KONINKLIJKE NEDERLANDSE
AKADEMIE VAN WETENSCHAPPEN

Academy Symposium:

Towards creating a minimal cell

Academy Lecture:

Jack Szostak - The Origins of Cellular life

(24 June 2015)

Professor Jack Szostak

Investigator, Howard Hughes Medical Institute, Professor of Genetics, Harvard Medical School, Professor of Chemistry and Chemical Biology, Harvard University, Alex Rich Distinguished Investigator, Massachusetts General Hospital.

Abstract

The origins of cellular life
The complexity of modern biological life has long made it difficult to understand how life could emerge spontaneously from the chemistry of the early earth. We are attempting to synthesize simple artificial cells in order to discover plausible pathways for the transition from chemistry to biology. Very primitive cells may have consisted of a self-replicating nucleic acid genome, encapsulated by a self-replicating cell membrane. A chemically rich environment that provided the building blocks of membranes, nucleic acids and peptides, along with sources of chemical energy, could have led to the emergence of replicating, evolving cells.

Short biography

Jack William Szostak (1952) is a Canadian American biologist of Polish British descent, Nobel Prize laureate, Professor of Genetics at Harvard Medical School and Alexander Rich Distinguished Investigator at Massachusetts General Hospital, Boston. Szostak has made significant contributions to the field of genetics. His achievement helped scientists to map the location of genes in mammals and to develop techniques for manipulating genes. His research findings in this area are also instrumental to the Human Genome Project.
Szostak grew up in Montreal and Ottawa. He attended Riverdale High School (Quebec) and graduated at the age of 15 with the scholars prize. He graduated with a B.Sc in cell biology from McGill University at the age of 19. In 1970, as an undergraduate, he participated in The Jackson Laboratory's Summer Student Program under the mentorship of Dr Chen K. Chai. He completed his PhD in biochemistry at Cornell University (advisor Prof. Ray Wu) before moving to Harvard Medical School to start his own lab at the Sydney Farber Cancer Institute. Howard Goodman lured him away to Massachusetts General Hospital and the Department of Molecular Biology. He was granted tenure and a full professorship at Harvard Medical School in 1988.
Szostak has made contributions to the field of genetics. He is credited with the construction of the world's first yeast artificial chromosome. That achievement helped scientists to map the location of genes in mammals and to develop techniques for manipulating genes. His achievements in this area are also instrumental to the Human Genome Project.

His discoveries have helped to clarify the events that lead to chromosomal recombination—the reshuffling of genes that occurs during meiosis—and the function of telomeres, the specialized DNA sequences at the tips of chromosomes.
In the early 90s his laboratory shifted its research direction and focused on studying RNA enzymes, which had been recently discovered by Cech and Altman. He developed the technique of in vitro evolution of RNA (also developed independently by Gerald Joyce) which enables the discovery of RNAs with desired functions through successive cycles of selection, amplification and mutation. He isolated the first aptamer (term he used for the first time). He isolated RNA enzymes with RNA ligase activity directly from random sequence (project of David Bartel).
Currently his lab focuses on the challenges of understanding the origin of life on Earth, and the construction of artificial cellular life in the laboratory.
Szostak has received several awards and honours for his contributions. He is a member of the National Academy of Sciences, American Academy of Arts and Sciences and New York Academy of Sciences. He was awarded the 2008 Dr H.P. Heineken Prize for Biochemistry and Biophysics, Royal Netherlands Academy of Arts and Sciences and the 2009 Nobel Prize for Physiology or Medicine, along with Elizabeth Blackburn and Carol W. Greider, for the discovery of how chromosomes are protected by telomeres.

Professor Cees Dekker, Bionanoscience, Delft University of Technology

Abstract

Towards division of synthetic cells
In this brief introduction I will propose a bottom up approach to building a synthetic cell. This involves a minimal form of cell division with a liposome filled with divisome proteins that can pinch off the liposome into two daughters. This approach requires building a minimal machinery to realize such a division process as well as control of the placement of the division proteins at the equator at mid-vesicle position. While we have not established this, I will present our experimental data on spatiotemporal Min protein oscillations – that control the location of the divisome – in live E. coli bacteria that are shaped into novel shapes such as rectangles, squares, triangles and circles. We study pattern formation in these geometries to understand the positional control.

Short biography

Prof. Cees Dekker (1959) is a scientist known for his research on carbon nanotubes, single-molecule biophysics, and nanobiology. Dekker's research style is characterized by a strong drive and enthusiasm for science, long-term vision, and experimental research directed at exploring novel phenomena in unknown territories.
He received a PhD in Experimental Physics at the University of Utrecht in 1988 and held several positions at the University of Utrecht, Delft University of Technology. In 2000, he was appointed in a regular full professorship in Molecular Biophysics at Delft, and in 2008 as a Distinguished University professor. Since 2010 Dekker also acts as the Director of the Kavli Institute of Nanoscience at Delft.
Dekker started his research on single carbon nanotubes in 1993 when he set up a new line of research to study electrical transport through single organic molecules between nanoelectrodes. In 1996 a breakthrough was realized with carbon nanotubes. In 1998, they were the first to build a transistor based on a single nanotube molecule. Since 2000, Dekker has shifted the main focus of his work towards biophysics where he studies the properties of single biomolecules and cells using the tools of nanotechnology. Dekker has been elected Member of the Royal Netherlands Academy of Arts and Sciences (2003) and Fellow to the American Physical Society and the Institute of Physics. He was awarded a number of national and international prizes, the 2003 Spinozapremie, the 2012 Nanoscience Prize, and 2015 Academy professor of the Royal Netherlands Academy of Arts and Sciences. He has more than 260 publications, including more than 20 papers in Nature and Science and his group work was selected as "breakthrough of the year" by the journal Science.

Professor Bert Poolman, Biochemistry, University of Groningen & Zernike Institute for Advanced Materials

Abstract

Towards a metabolism for synthetic cells
Cell volume regulation is crucial for any living cell because changes in volume determine the metabolic activity through *e.g.* changes in ionic strength, pH, macromolecular crowding and membrane tension. These physical chemical parameters influence interaction rates and affinities of biomolecules, folding rates, and fold stabilities *in vivo*. Understanding of the underlying volume regulatory mechanisms is of fundamental importance in biology, yet these factors are generally ignored in systems analyses of cellular functions. We study cell volume regulatory mechanisms in a context and at a level of complexity minimally needed for life. We aim to elucidate how the components of a regulatory circuit work together in a synthetic cell and control the internal physicochemical conditions. One of the challenges is to incorporate into synthetic cells an efficient pathway for ATP production and maintain energy homeostasis while the load on the system varies. I will present our recent work on osmoregulatory mechanisms of membrane transport and insights of cell volume regulation.

Short biography

Bert Poolman (1959) was trained in bioenergetics and microbiology and moved to biochemistry and biophysics in later years. Central questions in his research are: *How do molecules permeate biological membranes and how can one control solute fluxes?* Throughout his career, he has made contributions to the understanding of the dynamics and permeability of biological membranes and to the field of vectorial biochemistry, i.e. the role of electrochemical gradients in the fuelling and regulation of membrane transport. Poolman has a leading record in the energetics of membrane transport and cellular osmoregulation. He has advanced the field of ATP-binding cassette (ABC) transporters, one of the largest known protein families, by combining functional and structural studies. Poolman's group is also credited with several methodological advances, including the expression and quality control of membrane proteins, which are crucial for the *in vitro* reconstitution of cellular function and microscopy analysis of translocation processes *in vitro* and *in vivo*. A recent innovation is the development of a FRET-based sensor to probe macromolecular crowding in living cells

Poolman is professor of biochemistry at the University of Groningen. Since 2014 he also acts as Director of the Groningen Biomolecular Sciences and Biotechnology Institute. He is elected member of the Royal Netherlands Academy of Arts and Sciences (KNAW) and serves on the editorial board for the Faculty of 1000 and the Journal of Molecular Biology. After his PhD in 1987, he worked for a few years in industry (Genencor Inc, South San Francisco), and in 1990 he returned to the academia as KNAW fellow. In 2003, he was visiting professor at the California Institute of Technology, Pasadena. Poolman is recipient of several NWO Top and EU program grants and awarded a number of (inter)national prizes; in 2015 he was awarded an ERC Advanced Grant to support his research on ABC transporters and cell volume regulation. Poolman has published over 270 publications in peer refereed international scientific journals and a book on synthetic biology for layman audiences.

Professor Wilhelm T. S. Huck, Physical Organic Chemistry, Radboud University Nijmegen

Abstract

Towards an information carrier in synthetic cells
Living cells are extremely complex chemical reactors that are dominated by macromolecular crowding, interfaces, confinement, and compartmentalization. If we are to build a synthetic cell, we need to reconstruct this physical environment and understand its impact on key enzymatic processes in the cell,

including transcription and translation. We study cell-free gene expression in large numbers of picoliter droplets in microfluidic devices, while studying mRNA and protein production during changes in concentration of macromolecules, volume, and composition. I will show how crowding can lead to orders of magnitude faster transcription rates and how confinement leads to co-localization of transcription and translation. Furthermore, the inherent noise in cell free transcription translation systems increases significantly in viscous, crowded solutions. Our results indicate that the basic chemistry in cells differs strongly from dilute solutions typically studied in (bio)chemistry.

Short biography

Prof. Wilhelm T. S. Huck (1970) is Professor of Physical Organic Chemistry. He received his PhD (promoter Prof. David Reinhoudt) in 1997 from the University of Twente. After postdoctoral research with Prof. Whitesides at Harvard University, he took up a position in the Department of Chemistry at the University of Cambridge, where he was promoted to Reader (2003) and Full Professor of Macromolecular Chemistry (2007). He became Director of the Melville Laboratory for Polymer Synthesis in 2004 and in 2010 he moved to the Radboud University Nijmegen. His new group is focused on the physical organic chemistry of the cell and aims to elucidate, using model systems, the influence of the special nature of the cellular environment on complex reaction networks in cells. He was elected to the Royal Netherlands Academy of Arts and Sciences (KNAW) in 2012. He has published around 200 papers and supervised ~20 PhD students. His research group in Nijmegen is supported by an ERC advanced grant (2010) and a VICI award (2011).