



LINDAU  
NOBEL LAUREATE  
MEETINGS

64<sup>th</sup>

Lindau  
Nobel Laureate  
Meeting

Programme

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

## THE MEETINGS ONLINE

Lindau Blog

[blog.lindau-nobel.org](http://blog.lindau-nobel.org)

Lindau Mediatheque

[mediatheque.lindau-nobel.org](http://mediatheque.lindau-nobel.org)

Nobel Labs 360°

[nobellabs.lindau-nobel.org](http://nobellabs.lindau-nobel.org)

Lindau Alumni Community

[alumni.lindau-nobel.org](http://alumni.lindau-nobel.org)

Facebook

[www.facebook.com/LindauNobelLaureatesMeeting](http://www.facebook.com/LindauNobelLaureatesMeeting)

Twitter

[#lndm14](https://twitter.com/lindaunobel)

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With 37 Nobel Laureates and approximately 600 young scientists from more than 80 countries, the 64<sup>th</sup> 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 64<sup>th</sup> 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 traveling 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*



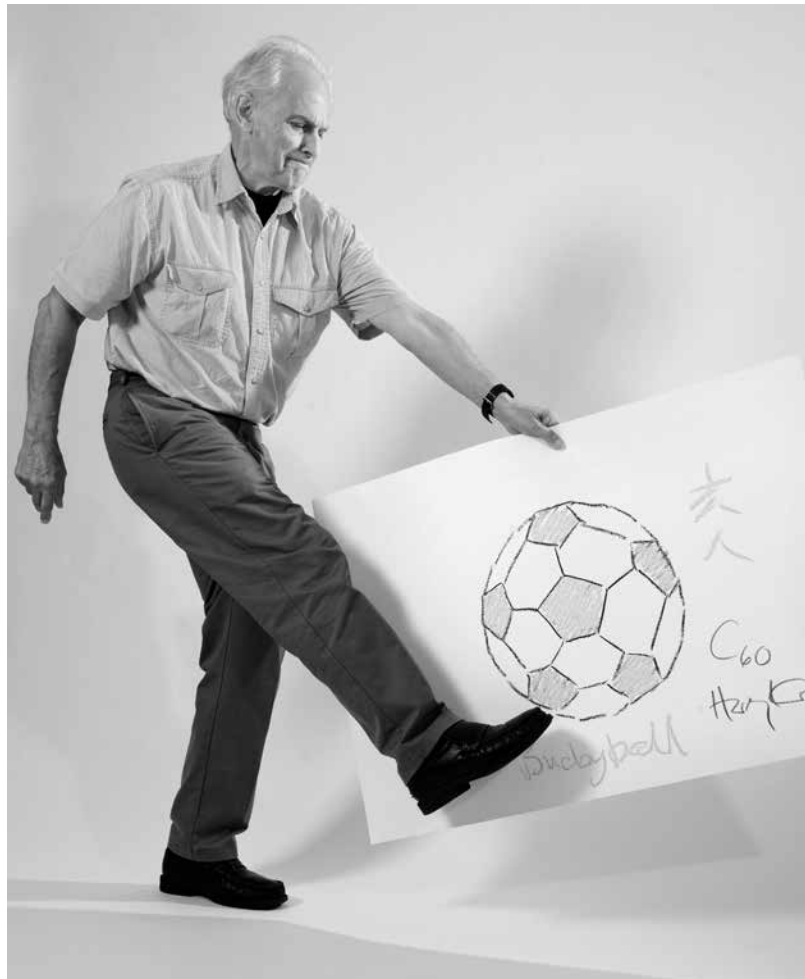
PETER AGRE WERNER ARBER FRANÇOISE BARRÉ-SINOUSSI  
 BRUCE A. BEUTLER J. MICHAEL BISHOP ELIZABETH H. BLACKBURN  
 MARTIN CHALFIE STEVEN CHU AARON CIECHANOVER JOHANN DEISENHOFER  
 MARTIN J. EVANS EDMOND H. FISCHER WALTER GILBERT JULES A. HOFFMANN  
 ROBERT HUBER TIM HUNT BRIAN K. KOBIŁKA WALTER KOHN JEAN-  
 MARIE LEHN BARRY J. MARSHALL HARTMUT MICHEL FERID MURAD  
 ERWIN NEHER BERT SAKMANN RANDY W. SCHEKMAN BRIAN P. SCHMIDT  
 HAMILTON O. SMITH OLIVER SMITHIES THOMAS A. STEITZ ROGER Y. TS'EN  
 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
07.00		<i>Science Breakfast</i>	<i>Science Breakfast</i>
		Science Breakfast upon invitation of	Science Breakfast upon invitation of
08.00		Australia	Else Kröner-Fresenius-Stiftung
09.00		<i>Lecture</i> Schekman	<i>Lecture</i> Barré-Sinoussi
		<i>Lecture</i> Warshel	<i>Lecture</i> Zinkernagel
10.00	Registration 10 - 20 hrs	<i>Lecture</i> Hoffmann	<i>Lecture</i> zur Hausen
		<i>Lecture</i> Beutler	<i>Lecture</i> Yonath
11.00		Coffee Break	Coffee Break
		<i>Lecture</i> Marshall	<i>Lecture</i> Steitz
12.00		<i>Lecture</i> Bishop	<i>Lecture</i> Kobilka
	<i>Lecture</i> Evans	<i>Lecture</i> Ciechanover	
13.00		<i>Lecture</i> Blackburn	<i>Lecture</i> Chu
14.00		Lunch Break upon invitation of Australia	Lunch Break
15.00	Opening Ceremony	<i>YS Discussions</i>	<i>YS Discussion</i>   <i>Lecture/Discussion</i>
16.00		Beutler   Bishop Blackburn   Evans Hoffmann   Marshall Warshel	Barré-Sinoussi Chu   Ciechanover   Kobilka   Steitz Yonath   Zinkernagel zur Hausen
17.00	Reception upon invitation of the Republic of Austria	Break	Break
	Concert Ensemble of the Vienna Philharmonic Orchestra	<i>Lecture &amp; Disc.</i>   <i>Master Classes</i>	<i>Presentation</i>   <i>Master Class</i>
18.00		Schmidt   Ciechanover Zinkernagel	offered by the European Commission   Lehn
19.00	<i>Social Function</i>	Break	Break
	Dinner at various locations limited attendance	<i>Social Function</i>	<i>Social Function</i>
20.00		International Get-Together upon invitation of Australia	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
21.00			
22.00			

# PROGRAMME OVERVIEW

	Wednesday, 2 July	Thursday, 3 July	Friday, 4 July
07.00	<i>Science Breakfast</i>	<i>Science Breakfast</i>	Baden-Württemberg Boat Trip to Mainau Island upon invitation of the State of Baden-Württemberg
	Science Breakfast upon invitation of	Science Breakfast upon invitation of	
08.00	Mars, Incorporated   McKinsey & Company, Inc.	Austrian Federal Ministry of Science, Research and Economy   German Cancer Research Center, DKFZ	
09.00	<i>Lecture</i> Smith	<i>Lecture</i> Michel	
	<i>Lecture</i> Agre	<i>Lecture</i> Deisenhofer	
10.00	<i>Lecture</i> Wüthrich	<i>Lecture</i> Huber	
	Coffee Break	Coffee Break	
11.00	<i>Lecture</i> Tsien	<i>Lecture</i> Arber	<i>Closing Panel Discussion</i>
	<i>Lecture</i> Lehn	<i>Lecture</i> Chalfie	Science for the Benefit of Mankind
12.00	<i>Lecture</i> Neher	<i>Lecture</i> Walker	Barré-Sinoussi, Bassioni, Mgone, Schmidt, Schütte
13.00	<i>Lecture</i> Sakmann	<i>Lecture</i> Smithies	
14.00	Lunch Break	Lunch Break	Lunch Break
15.00			
16.00	<i>Panel Discussion</i>	<i>Panel Discussion</i>	Farewell Ceremony
	Large Data and Hypothesis-Driven Science in the Era of Post-Genomic Biology Beutler, Bishop, Hoffmann, Schmidt	Academia and Industry: Exploring the Collaborative Landscapes of the Future Beutler, Goldman, Göttsche, Gomes, Malik, Wang	
17.00	Break	Break	Baden-Württemberg Boat Trip to Lindau upon invitation of the State of Baden-Württemberg
	<i>YS Discussions</i>	<i>YS Discussions</i>	
18.00	Agre   Lehn Neher   Sakmann   Smith Tsien   Wüthrich	Arber   Chalfie   Deisenhofer   Huber   Michel   Murad   Smithies   Walker	
19.00	Break	Break	
	<i>Presentation</i>	<i>Social Function</i>	
20.00	offered by the Global Young Academy	Bavarian Evening upon invitation of the Elite Network of Bavaria & Free State of Bavaria	
21.00	<i>Social Function</i>		
	Dinner		
22.00	Free Evening		



## 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.

<b>Partner Event</b>	<b>Women in Science: Fixing the Leaking Pipeline</b>
<b>07.00</b> Science Breakfast Forum am See	upon invitation of Australia <i>Elizabeth H. Blackburn</i> Department of Biochemistry and Biophysics, University of California <i>Suzanne Cory</i> Immediate Past President, Australian Academy of Science <i>Emma L. Johnston</i> School of Biological, Earth and Environmental Sciences & Evolution and Ecology Research Centre, UNSW Australia Director, Sydney Harbour Research Program, Sydney Institute of Marine Science <i>Brian P. Schmidt</i> The Research School of Astronomy and Astrophysics, The Australian National University <i>Moderator: Adam Spencer</i> Ambassador for Mathematics and Science, The University of Sydney Access: with online pre-registration only
<b>09.00</b> Plenary Lecture Inselhalle	<i>Randy W. Schekman</i> <b>Genes and Proteins that Control Secretion and Autophagy</b>
<b>09.30</b> Plenary Lecture Inselhalle	<i>Arieh Warshel</i> <b>Multiscale Simulations of the Functions of Biological Molecules</b>
<b>10.00</b> Plenary Lecture Inselhalle	<i>Jules A. Hoffmann</i> <b>Innate Immunity: From Flies to Humans</b>
<b>10.30</b> Plenary Lecture Inselhalle	<i>Bruce A. Beutler</i> <b>Deciphering Immunity by Making it Fail</b>
<b>11.00</b>	<b>Coffee Break</b> upon invitation of Australia
<b>11.30</b> Plenary Lecture Inselhalle	<i>Barry J. Marshall</i> <b>Man versus Helicobacter</b>

<b>12.00</b> Plenary Lecture Inselhalle	<i>J. Michael Bishop</i> <b>Forging a Genetic Paradigm for Cancer</b>
<b>12.30</b> Plenary Lecture Inselhalle	<i>Martin J. Evans</i> <b>Inheritance from Teratocarcinomas</b>
<b>13.00</b> Plenary Lecture Inselhalle	<i>Elizabeth H. Blackburn</i> <b>Adventures at the Ends of Chromosomes</b>
<b>13.30</b> Catering Tent	<b>Lunch Break</b> upon invitation of Australia Access: young scientists only
<b>15.30</b> Discussion Hotel Bay. Hof	<i>Bruce A. Beutler</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Evang. Hospital	<i>J. Michael Bishop</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Landratsamt	<i>Elizabeth H. Blackburn</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Altes Rathaus	<i>Martin J. Evans</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Hotel Bay. Hof	<i>Jules A. Hoffmann</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Forum am See	<i>Barry J. Marshall</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Altes Rathaus	<i>Arieh Warshel</i> <b>Discussion with young scientists</b>
<b>17.00</b>	<b>Break</b>

<b>17.30</b> Lecture & Disc. City Theatre	<i>Brian P. Schmidt</i> <b>Cosmology: An Example of the Process of Discovery</b>
<b>17.30</b> Master Class Altes Rathaus	<i>Master Class with Aaron Ciechanover</i> <b>Biology in the Service of Medicine</b> <i>Young scientists (tbd)</i> Access: with online pre-registration only
<b>17.30</b> Master Class Altes Rathaus	<i>Master Class with Rolf M. Zinkernagel</i> <b>Pandemic Threats</b> <i>Young scientists (tbd)</i> Access: with online pre-registration only
<b>19.00</b>	<b>Break</b>

HAVING A BRILLIANT THOUGHT?

Share it with us at  
[twitter.com](https://twitter.com/#lnlm14) (#lnlm14)



<b>19.30</b> Social Function Inselhalle	<b>International Get-Together</b> upon invitation of Australia
	<b>Welcome</b> <i>Countess Bettina Bernadotte</i> President of the Council
	<b>Welcome Address</b> <i>The Hon Andrew Robb AO MP</i> Australian Minister for Trade and Investment
	<b>Cultural Performance</b> <i>Genevieve Lacey</i> Recorder Virtuoso <i>Marshall McGuire</i> Harpist
	<b>Diving into Research</b> <i>Emma L. Johnston</i> School of Biological, Earth and Environmental Sciences & Evolution and Ecology Research Centre, UNSW Australia Director, Sydney Harbour Research Program, Sydney Institute of Marine Science
	<b>Master of Ceremonies</b> <i>Adam Spencer</i> Ambassador for Mathematics and Science, The University of Sydney
	<b>Dinner</b>
	<b>Dance</b>
	Access: all participants



<b>Partner Event</b>	<b>Science in Clinical Medicine</b>
<b>07.00</b> Science Breakfast Forum am See	upon invitation of Else Kröner-Fresenius-Stiftung <i>J. Michael Bishop</i> Director, The G.W. Hooper Research Foundation, University of California <i>Stephan Halle</i> Institute of Immunology, Hannover Medical School <i>Christoph Klein</i> Chair, Department of Pediatrics, Dr. von Hauner Children's Hospital, Ludwig Maximilians University Munich <i>Moderator: Susanne Schultz-Hector</i> Member of the Board, Else Kröner-Fresenius-Stiftung Access: with online pre-registration only
<b>09.00</b> Plenary Lecture Inselhalle	<i>Françoise Barré-Sinoussi</i> <b>On the Road Towards an HIV Cure</b>
<b>9.30</b> Plenary Lecture Inselhalle	<i>Rolf M. Zinkernagel</i> <b>Why do we not have a Vaccine Against HIV or Tuberculosis?</b>
<b>10.00</b> Plenary Lecture Inselhalle	<i>Harald zur Hausen</i> <b>Infections Linked to Human Cancers: Mechanisms and Synergisms</b>
<b>10.30</b> Plenary Lecture Inselhalle	<i>Ada E. Yonath</i> <b>Towards Control of Species-Specific Antibiotics Resistance</b>
<b>11.00</b>	<b>Coffee Break</b>
<b>11.30</b> Plenary Lecture Inselhalle	<i>Thomas A. Steitz</i> <b>From the Structure of the Ribosome to the Design of New Antibiotics</b>
<b>12.00</b> Plenary Lecture Inselhalle	<i>Brian K. Kobilka</i> <b>G Protein-Coupled Receptors: Challenges for Drug Discovery</b>

<b>12.30</b> Plenary Lecture Inselhalle	<i>Aaron Ciechanover</i> <b>The Revolution of Personalized Medicine: Are we going to Cure all Diseases and at What Price?</b>
<b>13.00</b> Plenary Lecture Inselhalle	<i>Steven Chu</i> <b>You can see a lot by observing: Optical Microscopy 2.0</b>
<b>13.30</b> Catering Tent	<b>Lunch Break</b> Access: for young scientists only
<b>15.30</b> Lecture & Disc. Altes Rathaus	<i>Edmond H. Fischer</i> <b>Cell Signaling by Protein Phosphorylation</b>
<b>15.30</b> Lecture & Disc. Landratsamt	<i>Walter Kohn</i> <b>Macular Distortation - Diagnosis and Correction</b>
<b>15.30</b> Lecture & Disc. Altes Rathaus	<i>Torsten N. Wiesel</i> <b>A Homage to David Hubel: Early days in our Studies of the Visual Cortex</b>
<b>15.30</b> Discussion Inselhalle	<i>Françoise Barré-Sinoussi</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion City Theatre	<i>Steven Chu</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Evang. Hospital	<i>Aaron Ciechanover</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Hotel Bay. Hof	<i>Brian K. Kobilka</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Hotel Bay. Hof	<i>Thomas A. Steitz</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Forum am See	<i>Ada E. Yonath</i> <b>Discussion with young scientists</b>

## TUESDAY, 1 JULY

<b>15.30</b> Discussion Altes Rathaus	<i>Rolf M. Zinkernagel</i> <b>Discussion with young scientists</b>
<b>15.30</b> Discussion Inselhalle	<i>Harald zur Hausen</i> <b>Discussion with young scientists</b>
<b>17.00</b>	<b>Break</b>
<b>17.30</b> Master Class Altes Rathaus	<i>Master Class with Jean-Marie Lehn</i> <b>Approaches to Molecular Drug Discovery</b> <i>Young scientists (tbd)</i> Access: with online pre-registration only
<b>Partner Event</b> <b>17.30</b> Presentation Inselhalle	<b>Excellence in Research – Europe’s Ticket to Our Future</b> 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. <i>Moderator: Mike W. Rogers</i> Research careers, Marie Skłodowska-Curie Actions DG Education & Culture, European Commission Access: all participants
<b>19.00</b>	<b>Break</b>
<b>19.30</b> Social Function Various Locations	<b>Academic Dinners</b> upon invitation of the Academic Partners Access: by invitation only
<b>19.30</b> Social Function Toskanapark	<b>Grill &amp; Chill: Connecting Cultures</b> upon invitation of the Council & Foundation Access: by invitation only

## WEDNESDAY, 2 JULY

<b>Partner Event</b> <b>07.00</b> Science Breakfast Forum am See	<b>Addressing the Challenges of Ageing Research through Cross-Disciplinary Collaboration</b> upon invitation of Mars, Incorporated <i>Elizabeth H. Blackburn</i> Department of Biochemistry and Biophysics, University of California, San Francisco <i>Hagen Schroeter</i> Director, Fundamental Health and Nutrition Research, Mars, Incorporated Adjunct Research Professor, Nutrition Dept., University of California, Davis <i>Young scientist (tbd)</i> <i>Moderator: Adam Smith</i> Chief Scientific Officer, Nobel Media AB Access: with online pre-registration only
<b>Partner Event</b> <b>07.00</b> Science Breakfast Hotel Bay. Hof	<b>Scientific Leadership in the 21st Century: Running Productive Labs, Leading Great People, Leading Self</b> upon invitation of McKinsey & Company, Inc. <i>Steven Chu</i> Physics Department, Stanford University <i>Frank Mattern</i> Director, McKinsey & Company, Inc. <i>Young scientist (tbd)</i> <i>Moderator: Matthias Evers</i> Principal, McKinsey & Company, Inc. Access: with online pre-registration only
<b>09.00</b> Plenary Lecture Inselhalle	<i>Hamilton O. Smith</i> <b>Synthetic Biology for Genetic Engineering in the 21st Century</b>
<b>09.30</b> Plenary Lecture Inselhalle	<i>Peter Agre</i> <b>Aquaporin Water Channels - from Atomic Structure to Malaria</b>

## WEDNESDAY, 2 JULY

<b>10.00</b> Plenary Lecture Inselhalle	<i>Kurt Wüthrich</i> <b>A Personal View of the History of Nuclear Magnetic Resonance in Biology and Medicine</b>
<b>10.30</b>	<b>Coffee Break</b>
<b>11.30</b> Plenary Lecture Inselhalle	<i>Roger Y. Tsien</i> <b>Molecules Against Cancer or for Long-Term Memory Storage</b>
<b>12.00</b> Plenary Lecture Inselhalle	<i>Jean-Marie Lehn</i> <b>Perspectives in Chemistry - Towards Adaptive Chemistry</b>
<b>12.30</b> Plenary Lecture Inselhalle	<i>Erwin Neher</i> <b>Short-Term Synaptic Plasticity</b>
<b>13.00</b> Plenary Lecture Inselhalle	<i>Bert Sakmann</i> <b>Cortical Circuit and Decision Making</b>
<b>13.30</b> Catering Tent	<b>Lunch Break</b> Access: for young scientists only
<b>15.30</b> Panel Discussion Inselhalle	<b>Panel Discussion: Large Data and Hypothesis-Driven Science in the Era of Post-Genomic Biology</b> <i>Bruce A. Beutler</i> Center for the Genetics of Host Defense, UT Southwestern Medical Center at Dallas <i>J. Michael Bishop</i> The G.W. Hooper Research Foundation, University of California <i>Jules A. Hoffmann</i> Molecular and Cellular Biology Institute, Université de Strasbourg <i>Brian P. Schmidt</i> The Research School of Astronomy and Astrophysics, The Australian National University <i>Moderator: Stefan H.E. Kaufmann</i> Director, Max Planck Institute for Infection Biology
<b>17.00</b>	<b>Break</b>

## WEDNESDAY, 2 JULY

<b>17.30</b> Discussion Landratsamt	<i>Peter Agre</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Altes Rathaus	<i>Jean-Marie Lehn</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Hotel Bay. Hof	<i>Erwin Neher</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Hotel Bay. Hof	<i>Bert Sakmann</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Evang. Hospital	<i>Hamilton O. Smith</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Forum am See	<i>Roger Y. Tsien</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Altes Rathaus	<i>Kurt Wüthrich</i> <b>Discussion with young scientists</b>
<b>19.00</b>	<b>Break</b>
<b>Partner Event</b> <b>19.30</b> Presentation Inselhalle	<b>Excellent Young Scientists Aiming to Change the World: The Global Young Academy</b> <i>Moderators:</i> <i>Heidi Wedel</i> Global Young Academy Berlin, Managing Director <i>Marc Creus</i> Global Young Academy member Group Leader at the Laboratory of Molecular Evolution at the Department of Chemistry, University of Basel Access: all participants
<b>20.00</b> Catering Tent	<b>Dinner</b> Access: young scientists only

WANT TO DISCUSS SCIENCE?

Visit the meeting blog at  
[blog.lindau-nobel.org](http://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**

<b>10.30</b> Plenary Lecture Inselhalle	<i>Ferid Murad</i> <b>Discovery of Nitric Oxide and Cyclic GMP in Cell Signaling and Their Role in Drug Development</b>
<b>11.00</b>	<b>Coffee Break</b>
<b>11.30</b> Plenary Lecture Inselhalle	<i>Werner Arber</i> <b>Biological Evolution in the Context of Cosmic Evolution and of Cultural Evolution</b>
<b>12.00</b> Plenary Lecture Inselhalle	<i>Martin Chalfie</i> <b>Tickling Worms: Surprises from Basic Research</b>
<b>12.30</b> Plenary Lecture Inselhalle	<i>John E. Walker</i> <b>Generating the Fuel of Life</b>
<b>13.00</b> Plenary Lecture Inselhalle	<i>Oliver Smithies</i> <b>Where do Ideas come from?</b>
<b>13.30</b> Catering Tent	<b>Lunch Break</b> Access: for young scientists only
<b>15.30</b> Panel Discussion City Theatre	<b>Panel Discussion: Academia and Industry – Exploring the Collaborative Landscapes of the Future</b> <i>Bruce A. Beutler</i> Center for the Genetics of Host Defense, UT Southwestern Medical Center at Dallas <i>Michel Goldman</i> Executive Director of the Innovative Medicines Initiative <i>Peter C. Gøtzsche</i> Director of the Nordic Cochrane Center <i>Renata Mota Gomes</i> University of Oxford, Cardiovascular Regeneration & Vascular Disease <i>Kemal Malik</i> Member of the Board of Management of Bayer AG, Innovations <i>Stan Wang</i> University of Cambridge, Department of Surgery & Gurdon Institute <i>Moderator: Adam Smith</i> Chief Scientific Officer, Nobel Media AB

<b>17.00</b>	<b>Break</b>
<b>17.30</b> Discussion Hotel Bayerischer Hof	<i>Werner Arber</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Hotel Bayerischer Hof	<i>Martin Chalfie</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Altes Rathaus	<i>Johann Deisenhofer</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Altes Rathaus	<i>Robert Huber</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Altes Rathaus	<i>Hartmut Michel</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Landratsamt	<i>Ferid Murad</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Forum am See	<i>Oliver Smithies</i> <b>Discussion with young scientists</b>
<b>17.30</b> Discussion Evang. Hospital	<i>John E. Walker</i> <b>Discussion with young scientists</b>
<b>19.00</b>	<b>Break</b>

## THURSDAY, 3 JULY

**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

## FRIDAY, 4 JULY

**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  
Toast by Simone Schwanitz (Permanent Secretary Ministry of Science,  
Research and the Arts, 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)****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](http://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 under-expression 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 <sup>1</sup>. 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. 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 from 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 blood-

stream 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 describing 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](http://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). Supremol ([www.Supremol.com](http://www.Supremol.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 Fcγ 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](http://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, tetrahydrobiopterin, 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 antacid, 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

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 programs 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 industries will also be discussed.

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*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.

*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-binding 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.

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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 (*Mycoplasma 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 re-

duced segments are viable. We are now refining our design so as to achieve a viable cell containing all 8 of the reduced segments.

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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 ratchet-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 enzymes. 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  $\alpha$ -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  $\alpha$ -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 extracel-

lular 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.

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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 neuromuscu-

lar 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, IF<sub>1</sub>, 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 F<sub>1</sub> ATPase, F<sub>0</sub> 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.

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*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.

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*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 Tuberculosis?**

*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 conclu-

sion 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:

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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*

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**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, Malik, Wang*

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**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*

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**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 ques-

## ABSTRACTS

tion 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.

### 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)<sup>1</sup>. Australia is taking steps to plan its own initiative.

The panel will briefly talk about their personal experiences, and how uni-



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versities 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<sup>1</sup>. 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 Re-

search 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.

<sup>1</sup> *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](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](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 pre-clinical 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

## ABSTRACTS

(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 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.

## ABSTRACTS

### FINDING ABSTRACTS TOO ABSTRACT?

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

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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

## ABOUT THE MEETINGS

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*

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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*

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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*

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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



## ABOUT THE MEETINGS

### *Programme Session Types*

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The 64<sup>th</sup> 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.

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Wissenschaftsgemeinschaft Gottfried Wilhelm Leibniz e. V.  
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# LINDAU ISLAND MAP



Inselhalle

Evangelisches Hospital

Toskanapark

City Museum

Landratsamt


City Theatre

Forum am See

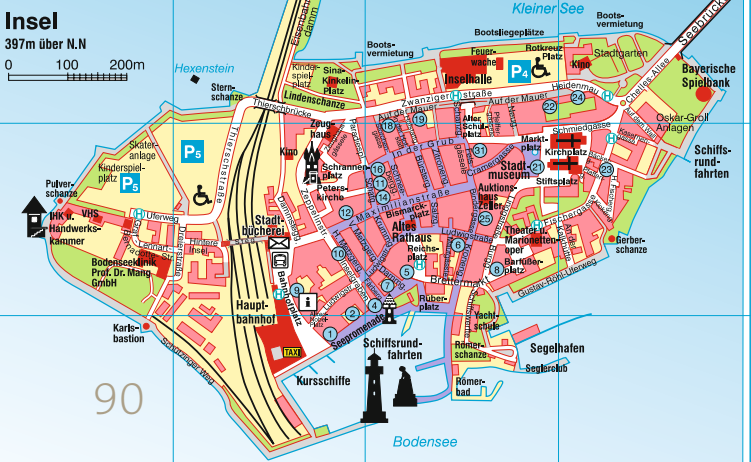
Altes Rathaus

Hotel Bayerischer Hof

Lindau Harbour

 Bus stop

# LINDAU VICINITY MAP



0 100 500 1000 m

# 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).

	earliest Saturday	Sunday	every hour at	latest		earliest Saturday	Sunday	every hour at	latest		
<b>Bus Line #1 from Oberhochsteg via ZUP to Main Station (Island)</b>					<b>Bus Line #1 from Main Station (Island) via ZUP to Oberhochsteg</b>						
Oberhochsteg	5.24	6.24	7.24	24 54	22.24	Hauptbahnhof/Insel	5.21	6.21	7.21	21 51	22.21
Rickenbach	5.25	6.25	7.25	25 55	22.25	Altes Rathaus	5.28	6.28	7.28	28 58	22.28
Bayerstraße	5.26	6.26	7.26	26 56	22.26	Stadttheater	5.30	6.30	7.30	30 00	22.30
Nobelstraße	5.27	6.27	7.27	27 57	22.27	Maxhof	5.31	6.31	7.31	31 01	22.31
Wannental	5.28	6.28	7.28	28 58	22.28	Toskana	5.33	6.33	7.33	33 03	22.33
Lugeck	5.29	6.29	7.29	29 59	22.29	Langenweg	5.34	6.34	7.34	34 04	22.34
Schule Reutin	5.30	6.30	7.30	30 00	22.30	Anheggerstraße (ZUP)	5.40	6.40	7.40	40 10	22.40
Wiedemannstraße	5.31	6.31	7.31	31 01	22.31	Bodensee-Gymnasium	5.41	6.41	7.41	41 11	22.41
Josefskirche	5.32	6.32	7.32	32 02	22.32	Blauwiese	5.42	6.42	7.42	42 12	22.42
Köchlin	5.34	6.34	7.34	34 04	22.34	Köchlin	5.43	6.43	7.43	43 13	22.43
Blauwiese	5.35	6.35	7.35	35 05	22.35	Josefskirche	5.44	6.44	7.44	44 14	22.44
Bodensee-Gymnasium	5.36	6.36	7.36	36 06	22.36	Wiedemannstraße	5.45	6.45	7.45	45 15	22.45
Anheggerstraße (ZUP)	5.40	6.40	7.40	40 10	22.40	Schule Reutin	5.46	6.46	7.46	46 16	22.46
Langenweg	5.41	6.41	7.41	41 11	22.41	Lugeck	5.47	6.47	7.47	47 17	22.47
Toskana	5.42	6.42	7.42	42 12	22.42	Wannental	5.48	6.48	7.48	48 18	22.48
Heidenmauer	5.43	6.43	7.43	43 13	22.43	Nobelstraße	5.49	6.49	7.49	49 19	22.49
Inselhalle	5.44	6.44	7.44	44 14	22.44	Bayerstraße	5.50	6.50	7.50	50 20	22.50
Hauptbahnhof/Insel an	5.46	6.46	7.46	46 16	22.46	Rickenbach	5.51	6.51	7.51	51 21	22.51
						Oberhochsteg an	5.53	6.53	7.53	53 23	22.53

	earliest Saturday	Sunday	every hour at	latest		earliest Saturday	Sunday	every hour at	latest		
<b>Bus Line #2 from Unterreitnau via ZUP to Main Station (Island)</b>					<b>Bus Line #2 from Main Station (Island) via ZUP to Unterreitnau</b>						
Unterreitnau	5.24	6.24	7.24	24 54	22.24	Hauptbahnhof/Insel	5.26	6.26	7.26	26 56	22.26
Eggatsweiler	5.25	6.25	7.25	25 55	22.25	Altes Rathaus	5.28	6.28	7.28	28 58	22.28
Schönau	5.28	6.28	7.28	28 58	22.28	Stadttheater	5.30	6.30	7.30	30 00	22.30
Entenberg	5.29	6.29	7.29	29 59	22.29	Maxhof	5.31	6.31	7.31	31 01	22.31
Hoyren	5.30	6.30	7.30	30 00	22.30	Toskana	5.33	6.33	7.33	33 03	22.33
Hochbuch	5.32	6.32	7.32	32 02	22.32	Langenweg	5.34	6.34	7.34	34 04	22.34
Heimesreutin	5.33	6.33	7.33	33 03	22.33	Anheggerstraße (ZUP)	5.40	6.40	7.40	40 10	22.40
Gstäudweg	5.34	6.34	7.34	34 04	22.34	Christuskirche	5.41	6.41	7.41	41 11	22.41
Schloß Moos	5.35	6.35	7.35	35 05	22.35	Schloß Moos	5.42	6.42	7.42	42 12	22.42
Christuskirche	5.36	6.36	7.36	36 06	22.36	Gstäudweg	5.43	6.43	7.43	43 13	22.43
Anheggerstraße (ZUP)	5.40	6.40	7.40	40 10	22.40	Heimesreutin	5.44	6.44	7.44	44 14	22.44
Langenweg	5.41	6.41	7.41	41 11	22.41	Hochbuch	5.45	6.45	7.45	45 15	22.45
Toskana	5.42	6.42	7.42	42 12	22.42	Hoyren	5.47	6.47	7.47	47 17	22.47
Heidenmauer	5.43	6.43	7.43	43 13	22.43	Entenberg	5.48	6.48	7.48	48 18	22.48
Inselhalle	5.44	6.44	7.44	44 14	22.44	Schönau	5.49	6.49	7.49	49 19	22.49
Westliche Insel	5.45	6.45	7.45	45 15	22.45	Unterreitnau an	5.53	6.53	7.53	53 23	22.53
Hauptbahnhof/Insel an	5.50	6.50	7.50	50 20	22.50						

	earliest Saturday	Sunday	every hour at	latest		earliest Saturday	Sunday	every hour at	latest		
<b>Bus Line #3 from Oberreitnau Nord via ZUP to Grenzsiedlung/Zech</b>					<b>Bus Line #3 from Grenzsiedlung/Zech via ZUP to Oberreitnau Nord</b>						
Oberreitnau Nord	5.23	6.23	7.23	23 53	22.23	Grenzsiedlung/Zech	5.25	6.25	7.25	25 55	22.25
Emersberg/Oberreitnau	5.24	6.24	7.24	24 54	22.24	Kunert	5.26	6.26	7.26	26 56	22.26
Marienplatz/Oberreitnau	5.25	6.25	7.25	25 55	22.25	Metzler	5.27	6.27	7.27	27 57	22.27
Kapelle	5.26	6.26	7.26	26 56	22.26	Gewerbegebiet	5.29	6.29	7.29	29 59	22.29
Paradies	5.27	6.27	7.27	27 57	22.27	Von-Behring-Straße	5.30	6.30	7.30	30 00	22.30
Schönau	5.29	6.29	7.29	29 59	22.29	Stadtwerke	5.30	6.30	7.30	30 00	22.30
Entenberg	5.30	6.30	7.30	30 00	22.30	Kamelbuckel	5.31	6.31	7.31	31 01	22.31
Hoyren	5.31	6.31	7.31	31 01	22.31	Buttlerhügel	5.32	6.32	7.32	32 02	22.32
Krankenhaus	5.33	6.33	7.33	33 03	22.33	Berliner Platz	5.33	6.33	7.33	33 03	22.33
Holbeinstraße	5.34	6.34	7.34	34 04	22.34	Jugendherberge/LIMARE	5.35	6.35	7.35	35 05	22.35
Am Torggel	5.35	6.35	7.35	35 05	22.35	Anheggerstraße (ZUP)	5.40	6.40	7.40	40 10	22.40
Aeschach	5.36	6.36	7.36	36 06	22.36	Aeschach	5.41	6.41	7.41	41 11	22.41
Anheggerstraße (ZUP)	5.40	6.40	7.40	40 10	22.40	Am Torggel	5.42	6.42	7.42	42 12	22.42
Jugendherberge/LIMARE	5.42	6.42	7.42	42 12	22.42	Holbeinstraße	5.43	6.43	7.43	43 13	22.43
Berliner Platz	5.43	6.43	7.43	43 13	22.43	Krankenhaus	5.44	6.44	7.44	44 14	22.44
Buttlerhügel	5.44	6.44	7.44	44 14	22.44	Hoyren	5.45	6.45	7.45	45 15	22.45
Kamelbuckel	5.45	6.45	7.45	45 15	22.45	Entenberg	5.46	6.46	7.46	46 16	22.46
Stadtwerke	5.46	6.46	7.46	46 16	22.46	Schönau	5.47	6.47	7.47	47 17	22.47
Von-Behring-Straße	5.46	6.46	7.46	46 16	22.46	Paradies	5.48	6.48	7.48	48 18	22.48
Gewerbegebiet	5.47	6.47	7.47	47 17	22.47	Kapelle	5.49	6.49	7.49	49 19	22.49
Metzler	5.48	6.48	7.48	48 18	22.48	Marienplatz	5.50	6.50	7.50	50 20	22.50
Versöhnerkirche	5.49	6.49	7.49	49 19	22.49	Oberreitnau Nord an	5.52	6.52	7.52	52 22	22.52
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						

	earliest Saturday	Sunday	every hour at	latest		earliest Saturday	Sunday	every hour at	latest		
<b>Bus Line #4 from Rehlings/Weißenberg via ZUP to Alwind</b>					<b>Bus Line #4 from Alwind via ZUP to Rehlings/Weißenberg</b>						
Rehlings/Weißenberg	5.23	6.23	7.23	23 53	22.23	Alwind	5.24	6.24	7.24	24 54	22.24
Lindenstraße/Weißenberg	5.25	6.25	7.25	25 55	22.25	Degelstein	5.25	6.25	7.25	25 55	22.25
Motzacher Wald	5.28	6.28	7.28	28 58	22.28	Ebnet	5.26	6.26	7.26	26 56	22.26
Motzsch	5.29	6.29	7.29	29 59	22.29	Johannes d. Täufer	5.27	6.27	7.27	27 57	22.27
Inselbrauerei	5.30	6.30	7.30	30 00	22.30	Enzisweiler Post	5.28	6.28	7.28	28 58	22.28
Rotmoosstraße	5.31	6.31	7.31	31 01	22.31	Schachener Hof	5.30	6.30	7.30	30 00	22.30
Rennerle	5.33	6.33	7.33	33 03	22.33	Schwesterberg	5.31	6.31	7.31	31 01	22.31
Friedhof Aeschach	5.34	6.34	7.34	34 04	22.34	Giebelbach	5.32	6.32	7.32	32 02	22.32
V.-Heider-Gymnasium	5.35	6.35	7.35	35 05	22.35	Wackerstraße	5.33	6.33	7.33	33 03	22.33
Anheggerstraße (ZUP)	5.40	6.40	7.40	40 10	22.40	Musikschule	5.34	6.34	7.34	34 04	22.34
Langenweg	5.41	6.41	7.41	41 11	22.41	Lärche	5.35	6.35	7.35	35 05	22.35
Musikschule	5.42	6.42	7.42	42 12	22.42	Anheggerstraße (ZUP)	5.40	6.40	7.40	40 10	22.40
Wackerstraße	5.43	6.43	7.43	43 13	22.43	V.-Heider-Gymnasium	5.41	6.41	7.41	41 11	22.41
Giebelbach	5.44	6.44	7.44	44 14	22.44	Friedhof Aeschach	5.42	6.42	7.42	42 12	22.42
Schwesterberg	5.45	6.45	7.45	45 15	22.45	Rennerle	5.43	6.43	7.43	43 13	22.43
Schachener Hof	5.46	6.46	7.46	46 16	22.46	Rotmoosstraße	5.45	6.45	7.45	45 15	22.45
Enzisweiler Post	5.48	6.48	7.48	48 18	22.48	Inselbrauerei	5.46	6.46	7.46	46 16	22.46
Johannes d. Täufer	5.49	6.49	7.49	49 19	22.49	Hasenbank	5.47	6.47	7.47	47 17	22.47
Ebnet	5.50	6.50	7.50	50 20	22.50	Schönbühl	5.50	6.50	7.50	50 20	22.50
Degelstein	5.51	6.51	7.51	51 21	22.51	Niederhaus	5.51	6.51	7.51	51 21	22.51
Alwind an	5.53	6.53	7.53	53 23	22.53	Rehlings/Weißenberg an	5.52	6.52	7.52	52 22	22.52







LINDAU  
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Alfred-Nobel-Platz 1  
88131 Lindau  
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