CONFERENCE HANDBOOK

# 7th RSC/SCI Symposium on Ion Channels as Therapeutic Targets

## Monday – Tuesday, 27th – 28th March 2023

Wellcome Genome Campus,
Cambridge, UK

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# Information for Delegates

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**Emergency Procedures**

In the event of a fire in your room:

- Leave immediately and close the door behind you.
- Raise the alarm by breaking the glass at nearest available alarm call point.
- Do not delay by collecting personal belongings.

If the alarm sounds, please:

- Leave the building by the nearest available exit.
- Proceed to the assembly point on the grass to the right of the conference centre building.
- Do not return to the building until authorised to do so.

Residents should familiarise themselves with escape routes before retiring to bed. Please note: There is a test fire alarm on a Wednesday morning, you may hear this if you wish to extend your stay.

**Security and Interruption**

The Security team will grant access to only those delegates that have registered to attend. Please also note that conference badges must be worn at all times (access may be denied if not worn), and that no flash photography or recording is permitted during the conference presentations.

**Smoking**

Smoking is not permitted in any rooms or buildings. There are designated smoking areas across the grounds, and delegates are asked NOT to smoke outside the conference centre, please.

**Internet Access**

The Wi-fi network is named 'conference guest'. Please follow the on-screen instructions. You will be required to validate your email address from the email message you receive to complete the registration process, otherwise, only 10 minutes of free Wi-Fi is granted.

**Twitter**

The hashtag is #IonChannels23. Delegates are asked not to tweet any images of slides or posters without the express permission of the presenter and, out of courtesy to our speakers, to refrain from taking photographs during the technical sessions when it could distract the presenter or members of the audience.

**Cloakroom and Luggage Storage**

Coat racks and luggage storage store is located behind the conference reception. Smaller lockers are located opposite reception, near the toilets, should you wish to use these, please request a token from the reception team.

**Drinks Reception, Conference Dinner and Bar**

At the end of the day on Monday, there will be a networking reception in the Event Space outside the Auditorium, in the exhibition and poster area. The networking reception will run from 17.05 to 18.45, there will be a short break before the conference dinner at 19.00 in Hinxton Hall. A bar is also available on site and open from 18.00 hours until mid-night. On Sunday the Graham Cameron Bar will be open from 18.00 hours until 23.00 hours.

**Information for residential delegates**

If you have booked accommodation at Hinxton Hall, please check-in at the Conference Centre Reception. Breakfast for residents will be served in the Restaurant from 7.30 - 9.00am. Please note that check-out is by 10:00 at the latest. Your bedroom key should be returned to the main reception desk in the Conference Centre.

# Information for Delegates

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**Poster Presenters**
Poster boards are located on the walls throughout the exhibition and catering areas, and poster presenters are asked to stand by their boards as much as possible during each catering break. Poster presenters are asked to remove their posters from the boards on Tuesday, before 16:45.

**Badges, Lanyards and Evaluation Forms**
Please hand in your delegate badges and lanyards to Hg3 Conferences team before you leave – they will be recycled. Please also be sure to complete an online post event evaluation form which will be sent out at the end of the conference – your feedback is most useful to us!

**Arrival and parking**
If you arriving to campus car, please approach the middle lane and a member of the security team will grant you access. You will then need to make your way to the Conference Centre Car Park (D). Once parked please walk towards to Conference Centre, which is the
opposite direction to where they drove in.
Please note that there is limited parking on-site and a space cannot be guaranteed.

**Trains to Cambridge**
A taxi may be booked to the nearest railway station which is Whittlesford Parkway, an eleven minute journey away from Cambridge railway station. Trains run approximately every 20 minutes.

**Taxis to Cambridge**
Please make your bookings direct with the Taxi's, but do not hesitate to ask the conference team for assistance if required. The approximate taxi journey time from the Genome Campus to Cambridge railway station is 20-30 minutes depending on traffic, and the approximate fares are £10 to Whittlesford Parkway and £18 to Cambridge railway station.

**Taxi Companies**
If you wish to make your own bookings, here are a few taxi suggestions:

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| **City Taxis** | 01223 832832 (Genome Campus' preferred taxi company, located locally)<br>https://www.cambridgecitytaxis.co.uk |
| **Camcab** | 01223 704704 / freephone 0800 783 1212<br>https://www.camcab.co.uk |
| **Panther Taxis** | 01223 715715 / 424424 / 523523<br>https://www.panthertaxis.co.uk/ |
| **Al CabCo Taxis** | 01223 313131 / 525555<br>http://www.a1cabco.co.uk/book-by-fax-or-email |
| **Ace Taxis** | 07424 102145 |

## Organisers

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*This symposium is organised by*
*The Royal Society of Chemistry's Biological and Medicinal Chemistry Sector (RSC-BMCS)*

*and The Society of Chemical Industry's Fine Chemicals Group (SCI-FCG)*

09.30 Registration and Refreshments

10.30 *Opening Remarks*
**Professor Brian Cox**, University of Sussex

**Session Chair:** Professor Brian Cox, University of Sussex

10.40 *Defective gating underlies a novel K2P channelopathy associated with sleep apnea*
**Professor Stephen Tucker,** University of Oxford

11.15 *Discovery of the TASK-1 and TASK-3 Channel Blocker BAY 2586116 for the Treatment of Obstructive Sleep Apnea (OSA)*
**Dr Michael Hahn,** Bayer AG Pharmaceuticals

11.50 Flash Poster Presentations

12.20 Lunch, Exhibitions and Posters

**Session Chair:** Dr Nigel Swain, Sosei Heptares

13.30 Dynamic action potential clamp to investigate ion channel pharmacology
**Dr Alexandra Pinggera,** Metrion Biosciences

13.50 *Functional Evaluation of Snake Neurotoxins and Recombinant Antibody Antivenoms via Automated Patch Clamp*
**Dr Damien Bell,** Sophion

14.10 *Identification of THIK-1 as a therapeutic target for neuroinflammatory diseases: discovery and characterisation of a selective THIK-1 blocker*
**Dr Anna Rowland,** Cerevance

14.30 *Discovery and characterisation of ETX-123, a novel Kv7.2/K7.3 activator for the treatment of Epilepsy*
**Dr Manuela Cerina,** Eliem Therapeutics

14.50 Refreshments, Exhibitions and Posters

**Session Chair:** Sarah Major, Evotec

15.20 *EVOchannel: tune in to safe molecules'*
**Dr Anna Carbone,** Evotec

15.55 *Discovery of CFTR Modulators for the Treatment of Cystic Fibrosis*
**Dr Alex Abela,** Vertex

16.30 *Positive Allosteric Modulators of GluN2B-Containing NMDARs as Enhancers of Synaptic Plasticity*
**Dr Jose Maria Cid,** Janssen R&D

17.05 Networking reception and Posters

19.00 Conference Dinner – Hinxton Hall

**Session Chair:** Dr Nadia Ahman, Charles River Laboratories

09.00 *The discovery of isocycloseram: a novel isoxazoline insecticide*
**Dr Mark Healy,** Novartis

09.35 *The discovery of isocycloseram: a novel isoxazoline insecticide*
**Dr Myriem El Qacemi,** Syngenta

10.10 *Discovery of Potent, Subtype-Selective GABAA alpha5 PAMs for the Treatment of Neurological Disorders from a NAM-to-PAM Switch*
**Dr Giuseppe Cecere,** F. Hoffmann-La Roche Ltd

10.45 Refreshment, Exhbition and Posters

**Session Chair:** Mike Clegg, MSD

11.15 *P2X ion channels as promising therapeutic and diagnostic targets: From the discovery of the first orthosteric P2X7R selective agonist to the development of optical probes for the imaging of P2X7R expression*
**Dr Anna Junker**, University of Muenster

11.50 *Cryo-EM Structural Studies of The Human TRPV4 Ion-Channel*
**Dr Simon Holton,** Nuvisan

12.25 *From High-Throughput Screening to Target Validation: Benzo[d]isothiazoles as Potent and Selective Agonists of Human TRPM5 Possessing In Vivo Gastrointestinal Prokinetic Activity in Rodents*
**Dr Luca Raveglia**, Evotec

13.00 Lunch, Exhibition and Posters

**Session Chair:** Dr Sarah Major, Evotec

14.10 Poster Prize Presentation

14.20 *Plugging the holes in antiviral therapy – Drug discovery potential of viroporins to treat SARS-CoV2*
**Dr Steve Griffin**, University of Leeds

14.55 Chemistry accelerated invention of a highly potent oral Nav1.8 channel blocker for the treatment of pain
**Dr Shawn Stachel**, MSD

15.30 Closing remarks
**Dr Sarah Major**, Evotec

15.40 Meeting Close

**Defective X-gating caused by *de novo* gain-of-function mutations in the TASK1 *(KCNK3)* K2P channel underlies a developmental disorder with sleep apnea**

*Stephen Tucker*

Kavli Institute for Nanoscience Discovery, University of Oxford, Oxford, UK

Sleep apnea is a common disorder that represents a global public health burden. *KCNK3* encodes TASK-1, a Two-Pore Domain (K2P) $K^+$ channel implicated in the control of breathing, but its link with sleep apnea remains poorly understood. We have recently described a novel developmental disorder with associated sleep apnea (DDSA) caused by rare *de novo* gain-of-function mutations in *KCNK3*. These mutations cluster around the 'X-gate', a gating motif which controls channel opening, and produce overactive channels that no longer respond to inhibition by G-protein coupled receptor pathways. However, despite their defective X-gating, these mutant channels can still be inhibited by a range of known TASK channel inhibitors. These results not only highlight an important new role for TASK-1 $K^+$ channels in development and their link with sleep apnea, but also identify possible therapeutic strategies.

## Discovery of the TASK-1 and TASK-3 Channel Blocker BAY 2586116 for the Treatment of Obstructive Sleep Apnea (OSA)

*Michael G. Hahn*

Medicinal Chemistry, Bayer AG, Pharmaceuticals, Wuppertal, Germany

TWIK-related acid-sensitive potassium (TASK) channels—members of the two pore domain potassium (K2P) channel family are found in neurons, cardiomyocytes and vascular smooth muscle cells, where they are involved in the regulation of heart rate, pulmonary artery tone, sleep/wake cycles and responses to volatile anaesthetics. K2P channels regulate the resting membrane potential, providing background $K^+$ currents controlled by numerous physiological stimuli, such as pH in case of TASK. As recently published, the unique inner X-gate[1] enables TASK channels to bind inhibitors with high affinity, extraordinary selectivity and extremely slow compound washout rates, which make these inhibitors attractive chemical starting points for the treatment of sleep apnea. Here we present a chain of translatability from a classical target driven drug discovery approach to represent a molecular association between a phenotypic in vivo disease model and human disease for OSA.

Initially, ultra-high throughput screening led to the identification of a novel highly potent and selective TASK-1/TASK-3 blocker class. Medicinal Chemistry efforts led to the lead structure BAY 1000493 (**1**) showing the required PK properties with high clearance and short half-life to avoid any systemic side effect. However, only moderate and short in vivo efficacy in the OSA pig model[2] was observed after nasal application. Consequently, our optimization strategy focused on improving in vivo efficacy and duration of action in the OSA-pig model. Finally, further extensive chemical optimization culminating in the identification of BAY 2586116 (**2**), which was in Phase II for the treatment of OSA[3]. The discovery of BAY 2586116 (**2**) and the structural activity relationship within this class will be presented.

#### References

1. Rödström, K.E.J.; Kiper, A.K.; Zhang, W.; Rinne, S.; Pike, A.C.W.; Goldstein, M.; Conrad, L.J.; Delbeck, M.; Hahn, M.G.; Meier, H.; Platzk, M.; Quigley, A. Speedman, D.; Shrestha, L.; Mukhopadhyay, S.M.M.; Burgess-Brow, N.A.; Tucker, S.J.; Müller, T.; Decher, N.; Carpenter, E.P.; *Nature* **2020**, *582*, 443-447.
2. Wirth, K.J.; Steinmeyer, K.; Ruetten, H.; *Sleep.* **2013**, *36*, 699-708.
3. Osman, A.M.; Mukherjee, S.; Altree, T.J.; Delbeck, M.; Gehring, D.; Hahn, M.; Lang, T.; Xing, C.; Mueller, T.; Weimann, G.; Eckert, D.J.; Chest, in press, https://doi.org/10.1016/j.chest.2022.11.024

## Dynamic action potential clamp to investigate ion channel pharmacology

***Alexandra Pinggera***, *Robert Kirby*

Metrion Biosciences LTD, Cambridge, UK

Whole-cell patch clamp electrophysiology is an indispensable technique to study the biophysical and pharmacological properties of ion channels. To investigate channels of interest in isolation, these experiments are often performed in recombinant systems with minimal expression of endogenous ion channels. However, under physiological conditions, the gating behaviour of ion channels is influenced by the presence of other conductances which consequently might also alter their pharmacology.

We therefore used the recently developed dynamic action potential-clamp (DAPC) technique to characterise the effect of different compounds targeting voltage gated sodium channels. DAPC enables currents recorded from a biological cell to be coupled in real time with an in-silico model cell to generate a hybrid neuron. In contrast to conventional patch clamp approaches, DAPC thus allows us to investigate the effect of different compounds on neuronal firing in recombinant cells. DAPC is therefore a valuable technique to characterise the effect of known and novel voltage gated sodium channel compounds under physiologically relevant firing patterns.

**Functional Evaluation of Snake Neurotoxins and Recombinant Antibody Antivenoms via Automated Patch Clamp**

*Kim Boddum[1], Line Ledsgaard[2], Marie Louise Laub Busk[1], Aneesh Karatt-Vellatt[3], John McCafferty[3], Andreas H. Laustsen[2],* ***Damian C. Bell[1]***

[1]Sophion, Sophion Bioscience A/S, Ballerup, Denmark, [2]Biotechnology and Biotherapeutics, Technical University of Denmark, Lyngby, Denmark, [3]IONTAS, IONTAS Ltd., Cambridge, UK

Snakebite was designated Neglected Tropical Disease (NTD) status by the WHO (2017), causing 100,000 yearly deaths and around 400,000 amputations. Each snake species has a unique venom, consisting of several dozen different toxins.

The century-old, traditional technique to generate snake antivenoms involved purifying antibodies from horse blood serum following immunization with snake venom. However, there are several drawbacks: equine-human immunoreactivity and side effects; batch-to-batch variation; specific to the snake venom used.

In the last decade, advances in antibody engineering have made antibody discovery and development more efficient and specific, including creating recombinant antivenom antibodies to target and neutralize key toxin peptides. One of the most medically relevant groups of snake toxins are the α-neurotoxins, targeting the nicotinic acetylcholine receptor (nAChR).

For over two decades automated patch clamp (APC) systems, have been used to advance our understanding of ion channel biophysics, pharmacology and their roles in physiology and disease.

Here, using QPatch II and Qube 384 APC, we functionally evaluate snake venom α-neurotoxins and anti-venom, toxin-neutralising IgG monoclonal antibodies (mAbs) on the muscle-type α1-nAChR.

## Identification of THIK-1 as a therapeutic target for neuroinflammatory diseases: discovery and characterisation of a selective THIK-1 blocker

***Anna Rowland***, *Kevin Doyle, Bernardino Ossola, Xiao Xu, Justin Powell, Giuliano Stiparo, Louise Dickson, Toni Cheung, David Cadwalladr, Keith Page, Nicol Brice, Mark Carlton, Lee Dawson, Rolan Bürli, Nicol Brice, Mark Carleton, Lee Dawson, Roland Bürli*

Drug discovery, Cerevance Ltd, Cambridge, UK

Neuroinflammation is a common underlying pathological feature of many neurodegenerative diseases. Thus, understanding the gene expression profile of microglia, the main immune cells of the central nervous system (CNS), and the changes in diseases will provide critical insight into neuroinflammatory pathology. Cerevance's proprietary Nuclear Enriched Transcript Sort Sequencing (NETSseq) platform allows for deep RNA-seq expression profiles (~12,000 genes) of distinct purified cell types, including microglia, from human post-mortem brain tissue. This technology has identified a highly specific expression of the tandem pore domain halothane-inhibited $K^+$ channel 1 (THIK-1) in microglia compared to other glial and neuronal cell types in the human brain. A hypothesis will be presented as to how a THIK-1 inhibitor may act as an anti-inflammatory therapy in the brain of patients suffering from neurodegenerative diseases. To test this notion, a high through-put screening campaign was performed and the first small-molecule THIK-1 inhibitor was identified. The in vitro pharmacological profile of a representative THIK-1 blocker, namely C101248, will be discussed in detail. Data will include inhibitory activity of C101248 for THIK-1 and other $K^+$ channels as well as its effects on microglia. The work presented will demonstrate the potential of the NETSseq platform to identify novel, unexplored and druggable microglia targets as potential therapies for neurodegenerative diseases.

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### Discovery and characterisation of ETX-123, a novel Kv7.2/K7.3 activator for the treatment of Epilepsy

***Manuela Cerina***[1]*, Shilina Roman*[1]*, Kathryn Oliver*[2,3]*, Edward Browne*[2]*, Christopher D Rundell*[4]*, Greg Iacobini*[4]*, Daniel Bakowski* [5]*, Shamila Griffiths*[6]*, Anthony M Rush*[7]*, David Witty*[3]*, Valer Morisset*[1,2,3]

[1]Department of Biology and Translational Science, Eliem Therapeutics, Cambridge, UK, [2]DMPK Department, Eliem Therapeutics, Cambridge, UK, [3]CMC Department, Eliem Therapeutics, Cambridge, UK, [4]Chemistry Department, Sygnature Discovery, Nottingham, UK, [5]Bioscience Department, Sygnature Discovery, Nottingham, UK, [6]Pharmacology Department, Labcorp, Harrogate, UK, [7]Neuroscience Department, Metrion Biosciences, Cambridge, UK

Potassium channels play a key role in the pathophysiology of epilepsy and other hyperexcitability-related diseases of the nervous system for which there are significant unmet medical needs. The Kv7.2/Kv7.3 heterometeric ion channel assembly is believed to be the molecular correlate of the M-current, which stabilizes the membrane potential and controls neuronal excitability. Activation of these channels is a validated mechanism for anticonvulsant activity in both animal models (Jones et al., 2021) and ongoing clinical trials (X-TOLE -NCT03796962). Ezogabine, a previously approved Kv7.2/Kv7.3 channel activator for the treatment of refractory partial-onset seizures, was a very efficient drug, despite suboptimal toleration. Ezogabine was withdrawn from the market for safety issues, which appear to be unrelated to the target itself. Therefore, the Kv7.2/Kv7.3 system remains a highly sought-after target for the treatment of epilepsy. Here, we report on a novel compound, ETX-123, differentiated from ezogabine by structural class, improved potency and selectivity, with encouraging anticonvulsant activity and tolerability. Electrophysiological recordings performed on transfected mammalian cells expressing Kv7.2/7.3 channels demonstrated that ETX-123 slowed down channel deactivation kinetics, increased the magnitude of the elicited-current and induced a leftward shift in the voltage-dependency. Although these effects were similar to those of ezogabine, ETX-123 is significantly more potent on Kv7.2/7.3, with an EC50= 7 nM versus EC50= 2 μM, for ezogabine. ETX-123 is also highly selective for Kv7.2/7.3 versus other Kv7 subtypes. For example, EXT-123 is ~14,000-fold less potent at Kv7.4, than at Kv7.2/7.3. As a reminder, Kv7.4 is hypothesised to play a role in urinary retention adverse effects observed with ezogabine (Splinter, 2021). ETX-123 also demonstrated a concentration-dependent modulation of neuronal excitability through hyperpolarization and inhibition of repeat firing evoked when rat dorsal root ganglion neurons were stimulated with a series of depolarising currents of increasing magnitude. In vivo, oral administration of ETX-123 (0.5-14 mg/kg) inhibited seizures evoked by ear electric stimulation in the rat maximal electroshock seizures model and demonstrated a 7-fold separation versus doses that induced motor impairment in the rotarod model. This data suggests that EXT-123 has encouraging properties for treating neuroexcitability disorders such as epilepsy, with a differentiated profile to ezogabine.

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**EVOchannel: tune in to safe molecules**

***Anna Carbone***

Late discovery, Ion Channels, Evotec, Hamburg, Germany

Ion channel disfunctions, due to genetic mutations or secondary defects, including exposure to drugs, are associated to numerous disease states (channelopathies). Furthermore, ion channels are important therapeutic target for several indications including pain, epilepsy, neurodegeneration, autoimmune disorders, and arrhythmia. About 20% of the marketed drugs target ion channels and there is a need to assess safety liabilities within the same protein family and across other ion channel families. Many drugs withdrawn from the market have been shown to cause cardiac related effects mediated by the block of the human ether-a-go-go hERG channel, which can result in fatal arrythmia. Platinum based chemotherapeutic drugs such as cisplatin and oxaliplatin, have been shown to alter the expression and activity of ion channels in DRG neurons and are known to cause chemotherapy induced neuropathic pain. Early identification of off-target compound activity can reduce safety-related attrition in development.

EVOchannel is a proprietary safety pharmacology platform providing project teams access to functional assays for ion channels to examine the effects and profile the propensity of drugs to cause Adverse Drug Reactions. EVOchannel offers the well-established cardiovascular (CiPA) panel, and a continuously expanding set of targets relevant to nervous system, kidney, muscular, pulmonary and secretory functions, tailored on the needs of the project. The wealth of in-house data from this platform is harnessed to develop Machine Learning tools, enabling predictions of safety profiles for small molecules.

## Positive Allosteric Modulators of GluN2B-Containing NMDARs as Enhancers of Synaptic Plasticity

***Jose Cid***[1]*, Carlos Martinez*[1]*, Josep Llavería*[1]*, Jesús Alcázar*[1]*, Ann Vos*[2]*, Hilde Lavreysen*[3]*, Ineke Fonteyn*[3]*, Ilse Van der Linden*[3]*, Juan Pita-Almenar*[3]

[1]Discovery Chemistry, Janssen R&D, Toledo, Spain, [2]Computational Chemistry, Janssen R&D, Beerse, Belgium, [3]Neuroscience Discovery, Janssen R&D, Beerse, Belgium

Synaptic plasticity is the ability of synapses to strengthen or weaken over time, in response to increases or decreases in their activity. This phenomenon is proposed to be the basis for learning and memory of neuronal networks and has the potential to recover from synaptic loss. Substantial evidence exists correlating synaptic dysfunction/loss with degree of cognitive impairment and late stages of Alzheimer's Disease (AD) for which synaptic plasticity represents a potential therapeutic approach.

NMDA receptors are glutamatergic receptors that can be activated precisely during the coincidence of excitatory synaptic transmission with neuronal activity. This precise activation of the NMDA receptor is key for synaptic plasticity and remodeling neuronal circuits. Each NMDA receptor contains different subunits: two GluN1 and two GluN2 divided into four subtypes A-D. The GluN2B subunit caught our attention. Its expression is developmentally regulated: a switch in GluN2B-containing receptors by GluN2A-containing receptors is seen after development which is associated with the closure of the "critical period of synaptic plasticity during brain development". GluN2B re-expression can restore critical period-like plasticity in adult sensory cortex, thus promoting learning and memory. Our aim is to identify PAMs of GluN2B function to enhance synaptic plasticity and improve learning and memory in neuronal circuits with synaptic loss such as aged/AD brains.

Here we report the structure activity relationship of a series of GluN2B PAMs pyridopyrazoles originated from a HTS campaign. Further characterization of advanced compounds revealed their potential as in vivo tools to understand the role of GluN2B in synaptic plasticity and their potential application in neurodegenerative diseases.

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## The discovery of the NMDA receptor NAM, MIJ821, a novel, rapidly acting antidepressant

***Mark Healy***

Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Cambridge, USA

The NMDA receptor has long been an attractive target for various neuroscience indications. Recently, an intranasal formulation of the -*S*- form of ketamine, esketamine, an NMDA receptor blocker, was approved as a rapidly acting antidepressant agent.

We have identified an NMDA NR2B subunit selective, negative allosteric modulator (NAM), with rapidly acting antidepressant clinical activity. We will present the discovery of MIJ821 (onfasprodil) in collaboration with biotech partners. We will include a story of scaffold morphing from a literature lead, balancing properties, in particular hERG and PGP efflux to ensure brain exposure, a target engagement imaging strategy, and a summary of the Phase 1 and Phase 2 clinical data that has led to this molecule moving into full clinical development.

## THE DISCOVERY OF ISOCYCLOSERAM: A NOVEL ISOXAZOLINE INSECTICIDE

**Myriem El Qacemi**, Jérôme Cassayre

Crop Protection Research, Syngenta Crop Protection, stein, Switzerland

Isocycloseram is a novel insecticide discovered at Syngenta Crop Protection. It is a member of the isoxazoline class of insecticides, which acts as a non-competitive antagonist of the invertebrate GABA receptor at a site distinct to that of fiproles and cyclodienes, resulting in excellent efficacy against invertebrate pests.

Innovative approaches for the delivery of modern agrochemicals such as multi-parameter optimization and faster cycles of Design-Synthesis-Test-Analysis (DSTA) were implemented during the research phase on the isoxazoline insecticidal class and led us to the discovery of Isocycloseram. The synthesis, optimization and biological efficacy aspects of this new chemical class will be presented.

# Discovery of First-in-Class Subtype Selective GABA$_A$ Alpha5 Positive Allosteric Modulators (PAMs) for the treatment of neurological disorders

***Giuseppe Cecere***

Roche Pharmaceutical Research and Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland

GABA$_A$ receptors are ligand-gated chloride channels and the main mediators of inhibitory synaptic transmission in the human brain. There are 19 genes encoding for GABA$_A$ receptor subunits that assemble as pentamers, with the most common stoichiometry of two α, two β, and one γ subunit. The α5 subunit-containing GABA$_A$ receptors are of particular interest given their specific expression pattern and physiological properties.[1-3] Multiple lines of evidence suggest that excessive neural activity in selected brain regions with consequent imbalance between excitatory/inhibitory neurotransmission underlie a variety of neurological disorders such as epilepsy, Autism Spectrum Disorder, Angelman Syndrome,[4] Schizophrenia and Alzheimer's disease. The presentation will highlight our efforts to discover highly potent, selective GABA$_A$ α5 PAMs from a program that had delivered Basmisanil,[5] a negative allosteric modulator (NAM) into clinical development. Key medicinal chemistry concepts involved in the optimization of the ligands and structural determinants underlining the NAM-to-PAM switch will be discussed. Finally, proof of concept studies in disease-relevant animal models with a selected PAM and further progression of the isoxazole-ether series to a clinical GABA$_A$ α5 PAM candidate Alogabat will be presented.

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2. Möhler, H., The rise of a new GABA pharmacology. *Neuropharmacology* **2011,** *60* (7), 1042-1049.
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### P2X ion channels as promising therapeutic and diagnostic targets: From the discovery of the first orthosteric P2X7R selective agonist to the development of optical probes for the imaging of P2X7R expression

*Andreas Isaak[1], Stephan Schmidt[1], Clemens Dobelmann[1], Friederike Theresa Fuesser[2], Katharina Sophie Erlitz[1], Oliver Koch[2], Thomas Budde[3], **Anna Junker[1]***

[1]1 European Institute for Molecular Imaging (EIMI), University of Muenster, Muenster, Germany, [2]Institut für Pharmazeutische und Medizinische Chemie , University of Muenster, Muenster, Germany, [3] Institut für Physiologie I, University of Muenster, Muenster, Germany

The purinergic P2X receptors belong to the family of ligand (ATP)-gated non-selective cation channels. Seven different P2X subunits (P2X1-7) have been identified, which form homo- or heterotrimeric P2X receptors [1]. The involvement of the P2XRs in a wide variety of physiological and pathophysiological processes such as synaptic transmission, regulation of neurotransmitter release, contraction of smooth muscles, inflammation, cancer and neuropathic pain [2–4] makes them highly promising targets for therapeutic and diagnostic applications. However, evaluating P2XR mediated effects requires the application of subtype-selective P2XR agonists. In the past, only a limited number of P2X receptor agonists derived from modifications of the endogenous ligand ATP (**1**), have been reported. Only a few of those compounds were well characterized for their functional activity and subtype selectivity at P2X receptors [5]. Therefore, the orthosteric ATP-binding site of the P2X receptors is poorly understood. Herein we present the first fully functional characterization of various ATP derivatives combined with in silico studies to advance the understanding of structure-activity and structure-selectivity relationships at the orthosteric binding sites of P2X receptors leading to the identification of the first P2X7R selective agonist [6].

*Figure 1: Dose-response curves of compound **2** in $Ca^{2+}$-flux-assays at P2X1-4 and P2X2/3 and in YO-PRO-1 uptake (superagonist) at P2X7R receptors (pooled data, n ≥ 3). Compound **2** bound to the P2X7R model.*

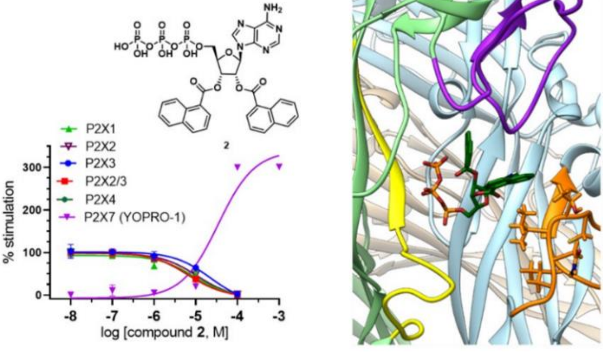


*Figure 2: Synthesis of optical probes for the imaging of P2X7R in vivo and dose-response curves of compounds **3c** and **4a** in patch-clamp recordings at P2X7R receptors (pooled data, n ≥ 3).*

Furthermore, we are highly interested in the diagnostic potential of P2XR imaging and report herein

the development of the first highly potent and P2X7R selective optical probe for the imaging of P2X7R expression in vitro and in vivo (data unpublished).

*References:*


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## Cryo-EM Structural Studies of The Human TRPV4 Ion-Channel

***Simon Holton***[1], *Alexander Ulrich*[1], *Mathieu Botte*[2], *David Gnutt*[3], *Ulrich Ebbinghaus-Kintscher*[3], *Vera Puetter*[1], *Michael Hennig*[2], *Holger Steuber*[1]

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The human transient receptor potential vanilloid 4 (hTRPV4) ion channel plays a critical role in a variety of biological processes. Its ion-channel gating properties can be activated by a broad spectrum of stimuli that includes heat, synthetic 4α-phorbols and several endogenous ligands. As the knowledge of its physiological roles has expanded, the interest in hTRPV4 as a potential therapeutic target has risen.

In this contribution we present the novel cryo-EM structure of the hTRPV4 determined in the presence of the archetypical phorbol acid agonist, 4α-PDD. The structure provides the first structural insights of hTRPV4 in an open conformation and reveals the underlying molecular mechanisms resulting in the opening of the central pore and activation of the ion-channel. Complementary mutagenesis experiments support the EM-identified binding site as well as allowing rationalization of disruptive mutants located outside of the 4α-PDD binding site.

The presented structural and biochemical data are a valuable tool to support the further exploration of TRPV4 biology and its pharmacological responses, as well as providing a great opportunity to support structure-guided design towards potent, selective and optimized novel drug molecules in a broad spectrum of human diseases.

# From High-Throughput Screening to Target Validation: Benzo[d]isothiazoles as Potent and Selective Agonists of Human TRPM5 Possessing *In Vivo* Gastrointestinal Prokinetic Activity in Rodents

***Luca Raveglia*[1]**, *Caterina Virginio*[2], *Richard Myers*[3]

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Transient receptor potential cation channel subfamily M member 5 (TRPM5) is a nonselective monovalent cation channel activated by intracellular $Ca^{2+}$ increase. This ion channel has been reported to be expressed in mammalian taste buds (in a subset of cells that co-express receptors for bitter, sweet and umami tastes), in distinct subsets of olfactory neurons and in the vomeronasal organ. TRPM5 is also expressed in tuft cells, which are taste-chemosensory epithelial cells of the small intestine and are suggested to be critical for protection during enteric infections and inflammatory responses. Currently, pharmacology associated with the activation of this ion channel is poorly understood and lack of potent and selective agonists hampers its clarification. With the aim of identifying potent and selective TRPM5 activators to help understanding the physiological and pathological role of TRPM5, particularly at the gastrointestinal level, a high-throughput screening (HTS) was run using a membrane potential assay technology, followed by automated patch clamp to validate the identified hits. Hit triaging followed by hit expansion activities allowed the selection of two promising hit series which entered the hit to lead phase. One of the two, the one described in this presentation, is represented by compound **1**, showing moderate agonist activity at TRPM5 ($pEC_{50}$=5.33). While optimization of TRPM5 activity to nanomolar levels and selectivity versus related cation channels was pretty straightforward, low metabolic stability remained an unresolved issue within this chemical series. We thus considered to shift the objective of the optimization of this series from systemic to local, luminally restricted TRPM5 agonist profile and we identified compound **2**, showing ideal DMPK properties for a compound acting locally at the intestinal level, with minimal absorption into systemic circulation. Compound **2** was tested *in vivo* in a mouse gut motility assay at 100 mg/kg, and demonstrated increased pro-kinetic activity.

SAR Exploration

HTS hit **1**
pEC50 = 5.33

**2**
pEC50 = 8.10

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**Plugging the holes in antiviral therapy – Drug discovery potential of viroporins to treat SARS-CoV2**

***Stephen Griffin***

Leeds Institute of Medical Research, School of Medicine, University of Leeds, Leeds, UK

SARS-CoV2 remains a pandemic virus, thought to be responsible for over 20M deaths since first emerging in 2019. Vaccination has weakened the link between infection and severe disease. However, for those unable to access or respond effectively to vaccines, antivirals are intended to make up the shortfall in protection, especially for vulnerable groups.

Worryingly, current NICE draft recommendations will leave the UK without licensed monoclonal antibody therapies, due mainly to a lack of randomised controlled trials for these agents in the Omicron era. NICE also recommend decreasing the number of early onset antiviral therapies to just a single agent; the protease inhibitor nirmatrelvir combined with a “ritonavir boost”, a.k.a. “Paxlovid” (Pfizer). New agents are desperately needed as second line or, ideally, as combinations to mitigate the emergence of resistance.

Ion channels play central roles in medicine as the focus of ~20% of marketed drugs. However, virus-encoded channels, “viroporins” , remain neglected by mainstream drug discovery. Viroporins perform essential functions for diverse pathogenic viruses. Most reside within virion, as well as cellular membranes, influencing egress and/or entry of infectious particles. The envelope (E) viroporin from SARS-CoV2 acts during viral egress, and, we hypothesise, influences virus entry.

Due to the urgency of the pandemic, we repurposed clinically advanced, direct-acting molecules with potency and specificity against SARS-CoV2 E. Diverse hits were active in vitro and showed overlapping yet distinct binding modes at the same binding site within the channel lumen. The screening lead displayed potent antiviral activity in culture, and a series of structural analogues provided the beginnings of a structure-activity relationship. We are currently confirming the provenance of this agent to ensure that drug "mispurposing" does not occur, as seen for certain entities progressed too soon into clinical studies. Importantly, repurposed compounds provide both a potential direct route into the clinic, as well as the structural basis for further bespoke inhibitor design.

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**Chemistry accelerated invention of a highly potent oral Nav1.8 channel blocker for the treatment of pain**

***Shawn Stachel***

Discovery Chemistry, Merck & Co., Inc., West Point, Pa, USA, Westpoint, USA

Nav1.8 is a tetrodotoxin resistant voltage-gated sodium channel primarily expressed in small to medium diameter sensory neurons, where it is thought to contribute to action potential generation. Data suggests Nav1.8 is an attractive target for chronic pain conditions. In support of this hypothesis, published knockdown and knockout studies, as well as studies with non-selective Nav 1.8 inhibitors, show that inhibiting Nav 1.8 function or expression produces analgesic-like effects in rodents. Furthermore, gain-of-function mutations in the human gene encoding NaV1.8 have been identified in patients with small-fiber neuropathy. Our team has succeeded in identifying inhibitors capable of selective inhibition of the Nav1.8 channel over other sodium channel isoforms. These compounds displayed activity in a humanized Nav1.8 rat, as well as primate in a capsaicin-sensitized thermode pharmacodynamic assay. Progress toward the lead identification, optimization, binding site elucidation and in vivo efficacy of these compounds will be discussed.

## Catalogue of Posters

| No. | Title | Authors | Affiliations |
|---|---|---|---|
| P01 Flash | Discovery of Novel Therapeutics Against Ion Channels Using the Salipro Technology | **Sara Bonetti**, Pilar Lloris-Garcerá, Anne-Sophie Tournillon, Stefan Klinter, Robin Löving, Jens Frauenfeld | Salipro Biotech, Teknikringen 38A, Stockholm, Sweden |
| P02 Flash | Pharmacology of Transient receptor potential cation (TRP) channels using different activation stimuli | András Horváth[1], Tom A. Goetze[1], Ilka Rinke-Weiß[1], Nadine Becker[1], Lukas Focke[2], Oliver Wehmeier[2], Ralf Schwandner[3], Niels Fertig[1], **Alison Obergrussberger[1]** | [1]Nanion Technologies GmbH, Munich, Germany, [2]AcCELLerate GmbH, Hamburg, Germany, [3]AssayWorks GmbH, Regensburg, Germany |
| P03 Flash | Thermo transient receptor potencial ion channels as a key molecular and functional landmark for neuropathic pain transduction in subsets of somatosensory neurons | **Angela Lamberti[1]**, Asia Fernandez Carvajal[1,2], Antonio Ferrer Montiel[1] | [1]Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanita, Universidad Miguel Hernandez, Elche,Spain, [2]Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanita, Universidad Miguel Hernandez, Elche,Spain |
| P05 Flash | Allosteric impact of different variants in RyR2, a cardiac $Ca^{2+}$ channel | **Yulia Einav[1]**, Oded Shor[2], Ayelet Shauer[2], David Luria[2] | [1]Faculty of Engineering and Digital Medical Technologies, Holon Institute of Technology, Holon, Israel, [2]Heart Institute, Hadassah-Hebrew University Medical Center, Jerusalem, Israel |
| P06 Flash | Measuring TRPC1/4/5 channels with chemical probes | **Aidan Johnson[1,2]**, Sebastian Porav[2], Hassane El Mkami[3], Christos Pliotas[4], Stephen Muench[4], Andrew Wilson[1], Robin Bon[2] | [1]School of Chemistry, University of Leeds, Leeds, UK, [2]Leeds Institute of Cardiac and Metabolic Medicine, University of Leeds, Leeds, UK, [3]School of Physics and Astronomy, University of St Andrews., St. Andrews, UK, [4]School of Biomedical Sciences, University of Leeds, Leeds, UK |
| P07 Flash | Targeted inhibition of the Hv1 proton channel as a potential anticancer therapy | **Martina Piga[1]**, Zoltán Varga[2], Ádám Fehér[2], Ferenc Papp[2], Eva Korpos Pintye-Gyuri[2], Tihomir Tomašič[1], Nace Zidar[1] | [1]Faculty of Pharmacy, Univeristy of Ljubljana, Ljubljana, Slovenia, [2]Faculty of Medicine, University of Debrecen, Debrecen, Hungary |
| P08 Flash | Identifying novel inhibitors of KNa1.1 (KCNT1) potassium channels using a structure-based approach | **Emily Caseley**, Stephen Muench, Katie Simmons, Jonathan Lippiat | School of Biomedical Sciences, University of Leeds, Leeds, UK |
| P09 Flash | Combining soft drug concept and protac technology as a safer treatment for neuropathic pain | **Georgia Goutsiou[1]**, Angela Lamberti[2], Asia Fernandez-Carvajal[2], Antonio Ferrer-Montiel[2], Tracey Pirali[1] | [1]Farmaceutical Sciences, Università del Piemonte Orientale, Novara, Italy, [2]Instituto de Biología Molecular y Celular, Universitas Miguel Hernandez, Elche, Spain |
| P10 Flash | A photoswitchable inhibitor of TREK channels to control pain specifically and reversible in wild-type and intact freely moving animals | Guillaume Sandoz | iBV, CNRS, Nice, France |
| P12 Flash | Identification of novel TMEM175 modulators using a high-throughput automated patch-clamp and solid-supported membrane- (SSM-) based electrophysiology platforms | Laura Hutchison[1], Maria Barthmes[2], Claire Brown[1], Andre Bazzone[2], Lesley Gerrard[1], **Elena Dragicevic[2]**, Cecilia George[2], Niels Fertig[2], David Dalrymple[1], Ian McPhee[1], David Pau[1] | [1]Ion Channel Group, SB Drug Discovery, Glasgow, UK, [2]Electrophysiology Team, Nanion Technologies, Munich, Germany |

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| P14 | Insights into *Leishmania donovani* potassium channel family and their biological functions | **Anindita Paul**, Shubham Sunil Chumbale, Anjana Lakra, Vijay Kumar, Dhanashri Sudam Alhat, Sushma Singh | Department of Biotechnology, National Institute of Pharmaceutical Education and Research, SAS Nagar, India |
| P15 | Virtual Ligand Screening Using an Evolutionary Algorithm and Combinatorial Compound Library Identifies Possible Activators of the KCNQ1 Voltage Sensor Domain | Jakob Schramm, **Georg Künze** | Institute for Drug Discovery, Leipzig University, Leipzig, Germany |
| P16 | Human Induced Pluripotent Stem Cell-Derived Nociceptors Suitable for Automated Patch Clamp High Throughput Pain Drug Discovery | Patrick Walsh[1], Aaron Randolph[2], Irene Lu[2], Rodolfo Haedo[2], Alison Obergrussberger[3], Vincent Truong[1], Tim Strassmaier[2], **Marc Rogers[1]** | [1]Biology, Anatomic Inc, Minneapolis, USA, [2]Scientific Operations, Nanion Technologies Inc, North Brunswick, USA, [3]Scientific Communications, Nanion Technologies GmbH, Munich, Germany |
| P17 | Detergent-free purification of membrane proteins using polymer lipid particle (PoLiPa) technology for use in Cryo-EM | **Jim Reid[1]**, Christopher Morton[1], Satya Bhamidimarri[1], Steven Hardwick[2], Dimitri Chirgadze[2], Stefanie Reich[1] | [1]Domainex LtD., Saffron Walden, UK, [2]Department of Biochemistry, University of Cambridge, Cambridge, UK |
| P18 | Development of TRPV2 inhibitors by molecular evolution of disulfide-rich peptides using the PERISS method | **Toshiaki Okada**, Tomohiro Yamaguchi, Hiroshi Matsukawa, Tadashi Kimura | R&D Division, Veneno Technologies Co. Ltd., Tsukuba, Japan |
| P19 | Automatic Analysis of Ligand Binding Sites in Ion Channel Families Using Sequence- and Structure-based Alignments | **Paul Kluge** | Institute for Drug Discovery, University of Leipzig, Leipzig, Germany |
| P20 | Molecular dynamics simulations and docking experiments on CNG channels and cGMP analogs identify structural determinants of ligand affinity and selectivity | **Palina Pliushcheuskaya[1]**, Sandeep Kesh[2], Frank Schwede[3], Francois Paquet-Durand[4], Vasilica Nache[2], Georg Künze[1] | [1]Institute for Drug Discovery, Medical Faculty, Leipzig University, Leipzig, Germany, [2]Institute of Physiology II, University Hospital Jena, Friedrich Schiller University Jena, Jena, Germany, [3]BIOLOG, Life Science Institute GmbH & Co KG, Bremen, Germany, [4]Cell Death Mechanism Group, Institute for Ophthalmic Research, University of Tübingen, Tübingen, Germany |
| P21 | Computational analysis and modelling of Ion Channels implicated in cardiac disease or liability: relationship to in vitro models of Inotropy and other cardiac safety markers | Robert Scoffin[1], Jeremy Billson[2], **Martin Slater[1]** | [1]Cresset Discovery, Cresset BMD Ltd, Cambridge, UK, [2]Board, Inocardia Ltd, Coventry, UK |
| P22 | Hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channel in CD4+ T-cell regulation | **Laura Vinnenberg[1]**, Johannes Greiff[1], Lisa Epping[1], Sven G Meuth[2], Heinz Wiendl[1], Thomas Budde[3], Petra Hundehege[1] | [1]Clinic of Neurology with Institute of Translational Neurology, University Hospital Münster, Münster, Germany, [2]Department of Neurology, University Hospital Dusseldorf, Dusseldorf, Germany, [3]Institute of Physiology I, Universtiy of Münster, Münster, Germany |

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| P23 | The role of kallikrein on Kv7 channels | **Nicole Rychlik [1]**, Paul Disse[2], Guiscard Seebohm[2], Sven G. Meuth[3], Thomas Budde[1] | [1]Institute of Physiology 1, University of Münster, Münster, Germany, [2]Institute for Genetics of Heart Diseases, University of Münster, Münster, Germany, [3]Neurological Clinic, University Hospital Dusseldorf, Dusseldorf, Germany |
| P24 | Cav2.3 phosphorylation in the pathophysiology of CDKL5 deficiency disorder: a new target for treatment | **Marisol Sampedro Castaneda[1]**, Lucas L Baltussen[1], Andre T Lopes[1], Yichen Qiu[2], Liina Sirvio[1], Simeon R Mihaylov[1], Suzanne Claxton[1], Jill C Richardson[3], Gabriele Lignani[2], Sila K Ultanir[1] | [1]Kinases and Brain Development Lab, The Francis Crick Institute, London, UK, [2]Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK, [3]UK Neuroscience Group, MSD R&D Innovation Centre, London, UK |
| P25 | Novel Mitochondrial KV 1.3 Inhibitors: Design, Synthesis and Biological Evaluation | **Marzia Fois [1]**, Špela Gubič[1], Xiaoyi Shi[2], Ildiko Szabo[3], Luis Pardo[2], Lucija Peterlin Mašič[1], Tihomir Tomašič[1] | [1]Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia, [2]Max-Planck Institute for Experimental Medicine, AG Oncophysiology, Göttingen, Germany , [3]Department of Biology, University of Padova, Padova, Italy |
| P26 | Cryo-EM structure of ion channel pannexin 1 using GeneArt and Salipro DirectMX platforms | **Ieva Drulyte[1]**, Aspen Rene Gutgsell[2], Pilar Lloris-Garcerá[3], Michael Liss[4], Stefan Geschwindner[2], Mazdak Radjainia[1], Jens Frauenfeld[3], Robin Löving[3] | [1]Materials & Structural Analysis, Thermo Fisher Scientific, Eindhoven, Netherlands, [2]Mechanistic & Structural Biology, Discovery Sciences, R&D, AstraZeneca, Mölndal, Sweden, [3]Salipro Biotech, Stockholm, Sweden, [4]GENEART GmbH, Thermo Fisher Scientific, Regensburg, Germany |

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## Discovery of Novel Therapeutics Against Ion Channels Using the Salipro Technology

***Sara Bonetti***, *Pilar Lloris-Garcerá, Anne-Sophie Tournillon, Stefan Klinter, Robin Löving, Jens Frauenfeld*

Salipro Biotech, Teknikringen 38A, Stockholm, Sweden

The Salipro technology stabilises ion channels and other membrane proteins in a lipid environment making them accessible for *de novo* development and characterisation of small molecules drugs and biologics. In our poster, we will present case studies on:

- Salipro Direct Membrane Extraction of ion channels into stable nano-membrane particles

- Small molecule ligand binding studies via SPR

- CryoEM structure determination of Salipro embedded ion channels (e.g., TRPV3)

- Antibody discovery by both *in vitro* phage display and *in vivo* immunization with subsequent B cell sorting.

P02

## Pharmacology of Transient receptor potential cation (TRP) channels using different activation stimuli

*András Horváth[1], Tom A. Goetze[1], Ilka Rinke-Weiß[1], Nadine Becker[1], Lukas Focke[2], Oliver Wehmeier[2], Ralf Schwandner[3], Niels Fertig[1], **Alison Obergrussberger[1]***

[1]Nanion Technologies GmbH, Munich, Germany, [2]AcCELLerate GmbH, Hamburg, Germany, [3]AssayWorks GmbH, Regensburg, Germany

Transient Receptor Potential (TRP) channels are widely distributed throughout the mammalian central and peripheral nervous systems. They can be directly activated by ligands, heat or cold and mechano-stimulation, and are important targets in drug discovery for the treatment of pain, respiratory diseases, cancer, immune disorders and others. Here, we studied the responses of TRPA1, TRPV1, TRPV3, TRPV4 and TRPM8 assay-ready and cultured cells activated using a variety of stimuli on automated patch clamp (APC) systems.

TRPA1 and TRPM8 are crucial in sensing noxious cold and inflammatory pain, responding to irritant environmental and food compounds, and metabolites produced during oxidative stress. TRPA1 is expressed in sensory neurons of the dorsal root ganglion (DRG) and trigeminal ganglion. Thus, TRPA1, and possibly TRPM8, antagonists are considered a promising approach for the treatment of acute and chronic pain. Desensitization is one of the biggest challenges for drug screening of TRPA1 channels. Here, we obtained IC50s obtained with short ligand exposure using a high throughput device, the SyncroPatch 384 (**Figure 1**). TRPM8 was activated repetitively activated using solution at 10°C on the Port-a-Patch using the temperature-controlled perfusion system at 10 °C. Capsazepine (10 µM) was used to block the activated current. TRPM8 was also activated by solution <18°C on the SyncroPatch 384 (**Figure 2**).

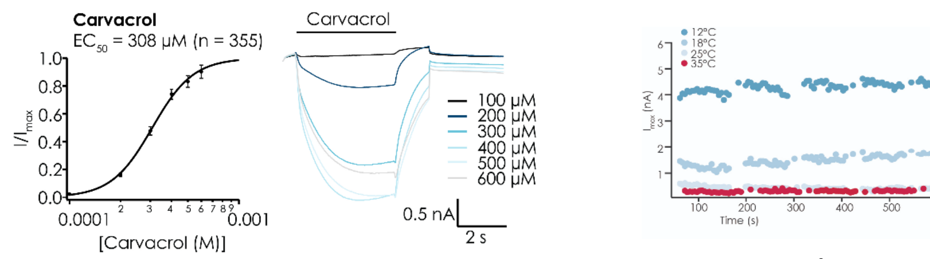


**Figure 1**

**Figure 2**

The TRPV1, 3 and 4 channels are ligand-gated, non-selective cation channels involved in nociception, and respond to elevated temperatures and compounds. Identifying compounds with differential effects on ligand vs heat activation may be crucial in the discovery of new treatments for pain with fewer side effects. Here, we developed robust methods for temperature and pharmacological activation to study differential effects of blockers. We used ligand activation (capsaicin, 2-APB, GSK1016790) and repeated heat activation of TRPV1, 3, 4 (Patchliner heated pipette, 37-45°C) followed by the addition of blockers (**Figure 3**). TRPV4 was activated by heat (38°C) and partially blocked by ruthenium red on the Port-a-Patch. In summary, we established a

range of reliable automated approaches to study temperature vs pharmacological influences on TRP channels.

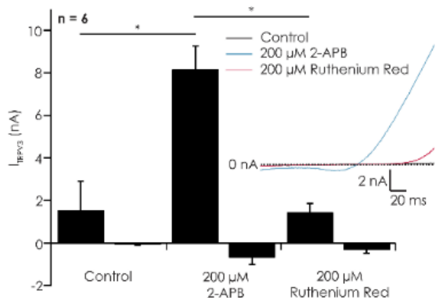


**Figure 3**

## Thermo transient receptor potencial ion channels as a key molecular and functional landmark for neuropathic pain transduction in subsets of somatosensory neurons

***Angela Lamberti[1]***, *Asia Fernandez Carvajal[1,2], Antonio Ferrer Montiel[1]*

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Chemotherapy-induced peripheral neuropathy (CIPN) is a challenging side effect arising from treatment of several anti-cancer agents that constitutes a major medical and societal problem because there is no effective prevention or treatment method [Lang-Yue H., et al., Neuropharmacology, 2019]. My project is focused on Paclitaxel, a taxane commonly used to treat cancers, which binds and stabilizes microtubules blocking cellular proliferation. However, the cellular mechanisms underlying Paclitaxel neurotoxicity are poorly understood [Yamamoto S., et al., Pharmacol., 2021]. Several studies have shown the involvement of thermoTRPs ion channels in several neuropathies [Aromolaran K. et al., Molecular pain, 2017].

The aim of my project is to investigate the role of three members of transient receptor potencial ion channels family (TRPs): TRPA1, TRPM8, and TRPV1 in Paclitaxel-induced nociceptor sensitization and to identify channel blockers that can be developed as therapeutics for reducing CIPN prevalence or sensory symptoms.
For this task, we have developed a long-term primary nociceptor culture that allows to mimic up to 2 drug cycles in vitro.

Results from calcium imaging suggest that two consecutive administrations of Paclitaxel, interspersed by a 3-day washing period, produce an increase in the size of the response and in the percentage of neurons responding to TRPA1, TRPM8 and TRPV1 agonists. This effect is notable 48 hours after the second exposure. Preliminary results from patch clamp show an increased spontaneous activity in Paclitaxel treated dorsal root ganglion neurons (DRGs). These results will be further electrophysiologically confirmed and correlated with the expression and activity of the thermoTRPs. Furthermore, we will test the effect of modulators of these ion channels currently under design as potential therapeutics to control CIPN.

In conclusion, once the involvement of these TRP ion channels in the induction of CIPN by Paclitaxel has been characterized, our goal will be to implement an in vitro model system more similar to the human one using sensory neurons from transdifferentiated human fibroblasts that could constitute a screening platform for the identification of new compounds able to reduce CIPN symptoms through the modulation of thermo TRP ion channels.

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### Allosteric impact of different variants in RyR2, a cardiac $Ca^{2+}$ channel

**Yulia Einav**[1], Oded Shor[2], Ayelet Shauer[2], David Luria[2]

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The cardiac ryanodine receptor RyR2 is a calcium ion release channel present in the cardiac muscle cells, which plays a major role in the regulation of $Ca^{2+}$ homeostasis in the heart. Pathological release of $Ca^{2+}$ via RyR2 leads to arrythmias associated with sudden cardiac death. Hundreds of RyR2 genetic variants are published, most of them have an unknown clinical significance. In order to predict pathogenicity of different RyR2 variants we developed a new Normal Mode Analysis (NMA)-based method that allows to study an allosteric effect of a single mutation on large protein tetrames, such as RyR2. Application of our Allosteric Entropy Change Method (AECM) to characterize and blindly classify 136 different variants of RyR2, some of which defined as clinically relevant and some as benign substitutions, allowed prediction of mutant pathogenicity with a value of 0.9 for the sensitivity and of 0.88 for the specificity of our approach. The pathological and the benign datasets were found to be statistically different by the means of vibrational entropy in a number of affected subunits, the extent of structural effect and the number of affected resedues overall. Description of the allosteric change in different RyR2 variants allows to get a more detailed picture of the channel critical regions, which may assist in a search of antiarrythmic therapeutics. Moreover, as many disease-causing mutations in various ion channels fall outside the ion pore or the gate region and show an allosteric effect, which molecular mechanism is rarely understood, AECM could be particarly useful in such cases. Therefore, our approach could be applied also to other ion channels, many of which are oligomers, and certainly to $Ca^{2+}$ channels other than RyR2.

## Measuring TRPC1/4/5 channels with chemical probes

**Aidan Johnson**[1,2], Sebastian Porav[2], Hassane El Mkami[3], Christos Pliotas[4], Stephen Muench[4], Andrew Wilson[1], Robin Bon[2]

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TRPC1/4/5 proteins form $Ca^{2+}$ - permeable ion channels that are present throughout the body with wide ranging functions. TRPC1/4/5 channels are implicated in heart disease, kidney function, and anxiety.[1] High resolution cryoEM structures have given structural insight into the mechanism-of-action of the highly potent inhibitory ligand Pico145, and this knowledge is used in guiding new ligand design.

This study uses spin-labelled ligands to further study these channels, for use in pulsed EPR-experiments such as PELDOR. It is believed that this approach can provide detailed structural information about the currently unknown open state of the channels. In conjunction with this, cryoEM is used to corroborate structural insights.

Using three newly developed spin-labelled ligands, each with nanomolar potency, initial PELDOR data were obtained. When using an inhibitory probe, analysis revealed intra-ligand distances consistent with calculated values for the closed channel. This protocol is being adapted for use with activating ligands. This will potentially reveal structural information about the open state of the channel, and the ratio of open to closed channels in an activated system.

## Targeted inhibition of the Hv1 proton channel as a potential anticancer therapy

**Martina Piga**[1], Zoltán Varga[2], Ádám Fehér[2], Ferenc Papp[2], Eva Korpos Pintye-Gyuri[2], Tihomir Tomašič[1], Nace Zidar[1]

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### Introduction

Voltage-gated proton channels are proton-selective voltage-dependent channels that have been found in mammalian and in cancer cells. They prevent intracellular acidification. However, when pathological conditions occur, tumor cells can adapt extremely well in the developed acid microenciroment.

The aim of our work is to discover and evaluate a series of new Hv1 inhibitors. At present, there are no selective inhibitors specific for Hv1 proton channels. A selective Hv1 inhibitor would allow to modulate the acidic tumor microenvironment.

### Materials and Methods

An open structure of the human Hv1 channel was used to perform virtual screening (VS) of an in-house library of compounds and selected known Hv1 inhibitors. Compounds were docked to the binding site of guanidine derivatives, on the voltage-sensing domain. A series of molecules was selected to be tested by manual patch-clamp on CHO (Chinese hamster ovary) and HEK (human embryonic kidney) cells expressing hHv1 and other channels. A small series of analogues was prepared by organic synthetic procedures and their identity and purity were evaluated by different spectroscopic and chromatographic techniques.

### Results and Discussion

Virtual screening results were evaluated, and a series of most promising hits were selected for biological evaluation on Hv1 channels. Seven hits were found to have an effect on proton currents (more than 50% block at 50 µM) and six of them had the same scaffold in their structure (Fig.1). Results obtained using the patch-clamp technique show that NZ-58, one of the hit molecules that showed the greatest effect, blocks dose-dependently the channels, it binds when the VSDs are resting or deactivated and that the binding rate is state independent; it is likely that it binds from the extracellular side. Most of the hit molecules turned out to have low selectivity: they also act on voltage-gated sodium and potassium channels. However, NZ-13, the scaffold itself and one of the hit molecules, had lower affinity for the other channels than for Hv1 and the smallest effect on T cell proliferation.

### Conclusion

By bringing together the knowledge and the results from ligand- and structure-based drug design, biophysical and pharmacological characterization, and medicinal chemistry methods, we have obtained a valid and solid starting point for the development of potential Hv1inhibitors. The selected promising hits will be used for further hit-to-lead optimization to obtain molecules with improved inhibitory potency, better hHv1 channel selectivity, and desired physicochemical properties.

# P07

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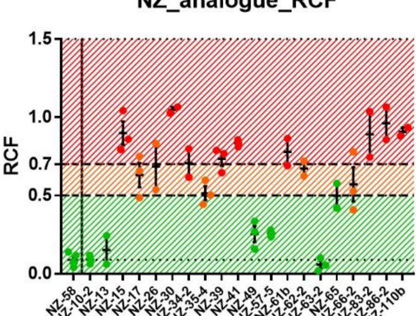

# Identifying novel inhibitors of KNa1.1 (KCNT1) potassium channels using a structure-based approach

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The *KCNT1* gene encodes the sodium-activated potassium ion channel subunit KNa1.1. Gain-of-function de novo mutations in this gene are associated with rare, severe, drug-resistant forms of childhood epilepsy; in addition to seizures, patients can also present with cognitive and behavioural disabilities, movement disorders and developmental delay. Existing treatments for these epilepsies are lacking, and off-label trials of the anti-arrhythmic drug quinidine, which is a KNa1.1 channel inhibitor, have been largely ineffective. This is principally due to off-target binding to the human ether-a-go-go-related gene (hERG) cardiac potassium channel, limiting dosing levels and leading to severe off-target effects. As such, the identification of specific small molecule modulators of the KNa1.1 ion channel represents an unmet clinical need.

We therefore aimed to use a structure-based approach to identify novel KNa1.1 channel inhibitors. We performed an *in silico* screen consisting of docking large commercially available compound libraries to the pore region of the chicken KNa1.1 cryo-electron microscopy structure using docking programs such as Glide. Compounds with favourable docking scores were purchased and were initially validated *in vitro* in a HEK293 cell line stably expressing a wild-type/Y796H gain-of-function heteromeric KNa1.1 channel, using a thallium-based fluorescence assay. Promising compounds were subsequently characterised further using patch clamp electrophysiology to quantify their potency and maximum channel inhibition and using cell viability assays to determine toxicity.

Using this methodology, we have so far identified 16 novel inhibitors of the human KNa1.1 channel with IC 50 values in the low micromolar range. These compounds have low toxicity, with many compounds not affecting cell viability at concentrations up to 30 µM. They also demonstrate significant structural diversity, increasing the likelihood of some of these compounds possessing favourable drug-like properties.

Together, we have used a structure-based approach to identify a structurally diverse series of novel KNa1.1 channel inhibitors, demonstrating the effectiveness of using such an approach when identifying small molecule modulators of ion channels. We are currently expanding on this work by assessing the pharmacokinetic and pharmacological properties of our inhibitors to identify potential drug-like molecules, in addition to carrying out structure-activity relationship studies to explore promising pharmacophores.

## Combining soft drug concept and protac technology as a safer treatment for neuropathic pain

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### Background

Chronic pain is a highly prevalent unmet medical need, which affects millions of people worldwide. TRPV1, a calcium permeable non-selective ion channel expressed in the nociceptive neurons, plays a crucial role in neuropathic pain transmission and modulation. Small molecule TRPV1 antagonists have been advanced into clinical trials for pain relief; however, their systemic use has been hampered by worrisome adverse effects such as hyperthermia. Hence, the development of effective and safe therapies is urgently required.

### Aims

To circumvent the systemic side effects of TRPV1 antagonists experienced so far, we are devoting several efforts at developing novel soft TRPV1 degraders for dermatological applications. In detail, we designed and synthetized PROTACs endowed with a predicted and controllable metabolism to nonactive and nontoxic metabolites after having exerted their local biological activity.

### Methods

The incorporation of a soft spot, namely an ester moiety, which undergoes predictable metabolism (*e.g.,* hydrolysis) in the blood circulation, represents a promising strategy to develop safer agents for topical applications. Furthermore, PROTACs technology has gained increasing interest for inducing degradation of proteins. Therefore, we combined the soft drug concept and the Proteolysis Targeting Chimeras (PROTACs) technology to develop different series of Soft-PROTACs targeting TRPV1 as effective and safer topical agents to tackle neuropathic pain. Notably, we exploited the versatility of Multicomponent Reactions (MCRs) to quickly assess to various Soft-TRPV1-PROTACs.

### Conclusions

Different series of Soft-TRPV1-PROTACs have been developed for topical applications as a safer and more effective therapeutic option for neuropathic pain. MCRs (*e.g.*, Passerini reactions) have been exploited to quickly prepare a large library of Soft-PROTACs' targeting TRPV1, a very challenging transmembrane protein to intercept compared to cytosolic proteins.

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### A photoswitchable inhibitor of TREK channels to control pain specifically and reversible in wild-type and intact freely moving animals

**Guillaume Sandoz**

iBV, CNRS, Nice, France

By endowing light control of neuronal activity, optogenetics and photopharmacology are powerful methods notably used to probe the transmission of pain signals. However, costs, animal handling and ethical issues have reduced their dissemination and routine use. Here we report LAKI(Light Activated $K^+$ channel Inhibitor), a specific photoswitchable inhibitor of the pain-related two-pore-domain potassium (K 2P) TREK and TRESK channels. In the dark or ambient light, LAKI is inactive. However, alternating transdermal illumination at 365 nm and 480 nm reversibly blocks and unblocks TREK/TRESK current in nociceptors, enabling rapid control of pain and nociception in intact and freely moving mice and nematode. These results demonstrate, *in vivo*, the subcellular localization of TREK/TRESK at the nociceptor free nerve endings in which their acute inhibition is sufficient to induce pain, showing LAKI potential as a valuable tool for TREK/TRESK channel studies. More importantly, LAKI gives the ability to reversibly remote-control pain in a non-invasive and physiological manner in naive animals, which has utility in basic and translational pain research but also in vivo analgesic drug screening and validation, without the need of genetic manipulations or viral infection.

## Identification of novel TMEM175 modulators using a high-throughput automated patch-clamp and solid-supported membrane- (SSM-) based electrophysiology platforms

Laura Hutchison[1], Maria Barthmes[2], Claire Brown[1], Andre Bazzone[2], Lesley Gerrard[1], **Elena Dragicevic[2]**, Cecilia George[2], Niels Fertig[2], David Dalrymple[1], Ian McPhee[1], David Pau[1]

[1]Ion Channel Group, SB Drug Discovery, Glasgow, UK, [2]Electrophysiology Team, Nanion Technologies, Munich, Germany

TMEM175 is a novel, constitutively active ion channel involved in regulating lysosomal pH and autophagy. Mutations in this gene impair normal lysosomal and mitochondrial function, thereby increasing aggregation of insoluble proteins such as phosphorylated α-synuclein, leading to symptoms typical of Parkinson's Disease (PD). Consequently, TMEM175 demonstrates significant potential as a key player in the treatment of PD. The lack of specific pharmacological tools has hampered further investigation into the exact role of TMEM175 in normal lysosomal function and pathological processes.

Advancements in high-throughput screening technologies have allowed rapid assessment of large numbers of compounds against ion channel drug targets using automated patch-clamp. We have successfully developed recombinant cell lines expressing wild-type (WT) TMEM175, a gain of function (Q65P), and loss of function (M393T) mutants using stably transfected HEK cells. Here, we report the characterization of the WT TMEM175 cell line performed using high-throughput automated patch-clamp electrophysiology and show reproducible concentration-response curves with the potassium channel inhibitor 4-aminopyridine (4-AP). A rapid and robust, automated high-throughput electrophysiology screening assay was subsequently developed to enable the identification of both activators and inhibitors of TMEM175.

Additionally, we have used solid-supported membrane- (SSM-) based electrophysiology (SSM-E) for TMEM175 recordings from lysosomal membranes purified and prepared from the WT TMEM175 cell line. Dose-dependent signal enhancement and inhibition of TMEM175 currents were successfully characterized. The SSM-E approach allows for stable and robust recordings from proteins residing in organellar membranes with a throughput of up to 10'000 data points per day.

In summary, the TMEM175 stable cell line was characterized using an automated patch-clamp and SSM-based electrophysiology. We developed and executed robust, high-throughput, and high-content direct electrophysiological intracellular screening assays, with unusually high success rates. As the TMEM175 channel has recently been suggested as an $H^+$ channel at low pH, we are now developing $H^+$ assays to be used in conjunction with $K^+$ assays. The successful development of TMEM175 electrophysiology assays capable of identifying novel pharmacological tools will enable investigation of the role of this exciting target in normal physiology and in disease.

**Insights into *Leishmania donovani* potassium channel family and their biological functions**

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*Leishmania donovani* is the causative organism for Visceral Leishmaniasis. Although this parasite was discovered over a century ago, nothing is known about role of potassium channels in *L. donovani.* Potassium channels are known for their crucial roles in cellular functions of various organisms. Our group has recently reported the presence of a calcium-activated potassium channel in *L. donovani*. This prompted us to look for other proteins which could be potassium channels and to investigate their possible physiological roles. Twenty sequences were identified in *L. donovani* genome and subjected to estimation of physio-chemical properties, motif analysis, localization prediction and transmembrane domain analysis. Structural predictions were also done. The channels were majorly a-helical and predominantly localized in cell membrane and lysosomes. The signature selectivity filter of potassium channel was present in all the sequences. In addition to the conventional potassium channel activity, they were associated with gene ontology terms for mitotic cell cycle, cell death, modulation by virus of host process, cell motility- to name a few. The entire study indicates the presence of potassium channel families in *L. donovani* which may participate in important cellular pathways. Due to their possible involvement in vital physiological processes in this pathogen, these potassium channels could be potential therapeutic targets against Visceral Leishmaniasis. Further functional validation of these ion channels is required to identify them as antileishmanial targets.

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### Virtual Ligand Screening Using an Evolutionary Algorithm and Combinatorial Compound Library Identifies Possible Activators of the KCNQ1 Voltage Sensor Domain

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Institute for Drug Discovery, Leipzig University, Leipzig, Germany

The KCNQ1-KCNE1 channel complex generates the slow delayed rectifier potassium current (I Ks) in the heart, which is important in controlling cardiac action potential duration and adaptation of heart rate in different physiological conditions. The I Ks channel is formed by the voltage-dependent, pore-forming α-subunit KCNQ1 and the regulatory β-subunit KCNE1. Mutations in any of these proteins can cause long QT syndrome (LQTS) – a condition in which the action potential duration is abnormally prolonged, which predisposes patients to a life-threatening cardiac arrhythmia. Pharmacological activation of KCNQ1 and I Ks is a possible therapeutic strategy to the treatment of LQTS. Some small-molecule activators of KCNQ1 have been developed, which could restore function of mutant KCNQ1 channels and represent a starting point for further drug development.

Here, we aimed at identifying ligands targeting the voltage sensor domain (VSD) of KCNQ1, which could offer a possibility to hyperpolarize the voltage-dependent activation of the KCNQ1 ion channel and increase the I Ks current. An evolutionary algorithm was used to virtually screen the combinatorial Enamine REAL Space library, which comprises 31B make-on-demand molecules, in a timely and efficient manner. Hit molecules were filtered for drug-likeness and the best-scoring molecules were validated by further docking and MD simulation experiments. Amongst the best-scoring ligands, molecules with tetrazole and sulfone functional groups were prevalent. The docking and MD simulations revealed hydrogen bond interactions with the first two gating charge residues on the S4 helix (Arg228, Arg231), which suggests that the identified ligands can stabilize the VSD in an active up-conformation. The computational binding free energies of the best ligands were comparable or substantially better than the energy of a previously identified azonaphthalene sulfonic acid-based activator of KCNQ1. The identified molecules can provide lead structures for further drug design efforts and can be evaluated for their ability to shift the voltage dependent activation of KCNQ1 in vitro.

## Human Induced Pluripotent Stem Cell-Derived Nociceptors Suitable for Automated Patch Clamp High Throughput Pain Drug Discovery

Patrick Walsh[1], Aaron Randolph[2], Irene Lu[2], Rodolfo Haedo[2], Alison Obergrussberger[3], Vincent Truong[1], Tim Strassmaier[2], **Marc Rogers[1]**

[1]Biology, Anatomic Inc, Minneapolis, USA, [2]Scientific Operations, Nanion Technologies Inc, North Brunswick, USA, [3]Scientific Communications, Nanion Technologies GmbH, Munich, Germany

There is an unmet need for novel non-addictive pain analgesics as the opioid epidemic continues. The ability to screen compounds on human sensory neuron nociceptors with high throughput would increase the efficiency and pace of preclinical pain drug discovery and improve translational success of new pain drug candidates. We have previously demonstrated that human nociceptors can be generated in an accelerated, scalable method from human induced pluripotent stem cells (hiPSCs), and that the hiPSC-derived nociceptors share similarities to human dorsal root ganglia based on whole-transcriptome profiling and expression of functional voltage- and ligand-gated channels important for nociception.

In this study, we utilise a novel dissociation method to enable automated patch clamp electrophysiological recordings of multiple ion channels in RealDRG™ cultures on the Patchliner and SyncroPatch 384 systems. The functional expression and biophysical and pharmacological properties of voltage-gated sodium (Na V) and potassium ion channels (K v), and ligand-gated ionotropic GABA and P2X receptors were studied over 14, 21 and 28 days in culture, along with excitability properties and action potentials in current clamp.

The percentage of cells with at least one evoked action potential increased from 42% to 77% over the course of maturation, with success rates decreasing from 56 to 35% as the cells matured. There was also an increase in voltage-gated sodium (Na V) and potassium (K v) currents over time in culture, with success rates ranging from 94-98% and 93-100%, respectively. Most neurons had tetrodotoxin-resistant (TTXr) sodium currents, with a trend of increasing number of cells with Nav current and fraction of TTXr current per cell. A ligand puff protocol was developed to reproducibly evoke ligand-gated GABA-A and P2X receptor ion channels without desensitisation. These findings demonstrate the ability to functionally screen multiple analgesia drug targets in human iPSC nociceptors using high throughput automated patch clamp systems.

**Detergent-free purification of membrane proteins using polymer lipid particle (PoLiPa) technology for use in Cryo-EM**

**Jim Reid**[1], Christopher Morton[1], Satya Bhamidimarri[1], Steven Hardwick[2], Dimitri Chirgadze[2], Stefanie Reich[1]

[1]Domainex LtD., Saffron Walden, UK, [2]Department of Biochemistry, University of Cambridge, Cambridge, UK

The structural and biophysical analysis of membrane proteins such as Ion channels, GPCRs and transport proteins is essential for modern drug discovery but has been limited by access to high quality purified protein and limitations of crystal formation. Contemporary techniques that rely upon detergent solubilisation of membrane proteins are greatly hindered by the challenges, time and costs associated with the bespoke method development needed for each purification. Domainex are developing a platform approach to membrane protein purification and structural analysis, enabled by polymer-based strategies, such as styrene maleic acid (SMA), that alleviate these issues. These solubilise cellular membranes and encapsulate membrane proteins that continually remain in their original native lipid environment, forming polymer lipid particles (PoLiPas). Thus, the membrane protein is presented in its folded state in solution, allowing purification using conventional techniques. Here, we showcase our system for rapid and generic preparation of high quality PoLiPa-purified proteins. To take advantage of this native lipid environment for structural studies, we also show how Cryo-EM can be used as a complimentary technique to visualise PoLiPa discs.

## Development of TRPV2 inhibitors by molecular evolution of disulfide-rich peptides using the PERISS method

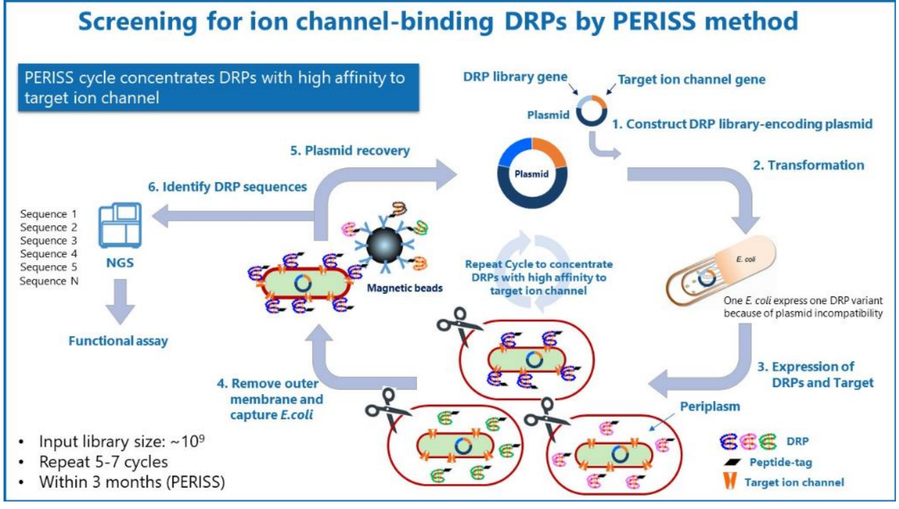
**Toshiaki Okada**, Tomohiro Yamaguchi, Hiroshi Matsukawa, Tadashi Kimura

R&D Division, Veneno Technologies Co. Ltd., Tsukuba, Japan

Several reports have shown that transient receptor potential cation channel subfamily V, member 2 (TRPV2), is a potential therapeutic target molecule for cardiac diseases such as dilated cardiomyopathy. Tranilast is an inhibitor of TRPV2 (IC50 =1 μM). In animal models and human clinical studies, the administration of tranilast has been reported to improve cardiomyopathy. If a more potent and TRPV2-selective inhibitor can be created, it may be developed as a more effective cardiomyopathy-improving therapeutic agent.

In this study, we explored the development of novel TRPV2 inhibitors with PERISS screening (Figure 1.) by taking advantage of the beneficial properties of DRPs as pharmaceuticals. GTx1-15 from tarantula venom was used as the scaffold for the DRP library. The gene library was constructed to introduce random substitution mutations in eight amino acids whose positions were determined by in silico calculations based on the three-dimensional structural model. First, we confirmed expression of TRPV2 protein in inner membrane of E. coli by western blotting. Next, we performed the PERISS screening to identify TPRV2-binding DRP sequences. After repeating PERISS for seven cycles, the plasmid was recovered, and the gene sequence of DRP was analyzed by next-generation sequencing. The amino acid sequences found at high frequencies were considered to be DRPs that bind strongly to TRPV2 and may inhibit the function of TRPV2 with high potency. Hence, we measured the activity of the top-ranking hit DRPs by electrophysiological assay using E. coli giant spheroplast expressing TRPV2. The results showed that one of the hit DRPs had TRPV2 inhibitory activity. This study showed that PERISS is a promising method for creating novel DRP-based inhibitors against ion channels.

Figure 1. PERISS method for the screening for ion channel-binding DRPs



### Automatic Analysis of Ligand Binding Sites in Ion Channel Families Using Sequence- and Structure-based Alignments

**Paul Kluge**

Insitute for Drug Discovery, University of Leipzig, Leipzig, Germany

The identification of conserved ligand binding sites in ion channel structures can provide valuable information for computer-aided drug discovery, e.g., for defining the binding pocket in ligand docking experiments for virtual screening or for estimating cross-reactions of potential drugs. However, to our knowledge, there exists no automatized tool that enables the large-scale detection and comparison of ion channel ligand binding sites. Research has been usually limited to the analysis of single (sub)families. Here we present an automatic workflow for the identification of conserved ligand binding sites, which can be applied to any ion channel family and allows the visualization and family-wise comparison of ligand-receptor interactions.

Our approach relies on the creation of sequence and structural alignments for all known ion channel structures available in the PDB, the grouping of ion channel structures according to TCDB notation, the automatic detection of protein-ligand contacts, and the identification of common binding sites by fraction of common contacts-based clustering.

We processed a total of 1054 PDB files that were separated into 62 families. After filtering the data, 852 PDB files and 40 families were used for analysis. The largest families were the transient receptor potential family (TRP), the glutamate-gated ion channel (GIC) family, and the voltage-sensitive NaV channel-like family with 114, 97, and 68 PDB files, respectively. We were able to identify a total of 545 ligand binding sites. The highest number of ligand binding sites could be found in the GIC family, the TRP family, and the voltage-sensitive calcium channel family with 74, 43, and 38 ligand binding sites respectively. For selected families, further analyses were conducted, eg. calculation of the degree of conservation and the comparison of ligand binding site identity among subfamilies.

We are implementing our database of ion channel-ligand binding sites in form of a web-accessible, graphical user interface, which could help to promote drug discovery research on ion channels.

**Molecular dynamics simulations and docking experiments on CNG channels and cGMP analogs identify structural determinants of ligand affinity and selectivity**

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Cyclic nucleotide-gated (CNG) ion channels are involved in signal transduction in retinal and olfactory systems. Their activation is triggered by binding of endogenous cyclic nucleotides (cGMP, cAMP). CNG channels have been implicated in the development of retinal degeneration diseases that can lead to vision loss. Overactivation of CNG channels due to elevated cGMP concentrations can lead to increased ion flux into rod photoreceptors and impairment or loss of rod function, followed by a secondary degeneration of the cone photoreceptors. Selective inhibition of the CNG channel expressed in rods could offer a pharmacological strategy to prevent rod overexcitation and maintain cone photoreceptor function. Here we have characterized the interactions of the rod and cone CNG channels with cGMP and a set of cGMP analogs and identified the structural determinants of ligand affinity and selectivity. Our approach included docking of cGMP-like ligands into the cyclic nucleotide binding domains of rod and cone channels to investigate the ligand modes of interaction, molecular dynamics simulations, and MM/GBSA energy calculations to obtain the total and per-residue binding energies for each ligand. Contact and per-residue decomposition analyses revealed the amino acids that contribute most to the binding process, which are overall similar in rod and cone CNG channel structures. In the rod CNG channel, Ser548, Arg561, and Thr562 form hydrogen bonds with the phosphate and phosphothioate moieties of cGMP ligands and make the energetically largest contributions. The substituted guanine ring takes part in energetically weaker, hydrophobic interactions with Val529, Ala566, Ile605, Leu606, and Lys608. The MM/GBSA energy values and ligand docking scores were highly correlated, whereas no correlation was found between these affinity metrices, and the experimental percentage current inhibition values determined for the cGMP-like ligands. This result suggests that additional binding parameters, such as ligand binding kinetics, need to be considered to be able to predict the activity of cGMP and its analogs on CNG channels. Furthermore, we discovered some amino acid differences between rod and cone CNG channels localized to the outer boundary of the cGMP binding pocket, which we will explore in future drug design experiments for their ability to make selective interactions.

## Computational analysis and modelling of Ion Channels implicated in cardiac disease or liability: relationship to in vitro models of Inotropy and other cardiac safety markers

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Cardiac safety is a major issue causing many late-stage drug development failures, and therefore the earliest possible prediction of cardiac liabilities has great value for drug discovery. In this work we demonstrate a powerful combination of in silico modelling and in vitro assay models which can be used as an early marker of potential downstream liabilities. The focus of the initial work was on Inotropy (positive and negative), but the methods employed have much broader applicability. Examples are given using $Ca^{2+}$ gated ion channel CaV 1.2 and $Na^{+}$ gated ion channels, including NaV 1.3 and NaV 1.5.

A combination of different modelling approaches are employed, depending on the background data available for each channel, and whenever possible a data fusion approach has been developed to give more robust predictions than would be possible using any one single standalone method. Principle approaches are molecular docking, structural minimisation, Electrostatic Complementarity (EC) and molecular dynamics.

The predictions from the in silico models are then able to be verified using the InoCardia assay platform, which enables the testing of candidate drugs against a single isolated cardiac myocyte in order to show the effects of specific modes of action on inotropy and the work cycle of the cell.

We also demonstrate a novel molecular similarity approach to defining activity space, again derived from inotropy data, but broadly applicable in other domains, which can then lead to alerting or screening applications for discovery and development programs.

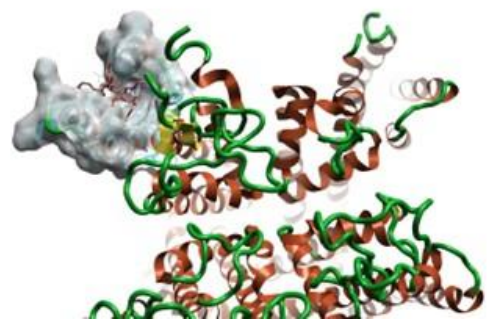

**Figure 1**

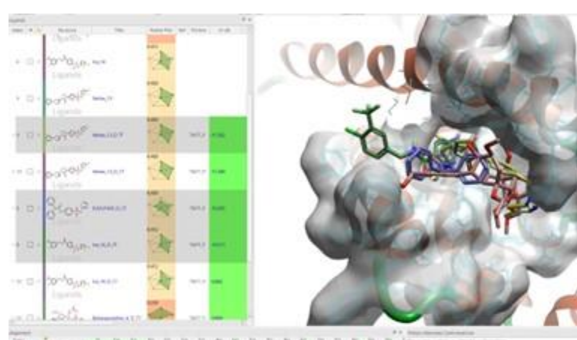

**Figure 2**

## Hyperpolarization-activated cyclic nucleotide-gated cation (HCN) channel in CD4+ T-cell regulation

**Laura Vinnenberg**[1], Johannes Greiff[1], Lisa Epping[1], Sven G Meuth[2], Heinz Wiendl[1], Thomas Budde[3], Petra Hundehege[1]

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Ion channels are fascinating proteins that are found in the cell membranes of all living cells. While the importance of ion channels for excitable cells is indisputable and research subject for a long time the significance for immune cell function is understudied. Knowledge of ion channels involved in differentiation, maintenance and activation of immune cells has increased in the last years. Identified candidates include the calcium release-activated calcium (CRAC), transient receptor potential (TRP), P2X, anion (VRAC) and diverse K+ channels (Kv1.3, TASK 1-3, TRESK, KCa3.1). Interestingly, T-cell activation involves redistribution of ion channels, upregulation of encoding genes and ionic currents [1-3]. Thus, selective ion channel modulators represent a promising therapeutic approach for the treatment of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [4,5].

A mathematical T-cell model was set up that holds all functionally expressed ion currents on human $CD4^+$ T-cells known yet including their individual current-voltage (IV)- and pH-dependencies. Simulation of T-cell electrophysiology led to the conclusion that there is a discrepancy in current amplitudes comparing experimental and *in-silico* data. Thus, pointing to a so far unknown, depolarizing ion conductance that is functionally affecting T-cell electrophysiology. HCN channels were considered good candidates for explaining this discrepancy [2].

It is known that HCN channels play crucial roles in a broad variety of electrically excitable (e.g. neurons, cardiomyocytes) and also non-excitable cell types, like kidney cells and mRNA expression of HCN2, HCN3 and HCN4 (but not HCN1) genes was detected in murine $CD4^+$ T-cells. However, neither pharmacological blockade with ivabradine, ZD7288 or EC18 nor $CD4^+$ specific knockout of the strong cAMP-dependent isoforms HCN2 and HCN4 using the Cre/loxP-System in mice revealed functional impact on cytokine secretion, proliferation or electrophysiological properties (unpublished data).

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**The role of kallikrein on Kv7 channels**

**Nicole Rychlik** [1], Paul Disse[2], Guiscard Seebohm[2], Sven G. Meuth[3], Thomas Budde[1]

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Multiple sclerosis (MS) is by far one of the most commonly occurring demyelinating neuroinflammatory diseases of young adults. MS is driven by a T-cell mediated attack where T-cells migrate across the disturbed blood brain barrier (BBB) leading to damaged myelin sheaths and oligodendrocytes in form of an autoimmune attack, thereby resulting in impaired electrical signal transduction, neurodegeneration and eventually permanent neurological deficits (Antel et al., 2012). Several mediators of the kallikrein-kinin system (KKS) have been identified to be critical contributors to MS pathogenesis and potent direct modulators of neurological functions (Göbel et al., 2016). In this context high levels of plasma prekallikrein (PK) could be observed in active central nervous system (CNS) lesions of MS patients (Göbel et al., 2019). Recently, Kv7 channels were found to be altered following demyelination thereby representing potential new molecular players. Several studies found upregulation of *KCNQ2* and *KCNQ3* transcripts in chronic active lesion in human MS brains (Boscia et al., 2021). This transient upregulation was followed by downregulation in chronic inflammatory-demyelinating gray matter areas in MS and EAE (Kapell et al., 2022).

In our study, we performed gene expression analysis following cuprizone-induced myelin loss showing decreased levels of *Kallikrein 6* in the auditory cortex (Au1) and the ventrobasal complex of the thalamus (VB) in mice. Also, the gene expression of *KCNQ3* were reduced in the VB and Au1. Whereas the expression of *KCNQ2* in the Au1 remained stable over time but was reduced in the VB. To study the electrophysiological properties of the Kv7.2 and Kv7.3 channels under the influence of kallikrein, the channels were expressed alone and together in *Xenopus laevis* oocytes. Characteristic M-currents showed a significant kallikrein-induced increase when Kv7.3 channel were expressed alone or together with Kv7.2.

As the role of the KKS in normal physiology and disease is still far from being understood, future studies have to identify the signaling pathways underlying the differential kallikrein effects in thalamus and cortex and to assess the involvement of Kv7 channels. Eventually a better understanding of the KKS may help to realize novel therapeutic approaches in MS injury treatment.

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## Cav2.3 phosphorylation in the pathophysiology of CDKL5 deficiency disorder: a new target for treatment

**Marisol Sampedro Castaneda[1]**, Lucas L Baltussen[1], Andre T Lopes[1], Yichen Qiu[2], Liina Sirvio[1], Simeon R Mihaylov[1], Suzanne Claxton[1], Jill C Richardson[3], Gabriele Lignani[2], Sila K Ultanir[1]

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CDKL5 deficiency disorder (CDD) is one of the most common types of genetic childhood epilepsy, affecting an estimated 1:40k newborns. The disease is caused by loss-of-function mutations in the gene encoding the brain-enriched Ser/Thr kinase CDKL5. Currently known physiological substrates of CDKL5 in the brain include proteins linked to microtubule function and DNA repair. How CDKL5 function impinges on neuronal excitability remains unknown. We present the identification of a novel physiological CDKL5 target, the alpha subunit of voltage-gated $Ca^{2+}$ channel Cav2.3 (encoded by *CACNA1E*) via a global phosphoproteomics screen in CDKL5 knockout mice. Cav2.3 is phosphorylated at Ser15 in the N-terminus, a region involved in G-protein modulation of the channel. In HEK cells expressing exogenous Cav2.3, loss of CDKL5-dependent phosphorylation leads to gain-of-function in Cav2.3 by slowing down channel inactivation. To assess changes in G-protein modulation, we used muscarinic acetylcholine receptor co-transfections and found that loss of Cav2.3 phosphorylation causes increased enhancement of $Ca^{2+}$ currents. Mice carrying a point mutation in the CDKL5 target residue (Ser15Ala) do not have spontaneous behavioural or EEG seizures. However, their behavioural characterization reveals motor, cognitive and social deficits, overlapping with CDKL5 KO mice phenotypes. We also find altered muscarinic neuromodulation in the CA1 region of the hippocampus, with larger afterdepolarizations and higher incidence of plateau potentials measured by whole-cell patch-clamp in acute slices. Finally, using a phospho-specific antibody, we show that S14 phosphorylation is reduced in iPSC derived neurons from CDD patients, indicating a conserved regulation. Our results show that CDKL5 dampens the impact of Cav2.3 currents on neuronal excitability by restricting channel open time, thus revealing Cav2.3 as a mechanistically relevant therapeutic target in CDD. Importantly, recently identified human point mutations in *CACNA1E* also lead to channel gain-of-function and early onset epilepsy, pointing at a central role for this channel in a converging disease pathway.

## Novel Mitochondrial KV 1.3 Inhibitors: Design, Synthesis and Biological Evaluation

**Marzia Fois** [1], Špela Gubič[1], Xiaoyi Shi[2], Ildiko Szabo[3], Luis Pardo[2], Lucija Peterlin Mašič[1], Tihomir Tomašič[1]

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KV1.3 is a transmembrane protein, expressed in cellular and in mitochondrial membrane, belonging to voltage-gated potassium channel KV1.x subfamily. KV1.3 has become an interesting target for anticancer therapy because a correlation between its expression and the development of cancer was demonstrated. It is overexpressed in different types of tumors and its activity is involved in cell proliferation and in the process of apoptosis.[1–3]

The aim of our work is to develop new inhibitors of the mitochondrial KV1.3 (mitoKV1.3) channel that would induce the apoptosis of cancer cells. We recently optimized the thiophene-based inhibitors and tested their ability to inhibit the proliferation of cancer cells that overexpress KV1.3, such as PDAC, Colo-357 and Panc-1.[4] Based on the results, we hypothesized that the inhibition of mitochondrial KV1.3 is required for a significant anticancer activity.

To improve the anticancer potential of KV1.3 inhibitors, we designed a series of mitoKV1.3 inhibitors composed of the thiophene-based KV1.3 inhibitor, a lipophilic alkyl linker and the cationic triphenylphosphonium$^+$ group (TPP$^+$). The anticancer activity of new compounds was investigated in Colo357 cancer cell models and mouse melanoma BF16F10 cells in which a significant toxicity was observed. The compounds were less cytotoxic in B16F10 C52 mouse melanoma cells in which KV1.3 was stably knocked down, so it appears that the effects depend on KV1.3 expression in mitochondria. Further biological evaluation is currently in progress.

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# Cryo-EM structure of ion channel pannexin 1 using GeneArt and Salipro DirectMX platforms

**Ieva Drulyte[1]**, Aspen Rene Gutgsell[2], Pilar Lloris-Garcerá[3], Michael Liss[4], Stefan Geschwindner[2], Mazdak Radjainia[1], Jens Frauenfeld[3], Robin Löving[3]

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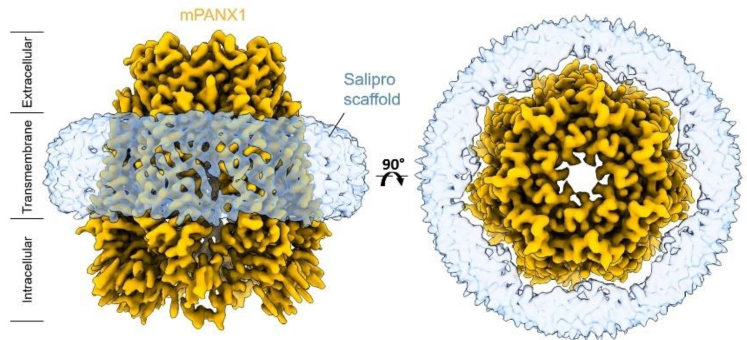
Cryo-electron microscopy (cryo-EM) is rapidly evolving to be the primary tool for the structure determination of membrane proteins[1,2]. Ion channels are particularly prominent examples since they are important drug targets, and their relatively large size is conducive to single-particle cryo-EM analysis. However, like all membrane proteins, the production of structure-grade recombinant ion channel proteins requires experience and expertise, often making this step the workflow bottleneck. Therefore, we asked whether it would be possible to leverage GeneArt™ services from Thermo Fisher Scientific with Salipro Biotech's expertise and the Salipro® platform technology for membrane proteins to generate high-quality pannexin 1 (PANX1) ion channel protein for structure-function analysis using SPR and cryo-EM. In this poster, we present the three stages of our approach – protein expression, generation of purified Salipro®-PANX1, and reconstruction of 3.1 Å cryo-EM map of mouse PANX1 (Fig. 1). Our cryo-EM structure mouse PANX1 represents the first published structure of a membrane protein extracted by Salipro nanoparticles directly from cells[3].

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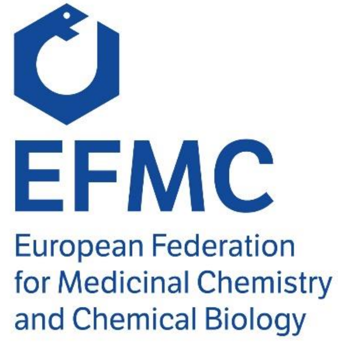

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