IP Provisions and ROI for State-Funded Stem Cell-Based Products and Technologies in California

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The California Institute of Regenerative Medicine (CIRM) reaches the end of its initial charter in 2017 and recently published its Transition Plan. The plan is a roadmap to sustained development of stem cell-based technologies in California. It also outlines oversight of intellectual property and revenue sharing provisions built into the institute's grants to for-profit and non-profit researchers. This article presents an overview of those provisions as they pertain to life sciences companies pursuing commercialization of stem cell technologies and products developed with funding from California's taxpayer-supported initiative.

PROPOSITION 71 AND THE FORMATION OF CIRM

Proposition 71 of 2004, also known as the California Stem Cell Research and Cures Act, was enacted by California voters to support stem cell research in the state. The act authorized the sale of general obligation bonds to allocate $3 billion dollars over a period of 10 years to stem cell research and research facilities. Although the funds could be used to advance all kinds of stem cell research, the act gives priority to human embryonic stem cell (hESC) research.

Proposition 71 created the California Institute for Regenerative Medicine (CIRM), which is in charge of making "grants and loans for stem cell research, for research facilities, and for other vital research opportunities to realize therapies" as well as establishing "the appropriate regulatory standards of oversight bodies for research and facilities development."

The initiative is novel in that it uses general obligation bonds, which usually finance brick-and-mortar projects, to underwrite science. By funding scientific research on such a large scale, the act gave California a role that is typically fulfilled by the U.S. federal government. Proposition 71 also established the state's constitutional right to conduct stem cell research.

Legal challenges, primarily to the aspects of the act that altered the state's constitution, delayed the start of the California research program. Since April 2006, however, CIRM has awarded 485 grants valued at $1.3 billion and, as of February 2012, had committed to funding another $586 million in awards.

CIRM's recent communications summarize voters' expectations as two-fold – "deliver hope for people suffering from a range of serious health conditions, and deliver an economic boost for the state." The institute's governing requirements, however, were written to ensure that California voters realize more tangible returns on their investment.

CIRM'S INTELLECTUAL PROPERTY PROVISIONS

Through the passage of Proposition 71, California is obligated to ensure that taxpayers receive real return on their investment in research. As such, the framers of CIRM's policies started with key provisions of The Bayh-Dole Act. Passed in 1980, Bayh-Dole regulates intellectual property (IP) ownership for inventions resulting from federal research funding. Its most important aspect is that it permits a university, small business, or non-profit institution to pursue ownership of an invention in preference to the government.

IP Ownership

CIRM's IP provisions ensure that grantees own all rights to their inventions. At the same time, recipients of CIRM research grants are obligated to file and report resulting patent applications. Grantees are responsible for the costs associated with filing and protecting such patent applications, but are allowed to recover the costs through license fees or other consideration.

As with Bayh-Dole, the intent of CIRM's IP ownership provision is to promote publicly beneficial research by academic institutions and small businesses. Funding through CIRM is structured to not only encourage research but to accelerate commercialization of stem cell-based technologies and products.

Licensing

To shorten the road to market, CIRM and its IP provisions require that grantees actively seek the development and commercialization of CIRM-funded discoveries, either in-house or through licenses and assignments to others. Further, the institute recognizes the value of both exclusive and non-exclusive licensing arrangements.

The former, an exclusive license, suggests that the invention is more advanced and is encouraged "if exclusivity is reasonably believed by the Grantee to be an economic incentive necessary to achieve commercial development and availability of the invention." In exchange for exclusivity, however, CIRM requires the grantee to document the development and commercialization capabilities of any intended exclusive licensee prior to entering into an exclusive license; to bear responsibility for all licensing activities for the invention, including ongoing reporting; to monitor and annually report to CIRM that the licensee performs according to established milestones and benchmarks; and to take reasonable action to enforce the terms of an exclusive license, including promptly reporting any material breach affecting any of the obligations to CIRM.

Should the grantee not be able or elect not to commercialize its CIRM-funded invention or technology, the institute requires that it make a reasonable effort to negotiate non-exclusive licenses for third-party development. Such agreements would make the discovery or invention available to added researchers and, perhaps, lead to a broader exploration of its potential applications.

March-In Rights

CIRM reserves the right to take charge of inventions resulting from its grant funding if the grantee, collaborator or exclusive licensee is not actively promoting its development. The institute is empowered to request that the grantee enter into appropriate licensing agreements with responsible applicants, under reasonable terms.

Should the grantee refuse to enter into such an agreement, CIRM "shall have the right to enter into such a license with an applicant on behalf" of the grantee, collaborator or its exclusive licensee if the party:

- Has not made reasonable efforts to achieve practical applications of a CIRM-funded invention or technology
- Has failed to provide or comply with a plan for patient access to a drug (as detailed later in this paper)
- Has unreasonably failed to use its CIRM-funded invention or technology to alleviate a public health emergency as declared by the Governor

Under its provisions, CIRM will promptly notify grantees or their collaborators or licensees of any "adverse determinations" and the institute's intent to exercise its march-in rights. CIRM will not proceed if the grantee takes prompt action to address the issue and resolves the matter in less than a year from the date of the march-in notice. Should the grantee elect instead to appeal the notice, it has 30 days to declare its intent and 60 days to submit its written appeal statement and supporting documentation. The provisions indicate that "absent extraordinary circumstances," the institute's governing board will issue its final decision on the appeal within 120 days of the march-in notice.

As with the Bayh-Dole Act, there are protections incorporated to make the march-in process fair. For instance, one consideration in taking march-in action will be "whether doing so will impinge upon the grantee's, collaborator's or exclusive licensee's academic freedoms." Yet the inclusion of march-in rights reiterates that the state's priority is to further the development and utilization of discoveries funded by taxpayers.

CIRM'S RETURN ON INVESTMENT POLICIES

The responsibility to generate and collect returns on investment (ROI) is behind CIRM provisions that go beyond the scope of those established by Bayh-Dole for federal funding. Consistent with the California Stem Cell Research and Cures Act, the CIRM IP policies take a more aggressive approach to realizing tangible economic benefits for the state and ensuring that research products reach Californians.

Biomedical Materials Requirements

Once a grantee has published papers or patents on a CIRM-funded invention or technology, it must make the publication-related biomedical materials available to other California researchers. Specifically, "[a] grantee shall share publication-related biomedical material for bona fide purposes of research in California. Such materials are to be shared without cost to the requestor or at the actual cost of providing the materials without an allocation of costs for overhead, research, discovery or other non-direct costs…."

There are exceptions to this requirement. For example, a grantee can teach the requestor to make the material. The obligation also may cease when the materials become broadly available commercially. The provision is designed to accelerate the sharing of discoveries and the scientific serendipity among California stem cell researchers, regardless of their affiliations and area of focus.

Revenue Sharing

In contrast to Bayh-Dole and the National Institutes of Health (NIH) at the federal level, CIRM has written revenue sharing requirements into its provisions. The rules, which apply to both non-profit and for-profit recipients, are designed to ensure that California taxpayers see a monetary return on their investment.

Grantees and collaborators who license their CIRM-funded discovery, invention or technology are required to pay approximately 25 percent of the net licensing revenue in excess of $500,000 into the state's general fund. (The institute does provide a formula for determining the proportional amount due for inventions co-funded by sources other than CIRM.)

Grantees and collaborators who elect to commercialize products developed through CIRM-funded research are subject to a four-tiered revenue sharing arrangement:

- Royalties of 3 percent per year on net commercial revenue above $500,000 up to three times the amount of the original CIRM grant.
- If net commercial revenue from a product developed through CIRM funding exceeds $250 million in any calendar year, the grantee shall pay a one-time payment of three times the initial grant amount to the state.
- If net commercial revenue from the product exceeds $500 million in any year, an additional one-time "blockbuster payment" of three times the initial grant shall be paid to California.
- A grantee or collaborator with aggregate CIRM grants amounting to more than $5 million is subject to late-stage revenue sharing of 1 percent of all net commercial revenue in excess of $500 million per year. This provision is valid for 20 years after the close of the grant for unpatented inventions or technologies or for the life of any patent covering the CIRM-funded discovery.

Access Requirements

Another CIRM mission is to make products resulting from state taxpayer funded research available to all Californians, regardless of their ability to afford them. The requirement states that grantees, collaborators or exclusive licensees of drugs resulting from CIRM-funded research "must submit a plan to afford uninsured Californians access to such a [d]rug." Added regulations stipulate that the access plan:

- Must be submitted to CIRM 90 days or more prior to the drug being commercialized in California.
- Must be consistent with industry standards at the time of commercialization.
- Will be subject to CIRM approval following a public hearing conducted by CIRM.
- Needs to cover only provision of the drug itself, not the costs of administering the drug or for any other medical procedures, protocols or attendants.

- Must provide the drug "at a price as provided in the California Discount Prescription Drug Program (commencing with California Health and Safety Code section 130500)" for California patients in that program or other programs that purchase the drug with California public funds. This regulation does not preclude other agencies or organizations from negotiating a lower price for the drug.

The grantee, collaborator or exclusive licensee is responsible for establishing that the proposed access plan satisfies these CIRM requirements.

CIRM IP PROVISIONS AND THE LIFE SCIENCE INDUSTRY

Because CIRM's IP provisions remain attached to the invention, the revenue sharing and access requirements will primarily fall to the enterprises that commercialize the CIRM-funded discoveries. Thus when CIRM announced its IP provisions, many predicted that the rules would dampen for-profit organizations' participation.

As demonstrated by earlier emerging technologies and new scientific and medical disciplines, however, commercial enterprises are typically not the source of basic scientific discovery and bench-scale testing. They rarely have time or resources to make breakthrough discoveries – and they can ill afford the dead ends and unexpected phenomena that complex science inevitably delivers. CIRM's model accounts for the potential value industry will realize – and build upon – via institute-funded research, facilities and resources.

Already the impact that CIRM has had on advancing drug development and disease modeling techniques based on stem cells has been phenomenal. Scientists working in the field, many in California and in CIRM-supported facilities, are refining breakthrough research methods to better understand the biology of disease as well as the workings of the healthy human body.

One such cutting-edge stem cell-based strategy has been dubbed "disease in a dish." The technique uses researchers' ability to reprogram almost any type of adult cell to become a "pluripotent" stem cell (iPS cell) – an embryonic-like cell with the potential to self-renew. These cells, with the addition of growth factors or chemicals, can be differentiated into cells from specific organs. That is, a researcher can take skin cells from a patient with Alzheimer's disease. Those cells can be transformed into iPS cells and then differentiated to produce brain cells. The resulting culture can provide the researcher with an endless supply of patient- and disease-specific cells that theoretically carry all the genetic and molecular changes that may have contributed to that individual's condition. The technique, which may also be used to grow new tissue for transplants, has accelerated research. It also is broadening the range of diseases that can be modeled.

By ensuring that early findings, techniques and biomaterials are shared among leading researchers in academic settings, CIRM intends to shorten the time until for-profit firms might license a promising technology or researchers may found their own firms to further develop their product. The institute's regulations ensure that promising techniques and materials are patented in a timely manner and that their IP is clean. Conducting due diligence on CIRM-funded projects should be made simpler by the institute's up-front involvement, and transparency across California's stem cell research centers should also give future investors confidence in underwriting the development of breakthrough therapies. Thus, the institute's IP provisions may diminish risk for the for-profit developers.

The added credibility afforded new technologies through the collaborative work of CIRM grantees is critical in the diseases for which regenerative medicine may prove most successful. The institute is funding translational project teams that are focused on identifying lead candidates for the treatment of several forms of cancer, Alzheimer's disease, diabetes, HIV/AIDS, heart disease, Parkinson's disease, multiple sclerosis, sickle cell disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), stroke and spinal cord injury, just to name a few.

These are serious, complex, often intractable conditions for which there are few or no treatments and for which drug development has proven difficult and expensive. Progress realized by CIRM grantees at the academic level will greatly enhance the biomedical industry's ability to make therapeutic products available to the patients who need them.

BIOMEDICAL COMPANIES' ACCOMMODATION OF THE REQUIREMENTS

Some years remain before stem cell-based products can be proven effective and safe. At the same time, aspects of the economic and political landscapes in California and the United States – especially as they pertain to CIRM's IP provisions and profit-sharing requirements – could have profound and unpredictable effects on future development. CIRM is anticipated to seek alternative funding sources to continue operations beyond 2017, so it is not yet clear which governmental agency will monitor and enforce the provisions going forward. Whether the U.S. healthcare reform package will extend medical insurance to a larger portion of Californians, and lessen the access accommodations for manufacturers, remains to be seen. The ability and willingness of commercial organizations and their investors to be among the first to advance a hESC-based product through the approval process also will depend on the health of the economy.

It is too early to gauge the costs and challenges to grantees and their collaborators in meeting their obligations to CIRM and the California taxpayers. Given the institute's success in accelerating discovery, however, clear – and clearly enforced – IP provisions are critical to the long-term viability of California's regenerative medicine industry.

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