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CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Memorandum

To: Members of the ICOC
From: Rosa Canet-Avilés, Chief Science Officer, CIRM
Re: CIRM iPSC Repository Closure
Date: May 20, 2025

From 2013 to 2018, CIRM funded the creation of a large research-grade induced pluripotent stem cell (iPSC) repository using blood or skin donated by more than 2000 participants. The goal was to enable iPSC-based modeling of polygenic, genetically complex diseases such as Alzheimer's disease, liver disease, neurodevelopmental disorders, and other diseases. The repository opened for business in September 2015, when the first three hundred lines became available to scientists worldwide. See Appendix A for a description of the iPSC repository, cell distribution data, and select outcomes.

The iPSC lines in the repository are owned by CIRM, while the underlying intellectual property is owned by multiple entities consolidated through Cellular Dynamics (now FUJIFILM Cellular Dynamics FCDI), who received a 2013 grant to generate the cell lines. Since 2018, FCDI has also been the CIRM iPSC repository manager, storing and fulfilling orders for the CIRM iPSC lines to academic, non-profit, and for-profit institutions, at no-cost to CIRM.

On October 7, 2024, FCDI informed CIRM that it will cease to manage the iPSC repository, with a July 16, 2025, termination date. FCDI suggested a potential new repository partner and offered their assistance in transitioning the iPSC repository to a new repository manager.

In planning the transition of the iPSC repository from FCDI to another partner, it became apparent that continued operations would incur substantial costs to CIRM (approximately $400k for the initial transfer and set-up, and an additional $300k per year for maintenance). The historical annual revenue from the repository falls short of the projected cost of operations by several hundreds of thousands of dollars, and this annual gap would need to be funded by CIRM indefinitely.

Given the large annual costs to CIRM for maintaining iPSC repository operations, due to lower than anticipated use and, consequently, insufficient revenue, the difficult decision has been made to cease operations of the CIRM iPSC repository. We will be announcing a sale of CIRM iPSC lines at a reduced price ending July 16, 2025, after which CIRM iPSC lines will no longer be available for purchase. CIRM will retain a minimal number of vials, representing all CIRM lines, in storage, in case future interest warrants revival of parts or all of the repository.

We recognize the significant contributions this repository has made to the scientific community over the past decade, and thank all donors, researchers, and partners who have made its success possible. While the decision to end operations was not made lightly, we remain

committed to supporting innovative and impactful stem cell research across California and beyond.

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Appendix A

CIRM human induced pluripotent stem cell (iPSC) Repository – Description, Cell Distribution, and Outcomes

Despite the significant financial gap between revenue and cost of operations, the CIRM iPSC repository has had an important impact. Below is a summary of the generation of the CIRM iPSC repository, the distribution of the CIRM iPSC lines, and a snapshot into the outcomes of their use. Even though sale of CIRM iPSC will end mid-2025, the iPSC lines that have been distributed to academic institutions and industry over the last 9.5 years will continue to support new discoveries about human biology and disease in the years to come.

Goal of CIRM iPSC repository initiative

The goal of CIRM's iPSC Initiative was to create a resource for the research and drug development community for modeling of prevalent, genetically complex diseases by creating comprehensive collections of research grade iPSC lines for reliable distribution worldwide.

CIRM provided a total of $32M that funded 9 awards:

i. 7 programs for the collection of tissue samples from hundreds of patients for each of the included diseases.
ii. 1 award for the standardized derivation of iPSC through a single site (FUJIFILM Cellular Dynamics, FCDI).
iii. 1 award for a repository (Coriell Institute for Biomedical Research, later transferred to FCDI).

Repository characteristics:

- Centralized iPSC repository
  - Lines owned by CIRM
  - Lines banked and distributed by FCDI
- 2,600 different iPSC lines generated from 2,184 unique donors, created with uniform production method
- Standardized consent language, consented appropriate for intended use
- Demographic, medical and/or diagnostic information available from each donor
- Self-reported ancestry of tissue donors: While most tissue donors identified as White (70%), given the size of the repository, it represents many donors of other ancestries, i.e., 5% Hispanic, 9% Asian, 5% African American, and 0.7% American Indian & Pacific Islander.
- For commercial use, customers can obtain a single licensing agreement; commercial license terms were negotiated before the repository was made
- Whole genome sequencing (WGS) data for 299 CIRM iPSC lines and single nucleotide polymorphism (SNP) data for all CIRM iPSC lines is available at dbGaP.

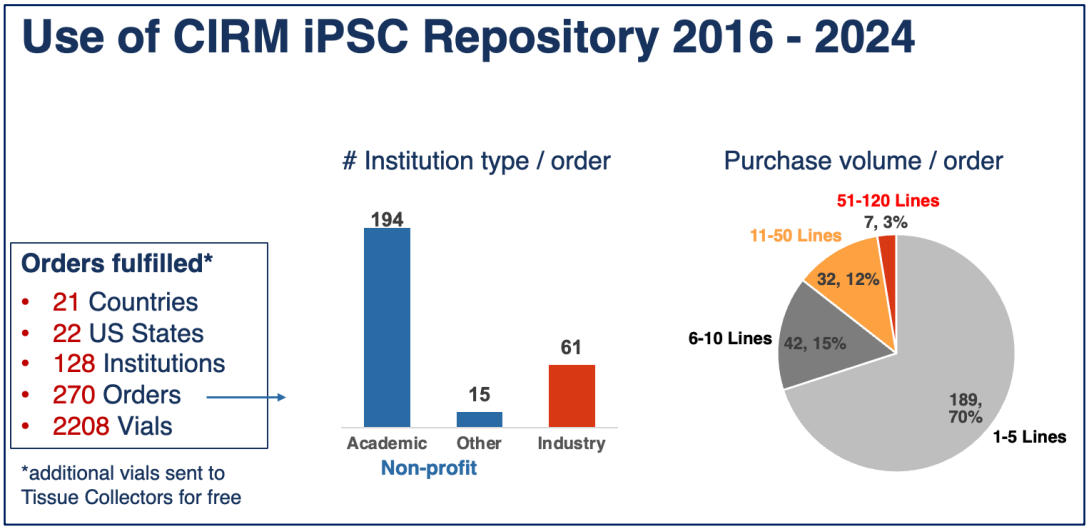
Increasing awareness of iPSC repository within the scientific community:

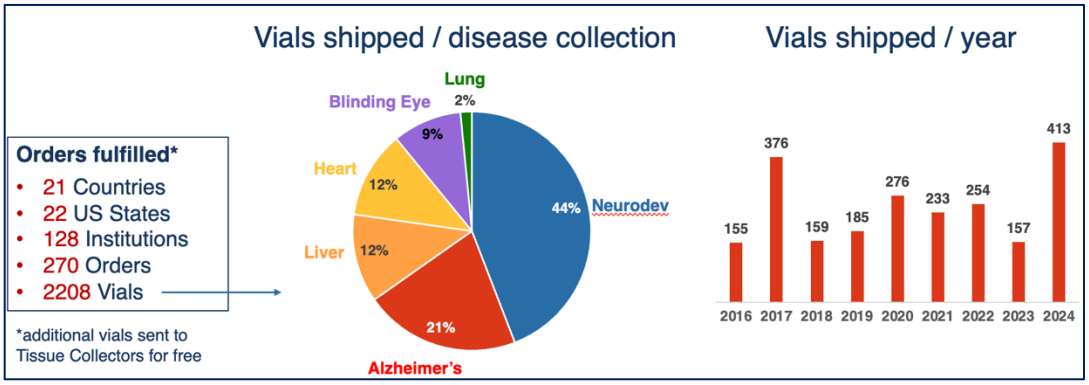
- Dedicated CIRM website

- Publication of a detailed description of this resource, Stem Cell Research 44 (2020) 101671
- Listed as a resource in relevant CIRM Program Announcements
- Advertised in CIRM presentations
- Registered iPSC lines with the hPSCreg project.

iPSC lines distributed

The repository started filling orders in 2016. By the end of 2024, more than 2200 vials of cells were purchased by non-profit and for-profit customers. In addition to iPSC lines distributed to customers, tissue collectors received lines corresponding to their tissue contributions for free, as part of their tissue collection agreements. See Figure for some additional details:





Since the goal of the repository was to enable modeling of prevalent, genetically complex diseases, large numbers of patients were recruited for a given disease. The assumption was that customers would acquire entire disease collections (dozens to hundreds of lines), to enable discovery of small phenotypic effect sizes. However, the volume of most purchases (85%) was low (1-10 lines), and only 3% of orders were for more than 50 lines.

The disease areas purchased most often were neurodevelopmental disorders, followed by Alzheimer's disease. Of note, 130 of the 270 orders were for control lines only.

A comprehensive outcomes analysis for the CIRM iPSC lines is beyond the scope of this document. A select set of studies from academic institutions is described next. Additionally, it is likely that some for-profit companies are using CIRM iPSC lines in target and biomarker discovery for select diseases, while others offer differentiated products to customers for their iPSC-based modeling needs.

Collaboration with the Broad institute

In 2019, CIRM established a collaboration with the Broad Institute of MIT and Harvard. Broad investigators purchased over 300 lines at a reduced price, whole genome sequenced 299 lines, and made that data available to interested researchers on dbGaP. They also shared SNP data for all CIRM iPSC lines, generated by FCDI as part of the QC process.

In vitro population studies

The size of the CIRM iPSC repository, and the uniform derivation and handling of the lines, lends itself to population studies. Of note, the following three examples make use of the large size of the CIRM iPSC repository, but do not rely on the diseases represented in the lines.

To enable use of large numbers of different cell lines to study the genetics of cellular phenotypes, the Broad investigators developed a 'cell villages' approach in which pools of ~100 cell lines are analyzed for cellular phenotypes. They developed a computational approach to de-convolute single cell findings from the villages using genomic information from individual donors. Different phenotypes displayed by cells from many lines in a single dish can thereby be attributed to specific lines through their genotypes. A manuscript describing a use case of this approach, using more than 100 CIRM iPSC lines, was posted to bioRxiv, and a study, using this approach, into the natural variation in viral susceptibility was published.

In a different large-scale approach, Broad investigators and colleagues used the SNP information (used for QC) associated with all CIRM iPSC lines to identify lines with extreme high and low polygenic risk scores for schizophrenia. A detailed analysis of these lines and their utility for modeling schizophrenia has been published.

Another customer of the iPSC repository, who purchased ~100 control lines, intended to perform genome wide association studies in a dish to assess the effects of common genetic variants on cellular phenotypes.

Disease modeling – liver disease

Several manuscripts have been published using the CIRM iPSC liver disease collection. The tissue collector who procured those samples, Jacquelyn Maher (UCSF), used 21 lines from Nonalcoholic Fatty Liver Disease (NAFLD) patients, and 16 lines from healthy control subjects to show that hepatocytes derived from NAFLD lines displayed a disease-specific gene expression profile and can be used for disease modeling. Relevant publications can be found here, here, and here.

A separate study, using 7 lines from the CIRM liver disease iPSC collection, led to the establishment of an in vitro model for non-alcoholic steatohepatitis (NASH).

A DISC2 award is utilizing CIRM liver iPSC to develop a screening tool to predict risk of NAFLD. A preprint describing this study can be found here.

Disease modeling – Alzheimer's Disease

Seven CIRM iPSC lines from the Alzheimer's disease collection were included in a study of APOE4's role in synapse loss and neurodegeneration in cerebral organoids.