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GLOBAL ANNUAL MEETING
SAN DIEGO | JUNE 23-27

Novel Translational Strategies for Drug Discovery

Andre Ghetti, PhD

Chief Executive Officer
AnaBios

AndrePGhetti



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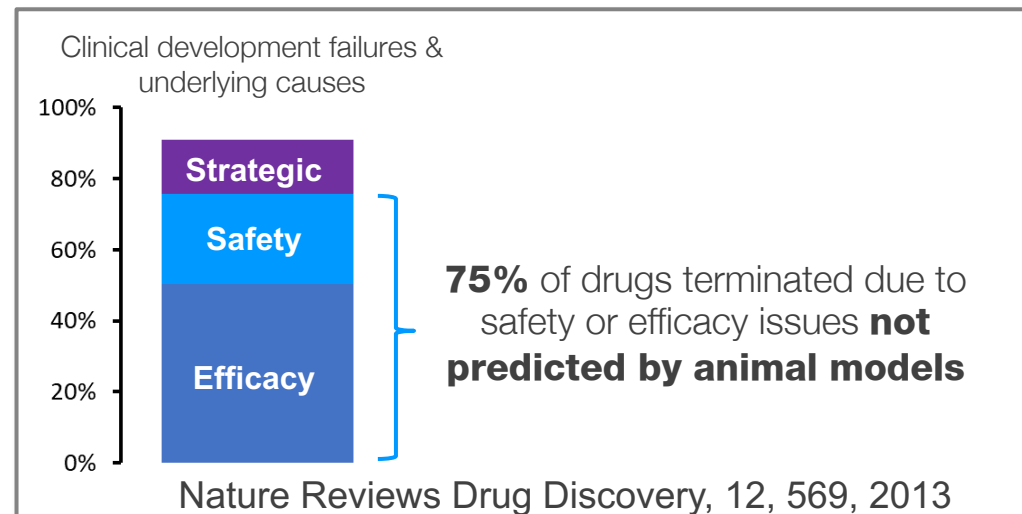
The Translational Challenge in Drug Discovery



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Clinical trial
failure rate >90%



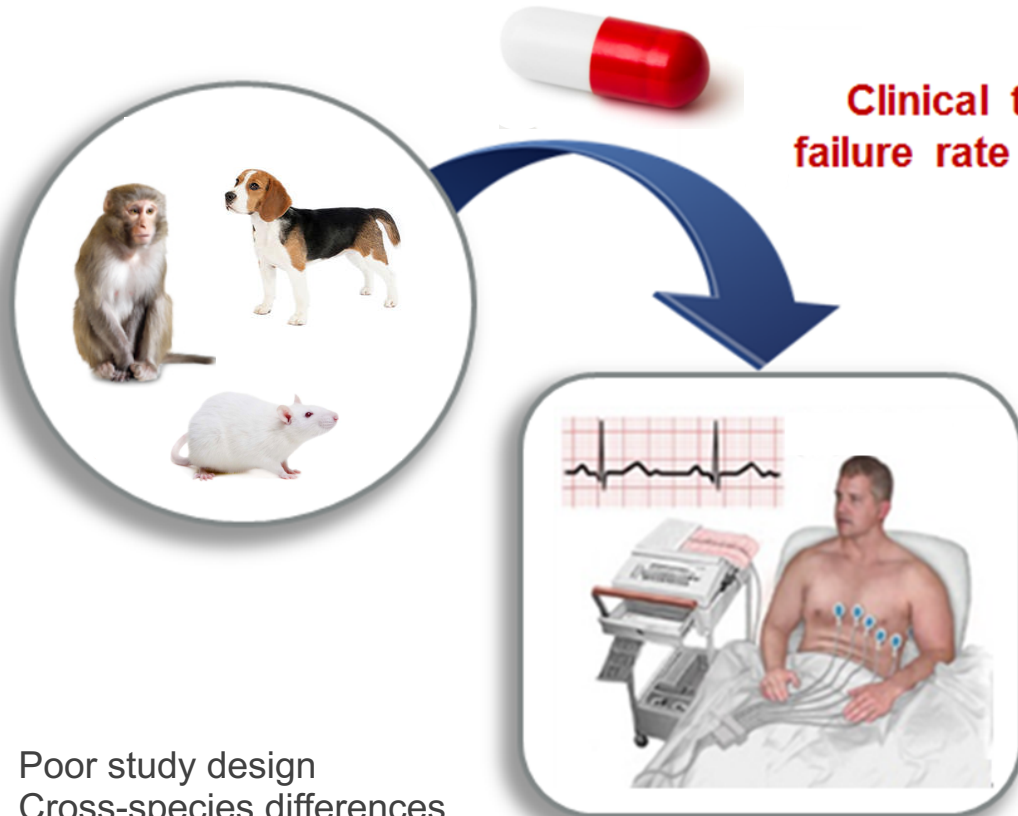
The Translational Challenge in Drug Discovery



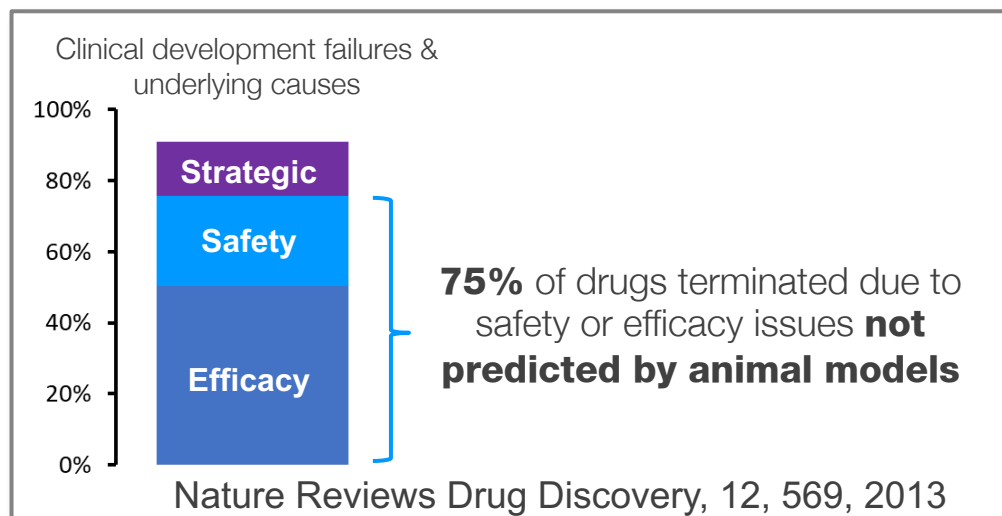
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Clinical trial
failure rate >90%



- Poor study design
- Cross-species differences
- Genetic uniformity of models
- Heterogeneity of patient population
- Poor understanding of disease mechanism



The Pain Patient Population is Heterogeneous

Sensory manifestation

Pain condition

Sensory loss > Thermal hyperalgesia >> Mechanical hyperalgesia

Thermal hyperalgesia > Mechanical hyperalgesia > Sensory loss

Sensory loss = Thermal hyperalgesia >> Mechanical hyperalgesia

Mechanical hyperalgesia > Thermal hyperalgesia > Sensory loss

Postoperative
Cancer
Renal colic
Trigeminal neuralgia
Child birth/labour
Mixed neuropathic
Osteoarthritis
Abdominal pain
Burn injury
Phantom limb
Postsurgical cancer pain
Trauma
Musculoskeletal (Low back/Neck)
Diabetic neuropathy (PDN)
Fibromyalgia
Acute migraine
Postherpetic neuralgia (PHN)
Central neuropathic
Chemotherapy induced
Dysmenorrhoea
Perioperative
Temporomandibular joint disease
Atypical facial pain
Inflammatory arthritis
Irritable bowel syndrome
Spinal cord / Nerve injury
Tension type headache
HIV related
Endometriosis
Herpes zoster infection
Myocardial infarction
Postmastectomy pain
Sickle cell disease
Somatoform pain disorders
Burning mouth syndrome
Pain-related funct. GI disorders
Intrauterine devices

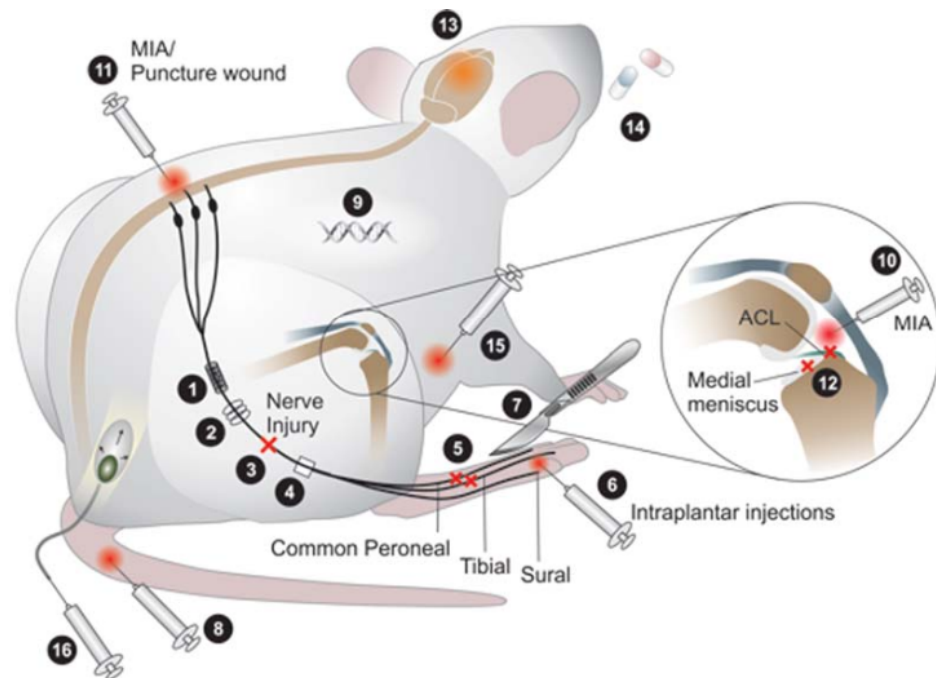
Baron et al., PAIN (2017)



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Unclear How Rodent Pain Models Map on the Diversity of Human Pain Patient Population



- 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



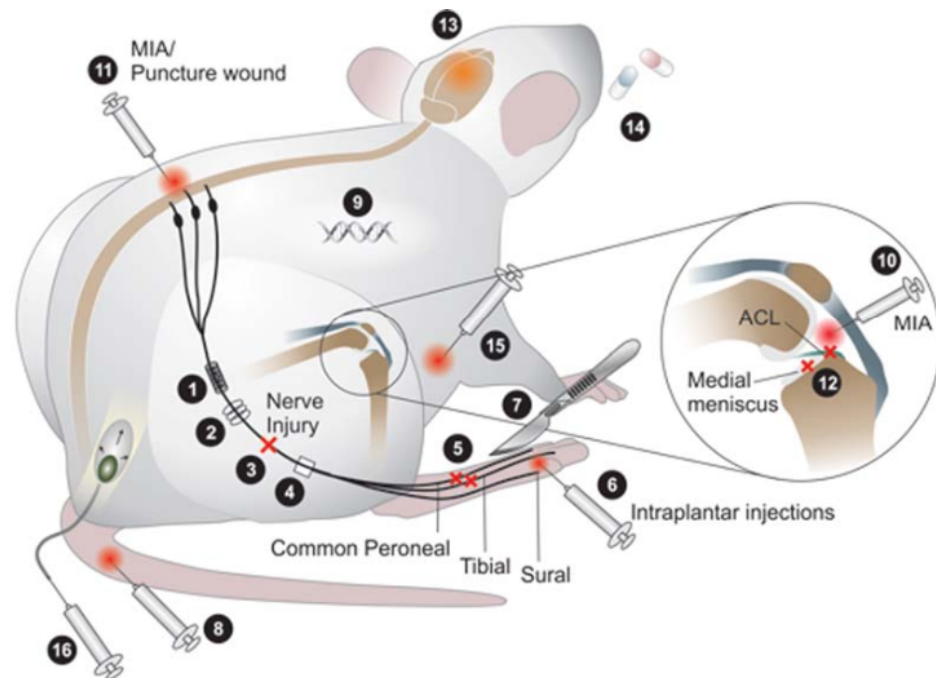
Postoperative
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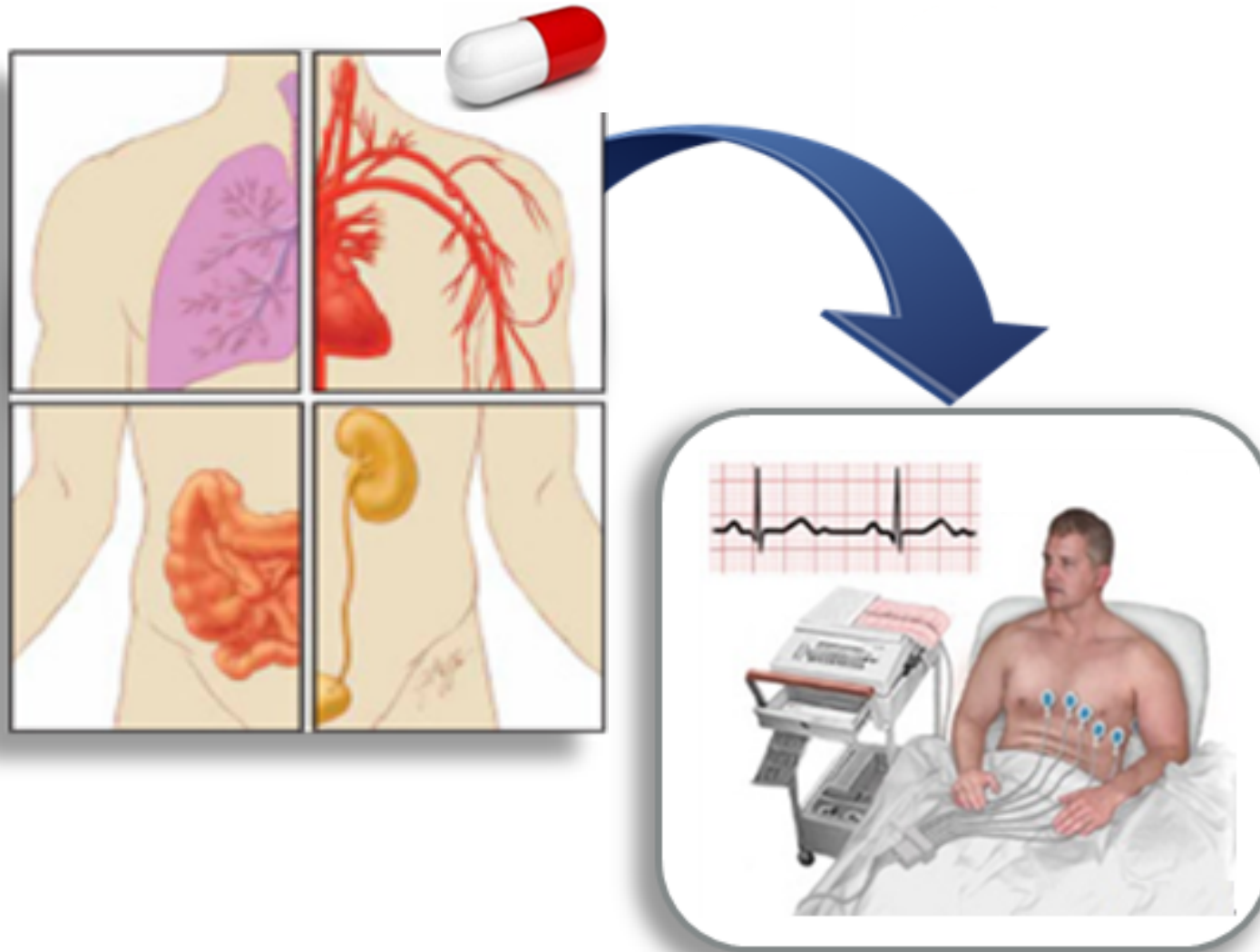
Rodent models do not help in matching a specific drug with the appropriate indication.



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



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Human Primary Hepatocytes in Drug Discovery



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Acknowledgement of the species differences in the DMPK profile of molecules

Hucker HB. Species differences in drug metabolism.
Annu Review Pharmacology. 1970;10:99-118

The use of human microsomes and hepatocytes is introduced

Houston JB. Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance.
Biochem Pharmacol. 1994;47(9):1469-1479.

Reduction of Ph-1 attrition due to issues related to pharmacokinetics or bioavailability

Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov.* 2004;3(8):711-715.

Drug Discovery Using Human Tissue from Disease Donors: Cystic Fibrosis Case Study



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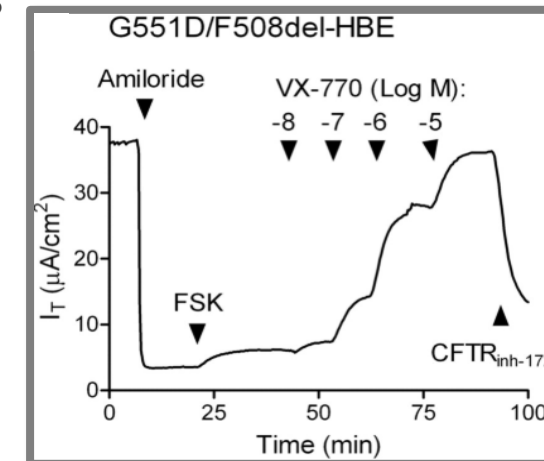
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Kalydeco for Cystic Fibrosis

- Genetic defect in CFTR chloride channel
- No relevant animal model
- Cultured bronchial epithelia isolated from human tissue
- Differentiated human epithelia show the same defective ion transport as observed in vivo
- Used as the key pharmacology model for Vertex CFTR modulators



Van Goor et al. (2006)





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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

Key Challenges of Human Tissue-Based Research

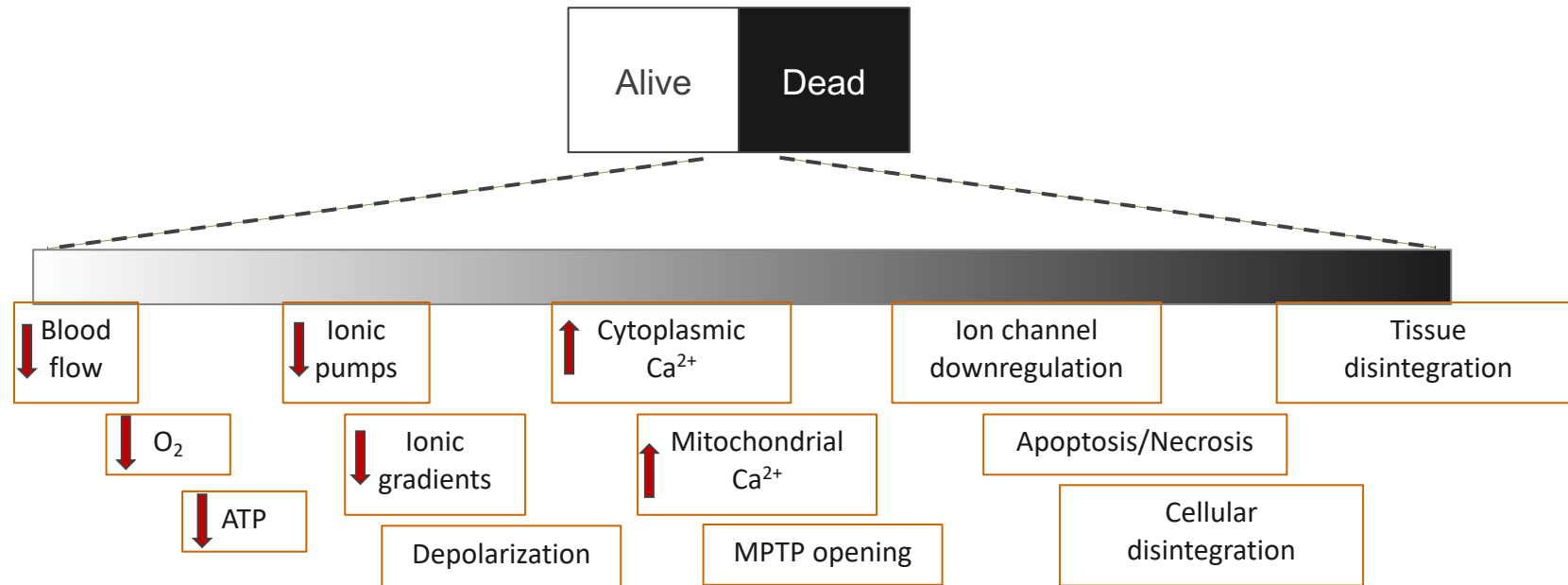
- *Viability*
 - *Functional assessment of drug effect*
 - *Data quality & reliability*
- *Velocity*
 - *Access*
 - *Scalability*
- *Variability*
 - *Recovery methods and timeline*
 - *Inter-donor variability*



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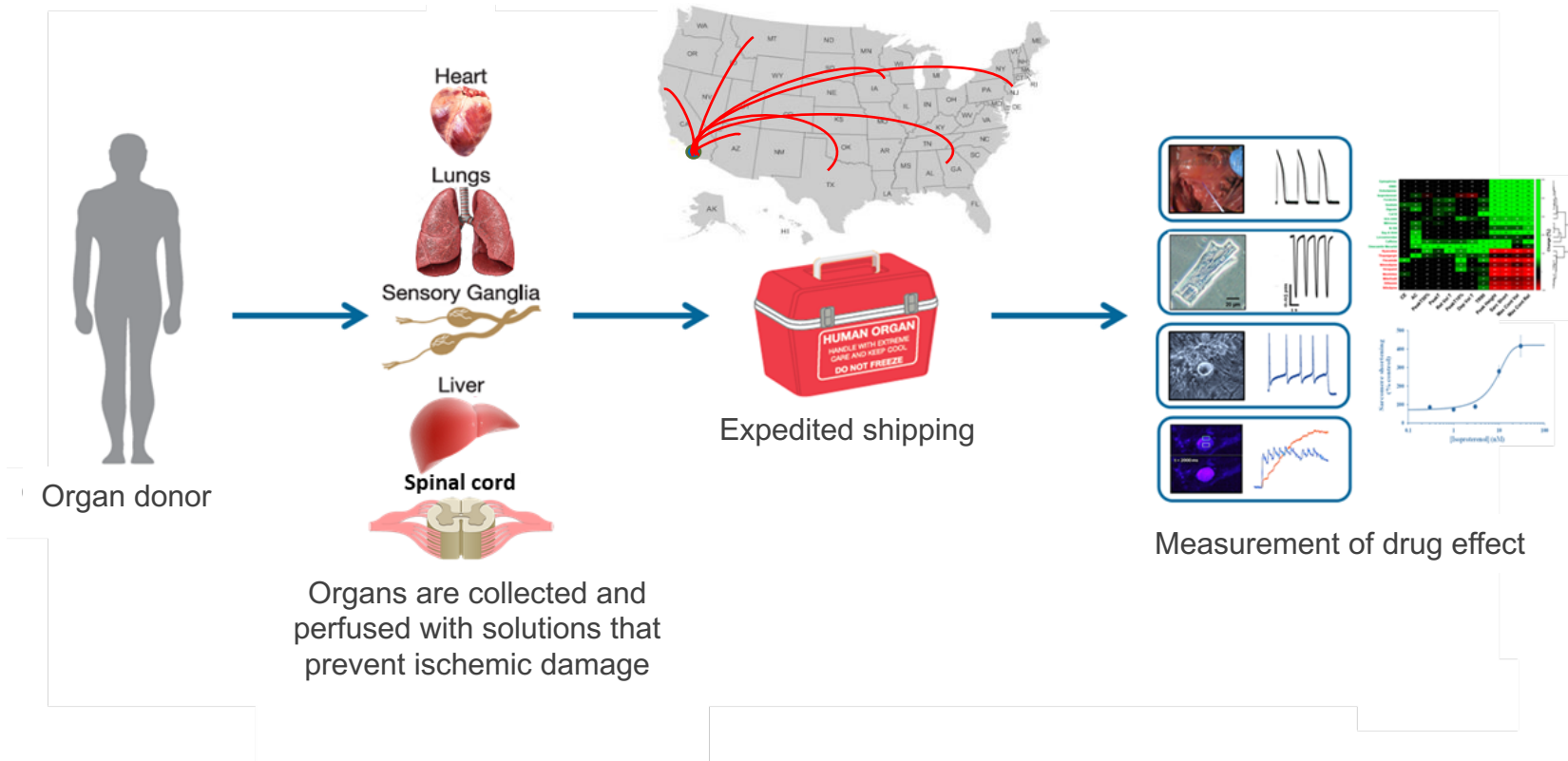
Cellular and Tissue Loss of Function is Process



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Enabling Drug Discovery in Human Tissues



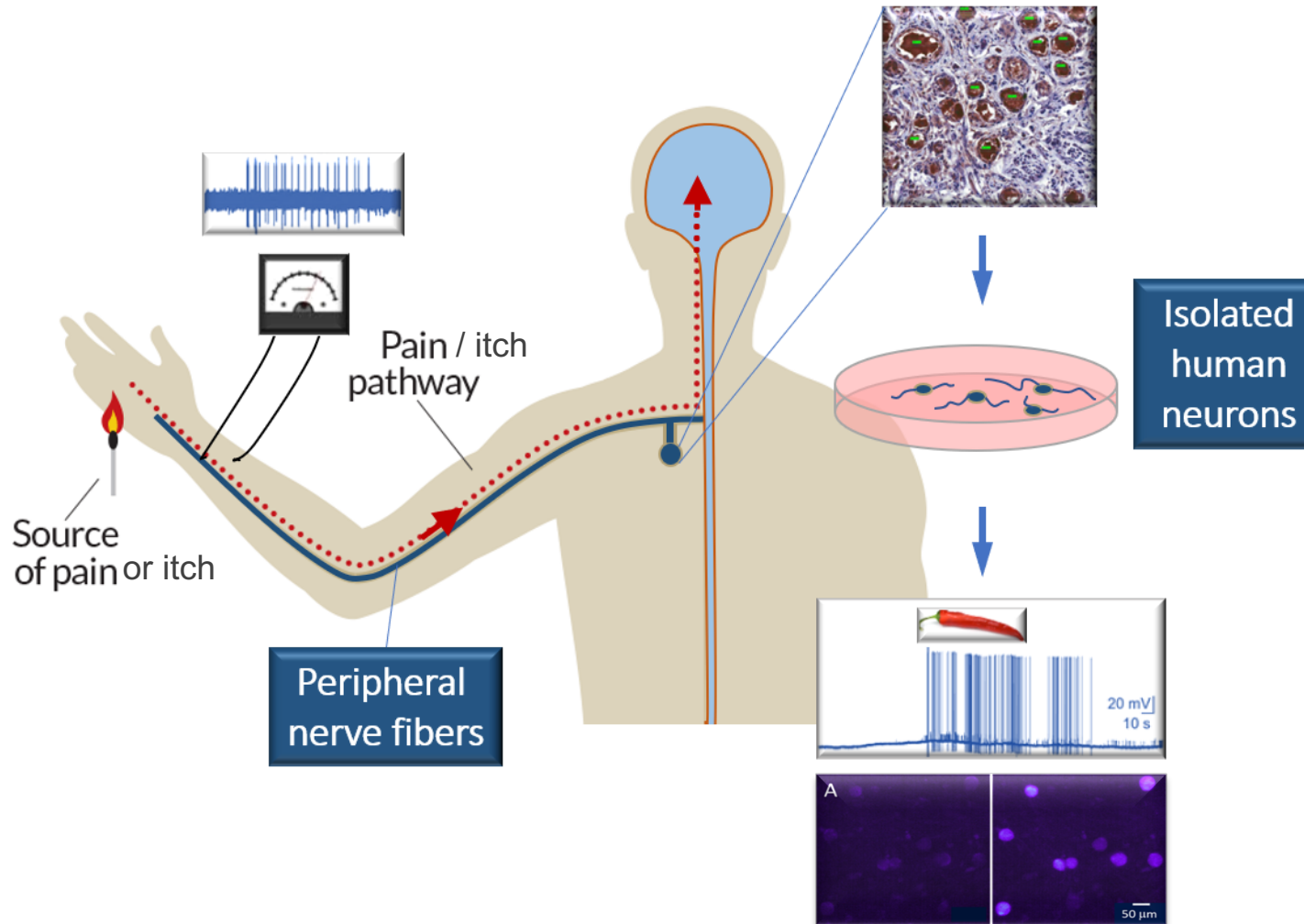
- ***Method standardization***
- ***Prevent ischemia and reperfusion injury***
- ***High volume of organs***
- ***Each sample is extensively annotated***



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Human Sensory Neurons for Pain Drug Discovery



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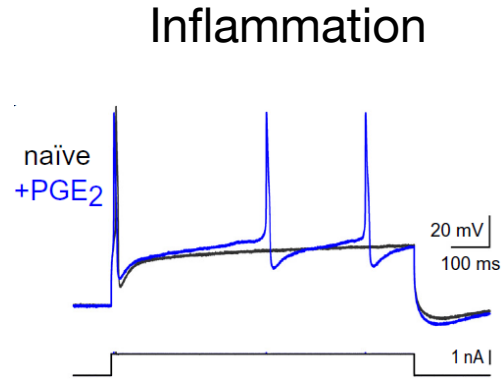
Assessment of Drug Activity in Pathological States



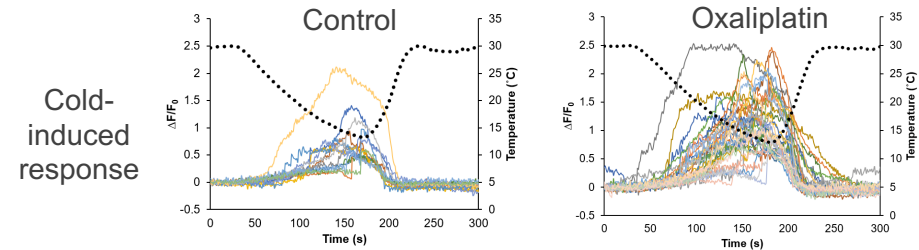
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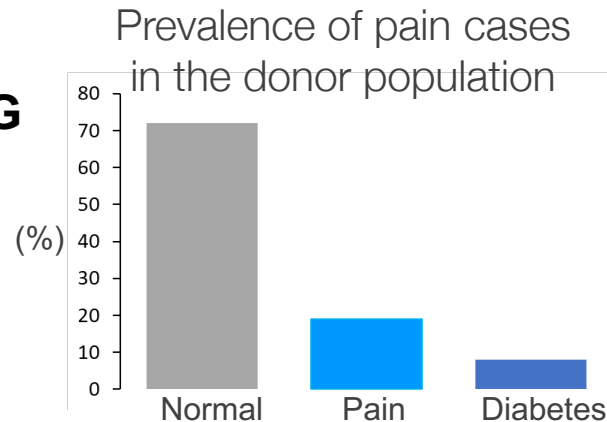
1- In vitro-sensitized hDRG



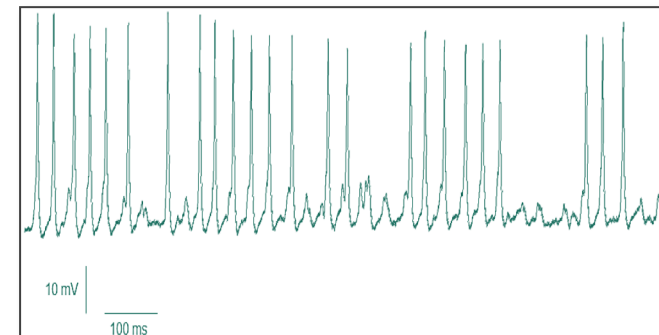
Peripheral neuropathy



2- Chronic pain donor hDRG



Spontaneous firing in hDRG neuron from chronic pain donor

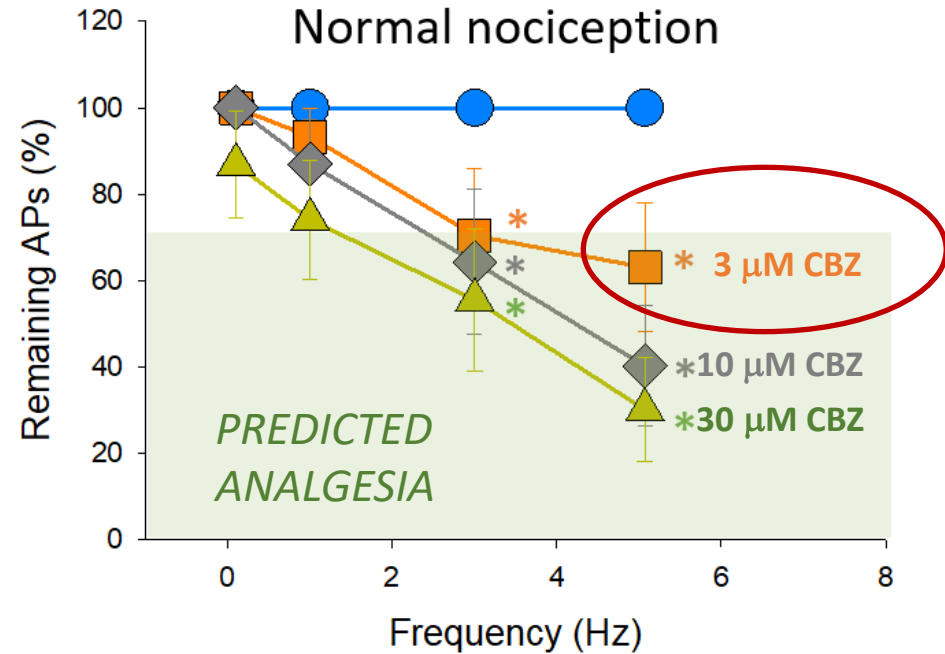
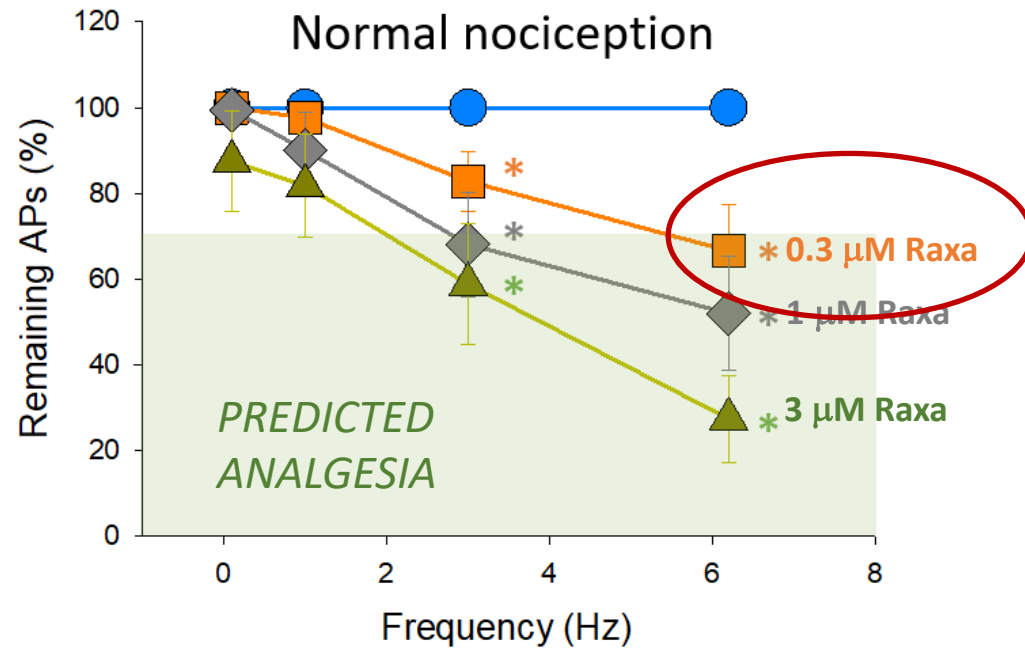


Inhibition of Human Sensory Neurons' Activity by Raxatrigine and Carbamazepine



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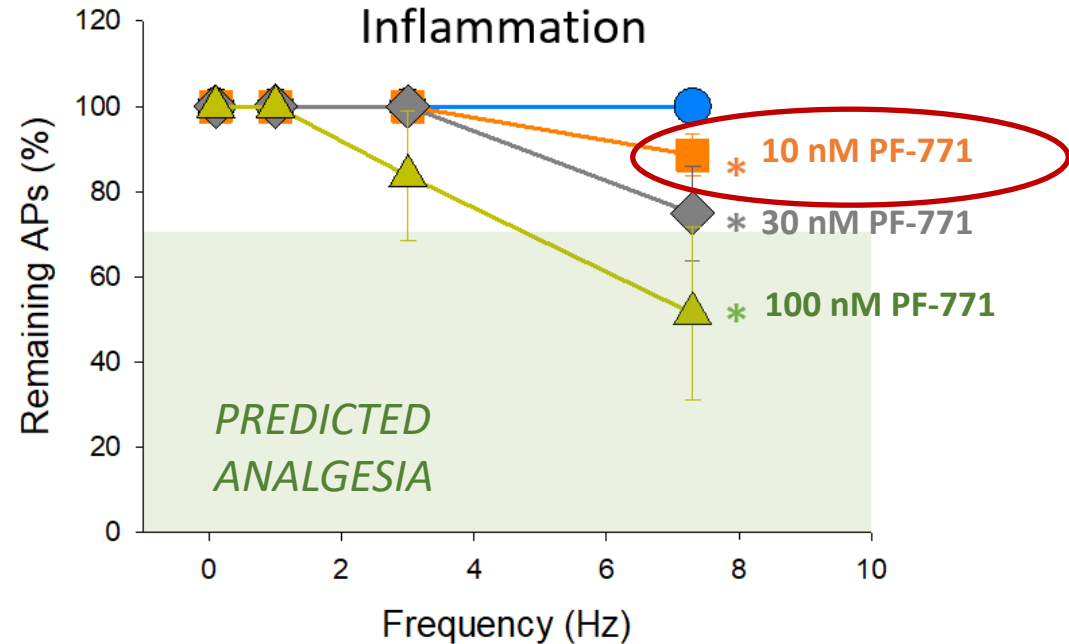
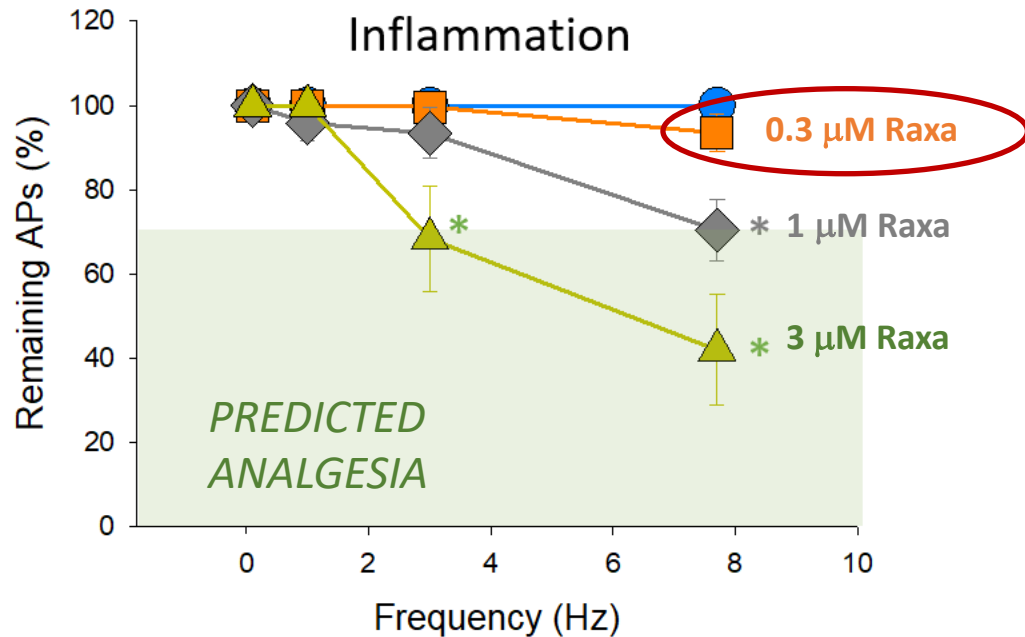


Sensory Neurons Sensitized With Inflammatory Agents Are Not Inhibited by Raxatrigine and PF-05089771

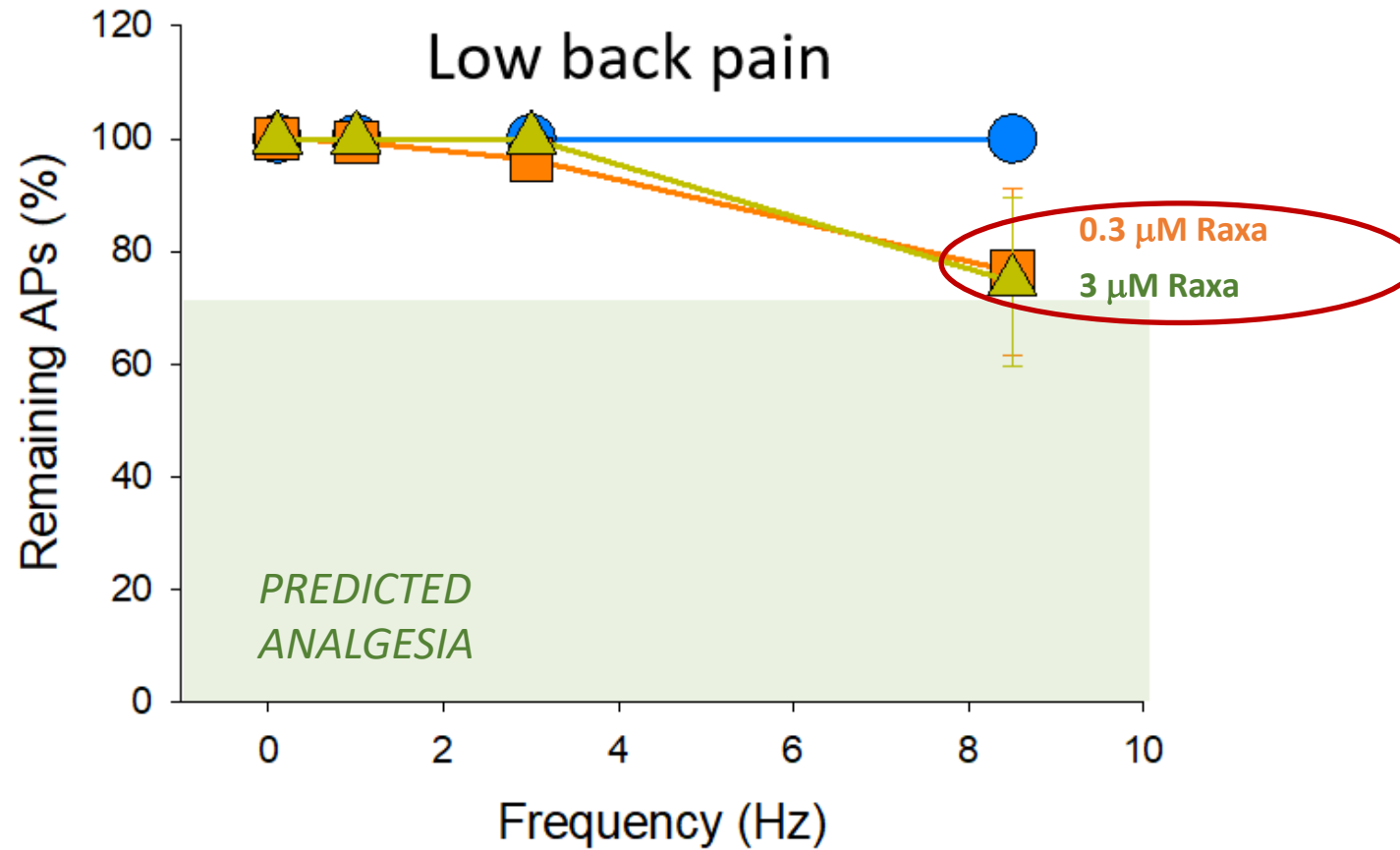


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Raxatrigine Fails to Inhibit the Activity of Human Sensory Neurons from Low Back Pain Donors



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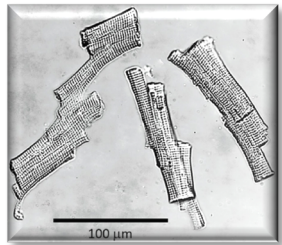
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Cardiac Safety Assessment in Human Heart Ex-Vivo

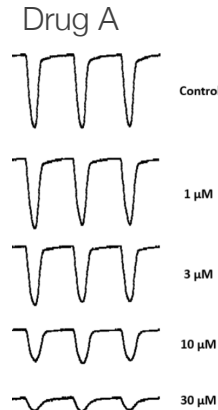


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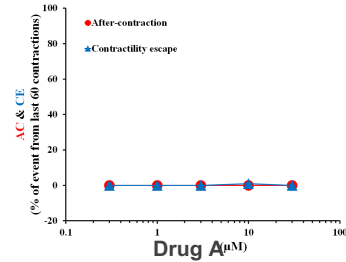
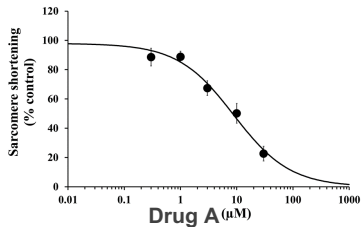
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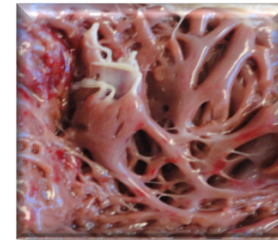
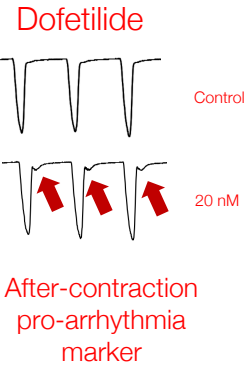
Human adult
cardiomyocytes



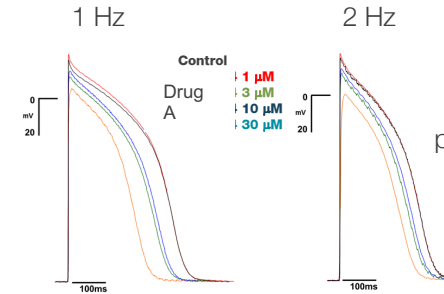
Reduction in
cardiomyocyte
contractility only
at very high
concentrations



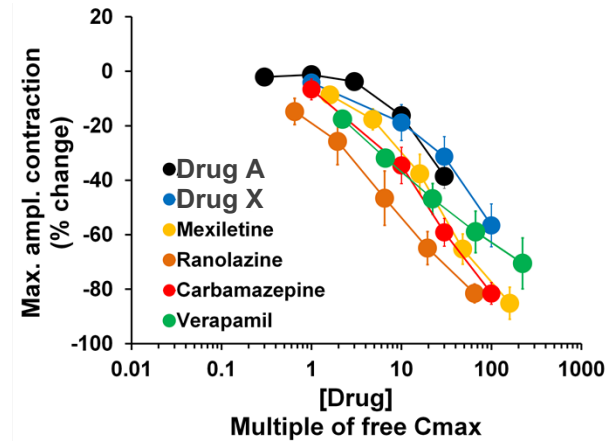
No evidence of
drug-induced
arrhythmia



Human adult ventricular
trabeculae



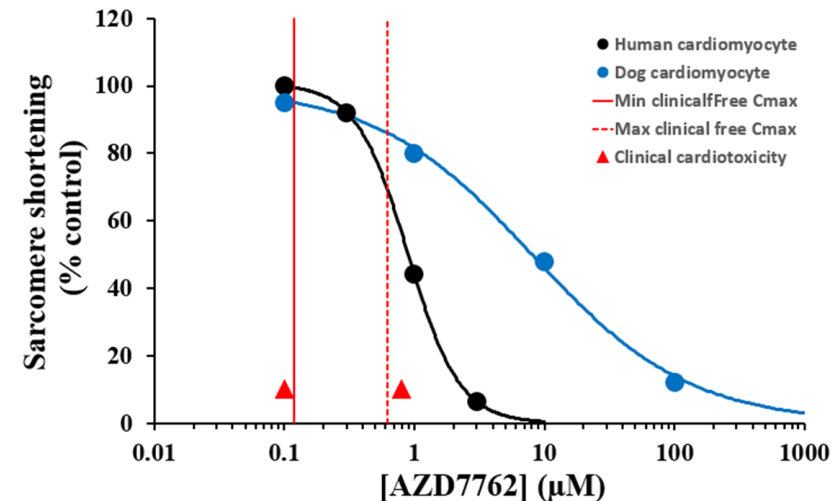
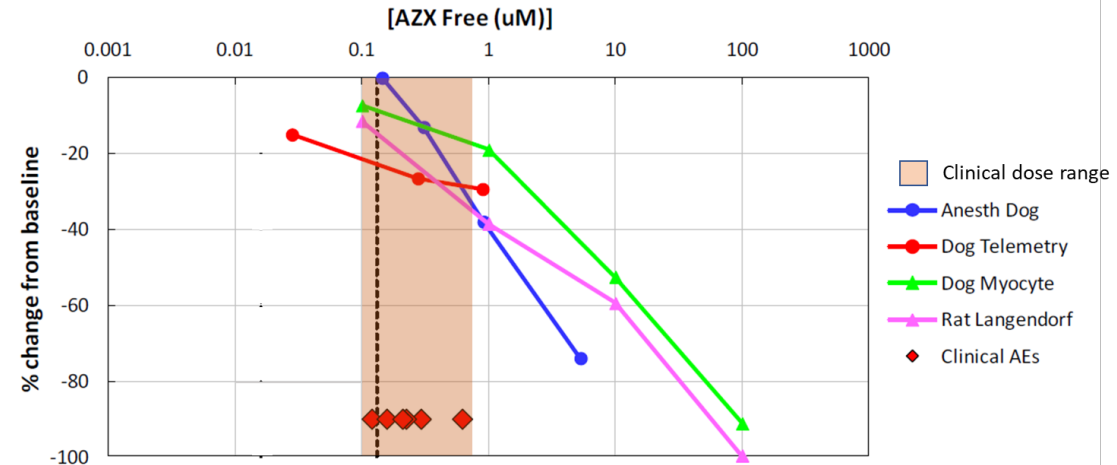
No evidence of
pro-arrhythmia markers
up to 30 µM



Cardiac safety margin
~100x of the target
effective
concentration

Poor Translation Can Result in Serious Adverse Events

- 1) AZD7762 is a potent and selective Chk1 kinase inhibitor for solid tumors
 - 2) Development halted due to serious AE
 - a) Decrease left ventricular ejection fraction
 - b) Increased troponin I
 - 3) In conscious dogs, transient dose-dependent decrease in contractility (-22% at high dose)
 - 4) No effects on systolic or diastolic arterial blood pressure
- Sausville et al. (2014)
- 5) In vitro human cardiomyocytes exhibit 10-30x higher sensitivity compared to dog myocytes
 - 6) Dogs are not good predictors of inotropy effects in human



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Human Ex-Vivo Systems are Increasingly Utilized in Translational Research



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Pfizer

BIOPHYSICAL AND PHARMACOLOGICAL CHARACTERISATION OF NATIVE HUMAN Na_v1.8 CHANNELS FROM ISOLATED DORSAL ROOT GANGLIA (DRG).
Liz Payne¹, Victor A. Panchenko², Andrea Ghetti², Ari Alexandrou², Paul E. Miller², Edward Stevens¹
¹Pfizer (Neurosciences), Cambridge, United Kingdom; ²Anabios, San Diego, CA, USA

Na_v1.7 is the dominant subtype underlying TTX-s currents in small diameter mouse & human DRGs.
Adrian J. Alexander¹, James Turner², C. Elizabeth Payne¹, Peter J. Cox¹, Victor A. Panchenko², Andrea Ghetti², Rebecca Prime¹, Rachel Doyle¹, Mark Chapman¹, Brian Marston¹, Paul E. Miller², Richard P. But¹, Edward B. Stevens¹

Analyst

PAPER

Long-term non-invasive interrogation of human dorsal root ganglion neuronal cultures on an integrated microfluidic multielectrode array platform†
H. A. Enright,^a S. H. Felix,^b N. O. Fischer,^a E. V. Mukerjee,^b D. Soscia,^b M. Mcnerney,^a K. Kulp,^a J. Zhang,^a G. Page,^c P. Miller,^a A. Ghetti,^c E. K. Wheeler^{a,b} and S. Pannu^a

frontiers in Physiology

Adult Human Primary Cardiomyocyte-Based Model for the Simultaneous Prediction of Drug-Induced Inotropic and Pro-arrhythmia Risk
Nathalie Nguyen, William Nguyen, Brynna Nguyen, Phachareeya Ratchada, Guy Page, Paul E. Miller, and Andrea Ghetti

Human-based approaches to pharmacology and cardiology: an interdisciplinary and intersectoral workshop
Blanca Rodriguez¹, Annamaria Carusi², Najah Abi-Gerges³, Rina Ariga⁴, Oliver Britton¹, Gil Bub⁵, Alfonso Bueno-Orovio⁶, Rebecca A.B. Burton⁷, Valentina Carapella⁸, Louie Cardone-Noote⁹, Matthew J. Daniels⁴, Mark R. Davies⁷, Sara Dutta¹, Andrea Ghetti³, Vicente Harmer¹, Ivan Kopjar¹, Pier Lambiasi¹⁰, Hua Rong Lu¹, Aurore Lyon¹, Ana Minchole¹, Anna Muszkiewicz¹, Julien Oster⁴, Michelangelo Paci¹¹, Elisa Passini¹, Stefano Severi¹², Peter Taggart¹⁰, Andy Tinker⁴, Jean-Pierre Valentin¹³, Andras Varro¹⁴, Mikael Wallman¹⁵, and Xin Zhou¹

PAIN

Human sensory neurons: Membrane properties and sensitization by inflammatory mediators
Steve Davidson^{a,1}, Judith A. Copits^{a,1}, Jingming Zhang^b, Guy Page^b, Andrea Ghetti^b, Robert W. Gereau IV^{a,2}

frontiers in Physiology

Action Potential Recording and Pro-arrhythmia Risk Analysis in Human Ventricular Trabeculae
Yusheng Qu¹, Guy Page², Najah Abi-Gerges², Paul E. Miller², Andrea Ghetti² and Hugo M. Vargas¹

exhibit similar pharmacology

Quantitative Comparison of Effects of Dofetilide, Sotalol, Quinidine, and Verapamil between Human Ex vivo Trabeculae and In silico Ventricular Models Incorporating Inter-Individual Action Potential Variability
Oliver J. Britton¹, Najah Abi-Gerges², Guy Page², Andrea Ghetti², Paul E. Miller² and Blanca Rodriguez²

Poster #W47

ACTION OF BIASED-MOR AGONISTS TO INHIBIT DEPOLARIZATION-INDUCED CALCIUM MOBILIZATION IN CULTURED HUMAN DRG NEURONS
S. P. Ameri¹, J. Zhang², P. E. Miller², Z. Rankovic², P. J. Hahn², D. L. Gerner², A. Ghetti²
¹NeuroSci Discovery, Eli Lilly & Company, Indianapolis, IN, USA; ²Anabios Corp., San Diego, CA, USA

frontiers in Physiology

New mechanism underlying IL-31-induced atopic dermatitis
Jianghui Meng, PhD,^{a,b} Masaki Moriyama, PhD,^a Micha Feld, PhD,^d Joerg Buddenkotte, MD, PhD,^{a,1} Timo Buhl, MD,^a Attila Szölösi, PhD,^b Jingming Zhang, PhD,^b Paul Miller, PhD,^b Andrea Ghetti, PhD,^b Michael Fischer, MD,¹ Peter W. Reeh, MD,¹ Chunxun Shan, PhD,^{a,b} Jiafu Wang, PhD,^a and Martin Steinhoff, MD, PhD^{a,b,c,d}

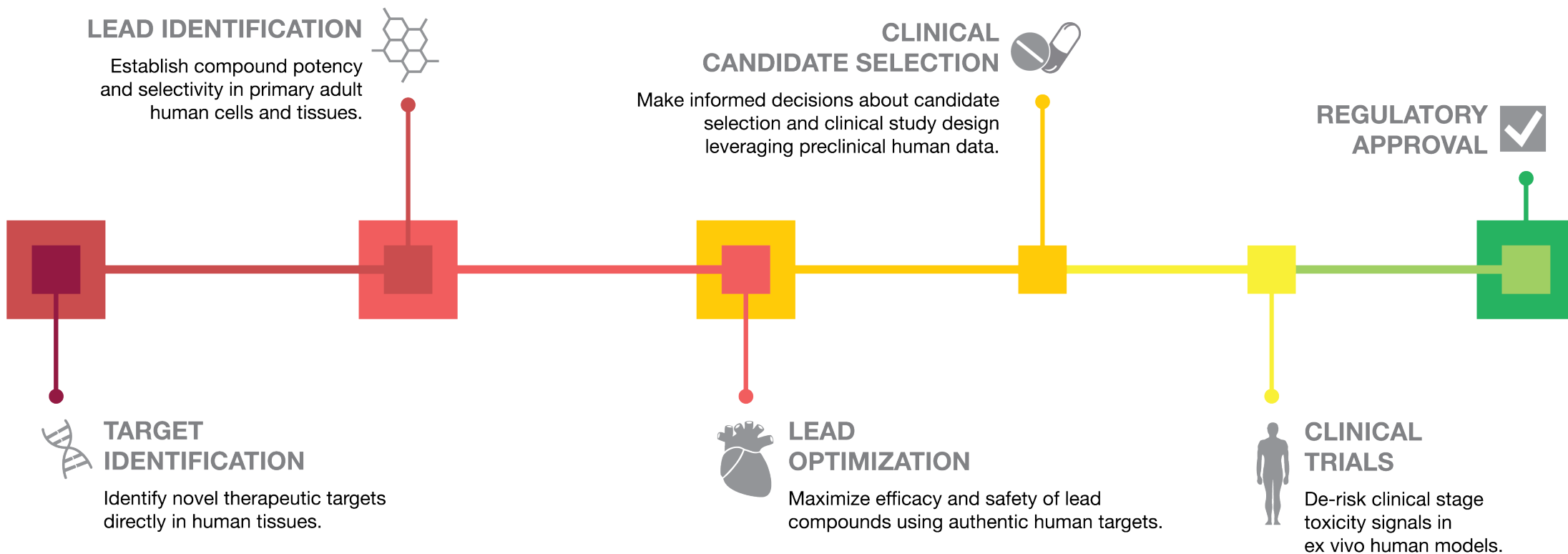
Systems/Circuits

The Cancer Chemotherapeutic Paclitaxel II and Rodent Sensory Neuron Responses to Activation of TLR4
Yan Li¹, Pavel Adamek¹, Haijun Zhang¹, Claudio Esteves Tatsuji¹, Laurence D. Rhee¹, Alyssa K. Kosturakis¹, Ryan M. Cassidy¹, Daniel S. Harrison¹, Juan P. Cata¹, Kenneth Ross M. Kennerly-Chapman¹, Abdul Basit Jawad¹, Andrea Ghetti¹, Husheng Yan¹

ORIGINAL ARTICLE

α-Conotoxin Vc1.1 inhibits human dorsal root ganglion neuroexcitability and mouse colonic nociception via GABA_B receptors
Joel Castro,¹ Andrea M. Harrington,¹ Sonia García-Caraballo,¹ Jessica Maddern,¹ Luke Grundy,¹ Jingming Zhang,² Guy Page,² Paul E. Miller,² David J. Craik,³ David J. Adams,⁴ Stuart M. Brierley¹

Human Tissues in Drug Discovery



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Summary

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



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



Quantitative assessment of potency



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Thank You

Andre Ghetti, PhD
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