REPROCELL

REPROCELL provides products and services across the entire drug discovery process

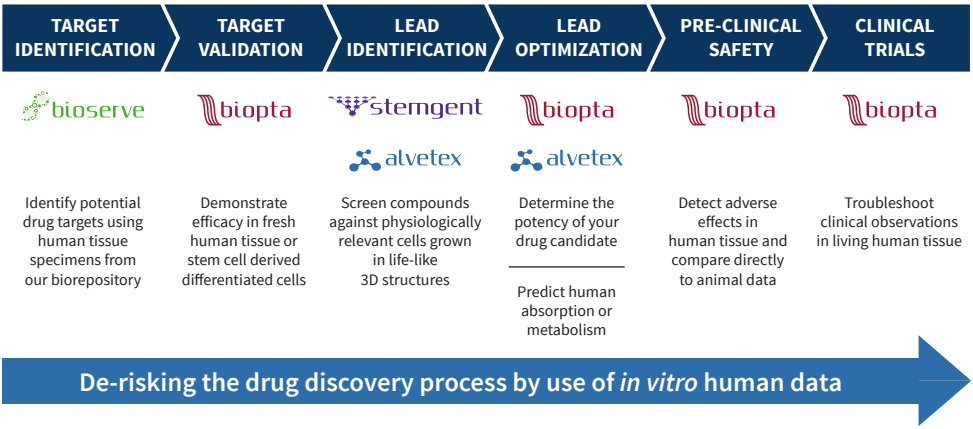
Stem Cells – 3D Models – Human Tissues – Predictive Assays

Why REPROCELL?

Clinical trials for Investigational New Drugs (IND) are perhaps the biggest cost associated with drug development. And yet, up to 90% of all INDs fail at some phase in clinical trials. This is mainly attributable to the fact that most IND research and development is done in animal models and cell culture. The translation of efficacy, clinical safety and toxicology data to humans is not assured.

The REPROCELL Group has ready access to live human tissues through our extensive clinical networks, in addition to human iPSC-derived 3D cell model systems to create custom assays that can provide predictive human data to de-risk your drug discovery programs. No other company has this unique combination of expertise and capabilities.

REPROCELL provides products and services across the entire drug discovery process



REPROCELL Brands

bioserve

- Extensive biorepository of human tissue samples
- Network of clinical sites for prospective sample collection
- Molecular services

stemgent

- RNA reprogramming systems and services
- Reagents for pluripotent cell culture and differentiation
- Extensive portfolio of small molecules

alvetex

- 3D cell culture technology creating *in vivo*-like cell environment
- Protocols for stem cell, oncology and other tissue research applications

biopta

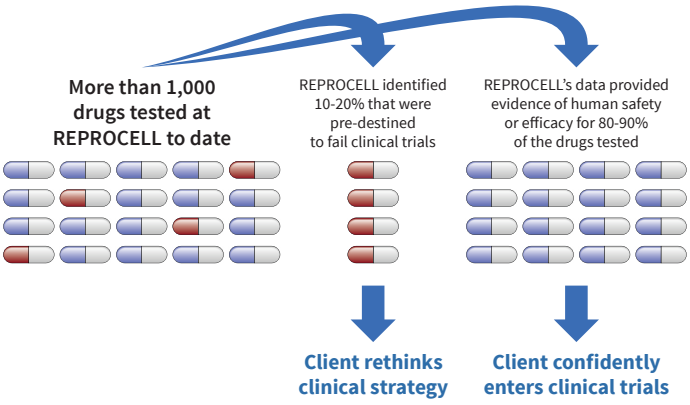
- Experts in human tissue research services for drug development
- Predictive safety, efficacy and ADME assays in human and animal tissues

REPROCELL's human tissue technology predicts clinical success by using the closest possible model of drug behavior in humans

REPROCELL offers contract laboratory services to pharmaceutical and biotechnology companies, providing data on the likely effects of drug candidates before they are given to human volunteers and patients. By understanding the safety and effectiveness of a drug in a pharmaceutical lab test, much more expensive clinical trials can be de-risked.

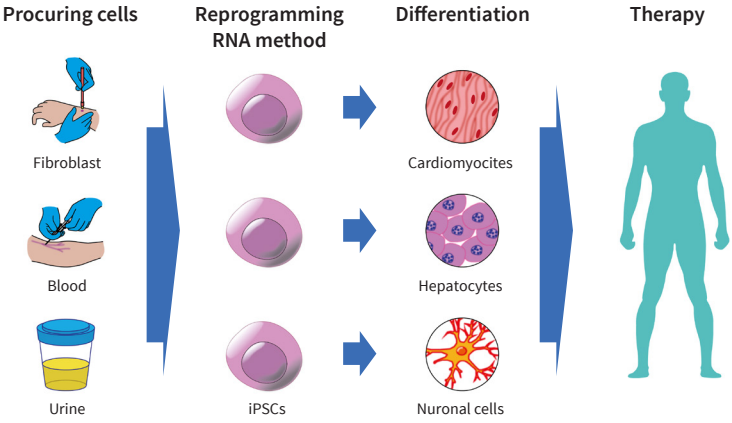
We help our clients manage risk and save money

Demonstrating human efficacy and safety at an early stage of development has an enormous commercial value to our clients' research programs. For 10-20% of the drugs we have tested, the client decided to rethink their clinical strategy which seemed likely to fail based on the human tissue data. We estimate that this has resulted in net savings of more than $55 billion in total costs for our clients.



More than **$55 billion** in wasteful costs have been avoided

REPROCELL's iPSC technology platform



1. Target Identification

Determine the biological origin of the disease and potential targets for intervention using human tissue samples. Investigate receptor sites on particular cells that may be abberantly expressed in the disease state.

The BioServe Global Human BioRepository

REPROCELL's BioServe's Global BioRepository is one of the largest commercial human tissue banks in the world.

All samples are linked to approximately 200 data points about demographic, phenotypic, pathology and diagnostic information and drug history.

We have it...

Our BioRepository contains more than 600,000 human serum, frozen tissue, DNA, RNA, FFPE and other samples collected from over 120,000 consented and anonymized patients on four continents.

Our network has it...

The BioServe Biospecimen Repository Network of partner organizations also provides broader access to rare samples and the ability to source material specific to your research needs through prospective collections.

Or, we can collect it

BioServe continues to establish procurement partnerships with speciality clinics around the USA in a number of indications/ diseases, including auto-immune, inflammatory and rheumatology, urology and oncology.

2. Target Validation

Determine the biological origin of the disease and potential targets for intervention using human tissue samples. Investigate receptor sites on particular cells that may be abberantly expressed in the disease state.

Assess the Efficacy of Your Drug Candidate in Diseased and Healthy Tissue

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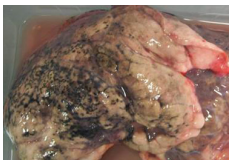
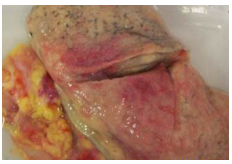
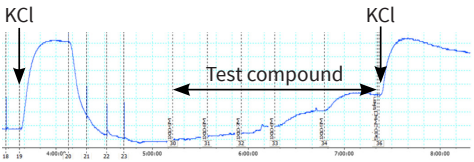
- Compare activation of potential target and functional response.
- Explore differences in drug response between patients and relate responses to clinical histories.



COPD lung



Healthy lung



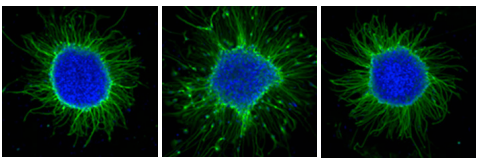
Measure bronchoconstriction or dilation

StemRNA™ Neuro —iPSC-derived Differentiated Neurons

stemgent

REPROCELL's Stemgent StemRNA Neuro* are differentiated using proprietary technologies that result in a mixed population of neuronal cell types.

- World's first commercially available iPSC-derived human neurons
- Displays highly complex networked morphology with synaptic junctions
- Alzheimer disease patient-derived and engineered mutant versions are available
- Clonally derived, highly consistent lot-to-lot performance, and stable phenotype



Neurite Outgrowth in 2D Culture. (**A.**) StemRNA Neuro, (**B.**) StemRNA Neuro AD-patient and (**C.**) StemRNA Neuro AD-mutant cells were first reformed into neurospheres and then allowed to attach to plates treated with Neuro Coat. Cells stained with DAPI (blue) and anti-TUJ-1 (green) fluorescent detection reagents.

(* Formerly known as ReproNeuro.)

3. Lead Identification

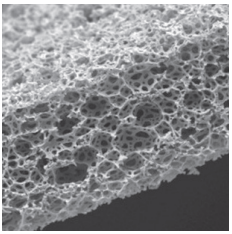
Perform high throughput screening of drug candidates on complex cell systems grown in 3D for physiologically meaningful data to identify potential leads.

Alvetex 3D Cell Culture Models

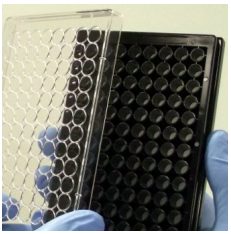
alvetex

3D cell cultures using REPROCELL's Alvetex technology deliver more *in vivo*-like results than traditional 2D monolayer cultures.

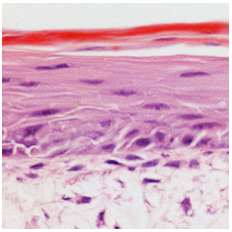
- Highly porous inert scaffold made from cross-linked polystyrene (200 µm thick).
- Suitable for a wide range of cell types including primary or iPSC-derived cells from most organs, various stem cells, cancer, and complex co-culture models.
- Automation – 96 well and 384 well plate formats compatible with high throughput screening and a variety of assays and techniques.
- Build more predictive biological models by maintaining *in vivo* physiological properties, enhancing cell viability and longevity.
- Simple histology, imaging and RNA/protein isolation analysis endpoints.
- Add perfusion in 3D for another step closer to *in vivo*.



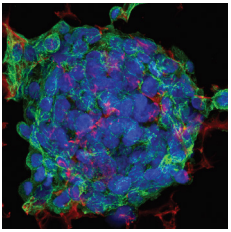
SEM of Alvetex Scaffold



96 well and 384 well plate formats available



Co-culture of primary keratinocytes and primary dermal fibroblasts forming a full-thickness human skin construct



Triple fluorescent staining of HepG2 cells grown in 3D on Alvetex Scaffold

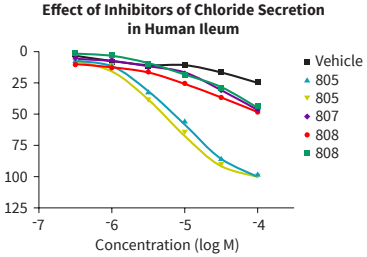
4. Lead Optimization

Accurately predict *in vivo* bioavailability and drug metabolism using human tissue, eliminating well known differences between human and alternative model systems.

Determine the Potency of Your Drug

- Compare the potency of your candidate drug versus other drugs on the market.

Small intestine ileum

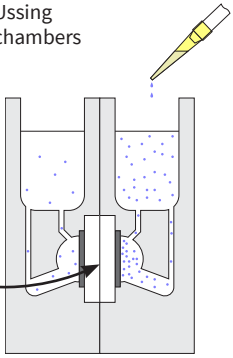


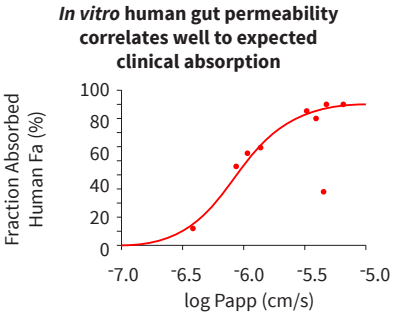
Increase the Confidence of Your First-in-Man Dose Estimate

- Measure compound permeability, transporter, or metabolic enzyme activity in human intestinal tissue in order to accurately predict *in vivo* bioavailability and drug metabolism.
- Eliminate well-known differences between human and animal or cell models in bioavailability and metabolism by using human tissue.

Healthy fresh small intestine

Ussing chambers





5. Pre-Clinical Safety

Are your test compounds safe in humans? Evaluate the pre-clinical safety of compounds using human tissue.

Find Out if Your Drug is Safe in Human Tissue Prior to Clinical Trials

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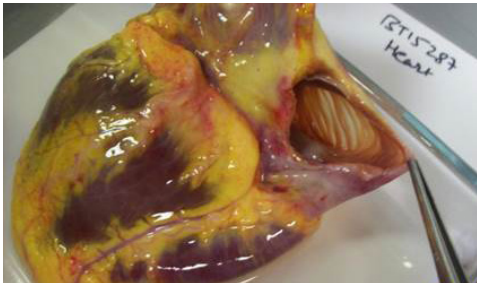
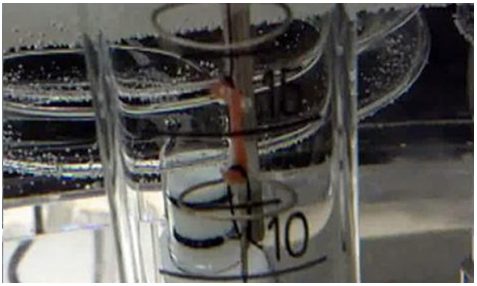
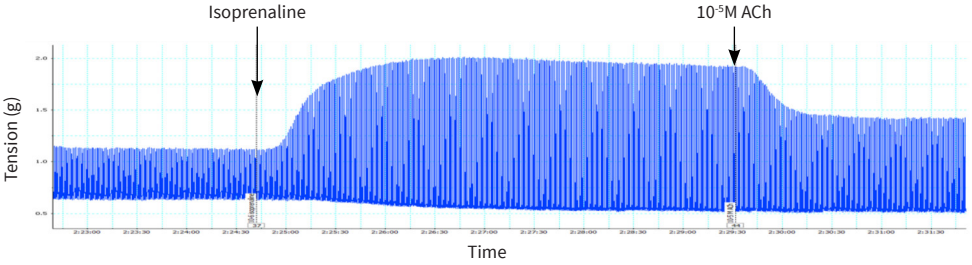
- Measure adverse effects on heart or lung muscle contractility or blood vessel contraction/ dilation.
- Conduct comparative studies across species.

Human heart



Force of contraction measured in organ baths





6. Clinical Trials

Troubleshoot clinical problems by investigating the mechanisms of clinically-observed adverse effects using human fresh tissues.

Investigate Unexpected Side Effects Observed in Clinical Trials

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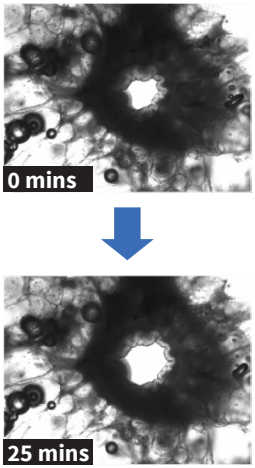
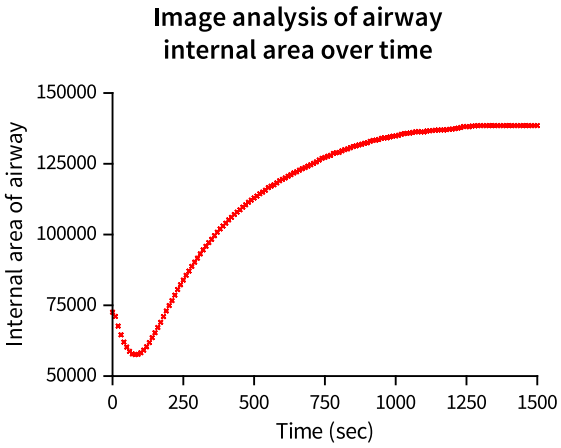
- Obtain independent verification of your clinical results.
- Examine adverse effects e.g. unforeseen effects on bronchiole dilation effecting airway internal area over time.



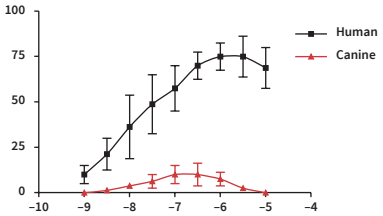


REPROCELL generates high quality translational data to help you make informed decisions during drug development.

Only a selection of our available tissues and assays is shown.
See our website or contact us for more information.

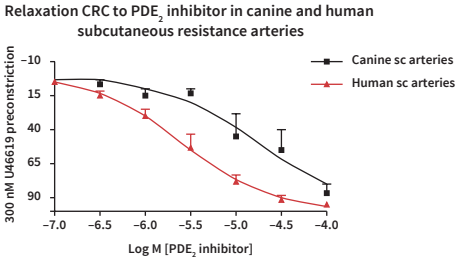
REPROCELL can directly compare drug responses across species, helping you to translate your data from preclinical animal species to humans

It is generally recognised that there is an over-reliance on animal models in the prediction of clinical effects, in particular with respect to the demonstration of efficacy in humans and the translation from preclinical species. Biopta's ability to perform comparative *in vitro* studies, including human tissue, highlights potential species differences early in the drug development process. This has become especially important in translational medicine, through preclinical safety studies and the need improve the prediction of efficacy by using phenotypically-relevant fresh diseased human tissue.



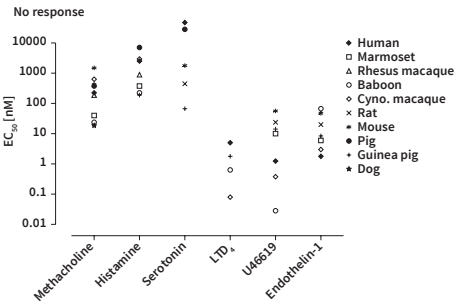
For example, the 5-hydroxytryptamine (5-HT, serotonin) pathway is more prominent in the coronary artery function of human than in canine tissues, a standard preclinical safety species and pig, a favoured cardiac model species. The above graph shows the marked differences in responses of isolated arteries to 5-HT between humans and dogs.

A further example below shows clear differences in the potency of a PDE type 2 inhibitor in humans and dogs, such that assessment of test compound effects in dogs would under-estimate the effect in humans.



It is not only in the vascular system that such differences exist between species.

A review of the literature illustrates that the potencies of various bronchoconstrictors differ markedly between the main preclinical species (see comparison below), with no species mimicking the human situation. Approximately one-third of all respiratory abnormalities during human clinical trials can be attributed to unforeseen drug-mediated changes in airway resistance. Taken together, these findings suggest that the prediction of human bronchoconstriction (and therefore airway resistance) could be vastly improved by greater use of human fresh bronchial tissues or by an early cross-species comparison between preclinical species to explore the relevance of the animal model to humans.



Adapted from:
Seehase *et al.* (2011) *J. Appl. Physiol.* 111:791-798
Downes *et al.* (1986) *J. Pharmacol. Exp. Ther.* 237:214-219

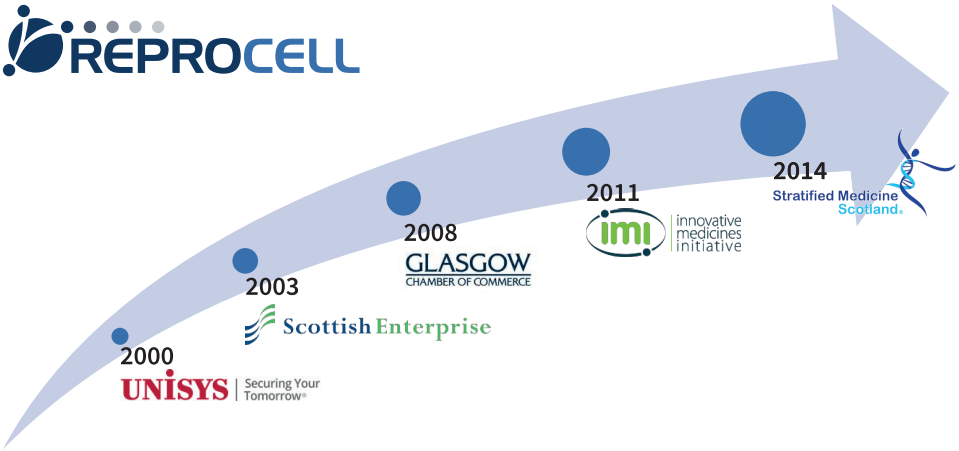
Although animal models continue to be a mainstay in the testing of potential new drug therapies, early cross-species comparisons with fresh functional human tissues increases confidence that the results will translate to patients. Moreover, such assays play an important role in the "3Rs", the refinement, reduction and replacement of tests in animals.

REPROCELL (formerly Biopta) has been providing contract research services to the pharmaceutical industry since 2002 and has established itself as the world leader in the use of fresh isolated tissues to better predict drug activity prior to clinical trials. The clear commercial benefits of reducing risk by generating early human data on safety, efficacy and absorption are making human tissue research a routine part of drug development. REPROCELL's expertise in all areas of human tissues research including sourcing, handling and experimenting on human tissue allows us to act as your "Human Tissue Research Department".

To discuss a comparative *in vitro* pharmacology study across species at REPROCELL please contact **info-emea@reprocell.com**

Award Winning Business

At REPROCELL, we have been awarded several titles for our work in human tissue research, including the Scottish Enterprise SMART Award (2003) and the Innovative Medicines Award (2012). Today, we are the preferred vendor of the Medicines Discovery Catapult (2019) and remain world-leaders in human tissue research globally.



Fulfilling Your Research Goals

REPROCELL work with a variety of clients, ranging from the top 20 Pharma to virtual biotechs. Numerous companies have also published using data generated in REPROCELL's labs. Below you can find a collection our client testimonials and publications.

Testimonials

"*[REPROCELL] has provided Proteon with high quality data in human tissue to guide dose selection for human clinical trials. The information has and will continue to be an important part of our nonclinical data for regulatory submissions.*" — **Senior Vice President and Chief Medical Officer, Proteon Therapeutics Inc.**

"*[REPROCELL's] human tissue services have played a critical part in our compound selection and have added considerable value to our lead compound. At our last round of funding, the investors were reassured by the presence of functional data on living human tissues.*" — **President & Head of R&D, Canadian Biotech.**

Publications

Lynch *et al*. **Comparison of the Intrinsic Vasorelaxant and Inotropic Effects of the Antiarrhythmic Agents Vernakalant and Flecainide in Human Isolated Vascular and Cardiac Tissues.** *Journal of Cardiovascular Pharmacology* 61:3 226–232 (2013).

Skinner *et al*. **The contribution of VEGF signalling to fostamatinib-induced blood pressure elevation.** *British Journal of Pharmacology* 171:9 2308-20 (2014).

Figure 1: Whole human organs and tissues can be obtained from our global network of biorepositories.

Figure 2: Patient derived cell lines can be obtained for iPSC transformation and differentiation.

Figure 3: Our scientists can then use these tissues to test the safety and pharmaco-kinetics of your test agent.

Figure 4: We can also measure test agent efficacy and investigate the cause of adverse drug reactions.

REPROCELL worldwide