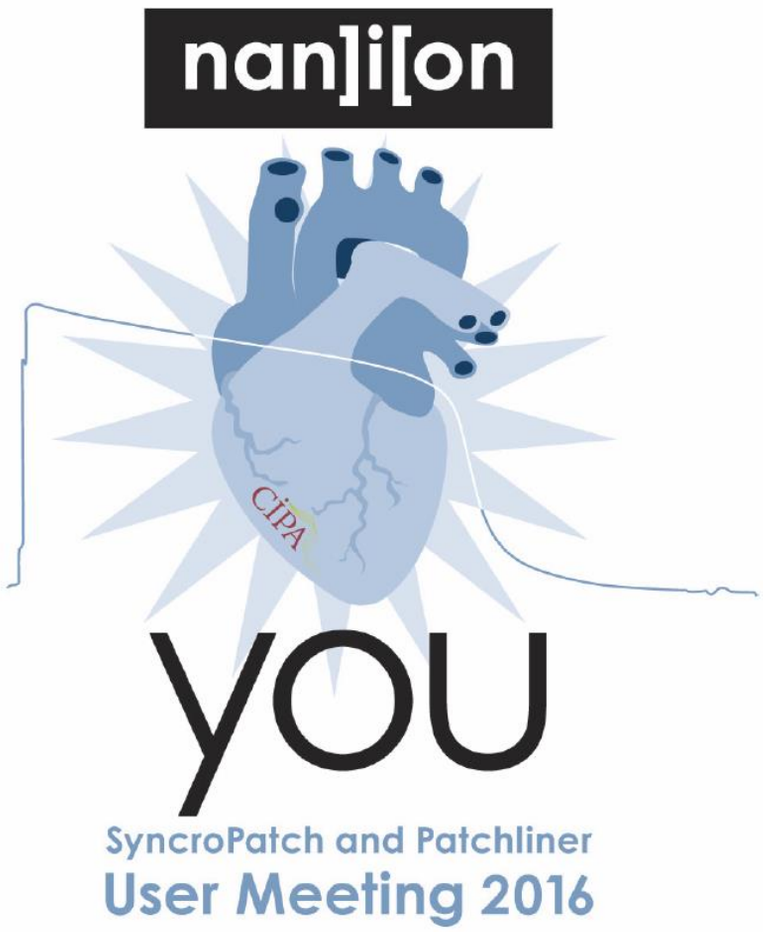
Nanion's 7th Annual User Meeting



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Welcome to Nanion's 7th Annual User Meeting

Table of Contents

Wednesday October 26

13:00 ▸ **Welcome reception**

13:30 – 13:50 ▸ **Welcome and introduction**
Niels Fertig, Nanion Technologies

Session 1 (chair: Niels Fertig)

Label free technologies in Safety Pharmacology

13:50 – 14:20 ▸ **Getting ready for CIPA – First steps with the CardioExcyte 96**
Fabian Haeusermann, Hoffmann-La Roche

14:20 – 14:50 ▸ **Towards exploration of 3D iPSC-CM models with the CardioExcyte 96**
Matt Burnham, AstraZeneca, United Kingdom

14:50 – 15:05 ▸ **News from the stem cell bench: present and future applications of cell-based assays**
Matthias Gossmann, Axiogenesis

15:05 – 15:20 ▸ **Electrophysiology in iPSC disease Modeling: Microelectrode Array (MEA), optogenetics and impedance approaches**
Sonja Stölzle-Feix & Elena Dragicevic, Nanion Technologies

15:20 – 16:20 ▸ **Refreshment Break & Poster Presentations**

Session 2 (chair: Andrea Brüggemann)

Ion channel Screening goes HTS

16:20 – 16:50 ▸ **Characterization of subtype selective KCNQ activators using the Synchropatch 384PE**
Chris Mathes, Icagen, USA

16:50 – 17:20 ▸ **Automated Electrophysiology Assay Development for MEM16A, a Calcium-Activated Chloride Channel using the Whole-Cell Configuration on the SyncroPatch 384PE**
Kaylee Choi, Amgen Inc., USA

17:20 – 17:50 ▸ **SyncroPatch 384PE: An Easy Approach to Difficult Target**
Andrea Brüggemann, Nanion Technologies

17:50 – 19:00 ▸ **Live demonstrations**

19:00 ▸ **Dinner**

Agenda

Thursday October 27

08:20 ▸ **Welcome**

Session 3 (chair: Maria Barthmes)

From ion channel Reconstitution to SSM on transporters All you can do with lipid bilayers

08:30 – 09:00 ▸ **Orbit16/Mini: Generic tools for the analysis of pore forming proteins**
Gerhard Baaken, Ionera, Germany

09:00 – 09:30 ▸ **Port-a-Patch Recordings of Purified TREK-2 K^+ Channels Reveal an Asymmetric Mechanosensitivity**
Stephen Tucker, University of Oxford, United Kingdom

09:30 – 10:00 ▸ **Introduction of the SURFE2R 96SE: A new tool for high throughput screening and characterization of membrane transporters and pumps**
Maria Barthmes, Nanion Technologies, Germany

10:00 – 10:40 ▸ **Refreshment Break & Poster Presentations**

Session 4 (chair: Claudia Haarmann)

New approaches in planar patch clamp

10:40 – 11:10 ▸ **Dynamic clamping on an MPA machine: adding virtual I_{K1} channels to cardiomyocytes**
Teun de Boer, University of Utrecht, The Netherlands

11:10 – 11:40 ▸ **Modelling the cardiac channelopathies using human induced pluripotent stem cells**
Divya Mirrington, University of Nottingham, United Kingdom

11:40 – 12:10 ▸ **Three Eighty Four – Current Clamp and more**
Claudia Haarmann, Nanion Technologies

12:10 – 13:00 ▸ **Lunch & Poster Presentation**

13:00 – 14:00 ▸ **Live Demonstrations**

Live Demonstrations:

SyncroPatch 384PE

Lab #1 ► **$GABA_A$**
768 parallel measurements of a stably transfected cell line expressing a cys-loop $GABA_A$ receptor
(Ilka Rinke)

Lab #2 ► **TRPC5**
Internal perfusion of Ca2+ to activate TRPC5 on the SyncroPatch 384PE
(Tom Goetze) (cell line kindly provided by Charles River)

Lab #2 ► **NaV1.5**
CIPA protocol to investigate the block of peak and late currents on the SyncroPatch384
(Markus Rapedius) (cell line kindly provided by Charles River)

Lab #2 ► **NaV1.8 (on demand)**
Assessment of Tetracaine sensitivity of Nav1.8 channels
activated from the slow-inactivated and resting states
(Markus Rapedius) (cell line kindly provided by Charles River)

Lab #2 ► **TMEM16a**
hTMEM16A/Ano1 channel gating is regulated by direct binding of intracellular Ca^{2+} and opens to conduct Cl^- ions. Using the internal perfusion system on the PE384/Felix the channel is activated by influx of free Ca^{2+}
(Nina Brinkwirth) (cell line kindly provided by SB Drug Discoveries)

SURFE²R 96SE & SURF²R N1

Lab #2 ► **PepT1**
Substrate affinity and inhibition of PepT1, a proton coupled peptide transporter
(Maria Barthmes)

Lab #2 ► **Sugar Transporters**
pH dependence of proton coupled sugar transporters. Discrimination of fast binding induced signals and transport induced signals
(Andre Bazzone)

Orbit Mini & Orbit 16

Showroom ► **Particle sizing**
Particle sizing through a nanopore in artificial lipid membranes
(Conrad Weichbrodt, Dr. Gerhard Baaken, Ionera Technologies GmbH)

Live Demonstrations:

Patchliner

Showroom ▸ Dynamic Patch Clamp (on demand)

The Patchliner is a fully automated patch clamp platform offering medium throughput and vast experimental freedom. Because of its high data quality, robust recordings and superior level of automation, the Patchliner is an exceptional tool routinely used by the pharmaceutical industry, CROs and academic institutions. We will show you some hot new stuff here: a cooled cell hotel, which keeps tricky cells such as iPS cells happy for a longer time. Furthermore, Christian is happy to introduce a new PatchControlHT version (2.0)! In addition to that, we can show some news on one of our development projects, dynamic clamp, which allows you to artificially equip your iPS cardiomyocytes with Ik1 and thus driving your resting membrane potential more negative!
(Sonja Stölzle-Feix, Christian Grad)

Maestro

Lab #3 ▸ Neuron & cardiomyocyte assay

During the Maestro multiwell MEA system (AxionBiosystems) demo, you will be able to experience the straight forward and high throughput approach to extracellular recording of neurons and cardiomyocytes. A range of neuronal and cardiac recordings will be shown, including safety, drug discovery and disease in a dish assays.
(Elena Dragicevic)

CardioExcyte 96

Lab #3 ▸ Optogenetic stimulation of cardiomyocytes

During the CardioExcyte96 demo, you will be able to experience the straight forward and high throughput approach to combined impedance and EFP recordings of iPS cardiomyocytes. A range of typical recordings with CiPA reference compounds will be shown. Furthermore, impedance toxicity assays on multiple other cells such as hepatocyte-like cells or proliferating cells will be shown.
We also have some hot new stuff coming up: A pioneering approach that allows optogenetic stimulation and the combined recording of electrophysiological and contractile parameters of iPS cardiomyocytes allows for a holistic understanding of the cells´ excitation-contraction coupling. Check it out!
(Ulrich Thomas, Krisztina Juhasz) (cells kindly provided by Axiogenesis)

Port-a-Patch

Showroom ▸ Stably transfected cells assays (on demand)

The Port-a-Patch is our miniaturized patch clamp system supporting giga-seal recordings from one cell at a time. It offers fast and easy access to high quality patch clamp data with only minimal training. Not only a powerful research tool but also ideal for educational purposes and quick tests of cells and ion channels. Check out our "Porti" and it´s multiple add-ons such as temperature control, internal perfusion and external perfusion!
(Patrick Mumm)

Abstracts Oral Presentations:

Session 1

Getting ready for CIPA – First steps with the CardioExcyte 96

Fabian Haeusermann, Hoffmann-La Roche

The recent progress in biosensor technology combined with availability of human stem cell-derived cardiomyocytes (SC-CMs) provides an exciting possibility to assess novel biomarkers of cardiac function in vitro. The goal of the present study was to evaluate the utility of the new hybrid instrument CardioExcyte 96 for multi-parameter profiling of endogenous responses in human SC-CMs. This integrative approach meliorates the screening pipeline by bridging single cell-based assays and ECG measurements for translational assessment.

Towards exploration of 3D iPSC-CM models with the CardioExcyte 96

Matt Burnham, Discovery Sciences, Alderley Park, Astrazeneca, UK

Stem cell cardiomyocyte (SCCM) based models show great promise for prediction of cardiotoxicity in drug discovery, and the formation of SCCM containing clusters, or spheroids, in 3D may provide additional physiological relevance and insight. However, generating data at scale using these advanced cell models can be challenging. We were able to perform label-free interrogation of the contracility and field potential of actively-beating SCCM spheroids alone, or with supporting fibroblast cells, using the CardioExcyte 96 platform, and were also able to pace the beat rate using electrical stimulation. Signal was particularly affected by spheroid size and proximity to the recording electrode, although spheroids containing only several hundred SCCM cells could be investigated. Custom designed 3D-printed plastic well inserts and the incorporation of magnetic nano-particle based reagents were explored to facilitate spheroid-to-electrode positioning in a simple manner. Pre and post-compound exposure beat rate, amplitude and field potential duration were detectable from the contracting spheroids. Further work is underway to improve the observed success rates and to understand the value of this approach to screening a 3D cellular phenotype as part of a cardiovascular toolkit of safety prediction screens.

News from the stem cell bench: present and future applications of cell-based assays

Matthias Gossmann, Axiogenesis AG, Germany

Cell-based assays play an outstanding role in the development of new hiPS-derived cell products. From earliest research over product development to final quality control, they provide deep insight into the fundamental functionality of the examined cells. Additionally, the application range of cell-based assays is still rapidly growing. The combination with new technologies broadens their application spectrum. One prominent example is the integration of optogenetic tools. By application of highly efficient molecular cargo delivery systems, hiPSC-derived cells can be modified by introducing new functions like light sensitive ion channels or calcium sensors. We present an overview of the current state in stem cell research and development as well industrial applications.

Electrophysiology in iPSC disease Modeling: Microelectrode Array (MEA), optogenetics and impedance approaches

Sonja Stölzle-Feix & Elena Dragicevic, Nanion Technologies

The Maestro, multi-well 768 channel microelectrode array (MEA) system (Axion Biosystems) provides measurements of extracellular electrophysiological activity of excitable cells over long periods of time. Each electrode is capable of capturing extracellular action potentials of excitable cells in ultra-high resolution (millisecond events with microvolt amplitudes), while multiple recording sites within each well allow population network activity measurements. Combined with Lumos, a state-of-the art multi-well optical stimulation device and Maestro APEX, the world's first robotic interface to automate the preparation, maintenance, and execution of MEA assays, Maestro brings the high throughput MEA research to the next level. The CardioExcyte is Nanion´s combined Impedance and extracellular field potential recording (EFP) system. Protocols for iPS cardiomyocytes from major cell suppliers are available, example data will be shown. Furthermore, a prototype of an optical stimulation lid is being developed at the moment. Optical in-vitro platforms will be of particular relevance in the early stages of drug discovery processes. Optogenetic stimulation and the recording of electrophysiological and contractile parameters of ChR2 (channelrhodopsin 2) transfected iPS Cor.4U cardiomyocytes were performed in a new assay approach, which allows a parallel investigation of impedance and EFP signals. This allowed a mechanistic understanding of cardiomyocyte cell physiology, which has been investigated over a physiological frequency range for stimulation (60-180 bpm).

Abstracts Oral Presentations:

Session 2

Characterization of subtype selective KCNQ activators using the Synchropatch 384PE

Chris Mathes, Icagen, USA

KCNQ2-5 (Kv7.2-5) are voltage-gated K^+ channels that underlie the neuronal M-current. These channels are expressed predominantly in the central and peripheral nervous systems. Small molecule pan-KCNQ openers, such as Retigabine, have been shown to reduce neuronal excitability thus providing a therapeutic approach to treat neuroexcitatory disorders such as Epilepsy, ALS and pain. Previously, Icagen scientists reported the discovery of ICA-27243, (N-(6-Chloro-pyridin-3-yl)-3,4-difluoro-benzamide), the first reported sub-type selective KCNQ2/Q3 opener. ICA-27243 has been shown to be active in a variety of rodent in vivo epilepsy and pain models, providing support for selective KCNQ2/3 openers as an anti- seizure or nociceptive therapeutic strategy. Nanion's Syncropatch 384PE offers a high throughput gigaseal electrophysiology platform which records high quality voltage clamp data from up to 384 individual cells or groups of cells simultaneously, providing reliable pharmacology and detailed biophysical characterization of channel gating. Using the Syncropatch 384PE we developed a KCNQ assay that accurately and reproducibly identifies selective activators of KCNQ2/Q3 with potencies comparable to those previously observed using either conventional patch clamp or PatchXpress automated electrophysiology recordings. Our results suggest that accurate pharmacology and high-throughput recordings of challenging targets like KCNQ channels can be achieved in a reproducible and reliable manner with the Syncropatch 384PE.

Automated Electrophysiology Assay Development for TMEM16A, a Calcium-Activated Chloride Channel using the Whole-Cell Configuration on the SyncroPatch 384PE

Kaylee Choi, Kathryn Henckels, John K. Sullivan, Joe McGivern Amgen Inc.

Transmembrane member 16A (TMEM16A), also known as anoctamin-1 (ANO1), is a calcium-activated chloride channel expressed by secretory epithelial cells, smooth muscle cells, sensory neurons, and some cancers. TMEM16A is activated directly by calcium when free intracellular levels are high, while the channel exhibits both voltage- and calcium-dependence at lower intracellular free calcium levels. TMEM16A antagonists represent an attractive new strategy to suppress the mucin hypersecretion and bronchoconstriction characteristic of uncontrolled severe asthma/COPD, and preclinical studies indicate they may also hold great promise for treating pulmonary hypertension, pain, and cancer.
To evaluate TMEM16A antagonists, we have developed the whole-cell patch-clamp assay in 384-format using the SyncroPatch 384PE on the FeliX platform. We have optimized the cell-catch step by tuning cell-catch pressure and time, and cell-dispense height and volume, resulting in 93% cell-catch success rate. We have also achieved fast calcium activation by optimizing internal perfusion pressure and time. Furthermore, we have shown stability of calcium-activated TMEM16A currents over 15-min recording time. Finally, we have obtained IC50 values for two known chloride channel inhibitors, niflumic acid and benzbromarone, that is similar to the potency reported in published literature.

SyncroPatch 384PE: An Easy Approach to Difficult Target

Andrea Brüggemann, Nanion Technologies

The SyncroPatch 384PE is not only a screening instrument for ion channels but also a very versatile instrument. It has great capabilities in assay development and handling of difficult targets. In this talk I would like to give you a short overview on the features of the SyncoPatch 384PE and how these can help you to screen your favorite targets. It will include TRPC5 activation by internal solution exchange and studies of CFTR. You can ask for your own favorite ion channels and I will try not to leave any wishes open

Abstracts Oral Presentations:

Session 3

Orbit16/Mini: Generic tools for the analysis of pore forming proteins

Gerhard Baaken, Ionera Technologies GmbH, Germany

High-throughput electrophysiological recordings from proteins in artificial membranes have a great potential for the investigation of non-patchable channel proteins and nanopore analytics. However in addition to parallelization and automation of lipid bilayer formation different protein reconstitution protocols are required depending on the concrete application.
In this talk the functional reconstitution of three classes of pore-forming proteins into suspended lipid bilayers on Ionera's Micro Electrode Cavity Array (MECA) within Nanion's Orbit devices will be presented. Three reconstitution strategies have been employed and optimized depending on the protein structure: self-insertion for pore-forming toxins, transfer from detergent micelles for porins and vesicle fusion for ion channels.

Port-a-Patch Recordings of Purified TREK-2 K+ Channels Reveal an Asymmetric Mechanosensitivity

Stephen Tucker, University of Oxford, United Kingdom

Mechanosensitive ion channels are gated open and shut by changes in membrane tension enabling the conversion of mechanical stimuli into changes in ionic composition and electrical signalling. However, the precise structural and biophysical mechanisms underlying these processes remain unclear. TREK-2 is a eukaryotic mechanosensitive ion channel that belongs to the Two-Pore Domain (K2P) family of K+-selective channels and is widely expressed in both the central and peripheral nervous system. I will discuss our recent structural, functional and computational studies which examine how TREK-2 responds to stretch-induced changes in the large lateral forces that vary with depth across the bilayer, and in particular how the asymmetric structure of the channel contributes to this process.

Introduction of the SURFE2R 96SE: A new tool for high throughput screening and characterization of membrane transporters and pumps

Maria Barthmes, Nanion Technologies, Germany

Solid supported membrane based electrophysiology provides the high signal amplification mandatory for the measurement of low transmembrane currents generated by pumps and transporters. Nanions SURFE2R devices base on this method. To enable measurement of transporter and pump activity with higher throughput and a high grade of automatization, necessary for efficient pharmacological research, Nanion developed the SURFE^{2}R 96SE. Here the SSM based method is briefly described and the technical features of the SURFE^{2}R 96SE are discussed. Finally several assays and data examples are presented.

Session 4

Dynamic clamping on an MPA machine: adding virtual I_{K1} channels to cardiomyocytes

Teun P. de Boer
Department of Medical Physiology, Division Heart & Lungs, University Medical Center Utrecht. Yalelaan 50, 3584 CM Utrecht, The Netherlands; t.p.deboer@umcutrecht.nl

Human pluripotent stem cell-derived cardiomyocytes (hPSC-CM) are an interesting source of cells for safety pharmacology. hPSC-CM can be differentiated to high purity in bulk, stored in liquid nitrogen and can be used in automated patch clamping machines to screen drug effects on human cardiomyocytes. Therefore, it is easy to understand why hPSC-CM are part of the CIPA proposal, but there are caveats that have to be taken into account.

Abstracts Oral Presentations:

A typical property of hPSC-CM is automaticity, the cardiomyocytes beat spontaneously, resembling cells in the sinoatrial node of the heart. The spontaneous beating is due to lack of IK1 ion channels, which cause hyperpolarisation and a stable resting membrane potential in the cells of the working myocardium. Work by our group has demonstrated that the depolarized state of hPSC-CM limits their usefulness in assays aimed at detecting proarrhythmic properties of drugs. In our study we observed EADs only with IKr block, not when blocking IKs, IK1, enhancing INa,late, blocking or enhancing ICa,L. This discrepancy with findings in adult cardiomyocytes is important, and can be explained by the immature phenotype of hPSC-CM.
Upregulation of IK1 channel expression is possible with recombinant viruses, however the expression level in individual cardiomyocytes cannot be controlled. As a more suitable alternative, dynamic clamping can provide virtual IK1 channels to a real biological hPSC-CM in a patch clamping experiment. Key benefits of this approach include full control of the added IK1 conductance to each cardiomyocyte, it can be applied to any hPSC-CM source and it can be coupled to automated patch clamping machines. Our group has developed a dynamic clamping system that can be fully controlled in an automated fashion via HEKA Patchmaster and PatchControlHT. In ongoing projects we are implementing the technique further with the Patchliner.

Modelling the cardiac channelopathies using human induced pluripotent stem cells

Dr Divya Rajamohan, Prof Chris Denning
Division of Cancer and Stem cells, School of Medicine, University of Nottingham NG7 2RD

The average drug takes 10-15 years of development, and millions of dollars to come to market. Between 1980 and 2009, one in seven licensed drugs had to be withdrawn due to unanticipated side-effects like cardiotoxicity and hepatotoxicity. These high rates of attrition are due to the use of sub-optimal, non-human in vitro screening assays in phase I drug trials.
Cardiomyocytes derived from human pluripotent stem cells (hPSC-CMs), comprising human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), are now emerging as a viable alternative for drug safety testing. They are 'human', and have been shown to respond predictably to over 60 different compounds that include modulators of ion channels, β (1-, and 2-) receptors, and muscarinic receptors. Furthermore, currently available high-efficiency cardiac differentiation protocols in concert with the high-content screening abilities of automated patch clamp devices, like the Patchliner® system, provide a platform for reliable and efficient drug candidate safety profiling and efficacy testing in industrial and academic settings.
In our labs we have used hPSC-CMs to models different cardiac channelopathies like the Long QT syndromes 1 and 2, and Catecholaminergic Ventricular Tachycardia (CPVT), with varying degrees of success. The foetal/neonatal-like phenotype of hPSC-CMs poses challenges to reliable disease modelling, and efforts are currently underway to push their structural and functional properties towards those seen in adult cardiomyocytes. While individual biochemical and mechanical cues provide incremental improvements in maturity, there has not yet been the leap needed to produce the adult CM phenotype. Whether this will ever be achieved is unknown but it might not be needed. Each improvement will extend the utility of hPSC-CMs further and they are already proving their worth.

Three Eighty Four – Current Clamp and more

Claudia Haarmann, Nanion Technologies

In this presentation I will be showing our latest data on stem-cell derived cardiomyocytes recorded on the SyncroPatch 384PE. We used the Cor.4Us (Axiogenesis) and Cellartis (Takara) cells. With those data I will take the opportunity to also introduce the new action potential analysis functions which come with our V1.5 software release (release date: Now! aka as User Meeting).
We also did some fun experiments with cells expressing NaV1.5 and ChR2 (Axxam) stimulating with light on the PE in both voltage and current clamp mode.

Abstracts Poster:

Poster #1:
Combining automated patch clamp, impedance and EFP of hiPSC-CMs

Camilla Larsson, Takara-Clonetech

Failure to correctly predict adverse cardiotoxic effects of new pharmaceuticals is the major cause of compound attrition during drug development as well as for withdrawal of drugs already on the market. This is partly due to lack of relevant human models for pre-clinical testing. With recent advances in the stem cell field it is now possible to generate human iPS cell-derived cardiomyocytes (hiPS-CM) that recapitulate the native behavior and accurately assess the pro-arrhythmic potentials of candidate drugs. At present, these cells are being actively investigated with high throughput technology, especially through the CiPA initiative, for their potential use as a model system for complete cardiac safety screening ("beyond hERG").
In this study, Cellartis® Cardiomyocytes applied in automated patch clamp platforms, the Patchliner, SyncroPatch 96 and SyncroPatch 384PE, were evaluated. Voltage-gated Na+ and Ca2+ currents could be reliably recorded in Cellartis Cardiomyocytes on all of these platforms, with values in good agreement with the literature, and a large proportion of the cells expressed Na and Ca currents (71% showed NaV current >-50 pA, 68% showed CaV current > -50 pA). NaV could be blocked by tetracaine, and CaV could be blocked by nifedipine with an IC50 in good agreement with the literature. This confirms that Cellartis Cardiomyocytes are suitable for use on high throughput automated patch clamp devices, providing an excellent assay for accurate drug safety testing in the light of the CiPA initiative.

Poster #2:
Effect of bispyridinium compounds on the activity of human a7-acetylcholine receptors using an automated patch clamp system

C. Scheffel[1,2*], K.V. Niessen[1], S. Rappenglück[2], K.T. Wanner[2], H. Thiermann[1], F. Worek[1], T. Seeger[1]
[1]Bundeswehr Institute of Pharmacology and Toxicology, Munich, Germany
[2]Department of Pharmacy – Center for Pharmaceutical Research, Ludwig-Maximilians-University Munich, Germany

Nicotinic Acetylcholine receptors (nAChRs) are a heterogeneous family of ligand-gated cation channels consisting of five heteropentameric or homopentameric subunits. nAChRs are implicated in pathological disorders in the CNS (e.g. Alzheimer's and Parkinson's disease, schizophrenia, depression and tobacco addiction) and in the PNS (e.g. congenital myasthenic syndrome, myasthenia gravis). Furthermore, these receptors are interesting therapeutic targets for the treatment of intoxications, e.g. by organophosphorus compounds (OPCs). Consequently, development of drugs that modulate function of nAChRs became increasingly interesting. Especially positive allosteric modulators (PAMs) that reduce or reverse nAChR desensitization are of therapeutic interest. Based on the lead structure MB327, an analogues series of different bispyridinium-non-oxime-compounds (BPs) was tested for their ability to prevent desensitization in order to unravel structural requirements mediating this effect.
To this end, cholinergic currents of human a7-nAChRs stably expressed in a CHO cell line (CHO/RIC-3/ha7-nAChR) were measured using whole-cell patch clamping under voltage-clamping conditions (-70 mV) performed with planar electrodes in an automatic system (Patchliner®, Nanion Technologies GmbH, Munich). Prior investigation of nicotine-induced currents showed a biphasic dose-response profile with increasing current amplitudes at low and declining amplitudes at high concentrations which seemed to be due to increasing receptor desensitization. Concerning the structure-activity profile of BP compounds co-applied with nicotine revealed two distinct intrinsic activities, i.e. inhibition or enhancement of nicotine-induced response depending on the substitution pattern of the pyridinium moieties. Enhancement of receptors by these compounds confirms the interaction on nAChRs as PAMs. This finding was proved that the tested compounds induced no receptor activation in absence of the orthosteric agonist nicotine, suggesting that their binding sites are spatially distinct from the orthosteric binding site.
The results are valuable basics for the development of potent PAMs for ha7-nAChR, allowing for initial structure-activity relations requested for predictive drug design.
Thereby, the automated patch clamp system serves as an effective tool for drug development, enabling prompt feedback of the intrinsic effects on the receptors mediated by the test substances.

Abstracts Poster:

Poster #3:
An Integrated and Innovative Service for Automatic Scoring of Cardiotoxicity Risks

Thierry Bastogne, Cybernano

This new integrated service is the result of a collaboration between Nanion and CyberNano to associate their innovations in terms of Data Acquisition and Data Analysis. The objective is to provide to all the users of the CardioExcyte 96 an efficient solution to evaluate risks of cardiotoxicity faster and safer. The complete workflow includes: data acquisition, data preprocessing, data compression and data analysis steps. As a result, a report is proposed to the experimenter with morphologic characteristics of the beatings, descriptive statistics, a risk scoring and a rank of the tested molecules. This service divides by ten the time of analysis of your data.

Poster #4:
Non-integrating, transient optogenetic modification of human iPSC-derived cardiomyocytes using ChR2 and GCaMP6f mRNAs

Benjamin Wolters[1], Ralf Kettenhofen[1], Jean Marc D'Angelo[2], Hirofumi Horai[2], Elena Dragicevic[3], Sonja Stoelzle-Feix[3], Matthias Beckler[3], Michael George[3], Leo Doerr[3], Ulrich Thomas[3], Niels Fertig[3]
[1] Axiogenesis AG, Cologne, Germany; [2] Hamamatsu Photonics, Massy, France; [3] Nanion Technologies, Munich, Germany

Monolayers of human iPSC-derived cardiomyocytes (hiPSCM) reveal spontaneous rhythmic beating which can be monitored either by means of microelectrode array recording of extracellular field potentials or by kinetic fluorescent plate readers using calcium- or voltage- sensitive dyes. Furthermore, the beat rate determines the duration of the field potentials (FPD) as well as the calcium transient (CTD) in a reverse usedependent manner. However, to understand drug mediated frequency changes, hiPSCM require a frequency correction of the FPD/CTD according to experimentally determined restitution curves or, preferably, cells can be paced by electrical means to beat at a constant rate.
To address this experimental limitation, we present a novel lipid-based transfection method which allows for a highly efficient and non-integrating optogenetic modification of hiPSCM using channelrhodopsin 2 and GCaMP6f (calcium sensor) mRNA. First, channel rhodopsin 2 mRNA was transfected into hiPSCMs which were then cultured and measured on Axion Maestro microelectrode arrays and CardioExcyte NSP96 plates. The channel rhodopsin 2 enabled the cells to be paced by optical stimulation (blue light) at defined rates for more than 2 weeks using the new Lumos light delivery system for the Axion Maestro or the CE96 optical stimulation system currently under development for CardioExcyte, respectively. Importantly, cells followed pacing frequencies from 1.5 Hz up to 5 Hz (higher frequencies were not tested). Additionally, transfection of the GCaMP6f mRNA into Cor.4U hiPSCM allowed for recording of calcium transients (Hamamatsu FDSS 7000EX) without addition of toxic chemical-based calcium dyes.
These data demonstrate novel tools to standardize, reduce costs, and greatly expedite drug safety screening in target organs of human origin while reducing animal usage.

Poster #5:
Excitatory Cortical Neurons (iCell GlutaNeurons) Derived from Human iPS Cells Create Functional Macro-Networks in vitro

Christian Kannemeier, Elisabeth Enghofer, Lisa Harms, Lori Norkosky, Rachel Lewis, and Brad Swanson Cellular Dynamics International, Inc., A FUJIFILM Company, Madison, WI USA

The ability to produce human neuronal populations from iPS cells combined with advancements in micro electrode array (MEA) instrumentation make it now possible to study human neuronal network activity in vitro. This poster presents data demonstrating the functional neuronal network properties of iCell GlutaNeurons, a human iPSC-derived excitatory cortical neuron population that enables electrophysiology and excitatory toxicity assays. Using single cell gene expression as a guide, we established a robust differentiation process starting from iPSCs that generates primarily cortical glutamatergic neurons. iCell GlutaNeurons react to increasing amounts of glutamic acid with increased cell death exhibiting excitatory toxicity. Pre-treatment of iCell GlutaNeurons with the NMDA and AMPA receptor inhibitors, AP5 and DNQX, inhibited excitatory toxicity. Most importantly, the cells show a robust formation of a synaptically-driven macro network over time with spontaneous, synchronous electrical activity in the MEA platform. The synchronous activity can be reversibly inhibited by AP5 and DNQX, thus demonstrating the ability to modulate iCell GlutaNeurons electrophysiological activity using pharmacology.

Abstracts Poster:

Poster #6:
Human iPSC-derived neurons for functional assessment of in vitro neurotoxicity and seizure liability

Dietmar Hess[1], Greg Luerman[1], Tristan Pritchard-Meaker[1], Elke Guenther[2], Heribert Bohlen[1]
[1] Axiogenesis AG, Köln, Germany; [2] NMI-TT GmbH, Reutlingen, Germany

In vitro pharmacology profiling of new chemical entities during early phases of drug discovery has recently become an essential tool to predict and avoid clinical adverse effects. While for cardiac safety testing, several validated platforms are available, specific in vitro neurotoxic panels are not, and only in vivo models are used. However, correlations between animal and human data are often weak; in addition, animal studies are expensive, ethically questionable and require large amounts of chemical compounds.
Here, we present two assay systems that address different in vitro neurotoxicity endpoints in a human system using induced pluripotent stem cell (iPSC)-derived neurons and multiwall microelectrode array (MEA)-technology. Peri.4U are iPSC-derived peripheral neurons that reveal clear burst-like activity after 3-4 day culture on MEA chips, indicating the presence and establishment of a functional neuronal network. Reference compounds with a known neurotoxic potential, such as neuroleptica, antidepressiva, neurotransmitter blockers, pesticides or plant toxins, were analyzed for their effect on neuronal network behavior. Peri.4U showed at least similar or even higher sensitivity to reference compounds compared to other neuronal in vitro models. This demonstrates the potency of Peri.4U for reliable detection and quantification of neurotoxic compound actions.
CNS.4U represent a highly physiological iPSC-based co-culture model of neurons (glutamatergic, GABAergic and dopaminergic) and astrocytes. CNS.4U rapidly form neuronal networks in culture and show synchronous network activity assessed by MEA technology over c. 5 weeks in culture. Here, we provide proof-of-concept results that demonstrate the suitability of CNS.4U for seizure liability assays based on dose-dependent reactivity to compounds that are known to affect seizure.

Poster #7:
Electrophysiology in iPSC disease modeling: microelectrode array (MEA) optogenetics and automated patch-clamp approaches

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Dissecting electrophysiological characteristics and distinct activity patterns of induced pluripotent stem cell (iPSC) derived neurons, recently became a priority in disease modeling research. Here, we describe different electrophysiological methods, used to achieve this goal.
Multi-well microelectrode array (MEA) systems (Axion Biosystems) provide simultaneous measurements of extracellular electrophysiological activity of excitable cells over long periods of time. Each electrode is capable of capturing extracellular action potentials of excitable cells in ultra-high resolution (millisecond events with microvolt amplitudes), while multiple recording sites within each well allow population network activity measurements. MEAs offer unbiased, label free, non-invasive recordings of natural cell functions, in a regulated physiological environment. Multiwell optogenetic stimulation further excels MEA-based disease modeling and drug discovery. These features enabled the usage of MEAs in development and characterization of in vitro disease models – Parkinson´s disease, ALS, epilepsy, fragile X, and autism – with the ultimate goal of identifying treatments. The high throughput and accuracy that Axion's MEA systems provide will significantly accelerate progress toward such treatments.
Automated, high-throughput planar patch clamp systems (Nanion Technologies), complement the need for predictive neurotoxicity screening in-vitro assays. Specialized protocols for reduced cell usage, increased throughput and integration into robotic environments improve cost efficiency, precision and are speeding up the HTS process of drug development and safety screening as a whole. Our special cell handling protocols enable usage of both control and patient derived, iPSC derived neurons on planar automated patch clamp systems. Our chip-based approaches, allow parallel patch clamp recordings without compromising neither data quality nor sophistication regarding technical features.
In summary, we present the data obtained from neuronal disease modelling experiments, by using both MEA and automated patch clamp approaches. These platforms together provide unmatched possibilities to study specific neurological disorders by developing phenotypic disease-in-a-dish cellular models.

Abstracts Poster:

Poster #8:
Pharmacological characterization of an amino acid transporter and his bacterial homologue with the Surfe²r

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The IDD in vitro biology department in Frankfurt has a long tradition of transporter drug discovery. Several techniques are established to find new small molecules to modulate the transporter function like fluorescence based flux assay, radioactive or MS based flux assays and even electrophysiological techniques like automated patch clamp or the Surfe2r technology. Our group has a more than ten years experience with this technology resulting in several project contributions for example the sodium-calcium-exchanger1 or the respiratory chain2. The recent project is for a Na^+-dependent transporter which is important in two indications relevant for Sanofi. No pharmacological tools are known for this transporter and the project team is searching for a small molecule inhibitor. The Sanofi compound library was screened with a fluorescence based membrane potential assay and the actives were validated with a MS-based substrate flux assay. The development of the first direct assay to measure the inhibition of transporter mediated currents with the Surfe2r technology is the topic of this poster.

Poster #9:
Assessment of pharmacological responses to cardioactive compounds in human induced pluripotent stem cell-derived (hiPSC) cardiomyocytes using MEA and calcium transient analysis

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Assessment of cardiac safety of drug candidates is highly important for effective drug development. Within the Comprehensive in vitro Proarrhythmia Assay (CiPA) consortium, hiPSC-derived cardiomyocytes are being evaluated for early prediction of drug-induced cardiac arrhythmias to refine the current ICHS7B guideline. Recently, we have developed a serum-free maturation medium (Pluricyte® Cardiomyocyte Medium) and hiPSC-derived ventricular cardiomyocytes (Pluricyte® Cardiomyocytes) that show a relatively mature phenotype, demonstrated by a high degree of ultrastructural sarcomere organization, low resting membrane potential, well defined action potential plateau and rapid depolarization. To understand the potential of Pluricyte® Cardiomyocytes for cardiac safety assessment, we measured the effects of a set of cardioactive compounds (including CiPA reference compounds) on the electrophysiology, using the Axion Maestro multiwell 768-channel platform, and on the calcium handling of Pluricyte® Cardiomyocytes, using the FDSS®/µCell platform. MEA analysis on the Axion Maestro multiwell 768-channel platform revealed field potential signals with robust sodium spikes and well-pronounced repolarization peaks. Both MEA and calcium transient analysis showed predictive and reproducible responses to cardioactive compounds, including tested low and high risk CiPA compounds.
Our data support the use of hiPSC-derived cardiomyocytes to predict cardiac safety of pharmaceuticals in humans, thereby improving preclinical testing strategies for the assessment of cardiac safety.

Poster #10:
Functional Characterization of Procaryotic NCX by Solid Supported Membrane Technology

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Sodium/calcium exchangers (NCXs) are membrane transporters which play an important role in Ca^{2+} homeostasis and Ca^{2+} signaling. Here, we use solid supported membrane (SSM) technology to performe functional analysis of NCX_Mj, an archaeal NCX isoform which has recently been crystalized. Using this approach we characterized the substrate affinity, ion specificity and inhibition by divalent cations of this archaeal exchanger protein. In conclusion we found a high functional similarity of NCX_Mj and eukaryotic NCX isoforms, although the prokaryotic protein lacks a large regulatory domain.

Abstracts Poster:

Poster #11:
Parallel reconstitution of bacterial toxins, porins and ion channels into suspended lipid membrane microarrays for high-throughput electrophysiology

Ekaterina Zaitseva[1,2], Gerhard Baaken[2], Mohamed Kreir[3], Conrad Weichbrodt[3], Sönke Petersen[2], Matthias Beckler[3], Federico Thei[4], Niels Fertig[3], Jan C. Behrends[1].
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We report on functional reconstitution of pore-forming proteins into suspended lipid bilayers on Micro Electrode Cavity Array (MECA). By optimizing protein concentration and facilitating spontaneous insertion with short voltage pulses just below the electroporation threshold, a controlled insertion of alpha-hemolysin was achieved. Exactly one pore per bilayer was inserted in over 50% of bilayers in the array, which is substantially higher than the 37% predicted by the Poisson distribution. We investigated and optimized insertion of outer membrane porins OmpF, MspA and OccK1 into bilayer arrays via detergent dilution. Best strategy was to use mild nonionic detergents and sequentially dilute protein stock solution to minimize influence of the detergent on the membrane. Protein injection in the immediate vicinity of a bilayer array and thorough mixing of the solution are decisive factors for homogeneous distribution of functional porins. Reconstitution via detergent micelles was found to be problematic for ion channels, but proteovesicle fusion was successful. The tetrameric potassium channel KcsA was expressed in vitro with cotranslational insertion into lipid vesicles or nanodiscs. Transfer from nanodiscs into suspended bilayers was shown to be inefficient. Additionally, the presence of nanodiscs substantially destabilized the membranes. For proteovesicles best fusion rates were achieved upon addition of negatively charged phospholipids followed by extrusion of the recovered proteovesicles through a polycarbonate filter.

Poster #12:
TRP-ing the light fantastic: Activation of TRPC5 and other channels using internal perfusion on an APC platform

Gesa Rascher-Eggstein, Andrea Brüggemann, Tom Goetze, Søren Friis, Markus Rapedius, Claudia Haarmanna, Ilka Rinke, Michael George and Niels Fertig
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Ion channels have been recognized as an important therapeutic target class for treating a number of different pathophysiologies. This target class is becoming even more important as the personalized medicine revolution evolves. However, a major limiting factor in the drug discovery process involving ion channels is the technically demanding electrophysiological assay which remains the gold standard since its discovery in the 1970's. Although automated patch clamp instruments have been successfully introduced in recent years, none of them combine the quality and flexibility of manual patch clamp with the throughput required for true high throughput screening (HTS) efforts. We present data on Nanion's SyncroPatch 384PE which is a high throughput giga-seal platform recording up to 768 experiments simultaneously. Using this system, biophysical properties of the ion channel can be studied and coupled with reliable pharmacology and complex effects of compounds. We show state dependent effects of tetracaine on NaV1.7. Additionally, a number of different TRP channels and chloride channels are activated by internal calcium. Furthermore, we show activation of TRPC5 and TMEM16A by perfusion of intracellular $Ca2^{+}$ and inhibition by external application of compounds.

Abstracts Poster:

Poster #13:
Precise control of temperature in artificial planar lipid bilayers to modulate different TRP channels

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Thermal Transient Receptor Potential (TRP) channels belong to the large family of TRP channels. They are an important class of receptors found widely distributed throughout the mammalian central and peripheral nervous systems. They have been shown to be directly activated by heat or cold in physiologically relevant temperature ranges, but are also activated by mechano-stimulation and various ligands. Understanding the mechanisms of temperature activation could lead to the discovery of novel compounds with differing effects on ligand activation and temperature activation for the treatment of pain and other disease states, with fewer side effects. We have employed parallel planar lipid bilayer instrumentation (Orbit mini, Nanion) to study different reconstituted thermo-TRP channels, particularly the purified human TRP-A1, -V1, -V3 and -M8 channels. Planar lipid bilayers can be formed in the Orbit family systems by painting lipids in organic solvents over Micro Electrode Cavity Array (MECA) chips, a 2 by 2 array of circular micro-cavities in a highly inert polymer. The reconstitution of TRP channels is achieved by adding the purified proteins directly to the bilayers.
In this study, we demonstrate the activation of the different TRP channels by cold and heat in a fully controlled environment using artificial membranes together with a Peltier element integrated in the Orbit mini setup to actively cool and heat the system to the desired temperatures (±1˚C) via an optional temperature control system. Furthermore, we compared our Q10 data from purified proteins to TRP channels expressed in HEK cells (Millipore, Chantest) using an automated patch clamp platform (Patchliner, Nanion) with temperature control.

Poster #14:
Cardiac drug and safety screening platforms for the future: Automated patch clamp, extracellular field potential and impedance approach

Gesa Rascher-Eggstein[1], Elena Dragicevic[1], Krisztina Juhasz[1], Sonja Stölzle-Feix[1], Ulrich Thomas[1], Nadine Becker[1], Leo Doerr1, Markus Rapedius[1], Matthias Beckler[1], Michael George[1], Andrea Brüggemann[1], Niels Fertig[1]
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Reliable and fast in-vitro cardiac safety screening are demand development of automated, high-throughput compatible drug evaluation systems. Also, recent rise in usage of iPSC cardiomyocytes (iPSCMs) provided more predictive model for cardiovascular risk assessment in-vitro assays. Together, automated, high-throughput electrophysiological assays and iPSCMs offer easy to use format for both academic research as well as pharmaceutical industry to perform screening of new drug candidates in a physiologically relevant environment.
For this purpose we have developed cell handling protocols for the use of iPSCMs on planar patch clamp systems (SyncroPatch 384/768 PE and the Patchliner). Additional data was generated on a hybrid screening instrument that combines impedance (cell contractility) with MEA-like extracellular field potential (EFP), the CardioExcyte96. The CardioExcyte 96 system provides a non-invasive, label-free, high temporal resolution approach for safety screening on iPSCMs. Also, EFP recordings were performed on the high-throughput and high-resolution Maestro MEA system.
We describe the development and optimization of cell-based assays that are sensitive and provide reproducible results for safety pharmacology. We present evaluation data from four major systems performed on iPSCMs, giving information on ionic currents, action potentials and activity patterns. Changes in the impedance signal indicate effects on cell contractility and shape whereas the field potential parameters provide information about the electrophysiological activity of the beating network of cells. In accordance with the Comprehensive In Vitro Proarrhythmia Assay (CiPA) guidelines, standard reference compounds were tested on iPSCMs. Example traces of action potential recordings, voltage-clamp measurements and also contractility and EFP/MEA recordings before and after compound applications were compared. To minimize cell usage on the automated patch clamp platforms, a protocol was developed to reduce the amount of cells per recording chamber to 400, thereby yielding highly cost efficient assays.
In summary, we show four complementary electrophysiology platforms, which provide unmatched information on a compound's safety profile. Reduced cell usage, increased throughput and integration into robotic environments improve cost efficiency, precision and are speeding up the whole HTS process of drug development and safety screening.

Our collaboration partners:

Anaxon: The Swiss biotech company Anaxon AG specializes in ion channel drug discovery. Proprietary assets include a comprehensive target catalogue and our innovative gene cloning technology. CRO assistance at distinct drug discovery stages is provided through custom specific collaborative framework. For fast into man projections patient specific cell based disease models are developed. We work on tiny aspects such as single base pair changes in human genes and thus scout for new effective drug targets. Like this we seek to reasonably contribute to translational biomedicine – think ion channel genes.

ApconiX Ltd combines a toxicology consultancy, with collectively over 200yrs drug discovery and development expertise, with a laboratory. The ApconiX laboratory has both conventional and automated electrophysiology platforms and offers ion channel screening, assay development and cardiac safety testing on a fee-for-service or research collaboration basis. Particular research interests of ApconiX are the use of hiPSC stem cells on automated platforms to improve predictivity of in vitro testing. ApconiX is also part of the CiPA initiative Ion Channel subteam generating data to shape future cardiac safety testing regulations.

Axiogenesis is a leading provider of commercial-grade in vitro differentiated cells derived from human induced pluripotent stem cells (iPSCs), along with validated assays, which enable drug development. Assays for each cell type have been developed for advanced drug discovery, safety pharmacology / in vitro toxicology, and disease / tissue modeling. Axiogenesis' innovative and proprietary cell types and assays accelerate and improve drug candidate selection, lower costs and thus increase overall drug development efficiency. Key products include Cor.4U cardiomyocytes, Peri.4U peripheral neurons, CNS.4U central nervous system cells, Dopa.4U dopaminergic neurons, and Astro.4U astrocytes. Products in development emcompass iPSC-derived sensory and cortical neurons, as well as matured cardiomyocytes.

Cellular Dynamics International (CDI), a FUJIFILM company, is a leading developer and supplier of human cells used in basic and translational research, drug discovery, toxicity testing, and regenerative medicine applications. Leveraging technology that can be used to create induced pluripotent stem cells (iPSCs) and differentiated tissue-specific cells from any individual, CDI is committed to advancing life science research and transforming the therapeutic development process in order to fundamentally improve human health. The company's inventoried iCell® products and donor-specific MyCell® Products are available in the quantity, quality, purity, and reproducibility required for drug and cell therapy development. For more information please visit www.cellulardynamics.com

17 of 20

CYBERnano is a CRO expert in Biosignal Processing & Biostatistics. Our computational innovations allow our clients to automate the analysis of their data in the aim to save a lot of time in their preclinical and clinical studies. We have developed services that are accessible through three platforms on the Internet for cell impedance signals, cardiomyocytes impedance and Quality-by-Design of molecules and nanoparticles. With the expertise of our innovations we divide by 10 the time of data analysis for biologists. CYBERnano analyzes your data up to 10 times faster than traditional workflow. Days or weeks become minutes.

Our collaboration partners:

Icagen partners with global pharmaceutical and biotech companies to generate high-quality, advanced leads. As a focused, Target-to-Lead (T2L) company, Icagen works with collaborators in multi-year, integrated drug discovery programs as well as piecemeal projects to fill-in the gaps of R&D efforts. Born from a biotech background and matured by pharma companies, Icagen brings to partners a North American team with over 20 years of experience in early discovery. The process of drug discovery starts with druggable targets. Icagen scientists have vast experience in target-based drug discovery, including ion channels, kinases, GPCR's and transporters. The Icagen team works with collaborators to determine target feasibility using state-of-the-art computational chemistry methods. Once a target is selected the team combines virtual screening, ultra-high throughput screening (uHTS), biology and medicinal chemistry to generate viable leads in an iterative process.

IONERA Technologies is a spin off from the University of Freiburg, founded in 2014 and located in Freiburg, Germany. Ionera's microelectrode cavity arrays (MECA-Chips) allow for automated and parallel recordings of membrane proteins reconstituted in planar lipid bilayers. Ionera's microchip devices are based on cavities of micrometer dimension, each of which contains an individual Ag/AgCl-microdisk as the active electrode. Because of their very small size, these microelectrodes can easily be arranged in dense arrays, therefore increasing the experimental throughput. Ionera's MECA16 and MECA4 chips are dedicated for the use in Nanion's bilayer systems, the Orbit-16 and Orbit Mini.

Metrion Biosciences is a UK-based CRO focussed on delivering a range of high-quality ion channel screening, cardiac safety profiling and drug discovery services on a fee-for-service or collaboration basis. Our aim is to provide ion channel electrophysiology expertise and high-quality screening assays as part of a dedicated and flexible service tailored to customer requirements. Customers can access Metrion's ion channel know-how and services at any point in their screening cascade. We offer a portfolio of services that add value to drug discovery programs by developing and de-risking ion channel modulators at all stages as they progress towards the clinic.

NMI TT Pharmaserrvices is a CRO dedicated to provide integrated experts services to our customers in Pharma, Biotech and Medtech.
Our business is focused on high quality products and services and R&D support in the fields of
Electrophysiology Services for Drug Discovery and Safety Pharmacology
Protein Profiling - Quality Control Pharma - High Content Analysis-Chromobodies® - Customised Cell Lines
NMI TT was established in 2002 as a fully-owned subsidiary of the Natural and Medical Sciences Institute (NMI), located in Reutlingen, (Stuttgart area, Southwest Germany), with a branch in Berlin, Germany.
http://www.nmi-tt.de/pharmaservices/

Our collaboration partners:

Pluriomics is a biotech company focusing on the development of fully functional human assay systems for use in cardiovascular drug discovery and development. Based on our novel proprietary methods for differentiation of stem cells we developed highly functional cell types like our Pluricyte® Cardiomyocytes. Pluricyte® culture systems are free of serum and other defined components. For more information, please visit www.pluriomics.com

ReproCELL: Established in 2004 by Kyoto University researchers, ReproCELL quickly became the leading company for stem cell research in Japan. Employing induced pluripotent stem cell (iPSC) technology developed by Professor Shinya Yamanaka (Nobel Laureate, 2014), ReproCELL was the first company to offer iPSC-derived human cardiomyocytes, hepatocytes and neuronal cells for research applications.
Together, the ReproCELL Group Companies (Stemgent, ReproCELL, Bioserve, Reinnervate and Biopta) now provide an integrated workflow Powering Translational Research with stem cells and drug discovery technologies for classic (small-molecule) drug research and cutting-edge Regenerative Medicine. As a global technology partner, ReproCELL has the history, expertise and flexibility to accelerate your research.

SB Drug Discovery specialises in development of ion channel cell lines for manual and automated electrophysiology screening assays. Our highly experienced cell biology and electrophysiology teams have collaborated to generate a panel of over 80 functionally characterised voltage & ligand gated ion channel cell lines for HTS, selectivity profiling and species cross-reactivity studies. SB Drug Discovery's services include custom ion channel cell line development, off-the-shelf cell line sales and contract ion channel screening.

Takara Bio Europe AB, formerly Cellartis AB, a subsidiary of Takara Bio Europe SAS, is focusing on stem cell derived products and services for drug discovery, disease modelling, and applications within regenerative medicine. The company leverages long-standing experience in stem cell handling and scale-up together with leading expertise in differentiation of cells into mature and functional human cells. Specifically, the company possesses broad expertise in human pluripotent stem cells, including both hiPSC and hESC and related media.
Takara Bio Europe AB is located in state-of-the-art facilities in Göteborg, Sweden.
For more information, visit our website: www.clontech.com

Thank you for attending our User Meeting!

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… and many more

Your Nanion Team