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your notes:
YOU MAKE YOUR GENE CHOICE....

....WE DELIVER AN ANALYSIS CONCEPT
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 $\alpha$, $\beta$ and $\delta$ 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 ($I_{Kr}$, 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.
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.
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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

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 / IC50 determination
Mechanism State- and use-dependence / site of action
Reference PAP-1 (IC50 value 77 nM)

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

A novel mutation in Kv1.1 channel causes episodic ataxia without myokymia. Human Lee et al. 2004
mutation 24: 23-36
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 / IC50 determination

**Mechanism** State- and use-dependence / site of action

**Reference** PAP-1 (IC50 value 209 nM)

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

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

ion channel genes worth analyzing together
Kv1.3

Shaker Related Potassium Channel
Ion Channel Gene Proficiency No. 20003

Draft screening report within 2 weeks **Turnaround**

**Species** Human

**Gene** KCNA3

**Protein** UniProt P22001

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

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

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

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

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

**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 Schmitz et al. 2005 autoimmune diseases. Mol. Pharmacol. 68: 1254–70

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 / IC50 determination
Mechanism State- and use-dependence / site of action
Reference PAP-1 (IC50 value 303 nM)

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 IKur 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 / IC50 determination
Mechanism State- and use-dependence / site of action
Reference PAP-1 (IC50 value 281 nM)

Kv1.5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation. Olson et al. 2006
Mutations in the Kv1.5 channel gene KCNA5 in cardiac arrest patients. Biochem. 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 / IC₅₀ determination

**Mechanism** State- and use-dependence / site of action

**Reference** PAP-1 (IC₅₀ value 26 nM)


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 / IC50 determination
Mechanism State- and use-dependence / site of action
Reference PAP-1 (IC50 value 185 nM)

Block of Kv1.7 potassium currents increases glucose-stimulated insulin Finol-urdaneta et al. 2004 secretion. EMBO Mol. Med. 4: 424–434
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 arrhythmias **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\textsubscript{50} determination

**Mechanism** State- and use-dependence / site of action

**Reference** PAP-1 (IC\textsubscript{50} value 306 nM)


Expression of KCNA10, a voltage-gated K channel, in glomerular endothelium and at the apical membrane of the renal proximal tubule. J. Am. Soc. Nephrol. 13:2831-2839 **Yao et al. 2002**
**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 / IC₅₀ determination

**Mechanism** State- and use-dependence / site of action

**Reference** TEA (IC₅₀ value 330 μM)

Novel mechanisms of trafficking defect caused by KCNQ1 mutations found in long QT [Sato 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

**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\textsubscript{50} determination

**Mechanism** State- and use-dependence / site of action

**Reference** Flecainide (IC\textsubscript{50} value 30 μM)


Novel mutations in the KCND3-encoded Kv4.3 K+ channel associated with autopsy-negative sudden unexplained death. Hum. Mutat. 33: 989–997
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 IKS 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 / IC50 determination

**Mechanism** State- and use-dependence / site of action

**Reference** Chromanol (IC50 value 2 μM), mefloquine (IC50 value 1.7 μM)

Novel mechanisms of trafficking defect caused by KCNQ1 mutations found in long QT **Sato et al. 2009**

Kv7.2

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

Draft screening report within 2 weeks **Turnaround**

**Species**
Human

**Gene**
KCNQ2

**Protein**
UniProt O43526

**Tissue**
Brain, skeletal muscle

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

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

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

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

**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**

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 / IC50 determination
Mechanism State- and use-dependence / site of action
Reference Linopiridine (IC50 value 13 μM)


Genetic association analysis of KCNQ3 and juvenile myoclonic epilepsy in a South Indian population. Hum. Genet. 113: 461-463
Kv7.5
KQT-like Potassium Channel
Ion Channel Gene Proficiency No. 20014

Draft screening report within 2 weeks

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 / IC₅₀ determination

**Mechanism** State- and use-dependence / site of action

**Reference** Flupiritine (IC₅₀ value 3 μM)

Localization of KCNQ5 in the normal and epileptic human temporal neocortex and hippocampal formation. Neuroscience 120: 353–364

KCNQ5 channels control resting properties and release probability of a synapse. Nat. Huang et al. 2011

Neurosci. 14: 840–847
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 / IC50 determination

**Mechanism** State- and use-dependence / site of action

**Reference** Linopirdine (IC50 value 11 μM)


Novel KCNQ2/Q3 agonists as potential therapeutics for epilepsy and neuropathic pain. J. **Fritch et al. 2010** Med. Chem. 53: 887–896
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 / IC50 determination

Mechanism State- and use-dependence / site of action

Reference Flupiritine (IC50 value 0.8 μM)


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
potassium channels

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**Kv10.1**

**Eag Related Potassium Channel**

**Ion Channel Gene Proficiency No. 20017**

Draft screening report within 2 weeks **Turnaround**

Human **Species**

**KCNH1 Gene**

UniProt 095259 **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: **Farias et al. 2004** 6996–7001

IGF-1 activates hEAG K(+) channels through an Akt-dependent signaling pathway in **Borowiec et al. 2007** breast cancer cells: role in cell proliferation. J. Cell. Physiol.212: 690–701
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, FH2 **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)


Sudden death associated with short-QT syndrome linked to mutations in HERG. Brugada et al. 2004 Circulation 109: 30–35
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\textsubscript{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\textsubscript{50} determination
Mechanism State- and use-dependence / site of action
Reference BaCl (IC\textsubscript{50} value 4 μM)

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_{ACh}) 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

**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**

**Function**
- ATP-activated K⁺ current in the heart (IₖATP)
- 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 / IC₅₀ value / diazoxide stimulation
- Mechanism: Site of action / ATP sensitivity
- Reference: Glibenclamide (IC₅₀ 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

The Kir6.2-F333I mutation differentially modulates KATP channels composed of SUR1 or SUR2 subunits. J. Physiol. 581: 1259–1269
rectifier channels
HCN cation channels
Mutations in the HCN ion channel, expressed in neurons of the CNS, are associated with epilepsy.

Image source: Anaxon AG

**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 If current **Function**

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

cAMP, KCNE2 **Interaction**

Ivabradine, clobradine, 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

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

**ion channel genes worth analyzing together**
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\textsubscript{50} value / Wash-out kinetics etc.

**Reference** Lidocaine (Tonic IC\textsubscript{50} value 570 μM)

Mutations of SCN1A, encoding a neuronal sodium channel, in two families with **Escayg et al. 2000**


Sodium channel alpha1-subunit mutations in severe myoclonic epilepsy of infancy **Wallace et al. 2003**

and infantile spasms. Neurology 61: 765–769
### 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 (%) / IC₅₀ value / Wash-out kinetics etc.

**Reference** Lidocaine (Tonic IC₅₀ value 1020 μM)

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

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

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**Table:**

- **Tissue:** Brain (neurons, microglia), utricular hair cells, corti organ
- **Function:** Excitability of neurons, generation of action potentials
- **Pathology:** Autism, epilepsy (EIEE11, BFNIS), late ataxia, pain, myoclonus, multiple sclerosis
- **Interaction:** Ankyrin G, β1 subunit, β2 subunit, calmodulin, Nedd4-2
- **Modulator:** Tetrodotoxin, saxitoxin, β-scorpion toxin Css-IV, veratridine, α-scorpion toxin, ATX-II
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, CID 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 (%) / IC50 value / Wash-out kinetics etc.
Reference Lidocaine (Tonic IC50 value 470 μM)

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

**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 (%) / IC50 value / Wash-out kinetics etc.

**Reference** Lidocaine (Tonic IC50 value 390 μM)


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

ion channel genes worth analyzing together
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 (%) / IC50 value / Wash-out kinetics etc.

Reference Lidocaine (Tonic IC50 value 330 μM)


Na(V)1.5 enhances breast cancer cell invasiveness by increasing NHE1-dependent H(+) efflux in caveolae. Oncogene 30: 2070–2076
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 (%) / IC50 value / Wash-out kinetics etc.

Reference Lidocaine (Tonic IC50 value 1260 μM)

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

Heterozygosity for a protein truncation mutation of sodium channel SCN8A in a Trudeau et al. 2006
patient with cerebellar atrophy, ataxia, and mental retardation. J. Med. Genet. 43:
527-530
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 (%) / IC50 value / Wash-out kinetics etc.
Reference Lidocaine (Tonic IC50 value 340 μM)

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

Paroxysmal extreme pain disorder M1627K mutation in human Nav1.7 renders DRG Sulayman et al. 2008
neurons hyperexcitable. Mol. Pain 4: 37
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 (%) / IC50 value / Wash-out kinetics etc.
**Reference** Lidocaine (Tonic IC50 value 610 μM)


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 (%) / IC50 value / Wash-out kinetics etc.

**Reference** Nifedipine / verapamil

CACNA1C polymorphisms are associated with the efficacy of calcium channel blockers. *Bremer et al. 2006*

Severe arrhythmia disorder caused by cardiac L-type calcium channel mutations. *Splawski et al. 2005*

Calcium channels

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 MVIIIC, 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 / IC50 determination

**Mechanism** State- and use-dependence / site of action

**Reference** ω-agatoxin-IVA (IC50 value 410 nM)

Two novel CACNA1A gene mutations associated with episodic ataxia type 2 and **Spacey et al. 2005**

Novel CACNA1A mutation causes febrile episodic ataxia with interictal cerebellar **Subramony et al. 2003**
钙离子通道

Cav3.2  T-Type Calcium Channel
Ion Channel Gene Proficiency No. 20402

Draft screening report within 4 weeks Turnaround

Human Species
CACNA1H Gene

UniProt 095180 Protein

Brain, ovary, placenta, vascular smooth muscle Tissue

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

Angina, epilepsy (CAE6, ELG6), sleep, breast cancer, autism, pain, cardiac hypertrophy Pathology

GNG2, KCNMA1, KDMSB, CACNA1s, CACNBs, CACNGs, NCAM Interaction

Kurtoxin, mibebradil, 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 / IC50 determination
Mechanism State- and use-dependence / site of action
Reference NiCl2 (IC50 value 11 μM)

calcium channels
chloride channels
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

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.
ion channel genes worth analyzing together

**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 (%) / IC50 value / Wash-out kinetics etc.

**Reference** 9-AC (IC50 value 14 μM)


Lyons et al. 2011


Trip et al. 2008
Two novel CLCN2 mutations accelerating chloride channel deactivation are Saint-Martin et al. 2009 associated with idiopathic generalized epilepsy. Hum. Mutat. 30: 397–405

Linkage and mutational analysis of CLCN2 in childhood absence epilepsy. Epilepsy Res. Everett et al. 2007 75: 145–153
trp channels
Subgroups

TRPC (TRPC1–TRPC7), TRPV (TRPV1–TRPV6),
TRPA1, TRPM (TRPM1–TRPM8),
TRPP (TRPP1–TRPP3, PKD1, PKD2, PKD3, PKD4, PKD5–PKD13),
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 (%) / IC₅₀ value / Wash-out kinetics etc.  
**Reference** Capsaicin (EC₅₀ value 110 μM)

The capsaicin receptor TRPV1 is a crucial mediator of the noxious effects of mustard *Everaerts et al.* 2011  
TRPV1 receptors in the CNS play a key role in broad-spectrum analgesia of TRPV1 *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 (%) / IC50 value / Wash-out kinetics etc.  
Reference 4α-PDD (EC50 value 880 nM)

Scapuloperoneal spinal muscular atrophy and CMT2C are allelic disorders caused by Deng et al. 2010  

Mutations in TRPV4 cause Charcot-Marie-Tooth disease type 2C. Nat. Genet. 42: Landouré et al. 2010  
170-174
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 pain. **Caspani et al. 2009**

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, Gaoq 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 (%) / IC50 value / Wash-out kinetics etc.

Reference Menthol (EC50 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 proliferation in pancreatic adenocarcinoma. Yee et al. 2010 Cancer Lett. 297: 49-55
crac channels
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

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
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 (%) / IC50 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

## 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 (%) / IC50 value / Wash-out kinetics etc.

**Reference** Thapsigargin


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 K₂ATP

**Readout** Current modulation (%) / IC₅₀ value / Wash-out kinetics etc.

**Reference** K₂ATP (EC₅₀ value 11 μM)

P2X(1) and P2X(3) purinergic receptors differentially modulate the inflammatory response in human osteoarthritic synovial fibroblasts. **Varani et al. 2010**

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 (%) / IC50 value / Wash-out kinetics etc.
Reference Bz–ATP (EC50 value 122 μM)

P2RX7, a gene coding for a purinergic ligand-gated ion channel, is associated with Lucae et al. 2006

P2RX7 gene is associated consistently with mood disorders and predicts clinical Soronen et al. 2011
cys-loop receptors
Light microscopy image of CNS tissue: Ganglion cells

Mutations in the GABA\textsubscript{\textalpha} ion channels, expressed in the CNS, are associated with epilepsy

Image source Anaxon AG

**Subgroups**

The LGIC class is made up of four different subfamilies including nicotinic acetylcholine receptors, glycine receptors, serotonin type 3 receptors and GABA\textsubscript{\textalpha} 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
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 (%) / IC50 value / Wash-out kinetics etc.

Reference Acetylcholine (EC50 value 662 μM)

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

Psychiatry 63: 630-638
**nAChR α4β2**

**Nicotinic Acetylcholine Receptor**

**Ion Channel Gene Proficiency No. 20902**

Draft screening report within 4 weeks **Turnaround**

**Human Species**

**CHRNA4 / CHRN2 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, α5, 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 (%) / EC50 value / Wash-out kinetics etc.

**Reference** Nicotine (EC50 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


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 (%) / EC50 value / Wash-out kinetics etc.

**Reference** 5-HT (EC50 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

<table>
<thead>
<tr>
<th>GlyR $\alpha 3$</th>
<th>Glycin Receptor Ion Channel Gene Proficiency No. 20904</th>
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<td>GLRA3 <strong>Gene</strong></td>
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<td>UniProt O75311 <strong>Protein</strong></td>
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<tr>
<td>Brain <strong>Tissue</strong></td>
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Neurotransmitter receptor, contributes to hyperpolarization **Function**

Migraine, pain, hyperekplexia, 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)


cys-loop receptors

\[ \alpha_1 \beta_2 \gamma_2 \]

GABA<sub>\alpha</sub> 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<sub>50</sub> submaximal concentration)

**Readout** Current modulation (%) / EC<sub>50</sub> value / Wash-out kinetics etc.

**Reference** GABA (EC<sub>50</sub> 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

ion channel genes worth analyzing together
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_{50} 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 development stages. Behav. Genet. 36: 577-590

Draft screening report within 2 weeks **Turnaround**

**Human** Species

**GABA\textsubscript{A}** Receptor

| Ion Channel Gene Proficiency No. | 20907 |

**Gene**

- GABRA3 / GABRB2 / GABRG2
- UniProt P34903 / UniProt P47870 / UniProt P18507

**Protein**

- Brain, adipose tissue

**Tissue**

**Function**

- Chloride ligand gated channel, inhibition of the activity of signal-receiving neurons (ISPS)
- 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\textsubscript{10} submaximal concentration)

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

**Reference**

- GABA (EC\textsubscript{50} value 33 μM)


- 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
**GABA<sub>α</sub> Receptor**  
**Ion Channel Gene Proficiency No. 20908**

**α<sub>5</sub>β<sub>2</sub>γ<sub>2</sub>**

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<sub>50</sub> submaximal concentration)

**Readout** Current modulation (%) / EC<sub>50</sub> value / Wash-out kinetics etc.

**Reference** GABA (EC<sub>50</sub> 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 and GABRB3 in a Chinese population affected by childhood absence epilepsy. Chin. Med. J. 117: 1497-1501

**ion channel genes worth analyzing together**
Draft screening report within 2 weeks **Turnaround**

**Human Species**

**Gene**

**Protein**

**Brain Tissue**

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

Epilepsy (JMES, 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_{50} 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 **Baur et al. 2010** while their binding is maintained. J. Neurochem. 115: 1478–1485.

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

Draft screening report within 2 weeks **Turnaround**

**Human Species**

**Gene**

GABRA4 / GABRB2 / GABRG2

**Protein**

UniProt P48169 / UniProt P47870 / UniProt P18507

**Tissue**

Brain, kidney

**Function**

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

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 (EC50 submaximal concentration)

Readout

Current modulation (%) / EC50 value / Wash-out kinetics etc.

Reference

GABA (EC50 value 19 μM) / lack of valium activity

Identification of significant association and gene-gene interaction of GABA receptor **Ma et al. 2005**


Egr3 stimulation of GABRA4 promoter activity as a mechanism for seizure-induced **Roberts et al. 2005**

Draft screening report within 2 weeks **Turnaround**

**Human Species**

**GABA**<sub>6</sub> / **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<sub>10</sub> submaximal concentration)

**Readout** Current modulation (%) / EC<sub>50</sub> value / Wash-out kinetics etc.

**Reference** GABA (EC<sub>50</sub> value 25 μM) / lack of valium activity

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Serotonin transporter and GABAA alpha 6 receptor variants are associated with neuroticism. Biol. Psychiatry 55: 244–249

GABA<sub>α</sub> Receptor
Ion Channel Gene Proficiency No. 20913

\[ \alpha_1\beta_1\gamma_2 \]

Draft screening report within 2 weeks **Turnaround**

**Human Species**

GABA<sub>α</sub> / GABBR1 / 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<sub>50</sub> submaximal concentration)

**Readout** Current modulation (%) / EC<sub>50</sub> value / Wash-out kinetics etc.

**Reference** GABA (EC<sub>50</sub> 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
GABA<sub>α</sub> 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<sub>50</sub> submaximal concentration)

**Readout** Current modulation (%) / EC<sub>50</sub> value / Wash-out kinetics etc.

**Reference** GABA (EC<sub>50</sub> value 26 μM) / loreclezole site confirmation

Maternal transmission of a rare GABRB3 signal peptide variant is associated with **Delahanty et al. 2011**


Hyperglycosylation and reduced GABA currents of mutated GABRB3 polypeptide in **Tanaka et al. 2008**

Remark: Anaxon is currently preparing the official application procedure for GLP accreditation by Swissmedic. Therefore, all GLP studies accomplished are termed “GLP Reference Study” for appropriate consideration.

The following wording is included in respective GLP statement section of every GLP study and is in line with current Swissmedic policies:

“The present study is a GLP Reference Study which will be used for the official GLP application procedure (Art. 5, GLPV, Swissmedic, Swiss Agency for Therapeutic Products).”

Our test facility has GLP operational status and the procedure thus allows to conclude every GLP Reference Study in compliant format. For any requested GLP study, please, contact us to set up your research project accordingly.
GLP 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-O-8

Auditing: Every 2 years by Swissmedic, 4 times in a year facility based inspections, each GLP Study

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-O-4

GLP archiving

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

Period: All GLP / NON-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
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 79 109 40 40
- **EMAIL:** office@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:** Study specific raw data and documents are archived for 10 years.