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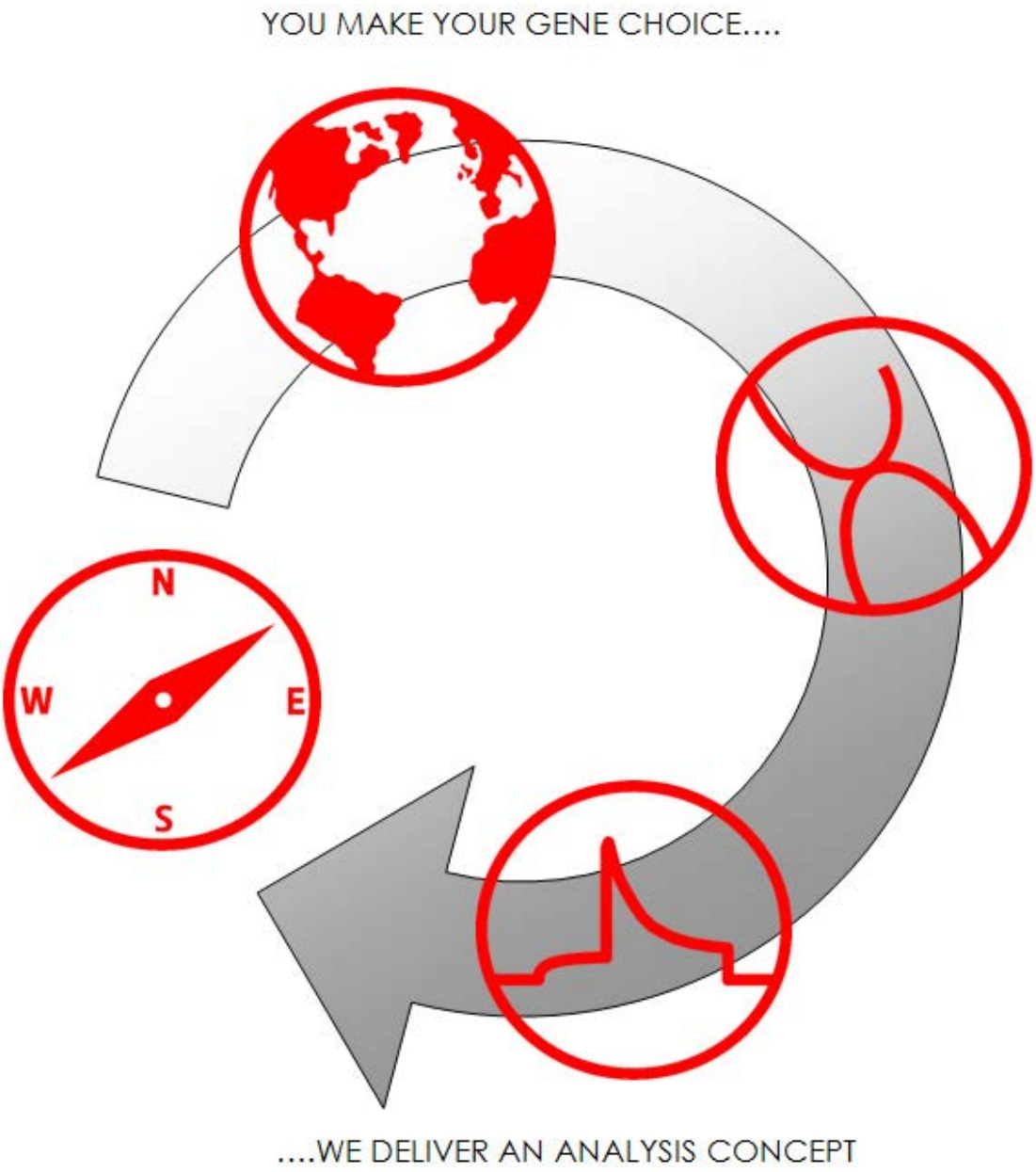
ION CHANNEL GENES WORTH ANALYZING TOGETHER

table of contents

your notes:


YOU MAKE YOUR GENE CHOICE....
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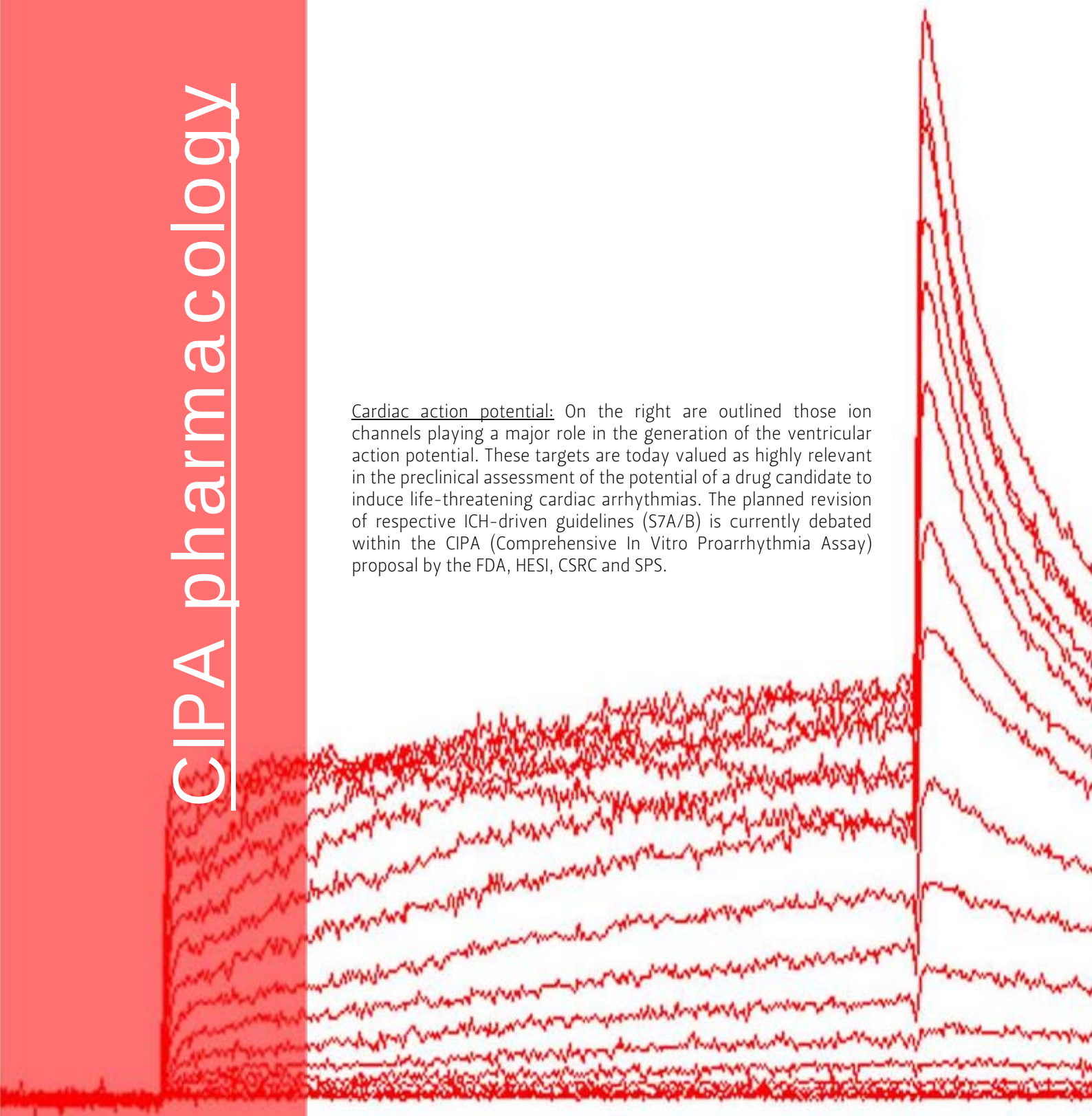
....WE DELIVER AN ANALYSIS CONCEPT

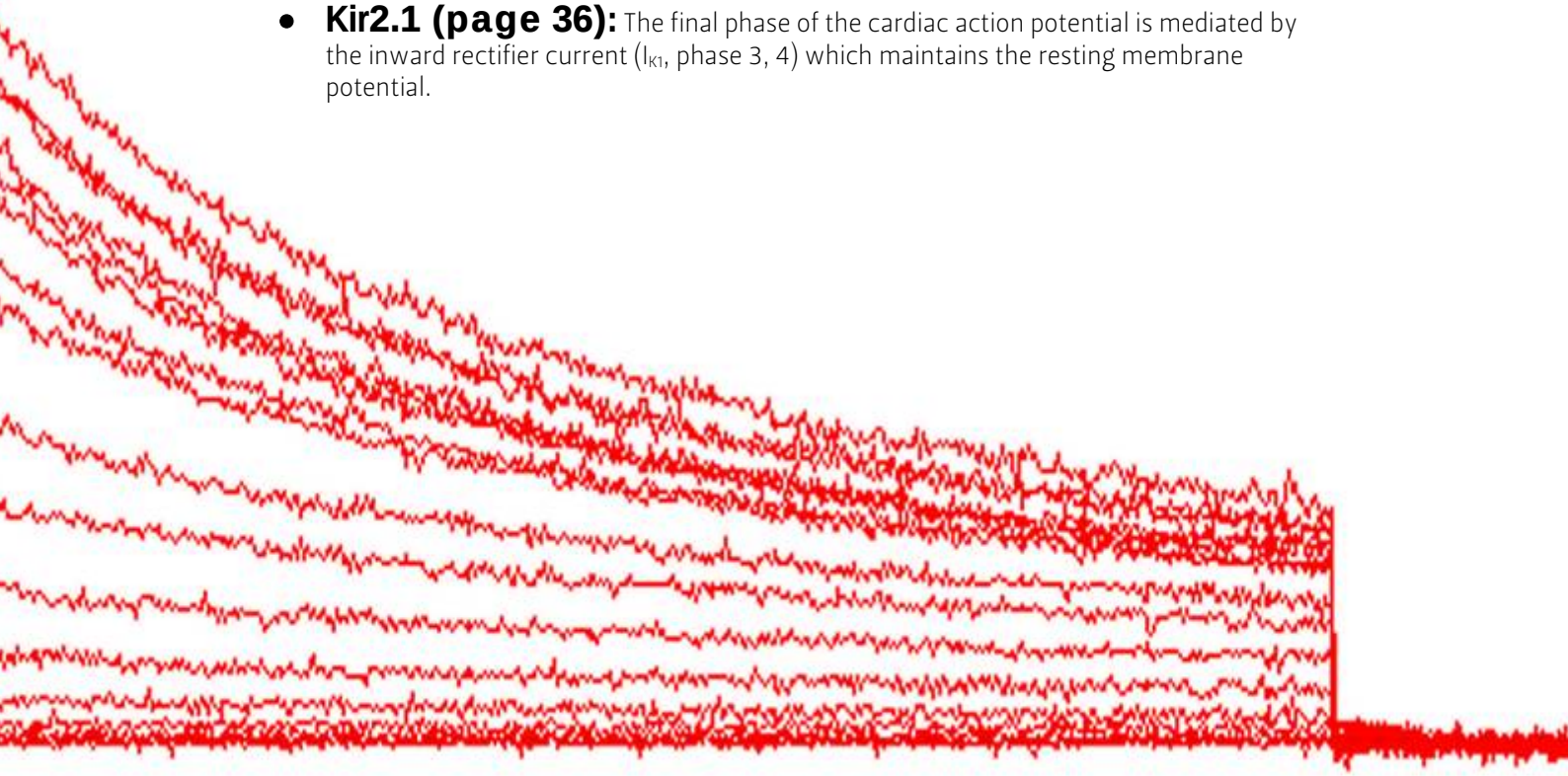
CIPA pharmacology

Cardiac action potential: On the right are outlined those ion channels playing a major role in the generation of the ventricular action potential. These targets are today valued as highly relevant in the preclinical assessment of the potential of a drug candidate to induce life-threatening cardiac arrhythmias. The planned revision of respective ICH-driven guidelines (S7A/B) is currently debated within the CIPA (Comprehensive In Vitro Proarrhythmia Assay) proposal by the FDA, HESI, CSRC and SPS.



selected CIPA ion channels:

- **hERG (page 33):** The human ether-a-go-go channel is a prominent target used for preclinical safety establishment and mediates the rapid delayed rectifier current (I_{Kr}, phase 3).
- **Cav1.2 (page 56):** The L-type calcium current (I_{Ca}, phase 2) is mediated by the calcium channel complex which is a multi-subunit arrangement of α, β and δ subunits.
- **Nav1.5 (page 50):** The sharp upstroke (I_{Na}, phase 0) initiates the cardiac action potential and is mediated by the Nav1.5 sodium channel.
- **KvLQT1/minK (page 26):** The paired expression of the KvLQT1 and minK subunits results in potassium currents resembling the slow delayed rectifier current (I_{Ks}, phase 3).
- **Kir2.1 (page 36):** The final phase of the cardiac action potential is mediated by the inward rectifier current (I_{K1}, phase 3, 4) which maintains the resting membrane potential.



ion channel genes....

New trends in the drug development arena indicate a global dogma shift.

Based on the dramatic increase in genetic and metabolic patient data, ambitious biomedical research programmes in the field of personalized medicine currently gain strong momentum.

During the past decade hundreds of genetic variations have been discovered by basic scientists that are linked to the risks of both rare and common diseases.

These major achievements have created a significant opportunity for many biotech companies to operate in modern diagnostics and clinical medicine.

New diagnostic tools will accelerate clinical trials and foster the definition of optimal endpoints for small patient clusters with specific pharmacogenomic profiles.

Therefore, the altered genes, proteins and molecular pathways may represent attractive new biomarkers and drug targets.

Whether or not the current success stories in pharmacogenomics (e.g. Crizotinib) are the exception or the rule depends on further development.

Due to the increasing understanding of the genetic bases of many disease classes, we expect to see more effective clinical trials in the future.

The Differentiated Drug Utility (DDU) approach helps to discover meaningful treatment responses and target these benefits to patient subgroups carrying individual genetic markers.

That's why we are convinced it's "worth" to handle such genes as promising hot spots in diagnostics and therapeutics.

....worth analyzing together

The advent of modern scientific approaches such as molecular genetics, bioinformatics, biophysics and nanostructures rapidly creates new research disciplines with vast numbers of specific experts now designing innovative drug discovery strategies.

In the neuroscience disease field, the economic interest to health insurers and pharmaceutical companies remains obvious. However, in spite of the large investments during the past years, these efforts haven't paid off so far.

One major reason for trial failure is the great variation of disease conditions present amongst different patient populations thus producing a huge scattering of treatment responses.

Not only contributes the Differentiated Drug Utility (DDU) approach to progress with rare and neglected diseases, but it may also help finding molecularly distinct subtypes of neuroscience diseases.

Clinical standardization is now keenly tailored to individual patient needs. It includes the detailed focus on well defined clinical endpoints combined with the specific selection of small trial subgroups exhibiting appropriate pharmacogenomic profiles.

In order to understand the numerous clinical facets of drug response and to explore all options for therapeutic prosperity, there is a need for bringing together experts from various disciplines and setting up a culture of strong interdisciplinary exchange.

We are active at the intersection of academia and industry to help companies integrate ion channel genomics into their drug discovery programmes.

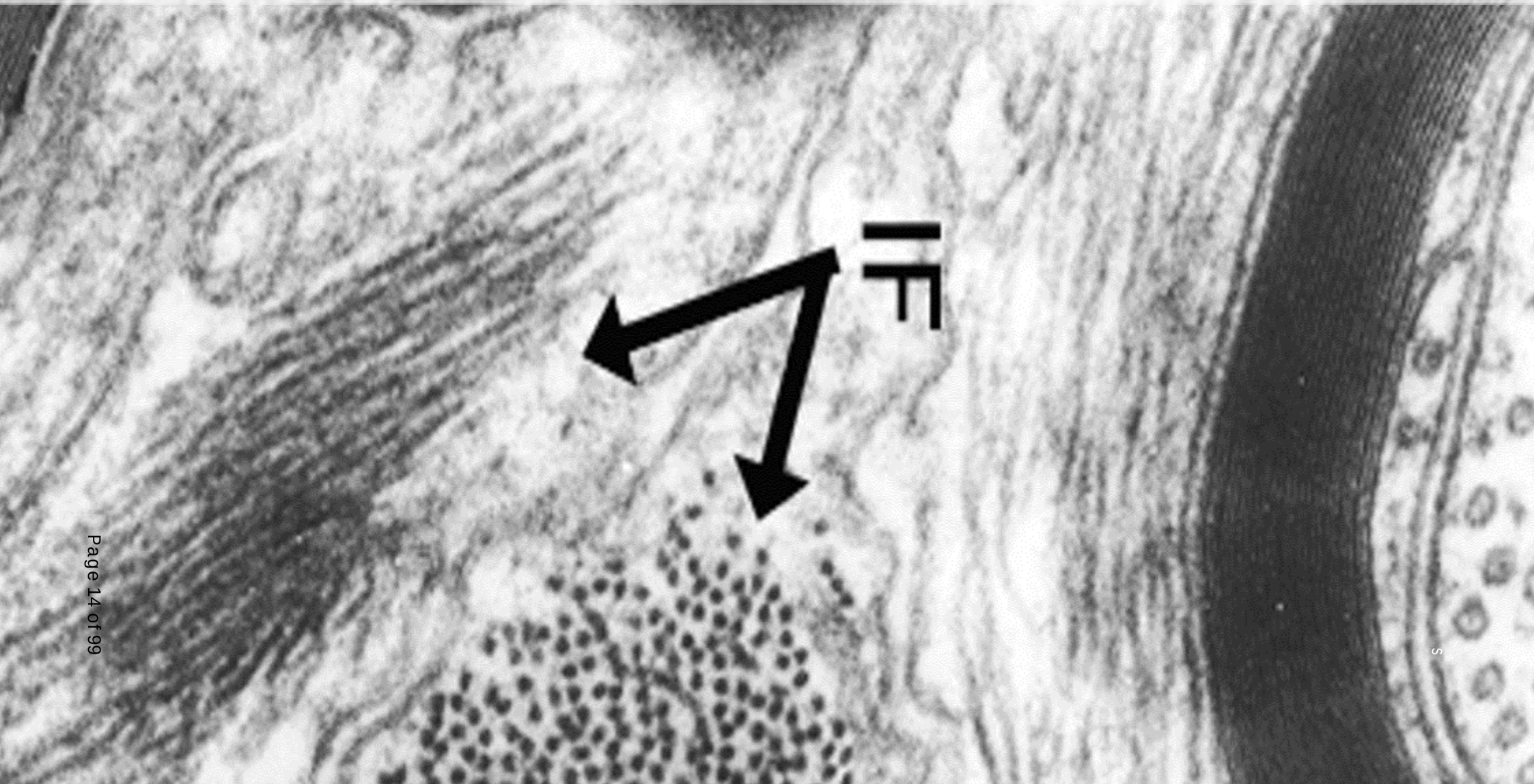
"Together" with our sponsors we are in a position to help translate basic discoveries successfully into new innovative therapies.

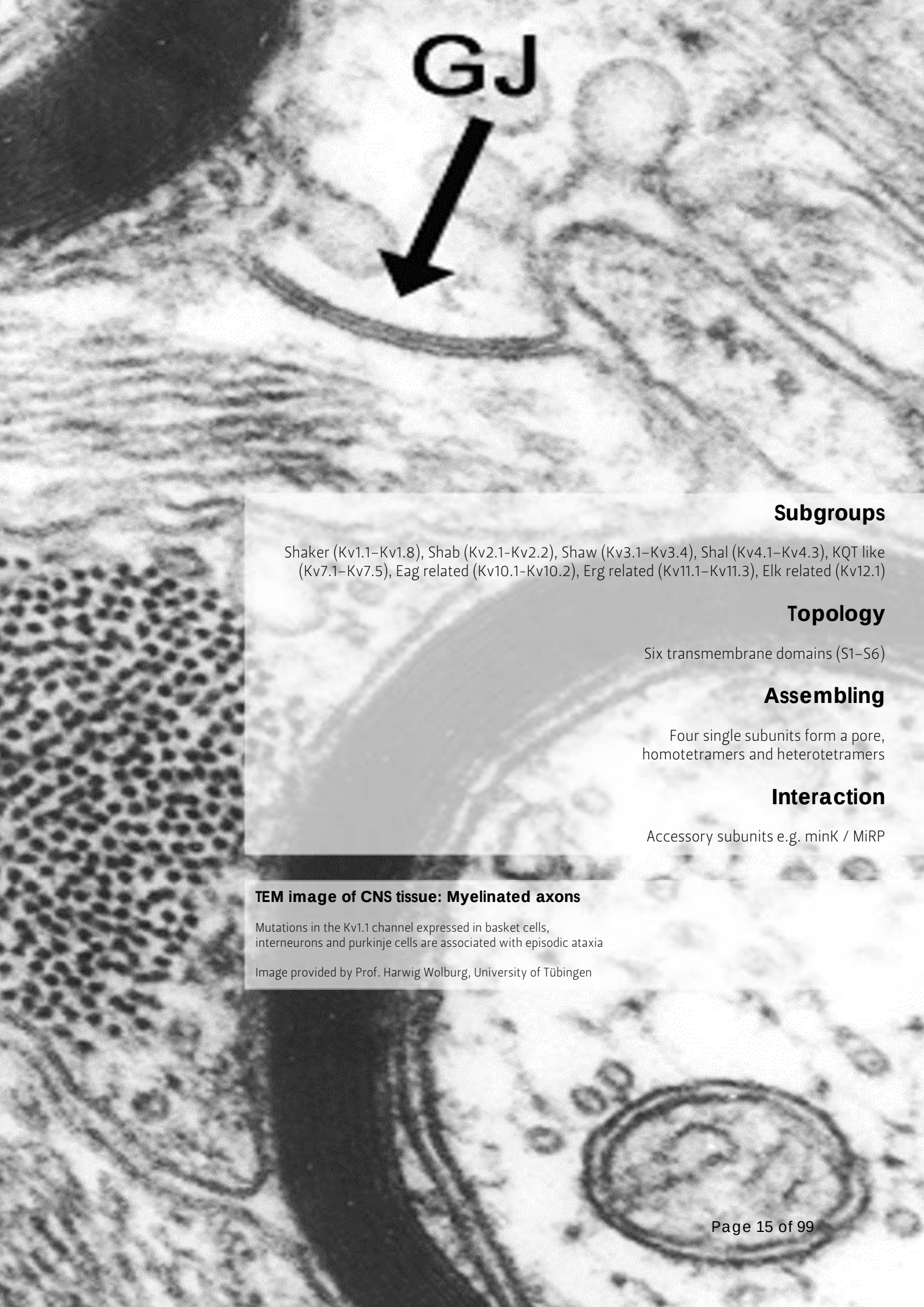
ion channel assays

browse our ion channel assays:

- Assay Sheets: On the following pages you find our ion channel assay sheets you can browse to search for your target of interest.
- Target Families: The genes are arranged in ten different ion channel families which are described briefly at the beginning of each section.
- Gene Sequence: Every ion channel gene included represents the validated human reference sequence (UniProt).
- Cell Background: Most ion channel genes are functionally expressed in both HEK-293 as well as CHO-K1 cell background.

potassium channels





Subgroups

Shaker (Kv1.1–Kv1.8), Shab (Kv2.1-Kv2.2), Shaw (Kv3.1–Kv3.4), Shal (Kv4.1–Kv4.3), KQT like (Kv7.1–Kv7.5), Eag related (Kv10.1-Kv10.2), Erg related (Kv11.1–Kv11.3), Elk related (Kv12.1)

Topology

Six transmembrane domains (S1–S6)

Assembling

Four single subunits form a pore, homotetramers and heterotetramers

Interaction

Accessory subunits e.g. minK / MiRP

TEM image of CNS tissue: Myelinated axons

Mutations in the Kv1.1 channel expressed in basket cells, interneurons and purkinje cells are associated with episodic ataxia

Image provided by Prof. Harwig Wolburg, University of Tübingen

Kv1.1

Shaker Related Potassium Channel
Ion Channel Gene Proficiency No. 20001

Draft screening report within 2 weeks **Turnaround**

Human **Species**

KCNA1 **Gene**

UniProt Q09470 **Protein**

Brain (neurons), cardiac and skeletal muscle tissue, retina, pancreas **Tissue**

Excitability of neurons and muscle **Function**

Isaacs syndrome, episodic ataxia, multiple sclerosis, epilepsy, stroke, seizure **Pathology**

Syntaxin 1A, Kv1.2, Kv1.4, Kv1.6, Kvβ1, Kvβ2, PSD95, SAP97, SNAP25 **Interaction**

Agitoxin-2, Dendrotoxin, Hongotoxin-1 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature

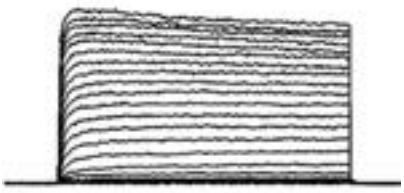
Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference PAP-1 (IC_{50} value 77 nM)



Functional analysis of a novel potassium channel (kcna1) mutation in hereditary myokymia. Neurogenetics 8: 131-135 **Chen et al. 2007**

A novel mutation in Kv1.1 channel causes episodic ataxia without myokymia. Human mutation 24: 23-36 **Lee et al. 2004**

Kv1.2

Shaker Related Potassium Channel
Ion Channel Gene Proficiency No. 20002

Draft screening report within 2 weeks Turnaround

Human Species

KCNA2 Gene

UniProt P16389 Protein

Brain (neurons), cardiac and smooth muscle tissue, retina, pancreas Tissue

Excitability of neurons and muscle Function

Blood pressure, cerebellar ataxic disease, multiple sclerosis, seizure Pathology

Kv1.1, Kv1.5, Kvβ1, Kvβ2, PSD95, RhoA, Caspr2, SAP97, SNAP95 Interaction

Margatoxin, Dendrotoxin, Tityustoxin Kα Hongotoxin-1 Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

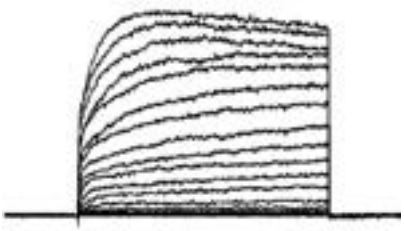
Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference PAP-1 (IC_{50} value 209 nM)



Structural Basis of the Selective Block of Kv1.2 by Maurotoxin from Computer Simulations. PlosONE 7: e47253 Chen et al. 2012

Fine-tuning of Voltage Sensitivity of the Kv1.2 Potassium Channel by Interhelix Loop Dynamics. J. Biol. Chem. 288: 9686-9695 Sand et al. 2013

Kv1.3

Shaker Related Potassium Channel
Ion Channel Gene Proficiency No. 20003

Draft screening report within 2 weeks **Turnaround**

Human **Species**

KCNA3 **Gene**

UniProt P22001 **Protein**

brain, lung, osteoclasts, T-lymphocytes, B-lymphocytes **Tissue**

T-lymphocyte activation, apoptosis, proliferation **Function**

Immune response, multiple sclerosis, rheumatoid arthritis, diabetes mellitus, asthma, cancer **Pathology**

Kvβ2, β1 Integrin, SAP97, ZIP **Interaction**

PAP-1, Margatoxin, Noxiustoxin, Charybdotoxin **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

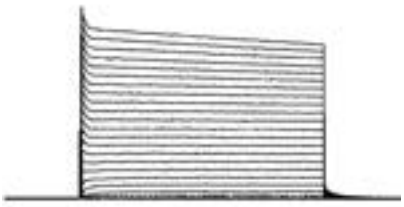
Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference PAP-1 (IC_{50} value 13 nM)



Design of PAP-1, a Kv1.3 blocker, or the suppression of effector memory T cells in autoimmune diseases. Mol. Pharmacol. 68: 1254–70 Schmitz et al. 2005

The potassium channel Kv1.3 is highly expressed on inflammatory infiltrates in multiple sclerosis brain. Proc. Natl. Acad. Sci. 102: 11094–9 Rus et al. 2005

Kv1.4

Shaker Related Potassium Channel
Ion Channel Gene Proficiency No. 20004

Draft screening report within 2 weeks **Turnaround**

Human **Species**

KCNA4 **Gene**

UniProt P22459 **Protein**

Neurons, oligodendrocytes, cardiac and skeletal muscle, pancreas **Tissue**

Excitability of neurons and muscle, cardiac transient outward potassium current **Function**

Myasthenia gravis, Ischemia, multiple sclerosis, neuropathic pain **Pathology**

KVβ, KChAP, α-actinin-2, SAP90, SAP97, σ-receptor, PSD-95, CamKII **Interaction**

Stichodactyla Toxin, TEA, 4-AP **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37˚C)

Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference PAP-1 (IC_{50} value 303 nM)

The molecular physiology of the Ito potassium current in normal and diseased myocardium. J. Mol. Cell. Cardiol. 33: 851–72 **Oudit et al. 2001**

Up-regulation of A-type potassium currents protects neurons against cerebral ischemia. J. Cereb. Blood Flow Metab. 31:1823-1835 **Deng et al. 2011**

Kv1.5

Shaker Related Potassium Channel
Ion Channel Gene Proficiency No. 20005

Draft screening report within 2 weeks **Turnaround**

Human **Species**

KCNA5 **Gene**

UniProt P22460 **Protein**

Cardiac and smooth muscle, colon, aorta, stomach and pulmonary artery, neurons, kidney **Tissue**

Excitability, repolarization cardiac action potential, insulin secretion, cardiac I_{Kur} current **Function**

Atrial fibrillation **Pathology**

Kvβ1, Kvβ2, Kvβ3.1, SAP97 , Src Tyrosine Kinase, caveolin , α-actinin-2 **Interaction**

α-linolenic acid, TEA, 4-AP **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

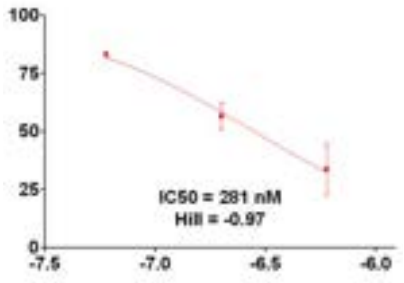
Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference PAP-1 (IC_{50} value 281 nM)



Kv1.5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation. Hum. Mol. Genet. 15: 2185–2191 **Olson et al. 2006**

Mutations in the Kv1.5 channel gene KCNA5 in cardiac arrest patients. Biochem. Biophys. Res. Commun. 354: 776–782 **Nielsen et al. 2007**

Kv1.6

Shaker Related Potassium Channel
Ion Channel Gene Proficiency No. 20006

Draft screening report within 2 weeks **Turnaround**

Human **Species**

KCNA6 **Gene**

UniProt P17658 **Protein**

Neurons, cardiac and smooth muscle tissue, ovary, testis **Tissue**

Excitability of expressing cells **Function**

Morvan's syndrome, Isaacs' Syndrome **Pathology**

Kv1.1, Kv1.2, Kvβ1, Kvβ2, Caspr2 **Interaction**

Margatoxin, Agitoxin-2, Hongotoxin-1 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

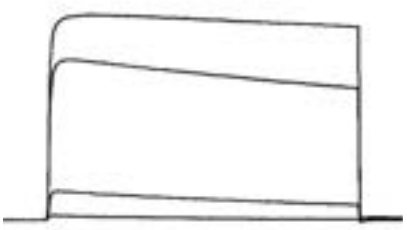
Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference PAP-1 (IC_{50} value 26 nM)



Position-dependent attenuation by Kv1.6 of N-type inactivation of Kv1.4 containing **Sabi et al. 2011** channels. Biochem. J. 438: 389-396

In silico detection of binding mode of J-superfamily conotoxin pl14a with Kv1.6 **Mondal et al. 2007** channel. In silico Biol. 7: 175-186

Kv1.7

Shaker Related Potassium Channel
Ion Channel Gene Proficiency No. 20007

Draft screening report within 2 weeks **Turnaround**

Human **Species**

KCNA7 **Gene**

UniProt Q96RP8 **Protein**

Placenta, pulmonary artery, heart, pancreas, skeletal muscle **Tissue**

Cardiac transient outward potassium current, Insulin secretion **Function**

Diabetes, obesity, anxiety, pain **Pathology**

MMP23 **Interaction**

Stichodactyla toxin , TEA, Conkunitzin-S1 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37˚C)

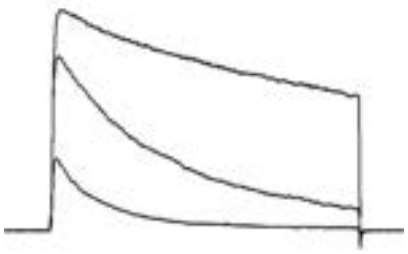
Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference PAP-1 (IC_{50} value 185 nM)



The molecular physiology of the Ito potassium current in normal and diseased myocardium. J. Mol. Cell. Cardiol. 33: 851–72 **Oudit et al. 2001**

Block of Kv1.7 potassium currents increases glucose-stimulated insulin secretion. EMBO Mol. Med. 4: 424–434 **Finol-Urdaneta et al. 2004**

Kv1.8

Shaker Related Potassium Channel
Ion Channel Gene Proficiency No. 20008

Draft screening report within 2 weeks Turnaround

Human Species

KCNA10 Gene

UniProt (Q16322) Protein

Kidney, inner ear, smooth muscle tissue, vascular endothelium Tissue

Renal potassium metabolism, regulation of vascular tone Function

Acquired arrythmias Pathology

KCN4B/POMP, cAMP, cGMP, KCNA4B Interaction

TEA, ketoconazole, verapamil, pimozide Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

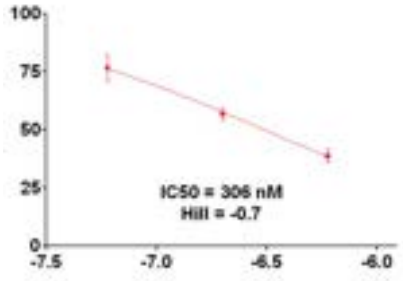
Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference PAP-1 (IC_{50} value 306 nM)



Specific expression of KCNA10, PXN and ODF2 in the organ of Corti. Gene Expr. Patterns. Carlisle et al. 2012
12: 172-9

Expression of KCNA10, a voltage-gated K channel, in glomerular endothelium and at the Yao et al. 2002
apical membrane of the renal proximal tubule. J. Am. Soc. Nephrol. 13:2831-2839

Kv3.3

Shaw Related Potassium Channel
Ion Channel Gene Proficiency No. 20009

Draft screening report within 4 weeks **Turnaround**

Human **Species**

KCNC3 **Gene**

UniProt Q14003 **Protein**

Brain, vascular smooth muscle cells, eye epithelium **Tissue**

repolarization of action potentials, facilitating repetitive high frequency firing **Function**

Spinocerebellar ataxia type 13, Alzheimer's disease **Pathology**

Protein Kinase C **Interaction**

AM 92016 hydrochloride, KN-93 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference TEA (IC_{50} value 330 µM)

Novel mechanisms of trafficking defect caused by KCNQ1 mutations found in long QT syndrome. J. Biol. Chem. 284: 35122-35133 **Sato et al. 2009**

Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci. Transl. Med. 1: 2ra6 **Goldman et al. 2009**

Kv4.3/KChIP2

Shal Related Potassium Channel
Ion Channel Gene Proficiency No. 20010

Draft screening report within 6 weeks **Turnaround**

Human **Species**

KCND3 / KChIP2 **Gene**

UniProt Q9UK17 / UniProt Q9NS61 **Protein**

Heart, brain, smooth muscle cells of myometrium, lung and colon **Tissue**

action potential shape and firing frequency of neurons, cardiac transient outward current I_{TO1} **Function**

Sudden unexplained death (SUD), spinocerebellar ataxia, Brugada Syndrome **Pathology**

Ca2+/Calmodulin-dependent kinase II , KChIP1, KChIP2, KCNE1-KCNE5 **Interaction**

Phrixotoxin-1, Heteropodatoxin-2 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37˚C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference Flecainide (IC_{50} value 30 µM)

Mutations in potassium channel KCND3 cause spinocerebellar ataxia type 19. Ann. Neurol. 72: 870-880 **Duarri et al. 2012**

Novel mutations in the KCND3-encoded Kv4.3 K+ channel associated with autopsy-negative sudden unexplained death. Hum. Mutat. 33: 989-997 **Giudicessi et al. 2012**

KvLQT1/minK

KQT-like Potassium Channel
Ion Channel Gene Proficiency No. 20011

Draft screening report within 2 weeks Turnaround

Human Species

KCNQ1 / minK Gene

UniProt P51787 / UniProt P15382 Protein

Heart, epithelial tissues, pancreas, intestine, stomach, kidney, lung, liver, thymus Tissue

Cardiac I_{KS} current, acid secretion into stomach, Cl- secretion into colon Function

Long QT, Jervell, Lange-Nielsen, Beckwith-Wiedemann syndrome, atrial fibrillation, cancer Pathology

KCNE1, KCNE3, Ca2+/calmodulin, PIP2, CALM Interaction

Azimilide, XE 991 dihydrochloride, linopirdine dihydrochloride Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference Chromanol (IC_{50} value 2 µM), mefloquine (IC_{50} value 1.7 µM)

Novel mechanisms of trafficking defect caused by KCNQ1 mutations found in long QT syndrome. J. Biol. Chem. 284: 35122-35133 Sato et al. 2009

Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci. Transl. Med. 1: 2ra6 Goldman et al. 2009

Kv7.2

KQT-like Potassium Channel
Ion Channel Gene Proficiency No. 20012

Draft screening report within 2 weeks **Turnaround**

Human **Species**

KCNQ2 **Gene**

UniProt O43526 **Protein**

Brain, skeletal muscle **Tissue**

Neuronal excitability, action potential propagation, neurotransmitter release, M-type current **Function**

Epilepsy, BFNS1, EBN1, EIEE7, myokymia, migraine, mental retardation **Pathology**

KCNQ3, PIP2, calmodulin, ankyrin **Interaction**

Flupirtine, retigabine, XE 991 dihydrochloride, linopirdine dihydrochloride **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference Linopiridine (IC_{50} value 4 µM)

Myokymia and neonatal epilepsy caused by a mutation in the voltage sensor of the **Dedek et al. 2001** KCNQ2 K+ channel. Proc. Natl. Acad. Sci. U.S.A 98: 12272-12277

A novel splicing mutation in KCNQ2 in a multigenerational family with BFNC followed **de Haan et al. 2006** for 25 years. Epilepsia 47: 851-859

Kv7.3

KQT-like Potassium Channel
Ion Channel Gene Proficiency No. 20013

Draft screening report within 2 weeks Turnaround

Human Species

KCNQ3 Gene

UniProt O43525 Protein

Brain, skeletal muscle Tissue

Neuronal excitability, responsiveness to synaptic inputs, M-type current Function

Epilepsy, BNFC2, EBN2, myokymia, migraine, convulsion Pathology

KCNQ2, KCNQ4, KCNQ5, PIP2, Calmodulin, ankyrin Interaction

Retigabine, flupirtine, XE 991 dihydrochloride, linopirdine dihydrochloride Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37˚C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference Linopiridine (IC_{50} value 13 µM)

A novel mutation of KCNQ3 gene in a Chinese family with benign familial neonatal convulsions. Epilepsy Res. 79: 1-5 Li et al. 2008

Genetic association analysis of KCNQ3 and juvenile myoclonic epilepsy in a South Indian population. Hum. Genet. 113: 461-463 Vijai et al. 2003

Kv7.5

KQT-like Potassium Channel
Ion Channel Gene Proficiency No. 20014

Draft screening report within 2 weeks Turnaround

Human Species

KCNQ5 Gene

UniProt Q9NR82 Protein

Brain, skeletal muscle, epithelial tissues, retina, vascular smooth muscle cells, myoblasts Tissue

Excitability of neurones, responsiveness to synaptic inputs, myogenesis, M-type current Function

Schizophrenia, cognitive impairment, retinal degeneration Pathology

KCNQ3, KCNQ4, calmodulin, DISC1, KCNE Interaction

Niflumic acid, retigabine, linopirdine, XE991 Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference Flupiritine (IC_{50} value 3 µM)

Localization of KCNQ5 in the normal and epileptic human temporal neocortex and hippocampal formation. Neuroscience 120: 353-364 Yus-Nájera et al. 2003

KCNQ5 channels control resting properties and release probability of a synapse. Nat. Neurosci. 14: 840–847 Huang et al. 2011

Kv7.2/Kv7.3

KQT-like Potassium Channel
Ion Channel Gene Proficiency No. 20015

Draft screening report within 4 weeks Turnaround

Human Species

KCNQ2 / KCNQ3 Gene

UniProt O43526 / UniProt O43525 Protein

Brain, skeletal muscle Tissue

Excitability, responsiveness to synaptic inputs, M-type current Function

Epilepsies, bipolar disorder, anxiety, dementia, BFNC, myokymia, neuropathic pain Pathology

Anchorin, calmodulin, KCNE, Nedd4-2, PIP2 Interaction

Linopirdine, XE991, oxotremorine-M, retigabine Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference Linopiridine (IC_{50} value 11 µM)

Modulation of KCNQ2/3 potassium channels by the novel anticonvulsant retigabine. Mol. Pharmacol. 58: 253-262. Main et al. 2000

Novel KCNQ2/Q3 agonists as potential therapeutics for epilepsy and neuropathic pain. J. Med. Chem. 53: 887-896 Fritch et al. 2010

Kv7.3/Kv7.5

KQT-like Potassium Channel
Ion Channel Gene Proficiency No. 20016

Draft screening report within 4 weeks **Turnaround**

Human **Species**

KCNQ3 / KCNQ5 **Gene**

UniProt O43525, UniProt Q9NR82 **Protein**

Brain **Tissue**

Excitability of neurones, responsiveness to synaptic inputs, M-type current **Function**

Seizure, schizophrenia **Pathology**

Calmodulin, kinase-1, Nedd4-2 **Interaction**

linopirdine, retigabine, XE991 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference Flupiritine (IC_{50} value 0.8 µM)

Regulation of the voltage-gated K(+) channels KCNQ2/3 and KCNQ3/5 by serum- and glucocorticoid-regulated kinase-1. Am. J. Physiol. Cell. Physiol. 295: C73-80 **Schuetz et al. 2008**

Regulation of the voltage-gated K(+) channels KCNQ2/3 and KCNQ3/5 by ubiquitination. Novel role for Nedd4-2. J. Biol. Chem. 282: 12135-12142 **Ekberg et al. 2007**

Kv10.1

Eag Related Potassium Channel
Ion Channel Gene Proficiency No. 20017

Draft screening report within 2 weeks **Turnaround**

Human **Species**

KCNH1 **Gene**

UniProt O95259 **Protein**

Brain, myoblasts at the onset of fusion **Tissue**

Cell proliferation **Function**

Cancer **Pathology**

KCNB1, KCNH5/EAG2, ALG10B, CaM, epsin, slop, KCR1 **Interaction**

Quinidine, astemizole, E-4031, terfenadine, dofetilide **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37˚C)

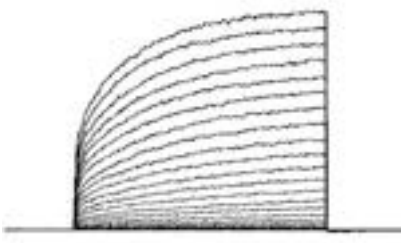
Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference Quinidine



Ether-a-go-go potassium channels as human cervical cancer markers. Cancer Res. 64: 6996-7001 **Farias et al. 2004**

IGF-1 activates hEAG K(+) channels through an Akt-dependent signaling pathway in breast cancer cells: role in cell proliferation. J. Cell. Physiol.212: 690-701 **Borowiec et al. 2007**

GLP: hERG

Eag Related Potassium Channel
Ion Channel Gene Proficiency No. 20018

Draft screening report within 2 weeks **Turnaround**

Human **Species**

KCNH2 **Gene**

UniProt Q12809 **Protein**

Brain, heart **Tissue**

Cardiac I_{KR} current, cell proliferation, cell migration **Function**

Long QT syndrome, atrial fibrillation, sudden infant death syndrome, cancer **Pathology**

KCNH6/ERG2, KCNH7/ERG3, ALG10B, KCNE1, KCNE2, CANX, cAMP, caveolin-1, FHL2 **Interaction**

Terfenadine, verapamil, dofetilide, cisapride, astemizole **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP / **ICHS7B-compliant GLP format**

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37˚C)

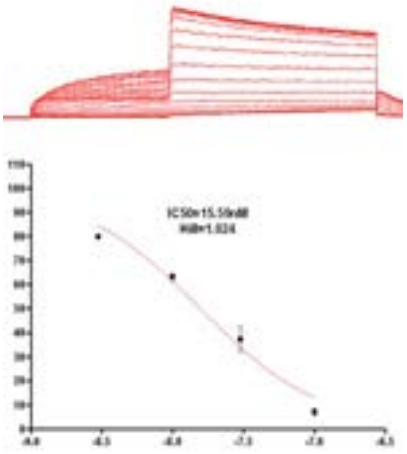
Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference E-4031 (IC_{50} value 15.59 nM), verapamil (IC_{50} value 441 nM)



Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. J. Cardiovasc. Electrophysiol. 16: 394-396 **Hong et al. 2005**

Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation 109: 30-35 **Brugada et al. 2004**

rectifier channels

Subgroups

Seven families Kir1-Kir7, channels demonstrate robust inward rectification

Topology

Two membrane spanning alpha helices denoted as M1 and M2

Assembling

Four identical subunits form a functional homotetramer, heterotetramers can combine with members of the same subfamily

Interaction

Maintaining resting potential, G-Protein activated channels, K-ATP channels

Light microscopy image of CNS tissue: Neurons

Mutations in the Kir4.1 expressed in astrocytes, are associated with epilepsy, ataxia, sensorineural deafness, tubulopathy

Image source Anaxon AG

Kir2.1

Inwardly-Rectifying Potassium Channel
Ion Channel Gene Proficiency No. 20101

Draft screening report within 4 weeks Turnaround

Human Species

KCNJ2 Gene

UniProt P63252 Protein

Heart, brain, vascular smooth muscle cells, skeletal muscles, lung, placenta, kidney Tissue

action potential waveform, neuron and muscle cell excitability, Cardiac I_{K1} current Function

Short QT syndrome type 3, long QT syndrome type 7 (Andersen-Tawil syndrome), ATFB9 Pathology

DLG4, TRAK2, Interleukin 16, PIP2 Interaction

Tertiapin-Q, ML 133 hydrochloride Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis / -50 mV to +110 mV

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference BaCl (IC_{50} value 4 µM)

A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. Circ. Res. 96: 800–7 Gudapakkam et al. 2005

Functional and clinical characterization of a mutation in KCNJ2 associated with Andersen-Tawil syndrome. J. Med. Genet. 43: 653-659 Lu et al. 2006

Kir3.1/Kir3.4

Inwardly-Rectifying Potassium Channel
Ion Channel Gene Proficiency No. 20102

Draft screening report within 6 weeks Turnaround

Human Species

KCNJ3 / KCNJ5 Gene

UniProt P48549 / UniProt P48544 Protein

Heart, brain Tissue

ACh-activated K+ current in the heart (I_KACh) Function

QT syndrome type 13, hyperaldosteronism type 3, adenocarcinomas, diabetes mellitus Pathology

Kir3.2, Kir2.1, P2Y, PIP2 Interaction

Tertiapin-Q, carbachol Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference Tertiapin-Q (IC_{50} value 9 nM)

The single nucleotide polymorphisms of Kir3.4 gene and their correlation with lone paroxysmal atrial fibrillation in Chinese Han population. Heart Lung Circ. 18: 257-261 Zhang et al. 2009

Identification of a Kir3.4 mutation in congenital long QT syndrome. Am. J. Hum. Genet. 86: 872-880 Yang et al. 2010

Kir6.2/SUR2A

Inwardly-Rectifying Potassium Channel
Ion Channel Gene Proficiency No. 20103

Draft screening report within 6 weeks **Turnaround**

Human **Species**

KCNJ11 / ABCC9 (SUR2) **Gene**

UniProt Q14654 / UniProt O60706 **Protein**

Heart **Tissue**

ATP-activated K+ current in the heart (I_KATP) **Function**

Congenital hyperinsulinism, PHHI, diabetes mellitus (NIDDM, TNDM3, PNDM), epilepsy **Pathology**

PKA, Kir6.1, SUR1, PIP2, ATP **Interaction**

Glibenclamide, tolbutamide, repaglinide **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis / -10 mV to -110 mV

Pharmacology Current modulation / IC_{50} value / diazoxide stimulation

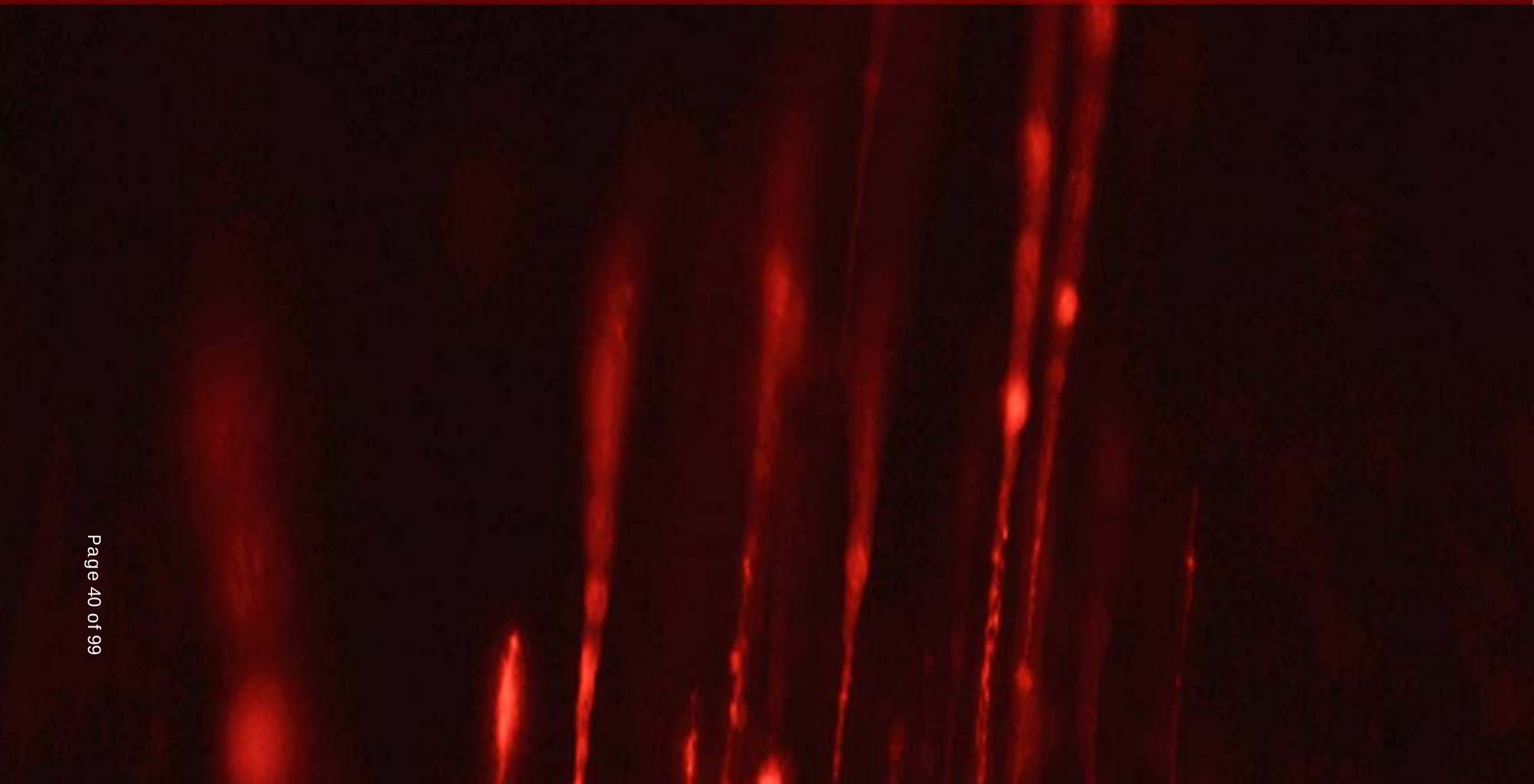
Mechanism Site of action / ATP sensitivity

Reference Glibenclamide (IC_{50} value 112 nM)

Mutations in the genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) in diabetes mellitus and hyperinsulinism. Hum. Mutat. 27: 220–231 **Gloyn et al. 2006**

The Kir6.2-F333I mutation differentially modulates KATP channels composed of SUR1 or SUR2 subunits. J. Physiol. 581: 1259–1269 **Tammaro et al. 2007**

hcn cation channels



Subgroups

Hyperpolarization-activated cyclic nucleotide-gated channels, four different members HCN1-HCN4

Topology

Six transmembrane domains (S1–S6)

Assembling

Four subunits form a functional channel, homotetramers and heterotetramers

Function

Nonselective gated cation channels, referred to as pacemaker channels, rhythmicity in brain and heart cells

Light microscopy image of CNS tissue: Growing neurons

Mutations in the HCN ion channel, expressed in neurons of the CNS, are associated with epilepsy

Image source Anaxon AG

HCN4

HCN-Gated Cation Channel
Ion Channel Gene Proficiency No. 20201

Draft screening report within 4 weeks Turnaround

Human Species

HCN4 Gene

UniProt Q9Y3Q4 Protein

Adult sinoatrial node (SAN), atrio-ventricular node (AVN), thalamus, olfactory bulb, taste cells Tissue

Electrical pacemaker activity, cardiac I_f current Function

Bradycardia, tachycardia, sick sinus syndrome (SS2), Brugada syndrome 8 (BRGDA8) Pathology

cAMP, KCNE2 Interaction

Ivabradine, cilobradine, zatebradine Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis / -40 mV to -110 mV

Pharmacology Current modulation / IC_{50} value

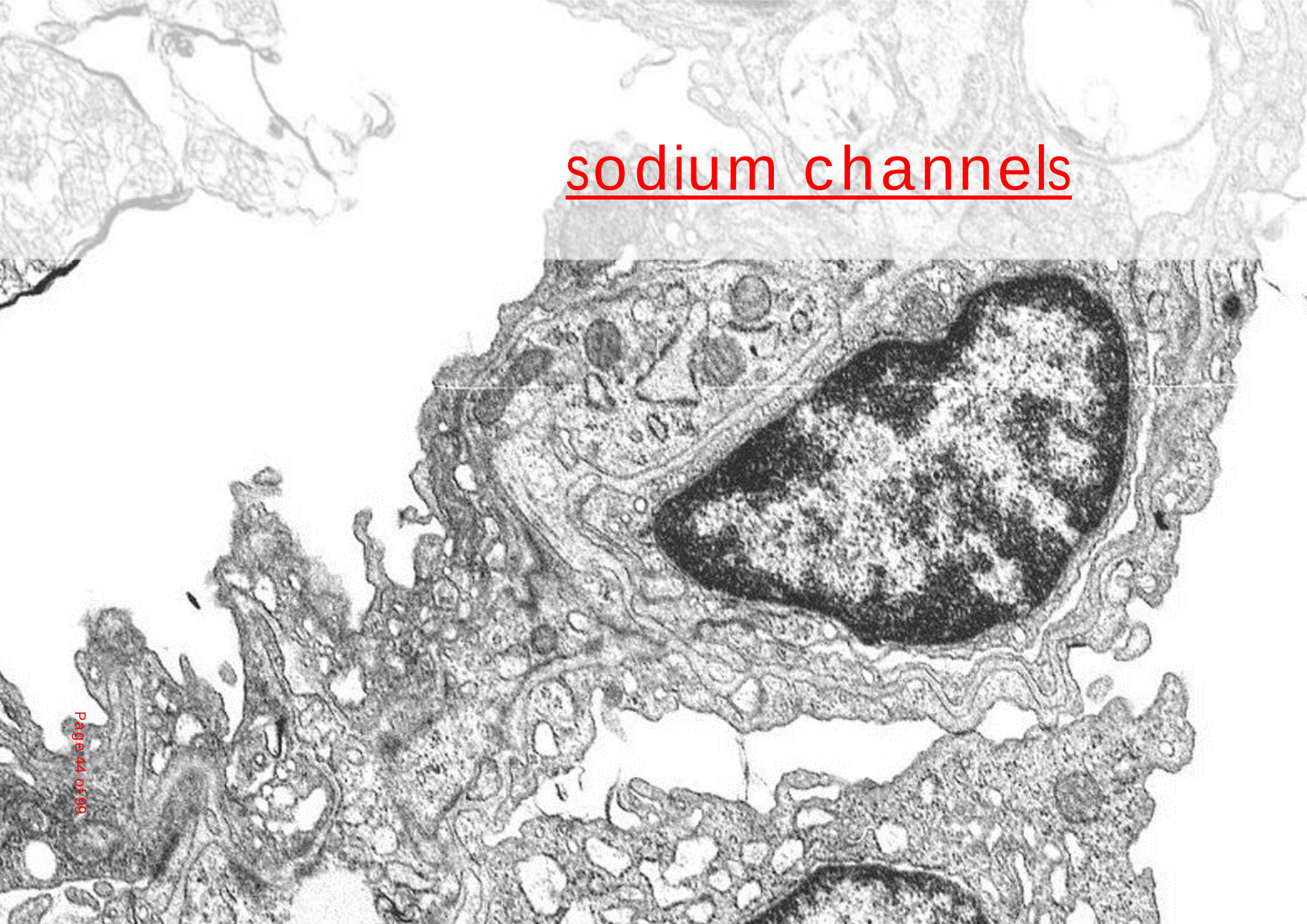
Mechanism Use-dependence / site of action

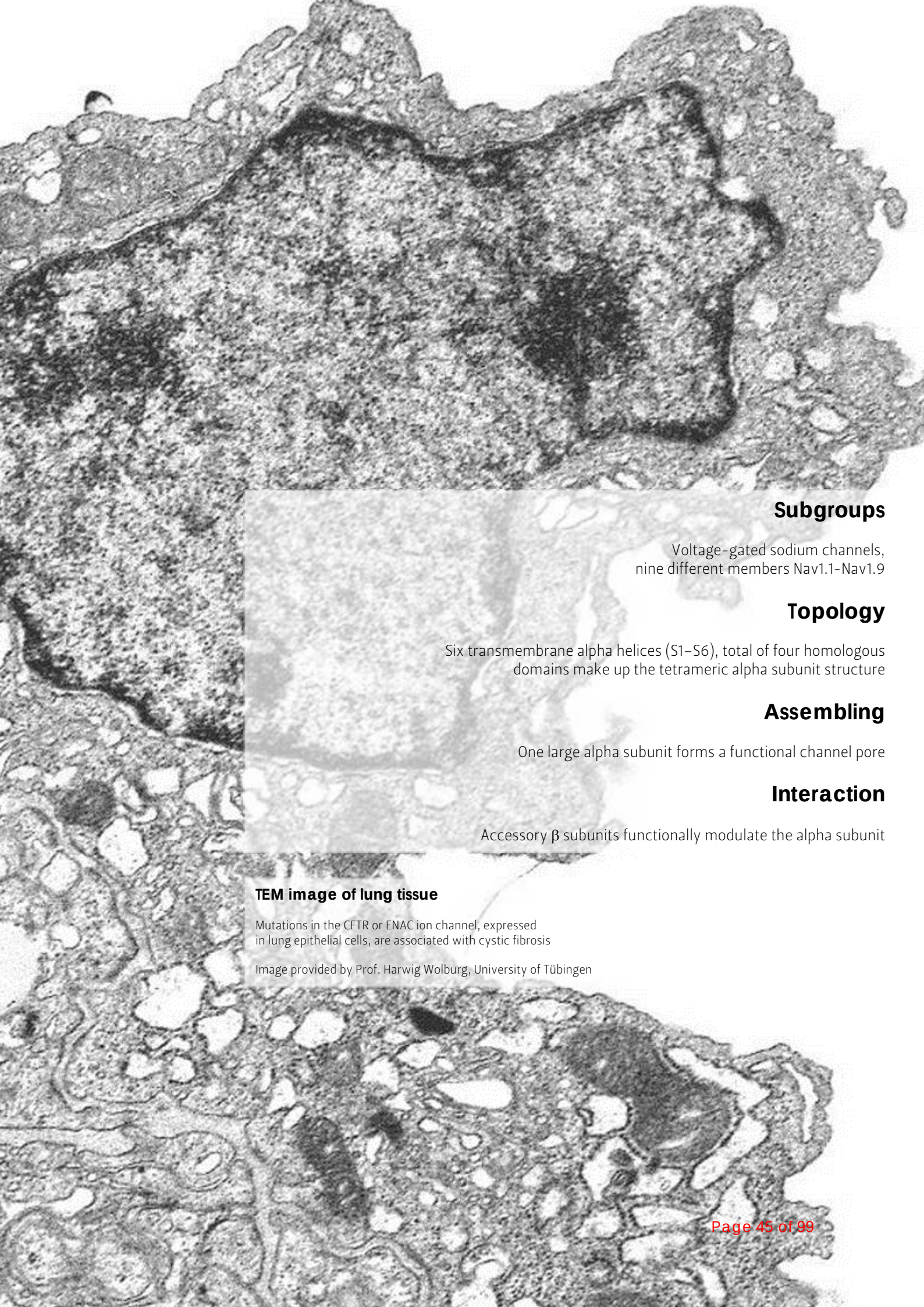
Reference Zatebradine (IC_{50} value 0.94 µM)

Functional characterization of a trafficking-defective HCN4 mutation, D553N, associated with cardiac arrhythmia. J. Biol. Chem. 279: 27194-27198 Ueda et al. 2004

Deep bradycardia and heart block caused by inducible cardiac-specific knockout of the pacemaker channel gene HCN4. PNAS 108: 1705–1710 Baruscotti et al. 2011

sodium channels





Subgroups

Voltage-gated sodium channels,
nine different members Nav1.1-Nav1.9

Topology

Six transmembrane alpha helices (S1–S6), total of four homologous domains make up the tetrameric alpha subunit structure

Assembling

One large alpha subunit forms a functional channel pore

Interaction

Accessory β subunits functionally modulate the alpha subunit

TEM image of lung tissue

Mutations in the CFTR or ENAC ion channel, expressed
in lung epithelial cells, are associated with cystic fibrosis

Image provided by Prof. Harwig Wolburg, University of Tübingen

Nav1.1

Voltage-Gated Sodium Channel
Ion Channel Gene Proficiency No. 20301

Draft screening report within 6 weeks **Turnaround**

Human **Species**

SCN1A **Gene**

UniProt P35498 **Protein**

Brain (neurons, glia) **Tissue**

Excitability of neurons, generation of action potentials **Function**

Pain, epilepsy (SMEI, GEFS+), migraine (FHM3), Rasmussen's encephalitis, autism **Pathology**

Alpha-1 syntrophin, β1 subunit, β2 subunit, calmodulin, Ca++, FHF4 **Interaction**

Tetrodotoxin, ATX-II, Bc-III, AFT-II **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Transient expression in HEK-293 cells

Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline Test pulse -100 to +10 mV / state dependent block

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Lidocaine (Tonic IC_{50} value 570 µM)

Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2. Nat. Genet. 24: 343–345 **Escayg et al. 2000**

Sodium channel alpha1-subunit mutations in severe myoclonic epilepsy of infancy and infantile spasms. Neurology 61: 765-769 **Wallace et al. 2003**

Nav1.2

Voltage-Gated Sodium Channel
Ion Channel Gene Proficiency No. 20302

Draft screening report within 6 weeks **Turnaround**

Human **Species**

SCN2A **Gene**

UniProt Q99250 **Protein**

Brain (neurons, microglia), utricular hair cells, corti organ **Tissue**

Excitability of neurons, generation of action potentials **Function**

Autism, epilepsy (EIEE11, BFNIS), late ataxia, pain, myoclonus, multiple sclerosis **Pathology**

Ankyrin G, β1 subunit, β2 subunit, calmodulin, Nedd4-2 **Interaction**

Tetrodotoxin, saxitoxin , β-scorpion toxin Css-IV, veratridine, α-scorpion toxin, ATX-II **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Transient expression in HEK-293 cells

Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline Test pulse -100 to +10 mV / state dependent block

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Lidocaine (Tonic IC_{50} value 1020 µM)

Impaired NaV1.2 function and reduced cell surface expression in benign familial neonatal-infantile seizures. Epilepsia 49: 1535-1545 **Misra et al. 2008**

SCN2A mutation associated with neonatal epilepsy, late-onset episodic ataxia, myoclonus, and pain. Neurology 75: 1454-1458 **Liao et al. 2010**

Nav1.3

Voltage-Gated Sodium Channel
Ion Channel Gene Proficiency No. 20303

Draft screening report within 6 weeks **Turnaround**

Human **Species**

SCN3A **Gene**

UniProt Q9NY46 **Protein**

Brain, injured neurons and spinal cord, heart **Tissue**

Excitability of neurons, generation of action potentials **Function**

Familial autism, deafness **Pathology**

Contactin, β1 subunit, β3 subunit, β8 subunit, calmodulin, LRP, C1D **Interaction**

Tetrodotoxin, AFT-II, Vinpocetine, Flecainide **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Stable expression in HEK-293 cells

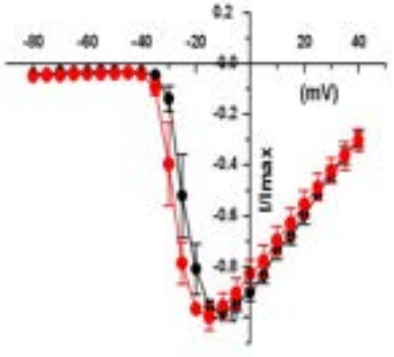
Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline Test pulse -100 to -10 mV / state dependent block

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Lidocaine (Tonic IC_{50} value 470 µM)



Sodium channels SCN1A, SCN2A and SCN3A in familial autism. Mol. Psychiatry 8: 186-194 **Weiss et al. 2003**

Genomic structures of SCN2A and SCN3A - candidate genes for deafness at the DFNA16 locus. Gene 264: 113-122 **Kasai et al. 2001**

Nav1.4

Voltage-Gated Sodium Channel
Ion Channel Gene Proficiency No. 20304

Draft screening report within 2 weeks **Turnaround**

Human **Species**

SCN4A **Gene**

UniProt P35499 **Protein**

Skeletal muscle **Tissue**

Generation and propagation of action potentials in muscle **Function**

Myotonia (PMC, PAM), periodic paralysis (HyperPP, HypoPP), congenital myasthenic syndrome **Pathology**

β1 subunit, syntrophin, calmodulin, DISC **Interaction**

Tetrodotoxin, saxitoxin, veratridine, grayanotoxin, AFT-II **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station / QPatch

Cell System Stable expression in CHO-K1 cells

Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline Test pulse -100 to -10 mV / state dependent block

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Lidocaine (Tonic IC_{50} value 390 µM)

Mutation screening in Korean hypokalemic periodic paralysis patients: a novel SCN4A Arg672Cys mutation. Neuromuscul. Disord. 14: 727-731 **Kim et al. 2004**

Severe neonatal episodic laryngospasm due to de novo SCN4A mutations: a new treatable disorder. Neurology 75: 641-645 **Lion-Francois et al. 2010**

GLP: Nav1.5

Voltage-Gated Sodium Channel
Ion Channel Gene Proficiency No. 20305

Draft screening report within 2 weeks **Turnaround**

Human **Species**

SCN5A **Gene**

UniProt Q14524 **Protein**

Cardiac muscle, brain (isoform 4), interstitial cells **Tissue**

Myocardial conduction, generation of action potentials and cell excitability **Function**

Romano-Ward, Brugada, Jervell, Lange-Nielsen, Long QT syndrome (LQT3), pain, cancer **Pathology**

β1, β2, β3, β4 subunit, syntrophin, NEDD4, NEDD4L, WWP2, calmodulin **Interaction**

Aconitine, veratridine, α-scorpion toxin, ATX-II, saxitoxin, tetrodotoxin **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP / ICHS7B-compliant GLP format

Analysis Platform Whole cell Patch-clamp station

Cell System Stable expression in HEK-293 cells

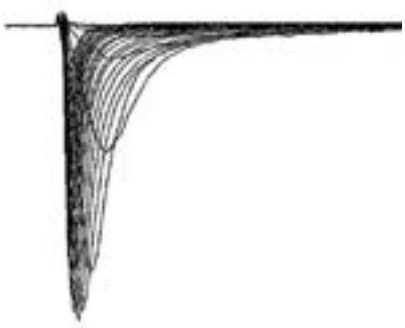
Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline Test pulse -100 to -20 mV / state dependent block

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Lidocaine (Tonic IC_{50} value 330 µM)



Identification of six novel SCN5A mutations in Japanese patients with Brugada syndrome. Int. Heart J. 52: 27-31 **Nakajima et al. 2011**

Na(V)1.5 enhances breast cancer cell invasiveness by increasing NHE1-dependent H(+) efflux in caveolae. Oncogene 30: 2070-2076 **Brisson et al. 2011**

Nav1.6

Voltage-Gated Sodium Channel
Ion Channel Gene Proficiency No. 20306

Draft screening report within 4 weeks **Turnaround**

Human **Species**

SCN8A **Gene**

UniProt Q9UQD0 **Protein**

Brain (neurons, glia), Smooth muscle myocytes, corti organ **Tissue**

Action potential initiation, propagation in excitable cells **Function**

Cognitive impairment with or without cerebellar ataxia (CIAT), epilepsy (EIEE13) **Pathology**

NEDD4, NEDD4L, β1, β2, β3, β4 subunit, calmodulin, FGF, MAPK14, ankyrin-G **Interaction**

Tetrodotoxin, flecainide, ATX-II **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Stable expression in CHO-K1 cells

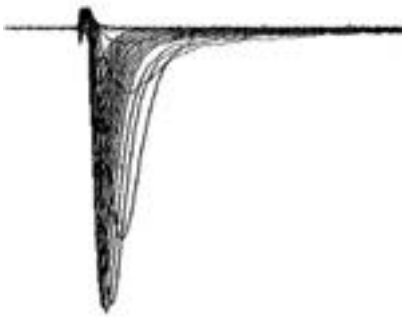
Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline Test pulse -100 to +10 mV / state dependent block

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Lidocaine (Tonic IC_{50} value 1260 µM)



De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. Am. J. Hum. Genet. 90: 502-510 **Veeramah et al. 2012**

Heterozygosity for a protein truncation mutation of sodium channel SCN8A in a patient with cerebellar atrophy, ataxia, and mental retardation. J. Med. Genet. 43: 527-530 **Trudeau et al. 2006**

Nav1.7

Voltage-Gated Sodium Channel
Ion Channel Gene Proficiency No. 20307

Draft screening report within 2 weeks **Turnaround**

Human **Species**

SCN9A **Gene**

UniProt Q15858 **Protein**

Sensory neurons, smooth myocytes, myenteric neurons, erythroid progenitor cells, immune cells **Tissue**

nociception signalling, sensory neuron excitability **Function**

Erythermalgia (IEM, PERYTHM), pain (CIP, PEPD), anosmia, epilepsy (GEFSP7), cancer **Pathology**

NGF, β1, β2 subunit, NEDD4, NEDD4L, calmodulin **Interaction**

Tetrodotoxin, α-scorpion toxin, lidocaine **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station / **QPatch + Nanion**

Cell System Stable expression in HEK-293 / CHO-K1 cells

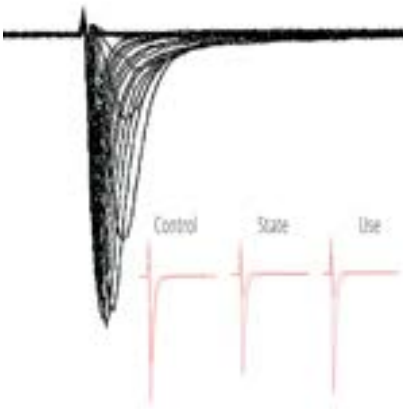
Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline Test pulse -100 to +20 mV / state dependent block

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Lidocaine (Tonic IC_{50} value 340 µM)



Mutation I136V alters electrophysiological properties of the Na(v)1.7 channel in a family with onset of erythromelalgia in the second decade. Mol. Pain 4: 1 **Cheng et al. 2008**

Paroxysmal extreme pain disorder M1627K mutation in human Nav1.7 renders DRG neurons hyperexcitable. Mol. Pain 4: 37 **Sulayman et al. 2008**

Nav1.8

Voltage-Gated Sodium Channel
Ion Channel Gene Proficiency No. 20308

Draft screening report within 6 weeks Turnaround

Human Species

SCN10A Gene

UniProt Q9Y5Y9 Protein

Brain (small-diameter DRG neurons, sensory neurons) Tissue

Excitability of neurons, nociceptive transmission Function

Multiple Sclerosis, neuropathic pain Pathology

β1, β2, β3 subunit, NEDD4, NEDD4L, PRX, FSTL1, PRX, DYNLT1, PDZD2, S100A10 Interaction

Tetrodotoxin, lidocaine, benzocaine, A-887826, A-803467 Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Transient expression in ND7/23 cells

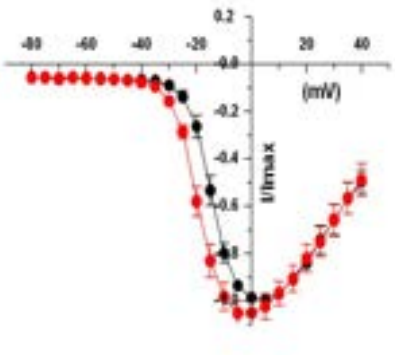
Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline Test pulse -100 to +10 mV / state dependent block

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

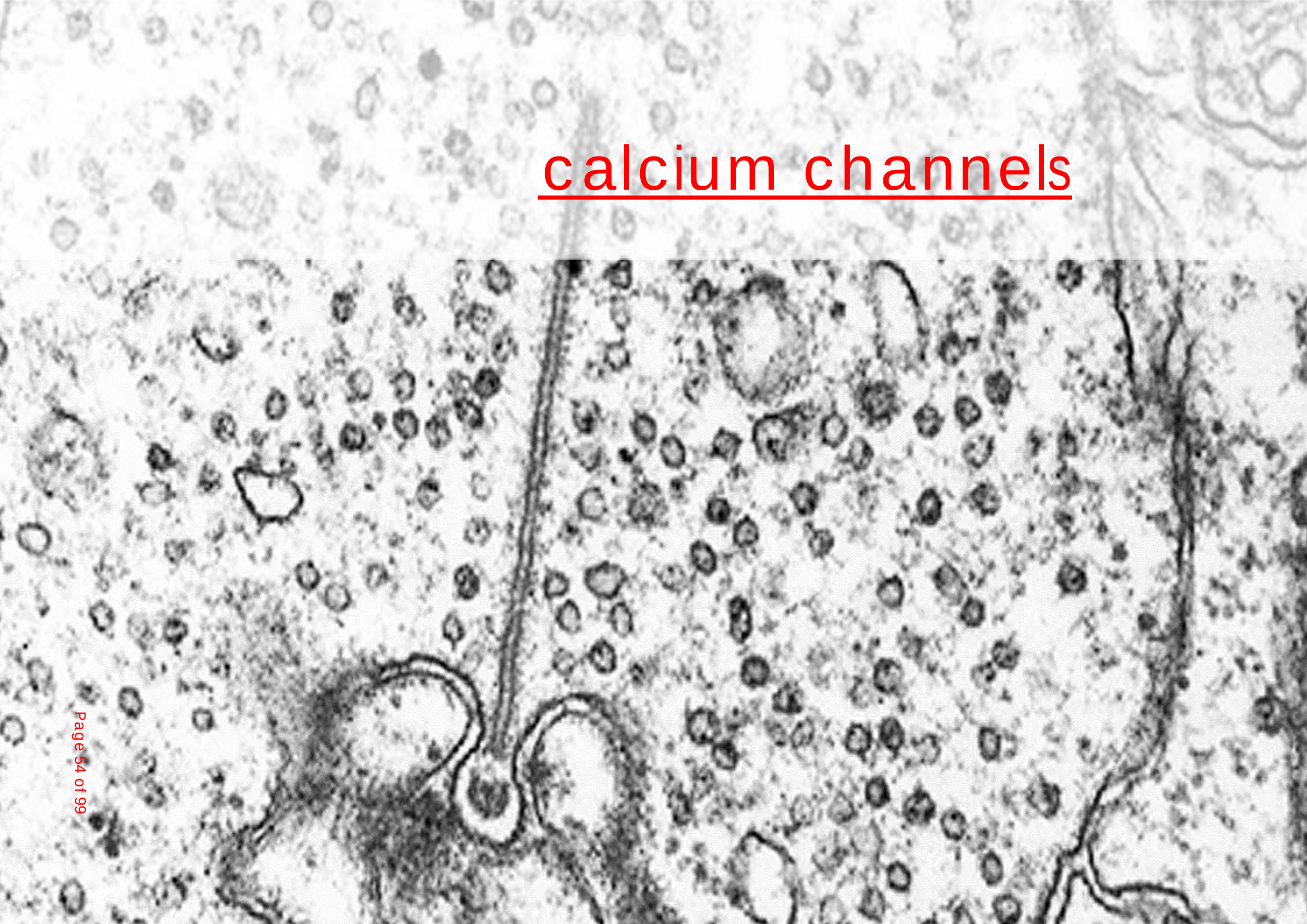
Reference Lidocaine (Tonic IC_{50} value 610 µM)

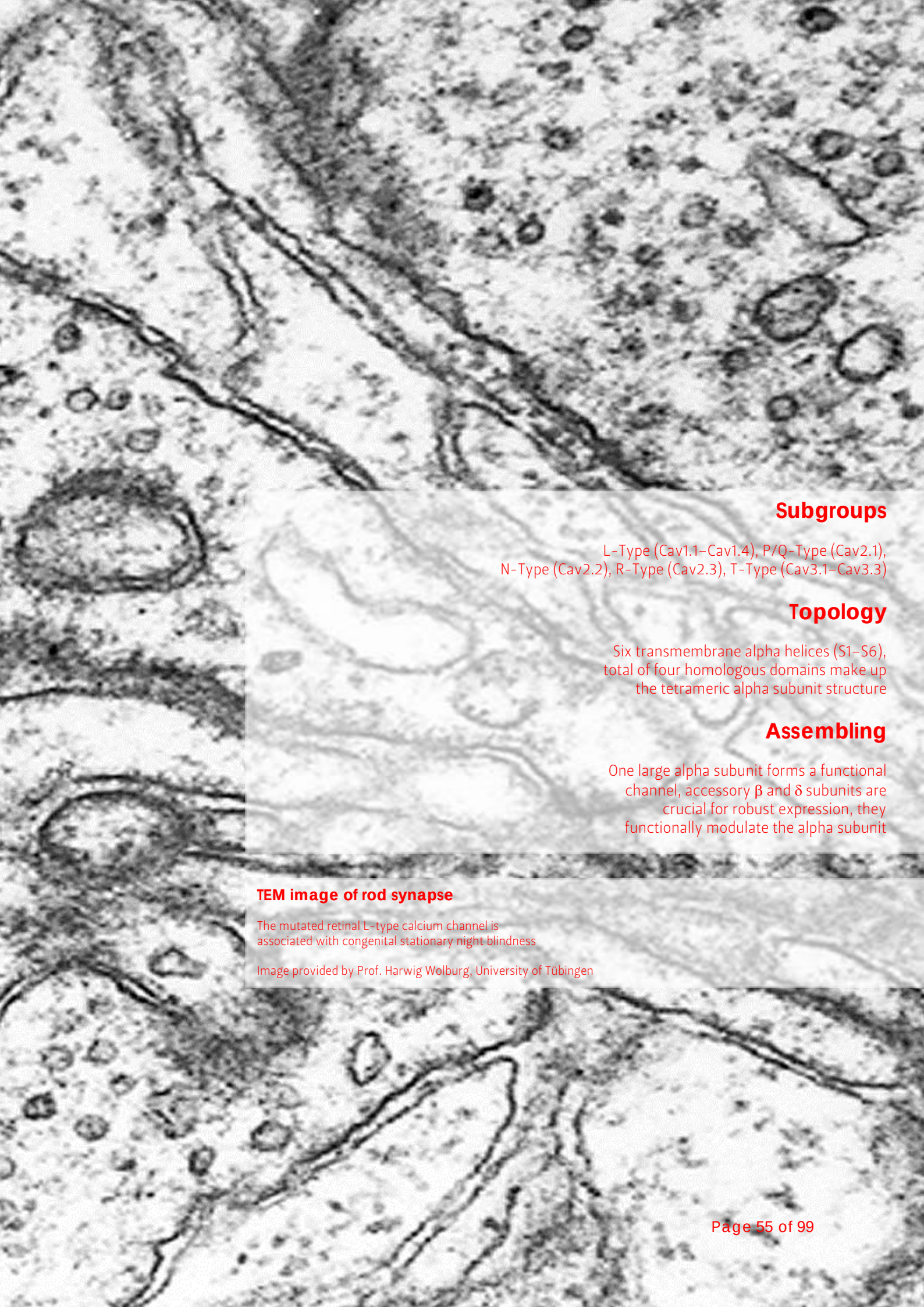


Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. J. Cardiovasc. Hong et al. 2005 Electrophysiol. 16: 394-396

Sudden death associated with short-QT syndrome linked to mutations in HERG. Brugada et al. 2004 Circulation 109: 30-35

calcium channels





Subgroups

L-Type (Cav1.1–Cav1.4), P/Q-Type (Cav2.1),
N-Type (Cav2.2), R-Type (Cav2.3), T-Type (Cav3.1–Cav3.3)

Topology

Six transmembrane alpha helices (S1–S6),
total of four homologous domains make up
the tetrameric alpha subunit structure

Assembling

One large alpha subunit forms a functional
channel, accessory β and δ subunits are
crucial for robust expression, they
functionally modulate the alpha subunit

TEM image of rod synapse

The mutated retinal L-type calcium channel is
associated with congenital stationary night blindness

Image provided by Prof. Harwig Wolburg, University of Tübingen

GLP: Cav1.2

L-Type Calcium Channel
Ion Channel Gene Proficiency No. 20401

Draft screening report within 6 weeks **Turnaround**

Human **Species**

CACNA1C / CACNA2D1 / CACNB2 **Gene**

UniProt Q13936 / UniProt P54289 / UniProt Q08289 **Protein**

Heart, brain, lymphocytes, prostate, bladder, uterus ,stomach, colon, placenta, adrenal gland **Tissue**

Ca2+ entry in excitable cells **Function**

Arterial hypertension, Long QT syndrome, schizophrenia, Timothy syndrome, BRGDA3 **Pathology**

Kir/Gem, CSN5/Jab1, β1-4 subunits, α2δ subunits, NF-κB, osteoprotegerin **Interaction**

Verapamil, nifedipine, kurtoxin, calcicludine, mibefradil, calciseptine, BAYK-8644 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP / ICHS7B-compliant GLP format

Analysis Platform Whole cell Patch-clamp station

Cell System Transient expression in CHO-K1 cells

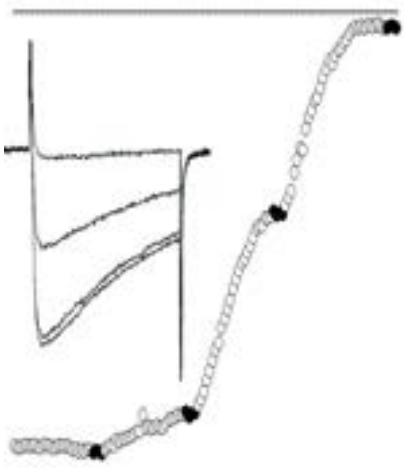
Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline Test pulse -80 to +0 mV / inward blocking potency

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Nifedipine / verapamil



CACNA1C polymorphisms are associated with the efficacy of calcium channel blockers in the treatment of hypertension. Pharmacogenomics 7: 271-279 **Bremer et al. 2006**

Severe arrhythmia disorder caused by cardiac L-type calcium channel mutations. Proc. Natl. Acad. Sci. 102: 8089-8096 **Splawski et al. 2005**

Cav2.1

P/Q-Type Calcium Channel
Ion Channel Gene Proficiency No. 20402

Draft screening report within 4 weeks **Turnaround**

Human **Species**

CACNA1A / CACNA2D1 / CACNB4 **Gene**

UniProt O00555 / UniProt P54289 / UniProt O00305 **Protein**

Brain **Tissue**

Pre-synaptic Ca2+ influx and neurotransmitter release in neurons, fast synaptic transmission **Function**

Migraine (FHM-1), ataxia (EA-2, SCA6), Benign paroxysmal torticollis of infancy, hemiplegia **Pathology**

β1-4 subunits, α2δ subunits, calmodulin, CaBP1, VILIP, mint, CASK, Syntaxin, SNAP25 **Interaction**

Kuratoxin, ω-agatoxin IIIA, ω-conotoxin MVIIC, ω-agatoxin-IVA, roscovitine **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

Mechanism State- and use-dependence / site of action

Reference ω-agatoxin-IVA (IC_{50} value 410 nM)

Two novel CACNA1A gene mutations associated with episodic ataxia type 2 and interictal dystonia. Arch. Neurol. 2: 314-316 **Spacey et al. 2005**

Novel CACNA1A mutation causes febrile episodic ataxia with interictal cerebellar deficits. Ann. Neurol. 54: 725-731 **Subramony et al. 2003**

Cav3.2

T-Type Calcium Channel
Ion Channel Gene Proficiency No. 20402

Draft screening report within 4 weeks **Turnaround**

Human **Species**

CACNA1H **Gene**

UniProt O95180 **Protein**

Brain, ovary, placenta, vascular smooth muscle **Tissue**

Pacemaker activity (brain, heart), hormone secretion, fertilization **Function**

Angina, epilepsy (CAE6, EIG6), sleep, breast cancer, autism, pain, cardiac hypertrophy **Pathology**

GNG2, KCNMA1, KDM5B, CACNA1s, CACNBs, CACNGs, NCAM **Interaction**

Kurtoxin, mibefradil, flunarizine, zonisamide, bepridil, nifedipine **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Pharmacology Current modulation / IC_{50} determination

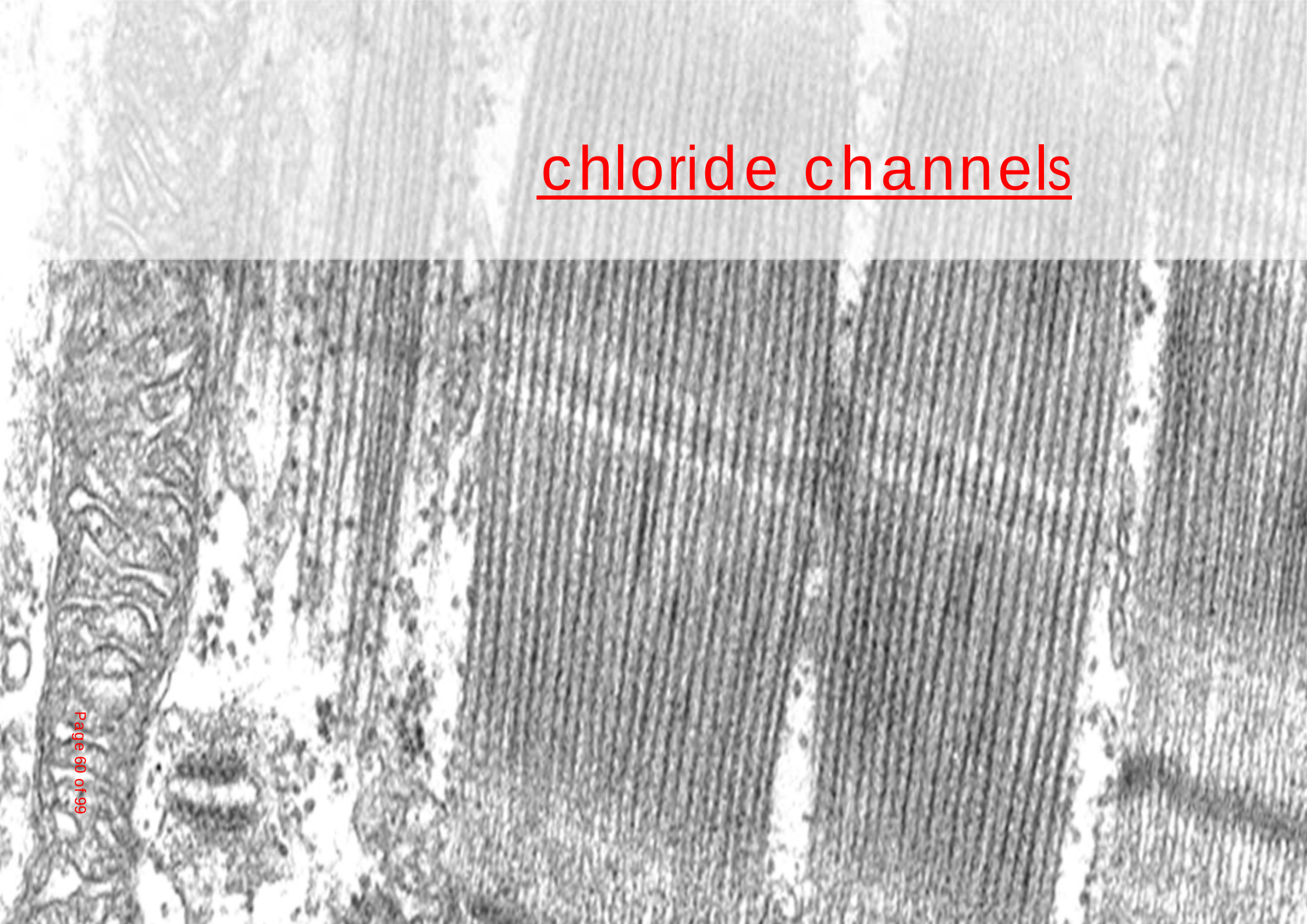
Mechanism State- and use-dependence / site of action

Reference $NiCl_2$ (IC_{50} value 11 µM)

CACNA1H mutations in autism spectrum disorders. J. Biol. Chem. 281: 22085-22091 **Splawski et al. 2006**

Extended spectrum of idiopathic generalized epilepsies associated with CACNA1H functional variants. Ann. Neurol. 62: 560-568 **Heron et al. 2007**

chloride channels



Subgroups

CLCN (CLCN1–CLCN7, CLCNKA, CLCNKB),
CLCA (CLCA1–CLCA4), CLIC (CLIC1-CLIC6),
chloride / anion conduction

Topology

Within the CLCN subfamily up to
18 α–helices make up the subunit structure,
17 of which are transmembrane domains

Function

Each protein forms a single pore, also homodimer
channels have been reported, cellular role for resting
membrane potential, cell volume and pH control

TEM image of striated muscle

Mutations in the ClCN ion channel, expressed in skeletal muscle cells,
are associated with myotonia congenita (Thomson's, Becker's)

Image provided by Prof. Harwig Wolburg, University of Tübingen

CLCN1

Voltage-Sensitive Chloride Channel
Ion Channel Gene Proficiency No. 20501

Draft screening report within 4 weeks **Turnaround**

Human **Species**

CLCN1 **Gene**

UniProt P35523 **Protein**

Skeletal muscle **Tissue**

Membrane potential stabilization, repolarization of skeletal muscle **Function**

Myotonia congenital (Thomsen's disease, Becker's myotonia), endomyocardial fibrosis **Pathology**

ATP **Interaction**

ASB-AAP34912 (Biozole), 9-anthracenecarboxylic acid (9-AC), zinc **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

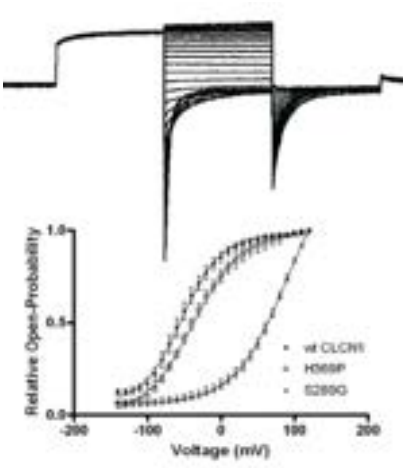
Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline Test pulse current activation -40 to +60 / -120 mV

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference 9-AC (IC_{50} value 14 µM)



In tandem analysis of CLCN1 and SCN4A greatly enhances mutation detection in families with non-dystrophic myotonia. Eur. J. Hum. Genet. 16: 921-929 **Trip et al. 2008**

Novel CLCN1 mutation in carbamazepine-responsive myotonia congenita. Pediatr. Neurol. 42: 365-368 **Lyons et al. 2010**

CLCN2

Voltage-Sensitive Chloride Channel
Ion Channel Gene Proficiency No. 20502

Draft screening report within 4 weeks **Turnaround**

Human **Species**

CLCN2 **Gene**

UniProt P51788 **Protein**

Brain, kidney, lung, gastrointestinal system **Tissue**

Maintains chloride ion homeostasis in cells **Function**

Epilepsy (EIG11, JAE2, IGEm, EJM8), generalized tonic-clonic seizures (GTCS) **Pathology**

Dynein, IFN-gamma, TGF-alpha, ATP **Interaction**

Lubiprostone, cadmium, zinc **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline Test pulse 0 to -120 mV / inward blocking potency

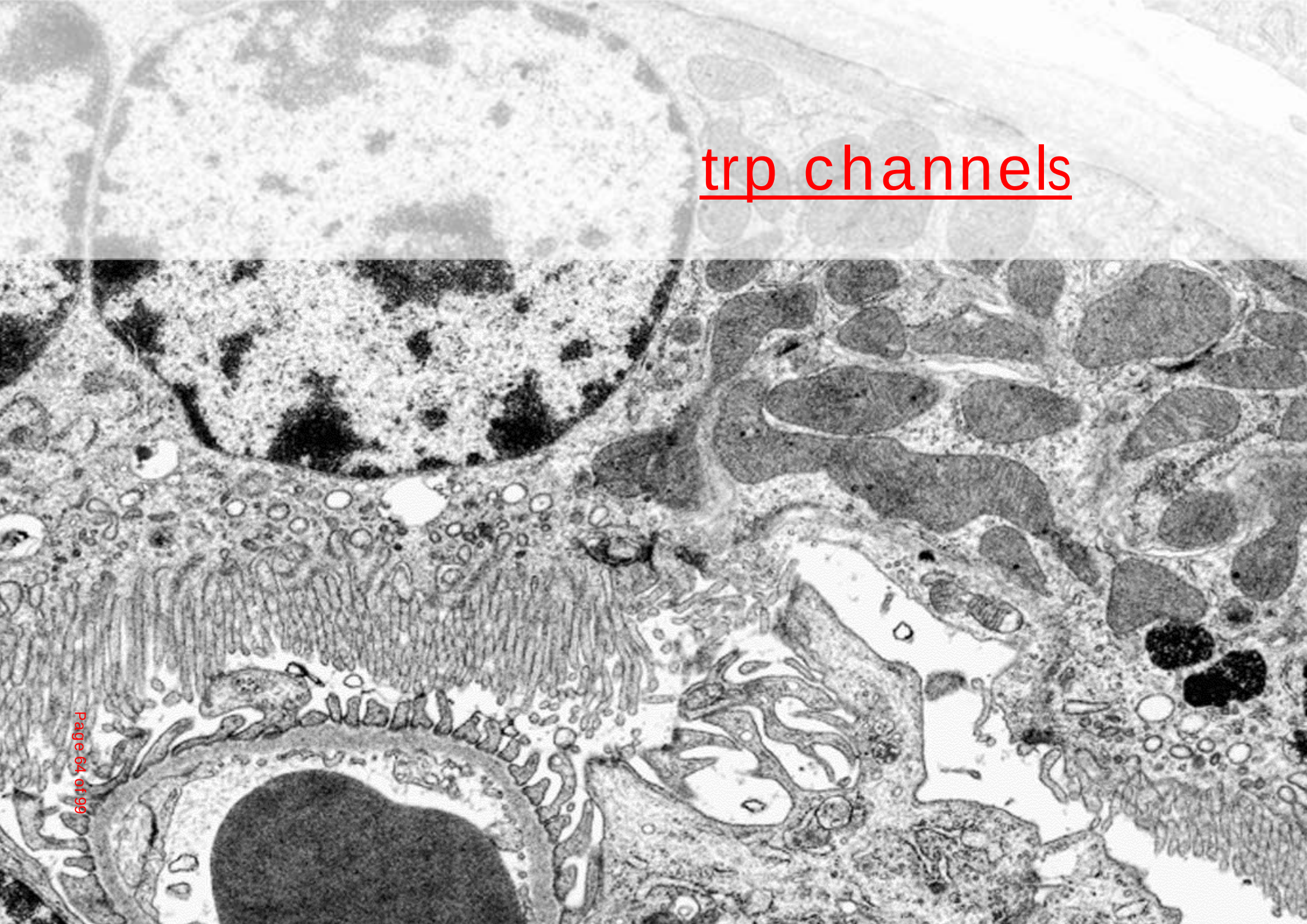
Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

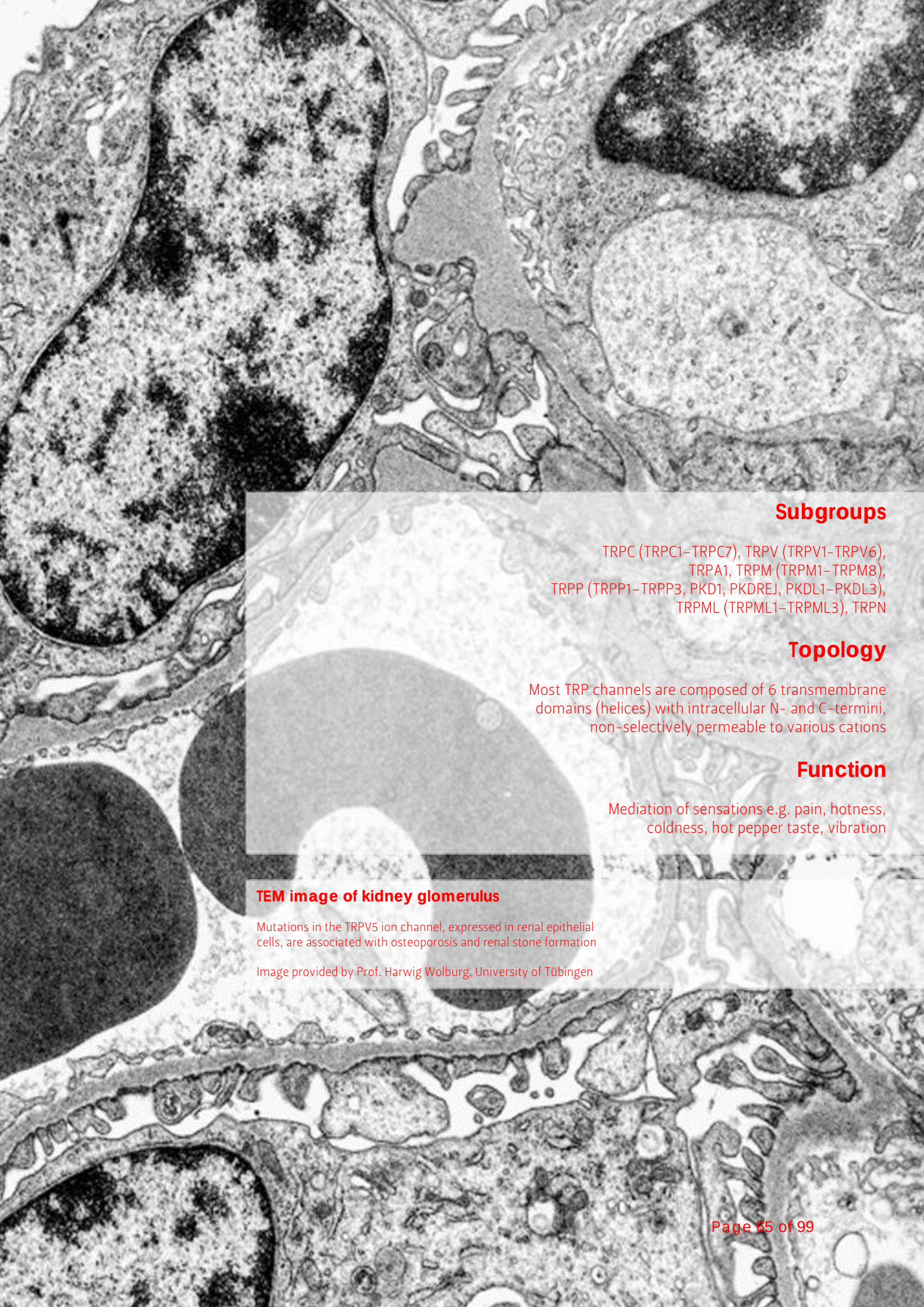
Reference Cadmium

Two novel CLCN2 mutations accelerating chloride channel deactivation are associated with idiopathic generalized epilepsy. Hum. Mutat. 30: 397-405 **Saint-Martin et al. 2009**

Linkage and mutational analysis of CLCN2 in childhood absence epilepsy. Epilepsy Res. 75: 145-153 **Everett et al. 2007**

trp channels





Subgroups

TRPC (TRPC1–TRPC7), TRPV (TRPV1-TRPV6),
TRPA1, TRPM (TRPM1–TRPM8),
TRPP (TRPP1–TRPP3, PKD1, PKDREJ, PKDL1–PKDL3),
TRPML (TRPML1–TRPML3), TRPN

Topology

Most TRP channels are composed of 6 transmembrane domains (helices) with intracellular N- and C-termini, non-selectively permeable to various cations

Function

Mediation of sensations e.g. pain, hotness, coldness, hot pepper taste, vibration

TEM image of kidney glomerulus

Mutations in the TRPV5 ion channel, expressed in renal epithelial cells, are associated with osteoporosis and renal stone formation

Image provided by Prof. Harwig Wolburg, University of Tübingen

TRPV1

Transient Receptor Potential Cation Channel
Ion Channel Gene Proficiency No. 20601

Draft screening report within 4 weeks **Turnaround**

Human **Species**

TRPV1 **Gene**

UniProt Q8NER1 **Protein**

Nociceptors, sensory neurons, brain, skin **Tissue**

Noxious chemical and thermal stimuli reception, apoptosis, temperature transducer for "heat" **Function**

Pain, incontinence, inflammation, thermoception **Pathology**

TRPV2, TRPV3, calmodulin, PI3 kinase, PRKCE, PRKCM, adenosine **Interaction**

Capsaicin, alpha-linolenic acid, reiniferatoxin, vanillotoxin, agatoxin 489, capsazepine **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC activation capsaicin / inward blocking potency

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Capsaicin (EC_{50} value 110 µM)

The capsaicin receptor TRPV1 is a crucial mediator of the noxious effects of mustard oil. Curr. Biol. 21: 316–21 **Everaerts et al. 2011**

TRPV1 receptors in the CNS play a key role in broad-spectrum analgesia of TRPV1 antagonists. J. Neurosci. 26: 9385–9393 **Cui et al. 2006**

TRPV4

Transient Receptor Potential Cation Channel
Ion Channel Gene Proficiency No. 20602

Draft screening report within 4 weeks **Turnaround**

Human **Species**

TRPV4 (VRL2, OTRPC4) **Gene**

UniProt Q9HBA0 **Protein**

Brain, liver, kidney, heart, testis, salivary gland, synoviocytes **Tissue**

Osmoreception, adherens junction **Function**

Brachyrachia (BRAK3), dysplasia (MTD, SMDK, SEDM, PSTD), atrophy (DSMAC, SPSMA), CMT2C **Pathology**

MAP7, Src family Tyr protein kinases, β-Catenin, calmodulin, aquaporin 5, pacsin 3 **Interaction**

4α-phorbol 12,13-didecanoate, anandamide, arachidonic acid, capsaicin, HC 067047 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC current activation 4α-PDD

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference 4α-PDD (EC_{50} value 880 nM)

Scapuloperoneal spinal muscular atrophy and CMT2C are allelic disorders caused by alterations in TRPV4. Nat. Genet. 42: 165-169 **Deng et al. 2010**

Mutations in TRPV4 cause Charcot-Marie-Tooth disease type 2C. Nat. Genet. 42: 170-174 **Landouré et al. 2010**

TRPA1

Transient Receptor Potential Cation Channel
Ion Channel Gene Proficiency No. 20603

Draft screening report within 4 weeks **Turnaround**

Human **Species**

TRPA1 (ANKTM1) **Gene**

UniProt O75762 **Protein**

Peripheral sensory neurons, hair cells, nociceptive neurons **Tissue**

Temperature transducer for "cold", nociceptive transduction, inflammation, inner ear function **Function**

Hereditary episodic pain syndrome, hyperalgesia, asthma, dentin sensitivity **Pathology**

Bradykinin, CYLD **Interaction**

Ruthenium red, gentamycin, gingerol, eugenol, mustard oil, cinnamaldehyde, allicin, menthol **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC current activation mustard oil

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Ruthenium red (IC_{50} value 74 nM)

A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome. **Kremeyer et al. 2010** Neuron 66: 671-680

The contribution of TRPM8 and TRPA1 channels to cold allodynia and neuropathic **Caspani et al. 2009** pain. PLoS One 4: e7383

TRPM8

Transient Receptor Potential Cation Channel
Ion Channel Gene Proficiency No. 20604

Draft screening report within 4 weeks **Turnaround**

Human **Species**

TRPM8 **Gene**

UniProt Q7Z2W7 **Protein**

Dorsal root ganglia neurons, prostate, lung, bladder **Tissue**

Temperature transducer for "cold", proliferation, generation of an action potential **Function**

Cancer, thermoception, neuropathic pain **Pathology**

PIP2, Gαq **Interaction**

Icilin, eucalyptol, menthol, capsaicin, ethanol, linalool, geraniol, capsazepine , BCTC **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37˚C)

Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC current activation menthol

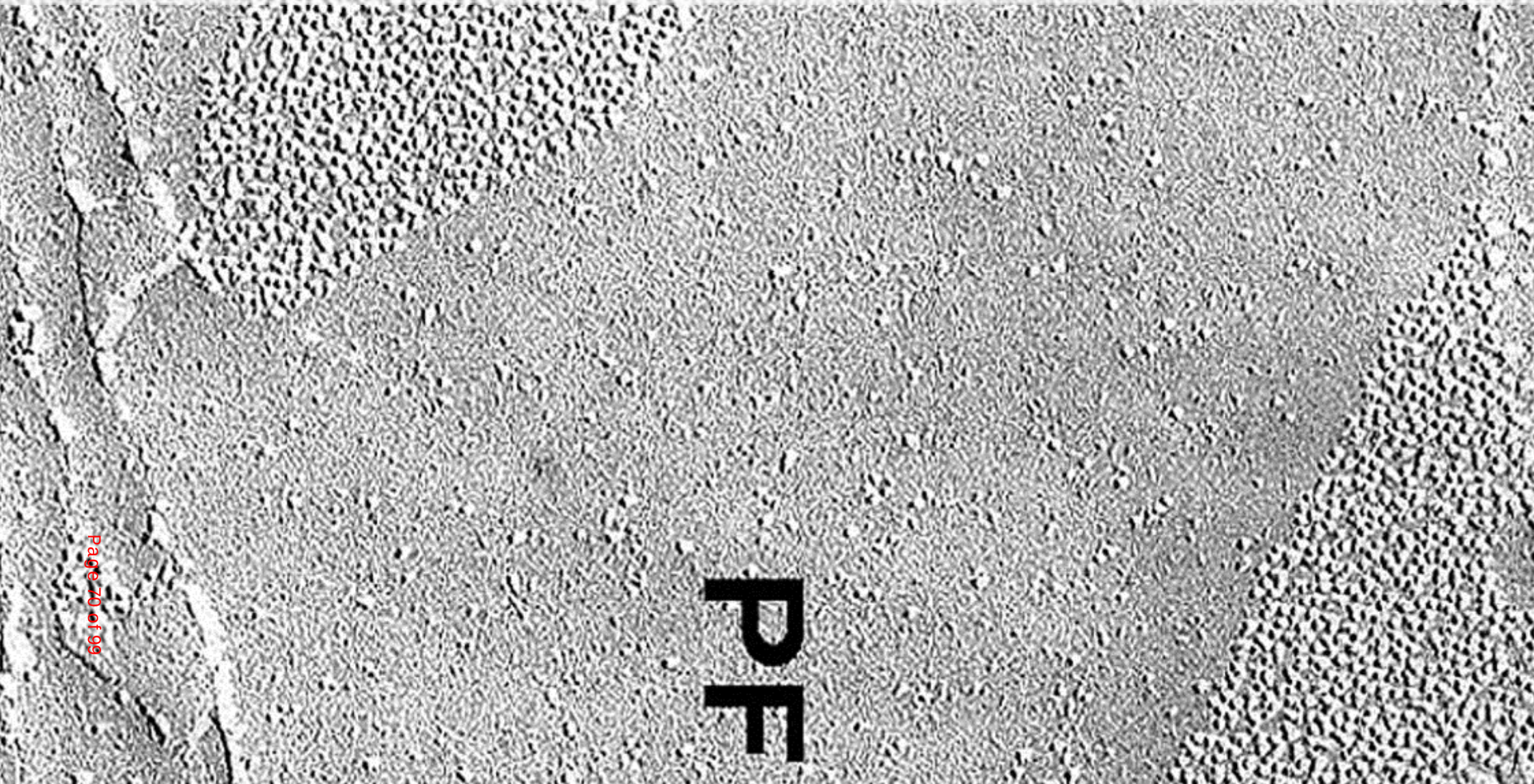
Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Menthol (EC_{50} value 1.4 µM)

Pharmacological and functional properties of TRPM8 channels in prostate tumor cells. **Valero et al. 2011** Pflugers Arch. 461: 99-114

Transient receptor potential channel TRPM8 is over-expressed and required for cellular **Yee et al. 2010** proliferation in pancreatic adenocarcinoma. Cancer Lett. 297: 49-55

crac channels



EF

Function

Activated upon the depletion
of internal calcium stores,
regulation of Ca^{2+} influx into cells

Mechanism

Aggregation of STIM (Ca^{2+} sensor) underneath
the cell membrane assembles ORAI
(pore-forming molecule, localized in the cell membrane)
into clusters, thereby activating the channel

Members

ORAI is encoded by ORAI1-ORAI3,
STIM is encoded by STIM1 and STIM2

TJ

Freeze-fracture image of endothelial cells

STIM/ORAI ion channel complexes, expressed in
endothelial cells, modulate proliferation and angiogenesis

Image provided by Prof. Harwig Wolburg, University of Tübingen

Stim1/Orai1

Calcium Release-Activated Calcium Channel
Ion Channel Gene Proficiency No. 20701

Draft screening report within 6 weeks **Turnaround**

Human **Species**

STIM1 (GOK) / ORAI1 (CRACM1) **Gene**

UniProt Q13586 / UniProt Q96D31 **Protein**

Almost ubiquitous ORAI1 tissue expression, absent in brain and cardiomyocytes **Tissue**

Calcium influx following depletion of intracellular Ca(2+) stores, activation of T-cells **Function**

Immune dysfunction (IDTICED1), cancer, ectodermal dysplasia **Pathology**

STIM2, ORAI3, EF-hand proteins EFCAB4B/CRACR2A, NFAT, ATP2C2, TRPC3, TRPC6, calmodulin **Interaction**

Thapsigargin, SKF 96365 hydrochloride, 2-APB, ML 9 hydrochloride, BTP2 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Study Outline Test pulse ramp -100 to +100 mV

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Thapsigargin

A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. **Feske et al. 2006** Nature 441: 179-185

Orai1/CRACM1 overexpression suppresses cell proliferation via attenuation of the store- **Hou et al. 2011** operated calcium influx-mediated signaling pathway in A549 lung cancer cells. Biochim. Biophys. Acta. 1810: 1278-1284

Stim1/Orai3

Calcium Release-Activated Calcium Channel
Ion Channel Gene Proficiency No. 20702

Draft screening report within 6 weeks **Turnaround**

Human **Species**

STIM1 (GOK) / ORAI3 **Gene**

UniProt Q13586 / UniProt Q9BRQ5 **Protein**

Almost ubiquitous ORAI3 tissue expression **Tissue**

Calcium influx following depletion of intracellular Ca(2+) stores, proliferation **Function**

Cell cycle control, inflammation, cancer **Pathology**

ORAI1, EF-hand proteins EFCAB4B/CRACR2A, NFAT, calmodulin **Interaction**

Thapsigargin, 2-APB, SKF 96365 hydrochloride, ML 9 hydrochloride, BTP2 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Study Outline Test pulse ramp -100 to +100 mV

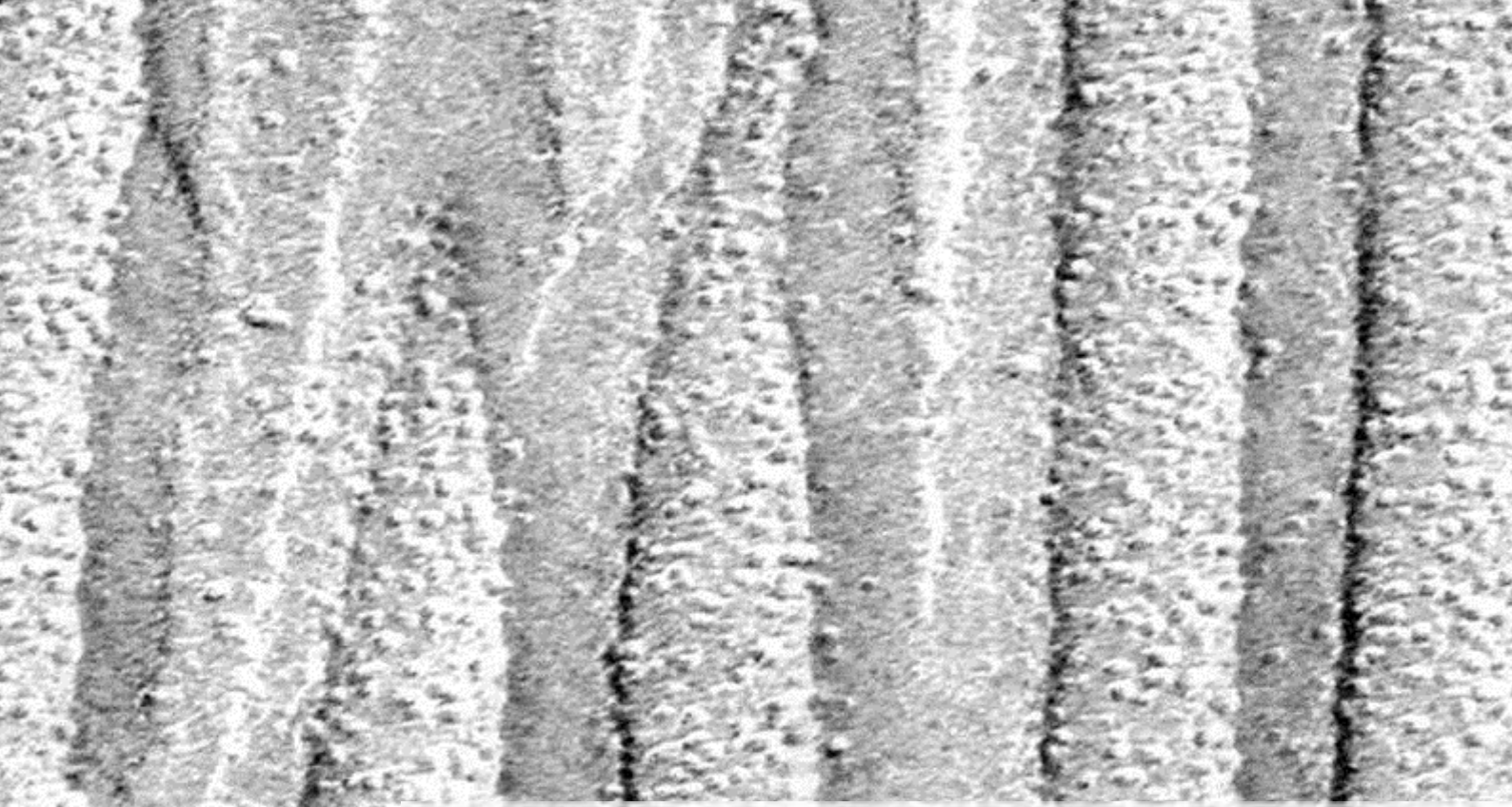
Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Thapsigargin

Down-regulation of Orai3 arrests cell-cycle progression and induces apoptosis in breast cancer cells but not in normal breast epithelial cells. J. Cell. Physiol. 226: 542-551 **Faouzi et al. 2011**

A novel native store-operated calcium channel encoded by Orai3: selective requirement of Orai3 versus Orai1 in estrogen receptor-positive versus estrogen receptor-negative breast cancer cells. J. Biol. Chem. 285: 19173-1983 **Motiani et al. 2010**

purinergic receptors



Subgroups

The ligand-gated purinergic receptor class is encoded by seven genes P2RX1-P2RX7

Topology

One molecule is composed of only two transmembrane domains and contains a large extracellular loop and intracellular carboxyl and amino termini

Assembling

Homomeric and heteromeric trimers make up a functional channel

Interaction

Activation by extracellular ATP

Freeze-fracture image of colon epithelial cells

P2X7 ion channels, expressed in enteric neurons, contribute to the progression of inflammatory bowel disease

Image provided by Prof. Harwig Wolburg, University of Tübingen

P2RX3

Purinergic Receptor
Ion Channel Gene Proficiency No. 20801

Draft screening report within 4 weeks **Turnaround**

Human **Species**

P2RX3 **Gene**

UniProt P56373 **Protein**

Nociceptive sensory neurons, myocytes, smooth muscle cells **Tissue**

Peripheral pain responses, urinary bladder volume reflexes, taste responses **Function**

Chronic pain, overactive bladder, hyperalgesia **Pathology**

P2RX2, IL-1β, PAR-2, oestrogen receptor ERα **Interaction**

ATP, Bz-ATP, suramin, Ro-51, NF-110, capsaicin, A-317491, TNP-ATP, purotoxin-1 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37˚C)

Cell System Stable expression in CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC current activation K_2ATP

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference K_2ATP (EC_{50} value 11 μM)

P2X(1) and P2X(3) purinergic receptors differentially modulate the inflammatory response in human osteoarthritic synovial fibroblasts. Cell. Physiol. Biochem. 25: 325-336 **Varani et al. 2010**

Potentiation of the P2X3 ATP receptor by PAR-2 in rat dorsal root ganglia neurons, through protein kinase-dependent mechanisms, contributes to inflammatory pain. Eur. J. Neurosci. 36: 2293-2301 **Wang et al. 2012**

P2RX7

Purinergic Receptor
Ion Channel Gene Proficiency No. 20802

Draft screening report within 4 weeks **Turnaround**

Human **Species**

P2RX7 **Gene**

UniProt Q99572 **Protein**

Brain (glia cells), antigen-presenting cells, heart, liver, skeletal muscle, pancreas, thymus, tonsils **Tissue**

Lysis of macrophages, fast synaptic transmission, release of proinflammatory cytokines **Function**

Leukaemia lymphocytic, inflammation, tuberculosis, depression, bipolar disorder, bone loss **Pathology**

ABL1, GRB2, NCK1, EMP3, pannexin-1, actin beta, supervillin, cAMP, CHAF1A **Interaction**

Suramin, ATP, Bz-ATP, AZ 11645373, ethidium bromide, uridine 5'-triphosphate **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 / CHO-K1 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC current activation Bz-ATP

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Bz-ATP (EC_{50} value 122 µM)

P2RX7, a gene coding for a purinergic ligand-gated ion channel, is associated with major depressive disorder. Hum. Mol. Genet. 15: 2438-2445 **Lucae et al. 2006**

P2RX7 gene is associated consistently with mood disorders and predicts clinical outcome in three clinical cohorts. Am. J. Med. Genet. B Neuropsychiatr. Genet. 156B: 435-447 **Soronen et al. 2011**

cys-loop receptors

Subgroups

The LGIC class is made up of four different subfamilies including nicotinic acetylcholine receptors, glycine receptors, serotonin type 3 receptors and $GABA_A$ receptors

Topology

Four transmembrane spanning domains TM1-TM4 form one receptor subunit

Assembling

Five or four subunits form a pore, homo- and heteromeric combinations are known

Interaction

Activation upon agonist binding

Light microscopy image of CNS tissue: Ganglion cells

Mutations in the $GABA_A$ ion channels, expressed in the CNS, are associated with epilepsy

Image source Anaxon AG

nAChR α7

Nicotinic Acetylcholine Receptor
Ion Channel Gene Proficiency No. 20901

Draft screening report within 6 weeks **Turnaround**

Human **Species**

CHRNA7 / Ric-3 **Gene**

UniProt P36544 / UniProt Q7Z5B4 **Protein**

Brain, lymphocyte, spleen **Tissue**

Neurotransmitter receptor, post- and presynaptic excitation **Function**

Alzheimer's disease, schizophrenia, juvenile myoclonic epilepsy, dementia, cancer **Pathology**

α2-α 5 subunit, β2, β4 subunit, Ric-3, PIK3R1, FYN, APP, adenylate cyclase 6, LYPD1 **Interaction**

Acetylcholine, choline, alpha-bungarotoxin, nicotine, PNU 282987, epibatidine **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

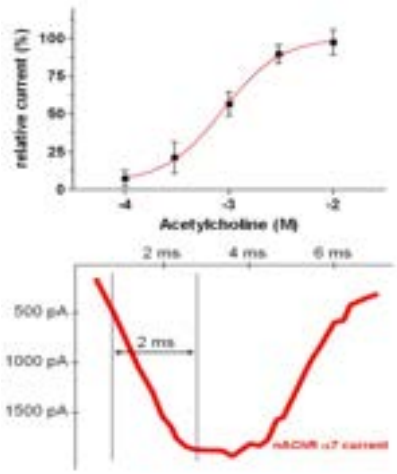
Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC activation Acetylcholine

Readout Current modulation (%) / IC_{50} value / Wash-out kinetics etc.

Reference Acetylcholine (EC_{50} value 662 µM)



Genetic Association Study of the Alpha 7 Nicotinic Receptor (CHRNA7) with the Development of Schizophrenia and Bipolar Disorder in Korean Population. Psychiatry Investig. 7: 196-201 **Joo et al. 2010**

Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. Arch. Gen. Psychiatry 63: 630-638 **Olincy et al. 2006**

nAChR α4β2

Nicotinic Acetylcholine Receptor
Ion Channel Gene Proficiency No. 20902

Draft screening report within 4 weeks **Turnaround**

Human **Species**

CHRNA4 / CHRNB2 **Gene**

UniProt P43681 / UniProt P17787 **Protein**

Brain **Tissue**

Neurotransmitter receptor, regulation of action potential, post- and presynaptic excitation **Function**

Hyperactivity disorder (ADHD), Parkinson, Alzheimer disease, epilepsy (ENFL1, IGE, JME) **Pathology**

CHRNB, Ric-3, α2, α3, α 5, α7 subunit, β2, β4 subunit, VSNL1, UBQLN1, CRELD2, YWHAH **Interaction**

Acetylcholine, nicotine, RJR 2403 oxalate, epibatidine, α-Conotoxin, Coclaurine **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC current activation Nicotine / Acetylcholine

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference Nicotine (EC_{50} value 14 µM)

Polymorphisms in the neural nicotinic acetylcholine receptor α4 subunit (CHRNA4) are associated with ADHD in a genetic isolate. Atten. Defic. Hyperact. Disord. 1: 19-24 **Wallis et al. 2009**

Autosomal dominant nocturnal frontal lobe epilepsy: a genotypic comparative study of Japanese and Korean families carrying the CHRNA4 Ser284Leu mutation. J. Hum. Genet. 56: 609-612 **Hwang et al. 2011**

5HT3A

5-Hydroxytryptamine Serotonin Receptor
Ion Channel Gene Proficiency No. 20903

Draft screening report within 4 weeks **Turnaround**

Human **Species**

HTR3A (5HT3R) **Gene**

UniProt P46098 **Protein**

Brain, testis, spleen, tonsil, intestine, uterus, prostate, ovary and placenta **Tissue**

Neurotransmitter receptor, fast, depolarizing responses in neurons **Function**

Migraine, serotonin syndrome, schizophrenia, motion sickness, bowel disorder, depression **Pathology**

HTR3B, HTR3C, HTR3D, HTR3E, Ric-3, HSPA5, calnexin **Interaction**

Serotonin, ondansetron, cisapride, granisetron, mirtazapine, MDL 72222 **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC activation 5-HT

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference 5-HT (EC_{50} value 2 µM)

The HTR3A polymorphism c. -42C>T is associated with amygdala responsiveness in **Kilpatrick et al. 2011** patients with irritable bowel syndrome. Gastroenterology 140: 1943-1951

Distinguishable haplotype blocks in the HTR3A and HTR3B region in the Japanese **Yamada et al. 2006** reveal evidence of association of HTR3B with female major depression. Biol. Psychiatry. 60: 192-201

GlyR α3

Glycin Receptor
Ion Channel Gene Proficiency No. 20904

Draft screening report within 2 weeks Turnaround

Human Species

GLRA3 Gene

UniProt O75311 Protein

Brain Tissue

Neurotransmitter receptor, contributes to hyperpolarization Function

Migraine, pain, yperekplexia, epilepsy, neurological disorder Pathology

ALDH7A1, NDRG3 Interaction

Glycine, Strychnine hydrochloride, Picrotoxin Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC activation Glycine

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference Glycine (EC_{50} value 29 µM)

Genetic variation of the human glycine receptor subunit genes GLRA3 and GLRB and susceptibility to idiopathic generalized epilepsies. Am. J. Med. Genet. 105: 534-538 Sobetzko et al. 2001

Recessive hyperekplexia mutations of the glycine receptor [alpha]-1 subunit affect cell surface integration and stability. Journal of Neurochemistry 111: 837–847 Villman et al. 2009

α1β2γ2

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20905

Draft screening report within 2 weeks **Turnaround**

Human **Species**

GABRA1 / GABRB2 / GABRG2 **Gene**

UniProt P14867 / UniProt P47870 / UniProt P18507 **Protein**

Brain **Tissue**

Major inhibitory neurotransmitter receptor **Function**

Epilepsy (JME5, CAE4, ECA2, GEFS+3, SMEI), convulsions (FEB8), tremor, autism, bipolar disease **Pathology**

UBQLN1, TRAK-1, PKC, DRD, PPP3CA, YWHAB, PIK3, KCTD, C1QBP, GABR (A, B, D, E, Q) **Interaction**

Bicuculline, muscimol, GABA, Flumazenil, Pentobarbital **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Stable expression in HEK-293 cells

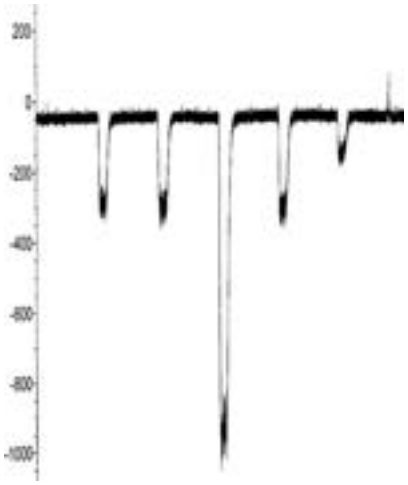
Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 7 µM)



Mutations in the GABRA1 and EFHC1 genes are rare in familial juvenile myoclonic epilepsy. **Ma et al. 2006** Epilepsy Res. 71: 129-134

Genetic investigation of chromosome 5q GABAA receptor subunit genes in **Petryshen et al. 2005** schizophrenia. Mol. Psychiatry 10: 1074-1088

α2β2γ2

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20906

Draft screening report within 2 weeks **Turnaround**

Human **Species**

GABRA2 / GABRB2 / GABRG2 **Gene**

UniProt P47869 / UniProt P47870 / UniProt P18507 **Protein**

Brain **Tissue**

Chloride ligand gated channel, inhibition of the activity of signal-receiving neurons (ISPS) **Function**

Childhood conduct disorder, drug dependence, autism, schizophrenia, epilepsy (ECA2, SMEI) **Pathology**

DRD5, GABARAP, UBQLN1, PRK (CB, CA), PPP3CA, TRAK2, KTCD, GABR (A, B, D, E, Q) **Interaction**

Bicuculline, gabazine, muscimol, GABA, picrotoxin, diazepam, flumazenil **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Stable expression in HEK-293 cells

Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 16 µM)

The role of GABRA2 in risk for conduct disorder and alcohol and drug dependence across developmental stages. Behav. Genet. 36: 577-590 **Dick et al. 2006**

The influence of GABRA2, childhood trauma, and their interaction on alcohol, heroin, and cocaine dependence. Biol. Psychiatry 67: 20-27 **Enoch et al. 2010**

α3β2γ2

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20907

Draft screening report within 2 weeks **Turnaround**

Human **Species**

GABRA3 / GABRB2 / GABRG2 **Gene**

UniProt P34903 / UniProt P47870 / UniProt P18507 **Protein**

Brain, adipose tissue **Tissue**

Chloride ligand gated channel, inhibition of the activity of signal-receiving neurons (ISPS) **Function**

Colour blindness, Rett syndrome, myopathy, autism, bipolar disorder, cancer, epilepsy **Pathology**

DRD5, GABARAP, UBQLN1, PRK (CB, CA), PPP3CA, TRAK2, KTCD, PIK3R1, GABR (A, B, D, E, Q) **Interaction**

Bicuculline, muscimol, GABA, picrotoxin, lorazepam, diazepam, flumazenil **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Stable expression in HEK-293 cells

Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 33 µM)

The gamma amino butyric acid (GABA) receptor alpha-3 subunit gene polymorphism in unipolar depressive disorder: a genetic association study. Am. J. Med. Genet. B Neuropsychiatr. Genet. 126B: 828-7 **Henkel et al. 2004**

Gamma-aminobutyric acid promotes human hepatocellular carcinoma growth through overexpressed gamma-aminobutyric acid A receptor alpha 3 subunit. World J. Gastroenterol. 14: 7175-7182 **Liu et al. 2008**

α5β2γ2

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20908

Draft screening report within 2 weeks **Turnaround**

Human **Species**

GABRA5 / GABRB2 / GABRG2 **Gene**

UniProt P31644 / UniProt P47870 / UniProt P18507 **Protein**

Brain **Tissue**

Chloride ligand gated channel, inhibition of the activity of signal-receiving neurons (ISPS) **Function**

Angelmann syndrome, autism, epilepsy (ECA2, SMEI), Prader-Willi Syndrome, bipolar disorder **Pathology**

UBQLN1, DRD5, PRK (CB / CA), PPP3CA, GABARAP, TRAK2, KTCD, STAT3, GABR (A, B, D, E, Q) **Interaction**

Bicuculline, muscimol, GABA, lorazepam, diazepam , flumazenil, picrotoxin **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Stable expression in HEK-293 cells

Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) /\ EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 14 µM)

The GABA type A receptor alpha5 subunit gene is associated with bipolar I disorder. **Otani et al. 2005** Neurosci. Lett. 381: 108-113

Case-control study and transmission/disequilibrium tests of the genes encoding GABRA5 **Lü et al. 2004** and GABRB3 in a Chinese population affected by childhood absence epilepsy. Chin. Med. J. 117: 1497-1501

α1β2

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20909

Draft screening report within 2 weeks **Turnaround**

Human **Species**

GABRA1 / GABRB2 **Gene**

UniProt P14867 / UniProt P47870 **Protein**

Brain **Tissue**

Lack of benzodiazepine activity, major inhibitory neurotransmitter receptor **Function**

Epilepsy (JME5, CAE4, ECA2, GEFS+3, SMEI), convulsions (FEB8), tremor, autism, bipolar disease **Pathology**

UBQLN1, TRAK-1, PKC, DRD, PPP3CA, YWHAB, PIK3, KCTD, C1QBP, GABR (A, B, D, E, Q) **Interaction**

Bicuculline, muscimol, GABA, Flumazenil, Pentobarbital **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 0.9 µM) / lack of valium activity

A residue close to α1 loop F disrupts modulation of GABAA receptors by benzodiazepines while their binding is maintained. J. Neurochem. 115: 1478-1485. **Baur et al. 2010**

The F-loop of the GABA A receptor gamma2 subunit contributes to benzodiazepine modulation. J. Biol. Chem. 283: 2702-2708 **Lummis et al. 2008**

ρ1

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20910

Draft screening report within 4 weeks **Turnaround**

Human **Species**

GABRR1 **Gene**

UniProt P24046 **Protein**

Brain, retina **Tissue**

Chloride ligand gated channel, inhibition of the activity of signal-receiving neurons (ISPS) **Function**

Fundus dystrophy, retinitis pigmentosa, tremor, bipolar schizoaffective disorder **Pathology**

SQSTM1, GABRR, MAPK1, SQSTM1, MAP1B, PRKCA, SLC6A9, P2RX2, PRKCA, CSNK2A1, MYC, PRKG1 **Interaction**

GABA, TPMPA, muscimol, picrotoxin, lorezepam, TBPS, isonipecotic acid **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 1.7 µM) / loreclezole biomarker

Variation at the GABAA receptor gene, Rho 1 (GABRR1) associated with susceptibility to bipolar schizoaffective disorder. Am. J. Med. Genet. B Neuropsychiatr. Genet. 153: 1347-1349 **Green et al. 2010**

GABRR1 and GABRR2, encoding the GABA-A receptor subunits rho1 and rho2, are associated with alcohol dependence. Am. J. Med. Genet. B Neuropsychiatr. Genet. 153: 418-427 **Xuei et al. 2010**

α4β2γ2

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20911

Draft screening report within 2 weeks Turnaround

Human Species

GABRA4 / GABRB2 / GABRG2 Gene

UniProt P48169 / UniProt P47870 / UniProt P18507 Protein

Brain, kidney Tissue

Chloride ligand gated channel, inhibition of the activity of signal-receiving neurons (ISPS) Function

Autism, Wolfram syndrome, epilepsy, status epilepticus, schizophrenia Pathology

PRKCG, GABR (A, B, D, E, Q) Interaction

Bicuculline, muscimol, GABA, lorazepam, flurazepam, flumazenil, bretazenil Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Stable expression in HEK-293 cells

Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 19 µM) / lack of valium activity

Identification of significant association and gene-gene interaction of GABA receptor subunit genes in autism. Am. J. Hum. Genet. 77: 377-388 Ma et al. 2005

Egr3 stimulation of GABRA4 promoter activity as a mechanism for seizure-induced up-regulation of GABA(A) receptor alpha4 subunit expression. Proc. Natl. Acad. Sci. 102: 11894-11899 Roberts et al. 2005

α6β2γ2

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20912

Draft screening report within 2 weeks **Turnaround**

Human **Species**

GABRA6 / GABRB2 / GABRG2 **Gene**

UniProt Q16445 / UniProt P47870 / UniProt P18507 **Protein**

Brain **Tissue**

Chloride ligand gated channel, inhibition of the activity of signal-receiving neurons (ISPS) **Function**

Antisocial personality disease, neurotic disease, canavan disease, depression, cancer **Pathology**

UBQLN1, GABR (A, B, D, E, Q) **Interaction**

Bicuculline, muscimol, GABA, lorazepam, flumazenil, bretazenil, picrotoxin **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Cell System Stable expression in HEK-293 cells

Discovery Screening 1 / 2 doses per molecule @ n=1 / n=2 cells

SAR Lead Optimization 4 doses per molecule @ n=3 cells

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 25 µM) / lack of valium activity

Serotonin transporter and GABAA alpha 6 receptor variants are associated with neuroticism. Biol. Psychiatry 55: 244-249 **Sen et al. 2004**

GABRA6 genetic polymorphism is associated with the risk of functional heartburn in Chinese. J. Gastroenterol. Hepatol. 22: 227-233 **Lee et al. 2007**

α1β1γ2

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20913

Draft screening report within 2 weeks Turnaround

Human Species

GABRA1 / GABRB1 / GABRG2 Gene

UniProt P14867 / UniProt P18505 / UniProt P18507 Protein

Brain Tissue

Chloride ligand gated channel, inhibition of the activity of signal-receiving neurons (ISPS) Function

Autism, bipolar disease, epilepsy Pathology

UBQLN1, KCTD, C1QBP, ARFGEF2, PIK3CA, AKAP5, GABR (A, B, D, E, Q) Interaction

Muscimol, bicuculline, Indiplon, GABA, lorazepam, picrotoxin, TBPS Modulator

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 10 µM) / loreclezole site confirmation

Investigation of autism and GABA receptor subunit genes in multiple ethnic groups. Collins et al. 2006
Neurogenetics 7: 167-174

GABA(B) receptor 1 polymorphism (G1465A) is associated with temporal lobe Gambardella et al. 2003
epilepsy. Neurology 60: 560-563

α1β3γ2

GABA$_A$ Receptor
Ion Channel Gene Proficiency No. 20914

Draft screening report within 2 weeks **Turnaround**

Human **Species**

GABRA1 / GABRB3 / GABRG2 **Gene**

UniProt P14867 / UniProt P28472 / UniProt P18507 **Protein**

Brain **Tissue**

Chloride ligand gated channel, inhibition of the activity of signal-receiving neurons (ISPS) **Function**

Angelman syndrome, Prader-Willi Syndrome, chronic insomnia, epilepsy (ECA5), autism **Pathology**

UBQLN1, PRKACA, ARFGEF2, GNB2L1, PPP2CA, GABR (A, B, D, E, Q) **Interaction**

Muscimol, bicuculline, Indiplon, GABA, lorazepam, picrotoxin, TBPS **Modulator**

Drug Perfusion Ultra-fast microfluidic molecule application (1 ms)

Data Format NON-GLP

Analysis Platform Whole cell Patch-clamp station

Condition Room temperature / physiological temperature (37°C)

Cell System Stable expression in HEK-293 cells

Biophysics IV-Curve / mutation analysis

Study Outline LGIC activation GABA (EC_{10} submaximal concentration)

Readout Current modulation (%) / EC_{50} value / Wash-out kinetics etc.

Reference GABA (EC_{50} value 26 µM) / loreclezole site confirmation

Maternal transmission of a rare GABRB3 signal peptide variant is associated with autism. Mol. Psychiatry 16: 86-96 **Delahanty et al. 2011**

Hyperglycosylation and reduced GABA currents of mutated GABRB3 polypeptide in remitting childhood absence epilepsy. Am. J. Hum. Genet. 82: 1249-1261 **Tanaka et al. 2008**

quality assurance

Anaxon AG is organized as a preclinical CRO test facility and is currently preparing it's GLP equivalent status at the new test facility site. The procedure allows to conclude a GLP reference study in compliant format.

Computerized systems: Electronic data are archived OFF-LINE after study completion (final report signed by study director) as for all other study specific data (paper, slides etc.).

Electronic SOP body: Anaxon AG promotes HYBRID versions of all SOPs. The approval is by wet ink on original paper document, distributed as file of the scanned paper document and archived as original paper.

Electronic archiving: It is ensured that archived electronic study data are never changed and protected against deletion. In any case, the archived electronic study data has READ-ONLY status for all facility users.

For any requested GLP Reference study, please, contact us to set up your research project accordingly.

quality assurance

Guidelines: ICH S7A/B, OECD Documents GLP and Compliance Monitoring Nr. 1-15 [C (97)186/Final], GLPV 18-05-2005 [RS 813.112.1]

QA Programme: Detailed description of Quality Assurance Programme (QAP) implemented as SOP document GE-0-8

Auditing: Every 2 years by authorities, every GLP Study is specifically inspected

personnel training

Documentation: Each employee maintains a personal GLP filer including a) CV, b) job position description, c) educational records, d) SOP confirmation records

GLP Training: Only GLP trained and technically skilled personnel participates in GLP Studies

Representation: The management of deputy responsibilities are defined in SOP GE-0-4

archiving

Archive: Solid and compliant archive location within appropriate test facility district

Period: All GLP Study filers along with complete facility documentation is subjected to a 10 years archiving phase.

SOPs: The comprehensive body of SOPs including all versions of documents is archived during complete test facility lifespan

how to order

....set up your ion channel study:

1) your gene of interest

- GENE: You announce your tailored ion channel gene sequence.
- DRUGS: You indicate your requested number of molecules to be assayed.
- FORMAT: You let us know your requested analysis format: GLP or NON-GLP.
- DOSES: You indicate your requested number of concentrations/replicates.

Please, contact us through phone or email:

- PHONE: +41 76 427 00 05
- EMAIL: studies@anaxon.net

2) final study outline

- OFFER: You receive from us a detailed quotation for your requested analysis.
- SHEET: You receive from us our standard drug sheet for molecule characterization.
- STUDY: You review our quotation and by written consent confirm your order.
- DRUGS: You ship to us the completed drug sheet along with your molecules.

Please, ship to us your molecules (solid material / stock solutions) along with drug sheet:

- DRUG SHEET: Specific molecule details as well as safety/stability characteristics
- MOLECULES: Containers including Test Item material OR stock solutions

3) our analysis data

- PLAN: We generate your specific study plan together with you.
- DRUGS: We confirm the successful receipt of your molecules and completed drug sheet(s).
- ANALYSIS: We start the analysis in line with your finalized study plan.
- REPORT: After completion of analysis we prepare a draft report for your review.

Our standard analysis package includes:

- DOCUMENTS: Quotation, CDA/MTA contracts, drug sheet, finalized study plan and report.
- ARCHIVING: GLP study specific data and documents are archived for 10 years.

contact us:

Anaxon AG
Schwarzenburgstrasse 265
3098 Berne
Switzerland

Phone: +41 76 427 00 05
Email: studies@anaxon.net
Internet: www.anaxon.net