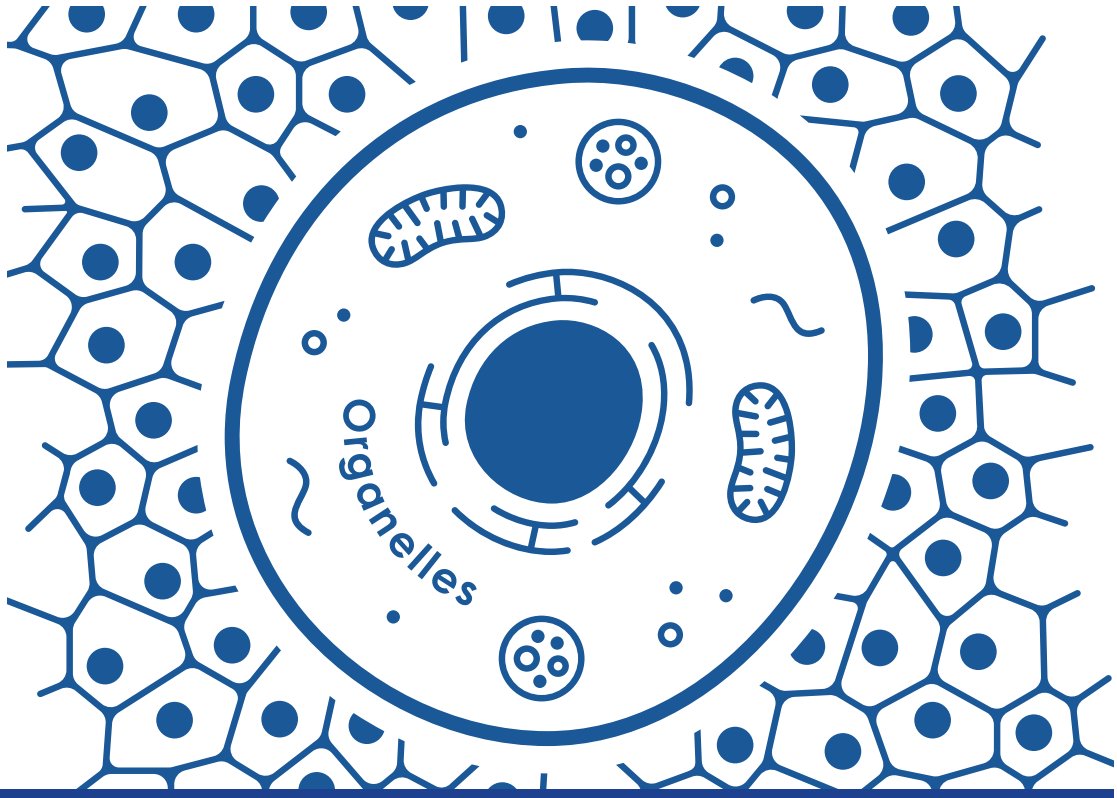

Nanion User Meeting 2024

Munich, Germany

Science, Workshops, Networking

Nanion User Meeting 2024 Agenda

Dates: October 22-23rd, 2024

Venue: Nanion Technologies HQ,

Tuesday, October 22nd

10:00 - 12:00 h CEST
User Workshop: SyncroPatch 384 (Registration required)

11:45 - 13:00 h CEST
Registration & welcome bites

13:00 - 13:15 h CEST
Niels Fertig (Nanion Technologies)
Welcome words

13:15 - 13:40 h CEST
Martin Gunthorpe (Autifony Therapeutics)
K_V3 channel positive allosteric modulators as a precision medicine approach for the treatment of progressive myoclonic epilepsy

13:40 - 14:05 h CEST
Joachim Wegener (University of Regensburg & Fraunhofer EMFT)
Profiling GPCR pharmacology using impedance monitoring of cell-based assays

14:05 - 14:30 h CEST
Christian Grimm (Ludwig-Maximilian University)*
A small GTPase is a direct effector of the intracellular Ca^{2+} channel TPC2 regulating melanoma progression through modulation of the Wnt signaling pathway

14:30 - 14:35 h CEST
Poster flash talks (x2, 2 min each)

14:35 - 16:00 h CEST
Instrument demos & Networking

16:00 - 16:25 h CEST
Alexandre Santinho (Oria Bioscience)
Inside out: Pioneering the future of organellar target screening

16:25 - 16:50 h CEST
Adriana Bizior (SB Drug Discovery)
Utilising SURFE^{2}R technology to accelerate transporter drug discovery

16:50 - 17:15 h CEST
Surabhi Rajendra Kokane (Stockholm University)
PI-(3,5)P2 mediated oligomerization of the endosomal Na^+/H^+ exchanger NHE9

17:15 - 17:40 h CEST
Ulrich Hammes (Technical University Munich)
Substrate recognition and transport mechanism of the pin-formed auxin exporters

17:40 - 17:45 h CEST
Poster flash talks (x2, 2 min each)

17:45 - 18:45 h CEST
Posters & networking

19:00 - 23:00 h CEST
Dinner hosted by Nanion Technologies
Fräulein Wagner, Am Bavariapark 16, 80339 Munich

*This talk will be only available to the attendees on-site. It will not be broadcasted to the virtual attendees

Wednesday, October 23rd

08:45 - 09:15 h CEST
Coffee & tea

09:15 - 09:40 h CEST
Stefan Kubick (B4 PharmaTech)
Cell-free systems for the production and functional characterization of membrane proteins

09:40 - 10:05 h CEST
Gregor Anderluh (National Institute of Chemistry)
Pore forming toxins: from molecular mechanisms to nanosensing

10:05 - 10:30 h CEST
Tobias Ensslen (Hahn-Schickard Institute)
Real-Time Peptide Differentiation: Insights from Nanopore Technology

10:30 - 11:00 h CEST
Coffee break

11:00 - 11:25 h CEST
Jamie Bhagwan (Axol Bioscience)
Chamber-specific pharmacological responses of axoCells™ hiPSC-derived Atrial and Ventricular Cardiomyocytes on the FLEXcyte96 platform

11:25 - 11:50 h CEST
Jieun An (NEXEL)
Utilizing Cardiosight®-S with the CardioExcyte96 for Cardiotoxicity Screening

11:50 - 12:15 h CEST
Jamie Vandenberg (Victor Chang Cardiac Research Institute)
High throughput phenotyping of cardiac ion channel variants

12:15 - 13:30 h CEST
Lunch

13:30 - 13:55 h CEST
Janina Sörmann (University of Copenhagen)*
Leveraging Machine Learning tools to design hASIC1a modulators

13:55 - 14:20 h CEST
Rajnish Ranjan (EPFL)
CHANNELOME: Towards a paradigm shift in drug screening

14:20 - 14:45 h CEST
Karen Elvers & Iwan Williams (Cardiff University)
Enabling Drug Discovery with the SyncroPatch 384

14:45 - 15:10 h CEST
Alexandr Ilyaskin (Friedrich-Alexander-Universität)
Structure-based analysis of proteolytic and ligand-mediated ENaC activation

15:10 - 15:20 h CEST
Ali Obergrussberger (Nanion Technologies)
Closing words

MEMBRANE PHYSIOLOGY SYMPOSIUM

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Speakers:

Dr. Mustafa Djamgoz - Imperial College of London
Dr. Teresa Giráldez - Universidad de La Laguna
Dr. Tamer Gamal El-Din - University of Washington
Dr. Filip Van Petegem - University of British Columbia
Dr. Hiro Furukawa - Cold Spring Harbor Laboratory
Dr. Gerald Zamponi - University of Calgary
Dr. Alfred L. George Jr. - Northwestern University
Dr. Olive Burata - University of California San Francisco
Dr. Matthias Quick - Columbia University
Dr. Baron Chanda - Washington University in St Louis
Dr. Adam Cohen - Harvard University
Dr. Terry Hébert - McGill University
Dr. Howard Young - University of Alberta
Dr. Isabelle Deschenes - The Ohio State
Dr. Brooke Ahern - US Army DEVCOM
Dr. Heike Wulff - University of California Davis
Dr. David Weaver - Biohaven
Dr. David Chiang - BWH Harvard
Dr. John Graef - Sarepta Therapeutics
Dr. Merritt Maduke - Stanford University

October 22nd

13:00 - 14:35 h CEST

Dr. Niels Fertig

Nanion Technologies

What is new at Nanion?

For over two decades, Nanion Technologies has been a leader in providing diverse solutions for electrophysiologists worldwide. Our innovative work in ion channel APC electrophysiology, cell viability and contraction monitoring, and electrogenic transporter research supports high-throughput capabilities. Niels Fertig will highlight our significant milestones and achievements from the past year, showcasing our ongoing efforts to advance electrophysiology and support groundbreaking research.

Session: Allosteric channel modulation
Chair: Markus Rapedius (Product Manager APC Chips)

Martin Gunthorpe

Autifony Therapeutics

K_v3 channel positive allosteric modulators as a precision medicine approach for the treatment of progressive myoclonic epilepsy

Autifony Therapeutics is a clinical-stage biotech company dedicated to new ion channel medicines for rare CNS disorders. Its lead programme is based on novel, first-in-class, positive allosteric modulators (PAMs) of Kv3 channels for which the site and mechanism of action is now resolved by Cryo-EM. Kv3 channels exhibit ultra-fast kinetics enabling neurons to fire action potentials at high frequencies, control neurotransmitter release, and fine-tune neuronal activity in the brain. Identification of a human causal mutation (R320H) that, through Kv3.1 loss of function, causes a rare epilepsy highlights this important role. The potential of Kv3 PAMs as novel therapeutics to treat epilepsy as well as additional diseases in which evidence of interneuron dysfunction is implicated in the underlying pathology will be highlighted.

Joachim Wegener

University of Regensburg & Fraunhofer EMFT

Profiling GPCR pharmacology using impedance monitoring of cell-based assays

G-protein coupled receptors (GPCRs) are among the most heavily addressed drug targets in medicinal chemistry and pharmacology. Non-invasive impedance analysis of cells grown on thin film electrodes has attracted considerable attention in the field as it allows monitoring the response of target cells with endogenous receptor expression in real time and label-free. The disposable electrodes are integrated into regular cell culture dishes of various formats up to 96well multi-well plates. This webinar will explain the technology and the underlying physical principles. It will focus on several different approaches how label-free impedance measurements help to characterize the pharmacology of GPCRs in cell-based assays.

Christian Grimm

Ludwig- Maximilian University

A small GTPase is a direct effector of the intracellular Ca^{2+} channel TPC2 regulating melanoma progression through modulation of the Wnt signaling pathway

Melanoma is the deadliest form of skin cancer. It arises from pigment producing melanocytes. Extensive ultraviolet light exposure is a major cause of melanoma and individuals with low levels of melanin are at particular risk. Humans carrying gain-of-function polymorphisms in the melanosomal/endolysosomal two-pore cation channel TPC2 present with hypopigmentation, blond hair, and albinism, and may bear a higher risk for melanoma development. Vice versa loss of TPC2 is associated with decreased cancer/melanoma proliferation, migration, invasion, tumour growth and metastasis formation, and TPC2 depleted melanoma cells show increased levels of melanin. We show here that a small GTPase, highly abundant in melanoma strongly enhances, through direct protein-protein interaction the activity of TPC2 and that the effects of TPC2 on melanoma hallmarks, in vitro and in vivo strongly depend on this GTPase, which controls TPC2 activity to modulate components of the Wnt signaling pathway, in particular GSK3β-mediated degradation of MITF, a major regulator of melanoma development and progression.

October 22nd

16:00 - 17:45 h CEST

Session: Membrane transporters in drug discovery
Chair: Cecilia George (Senior Sales Manager SURFE²R / Senior Scientist)

Alexandre Santinho
Oria Bioscience

Inside Out: Pioneering the future of organellar target screening

Cellular organelles are central to vital processes within our cells. Researchers have ingeniously tackled the challenge of studying therapeutic targets within these organelles for decades. In recent years, Oria Bioscience has developed a breakthrough technology that isolates organelle vesicles. In this talk, we will show the unique expertise we've gained in understanding organelles' biomechanical and biophysical properties, which is crucial for their study through automated electrophysiology. Our collaboration with Nanion has enabled us to test ion channel activity in microfluidics-generated organelles, beginning with the lysosome. At Oria, we are positioning ourselves as a provider of standardized & viable organelles for both automated and solid-supported membrane electrophysiology. We aim to establish a robust, reliable, reproducible framework for organelle-based screening.

Adriana Bizior
SB Drug Discovery

Utilising SURFE²R technology to accelerate transporter drug discovery

Numerous platforms offer insights into function, activity, and pharmacology of transporter proteins, however, lack of specific tools allowing for rapid investigation in their native environment is still an obstacle for drug discovery. SURFE²R technology presents a novel high throughput method to resolve this challenge. Using enriched lysosomal or membrane fractions from recombinant cell lines we have successfully developed assays to investigate multiple transporters and channels. SURFE²R technology has the potential to facilitate reliable compound screening, enabling discovery of novel modulators and aiding the advancement of knowledge of transporter proteins and their role in normal physiology and disease.

Surabhi Rajendra Kokane
Stockholm University

PI-(3,5)P2 mediated oligomerization of the endosomal Na^+/H^+ exchanger NHE9

NHE9 (SLC9A9) is pivotal in maintaining intracellular pH, sodium levels, and cell volume regulation. Its activity has been closely associated with diseases such as glioblastoma, autism spectrum disorders, and ADHD. Here, we present the cryo-EM structure of the NHE9 homodimer at 3.2 Å and 3.6 Å resolutions. The structure uncovers previously unknown features of the loop domain in NHE9, having two β-hairpin strands positioned approximately 15 Å above the dimerization interface. This domain interacts with the endosome-specific lipid PI-(3,5)P2. A combination of thermal-shift assays and solid-state membrane electrophysiology confirms the specific binding of PI-(3,5)P2 to NHE9. Furthermore, we establish that this lipid enhances sodium binding.

Ulrich Hammes
Technical University Munich

Substrate recognition and transport mechanism of the pin-formed auxin exporters

PIN-FORMED transporter are key players in polar auxin transport. In Arabidopsis there are five canonical, plasma membrane-localized PINs, that possess a long-disordered loop which is subject to regulation by kinases. Mutants in these genes display severe phenotypes. The two short PINs, PIN5 and PIN8, localize to the ER and their physiological role is less clear. PIN6 is intermediate and shares features of long as well as short PINs. Recently, a total of nine structures of three PINs were published and significantly advanced our understanding of this family of transporters. In this presentation, I will compare the structures and explain the transport mechanism. I will also share recent data about what determines substrate specificity and binding of substrates in PIN and how we use SURFE²R to address these questions and discuss the limitations and pitfalls we encountered along the way.

October 23rd

09:15 - 10:30 h CEST

Join us at the meeting dinner tonight!

Dinner will take place on October 22nd at the Fräulein Wagner!

Session: Understanding pores and toxins
Chair: Conrad Weichbrodt (Product Manger Orbit systems)

Stefan Kubick
B4 PharmaTech

Cell-free systems for the production and functional characterization of membrane proteins

Membrane proteins are key targets in both functional characterization and structural studies. Recently, cell-free systems, particularly eukaryotic ones, have emerged as efficient tools for rapidly producing a wide range of proteins. Many of these proteins require posttranslational modifications to function optimally. To date, several membrane proteins expressed *in vivo* closely mimic their authentic counterparts in function, antigenicity, and immunogenicity. Cultured eukaryotic cells perform essential modifications like glycosylation, phosphorylation, and palmitoylation. We have developed a method for creating translationally active eukaryotic lysates, preserving the membrane vesicles and their functionality, enabling advanced protein synthesis.

Gregor Anderluh
National Institute of Chemistry

Pore forming toxins: from molecular mechanisms to nanosensing

Pore-forming toxins are an important group of natural toxins. They act by forming pores of nm dimensions in cell membranes, which disrupts normal functioning of cells and can even lead to cell death. Many examples of pore forming toxins families exis t in all domains of life. Nep1-like proteins are important microbial effectors that disrupt plant membranes. They form small transient pores, which can be observed by a planar lipid bilayers approach using model membranes composed of sphingolipids purified from plants. The varying levels of conductances and noise indicated that pores differ in their architecture and size. We will also show how pore-forming toxins can be employed for sensing of macromolecules.

Tobias Ensslen
Hahn-Schickard Institute

Real-Time Peptide Differentiation: Insights from Nanopore Technology

While DNA sequencing by nanopores is established, no similar method exists for proteins and peptides. Initial attempts at peptide sequencing by nanopores used a DNA-peptide hybrid threaded through a nanopore by a helicase enzyme but faced intrinsic limitations. We present an alternative using a wt-Aerolysin pore in the trapping regime for peptide differentiation. We generated 6 decapeptides of identical composition and molecular weight but different sequences. Each peptide's ladder produced unique maxima in the histogram of relative blocked current levels, correlating with sequence lengths. We demonstrated in-situ peptide ladder generation via exopeptidase degradation, enabling real-time sequence monitoring. This approach is reproducible, parallelizable, and automation-friendly.

October 23rd

11:00 - 12:15 h CEST

Session: Cardiac research insights
Chair: Elena Dragicevic (Global Marketing Manager)

Jamie Bhagwan
Axol Bioscience

Chamber-specific pharmacological responses of axoCells™ hiPSC-derived Atrial and Ventricular Cardiomyocytes on the FLEXcyte 96 platform

In recent years, hiPSC-CMs have found great utility for *in vitro* studies as a physiologically relevant source of material. However, less work has been performed assessing pharmacological responses on atrial hiPSC-CMs. Here, we show that axoCells™ hiPSC-derived Atrial and Ventricular Cardiomyocytes show differential contractility responses when measured on the FLEXcyte 96 platform, including beat rate, beat duration and contractile force. Furthermore, chamber-specific responses were observed upon addition of specific classes of compounds such as GPCR agonists and K^+ channel antagonists. These insights illustrate the power of being able to simultaneously record contractility in a multi-well format to test a range of compounds at multiple concentrations for more faithful medium to high throughput drug screens *in vitro*.

Jieun An
NEXEL

Utilizing Cardiosight®-S with the CardioExcyte 96 for Cardiotoxicity Screening

Cardiosight®-S provides an *in vitro* test system that recapitulates native human cardiac myocyte physiology and function while the CardioExcyte 96 system provides a non-invasive, label-free, and high-throughput platform for monitoring EFP and impedance. Combining Cardiosight®-S with the CardioExcyte 96 allows for the measurement of stable signals with physiological trace shapes and accurately assesses the feasibility of evaluating the cardiac safety of drugs. This combination highlights the ease of generating robust and relevant data on cardiac electrophysiological characteristics, suggesting that Cardiosight®-S together with CardioExcyte 96 can be effectively used as a model in the drug development process.

Jamie Vandenberg
Victor Chang Cardiac Research Institute

High throughput phenotyping of cardiac ion channel variants

Advances in next-generation sequencing have been exceptionally valuable for identifying variants in medically actionable genes. However, for most missense variants there is insufficient evidence to permit definitive classification of variants as benign or pathogenic. To overcome the deluge of Variants of Uncertain Significance, there is an urgent need for high throughput functional assays to assist with the classification of variants. Advances in parallel planar patch clamp technologies has enabled the development of automated high throughput platforms capable of increasing throughput 10- to 100-fold compared to manual patch clamp methods. Automated patch clamp electrophysiology is poised to revolutionize the field of functional genomics for inheritable cardiac ion channelopathies. In this presentation I will outline the development of high-throughput automated patch clamp assays to assess cardiac ion channel variants, clinical application of these assays and where the field is heading.

research ins]i[ghts

cardiac safety symposium 2025

When: May 21st, 2025
Where: Virtual
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Safety pharmacology

Cardiotoxicity

Ion channels

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October 23rd

13:30 - 15:20 h CEST

Session: Ion channels in drug discovery
Chair: Fitzwilliam Seibertz (Scientific Sales)

Janina Sörmann
University of Copenhagen

Leveraging Machine Learning tools to design hASIC1a modulators

Stroke is a leading cause of death and adult disability, with numbers rising due to population aging and increasing risk factors. Acid-sensing ion channels (ASICs) in the central nervous system contribute to tissue damage after ischemic stroke but are underexplored therapeutic targets due to the lack of potent and selective inhibitors. We developed hASIC1a modulators by integrating the machine learning tools RFdiffusion, ProteinMPNN, and AlphaFold in the drug discovery process and combining it with functional analysis on the SyncroPatch 384. These computationally designed modulators offer high specificity, efficacy, and cost-effective synthesis, broadening accessibility for stakeholders.

Rajnish Ranjan
EPFL

CHANNELOME: Towards a paradigm shift in drug screening

Voltage-gated ion channels (VGICs) are essential proteins that regulate electrical signals in cells, making them critical for research in physiology and drug discovery. The traditional patch-clamp method, though effective, is limited in scale, hindering comprehensive VGIC research and drug screening. Automated patch-clamp systems have advanced the field, enabling high-throughput recordings, but many studies still rely on incomplete data, labeling drugs as "specific blockers" after limited testing. To address this, we developed an AI-based tool for comprehensive VGIC drug screening. Using stable CHO cell lines and automated systems, we screened 10 drugs across all major VGICs within a week.

Karen Elvers & Iwan Williams
Cardiff University

Enabling Drug Discovery with the SyncroPatch 384

There is little doubt that the therapeutic potential of drugs that specifically target ion channels has been largely untapped due to the technological challenge of the high-throughput electrophysiology required to screen and evaluate potential modulators of ion chancel function. In this regard, high-throughput electrophysiology platforms such as the SyncroPatch 384 represent a significant step-change and provide a capability that allows us to explore therapeutic targets that were previously technically intractable. In this presentation, we will discuss two separate applications of the SyncroPatch 384: 1) the development and optimisation of an assay suitable for the detection of modulators of a ligand-gated ion channel; and 2) the characterisation of an assay for an ion channel that regulates the function of lysosomes and which has been implicated in the pathophysiology of disorders associated with a dysfunction of lysosomal biology.

Alexandr Ilyaskin
Friedrich-Alexander University

Structure-based analysis of proteolytic and ligand-mediated ENaC activation

The epithelial sodium channel (αβγ-ENaC) is critically important for maintaining extracellular volume, blood pressure, and pulmonary fluid clearance. Its unique feature is proteolytic activation, which is based on the release of autoinhibitory peptides from α- and γ-ENaC. The channel is also stimulated by a small molecule activator S3969. Using recently published ENaC structures, we characterized two binding sites for autoinhibitory peptides in the α- and γ-subunit and identified a novel binding site for S3969 in β-subunit. Based on these results, we hope to identify novel ENaC modulators with possible (patho-)physiological implications by using virtual screening in combination with automated patch-clamp recordings.

Posters

Poster board #1. "The functional rescue of novel epilepsy-linked missense mutations in the human GABA transporter 1 by pharmacochaperoning"
Presenter: Nikita Shah (Medical University of Vienna)

Poster board #2. "Utilizing Solid Supported Membrane Electrophysiology (SSME) to Accelerate Discovery of TRPML1 Modulators"
Presenter: Adriana Bizior (SB Drug Discovery)

Poster board #3. "Exploring Membrane Proteins: Production, Function, and Structure via Cell-Free Protein Synthesis"
Presenter: Fang Dong

Poster board #4. "Beyond the Analgesic Flupirtine Towards Safe K_v7.2/3 Channel Activators"
Presenter: Frieda-Marie Bartz (University of Greifswald)

Poster board #5 "Development of Slo3-specific ion channel inhibitors"
Presenter: Teresa Mittermair (Münster University)

Poster board #6 "HTS and Lysopatch? New frontiers of Organellar Electrophysiology"
Presenter: Anna Mondini (Axxam SpA)

Poster board #7 "Local anesthetic reversal drug phentolamine inhibits voltage-gated sodium channels"
Presenter: Idil Toklucu(Uniklinik RWTH Aachen University)

Poster board #8 "*In Vitro* Systems for the Assessment of Chronic Cardiotoxic Effects: News from the HESI Stem Cell Working Group"
Presenter: Matthias Gossmann (innoVitro GmbH)

We welcome your feedback about the user meeting!

Notes

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