FREQUENTLY ASKED QUESTIONS:

REPROCELL Custom iPSC Services

Questions about the StemRNA 3rd Gen Reprogramming Technicology and Service Packages

1. Why use mRNA for reprogramming?

Using mRNA for reprogramming provides the optimal combination of efficiency, speed, quality, and clinical relevance.

- **mRNA reprogramming provides the highest efficiency** (number of iPSC colonies per starting target cell) of any common reprogramming method, yielding up to 4% efficiency. This can mean the difference between success and failure of the project when reprogramming target cells from actual patients, rather than controls chosen for ease of use.
- **mRNA reprogramming provides high quality iPSCs in the shortest time**, allowing the project to quickly proceed to the next step. iPSCs reprogrammed with mRNA do not retain reprogramming vectors, meaning that no time-consuming vector screening is required, as mRNA is cleared from the cell within 18 to 24 h after transfection. mRNA-reprogrammed iPSCs show the lowest rates of genetic abnormalities such as aneuploidy, compared to the starting target cell, at the chromosomal level.
- **mRNA reprogramming allows easy access to clinically-relevant iPSCs,** insuring that work won't need to be repeated as you move from research to clinical development. Therapeutic mRNA is currently being investigated in clinical trials in several disease areas, showing the synthesis of clinical grade RNA is readily accessible. Other reagents used in RNA reprogramming are also available GMP grade.

2. What is the StemRNA 3rd Gen Reprogramming Technology?

The StemRNA 3rd Gen Reprogramming Technology is a non-integrating system that uses RNA only to reprogram somatic cells into iPSCs. The reprogramming kit contains six reprogramming mRNAs (OCT4, SOX2, KLF4, c-MYC, NANOG, LIN28), three immune ablating mRNAs and a proprietary miRNA cocktail. Using our footprint-free technology all RNA is cleared from the cells and degraded 18-24 h after delivery into the somatic cell.

3. What does REPROCELL's iPSC reprogramming service include?

Every service project is milestone-based and customizable to meet your needs. For induced pluripotent stem cell (iPSC) services, REPROCELL can perform donor tissue collection, sample quarantine, derivation of primary cell lines, RNA-based iPSC reprogramming, expansion, characterization, cryopreservation, and differentiation into particular cell types. Our standard quality control package includes mycoplasma, infectious disease check, STR analysis and live-staining for certain pluripotency markers. Additionally, our in-house services team can provide more detailed characterizations such as pluripotency analysis by immunocytochemistry, flow-cytometry and functional pluripotency by tri-lineage differentiation. Additional characterization services can be modified to fit the specific needs of the project and performed by REPROCELL's strategic partners. Examples of assays include: karyotyping, cell banking, genome-editing, teratoma formation, CGH/SNP arrays, etc.

4. What kind of primary cell types can be reprogrammed with the StemRNA 3rd Gen Reprogramming Technology?

The primary cell types that can be reprogrammed with the StemRNA 3rd Gen Technology includes primary fibroblasts (adult and neonatal), endothelial progenitor cells derived from blood and urine progenitor cells. For additional human and non-human cell types (which have no standard reprogramming protocol yet) using our StemRNA 3rd Gen Reprogramming Technology we offer a milestone-based developmental service projects. For iPSC services, REPROCELL can procure starting cell sources such as blood, urine and skin through our extensive custom collection network and establish patient-derived primary somatic cell lines

5. What are the timelines and costs for your iPSC reprogramming service?

REPROCELL is committed to customizing a unique reprogramming service project based on your needs and your budget. The StemRNA 3rd Gen iPSC technology is one of the fastest and most efficient iPSC reprogramming technologies available. This technology does not require any downstream screening once the iPSC lines are generated. By day 10-15 iPSC clones are mature enough to be expanded and then ready-to-use after additional 2-3 weeks of expansion and banking. We also offer the option for a bulk reprogramming package where one iPSC line is generated by pooling clones and is therefore available for use even faster. All service costs depend on the primary starting cell lines, the number of lines to be reprogrammed and the extent of the quality control and your characterization needs (karyotyping, genome arrays, pluripotency assays, etc.).

If considering the timeline of a more extensive service projects which would include tissue collection timelines, primary cell line derivation, further expansion and banking of cells, etc. we generally like to suggest that once we have sourced the correct patient tissue, we can deliver a final product in the timeline of 3-4 months.

6. Can you source the donor or patient tissue for us as well?

Yes, REPROCELL's BioServe brand is well known for a vast biorepository of over 600,000 clinical samples from over 120.000 patients, global partner network and prospective sample collection services. The Biopta brand also has a wide tissue network and 24/7 operation and systems for collection and receipt of fresh human tissues out of regular hours.

7. Can you reprogram a patient sample from your existing BioServe patient biorepository?

We validated the StemRNA 3rd Gen Technology for reprogramming of primary fibroblasts (adult and neonatal), endothelial cells derived from either peripheral or cord blood (fresh or frozen MNCs), and fresh urine cells. We are also in the process of extending this application to more primary cell types. Therefore, we offer our customers access to our sample collection expertise and networks for collecting primary samples for your reprogramming project. As most of our existing Bioserve patient biorepository consist of human serum, DNA, RNA, and FFPE samples these samples are not suitable for generating iPSCs.

8. Will you keep a stock of the patient material or patient-derived iPSCs yourself?

Upon completion of the reprogramming service project, all patient material that was provided by you for us to carry out the reprogramming services, as well as the patient-derived iPSCs will be returned and sent to you. You

have the option to (i.) accept the return of the material at your expense (ii.) pay an archiving cost for further storage or (iii.) request for destruction. In case patient samples were sourced by us, such samples shall remain our property.

9. Which location are your iPSC services provided from?

UK (Glasgow, Scotland), US (Maryland), Japan (Yokohama).

10. What are the differences between the UK/US/Japan iPSC service labs?

All three sites use the same Standard Operating Procedures (SOPs). Some of the outsourcing partners for quality control assays may differ, but the service packages are the same. This allows us the unique opportunity to conduct projects at the location where we have the easiest access to patient samples to fit your program needs.

11. Can you provide iPSC differentiation services as well? Which cell types?

Yes. REPROCELL was the first company to commercialize differentiated iPSC cells. We regularly differentiate iPSCs into cardiomyocytes, hepatocytes and neurons in our service labs in all three sites. We have in-house protocols but can also follow the customer's specific protocol. For interest in differentiation service projects of other (e.g. muscle cells) or more specialized cell types (e.g. RPE's, dopaminergic neurons, sensory neurons etc.), we should be able to accept the project after consulting with the client and understanding more of the specific needs (kind of cell types, number of cells per run required etc.).

Questions about Competitors / Pricing

1. Why is your method (3rd Gen RNA) better/ different compared to other reprogramming technologies on the market?

- The 3rd Gen RNA Reprogramming Technology is unique to REPROCELL and is the fastest, cleanest technology.
- The 3rd Gen RNA is the only RNA-based technology that can reprogram adult and neonatal fibroblasts as well as blood and urine derived cells into iPSCs. This is a highly valuable feature in case it is not feasible to procure a skin punch biopsy from a patient. Some companies provide mRNA-based iPSC generation services using our discontinued 1st or 2nd Gen RNA technology (both replaced by the 3rd Gen Technology) which only works reliably on (neonatal) fibroblasts, with longer non-xeno protocols using conditioned medium and generates iPSCs less efficiently.
- Most other companies only offer reprogramming with Sendai Virus or Episomal DNA. These technologies have the potential for either sustainability or integration of the expression vector and hence require downstream screening to ensure the vector is not remaining in the cells. There may be a risk of spontaneous differentiation once the vector cleared and the cells need to maintain the pluripotent state independently.
- The 3rd Gen Technology can easily reprogram refractory and/or low proliferative cell lines.

2. Can I get a discount on multiple iPSC lines?

Every contract is handled independently, so please check with your local Sales Managers. This is more likely in case we can get all donor samples at the same time since we can perform many steps in parallel. Another discount way to get a discount is to use other services we provide such as iPSCs differentiation services into relevant cell types.

Questions about License Model / Freedom to Operate

1. Can I use the iPSCs for a cell therapy program we are working on?

REPROCELL's current service offering are for research use only and does not consent the iPSCs generated to be used for clinical/cell therapy purposes. Projects that intend to use the iPSCs for therapeutic and/or clinical use would need a separate agreement and will be evaluated on a case by case basis.

2. Can you provide clinical-grade reprogramming services?

REPROCELL is building a GMP facility in Japan that will be able to perform this service on a small-scale by the end of 2018. The reprogramming RNAs and culture media can be made to GMP-grade. Please inquire about costs.

3. Is commercial sale of iPSC products allowed and what is my Freedom to Operate?

Yes. Internal R&D use or commercial sales of products or services using differentiated iPSCs or derivatives is allowed. There are no upfront fees, annual maintenance fees or royalties if the customer does not commercialize the product. The freedom to operate will be detailed in the User Agreement that will be sent to you together with the service contract. Distribution (passing and sale) of undifferentiated iPSCs is by default not allowed without REPROCELL's explicit written permission.

4. Can I sell the undifferentiated iPSCs to other companies/ universities, etc.?

No, selling of undifferentiated iPSCs is by default not allowed. Exceptions can be made upon REPROCELL's written permission.

5. We would like to use these iPSCs for a research collaboration/ consortium where we will be reimbursed on cost recovery basis. For participation we would need to pass the undifferentiated iPSCs to another partner for genome-editing/ differentiation/ automated scale-up, etc. Is this possible?

Passing undifferentiated iPSCs to third parties amongst academic research groups/partners is allowed. Please inquire more information about specific cases. For example, if such transfer involves transfer of ownership of iPSCs.

6. We are partnering with another commercial company who will be genome-editing these iPSC lines for us. Can I send them the undifferentiated iPSCs?

Passing undifferentiated iPSCs to third parties for genome-editing is allowed as long as this is not for commercial sale, or the third party will not be selling derivatives of the cells for commercial gain. REPROCELL has a collaborative partnership with improved, highly efficient genome-editing capability using CRISPER/Cas9 technology. Please contact us for more information.

7. Can I differentiate the iPSCs into neurons/hepatocytes/cardiomyocytes, etc. for providing commercial (screening) services to other companies?

Yes, a fee will apply for commercializing differentiated iPSCs. Please contact us for more information.

8. Can I sell differentiated iPSC cells to other companies/ universities, etc?

REPROCELL has a collaborative partnership with improved, highly efficient genome-editing capability using CRISPER/Cas9 technology. Please contact us for more information.

9. We are partnering with other companies/ university labs who have a specialist differentiation protocol and we want them to differentiate our iPSC cell lines. Can I send them the undifferentiated iPSCs?

Passing undifferentiated iPSCs to third parties for specialist differentiation protocol is allowed as long as this is not for commercial sale, or the third party will not be selling derivatives of the cells for commercial gain. We have our own in-house expertise for differentiation. Please contact us for more information.

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