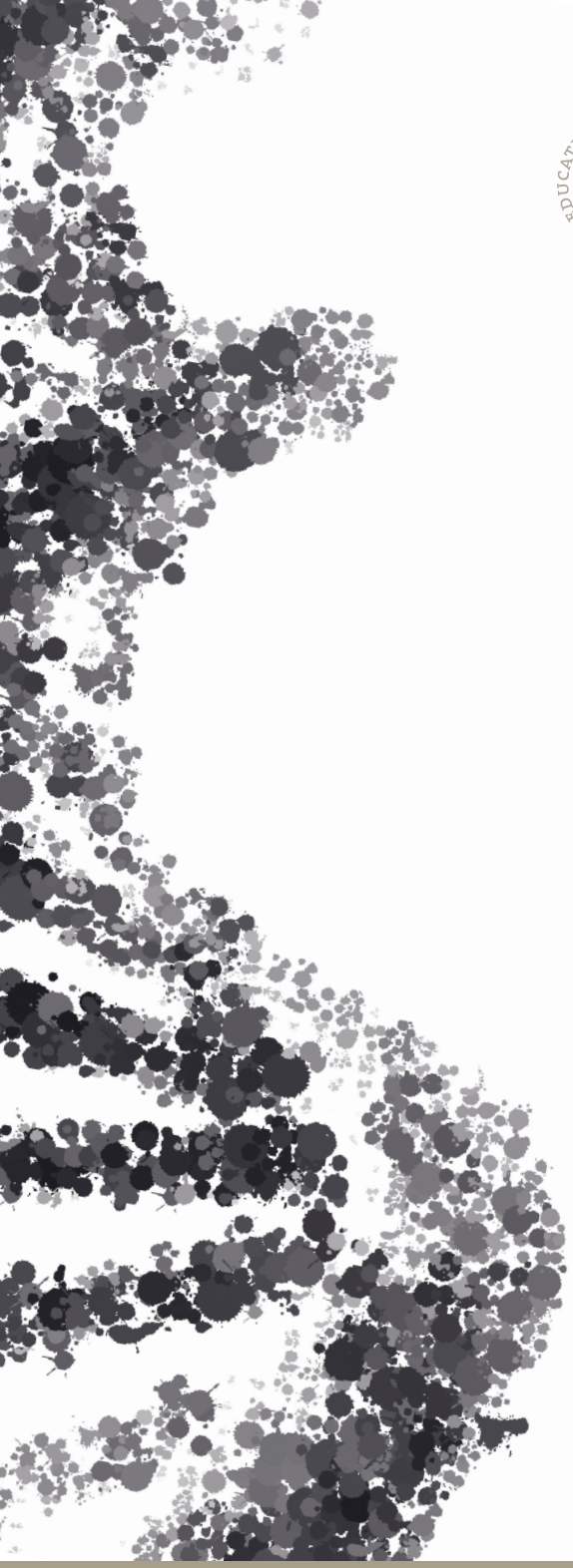

LINDAU
NOBEL LAUREATE
MEETINGS

64th Lindau Nobel Laureate Meeting

Programme

29 June – 4 July 2014
Lindau & Mainau Island, Germany

THE MEETINGS ONLINE

Lindau Blog
blog.lindau-nobel.org

Lindau Mediatheque
mediatheque.lindau-nobel.org

Nobel Labs 360°
nobellabs.lindau-nobel.org

Lindau Alumni Community
alumni.lindau-nobel.org

Facebook
www.facebook.com/LindauNobelLaureatesMeeting

Twitter
twitter.com/lindaunobel (#lnlm14)

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WELCOME

With 38 Nobel Laureates and approximately 600 young scientists from more than 80 countries, the 64th Lindau Nobel Laureate Meeting is a landmark on the agenda of the international scientific dialogue. The most esteemed scientists of our times and promising young talents will share their enthusiasm for science, discuss the latest research findings, and help expand a community across generations, cultures and disciplines. It is a great pleasure for the Council for the Lindau Nobel Laureate Meetings and the Foundation Lindau Nobel Laureate Meetings to welcome our appreciated guests.

Since 1951, Nobel Laureates in physiology or medicine, physics, and chemistry have gathered annually in Lindau to mentor and inspire the next generation of excellent scientists. From their beginnings in 1951, the Lindau Meetings have evolved into an international forum for global debate. The 64th Lindau Nobel Laureate Meeting is dedicated to physiology/medicine. Once again, Nobel Laureates have been invited to lecture on a topic of their deliberate choice and showcase the wide range of research fields.

The Lindau Nobel Laureate Meetings have always encouraged promising and passionate young scientists from around the globe not only to strive for excellence in their fields of research but also to look beyond their actual research.

This year´s meeting will again stimulate the valuable exchange of knowledge and ideas. Our leitmotif "Educate. Inspire. Connect." embodies a holistic and therefore sustainable understanding of the concept of learning. At the Lindau Nobel Laureate Meetings, education means more than learning from textbooks. It should be part of everyone's education to make inspiring and lasting experiences and share them with others. This approach distinguishes the Lindau Meetings from common scientific conferences.

In order to foster the understanding of science in society, our "Mission Education" comprises various initiatives and projects, including the Lindau Mediatheque, educational films, the initiative Teaching Spirit and the travelling exhibition "Sketches of Science". They all have the potential to generate public awareness of the importance and fascination of science and research.

The council and the foundation would like to express their gratitude to the participating Nobel Laureates, this meeting's scientific chairs, our academic partners from all continents, the donors and benefactors as well as all supporters for their continuous commitment to our Mission Education. We welcome you to join and share an unforgettable experience.

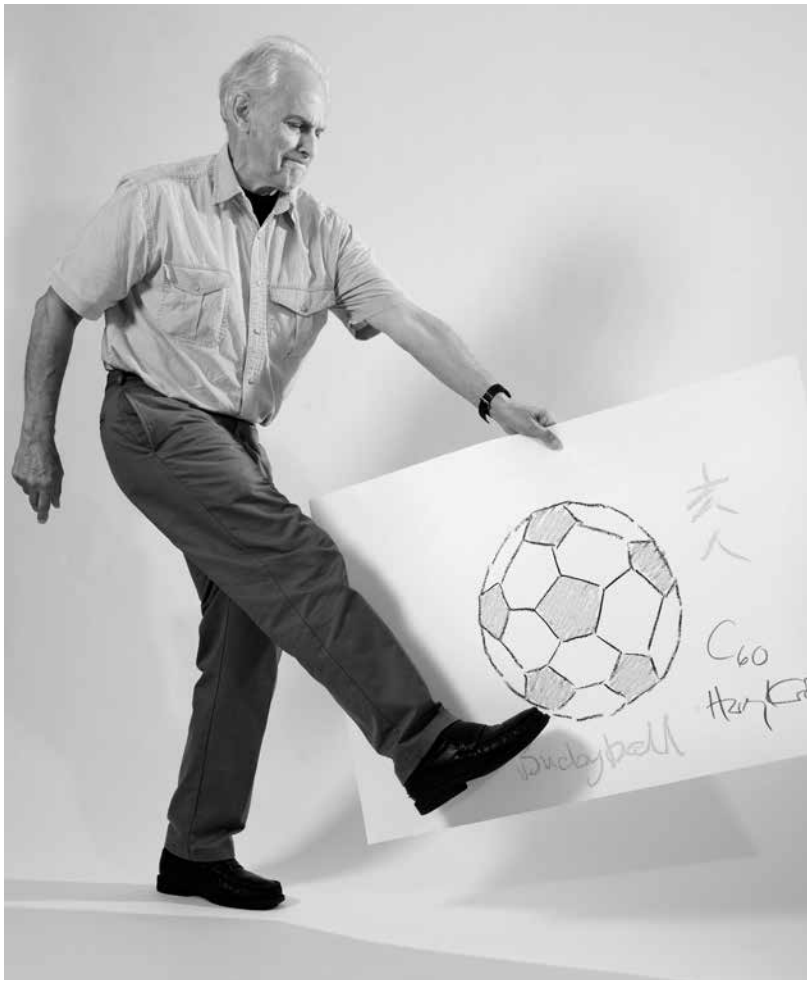
Council for the Lindau Nobel Laureate Meetings

Foundation Lindau Nobel Laureate Meetings

PETER AGRE WERNER ARBER FRANÇOISE BARRÉ-SINOUSSI
BRUCE A. BEUTLER J. MICHAEL BISHOP ELIZABETH H. BLACKBURN
MARTIN CHALFIE STEVEN CHU AARON CIECHANOVER
JOHANN DEISENHOFER MARTIN J. EVANS EDMOND H. FISCHER
WALTER GILBERT JULES A. HOFFMANN ROBERT HUBER
TIM HUNT BRIAN K. KOBILKA WALTER KOHN JEAN-MARIE LEHN
BARRY J. MARSHALL HARTMUT MICHEL FERID MURAD
ERWIN NEHER RICHARD J. ROBERTS BERT SAKMANN
RANDY W. SCHEKMAN BRIAN P. SCHMIDT HAMILTON O. SMITH
OLIVER SMITHIES THOMAS A. STEITZ ROGER Y. TSIEN
JOHN E. WALKER ARIEH WARSHEL TORSTEN N. WIESEL
KURT WÜTHRICH ADA E. YONATH ROLF M. ZINKERNAGEL
HARALD ZUR HAUSEN

PROGRAMME OVERVIEW

	Sunday, 29 June	Monday, 30 June	Tuesday, 1 July	Wednesday, 2 July	Thursday, 3 July	Friday, 4 July
07.00		*Science Breakfast* **ScienceBreakfast** upon invitation of Australia	*Science Breakfast* **Science Breakfast** upon invitation of Else Kröner-Fresenius-Stiftung	*Science Breakfast* **Science Breakfast** upon invitation of Mars, Incorporated / McKinsey & Company, Inc.	*Science Breakfast* **Science Breakfast** upon invitation of Austrian Federal Ministry of Science, Research and Economy / German Cancer Research Center, DKFZ	**Baden-Württemberg Boat Trip** to Mainau Island upon invitation of the State of Baden-Württemberg
08.00						
09.00		*Lecture* Schekman *Lecture* Warshel *Lecture* Hoffmann *Lecture* Beutler	*Lecture* Barré-Sinoussi *Lecture* Zinkernagel *Lecture* zur Hausen *Lecture* Yonath	*Lecture* Smith *Lecture* Roberts *Lecture* Agre *Lecture* Wüthrich	*Lecture* Michel *Lecture* Deisenhofer *Lecture* Huber *Lecture* Murad	
10.00		Coffee Break	Coffee Break	Coffee Break	Coffee Break	
11.00		*Lecture* Marshall *Lecture* Bishop *Lecture* Evans *Lecture* Blackburn	*Lecture* Steitz *Lecture* Kobilka *Lecture* Ciechanover *Lecture* Chu	*Lecture* Tsien *Lecture* Lehn *Lecture* Neher *Lecture* Sakmann	*Lecture* Arber *Lecture* Chalfie *Lecture* Walker *Lecture* Smithies	*Closing Panel Discussion* Science for the Benefit of Mankind Barré-Sinoussi, Bassioni, Mgone, Schmidt, Schütte
12.00						
13.00						
14.00		**Lunch Break** upon invitation of Australia	**Lunch Break**	**Lunch Break**	**Lunch Break**	**Lunch Break**
15.00	**Registration** 10 - 20 hrs					
16.00	**Opening Ceremony**	*YS Discussions* Beutler | Bishop Blackburn | Evans Hoffmann | Marshall Warshel	*YS Discussion* Barré-Sinoussi Chu | Ciechanover | Kobilka | Steitz Yonath | Zinkernagel zur Hausen *Lecture/Discussion* Fischer Kohn Wiesel	*Panel Discussion* Large Data and Hypothesis-Driven Science in the Era of Post-Genomic Biology Beutler, Bishop, Hoffmann, Schmidt	*Panel Discussion* Academia and Industry: Exploring the Collaborative Landscapes of the Future Beutler, Goldman, Gøtzsche, Gomes, Wang	**Farewell Ceremony**
17.00	Reception upon invitation of the Republic of Austria	**Break**	**Break**	**Break**	**Break**	
18.00	**Concert** Ensemble of the Vienna Philharmonic Orchestra	*Lecture & Disc.* Schmidt *Master Classes* Ciechanover Zinkernagel	*Presentation* offered by the European Commission *Master Class* Lehn	*YS Discussions* Agre | Lehn Neher | Roberts Sakmann | Smith Tsien | Wüthrich	*YS Discussions* Arber | Chalfie | Deisenhofer | | Huber | Michel | Murad | Smithies | Walker	**Baden-Württemberg Boat Trip** to Lindau upon invitation of the State of Baden-Württemberg
19.00	*Social Function*	**Break**	**Break**	**Break**	**Break**	
20.00	**Dinner** at various locations limited attendance	*Social Function* **International Get-Together** upon invitation of Australia	*Social Function* **Academic Dinners** at various locations upon invitation of the Academic Partners or **Grill & Chill** upon invitation of the Council & Foundation and City of Lindau with the Lindau Citizens	*Presentation* offered by the Global Young Academy *Social Function* **Dinner**	*Social Function* **Bavarian Evening** upon invitation of the Elite Network of Bavaria & Free State of Bavaria	
21.00				**Free Evening**		
22.00						



SKETCHES OF SCIENCE

Exhibition

Japan, OIST Okinawa Institute of Science and Technology | May – June 2014
Japan, Tohoku University | July – September 2014
Korea | October – November 2014
USA, UC Davis | December – February 2015
Deutschland, Hannover Messe | April – Mai 2015

10.00
Registration
Inselhalle

Meeting Registration
from 10.00 – 20.00 hrs continuously

15.00
Opening Ceremony
Inselhalle

Opening Ceremony

Welcome
Countess Bettina Bernadotte
President of the Council

Welcome Address
Klas Kärre
Chairperson of The Nobel Assembly Physiology and Medicine at Karolinska Institutet

Welcome Address
Johanna Wanka
Federal Minister of Education and Research, Germany

Induction of a New Member to the Honorary Senate of the Foundation Lindau Nobel Laureate Meetings
Hansjörg Wyss
Chairman, Wyss Foundation, Switzerland

Launch of the Science TV Channel 'ARD-alpha'

The IGNORANCE Study
Hans Rosling
Karolinska Institutet, Sweden

Access: all participants

16.30

Break

17.00
Concert
City Theatre

Reception & Concert
Ensemble of the Vienna Philharmonic Orchestra
Reception upon invitation of the Austrian Federal Ministry of Science, Research and Economy
Access: Laureates, young scientists, guests

19.00
Dinner
Various Locations

Dinner
Please see your personal agenda for details.

Partner Event

07.00 Science Breakfast, Forum am See

Women in Science: Fixing the Leaking Pipeline

upon invitation of Australia

Elizabeth H. Blackburn
Department of Biochemistry and Biophysics, University of California

Suzanne Cory
Immediate Past President, Australian Academy of Science

Emma L. Johnston
School of Biological, Earth and Environmental Sciences & Evolution and Ecology Research Centre, UNSW Australia
Director, Sydney Harbour Research Program, Sydney Institute of Marine Science

Brian P. Schmidt
The Research School of Astronomy and Astrophysics, The Australian National University

Moderator: Adam Spencer
Ambassador for Mathematics and Science, The University of Sydney

Access: with online pre-registration only

09.00 Plenary Lecture, Inselhalle

Randy W. Schekman
Genes and Proteins that Control Secretion and Autophagy

09.30 Plenary Lecture, Inselhalle

Arieh Warshel
Multiscale Simulations of the Functions of Biological Molecules

10.00 Plenary Lecture, Inselhalle

Jules A. Hoffmann
Innate Immunity: From Flies to Humans

10.30 Plenary Lecture, Inselhalle

Bruce A. Beutler
Deciphering Immunity by Making it Fail

11.00

Coffee Break
upon invitation of Australia

11.30 Plenary Lecture, Inselhalle

Barry J. Marshall
Man versus Helicobacter

12.00 Plenary Lecture, Inselhalle

J. Michael Bishop
Forging a Genetic Paradigm for Cancer

12.30 Plenary Lecture, Inselhalle

Martin J. Evans
Inheritance from Teratocarcinomas

13.00 Plenary Lecture, Inselhalle

Elizabeth H. Blackburn
Adventures at the Ends of Chromosomes

13.30 Catering Tent

Lunch Break
upon invitation of Australia

Access: young scientists only

15.30 Discussion, Hotel Bay. Hof

Bruce A. Beutler
Discussion with young scientists

15.30 Discussion, Evang. Hospital

J. Michael Bishop
Discussion with young scientists

15.30 Discussion, Landratsamt

Elizabeth H. Blackburn
Discussion with young scientists

15.30 Discussion, Altes Rathaus

Martin J. Evans
Discussion with young scientists

15.30 Discussion, Hotel Bay. Hof

Jules A. Hoffmann
Discussion with young scientists

15.30 Discussion, Forum am See

Barry J. Marshall
Discussion with young scientists

15.30 Discussion, Altes Rathaus

Arieh Warshel
Discussion with young scientists

17.00

Break

17.30
Lecture & Disc.
City Theatre

Brian P. Schmidt
Cosmology: An Example of the Process of Discovery

17.30
Master Class
Altes Rathaus

Master Class with Aaron Ciechanover
Biology in the Service of Medicine
Young scientists (tbd)
Access: with online pre-registration only

17.30
Master Class
Altes Rathaus

Master Class with Rolf M. Zinkernagel
Pandemic Threats
Young scientists (tbd)
Access: with online pre-registration only

19.00

Break

HAVING A BRILLIANT THOUGHT?

Share it with us at
twitter.com (#lnlm14)

19.30
Social Function
Inselhalle

International Get-Together
upon invitation of Australia

Welcome

Countess Bettina Bernadotte
President of the Council

Welcome Address

The Hon Andrew Robb AO MP
Australian Minister for Trade and Investment

Cultural Performance

Genevieve Lacey
Recorder Virtuoso

Marshall McGuire
Harpist

Diving into Research

Emma L. Johnston
School of Biological, Earth and Environmental Sciences & Evolution and Ecology Research Centre, UNSW Australia
Director, Sydney Harbour Research Program, Sydney Institute of Marine Science

Master of Ceremonies

Adam Spencer
Ambassador for Mathematics and Science, The University of Sydney

Dinner

Dance

Access: all participants

Partner Event

07.00 Science Breakfast, Forum am See

Science in Clinical Medicine

upon invitation of Else Kröner-Fresenius-Stiftung

J. Michael Bishop
Director, The G.W. Hooper Research Foundation, University of California

Stephan Halle
Institute of Immunology, Hannover Medical School

Christoph Klein
Chair, Department of Pediatrics, Dr. von Hauner Children's Hospital, Ludwig Maximilians University Munich

Moderator: Susanne Schultz-Hector
Member of the Board, Else Kröner-Fresenius-Stiftung

Access: with online pre-registration only

09.00 Plenary Lecture, Inselhalle

Françoise Barré-Sinoussi
On the Road Towards an HIV Cure

9.30 Plenary Lecture, Inselhalle

Rolf M. Zinkernagel
Why do we not have a Vaccine Against HIV or Tubercolosis?

10.00 Plenary Lecture, Inselhalle

Harald zur Hausen
Infections Linked to Human Cancers: Mechanisms and Synergisms

10.30 Plenary Lecture, Inselhalle

Ada E. Yonath
Towards Control of Species-Specific Antibiotics Resistance

11.00

Coffee Break

11.30 Plenary Lecture, Inselhalle

Thomas A. Steitz
From the Structure of the Ribosome to the Design of New Antibiotics

12.00 Plenary Lecture, Inselhalle

Brian K. Kobilka
G Protein-Coupled Receptors: Challenges for Drug Discovery

12.30 Plenary Lecture, Inselhalle

Aaron Ciechanover
The Revolution of Personalized Medicine: Are we going to Cure all Diseases and at What Price?

13.00 Plenary Lecture, Inselhalle

Steven Chu
You can see a lot by observing: Optical Microscopy 2.0

13.30 Catering Tent

Lunch Break

Access: for young scientists only

15.30 Lecture & Disc., Altes Rathaus

Edmond H. Fischer
Cell Signaling by Protein Phosphorylation

15.30 Lecture & Disc., Landratsamt

Walter Kohn
Macular Distortation - Diagnosis and Correction

15.30 Lecture & Disc., Altes Rathaus

Torsten N. Wiesel
A Homage to David Hubel: Early days in our Studies of the Visual Cortex

15.30 Discussion, Inselhalle

Françoise Barré-Sinoussi
Discussion with young scientists

15.30 Discussion, City Theatre

Steven Chu
Discussion with young scientists

15.30 Discussion, Evang. Hospital

Aaron Ciechanover
Discussion with young scientists

15.30 Discussion, Hotel Bay. Hof

Brian K. Kobilka
Discussion with young scientists

15.30 Discussion, Hotel Bay. Hof

Thomas A. Steitz
Discussion with young scientists

15.30 Discussion, Forum am See

Ada E. Yonath
Discussion with young scientists

TUESDAY, 1 JULY

15.30
Discussion
Altes Rathaus

Rolf M. Zinkernagel
Discussion with young scientists

15.30
Discussion
Inselhalle

Harald zur Hausen
Discussion with young scientists

17.00

Break

17.30
Master Class
Altes Rathaus

Master Class with Jean-Marie Lehn
Approaches to Molecular Drug Discovery
Young scientists (tbd)
Access: with online pre-registration only

Partner Event
17.30
Presentation
Inselhalle

Excellence in Research – Europe's Ticket to Our Future
The European Commission presents research career opportunities in the "Excellence" pillar of Horizon 2020; the largest international research programme; and the EURAXESS-Scientists in Motion services platform for scientists globally. The presentation will also cover the relevant activities of the ERC and the FET Open initiatives.
Moderator: Mike W. Rogers
Research careers, Marie Skłodowska-Curie Actions
DG Education & Culture, European Commission
Access: all participants

19.00

Break

19.30
Social Function
Various Locations

Academic Dinners
upon invitation of the Academic Partners
Access: by invitation only

19.30
Social Function
Toskanapark

Grill & Chill: Connecting Cultures
upon invitation of the Council & Foundation
Access: by invitation only

WEDNESDAY, 2 JULY

Partner Event
07.00
Science Breakfast
Forum am See

Addressing the Challenges of Ageing Research through Cross-Disciplinary Collaboration
upon invitation of Mars, Incorporated
Elizabeth H. Blackburn
Department of Biochemistry and Biophysics, University of California, San Francisco
Hagen Schroeter
Director, Fundamental Health and Nutrition Research, Mars, Incorporated
Adjunct Research Professor, Nutrition Dept., University of California, Davis
Young scientist (tbd)
Moderator: Adam Smith
Chief Scientific Officer, Nobel Media AB
Access: with online pre-registration only

Partner Event
07.00
Science Breakfast
Hotel Bay. Hof

Scientific Leadership in the 21st Century: Running Productive Labs, Leading Great People, Leading Self
upon invitation of McKinsey & Company, Inc.
Steven Chu
Physics Department, Stanford University
Frank Mattern
Director, McKinsey & Company, Inc.
Young scientist (tbd)
Moderator: Matthias Evers
Principal, McKinsey & Company, Inc.
Access: with online pre-registration only

09.00
Plenary Lecture
Inselhalle

Hamilton O. Smith
Synthetic Biology for Genetic Engineering in the 21st Century

9.30
Plenary Lecture
Inselhalle

Richard J. Roberts
Bacterial Methylomes

10.00
Plenary Lecture
Inselhalle

Peter Agre
Aquaporin Water Channels - from Atomic Structure to Malaria

10.30
Plenary Lecture
Inselhalle

Kurt Wüthrich
A Personal View of the History of Nuclear Magnetic Resonance in Biology and Medicine

11.00

Coffee Break

11.30
Plenary Lecture
Inselhalle

Roger Y. Tsien
Molecules Against Cancer or for Long-Term Memory Storage

12.00
Plenary Lecture
Inselhalle

Jean-Marie Lehn
Perspectives in Chemistry - Towards Adaptive Chemistry

12.30
Plenary Lecture
Inselhalle

Erwin Neher
Short-Term Synaptic Plasticity

13.00
Plenary Lecture
Inselhalle

Bert Sakmann
Cortical Circuit and Decision Making

13.30
Catering Tent

Lunch Break
Access: for young scientists only

15.30
Panel Discussion
Inselhalle

Panel Discussion: Large Data and Hypothesis-Driven Science in the Era of Post-Genomic Biology

Bruce A. Beutler
Center for the Genetics of Host Defense,
UT Southwestern Medical Center at Dallas

J. Michael Bishop
The G.W. Hooper Research Foundation, University of California

Jules A. Hoffmann
Molecular and Cellular Biology Institute, Université de Strasbourg

Brian P. Schmidt
The Research School of Astronomy and Astrophysics,
The Australian National University

Moderator: Stefan H.E. Kaufmann
Director, Max Planck Institute for Infection Biology

17.00

Break

17.30
Discussion
Inselhalle

Peter Agre
Discussion with young scientists

17.30
Discussion
Altes Rathaus

Jean-Marie Lehn
Discussion with young scientists

17.30
Discussion
Hotel Bay. Hof

Erwin Neher
Discussion with young scientists

17.30
Discussion
Landratsamt

Richard J. Roberts
Discussion with young scientists

17.30
Discussion
Hotel Bay. Hof

Bert Sakmann
Discussion with young scientists

17.30
Discussion
Evang. Hospital

Hamilton O. Smith
Discussion with young scientists

17.30
Discussion
Forum am See

Roger Y. Tsien
Discussion with young scientists

17.30
Discussion
Altes Rathaus

Kurt Wüthrich
Discussion with young scientists

19.00

Break

Partner Event
19.30
Presentation
Inselhalle

Excellent Young Scientists Aiming to Change the World: The Global Young Academy

Moderators:

Heidi Wedel
Global Young Academy Berlin, Managing Director

Marc Creus
Global Young Academy member
Group Leader at the Laboratory of Molecular Evolution at the Department of Chemistry, University of Basel

Access: all participants

20.00
Catering Tent

Dinner
Access: young scientists only

WANT TO DISCUSS SCIENCE?

Visit the meeting blog at
blog.lindau-nobel.org

Partner Event
07.00
Science Breakfast
Forum am See

Predicting Phenotypes from Genotypes — a Brave New World?
upon invitation of the Austrian Federal Ministry of Science, Research and Economy

Katarzyna Niespodziana
Medical University of Vienna

Oliver Smithies
Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill

Moderator: Magnus Nordborg
Gregor Mendel Institute, Vienna

Access: with online pre-registration only

Partner Event
07.00
Science Breakfast
Hotel Bay. Hof

From Cancer Research to Personalized Medicine
upon invitation of German Cancer Research Center, DKFZ

Christiane Opitz
Head Junior Research Group Brain Cancer Metabolism, German Cancer Research Center

Stephan Pfister
Head Division of Pediatric Oncology, German Cancer Research Center

Otmar D. Wiestler
CEO and Scientific Director, German Cancer Research Center

Moderator: Stefanie Seltmann
Head Press and Public Relations, German Cancer Research Center

Access: with online pre-registration only

09.00
Plenary Lecture
Inselhalle

Hartmut Michel
Membrane Proteins: Importance, Functions, Mechanisms

09.30
Plenary Lecture
Inselhalle

Johann Deisenhofer
Structural Studies on Cholesterol Transport

10.00
Plenary Lecture
Inselhalle

Robert Huber
Structural Biology and Its Translation Into Practice and Business: My Experience

10.30
Plenary Lecture
Inselhalle

Ferid Murad
Discovery of Nitric Oxide and Cyclic GMP in Cell Signaling and Their Role in Drug Development

11.00

Coffee Break

11.30
Plenary Lecture
Inselhalle

Werner Arber
Biological Evolution in the Context of Cosmic Evolution and of Cultural Evolution

12.00
Plenary Lecture
Inselhalle

Martin Chalfie
Tickling Worms: Surprises from Basic Research

12.30
Plenary Lecture
Inselhalle

John E. Walker
Generating the Fuel of Life

13.00
Plenary Lecture
Inselhalle

Oliver Smithies
Where do Ideas come from?

13.30
Catering Tent

Lunch Break
Access: for young scientists only

15.30
Panel Discussion
City Theatre

Panel Discussion: Academia and Industry – Exploring the Collaborative Landscapes of the Future

Bruce A. Beutler
Center for the Genetics of Host Defense,
UT Southwestern Medical Center at Dallas

Michel Goldman
Executive Director of the Innovative Medicines Initiative

Peter C. Gøtzsche
Director of the Nordic Cochrane Center

Renata Mota Gomes
University of Oxford, Cardiovascular Regeneration & Vascular Disease

Stan Wang
University of Cambridge, Department of Surgery & Gurdon Institute

Moderator: Adam Smith
Chief Scientific Officer, Nobel Media AB

17.00

Break

17.30
Discussion
Hotel Bayerischer Hof

Werner Arber
Discussion with young scientists

17.30
Discussion
Hotel Bayerischer Hof

Martin Chalfie
Discussion with young scientists

17.30
Discussion
Altes Rathaus

Johann Deisenhofer
Discussion with young scientists

17.30
Discussion
Altes Rathaus

Robert Huber
Discussion with young scientists

17.30
Discussion
Altes Rathaus

Hartmut Michel
Discussion with young scientists

17.30
Discussion
Landratsamt

Ferid Murad
Discussion with young scientists

17.30
Discussion
Forum am See

Oliver Smithies
Discussion with young scientists

17.30
Discussion
Evang. Hospital

John E. Walker
Discussion with young scientists

19.00

Break

19.30
Social Function
Inselhalle

Bavarian Evening
upon invitation of the Elite Network of Bavaria
and the Free State of Bavaria

Words of Welcome
Ludwig Spaenle
Bavarian State Minister of Education, Science and the Arts

Bavaria - Land of Science and Research
Bert Sakmann
Max Planck Institute of Neurobiology

Current Research Projects in the Elite Network of Bavaria
Katarzyna Bieńkowska, Henning Hintzsche

Presentation of the Elite Network Design Award
Michael Wolf

Bavarian Music & Folk Dance

Bavarian Buffet Dinner

Access: all participants

07.15
MS Sonnenkönigin

Baden-Württemberg Boat Trip to Mainau Island
upon invitation of the State of Baden-Württemberg
Access: Laureates, young scientists, guests;
access for Media by invitation only

07.15
Lindau Harbour

Check in (Lindau)

07.45
Lindau Harbour

Departure (Lindau)

08.00
Bad Schachen

Arrival (Hotel Bad Schachen)

08.15
Bad Schachen

Departure (Hotel Bad Schachen)

Welcome
Klaus-Peter Murawski
State Secretary and Head of the State Chancellery Ministry of State
Baden-Württemberg

10.20
Mainau Island

Arrival (Mainau Island)

11.00
Closing Session
Mainau Island
Castle Meadow

Panel Discussion: Science for the Benefit of Mankind

Françoise Barré-Sinoussi
Département de Virologie, Institut Pasteur, France

Ghada Bassioni
Associate Professor and Head of the Chemistry Department,
Ain Shams University, Cairo, Egypt
Lindau 2012 Alumna

Charles Mgone
Executive Director, European and Developing Countries Clinical Trials Partnership (EDCTP)

Brian P. Schmidt
The Research School of Astronomy and Astrophysics,
The Australian National University

Georg Schütte
State Secretary, German Federal Ministry of Education and Research

Moderator: Geoffrey Carr
Science Editor, The Economist

Access: all participants

13.00
Lunch Break
Mainau Island

Lunch Break
upon invitation of the State of Baden-Württemberg

15.30
Castle Courtyard

Conclusion & Farewell

Countess Bettina Bernadotte
President of the Council

16.30
Mainau Harbour

Departure (Mainau Island)
Baden-Württemberg Boat Trip to Lindau
upon invitation of the State of Baden-Württemberg

Access: Laureates, young scientists, guests;
access for Media by invitation only

18.30
Bad Schachen

Arrival (Hotel Bad Schachen)

18.45
Lindau Harbour

Arrival (Lindau)

FRIDAY, 4 JULY

Note:

For all participants departing on Friday and not returning to their hotel: No travel luggage may be taken on the boat. Two luggage buses will be available; please place your luggage accordingly.

Bus 1: to "Mainau Island": for those not returning to Lindau. Pick-up at main entrance on Mainau Island.

Bus 2: to "Lindau": for those leaving directly after their return to Lindau. Pick-up at Lindau harbour.

Certificates of Attendance will be available on the boat.

MISSED SOMETHING?

Watch it online at
mediatheque.lindau-nobel.org

LECTURE ABSTRACTS *(in alphabetical order by last name)*

Peter Agre

Aquaporin Water Channels - from Atomic Structure to Malaria

Session: Wednesday, 2 July 2014, 10.00 hrs

Aquaporin (AQP) water channel proteins enable high water permeability in certain biological membranes. Discovered in human red cells but expressed in multiple tissues, AQP1 has been thoroughly characterized and its atomic structure is known. Expression patterns of the 13 known human homologs predict phenotype. Individuals lacking Colton blood group antigens have mutations in AQP1. In people with no AQP1, lack of water causes defective urine concentration and reduced fluid exchange between capillary and interstitium in lung. Mutations in AQP0, expressed in lens fiber cells, result in familial cataracts. Mutations in AQP2, expressed in renal collecting duct principal cells, result in severe nephrogenic diabetes insipidus. AQP2 underexpression is found in disorders with reduced urinary concentration, AQP2 overexpression in those with fluid retention.

Mistargeting of AQP5, normally expressed in the apical membranes of salivary and lacrimal gland acini, can occur in Sjogren's syndrome. Aquaporins also are implicated in brain edema and muscular dystrophy (AQP4), anhidrosis (AQP5), renal tubular acidosis (AQP6), conversion of glycerol to glucose during starvation (AQP7 and AQP9) and cystic fibrosis (several aquaporins). Aquaporins provide rootlet water uptake and turgor in plants. Recent work has delineated roles for aquaporins in parasitic diseases including malaria.

Werner Arber

Biological Evolution in the Context of Cosmic Evolution and of Cultural Evolution

Session: Thursday, 3 July 2014, 11.30 hrs

After reconsidering the very long time periods in cosmic evolution, we will focus our attention to the evolutionary development of living organisms on our planet Earth. The genetic variants (mutations), which are occasionally produced, are alterations in the linear sequences of nucleotides of double-

stranded DNA molecules and they drive biological evolution. In the past 70 years, scientific investigations have revealed that a remarkable number of specific molecular mechanisms of genetic variation contribute to evolutionary progress. We can classify these mechanisms into three natural strategies of genetic variation according to specific qualities of their contributions to biological evolution: local DNA sequence changes, intragenomic rearrangements of DNA segments, and the acquisition of a segment of foreign DNA by horizontal gene transfer. Products of so-called evolution genes are thereby involved in cooperation with a number of non-genetic elements. We can conclude that "natural reality" actively takes care of biological evolution. This includes both, the largely contingent production of genetic variants and a drastic limitation of the rates of genetic variation. On the basis of available scientific knowledge we will discuss world view-related aspects and concerns on the long-term sustainability of evolutionary developments on our planet Earth in the context of the cultural evolution of humankind. In conclusion, we recommend respecting the scientifically identified laws of nature for any intended cultural application of scientific knowledge to the benefit of humankind and its environment.

Françoise Barré-Sinoussi

On the Road Towards an HIV Cure

Session: Tuesday, 1 July 2014, 09.00 hrs

Since the first cases of AIDS in 1981 and the identification of its etiological agent in 1983, much progress has been made in both the development of tools to prevent and treat HIV infection and the access to these tools. In particular, the wide array of antiretroviral treatments that now exists has considerably transformed the face of the infection from a lethal disease to a chronic condition. Today, thanks to unprecedented international efforts, the more than 10s of millions of people living with HIV have access to these life-saving treatments in resource-limited countries.

However, the sustainability of these life-long therapies is a real challenge both for the patients who have to meticulously take them each day and for the global economy considering their cost. Indeed, these antiretroviral treat-

ments are not curative as HIV latently persists in reservoir cells and in many compartments of the host.

Novel therapeutic strategies that would cure HIV infection or at least induce a sustainable remission in patients without the need to further take medication are thus an absolute necessity. The increased knowledge of HIV reservoirs and of the mechanisms of persistence as well as reports of proof of concept studies, have generated great optimism in the scientific community, which now believe that sustainable remission of HIV infection is an achievable goal.

In 2010, the International AIDS Society launched the "Towards an HIV Cure" initiative with the aim to mobilize the scientific community and accelerate research on this topic, which has since then become a priority in the HIV science agenda.

Recommended Readings:

1. *Towards an HIV cure: a global scientific strategy.*
   International AIDS Society Scientific Working Group on HIV Cure, Deeks SG, Autran B, Berkhout B, Benkirane M, Cairns S, Chomont N, Chun TW, Churchill M, Di Mascio M, Katlama C, Lafeuillade A, Landay A, Lederman M, Lewin SR, Maldarelli F, Margolis D, Markowitz M, Martinez-Picado J, Mullins JI, Mellors J, Moreno S, O'Doherty U, Palmer S, Penicaud MC, Peterlin M, Poli G, Routy JP, Rouzioux C, Silvestri G, Stevenson M, Telenti A, Van Lint C, Verdin E, Woolfrey A, Zaia J, Barré-Sinoussi F.
   Given the limitations of antiretroviral therapy and recent advances in our understanding of HIV persistence during effective treatment, there is a growing recognition that a cure for HIV infection is both needed and feasible. The International AIDS Society convened a group of international experts to develop a scientific strategy for research towards an HIV cure. Several priorities for basic, translational and clinical research were identified. This opinion article summarizes the recommendations of the group to funding agencies and to the international community.
   Nat Rev Immunol. 2012 Jul 20;12(8):607-14.

2. *HIV cure research: Advances and prospects.*
   Passaes CP, Sáez-Cirión A.
   Thirty years after the identification of HIV, a cure for HIV infection is still to be achieved. Advances of combined antiretroviral therapy (cART) in recent years have transformed HIV infection into a chronic disease in patients on cART. However, in spite of this favorable outcome, cART is not curative and patients are at risk of developing non-AIDS malignancies. Moreover, universal access to cART is still restricted by financial obstacles. This review discusses the most recent strategies that have been developed in the search for an HIV cure and to improve life quality of people living with HIV.
   Virology. 2014 Apr; 454-455C:340-352.

Bruce A. Beutler

Deciphering Immunity by Making it Fail

Session: Monday, 30 June 2014, 10.30 hrs

Infectious microbes collectively represent the strongest selective pressure operating on our species, and over hundreds of millions of years, drove the evolution of the sophisticated immune system we have today. While the general outlines of immune sensing, signaling, and effector function have been learned, we are far from achieving a comprehensive mechanistic understanding of immunity. We have limited ability to predict who will respond to a vaccine, for example, or who will develop autoimmunity. The total number of genes important for immunity and their identity remains unknown. Among those genes that are known, only rather sketchy inferences about function may be drawn in most instances. The initial goal of cataloguing all genes needed for robust immune function has advanced recently, as new technologies permit almost instantaneous identification of mutations that cause phenotype. It has thus become possible to randomly alter the genome of mice using a point mutagen, breed them to bring mutations to homozygosity, and screen them to identify impairment of immune function. As soon as data on function are developed, it is usually possible to declare the cause of any observed phenovariance. At present, it is possible to survey the effects of approximately 50,000 mutations that affect coding sense each year. Mutations affecting the antibody response, innate immune responses, and maintenance of immunological homeostasis are detected regularly, and many are "new," affecting genes not previously known to participate in the immune response.

J. Michael Bishop

Forging a Genetic Paradigm for Cancer

Session: Monday, 30 June 2014, 12.00 hrs

It is now axiomatic that, no matter what its causes, cancer ultimately arises from the malfunction of genes. A number of clues prefigured this paradigm: the persistence of the malignant phenotype through countless cell divisions; the mutagenicity of various agents that can cause cancer; the presence of chromosomal abnormalities in cancer cells; the occasional instances in which cancer presents as a familial disease; and the predisposition to cancer that accompanies heritable deficiencies in DNA repair. In concert, these findings pointed to an altered genome as the underpinning of cancer. It was the study of RNA tumor viruses, however, that first fingered potentially tumorigenic culprits among the genes of normal cells: "proto-oncogenes" that can be converted to "oncogenes" by genetically dominant gain of function. A variety of genetic anomalies inflict gain of function on proto-oncogenes in human cancer, and there is persuasive evidence that these anomalies contribute to tumorigenesis. Meanwhile, hints emerged that cancer cells might also suffer from recessive deficiencies that contribute to the neoplastic phenotype. The first tangible sighting of such a deficiency came from the discovery of a focal chromosomal deletion that creates a hereditary predisposition to childhood retinoblastoma. Exploration of this deletion uncovered the first of many "tumor suppressor genes," homozygous deficiencies of which contribute to tumorigenesis. Combinations of wayward proto-oncogenes and defective tumor suppressor genes are present in most, if not all human cancers, having accrued in a stepwise fashion to drive the clonal development and diversification that lead to malignancy – a maladaptive form of Darwinian evolution in miniature. The growing power of genomic science promises to bring us a comprehensive inventory of the genetic maladies in human cancer and the particular tumors in which each of the various maladies may be culpable. The resulting genetic fingerprints should strengthen our approach to virtually every aspect of cancer, including predisposition, cause, pathogenesis, detection, taxonomy, therapy, prognosis and prevention. The forging of the genetic paradigm for cancer provides a powerful example of the unexpected ways in which science can unveil the secrets of nature to the benefit of human health and welfare.

Recommended Readings:

Bishop, J. M. Cancer: The Rise of the Genetic Paradigm. Genes and Development 9:1309-15 (1995)

Strattan, M.R. Exploring the Genomes of Cancer Cells: Progress and Promise. Science 331: 1553-8 (2011)

Elizabeth H. Blackburn

Adventures at the Ends of Chromosomes

Session: Monday, 30 June 2014, 13.00 hrs

What keeps chromosome ends from eroding away and degrading as we age? Telomeres, the protective tips that 'cap' and stabilize the ends of chromosomes are important for this. In mammals, each telomere consist of several kilobases of TTAGGG-sequence DNA repeats, bound by proteins ("shelterins") that make a sheath protecting the telomeric DNA. The integrity of telomeres plays essential roles in human health.

We discovered a special evolutionarily conserved enzyme in cells, telomerase, that adds telomeric DNA to telomeres, replenishing them to counteract the progressive shortening that otherwise often occurs. Telomerase is critical for long-term eukaryotic cell genomic stability, yet curiously, in humans telomere maintenance seems to be limiting throughout our lifespan, and the loss of telomeric protective function plays roles in disease processes.

Telomere shortening in normal cells in humans has been associated with aging-associated diseases – including pulmonary fibrosis, cardiovascular disease, some cancers, diabetes, immune dysfunction and pro-inflammatory states – and higher risks of mortality 1. Telomere shortening potentially plays causal roles in at least some of these disease processes: individuals born with a mutation causing them to have insufficient telomerase enzyme or telomere-maintenance proteins have shorter-than-normal telomeres and suffer premature aging syndromes, including increased incidences of cancers.

Our collaborative studies have shown that telomere maintenance is affected by various events and conditions of life 2. Accelerated telomere shortening in humans is related to – or perhaps caused by – factors including chronic psychological stress, traumatic and chronic stressful life events, some of which in turn are associated with higher risks of aging-related diseases. Physical activity appears to alleviate the impact of stress on leukocyte telomere shortening. Thus, intervention studies are underway to identify how much some of the malign influences on telomere maintenance may be counteracted by preventive actions.

Reading:

1. *Blackburn E. Telomeres and Tetrahymena: an interview with Elizabeth Blackburn. Dis Model Mech. 2009 Nov-Dec;2(11-12):534-7. doi: 10.1242/dmm.003418. Epub 2009 Oct 19. No abstract available. PMID: 19841239*

2. *Blackburn EH, Epel ES. Telomeres and adversity: Too toxic to ignore. Nature. 2012 Oct 11;490(7419):169-71. doi: 10.1038/490169a. No abstract available. PMID: 23060172*

Martin Chalfie

Tickling Worms: Surprises from Basic Research

Session: Thursday, 3 July 2014, 12.00 hrs

Research, at least my research, has never been linear. I have found that my lab and I often double back on problems after years of inactivity or go off in entirely new directions as dictated by the work and people's interests. This lack of direction results, at least in part, from the fact that I am a geneticist and mutants have an annoying, yet wonderful, habit of leading one into new areas of study. I will describe how a simple assay to look for mutants in the nematode Caenorhabditis elegans that are insensitive to touch (stroking animals with an eyebrow hair glued to a toothpick) led me and my lab to investigate problems in cell determination, cell differentiation, mechanosensory transduction and modulation, and neural circuitry and the integration of sensory signals. Along the way, these studies resulted in the introduction of green fluorescent protein (GFP) as a biological marker, several other methods, and maybe even some insights into a few human diseases. Although we actually have answered some of the questions we

set out to study, the excursions far from what I thought I was studying have often been the most exciting.

Steven Chu

You can see a lot by observing: Optical Microscopy 2.0

Session: Tuesday, 1 July 2014, 13.00 hrs

Biological research and medicine were transformed by the invention and improvement of the optical microscope. Since the early 1990s, there has been another revolution in optical imaging, and manipulation of individual biological molecules and bio-molecular systems have been demonstrated and applied to a wide variety of systems. Most recently, innovations in "super-resolution" optical imaging, such as STORM and PALM have been used to construct biological images with ~ 10 nm resolution. With bright optical probes and corrections to the slight differences in sensitivity to the CCD or CMOS camera, < 1 nm resolution is possible in biological samples in water. Recent applications of super-resolution imaging to cancer signaling, and bio-films will be discussed.

Finally, the development of sub-wavelength micro-spectroscopy in the fingerprint region of the infrared spectra (wavelength = 4 – 12 μm) to observe changes in biological states with 20 nm spatial resolution will be outlined.

Aaron Ciechanover

The Revolution of Personalized Medicine:
Are we going to Cure all Diseases and at What Price?

Session: Tuesday, 1 July 2014, 12.30 hrs

Many important drugs such as penicillin, aspirin, or digitalis, were discovered by serendipity - some by curious scientists who accidentally noted a "strange" phenomenon, and some by isolation of active ingredients form plants known for centuries to have a specific therapeutic effect. Other major drugs like the cholesterol reducing statins were discovered using more advanced technologies, such as targeted screening of large chemical libraries. In all these cases, the mechanisms of action of the drug were largely

unknown at the time of their discovery, and were unraveled only later. With the realization that patients with apparently similar diseases at diagnosis – breast or prostate cancer, for example - respond differently to similar treatments, and that clinical behavior of the disease is different in different patients, we have begun to understand that the mechanistic/molecular basis of what we thought is the same disease entity, is different. Thus, breast cancer or prostate cancers appear to be sub-divided into smaller distinct classes according to their molecular characteristics. As a result, we are exiting the era where our approach to treatment of these and many other diseases is "one size fits all", and entering a new era of "personalized medicine" where we tailor treatment according to a patient's molecular/mutational profile. Here, unlike the previous era, an understanding of the mechanisms will drive the development of new drugs. This era will be characterized initially by the development of technologies where sequencing and data processing of individual genomes will be fast (few hours) and cheap (<US$ 1,000), by identification and characterization of new disease-specific molecular markers and drug targets, and by design of novel, mechanism-based drugs to modulate the activities of these targets. It will require a change in our approach to scientific research and development and to education, where interdisciplinarity will dominate and replace in many ways, traditional discipline-oriented approaches. Entry into this era will be also accompanied by complex bioethical problems, where detailed genetic information of large populations in developed countries will be available, and protection of privacy will become an important issue for health authorities.

Johann Deisenhofer

Structural Studies on Cholesterol Transport

Session: Thursday, 3 July 2014, 09.30 hrs

Cholesterol has two essential functions in our bodies: It is an important component of cell membranes and it serves as the starting material for the synthesis of bile acids, steroid hormones, and other compounds. The human body obtains necessary cholesterol by intracellular synthesis and by dietary uptake. Cholesterol is packaged in the liver and transported in the bloodstream primarily in the form of low density lipoprotein (LDL), a complex of phospholipids, cholesterol, cholesteryl esters, and apolipoprotein B.

The LDL receptor, a membrane anchored protein of 839 amino acids, mediates the uptake of LDL into the cellular interior. This receptor binds LDL at neutral pH with high affinity, and releases it when the pH drops below ~6, as happens in endosomes during endocytosis. A crystallographic study of the extracellular portion of the receptor (amino acids 1-699) in its low-pH form shows the protein in a conformation that disables binding of LDL.

The protein PCSK9 (Proprotein Convertase Subtilisin Kexin 9), discovered in 2003, lowers the efficiency of the LDL uptake system by accelerating the degradation of LDL receptors. PCSK9 has therefore become a target for newly developed drugs that can disrupt its interaction with the receptor and thus complement the statins in lowering the blood LDL level.

In my talk I will describe structures of LDL and the LDL receptor, as well as details of the interaction between PCSK9 and the LDL receptor.

Martin J. Evans

Inheritance from Teratocarcinomas

Session: Monday, 30 June 2014, 12.30 hrs

The techniques and concepts that have resulted in the identification and isolation of embryonic stem cells have come from studies with mouse teratocarcinomas. Embryonic stem cells isolated from normal mouse embryos may be grown in tissue culture and new genetic modifications introduced into them. They may then be used to form chimeric mice, which are able to transmit the new mutations in their germ line. This has resulted in fully experimental mammalian genetics.

In addition to this genetic inheritance we might also consider the huge impacts of these ideas. Developmental cell biology now informs us about the plasticity as well as stability of the differentiated state, and stem cell biology is becoming a powerful new paradigm for clinical advances. The future of stem cell therapies will be discussed.

Edmond H. Fischer

Cell Signaling by Protein Phosphorylation

Session: Tuesday, 1 July 2014, 15.30 hrs

Signal transduction by protein phosphorylation represents one of the most prevalent mechanisms by which eukaryotic cellular events are regulated. It is involved in the control of many physiological processes and pathological conditions including bacterial and viral diseases. Emphasis will be placed on cellular regulation by tyrosine phosphorylation implicated in cell growth, differentiation and transformation, bringing into play a diversity of tyrosine kinases of viral or cellular origin or linked to growth factor receptors. These receptors transduce their signal by recruiting adaptor proteins interacting with one another through binding modules (SH2, SH3, WW, PH, PDZ, etc.) thereby initiating a diversity of signaling cascades. Examples decribing how a few of these are utilized will be presented. Regulation of signal transduction also involves protein tyrosine phosphatases (PTPs), an expanding family of transmembrane and intracellular enzymes that catalyze the reverse reaction. Most PTP receptor forms have the structural characteristics of cell adhesion molecules which suggests that they must be involved in – or be regulated by – cell-cell or cell-matrix interaction. Their involvement in oncogenesis will be presented. In contrast to the old view when metabolic pathways were represented by simple linear arrays of enzymes working successively on one another, we know today that cell signaling brings into play entire networks of enzymes, receptors and channels, a plethora of sub-cellular elements plus environmental factors such as the scaffolding proteins, chaperones, targeting subunits etc., all interacting and communicating with one another. We must comprehend the cross-talk that takes place among all these elements if we really want to understand how the cell functions. Only then will we be able to embark on a rational approach to therapeutics.

Jules A. Hoffmann

Innate Immunity: From Flies to Humans

Session: Monday, 30 June 2014, 10.00 hrs

Flies challenged with bacteria or fungi rapidly transcribe a battery of genes encoding potent antimicrobial peptides which oppose the invading microorganisms. Genetic analysis has identified two signaling cascades which control their expression: (1) the Toll pathway, activated in response to fungi and Gram-positive bacteria, has significant similarities with the Toll-like receptor (TLR) pathway in mammals, and (2) the Drosophila immune deficiency (IMD) pathway controls infection by Gram-negative bacteria, and exhibits stringent similarities with the mammalian TNF-Receptor pathway. The roles of innate immunity in both phyla will be discussed, as well as the origin of this first-line defense, which is now understood to have originated with the first multicellular organisms.

Robert Huber

Structural Biology and Its Translation into Practice and Business: My Experience

Session: Thursday, 3 July 2014, 10.00 hrs

As a student in the early 1960s, I had the privilege to attend winter seminars organized by my mentor, W. Hoppe, and by M. Perutz, which took place in a small guesthouse in the Bavarian-Austrian Alps. The entire community of a handful of protein crystallographers assembled in a room which served as living and dining room and as auditorium for the lectures. Today structural biologists organize large congresses with thousands of attendants and there exist many hundreds of laboratories specialized in this field. It appears to dominate biology and biochemistry very visibly if we count covers in scientific journals displaying macromolecular structures.

Structural biology was successful, because it was recognized that understanding biological phenomena at the molecular and atomic level requires that we see these molecules. Structural biology revealed the structure of genes and their basic mechanism of regulation, the mechanism of enzymes' function, the structural basis of immune diversity, the mechanisms of energy production in cells by photosynthesis and its conversion into energy-rich chemical compounds and organic material, the mechanism that makes muscle work, the architecture of viruses and multi-enzyme complexes, and

many more.

New methods had a profound impact on the development of structural biology. Methods seemed to become available in cadence with the growing complexity of the problems and newly discovered methods brought biological problems within reach for researchers, a co-evolutionary process of the development of methods and answerable problems.

An important additional incentive for structural biology came from its potential application for drug design and development by the use of knowledge of drug receptors at the atomic level. The commercial interest in application spurred this direction of research enormously.

My lecture will start out with the history of protein crystallography and describe the major factors contributing to its development, illustrated with examples contributing to our understanding of the physical and chemical basis behind biological phenomena. I then will let you share my experience with the foundation and development of two biotech companies with different business models, but both based on basic academic research in structural biology: Proteros (www.Proteros.com) offers enabling technology services for pharmaceutical and crop science companies imbedding all steps of the workflow that molecular and structural biology can provide, and commands and uses its platform for the generation of leads from identified targets to in vivo proof of concept (PoC). Suppremol (www.Suppremol.com) specializes in the development of novel immunoregulatory therapeutics for the treatment of autoimmune diseases on the basis a recombinant, soluble, non-glycosylated version of the human Fcg receptor IIB.

Brian K. Kobilka

G Protein-Coupled Receptors: Challenges for Drug Discovery

Session: Tuesday, 1 July 2014, 12.00 hrs

G protein-coupled receptors (GPCRs) conduct the majority of cellular responses to hormones and neurotransmitters, and are therefore the largest group of pharmaceutical targets for a broad spectrum of diseases. Identification of genes for GPCRs, initially through cloning and subsequently through

database mining, raised hopes for the rapid discovery of new therapeutics. However, the number of new approved drugs for GPCR targets over the past two decades has fallen short of expectations. I will discuss challenges in GPCR drug discovery and the potential impact of structural biology and other scientific advances on future drug discovery efforts.

Walter Kohn

Macular Distortation - Diagnosis and Correction

Session: Tuesday, 1 July 2014, 15.30 hrs

Age-related Macular Degeneration (AMD) is globally the leading cause of blindness for persons aged 65 or over. Early stages or mild forms of AMD allow some vision, though distorted. Our research aims to diminish the perceived distortions. A status report, including a demonstration, will be presented.

Jean-Marie Lehn

Perspectives in Chemistry - Towards Adaptive Chemistry

Session: Wednesday, 2 July 2014, 12.00 hrs

Supramolecular chemistry lies beyond molecular chemistry. It aims at implementing highly complex chemical systems from molecular components held together by non-covalent intermolecular forces and effecting molecular recognition, catalysis and transport processes.

A further step consists in the design of systems undergoing self-organization, i.e. systems capable of spontaneously generating well-defined functional supramolecular architectures by self-assembly from their components, thus behaving as programmed chemical systems.

Supramolecular chemistry is intrinsically a dynamic chemistry in view of the lability of the interactions connecting the molecular components of a supramolecular entity and the resulting ability of supramolecular species to exchange their components. The same holds for molecular chemistry when the molecular entity contains covalent bonds that may form and break reversibility, so as to allow a continuous change in constitution by reorganiza-

tion and exchange of building blocks. These features define a Constitutional Dynamic Chemistry (CDC) on both the molecular and supramolecular levels. CDC takes advantage of dynamic constitutional diversity to allow for variation and selection in response to either internal or external factors to achieve adaptation.

The implementation of selection in chemistry introduces a fundamental change in outlook with respect to the usual molecular chemistry. The combination of dynamics and reversibility with constitutional and structural diversity points towards the emergence of Adaptive and Evolutive Chemistry Illustrations from applications of this approach to biochemical systems will be given.

References:

Lehn, J.-M., From supramolecular chemistry towards constitutional dynamic chemistry and adaptive chemistry, Chem. Soc. Rev. 2007, 36, 151.

Lehn, J.-M., Perspectives in Chemistry – Steps towards Complex Matter, Angew. Chem. Int. Ed. 2013, 52, 2836-2850.

Barry J. Marshall

Man versus Helicobacter

Session: Monday, 30 June 2014, 11.30 hrs

Please see mediatheque.lindau-nobel.org for an online abstract.

Hartmut Michel

Membrane Proteins: Importance, Functions, Mechanisms

Session: Thursday, 3 July 2013, 09.00 hrs

Biological membranes define and compartmentalize the cells of higher organisms. Consisting of membrane proteins and lipids, they are basically impermeable for ions and polar substances, so that electric voltages ("membrane potentials") and substance gradients across membranes can be generated and maintained. Thus membranes form barriers, and information and substances have to be transferred across these membranes.

Compared to membrane lipids, membrane proteins are more active players

in biological membranes. They catalyze:

(i) transmembrane transport, for example, specific uptake of nutrients and substrates, exchange of ions, and excretion of waste products and extracellular proteins across biological membranes;

(ii) biological electron transfer and energy conservation in photosynthesis and respiration;

(iii) signal reception, signal transduction across the membrane and amplification;

(iv) enzymatic reactions with preferentially hydrophobic substrates.

It is our aim to understand the function of membrane proteins and their mechanism of action. In addition, most drugs available to treat diseases act by inhibiting or activating a certain membrane protein. Therefore determining structure of membrane proteins is extremely interesting for drug design and virtual screening. However, membrane proteins are difficult to study because of material limitations caused by insufficient availability of membrane proteins and their instability. At present, the atomic structures of approximately 440 membrane proteins are known compared to tens of thousands of water soluble proteins. Moreover, the structures of only 30 human membrane proteins (of about 6000 to 8000) have been determined.

Methods of membrane protein structure determination as well as several recent successes of the author's lab with membrane proteins of potential medical interest, will be presented.

Ferid Murad

Discovery of Nitric Oxide and Cyclic GMP Cell Signaling and Their Role in Drug Development

Session: Thursday, 3 July 2014, 10.30 hrs

The role of nitric oxide in cellular signaling in the past three decades has become one of the most rapidly growing areas in biology. Nitric oxide is a gas and a free radical with an unshared electron that can regulate an ever-growing list of biological processes. Nitric oxide is formed from L-arginine

by a family of enzymes called nitric oxide synthases period. These enzymes have a complex requirement for a number of cofactors and regulators, including NADPH, tetrahydrobioterin, flavins, calmodulin and heme. The enzymes are present in most cells and tissues. In many instances, nitric oxide mediates its biological effects by activating the soluble isoform of guanylyl cyclase and increasing cyclic guanine nucleotide monophosphate (GMP) synthesis from Orotidine triphosphate (OTP). Cyclic GMP, in turn, can activate cyclic GMP-dependent protein kinase (PKG) and can cause smooth muscles and blood vessels to relax, decrease platelet aggregation, alter neuron function, etc.

These effects can decrease blood pressure, increase blood flow to tissues, alter memory and behavior, decrease blood clotting, etc. The list of effects of nitric oxide that are independent of cyclic GMP formation is also growing at a rapid rate. For example, nitric oxide can interact with transition metal such as iron, thiol groups, other free radicals, oxygen, superoxide anion, unsaturated fatty acids, and other molecules. Some of these reactions result in the oxidation of nitric oxide to nitrite and nitrate to terminate the effect, while other reactions can lead to altered protein structure function and/or catalytic capacity. These effects probably regulate bacterial infections, inflammation of tissues, tumor growth, and other disorders. These diverse effects of nitric oxide that are cyclic GMP dependent or independent can alter and regulate numerous important physiological events in cell regulation and function. Nitric oxide can function as an intracellular messenger, an antacoid, a paracrine substance, a neurotransmitter, or as a hormone that can be carried to distant sites for effects. Thus, it is a unique molecule with an array of signaling functions. However, with any messenger molecule, there can be too little or too much of the substance, resulting in pathological events.

Some of the methods used to regulate either nitric oxide formation metabolism, or function have been in clinical use for more than a century, such as with the use of organic nitrates and nitroglycerin in angina pectoris that was initiated in the 1870s. Inhalation of low concentrations of nitric oxide can be beneficial in premature infants with pulmonary hypertension and

ABSTRACTS

increase survival rates. Ongoing clinical trials with nitric oxide synthase inhibitors and nitric oxide scavengers are examining the effects of these agents in septic shock, hypotension with dialysis, inflammatory disorders, cancer therapy, etc. Recognition of additional molecular targets in the areas of nitric oxide and cyclic GMP research will continue to promote drug discovery and development program s in this field. Current and future research will undoubtedly expand the clinician's therapeutic armamentarium to manage a number of important diseases by perturbing nitric oxide formation and metabolism. Such promise and expectations have obviously fueled interests in nitric oxide research for a growing list of potential therapeutic applications. There have been and will continue to be many opportunities from nitric oxide and cyclic GMP research to develop novel and important therapeutic agents. There are presently more than 80,000 publications in the area of nitric oxide research. My lecture will discuss our discovery of the first biological effects of nitric oxide and how the field has evolved since our original reports in 1977. The possible utility of this signaling pathway to facilitate novel drug development and the creation of numerous projects in the pharmaceutical and biotechnology industrials will also be discussed.

References:

1. *Murad F. Discovery of some of the biological effects of nitric oxide and its role in cellular signaling. Nobel Lecture. Bioscience Reports 19: 133-154. 1999 and Les Prix Nobel. 1998 (the Nobel Prizes. 1998). pp. 273-307. 1999.*
2. *Murad F. Shattuck Lecture. The Discovery of nitric oxide and cyclic GMP in cell signaling and their role in drug development. New England J. Med 355. 2003- 2011. 200 6.*

Erwin Neher

Short-Term Synaptic Plasticity

Session: Wednesday, 2 July 2014, 12.30 hrs

Our brain is a network of about 10^{11} neurons, which are connected via synapses. A neuron typically receives input from about 10000 other neurons, which can be either excitatory or inhibitory. The neuron integrates these inputs and generates an action potential, when its membrane potential

surpasses a certain threshold. In synaptic transmission neurotransmitter is released upon an increase in intracellular calcium concentration ([Ca^{++}]) in the presynaptic terminal. Neurotransmitter diffuses across the synaptic cleft and opens ion-selective channels in the postsynaptic membrane.

Synaptic strength (the size of the signal in the postsynaptic neuron, elicited by a nerve impulse in the presynaptic one) displays 'plasticity' - unlike signal transfer across elements in a digital computer. The term 'synaptic plasticity' describes the fact that connection strengths between the neurons of our brain change constantly in a use-dependent manner. These changes occur on many time scales and underly many of the computational capabilities of our brain. Long term changes, such as 'long-term potentiation' and 'long-term depression' are being studied intensely, since they are believed to underly learning and memory. Short-term changes, on the other hand, are in no way less important, since they subserve basic signal processing tasks, such as adaptation, gain control, filtering, short-term memory etc. Molecular mechanisms for this, so-called 'short-term plasticity', are still a matter of debate. In my laboratory we are studying the dynamics and pharmacology of short-term plasticity in a particular synapse, which has very special features for electrophysiological investigations:

The 'Calyx of Held', a glutamatergic presynaptic terminal in the auditory pathway, is a giant synapse, which is large enough that quantitative biophysical techniques, such as voltage clamp, Ca^{++} fluorimetry, and Ca^{++} ion uncaging can be applied. Using these experimental tools, the role of Ca^{++} and other second messengers in neurotransmitter release can be conveniently studied (see E. Neher and T. Sakaba, 2008, Neuron 59, 861-872 for review). We identified specific roles of Ca^{++} in the triggering of release and in the maintenance of release during sustained high-frequency stimulation (Lipstein et al., 2013, Neuron 79. 82-96), as well as influences of other signaling pathways, which modulate amount and kinetics of short-term plasticity. A better understanding of these phenomena will not only clarify mechanisms of signal processing in dedicated brain circuits, but also provide explanations regarding the question how our brain is able to rapidly switch between distinct states, such as various forms of sleep and wakefulness.

Richard J. Roberts

Bacterial Methylomes

Session: Wednesday, 2 July 2014, 09.30 hrs

We have become accustomed to describing genomes as strings of A's, C's, G's and T's. This is how DNA sequencing results are reported and then stored in the sequence databases. But we know that almost universally DNA carries modifications, such as methylation, which play a key role in many biological events. In humans, m5CpG and its oxidized product hm5C are important epigenetic elements that can affect embryonic development and differentiation. Prokaryotic genomes are also methylated, but with just a few exceptions – such as protection for restriction enzymes, marking parental strand during mismatch repair and involvement in cell cycle control – rather little is known of their function. A major reason for this is that the complete analysis of methylation patterns in bacterial genomes has been extremely difficult if not impossible. Bisulfite sequencing can be used, with difficulty, to probe m5C modification, but m4C and m6A modifications, which are promiscuous in bacterial genomes, have proved almost impossible to investigate.

Within the last two years, however, a new technology, SMRT™ sequencing, has been developed by Pacific Biosciences that permits both the DNA sequence and its methylation pattern to be determined simultaneously. This has provided a breakthrough in analyzing bacterial methylation by enabling DNA methyltransferase (MTase) recognition specificities to be determined in an almost trivial fashion. It provides a unique insight into prokaryotic biology and reveals extremely interesting patterns of methylation that await biological function determination. Whole genomes can be scanned in a single experiment with ease. Many exciting new findings are emerging and complete methylomes for more than 500 bacterial and archaeal genomes are now known. Some MTases are part of restriction-modification systems, which protect bacteria from phage infections and prevent foreign DNA from entering the cells. For Type I and Type III restriction systems this also means that the restriction enzyme recognition sequences will also become known because the specificity is determined by the methylase in the case of

the Type III enzymes and by a common specificity subunit in the case of the Type I enzymes. This analysis used to take months for one enzyme and was rarely undertaken. Some new types of MTases have been found and because many MTases are not associated with restriction systems it is probable that new functions await discovery. A door has been cracked open that promises a new dimension in the study of genomes.

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2. *Murray, I.A., Clark, T.A., Morgan, R.D., Boitano, M., Anton, B.P., Luong, K., Fomenkov, A., Turner, S.W., Korlach, J., Roberts, R.J. Nucleic Acids Res. 40: 11450-11462 (2012). The methylomes of six bacteria.*

Bert Sakmann

Cortical Circuit and Decision Making

Session: Wednesday, 2 July 2014, 13.00 hrs

To delineate the anatomical and functional basis of behaviours, like decision making, the representation of stimuli in the sensory cortex must be understood at the cellular level. In rodent cortex, tactile stimuli are represented almost simultaneously in a cell type-specific way in all cell cortical layers. Representation is also distributed over several cortical columns but the spread depends on the cell type (De Kock et al., 2007). The main cortical output cells are tufted pyramids in layer 5. In one subclass named layer 5B, thick-tufted cells have electrically excitable dendrites (Larkum et al., 2001). The function of thick-tufted cells, which span almost the entire cortical width, could be the detection of near simultaneous electrical activity in different cortical layers. Anatomical reconstruction of different cell types and registration into a standard reference frame of vibrissal cortex (Oberlaender et al., 2010) suggest that thick tufted cells are tuned to detect touch from input via lemniscal and paralemniscal thalamocortical projections (Oberlaender et al., 2011). Thick-tufted cells project to thalamus where the output spike pattern is filtered to provide a feedback signal to cortical thick-tufted cells depending on behavioral state.

Randy W. Schekman

Genes and Proteins that Control Secretion and Autophagy

Session: Monday, 30 June 2014, 09.00 hrs

The broad outlines of the secretory pathway were established by pioneering EM and cell fractionation experiments conducted by George Palade in the 1960s. Beginning in the mid 1970s and early 80s, my laboratory isolated a series of conditionally lethal, temperature-sensitive mutations that block secretion at one of several sequential stages along the pathway established by Palade. Concurrently, James Rothman's laboratory established a cell-free reaction that reproduced vesicular traffic within the Golgi apparatus, and several of the proteins he isolated with this functional assay matched the Sec proteins we identified. Using a cell-free vesicle budding reaction, my laboratory isolated a complex of Sec proteins that comprise a coat, COPII, responsible for cargo vesicle traffic from the endoplasmic reticulum.

Autophagosomes mature by the addition of membrane material from various intracellular sources and the attachment of peripheral proteins that remain bound through a covalent lipidation reaction. However, the origin and the mechanism of generation of the pre-autophagic membrane are poorly understood. We addressed this question with the development and analysis of a cell-free reaction that reproduces the lipidation of a major peripheral autophagosomal protein, LC3. A crude membrane fraction isolated from cells deficient in lipidation was mixed with cytosol harvested from normal cells that were untreated or subjected to a stress regimen known to induce autophagy. On addition of ATP, incubation of the mixture resulted in the formation of lipidated LC3. The reaction requires both membranes and cytosol, and was found to be stimulated 2- to 5-fold when the cytosol was taken from stress-induced cells. Autophagosome maturation requires a class III PI-3 kinase (VPS34 homolog); LC3 lipidation in our cell-free reaction is inhibited by inhibitors of this kinase, and by the addition of a peptide containing a PI3P-bnding sequence, the FYVE domain. Using cell fractionation techniques we have identified the ER-Golgi intermediate (ERGIC) compartment as the major site for lipidation of LC-3. This cell-free reaction may now be used to understand the molecular mechanism of autophagosome

maturation.

References:

[1] Schekman, R. (2002) SEC mutants and the secretory apparatus. Nature Medicine 8, 1055-1058.

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Brian P. Schmidt

Cosmology: An Example of the Process of Discovery

Session: Monday, 3 July 2014, 17.30 hrs

The past century has seen our understanding of the universe rise from essentially nothing to our current state where we have a highly successful model of the cosmos. Theory now is able to predict the broad range of increasingly detailed observations astronomers collect from the elemental production of the big bang, to the distribution of galaxies, but the result is highly unsatisfactory. To explain our universe we need to suppose that 95% of the Universe is made of types of matter and energy that are not yet identified. Yet, this model of the universe continues to be vindicated with experiment after experiment bearing out the predictions of the theory. In my lecture I will discuss the process of discovery that has led to our current model of the universe, focussing on where humanity went right, and where it went wrong. I will describe my vision of how the scientific process works, ponder the nature of reality, and predict where it all might lead into the future.

Hamilton O. Smith

Synthetic Biology for Genetic Engineering in the 21st Century

Session: Wednesday, 2 July 2014, 09.00 hrs

Synthetic biologists seek to design, build, and test novel biological systems. We have chemically synthesized a bacterial genome (Mycoplsama mycoides, 1078Kb) and brought it to life by transplantation into the cytoplasm of a related species. We are interested in reducing the gene content of this

"synthetic cell" to help us understand the minimal requirements for simple cellular life. Using Tn5 transposon mutagenesis we have identified 438 genes that are apparently non-essential out of a total of 911 genes. Using this information, we have designed reduced versions of 8 overlapping segments of the genome. We have now built and tested each of the 8 reduced segments, and they are all viable in the context of the remaining 7/8th wild type genome. When all 8 of the reduced segments are combined, the resulting reduced genome is not viable. However, several combinations of reduced segments are viable. We are now refining our design so as to achieve a viable cell containing all 8 of the reduced segments.

References:

1. *Lartigue C, Vashee S, Algire MA, Chuang RY, Benders GA, Ma L, Noskov VN, Denisova EA, Gibson DG, Assad-Garcia N, Alperovich N, Thomas DW, Merryman C, Hutchison CA III, Smith HO, Venter JC, Glass JI. (2009) Creating Bacterial Strains from Genomes that have been Cloned and Engineered in Yeast. Science, advance online publication doi:10.1126/science.1173759. http://www.bio.davidson.edu/molecular/restricted/2010/Genome_Reboot.pdf*

2. *Gibson DG, Glass JI, Lartigue C, Noskov VN, Chuang RY, Algire MA, Benders GA, Montague MG, Ma L, Moodie MM, Merryman C, VAshee S, Krishnakumar R, Assad-Garcia N, Andrews-Pfannkoch C, Denisova EA, Young L, Qi ZQ, Segall-Shapiro TH, Calvey CH, Parmar PP, Hutchison CA 3rd, Smith HO, Venter JC (2010). Creation of a bacterial cell controlled by a chemically synthesized genome. Science 329, 52-56. https://www.sciencemag.org/content/329/5987/52.full.pdf*

Oliver Smithies

Where do Ideas come from?

Session: Thursday, 3 July 2014, 13.00 hrs

At many times in your scientific lives, you will hopefully have ideas – good or not so good – that will determine what you will do next. Where do ideas come from? My intention is to tell you where some of mine came from, and particularly those when I was as young as you. Some useful principles emerge.

Thomas A. Steitz

From the Structure of the Ribosome to the Design of New Antibiotics

Session: Tuesday, 1 July 2014, 11.30 hrs

Structural studies of the ribosome exemplify the evolution of structural studies in cell biology from the early negatively stained images of macromolecular assemblies in whole cells, to a detailed atomic understanding of the mechanisms of action of a large assembly. The earliest electron microscopic (EM) images by George Palade capturing the ribosome in the cell were initially called Palade particles. Biochemical studies in the 60s showed that the larger subunit of this 2.6 MDal RNA-protein assembly catalyzed peptide bond formation while interactions of the anticodon of tRNA with mRNA bound to the small subunit effected translation of the message; the binding of the aminoacyl-tRNA to the A site and binding of the peptidyl-tRNA to the P site were identified, and translocation of the peptidyl-tRNA from the A site to the P site following peptide bond formation was hypothesized. Proceeding from the early reconstructions of the shapes of the two interacting subunits from negatively stained images by Jim Lake (1976) to the current atomic resolution structures of the 70S ribosome and of its large and small subunits captured in various functional states, the mechanistic level of structural insights into ribosome function now exceeds that achieved in the early structural studies of lysozyme, carboxypeptidase and ribonuclease.

Mechanistic details of the decoding of messenger RNA at the atomic level have been derived by the Ramakrishnan lab from 3.0 Å resolution structures of the 30S ribosomal subunit complexed with mRNA and tRNA substrate fragments as well as more recent structures of tRNA substrates or fragments complexed with the 70S ribosome determined at resolutions between 3.7 Å and 2.8 Å by the Noller and Ramakrishnan labs. Structural insights into the peptidyl transferase reaction, as well as its inhibition by antibiotics, have come from structures of substrate and intermediate complexes with the 50S ribosomal subunit at resolutions that range variously between 3.3 Å and 2.3 Å from the Steitz lab. The first atomic model of the 70S ribosome derived from a 5.5 Å resolution map by the Noller lab using the atomic structures of the 30S and 50S subunits showed the interactions between the

two subunits and the general positions of tRNA molecules bound to the A-, P- and E-sites, while the most recent higher resolution structures of the 70S ribosome show further details of the interactions made by tRNAs with the P site and E site. Also, a more complete and detailed structure of the ligand free 70S E. coli ribosome from the Cate lab has shown two conformations of the "head" domain of the small subunit that is related to the process of tRNA and mRNA translocation. Structures of the release factors 1 and 2 and the appropriate mRNAs bound to the 70S ribosome calculated from the Noller and Ramakrishnan labs provide insights into the termination of polypeptide synthesis. More recent crystal structures of the 70S ribosome captured in various states of tRNA delivery by elongation factor Tu and the post-translocation state by elongation factor G from the Ramakrishnan lab have shown EF-Tu delivering an aminoacyl-tRNA and EF-G promoting translocation as well as rachet-like relative rotations of the large and small subunits. Most recently, we have obtained the structure of the 70S ribosome with EF-G in a compact pre-translocation state which suggests how EF-G promotes translocation; our recent structure with a back-translocation factor, LepA, bound to the ribosome suggests how back translocation is achieved.

Also recently, we have also obtained structures of the 70S ribosome with protein factors. The protein factor EFP stimulates the formation of the first peptide bond, and our structure of the 70S ribosome with f-met-tRNA and EFP bound shows that the EFP binds adjacent to the P-site tRNA interacting with both the anticodon stem-loop and the acceptor stem. It is presumably positioning the P-site tRNA for peptide bond formation. We have also determined the structures of the 70S ribosome with two different hibernation factors. One binds the A site on the 30S subunit that overlaps with the P-site and A-site tRNAs, thereby preventing their binding. The other factor binds near the 3' end of the 16S rRNA where the Shine-Delgano m-RNA sequence binds, which would also prevent the initiation of protein synthesis.

These structural studies of the ribosome not only provide a detailed look at the process of protein synthesis, but also demonstrate that the ribosome a ribozyme and that rRNA undergoes substrate ligand-induced conformational changes in order to achieve specificity, just as is seen in protein en-

zymes. The ribosome is 2/3 RNA and 1/3 protein. Our structural studies of the Haloarcula marismortui (Hma) large subunit showed that the site of peptide bond formation (the peptidyl transferase center) consists entirely of rRNA and our structures of many different complexes of the large subunit with various substrate, intermediate and product analogues, along with kinetic and biochemical studies of others, have illuminated the mechanism of peptide bond formation. Binding of the correct substrate to the A site results in a conformational change in the rRNA and a reorientation of the peptidyl group of the P-site substrate. The 2'OH of A76 of the A-site tRNA is H-bonded to the α-amino group of the A-site substrate. This structure of the pre-reaction substrate complex and other kinetic and biochemical data support a proton shuttle mechanism in which the 2'OH of A76 receives a proton from the attacking α-amino group thereby enhancing its nucleophilicity, while it donates a proton to the 3' oxygen of A76 of the peptidyl-tRNA as it is being deacylated. A movie of this process (with music) based on many structures will show the mechanism of peptide bond formation.

The ribosome is a major target of antibiotics which are seen to bind either the large or the small subunit or to both subunits simultaneously. We have determined the structures of many different families of antibiotics bound to the Hma large subunit or to the Thermus thermophilus (T.th.) 70S ribosome, and those structures inform how the various antibiotics inhibit protein synthesis by the ribosome. They also suggest why various resistance mutations in the ribosome make the ribosome insensitive to specific antibiotics. We have also determined the structures of complexes of mutant ribosomes with antibiotics to validate the proposed mechanisms of antibiotic resistance produced by the mutations.

The rise of antibiotic-resistant bacteria is becoming a major global health problem. MRSA is reported to now result in about 100,000 deaths annually world-wide. The structures of our antibiotic complexes with the ribosome are currently being used for structure-based drug design to create new compounds that are effective against MRSA and other antibiotic-resistant bacterial strains. The strategy being employed by Rib-X Pharmaceuticals, Inc. (now Melinta Therapeutics, Inc.), in New Haven, Connecticut is to design

new compounds that chemically link a portion of one known antibiotic to a part of another antibiotic that is observed to bind to an adjacent site.

Using computational approaches for the design of new compounds, many cycles of compound synthesis and evaluation are resulting in new potential antibiotics that are effective against resistant strains are being created. One compound made by Rib-X Pharmaceuticals, Radezolid, has successfully completed phase II clinical trials and many other compounds are in their antibiotic development pipeline.

Our structural studies of the ribosome and its complexes with many functionally important ligands are not only providing important insights into how this macromolecular machine works, but are now also leading to practical benefits to human health.

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Roger Y. Tsien

Molecules Against Cancer or for Long-Term Memory Storage

Session: Wednesday, 2 July 2014, 11.30 hrs

For cancer diagnosis and therapy, we are developing activatable cell-penetrating peptides (ACPPs), synthetic molecules with a novel amplifying mechanism for homing to diseased tissues. ACPPs are polycationic cell-penetrating peptides whose cellular uptake is minimized by a polyanionic inhibitory domain and restored if the peptide linker connecting the two

domains is cleaved. Local activity of specific proteases cuts the linker and causes amplified adhesion and uptake in tumors. ACPPs sensitive to matrix metalloproteinases 2 and -9 enable magnetic resonance imaging (MRI), fluorescence-guided surgery, delivery of chemotherapy, and radiosensitization. We have also developed fluorescent peptides that light up peripheral nerves to show surgeons where not to cut.

We are testing the hypothesis that life-long memories are stored as the pattern of holes in the perineuronal net (PNN), a specialized form of extracellular matrix deposited around selected neurons during critical periods of brain development. The PNN can be modified enzymatically and is interrupted by holes where synapses occur. We postulate that the PNN contains long-lived molecules and that new memories are recorded by carving new holes to form novel synapses or by expanding existing holes to strengthen old synapses. Experimental tests are underway.

References:

Crisp et al (2014) Dual targeting of integrin alpha-v beta-3 and matrix metalloproteinase-2 for optical imaging of tumors and chemotherapeutic delivery. Mol Cancer Ther. 2014 Apr 15. [Epub ahead of print]

Tsien (2013) Very long-term memories may be stored in the pattern of holes in the perineuronal net. Proc. Natl. Acad. Sci. USA. 110: 12456-61

John E. Walker

Generating the Fuel of Life

Session: Thursday, 3 July 2014, 12.30 hrs

The lecture will be devoted to the topic of how the biological world supplies itself with energy to make biology work, and what medical consequences ensue when the energy supply chain in our bodies is damaged or defective. We derive our energy from sunlight, which, via photosynthesis in green plants, provides high energy components in the foods that we ingest. We harvest that energy, effectively by "burning" (oxidising) the high energy components, releasing cellular energy in a controlled way to generate the fuel of life, in the form of the molecule known as adenosine triphosphate (or ATP for short). The key steps in this process take place in the mitochondria

inside the cells that make up our tissues. They serve as biological "power stations" that contain millions of tiny molecular turbines, the ATP synthase, that rotate rather like man-made turbines churning out the cellular fuel in massive quantities, which is then delivered to all parts of our bodies to provide the energy to make them function. Each of us makes and expends about 60 kg of this fuel every day of our lives. Defects in the fuel supply process are increasingly being recognised as important components of complex human diseases such as cancer, neurodegeneration and neuromuscular diseases, and they may also be part of the process of ageing.

The ATP synthases found in mitochondria eubacteria and chloroplasts have many common features. Their overall architectures are similar, and they all consist of two rotary motors linked by a stator and a flexible rotor. When rotation of the membrane-bound rotor is driven by proton motive force, the direction of rotation ensures that ATP is made from ADP and phosphate in the globular catalytic domain. When ATP serves as the source of energy and is hydrolysed in the catalytic domain, the rotor turns in the opposite sense and protons are pumped outwards through the membrane domain, and away from the catalytic domain. Although, the ATP synthases from mitochondria, eubacteria and chloroplasts have many common features in their catalytic mechanisms, they differ fundamentally in the energy cost that is paid to make each ATP molecule, and the most efficient ATP synthase is found in the mitochondria of multicellular animals. The ATP synthases in unicellular organisms, and chloroplasts, pay various higher costs that seem to reflect the supply of available energy in the biological niches that they inhabit. The ATP synthases also differ significantly in the way they are regulated. Eubacteria have evolved a range of mechanisms of regulation, and the chloroplast enzyme is rendered inactive by a redox mechanism in the hours of darkness. Mitochondria contain an inhibitor protein, IF1, which inhibits ATP hydrolysis but not ATP synthesis. Its in vitro mechanism has been studied in great detail, but its in vivo role is mysterious, and suppression of expression of the protein appears not to influence respiration.

Arieh Warshel

Multiscale Simulations of the Functions of Biological Molecules

Session: Monday, 30 June 2014, 09.30 hrs

Despite enormous advances in structural studies of biological systems we are frequently left without a clear structure–function correlation and cannot fully describe how different systems actually work. This introduces a major challenge for computer modeling approaches that are aimed at a realistic simulation of biological functions. The unresolved questions range from the elucidation of the basis for enzyme action to the understanding of the directional motion of complex molecular motors. Here we review progress in simulating biological functions, starting with the early stages of the field and the development of QM/MM approaches for simulations of enzymatic reactions. We provide overwhelming support for the idea that enzyme catalysis is due to electrostatic preorganization and then move to the renormalization approaches aimed at modeling long-time processes, demonstrating that dynamical effects cannot change the rate of the chemical steps in enzymes. Next we describe the use of our electrostatic augmented coarse-grained (CG) model and the renormalization method to simulate the action of different challenging complex systems. It is shown that our CG model produces, for the first time, realistic landscapes for vectorial process such as the actions of F1 ATPase, Fo ATPase and myosin V. Significantly, at present, to the best of our knowledge, these are the only studies that consistently reproduced (rather than assumed) a structure-based vectorial action of molecular motors. The emerging finding from all of our simulations is that electrostatic effects are the key to generating functional free energy landscapes.

References:

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Coarse-Grained (Multiscale) Simulations in Studies of Biophysical and Chemical Systems, S. C. L.Kamerlin, S. Vicatos, A. Dryga and A. Warshel, Ann. Rev. Phys. Chem. 62,41 (2011).

Torsten N. Wiesel

A Homage to David Hubel: Early days in our Studies of the Visual Cortex

Session: Tuesday, 1 July 2014, 15.30 hrs

Dr. Wiesel will commemorate his dear friend and colleague David Hubel, who died last fall. Nearly half a century ago, the two scientists carried out experiments on the visual cortex in cats and monkeys over a period of nearly 20 years, and Dr. Wiesel will tell the story of the wonders they revealed in the structure, function and development of the visual system.

Kurt Wüthrich

A Personal View of the History of Nuclear Magnetic Resonance in Biology and Medicine

Session: Wednesday, 2 July 2014, 10.30 hrs

In 1952, Felix Bloch and Edward Purcell were awarded the Nobel Prize in Physics for the description of the phenomenon of nuclear magnetic resonance (NMR). Over the years, NMR has been used in a wide range of fundamental studies in physics, and in the 1960s it became an important analytical tool in all branches of chemistry. Based on novel concepts and advances in instrumentation and computation, exciting developments in the early 1970s laid the foundations for magnetic resonance imaging (MRI) being a key technique in medical diagnostics today, and for NMR spectroscopy being a widely applied technique in modern structural biology. Here, I will review some basic concepts that enabled these developments.

References:

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Nuclear magnetic resonance — from molecules to man.

Wüthrich, K. (2003) Angew.Chem. Int. Ed. 42, 3340–3363.
NMR studies of structure and function of biological macromolecules (Nobel Lecture).

Ada E. Yonath

Towards Control of Species-Specific Antibiotics Resistance

Session: Tuesday, 1 July 2014, 10.30 hrs

Ribosomes, the universal cellular nan-machines that translate the genetic code into proteins, are targeted by many antibiotics that paralyze them by binding to their functional sites. The three-dimensional structures of complexes of ribosomes from genuine pathogens and pathogen-model with ribosomal antibiotics revealed their binding modes, inhibitory actions and synergism pathways. They also indicated the principles of differentiation between patients and pathogens, suggested the species-specific mechanisms leading to bacterial resistance, and paved the way towards improvement of existing antibiotics, as well as towards the design of advanced therapeutics capable of minimizing antibiotic resistance.

Rolf M. Zinkernagel

Why do we not have a Vaccine Against HIV or Tubercolosis?

Session: Tuesday, 1 July 2014, 09.30 hrs

Analysis of the immune system is fascinating and progressing rapidly. As a field of medical enquiry, it has however, drifted and turned purely academic. This is because interest and appreciation of protective immunity in infectious disease medicine has been overtaken by 'l'art pour l'art' of so-called 'basic immunology'. This development deprives much of immunological sciences of the biological basis and understanding that is linked to co-evolution of infectious agents and hosts' protective immunity. It is this co-evolutionary context that renders this field so different from studying yeast, bacteria, fibroblasts, lymphocytes or neuronal cells in splendid isolation in in vitro model situations, where everything is possible (and permitted or mistakes forgiven without repercussions) because the co-evolutionary context is ignored.

I shall explain why we have excellent vaccines against acutely lethal (childhood) infections but not against most slow, chronic persistent infections or tumors, which usually kill us late i.e. after reproduction. Another conclusion is that so-called 'immunological memory' of course exists, but only in particular experimental laboratory models measuring 'quicker and better' responses, which often do correlate with, but are not the key, mechanisms of protection. Protection depends on pre-existing neutralizing antibodies or pre-activated T cells at the time of infection. This is well documented by the importance of maternal antibodies at birth for survival of offspring. Importantly, both high levels of antibodies in mothers are driven by antigen reencounter. This of course has serious implications for our thinking about old, and hopes for new, vaccines.

Further readings:

1. *Zinkernagel RM, Ehl S, Aichele P, Oehen S, Kundig T and Hengartner H (1997) Antigen localisation regulates immune responses in a dose- and time-dependent fashion: a geographical view of immune reactivity. Immunol Rev 156:199-209*
2. *Zinkernagel RM (2001) Maternal antibodies, childhood infections, and autoimmune diseases. N Engl J Med 345:1331-1335*
3. *Zinkernagel RM and Hengartner H (2004) On immunity against infections and vaccines: credo 2004. Scand J Immunol 60:9-13*

Harald zur Hausen

Infections Linked to Human Cancers: Mechanism and Synergisms

Session: Tuesday, 1 July 2014, 10.00 hrs

Slightly more than 20% of the global cancer incidence is presently being linked to viral, bacterial, or parasitic infections. The mechanisms by which these agents mediate malignant transformation differ substantially. Some contribute directly, frequently integrating their genome into chromosomal DNA, others may persist episomally. Persistence of the respective DNA is required to maintain the malignant phenotype of the affected cells. Indirect contributions may involve immunosuppression, induction of reactive oxygen radicals, amplification of latent tumor virus DNA, induction of mutations and translocations, and prevention of apoptosis. Even in case of direct contributions to carcinogenesis additional modifications of host cell genes are required prior to onset of malignant growth. The required number of these genetic or epigenetic changes determines the latency period between

primary infections and malignant proliferation. In most cases it varies between 10 and 60 years.

Interactions of potentially carcinogenic infections with other mutagenic factors (e.g. chemical carcinogens, irradiation, hormones, inflammations, specific virus infections) emerges more as rule than exception. Nevertheless, the identification of potentially carcinogenic infectious agents permitted novel approaches in cancer prevention and identification of persons at risk for specific cancers. The emerging picture of the role of infections in human carcinogenesis, however, results in great difficulties to apply criteria outlined by Koch, later by Hill and others, to define causality.

Recommended Readings:

zur Hausen H., de Villiers, E.-M.: Prenatal Infections with Subsequent Immune Tolerance Could Explain the Epidemiology of Common Childhood Cancers. World Cancer Report 2014, pages 261-265, IARC Lyon

zur Hausen, H. de Villiers, E.M. Cancer « causation » by infection – individual contributions and synergistic networks. Seminars in Oncology, in print.

PANEL DISCUSSION ABSTRACTS

Beutler, Bishop, Hoffmann, Schmidt

Large Data and Hypothesis-Driven Science in the Era of Post-Genomic Biology

Session: Wednesday, 2 July 2014, 15.30 hrs

Canonically, biology including medicine considers hypothesis-driven research as its ultimate goal. In biomedicine, experimental proof of a hypothesis is sometimes translated into a clinical intervention, a process termed translational medicine. With recent achievements in genomics and other biomics increasingly large datasets are being generated which, e.g., allow assessment of genetic variability of humans and their predisposition to certain diseases. Some scientists take the position that this approach lacks any hypothesis and sometimes disqualify it as fishing experiment. Others argue instead that new hypotheses can be generated through analysis of large datasets which can subsequently be contested in specific analytical systems. However, large datasets and hypothesis-driven research are not mutually exclusive. Rather they are complementary and when applied in an iterative way can provide deep insights into biological and medical phenomena leading to a systems biologic view of life.

This topic – and in particular the place of biology in this endeavor – will be discussed in the panel discussion with several Nobel Laureates.

Beutler, Goldman, Gøtzsche, Gomes, Wang

Academia and Industry – Exploring the Collaborative Landscapes of the Future

Session: Thursday, 3 July 2014, 15.30 hrs

Collaborations between academia and industry most probably play an important role at some point in almost every biomedical scientist's life. Lately there has been much talk about industry's desire to encourage a 'new' landscape of openness in its relationships with academia, while academics are themselves exploring new models for how to share information. Worldwide, universities are under pressure to demonstrate the applied benefit of

their research, promoting a move towards increased liaison with industry.

However, against this background many scientists question the wisdom of the move towards application-focused research goals, and criticism of industry's motives is common. This panel discussion brings together voices from across the spectrum of opinions to explore the collaborative options open to biomedical research scientists of the future. And, this being all about collaboration, the audience will be encouraged to participate!

Barré-Sinoussi, Bassioni, Mgone, Schmidt, Schütte

Science for the Benefit of Mankind

Session: Friday, 4 July 2014, 11.00 hrs

The last will of Alfred Nobel states that the prizes should be given to those who have conferred the greatest benefit to mankind.

Looking backward, it is rather easy to identify a great number of inventions and discoveries that have greatly contributed to the benefit of mankind, if not even seriously influences its development. Yet, identifying fields of science and research that will accomplish the same for the future is much more difficult.

The definition of "benefit to mankind" alone is quite challenging. In terms of healthcare, needs vary greatly in different parts of the world, and the question of what is beneficial to whom is quite complicated to answer. Furthermore, the conditions for conducting science and research are very heterogeneous in different countries as well.

How can "benefit" be distributed fairly? What responsibility do scientists have, towards society, towards mankind? Does it make sense to devote oneself to a defined goal (of achieving a major impact)?

The panelists will also try a bold look into the future as to where "beneficial" future developments and discoveries might be, and which of the many roads a young scientist might take to get there.

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SCIENCE BREAKFAST ABSTRACTS

Science Breakfast upon invitation of Australia

Women in Science: Fixing the Leaking Pipeline

Session: Monday, 30 June 2014, 07.00 hrs

A panel led by Professor Suzanne Cory, Immediate Past President of the Australian Academy of Science, Nobel Laureates Professor Elizabeth Blackburn and Professor Brian Schmidt, together with marine biologist Professor Emma Johnston, Director of Sydney Harbour Project, and moderated by science communicator Adam Spencer, will discuss the contributions of women to the progress of science and why women often either reject science as a career choice or depart prematurely.

If we are to fully benefit from the talents of women in the scientific and technological workforce, actions that encourage greater gender equity are required. Some countries are already taking steps to ensure greater representation of women in science. For example many universities and research institutions in the UK are members of the Scientific Women's Academic Network (SWAN) Charter, which is committed to the advancement and promotion of careers of women in science, technology, engineering, medicine and mathematics (STEMM)[1]. Australia is taking steps to plan its own initiative.

The panel will briefly talk about their personal experiences, and how universities and institutes could encourage women to reach their full potential as scientific researchers. This will be followed by a question and answer session.

References

1. *Athena SWAN Charter for women in science. http://www.athenaswan.org.uk/content/history-and-principles*

Science Breakfast upon invitation of Else Kröner-Fresenius Stiftung

Science in Clinical Medicine

Session: Tuesday, 1 July 2014, 07.00 hrs

Clinical medicine is increasingly influenced by systematic scientific approaches, working along mechanistic concepts of genes, gene expression or signalling pathways rather than along symptoms or organs. How much scientific knowledge does a modern physician therefore need to possess? Does exposure to science make a better general practitioner?

The progress of medical research needs the contribution of: (i) the scientist pursuing fundamental mechanisms and guided by the quest of knowledge, as well as (ii) the clinician, who is mainly driven by the desire to help his patients. The clinician is capable of recognizing the clinical potential of new ideas, and has access to patients or patient material for validation of laboratory results, while the scientist has the training and the time to delve deep into complex experimental models and techniques.

It is clear that these two worlds must meet for medicine to substantially move forward. The obvious and classical model to achieve this is to amalgamate the scientist and the clinician in one person, the clinician scientist. From a recent survey (unpublished) amongst medical scientists we have learned that clinician scientists, who are in a position to divide their time between laboratory and clinic, are highly satisfied.

However, the worlds of science and medicine appear to drift apart: fewer and fewer doctors take on the double challenge of both research and patient care.

Is it the pressure of profitability of patient care that leaves no room for research? Is it the increasing burden of family obligations or the increasing longing for work-life-balance that makes doctors go home when their clinical shift ends instead of going to the laboratory? Has science become too complex to be mastered successfully with less than a fulltime commitment? Why are there so few Nobel Prizes in Physiology or Medicine held by clinicians?

Science Breakfast upon invitation of Mars, Incorporated

Addressing the Challenges of Ageing Research through Cross-Disciplinary Collaboration

Session: Wednesday, 2 July 2014, 07.00 hrs

The number of people over 65 years old worldwide is expected to triple by 2050[1]. As life expectancy rises, ageing populations are increasingly being seen as a looming social and economic challenge of urgent global importance. At the Mars, Incorporated Science Breakfast, Adam Smith (Chief Scientific Officer of Nobel Media) will moderate a panel discussion focusing on the role of cross-disciplinary collaboration in driving ageing research to address the challenges we expect to face.

The panel will feature the views of Prof. Elizabeth Blackburn (Physiology or Medicine Nobel Laureate) and Dr. Hagen Schroeter (Director, Fundamental Health & Nutrition Research, Mars, Incorporated) as well as a selected young researcher. Prof. Blackburn was awarded the Nobel Prize for Physiology or Medicine in 2009 for her discovery of telomeres. She is the Morris Herzstein Professor in Biology and Physiology at the Department of Biochemistry and Biophysics, University of California, San Francisco, and a leader in the area of telomere and telomerase research. She discovered the molecular nature of telomeres – the ends of eukaryotic chromosomes that serve as protective caps essential for preserving the genetic information – and the ribonucleoprotein enzyme, telomerase. Prof. Blackburn is harnessing telomere biology to contribute to a cross-disciplinary approach to healthy ageing.

Dr. Hagen Schroeter is Director of Fundamental Health & Nutrition Research for Mars, Incorporated and Adjunct Research Professor at the Nutrition Department, University of California, Davis. Dr. Schroeter will provide background information on the fundamental research programs in health and nutrition advanced by Mars, Incorporated and collaborators in academia, industry, and government. A main research focus aims at understanding the molecular and cellular mechanisms underlying the beneficial effects of flavanols – a plant-derived nutrient - in maintaining cardiovascular and cognitive health as we age. Dr. Schroeter led Mars' involvement in FLAVIOLA

– a pan-European collaborative research project supported by the European Union and dedicated to state-of-the-art research into flavanols, their health benefits and their potential applications in the context of public health.

The Mars, Incorporated Science Breakfast will bring together the views of Laureates, industry scientists and young researchers - both on the panel and in the audience - to trigger robust discussion on the role of science and cross-disciplinary collaboration in healthy ageing research.

[1] *United Nations, Department of Economic and Social Affairs, World Population Prospects: 2012 Revision, June 2013, http://esa.un.org/unpd/wpp/index.htm*

* Please note:

Participation in the Preparatory Event is essential for all attendees of the Science Breakfast supported by Mars, Incorporated. The Preparatory Event will take place the day before the Science Breakfast at 07.00 on Tuesday, July 1st. It will consist of mini-lectures given by Prof. Elizabeth Blackburn and Dr. Hagen Schroeter on their research and will provide the necessary background information to promote debate and discussion at the Science Breakfast.

Science Breakfast upon invitation of McKinsey & Company, Inc.

Scientific Leadership in the 21st Century: Running Productive Labs, Leading Great People, Leading Self

Session: Wednesday, 2 July 2014, 07.00 hrs

Leadership can be defined in many ways. While definitions might vary, it is clear that leadership is not about seniority or titles, and it should not be confused with management. Leadership is about mobilizing groups of people – and by doing so creating exceptional value beyond what individuals can achieve – toward the achievement of a goal, including of course leading self. In science, the importance of individual excellence is well known and documented, in fact at times combined with the prejudice that most scientists act alone or in very small teams.

At the same time, biopharmaceutical and biomedical sciences have become

highly multidisciplinary fields and new technological opportunities are continuously emerging, offering unprecedented opportunities (e.g., cell-based approaches; real-world patient data; high-throughput sequencing). Our experience from working with R&D industry leaders and their organizations suggests indeed that scientific excellence, focus, and cross-functional ways of working are important predictors of success. At the lab level, not surprisingly, we have identified collaboration as a critical success factor, next to talent (Edwards et al., 2011). We have coined the term "scientific leadership" to describe what matters in biopharmaceutical and biomedical sciences more than anywhere else – successful leaders need to have depth and master the science but, at the same time, be capable to motivate and mobilize ever more cross-functional teams to overcome the important biomedical and biopharmaceutical challenges of our time.

As if this would not be difficult enough, today's volatile environment is providing science leaders challenges unseen in history. Science leaders are facing an unprecedented set of opportunities, increasingly deep but also hard-to-interpret insights into the science of disease mechanisms, at times overwhelming richness of knowledge and a 24/7 information flow that is hard to master by any single human individual, and, lastly, an ever more global and connected world, also between industry and academia.

We believe that mastering "scientific leadership" is becoming an extremely important capability in the 21st century, both in academia and in industry. It becomes relevant for today's students, post-docs/scientists, but also scientists and leaders in industry. This begs the question of how one can understand, let alone acquire such leadership skills. Learning by doing and exposure to mentors are certainly important components, but as a first step we need to define what "scientific leadership" is and what it takes. Hence, we believe it will benefit the progress of science if we facilitate the dialogue between highly experienced and senior science leaders – reflecting on their path to success – young scientists, and successful business leaders. This cross-disciplinary dialog has the potential to derive learnings that can equip the next generation of leaders with what it takes to be successful in the 21st century.

References:

1 – Michael Edwards et al. "Managing the health of early-stage discovery"; Nature Drug Discovery Reviews; Vol. 12 (page 171f.), March 2011

2 – Interviews with 21st century business leaders at http://www.mckinsey.com/insights/leading_in_the_21st_century/interviews_with_leaders

3 – McKinsey experiences in biopharmaceutical R&D, including relevant publications at http://www.mckinsey.com/client_service/pharmaceuticals_and_medical_products/expertise/research_and_development

Science Breakfast upon invitation of the Austrian Federal Ministry of Science and Research and Economy

Predicting Phenotypes from Genotypes — a Brave New World?

Session: Thursday, 3 July 2014, 07.00 hrs

Considerable progress is being made in understanding how genetic variation translates into phenotypic variation, and how this translation is affected by the environment. We are beginning to understand the causes of human variation, whether it be height, skin color, or susceptibility to disease. Analogously, breeders are dissecting the basis for variation in crop yield and resistance to pests, and evolutionary biologists the basis for natural adaptation. The possibilities have caught the attention not only of Hollywood, which, in movies like "GATTACA" (1997), envision a dystopian future of genetic determinism, but also of Wall Street, which touts "personalized medicine" as the future of healthcare.

But what are the biological realities behind this? To what extent can we actually predict phenotype from genotype? Beyond prediction, will it be possible to manipulate the genome to change the phenotype in predictable ways? What are the technical, fundamental biological, and ethical limitations?

Science Breakfast upon invitation of the German Cancer Research Center, DKFZ

From Cancer Research to Personalized Medicine

Session: Thursday, 3 July 2014, 07.00 hrs

Cancer is a disease characterized by genetic alterations of affected cells.

Large scale sequencing analyses covering the entire genome demonstrate a high variability of these changes between individual patients. Such studies are now used as a basis for personalized treatment plans. These fascinating new developments towards individualized cancer medicine will be highlighted by our panel. Professor Otmar Wiestler, CEO and Scientific Director of the German Cancer Research Center, DKFZ, will give an overview of highly innovative developments at the DKFZ.

Pediatric Neurooncology is currently a vibrant field of research with major achievements in the last few years, to unravel the molecular basis of childhood brain tumors and translate molecular findings into clinical practice. This is desperately needed from a clinical perspective, since brain tumors have become the number one cause of cancer-related mortality in children. The group of Stephan Pfister, Pediatric Neurooncology, aims to bridge the gap between generating genomic screening data and exploiting these data for the benefit of patients. This includes the identification, validation and clinical application of prognostic and predictive biomarkers as well as functional characterization of newly identified mutations in different childhood brain tumors. Another major focus of the group involves the systematic preclinical testing of novel drug targets, often in combination with established cytotoxic drugs and/or chemotherapy to develop and validate and treatments based on the genetic/molecular signature of the individual tumor ("personalized oncology"). Another focus will be the detection of tumor-specific alterations in body fluids, such as cerebrospinal fluid, and plasma, which can be exploited for molecular diagnostics, tumor cell clearance (minimal residual disease), monitoring of the disease, detection of molecular drug targets, and primary resistance mechanisms.

The Junior group of Christiane Opitz, Brain Cancer Metabolism, identified a metabolic pathway of the essential amino acid tryptophan as a key element promoting malignant brain tumors. Tryptophan metabolites activate the dioxin receptor resulting in enhanced invasiveness and clonogenicity of brain tumor cells. As different dioxin receptor ligands exert diverse biological effects, it is expected that tryptophan metabolites will activate other signaling pathways beyond the classical and well-studied exogenous ligand

ABSTRACTS

dioxin. Inhibition of the dioxin receptor may open a new approach for cancer therapy. Furthermore, there is preliminary evidence that several enzymes implicated in nicotinamide metabolism are overexpressed in brain tumors. Christiane Opitz´s group performs small molecule screens to identify inhibitors of the respective enzymes. In addition, nicotinamide will be measured in biofluids of brain tumor patients and correlated with the activity of the respective enzymes in the tumor tissue; this will be done with the aim of identifying biomarkers for the activity of nicotinamide metabolism for future stratification of patients to treatment with inhibitors of this pathway.

FINDING ABSTRACTS TOO ABSTRACT?

Visit the laureates in their labs:
nobellabs.lindau-nobel.org

Henri Matisse, Ikarus (VIII), 1947 © Succession Matisse, VG Bild-Kunst, Bonn 2014

VARIATION – IMPROVISATION by Henri Matisse

5 April – 31 August 2014
City Museum Lindau
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ABOUT THE MEETINGS

The Meetings

The Lindau Nobel Laureate Meetings – established in 1951 – provide globally recognised forums for the exchange of knowledge between Nobel Laureates and young scientists. They inspire scientific generations and build sustainable networks of young scientists from around the world.

The participants at the Lindau Meetings are characterised by diversity. They all come from a variety of national and scientific backgrounds and have very different ways of communicating. This makes the Nobel Laureate Meetings unique in the world and a model of the kind of visionary cooperation which science will increasingly need in the future. Furthermore, scientific progress will need to be firmly anchored in international and interdisciplinary networks of individuals working together. Lindau provides the stimulus for such networks to take root and grow.

The original idea of the meetings goes back to the two Lindau physicians Dr. Franz Karl Hein and Professor Dr. Gustav Wilhelm Parade as well as Count Lennart Bernadotte af Wisborg, a member of the Swedish royal family who quickly became the spiritus rector of the Lindau Meetings. It was him who recognised the significance of the meetings for the reconciliation of the peoples of post-war Europe early and thus systematically developed it to an international forum for the exchange of knowledge between nations, cultures and disciplines.

The Organisers

The Council for the Lindau Nobel Laureate Meetings and the Foundation Lindau Nobel Laureate Meetings organise the annual meetings. The Executive Secretariat is responsible for their planning and realisation.

Countess Bettina Bernadotte af Wisborg is president of the council, which sets the course for the Lindau Meetings' concept and programme. Internationally accredited scientists from the fields of medicine, physics, chemistry and the economic sciences are members of the council. The work of the council benefits from the commitment of the secretaries of the assemblies

responsible for awarding the Nobel Prizes: at least one of the two scientific chairpersons of each conference is a member of the institutions that select the Nobel Laureates.

The foundation was founded in the year 2000 by the council and the Bernadotte family on the initiative of 50 Nobel Laureates. Prof. Dr. h.c. Wolfgang Schürer serves as the chairman of the board of the foundation. Joint initiatives regarding the advancement of the Lindau Meetings and the establishment of an international network of academic partners are key priorities besides ensuring sustainable funding.

The Lindau Meetings enjoy widespread support. More than 270 Nobel Laureates are members of the founders' assembly of the foundation and demonstrate – through their membership and their participation in the Lindau Dialogue – their support for the principle of the Lindau Nobel Laureate Meetings. Personalities from the worlds of science, politics and industry have been inaugurated into the foundation's honorary senate in recognition of the special commitment they have shown towards scientific excellence and the promotion of young scientists.

Funding of the Lindau Nobel Laureate Meetings

The Lindau Nobel Laureate Meetings are enabled thanks to the support received from companies, associations and private patrons, on the one hand, and from national and state ministries, the International Lake Constance Conference and the European Commission on the other.

International companies, selected foundations, associations and private patrons assure the material basis for the Lindau Meetings by making donations to the assets of the Foundation Lindau Nobel Laureate Meetings. Interest earned on the endowment, plus additional annual contributions by benefactors cover the budget of the Lindau Meetings. Donations in kind also play an important role in raising the professional level of the Meetings. The success of the Lindau Meetings can also be attributed not least to the commitment shown by the Nobel Laureates, members of the council and the board of the foundation during the preparation, realisation and evaluation

ABOUT THE MEETINGS

of the meetings. They all give their support on a pro bono basis.

A full list of supporters is enclosed in this programme.

The Academic Partners Network

The Lindau Nobel Laureate Meetings interact closely with a global network of academic partners to identify highly-talented young scientists and to nominate them for participation. Partners include national academies of science, ministries, research institutions, top-ranking universities, foundations and international scientific organisations. Without this support, the Lindau Nobel Laureate Meetings would not be able to identify and invite the most gifted scientific talents world-wide.

The world's best young scientists of tomorrow submit applications to attend the Lindau Nobel Laureate Meetings. An international, multi-stage selection process makes sure that the scientific elite of the future is able to come together with the Nobel Laureates in Lindau. Every year, several thousand young scientists worldwide apply.

A full list of academic partners can be found in the Participants Directory.

Lanyard Color Key

Turquoise	Nobel Laureates
Grey	Young Scientists
Red	Guests
Yellow	Journalists
Lime Green	Host Families
Purple	Lindau Citizens
White	Lindau Alumni (from 1984)
Brown	Contractors of Third Parties
Orange	Contractors
Green	Council & Foundation
Black	Staff of the Executive Secretariat

Programme Session Types

The 64th Lindau Nobel Laureate Meeting features a variety of session formats.

In general, the mornings usually offer plenary formats, while the afternoons add more interactive elements.

Plenary Lecture

Plenary lectures are given by Nobel Laureates only. They may choose a topic of their liking – be it their Nobel Prize research, be it something else. As the time is limited to thirty minutes, there is usually no discussion.

Plenary Panel Discussion

In a plenary panel discussion, several panelists jointly discuss one topic. This year, three discussions are offered: on Wednesday ("Large Data and Hypothesis-Driven Science in the Era of Post-Genomic Biology"), on Thursday ("Academia and Industry – Exploring the Collaborative Landscapes of the Future") and on Friday ("Science for the Benefit of Mankind").

Discussion Sessions

In the afternoon, all lectures held in the morning can be discussed in a separate discussion session. These research-oriented discussions are strictly limited to Laureates and young scientists, and switching between sessions should be avoided.

Master Class

This format will offer a most intense exchange between young scientists and Laureates, as selected young scientists present their research and then engage in an in-depth discussion with a Laureate. Attendance requires online pre-registration.

Science Breakfasts

Science breakfasts are additional options for a more informal exchange. They are organised by Lindau's partners, featuring talks, discussions and a joint breakfast with a Nobel Laureate. Attendance requires online pre-registration.

The Lindau Nobel Laureate Meetings would like to thank all maecenates, patrons and donors for their contributions to the endowment of the foundation.

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LINDAU VICINITY MAP
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B 31
Hengnau
Bruggach
Taubenberg
Bahnholz
Paradies
Dachsberg
Paradiesweg
Dunkelbuchweg
Trimm-Dich-Pfad
Diepoldsberg
Oberrengersweiler
Campingpark Gitzenweiler Hof
Metzlers
Grübels
Weißensberger Weiher
B 12
Rehlings
Niederhaus
Weissens-berg
B 308
Anschlußstelle Sigmarszell
Zeisertsweil
Ringoldsberg
Tunnel
Schönau
Schönbühl
Kemptener Str.
Tobel
Witzign
Entenberg
Hochbuch
Heimesreutin
Golfplatz
Waldeinpfad
Schießstand
Motzach
Streitelsfingen
Bösenreutin
A 96
Bettnau
Bodolz
Enzisweiler
Hoyren
LI 16
Wasserburg
Bichelweiher
Aeschach
Wannental
Schachen
Reutenen
Friedrichshafener Straße
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Reutiner Straße
Lugeck-siedlung
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Reutin
Ricken-bach
Schachener Straße
Wackerstraße
Villa Lindenhof
Lindenhofpark
Strandbad Bad Schachen
Alter Friedhof Park
Kolpingstr.
B 12
Aeschacher Bad
Am Alpengarten
Ladestraße
Eislaufplatz
Strandbad Eichwald
Eichwaldstraße
ADAC
Anschlußstelle Lindau
Klaranlage
Bregenzer Straße
Zech
Kleiner See
Insel Hoy
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397m über N.N
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Hexenstein
Kleiner See
Bootsvermietung
Bootsliegeplätze
Seebrücke
Bayerische Spielbank
Inselhalle
Lindenschanze
Oskar-Groll Anlagen
Schiffsrundfahrten
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Stadtmuseum
Hauptbahnhof
Karlsbastion
Seehafen
Schiffsrundfahrten
Kursschiffe
Römerschanze
Segelhafen
Gerberschanze
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PROLINDAU MARKETING
Park-Camping am See
Sporthafen
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BUS LINES & TIME TABLE

Special Operating Hours during the Meeting

On Monday night, 30 June, the last buses leave at 00.40 hrs from the central connection point (ZUP) and serve all stops along their lines.

On Tuesday night, 1 July and Thursday night, 3 July the last buses leave at 23.40 hrs from the central connection point (ZUP) and serve all stops along their lines.

How to Read the Time Table

The time table on the opposite page shows operating hours and departure times for all four lines and both directions. The first three columns (earliest, Saturday, Sunday) indicate when the earliest bus runs from each stop, while the last columns show the last service. The two middle columns (every hour at) show when buses depart between the first and last service. Example: 24/54 means that this bus departs from the station every hour at minute 24 and 54 (e.g. at 15.24 hrs and 15.54 hrs).

Bus Line #1 from Oberhochsteg via ZUP to Main Station (Island)

	earliest	Saturday	Sunday	every hour at		latest
Oberhochsteg	5.24	6.24	7.24	24	54	22.24
Rickenbach	5.25	6.25	7.25	25	55	22.25
Bayerstraße	5.26	6.26	7.26	26	56	22.26
Nobelstraße	5.27	6.27	7.27	27	57	22.27
Wannental	5.28	6.28	7.28	28	58	22.28
Lugeck	5.29	6.29	7.29	29	59	22.29
Schule Reutin	5.30	6.30	7.30	30	00	22.30
Wiedemannstraße	5.31	6.31	7.31	31	01	22.31
Josefskirche	5.32	6.32	7.32	32	02	22.32
Köchlin	5.34	6.34	7.34	34	04	22.34
Blauwiese	5.35	6.35	7.35	35	05	22.35
Bodensee-Gymnasium	5.36	6.36	7.36	36	06	22.36
Anheggerstraße (ZUP)	5.40	6.40	7.40	40	10	22.40
Langenweg	5.41	6.41	7.41	41	11	22.41
Toskana	5.42	6.42	7.42	42	12	22.42
Heidenmauer	5.43	6.43	7.43	43	13	22.43
Inselhalle	5.44	6.44	7.44	44	14	22.44
Hauptbahnhof/Insel an	5.46	6.46	7.46	46	16	22.46

Bus Line #1 from Main Station (Island) via ZUP to Oberhochsteg

	earliest	Saturday	Sunday	every hour at		latest
Hauptbahnhof/Insel	5.21	6.21	7.21	21	51	22.21
Altes Rathaus	5.28	6.28	7.28	28	58	22.28
Stadttheater	5.30	6.30	7.30	30	00	22.30
Maxhof	5.31	6.31	7.31	31	01	22.31
Toskana	5.33	6.33	7.33	33	03	22.33
Langenweg	5.34	6.34	7.34	34	04	22.34
Anheggerstraße (ZUP)	5.40	6.40	7.40	40	10	22.40
Bodensee-Gymnasium	5.41	6.41	7.41	41	11	22.41
Blauwiese	5.42	6.42	7.42	42	12	22.42
Köchlin	5.43	6.43	7.43	43	13	22.43
Josefskirche	5.44	6.44	7.44	44	14	22.44
Wiedemannstraße	5.45	6.45	7.45	45	15	22.45
Schule Reutin	5.46	6.46	7.46	46	16	22.46
Lugeck	5.47	6.47	7.47	47	17	22.47
Wannental	5.48	6.48	7.48	48	18	22.48
Nobelstraße	5.49	6.49	7.49	49	19	22.49
Bayerstraße	5.50	6.50	7.50	50	20	22.50
Rickenbach	5.51	6.51	7.51	51	21	22.51
Oberhochsteg an	5.53	6.53	7.53	53	23	22.53

Bus Line #2 from Unterreitnau via ZUP to Main Station (Island)

	earliest	Saturday	Sunday	every hour at		latest
Unterreitnau	5.24	6.24	7.24	24	54	22.24
Eggatsweiler	5.25	6.25	7.25	25	55	22.25
Schönau	5.28	6.28	7.28	28	58	22.28
Entenberg	5.29	6.29	7.29	29	59	22.29
Hoyren	5.30	6.30	7.30	30	00	22.30
Hochbuch	5.32	6.32	7.32	32	02	22.32
Heimesreutin	5.33	6.33	7.33	33	03	22.33
Gstäudweg	5.34	6.34	7.34	34	04	22.34
Schloß Moos	5.35	6.35	7.35	35	05	22.35
Christuskirche	5.36	6.36	7.36	36	06	22.36
Anheggerstraße (ZUP)	5.40	6.40	7.40	40	10	22.40
Langenweg	5.41	6.41	7.41	41	11	22.41
Toskana	5.42	6.42	7.42	42	12	22.42
Heidenmauer	5.43	6.43	7.43	43	13	22.43
Inselhalle	5.44	6.44	7.44	44	14	22.44
Westliche Insel	5.45	6.45	7.45	45	15	22.45
Hauptbahnhof/Insel an	5.50	6.50	7.50	50	20	22.50

Bus Line #2 from Main Station (Island) via ZUP to Unterreitnau

	earliest	Saturday	Sunday	every hour at		latest
Hauptbahnhof/Insel	5.26	6.26	7.26	26	56	22.26
Altes Rathaus	5.28	6.28	7.28	28	58	22.28
Stadttheater	5.30	6.30	7.30	30	00	22.30
Maxhof	5.31	6.31	7.31	31	01	22.31
Toskana	5.33	6.33	7.33	33	03	22.33
Langenweg	5.34	6.34	7.34	34	04	22.34
Anheggerstraße (ZUP)	5.40	6.40	7.40	40	10	22.40
Christuskirche	5.41	6.41	7.41	41	11	22.41
Schloß Moos	5.42	6.42	7.42	42	12	22.42
Gstäudweg	5.43	6.43	7.43	43	13	22.43
Heimesreutin	5.44	6.44	7.44	44	14	22.44
Hochbuch	5.45	6.45	7.45	45	15	22.45
Hoyren	5.47	6.47	7.47	47	17	22.47
Entenberg	5.48	6.48	7.48	48	18	22.48
Schönau	5.49	6.49	7.49	49	19	22.49
Unterreitnau an	5.53	6.53	7.53	53	23	22.53

Bus Line #3 from Oberreitnau Nord via ZUP to Grenzsiedlung/Zech

	earliest	Saturday	Sunday	every hour at		latest
Oberreitnau Nord	5.23	6.23	7.23	23	53	22.23
Emersberg/Oberreitnau	5.24	6.24	7.24	24	54	22.24
Marienplatz/Oberreitnau	5.25	6.25	7.25	25	55	22.25
Kapelle	5.26	6.26	7.26	26	56	22.26
Paradies	5.27	6.27	7.27	27	57	22.27
Schönau	5.29	6.29	7.29	29	59	22.29
Entenberg	5.30	6.30	7.30	30	00	22.30
Hoyren	5.31	6.31	7.31	31	01	22.31
Krankenhaus	5.33	6.33	7.33	33	03	22.33
Holbeinstraße	5.34	6.34	7.34	34	04	22.34
Am Torggel	5.35	6.35	7.35	35	05	22.35
Aeschach	5.36	6.36	7.36	36	06	22.36
Anheggerstraße (ZUP)	5.40	6.40	7.40	40	10	22.40
Jugendherberge/LIMARE	5.42	6.42	7.42	42	12	22.42
Berliner Platz	5.43	6.43	7.43	43	13	22.43
Buttlerhügel	5.44	6.44	7.44	44	14	22.44
Kamelbuckel	5.45	6.45	7.45	45	15	22.45
Stadtwerke	5.46	6.46	7.46	46	16	22.46
Von-Behring-Straße	5.46	6.46	7.46	46	16	22.46
Gewerbegebiet	5.47	6.47	7.47	47	17	22.47
Metzeler	5.48	6.48	7.48	48	18	22.48
Versöhnerkirche	5.49	6.49	7.49	49	19	22.49
Kopernikusplatz/Zech	5.52	6.52	7.52	52	22	22.52
Leiblachstraße	5.52	6.52	7.52	52	22	22.52
Grenzsiedlung/Zech an	5.55	6.55	7.55	55	25	22.55

Bus Line #3 from Grenzsiedlung/Zech via ZUP to Oberreitnau Nord

	earliest	Saturday	Sunday	every hour at		latest
Grenzsiedlung/Zech	5.25	6.25	7.25	25	55	22.25
Kunert	5.26	6.26	7.26	26	56	22.26
Metzeler	5.27	6.27	7.27	27	57	22.27
Gewerbegebiet	5.29	6.29	7.29	29	59	22.29
Von-Behring-Straße	5.30	6.30	7.30	30	00	22.30
Stadtwerke	5.30	6.30	7.30	30	00	22.30
Kamelbuckel	5.31	6.31	7.31	31	01	22.31
Buttlerhügel	5.32	6.32	7.32	32	02	22.32
Berliner Platz	5.33	6.33	7.33	33	03	22.33
Jugendherberge/LIMARE	5.35	6.35	7.35	35	05	22.35
Anheggerstraße (ZUP)	5.40	6.40	7.40	40	10	22.40
Aeschach	5.41	6.41	7.41	41	11	22.41
Am Torggel	5.42	6.42	7.42	42	12	22.42
Holbeinstraße	5.43	6.43	7.43	43	13	22.43
Krankenhaus	5.44	6.44	7.44	44	14	22.44
Hoyren	5.45	6.45	7.45	45	15	22.45
Entenberg	5.46	6.46	7.46	46	16	22.46
Schönau	5.47	6.47	7.47	47	17	22.47
Paradies	5.48	6.48	7.48	48	18	22.48
Kapelle	5.49	6.49	7.49	49	19	22.49
Marienplatz	5.50	6.50	7.50	50	20	22.50
Oberreitnau Nord an	5.52	6.52	7.52	52	22	22.52

Bus Line #4 from Rehlings/Weißensberg via ZUP to Alwind

	earliest	Saturday	Sunday	every hour at		latest
Rehlings/Weißensberg	5.23	6.23	7.23	23	53	22.23
Lindenstraße/Weißensberg	5.25	6.25	7.25	25	55	22.25
Motzacher Wald	5.28	6.28	7.28	28	58	22.28
Motzach	5.29	6.29	7.29	29	59	22.29
Inselbrauerei	5.30	6.30	7.30	30	00	22.30
Rotmoosstraße	5.31	6.31	7.31	31	01	22.31
Rennerle	5.33	6.33	7.33	33	03	22.33
Friedhof Aeschach	5.34	6.34	7.34	34	04	22.34
V.-Heider-Gymnasium	5.35	6.35	7.35	35	05	22.35
Anheggerstraße (ZUP)	5.40	6.40	7.40	40	10	22.40
Lärche	5.41	6.41	7.41	41	11	22.41
Musikschule	5.42	6.42	7.42	42	12	22.42
Wackerstraße	5.43	6.43	7.43	43	13	22.43
Giebelbach	5.44	6.44	7.44	44	14	22.44
Schwesternberg	5.45	6.45	7.45	45	15	22.45
Schachener Hof	5.46	6.46	7.46	46	16	22.46
Enzisweiler Post	5.48	6.48	7.48	48	18	22.48
Johannes d. Täufer	5.49	6.49	7.49	49	19	22.49
Ebnet	5.50	6.50	7.50	50	20	22.50
Degelstein	5.51	6.51	7.51	51	21	22.51
Alwind an	5.53	6.53	7.53	53	23	22.53

Bus Line #4 from Alwind via ZUP to Rehlings/Weißensberg

	earliest	Saturday	Sunday	every hour at		latest
Alwind	5.24	6.24	7.24	24	54	22.24
Degelstein	5.25	6.25	7.25	25	55	22.25
Ebnet	5.26	6.26	7.26	26	56	22.26
Johannes d. Täufer	5.27	6.27	7.27	27	57	22.27
Enzisweiler Post	5.28	6.28	7.28	28	58	22.28
Schachener Hof	5.30	6.30	7.30	30	00	22.30
Schwesternberg	5.31	6.31	7.31	31	01	22.31
Giebelbach	5.32	6.32	7.32	32	02	22.32
Wackerstraße	5.33	6.33	7.33	33	03	22.33
Musikschule	5.34	6.34	7.34	34	04	22.34
Lärche	5.35	6.35	7.35	35	05	22.35
Anheggerstraße (ZUP)	5.40	6.40	7.40	40	10	22.40
V.-Heider-Gymnasium	5.41	6.41	7.41	41	11	22.41
Friedhof Aeschach	5.42	6.42	7.42	42	12	22.42
Rennerle	5.43	6.43	7.43	43	13	22.43
Rotmoosstraße	5.45	6.45	7.45	45	15	22.45
Inselbrauerei	5.46	6.46	7.46	46	16	22.46
Hasenbank	5.47	6.47	7.47	47	17	22.47
Schönbühl	5.50	6.50	7.50	50	20	22.50
Niederhaus	5.51	6.51	7.51	51	21	22.51
Rehlings/Weißensberg an	5.52	6.52	7.52	52	22	22.52

Opening Hours Registration Desk

Sunday, 29 June	10.00 – 20.00
Monday, 30 June	08.30 – 14.00
Tuesday, 1 July	08.30 – 19.00
Wednesday, 2 July	08.30 – 19.00
Thursday, 3 July	08.30 – 14.00

Onsite Contacts

The office can be reached during the meeting as follows:

Registration Desk	+49 8382 260-633	Fax -660
Press Office	+49 8382 260-632	
email	info@lindau-nobel.org	
Emergency	112	
Taxi/cab	+49 8382 6006 or +49 8382 4455	

Scientific Chairmen of the 64th Lindau Nobel Laureate Meeting

Stefan H. E. Kaufmann
Director, Max Planck Institute for Infection Biology, Berlin, Germany
Professor for Microbiology and Immunology, Charité University Clinics, Berlin, Germany

Klas Kärre
Chairperson, Nobel Assembly for Physiology or Medicine at Karolinska Institutet, Stockholm, Sweden
Professor in Molecular Immunology, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden

Future Meetings

5th Lindau Meeting on Economic Sciences
19 – 23 August 2014

4th Interdisciplinary Lindau Nobel Laureate Meeting
28 June – 3 July 2015

66th Lindau Nobel Laureate Meeting (Physics)
26 June – 1 July 2016

Programme Editors: Susanne Wieczorek , Wolfgang Huang, Katja Merx, Nikolaus Turner

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Alfred-Nobel-Platz 1
88131 Lindau
Germany

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