Cell Stem Cell
Forum

Public Private Partnerships: A Marriage of Necessity

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Harnessing the unprecedented flexibility that iPSC technology and gene editing offer academic and industry-based researchers requires developing an interactive model of collaboration. Such a model will have to leverage the basic research expertise in academia with the pharmaceutical industry's knowledge in manufacturing and high throughput technology to be successful.

Moving toward Translation

The recent discovery that any somatic cell can be turned into a pluripotent cell or directly reprogrammed into a different lineage using only a small number of well-defined inducing agents has heralded a new era of possibilities. The ability to use either method to define intermediate stages at which cells can be expanded and purified makes it possible to obtain sufficient numbers of differentiated cells for a variety of purposes, including screens (Figure 1) and autologous therapy.

Using patient-derived cells, researchers can now coordinate stage-specific differentiation into rare, difficult to obtain, differentiated cell phenotypes, which allows them to examine the etiopathology of a particular human disease in vitro or in vivo without the confounding influences of immortalization, genotypic background, and allelic variability. The relative ease of this process and its high degree of fidelity allows this paradigm to be generalized so that studies can be performed not just on single cell lines from individual patients but on entire panels, including multiple lines per patient.

It is therefore now possible to consider obtaining cells from a series of patients with an obscure disease, transforming those somatic cells into induced pluripotent stem cells (iPSCs), and growing them in sufficient numbers to make this rare phenotype widely available to individual investigators, thus allowing them to assess the phenotype in a multitude of differentiated cell types. Cell sample is no longer limiting, and sufficient cells are available that large-scale screens that use billions of cells are now possible.

This ability to obtain useful information from patient-specific iPSC lines has been further enhanced by our ability to edit the human genome using gene engineering technologies whose efficiency has seen a dramatic improvement in the last decade. Improvements in homologous recombination technologies and in harnessing various DNA repair mechanisms using integrases, nucleases, meganucleases, recombinases, and transposases have allowed researchers to construct reporters in safe harbor sites, edit the genome to repair the altered site for isogenic controls, and to consider "personalized medicine" as a potential therapeutic strategy (Rao, 2011). Using these varied tools and expertise, however, will require skill sets that are not currently present solely in either industry or academia and will require the formation of new partnerships.

Why Academic Efforts Alone Are Not Sufficient

Although the technological breakthroughs have been dramatic and have occurred in the academic domain, several hurdles still remain before academic scientists will be able to transform these technological advances into cell-based products for translational science for screening or therapy. Some of these issues may seem obvious, such as simply setting up a new process in a laboratory and performing activity on a reasonable scale for screening with primary cells. Other obstacles are not as obvious. For example, most consent forms written in the past did not take into account the potential use of donated cells for screening or therapy and the recent advances in whole-genome sequencing. As a result, many existing lines simply cannot be used for screening purposes. Other consent agreements allowed use of the tissue sample obtained for very narrow or specific research purposes and thus do not permit their usage for making iPSC lines. These issues are relatively straightforward to fix, and indeed many efforts along those lines have already been made (Lowenthal et al., 2012).

Other obstacles, however, are more subtle, and creating meaningful solutions is not trivial. An example of one such issue is the fact that granting mechanisms historically developed budgets related to supplies based on a rule of thumb of how much was spent per person in a laboratory. Currently, grants are also given over shorter time periods than in the past with competitive renewal requirements over that short timeframe. These circumstances often mean that grants cover a period spanning 1 to 3 years with an annual renewal process based on progress made. However, these grant processes and timelines are extremely difficult for an average researcher to adhere to while demonstrating sufficient progress. For example, making a well-characterized iPSC line takes about 8 months if one includes the time required to thoroughly characterize the cells, store sufficient numbers of cells for use and distribution, and grow to sufficiently long passages to obtain the requisite epigenetic stability. Differentiating them into appropriate phenotypes requires additional time, and with human cells, this correlates with our own prolonged developmental stages such that the differentiation into mature cell phenotypes takes weeks and months (Ginis et al., 2004).

Two additional problems, which I call the "big science" issue, compound the

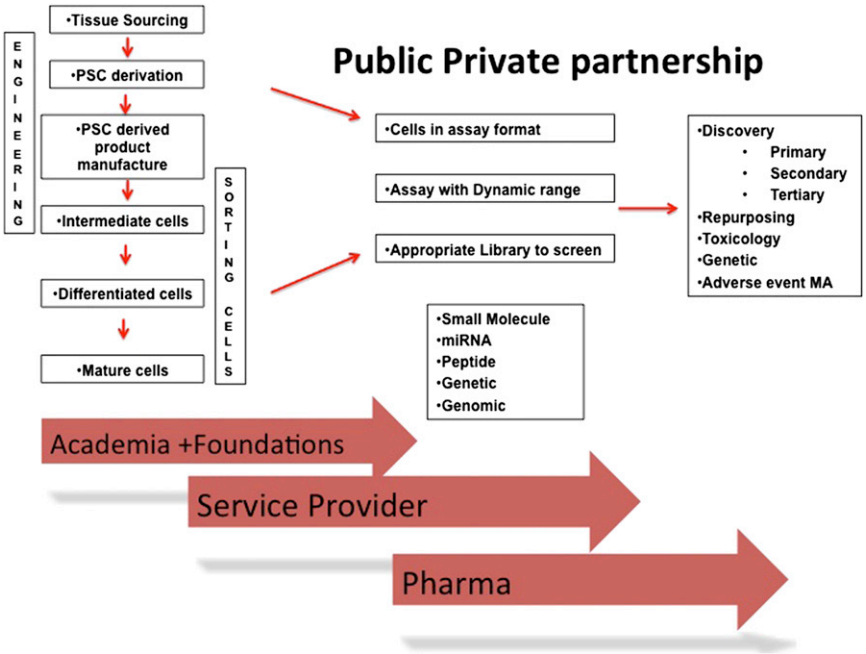

Figure 1. Partnership Opportunities in Screening

The different steps in a screening process are illustrated and the possible roles of academia, foundations, service providers, and pharmaceutical companies are illustrated. In an ideal collaboration, academia would develop the cells and protocols and transfer them to a service provider, who would scale up the assay and deliver the cells to pharma, who would run the assay for discovery or other kinds of screens.

problem. While small laboratories can easily make iPSCs, making a differentiated cell of an appropriate phenotype requires skills and expertise that are different from the molecular skills required to perform engineering, and these are in turn different from the skills required to perform next-generation sequencing and handle these databases. Most laboratories are not of the size and scale that allows one to maintain the necessary infrastructure to perform all of these experiments, and the few large centers that have recognized this problem (Ginis et al., 2004; Lowenthal et al., 2012) have used a core model that uses different core facilities, which often are not sufficiently coordinated to effectively work together throughout this multistep process. As a result, while big science is required, academic institutions and labs don't have the means to do this, and even when they do, the appropriate funding or review processes to enable such cross-disciplinary activity is lacking.

The NIH has recognized this inability as a problem and has made efforts to fund such cores, but within current budget climates such efforts are limited and still remain distributed over multiple institutions (Hazard et al., 2011). The only other organizations that can collate all of these efforts under one roof are foundation-funded efforts or pharmaceutical-company-lead efforts.

Why Industry Alone Has Been Unable to Respond to the Challenge with Pluripotent Cells

One might imagine that if academics cannot perform big science because of time, process, and infrastructure issues, then perhaps such experiments are best left to industry, and indeed one could make a reasonable argument as to why this has worked in the past and should work for iPSCs and their derivatives. However, upon closer examination, several explanations arise as to why this has not happened and why it might actually be difficult for pharmaceutical companies to do this alone (see Figure 1). Many of these issues are common to other avenues of research, and I won't belabor them here. Briefly, they include the inability to share information, the lack of incentive to publish, their own R&D budget cuts, and quarter to quarter productivity demands that are difficult for an R&D organization to meet (Pienta, 2010). Instead, I would like to emphasize that there are specific obstacles presented by industry-based approaches that have more direct relevance to stem cell research that concern issues regarding licensing and access to tissue and replication of existing data from laboratory-scale processes and transfer of such to a large scale.

The process of making iPSC lines includes tissue sourcing and consent issues that are difficult for pharmaceutical companies to overcome, material ownership interests in the cells, process patents, and issues with patent ownership regarding reagents used for iPSC generation, such as vectors that went into the cells and patented protocols for obtaining specific differentiated cell types (Bubela et al., 2012). Obtaining such licenses is a time consuming, expensive, and difficult task, because each group has an exaggerated sense of their component's importance in the overall process. This problem is further compounded by the fact that in general one would like to run panels of lines, each of which may be generated by a different group with different licensing demands.

Even if licensing demands can be met, there are additional problems to working with human tissue related to testing samples, issues of privacy, and the consent restrictions that may accompany tissue donation (Lowenthal et al., 2012). These restrictions are easily surmountable for academic hospital-based investigators, but are an additional hurdle for pharmaceutical-based investigators.

Even in cases when pharmaceutical-based investigators may be willing to address these consent issues, financial concerns may dissuade them. Pharmaceutical companies have already developed a strong record in using primary cells for their screens, and so developing models based on iPSCs may not be considered advantageous from a business perspective. Furthermore, in light of the budgetary constraints and layoffs facing the industry, the substantial resources and determination needed to mount game-changing efforts that would not be realized for many years may be lacking.

Can Working Together Work, and If So, What Would It Take?

One can imagine several solutions to such an impasse, and indeed, several efforts

are underway. One approach that is being undertaken by foundations, the NIH, and some of the state funding initiatives is the generation of large panels of lines and making them available to both academic and nonacademic entities for use. Examples of such initiatives include the STEMBANCC initiative (http://blogs.nature.com/news/2012/12/e50-million-project-aims-to-produce-1500-stem-cell-lines-for-drug-discovery.html), the NYSCF initiative (http://www.NYSCF.org), and the CIRM initiative (http://www.cirm.ca.gov). In each case, the public entity has made an effort to resolve the tissue sourcing issue by ensuring that pharma will have access to the iPSC lines and that large panels of disease-specific lines will be available. In many of these initiatives, the public entity has also asked private tool and reagent providers to provide the scale required to manufacture and differentiate the cells.

A slightly different example is that of a service provider, in collaboration with academic scientists, generating the data required for pharmaceutical companies to adopt a primary cell screen for toxicology assays. A smaller-scale example of this approach was taken by the Parkinsons Disease foundation, which contracted with Life Technologies to develop key tools required by researchers and pharma (https://www.michaeljfox.org/foundation/researchers.php?id=1110).

In this case, the tools were developed to screen for factors involved in the LRRK2 pathway, which is commonly mutated in Parkinson's disease patients, and further leveraged the industry expertise with Life Technologies performing the screen in patient-specific populations. Similarly, GE has made commitments with academic partners for the large-scale manufacture of human cardiomyocytes. More importantly, they compared the human cardiomyocytes side by side with cardiomyocytes from other species (Peng et al., 2010) and showed that this approach was worth the cost difference (http://www.nibib.nih.gov/nibib/file/NewsandEvents/SymposiumandWorkshops/AIMBE2012/S2_NThomas_StemCellTechForPreClinicalDrugDiscovery.pdf). In both examples cited above, neither GE nor Life Technologies alone could have developed the models or tested them, but rather, each needed to work with academic experts and even other service providers and foundations to garner the necessary infrastructure and expertise required to make a commercially viable resource.

A third example is the model of investigators working directly with pharmaceutical companies in a collaboration that is somewhat different from past partnerships where academia looked to pharma as an outlet for licensing promising technologies. In a study reported in this issue of *Cell Stem Cell*, Nissim Benvenisty and colleagues have used this creative approach. Ben-David et al. (2013) developed a high-throughput assay to screen for compounds that were toxic to stem cells, but not to differentiated progeny, in an effort to increase the purity of differentiation cultures (Ben-David et al., 2013). It is important to note that these results could not have been obtained without such a partnership, not from a lack of ingenuity or ideas but more simply because it would not be possible to identify the best targets for such a screen without access to the compounds and their associated databases. Indeed, our own earlier efforts for developing a "stem cell kill" assay (Han et al., 2009) in an academic setting, while showing proof of principle, could simply not perform the experiment as rigorously and elegantly as Dr. Benvenisty.

In each of these examples one can see that no single entity could have completed the process independently of the other. However, working together, these separate actors could harness complementary expertise and access to unique resources to effectively leverage the potential of iPSCs.

In Closing

Public private partnerships may be a way to accelerate the field. Academic centers can generate panels of lines and develop protocols to differentiate the cells. In parallel, service providers can provide these differentiated cells in assay-ready formats to pharmaceutical companies, and these companies can focus on running screens with their annotated compound libraries and depth of expertise in medicinal chemistry to develop products. A key to any partnership is understanding the legal obligations and clarifying patent and ownership issues. I believe that this agreement is certainly possible and is necessary given the present constraints.

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