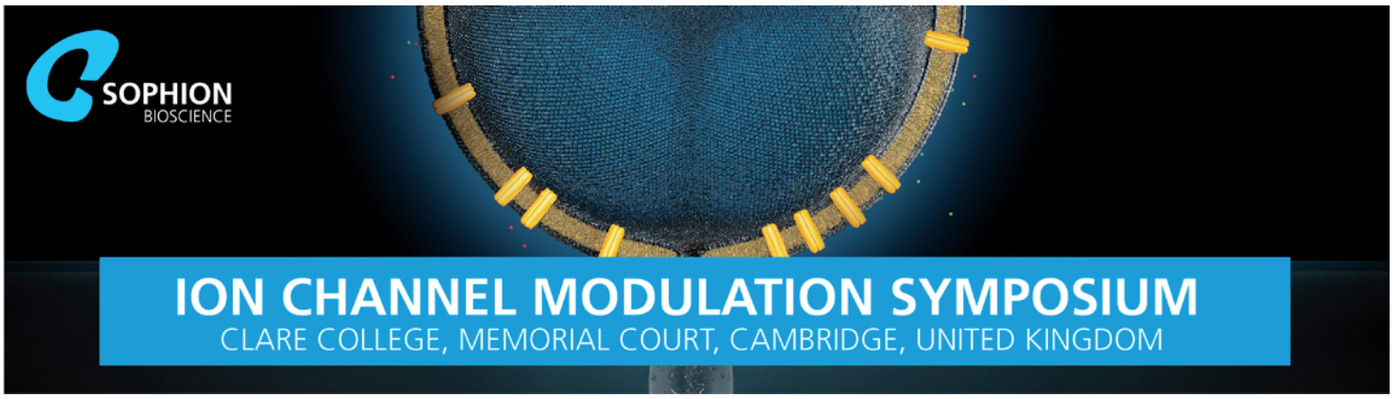

Agenda - 20th June, 2018

08.00	Registration - Tea/Coffee
09.00	Welcome Remarks
	Session 1 - Chair: Professor David Wyllie - Edinburgh University, UK
09.15	Professor Matthew Nolan - Edinburgh University, UK *Diverse computational roles for HCN1 ion channels in behaviour*
09.40	Dr Hongjie Yuan - Emory University, USA *GRIN mutations in neurological diseases: from molecular mechanism to rescue pharmacology*
10.05	Dr Stephen Brickley - Imperial College London (ICL), UK *Age-related changes in synaptic transmission during cognitive decline*
10.30	Tea/Coffee, Exhibits and Posters
11.15	Professor Hirokazu Hirai - Gunma University Graduate School of Medicine, Japan *GABA-B receptor and type 1 metabotropic glutamate receptor (mGluR1) as therapeutic targets for hereditary spinocerebellar ataxia*
11.40	Professor Jian Yang - Columbia University, USA *Antiarrhythmic natural compounds and structural basis of modulation of an endolysosomal calcium channel*
12.05	Professor Lucia Sivilotti - University College London (UCL), UK *Agonist efficacy in Cys-loop ion channels: the single molecule view*
12.30	Lunch
	Session 2 - Chair: Professor Derek Bowie - McGill University, Canada
14.00	Professor Annette Dolphin - University College London (UCL), UK *Neuronal calcium channel trafficking and function: relevance to chronic pain*
14.25	Professor Yasuo Mori - Kyoto University, Japan *Redox biology of TRP channels*
14.50	Professor Uwe Rudolph - McLean Hospital and Harvard University, USA *Towards a circuit-based pharmacology of GABA-A receptors*
15.15	Tea/Coffee, Exhibits and Posters
16.00	Assistant Professor Saviero Gentile - Loyola University Chicago, USA *Cancer as channelopathy: Activating potassium channels as a novel and safe therapeutic approach against cancer*
16.25	Professor Diane Lipscombe - Brown University, USA *Cell-specific splicing of neuronal calcium channels: Function, pharmacology and targets*
16.50	Professor Anders Jensen - Copenhagen University, Denmark *Probing the molecular basis for potency- and efficacy-based subtype-selectivity exhibited by benzodiazepine-site modulators at GABA-A receptors*
17.15	Wrap Up
17.30	Drinks Reception in the Scholar's Garden
18.30	Dinner in the Great Hall of Clare College

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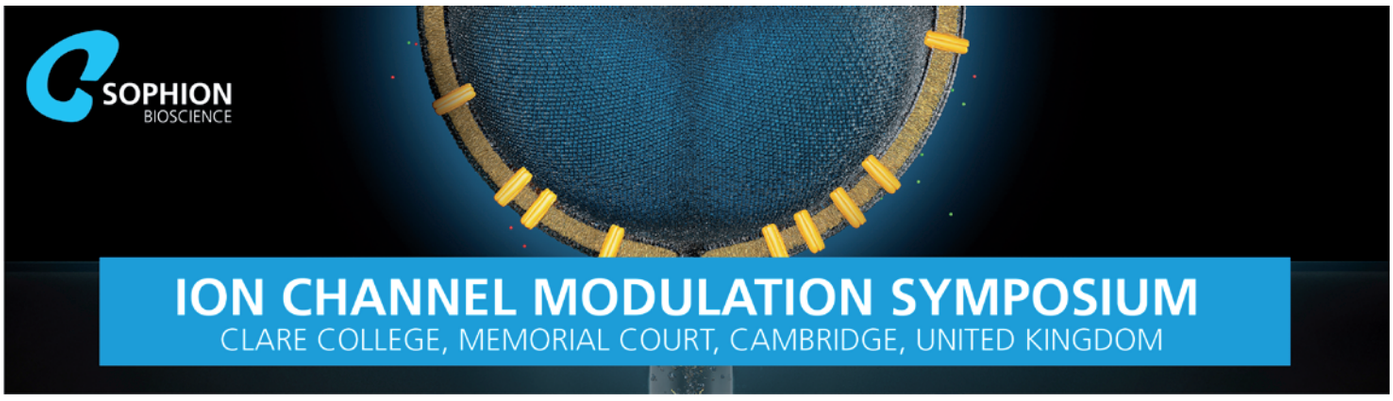

Agenda - 21st June, 2018

08.00	Tea/Coffee
09.00	Welcome Remarks
	Session 3 - Chair: Professor Stephen Tucker - Oxford University, UK
09.15	Professor David Beech - Leeds University, UK *Piezo1 channel function and small-molecule modulation*
09.40	Professor David Bennett - University of Oxford, UK *The role of $Na_V1.7$ in human pain disorders*
10.05	Professor Jun-ichi Okada - University of Tokyo, Japan *Cardiac safety assessment of drugs based on a hybrid system combining automated patch clamp and heart simulator*
10.20	Tea/Coffee, Exhibits and Posters
11.20	Professor Bonnie Wallace - Birkbeck College, University of London, UK *Voltage-gated sodium channels: structure, function and disease*
11.45	Professor Dr. Gary Lewin - Max-Delbrück-Center for Molecular Medicine, Germany *Modulating force sensing channels by voltage and small molecules*
12.10	Professor Nikita Gamper - Leeds University, UK *Modulation of Kv7 potassium channels by intracellular zinc*
12.35	Lunch
	Session 4 - Chair: Professor Martin Gosling - Sussex University, UK
14.00	Professor Thomas Jentsch - Max-Delbrück-Center for Molecular Medicine, Germany *The volume regulated anion channel VRAC: structure-function and surprising roles*
14.25	Professor David Sheppard - Bristol University, UK *Cystic fibrosis: rescuing defective chloride channels with small molecules*
14.50	Associate Professor Bo Hjorth Bentzen - Copenhagen University, DK *Modulation and anti-arrhythmic potential of SK channels*
15.15	Professor Raimund Dutzler - Zurich University, Switzerland *Mechanism of ion conduction and gating in the calcium-activated chloride channel TMEM16A*
15.40	Wrap Up

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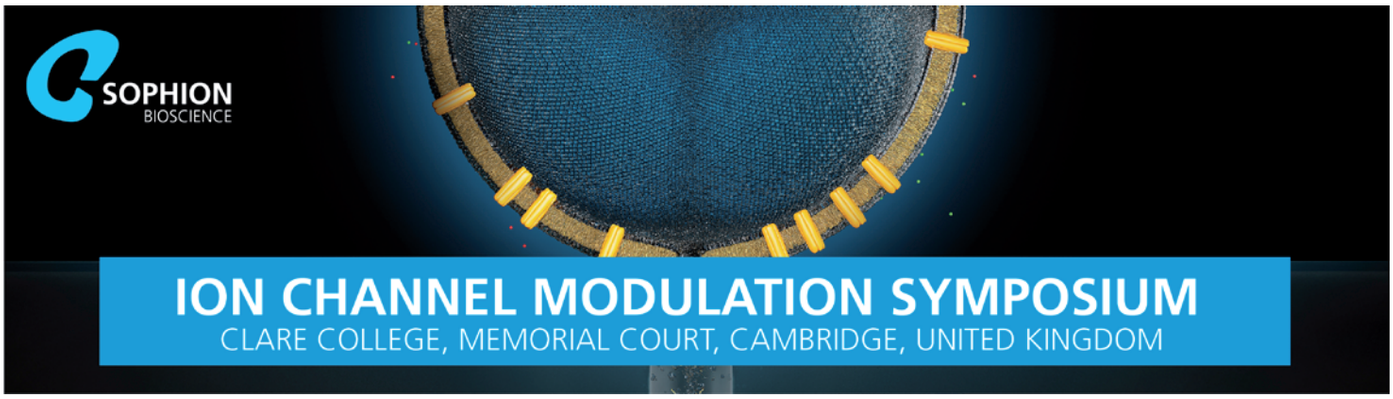


Biographies - Advisory board

Martin Gosling- Sussex University, UK

Martin has devoted his research career to realising the therapeutic potential of ion channels in both industrial and academic settings.Subsequent to completing a BSc degree in Pharmacology at the University of Leeds, Martin received his PhD from the Department of Pharmaceutical Sciences at the University of Aston in Birmingham by studying ion channels in bone and muscle cells. His ion channel research continued throughout his post-doctoral studies at Imperial College and in 1998 Martin was appointed as lecturer in Vascular Physiology at Imperial College School of Medicine. Martin joined Novartis in 2001 in the Respiratory Diseases Area based in Horsham UK, and established an industry leading ion channel discovery group focused upon programs for the treatment of respiratory, CNS, inflammatory and cardiovascular diseases. Martin and his associated teams made pivotal contributions to the identifi cation of numerous clinical candidates, several of which are still progressing through clinical development. In 2014 Martin joined the University of Sussex, establishing a group developing respiratory therapeutics programs and collaborating with colleagues in CNS ion channel drug discovery. Martin is also a founder and Chief Scientific Officer of Enterprise Therapeutics, a Sussex-based respiratory biotech company.

Derek Bowie - McGill University, Canada

Dr. Derek Bowie is the Director of the FRQS-funded research group, GEPROM, and has been a Professor at McGill University since 2002. He is the recipient of the Canada Research Chair award in Receptor Pharmacology and serves on the editorial boards of the Journal of Physiology, Current Neuropharmacology and Channels. Dr. Bowie earned his Ph.D. at the University of London after completing his undergraduate degree at Strathclyde University in Scotland. He then carried out postdoctoral training in France (Université Louis Pasteur), Switzerland (University of Zurich) and the USA (National Institutes of Health) before holding a faculty position at Emory University in Atlanta. The Bowie lab focuses on the structure-function properties of ionotropic glutamate receptors, GABA-A receptors and sodium channels as well as examining their role in neuronal circuit behaviour.

David Wyllie - Edinburgh University, UK

My long-standing research interest is in ligand-gated ion channels (LGICs) – specialized pore-forming membrane proteins that are activated by neurotransmitters during 'fast' chemical synaptic transmission. In particular my lab studies LGICs activated by L-glutamate – the major excitatory neurotransmitter in the mammalian brain. Although glutamate activates several different classes of LGIC one in particular, the N-methyl-D-aspartate receptor (NMDAR) has been a major focus for our research. Through electrophysiological studies, my lab has contributed signifi cantly to our understanding of the structure-function properties and physiological roles of the various subtypes of NMDARs. NMDARs play pivotal roles in both normal and abnormal brain function. In early life for instance, they ensure that the correct wiring pattern is laid down in the developing brain. Furthermore, activation of NMDARs is required to learn certain tasks and store memories. However, both over- and under-activation of NMDARs can be deleterious for normal brain function. For example, during a stroke excessive activation of NMDARs contributes signifi cantly to neuronal loss, while NMDAR dysfunction is thought to contribute to diseases such as Alzheimer's, Parkinson's and Schizophrenia. More recently it is now recognised that de novo mutations in the protein sequence of NMDARs can lead to intellectual disability. Directly related to our structure-function studies of NMDARs we use pre-clinical models of single gene causes of neurodevelopmental disorders (such as fragile X syndrome) to study the properties of altered synaptic function and to assess the extent to which pharmacological intervention can ameliorate the changes that are observed in such models. A more recent focus of our research is the electrophysiological and functional characterization of defi ned neuronal and glial populations derived from human embryonic stem cells and induced pluripotent stem cells and specifi cally those from individuals suffering from neurodevelopmental and neurodegenerative diseases. Our work seeks to assess the electrophysiological profi le of such neurons in order to further our understanding of these debilitating diseases. Our overall aim is to develop an integrated approach to research that begins with the study of single protein molecules and synaptic function and extends, through collaboration with colleagues, to whole animal studies with an ultimate goal of the clinical study and treatment of disease.

Stephen Tucker - Oxford University, UK

Stephen Tucker is a Professor of Biophysics in the Clarendon Laboratory at the University of Oxford, and also Director the Wellcome Trust PhD programme in Ion Channels and Disease. After studying Biochemistry at Oxford he did his PhD at the Institute of Molecular Medicine at the John Radcliffe Hospital studying the CFTR chloride channel. After this he went to the Vollum Institute, Oregon USA for two years as a Wellcome Trust International Prize Travelling, and in 1996 he returned to Oxford as a Wellcome Trust Career Development Fellow where he worked closely with Prof Dame Frances Ashcroft, FRS on the ATP-sensitive K^+ channel and other inwardly-rectifying K^+ channels. In 2000 he was awarded a Royal Society University Research Fellow in the Dept Physiology, and in 2008 he was appointed to a University Lecturership in the Dept Physics. In 2015 he was made a Professor of Biophysics in the Dept Physics, and is currently a fellow of Green Templeton College, Oxford. The Tucker lab employs a wide range of structural, functional and computational approaches to study ion channels, and current work is focussed on the Two-Pore domain (K2P) family of potassium channels.

Biographies - Speakers

David J Beech - Leeds University, UK

David Beech graduated in Pharmacology from the University of Manchester UK in 1985 before PhD study with Thomas Bolton at St George's Hospital Medical School London and postdoctoral training with Bertil Hille at the University of Washington Seattle USA. In 1992 he established an independent research group at the University of Leeds UK, funded initially by a Wellcome Trust Postdoctoral Career Development Fellowship and then a full university professorship since 2000, moving from the Faculty of Biological Sciences to the Faculty of Medicine and Health in 2013. His research is focussed on calcium-permeable non-selective cationic channels of mammalian cells – their mechanisms, roles and potential as new therapeutic targets. He is particularly interested in the idea that the channels importantly sense physical and chemical factors to regulate cardiovascular and metabolic health. He has trained 74 postgraduate and postdoctoral research scientists, published 150 peer-reviewed articles (including 2 in Nature and 4 in Nature sister journals) and delivered 157 invited lectures worldwide. He was elected to Fellowship of the Academy of Medical Sciences in 2013 and became a Wellcome Trust Investigator in 2016 and British Heart Foundation Programme Grant Holder in 2018. Since 2016 he has been Director of the Leeds Institute of Cardiovascular and Metabolic Medicine, a research and teaching organisation of over 200 staff in the School of Medicine at Leeds. He founded and continues to direct the British Heart Foundation 4-Year PhD Programme in Cardiovascular Disease and Diabetes and the Multidisciplinary Cardiovascular Research Centre, a pan-university / teaching hospital structure for all cardiovascular research in the Leeds region

David Bennett - University of Oxford, UK

David is Professor of neurology and neurobiology at the University of Oxford and honorary consultant neurologist. His subspecialty interest is peripheral neuropathy and neuropathic pain; he administers the neuropathy and pain channelopathy clinic at Oxford University Hospitals. He completed neurology training in London and moved to Nuffield Department of Clinical Neuroscience, Oxford in 2012. He is currently a senior Wellcome clinical scientist. His research interest is to understand the process of nerve injury and repair and prevent unwanted outcomes such as neuropathic pain. He takes a broad experimental approach to this problem ranging from understanding ion channel biology to clinical trials.

Stephen Brickley - Imperial College London (ICL), UK

Stephen Brickley is a Reader in Neuroscience for the Department of Life Sciences and member of the Centre for Neurotechnology at Imperial College London. His laboratory specializes in functional & anatomical techniques to study connectivity between neurons during the ageing process. He is a Fellow of the Royal Society of Biology, external examiner for the Department of Neuroscience, Physiology and Pharmacology at UCL and Associate Editor for Frontiers in Molecular Neuroscience.

Annette C. Dolphin - University College London (UCL), UK

Annette Dolphin received her BA in Natural Sciences (Biochemistry) from the University of Oxford and her PhD from University of London, Institute of Psychiatry. She then held postdoctoral fellowships at the College de France in Paris, and at Yale University, before returning to the UK to the National Institute for Medical Research, London; followed by a lectureship in the Pharmacology Department of St. George's Hospital Medical School, London University. She was appointed Chair of the Department of Pharmacology at Royal Free Hospital School of Medicine, London University in 1990, and moved to University College London in 1997. She is a Professor of Pharmacology in the Department of Neuroscience, Physiology and Pharmacology at UCL. She was elected to the Academy of Medical Sciences in 1999, and the Royal Society in 2015. She is a Wellcome Trust Senior Investigator and held a Royal Society Leverhulme Trust Senior Research Fellowship (2016-17).

Raimund Dutzler - Zürich University, Switzerland

In 1994 Raimund graduated in Biochemistry from the University of Vienna before undertaking his PhD in Biophysics at the University of Basel. From 1994 to 1998 Raimund had a postgraduate studentship with Prof. Tilman Schirmer at the University of Basel. In 1999 he became a Postdoctoral Associate with Prof. Roderick MacKinnon, The Rockefeller University, New York, a position that he held until 2003 when he became Assistant Professor (tenure-track) in the Department of Biochemistry, University of Zurich. In 2009 Raimund was appointed Professor of Biochemistry, Department of Biochemistry, at the University of Zurich.

Nikita Gamper - Leeds University, UK

Nikita Gamper got his PhD in Physiology at Sechenov Institute of Evolutionary Physiology and Biochemistry (St Petersburg, Russia). After postdoctoral work at Tuebingen University (Germany) and at the University of Texas Health Science Center at San Antonio (USA). He joined Faculty of Biological Sciences at the University of Leeds where he is currently appointed as Professor of Neuroscience. He also holds a position of Adjunct Professor of Pharmacology at the Hebei Medical University, Shijiazhuang, China. His group studies molecular and cellular mechanisms of nociception. Specifically, the group investigates regulation of ion channels that control or influence excitability of peripheral 'pain' neurons; the group is also interested in the modulation of different neuronal ion channels by G protein-coupled receptors (GPSRs) and in GPCR signalling networks of sensory neurones.

Biographies - Speakers

Hirokazu Hirai - Gunma University, Japan

Dr Hirai is the Professor and Chair in the department of Neurophysiology & Neural Repair, Graduate School of Medicine, and Director of Biosignal Genome Resource Center in Gunma University. He serves as Deputy Director of General Affairs in the Japan Neuroscience Society. His research is focused on synaptic plasticity in the cerebellum and pathophysiology underlying neurodegenerative diseases, principally the autosomal dominant form of spinocerebellar ataxia type 1 and type 3 (SCA1 and SCA3). Hirai and his colleagues identified that GluA2 subunit of the AMPA-type glutamate receptor in cerebellar Purkinje cell is phosphorylated by PKC at the position of Ser 880, which leads endocytosis of AMPA receptors, resulting in expression of LTD at parallel fiber to Purkinje cell synapses. More recently, Hirai and his colleagues found that impairment of mGluR1 signalling is a main cause of cerebellar ataxia found in SCA1 and SCA3, and pharmacological rescue of mGluR1 signalling significantly alleviates the ataxia in the SCA1/SCA3 model mice.

Bo Hjorth Bentzen - Copenhagen University, Denmark

The focus of associate prof. Bo Hjorth Bentzen's research group is to understand the mechanism of cardiac arrhythmia and to find new opportunities for treatment of these. To this end, we work with a broad range of model system ranging from electrophysiological recordings on single cells and zebrafish, to isolated perfused hearts and recordings on conscious large animals. This work has included investigating the mechanism of inherited cardiac arrhythmia and discovering and validating new ion channel drug target for the treatment of cardiac disorders such Long-QT syndrome, ischemia-reperfusion injuries and atrial fibrillation.

Anders A Jensen - Copenhagen University, Denmark

Anders A Jensen obtained his PhD degree from the University of Copenhagen in 2001, and he has been Associate Professor and heading his own research group at this university since 2007. The primary research focus of the Jensen group is molecular pharmacology aspects of Cys-loop receptors, a family of pentameric ligand-gated ion channels mediating the fast signalling of the neurotransmitters acetylcholine, serotonin, γ-aminobutyric acid (GABA) and glycine. A major interest of the group is to identify and develop novel ligands targeting these receptors and to delineate their mechanisms of action at the receptors.

Thomas Jentsch - Max-Delbrück-Center for Molecular Medicine, Germany

Thomas Jentsch studied human medicine from 1972 to 1978 at the Free University of Berlin (FU Berlin) and from 1974 to 1980 physics at the FU Berlin. In 1979, he received his medical degree and earned his diploma in physics. Thomas Jentsch graduated in 1982 with a PhD rer. nat. in physics at the Fritz Haber Institute of the Max Planck Society and the FU Berlin and 1984 Dr med. med. at the FU Berlin. Afterwards, he was a research assistant at the Institute of Clinical Physiology at the Charité Berlin on the Campus Benjamin Franklin. Between 1986 and 1988, he was a postdoc in the department of Harvey F. Lodish at the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology. From 1988 to 1993 Jentsch was Research Group Leader at the Centre for Molecular Neurobiology Hamburg (ZMNH), University Medical Centre Hamburg-Eppendorf. From 1993 to 2006 he was Professor and Director of the Institute of Molecular Neuropathobiology at the ZMNH, from 1995 to 1998 and again from 2001 to 2003 also Director of the ZMNH. Since 2006, Jentsch is full professor at the Charité Berlin. He is head of the research group Physiology and Pathology of Ion Transport at the Leibniz Institute of Molecular Pharmacology and the Max Delbrück Centre for Molecular Medicine. Since 2008 Jentsch is the first researcher of NeuroCure. In 2015, The Journal of Physiology honoured him and his associates with a special issue for the discovery of chloride channels and chloride transporters 25 years ago. On May 2, 2017, the medical faculty of the University of Hamburg awarded him an honorary doctorate.

Gary Lewin - Max-Delbrück-Center for Molecular Medicine, Germany

Gary is Manx and was born 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. McMahons lab at St. Thomas's Hospital Medical school in the Sherrington school of Physiology in London. He received his PhD in February 1990. From London, he then moved to do post-doctoral work in the lab of Professor Lorne Mendell in the Department of Neurobiology and Behavior at the State University of 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 or hyperalgesia and pain. These findings formed the mechanistic basis of anti-NGF medication, like Tanezumab, that holds great promise for the treatment of inflammatory pain. In 1993 he received a von Humboldt Fellowship to work in the department of Neurobiochemistry at the Max-Planck Institute for Psychiatry in Munich under the directorship of Professor Yves-Alain Barde. In February 1996, he took up an appointment as an independent Group Leader at the MDC in Berlin. The projects in his lab now focus more 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.

Biographies - Speakers

Diana Lipscombe - Brown Institute, USA

Diane Lipscombe is Director of the Brown Institute for Brain Science and Professor of Neuroscience. Diane Lipscombe has studied voltage-gated calcium ion channels -- their function, pharmacology and modulation for over 30 years. The lab has shown how cell-specific control of ion channel composition through RNA splicing impacts animal behaviour and drug sensitivity. Lipscombe has also demonstrated the impact on channel function of rare mutations in calcium ion channel genes associated with disease in humans and, is involved in a collaborative effort to identify gene suppressors of animal models of familial Amyotrophic Lateral Sclerosis.

Yasuo Mori - Kyoto University, Japan

Yasuo Mori earned PhD in molecular genetics at Kyoto University Graduate School of Medicine. His research field has been mainly in molecular physiology of calcium channels including voltage-dependent calcium channels (neuronal Ca_V2 channels that trigger neurotransmitter release) and calcium-permeable TRP cation channels (TRPM, TRPC, and TRPA subfamilies mediating different pathways of calcium-dependent signal transduction) for nearly 30 years. Recently, he is very much interested in studying calcium channels, particularly TRP channels, in the context of redox biology by resolving the complex relationship between calcium channels and redox species including nitric oxide, reactive oxygen species, and molecular oxygen. He considers direct modification of calcium channel proteins as the most important clue to understanding this issue.

Matthew Nolan - Edinburgh University, UK

Matt Nolan is Professor of Neural Circuits and Computation at the University of Edinburgh. His research group aims to understand how computations important for cognition are implemented by neural circuits in the brain. His current focus is on how memory and sensory stimuli are combined by neural circuits that tell us where we are. Before moving to Edinburgh, Matt was a postdoc at Columbia University working with Eric Kandel and prior to this, he did his PhD and a short postdoc at the University of Aberdeen with Steve Logan And Dave Spanswick.

Jun-ichi Okada - University of Tokyo, Japan

Jun-ichi Okada is the director of the UT-Heart Inc. and a project lecturer of the University of Tokyo. He obtained his BSc and MSc degree in engineering from the Nagoya Institute of Technology and his PhD in science from the University of Tokyo in 2004. He has been working on the development of a three-dimensional, multi-scale, multi-physics heart simulator (UT-Heart). In particular, his research focuses on its application to clinical medicine and pharmacology. In 2015, he reported a novel proarrhythmic risk assessment system combining in vitro channel assays using the automated patch clamp technique and in silico simulation of cardiac electrophysiology using a UT-Heart. Recently, he extended this approach and developed a comprehensive hazard map of drug-induced arrhythmia based on the exhaustive in silico ECG database of drug effects in the hope that anyone can assess the arrhythmogenic risk of compounds without the use of expensive computers.

Saviero Gentile - Loyola University Chicago, USA

Dr Saverio Gentile received a PhD in neuroscience and cell biology from the Zoological Station "A. Dohrn" in Naples, Italy and Universita' degli Studi Della Calabria Italy. As a postdoctoral fellow at the National Institute of Environmental Health Sciences (NIEHS/NIH) and later in the Cardiology Department at Duke University Dr Gentile studied the non-genomic hormonal regulation of ion channels. As an independent investigator at Loyola University, Dr Gentile scientific interests focus on the role of ion channels in cancer biology and on establishing a therapeutic approach by pharmacologically targeting ion channels that are expressed in cancer cells. Recent discoveries in Dr Gentile's lab have brought to light important roles of K+ channels in controlling several hallmarks of cancer including growth/antigrowth signalling, cell death evasion, metabolism, tissue invasion, and metastasis.

Uwe Rudolph - McLean Hospital and Harvard University, USA

Uwe Rudolph graduated from the Medical School of the Freie Universitaet Berlin, where he also obtained a research-based doctorate for biochemical studies on G proteins. After a postdoctoral fellowship at Baylor College of Medicine in Houston, TX, he moved to the University of Zurich, where he and his colleagues generated and analyzed knock-in and knock-out mice to identify physiological and pharmacological functions of GABAA receptor subtypes. Since 2005 he is working at McLean Hospital in Belmont, MA and Harvard Medical School, where he is currently a Professor of Psychiatry. At McLean Hospital, his laboratory focuses on identifying the function of GABAA receptor subtypes in defined cell types and circuit locations, and – using chromosome engineering techniques – on copy number variations as genetic risk factors for psychiatric disorders.

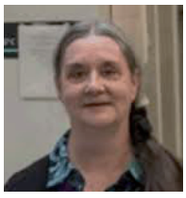
David Sheppard - Bristol University, UK

David N. Sheppard is Professor of Physiology at the University of Bristol. He uses single-channel recording to investigate how cystic fibrosis (CF) mutations disrupt cystic fibrosis transmembrane conductance regulator (CFTR) function and the action of small molecules that rescue or bypass mutant CFTR.

Biographies - Speakers

Lucia Sivlotti - University College London (UCL), UK

Lucia Sivilotti graduated in Pharmaceutical Chemistry from the University of Ferrara. Her PhD work at St Bartholomew's Medical School, London, provided the first description of GABAC receptors. After postdoctoral work on pain sensitization in the spinal cord, she specialised in single-channel recording on pentameric ligand-gated ion channels. Her work on glycine and nicotinic channels showed that agonist efficacy is determined early in channel activation, by access to a pre-open intermediate state. Lucia works at UCL, where she is the AJ Clark Professor of Pharmacology.



Bonnie Wallace - Birkbeck College, University of London, UK

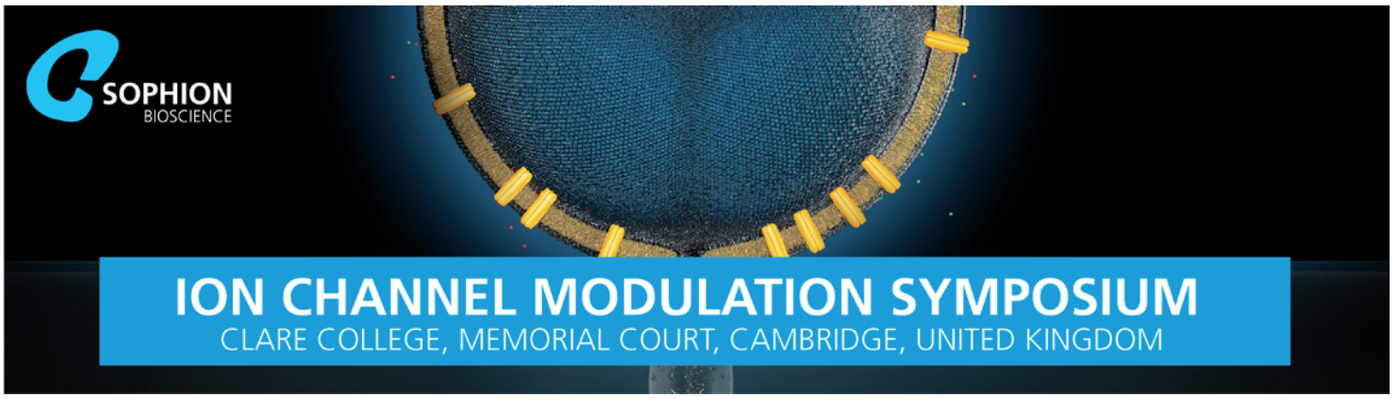
Bonnie Ann Wallace is Professor of Molecular Biophysics in the Institute of Structural and Molecular Biology at Birkbeck College, University of London. She obtained her PhD in Molecular Biophysics and Biochemistry from Yale University and did postdoctoral work (as a Jane Coffin Childs fellow) at Harvard and at the MRC Lab of Molecular Biology in Cambridge. She was an Associate Professor of Biochemistry at Columbia University, before moving to Rensselaer Polytechnic Institute as Professor of Chemistry and Director of the Center for Biophysics. She moved her lab permanently to London following a sabbatical visit (as a Fogarty Fellow) to Birkbeck. She was the first recipient of the Dayhoff Award of the U.S. Biophysical Society (for the best young female biophysicist in America) and received the Irma T. Hirschl Award, and the Camille and Henry Dreyfus Teacher-Scholar Award, and was previously named one of the dozen top young scientists in America by Fortune Magazine. She received the 2010 AstraZeneca Award from the Biochemical Society and the 2009 Interdisciplinary Prize from the Royal Society of Chemistry and was recently elected an Honorary Member of the British Biophysical Society and a Fellow of The (U.S.) Biophysical Society. Her principal research interests are in the structure and function of voltage-gated sodium channels, and the development of new methods and bioinformatics tools for characterising proteins.

Jian Yang - Columbia University, USA

Dr Jian Yang is currently Professor in the Department of Biological Sciences at Columbia University and Principal Investigator and Director of the Ion Channel Research and Drug Development Center (ICDC) at the Kunming Institute of Zoology of the Chinese Academy of Sciences. He obtained his B.S. degree at Peking University in 1982, M.S. degree at the Shanghai Brain Research Institute in 1985, and PhD degree at the University of Washington in Seattle in 1991, and performed postdoctoral research at Stanford University and the University of California, San Francisco. He became Assistant Professor in the Department of Biological Sciences at Columbia University in 1997, Associate Professor in 2002 and Professor in 2009. Dr Yang's research focuses on ion channel structure, function, disease mechanisms and drug discovery, and cellular calcium signalling and homeostasis, and uses a combination of approaches including molecular biology, biochemistry, cell biology, patch-clamp, X-ray crystallography, cryo-EM and confocal microscopy. His research areas include (1) Studying the structure, function and regulation of calcium-conducting channels, including voltage-gated calcium channels (VGCCs), transient receptor potential (TRP) channels, and cyclic nucleotide-gated (CNG) channels; (2) Searching for active natural compounds and developing new drugs targeting these (and other) channels and elucidating their action mechanisms. (3) Investigating at the molecular, cellular and animal levels the pathogenic mechanisms of human diseases (including autism spectrum disorder and autosomal dominant polycystic kidney disease) caused by or associated with mutations and/or dysfunction of VGCCs and TRP channels.

Hongjie Yuan - Emory University, USA

By training, Dr Yuan is an MD/PhD neuroscientist interested in roles of ion channels in neurological disorders. He is currently an Assistant Professor in the Department of Pharmacology and Deputy Director in the Center for Functional Evaluation of Rare Variants (CFERV) at Emory University School of Medicine. His current research is focused on human glutamate receptor mutations associated with neurological disorders. Dr Yuan utilizes a multidisciplinary approach to translate basic research involving human glutamate receptor mutations toward a therapeutically-relevant understanding of the NMDA receptors function in pediatric neurological disorders. Dr Yuan's research program also explores new approaches to the clinical treatment of a subset of neurodevelopmental disorders.



Poster Abstracts

NMDA receptor modulators in QPatch

Ezio Bettini
Leeds University, UK

N-methyl-D-aspartate receptors (NMDARs) are ionotropic glutamate receptors permeable to Ca^{2+}, Na^{+} and K^{+}. To be activated, they need to bind to glutamate (via GluN2 subunits), glycine (via GluN1) and release the Mg2+ blockade by membrane depolarization. The majority of NMDARs are tetrameric complexes, consisting of two glycine-binding GluN1 subunits and two glutamate-binding GluN2 subunits. GluN1 is coded by a single gene with at least eight different splice variants; four different GluN2 genes originate GluN2A, GluN2B, GluN2C, and GluN2D subunits.
CHO cell lines stably expressing diheteromeric NMDARs (hGluN1-hGluN2A, hGluN1-hGluN2B, hGluN1-hGluN2C or hGluN1-hGluN2D) were generated in Evotec. Few methodologies, which can be applied to characterize various classes of NMDA receptor modulators in recombinant cell lines, were set up using QPatch automated system. Such methodologies include: protocol for recording outward current in presence of 1 mM Mg^{2+}, protocol for measuring onset/offset kinetic of modulators effect on NMDAR, protocol for measuring glutamate deactivation kinetic in presence of NMDAR modulators. Selected QPatch protocols will be illustrated with specific examples.

Optical modulation of ion channels using Qube Opto

Kim Boddum
Sophion Bioscience, Denmark

The discovery of light-activated ion channels has paved the way for many exciting developments in the field of optogenetics. These ion channels change their conformation following optical stimulation allowing ions to pass through their pore. Since their discovery, many genetically engineered versions have been generated, exhibiting a broad spectrum of biophysical properties. A further technique to optically modulate ion channels is through the use of caged or photo-switchable compounds. Optical modulation of ion channels is traditionally studied using a manual patch clamp system combined with a light source. This approach, however, is limited by very low throughput. In the present work we show data recorded using a 384-well based automated patch clamp system equipped with 384 integrated light sources (Qube Opto).

Methods and results

HEK293 cells stably expressing Channelrhodopsin 2 (ChR2) were electrophysiologically characterized using blue light pulses (λ = 470 nm).
A light activation curve of the channel was recorded by application of various light intensities. It was further shown that ion selectivity and activation kinetics are in agreement with literature values. In a similar experiment, Halorhodopsin iC^{++}, a light-activated chloride pump, recombinantly expressed in HEK293 was characterized.

Rubi-GABA is a caged version of GABA that is released following exposure to blue light. Using this compound in combination with Qube Opto, GABAA receptors were studied. With the optical capability of Qube Opto in combination with the microfluidic flow channel of the QChip, the exposure time of a ligand can be better controlled and drastically reduced. Uncaged ligands can be rapidly washed out thereby reducing ligand exposure time approaching that of a synaptic response.

Conclusion

We provide compelling evidence that it is possible to study ion channels modulated by light on a high throughput patch clamp platform. This new capability opens the door for many novel applications in the field of ion channel research.

The citrus flavanone hesperetin preferentially targets the slow inactivation of a human cardiac Na^+ channel mutation responsible for a LQT3 syndrome

Julio Alvarez Collazo
KU Leuven, Belgium

The citrus flavanone hesperetin (HSP) has been proposed for the treatment of several human pathologies, but its cardiovascular actions remain largely unexplored. Here we determined the effects of HSP on the cardiac electrical and contractile activities and on aortic contraction. We further evaluated the action of HSP on the voltage-gated Na^+ channel $Na_V1.5$ and compared it to its effects on a recombinant $Na_V1.5$ channel baring a mutation (R1623Q) associated with lethal ventricular arrhythmias in the Long QT syndrome subtype 3 (LQT3).

Experimental approach: We used cardiac surface electrogram and contraction force recordings to evaluate HSP effects in isolated rat hearts and aortic rings. Whole-cell patch-clamp was used to record voltage-dependent Na^+ currents (INa) in rat ventricular cardiomyocytes and in HEK293T cells expressing $hNa_V1.5$ wild type (WT) or mutant channels.

Key results: HSP blocked the rat and human $Na_V1.5$ channels in voltage-dependent manner with an effective inhibitory concentration (IC_{50}) of ≈100 μM. Its inhibition was ineffective by disruption of the F1760 residue. HSP preferentially accelerated the inactivation phase of INa and decreased the Na+ net influx into the cell. These effects were more marked in the R1623Q mutant and occurred at concentration were HSP had minor effects on cardiac electrical and contractile activities and poor vasodilatory action.

Conclusions and implications: HSP preferentially accelerates the inactivation phase of INa, more markedly in the mutant R1623Q. HSP could be used as a template to develop drugs against lethal cardiac arrhythmias in LQT3.

$Na_V1.5$ *big late*: An inactivation deficient mutant of $Na_V1.5$ as screening tool for late sodium currents of the cardiac action potential

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Torsades de pointes (TdP) is a potentially fatal type of a ventricular tachcardia associated with delayed repolarization of the cardiac action potential. The major reason for pharmacologically induced TdP is the blockade of the voltage-gated potassium channel ($K_V11.1$ or hERG current, I_{Kr}). Therefore, the main focus of pre-clinical in vitro tests has been set on detection of I_{Kr} blockade to effectively discard drugs with a propensity to induce TdP. However, not all compounds that block I_{Kr} will eventually induce tachyarrhythmia and, therefore, a detected block of I_{Kr} alone is not specifically predictive for delayed repolarization and TdP. Not all known I_{Kr} blockers cause significant arrhythmia because effects caused by induced reduction of potassium outward currents may be counterbalanced by a reduced calcium inward current (I_{CaL}) or late inward sodium current (I_{NaL}). HERG and L-type calcium currents ($Ca_V1.2$) can easily be assessed in *in vitro* systems using electrophysiology methods (e.g. patch-clamping). Since the physiological late sodium current exhibits only tiny current amplitudes, I_{NaL} needs to be increased for drug screening by decreasing or slowing the inactivation of $Na_V1.5$ channels. This can be pharmacologically achieved by adding e.g. a sea anemone toxin II (ATX-II), which binds to the extracellular linker of segments S3-S4 of domain IV or by using inactivation modifying mutations.
For this study a cell line stably expressing a mutated $Na_V1.5$ (CW) channel was generated and validated using known I_{NaL} blockers. The substitution L409C/A410W was found to lead to a inactivation-deficient mutation. The mutation is localized in DIS6 and presumably prevents access of the intrinsic fast inactivation particle to the inner cavity.
During pharmacological validation using manual and automated (QPatch™) patch-clamping, IC_{50} values differed by less than a factor of two between ATXII stimulated and CW mutated $Na_V1.5$ channels. Besides shorter duration of I_{NaL} experiments and larger current amplitudes, also the observed conserved sensitivity to ATXII and overall reduced assay costs are strong arguments to screen late sodium currents in mutated rather than in pharmacologically stimulated $Na_V1.5$ channels.

$GABA_A$ receptor pharmacology measured in rat hippocampal astrocytes and stably expressing HEK cells on an automated patch clamp setup (QPatch)

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GABA is the major inhibitory neurotransmitter in the CNS and is exerting its effect by binding to GABA receptors. The importance of GABA in the CNS is underscored by the devastating consequences of dysfunctional GABA signaling. Consequently, pharmacological manipulation of GABA receptors, such as the ion channel $GABA_A$, has a large therapeutic potential. The patch clamp technique is the gold standard for assessing compound effects on ion channels, however, such studies have traditionally been limited by the labour-intensive and low-throughput nature of the method.
Here we perform a thorough pharmacological $GABA_A$ receptor evaluation, employing our Automated Patch Clamp (APC) platform, QPatch, in high-throughput (HTX) mode. This setup allows the patching of ten cells per recording site, and recordings of 48 sites in parallel, resulting in high quality, medium throughput electrophysiological measurements.
We present the evaluation of both a single $GABA_A$ receptor clone (α5β3γ2), stably expressed in a HEK cell line, and of the heterogeneous GABA receptor population of cultured primary hippocampal astrocytes. In GABAA(α5β3γ2)-HEK293 cells, 100 µM GABA elicited a 1.98 nA (± 0.64 nA) response (peak current) per cell and the EC_{50} value was 12.2 µM (CI95%: 11.1 µM - 13.4 µM). This current was both bicuculine and picrotoxin sensitive and potentiated by diazepam. The astrocytes displayed a 70.2 pA (± 38.3 pA) current in response to 3 mM GABA. The EC_{50} value was 161 µM (CI95%: 91.2 µM – 287 µM) and the current was completely blocked by picrotoxin.
This study demonstrates that it is possible to perform medium throughput electrophysiological evaluation of $GABA_A$ receptor pharmacology in both stably expressing cells and primary astrocytes using the APC platform, QPatch.

Gating mechanism of diamide insecticide-induced Ca^{2+} release channels

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Diamide insecticides including flubendiamide show agonistic effects on lepidopterous ryanodine receptor (RyR) channels responsible for Ca^{2+} release from the sarco/endoplasmic reticulum. Here, we characterized protein domains important to the selective flubendiamide action in lepidopterous RyRs. In silkworm RyR (sRyR), replacement of the divergent region 1 (DR1), poorly conserved among species, with DR1 from rabbit RyR2, significantly impaired the Ca^{2+} release response to flubendiamide, but spared receptor sensitivity to caffeine, a universal RyR activator. Flubendiamide-acyl imidazol (flubendiamide–AI), the labeling probe with the reactive AI attached to the aliphatic amide moiety, was predominantly incorporated into the peptide sequence TLQLGISILR (3,906–3,915) of the cytoplasmic central domain adjacent to DR1 in sRyR. Importantly, replacement of T3906 with alanine abolished flubendiamide–AI incorporation but retained intact flubendiamide sensitivity in sRyR. Furthermore, the mutations G4866E and I4709M corresponding to the diamide-resistant mutations identified at the transmembrane region in RyR of the diamondback moth, abolished the flubendiamide response, but retained flubendiamide–AI labeling or the caffeine response in sRyR. Our findings suggested that flubendiamide directly binds to DR1 with its aliphatic amide moiety oriented towards T3906 of the central domain, which serves as the reaction site for the AI moiety of flubendiamide–AI in sRyR, to impinge the S4 segment in opening the Ca^{2+}-permeable channel pore of sRyR. Thus, diamides differ from non-selective modulators such as caffeine in binding to DR1, which may provide an important basis for designing a class of compounds that selectively activate RyRs in specific insect taxa or mammalian RyR subtypes.

Protein kinase Cγ modulation of voltage gated sodium channel properties in mature Purkinje cells contributes to the motor coordination

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Protein kinase Cγ (PKCγ) is expressed exclusively in neurons of the brain and spinal cord. PKCγ-deficient mice have been shown to exhibit normal cerebellar long-term depression (LTD) but deficient pruning of climbing fibers (CFs) onto developing Purkinje cells (PCs) and impaired motor coordination. These data suggest a critical role for PKCγ in brain development and a possible contribution to developmental abnormalities leading to motor deficits. However, the physiological significance of PKCγ in mature animals has remained unknown. To clarify the role of PKCγ in mature mouse PCs, we compared the electrophysiological properties of PKCγ-null PCs with those of wild-type (WT) PCs. After confirming no difference in CF-PC (except for multiple innervation) and PF-PC synaptic transmission between WT and KO mice, we examined miniature inhibitory postsynaptic currents (mIPSCs) at interneuron – PC synapses, which also showed no significant difference between WT and KO mice. We next explored the firing properties of PCs and found the significantly higher threshold for action potential generation in KO mice than in WT mice. Then, we examined whether viral vector-mediated re-expression of PKCγ in the PCs of matured PKCγ-KO mice rescued the defects observed in KO mice. The rescue of PKCγ significantly restored the action potential threshold and the behavioral performance, while the multiple CF innervations of PCs remained unaltered. Additionally, we found the impaired voltage gated sodium channel (VGSC) currents in the KO mice PCs, and that was significantly rescued by the re-expression of PKCγ.
These results suggest that, through the regulation of VGSCs, PKCγ modulates the threshold for action potential generation, potentially shapes the firing property in PCs and critically regulates motor function in adult mice independent of multiple CF innervations of PCs and cerebellar LTD.

Development of a novel screening system to identify activators of Two-pore domain potassium channels (K2Ps)

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Two-pore domain potassium channels (K2Ps) are characterised by their four transmembrane domain, two-pore topology. They carry background (or leak) potassium current in a variety of cell types, including those with important pathophysiological roles. However, they have proved a difficult target class to modulate with small molecules and there is a lack of useful specific pharmacological tools which target K2Ps. This in turn has limited the interrogation of the precise physiological function of K2Ps and efforts to generate K2P targeting therapeutics.

The aim of this work was to develop a cellular system to identify activators across all the described subclasses of K2P channels. Generation of cell lines stably over-expressing ion channels can be challenging for a number of reasons including inherent toxicity. Moreover, the ability to identify channel activators can be compromised by systems in which the target is expressed at high levels. To avoid these issues we used BacMam to express Ion channels in mammalian cells. BacMam offers a number of advantages, including safety and reduced time, compared to generating stable cell lines, but importantly it allows the precise titration of expression of the gene of interest. This enabled us to generate cell systems in which we were able to intricately and robustly select a level of K2P expression in functional assays, optimized for the identification of channel activators.

Using an initial representative group of channels (THIK1, TWIK1, TREK2, TASK3 and TASK2) this system was used to screen a 10k representative set of the full LifeArc compound collection and a library of 1k FDA approved compounds. A thallium based system was used on the FLIPR (Molecular Devices). Good screening statistics were observed for all channels tested and a number of diverse and novel activators were identified. Activators were also screened in concentration-response format across all channels to investigate selectivity.

An exemplar novel activator identified was Terbinafine, which was shown to be a TASK3 activator using the thallium flux system and had a pEC50 of 6.2. Activity was confirmed using whole cell patch clamp electrophysiology. It is the first identified selective TASK3 activator, displaying no activation at other K2Ps screened. Interestingly, Terbinafine showed an increased level of activation versus the pathophysiological G236A variant compared to the wild type TASK channel.

Development and validation of ligand-gated ion channel assays using the Qube 384 automated electrophysiology platform

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Ligand-gated ion channels are of particular interest to the pharmaceutical industry for the treatment of diseases from a variety of therapeutic areas including CNS disorders, respiratory disease and chronic pain. Ligand-gated ion channels have historically been investigated using fluorescence-based and low throughput patch-clamp techniques. However, with the development of the Qube 384 automated patch-clamp system, the rapid exchange of liquid and direct measurement of ion channel currents on a millisecond timescale is now possible at a greater throughput than previously possible. Here, we have used the Qube platform to develop assays against two ligand-gated families: 1) the P2X receptor and 2) the GABA receptor families. The P2X family is comprised of 7 family members, which are cation permeable and gated by the binding of extracellular ATP. We have assessed both agonist and antagonist pharmacology of 4 members of the P2X family, $P2X_1$, $P2X_2$, $P2X_3$ and $P2X_4$, as well as two species homologs, $rP2X_3$ and $gpP2X_3$. The $GABA_A$ α1β3γ2 receptor is a chloride permeable ion channel gated by the binding of GABA. We utilized stacked liquid addition to assess the open state kinetics of the channel and to investigate the effects of a positive allosteric modulator on channel function. As such, we have successfully characterized and developed assays for both the P2X receptor and GABA receptor families and present EC/IC_{50} data for antagonists and positive allosteric modulators.