35th ALTENBERG WORKSHOP IN THEORETICAL BIOLOGY

A Revised Theory of Cancer

organized by

Mina J. Bissell, Ingemar Ernberg, and Bernhard Strauss

November 9–12, 2017

KLI, Klosterneuburg

Austria

This Workshop is dedicated to the memory of Susan Lindquist (Whitehead Institute, MIT, USA) and George Klein (Karolinska Institute, Sweden), two brilliant and amazingly successful scientists who have embraced ‘a revised theory of cancer’ late in their scientific careers.

Welcome

to the 35th Altenberg Workshop in Theoretical Biology. The Altenberg Workshops are interdisciplinary meetings organized by the KLI in Klosterneuburg, Austria. The workshop themes are selected for their potential impact on the advancement of biological theory. Leading experts in their fields are asked to invite a group of internationally recognized scientists for three days of open discussion in a relaxed atmosphere. By this procedure the KLI intends to generate new conceptual advances and research initiatives in the biosciences. We are delighted that you are able to participate in this workshop, and we wish you a productive and enjoyable stay.

Gerd B. Müller
President

The topic

Ever increasing amounts of DNA sequence-based “cancer mutation” data have added much to our understanding of the human genome over the past decade. However, whereas detailed sequencing has helped delineate new pathways and has led to limited progress in some cancer types, it has not delivered a real breakthrough in our understanding of cancer initiation, progression, and treatment approaches. We believe it is time to reassess some of the scientific concepts that underpin current mainstream cancer research, such as the “Somatic Mutation Theory” of cancer in light of solid experimental data and alternative theoretical concepts that have accumulated over several decades in different areas of cell and cancer biology as well as big data analysis methodologies. The workshop is anticipated to start the process of integrating these insights into a new framework of “a revised theory of cancer.”

Aims

The overall aim of the workshop is to formulate and publish in the following year a conceptual framework of cancer theory, based on contributions of the participants. The workshop provides a forum to generate specific answers in the below broad areas of cancer research. These headings are only meant to serve as structural pointers that may act as starting points for in depth, detailed discussions.

A: Recent cancer data and current theoretical concepts

The presence/absence of specific theoretical concepts in current cancer research will be discussed around the following questions: Which basic science concepts, such as the “Somatic Mutation Theory of Cancer” are supported by data, and what data is conflicting with certain concepts? What are the main issues and new questions that have emerged over the past decade as a result of large genomic cancer screening efforts? What alternative, evidence based concepts exist that are not part of mainstream cancer theory, or need testing?

Desired outcomes:

- Overview of implicit and explicit hypotheses currently applied in cancer research
- Alternative hypotheses that are supported by data
- Alternative hypotheses that need testing

B: Cancer causation and progression

This theme should help address the following questions: What are the fundamental cellular and molecular mechanisms that are involved in cancer initiation and progression? What are newly emerging epigenetic mechanisms? What is the role of the tumor microenvironment in cancer initiation, progression, and therapy? How can tissue level mechanisms be investigated and utilized for therapy?

Desired outcomes:

- A revised model of cancer causation and progression
- New evidence based definitions for tissue level mechanisms

C: New data analysis approaches for new insights

What can Big Data analytics and network science approaches contribute to our mechanistic understanding of cancer? This theme should prompt discussions about whether new correlations can be found in existing data, and what data needs to be collected to gain better meaningful insights. Do new data analysis methods lead to new general concepts that can be useful for basic experimental cancer research? What new theory frameworks that are currently not used by cancer research can be applied to the cancer problem?

Desired outcomes:

- Strategies to mine existing cancer data for new causal relationships
- Computational strategies to test new hypotheses on large data sets
- Hypothesis driven analytics tools and AI applications for disparate cancer data

Format

Workshop sessions comprise two 20-minute talks followed by at least 30 minutes of discussions, followed by breaks. Each workshop day has allocated at the end 1.5 hours of time for synopsis and interaction. After the final session on Sunday morning additional time is planned for discussing future plans, collaborations, and further workshop outcomes.

Manuscript preparation and publication

The 35th Altenberg Workshops in Theoretical Biology is sponsored by the KLI, the Breast Cancer Research Foundation, the Company of Biologists, Novartis, and Nature. In turn, we ask participants to contribute a paper to a volume edited by the organizers. Altenberg Workshop results are usually published in the Vienna Series in Theoretical Biology (MIT Press). The volume will further develop the novel ideas and concepts generated as a result of the workshop. The contributors are not necessarily limited to the original participants; they may be complemented by experts on those topics that emerge as important and may include co-authors invited at the discretion of the participants. Because of the explicit interdisciplinary nature of the effort, the outcome should be attractive to a wide range of experts in the medical and natural sciences as well as in the humanities.

We expect that participants will revise their drafts as a result of our discussions at the workshop and the ensuing review process. We are aiming for a March 15th, 2018, date for receipt of finished manuscripts for publication. The length of the contributions should be approximately 8,000 words. The use of figures and photographs is highly encouraged. All contributions will be edited for style and content, and the figures, tables, and the like will be drafted in a common format. The editors will send specific instructions after the workshop.

Mina J. Bissell, Ingemar Ernberg, and Bernhard Strauss

Participants

MARTA BERTOLASO **m.bertolaso@unicampus.it**

Campus Bio-medico University of Rome
Via Álvaro del Portillo, 21
00128 Rome
ITALY

MINA J. BISSELL **mjbissell@lbl.gov**

Lawrence Berkeley National Laboratory
One Cyclotron Road
Berkeley, California 94720
USA

CÉDERIC BLANPAIN **cedric.blanpain@ulb.ac.be**

Université Libre de Bruxelles (ULB)
Laboratory of Stem Cells and Cancer
Route de Lennik, 808 – Campus Erasme
Bâtiment C – Room C6-131
BELGIUM

PETER CSERMELY **csermelynet@gmail.com**

Semmelweis University
PO Box 2
H-1428 Budapest
HUNGARY

PAUL C.W. DAVIES **Paul.Davies@asu.edu**

Beyond: Center for Fundamental Concepts in Science
Arizona State University
P.O. Box 870506
Tempe, AZ 85287–0506
USA

INGEMAR ERNBERG **ingemar.ernberg@ki.se**

Dept. of Microbiology, Tumor and Cell Biology (MTC)
Karolinska Institute
MTC, Karolinska Institutet, Box 280,
17177 Stockholm
SWEDEN

CYRUS M. GHAJAR **cghajar@fredhutch.org**

Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North
M5-A864, Seattle, WA
USA

VERA GORBUNOVA **vera.gorbunova@rochester.edu**

University of Rochester
1720 W. Bloomfield Rd
Honeoye Falls, NY 14472
USA

EDOUARD HANNEZO **edouard.hannezo@ist.ac.at**

Institute of Science and Technology Austria
Am Campus 1
A – 3400 Klosterneuburg
AUSTRIA

SUI HUANG **sui.huang@systemsbiology.org**

Institute for Systems Biology
401 Terry Ave N.
Seattle, WA 98109
USA

GIORGIO INGHIRAMI **ggi9001@med.cornell.edu**

Weill Cornell Medicine
1300 York Avenue
New York, NY
USA

BARBARA MARTE **b.marte@nature.com**

Nature
4 Crinan Street
London N1 9XW
UK

JÖRG MENCHE **jmenche@cemm.at**

CeMM Research Center for Molecular Medicine of the
Austrian Academy of Sciences
Lazarettgasse 14
A-1090 Vienna
AUSTRIA

TIM NEWMAN **T.Newman@dundee.ac.uk**

College of Life Sciences
University of Dundee
Dow Street
Nethergate, Dundee DD1 4HN
UK

LARRY NORTON **nortonl@mskcc.org**

Memorial Sloan Kettering Cancer Center
300 E. 66th Street
New York, NY 10065
USA

JACQUES POUYSSEGUR **jpouyssegur@centrescientifique.mc**

Institute of Research on Cancer and Aging (IRCAN)
University of Nice-Sophia Antipolis -CNRS-Inserm
Centre A. Lacassagne
06189 Nice
FRANCE

JACCO VAN RHEENEN **j.vanrheenen@hubrecht.eu**

Hubrecht Institute and UMC Utrecht
Uppsalalaan 8
3584CT Utrecht
The NETHERLANDS

KAHN RHRISSORRAKRAI **krhriss@us.ibm.com**

IBM Research
1101 Kitchawan Road
Yorktown Heights, NY 10598
USA

TOBIAS SJÖBLOM **tobias.sjoblom@igp.uu.se**

Uppsala University
IGP, Dag Hammarskjölds v 20
SE-751 85 Uppsala
SWEDEN

BERNHARD STRAUSS **b.strauss@gurdon.cam.ac.uk**

The Gurdon Institute
University of Cambridge
Tennis Court Road
CB2 1QN
UK

EMMY VERSCHUREN **emmy.verschuren@helsinki.fi**

Institute for Molecular Medicine Finland (FIMM)
University of Helsinki
Tukholmankatu 8
00290 Helsinki
FINLAND

VALERIE WEAVER **Valerie.weaver@ucsf.edu**

University of California, San Francisco
513 Parnassus Avenue HSE 560
San Francisco, CA 94143
USA

A Revised Theory of Cancer

Thursday 9 November	Afternoon	Keynote Lecture and Panel Discussion
5.00 pm - 5.10 pm	G. B. Müller President KLI	Welcome Address
5.10 pm - 5.30 pm	B. Strauss	Why We Need a Revised Theory of Cancer
5.30 pm - 6.10 pm	M.J. Bissell	Why Don't We Get More Cancer?
6.10 pm - 6.20 pm	J. van Rheenen	The Live View of Cancer
6.20 pm - 6.30 pm	S. Huang	A Systems View of Cancer: "What Does Not Kill Me Only Makes Me Stronger"
6.30 pm - 7.00 pm	Panel discussion	(Workshop participants present)
7.00 pm - 7.45 pm	Networking reception	
8.00 pm		Welcome dinner, Vienna

Friday 10 November	Morning	Theories in Cancer Research	Chair: M.J. Bissell
9.30 am - 9.45 am	M. J. Bissell, I. Ernberg, B. Strauss	Workshop Aims, Structure, and Desired Outcomes	
9.45 am - 10.05 am	M. Bertolaso	A Disease of Biological History: A Dynamic and Relational View of Cancer	
10.05 am - 10.25 am	S. Huang	Towards a Unifying Theory of Cancer: On the Intrinsic Inevitability of Cancer	
10.25 am - 11.00 am	Discussion		
11.00 am - 11.20 am	Coffee		
11.20 am - 11:40 am	P. Davies	Cancer as a Reversion to an Ancestral Phenotype	
11:40 am - 12.00 am	I. Ernberg	Intercellular Cancer Cell Heterogeneity Beyond Genes and Epigenetics	
12.00 am - 12.30 pm	Discussion		
12.30 pm - 2.00 pm	Lunch	at the KLI	

Friday 10 November	Afternoon	Cancer Initiation and Progression	Chair: I. Ernberg
2 pm - 2.20 pm	C. Blanpain	Cancer Cell of Origin and Tumor Heterogeneity	
2.20 pm - 2.40 pm	T. Newman	Simple Models of Rare Events Giving Insights into Cancer Initiation and Metastasis	

2.40 pm - 3.10 pm	Discussion	
3.10 pm - 3:45 pm	Coffee	
3.45 pm - 4.05 pm	E. Hannezo	Defining the Clonal Dynamics of Skin Tumor Initiation
4.05 pm - 4.25 pm	J.van Rheenen	Intravital Imaging of Cancer Cells and Their Microenvironment
4.25 pm - 4.55 pm	Discussion	
4.55 pm - 6.00 pm	Synopsis	Review of discussions of day one
6.00 pm		Free evening

Saturday 11 November	Morning	What We Can Learn from the -Omics View of Cancer	Chair: S. Huang
9.30 am - 9.50 am	K. Rhrissorrakrai	An -Omic Centric Approach to Advancing Precision Oncology	
9.50 am - 10.10 am	P. Csermely	Adaptation of Cancer Cell Networks	
10.10 am - 10.30 am	J. Menche	Network Approaches in Medicine: From Protein-Protein to Drug-Drug Interactions	
10.30 am - 11.00 am	Discussion		
11.00 am - 11.20 am	Coffee		
11.20 am - 11.40 pm	T. Sjöblom	How Should We Go About to Discover Truly Useful Cancer Biomarkers?	
11.40 am - 12.00 am	E. Verschuren	Histopathology-Specific Phenotypes as Disease Vulnerabilities	

12.00 am - 12.30 am	Discussion	
12.30 pm - 2.00 pm	Lunch	at the KLI

Saturday 11 November	Afternoon	Cancer Physics, Metastasis, and Metabolism Point to New Treatment Approaches	Chair: P. Davies
2.00 pm - 2.20 pm	V. Weaver	Interplay Between Extrinsic and Intrinsic Force Regulates Cancer Progression and Treatment Response	
2.20 pm - 2.40 pm	C. Ghajar	Targeting Dormant Tumor Cells for Metastasis Prevention	
2.40 pm - 3.10 pm	Discussion		
3.10 pm - 3:30 pm	Coffee		
3.30 pm - 3.50 pm	J. Pouyssegur	Targeting Acidic, Nutritional and Oxidative Stresses in Cancer	
3.50 pm - 4.10 pm	L. Norton	Evolving Concepts Concerning the Nature of Neoplasia	
4.10 pm - 4.40 pm	Discussion		
4.40 pm - 6.00 pm	Synopsis	Review of discussions of day two	
6.00 pm		Departure for dinner to a local “Heurigen”	

Sunday 12 November	Morning	Lessons from the Vascular Niche and Cancer Resistant Mammals Chair: V. Weaver
9.30 am - 9.50 am	G. Inghirami	The Maladapted Vascular Niche Initiates Tumor Stem Cells, and Fosters Metastasis and Chemoresistance by Supplying Aberrant Angiocrine Factors
9.50 am - 10.10 am	V. Gorbunova	Lessons from Cancer-Resistant Species of Mammals
10.10 am - 10.40 am	Discussion	
10.40 am - 11.00 am	Coffee	
11.00 am - 12.30 pm	Synopsis	Open questions, future plans
12.30 pm - 2.30 pm	Lunch	at the KLI
2.30 pm		Departure for sightseeing & dinner in Vienna

Abstracts

Bernhard STRAUSS
University of Cambridge

Why We Need a Revised Theory of Cancer

Most current research efforts to understand cancer, and to find a cure are firmly based on the somatic mutation theory of cancer. The narrative that “cancer is a disease caused by mutations” has particularly gained dominance since the sequencing of the human genome made it appear plausible that most human diseases can ultimately be explained and treated at the genomic level. However, large sequencing data sets of cancer tissue samples have shown that simple causal relationships between specific mutations and cancer phenotypes do not exist in the great majority of cancers. Moreover, outcome data of several clinical trials carried out in the past five years that have used an “actionable target” based treatment approach are now available. These approaches, trying to specifically correct the effect of certain mutations, have unfortunately been clearly less successful in the clinic than other approaches. This situation needs to be explained from a history of science perspective, and changed by using an alternative theory framework to find more effective approaches to understand and treat cancer. In this talk I will suggest that we are currently in a good position to propose such an alternative framework, based on several lines of evidence that have accumulated over many decades.

Biosketch:

Bernhard Strauss is a senior research fellow at the Gurdon Institute, University of Cambridge and the Institute of Cancer Research, London. He is currently working on signaling interactions between cell cycle checkpoints and the extracellular environment using human organoid culture systems with defined extracellular matrices. Bernhard Strauss has previously studied cell cycle

regulators in knock out mouse models and pioneered FRET based cell cycle analysis in early mouse embryos. After undergraduate studies in Medicine and Biology at university of Vienna, Austria, he obtained his PhD at the University of Cambridge where he worked on the role of cell shape in mitotic spindle orientation and cell fate specification. As an inventor of life science technology solutions Bernhard has commercialized products in the areas of live imaging microscopy, microfluidics, and high-throughput sample preparation.

Mina J. BISSELL

Lawrence Berkeley National Laboratory

Why Don't We Get More Cancer?

It should be clear by now that cancer is a tissue- and organ-specific disease. Thus to understand a given malignancy, we could do well to know the biology of the normal tissue and the organ from which the malignant tumor develops.

To understand initiation of breast tumors, one must consider the health of the entire organ within the context of the individual: the age of the individual and the medical condition, not only the cells that become, or have become, malignant, but the entire tissue and the microenvironment of the cells that have been targeted to become tumors.

I will discuss three fundamental questions: 1) How do epithelial cells know when to stop growing, and why malignant cells don't? 2) What is the basis of tissue- and organ- specificity? And 3) How do physical and biochemical signals help make a tissue?

We have shown that unless the architecture of the tissue is severely compromised, the cells will not become malignant or invade. Indeed, we can revert the malignant cells to 'normal phenotype' despite myriads of mutations, deletions and amplifications if we restore the architecture. We now have discovered new pathways that regulate growth and quiescence in human breast cells[1], an intricate mechanism by which the ECM and cytoskeletal connections may interact with the nucleus and chromatin[2], and how the morphogenetic signaling loop in breast epithelial tissue is maintained.[3?]

This is a tale of how form and function integrate: From laminins to lamins, P53, HOX D10 and back to laminins.

1) Cell Report, 2017

2) J. Cell Science, 2017

3) E.Life (in Press)

Biosketch:

Mina J. Bissell is Distinguished Scientist, the highest rank bestowed at Lawrence Berkeley National Laboratory (LBNL) and serves as Senior Advisor to the Laboratory Director on Biology. She is also Faculty of four Graduate Groups in UC Berkeley: Comparative Biochemistry, Endocrinology, Molecular Toxicology, and Bioengineering (UCSF/UCB joint program). Having challenged several established paradigms, Bissell is a pioneer in breast cancer research and her body of work has provided much impetus for the current recognition of the significant role that extracellular matrix (ECM) signaling and microenvironment play in gene expression regulation in both normal and malignant cells. Her laboratory developed novel 3D assays and techniques that demonstrate her signature phrase: after conception, "phenotype is dominant over genotype."

Bissell earned her doctorate in microbiology and molecular genetics from Harvard Medical School, won an American Cancer Society fellowship for her postdoctoral studies, and soon after joined LBNL. She was the founding Director of the Cell and Molecular Biology Division and later the Associate Laboratory Director for all Life Sciences at Berkeley Lab where she recruited outstanding scientists and developed a strong program in cell and molecular biology and breast cancer.

Bissell has published more than 400 publications and is one of the most sought-after speakers in the field. She has received numerous honors and awards, which include: U.S. Department of Energy's E.O. Lawrence Award, AACR's G.H.A. Clowes Memorial Award, the Pezcoller Foundation-AACR International Award, Susan G. Komen Foundation's Brinker Award, BCRF Foundation's Jill Rose Award, Berkeley Lab's inaugural Lifetime Achievement Prize, American Cancer Society's Medal of Honor, MD Anderson Cancer Center's highest honor – the Ernst W. Bertner Award, the Honorary Medal from the Signaling Societies in Germany, ASCB's highest honor – the E.B. Wilson Medal, and the 2017 AACR Award for Lifetime Achievement in Cancer Research. Bissell is an inspiring mentor and in her honor, the University of Porto, Portugal established the Mina J. Bissell Award which is given every three years to a person who has dramatically changed a field. She is the recipient of Honorary Doctorates from both Pierre &

Marie Curie University in Paris, France, and University of Copenhagen in Denmark. Bissell is not only an elected Fellow of most U.S. honorary scientific academies, including National Academy of Sciences (NAS), National Academy of Medicine (NAM), and American Philosophical Society (APS), but she also sits on many national and international scientific boards and continues to engage in full-time research, among other scientific activities.

Marta BERTOLASO

Campus Bio-medico University of Rome

A Disease of Biological History: A Dynamic and Relational View of Cancer

To tame the complexity and overcome some serious anomalies encountered by cancer research, the tools of Systems Biology – whole-genome or supra-cellular models and concepts – were introduced to analyze relationships among a huge number of factors. Systemic approaches do not merely provide technical tools to examine large datasets, nor are they simply opposed to “mechanistic” or “reductionist” approaches that look at components (single cells, individual macromolecules). Rather, according to my philosophical analysis, they drive research questions towards the dynamic maintenance of functional unity of biological entities. Cancer comes to be seen as a disease of biological history, a disruption of the ongoing relational interactions that constitute an organism. I will show that such a dynamic and relational view generates a new view of cancer and new theoretical concepts, transforms scientific practice, centering it on ‘explanatory relevance’, and produces a new view of long-term advancement of cancer research.

Biosketch:

Marta Bertolaso is Associate Professor for Philosophy of Science in the Faculty of Engineering and at the Institute of Philosophy of the Scientific and Technological Practice at University Campus Bio-Medico of Rome. Her research projects deal with new epistemological and philosophical challenges in the fields of biological and systemic development (with a special focus on cancer), scientific advancement, *in silico* medicine, modeling and validation processes. She has been lecturer for philosophy of science and bioethics in different universities in Italy and at the Center for Mathematical Philosophy (MCMP) at Ludwing-Maximillians- Universitat in Munich (Germany), at the Department of Philosophy at Washington University of St. Louis (USA), at Universidad Popular

Autónoma del Estado de Puebla (Mexico). Among her last publications there are Philosophy of Cancer – A Dynamic and Relational View. Springer Series in "History, Philosophy & Theory of the Life Sciences", 2016, and The Future of Scientific Practice: 'Bio-Techno-Logos', Pickering & Chatto Publishers, London, 2015. She is Editor of the Springer Series on "Human Perspectives in Bio-Medicine and Technology."

Sui HUANG

Institute for Systems Biology, Seattle

Towards a Unifying Theory of Cancer: On the Intrinsic Inevitability of Cancer

We present a vision towards a unifying theory of cancer that helps to explain the apparent, perhaps intrinsic inevitability of cancer as a manifestation of metazoan life. We require that all elements of such a theory not only be consistent with empirical observations, but also be grounded in “first principles” of dynamical systems theory. The latter encompasses mathematical principles that explain how gene regulatory and cell-communication networks produce robustness of complex phenotypes and directionality of development. This theory, in which cancer cells are trapped in abnormal “attractor states”, predicts the multiplicity of non-genetic causes of cancer and its self-organizing complexity – both defy the orthodoxy of genetic mutations as the cause of cancer. Our theory explains why oncogenesis recapitulates ontogenesis (cancer as immature tissue) and phylogenesis (cancer as cellular atavism), and why tumors not only resist, but also become more aggressive when treated – following Nietzsche’s, “What does not kill me makes me stronger.”

Biosketch:

Sui Huang, MD, PhD, studied medicine, molecular biology and physical chemistry at the University of Zurich in the 1990s as the first awardee of the Swiss National Foundation MD-PhD program. As postdoc and faculty at Harvard Medical School in Boston, Dr. Huang worked with Donald Ingber and Judah Folkman on cell fate regulation and tumor angiogenesis. He then helped establish an institute at the University of Calgary dedicated to biocomplexity and cancer drug discovery alongside Stuart Kauffman before joining the Institute for Systems Biology in Seattle in 2011. His current work uses omics technologies combined with theory of non-linear dynamical systems and “big data” analysis to

understand fundamental principles of cell fate decisions in development and cancer. Sui Huang's broader interest is the formalization of the problem of genotype-phenotype mapping by emphasizing complex systems dynamics, critical phenomena, phenotype plasticity and non-genetic as well as non-Darwinian processes.

Paul C.W. DAVIES

Arizona State University

Cancer as a Reversion to an Ancestral Phenotype

Although cancer is one of the most intensively studied phenomena in biology and occurs in almost all multicellular species, an explanation for its existence and properties within the context of evolutionary history has received comparatively little attention. However, progress in treatment and prevention depends on a deeper understanding of the biology of cancer. Many of the hallmarks of cancer are reminiscent of unicellular, or early-stage metazoan life, suggesting that neoplasms represent a type of throwback or re-expression of ancestral traits. This basic idea has recently been developed into the so-called atavistic theory of cancer, which seeks to trace cancer's deep evolutionary roots to make specific predictions about gene expression in tumorigenesis. New data strongly supports the basic hypothesis.

Biosketch:

Paul Davies is a theoretical physicist, cosmologist, astrobiologist and best-selling science author. He is Regents' Professor at Arizona State University, where he is Director of the Beyond Center for Fundamental Concepts in Science and co-Director of the Cosmology Initiative. He previously held academic appointments in physics, mathematics and astronomy in the UK and Australia. He is also a Fellow of University College London, a Visiting Professor of Bioengineering at Imperial College London and a Visiting Professor of Physics at the University of New South Wales. He has published about 30 books and hundreds of research papers and review articles across a range of scientific fields. His research interests have focused mainly on quantum gravity, early universe cosmology, the theory of quantum black holes and the nature of time. He has also made important contributions to the field of astrobiology, and was an early advocate of the theory that life on Earth may have originated on Mars. For several years he

has also been running a major cancer research project, and developed a new theory of cancer based on tracing its deep evolutionary origins. Among his many awards are the 1995 Templeton Prize, the Faraday Prize from The Royal Society, the Kelvin Medal and Prize from the Institute of Physics, the Robinson Cosmology Prize and the Bicentenary Medal of Chile. He was made a member of the Order of Australia in the 2007 Queen's birthday honors list and the asteroid 6870 Pauldavies is named after him. His more recent books include *About Time, The Origin of Life, The Goldilocks Enigma: Why Is the Universe Just Right for Life?, How to Build a Time Machine* and *The Eerie Silence: Are We Alone in the Universe?*

Ingemar ERNBERG

Karolinska Institute, Stockholm

Intercellular Cancer Cell Heterogeneity beyond Genes and Epigenetics

Genetic and to some extent epigenetic heterogeneity within a cancer cell population are well established phenomena. But there is a third level of singular cell heterogeneity that results from stochastic noise in transcription and intercellular networks.

This observed intercellular heterogeneity within a clonal cell population can be mapped as dynamical states clustered around an attractor point in gene expression space, owing to a balance between homeostatic forces and stochastic fluctuations. These dynamics have led to the formulation of a conceptual cancer cell attractor model, with implications for both carcinogenesis and new therapeutic concepts. Immortalized and malignant EBV-carrying B-cell lines were used to explore this model and characterize the detailed structure of cell attractors.

Any subpopulation selected from a population of cells repopulated the whole original basin of attraction within days to weeks. Cells at the basin edges were unstable and prone to apoptosis. Cells continuously changed states within their own attractor, thus driving the repopulation, as shown by fluorescent dye tracing. Transcriptome analyses suggest that these forces result from high-dimensional dynamics of the gene regulatory network.

We propose that this phenomenon can be generalized to all cancer cell populations and that it represents intrinsic behaviors of tumor cells, offering an additional characteristic governing phenotype.

Biosketch:

Professor Ingemar Ernberg is a Professor of Tumor Biology. Ernberg completed his PhD thesis at Karolinska Institutet with George Klein in 1979, and obtained

his MD degree in 1984, followed by studies abroad in Omaha, Nebraska 1986 and at the MRC Laboratory of Molecular Biology in Cambridge UK 1988-1990. He was secretary of science at the Swedish Cancer Society 1983-93. He was the first chair of the new department of Microbiology and Tumorbiology Center (MTC) at Karolinska Institutet 1993-1999. He is now the chairperson for the Karolinska Institute (KI) Cancer Network organizing 135 research groups. He has been the coordinator for KI collaborations with China, while he heads his research group of 10 at MTC.

Ingemar Ernberg's work deals with tumor viruses in man, cancer genetics, lymphoma biology, transcriptional regulation (HIV, EBV) and epigenetics (methylation). He has authored more than 250 publications. Seminal discoveries of his team have established that the B-lymphocyte is the site of EBV-latency in vivo (Gratama et al, PNAS, 1988), and that EBV expression is regulated by epigenetic methylation. More recent interests have dealt with genomic signatures and global gene expression profiles, as well as designing methods to allow quick analysis of the normal gut flora. This has led to an increasing interest in tissue biology, self-organization of biological systems and the possibilities and limits of simulations *in silico* as an additional scientific tool.

Cédric BLANPAIN

Unversité Libre de Bruxelles

Cancer Cell of Origin and Tumor Heterogeneity

Different theories have been proposed to explain tumor heterogeneity including the cancer cell of origin. Here, we have developed new genetically engineered mouse models allowing lineage tracing together with oncogenic activation in different cell lineages of the skin epidermis and the mammary gland and assessed whether the cancer cell of origin controls tumor heterogeneity. I will present evidence that the cancer cell of origin controls tumor heterogeneity and the underlying molecular mechanisms by which the cancer cell of origin controls tumor differentiation, stemness, EMT, resistance to therapy and metastasis in primary tumors. These results have important implications for our understanding of the mechanisms controlling tumor heterogeneity and the development of new strategies to block tumor initiation, progression, metastasis and resistance to therapy.

Biosketch:

Cédric Blanpain is MD/PhD and board certified in internal medicine from the Université Libre de Bruxelles, Belgium.

Cédric Blanpain is full professor, WELBIO investigator and director of the laboratory of stem cells and cancer at the Université Libre de Bruxelles. His research group uses lineage-tracing approaches to study the role of SCs during development, homeostasis and cancer. His group uncovered the existence of stem cells and progenitors acting during homeostasis and repair of the epidermis and uncovered a novel paradigm of lineage segregation in the mammary gland and prostate. His lab pioneered the use of mouse genetics to identify the cellular origin of epithelial cancers. They identified the cancer cell of origin and the mechanisms regulating the early steps of tumor initiation in skin basal cell carcinoma, skin squamous cell carcinoma and PIK3CA mediated mammary

tumors. His lab has developed novel approaches to unravel the mode of tumor growth within their natural environment and to understand the mechanisms regulating cancer stem cell functions.

Cedric Blanpain received several prestigious and highly competitive awards including EMBO Young investigator award, ERC starting and ERC consolidator grants, the outstanding young investigator award of the ISSCR 2012, the Liliane Bettencourt award for life sciences 2012, Joseph Maisin Award for basic biomedical Science 2015. He has been elected member of the EMBO in 2012, the Belgian Royal Academy of Medicine, and the Academia Europa.

Tim NEWMAN
University of Dundee

Simple Models of Rare Events Giving Insights into Cancer Initiation and Metastasis

I will present findings from two projects both utilizing the same underlying model of rare events. The first is a null model of cancer initiation, with the rare event being immune system escape that can explain cancer incidence across a wide range of cancer types, including gender differentials. The second project uses a similar approach, applied to metastatic colonization, and provides insights into how rare random events can appear strongly deterministic. Both projects are overt counterpoints to the paradigm of "cancer as a genetic disease". Yes, cancer is a genetic disease (and water is a molecular liquid), but additional paradigms are absolutely required to understand cancer progression in humans.

Biosketch:

Tim Newman was educated in theoretical and statistical physics, and since 2000 has applied ideas from these fields to diverse areas of the life sciences: ecology, development, gene regulation, DNA repair and cancer. Tim's group has focused in recent years on "simple" approaches to modeling and understanding biological systems. Tim worked at Arizona State University from 2002 to 2010, and since 2011 has worked at the University of Dundee, both in research and more recently in senior management. He will be leaving Academia at the end of 2017 to pursue projects as an independent scientist and thinker.

Edouard HANNEZO

Institute of Science and Technology Austria, Klosterneuburg

Defining the Clonal Dynamics of Skin Tumor Initiation

The changes in cell dynamics after oncogenic mutation that lead to the development of tumors are currently unknown. Here, using skin epidermis as a model, we assessed the effect of oncogenic hedgehog signaling in distinct cell populations and their capacity to induce basal cell carcinoma, the most frequent cancer in humans. We found that only stem cells, and not progenitors, initiated tumor formation upon oncogenic hedgehog signaling, mirroring the homeostasis, spatial organization and hierarchy of the tissue. Modeling reveals that cancer initiation is a stochastic process in which cells continue to make random fate decisions as they do during normal homeostasis. Our work reveals that the capacity of oncogene-targeted cells to induce tumor formation is dependent not only on their long-term survival and expansion, but also on the specific clonal dynamics of the cancer cell of origin.

Biosketch:

Edouard Hannezo is an Assistant Professor of Theoretical Biophysics at IST (Institute for Science and Technology), Austria (2017 onwards). He did his PhD at the Institut Curie in Paris, developing mechanical descriptions of epithelial cells and tissues, before moving to Cambridge University for a post-doc working on stochastic models of stem cell fate in development, homeostasis and cancer initiation, as well as the dynamics of branching morphogenesis in different mammalian organs.

Jacco van RHEENEN
Hubrecht Institute and UMC Utrecht

Intravital Imaging of Cancer Cells and Their Microenvironment

Over the years, we have developed techniques to visualize the behavior of individual cells in living mice at sub-cellular resolution (IVM). In this talk I will discuss how we have used these techniques to study the microenvironment of tumor cells that drives tumor growth and metastasis. For example, I will show that mammary tumor cells that are surrounded by T cells acquire migratory properties. An additional aspect that complicates the tumor microenvironment is that cells may exchange active biomolecules through the release and uptake of extracellular vesicles (EVs). Our data shows, in living mice, that malignant tumor cells, through transfer of EVs, enhance the migratory behavior and metastatic capacity of more benign cells. Taken together, our data exemplify that tumor heterogeneity and the tumor microenvironment are far more complex than currently anticipated, which has profound consequences for our ideas on the mechanisms of tumor progression and for designing optimal treatment strategies.

Biosketch:

Jacco van Rheenen did his PhD at the Netherlands Cancer Institute and his postdoc at the Albert Einstein College of Medicine in New York. In 2008 he was appointed as group leader at the Hubrecht Institute. In 2009, he was awarded a VIDI grant and a research grant from the Dutch Cancer Society. In 2012, he was awarded a research grant from the Association for International Cancer Research (who have now rebranded as Worldwide Cancer Research), and in 2013 a research grant from Netherlands Organisation for Scientific Research. In 2013, he received the Stem Cells Young Investigator Award. In July 2014 he was appointed full professor in Intravital Microscopy at the University Medical Center Utrecht. In 2015, he was awarded an ERC consolidator grant. In 2017, he

received the Joseph Steiner Award for Cancer Research. In October 2017, he will move his lab to the Netherlands Cancer Institute.

Kahn RHRISSORRAKRAI
IBM Research, Yorktown Heights

An -Omic Centric Approach to Advancing Precision Oncology

In recent years incredible efforts and resources have been applied towards the realization of personalized, precision oncology. With each new large-scale -omic study, our appreciation of the complexity and heterogeneity of cancer has only grown. To achieve durable clinical benefit for more patients, we likely need to move beyond a tissue-based approach for diagnosis and treatment to one that is driven by the specific molecular mechanisms behind a particular patient's disease, and to treat according to those mechanisms rather than by site. Our goal is to develop an effective human-machine interface for this genomic analysis that would ultimately present potentially clinically actionable calls for individual patients in a more timely and efficient manner. To address this challenge, we are pursuing several avenues of study, including checkpoint immunotherapy response and mechanisms of drug resistance, and plan to leverage insights made there within our integrative cancer analysis system, Watson Genomic Analytics, which is trained to analyze molecular data and provide clinically actionable insights that are supported by all available relevant evidence.

Biosketch:

I received my M.S. (2006) and Ph.D. (2012) in Computational Biology from New York University with primary focus on the condition-specific usage of functional models in C. elegans development. At IBM, I have studied problems related to network analysis/inference, challenge-based approaches for answering complex biological questions, and cancer genomic analysis focused on drug response, drug resistance and immunotherapy response biomarkers.

Most recently, I've been working with a team of researchers and developers to create Watson Genomics, a system designed to support clinical oncologists make better treatment decisions by performing a genomic analysis of the patient

and recommending therapies that are specific to the genetic alterations they possess. This work leverages expertise from across domains - cancer biology, cell biology, machine learning, network analysis, natural language processing - and is being offered as a cloud-based service that reduces what was formally a weeks-long manual analysis of a patient's genomic profile to a minutes-long analysis.

Peter CSERMELY

Semmelweis University, Budapest

Adaptation of Cancer Cell Networks

Network-based adaptive mechanisms mobilize cancer cell 'creativity' to survive in an unpredictable environment. Adaptation starts with a dominance-shift from network core-driven processes to changes in the network periphery, leading to 'creative' shortcuts between distant network regions. This may change the network from a rigid to a plastic state. Rigid networks have a dense core, disjunct modules, hierarchy, small network entropy, and sink-dominance leading to a few attractors. Plastic networks have a fuzzy core, overlapping modules, less hierarchy/more loops, large network entropy, and source-dominance leading to many attractors. Finally, the periphery may remodel the core thus encoding novel information. These changes (and their multi-cellular expansions) increase system-level cancer evolvability. Using a dynamic model of cancer signaling combined with transcriptome and mutation profiles allows the exploration of specific cancer cell attractors (reflecting cell phenotypes, e.g. proliferation, apoptosis, metastasis, etc.). Moreover, this dynamic signaling model is able to predict compound combination outcomes in a dose-dependent manner.

Biosketch:

Peter Csermely is a professor of network science at the Semmelweis University (Budapest, Hungary; http://linkgroup.hu) and a founder/advisor of the Turbine startup establishing a dynamic cell model to predict anti-cancer combination therapies (http://turbine.ai). He wrote and edited 13 books and 270 research papers with over 14,000 Google Scholar citations. Dr. Csermely is a member of the Hungarian Academy of Sciences and Academia Europaea, was the member of the Wise Persons' Council of the president of Hungary, an Ashoka Fellow, a Fogarty, a Howard Hughes and a Rockefeller Scholar, as well as a Templeton Awardee. From 1995 he established several talent support programs including

the Hungarian Talent Support Council involving more than 200,000 people. In 2012 he became the president of the European Council for High Ability, which started a European Talent Support Network now having more than 300 nodes in 39 countries in Europe and other continents (http://etsn.eu/map-of-etsn).

Jörg MENCHE

CeMM Research Center for Molecular Medicine of the Austrian Academy of Science

Network Approaches in Medicine: From Protein-Protein to Drug-Drug Interactions

Network medicine is an emerging interdisciplinary approach towards understanding human disease. The ever growing wealth of data, from individual genome sequencing to population-wide health records, reflects the many levels of organization that play a role in disease phenomena, from protein-DNA interactions to signal transduction, from metabolism to social interactions implicated in disease transmission. In view of the complicated interactions within and across these levels, network science may provide invaluable tools to help disentangle this enormous complexity and understand disease phenomena in a holistic fashion. In my talk I will highlight recent advances in projecting diseases onto protein-protein interaction networks and discuss our latest effort in systematically mapping drug-drug interactions.

Biosketch:

Jörg Menche studied physics in Leipzig, Recife and Berlin. During his Ph.D. at the Max-Planck-Institute for Colloids and Interfaces in Potsdam he specialized in network theory. For his postdoc he moved to Boston to work with Albert-László Barabási at Northeastern University and Dana Farber Cancer Institute. In close collaboration with Joseph Loscalzo at Harvard Medical School and Marc Vidal at Dana Farber he used network theory to elucidate the complex machinery of interacting molecules that constitutes the basis of (patho-) physiological states. In 2015 Jörg joined the CeMM Research Center for Molecular Medicine in Vienna as Principal Investigator. His group applies diverse computational and mathematical approaches to help understand and interpret large post-genomic datasets. Major areas of interest of his group are network-based approaches to

rare diseases, understanding the basic principles of drug-drug interactions and virtual reality data visualization technologies.

Tobias SJÖBLOM
Uppsala University

How Should We Go About to Discover Truly Useful Cancer Biomarkers?

The number of regulatory approved biomarkers for early detection of cancer is low considering the significant research efforts spent to discover them. A large body of literature describes challenges and reasons for failure in cancer biomarker discovery, but there is essentially no literature on strategies that maximize chances of success. Shortcomings in study design combined with undersized or otherwise suboptimal patient cohorts are key reasons for this underperformance. For a fresh take on cancer biomarker discovery, we have worked with a team of statisticians to develop a cogent statistical framework for plasma biomarker discovery and validation, created analytical expressions to compute study group sizes, collected a large population-based set of pre-analytically standardized blood samples from many different tumor types, and performed initial analyses to support a novel approach. I will discuss insights, fears and hopes ahead of a full-scale attack on this central problem.

Biosketch:

Tobias Sjöblom is Professor in Tumor Genetics at Uppsala University, Sweden. His thesis work concerned new applications of tyrosine kinase inhibitors in cancer therapy. During his postdoctoral fellowship with Bert Vogelstein at the John Hopkins University, he performed the first exome-wide mutational analyses of any human disease, namely breast and colorectal cancers. His current research interests include the somatic genetic basis of colorectal cancer, phenotypes of cancer mutations, and development of diagnostic and therapeutic methods based on somatic mutations. He is Program Director for U-CAN, a longitudinal cancer biobanking initiative encompassing >13.000 patients to support academic and corporate cancer biomarker research, Biobank Sweden

(national scientific infrastructure for sample based research), and Partnership for Precision Medicine in Cancer (a national network to support PCM research).

Emmy VERSCHUREN
University of Helsinki

Histopathology-Specific Phenotypes as Disease Vulnerabilities

Tumors are complex ecosystems in which gene-environment interactions constitute a dynamic equilibrium that evolves over time. Using immunocompetent mouse models, we study gene-phenotype relationships across the histopathological diversity of non-small lung cancer (NSCLC) tumors. We find that while genetic drivers define histopathology spectra, these critically depend on the tumor's cell of origin. Importantly, phenotypic diversity in oncogenic signaling, immune microenvironments, and metastatic propensity align more closely with histotype, rather than driver genotype. This determines histotype-specific therapeutic sensitivity, adaptive resistance mechanisms, and combinatorial drug sensitivity. Finally, using tumor explants, we show that responses to combination treatment with signaling inhibitors correspond with spatially-defined targeted pathway activities. Our work implies the existence of NSCLC histopathology-specific phenotypes, and cautions against an over-reliance on genetic markers in personalized diagnostic settings. Our future aim is to address whether histopathology-specific phenotypes are targetable by minimally invasive treatments or physiological adaptations.

Biosketch:

Emmy Verschuren is a Dutch cancer biologist interested in understanding how environments can be optimized to promote health. She graduated cum laude from the University of Groningen, with a Master's in tumor immunology. Her PhD and postdoc trained her in notable labs at the ICRF/CRUK, UCSF, Stanford University and Genentech Inc. Her postdoc on cell cycle biochemistry was awarded a Damon Runyon Fellowship. In 2009, she became the first international FIMM-EMBL Group Leader recruit at the newly founded Institute for Molecular Medicine Finland (FIMM). Her biggest funding success to date was the

public-private IMI consortium PREDECT (’11-’16), for which she academically coordinated the development of complex target validation models. She is an EACR Board Member since 2012, and helps organize its biannual Congress and Goodbye Flat Biology Conference. Her group studies *in vivo* and *ex vivo* models of lung cancer, aimed to improve the prognosis of locally-treated patients.

Valerie WEAVER
University of California, San Francisco

Interplay between Extrinsic and Intrinsic Force Regulates Cancer Progression and Treatment Response

Cells experience force and possess a mechanotransduction machinery to detect physical cues from their microenvironment and to transduce and biochemically amplify these signals to modulate their fate. Tumors show increased cell and tissue level forces and transformed cells exhibit a perturbed mechanophenotype. We have been studying how cells transduce mechanical cues to regulate their behavior and how altered force compromises tissue homeostasis to drive malignancy, metastasis, and treatment response. We found that the tumor ECM in breast, pancreas, skin and glioblastomas is remodeled and stiffened. We determined that the magnitude of the ECM stiffening and the nature of the collagen crosslinks correlate significantly with tumor progression and aggression. A stiffened ECM compromises tissue differentiation and organization by activating ion channels and promoting integrin focal adhesion (FA) assembly that potentiate transmembrane receptor signaling and induce cytoskeletal remodeling and actomyosin contractility. Sustained tumor mechanosignaling synergizes with cancer cell expressed oncogenes (Ras, myc, ErbB2, ZNF217) and reduces the level of tumor cell expressed tumor suppressor genes (PTEN, BRCA1, miRs e.g. 203) to drive transformation and foster an epithelial to mesenchymal transition (EMT). Consistently, our studies illustrated how inhibiting ECM stiffening restores tumor suppressor function and reduces oncogenic signaling to prevent malignancy and abrogate metastasis, and how enhancing ECM stiffness promotes malignant transformation and induces an EMT to drive metastasis. We determined that cells respond to a stiffened ECM by "tuning" the magnitude of their actomyosin tension to align with the stiffness of their surrounding microenvironment. Elevated cellular actomyosin tension in turn fosters focal adhesion assembly and activates ion channels to enhance signaling through RhoGTPases, Stats, ERK, PI3 kinase, Jnk, Wnt, NFkappa B and Notch (etc) that

promote cell proliferation, enhance cell survival, and drive tumor cell invasion and dissemination. Importantly, we also find that a stiffened ECM also modulates the tumor vasculature directly and indirectly to drive angiogenesis and eventually compromise vascular integrity to induce hypoxia and alter tumor metabolism. In addition, a stiffened ECM indirectly and directly alters tumor immunity to promote tumor progression and compromise treatment efficacy. For instance, a stiff ECM stimulates tumor cell expression of Stat3 that promotes the expression and release of chemokines and cytokines that stimulate immune cell infiltration. The infiltrating immune cells (macrophages, neutrophils) thereafter secrete large quantities of TGF beta that further induce ECM remodeling and drive immune suppression. A stiffened ECM also directly fosters a pro-tumorigenic immune suppressive microenvironment by changing the immune cells response to soluble factors. These data support the notion that a progressively remodeled and stiffened ECM promotes malignancy and metastasis by directly altering the tumor phenotype and by indirectly regulating the vascular and immune microenvironment. Interestingly, we determined that genetic alterations that increase levels and/or activity of key oncogenes including Ras and loss of key tumor suppressor genes including TGFbeta receptor 2 “tune” the intrinsic tension response of the tumor cells to promote malignancy by potentiating mechanosignaling and by fostering ECM remodeling and stiffening. I will discuss findings from my group that support a role for both intrinsic and extrinsic mechanical force in solid tumors and discuss how these observations provide insight to guide and improve cancer diagnosis and therapy.

Biosketch:

Dr. Weaver is currently the Director of the Center for Bioengineering and Tissue Regeneration in the Department of Surgery, and is a Professor in the Departments of Surgery, Anatomy and Bioengineering and Therapeutic Sciences at UCSF in San Francisco, CA. Her education took place in Canada, with a bachelor’s degree in Chemistry from the University of Waterloo, an Honors Bachelor’s and PhD degree in Biochemistry from the University of Ottawa with a two year postdoctoral training at the Institute for Biological Sciences, National Research Council of Canada and a 5 year postdoctoral tenure at the Lawrence

Berkeley National Laboratory at UC Berkeley with Dr. Mina J Bissell. Dr. Weaver was recruited to the University of Pennsylvania in Philadelphia where she joined the faculty in the Department of Pathology as an Assistant Professor and was appointed a full member of the Institute for Medicine and Engineering. In mid-2006 she relocated to UCSF in San Francisco as an Associate Professor in the Department of Surgery with a joint appointment in Anatomy to take on the Directorship of the Center for Bioengineering & Tissue regeneration. She was invited to join the UCSF Cancer Center and Stem Cell Programs in 2007 and was cross appointed to the newly formed Department of Bioengineering and Therapeutic Sciences in 2008 and was promoted to full Professor in 2010. Dr. Weaver has over 20 years of experience in leading interdisciplinary research in oncology, including leadership of significant program projects including the Bay Area Physical Sciences and Oncology program and the UCSF Tumor Microenvironment Brain Program that merge approaches in the physical/engineering sciences with cancer cell biology and emphasize the role of the tumor microenvironment. Dr. Weaver has been recognized for her research and leadership through receipt of several awards including the DOD BCRP Scholar award in 2005 and the DOD BCRP Scholar expansion award in 20013 for exceptional creativity in breast cancer research and the ASCB WICB Midcareer award for sustained excellence in cell biology research in 2014. Most recently she was elected as the chair of the AACR TMEN working group in 2015. Her research program focuses on the contribution of force, cell-intrinsic as well as extracellular matrix, to breast, pancreatic and glioblastoma tumor development and treatment.

Cyrus M. GHAJAR

Fred Hutchinson Cancer Research Center, Seattle

Targeting Dormant Tumor Cells for Metastasis Prevention

In a significant fraction of breast cancer patients, distant metastases emerge after years or even decades of latency. How disseminated tumor cells (DTCs) are kept dormant, and what wakes them up, are fundamental problems in tumor biology. To address these questions, we use metastasis assays in mice and zebrafish and have determined that the perivascular niche of distant sites like the lung, bone marrow, and brain regulate DTC dormancy. We have developed organotypic microvascular niches to specify that endothelial cells regulate breast cancer cell growth, and applied proteomics to identify endothelial-derived mediators of DTC dormancy. More recently, we have begun to explore whether the perivascular niche confers therapeutic resistance to DTCs. I will present data that suggests strongly that the perivascular niche regulates therapeutic resistance of DTCs in a manner that is independent from its role in regulating DTC growth. We have uncovered mediators of perivascular signaling that, when targeted, cause dormant DTCs to respond robustly to chemotherapy. Critically, inhibiting these mediators causes chemosensitization without inducing dormant DTCs to re-enter the cell cycle. We are currently testing this treatment paradigm in pre-clinical models to determine the efficacy in killing dormant DTCs through this approach. I will discuss pre-clinical trial design and important caveats to accurately gauging whether eradication of dormant DTCs significantly prolongs metastasis-free survival.

Biosketch:

Cyrus Ghajar directs the Laboratory for the Study of Metastatic Microenvironments (LSM^2) (URL: http://research.fhcrc.org/ghajar/en.html) within the Fred Hutchinson Cancer Research Center's Translational Research Program. Broadly, he is interested in how distant tissue microenvironments

influence the behavior of disseminated tumor cells (DTCs). Specifically, his laboratory is working to understand how tissues like lung, liver, bone marrow, brain and lymph nodes regulate survival, growth and therapeutic resistance of DTCs, and how local and systemic changes awaken DTCs. His ultimate interests lie in targeting dormant DTCs to prevent metastasis.

Jacques POUYSSEGUR
University of Nice – Sophia Antipolis – CNRS-Inserm

Targeting Acidic, Nutritional and Oxidative Stresses in Cancer

In metazoans, sensing the availability of oxygen and key nutrients (glucose, amino acids, fatty acids) is integrated with growth factor and hormone signaling. This multiple nutrient and energy checkpoint converges on the activation of the master protein kinase TORC1, critical for engaging cells in the cell cycle and promoting growth. Cells have evolved sophisticated regulatory systems to rapidly respond to several lethal stressors including metabolic acidosis, nutritional depletion and reactive oxygen species. Cancer cells respond in multiple ways to escape and thrive under these microenvironmental stresses, thus offering several strategies to combat cancer resilience before and after therapeutic treatment. In this lecture we will discuss how we can exploit cancer vulnerabilities (metabolic tumor acidosis, amino acid depletion and oxidative stress) to propose novel anticancer targets capable of either arresting tumor growth or killing cancer cells.

Biosketch:

Currently Dr. Pouyssegur's group pursues, at a fundamental level, the physiological role of key targets induced by nutritional stress and hypoxia in tumors. The focus is on tumor aberrant glucose metabolism (Warburg effect), glycolysis, autophagy, and nutrient import driven by HIF, with a special focus on translational research. Numerous anticancer targets disrupted by ZFN & CRISPR/Cas9 are in the process of being validated in preclinical mouse models by his team (carbonic anhydrases CA9, CA12, CA2, bicarbonate transporters NBCs, MonoCarboxylate Transporters MCT1, MCT4, their chaperone CD147/Basigin and amino acid transporters LAT1/CD98, xCT, ASCT2…). His team has made substantial contributions to the areas of cell surface glycoproteins, metabolism, intracellular pH regulation, identification of human

Na/H exchangers and established that intracellular pH and MAP kinase (ERKs) signaling are critical for cell cycle entry.

Larry NORTON

Memorial Sloan Kettering Cancer Center, New York

Evolving Concepts Concerning the Nature of Neoplasia

Almost all contemporary therapeutic strategies for epithelial cancers are founded on the concept that the primary defect is aberrant mitotic regulation of the cancer cells. The 19th century idea that metastases were due to mechanical forces, long regarded as archaic, are yet still influencing surgical approaches. However, new discoveries in cancer biology may be converging on a different concept of the nature of malignancy. That new concept could have profound therapeutic implications. Factors to be considered include the ubiquity of sigmoid growth patterns (of proven utility in designing chemotherapy regimens), the biology of site-specific metastatic behaviors, the profound influences of the microenvironment around and within malignant tumors, non-cellular information transfer mechanisms and the importance of cancer cell mobility. This line of thinking yields the growth equation:

$$dN(t)/dt = k1*N^{[D(t)/3]} – k2*\{N(t) – N^{[D(t)/3]}\},$$

where dN(t)/dt is the growth rate of N tumor cells at time t, k1 is a constant reflecting the mitotic gain vs. cell losses of tumor cells in contact with the microenvironment, k2 reflects the mitotic gain vs. cell losses of tumor cells not in contact with the microenvironment, and D is related to the fractal dimension of the tumor architecture, which is expressed as a function of time, because it could change in response to intrinsic changes (including mutations) or extrinsic changes (including therapy). These parameters are measurable and the impact of their perturbation quantifiable with theoretical and practical implications to be discussed.

Biosketch:

Dr. Larry Norton, Norna S. Sarofim Chair of Clinical Oncology and Director, Lauder Breast Center, Memorial Sloan Kettering Cancer Center, is Professor of Medicine at Weill-Cornell Medical College. He is a founder of the Breast Cancer Research Foundation and has served as its Scientific Director since the Foundation's inception in 1993. Dr. Norton has served on, or chaired, numerous committees of the National Cancer Institute, National Institutes of Health, and the Institute of Medicine of the National Academy of Sciences and has served as President of the American Society of Clinical Oncology among other leadership roles.

Dr. Norton has dedicated his life to the eradication of cancer by activities in medical care, laboratory and clinical research, advocacy, and government His research is broad, but he is best known for mathematical modeling in therapeutic development. He has been involved in the development of several effective agents including paclitaxel and trastuzumab. He co-invented the Norton-Simon Model of cancer growth which has broadly influenced cancer therapy, and more recently the self-seeding concept of cancer metastasis and growth. He is the Principal Investigator of an NCI Program Project Grant in Models of Human Breast Cancer and author of more than 350 published articles and many book chapters.

Among many honors, he received ASCO’s Karnofsky and Bonadonna Awards, the McGuire Lectureship at the San Antonio Breast Cancer Symposium, MSKCC's Whitmore Award for Clinical Excellence, the Columbia University’s Gold Medal for Outstanding Achievement in Medical Research as well as the Thomson Reuters Highly Cited Researcher Certificate.

Giorgio INGHIRAMI

Weill Cornell University, New York

The Maladapted Vascular Niche Initiates Tumor Stem Cells, and Fosters Metastasis and Chemoresistance by Supplying Aberrant Angiocrine Factors

We have set forth the transformative concept that tumor growth is not merely cell autonomous but rather requires the interaction of tumor cells within a pro-tumorigenic niche. We have shown that endothelial cells (ECs) within the tumors comprise of specialized vascular elements that are not just passive conduits to deliver nutrients. Conversely, maladapted tumor ECs establish a pro-tumorigenic niche, which via paracrine/angiocrine factors, directly induces the generation of tumor initiating cells (TICs). Tumors subvert the physiological function of the ECs by provoking aberrant expression of angiocrine factors, i.e.Jaggd-1, Jagged-2, Dll4, IGF1, and proteases, by downregulating tumor suppressor genes, such as IGFBP7, thus igniting tumor invasion, metastasis, and conferring chemoresistance. We predict that selective targeting of the perfusion-independent functions of ECs blocking the FGF4-FGFR1/Jagged1-Notch2 loop, or infusing IGFBP7 as well as other angiocrine factors (i.e. CXCR4/CXCR7, Selectins) could diminish the frequency of TICs, enhance chemosensitivity, and prevent clinical relapse.

Biosketch:

Giorgio Inghirami is a clinical scientist and Hematopathology practitioner. His main interest lays in the dissection of the molecular mechanisms leading to the transformation and maintenance of neoplastic phenotypes of lymphoma. In particular, his group has dissected the oncogenic properties of genomic aberrations associated with T-cell lymphoma, mainly Anaplastic Large Cell Lymphoma (ALCL). Over the years he has developed novel mouse models and applied genomics approaches (WES, total RNA, ERBSS, ATACseq,

metabolomics and proteomics HTP platforms) to define the mechanisms of actions leading to lymphoma. These approaches have highlighted new scenarios, demonstrating that the lymphoma phenotypes depend on dynamic and conflicting forces, which continuously forge tumor clones and their evolution and on the close relationship between tumor cells and their microenvironment. Deep sequencing approaches and single cell analyses have been recently applied to picture the clonal complexity of lymphomas and their normal counterpart elements. His laboratory has pioneered different 2D and 3D models using engineered normal lymphocytes and lymphoma cells from primary or Patient Derived Tumor Xenograft (hPDTX) models to generate drug response signatures in cancer patients. His group has collaborated with many scientists and more recently he has established a program project to interrogate the role of endothelial cells in sustaining leukemia and other human cancers in collaboration with Drs. Shahin Rafii and Olivier Elemento, leaders in their respective fields.

Vera GORBUNOVA

University of Rochester, Rochester, River Campus

Lessons from Cancer-Resistant Species of Mammals

Animals have evolved a dramatic diversity of aging rates, from 2 years maximum lifespan in a shrew to over 200 years in a Bowhead whale. Mammalian species also vary greatly in susceptibility to cancer, with longer-lived species being more cancer resistant. We study naturally evolved mechanisms of cancer resistance in long-lived mammalian species. The naked mole rat is a small rodent characterized by very low cancer incidence and a 30 year maximum lifespan. We previously showed that multiple naked mole rat tissues produce abundant high molecular weight hyaluronic acid (HMW-HA) that prevents cancer development. We have also identified distinct mechanisms of cancer resistance in the blind mole rat, which rely on an interferon-mediated necrotic response. Our current studies are also focused on cancer resistance mechanisms in the bowhead whale. Our goal is to ultimately apply these new mechanisms to prevent or treat cancer in human patients.

Biosketch:

Vera Gorbunova is a Professor of Biology at the University of Rochester and a co-director of the Rochester Aging Research Center. Her research is focused on understanding the mechanisms of longevity and genome stability and on the studies of exceptionally long-lived mammals. Dr. Gorbunova earned her B.Sc. degrees at Saint Petersburg State University, Russia, and her Ph.D. at the Weizmann Institute of Science, Israel. Dr. Gorbunova pioneered comparative biology approaches to study aging and identified rules that control evolution of tumor suppressor mechanisms depending on the species lifespan and body mass. Dr. Gorbunova also investigates the role of Sirtuin proteins in maintaining genome stability. More recently the focus of her research has been on the longest-lived rodent species, the naked mole rats and the blind mole rat. Dr. Gorbunova identified high molecular weight hyaluronan as the key mediator of

cancer-resistance in the naked mole rat. Her work received awards from the Ellison Medical Foundation, the Glenn Foundation, American Federation for Aging Research, and from the National Institutes of Health. Her work was awarded the Cozzarelli Prize from PNAS, the prize for research on aging from ADPS/Allianz, France, the Prince Hitachi Prize in Comparative Oncology, Japan, and the Davey prize from the Wilmot Cancer Center.

Barbara MARTE

Nature, London

Biosketch:

Barbara Marte is a Senior Editor with Nature, based in London. She did a Diploma in Human Biology at the University Marburg, her PhD at the University Basel and a postdoctoral fellowship at the Imperial Cancer Research Fund in London. Barbara joint Nature in 1997 and is responsible for covering cancer at Nature.


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