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2022 RITA LEVI-MONTALCINI LECTURE by Nobel Laureate David Julius

&

INTERNATIONAL WORKSHOP 'FROM TOUCH TO PAIN'

ABSTRACTS & BIOGRAPHIES

AUDITORIUM MAXXI- MUSEO NAZIONALE DELLE ARTI DEL XXI SECOLO (Rome)

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Nobel Laureate

David Julius
Morris Herzstein Chair in Molecular Biology and Medicine, Professor and Chair in the Department of Physiology, University of California

ABSTRACT

Gut Feelings: probing mechanisms of visceral pain

Gastrointestinal discomfort and pain are associated with inflammatory and post-inflammatory disorders (such as irritable bowel syndrome) that can leave sufferers with chronic visceral pain and hypersensitivity long after signs of tissue injury and inflammation have resolved. IBS and other such functional pain disorders also show a substantial sex disparity, with about three-fold greater prevalence among women than men. This seminar will focus on interactions between primary afferent nerve fibers and sensory neuroendocrine cells in the gut, with the goal of understanding how these interactions contribute to acute and persistent visceral pain in males and females.

Biography

David Julius, a native of New York City, received his undergraduate degree from MIT, where he worked with Alexander Rich studying mechanisms of tRNA aminoacylation. He then moved to the University of California at Berkeley for graduate studies with Jeremy Thorner and Randy Schekman, elucidating mechanisms of peptide hormone processing and secretion in yeast, followed by postdoctoral studies with Richard Axel at Columbia University, where he identified genes encoding members of the serotonin receptor family. David then joined the faculty at the University of California, San Francisco, where he is currently the Morris Herzstein Chair in Molecular Biology and Medicine and Professor and Chair in the Department of Physiology.

A major focus of David's work is to elucidate molecular mechanisms of somatosensation and pain, and sensory adaptation. His group has exploited the properties of natural products to discover a family of thermo- and chemo-sensitive ion channels that enable sensory nerve fibers to detect hot or cold temperatures and other noxious stimuli. With the aid of genetic, electrophysiological, and behavioral methods, they have determined how these ion channels contribute to pain sensation, and how channel activity is modulated in response to tumor growth, infection, or other forms of injury that produce inflammation and pain hypersensitivity.

David is a member of the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, the Hungarian Academy of Sciences (Honorary), and the Norwegian Academy of Science and Letters (Foreign Member). His work has been recognized by numerous awards, including the Shaw Prize in Life Sciences and Medicine, the Canada Gairdner International Award, the Breakthrough Prize in Life Sciences, and the Nobel Prize in Physiology or Medicine.

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Bailong Xiao
School of Pharmaceutical Sciences & Tsinghua-Peking Joint Center for Life Sciences, IDG/McGovern Brain Research Institute, Tsinghua University, Beijing, China

ABSTRACT

Feeling Force with PIEZOs

PIEZO1 and PIEZO2 have been identified by Patapoutian and colleagues as bona fide mechanoreceptors, which mediate the sense of gentle touch, proprioception, blood pressure, tactile pain and regulate cardiovascular function and bone formation and remodeling. To understand how PIEZOs function as mechanically activated cation channels to effectively convert piconewton-scale forces into selective cation permeation, we have first determined the cryo-EM structures of PIEZO1 and PIEZO2. PIEZOs possess a unique 38-transmembrane (TM) helix topology and form bowl-shaped trimers comprising a central ion-conducting pore with an extracellular cap and three curved and non-planar blades with intracellular beams, which may undergo force-induced deformation within lipid membranes. To explore the mechano-gating dynamics of PIEZO channels in lipid membranes, we have determined the curved and flattened structures of PIEZO1 reconstituted in liposome vesicles, directly visualizing the substantial deformability of the PIEZO1-lipid bilayer system and an in-plane areal expansion of approximately 300 nm2in the flattened structure. The curved structure of PIEZO1 resembles the structure determined from detergent micelles, but has numerous bound phospholipids. By contrast, the flattened structure exhibits membrane tension-induced flattening of the blade, bending of the beam and detaching and rotating of the cap, which could collectively lead to gating of the ion-conducting pathway. On the basis of the measured in-plane membrane area expansion and stiffness constant of PIEZO1, we calculate a half maximal activation tension of about 1.9 pN nm-1, matching experimentally measured values. Thus, our studies have provided a fundamental understanding of how the notable deformability and structural rearrangement of PIEZO achieve exquisite mechanosensitivity and unique curvature-based gating in lipid membranes.

Biography

Dr. Bailong Xiao is a Professor at the School of Pharmaceutical Sciences in Tsinghua University, as well as a Principal Investigator at the Tsinghua-Peking Center for Life Sciences, the IDG/McGovern Institute for Brain Research, and the Beijing Advanced Innovation Center for Structural Biology. He obtained his B.S. degree from the Sun Yat-Sen University in China in 2001, and did his PhD study in the University of Calgary in Canada from 2001 to 2006, focusing on the structure-function relationship of the cardiac Ryanodine Receptor. From 2007 to 2012, he conducted his postdoctoral training with Dr. Ardem Patapoutian at the Scripps Research Institute in the United States, where he made contributions to the establishment of the mechanically activated PIEZO channel family and the identification of STIM1 as a novel temperature sensor. After joining the faculty of the School of Pharmaceutical Sciences in Tsinghua University in 2013 as an Assistant Professor, he has established a multidisciplinary research program to advance the understanding of the structure-function relationships as well as physiological and pharmacological regulations of PIEZO channels.

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ABSTRACT

Vera Moiseenkova-Bell
Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

TRPV Channels Gating by Endogenous and Exogenous Modulators

Transient Receptor Potential channels from the vanilloid subfamily (TRPV) are a group of cation channels that play a critical role in a variety of physiological and pathophysiological
processes. They are modulated by a variety of endogenous stimuli as well as a range of natural and synthetic compounds. Their roles in human health make them of keen interest, particularly from a pharmacological perspective. However, despite this interest, the complexity of these channels has made it difficult to obtain high resolution structures until recently. With the cryoelectron microscopy (cryo-EM) resolution revolution, our laboratory produced several TRPV channels structures and determine mechanisms of TRPV channels activation, inhibition and desensitization. This newly obtained information could guide us towards the design of novel TRPV channles specific therapeutic molecules.

Biography

Dr. Moiseenkova-Bell is a membrane protein biochemist and a structural biologist with expertise in cryo-electron microscopy (cryo-EM). Her research is focused on structure-function analysis of Transient Receptor Potential (TRP) channels and their interaction with agonists/antagonists to enhance our understanding of their function at the molecular level. In addition, her laboratory research program seeks to understand how TRP channels regulate cellular functions and the role of their dysregulation in human disease.

After obtaining a M.S. degree in Physics from Moscow State University in 1999, Dr. Moiseenkova-Bell switched to a biological research area and received Ph.D. in Cellular Physiology & Molecular Biophysics from the University of Texas Medical Branch in 2004. During her graduate work, she was the first to develop a methodology for overexpression and purification of functional TRP channels for structural studies. As a postdoctoral fellow, Dr. Moiseenkova-Bell continued her work on TRP channels at Baylor College of Medicine (BCM). During her training at BCM, she was the first researcher to solve and report the structure of a TRPV1 channel using cryo-EM. Because of this achievement, she received the Ruth McLean Bowman Bowers Excellence in Research Award from BCM. In 2009, Dr. Moiseenkova-Bell joined Department of Pharmacology at Case Western Reserve University (CWRU) as a tenure track Assistant Professor and was promoted to Associate Professor with tenure in 2016. Dr. Moiseenkova-Bell moved to University of Pennsylvania in 2018, where she is a Full Professor and she is continuing her work on understanding molecular mechanisms of TRP channel activation, inhibition and desensitization using cryo-EM at the Department of Systems Pharmacology and Translational Therapeutics. She is also a Faculty Director of the Beckman Center for Cryo-EM and Electron Microscopy Resource Laboratory at the University of Pennsylvania.

In the past twelve years, Dr. Moiseenkova-Bell established herself as an independent scientist and as an expert in the field of TRP channels, focused on structural and functional analysis. She has published papers in Journal of Biological Chemistry, Journal of General Physiology, Molecular and Cellular Biology, Structure, Cell Reports, Nature Communications, Nature Structural and Molecular Biology. She has given numerous invited seminars and presentations both at the national and international levels. Dr. Moiseenkova-Bell has secured funding for her research from American Lung Association, American Heart Association, Mt. Sinai Foundation, Pfizer and NIH.

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ABSTRACT

Gary Lewin
Molecular Physiology of Somatic Sensation, Max Delbrück Center for Molecular Medicine, Berlin

Molecular tethers and novel ion channels required for touch

The fingertip feel of the finest silk requires mechanoreceptors in the skin that are able to detect nanometer scale mechanical deflections. The sensory transduction events required for our sense of touch are widely accepted to be due to the opening of fast mechanosensitive ion channels. However, work from model organisms like flies and worms has long suggested that sensory transduction channels may be tethered and gated by movement of the extracellular matrix. We have provided evidence that proteinaceous extracellular tethers are required for normal touch receptor function and such proteins may convey force from the matrix to mechanosensitive ion channels (Hu et al 2010; Chiang et al 2011). The molecular identity of such tether proteins was, however, unknown. Using mouse genetics and highly site-specific proteases we have now identified at least one component of such "touch tethers". The mechanosensitive ion channel, PIEZO2 is regulated by stomatin-like protein-3 oligomers (STOML3) and the Stoml3gene is, like Piezo2,genetically required for normal touch. However, both these proteins are dispensable for mechanotransduction in more than half of all touch receptors. In this lecture I will show evidence that a second mechanosensitive ion channel ELKIN1 is required for touch transduction in a Piezo2 independent manner. We conclude that there are multiple molecular players in touch transduction that work together to build receptors capable of detecting nanoscale mechanical events.

The Piezo2 ion channel is genetically required for normal touch sensation in mice, but is dispensible for the function of more that 50.

Biography

Gary is Manx and grew up in Douglas on the Isle of Man.He received his first degree in Physiology and Pharmacology from Sheffield University in 1986, then worked on his doctoral thesis in Stephen B. McMahon's lab at St. Thomas's Hospital Medical school in London. He received his Ph.D. in February of 1990.

He then moved to the lab of Professor Lorne Mendellin New York at Stony Brook. He worked in Lorne's lab for almost four years and in the last year he was appointed Research Assistant Professor. It was in Lorne Mendell's laboratory that Gary discovered that NGF is a critical mediator of hyperalgesia and pain. These findings formed the mechanistic basis of anti-NGF medication, like Tanezumab, that hold great promise for the treatment of inflammatory pain.

In 1993 he received a von Humboldt Fellowshipto work in the department of Neurobiochemistryat the Max-Planck Institute for Psychiatry in Munich under the directorship of Professor Yves-Alain Barde. In February of 1996 he took up an appointment as an independent Group Leader at the MDC in Berlin. The projects in his lab first focused on the molecular basis of sensory neuron mechanotransduction and sensory ion channels. In 2003 Gary obtained a joint appointment at the Charité University Medical Faculty as a full Professor. The lab recently developed small drug-like molecules that can interfere with touch sensation and can be used to treat pain. Over the last 10 years the Lewin lab has pioneered the molecular exploitation of extreme physiology observed in the naked mole-rat and other African rodents. The lab has broadened its outlook and now looks at molecules that may promote metabolic health inspired by the phenomenal fitness and longevity of the naked mole-rat.

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Mathew Diamond
Scuola Internazionale Superiore
di Studi Avanzati, Trieste

ABSTRACT

How touch is processed to support multiple percepts

When we consider the processing of a tactile stimulus, it is natural to focus on transduction mechanisms, the subsequent neuronal coding, and the perceptual outcome of this process. But a second percept, explicitly or implicitly, accompanies the tactile experience – the feeling of time occupied by that stimulus. To explore the connection between stimulus perception and time perception, we begin with human and rat psychophysics. When subjects judge the duration of a vibration applied to the fingertip (human) or whiskers (rat), increasing stimulus intensity leads to increasing perceived duration. Symmetrically, increasing vibration duration leads to increasing perceived intensity. From this relationship, we build a computational framework where the vibration-evoked firing early in the processing stream is accumulated by two integrators, in parallel, each integrator giving rise to a corresponding percept (intensity and duration). This framework predicts that direct intervention on the activity of sensory cortex will have perceptual effects on both intensity and duration, and we verify this by optogenetics in rats. Time is a sense without a sensory system; our experiments show how touch can be "highjacked" to supply the sensory input giving rise to perceived time.

Biography

Mathew Diamond obtained his BSc in Engineering Science at the University of Virginia (USA) in 1984 and his PhD in Neurobiology at the University of North Carolina (USA) in 1989.

After a postdoctoral position at Brown University and an Assistant professor position at Vanderbilt University, Diamond joined the International School for Advanced Studies (SISSA). Since 2000 he has been a SISSA professor of Cognitive Neuroscience and Director of the Laboratory of Tactile Perception and Learning.

He serves on the faculty of: SISSA Phd in Cognitive Neuroscience; SISSA PhD in Theoretical and Scientific Data Science; Università Ca' Foscari (Venice)/SISSA Master's degree in Computational Neuroscience

Diamond's research is done through the SISSA Tactile Perception and Learning Laboratory. The lab aims to understand the neuronal language of memory and perception – how brain activity gives rise to meaningful percepts, how these are stored and recalled to guide decisions. Besides publications in journals, other work includes the 2011 and 2020 editions of the popular textbook From Neuron to Brain (Oxford Univ Press). The lab has trained 17 PhDs and 16 postdocs; among these, twelve nations are represented.

Additionally, Diamond serves as the SISSA International Relations Delegate (2015-present). Recent efforts concern setting up SISSA programs to host scholars (from PhD to faculty) fleeing from war. In the last several months, the Afghanistan and Ukraine crises have been pressing.

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Paul Heppenstall
Scuola Internazionale Superiore
di Studi Avanzati, Trieste

ABSTRACT

Developing tools to target Primary Afferent Subtypes

A number of recent mouse genetic studies have demonstrated that distinct subpopulations of primary afferent contribute to behavioral responses to different types of mechanical, thermal and chemical nociceptive stimuli. Focusing on work from my laboratory in which we have targeted populations of sensory neuron defined by their Trk receptor expression, I will discuss how opto- and pharmacogenetic approaches can be used to control sensory input from the periphery and thus regulate behavior in transgenic mice. Taking this approach further I will show how these genetic strategies can also be translated into pharmacological technologies by means of the ligands that bind to membrane receptors expressed on these distinct populations of neuron. Using BDNF and NGF as examples, I will describe how cargoes such as photosensitizers can be attached to these molecules and delivered in vivo in mice. Application of light to the skin then results in retraction of neurons from their end organs and long-term reversal of pain behavior in animal models of acute, inflammatory and neuropathic pain. Finally, I will discuss how this technology can be applied to other ligands with the ultimate aim of gaining optical and chemical control over neuronal activity, thus inhibiting pain and itch at its source.

Biography

Paul Heppenstall trained as a physiologist at the University of Edinburgh for his PhD, before moving to the Max Delbrueck Centrum, Berlin for postdoctoral training. In 2002, he was awarded a Junior Professor position in the Department of Anaesthesiology, Charité, Berlin where he started his own research programme in molecular pain research. In 2008, he moved to EMBL Rome where he led a research group studying the molecular physiology of somatosensation. In 2011, this was supplemented by a joint group leader position at the Molecular Medicine Partnership Unit (MMPU) in Heidelberg. Since 2018 he has been a full professor at SISSA. Paul has been working in pain research for more than 25 years and has made contributions to spinal cord physiology and pharmacology, sensory mechanotransduction, and peripheral nervous system biology. A major focus of his laboratory is to now translate research findings into new treatments for pain and itch.

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ABSTRACT

Silvia Marinelli
European Brain Research Institute (EBRI)
'Rita Levi-Montalcini'
Group Leader Laboratory 'Neurons and microglia in the physiopathology of cortical microcircuits'

TRPV1 and NGF signals in the brain

In my presentation I will talk about the TRPV1 and NGF signals in the brain in both physiological and diseased conditions, including neuropathic pain. I will first provide separate evidence on the functional expression of these two systems in the microglia and their capability in regulating microglia to neuron communication. Next, I will show our recent findings on the interaction between TRPV1 and NGF signals and their relationship in the prefrontal cortex of transgenic mice.

Overall, we can sum up a different and diverse reciprocal interactivity of the two systems in the brain, with respect to the peripheral nervous system.

Biography

Born in Rome, Italy, Silvia Marinelli obtained her PhD in Neuroscience at University of Rome Tor Vergata after spending some years at the University of Sydney (Australia) where she studied the cellular mechanisms of descending control of pain transmission and gained interest in ion channels, i.e. TRPV1, involved in pain transmission at brain level.

She later joined the group of Alberto Bacci at the European Brain Research Institute (EBRI) 'Rita Levi-Montalcini', in Rome. There, she studied and identified specific forms of synaptic plasticity in cerebral cortex microcircuits. She is currently group leader of the laboratory Neurons and microglia in the physiopathology of cortical microcircuits at EBRI. One of the main research interests of her laboratory is looking into the cross-talk between microglia and neurons with the aim of uncovering specific signals underlying the neuro-immune communication.

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ABSTRACT

Moses Chao
Depts of Cell Biology, Physiology & Neuroscience
and Psychiatry
NYU Langone Medical Center

Independence of neurons for trophic factors
Little is known about how neurons become independent of trophic support. Answering this question will provide insight into how neurons avoid cell death and persist for a lifetime. An increased resistance to loss of trophic factors represents a protective mechanism to prevent neurodegeneration.

Biography

Moses V. Chao is Professor of Cell Biology, Physiology & Neuroscience and Psychiatry at NYU School of Medicine. His research interests lie in defining mechanisms used by trophic factors to change synaptic plasticity. Chao served as Senior Editor for the Journal of Neuroscienceand is a member of the Advisory Boards for the Simons and Pritzker Foundations, Target ALS and the Crick and Weizmann Institutes. Chao was President of the Society for Neuroscience in 2012. He is a recipient of the Zenith Award, a Jacob Javits Neuroscience Investigator Award, a Guggenheim Fellowship and the Julius Axelrod Prize.

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ABSTRACT

Simona Capsoni
Associate Professor,Physiology Section, Department of Neuroscience and Rehabilitation University of Ferrara; Bio@SNS, Laboratory of Biology, Scuola Normale Superiore, Pisa

Genetic painlessness diseases: lessons from the NGF-TrkA system

Nerve growth factor (NGF), by binding to TrkA and p75NTR receptors, regulates the survival and differentiation of sensory neurons during development and mediates pain transmission and perception during adulthood, by acting at different levels of the nervous system. This notion is also supported by the finding that mutations in the TrKA and NGF genes cause the painlessness diseases Hereditary Sensory and Autonomic Neuropathy type IV (HSAN IV) and V (HSAN V), respectively. Here we shall review the consequences of the R649W mutation in the TrkA gene and of the R100W mutation in the NGF gene. Each of them results in specific clinical signs: NGFR100Wdetermines congenital pain insensitivity with no overt cognitive disabilities, whereas TrkAR649Walso result in intellectual disability and anhidrosis. Here we will compare behavioral, biochemical, and histological findings in knock-in mice for these mutations to understand not only the possible mechanisms underlying the phenotype distinguishing HSAN IV from V, but also to highlight new roles of the NGF signalling system in central pathways controlling pain perception.

Biography

Simona Capsoni received her DVM degree in 1990 and a PhD in Chemotherapy (1995) at University of Milan, Italy. During her studentship she spent more than one year at the Section on Pharmacology, NIMH, NIH (Bethesda, USA). In 1996, she received a fellowship to be trained as industrial researcher. During that period, she spent one year at the International School for Advanced Studies in Trieste (ISAS, Italy) and then she moved to Fidia Pharmaceuticals in Abano Terme (Italy).

In 1998, SC moved back to ISAS and started her research on neurotrophins and Alzheimer's disease and a long-lasting collaboration with Prof. Antonino Cattaneo. She characterized neurodegenerative phenotype of the AD11 anti-Nerve Growth Factor (NGF) mouse model. In 2000 she started to set up the intranasal method to deliver NGF to the brain. In 2002 SC became the Head of the AD Research Program at Lay Line Genomics S.p.A., a biotech company spin-off of ISAS. In that period, she started to characterize the mutant form of human NGF, painless NGF (hNGFp).

In 2008 she moved to the European Brain Research Institute where she continued to characterize hNGFp and she had the opportunity to have as co-supervisor prof. Rita Levi-Montalcini on the characterization of the effects of NGF deprivation on chicken embryo development.

In 2010 she joined the Bio@SNS Laboratory of Biology at Scuola Normale Superiore in Pisa (Italy) as contract junior professor where she discovered that NGF and hNGFp can affect the pathophysiology of glial cells, in particular microglia. At the same time, she started the line of research on NGF signalling system in painlessness diseases. In 2016 SC became Associate Professor of Physiology at University of Ferrara and Scuola Normale Superiore where she is continues her research on the therapeutic application of hNGFp.

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ABSTRACT

Fabrizio Benedetti
Professor, University of Turin Medical School, Neuroscience Dept, Turin, Italy
Director, Program in Medicine and Physiology of Hypoxia, Plateau Rosà, Italy/Switzerland

Relieving pain with words and drugs: a common mechanism of action

Although placebos have long been considered a nuisance in clinical research, today they are an active and productive field of research in neuroscience because they represent an excellent model to understand how social interaction and the doctor's words may affect the patient's brain and illness. Because of the involvement of many mechanisms, they can actually be viewed as a melting pot of concepts and ideas for neuroscience. For example, brain mechanisms of expectation, anxiety, reward are all involved, as well as a variety of learning phenomena, such as Pavlovian conditioning, cognitive and social learning. There is also some evidence of different genetic variants in placebo responsiveness. Overall, the concept that is emerging today is that placebos, words and drugs share common mechanisms of action.

Biography

Fabrizio Benedetti, MD is Professor of Neurophysiology and Human Physiology at the University of Turin Medical School, Turin, Italy, and Director of Medicine and Physiology of Hypoxia at Plateau Rosà, Switzerland. He has been nominated member of The Academy of Europeand of the European Dana Alliance for the Brain. He is author of the book Placebo Effects (Oxford University Press, 3rd Edition, 2020), which received the Medical Book Award of the British Medical Association. In 2012 he received the Seymour Solomon Award of the American Headache Society, in 2015 the William S Kroger Award of Behavioral Medicine from the American Society of Clinical Hypnosis. In 2015 he was nominated member of the Council of Scientists of the Human Frontiers Science Program Organization.