Stem Cell Services

REPROCELL Discovery Technologies

Latest Generation RNA Technology

REPROCELL is the exclusive provider of the **Stemgent® StemRNA™ 3rd Gen** reprogramming technology — the most rapid, robust, and clinically-relevant integration-free method on the market. REPROCELL offers custom iPSC production services to clients in industry and academia with over 15 years' experience as leaders in stem cell research. The third generation RNA technology is faster, more stable and footprint-free, allowing REPROCELL to deliver iPSCs in around half the time of its competitors.

REPROCELL's iPSC Contract Services

- Global custom service and research labs in America, Europe and Asia
- Fresh, normal or diseased tissue available through our custom collection network
- Establishment of patient-derived primary somatic cell lines as part of the standard service
- Reprogramming of multiple human and non-human cell types
- Cryopreserved patient-derived primary cells and iPSCs expanded and provided
- Management of projects based on milestone achievements for flexible project customization and fair value

Comparison of Current Non-Integrative Reprogramming Technologies[1]

Reprogramming technology	**Sendai** ThermoFisher	**Episome** Thermofisher	**StemRNA 1st & 2nd Gen** REPROCELL (Stemgent[2])	**StemRNA 3rd Gen** REPROCELL (Stemgent[2])
Non-integrative	✔	?	✔	✔
No vector retention	✖	✖	✔	✔
DNA-free/Virus-free	✖	✖	✔	✔
No screening required	✖	✖	✔	✔
Normal karyology and stability of iPSC	++ [3]	+ [3]	+++ [3]	+++
Reprogramming efficiency	++ [3] 0.08%	+ [3] 0.01%	++ [3] 1%	++ 2-4%
Reprograms refractory patient lines	✖	✖	✔	✔
Time to usable iPSCs	**8-10 weeks** (Passage 10+)	**10-12 weeks** (Passage 10+)	**5-6 weeks** (Passage 4-5)	**4 weeks** (Passage 4-5)

[1] Data based on fibroblast reprogramming. [2] Stemgent Inc. was acquired by REPROCELL Inc. (Japan) in 2014. [3] Based on Schlaeger *et al.*, *Nature BioTechnol*. 2015.

Five reasons to choose **StemRNA 3rd Gen** reprogramming

1. **No screening of iPSCs required**
Non-viral, non-DNA, non-integrating cellular RNA reprogramming allows for the generation of clinically-relevant iPSC lines without the need to screen clones for vector retention (footprint-free) — this saves you time and money!

2. **Robust and consistent**
A unique microRNA cocktail increases the overall efficiency and enables success for refractory or difficult-to-reprogram patient-derived samples across multiple different somatic cell types.

3. **Most-efficient and fastest reprogramming kinetics**
High reprogramming efficiencies of between 1-4% of primary cells, depending on the cell type, with iPSCs ready to be expanded by day 10-14.

4. **High quality iPSCs**
Our generated iPSCs are robust in culture, and display very low clone-to-clone variability with normal karyology. These easy-to-maintain reprogrammed cell lines can be used by anyone even with minimal cell culture experience, eliminating the need for high level stem cell expertise.

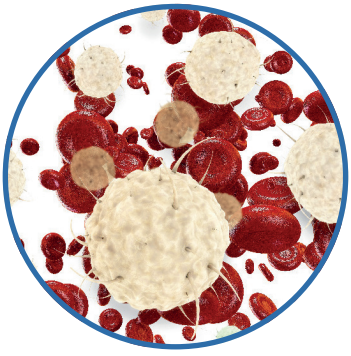
5. **Safe and clinically compatible**
The non-modified RNAs of our StemRNA 3rd Gen technology are synthesized using a GMP-compatible manufacturing process. The reprogramming protocol and the iPSC maintenance medium (NutriStem® hPSC XF Medium) are chemically defined, xeno-free and serum-free. NutriStem is produced under cGMP compliance, with an FDA drug master file available. The iPSCs are cryopreserved in ReproCryo™ DMSO-free medium.

TISSUE PROCUREMENT	CELL LINE ESTABLISHMENT	REPROGRAMMING	EXPANSION/ BANKING	CHARACTERIZATION	DIFFERENTIATION
• Blood • Skin punch biopsy • Urine	• EPCs • Fibroblasts • UPCs	• Non-integrating RNA	• Clonal selection • Cryopreservation	• Immunocytochemistry • *In vitro* differentiation • Karyotyping	• Cardiomyocytes • Neurons • Hepatocytes

Which cells can be reprogrammed?

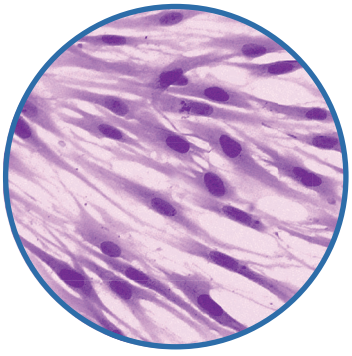
Human Blood

- Target cell type: **Endothelial Progenitor Cells (EPCs)**
- Sample submission: Fresh peripheral or cord blood or cryopreserved EPCs



Human Skin

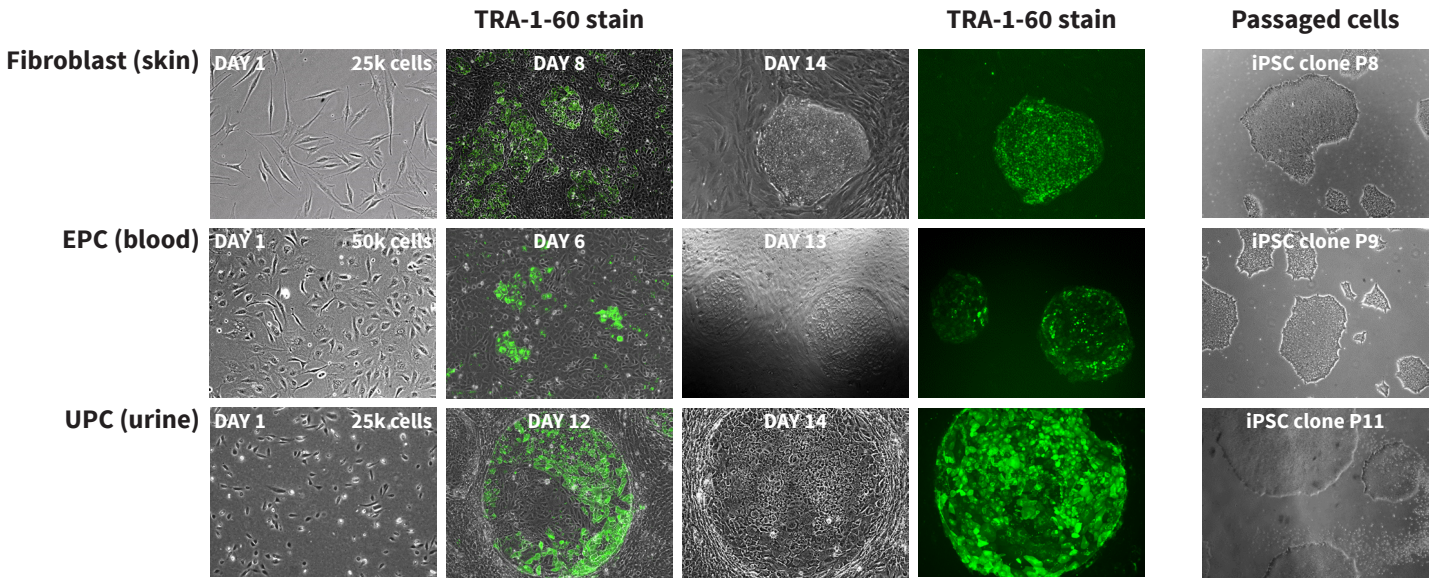
- Target cell type: **Adult dermal and neonatal Fibroblasts**
- Sample submission: Fresh skin biopsy or cryopreserved fibroblast cell lines



Human Urine

- Target cell type: **Urine-derived Progenitor Cells (UPCs)**
- Sample submission: Fresh human urine or cryopreserved UPCs

Reprogramming timeline



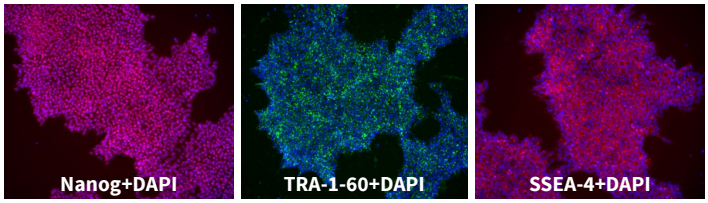
Reprogramming protocol:

- No conditioned medium
- No feeders
- No small molecules
- No screening required
- No cell passage or splitting

iPSC Colony Morphology and Pluripotency.

Primary somatic cells at Day 1 and morphology of emerging iPSC colonies are shown at progressively later stages. The pluripotency marker TRA-1-60 shows increasing levels of expression with iPSC maturity. Expanded iPSC clones (passaged cells) illustrate stable iPSC lines out beyond passage 8.

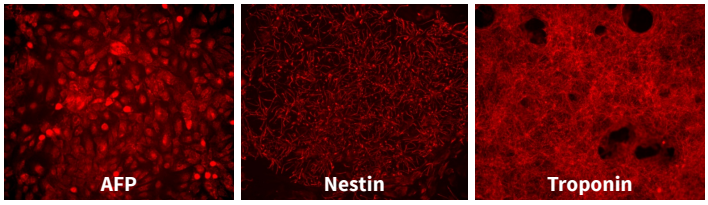
Pluripotency



Immunocytochemical Staining of Urine-derived iPSCs.

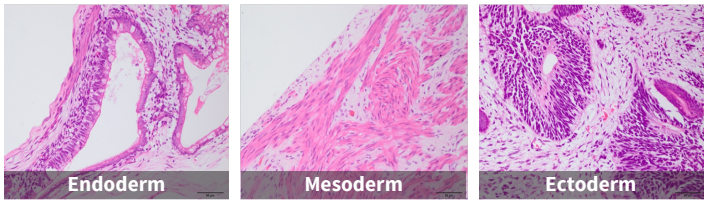
The morphology and expression of key pluripotency markers and DAPI are shown by immunostaining of UPC-RNA-iPSCs (passage 7) with various antibodies.

Differentiation



Validation of Tri-lineage Differentiation of Urine-derived iPSCs.

In vitro differentiation of UPC-RNA-iPSCs (passage 11) into early endoderm (AFP), neuronal cells (nestin) and cardiomyocytes (Troponin T) is shown by immunocytochemistry.



Validation of Tri-Lineage Differentiation of EPC-derived iPSCs.

Histological analysis of teratoma resulting from the injection of EPC-RNA-iPSCs (passage 13) into the kidney capsule of immunocompromized mice.

"For human fibroblast reprogramming, the StemRNA 3rd Gen reprogramming system is outstanding for efficiency & clinical relevance."

— Dr. Marco Poleganov, Head of Stem Cells & Reprogramming, BioNTech RNA Pharmaceuticals GmbH

"Next generation, clinically-relevant iPSC reprogramming"

What does a typical reprogramming project include?

- Each project gets a dedicated Study Director to customize and support your needs throughout the entire project.
- Our broad capabilities allow for customized optimization of transcription factors, culture conditions and protocol development for your unique project.
- Through our human tissue procurement network (BioServe or Biopta clinical partners) we can ethically source fresh samples of healthy or diseased clinical material, or you can provide the source material for reprogramming.
- We establish the primary cell cultures, expand, archive and provide the cryopreserved cells as part of the service.
- Our highly skilled stem cell scientists have extensive experience with derivation of primary cell lines from multiple cell sources and using these newly established low passage cell lines in RNA reprogramming to achieve optimal results.
- Cryopreserved iPSCs are provided to you from expanded-out clonal lines with validation data, according to the service level package that you have selected.
- Our research labs can also offer differentiation services into custom-engineered somatic cells based on your requirements.

REPROCELL has reprogramming technical experts and stem cell laboratories on three continents. Above: REPROCELL's stem cell laboratories around the world: **A**: Centre for Predictive Drug Discovery in REPROCELL Europe (Glasgow, Scotland), **B**: REPROCELL USA (Beltsville, MD) and **C**: REPROCELL HQ (Yokohama, Japan). Contact information is provided below if you wish to visit or discuss a service project performed by our highly experienced staff.

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