An *Ex Vivo* Human Model of Pain for Enabling Translational Research and Drug Discovery

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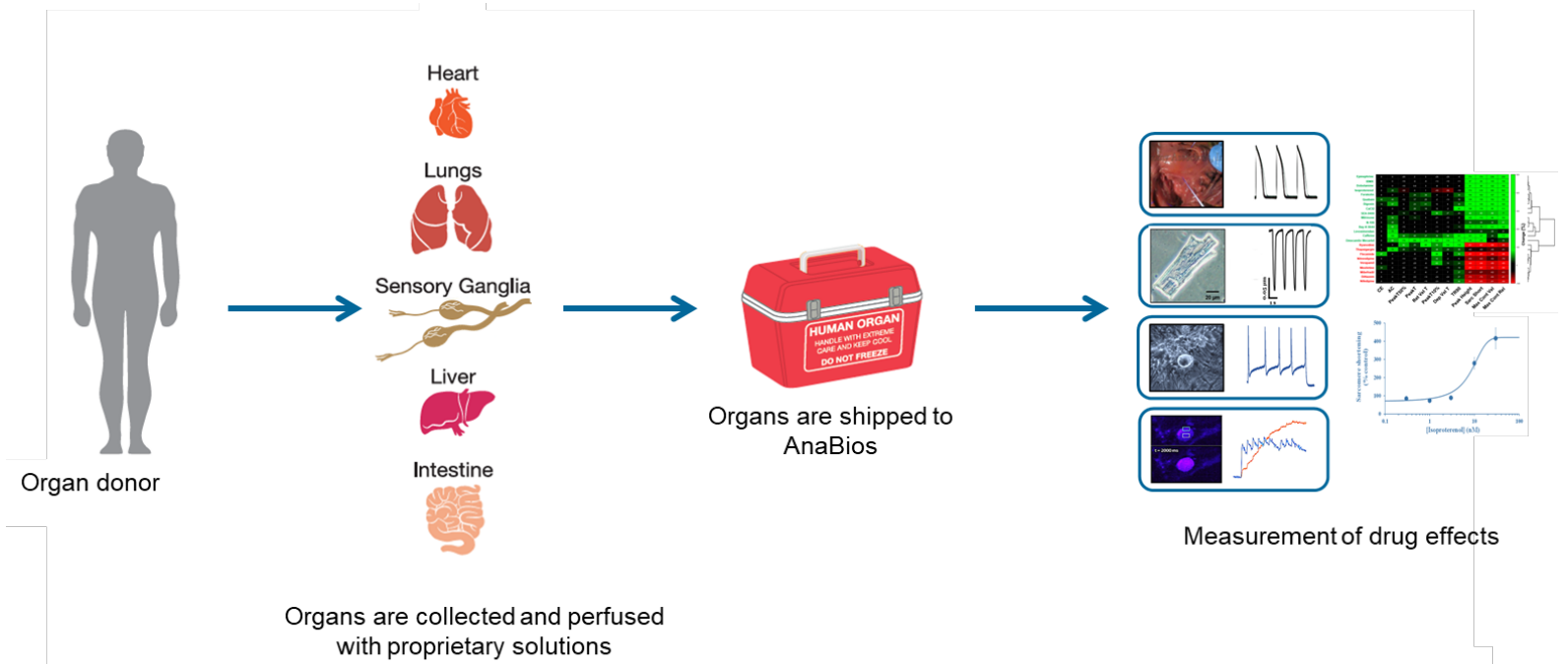
AnaBios studies drug effects directly on

isolated human organs and tissues

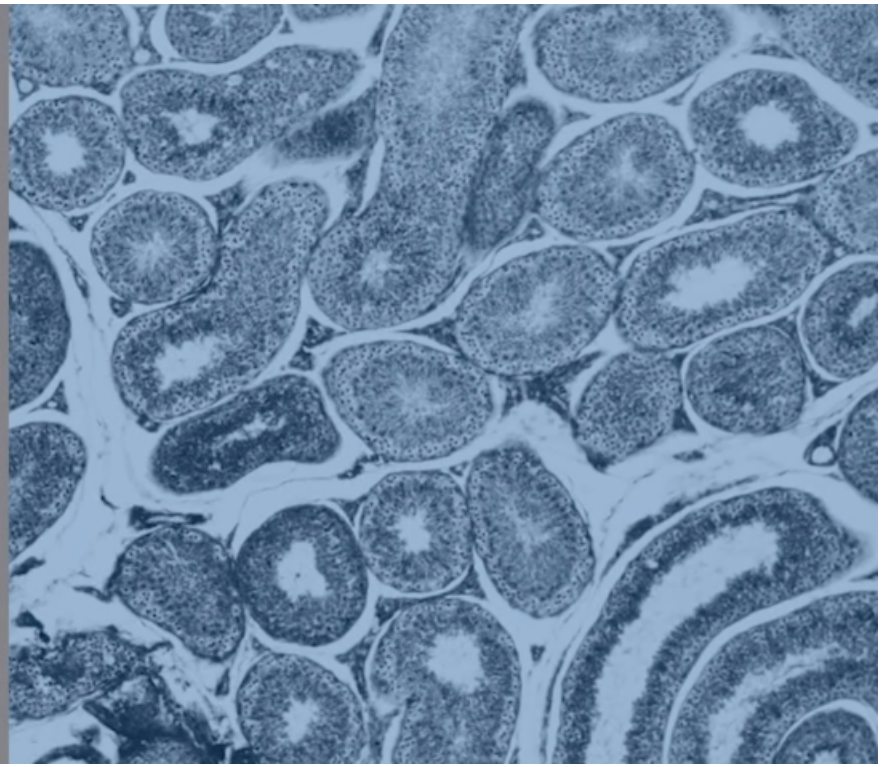
Enabling Drug Discovery in Human Tissues



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

A variety of Tissues are Available From
Healthy or Diseased Donors

- Heart
- DRG
- Spinal Cord
- Liver
- Kidney
- Lung



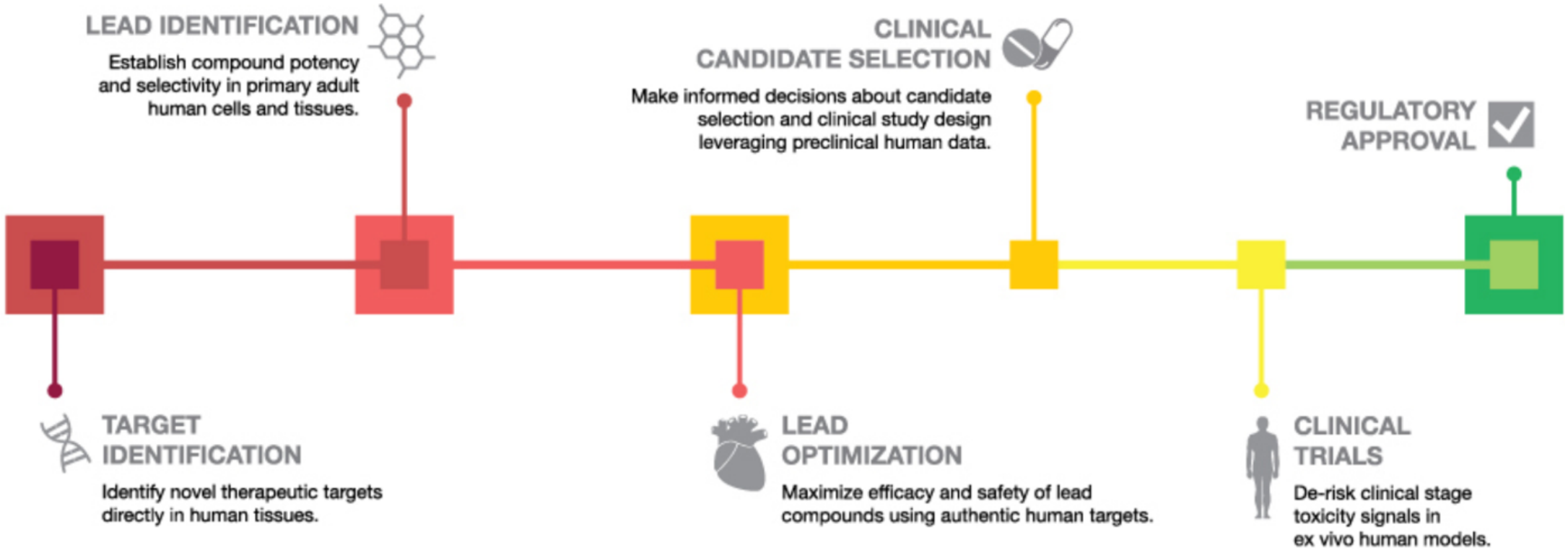
Predictive of clinical outcomes

Lower development risks related to interspecies differences

Study of drug action in healthy or pathological states

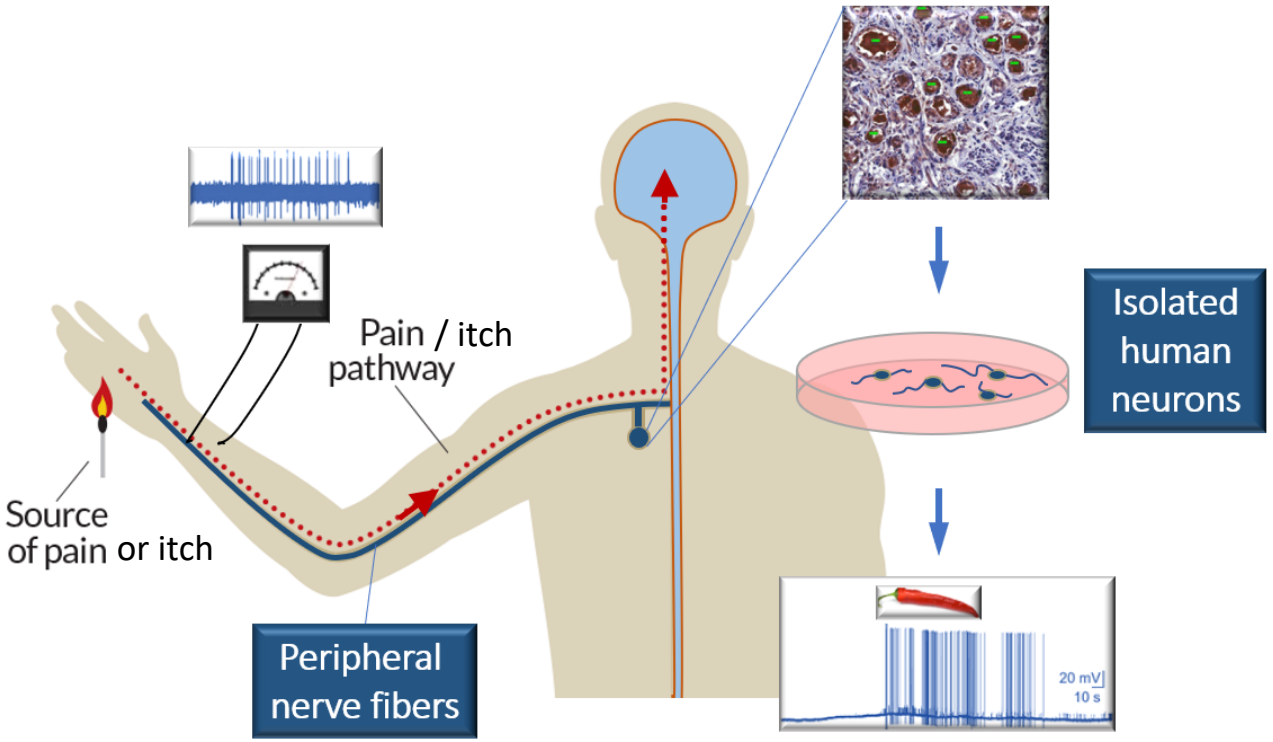
Reliable assessment of potency to guide first in human dosing

Human Tissues in Drug Discovery

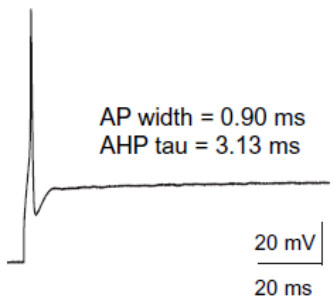


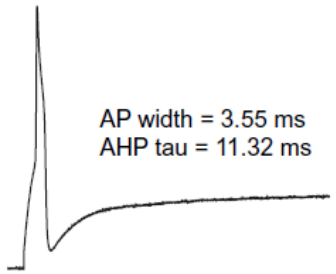
Screening and Profiling of New Potential Analgesics in Human Sensory Neurons

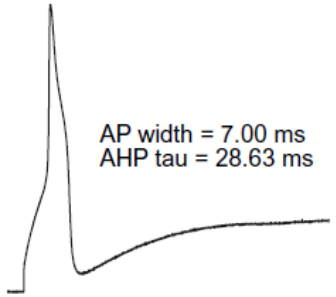
AnaBios Studies the Activation of Peripheral Sensory Neurons in Vitro

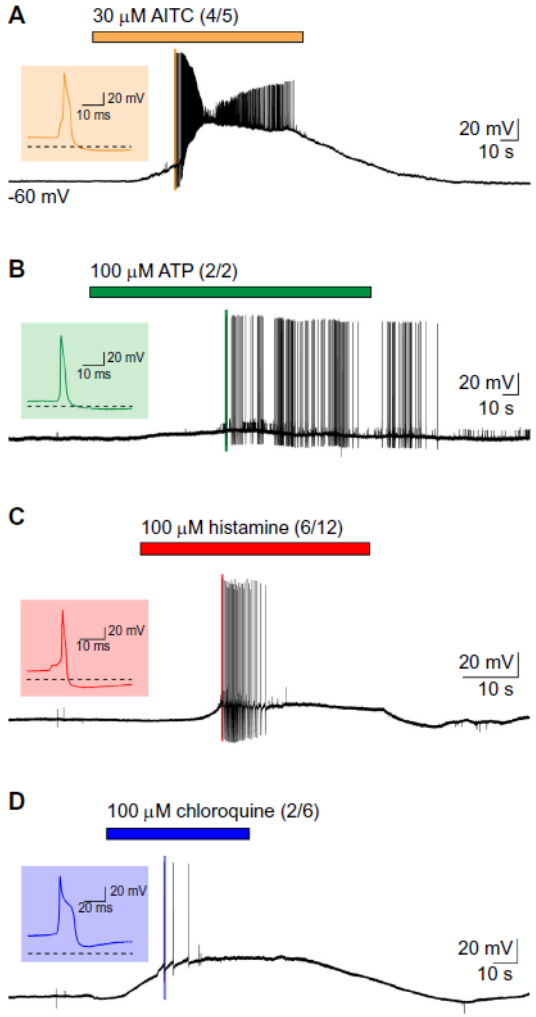


Properties of hDRG Neurons in Culture





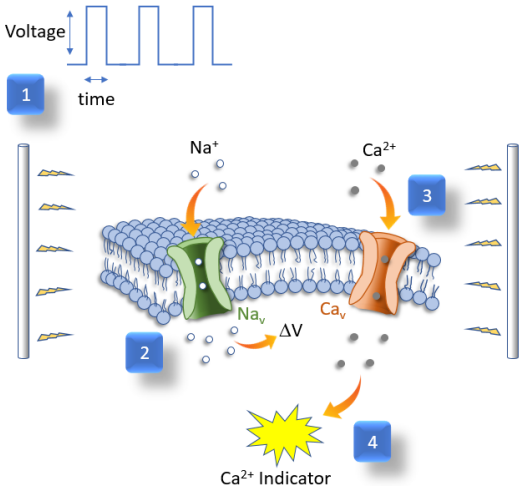


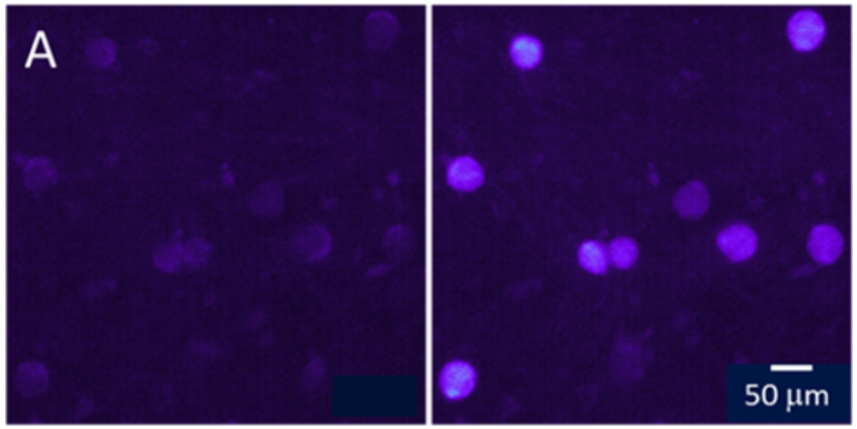


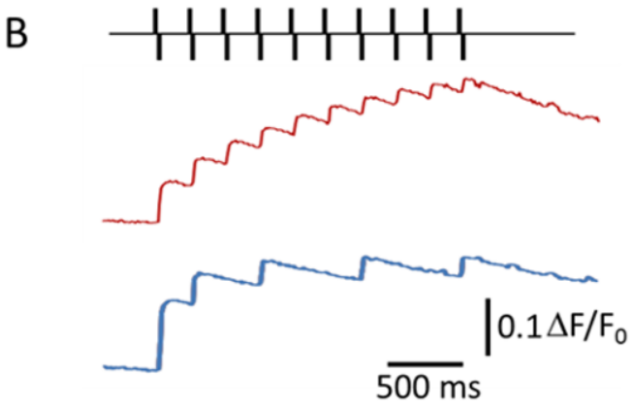
- Exhibit expected biophysical and pharmacological properties
- Responses to nociceptive agents
- Amenable to electrophysiology, calcium imaging, electrical field stimulation, gene delivery
- Useful for studying a variety of targets:
- Voltage gated Na^+, Ca^{2+}, K^+, Cl^- channels
- TRP channels
- GluR channels, mGluR receptors
- GABA receptors
- Opioid receptors

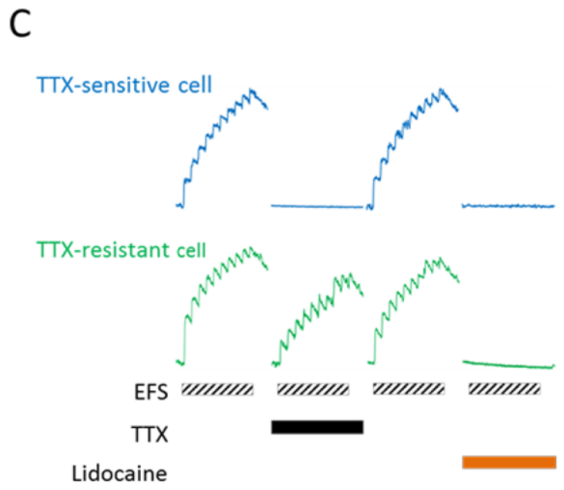
Davidson et al., PAIN (2014)

Screening Platform: hDRG Activation by Electrical Field Stimulation



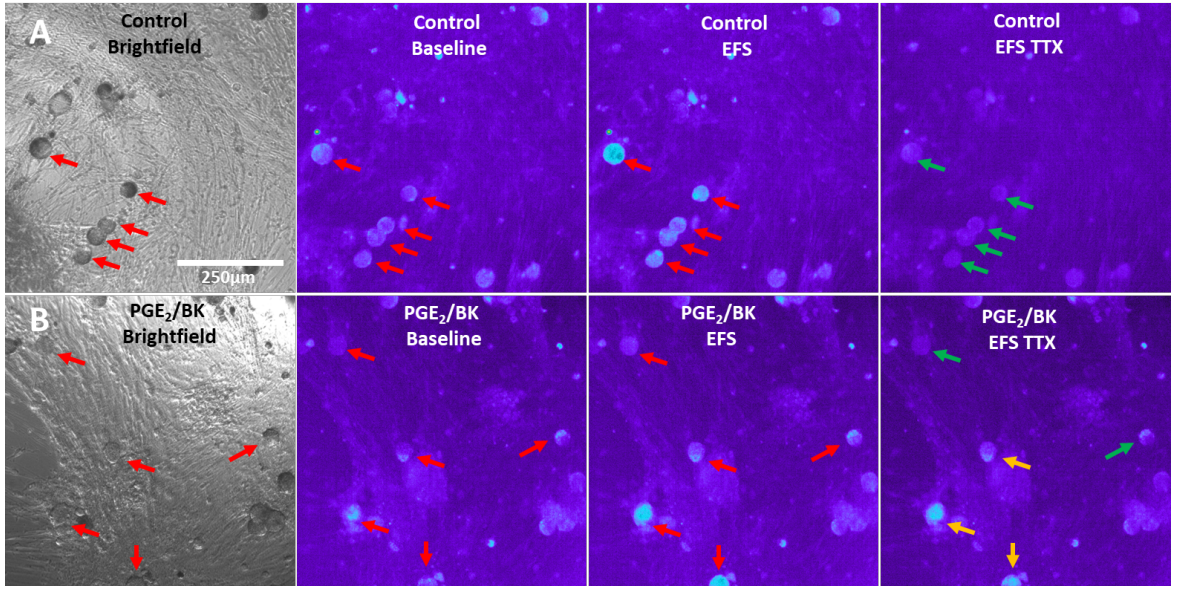


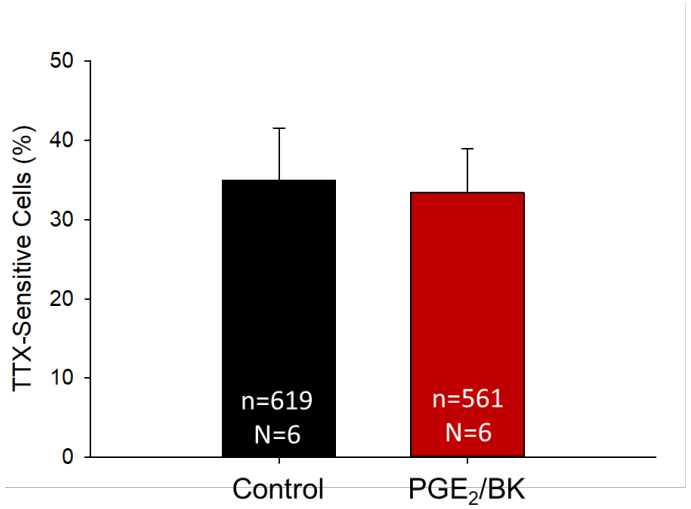


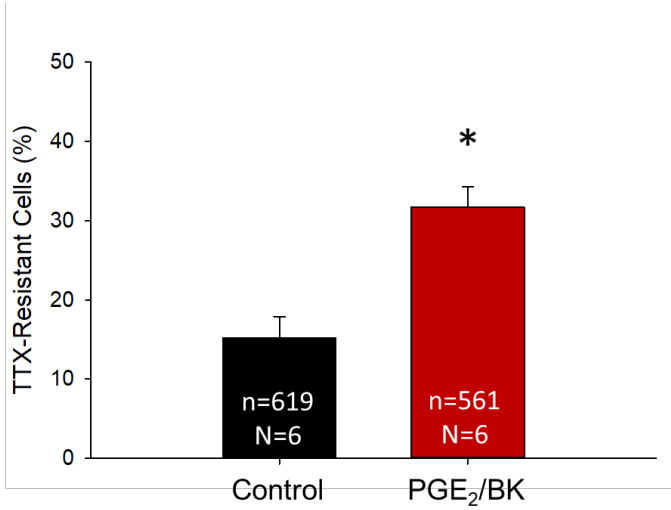


- Parallel interrogation of large neuronal populations comprising diverse phenotypes
- Identification of different neuronal classes
  - Cells expressing TTX_R vs. TTX_S Nav channels

Validation of an inflammatory pain model by Electrical Field Stimulation

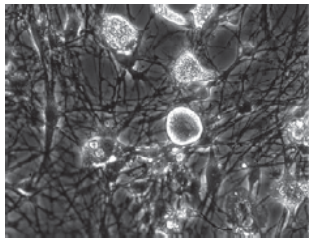


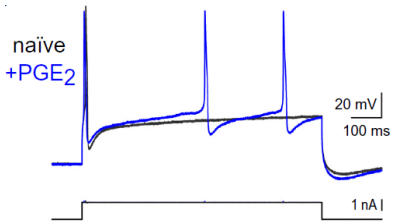




Electrophysiology-based Profiling of Drug Candidates in Human Sensory Neurons

Assessment of Drug Efficacy in Human Target Tissue in Pathological States

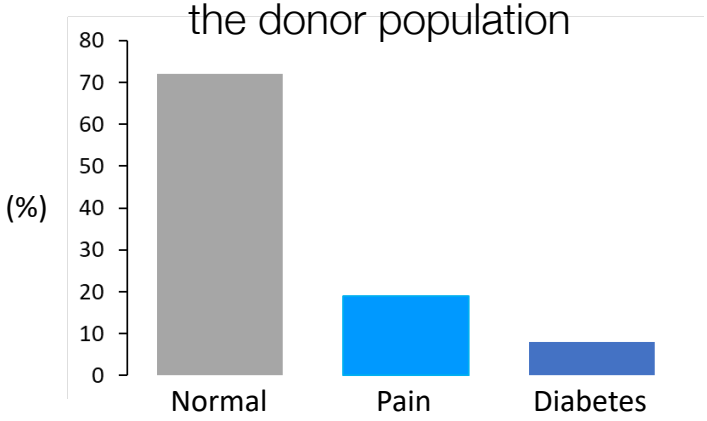




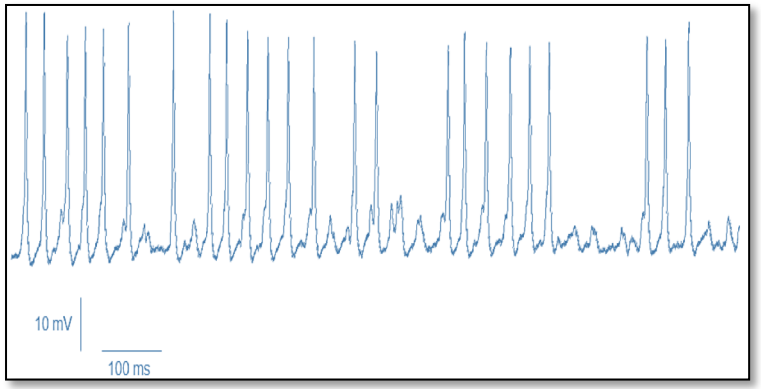
In vitro models of pathological states:

- Inflammation
- Peripheral neuropathy
- Chemotherapy-induced pain

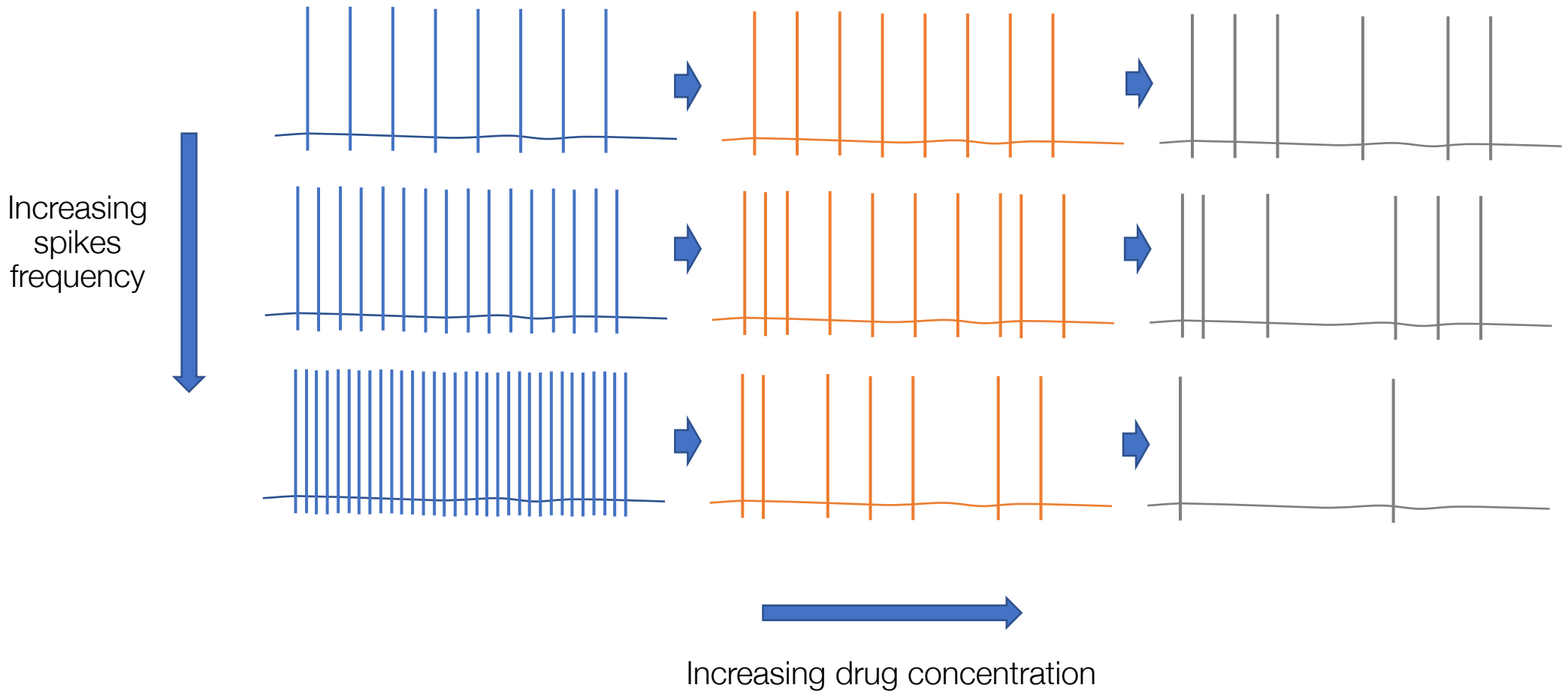
Prevalence of pain cases in the donor population



Spontaneous firing in hDRG neuron from chronic pain donor

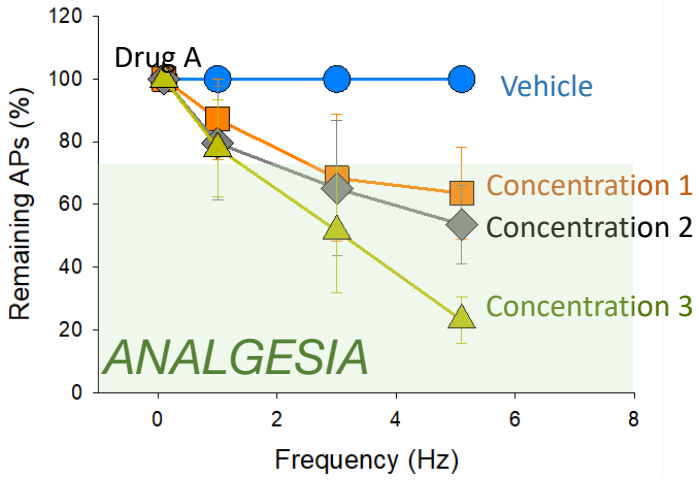


State- and Dose-dependent Inhibition of Neuronal Activity



Measuring Drug Effects on Human Nociceptor Action Potentials

- Human DRG neurons are patched in whole cell mode and V_m is recorded using current clamp
- Trains of 120 action potentials are induced at different frequencies (0.1 Hz, 1 Hz, 3Hz and 10Hz)
- For each frequency 3 concentrations of the test article are applied
- The fraction of remaining action potentials is calculated for each stimulation frequency and drug concentration

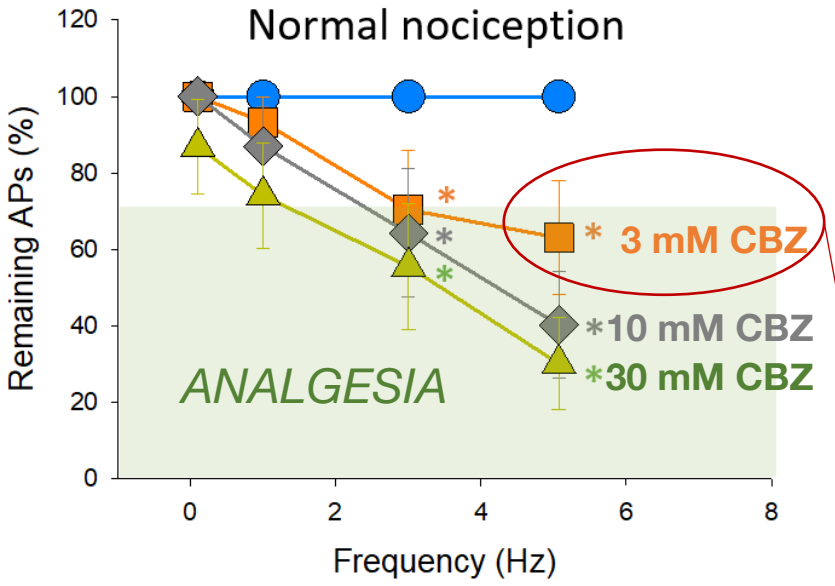


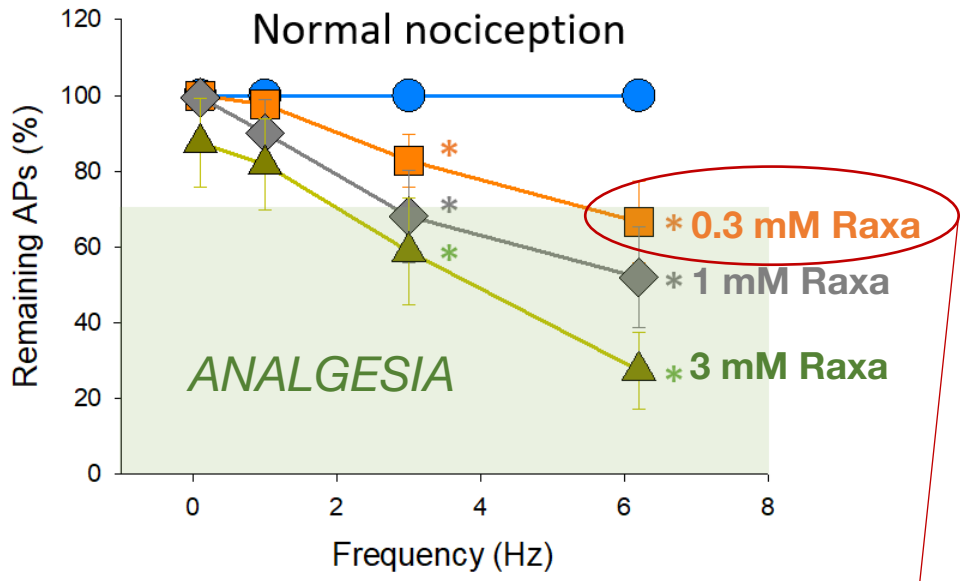
- ***Physiological response***
- ***Quantitative assessment of potency***
- ***Use dependence***

Examples and Case Studies: 1

Pain Drug Discovery

Inhibition of Human Peripheral Neurons' Activity by Carbamazepine and Raxatrigine





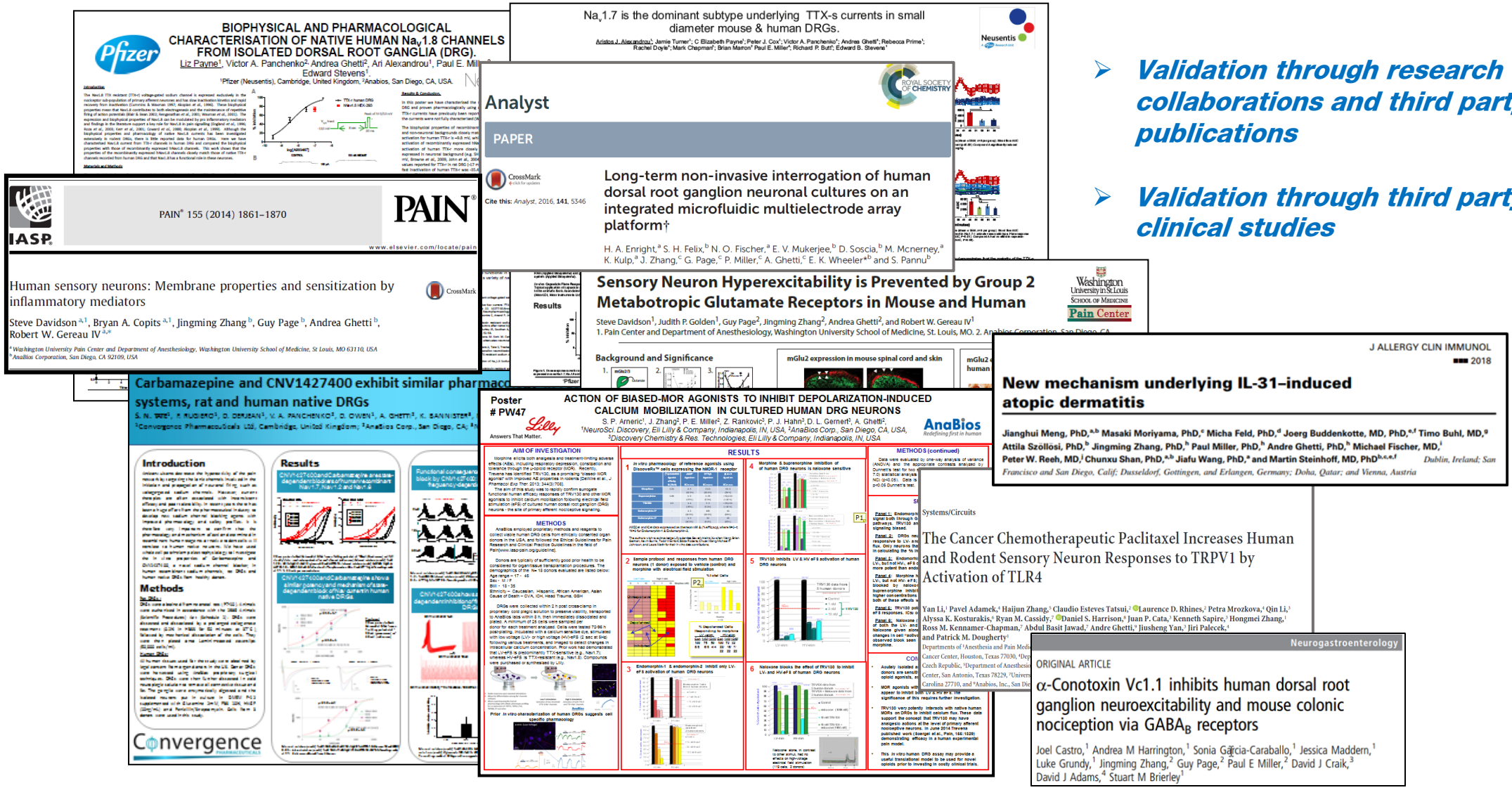
Human neuron-based assay can explain the analgesic effect of Carbamazepine and Raxatrigine in trigeminal neuralgia

Clinical outcome of
PF-771, Raxatrigine and Carbamazepine

DrugA	PF-05089771	BIIB074 (Raxatrigine)	Carbamazepine
Selectivity	Nav1.7	Nav1.7> other Nav NOT Nav1.8	All Nav
Clinical outcome	Post-surgical pain: ✗ Diabetic neuropathy: ✗	Trigeminal neuralgia: ✓ Low back pain: ✗	Trigeminal neuralgia: ✓

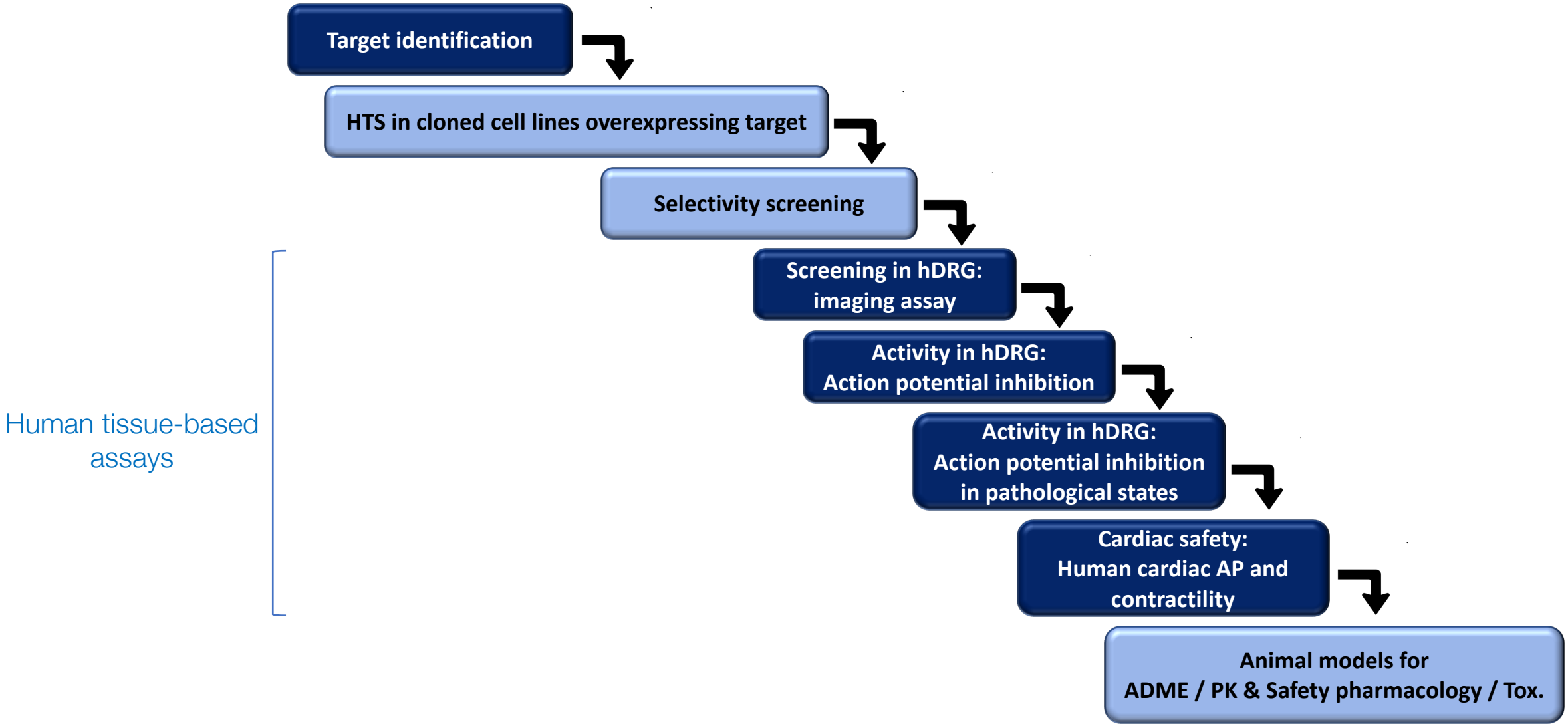
- Predictive outcomes using our human-based assay

AnaBios' Human-Focused Strategy is Extensively Validated



- ***Validation through research collaborations and third party publications***
- ***Validation through third party successful clinical studies***

AnaBios' Human-Focused Strategy for Pain Drug Discovery



Assessment of drug effects in *ex vivo* human models

Study of drug action in the context of pathological states

Bypass cross-species differences

Measure drug effects and potency across authentic human neuronal populations

Maximize opportunities for successful translation

An *ex vivo* human model of pain for enabling translational research and drug discovery

Thank You