Predicting Contractility Risk of Cancer Agents with Adult Human Primary Cardiomyocytes

58th Annual SOT Meeting

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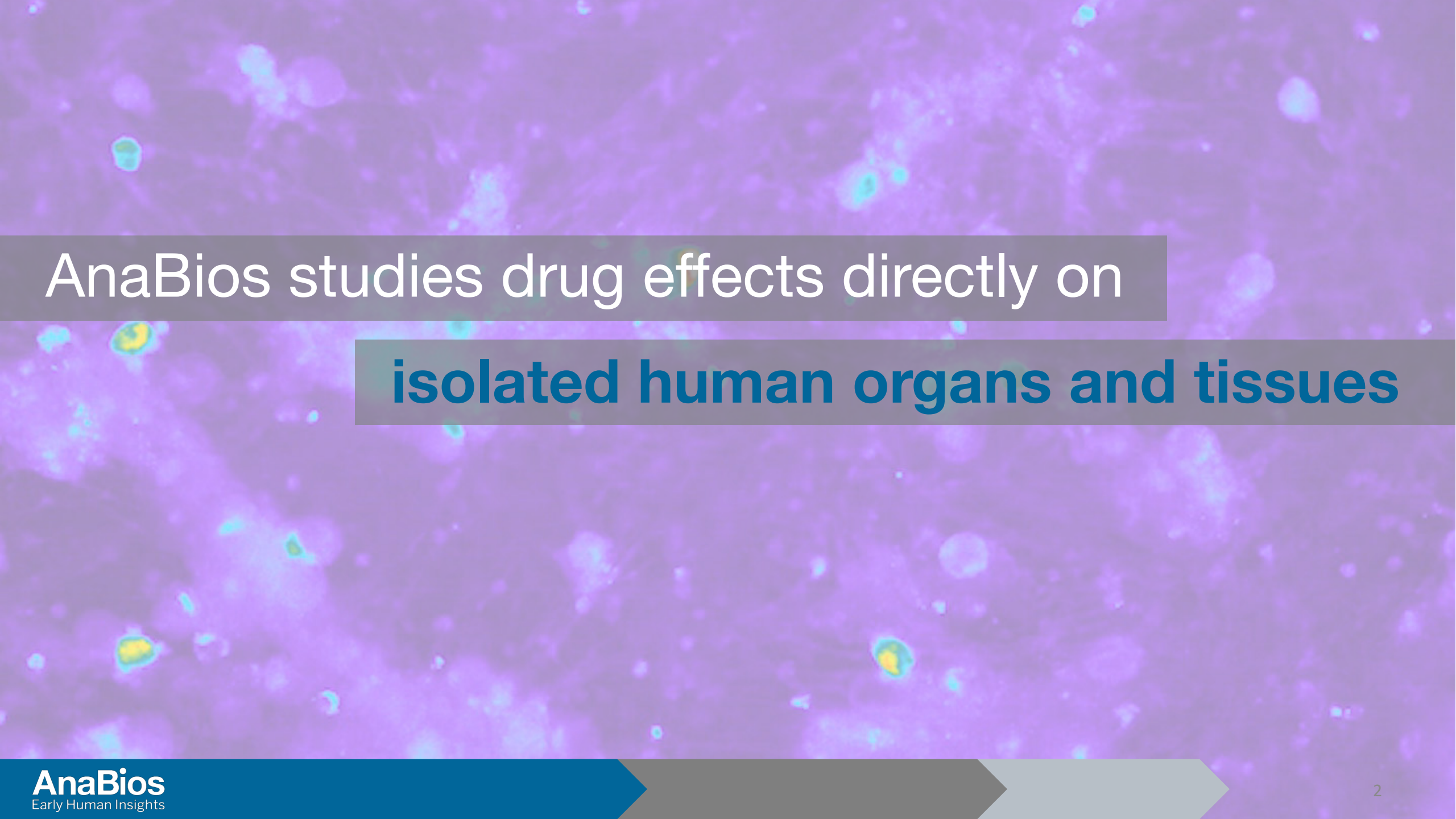
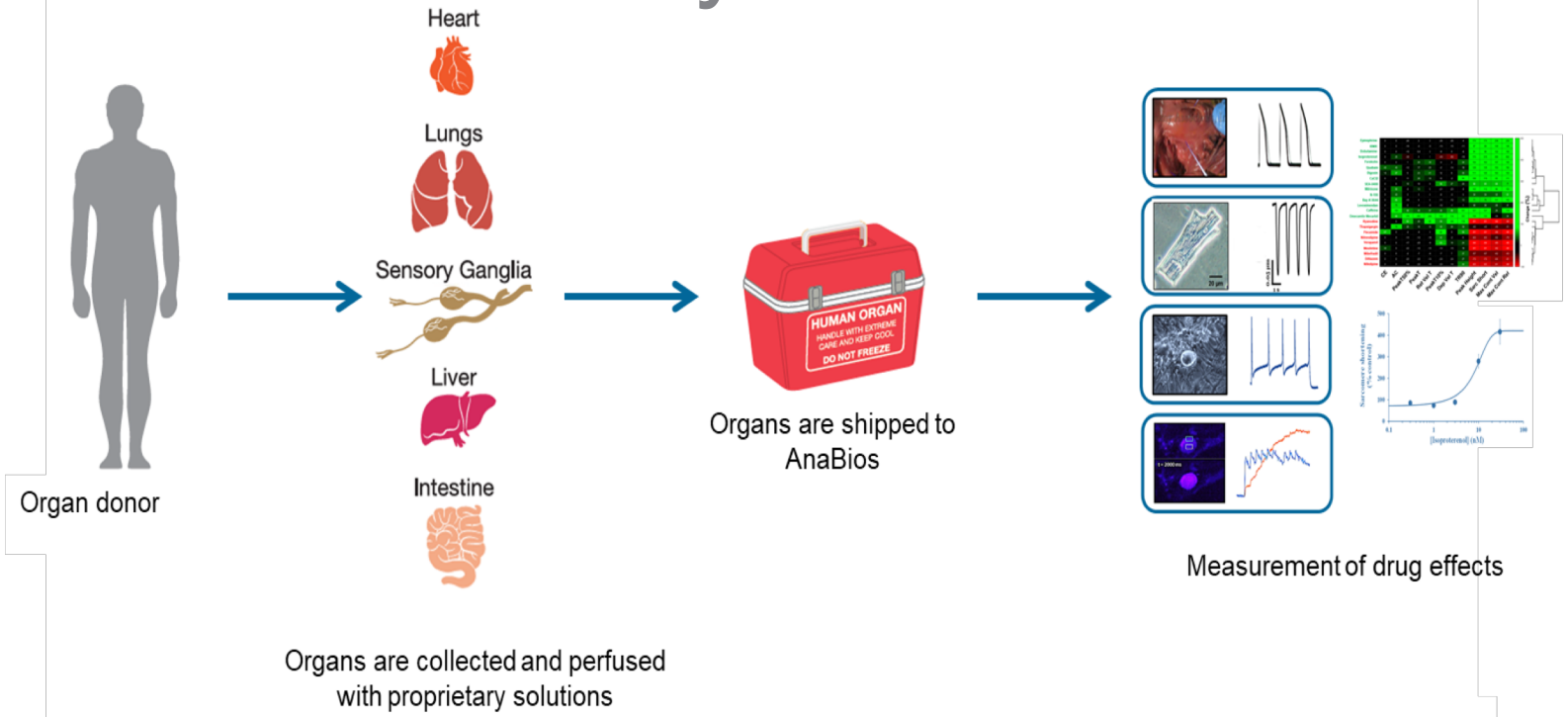
AnaBios
Early Human Insights

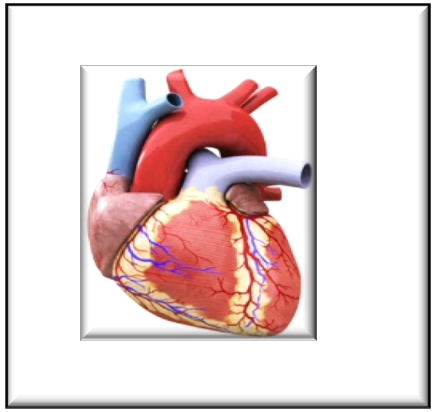

AnaBios studies drug effects directly on
isolated human organs and tissues

Enabling Drug Discovery
in Human Healthy and Diseased Tissues



- Tissue harvesting methods and solutions are designed to avoid ischemic damage and reperfusion injury
- Complete chain of custody, processing methods and rigorous QC ensure excellent tissue quality
- Large U.S.A.-based network ensures the availability of samples
- Excellent heart quality permits integrated human cardiac drug discovery at the preclinical stages

Comprehensive Drug Discovery
in Ex-Vivo Healthy Human Cardiac Models



> 1000 **ex vivo** human hearts tested

CELL-BASED ASSAYS
(Optimization of drugs)

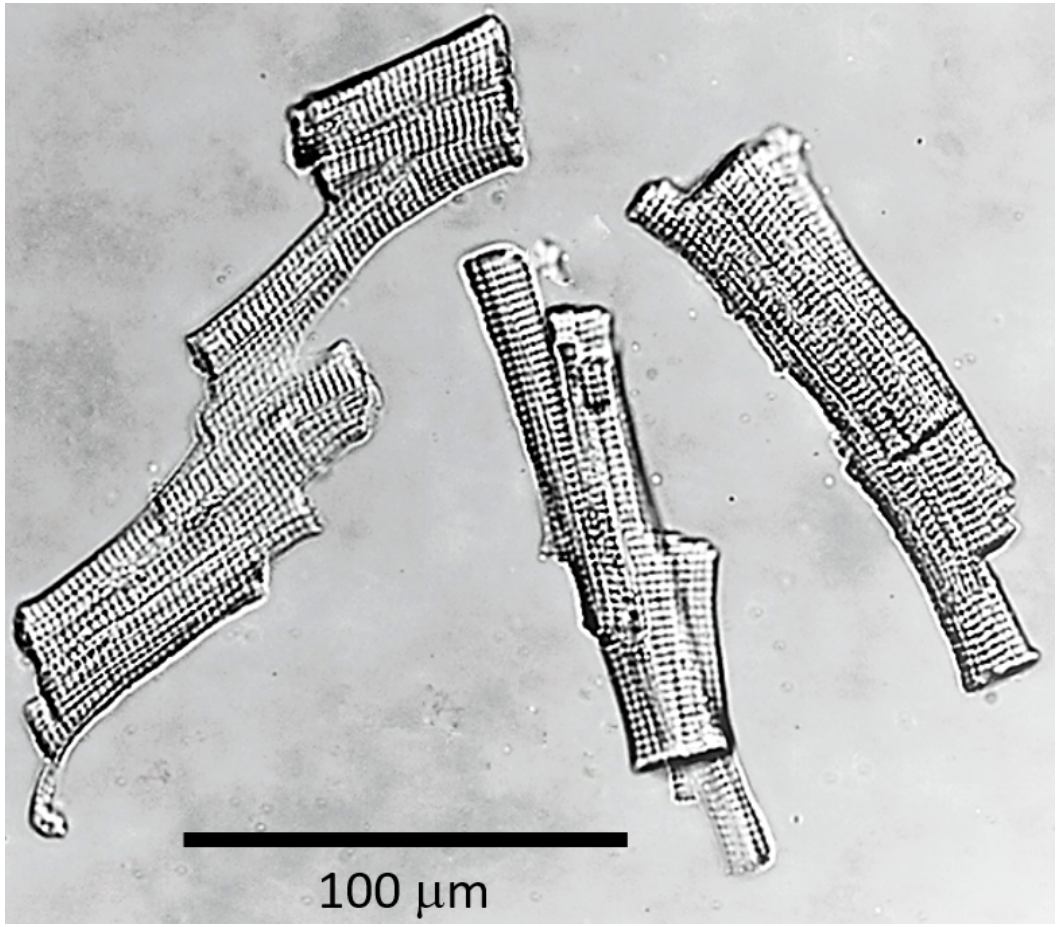
- **Pro-arrhythmia & Inotropy** *Ventricular Myocytes*
- **Arrhythmia & Inotropy** *Atrial Myocytes*
- **Ca^{2+} Assay** *Ventricular Myocytes*
- **Ion Channel** *Ventricular & Atrial Myocytes*
- **Action Potential** *Ventricular & Atrial Myocytes*
- **Cardiac Fibrosis** *Cardiac Fibroblasts*

TISSUE-BASED ASSAYS
(Nomination of drugs)

- **Pro-arrhythmia** *Action Potential Ventricular Trabeculae*
- **Inotropy** Contractility *Ventricular & Atrial Trabeculae*
- **Chronotropy** Spontaneous Action Potential *Sinoatrial Node*
- **Vaso-constriction Dilation** *Coronary Rings*

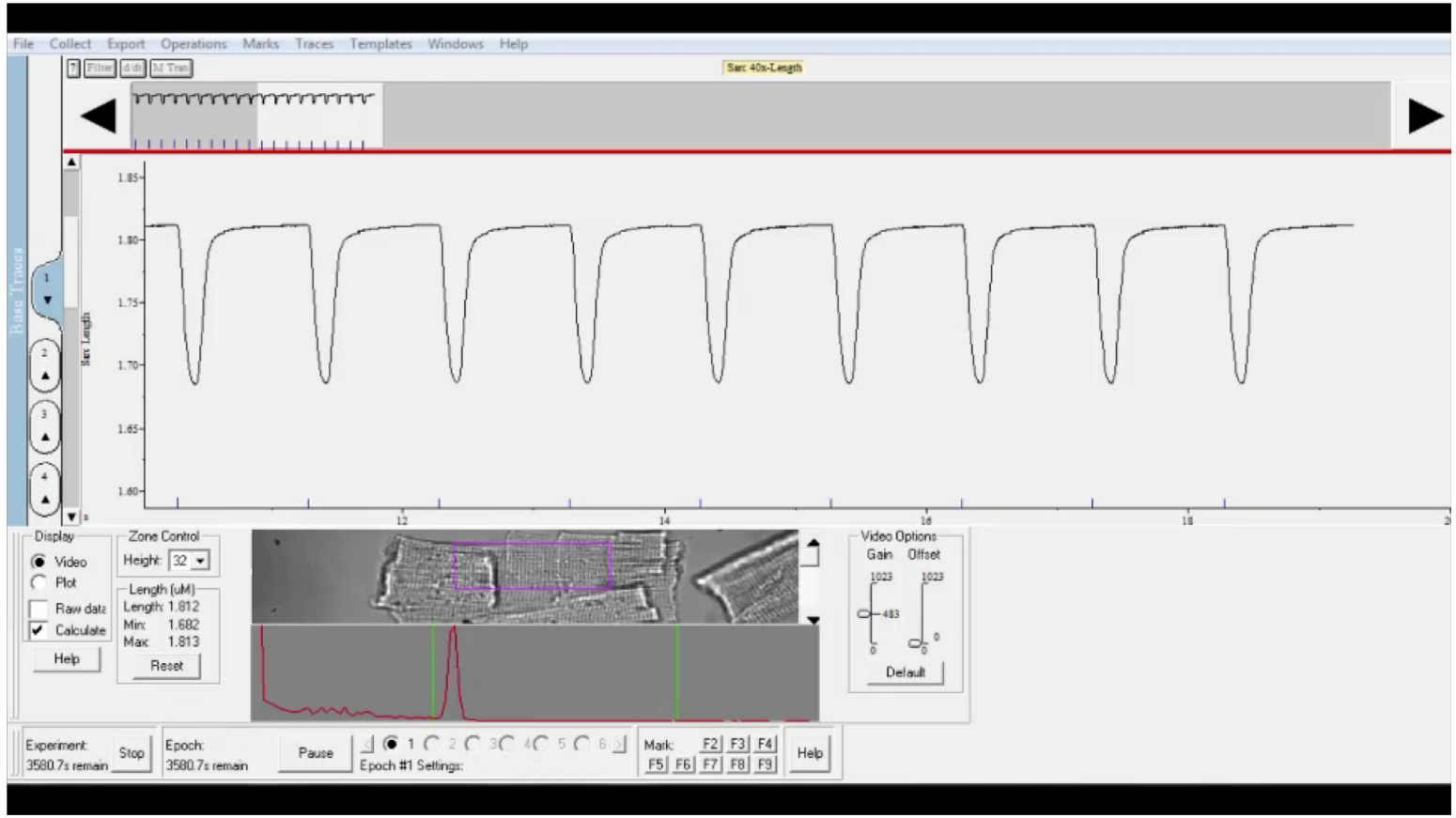
New Isolation Method Provides High Yield of Cardiomyocytes

> 1000 **ex vivo** human hearts tested



Non-Invasive Measurement of Contraction

Full Retention of Cardiomyocyte Functionality



- Bright-field imaging
- Low technical complexity
- No cytotoxic fluorescent reagents
- High information content

IonOptix: Sarcomere shortening measured by digital cell geometry tracking; stimulation frequency 1Hz

Inhibition of Kinase Activity to Control Tumor Growth

Can Lead to Cardiotoxicity

Dysregulation of tyrosine kinases

Progression to many cancers

Tyrosine Kinase inhibitors (TKIs)
effective cancer treatment

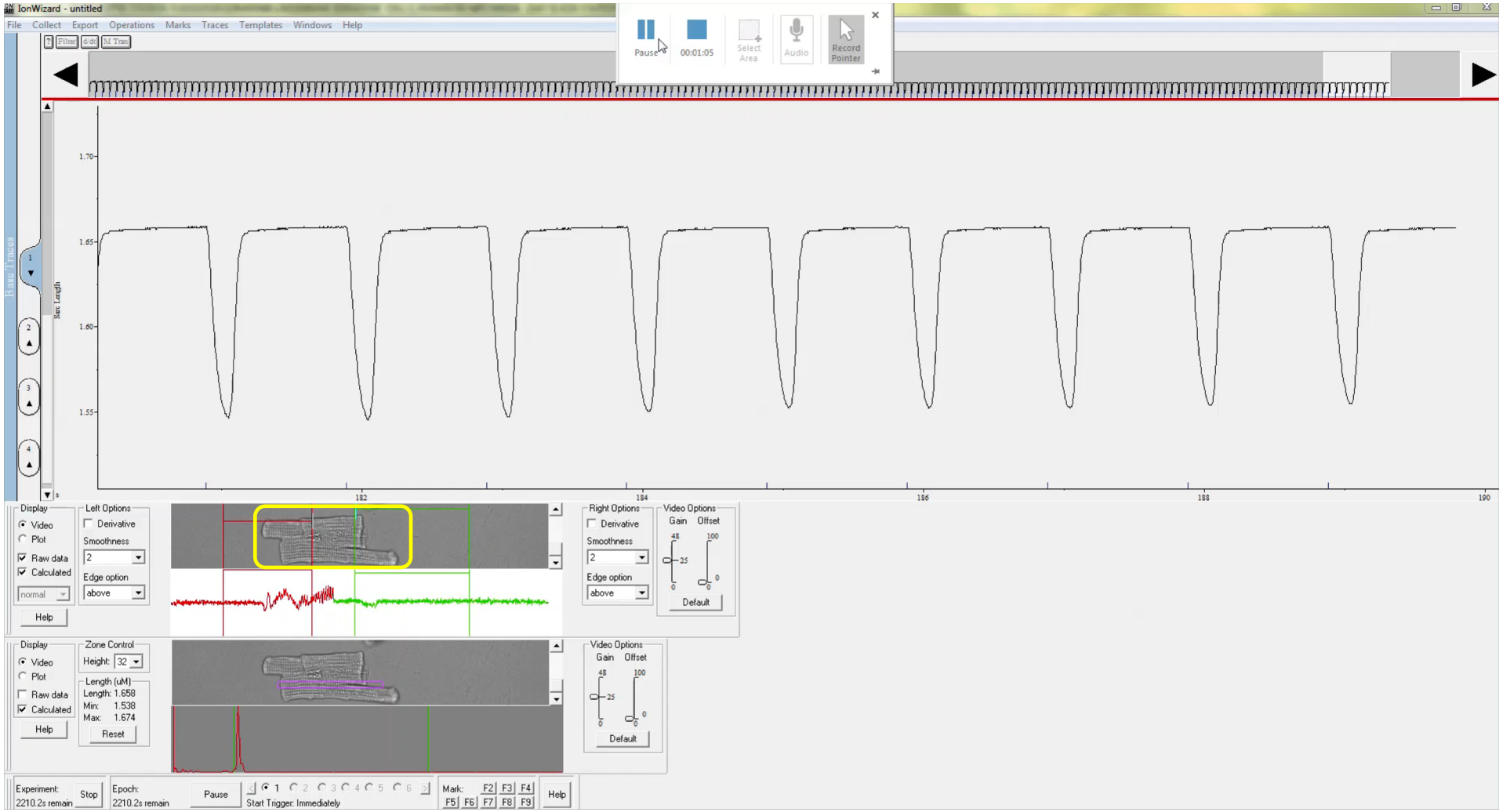
TKIs induce cardiotoxicity
heart failure
reduced left ventricular ejection fraction
myocardial infarction
arrhythmias

Validating Clinical Relevance of Cancer Agents

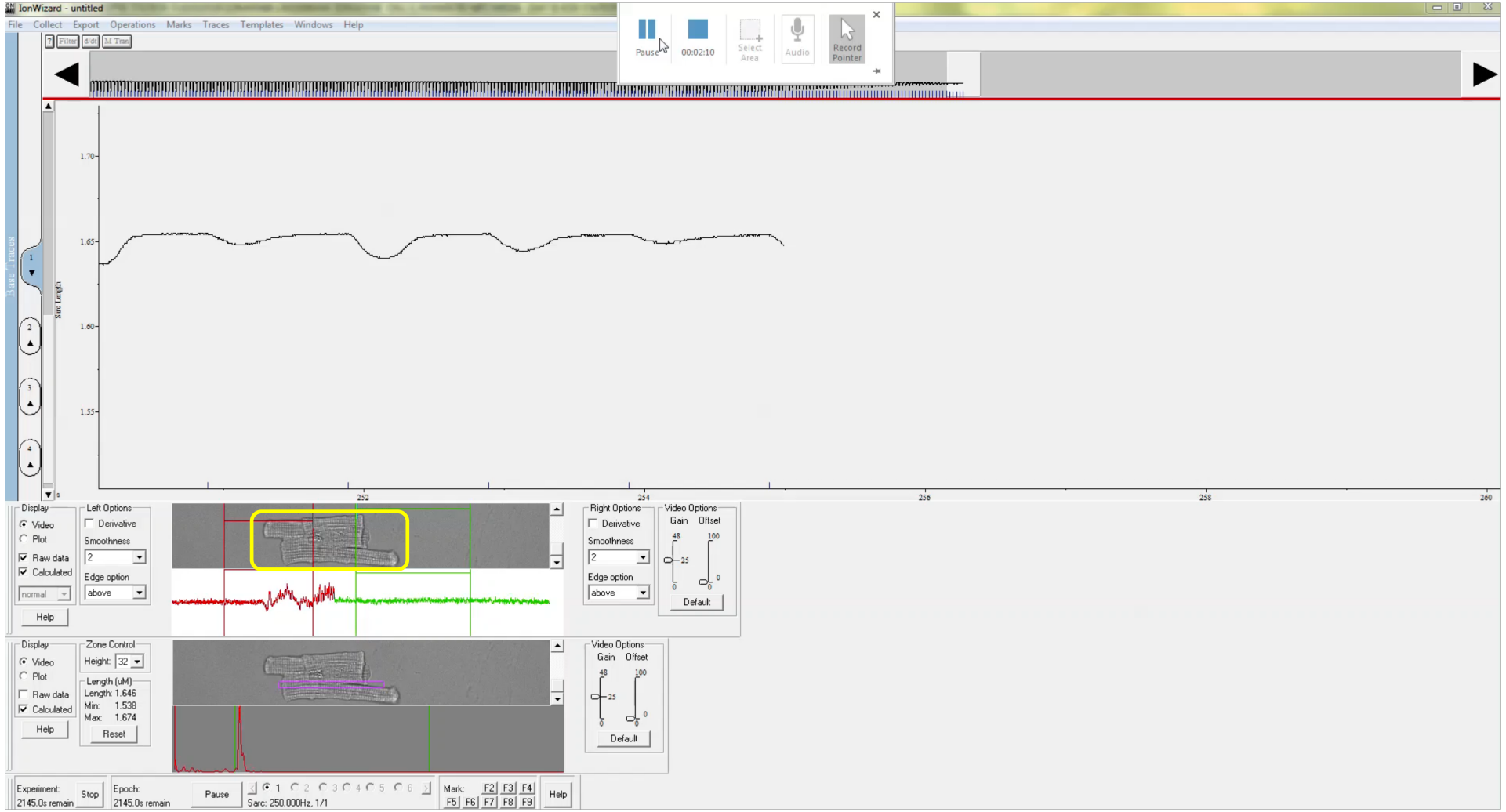
- Validated 9 clinically well-characterized controls :

1) 4 cardiotoxic TKIs (Sorafenib, Vandetanib, AZD7762, Imatinib)
2) 4 safe TKIs (Erlotinib, Dasatinib, Afatinib, Gefitinib)
3) One cardiotoxic anthracycline (Doxorubicin)
4) Each drug was tested at multiples of the Cmax
5) Each concentration was perfused for 5 mins

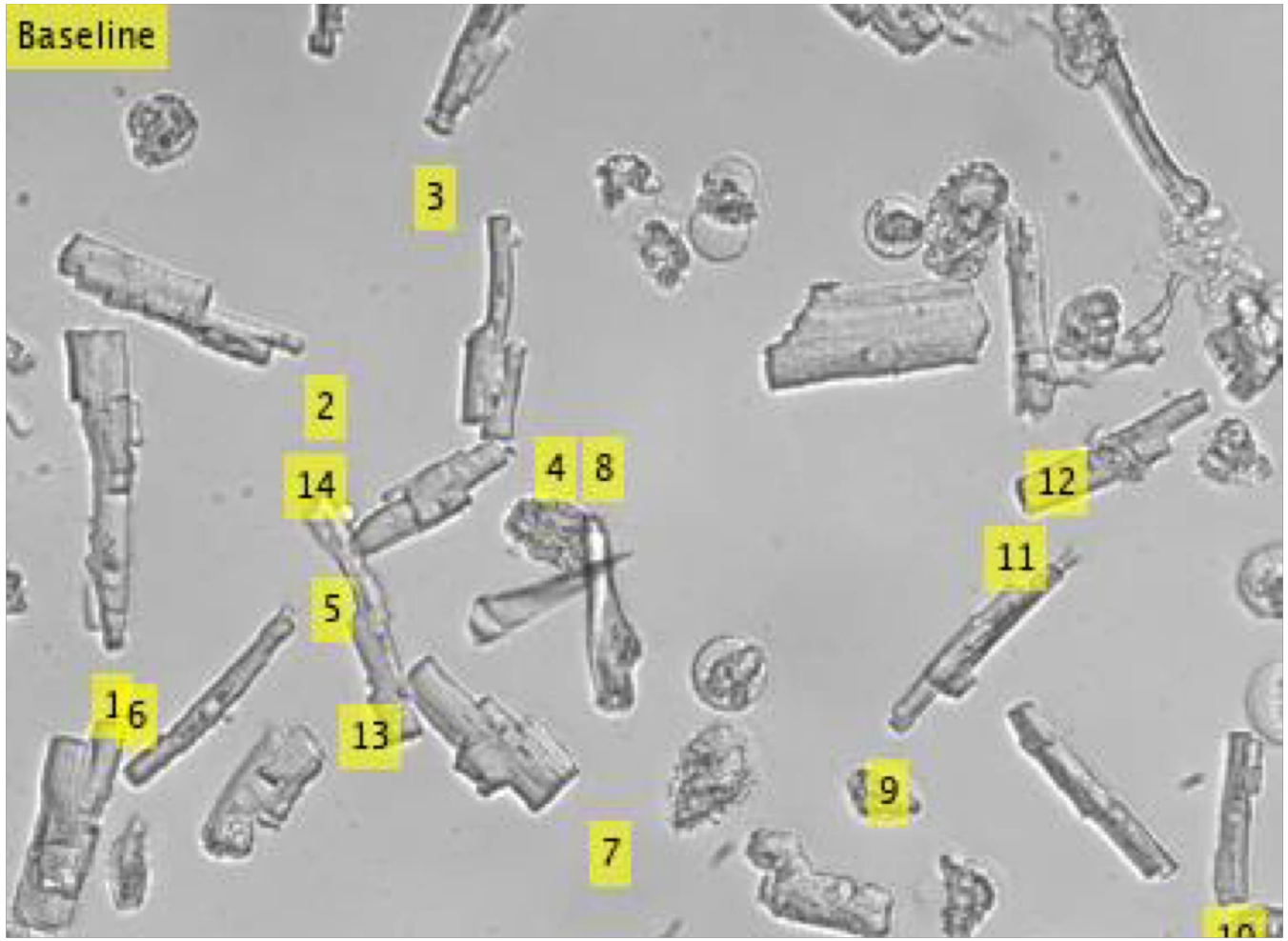
Sorafenib Induces Functional Cardiotoxicity
in Human Cardiomyocytes



Sorafenib Induces Structural Cardiotoxicity
in Human Cardiomyocytes

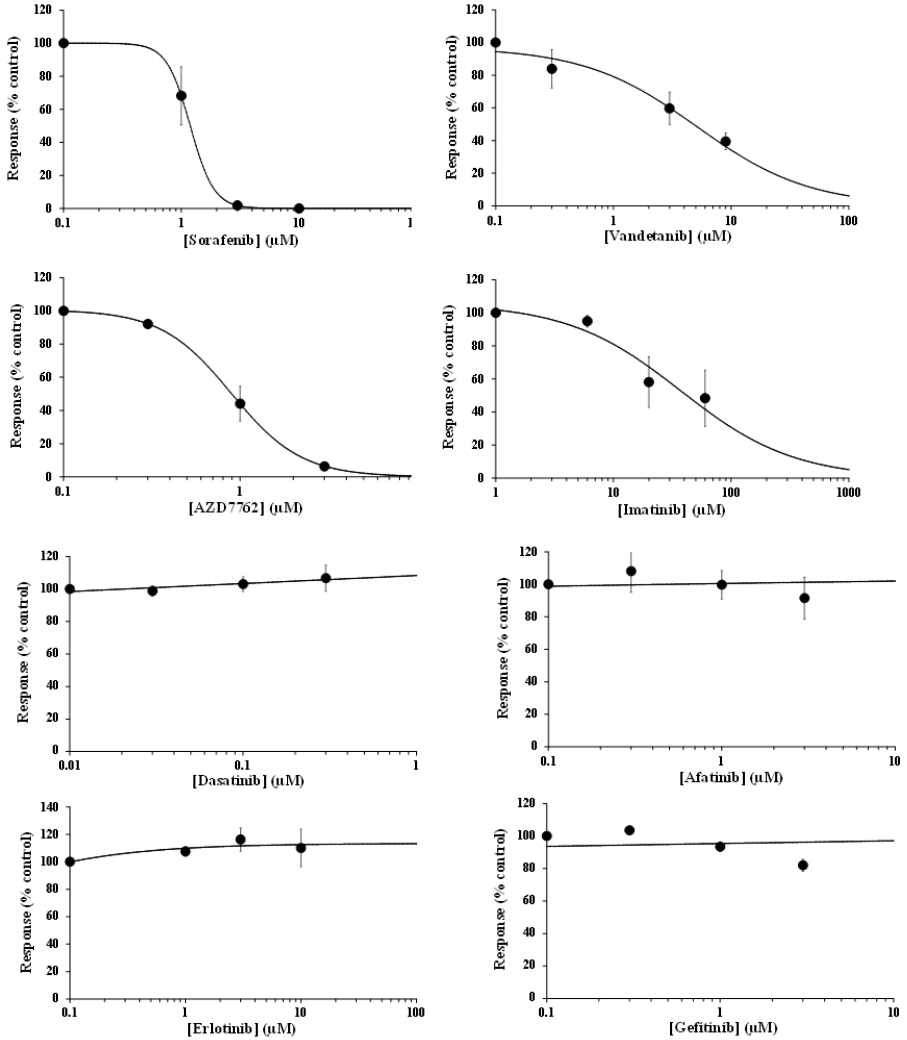


Afatinib Induces No Functional or Structural Cardiotoxicity in Human Cardiomyocytes



0.3μM = 3-fold Cmax
1μM = 10-fold Cmax
3μM = 30-fold Cmax

Tyrosine Kinase Inhibitors Affect Human Cardiomyocyte Contractility



TKI	Clinical contractility risk	Human cardiomyocyte contractility	Cmax (µM)	IC_{50} (µM)	Ratio (IC_{50}/C_{max})
Sorafenib			3.4	1.2	0.35
Vandetanib			1.8	4.6	2.55
AZD7762			0.12	0.8	6
Imatinib			5	44	8
Erlotinib			2.5	>10*	>4
Dasatinib			0.01	>0.3	>30
Afatinib			0.1	>3	>30
Gefitinib			0.1	>3	>30

Similar human cardiac tissue data recently published by Schneider C et al., 2018 Nature Scientific Reports
**: Limit of solubility*

Risk
No risk

Sorafenib Decreases Force in Contracting Human Myocardia

www.nature.com/scientificreports

SCIENTIFIC REPORTS

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The Anti-Cancer Multikinase Inhibitor Sorafenib Impairs Cardiac Contractility by Reducing Phospholamban Phosphorylation and Sarcoplasmic Calcium Transients

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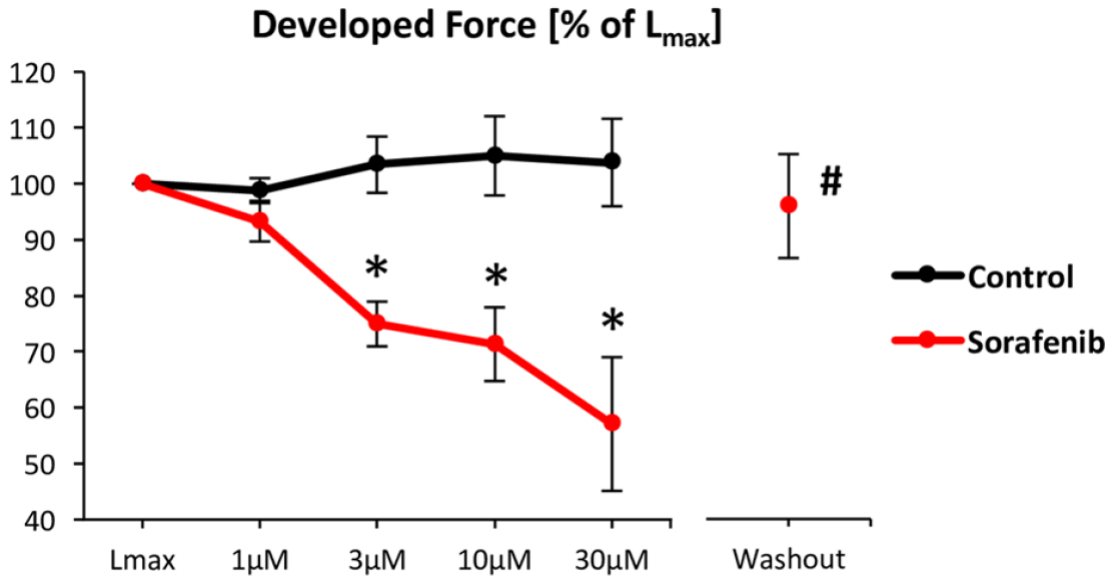
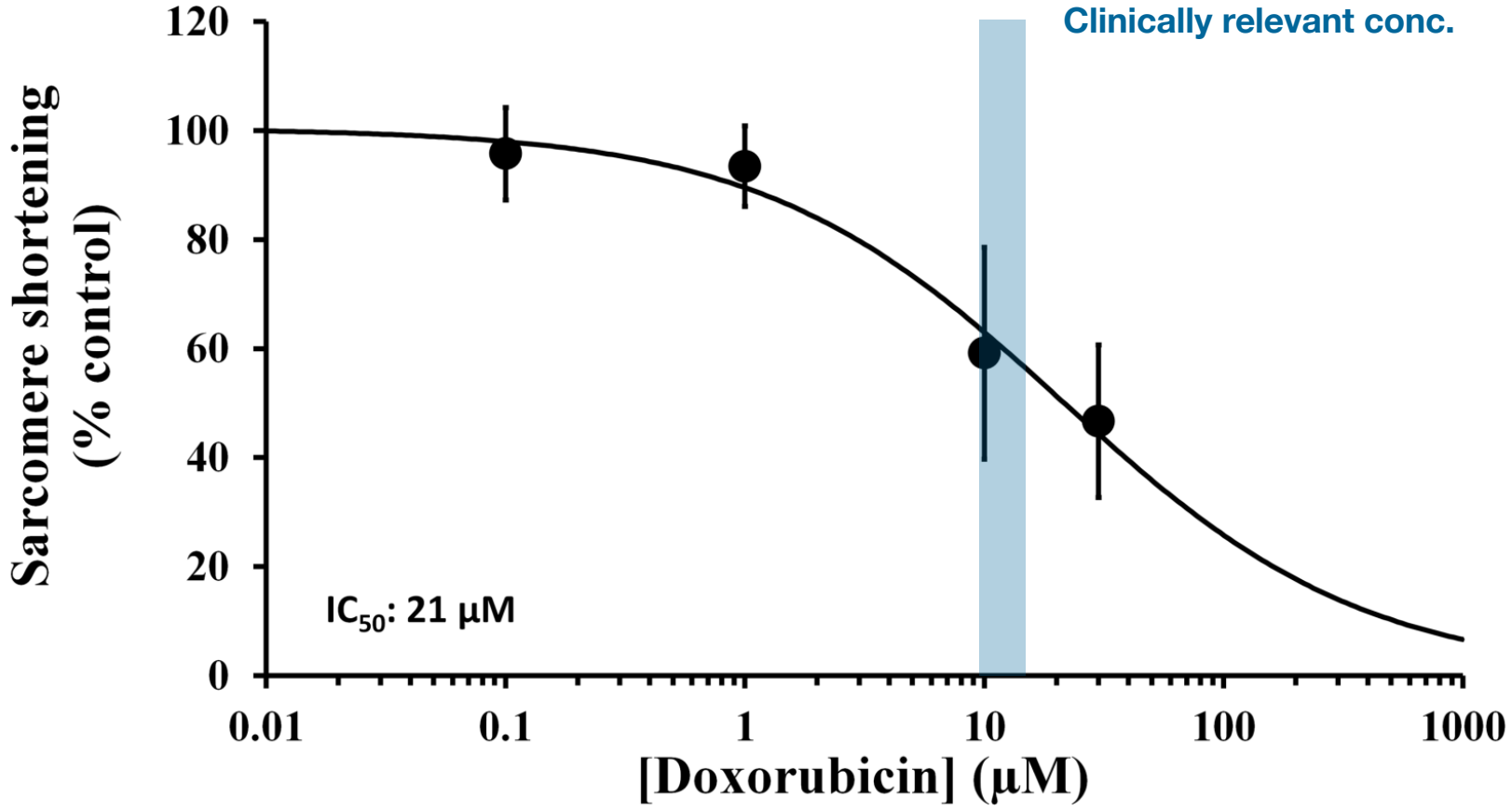
Christopher Schneider[1], Markus Wallner[1,2], Ewald Kolesnik[1], Viktoria Herbst[1], Heinrich Mächler[3], Martin Pichler[4,5], Dirk von Lewinski[1], Simon Sedej[1,6] & Peter P. Rainer[1,7]

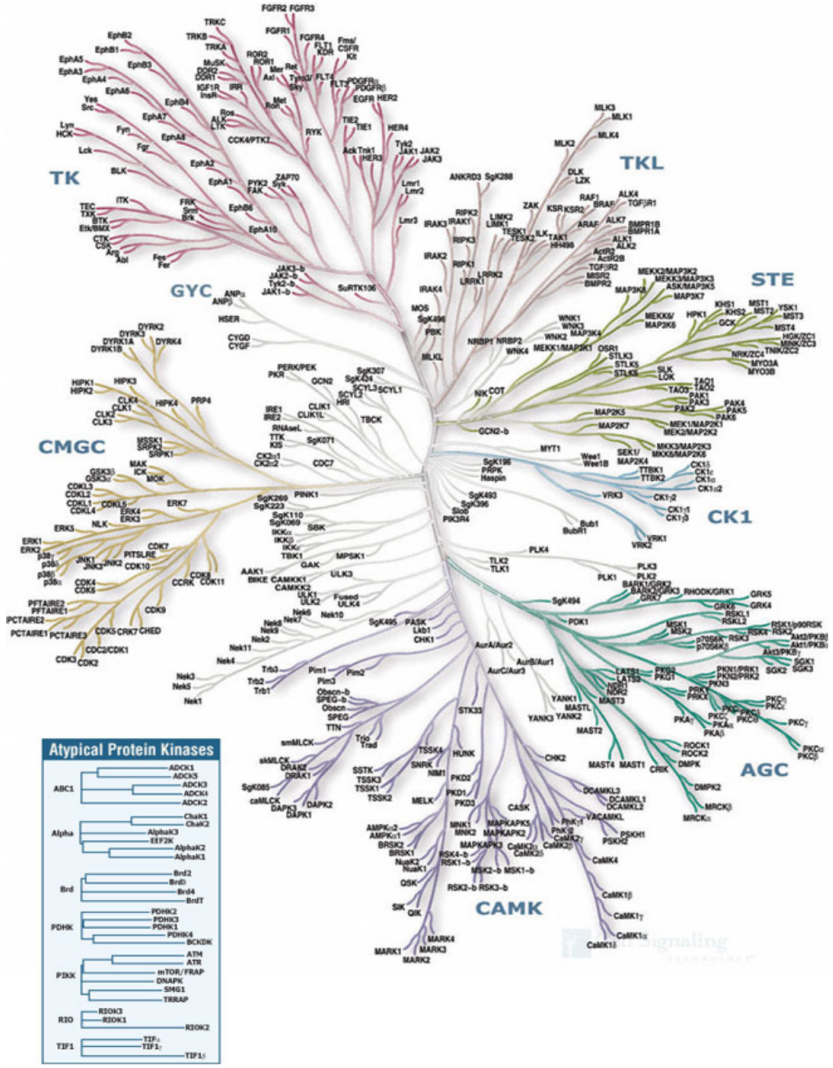


amplitude, and slowed cytosolic calcium removal. These results indicate myocyte intrinsic cardiotoxicity irrespective of effects on the vasculature and chronic cardiac remodeling.

Doxorubicin, Anthracycline Agent, Decreases Human Cardiomyocyte Contractility



Protein Kinases in Human Cancer



Cancer-driving kinases

Expression and role of kinases in cancer are well understood

Protein Kinases in Human Heart

Heart kinases

- **Expression & function of kinases in cardiac tissue are poorly characterized**
- **Mechanism(s) of KI-induced cardiotoxicity are not fully understood**

Human Heart Kinome Profiling

Phase 1

Gene expression analysis

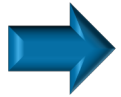
Full profile of kinase expression in human heart

Enable efficient selection of ***relevant*** kinases for selectivity screening to minimize the chance of cardiac side effects

Phase 2

Functional profiling of different chemotypes

Company KI chemical space
Select 300-400 KIs



Contractility assay in human cardiomyocytes

Identify the chemotypes most frequently associated with reduction in cardiac contractility

- **Establish a Company Proprietary human-relevant database covering the cardiac kinome**
- **Enable efficient data-driven selection of leads with lowest cardiotoxicity risk**
- **Significant opportunity for competitive advantage**

Adult Human Cardiomyocyte Model

Early Primary Screening Tool for Cancer Agents

- Provides an integrative assessment with a physiologically functional cell
- Differentiates cardiotoxic from safe cancer drugs
- Predictive of clinical outcomes
- Mechanistic investigations are in progress

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