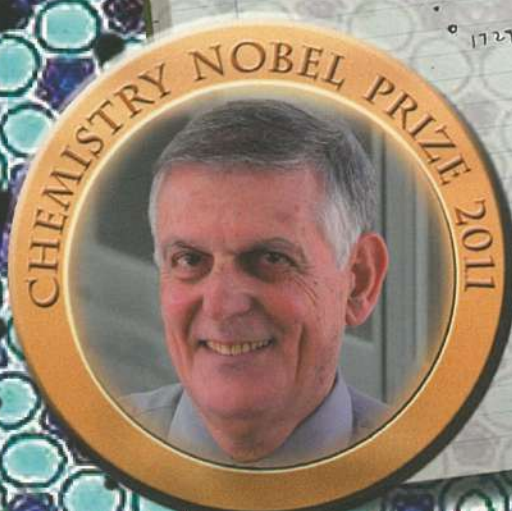




# CHEMISTRY IN ISRAEL

Bulletin of the Israel Chemical Society

www.chemistry.org.il | No. 26 | February 2012

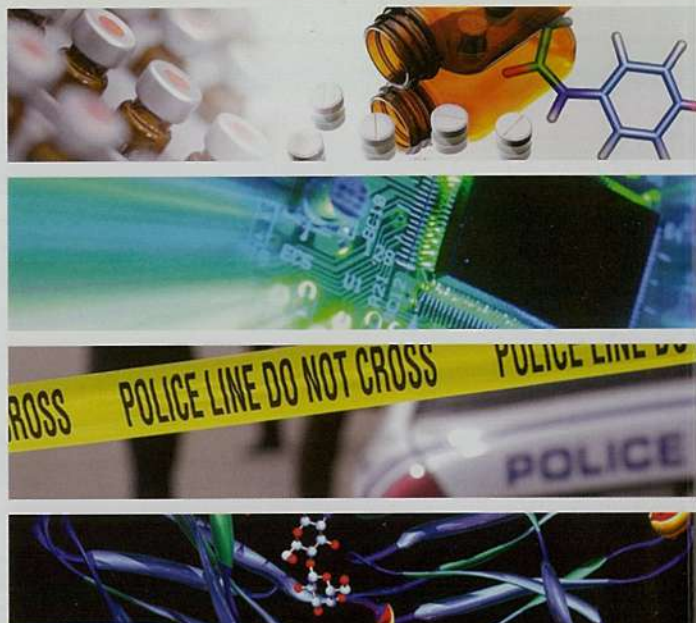


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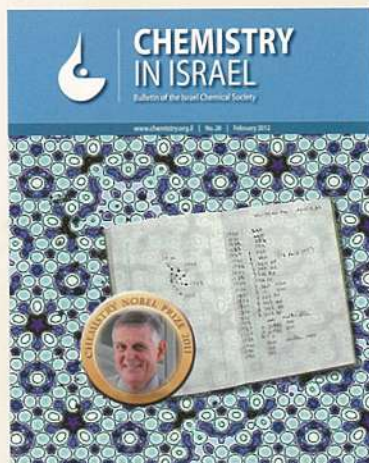


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**Cover:** The cover illustration celebrates the 2011 Chemistry Nobel Prize awarded to Professor Dan Shechtman of the Technion – Israel Institute of Technology. The cover shows Shechtman's lab notebook, documenting his discovery of quasicrystals while examining rapidly quenched Al-Mn alloys with TEM. The left-hand page shows his sketch of part of the 10-fold diffraction pattern, with labels of diffraction spots used for dark field TEM plates listed on the right. Photos courtesy of the Ames Laboratory, which is operated by Iowa State University. The background illustrates an atomic model of an aluminium-palladium-manganese (Al-Pd-Mn) quasicrystal surface (B. Unal et al. *Phys. Rev. B*, 2007, 75, 064205).

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## TABLE OF CONTENTS

### Editorial

- 5 Letter from the president**  
Prof. Ehud Keinan, President of the Israel Chemical Society
- 7 Letter from the editor**  
Prof. Matityahu Fridkin, Editor-in-chief

### In Memoriam

- 8 Prof. Israel Dostrovsky**

### Invited Scientific Contributions

- 10 Forging the Missing Link between Molecular Chirality and Crystal Morphology following Pasteur's Famous Experiment**  
Meir Lahav and Leslie Leiserowitz
- 24 Molecular Self-Assembly of Small Aromatic Peptides: A New Frontier in Organic Nanotechnology**  
Ehud Gazit

### Report on Meetings

- 32 The Israel Chemical Society celebrates the International Year of Chemistry**  
Ehud Keinan and Yael Schuster
- 46 The 76<sup>th</sup> Annual Meeting of the Israel Chemical Society**  
Ehud Keinan
- 55 The 77th Annual Meeting of the Israel Chemical Society**
- 56 The ICS Prizes for 2010**
- 58 The 9th meeting of the Section of Medicinal Chemistry of the Israel Chemical Society**  
Ora Schueler-Furman, David Stepensky, Arie Gruzman

### From the Archives

- 64 Gertrude B. Elion and the Design of Selective Chemotherapeutic Agents**  
Bob Weintraub



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# 268

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# Letter from the president

**Prof. Ehud Keinan**

President of the Israel Chemical Society

## Dear Colleague,

The year of 2011 was an exciting year for all of us, marked by an avalanche of events related to the international Year of chemistry (IYC2011). Some of these events, including the opening ceremony of the IYC2011 in the Knesset, the issuing of two Israeli stamps that commemorated the IYC2011 and the Chemistry Nobel Prizes awarded to Israeli scientists, and the M2V relay race, are covered by a detailed report in this issue. For ICS members there could not be a happier way to conclude the Year of Chemistry than receiving the great news from Stockholm that the 2011 Chemistry Nobel Prize was awarded to Prof. Dan Shechtman.

It has been already two years since the *Israel Journal of Chemistry* joined the prestigious publishing house of Wiley-VCH and became the official journal of the ICS. I am proud to serve as Editor-in-Chief of this journal and follow with much satisfaction its ever-increasing popularity and worldwide visibility with 12 issues published every year. The Journal concluded the Year of Chemistry by a special issue on quasicrystals, dedicated to the topic of the Nobel Prize.

The main event of the IYC2011 in Israel was the "Chemistry Week" (7-10 February, 2011), which included the ICS 76th Annual Meeting, the 14th Conference of the Israel Analytical Chemical Society, and a huge exhibition of equipment and scientific instrumentation. It was a very large scientific event with about 3000 participants. The 76th Meeting, which is also covered separately in this issue, was organized by Bar Ilan University with Professor Jean-Paul (Moshe) Lellouche as Chairman. Following our long tradition we've hosted in this meeting delegation of world-renowned scientists from Academia Sinica of Taiwan.

In addition, we held three international conferences: the Schulich Conference on "Chemical synthesis of peptides and proteins" was organized by me at the Technion in March 13, 2011; An international conference on "Frontiers in Chemistry", honoring the three 2011 Chemistry Wolf Prize Laureates, was also organized by me at the Technion in May 30, 2011; and the Israel-Italy binational conference on "Frontiers in Organic Chemistry" was organized by Prof. Arkadi Vigalok of Tel Aviv University in December 13-14, 2011 at the Dan Panorama hotel in Tel Aviv, representing the growing cooperation between the ICS and the Italian Chemical Society. Among other events, we had several other scientific conferences around the country, popular lectures to the public, the "Researchers' Night" at the Museum of Science, and a public experiment, which was registered in the Guinness Book of Records.

Our international activities are expanding with significant growth of representation in EuCheMS. Prof. Ilan Marek of the Technion was elected to serve as President of the EuCheMS Organic Division and I was elected to serve as a member of the EuCheMS Executive Board.

Following the recent elections to the ICS bodies, I wish to thank you for your trust in me and in all members of our Executive Board. I thank the three members who have completed the job, Mr. Yashar Ben Mordechai Dr. Levi Gottlieb and Dr. Nitza Barnea, and welcome the new members, Mr. Malachy Alper, Prof. Avi Domb and Dr. Dorit Teitelbaum. Finally, I wish to thank Prof. Mati Fridkin and Ms. Hanna Attali for a fine job in continuously upgrading the international stature of *Chemistry in Israel*. I thank the authors who have contributed articles to this issue and I encourage all of you to contribute future articles to this journal.

**Ehud Keinan, President**





# האקדמיה של ברגל

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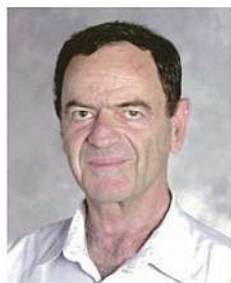
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## Letter from the editor

**Prof. Matityahu Fridkin**  
Editor-in-chief

In the last issue of *Chemistry in Israel* we congratulated Prof. Ada Yonath, Laureate of the 2009 Nobel Prize in Chemistry. Now we extend our heartiest and warmest congratulations to Prof. Dan Shechtman of the Department of Materials Engineering of the Technion, who recently won the 2011 Nobel Prize in Chemistry. The Prize was awarded for his outstanding discovery of the quasi-periodical crystals. As explained by the Nobel Prize committee, "The Shechtman's findings fundamentally changed the way in which we think about the structure of the materials that surround us." The Nobel recognition of Shechtman's achievements was a great day for the State of Israel, for the Technion, and for the entire chemical community in Israel, YISHAR KOACH!!

Prof. Israel Dostrovsky, one of the foremost Israeli scientists, one of the founders of the Weizmann Institute of Science and its fifth president, passed away. In his memoriam a press release of the Weizmann Institute is provided herein.

Profs. Meir Lahav and Leslie Leiserowitz, winners of the 2010 ICS Medal, summarize here their studies on crystal growth involving oriented nucleation "Forging the missing link between molecular chirality and crystal morphology following Pasteur's famous experiment".

Prof. Ehud Gazit of Tel Aviv University has contributed much to our understanding of how nano-scale well-ordered structures are formed, a central theme in nano-science and nano-technology. He summarizes here these investigations in his article "Molecular self-assembly of small aromatic peptides: a new frontiers in organic nanotechnology".

The highlights of the 76<sup>th</sup> ICS meeting, held in February 7-8, as part of the Chemistry Week at the David Intercontinental Hotel in Tel-Aviv, are outlined by Prof. Ehud Keinan and Dr. Yael Schuster of the Technion.

Drs. Ora Schuster, David Stepansky and Arie Gruzman report on the 9th meeting of the Medicinal Chemistry Section of the ICS, held in March 8th, 2011 in the Weizmann Institute of Science.

Finally, Dr. Bob Weintraub, Director of the Libraries at the Sami Shamoon College of Engineering, tells a fascinating story of Gertrud B. Elion, Laureate of the 1988 Nobel Prize in Physiology and Medicine, on the design of selective chemotherapeutic agents.

On behalf of the Editorial Board I would like to thank Prof. Ehud Keinan for his support and encouragement in the various stages of production of the current issue. Special thanks go to all authors of this issue and those who will contribute to the future issues of this important bulletin.





## **Prof. Israel Dostrovsky** 1918 – 2010

**Prof. Israel  
Dostrovsky, One of  
Israel's Foremost  
Scientists, Among  
the Founders of the  
Weizmann Institute  
of Science and the  
Fifth President of  
the Institute, Passes  
Away at Age 92**



Prof. Israel Dostrovsky was born in Odessa, the former USSR, in 1918 and arrived in Eretz-Israel in 1919. After attending primary and secondary school in Jerusalem, he went to study in England and received a B.Sc. in chemistry in 1940 and a Ph.D. in physical chemistry in 1943, both from University College, London. After working as a lecturer in chemistry at University College, he joined the Weizmann Institute in 1948, shortly before the Institute's dedication. Immediately upon joining the staff of Weizmann, he was appointed Head of the Isotope Research Department, a position he held for 17 years. Between 1971 and 1975 he served as the Institute's Vice President and President, and in 1975 he was named Institute Professor, a prestigious title awarded by Weizmann faculty and administration to outstanding scientists who made significant and meaningful contributions to science or to the State of Israel. Between 1980 and 1990, he served as Director of the Center for Energy Research at the Institute. When he turned 80, the Israel Academy of Sciences and Humanities held a special scientific conference in Jerusalem and at Weizmann to honor the occasion.

Prof. Dostrovsky's government appointments included Director of Research at the Israel Atomic Energy Commission, 1953-1957; Chairman of the National Council for Research and Development, 1959-1961; Director-General of the Israel Atomic Energy Commission, 1965-1971; and Chairman of Israel's Desalination Committee, 1966-1981. Between 1973 and 1981 he served as a member of the Scientific Advisory Committee of the United Nations' International Atomic Energy Agency in Vienna, and between 1991 and 1993 he was a member of the Executive Committee of the International Energy Agency's SolarPACES project.

Prof. Dostrovsky belonged to several professional societies: Israel Chemical Society, Israel Physical Society, American Chemical Society, American Physical Society and Royal Chemical Society of Great Britain. He was a member of the Israel Academy of Sciences and Humanities and an honorary life member of the New York Academy of Science. He received the Ramsey Medal and Prize, 1943; Tel Aviv's Weizmann Prize, 1952; honorary doctorates from Tel Aviv University, 1973, and the Technion-Israel Institute of Technology, 1994; and the Israel Prize, 1995.

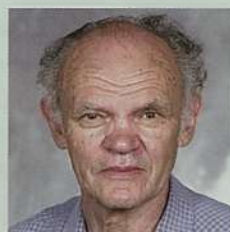


# Forging the Missing Link between Molecular Chirality and Crystal Morphology following Pasteur's Famous Experiment

**Meir Lahav and Leslie Leiserowitz**



**Meir Lahav** did his M.Sc. studies at the Hebrew University of Jerusalem and Ph.D. studies at the Weizmann Institute of Science with G. M. J. Schmidt in the field of solid-state chemistry. After two years at Harvard with P. D. Bartlett, he returned to the Weizmann Institute in 1971. His fields of interest include solid-state chemistry, surface chemistry, stereochemical studies of crystal nucleation and crystal growth, and the origin of homochirality on Earth. In 2006, he was awarded the Chirality Medal established by the Italian Chemical Society.



**Leslie Leiserowitz** obtained his M.Sc. degree at the University of Cape Town and a Ph.D. in chemical crystallography with G. M. J. Schmidt at the Weizmann Institute of Science. After a one-year Post Doc at the University of Heidelberg, he returned to the WIS in 1968. His fields of interest include molecular interactions, crystal growth and nucleation, grazing incidence X-ray diffraction, and studies on malaria.

Meir Lahav and Leslie Leiserowitz share the Prelog Medal of Stereochemistry 1987, The prize of the Israel Chemical Society in 1999, the Aminoff Prize of the Swedish Academy of Science 2002, and the Medal of the Israel Chemical Society 2009. They are members of Leopoldina Nationale Akademie der Wissenschaften.



## Forging the Missing Link between Molecular Chirality and Crystal Morphology following Pasteur's Famous Experiment

Meir Lahav and Leslie Leiserowitz

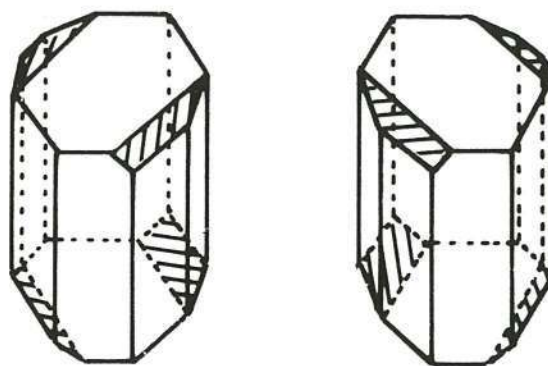
At the opening ceremony of the 75<sup>th</sup> Israel Chemical Society meeting we were awarded the 2009 ICS medal. We thank the ICS for bestowing this prestigious honor upon us, which made us cast our minds on the debt we owe to the people with whom we had worked over the years, as acknowledged at the end of this article.

The work described here is the fruit of intense and exciting effort, clearly revealing that we stood on the shoulders of scientists well before our time. Indeed, our starting point is the classic experiment by Pasteur on the separation of enantiomorphous crystals of a tartaric acid salt. Pasteur was at home both in the disciplines of chemistry and crystallography. In this respect, we (ML & LL) had taken advantage of differences in our academic background. ML in chemistry, and LL in X-ray crystallography. We both did our PhD studies in the Dept. of X-ray crystallography under the stimulating supervision of the late Professor Gerhard Schmidt in solid-state chemistry, ML on topochemistry of polymerization reactions and LL in crystal thermochromism. Following our post doctoral studies, and return to the WIS (Dept of Structural Chemistry), ML engaged on a project of 'absolute' asymmetric synthesis in crystals, which was essentially virgin territory at the time and LL started working on packing modes in crystals, with a focus H-bonding systems, in particular validating weak C-H...X H-bonds and O...O electron lone pair repulsions. In the 1970's we joined forces and initiated a project on mapping the reaction coordinates *in-situ* in host-guest complexes, by combined chemical and crystallographic methods. Following this study, an original stereochemical approach was initiated involving the control of nucleation, growth, dissolution, polymorphism and structure of molecular crystals both in solution and at the air-water interface, with the aid of "tailor-made" auxiliaries. The auxiliaries were of two types; additives with a structure akin to that of the host molecule to be crystallized, which acted as inhibitors of crystal nucleation and growth in solution. These studies resulted, amongst others, in a general revision in the structures of mixed crystals, following a discovery that racemic  $\alpha$ -amino acids undergo separation into enantiomers within the centro-symmetric crystals

of glycine. The second type of auxiliary comprised crystalline monolayers of long-chain amphiphiles, which acted as nucleators of three-dimensional crystals at the air-water interface by virtue of epitaxy. Following these studies we determined, at near atomic resolution, the two-dimensional structure of clusters which served as crystal nucleators. Here we were among the pioneers in applying grazing incidence X-ray diffraction using synchrotron light. This approach provided general insight on the early events of crystal nucleation at the molecular level, in particular the freezing of super-cooled water. More recently ML has engaged on studies relating to the Origin of Homochirality on Earth, and LL has been engaged on work in the field of Malaria.

## Introduction

The manual separation of the enantiomorphous crystals of sodium ammonium tartrate tetrahydrate (Fig. 1) by Pasteur in 1848<sup>1</sup> laid the foundations of modern stereochemistry. The experiment demonstrated that certain classes of molecules display enantiomorphism even when dissolved in solvent. The success of his findings depended on two central but not commonly encountered properties of racemates, spontaneous resolution into enantiomorphous crystals and the expression of hemihedral faces that make such crystals



**Figure 1.** Enantiomorphous crystals of sodium ammonium tartrate.4H<sub>2</sub>O.



non superimposable to one another. The observations by Pasteur paved the way for the inspired suggestion, about 20 years later, by van't Hoff<sup>2</sup> and by Le Bel<sup>3</sup> of a tetrahedral arrangement of bonds around the carbon atom.

The above findings raised two fundamental questions: the absolute configuration of chiral molecules, and how a molecule of a given configuration shapes the enantiomorphous morphology of the crystal. In the absence of such knowledge, Fischer<sup>4</sup> and Rosanoff<sup>5</sup> introduced, at the turn of the 19<sup>th</sup> Century, an arbitrary convention for the absolute configurations of the L and D forms of glyceraldehyde and alanine, via which the configurations of other molecules such as sugars and peptides were correlated by chemical degradation.

The introduction of X-ray diffraction of crystals in 1912 paved the way for the determination of crystal structure at the atomic level. However the X-ray diffraction data from a crystal composed of chiral molecules of single handedness, cannot yield the absolute configuration of the constituent molecules, when there is no effect of anomalous X-ray dispersion. Under such conditions the crystal structure and its mirror image will yield the same X-ray diffraction intensity pattern, as a consequence of Friedel's law, which states that the X-ray diffraction intensities from opposite sides of a set of  $h,k,l$  crystal planes,  $F(h,k,l)^2 = F(\bar{h},\bar{k},\bar{l})^2$ .

In 1951, Bijvoet et al. assigned the absolute configuration of (+)-tartaric acid by applying the method of anomalous scattering of X-rays to the chiral crystals of sodium rubidium tartrate.<sup>6</sup> This method was first introduced by Nishikawa and Matsukawa<sup>7</sup> in 1928 and independently by Coster, Knol and Prins<sup>8</sup> in 1930 for determining the sense of polarity of ZnS crystals.

Although crystal structures could be determined and it was already possible to assign the absolute configuration of chiral crystals, the perplexing link between molecular chirality and the morphology of chiral crystals, was still to be forged. The asymmetric morphology expressed by hemihedral ( $h,k,l$ ) and ( $\bar{h},\bar{k},\bar{l}$ ) faces, which are not related by crystal symmetry, manifests itself in their different rates of growth. This phenomenon involves a complex interplay between the contributions of the internal crystal structure and of the solution-surface interactions to facial growth rate.

An attempt to assign the absolute configuration of resolved tartaric acid by comparing the relative ease of binding of an oncoming tartaric acid molecule to

opposite hemihedral faces, was reported by Waser<sup>9</sup> in 1949. He took into account only intermolecular distances between the crystal and the to-be-attached molecule. Waser ignored, however, the determining role played by solvent in the growth of the two faces, as pointed out by Turner and Lonsdale.<sup>10</sup> They claimed that the difference in development of the two opposite hemihedral faces must have been due to solvent-surface interactions.

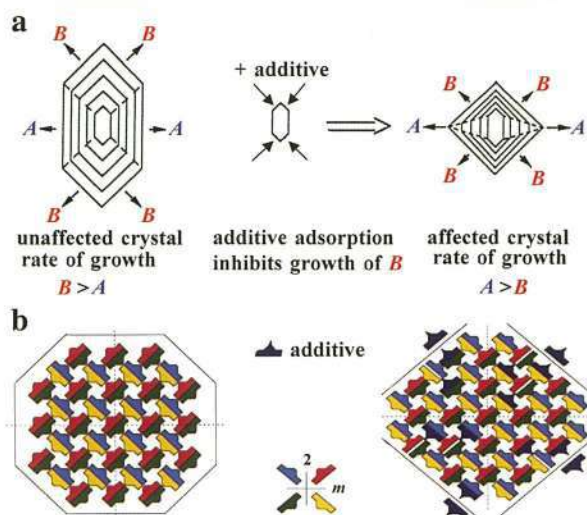
In the course of our studies on crystal and morphology engineering with "tailor-made" auxiliary molecules, it became possible not only to manipulate the morphology of crystals in a rational manner, but also to correlate directly between molecular enantiomerism and crystal enantiomorphism, thus providing a method independent from that of Bijvoet for the direct assignment of the absolute configuration of chiral molecules and the absolute structure of polar crystals.<sup>11</sup> In this way it became possible to assign the absolute molecular structure of a variety of molecular systems, such as  $\alpha$ -amino acids, sugars and steroids.

The interplay between the contributions of the internal crystal structure and of the solution-surface interactions in determining crystal morphology was clarified via the role played by the "tailor-made" additives on crystal nucleation, growth, morphology and structure, namely by examining the changes imposed by the additives on the system.<sup>12-14</sup> This approach also helped to extend the Pasteur experiment of sorting enantiomorphous crystals which do not express hemihedral faces, to elaborate a new method for the resolution of enantiomers on a large scale, to elucidate the role played by solvents on crystal growth and dissolution, provide a revision of the structure of mixed crystals, make an intelligent selection of etchants for the investigation of dislocations in crystals, and present evidence in favor of two-dimensional self assembly of amphiphilic molecules at the air-water interface.

### A bridge between crystal structure, morphology and molecular chirality

From a systematic study of a variety of organic compounds crystallized in the presence of additives of molecular structure similar to the structures of the corresponding substrate molecules and so-labeled "tailor-made" additives, it was possible to deduce a stereochemical link between the structures of the





Scheme 1

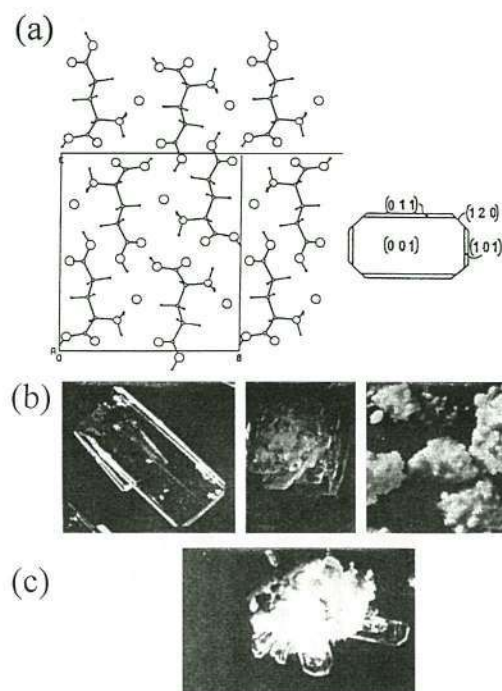
affected crystal surfaces and the molecular structure of the additive.<sup>13</sup> We could infer that the “tailor-made” additive is stereoselectively recognized and adsorbed on the growing crystals, but only at certain surfaces and then with the part of the adsorbate that differs from that of the substrate emerging from the crystal. This selective adsorption of the “tailor-made” additive at crystal faces and concomitant inhibition of their growth is depicted in Scheme 1a,b, highlighting in (a) the general effect of additive bound to the diagonal faces and how this process is manifested at the molecular level in (b).

We now examine how this approach can be applied for modification of the Pasteur experiment of sorting enantiomorphous crystals that do not express hemihedral faces, and for the assignment of absolute configuration of chiral molecules.

### Separation of enantiomorphous crystals by manual sorting

Enantiomorphous crystals behave alike in their interactions towards external environment. However, an enantio-pure additive that will interact enantioselectively with the faces of the chiral crystals, should affect the growing faces of the two enantiomorphs differently. Consequently, a enantiomerically pure inhibitor,  $S^*$

consisting of a slightly modified  $S$  molecule will be, in general, adsorbed only at the crystal surface of the ( $S$ )-enantiomorph and not at the surfaces of the ( $R$ )-crystal. This stereoselective adsorption causes a delay in the nucleation of the ( $S$ )-crystals associated with drastic morphological changes that allow visual identification and manual separation of the two enantiomorphs.<sup>15,16</sup> This principle is illustrated here with the racemic glutamic acid HCl (GluHCl), which undergoes spontaneous separation to yield a conglomerate mixture of ( $R$ ) and ( $S$ ) plate-like crystals that do not express hemihedral faces.<sup>17</sup> Fig. 2 shows how adsorption of  $S$ -lysine (Lys) additive causes ( $S$ )-GluHCl crystals to grow as thinner and thinner plates and finally as powder at higher inhibitor concentrations, while the ( $R$ )-GluHCl crystals preserve their original morphology. This correlation



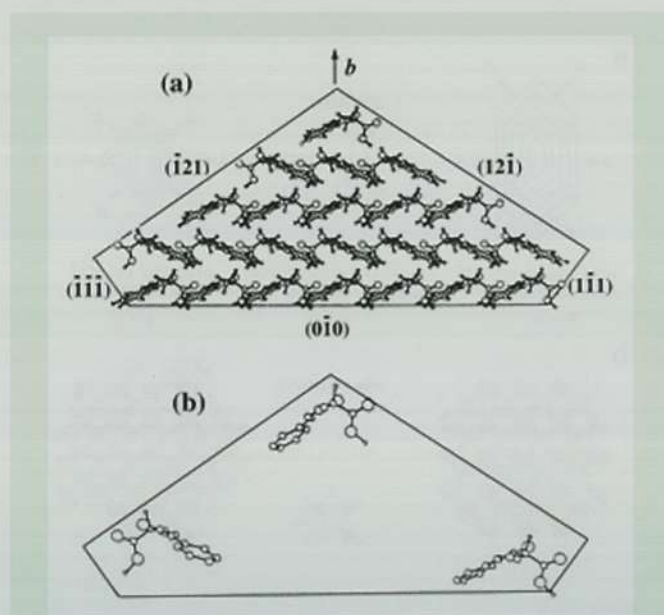
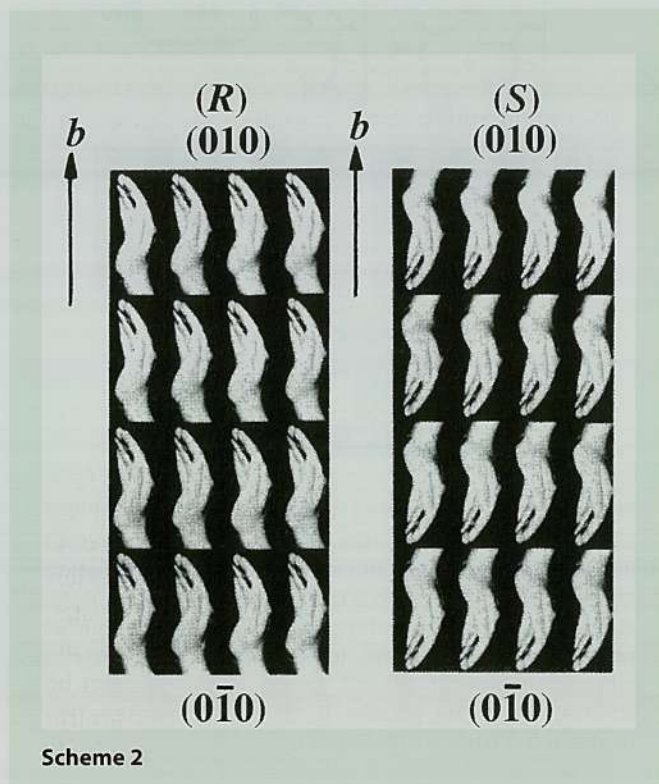
**Figure 2.** (a) The packing arrangement and plate-like {001} morphology of ( $S$ )-Glu.HCl. (b) Growth of crystals from a solution of  $S$ -Glu.HCl in the presence of increasing concentration of additive  $S$ -Lys shown from left to right, starting with the pure habit, yielding thinner and thinner plates and finally powder. (c) Crystals obtained from a racemic solution of Glu.HCl, grown in the presence of additive  $S$ -Lys. The powder is ( $S$ )-Glu.HCl, whereas the unaffected crystals are ( $R$ )-Glu.HCl.



between the crystal and the additive can also be applied as a method for the assignment of the configuration of chiral molecules on a relative basis.

### Absolute configuration assignment of polar crystals

To demonstrate the method we first focus on polar crystals composed of chiral-resolved molecules. The method involves the principle of fixing the orientation of the constituent molecules *vis-a-vis* the polar axis, or axes, of the crystal and subsequently determine the absolute configuration of the chiral molecules. This principle is depicted in Scheme 2, which shows two enantiomorphous sets of hands arranged in a lattice, right hands forming a (*R*) crystal and left hands forming a (*S*) crystal. The fingers of the hands are exposed at the (010) face of the right-handed ‘molecules’ and, by symmetry, at the (0  $\bar{1}$  0) face for the left-handed ‘molecules’. Thus, by determining at which face of the crystal specimen the fingers or wrists are exposed, the handedness of the constituent molecules may be assigned. This step may be performed via the mechanism of adsorption-



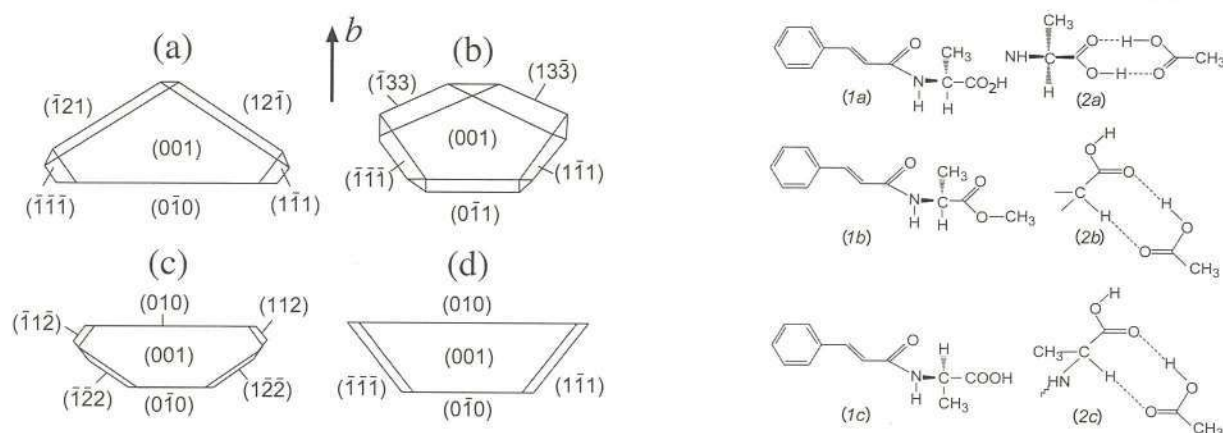
**Figure 3.** (a) Packing arrangement of *E*-cinnamoyl-(*S*)-alanine delineated by the faces observed in the pure crystal grown from methanol. (b) Orientations of only three host molecules *vis-a-vis* the crystal faces to envisage the effect thereon by the additives **1b** and **1c** and acetic acid solvent.

inhibition described above, using appropriate “tailor-made” additives.

We illustrate this approach with the example of *N*-(*E*-cinnamoyl) alanine.<sup>18</sup> Molecules of *N*-(*E*-cinnamoyl)-*S*-alanine (**1a**) crystallize in monoclinic space group  $P2_1$ . The packing arrangement delineated by the crystal faces as grown from methanol solution is shown in Fig. 3. The molecules are arranged such that the carboxyl groups emerge at the two {111} faces and the C(chiral)-H bonds are directed along the +*b* axis. In a study on the effect of “tailor-made” additives on the morphology of pure *E*-cinnamoyl-(*S*)-alanine (**1a**, Fig. 4a), it was found, as expected, that the methyl ester (**1b**), of the same absolute configuration as the host molecule (**1a**), induced large {111} faces (Fig. 4b), since the O-CH<sub>3</sub> group replaces a O-H group emerging from such faces. “Tailor-made” additive *E*-cinnamoyl-*R*-alanine (**1c**) of configuration opposite to that of the host induced, as expected, a (010) face (Fig. 4c), because of an interchange of CH<sub>3</sub> and H at the guest asymmetric carbon so that the C-CH<sub>3</sub> guest moiety replaces the emerging host C-H bond.

It was found that solvent may act in a manner similar to the “tailor-made” additives, for example, by growing





**Figure 4.** Morphologies of measured crystals of *N*-(*E*-cinnamoyl)-(*S*)-alanine. (a)–(c) refer to crystals grown from methanol: (a) pure crystal, (b) grown in the presence of the methyl ester (1b), (c) grown in the presence of *E*-cinnamoyl-(*R*)-alanine (1c) and (d) pure crystal grown from acetic acid.

*E*-cinnamoyl-(*S*)-alanine from acetic acid<sup>19</sup> instead of methanol. Acetic acid is a solvent which can selectively bind at the exposed carboxylic acid groups of the two  $\{1\bar{1}1\}$  faces, forming a hydrogen-bonded dimer (2a). Acetic acid can also bind to the  $\text{CHCO}_2\text{H}$  moiety of cinnamoylalanine *via* a cyclic dimer (2c) on the (010) face. The dimer (2b) is the motif adopted by acetic acid in its own crystal structure,<sup>20</sup> forming a  $\text{C-H}\cdots\text{O}$ (carbonyl) interaction.<sup>21</sup> Crystallization of *E*-cinnamoyl alanine (1a) from glacial acetic acid yields crystals with the morphology shown in Fig. 4d, in keeping with expectation.

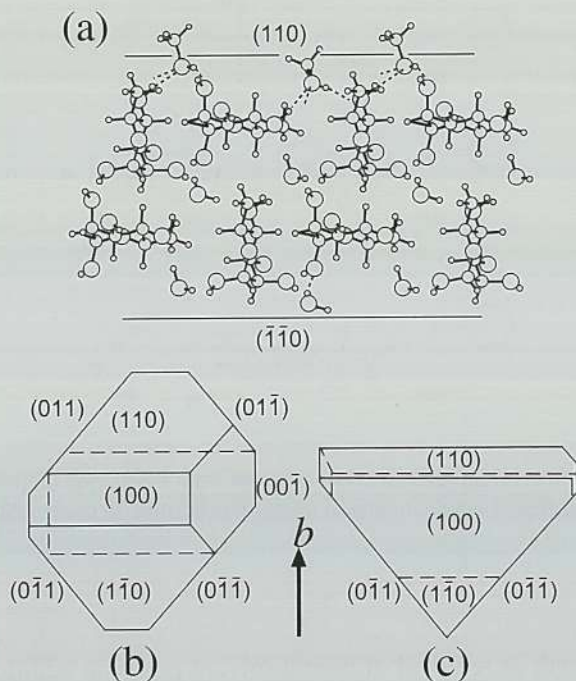
### Solvent-surface interactions for absolute structural assignment of polar crystals

Solvent has a strong influence on the habit of crystalline materials; however, the role played by solvent-surface interactions in enhancing or inhibiting crystal growth had long been a matter of debate. Till about the 1980's, there had been two different approaches to help clarify this point. In one approach, favorable interactions between solute and solvent on specific faces leads to reduced interfacial tension, causing a transition from a smooth to a rough interface and a concomitant faster surface growth.<sup>22</sup> Alternatively, it has been proposed that preferential adsorption at specific faces will inhibit their

growth as removal of bound solvent poses an additional energy barrier for continued growth. Our studies on the role played by “tailor-made” additives are in keeping with the latter approach. Therefore, solvents may act in a manner similar to “tailor-made” additives.<sup>14</sup> This effect is illustrated with the use of solvent for the determination of the absolute configuration of molecules packing in polar crystals that are crystalline solvates and where the solvent of crystallization plays the dual role of solvent and solute. Such crystals were grown in the added presence of “tailor-made” solvent, which is a slightly modified version of the solvate solvent. When crystalline hydrates were grown from aqueous solution in the added presence of methanol (the “tailor-made” solvent), it was found that the change in morphology was interpretable<sup>14,23</sup> in a manner akin to the effect of a “tailor-made” inhibitor.

For this purpose, we made use of the crystal structure of  $\alpha$ -rhamnose monohydrate, which embodies a polar arrangement (Fig. 5a) in space group  $P2_1$  and, when grown from pure aqueous solution, displays a bipyramidal morphology (Fig. 5b). The two O-H bonds of the hydrate water molecules are oriented exclusively towards the  $+b$  direction of the crystal. A methanol molecule may replace a water molecule at the (110) face of the crystal by virtue of a hydrogen bond of the OH group such that the methyl group protrudes from the surface and perturbs the regular growth along





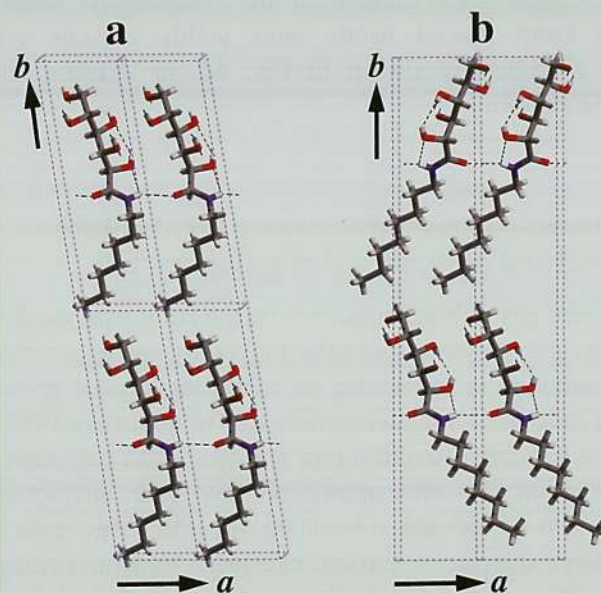
**Figure 5.** (a) Packing arrangement of  $\alpha$ -rhamnose monohydrate crystal viewed along the  $a$  axis; the OH bonds of the hydrate water molecules point towards the  $1b$ , but not the  $2b$ , direction; replacement of water by methanol on the  $\{110\}$  faces is depicted; (b, c) Morphology of  $\alpha$ -rhamnose monohydrate crystals grown from aqueous solution and 9:1 methanol:water solution, respectively, as viewed along the  $a$  axis.

the  $+b$  direction but not towards the  $-b$  direction of the crystal. Consequently, the addition of methanol as cosolvent changes the bipyramidal crystal morphology into pyramidal (Fig. 5c). A similar change in crystal morphology was accomplished on growing crystals of asparagine monohydrate, which does not exhibit polar axes, in the presence of methanol.<sup>23,24</sup>

Direct assignment of the absolute configuration of chiral-resolved molecules by the difference in wetting properties of hydrophobic and hydrophilic crystal faces was made possible<sup>25</sup> using crystals of the class belonging to chiral-resolved alkyl gluconamides,  $C_nH_{2n+1}NHCO(CHOH)_4CHOH$ ,  $n=7-10$ . The molecules crystallize as plates in an arrangement<sup>26</sup> akin to that depicted in Scheme 2, namely head-to-tail, as shown in Fig. 6. Thus, one face of the plate crystal is hydrophobic

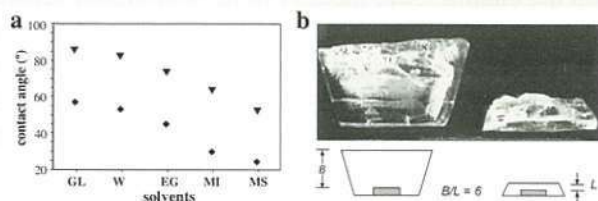
and the opposite face is hydrophilic. Contact angle measurements with a variety of polar solvents deposited on the opposite plate-like faces of specimen crystals could establish which face is hydrophobic and which is hydrophilic (Fig. 7a). This information fixes the orientation of the constituent molecules along the polar  $b$ -axis of the crystal specimen and consequently their chirality.

These wettability experiments also led to crystal growth experiments on these systems to help determine the role of solvent on crystal growth. In the absence of a difference in the effect of binding of solvent at the opposite hemihedral plate faces of the alkyl gluconamides these two faces should grow at the same rate,<sup>10</sup> as already alluded to in the discussion on the experiment by Waser.<sup>9</sup> A pronounced difference in growth rate must then be associated with differences in solvent-surface interactions. In  $CH_3OH$  solution the polar plate-like crystals of the octyl derivative ( $n = 8$ ) were found to grow almost four times faster at the hydrophobic side than at the hydrophilic side (Fig. 7b).<sup>27</sup> This result is completely in keeping with the observation that water and other polar solvents wet the hydrophilic face more strongly than the opposite hydrophobic face. It is noteworthy that at the hydrophilic face, solvent



**Figure 6.** Packing arrangements of  $n$ -heptyl and  $n$ -octyl gluconamides viewed along their  $c$  axes.





**Figure 7.** (a) Contact angle measurements on the hemihedral faces of N-n-octyl-gluconamide crystals grown in methanol: GL, glycerol; W, water; EG, ethylene glycol; MI, methylene iodide; MS, mother solution (methanol). (u) hydrophilic (010) face; (t) hydrophobic (00) face. (b) Morphology of crystals grown from seeds, which can be observed as an opaque shadow at the bottom. Thickness of added material on the hydrophobic surface is denoted as B and that added on the hydrophilic surface is denoted as L. The B/L ratio has an average value of about 5.

methanol can form O··H-O H-bonds with the terminal hydroxyl groups of two neighboring chains, since the translation separation distance between them is *ca* 5 Å. The role played by solvent-surface interactions in determining the relative rates of growth at the opposite ends of the polar axis has been reviewed in Ref. 28.

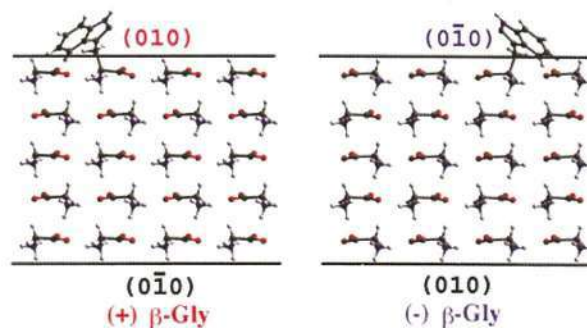
### Assignment of absolute configuration of a polar, pseudo-centrosymmetric crystal

Growth measurements of  $\beta$ -Gly crystals in 1:1 ethanol-water solutions revealed much faster growth at one end of the needle-like crystal, corresponding to the polar *b*-axis, than at the opposite end.<sup>29a</sup> The basic question in crystal growth was at what end of the polar axis does  $\beta$ -Gly grow faster.

An attempt to assign the sense of polarity of specimen crystals of the  $\beta$ -polymorph of glycine ( $\beta$ -Gly), space group  $P2_1$ , by the Bijvoet method was unsuccessful because the arrangement of the relevant O, N, C anomalous X-ray scatterers is near centrosymmetric (space group pseudo- $P2_1/m$ ). “Tailor-made” additives were used for the assignment of the sense of polarity of specimen crystals, employing tryptophan (Trp).<sup>29a</sup> For convenience, we define the two enantiomorphous crystals of  $\beta$ -Gly as follows: the enantiomorph in which the Gly C-H bonds point along the  $+b$  direction, which would emerge from the (010) face, is defined

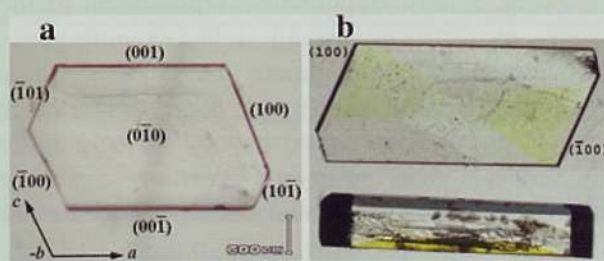
as (+) (Fig. 8 left). Hypothetical replacement of these H atoms by deuterium would yield Gly molecules of “*R*-configuration.” By symmetry, the Gly molecules of the (−) enantiomorph, whose C-H bond vectors emerge from the (0  $\bar{1}$  0) face, would be of “*S*-configuration” (Fig. 8 right). Thus, on crystal growth, *R*-amino acid additives are expected to bind selectively to the (010) face of (+)  $\beta$ -Gly and *S*-amino acids onto the (0  $\bar{1}$  0) face of (−)  $\beta$ -Gly. Crystallization of  $\beta$ -Gly in 1:1 ethanol:water solutions in the presence of racemic Trp yielded, as expected, the formation of short prismatic crystals due to enantioselective binding of the additive followed by retardation of crystal growth at either (010) or (0  $\bar{1}$  0) face of the (+) and (−)  $\beta$ -enantiomorphs, respectively. Therefore, we concluded that  $\beta$ -Gly grows faster at the C-H exposed side than at the opposite N-H exposed side, which was interpreted in terms of solvent surface interactions.<sup>29a, 28</sup>

To differentiate between the (+) and (−)  $\beta$ -enantiomorphs grown in the presence of racemic Trp, we colored them enantioselectively by growing the  $\beta$ -Gly crystals in aqueous solutions in the presence of mixtures of 2% *R,S*-Trp and 0.1% of either *R*- or *S*-N<sup>c</sup>-(2,4-dinitrophenyl)lysine (DNPLys).<sup>29b</sup> The  $\beta$ -Gly plate-like crystals grown in the presence of *S*-DNPLys appeared as a mixture of colorless (+)-enantiomorphs (Fig. 9a) and (−)-enantiomorphs colored only at the (0  $\bar{1}$  0) face (Fig. 9b).



**Figure 8.** (a, b) Packing arrangements of the (+)- and (−)- $\beta$ -polymorphs of Gly delineated by the {0  $\bar{1}$  0} crystal faces and showing the adsorption of *R*- and *S*-Trp molecules, respectively.





**Figure 9.** Crystals of  $\beta$ -Gly grown from aqueous solutions in the presence of a mixture of 2% *R,S*-Trp and (a) 0.1% *S*-DNPLys or (b) *R*-DNPLys. Note in (b) two views of the same yellow colored crystal; bottom, view along *c* direction showing the color at only one side, and top, view along the *b* direction showing coloring in the (100) and ( $\bar{1}00$ ) sectors.

### Centrosymmetric crystals as a means for separation of enantiomeric territories and assignment of molecular chirality

In contrast to the situation for chiral crystals, it had not been generally appreciated that in centrosymmetric crystals the orientations of the constituent enantiomeric molecules are unambiguously assigned with respect to the crystal axes, from a conventional structure determination. Thus, the known orientation of the two enantiomeric molecules in a centrosymmetric crystal can be exploited for the direct assignment of absolute configuration of chiral-resolved molecules, provided the structural information embedded in the racemic crystal can be transferred to chiral additive molecules. The direct assignment of the absolute configuration of such chiral resolved additives may thus be determined through the morphological changes they induce selectively on one set of enantiotopic faces of centrosymmetric crystals with appropriate packing features.

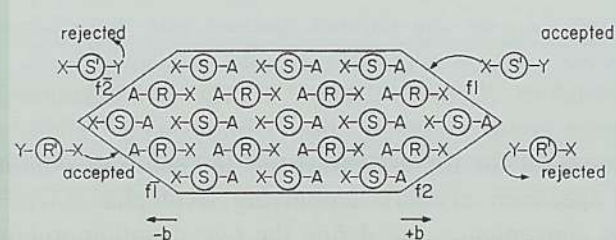
A prerequisite for application of this method is that within the centrosymmetric racemic crystal a specific functional group attached to a (*R*)-molecule points toward the face *f*1 but not toward the opposite face  $\bar{f}1$  (Scheme 3). By symmetry, the same functional group attached to a (*S*) molecule will emerge at the enantiotopic face  $\bar{f}1$ , but not at *f*1. Crystallization of a centrosymmetric crystal in the presence of a chiral additive *R'* designed so that it will fit in the site of a (*R*) molecule on the growing crystal faces  $\bar{f}1$  or  $\bar{f}2$  but

not on the enantiotopic faces *f*1 or *f*2, will hinder growth in the  $-b$  direction but not in the  $+b$  direction (Scheme 3). By virtue of symmetry, the enantiomeric additive *S'* will inhibit growth perpendicular to faces *f*1 and *f*2, while racemic additives *R',S'* will inhibit growth in both directions,  $+b$  and  $-b$ .

We first applied this method for the assignment of the absolute configuration of threonine from both the morphological changes induced by this molecule on the centrosymmetric crystals of racemic (*R,S*)-serine as well as by the distribution of the guest additives in the host crystal.<sup>30</sup> Here we shall rather focus on the use of the centrosymmetric  $\alpha$ -polymorph of crystalline glycine +  $\text{H}_3\text{NCH}_2\text{CO}_2^-$ , which is achiral in solution, for the assignment of absolute configuration of  $\alpha$ -amino acids.<sup>14,31,32</sup>

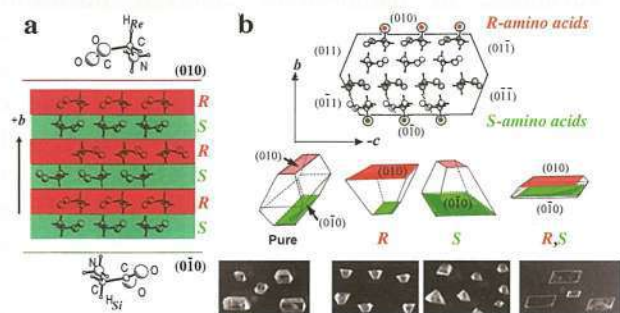
When grown from aqueous solutions, Gly crystallizes in its centrosymmetric  $\alpha$ -form, space group  $P2_1/n$ , assuming a chiral conformation therein. In the crystal, the  $\text{C-H}_{re}$  vector of Gly molecules in *R*-layers parallel to the *ac* plane points toward the  $+b$  direction emerging perpendicular to the (010) face (Fig. 10a) whereas the  $\text{C-H}_{si}$  vector of Gly molecules in *S*-layers (also parallel to the *ac* plane) points toward the  $-b$  direction emerging perpendicular to the (0 $\bar{1}$ 0) face. The other C-H bond of the  $\text{CH}_2$  group lies within the crystalline *ac* plane. Thus the  $\alpha$ -Gly crystal is composed of chiral layers, parallel to the *ac* plane, of alternating symmetry, colored in red and in green (Fig. 10a).

When  $\alpha$ -Gly crystals are grown in aqueous solutions in the presence of racemic mixtures of amino acids they display a plate-like morphology expressed via the enantiotopic (010) and (0 $\bar{1}$ 0) faces (Fig. 10b). During growth, the *R*-amino acids interact enantioselectively



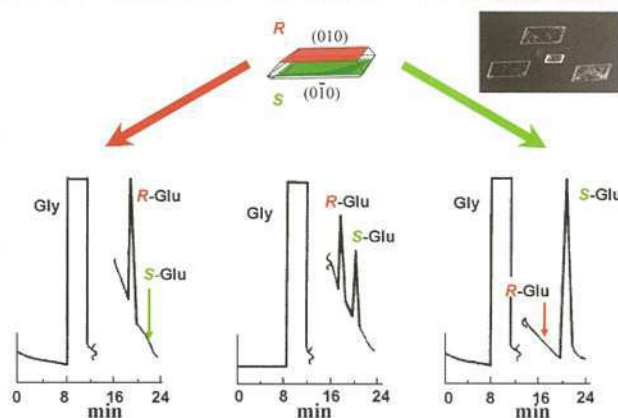
**Scheme 3.** The adsorption of enantiopure additives onto enantiotopic faces of a centrosymmetric crystal.





**Figure 10.** (a) Packing arrangement of  $\alpha$ -Gly with the crystal heterochiral layers of chiral Gly molecules colored in red and green; (b) Morphology and photographs of the crystals of pure  $\alpha$ -Gly as well as (c–e) grown in the presence of enantiomeric *R* and *S*, and racemic *R,S*  $\alpha$ -amino acid additives.

with the (010) face by virtue of their  $\alpha$ -amino acid moieties and thus replace “red” glycine host molecules so that their side chains emerge from the crystal surface and thus do not interfere with the intralayer binding process. A minor fraction of these amino acid guest molecules would be occluded within the bulk of the  $\alpha$ -Gly crystal on growth. By symmetry, the *S*-amino acids would be occluded into the bulk of the  $\alpha$ -Gly crystal through the (0  $\bar{1}$  0) face. As a result of this process, racemic  $\alpha$ -amino acids can undergo segregation into enantiomers upon occlusion within  $\alpha$ -Gly crystals (Fig. 11). Furthermore, if  $\alpha$ -Gly crystals are grown at an interface that blocks growth at one of the enantiotopic faces, say (010), then only the *S*-enantiomer of the racemic  $\alpha$ -amino acids will be occluded within the crystals through their (0  $\bar{1}$  0) face exposed to solution thus “converting” the achiral host  $\alpha$ -Gly crystal into a homochiral mixed crystal of single handedness of symmetry  $P2_1$ . This transformation can be illustrated with  $\alpha$ -Gly crystals grown in the presence of *N*ε-(2,4-dinitrophenyl)-*S*-lysine. Crystals that exposed only their (010) face to solution during growth had not occluded the yellow dye and therefore are white whereas the crystals exposing to the solution the (0  $\bar{1}$  0) face during growth are yellow (Fig. 12). By applying the same principles, we have assigned the absolute configuration of the dipeptide glycyl-leucine that induced a change in the morphology and underwent segregation upon enantioselective occlusion within glycyl-glycine crystals.<sup>33,34</sup> These studies were applied to constitute a model on mirror symmetry breaking of relevance to the origin of homochirality on Earth.<sup>34</sup>



**Figure 11.** Enantiomeric HPLC analyses of the occluded additives in plate-like crystals of glycine grown in the presence of *R,S*-glutamic acid; (left to right) sample taken from the  $+b$  pole, sample from a whole crystal and sample taken from the  $-b$  pole.

### Etch-pits on chiral surfaces of centrosymmetric crystals for chirality assignment

Partial dissolution of crystals in the presence of additives may induce formation of well-shaped etch-pits on particular crystal faces. Crystal dissolution invariably begins at sites of emerging dislocations.<sup>35</sup> Subsequently, etch-pits are formed at the dislocation centers on those faces at which the additives are bound. Therefore, it was anticipated that “tailor-made” growth inhibitors of



**Figure 12.** Photographs of white crusts and yellow crusts of glycine crystals grown at the air/aqueous solution interface in the presence of *N*ε-(2,4-dinitrophenyl)-*S*-lysine and leucine in a ratio  $S/R > 1$  and  $S/R < 1$ , respectively. The white crystals exposed their (0  $\bar{1}$  0) face towards the solution whereas the yellow crystals exposed their (00) face.



a given face would operate as “tailor-made” etchants of the same face. This approach was tested on several crystals,<sup>24</sup> which we illustrate with one example.

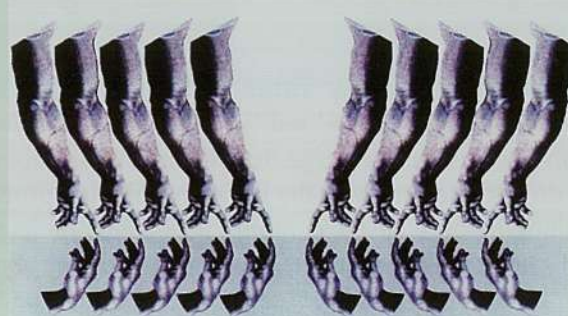
{010} plates of  $\alpha$ -Gly crystals were partially dissolved in an undersaturated solution of Gly containing variable amounts of another type of  $\alpha$ -amino acid. When *R*-alanine was present in the solution, well-developed etch-pits were formed only on the (010) face, whereas the (0  $\bar{1}$  0) face dissolved smoothly (Fig. 13a). As expected, *S*-Ala induced etch-pits on the (0  $\bar{1}$  0) face exclusively. The role played by dislocations for inducing etch pit formation was also demonstrated. A Gly crystal was cleaved to expose (010) and (0  $\bar{1}$  0) faces, each etched with racemic Ala, revealed mirror-symmetry related patterns (Fig. 13b).<sup>24</sup>

The same type of chiral selectivity holds for an enantiomorphous pair of crystals dissolved in the presence of a chiral additive; only one of the enantiomers is etched, as was demonstrated for conglomerate mixtures of glutamic acid.HCl and asparagine.H<sub>2</sub>O.<sup>24</sup> This simple method also differentiates between enantiomorphous crystals which do not express hemihedral faces.

### Absolute configuration assignment of amphiphiles forming self-assembled crystalline monolayers at the air-water interface

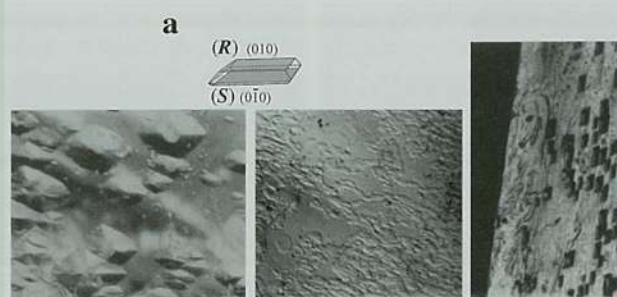
The opposite faces of a centrosymmetric crystal that are chiral and thus of opposite handedness, were used

to advantage to demonstrate epitaxial nucleation by an ordered monolayer composed of amphiphilic molecules of a single handedness at the air-aqueous solution interface. Scheme 4, left depicts a layer of amphiphilic left hands in contact at an interface with an underlying layer of right hands that represents the uppermost molecular layer of a to-be-nucleated three-dimensional (3-D) crystal; by symmetry, the layer of amphiphilic right hands makes equivalent contact with the uppermost layer of left-handed molecules of the 3-D crystal (Scheme 4, right).



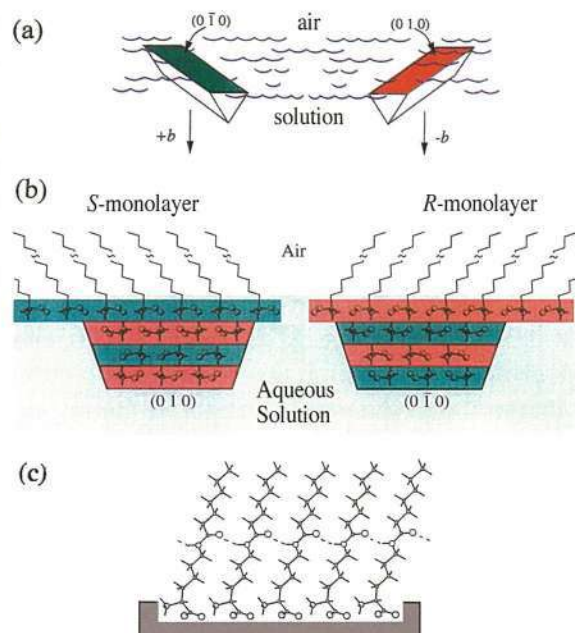
Scheme 4

This principle was applied for the induced nucleation, at the air-aqueous solution interface, of  $\alpha$ -Gly via its two enantiotopic {010} faces (Fig. 10), when grown in the presence of the natural hydrophobic  $\alpha$ -amino acids of single-handedness such as *R*- or *S*-leucine. Such solutions resulted in the formation of floating pyramidal-shaped Gly crystals oriented with their “red” basal (010) or “green” (0  $\bar{1}$  0) face to air depending upon the chirality, *R* or *S*, of the additive (Fig. 14a).<sup>36</sup> This result suggested that if amphiphilic  $\alpha$ -amino acids formed ordered monolayers on the aqueous Gly solution surface, with a structure akin to that of the “red” (010) or “green” (0  $\bar{1}$  0) layer of  $\alpha$ -Gly, as depicted in Fig. 14b, the chirality of the amphiphile could be determined via assignment of the nucleated  $\alpha$ -Gly face at the air-solution interface. This prediction was realized using the  $\alpha$ -amino acid amphiphile,  $+H_3NCHXCO_2^-$ ,  $X = C_nH_{2n+1}CONH(CH_2)_4$ ,



**Figure 13.** (a) Photographs of the (010) and (010) faces of a plate-like  $\alpha$ -Gly crystals after etching in the presence of *R*-alanine; (b) The (010) and (00) faces of a cleaved  $\alpha$ -Gly crystal subsequently etched in the presence of *R,S*-alanine.





**Figure 14.** (a) Schematic view of floating crystals of  $\alpha$ -glycine of pyramidal shape obtained when grown in the presence of hydrophobic (left) *S*, and (right) *R*,  $\alpha$ -amino acid. (b) Schematic view of pyramidal crystals, incorporating molecular packing arrangement, of  $\alpha$ -glycine grown under monolayers of amphiphilic *S* and *R*  $\alpha$ -amino acids, the packing arrangement of which for  $C_{17}H_{33}CONHC_4H_8CH(NH_3^+)CO_2^-$ , as determined by GIXD, is shown in (c). The upper section of the chain has been removed.

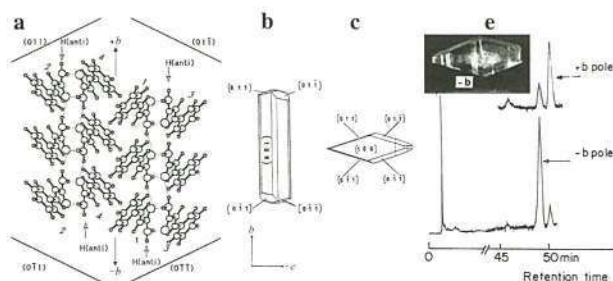
$n = 17$ , as the  $\alpha$ -Gly nucleating agent.<sup>37</sup> The importance of this experiment, however, was more along the line of demonstrating that certain amphiphilic monolayers can spontaneously form 2-D crystals at the air-solution interface at a time when grazing incidence X-ray diffraction (GIXD) measurements of amphiphilic monolayers at the air-water interface had still not been undertaken. Indeed, eventual GIXD studies of the  $\alpha$ -amino acid amphiphiles  $n = 15, 17$  yielded diffraction patterns that not only confirmed the monolayer crystallinity, but also yielded the molecular arrangement, revealing that the glycyl +  $H_3NCHXCO_2^-$  moieties adopted a motif (Fig. 14c) akin to that of the layer structure of  $\alpha$ -Gly.<sup>38</sup>

## "Absolute" asymmetric synthesis in centrosymmetric crystals

In the above examples involving growth of a crystal in the presence of a "tailor-made" growth inhibitor, either the host crystal and the additive molecule were both chiral or the host crystal was centrosymmetric, composed of either a racemate or of achiral molecules, and the additive was chiral.

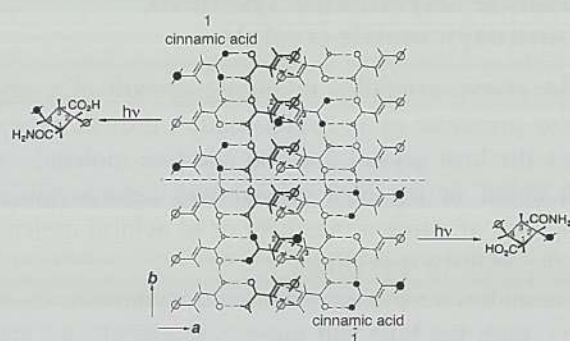
These studies were extended to centrosymmetric crystals where both the host and guest components are achiral molecules. Selective occlusion of the guest into a subset of host sites led to a loss of crystal inversion symmetry **1**. This reduction in crystal symmetry was manifested by photoreaction between host and guest, yielding a homochiral product, whose absolute handedness could be assigned from the knowledge of the structure of the crystal surface across which the guest was adsorbed and occluded.

In the specific example, additive *E*-cinnamic acid  $C_6H_5-CH=CH-CO_2H$ , induced a loss of the center of inversion in the crystal of *E*-cinnamamide  $C_6H_5-CH=CH-CONH_2$  which, in pure form, appears in a centrosymmetric monoclinic arrangement, space group  $P2_1/c$ . The crystal structure (Fig. 15a) is composed of H-bonded dimers interlinked by N-H $\cdots$ O bonds to form a ribbon-like motif that runs parallel to the *b*-axis. *E*-cinnamic acid was preferentially occluded through only half of the  $\{011\}$  surface sites of the crystal



**Figure 15.** Packing arrangement of *E*-cinnamamide viewed along the *a*-axis delineated by the  $\{011\}$  faces; (b, c) morphology of *E*-cinnamamide crystals, pure and grown in the presence of cinnamic acid; (d) HPLC analysis of the products obtained at the +*b* and -*b* poles of the host crystal.





**Figure 16.** Ribbons, along the *b* axis, of H-bonded molecules composed of *E*-cinnamamide (open circles) and occluded guest *E*-cinnamic acid molecules (full circles). The latter were adsorbed through site 1 at the  $+b$  end and site  $-1$  at the  $-b$  end, leading to two enantiomorphous domains joined at the central dotted line. Shown also are the ribbons related by translation along the *a* axis so depicting the close 4 Å contact between C=C double bonds related by a center of inversion. Also shown are two enantiomorphous cyclobutane photodimers between the host and occluded guest from the top and bottom halves of the crystal.

at the opposite ends of these ribbons, resulting in a change in crystal morphology, (Figs. 15b and 15c) and a reduction in crystal symmetry, whereby the affected crystal was composed of two enantiomorphous halves of at most  $P2_1$  symmetry. This reduced symmetry was proven photochemically.<sup>39</sup> Ultraviolet irradiation of *E*-cinnamamide yields centrosymmetric photodimers, by virtue of a cyclobutane ring formation involving pairs of close packed  $>C=C<$  bonds across centers of inversion (Fig. 16). Replacement of one of such a pair by *E*-cinnamic acid resulted in the formation of asymmetric cinnamamide–cinnamic acid photodimers of opposite chirality at the two enantiomorphous halves of the mixed crystal, with an enantiomeric ratio of 60:40 at each opposite half (Fig. 15d). This absolute configuration of the C4 rings follows directly from the orientation the acid molecule adopts upon insertion into the growing crystal. The four C-atoms of the C4 ring formed by occlusion of the acid at the  $+b$  pole of the crystal were of *R*-absolute configuration, whereas that formed at the  $-b$  side were of *S*-configuration.<sup>39</sup> The predicted configuration was confirmed by an independent Bijvoet analysis.

## Summary and conclusions

The use of “tailor-made” additives, or indeed solvent in favorable cases, on crystallization and dissolution processes provides an approach for the assignment of absolute configuration of chiral molecules, independent of the Bijvoet method. More important, this method, by virtue of its experimental and conceptual simplicity, provides a tangible and easily understood correlation between molecular chirality and crystal morphology, growth, dissolution, solvent-surface interactions and structure, and so easily amenable to students of stereochemistry. In addition this approach has provided deep practical and theoretical insight in the nucleation and growth of crystals on the molecular level as well in the development of a new method for large-scale resolution of enantiomers by crystallization<sup>40</sup>.

**Acknowledgments** We are indebted in particular to Lia Addadi, the late Ziva Berkovitch-Yellin, Isabella Weissbuch, Ronit Popoviz-Biro, Edna Shavit and Doctoral and Post-Doctoral students who participated in the work described above. We also acknowledge collaboration with Jakob Sagiv in the early studies at the air-water interface. The grazing incidence X-ray diffraction studies of films at liquid surfaces would not have been possible without the collaboration of the Danish physicists Jens Als-Nielsen and Kristian Kjaer. Finally, most of the studies described above performed by our group had been supported by the Israel Science Foundation.

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# Molecular Self-Assembly of Small Aromatic Peptides: A New Frontier in Organic Nanotechnology

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Prof. Ehud Gazit is Tel Aviv University Vice President for Research and Development and the incumbent of the Chair for Nano-Biology. Gazit received his B.Sc. summa cum laude after completing his studies at the Special Program for Outstanding Students at Tel Aviv University, and his Ph.D. (with highest

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## ABSTRACT

The controlled assembly of well-ordered structures at the nano-scale is a central theme for nano-science and nanotechnology. A new and important direction is the use of organic building blocks, rather than inorganic or pure carbon elements, for this purpose. Nanotechnology that is based on organic chemistry offers facile synthesis, chemical diversity, versatile deposition methods, and biocompatibility. We have established the diphenylalanine aromatic motif as a key structural element for nanotechnology. This simple aromatic building block and its analogues can form nanostructures of various geometries including nanotubes, nano-spheres, nano-plates, nano-fibrils, and hydrogels of nano-scale order. All these structures are being formed by bottom-up self-assembly under mild conditions and show remarkable chemical, mechanical, optical, and piezoelectrical properties. We also established methods for the controllable deposition of these structures in ordered arrays using unidirectional axial growth, physical vapor deposition, inkjet printing, lift-off techniques and more. The application of the new family of nanostructures was already demonstrated in the fields of ultra-sensitive biosensors, energy storage, composite materials and more.

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## Introduction

Molecular self-assembly of elementary building blocks to form well-ordered structures at the nano-scale is the key direction for fabrication of functional supramolecular assemblies of nano-scale dimensions [1]. Early work on functional nano-scale chemical entities started with the discovery of carbon buckminsterfullerene and later on carbon nanotubes. These pure carbon structures show unique physical properties and they are being extensively studied for their application in materials and devices. Another important group of nano-scale assemblies is based on inorganic materials in which two-dimensional layers of metallic derivatives such as tungsten disulfide, vanadium oxide and manganese oxide are forming curved tubular and spherical structures [2]. Also these inorganic nanostructures are being extensively studied for various applications including solid lubricants and additive to composite materials.

Despite the very important properties of the carbon and inorganic nanostructures they have some inherent limitations than could be overcome by use of organic nanostructures. These include the relatively complicated synthesis of functional derivatives, the limitations in their use at a bottom-up self-assembly processes, their limited biocompatibility, and their cost. Organic chemistry offers a very rich array of synthesis techniques, the controlled tunability of physical and chemical properties, the ability for facile up-scaling of the synthesis, the small size of elementary building blocks, and their straightforward interface with the biological world. In many senses, new organic nanotechnology is parallel to the transition from traditional materials to organic polymers of desirable properties such as polyamides (from the aliphatic Nylons to the aromatic Kevlar and Nomex), polytetrafluoroethylene (Teflon), polyvinylchloride (PVC), polypropylene, polyester and many more. Indeed, the utilization of organic chemistry for the design and synthesis of new polymers had revolutionized the material world of the 20<sup>th</sup> century. We predict such a revolution when organic chemistry will be further employed for the design and synthesis of novel nano-materials at the 21<sup>st</sup> century.

Indeed much effort has been invested toward the development of organic building blocks for nanotechnology. Much of the activity was devoted towards the use of biological building blocks as

biology represent the most vivid example of functional nanotechnology with nano-scale elements such as motors, sensors, cables, signal processing units, chemo- and photo-receptors, delivery vehicles, structural reinforcement elements, and more. Moreover, in addition to the discussion at the previous paragraph, prior to the use of synthetic polymers much of the earlier processed materials were based on biological polymers such as wood, paper, wool, flax, cotton, silk, and natural rubber.

Thus there is a genuine quest for the development of new nanotechnological building blocks that will be based on organic elements and in particular biological ones. The studied building blocks for nanotechnology include proteins, carbohydrates, and even DNA elements. The central research direction is directed towards the design and characterization of simple organic building blocks that, as the synthetic polymers, could be synthesized easily and efficiently and in addition poses unique chemical and physical properties.

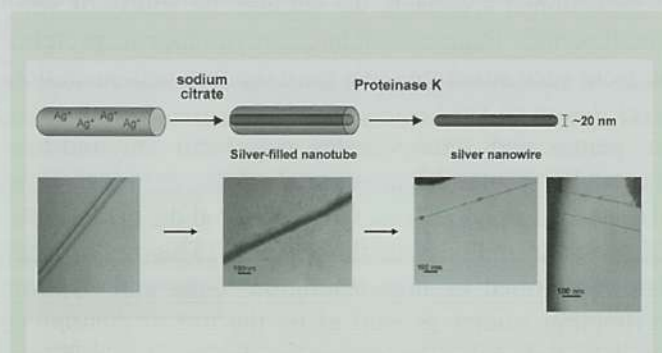
## The discovery of the diphenylalanine motif

We have been involved in the last decade in the study of the molecular recognition and self-assembly by peptides and proteins. The work was initiated by our interest in the process of amyloid fibril formation. Amyloids are nano-scale fibrillar assemblies of 7-10 nm in diameter of remarkable nearly-crystalline internal order that are involved in major human disorders such as Alzheimer's disease, Parkinson's disease and Type II diabetes. Using a reductionist approach, we studied the ability of very small peptide fragments of large amyloidogenic proteins to form such structures. We gave the first demonstration ever that even very short peptide fragments, such short as penta- and tetra-peptides can form amyloid-like assemblies [3-4]. When we studied the chemical basis for the assembly process, we discovered the central role of aromatic moieties in this process. This notion was later confirmed by high-resolution X-ray and electron diffraction studies as well as by the use of theoretical models and molecular dynamics studies. A significant part of the work in our laboratory, out of the scope of this review, is related to the inhibition of the formation of the amyloidal nano-fibrils and small oligomers by molecular design of inhibitors that interfere with the process of molecular recognition and self-assembly [5-8].



On our path to determine the smallest amyloid-forming peptide motifs, we studied the core recognition module of the Alzheimer's  $\beta$ -amyloid polypeptide. We discovered that this simple aromatic diphenylalanine peptide form well-ordered and hollow nanotubes of remarkable persistence length (of several microns) at high efficiency [9]. The ultrastructure of the nanotubes was visualized using electron microscopy (both transmission and scanning electron microscopy) as well as atomic force microscopy (AFM). Very interestingly, unlike many other nanostructures, an inherent property of the peptide nanotubes is their dispersity. The tubes appear as discrete entities that do not aggregate or form bundles.

The ability to use these nanotubes as degradable casting mould to fabricate metal nano-wires of high aspect ratio was demonstrated [9]. The preferential entrance of silver ions to the inner lumen of the tube was followed by chemical reduction into elementary silver and degradation of the peptide cast by proteolytic enzyme to result in silver nano-wires of 20 nm in diameter [9] (Figure 1). Following this work, we had demonstrated our ability to fabricate co-axial nano-cable. In this later case instead of degradation of the peptide cast, thiol conjugated building blocks were used followed by binding of gold nano-particles and enhancement by gold ions to end up with co-axial silver-peptide-gold cables [10].



**Figure 1:** The use the aromatic dipeptide tubes as degradable casting mould for the fabrication of metallic objects of high aspect ratio. The use of chemical reduction techniques together with enzymatic degradation is used to fabricate silver nanowires with a diameter of about 20 nm [Reches and Gazit (2003) *Science* **300**, 625-627].

To make nanostructures that are resistant to proteolytic degradation, instead of the natural L-amino-acids, the stereoisomer D-amino-acids were used. The all-D diphenylalanine analogue forms nanotubes that are ultrastructurally identical to those formed by the all-L building blocks. Yet these nanotubes are completely resistant to degradation by proteolytic enzymes which are stereo-specific [9]. Such resistant nanotubes could be useful for use of the assemblies in nano-fluidic devices. We indeed demonstrated the ability to integrate the tubes in conventional lithography process to fabricate functional nano-fluidic devices in which flow of liquid occurs through the hollow peptide nanotubes [11].

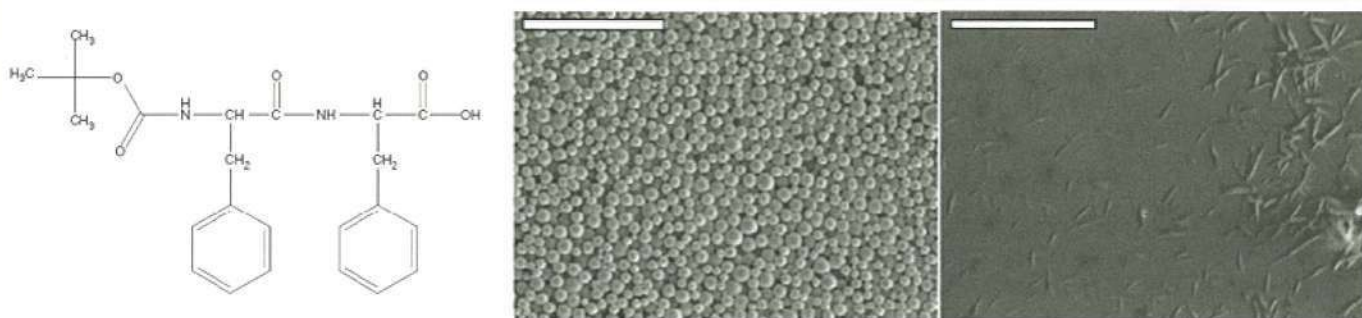
### Formation of nanostructures by analogues

Following our studies of the diphenylalanine building block we had investigated other aromatic dipeptide motifs. When we studied the simpler diphenylglycine motif, in which the aromatic moiety is conjugated directly to the C- $\alpha$  backbone of the peptide, we discovered the formation of spherical nano-assemblies that had similar dimensions as the nanotubes [12]. Similar nano-spheres were obtained when a tripeptide containing thiol, Cys-Phe-Phe, was used. Also the modification of the diphenylalanine peptide with a thiolating agent resulted in the formation of similar nano-spheres [12]. Also the bulkier dinaphthylalanine aromatic dipeptide formed ordered structures although these structures were less rigid, as inferred by their persistence length [13].

Other interesting property of the diaromatic peptide motifs were discovered when blocked analogues (either at the C-terminal or the N-terminal) were used. These building blocks formed various ordered assemblies at the nano-scale. Ordered bundled structures were also formed when a cyclic C-to-N dipeptide was studied. In this case, bundles of nanotubes were formed [13]. We also revealed that a non-charged peptide analogue, Ac-Phe-Phe-NH<sub>2</sub>, self-assembled into similar tubular structures [14]. These observations are consistent with the notion that it is mainly the interaction between the aromatic moieties in form of  $\pi$ - $\pi$  stacking provides the energetic contribution as well as the order and directionality for the formation of such structures.

We also explored the self-assembly of other homo-aromatic dipeptides in which their phenyl side-chains





**Figure 2:** Formation of either tubular (right) or spherical (middle) nanostructures by tert-butyloxycarbonyloxy-diphenylalanine (left) as described at Adler-Abramovich and Gazit (2009) *J. Pep. Sci.* **14**, 217-223 [21]. Scale bar is 20 μm.

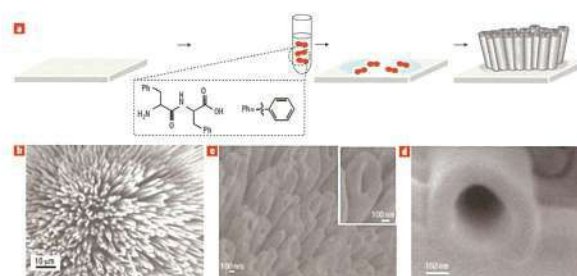
are modified with halogen atoms (di-para-fluoro-Phe, di-pentafluoro-Phe, di-para-iodo-Phe), additional phenyl groups (di-4-phenyl-Phe), or with nitro substitutions (di-para-nitro-Phe) [14]. In all cases, various ordered nanostructures were formed. As a rule, it appears that for the formation of the nanostructures there is a need for two identical aromatic moieties conjugated by a planar amide bond.

When N-terminal modified analogue, in which the amino-terminal was modified with the fluorenylmethyloxycarbonyl (Fmoc) protecting groups, was studied we observed the formation of rigid hydrogels [15]. While these gels contained more than 99% water, their mechanical rigidity is evident and confirmed by rheology. Environmental scanning electron microscopy (E-SEM) analysis under humid conditions revealed the existence of well-ordered fibrillar network within the gel which serves as a skeleton to allow the mechanical rigidity. These hydrogels were used for the slow release of drug as well as scaffold for cell growth with tissue engineering applications envisioned [15].

The study of various N-modified analogues of the diphenylalanine building blocks also revealed the fact that some peptides could form wither spherical or tubular assemblies under different conditions. The *t*-BOC (*N*-tert-butoxycarbonyl) modified peptide was shown to form alternatively tubular or spherical structures at various ratios between water and ethanol in the solution [16]. Very intriguingly, we could observe a clear case of phase separation as the solution contained **either** tubular or spherical assemblies but not a mixture of the two

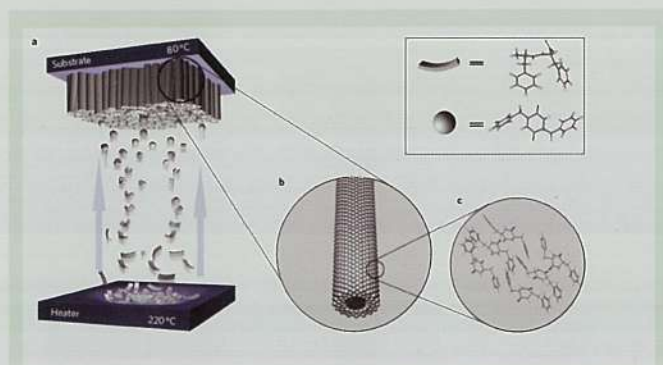
forms [16] (Figure 2).

Deposition and orientation methods of the assemblies We were not only able to form these various nano-assemblies but also to deposit and orient them on various surfaces. We demonstrated the ability to form nano-forests (dense arrays of nanotubes) when the growth of nanotubes was initiated by the evaporation of a solution



**Figure 3:** Vertically aligned diphenylalanine-based nanotubes self-assembled into a peptide nanoforest. a, A possible model for the formation of the aligned peptide nanotubes array. Applying the dipeptide monomers dissolved in the organic solvent onto siliconized glass resulted in the formation of a vertically aligned array of peptide nanotubes. b, SEM analysis of the vertically aligned peptide nanotubes. c, Cold field-emission gun high-resolution scanning electron microscope (CFEG-HRSEM) analysis of the nanotubes array. The inset represents higher magnification of the aligned nanotubes. d, High-magnification micrograph (x120,000) of one individual nanotube of the array obtained by CFEG-HRSEM. [Rechess and Gazit (2006) *Nature Nanotech.* **1**, 195-200].





**Figure 4:** Proposed assembly mechanism for the formation of vertically aligned peptide nanotubes. a, Schematic of the vapour deposition technique. During evaporation, the diphenylalanine peptide, which is heated to 220 °C, attained a cyclic structure (Cyclo-Phe-Phe peptide) and then assembled on a substrate to form ordered vertically aligned nanotubes. b, Illustration of a single peptide nanotube composed mainly of Cyclo-Phe-Phe peptide. c, Molecular arrangement of six Cyclo-Phe-Phe peptides after energy minimization. A stacking interaction between aromatic moieties of the peptides is suggested to provide the energetic contribution as well as order and directionality for the initial interaction [Adler-Abramovich et al. (2009) *Nature Nanotech.* **4**, 849-854].

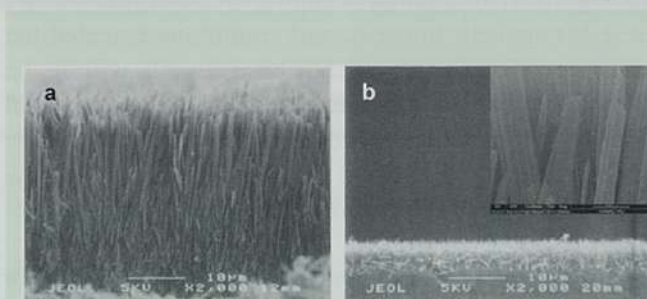
of building blocks dissolved in hexafluoroisopropanol (HFIP) [17]. The rapid evaporation of the fluorinated alcohol resulted in a unidirectional axial growth of the peptide nanotubes (Figure 3). Electron microscopy visualization of peptide nanotube arrays demonstrated in the rapid formation in some of the cases incomplete closure of the tubular structure occurs suggesting that as with other nanostructure the formation of closed assemblies is achieved by the curving of a two dimensional layers.

Horizontal orientation of the nanotubes was obtained when the nanotubes were coated with ferrous-ferric oxide magnetic nano-particles and small (0.5 Tesla) external magnetic force was applied. A clear reorientation of the tubes from a random distribution to an orientation along the magnetic field is observed [17]. The orientation of non-modified nanotubes was obtained when a much larger (up to 12 Tesla) magnetic field was applied [18]. This is most likely due to the diamagnetic properties of the aromatic moieties which are quite small for each system but results at larger cumulative properties when a large array of diamagnetic elements is formed as in the case of nanotubes with micro-scale length.

Other methods of deposition were based on the physical vapor deposition of these structures which included heating of the peptide building blocks under high vacuum and their growth on a target surface [19] (Figure 4). The duration of the deposition process allows the precise control of the thickness of the peptide array (Figure 5). Peptide nanostructures were also deposited by the use of inkjet technology in which the peptide building blocks were used as “ink” for printed of these structures on different surfaces including plastic and the conductive ITO (indium tin oxide)-coated plastic [16].

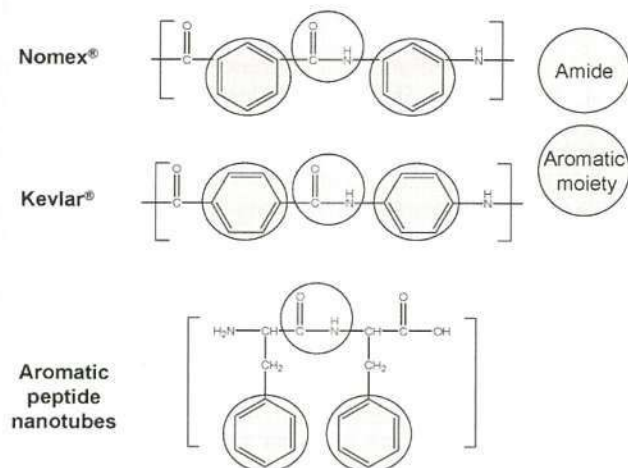
### Physical and chemical properties of the nanostructures

We could clearly predict a very high rigidity of the structures based on their extraordinary persistence length. Yet, direct mechanical measurement using AFM indentation techniques were employed to determine directly the rigidity of the structures. For the nanotubes, an averaged point stiffness of 160 N/m was measured and a Young's modulus of 20 GPa was calculated using finite element analysis [20]. This very high value was also confirmed independently by another group using a bending beam model [21]. At that time, it was claimed that the peptide nanotubes are the most rigid self-assembled organic nanostructures. Yet, the nanospherical



**Figure 5:** Control of the self-assembly process of the peptide nanotubes by physical vapour deposition (PVD) a, Side view of vertically aligned ADNTs demonstrating the elongated micrometer tubes, with a thickness of 40 μm. b, Side view of vertically aligned ADNTs demonstrating the elongated micrometer tubes, with a thickness of 5 μm. The inset shows a high-resolution SEM image of the ADNTs. [Modified from Adler-Abramovich et al. (2009) *Nature Nanotech.* **4**, 849-854].





**Figure 6:** Comparison of peptide aromatic polyamides and the aromatic peptide nanotubes building blocks sharing common structural features of planar amide bond that allow staking and hydrogen bonds and ordered aromatic moieties that allow organization into compact crystalline regions [Gazit (2007) *Chem. Soc. Rev.* **36**, 1263–1269].

fabrication techniques [23]. Other observed physical properties of the nanotubes included non-linear optic phenomena [24] and high piezoelectricity [25].

### Applications of the organic nanostructures

Various technological applications of the peptide nanostructures were already explored. The first one was the modification of electrodes for electrochemical biosensing. The increase in the surface area of the electrode resulted in a marked increase of sensitivity [26–27]. Later studies compared the increase in sensitivity of peptide nanotube modified electrodes as compared to carbon nanotube modified electrodes and higher sensitivity was observed with the former [28]. While the modification of electrochemical sensors electrode is an important direction other directions are being explored including the modification of field effect transistors (FET) gating.

Similar to the modification of electrodes for electrochemical sensing, we modified electrodes for electrostatic energy storage using ultra-capacitors. The electrodes were modified with array of nanotubes deposited by physical vapor deposition as described above and the electrostatic storage was measured [19]. It was clearly demonstrated that the increase in the functional surface of the electrodes and a marked increase in the energy storage capacity. The modified electrodes were shown to be stable in thousands rounds of charge and discharge [19].

Another direction that was already explored is the use of the peptide nanostructures as fillers for the formation of improved composite materials. When the peptide nanotubes were added to epoxy resin and the mechanical properties were study. The addition of the tubes resulted in a maximal increase of about 70% in shear strength and 450% in peel strength as compared to neat epoxy while preserving the thermal and elongation properties of the resin [29]. This effect exceeds the reinforcement effect of several known inorganic nanofillers, positioning the peptide nanotubes as excellent nanofillers in composite materials. This further suggests the usefulness of the assemblies for the reinforcement of composite materials.

### Conclusions

assemblies revealed even higher mechanical rigidity. When we studied the rigidity of the nano-sphere using indentation techniques, the structure could not be deformed by any metallic cantilever and we had to use a diamond cantilever. Indeed, an averaged point stiffness of up to 900 N/m was measured and a Young's modulus of up to 275 GPa was calculated [22]. This is especially intriguing as this is higher than many metals and even steel. The molecular basis for the remarkable rigidity is not full understood. Yet the similarity of the building blocks to the ultra-rigid aramid polymers is evident (Figure 6).

The peptide nanostructures show not only remarkable mechanical stability but also high thermal and chemical stability. The tubular structures are stable at temperatures over 250° C as observed by thermogravimetric analysis (TGA) and visualization by microscopy techniques [23]. The peptide nanostructures also had remarkable stability in various solvents including acetone, acetonitrile, dichloromethane, and other organic solvents and at acidic and basic conditions. This clearly suggests that the peptide structures could be compatible with various



Based on our studies of the mechanism of amyloid self-assembly by extremely short peptide motifs, we discovered the ability of the diphenylalanine and its related structural family to form well-ordered structures at the nano-scale. Nanostructures of various geometries could be formed and these assemblies could deposit and orientated on various surfaces. The unique physical and chemical properties of these nanostructures were already utilized for various technological applications. We believe that the dipeptide aromatic motif represents a new front in organic nanotechnology and many more technological applications could be developed. Open and intriguing scientific question remain on the exact mechanism that lead to the remarkable mechanical rigidity of these structures and precise steps in the early events that lead to the formation of these structures.

## Acknowledgements

I would like to greatly acknowledge the contribution of my students and members of the research group, current and former, as well as our many collaborators. The work described here is the result of inspiration and hard work of many. I was fortunate to take part in this journey with my group members and collaborators.

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# The Israel Chemical Society celebrates the International Year of Chemistry<sup>1</sup>

**Ehud Keinan\* and Yael Schuster**

Following a proposal made by the International Union of Pure and Applied Chemistry (IUPAC) and the United Nations Educational, Scientific and Cultural Organization (UNESCO), the General Assembly of the United Nations has declared the year of 2011 as the International Year of Chemistry (IYC2011). The year 2011 marks the 100th anniversary of the Nobel Prize in Chemistry awarded to Marie Skłodowska Curie, highlighting the role of women in chemistry and other sciences. This year also marks the 100th anniversary of the founding of the International Association of Chemical Societies, which promotes international communication and cooperation among all chemists.

As chemists, we wish to convey a message to the public that Chemistry is a fascinating science that offers outstanding opportunities for the young generation. Chemistry is called *the Central Science* because it is concerned with the material world on a molecular level, dealing with the structures of molecules, their interactions with other molecules and with all forms of energy. Therefore, Chemistry has always played and will continue to play a central role in all basic and applied fields of science, including physics, biology, medicine and all technological disciplines. Consequently, the chemical sciences and chemical industry hold the keys

for solving severe global problems, including the ever increasing demand for energy, food, better human health, fresh water, clean air, raw materials, quality of life, etc.

Chemistry has always been a prominent area of scientific and technological excellence in the State of Israel. Israel is home to about 7,000 chemists, 5,000 chemical engineers, and 1,000 chemistry teachers. The Israeli chemical industry has contributed significantly to the national economy, with chemical products constituting about 25% of the country's exports. Two of the State's nine Presidents, Prof. Chaim Weizmann and Prof. Ephraim Katzir, were world-renowned chemists. All four Nobel Prizes in science awarded so far to Israeli scientists, Professors Avram Hershko (2004), Aaron Ciechanover (2004), Ada Yonath (2009), and Dan Shechtman, were Chemistry Prizes.

The Israel Chemical Society (ICS), founded in 1933 as a non-profit organization, aims at the promotion of chemical research and development, chemical industry and chemical teaching, as reflected by its diverse membership, including academic faculty members and students, industrial chemists, chemical engineers and chemistry teachers. The overarching goals of the ICS perfectly match the global goals of the IYC2011

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<sup>1</sup> A previous version of this article has been published in the *Israel J. Chem.* 2011, 51, 688–697.



- increasing the public appreciation and awareness of chemistry and, in particular, increasing the interest of young people in chemistry and chemical education in order to ensure that first-rate minds continue to be attracted to and challenged by the *Central Science*.

All members of the ICS, including chemists, chemical engineers, and chemistry teachers, share the excitement and pride of being Israeli chemists. The ICS has joined its sister societies around the globe with over a dozen original endeavors for the International Year of Chemistry, three of which are reported here: the Launch Ceremony in the Knesset, the issuing of new stamps, and participation in the 3rd Israel Mountain-to-Valley relay race.

### Launching of IYC2011 in the Knesset

Israel opened the International Year of Chemistry on January 4th, 2011, even before the official international ceremony at the UNESCO World Headquarters in Paris, Jan.27--28, 2011. Remarkably, Israel has been the only country where such an event was hosted by its Parliament. The ICS and the Knesset Science and Technology Committee jointly organized the launch, which was attended by several hundreds distinguished guests (Figures 1 and 2), including Government Ministers, Knesset Members, Supreme Court Judges, Governor of the Bank of Israel, University Deans and Rectors, President of the Israel Academy of Sciences and Humanities, officials of the Israel Ministry of Education, leaders in academia and chemical industry, professors, chemistry teachers, and students from all Israeli universities and colleges.

The Knesset lobby was decorated with many colorful posters depicting how chemistry benefits humankind (Figure 3). The posters, which were provided by Prof. Attila Pavlath, former President of the American Chemical Society, were translated into Hebrew by the ICS and printed by the Ministry of Education. All guests received T-shirts depicting the International logo of the IYC2011 and the motto "Chemistry is everything." Indeed, the entire event was produced by chemists. For example, Yury Tulchinsky, the concert pianist who welcomed the attendees into the Knesset auditorium with wafting sounds of piano music, is a chemistry graduate student of the Technion.



**Figure 1.** Distinguished guests at the Knesset event.



**Figure 2.** Three school pupils who won medals in recent International Chemistry Olympiads are applauded by the audience at the Knesset ceremony. Standing from left: Moshe Michael Michalshvili (Bronze Medal, 2010, Tokyo) Eviatar Dgani (Bronze Medals, 2009, Cambridge and 2010, Tokyo) Assaf Mauda (Silver Medal, 2008 Budapest, Gold Medal, 2009, Cambridge and Gold Medal, 2010, Tokyo), all wearing T-shirts with the Hebrew version of the IYC2011 logo.



**Figure 3.** Display of posters, which depict how chemistry benefits humankind, were provided by Prof. Attila Pavlath of the ACS and translated into Hebrew by the ICS.





**Figure 4.** Distinguished guests at the Knesset event. Top row, from Left: MK Reuven (Rubi) Rivlin, Speaker of the Knesset, Knesset Member Meir Sheerit, Head of the Knesset's Science and Technology Committee, Prof. Daniel Hershkowitz, Minister of Science and Technology, Prof. Ruth Arnon, President of the Israeli Academy of Sciences and humanities, Prof. Nicole Moreau, President of IUPAC, Prof. Ulrich Schubert, President elect of EuCheMS, Prof. Stanley Fischer, Governor of the Bank of Israel, Prof. Francois Diederich, Department of Chemistry and Applied Biosciences ETH Zurich.

The program started with MK Reuven (Rubi) Rivlin (Figure 4), the Knesset Chairman, who welcomed the audience, emphasizing the importance of scientific research and education for the State of Israel. Prof. Ehud Keinan, President of the ICS, delivered the opening remarks, outlining the roots and goals of the ICS and the IYC2011. MK Meir Sheerit, Chairman of the Knesset Science and Technology Committee, reminded the audience that he started his career as a chemistry student and a high school chemistry teacher. He stressed the importance of a strong scientific education in all academic pursuits, allowing a student to see the order and logic in the natural world, and such a solid base is necessary before becoming a scientist. Sheerit ended with a challenge to the Ministry of Education to revert to

the basics and emphasized the crucial need to expose all Israeli pupils to rigorous scientific learning.

The next speaker was Prof. Daniel Hershkowitz, Minister of Science and Technology, former Dean of the Faculty of Mathematics at the Technion as well as Rabbi of a Haifa neighborhood. He sketched his vision for the future of science in Israel as a technological power. Although small in size, Israel is clearly on par with the world's scientific superpowers. Prof. Hershkowitz portrayed scientists as tourists who are trying to uncover the laws of nature, hoping that Israeli chemists have successful scientific journeys to continually uncover the secrets of nature for the benefit not only of the State of Israel but for the whole world.



The next speaker was Prof. Ruth Arnon, the first female President of the Israel Academy of Sciences and Humanities. She is one of Israel's top-ranking chemical immunologists and former Vice-President of the Weizmann Institute of Science. Her long, successful career has included the Wolf, Rothschild, and Israel prizes, and co-inventing the Copaxone drug for Teva Pharmaceuticals. She underscored the crucial role of chemistry in education because everything in the universe is made up of chemical elements. The recent decline in education, in particular chemical education, strengthens the need for improving chemical awareness and recognition. She ended on a positive note, remarking that awarding of the ICS medals at this ceremony celebrates Israel's strengths in chemistry, and that the creativity represented by the Medal Laureates will certainly promote the chemical industry.

The guests were then entertained by an outstanding vocal performance of Albinoni's Adagio in G Minor by two Technion doctoral students in Chemistry (Figure 5), Ms. Renana Poranne (soprano) and Ms. Moran Shalev (mezzo-soprano), who were accompanied on the piano by Biotechnology Engineering student, Mr. Amit Blum.

Prof. Nicole Moreau, President of IUPAC (Figure 3), welcomed the enthusiastic participation of Israel in the International Year of Chemistry. IUPAC is an international umbrella organization for all chemical societies. Its relationship with UNESCO, along with

some crucial help from Ethiopia, enabled this year to be named the IYC2011. Because of the unique design, in which each country is responsible for its own planning, the influence of IYC2011 is expected to extend long after the year has ended. Prof. Moreau made an amusing comment about the fact that this program preceded the official launch of IYC2011 in Paris, indicating that this practice is in keeping with the Jewish tradition of starting all holidays on the preceding evening.

Prof. Ulrich Schubert, President elect of the European Association of Chemical and Molecular Sciences (EuCheMS), who is Professor of Chemistry at the University of Technology in Vienna, lauded Israel's appreciation of chemistry, highlighted by the fact that no other parliament in the world has opened its doors to an event like this. Since the language of chemistry is the same all over the world, independent of race, nation, or religion, it can be a problem-solving role model for all. Professor Schubert ended with wishes of a successful, peaceful year of chemistry.

The speeches were followed by the unveiling of two new Israeli stamps commemorating the IYC2011 (Figure 6). The ceremony included MK Meir Sheetrit; Mr. Sasi Shilo, Chairman of the Israel Postal Company; Mr. Yaron Razon, Director of the Philatelic Service; and Mr. Asher Greenbaum, deputy CEO of Israel Chemicals Ltd., Board member of the ICS and chairman of the chemical, pharmaceutical, and environmental division of the



**Figure 5.** Performing at the Knesset: from left, Ms. Renana Poranne (soprano) and Ms. Moran Shalev (mezzo-soprano), both Ph.D. candidates at the Schulich Faculty of Chemistry of the Technion.



**Figure 6.** Two new Israeli stamps are exposed at the Knesset. From left: MK Meir Sheetrit, Mr. Yaron Razon, Director of the Philatelic Service, Mr. Asher Greenbaum, deputy CEO of Israel Chemicals Ltd. and member of the ICS Board, Mr. Sasi Shilo, Chairman of the Israel Postal Company.





**Figure 7.** The ICS Gold Medal is being awarded to Mr. Eli Hurvitz. From left: Prof. Ruth Arnon, MK Meir Sheetrit Mr. Eli Hurvitz and Prof. Keinan.



**Figure 8.** Mr. Eli Hurvitz. Is being decorated with the IYC2011 pin by Prof. Keinan.

Manufacturers' Association. These stamps are based on a graphical depiction of the scientific achievements for which two Nobel prizes in chemistry awarded to Israeli scientists. Mr. Shilo made a convincing description of the strength and power stamps have to educate and unify people of different cultures. A full description of the development of the IYC11 stamps is given below.

The presentation of the stamps was followed by a lecture entitled "Chemistry is everything" by Prof. Ehud Keinan, who punctuated his talk with many famous quotes by scientists. He began with Marie Curie's whimsical description of the unique, intellectually rewarding experience of being an active scientist: "a scientist in his laboratory is not a mere technician: he is also a child confronting natural phenomena that impress him as though they were fairy tales," and that of Sir Francis Bacon: "they are ill-discoverers that think there is no land, when they can see nothing but sea." He demonstrated the absolute unpredictability of science, bringing up laughable predictions by famous scientists about the future, such as Lord Kelvin's claim, in 1885, that "heavier-than-air flying machines are impossible," and the statement by Nobel Laureate Sir George P. Thomson, who said in 1956 that "the possibilities of travel in space seem at present to appeal to schoolboys more than to scientists," just 1 year before the Sputnik launch, 4 years before the space travel of Yuri Gagarin, and 13 years before the first landing on the moon. Keinan further supported the notion of unpredictability of science by the colossal failure of the commission of respectful

scientists nominated by President Franklin D. Roosevelt in 1937 to predict technical and industrial developments of the following 20--30 years. Using another citation by Thomas Jefferson that "Liberty is the great parent of science and of virtue; and a nation will be great in both in proportion as it is free," he reached the conclusion that academic freedom must be preserved and that control over scientific research and the entire higher education system should be kept away from zealous governmental administrators who are sure they can predict the future and tell scientists where to invest their efforts.

Keinan presented the central role that chemistry plays in all scientific disciplines, as well as in dealing with the most pressing global problems. Finally, he brought up the great benefits to the national economy that arise from intense scientific activities, as described by the recent bestseller "Start-Up Nation" by Dan Senor and Saul Singer. Prof. Keinan, who serves also as Chairman of the National Chemistry Committee of the Ministry of Education, expressed deep concerns about the national educational policy. In contrast to the self-evident success story of science and the economy in the State of Israel based on the past six decades, the current policy of the Ministry of Education results in a very narrow exposure of the Israeli pupils to the sciences, with only 20% of them achieving matriculation in science. This situation puts much responsibility on the shoulders on non-governmental organizations, including the ICS, to promote science education through joint efforts of academia, schoolteachers and industry. Reinvigoration of



the country's scientific awareness is the most important goal of IYC2011 in Israel.

The next highlight of the program was the awarding of three prestigious ICS prizes: the ICS gold medal to Mr. Eli Hurvitz of Teva Pharmaceuticals and to Prof. Meir Wilchek of the Weizmann Institute of Science, and the ICS Industrial Green Chemistry award to Mr. Malachi Alper of Paz Ashdod Refinery Ltd.

**ICS gold medal to Mr. Eli Hurvitz** (Figures 7 and 8). This year is the first time that the ICS gold medal, the highest honor of the ICS, has been awarded to a non-chemist for his outstanding contributions to the chemical industry: Mr. Eli Hurvitz, who transformed Teva Pharmaceuticals into the largest company in Israel, a key element in the Israeli economy, and the number one generic manufacturer worldwide. He has led the Teva group for 35 years and brought it from a small, unknown pharmaceutical company to its standing today as a world leader in generic pharmaceuticals. These great achievements were attained by implementing a culture of excellence and strategic management based on a long-term vision of the future leadership of the company. Teva currently employs about 40,000 employees in dozens of factories and subsidiaries around the world, yet it retains its core management and development in Israel with about 6000 employees.

Eli Hurvitz was born in Jerusalem in 1932. In 1953, after graduating from the Hebrew University economics school in Tel Aviv, he began his career as a junior employee in the drug company Asia. In 1976 he was appointed to the position of CEO and, over time, orchestrated the merger of several pharmaceutical companies into the company named Teva, which he then headed for many years until 2009.

In addition to his great responsibilities at Teva, Eli was also recruited for the support of many social, cultural, and scientific activities in Israel. He has held a long list of public positions, including President of the Manufacturers Association, Chairman of the Federation of Economic Organizations, Chairman of the Israel Export Institute, Chairman of the Board of Bank Leumi, Chairman of the Israeli Task Force, Chairman of the Jerusalem Development Authority, member of the Advisory Committee of the Bank of Israel, member of the Board of Governors of the Weizmann Institute and Tel Aviv University, and many more. He has received

many and varied awards for his civic and industry activities, including honorary doctorates from the Technion, Weizmann Institute, Ben Gurion University, Tel Aviv University, and Bar Ilan University. He won the Industry Prize, and the State of Israel Jubilee Award for lifetime achievement and special contributions to the state.

Eli Hurvitz's acceptance speech was peppered with jokes and deeply philosophical remarks on the boundaries of nature and science. There are billions of people in the world who live off what they have made, he said, not what nature gave them. His message was not that we should use science try to squeeze the most out of nature, but rather that human abilities and nature's limitations are what allow science to create new possibilities. The number of people who can enjoy these materials is confined only by the boundaries of our imaginations, and not the boundaries of nature. As someone who is intimately familiar with the workings of an international company and encounters dilemmas every day, he knows the distance between goals and the day-to-day details, and without high goals this gap cannot be filled with any real substance. It is through human curiosity and scientific power that we can achieve the highest of all scientific goals.

**ICS gold medal to Prof. Meir Wilchek** (Figure 9). Prof. Wilchek is the father of the technology known as affinity chromatography, which is used to separate and purify proteins in any biochemical laboratory and the pharmaceutical industry worldwide. This technology led to the establishment of more than 75 high-tech companies worldwide, with sales of over 70 billion dollars this year. Yet, most remarkable of all, this groundbreaking method was not patented. Prof. Wilchek felt that his research was funded by the public, and so it should be publicly available. In order to succeed, Wilchek said, you need money, patience, and luck. Since money is something we don't have in Israel, one must succeed on patience and luck alone.

Prof. Wilchek was born in Warsaw, Poland, in 1935. During World War II he was taken to Siberia from the Soviet Union. His father, the rabbi of Warsaw, was killed along with most of his family. In 1949, he immigrated to Israel with his mother and sister, and settled in Rehovot. After completing his military service in the Air Force, he studied chemistry and physics at Bar Ilan University, receiving his first degree in 1960, followed by his Ph.D.





**Figure 9.** The ICS Gold Medal is being awarded to Prof. Meir Wilchek. From left Prof. Ruth Arnon, MK Meir Sheerit, Prof. Meir Wilchek and Prof. Ehud Keinan.



**Figure 10.** Mr. Malachi Alper, CEO of Paz Ashdod Refinery Ltd. receives the ICS Industrial Green Chemistry award. From left: Mr. Yehuda Segev, Director General of the Manufacturers' Association of Israel (MAI), Prof. Ruth Arnon, MK Meir Sheerit, Mr. Malachi Alper and Prof. Ehud Keinan.

in 1965 from the Weizmann Institute of Science in the Department of Biophysics where he later became a faculty member. He filled various senior positions at the Weizmann Institute, including Department Head of Biophysics, Head of the Professors' Council, and Dean of the Faculty of Biochemistry and Biophysics. He was a visiting scientist at the U.S. National Institutes of Health and served as an advisor to biotechnology companies and public committees.

Prof. Wilchek has published more than 400 scientific papers. In 1968, he and his colleagues developed "affinity chromatography", which revolutionized the isolation of biochemical materials and opened the door to new opportunities in biology, biotechnology, chemistry, nanotechnology, physics, and many other fields. This method has contributed to many developments in life sciences, such as increased understanding of DNA and development of protein chips. It has had an especially profound impact on the field of medicine, accelerating the development of protein-based drugs. Moreover, Prof. Wilchek also developed the Avidin-Biotin technology, which is used to diagnose diseases, isolate biological materials for biotechnological or nano-technological purposes, and for biomedical research. This system has enabled many laboratories to give up their need for radioactive materials.

Prof. Wilchek has been awarded honorary doctorate degrees from the University of Waterloo (Canada), Bar

Ilan University, University of Jyväskylä (Finland), and Ben Gurion University. He is the recipient of the Wolf Prize for Medicine, the Israel Prize for Biotechnology, the Outstanding Clinical Chemist Prize from the International Federation of Clinical Chemists, the Christian B. Abfinsen Prize of the Protein Society, the Willheim Exner Medal from Austria, and the Emet Prize in Chemistry. He is a member of the Israel Academy of Sciences, honorary member of the American Society of Biological Chemists, and a foreign member of the Institute of Medicine of the National Academy of Sciences. At the Weizmann Institute he holds the Marc Gutwirth Chair of Molecular Biology.

**ICS Industrial Green Chemistry award to Paz Ashdod Refinery Ltd** (Figure 10). Mr. Malachi Alper, CEO of the Paz Ashdod Refinery, received the award for outstanding achievements in environmental protection through remarkable reduction of industrial waste, reduced emission of greenhouse gases, and noteworthy conservation of energy. Within the past three years he refinery invested over \$115 million in new facilities that reduce emission of toxic waste and significantly preserve energy. For example, a recently constructed catalytic facility that is based on three successive catalytic reactions removes sulfur dioxide from the effluent gas, bringing its emission down to one-tenth of the legal level. Similar achievements were recorded with reduction of carbon dioxide emission and with detoxification of sewage using bioreactors. The refinery, 4 km north of



the city of Ashdod, was established in 1973 to meet the challenges of increased energy demands by the growing Israeli economy. The refinery received crude oil from the port of Ashdod and from the Eilat-Ashkelon crude oil pipeline. Using natural gas as a non-polluting energy source for production of electricity, steam, and heat, the plant is also connected to the national natural gas pipeline.

The program concluded with another remarkable vocal performance by chemistry graduate students Renana Poranne and Moran Shalev, who were accompanied on the piano by Biotechnology Engineering student Amit Blum.

### The IYC2011 stamps

Postal stamps are an excellent means to deliver messages to the general public. For this reason, the ICS applied to the Israel Philatelic Service with a request to issue a stamp commemorating the IYC2011. Nevertheless, considering the fact that national postal services worldwide every year reject hundreds of thousands of stamp proposals, the chances were quite slim. Furthermore, the process of issuing a new stamp takes time. Proposals for 2011 had to reach the Philatelic Service no later than October 2009. And we sent our stamp proposal five months after the deadline. Nevertheless, Israel is known to be the country of unlimited opportunities and, as David Ben Gurion used to say, "In Israel, anyone who doesn't believe in miracles is not a realist."

Obviously, the response from Mr. Yaron Razon, director of the Philatelic Service, arrived on April 29, 2010 with much surprise. His acceptance of our proposal marked the beginning of very successful collaboration between the ICS and the Philatelic Service. Issuing of stamps is very long and detailed, with many steps including careful design, approval by the Government of Israel and a complex printing process (by the Royal Joh. Enschedé print, The Netherlands). In order to make the stamps available for January 4th, all this had to be accomplished in record time. It was a joint effort of many enthusiastic people. The ICS established an *ad-hoc* stamp committee, including Prof. Zvi Rappoport of the Hebrew University of Jerusalem, Prof. Joel Sussman of the Weizmann Institute of Science, and Prof. Ehud Keinan of the Technion. The team of the Philatelic Service included Mr. Yaron Razon and Mr. Gideon Marinsky, and the

stamp artist, Mr. Haim Kivkovic. Dr. Michael Pique of The Scripps Research Institute provided additional help.

A highly productive meeting of all parties was held in the morning of June 30, 2010 in the main office of the Philatelic Service in Jaffa. One major achievement was that the Philatelic Service accepted the ICS request to issue two stamps rather than one, in order to give separate recognition to the two Nobel Prizes in Chemistry awarded to Israeli scientists. Discussing the stamp graphics we learned from Mr. Yaron Razon that personal portraits are used on official stamps only *post-mortem*, a nod to Jewish tradition. Accordingly, the ICS proposal to depict the crystallographic molecular structures of the relevant molecules was accepted. While the small protein ubiquitin could easily fit on a stamp, the extremely large and complex structure of the ribosome became a major challenge for the stamp artist. Much help was received from a crystallographer at the University of Hamburg, Dr. Joerg Harms, who transformed the results from a 2001 paper published by Prof. Ada Yonath and her coworkers in *Nature* to an aesthetically pleasing image with appropriate colors, showing the large ribosomal subunit.

The next six months represented a continuous struggle to complete all the necessary technical and administrative tasks for the date of issue to coincide with the IYC2011 Launch Ceremony in the Knesset on January 4, 2011. Indeed, the impossible happened and the stamps were ready in time.

**The ubiquitin stamp: a protein destructor.** The stamp (4.20 NIS, Figure 11) refers to a very basic scientific question: why must our proteins die, so that we may live? Proteins are the machines that drive our bodies, responsible for all our activities. But on a daily basis our bodies destroy up to 10% of our proteins and generate new ones instead. This phenomenon raises interesting questions: why does this process occur at all, and how? Which diseases would result, if this mechanism were to fail? How can we cure such diseases? As part of the body's quality control mechanism, proteins are destroyed after fulfilling their specific function, if they have been damaged by heat, by pollutants, by genetic mutation, or simply because they are no longer needed. Professors Aaron Ciechanover and Avram Hershko of the Technion -- Israel Institute of Technology, and Irwin Rose of the University of California, Irvine, USA, were jointly awarded the 2004 Nobel Prize in





**Figure 11.** The two Israeli stamps and date of issue envelope commemorating the IYC2011 depict the scientific achievements for which two Nobel prizes in chemistry were awarded to Israeli scientists.

Chemistry for discovering the mechanism that removes damaged or unnecessary proteins. These proteins are labeled for destruction by another small protein called ubiquitin, whose general structure is shown on the stamp. The illustration was adopted from W. J. Cook and coworkers, *Journal of Molecular Biology*, 1987, 194, 531-544. Once tagged by this “kiss of death,” the labeled proteins are removed by the proteasome, while healthy, untagged proteins are spared. Aberrations in this protein destruction process may result in numerous sicknesses, including certain types of cancers and brain diseases. Many pharmaceutical companies are working to develop drugs to combat such diseases. One such drug to treat multiple myeloma, which is a form of blood cancer, is already being used clinically.

**The Ribosome stamp: a protein constructor.** The stamp (6.10 NIS, Figure 11) refers to another basic scientific question: how does the ribosome translate DNA code into life? The ribosome is the biological machine in every

living cell that makes proteins from amino acids. Genetic information, which is stored in our DNA, is copied into RNA, which is then read by the ribosome. This process is known as translation of the genetic information from RNA into proteins, which in turn control the structure and function of all living organisms. The ribosome is a huge machine, consisting of three RNA chains and more than 50 different proteins. Understanding the ribosomal structure and its operating mechanism is critical for the scientific understanding of all kinds of life. In particular, this insight into the life of pathogenic bacteria opened the door to the use of ribosomes as an important target for new antibiotics. Many of today's antibiotics cure various diseases by blocking the function of bacterial ribosomes. The 2009 Nobel Prize in Chemistry was awarded jointly to professors Ada E. Yonath of the Weizmann Institute of Science, Venkatraman Ramakrishnan of the Medical Research Council, Cambridge, UK, and Thomas A. Steitz of Yale University, USA. They showed what the ribosome looks like and how it functions at the atomic level. All three used X-ray crystallography methods to solve the ribosome structure. The image on the stamp (contributed by Dr. Joerg Harms of the University of Hamburg), which is adopted from a paper published by Ada Yonath and her coworkers (Schlunzen et al., *Nature*, 413, 814-21, 2001), shows a view into the tunnel of the large ribosomal subunit from which the newly constructed chain of amino acids exits. This huge structure shows the ribosomal proteins (orange), the ribosomal RNA (blue and pink), and the antibiotic erythromycin (red).

In collaboration with the Philatelic Service, the ICS designed (with the help of Ms. Dina Mid of the Technion graphics department) and issued a Souvenir Leaf in limited edition (Figure 12). This collector's item features the six metals that were known at the Biblical times: “Only the gold, and the silver, the brass, the iron, the tin, and the lead...” Numbers 31:22. Interestingly, whoever translated the Bible from Hebrew to English probably had a limited background in chemistry, incorrectly translating to brass the original term *nehoshet* (copper).

### The Mountain to Valley race

The Mountain to Valley (M2V, *Har La'Emek* in Hebrew) race is the longest and most challenging relay

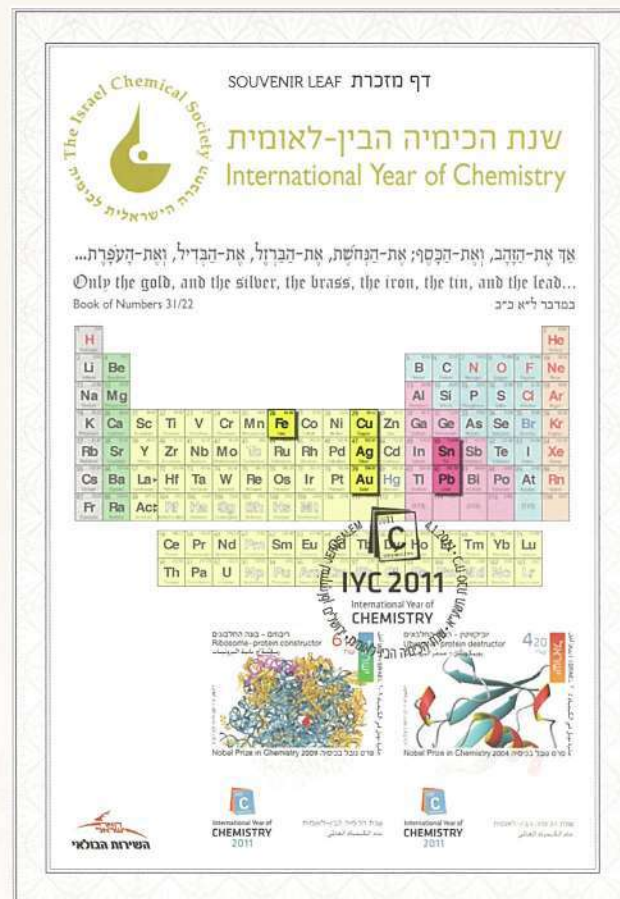


race in Israel, featuring 212 kilometers of dirt roads and mountainous paths from the foot of Mount Hermon along the vistas of the Hula Valley, the mountainous Jordan River, Sea of Galilee, the Beit Netofa Valley and the lower Galilee, the Jezreel Valley, all the way to the communal village of Timrat. This northern part of Israel in the spring season, on the first full-moon night after Passover, probably displays the most beautiful natural scenes of the country.

Over 260 groups totaling over 1800 runners, most of them in teams of 8, took part in the 3rd M2V race, May19-20, 2011. These teams participated in either competitive or a non-competitive race. With a route comprising 24 legs of 6--14 km each, every runner on a team of 8 completed three legs, approximately 25 km in total, each time passing the relay bracelet to the next member of the team. Smaller teams included 6, 4 or 2 runners (men, women or mixed teams) rotating among themselves. In addition, a few "ultra runners" completed the entire route of 212 km in about 30 hours, demonstrating outstanding physical and mental fitness.

**The ICS teams.** Two mixed teams of 8 runners each represented the ICS. The teams, named Ubiquitin and Ribosome, included faculty members and graduate students from the chemistry departments of all of Israeli universities. The team members were easily identified by their yellow and white running shirts (Figures 14-16), featuring either the ubiquitin or the ribosome stamp on the front and the ICS logo on the back along with the Hebrew version of the IYC2011 logo and that of the teams' sponsor, Oil Refineries Ltd. (ORL), Haifa. Although participating in the non-competitive category, both teams completed the route in a little over 20 hours, matching the top 30% of the competitive teams.

The 8 members of the Ubiquitin team were led by Dr. Alex M. Szpilman of the Technion whose lab focuses on organic synthesis of biologically active natural products and synthetic methodology. Alex received his Ph.D. degree from the Weizmann Institute of Science with Prof. Mario D. Bachi and later was a postdoctoral fellow at the ETH Zurich with Prof. Erick Carreira. Other team members were: Prof. Ehud Keinan of the Technion and The Scripps Research Institute, President of the ICS and Editor-in-Chief of the IJC; Dr. Micha Fridman, a Senior Lecturer at Tel Aviv University who received his Ph.D. at the Technion with Prof. Timor Baasov and was a postdoctoral fellow at Harvard University with Prof.



**Figure 12.** The souvenir leaf depicting the stamps with the first-day-of-issue cancellation. The six metals highlighted on the periodic table are mentioned in a single biblical phrase: "Only the gold, and the silver, the brass, the iron, the tin, and the lead..." Numbers 31:22.

Daniel Kahne; Prof. Gerardo Byk of Bar Ilan University, who focuses on the development of novel nanometric, high throughput screening suited for in vivo screening of small molecules; Dr. Claudia M. Barzilay, researcher and Senior Advisor at Bargal-Analytical Instruments -- born in Peru she obtained all her degrees at the Technion, including Ph.D. with Prof. Zeev Gross, and following a postdoctoral research with Prof. Paul A. Wender at Stanford University, she was a Lecturer at the department of Medicinal Chemistry at the Hebrew University of Jerusalem until 2009; Ms. Natalie Reznikov, a graduate student in the Department of Structural Biology, the Weizmann Institute of Science; Mr. Niv Yardeny, a graduate student at Ben-Gurion University, finishing his





**Figure 13.** The framed IYC2011 stamps and date of issue envelope (gift from the Israel Philatelic Service) are being awarded by Prof. Keinan to the three Israeli Nobel Prize Laureates, Professors Avram Hershko (2004), Aaron Ciechanover (2004) and Ada Yonath (2009).

M.Sc. degree on hypervalent silicon compounds under Prof. Daniel Kost; and Mr. Michael Morozov, an M.Sc. student at the Weizmann Institute of Science under Prof. Milko van der Boom, focusing on surface chemistry of organometallic compounds.

The 8 members of the Ribosome team were led by Prof. Michael M. Meijler of Ben-Gurion University, a native of The Netherlands. While studying chemistry at the University of Amsterdam he was also a competitive distance runner. Specializing in the 3000 m steeplechase, he won the Israel championship in 1999, 2001, and 2002. After earning a Ph.D. degree from the Weizmann Institute of Science with Prof. Abraham Shanzer he was a postdoctoral fellow at The Scripps Research Institute with Prof. Kim Janda. His research focuses on the elucidation of chemical communication within and between species. The Ribosome team also included: Prof. Alon Hoffman of the Technion, who focuses his research on experimental surface science and thin films, and, in particular, on diamond surfaces using electron spectroscopic and microscopic methods, deposition of diamond films onto different substrates and studying their properties; Ms. Alina Amel, an M.Sc. student at the Technion with Prof. Efrat Lifshitz, as well as a triathlete, cyclist, runner, and swimmer; Dr. Eyal Gur, a competitive distance runner as well as a Lecturer at

Ben-Gurion University, focusing his research on protein quality control mechanisms in bacteria, especially on ATP-dependent protein degradation; Ms. Neta Rosenstein, a triathlete who recently obtained her B.Sc. degree in Chemistry and Materials Engineering at the Technion; Dr. Daniel Mohr, a marathon runner and a native of Northern Germany, who obtained his Ph.D. degree at the University of Münster and is now a postdoctoral fellow at the Weizmann Institute of Science with Prof. Lucio Frydman; Mr. Ori Gidron, a Ph.D. student at the Weizmann Institute of Science with Prof. Michael Bendikov, who has discovered a new family of organic electronic materials; and Mr. Gary Zaiats, a Ph.D. student at the Technion with Prof. Efrat Lifshitz, working on solar energy.

**The trail.** The breathtaking 212 km trail, which took most teams about 20-24 hours to complete, started at the foot of Mount Hermon at *Qala'at Namrud* (Nimrod Fortress), which was built in 1229 by Al-Aziz Uthman, nephew of Saladin. *Leg 1* descended steeply from the ancient fortress down the scenery road that connects Neve Ativ to the Banias Nature Reserve, overlooking Katef Sion to the north and entire Hula valley to west and south. *Leg 2*, from Banias to Kibbutz Shamir, followed the old patrol route of the pre-1967 war, a poor gravel road connecting old guard posts at the foot of the



abandoned Syrian outposts of Tel Fahr and Tel Azaziat. *Leg 3* descended from Kibbutz Shamir, passing Kibbutz Lehavot Habashan and many agricultural fields, to the pecan grove located on the western bank of the Jordan River. *Leg 4* continued along the eastern canal of the Jordan River to the Agmon Ha'Hula nature reserve. *Leg 5* encircled the southwest side of the Agmon Ha'Hula lake, continuing to the junction of the east and west canals and then along the western bank of the Jordan River all the way to the Pkak Bridge. *Leg 6* crossed the bridge, continued along the eastern bank of the Jordan River, passed areas suspected to be old Syrian mine fields and finally ascended to the Benot Ya'aqov Bridge. *Leg 7* crossed the Jordan River again to the west, to the communal village of Karkom via the Hilly Jordan Route, passing the Kfar Hanassi hydraulic station and the Atara Fortress. *Leg 8* went along the Karkom road until the Amnon--Almagor junction, followed by a steep descent towards Kfar Nahum (Capernaum) on the northern shores of Lake Kinneret (Sea of Galilee).

*Leg 9* started at Capernaum, one of the key sites for Christian pilgrims with a number of wonderful churches, and followed the walkway at the banks of the Sea of Galilee. A steep climb to the Sapir water pumping station, where water is pumped from Lake Kinneret to the National Water Carrier (NWC), was followed by a very steep descent to road 90 that leads to Tiberias. *Leg 10* went from the Sapir site all the way to the Tzalmon Prison, suddenly changing its character from mostly descending to mostly ascending with the crossing of the Amud Stream. *Leg 11* descended to the Tzalmon stream, then up a difficult ascent to a ridge northwest of the village of Eilabun, bypassing the village and reaching the Eilabun--Maghar road. *Leg 12* departed from Eilabun along the NWC at the northern border of the green Netofa Valley below the villages of Avtalion and Arraba. *Leg 13* continued along the NWC, passing mostly flat terrain, alongside the road to Kfar Manda, encircling the Eshkol Water Treatment Reservoir and rising to Tel Hanaton. *Leg 14* went from Kibbutz Hanaton to the village of Alon Hagalil. *Leg 15* continued to the Zarzir junction along a scenic route leading to the Tzipori Stream, crossing it and ascending to the Kaabiya--Zarzir road. *Leg 16* headed south to the village of Alonei Abba, passing the village of Beit Lechem Haglilit on dirt roads through forests of pine trees and old oaks to the Alonei Abba nature reserve.



**Figure 14.** Part of the Ubiquitin team at start line. From left: Claudia Barzilay, Gerardo Byk, Ehud Keinan and Micha Fridman.

*Leg 17* crossed the village of Alonei Abba towards Kibbutz Alonin via agricultural fields, passing through the southern part of Alonin, ascending towards Tivon and descending towards the National Park of ancient Beit Shearim. *Leg 18* continued to the Alexander Zaid statue that overlooks the Jezreel valley, passing agricultural fields to the historic railroad station at Kfar Yehoshua. *Leg 19* continued through the fields, crossing the Kishon stream, and climbing through the village of Yoqneam, Kibbutz Hazorea, and Hashalom valley along an old route from the times of the British Mandate, to the Typhoon amusement park near Kibbutz Ramat Hashofet. *Leg 20* continued southward parallel to the Haemek--Ein Hashofet road in the direction of Kibbutz Hazorea. *Leg 21* continued along the Kishon Stream all the way to Moshav Hayogev. *Leg 22* went through Hayogev, crossing the Kishon again and climbing along the man-made canal of the Barukh Reservoir, bypassing





**Figure 15.** Part of the Ubiquitin team at finish line. From left: Ehud Keinan, Alex M. Szpilman, Mr. Niv Yardeny and Natalie Reznikov.



**Figure 16.** Happy ending of the Ribosome team at the M2V finish site. Standing (from left): Ehud Keinan, Daniel Mohr, Gary Zaiats, Eyal Gur, Alon Hoffman, and Ori Gidron; sitting: Neta Rosenstein, Michael Meijler, Alina Amel and Claudia Barzilay.

Moshav Kfar Barukh and the old entrance to the Ramat David Air Force Base all the way to Moshav Kfar Barukh. *Leg 23* continued to Kibbutz Yif'at, passing through almond orchards, crossing road 75, and finally reaching the Mekorot pump facility near Ma'alul. *Leg 24* left Ma'alul with a difficult climb through pine forests, crossing the village of Timrat down to the finish line at the nature reserve of *Faidherbia albida* (also known as *Acacia albida Delile*), which is the northernmost natural populations of this beautiful African tree.

**A unique experience.** The breathtaking mountainous scenery, the nocturnal landscape of the Galilee at full moon, and the amazing sunset and sunrise were more than fair reward in exchange for the physically demanding route and the sleepless 24-hour period under very hot day hours and a cold night. The complex teamwork with constant troubleshooting, unexpected challenges and necessary group effort became an interesting social experience within each team and among the teams. The two ICS teams developed strong friendship and collegiality that will last, no doubt, for many years to come.

The relay race could not take place without the wonderful support provided by the community of Timrat and

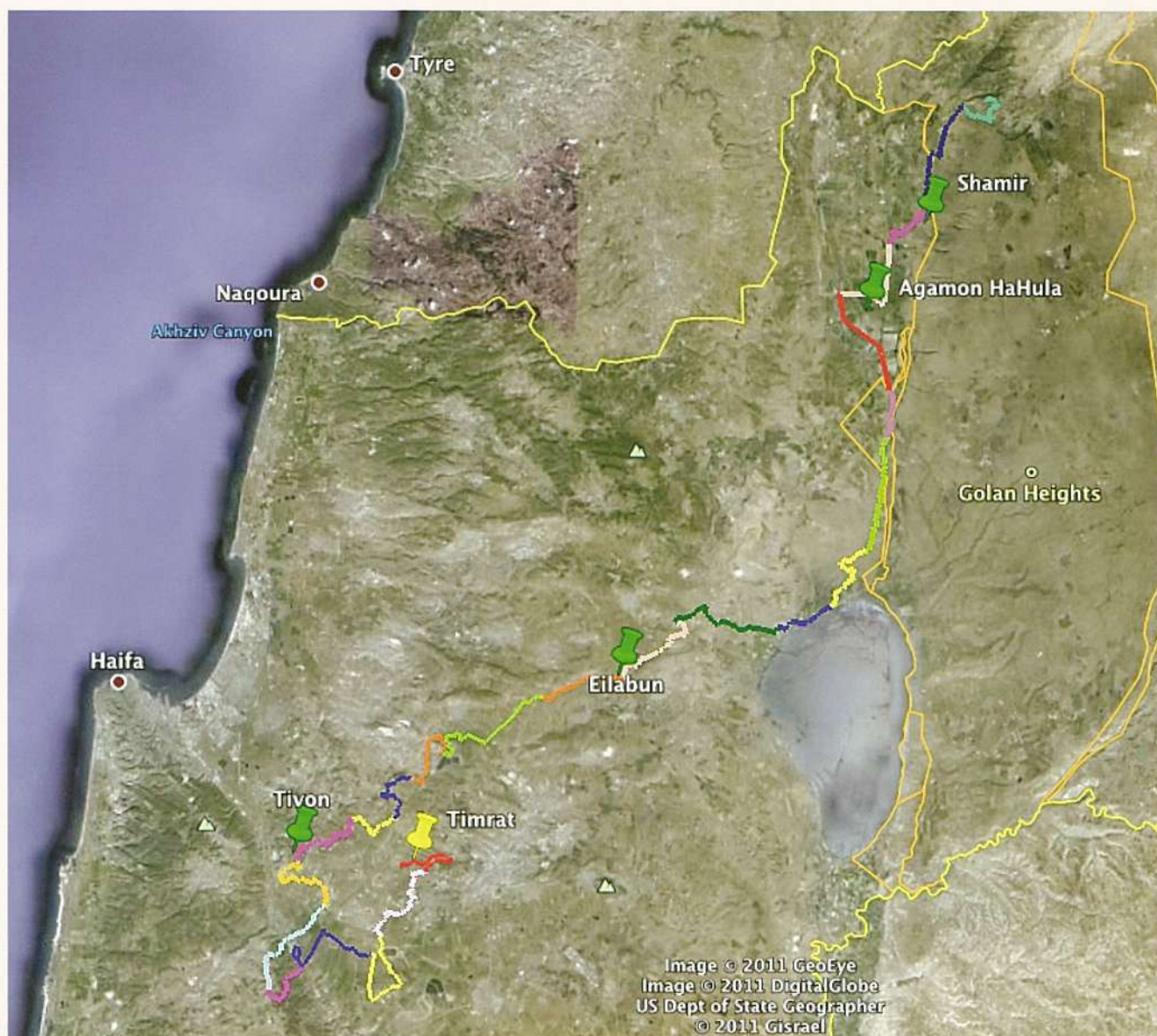
several hundred volunteers from Timrat and neighboring villages, who manned the relay stations and assisted with the logistics over the course of the race. These dedicated volunteers registered the incoming and outgoing runners, solved logistic problems, made sure that each runner was appropriately equipped for night running, and kept everyone on track with hundreds of visible signs along the 212 Km of trails. They even worked as paramedics in some cases of minor injuries, and plied the runners with homemade cakes, dried fruits, and drinking water. Thus the arrival at each station became like homecoming.

### Other events

This article covers only three out of many ICS events that highlight the IYC2011 calendar. The most prominent event, which is covered separately in this issue, was the "Chemistry Week", held in Tel Aviv, February 7-10, 2011, featuring the 76th Annual ICS Meeting, the 14th Isranalytica conference and a large exhibition of scientific equipment and instrumentation with close to 3000 participants.

Other noteworthy events were the International Conference on Art, Science and Technology held





route

in Carmiel, the Schulich Conference on “Chemical synthesis of peptides and proteins” held at the Technion in March 13, 2011; the international conference on “Frontiers in Chemistry”, honoring the three 2011 Wolf Prize Laureates in Chemistry, held at the Technion in May 30, 2011. the Israel-Italy binational conference on “Frontiers in Organic Chemistry” held at the Dan Panorama hotel in Tel Aviv in December 13-14, 2011,

the “Researchers’ Night” at the Museum of Science, the public experiment, which was registered in the Guinness Book of Records, and more. All indications show that IYC2011 marked a new era in the awareness and appreciation of the public for the chemical sciences, chemical industry, and chemical education in the State of Israel.



# The 76<sup>th</sup> Annual Meeting of the Israel Chemical Society

**David Intercontinental  
Hotel, Tel Aviv  
February 9-10, 2011**

**E. Keinan<sup>[a]</sup>**

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The 76<sup>th</sup> ICS Annual Meeting, which was part of the “Chemistry Week”, represented one of the major scientific events in the International Year of Chemistry (IYC2011). The meeting was organized by Bar-Ilan University with Prof. Jean-Paul (Moshe) Lellouche serving as Chairman. Since its establishment in 1933, the ICS Annual Meetings have always been an attractive, colorful celebration of the Israeli chemical science, bringing together researchers from academia, chemical education, chemical industry, government laboratories and guests from abroad.

Combined with the 14<sup>th</sup> Isranalytica meeting of the Israel Analytical Chemical Society, the two consecutive scientific meetings offered a unique synergistic opportunity to celebrate a week of chemistry. This 4-day event, which was accompanied by a very large exhibition of scientific equipment and instrumentation, highlighted the scientific and societal impacts of the chemical sciences, boosting public awareness and appreciation of chemistry in the context of the IYC2011. About 3000 participants took part in this chain of events, attending the rich scientific Program which included plenary and keynote lectures, invited lectures in many parallel symposia, poster sessions, specific sessions on industrial chemistry and intellectual property, a job fair, etc.





Chi-Huey Wong



Andrew H.-J. Wang

Chung-Hsuan  
(Winston) Chen

Ming-Daw Tsai



Shang-Cheng Hung



Huan-Cheng Chang



Yu-Ju Chen

**Figure 1.** Members of the Academia Sinica delegation

The unique tradition of the ICS, which has already attracted much worldwide attention and interest, has been the custom to invite to each meeting a delegation of eminent chemists from a top institution outside of Israel, to present plenary and keynote lectures. This initiative has created outstanding opportunities for many Israeli scientists, and particularly for graduate students and young scientists, to interact with top-tier chemists, thus enhancing prospects for networking, scientific collaboration, extensive exchanging of ideas and securing mutual visits of students and faculty members. Each visit of these delegations has left a long trail of postdoctoral fellowships, Sabbatical programs of Israeli scientists, joint research proposals and other fruitful international activities. The ICS has already hosted distinguished delegations 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), and the Chemical Society of Japan and Japan Society for the

### Promotion of Science (2010).

In 2011 the ICS was proud to host a delegation of world-renowned scientists from Academia Sinica who represented the strong Taiwanese chemical sciences: President of Academia Sinica, Prof. Chi-Huey Wong, Vice President, Prof. Andrew H.-J. Wang, Distinguished Research Fellows Dr. Chung-Hsuan Chen, Dr. Ming-Daw Tsai, and Dr. Shang-Cheng Hung, and Research Fellows Dr. Huan-Cheng Chang, and Dr. Yu-Ju Chen. All delegation members were awarded with a lifetime Honorary Membership of the ICS.



Plenary lecture



Exhibition of scientific equipment



Poster session





Prof. Abraham  
Nudelman



Prof. Jacob Klein



Prof. David Avnir



Prof. Nissim Garti



Prof. Timor Baasov

**Figure 4.** Israeli plenary lecturers

The opening session included greetings by the Minister of Science, Prof. Daniel Hershkowitz, who highlighted the importance of the chemical sciences to the economy of the State of Israel as reflected by rich and diverse academic and industrial research and development. It was the first time in the ICS history that we hosted the President of the American Chemical Society in our annual meeting. The ACS President, Dr. Nancy B. Jackson arrived from the USA for this event accompanied by Dr. Bradley D. Miller, Director of the ACS International Activities. In their several meetings with the ICS Executive Board and other ICS members we delineated some modes of collaboration between the ICS and the ACS. The Representative of Taipei Economic and Cultural Office in Tel Aviv (equivalent to an Ambassador of Taiwan to Israel), Mr. Liang-Jen Chang, also attended the opening ceremony and greeted the Taiwanese delegation and all other participants. Prof. Chi-Huey Wong spoke on behalf of Academia Sinica. Both Prof. Eli Grushka, President of the Israel Analytical Chemical Society and Prof. Ehud Keinan spoke about the attractive opportunities in future collaboration between the two societies, which started with the successful organization of this "Chemical Week". The annual meeting has always been the forum in which the ICS prizes have been awarded, mostly during the opening ceremony. More details about these prestigious prizes are given in the following pages in this issue.

The scientific program included two very busy and long days, covering all facets of modern, interdisciplinary chemical research, including 9 plenary lectures, 18

symposia and 2 poster sessions. Overall, the meeting included over 90 keynote, invited and contributed lectures and over 200 posters. The following paragraphs highlight the plenary and keynote lectures.

**Prof. Chi-Huey Wong** of Academia Sinica delivered the first plenary lecture on "Chemical approach to post-translational glycosylation." He explained that protein glycosylation is the most complex post-translational process with more than 90 percent of human proteins being glycosylated. Yet, the significance of glycosylation at the molecular level is not well understood, and as such the pace for the development of carbohydrate-based drugs and diagnostic tools is relatively slow. It is thus important to develop new tools to study the effect of glycosylation on the structure and function of proteins and other biologically active molecules. The lecture focused on the development of new methods for the synthesis of homogeneous glycoproteins with well-defined glycan structures, glycan arrays for the high-throughput analysis of protein-glycan interaction and the design of click-induced fluorescence probes for identification of new cancer biomarkers for diagnosis and drug discovery. New glycoprotein vaccines have been designed and developed to tackle the problems of influenza and breast cancer.

**Prof. Abraham Nudelman** of Bar Ilan University delivered the second plenary lecture on "Improving drugs by the prodrug approach – highlights from 40 a review of provided lecture years of research." The many years of research in the field of prodrugs. The various investigational approaches towards their design and study were presented, culminating with the most



recent discoveries of prodrugs useful for the treatment of schizophrenia, neuropathic pain and cancer.

**Prof. Andrew H.-J. Wang** of Academia Sinica delivered the third plenary lecture on "Structure and function of enzymes relevant in drug discovery." He demonstrated that protein synchrotron crystallography is a powerful tool for drug discovery. Many important drug targets can be analyzed with relevant ligands bound at the active site. The lecture discussed the several enzymes and protein regulators useful for such as prenyltransferases, antibiotics development, which are involved in many biological pathways, and thus are useful for developing new drugs for various diseases. In addition, dehydrosqualene synthase has been tested as the target for treating infections by methicillin-resistant *S. aureus* (MRSA). Squalene synthase inhibitors for cholesterol-lowering activity in humans bind to CrtM and block the biosynthesis. Another study related of staphyloxanthin *in-vitro* to MRSA was on TcaR and IcaR, weak and strong negative regulators of transcription of the *ica* locus, respectively. They prevent the production of poly-N-acetylglucosamine and biofilm formation in *S. aureus* and *S. epidermidis*. The 3D structure of TcaR was solved in its apo form and in complex with salicylate, as well as several aminoglycoside and beta-lactam antibiotics. The results support a general mechanism for antibiotics in regulating TcaR-DNA interaction and thereby promote the understanding of the effect of antibiotic exposure on bacterial antibiotic resistance through biofilm formation.

**Prof. Jacob Klein** of the Weizmann Institute of Science, winner of the ICS Prize, delivered the fourth plenary lecture on "Hydrated charges as molecular ball-bearings: exploring a new paradigm." The effect of hydration layers, that form about charged species in aqueous media, in modifying short-ranged forces between charged surfaces, has long been known. In recent years several new features of water in thin films have been revealed, in particular its persistent fluidity when confined to sub-nanometer layers. The role of the thin hydration layers in modulating shear forces between sliding surfaces has been elucidated, and its possible role in the uniquely-efficient lubrication of surfaces in biological systems has been studied. The lecture reviewed these findings and described recent

advances in this area. In particular, the combination of the supramolecular benefits of polymer brushes together with the highly hydrated nature of zwitterionic phosphorylcholine monomers was shown to provide important advantages in designing extremely efficient boundary lubricants. This new paradigm of hydration lubrication was extended to other supramolecular assemblies, such as liposomes, and possibly to tissue engineering in regenerative medicine.

**Prof. David Avnir** of the Hebrew University of Jerusalem, winner of the ICS Prize, delivered the fifth plenary lecture on "Organically doped metals: a new family of functional materials." These new materials, denoted dopant@metal, enable the incorporation and entrapment of small organic molecules, polymers, biomolecules, and nanoparticles within metals. The new materials combine the diverse properties of organic molecules with the traditional properties and applications of metals, such as conductivity and catalytic activity. This new approach was demonstrated with silver, copper, gold, magnetic cobalt, iron and palladium. These materials, having the structure of entrapped organic compounds within agglomerated nanocrystals, are produced by either homogeneous or heterogeneous reduction of the metal cations in water or DMF, by electrochemical entrapments and by thermal decompositions of metal carbonyls. The organic component varied between less than 1% (doping) and 25% (hybrid formation). Useful applications of the new materials were demonstrated, including alteration of classical metal properties, such as conductivity, induction of un-orthodox properties to metals, such as rendering a metal acidic or basic, formation of new catalysts, such as metals doped with organometallic complexes, creation of materials which are at the border between polymeric and metallic, formation of bioactive metals by entrapment of enzymes, induction of chirality within metals, induction of corrosion resistance in iron, and formation of efficient biocidal materials.

**Prof. Nissim Garti** of the Hebrew University of Jerusalem delivered the sixth plenary lecture on "New fluid lyotropic mesophases vehicles for solubilization and on-demand delivery transmembrane and transdermal of bioactives". The properties, structure and transitions of lyotropic liquid crystalline





**From left:** Prof. Chi-Huey Wong, President of Academia Sinica; Prof. Ehud Keinan; Prof. Daniel Hershkowitz, Minister of Science; Mr. Liang-Jen Chang, Representative of Taiwan



**From left:** Prof. Ehud Keinan; Dr. Nancy B. Jackson, ACS President; Prof. Jean-Paul (Moshe) Lellouche, Chairman of the 76<sup>th</sup> ICS Meeting

mesophases were studied for food and cosmetic applications. By manipulating the critical packing parameters of certain surfactants using a third component, two new fluid modified lyotropic liquid crystals which are stable at room temperature were obtained. The first is a fluid discontinuous micellar cubic mesophase (QL) and the other is a fluid reverse hexagonal mesophase (modified HII). These mesophases, characterized by SAXS, Cryo-TEM, DSC, and rheology, were designed for transdermal and oral applications. Dispersing them in an aqueous phase forms soft particles, termed Micellosomes and modified Hexosomes. Their very large interfacial surface area, the water channels and the lipid layer allow for solubilization of nutraceuticals, bioactives, aromas, antioxidants, drugs, peptides, DNA, enzymes and proteins. Various ‘facilitators’ were embedded at the vehicles’ interfaces, such as membrane recognition compounds, piercing agents, worming agents and enzymes, in order to enhance the delivery of the bioactive species in transdermal applications and across intestines membranes.

**Dr. Ming-Daw Tsai** of Academia Sinica delivered the seventh plenary lecture on “Structure and mechanism of a viral DNA polymerase with G:G specificity”. The structure of the enzyme-DNA-MgdNTP ternary complex of a DNA polymerase was solved by NMR. DNA polymerase X (Pol X) from African swine fever virus, the smallest known nucleotide polymerase, can catalyze both G:C and G:G with similar efficiencies. Pol X was found to be an extremely low fidelity

polymerase, which may be involved in the mutagenic viral DNA base excision repair pathway. Using both steady-state and pre-steady-state kinetics, it has been found that Pol X binds dGTP to form a productive binary complex with an altered substrate binding order. The structures of Pol X and its ternary complex with DNA and dGTP were studied by NMR, and they resemble the C-terminal half of DNA polymerase beta. In the ternary complex of Pol X with DNA and a mismatched G:G pair, the G:G mispair forms Hoogsteen base-pairing in the Pol X active site, with the incoming dGTP in *syn* conformation, while the template G is in an *anti* conformation. dGTP formed a Pol X/dGTP binary complex with a *syn* conformation. Thus, the formation of a binary complex between Pol X with dGTP accelerates the G:G mispair reaction, explaining the low fidelity of catalysis.

**Prof. Timor Baasov** of the Technion delivered the eighth plenary lecture on “To fix nature’s mistakes: repairing human faulty genes by sugars-based small molecules”. The treatment of genetic disorders represents a major challenge of modern medicine. While major advancements have been made in gene therapy, it is still far from achieving clinical success. One alternative method that has emerged recently is suppression of pathogenic nonsense mutations through induction of translational read-through of the in-frame stop mutations. Aminoglycosides were the first promising drugs in this respect, demonstrating the ability of certain aminoglycosides to induce the mammalian ribosome to read-through premature



stop codon mutations and therefore partially restore the production of full-length functional proteins. Unfortunately, the high toxicity of these drugs has limited their clinical use. Structural information of the bacterial ribosome complex with aminoglycosides has shed light on their mechanism of action as antibiotics. Yet, no crystal structure of the human ribosome is available and the mechanism of aminoglycoside-induced read-through is unknown. A series of new derivatives of clinical aminoglycosides were designed and synthesized and studied for their ability to read-through stop codon mutations *in-vitro* and in animal models of cystic fibrosis. Some of them demonstrated exceptional improvement in stop-codon read-through activity and low toxicity. The structure-activity-toxicity relationships of these drug candidates in their eukaryotic vs. prokaryotic selectivity were examined. The crystal structures of designed molecules in complex with the *H. sapiens* 18S cytoplasmic A site RNA construct was solved.

**Dr. Chung-Hsuan (Winston) Chen** of Academia Sinica delivered the ninth plenary lecture on “Biological mass spectrometry development and its applications”. Mass spectrometry has played a key role in biomarker discovery. Thousand of proteins can be analyzed to compare protein profiles between patients and normal controls. Nevertheless, the progress so far is still quite limited due to (1) low analysis speed (2) low detection sensitivity and (3) lack of capability for the detection of proteins with post-translation modification. These problems were addressed by developing novel mass spectrometry technologies, such as (1) Broad Range Mass Spectrometer to cover mass range from atom to cell, (2) Accelerator Biological Mass Spectrometer to reach single ion detection of ultra-large biomolecules, such as IgM, and (3) Portable Multiple Function Biomolecular Mass Spectrometer to carry out biomedical sample analysis *in-situ* and in real-time. Several biomedical applications of these novel instruments were discussed.

**Prof. Arkadi Vigalok** of Tel Aviv University, winner of the Excellent Young Scientist Prize, delivered a keynote lecture on “Organic synthesis without organic solvents represent the biggest solvents.” pollution problem of many synthetic organic processes. As the most abundant and environmentally friendly

solvent, water is considered an attractive alternative and yet, very few synthetic organic transformations are performed with water as a solvent. The stumbling block in the use of water, instead of organic solvents, is the very low solubility of most of the organic compounds in aqueous media. New ideas were discussed on using this low solubility in the design of efficient organic syntheses often unattainable in the organic media. A new family of catalysts that utilize amphiphilic chiral block copolymers as multidentate ligands for transition metal-catalyzed organic transformations was presented. Upon dissolution in water, these copolymers form micelles with the hydrophilic external corona and hydrophobic inner core. The latter serves as the reaction media for poorly soluble organic molecules with the transition metal catalysts attached to each of the repeating units of the hydrophobic polymer. A particular emphasis was placed on the effect of the micellar assembly on selectivity of the metal-based catalysis. General strategies for performing common organic reactions under the “on water” conditions were presented. Radical transformations with hydrophobic aldehydes were found to proceed with High efficiency upon stirring with water in air. Importantly, in all described directions recycling of the aqueous media were achieved.

**Prof. Leeor Kronik** of the Weizmann Institute of Science, winner of the Excellent Young Scientist Prize delivered a keynote lecture on “Understanding organic-based interfaces from first principles: challenges and progress.” Organic-based interfaces in general, and organic/inorganic interfaces in particular, present a research area of intense fundamental interest, with strong implications for organic and molecular electronics. Their study requires working and thinking in two worlds - the molecular and the non-molecular - that differ in their electronic structure and chemical properties, as well as in the experimental tools used in their study. The lack of well-established “chemical intuition” for such interfaces provides strong motivation to study their behavior from first principles calculations. The unique challenges posed by these interfaces to first principles calculations based on density functional theory (DFT) were presented. The systematic inclusion of physical ingredients that are missing in common approximate DFT calculations show how the calculations allow for



quantitative accuracy in comparison to DFT, which enables to experiment on interesting prototypical systems. Such calculations were presented together with a host of other theoretical approaches - from simple electrostatic models, through tight-binding calculations, to many-body perturbation theory. The aim is to identify novel collective inter-molecular and molecule-substrate interactions that often dominate the interface properties.

**Dr. Shang-Cheng Hung** of Academia Sinica delivered a keynote lecture on "Synthesis of cell-surface heparan sulfate oligosaccharides and their interaction The cell-surface heparan sulfate with proteins." (HS), which is a linear polysulfated polysaccharide belonging to the family of glycosaminoglycans, consists of an uronic acid ( $\beta$ -D-glucuronic acid or  $\beta$ -L-iduronic acid) and an  $\alpha$ -D-glucosamine alternately linked in a 1 $\rightarrow$ 4 fashion. The multifaceted roles of these sugars in biological processes are reflected by the continually increasing number of HS-binding proteins being identified. Regulation of the biological activity of several proteins in the coagulation cascade along with many other processes of biomedical importance including growth factor interactions, viral entry, and angiogenesis are just a few of their currently acknowledged functions. A concise synthesis of HS oligosaccharides and their interaction with proteins was presented. **Dr. Huan-Cheng Chang** of Academia Sinica delivered a keynote lecture on "Fluorescent nanodiamonds for super-resolution bioimaging and long-term cell tracking." Nanodiamonds have received increasing attention for promising biomedical applications. This material is highly biocompatible, non-toxic, and can be easily conjugated with bioactive molecules. Recently, nanoscale diamond particles have been applied as fluorescent biolabels and therapeutic agents. The fluorescence, arising from photoexcitation of color centers, can be substantially enhanced when type Ib diamond nanocrystals are bombarded by a high-energy particle beam and then annealed to form negatively charged nitrogen-vacancy centers. The center absorbs strongly at 560 nm, fluoresces efficiently at 690 nm, and is exceptionally photostable (without photoblinking and photobleaching). It is an ideal candidate for super-resolution imaging with stimulated emission depletion (STED) microscopy and long-term cell tracking and sorting with flow

cytometry. The lecture summarized recent advances in the development of fluorescent nanodiamonds (FNDs) for optical bioimaging and biolabeling with single particle sensitivity, long-term tracking capability, and nanometric resolution.

**Prof. Yoram Oren** of Ben Gurion University of the Negev delivered a keynote lecture on "The effect of biofilms and associated components on mineral scaling Membrane fouling is on reverse osmosis membranes." one of the major factors that limit recovery in reverse osmosis desalination. Fouling and biofouling may occur by accumulation and adsorption of inorganic particles, microorganisms, macromolecules and corrosion products on membrane surfaces. Mineral salt scaling is another major foulant that limits the recovery in reverse osmosis desalination processes. The primary mineral salt scalants that are typically of concern in inland water desalination are calcite, gypsum, barite, and calcium phosphate in particular. During the desalination process of any kind of water, fouling and scaling always appear together, however to different extents, on the membrane surface. In order to properly mitigate these phenomena, it is important to understand how mineral salt scaling is affected by the presence of a biofilm and its separate components. In order to address the above coupled fouling and scaling problem, a systematic surface scaling study was carried out, with gypsum as the model scalant, to evaluate the kinetics of surface crystallization in the presence of a biofilm. In addition, calcium phosphate mineralization from a simulated secondary wastewater solution was studied under the influence of the different components comprising the biofilm extracellular polymeric substances (EPS). The presence of a biofilm on the membrane surface was found to significantly affect the single crystal growth rates and increase the rates of nucleation. Moreover, gold wafers to which typical biopolymer components of the EPS are attached, and incubated in a simulated wastewater solution for 10 and 20 days, showed that the rate of calcium phosphate mineralization is in the order: alginic acid > fibrinogen > BSA > medium MW chitosan on the surface.

**Dr. Yu-Ju Chen** of Academia Sinica delivered a keynote lecture on "A simple label-free proteomic strategy towards comprehensive proteomic signatures:





Professors David Avnir (left) and Jacob Klein (right) receive the ICS Prize from Prof. Keinan during the festive dinner

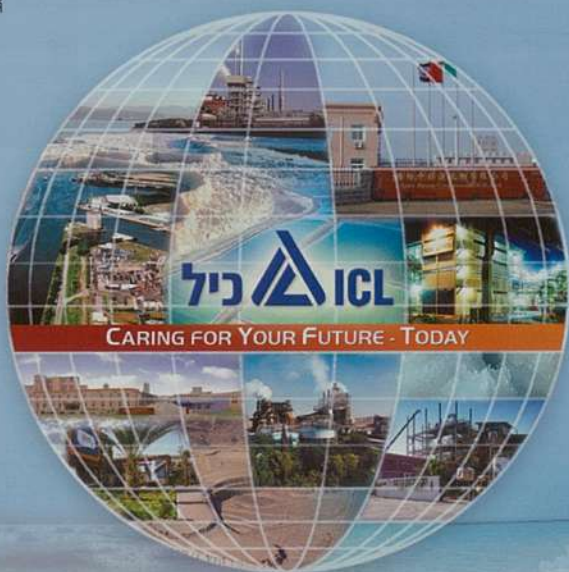


opportunities for mining therapeutic targets and biomarkers." Many studies have shown that aberrant membrane protein expression and post-translational modification, such as phosphorylation, glycosylation and nitrosylation, are associated with various diseases. Quantitative proteomics approaches may provide an in-depth view of the disease-specific expression, which potentially enhances our understanding on the underlying disease mechanisms as well as the opportunity for biomarker and drug target discovery. Towards highly sensitive and robust quantitation, a simple and efficient label-free strategy was presented, which combines liquid chromatography alignment and informatics tools for multiplexed proteomic profiling of membrane proteome and post-translational modifications. On the standard protein level, reliable linear correlation can be obtained with 4000-fold dynamic range ( $R^2=0.99$ ). On the proteome-scale, the combination of a reproducible enrichment protocol and a robust nanoUPLC-MS/MS demonstrated high quantitation accuracy ( $1\pm0.32$ ) and precision ( $<10\%$ ). To further explore the opportunity of biomarker and drug target candidate discovery by the proteomics strategy, its application on cancer tissues and stem cells was presented. With the reproducible enrichment protocol, the approach can be applied for quantitation of protein modification. Good accuracy and precision were obtained for phosphoproteomics and S-nitrosylomics and applied to the first delineation of differential phosphoproteomics profiles of cancer invasion cell model.

**Prof. H. D. Wagner** of the Weizmann Institute of Science delivered a keynote lecture on "The mechanistics of small objects: selected experiments from various landscapes." He focused on the testing of very small objects belonging to various areas, for example carbon and tungsten sulfide nanotubes in the composites area, Nickel micropillars in metallurgy, and hair cilia and dentin pillars in biology. Some of the recent experimental and theoretical results regarding materials mechanics at the nanoscale were reviewed. The main focus of the presentation included carbon and tungsten sulfide nanotubes, and nanotube-based composite materials. Such developments were shown to present significant practical challenges, in particular for attempts to probe the properties of individual nanotubes by means other than computer simulations, and for attempts to optimize the mechanical properties of nanocomposites, especially biological nanocomposites. Polymer-nanotube composite mechanics, including interfacial adhesion and toughness issues, as well as mechanical testing of biological structures with a nanoindenter were presented. Measurements of stiffness of individual WS2 fullerene-like nanoparticles, which are 80nm or larger using high-resolution scanning electron microscope (HRSEM) were also presented.

A festive dinner, kindly sponsored by the Representative of Taipei Economic and Cultural Office in Tel Aviv was held in the evening of the first day with the participation of the Representative, Mr. Liang-Jen





כימיקלים לישראל בע"מ (כיל) הנה חברה רב-לאומית הפועלת בעיקר בתחומי הדשנים והכימיקלים המיוחדים. לכיל - מעמד מרכזי בעולם בשוקי האשלג, הברום, החומצה הזרחתית הנקייה, הפוספטים המיוחדים, מעכבי בעירה על בסיס ברום וזרחן וכימיקלים למניעת התפשטות שריפות. כ-94% מהמכירות הינם בשווקים בינלאומיים מחוץ לישראל וכ-50% מהייצור הינו מחוץ לישראל.

**לכיל** זיכיונות ארוכי טווח למינרלים המצויים בים המלח המאפשרים הפקת מוצרים ייחודיים בעלויות תחרותיות. **כיל** מפיקה מים המלח אשלג, ברום, מגנזיום, מוצרי מגנזיה ומלחים שונים. כמו כן **כיל** כורה פוספטים מהנגב וכן אשלג ומלח ממכרות באנגליה ובספרד. **לכיל** מפעלי ייצור, מערך משרדי שיווק, מסופים, מחסנים ומרכזי הפצה ברחבי העולם. **כיל** נהנית מיתרונות במערך ההפצה והלוגיסטיקה בזכות הקרבה של מרכזי הייצור של החברה לנמלים בישראל ובאירופה. **כיל** הנה חברה ציבורית הנסחרת בבורסה בתל-אביב (TASE: ICL).

Chang, the Taiwanese delegation, ACS President, Dr. Nancy B. Jackson, Director of the ACS International Activities, Dr. Bradley D. Miller, winners of the ICS medal, Prof. Meir Wilchek and winners of the ICS Prize of Excellence, Prof. David Avnir and Prof. Jacob Klein. The pleasant evening including the prize award ceremony to Professors Avnir and Klein and awarding the ICS Honorary Membership to all members of the delegation, as well as to Dr. Nancy B. Jackson. The audience was entertained by an outstanding vocal performance by Ms. Moran Shalev (mezzo-soprano), who was accompanied on an electrical organ by Biotechnology Engineering student, Mr. Amit Blum.

Fife posters were selected by the Poster Committee for the following prizes, which were awarded at the end of the second day.

The 1<sup>st</sup> best poster prize of the PCCP was awarded to Elul Shaltiel, Yair Cohen, Doron Aurbach, Bar-Ilan University and the Negev Nuclear Center for their poster "The influence of the geometry in simulation studies of charge/discharge processes of Li-ion batteries."

The 2<sup>nd</sup> best poster prize of the PCCP was awarded to Ori Gidron, Afshin Dadvand, Dimitri F. Perepichka and Michael Bendikov of the Weizmann Institute of Science for their poster "Towards 'green' electronic materials: A-oligofurans as semiconductors."

The 1<sup>st</sup> best poster award of the ICS was given to Tal Gitelman, Haim Cohen, S. Leiman, S. Sternklar, Ariel University Center & the Ben-Gurion University of the Negev, "Enhancing the sensitivity of material characterization with Raman scattering using a photonic fiber and nanoparticles (SERS)."

The 2<sup>nd</sup> best poster award of the ICS was given to Yakov Ginzburg, Yuval Vidasky, Amos Ben-Asuly, N. Gabriel Lemcoff of Ben-Gurion University of the Negev for their poster, "Three-point chelated olefin metathesis ruthenium catalysts."

The Bargal poster prize was awarded to Lilia Reytmann and Edith Tshuva of the Hebrew University of Jerusalem for their poster, "Vanadium bisphenolato complexes of different oxidation states as anticancer agents."





# The 77<sup>th</sup> Annual Meeting of the Israel Chemical Society

Conference and Exhibition February 07-08, 2012  
Kfar HaMaccabiah Congress Center, Ramat Gan

אוניברסיטת  
בן-גוריון בנגב

## Scientific Program

### Day 1 - 7/02/2012

- Organic Chemistry
- Nano and Materials
- Green Chemistry
- Chemical Biology
- Inorganic and Organometallic Chemistry
- Bioorganic and Medicinal Chemistry
- Supramolecular Chemistry
- Renewable Energy
- Chemical Education

### Day 2 - 8/02/2012

- Biophysical Chemistry
- Organic Chemistry
- Molecular Electronics
- Physical Chemistry
- Analytical and Environmental Chemistry
- Structural Biology
- Polymer Chemistry
- Industrial Chemistry

## Delegation

Distinguished researchers  
from the University of  
California, Berkeley

**Berkeley**  
UNIVERSITY OF CALIFORNIA



**Prof. Daniel M. Neumark**  
Department Chairperson,  
Department of Chemistry  
Joel Hildebrand Distinguished  
Professor



**Carlos J. Bustamante**  
Professor of Chemistry, Physics  
and Molecular and Cell Biology



**Prof. Ronald C. Cohen**  
Director, Berkeley Atmospheric  
Science Center, Professor of  
Chemistry and of Earth and  
Planetary Sciences



**Prof. Richmond Sarpong**  
Associate Professor of  
Chemistry



**Prof. Gabor A. Somorjai**  
Professor of Chemistry



**Prof. Dean Toste**  
Associate Professor of  
Chemistry

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Free parking at Kfar HaMaccabiah Congress Center.

Free shuttle service is available on both mornings (08:00-08:30) of the conference from Hashalom (Azrieli) Train Station to Kfar HaMaccabiah Congress Center.

Spaces are limited, please register on-line for the shuttle service.

The service is on a first come first served basis.

For more information please contact Mrs. Daniela Levin

Tel: +972-(0)8-931-3070 Fax: +972-8-931-3071 E-mail: daniela@bioforum.co.il Site: www.bioforum.co.il



[www.chemistry.org.il/77](http://www.chemistry.org.il/77)



## The ICS Prizes for 2010

### ICS Medal



*Prof. Meir Wilchek*



*Mr. Eli Hurvitz*

**PROFESSOR MEIR WILCHEK**  
**Weizmann Institute of Science**

For developing the technology of affinity chromatography which is used for protein purification, revolutionized the pharmaceutical industry, generating numerous biotechnological companies and significant research and industrial activities worldwide.

**MR. ELI HURVITZ**  
**Teva Pharmaceutical Industries Ltd.**

For his unique contributions to the chemical industry, for turning Teva into a flagship company of the Israeli industry and the worldwide leader of generic drug manufacturing.

### Prize for Excellence



*Prof. David Avnir*



*Prof. Jacob Klein*

**PROFESSOR DAVID AVNIR**  
**Hebrew University of Jerusalem**

For his discoveries and pioneering studies on entrapment of organic compounds in sol-gel materials.

**PROFESSOR JACOB KLEIN**  
**Weizmann Institute of Science**

For his discoveries and seminal contributions to the physical chemistry of soft matter and interfaces, providing fundamental insight on processes such as biological lubrication.

### ICS Outstanding Young Scientist



*Prof. Leeor Kronik*

**Prof. Leeor Kronik**  
**Weizmann Institute of Science**

For his path breaking work in computational materials science and, in particular, for the development of new and innovative methods and tools relevant to central problems in interfacial and solid-state chemistry.



*Prof. Arkadi Vigalok*

**Prof. Arkadi Vigalok**  
**Tel Aviv University**

For his outstanding and pioneering contributions in metal-mediated formation of carbon-fluorine bonds and in the synthesis and application of calixarene compounds as ligands in metal-mediated transformations.

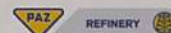
### ICS Chemical Green-Industry



*Mr. Malachi Alper*

**Mr. Malachi Alper, CEO**  
**Paz Ashdod Refinery Ltd.**

For excellence in environmental protection and for contributions to industrial waste reduction, efficient energy consumption, and reduced emission of greenhouse gases.





## The Excellent Teacher



Mrs. Adina Shenfeld

**MRS. ADINA SHENFELD**  
**"Rogozin" High School, Kiryat Ata**  
**and ORT Kiryat Motzkin**

For her outstanding contribution to chemistry teaching as a teacher and an instructor on the regional and national levels, and for implementing innovative teaching methods and advanced teaching programs.

## The Young Teacher



**MRS. NURIT DEKALO**  
**Yarkon High School**

For extraordinary devotion to chemistry teaching that produced outstanding students, for making chemistry a prestigious, highly demanded subject at his school.

## Lise Meitner Prize



**DANA KERPEL**  
**Tel Aviv University**  
 Thesis Advisor: Dr. Oded Hod

## Ph.D. Excellent Student



**Yael (Elaine) Schuster**  
**Technion - Israel Institute of**  
**Technology**  
 Thesis Advisor: Prof. Mark Gandelman



**MAHMOOD HAJ-YAHYA**  
**Ben Gurion University of the**  
**Negev**  
 Thesis Advisor: Prof. Ashraf Brik



**ELAD MENTOVICH**  
**Tel Aviv University**  
 Thesis Advisor: Dr. Shachar Richter



**DAVID EISENBERG**  
**The Hebrew University of**  
**Jerusalem**  
 Thesis Advisor: Dr. Roy Shenhar



**KEREN STIMLER**  
**Weizmann Institute of Science**  
 Thesis Advisor: Prof. Dan Yakir



**HADAS SKAAT**  
**Bar Ilan University**  
 Thesis Advisor: Prof. Shlomo Margel



# The 9th meeting of the Section of Medicinal Chemistry of the Israel Chemical Society

## Meeting Report

Ora Schueler-Furman<sup>[1]</sup>, David Stepensky<sup>[2]</sup>, Arie Gruzman<sup>[3]</sup>



### Ora Schueler-Furman

Dr. Ora Schueler-Furman received her B.Sc. in Biology from the Hebrew University of Jerusalem in 1992. She then joined the group of Prof. Hanah Margalit at the Department of Microbiology and Molecular Genetics in the Faculty of Medicine for her M.Sc. Studies, where she characterized the evolutionary conservation of salt bridges in proteins. She then continued with Ph.D. studies under the joint guidance of Prof. Hanah Margalit and Prof. Ron Elber, then at the Fritz Haber Research Center for Molecular Dynamics in the Institute of Chemistry of the Hebrew University. During her postdoctoral studies in the group of Prof. David Baker at the University of Washington. Dr. Schueler-Furman joined the Department of Microbiology and Molecular Genetics at the Faculty of Medicine of the Hebrew University of Jerusalem in 2005. Her research focuses on the fundamental principles that govern protein binding affinity and specificity. Her group develops and applies tools for the structure-based characterization, modeling and manipulation of peptide-mediated protein interactions. In addition, she applies computational robotics tools to model protein motion.



### David Stepensky

Dr. David Stepensky received B.Sc. in Pharmaceutics from The Hebrew University of Jerusalem, Israel, in 1996. After that he joined the research group of Prof. Amnon Hoffman at the Department of Pharmaceutics at The Hebrew University and studied pharmacokinetic and pharmacodynamic aspects of drug treatment during his Ph.D. studies (direct track, graduated Summa cum Laude). David received research specialization in the field of antigen presentation and tumor immunology during his post-doctoral studies in the group of Prof. Lea Eisenbach at Dept. of Immunology, Weizmann Institute of Science, Rehovot, Israel. After that David completed second post-doctorate in the field of antigen presentation in the group of Prof. Peter Cresswell at Dept. of Immunobiology, Yale University, USA. Dr. Stepensky joined the Dept. of Clinical Pharmacology at the Ben-Gurion University of the Negev in 2007. His research focuses on development of targeted drug delivery systems and analysis of pharmacokinetic/pharmacodynamic aspects of drug treatment.

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[2] Dept. of Clinical Pharmacology and School of Pharmacy, Faculty of Health Sciences, Ben-Gurion University of The Negev, Israel, 84103

[3] Division of Medicinal Chemistry, Dept. of Chemistry, Faculty of Exact Science, Bar Ilan University, Ramat Gan, Israel, 52900





#### Arie Gruzman

Dr. Arie Gruzman received his B.Sc. in Medicinal Chemistry from the Bar Ilan University, Israel, 1995. He carried out his direct doctoral studies at Department of Pharmacology, School of Pharmacy, The Hebrew University of Jerusalem in the laboratory of Professor Shlomo Sasson. Arie received his Ph.D. at 2003 (Summa cum Laude). He then joined the group of Professor Vishvanath Lingappa at the Dept. of Physiology at the University of California and California Pacific Medical Center Research Institute both in San Francisco for a postdoctoral training until 2007. Dr. Gruzman became a faculty member in the Department of Chemistry at Bar Ilan University in October 2009. His research focuses on development of new drugs for the treatment of diabetes, ALS, prostate cancer and arrhythmia.

The 9<sup>th</sup> meeting of the Section of Medicinal Chemistry of the Israel Chemical Society was held on March 8th 2011. Close to 200 participants from both Industry and Academia gathered at the Weizmann Institute for an intensive day of Lectures, Poster presentation, and vivid informal scientific discussions. The Commercial exhibits were an integral part of the congress program and represented a unique opportunity for companies to present and promote their products to the numerous scientists involved in organic and medicinal chemistry. The Section of Medicinal Chemistry was founded in 2002 by Professor Matityahu Fridkin from the Weizmann Institute, Professor Abraham Domb from the Hebrew University and Jeff Sterling from Teva, with the goal to promote the study and research of Medicinal Chemistry in Israel. Its central role since then was well highlighted by the diversity of the program and the large number of researchers from a variety of disciplines, including Chemistry, Pharmacology, Life Sciences and Medicine. This year, the meeting was organized by Dr. Arie Gruzman from Bar Ilan

University, Dr. David Stepensky from the Ben Gurion University of the Negev, and Dr. Ora Schueler-Furman from The Hebrew University of Jerusalem.

As every year, the main highlights of the program included sessions with scientific lectures, a poster session, and award ceremonies.

#### Awards

The Chorev Award was established by Professor Michael Chorev from the Harvard Medical School within the frame of the Medicinal Chemistry Section. The **Award for distinguished contributions to the Industrial Medicinal Chemistry field for a scientist in industry** was presented this year, to **Yaacov Herzig** from TEVA, a pioneer of Medicinal Chemistry in Industry in Israel, for his contribution to the development of new drugs and the advancement of the drug industry in Israel. Yaacov Herzig has been worked in pharmaceutical chemistry for his entire professional life. Some of the projects in which he was involved lead to discovery of biological active compounds, while several of them were self-generated. For example, Yaacov Herzig was involved in development of new anti-epileptic compounds, anti-cholinesterase agents for Alzheimer's treatment and TACE (Tumor necrosis factor- $\alpha$ -Converting Enzyme) inhibitors for cancer treatment.

**Adi Haber** from the Technion and **Nir London** from the Hebrew University received the **Chorev Prize for two graduate students for their outstanding research advances and achievements in the field of Medicinal Chemistry**. Each presented a lecture about their work.

**Adi Haber** is a student in the group of Professor Zeev Gross at the Technion, the Israeli Institute of Technology in Haifa. She works on the development of new approaches to prevent cholesterol accumulation within arterial macrophages, a preliminary stage in formation of atherosclerotic plaques, which eventually results in myocardial infarction. Cellular cholesterol levels are governed by two lipoprotein-mediated pathways: its uptake is mediated by low density lipoprotein (LDL) and its efflux is mediated by high density lipoprotein (HDL). In her work, Adi demonstrated that the iron(III) complex of a bipolar corrole (1-Fe) binds spontaneously and with high affinity to lipoproteins in human serum. The conjugated corrole protects HDL and LDL against lipid peroxidation and protein





Group picture of the participants of the 9<sup>th</sup> meeting of the Section of Medicinal Chemistry of the Israel Chemical Society

nitration, thus preventing the loss of the formers anti-atherogenic activities and reducing the pro-atherogenic properties of the latter. The extremely strong binding of 1-Fe to lipoproteins suggests that it will be carried all the way to the arterial wall, where the need for its protective action against the atherogenicity-inducing damage to oxidized lipoprotein(s) is most crucial.

**Nir London** is a student in the group of Dr. Ora Schueler-Furman at the Faculty of Medicine of the Hebrew University of Jerusalem. He works on the development and application of tools in computational structural biology to characterize, model and manipulate peptide-mediated protein interactions. A substantial fraction of known protein-protein interactions are mediated by short flexible peptides, and the explicit modeling of this flexibility poses a major challenge for docking programs.

Nir London developed in collaboration with Barak Raveh from the group a protocol Rosetta FlexPepDock that incorporates the considerable peptide flexibility upon binding to its protein receptor, and consequently allows for highly accurate structural modeling of peptide-mediated interactions (Implemented as a server at <http://flexpepdock.furmanlab.cs.huji.ac.il>). Nir then used this protocol to analyze specific peptide-protein interactions to define their binding specificity, and to design potential new inhibitors. As an example, he was able to refine and extend the repertoire of proteins that undergo farnesylation by Farnesyltransferase by evaluating which c-terminal peptide sequences this enzyme can bind.

Finally, two prizes were awarded to the winners of the **best poster competition**: Among the 31 posters, **Hadas**



**Sneh-Edri** (intracellular organelles targeting) from the group of Dr. David Stepensky from the Department of Pharmacology at Ben Gurion University in the Negev, and **Pinchas Zer Aviv** (development of new anti prostate cancer drugs), from the group of Dr. Arie Gruzman in the Department of Chemistry at Bar Ilan University were selected.

The main program included lectures organized into four sessions, namely peptide and protein drugs, drug design and synthesis, new drugs for therapy of neurodegenerative diseases, and anticancer and antibacterial drugs. These lectures blended nicely Academy and Industry, and highlighted the wide variety of interesting and timely topics studied in the field.

### Peptide and protein drugs

**Gonen Ashkenasy** from Ben Gurion University presented the design and kinetic analysis of simple peptides that form soluble one-dimensional  $\beta$ -sheet aggregates and can significantly accelerate their ligation and self replication. He discussed the relevance of close analogs of Glu-(Phe-Glu) $_n$  peptides to early molecular evolution, given their shorter length compared to previously reported relatively long  $\alpha$ -helical peptides that undergo self assembly, and the added functionality of  $\beta$  sheets.

**David Margulies** from the Weizmann Institute of Science described step by step his design of dynamic synthetic receptors inspired by proteins. His biomimetic design includes artificial enzyme-linked receptors that initiate catalytic drug release upon binding to specific growth factors: upon dimerization, a catalytic cyclic peptide encoded in one receptor chain can cleave and activate a prodrug in the second receptor chain. In addition, he devised combinatorial sensory systems that can potentially differentiate between a wide range of closely related protein isoforms or glycoforms. Such tools can be used to detect and regulate important cellular processes.

**Yoram Shechter** from the Weizmann Institute of Science presented the development of different technologies that increase the lifetime of peptide and protein therapy by slowing their activation process. This includes modifications of peptide drugs to turn them into slowly reactivable prodrugs, reversible pegylation, the engineering of prolonged-acting prodrugs by introducing a hydrolyzable albumin-binding probe, and strategies

for the delivery of neuropeptides from the periphery to the brain.

### Drug Design & Synthesis

Prof. Amiram Goldblum dedicated this session to the memory of **Dr. Claude Cohen**, who passed away last year. Dr. Cohen was a pioneer in Rational Drug Design who made seminal contributions to the development of the methods and techniques used today in drug discovery, when working first at Roussel-Uclaf (now Sanofi-Aventis) as Head of Department of Theoretical Medicinal Chemistry, later at Ciba-Geigy (now Novartis) as Head of Molecular Modeling and Drug Design, and finally at Synergix which he founded in 1996. Dr. Cohen developed an array of methods for three-dimensional drug design that were applied to discovery projects in therapeutic areas such as CNS, CVS, Infection & Immunity and Oncology. He contributed to the discovery of several drugs including Valsartan (Diovan), which grossed \$5 billion in 2008. In 2009, Claude was recognized as an ACS Hero of Chemistry together with his team from Novartis, for their discovery and development of Aliskiren, the first-in-its class renin inhibitor.

**Hanoch Senderowitz** from Bar Ilan University presented a tool for biasing conformational ensembles towards bioactive-like conformers for ligand-based drug design. The challenge for the development of reliable pharmacophore models in computer-aided drug design is to identify the bioactive conformation of the compound - when it is bound to the target protein. Since this is not necessarily its lowest energy conformation, other parameters need to be identified that can identify, or at least enrich this conformation among models. In his study, Hanoch Senderowitz investigated a number of different criteria that could be used to focus on relevant ligand conformations, using distinct training and test sets of drug compounds. His final protocol involves a crucial initial prefiltration step in which ligands for which the probability of finding bioactive-like conformations is low are removed. Then, filtration is applied based on a unique combination of 2D/3D ligand properties identified during the optimization. The latter step shows 80% success rate and considerably reduces the number of conformations to consider.

**Igor V. Komarov** from Taras Shevchenko University



and ENAMINE, Ukraine, described an approach for the exploration of chemical space for the need of Medicinal Chemistry that focuses on conformationally restricted diamines and amino acids as building blocks for drug design. He demonstrated an impressive ability to efficiently synthesize a library of both known and new compounds. X-Ray studies of derivatives of the synthesized compounds confirmed calculated results.

**Lior Zelikovich** from ChemAgis talked about how to minimize impurities in the manufacturing process of active pharmaceutical ingredients. The “quality by design” methodology that he presented aims at identifying the origin of these impurities, the study of the mechanism of their formation, and their prevention - as early as possible during the development of the manufacture process. This optimizes the ability to obtain optimal protocols for the creation of high-quality products.

### New Drugs for Therapy of Neurodegenerative Diseases

**Nava Zisapel** from Tel Aviv University described her studies on familial amyotrophic lateral sclerosis (fALS). This disease is increased in patients with mutant Cu/Zn-superoxide dismutase (G39A hSOD), which misfolds and binds to new targets, a “gain-of-function” event that is thought to lead to neuronal damage. Using a fluorescence resonance energy transfer (FRET) based, live cell screening system, as well as a pull-down immunoprecipitation assay, her group was able to identify important new partners: Cytosolic malate dehydrogenase (cytMDH) is a key component of the malate aspartate shuttle which controls brain mitochondrial NADH/NAD<sup>+</sup> balance vital to neurons. Malate-aspartate shuttle dysfunction may explain the damage to neurons and the vulnerability to impairments of glycolytic pathways in ALS and provide a new target for the development of potential therapies for neurodegenerative diseases. Inhibiting or abrogating G93A-hSOD1-cytMDH interaction may alleviate the toxic gain of interaction of the mutant protein.

The group of **Moussa Youdim** from the Technion was among the first to propose multi-target therapies, namely to develop compounds that target several sites. The important advantages of such multi-target drugs lies both in their reduced side effects, as well as reduced costs. In order to address neurodegenerative

diseases such as Parkinson and Alzheimer's disease, the proposed therapeutic strategy promotes candidates that are designed expressly to act on multiple neural and biochemical targets involved in the neurodegenerative and pathological processes and to possess neuro-protective and neuro-restorative activities. These were achieved by the use of functional moieties that target an array of pathological pathways which induce neuronal death. Prof. Youdim described how starting from an anti-Parkinson drug rasagiline (Azilect), his group designed Ladostigil to possess anti-depressant, anti-Parkinson and anti-Alzheimer's disease activities (in Phase IIB trial), and described his recent development of another set of multi target drugs with neuro-protective but also neuro-rescue and neuro-restorative activities.

The research in **Shai Rahimipour's** group at Bar Ilan University focuses on the development of agents to prevent amyloid beta peptide (Abeta) aggregation. According to the amyloid hypothesis, accumulation of Abeta in the brain and its oligomerization to toxic species is the primary pathogenic event in Alzheimer's disease. The strategy employed involves surface-modified proteinaceous particles that contain multiple copies of an Abeta-recognizing motif that compete with Abeta and prevent its aggregation, thereby directly reducing its toxicity to the cells. Importantly, the designed particles target and deliver Abeta to macrophages for efficient clearance through a non-Abeta-mediated phagocytotic mechanism and thus mimic to some extent the capability of Abeta antibodies to clear Abeta.

### Anticancer & Antibacterial Drugs

**Gary Gellerman** from the Ariel University Center of Samaria reported the development of new, highly efficient strategies for the synthesis of established as well as novel 9-anilinoacridine (9-AA) conjugates as non-DNA damaging anticancer candidates. This allows for quick synthesis of 9-AAs with variable spacer lengths and charged, polar or hydrophobic residues at desired positions, which can increase binding affinity, conformation stability and/or biological activity. In vitro biological results on a wide spectrum of cancer cell lines indeed identified submicromolar hits with moderate DNA damage.

**Michael Meijler** from Ben-Gurion University, highlighted the importance of bacterial communication for coordinated action, and suggested a strategy to inhibit



virulence by interfering with bacterial communication. Towards this goal, his group synthesizes quorum-sensing compounds and derivatives to research their way of action and to develop inhibitors. In particular, they developed a series of molecules that covalently attach to the receptor and thereby block the high affinity interaction responsible for quorum sensing in *Pseudomonas aeruginosa*. Extending his view, he also studies quorum-sensing molecules as means for interkingdom communication of prokaryotes with their eukaryotic hosts.

**Eylon Yavin** from The Hebrew University of Jerusalem described the design of selective DNA photo-cleavage agents. One system involves triplex forming oligonucleotides: a conjugate made of a DNA/LNA mixmer 5'-end modified with L-Trp (or Gly) followed by a cyanine dye (either thiazole orange or thiazole red) was shown to nick and linearize specific plasmid DNA (containing the target sequence, but not a scrambled control sequence) upon light activation. Another system currently evaluated consists of PNA constructs that contain a c-terminal cell penetrating peptide (8 D-Lysines) and an N-terminal Trp-cyanine dye as DNA photo-cleavage agents.

The meeting was supported by Teva, SciFinder, Golan Heights Winery, Sigma-Aldrich, Di-Chem, Enamine (Ukraine), Lumitron, Mercury, the Faculty of Medicine and the Institute of Drug Research in the School of Pharmacy of the Hebrew University of Jerusalem, the Grass Foundation and the Weizmann Institute of Science Goldschleger Foundation.

The Advisory Board consisted of Prof. Matityahu Fridkin from the Weizmann Institute, Prof. Eli Breuer from the Hebrew University, and Prof. Abraham Nudelman from Bar Ilan University. During the congress, Dr. Rafael Nudelman (TEVA) was elected as a new head of Israel Association of Medicinal Chemistry. Dr. Arie Gruzman from Bar-Ilan University and Dr. Masha Niv from Hebrew University, have joined the board of the association. Dr. Gruzman will act as the vice president and Dr. Niv will be the secretary. The next congress is planned for March 2012.



# Gertrude B. Elion and the Design of Selective Chemotherapeutic Agents

**Bob Weintraub**

Ms. Gertrude B. Elion and Dr. George Hitchings, working together, and Sir James W. Black, discovered “principles for drug treatment which have been applied successfully to the treatment of a wide variety of serious illnesses.” For this work the three were awarded the 1988 Nobel Prize in Physiology or Medicine.

During the early 1950's Elion and Hitchings “published the hypothesis that, with the aid of drugs, it should be possible to, selectively inhibit the synthesis of nucleic acids used by e.g. cancer cells and bacteria, without simultaneously impeding the growth of normal cells. In these days our knowledge of how nucleic acids were synthesized within the cell was very limited. However, it was known that cells used certain simple building blocks in the manufacture of their nucleic acids. Elion and Hitchings studied how false building blocks, the so-called antimetabolites, could be used to interrupt cellular growth. As early as 1951, they discovered a compound, 6-mercaptopurine, which was used successfully in a hitherto incurable form of leukemia. Through a simple chemical alteration of the 6-mercaptopurine structure, they developed another drug, azathioprine (1957) which inhibited the property of white cells to reject transplanted organs. Twenty years later, one of the world's leading transplant surgeons asserted that, as a result of the discovery of this immunosuppressant drug, 20,000 individuals had been able to receive a new kidney.

Furthermore, a new strategy for the treatment of gout with allopurinol was developed by Elion and Hitchings in 1963.

Hitchings and co-workers also developed the anti-malarial drug pyrimethamine (1950) and the anti-bacterial agent trimethoprim (1956). An important observation of theirs was that the effects of both of these drugs were enhanced by sulfonamides, which led to the use of the trimethoprim-sulfa combination in the treatment of severe bacterial infections, such as those encountered in AIDS patients, and also in an important antimalarial preparation. A subsequent outcome of Elion's and Hitchings' research programme was the successful development of the first effective antiviral drug, acyclovir, which is used against infections caused by e.g. the herpes virus. The virus-infected cell is tricked into transforming acyclovir into a compound which inhibits cell growth and thereby suppresses the ability

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of the virus particle to reproduce. Only cells infected by the virus are attacked. (Prof. Folke Sjöqvist, Nobel Prize Presentation Speech)

Elion in discussing how it feels to be honored with the award of the Nobel Prize: "It's very nice but that's not what it's all about. I'm not belittling the prize. The prize has done a lot for me, but if it hadn't happened, it wouldn't have made that much difference...When you meet someone who has lived for twenty-five years with a kidney graft, there's your reward."

### Gertrude B. Elion

Gertrude B. Elion (1918-1999) was born and grew up in New York City. Her parents were Jewish immigrants, her father from Lithuania and her mother from an area of Russia that is now part of Poland. When she was 15 her grandfather, whom she loved dearly, died slowly and painfully of stomach cancer, "I decided that nobody should suffer that much." "That was the turning point. It was as though the signal was there: 'This is the disease you're going to work against.' I never really stopped to think about anything else. It was that sudden...."

Elion attended college during the years of the great depression. She earned her undergraduate degree in Chemistry (1937) from Hunter College, at that time the women's branch of the City University of New York.

Due to lack of money, the opportunity to continue on directly to graduate school was not open to her. Despite having graduated Hunter College with the highest honors, Elion was not offered financial assistance from any of the 15 graduate schools that she applied to. She sought professional employment, but "Jobs were scarce and the few positions that existed in laboratories were not available to women." Elion held a series of temporary jobs both in and out of chemistry. With savings and while working, she enrolled in New York University for her masters degree studies. She was the only female in her graduate chemistry class, "but no one seemed to mind, and I did not consider it at all strange." Elion earned her M. S. degree in chemistry from New York University in 1941, with a thesis on the reaction of guanidine derivatives with glucose. Around this time Elion was engaged to be married when her fiancé



Gertrude B. Elion, (Image courtesy of Wellcome Library, London.)

died of subacute bacterial endocarditis. A few years later with the advent of penicillin he would have been saved. "It reinforced in my mind the importance of scientific discovery..."

She never married.

The war changed the situation as to the employment of women. Jobs for women in chemistry were opening up. Elion found work in laboratories but still not in research as she wanted. The break came in 1944 when she found employment with Burroughs Wellcome, now part of GlaxoSmithKline, as a research chemist working with Dr. George Hitchings. Hitchings "talked about purines and pyrimidines, which I must confess I'd never heard about up to that point, and it was really to attack a whole variety of diseases by interfering with DNA synthesis. This sounded very exciting." It was ten years before the discovery of the double helix. Elion (1990): "I originally set out thinking, I'm going to stay here as long



as I continue to learn. Here I am, 46 years later and I'm still learning." After Hitchings retirement in 1967, Elion became head to the department of experimental therapy.

Elion began doctoral studies at Brooklyn Polytechnic Institute at night, part-time, but left after two years when informed that to continue she would have to give up her job and become a full time student. She never earned a Ph.D. degree. She held 25 honorary doctorates, including one from Brooklyn Polytechnic Institute, which she thought of as *poetic justice*.

### 6-Mercaptopurine (6-MP): The first major drug to fight Leukemia.

Elion was assigned to work with purines, including adenine and guanine. "Few chemists were interested in the synthesis of purines in those days and I relied mainly on methods in the old German literature. The transformation reactions were carried out mainly by the methods of Emil Fisher and the syntheses from pyrimidine intermediates by the methods of Traube. The direct replacement of oxygen by sulfur by the method of Carrington also proved to be exceedingly useful for synthesizing the mercaptopurines."

Hitchings and Elvira Falco had devised a screening test using *Lactobacillus casei* as the biological object. Hitchings: "Thus, we used *L. casei* as a 'black box' of enzymes and metabolic pathways concerned with the biosynthesis of nucleic acids...In the beginning, we proposed to make variants of the heterocyclic basis of nucleic acids, mostly variants of the functional groups, to see whether these, as probes, could reveal anything about nucleic acid biosynthesis. It was soon apparent that some of these variants could jam the works in a reversible fashion so that there was much to be learned from this kind of probe...In 1944, at about the time we had decided we really had established this system as a working tool, Trudy Elion joined us and got involved in the purine field." (Hitchings and Elion, 1985)

Gertrude Elion: "At the beginning . . . it was my job to find out how to make [compounds]. So I'd go to the library, look up the old literature to see if I could figure out how to do it . . . I would just go ahead and make the compounds, and then the question was, well what

do we do with these compounds? How do we find out if they really do anything? [Working with a microorganism like *Lactobacillus casei*] you could throw it in a defined medium and you could tell when you added something that was a real growth antagonist, then analyze why it was an antagonist. We knew that this organism would grow and from that it could make DNA and folic acid . . . You could make everything just from the amino acids, medium, and folic acid, and so on. We knew folic acid was essential, or if you could replace folic acid with a purine, it would grow . . . It would make lactic acid. If the organisms didn't grow, we knew we had something and we might be antagonizing folic acid or it might be antagonizing the purine. So you could with that one organism really make an analysis of three different kinds. You could add purine or folic acid and reverse the antagonism . . . [We] didn't know the structure of DNA, because nobody did at the time, but [we] knew what the building blocks were, and so we were starting really at the very basic portion of the DNA and saying we don't know how it gets to be DNA . . . but let's find out how we can deal with it . . . One of the things we had in mind was to inhibit what kills cancer cells." (Biographical Memoirs, National Academy of Sciences)

In 1948, they discovered that 2,6-diaminopurine inhibited the growth of *L. casei*, and the inhibition was reversed by adenine but not by other natural purines. They deduced that adenine and 2,6-diaminopurine are anabolized by the same enzyme and that the product of diaminopurine anabolism interfered with purine interconversion. This understanding was a major breakthrough. Elion showed that on leukemic mice and that on in vitro exposure to leukemic cells that 2,6-diaminopurine interfered with the formation of leukemia cells. That enzyme was reported in 1955 by Arthur Kornberg to be adenylyl pyrophosphorylase.

The compound 2,6-diaminopurine was tested on patients. It was found that despite improvement in their condition that the patients relapsed. Hitchings and Elion: "Diaminopurine served to give us a thrill and put us on the emotional roller coaster that was familiar to everybody who was working in cancer chemotherapy in those days. We saw remissions that gave us joy, but almost all were followed by relapse. An example of what diaminopurine did is best illustrated by the case history of J.B., a 23-year-old woman, who, after very



brief therapy, went into a prolonged remission. She was treated with a course of diaminopurine, combined with other drugs. She went into complete remission, stayed in remission for over two years, married, and bore a child. About the time the original diagnosis was being called into question, and the bone marrow slides were being reviewed by experts, she confirmed the diagnosis by relapsing." By 1951 the group had tested over 100 purines in the laboratory and discovered that the compound 6-mercaptopurine (6-MP) formed by the substitution of oxygen by sulfur at the 6-position of the diaminopurine was active against rodent tumors and leukemia.

At that time, the median life expectancy for terminally ill children with acute leukemia was between 3 and 4 months; only 30% lived for as long as one year. Children treated with 6-MP experienced complete remissions and then later relapsed and died. Elion: "The addition of 6-MP to the antileukemia armamentarium increased the median survival time to 12 months in these children, and a few remained in remission for years with 6-MP and steroids. This convinced us, as well as many other investigators in the cancer field, that antimetabolites of nucleic acid bases were fruitful leads to follow." "And for eighteen years of my life, I tried to make 6-mercaptopurine better. I was insistent that this was going to work..." Today 6-MP when used in chemotherapy in combination with three or four other drugs to produce and consolidate remission, almost 80% of children with acute leukemia are cured.

Another product of this stage of the research is thioguanine, synthesised before 6MP, which has found use in the treatment of acute myelocytic leukemia in adults.

Elion: "We get letters from people all the time, from children who are living with leukemia. And you can't beat the feeling that you get from those children."

### **Allopurinol: Gout**

Elion and Hitchings searched for a compound to potentiate the activity of 6-MP. "Since we knew that 6-thiouric acid was one of the principal products of 6-MP catabolism, it seemed possible that we could interfere

with this oxidation by inhibiting the enzyme responsible for it, xanthine oxidase." The compound they choose to study, based on previous work from their lab, was a pyrazolopyrimidine, a hypoxanthine analog, allopurinol. With the collaboration of Wayne Rundles, they found the desired increase in activity, but it was accompanied by a proportional increase in toxicity. "Xanthine oxidase is responsible not only for the oxidation of 6-MP, but also for the formation of uric acid from hypoxanthine and xanthine. Consequently, treatment with allopurinol produces a marked decrease in both serum and urinary uric acid. This presented the possibility of a unique approach to the treatment of gout and other forms of hyperuricemia." Allopurinol has been shown to be a safe and effective drug for long-term treatment. Since that time, tophaceous gout has disappeared and renal complications of gout have become rare. Allopurinol is also effective for leishmaniasis and Chagas' disease.

### **Azathioprine: Organ Transplants**

Dr. Robert Schwartz, working with William Dameshek, showed that 6-MP was useful as an immune system suppressant. Encouraged by Schwartz's work, Dr. Roy Calne looked into the effect of 6-MP on kidney transplant rejection. Elion gave him samples of related compounds that were suitable candidates for immune system suppression. Doctors had worked out the surgical procedure for kidney transplant but had not solved the problem of tissue rejection. In 1960, using one of these compounds, azathioprine--an imidazolyl derivative of 6-MP, Dr. Calne successfully transplanted a kidney into a collie named Lollipop. In 1961, Dr. Joseph E. Murray carried out the first successful kidney transplant between unrelated humans. "Our third patient, transplanted in April 1962, was treated with azathioprine following a cadaveric renal allograft. He survived over one year and was the world's first successful unrelated renal allograft." For work in this field, Dr. Murray, together with E. Donnall, was honored by the award of the Nobel Prize in Physiology or Medicine in 1990. Azathioprine made organ transplants possible by preventing rejection of kidneys transplanted between unrelated donors. It has become a mainstay in kidney transplantation. Tens of thousands of kidney transplants are carried out every year. Other transplants have now also become possible.



### Acyclovir: The first medication effective against viruses

Antivirals was a field that drug companies stayed away from. The few known effective compounds were toxic to the cells. Then in the late 60's, a natural product isolated from a sponge showed a therapeutic index a little better than what was found before. Elion: "It was a purine, and I had been working all my life on purines. People hadn't been working with purines as antivirals. They had been looking at pyrimidines and those were pretty toxic. Why not go back and see if some of our purines aren't antiviral? It had an unnatural sugar on it. So we began to make these modified sugars, and we found things that were just as good, or better, than this thing that was found in a sponge."

In the meantime, Dr. Schaeffer came to work for us in 1970. He had been playing around with the sugar molecule on these bases. Instead of the whole ring system, he'd made just a piece of the sugar. He saw that you don't need the entire sugar to bind to the enzyme he was working with. The enzyme will recognize even this one piece. That sounded like a good idea to exploit, so we put his false sugar on the purines we were working with. We tested it on herpes virus and, lo and behold, this compound had high activity. Amazingly, they were very non-toxic...Why is that the case? We put all our efforts into finding out what was going on in a virus-infected cell. Then we began to find that these non-toxic compounds were actually being activated by the virus itself. The virus was converting it to the toxic compound. It took three more steps to get to the really active antiviral compound."

Acyclovir is used today in the treatment of conditions in which the herpes virus is present: first episodes of genital herpes infection, herpes zoster, prevention of herpes infection in immunosuppressed patients, herpetic encephalitis, and others. François Chast: "The discovery of acyclovir was a major therapeutic breakthrough per se, but the lessons learned from its history have also turned out to be extremely fruitful for subsequent research on antivirals, mostly in connection with AIDS. In-depth study of its mechanism of action has led to a better grasp of the enzymatic differences between healthy and virus-infected cells and helped assess the impact of the specific properties of enzymes on their therapeutic applications."

The introduction of acyclovir was undoubtedly the high point of Elion's career. It is a remarkable fact that, more than fifty years after she began her work, the discoveries of this extraordinary pharmacologist were still indispensable and unsurpassed therapeutic tools."

G.B. Elion (1985) : "In closing, I wish to espouse the concept that ignorance of the law is no excuse. We must certainly continue to pursue basic research and to probe Nature for her undiscovered laws, but let us not ignore the clues along the way. Chemotherapeutic agents are not only ends in themselves, they are also beginnings. They are the tools which help us to answer the whys and the wherefores. Unless we use drugs as tools, we will have thrown away the keys and gone searching for new locked doors. Each door we open may lead to a new maze, but an unlocked door leads nowhere. Let us not rely on the excuse that we do not yet know enough to design selective chemotherapeutic agents. Until that time comes, in the words of Admiral Farragut, 'Damn the torpedoes. Full speed ahead.' Selectivity must be our goal and understanding its basis, our guide to the future."

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# "המסלול הירוק" של בזן

הגנת הסביבה, היא חלק נכבד מהפעילות האסטרטגית של קבוצת בזן כמו גם פיתוח בר-קיימא. בפועל, משמעות הדבר היא כי בזן שואפת באופן מתמיד לפתח ולייצר מוצרים ירוקים, נקיים יותר, כאלה שלא רק יצמצמו ככל הניתן את הפגיעה בסביבה, אלא גם יעשו זאת לכל אורך מסלול חייהם - החל משלב הייצור, דרך השימוש במוצר ועד סופו. כזה הוא למשל "המסלול הירוק" של בזן הכולל בין היתר את המוצרים הבאים:

## דלקים נקיים, דלי גופרית

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## ביטומן משופר

חומר המתווסף אל תערובת האספלט המשמש לסלילת כבישים. הביטומן המשופר מאפשר הכנת תערובות אספלט לריבוד כבישים בתנאים נוחים וידידותיים יותר לסביבה.

## מיד"ן : מתקן ייצור דלקים נקיים

מטרתו של המתקן שהקמתו הולכת ונשלמת בהשקעה חסרת תקדים, הינה להפוך את חומרי הגלם לתזקיפים באיכות גבוהה הרבה יותר. כך למשל, הסולר אשר מתקן זה ייצר, צפוי להיות איכותי אף יותר מהתקן המקובל. פעילותו של המתקן, לא תוסיף פליטות מבתי הזיקוק ובסופו של דבר תביא להפחתת הזיהום מכלי הרכב בכבישים, כתוצאה מהשיפור באיכות הסולר לתחבורה שיהיה בשימוש בארץ.

## המעבר לגז טבעי

החל מחודש מאי 2011 כדי להבטיח אספקה סדירה, חתמה הקבוצה על הסכם אספקת גז עם שני ספקי גז טבעי. מבחינת בזן בכלל, ותהליך הייצור בפרט, מדובר בלא פחות ממהפכה. היתרונות הסביבתיים והכלכליים לשימוש בגז הם רבים, וכבר כיום ניתן לראות כי רמת הפליטות ממתקני הייצור הופחתה באופן משמעותי.

## משאבים מתחדשים

בזן ממשיכה ומיישמת בשטחה פרויקטים סביבתיים שונים כמו התהליך הייחודי לטיפול בתמלחות הנוצרות בתהליכי הייצור, דבר שיפסיק את הזרמתן לנחל קישון. בתהליך, אשר מבוצע על ידי חברת משאבים מתחדשים, מטופלות מטהורות, ושובות לשימוש חוזר בתהליך - פתרון שהוא סביבתי וחסכוני כאחד.



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