DISTRIBUTION PRINCIPLES FOR BROAD CELL LINE FACTORY

Background:

In late 2013, a group of investigators from the Broad Institute and collaborating hospitals recognized a joint opportunity to accelerate the generation of patient derived, genetically characterized cancer models and reducing barriers to access. To test this concept, we received IRB approval (#13-185B) to launch a Cell Line Factory pilot to serve the scientific community and determine feasibility and best practices.

During the pilot period, the IRB mandated that distribution of new models and data be limited to co-Investigators (those that provided samples or were deeply committed to characterizing biology of new models and sharing knowledge). The co-Investigators and the IRB agreed that once feasibility had been established, that working together with an appropriate biorepository to draft a new IRB to facilitate access more broadly would be important.

Project overview and progress:

Over the last 24 months, the pilot has been extremely successful with the partnership of many co-PIs, clinical teams and Institutions. The team has processed 613 samples from 403 patients across 18 pilot cohorts, attempting to propagate samples under a diversity of culture conditions. Overall, we have observed a 56% success rate in enabling samples to proliferate to 5 doublings and 53% of the tumor-derived models have validated by sequencing.

Our process has 6 phases, with fully integrated LIMS and JIRA tracking throughout as well as QC checkpoints:

1. **Initiation (p0-p1).** Tissue samples of many types are dissociated into single cell suspensions and are initiated under a defined series of standard culture conditions as well tissue specific conditions.
2. **Nursery (p1-p5).** Cells are propagated for an initial five doublings.
3. **Verification (>p5).** QC confirmation step. DNA samples submitted to Broad’s Genomics Platform for Rapid Cancer Genomics Panel, consisting of 2500 amplicons (cancer mutations, chromosome alterations, gender, fingerprinting, mycoplasma, 5 day turn around).
4. **Expansion (p6-p10).** Expansion to 10 vials and additional passages. Testing of viability post freeze/thaw.
5. **Performance Testing.** Complete genomic analysis (WES and/or RNAseq). Testing of compatibility with standard media conditions, biological QC in collaborators’ labs (where appropriate), compatibility with large scale screening.
6. **General Distribution.** (Vendor TBD). Default scenario triggered by 9 months post expansion or publication.
We have completed the generation of the first set of CCLF cell lines, which will constitute our v1.0 release. This set will include approximately 30 high purity tumor models and 40 normal models. We would like distribution to go live with these models on or before May 2, 2016.

Looking forward, we expect to complete 100-300 models per year after that for the next 7 years (total target: 2000 cancer cell lines)

Possible guiding principles for distribution:

Our goal is to identify a mission-driven distribution partner that will optimally help us achieve the following guiding principles:

1. Making models and data available broadly will maximize the impact of our project. Success of the Cell Line Factory project will be ultimately measured by the impact we are having in accelerating cancer therapeutics; thus making models and data broadly accessible will propel our success.

   a. Ensuring ease of access: We may wish to establish either one or multiple biorepositories. However, no biorepository should constrain others’ ability to distribute models and data, as this would suppress success.

   b. Recognizing contributions: It will be highly desirable to have a mechanism to recognize individuals and institutions that were responsible for the generation of each cell line. For instance, the repository should list key people and institutions on the homepage for each cell line and, publications using CCLF models should cite the source page(s).

   c. Benefits for collaborating institutions: We believe that models should be broadly available. However, some institutions will have made larger investments in helping to establish the new models than others. Therefore, there should be a fair mechanism to appropriately incentivize and recognize institutions in a manner proportional to their investment.

   d. Discounts for academia: While facilitating access by both academic and biopharmaceutical researchers should maximize success; it would seem reasonable to ensure that academic researchers may obtain samples at reduced rates.

2. Our project should adhere to best practices for patient protection and privacy. Cancer cell lines come from cancer patients. Our biorepository plans must keep this in the forefront of our thinking.
a. **Ensuring consent:** The availability of models will be ultimately governed by whether patients have consented to such distribution. Thus, it will be desirable for the biorepository and the Broad to work closely together to track consent status.

b. **Provision to withdraw samples:** If a cancer patient requests that their model/data be withdrawn from the biorepository, we will work with the IRB and the biorepository to determine how best accommodate these requests.

c. **Protecting privacy:** While federal regulations and policies do not currently consider genomic data to be protected health information, we must consider that distribution of raw sequencing data could facilitate patient re-identification. Thus, it will be highly desirable for the biorepository to have mechanisms to distribute data (for instance, metadata) in a manner that is consistent with best practices for genomic privacy.

3. **We should commit to continually re-evaluating whether our plans are achieving the desired outcomes.** As time passes, we should work together to continually evaluate whether the initial distribution plan is working, and whether it continues to serve our needs. If it does not, there should be a mechanism to reconvene and modify our plan(s).

   a. **Framework for expeditious MTA agreement:** It will likely be desirable for the biorepository(s) to have infrastructure to facilitate rapid MTA agreement, with a goal to be as efficient as Addgene is for plasmid MTAs.

   b. **Intellectual property considerations:** As products of nature, cell models are unlikely to be patentable (except in rare circumstances). Furthermore, protecting models will likely reduce their potential for impact since access will be far more challenging.

   c. **Preventing re-distribution:** It would seem reasonable for individual labs to not be allowed to redistribute models without express consent from the biorepository(s). co-PIs should have access to all models from the project.

   d. **Diligence provision:** There should be a mechanism to withdraw the entire collection of cell lines and data from the biorepository and create a new plan if the biorepository fails to distribute models and data easily and rapidly.