Advancing Analgesic Drug Discovery with a Novel Translational Strategy

Andre Ghetti, Ph.D.
Chief Executive Officer

AnaBios Corporation

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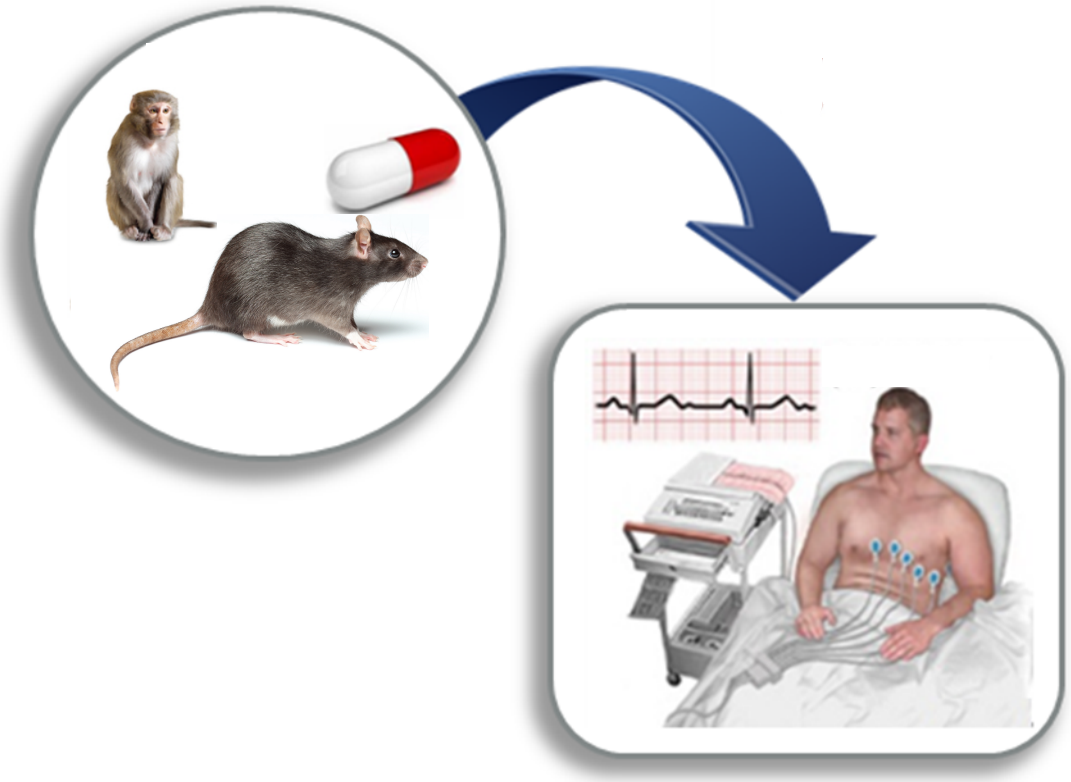
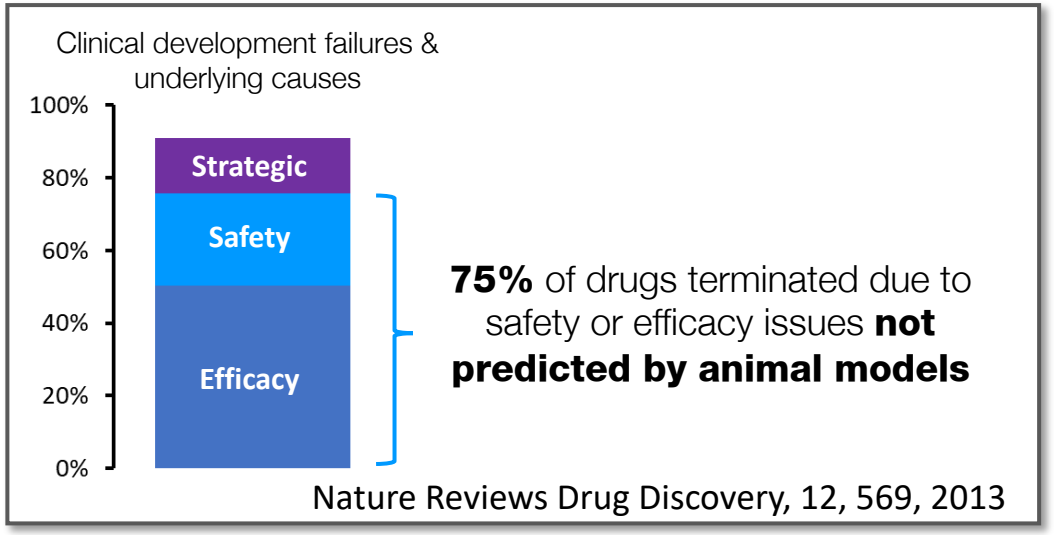
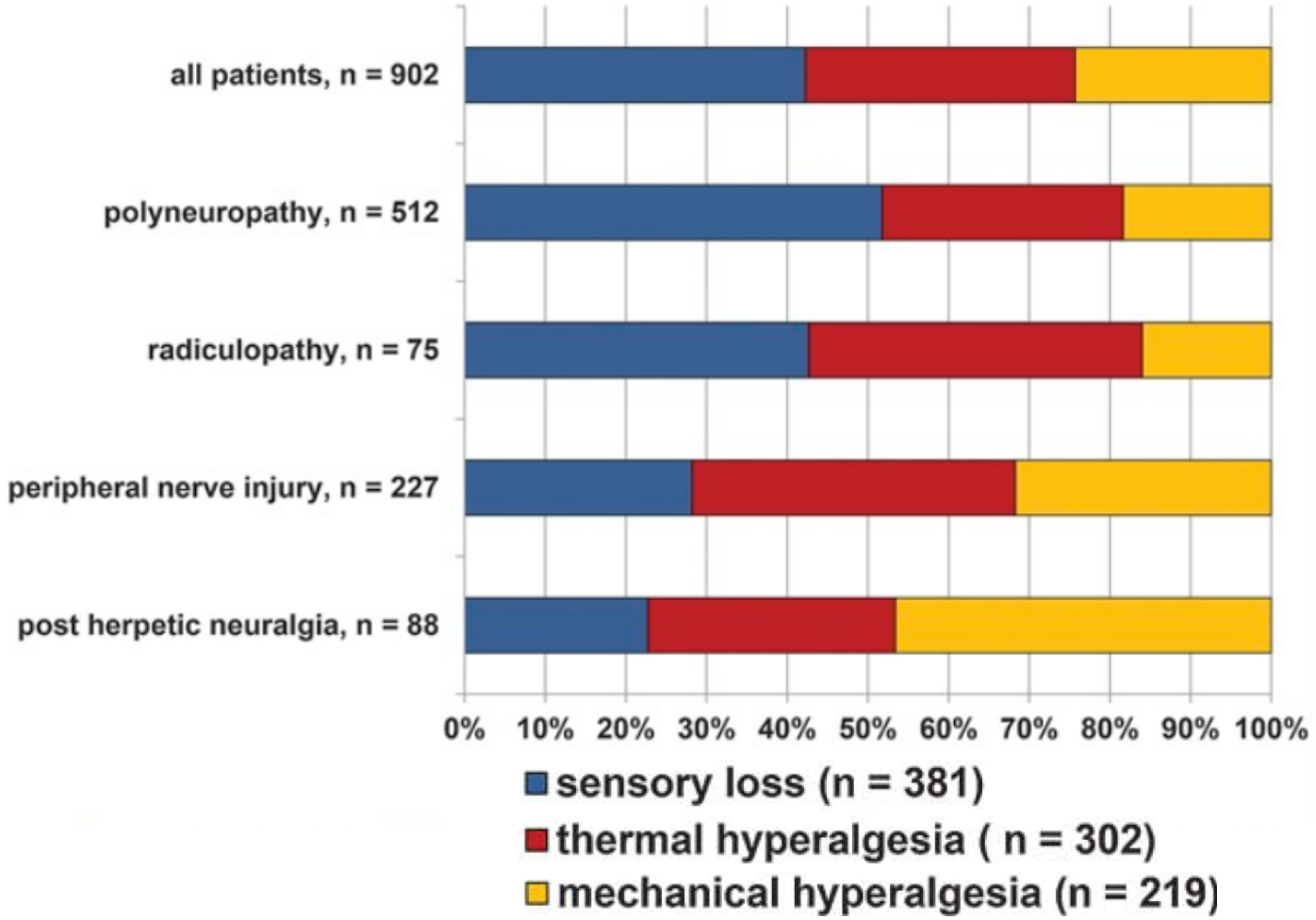
The Translational Challenge in Drug Discovery





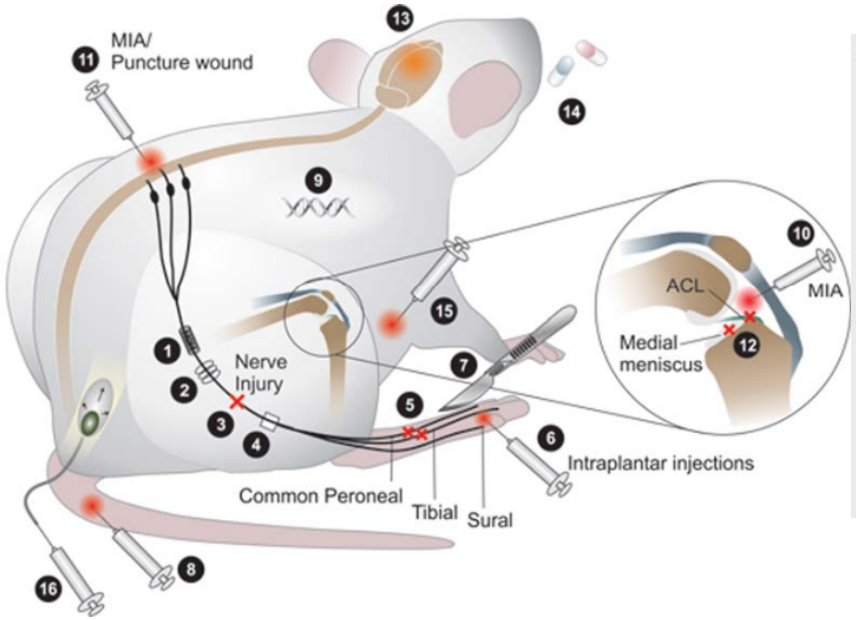
The Pain Patient Population is Heterogeneous



Patients with peripheral neuropathic pain of several etiologies were tested to assess their sensory profiles

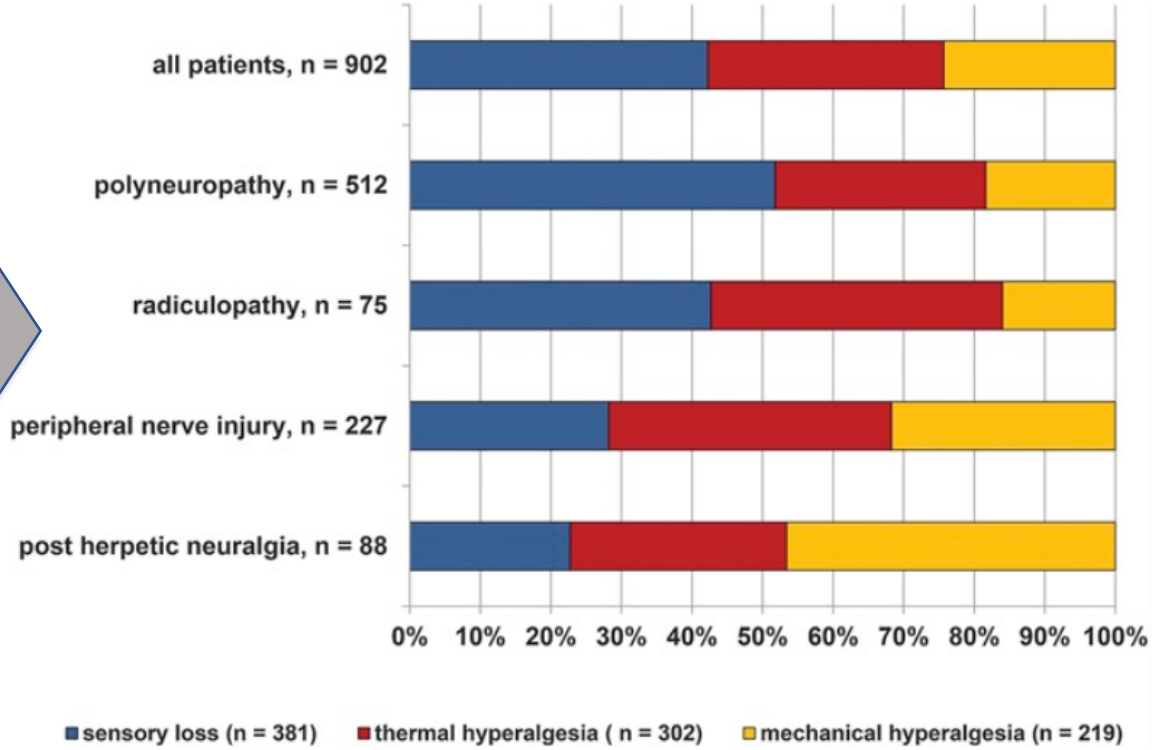
German Neuropathic Pain Research Network (DFNS), EUROPAIN, and NEUROPAIN consortia; Baron et al., PAIN (2017)

Unclear How Pain Models Map on the
Diversity of Human Pain Conditions



1 → 5 Nerve injury
6 Chemical irritants
7 Incision wound
8 Collagen injection
9 Transgenic animals
10 → 11 Chemically-induced arthritis
12 Mechanically-induced arthritis
13 Migraine
14 Pharmacological agents
15 Systemic Injection
16 Distension

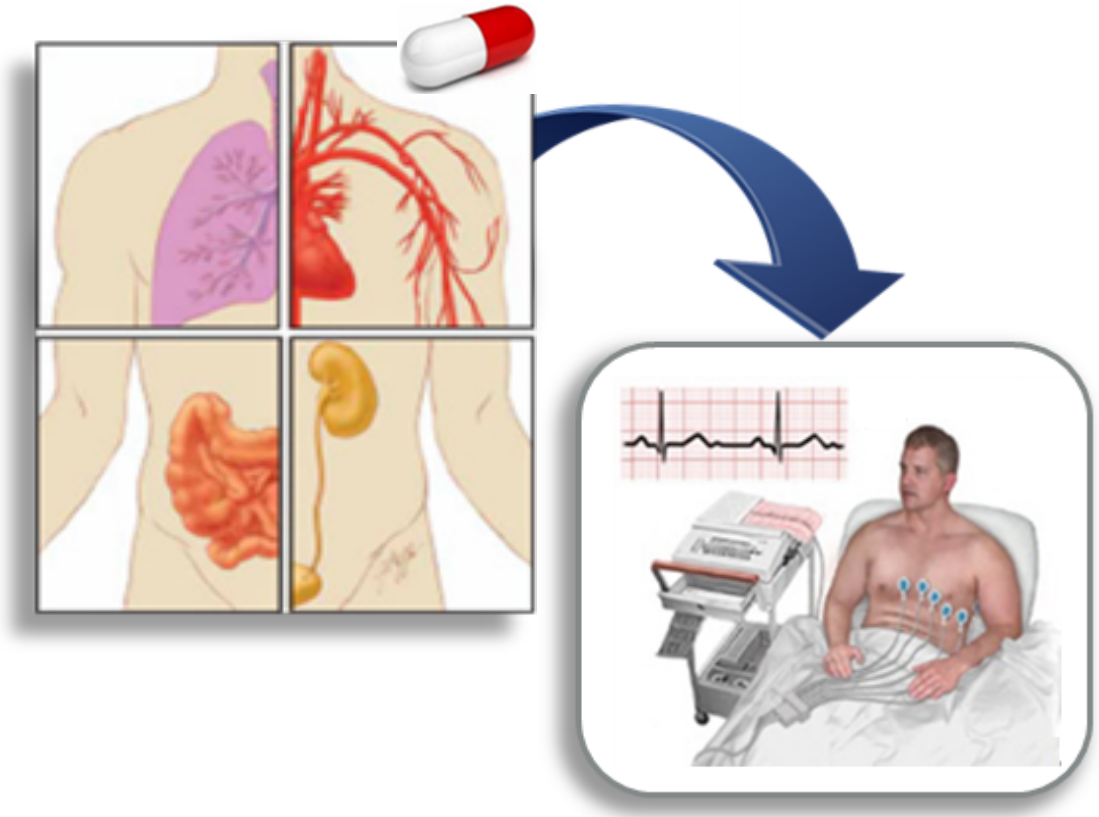
?



Baron et al., PAIN (2017)

Rodent models do not help matching a specific drug with the appropriate indication

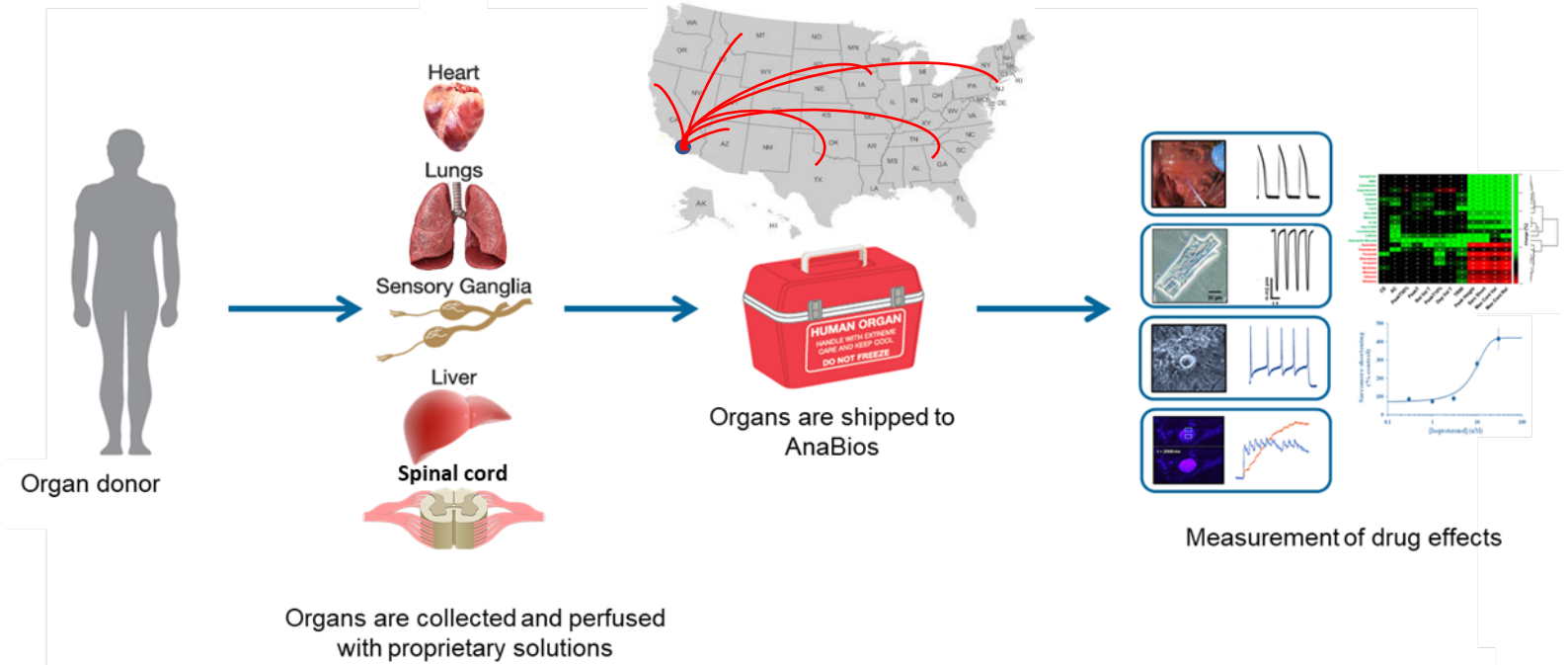
Enabling the Ex-Vivo Study in Human Primary Cells and Tissues to Improve Translational Research



Challenges to the Use of Human Tissue
in Pharmaceutical Research

- *Viability* — *Proprietary solutions to prevent cold ischemia- and reperfusion-injury*
- *Access* — *Network of partnering hospitals in the U.S.A.*
- *Reproducibility* — *Standardized recovery methods; quality control; medical history*

Enabling Drug Discovery in Human Tissues



- Advanced procurement methods ensure sample viability
- Rigorous QC guarantees tissue quality
- U.S.A.-based network: high ethical standards and large donor population

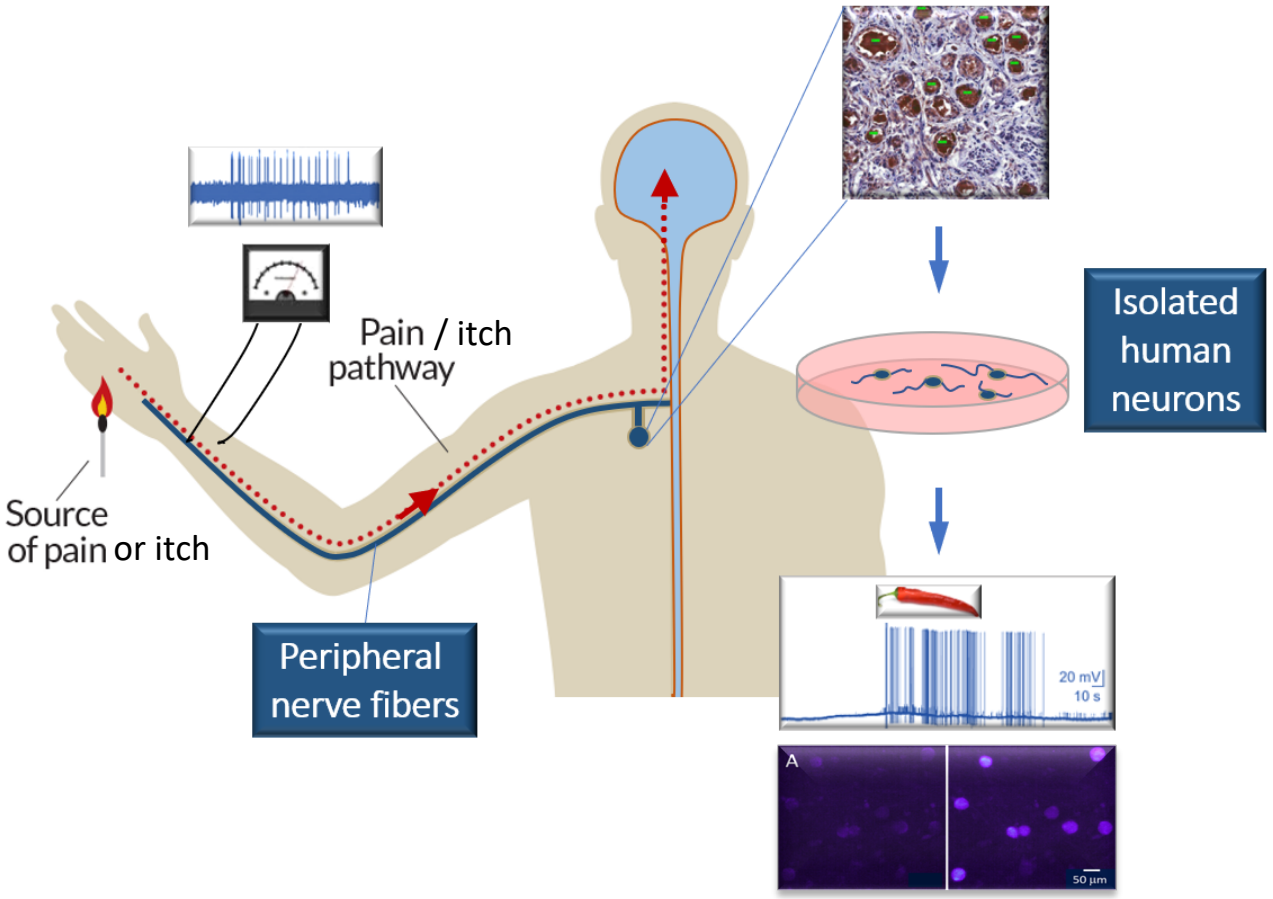
Predictive of clinical outcomes

Lower development risks related to interspecies differences

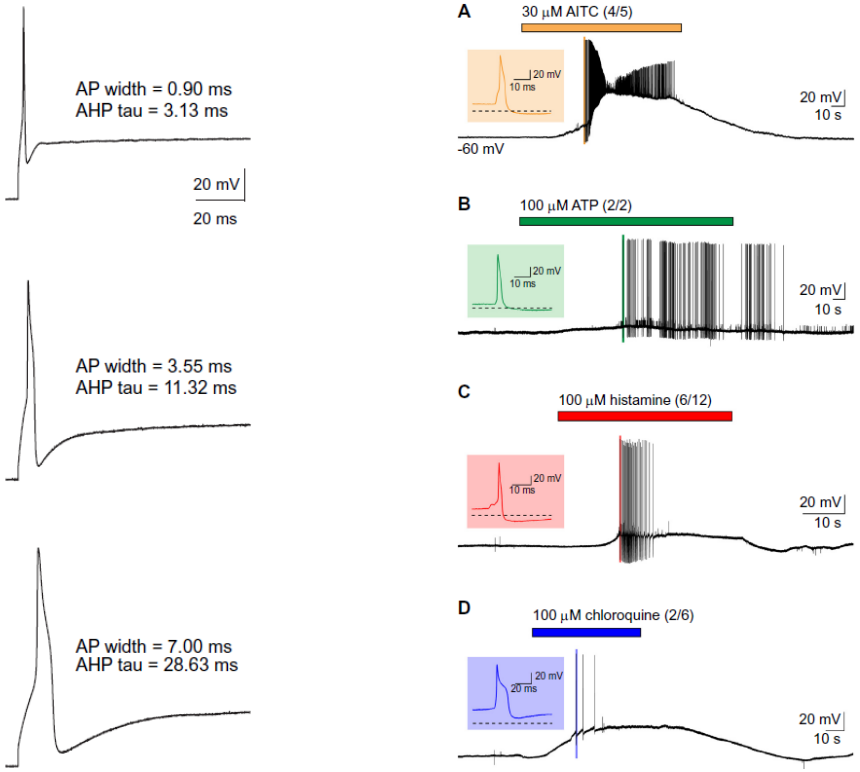
Study of drug action in healthy or pathological states

Reliable assessment of potency to guide first in human dosing

Human Sensory Neurons for Pain Drug Discovery



hDRG Neurons in Culture Exhibit a Stable Phenotype
and Respond to Algogenic and Pruritogenic Agents



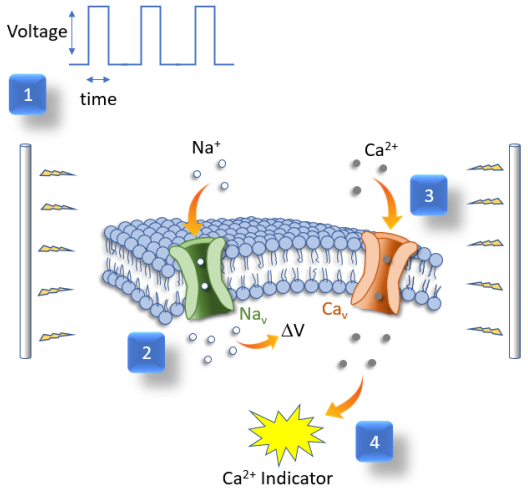
Davidson et al., PAIN (2014)

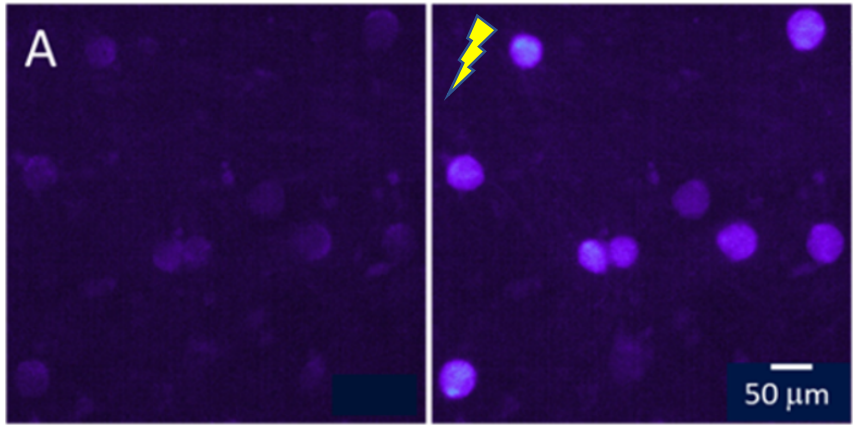
- Amenable to electrophysiology, calcium imaging, electrical field stimulation, gene delivery

Possible to study a variety of targets:

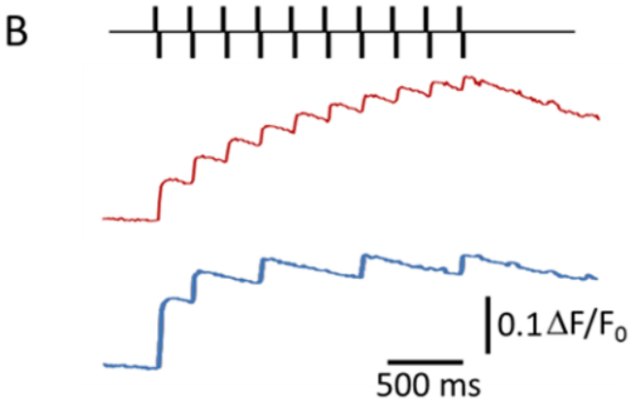
- Voltage-gated Na^+, Ca^{2+}, K^+, Cl^- channels
- TRP channels
- GluR channels, mGluR receptors
- GABA receptors
- Opioid receptors

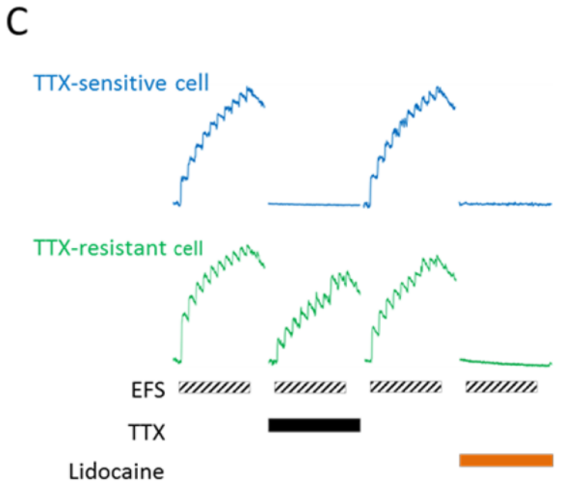
hDRG Functional Profiling in High Throughput Assays

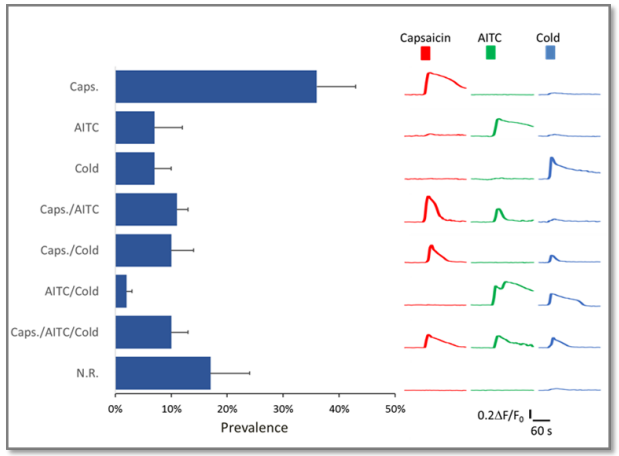




- Parallel interrogation of large neuronal populations
- Allows identification of different neuronal classes

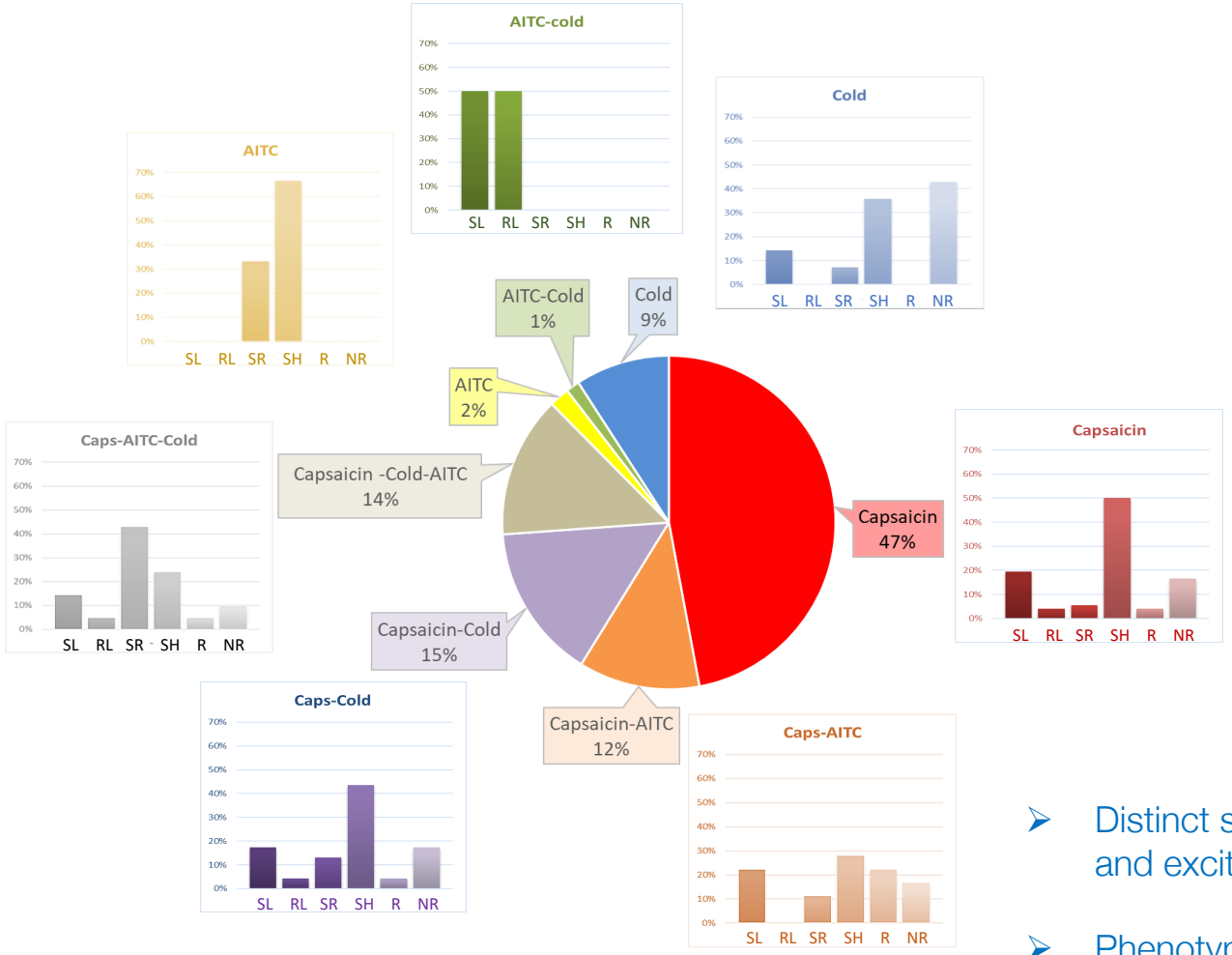






Phenotypic Profiling of hDRG Neurons Based on Responses to EFS and Agonists

Na_v profiles

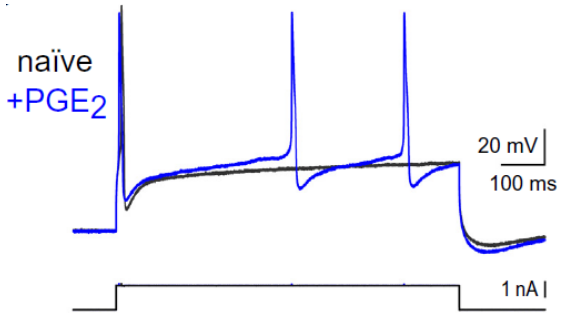


- Distinct sub-populations with defined sensitivity and excitability
- Phenotypes change in pathological states

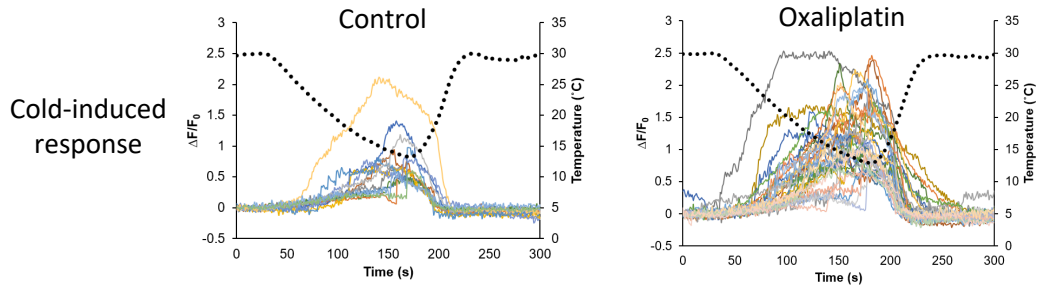
Assessment of Drug Activity in Pathological States

1- In vitro-sensitized hDRG

Inflammation

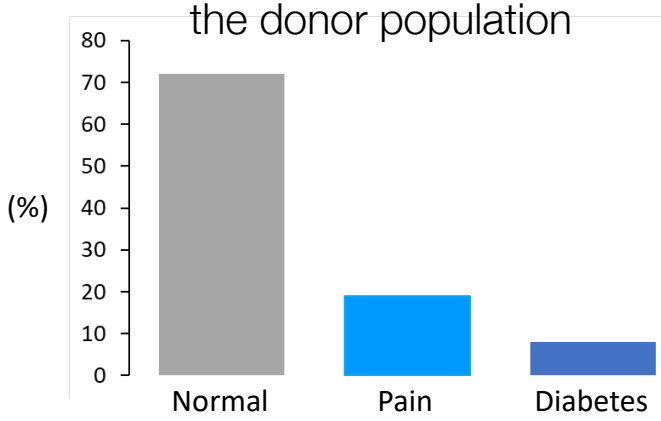


Peripheral neuropathy

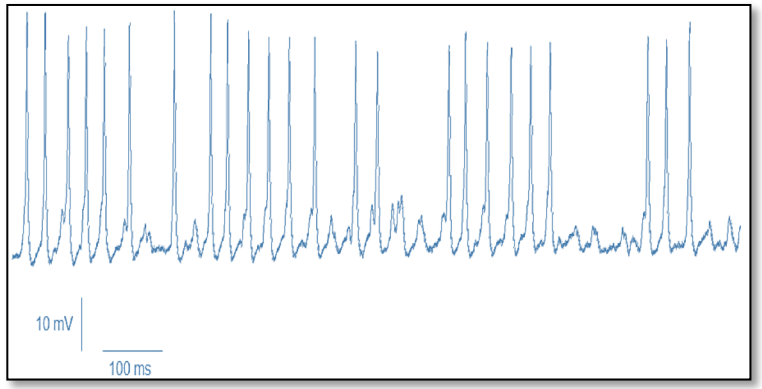


2- Chronic pain donor hDRG

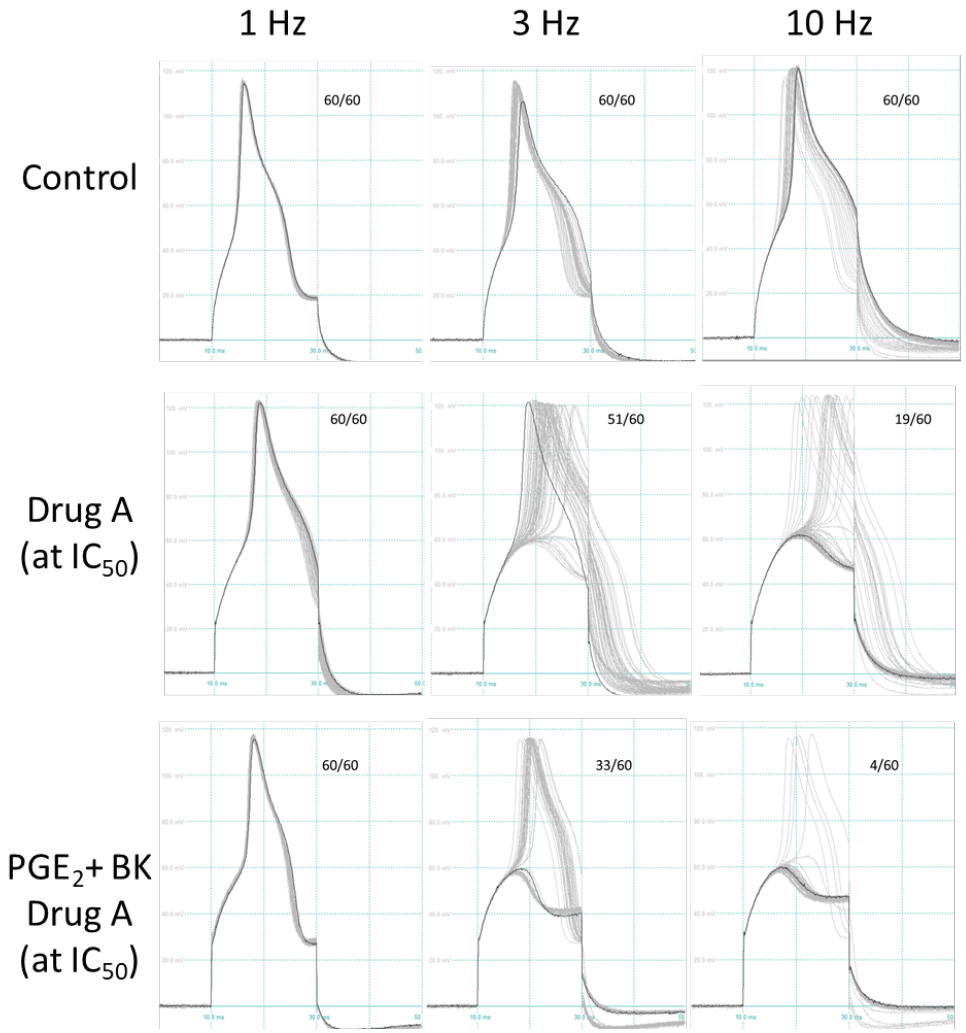
Prevalence of pain cases in the donor population

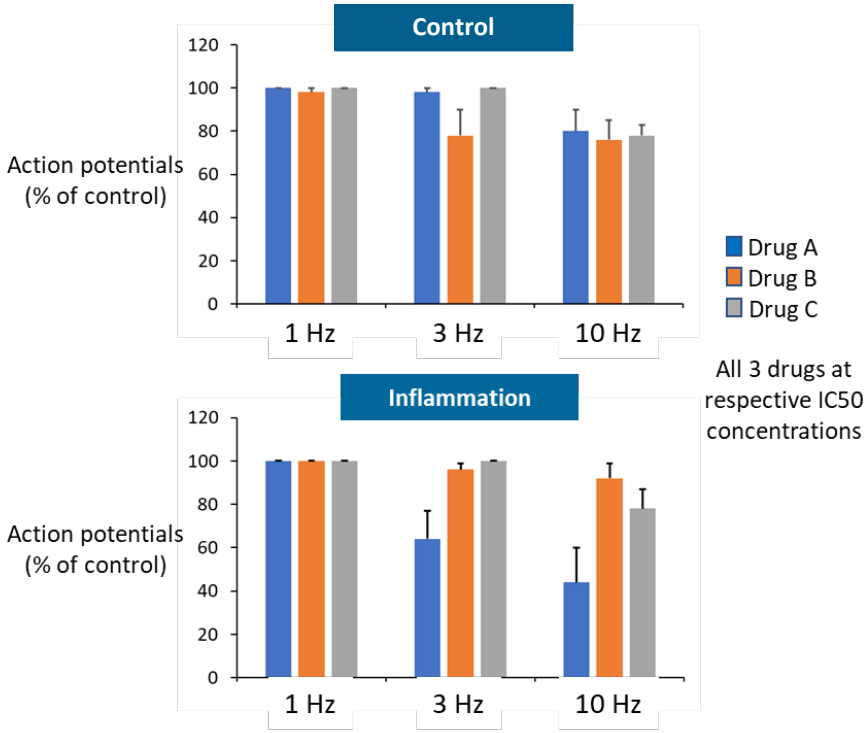


Spontaneous firing in hDRG neuron from chronic pain donor



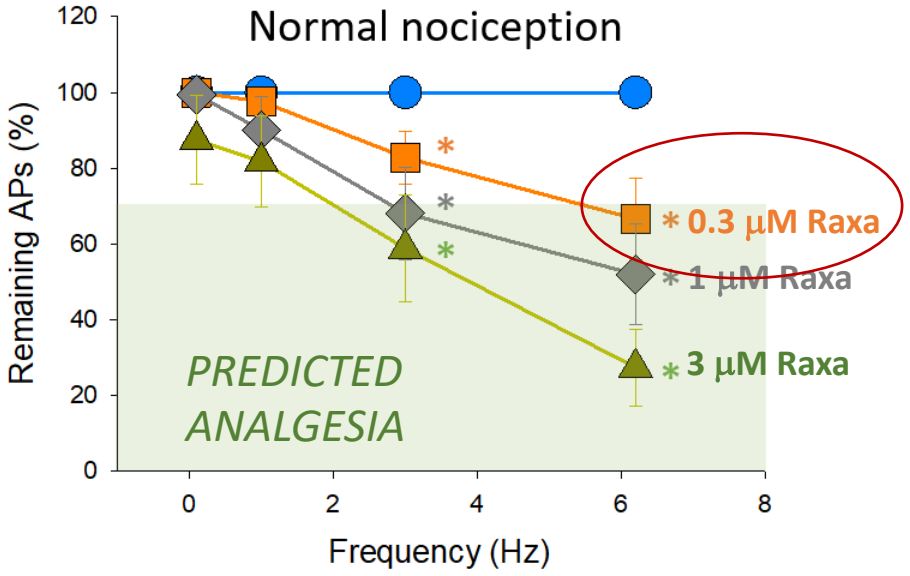
Identification of Na_v Blockers That Inhibit Action Potentials
in Neurons Sensitized With Inflammatory Agents

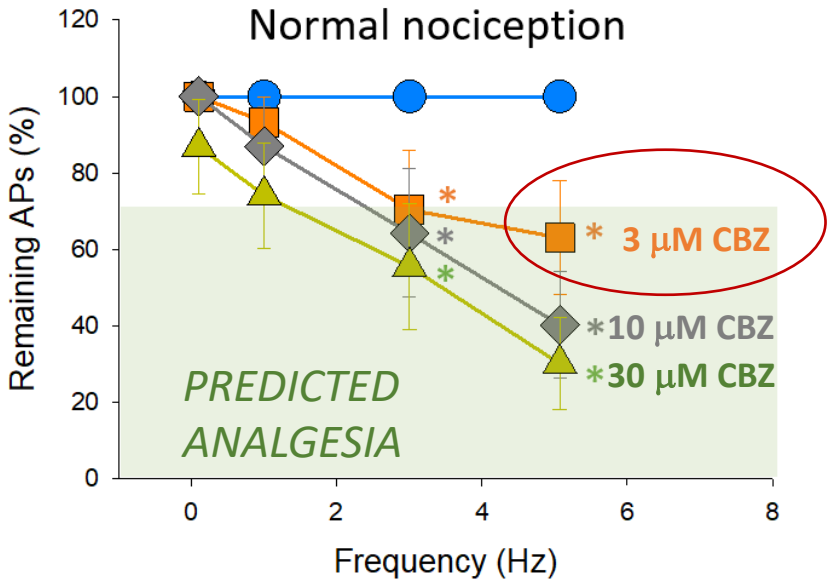




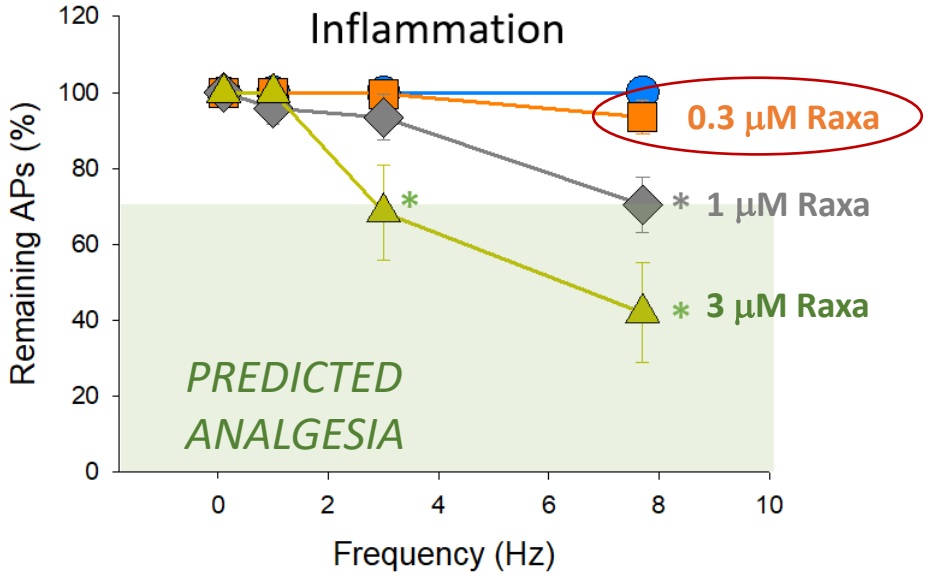
All 3 drugs at respective IC50 concentrations

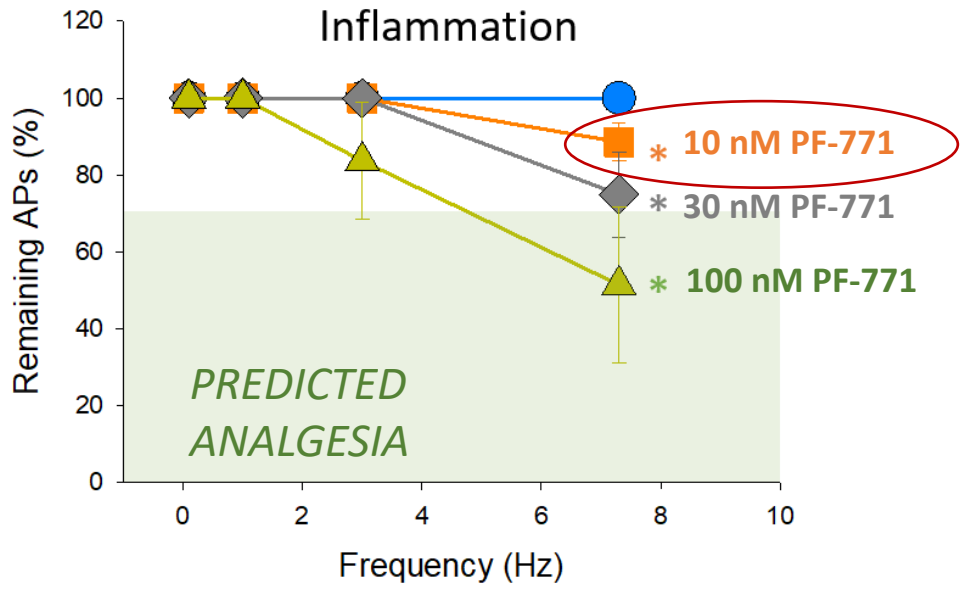
Inhibition of Human Peripheral Neurons' Activity by Raxatrigine and Carbamazepine





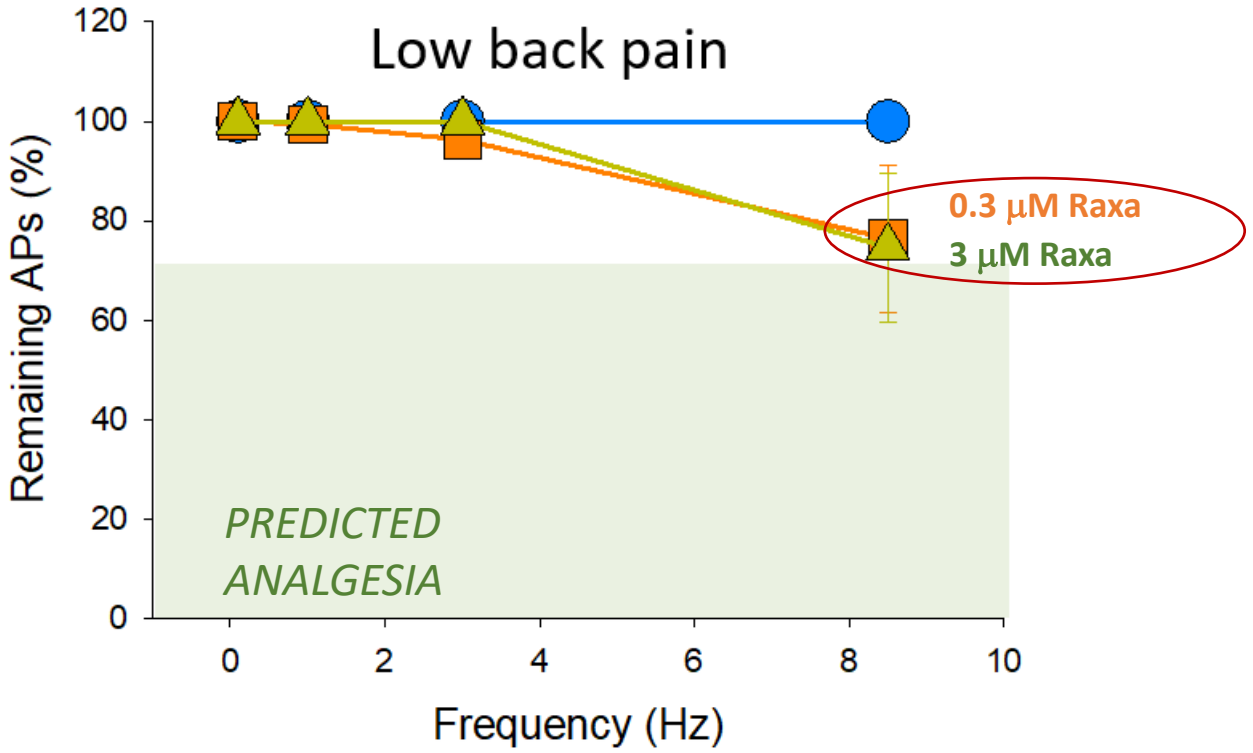
Inhibition of Human Peripheral Neurons' Activity by Raxatrigine and PF-05089771



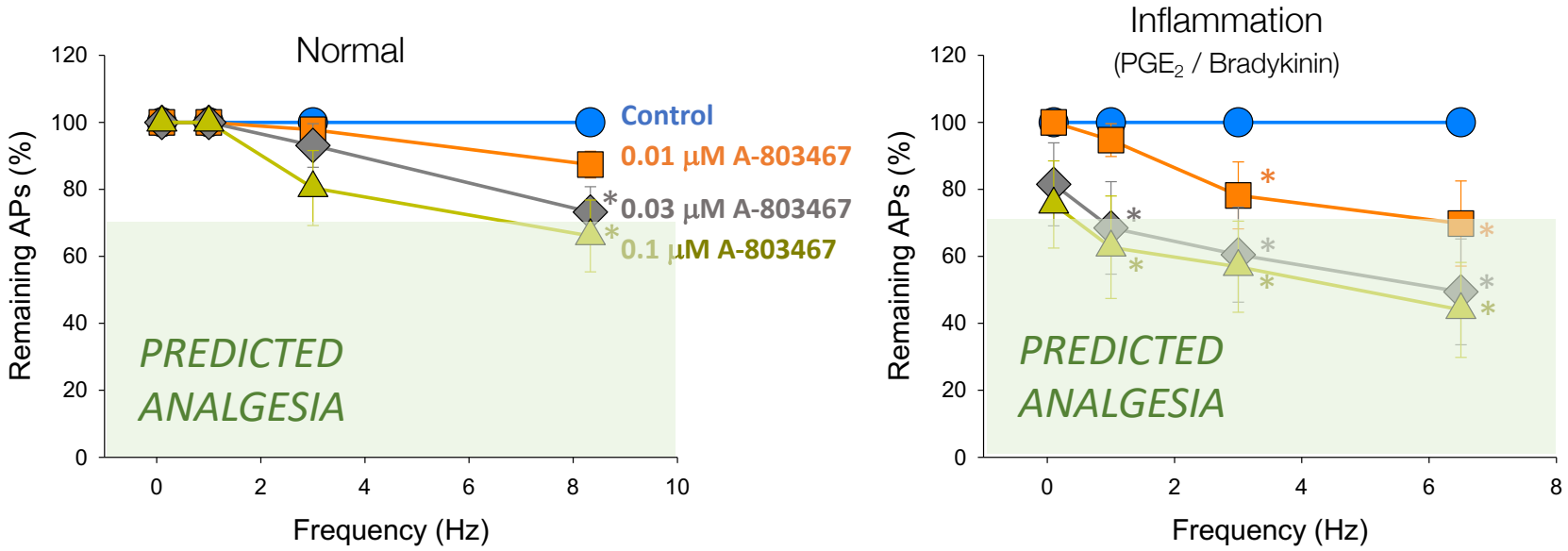


Raxatrigine Fails to Inhibit the Activity of Human DRG Neurons

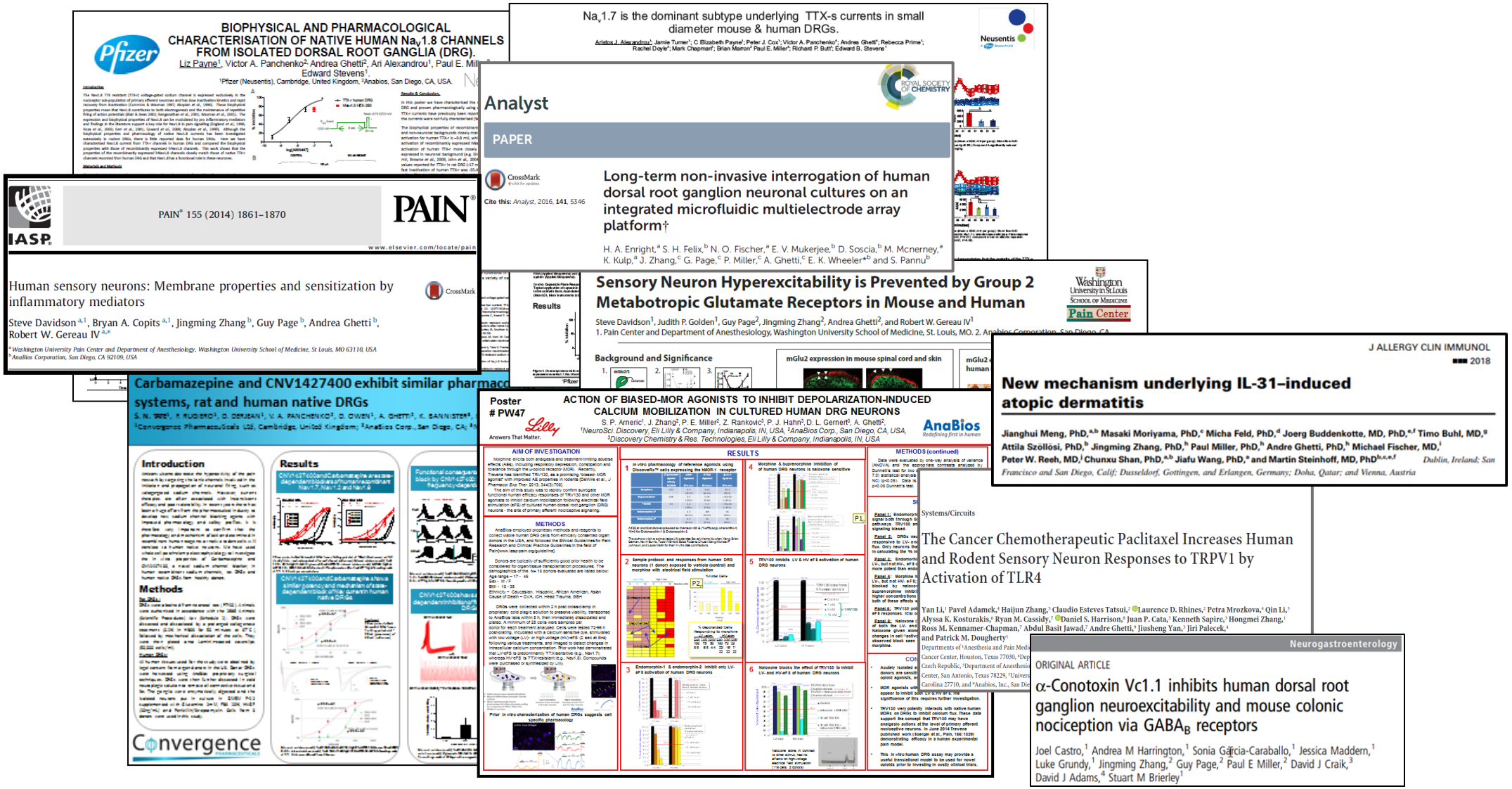
from Low Back Pain Donors



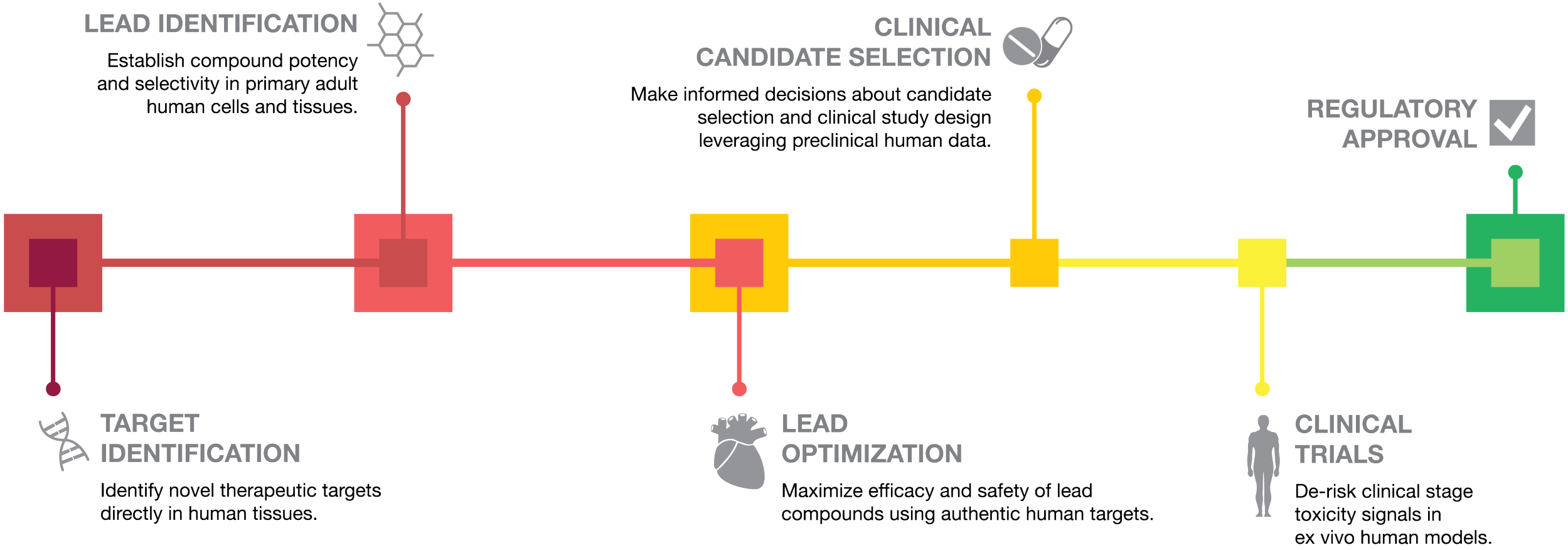
Reference Drug With $Na_v1.8$ activity: A-803467



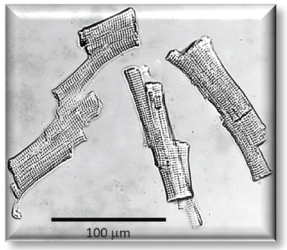
AnaBios' Human-Focused Strategy is Extensively Validated



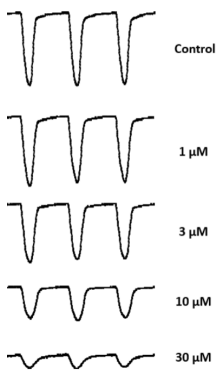
Human Tissues in Drug Discovery

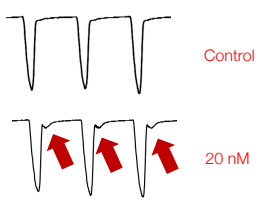


Cardiac Safety Assessment
in Human Heart Ex-Vivo

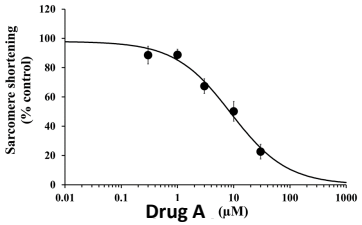


Human adult cardiomyocytes

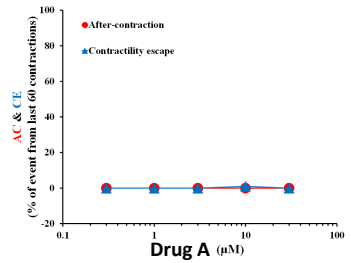




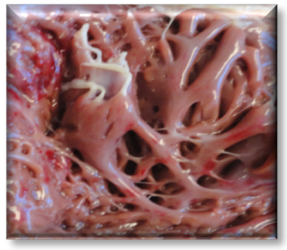
After-contraction pro-arrhythmia marker



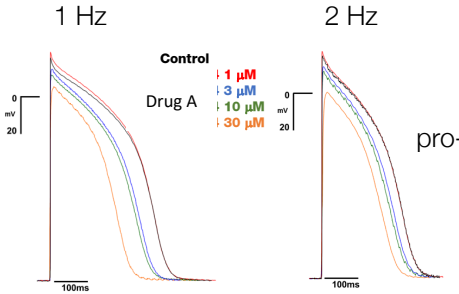
Reduction in cardiomyocyte contractility only at very high concentrations



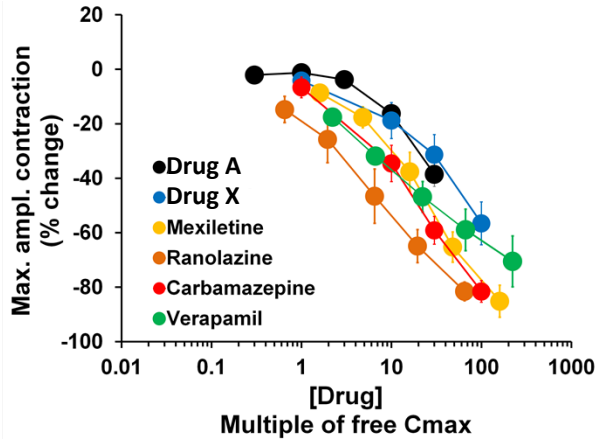
No evidence of drug-induced arrhythmia



Human adult ventricular trabeculae



No evidence of pro-arrhythmia markers up to 30 µM



Cardiac safety margin ~100x of the target effective concentration

Assessment of drug effects in ex-vivo ***human*** models

Study of drug action in the context of **pathological** states

Quantitative assessment of potency