Policy Framework for Intellectual Property Derived from Stem Cell Research in California:

Interim Report to the California Legislature Governor of the State of California California Institute for Regenerative Medicine

August 2005

CALIFORNIA COUNCIL ON SCIENCE AND TECHNOLOGY
INTELLECTUAL PROPERTY STUDY GROUP

California Council on Science and Technology
Intellectual Property Study Group

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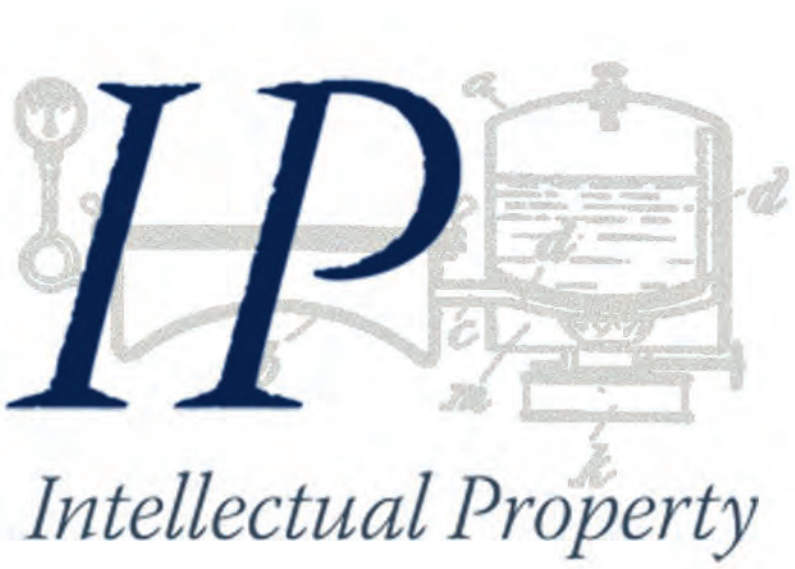

Interim Report to the
California Legislature
Governor of the state of California
California Institute for Regenerative Medicine

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Letter from CCST Leadership

It is often said that California is the nation's high-tech leader. Certainly, the size of California's science and technology sector, its leading public and private research institutions, and world-renowned high-tech business community bear ample witness to this statement by simple scale and scope. But what drives the state's true leadership position is not just the size of its science and technology sector, the total dollar amount of its research and development activities, or number of patents earned. It is California's willingness to look ahead, take risks, set the standards for performance, and then excel in highly competitive arenas.

The approval by voters of Proposition 71, and the resulting California Institute for Regenerative Medicine (CIRM), is the most recent example of this state taking the lead on an important issue. CIRM is a historic state-funded research and development initiative that far exceeds any comparable state investment in the country. Its goal is to serve a key role in the advancement of stem cell research, a field of exploration and discovery that in many ways is in its early stages, yet holds much promise to increasing our understanding of how cell lines develop and regenerate. The hope is that this research will lead, in time, to therapies and treatments for diseases and conditions that, to date, have been intractable or deadly.

CIRM is faced with many challenges. It is a new organization currently engaged in the process of writing many of its own rules, because there are no precedents for establishing a state-level research institute of this magnitude.

It is not easy to break new ground. CIRM involves a significant investment for California and many interests are at stake. This interim report provides policy recommendations to the California Legislature, the Governor and CIRM about how to address an important infrastructure challenge: establishing a consistent and workable set of intellectual property policies for stem cell research that will best serve the interests of the state, the public and the research community. The analysis and recommendations CCST provides here are an interim step to another unprecedented project, that of designing a comprehensive set of intellectual property policies for the state. CCST's final report on that topic will be completed in December of this year.

In approaching this project, CCST has brought together a team of experts and leaders from the high-tech community representing business and industry, venture capital, academia, and government. These individuals have taken their responsibilities very seriously and have volunteered a tremendous amount of time and effort to the project despite their own significant other commitments. The resulting consensus report reflects a great deal of discussion and review.

It is our hope that the results serve as a useful guide for CIRM as it continues to establish the policies that will guide its work for the next decade and beyond. We also believe that this report will be of use to state legislators and other state leaders as they continue to consider how best to encourage exploration and innovation in California.

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Preface

Innovative technologies and their underlying intellectual property (IP) are the fundamental drivers of California's high-tech economy. In general, the way that IP is handled creates the environment in research institutions and in business and industry necessary for risk taking and the investment of capital to translate creative ideas to marketable products, and subsequent attendant benefits. Time-tested models in the private sector and at the federal level show that uniform IP policies create efficiencies in time and money, reduce barriers, and increase opportunities for the development of new products and services.

At the state level, however, a comprehensive and coherent policy does not yet exist either for state-generated works or for state-funded works developed by third parties. A 2000 State Auditor's report noted that California's approach to IP management is Balkanized and its policies are splintered among the various state agencies. The result is that each agency is free to negotiate its own contracts with the institutions that perform research and development with state funds, which includes universities and small and large businesses. Among the consequences of this splintered set of policies is a lack of consensus about IP data, incomplete understanding of the research enterprise and technology transfer, and few, if any, incentives to develop state-funded IP into marketable products.

In order to help state policymakers design an IP policy framework appropriate for California's current economy, the Legislature through ACR 252 requested that the California Council on Science and Technology (CCST) conduct an analysis of whether and how to implement a set of consistent statewide policies. This analysis is scheduled for completion in late 2005.

After the passage of ACR 252 in September 2004, a major new initiative passed in the November 2004 elections that held significant ramifications for IP policy in California. Proposition 71, the Stem Cell Research and Cures Initiative, calls for awarding $3 billion over the next ten years to fund stem cell research and creation of the California Institute for Regenerative Medicine (CIRM). The Independent Citizens Oversight Committee (ICOC), which has been charged with establishing CIRM and implementing Proposition 71, is faced with many significant challenges, including that of establishing policies for the appropriate administration of IP generated through CIRM-funded research. Because CCST had already undertaken the task of developing IP policy recommendations for the state requested by ACR 252, many in the state felt that the Study Group assembled by CCST also would be the most effective body to advise the ICOC and CIRM on developing a sound and coherent set of IP management policies.

Consequently, legislators authored ACR 24, which requests that CCST expand the scope of the Study Group to include contracts, grants and agreements developed under Proposition 71.[♦] This interim report is a response to the original draft of ACR 24 as amended in April 2005. In mid July, several additional amendments were added to ACR 24 with new directives for the Study Group. These are addressed in an addendum at the end of the report.

♦ ACR 24 of the 2005-06 Regular Session, (Mullin), Amended 4/21/05.

In order to conduct this study, CCST convened two groups: a Study Group and a Working Group. The Study Group consists of a diverse collection of 17 leaders from California's science and technology (S&T) community representing a range of experience, expertise, and perspectives in research management, inventor to IP process, federal and state IP process and technology transfer, economics, and public policy.

The Study Group is co-chaired by Alan Bennett, associate vice chancellor for Research, University of California, Davis, and Stephen Rockwood, executive vice president, Science Applications International Corporation. Five of the members are associated with CCST as Council members or Fellows. In addition, there are 11 members in the Working Group, which consists of subject matter experts familiar with IP issues and with the policy interface between the state government and the research community. The two groups represent a broad spectrum of IP-related expertise from many of California's leading institutions, both public and private. In addition, the report has benefited from the input of nearly 50 peer reviewers, both in and outside of CCST, from private foundations, government agencies, academia, venture capital firms, and high-tech industry, both biotechnology and other.

This is an interim report (August 2005) intended primarily to advise CIRM as it develops its IP policies. CCST's final report to the Legislature is scheduled for completion in December 2005. Given the urgency of launching the new CIRM, we focus in this report on IP policy issues that are particular to the unique circumstances of CIRM's creation and implementation. The following analysis and recommendations, while intended to be consistent with those under development for our final report, should not be construed as a comprehensive set of guidelines for the state of California.

Executive Summary

Proposition 71, approved by California's voters in November 2004, requires that the Independent Citizens Oversight Committee (ICOC) of the California Institute for Regenerative Medicine (CIRM) set intellectual property (IP) standards that "balance the opportunity of the state of California to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials with the need to assure that essential medical research is not unreasonably hindered by the intellectual property agreements." [1]

The purpose of this interim report is to discuss the likely benefits associated with IP created under CIRM funding, describe some existing models for handling IP, and suggest some approaches to the treatment of IP that benefit CIRM and the state. This report provides brief background on the federal Bayh-Dole Act, special considerations about biomedical research, kinds of intellectual property, and California's return on its investment. It then discusses factors that CIRM will need to consider in the establishment of its IP policies, and presents specific recommendations.

In formulating CIRM's policies to handle intellectual property, ICOC members and state leaders must realize that this field of research is in its very early years. A significant portion of the funding that CIRM will give out will support basic research; the output of this basic and applied science will largely be research tools, databases of scientific data, research publications, and most important, a step forward in the understanding of the science, paving the way for additional research. A small number of research discoveries may lead to therapeutic or diagnostic technologies, and it is impossible to discern in advance which discoveries have this potential. In all likelihood, the development of effective therapies from CIRM-sponsored research is at least ten to twenty years away.

In the life sciences, the development of a new drug or FDA-approved treatment from a research finding typically takes at least a decade, and it takes private investments in excess of several hundred million dollars in the development process to bring a product to market.

In response to the high degree of public interest in the implementation of Proposition 71 and numerous policy discussions that have unfolded in the months since its approval, we urge CIRM and the state to proceed with caution and not to set overly prescriptive policies for IP derived from stem cell research. We conclude that some Californians have unrealistically optimistic expectations about the likely financial returns to the state from its investment in stem cell research, especially in the short run.

Stem cell research has been promoted as holding a great deal of promise for California. Taxpayers' return on investment is one issue that figured prominently in literature used to promote Proposition 71 prior to the election and in subsequent discussion of its administration.[2] In turn, legislators have proposed that CIRM's IP policy should seek to generate substantial new revenues for the state, new funds for further research by CIRM, and favorable pricing for

[1] Health & Safety Code §125290.30(h)s.

[2] http://www.voterguide.ss.ca.gov/propositions/prop71-title.htm.

therapies derived from CIRM's research. We find that these proposals, and the statements and studies on which they are based, including the economic impact analysis that was released during the campaign by the proponents of Proposition 71, are based on unrealistic assumptions about the potential economic impact of CIRM's research program.[3] In particular, although the amount of funds that will be focused on stem cell research – about $300 million per year for 10 years – is substantial, it must be put in the context of the nearly $14 billion annually in federally funded research in the state's institutions of higher education, private research institutes and national laboratories, and $45 billion annually in industry funded R&D.[4] All interested parties must be mindful of overestimating both the projected revenue stream from IP generated by CIRM-funded grants and the timeline to achieve it.

While expectations of a short-term revenue stream and quick availability to the public of new treatments may well be overstated, CIRM-funded research can, nonetheless, be expected to benefit the state in significant ways, particularly in the long term. The greatest potential long-run benefit arising from CIRM's research will be improvements in the quality of life of citizens who now suffer from debilitating degenerative disease and traumatic injuries. CIRM's research grants may also add to the considerable attractiveness of California as a location for biotechnology research firms, but this effect is not likely to be large in the near term. Because a large portion of the research will be basic in nature, particular attention needs to be paid to the treatment and dissemination of research tools and databases. Making research tools developed with CIRM funding largely available to other scientists for use in ongoing research would be consistent with the language of Proposition 71, which specifies that CIRM is expected to assure that "essential medical research is not unreasonably hindered." This is a standard policy for research funded by the National Institutes of Health (NIH) and should be encouraged by CIRM.[5] We recommend that exclusive licenses to research tools, if used, should retain rights for the grantee and the CIRM research community to continue to use the IP for research purposes. CIRM also should encourage researchers to make databases as widely available as possible, while at the same time recognizing the need to maintain quality data. Scientific and research progress in stem cell research, like other research, will depend on researchers' ability to access and use information in the public domain and to combine public and proprietary data into new databases, as well as to re-evaluate and reuse existing data.

CIRM's mission, as a new state agency, is to make grants and provide loans for stem cell research and training, research facilities, and other vital research opportunities, with an ultimate goal of discovering and developing new ways of treating degenerative diseases. The primary objectives of CIRM IP policies should be to maximize CIRM's effectiveness in supporting this mission. Examples of such objectives might be:

- Support the open dissemination of research results and transfer of knowledge where appropriate;
- Ensure that discoveries and research tools that are useful for further research are made broadly available to the research community;
- Encourage practical application of CIRM-funded research results for the development of medical therapies that benefit the public;

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[3] Laurence Baker and Bruce Deal, Economic Impact Analysis: Proposition 71, California Stem Cell Research and Cures Initiative. Analysis Group, Inc. (Sept. 14, 2004) pp. 2-3.

[4] National Science Board, 2004. Science and Engineering Indicators.

[5] http://ott.od.nih.gov/pdfs/64FR72090.pdf.

- Accelerate the transition of discoveries from research to commercially available diagnostics and treatments;
- To the extent possible, balance existing investments with state investments such that each receives appropriate returns;
- Promote collaboration between commercial entities and non-profit research institutions;
- Encourage private investors to invest in further research and development of new technologies resulting from CIRM-funded research;
- Minimize costs of administering policies; and
- Be mindful of the time delay and private investment needed before significant benefits accrue to the state.

Models for IP Policy

Research, especially in universities and non-profit institutions, receives funding from many sources, including federal and state agencies, private industry and non-profit organizations. Ownership of any IP generated by such research, and the details of how it is managed, depends on the source of funding, but generally converges on high-level objectives such as ensuring broad dissemination of research results and managing inventions for the public benefit.

Bayh-Dole rationalized and simplified the process of moving technologies generated by federally funded research from university laboratories to the private sector.

The Bayh-Dole Patent and Trademark Amendments Act of 1980 (Bayh-Dole) led to the development of consistent patent policies for federally funded research conducted at universities and in small businesses. It permitted grantees to own inventions resulting from federally funded research, which they could then license to other entities, including to private firms willing to invest in commercialization. Many research universities and labs began to encourage faculty and other researchers to identify and report discoveries that could be patented to encourage commercial development. Many institutions established technology transfer offices to handle patent prosecution and licensing.

There is a general consensus that Bayh-Dole rationalized and simplified the process of moving technologies generated by federally funded research from university laboratories to the private sector. Bayh-Dole is considered to have contributed positively to the development of some technologies that may not have been made available to the public in its absence.[6]

In many ways, the situation in California today regarding treatment of IP resulting from state-funded research resembles the federal situation in the late 1970s prior to the passage of Bayh-Dole: contracting is possible, but complicated. The absence of clear guidance leads to considerable time and costs associated with negotiating the handling of IP stemming from state funded research.

State level policies in California are not uniform and do not have a common set of clearly stated objectives.

[6] Jerry G. Thursby and Marie C. Thursby, "University Licensing under Bayh-Dole: What are the Issues and Evidence?" (May 2003) p.9.

As CIRM develops its IP policies, consideration should be given to the likely circumstance where CIRM funds would be deployed alongside federal funds, or potentially leveraged with federal funds in the same research project. To minimize confusion and maximize the return on grant funds, CIRM's policies should be consistent with Bayh-Dole. This is not to say that CIRM's policy needs to be identical to Bayh-Dole, but its provisions should not conflict with Bayh-Dole in ways that would lead to the creation of confusing, conflicting, or convoluted funds management administration by institutions, ultimately impeding the conduct of research.[7]

Ownership of Intellectual Property

Ownership of intellectual property resulting from sponsored research is a central issue in establishing an intellectual property policy and allowing ownership to reside with the grantee is the central feature of the Bayh-Dole Act. From this central feature of IP ownership, many other policy considerations followed. In considering the issue of IP ownership for CIRM, it is important to consider: 1) the relative importance of a policy that is consistent with federal (e.g. Bayh-Dole) statute and policy, 2) who is best able to manage the resulting IP, and 3) the existing financial models that are in place to make appropriate investments in protecting very early-stage research results.

Clearly, consistency with federal statutes and policy suggest that ownership of IP resulting from CIRM-sponsored research should reside with the grantee. In considering who is best able to manage IP resulting from university research, strong arguments have been made that IP management should occur at a level that is as close as possible to the research itself – and perhaps more importantly – as close to the researchers as possible. This conclusion was a central feature of the California Technology Trade and Commerce Agency report of 2003, which recommended that the University of California decentralize its technology transfer programs to the local campus level.[8] Because IP resulting from basic research is very early stage, the ability to manage this IP is also related to the institutional capacity to invest in filing patent applications before there is any prospect of a return on that investment. Thus, if CIRM or a surrogate agency were to manage IP resulting from its sponsorship, an allocation of additional funds would be required to invest in patent filings as the research results emerged from the laboratory. Research universities and not-for-profit research institutes have addressed this issue over the last 20 years and have either established fund sources to support patent filings or utilize the royalty stream resulting from past inventions to support the costs of new patent filings.

Based on compliance with Bayh-Dole, as well as who is best able to manage the resulting IP and having existing financial models to invest in patent filings, we find that there are compelling reasons to recommend that ownership of IP resulting from CIRM-sponsored research reside with the grantee. This will provide a policy framework that will not conflict with federal statutes and policy, but more significantly recognizes the importance of the researchers themselves in helping to manage and advance the IP as well as the existing institutional infrastructure to manage and fund investments in IP protection.

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[7] In the version of ACR 24 amended 7/13/05, other programs such as the William and Melinda Gates Foundation and the AIDS Initiative were cited as additional possible points of comparison for CIRM policy. While these programs employ interesting approaches to handling of IP, there are differences between the functions they perform and the role CIRM will play; in addition, both are too recent to have an established track record. A more complete discussion of these has been included in an addendum at the end of the report.

[8] Lon Hatamiya, Jeff Newman and Jessie Szeto, Recommendations on Streamlining the University of California Technology Transfer Process California Department of Technology, Trade, and Commerce (Sept. 19, 2003).

Return on Investment

The Legislature, through ACR 24 (as amended in April 2005),[9] asked the Study Group to give particular consideration to the generation of "public benefit" via state revenues, favorable pricing, revenue sharing, and reinvestment into research.

All of these issues were debated extensively at the federal level prior to and following the passage of Bayh-Dole in 1980, and continue to be a subject of discussion today by federal agencies such as the National Institutes of Health.

State Revenues and Revenue Sharing

There are several ways for the state to benefit from IP generated by CIRM-funded research. In most ways, this IP will be no different than any other state-funded biomedical IP generated in California. There are, however, some aspects of CIRM-funded IP that merit special consideration, because of the nature of the research and because of current federal policies.

First, in contrast to research in other areas such as information technology, the IP generated by CIRM-funded research will likely involve:

- A longer time to develop into useful products;
- A greater cost to develop than other IP (because of the longer time necessary and highly regulated development environment); and
- A much higher level of public visibility and scrutiny than most research programs.

Second, as is well known, the federal government has restricted federal funding for human embryonic stem cell research to a limited set of stem cell lines extant at the time the relevant federal policy was issued in 2001.[10] In the future, it is possible that current federal restrictions will be changed. To the extent that CIRM funding can be used to leverage federal funds, this should be encouraged, as it will maximize the effectiveness of the state's investment in stem cell research.

In any scenario, it will take many years for the state to accrue benefits from CIRM-funded research. Moreover, within the state, the high level of expectation about return on its investment is unusual in research. At the federal level, this has not been much of an issue in the 25 years since the passage of Bayh-Dole. Instead, after considerable debate, the NIH decided that the single most important goal for biomedical research was the rapid development and commercialization of products, and that direct financial considerations should be secondary.

Regardless of CIRM's IP policies, long time periods are required to do research and develop useful and safe biomedical products and therapies and usher them through the regulatory approval process. CIRM-funded innovations and the revenues generated from them cannot realistically be expected to have any significant effect on the state's revenues for the immediate future.

In the near term, economic benefits will most likely accrue to the state from its investment in the stem cell initiative through retention and recruitment of high-quality research personnel and enhanced business activity in support of research institutions and programs.

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[9] ACR 24 of the 2005-06 Regular Session, (Mullin), Amended 4/21/05.

[10] Address to the Nation on Stem Cell Research, 2 Pub. Papers 953 (Aug. 9, 2001); see also Press Release, The White House, Fact Sheet: Embryonic Stem Cell Research, http://www.whitehouse.gov/news/releases/2001/08/print/20010809-1.html.

Regarding benefits from new discoveries, the primary IP derived from CIRM-funded research in this early period will be either research tools or inventions that have therapeutic promise, but for which much more research funded by venture capital and companies will be required to determine their optimal use and commercial viability.

Over time, the returns on CIRM investments in research will have to be evaluated by considering the full scope of the benefits that medical research offers to society. Conventional thinking measures traditional quantifiable investments, both direct (dollars spent) and indirect (jobs created, total sales, etc.). More difficult, although still possible to measure, are cost savings from diagnostic and treatment procedures for particular diseases, increases in life expectancy, and improvements in the standard of living.

Royalty Revenues

The expectation exists that CIRM's IP policy needs to direct a revenue stream to the state. It is critical that this expectation not work against CIRM's primary mission, which is to fund research with the goal of discovering and developing new ways of treating degenerative diseases.

The desire for a substantial return on investment, in particular if that in turn drives high royalty rates on early stage research products, should be balanced with the need to create incentives for the much greater commercial investment that is necessary to develop useful treatments and therapies. A requirement that the state be entitled to a royalty stream from any commercialization of CIRM-funded therapeutics is likely to create disincentives to invest; more importantly, such a requirement may also impact CIRM's ability to use tax-exempt bonds to fund research which will cost the state much more in terms of the cost of bonds than it could ever hope to realize through royalty revenues.

The expectation that CIRM's IP policy needs to direct a revenue stream to the state should not work against CIRM's primary mission...to discover and develop new ways of treating degenerative diseases.

Thus, CIRM's IP policy should focus on providing incentives for commercial investment and development of new technologies within the state of California. That strategy will potentially contribute the largest economic impact of the initiative in the near term through job creation.

The overriding IP consideration for grantees should be to move technology from research to other entities as effectively as possible for the public benefit.

Even though we do not recommend any form of direct royalty revenue sharing with the state because of the likely impact on tax-exempt bond status, some portion of royalties could be used to support additional research or for other purposes that support CIRM's mission (see below). In considering how royalty revenues could be used, several details need to be addressed to ensure that the appropriate incentives remain in place to support effective IP management. Some of the issues include:

- Permit grantees to recover all direct expenses incurred in pursuing patent protection and licensing opportunities.

- Begin royalty revenue sharing only when certain landmarks have been passed, e.g. net revenues exceeding $500,000/year, to avoid the administrative inefficiency of dealing with marginal amounts of money and to help grantees offset the cost of the risks they make in IP that is ultimately unsuccessful, thereby providing an incentive to take such risks.
- Allow grantees to share any licensing income with inventors, in accordance with their established institutional policies. This requirement is dictated under federal funding regulations, and serves as an incentive for the inventor to participate in the time-consuming process of obtaining patent protection and to help a potential licensee fully utilize a technology. Furthermore, many institutions have employment agreements/contracts under which they are required to share such income according to pre-established formulas.
- Enable grantees to fulfill their other mandatory obligations. For example, when an invention includes a co-inventing/co-owning institution, and the grantee is managing the invention on behalf of both parties, it may be legally obligated to share a specified portion of any income it receives with the co-inventor/co-owner.

Reinvestment into Research

An option is to direct a share of royalty revenues to fund further stem-cell related research and education, which is consistent with the objectives of CIRM and with the mission of non-profit research institutions. This option also minimizes potential conflicting requirements with Bayh-Dole for non-profits that also have federally funded research in this area. Bayh-Dole requires non-profit grantees to use net licensing revenues for research and education. As with IP ownership, consistency with the requirements of other providers of research funding will allow CIRM grantees to leverage such funds where available and appropriate, and avoids the necessity and expense of complex administration or of isolating CIRM-funded research activity.

Favorable Pricing

There has been much discussion of requiring that CIRM-funded drugs and medical treatments be made available to consumers at "reasonable prices." While certainly a well-intentioned public policy objective, the pricing of future treatments and therapies is not directly an IP policy issue. The linkage of such an important healthcare financing policy with IP policy, and the subsequent management of IP, may have unfortunate and unintended consequences. Experience at the federal level strongly suggests that it would actually *hinder* the availability of medical advances, rather than make them more widely available.

The NIH concluded that ensuring royalties and monitoring returns was a less important issue than expeditious development of new products.

In 1989, NIH implemented a reasonable pricing policy for its Cooperative Research and Development Agreements (CRADAs). Under this policy, potential collaborators had to agree to "a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public." [11] Ultimately, the policy had a chilling effect on the NIH's relationship with industry. Many companies considered "reasonable pricing" a means of price control and simply declined

[11] Report of the NIH Panels on Cooperative Research and Development Agreements, July 21 and September 8, 1994, p.27.

further interaction with NIH, leading to a zero growth rate of CRADAs. The NIH chartered review panels that concluded that ensuring royalties and monitoring returns was a less important issue than expeditious new product development. Consequently, the policy was revoked in 1995, and CRADA growth rebounded.

The issue of affordable pricing of treatments and therapies that may emerge from CIRM-funded research, however, must be addressed. In all likelihood, new treatments and therapies will not emerge for several years, so there is sufficient time to seek the advice and counsel of a wide range of experts and deliberate carefully. To that end, we recommend that a more detailed examination begin in the near future that engages the full range of non-IP technical expertise required to lay out the key issues involved in reasonable or favorable pricing. Among the kinds of expertise needed are healthcare financing, health insurance, and business development. Members of ICOC and Legislature also should be part of that deliberative process as it proceeds, and before policy decisions are made.

Recommendations

Our recommendations are consistent with general principles we are likely to recommend for state-funded research in the Study Group's final report to be completed later this year. These general principles assert that the IP policy:

- Is to be consistent with the Bayh-Dole Act.
    - This principle can play out in many ways that are of benefit to the public. In particular, ownership of IP resides with the grantee, who is required to diligently develop IP for the public. In addition, the balance of any net royalties must be used to support research and education activities.
- Creates incentives for commerce in California from state-funded research to the greatest extent possible.
- Encourages timely publication of results to diffuse knowledge widely, and provide guidance on the kinds of data that are desired to be placed in the public domain or available under open source, Creative Commons, or other broad-use licenses, including software and special databases.
- Requires diligent development of IP into products that benefit the public.

With these general principles in mind, we recommend that CIRM consider policies that accomplish the following:

- Permit grantees to own IP rights from CIRM-funded research.
- Require grantees (institutions, individuals, or both) to provide a plan describing how IP will be managed for the advancement of science and California public benefit.
- Grant basic research funds without requiring grantees to commit to providing a revenue stream to the state. If, however, a revenue stream develops over time, revenues will be reinvested in research and education.
- Generally make CIRM-developed research tools widely available to other researchers.
- Require diligent efforts to develop CIRM-funded IP into therapeutics and diagnostics that can benefit the public.
- Retain within CIRM Bayh-Dole-like rights to step in if the owner of IP is not undertaking appropriate steps to transfer technology to benefit the public.

- Leave license particulars to the owner who is in the best position to judge how best to ensure that discoveries are made widely available through commercialization or otherwise.
- Reserve the right to use IP by or on behalf of CIRM.
- Establish and maintain a CIRM database to track all IP generated through CIRM funding.

Finally, in the time available to prepare this interim report, we were only able to begin to explore options for returns on investment. In light of the tremendous level of public expectations about benefits to California, we also recommend that CIRM, to the extent possible, fund further research on models to optimize returns to the state. In addition, we recommend that a more detailed examination begin in the near future that engages the full range of non-IP technical expertise required to identify and deliberate over key issues involved in reasonable or favorable pricing of treatments and therapies derived from CIRM-funded research.

Conclusions

With the creation of CIRM and the commitment to invest $3 billion in stem cell research, California is setting a precedent that is being closely watched by the nation and the world. The size and visibility of the public investment approved by voters through Proposition 71, and operationalized by CIRM, is creating high expectations for measurable impacts over the next decade. As it establishes policies for IP, CIRM will be defining a fundamental framework to be used by the research institutions and businesses that will translate creative ideas into tangible products. The careful management of the IP derived from CIRM-funded research will be critical in determining how well the intellectual outputs of this public investment are translated into useful products, therapies and treatments. We believe this interim report addresses the key issues that CIRM needs to consider as it undertakes this important task.

1. Introduction

Proposition 71, approved by California's voters in November 2004, requires that the Independent Citizens Oversight Committee (ICOC) of the California Institute for Regenerative Medicine (CIRM) set intellectual property (IP) standards that "balance the opportunity of the state of California to benefit from the patents, royalties, and licenses that result from basic research, therapy development, and clinical trials with the need to assure that essential medical research is not unreasonably hindered by the intellectual property agreements." [12] New discoveries and inventions created under research funded as a result of Proposition 71 that result in new therapies and treatments for degenerative diseases will eventually benefit California. There are, however, many ways that these benefits may be manifested, including the prestige associated with being the nation's leader in stem cell research, which will help retain current and attract new intellectual talent to the state; economic development in the state, including employment; tax revenue from new business that may be attracted to the state and commercialization of products stemming from CIRM-funded research; and, over time, reduced costs for healthcare as a result of emerging stem cell therapies for chronic diseases.

The purpose of this interim report is to discuss the likely benefits associated with IP created under CIRM funding, describe some existing models for handling IP, and suggest some approaches to treatment of IP that might be beneficial to CIRM and to the state. This report responds to the April 2005 version of ACR 24, which specifically requests:

> "That the Study Group shall study how the commercialization of technology developed with the investment of taxpayer dollars in the form of contracts, grants, and agreements could generate some public benefit, including, but not limited to, state revenues, favorable pricing, revenue sharing, [and] reinvestment into research…" [13]

This report provides a brief background on the Federal Bayh-Dole Act, special considerations about biomedical research, kinds of intellectual property, and California's return on investment. It then discusses factors that CIRM will need to consider in the establishment of its IP policies, and presents specific recommendations. Additional amendments added to ACR 24 in mid July 2005 are addressed in an addendum at the end of the report.

[12] Health & Safety Code §125290.30(h).

[13] ACR 24 of the 2005-06 Regular Session (Mullin), Amended 4/21/05.

2. Proposition 71 and Biomedical Research

The state of California has shown bold initiative with the creation of CIRM and the associated funding allocation of $3 billion for stem cell research over the next ten years. Several states are seeking to bolster or develop their own programs in response to California's example: in New York, the Starr Foundation has recently awarded $150 million for stem cell research to a group of three institutions, citing a need to keep New York competitive as California "races ahead in this crucial field." [14] The fact that California's initiative passed by a substantial margin[15] suggests that its citizens believe that stem cell research is potentially valuable to the advancement of medical science, and hence worth funding on humanitarian grounds.

In response to the high degree of public interest in the implementation of Proposition 71 and the numerous policy discussions that have unfolded in the months since its approval, we find it necessary to urge CIRM and the state to proceed with caution and not set overly prescriptive policies for IP derived from stem cell research. We conclude that some Californians have unrealistically optimistic expectations about the likely financial returns to the state from its investment in stem cell research, especially in the short run. Some statements about these returns verge on hyperbole.

Stem cell research has been promoted as holding a great deal of promise for California. Taxpayers' return on investment is one issue that figured prominently in literature used to promote Proposition 71 prior to the election and in subsequent discussion of its administration.[16] In turn, legislators have introduced state revenue, favorable pricing, revenue sharing, and reinvestment into research as issues that should be considered in framing an IP policy for the stem cell initiative. We find that much of this literature, including a prominently cited economic impact analysis released shortly before the election, provide unrealistic expectations for the potential economic impact of Proposition 71.[17] In particular, although the amount of funds that will be focused on stem cell research – about $300M per year for 10 years – is substantial, it must be put in the context of the nearly $14B annually in federally funded research in the state's institutions of higher education, private research institutes and national laboratories, and $45B annually in industry funded R&D.[18] All interested parties must be mindful of overestimating both the projected revenue stream from IP generated by CIRM-funded grants and the timeline to achieve it.

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[14] The institutions are Weill Medical College of Cornell University, Rockefeller University and Memorial Sloan-Kettering Cancer Center; see Richard Peréz-Peña, "3 City Institutions to get $50 Million for Stem Cell Research," The New York Times, 5/23/05.

[15] The vote was officially tallied at 59.1% for, 40.9% against, and 5.6% votes not cast. Office of the Secretary of State, State of California, State Ballot Measures, http://www.ss.ca.gov/elections/sov/2004_general/formatted_ballot_measures_detail.pdf (last visited 4/21/05).

[16] http://www.voterguide.ss.ca.gov/propositions/prop71-title.htm.

[17] Laurence Baker and Bruce Deal, Economic Impact Analysis: Proposition 71, California Stem Cell Research and Cures Initiative. Analysis Group, Inc. (Sept. 14, 2004) pp. 2-3.

[18] National Science Board, 2004. Science and Engineering Indicators.

In formulating CIRM's policy to handle intellectual property, ICOC members and state leaders must realize that despite the enormous promise of stem cell research, this field of research is in its very early years. Stem cell research, particularly human stem cell research, is worth undertaking for many reasons. One reason is to advance basic science to promote further understanding of biological processes, and much of this kind of research is just beginning. A significant portion of the funding that CIRM will grant will support this kind of research; the output of this basic and applied science will largely be additional stem cell lines with broad capabilities, research tools, databases of scientific data, research publications, and most important, a step forward in the understanding of science, paving the way for additional research. A small number of research discoveries may lead to therapeutic or diagnostic technologies, and it is impossible to discern in advance which discoveries have this potential. In all likelihood, the availability to the public of effective therapies from this basic research is at least ten to twenty years away.

While expectations of a short-term revenue stream and quick availability to the public of new treatments may well be overblown, CIRM-funded research can, nonetheless, be expected to benefit the state in significant ways. In the near term, benefits will accrue to the state from its investment in the Stem Cell Initiative through retention and recruitment of high-quality research personnel to the state and through enhanced business activity in support of California research institutions and programs. In the longer term, the state will realize the majority of its economic return on investment from the creation of new high-tech jobs and businesses, stimulation of the economy, and the tax revenues derived from commercialization of the research results into new products and therapeutic treatments for a wide variety of debilitating illnesses. Although these impacts are not likely to accrue quickly in the near term, they have the potential to be substantial.

To put this ambitious goal in perspective, a similarly challenging research initiative, the so-called war on cancer, has been waged for more than three decades and is only now beginning to result in lower death rates from cancer. In the life sciences, the development of a new drug or FDA-approved treatment from a research finding typically takes at least a decade, and it takes private investments in excess of several hundred million dollars in the development process to bring a product to market. Figure 1 shows a case study on the development of Rituxan®, a cancer treatment; although atypically rapid, this process nonetheless took eight years. Another important example is shown in Appendix C, the story of the development of effective therapies for childhood leukemia. Simply stated, in the biological sciences, the investments of time and money in development and commercialization activities typically far exceed those required in the original basic research. IP policies applied to CIRM-funded activities must acknowledge these typical aspects of biomedical research to assure that the state ultimately accrues the most benefits for its taxpayers. We strongly recommend that the ICOC, drawing on its considerable expertise and access to other national experts and networks, take the time it needs to set policies that will serve the best interests of the science, the state and its citizens, and the researchers and institutions that will conduct the research.

Drug Development: A Case Study

Rituxan®, Biogen Idec, Cambridge, MA

The product development cycle for new drugs and biologics is lengthy and uncertain. Researchers must conduct three phases of clinical trials to show that a drug's benefits outweigh its side-effects, and that its therapeutic action works better than a placebo. Depending on the complexity of the new drug and the nature of the disease being treated, it may take thousands of patients and several years before statistically significant data emerge to confirm that a drug works.

In November 1997, the FDA approved the first new single agent therapy in a decade for non-Hodgkin's B-cell Lymphoma, a cancer that attacks the lymph system. This revolutionary new therapy, named Rituxan®, was co-developed by IDEC Pharmaceuticals in San Diego, now Biogen Idec, and Genentech in South San Francisco. Rituxan® belongs to a special class of drugs called monoclonal antibodies, and is the first of its kind to be approved for use in the U.S. Scientists create monoclonal antibodies through genetic engineering, producing hybrid cells that contain the desired characteristics, such as antibodies to a certain disease, and an absence of any substance that might provoke an immune response in the patient.

IDEC initiated its anti-cancer program in 1990, when researchers began screening compounds for demonstrated anti-cancer activity. In early 1991, researchers noted such properties in the monoclonal antibody that they later developed into Rituxan®. Animal studies confirmed the existence of anti-cancer activity, and IDEC began Phase I clinical trials in 1993, moving on to Phase II the following year. 1995 brought a collaboration with Genentech for the further development and commercialization of the drug, along with the onset of pivotal Phase III trials. The companies announced positive results of the trials in December 1996, nearly two years later, and submitted an application for FDA approval in March of 1997. The FDA speedily reviewed the application, granting its approval in November, and Rituxan® became available in December, Even with an extremely promising drug candidate from the outset, and an accelerated FDA review process, the development and commercialization of Rituxan® required nearly eight years and over $110 million to accomplish.

The Clinical Trials Process

PHASE I SAFETY	PHASE II SAFETY AND EFFICACY	PHASE III CONTROLLED SAFETY AND EFFICACY
The therapy is tested on a small number of people, typically healthy volunteers, to ensure that there are no adverse results from its use.	A larger trial is conducted on patients, to assess the effectiveness of the therapy in treating the targeted disease.	Therapies that show promising results in Phase II move on to larger-scale clinical evaluation to verify these results. Depending on the targeted disease and statistical requirements, this phase may require hundreds or thousands of patients.

The Path to Discovery – *Rituxan® for the Treatment of Non-Hodgkin's Lymphoma*

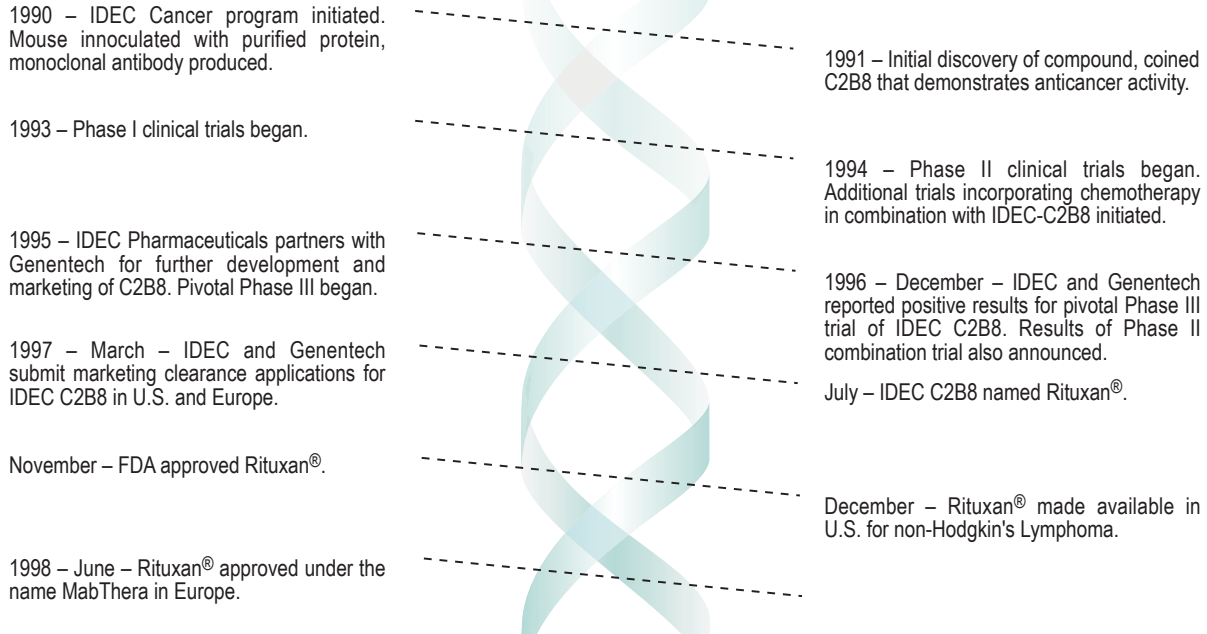

Figure 1: Drug Development: A Case Study (courtesy of California Healthcare Institute)

Figure 2 illustrates the typical progression of a new therapy from basic research, to further development, to going through the regulatory approval process, to the point where it is marketable and potentially usable by the medical community.

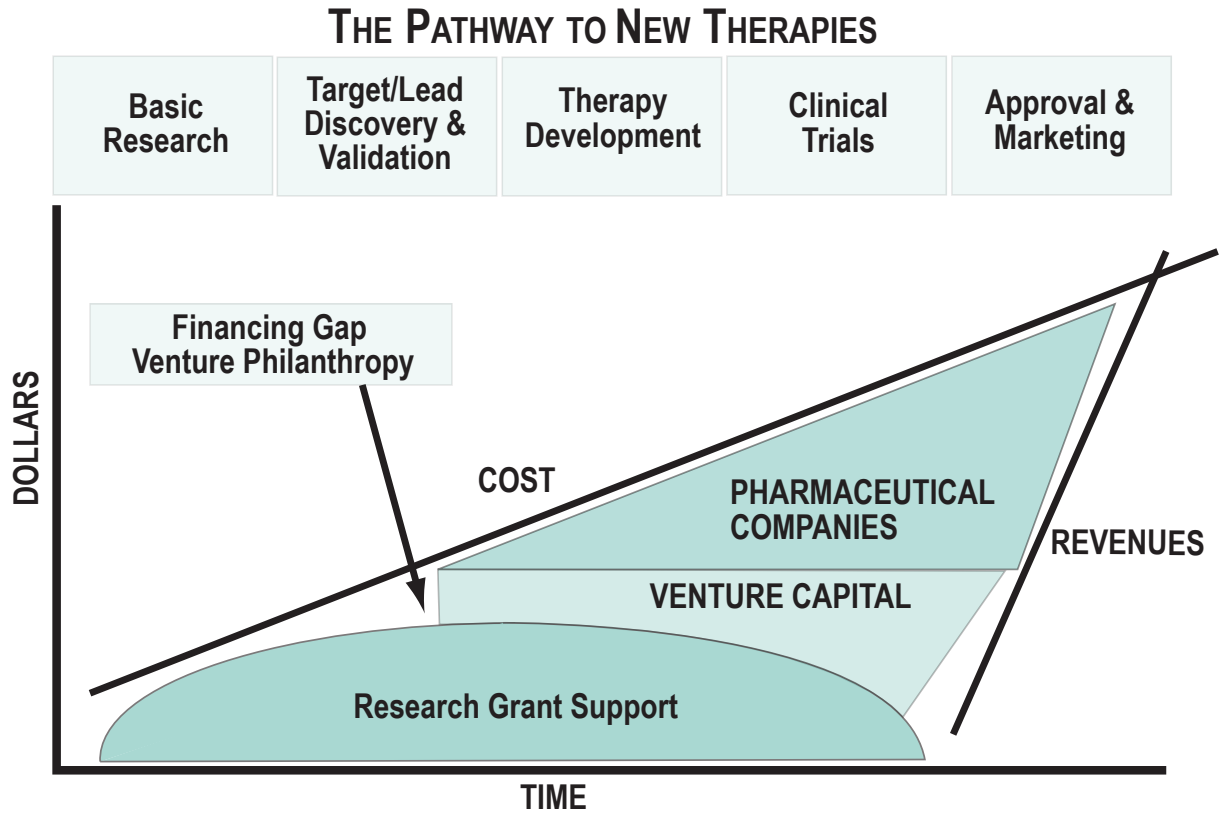

Figure 2: Development of New Therapies. (courtesy of Fred Gage, The Salk Institute and Larry Goldstein, Howard Hughes Medical Institute, University of California, San Diego)

In the life sciences, the development of a new drug or FDA-approved treatment from a research finding typically takes at least a decade, and it takes private investments in excess of several hundred million dollars in the development process to bring a product to market.

As the figure demonstrates, new therapies must go through five stages before reaching the point where they can be commercialized. The funds required to develop a therapy increase substantially after the basic research and validation stages; as the figure also shows, pharmaceutical companies shoulder the bulk of the financing burden in the later and more expensive stages of development (therapy development, clinical trials, approval and marketing). Commercial investment in this inherently risky process is less likely to occur if the potential new therapy is also burdened with the "stacking" of royalty payments back to too many parties. Indeed, IP policies that fail to create incentives for commercialization by the private sector have the potential to diminish rather than enhance economic impacts that will benefit the state through new jobs, new businesses, tax revenues for the commercialization of research results into new products and therapeutic treatments, and reductions in the state's healthcare costs for chronic debilitating diseases that may be benefited by stem cell therapies.

3. Background: The Bayh-Dole Act

Research, especially in universities and other non-profit research institutions, receives funding from many sources, including federal and state agencies, private industry and non-profit organizations. Ownership of any IP generated by such research, and the details of how it is managed, depends on the source of funding, but generally converges on high-level objectives such as ensuring broad dissemination of research results and managing inventions for the public benefit.

Up through the 1970s, agreements on ownership of inventions derived from federally funded research were negotiated individually with each government agency. The results were inconsistencies and high transaction costs that too often contributed to ineffective transfer of university IP to technologies for commercialization. Moreover, many promising federally funded research discoveries were not being transformed into widespread use because IP rights were not being claimed. Without IP protection, companies had insufficient incentives to invest in transforming the research discoveries to marketable products.

The Bayh-Dole Patent and Trademark Amendments Act of 1980 (Bayh-Dole) led to the development of consistent invention policies for federally funded research conducted at universities and in small businesses. It permitted grantees to patent inventions resulting from federally funded research, which they could then license to other entities, including to private firms willing to invest in commercialization.[19] Many research universities and labs began to encourage faculty and other researchers to identify and report discoveries that could be patented for commercial development. Many institutions also established technology transfer offices with their own resources to handle patent prosecution and licensing.

While it is difficult to measure the direct effect of Bayh-Dole on technology transfer, by rationalizing and simplifying the process of moving technologies generated by federally funded research from university laboratories to the private sector, Bayh-Dole is generally considered to have contributed positively to the development of some technologies that may not have been made available to the public in its absence.[20] Appendix B provides additional analysis of Bayh-Dole.

Bayh-Dole rationalized and simplified the process of moving technologies generated by federally funded research from university laboratories to the private sector.

Bayh-Dole provides guidance on the handling and ownership of federally funded IP. In contrast, state level policies in California are not uniform and do not have a common set of clearly stated objectives.

In many ways, the situation in California today regarding state-funded research resembles the federal situation in the late 1970s prior to the passage of Bayh-Dole: contracting is possible, but complicated. The absence of clear guidance leads to considerable time and costs associated

[19] David C. Mowery, "The Bayh-Dole Act and High-Technology Entrepreneurship in U.S. Universities: Chicken, Egg, or Something Else?" prepared for the Eller Center conference on Entrepreneurship Education and Technology Transfer (U. of Arizona, January 21-22, 2005) pp. 14-15.

[20] Jerry G. Thursby and Marie C. Thursby, "University Licensing under Bayh-Dole: What are the Issues and Evidence?" (May 2003) p. 9.

with negotiating the handling of IP stemming from state funded research. The University of California, for example, entered into 900 contracts with 74 state agencies for a total of $220 million in 2003, most of which had to be negotiated individually. UC estimates that if the 900 state awards had been federal awards (or implemented in a streamlined manner similar to federal awards), UC and perhaps also the state would have saved over $1.1 million in streamlined invoicing, record keeping, and administrative issues.[21]

Most university research relies on multiple sources of support, and universities must take great care to ensure that researchers do not operate under conflicting terms and restrictions in the ways IP generated by their research is to be handled. Since the vast majority of research funding at most universities and non-profit research laboratories comes from federal agencies, policies for the management of IP at those institutions are driven by the provisions of Bayh-Dole. The role of technology transfer offices at universities and non-profit research institutions is to negotiate compromises between all affected parties in such instances.[22] It is not the role of the state agencies, like CIRM, to fund technology transfer offices directly, but by streamlining and standardizing state-funded IP policies, the complications and administrative costs associated with managing conflicting obligations can be reduced all around.

State level policies in California are not uniform and do not have a common set of clearly stated objectives.

As CIRM develops its IP policies, consideration should be given to the likely circumstance where CIRM funds would be leveraged with federal funds. At a minimum, CIRM should recognize that institutional policies will be driven by Bayh-Dole. To minimize confusion and maximize the return on grant funds, CIRM's policies should be consistent with Bayh-Dole. This is not to say that CIRM's policies need be identical to Bayh-Dole, but its provisions should not conflict with Bayh-Dole in ways that would lead to the creation of confusing, conflicting, or convoluted funds-management administration by institutions, ultimately impeding the conduct of research. Consistency between federal and state policies would avoid conflicts in determining ownership and royalties from cumulative research results involving related projects, possibly supported by a variety of funding sources. In addition, CIRM should avoid adopting a set of IP policies that make the prospective financial returns for inventions made with CIRM grants less attractive than those for comparable NIH grants. A likely unintended consequence could be that the best researchers and institutions would favor types of research funded by the latter (in the event that NIH grants were to become available for the type of research funded by CIRM).

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[21] Alan Bennett, "University of California Agreement," University of California, Davis, Transfer Office and Office of the President (Davis, California, 2004), p. 1.

[22] Sean M. O'Connor, "Intellectual Property Rights and Stem Cell Research: Who Owns the Medical Breakthroughs?" New England Law Review (Vol. 39) p. 705.

4. Objectives to Consider for CIRM IP Policies

In most ways, IP derived from CIRM-funded research will be no different than that of any state-funded biomedical IP generated in California. For that reason, treatment of this IP should be consistent with whatever statewide policies may be developed and adopted following the release of our final recommendations to the California Legislature in December 2005.

There are, however, some aspects of CIRM-funded IP that merit special consideration, because of the nature of the research and because of current federal policies.

First, in contrast to research in other areas such as, for example, information technology, the IP generated by CIRM-funded research will likely involve:

- A longer time to develop into useful products
- A greater cost to develop than other IP (because of the longer development time necessary and highly regulated development environment)
- A much higher level of public visibility and scrutiny than most research programs

Second, as is well known, the federal government has restricted federal funding for human embryonic stem cell research to a limited set of stem cell lines extant at the time the relevant federal policy was issued in 2001.[23] This federal funding restriction was, in fact, the major impetus behind Proposition 71. In order to ease compliance with the federal funding restriction, institutions may choose not to leverage their federal funds (by matching, or in-kind arrangements) with CIRM funds used for research on embryonic stem cell lines ineligible for federal funding. However, CIRM-funded research with cell lines listed on the National Institutes of Health registry of human embryonic stem cell lines eligible for federal funding, and CIRM-funded research using adult stem cells could be used to leverage federal funds. In addition, in the future, it is possible that current federal restrictions will be changed. To the extent that CIRM funding can be used to leverage federal funds, it should be encouraged, as it will maximize the effectiveness of the state's investment in stem cell research. As a consequence, it may be prudent to model CIRM's IP policy to be consistent with the provisions of Bayh-Dole, with some deviations or exceptions that do not go so far as to conflict with the requirements of Bayh-Dole. Similarly, CIRM may also want to model its policies on sharing research materials and tools with applicable policies developed by the National Institutes of Health.

Third, universities and other non-profit research institutions will be key participants in conducting the basic stem cell research funded by CIRM. To succeed, CIRM must provide an attractive source of research support to talented scientists who are the most likely to produce the most important research. As a result, CIRM's policies must not differ dramatically from the prevailing research and academic policies that enable those researchers to make and receive credit for significant contributions at the frontiers of science. For instance, universities preserve the rights of their researchers to freely publish their research results. Among them, the UC system has articulated some fundamental principles to which its campuses must adhere with

[23] Address to the Nation on Stem Cell Research, 2 Pub. Papers 953 (Aug. 9, 2001); see also Press Release, The White House, Fact Sheet: Embryonic Stem Cell Research, http://www.whitehouse.gov/news/releases/2001/08/print/20010809-1.html.

respect to research results. These principles take the form of UC Presidential Policy, and are generally consistent with most other academic institutions. Among other things, these policies include preserving the researcher's ability to openly disseminate research results and making laboratory innovations available for public benefit in a timely manner.[24]

CIRM's mission, as a new state agency, is to make grants and provide loans for stem cell research and training, research facilities, and other vital research opportunities, with an ultimate goal of discovering and developing new ways of treating degenerative diseases. The primary objectives of CIRM IP policies should be to maximize CIRM's effectiveness in supporting this mission. Examples of such objectives might be:

- *Support the open dissemination of research results and transfer of knowledge, where appropriate.* Widespread dissemination of research results is essential for the advancement of stem cell science and the development of practical application.
- *Ensure that discoveries and research tools that are useful for further research are made broadly available to the research community.* Accessibility of research tools ranging from cell lines to reagents to software programs is essential for the advancement of stem cell science.
- *To the extent possible, preserve the ability for grantees to leverage non-CIRM funds in their stem cell-related research.* Ideally, CIRM's IP policies would not conflict with the obligations associated with other sources of research funds. Under federal funding, for example, a non-profit recipient of funds generally retains ownership of its inventions and must ensure that any net proceeds from licensing the inventions be used to support further scientific research and education. Any CIRM policy to the contrary would prevent a grantee from fully leveraging federal funds.
- *Encourage practical application of CIRM-funded research results for the broad public benefit.* The ultimate goal of CIRM is to provide public availability of scientific advances such as diagnostics, drugs and other treatments. This goal cannot be accomplished without industry involvement. In the pharmaceutical and biotech industries, where a tremendous investment is required to take a drug through development and regulatory hurdles, companies usually require exclusive access to a promising new discovery in order to justify such an investment. Such exclusive access is achieved through use of the patent and licensing system. Other types of research results can be made broadly available on a nonexclusive basis.
- *Accelerate the transition of discoveries from research to commercially available diagnostics and treatments*. The primary goal of CIRM is to generate new methods of treating chronic degenerative diseases. All of CIRM's IP policies need to be crafted with this fundamental premise in mind. It will be important to avoid introducing any policies that would slow down, inhibit, or prevent this transfer process. This approach is consistent with that of the NIH, which has affirmed that the primary consideration in government-funded biomedical research needs to be accelerating research into the development and commercialization of diagnostics and therapies.
- *To the extent possible, balance existing investments with state investments such that each receives appropriate return.* As noted above, there are several possible models to apply for determining how any revenue stream is directed.

[24] http://www.ucop.edu/ott/preamble.pdf.

- *Promote collaboration between commercial entities and non-profit research institutions.* Close collaboration between such entities is often critical to bridge the gap between early stage discoveries and products for the diagnosis and treatment of injury and disease.
- *Encourage private investors to invest in further research and development of new technologies resulting from CIRM-funded research.* Venture capital investment plays a critical role in the development of IP after initial research and before late-stage R&D which is more generally funded by private industry.
- *Minimize costs of administering policies.* To minimize costs and administrative burden, CIRM should strive for a uniform and streamlined process for administering its grants and resulting IP. For example, permitting grantees to administer inventions in accordance with their established policies (to the extent such policies are consistent with CIRM's objectives) would relieve CIRM of this administrative effort and expense.
- *Be mindful of the time delay and private investment needed before significant benefits accrue to the state.*

Any IP model must be developed with consideration for the different kinds of IP which CIRM-funded research may generate. These are detailed in Table 1, and described further in Appendix A.

Particular attention needs to be paid to the treatment and dissemination of research tools and databases. Making research tools developed with CIRM funding largely available to other scientists for use in ongoing research would be consistent with the language of Proposition 71, which specifies that CIRM is expected to assure that "essential medical research is not unreasonably hindered." This is a standard policy for research funded by the National Institutes of Health[25] and should be encouraged by CIRM.

In their proposals, CIRM grantees should discuss the anticipated research tools to be created and how and when they intend to make them available to other researchers, particularly CIRM-funded researchers.

Creators of IP that falls into the "research tools" category have several options. Grantees may choose not to file patents on research tools. Alternatively, they may choose to file patents, in which case they have, in turn, a number of other options. They can grant royalty-bearing, nonexclusive licenses to others who wish to use the research tools or, when the research tool needs further development, they can grant exclusive licenses to encourage a company to further develop and commercialize the invention. Each of these approaches supports wide availability to the research community for further development and the overall advancement of the science. We recommend that exclusive licenses, if used, should retain rights for the grantee and the research community to continue to use the IP for research purposes.

[25] http://ott.od.nih.gov/pdfs/64FR72090.pdf.

Table 1: Expected Output from Stem Cell Research and the Applicability of Intellectual Property Protection

Expected Output	Definitions	Applicable Intellectual Property Protection[26]
Patentable Inventions	Discoveries that advance science and enable new useful applications, notably including therapeutics or diagnostic tools. Such discoveries are often patented, and licensed in a manner that will promote the development and availability of products embodying the invention. When significant further investments are required to take a promising research result to a viable product, exclusive licensing may be the best model to benefit the public, by inducing private industry to make the significant investment to further develop the research into a product. In other cases, nonexclusive licenses can encourage widespread development and adoption of new patentable discoveries. For effective technology transfer, more than patents must sometimes be licensed; biological materials and equipment and associated know-how may be transferred through material transfer agreements.	Patent Trade Secret
Research Tools	Inventions that broadly facilitate subsequent research, including both methods (e.g., Polymerase Chain Reaction (PCR) a technique for amplifying DNA to facilitate cloning and sequencing) and products (e.g., specific cell lines, such as embryonic stem cells, DNA clones, or antibodies). This IP may be patented or not, but is best managed through strategies that ensure widespread dissemination and use. Research tools are often shared freely and without any formal agreement; however, if the provider of research tools wishes to control dissemination of the research tool, a material transfer agreement may be used.	Patent Trade Secret Physical Property Right
Computer Programs	Computer programs for a variety of purposes, including analyzing data. Computer programs are automatically protected by copyright law, and may be made available to research communities or the public through open source licensing or dedication to the public domain; if further investments are needed to refine the program to make it more useful, proprietary licensing may be appropriate.	Patent Trade Secret Copyright
Databases	Compilations of data, typically generated from research, sometimes from one source, but often combined from many sources. Original databases are protected by copyright law and there have been several legislative bills in recent years seeking to extend this protection. Databases may be shared without restriction, or licensed to research communities, to promote the advancement of science. When developed by private industry or under private funding, databases may be licensed as a commercial asset.	Trade Secret Copyright
Research Articles	Publishable scientific articles protected by copyright law. Although it is common for publishers to request or require researchers to assign copyrights as a condition of publication, published work is widely available to the research community via digital libraries, open licensing, and pre-print servers.	Copyright

[26] See Appendix C for more detailed discussion of these types of IP.

Researchers increasingly need access to large amounts of data, generally available in electronic form. As generators and users of databases, researchers are dependent on database information, which must be gathered and entered, updated regularly, with quality controls implemented to be sure the data is accurate and the database remains useful. Databases can be made available for a fee or for free. In addition, many research enterprises maintain "proprietary" databases to which they have dedicated significant resources and which they may or may not make available to others. Even if the research relies on access to a database that is not available for others to use, the results of research conducted with the aid of the database should be widely disseminated.

CIRM should encourage grantees to make CIRM-funded databases as widely available as possible. However, if a proprietary database is necessary to move a grantee's stem cell research forward faster, proprietary databases may be developed for and used in that research. The success of CIRM will depend greatly upon researchers' ability to access data and information, often for multiple purposes. Scientific and research progress in stem cell research, like other research, will depend on researchers' ability to access and use information in the public domain and to combine public and proprietary data into new databases, as well as to re-evaluate and reuse existing data.

Research tools may include biological material such as cell lines, monoclonal antibodies, reagents, software programs, data and databases, and other inventions. In the IP management plans they submit with each proposal, CIRM grantees should discuss the research tools they anticipate creating and whether and how they intend to make them available to other researchers, particularly CIRM-funded researchers. Some approaches might be:

For biological material, licenses will typically be nonexclusive for the area of research. Biological materials may also be placed in repositories to store, reproduce and transmit the materials.

For software, internal use licenses will typically be nonexclusive; but if a company will add value and further develop the software, commercialization licenses would generally be exclusive, perhaps for a limited period of time and a specific area or areas of science. Alternatively, software may be made broadly available through open source licensing or affirmatively put in the public domain for use by anyone.

For data and databases, CIRM should encourage wide accessibility of public and proprietary data for the benefit of researchers. If a company has proprietary data or databases that will enhance the likelihood of therapy development, exclusive licenses may be appropriate, provided the results of the research can be freely shared.

The overriding IP consideration for grantees should be to move technology from research to other entities as effectively as possible for the public benefit.

For inventions, grantee should license as appropriate for the stage of development of the invention, taking into consideration the requirements for effective diligent commercialization and public availability as quickly as possible.

In all cases, grantees should be obliged to disclose to CIRM the patentable inventions and other intellectual creations that result from CIRM-funded research; if they believe that the creations would be most effectively disseminated and most effectively foster significant ongoing scientific progress through dedication to the public domain or open source licensing, CIRM should respect this decision. Most important, CIRM grantees should be expected to reserve the right to use the technology for their own research and education purposes and to allow

other non-profit institutions to do so as well, even in cases where an exclusive commercial license is granted for the commercial development of a product.

A sample of National Institutes of Health guidelines concerning research tools can be found in Appendix D.

5. California's Return on Investment

The language of Proposition 71, Section 3, states that its intent is to "protect and benefit the California budget: … by providing an opportunity for the state to benefit from royalties, patents, and licensing fees that result from the research." In turn, the Legislature, through ACR 24 (as amended in April 2005), asked the Study Group to give particular consideration to the generation of "public benefit" via state revenues, favorable pricing, revenue sharing, and reinvestment into research.[27]

All of these issues were debated extensively at the federal level prior to and following the passage of Bayh-Dole in 1980, and continue to be a subject of discussion today by federal agencies such as the National Institutes of Health (NIH). These discussions may prove to be of value to CIRM as it considers how to maximize the state's return on investment, both directly and indirectly.

Ownership of Intellectual Property

Ownership of intellectual property resulting from sponsored research is a central issue in establishing an intellectual property policy, and allowing ownership to reside with the grantee is the central feature of the Bayh-Dole Act. From this central feature of IP ownership, many other policy considerations followed. In considering the issue of IP ownership for CIRM, it is important to consider: 1) the relative importance of a policy that is consistent with federal (e.g. Bayh-Dole) statute and policy, 2) who is best able to manage the resulting IP, and 3) the existing financial models that are in place to make appropriate investments in protecting very early-stage research results.

Clearly, consistency with federal statutes and policy suggest that ownership of IP resulting from CIRM-sponsored research should reside with the grantee. In considering who is best able to manage IP resulting from university research, strong arguments have been made that IP management should occur at a level that is as close as possible to the research itself – and perhaps more importantly – as close to the researchers as possible. This conclusion was a central feature of the California Technology, Trade and Commerce Agency report of 2003 which recommended that the University of California decentralize its technology transfer programs to the local campus level.[28] Because IP resulting from basic research is very early stage, the ability to manage this IP is also related to the institutional capacity to invest in filing patent applications before there is any prospect of a return on that investment. Thus, if CIRM or a surrogate agency were to manage IP resulting from its sponsorship, an allocation of additional funds would be required to invest in patent filings as the research results emerged from the laboratory. Research universities and not-for-profit research institutes have addressed this issue over the last 20 years and have either established fund sources to support patent filings or utilize the royalty stream resulting from past inventions to support the costs of new patent filings.

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[27] Op. cit.

[28] Lon Hatamiya, Jeff Newman and Jessie Szeto, Recommendations on Streamlining the University of California Technology Transfer Process California Department of Technology, Trade, and Commerce (Sept. 19, 2003).

Based on compliance with Bayh-Dole as well as who is best able to manage the resulting IP and having existing financial models to invest in patent filings, we find that there are compelling reasons to recommend that ownership of IP resulting from CIRM-sponsored research reside with the grantee. This will provide a policy framework that will not conflict with federal statutes and policy, but more significantly recognizes the importance of the researchers themselves in helping to manage and advance the IP as well as the existing institutional infrastructure to manage and fund investments in IP protection.

Defining "Return on Investment"

As noted earlier, there are several ways for the state to benefit from IP generated by CIRM.

In the near term, economic benefits will most likely accrue to the state from its investment in the Stem Cell Initiative through retention and recruitment of high-quality research personnel and enhanced business activity in support of research institutions and programs.

Regarding benefits from new discoveries, the primary IP derived from CIRM-funded research in this early period will be either research tools or inventions that have therapeutic promise, but for which much more research funded by venture capital and companies will be required to determine their optimal use and commercial viability.

To help understand how returns on CIRM investments in research can be evaluated, one can first consider the full scope of the benefits that medical research offers to society. Conventional thinking measures traditional quantifiable investments, both direct (dollars spent) and indirect (jobs created, total sales, etc.). Less evident in the near term, but potentially measurable are cost savings from diagnostic and treatment procedures for particular diseases, increases in life expectancy, and improvements in the standard of living. According to one analysis[29] gains associated with the prevention and treatment of cardiovascular disease through the 1970s and 1980s substantially outweighed R&D costs in this area. While this estimate is considered high by some experts, it is apparent that in defining how the state's investment is to be "recouped," CIRM needs to make sure that the broader perspective of the potential value of its funded research is kept in mind.

In addition, analyses show that research investment has spawned the establishment of many new companies in California, which in turn supports the state's economic growth. A 2004 report by the state's biomedical industry prepared for the California Healthcare Institute (CHI)[30] by PricewaterhouseCoopers found that California universities and research institutes have spun off 732 companies. These companies bring significant jobs, tax revenues, new products, and intellectual and scientific capital to the state. According to this report, the 2,600 biomedical companies in California generate over 230,000 jobs, making the biomedical industry a leading employer in the state. The jobs in this sector pay an average salary of $67,000 per year, thereby contributing substantially to income tax revenues to the state. These companies generate $32.3 billion in worldwide revenues, and on average invest 48% of those revenues back into research and development activities. These companies also attract further investments to California, with over $4 billion coming from alliances with big pharmaceutical companies, and $2.1 billion from venture capital.

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[29] *Exceptional Returns: The Economic Value of America's Investment in Medical Research* http://www.fundingfirst.org

[30] California Healthcare Institute, California's Biomedical Industry: 2004 Report (http://chi.org/home/template5.php?pid=34&subSel=3&subSel=3) p.11.

State Revenues from IP

Some who are concerned about state expenditures in this period of tight budgets have proposed that the state seek to maximize its revenues from CIRM-funded inventions, with the goal of either recovering the cost of the institute or helping to solve the state's fiscal problems. In any scenario, and regardless of CIRM's IP policies, CIRM-funded innovations and the revenues generated from them cannot realistically be expected to have any significant effect on the state's revenues for the immediate future.

The NIH concluded that ensuring royalties and monitoring returns was a less important issue than expeditious development of new products.

The expectation exists that CIRM's IP policy should direct a revenue stream to the state. This high level of expectation about return on its investment is unusual in research. At the federal level, this has not been much of an issue in the 25 years since the passage of Bayh-Dole. Instead, after considerable debate, the NIH decided that the single most important goal for biomedical research was the rapid development and commercialization of products, and that direct financial considerations should be secondary.

This expectation, however, should not work against CIRM's primary mission, which is to fund research with the goal of discovering and developing new ways of treating degenerative diseases.

Royalty Revenues and Revenue Sharing

At least in the near term, and possibly in the longer term (10-15 years), the primary IP derived from CIRM-funded research and development will be either research tools or inventions that have therapeutic promise, but for which much more research funded by venture capital and companies will be required to determine their optimal use and commercial viability.

Royalty revenue sharing may have negative impacts on both non-profit and for-profit grantees. Revenue sharing imposed by CIRM on its non-profit grantees may act as a disincentive to invest the effort and cost necessary to secure patent protection, find an appropriate licensee, and ultimately transfer a promising technology to the commercial sector for the development of treatments and drugs that prove beneficial to the general public. In addition, for non-profit grantees, a royalty sharing requirement could, depending on how it is administered, prevent them from maximizing the impact of CIRM funding by using it to leverage federal funds, since federal funding rules require them to use net royalties for education and research purposes. Royalty revenue sharing imposed on for-profit grantees could discourage their participation in CIRM funding altogether.

In addition, income on royalties from licenses is not guaranteed, and is often modest. For example, a study of University of California inventions over two decades (1975-1995) showed that only 1 in 400 inventions could be expected to bring in over $1 million in licensing revenue over its entire life.[31] In addition, according to a recent national Association of University Technology Managers (AUTM) survey, universities, on average, produce one commercially significant invention for every $2.5 million of research funding.[32] Consequently, if CIRM were to award the full $3

[31] Considerations in Developing an Intellectual Property Model for Research Grants Awarded by the California Institute for Regenerative Medicine," University of California, The Burnham Institute, Stanford University, and University of Southern California (2004) p. 3.

[32] AUTM Licensing Survey: FY 2002, Ed. Ashley J. Stevens (Association of University Technology Managers, 2003).

billion in research funding (ignoring the amounts that will be used for facilities and to pay interest on the bonds), one might expect around 1,200 total inventions from this investment, of which only 3 to 4 might earn more than $1 million in licensing income over their entire lifetimes.

The issue of whether or not to require recipients of research grants to compensate the state in the event they realize income from the commercialization of IP created under state funding was explored by the state-funded Breast Cancer Research Program (BCRP), administered by the University of California. The BCRP explored the advantages and disadvantages of a number of approaches,[33] ultimately deciding not to impose any kind of compensation requirement, preferring instead to encourage maximum participation in the program.

The desire for substantial return on investment, in particular if that in turn drives high royalty rates...should be balanced with the need to create incentives for the much greater commercial investment that is necessary to develop useful treatments and therapies.

It should also be noted that at the federal level, after considerable debate, the NIH decided that the single most important goal for biomedical research was the rapid development and commercialization of products, and that direct financial considerations should be secondary.[34]

The desire for substantial return on investment, in particular if that in turn drives high royalty rates on early stage research products, should be balanced with the need to create incentives for the much greater commercial investment that is necessary to develop useful treatments and therapies.

Instead, CIRM should focus on providing incentives for commercial investment and development of new technologies within the state of California. That strategy will potentially contribute the largest economic impacts of the initiative in the near term through job creation.

Nevertheless, if CIRM determines that royalty revenue sharing is not counter to CIRM's broader mission and is the best way to satisfy public expectations, there are models that could be explored in more detail that would:

- Permit grantees to recover all direct expenses incurred in pursuing patent protection and licensing opportunities.
- Begin royalty revenue sharing only when certain landmarks have been passed, e.g. net revenues exceeding $500,000/year, to avoid the administrative inefficiency of dealing with marginal amounts of money and to help grantees offset the cost of the risks they make in IP that is ultimately unsuccessful, thereby providing an incentive to take such risks.
- Allow grantees to share any licensing income with inventors, in accordance with their established institutional policies. This requirement is dictated under federal funding regulations, and serves as an incentive for the inventor to participate in the time-consuming process of obtaining patent protection and to help a potential licensee fully utilize a technology. Furthermore, many institutions have employment agreements/contracts under which they are required to share such income according to pre-established formulas.

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[33] Charles L. Gruder, "Options for Requiring For-profit Grantees to Compensate the State," University of California Special Research Programs (1994).

[34] Ibid.

- Enable grantees to fulfill their other mandatory obligations. For example, when an invention includes a co-inventing/co-owning institution, and the grantee is managing the invention on behalf of both parties, it may be legally obligated to share a specified portion of any income it receives with the co-inventor/co-owner.
- Direct any shared revenues to fund further stem-cell related research and education, which is consistent with the objectives of CIRM and with the mission of non-profit research institutions, and minimizes potential conflicting requirements with Bayh-Dole for non-profits that also have federally funded research in this area.

Figure 3a shows a typical model for research output at a non-profit research institution. Figure 3b shows two models for revenue distribution. Variations occur in each type of institution, but the path of outputs suggests the complexity of the interactions between researchers and any net revenues downstream.

If CIRM were to consider royalty returns to the state, it may be most efficient for CIRM to handle the infrastructure itself, or to create a Joint Powers Authority to handle it.

From Research to Commercial Product: Typical Research Output at a Non-Profit Research Institution

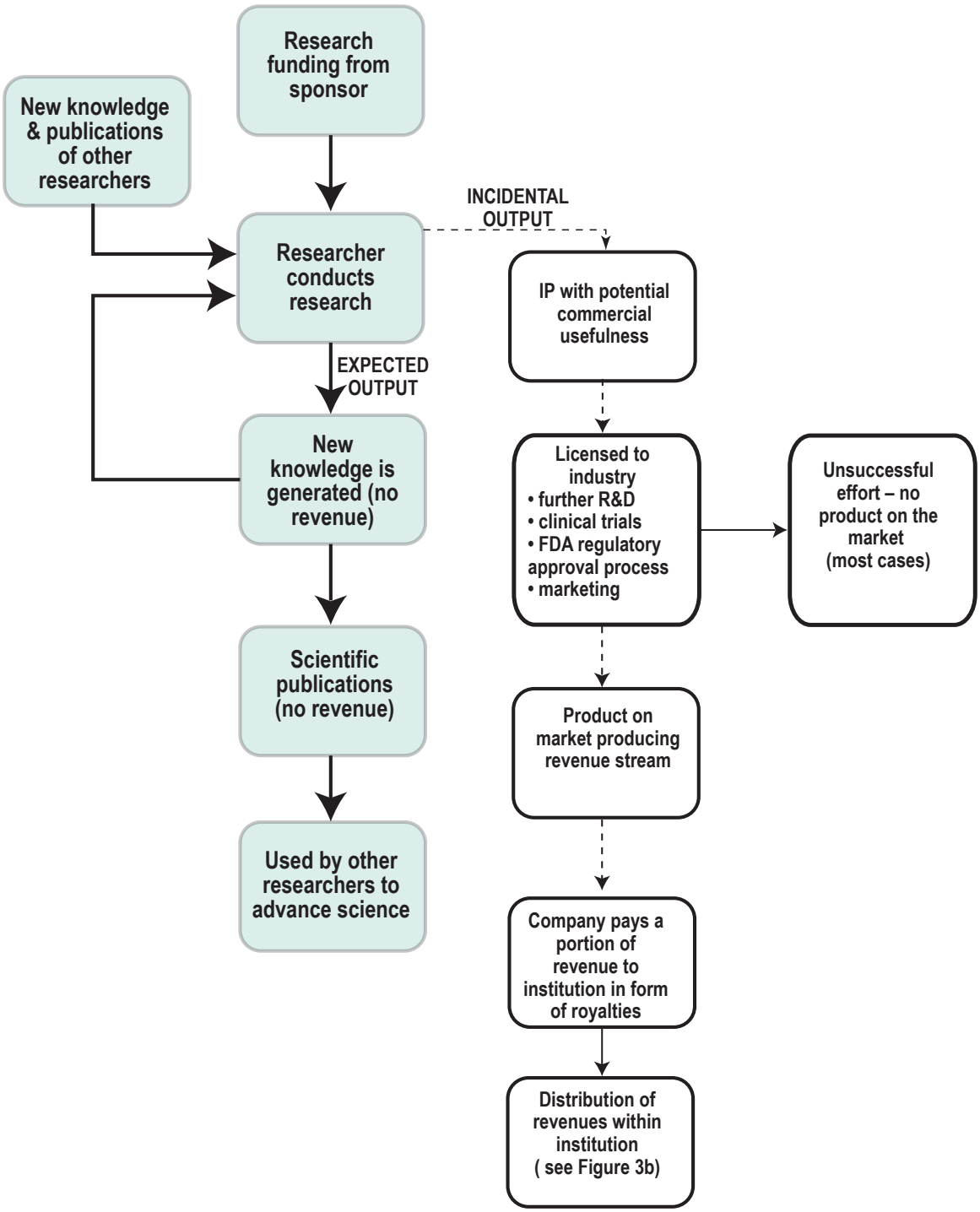

Figure 3a: From Research to Commercial Product. This figure illustrates the typical pathway for knowledge generated by research at a non-profit research institution (left) and the steps following the incidental production of IP with commercial usefulness (right).

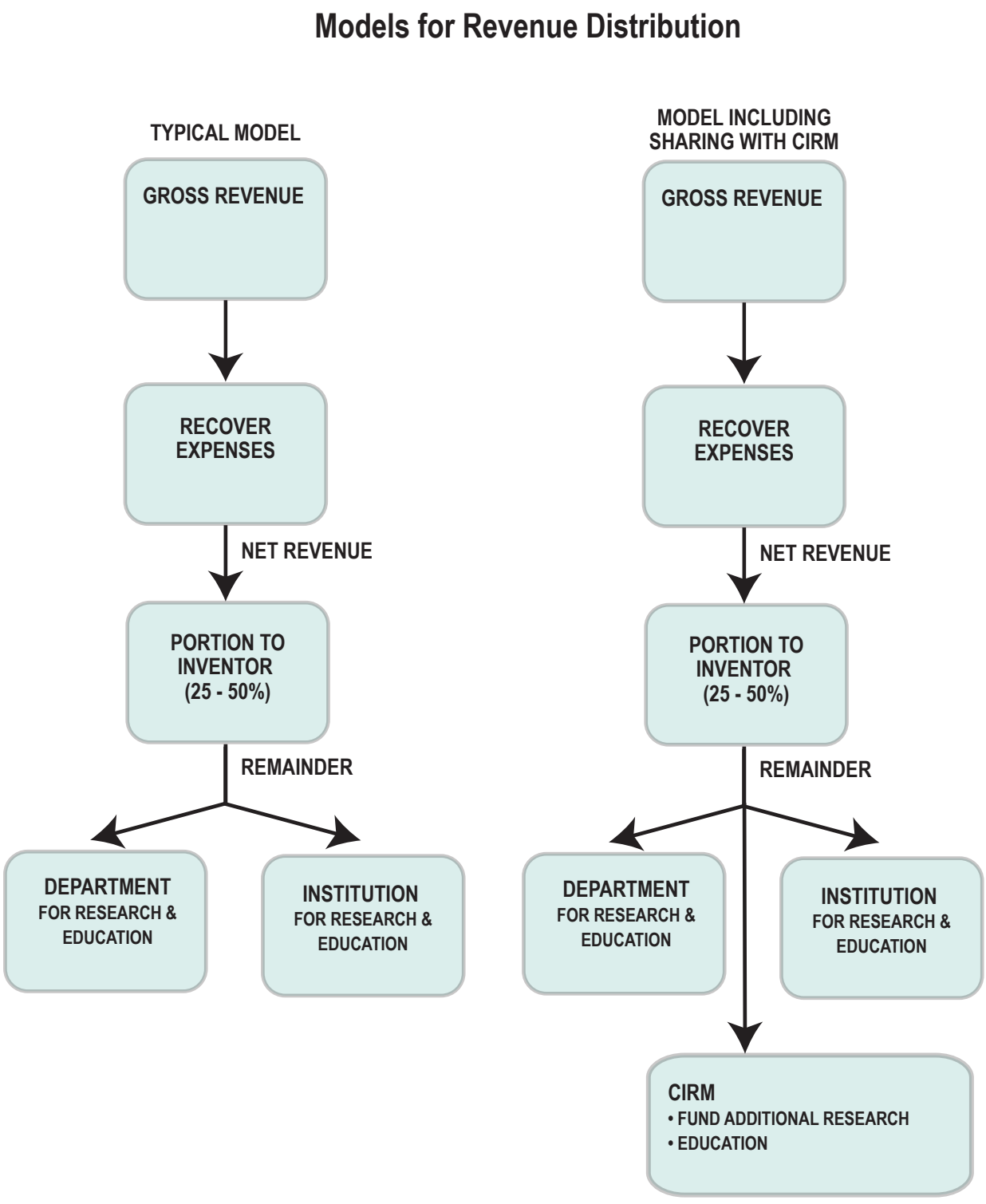

Figure 3b: Models for Revenue Distribution. At left is a typical model for revenue distribution at a university or other non-profit research institution. At right is a potential variation of this model including CIRM as a beneficiary of the net revenue.

Reinvestment into Research

This issue is closely tied to revenue sharing, as the flow of revenue first needs to be determined before consideration can be given to how much can be reinvested in research. CIRM's potential non-profit grantees, based on Bayh-Dole requirements, already have policies in place that require net licensing revenue to be used only for research and education. The federal government imposes this as a condition of its funding to non-profits. As with IP ownership, consistency with the requirements of other providers of research funding will allow CIRM grantees to leverage such funds where available and appropriate, and avoids the necessity, expense and administrative burden of isolating CIRM-funded research activity.

It should be noted that reinvestment into research based on any revenue flow back to the state would be most effectively guaranteed if the revenue were either returned directly to CIRM or to a special research account managed by the state (similar to the Breast Cancer Research Account), as opposed to the state's general fund.

Favorable Pricing

There has been much discussion of requiring that CIRM-funded drugs and medical treatments be made available to consumers at "reasonable prices." While certainly a well-intentioned public policy objective, the pricing of future treatments and therapies is not directly an IP policy issue. The linkage of such an important healthcare financing policy with IP policy, and the subsequent management of IP, may have unfortunate and unintended consequences. Experience at the federal level strongly suggests that it would actually hinder the availability of medical advances, rather than make them more widely available.

CIRM's most important objective is to fund stem cell research and make available to the public new and innovative treatments for a number of diseases. The example of the NIH experience suggests that an explicit requirement for reasonable pricing will probably drive away industry, which will be the critical partner in bringing treatments from concept to reality, and will effectively erect an insurmountable barrier to the commercialization of the products of CIRM-funded research. In 1989, NIH implemented a reasonable pricing policy for its Cooperative Research and Development Agreements (CRADAs). Under this policy, potential collaborators had to agree to "a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public." [35] Ultimately, the policy had a chilling effect on the NIH's relationship with industry. Many companies considered "reasonable pricing" a means of price control and simply declined further interaction with NIH, leading to a zero growth rate of CRADAs. The NIH chartered review panels that concluded that ensuring royalties and monitoring returns was a less important issue than expeditious new product development. Consequently, the policy was revoked in 1995, and CRADA growth rebounded.

The issue of affordable pricing of treatments and therapies that may emerge from CIRM-funded research, however, must be addressed. In all likelihood, new treatments and therapies will not emerge for several years, so there is sufficient time to seek the advice and counsel of a wide range of experts and deliberate carefully. To that end, we recommend that a more detailed examination begin in the near future that engages the full range of non-IP technical expertise required to lay out the key issues involved in reasonable or favorable pricing. Among the kinds of expertise needed are healthcare financing, health insurance, and business development. Members of the ICOC and the Legislature also should be part of that deliberative process as it proceeds, and before policy decisions are made.

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[35] Report of the NIH Panels on Cooperative Research and Development Agreements, July 21 and September 8, 1994, p.27.

6. Recommendations for CIRM IP Policies

Our recommendations comport with general principles we are likely to recommend for state-funded research in the final report of this Study Group. These general principles assert that the IP policy:

- Is to be consistent with the Bayh-Dole Act.
    - o This principle can play out in many ways that are of benefit to the public. In particular, ownership of IP resides with the grantee, who is required to diligently develop IP for the public. In addition, the balance of any net royalties must be used to support research and education activities.
- Creates incentives for commerce in California from state-funded research to the greatest extent possible.
- Encourages timely publication of results to diffuse knowledge widely, and provide guidance on the kinds of data that are desired to be placed in the public domain or available under open source, Creative Commons, or other broad-use licenses, including software and special databases.
- Requires diligent development of IP into products that benefit the public.

CIRM may want to adopt interim policies guided by this report, and to adopt final IP policies after review of the CCST recommendations for all state IP to be published in December 2005.

With these principles in mind, we recommend that CIRM consider policies that accomplish the following:

1. Permit grantees to own IP rights from CIRM-funded research.

To encourage the greatest participation in CIRM-funded research, by both for-profit and non-profit entities, grantees should be permitted to own IP that they create in projects fully or partially funded by CIRM. From a grantee's perspective, this avoids "fractionating" the research results from a given researcher/laboratory. This approach is consistent with the Bayh-Dole Act and with the requirements of most other funding entities, thus allowing grantees to leverage federal and other funds (where available and appropriate) and avoiding the administratively burdensome need to isolate CIRM-funded research to prevent conflicting obligations from the use of third party funding. Allowing ownership to reside with the grantee also avoids fractionating the research results from a given laboratory. However, CIRM should retain the ability to acquire IP rights – so-called "march-in" rights – if grantees do not show diligence in developing and applying the technology (see recommendation 5 below).

2. Require that grantees (institutions, individuals, or both) provide a plan describing how IP will be managed for the advancement of science and California public benefit.

Although such a plan is not customary for research grants, the public interest in this initiative and the calls for accountability suggest that developing a plan is a political necessity.

As the nation's first major state-funded stem cell research agency, CIRM will attract considerable interest nationwide. Due to the national (and international) nature of the biomedical research, both not-for-profit and for-profit, it is not realistic to expect that every CIRM discovery or invention will be licensed and developed exclusively in California. However, to help ensure that CIRM-funded research provides substantial benefit to California's economy, it would be advisable to incorporate a section of the grant application that asks potential grantees to explain how the work is expected to benefit the state of California and how specific IP management strategies will attempt to direct commercialization opportunities to the state. Evaluating these potential contributions should be at the discretion of CIRM.

3. Grant basic research funds without requiring that grantees commit to providing a revenue stream to the state. If, however, a revenue stream develops over time, revenues will be reinvested in research and education.

The state and CIRM must take care not to create financial burdens that discourage or impede the rapid development of therapies for the public good. Direct revenue sharing would take years to benefit the state and run contrary to the terms of most federal funding, which specifies that excess revenues can only be used to support research and education. There are multiple examples of the negative effects that policies requiring direct revenue sharing at the federal level have had on the technology transfer process. We believe that a CIRM IP policy that benefits the state by revenue sharing would not be appropriate and could well have the unintended consequence of decreasing, rather than increasing, the long-term economic benefits to the state.

If after thorough review of the likely pros and cons, CIRM deems revenue sharing essential, we recommend that a percentage of net revenues above a reasonable threshold (e.g., $500,000) be redirected to CIRM for continued support of research or educational missions.

4. Generally, make CIRM-developed research tools widely available to other researchers.

In any licensing of CIRM-funded inventions, especially those that are useful in future research activities, it should be made clear that grantees should be expected not only to reserve their own right to use the invention for research and educational purposes, but to share their CIRM-funded research tools with as few encumbrances as possible, especially for use in other CIRM-funded research. This is an important part of fulfilling CIRM's objective of facilitating stem cell and regenerative medicine overall.

Grantees should ensure that third party agreements, e.g., for access to research materials, preserve their ability to broadly share research tools and data, and to publish freely as appropriate.

In their grant applications, applicants should be expected to provide a plan describing how IP will be managed to ensure that research tools will be made broadly available for the further advancement of science. This is consistent with the requirements of many NIH request for proposals (RFPs).

5. Require diligent efforts to develop CIRM-funded IP into therapeutics and diagnostics that can benefit the public.

Exclusive commercial licenses issued by the grantee for the commercialization of CIRM-funded research should include a provision requiring the recipient of the license to diligently

develop the licensed invention, or to use it in a manner that benefits the state. An example would be the establishment of milestones toward commercialization. Such a provision permits the grantee to terminate the license if the licensee is unwilling or unable to move an invention forward in an appropriate and timely manner. Since diligence terms are case-specific, it is important that CIRM not impose any specific parameters in this area.

If a grantee chooses not to move forward with commercial development or use of a CIRM-funded invention, it should be required to notify CIRM and provide CIRM the opportunity to do so, either through an exclusive license to the grantee's interest in the technology or by permitting CIRM to take title to the invention (but only to the extent that the grantee is legally able to transfer title – e.g., if federal funds are used to create the invention, the grantee is usually prohibited by law from transferring title).

Inventions made under CIRM funding should be promptly reported to CIRM by the grantee office responsible for such matters. As discussed above, where an industry investment is required to develop a product and take it through the regulatory process, companies usually require exclusive access in order to justify such an investment. This is usually achieved through use of the patent system. To preserve the ability to secure the patent protection necessary for exclusive access, CIRM must be able to receive invention reports in confidence. In addition to initial invention reports, in order to monitor the diligent development of CIRM-funded inventions, CIRM should require annual reports on invention utilization as well.

6. Retain within CIRM Bayh-Dole-like rights to step in if the owner of IP is not undertaking appropriate steps to transfer technology to benefit the public.

CIRM may want to consider retaining the right to step in if it is clear that effective steps are not being taken within a reasonable time to achieve practical application of a CIRM-funded invention. Such right could include CIRM's ability to require the grantee to grant a license to a responsible applicant on reasonable terms. However, great caution should be taken with implementing such a right. At the federal level, such "march-in" rights are similarly provided to the federal government, but with a process of checks and balances. Early on, industry was concerned about the uncertainty introduced by the federal "march-in" rights and showed a great deal of reluctance to invest in federally-funded inventions. While some still express concern over this issue, it has been largely mitigated by the fact that the federal government has not yet exercised this right.

7. Leave license particulars to the owner who is in the best position to judge how best to ensure that discoveries are made widely available through commercialization or otherwise.

As noted earlier, CIRM should avoid overly prescriptive policies for IP derived from CIRM-funded research. In general, grantees are in the position to know how their IP could be commercialized, and have the expertise to negotiate deals with the private sector with the goal of successful commercial development. Moreover, grantees are in a position to monitor licensees to ensure that they are being diligent in their efforts to develop useful products.

8. Reserve the right to use IP by or on behalf of CIRM.

CIRM should receive a non-exclusive, royalty-free license to all CIRM-funded inventions for use to practice and have practices for or on behalf of CIRM. The license should include the right to allow other CIRM grantees to use such inventions in their CIRM-funded research activities.

This is consistent with policy at federal agencies (e.g., NASA) and will help ensure that CIRM is able to effectively facilitate research and development of therapeutics and diagnostics.

9. Establish and maintain a CIRM database to track all IP generated through CIRM funding.

In order to effectively keep track of IP generated through CIRM-funded research, it will be essential to establish a database to track it and an office to collect and update the information. Such a database would be a useful source of information to other stem cell researchers, including CIRM-funded researchers, and to companies interested in commercial development of stem cell technology. Although it would represent an added responsibility, we believe that CIRM would be the logical repository for tracking IP generated through research that it funds. CIRM should require that all grantees report regularly about the IP generated with CIRM funds in a form that can be readily introduced into a database. This would enable CIRM to more accurately inform the state of all the benefits derived from CIRM–funded research. CIRM may wish to contract out this responsibility, but the office should remain under CIRM jurisdiction. The most likely alternative to a CIRM-administered office would be a state agency, which we believe would complicate matters unnecessarily.

In the time available to prepare this interim report, we were unable to fully explore several important areas. In light of the tremendous public expectations about benefits to California, we also recommend that CIRM, to the extent possible, fund further research in the following areas so as to inform fully policymakers in the following areas:

- optimizing returns to the state and recoupment strategies;
- ways to create incentives to develop therapies and treatments for orphan diseases;
- sharing of research tools and data to best meet the state's interests, for example, licensing policies for database access that enable data access and sharing;
- strategies to ensure that research publications are made widely available on an open access basis;
- ways to manage potential firewalls between NIH- and CIRM-funded stem cell research.

Finally, we recommend that a more detailed examination begin in the near future that engages the full range of non-IP technical expertise required to identify and deliberate over the key issues involved in reasonable or favorable pricing of treatments and therapies that emerge from CIRM-funded research.

Conclusions

With the creation of CIRM and the commitment to invest $3 billion in stem cell research, California is setting a precedent that is being closely watched by the nation and the world. The size and visibility of the public investment approved by voters through Proposition 71, and operationalized by CIRM, is creating high expectations for measurable impacts over the next decade. As it establishes policies for IP, CIRM will be defining a fundamental framework to be used by the research institutions and businesses that will translate creative ideas into tangible products. The careful management of the IP derived from CIRM-funded research will be critical in determining how well the intellectual outputs of this public investment are translated into useful products, therapies and treatments. We believe this interim report addresses the key issues that CIRM needs to consider as it undertakes this important task.

7. Appendices

The first four appendices are intended as resources to supplement the body of the report. They include sections prepared by Study and Working Group members to expand upon key points and relevant examples of IP policies and development.

Appendix A explains the different types of intellectual property in greater detail, explaining what each entails, how they apply to biotechnology research, and the different kinds of protection that they offer.

Appendix B provides greater detail on the Bayh-Dole Act, the federal IP policy used as a reference point throughout this report, and how the Bayh-Dole Act might apply to research institutions which may receive CIRM funding.

Appendix C is an example of how research led to the development of an effective therapy for childhood leukemia. It provides a valuable timeline for the process and illustrates the different stages of the research and development process along the way. This document is part of the "Beyond Discovery" educational series and is reproduced courtesy of the National Academy of Sciences.

Appendix D provides key excerpts from guidelines for disseminating research resources arising out of NIH-funded research. CIRM will be performing a function similar to the NIH in funding research, although on a much smaller scale. The NIH policy is an instructive example on how an institution such as CIRM might implement a set of policies on dissemination research resources.

Appendix A: Types of Intellectual Property

James Pooley and Katherine Nolan-Stevaux

Different forms of intellectual property are used to protect diverse discoveries. This appendix offers a brief primer on patent, trade secret, and copyright protection, focusing specifically on how each relates to biological, biotechnological, or pharmaceutical discoveries, and illustrates how some discoveries may be protected by combinations of different intellectual property regimes.

Patents provide exclusive protection for inventions for a limited time period. For twenty years from the application date, a patent holder may exclude others from making, using, or selling the patented material. Patents enable protection of human-made inventions that are novel, useful, and inventive compared to what is publicly available. Consequently, research tools in biology, chemistry, engineering, and computer science are often patented. To obtain a patent, an inventor must file an application with the United States Patent and Trademark Office, which will determine whether the invention meets the patentability requirements, and if so, will issue the patent. In return for full public disclosure of the invention in the body of a patent, the inventor obtains the right to exclude others from practicing the invention. Thus, during the life of a patent, no one else may make, use, sell, or offer for sale any product or method that is covered by that patent. Once the patent expires, anyone may use the invention without restriction. For example, after a patent on a pharmaceutical drug expires, generic drug companies may manufacture and sell generic versions of the drug.

Patents are commonly used to protect biological, biotechnological, or pharmaceutical research tools. Although genes as they exist in the human body may not be patented, upon isolation from an organism, they are appropriate patentable subject matter in many countries. Accordingly, substances purified or isolated from nature, such as human hormones like insulin, and substances created in the laboratory, such as the cholesterol lowering drugs called statins, are frequently patented. In addition, living materials, such as cultured cell lines or stem cells, may be patented once isolated from their natural environment. Even the research methods by which such cell lines are isolated may be protected through patenting. Although patenting an invention can be expensive, many view the exclusive rights to the invention as worth the cost.

In contrast to patents, **trade secrets** exist as long as the information remains secret. Any information or invention that provides actual or potential value to its holder qualifies for trade secret protection, provided that such information is not generally known or easily discoverable. In order for an invention to acquire trade secret status, the inventor must undertake reasonable efforts to keep the invention secret. For example, documents describing the trade secret should be marked confidential, kept in a secure location, and access to that location should be restricted. Individuals with access to the trade secret should sign confidentiality and non-disclosure agreements in order to preserve the trade secret. Anyone who uses improper means to obtain a trade secret will be liable to the owner. However, others may independently discover a trade secret without incurring liability, if they do not employ improper means. In such a scenario, as long as the invention remains secret, it remains a trade secret; however, once the invention becomes publicly available, trade secret protection ends. Thus, the scope of trade secret protection may be broad and potentially permanent, but unlike patents, trade secrets do not provide exclusive protection.

Trade secret law may protect biological or pharmaceutical research at select times in a research program. Prior to the publication of a patent application, trade secret protection enables an inventor to ensure that the invention is not disclosed publicly. However, once the application is published, trade secret protection ends and, if the patent issues, the invention will benefit from patent protection. If the invention is not patentable or the inventor elects not to seek patent protection, trade secret law may protect the invention indefinitely or until patentable research tools have been generated using the trade secret. For example, prior to publishing their own results, researchers may agree to share a mouse model of Alzheimer's disease with an academic laboratory subject to a material transfer agreement (MTA), requiring the receiving researchers' assurance that no for-profit research will be conducted using the mice and that none of the research will be shared with for-profit institutions. Researchers receiving materials under an MTA sign confidentiality and non-disclosure agreements designed to ensure that the invention remains a trade secret.

Unlike patent and trade secret protection, which focus on protecting ideas and information, **copyright** protects original expression recorded in a tangible medium. Copyright protection lasts longer than patent, extending 70 years beyond the life of an individual author, or, for institutional authors like companies, either 95 years from publication or 120 years from creation, whichever is shorter. Although most commonly associated with protection of literary, dramatic, or musical works, including scientific publications, copyright also protects aspects of computer software. Essential functional components of software may not be copyrighted, but creative elements, such as a novel search mechanism, are eligible. Unlike patents, which require government review and validation, copyright protection begins at the moment of creation (although copyrights can be registered with the federal government to ensure robust remedies for infringement). Similar to trade secret, copyright does not provide protection against independent development by others. However, copyright differs from both patent and trade secret by providing a fair use exception, which enables some copying of a "work" subject to the nature of the use, the type of work, the amount of the work used, and the effect of the copy on the market for the original work.

In terms of biological, biotechnological, or pharmaceutical inventions, copyright often protects tools used in bioinformatics, or the use of mathematical, statistical, and computing methods to solve biological problems. In the post-genomics era, bioinformatics includes analyses of gene products (e.g., comparison of gene expression profiles), descriptions of protein interactions in cells or organisms, and analyses and comparisons of sets of experiments, such as the effort to assemble gene expression profiles from different human tumors to identify new genes involved in cancer initiation and progression. Copyright may protect aspects of the software tools used for the analysis of these complex problems and the websites through which researchers access such information from databases.

Recent developments in biology illustrate how patent, trade secret, and copyright converge to protect particular aspects of new technologies. For example, gene expression profiling experiments require the use of multiple inventions protected by different intellectual property approaches. First, the products of active genes, or transcripts, are isolated from tissues or cell lines. Both the method of isolation as well as the cell line may be patented. Second, these transcripts are washed over a DNA gene chip, upon which portions of every gene in a given organism is affixed, with the transcripts binding specifically to their respective gene. Patents may protect the manufacturing method for the DNA chip and the isolated genes spotted on the chip. In addition, trade secret may protect the organization of the genes on the chip, the selection of specific portions of the genes fixed on the chip, and the types of internal controls employed. Third, a patented machine scans the chip, translating binding patterns

into raw data, and computer software transforms the raw data into a list of genes, in order of their level of activity. Different software may be employed to identify clusters of genes with similar activity patterns. Aspects of these computer programs may be protected through either patent or copyright. Fourth, a researcher may compare this dataset with a database of similar gene expression profiles, again employing software that may be in part both patented and copyrighted. In addition, the database may be proprietary, using trade secret protection to protect its contents. Thus, biological research today often employs multiple types of intellectual property to protect distinct parts of a research program.

Appendix B: The Bayh-Dole Act and CIRM

Wendy Streitz and Richmond Wolf

Background

Prior to the 1980 passage of The Patent and Trademark Law Amendments Act (P.L. 96-517 and P.L. 98-620), better known as the Bayh-Dole Act, there was no consistent federal policy concerning ownership of inventions made through the use of federal funds. Agreements on ownership of inventions were negotiated individually with each federal agency, resulting in inconsistencies and high transaction costs. By 1980, the government held title to approximately 28,000 patents, of which fewer than 5% were licensed to industry for the development of commercial products. Congress passed the Bayh-Dole Act with a primary objective of promoting public benefit from government-funded research, or in the Act's own words, to "use the patent system to promote the utilization of inventions arising from federally supported research or development." It was anticipated that, not only would the public benefit from the availability of goods and services that would otherwise be unavailable, but the U.S. economy would benefit as well. It was also anticipated that a uniform federal policy would substantially reduce the transaction costs of awarding research contracts and grants.

Elements of Bayh-Dole

The Bayh-Dole Act originally applied to non-profit organizations and small businesses; it was extended to include large businesses by a February 18, 1983 Presidential Memorandum. Under the Bayh-Dole Act, recipients of government contracts and grants may take title to inventions they make with the use of federal funds in return for a commitment to diligently pursue the timely development of those inventions into products and services that can benefit the public. To provide further incentive for diligence, grantees may retain any income received through their commercialization of a government-funded invention.

Some important elements of Bayh-Dole are:

- The Bayh-Dole Act applies to all federal grantees, including universities, small businesses, industry, research foundations, etc.
- Grantees may own inventions they make with the use of federal funding.
- Grantees must disclose such inventions to the federal funding agency and report annually on the utilization of each invention.
- Grantees must notify the federal government in a timely manner if they choose not to pursue rights in an invention so that the federal government may maintain the rights. In the event that the federal government declines its rights, the inventor(s) may petition the government to have the rights assigned to them.
- The federal government retains a nonexclusive, nontransferable, royalty-free license to practice the invention for use by or on behalf of the government.
- To ensure diligence, if the grantee does not pursue patent protection within certain time limits, the federal government can take title to the invention.

- To ensure diligence, if the grantee does not take reasonable steps to achieve practical application of the invention, the federal government can exercise a march-in right to enable another party to make use of the patent rights.
- The Act is silent on copyright issues.

In the case of a non-profit grantee, the following also apply:

- Title may not be transferred to a third party except under very limited circumstances.
- To ensure that federally funded inventions contribute to the economic development of the U.S., products that are sold in the U.S. must be substantially manufactured in the U.S.
- Reasonable efforts must be made to license to small businesses. This requirement fosters regional economic development, supports the formation of new companies, and strengthens existing small businesses.
- Net royalties received by the grantee must be shared with the inventor(s). This provides an incentive for researchers to actively participate in the technology transfer process and promotes further innovation.
- The balance of any net royalties must be used to support research and education activities.

Conflicts with Federal Funding

Although most research institutions receive research funding from a number of sources, the vast majority comes from the federal government (e.g., in a recent fiscal year at a major west coast research institution, less than one percent of all extramural research sponsors were federal government organizations, but the funding from these federal government organizations accounted for over 70% of total extramural research funding at the institution). Since Bayh-Dole applies if *any* amount of federal funds are used in the creation of an invention, there is a very good chance that an invention made at a university will fall under Bayh-Dole. This could happen through the existence of a co-inventor who receives federal funds, or from an unanticipated convergence of separately funded research projects in a lab.

If a research institution were to accept research funds with obligations that conflict with Bayh-Dole (e.g., with title going to the sponsor) and federal funds were to become involved in the creation of an invention, the institution would be in the untenable position of either violating federal law or breaching a legal agreement with the other sponsor. To prevent such a situation from occurring, research institutions generally do not accept funding that conflicts with the requirements of Bayh-Dole. In the rare case that a research institution does accept such funds, it must put processes in place to rigorously ensure that no federal funds become involved in the research. Not only is this administratively burdensome, it can entail limiting funding opportunities for an entire lab as well as limiting with whom a researcher may and may not collaborate.

The following are some of the areas of potential conflict with Bayh-Dole. If a research agreement were to contradict any of these elements, the research funding could very well be less attractive than funding from another source.

- Title to inventions – Non-profit organizations are generally prohibited from transferring title to inventions made under Bayh-Dole.

- Use of net royalties – Use of net royalties by non-profit organizations for any purpose other than research or education is prohibited under Bayh-Dole.
- Sharing royalties with inventors – Non-profit organizations are required to share net royalties from federally-funded inventions with their inventors.
- Government purposes licenses – The federal government retains a non-exclusive license to practice federally-funded inventions for use by or on behalf of the government; any licenses to other sponsors must be subject to the government's rights.
- Reversionary rights – If the grantee chooses not to pursue an invention or if it does not file patents within certain time limits, title to federally funded inventions can revert to the government. The government also has the right to take title if the grantee is not taking reasonable steps to achieve practical application of an invention. Any rights granted to other sponsors must be subject to the government's rights.

Federal Funds and Stem Cell Research

Currently, federal funds cannot be used in research involving human embryonic stem cells unless the cell lines are one of a few dozen that meet criteria established by presidential policy announced on August 9, 2001, as indicated in the National Institutes of Health (NIH) stem cell registry. But federal funds *can* be used with the stem cell lines on the NIH registry, as well as in research using non-embryonic stem cells (e.g. adult stem cell lines), and closely related research that doesn't actually make direct use of stem cells. It also seems more than likely that the current federal restrictions will relax sometime in the next few years.

It will be necessary for CIRM to fund innovation at the highest level, and to do that, funding is likely to be co-mingled with federal money. Such leveraging of federal funds is arguably in the best interests of CIRM and the advancement of the research. However, this has the potential to create a conflict in terms of tier, particularly in the case of reversionary rights, royalty sharing, and assignment of rights. To ensure that this does not happen, it will be necessary to create rules that link the rights held by the federal government with the rules for compliance under CIRM funding. To avoid any disparity between the two sources of money, institutions may refuse to take CIRM funding, and if the federal guidelines on embryonic stem cell research are relaxed, it could put CIRM at a tremendous disadvantage in terms of funding the highest quality research projects. Many other states are currently considering ways to incentivize their own stem cell research programs – if they are able to take advantage of federal funds, especially if current restrictions are relaxed, California will find itself at a disadvantage.

Resources

The Bayh-Dole Act: http://straylight.law.cornell.edu/uscode/html/uscode35/usc_sup_01_35_10_II_20_18.html

"The Bayh-Dole Act: A Guide to the Law and Implementing Regulations", COGR Brochure, October 1999: http://straylight.law.cornell.edu/uscode/html/uscode35/usc_sup_01_35_10_II_20_18.html

"University Technology Transfer: Questions and Answers", COGR Brochure, October 1999: http://www.cogr.edu/docs/BayhDoleQA.htm

Appendix C: Beyond Discovery: Curing Childhood Leukemia

THE PATH FROM RESEARCH TO HUMAN BENEFIT™

CURING CHILDHOOD LEUKEMIA

Cancer is an insidious disease. The culprit is not a foreign invader, but the altered descendants of our own cells, which reproduce uncontrollably. In this civil war, it is hard to distinguish friend from foe, to target the cancer cells without killing the healthy cells. Most of our current cancer therapies, including the cure for childhood leukemia described here, are based on the fact that cancer cells reproduce without some of the safeguards present in normal cells. If we can interfere with cell reproduction, the cancer cells will be hit disproportionately hard and often will not recover.

The scientists and physicians who devised the cure for childhood leukemia pioneered a rational approach to destroying cancer cells, using knowledge about the cell built up from a series of basic research discoveries earlier in this century. That research had shown that the machinery of the cell is based on a large set of chemical reactions that follow one after another like the steps in a production line. These reactions, known as the cell's metabolism, convert food to fat, muscle, and energy—with the starting materials for each step supplied by the previous step. Any one of the many production lines will grind to a halt if one of its steps is faulty. The scientists' approach was to take a chemical that they knew was essential for cell reproduction—a building block for making DNA—and modify it so that it jammed the cell's works when the cell mistook it for the usual chemical. Such deliberately defective materials are called antimetabolites. Many of them are now used as drugs to treat not only cancer, but also gout, bacterial infections, viral infections, and many other illnesses.

The fight against cancer has been more of a war of attrition than a series of spectacular, instantaneous victories, and the research into childhood leukemia over the last 40 years is no exception. But most of the children who are victims of this disease can now be cured, and the drugs that made this possible are the antimetabolite drugs that will be described here. The logic behind those drugs came from a wide array of research that defined the chemical workings of the cell—research done by scientists who could not know that their findings would eventually save the lives of up to thirty thousand children in the United States.

A Life Is Saved

Suddenly, it seemed, Debbie Brown became permanently tired. She was so tired that she had to crawl up the stairs, and with any slight contact, she bruised. It was 1954, and Debbie, age 9, had leukemia.

A year earlier, Debbie would have died within months. But it was 1954, and

As many as twelve different drugs, often used in complex combinations and joined with transfusions and radiation therapy, provide doctors with the arsenal needed to combat childhood leukemia, a disease now defeated in nearly 80 percent of cases. (Photo courtesy of the National Cancer Institute)

NATIONAL ACADEMY OF SCIENCES

Courtesy of the National Academy of Sciences

Debbie's doctor knew about Dr. Joseph Burchenal's work at Memorial Sloan-Kettering Hospital in New York. After a referral, Burchenal's team gave Debbie two experimental drugs, 6-mercaptopurine (6-MP) and methotrexate—and a chance for survival.

The scientists who developed those drugs, which are still used in leukemia chemotherapy, did not stumble upon them in nature or in the laboratory. Instead, they set out to design the drugs, which were among the first ones ever made to order.

Without the drugs, Debbie had a life expectancy of 3 months; with them, she became perhaps the first long-term survivor of childhood leukemia. Although a cure was never mentioned, her visits to Burchenal became less frequent. In 1969, she had her first child, and she now teaches at a school in New Jersey.

The story of childhood leukemia did not end in 1954. In that year, Debbie was a lucky exception. To reach the nearly 80% cure rate of childhood leukemia seen today, doctors have had to marshal up to 12 drugs, used in complex combinations, and add transfusions and radiation therapy. But the drugs that gave doctors hope that this fast-moving disease was even worth tackling were the ones that cured Debbie Brown—the "antimetabolites."

Defining the Target

The cell is the fundamental unit of life. A human being starts as a single cell—a tiny fertilized egg—which grows and divides to produce the more than 10 million million (10,000,000,000,000) cells of an adult. The drugs directed at Debbie's cancer cells were aimed at specific protein molecules in these abnormal cells. A prerequisite for designing the drugs was a detailed understanding of the contents and workings of cells. Scientists had been looking at cells since 1655, the year in which Robert Hooke described the characteristic box-like shapes that he saw in cork. But for a long time they were hard put to understand them. What were the cells doing, and how were they able to grow and divide?

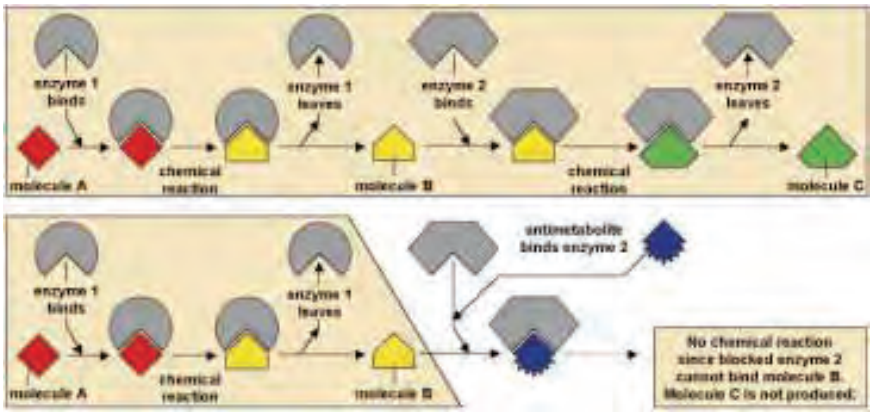
The age-old process of fermentation gave scientists a clue to one cellular activity: yeast cells could make alcohol. As the understanding of chemistry developed, it became clear that fermentation was a chemical reaction. Something was driving the chemical reaction, and the first step was to describe that entity. In 1878, W. Kühne defined an "enzyme" as something that directed chemical reactions—something that was inside, but separable from, the cell. Kühne's idea was rejected by Louis Pasteur, the originator of the germ theory of infectious disease. Pasteur maintained that fermentation was inseparable from living cells—that it was a special property of the organism as a whole and not of one of its parts. Pasteur's theory died in 1897, when E. Buchner ground up yeast cells so that they all burst. Buchner showed that fermentation still took place in the remaining extract of destroyed cells, just as Kühne would have predicted.

As scientists analyzed more and more reactions in cell extracts, it became clear that enzymes are the workhorses that drive all of the chemical reactions in the cell. But to see exactly what an enzyme was, scientists had to separate enzymes from the other components of the cell. In 1926, James Sumner of Cornell University successfully purified an enzyme called urease. He could finally prove that urease, the agent responsible for driving an important chemical reaction in cells, was a large protein molecule.

Locks and Keys

Once pure enzymes were in hand, the activities of these crucial proteins could be studied and manipulated in a predictable, controlled environment. Those studies helped to establish that enzymes are finicky. Like an assembly-line robot, a given enzyme can only pick up a particular part, and it always makes the same product. This idea had been proposed by Emil Fischer in 1894, before pure enzymes were available. Fischer assembled a set of chemicals that were similar to each other, but not identical. Enzymes in the cell were able to differentiate between these chemicals, and Fischer suggested that the starting chemical was like a key that fits perfectly into its lock (the enzyme)—an analogy that is still used today.

From this point to the anti-leukemia drugs, the remaining intellectual leap was the recognition that a defective key could jam the lock. The first defective key that was useful in medicine was a dye called Prontosil. The German fabric industry had long been using similar dyes, all containing a chemical group called the sulfonamide group, because these dyes did not bleed when applied to silk or wool. Prontosil's debut in biological research came in 1935, when Gerhard Domagk casually included it in a group of chemicals that he was testing for their ability to stop mouse cells from engulfing bacteria. Prontosil had no effect on this process, but he observed that it kept the



Schematic representation of a metabolic production line: To start this chain of chemical reactions, enzyme 1 binds molecule A and converts it to molecule B. Molecule B then binds to a different enzyme, enzyme 2, and is changed to molecule C. Molecule C will then bind to a third enzyme to continue the process of converting molecule A into a substance needed by the cell. If an antimetabolite binds tightly to enzyme 2, it will prevent the conversion of molecule B to molecule C and could thereby block cell growth.

mouse that had been inoculated with bacteria alive. Prontosil and similar sulfonamides soon became the first effective antibacterial agents, and this landmark in medicine resulted in the awarding of a Nobel Prize to Domagk in 1939. By 1943, nearly 10 million pounds of sulfonamides were being produced each year. They played a critical role in fighting infections during World War II, although other antibiotics, such as penicillin, were soon to overshadow them.

Blocking the Production Line

Sulfonamides worked, but no one knew how. D. D. Woods and Paul Fildes, of the Bland Sutton Institute of Pathology in London, suggested in 1940 that sulfonamides starved the cells by interfering with chemicals, termed essential metabolites, that were needed for cell growth. They defined essential metabolites as any of the chemical intermediates in the assembly lines for making complex biomolecules (such as proteins or DNA) from simple organic chemicals.

The idea that cells require specific chemicals was consistent with nutritional studies. For example, vitamins are chemicals that animals need (if only in tiny amounts) for survival. Vitamin research began with trial-and-error dietary cures for several medical disorders: limes for scurvy, cod liver oil for rickets, rice husks for beriberi, and liver for pernicious anemia. During the 1930s and 1940s, various workers isolated vitamins, the active components of such remedies.

Meanwhile, others worked on defining what the tiny single-cell organisms known as bacteria need to live and grow. This was no simple matter: most bacteria need a complex mixture of chemicals. But those who persisted found out that there is a hierarchy of bacterial needs and abilities. Some bacterial assembly lines can be thought of as starting by putting together a tire and a hubcap, and others as needing to be supplied with preformed wheels. Earlier results had been varied and confusing precisely because different bacteria pick up the construction process at different points in each multistep reaction pathway. Once the concept of these pathways was in place, it was clear that blocking one of them should stop the cell in its tracks, but that supplying a chemical beyond the blocked point would circumvent this block.

Woods guessed that sulfonamides were blocking a pathway by mimicking an essential metabolite. He tested a number of chemicals that looked like the sulfonamides and found that large amounts of one of them, p-aminobenzoic acid (PABA), could be used to bypass the sulfonamide block. We now know that the sulfonamides do, indeed, beat out PABA for access to a particular enzyme, thus preventing that enzyme from converting PABA to the next chemical in the pathway.

Early Chemotherapy

Before the 20th century, treatments for diseases had arisen somewhat haphazardly. Early doctors touted salves and balms of varied usefulness, but the active components were rarely known, and how they worked remained mysterious.

The originator of the modern culture of drug treatment was Paul Ehrlich, who, in the late 19th century, began the search for specific chemicals that could be used to target specific diseases. Ehrlich's drug treatment, or chemotherapy, was too toxic for humans, but the sulfonamides were far more successful, and the other antibiotics that followed and cured previously

fatal diseases cemented the idea of chemotherapy in the minds of physicians. But those drugs were all for infectious diseases. Cancer, the disease that comes from within, was another matter, and in the 1930s the only available treatments for it were surgery and radiation.

The first chemotherapeutic agent for cancer came from warfare. Mustard gas was first used in World War I as a weapon, but in 1942 Alfred Gilman and Fred Phillips administered it first to mice and then to a person with lymphoma. The patient showed some improvement, and chemical relatives of mustard gas were developed and used to treat various cancers.

For leukemia, mustard gas and radiation were of little use, and surgery was impossible because leukemia is a disease of the blood and bone marrow. The disease was first described in 1845 by Rudolf Virchow, a remarkable man involved in medicine, anthropology, public health, and politics. What Virchow saw when he looked at the blood of leukemia patients was a huge proliferation of white blood cells at the expense of both the red blood cells, which carry oxygen, and the platelets, which are needed for blood clotting. The leukemia patient often has intense bone pain as the white blood cells proliferate furiously in the bone marrow, but it is uncontrolled bleeding or infection that is usually the fatal event.

The most voracious of the leukemias, acute lymphocytic leukemia, occurs almost exclusively in children. Without treatment, the children seldom survive beyond 3 months after diagnosis. This rapid decline led many to see childhood leukemia as a lost cause, a problem not worth tackling. Luckily, a few scientists and doctors saw the severity of the disease as an advantage for testing their new treatments. With no other prospects, the children with leukemia had nothing to lose. This gave researchers an opportunity to see whether chemotherapy would work against cancer. Their jumping-off point was interference with the building blocks that make up DNA.

A Leap of Faith

We now know that DNA is the stuff from which genes and chromosomes are made. But the study of DNA had a rather messy start, when in 1868 Friedrich Miescher, working in Tübingen, Germany, isolated nuclei from the pus cells in discarded bandages. Miescher found that the nuclei, which we now know as the cell compartments that hold the DNA, contained an unusual phosphorus-containing chemical. Over the next 50 years, scientists isolated the bases and sugars that make up DNA and determined their structures (the arrangements of their atoms). There are four bases: the two purines called adenine (A) and guanine (G), and the two pyrimidines called cytosine (C) and thymine (T). Long strings of these bases are linked together by intervening sugar and phosphate molecules to make up DNA, and each of our chromosomes is formed from one enormously long DNA molecule.

In 1942, George Hitchings set out to design and synthesize antimetabolites based on the DNA bases.

Curing Childhood Leukemia—A Chronology of Selected Events

This timeline shows the chain of basic research that led to the discovery of a cure for childhood leukemia.

1845
Rudolf Virchow describes leukemia as a disease of the blood.

1878
W. Kühne names the agents from living cells that direct chemical reactions "enzymes."

1894
Emil Fischer proposes the lock-and-key hypothesis for enzyme action.

1908
Paul Ehrlich outlines his concept of chemotherapy: chemicals can be used to selectively interfere with the growth of infectious agents.

1926
James Sumner purifies the enzyme urease, and demonstrates that enzymes are proteins.

1935
Gerhard Domagk discovers the antibacterial action of the sulfonamide, Prontosil.

1940
D. D. Woods and Paul Fildes propose that sulfonamides work as antimetabolites.

1942
Alfred Gilman and Fred Phillips achieve a partial remission after administering mustard gas to a human with lymphoma.

1948
Sidney Farber reports temporary remissions in several cases of childhood leukemia after treatment with aminopterin.

1948
Gertrude Elion and George Hitchings make 2,6-diaminopurine, and Joseph Burchenal uses it to get two remissions in adults with leukemia.

Remarkably little was known about DNA. Hitchings did not know any details of the pathways that he was proposing to block (the production lines that make the DNA bases). Not until 2 years later was DNA shown to be the cell's information store; and the double-helix structure of DNA, which made it clear how the DNA could be "unzipped" to be read or copied, was not to be discovered until 1953, by James Watson and Francis Crick. (For additional information about this and other related discoveries, see "Human Gene Testing" posted on the Beyond Discovery website.) All Hitchings knew was that cells needed DNA to divide; therefore, if he could block the cells from making new DNA bases or cause the cells to include defective bases in their DNA, the cells should be unable to reproduce themselves.

The first thing that Hitchings needed was a way to test potential new drugs simply and cheaply. The solution, developed in his laboratory by Elvira Falco, was a test system using Lactobacillus casei (L. casei for short). This bacterium would grow on milk or in a synthetic medium as long as it was supplied with either a liver preparation called "L. casei factor," or both a purine (A or G) and thymine (T).

Gertrude Elion joined Hitchings' group in 1944, one of the few women finally gaining access to the male-dominated arena of chemistry. She started synthesizing an astonishing array of chemicals that were similar, but not identical, to the purines in DNA. By 1951, Elion had made and tested over 100 of these modified purines. Some of them slowed or stopped the growth of L. casei, and Elion could then test which production line they were jamming by adding an excess of thymine or one of the purines. In sufficient quantities, these "true" metabolites could overwhelm the effect of an antimetabolite on a given enzyme, or supply the final product of a pathway, thus making early blockages irrelevant.

Once Elion had identified chemicals that slowed down L. casei, she was ready to try them out on a human disease. Hitchings had begun the research program with the idea that rapidly dividing cells would have a more urgent need for DNA than sluggish cells and would therefore be hit harder by drugs that restricted the supply of the DNA building blocks. Now he had only to select his targets from among the types of cells that grow speedily: bacteria, protozoa, and cancer cells. Leukemia was one of the first targets, both because there were no existing therapeutic options for patients and because a mouse model of the disease was available for initial drug testing.

Although Hitchings and Elion began their antimetabolite program earlier, the first leukemia remission was achieved by another group of workers. Sidney Farber, of Boston's Children's Hospital, tested the effect of the vitamin folic acid on cancer and concluded that it made matters worse. His conclusion is now in doubt (and the rationale for testing folic acid has died with him), but it inspired chemists at Lederle Pharmaceuticals to make antimetabolites resembling this molecule that would block the action of folic acid. An early attempt, aminopterin, was rushed into clinical

1953
The US National Cancer Institute (NCI) is founded.

1953
The US Food and Drug Administration approves 6-mercaptopurine (6-MP), made by Elion and Hitchings two years earlier.

1957
At the NCI, Emil Frei and Emil Freireich start a double-blind clinical trial using 6-MP and methotrexate in combination.

1959
The NCI team tries continuing chemotherapy during remission.

1960
Roy Calne uses 6-MP for kidney transplants in dogs.

1963
Allopurinol used in leukemia trial reduces amount of uric acid; soon after allopurinol is used to treat gout.

1963
NCI trial of methotrexate in the spinal cord reduces recurrence of childhood leukemia.

1970
Five year survival for childhood leukemia increases to 50%.

1978
Burroughs Wellcome team makes acyclovir, an effective treatment for genital herpes, cold sores, shingles, and chicken pox.

1988
Gertrude Elion and George Hitchings awarded the Nobel Prize in Physiology or Medicine.

1994
In a study using four intensive treatment regimens, 95% of childhood leukemia patients were disease free after four years. Treatment of the general population is not yet this successful.

In the 1940s, George Hitchings (left) pioneered the design and synthesis of antimetabolites, the class of drugs that could be used to destroy cancer cells. Joseph Burchenal (right) of Memorial Sloan-Kettering Hospital in New York City administered these drugs to leukemia victims and succeeded in inducing cancer remissions in some cases. (Memorial Sloan-Kettering Cancer Center)

trials just a year after the structure of folic acid had been reported. In 1948, the Farber team reported that treatment with aminopterin had resulted in temporary remissions in several cases of childhood leukemia. The remissions were rare and brief, but an encouraging start. Another variant of folic acid, called methotrexate, was developed within a year, and this antimetabolite became a mainstay of leukemia chemotherapy.

Elion's first success came in 1948 with a chemical called 2,6-diaminopurine, which had two amine groups protruding from the normal purine structure. In tests with the L. casei bacterium, it blocked the conversion of adenine into a DNA building block. Elion and Hitchings sent 2,6-diaminopurine to Joseph Burchenal at the Memorial Sloan-Kettering Hospital in New York City for testing, initially in mice. Burchenal succeeded in getting two remissions in adults who had leukemia, but for most patients the drug was too toxic: the nausea and vomiting were intolerable.

To make the successful antimetabolite, 6-mercaptopurine or 6-MP, Elion replaced an oxygen atom on the purine ring with a sulfur atom. This chemical not only had antitumor activity in mice, but it produced remissions, without undue toxicity, in children who had acute leukemia. In the few days after news of the clinical success with 6-MP broke, Hitchings received over 600 phone calls. The excitement about 6-MP was so great that the US Food and Drug Administration approved its use late in 1953—only 10 months after clinical trials began, and 7 months before all the data supporting its effectiveness were made public.

Systematic Medical Research

The two drugs that would cure Debbie Brown in 1954 were now established. But for most patients and their doctors, this was only the beginning. With the combined use of methotrexate and 6-MP, the average survival time for childhood leukemia had been extended from just 3 months to a year. For much of the extra time, the children were in remission, showing no external signs of the disease. Early in these studies, the scientists, doctors, and patients hoped that the children were permanently cured. But almost inevitably the cancer came back. And when it came back it was usually resistant to the drugs that had been used the first time.

The great success of antibiotics had set the tone for medical treatment in this period. Everyone expected "a magic bullet," a single drug that could eliminate all signs of disease. Gradually, the researchers and doctors saw that no one drug would be enough for childhood leukemia. They would have to carry out more precise clinical trials to determine exactly which combination, dose, and frequency of drugs would be best.

The focus for the next stage was the US National Cancer Institute (NCI) in Bethesda, Maryland, which was founded in 1953. In an extraordinary confluence

Gertrude Elion received the Nobel Prize in Physiology or Medicine in 1988, together with George Hitchings, for their work on the design of drugs to cure childhood leukemia and other diseases. (Photo courtesy of Reportagebild, Stockholm, Sweden)

of talent and names, Emil Frei III and Emil J. Freireich joined the NCI in 1955 to lead leukemia-drug trials. The conciliatory Frei and the confrontational Freireich worked together with their chief, C. Gordon Zubrod, to modernize chemotherapy trials. Before their work, drug trials were often anecdotal and usually inconclusive. The first step for the NCI doctors was to define a "remission." Rather than trying to assess some vague measure of a patient's well-being, the doctors counted the number of leukemic cells in bone-marrow samples. They then initiated trials in which all patients were given the same treatment program. Other doctors believed that treatment should be customized for each patient, but with this approach the results of any study would always be confusing. Frei and Freireich also devised the concept of a double-blind study, in which neither patient nor doctor knows who is getting which treatment. This was essential to avoid any bias that might creep in if the doctor or patient hoped that a particular treatment would be better.

In one of the early trials, the NCI doctors showed that transfusing patients with fresh supplies of blood platelets could prevent serious bleeding. That kept the patients alive for long enough to reap the benefits of new drugs—drugs from varied sources, including plants. With the new drugs, obtaining remissions became almost routine. But still the cancer would return in most cases. What did the doctors need to do to wipe out the cancer once and for all? Frank Schabel and Howard Skipper, working at the Southern Research Institute, used mice to show that a single leukemic cell was all that was needed to start a fatal process. The task was thus defined: to wipe out every last leukemic cell. That led the doctors to try continuing chemotherapy past the time when all signs of the disease had disappeared. And mathematical modeling by Schabel and Skipper of the growth of the cells gave the doctors an estimate of how hard, how often, and for how long they would have to hit the cancer. Knowing that a number of their drugs had different, nonoverlapping side effects, the doctors took another critical step: they began to use new combinations of drugs, hitting the cancerous cells from several directions at once.

The final step in converting remissions to cures was the identification of the brain and spinal cord as an important hideout for the cancer cells. Because the central nervous system is separated from the blood, and thereby protected from bloodborne diseases and toxins, the anti-leukemia drugs were not getting into these areas. The doctors therefore began to inject drugs directly into the spinal-cord canal and to target radiation specifically to the head. The combination of these treatments and the newer drugs has increased the cure rate for childhood leukemia to nearly 80%. But the drugs of choice for maintaining remissions are still 6-MP and methotrexate.

New Horizons

Hitchings had envisioned the antimetabolites as a therapy for any number of diseases; leukemia was merely the first to be tested. The path to the first of two unexpected uses began with Robert Schwartz, of Tufts University. Inspired by the knowledge that the antimetabolites hit certain immune cells in the blood particularly hard, he found that 6-MP could stop the immune system of rabbits from responding to a foreign protein. Roy Calne, of the Royal Free Hospital in London, heard about Schwartz's finding and put the immunosuppresive effect of 6-MP to work. The drug reduced the immune system's rejection of transplanted kidneys in dogs and so lengthened the time that the dogs retained the kidneys. He then tested a pro-drug of 6-MP that Elion had made called Imuran ™ and found it even more effective (a pro-drug is a drug that is administered in one form and then releases the active component, in this case 6-MP, in the body). Imuran remains in use for human kidney transplants today.

Antimetabolites were next used to treat gout, a disease in which the body accumulates too much of a chemical called uric acid. Crystals of uric acid build up in the joints of patients and cause painful arthritis. The treatment for gout, a drug called allopurinol, was first used in a leukemia trial. Elion and Hitchings, in collaboration with Wayne Rundles and hematologists at Duke Medical Center in North Carolina, were using allopurinol to increase the potency of 6-MP by jamming the enzyme that destroys 6-MP in the body. The approach was partially successful, but the combination of 6-MP and allopurinol was not only more effective but also more toxic. The scientists knew that the target for allopurinol was the enzyme that made uric acid, so they looked at how much uric acid the patients in the trial were excreting in their urine. They found that the drug was working: allopurinol was blocking formation of uric acid. Further trials proved that it could reverse the accumulation of uric acid and thus relieve the symptoms of gout—a major medical triumph.

In 1968, Elion and others on the Burroughs Wellcome team decided to look at whether the

In 1989, childhood leukemia survivors staged a reunion at Memorial Sloan-Kettering Hospital in New York City to celebrate the individuals and institutions that played a role in their cure. Without their treatments, it is unlikely that any would have survived to adulthood. (Harry Heleotis, NYC)

antimetabolites they had synthesized could be used to slow down viruses. The last of a series of chemicals that they tried was a version of guanine in which the sugar ring attached to it in DNA was opened and shortened. This chemical, called acyclovir, is now an effective treatment for various herpes virus infections, including genital herpes, cold sores, shingles and chickenpox. Acyclovir is an extremely effective drug; only viruses have enzymes to convert it into a toxic form that then blocks the construction of viral DNA, so the drug is far less toxic to humans than are many other antimetabolites.

In 1988 the Royal Swedish Academy of Sciences awarded Elion and Hitchings the Nobel Prize in Physiology or Medicine for introducing to drug discovery "a more rational approach based on the understanding of basic biochemical and physiological processes." Their approach is now used widely; these days, researchers (who can now determine the exact structure of enzymes) have the help of computers to design defective keys for an enzyme lock. To find more powerful, less toxic drugs, researchers will need to find enzymes that, like the target of acyclovir, are specifically required by the viruses or cells that cause a particular disease. Every year, many potential targets for antimetabolites are being discovered by the basic research that is rapidly unraveling the chemistry of the cell, the same type of research that suggested that antimetabolites could be used to cure childhood leukemia.

No one knows what the next successful drug target will be, nor what type of human suffering it will relieve. But whatever the new cures, the credit for them will belong to more than those who make the final breakthrough. Much credit should also go to the worldwide team of biologists and chemists, each of whom may spend a lifetime teasing out the workings of one or two of the cell's thousands of activities. On the foundations of these discoveries will come great benefits to human welfare. And many scientists will be able to stand with great pleasure among survivors of deadly diseases.

This article was written by science writer William Wells, with the assistance of Gertrude Elion and John Laszlo, MD, for Beyond Discovery™ The Path from Research to Human Benefit, a project of the National Academy of Sciences.

The Academy, located in Washington, DC, is a society of distinguished scholars engaged in scientific and engineering research and dedicated to the use of science and technology for the public welfare. For over a century, it has provided independent, objective scientific advice to the nation. The project's web site is accessible at http://www2.nas.edu/bsi, from which the full text of all articles in the series can be obtained.

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Appendix D: Excerpts from Guidelines for Disseminating Research Resources Arising Out of NIH-Funded Research[36]

Definition of Research Tools

The definition of research tools is necessarily broad, and it is acknowledged that the same material can have different uses, being a research tool in some contexts and a product in others. In determining how an NIH-funded resource that falls within the definition should be handled, Recipients should determine whether: (1) The primary usefulness of the resource is as a tool for discovery rather than an FDA-approved product or integral component of such a product; (2) the resource is a broad, enabling invention that will be useful to many scientists (or multiple companies in developing multiple products), rather than a project or product-specific resource; and (3) the resource is readily usable or distributable as a tool rather than the situation where private sector involvement is necessary or the most expedient means for developing or distributing the resource. Recipients should ensure that their intellectual property strategy for resources fitting one or more of the above criteria enhances rather than restricts the ultimate availability of the resource. If Recipient believes private sector involvement is desirable to achieve this goal, Recipient should strategically license the invention under terms commensurate with the goal.

Use of Simple Letter Agreement

Recipients are expected to ensure that unique research resources arising from NIH-funded research are made available to the scientific research community. The majority of transfers to not-for-profit entities should be implemented under terms no more restrictive than the Uniform BioMaterial Transfer Agreement(UBMTA). In particular, Recipients are expected to use the Simple Letter Agreement provided below, or another document with no more restrictive terms, to readily transfer unpatented tools developed with NIH funds to other Recipients for use in NIH-funded projects. If the materials are patented or licensed to an exclusive provider, other arrangements may be used, but commercialization option rights, royalty reach-through, or product reach-through rights back to the provider are inappropriate.

Similarly, when for-profit entities are seeking access to NIH-funded tools for internal use purposes, Recipients should ensure that the tools are transferred with the fewest encumbrances possible. The Simple Letter Agreement may be expanded for use in transferring tools to for-profit entities, or simple internal use license agreements with execution or annual use fees may be appropriate.

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[36] Department of Health and Human Services, National Institutes of Health, "Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research, Resources: Final Notice, Federal Register Vol. 64, No. 246 (December 23, 1999) pp. 72090-72096, http://ott.od.nih.gov/pdfs/64FR72090.pdf.

Simple Letter Agreement for the Transfer of Materials

In response to RECIPIENT's request for the MATERIAL [insert description] _____the PROVIDER asks that the RECIPIENT and the RECIPIENT SCIENTIST agree to the following before the RECIPIENT receives the MATERIAL:

1. The above MATERIAL is the property of the PROVIDER and is made available as a service to the research community.

2. THIS MATERIAL IS NOT FOR USE IN HUMAN SUBJECTS.

3. The MATERIAL will be used for teaching or not-for-profit research purposes only.

4. The MATERIAL will not be further distributed to others without the PROVIDER's written consent. The RECIPIENT shall refer any request for the MATERIAL to the PROVIDER. To the extent supplies are available, the PROVIDER or the PROVIDER SCIENTIST agree to make the MATERIAL available, under a separate Simple Letter Agreement to other scientists for teaching or not-for-profit research purposes only.

5. The RECIPIENT agrees to acknowledge the source of the MATERIAL in any publications reporting use of it.

6. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Unless prohibited by law, Recipient assumes all liability for claims for damages against it by third parties which may arise from its use, storage or disposal of the Material except that, to the extent permitted by law, the Provider shall be liable to the Recipient when the damage is caused by the gross negligence or willful misconduct of the Provider.

7. The RECIPIENT agrees to use the MATERIAL in compliance with all applicable statutes and regulations.

8. The MATERIAL is provided at no cost, or with an optional transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs. If a fee is requested, the amount will be indicated here: _____

The PROVIDER, RECIPIENT and RECIPIENT SCIENTIST must sign both copies of this letter and return one signed copy to the PROVIDER. The PROVIDER will then send the MATERIAL.

Provider Information and Authorized Signature

Provider Scientist:_____

Provider Organization:_____

Address:_____

Name of Authorized Official:_____

Title of Authorized Official:_____

Certification of Authorized Official: This Simple Letter Agreement ___has ___has not [check one] been modified. If modified, the modification are attached.

_____

(Signature of Authorized Official) (Date)

Recipient Information and Authorized Signature

Recipient Scientist: _____

Recipient Organization: _____

Address: _____

Name of Authorized Official: _____

Title of Authorized Official: _____

Signature of Authorized Official_____

Date: _____

Certification of Recipient Scientist: I have read and understood the conditions outlined in this Agreement and I agree to abide by them in the receipt and use of the MATERIAL.

_____

(Recipient Scientist) (Date)

Ensuring Consistent Obligations

Recipients must ensure that obligations to other sources of funding of projects in which NIH funds are used are consistent with the Bayh-Dole Act and NIH funding requirements. Unique research resources generated under such projects are expected to be made available to the research community. Recipients are encouraged to share these Guidelines with potential co-sponsors. Any agreements covering projects in which NIH funds will be used along with other funds are expected to contain language to address the issue of dissemination of unique research resources. Examples of possible language follow. The paragraphs are presented in a "mix and match" format:

The project covered by this agreement is supported with funding from the National Institutes of Health. Provider agrees that upon publication, unpatented unique research resources arising out of this project may be freely distributed.

In the event an invention is primarily useful as a research tool, any option granted shall either be limited to a non-exclusive license or the terms of any resulting exclusive license shall include provisions that ensure that the research tool will be available to the academic research community on reasonable terms.

Provider agrees that Recipient shall have the right to make any materials and inventions developed by Recipient in the course of the collaboration (including materials and inventions developed jointly with Provider, but not including any Provider materials (or parts thereof) or Provider sole inventions available to other scientists at not-for-profit organizations for use in research, subject to Provider's independent intellectual property rights.

Subject to Recipient's obligations to the U.S. government, including 37 CFR Part 401, the NIH Grants Policy Statement, and the NIH Guidelines for Obtaining and Disseminating Biomedical Research Resources, Recipient grants to Sponsor the following rights:

Limiting Exclusive Licenses to Appropriate Field of Use

Exclusive licenses for research tools (where no further research and development is needed to realize the invention's usefulness as a tool) should generally be avoided except in cases where the licensee undertakes to make the research tool widely available to researchers through unrestricted sale, or the licensor retains rights to make the research tool widely available. When an exclusive license is necessary to promote investment in commercial applications of a subject invention that is also a research tool, the Recipient should ordinarily limit the exclusive license to the commercial field of use, retaining rights regarding use and distribution as a research tool. Examples of possible language include:

Research License means a nontransferable, nonexclusive license to make and to use the Licensed Products or Licensed Processes as defined by the Licensed Patent Rights for purposes of research and not for purposes of commercial manufacture, distribution, or provision of services, or in lieu of purchase, or for developing a directly related secondary product that can be sold. Licensor reserves the right to grant such nonexclusive Research Licenses directly or to require Licenses on reasonable terms. The purpose of this Research License is to encourage basic research, whether conducted at an academic or corporate facility. In order to safeguard the Licensed Patent Rights, however, Licensor shall consult with Licensee before granting to commercial entities a Research License or providing to them research samples of the materials.

Licensor reserves the right to provide the Biological Materials and to grant licenses under Patent Rights to not-for-profit and governmental institutions for their internal research and scholarly use.

Notwithstanding anything to the contrary in this agreement, Licensor shall retain a paid-up, nonexclusive, irrevocable license to practice, and to sublicense other not-for-profit research organizations to practice, the Patent Rights for internal research use.

The grant of rights provided herein is subject to the rights of the United States government pursuant to the Bayh-Dole Act and is limited by the right of the Licensor to use Patent Rights for its own research and educational purposes and to freely distribute Materials to not-for-profit entities for internal research purposes.

Licensor reserves the right to supply any or all of the Biological materials to academic research scientists, subject to limitation of use by such scientists for research purposes and restriction from further distribution.

Licensor reserves the right to practice under the Patent Rights and to use and distribute to third parties the Tangible Property for Licensor's own internal research purposes.

Appendix E: Legislative Requests Assembly Concurrent Resolutions 252 (Chaptered) and 24 (Pending)

BILL NUMBER: ACR 252 CHAPTERED[37], RESOLUTION CHAPTER 190
FILED WITH SECRETARY OF STATE SEPTEMBER 14, 2004
ADOPTED IN SENATE AUGUST 26, 2004, ADOPTED IN ASSEMBLY AUGUST 18, 2004
INTRODUCED BY Assembly Member Mullin, JULY 8, 2004
Assembly Concurrent Resolution No. 252--Relative to the California Council on Science and Technology.
LEGISLATIVE COUNSEL'S DIGEST
ACR 252, Mullin. California Council on Science and Technology.

This measure would request the California Council on Science and Technology to create a study group, as specified, on how the State of California should treat intellectual property created under state contracts.

WHEREAS, California is home to many of the world's top research universities, national laboratories, and leading-edge high technology companies that generate significant intellectual property; and

WHEREAS, It is in the interest of the state to ensure that the results of state-funded research are promptly protected and developed; and it is in the interest of the state to facilitate, promote, and enhance technology transfer programs that will facilitate the transfer of technology into the marketplace for the public benefit; and

WHEREAS, The State of California supports the establishment of government-university-industry partnerships to develop leading-edge research results that would encourage economic development through growth of small business, development of emerging industries, and creation of jobs within the state; and

WHEREAS, The Bureau of State Audits Report, "State-Owned" Intellectual Property, November 2000, stated that policies and guidelines should be established to assist state agencies in determining how best to administer state-owned intellectual property so that it can be utilized in the best interests of the public; and

WHEREAS, The Legislature supports the use of efficient models to develop and streamline infrastructures, policies, and processes for the management of intellectual property developed under state funding in order to stimulate economic development in the state similar to the approach used by the federal government; and

WHEREAS, A comprehensive intellectual property policy can foster major technological developments; and

WHEREAS, In this time of fiscal crisis, it is necessary for the state to create public-private partnerships; and

WHEREAS, The California Council on Science and Technology has a proven record of accomplishment in providing timely, impartial analyses of complex issues for the legislative and executive branches of government, including energy research in the Public Interest Energy Research Program, Critical Path Analysis of California's Science and Technology Education System and Nanoscience and Nanotechnology: Opportunities and Challenges in California; now, therefore, be it

Resolved by the Assembly of the State of California, the Senate thereof concurring, That the Legislature requests the California Council on Science and Technology to create a special study group to develop recommendations to the Governor and the Legislature on how the state should treat intellectual property created under state contracts, grants, and agreements, including, but not limited to, the following:

(1) Promoting the utilization of intellectual property arising from state-supported contracts, grants, and agreements.

(2) Encouraging maximum participation of small business firms in those state-supported awards.

(3) Promoting collaboration between commercial concerns and nonprofit organizations, including universities.

(4) Ensuring that the intellectual property created by nonprofit organizations and small business firms is used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery.

(5) Promoting the commercialization and public availability of that intellectual property made in the state by California and United States industry and labor.

(6) Ensuring that there are mechanisms in place that allow the state to obtain certain minimal rights in state-supported intellectual property to meet the needs of the state and protect the public against nonuse or unreasonable use of that intellectual property.

(7) Minimizing the costs of administering policies in this area; and be it further

Resolved, That the Legislature requests the California Council on Science and Technology, upon creation of the study group, to work with its sustaining institutions, state agencies, including the office of the Attorney General, and other organizations, to complete this study. Members of the study group are to include, but are not limited to, the following:

(1) The Department of General Services.

(2) Experts in contract and licensing with the state and federal governments.

(3) Research and development practitioners.

(4) Experts in technology transfer.

(5) Individuals representing the public interest; and be it further

Resolved, That the Chief Clerk of the Assembly transmit copies of this resolution to the Attorney General and the Department of General Services.

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[37] http://www.leginfo.ca.gov/pub/03-04/bill/asm/ab_0251_0300/acr_252_bill_20040914_chaptered.html, accessed 6/3/05.

BILL NUMBER: ACR 24 AMENDED BILL TEXT[38] (PENDING)
AMENDED IN ASSEMBLY APRIL 21, 2005
INTRODUCED BY Assembly Member Mullin
FEBRUARY 22, 2005
Assembly Concurrent Resolution No. 24 – Relative to the California Council on Science and Technology.
LEGISLATIVE COUNSEL'S DIGEST
ACR 24, as amended, Mullin. California Council on Science and Technology.

This measure would request the California Council on Science and Technology to expand its study group on how the State of California should treat intellectual property created under state contracts to include contracts, grants, and agreements developed under Proposition 71 of the November 2, 2004, general election *and to study how the commercialization of technology developed with the investment of taxpayer dollars could generate a public financial benefit.*

Fiscal committee: yes.

WHEREAS, California is home to many of the world's top research universities, national laboratories, and leading-edge high technology companies that generate significant intellectual property; and

WHEREAS, It is in the interest of the state to ensure that the results of state-funded research are promptly protected and developed; and

WHEREAS, The commercialization of technology developed with the investment of taxpayer dollars in the form of contracts, grants, and agreements could generate some public benefit, including, but not limited to, state revenues, favorable pricing, revenue sharing, and reinvestment into research; and

WHEREAS, It is in the interest of the state to facilitate, promote, and enhance technology transfer programs that will facilitate the transfer of technology into the marketplace for the public benefit; and

WHEREAS, The Legislature supports the use of efficient models to develop and streamline infrastructures, policies, and processes for the management of intellectual property developed under state funding in order to stimulate economic development in the state similar to the approach used by the federal government; and

WHEREAS, The voters approved the passage of Proposition 71, California Stem Cell Research and Cures Act, which establishes the California Institute for Regenerative Medicine to regulate stem cell research and provide funding, through grants and loans, for this research and research facilities; and

WHEREAS, The passage of Proposition 71 heralds a new era for the future of medicine and the way diseases are treated; and

WHEREAS, The development of innovative technologies is fundamental to the California economy; however, lack of understanding about the research enterprise and technology transfer, as well as lack of clarity concerning the role of the state government, if any, in developing intellectual property into marketable products make it difficult for the state to design an effective intellectual property policy; and

WHEREAS, The Legislature approved Assembly Concurrent Resolution No. 252 of the 2003-04 Regular Session, which requests the California Council on Science and Technology to establish a study group to develop recommendations to the Governor and the Legislature on how the state should treat intellectual property made under state contracts, grants, and agreements; and

WHEREAS, The scope of the study does not include the contracts, grants, and agreements developed under Proposition 71; now, therefore, be it

RESOLVED by the Assembly of the State of California, the Senate thereof concurring, that the Legislature requests the California Council on Science and Technology to expand the scope of the study group on how the state should treat intellectual property created under state contracts, grants, and agreements, to include contracts, grants, and agreements developed under Proposition 71; and be it further

RESOLVED, That the Legislature requests the study group to study how the commercialization of technology developed with the investment of taxpayer dollars in the form of contracts, grants, and agreements could generate some public benefit, including, but not limited to, state revenues, favorable pricing, revenue sharing, and reinvestment into research; and be it further

RESOLVED, That the Legislature requests the California Council on Science and Technology to expand the membership of the study group to include representatives from the Independent Citizen's Oversight Committee created pursuant to Proposition 71; and be it further

RESOLVED, That the Chief Clerk of the Assembly transmit copies of this resolution to the Attorney General, the Department of General Services, and to the author for appropriate distribution

[38] http://info.sen.ca.gov/pub/bill/asm/ab_0001-0050/acr_24_bill_20050421_amended_asm.html.

Appendix F: Intellectual Property Study Group

CO-CHAIRS

ALAN B. BENNETT
Associate Vice Chancellor for Research, University of California, Davis
Executive Director, Public Intellectual Property Resource for Agriculture

Alan Bennett currently serves as the associate vice chancellor for research at the University of California, Davis where he is responsible for technology transfer, strengthening research-based alliances with industry and supporting technology-based economic development in the Sacramento/Davis region. He also serves as the founding executive director of the Rockefeller Foundation-supported Public Intellectual Property Resource for Agriculture (PIPRA); an organization comprised of 25 universities dedicated to the collective management of intellectual property to support broad commercial innovation as well as humanitarian uses of technology in agriculture. From 2000-2004, Bennett served as the executive director of the University of California Systemwide Office of Technology Transfer and Research Administration. He earned B.S. and Ph.D. degrees in plant biology at UC Davis and Cornell University, respectively; and joined the UC Davis faculty in 1983.

STEPHEN D. ROCKWOOD
Executive Vice President
Science Applications International Corporation (SAIC)

Stephen D. Rockwood is executive vice president and member of the Board of Directors, Science Applications International Corporation, San Diego, 1986-present. Rockwood is former associate director for Defense Research Programs, Los Alamos National Laboratory.

Rockwood received a M.S. and Ph.D. in physics from the California Institute of Technology. His awards and honors include the Air Force Scientific Achievement Award, 1971 and the Los Alamos National Laboratory Distinguished Performance Award, 1979. He is a member of Phi Beta Kappa, the American Physical Society, the New York Academy of Science, and the American Association for the Advancement of Science.

MEMBERS

SUSAN V. BRYANT
Professor of Developmental and Cell Biology
Dean, School of Biological Sciences
University of California, Irvine

Susan Bryant obtained her undergraduate degree at King's College and her Ph.D. at St. Mary's Hospital Medical School, University of London. She moved to the U.S. to study regeneration as a postdoctoral fellow at Case Western Reserve University, and was recruited as the first woman on the faculty in Biology at the University of California, Irvine.

Dr. Bryant has served on several national committees, including advisory boards for the VA Office of Regeneration Programs, and for the Indiana University Axolotl Colony. She also serves on the editorial boards of several journals in her field. In 2001, she was elected a fellow of the American Association for the Advancement of Science. Along the way, she has held several leadership positions, including program director at the National Science Foundation, assistant vice chancellor for Plans and Programs and department chair at UCI, culminating in being appointed dean of the School of Biological Sciences in 2000. In 1987, she was awarded one of the first UCI Pacesetter Awards for contributions to women at UCI, and in 2005, she was elected a fellow, the highest honor bestowed by the Association for Women in Science.

RONALD W. COCHRAN
Laboratory Executive Officer
Lawrence Livermore National Laboratory (LLNL)

As laboratory executive officer, Ronald Cochran assists the laboratory director and associate directors in representation of LLNL, internally and externally. Responsibilities for this position also include oversight of the Congressional Affairs operational area. Prior to his current position, Cochran served as deputy associate director for Laser Programs and deputy associate director for the Advanced Processing Technology Program. He held a position in the Department of Energy, Office of the Secretary as director of the New Production Reactor Program, and as special assistant to the deputy secretary. He also served as deputy manager in the Department of Energy's Albuquerque Operations Office, providing administrative oversight of two national laboratories.

Cochran earned a B.S. in metallurgical engineering from the University of Tennessee and an M.S. in metallurgical engineering from Ohio State University. Professional organization memberships include the American Society for Metals, the American Association for the Advancement of Science, and the American Nuclear Society.

LAWRENCE B. COLEMAN
Vice Provost for Research
University of California

Lawrence B. Coleman is the vice provost for research, University of California and professor of physics at the University of California, Davis. He served as chair of the University-wide Academic Senate in the 1999-2000 academic year following a year as vice chair of the UC Senate. Arriving at Davis in 1976, he was promoted to associate professor in 1982. While at the UC Davis, he has held the positions of chair, Davis Division of the Academic Senate; director, The Internship and Career Center; acting vice provost–of Academic Programs and dean–of Undergraduate Studies; and acting associate vice chancellor–of Academic Programs.

Coleman's previous affiliations include: postdoctoral research investigator, Department of Physics, University of Pennsylvania, 1975-1976, and research fellow, Department of Physics, University of Pennsylvania, 1970-1975. Coleman received a Ph.D. from the University of Pennsylvania in experimental condensed matter physics, and a B.A. in physics from The Johns Hopkins University.

CYNTHIA CURRY
Senior Staff Counsel, California Department of General Services
Office of Legal Services

Curry is a senior staff counsel with the State of California, Department of General Services, Office of Legal Services. She has been with the state for 10 years, and her main area of practice is contract law, with an emphasis in information technology.

MICHAEL D. GOLDBERG
General Partner
MDV-Mohr, Davidow Ventures

As a general partner at MDV, Goldberg leverages valuable entrepreneur and investor experience from his more than 20 years of work in the life sciences industry including biotechnology, pharmaceuticals, health services and healthcare information technology.

Prior to joining MDV, Goldberg was managing director of Jasper Capital and co-chair of the California Research and Cures Coalition. He has also held senior management and operations roles including serving as chairman of OnCare, an oncology practice management company he founded in 1995. Until 1999, he also served as OnCare's chief executive officer. Previously, Goldberg was founder and chief executive officer of Axion Inc., a cancer-focused healthcare service company he started in 1987 and sold to Bristol-Myers Squibb in 1996. Goldberg received a B.A. from Brandeis University and an M.B.A. from Stanford Graduate School of Business.

GINGER L. GRAHAM
President and Chief Executive Officer
Amylin Pharmaceuticals, Inc.

Ginger L. Graham is president and chief executive officer of Amylin Pharmaceuticals, Inc. Ginger is the former group chairman, Office of the President, for Guidant Corporation located in Indianapolis, Indiana. From 1993 to 2000, Ms. Graham was president and CEO of Advanced Cardiovascular Systems, and with the creation of Guidant in 1994, she became president of the Vascular Intervention business group. Ms. Graham started her career with Eli Lilly and Company and served in a number of management positions. Her diverse career path gave her the opportunity to work in a variety of industries including agriculture, cosmetics, pharmaceuticals, investment banking and medical technology.

Ginger received a Bachelor of Science degree in agricultural economics from the University of Arkansas. She also holds a Master of Business Administration degree from Harvard University.

WAYNE C. JOHNSON
Vice President, Worldwide University Relations
Hewlett-Packard

Wayne C. Johnson is the vice president for Hewlett-Packard Company's worldwide University Relations. He is responsible for higher education programs in research, marketing and sales, recruitment, continuing education, public affairs and philanthropy.

Johnson joined HP in July 2001 from Microsoft's University Relations Department. From 1967 to 2000, he held a variety of positions at the Raytheon Company in Lexington, Massachusetts, including national sales manager for Wireless Solutions, manager of International Financing and Business Development in Wide Area Surveillance Programs, manager of Administration and Strategic Planning, and manager of Program Development and Operations for Technical Services. He was an adjunct professor of Management at Boston University from 1977 to 1999.

Johnson received his B.A. from Colgate University, Hamilton, New York, and his M.B.A. from Boston College's Carroll School, Boston, Massachusetts.

KATHARINE KU
Director, Office of Technology Licensing
Stanford University

Katharine Ku is director of the Office of Technology Licensing (OTL) at Stanford University. OTL is responsible for the licensing of various state-of-the-art university technologies such as biotechnology and semiconductor inventions, software, medical instrumentation, etc. From 1994-98, Ku was also responsible for Stanford's Sponsored Projects Office, which handles research contracts and grants for the University. Prior to 1991, Ku was vice president, Business Development at Protein Design Labs (PDL), Inc. Prior to PDL, Ku spent 12 years at Stanford in various positions, was a researcher at Monsanto and Sigma Chemical, administered a dialysis clinical trial at the University of California, and taught chemistry and basic engineering courses.

Ku has been active in the Licensing Executive Society (LES), serving as vice president of the Western Region, trustee, and various committee chairs. She recently received the Association of University Technology Managers Bayh-Dole Award for her efforts in university licensing. Ku has a B.S. in chemical engineering from Cornell University, an M.S. in chemical engineering from Washington University and is a registered patent agent.

MEYYA MEYYAPPAN
Director, Center for Nanotechnology
NASA Ames Research Center

Meyya Meyyappan is director of the Center for Nanotechnology as well as senior scientist at NASA Ames Research Center. He is a founding member of the Interagency Working Group on Nanotechnology (IWGN) established by the Office of Science and Technology Policy. The IWGN is responsible for putting together the National Nanotechnology Initiative.

Dr. Meyyappan is a fellow of the Institute of Electrical and Electronics Engineers (IEEE) and the Electrochemical Society. In addition, he is a member of American Society of Mechanical Engineers, Materials Research Society, American Vacuum Society and American Institute of Chemical Engineers. For his work and leadership in nanotechnology, he has been awarded NASA's Outstanding Leadership Medal and Arthur Flemming Award by the Arthur Flemming Foundation and George Washington University. For his contributions to nanotechnology education and training, he has been awarded the 2003-2004 Engineer of the Year award by the San Francisco section of the American Institute of Aeronautics and Astronautics (AIAA). In 2004, he was honored with the President's Meritorious Award for his contributions to nanotechnology.

ROGER G. NOLL
Morris M. Doyle Centennial Professor in Public Policy, Department of Economics
Professor of Political Science (by courtesy), School of Humanities and Sciences
Stanford University

Roger G. Noll is the Morris M. Doyle Centennial Professor of Public Policy in the Department of Economics at Stanford University. He also has a long affiliation with the Brookings Institution in Washington, D.C., where he has been a senior fellow, a visiting fellow, and a non-resident senior fellow. He served as a member of the California Council on Science and Technology from 1995-2000, and is now a fellow.

Noll holds a Ph.D. in economics from Harvard University and his distinguished career includes service as director of the Public Policy Program at Stanford and visiting positions at the University of Michigan and the University of California, San Diego. Noll has won a Guggenheim Fellowship, the Book Award of the National Association of Educational Broadcasters, and the Distinguished Service Award of the Public Utilities Research Center. He received the 1994 Rhodes Prize for Undergraduate Teaching from Stanford University.

JAMES POOLEY
Partner
Milbank, Tweed, Hadley & McCloy LLP

James Pooley is a partner in Milbank's Intellectual Property Group, specializing in the litigation and trial of patent, trade secret, copyright, and technology-related commercial litigation, in state and federal courts, and before the International Trade Commission. Mr. Pooley has practiced in Silicon Valley since 1973, establishing a national reputation as trial counsel in some of the most difficult and high visibility cases involving intellectual property. His successful patent infringement defense of Adobe Systems was recognized by the National Law Journal as the only IP case among its Top Defense Verdicts of 1997, and a record settlement for ESS Technology in a software copyright case led to his being honored as a 2003 Lawyer of the Year by *California Lawyer Magazine*.

He is a director and officer of the National Inventors Hall of Fame and of the American Intellectual Property Law Association, where he will become president in 2007. Mr. Pooley graduated from Columbia School of Law as a Harlan Fiske Stone Scholar in 1973, and holds a Bachelor of Arts, with honors, from Lafayette College.

PAMELA SAMUELSON
Professor, School of Information Management and Systems
University of California, Berkeley

Pamela Samuelson is a professor at the University of California at Berkeley with a joint appointment in the School of Information Management and Systems and the School of Law. She is also co-director of the Berkeley Center for Law and Technology. Her principal area of expertise is intellectual property law. She has written and spoken extensively about the challenges that new information technologies are posing for public policy and traditional legal regimes and is an advisor for the Samuelson Law, Technology and Public Policy Clinic. Since 2002, she has also been an honorary professor at the University of Amsterdam. Professor Samuelson holds a B.A. and M.A. from the University of Hawaii and a J.D. from Yale University.

From 1997 through 2002, Samuelson was a fellow of the John D. & Catherine T. MacArthur Foundation. She is also a fellow of the Association of Computing Machinery. In 2001, she was appointed to a UC Berkeley Chancellor's Professorship for distinguished research, teaching and service for her contributions to both Boalt Hall and the School of Information Management and Systems.

ROBERT SPINRAD
Retired Vice President, Technology Strategy
Xerox Corporation

Bob Spinrad built his first computer in 1953 out of discarded telephone switching equipment. Playing with his creation sparked a life-long fascination with information technology and its effects on our lives. Spinrad worked as a senior scientist at Brookhaven National Laboratory before joining Xerox in 1968, where, over the years, he held various engineering, programming and research management positions. He last served as vice president, Technology Strategy.

In addition to other work for these organizations, Spinrad has also served in various advisory roles at Harvard, Stanford, the Massachusetts Institute of Technology, the University of California, the Jet Propulsion Lab, EDUCOM, the Council on Foreign Relations, the National Science Foundation, the National Academy of Sciences, the National Academy of Engineering, the National Research Council, the Council on Library and Information Resources, Lawrence Livermore National Laboratory, the Defense Department's Advanced Research Projects Agency, Bell Labs, the International Institute for Applied Systems Analysis, Digital Pathways, Inc., The Information Society and the McGraw-Hill Encyclopedia of Science & Technology.

Spinrad holds a Ph.D. from the Massachusetts Institute of Technology and M.S. and B.S. degrees from Columbia. He is also a licensed Professional Engineer (New York).

RICHMOND WOLF
Director, Office of Technology Transfer
California Institute of Technology

Richmond Wolf is the director of the Office of Technology Transfer at the California Institute of Technology (Caltech), a non-profit university that also manages the Jet Propulsion Laboratory (JPL) for NASA. He is responsible for the management of the intellectual property portfolio developed at Caltech and JPL, which includes over 2000 issued and pending patents. Dr. Wolf has experience working with start-up companies from Caltech and JPL in areas of business and product development, and he was a co-founder of two companies, WebEventBroadcasting and Xen Golf. Dr. Wolf is a member of the board of directors of Alexandria Real Estate Equities (NYSE:ARE). He is or has been an observer to the board of directors of Agorare Global, Oraxion, Insert Therapeutics, Aonex, Nanotechnica, Wavestream, and Vasgene, and he is or has been a member of the advisory board of ITU Ventures, Oak Grove Systems, the Los Angeles Regional Technology Alliance, and the Egg Factory. Dr. Wolf is a graduate of Princeton University *cum laude*, received a Ph.D. from Caltech, and he is also a registered patent agent.

JULIE MEIER WRIGHT
President and CEO
San Diego Regional Economic Development Corporation

Julie Meier Wright has served as president and chief executive officer of the San Diego Regional Economic Development Corporation (EDC) since August 1997. EDC is the premier business development organization for the greater San Diego region.

Prior to coming to San Diego, Ms. Wright served as California's first Secretary of Trade and Commerce and a member of Governor Pete Wilson's Cabinet from 1991 to 1997. In 2003, she served on gubernatorial candidate Arnold Schwarzenegger's Economic Recovery Council. She currently serves as a senior advisor to the California Budget Education and Action for Reform project and a member of the California Council for Regional Leadership. Prior to her time in public service, she spent 25 years in executive marketing and public affairs positions in the private sector, including 14 years with TRW Inc., now a part of Northrop-Grumman.

Ms. Wright holds a Bachelor of Arts degree in Criminology from the University of Maryland. She has completed the Stanford University Advanced Management College, the Stanford Financial Seminar, and a special program on competitiveness at Harvard University.

Appendix G: Intellectual Property Working Group

ELLEN R. AURITI
Executive Director, Academic Legislative Affairs and Research Policy
Office of Research
University of California Office of the President

Ellen R. Auriti is the executive director of Research Policy and Legislation in the Office of Research at the University of California. The Research Policy Unit of the Office of Research provides coordination and guidance on systemwide research policy issues, working with the University's campuses and with other units within UCOP on developing and revising systemwide research policies and guidelines, developing University positions on public policies and proposals affecting research, and coordinating with campuses regarding significant legislative and regulatory changes affecting research.

Ellen received a B.A. from Yale University, and a J.D. from UC Berkeley's Boalt Hall School of Law. Prior to joining the University of California, Ellen was an attorney with Morrison & Foerster in San Francisco.

HALL P. DAILY
Assistant Vice President, Government & Community Relations
California Institute of Technology

Hall P. Daily is the assistant vice president of Government & Community Relations at the California Institute of Technology in Pasadena, California. He came to Caltech in 1987 as assistant director of Public Relations after a 15-year career in journalism. Prior to his association with Caltech, Daily was an editor and reporter for The Associated Press, the San Jose Mercury News and the Pasadena Star-News.

Daily represents Caltech on the Association of Independent California Colleges and Universities and serves as treasurer of its executive committee. In addition, he represents the state's private universities and colleges on the statewide GEAR UP implementation task force. Daily currently serves as board vice president of El Centro de Accion Sociale in Pasadena, and board member of the Pasadena Police Activities League. In addition, he serves on the convening committee of Pasadena: City of Learning.

WILLIAM J. MCLEAN
Former Director, Combustion Research Facility
Sandia National Laboratories

William J. McLean is former director of the Combustion Research Facility (CRF) at Sandia National Laboratories in Livermore, California. The CRF is a U.S. Department of Energy, Office of Basic Energy Sciences User Facility dedicated to advancing the science and technology of combustion and related energy systems. He is also responsible, under Sandia's Energy and Critical Infrastructure Strategic Business Unit, for overall program management of Sandia's Energy Efficiency research programs. He maintains close association with the U.S. Department of Energy (DOE) research programs sponsored by the Office of Science and the Office of Energy Efficiency and Renewable Energy.

Dr. McLean received his undergraduate and graduate education in mechanical engineering at the University of California, Berkeley, and was associate professor of mechanical engineering at Cornell University before joining Sandia twenty-five years ago.

BARBARA L. MORROW
Vice President-General Counsel
California Healthcare Institute (CHI)

Barbara L. Morrow joined CHI in September 2002 as vice president-general counsel. Morrow was vice president-legislation of the Civil Justice Association of California (CJAC), a coalition of businesses, individuals, and local government groups, where she oversaw the lobbying program. In that position, Morrow managed a wide range of civil liability and procedural issues, including product liability, arbitration, protective orders, summary judgment law, the unfair competition law, class actions, punitive damages, toxic torts, and construction defect law. Prior to joining CJAC, Morrow served as a legislative aide to Assemblyman Tom Bordonaro (R-Santa Barbara). From 1990-1996, Morrow was in-house counsel to Yamaha Motor Corporation in Cypress, California, where she focused on product liability litigation on a nationwide basis. Ms. Morrow holds a bachelor's degree in business administration from Georgia State University and juris doctor degree from Whittier College School of Law.

KURT C. OLSEN
Director of the California Legal and Patent Center
Sandia National Laboratories

Kurt C. Olsen is the principal attorney for Sandia National Laboratories in Livermore, California. He specializes in intellectual property licensing, and manages the patent department.

Working with the staff of Senators Jeff Bingaman (D-New Mexico) and Pete Domenici (R-New Mexico), Kurt developed concepts for protecting know-how in cooperative research and development agreements (CRADAs). Know-how protection was adopted in the Technology Transfer Act of 1989 (15 USC 3710a(c)(7)). His concept for waiver of government licenses to summon private risk capital investment was sponsored by Senator Bingaman and became law in 2000 (15 USC 3710a(b)(6)).

Kurt's early patent work was on computerized speech recognition at Bell Telephone Laboratories in Murray Hill, New Jersey. His undergraduate degree is in mechanical engineering from the University of Colorado, and his law degree is from Cleveland Marshall College.

SALLY O'NEIL
Manager, Industrial Contracts Office
Stanford University

Sally O'Neil manages the Industrial Contracts Office team. In this position, she handles sponsored research agreements, consortium agreements, and master agreements and negotiates and administers agreements for sponsored research with industrial sponsors, including intellectual property, licensing, and publication provisions, for the Engineering, H&S, and Medical Schools. She also serves as liaison between the Office of Sponsored Projects and Office of Technology Licensing. She is responsible for specific departments within the School of Medicine, and Engineering.

She earned a B.A. in English (Oberlin College), an M.A.T. in English (University of Chicago), and M.J. (University of California, Berkeley), and a J.D. (University of Santa Clara). Ms. O'Neil is a member of the State Bar of California, American Bar Association, and Santa Clara County Bar Association.

VALERIE D. PURNELL
Associate Director, State Governmental Relations
University of California Office of the President

As associate director of the University of California's Office of State Governmental Relations, Valerie Purnell is one of two senior lobbyists representing UC before the legislative and executive branches of California government. Ms. Purnell shares the tasks of identifying policy issues relevant to UC, devising the legislative strategies necessary to achieve the university's objectives, and analyzing the intent and potential effect of proposed legislation on the university.

Prior to taking her current position in 1994, Ms. Purnell worked for five years with Children Now. There she held the positions of principal lobbyist, media spokesperson, and later, director of External Relations. In addition to her work in education, Ms. Purnell has had more than twelve years experience as a health policy advocate having worked for organizations such as Health Access, and the public interest law firm, Public Advocates, Inc.

Ms. Purnell received her law degree from the University of California, Hastings College of the Law, studied medical sociology at the University of California, San Francisco, and received her undergraduate degree from Pitzer College of the Claremont Colleges.

HEATHER RICHMAN
Associate Director of Government Relations
Stanford University

Heather Richman is the associate director of Government Relations at Stanford University with her focus being on state issues. She joined the Stanford team in 2004 after working over five years for U.S. Senator Charles Schumer (D-NY) on appropriations, tax and budget issues. Prior to her time in Washington, DC, Heather worked for U.S. Senator Barbara Boxer in her San Francisco office.

KRISTIN SOARES
Associate Vice President of External Relations
Office of State Government Relations
University of Southern California

Kristen Soares, associate vice president of External Relations, State Government Relations, represents USC in public policy arenas involving education, research and public service. Based in Sacramento, she works directly with members of the Legislature and officials in the executive branch to stimulate government actions that enhance the university's ability to carry out its mission. She is also responsible for coordinating these activities with USC's federal relations office. Ms. Soares has been with USC since 1998 having served as assistant vice president of External Relations and director of State Government Relations. Ms. Soares is a member of the Association of Independent California Colleges and Universities (AICCU) Executive Committee and the Policy Council for the California Chamber of Commerce.

WENDY STREITZ
Director, Policy, Analysis and Campus Services
University of California, Office of Technology Transfer

Wendy Streitz is director of the Policy, Analysis, and Campus Services Unit, Office of Technology Transfer at the University of California. Prior to joining the University of California, she served as associate director, Intellectual Property and Technology Transfer at Auburn University. Ms. Streitz has a BSE from Harvey Mudd College and an MSEE from Johns Hopkins University, and has spent twelve years in industry in the field of signal processing.

Appendix H: Reviewers

The California Council on Science and Technology has the highest principles in providing independent, objective and respected work. The Council is in itself a review process in that all work that bears the Council's name is reviewed by Council members, Fellows, and outside experts. The Council seeks guidance and approval of outside experts for peer review. This results in a protocol that ensures the issue is well addressed, the response is targeted, and the results are clear and sound.

In all, this report reflects the input and expertise of nearly 50 people in addition to those in the Study and Working Groups, including experts from academia, high-tech industry (both biotechnology and other), government agencies, the national laboratories, venture capital corporations, and private foundations.

We wish to extend our sincere appreciation to the external reviewers listed below, whose expertise and diligence in reviewing this report has been invaluable, both in rigorously honing the accuracy and focus of the work and in ensuring that the perspectives of their respective areas of expertise and institutions were taken into account. Without the insightful feedback that these reviewers generously provided, this report could not have been completed.

We also wish to extend particular appreciation to the California State Attorney General's Office for consulting with the Study Group throughout the preparation of this report.

Elbert W. Branscomb
Associate Director, Biosciences
Lawrence Livermore National Laboratories

George Cunningham
Chief, Genetic Disease Branch
California Department of Health Services

Molly Holman
Amylin Pharmaceuticals

Edward K. Kawahara
Principal Consultant, California Economic Strategy Panel
California Labor and Workforce Development Agency

Saskia Kim
Senate Office of Research

Gus A. Koehler
Time Structures

David C. Mowery
William A. & Betty H. Hasler Professor of New Enterprise Development
Haas School of Business, University of California, Berkeley

Darci Sears
Legislative Director
Office of Assembly Member Gene Mullin

Appendix I: California Council on Science and Technology

CALIFORNIA COUNCIL ON SCIENCE AND TECHNOLOGY

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Vice Provost for Research and Professor of Biological Sciences
University of Southern California

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University of California, Merced

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Andrew Viterbi
President
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Max T. Weiss
Retired Vice-President and General Manager
Northrop Grumman Corporation

8. Addendum

By Alan B. Bennett and Stephen D. Rockwood

Co-Chairs, IP Study Group

Overview of the History of ACR 24

When CCST's Study Group undertook this project earlier this year in response to ACR 252 (chaptered), it set out to provide a framework for intellectual property policy for CIRM and the state. ACR 24 (pending) was subsequently authored to request CCST consider the disposition of IP derived under Proposition 71 and produce recommendations for the state to consider. The Study Group worked to respond to Assembly draft of ACR 24. It understood at the time that ACR 24 had not yet been passed and that it could potentially be subject to change. In keeping with its original timeline to produce an interim report by late June/early July, the Study Group completed its deliberations and the report underwent external peer review by late June. As the report was going into production, the Senate Health Committee added several amendments on July 13 that requested the Study Group to expand the scope of the project to address some additional concerns.

While we recognize the importance of the amendments in the revised ACR 24, we do not believe that they will affect the Study Group's conclusions and recommendations for intellectual property policy as set forth in the interim report.

This addendum contains our reply to the amendments. Some, as indicated below, will be explored more fully by the Study Group and will be incorporated in its final report that will be completed later this year. Others are beyond the scope of this group's expertise and experience and will need to be studied more thoroughly elsewhere.

Amendments to ACR 24 as of July 13, 2005

Resolved, That the Legislature requests the study group to develop general guidelines or criteria to define how the state can achieve maximum public benefit from research funded under Proposition 71.

This interim report provides an overview of California's potential return(s) on investment from IP generated by CIRM-funded research in Section 5. Our analysis provides background and context for the typical generation of revenues and benefits from biomedical research, and offers guidelines for the disposition of revenues from IP generated by CIRM-funded research. The definition of maximum benefit (monetary and otherwise) and the determination as to how the state can achieve it are broad subjects in need of further investigation.

Resolved, That the Legislature requests that the options and recommendations identified by the study for Proposition 71-funded research reflect the constraints posed by the use of tax-exempt bonds for research and represent options and recommendations that are consistent with the goal and intent of using tax-exempt bonds to fund the research, including options and recommendations for achieving accessibility and affordability of treatments, products, and therapies resulting from Proposition 71 funded research.

CCST has consulted with Orrick, Herrington & Sutcliffe, LLP, the bond counsel retained the State Treasurer's Office, in order to assess the scope of the issues involved in the use of tax-exempt versus taxable bonds. Although the ultimate disposition on several issues related to the use of tax-exempt bonds will be dependent upon decisions yet to be rendered by the Internal Revenue Service, the direct return of intellectual property or its licensing revenue to the state appears to be in conflict with using tax-exempt bonds to fund Proposition 71 research. In this regard, the report's recommendations would appear to be consistent with the use of tax-exempt bonds. Full consideration of this issue, and the consideration of other potential mechanisms to utilize a portion of licensing revenue to meet state needs is beyond the scope of this Study Group's charge and will need to be studied further by the Treasurer's Office and the State Attorney General's Office in consultation with the IRS.

Resolved, That the Legislature requests that the [California] Council on Science and Technology establish a review group that shall include representatives of bond counsel firms, the Legislative Analyst, the Treasurer's Office, consumer and public interest groups, and foundations engaged in funding biomedical research to review and comment on the study and options and recommendations for generating public benefit from commercialization of technology developed with Proposition 71 funds prior to their release and that the Council compile those comments in the report.

The Study Group incorporates a broad range of experts involved with the creation of and administration of IP policy in a variety of institutions. The interim report has been reviewed by external reviewers (Appendix H) and the CCST Board and Council (Appendix I) in accordance with CCST's peer review procedures. The current report reflects the input and expertise of both the Study Group members and those who reviewed the report. Upon its release, we anticipate that the interim report will attract commentary from the groups and organizations listed above as well as others. It is our hope that the document serves as a constructive starting point for additional discussion and we look forward to whatever commentary and analysis may be offered by these other groups.

Resolved, That the Legislature requests that the [California] Council and Science and Technology complete its study by November 1, 2005 and report its options and recommendations for generating public benefit from commercialization of technology developed with Proposition 71 funds to the Health Committees of the Senate and Assembly no later than January 1, 2006 for consideration in developing further policies in this area.

This interim report is being released prior to November 1 because the Study Group has completed its initial analysis, and we believe it will be of use to the state and to CIRM as it begins the process of developing IP policies. The final report with recommendations for the state of California, as requested by ACR 252, will be released at the end of 2005 as originally scheduled.

Consideration of Additional Models for Managing IP

It has been noted that, in addition to the National Institutes of Health (NIH), there are other organizations that may be compared with CIRM for the purposes of proposing IP policies. While it is the Study Group's belief that the NIH is the most appropriate institution to use as a reference point in examining possible policies for CIRM, two programs mentioned in the amended ACR 24 merit consideration. The International AIDS Vaccine Initiative (IAVI) and the Grand Challenges in Global Health Initiative have initiated new strategies for IP that "commit funding recipients and entities seeking to commercialize research to ensure

that resulting therapies and products are accessible and affordable to designated low-income populations." These non-governmental organizations are substantially different from CIRM, as a state agency, in many respects, but offer some interesting points of comparison with regards to their IP policies.

The International AIDS Vaccine Initiative (IAVI) is a not-for-profit organization in operation in 23 countries. Since its inception in 1996, IAVI has invested more than $100 Million in AIDS vaccine development. Funding comes from the Bill & Melinda Gates Foundation; the Rockefeller, Starr and Sloan Foundations; the World Bank; Becton, Dickinson & Co.; the European Union; and the governments of Canada, Denmark, Ireland, the Netherlands, Norway, Sweden, the United Kingdom, and the United States. IAVI manages a portfolio of R&D projects that focus on new concepts for vaccine development. The funds are dedicated to supporting development of new product development candidates and research on difficult technical problems that impede the translation of basic research into easily usable products and therapies. If an AIDS vaccine is developed with IP-derived from IAVI support, it will be made affordable in developing countries.

IAVI's vaccine research program supports projects that bridge the gap between fundamental research and product development efforts, with a focus on applied research and vaccine design. IAVI seeks to harness the global talent and infrastructure necessary to work on complex applied research problems. Among the goals of IAVI is to support new kinds of consortia that would not otherwise occur by identifying key problems to be solved, and then identifying collaborators in wide ranging institutions to work on those issues. A current example, begun in 2002, is the Neutralizing Antibody Consortium, which has made progress towards understanding the large scientific challenge of designing immunogens for eliciting broadly neutralizing antibodies against HIV. Several other models are also underway or in development, and the technical problems being worked on are exceedingly complex.

The Grand Challenges in Global Health Initiative is a $482 M effort supported by the Bill and Melinda Gates Foundation, the Wellcome Trust in the United Kingdom, and the Canadian Institute for Health Research. The $450 M in funding from the Gates Foundation includes $200 M managed by the Foundation for the National Institutes of Health.

The Grand Challenge was launched in 2003 with the goal of instigating the development of research projects that would apply innovation in science and technology to the greatest health problems of the developing world. The key focus of this challenge is to improve global health technologies. 43 grants, for a total of $436.6 M, were announced in late June. These grants involved scientists in 33 countries.

Some projects will improve on existing technologies; others will attempt to develop entirely new technological approaches. The range of projects include developing low-cost technologies for formulating vaccines that do not require refrigeration, and single-dose vaccines; new strategies for HIV vaccines; and new, low cost diagnostics for serious diseases. Of the initial grants, nearly all represent new consortia of academic, nonprofit, and for-profit institutions.

Management of IP by these initiatives

The IP derived from IAVI funding is owned and managed by the inventors. The individually negotiated IP agreements require that vaccines developed using IP derived with IAVI funding must be provided in poor countries at a reasonable price, as based on the income level of the country and other factors. IAVI envisions that its funding is supporting research that will bridge the gap between the basic research and the proofs of concept that overcome the large

technical challenges the currently exist. The IP associated with the proofs of concept will then be licensed by industry, which will play its traditional role in advanced product development and commercialization of the vaccines. In poor countries, those vaccines would be delivered at reasonable prices. The initiative does not establish restrictions in other markets or for use of the IP for other applications.

The Grand Challenge initiative handles IP through a new concept called a "global access strategy." It does not have an IP policy *per se*. Instead, IP is dealt with in the terms and conditions of each grant award. Grantees must develop a Global Access Plan that specifies how current and newly generated IP will be managed so as to facilitate access of new products and therapies to those most in need in the developing world. Each grantee must develop its own response to the objectives of the global access strategy that describes their thought processes about developing a useable product, producing a product maturation plan, criteria for selecting research and commercial partners, and other issues.

The global access strategy is causing grantees to push the envelope in thinking about how to eventually develop licensing agreements that enable access by poor countries. To date, most grantees are still developing their global access plans and other documents, such as project management charters. The Gates Foundation and the FNIH, which will each manage about half of the grants, realize the uniqueness of this approach, and anticipate an iterative process with the grantees over time through which many lessons will be learned and best practices will emerge.

In many ways, these initiatives are quite innovative. However, the new aspects of both initiatives focus primarily on how IP is licensed and used after it is generated. Ownership will reside with the grantee. The general principles for IP ownership for these initiatives are consistent with the general principles put forward in this report, that IP policy:

- Is to be consistent with Bayh-Dole, where ownership of IP resides with the grantee
- Create incentives for commerce to the greatest extent possible
- Encourage timely publication of results to diffuse knowledge widely, and
- Requires diligent development of IP into products that benefit the public.

The newness of these initiatives does not enable us to point to successful models. It is too soon, therefore, to recommend to the state and to CIRM wholesale adoption of the processes used in either of these initiatives. The efforts of IAVI and the Grand Challenges, however, have succeeded in catalyzing principal investigators, business managers, and technology transfer executives and managers to begin thinking in new ways about licensing strategies to ensure low-cost treatments to people in the poorest countries in the world. To the extent that these new explorations may help CIRM think about ways that licensing agreements based on IP derived from CIRM-funded grants – which in and of itself is still several years away -- can be structured in ways that benefit a particular class of California citizens (low-income individuals), then we encourage ongoing discussions between CIRM and the leaders of these initiatives.

It seems most important in the near term that the general principles offered in this interim report guide CIRM's initial policy making related to ownership of IP and its diligent development into products that benefit the public. During the next decade, we expect that many lessons will be learned from IAVI and the Global Health Challenge, and perhaps other public-private partnerships, and that best practices will emerge. It is still apparent to us, however, that CIRM, by design and given the basic and early applied nature of the stem cell research to be conducted, especially in the next several years, is much more similar in its goals to the NIH than a private

or public charity. Therefore, consistency with the objectives Bayh-Dole would provide the best incentives to the community of researchers and commercial entities that ultimately will harness the creative spirit required to develop breakthroughs and applications to new treatments and therapies.

For additional information on these two initiatives, see:

The International AIDS Vaccine Initiative -- http://www.iavi.org

The Grand Challenges in Global Health Initiative – www.gatesfoundation.org and www.fnih.org

Conclusion

The Study Group was convened to examine the specific question on how to establish an intellectual property framework for the state of California. There is no precedent for the creation of such a statewide policy framework, just as there is no precedent for a state-supported basic research institution on the scale of CIRM. It is perhaps inevitable that the creation of completely new institutions and policies will invite speculation. As noted both in ACR 24 and elsewhere, there is a wide range of other issues that need to be addressed in the creation and administration of CIRM and state funded IP in general. The Study Group has done its best to answer the mandate set forth in the original scope of the project, which focuses on a framework for IP policy. It is our hope that other committees and organizations can give the additional issues cited in the amended ACR 24 the full analysis and attention that they deserve.

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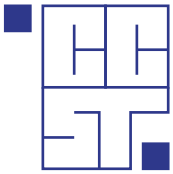

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