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The Signer DNA-Symposium in Bern

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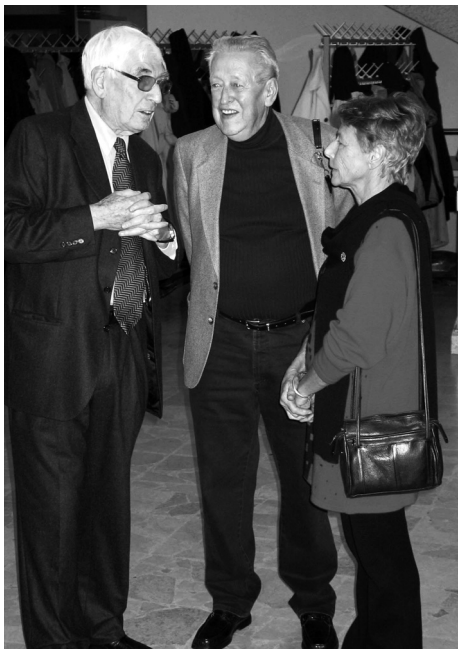
Abstract: As the year 2003 was not only the 50th anniversary of the discovery of the DNA structure but also the 100th birthday of Rudolf Signer, the Department of Chemistry and Biochemistry at the University of Bern organized a Symposium on November 28th, in order to honour the pioneering work of its former faculty colleague Rudolf Signer. The invited symposium speakers covered a number of aspects related to the person and work of Rudolf Signer as well as ongoing research on the structure, function and use of DNA and nucleic acids.

Keywords: DNA · Double helix · Nucleic acids · RNA · Rudolf Signer

The famous *Nature* paper by James Watson and Francis Crick describing the DNA structure marks the birth year of modern molecular biology, but their work would not have been possible without the good X-ray diffraction data collected by Rosalind Franklin. As acknowledged by Maurice Wilkins in his Nobel-lecture, the generation of X-ray diffraction data was critically dependent on the high-quality DNA provided by Rudolf Signer who was a Professor of organic chemistry in Bern. In addition to his contribution for the elucidation of the DNA structure, his important work established DNA as a high molecular weight macromolecule. Furthermore, Rudolf Signer was a unselfish and generous personality, as he offered his high-quality DNA samples to anyone interested within the scientific community. In order to dignify the person and work of Rudolf Signer, the symposium speakers covered not only historical aspects, but also showed results from ongoing research revealing the potential of nucleic acids for a variety of applications including molecular diagnostics, biochemical catalysis, drug discovery and therapy.

The symposium was officially opened by ***Gerhard Jäger,*** the Dean of the science faculty at Bern University. ***Christian Leumann,*** head of the Department for Chemistry and Biochemistry, gave a short introduction into the person and work of Rudolf Signer. He highlighted his scientific achievements and also appreciated his unusual generosity in distributing the DNA samples to interested researchers. Christian Leumann emphasised that the symposium should not only serve to publicise Signer's largely forgotten scientific contributions, but also shed light on present and ongoing research.

The first scientific session chaired by *Jack D. Dunitz* (ETH Zürich) began with a talk given by ***Michael Famulok*** from the University of Bonn (Germany) entitled 'Ribozymes for Drug Screening'. Michael Famulok pointed out that specific target-binding RNA molecules, commonly designated as aptamers, can be obtained by *in vitro* selection of combinatorial nucleic acid libraries. These RNA aptamers can be used for a variety of applications including the specific inactivation of target structures upon aptamer binding. While modern technology allows the selection and identification of aptamers in a short time, the use of these nucleic acids within intact cells is still hampered by the limited stability of RNA. Michael Famulok presented various experimental strategies to couple aptamers with reporter groups, thus allowing to monitor competitive binding of small molecules to the RNA binding site by changes in fluo-



The son of Rudolf Signer, Peter Signer and his wife chatting with Jack Dunitz (left).

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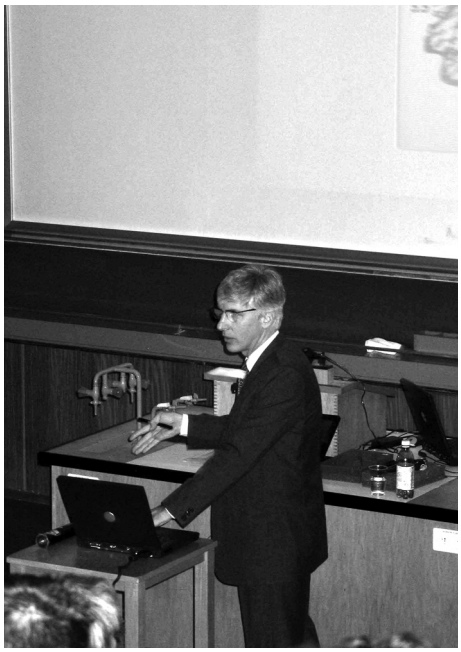
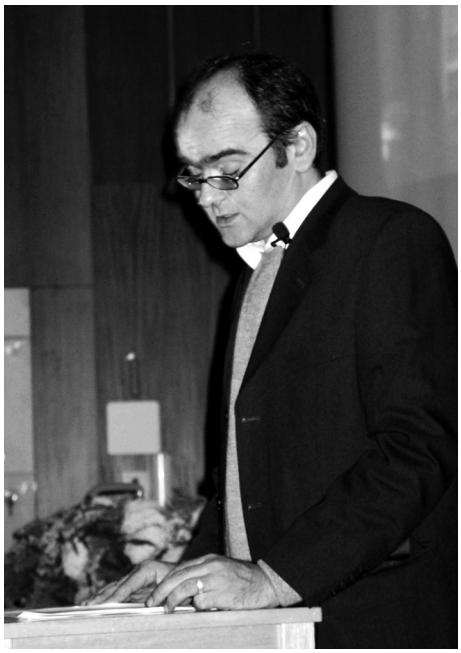


Timothy Richmond explaining the nucleosome structure.



Matthias Meili introducing the work and life of Rudolf Signer to the audience.

rescence emission. The approaches allowed him to identify substances binding to the HIV Rev protein and inhibiting HIV replication. He is now using these technologies to investigate multi-protein complexes.

The next talk by ***Timothy Richmond*** (ETH Zürich) on 'DNA in Chromatin' allowed a fascinating view on the nucleosome core. He showed the structure of histones within the nucleosome octamer and the 147 bp of DNA wrapped around the histones at a resolution of 1.9 Å. A picture showing the nucleosome in the presence of water and ions illustrated the role of water for the movement of DNA on the octamer surface. While naked DNA shows a relatively uniform structure, the packaging of DNA causes major differences in the structural organization of DNA. Richmond's high-resolution structure enabled the persistently tight curvature of nucleosome core DNA which causes it to adopt a stretched conformation *in vivo* to be visualized. The excess curvature of nucleosomal DNA stems predominantly from the roll rather than the tilt parameter. He observed that DNA segments bent into the minor groove are either alternately shifted or kinked, and he discussed the implications of these findings for transcription factor binding and gene activation.

During the lunch break many of the symposium participants enjoyed a project called 'HUGO hat Töne' created by *Daniel Schümperli, Rudolf von Steiger,* and *Lukas Frey.* A computer translated the DNA sequence of human chromosome 23 into a series of sounds, thus creating 'genomic' music. DNA is not only an aesthetically pleasing molecule, it can also be used as a template for music.

The afternoon session chaired by *Hans-Beat Bürgi* began with a presentation by ***Matthias Meili***, a biochemist now working for the 'NZZ am Sonntag'. He is owed the merit of bringing the forgotten contributions of Rudolf Signer to a broader audience. The science journalist Matthias Meili reported on his research on the life and scientific contributions of Rudolf Signer (M. Meili, 'Signer's Gift – Rudolf Signer and DNA', *Chimia* **2003**, *57*, 735–740). He reported on the scientific stations of Signer, which led him as a student of Hermann Staudinger from Zürich to Freiburg/Br. and then to Bern, where he carried out his important DNA work. In 1938, Signer published an often cited paper in *Nature,* where he measured the physical characteristics of native DNA, describing it as a long, high-molecular weight thread-like molecule. He also emphasised the generosity of Signer, who distributed his DNA samples to interested scientists at the occasion of a meeting of the Faraday society in London.

Hans Trachsel (University of Bern) talked about the regulation of gene expression in ribosomes. Starting with a historical excursion, he featured the classical experiments he performed when using the Schreier-Staehelin *in vitro* translation system. This assay system directs translation of globin mRNAs in rabbit reticulocyte extracts only in the presence of added initiation factors and was thus ideally suited to study the factors mediating translation initiation. This work allowed the purification of translation initiation factors and studies on their regulation, as pointed out by the example of eIF-2 phosphorylation. Phosphorylation of this translation initiation factor precludes its function and inhibits binding of the $tRNA_i^{Met}$ to the small ribosomal subunit. The speaker then switched to ongoing research which involves investigations of translation initiation factor structures and closed by presenting an up-to-date model of

Former coworkers of Rudolf Signer: W. Reichenberger, H. Türler and K. Naef (from left to right).

Albrecht Eschenmoser lecturing.

Logos of the sponsors.

translation and its regulation in eukaryotes.

In the following talk, ***Robert Häner*** (University of Bern) featured nucleic acids as targets of destruction and objects of construction. Destruction of nucleic acids is often desired in biomedicine, as for example dysregulated expression of oncogenes can be a cause of cancer. Robert Häner presented several experimental approaches which prevent or impair the expression of genes. While binding of antisense RNA to the mRNA prevents efficient translation and also recruits RNaseH to destroy the duplex RNA, another strategy employs sequence-specific RNAs coupled to a cleaver such as the metal europium. He started the second part of his talk by presenting the title page of Jim Watson's book 'The Double Helix' which falsely displays the famous double helix in the left-handed form. He then presented various methods for structural stabilisation of abasic DNA and the synthesis of hairpin DNA.

The next lecture entitled 'DNA Analogues for Antisense Applications and More' was given by ***Christian Leumann*** (University of Bern). He pointed out that oligonucleotides can be used for a variety of applications ranging from molecular diagnostics (gene arrays) to oligo-based therapeutics and specific catalysis of reactions. The speaker presented the concept of HNAs (hexitol nucleic acids) which contain a phosphorylated 1,5-anhydrohexitol backbone and LNAs (locked nucleic acids). These novel oligonucleotide analogues are capable of recognising complementary DNA and RNA with very high affinities and can be efficiently transfected into cells. Another class of oligodeoxynucleotide analogues are the tricyclo-DNAs which can form stable Watson-Crick base-pairs with other nucleic acids and have antisense properties. They display an increased thermal and cellular stability and efficiently interfere with splicing of the pre-mRNA encoding cyclophilin A. The suitability of chimeric DNA/RNA triplex-forming oligonucleotides for inhibition of gene expression and of so-called molecular beacons as biosensors was discussed.

In the last session with *Christian Leumann* as chairman, ***Albert Eschenmoser*** (ETH Zürich and The Scripps Research Institute, La Jolla, USA) gave a talk entitled 'The Quest for a Chemical Etiology of Nucleic Acid Structure'. In other words: was there genetic material before RNA appeared as an information carrier? Interest in this kind of research was sparked by the early experiments of Stanley Miller who showed that some amino acids can be found after boiling of organic compounds. Recent data from Miller's laboratory also allow the theory of a 'cold origin of life', as a frozen ammonium cyanide solution stored at –78 °C for 27 years contained a wide variety of pyrimidines and purines. Why is RNA used in nature and not the pyranosyl isomer of RNA or pentopyranosyl-(4',2') oligonucleotides? A possible clue comes from the finding that pyranosyl RNA and RNAs are not able to form duplexes with each other, which would preclude information exchange between these two molecules. These data suggest that pyranosyl RNA is unlikely to be the genetic material preceding RNA. Therefore, the quest for a chemical etiology of nucleic acid structure goes on.

Last, but not least, ***Hans Beat Bürgi*** (University of Bern) made some concluding remarks. He acknowledged the sponsors of the symposium and also expressed his thanks to all speakers, discussion partners and the large and interested audience, which together made this symposium a great success.

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