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CFTR



The Israel Chemical Society (ICS: www.chemistry.org.il)



The Israel Institute of Chemical Engineers (IIChE: www.iiche.org.il)



The Israel Society of Chemical Engineers and Chemists (ISCEC)





The Conference of the Association of Engineers, Architects and Graduates in Technological Sciences in Israel on the subject of

Natural Gas in Israel - Engineering and Industry

September 20, 2016, at Bar-Ilan University, Israel

The discovery of the large gas reserves off the shores of Israel has led to a revolution in Israel's energy industry.

The transition to natural gas as Israel's main energy source has extensive influence on the economy, industry and the environment.

This step will require risk management in order to assess the mix of fuel types in creating reliable and available electric energy in Israel.

Prominent members of the government ministries, Israeli industry and academia will participate in the conference, in order to provide the best and most professional review possible with regard to the subjects in question.

Companies that are interested in taking part in the commercial exhibition should contact: Orel Lahav, **03-5205827**, **orel@aeai.org.il Conference website: http://www.ngi.org.il**

Association of Engineers and Architects, Shani Harpaz Tl. 03-5205808, Fax 03-5272496, shani@aeai.org.il

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Dear Friends,

It is an honor for me to introduce this 2nd edition of the Journal of the Israel Society of Chemical Engineers and Chemists at the Association of Engineers and Architects in Israel, in cooperation with the Israel Chemical Society and the Israel Institute of Chemical Engineers.

The Israel Society of Chemical Engineers and Chemists is one of the largest professional societies at the Association of Engineers, Architects and Graduates in Technological Sciences in Israel. The association is a representative umbrella organization that incorporates tens of thousands of engineers, architects and academics in technological professions, based on their fields of knowledge and endeavor. The association makes connections between academic study and thinking and their practical application at Israel's industrial and hi-tech facilities.

Working alongside the Israel Society of Chemical Engineers and Chemists at the association are the Israeli Society of Mechanical Engineers, the Israeli Society of Safety Engineers, the Israeli Society of System Engineering, the Data Science Society, the Israeli Society of Electric and Electronics Engineers, the Israeli Association of Construction and Infrastructure Engineers, the Israeli Society of Industrial and Management Engineers, the Israel Association of Municipal Engineers and the Israeli Institute of Architects and Town Planners.

Our Vision

- Professional and technological development of Israel's engineers in all branches of engineering, architecture and technological professions, due to the understanding of the importance of technological development to the individual, the advancement of the Israeli economy and society, the development of the younger generation and as a contribution to the community and humanity as a whole in an ever- changing global era.
- · Amalgamation of the entire body of Israeli engineers

under one roof - one community that learns, shares, develops and contributes.

• Creating collaboration for the purpose of brainstorming and interdisciplinary cooperation.

Our Method

- Collaborations with central parties in the community: industrial and hi-tech facilities, academic engineering faculties, the engineering student body, international organizations, the education system, government ministries and parliamentary committees.
- Establishing new societies based on fields of interest.
- Promoting women and minorities in the various fields of engineering and management.
- Organizing conferences, exhibitions, seminars and professional tours of engineering plants in Israel and overseas.
- Organizing workshops, courses and certification training in various engineering fields.
- Promoting legislation and involvement in the decision making process in Israel's government systems.
- Encouraging initiatives for the advancement of the younger generation.
- Encouraging innovation and entrepreneurship through projects.
- Publishing professional journals in various fields of engineering.

We invite you to take part in our extensive activities and contribute your knowledge and experience to the entire community of engineers and architects.

We hope that this journal will serve as a source of enriching and reliable knowledge, and will be of help to you in your various fields of expertise.

Best Wishes,

Ehud Noff

Chairman of the Association of Engineers, Architects and Graduates in Technological Sciences in Israel



Dear Readers,

Welcome to the second issue of the Israel Chemist and Engineer (ICE) online magazine. This is a joint venture of the Israel Chemical Society (ICS), the Israel Society of Chemical Engineers and Chemists (ISCEC) at the Association of Engineers, Architects and Graduates in Technological Sciences in Israel (AEAI) and the Israel Institute of Chemical Engineers (IIChE).

We hope you will find the magazine interesting and will be inspired to contribute to future issues. You will find articles describing the fight for a cure for cystic fibrosis, the use of titanium in the oil refining and petrochemical industry, and several aspects of the conversion of phosphate rock into phosphoric acid. In addition, there are two fascinating articles of historical interest, one on Tadeus Reichstein who performed the first synthesis of vitamin C and one on Chaim Weizmann and the trials and tribulations he experienced in producing acetone for the allies during the First World War. In an effort to reveal the personalities behind the impressive CVs, we include the profiles of six Israeli chemists who were awarded prizes at the 2015 or 2016 ICS meetings. In addition, there are reports of the 2016 ICS meeting and the 7th National Graduate Student Symposium in Organic Chemistry. Finally, we have reproduced the poster that Daniella Goldfarb presented at the 2016 ICS meeting on the gender balance in chemistry in Israel. While approximately 50% of graduating PhDs are women, and there is some improvement at the senior lecturer/assistant professor level, there is still considerable imbalance at the full professor level. We will be pleased to publish any suggestions for improving the situation.

In future editions, we hope to have profiles of the various chemical industries that contribute to Israel's economy, articles on the various careers open to chemists and chemical engineers in Israel, and a discussion of the future of chemistry education in our high schools which directly impacts recruitment to chemistry and engineering degrees in the universities.

If you have other suggestions for future editions or would like to contribute an article, please contact me at gordon@biu.ac.il.

Arlene D. Wilson-Gordon Professor Emerita Chemistry Department, Bar-Ilan University ICE Editor



Dear Fellow Chemists and Chemical Engineers,

It is with much satisfaction that we celebrate the second issue of ICE. This new format of the old ICS Bulletin unites the three major Israeli organizations of chemists and chemical engineers under the leadership of Editor-in-Chief Prof. Arlene Wilson-Gordon. In less than a year, the ICE magazine has reached maturation and much visibility not only within the State of Israel, but also worldwide. It represents a successful collaboration among multiple organizations, all striving to promote the chemical sciences and engineering, chemical industry and chemistry education.

I am sure that all ICS members have been watching with gratification the enormous progress of our official journal, the Israel Journal of Chemistry (IJC) over the past few years. Since we transferred this journal to the Wiley-VCH publishing house in 2010, it has climbed up to unprecedented heights in terms of impact factor, usage index and relative rating among the chemistry journals around the world. We are pleased to see that both the IJC and ICE significantly influence the scientific community, as well as the general public and government agencies.

Many exciting events took place in our community over the past year. A year ago, in our 80th Annual Meeting we hosted a prestigious delegation from Stanford University, including two Nobel Prize Laureates. The 81st Meeting of this year was equally exciting, sharing our science with a distinguished delegation of nine world leaders from five different Texas universities. Much of that is summarized in my Conference Report in this issue. Certainly, we remember other remarkable events that took place recently. The 6th EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry was held in the Weizmann Institute last November under the responsibility of the Medicinal Chemistry Section of the ICS. The 7th National Graduate Student Symposium in Organic Chemistry (also summarized in this issue) took place last December in Ariel University.

Other exciting events are coming soon. In May, two teams of ICS runners, including myself, completed the 2016 Mountain-

to-Valley relay race (also reported in this issue). In June 1, 2016, just one day before the Wolf Prize ceremony in the Knesset, we had a special symposium at the Technion, honoring the two prize Laureates in Chemistry, K.C. Nicolaou and Stuart Schreiber. Later, we'll have the annual meeting of our Graduate Students Division and the 14th MCS-ICS meeting. The major event upcoming event will be our 82nd Annual Meeting, which will be held In February 2017 under the responsibility of Bar-Ilan University with Prof. Bilha Fischer as Chairperson. In that meeting we'll host a respectable delegation of scientists from LMU-Munich. The 6th Angewandte Symposium, which will follow the ICS meeting, will be done jointly by the ICS, the German Chemical Society (GDCh), Angewandte Chemie and the IJC.

I wish to conclude with a personal note. I've never predicted that upon becoming an Emeritus Professor my overall load of professional commitments would increase rather than shrink. It is already my third term as ICS President, my 9th year as Editor-in-Chief of the IJC and 9th year as Chairman of the Advisory Council of High School Chemistry Education at the Ministry of Education. My involvement with the Wolf Foundation has increased, as well as my function in the international organizations of chemistry, now serving on the Bureau of IUPAC after completing my term in EuCheMs Board. In addition to my research program and public writing, taking a management role in the new Technion campus in China has been quite challenging. Leonardo da Vinci used to say, "Time stays long enough for anyone who will use it." And Johann Wolfgang von Goethe said, "We always have time enough, if we will but use it aright." I've noticed that both of them kept away from the TV, YouTube and the social networks.

Enjoy your reading, **Prof. Ehud Keinan** President, the Israel Chemical Society



Dear chemical engineers, chemists, teachers of chemistry and all readers who are interested in chemistry and chemical engineering,

I hope you enjoyed the 1st issue with its diverse topics in chemistry, chemical engineering chemical education, and history in chemistry. It inspired us to prepare the 2nd issue. We see our mission as the dissemination of knowledge and education of a new generation of scientists, 'changemaking' engineers, educators, and managers. A 'changemaking' engineer is a creative person who can change the world for the better. We have to develop creative engineers who can solve current and future problems in industry, science, and society. Usually an engineer is "burdened, connected" by different algorithms, standards, codes, and specifications. An engineer works in a "rigid framework". Our task is to "emancipate" him, to give freedom for creative work, creative thinking. This new approach is reached by use of humanitarian aspects in engineering and scientific teaching and education. Certainly we should learn to approach everything with a positive mindset.

Chemical enterprises have many problems and you will find new solutions in the selection of materials, corrosion control, new technologies, to name a few.

2016 is full of events in different fields of chemistry and

chemical engineering. The current magazine will inform you about this too. I will mention only some of them and you can find information on the website www.engineers.org.il. The conference "Natural Gas in Israel: Present and Future" will be held on September 20, 2016 at Bar-Ilan University, Ramat Gan. The chemical seminar "Technologies: Pros and Cons. Chemistry and Life. How to be successful?" will be held on June 5-8, 2016 at the Dead Sea with invited lectures by the Nobel Laureate in Chemistry 2011, Prof. Dan Shechtman, and the President of the Israel Chemical Society Prof. Ehud Keinan. The 12th biannual conference of the Israel Corrosion Forum will be held on November 24, 2016 in Tel Aviv.

Now we invite you to start your journey into the amazing world of chemistry, chemical technology and chemical education. I am sure that reading this magazine will enrich your knowledge.

Dr. Alec Groysman

Chairman, the Israel Society of Chemical Engineers and Chemists at the Association of Engineers and Architects in Israel (AEAI)

Fighting Cystic Fibrosis: In Search of a Cure

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Abstract: Cystic Fibrosis (CF) is the most common lethal genetic disease among Caucasians with an estimated worldwide patient population of 70,000 (~30000 in the US; ~650 in Israel), and a median survival age in the late thirties. Years of efforts, both in basic research and in translation research, have led to significant increases in both the lifespan and quality of life of CF patients, mainly through treating the symptoms of the disease.

CF puts an enormous burden, both emotional and economical on CF patients, their families and the public healthcare system. It was estimated that the US market for the treatment of CF related pulmonary symptoms grew more than 15% annually to \$397M, from 2000 to 2007. These numbers are expected to further increase with the anticipated increase in the lifespan of CF patients.

CF is caused by mutations to a protein named the cystic fibrosis transmembrane conductance regulator (CFTR). The mutant proteins cannot form into the completely assembled machine that is required to efficiently transport chloride ions across the cell membrane in order to keep the mucus layer lining the surface of the lung moist. The dehydrated mucus is readily colonized by bacteria, ultimately resulting in chronic disease and lung failure.

While the details of the assembly process are not fully understood, ample experimental evidence suggests that increasing chloride conductance by stabilizing the weak structure of the mutant protein or stabilizing its chloride-conducting conformation can alleviate most of CF pathologies. Indeed, two orally available drugs which were recently approved by the FDA can do just that. Lumacaftor stabilizes mutant CFTR channels and increases their number at the cell membrane while Kalydeco (ivacaftor) is able to increase chloride conductance through these channels by keeping them open for longer periods of time. When co-administered, these two compounds can treat the majority of CFTR patients. Yet the efficacy of this treatment is still questionable and new and better drugs for CF patients are still badly needed.

Here we review the pathophysiology of CF, the molecular basis of the disease and some of the available treatments with emphasis on the development of CFTR modulators.

1. Cystic Fibrosis (CF)

1.1 Disease Characteristics

Cystic Fibrosis (CF) is the most common lethal monogenic disease among Caucasians. It affects about one in 3500 individuals leading to a current worldwide patient population of ~70,000 with about half located in the US. In Israel there are currently ~650 CF patients. Due to the relatively small number of patients, CF is defined as an orphan disease (according to US criteria, an orphan disease is a disease that affects fewer than 200,000 people). CF results in chronic obstruction in multiple organs and consequently in an array of pathologies including depressed lung function, inflammation and chronic

Hanoch Senderowitz completed his Ph.D. studies in computational organic chemistry with Professor Benzion Fuchs at Tel Aviv University in 1993 doing computational work on steric and stereoelectronic effects. Between 1993 and 1997, he was a Post Doctorate Fulbright Fellow with Professor Clark Still in the MacroModel development team at Columbia University developing enhanced sampling methods and QM-based carbohydrate force fields. In 1997, Dr. Senderowitz returned to Israel and joined the pharmaceutical industry first at Peptor Ltd. and latter at EPIX Pharmaceutical where he held the position of Executive Director Computational Development. In 2009 Dr. Senderowitz was appointed as an associate



professor at the Department of Chemistry, Bar-Ilan University where he currently heads the laboratory of molecular modeling, computer aided drug design and chemo-informatics. His research focuses on modeling the structure and mode of action of pharmaceutically relevant bio-targets, studying the factors governing the interactions between such targets and their ligands, and predicting the pharmacological profile of drug candidates.



Figure 1: Increase in life expectancy of CF patients. Taken from http://www.newhealthguide.org/Cystic-Fibrosis-Life-Expectancy.html



Figure 2: Chloride conductance via normal CF channels located at the cell membrane leads to hydration of the mucus layer lining the epithelial cells of the lungs and to its facile clearance from the body (left). Mutant CFTR channels are either completely absent from the cell membrane or, if present, their chloride conductance efficiency is impaired. This leads to the dehydration of the mucus layer and to its subsequent colonization by bacteria. As the disease progresses, the bacteria form biofilms which are resistant to antibiotics. Taken from http://cyfbin.weebly.com/cyfb.html

lung disease, pancreatic and digestive insufficiency, bowel obstruction, diabetes, hepatic damage and male sterility. As a result of the development of multiple therapies, the median survival age of CF patients has steadily increased from about 20 years in the eighties to about 40 years today (Figure 1). Yet even today there is no global cure for CF and most of the treatments available to CF patients are symptomatic ^[1, 2].

1.2 What Causes CF

CF is caused by mutations in the gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR is a 1480 residues long membrane glycoprotein localized to the apical surface of epithelial cells that line ducts of glands and airways and functions as a chloride channel, transporting chloride ions from the intra-cellular matrix to the extra-cellular milieu. There are currently more than 2000 known mutations associated with CFTR ^[3] with different prevalence and symptom severity and all compromise the ability of the protein to conduct chloride ions across cell membranes ^[4].

Impaired chloride conductance disrupts the ion-liquid balance across the epithelial cells lining the respiratory system, leading to dehydration of the mucus layer lining the lungs and in turn to its reduced clearance. Since there is no sufficient clearance of the mucus it is colonized by bacteria, ultimately resulting in chronic lung disease and lung failure (Figure 2).

2. The Molecular Basis of CF

2.1 The Structure of CFTR

As noted above, CF is caused by mutations to CFTR. CFTR is a member of the ABC (ATP-binding cassette) transporter family ^[5] but has a unique functionality being the only ion channel in this group ^[4]. Nevertheless, CFTR architecture is similar to that of other ABC transporters and its structure comprises two membrane spanning domains (MSDs) connected through four intra-cellular loops (ICLs) to two nucleotide binding domains (NBDs). In addition, CFTR features a unique intrinsically disordered R-region which is located at the sequence level between NBD1 and MSD2 (Figure 3) ^[4, 6-11]. Despite years of efforts, the crystal structure of full length CFTR is unavailable and the only direct structural information of the full channel comes in the form of low resolution electron microscopy maps. Yet multiple homology models of CFTR have been reported in the literature ^[12-20].

2.2 The Mechanism of Action of CFTR

The gating of the CFTR channel is controlled by the binding and hydrolysis of ATP. Gating requires the prior

phosphorylation of the regulatory (R) domain by protein kinase A (PKA). Following phosphorylation, the R domain undergoes a conformational change that allows for the binding of two ATP molecules to the interface between NBD1 and NBD2. This binding event leads to the dimerization of the two domains and to subsequent channel opening. Hydrolysis of one ATP molecule weakens the NBD1:NBD2 interaction, leading to dimer dissociation and subsequent channel closure (Figure 4) ^[21, 22].

2.3 Mutations in CFTR

More than 2000 mutations to the gene coding for CFTR are reported in the literature ^{[3].} These are primarily organized in two databases. The CFTR1 database (http://www.genet. sickkids.on.ca/Home.html) contains clinical information related to the details of discovery of specific mutations. More detailed and expert-reviewed functional and clinical information on a subset of CFTR mutations can be found in the CFTR2 database (http://cftr2.org/) ^[23]. Mutations in this database are classified according to the different mechanisms by which they are known to operate (see below). Both databases are continuously updated with new mutations as these are identified, and with new information related to their mechanisms of action as these are elucidated.

CFTR mutations are classified into six classes (see Figure 5) ^[24-26]. All mutations compromise the ability of the protein to conduct chloride ions. Class I mutations produce premature termination signals (premature stop codons) that result in incomplete translation of CFTR and in its (almost) complete absence from the cell membrane. Class II mutations produce a misfolded protein which fails to mature and consequently does not traffic to the correct cellular location (i.e. cell membrane). Class III mutations produce enough mature CFTR at the cell membrane but interfere with the gating process of the protein reducing its open probability (i.e., the amount of time the protein maintains an open, chlorideconducting conformation). Class IV mutations are located along the chloride conductance pathway reducing chloride transport. Class V mutations result in alternative splicing that disrupts mRNA processing by generating both alternative and normal transcripts, albeit the latter in minor amounts. This leads to extremely reduced amounts of normal CFTR protein at the cell membrane. Finally, class VI mutations reduce the stability of the protein in the apical cell membrane thereby increasing its turnover rate and reducing its chloride conductance. Importantly, some of the CF-causing mutations can be classified into several classes.

The most common CF-causing mutation is the deletion of the codon for phenylalanine 508 (F508del) in the primary



Figure 3: Schematic representation of CFTR. Taken from http://www.hopkinscf.org/what-is-cf/basic-science/cftr/structure/



Figure 4: The gating cycle of CFTR. Taken from https://en.wikipedia.org/wiki/ATP-binding_cassette_transporter

sequence of wild type CFTR ^[3, 27, 28]. This is a class II mutation found in over 90% of CF patients. Structurally, this mutation is located at the interface between NBD1 and the 4th intracellular loops which forms part of the second membrane spanning domain (MSD2). At the level of NBD1, the F508del mutations leads to increased aggregation propensity and to reduced thermal stability and folding yield. At the level of the full length protein, this mutation leads to impaired interactions of NBD1 with other CFTR domains ^[29-36]. This in turn leads to a CFTR channels that are incorrectly or



Figure 5: CFTR mutations. Taken from https://www.researchgate.net/figure/266206301 fig1 Figure-2-Classes-of-CFTR-gene-mutations-The-aim-of-stratification-of-CFTR-mutations

incompletely folded and consequently become targeted to endoplasmic reticulum (ER)-associated degradation ^[37]. The few mutant chloride channels that pass the quality control or simply escape the ER before degradation are eventually incorporated into the plasma membrane. However, these are thought to represent less than 5% of the level observed in cells expressing wt-CFTR and in addition are characterized by an open probability about 15 fold lower than that of wt-CFTR ^[38, 39] (i.e., class III mutation) and by impaired membrane stability ^[40] (i.e., class VI mutation), resulting in a commensurate low total whole-cell chloride conductance. CF patients bearing the F508del mutation can be treated with the Orkambi combotherapy which was recently approved by the FDA (see below).

Another common mutation is glycine-to-aspartate at position 551 (G551D) in the signature motif of NBD1 ^[41]. This mutation is categorized as a class III mutation (defective regulation) and appears in ~4% of CF patients ^[42]. The resulting mutant can traffic normally to the apical membrane and is normally phosphorylated ^[43], but is characterized by a drastically reduced channel activity due to an extremely low open probability, ~1% compared to that of wt-CFTR ^[41]. CF patients bearing the G551D mutation can be treated with Kalydeco which was approved by the FDA in 2012 (see below).

Class I mutations (defective protein production) are found in ~10% of CF patients and the most common ones are G542X and W1282X, the latter being particularly common in Ashkenazi Jews ^[44].

Overall, understanding the different molecular mechanisms of CFTR dysfunction caused by different mutations is necessary in order to provide the scientific basis for the development of drugs for mutation-specific therapy of CF.

3. CF Therapies

As discussed above, CF leads to an array of pathologies affecting multiple organs in the body. Furthermore, the severity of the disease and its symptoms are determined by the specific genotype of each individual. Thus, (1) there is no off-the-shelf treatment available to all CF-patients and in order to achieve optimal results, treatment regimes should be patient-tailored, (2) the optimal treatment involves multiple pharmaceutical interventions. Indeed a range of medicines is required to treat the multi-organ pathologies characteristic of CF at the symptomatic level. Moreover, even the Orkambi medicine that treats the underlying defect of the disease by modulating the behavior of CFTR itself is in fact a combo-therapy composed of ivacaftor and lumacaftor (see below). Figure 6 provides an overview of the CF drug discovery pipeline.

While the focus of this review is on CFTR modulators, we begin by a short description of some of the therapeutic agents available to treat CF symptoms.

3.1 Symptomatic Treatments^[45, 46]

3.1.1 Antibiotic Therapy

Colonization of the respiratory tract by bacteria is at the root of the declining respiratory function and consequent mortality of most CF patients. Microbial colonization typically begins early at childhood and the bacteria profile changes with age. With time, repeated infections compromise the integrity of the lung structure leading eventually to lung failure. Keeping the lungs of CF patient bacteria-free, or at least reducing the microbial burden as much as possible, is therefore of paramount importance in the treatment of CF. In this battle, antibiotics plays a pivotal role.





CF patients are typically subjected to frequent mucus screening for the early detection of pathogens and based on the results are treated with a variety of antibiotics such as flucloxacilin, tobramycine, and azithromycin, administered either by inhalation or intravenously. In certain countries (e.g., the UK) antibiotic treatment begins early in life to stave off bacterial colonization. This treatment strategy however is not standard practice in the US.

3.1.2 Mucolytic Therapy

As noted above, a dehydrated, sticky mucus layer lining the lungs is a hallmark of CF. Re-hydrating the mucus layer and/ or reducing its viscosity is therefore a viable therapeutic approach.

The mucus of CF patients is a complex mixture consisting of mucin, extracellular DNA and other polymeric substances. Mucolytic agents in clinical use include N-acetylcysteine (marketed as Mucomyst) for breaking disulfide bridges in mucin glycoproteins and recombinant human DNAse I (marketed as Pulmozyme) for DNA cleavage. In addition, osmotic agents (e.g., inhaled saline solution) are also used to thin the mucus layer and facilitate its expectoration. These agents likely work by increasing the osmolyte concentration outside the cell, thereby increasing the diffusion of water molecules across the cell membrane and into the mucus layer.

3.1 Treatments Targeting CFTR

The growing understanding of the molecular basis of CF pathologies has stimulated the development of CFTR-targeting pharmacological agents, termed CFTR modulators with the hope to repair the underlying defects in CFTR.

CFTR modulators can be classified according to the underlying defect they seek to repair. CFTR potentiators are compounds that interact with mutated CFTR channels already present at the cell membrane to increase their open probability. This could be achieved either by prolonging the open time of the channel and/or by increasing the opening rate. Potentiators may therefore be applicable to mutation classes III - VI, which are characterized by full length CFTR that reaches the cell surface but exhibits reduced ion transport activity owing to abnormal channel gating (class III and IV) or reduced number of active channels (class V and VI). In contrast, CFTR correctors (also known as pharmacological chaperones) are compounds that correct the folding defect of mutated CFTR and consequently increase the number of CFTR channels in the cell membrane. Correctors may therefore be applicable to class II mutations, which are characterized by defective protein processing. Finally, compounds which exert their

effect by reading through premature termination codons (PTCs) allow the ribosome to ignore the faulty stop signal and continue translation of the mRNA, resulting in the formation of a functional protein. PTCs are therefore applicable to class I mutations.

3.1 Challenges in the Development of CFTR Modulators

Efforts towards the development of CFTR modulators of all three types have been going for over a decade. Yet these efforts are complicated by numerous challenges including: (1) The challenging nature of the required pharmaceutical intervention and the resulting pharmacological characteristics of putative modulators; (2) The lack of structural and mechanism of action (MOA) data relevant to rational drug design; (3) The need to overcome potential compliance issues.

As opposed to more common drugs which typically exert their effect by agonizing/antagonizing a bio-target through binding into well-defined endogenous or allosteric sites, it is unclear whether CFTR has sites suitable for the binding of correctors, and, except of the ATP binding site, sites appropriate for the binding of potentiators. Moreover, while potentiators are likely to bind to CFTR in its mature state, correctors may also bind to intermediate states encountered during CFTR's folding process.

CFTR modulation requires the pharmaceutical intervention in cellular processes such as translation, folding, trafficking and gating, all of which are multistep and involve multiple cellular factors. Thus, restoring these processes to their normal behavior could in principle be achieved by drug interactions with other, often cell type specific ^[47] cellular targets such as the chaperones, glycosylation enzymes and phosphorylation/ dephosphorylation enzymes which control the gating cycle.

However, these targets are non-specific and consequently, interference with their functionality may lead to undesirable side-effects. Therefore, in order to prevent potential selectivity issues, it is preferable that CFTR correctors and potentiators exert their effect by directly interacting with the mutant CFTR channel. Similarly, read-through of premature termination codons should selectively induce ribosomal read-through of faulty but not of normal termination codons.

A second challenge in the development of CFTR modulators stems from the lack of accurate structural and MOA data relevant to rational drug design. A high-resolution crystal structure of full length CFTR is currently unavailable and only lower-resolution structures have been published ^[48, 49]. Currently available CFTR models are inherently approximate.

Finally, potential compliance issues dictate an oral mode of administration to newly developed CFTR modulators in order not to inconvenience CF patients by further complicating their treatment regime. This requirement strongly restricts the chemical space in which new CFTR modulators could be searched for.

3.2 Strategies for the Development of CFTR Modulators

Strategies for the development of new CFTR modulators can be broadly divided into two classes, namely: (i) brute force methods and (ii) structure-based methods.

Brute force approaches utilize high-throughput screening (HTS) assays to discover new drug candidates. This search strategy attempts to cover as large a region of chemical space as possible, by testing large libraries of compounds in search for those that exhibit the required behavior (i.e. active hits). Thus, the resources required, in terms of both time and cost, linearly scale with the number of compounds to be screened. In contrast, structure-based methods rely on prior knowledge of the target or ligand structures to perform a more sophisticated search through the chemical space.

3.2.1 Brute Force Methods

Several HTS campaigns for the discovery of CFTR modulators have been reported in the literature and have led to the identification of several different structural classes of potentiators.

Yang et al. ^[50] identified six novel classes of high affinity potentiators of F508del-CFTR by screening 100,000 diverse small molecules using an iodide uptake functional assay in epithelial cells co-expressing F508del-CFTR and a high sensitivity halide indicator. Thirty-two compounds with submicromolar potency were identified, which corresponds to a hit rate of 0.03%. Further screening of over 1000 structural analogues revealed a series of tetrahydrobenzothiophenes that activated F508del-CFTR Cl⁻ conductance reversibly with Kd < 100 nM. The importance of this study lies not so much in the discovered compounds but rather in the development of a HTS methodology which was subsequently used in many other similar campaigns ^[47].

Perhaps the most successful HTS campaign for the discovery of CFTR potentiators was conducted by the Vertex group ^[51, 52]. This group has reported the HTS of over 220,000 compounds for F508del-CFTR potentiation using NIH/3T3 cells overexpressing F508del-CFTR. The resulting hits were subsequently optimized into drug candidates culminating in the development of VX-770, the first orally available CFTR

potentiator approved by the FDA and marketed under the trade name Kalydeco (see below).

Fewer CFTR correctors have been reported in the literature. Pedemonte et al.^[47] have screened 150,000 diverse compounds using the above-mentioned iodide flux assay. Several classes of F508del-CFTR correctors were identified and subsequently optimized to improve correction, potency and efficacy. This led to the development of e.g., corr-4a which is extensively used as a tool compound and as standard against which to measure newly discovered correctors.

The Vertex group has also performed the most successful HTS campaign for the discovery of CFTR correctors ^[52]. Over 160,000 compounds were screened for F508del-CFTR correction. Hits were verified using an array of functional assays and subsequently optimized into drug candidates culminating in the development of corrector VX-809 which forms part of the recently FDA approved Orkambi combotherapy (see below). Subsequent optimization led to corrector VX-661 which is currently in clinical trials for the treatment of CF patients homozygous to the F508del mutation.

HTS assays were also applied to the identification of compounds capable of overcoming PTCs. PTC Therapeutics used a luciferase reporter gene system for the screening of over 800,000 compounds in an attempt to identify new agents able to induce translational read through [53]. Multiple chemical scaffolds were identified and subsequently optimized through extensive medicinal chemistry efforts, leading to the development of PTC-124 (Ataluren), a novel, orally bioavailable compound that exhibits PTC suppression at concentrations readily achievable in serum. Unfortunately, Phase III clinical trials did not show significant improvement in forced expiratory volume (FEV1) measurements upon Ataluren treatment [54] (FEV1 is the volume of air that can forcibly be blown out in one second, after full inspiration and is the most common endpoint in clinical trials of CF therapies). However, stabilization of lung function was observed in a subset of patients and a new Phase III trial in that subgroup is ongoing [55].

3.2.2 Structure-Based Approaches

Structure-based approaches rely on structural knowledge of the biological target (target-based approaches) or its ligands (ligand-based approaches) in order to perform a more sophisticated search through the available chemical space, thereby increasing the efficiency of the screening procedure. Target-based approaches use information on the structure of putative binding sites in order to identify sets of compounds which best match them. Ligand-based approaches retrieve sets of compounds based on similarity to known active ones.



Figure 7. A pharmacophore model of CFTR potentiators. Blue, red, green and black spheres represent, respectively, H-bond donor, H-bond acceptor, aromatic ring, and excluded volume features. The overall shape of the pharmacophore model is depicted in grey.



Figure 8: CFTR potentiators.

As an example of a ligand based approach, Springsteel et al.^[56] used a series of 77 benzoflavone analogues to examine activation of G551D-CFTR and formulated a fourpoint pharmacophore model featuring a hydrogen bond acceptor, an aromatic ring and two hydrophobic groups. The pharmacophore model suggested a common binding mode for the flavones and other known CFTR potentiators at one of the NBD sites, and may therefore be used for the virtual screening



Figure 9: CFTR correctors.

of novel potentiators. Another pharmacophore model was derived based on known CFTR potentiators and used for the virtual screening of a database of ~750,000 compounds (see Figure 7). This effort has led to the discovery of a few new potentiators which although not optimized into drug candidates, served as useful research tools.

As an example of a structure-based approach, Kalid et al. ^[57] have used a CFTR model for the in silico screening of CFTR

modulators targeting three putative inter-domain binding sites. A total of 496 candidate compounds from all three sites were tested using a functional iodide flux corrector assay ^[47]. Fifteen compounds, representing diverse chemotypes, were identified as F508del-CFTR folding correctors corresponding to a 3% hit rate, ~10-fold higher than hit rates obtained in corresponding HTS campaigns. The same binding sites also yielded potentiators and, most notably, compounds with a dual corrector-potentiator activity.

Some of the CFTR potentiators and correctors identified by the above described (and other) screening efforts are presented in Figures 8 and 9, respectively. For the benefit of CF researchers, these compounds are today distributed, free of charge, to the scientific community by the Cystic Fibrosis Foundation (www.cff.org).

3.3 CFTR Modulators Approved by the FDA

To date, only two orally-bioavailable CFTR modulators have been approved by the FDA. The first of these compounds is Ivacaftor marketed under the name Kalydeco (Figure 10). Kalydeco is a potentiator (i.e., a compound acting on CFTR channels already in the cell membrane to increase their open probability) discovered by Vertex Pharmaceuticals through the optimization of hits discovered in a high throughput screening (see section 3.2.1 above). The compound was originally approved for the treatment of CF patients bearing the G551D (class III) mutation. However, it was soon realized that this compound is able to potentiate additional CFTR mutations and today, it is approved for the treatment of CF in patients age 2 years and older who have one of the following mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or R117H. Interestingly, the binding site of Kalydeco is not known, yet its ability to potentiate multiple mutations residing in different domains of CFTR may suggest binding to an allosteric site.



Figure 10: The structure of ivacaftor.

The efficacy of Kalydeco was evaluated in two randomized, double-blind, placebo-controlled clinical trials in 213 clinically stable patients with CF, 109 receiving the compound 150 mg twice daily. Trial 1 evaluated 161 patients with CF who were 12 years of age or older with FEV1 at screening between 40-90%. Trial 2 evaluated 52 patients who were 6 to 11 years of age with FEV1 at screening between 40-105%. Patients in both trials were randomized 1:1 to receive either Kalydeco or placebo every 12 hours with food containing fat for 48 weeks in addition to their prescribed CF therapies. The primary efficacy endpoint in both studies was improvement in lung function as determined by the mean absolute change from baseline in FEV1 through 24 weeks of treatment.

In both studies, treatment with Kalydeco resulted in a significant improvement in FEV1. The treatment difference between Kalydeco and placebo for the mean absolute change in FEV1 from baseline through week 24 was 10.6 percentage points (P < 0.0001) in Trial 1 and 12.5 percentage points (P < 0.0001) in Trial 2. These changes persisted through 48 weeks. Improvements in percent predicted FEV1 were observed regardless of age, disease severity, sex, and geographic region. In addition, people over 12 years old who took Kalydeco reported less coughing, less mucus and less trouble breathing compared with people who took placebo (no beneficial effect in these parameters was reported for children under 12 years old). Moreover, nearly 70% of the people over 12 years old taking Kalydeco did not have a pulmonary exacerbation during the trial as opposed to only $\sim 40\%$ of the people taking placebo. Finally, in both trials patients on the medicine gained ~6 pounds during the 48 weeks treatment compared to patients taking placebo^[58].

In parallel with the Kalydeco discovery effort, Vertex Pharmaceutical was also engaged in the discovery and development of a CFTR corrector (i.e., a compound that would correct the folding defect in CFTR and increase the number of channels at the cell membrane) for the treatment of CF in patients homozygous to the (most common) F508del mutation. These efforts culminated in the development of XV-809, later called lumacaftor (Figure 11).



Figure 11: The structure of lumacaftor.

Similar to Kalydeco, the binding site of lumacaftor on CFTR was not determined. Some evidence suggests that this compound binds to the first trans-membrane domain^[59] whereas others suggest binding to the region of the missing F508, at the interface between NBD1 and ICL4 (the 4th intracellular loop)^[60]. A putative binding mode of lumacaftor to this site is shown in Figure 12.



Figure 12: A putative binding mode of lumacaftor at the interface between NBD1 and ICL4. The protein is shown as a ribbon diagram color coded according to its secondary structure (red: alpha-helices; blue: beta-sheets). Lumacaftor is presented in sticks-and-balls. Left: Global view; Right: Close up.

Unfortunately, lumacaftor, when administered alone, did not meet all the biological endpoint in clinical trials^[61]. This is perhaps not surprising since F508del-CFTR channels that are able to incorporate to the cell membrane are poor Cl⁻ conductors due to low open probability and poor membrane stability.

Realizing that, Vertex Pharmaceutical has launched a series of clinical trials co-administering lumacaftor with Kalydeco under the assumption that the former compound will increase the number of CFTR channels at the cell membrane while the latter, will increase their open probability. Indeed, this corrector-potentiator combination, called Orkambi met the clinical endpoint and was recently approved by the FDA for the treatment of CF patients homozygous to F508del.

The efficacy of Orkambi was evaluated in two randomized, double-blind, placebo-controlled, 24-week clinical trials in 1108 clinically stable patients with CF of whom 369 patients received the compound twice daily ^[62,63]. Trial 1 evaluated 549 patients with CF who were aged 12 years and older with FEV1 at screening between 40-90%. Trial 2 evaluated 559 patients aged 12 years and older with similar FEV1 values. Patients in both trials were randomized 1:1:1 to receive either Orkambi (lumacaftor 400 mg every 12 hours/ivacaftor 250 mg every 12 hours) or lumacaftor 600 mg once daily/ivacaftor 250 every 12 hours or placebo.

Patients took the study drug with fat-containing food for 24 weeks in addition to their prescribed CF therapies. The primary efficacy endpoint in both trials was change in lung

function as determined by absolute change from baseline in FEV1 at week 24, assessed as the average of the treatment effects at week 16 and at week 24. In both trials, treatment with Orkambi resulted in a statistically significant improvement in FEV1. This positive effect persisted throughout the 24-week treatment period regardless of age, disease severity, sex, and geographic region.

4. Conclusions and Outlook

A survey of the CF drug development pipeline (Figure 6) reveals an exciting combination of drugs for treating the symptoms associated with CF with drugs addressing the underlying cause of the disease. The former have been extremely successful in increasing the lifespan and improving the quality of life of CF patients, while the latter, although relatively new in the market, are already showing promising results.

Besides bringing new hope to CF patients, the main importance of Kalydeco and Orkambi lies in establishing a proof of concept that restoring chloride conductance to levels sufficient for the amelioration of CF-related pathologies is indeed achievable through the oral administration of drug compounds. This has inspired many pharmaceutical companies to embark on drug discovery projects for CF. Indeed additional drugs are already in advanced clinical studies and are expected to reach the market in the near future. Yet, there is a clear need for the development of additional drugs, in particular for CF patients with rare mutations. An interesting approach in this respect which recently has shown some promising results is gene therapy which in principle is not limited to specific mutations [64, 65].

To date, the development of CFTR modulators has been primarily based on brute force rather than on rational design approaches. This is largely due to the fact that the type of information required for the successful application of rational methods, namely, the availability of a high resolution structure, relevant to drug discovery, of full-length CFTR and detailed mechanism of action information on CFTR modulators has not been available and in fact is still lacking.

Nevertheless, we believe that this missing information could be obtained and successfully applied to the discovery of new CFTR modulators. Indeed multiple efforts are currently underway for obtaining a higher resolution structure of full length CFTR using electron microscopy, for designing new CFTR constructs with improved solubility and crystallization propensity and for the development of CFTR domain-specific assays. These efforts will likely result in the discovery of new classes of CFTR modulators. Overall new hope is looming for CF patients.

5. References

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Titanium-Based Anticancer Agents: Developmental Stages toward the Dream Drug

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Abstract: Chemotherapy is the leading line of treatment for various cancer diseases and, in particular, the metallodrug cisplatin is highly effective towards specific tumor types. Its limitations regarding narrow activity range, resistance development, and severe side effects have triggered study on various other metals. Titanium complexes have been recognized as promising alternatives for more than two decades due to their higher activity range and reduced toxicity; nevertheless, their limitation lies in their general hydrolytic instability. The first generation of advanced anticancer titanium complexes that we have introduced and analyzed relies on bis(phenolato) tetradentate ligands with two labile monoanionic groups that were thought to be essential based on the known mechanism of cisplatin. Complexes of this family demonstrated activity mostly higher than that of cisplatin toward a wide range of cells, with in vivo efficacy and a degree of cancer selectivity. Additionally, they are markedly more hydrolytically stable than previously known titanium compounds,

Introduction

Cancer diseases are a leading cause of death worldwide. In fact, more than seven million people die annually from cancer, representing over 10% of all human deaths. The most common therapeutic approach includes chemotherapy. Despite the side effects often accompanying this type of treatment, its high effectiveness makes it the main approach for dealing with various tumors. Nevertheless, due to the common limitations of known drugs often relating to limited activity range, resistance development, and toxicity profiles, the search for new anticancer chemotherapeutic agents is evergrowing. Herein the requirements of a potent anticancer drug are overviewed, with a particular focus on the developmental stages of titanium-based compounds, as a newer generation of metallodrugs that follow the discovery of cisplatin.

Concerning Activity and Selectivity

The main requirement of a drug is to be effective; namely, to effectively inhibit cancer cell growth. Cisplatin is a platinumbased inorganic compound that is considered highly effective eventually yielding defined oxo-bridged clusters within several hours in water solutions. Such bulky clusters demonstrated themselves cytotoxicity but only when formulated, implying that: (a) accessibility is an important factor and (b) labile ligands are not needed for the activity. The second generation of complexes developed in our group addressed these aspects, providing the desired combination of particularly high cytotoxic activity and in vivo efficacy, wide activity range also toward the NCI-60 panel of the National Institute of Health (NIH), selectivity to cancer cells and no clinical signs of toxicity to treated animals, hydrolytic stability with no decomposition for weeks in biological environments, and accessibility whereby all activity aspects are obtained independently of formulations. Preliminary mechanistic insights point to controlled rather than instant cell death. Future research directions include profound mechanistic analyses as well as developing tumor targeting strategies, while proceeding toward clinical development.

Born in 1975, Edit Tshuva conducted her Ph.D. studies under the supervision of Prof. Moshe Kol at Tel-Aviv University, working on group IV metal complexes as catalysts for the polymerization of alpha-olefins. After graduating in 2001, she spent two years at The Massachusetts Institute of Technology (MIT) working as a postdoctoral fellow under the supervision of Prof. Stephen J. Lippard on synthetic models for metalloenzymes. In 2003 she joined the Hebrew University of Jerusalem as a Senior Lecturer, and was promoted



to Associate Professor in 2009. Her research group is interested in various topics that relate to synthetic bioinorganic chemistry, applying coordination chemistry techniques in the synthesis and investigation of transition metal complexes that have valuable biological and medicinal applications. Edit Tshuva is currently a member of the Israeli Young Academy, the Global Young Academy, the International Union of Pure and Applied Chemistry, and the editorial boards of Structural Chemistry and Journal of Visualized Experiments, as well as holds the position of Head of the School of Master Studies of the Faculty of Science at the Hebrew University.



Scheme 1. (a) Cisplatin; (b) titanocene dichloride; (c) budotitane.

toward a number of tumors and has been employed in the clinic for over 30 years (Scheme 1a).¹⁻⁸ In fact, it is reported that cisplatin may completely cure up to 80% of specific cancer types (ovarian, testicular), assuming that they are diagnosed at relatively early stages. Nevertheless, cisplatin suffers from two main limitations; its activity range is rather narrow, and it is only effective toward a number of tumors whereas others either do not respond to the treatment or can develop resistance. Additionally, severe side effects resulting from poor selectivity to cancer tissue further inhibit its utility.⁹ The pros and cons of cisplatin have triggered wide research on other metallodrugs with the aim to overcome the drug limitations.

Among metals studied as platinum alternatives,¹⁰⁻¹⁶ titanium showed promising results.^{13, 14, 17-22} The big advantage of the titanium metal is its biocompatibility; titanium oxide is a known safe material with no known side effects or any dietary restrictions, and is often found in food, cosmetic, or drug products.²³ This makes this metal attractive for exploration as a potential drug.

Titanocene dichloride (Scheme 1b) and budotitane (Scheme 1c) reached clinical trials already in the 1990s due to their wider activity range, being active also toward cells resistant to cisplatin.²⁴⁻²⁷ Additionally, reduced side effects were indeed reported, most of which were reversible - a clear advantage for patient quality of life. These observations marked titanium as highly attractive for further exploration.

Now Concerning also Stability

The titanium complexes titanocene dichloride and budotitane failed the clinical trials.²⁴⁻²⁷ Their main limitation was rapid hydrolysis in biological environments. As cisplatin operates by chelate binding to DNA through the positions of the cis labile chloro ligands that hydrolyze in the cell,^{3, 4} it was reasonable to maintain an equivalent structure with two cis labile ligands also in the titanium derivatives; nevertheless, as titanium is a hard oxophilic metal that rapidly reacts with water, the labile groups in titanocene dichloride (Cl) and in budotitane (OEt) hydrolyzed within seconds to minutes in water far



Figure 1. First generation of phenolato titanium complexes; $LTiX_2$ type (X = OiPr); representative X-ray structure.

before reaching the cells; consequently, the inert ligands (Cp, diketonato) hydrolyzed within a few hours, leading to formation of various unidentified oxo-bridged aggregates.^{14, 28-30} Accompanied by formulation problems, these obstacles prevented these compounds from progressing further to the clinic. It thus became evident that in order to proceed with studies on titanium compounds as anticancer drugs, hydrolytic stability should be seriously addressed.

Phenolato Compounds - 1st Generation LTiX₂ Complexes

Many studies focused on derivatives of titanocene dichloride and budotitane, namely, titanium complexes of substituted Cp rings and diketonato ligands, some producing markedly improved features.^{17, 22, 31} We, however, chose to go on a different path, and employ a different ligand system based on phenolato donors.^{30, 32} A chelating ligand with such donors should strongly bind the metal and inhibit hydrolysis. To maintain the general structure assumed to be of importance, the first generation of the complexes that we introduced for anticancer applications relied on a schematic design that included two labile monoanionic and monodentate ligands, and a tetradentate dianionic bis(phenolato) inert ligand for maximal stability. Such complexes had previously been studied for catalytic applications and a wide variety of derivatives may conveniently be obtained based on straightforward syntheses from numerous available starting materials.³³⁻³⁷ Thus, a new family of "salan" based diaminobis alkoxo-bis(phenolato) anticancer complexes was developed (Figure 1).³⁸

Concerning Activity, Selectivity and Stability

The salan complexes revealed incredibly high activity toward a wide variety of cell types (Figure 2).³⁸⁻⁴¹ Activity higher than that of cisplatin was mostly recorded, with inhibition concentration of 50% (IC_{50}) values in the low micromolar range for leading derivatives. Among the cancer cells responding to the salan titanium complexes are human colon, ovarian, cervix, melanoma, lung, leukemia, breast, and more (Figure 2). Additionally, activity was also recorded toward



Figure 2. Cytotoxic activity of several salan titanium complexes of $LTiX_2$ type and known compounds towards representative cell lines as presented by different bar colors (human: A375.S2 – skin, NCL-H 1229 – non-small-lung, HeLa - cervix, HT-29 – colon, OVCAR – ovarian, U937 – leukemia; murine: 4T1 – breast, Panc1 – pancreas); results are presented as IC_{s0} values: concentration that inhibits 50% of cell growth; lower bar indicates higher activity.



Figure 3. In vivo results showing tumor size in treated and untreated immune deficient (nude) mice (N=5) with sub-cutaneous inoculation of HT-29 colon cells; the complex of the $LTi(OiPr)_2$ type was injected IP every other day for 3 weeks when the experiment was terminated. Control mice were injected with PBS.

lines resistant to cisplatin, as observed with known titanium complexes.³⁹ This observation further establishes the wider activity range of titanium as it does not follow the resistance mechanism involving cisplatin. An observed reactivity also toward multi-drug-resistant (MDR) cells further contributed to the high potential of these compounds for utility toward a wide range of cancer types.³⁹ Importantly, in vitro combination studies with cisplatin revealed synergistic behavior for some

derivatives toward colon and non-small-lung cells,⁴² further emphasizing the potential application of these compounds in combination treatments, which are frequently employed for achieving optimal effects with reduced side effects.

Leading salan titanium complexes were also evaluated on noncancerous cells to establish possible toxicity and selectivity. Reduced activity was recorded on primary mouse cells,³⁹ as well as no decrease in viability in treated zebra fish embryos.⁴³ Additionally, leading compounds were analyzed in vivo on murine models both by us and by others.⁴⁴⁻⁴⁶ Clear efficacy was recorded (Figure 3) and, most notably, no clinical signs of toxicity were detected in the treated mice; mice appeared healthy, with no weight or hair loss, no grooming or behavioral signs of stress, no swellings or eye infections, no signs of food or fluid deprivation, and no mortality occurring during the period of the experiment. The clinical signs of mice treated with cisplatin as control clearly demonstrated various signs of stress.

Hydrolytic stability was evaluated based on a comparative method, by adding 10% D_2O to a deuterated organic solution of the complexes and monitoring the reactivity with time by NMR.^{40, 41, 47} The employment of only 10% D_2O was dictated by the insufficient solubility of some derivatives at pure water solutions; thus, despite not mimicking exactly the biological environment, this method provided a convenient tool to compare among derivatives.

The salan complexes in general demonstrated enhanced stability relative to the known titanocene dichloride and



Figure 4. Hydrolysis products of first generation of phenolato titanium complexes: representative X-ray structures; Ligands with NMe gave trimers (a) and those with NH gave dimers (b)

budotitane complexes and, additionally, underwent defined hydrolysis processes rather than forming unidentified aggregates.^{40, 41} The labile ligands, mostly isopropoxo, decomposed within several hours rather than minutes, yielding highly stable and defined oxo-bridged clusters (Figure 4). Complexes with N-Me groups generally yielded trimers, whereas those of NH moieties yielded dimers.^{40, 41, 48-50} Nevertheless, one main cluster was obtained per reaction, where in each cluster, each titanium center was bound to the inert salan ligand, with no hydrolysis of the latter for days and weeks in water solutions.

Numerous derivatives of the salan titanium complexes have been studied by us, as well as others.^{38, 40, 41, 47-59} The main structure-activity relationships identified include the following: (a) in general, structural parameters on the ligand strongly influenced the performance of the complex; as evidence, asymmetric complexes with two differently substituted aromatic rings often presented activity higher than those of the symmetrical analogues and their equimolar mixtures,^{52, 53} emphasizing the importance of fine tuning ligand properties to maximize complex activity; (b) higher stability mostly resulted in higher cytotoxicity;⁴⁰ interestingly, an equivalent family of bis(phenolato) complexes based on branched ONNO ligand connectivity was of markedly reduced stability and activity;^{60, 61} (c) halogenations at positions ortho to the binding phenolato donors substantially increased even further the hydrolytic stability, with $t_{1/2}$ for labile ligand hydrolysis in 10% D₂O solutions of over a week, producing the complexes of the highest stability and activity;⁴⁰ (d) cis configuration of the labile ligands was not essential, as equivalent trans salen complexes gave comparable hydrolytic reactivity and cytotoxicity;62,63 (e) steric bulk had a generally negative effect on activity;^{41,47,50,52} this has implied that insufficient solubility or inability to penetrate through the cell membrane, which is a size-dependent process, may damage the biological accessibility, and thus may also be of concern.49

Now Concerning also Accessibility

Particularly large derivatives of the phenolato salan titanium complexes of the LTiX, type showed inactivity toward cancer cells regardless of their stability,^{40, 41, 52} raising the issue of accessibility. Additionally, some particularly small complexes of NH groups were active despite being of markedly lower stability,⁴⁹ raising the hypothesis that the hydrolysis product, namely the oxo-bridged dimer, serves as the active species in the cell. Additionally, as such clusters are obtained within hours in 10% water solutions even for the more stable derivatives,⁴⁰ and cytotoxicity increases with incubation time up to 72 hours with cells at 100% aqueous environment,³⁸ the clusters were suspected as the cellular active species and were therefore analyzed directly for their cytotoxicity; surprisingly, they were found inactive.^{40,41,49} These observations combined, together with the activity of salen complexes with trans labile ligands giving similar clusters in water,^{62, 63} led us to propose that the clusters are indeed active when formed in the cell, vet, as other particularly large complexes, are inaccessible when administered directly; namely, of insufficient solubility and/or cannot penetrate through the cell membrane. Thus, the clusters were put in particular nano-formulations that assists in improving both features. Indeed, the clusters and other particularly bulky complexes that were inactive when studied directly, were highly cytotoxic when administered in the nano-formulated form.^{64, 65} These observations provided an important milestone in the development of potent titaniumbased anticancer drugs; aside from identifying an active species performing in the cell, we have proved that the combination of high anticancer activity and stability for days in water may be achieved with complexes of the bio-friendly titanium metal. As the active clusters do not include any labile groups, it was clear that a new structural design should enable producing mononuclear titanium complexes of only inert ligands, and thus markedly improved stability. Importantly, it became evident that when considering the requirement of a potent drug, accessibility cannot be neglected.



Figure 5. Second generation of phenolato titanium complexes; LTi type; L is tetrakis(phenolato) system; representative X-ray structure.



Phenolato Compounds - 2nd Generation LTi Complexes

According to the realization that labile ligands are not required for the anticancer activity of titanium complexes, and as those were the ones first to hydrolyze, a new window of possibilities now opened for the design of titanium complexes stable for days in biological environments. Thus, the new generation of compounds is based on a single hexadentate ligand to coordinatively saturate the metal center, with four covalent donors to accommodate the Ti(IV) oxidation state and two additional coordinative atoms. Additionally, such complexes, if indeed found active and stable, will lead to cancer cell growth inhibition without mandatory preceding hydrolysis steps, which are often accompanied by release of undesired, potentially toxic, side products, such as the free labile ligands (e.g. isopropanol for isopropoxo complexes).

Concerning Activity, Selectivity, Stability, and Accessibility

The first family of LTi compounds that we developed relied on a diamino-tetrakis(phenolato) system (Figure 5).64-66 Such complexes were indeed stable for days in water solutions, due to the absence of labile groups and the highly chelating nature of the ligands with all-phenolato donors, providing particularly strong bonds to the titanium metal center. Nevertheless, when analyzing cytotoxic activity of such complexes, high activity was recorded again - only in formulation. It was thus evident that the complexes were still too bulky to assess the cellular target as are. Notably, when formulated, in vivo activity was also recorded for a representative complex toward a human colon cancer model in nude mice, again, with no clinical signs of toxicity (Figure 6a).⁶⁶ The activity of this complex was also evaluated toward the non-cancerous human lung fibroblast cells and markedly reduced impact was observed (Figure 6b).⁶⁶ These observations combined certainly point to a degree of selectivity to cancerous tissue which may potentially lead to reduced side effects, as we generally expect of the bio-friendly titanium metal.

Figure 6. (a) top: In vivo results showing tumor size in treated and untreated immune deficient (nude) mice (N=10) with sub-cutaneous inoculation of HT-29 colon cells; the tetrakis(phenolato) complex of the LTi type was injected IP as is, without formulations every other day for 3 weeks when the experiment was terminated. Control mice were injected with PBS; bottom: solid tumors at the termination of the experiment; upper panel - control mice; lower panel - treated mice (2/5 were devoid of tumors). (b) Cell growth inhibition dependence on concentration of the titanium tetrakis(phenolato) complex of the LTi type; A2789 – human ovarian cancer cells; MRC-5: human non-cancerous lung fibroblast cells.



Figure 7. Second generation of phenolato titanium complexes; LTi type; L is bis(alkoxo)-bis(phenolato) system; representative X-ray structure.



Figure 8. In vivo results showing percent survival in treated and untreated mice (N=10) with sub-cutaneous inoculation of T-25 lymphoma cells; the bis(alkoxo)-bis(phenolato) complex of the LTi type was injected IP every other day for 4 weeks when the experiment was terminated. Control mice were injected with PBS.

With the aim to develop complexes that will demonstrate the desired combination of all required features and yet, be accessible and active as are without depending on formulations, we proceeded a step further in reducing the complexes' steric bulk. Thus, phenolato moieties were replaced with aliphatic alkoxo ligands.⁶⁷ Nevertheless, when comparing bond strengths, phenolato donors provide stronger bonds to the titanium metal than do aliphatic ones. Indeed, a control complex with all four aliphatic donors in a single hexadentate ligand decomposed within hours in mixed water/ methanol solutions and was inactive toward cancer cells.⁶⁷ This observation evinced that phenolato coordination, despite increasing steric bulk and hence damaging accessibility, was essential for hydrolytic stability.

An optimal balance between stability and accessibility was obtained upon the development of the second family of complexes of the second generation LTi type (Figure 7).⁶⁷ Replacing only two of the phenolato donors in the tetrakis

(phenolato) system with aliphatic ones while maintaining the other two in a bis(alkoxo)-bis(phenolato) system provided complexes that are both stable for weeks in water, and with particular ligand substitutions - active toward cancer cells also independently of formulations.

In vitro activity of the bis(alkoxo)-bis(phenolato) complexes gave IC₅₀ values in the low micromolar range, again, mostly higher than that of cisplatin.⁶⁷ Comparing the activity toward a line resistant to cisplatin vs. its equivalent sensitive line produced similar activity, where the titanium is again not influenced by the platinum resistance.⁶⁷ When analyzing non-cancerous human lung fibroblast cells, reduced impact was again recorded. A leading complex also underwent in vivo analysis toward a murine lymphoma model and showed high efficacy (Figure 8) accompanied by no clinical signs of toxicity in the treated animals. In fact, similar in vivo results were obtained when the compound was administered as is, without formulations, directly to the animal. It is thus clear that this compound combines activity and selectivity with biological accessibility.⁶⁷

The wide activity of the leading LTi complex toward numerous cell lines was also confirmed by the results toward the NCI-60 analysis performed by the NIH.⁶⁷ Altogether 57 lines were evaluated, and high activity was recorded toward all lines, including MDR lines, with average GI50 (growth inhibition 50%) of $4.7 \pm 2 \mu$ M. Additionally, cancer types especially sensitive to the titanium complexes were identified, which includes colon and most types of melanoma (Figure 9). Importantly, COMPARE analysis, which correlates the reactivity pattern to those of known drugs, did not identify any known drug with high correlation factor, which indicated that the mechanism of this titanium complex is distinct and it thus may be especially effective in combination therapy - a common treatment regime for cancer diseases.

When comparing the leading LTi complex to its earlier generation analogues of the LTiX₂ type, its main advantage lies in its incredibly high water stability. Not only did the complex maintain its structure after days in water according to NMR analysis, but it also did not decompose at acidic conditions of pH = 5.5.⁶⁷ Moreover, the complex showed negligible loss of activity following pre-incubation in biological medium for up to a full week (!) before adding cells and measuring cytotoxicity (Figure 10).⁶⁷ This result is exceptional considering that previously known compounds lost activity following ca. 3 hours of pre-incubation in medium, and salan LTiX₂ complexes of the 1st generation lost activity after ca. 24 hours.³⁹ It is thus obvious that these complexes are especially resilient, combining all requirements that we have of a potent drug: wide activity, selectivity, stability and accessibility.



Figure 9. Relative sensitivity of cell-lines of the NCI-60 to bis(alkoxo)-bis(phenolato) titanium complex of the LTi type; the delta between the mean growth inhibition of 50% (GI50) value toward all cell lines and the GI50 value toward each cell line (μ M) is presented on Y axis. Data for cell lines that were particularly sensitive to the titanium complex LTi appear above X axis, and for relatively resistant cell-lines appear below.



Figure 10. Dependence of human cancer colon HT-29 cell viability on administered concentration of the bis(alkoxo)-bis(phenolato) titanium complex of the LTi type following pre-incubation in 0.5% DMSO cell growth medium for varying periods prior to administration to the cells for additional standard 3 days incubation.

So How Does It All Work?

After achieving the basic requirements of wide activity, selectivity, stability and accessibility, we face another important requirement - elucidating the mechanism of cellular operation of these new potential drugs. This is essential not only for advancing basic science, but also for utility, to eventually gain FDA approval for use of the titanium complexes as drugs. Having established that labile ligands are not required for the activity of titanium complexes, on one hand enabled us to make a substantial breakthrough in the development of superior more stable agents; nevertheless, on the other hand, it proved that the mechanism is different than that of cisplatin, leaving us puzzled as to the type of interactions that occur with the yet unidentified cellular target. Thus, many efforts are currently devoted to mechanistic studies on these promising drug candidates.

Now Concerning also Mechanistic Aspects

Preliminary mechanistic studies were performed with both the 1st generation and 2nd generation of phenolato titanium complexes. A leading LTiX₂ complex showed the following:⁴⁶ (a) cellular accumulation increasing with time;^{43, 68} (b) interruption to cell cycle, where cells were halted at the G1 stage; (c) some buildup of proteins that normally take part in apoptotic pathways, including p53 and caspases (Figure 11); (d) buildup of apoptotic cells with time following treatment. These results supported the earlier study with a different derivative showing buildup of apoptotic treated HeLa cells.⁵⁶ A leading LTi complex showed the following:67 (a) again, buildup of apoptotic cells with time following treatment (Figure 12); (b) cell penetration reaching maximal influx following ca. 24 hours from administration; (c) maximal cytotoxic activity following ca. 48 hours of incubation with cells. Altogether, these observations support controlled and programmed cell death through apoptotic pathways, rather than by instant necrosis. Additional massive mechanistic study is required to fully elucidate the mode of operation of these complexes and the particular interactions involved.



Figure 11. Effect of the titanium complex of the $\text{LTi}(\text{OiPr})_2$ type on (a) p21 levels and (b) the accumulation of active caspase3 in human cancer colon HT-29 and ovarian A2780 cells.



Figure 12. Apoptosis assay for human cancer colon HT-29 cells, showing cells in early or late apoptotic stages following exposure to the bis(alkoxo)-bis(phenolato) titanium complex of the LTi type for (a) 0 (control), (b) 9, (c) 24, (d) 48 hours.

Perspective, Where Do We Go from Here?

Having established the high performance of the latest derivatives of the anticancer titanium complexes in all basic aspects makes them particularly attractive as drug candidates. A big open question nonetheless remains regarding their mechanism of operation. Thus, a profound study from both the chemical and biological sides is underway. The most important mechanistic questions are (a) what is the active species?; (b) what is the cellular target?; and (c) what are the interactions between them? Having identified cytotoxic complexes that are highly stable and maintain their nature in the biological environment implies that we have answered question 1, and the active species is the complex administered. The various preliminary mechanistic clues already gained imply that DNA is either directly or indirectly involved, as apoptotic pathways are induced and cell cycle is interrupted by the titanium complexes. It is now a great challenge to identify the particular interactions involving the titanium complexes that enable the selective inhibition of cancer cell growth.

The next desired path is obviously to consider the phenolato titanium complexes for utility in the clinic as anticancer drugs. A long road is still ahead of us before a dream drug can be marketed. Various additional more relevant in vivo models should be investigated, the therapeutic window should be determined, and specific target diseases should be identified. Having established the cells especially sensitive to the leading titanium complex of the NCI-60 panel is an important milestone that will direct future analyses, both in vitro and in vivo, both alone and in combination with known effective drugs. Hopefully, human clinical trials will rapidly follow.

Another future direction involves tumor targeting of the leading anticancer titanium agents. Despite the selectivity to cancer tissue, any potential drug would significantly benefit from specific targeting to the tumor cell based on the different conditions characterizing it. We are thus currently exploring various paths toward this goal, which, if achieved, would improve all aspects required of the dream drug: activity, selectivity, stability, and of course - accessibility.

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The 17th Conference for Non-Destructive Testing of the Israeli Branch of Non-Destructive Testing at the Association of Engineers in Israel In cooperation with ISRANDT - the Israeli National Society for Non-Destructive Testing

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Use of Titanium in the Oil Refining and Petrochemical Industry

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Abstract: The aim of this work is to analyze the physicochemical properties of titanium alloys, their chemical resistance in different media, advantages, corrosion phenomena and limitations, experience and examples of application at oil refinery and petrochemical units, problems, and solutions.

Introduction

Titanium has found wide application in different industries and spheres of life: from spacecraft, aircraft and missiles to laptops, body implants, architecture, and in jewelry and decorations as the beautiful yellow coating titanium nitride (instead of gold). Although titanium alloys were originally developed in the early 1950s for aerospace applications where their high strength-to-density ratios were especially attractive, the chemical industry was the first where titanium began to be used because of its high corrosion resistance to diverse media ^[1-6]. When the price of titanium tubing fell during the 1960s, it became possible commercially to exploit the resistance of the metal to attack by brackish, saline and cooling water, and other media (hydrocarbons containing HCl, H₂S, NH₂, and organic acids) of oil refineries. Titanium heat exchangers, piping, vessels, tanks, valves and other equipment in different applications have been used since 1967 in oil refining and petrochemical plants^[7]. It is the combination of high corrosion resistance, high strength and low density that has led to the increased use of titanium in the oil refining and petrochemical industry from 1970 onwards. Titanium is no longer regarded as a new metal or an unusual one used solely for aerospace applications, but simply as another high-performance material available to the design engineer. Nowadays there is nearly 50 years' experience of the use of titanium as a construction material in the oil refining and petrochemical industry [7-11]. Only a few cases of failure have occurred.

In physical appearance, titanium is a beautiful lustrous white metal with a silver color like steel. It is easy to confuse with stainless steel on the basis of its appearance alone. One important physical property of titanium, its lightness, can easily identify it. The physicochemical properties and chemical resistance of titanium alloys to different media, advantages, corrosion phenomena and limitations, experience of applications at oil refinery and petrochemical units, problems and solutions are described in this work.

My personal prologue

When I began working as a corrosion engineer at the oil refinery in 1990, the chief chemist once called me and gave me a shiny thin tube about 10 cm length and 1 cm in diameter, and asked me to determine which material the tube was made of. He also said that I should not use chemical analysis. I remembered a story how Archimedes uncovered a fraud in the production of a golden crown commissioned by Hiero II, a king of Syracuse. He tested whether it was pure gold or a mixture of gold and silver, according to the volume and mass of the crown (density). Therefore, I decided to determine the density of the shiny small tube. Weighing it and measuring its volume, I obtained the density 4.5 g/cm³. This value is nearly half that of stainless steel which was my first guess when I saw the tube - so a light metal! There was no internet

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Alec Groysman has experience in corrosion and corrosion control in the oil refining and petrochemical industry. He is a lecturer of the courses "Materials and Standards in Oil and Gas Engineering" and "Corrosion and Corrosion Control" at the Technion (Haifa, Israel).



His first book "Corrosion for Everybody" published by Springer in 2010 received the innovation award winner of Materials Performance Readers' choice in 2012 year in the USA. His new book "Corrosion in Systems for Transportation and Storage of Petroleum Products and Biofuels" is published in 2014 by Springer.

He has special interests in materials and corrosion education and in searching for relationships between materials, corrosion, art, history and philosophy.

Dr. Alec Groysman is the chairman of the Israeli Association of Chemical Engineers and Chemists.

Alloy		C _{max}	N _{max}	O _{max}	H _{max}	Fe _{max}	Мо	Ni	Pd	Ti
Grade	UNSª									
1	R50250	0.1	0.03	0.18	0.015	0.2				Rem.⁵
2	R50400	0.080	0.03	0.25	0.015	0.3				Rem. ^₅
4	R50700	0.1	0.05	0.4	0.015	0.5				Rem. [♭]
5°	R56400			0.2		0.25				90
7	R52400								0.12-0.25	Rem. ^₅
12	R53400	0.080	0.03	0.25	0.015	0.3	0.2-0.4	0.6-0.9		Rem. [♭]
16	R52402								0.04-0.08	Rem. ^b

Table 1. Chemical composition of titanium alloys (wt%) [12, 13]

^aUNS - Unified Numbering System.

^bRem.= Remainder.

^cGr.5 - Ti-6Al-4V (6 % Al; 4 % V). Ti Gr.4 and Gr.5 have the highest hardness and are thus most resistant to erosion.

in those times. I took the encyclopedia and found that only one metal had this density (4.5 g/cm^3) - titanium. Thus, I began my acquaintance with titanium at the oil refinery. In 10 years more than 45 heat exchangers in different applications were functioning at oil refinery units.

Properties of titanium

The density (4.5 g/cm³) of titanium is midway between those of the light alloys of aluminum (2.7 g/cm³), and magnesium (1.74 g/cm^3) and those of steel (7.87 g/cm^3) and nickel alloys (8.4-8.9 g/cm³). In alloy form, titanium retains useful strength at temperatures substantially higher than those considered safe for the more conventional light alloys and is an attractive metal for applications demanding high specific strength at temperatures ranging from sub-zero to ~250°C. When titanium is alloyed with Al, Sn, Zr, Nb, Mo, and Si, it can be used up to ~600°C. Titanium loses strength when heated and at 300°C it is half as strong as at 20°C. This feature must be taken into account when using it at elevated temperatures. Titanium is as strong as steel but 45% lighter at ambient temperatures. It is twice as strong as aluminum, but 60% heavier. Titanium is not as hard as some grades of heat-treated steels, it is nonmagnetic and a poor conductor of heat and electricity.

Titanium at high temperatures (600-1,000°C) greedily absorbs nitrogen, oxygen, hydrogen and carbon from the atmosphere and becomes brittle and unsuitable for practical purposes. Therefore, it had been impossible to obtain pure titanium and so it had not been used for many years. Titanium became a commercial reality only in the 1950s. All high temperature processes with titanium (including welding) must be done in vacuum or in an atmosphere of inert gas (argon or helium).

Another important characteristic of titanium is its corrosion resistance in a wide range of chemical and natural media, particularly with respect to general corrosion, pitting corrosion, stress corrosion cracking (SCC), microbiologically induced corrosion (MIC), erosion and cavitation. In many applications, especially where the material is used in the presence of chlorides, its corrosion resistance is far superior to those of stainless steels. We should remember these properties of titanium when using it at refinery units. There are about 40 grades of Ti alloys differing in composition and, as a result, in mechanical properties and chemical resistance. Five of these grades (Gr.1, Gr.2, Gr.7, Gr.12, and Gr.16) are used in the oil refining industry (Table 1).

Chemical resistance of titanium alloys

Titanium is a reactive metal: $E_{Ti}^{2+} = -1.63$ V_{SHE} (SHE - Standard Hydrogen Electrode) at 25°C^[14].

For comparison, $E_{A1}^{\circ 3+}$ =-1.66 V_{SHE} at 25°C. However, the chemical resistance of titanium and its alloys is due to the fast formation of a tenacious, hard, tightly adherent protective titanium dioxide surface layer (TiO₂). Therefore, if titanium is immersed in an aqueous solution of electrolytes the electrode potential of the surface (not pure Ti but TiO_2) is more positive and can reach -0.7 V_{SCE} (-0.383 V_{SHE}) (SCE - Saturated Calomel Electrode) in HCl and H_2SO_4 to -0.1 V_{SCE} (+0.217 V_{SHE}) in sea water at 25°C. Titanium dioxide as a white pigment has a wide range of applications, from paints to polymeric materials, sunscreen, toothpaste, paper, and food coloring. Actually, three titanium oxides (similar to the three iron oxides formed on an iron surface at high temperature) are formed: TiO (close to the titanium surface), Ti₂O₂ (intermediate layer), and TiO₂ (outer layer close to the atmosphere or other medium). Thus, titanium alloys have a tendency to be spontaneously passivated at ~20°C and this behavior is retained at 250°C in the presence of an oxygen source. Oxidizing conditions are heating in air (thermal oxidation), anodic polarization in an electrolyte, and exposure to HNO₂; the thickness of the oxide layer on titanium

T°C	24							52					66					
Conc. of HCl, wt %	5	6	8	9	17.3	26	1.4	5.8	6	7	11.5	1	1.5	1.7	2	3	4.7	
Corr. Rate, mm/y	0	0.07	0.2	0.25	0.51	2.59	0.02	0.51	0.68	1.27	3.07	0.01	0.02	0.13	0.61	1	7.08	

Table 2. Corrosion of Ti Gr.2 in naturally aerated HCl solutions at different temperatures^[1]

T°C			24				5	2		66				
Conc. of HCl, wt %	6	8	10	12	28.5	3	4	5.9	7	2.4	3.6	5.9	7	
Corr. Rate, mm/y	0.008	0.008	1.4	2.54	5.58	0	0.001	0.518	5.30	0.01	0.03	0.51	8.98	

Table 3. Corrosion of Ti Gr.12 in naturally aerated HCl solutions at different temperatures^[1]

T°C	24							66							
Conc. of HCl, wt %	9	18	20	26.5	27	9	11.5	14.7	16.8	19	21.9	6	9.6	11.5	16.8
Corr. Rate, mm/y	0	0	0.01	0.02	0.70	0.008	0.02	0.03	0.06	0.08	0.41	0.01	0.03	0.04	0.13

Table 4. Corrosion of Ti Gr.7 in naturally aerated HCl solutions at different temperatures^[1]

increases with time: from 1-2 nm to 6 nm during 70 days, and then to 11 nm after 1.5 year, and even to 25 nm after 4 years (in natural conditions). Chemical resistance of titanium can be enhanced by increasing the surface oxide film thickness, alloying titanium with certain elements, and adding inhibitors (oxidizing compounds) to the media. Anodization thickens the oxide layer to give a beautiful colorful spectrum.

Usually naturally formed TiO_2 films are invisible to the eye. This oxide layer is highly chemically resistant and is attacked by only hot concentrated HCl, H_2SO_4 , NaOH, and HF (see below). Without the protective dioxide layer TiO_2 , titanium would dissolve rapidly in most solutions.

Corrosion of titanium

The following corrosion phenomena can occur with titanium: general corrosion, pitting corrosion, crevice corrosion, SCC, hydrogen embrittlement, fatigue, erosion, and galvanic corrosion. SCC, hydrogen embrittlement, and fatigue are called environmentally assisted cracking.

General corrosion

Titanium offers moderate resistance to some mineral (inorganic) (HCl, H_2SO_4 , H_3PO_4) and organic acids. Titanium oxides are not soluble in most inorganic acids. The corrosion rate depends on acid type, its concentration, and temperature. Amine corrosion inhibitors are not effective for protecting titanium. Titanium is very resistant to HNO₃ up to its boiling

point. The corrosion rate of titanium in diluted HCl (up to 5 wt%) is very low at 24°C. Significant corrosion of Ti Gr.2 (> 0.2 mm/y) occurs at concentrations of HCl greater than 8 wt% at 24°C and greater than 1.5 wt% at 52-66°C (Table 2). For Ti Gr.12, considerable corrosion begins at concentrations of HCl greater than 8 wt% at 24°C, and greater than 4 wt% at 52-66°C (Table 3). For Ti Gr.7, severe corrosion begins at concentrations of HCl greater than 26.5 wt% at 24°C, greater than 15 wt% at 52°C and greater than 11 wt% at 66°C (Table 4). Titanium is not resistant to HF solutions at all.

Titanium is resistant to most organic acids over a wide range of concentrations. However, it severely corrodes in formic acid (>10 wt%), oxalic acid (even in dilute solutions), and in citric acid (50 wt% at 100°C). Alloying additions of Mo and Ni (Ti Gr.12) reduce the susceptibility of Ti to anodic dissolution. The latter additions increase the alloy strength at the expense of ductility. Palladium is added in small concentrations (0.04 to 0.25 wt%) (Ti Gr.7, Ti Gr.16 - see Table 1) to increase the corrosion resistance of titanium in reducing acid environments. Titanium exhibits low corrosion rates in alkaline solutions (NaOH, KOH) at low and moderate concentrations and temperatures. Titanium is not resistant in strong caustic solutions (pH > 12, T > 80°C) (1).

 $2\text{Ti}_{(s)} + 2\text{NaOH}_{\text{conc.}} + 2\text{H}_2\text{O}_{(1)} \rightarrow 3\text{H}_{2(g)} + 2\text{NaTiO}_{2(aq)}$ (1) However, titanium is resistant to aqueous ammonia (NH₄OH) at all concentrations and temperatures and to anhydrous ammonia. Thus, titanium can be considered as an amphoteric metal, which means that it dissolves both in concentrated acids and alkalis. Titanium is resistant to solutions of alcohols, aldehydes, esters, ketones, and hydrocarbons. Aeration may be required to maintain its passivity. Titanium alloys are highly resistant to air, sea water, fresh water, steam (up to 400°C), H_2S and CO_2 , aqueous solutions of neutral salts (up to 100°C, even more resistant than stainless steel), dilute HCl (up to 5 wt% at 24°C), hypochlorites (HOCl, NaOCl, Ca(OCl)₂), ammonium chloride (NH₄Cl), amine chloride, and ammonium bisulfide (NH₄HS). They also are resistant to concentrated NaCl, CaCl₂ and MgCl₂ aqueous solutions containing sulfur (120 g/l) and at pressure 7 MPa H_2S up to $180°C^{[10]}$. Above this temperature, the titanium alloys are susceptible to localized attack.

Allowable corrosion rate of titanium

The allowable corrosion rate is the maximum (acceptable, permissible) value for which the equipment or construction can serve without failure during a defined period (design life). This value is defined from experimental data about general (uniform) corrosion rate and depends on the type of metal, requirements of a specific industry, and the type of equipment (the type of the material and its thickness). Allowable corrosion rates are very important parameters for designers and engineering personnel at oil refineries. These values allow decisions to be made about the correct and proper application of corrosion control measures. For carbon steel heat exchanger tubes in oil refining and petrochemical industry, the allowable corrosion rate is defined as 0.11 mm/year^[14]. For titanium heat exchanger tubes this value should be defined. The design life of heat exchangers is 15 years in the oil refining and petrochemical industry. The widespread wall thickness of heat exchanger titanium tubes is 0.9 mm (instead of 2.336 mm for carbon steel). The allowable corrosion rate of titanium tubes in this particular case is

$$\frac{0.9 \text{ mm} \cdot 0.7}{15 \text{ years}} = 0.04 \frac{\text{mm}}{\text{year}} \tag{1}$$

where 0.7 is the safety factor. This means that we may only use heat exchangers up to a corrosion wear (from a mechanical point of view - strength of remaining tube material) of 70% ^[14]. Thus, the allowable corrosion rate (0.04 mm/year) of titanium tubes is one third of that of carbon steel (0.11 mm/ year). We can emphasize that corrosion rates of titanium in most media are much lower than the allowable value 0.04 mm/ year because of the presence of the protective film TiO₂ on the titanium surface and its growth during service. As a result, titanium equipment is often designed with a zero corrosion allowance in passive conditions in different media of the oil refining and petrochemical industry.

Pitting corrosion

Titanium is highly resistant to pitting attack in chloride media and failures are very rare. This is explained by the protective oxide film which exhibits very high anodic pitting potentials in chloride solutions: +5 to +10 V (versus SCE).

Crevice corrosion

Titanium with a passive film is susceptible to crevice corrosion, similar to other metals and alloys with passive films (stainless steels, aluminum, and nickel alloys). Crevice corrosion on titanium can occur under metal joints, non-metal gaskets, or under deposits. Temperature and pH are critical factors for the occurrence of crevice corrosion on titanium. Crevice corrosion does not occur at pH > 10. Initiation can occur rapidly at pH <7, titanium chlorides formed within the crevice are hydrolized, forming HCl (pH < 1) and titanium oxide/hydroxide corrosion products. At 7 < pH < 10, crevice attack can also occur. At pH < 7 and $T > 80^{\circ}C$, the resistance of titanium alloys to crevice corrosion depends on the presence of noble metal alloying additions of Mo, Pd, and Ru. Titanium alloys (Gr.7, Gr.16, Gr.12) are susceptible to crevice corrosion when subject to "dry" amine salts. Addition of liquid water (~1 wt%) in the overhead at the crude distillation column is required to passivate the titanium alloys and thus to prevent under deposit "dry" amine salt crevice corrosion. Ti Gr.7 contains 0.12-0.25 wt% Pd and its resistance to crevice corrosion is very high. Ti Gr.16 contains 0.04-0.08 wt% Pd and its resistance to crevice corrosion is significantly less than that of Ti Gr.7.

Ti Gr.12 contains 0.3 wt% Mo and 0.8 wt% Ni, has improved strength compared to unalloyed Ti Gr. 2, and is used when crevice corrosion under salt deposits is expected in the overhead of atmospheric and vacuum columns (Figure 1).

In spite of the formation of salt deposits on Ti Gr.12 tubes, they can serve with these deposits (in the case of insufficient water wash) without failure for more than 20 years (current experience). Removing and cleaning titanium tubes from salt deposits should be carried out every 4 years. Titanium tubes after 20 years of service in the overhead of atmospheric and vacuum columns have good appearance while carbon steel undergoes severe corrosion (see Figure 1c).

Specific case of crevice corrosion

Once, during the assembling of heat exchanger tube bundle made from Ti Gr.2, carbon steel parts were welded in the vicinity of titanium tubes. Nobody noticed that iron particles



Figure 1. a Titanium Gr.12 tube bundle of the condenser in the overhead at the vacuum unit. **b** Carbon steel inlet of hydrocarbons containing small concentrations of HCl and H_2O (T = 50°C). **c** Corroded carbon steel inlet after 4 years. As opposed to this, titanium tubes have good appearance (see **a**).

were smeared on the titanium tubes. Several months after the beginning of service of the titanium heat exchanger with cooling water (aqueous solution of electrolytes), leaks from the titanium tubes were detected. Visual examination of titanium tubes revealed corrosion holes formed on the outer surface. This phenomenon is called 'smeared iron pitting' occurring because of galvanic corrosion of iron particles adhered on titanium. The resulting corrosion product is acidic ferric chloride (FeCl₂) which attacks the titanium surface under iron particles where they breach the passive titanium oxide film. Usually 'smeared iron pitting' occurs at $T > 80^{\circ}C$ but sometimes at lower temperatures in electrolyte solutions. Ti Gr.7, 12, and 16 are more resistant to this attack. The general rule is that in no case should work with carbon steel and low-alloy steels (i.e. welding, tooling, cutting) be carried out when titanium parts are fabricated in the vicinity. Stainless steel tools are recommended for use on titanium. If, however, smeared iron particles are present on titanium, they should be removed by immersion in aqueous solution of mixture HNO, and HF for several minutes.

Stress corrosion cracking (SCC)

The majority of titanium alloys are resistant to SCC which can occur in pure methanol and aqueous halide (Cl⁻, Br, I⁻) solutions. The addition of 2 wt% H_2O to methanol inhibits the SCC of titanium.

Hydrogen damage (hydriding, hydride embrittlement, hydrogen-induced cracking)

The oxide film on titanium is an effective barrier to hydrogen atom intrusion. Disruption of this film allows easy absorption of hydrogen atoms. However, the presence of ~2 wt% of H₂O or O₂ passivates the titanium surface, forming again an effective barrier for hydrogen atoms up to $T = 300^{\circ}C$ and P =55 bar. At T < 80°C, hydrogen atom diffusion is very slow and atoms remain on the surface. At $T > 80^{\circ}C$ atomic hydrogen penetrates into the titanium lattice leading to the formation of titanium hydrides (TiH₂) in the alloy microstructure. Brittle titanium hydrides (dark, acicular needle-like structured platelets) can lead to a loss of mechanical properties (ductility, toughness) and then embrittlement (crack) under applied stresses. Hydriding occurs when titanium corrodes actively (when protective dioxide film is absent or disturbed) or titanium is coupled to a less noble corroding metal/alloy (i.e. carbon steel). The most favorable conditions for hydriding are: pH < 3 or pH > 12; generating nascent hydrogen on a titanium surface (which can occur from a galvanic couple; an impressed cathodic current; damage to the protective titanium dioxide layer, i.e. abrasion or smeared iron); T > 80°C (where the diffusion rate of hydrogen atoms into titanium is significant). In order to prevent hydrogen damage, these conditions must be avoided. Therefore, galvanic contacts of titanium tubes with carbon steel tube sheets, baffles and shells must be excluded. Like arsenic, antimony and cyanide species, the sulfides act as a hydrogen recombination poison (that is, prevent the recombination of atomic hydrogen) and enhance hydrogen uptake by titanium. No hydrogen absorption and embrittlement occur when titanium contacts fully passive alloys (stainless steels and nickel alloys).

Impressed cathodic potentials below the hydrogen evolution line should be avoided. High-temperature (> 80°C) alkaline conditions should be avoided as they may cause hydrogen uptake (as a result of general corrosion) and embrittlement of titanium alloys.

It is important to emphasize that the same deleterious titanium hydride which is formed inside the microstructure when atomic


Figure 2. Examples of galvanic corrosion after 4 years of service. T=30-35°C.

a, **b** Ti Gr.2 tubes. Baffles and tie rods - carbon steel. Medium - hydrocarbons + water condensate after separation tank (drum) at the crude oil atmospheric unit. Solution - baffles and tie rods must be made from SS 304.

c Tubes - Ti Gr.2. Tube-sheet - Admiralty brass (copper-zinc alloy). Medium - cooling water. Electric potentials are -0.10 V of Ti Gr.2 and -0.29 V (vs. SCE) of Admiralty Brass (see Table 5). The latter worked as anode relatively to titanium cathode and corroded. Solution - the tube-sheet must be made from Ti Gr.2 or carbon steel cladded with Ti Gr.2.

d Tubes - Ti Gr.2. Tube-sheet - carbon steel coated with epoxy-ceramic coating system. Medium - cooling water.

Solution: (a) In no case to paint anode (carbon steel tube-sheet); (b) The tube-sheet must be made from Ti Gr.2, or SS 316, or carbon steel cladded with Ti Gr.2.

Metal/Alloy	Pt	SS 316°	SS 304°	Moneld	Hastelloy ^e	Ti	SS 316 ^f	Adm. brass ⁹	CS ^h
E, V vs SCE ^b	+0.15	-0.05	-0.08	-0.08	-0.08	-0.10	-0.18	-0.29	-0.61

Table 5 Galvanic series in flowing sea water^a [1]

^aSome metals and alloys are shown. Velocity: 4 m/s. T = 24°C.; ^bE, V vs SCE - electrode potential in Volt versus saturated calomel electrode. ^cAustenitic stainless steels in passive state; ^aMonel - Alloy 400, copper-nickel alloy; ^eHastelloy - 'C-type' alloys (C-276, C-22, C-2000), nickel alloys. ^fSS 316 - Austenitic stainless steel in active state; ^gAdm. brass - Admiralty brass (copper-zinc alloy). ^hCS - Carbon steel.

hydrogen penetrates, and then can cause environmentally stress cracking of titanium alloys, can play the positive role of catalyst of hydrogenation of some organic compounds and as a reducing agent in powder metallurgy.

Pyrophoricity

Pyrophoricity is a spontaneous combustion of a material upon exposure to air (atmospheric oxygen). Pyrophoric means 'fire-bearing' from Greek. Pyrophoric substances ignite spontaneously in air at $T \le 55^{\circ}$ C. Most materials are not pyrophoric unless they are in a very finely divided state: dust, powder, fine particles, thin sections, fine turnings, thin slices, or small chips. Examples are iron sulfides, some reactive metals (Ti, Mg, Al, even Fe) and hydrocarbon sludge (wastes formed at oil refineries and petrochemical plants). When titanium severely corrodes (oxidizes) forming a high surface area (sponge-like structure), it can be pyrophoric. Burning titanium produces little smoke. Iron sulfides (Fe S) are formed on carbon steel surfaces as a result of corrosion by H₂S, then can be oxidized exothermically (release of heat energy) and eventually be ignited. This occurs when equipment is taken out of service and exposed to air. Namely, when the tube bundle in heat exchanger is taken out but removal of iron sulfide is delayed. In this case, iron sulfide smolders and then ignites. The empty heat exchanger shells on each side and interconnected piping act like a chimney, increasing the severity. Precautions are to keep the equipment wet enough so that oxidation heat is removed by evaporation and ignition cannot occur.

Biofouling and MIC

Since titanium is nontoxic, it is susceptible to biofouling (~0.5 kg·m⁻²·year⁻¹) when immersed in seawater ^[15]. However, microorganisms do not attack dioxide film and titanium remains resistant to localized corrosion. Water velocities greater than 2 m/s reduce the extent of biofouling. Ozone, UV (ultraviolet light) and chlorination help in controlling biofouling on titanium.

Galvanic corrosion

Titanium is corrosion resistant in many media and is often the more noble metal (the cathode) in a galvanic couple. Rapid corrosion of the less noble alloys (carbon steel, copper alloys) occur when these materials contact titanium (Figure 2). Therefore, these contacts must be avoided.

Titanium may be safely coupled to stainless steel (in their passive condition), nickel alloys (i.e. Hastelloy C 276, Inconel 625), and nickel-copper Alloy 400 (Monel) which have similar electric potentials (Table 5).

Erosion, erosion-corrosion, and cavitation

Titanium is highly resistant to erosion and cavitation as a result of its hard adhered dioxide layer TiO_2 (ceramic material). For instance, Ti Gr.2 gave a minimal flow enhanced corrosion rate of 0.01 mm/year (comparing with stainless steel) at sea water velocity of 35 m/s (in the absence of suspended particles) at 25°C. High local turbulence, impingement and cavitation favor erosion of titanium. Inlet turbulence in shell and tube heat exchanger, entrained gas bubble and mist-laden vapor impingement, and the presence of corrosives (i.e. HCl drops) can result in erosion-corrosion of titanium in very rare cases (Figure 3).



Figure 3. Overhead condenser at the vacuum unit. Medium: hydrocarbons with contaminants HCl and H_2O (T = 50°C, 4 years). **a** Erosion-corrosion of the impingement plate (Ti Gr.2). **b** Magnification of the picture a.

The harder higher-strength titanium alloys (Ti Gr.4 and Ti Gr.5) are more resistant to erosion than Ti Gr.2 (Table 6).

Titanium Grade	2	4	5
Hardness Brinell (HB)	160	265	379

Table 6 Hardness of some titanium alloys

Experience of use of titanium alloys at oil refinery and petrochemical units

Two-phase mixtures of hydrocarbons and water condensate containing HCl, H_2S and NH_3 forming in the overhead in crude oil distillation and FCC (Fluid Catalytic Cracking) fractionation columns are aggressive to carbon steel, copper

alloys and copper-nickel alloys. Usually heat exchangers and condensers made from these materials serve 2-4 years, when economical design life is 15 years. The service life of this equipment was extended to 20 and more years after replacing them with titanium. Five types of titanium alloys (of different grades -Ti Gr.1, Ti Gr.2, Ti Gr.12, Ti Gr.7, and Ti Gr.16) are used as construction material in equipment of the oil refining and petrochemical industry. Titanium heat exchangers and condensers (shells, tubes, baffles, tie rods, and spacers), air coolers (tubes and header boxes), piping, and pressure vessels can be used in:

- the overhead at crude oil distillation atmospheric and vacuum columns (the medium: two-phase mixtures of hydrocarbons and aqueous solutions of H_2S , HCl, NH_3 , amine neutralizers, and amine corrosion inhibitors);

- the overhead at FCC fractionation column;
- delayed coking units (DCU);
- the overhead condensers in sour water strippers (SWS);
- hydrodesulfurizer (HDS) (to 170°C and 50 bar);
- cooling water systems.

The FCCU and DCU fractionation overhead streams in addition to hydrocarbons and water condensate containing large concentrations of NH_3 and H_2S along with small amounts of HCN, HCl, SO_2 , and CO_2 . Ammonium polysulfide or proprietary amine corrosion inhibitors are sometimes injected in these overhead condensing systems to control corrosion. Sour waters are stripped in SWS to remove H_2S and NH_3 . The condensed overhead water in SWS can contain up to 40 wt% NH_4HS along with cyanides and chlorides (~100 ppm). Cooling water systems can contain different salts and their concentrations at about neutral pH: brackish water, sea water, and potable water.

In spite of successful use of titanium as construction material in the oil refining and petrochemical industry, some limitations exist.

Limitations of use of titanium alloys

Certainly there is no material with only desired properties. Titanium has also some disadvantages which limit its use. Misapplication of titanium or operation of titanium equipment beyond established process limits can result in failures which are described below.

Titanium is prone to crevice corrosion under deposits (dry amine salts at ~121°C or smeared iron particles), hydrogen embrittlement, and galvanic corrosion of other alloys. Temperature limitation of use of Ti Gr.2 in the overhead at crude oil distillation units, FCCU, DCU and SWS is 121°C. Ti Gr.12 in the overhead condensers can be used up to 171°C where formation of solid, dry amine salt is avoided. Proper water wash or selection of amine neutralizers is important in ensuring the successful use of titanium. Contacting titanium with more active alloys (carbon steel, copper alloys) can cause their galvanic corrosion. Titanium may contact austenitic stainless steels without fear of galvanic corrosion. The factors that influence the breakdown of passivity on titanium alloys are temperature, pH, halides (F-, Cl⁻, Br⁻, I⁻), and elemental sulfur. Titanium alloys are resistant to dilute HCl (up to 5 wt%) at ambient temperatures, formic and acetic acids (up to 10 wt%) up to 100°C. Titanium alloys are not resistant to concentrated HCl. Addition of corrosion inhibitor sodium molybdate (Na₂MoO₄) to HCl aqueous solutions significantly reduces corrosion rate and hydrogen pick up. Titanium is not resistant to concentrated NaOH and KOH (pH > 12) and diluted NaOH (2 wt%) with addition of H₂O₂ (1 wt%). Injection of corrosion inhibitors sodium silicate (1 wt% Na₂SiO₂) and sodium hexametaphosphate (0.05 wt%) $(NaPO_{2})_{\epsilon}$) to the latter alkaline-peroxide solution significantly decreases corrosion of titanium^[16].

Fouling in titanium heat exchangers

Fouling is the accumulation of unwanted material on solid surface of equipment and structures. One of serious problems is a formation of fouling (scale and deposits) on titanium tubes, tube-sheets and plates in heat exchangers from cooling waterside (Figures 4 and 5). Usually this is similar to the formation of scale and deposits on other materials with passive films, such as stainless steel and copper alloy heat exchange surface.



Chemical composition of the scale depends on the source of cooling water, its treatment before use in the system (i.e. use of precipitation tanks for removing Ca^{2+} and Mg^{2+} ions - hardness salts), treatment during use (injection of anti-scaling agents, keeping recommended pH and ion composition), and operating conditions (temperature, flow velocity, realization of reversal flow - back flushing).

In spite of different thermal conductivity of various alloys, their nature does not influence the chemical composition of scale and deposits formed on their surfaces. Any sudden changes in the abovementioned factors can result in scale formation. The chemical nature of the scale and alloy influence the extent of the adherence of the scale to metal surface and, as a result, the procedure of removing and cleaning. It is impossible to decide about the cleaning procedure without opening the equipment (heat exchanger, condenser, pipe) and identifying the chemical composition of the scale. In most cases, scale is composed of CaCO₃ and MgCO₃ (see Figure 5). Sometimes CaSO₄ is also included in deposits. Chemical cleaning from carbonate scale (CaCO₂, MgCO₂) is often carried out with aqueous solution of citric acid (5-8 wt%). Corrosion rate of titanium in solutions of citric acid (5-8 wt%) is less than 0.01 mm/y (when allowable value is 0.04 mm/y), therefore it is not necessary to inject corrosion inhibitor during the cleaning with citric acid. Carbonate scale from titanium surface may be removed also by HCl (5 wt%).

If cooling water is treated by corrosion inhibitors (zincphosphate-phosphonate), deposits can contain calcium and zinc phosphates and calcium sulfates, and can even clog the inner surface of titanium tubes after 4 years of service (see Figure 5a). Plate heat exchangers (because of close position of plates) can be clogged even after one year of service (see Figure 5b,c). Sometimes corrosion products (iron hydroxides/ oxides) may be present in deposits. Carbonates, sulfates, phosphates and hydroxides have different solubility in cleaning acid solutions.



plates (Ti Gr.1) after one year of service (**b**, **c**). White-grey deposits: calcium phosphate, zinc phosphates, and calcium sulfates. $T = 30-35^{\circ}C$. P = 4-5 bar.

Slow water velocity and absence of sufficient concentration of anti-scaling agent result in the precipitation of deposits. In order to diminish and prevent fouling, the following solutions and recommendations should be carried out:

(a) To clean inner surface of titanium tubes by means of aqueous solution HCl (2-5 wt%). It is important to emphasize that this dilute HCl solution does not require corrosion inhibitor as sometimes is recommended. It is possible to clean also with citric acid (5-8 wt%) but it is more expensive.

(b) To keep cooling water velocity more than 1.2 m/s.(c) To optimize the concentration of anti-scaling agent.

(d) To perform periodical reversal flow (flushing) in heat exchangers (once in 3-4 months).

Conclusions

1. Experience of use of titanium alloys (five grades) as construction material for heat exchangers, condensers and other equipment for different services and applications at oil refinery and petrochemical units during 20-40 years proves its high durability and benefits.

2. Titanium alloys Ti Gr.2 and Ti Gr.12 can be used in contact with hydrocarbons, H_2O , HCl (diluted), H_2S and NH_3 up to 121°C and 171°C at 1 bar respectively. It is necessary to prevent formation of solid ammonium or amine chloride salts in titanium heat exchangers. Water wash and suitable amine injection should be used. Ti Gr.12 in some cases is resistant to solid ammonium or amine chloride salts.

3. Titanium alloy Ti Gr.2 can replace carbon steel, copper alloys and copper-nickel alloys in the overhead service at FCCU fractionation column where H_2S and NH_3 are the corrosion problem. Copper and nickel are not resistant both to H_2S and NH_3 .

4. Titanium alloys Ti Gr.1 and Ti Gr.2 are recommended for use in cooling water containing large concentrations of chlorides and sulfates (i.e. sea water, brackish water or potable water) at neutral pH at 10-40°C and 5 bar.

5. Titanium alloys are susceptible to crevice corrosion, therefore, special attention must be paid to tube-to-tube sheet joints, gasket-to-metal flanges and other seal joints, and weld joints.

6. In no case should titanium be used in contact with less noble alloys (carbon steel, copper alloys) in electrolyte solutions, otherwise galvanic corrosion of the latter can occur. Tube-sheets and tube bundle parts (baffles, tie rods, bolts) should be made from suitable materials (usually SS 304 or SS 316), not carbon steel, to prevent possible galvanic corrosion and to optimize bundle life.

7. Use of the thinner wall titanium tubes (0.9 mm wall thickness instead 2.336 mm for carbon steel tubes), requires appropriate handling of bundles. This situation also requires closer baffle spacing to prevent excessive tube vibration that can result in premature fatigue failures. It is recommended to install extra vibration dampening bars between the baffles to provide additional support for the titanium tubes. It is not a good practice to retube an existing carbon steel bundle with titanium tubes.

8. It is forbidden to weld carbon steel in the vicinity of unalloyed titanium (Ti Gr.1, Ti Gr.2) equipment or to use iron instruments when titanium parts are fabricated. Iron particles can be smeared on titanium surface and then cause crevice corrosion of titanium. Smeared iron particles on titanium should be removed by means of aqueous solution HNO_3 and HF. Stainless steel tools should be used on titanium.

9. Scale and deposits can be formed on titanium in cooling water service. Cleaning with dilute aqueous HCl solution (not more than 5 wt% HCl) without corrosion inhibitor can be used for removing carbonates, sulfates and phosphates.

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Phosphate Rock Conversion into Phosphoric Acid: Chemistry, Chemical Engineering and Corrosion Control

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Abstract: Phosphate rock (PR) and phosphoric acid (PA) are the central subjects of a worldwide economic sector supplying chemicals for the fertilizer, metal, food, medicine and dentistry sectors. PA is a triprotic acid that ionizes in three steps: $H_2PO_4 \leftrightarrow H^+ + H_2PO_4^- \leftrightarrow 2 H^+ + HPO_4^{-2} \leftrightarrow 3 H^+ + PO_4^{-3}$. [1]

It is produced by chemical reactions of PR with mineral acids: sulfuric (H₂SO₄) or hydrochloric (HCI) and posterior separation by filtration and evaporation or solvent extraction. The corrosivity of the reaction system depends on two main chemical factors: the chloride and fluoride content of the PR and the chemical interaction between the HF formed during the acid leaching and the SiO₂, Al₂O₃ and MgO present in the PR. Therefore, it is a common industrial practice to add SiO₂ and Al₂O₃ containing clays, or acid-soluble silicates to reduce the corrosion effects. The PR and PA industry is spread out in countries of four continents: Asia, Africa, America and Europe, which operate PR mines, PA production plants and produce phosphatic fertilizers. The chemical reactions, the corrosion problems and the solutions implemented are illustrated and discussed, based on the authors experience and knowledge

Introduction

PA is an important industrial chemical, used as an intermediate in the fertilizer industry ^[1,2], for metal surface treatment in the metallurgical industry ^[3,4], water purification and as an additive in the food industry ^[5]. Cola-type beverages and fruit juices contain food-grade PA to impart acid taste and to avoid sedimentation of iron hydroxides. Corrosion protection

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Hebrew. He has worked as a corrosion consultant and professor in Israel, the United States, Latin America, Spain, South Africa and France. During the IMRS Congress in August 2010, Mexico, he received a "Distinguished Service Award" from NACE International and the NACE Central Mexico Section. He is a member of the National System of Researchers in Mexico. He has been a NACE International member for 25 years. mschorr2000@yahoo.com of steel infrastructure assets and industrial equipment is achieved applying a phosphatization process, based on PA^[6]. A singular application is the manufacture of artificial apatite for coating stainless steel orthopedic implants in the human body.

Table 1 presents the chemical composition of different PRs from several countries, showing the great diversity and, consequently, their chemical behavior during conversion into PA.

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Constituent	Florida, U.S.A.	North Carolina, U.S.A.	Palfos, RSA	Pesca, Colombia	Hazara, Pakistan	Monte Fresca, Venezuela	Araxa, Brazil	Hidalgo, Mexico	Sahara, Morocco	Safi, Morocco	Ruseifa, Jordan	Oron, Israel
P205	31.2	29.7	39.9	20.5	28.5	34.18	35.5	43.3	34.2	32.4	33.4	29.8
CaO	45.0	47.4	1	29.0	41.9	42.30	47.3	46.3	50.3	49.9	51.0	51.0
CI	0.05	0.015		0.001	0.03	100-340-00 100-340-00	0.001	0.02	0.02	0.02	4.2	0.03
F	3.60	3.53	2.35	2.0	2.92	2.94	2.54		3.8	4.1	4.9	3.8
SiO ₂	9.48	1.73	1.0	39.2	23.2	10.29	0.41	2.8	22	2.85	0.2	0.68
Fe ₂ O ₃	1.33	0.79	(a)	0.8	1.85	0.66	2.42	-	0.22	0.70	0.3	0.2
Al ₂ O ₃	1.76	0.53	0.35	1.1	1.0	1.15	0.32	1.11	0.48	0.40	1.001	0.3
MgO	19 0 3	0.79	0.51	0.09	0.13	0.21	0.07	2.17	0.12	0.70	1000	000
Na ₂ O	0.89	0.98		0.14	0.16	1.30	0.03	0.05		0.90		100
K ₂ O	0.11	0.17	1.0	0.14	0.31	0.18	0.10			0.10	4.5	123
CO ₂	3.48	4.18	1.0	3.0	1.1		1.7	0.02	2.7	4.1	10 0 10	7.8
Organic C	2.18	1.38	1000	0.3	0.18	-	<0.1	2	0.06	(24)		0.6
Total S	1.05	1.1		0.1	0.18	-	1.52	-	P243E08	0.20	-	

Table 1: Chemical composition of phosphate rocks

The corrosivity of phosphate ores, used in the production of PA depends on two main chemical factors: the chloride content and the interaction between HF formed in the PA reaction slurry with SiO₂, Al₂O₃, and MgO present in the ore ^[7,8].

Corrosion events occur mainly in the reaction system, taking place under severe hydrodynamic operating conditions, which include agitation of an erosive slurry and high temperature, 70-80 C. To prevent these pernicious events, industrial plant equipment is fabricated from corrosion-resistant alloys (CRA) plastics and elastomers ^[9].

Phosphoric acid production

Two main processes are used to produce PA: the wet process (WPA) by attack with H_2SO_4 and a novel process by attack with HCl followed by separation of PA applying solvent extraction (SX) technology. The composition and purity of the PA obtained by these processes depend upon the mineral and chemical composition of the PR and the acid used.

The wet process consists of three main stages:

1. Acidulation of PR by H_2SO_4 ; the overall reaction with fluoroapatite is usually expressed as:

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 $Ca_{10}(PO_4)_6F_2 + 10 H_2SO_4 \Rightarrow 10CaSO_4 + 6H_3PO_4 + 2HF.$ [2]

2. The hydrogen fluoride reacts with any active silica present to form silicon tetrafluoride:

$$4 \text{ HF} + \text{SiO}_2 \rightarrow \text{SiF}_4 + 2 \text{ H}_2\text{O}, \qquad [3]$$

3. which volatilizes as such or hydrolyzes to fluorosilicic acid, forming silica deposits:

$$3\operatorname{SiF}_4 + 2\operatorname{H}_2\operatorname{O} \to 2\operatorname{H}_2\operatorname{SiF}_6 + \operatorname{SiO}_2.$$
 [4]

During the acidulation, a thick slurry is formed containing 30% of solid particles, mainly gypsum (CaSO₄) and unreacted PR components.

2. Filtration, to separate the solid particles from the filter acid, $30\% P_2O_5$ (50% PA).

3. Concentration, by evaporation of the filter acid to merchant-

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Figure 1: Typical wet process acid plant, showing three stages and industrial equipment.

grade PA, 54 % P₂O₅ (70% PA).

A schematic diagram of a typical WPA plant presents the process three stages and the diverse plant equipment and the products (Figure 1).

The solvent extraction process (SX)

PR is reacted with HCl to form an aqueous reaction mixture comprising PA and CaCl₂:

$$\operatorname{Ca}_{3}(\operatorname{PO}_{4})_{2} + 6 \operatorname{HCl} \rightarrow 2 \operatorname{H}_{3}\operatorname{PO}_{4} + 3 \operatorname{CaCl}_{2}.$$
 [5]

PA is extracted by contacting the mixture with a lower aliphatic alcohol (RCH₂OH). The aqueous extract is separated from the solvent extract, it is washed with water to release PA which is concentrated by distillation to produce food grade, pure PA. Sometimes, the wet process (PR reacted with H_2SO_4) is integrated into the SX process (Figure 2). In this version, the slurries obtained by treatment with H_2SO_4 (wet process) and with HCl (SX process) are mixed, and subsequently, the PA is extracted with an aliphatic alcohol ^[10,11]. The HCl is generated as a byproduct at adjacent chemicals plants.

Chemistry of phosphate rock impurities

PR is the principal source of dissolved and suspended impurities

in WPA. Other impurities such as Cl⁻ may be introduced in process water, particularly brackish water ^[12]. Sometimes contaminated H₂SO₄ obtained from the hydrometallurgical industry introduces additional impurities. Cl⁻ and F⁻ are particularly corrosive, other impurities that affect production are SiO₂, Al₂O₃, MgO, alkali metal salts, SO₄²⁻, S²⁻, organic matter, and oxidizing agents.

The Cl⁻ ion is adsorbed on metal surfaces and replaces adsorbed oxygen or water molecules. During attack on stainless steel, chlorides of iron, nickel, and chromium are formed; these are highly soluble in PA because of its complexing of cations of the transition group elements. The corrosivity of the halogen acids: HCl and HF, and of the halide ions Cl⁻ and F⁻, that dissolve in strong mineral oxygen-acid, such as H_3PO_4 and H_2SO_4 , is related to the physicochemical properties of the halogens, their electronegativity, ion size, and ionic character of the HX molecule that indicates their high chemical reactivity ^[13].

The interaction of HF with SiO₂, Al₂O₃ and MgO

The CaF₂ constituent of the fluorapatite reacts with H_2SO_4 during acidulation to produce HF which may form HF^{2-} , and F⁻ ions, depending on the hydrogen ion activity of the solution. HF reacts with any active silica, alumina and magnesia compounds in the rock to form acid-soluble silicon fluoride and aluminum fluoride complexes and salts, e.g., $(SiF_6)^{-2}$, $(AlF_6)^{-3}$, and MgSiF₆. Other reactions that decrease



Figure 2: Diagram of the phosphoric acid solvent extraction process.

corrosion include formation of partially soluble metal fluoride complexes with Fe⁺³, Ca⁺², K⁺ and Na⁺, and formation of insoluble fluoraluminates and fluorosilicates that settle on equipment surfaces ^{[14,15].}

Becker ^[7] states that, according to his personal experience, acceptable corrosion rates are obtained when $F/SiO_2(\%)$ weight ratio) in the phosphate ore is held below the threshold value of 1.4. A more accurate and complete calculation of the complexing ratio is based on the stoichiometry of the complex-forming reaction between F⁻ and equivalent SiO₂, Al₂O₃, MgO:

24 HF + 2 SiO₂ + Al₂O₃ + MgO \rightarrow H₂SiF₆ + 2 H₃AlF₆ + MgSiF₆ + 8H₂O. [6]

The chemical equivalent ratio is:

$$\frac{\frac{\%F}{19}}{\left(\frac{\%SiO_2}{15} + \frac{\%Al_2O_3}{17} + \frac{\%MgO}{20.2}\right)}.$$
[7]

An equivalent ratio, $F/(SiO_2+Al_2O_3+MgO) > 1$, indicates the presence of non-complexed fluoride and, consequently, enhanced corrosivity during production of WPA. When the equivalent ratio is < 1, the ore contains enough SiO_2 , Al_2O_3 and MgO to ensure the formation of non-corrosive fluoride complexes.

Corrosivity of phosphoric acid

The PA plants, both implementing the wet and the SX processes, have a high level of corrosion risk resulting from several corrosion common characteristics: they handle and process aggressive mineral acids such as H_3PO_4 , H_2SO_4 , HF and HCl; operate under severe hydrodynamic conditions that include mineral leaching, chemical reaction, agitation, circulation at high flow velocities and distillation. Furthermore, they operate at relatively elevated temperatures to accelerate the chemical reactions^[16].

Many forms of corrosion, mainly localized, are encountered in PA production plants and facilities. The most common type is erosion-corrosion (EC), generated by the joint, simultaneous action of mechanical erosion and electrochemical corrosion (^{17,18}]. Testers for the study and measurement of EC were developed and built by the corrosion and materials section of IMI-TAMI Institute for Research and Development Ltd, Haifa, now a part of Israel Chemicals Ltd. (ICL)^[19]. The electronic part of these testers was designed by Ch. Yarnitzky, Technion-Israel Institute of Technology ^[20].

The addition of fluoride complexants

The addition to the phosphate ore or to the WPA reaction system, of fluoride complexants: clays, amorphous silica or acid-soluble silicates improves the system chemical reactions. The addition of such minerals has other positive influences, e.g., increased plant capacity by improving filtration rate, higher filter acid strength, control of HF emission and F-content in the final product. Based on their influence during the production of WPA, clays are considered as chemical modifiers of the PR, since its chemical behavior changes as a result of clay addition ^[14,15].

The selection of a suitable clay and the amount to be added must be based on a thorough analysis of the PR, the clay components, their chemical and physical nature (amorphous or crystalline) and their reactivity with different acids present in the reaction slurry: H_3PO_4 , H_2SO_4 , HF, H_2SiF_6 , and HCl. Several properties are required from a suitable clay to improve the chemical performance during WPA production, namely:

- A high degree of chemical reactivity of the SiO₂ and Al₂O₃ components. In general, amorphous minerals are more reactive than crystalline ones. For instance, quartzite (sand) does not react quickly with HF. In that case, HF in the liquid phase and SiO₂ as a solid suspension will coexist in the slurry and enhance the erosion-corrosion effects. On the other hand, porcelanite is more reactive due to its amorphous state.
- A very low content of impurities, to avoid contamination of the PA product, e.g. iron, copper and heavy metals such as Cd, Pb, Ti, Sr; radionuclides and organic matter.
- A low content of crystallization and bounded water, which may rise to 25%, to save in transportation, storage and handling expenses.
- Low price and easy, local availability.

Conclusions

PA is an important chemical used in many industries; its composition, purity and applications depend upon the composition of the PR. The interaction between HF and SiO₂, Al_2O_3 and MgO in the WPA reaction system is quantitatively expressed by a chemical equivalent ratio: $F/(SiO_2 + Al_2O_3 + MgO)$. Mineral modifiers such as clays and silicates are added to the PR or the WPA reaction system to modify the PR concentration, to amend their behavior, to reduce corrosion and overcome problems in WPA production.

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Tadeus Reichstein (1897-1996): Vitamin C, The Hormones of the Adrenal Cortex, Ferns and Insects

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Fig. 1: Tadeus Reichstein, ca. 1937.

Tadeus Reichstein's (Fig. 1) most notable scientific contributions are the achievement of the first synthesis of vitamin C and his work on the isolation and elucidation of the adrenal cortex hormones.

Robin Fåhraeus, member of the Swedish Royal Academy of Sciences, addressing the Nobel Prize laureates for Medicine or Physiology for 1950 [1]: "Doctor Philip Hench, Professor Edward Kendall and Professor Tadeus Reichstein. Together your researches have contributed to the enlightenment of the extremely complicated physiological chemistry of the suprarenal glands which since their discovery for a long time have been assumed to play no other part than to fill up the vacuum between the kidneys and the diaphragm. Your contributions have already fulfilled the hopes of therapeutic successes in a field hitherto almost inaccessible." The group of Reichstein and that of Kendall and Hench worked in parallel, both groups achieving the isolation of cortisone about the same time.

M. Rothschild [2]: "Many people were surprised at the fact that Tadeus did not receive the Nobel Prize for the synthesis of vitamin C, or at least shared the honor with Szent-György and perhaps Oppenauer [Reichstein's student]. It was recognized that the work had laid the foundation stone for the modern bridge spanning organic chemistry and medicine. This bridge was one of Reichstein's most cherished objectives."

Tadeus Reichstein:

Tadeus Reichstein^[1-5] was born into a Jewish family in Wloclawek, Poland (then part of Russia), in 1897. His early childhood was spent in Kiev. Here he experienced the terror of pogroms. His father, fearing for the safety of his children, moved the family first to Germany and then to Switzerland. Reichstein earned his doctorate in 1922 in chemical engineering with a specialty in organic chemistry at the Eidenössische Technishce Hochschule [ETH]. He carried out his research under the supervision of Prof. Hermann Staudinger, in part, on the chemistry of compounds similar to atropine. Upon completing the requirements for his doctorate, he continued on to study the composition of the flavoring substances of roasted coffee. Reichstein then continued to work on this subject for the next nine years, being financed by the small industrial firm Kathreiners Melzkaffee. His work became the basis for the production of the modern powdered

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extracts of coffee. In 1929 he qualified as lecturer at the ETH and in 1931 he was appointed assistant to Leopold Ruzicka. Reichstein stayed at ETH until 1938. He then joined the faculty of the University of Basel as Head the Department of Pharmacy and Director of the Pharmaceutical Institute, where he remained. In 1946, in addition to his other responsibilities, Reichstein was appointed Director of the Institute of Organic Chemistry.

Reichstein [6,7] was greatly influenced by Ruzicka, who was also a student of Staudinger. Ruzicka was gifted in discovering methods for investigating natural products. "It was one year in the Christmas holidays that Leopold Ruzicka showed me for the first time what research is all about. Later on he harangued me into giving it a try." Before the war, Ruzicka had 15 scientists in his laboratory, about 7 of whom were Jewish. Leo Sternbach, a Jewish employee of Ruzicka, recalled^[1], "But the ETH was not free of anti-Jewish hostility. The rabble-rousing attacks bounced off Professor Ruzicka. He did whatever he could to encourage his Jewish colleagues." George Rosenkranz, another Jewish employee of Ruzicka, recalled Ruzicka being a sort of guardian to the Jewish staff at the institute. "He was protecting the Jews in Zurich. There was a lot of pressure on him, so we got together and we decided to leave Switzerland to protect him. "Owing to unexpected administrative complications, Reichstein had to leave Ruzika's laboratory in 1938 and was offered a position in Basel. Rothschild^[2]: "No other Swiss University would, at that time, have had the courage to nominate a Jew of Polish origin for a chair." His appointment was due to the influence of Fritz Hauser, Head of the Department of Education, and an ardent anti-Nazi. Dr. Chaim Weizmann repeatedly urged Prof. Reichstein to settle in Israel. Reichstein, having experienced the Russian pogroms and the Holocaust, could not take such a step. He visited and lectured in Jerusalem.

Vitamin C:

In 1933 Reichstein and his group reported the first synthesis of ascorbic acid. This came as a result of his interest in working on compounds of medical interest. A year after the publication of the synthesis, Reichstein and Grüssner described a biotechnological route that allowed the readily available D-glucose to be used as a raw material. This was the first practical synthesis of vitamin C and it remains today, with slight modifications, the most important synthetic pathway for its manufacture. The main problem was the transformation of D-sorbitol into L-sorbase.

Reichstein described his success in the discovery of the practical synthesis of vitamin $C^{[2]}$: "In the first place I owe my

success to a small insect Drosophila melanogaster. We had before us the problem of obtaining substantial quantities of L-sorbose, a well-known sugar, but which was not commercially available. It was known, however, that 'Sorbose bacteria' - at this time thought to be the slime producing micro-organism called 'mother of vinegar' - are the activating organisms which transform L-sorbitol into L-sorbose. All five 'bureaux of Schimmelcultures' sent me living cultures of bacteria but none produced sorbose or only traces. I found a clue in a 19th century publication by C. Bertrant. In order to catch wild efficient bacteria [the fruit fly has the active bacteria in its intestine] he put some aqueous sorbitol solution in a cup with a little wine and vinegar and stood it outside at night, under cover of the roof, in September and October. Without much hope - for it was late October and cold with not an insect to be seen - I filled six glasses with aqueous sorbitol and added some yeast extract, some red wine and vinegar to produce pH 5. This is the optimal acidity for the growth of the organism (now known to be Acetobacter suboxydans). The low pH inhibits the growth of other bacteria. The cups were left outside on the windowsill over the weekend, and on Monday morning they all contained solid residues. Three of these consisted of sticky masses of solid sorbitol while the others contained crystals which turned out to be pure sorbose. In one of these was a drowned Drosophila and from one of its legs long sorbose crystals had grown to the surface. It was easy to nucleate the bacteria on fresh medium and in a few days we had 100 g of pure sorbose crystals. Acetonation and oxidation etc. succeeded as planned and thus Vitamin C was produced in a suitably commercial way."

The Hormones of the Adrenal Cortex:

Tadeus Reichstein, together with his colleagues, started the study of the adrenal cortex by extracting a ton of the adrenal glands of cattle: 1,000 kg adrenals from cattle gave in the case of industrial extraction an extract with about 1 kg of dry residue. The activity of this extract could be concentrated to about 25g.

Rothschild ^[2]: "Reichstein isolated about thirty closely related but distinct hormones, the so-called corticosteroids-from the cortex, most which he obtained in pure crystalline form. They included the famous Compound E, now known as cortisone. The biological effects of these hormones included, among other functions, the control and metabolism of sugar, nervous development, anti-inflammatory qualities, and control of the development of heart muscles, of sex hormones and of the immune response. From the clinical aspect these hormones were of great importance for the treatment of Addison's disease, cases of dysfunction of the adrenal cortex and certain inflammatory conditions of both animals and man. The final triumph in the elucidation of the corticosteroids came with the isolation of Kendall's 'amorphous fraction', aldosterone (the most potent mineralocorticosteroid, which controls the body's salt balance). This was accomplished with a happy and fruitful collaboration with Sylvia Simpson and her husband-to-be, James Tait. These two scientists evolved a most sensitive method for estimating minute quantities of electrocortin (now known as aldosterone) in adrenalectomized rats by injecting them with radioactive isotopes before the administration of the assayed steroids. The elucidation of the nature, isolation, structure and crystallization of the 'amorphous fraction', announced in a lecture in Basel in 1954, was cause for worldwide congratulation for Reichstein and the Taits."

Professor G. Liljestrand, from the Nobel Prize presentation speech^[1]: "Professor Tadeus Reichstein. To you and your coworkers we owe the first isolation of four active hormones from the adrenal cortex, the first synthesis of one of them, the proof of the steroid nature of said hormones, and numerous details on the structure and properties of these important bodies. In this way the wearisome road to synthesis was smoothed, and new medicaments created. Your discoveries in this field are of fundamental importance."

Ferns, Butterflies, and an Aposematic Grasshopper from Israel:

Reichstein at age 75 announced that he was abandoning the study of organic chemistry and would concentrate on a special field of botany, the cytogenics of ferns. The chemistry of plants was a subject in which Reichstein had long been interested, in fact, since the days of the aroma of roasted coffee, so it was not as strange a departure as it must have seemed to many. Reichstein studied the polyploid fern complexes and reticulate evolution in the genus Asplenium. He raised the plants and performed the hybridization experiments in his greenhouses. Reichstein: "Over a period of twenty years, we succeeded in clarifying the inter-relationship of various genera of Asiatic ferns — down to the last detail — and we were able to establish clearly the ancestral taxa, the polyploidy species that had arisen through hybridization and polyploidia and the numerous (sterile) hybrids." Reichstein published over 100 papers on ferns.

Reichstein's interest in steroids led to collaboration with Miriam Rothschild on butterflies. At first he was hesitant, saying that his only interest was in steroids, and until that time steroids had never been found in insects. Rothschild responded^[2], "Professor Reichstein, if you let me work in your laboratory, I will find you steroids in old boots." Rothschild^[2]: "Altogether we recorded and identified twenty-five different



Fig. 2: Photograph of leaves and stems of Calotropis procera (Sodom Apple) in the drug collection of Prof. Tadeus Reichstein at the University of Vienna. This sample was collected by Prof. L. Fishelson of Tel Aviv University in July, 1965, at Ein Gedi.

cardenolides from various insects; the Monarch butterfly, reared on Asclepias curassavica yielded ten, five of which were identified as calactin, calotropin, calotoxin, calotropagenin and uzarigenin. Of these the four main compounds yielded pure or nearly pure crystals. Cardenolides were also found in the butterfly's eggs. Reichstein elucidated the hitherto unknown structure of catactin. At that moment in time it was a minitriumph, but he was never persuaded to take a real interest in the insects themselves, although he was delighted to find the same cardenolides in Danaus and in the defensive spray of an aposematic grasshopper, which came from Israel."

The story behind one research collaboration:

The Sodom Apple (Fig. 2) can be seen in the area around the Dead Sea and Ein Gedi. Reichstein, together with others, studied this plant. See "Cardenolides (Heart Poisons) in a Grasshopper feeding on Milkweeds," by J. v. Euw, L. Fishelson, J. A. Parsons, T. Reichstein & Miriam Rothschild, Nature (1967), 214, 35: "A North African grasshopper (Poekilocerus bufonius, (Pyrgomorphidae)), with warning coloration and which feeds on milkweeds (Asclepiadaceae) contains cardenolides similar to those found in the plant. These heart poisons which, like digitalis, excite nausea and vomiting are found in the insect's body tissues and can also be ejected in solution from its defensive glands. They thus form part of the grasshopper's defense mechanisms."

I asked Prof. L. Fishelson, Professor Emeritus Tel Aviv University, for his recollections of this project. He wrote to me as follows (2010):

"To respond to your letter I must dig into the far past. My



Fig. 3: Poekilocerus bufonius with Calotropis procera. Eilat, Israel.

dear friend, the late Miriam Rothschild, had a similar interest in insects that I had, namely, the correlation of observed phenomena with morphological-behavioral adaptations. After I published my first paper on food and the gland of Poecilocerus bufonius (Fig. 3) we discussed the possibility to invite the now late Prof. Reichstein to study the chemical nature of the defensive substances used by the grasshopper. He was enthusiastic about this and so I started to collect and dry the shrub Calotropis procera and the secretions produced by the gland of the insect, and send them to Basel. At some stage of this cooperation, 1966?, I was invited by Miriam to join her and Tadeus in Basel, to discuss the joint study. It was a remarkable experience for me, to sit and talk with such two remarkable persons. And it was extremely exciting to do this in his lab and then over a lunch in the Hotel Am Rein, followed by Zionist talk on the historic balcony of Herzl (Fig. 4). Following this we continued for years to exchange greetings and information.

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Flora of Israel Online, Hebrew University of Jerusalem; Prof. C. Kletter, Department of Pharmacognosy, University of Vienna, for photograph of leaves and stems of Calotropis procera in the drug collection of Prof. Reichstein at the University of Vienna. Photograph of Prof. Reichstein courtesy of ETH Bibliothek. Photograph of Theodor Herzl by E. M. Lilien (1901).



Fig. 4: Theodore Herzl at the fifth Zionist Conference in Basel, in December 1901. Prof. Fishelson recollects discussing Calotropis procera with Prof. Tadeus Reichstein and Dame Miriam Rothschild at the Hotel Am Rein and Zionist talk on the historic balcony of Herzl.

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Acetone: Science, Business and Politics -100 Years since Dr. Chaim Weizmann's Acetone Patent

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Preface

In the Weizmann Institute campus in Rehovot, at the entrance to the burial ground of Dr. Chaim Weizmann, the first President of the State of Israel and founder of the research institution that bears his name, there is a marble plaque with an excerpt from a speech which he delivered in 1946 that reads :

"I feel sure that Science will bring to this land both peace and a renewal of its youth creating here the springs of a new spiritual and material life. And here I speak of Science for its

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I. Member, Executive Board, Weizmann Institute. Since 2011, Emeritus Prof. at Weizmann engaged in advancing a project with applicable potential.

Jehuda Reinharz was born in Haifa, Israel, in 1944 and earned his doctorate in modern Jewish history from Brandeis University in 1972. In 1994, he became the seventh President of Brandeis University and, in 2011, was named President of the Mandel Foundation. He is the author of two books on Chaim Weizmann and is currently co-authoring a third volume with Professor Motti Golani. Professor Reinharz is the recipient of seven honorary doctorates. In addition, he is an elected member of both the American Academy



of Arts and Sciences and the Council on Foreign Relations.



Fig. 1. Marble plaque with excerpt from Weizmann's 1946 speech

own sake, and of Applied Science" (Emphasis by the authors).

One can assume that the vision expressed in this excerpt from

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Prof. Eliyahu Rosenthal - Graduated from the Hebrew University in Jerusalem (MSc. and PhD in hydrogeology and hydrogeochemistry). Postgraduate studies were completed in France and in the USA. Senior scientist and Head of Scientific Projects in the Israel Water Commission. Professor at the Dept. of Geophysics and Planetary Research, Tel Aviv University. Professional experience includes multiaguifer systems, deepseated thermo-mineral brines and geogenic salinization processes.



Member of Israel Delegation to the Peace Treaty Negotiations with Jordan (Water Issues). Since retirement, active in the Weizmann Archives.



[Price 6d.]

Fig. 1. British Patient of Dr. Chaim Weizmann on the production of Acetone and Butanol, submitted on March 29th, 1915

Weizmann's speech in 1946 is based on the long, personal experience of Weizmann as a prolific academic scientist, who published over 100 scientific papers and made numerous useful inventions in both chemistry and biotechnology, many of which were then translated into important industrial products. In addition, it is admirable that throughout his scientific career, Weizmann devoted much of his time to promote his Zionist ideals and served as one of the most important leaders of the World Zionist Organization between the two World Wars.

On March 29th, 2015, we marked the 100th anniversary of the submission by Dr. Chaim Weizmann of the famous patent (see Fig. 2) for the process of production of acetone by bacterial fermentation of maize starch.

What is acetone and why was it of such historical importance? Acetone is an organic solvent that nowadays is commonly known for its extensive use in removing nail varnish and as a paint solvent. However, in 1914, at the beginning of World War I, Britain found itself in desperate need of large amounts of acetone for the explosives and munitions industry, and its production by Weizmann's novel biotechnological process significantly contributed to the war effort.

We believe it is important to recount the historical context and details of this invention, not only from the very interesting scientific and technological aspect, but also because of its political impact on the establishment of the State of Israel and the development of Israel's scientific and industrial infrastructure. In this article, we choose to focus on the events that led to Weizmann's scientific discovery of the fermentation process for the production of acetone, its significant industrial application and its business outcome, until 1926.

The Academic Research Years

Early in his life, Weizmann became interested in following a scientific career. In 1894, at the age of 18, immediately after finishing his high school studies in Pinsk, he traveled to Germany to study chemistry at the Darmstadt Polytechnicum. Two years later he moved to Berlin and continued his studies at the prestigious Berlin Polytechnic Institute, which at that time was considered one of the three best universities in Europe. After his graduation in 1897, he decided to move to the University of Fribourg in Switzerland to work on a doctoral thesis whose subject was the synthesis of novel dyestuff compounds. In 1899, Weizmann submitted his thesis and was awarded the degree of PhD 'Summa cum laude'.

As is the case nowadays, in those years, young PhD's had a difficult task finding a job or position in the universities. Finally, after two years, he managed to obtain a position as assistant teacher of chemistry at the University of Geneva. The salary he received was very low and insufficient to sustain him. Fortunately, using his German scientific connections, he also obtained a small salary as a consultant for the Bayer Chemical Company in Germany. Together with a colleague from Geneva University, Dr Chris Deichler, he signed a contract in 1902 with Bayer to prepare novel synthetic methods to produce naphtacene and derivatives. In this contract, Weizmann and Deichler agreed to inform and assign all their rights to Bayer on any new invention that they might make during their employment, and Bayer would submit patents on their behalf. As an incentive, Bayer paid them 3,000 German marks each with the promise of a small percentage of any profits that Bayer would make on any products emanating from their inventions. Weizmann and Deichler consequently invented a new synthetic method for the synthesis of naphtacene and some derivatives, for which Bayer submitted a patent in 1902. After its submission, Weizmann and Deichler published their research results in the scientific literature.



Fig. 3. Staff of the Department of Organic Chemistry, University of Manchester, 1911. A number of members of the department are identified, including the Chair, Prof. William Perkin Jr., Prof. Harold Dickson, Dr. Chaim Weizmann, Dr. Arthur Lapworth, brother-in-law of Prof. Perkin who was later chosen to replace him as Chair and two assistants to Dr. Weizmann, Harold Davies and Mr. Mumford, who worked with him in the production of acetone. The only woman in the picture, Miss Cliffe, was most likely the secretary of the department.

In 1903, his contract with Bayer ended, and Weizmann came to the conclusion that as a Jew in continental Europe, he did not have a good enough chance to advance his career, and thus decided to apply for a position in England and the USA. He obtained a letter of recommendation from Prof. Grabbe from the University of Geneva, and applied for a position to Prof. William Perkin, Jr., Chair of Organic Chemistry Department at the University of Manchester, a well-known chemist, who had also studied in Germany. Prof. Perkin invited him for an interview and offered him a fellowship as Assistant Lecturer at the Owens College in Manchester. Weizmann accepted and arrived in Manchester in July 1904.

Prof. Harold Dickson, the Director of Laboratories at the university, offered Weizmann space in a small basement laboratory where he could conduct his own research together with students. Weizmann quickly established his lab and within three months, in collaboration with Prof. Perkin and his assistant, Mr. Pickeles, he published an important paper in the prestigious journal "Proceedings of the Chemical Society" on the isolation and synthesis of anthracene derivatives, which were needed for their valuable dyeing properties. Prof. Perkin was very impressed with this achievement, gave him three more students to work with and more freedom to develop other research interests. At the same time, Weizmann also began teaching chemistry to students, and his lectures became so popular that in December 1904, when Perkin founded the Manchester Chemical Society, he nominated Weizmann as its Secretary. Weizmann's continuing relationship with Perkin was excellent, and in July 1905 Perkin appointed him to the rank of Assistant to the Head of Department (see Fig. 3), and as tutor and demonstrator in the students' Organic Chemistry laboratory. By now, Weizmann was confident that his academic career would rapidly advance at the university.

Research Interests with Industry

Although Weizmann, in those early years in Manchester, still had difficulties with the English language, he nevertheless developed many professional and social relationships with leading university scientists, with prominent members of society, and with politicians. Weizmann befriended C. P. Scott, the editor of the influential newspaper, The Manchester Guardian, and through him became acquainted with Arthur Balfour, who had resigned in 1905 as Prime Minister but was a member of the British Parliament from Manchester, and one of the leaders of the Conservative Party. More and more, Weizmann found himself moving in the circles of science, applications and politics and he tried to use these relations to advance his goals. He also became friends with Mr. Charles Dreyfus, who was one of the leaders of the Jewish community and active in the local Zionist Organization. Dreyfus regarded Weizmann as a very knowledgeable scientist and offered him a job as a chemist in his chemical industry, Clayton Aniline, where he could work during his vacation time from the university. Prof. Perkin gave Weizmann his approval of the work offer, provided it would not interfere with any of Weizmann's responsibilities at the university as a tutor of students and Assistant Lecturer, and that research for the company would be done at his University laboratory with his students. Weizmann began to work for the company and, within a short time, developed a novel method to produce camphene and together with the company he submitted a Patent in 1906. He continued working for Dreyfus and in 1907, together with Perkin, they developed a new method to synthesize camphor, a compound known for its aromatic odor.

In his laboratory at the University, Weizmann began devoting his research efforts to produce synthetic rubber, which in those days was still produced from the natural caoutchouc resin or latex harvested from certain trees in the Far East. Since natural rubber was found to consist of a polymer of the molecule isoprene, many laboratories at that time were attempting to discover a more economic way to synthesize it. Weizmann thought that isoprene could be synthesized from the higher alcohols, butanol or amyl-alcohol, and decided to study methods to produce such higher alcohols by bacterial fermentation of sugars. The research was carried out in collaboration with Prof. Perkin and was funded by the Strange & Graham Company, London, where Perkin served as scientific advisor. In 1910, Perkin offered Weizmann a position there as his assistant and promised him 33% of any profits or royalties which he might receive from the company for his work on the synthetic rubber project. Weizmann readily agreed, but since the project required the development of fermentation processes for production of butanol, he proposed including Prof. August Fernbach (see Fig. 4) from the Pasteur Institute



Fig. 4. Left: Prof. Auguste Fernbach (1860-1938), PhD. Institute Pasteur, Paris, Director of Services de Fermentations (1900-1935). Right: Moise Schoen (1884-1938), Chemical Engineer, Assistant to Prof. A. Fernbach in the Services de Fermentations at Institute Pasteur, Paris (1908-1935).

in Paris, an expert in fermentations. Since Perkin did not have any knowledge in fermentation, he agreed with Weizmann's suggestion and in the autumn of 1910 they signed an Anglo-French Cooperation Agreement and formed a syndicate, whose goal was to develop methods for the production of butanol and amyl alcohol by fermentation which, in turn, would be used as the basic molecules for the synthesis of synthetic rubber.

Weizmann visited Fernbach in Paris at the beginning of 1911, and they reached an agreement on how to divide any income that might emanate from their joint research efforts. They worked together for a period with Fernbach's assistant, Moses Schoen (see Fig. 4), and together found a mixture of bacterial species that could ferment starch from potatoes and produce small amounts of amyl alcohol. Weizmann took some of the amyl alcohol back to Manchester, and in the autumn of 1911 discovered a chemical process to produce isoprene from the alcohol. Weizmann then wrote to Mr. Edward Halford Strange, who was a chemist who had graduated with an MSc degree from the University of Manchester and was the owner of the company that was supporting the research activities of the Anglo-French Syndicate, suggesting to patent and publish the new method in the literature. Strange declined because he wanted to keep the developments as a secret of the Company. Meanwhile, in June 1911, Fernbach isolated a new bacteria that he named FB, which fermented starch from potatoes and produced butanol as well as small amounts of acetone. In 1912, Strange and Fernbach submitted a Patent for the bacteria and its use in the fermentation process and sent Weizmann a sample of the FB bacteria for testing in Manchester .

On the basis of these discoveries and developments, Perkin advised Strange that it would be worthwhile to publish the

potential use of amyl alcohol and butanol for the synthesis of isoprene among investors, to interest them in investing in the establishment of an industrial facility to produce synthetic rubber. This decision started a chain of events resulting in scientific and political turmoil. Edward Strange hired Dr. Otto Hehner to compile a scientific report on the fermentation process that produces amyl and butyl alcohols. Dr. Hehner exaggerated in his description of the yields of butanol that were obtained from the fermentation of maize starch, when essentially those yields were obtained by fermentation of potato starch. Strange asked Perkin to support the report and to deliver some lectures on the processes that had been developed. Together they wrote a very appealing document for an IPO (Initial Public Share Offer) and submitted it on June 29th 1912 to the London Stock Exchange. It immediatiely attracted a lot of interest and enabled Strange to raise 75,000 Pounds (£) to build up a fermentation facility which they named Synthetic Products Company (SPC). The sum raised as the result of the initial public share sale of SPC, was unprecedented, especially in comparison to the salary of Weizmann who, as a senior scientist in the University, earned 600 £/annum.

Interestingly, neither Weizmann nor Fernbach were informed about the SPC stock sale nor the large sum of money that was raised. Naturally, they were both very offended since neither had been consulted on the issue nor given any credit for their original work. Weizmann, in particular, felt offended because he had not been given any credit in the well-attended lecture that Perkin had delivered on June 17th 1912 at the Society of Industrial Chemists on fermentation developments and discoveries. Moreover, they were very concerned that the document which Strange and Perkin presented for the public share offer was full of exaggerations and misinformation. Fernbach and Weizmann decided to end their cooperation with Strange's company until they had negotiated and received a fair share of the proceeds, as well as shares in the SPC company.

At this point, a serious dispute began among the four members of the original syndicate. On one side stood Perkin, who received a generous retainer from Strange but who had almost no involvement in the developments of the fermentation, and on the other side stood Fernbach and Weizmann, who felt cheated and demanded a fair share of the proceeds. Perkin, fearing that his income from Strange was at stake, decided to remove Weizmann from the Company by informing him that, according to his contract with the university, he had promised not to perform research outside that institution. Weizmann reacted by writing to Strange about his difficulties with Perkin and that he was considering to resign from the university, and asked Strange whether he would hire him as a Company scientist. Strange, being very concerned about the dispute that was developing among his scientific collaborators, asked Perkin, who still was Weizmann's supervisor at the university, to convince the latter to continue cooperating with the company. But Weizmann refused to come to terms with Perkin and what followed was an irreparable breakdown in the relations between the two.

At the same time, Strange requested a meeting with Fernbach to try and convince him to continue working with SPC and provide further reports on his results to the shareholders. However, Fernbach, aware that the scientific reports of Strange to the shareholders contained misinformation, hesitated and postponed the meeting with Strange until he had a chance to discuss the issues with Weizmann, whose scientific contributions he greatly respected. Fernbach invited Weizmann to a meeting in Paris to discuss a joint strategy on how to deal with the company of Strange and Perkin. They reached an agreement on how they would split between them any monetary benefits that they might receive from Strange and Perkin. Weizmann returned to Manchester, but to his dismay, after a short while he heard that Fernbach had reached an agreement with Strange and Perkin without consulting him. Weizmann, once again hurt and betrayed, contracted a lawyer to consider his next steps. His friends at the university, Professors Arthur Schuster, Samuel Alexander and Ernest Rutherford, with whom he often consulted, recommended that he completely stop cooperation and cut all relations with SPC, and hinted that the university authorities were also not happy about his significant research involvement in the Company. Weizmann accepted their recommendation, and in the autumn of 1912 he discontinued all his scientific contacts with Fernbach, Perkin and Strange. He further wrote to Strange that, as of that date, he was free to independently pursue any future topic of research.

In December of 1912, Perkin accepted the nomination of Professor and Chair of Chemistry at the prestigious Oxford University and decided to avenge Weizmann's decision to quit the scientific partnership with him, Strange and Fernbach. Perkin decided to disavow the verbal promise he had given Weizmann that in the event he would leave Manchester University he would recommend Weizmann as his heir to the Chair of Organic Chemistry. Perkin viciously spread the word at the university that the only thing that interested Weizmann was not science but money, and that he even had plans to move to live in Palestine. Perkin recommended to the University Search Committee, which until then had not interviewed a single candidate, that they should appoint his brother-in-law, Dr. Arthur Lapworth, an inorganic chemist, as his heir to the Chair of Organic Chemistry (see also Fig. 2). Dr. Lapworth was appointed to the position in May 1913 without resorting to any public tender or search and Weizmann was appointed Reader in Biochemistry, which is today's equivalent to the rank of an Associate Professor, but was freed from the obligation to report to the new Chair, Prof. Lapworth.

The fact that Weizmann was not appointed Professor was a very serious blow to his self esteem as this also meant that he could not be accepted as a member of the very prestigious Royal Society. In his despair Weizmann went for the easy explanation; he decided that the motive behind Perkin's attitude towards him was based on professional envy and anti-Semitism.

It is probably right to assume that Weizmann suffered the major damage from the rupture of the complex relations which he had developed with Perkin, Strange and Fernbach over the years. His scientific stature as the potential heir to Perkin's Professorial Chair had suffered a severe blow, not to mention the loss of his added income from the company. Depite his anger and hurt, Weizmann returned to his laboratory at the university and immersed himself in research with his students. In parallel, however, he also began devoting more of his time to his real passion, to advance the politics of Zionism.

Weizmann's invention for the production of acetone by fermentation

After his promotion by the university, Weizmann was an independent senior scientist without teaching duties, and his augmented salary allowed him more time for independent research. Weizmann and his students continued their research on the fermentation of starch using different bacterial species. Towards the end of 1913, Weizmann made a secret agreement with his Zionist friend, Mr Julius Simon, to financially support his research program on synthetic rubber. In return for his investment, Weizmann promised him 50% of any income that he might receive on developments to produce synthetic rubber. Weizmann now focused on bacteria that could produce by fermentation higher yields of butanol and amyl alcohol than in the past. His investigations with the FB bacteria that Fernbach had isolated and given him in 1912, revealed that it could only ferment potato starch under anaerobic conditions (without oxygen) but could not ferment starch from maize. Therefore, he decided to find bacteria which would directly ferment maize under aerobic conditions, and produce higher yields of butanol and amyl alcohol. After much research, he isolated such bacteria, which he characterized as a Clostridium Acetobutylicum species, and named it BY.

It is important to explain in more detail the process of isolation and characterization of Weizmann's BY bacterium, the reason being that this became an issue of utmost importance in the long and contentious dispute between Weizmann and the SPC Article on History of Chemistry

company members, Strange and Fernbach.

Weizmann isolated his BY bacteria from the commercially available Fitz bacterial mixture, the details of which had been published several years earlier in a book on microorganisms by Prof. Emile Duclaux from the Pasteur Institute in Paris. Fernbach had also isolated his FB bacteria from the same publicly available non-confidential source. Duclaux had also published a new method to activate certain properties of bacteria by briefly exposing them to heat. Weizmann had a vast knowledge of the scientific literature, including the 1909 papers of Bredemann, a Russian scientist who had reported on his results with bacteria that ferment starch, and he decided to isolate a bacteria from the Fitz mixture that would ferment starch from maize, using the heat treatment of Duclaux. Weizmann suspended the Fitz bacterial mixture in water and placed it in a bath with boiling water for a few minutes. All the bacteria died except for spores of bacteria that were heatresistant and survived the treatment. The bacteria that grew from these spores were heat-treated again, and this process was repeated ten times. From the bacteria which grew from the spores that had survived the repeated heat treatments, Weizmann isolated the BY species and was delighted to find that these bacteria had markedly different properties from the Fernbach FB bacteria.

In contrast to the FB bacteria of Fernbach, the BY bacteria were capable of directly fermenting starch from maize because, as he discovered, they contained the maltase enzyme that breaks down starch into sugars, which are then fermented. In addition, the BY bacteria were not sensitive to oxygen so the fermentation could be done under much more efficient aerobic conditions. Another proof of the difference between the FB and BY bacteria was that FB could be grown on plates with gelatin (a protein rich in collagen), whereas the BY bacteria caused the liquidification of gelatin and were only able to grow on plates with agar (a gel from sea algae). Weizmann found that during their growth, the BY bacteria secrete a proteolytic enzyme which breaks down gelatin into amino acids, which the bacteria then use as a nutrient. The finding of enzymes which degrade proteins and starch in the BY bacteria provided conclusive proof that the FB and BY bacteria had different properties. For all these reasons, Weizmann concluded that his BY bacteria differed substantially from the Fernbach FB bacteria. Of course, nowadays, with the available DNA and RNA analytical technologies, it would have been very simple to prove that the two bacteria were completely different.

Weizmann analyzed the products of the maize starch fermentation by the BY bacteria and found the two alcohols, butanol and amyl alcohol, but to his surprise, the most abundant product was acetone. Since Weizmann at that





time was particularly interested in the two alcohols because they were the basic compounds to produce isoprene for his synthetic rubber project, he did not pay much attention to the presence of rather large amounts of acetone. The separation of each of the products was achieved by fractionation distillation at different temperatures.

Acetone and its importance in the first World War

On August 3rd 1914, Britain declared war on Germany and the British Navy soon discovered that their factories for munitions and explosives had run out of stocks of acetone. Acetone was an important solvent used in the production of the Cordite propellant, which fires the heavy shells from the big naval guns. Pretreatment of the gunpowder with acetone prevented the abrasion of gun barrels and the release of smoke after firing and this made it difficult for the enemy to identify the location of the guns. Acetone in those days was produced in Germany, Russia and Finland but, due to the hostilities, the supplies of acetone were completely stopped. The method used to prepare acetone was by pyrolysis (high temp. heating of dry wood), an inefficient method that yielded only one ton of acetone per 80-100 tons of wood. Britain was incapable of providing such large amounts of wood and the alternative to import it was highly impractical. Thus the British Navy Admiralty and the Ministry of Munitions were desperately searching for alternative sources of acetone.

As mentioned before, the SPC company owned by Edward Strange started, in 1912, to produce some quantities of acetone and butanol by fermentation of potato starch with the Fernbach FB bacterium. At their facility in Kings Lynne, they produced acetone until June 1914 but stopped due to low demand. However, in September 1914, Strange realized that there was an urgent need to produce acetone for the war effort, so they restarted production. Strange contacted Nobel Explosives in Scotland and offered them a demonstration of their capabilities to produce acetone. Nobel Explosives sent their scientific director, Dr. Rintoul, to assess the SPC process and concluded that it was not very efficient as the fermentation only yielded 4% of acetone from the amount of potato starch. Nevertheless, due to the acute shortage, Dr. Rintoul gave SPC a contract to provide 7 tons of acetone per week. In practice, SPC managed to produce only one ton per week of not very pure acetone. The British Government, dissatisfied with the results of Strange's SPC production, contacted Prof. Perkin in Oxford University, who had proposed a chemical process to produce acetone from ethanol, the alcohol that is readily available from fermentation of grain by yeasts during the production of beer. Perkin, who had also left SPC, convinced the Government to build for him a facility where he would use his method to produce 100 tons of acetone per month. In reality, the Perkin facility could produce no more than 16 tons of acetone per month.

Following the recommendation of a colleague from the university, Weizmann wrote to Dr. Rintoul in January 1915 about his fermentation process and its ability to produce acetone. Dr. Rintoul visited his laboratory in February of 1915 and was so impressed that he returned two weeks later with a team of experts when Weizmann demonstrated his ability to produce 2 kg of pure acetone using a small lab scale fermentor. Dr. Rintoul and his team were very excited as it was the first time they had seen such an efficient system, and they recommended that Weizmann submit a Patent for his bacteria and production process. He also proposed that Weizmann sell his Patent to Nobel Explosives and asked him to start producing as much acetone as he could. Dr. Rintoul then told him that a proposal to the Government would be made to help him move his process to an industrial scale. Ironically, the sale of the Weizmann patent to Nobel Explosives did not materialize because of a large explosion that occurred at the Nobel Plant. As a result, Dr. Rintoul feared that the production of acetone would increase the danger of future explosions. Dr. Rintoul also reported his findings on the Weizmann acetone production process to Colonel Sir Frederick Nathan, Director of the Nobel Explosives Company in Scotland, and who also served as a consultant on explosives to the First Lord of the Admiralty, Winston Churchill. Sir Frederick Nathan was Jewish and had been a highly decorated artillery officer in the Boer War in South Africa. He knew Churchill from those days. As soon as he heard that the Weizmann process fermented the cheaper maize starch in an aerobic fermentor, Sir Nathan warmly supported the idea because it had a significant advantage and he understood that the British explosives industry could rapidly become self-sufficient in acetone. In April 1915, Weizmann and Sir Nathan met and discussed the conditions to apply fermentation on an industrial scale. Nathan arranged for a demonstration of the Weizmann process at the Nicholson Gin Factory in London, where there was a large fermentor that was placed at his disposal. The large scale experiment was a big success, and proved that the process was very efficient as it produced 12 tons of acetone from 100 tons of maize. Weizmann and Nathan also agreed that the processing of the patent that Weizmann had just submitted on the fermentation process should be frozen: the patent application would be assigned to the Government and kept as a state secret for the duration of the war. Weizmann in a well-planned chivalrous gesture, declined any compensation for the patent until the end of the war, when the patent would be returned to him and he could commercialize it without any restrictions. It is assumed that Weizmann's desire was to mimic what he had found common in English elite circles as "the proper way to behave" and not appear to be taking advantage of the dire military situation. Nathan was only too pleased with this arrangement and authorized it on May 12th 1915.

Nathan and the Ministry of Munitions were very pleased with the results of the Weizmann process and agreed to pay the salary of Mr. Harold Davies, Weizmann's close assistant in the university who had moved to London. In addition, the Government approved the construction of two new fermentation facilities under Weizmann's direction that would produce 2000-3000 tons/year of acetone. Until the new facilities were operational, they ordered a number of beer breweries and whiskey distilleries to start producing acetone in their fermentors, using the Weizmann process.

The rumors about the success of the Weizmann acetone production process and his patriotic gesture not to ask for compensation reached Winston Churchill at the Admiralty and the Munitions Minister, David Lloyd George. Weizmann, in his autobiography, writes that Churchill met with him and asked whether he could produce 30,000 tons/year acetone. This amount was exorbitant, since the more realistic needs by the industry were around 3,000 tons/year. In May 1915, Churchill was forced to retire after the defeat the British Navy suffered at the ill-fated Gallipoli campaign, and Arthur Balfour, whom Weizmann had met through C.P. Scott in Manchester, was appointed First Lord of the Admiralty in his place.

Weizmann who until that time was practically unknown, was appointed by Arthur Balfour as a paid advisor to the Admiralty on the subject of acetone, and as an advisor on chemical affairs to the Minister of Munitions. Following these official appointments, Weizmann received a special leave of absence from the University of Manchester and moved to London. He never returned to the university. In London, the Ministry of Munitions had prepared a research laboratory for him at the famous Lister Institute, the expenses of which were covered by the Government. At the Lister Institute, Weizmann investigated potential warfare uses for the fermentation side products, butanol and amyl alcohol, that were also obtained in large quantities from his fermentation process. Weizmann managed to chemically convert the alcohols into benzene and toluene, which are the primary products for the preparation of two important explosives, TNT and picric acid.

In December, 1915, Prof. Harold Dickson from Manchester University wrote to Weizmann informing him that Mr. Strange had paid him a visit after he had heard that Weizmann was working for the Government on the production of acetone. Strange asked details about the Weizmann process that Dickson refused to reveal. Strange told him that he no longer had connections with Prof. Perkin and that he was eager to renew his relationship and collaboration with Weizmann. Dickson suggested that Weizmann meet with Strange in an attempt to renew their collaboration. Weizmann replied that he had no interest in meeting Mr Strange and that the process he was using was a state secret that belonged to the British Government, and he had no authority to disclose any details. He emphasized, however, that his new process for the production of acetone was different from that used by Prof. Fernbach at SPC.

Some days later, Weizmann received a letter from Strange trying to convince him to meet with him and Fernbach in order to renew their old Syndicate collaboration agreements from 1910, for their mutual benefit. Weizmann guessed that the efforts of Strange to come to terms with him were mainly due to the bleak prospects of his company and on 17th December 1915 replied that he did not see any merit in meeting with him and Fernbach. He would only consider and respond if they sent him a written proposal based on the understandings attained during the intensive negotiations of 1912-1913, which had fallen through because they were unable to agree on terms.

In view of Weizmann's refusal to meet him, Strange wrote to Lord Moulton, who was the Chair of the Committee on Explosives at the Ministry of Munitions asking to meet him on an important issue relating to Weizmann. Strange also sent him various documents which he hoped would demonstrate that Weizmann was using their fermentation know-how and the FB bacteria of Fernbach. Lord Moulton, who resented the fact that Weizmann did not report to him and maintained direct communications with the Minister, David Lloyd George agreed to meet with Strange. Lord Moulton was nevertheless surprised to hear that Strange suspected Weizmann had stolen and used Fernbach's bacterium for the fermentation process. This he reported to Sir Nathan, who was responsible for the acetone project. One of the reasons for the aggressive claims of Strange and his threats to take Weizmann to court were because in March, 1916, the British Government, under the Defence of the Realm Act (DORA), issued an emergency decree to take over the acetone production facilities of SPC in Kings Lynne which used Fernbach's FB bacteria to ferment potato starch. The Government ordered a change in the fermentation process to the Weizmann BY bacterium using maize and under his direction. The take-over of SPC by the Government and placing it under the direction of Weizmann was a very strong blow for both Strange and Fernbach and unwilling to fight the British Government, they decided to fight it by discrediting Weizmann.

Following the report of Lord Moulton and after meeting with Weizmann, Sir Nathan realized how complicated the issue had become. He wanted to prevent the brewing dispute from reaching a public lawsuit in court at the height of waging a very difficult world war. Therefore Nathan invited all the parties to a meeting with the participation of Strange, Fernbach, Weizmann, Moulton and their respective lawyers, as well as Weizmann's patent agent Mr. Atkinson Adam. Adam declared at the meeting that the claims of Strange and Fernbach had no basis because Weizmann's fermentation process was based on a very different bacterium to the FB bacterium that Fernbach and Strange used. In addition, he declared that the whole process belonged to the British Government and if they were interested in pursuing their claims in court, they would be dealing with the Government. As a result of these very blunt declarations, Strange and Fernbach decided to discontinue their plans to bring the case to court, although their lawyers continued to issue threats and demands to hold an arbitration for a long while after. By the summer of 1916, Strange realized that the Government sided with Weizmann and had no interest in entering into lengthy litigation during a disastrous war that was claiming hundred of thousands of British and allied casualties. Therefore they stopped their harassments and decided to wait for a more opportune occasion. Weizmann understood that the dispute was not over and he began collecting all possible evidence which might help prove in court the significant differences between his and Fernbach's bacteria and their fermentation processes.

In parallel, however, Fernbach and Strange decided, during the summer of 1916, to interest the French and Italian Governments in their fermentation process for the production of acetone. The French Ministry of Armaments invited them for a demonstration of their process with the FB bacteria but to their dismay, the demonstration failed miserably. Since France and Italy were in alliance with Britain during the war, these countries asked the British Government for its assistance, and Weizmann was asked to travel to France to demonstrate his process. In September 1916, Weizmann and Mr. Davies traveled to war-torn France and successfully demonstrated their fermentation process. Upon his return to London, Weizmann wrote to Sir Graham Greene at the Ministry of Munitions recommending that the British Government allow the French Ministry of Armaments to start producing acetone using his bacteria and his methods. Weizmann added that Mr. Davies would be willing to facilitate the transfer of technology to the French. Weizmann also revealed in his letter that a French official had told him about the failure of the Fernbach process, and that Strange and Fernbach had accused Weizmann of stealing their bacteria and claimed that the entire British fermentation process belonged to Fernbach. The Ministry of Munitions and the Admiralty gave their consent to transfer, under contract, the Weizmann fermentation technology and bacteria to the French, and Mr. Davies started producing acetone at a facility in France.

However, Weizmann's worries were not yet over, and there was another obstacle to overcome. The fermentation processes of both Weizmann and Fernbach were based on the use of starch from potatoes or maize. However, due to the massive mobilization and manpower recruitments for the war effort, the agricultural production of Britain, especially that of potatoes and of maize (for animal feed), were becoming scarce. The British Government was importing increasing amounts of potatoes and maize from the USA to feed the troops and population, but many of the cargo ships were sunk by German submarines in the Atlantic and their precious cargo was lost. In view of the shortages, Weizmann came up with the idea to use chestnuts as a source of starch. Chestnuts were abundant in the country forests and not used for human consumption or as animal feed, so the Government initiated a campaign to induce children to collect chestnuts and bring them to a central depot, with a small payment as reward. Unfortunately, the acetone yields obtained from the fermentation of chestnuts were much lower than from maize because the starch content of chestnuts is less than half.

A decision was made by the Ministry of Munitions to look for an American company that would receive, under a secrecy agreement, the Weizmann fermentation technology and produce and ship the acetone to Britain. Representatives of the Ministry looked for a suitable company that would be willing to produce acetone. They found a company called Commercial Solvents Com. (CSC) in Terre Haute, Indiana, which had sizable fermentation capacities. The company owners signed an agreement whereby they would receive the Weizmann fermentation process, including the BY bacteria, and commit to exclusively produce and supply acetone for the British Government until the end of the war in Europe. Since maize was plentiful in America, CSC very quickly managed to produce large quantities of acetone which they then sent to Britain in drums on navy ships. In 1917, when the USA joined the allies in the war in Europe, the British Government authorized CSC and the US Government to invest in additional fermenters, also in Toronto, Canada, so as to increase production capacity for the American and Canadian explosives industry that also required acetone.

Weizmann's many contributions to British war efforts were highly appreciated by various prominent members of the Government. After the resignation of the Government of Herbert Asquith in December 1916, the two Ministers with whom Weizmann had frequent personal contacts, David Lloyd George at the Munitions Ministry, and Arthur Balfour at the Admiralty, were respectively appointed in January 1917 as Prime Minister and Minister for Foreign Affairs. It is appropriate to mention here that without doubt the personal relationships that Weizmann had established with both these leaders during the years 1915-1917, as well as with many prominent Jewish leaders like Herbert Samuel, who had served as Home Secretary in the Asquith cabinet, Israel Sieff, Simon Marks, Harry Sacher, Julius Simon, Samuel Tolkowsky and others, significantly contributed to advance the ideas and agendas of the Zionist movement, which culminated in the Balfour Declaration of November 2nd, 1917 which stated: "His Majesty's Government views with favor the establishment in Palestine of a national home for the Jewish people."

Many articles and book chapters have appeared during the years that review the scientific and political contributions of Weizmann to the Balfour Declaration. In the present article, we shall refrain from expanding on this well-reviewed subject.

Commercialization of the Acetone Patents after the War

Following the end of the War in Europe in November, 1918, Weizmann requested that the Admiralty return to him the rights to his 1915 patent application. As mentioned previously, the Patent itself had been kept a state secret during the war and had not been processed, at Government request. The Patent was finally awarded by the British Patent office on March 6th, 1919, and Weizmann obtained permission to commercialize its use in any territory he wished. The invention had not been publicly published anywhere else, so Weizmann, in order to protect his invention from competitors and with the aid of his patent agent, Atkinson Adam, applied for patents in various European countries in addition to the USA, Canada and India. All patents were awarded for the customary exclusivity duration of 17 years.

Adam also advised him to establish a limited company that would own and protect Weizmann's intellectual property and would facilitate negotiations to award licenses to interested companies. They chose the name The Organic Research Company (ORC). Weizmann and Adam subsequently wrote to the managers of CSC in Indiana informing them that ORC now owned the patent, which was awarded in Britain in 1919, and if they were interested in continuing to produce and sell acetone and butanol, ORC would be willing to negotiate for a license. The management of CSC was caught off guard since they had been under the impression that the British Government would allow them to continue producing and selling acetone and butanol. With the help of the Director of the Weizmann Archives, Mrs. Merav Segal, we found a copy of the license agreement that Weizmann signed with CSC, initially in 1919. This brief agreement was subject to US Patent office approval and award of the Weizmann Patent as submitted in the USA. Later on, in 1921, it evolved into a full license agreement document between ORC and CSC. We assume that Adam's role as party to the Agreement may be due to the fact that, according to English law, all private limited companies need to have at least two shareholders. Another consideration could have been to compensate for Adam's fees.

It is noteworthy that the license agreement that Weizmann and Adam signed with CSC in 1921 is, in essence, very similar to the standard license agreements that Yeda R&D Company, the commercial arm of the Weizmann Institute of Science signs nowadays with commercial entities on patents of Weizmann Institute scientists/inventors. It was particularly interesting to read the royalty clauses of the agreement that ORC would receive from CSC on the sales of acetone and butanol. ORC was promised, on average, one pound Sterling (£) per ton of acetone or butanol sold to third parties. As an example, from the 1929 Annual Report of CSC to its public shareholders, we learn that CSC sold that particular year 60,000 tons of acetone and was paid a total of 60 million pounds (1000 £/ton), of which CSC paid Weizmann approximately £60,000. Using an internet application that converts the value of one pound sterling in 1929 to the equivalent economic value of one pound

sterling in 2012, the value would increase 120 to 248-fold, depending on which index is used (cost of living, purchasing power, inflation, devaluations, etc). These calculations imply that the payment that Weizmann received in 1929 would be the equivalent in 2012, of a dollar value of \$7-15 million. Although this sum sounds very high, it is quite possible that today Weizmann could have negotiated and received a much higher figure. The reason being that the fermentation process and the bacteria, which Weizmann licensed exclusively to CSC, was already well-established and tested on an industrial scale, so CSC did not have to invest in any development of technology or infrastructure. The British and US Governments had invested, during the years 1917-1918, in the expansion of the fermentation facilities of CSC so that CSC was able to produce large amounts of acetone and butanol very quickly, and made a huge profit. Towards the second half of 1920s the demand for acetone declined but there was a big increase in the demand for butanol which yielded big royalties to Weizmann. The royalties that CSC paid to Weizmann were at a rate of 0.1% of sales and would be considered very low in 2012. In recent years, the inventors and technology transfer organizations of universities are usually able to negotiate higher rates of royalties based on sales of a product, especially if the technology or product is protected by a world-wide patent that has 17 years of exclusivity, is mature, and ready for production. Interestingly, we also did not find any evidence during our research that Weizmann gave any portion of his income to his scientific assistants who worked with him on the discovery, or to the university where he carried out the initial research, as is customary today. Weizmann, as mentioned before, also had an agreement with Mr. Julius Simon from the Zionist Organization, to split any income that he might receive from the synthetic rubber project, but since acetone had no connection to the rubber project, no mention was found regarding this agreement.

Weizmann continued to receive royalties from CSC until the expiry of the patent in 1936. The significant income allowed him and his family to live a very comfortable life. The income also enabled Weizmann to travel extensively around the world and to serve without a salary for many years as the elected President of the World Zionist Organization. During the years between the two world wars, Weizmann, together with Sigmund Freud and Albert Einstein, was amongst the most recognized and famous Jewish personalities.

The London Trial on the Infringement of the Weizmann Patent

In 1923, after a lot of effort, Strange and Fernbach managed to get back from the British Government the ownership of the SPC facility which had been taken from them by decree during the war in March, 1916. Weizmann produced acetone for the Government at the SPC facility during the years 1916-1918, using his bacteria. Strange and Fernbach refurbished the fermentation equipment and started to produce acetone and solicit clients to buy their product. CSC was very surprised to find out about the new competitor in the market and asked SPC how they were producing acetone. To their surprise Strange and Fernbach replied that they had their own bacteria, and the fermentation process that Weizmann had patented was essentially copied from them. Furthermore, in their opinion, the British Patent Office should never have approved Weizmann's patent.

The management of CSC was very concerned about these allegations, since they were not aware of the long, simmering dispute that existed between Weizmann, Strange and Fernbach ever since the early stages of the war. CSC management demanded to hear Weizmann's side of the story, whereby Weizmann denied all allegations that he had stolen the bacteria and information from Fernbach. Weizmann's Patent agent, Atkinson Adam, provided documents that convinced CSC that the SPC claims were false and that there were grounds to sue them for the infringement of Weizmann's patent.

Fernbach and Strange didn't give up and started a malicious campaign to destroy Weizmann's reputation by publishing accusations in Jewish newspapers and Zionist forums that Weizmann was a thief and a liar. Fernbach's Jewish assistant at the Pasteur Institute, Mr. Moses Schoen, who was connected to SPC was one of the accusers who tried to defame Weizmann in Zionist circles in Europe. He claimed that Weizmann had also duped the British Government about his invention during the war. Schoen wrote to the heads of the Zionist Organization recommending that they steer away from Weizmann because in the pending court trial in London, Weizmann was going to be found guilty of fraud, and this would besmirch the Zionist Organization. Naturally, all this took its toll on Weizmann who felt depressed by these defamations, and many of his colleagues tried to convince him to accept an arbitration and come to terms with Strange and Fernbach. On the other hand Atkison Adam and the lawyers of CSC had done a lot of research on the allegations of SPC and were well educated on the many differences between the FB and BY bacteria. They eventually convinced Weizmann to counter sue SPC for patent infringement in the London High Court. At the same time, Weizmann's lawyers warned him that if he agreed to an arbitration and reached a compromise with Strange and Fernbach, it would be considered a confession of guilt and cause irreparable damage to his reputation. So Weizmann decided to fight for his good name, and the CSC lawyers prepared and submitted a lawsuit to the High Court in London.

The lawsuit drew a lot of public attention, because it was the first time that the ownership of a complex bacteriological process and the reputation of scientists from famous institutions was at stake. The appointed trial judge was Justice M. Romer, and the first hearing began in January, 1926. Since the scientific questions were so complex that only a few people with a scientific background were able to understand the issues, Justice Romer decided to nominate a number of experts who would provide, under oath, explanations to the Court. The defendants, SPC who had infringed Weizmann's patent, claimed in their defense that the patent should be invalidated because the fermentation process by a bacteria that produced acetone had already been discovered and patented by Prof. Fernbach in 1912 and that Weizmann, who had spent some time in Fernbach's laboratory at the Pasteur Institute, had received a sample of this bacteria and taken it back with him to Manchester. Weizmann, in his testimony, confirmed that he had received the FB bacteria from Fernbach, but claimed that in the experiments he did with the FB bacteria in Manchester, he found that FB was incapable of fermenting maize starch, and could ferment potato starch only under anaerobic conditions. Fernbach, in his testimony, admitted that FB bacteria could ferment maize starch only after it was first treated with acid (hydrolysis), which breaks down starch into glucose, and that FB was sensitive to oxygen.

Weizmann testified at length on the reasons that led him to search for a bacteria that would directly ferment maize starch under aerobic conditions. He described in detail the isolation of the heat-resistant spores from the commercially available Fitz bacterial mixture, explaining that information about this bacterial mixture was publicly available, and that Fernbach himself had purchased it from the same source. Weizmann also described in detail the various differences he found between the BY bacteria that he had isolated and characterized, and the FB bacteria of Fernbach.

Justice Romer decided to nominate two well-known experts in bacteriology, Prof. Sir Frederick Andrewes and Mr. H. Ballantyne, to perform, in their own laboratories, fermentation experiments with the two types of bacteria: the FB of Fernbach was to be taken from the bacterial stock that had been deposited with the Government by SPC when they started producing acetone in 1915 in their Kings Lynne facility, and the BY bacteria that Weizmann used at the same SPC facility, after it had been taken over by the Government in the spring of 1916. Justice Romer asked the two bacteriologists to perform the fermentations in their respective laboratories exactly according to the protocols that were used in each of the cases at Kings Lynne, and to report their findings to the Court. The experts worked on their assignment in their individual laboratories for several weeks, and then testified in Court that the two bacteria were very different one from the other in their fermentation capabilities, as Weizmann had indicated. Fernbach was flabbergasted, and came up with a new story, telling the Court that, in 1912, he had isolated another bacteria, which he called 160X, and that this other bacteria had the same properties as the BY of Weizmann. He claimed that he had mentioned this to Weizmann, and as evidence, he showed the Court a letter he had received in 1912 from Weizmann asking if he could receive a sample of this new bacteria. During cross examination, CSC lawyers asked Fernbach whether he had replied to the letter and if he had sent Weizmann the bacteria. Fernbach was forced to admit that he had not answered because his relationship with Weizmann had already gone sour. Fernbach's testimony that he had not sent him the bacteria dismissed one of his most important accusations, that Weizmann had stolen his secret information and new bacteria.

Yet another secret which Fernbach claimed that Weizmann stole from the Pasteur Institute was the technique used for the selection of the BY bacteria, which was based on the exposure of bacteria to heat. Weizmann dismissed this claim by showing the Court the 1911 publication of Prof. Duclaux from the Pasteur Institute, in which he wrote all the details for the heat treatment and selection of heat-resistant bacteria.

Towards the end of the trial, Justice Romer, who had become very involved in all the scientific details of the case and often consulted with the experts he had nominated, came back to an issue which the CSC lawyers had asked Fernbach during their cross-examination. Fernbach was asked why, if already in 1912 he had in his possession the 160X bacteria that, according to him, could ferment maize, didn't he use it to produce acetone and butanol at their SPC fermentation facility, and why again he did not use it in 1916 when he had made a demonstration to the French Government. Justice Romer wrote in his detailed verdict (54 pages), that Fernbach's replies to this question were very vague and unreliable, and that the defendants were unable to provide evidence that they indeed had in their possession in 1912 a bacteria whose properties were identical to those of the Weizmann BY bacteria.

A further claim of the defendants was that the Weizmann patent of 1915 should be invalidated on the grounds that it was not a novel invention, because a fermentation process that produced acetone had already been 'reduced to practice' in 1913-1914 at the SPC facility in Kings Lynn. Justice Romer wrote that their argument was not acceptable on the grounds that experts of the British Government had concluded, in 1916, that acetone production with the FB bacteria was inefficient. The Government itself then took steps to take over the SPC facility and convert it into the much-improved Weizmann bacterial process, and this significantly contributed to the war effort.

In his detailed verdict of March, 1926, Justice Romer accepted all the Weizmann and CSC arguments and rejected all the defendants' claims, and ruled that SPC had infringed the Weizmann patent. Moreover, Justice Romer ordered the defendants to retract their accusation that Weizmann's actions were motivated by malicious intent, and wrote that there was no truth in the further accusations of Strange and Fernbach that Weizmann had used information belonging to SPC in his experiments to isolate the BY bacteria.

The Judge also wrote that: "through the Defendants' evidence, many of the witnesses have been looking at opportunities to damage the character or honesty of Dr. Weizmann and I cannot see the slightest evidence that Dr Weizmann has done anything that an honest man ought not to do."

The Judge then forbade SPC to produce acetone, ordered them to cancel all the contracts they had made, and pay damages to CSC. He also ordered them to pay the expenses of the expert scientists that the Judge had called upon in order to assist him in the trial.

Weizmann was very satisfied with the verdict of March, 1926 that proved his innocence. However, to his dismay, even after publication of his complete vindication in the trial, people associated with Strange and Fernbach (mainly in Eastern Europe Jewish communities such a Riga where the news about the London trial had not reached) continued to spread slander about Weizmann. Anonymous letters claimed that the London trial was a farce because Prof. Fernbach hardly spoke any English and his testimony was misunderstood. Weizmann's lawyers, and those of the Zionist Organization, were adamant in their desire to defend Weizmann, and sent letters to the newspapers and perpetrators of the slander demanding they desist or be sued for libel.

Another outcome of Weizmann's victory in the London trial was that it received a lot of attention among jurists and lawyers who dealt with Intellectual Property. In 1930, the precedent of the verdict of Justice Romer was also recognized in US Courts, when another American company, United Solvents, tried to infringe the Weizmann patent which had been licensed to CSC (then also called Butacet). The Judge in Delaware quickly ruled in favor of Butacet and forced United Solvents to pay damages.

The verdict in the Weizmann Patent Trial of 1926 bears some similarity to the long and detailed verdict written by US Federal Justice, Naomi Buchwald, in 2006 during a trial in which the Weizmann Institute of Science brought to court two large pharmaceutical companies, Imclone and Aventis (formerly Rhone-Poulenc) claiming that they had stolen the invention of a group of three Institute scientists, led by Prof. Michael Sela. In a landmark and unprecedented ruling, Judge Buchwald ordered the US Patent office to remove the names of the Rhone-Poulenc inventors from the Patent and replace them with the Weizmann Institute inventors. This decision also meant that the Weizmann Institute was awarded sole ownership of the valuable invention. Although almost 80 years separate between the two trials, it is interesting to note that, as in the Strange and Fernbach case, the Judge wrote in his summation that he was impressed by the integrity of the Institute scientists who appeared before the Court, who had been innocently unaware that their important invention had been stolen from them by former collaborators.

Epilogue

The disputes that developed during those years among the various scientific collaborators of Dr. Weizmann are in a way similar to those which, nowadays, are sometimes encountered between inventors and collaborators in academic institutions. It is interesting to note that a breakdown in relationships generally occurs when the scientific collaborators and partners realize that their joint research results might yield significant financial benefits and as lawyers and financial investors become involved.

Dr. Weizmann's scientific and business activities during the two decades (1904-1926) in which he managed to advance a significant number of scientific applications and patents, often caused him anguish and frustration. However, later on, and to his great satisfaction, these activities culminated in some very important financial benefits which also enhanced his reputation and enabled him to devote most of his time to his Zionist goals.

If experience is defined as "The knowledge or mastery of an event or subject gained through involvement in or exposure to it." (Oxford English Dictionary), then it is safe to assume that Weizmann learnt a lot from the 'messy affair' of the acetone patent. It most likely strengthened his character and contributed to his self esteem, and the experience helped him become one of the most important Jewish leaders in the period between the two world wars.

Moreover, the Weizmann acetone affair, which brought Science, Business and Politics to a mutual crossroad, may very well have been a driving force to implement very important scientific and management guidelines during Weizmann's establishment, in 1933, of the Sieff Institute of Research in Rehovot, (the predecessor of the Weizmann Institute of Science), as well as in the Palestine Pharmaceutical Products (PPhP) company, which he founded in 1941 adjacent to the Sieff Institute.

Acknowledgments

We wish to express our deep gratitude to Mrs. Merav Segal, the Director of the Weizmann Archives at the Weizmann Institute and to Dr. Netta Maoz for their very valuable assistance in finding relevant historical documentation for this article. We also wish to thank Mrs. Jean Pnini for her excellent contribution to the editing.

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Profile of Gil Alexandrowicz: Recipient of 2015 ICS Prize for the Outstanding Young Scientist

by Simone Somekh



Both of Gil Alexandrowicz's parents were scientists. However, the renowned Israeli scientist and winner of the 2015 ICS Excellent Young Scientist Prize, did not see himself as a scientist when he was a teenager. "It didn't even cross my mind to study chemistry or physics," he said. Today he runs one of the most successful labs at the Technion, merging physics, chemistry, and chemical engineering.

Alexandrowicz was born in Jerusalem in 1973 and decided

to study physics after he finished his military service. During his third year of his BSc, drawn by the enthusiasm of Prof. Noam Kaplan at Hebrew University, he decided to become an experimental physicist and enrolled in the MSc program of the institute. "Kaplan was my supervisor, and he showed me the importance of curiosity and intuitiveness in the research process."

During his MSc he studied electron resonance. "We used

resonance to achieve electron motion inside solids."

After graduation, he worked for two years in a start-up company called TopSpin Medical, which operated in the medical field. Alexandrowicz was able to use his physics expertise to help create a device which diagnosed the presence of vulnerable plaque and ultimately prevented heart attacks. The physicist enjoyed his job – however, he missed academic life.

"I am curious by nature," he said. "I was eager to study." And so he did. He flew to Cambridge for an interview and was accepted for a doctorate. He was one of the first students to ever receive the prestigious Bill Gates scholarship, which allowed him to move to the United Kingdom with his wife and their daughter, who was three-months old. At Cambridge, he studied the structure and motion of molecules on surfaces, bringing his ideas from the field of magnetic resonance in which he had worked before. The research was so successful that he ended up staying there for his post-doctorate, as well.

In the beginning, life in Cambridge wasn't so easy. Alexandrowicz, his wife, and their daughter were far from their family in Israel, and they had to adjust to a whole new world. Despite this initial challenge, the atmosphere in the lab was very nice, he says, with students from Egypt, Singapore, China, and Scotland.

After seven years in Cambridge, Gil received an offer to open his own lab at the Technion in Haifa. In 2010, he moved back to Israel with his family (which included an addition — a baby boy) and established his group, composed of chemical engineers, chemists, and physicists, with one goal: building a new helium-3 spin echo spectrometer (HSE), the apparatus he had helped to build in Cambridge.

Despite the efficiency of the team, which managed to build the ultra-sophisticated machine, Alexandrowicz soon hit a wall: there was no helium-3 available for purchase. The gas, which was crucial to make the spectrometer work, is very rare and expensive.

"There was a worldwide shortage of helium-3. I was stuck," he recalled. "Then I realized I could use my machine to do

other experiments, particularly to separate water molecules, a practice that is impossible with any conventional device."

The change of direction was a clear sign of Alexandrowicz's out-of-the-box thought process. His team managed to use the HSE spectrometer to separate the water molecules, and received worldwide praise for this important achievement. In the meanwhile, Gil was finally able to purchase helium-3 and finished building the machine for its original use.

Currently, he is building a new spectrometer and his team is helping a Canadian group of researchers to build a similar device.

Alexandrowicz is enjoying the Technion. "I receive a lot of support for my research, it's a great place," he said. However, he's not as happy when it comes to Israel as a whole. The professor feels like the country is slowly worsening in terms of tolerance and education. "While the academia is a great oasis, the general trend is worrying me."

The researcher dedicates most of his time to the lab, yet he is glad to show both of his children that he enjoys his profession. In his free time he likes to hike and he recently started surfing.

To the new generation of researchers, Alexandrowicz says: "Don't be afraid to shift from one field to another. Never underestimate the power of teamwork. And, ultimately, being passionate is the key to success."

Simone Somekh was born in Italy in 1994. He studies at Bar-Ilan University and works as a freelance writer. His works have been published in The Jerusalem Post, The Times of Israel, and Wired Italy.

His Twitter account: (@simonsays101) and his website: www.simonesomekh.com



Profile of Rafal Klajn: Recipient of 2015 Prize for the Outstanding Young Scientist

by Simone Somekh



Born in Poland in 1982, Rafal Klajn was first exposed to the world of chemistry at the age of 12, when he attended his first chemistry class. The teacher was an enthusiastic lecturer, one of the very few who took the effort to set up a small laboratory and to organize practical classes for the students.

Passionate about both chemistry and architecture — "Both deal with elegance in design and execution," he said, quoting writer Philip Ball — Klajn completed his undergraduate studies at the University of Warsaw, and subsequently moved to Chicago, obtaining a PhD in Chemical and Biological Engineering at Northwestern University.

"I chose an academic career rather than one in industry for the intellectual freedom," said Klajn. "Academia allows me to work on things that are fundamentally interesting rather than immediately useful." The professor enjoys being part of a worldwide network of scientists.

In 2009, Klajn relocated to Israel and joined the Weizmann Institute. "I was attracted to the curiosity-driven research of the Institute," he explained. "Despite its relatively short life, its scientists have made numerous important discoveries. It's also quite inspiring to interact with colleagues from different fields, such as astrophysics and systems biology."

In his lab at Weizmann, Klajn is studying systems that combine chemical reactions with self-assembly processes. This broad field of chemistry includes concepts ranging from motion on the molecular scale to assembly of colloidal particles.

"To me, the essence of chemistry is captured in the Chinese word for 'chemistry,' which translates into 'the study of change.""

One of Klajin's main interests, in fact, is a class of molecules known as molecular switches, capable of performing controlled motions when subjected to external stimuli. These switches, explained Klajn, allow us to construct so-called "smart" materials.

"We are also very interested in studying and trying to mimic the ways reactions and self-assembly processes occur in nature. Hence, we are very much into problems such as reactions in confined spaces, compartmentalization, templating, multivalency, energy-dissipating system and materials. These concepts are closely related to one of the biggest outstanding questions in science, namely, the origin of life on Earth."

Among his many discoveries, Klajn recalled finding that cubic magnetic nanoparticles can spontaneously assemble into helical superstructures, and demonstrating that lightresponsive nanoparticles can act as catalysts for chemical reactions.

The lab has hosted students and researchers from China, Croatia, Germany, India, Israel, Korea, Latvia, Poland, Portugal, Spain, and the United States.

At Weizmann, Klajn is also teaching a course entitled "Colloidal and supramolecular chemistry." In class, he enjoys the interactions with the students, to the extent that he even likes being interrupted by the "often excellent questions."

Chemists are privileged people, he explained, mentioning the feeling of being the only person on the planet to ever hold in their hands a particular chemical compound. "Never lose curiosity," said Klajn. "While experimenting, always look for the unexpected. Don't be afraid of exploring new territories. And keep up with the recent literature."



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Shlomo Magdassi, Printing The Future of Chemistry

by Simone Somekh



When Shlomo Magdassi was 10 years old, he already knew he wanted to be a chemist. He enjoyed doing all sorts of experiments that involved electrolysis and producing gases. So when he completed his army service, it was more than obvious that he would enroll in the chemistry department of Hebrew University.

Born in 1954 in Ramla to parents who emigrated from Iraq, Magdassi moved to Jerusalem after serving in the army and spent almost his entire academic career at the Hebrew University, where he received his doctorate. He did his post-doc in Columbus, Ohio, researching colloid science and emulsions in the school of pharmacy; he was then offered the opportunity to start his own lab at the Hebrew University and decided to return to Israel.

In his Jerusalem lab, the professor directed his research towards nanomaterials and started several research projects about digital printing, which at the time was a completely new field.

"Digital printing with nanoparticles can be useful for multiple functions, from conducting electricity to emitting light, from sensing humidity to sensing touch," he explained. In recent years his lab licensed several of his printing and coating technologies to produce new products. DipTech, for instance, is a Kfar Saba -based company that produces digital printers and inks for a longlasting glass printing solutions. With Magdassi's technology, the inkjet ink becomes an inherent part of the glass itself, creating new frontiers for architecture and design. Another example for licensed technology is BrightSource, which launched in 2010 the Ivanpah Project in California. The project — operational since December 2013 - is a solar thermal power plant which supplies electricity to over 140,000 homes in the area, while the invention (together with Prof. Mandler) provides the heat resistant solar absorber .

Other projects include NanoDimension, established in 2012, operative in the research and development of advanced 3D printed electronics, and ClearJet, which uses inkjet technologies to produce touch screens. Magdassi was also recently appointed as director of the new 3D printing center at the Hebrew University.

So far, Prof. Magdassi has authored more than 200 publications and leads a large research group, to which he welcomes numerous international students. "My students need to be curious and highly motivated," he said. "They need to be hungry... in a good way."

The researcher is currently spending a sabbatical in Singapore, working on a collaborative research program between Nanyang Technological University (NTU), The Hebrew University of Jerusalem and Ben-Gurion University of the Negev. The program, "NEW", is aimed at studying and using nanomaterials for water and energy management. It is part of the international collaboratory Campus for Research Excellence and Technological Enterprise (CREATE), which is under the National Research Foundation of Singapore. Magdassi, describes his experience in Singapore and collaboration with NTU researchers as "excellent." "I wish we could adapt some of the Singaporean attitudes to our labs," he said. "For instance, the long-term planning and the very strong governmental support received for the research. I also enjoy the general atmosphere in Singapore; people have a strong sense of respect for each other, something that we should strengthen in our country ."

While in Singapore, Magdassi holds regular meetings on Skype with his students to follow their research projects. Even during the interview, he received several WhatsApp messages from them. "WhatsApp is constantly making sure that I am still connected to my lab," he joked. Magdassi is married and has two children; his son is an industrial designer and his daughter is a student at the Hebrew University.

As the winner of the 2015 ICS-ICL Prize for Technological Innovation, Magdassi has some advice for the aspiring chemists out there: "Follow your intuition and reinvent yourself. Don't be stuck in one single field. Don't be afraid to explore new field and to get out of your comfort zone."

Profile of Dima Gelman: Recipient of 2014 Prize for the Outstanding Young Scientist

by Simone Somekh



Born in 1974 in Chelyabinsk, a former Soviet Union industrial city (the city is otherwise known for the meteor crash in 2013) to parents who were engineers, Dima Gelman always knew he wanted to be a chemist. As a youngster, he didn't like mathematics, but was fond of science, which he started learning from a young age. "At the age of 12 I prepared my first Berthelot's salt."

When he was 16 years old, Gelman decided to move to Israel and made Aliyah alone. "I was seeking adventures," he recalled. "Though life was different in Israel, my transition was easy as I was young and unpretentious." Gelman spoke very little Hebrew and no English at the time, but he learned both languages and completed his high school matriculation at the Wizo-Hadassim boarding school in Even Yehuda, not far from Netanya.

After graduation, he decided to sign up for a program that would allow him to pursue an academic degree before serving in the military. It's no surprise that the choice immediately fell on chemistry.

After completing his military service in the armored corps of IDF, Gelman returned to the lab of Prof. Jochanan Blum, his MSc supervisor, and began working on cross-coupling chemistry, at that time a challenging branch of organometallic synthetic chemistry. During his PhD, he met his wife Faina, who was also working in Prof. Blum's group. The two subsequently searched for positions abroad as postdocs in the same institute; in 2002, they both found a place at the Massachusetts Institute of Technology. "We worked in two different labs: Faina - with Prof. Alex Khlibanov and I – with Prof. Steve Buchwald, but were in the same building," said Dima.

"Researching at the MIT was an amazing professional experience," he said. It was at a time when scientific search engines had only just become accessible to scientists in the States but were still not popular in Israel. "Today the difference isn't so big anymore, but at that time, I was charmed by the immediate access to information," claimed Gelman.

As soon as they completed their postdocs, Dima was offered the opportunity to open a new lab at the Hebrew University, and so they moved back to Jerusalem. "I feel at home in Israel," said Gelman.

"Starting a new lab is not easy," he explained, "but I received a lot of support from my former supervisor, Prof. Blum, to make the first steps in the Israeli academia." In the lab, Gelman and his team develop a new family of very modular multifunctional transition metal catalysts, whose properties can be easily modified via "Lego"-type structural transformations according to the desired application.

The group was very diverse – just as his current team is – with students and researchers from Israel, Poland, France,

Russia, India, and other countries. "My lab has always been characterized by diversity: I have Jews, Christians, and Muslims, both religious and secular. I believe this is the way to go because diversity is a driving force behind evolution and progress."

Along with chemistry, Gelman has another passion: animals, especially French bulldogs, pictures of which cover a wall of his office at the Givat Ram campus of the Hebrew University. For many years, he's dreamed of pursuing a degree in veterinary science, and now the time might have come for him to follow this dream, as well.

"My advice for the aspiring chemists and young researchers is to keep experimenting," he said.

Simone Somekh was born in Italy in 1994. He studies at Bar-Ilan University and works as a freelance writer. His works have been published in The Jerusalem Post, The Times of Israel, and Wired Italy.

His Twitter account: (@simonsays101) and his website: www.simonesomekh.com



Profile of Abraham Nitzan: Recipient of 2014 ICS Gold Medal

by Arlene D Wilson-Gordon



The distinguished Israeli theoretician Abraham Nitzan was born in Tel Aviv in 1944 to a family of Polish origin. From his earliest years, he was fascinated by science and was an avid reader of all the popular science magazines then available. His interest in science was encouraged by his older brother who was nine years his senior and a pediatrician by profession. Like many professional chemists, Nitzan had a lab at home where he performed experiments, many of which would be considered too dangerous for children nowadays. For example, he investigated the effect of sodium pellets supplied by his brother on the puddles near his home! At his high school, he received an excellent education in physical sciences which consisted of mathematics, physics and chemistry as a coherent unit. Nitzan feels that the change to separate subjects in the Israeli matriculation has been detrimental to chemistry and has contributed to the decrease in the number of schools that offer chemistry as a matriculation subject.

Aged only 17, Nitzan applied to the Hebrew University to study chemistry but was rejected due to his young age and the fierce competition for places. Instead, he was accepted to study physics which was at the time less popular. Not easily deterred, he successfully appealed and studied for both the BSc and MSc in chemistry at the Hebrew University. There, under the tutelage of the well-known physical chemist Gidon Czapski, he studied the radiation chemistry of aqueous solutions and acquired his life-long interest in theoretical chemical physics. After completing his army service, Czapski advised him to move to Joshua Jortner's vibrant group at the Department of Chemical Physics in Tel Aviv University for his doctorate. He flourished in that stimulating and demanding environment where it was not unusual for papers to be written in the small hours of the morning. His thesis focused on the theory of non-radiative transitions in large molecules and was based on concepts developed in nuclear physics.

After completing his doctorate in 1972, Nitzan moved to MIT for a postdoctoral fellowship with John Ross where he studied the kinetics and diffusion of chemical instabilities using classical statistical mechanics. After a year as an assistant professor at Northwestern University where he met Mark Ratner, his collaborator for many years to come, and also collaborated with Karl Freed and Morrel Cohen of the University of Chicago on the study of disordered condensed phases, he returned to Israel in 1975 with his wife and a small daughter born during his stay at MIT. He was offered academic positions at the Hebrew University, Weizmann Institute and Tel Aviv University and decided to return to Tel Aviv University where he has spent most of his career apart from numerous visits to universities and research institutes abroad. During one such visit to Bell Labs, a second daughter was born. He says that at no time did he consider a career outside academia. His enthusiasm for academic research has inspired both his daughters: his older daughter is a mathematician at Georgia Tech and his younger daughter is doing a postdoc in psychology in Boston.

Nitzan's wide-ranging research interests can be summed up by the title of his book published in 2006 by Oxford University Press: "Chemical Dynamics in Condensed Phases: Relaxation, Transfer, and Reactions in Condensed Molecular Systems" which arose from various courses that he has taught throughout his career. Within this general theme, he has identified and often pioneered many subjects. He is particularly proud of his work (with Joel Gersten from the University of New York) in the 1980s on surface-enhanced spectroscopies that later led to the development of the field of molecular plasmonics and his more recent work on molecular electronics, for both of which he was awarded the Emet Prize for chemistry in 2012. Indeed, Nitzan has won many awards and distinctions including the 2003 ICS prize for an outstanding scientist, the 2010 Israel prize in chemistry and the 2014 ICS medal. He is a member of the Israel Academy of Sciences and Humanities since 2009, a foreign honorary member of the American Academy of Arts and Sciences since 2006 and a foreign associate of the National Academy of Sciences (USA) since 2015.

Nitzan says that the recurring theme in his extensive work is the use of similar fundamental concepts and techniques to study different systems and their applications. When his long list of publications is viewed by an outsider, it seems as if the flow from subject to subject is smooth and well-planned, like a well-orchestrated symphony, yet Nitzan admits that his greatest challenge lies in deciding when to abandon a particular line of research and which new directions to pursue. For example, he abandoned his research on ion diffusion via biological membranes when he realized that he would have to devote substantial time to study the necessary biology. This illustrates Nitzan's rigorous approach to research: he does not seek shortcuts and likes to be in control of all aspects of the research. In addition, Nitzan enjoys teaching basic and advanced courses to undergraduates as well as interacting with the many graduate students and postdocs he has mentored.

In addition to teaching and research, Nitzan has served in a number of academic administrative roles, such as head of the School of Chemistry, dean of the Faculty of Exact Sciences, head of the faculty teaching committee, member of the university promotions committee, senate representative in the university central steering committee and board of trustees and director of the Sackler Advanced Studies Institute at Tel-Aviv University. He has also contributed to the wider community by serving as a member of the Ministry of Education topical committee on chemistry.

When asked whether there are any changes he would make in his university, he says that he thinks that the transfer of biochemistry from the School of Chemistry to the Faculty of Life Sciences is regrettable. He feels that chemistry should reclaim its rightful place as the central science between physics and biology. In addition, he would like to see more women in the faculty (there is only one woman in his own department). He feels that the brain drain of Israeli scientists is inevitable due to the international nature of modern science but would like to see Israeli universities attracting faculty from other countries, especially in specialities where there is a shortage of suitable candidates. Nitzan has thoroughly enjoyed his career as an academic scientist and would strongly recommend academic life to young gifted scientists although he feels that the many demands made of young academics have somehow destroyed the "freedom to dream" that once existed. Given a "magic wand" he would restore that essential freedom. On balance, he is pleased by the level of the young scientists recruited to Israeli universities and believes that we should be proud of the achievements of Israeli scientists. When he is not busy with his research, Nitzan (who has remarried) enjoys spending time with his grandchildren and his wife, and collecting tortoises (not live ones).

Now at the age where many people slow down, Nitzan has recently taken on a new challenge as Professor of Chemistry at the University of Pennsylvania. He has already begun to build a research group there and next year will begin teaching. When asked about his plans for the future, he says "to do good science."

Arlene Wilson-Gordon was born in Glasgow, Scotland. She completed her BSc (Hons) at Glasgow University and her DPhil at Oxford University under the supervision of Peter Atkins. After a postdoc at the Hebrew University with Raphy Levine, she joined the faculty at the Department of Chemistry, Bar-Ilan University, where she rose to the rank of Professor and in 2015, Professor Emerita. Her research interests lie in the field of theoretical quantum and nonlinear optics. She is the editor of



the Israel Chemist and Engineer, an online magazine for all who are interested in chemistry and chemical engineering.
Profile of Emanuel Peled: Recipient of 2015 ICS Prize for the Outstanding Scientist

by Lior Elbaz



Emanuel Peled was born in 1942 in Israel to a well-established Israeli family. He is the fifth generation of his family in Israel, a family that helped build important parts of Israel, the founders of Rosh-Pina, Yavniel and his birth place and current home: Even Yehuda. Initially, Even Yehuda was just two shacks: his grandparents, mom and aunt lived in one of them, and 20 bachelors lived together in the other. Since then, Even Yehuda has become a flourishing agricultural center in the Sharon region and the home of over 12,000 residents today. As the son of Halutzim (Zionist pioneers), it was natural to send him to study at Rupin, an agricultural school not too far from his home. During these years, Emanuel became interested in radio-communication (became a ham radio operator), built a transmission station and contacted radio fans from more than 80 different countries, from America to North Africa to Australia - he still holds on to their ID cards (cards exchanged by radio fans to prove they communicate with each other). In contrast to expectations, during his days at Rupin, Emanuel became interested in chemistry due to the influence of Gonda, his chemistry teacher. This was the first milestone in his path to becoming one of the leading chemists in Israel. After graduating from Rupin, Emanuel enlisted in the Israeli Defense Forces and became a medic in the Israeli Armored Forces. Immediately after his military service he followed his passion for sciences and chemistry and decided to study chemistry. At that time, there were only two options in Israel: The Technion and the Hebrew University. After obtaining his bachelor's degree in 1965 from the Hebrew University, he decided to continue his studies and signed up for the graduate school at the same university. Following the introduction of the first linear accelerator in Israel, he became interested in radiochemistry and looked for a good mentor in this field. He did his MSc (1967) and PhD (Summa cum laude, 1972) with Professor Gidon Czapski on the radiochemistry of aqueous solutions. Like many others from his generation, his plans were interrupted by several of the hardest and most critical wars Israel has known: he fought in the Six Days' war (the 1967 war), the battle of Karameh (1968) and the Yom Kippur war (the 1973 war).

After obtaining his PhD, Emanuel started working in a newly established lab - the first electrochemistry lab in Israel, Professor Eliezer Gileadi's lab at Tel-Aviv University. Over there he worked on the development of methods for electroplating of aluminum. After a couple of years of working in electrochemistry, he was convinced he should build his academic career as an electrochemist. He realized that there was very little known in this growing field which had many prospects. Emanuel also says that electrochemistry is an overlap between his passion for radio, electronics and chemistry, since the passing of current through liquids, solids and their interfaces has always fascinated him. He is proud to say that in his time, researchers had to build their instruments from scratch. As a prominent researcher, he became a lecturer at the Tel Aviv University in 1973. When asked, "What was your motivation to do scientific work?" he answered, "I wanted to do good, reliable, innovative and interesting science and the guideline for my work is to do science that will help keep Israel safe and will contribute to its economy." In many ways, this is not surprising when looking back at his life and his strong connection to this country. Emanuel also calls his work "Directed Science", which he describes as basic science directed towards applicable goals or products that will have significant impact on people's lives. Emanuel decided to focus his studies on energy-related work, mainly on batteries and fuel cells. Today, Professor Emanuel Peled is a world-renowned scientist in these fields of research. He has published more than 170 papers and holds 47 patents and patents pending. The large number of patents reflects his sustained contribution to the development of advanced electrochemical power sources. For his achievements in the field of electrochemical power sources, he received the Electrochemical Society Battery Division Research Award, the Landau Research Award, the Award of the International Battery Association (IBA) and the 2015 Israel Chemical Society Outstanding Scientist Award. He was also recently elected as a Fellow of the Electrochemical Society.

According to Emanuel, his greatest and most important scientific contribution is the invention and development of the solid-electrolyte-interphase (SEI) model developed in 1979 for nonaqueous alkali-metal batteries. This model constitutes a paradigm change in the understanding of lithium batteries and has enabled the development of safer, durable, higherpower and lower-cost batteries. At first, fellow scientists in his field did not recognize this groundbreaking development and continued to use the Butler-Volmer equation, in which direct electron transfer from the electrode to lithium cations in the solution is assumed. It was common knowledge that the "passivating" layer on lithium anode must be eliminated. The SEI model showed that this is the wrong approach; the Butler-Volmer equation is not applicable and lithium batteries cannot function at all without a proper SEI that prevents electron transport to the solution. Thus the electrolyte has to contain a proper SEI precursor. The SEI determines the safety, cycle life, power and shelf life of the lithium batteries. The SEI model was the first to explain the electrochemistry of the lithium batteries. It took many years for the scientific community to accept the SEI model, until Prof. Jeff Dahn, a pioneer in the development of Li-ion batteries, started using it in 1989. Since then it has become the gold-standard model for studying the kinetics of lithium during battery charge and discharge processes, lithium-anode corrosion, the resistivity of the SEI, the growth rate of the SEI, the exchange-current density and for the "Tafel" slope and its dependence on SEI thickness. At present, in most of the articles on the electrochemistry of lithium and sodium batteries (over 30,000), the SEI model is used to analyze the experimental results. Only four electrochemical power sources are capable of achieving the 500 km driving range goal of EVs. These are lithium/sulfur, lithium/air, sodium/air and fuel cells. Emanuel Peled has made significant contributions to each of them. Emanuel pioneered the development of the rechargeable lithium/sulfur battery. He was the first to develop a lithium/sulfur cell that consists of a porous carbon electrode loaded with sulfur. His work is seminal in advancing knowledge related to this battery. He was the first to publish a paper on a novel molten-sodium/ oxygen (air) rechargeable cell. In the field of fuel cells (FCs), he has made some major contributions. A high performance and very-low-cost nanoporous proton-conducting membrane (NP-PCM) has been developed. With the use of this membrane, several fuel cells have been developed, including a direct methanol and, for the first time, a direct ethylene glycol fuel cell and a hydrogen tribromide fuel cell. These three fuel cells have demonstrated world-record powers. Methanol and ethylene glycol are produced from natural gas and can be used as alternative fuels for transportation. A low-cost high-power hydrogen tribromide unified regenerative fuel cell (RFC) was developed for the first time. The technology was transferred to Enstorage which scaled it up to 50kW grid connected unit. He is a co-founder of three energy related start-up companies based on technology developed in his laboratory: Chemtronics (lithium battery meter), Enstorage (RFC) and Honeycomb (a 3D micro battery). As a testament to Emanuel's impact on his field and on the development of energy technologies, he has been frequently asked to serve as a consultant to Israeli companies such as Tadiran and Rafael, the Israeli Department of Defense, The US Department of Defense, NASA and many other small companies. Last, but definitely not least, Emanuel is the proud father of four sons, two PhDs in electro-optics, one computer engineer and one fighter pilot in the Israeli Air Force. He is also grandfather to 13 grandchildren whom he likes to visit at least once a week.

From the author: Speaking not only for myself but for the whole Israeli electrochemical community, Emanuel has always been an inspiration in the field, his versatility and deep knowledge has contributed to all of us, not only through his scientific communications but also through insightful meetings with him. From my personal experience, his door is always open and he likes to help and collaborate with young ambitious fellow electrochemists. He is a kind and very modest person.

Dr. Lior Elbaz has a B.Sc., M.Sc. and Ph.D. in chemical engineering, all from the Ben-Gurion University, Israel. During his graduate studies, he became an expert in electrochemistry and electrocatalysis. He used his expertise to develop alternative energy technologies. After finishing his Ph.D. he joined the MPA11 group, at the Materials Physics & Applications Division at the Los Alamos National Laboratory, a world leader in the development of fuel cell technology, where he developed new catalysts,



and materials for fuel cells, in order to reduce their price and increase their durability. After almost four years at Los Alamos, Lior came back to Israel to take a faculty position at the Department of Chemistry, Bar-Ilan University, where he heads the alternative Energy Lab.



GENDER BALANCE IN CHEMICAL SCIENCES IN ISRAEL

Daniella Goldfarb

Chemical Physics Department, Weizmann Institute of Science, Rehovot, Israel

The purpose of the poster to increase the awareness of the Chemistry communityin Israel to poor gender balance in the Chemistry departments in Israel. Although the % of PhD women graduates from Departments of Chemistry in the Israeli Universities is relatively high, the representation of women in the academic staff, assistant professor (senior lecturer, senior scientist), associate professor and full professor, is still low. Here I present some statistics to highlightthe current state. Comparison to some top Chemistry departments in the world will as well. I hope that this poster will trigger some discussion and will lead to some activities within the Israeli Chemical Society to encouragea heathier gender balance in Chemistry in Israel.

see poster on the next page

Prof. Daniella Goldfarb received a BSc in chemistry from the Hebrew University of Jerusalem, an MSc at the University of Rhode Island, and a PhD at the Weizmann Institute. Following postdoctoral studies at the University of Houston, she joined the Weizmann Institute in 1987 and was promoted to Full Professor in 1998. She is the incumbent of the Erich Klieger Professorial Chair in Chemical Physics. At the Weizmann Institute, she has chaired the Chemistry Board of Studies at the Feinberg Graduate School, and was Head of the Department of Chemical Physics. She has served as the Institute's Chair of the Council of Professors, and in 2014 became the President's Advisor for Advancing Women in Science.

Prof. Goldfarb's research interests are methodological developments of electron paramagnetic resonance (EPR) spectroscopy and dynamic nuclear polarization (DNP) and the application of advanced EPR spectroscopy to biophysics and porous materials.

Prof. Goldfarb has served as president of the European Federation of EPR Groups and currently is the president of the International Magnetic Resonance Society. She has been the chair of the editorial board of Physical Chemistry Chemical Physics since 2012-2014. Among her awards are the Silver Medal in Chemistry by the International EPR Society, the Bruker BioSpin Lectureship by the Royal Society of Chemistry, the Zavoisky Award from the Zavoisky



Physical Technical Institute of the Russian Academy of Sciences, and the Kolthoff Prize from the Technion-Israel Institute of Technology. Finally, she is a fellow of the International Society of Magnetic Resonance and of the Royal Society of Chemistry. Prof. Goldfarb is married and has two daughters.







The Israeli U produce 50% Chemistry PhD graduates – So where is the leak in the pipeline?





Why we want a better gender balance?

Maximize use of human resources – pure economic argument Equality leads to a better society Diversity leads to a better workplace.

What can we do about it?

Awareness – look at the numbers and realize that there is a problem. **Think about it. Talk about it. Care about it.** Be aware of **unconscious gender bias** and its effects on recruitment and evaluation. Get the right training to minimize it. Encourage and empower excellent female PhD students. Any other ideas are welcome.

The 7th National Graduate Student Symposium in Organic Chemistry

Haim Katz, Elena Ragozin, and Flavio Grynszpan* Department of Chemical Sciences, Ariel University, Ariel 40700, Israel. *E-mail: flaviog@ariel.ac.il

The 7th National Graduate Student Symposium in Organic Chemistry took place on December 17th 2015. This symposium is organized every year by a different research university. This year, Ariel University had the honor to host this event, closing the first cycle. About 90 participants from both industry and academia from all over the country gathered at Ariel University for an exciting day of high-quality lectures, poster



Figure 1: The organizing committee of the symposium: From left: Elena Ragozin, Haim Katz and Flavio Grynszpan celebrate Prof. Haim Cohen's 70th birthday during the opening ceremony.

presentations, and intense informal scientific discussions. The commercial exhibits of our generous sponsors were an integral part of the program and represented a unique opportunity for companies to display and promote their products to numerous young scientists involved in different aspects of organic chemistry.

The relatively new tradition of National Graduate Student Symposia started in 2008 at the Technion as an initiative of the Israel Chemical Society. This event, under the umbrella of the Graduate Student Division, brings together graduate students, postdocs, faculty members and representatives from industry, involved in different areas of organic chemistry, and provides a fantastic opportunity for young scientists to present their work to their peers in a very professional framework. The success of this series is highlighted by the large number and diversity of participants, and from the presentations reflecting



Figure 2: Snapshot of the audience.

a variety of related disciplines, including synthetic organic chemistry, organometallic chemistry, bioorganic chemistry, computational chemistry, pharmacology, life sciences and medicinal chemistry, among others.

This year, the meeting was organized by Mr. Haim Katz, Ms. Elena Ragozin and Dr. Flavio Grynszpan from Ariel University. As each year, the main highlights of the program included a world-class keynote speaker, three sessions packed with scientific lectures and a poster session. Cash prizes were



Figure 3: From left: Flavio Grynszpan and Michael Montag awarding the best oral presentation prize to Ms. Neta Elool Dov.

awarded for the best oral and best poster presentations.

In addition, this year we also had a special round table led by Prof. Reshef Tenne dealing with the topic: "How to plan your postdoc position." A panel featuring members of academia and industry addressed the question: Is my PhD a real advantage? We also had a "resume and interviewing" booth set up by the well-known high tech and biotech recruiting firm, Nisha Group, which offered improvement tips to participants! During the opening ceremony we celebrated the 70th birthday of Prof. Haim Cohen (Fig. 1) whom we would like to thank for his help in organizing this event.

The scientific program included an outstanding keynote speaker followed by seven short lectures, divided into two morning sessions, and one afternoon session, a round table with Prof. Reshef Tenne and a panel discussing the advantages of a PhD degree. Pizza made *in situ* and refreshments were served.

Keynote Presentation

Prof. Itamar Willner (HUJI) opened the scientific program with his inspiring lecture entitled, "DNA Nanotechnology: From basic science to applications." He began by describing how the base sequence of nucleic acids encodes structural information and how the information in the biopolymer can be adapted and implemented to develop DNA machineries for amplified sensing, for switchable control of fluorescence properties on plasmon surfaces, and for development of stimuli cages and shape-memory hydrogels with great potential for controlled drug delivery. In a detailed and impressive tourde-force, Prof. Willner described his work on DNA machines (molecular tweezers, walkers and rotors) operating in solution and on surfaces. He also presented interlocked DNA catenanes and rotaxanes developed by his group and their use for the programmed, switchable, dynamic reconfiguration of gold nanoparticles as well as the generation of DNA-based shape-memory hydrogels. The topics of Prof. Willner's stimulating and thought-provoking talk resonated in informal conversations among participants throughout the day.

Morning session

The first talk of the morning was delivered by Mr Ori Shalev. Ori is a graduate student in the lab of Prof. S. Biali at the Hebrew University of Jerusalem. His presentation entitled, "Incorporation of three or two double bonds at the methylene bridges of the calix[4]arene Scaffold" set a very high standard for the rest of the young speakers. Ori discussed, in a very clear and interesting way, chemical modifications of calix[n] arenes that are difficult to perform, and their conformational analysis. Calix[4]arenes are macrocyclic molecules that can adopt four different conformations. In the cone conformation, the inner cavity and functional groups of the calixarenes make them potential molecular hosts likely to form complexes with ions or small molecules. A structural modification of interest involves the incorporation of exocyclic double bonds to the bridges of the calix[n]arenes. Such systems, possessing several double bonds "radiating" from the center of the macrocycle, can be viewed as the calixarenes analogues of the [n]radialenes. In his talk, Ori reported the preparation and structural characterization of calix[4]arene derivatives with two distal or three exocyclic double bonds.

After a short coffee break, the morning session continued with a gripping lecture delivered by Ms Yael Nissinkorn. Yael, from the Margulies Lab at WIS, talked about "A new class of fluorescent probes that can track protein structural changes and binding interactions." Fluorescent probes to detect and follow protein activity are known but are not very effective when targeting protein surfaces outside the binding site. Yael



Figure 4: Exhibition of equipment and scientific instrumentation.

described the difficulties involved in selectively recognizing protein surfaces and showed us how to evade that problem by an environmentally sensitive receptor coupled to a Histag. Using their ingenious technique, Yael and her co-workers were able to track various protein-surface modifications and binding interactions.

Ms Michal Roth works at Tel Aviv University in Prof. D. Shabat's lab. In her presentation, Michal described the use of self-immolative dendrimers to generate hydrogels with interesting and diverse physical properties. These hydrogels display a special ability, which is the spontaneous degradation upon exposure to a specific stimulus. Practical applications of this system, such as triggered drug delivery, make these hydrogels a very exciting development in the field.

The last talk of the morning session was delivered by Mr Regev Parnes from the Pappo Lab at Ben-Gurion University.

Regev's impressive lecture on "Multi-component reactions based on thionium-ion chemistry" centered on the idea of generating thionium-ions in situ while avoiding the need for harsh acid catalyzed conditions and stoichiometric amounts of the activator. Regev described, with mechanistic detail, how Pummere/aldol or Pummere/Friedel-Crafts reactions can be efficiently performed in a region-, chemo- and stereo-selective fashion using a smart and swift transformation involving the generation of the key thionioum-ion in situ.

Round Table with Prof. Reshef Tenne

Prof. Reshef Tenne (WI) shared with us some important thoughts about the strategy involved while planning for a postdoc position. Prof. Tenne started by emphasizing the great importance of writing a research proposal, and suggested that every PhD candidate should give it a shot during the last months of his/her program. The skills required to write a scientific proposal are particularly important if the candidate is considering an academic position after the postdoc period.

Prof. Tenne indicated that the proposal, as the postdoc period itself, must excel in two fundamental areas. First, the proposal has to deal with an advanced scientific field, one where other Israeli researchers are scarce and where the candidate can make a unique and significant contribution. Second, the area of scientific investigation during the postdoc period should be different from the doctoral thesis topic in order to demonstrate the creativity and flexibility required for a career as a PI. In addition, Prof. Tenne mentioned the advantages of doing a postdoc in Europe. These advantages include scientific networking in the EU that may become instrumental in promoting future collaborations and improving the chances of success in winning European research grants, such as those of the European Research Council (ERC), German-Israel Foundation (GIF), etc.

Afternoon session

The afternoon session started with an excellent synthetic lecture given by Dr Fa-Guang Zhang. Dr Zhang, who works with Prof. Ilan Marek at the Technion, spoke about the "Brook rearrangement as a trigger for ring-opening of strained carbocycles" as a strategy to build valuable molecules from relatively simple starting materials. Fa-Guang presented a one-pot method for preparing a large variety of linear amides, all of them including a quaternary carbon stereo center, in good yields from simple cyclopropenyl starting materials. He described in detail his synthetic approach including the tandem diastereoselective carbometallation of a given cyclopropane followed by nucleophilic addition to acylsilane, Brook rearrangement and finally selective ring opening to the desired linear amide.

The second lecture of this session was delivered by Ms Neta Elool Dov from the van der Boom Lab at the Weizmann Institute.

Neta gave a fantastic lecture dealing with "Stimuli responsive metallo-organics for the formation of electrochromic devices." Neta introduced molecular assemblies built from metal polypyridyl complexes cross-linked with PdCl₂. These polypyridyl complexes are considered ideal chromophores for fabricating electrochromic materials due to their excellent stability and light absorption that significantly depends on their oxidation state. Neta used a spin-coating process to generate molecular assemblies based on these complexes. The polymer coatings exhibit high coloration efficiencies and are extremely stable; they are thermally robust and present exceptionally high (spectro)electrochemical performances. A first generation solid-state set-up was demonstrated showing great potential for interesting applications in molecular electronics, sensor, solar cells and data storage among others.

The last talk was delivered by Ms Lena Mostinski from the Tsvelikhovsky Lab at the School of Pharmacy of the Hebrew University of Jerusalem. Lena is particularly interested in the synthesis of tricyclic angularly fused ring molecular patterns which are shared by a wide variety of bioactive molecules of natural origin. Her work is focused on the development of a general synthetic strategy for the construction of the angularly fused tricyclic skeleton common to the Teucrolivin, the Arteannuin and the Alliacane families of natural products. Lena described a new successful approach to the synthesis of compounds that closely resemble the natural tricyclic scaffold and could potentially become valuable drugs/therapeutic agents. The novel synthetic compounds were submitted to various biological activity assays and have already shown promising bioactivity.

Panel with members of industry and academia

The last afternoon session hosted a panel with experts representing various aspects of the industry and business sector and concentrated on employment opportunities for young chemists holding a PhD degree. The panel was headed by Prof. Haim Cohen from Ariel University and included Dr Itsik Bar Nahum from Adama, Dr Lena Lerman from Teva, Ms Odelia Segev from Nisha and Dr Eric Messika from Coronis Partners. Each member of the panel described different aspects of employment opportunities for young scientists, in general, and doctors in chemistry, in particular. From the recruiting company's point of view, there is a steadily growing demand for PhD chemists in the central and southern regions of Israel. Ms Segev also mentioned that in some cases the research experience of the PhD candidate can be considered as actual years of working experience, especially for the first industrial job. Both representatives of the large industrial companies -

Teva and Adama – said that they prefer to build heterogeneous working teams, including engineers, second and third degree, and chemists after postdoc. A PhD graduate always starts at a higher salary level and typically advances to higher positions with increased responsibilities in the company. Dr Messika from Coronis Partners pointed out that from the "business" point of view, doing an MBA in addition to the PhD can open up interesting opportunities away from the bench and lead to a higher income level corresponding to key managerial positions, when compared with purely scientific professionals.

Awards

The award for the best oral presentation was presented this year to Neta Elool Dov from the Weizmann Institute. Neta is a student in the group of Prof. M. van der Boom. She works on the development of stimuli responsive metallo-organics for the formation of electrochromic devices.

Finally, 20 excellent posters were displayed and the prize for the best poster presentation was awarded to Ms. Hila Sameach for her work entitled, "Structural and dynamics characterization of the Cu(I) E.coli metal sensor CueR in the DNA bound state". Hila is a student working in the lab of Dr Sharon Ruthstein in the Department of Chemistry at Bar-Ilan University.

Links to the abstracts of all oral and poster presentations, as well as to the photo-gallery of this symposium, can be found at http://www.ariel.ac.il/sites/organic-chemistry-symposium.

The next 8th symposium is planned for the last quarter of 2016 and will presumably be held at the Technion, Haifa, starting a new cycle of successful meetings.

Needless to say, we owe special thanks to all our sponsors: Ariel University, Teva, Labotal, Scifinder – Arad Ofir, BioAnalytics, Nisha, Yair Technologies and Tzamal D-Chem, for their financial support. We could not have done it without their help!

Acknowledgments

We wish to thank Prof. Haim Cohen and Prof. Gary Gellerman from Ariel University for their assistance and strategic discussions during the organization of the symposium. We thank Ms Efrat Antman for her invaluable technical assistance. We also wish to thank Ms Olga Chovnik, Ms Barbara Kazanski and Dr Palaiappan Subramanian for chairing the scientific sessions and to Dr. Subramanian for his assistance in summarizing a presentation.

The 81st Annual Meeting of the Israel Chemical Society and Exhibition¹

February 9-10, 2016, David Intercontinental Hotel, Tel-Aviv, Israel

Ehud Keinan

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The Annual Meetings of the ICS have become a permanent part of the scientific landscape of the Israeli scientific community. These colorful events usually take place in early February, which is the inter-semester break of all Israeli universities at the end of the short rainy season in Israel. The responsibility for the meetings has been revolving in a 6-year cycle among the chemistry departments of the 6 major research universities in a constant order: Tel Aviv University (TAU), Bar-Ilan University (BIU), Ben-Gurion University of the Negev (BGU), the Weizmann Institute of Science (WIS), the Hebrew University of Jerusalem (HUJ), and the Technion - Israel Institute of Technology. Thus, looking back at the ICS history of the past 2 decades, the School of Chemistry at Tel Aviv University has taken responsibility for organizing the 63rd Meeting (1998), the 69th Meeting (2004), the 75th Meeting (2010), and now the 81st Meeting (2016).

Another unique tradition of the ICS, which had already attracted much worldwide attention and interest, has been the hosting of high profile delegations of scientists from top academic institutions worldwide who present plenary and invited lectures. This initiative has created outstanding opportunities for many Israeli scientists, and particularly for graduate students, to interact with top-tier chemists, thus enhancing prospects for networking and scientific collaboration. Each visit of these delegations has resulted in many mutual visits of students and faculty members, postdoctoral and sabbatical programs, joint research proposals and other fruitful international activities. The ICS had already hosted delegations of distinguished scientists from The Scripps Research Institute (1997), California Institute of Technology (1998), University of Cambridge, UK (1999), ETH-Zurich (2000), Columbia University (2001), University of California at Santa Barbara (2006), the Max Planck Society (2009), the Chemical Society of Japan and the Japan Society for the Promotion of Science (2010), Academia Sinica (2011), the University of California at Berkeley (2012), the University of Oxford (2014) and Stanford University (2015). This year we had the pleasure of hosting a delegation of 9 outstanding scientists from major universities of the State of Texas (Figure 1).

The Organizing Committee included Micha Fridman and Amir Goldbourt as Chairmen, Roey J. Amir, Roman Dobrovetsky, Yuval Ebenstein, Sharly Fleischer, Omry Morag and Yael Roichman, all of the School of Chemistry, Raymond & Beverley Sackler Faculty of Exact Sciences at Tel Aviv University. The actual operation, including all technical aspects, administration, organization of the exhibition, promotion, etc. was carried out by an experienced team of



Figure 1. A traditional ICS autographed poster, displaying members of the delegation from Texas (top two lines) and laureates of the major ICS prizes.



Figure 2. Collage of random photos that reflect the general atmosphere of the 81st ICS Meeting.

Diesenhaus-Unitours Incoming Tourism Ltd. Conventions Department, mainly by Anat Reshef, Tsipi Laxer and Magali Mizrahi.

Nearly 800 participants enjoyed a broad range of over 100 lectures on diverse subjects, including more than 20 plenary and keynote lectures, over 210 posters, special symposia and discussion groups, as well as a large commercial exhibition by 20 providers of lab equipment, scientific instrumentation, chemicals, materials, services of analytical chemistry and diagnostics, publishing houses and management of intellectual property. The companies represented in the exhibition included Arad – Ophir Ltd., Medent Ltd Scientific Equipment, Bargal Analytical Instruments Ltd., Mercury Scientific & Industrial Products Ltd., BioAnalytics Ltd., Meshulam Avni & Son Ltd., Bruker Scientific Israel Ltd., Pearl Cohen Zedek Latzer Baratz, Dr. Golik Scientific Solutions, S.L. Moran Ltd., Eldan Electronics Instruments Co. Ltd., Sigma-Aldrich Israel Ltd., Gas Technologies O.B. Ltd., Silicol Scientific Equipment Ltd.,

Holland-Moran Ltd., Tzamal D-Chem Laboratories Ltd., Iner-Tech Ltd., Waters (TC) Israel Ltd.

As in previous years, the conference center of the David Intercontinental Hotel offered convenient space for the parallel sessions, exhibition and poster sessions, along with excellent food services. The hotel location at the Mediterranean beaches at the southern part of Tel Aviv offered pleasant strolls along the coastal promenade to the scenic harbor of ancient Jaffa, to outdoor cafés and art galleries, the famous flea market and the adjoining historic neighborhoods of early Tel Aviv, such as the trendy Neve Tzedek district. The Tel Aviv weather in this period of early February was typically dry, sunny and pleasant, not too cold for outdoor activities. Indeed, this attractive setup provided good reasons for several participants and guests to extend their stay by a few more days to explore the country.

The various presentations, colorful poster sessions, exhibition and other activities created a vivid atmosphere with vibrant discussions, exchange of information and social gathering, all reflected by the collage of photographs (Figure 2).

Welcoming reception

The welcoming reception dinner took place in the authentic Yemenite restaurant Maganda, located in one of the oldest neighborhoods of Tel Aviv. In addition to all the members of the Texas delegation, members of the ICS Executive Board and the Organizing Committee attended the event. Following his welcoming greetings, Keinan explained to the group the background of the Maganda restaurant. In 1927 the family of Zadok Habura immigrated from Yemen and built their home on a piece of land they purchased at 26 Rabbi Meir Street in the neighborhood of "Kerem Hatemanim" (The Yemenite vineyard) district in Tel Aviv. The authentic Yemenite menu was based on the original home cooking. The youngest son in the family resembled a key character named "Maganda" of a popular African movie. Thus, he was nicknamed Maganda, and that name was adopted also for the family operated restaurant the brothers opened in 1965.

Opening Ceremony

On Tuesday morning, February 9th, Dr. Micha Fridman and Prof. Amir Goldbourt, Chairmen of the Organizing Committee, opened the 81st Annual Meeting by greeting the large audience and the distinguished guests, the participants, sponsors and exhibitors, as well as the organizing company, for making this meeting possible. They explained that the meeting brings together over 800 participants from academia, industry and education to discuss all aspects of chemistry. The twoday meeting was planned to include five plenary talks, four parallel sessions with 75 speakers, and a special session on Chemistry Education. The Meeting also features 'flash talks' delivered by graduate students and post-doctoral fellows to promote and highlight a selected number of excellent poster presentations out of more than 200 posters. They explained that they made great efforts to bring together Israeli scientists, practitioners, students, industrial leaders and teachers, as well as representatives from several other countries. Finally, they acknowledged the significant help of all members of the Organizing Committee, the ICS Project Manager, Ms. Liraz Maanit and the ICS President.

Prof. Ehud Keinan, President of the ICS, welcomed all ICS members and the distinguished guests from Texas and the ACS, mentioning the sequence of events that made it possible, particularly the vision of Prof. Jonathan Sessler, who has initiated and supported the idea of organizing a delegation from several universities in Texas.

Keinan mentioned some of the most prominent achievements of the ICS during the past year, starting with its two successful journals. The Israel Chemist & Engineer (ICE), which is the new form of the known ICS Bulletin, has appeared in a new format, unifying the three major organizations of chemists and chemical engineers in Israel. Under the leadership of Prof. Arlene Gordon as Editor-in-Chief, the first published issue has already attracted much attention worldwide. Relating to the ICS official journal, Israel Journal of Chemistry (IJC), he pointed out that the achievements of this journal can be appreciated by many of the Texan guests because several of them hold major editorial responsibilities with the ACS journals. It is well known that the usage is rapidly becoming a more reliable criterion to represent the journal popularity than the impact factor. The usage of IJC has increased heavily over the past two years, at a rate much higher than typical for chemistry journals. It is noteworthy that this journal was essentially unknown before it was transferred to the Wiley-VCH publishing house.

Referring to the ICS events of last year, he mentioned the 80th Annual Meeting of the ICS, which was held in the same venue, David Intercontinental Hotel, in February 17-18, 2015 with a prestigious delegation from Stanford University, including Nobel Prize Laureates Michael Levitt and W. E. Moerner. Another successful event was the 6th EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry, which was held in the Weizmann Institute in November 15-18, 2015. It was a joint event with the 13th Annual Meeting of the Medicinal Chemistry Section of the ICS. The European Federation for Medicinal Chemistry (EFMC) and ChemBridge Corporation have been organizing this series of the International Symposia on Advances in Synthetic and Medicinal Chemistry since 2004. The first symposium was held in Moscow, followed by St. Petersburg in 2007 and 2011, Kiev in 2009 and again Moscow in 2013. During the meeting Prof. Paul A. Wender of Stanford University received the 2015 MCS-ICS Award for Excellence in Medicinal Chemistry in Memory of Barry Cohen.

The 7th National Graduate Student Symposium in Organic Chemistry took place on December 17th 2015 in Ariel University (see report in this issue). The series of national graduate student annual symposia has already become a tradition that was initiated in 2008 at the Technion. This annual gathering has led to the establishment of the Graduate Student Division (GSD) of the ICS. Graduate students Haim Katz and Elena Ragozin, assisted by Dr. Flavio Grynszpan, all of Ariel University, organized the meeting. The program included a keynote lecture by Prof. Itamar Willner of the Hebrew University, six lectures by graduate students, a poster session and a commercial exhibition. The 8th GSD symposium is planned for the end of 2016 at the Technion. Thus the GSD is now well established with good representation of all universities.

The coming year will also be full of exciting events. The 82nd Annual Meeting of the ICS will be held In February 2017. It will be organized under the responsibility of Bar Ilan University with Prof. Bilha Fischer as Chairperson. The event will be jointly organized by four entities: The Israel Chemical Society, The Gesellschaft Deutscher Chemiker (German Chemical Society, GDCh), Angewandte Chemie and the Israel Journal of Chemistry. The cluster of events will include the 6th Angewandte Symposium. In addition, we'll have several specific meetings, including the Wolf Prize Meeting, which will be held in the Technion in June 1st 2016. This special symposium will honor the two Laureates of the 2016 Wolf Prize in Chemistry, K. C. Nicolaou of Rice University and Stuart Schreiber of Harvard University. The 2016 MCS-ICS meeting will be held as usual by the end of the year. As in previous years, the ICS will send two teams of runners to the Mountain-to-Valley relay race (M2V), which will take place from May 19-20, 2016.

Referring to the ICS membership fees, Keinan announced the unprecedented decision made recently by the Managing Board: those who will join the ICS in February and March this year will enjoy free membership for three years. This decision reflects the idea that we consider the number of members more important than the membership fees and that the ICS should rely on the more significant income from corporate membership rather than from individual fees. The relations with all international organization of chemistry, including the



Figure 3. Honorable ICS Membership is award to members of the Texan delegation and to Prof. Donna Nelson of the ACS. Top row from left: Anslyn, Gabbai, Gladysz. Second row: Liu, Miljanic, Romo. Third row: Rossky, Yakobson, Sessler. Third row: Nelson, Chairmen Micha Fridman and Amir Goldbourt. Bottom from left: Romo, Gladysz, Gabbai, Liu, Anslyn, Nelson, Yakobson, Miljanic, Sessler, Rossky, Bradley Miller of the ACS, Keinan.



Figure 4. Guest speakers. First row from left: Boris I. Yakobson, Jonathan Sessler, Hung-Wen (Ben) Liu, John A. Gladysz. Second row from left: Peter Rossky, François P. Gabbaï, Daniel Romo, Ognjen S. Miljanic. Second row from left: Eric V. Anslyn, Donna Nelson, Chuck Ashley of the U.S. Embassy.

EuCheMs, FACS, IUPAC, ACS and other Chemical Societies, have intensified and strengthened. Keinan mentioned that although he has completed his term as a Board Member of EuCheMs, he was elected as a Member of the IUPAC Bureau for the next 3 years.

Finally, he thanked the many people who joined forces in making this event possible, including the Chairpersons Micha Fridman and Amir Goldbourt, the organizing committee from Tel Aviv University. Anat Reshef, Tsipi Laxer and Magali Mizrahi of Diesenhaus-Unitours Ltd., and the ICS Project Manager, Ms. Liraz Maanit.

At the end of his welcoming address, Keinan presented the Honorable ICS Membership award (Figure 3) to all 9 members of the Texan delegation and to Prof. Donna Nelson, President of the American Chemical Society. In a way, Prof. Nelson is also associated with Texas because she received her PhD degree in chemistry from the University of Texas at Austin under Michael J. S. Dewar. It has become a remarkable tradition that the ICS has been hosting the Presidents of the ACS at many of its annual Meetings.

Mr. Chuck Ashley, the Environment, Science & Technology, and Health Affairs Officer at the U.S. Embassy in Tel Aviv, greeted the organizers, ICS Members and the delegation of Scientists from Texas, and conveyed the warm greetings from Ambassador Daniel Shapiro.

"I want to begin by giving chemists the recognition and appreciation they deserve, as chemists have advanced scientific knowledge and developed so many products that we now take for granted. Pharmaceuticals, fertilizers, and fuels; soaps and shampoos; paints and plastics, and the list seems endless.

Today we face many challenges that require both a sound base of scientific evidence and a coordinated international response. Climate change, pollution, water scarcity, and communicable diseases are just a few examples. And chemists can make valuable contributions in addressing each of these. Science does more than support decision-making. It produces bonds; not only bonds between atoms and molecules, but also bonds between people, institutions, and nations. Simply put, science is a vital ingredient for good government and public policy.

That's why the United States has integrated science into formulation and implementation of foreign policy too. That's also why the USA Secretary of State has his own Science & Technology Advisor. Furthermore, through partnerships with the American Association for the Advancement of Science and the National Academies of Science, the State Department recruits scientists who better equip us to manage issues at the intersection of science and foreign policy. The State Department also shares US scientific expertise with other nations for mutual benefit. The USA Science Envoys and Science Fellows programs send USA scientists to other countries to promote the value of science-based decision-making, build enduring relationships, and cooperate on policy development.

Obviously, the USA is not the source of all knowledge, and the American people wishes to learn much from others. The Fulbright program, for example, involves a two-way exchange of knowledge that increases mutual understanding between peoples and nations. The Middle East Regional Cooperation (MERC) program supports collaborative research projects between scientists in Israel and Arab countries. MERC fosters relationships, builds trust, and produces science that benefits Israelis and Arabs alike.

In Israel, the USA offers three binational foundations that facilitate cooperative research and development between the USA and Israeli scientists and private companies. The Binational Science Foundation (BSF) supports cooperation on basic science. The Binational Agricultural Research & Development (BARD) foundation promotes scientific cooperation in agricultural-related fields. The Binational Industrial Research & Development (BIRD) foundation advances industrial research and development cooperation in the private sector.

Science brought us together today, and science is bringing both nations together too. And science has never been more vital to the conduct of foreign affairs as it is in our times. I wish all participants a fruitful conference and hope that it planted the seeds for new collaborations and closer relations between Americans and Israelis."

Prof. Donna Nelson, ACS President, greeted the audience in the name of 160,000 ACS members. She explained that whether our practice of chemistry in is in the classroom, lab, or the media, building relationships, building bridges, and building trust must be a central product of our work. "We as chemists, chemical engineers, and chemistry educators can do this, because we speak a common language through a shared understanding of the details of science at a molecular level.

The quality and value of our combined efforts originate in our peer review. Irrespective of borders and language, we operate together within the scientific culture to quality assure research outcome validity and reliability. As the next few days of our convening and networking ensue, it was my hope that we have occasion to give some thought to how we might build community around our shared language of science and our shared culture of peer review. The process can build a safer, more peaceful, and more secure future for us all.

Over the last fifty years, our profession of chemistry has borne witness to remarkable changes in the form and content of its practice. With growth in global political, economic, and technological interdependency, the transfer of chemical knowledge and professionals across borders has accelerated and become more prevalent – and our concomitant responsibilities as chemists, chemical engineers, and chemistry educators – to use our technical expertise and practical knowledge for a safer and more secure global future.

Scientific cooperation through professional society interactions and exchange activities provides an opportunity to move forward with science-based multilateral diplomatic efforts – many of which can favorably impact economic growth, quality of life, and the health and security of the Earth. We must better understand and optimize how chemical practitioners experience and use their expertise and knowhow in transnational contexts, especially where science can help provide a means to sustained diplomatic dialog and the resolution of conflict.

Five questions related to chemists working transnationally warrant further consideration and inquiry. (a) What is the current nature of the chemist's experience in a globalized practice? (b) How can that be optimized for diplomacy, conflict resolution, and creating safer and more secure futures? (c) What are the role and potential impacts of the professional society in fostering this activity? (d) Which agencies, authorities and civil society organizations should professional societies engage in order to carry out this activity? (e) How do we best measure and communicate success among the scientific and diplomatic communities?

The conduct, communication, and use of chemistry are intrinsically global, and we as chemists are increasingly important in addressing many critical global issues, where our science offers a diplomatic opportunity to resolving conflict, and creating safer and more secure futures for humankind."

To demonstrate the latter points she referred to her recent experience in Paris and Morocco. She was scheduled to visit Paris just one week after the deadly terrorist attacks of November 13. Her plan was to stop on the way back from Morocco to see members of the French chemistry community. In Morocco she attended the conference Malta VII, Frontiers of Science: Research & Education in the Middle East, a Bridge to Peace. This biennial gathering, which was organized by the Malta Conferences Foundation President Dr. Zafra Lerman, convened scientists from 15 countries representing the Middle East and Morocco and for many provided their only opportunity to exchange scientific ideas, build collaborations and international partnerships, and discuss common problems in the region.

The conference mood and discussions, juxtaposed with the news from Paris, confused expectations. Paris is typically associated with thoughts of romance rather than conflict, and the violence it witnessed contrasted with the conference's goals of peace. France's admirable and deliberate openness and fundamental commitment to "liberté, égalité, fraternité" can also bring vulnerability. It raised a question whether terrorism would impact science and can science impact terrorism? This was answered in an article by Alain Fuchs, president of the French National Center for Scientific Research (CNRS): "Following the attacks perpetrated in Paris last week, the CNRS makes a strong appeal for new multidisciplinary research projects capable of exploring all the potential issues and challenges that surround these tragic events, paving the way for durable solutions. Research and politics are distinct. But this is a rare opportunity for researchers to express a form of solidarity with all those who, directly or indirectly, have been affected by the terrible events which, as we all know, can happen again."

Prof. Nelson summarized that "Obviously science diplomacy has a role in making the world more secure. One example of best practice combines professional activities with student education. For instance, as the use of dangerous chemicals became more routine, not only did chemists practice greater safety, but also chemical safety was increasingly introduced to students via basic university training. Following this precedent, chemical security and science diplomacy should be similarly enhanced at both levels: Not only should we increase awareness of these in the chemical community, but also we should introduce them to students at an early stage. Promoting codes of conduct and of ethics among scientists and students will lead by example and build trust among scientists. Life – and science – must go on."

Prof. Jonathan Sessler, head of the Texas delegation, greeted the audience on this wonderful celebration of chemistry. He mentioned that chemistry is taken very seriously in the State of Texas and its universities. He remembered that the idea of having a Texas delegation was born in Shanghai during the 4th International Conference on Molecular Sensors and Molecular Logic Gates (MSMLG2014), which was held in East China University of Science and Technology in November 9-12, 2014. On the first evening of that conference Jonathan Sessler and Eric Anslyn shared a bottle of whisky with Doron Shabat of Tel Aviv University, Milko van der Boom and David Margulies, both of the Weizmann Institute. The original idea was to assemble a delegation exclusively from the University of Texas at Austin. Nevertheless, a month later, while spending the month of December 2014 as a visiting professor in the Technion, Sessler had a chance to discuss the idea with Keinan and they decided to expand the delegation to include all major Texas universities. He used this anecdote to support the notion that internationalization and cooperation is ultimately a human enterprise. Sessler himself remembers vividly many visits to the State of Israel in which he met many old friends and always made new friends. Long ago, very early in his career, he spent a whole year in the Hebrew University of Jerusalem (HUJ) and even had a chance to pick up the Hebrew language at a reasonable level. He studied "Shana Bet" chemistry and was fortunate to have Dani Gibson among his many talented classmates and to enjoy a few exciting ski adventures together on Mt. Hermon. Their TA was Avi Bino and Jonathan traces his love of inorganic chemistry back to those days. He closed his remarks by noting that Israel was a country that foreigners either never visited or visited many times. He expressed his wish, hope, and expectation that all members of the Texas Delegation would soon be regular visitors to Israel and frequent participants at the ICS meetings.

Plenary Lectures

Considering the constraints of a two-day program the organizing committee selected the many presentations of the distinguished presentations as either plenary or keynote lecturers based on considerations of topics and balance of research fields (Figure 4).

Boris I. Yakobson of Rice University delivered the first plenary lecture on "Theory of nanostructure synthesis examples of recent advances: nanotubes, graphene, and 2D boron." He mentioned that a recent C&EN cover article offers a retrospect of nanotube research within a framework of Gartner's hype peak, tacitly inviting the readers to gauge the peak phases for graphene or 2D materials "beyond graphene". In such a large timeframe, one ponders why the progress in theory of nanotube synthesis has been so slow, with the origin of helical symmetries, pointed to in 1991 by Iijima, having taken two decades to yield a formula $R \sim \sin x$ (growth rate R, helical angle x). Analysis of the interplay between the kinetics and thermodynamics nucleation and growth on solid catalysts reveals sharply peaked abundance distribution A \sim $x \exp(-x)$, and explains the puzzling (n, n-1) types observed in many laboratory syntheses. Building on this approach in case of graphene, a similar combined analysis of the nucleation and growth (implemented with the DFT and Monte Carlo models) explains the low symmetry shapes of islands growing on certain substrates. He also discussed a non-carbon example of emergent interest, the 2D pure boron, where theoretical analyses of nucleation and growth-type selection (on metal substrates) predict specific structures, which now seem to appear in experiments.

Hung-Wen (Ben) Liu of the University of Texas at Austin delivered the second plenary lecture on "Mechanistic studies of an unusual C-O bond formation in fosfomycin biosynthesis". He explained that the O2-activating, non-heme iron enzymes catalyze a wide range of oxidation reactions with important biological implications, such as DNA repair, hypoxic response, collagen biosynthesis, and histone demethylation. Most of these enzymes possess a single iron center coordinated by two His and one Asp/Glu residues in a tridentate binding motif referred to as the '2-His-1-carboxylate facial triad'. Understanding the mechanism of O2-activation by these enzymes may provide key insights into the source of their diverse substrate specificities despite similarly coordinated active site metal centers. HppE is a unique member of this class of enzymes and functions as an iron-dependent epoxidase to convert (S)-2-hydroxypropyl-1-phosphonate (S-HPP) to the antibiotic fosfomycin. The reaction catalyzed by HppE is unusual, because it involves the 1,3-dehydrogenation of a secondary alcohol to an epoxide. Several mechanisms have been proposed for HppE catalysis,

and these are differentiated primarily in terms of the identity of the O_2 -activated iron complex that abstracts a hydrogen atom from C1 of S-HPP to initiate epoxide ring closure. The recent results from his group have shown that the preferred cosubstrate is H_2O_2 and that HppE uses an iron (IV)-oxo complex as the hydrogen atom abstractor. He presented these results along with recent studies using radical probes to gain insight into the mechanism of this enzyme.

Emanuel Peled of Tel Aviv University, winner of the 2015 ICS Prize of Excellence, delivered the third plenary lecture on "Study of high performance silicon based anodes for electric vehicles (EVs) batteries." He explained that in order to increase the energy density of the lithium battery, better anodes and cathodes are still required. Silicon has attracted much attention because its theoretical capacity is 4200 mAhg⁻¹, an order of magnitude greater than that of graphite. Nevertheless, the main disadvantage of high-capacity anode materials is their very large volume expansion and contraction (~320 %) during Li insertion/de-insertion, followed by cracking and pulverization of the anode material. Si nanostructures have the advantage of a shorter diffusion distance for lithium species, which can improve the power performance of the battery. Study of large surface capacity anodes (high Si loading) is almost nonexistent. He showed that, in addition to the synthesis and characterization of novel three-dimensional high-capacity SiNWs and SiNPs-based anodes, his group focused on studying their degradation mechanisms. They have been able to produce remarkably high loadings of 3-15 mAh/cm², very low irreversible capacity (of the order of only 10 % for the 3-4 mAh/cm² samples), current efficiency greater than 99.5 % and a fast charge-discharge rate (up to 2.7C (20 mA/cm²), which is not common for silicon anodes). These properties meet the requirements of lithium batteries for portable and electric-vehicle applications. These SiNWs-based binder free anodes and the SiNPs anodes have been cycled for 200-300 cycles, exhibiting a stable cycle life after which, at least 70-80 % are still connected to the substrate. The thickness and the resistance of the solid electrolyte interphase grow with time and with cycling. The structure and composition changes of the SiNWs, the SiNPs and of the SEI was reported.

Eric V. Anslyn of the University of Texas at Austin, delivered the fourth plenary lecture on "Differential sensing – concepts and applications." He explained that the mammalian senses of taste and smell utilize a series of cross-reactive receptors, rather than highly selective receptors. His group mimics this principle with a series of synthetic and designed receptors for the analysis of complex analytes in real-life settings. The receptors derive from a combination of rational chemical design and modeling, with combinatorial synthesis techniques. Optical signaling often derives either from indicator-displacement assays, or direct modulation of the spectroscopy of the receptor. He showed that a union of designed receptors targeted to a class of analytes, with combinatorial methods, gives fingerprints that differentiate between the individual members of the analyte class. The strategy is to use a core-binding element that imparts a bias to each and every member of the library, ensuring affinity of the library members for the class of analytes being targeted. The design of this core derives from standard molecular recognition principles: preorganization, complementary, pair-wise interactions between receptor and analyte, and desolvation. Imparting a bias to the affinity of the library members dramatically reduces the diversity space needed in the library. The fingerprints of the solutions are created using artificial neural networks, principle component analysis, and/or discriminate analysis. The technique represents a marriage of supramolecular chemistry and pattern recognition protocols, and has become known as differential sensing. A variety of examples were presented, ranging from applications in the biological sciences to commercial beverage analysis.

Yoram Cohen of Tel Aviv University, winner of the 2015 ICS Prize of Excellence, delivered the fifth plenary lecture on "From supramolecular chemistry and model systems to microstructure of the central nervous system: a look from diffusion NMR and MRI." He explained that pulsed-field gradient spin-echo (PGSE) NMR technique used for measuring diffusion with NMR is more than 50 years old and diffusion MRI is widely used to study the central nervous system (CNS). He presented examples of the application of diffusion NMR in supramolecular chemistry, with special emphasis on hydrogenbonded molecular capsules, which, even more than a decade later, are the best examples to demonstrate the added value of diffusion NMR in elucidating the structure of supramolecular systems in solution. In confined space where diffusion is non-Gaussian, diffusion NMR may, in principle, be used for gleaning microstructural information. He also presented structural information and the diagnostic power of q-space diffusion MRI (QSI), followed by more recent applications of angular double PGSE NMR and MRI to obtain detailed microstructural information in model systems where the ground truth is known as well as in complex systems, neuronal tissues and animal CNS. Finally, he described the development of new anti-biofilm agents that resulted from an attempt to prepare new xenon NMR biosensors.

Keynote Lectures

Jonathan Sessler of the University of Texas at Austin, Austin, spoke about "Expanded porphyrins based on pyrrole, pyridine, thiophene and furan." He explained that expanded porphyrin is a term his group introduced into the literature in 1988 to describe larger homologues of natural and synthetic tetrapyrrolic macrocycles. These systems have seen application in areas as diverse as anion recognition and transport, self-assembly, liquid-liquid ion extraction, photodynamic therapy, and anticancer drug development. In this lecture, particular emphasis was placed on systems that support unexpected electronic configurations, including unusual [4n+1] p-electron semi-aromatic peripheries, and new compounds that may provide experimental support for the long-sought, but hitherto elusive concept of 3-dimensional aromaticity.

Assaf Friedler of the Hebrew University of Jerusalem, spoke about "New methods for peptide cyclization and acetylation." He pointed out that his group is interested in using peptides for the quantitative biophysical and structural analysis of proteinprotein interactions in health and disease. Based on this, they develop lead peptides that modulate PPI for therapeutic purposes. To improve the lead peptides, they are developing new synthetic methods for peptide modifications. He presented a new approach for peptide cyclization during solid phase synthesis under highly acidic conditions. This approach involves simultaneous in situ deprotection, cyclization and TFA cleavage of the peptide, which is achieved by forming an amide bond between a lysine side chain and a succinic acid linker at the peptide N-terminus. The reaction proceeds via a highly active succinimide intermediate, which was isolated and characterized. The new methodology is applicable for the formation of macrocycles in solid phase synthesis of peptides and organic molecules. They also developed a new general N-acetylation method for solid phase synthesis. Malonic acid is used as precursor and the reaction proceeds by in situ formation of a reactive ketene intermediate at room temperature.

Ralf Metzler of the University of Potsdam spoke about "Ergodicity violation and ageing: from granular gases to living cells." He mentioned that in 1905 Einstein formulated the laws of diffusion, and in 1908 Perrin published his Nobelprize winning studies determining Avogadro's number from diffusion measurements. With similar, more refined techniques the diffusion behavior in complex systems, such as the motion of tracer particles in living biological cells, is nowadays measured with high precision. Often the diffusion turns out to deviate from Einstein's laws. He discussed the basic mechanisms leading to anomalous diffusion and pointed out the physical consequences. In particular, the unconventional behavior of non-ergodic, ageing systems was discussed within the framework of different stochastic processes with concrete examples, including granular gases, biological cells, lipid membranes, and interacting many particle systems.

Danny Porath of the Hebrew University of Jerusalem spoke

about "The quest for charge transport in single adsorbed long DNA-based molecules." He explained that DNA and DNA-based polymers have been at the focus of molecular electronics owing to their programmable structural versatility. The variability in the measured molecules and experimental setups, caused largely by the contact problem, has produced a wide range of partial or seemingly contradictory results, highlighting the challenge to transport significant current through individual DNA-based molecules. A well-controlled experiment that would provide clear insight into the charge transport mechanism through a single long molecule deposited on a hard substrate has never been accomplished. He reported on detailed and reproducible charge transport in G4-DNA, adsorbed on a mica substrate. Using a novel benchmark process for testing molecular conductance in single polymer wires, they observed currents of tens to over 100 pA in many G4-DNA molecules over distances ranging from tens to over 100 nm, compatible with a long-range thermal hopping between multi-tetrad segments. With this report, his group answered a long-standing question about the ability of individual polymers to transport significant current over long distances when adsorbed a hard substrate, and its mechanism. These results may re-ignite the interest in DNA-based wires and devices towards a practical implementation of these wires in programmable circuits.

Rafal Klajn of the Weizmann Institute of Science, winner of the ICS Young Scientist Prize, spoke about "From dynamically self-assembling materials to chemical reactivity in confined environments." He explained that living organisms are the most prominent examples of systems self-assembled and performing useful functions under far-from-equilibrium conditions. Inspired by Nature, his group has designed new materials whose properties and functions can be "turned on" and "off" on demand, using external stimuli as inputs. Among the different external stimuli, they focus on magnetic fields and light since these can be delivered instantaneously and into a precise location. He discussed molecular switches and inorganic nanoparticles as the key building blocks of new dynamically self-assembling materials. These materials hold promise for new applications as diverse as light-controlled catalysis, or manipulating non-magnetic objects with the help of magnets.

John A. Gladysz of Texas A&M University spoke about "Werner complexes: a new class of chiral hydrogen bond donor catalysts for enantioselective organic reactions". He pointed out that salts of the chiral tris(ethylenediamine)-substituted octahedral trication $[Co(en)_3]^{3+}$, and related species, have played important historical roles in the development of inorganic chemistry and stereochemistry. As Werner described in 1912, the two enantiomers, commonly designated L and D, can be separated by crystallization of the diastereomeric tartrate salts. However, despite the low cost and ready availability of the building blocks, there have been no applications in enantioselective organic synthesis. His group has found that $[Co(en)_3]^{3+}$ and related cations can be rendered soluble in organic solvents by using lipophilic anions. Suitably functionalized derivatives act as highly enantioselective catalysts for a variety of carbon-carbon bond forming reactions. The mechanisms involve outer sphere activation of the electrophile by hydrogen bonding to the NH moieties. Other types of metal-containing chiral hydrogen bond donors are also effective, including a chelate of the CpRuL fragment.

Arie Gruzman of Bar-Ilan University spoke about "Rational design and synthesis of novel peptidomimetic drug candidates for prostate cancer treatment. He explained that despite progress in early diagnostics and treatment, prostate cancer is still one of the most devastating male diseases. Thus, the development of anti-prostate cancer drugs remains urgent. Prostatic acid phosphatase (PAcP) has been implicated in the pathogenesis of prostate cancer. In prostate epithelial cells PAcP is presented in two distinguished isoforms: extracellular and nuclear. These populations differ from each other by function, enzymatic activity and by protein folding. Secreted PAcP upregulates cancer growth of prostate epithelial cells (prooncogenic), whereas the nuclear form inhibits it (antioncogenic). His group hypothesized that the primary factor that regulates the secretion of prooncogenic PAcP is appropriate its signal sequence cleavage. In fact, any secretory protein should lose its signal sequence in order to be properly secreted. They established a new mechanism-based anticancer drug discovery approach for prostate cancer therapy: the inhibition of signal peptides SP1, the enzyme that cleaves PAcP signal sequence. Such inhibition should prevent the secretion of prooncogenic PAcP and slows prostate cancer progression. Using homology computer modeling they built a virtual human SP1 model. Based on signal sequences of PAcP, a series of potential SP1 inhibitors, both peptide-based and peptidomimetics were designed and synthesized. One of synthesized molecules was active in vitro in prostate cancer model. The compound decreased the secretion of PAcP from prostate cancer cells and showed cytotoxic activity. Non-cancer cells were not affected by the compound. Innovative drug development approach, which is based on inhibiting PAcP secretion and in silico SP1 model, was not previously described in the scientific literature.

Peter Rossky of Rice University spoke about "Electronic excited state relaxation in complex systems: two stories of harmony between theory and experiment." His presentation focused on progress in their ability to understand, at the level of atoms and on the time scale of femtoseconds, the molecular rearrangements and time-dependent processes

that occur following electronic excitation by light when these changes take place in liquid solutions or in unstructured solid materials, including those occurring in biological and synthetic polymeric materials. Computational models and experiment are increasingly able to simultaneously describe these processes, greatly enhancing the information that can be learned about chemistry from the combined theoretical and experimental analysis. He discussed two example cases with focus on how time-dependent simulations of quantum phenomena can directly inform on mechanisms. The first case is one where both the complex system and electronic process are relatively "simple": his group study the electronic excited state relaxation of photoexcited anionic water clusters to understand the measured cluster size dependence of the ground state recovery rate and how those values come about. In the second, they study far more complex molecular systems based on a simple semi-empirical electronic structure method. Analysis of the evolution of electronic excited states in representative conjugated molecular systems, particularly relevant to the function of plastic solar cells, were discussed, including the processes underlying exciton migration and exciton dissociation, and the impact of interfacial structure and of extrinsic electric fields.

Amit Meller of the Technion spoke about "Single-molecule sensing and characterization of native, unlabeled proteins using solid-state nanopores." He explained that nanopores (NPs) are single molecule biosensors, which utilize electrokinetic focusing and transport to detect and characterize unlabeled biomolecules. Controlling and tuning the capture rate and the translocation speed of biomolecules through the NP are crucial features to allow sensing of fine biomolecular features within the experimental bandwidth limitations. His group recently developed methods to enhance the resolution of native, unlabeled proteins sensing by radically enhancing their residence time while in the pore, and improved nano-sensor morphology. These improvements allowed them to sense and characterize individual native (chemically unmodified) proteins. Specifically, they demonstrated the discrimination among two, unlabeled, ubiquitin protein dimers, which only possess a slightly different 3D structure and having the same amino-acid sequence. Furthermore they were able to directly sense and map individual transcription-factors bound to their target ds-DNA. The ability to analyze biomolecular complexes, fine features along DNA strands and small proteins in their native folded state at the single molecule level opens up broad opportunities in biomedical research and in biochemistry.

Gil Alexandrowicz of the Technion, winner of the ICS Young Scientist Prize, spoke about "Studying surfaces with magnetically-manipulated atomic and molecular beams." He pointed out that in his group they use atomic and molecular beams with the aim of studying the structure and dynamics of surfaces on the atomic scale. He briefly explained what kind of magnetic manipulations they use and what they gain from this approach. Magnetic manipulations on a helium-3 atomic beam allow them to perform atom-interferometry experiments and study atomic-scale motion, which takes place on very fast time scales (pico to nano-seconds). In a recent study they exploited this technique to study the influence of an atomic step on the ultra-fast diffusion of an adsorbed atom. They also magnetically manipulate molecular beams. In this case, the manipulations allow them to separate spin isomers. For example, they used this approach to separate ortho and para H₂O molecules. One potential application of this molecular beam separation technique is a new spectrometer they are currently working on, an instrument, which should enable ultra-sensitive NMR experiments of water surfaces in the near future.

François P. Gabbaï of Texas A&M University lectured on "Lewis acidic properties of organo-antimony compounds: application in anion sensing and catalysis." He showed that the oxidation of organo-antimony(III) derivatives provides access to Lewis acidic antimony(V) derivatives, which can be used in a number of applications ranging from anion sensing to organic reaction catalysis. The first part of the presentation was dedicated to the chemistry of Lewis basic bidendate distibines and their oxidative conversion into the corresponding distiboranes. These distiboranes behave as bidendate Lewis acids and readily chelate anions, such as the fluoride anion. In the second part of the presentation, he described how stibines of general formula R3Sb could be oxidized even when ligated to transition metal complexes (M). This oxidation induces the formation of a $M \rightarrow Sb$ interaction, which results in a drastic increase in the Lewis acidity of metal center. Using a family of gold stibine derivatives, he demonstrated that such coordinated stibine oxidation reactions can be used to afford potent hydroamination catalysts.

Daniel Romo of Baylor University spoke about "Bioactivityguided retrosynthesis: "upping the ante" for natural product total synthesis." He explained that in recent years, great efforts have been made to improve the efficiency of the total synthesis of complex bioactive natural products through atom and step economy, avoidance of protecting groups, development of complexity-generating cascade processes minimizing step count and purifications. His group's continued interest in understanding the mechanism of action of bioactive natural products, including identification of their cellular receptors, has led us to consider adding another requirement to their retrosynthetic strategies. Namely, they have sought to introduce a hypothesized pharmacophore early in the synthetic sequence to enable biological studies to be initiated at an early stage of a total synthesis effort. This approach is most readily applicable to natural products that likely covalently modify their putative cellular receptors, however application to non-covalent protein interactors is also beginning to show promise. Several case studies implementing this strategy were presented along with biological studies.

Shimon Vega of the Weizmann Institute of Science spoke about "Some new insights into the dynamic nuclear polarization mechanism in solids." He explained that dynamic nuclear polarization has become an integral part of magnetic resonance spectroscopy. This sensitivity enhancement mechanism has been implemented in NMR and MRI experiments for the study of structure and folding of protein, molecular composition of surfaces, metabolic pathways, differentiation between tissues and much more. Introduced more than sixty years ago, DNP relies on our ability to transfer electron polarization to nuclear polarization by microwave saturation of the transitions of unpaired electrons that are coupled to the nuclei of interest. The basic theoretical models explaining the DNP phenomena were established already forty years ago and most experimental observations were interpreted using these models. Only in the last decade or so with the significant increase of NMR and MRI applications involving DNP it has become apparent that the basic theoretical models were not sufficient to account for all experimental observations. Using his group's hybrid EPR-NMR spectrometer they have been following the frequency dependence of the electron and nuclear polarizations during MW irradiation on samples containing nitroxide TEMPOL and trityl radicals. Detecting frequency swept ELDOR and DNP enhancement profiles at low temperatures, they showed that the standard thermal mixing model for describing DNP cannot describe their experimental observations. He presented a comprehensive description of the different mechanisms contributing to the DNP enhancement in radical containing amorphous solids, including the indirect and heteronuclear cross effect mechanisms. In addition, he reported on the influence of sample rotation during magic angle spinning on these processes. All explanations were accompanied by experimental DNP results.

Ori Cheshnovsky of Tel Aviv University spoke about "Super resolution microscopy based on photo-modulated reflectivity." He explained that far-field super-resolution (SR) microscopy has developed to be an important tool in life sciences. However, it relies on, and therefore is limited by the ability to control the fluorescence of label molecules. His group introduced a new far field label-free SR methodology that is based on the nonlinear response of the reflectance to photo-modulation. It relies on the ability to photo-excite a temperature and charge carrier's spatial distribution inside the diffraction-limited spot by an ultra-short pump pulse. An overlapping delayed probe



Figure 5. ICS Award Ceremony. Top row from left: Dorit Taitelbaum and Keinan with Dorota Czarkie; Taitelbaum, Yousif Sahly of Teva Pharmaceuticals and Keinan with Michael Koifman; Taitelbaum, Yousif Sahly and Keinan with Shai Shahar. Second row: the Chemical Green-Industry Prize is awarded to Shelly Sela, Moshe Nitzan and Yehezkel Moshe of Bromine Compounds Ltd. The Technological Innovation Prize is awarded to Prof. Moshe Kol by Eddy Kaufman of ICL-Innovation and Keinan; Dani Shahar and Keinan present the Best Poster award to Tamar Yelin. Third row, Shahar and Keinan present the Best Poster award to Shimrit Ohayon, Alina Khersonsky and Amir Hevroni.

pulse monitors reflectance changes. Spatial resolution within the diffraction-limited spot is enhanced due to nonlinearities in photo-modulated properties of the matter. The method is suitable for characterization of semiconductors and metals in vacuum, ambient, and liquid, semi-transparent and opaque systems, ultrathin and thick samples alike. Examples of such resolution enhancement due to nonlinearities (lateral and vertical) were presented: The change of thermo-reflectance of VO₂ upon its characteristic insulator-to-metal transition at ~340 K, the heating process of a nanostructured silicon or gold surfaces, and the nonlinear response of photo-modulated Raman spectra. Resolution down to 85 nm was demonstrated.

Ognjen S. Miljanic of the University of Houston spoke about "Fluorinated porous materials: from metal-organic frameworks to molecular crystals." He explained that p-porous materials have numerous applications, most of which are related to energy and fuels. The field of porous materials has grown rapidly during the past two decades by the development metalorganic (MOFs) and covalent organic frameworks (COFs). These modularly synthesized materials offer essentially infinite possibilities for structural variation, and therefore allow for the preparation of materials with tailored thermal and chemical stabilities, pore sizes, shapes, and internal functionalities. However, COFs and MOFs are not perfect: as insoluble solid-state structures, they have essentially no solution processability, and many of MOFs and COFs are also hydrolytically sensitive. Work in his group has made significant strides towards addressing both of these challenges by creating porous molecular crystals, in which individual building blocks are held together only by noncovalent interactions: hydrogen bonding and $[\pi^{\bullet\bullet\bullet}\pi]$ stacking. These structures are fundamentally interesting and quite rare molecules that prefer to closely pack in the solid state. At the same time,



Figure 6. ICS awards for Excellent Graduate Students are presented to the winners by Keinan and a representative of the relevant Department. Top row from left: Ido M. Herzog of the Tel-Aviv University with Gil Markovich; Elena Ragozin of Ariel University with Haya Kornweitz; Efrat Levin of Ben-Gurion University with Gabriel Lemcoff. Second row: Sigalit Meker of the Hebrew University with Assaf Friedler; Diana Meltzer of Bar-Ilan University with Bilha Fischer; Arseni Kostenko of the Technion receives the Lise Meitner Prize from Keinan and Miri Karni. Third row: Mother of Sivan Refaely-Abramson of the Weizmann Institute of Science with Reshef Tenne; Noam Adir, Dean of the Schulich Faculty of Chemistry receives the award for Rami Batrice.

these materials promise to be practical, since they are soluble, easily characterized, and highly thermally, hydrolytically, and chemically stable. In addition, their noncovalent connections can expand or shrink in response to adsorbed analytes, thus constituting a piezochromic sensing mechanism. These structures have been used as adsorbents for fluorinated pollutants, hydrocarbons, and anesthetics. He surveyed his group's research results, and also described two other classes of porous materials prepared by his group: fluorinated MOFs and the emergent class of porous macrocycles, known as cyclobenzoins, which can be synthesized in a single step from commercially available starting materials.

Zeev Gross of the Technion spoke about "Sustainable metal catalysts for energy-relevant processes." He pointed out that limiting catalytic reactions involved in energy-relevant process include the two-electron reduction of protons to hydrogen gas, the selective reduction of oxygen to water, and photoassisted uphill reactions. His group has introduced complexes of corroles with first-row transition and post-transition metal ions that may resolve critical issues involved in these electroand photo-catalytic processes. This is accompanied with mechanism of action studies, for assisting in the design of optimally performing catalysts, achieved by variations in the identity of M, X, and Ar in the structure of the complexes.

Diana Golodnitsky of Tel Aviv University spoke about "Novel polymer-in-ceramic electrolytes; ion-transport phenomena." She explained that solid electrolytes could revolutionize battery and supercapacitor technology because of their nontoxicity, stability during operation and enhanced safety. The major limitation of solid electrolytes is their low ionic conductivity at room temperature, and intricate ion transport complicated by grain-boundary phenomena. Her group has developed novel polymer-

in-ceramic composite electrolytes with high ion-conduction properties, prepared by electrophoretic deposition. Nanoparticles of LiAlO₂, Li₁₀SnP₂S₁₂, and some ion-conducting glasses were used as ceramic matrices. Polyethyleneimine (PEI) and polyethylene oxide (PEO) were tested as binders and lithium-ion-conducting mediums. Their recently developed simplified Poisson-Boltzmann model reveals that the adsorption of PEI on the surface of ceramic particles increases zeta potential, repulsion forces between the particles and their deposition rate. The electrophoretic deposition of PEO and nanoceramic powders occurs from the individual entities. They have succeeded in depositing films containing 5 to 40 % PEO, which are homogeneous in composition and uniform in thickness. XRD and DSC tests showed that the crystallinity of the polymer confined in the pores of ceramics, is suppressed. This was expected to improve the ionic conductivity of composite electrolytes saturated with LiI salt. However, on the basis of ACimpedance, NMR and high-resolution X-ray tomography data, they suggest that the high ionic conductivity (0.5 mS/cm) and low activation energy (2.3 kJ/mole) are brought about by the parallelto-the-current-path grain boundaries between the excess of LiI and ceramic nanoparticles, and not by the confined-in-ceramic polymer. It is obvious that the nanoarchitecturing of ordered, fast-ion-conduction paths and the elimination of perpendicular blocking grain boundaries will reduce the effect of high-resistant grains.

David Tannor of the Weizmann Institute of Science spoke about "Laser control of chemical reactions: where are we and where are we going?" He presented an overview of laser control over chemical reactions, with an emphasis on time-dependent methodologies. It included a review of the pump-dump scheme, optimal control theory for design of optimally shaped laser pulses, learning algorithms, deciphering excited state potential energy surfaces from multiple-pulse spectroscopy and recent work toward controlling multi-electron motion.

The ICS Awards Ceremony

Following the ICS tradition, all prizes were awarded either at the Awards Ceremony (Figure 5), which took place in the afternoon of February 9th, or during the Gala Dinner the same evening. The ICS Prizes of excellence and the Excellent Teachers prizes were sponsored by Teva Pharmaceuticals Ltd.

The 2015 ICS-ICL Prize for Technological Innovation, which is sponsored by ICL Innovation Ltd., was awarded to Prof. Moshe Kol of Tel-Aviv University for his profound and lasting impact on the field metal-catalyzed olefin polymerization. In the past 15 years, Prof. Kol and his group have developed novel families of homogeneous catalysts for polymerization of alpha-olefins and the ring-opening polymerization of cyclic esters for the preparation of environmentally friendly plastics. They designed and synthesized new chelating ligands and their complexes with transition metals, as well as with main-group elements, and applied them as single-site catalysts in various transformations. Several of these novel catalysts are known worldwide as the Kol-type catalysts.

In 2000 they introduced the Salan-zirconium catalysts, which enabled the first living and isospecific polymerization of high-olefins at room temperature, and had a major effect on the worldwide research in this field. Their Salalen-titanium complexes and related families of catalysts had unique ability to direct incoming substrate molecules, and led to polypropylene with unprecedented isotacticity and a recordhigh melting point. In 2015 they also developed heteroselective aluminum catalysts for lactide polymerization that operate by alternating polymeryl-exchange between enantiomeric catalytic molecules. Their recently developed polypropylene catalysts led to an intensive collaboration with ExxonMobil Company. Prof. Kol has published about 100 research articles, two book chapters and 17 patent applications, 13 of which in the past five years. His work has been cited over 4100 times with H-Index 40.

The 2015 ICS Prize for Excellence in Chemistry Teaching was shared by two teachers. Dr. Dorota Czarkie of Ahad Ha'am High School, Petah Tikva, and the Open University, received the Prize for excellence in teaching, for development of innovative teaching methods and novel laboratory experiments, as well as new high school courses and learning materials at the Open University; for collaborative learning and personal contact with her students, thereby leading them to extraordinary academic achievements. Mr. Michael Koifman of the Baruch Venger high School Ort Psagot, Carmiel, received the Prize for excellence in teaching chemistry and biology, including the development of learning materials for students in the high school and the Museum of Science, Madatech; for creativity and pedagogical initiatives, including support for other teachers, development of innovative laboratory experiments, and leading the student to academic excellence.

The 2015 ICS Prize for the Outstanding Young Teacher was awarded to Mr. Shai Shahar of the Hebrew Reali School of Haifa and the Open University, for excellence in education and chemistry teaching in high school and at the Open University, for developing novel learning materials tailored for the students, promoting chemistry through innovative initiatives, such as learning through projects and joint activities between students and their parents.

The 2015 ICS Prize for the Excellent Graduate Student was awarded to seven PhD students, one from each of the seven research universities that have a chemistry department (Figure 6).

Rami Batrice of the Technion works on actinide coordination chemistry and catalysis under the supervision of Moris Eisen. He has uncovered a series of previously unseen catalytic reactions utilizing uranium and thorium complexes. Most notable of these is the catalytic cyclotrimerisation of terminal alkynes, the addition of protic nucleophiles to various heterocumulenes, including the first formal addition of a C-H bond across an unsaturated carbon-heteroatom bond, and the catalytic addition of alcohols to carbodiimides. The latter process has long thought to be forbidden owing to the high barrier of actinide-oxygen bond scission. His research has also resulted in the development of novel actinide complexes bearing bridged pyrrolyl moieties displaying an unusual pentahaptic coordination of the heterocycle, and phenoxyimine ligands capable of undergoing a rare intramolecular ortho-activation of the ligand architecture.

Ido M. Herzog of the Tel-Aviv University received his BSc in Chemistry and Biology from the school of chemistry at Tel-Aviv University. His PhD program under Micha Fridman focuses on the design, development and mechanistic study of membrane-disrupting antimicrobial agents. By utilizing the differences between mammalian and bacterial membrane compositions he successfully developed membrane-disrupting agents that have already demonstrated enhanced selectivity to bacterial membranes. His research has significantly contributed to the revived interest in bacterial membranes as targets for antibiotics development.

Efrat Levin of Ben-Gurion University of the Negev works for her PhD degree under N. Gabriel Lemcoff on photocontrolled olefin metathesis. As the ability to selectively guide consecutive chemical processes towards a preferred pathway by using light of different frequencies is an appealing concept, her research involved two photochemical reactions: photo-activation of a sulfur-chelated olefin metathesis catalyst and photo-labile super-silyl protecting group. Depending on the steric stress exerted by a photo-removable neighboring chemical substituent, she demonstrated the selective formation of either five or six membered ring products by light-triggered reactions. This chromatic orthogonal study led to a novel catalyst design, which could be activated by UV-A irradiation and irreversibly decomposed by UV-C light. The possibility to control catalysis by using light of different frequencies opens the pathway for stereolithographic applications and light guided chemical sequences.

Sigalit Meker of the Hebrew University focuses her research under Edit Y. Tshuva on the development of titanium-based

anti-cancer agents, which feature activity toward various cancer cells and low intrinsic toxicity, compared with other chemotherapeutic drugs. She is interested in developing soluble, hydrolytically stable, anti-tumoral Ti(IV) complexes based on hexadentate phenolato ligands. She is also investigating the mechanism of these agents, particularly the nature of the active species, the in vitro and in vivo activity, cellular distribution, and selectivity toward non-cancerous cells. This is accomplished by the employment of organic and inorganic syntheses, spectroscopic methods, and cellular biology techniques.

Diana Meltzer of Bar-Ilan University works under Bilha Fischer on the design, synthesis and evaluation of novel nucleotide and methylenediphosphonotetrathioate analogs, as potential drugs for the treatment of several conditions, including inflammatory bowel diseases (IBD), deposition of pathological calcium-pyrophosphate-dihydrate, and disorders involving excess of zinc-ions. She established a comprehensive structure-activity-relationship for UDP/UTP analogues useful for the development of hP2Y6/hP2Y2 receptor antagonists/ agonists, as potential drugs for the treatment of IBD. She also developed novel nucleoside-5'-tetrathiobisphosphonate analogs as biocompatible chelators of zinc and novel hybrids of methylene-diphosphono-tetrathioate and crown-ether rings as selective zinc chelators, which may be useful for the treatment of health disorders involving zinc binding enzymes or excess zinc.

Sivan Refaely-Abramson of the Weizmann Institute of Science works under Leeor Kronik on electronic and optical excitations from an optimally-tuned range-separated density functional approach. Understanding and predicting spectroscopic properties of materials is crucial for device characterization and design in general and for organicphotovoltaics in particular. She has developed and applied a new method for predicting crucial spectroscopic properties of both gas-phase and solid-state systems accurately and efficiently within density-functional theory, by combining its time-independent and time-dependent forms. This is achieved using the relatively new concept of an optimally-tuned rangeseparated hybrid functional, where a first-principle parametertuning procedure is applied separately for each system. This method supplies highly accurate results for the electronic structure and the optical excitations of molecular systems as well as solid-state molecular crystals of photovoltaic interest, opening the door to studies of materials of increasing size and complexity.

Elena Ragozin of Ariel University works under Gary Gellerman and Michael Zinigrad on the development of novel platforms for conjugation and simultaneous delivery of anticancer drugs.



Figure 7. ICS awards presented at the Gala Dinner by Keinan and Dr. Raphael Nudelman of Teva Pharmaceutical Industries Ltd. Top row from left: ICS Medal to Zvi Rappoport and Reshef Tenne, Honorable Member of the ICS to Amitai E. Halevi. Second row: ICS Prize of Excellence to Emanuel Peled and Yoram Cohen, ICS Excellent Young Scientist Prize to Gil Alexandrowicz. Third row: ICS Excellent Young Scientist Prize to Rafal Klajn, general view of the dinner hall, Peled signing the poster shown in Figure 1.

This research is driven by the need for selective anti-cancer compounds having minimal side effects. She designs "cocktail drug platform" that would provide, upon linkage to the given carrier, the desired selectivity. She has developed a model of targeted drug delivery to gain controllable drug penetration into the cancer cells using a specific peptide carrier, which binds to the somatostatin receptor.

Arseni Kostenko of the Technion received his BSc cum laude in 2009 in molecular biochemistry. He continued directly to a PhD program under the supervision of Yitzhak Apeloig, focusing on radical reactions of silanes and the development of transition metal complexes that catalyze such reactions. He combines experiment with theory using quantum mechanical computational methods. He received the Schulich Prize of Excellence for outstanding graduate students. The 2015 Lise Meiner prize was awarded to him for using theory innovatively to support the spectroscopic observation of the first triplet diradical resulting from thermal rotation around an E<C=>E bond, where E is Si, and for his 2015 Angew. Chem. paper "Observation of a Thermally Accessible Triplet State Resulting from Rotation around a Main-Group Bond."

The 2015 Tenne Family Prize in memory of Lea Tenne for Nanoscale Sciences was awarded to Prof. Taleb Mokari of Ben-Gurion University of the Negev for his discoveries of novel synthetic approaches of high quality semiconductor nano-crystals, hybrid nanoparticles and nanowires. This year the award ceremony took place during the Nano-Israel 2016, which was held in Tel Aviv on February 22-23, 2016.

Taleb Mokari received his BSc in 2000 and PhD in physical chemistry in 2006 (summa cum laude) from the Hebrew University of Jerusalem under Prof. Uri Banin, investigating the synthesis of hybrid nanoparticles. He was a Fulbright and an Ilan Ramon postdoctoral fellow with Prof. Peidong Yang

at the University of California, Berkeley for one year, and in 2007 he joined the Molecular Foundry at Lawrence Berkeley National Laboratory as a staff scientist. In 2009 he joined the department of chemistry and the Ilse Katz Institute for Nanoscience and Nanotechnology at Ben-Gurion University of the Negev and was promoted to Associate Professor in 2012. His research focuses on the chemical and physical properties of inorganic nanostructures. His group specializes on gasand solution-phase synthesis of nanostructures, studying their fundamental physical and chemical properties and their potential applications for renewable energy. Mokari won prestigious research grants, including the ERC starting grant and the Marie Curie grant. His long list of awards includes the Krill Award for Excellence in Scientific Research (2011) and the Toronto prize (2015). In 2012, he was appointed member of the new "Young Israel Academy". He has published 53 research papers with more than 3360 citations and H-index of 24.

The 2015 ICS Prize for the Chemical Green-Industry was awarded to Bromine Compounds Ltd. (ICL Neot Hovav) for research, development and production of compounds that help protecting the environment and for the significant reduction of the environmental footprint of the factory. Bromine Compounds was established in 1978 and over the years it acquired an international leadership position in the research and development of processes that formed the basis for advanced bromine-based products, such as fire-retardants, materials for deep-sea drilling of oil and gas, water treatment, paper, textiles and more. The company developed a "sustainability index" for prioritizing research and development of new products, considering not only the direct effect of the product on the environment, but also the contribution to a greener and safer world. Along with all these, the plant adopted a strict policy of reducing its environmental footprint, based on the stringent requirements of the European Union. Since 2013, the company has switched all operations to natural gas as a fuel. They adopted the Voluntary Emission Control Action Program (VECAP), and also participate in the international Responsible Care program, and implemented measures for compliance with the policy of "green factory." The prize was presented to three representatives of the company: Site Manager of Neot Hovav Moshe Yehezkel, Senior Vice President, ICL IP Operations Moshe Nitzan and Environment Manager Shelly Sela.

Gala dinner

About 100 distinguished guests attended the Gala Dinner, which, in the long tradition of the ICS, is the occasion of awarding the major ICS prizes (Figure 7). For many people this award ceremony has been the most moving and exciting part of the entire conference. Keinan invited Dr. Raphael Nudelman, who represented Teva Pharmaceutical Industries Ltd. to join him for the ceremony. Nudelman is Associate Director and Head of Chemical & Computational Toxicology at Teva, also serving as President of the Medicinal Chemistry Section (MCS) of the Israel Chemical Society. He said that Teva is proud to sponsor most ICS prizes and mentioned the fabulous, many year relationships of the ICS and Ehud Keinan with Teva.

The 2015 ICS Gold Medal was jointly awarded to two laureates. Prof. Zvi Rappoport of the Hebrew University of Jerusalem received the medal for comprehensive deciphering of the mechanisms of important chemical reactions and for characterizing reactive intermediates, thus equipping organic chemists with tools for better controlling their reactions; for significantly advancing the Israeli chemical community through establishing an influential school of physical organic chemistry and by refining the organic chemistry literature. Prof. Reshef Tenne of the Weizmann Institute of Science received the medal for his discoveries of the inorganic fullerene-like nanospheres and nanotubes, which represent a new class of nanomaterials, for elucidating their unique properties and for employing them in a broad range of useful applications.

Prof. Zvi Rappoport was born in 1936 in Jerusalem, received his MSc in chemistry (1959), PhD (with Saul Patai, 1962) from the Hebrew University and was a postdoc in UCLA (1963-1965) with Saul Winstein. In 1965 he joined the Hebrew University for his entire career. Prof. Rappoport is known as the founding father of physical and mechanistic organic chemistry in Israel and one of the a worldwide leaders in the field. He pioneered the study of vinyl cations, vinylic nucleophilic substitution, the selectivity-reactivity relationships, stable enols and vinylic propellers. He published over 300 papers and reviews in leading journals and his research is widely cited by most textbooks of organic chemistry. His list of awards includes the Kolthoff Prize, the Lise Meitner-Alexander von Humboldt Research Award, the Gold Commemorative medal of Masaryk University, Czech Republic, Laurea Honoris Causa from University of Cagliari and the 2006 Israel Prize in Chemistry. One of his most celebrated contributions to science is the renowned series "The Chemistry of the Functional Group" (Patai's series) of which he edited more than 70 books. This legendary book series has brought the Israeli chemistry to every chemistry department worldwide. Zvi Rappoport has mentored generations of students, thus creating a strong Israeli school of physical organic chemistry. He is also an avid stamp collector and his particular expertise in "chemistry on stamps" has been recognized worldwide.

Prof. Zvi Rappoport responded: "I want to thank the ICS and Ehud Keinan for organizing these special meetings for

so many years. It is a very special experience and pleasure to attend these conferences, especially as you become older. I have been teaching in the Hebrew University for more than 55 years and it is very rewarding to see students from these 55 years. Even those who didn't want to talk to me at the time are now coming in a friendly way, congratulating me and sharing with me stories of the old days. I also want to thank those who recommended me for this award. It is not obvious because there are many other candidates. When hearing the citation, naming me as a pioneer of physical organic chemistry in the State of Israel, I thought I would clarify this point. I was not the first one, we all follow the steps of others and I would like to state that Amitai Halevi, who is here tonight, was practicing physical organic chemistry long before I knew the meaning of this term. In addition to him there were 2-3 other Israeli pioneers before my time. I should also stress that although I received the ICS medal for scientific achievements, my students have done the actual work. In particular, I would like to mention the names of two of them who were killed in the Yom Kippur war of 1973, Aharon Gal and Motti Tuval and I would like to remember them on this occasion."

Prof. Reshef Tenne was born in Kibbutz Usha (1944), obtained his BSc (1969), MSc (1971), PhD (1976) in chemistry from the Hebrew University, postdoc at the Battelle Institute in Geneva, joined the Weizmann Institute in 1979. He published over 300 papers and 70 invited chapters and review articles. His main focus is the synthesis, characterization and applications of novel inorganic nanomaterials nicknamed inorganic fullerenelike structures and inorganic nanotubes. Since his discovery of these structures in 1992, he has become the worldwide pioneer and leader of the field. He found that these materials have a very broad spectrum of useful applications, including superior lubrication properties when mixed with various fluids, coating of various medical devices to improve their entry-retrieval, nano-size superconductors, components for reinforcing polymer nanocomposites, sensors for aerospace technologies and for tissue engineering, etc. Tenne serves as Chief Scientific Advisor of companies that were established on these technologies, NanoMaterials and Apnano Materials. Tenne's long list of awards includes the Kolthoff Prize, the Rafael Prize for Excellence in Science, the Materials Research Society Medal, the Landau Prize in Nanotechnology, the ICS Prize of Excellence and the Rothschild Prize in Physical Sciences and Chemical Sciences. He is a Fellow of the Royal Society of Chemistry, the Israel Academy of Sciences and Humanities, and Academia Europaea.

Prof. Reshef Tenne responded by thanking the ICS and its President for this distinguished award. "It is important to acknowledge that I could do all this wonderful work in a wonderful place, the Weizmann Institute, which is a tremendous

place to do science, particularly Blue-Sky science. It is a place where one can do innovative science even in the absence of outside support, one can develop a product and bring it all the way to the marketplace and educate outstanding students who continued their career in both academia and industry. I would like to thank my family. This afternoon Keinan had mentioned the Lea Tenne Prize, which commemorates my late wife. It is based on a contribution of my family to the ICS to recognize leading Israeli scientist in the nano-scale sciences. I am very proud of this prize, by the recipients of this prize and the tradition that has been created. I would like to mention here Prof. Moshe Levi, my dear friend who passed away few months ago. He was a visionary scientist and we have done many things together and his passing was a great personal loss for me. Finally, I wish to thank all members of my family, particularly my wife Ella who could not attend this event because she is sick today."

The 2015 Honorable Member of the ICS Award was presented to Prof. Amitai E. Halevi of the Schulich Faculty of Chemistry, the Technion, for his long scientific leadership in the field of Physical and Theoretical Organic Chemistry, and for his major contributions to higher education in the State of Israel.

Keinan explained that the fascinating biography of Prof. Halevi (born in New York, 1922) includes service in the US Air Force during WWII, violin practice, service in the Hagana, Talmud studies and much more. He received his BA from the University of Cincinnati, MSc from the Hebrew University and PhD (1952, with Christopher Ingold) from University College London. He joined the Hebrew University (1952) but moved to the Technion (1955) upon request from David Ginsburg, became Professor in 1964 and Professor Emeritus in 1990. Prof. Halevi is most known for his experimental and computational studies of isotope effects on molecular properties, equilibria, and kinetics; and the dependence of reaction mechanisms on state-, orbital- and spin-symmetry. His collaborative research took him to Cornell University, ETH Zürich, Brookhaven National Laboratory, Oregon State University, Univ. of Oregon, Argonne National Laboratory, Purdue University, Weizmann Institute, Univ. College London, UC Irvine, Ben-Gurion University, MPI Mülheim/ Ruhr, University of Munich, University of Frankfurt, Univ. of Heidelberg, University of Graz, Univ. of Paris, Clarkson University, CalTech, MPI Heidelberg, Simon Frazer University, and the Univ. of Wisconsin. At the age of 94, he still publishes single-authored research papers, some of which challenge well-established theories, such as the Woodward-Hoffmann rules and Perrin's theory concerning isotope effects on acidity.

We all know that every university and every academic

department has a recognizable character and unique culture, which distinguishes it from other universities and departments. We easily recognize universities that radiate a pleasant ambience and good values across the campus at all levels, including faculty members, students, technical stuff and administrative personnel. This character does not come by chance; it stems from the hard work of a few outstanding people, who make it happen. Very often, those characterdetermining people are too humble and too busy to stand at the front to collect the credit they deserve. Like the engines of a big ship, they push forward the heavy vessel while staying almost invisible. Furthermore, similar to the social behavior of human beings, young universities take the older and more experienced ones as role models. Consequently, the expanse of influence by those human engines is much broader than their domestic arena. Thus, Amitai Halevi is being recognized as Honorable Member of the ICS for significantly advancing not only the Technion, but also the entire network of higher education in the State of Israel.

As Dean of the Faculty of Chemistry (1983-85), Prof. Halevi steered the Faculty over the turbulent waters of one of its lowest points in history. He influenced the Technion as a member of the Academic Development Committee, the Committee for Senior Faculty Appointments and the Committee for Appointment of Research Professors. As president of the Disciplinary Tribunal for Academic Staff, he made an impact on ethical conduct. Via the Review Committee on Operations and Functions of the VP for Finance and Administration he helped shaping the Technion administration. He also acted as the Senate Representative in the Board of Governors, as member of the Senate Steering Committee and the Committee for Election of the President, where he took part in shaping the Technion management. As Dean of the Technion Graduate School (1969-71) he revolutionized and shifted the conceptual basis of the Ph.D. programs from applied to basic science.

In his introductory remarks, Keinan also mentioned that the title Honorable Member is probably better described as Cherished Member, and Amitai Halevi is certainly cherished by all ICS members. Keinan turned the attention of Prof. Donna Nelson, ACS President, that Amitai has been a member of the ACS continuously for 73 years, since 1943, which is quite remarkable. Referring to Halevi's biography, Keinan commented that in our time it is quite uncommon for graduate students to complement their income by producing detonators and explosives for the Israeli Defense Force. While a student in the Hebrew University during the pre-State time Halevi made his living by producing detonators for the Israeli military industry. In addition to being a gifted translator of poetry from Hebrew to English and from English to Hebrew, Amitai is a relentless scientist. He has challenged twice the American scientific establishment by publishing a book on Orbital Symmetry and Reaction Mechanisms, which criticizes and simplifies the Woodward-Hoffmann's rules. In recent years he challenged the well-established theory of Charles Perrin on isotope effects.

Prof. Amitai Halevi responded by thanking Keinan for his generous introduction and said that he was deeply gratified to have been chosen by the Israel Chemical Society to be its Honorable Member for 2015, and was sorry that Ada, his wife for over 69 years, couldn't attend this event. He admitted that the award came to him as a surprise: "It is not my intention to belittle my achievements as a chemist; it would be an insult to the committee that decided to grant it to me. Nevertheless, it is a fact that my career as a practicing chemist came to an end when I retired from the Technion a quarter of a century ago.

True, I published a research paper two years ago and a brief follow-up last year, but that was in order to clarify – once and for all – a point in the theory of isotope effects that had been settled over 50 years ago. My only other publication since retirement is a translation into Hebrew of a poem by the late American author John Updike. It was published in Itton 77, a journal of Hebrew, non-chemical literature. Therefore, I understood that the committee had something more in mind when they chose me as Honorable Member for 2015. There is a more than a hint of it in Professor Keinan's introduction.

I am one of the few surviving members of a group of Israeli chemists who were research students or junior faculty members in the last years of the British Mandate. We were coopted as scientists into the defense forces of the 'State in the Making' and served as such in the War of Independence. With the establishment of the State of Israel, some of us remained in the defense establishment and made important anonymous contributions to the security of the state and its citizens. Others opted for applied research in the laboratories of the growing chemical and pharmaceutical industries.

The remainder, and I among them, returned to the Israeli academic scene. Resisting the temptation to emigrate to greener pastures, we modernized research and teaching in the existing academic institutions, set up departments of chemistry in the newly established universities, and taught chemistry to generations of students. Over the years we, our students and our students' students, succeeded in making Israel a center of chemical research. The world-wide respect currently held by Israeli chemistry – academic and industrial – is due in no small measure to the devotion and perseverance of this group of chemists, most of whom are no longer with us. I am proud to accept the award on their behalf. Thank you."

The 2015 ICS Prize of Excellence was awarded to two professors of the School of Chemistry of Tel Aviv University. **Prof. Emanuel Peled** received the Prize for his seminal contributions to the field of battery science, particularly the introduction of the solid-electrolyte-interface model. **Prof. Yoram Cohen** received the Prize for his pioneering contributions to the application of diffusion NMR in supramolecular chemistry and biomedicine.

Prof. Emanuel Peled, incumbent of the Nathan Cummings Chair of Pure and Applied Electrochemistry, is the inventor and developer of the solid-electrolyte-interphase (SEI) model for non-aqueous alkali-metal batteries. This model, which was cited over 15,000 times, constitutes a paradigm change in the understanding of lithium batteries and has thus enabled the development of safer, durable, higher-power and lowercost lithium batteries for portable and EV applications. He developed many batteries and fuel cell systems, including direct methanol and direct ethylene glycol fuel cells. He was the director of the Wolfson Applied Material Research Center, the Gordon Center of Energy Studies, the Fuel Cells and Battery Center. He has published over 180 papers and 47 patents on ESI, electrochemistry of fuel cells membranes and catalysts, super capacitors, metals and alloys, 3D-micro- and nanobattery architectures, as well as characterization of innovative materials for advanced electrochemical power sources. He is a co-founder of the startup companies Chemtronics, EnStorage and Honeycomb.

Prof. Yoram Cohen graduated (Summa Cum Laude, 1987) from the Hebrew University, was a Fulbright postdoc at UCSF and joined Tel Aviv University in 1992. He established the experimental MRI unit of Tel Aviv University, served as Head of the Strauss Center for Computational Neuro-Imaging and was Head of the School of Chemistry. His research ranges from supramolecular chemistry in solution and molecular capsules to the applications of advanced MRI techniques for studying structure and pathologies in the central nervous system with special emphasis on diffusion NMR and MRI. He received the Pulver Award, the Gerhard MJ Schmidt Award, the Juludan Award, the Brown Roger-Ziguel Award, the Josefa and Leonid Olschwang Award and was nominated Fellow of the International Society of Magnetic Resonance in Medicine. He holds the Joshua Jortner Chair in Chemistry.

In their response both Emauel Peled and Yoram Cohen commented that they were very honored to get this highly prestigious prize and thanked the ICS, their many good students and family. Cohen mentioned that he is grateful to his teachers from the Hebrew University, Tel Aviv University, as well as the organizers, particularly Micha Fridman, Amir Goldbourt, and Keinan for the non-trivial service in the ICS over so many years.

The 2015 ICS Excellent Young Scientist Prize was jointly awarded to two laureates. Prof. Gil Alexandrowicz of the Technion received the prize for his work on the use of magnetically manipulated atomic and molecular beams for study of surface structure and dynamics, which elegantly combines the diverse fields of molecular beams, spin chemistry and surface science. Dr. Rafal Klajn of the Weizmann Institute of Science received the prize for his original contributions to stimuli-responsive nanomaterials and chemistry in confined spaces.

Gil Alexandrowicz (born 1973, Israel), BSc and MSc in Physics from the Hebrew University and PhD from the University of Cambridge, UK (2005, with John Ellis). He joined the Technion in 2008 after 3 years of postdoc work in Cambridge. He focuses on a unique helium-spin-echo apparatus, capable of measuring structure and ultra-fast (10-12 sec) dynamics on the atomic scale. This combination of length and time scales is completely inaccessible using conventional technology. He succeeded in measuring the structure of water molecules on metallic surfaces, the motion of CO molecules on a copper surface, ultra-high-resolution measurements of surface phonons and the effect atomic steps have on the correlated diffusion of sodium atoms on a copper surface. In addition, he developed numerical approaches for data interpretation. Another research effort was initiated when he magnetically focused a molecular beam of water and separated, for the first time, ortho and para water (Science 2011). He then demonstrated the high purity of his source and the ability to store the ortho-water. One exciting application of his orthowater beam is the development of a unique apparatus capable of performing NMR measurements of a single surface layer of water. His ERC project revolutionizes the NMR measurements of surfaces.

Alexandrowicz responded by thanking his family and many students and postdocs, and the ICS. He admitted that this is great honor for him considering those outstanding Israeli scientists, who received this prize in the past.

Rafal Klajn (born 1982, Poland) received his BSc and MSc in Chemistry from the University of Warsaw (2004, Summa Cum Laude) and PhD from Northwestern University (2009, with Bartosz A. Grzybowski). Since joining the Weizmann Institute he focused on developing new dynamically selfassembling materials, and investigating chemical reactivities inside synthetic confined environments. These efforts are inspired by the concept that in the course of evolution, Nature has evolved dynamically self-assembling materials that perform functions essential to life, and macromolecular machineries capable of carrying out chemical reactions with unprecedented rates, yields, and selectivities. Rafal's group approaches dynamic materials on the basis of stimuliresponsive nanoparticles: they showed, for example, that magnetic nanocrystals could be assembled into previously unknown helical superstructures, and that self-assembly of nanoparticles decorated with monolayers of photoresponsive molecules could be directed with light of specific colors. In the course of these studies, the group showed that when their nanoparticles assembled, they could efficiently trap various molecules from the surrounding solution. This finding has opened the way to investigate chemical reactivities in confined spaces under out-of-equilibrium conditions (Science, Nature Chemistry, Small, Nature Nanotech, Nature Commun., JACS and Angew. Chem.).

Klajn responded by thanking the ICS and President Keinan. "I would like to make some personal comments. I am very honored by being elected for this prize and I wish to thank my colleagues at the WIS for believing in me. This is not trivial because I received my PhD from Northwestern University only six years ago and I have never lived in Israel before then. Nobody in Israel knew me at that time and despite this fact they took a major risk by offering me a faculty position. Today, I am very happy to take part in this amazing event and be part of the vibrant scientific community of Israel. Finally, I would like to thank my wife Alexandra without whom nothing would be possible."

Closing Ceremony

The ICS Prize for an Excellent Posters where awarded to Alina Khersonsky (with Doron Pappo) of Ben-Gurion University for Poster 36: "Synthesis of polyarenes by sequential oxidative cross-coupling of phenols with arenes," Amir Hevroni (with Gil Markovich) of Tel Aviv University for Poster 53: vt-stm studies of superparamagnetism and the verwey transition in magnetite nanocrystals;" Shimrit Ohayon (with Ashraf Brik) of the Technion for Poster 23: "Assay development and inhibition of deubiquitinases;" Tamar Yelin (with Richard Korytar, Nirit Sukenik, Ran Vardimon, Bharat Kumar, Colin Nuckolls, Ferdinand Evers and Oren Tal) of the Weizmann Institute of Science for Poster 97: "The upper limit of conductance across a single molecule." The awards were presented to the four posters by Keinan and Dani Shahar of Bioanalytics, the awards sponsor (Figure 5).

Keinan announced that the 82nd Annual Meeting of the Israel Chemical Society will be held in February 2017 in Tel Aviv under the theme "The Next 50 Years". The event will be jointly organized by four entities: The Israel Chemical Society (ICS), The Gesellschaft Deutscher Chemiker (German Chemical Society, GDCh), Angewandte Chemie and the Israel Journal of Chemistry (IJC). The cluster of events will include the ICS Meeting and the 6th Angewandte Chemie Symposium. The past Angewandte Symposia took place in Japan (2011), China (2011), Korea (2012), Germany (2013) and the 5th symposium will be held in India (2016).

The GDCh and Angewandte Chemie will join the ICS annual meeting with delegations of German and international speakers reinforced by representatives of the GDCh and Wiley-VCH, as well as the Ambassador of Germany to Israel. This joint conference will celebrate several events, including 50 years of diplomatic relations between Israel and Germany and 150th anniversary of DChG, the predecessor organization of GDCh.

Reference

1. For a full version of this report, see

http://onlinelibrary.wiley.com/doi/10.1002/ijch.201610100/abstract?campaign=woletoc

The 2016 Mountain-to-Valley Relay Race (M2V) May 19-20, 2016

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The Mountain-to-Valley relay race (M2V) is the first of its kind in Israel and, this month, it took place for the 8th consecutive year. The M2V Association, a non-profit organization, whose goal is to encourage long-distance running and the connection to nature and the environment, organizes the race. The organizers, mainly residents of Timrat, were inspired by a similar race in the USA. The race is held annually, on the first full moon after Passover, along the spectacular views of Northern Israel. The long route of nearly 220 Km begins at Tel Hai and continues along the vistas of the Hula Valley, the Jordan River, Sea of Galilee, Beit Netofa Valley, much of Jezreel Valley, finishing in Timrat.

The route is divided into 24 segments, each about 6-13 Km long on heterogeneous terrain, mostly mountainous dirt roads. The 1st segment goes from Tel Hai to Dagi Dafna, 2nd to the Shamir Reservoir, 3rd to Lehavot Habashan, 4th to Notera, 5th to the Pkak Bridge, 6th to the Benot Ya'aqov Bridge, 7th to Karkom, 8th to Kfar Nahum, 9th to the Sapir Site, 10th to the Tzalmon Prison, 11th to Eilabun, 12th to Arabe-Avtalion, 13th to Hosheaya, 14th to Shimshit, 15th to the Zarzir Junction, 16th to the railroad station of Kfar Yehoshua, 19th to Ramat Hashofet, 20th to Hazorea, 21st to Kishon, 22nd to Gevat, 23rd to Kfar HaHoresh, and 24th to the finishing line below the village of Timrat at the nature reserve of the beautiful African tree Faidherbia albida (in Hebrew: Shitta Malbina).

Most of the teams include 8 runners who rotate among themselves, but there are also smaller teams of 6, 4, 2, and even a few "ultra-runners" who complete the entire route alone (the equivalent of 5 marathons!). More than 1000 teams participated, totaling approximately 8,000 runners, including employees of Israeli companies, governmental agencies, nonprofit organizations, guests from abroad and other groups.

Each 8-runner team was split into two independent quartets, each using their own car. Thus, while one team member was running along his/her segment, the other three drove to the next exchange station and waited there for the runner. After exchanging with a fresh runner they moved with their car to the next station (usually using the Waze application) until they



Figure 1. Collage of photos taken throughout the M2V race.

completed the first 4 segments. At that point the other quartet started their 4 segments and the first quartet could take a rest for about 4 hours.

The responsibility of the race organizers covered not only the starting and finishing points, but also the exchange stations, readily available medical teams and other necessary aid to runners, as well as marking the route with clear signs that were visible day and night. The running teams were responsible for their transport between the exchange stations as well as their food, other supplies and compulsory equipment, such as water, a head flashlight, a light reflecting vest and a red flashing light on back for the night runs. In addition to the team number, each runner carried the race bracelet on the wrist and passed it to the next runner at the exchange stations. The exchange event and the exact timing were recorded electronically at each station.

The relay race could not take place without the wonderful support provided by the hundreds of volunteers, many of them from the community of Timrat and other neighboring villages. In each of the 24 stations there were several volunteers who registered the incoming and outgoing runners and assisted with the wide range of logistics, providing the runners with snacks, dried fruit and drinking water and even took care of some minor injuries. Ms. Liraz Maanit, the ICS Project Manager, who resides with her family in Kibbutz Hazorea had reserved in advance three fully furnished rooms in the Kibbutz, and even provided plentiful fruits and snacks, so that all runners could enjoy a refreshing resting site for part of the night. The collage of photos (Figure 1), mostly taken by cellular phones by the runners gives a general impression of the M2V experience.

The ICS running teams

This is the 6th time that ICS teams have participated in the race. This year, two teams of 8 runners each, represented the ICS (Figure 2). The teams consisted of graduate students, industrial chemists and faculty members at academic institutions, and every runner completed about 28 Km. Although both teams elected the non-competitive option, they completed the route in good timing of approximately 23 hours, running at an average speed of 10Km/h. Prof. Alex M. Szpilman was the Team Captain of ICS 1 and Prof. Gerardo Byk was Team Captain of ICS 2.

Israel Chemical Society 1 included 8 runners: Prof. Alex M. Szpilman, a native of Denmark, who received his MSc degree from the Technical University of Denmark and PhD from the Weizmann Institute of Science under Prof. Mario D. Bachi. He was a Carlsberg Postdoctoral Fellow at the ETH Zürich with Prof. Erick M. Carreira before starting his independent academic career at the Technion. He has recently moved to the Department of Chemical Sciences at Ariel University. His research focuses on the design of new reactions and catalysts for organic synthesis, as well as the study of biologically active natural products. Alex has organized the ICS running teams for the M2V races continuously since 2010. In addition to long distance running on beautiful countryside trails, his other hobbies include cooking, playing musical instruments, listening to music and spending time with his family.

Dr. Leora Shapiro has recently completed her PhD at the Hebrew University of Jerusalem under Prof. David Avnir. Her research focused on the entrapment of catalysts within catalytic metals by reducing metal ions in the presence of catalysts in an aqueous solution. Her MSc degree under Prof. Daniel Mandler focused on thin films for selective electrodes. She has also worked at Sol-Gel Technologies Ltd., developing silica-based encapsulation for drug delivery systems. Besides chemistry, running is her great passion. She routinely runs with her group "Mishehu Larutz Ito" (someone to run with) at least twice a week. Earlier this year she participated in the Jerusalem Marathon. This is her third time representing the ICS in the M2V race.

Hai Haham is a PhD student under Prof. Shlomo Margel at the Institute of Nanotechnology and Advanced Materials of Bar-Ilan University. His research focuses on the synthesis and characterization of functional iron-containing magnetic nano-particles of narrow size distribution, for environmental remediation applications. His goal is to develop nano-toolkit technologies with which to address water contamination problems, which may find industrial applications.

Niv Yardeny received his BSc and MSc from Ben Gurion University under Prof. Daniel Kost, focusing on hypercoordinated silicon complexes. Currently, he is a project manager of "On Target Chemistry", based in Ness-Ziona, which provides organic synthesis and analytical services. In the past Niv was attracted to various sports, specializing in judo. He has been a member of the ICS teams in the M2V races for the past 6 years. Niv (33) resides in Rehovot with wife Smadar and daughter Noga.

Arthur Shapiro has completed his BSc at the Technion and is currently a direct-track PhD student in physical chemistry under Prof. Efrat Lifshitz at the Technion. His research focuses on quantum dots of the IV-VI family, including PbSe and PbSe/PbS, their preparation and characterization, aiming at assembling them for field effect transistors. Sport has always been an integral part of his life and this is the third time for him with the M2V race.

Ariel Abrahamov was a field salesperson before moving to the field of international freight forwarding. He enjoys various types of sport, particularly Shotokan karate (black belt degree, 1st Dan), trail running and tennis. Ariel (38) lives in Kiryat Motzkin with his family, including daughter (10) and son (6).



Figure 2. The two teams at the Finish zone. ICS 1 (left photo), from left: Leora Shapiro, Alex M. Szpilman, Hai Haham, Niv Yardeni, Arthur Shapiro, Ariel Abramov, Rami Zhelinger and Yaniv Bouhadana. ICS 2 (right photo), from left: Ehud Keinan, Deepak Kumar Khajuria, Raz Jelinek, Gerardo Byk, Roni Peretz, Priel Levy, Olga Chovnik and Marco Bugnola.

Rami Zhelinger is a member of Kibbutz Yagur and an entrepreneur. He holds a BSc degree in physics from Ben-Gurion University and an MSc in electrical engineering and electronics from Tel Aviv University. He has served as Chairman of Balagan Ltd. and Free Time Ltd. He founded and managed several startup companies, including Just Ask Ltd.

Dr. Yaniv Bouhadana received his PhD degree in 2011 from Bar-Ilan University, majoring in water desalination using electrochemical means and later was a postdoctoral fellow at the Bar-Ilan Institute of Nanotechnology & Advanced Materials (BINA) for 5 years. He received his MSc degree with distinction (cum laude) in 2007 from Bar-Ilan University, majoring in materials science and nanotechnology.

During his undergraduate studies and before he gained experience with the hi-tech industry, working for Orziv Ltd. (Tami 4, Nilimendix, Ionmed, Polgen etc. and the Military Industries). Currently he is a senior software developer at SwitchBee Ltd.

Israel Chemical Society 2 included 8 runners: **Prof. Gerardo Byk**, member of the Laboratory of Nano-Biotechnology, Department of Chemistry at Bar-Ilan University since 1998. His laboratory focuses on the design, synthesis and applications of biocompatible polymeric nanoparticles for cell tracking, drug delivery and in vivo imaging. His group also develops novel multicomponent reactions (MCRs), aiming at obtaining in one pot, analogs of complex natural bioactive molecules for biologically activity optimization. He has participated in the ICS teams for the M2V races since 2011. Prof. Ehud Keinan of the Schulich Faculty of Chemistry, Technion, received his PhD from the Weizmann Institute and was a postdoc at the University of Wisconsin. His research interests include biocatalysis with antibodies and synthetic enzymes, organic synthesis, molecular-computing, supra-molecular chemistry, improvised explosives and drug discovery. He was Dean of the Schulich Faculty of Chemistry, an Adjunct Professor at The Scripps Research Institute, founder and first Head of the Institute of Catalysis at the Technion and founder of two startup companies. Since 2009 he is President of the Israel Chemical Society, Editorin-Chief of the Israel Journal of Chemistry, member of the IUPAC Bureau, Council member of the Wolf Foundation, and Chairman of the Advisory Council of High School Chemistry Education. Since 2015 he is the Pro-Vice Chancellor and Dean of Sciences of Technion-Guangdong. In 2010 he initiated the long tradition of active participation of ICS teams in the M2V races.

Roni Peretz received his BSc degree in materials science and chemistry from the Technion. He is a program manager in XwinSys, a start-up company of about 15 employees, which builds machines for quality control in the semiconductor industry using both optical and X-ray technologies. He has been a member of the ICS teams for the M2V races for the past 3 years.

Marco Bugnola is an Italian citizen, did his BSc and MSc in Padova under Dr. Marcella Bonchio, focusing on photocatalysts for CO2 reduction. In 2014 he started his PhD research at the Weizmann Institute under Prof. Ronny Neumann, focusing on polyoxometalates and their oxidation reactions. In 2015, he represented the Weizmann Institute in the first Israeli academic rowing competition against Tel-Aviv University, and this is his second time in the M2V race.

Olga Chovnik has completed her BSc in molecular biochemistry at the Technion before moving to the Weizmann Institute. Her MSc research under Dr. Rafal Klajn focused on photoswitchable nanoparticles as a model system to crystallization process. Since 2014 she is a PhD student under Prof. Milko van der Boom, focusing on halogen-bond-based 3D networks. Olga enjoys various sports, she represented the Weizmann Institute in the 2015 rowing competition against Tel-Aviv University, and this is her second year with the ICS runners in the M2V race.

Prof. Raz Jelinek holds the Carole and Barry Kaye Chair in Applied Science at the Department of Chemistry of Ben-Gurion University. Raz received his BSc from the Hebrew University and PhD from the University of California at Berkeley. In 1996 he joined the Department of Chemistry at Ben-Gurion University. His diverse research program includes "bottom-up" chemistry, bio- and chemo-sensors, amyloid peptides, membranes, and carbon nanoparticles. Raz is an avid runner and hiker, who has already participated 3 times in the M2V race, and hiked half of "shvil Israel."

Dr. Deepak Kumar Khajuria completed his PhD in pharmacology in 2014 in Rajiv Gandhi University of Health Sciences at Bangalore, India, focusing on the development and screening of novel drug formulations and combinations for postmenopausal and immobilization osteoporosis in animal models. His postdoctoral research at the Indian Institute of Science (IISc) at Bangalore focused on lab-on-chip (3D microfluidic devices) for bone tissue engineering and drug screening applications. In Dec 2015, he joined the research group of Prof. Shlomo Margel and Prof. David Karasik at the Musculoskeletal Aging Lab at Bar-Ilan University, focusing on the development of nanoparticle-based therapeutic interventions, which is directed against the musculoskeletal degenerative diseases such as osteoporosis, osteoarthritis and sarcopenia.

Priel Levy has recently completed his MSc degree in computer science at Bar-Ilan University. This is the third year he has enjoyed the M2V race with the ICS.

The Rotal Group sponsored the ICS teams for the second time, covering much of the registration fees and the beautiful

athletic shirts, which displayed the ICS logo and the phrase "Chemistry is everything". The Rotal Group is a family business, established in 1963 by Bernhard Rosenthal, a descendent of a long line of German industrialists. Since 2003, the business has been managed by Meir Tal (Rosenthal). The Rotal Group consists of three companies: Rotal Industries and Trading, Rotal Adhesives and Chemicals, and Lachman Ltd. Their client base consists of the majority of sophisticated industrial companies in Israel to whom they supply industrial adhesives, electronic adhesives, special lubricants, metal work liquids, soot reduction additives, environmentally friendly cleaning products, dispensing equipment, and control and measurement equipment.

Why we do it?

Many people fail to understand the motivation of intelligent, civilized and sane people to spend a full day and night with little sleep, sweating over dusty dirt roads and hostile insects under a blazing heat of a typical May day and a cold night, conditions that remind many of their mandatory military service. Those who have repeatedly participated in the M2V race would describe it as unique, very intense experience. It is certainly intense on the personal level, where "The Loneliness of the Long Distance Runner" is not just a book or a movie. It is a personal, several hour experience of every runner who needs to constantly balance their capabilities against the changing demands of the route, temperatures, humidity and terrain. It is a continuous decision making process on how far can one push one's heart, lungs and muscles without taking too much risk.

It is also an intense group experience and group dynamics within a small group of people of diverse backgrounds, spending many hours together, sharing life experience, personal stories and anecdotes, developing friendships and enjoying time together. Beyond the physical effort, every group shares the magnificent countryside scenery of northern Israel, which is so diverse and keeps changing dramatically under daylight and moonlight. The team members, regardless of their age and personal background, get to know one another, share exceptional memories, amusement, companionship and the challenging group effort. Therefore, it is not surprising that those who had a chance to experience the M2V race, even once, come back every year, almost religiously, driven by unforgettable memories. It is not surprising that every year in January, within merely two hours of opening electronic registration, about 10,000 runners register fanatically, to make sure they don't miss the next M2V race.





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