

Meeting Report

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Thickets and gaps blocking stem cell science

Monya Baker¹

Cross-institutional collaborations could advance stem cell science

A million fixes can add up to one big mess. If everyone holds tight to his own tools, few work well. These were the grand problems identified in an all-day workshop on barriers to stem cell research and collaborative efforts to remove them. The workshop was organized by the Berkeley Stem Cell Center and held at the University of California, San Francisco campus on 6 February.

Tools refers to the data, materials and intellectual property (IP) that researchers need to make scientific discoveries. The million fixes refers to the myriad regulations and practices covering human embryonic stem (ES) cell research. Societies generally agree that destroying, creating or manipulating embryos requires ethical oversight, even to pursue the ethical good of potential therapies; to this end, various societies created various regulations. Sharing data can move science collectively forward but also cost individual scientists time and prestige. The result is that experts, materials and scientific progress stall when they cross regional barriers.

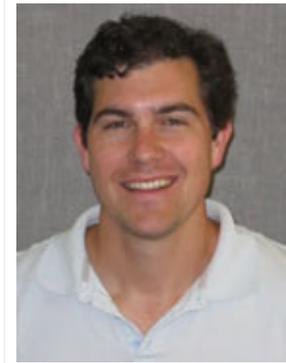
At a meeting so close to Silicon Valley, it's not surprising that one proposed solution to everything was a giant, collaborative database: ethical oversight committees could flag and track discrepancies; researchers and lawyers could find fragmented IP to bring together; and scientists would stop duplicating each others' efforts because they could find the data and collaborators they needed.

Kumbaya.

That's what Ed Pinhoet, vice-chair of the governing board of the California Institute of Regenerative Medicine (CIRM), based in San Francisco, said in sarcasm toward the end of the day as he urged participants to have realistic expectations and to remember that worthwhile collaborations require worthwhile projects. Still, he called the meeting of lawyers, scientists, academics and activists a "historic event" because so many sectors were engaged in how biomedical science can and should move forward.

What follows is my highly selective and condensed version of the meeting. A fuller account will be made available from the [Berkeley Science, Technology, and Society Center](#).

Most of the day was spent defining barriers and then defining the barriers to lowering the barriers. Problems fall into two classes: thickets in which one entity's stance blocks another's ability to operate (think of conflicting regulations or access to IP) and gaps in which resources are immature or insufficient (think of cell banks or an understanding of differentiation).



David Winickoff,
Berkeley Science
Technology and
Society Center



Alan Trounson,
California Institute of
Regenerative
Medicine

IP drag

CIRM president Alan Trounson described the route through which multiple technologies result in a few therapies: technologies must be patentable so that investors can get a return on their investment, he said, but IP can also clog the pipeline. "Biotech companies come and they go, and their IP gets stuck," he said. "We need agreements in place that don't block the pipeline."

What shape those agreements might take was unclear. Alan Bennett of the University of California, Davis described the IP-pooling agency he directs. [The Public Intellectual Property Resource for Agriculture](#) (PIPRA), based at UC Davis, was formed when a bunch of agricultural colleges came together as a one-stop shop to license the complementary pieces of IP necessary for engineering new crops and other products. Revenues generated by the licenses are shared according to a preagreed formula among the universities. The audience seemed both highly interested in this as a potential model and highly sceptical. One difficulty in transferring the idea to stem cells is that biomedical science anticipates higher revenues and, so, higher stakes. Also, PIPRA got started under the aegis of the philanthropic Rockefeller Foundation. Even so, Bennett said it took about two years of meeting with high-level university administrators and tech transfer officers before cooperation could get underway.

Sean O'Conner, a professor at the University of Washington School of Law, in Seattle, proposed that patent enforcement similar to that practiced in Japan and South Korea could make technologies more accessible. In those countries, a patented technology can be used freely for research and development (R&D). Only when that R&D yields a product that could produce revenues are the patents considered.

Right now, no one is really sure what current patents cover and who holds them. Challenges to broad patents covering the derivation of human ES cells are still unresolved (see [A patent challenge for stem cells](#)). In the United States, there are overlapping IP claims covering similar cells. Joydeep Goswami of Invitrogen Corp., in Carlsbad, California, said that many early patents were issued when no one really knew what the cells were capable of. Thus both Osiris Therapeutics Inc., in Baltimore, and Cytori Therapeutics Inc., in San Diego, have overlapping claims over mesenchymal stem cells. Geron Corp., in Menlo Park, California, and Q Therapeutics Inc., in Salt Lake City, Utah, have overlapping claims over oligodendrocytes. And the tools used to work with stem cells—antibodies, growth factors, separating and sorting technologies—also have IP issues that stymie technology development.



Jeanne Loring,
Scripps Research
Institute

Scientific data flow

Getting a notion of what patents exist could be a precursor to combining patents in productive ways and clearing the 'patent thicket' in which researchers don't develop products because necessary steps are blocked by IP claims. Another hindrance is that scientists aren't always sure what they should expect from different cell lines grown under different conditions.

"We need a database with all the molecular markers and how they change in a culture dish," said Mike West, founder of Geron and former president of Advanced Cell Technology Inc., in Los Angeles. "I don't know how the field can progress without the map."

Scientists argue broadly for sharing resources, but there are

Scientists argue broadly for sharing resources, but there are powerful disincentives not to do so, said Pam Samuelson, a professor at the Boalt School of Law at University of California, Berkeley. Sharing data can dissipate the rewards gained from the hard work of data collection and can jeopardize trade secrets. Scrubbing and formatting data so it can be shared without violating subjects' privacy takes considerable time. "There's no reward for doing it, and no penalty for not doing it," she said. The first scientists to share data have little to gain, and those with the biggest data sets have the most to lose. Similar constraints exist in sharing research materials.

Samuelson and participants discussed several strategies to promote data sharing. Default standards would make reformatting easier. But there should also be a system of carrots and sticks. People who share useful data or materials should be rewarded; perhaps the number of times a dataset is downloaded could be tracked and acknowledged. Researchers who don't share should be excluded from future grant applications or using other resources.

Scientists cannot rely on getting the data or materials they need from other researchers, and resources are squandered when scientists duplicate efforts, said Jeanne Loring, of The Scripps Research Institute, in La Jolla, California, and Jon Auerbach, CEO of GlobalStem Inc., in Rockville, Maryland, and chair of the standards committee for the International Society for Stem Cell Research, based in Northbrook, Illinois. The research community needs a system of repositories that can supply cell lines. "One bank in the UK and one bank in Wisconsin isn't enough," said Auerbach. "But you don't need a bank in every state or institution."

The solutions, they said, are registries, repositories, databases and common standards for supplying information and other resources. Ideally, a registry for scientists would describe genomic stability over time, cell lines' differentiation tendencies and marker expressions, and the tests used for assessing particular lines. However, if researchers are to trust such data, stakeholders must agree on definitions, methodologies, protocols and reference standards. Ideally, the same factors would be measured across multiple cell lines in multiple labs, but such efforts are difficult because of differences in funding.

Regulatory detangling

The scope for collaborative efforts seemed most ripe in the conflicting regulations that researchers encounter. Susan Stayn from Stanford University, in Palo Alto, California, outlined no fewer than 10 sources of regulations and guidelines that a stem cell researcher might have to follow. Before giving permission for researchers to use an ES cell line, oversight committees at each institution have to research whether the line was derived under conditions that conform to both the particular institution's and the particular state's ethical guidelines. This can be murky.

Geoff Lomax of CIRM described how complicated Embryonic Stem Cell Research

We need someone to mobilize the effort to map the human embryo. I don't know how the field can progress without the map.

Michael West

Founder of Geron Corp.

Oversight (ESCRO) research could become. Consider if a couple had embryos created at an infertility clinic but no longer needs them to get pregnant. It is possible that an egg donor was paid to supply eggs for the embryo creation. Could these embryos be used to derive stem cell lines? Various regulations would cover the situation. Should the situation fall under rules governed by gamete consent or paid donors? What if the clinic cannot verify that the woman for whom the embryo was intended was also the egg donor?

A trusted registry showing the conditions under which cell lines were derived could shrink regulatory delays and prevent ESCRO researchers from having to repeat each other's work establishing appropriate provenance of the line.

Scientific institutions can be surprisingly hungry for guidance, said Alta Charo, a law professor at the University of Wisconsin–Madison who was on the National Academy of Sciences committee that drafted guidelines for ES cell research. In fact, institutions wanted regulations to be more specific. The idea was that the public could be more reassured that researchers weren't participating in a 'Wild West' science where anything goes, but the line between necessary and onerous regulations is blurry. Before expanding regulations, experts must explicitly assess whether they cover areas that touch on broad or deep societal concerns. Otherwise, the danger of 'regulatory creep' is real.



Alta Charo, University of Wisconsin-Madison

Pleas for forward thinking

UC Berkeley's Charis Thompson proposed a database solution that would shift the very notion of informed consent. Currently, people who provide biological samples do so for altruism or money; once the sample is taken, neither side expects to hear from the other again. Often, experiments that were unanticipated when the sample was taken cannot be performed because consent wasn't granted. Further, patient privacy is getting harder to guarantee because samples can now be more easily matched to individual patients. She proposed that the incentive for research subjects should be to gain information. As information was gleaned from research, personalized information could be fed back to patients. This would allow additional data collection and would build in a procedure for renewing consent. She proposed that independent centres and repositories be set up to handle the process. Several heads nodded during the presentation, but many issues were left unaddressed. What if family members or subjects don't want information released? How can patients make sure their information isn't accessed without their consent?



Hector Preciado, Greenlining Institute

Bernard Siegel of the Genetics Policy Institute, based in Wellington, Florida; Hector Preciado from the Greenlining Institute, of Berkeley, California; and Jeff Sheehy, a CIRM board member and patient advocate, urged participants to consider patient advocates for collaborative projects. Researchers and policymakers must consider social issues thoroughly before any potential policy applications, particularly in regard to diversity and under-served communities, said Preciado. "A lot of time a policy is developed and then it is 'Oh, what about them' and those can turn into roadblocks. And those can be prevented if you have the right people at the table to start."

Planning future projects

Conference organizer David Winickoff asked conference attendees to put their heads together to decide what kinds of efforts could be useful for resolving these issues.

Many attendees worried that an overambitious project would get nowhere and felt that the first database should be designed for ethical oversight committees to use to assess provenance. Pinhoet warned attendees to make sure that any project could be updated easily and wouldn't require chronic redesigns. "The cost to set it up is trivial," he said. "It's the cost to maintain it."

As for amassing scientific data, Robert Tjian, codirector of the Berkeley Stem Cell Center, thought it was too early. "We don't know enough to even know what the science would be."

But efforts are already underway. Several speakers referred positively to the newly launched [hESCreg](#) in Europe as a model for how a registry could be useful. Among other information, the hESCreg lists contact information for requesting cell lines, plus information on cell lines' derivation and the assays performed for the presence of cell markers and differentiation. A company called [StemCore](#), based in Wellesley, Massachusetts, has set up a registry and says it will include cell lines whose provenance and procurement are vetted by stem cell research oversight committees. Loring thought that one solution would be to store simple scientific data that is less open to overinterpretation, and said she'd started [setting up a database](#) as well. The University of Massachusetts Medical School, in Worcester, has received a multimillion dollar grant to develop an ES cell bank and registry, and representative Mai Luong welcomed collaborators.

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