Re-Examining the Need for Innovation Capital to Advance Life Science Development in Indiana

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Prepared for: BioCrossroads

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The Business *of* Innovation

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ACRONYMS AND SHORT FORMS

CICP	Central Indiana Corporate Partnership
CTSA	(NIH) Clinical and Translational Science Award
CTSI	(Indiana) Clinical and Translational Sciences Institute
FDA	Food and Drug Administration
FoF	fund of funds
IEDC	Indiana Economic Development Corporation
IP	Intellectual property
IU	Indiana University
MINT	Merck Initiatives for New Targets
NCATS	National Center for Advancing Translational Sciences
NIH	National Institutes of Health
OECD	Organization for Economic Cooperation and Development
PhRMA	Pharmaceutical Research and Manufacturers of America
R&D	Research and development
SBIR	Small Business Innovation Research
SPARC	Strategic Pharma-Academic Research Consortium
TPP	(Battelle) Technology Partnership Practice
VA	Veterans Administration

PROLOGUE

Since our founding in 2002, BioCrossroads has pursued our first and best mission to serve as a catalyst for advancing economic opportunity through innovation across Indiana's impressive life science sector. Within that mission, our particular focus has been the formation and growth of new life science companies that can leverage the state's deep and diverse life sciences research and industrial base, and set the stage for this key sector's continuing vitality and development in the 21st century. As we knew from the start—and have seen validated many times since—such a strategy can only succeed if innovation has sufficient and constant access to capital.

It has now been ten years since BioCrossroads' first formation and funding of a unique venture capital strategy for Indiana—a $73 million institutional investor fund of funds (FoF) vehicle called the "Indiana Future Fund," whose purpose was to make critically needed capital available to early-stage Indiana companies to spur innovation. Over that same decade, philanthropy has made additional key investments, as have a variety of State, university and private sources, resulting in an overall strengthening of our life science community and laying the foundation for a productive strategy to assure our future competitiveness in this global sector of opportunity.

Battelle Technology Partnership Practice, the premier experts in analyzing and charting the development of America's life sciences sector within and across all fifty states, has taken an in-depth look at Indiana's life science landscape, including available capital and innovation outputs for the decade prior to the formation of the Indiana Future Fund (1993 to 2002), the decade this FoF strategy was implemented (2003 to 2012), and a look forward to what comes next. Capital, for purposes of this study, includes not only risk capital in all of its stages, but also federal and state grant funds, philanthropic investment, and other corporate and private support. Re-examining the history and full economic impact of capital on innovation is important to inform decision-makers and stakeholders of the type of public-private partnership efforts that are needed to catalyze and sustain our life sciences innovation ecosystem for the future, as well as to consider how the need for capital to fuel innovation is evolving. For this new study, Battelle looked at extensive data and conducted a series of key interviews. These interviews, along with data and accompanying analysis of activity over the past 20 years, form the basis of the following report.

The overall message here is a hopeful one. Clear gains in measures of innovation occurred over the past decade, when contributors to Indiana's capital markets—the State, universities, industry, philanthropy, and groups like BioCrossroads—all enacted targeted strategies to advance growth. Indiana's gains in life science innovation capital in the decade since 2003 have generally outpaced the nation. More capital was available, from State programs, university sources, seed funds, and the Indiana-based philanthropic foundation community. Significant leverage was achieved for those companies receiving capital,

especially when compared (as the report also does) to the far more modest record of the prior decade. Since 2003, many more companies have achieved growth directly from Indiana-based sources of capital, an astounding jump from five companies in the prior decade prior to 160 companies for the period from 2003 to 2012. Other essential commercialization measures, such as overall patent generation, venture capital, and university technology transfer, also trended positively.

In the midst of our laudable progress over the past ten years, the marketplace has not been static. And now, the decade ahead holds even more challenges, as advanced therapeutic pursuits in fields such as cancer, Alzheimer's disease and metabolic disorders range increasingly across the high frontiers of emerging scientific knowledge; federal funding for life sciences research decreases; risks associated with innovation accordingly continue to rise; and the recent shift in U.S. capital markets to fewer, larger venture capital firms that in turn make fewer and later-stage investments appears to extend into the foreseeable future. In the face of these challenges, Battelle has listed a series of recommendations that we believe can begin new and important conversations, all aimed at continuing to drive innovation forward and strengthen our life sciences community. These recommendations underscore the importance of active early-stage investments; a focus on finding, retaining and growing entrepreneurial talent; the increasing need for multiple and complementary strategies to de-risk early-stage research and technology; and expansion of university-industry partnerships to advance translational or "use-inspired" research and to leverage our life science industry strength to further life science innovation here.

Indiana is unique in the richness of our academic and corporate life science assets, coupled with our unmatched tradition of genuine collaboration and partnership. We are home to significant corporate operations from medical devices to therapeutics and diagnostics to ag-biosciences, each and all of which take active roles in supporting the life sciences community while directing billions of dollars in research annually. Our research universities have launched early-stage seed investment funds and partnered to support one of the nation's top NIH-sponsored Clinical and Translational Science Institutes. The State of Indiana has shown its support through the 21st Century Fund, Investment Tax Credits, and early and substantial funding for the industry-led Indiana Biosciences Research Institute. We are home to an active philanthropic community that has advanced our research institutions with hundreds of millions of dollars for research and programs, and worked with other collaborative organizations to assess and study important trends. Throughout, BioCrossroads has been privileged to serve as a connecting point for each of these groups, to understand the broader environment and its implications for Indiana, and accordingly, to facilitate investments and partnerships to safeguard strengths and accelerate growth. The assets we share, and our shared determination to grow them far more through the advance of promising innovation, will continue to enable Indiana to thrive over the decade ahead—and far beyond.

This is an important and timely report. And certainly, it is appropriate here to thank those whose efforts have made it possible: the Lilly Endowment, through a generous grant to the CICP Foundation on behalf of BioCrossroads, that provided the essential funding; our colleagues at the Battelle Technology Partnership Practice, who know both Indiana and the life sciences sector well, and have drawn on their substantial expertise to provide a helpful and comprehensive study; and my colleague at BioCrossroads,

Nora Doherty, Vice President for Finance and Managing Director of the Indiana Seed Funds, who came up with the idea of this report in the first place, and then guided the work of many others to ensure its success.

Sincerely,

David L. Johnson
President and CEO, BioCrossroads

October 2014

EXECUTIVE SUMMARY

As Indiana looks to accelerate and position its economy for future growth in the aftermath of the recent Great Recession and weak economic recovery, there is a growing recognition of the importance of advancing innovation as a driver of economic competitiveness. According to the National Research Council in a recent report, *Rising to the Challenge*, the capability to innovate is fast becoming the most important determinant of economic growth and a nation's ability to compete and prosper in the 21st century global economy.[1]

For Indiana, one of its strongest industry clusters for innovation is found in the life sciences. This strength in life science development presents a high growth opportunity for Indiana. Economic output of the life science industry has expanded significantly over the past decade, well outperforming the overall U.S. economy.[2] Looking forward, major new opportunities in the life sciences are emerging in areas of innovation such as tissue engineering, stem cell therapies, immunotherapies and personalized medicine, joining traditionally strong markets in cardiovascular disease, diabetes, and neuroscience. Overall, innovation is recognized as a critical driver for life science development, generating a significant level of its future revenues.

The imperative of advancing economic opportunity and growth in the life sciences through innovation was the reason for launching BioCrossroads in 2002. The mission of BioCrossroads is to serve as a catalyst for the continued growth of Indiana's robust life science industry by engaging industry, university, health care, philanthropic and state government stakeholders. Of particular concern for Indiana is ensuring the formation and growth of new life science companies thereby leveraging the life science research base and industry anchors in Indiana—churn that is necessary in building a dynamic and healthy life science community. Successful new company formation, increased innovation, and subsequent economic growth are all highly correlated to the amount of innovation capital, i.e., capital used to fund and advance life science innovation, which is able to be accessed.

After more than a decade in action, BioCrossroads can point to significant program activities and successes in its efforts to catalyze life science innovation capital as a means to advance the life science industry in Indiana. These efforts to generate life science innovation capital include recent initiatives in Indiana to promote collaborations with industry and universities—such as the newly launched Indiana Biosciences Research Institute and the ongoing Indiana Clinical and Translational Sciences Institute. Indiana has also been successful in generating local funding for early stage investment, engaging Indiana's own angel investors, corporate funding arms, the philanthropic community and state government, while also building broader connections and relationships with national venture capital firms for follow-on funding to enable the long-term success of Indiana's high growth potential, emerging life science companies.

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[1] Charles W. Wessner and Alan Wm. Wolff, Eds. "Rising to the Challenge: U.S. Innovation Policy for the Global Economy." 2012. The National Academies Press, Washington, DC., page xiii.

[2] Battelle/BIO State Bioscience Jobs, Investments and Innovation 2014.

Indiana is Well-Positioned in Life Science Industry Development and Innovation

Indiana ranks in the top three states in its life science industry specialization, and stands out in the diversity of its life science industry base. Indiana has industry specializations far greater than the national average in three of the five subsectors of the life science industry, including Drugs and Pharmaceuticals, Medical Devices and Equipment, and Agriculture Feedstock and Chemicals. Indiana also has a substantially higher concentration of total private sector employment in Bioscience-related Distribution at 19 percent above the national average.

As a leading advanced manufacturing industry, the life science industry cluster in Indiana pays high wages as a result of its extensive high-skilled workforce involving technicians, machinists, engineers and scientists. The life science industry average wage in Indiana stood at $87,757 in 2012. This is more than double the total private sector annual wage in Indiana of $41,356.

Typical of manufacturing industries, the life science industry in Indiana has very strong supply-chain relationships, which together with the spending of its high wage workforce, makes the life science industry a critical economic driver for Indiana. For every one life science job in Indiana, another 4.3 jobs are generated. This means the 57,644 workers directly employed in the life science industry in Indiana help generate another 247,869 jobs, and as a result, have a total employment impact of 303,692 jobs in Indiana. This represents just under 13 percent of Indiana's total private sector.

Indiana has a sizable university research base in the life sciences. In 2012, Indiana had $578 million in university life science research across all of its research universities—representing approximately 50 percent of all university research funding in Indiana. While this university research base complements the strong life science industry presence with a source of new basic science discoveries and access to top talent and scientific expertise, often overlooked is that, by itself, this university research base is also an economic driver.

Indiana is also well-positioned in generating life science inventions. A direct measure of inventions in the life sciences is the number of patents awarded for life science innovations. Patents represent the way businesses, universities and individuals protect intellectual property (IP) that they invent. From 2009 to 2013, Indiana inventors generated 3,420 life science-related patents. This places Indiana 12th in the nation, and in the same range as states such as Maryland, Ohio, Texas, North Carolina and Washington. Indiana's number of patents particularly stands out in the areas of surgical and medical instruments, drugs and pharmaceuticals and biotechnology.

This study analyzes the life science innovation landscape for the decade prior to Indiana undertaking its formal life science capital strategies (1993–2002), the decade these strategies were implemented (2003–2012/13), and a look forward to what the future might hold. This look back is important for reminding current decision-makers and stakeholders of the types of public-private partnership efforts required to catalyze and sustain Indiana's life science innovation ecosystem for the future. In its look forward, this study considers how the need for capital to fuel life science innovation is evolving in Indiana as the state's life science innovation ecosystem has matured and is being reshaped by global forces in the competition for life science innovation.

An analysis of life sciences innovation capital needs to begin with university and industry efforts in research and development. Innovative new products in the life sciences are very dependent upon research discoveries and advances in scientific knowledge. This is the reason why the life sciences are the largest area of industry research and development in the U.S.

Still, life sciences research activity is just the start to realizing industrial returns from innovation. The commercialization process in the life sciences is often lengthy, costly and uncertain. This difficult commercialization process in the life sciences is due not only to the complexity of new therapeutics and devices innovations, but also to the extensive clinical testing required for new product approvals and compliance with associated regulatory hurdles.

The definition of innovation capital for the life sciences needs to reflect the close ties to research and development efforts and the more extensive efforts needed to commercialize life science innovations. Capital, for purposes of this study, includes funding to advance:

- Life science research
- Technology commercialization
- Venture formation and growth.

These categories of innovation capital represent a continuum in the advancement of commercialization as illustrated in Figure ES-1.

The funding sources of life science innovation capital are also quite broad. These sources include not only providers of risk capital across all of its stages, but also federal and state grant funds, philanthropic investments, and other corporate and private support.

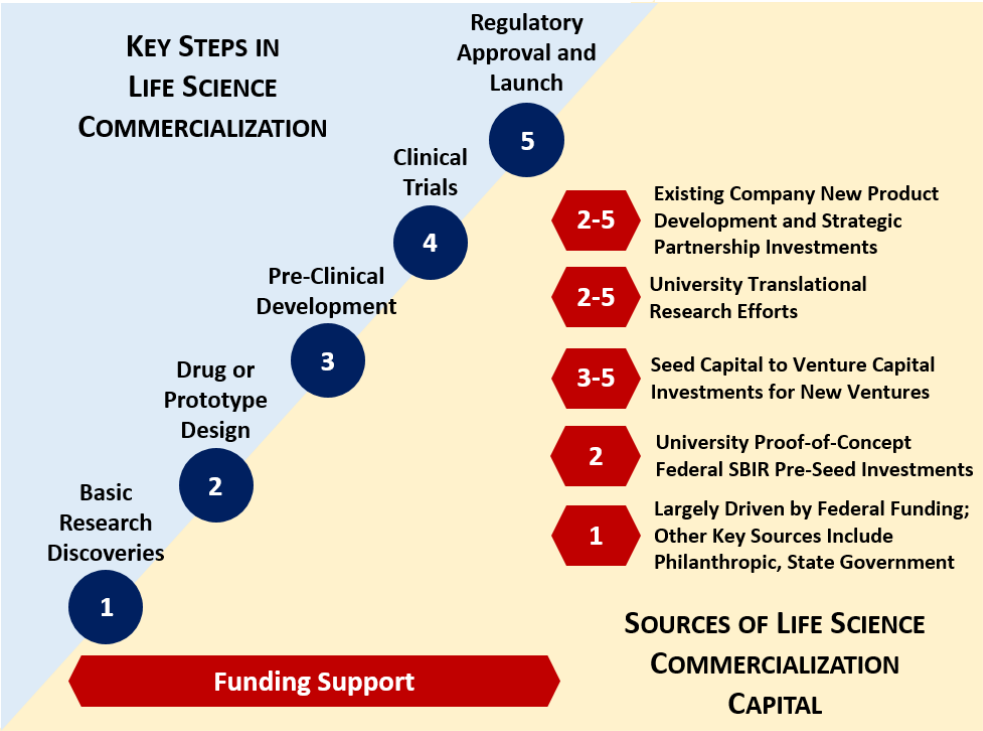

Figure ES-1. Life Science Innovation Continuum with Range of Sources for Innovation Capital

Recapping the Differences between the Decades

The formal life science innovation capital strategies implemented in Indiana have made a considerable difference to the innovation environment and are generating a marked change from the decade before these efforts were undertaken. The evidence suggests just how striking these improvements in Indiana's life science innovation activities have been.

Indiana took a major step forward over the last decade in generating additional sources of life science innovation capital from nationally available sources.

- In the decade before 2003, the vast majority of life science innovation capital in Indiana came from university life science research and industry research. Both technology commercialization funding and venture development funding were quite limited.
- In the decade since 2003, in addition to industry and university research continuing to grow, there was a substantial rise in technology commercialization and venture development funding.

The gains made by Indiana in life science innovation capital in the decade since 2003 have generally outpaced the nation. Indiana recorded higher growth than the nation in university life science research, industry life science research and venture capital funding. One area of concern, though, is in NIH research funding where Indiana lagged slightly behind the national average.

The considerable rise of life science innovation capital for technology commercialization and venture development in the decade since 2003 stands out in Indiana. It reflects the growing funding support for technology commercialization and venture development primarily from philanthropic and state sources in a range of new mechanisms such as seed capital investment funds, fund of funds to invest in venture capital, state tax incentives for angel investment, and university proof-of-concept and early-stage company formation funding (Indiana-based sources of innovation capital).

Of particular importance over the past decade is the role that the Indiana-based philanthropic foundation community has continued to play as a critical source of life science innovation capital. The Indiana-based philanthropic foundation community has provided both an important source of funding for advancing life science research capabilities and a strong source of support for the organizations engaged in technology commercialization.

Indiana's efforts to advance life science innovation capital for commercialization and venture funding of emerging life science companies in the decade since 2003 have generated measurable results:

- Indiana-based sources for commercialization and venture development invested in a total of 160 emerging life science companies in the decade since 2003. These 160 firms received a total of $154 million of commercialization and venture funding across all Indiana sources, such as from the BioCrossroads' seed funds, Indiana's Fund of Funds, the State of Indiana's venture capital investment tax credit, and the 21st Century Fund, which generated an additional $323 million or a leverage ratio of $2.10 for every $1 of funding.
- There is a demonstrated connection across the life sciences innovation continuum with 45 of the 160 emerging life sciences companies receiving funding from more than one Indiana-based source of innovation capital.

More broadly, the overall performance of Indiana across the continuum in generating innovations appears to be on the rise. Not only has Indiana raised its performance in advancing commercialization across most measures, but its share of national activity in many key measures of commercialization performance has also improved, including overall patent generation, venture capital investment, and university technology transfer activity.

Most importantly, the increase in innovation capital has enabled Indiana's life science industrial base to remain highly concentrated at a time in which the industry sector has experienced significant changes. This is keenly observed in light of the recent impact of the pharmaceutical industry's loss of employment in Indiana. Recognizing that the industry is subject to national and global market pressures and changes in regulations, it is critically important that a state's industrial base remain nimble and flexible to ever mounting pressures and changes—highlighting even further the importance of innovation capital in the decade to come – and the need to increase the number of new firms and a net increase of companies and jobs to insure Indiana remains a global player.

Future Needs and Emerging Trends Shaping Life Science Innovation Capital

Indiana has clearly accomplished much with its formal strategies to advance life science innovation capital. The last decade has seen Indiana forge its own unique solutions to the challenges of increasing life science innovation capital needed to fuel the growth of the life science industry.

At the same time, however, new challenges to advancing life science innovation are emerging. The convergence of three key challenges is making early stage investments fill a larger and more critical gap and creating the need for new interventions to further collaborative research and development between universities and industry. These three key challenges are:

- Increasing pressure on existing large biopharmaceutical and medical device companies to generate greater returns from R&D investments and pursue partnership opportunities to de-risk promising new therapeutics and devices
- The shift to fewer, larger venture capital firms that in turn are making more of their investments in later stage, less risky ventures
- The decline in federal funding for basic research.

It is essential to step back and ask how Indiana can best compete in this new environment.

How Indiana Can Compete for Future Growth in Life Science Development

The analysis of life sciences development in Indiana points to Indiana's existing industrial base as the state's most significant life sciences asset. The one constant over the past 20 years in Indiana's life sciences development has been the size and diversity of the state's life science industry base. This significant industry base is hard for other states to replicate. It provides critical knowledge and access to life science markets and, in itself, is a major driver of innovation investments. Over the past decade, this industry base has increased its focus on innovation as demonstrated by strong growth in industry-led life science research and development and substantial gains in total life science patent activity in Indiana.

By contrast, Indiana's university and academic medical center activities, while offering many partnership opportunities to work with industry, remain ranked in the middle quintile among life science research institutions in the nation. Indiana does not match today nor is it likely to match the life science basic research funding levels of top life science states such as Massachusetts, Maryland or North Carolina in the future. However, because of its significant industry research base, its creation of new types and forms of intermediary organizations such as the Indiana Biosciences Research Institute, and the promise of increased industry and university collaboration in the future, Indiana can advance new strategies for growth in today's fast changing life sciences innovation environment in ways competitor states and regions or countries may not be able to do. These new strategies offer Indiana universities the opportunity to be a national leader in advancing industry-university partnerships designed to create innovation to further life science industry growth.

Furthermore, Indiana's efforts to catalyze sources of innovation capital are modest and targeted at the early stages of commercialization and new firm formation. Indiana is not a money centered location with major national investment banks and venture capital firms, such as Boston, San Francisco, New York or Chicago. Rather than leveraging an industry strength in financial services, Indiana must seek to create a targeted focus on ensuring sufficient sources of capital to enable innovation to occur and then facilitate connections to national sources of financial capital. Despite the successes of Indiana's efforts in promoting investment by angel investors, seed capital investment, and engaging non-state resident venture capital, there is a need to significantly increase early-stage pre-seed and seed investments to advance innovation.

Specific Steps Recommended for Indiana

Based on the global market challenges, analysis of the current state of Indiana's innovation ecosystem, and guidance from Indiana's stakeholders and national innovation capital experts, five broad recommendations emerge regarding the critical steps in a future innovation capital strategy for Indiana:

- **Ensure there is a sufficient level of indigenous early-stage life science innovation capital to generate high quality deal flow of emerging life science companies in Indiana and facilitate connections to follow-on national venture capital funding.**
- **Improve development of entrepreneurial talent to lead life science innovations.**
- **Enhance the commercialization of university research discoveries and technology advances through initial technology and market validation activities.**
- **Enable Indiana to stand out as a global leader in university-industry partnerships to advance translational or "use-inspired" research.**
- **Leverage Indiana's existing life science industry strengths to further life science innovation within Indiana.**

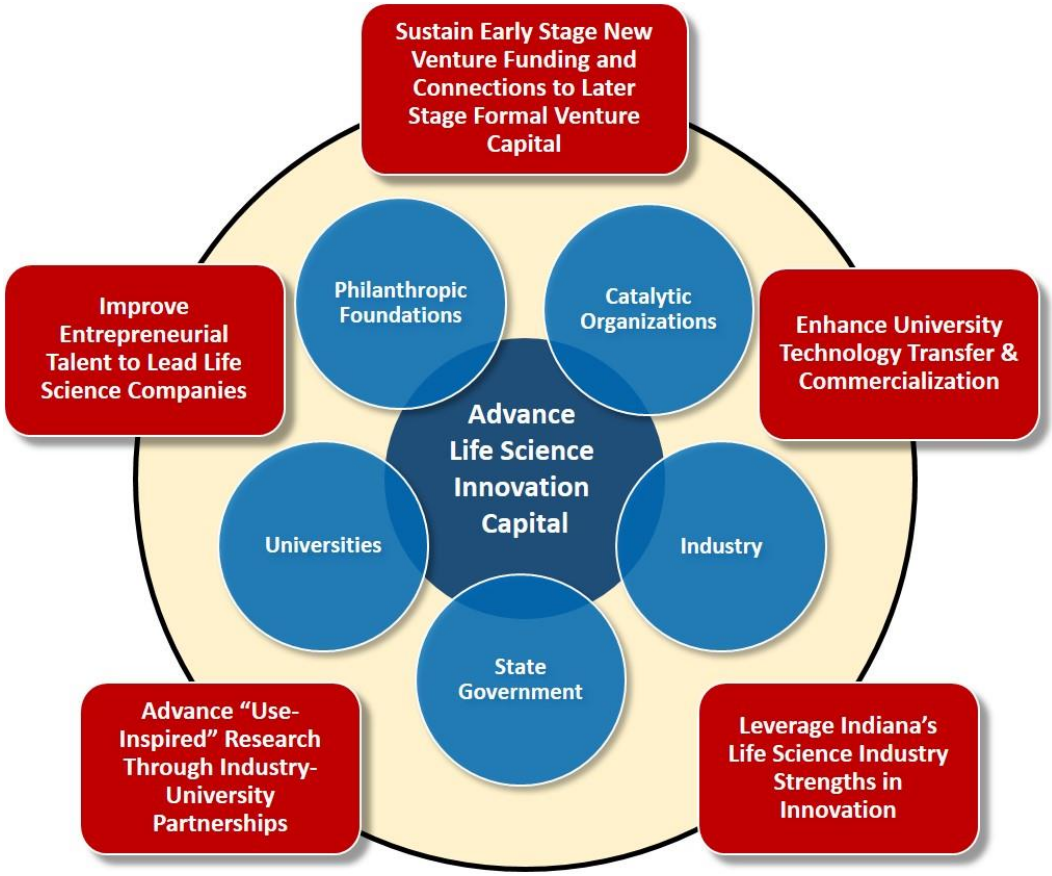

Figure ES-2. Depiction of Key Recommendations

A summary of the specific actions to be considered to advance each of these five recommendations is set out in Table ES-1, along with the wide range of stakeholders needed to help in the advancement and implementation of these recommendations.

By focusing on these recommendations, Indiana can build upon its distinct assets and competitive advantages and address specific weaknesses to grow its life science industry through innovation. The specific steps touch upon the complex nature of life science innovation capital, recognizing its continuum across research activities, technology commercialization, new firm formation, clinical testing, and new product scale-up and launch. All aspects of the innovation continuum are under stress in today's changing world of life science innovation where open innovation models are being increasingly embraced by industry, the challenge of de-risking new technology is rising in importance, and the funding gaps between research and early rounds of venture capital are growing for new firm formation. The specific recommended steps address these issues in a tailored and measured way for Indiana.

Table ES-1. Specific Actions to be Considered and Stakeholder Engagement Needed for each of the Five Proposed Recommendations

Proposed Recommendations	Specific Actions to be Considered	Key Stakeholders
Sustain sources of indigenous early-stage life sciences innovation capital and connections to follow-on national venture capital funding.	• Continue to provide local seed capital funding in Indiana • Enhance the tax incentives for early stage investment • Support "smart" angel investing • Continue support of University-sponsored Seed Funds • Reinvent the 21st Century Fund to focus on proof-of-concept/prototype development • Capitalize a third Fund-of-Funds for connections to sources of follow-on venture capital investments	• BioCrossroads • State Government • Angel investors • Universities • Indiana institutional investors
Improve Life Sciences Entrepreneurial Talent Development	• Establish a life sciences entrepreneurial development effort involving mentoring by serial entrepreneurs and growing next generation of talent among top graduate students	• BioCrossroads • Universities and Colleges • Philanthropic Foundations • State Government • Industry
Enhance Technology Transfer and Commercialization	• Increase technology and market validation activities at universities • Examine feasibility and benefit of separate technology transfer office at IU School of Medicine • Advance closer alignment to health care system	• Universities • Health Care Systems • State Government
Advance "Use-Inspired" Research	• Advance the ongoing activities of the Indiana Biosciences Research Institute and Indiana Clinical and Translational Sciences Institute/SPARC • Pursue implementation of additional university-industry collaboration opportunities set out in *Advancing Indiana's Life Sciences Competitiveness and Strategic Collaborations* in Health Informatics, Global Health and Plant Improvement	• Industry • Universities • Philanthropic Foundations • State Government • BioCrossroads
Leverage Indiana's Existing Industry Strengths	• Enhance the incentives for industry innovation in Indiana, including modifying the state's R&D tax credit to be refundable for small companies and adding a larger incentive for industry research costs with universities and other Indiana companies.	• State Government • Industry • BioCrossroads

INTRODUCTION:
WHY BROAD-BASED LIFE SCIENCE INNOVATION CAPITAL MATTERS

As Indiana looks to accelerate and position its economy for future growth in the aftermath of the recent Great Recession and weak economic recovery, there is a growing recognition of the importance of advancing innovation as a driver of economic competitiveness. According to the National Research Council in a recent report, "Rising to the Challenge," the capability to innovate is fast becoming the most important determinant of economic growth and a nation's ability to compete and prosper in the 21st century global economy.[3]

To effectively compete for innovation and technology development, it is well understood that each state has specific industry clusters through which it is uniquely positioned for growth due to factors of comparative advantage. The National Governors Association's advice to states across the nation with regard to best practices for global competitiveness includes the opinion that:

> *Each state must exploit the unique advantages it has relative to other states and build on the strengths found in its local "clusters of innovation"—distinct groups of competing and cooperating companies, suppliers, service providers and research institutions."*[4]

For Indiana, one of the strongest industry clusters for innovation is found in the life sciences. This strength in life science development presents a high growth opportunity for Indiana. Economic output of the life science industry has expanded significantly over the past decade, well outperforming the overall U.S. economy.[5] Looking forward, major new opportunities in the life sciences are emerging in areas of innovation such as tissue engineering, stem cell therapies, immunotherapies and personalized medicine. Overall, innovation is recognized as a critical driver for life science development, generating a significant level of its future revenues. An Organization for Economic Cooperation and Development (OECD) study, *The Bioeconomy to 2030,* estimates that recognized advances in biological sciences with a high probability of reaching the market could contribute up to 80 percent of pharmaceutical and diagnostic revenues in 2030.[6] The life sciences represent an industry cluster where states that succeed in advancing innovation have a much higher likelihood of gaining competitive advantage that in turn drives economic growth.

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[3] Charles W. Wessner and Alan Wm. Wolff, Eds. "Rising to the Challenge: U.S. Innovation Policy for the Global Economy." 2012. The National Academies Press, Washington, DC., page xiii.

[4] National Governors Association, "A Governor's Guide to Trade and Global Competitiveness," 2002.

[5] Battelle/BIO State Bioscience Jobs, Investments and Innovation 2014.

[6] OECD, The Bioeconomy to 2030, 2009, page 199.

The imperative of advancing economic opportunity and growth in the life sciences through innovation was the reason for launching BioCrossroads in 2002. The mission of BioCrossroads is to serve as a catalyst for the continued growth of Indiana's robust life science industry by engaging industry, university, health care, philanthropic and state government stakeholders. Of particular concern for Indiana is ensuring the formation and growth of new life science companies thereby leveraging the life science research base and industry anchors in Indiana—churn that is necessary in building a dynamic and healthy life science community. Successful new company formation, increased innovation, and subsequent economic growth are all highly correlated to the amount of innovation capital that is able to be accessed.

After more than a decade in action, BioCrossroads can point to significant program activities and successes in its efforts to catalyze life science innovation capital as a means to advance the life science industry in Indiana. These efforts to generate life science innovation capital include recent initiatives in Indiana to promote collaborations with industry and universities—such as the newly launched Indiana Biosciences Research Institute and the ongoing Indiana Clinical and Translational Sciences Institute. Indiana has also been successful in generating local funding for early stage investment, engaging Indiana's own angel investors, corporate funding arms, the philanthropic community and state government, while also building broader connections and relationships with national venture capital firms for follow-on funding to enable the long-term success of Indiana's high growth potential, emerging life science companies.

This study analyzes the life science innovation landscape for the decade prior to Indiana undertaking its formal life science capital strategies (1993–2002), the decade these strategies were first implemented (2003–2012/13), and a look forward to what the future might hold. This look back is important for reminding current decision-makers and stakeholders of the types of public-private partnership efforts required to catalyze and sustain Indiana's life science innovation ecosystem for the future. In its look forward, this study considers how the need for capital to fuel life science innovation is evolving in Indiana as the state's life science innovation ecosystem has matured and is being reshaped by global forces in the competition for life science innovation.

Assessing the history and past results and evolving need for life science innovation capital requires a careful, independent and objective assessment. BioCrossroads retained the Battelle Technology Partnership Practice (TPP) to conduct this assessment. Battelle TPP is the technology-based economic development consulting practice of the world's largest, non-profit research and development organization, and is nationally recognized for its thought leadership and expertise in assessing and planning for innovation-driven initiatives, particularly, life science development strategies. From its past work, Battelle TPP is also very familiar with Indiana having prepared the original report identifying Indiana's life science strengths, opportunities, and challenges for life science development in February 2002, as well as the more recent strategic assessment of the opportunities for industry-university-health care partnerships in Indiana in 2012.

SETTING THE CONTEXT: AN UPDATE ON INDIANA'S LIFE SCIENCE DEVELOPMENT TRENDS AND EMERGING CHALLENGES FOR LIFE SCIENCE INNOVATION

The focus on advancing life science development in Indiana through innovation has been a cornerstone of the efforts of industry, university, health care, government and philanthropic stakeholders since the early 2000s. To help set the context for this study, it is critical to examine:

- *The current position of Indiana's life science industry development*
- *The broad challenges facing life science innovation across the U.S.*

The State of Indiana is Well-Positioned in Life Science Industry Development

Indiana ranks in the top three states in its life sciences industry specialization, with more than double the share of total private sector employment found in the life sciences than in other states across the nation according to the *2014 State Bioscience Jobs, Investments and Innovation Report* recently issued by the Biotechnology Industry Organization[7]. What also stands out for Indiana is the diversity of its life science industry base. Indiana has industry specializations far greater than the national average in three of the five subsectors of the life science industry, including Drugs and Pharmaceuticals, Medical Devices and Equipment, and Agriculture Feedstock and Chemicals. Indiana also has a substantially higher concentration of total private sector employment in Bioscience-related Distribution at 19 percent above the national average. The one life science subsector where Indiana is below the national level of industry specialization is in Research, Testing and Medical Laboratories. Still, this life science industry subsector is the fastest growing one in Indiana.

As a leading advanced manufacturing industry, the life science industry cluster in Indiana pays high wages as a result of its extensive high-skilled workforce involving technicians, machinists, engineers and scientists. The life science industry average wage in Indiana stood at $87,757 in 2012. This is more than double the total private sector annual wage in Indiana of $41,356.

Typical of manufacturing industries, the life science industry in Indiana has very strong supply-chain relationships, which together with the spending of its high wage workforce, makes the life science industry a critical economic driver for Indiana. For every one life science job in Indiana, another 4.3 jobs are generated. This means the 57,644 workers directly employed in the life science industry in Indiana

[7] Ibid. Industry specialization measures the relative size of a state's life science industry base compared to the nation. A high industry specialization reflects the broader competitiveness of a state for that industry.

help generate another 247,869 jobs, and as a result, have a total employment impact of 303,692 jobs in Indiana. This represents just under 13 percent of Indiana's total private sector.

Indiana also has a sizable university research base in the life sciences. This is important given the strong ties between life science innovation and basic research discoveries, which helps distinguish the life sciences from other technology sectors. Academic studies have found that many of the most important therapeutic drugs introduced between 1965 and 1992 had their origins in public sector research conducted in universities, NIH and non-profit research institutions.[8] In 2012, Indiana had $578 million in university life science research across all of its research universities—representing approximately 50 percent of all university research funding in Indiana. While this university research base complements the strong life science industry presence with a source of new basic science discoveries and access to talent and scientific expertise, often overlooked is that, by itself, this university research base is also an economic driver.

Much of Indiana's university research funding in the life sciences comes from federal, philanthropic and industrial sources. Indiana's ability to attract growing university

The life science industry is best understood as a grouping of diverse industries with a common link – the application of biological scientific knowledge as to how living organisms function to specific products and services involving health care, agriculture and food, and industrial chemicals. The Biotechnology Industry Organization, with technical assistance from Battelle, has set out 25 detailed industries organized into five primary subsectors to represent the life science industry:

Drugs and Pharmaceuticals involving traditional small molecule drugs, vaccines, biotechnology-based therapeutics (such as monoclonal antibodies), and diagnostic substances, among other products. These drugs and pharmaceuticals are focused not only on human health, but animal health markets.

Medical Devices and Equipment involving a wide range of products, such as orthopedic/prosthetic implants, vascular stents and other implantable devices, bioimaging equipment, surgical instruments and supplies and dental instruments and materials, among others.

Research, Testing and Medical Laboratories involving more product development services to existing bioscience companies as well as product development activities of emerging bioscience companies that have not yet reached the market. These services include preclinical drug development, drug delivery systems, clinical trials contract research services, research and laboratory support and other applied research needs.

Bioscience-Related Distribution has become a highly specialized technical area to bring agricultural, drugs and medical devices to market. Among the specialized technologies required is cold storage, highly regulated product monitoring and advanced distribution applications.

Agricultural Feedstock and Chemicals involving products such as fertilizers, pesticides, corn and soybean oil, ethanol and biodiesel fuels, as well as biodegradable materials and biocatalysts synthesized from plant-based feedstock.

[8] Paula Stephan, How Economics Shapes Science, Harvard University Press, 2012, page 207.

research funding brings new income and wealth to the state and results in measurable statewide economic impacts. In order to conduct research, universities purchase goods and services from local suppliers and employ local residents. These purchases and wages are circulated in the state's economy to other businesses and workers who in-turn purchase goods and services from other local companies, who employ and pay wages and salaries to other workers through successive cycles of revenues and purchases. As a result, the total economic activity supported by university research is greater than simple R&D expenditures. It is estimated that the $578 million in university life science research translates into a total economic impact of nearly 8,000 jobs for Indiana's economy.

Indiana is also well-positioned in generating life science inventions. A direct measure of inventions in the life sciences is the number of patents awarded for life science innovations. Patents represent the way businesses, universities and individuals protect intellectual property (IP) that they invent. It is through patents that many companies are able to protect their innovations from being replicated. As Scientific American explains in its recent Worldview Scorecard on Biotechnology: "Biotechnology innovation – like that of many other businesses – relies on strong IP protection. In short, fewer innovators would take the risk of time and investment without some hope of capturing a return."[9]

From 2009 to 2013, Indiana inventors generated 3,420 life science-related patents. This places Indiana 12th in the nation, and in the same range as states such as Maryland, Ohio, Texas, North Carolina and Washington. Indiana's number of patents particularly stands out in the areas of surgical and medical instruments, drugs and pharmaceuticals and biotechnology.

The Challenges of Advancing Life Science Innovation Looms Large

Indiana's effort in life sciences research and patented inventions is just the start to realizing industrial returns from innovation. The discoveries that generate patents must still be developed into viable technology solutions and commercial products to meet the needs of customers in the marketplace. For the life sciences, this process of innovation is lengthy, complex, costly and uncertain.

Part of the challenge to life science commercialization is due to the need for clinical testing in humans and lengthy regulatory reviews before a new innovative medical product can obtain the approval by the U.S. Food and Drug Administration (FDA) to be introduced into the market. Still, even before a new medicine or device can reach this stage of clinical testing and FDA review/approval, there is considerable time and effort required for drug discovery or prototype development and preclinical testing. All of these steps take substantial capital investments. The full continuum for life science innovation, with likely sources of innovation capital at each stage, is set out in Figure 1.

[9] Scientific American, Worldview Scorecard: A Global Biotechnology Perspective, Special Report, 2014, page 36

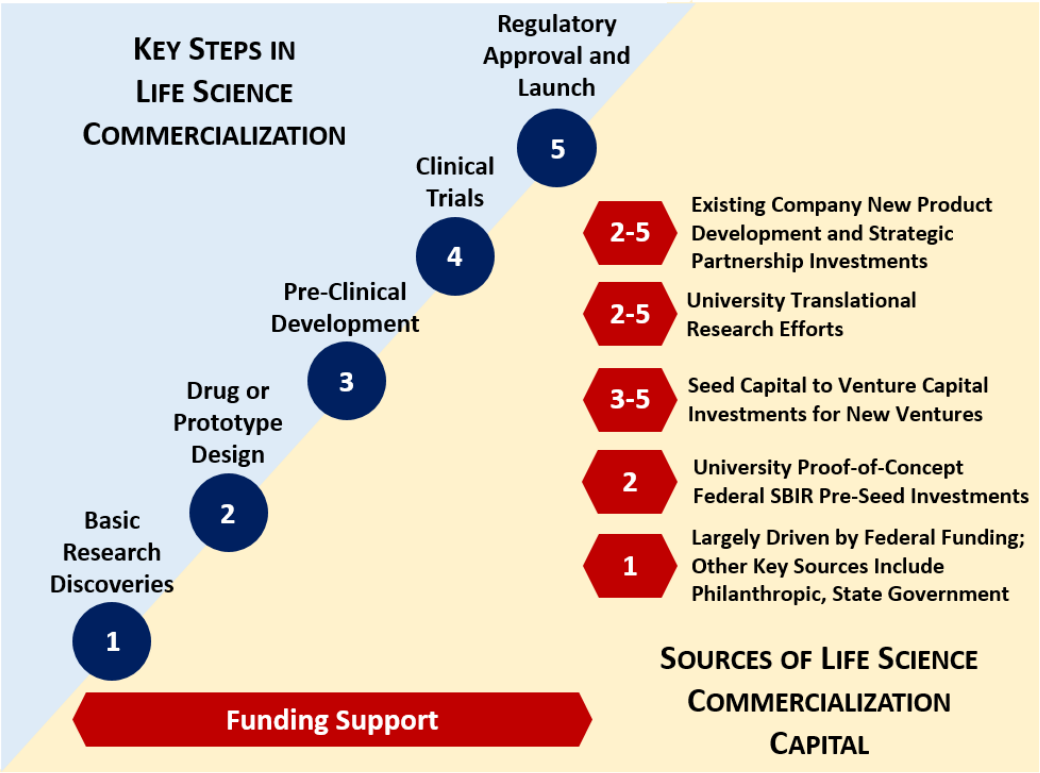

Figure 1. Life Science Innovation Continuum with Range of Sources for Innovation Capital

The Pharmaceutical Research and Manufacturers of America (PhRMA) reports a wide range of challenges to advancing life science innovation:[10]

- **The length from discovery to patient now exceeds a decade.** The time for a new medicine to complete the journey from initial discovery to patients is now between 10 to 15 years. This starts with up to three to six years to identify a lead compound, determine how best to design as a new medicine, and conduct initial testing on model organisms. It is then followed by nearly six to seven years to complete the full three phases of clinical trials required, and another six to ten months for FDA review, if all goes well.

  While not as arduous as new medicines, innovative medical devices also have a significant prototyping and preclinical testing period, which can require continued advances in the design and development of an innovative device to miniaturize, ensure it is biocompatible, or address human factors and surgical tools to enable it to be successful as a medical treatment.

- **The complexity of life science innovation is on the rise.** As medical innovators tackle more chronic and difficult diseases and medical conditions with advances in biological and other scientific knowledge, it is no surprise that the development hurdles mount as well. In particular, there is a growing focus on applying the molecular and genetic understanding of diseases to new drug and medical device strategies, such as immunotherapies and regenerative

[10] PhRMA, 2014 Profile of the Biopharmaceutical Research Industry.

approaches, as well as advancing more targeted medicine approaches that combine diagnostics and new medicines in ways that build upon an individual's specific genomics make-up and the promise of more personalized medicine. All of these scientific advances to address more complex diseases and medical conditions also place a challenge on the regulatory review process and how to measure the effectiveness of new medical approaches.

- **The costs of life science commercialization are continuing to increase.** PhRMA reports that the average cost to develop one new approved drug, including the cost of failures, has risen from an average of $140 million in the mid-1970s to $320 million in the mid-1980s to $800 million in the late 1990s to $1.2 billion in the early 2000s. This nearly 10-fold increase far outpaces the growth of inflation or overall economic activity.

- **And the uncertainty of success in life science commercialization is high.** For a new medicine entering clinical trials, there is only a 16 percent chance of being approved. Even for premarket approvals of innovative medical devices, the average approval rate over the past five years has been just under 72 percent.

  Beyond the uncertainties of FDA approval, marketing a new medicine or medical device to patients requires an even higher hurdle—reimbursement by insurance companies. Today, with the shift towards more health outcomes effectiveness research, it is harder for new medicines and medical devices to win reimbursement from insurance providers.

These challenges to life science commercialization have resulted in a difficult funding climate for advancing life science innovation. For larger, established life science companies, these challenges, combined with the loss of revenues for drug and pharmaceutical companies from expiring patents on major blockbuster drugs and the subsequent rise of competition from generics, is creating a climate where there are more cost constraints on research and development and a more focused effort on near-term results.

At the same time, venture capital funding in the life sciences is on the decline in recent years, falling in 2012 and 2013 despite the economic recovery. Life science venture capital must compete with alternative opportunities in social media and other information technology fields that offer high returns in the near-term and often face less risk. Not surprisingly, many life science venture capitalists have shifted their focus to only funding emerging life science companies once they are ready to enter clinical trials. The number of venture capital deals in the life sciences at the start-up/seed stage over the period 2009 to 2013 is well below those in follow-on rounds of venture capital funding.

There is also a significant change in the number and size of life science venture capital funds with a trend towards fewer and larger life science venture capital firms, which in turn is **making it much harder in today's environment to find early stage money than in the past.** The fewer and larger life science venture capital firms today are seeking larger initial investments, larger overall investments, and larger valuation requirements for investments—which speaks to the declining investment in early stage deals. Given the uncertainties of FDA regulatory processes and growing emphasis on cost effectiveness to gain

market entry, there is also a need for venture capital firms to have in place larger reserves for carrying a company much longer through its development. As a result, the number of venture capital investments is being ratcheted down in order to preserve funding for existing portfolio companies. The bottom line is that venture capitalists are no longer investing based on the technology, but now are considering much more heavily the stage of development, preferring to invest when the technology is ready for clinical trials, if not already advanced beyond them.

Further exacerbating the funding situation for life science commercialization is that federal National Institutes of Health (NIH) funding is on the decline. After reaching nearly $29 billion in 2010, with the addition of $4.6 billion in stimulus funding, NIH extramural funding has been at just over $22 billion for 2012 and 2013. The difficult federal budget situation is likely to continue to place significant constraints on the growth of NIH funding in the years ahead.

The result of this difficult funding environment for life science innovation by industry, venture capital and federal sources is leading to increased emphasis on research and development partnerships between industry and universities. Major life science companies, from Johnson & Johnson to Pfizer to Merck, all have growing partnership initiatives with universities.[11] Many of these efforts are focused on proof-of-concept funding to "de-risk" innovative discoveries and lay the groundwork for future licensing by life science companies.

NIH is also emphasizing collaboration. The Clinical and Translational Science Awards were a first step to create institutional homes within academic institutions able to help in advancing promising discoveries through clinical testing. Recently, NIH launched its newest institute, the National Center for Advancing Translational Sciences (NCATS), whose mission incorporates the Clinical and Translational Science Awards, and more broadly seeks to enhance the development, testing and implementation of diagnostics and therapeutics using innovative methods and technologies through partnerships. Furthermore, NIH launched, through its Foundation, a new Accelerating Medicines Partnership with ten biopharmaceutical companies and several non-profit/philanthropic organizations to develop new diagnostics and treatments in three disease areas – Alzheimer's disease, Type 2 Diabetes and autoimmune disorders of Rheumatoid Arthritis and Lupus.

Philanthropic foundations are also recasting themselves to advance innovative partnerships with universities and industry to advance life science commercialization. The Gates Foundation has been at the forefront of this movement, with focused solicitations seeking solutions to global health issues rather than simply advancing new research. Other foundations are following this lead, including the Juvenile Diabetes Research Foundation and Multiple Myeloma Foundation, which each have focused on

[11] Johnson & Johnson has established four Innovation Centers that emphasize proof-of-concept funding and a co-creation model approach; Pfizer has advanced Centers for Therapeutic Innovation involving master agreements with universities to collaborate on advancing promising discoveries; Bayer has advanced significant collaboration agreements with European and U.S. institutions as well as supported funding through a crowdsourcing effort that gives them a first look at new discoveries going through proof-of-concept funding; and Merck has over 50 university collaborations through its Merck Initiatives for New Targets (MINT) as well as recently establishing a California Institute for Biomedical Research that offers drug screening and animal models for new spin-off companies.

proof-of-concept and other commercialization funding to move discoveries through the innovation continuum and into clinical trials, with a combined 70 clinical trials now being supported by their efforts.

How Indiana is able to address these challenges to life science innovation is of critical importance to the state's future success in life science development. Sustaining and strengthening Indiana's life science industry competitiveness will require strategies to "work around" the resource challenged environment that currently prevails nationally.

LIFE SCIENCE INNOVATION CAPITAL: MEASURING ITS AVAILABILITY AND RESULTS

Given the close interplay in the life sciences among university research, technology commercialization, new venture development, and existing companies' new product development, life science innovation capital needs to be broadly defined. Capital, for purposes of this study, includes not only risk capital in all of its stages, but also federal and state grant funds, philanthropic investments, and other corporate and private support.

In light of the fact that the scope of the definition for life science innovation capital is quite broad, this assessment considers funding to advance:

- Life science research
- Technology commercialization
- Venture formation and growth.

To take stock of Indiana's position, a wide variety of sources have been tracked to account for the availability of life science innovation capital. These sources of life science innovation capital include those that are nationally available and those that are specific to Indiana-based activities found across universities, non-profit organizations and state government.

Included among the nationally available sources of life science innovation capital are:

- **Industry research expenditures in the life sciences.** Innovative new products in the life sciences are very dependent upon research discoveries and advances in scientific knowledge. This is the reason why the life sciences are the largest area of industry research and development in the U.S.

- **University research expenditures in the life sciences** from all funding sources, including federal, state, philanthropic, institutional and industry. This is the most comprehensive measure of university research and provides an examination not only for overall life science research, but by detailed fields of medical sciences, biological sciences, agricultural sciences, bioengineering and other life sciences, such as nursing, pharmacy and allied health.

- **National Institutes for Health (NIH) research funding** to Indiana universities, non-profit research institutions, hospitals and industry. While the vast majority of NIH research funding goes to universities and is captured in the university research expenditures, it is important to examine the level of NIH research funding since its rigorous peer-review makes it the "gold standard" for biomedical research, and has been a critical driver for advancing life science discoveries.

- **Federal Small Business Innovation Research (SBIR) awards** support technology commercialization for small businesses through a competitive awards process. Each federal

agency with extramural research and development (R&D) budgets that exceed $100 million is required to allocate 2.5 percent of its R&D budget to the SBIR program. These federal agencies develop specific technology topic areas that they are seeking small businesses to address. The SBIR program provides funding in phases, with the first phase being focused on validating the technical feasibility and the second phase on further product development and evaluating the commercialization potential. For NIH, phase one awards cannot exceed $150,000 and phase two awards cannot exceed $1,000,000.

- **Angel investor funding** represents start-up capital provided by high-net worth individuals, often retired entrepreneurs and executives, to bridge the gap between funding from friends and family and funding from formal venture capital funds. These angel investors also are an important source of management advice and contacts for entrepreneurs.
- **Venture capital funding** is a more organized form of risk capital investment in emerging new technology ventures. Typically, venture capital firms raise funding from pension funds, endowments, foundations and high-net-worth individuals to form a venture fund. This fund is then invested in the most promising emerging companies typically over the course of ten years. Venture funding is provided in multiple rounds, where at each point the emerging new technology venture must meet certain milestones to receive additional funds needed for growth. Venture capital investors take an active role in overseeing their investments, including taking a seat on the boards of directors, shaping a company's management team, and providing an ongoing source of strategic counsel on all aspects of the company's operations, marketing and financial management.

Indiana-based specific sources of life science innovation capital, meanwhile, reflect the growing funding support for technology commercialization and venture development primarily from philanthropic and state sources in a range of new mechanisms such as seed capital investment funds, fund of funds to invest in venture capital, state tax incentives for angel investment, and university proof-of-concept and early-stage company formation funding, including:

- **21st Century Research and Technology Fund**, which was created in 1999 by the General Assembly to help diversify the state's economy by encouraging development and commercialization of advanced technologies in Indiana. Initially, the Fund emphasized the creation of academic-commercial partnerships to promote research activity and stimulate the transfer of research and technology into marketable products, including matching funds to universities for specific research centers and commercialization activities. Over time, the Fund shifted to more company specific funding, particularly for matching grants for phase one SBIR funding and later stage commercialization financing. In 2005, the Fund was integrated as a part of the Indiana Economic Development Corporation (IEDC). Then, in 2010, the IEDC selected Elevate Ventures, a non-profit venture development organization, to manage the Fund subject to the approval of the IEDC Board.

- **University technology commercialization funding**, largely undertaken at Purdue University and Indiana University, the state's two top-tier public research universities. These university technology commercialization funding activities involve a range of activities to accelerate the commercialization of early-stage technologies into new ventures through modest investments combined with management assistance in technology assessment, market analysis and business planning.
- **BioCrossroads Seed Capital Funding**, which provides a source of early stage capital needed for life science businesses to commercialize and validate their technology and begin the road to growth prior to their ability to attract capital from venture capitalists. Multiple seed funds have been organized by BioCrossroads totaling $14.25 million from a variety of state, philanthropic and industry support.
- **Indiana's Life Science Venture Fund of Funds** is focused on bringing life science venture capital funding to Indiana. Through a FoF model, investments are made in a portfolio of venture funds with the assistance of a general fund manager, who helps select those venture funds best-suited for Indiana. The FoF approach mobilizes life science venture capital investors who are willing to consider investing in emerging life science companies located in the state. In 2003, BioCrossroads established the Indiana Future Fund to bring venture financing to Indiana, investing $73 million across six venture capital firms. In December 2009, BioCrossroads established the $58 million INext Fund as a successor fund to the Indiana Future Fund, with four venture capital firms receiving investments.
- **State of Indiana Venture Capital Investment Tax Credit**, a program that improves access to capital for fast-growing Indiana companies by providing individual and corporate investors an additional incentive to invest in early stage firms. Investors who provide qualified debt or equity capital to Indiana companies receive a credit against their Indiana tax liability of 20 percent of their investment, not to exceed $1 million. If the amount of credit exceeds the taxpayer's state tax liability for that taxable year, the taxpayer may carry over the excess credit for a period not to exceed the taxpayer's following five taxable years. A taxpayer is not entitled to a carry back or a refund of any unused credit amount. Only investments in Qualified Indiana Businesses first certified by the Indiana Economic Development Corporation are eligible for the credit.
- **The Indiana Biosciences Research Institute** (IBRI) was launched in 2013 as a statewide public-private partnership with an initial $25 million state commitment that has now been matched by corporate and philanthropic funders. The Institute is developing a novel operating model, with industry providing a major source of funding and defining the Institute's research focus to optimize commercialization opportunities. Industry executives from Eli Lilly and Company, Roche Diagnostics, Dow AgroSciences, Indiana University Health, Cook Medical and Biomet have been critical in advancing the Institute in partnership with BioCrossroads, state government and Indiana's research institutions. The Institute will initially focus on the most pressing global and

local interrelated human health issues: cardiovascular disease, diabetes, obesity and nutrition. These interrelated metabolic disorders are a major economic burden and a leading cause of death in the United States.

- **Philanthropic Funding** – Even though philanthropic funding is found across all components of innovation capital, it is important to recognize its significant contribution to advancing Indiana-based efforts. Therefore, in the analysis set out below, philanthropic funding is tracked by component of innovation capital.

For each source of innovation capital, there are outcomes and results that can assessed relative to the productivity and impact of that capital. These are highlighted below.

For life science research there are a variety of measures to track how research is leading to new discoveries and the creation of new intellectual property.

- Patents represent perhaps the most universal and easily identified form of intellectual property resulting from research and development activities by companies, universities and individuals. It is through patents that many companies are able to protect their innovations in products from being replicated. For the life sciences, patents are the primary means by which intellectual property is protected.
- For universities, the level of disclosures is another measure of university technology transfer activity and the most closely associated with direct research activities. A disclosure represents the first step in the identification of new intellectual property and is generated by a university faculty member (and sometimes by graduate and postdoctoral students doing research).

For technology commercialization, there are a variety of measures:

- University licenses to company
- University start-up companies
- Companies assisted by Indiana sources of technology commercialization capital.

For advancing venture development:

- Leverage – For emerging life science companies tapping Indiana sources of life science innovation capital, how much additional funding was leveraged or received in the form of additional outside capital investments where sources of Indiana funds would include university sources, 21st century fund, BioCrossroads seed investments, Fund of Funds).
- Breadth of Innovation System – Have the efforts by Indiana been reinforcing so that there is an ever increasing number of companies receiving assistance across the life science innovation continuum.

Bringing together all of these elements into an analysis of Indiana's situation offers important insights into the availability and performance of innovation capital over time in advancing life science industry development.

A Contrast of Times: Life Science Innovation Capital across Two Decades

The following assessment considers the record of success and evolving needs for innovation capital to advance life science innovation in Indiana over the periods:

- *1993 to 2002, corresponding to the decade before Indiana had undertaken a formal life science innovation capital strategy; and*
- *2003 to 2012, the first decade in which Indiana had a formal life science capital strategy, generally corresponding to the launch of the collaboration and investment programs of BioCrossroads.*

For each of these periods, the preliminary assessment considers:

- *The state of life science industry development in Indiana;*
- *The availability of life science innovation capital from a wide variety of sources; and*
- *The output resulting from access to life science innovation capital in terms of innovations generated, technology transfer and new companies formed.*

Analyzing these two time periods offers a rich contrast and a clear view on how far Indiana has come in advancing its life science innovation ecosystem.

The Decade Before 2003

This section examines status quo for the time period prior to the launching of a formal life science innovation capital strategy for Indiana.

Life Science Industry Development

The life science industry was already serving as a leading sector of Indiana's economy during the 1993 to 2002 period. As the December 2000 Battelle study for CICP, *Nurturing Central Indiana's Pillar Industries For 21st Century Midwestern Pre-Eminence,* noted:

> This [life science] industry is growing in employment, increasing jobs by 33 percent between 1989 and 1998. Central Indiana has a concentration rate [in life science industry employment] of 50 percent greater than the nation. It offers high quality, high paying jobs, averaging $78,600 per employee, 2.5 times better than the average for the

region. Almost half of the region's life science industry (45 percent) is represented by pharmaceutical preparations with 10,000 workers.

Central Indiana's life science industry is more manufacturing-intensive than the national sector as a whole including, besides pharmaceuticals, surgical and medical instruments and medical laboratories, all primarily export industries.

At the state level, by 2001, Indiana's life science industry already stood out as a leading economic driver. Life science employment in 2001 reached 52,442 across 1,522 business establishments. Compared to the national footprint of the life science industry, Indiana stood 56 percent higher in its industry concentration than the national average—making Indiana one of the most specialized states in life science industry activity.

In 2001, the largest and most specialized life science industry subsector in Indiana was drugs and pharmaceuticals, with 18,536 jobs and a level of industry concentration nearly three times the U.S. average. Medical devices and equipment was another large and highly specialized life science subsector, with employment of 12,862 and a level of industry concentration 71 percent higher than the national average. Finally, agricultural feedstock and chemicals stood out as a niche industry subsector in Indiana with employment of 4,777 and a level of industry concentration more than double the national average.

Availability of Life Science Innovation Capital

Outside of life science research funding, there was little life science innovation capital for technology commercialization or venture development over the 1993 to 2002 period in Indiana.

As Table 1 illustrates, across industry and universities, Indiana had nearly $10 billion in life science innovation capital for research. By comparison, the levels of life science innovation capital for technology commercialization and venture development were each under $100 million for the decade.

Towards the end of the 1993 to2002 decade, initial efforts were already underway to promote innovation capital in Indiana. One notable effort was the launching of the 21st Century Fund by the State of Indiana in 1999. A number of Indiana life science stakeholders interviewed by Battelle viewed this effort as a tipping point that began a wave of awareness of the need for investment capital for spurring innovation. A collateral benefit included enhancing intra- and inter-university partnerships helping to foster a more collaborative environment in which research strengths were leveraged. However, other Indiana life science stakeholders noted concerns regarding the initial emphasis of the 21st Century Fund on university research efforts and its lack of effectiveness in mobilizing private sources of innovation capital for Indiana.

It is also notable that beginning in 2000, Indiana-based foundations—led by the Lilly Endowment Inc.—began to provide support for research at Indiana universities to spur innovation in emerging areas such as genomics, bioinformatics and medical informatics, as well as initial support for new university efforts

related to the commercialization and formation of new ventures, such as the Purdue Discovery Park and Rose Hulman Ventures.

Table 1. Total Amount of Life Science Innovation Capital in Indiana, 1993 to 2002

Type of Life Science Innovation Capital	Specific Source	Amount of Funding	Share of U.S. Funding
Life Science Research	University Life Science Research Expenditures	$2,218,146,000	1.48%
	NIH Research Funding	$1,139,816,301*	1.0%
	Indiana-based Foundations	$155,000,000	n/a
	Industry Life Science R&D Funding (est.)**	$7,600,000,000	4.0%
	21st Century Fund for University	$20,300,000	n/a
Technology Commercialization F	NIH SBIR	$21,824,934	0.82%
	21st Century Fund for Industry	$8,200,000	n/a
	Indiana-based Foundations	$52,600,000	n/a
	University–own Sources	0	n/a
Venture Development	Angel Investor Funding	Not Known	n/a
	Venture Capital Funding	$80,060,000	0.16%

* The vast majority of NIH research funding goes to universities, and that funding is captured in university life science research expenditures. Still, it is important to note NIH funding separately since it is often considered to be the "gold standard" of biomedical research funding.

** Industry life science R&D was estimated from annual total R&D using share of life science patents to total patents as a proxy for industry life science activity.

In life science research funding, Indiana had a mixed record of growth and stood in the second tier of states in its funding level. It did well in overall university life science research funding, but did not keep pace with the growth in NIH funding.

In university research funding from all sources over the 1993 to 2002 period:

- Indiana started the period with $153,480 million in life science research funding and by 2002 had grown to $327,620 million, a gain of 113.5 percent.
- Indiana outpaced overall growth in total life science funding in the U.S. by a significant level, 113.5 percent growth versus 100.2 percent growth.
- Indiana had a stronger relative growth than the nation in every research field other than bioengineering, led by agricultural and other life science fields such as nursing, pharmaceutical sciences, and public health.
- Indiana ended the period ranked 22nd among all states in life science university research expenditures in 2002 compared to 25th in 1997, the first year data is available.

Table 2. Percentage of Growth in University Life Science Research, 1993 to 2002 (Total and by Field)

Reporting Entity	Total Life Sciences	Medical Sciences	Agricultural Sciences	Biological Sciences	Bioengineering	Other Life Science
Indiana	**113.5%**	**118.8%**	**101.1%**	**92.7%**	**78% (97-02)**	**224.2%**
U.S.	**100.2%**	**115.8%**	**57.2%**	**86.7%**	**266.3% (97-02)**	**107.5%**

Source: National Science Foundation, University Research Expenditures Database; Calculations by Battelle

In NIH funding to Indiana – the gold standard in biomedical research funding – which predominantly goes to universities, but also support hospitals, non-profit research organizations and industry:

- Indiana rose from $88 million to $167.3 million, a gain of 90.1 percent
- This fell short of the U.S. growth of 131 percent
- By 2002, Indiana's share of NIH funding reached 0.95 percent—it had been as high as 1.03 percent in 1995.

The 1993 to2002 period was marked by very limited venture capital funding to Indiana life science companies.

- Limited life science venture capital was available in Indiana over the 1993 to 2002 period, reaching just $80 million compared to $53.6 **billion** nationally.
- Only 14 companies in Indiana received venture capital funding over the 1993 to 2002 period, compared to 2,893 nationally. Only two venture capital transactions during this period totaling $8 million in equity involved some portion of investment by indigenous venture capital firms.
- Across all industries, Indiana generated just over $1 billion in venture capital funding across 84 companies. The life sciences comprised just under 8 percent of total state venture capital funding and under 17 percent of the companies receiving venture capital investments. There were only three total venture capital firms investing in life science companies headquartered in Indiana as of 1995, and none prior to that time. The number of Indiana venture capital firms investing in life science companies doubled by 2002 to six, but this still represented a very limited pool of locally-based venture resources and the vast majority of deals were financed through out-of-state sources.

Table 3. Total VC Investments in Indiana and U.S., 1993 to 2002

Metric	Indiana VC Investment				U.S. VC Investment		
	Life Science	All Industries	Life Science Share of Total	IN Life Science Share of U.S. Biosciences	Life Science	All Industries	Life Science Share of Total
Number of VC Deals	25	147	17.01%	0.31%	8,171	42,877	19.06%
Companies Invested In	13	84	15.48%	0.47%	2,754	17,337	15.89%
Investment Value in $Millions	80	1,040	7.70%	0.16%	50,349	353,329	14.25%

- Interviews with Indiana life science stakeholders reinforced the fact that Indiana missed out on life science innovation capital beyond the research stage. According to the stakeholders:
  - There were only a few angel investors and no organized sources of life science innovation capital available, which meant that companies had to seek capital on the coasts which was very difficult to do and often led to companies relocating.
  - More generally, the lack of innovation capital was just a symptom of a poorly functioning life science innovation ecosystem supporting the commercialization and formation of new life science businesses in Indiana:
    - There was a lack of networking to trusted sources of capital and value-added mentoring and business services for life science entrepreneurs and emerging companies, which limited their growth.
    - There was minimal connection between entrepreneurs and universities, and the business environment in the life sciences focused more on competition than on collaboration.
    - Overall, it was perceived that Indiana was not a friendly environment for entrepreneurs due to its risk adverse culture and the conservative nature of the small amount of capital that did exist.

Results/Impact of Life Science Innovation Capital in Indiana

Total life science patent activities in Indiana over the 1993 to 2002 decade, which are primarily generated by industry, reached 4,323 or 2.4 percent of the national patents. While a substantial number, the generation of life science patents in Indiana was below Indiana's share of national industry life science research funding of 4 percent as well as below Indiana's share of national industry life science employment of 3.5 percent.

In university technology transfer, though, Indiana performed relatively well to the national average over the period 1993 to2002. Indiana universities were slightly higher than the U.S. in disclosures, licenses and start-ups per $10 million of funded research compared to the U.S. average for all universities. Only in patent applications per $10 million of funded research did Indiana fall below the national average.

Relative to Indiana universities' share of national life science research funding of 1.48 percent for the 1993 to2002 period, Indiana outperformed its share of activity in university technology transfer measures, except in patent applications.

Table 4. University Technology Transfer Performance Metrics, Indiana Universities and U.S. Average for all Universities, per $10 Million Expenditures of Funded Research, 1993 to2002

Mode of Technology Transfer	Indiana	U.S. Average	Indiana Share of U.S.
Disclosures	4.30	4.25	1.77%
Patent Applications	2.35	2.94	1.40%
Licenses	1.78	1.28	2.42%
Start-Ups	0.12	0.11	1.86%

Source: Association of University Technology Managers, Annual Reports on University Licensing Activities; Calculations by Battelle

Of the investments in life science firms that were made during the time period, the results/impact were not very promising:

Leverage – Total innovation capital investments using state sponsored sources of $28.5 million, mainly in the form of 21st Century Fund awards, generated $9.9 million in additional /follow-on funding. Additional investment capital across all sources of aggregate leverage was made up of approximately 80 percent venture capital investments unconnected to Indiana state sponsored sources and 20 percent federal SBIR grant awards.

Breadth of Innovation System – Given the limited availability of Indiana-sponsored sources of funding, it was not possible to assist companies across the life science innovation continuum. Two of the 25 companies assisted by the 21st Century Fund (Endocyte and Optosonics) were successful in generating non-state sources of innovation capital involving SBIR and venture capital investment.

Summary of the Decade

The analysis of the 1993 to2002 decade reveals the chasm found in Indiana for life science innovation capital before Indiana's formal life science innovation capital strategy was launched with the formation of BioCrossroads. Life science innovation capital was concentrated at two ends of the innovation continuum—basic research and existing industry research and development. Quite pronounced was the lack of life science innovation capital to generate new life science businesses, to commercialize university research, and to partner with Indiana's existing life science industry base.

This condition points to how siloed life science development was in the 1990s and early 2000s in Indiana. Life science companies primarily relied on their own efforts to drive innovation and often viewed other industry players as competitors. Universities, for their own part, focused primarily on growing their research capacities at a time when exciting advances in biotechnology were taking hold as a new research paradigm. And new and emerging life science companies were largely ignored, not well-served by the business environment in Indiana, and not viewed as critical partners to universities and established companies in advancing innovation.

Still by the end of the period, a shift was evident:

- Creation of the Indiana Health Industry Forum focused on broad industry networking helped to define a more collaborative environment for the life science industry in Indiana.
- Launching of the 21st Century Fund in 1999 helped raise the awareness of the need for investment capital for spurring innovation.
- University technology transfer and commercialization of research discoveries began to take root.
- Growing appetite to advance technology-based entrepreneurship in the life sciences was taking hold, especially as the State of Indiana's organized venture firm, CID, demonstrated new information technology start-ups were possible in Indiana.

Case Studies From the Decade 1993–2002

In the decade 1993–2003, two examples of successful life science commercialization efforts stand out in demonstrating the potential for Indiana to advance its life science industry through innovation.

Cook Biotech

Cook Biotech is an example of how Indiana life science innovation can benefit Indiana's existing life science industry base. Established in 1995 following a Purdue University biomedical engineering research team's discovery of the unique properties of porcine small intestinal submucosa, Cook Biotech emerged as a world leader in regenerative medicine, developing advanced soft-tissue-repair products, including treatments for hernia, fistula and wound care. As it commercialized the technology from Purdue University, Cook Biotech was an early recipient of a Center of Excellence award from the 21st Century Fund in 1999 to lead a Consortium for Tissue Engineering of Living Replacement Vessels and Organs Starting from Natural Scaffold Biotechnology that involved several Indiana universities and health care providers – one of the earliest industry-university research partnerships focused on commercialization. Today, Cook Biotech operates as one of Cook Group's medical manufacturing companies.

Endocyte

Endocyte is an example of the potential for university discoveries to lead to a publicly traded life science company advancing innovative new drug products through the later stages of clinical trials – all the while creating deep roots in Indiana. Its technology is based on research published in 1991 by two Purdue researchers who were the first to discover a mechanism to deliver bioactive molecules inside cells. The company was formally launched in 1996 as a university spin-out after further years of continuing research advancement when it was ready to begin developing its prototypes and planning for its clinical testing. Then, beginning in the early 2000s the company received several rounds of venture capital that supported its development until it was able to go public in 2011 based on promising advances in clinical trials.

The most critical challenge for Endocyte was how to navigate bringing together the early-stage risk funding needed to bridge from a university-based technology project to a venture capital ready firm. One key to the success of Endocyte was the early support it received from Purdue University in its formation and development. Purdue University's support ranged from providing opportunities to further the initial research discoveries to agreeing to licensing terms that allowed the company to grow and raise capital to finding space to start and expand an emerging company. Along the way, Endocyte made use of federal SBIR funding and then received a critical Center of Excellence grant from the 21st Century Fund in 1999 that proved very helpful in furthering the development of its first prototype. In the early 2000's, Endocyte was one of the first Indiana-based life science companies to receive venture capital funding through three of the venture capital firms invested in by the Indiana Future Fund. Endocyte has raised over $500 million in outside capital.

Endocyte is now giving back to Indiana by growing its operations in the state, currently employing approximately 90 professionals, and entering into substantial research funding with Purdue University.

Life Science in the Decade Since 2003

This subsection highlights the changes that occurred after the formal life science innovation capital strategy for Indiana was launched by BioCrossroads in late 2003. The discussion focuses on the growth of the Life Science industry, the availability of innovation capital for the Life Science industry, and the results and impacts associated with greater Life Science innovation capital in Indiana.

Life Science Industry Development

Industry trends reflect that Indiana continued to grow in its life science industry employment at a pace faster than the U.S. over the time period of 2001 to 2012; however, since the recession, Indiana has had modest declines in its life science industry while the U.S. has remained largely flat.

- In the longer-term period of 2001 to 2012, Indiana's life science industry grew by 9.9 percent, outpacing national life science industry growth of 7.4 percent and serving to offset the longer-term declines in the total private sector industry.
- This longer-term growth in Indiana's life science industry was led by strong growth in the Medical Devices and Equipment subsector and Bioscience-related Distribution subsector, both of which well outpaced national trends for these subsectors. Research, Testing and Medical Laboratories also recorded healthy employment gains over this longer term period.

Table 5. Employment Changes in Life Science Industry and Subsectors, Comparing Indiana and U.S., 2001 to2012

Industry	Employment Change, 2001–2012	
	Indiana	U.S.
Total Private Sector	**-2.7%**	**1.0%**
Total Life Science	**9.9%**	**7.4%**
Agricultural Feedstock & Chemicals	2.4%	-1.5%
Bioscience-related Distribution	21.7%	6.3%
Drugs & Pharmaceuticals	-20.9%	-7.1%
Medical Devices & Equipment	46.5%	1.5%
Research, Testing, & Medical Laboratories	13.7%	28.1%

Source: IMPLAN, includes Puerto Rico in U.S. totals.

Still, the sharp decline in recent years in the Drugs and Pharmaceuticals subsector employment has held back Indiana's life science industry growth.

Since 2001, Indiana's Drugs and Pharmaceuticals subsector employment has declined by nearly 21 percent, outpacing the broader national decline in this subsector of 7.1 percent. This fall-off in the Drugs and Pharmaceutical subsector reflects changes in the health care market, global competition, and the

rise of generic drugs. It also reflects a broader trend in outsourcing of traditional pharmaceutical industry research activities to contract research organizations, which helps to explain one factor in the fast growth of the Research, Testing and Medical Laboratories subsector nationally.

In Indiana, a direct shift of workers from the Drugs and Pharmaceuticals subsector to the Research, Testing and Medical Laboratories subsector occurred with the strategic research and development collaboration in 2008 between Eli Lilly and Company and Covance, a leading contract research organization. This strategic collaboration resulted in the transfer of Lilly's early drug development campus in Greenfield, Indiana and about 260 Lilly employees to Covance, along with an agreement for Covance to provide Lilly with a broad-range of drug development services over the next ten years that limited the employment growth of Eli Lilly and Company that would have otherwise taken place. Since that time, Covance's operations in Indiana have continued to expand as it now serves a broader range of biopharmaceutical companies in Indiana and other states. Similarly, the sale of the Lilly Tippecanoe Laboratories manufacturing facility in Lafayette, Indiana to Evonik Industries AG in 2009 resulted in the transfer of 700 employees. It is likely this employment is now found outside of Drugs and Pharmaceuticals as Evonik is likely to be classified as a more general chemicals company.

Still, the Drugs and Pharmaceuticals subsector is a very important one in Indiana, and the broader structural changes taking place in this subsector add a level of caution in taking for granted this key subsector of the life science industry in Indiana. Employment declines in this subsector make the imperative of succeeding in life science innovation even more pressing if Indiana is to recover lost ground.

Availability of Life Science Innovation Capital

The total amount of life science innovation capital in Indiana rose sharply over the decade since 2003.

What stands out is the range of new types of life science innovation capital available, including:

- University sources of life science innovation capital through Purdue's Emerging Innovation Fund and Trask Funds, and Indiana University's Innovate Indiana Fund
- Seed capital available through BioCrossroads
- State support through the Venture Capital Investment Tax Credit
- State of Indiana, University Foundations, and Corporate fiduciary investment in FoF vehicles– Indiana Future Fund and INext Fund.

At the same time, industrial life science R&D funding is estimated to have also increased substantially reflecting both underlying growth in industry research funding in Indiana and increased share of life science patent activity.

As Table 6 indicates, these growing sources of funds reflect both the progress made by Indiana in advancing a more formal life science capital strategy and the growing awareness of the importance of having available life science innovation capital to advance industrial development.

Table 6. Total Amount of Life Science Innovation Capital in Indiana Over the 2003 to 2013 Period

Type of Capital	Specific Source	Amount of Funding	Share of U.S. Funding
Life Science Research	University Life Science Research Expenditures	$4,852,745,000	1.54%
	NIH Research Funding[(a)]	$2,102,108,944	0.93%
	Industry Life Science R&D Funding (estimate)[(b)]	$19,766,000,000 (2003 to2011)	6.9%
	21st Century Fund for Universities	$4,600,000	n/a
	Indiana-based Foundations[(c)]	$373,000,000	n/a
Technology Commercialization	NIH SBIR	$66,234,588	1.01%
	Federal Qualifying Therapeutic Discovery Program Grant	$10,293,530	1%
	21st Century Fund for Industry	$73,200,000	n/a
	Indiana-based Foundations[(d)]	$60,750,000	n/a
	University –own Sources	$2,250,000	n/a
Venture Development	Angel Investor Funding[(f)]	$94,031,825	n/a
	Venture Capital Funding Equity (not including acquisition deals)	$349,000,000	0.35%

(a) The vast majority of NIH research funding goes to universities, and that funding is captured in university life science research expenditures. Still, it is important to note NIH funding separately since it is often considered to be the "gold standard" of biomedical research funding.

(b) Industry life science R&D was estimated from annual total R&D using share of life science patents to total patents as a proxy for industry life science activity.

(c) $223 million from Lilly Endowment; $100 million from Regenstrief Foundation; $50 million Richard M. Fairbanks Foundation.

(d) $57 million from Lilly Endowment; $3.75 million from Richard M. Fairbanks Foundation

(e) Includes $770,000 Purdue Emerging Industry Fund and $1.4M Indiana Innovation Fund that went to emerging life sciences companies. Purdue's Trask Fund also accelerates life science technologies but goes to faculty members for proof-of-concept and no data was available to connect that funding to emerging life science companies.

(f) Based on certified State of Indiana venture capital investment tax credit of 20 percent to life sciences companies of $18,806,365 – which is the equivalent of $94,031,825 in total investment. It is assumed that these are angel investor investments since there are very few Indiana sources of formal venture capital.

Life science research funding is no longer in a strong growth trajectory, reflecting broader national trends.

In university research funding from all sources over the 2003 to 2012 period:

- Indiana grew by a more modest 53 percent, which was slightly off the national rate of 58 percent.
- Compared to the nation, Indiana fared better in the growth of medical sciences and agricultural sciences, but lagged substantially behind the national growth rate in biological sciences and bioengineering.
- Still for the most recent reporting year, 2012, Indiana declined in total university life science funding – falling from $580.7 million in 2011 to $577.9 million in 2012, while the nation held steady.
- Indiana started and ended the period ranked 21st in the nation among states in life science university research expenditures. Indiana had improved to 19th in the nation in 2004 before slipping back to 21st in 2012.

Table 7. Percentage Growth in University Life Science Research, 2003 to2012 (Total and by Field)

Reporting Entity	Total Life Science	Medical Sciences	Agricultural Sciences	Biological Sciences	Bioengineering	Other Life Science
Indiana	**53%**	**68%**	**33%**	**37%**	**61%**	**136%**
US	**58%**	**59%**	**29%**	**57%**	**181%**	**94%**

The same pattern held for NIH funding, which is current through 2013:

- Indiana's overall growth in NIH funding was well off from the prior decade and slightly lagged the national average over the 2003 to 2013 period – growing 2.6 percent in Indiana compared to 2.9 percent nationally.
- Since 2011, Indiana's NIH funding has fallen sharply, from $213.8 million in 2011 down to $187.1 million in 2013. This represents a decline of 12.5 percent for Indiana, more than double the decline nationally of 6.1 percent.

The decade since 2003 saw a strong increase in venture capital funding for the life sciences, and most notably, a shift in Indiana towards life sciences as a leading technology area for venture capital.

- **Indiana has made substantial gains in life science venture capital investment over the past decade.** Total venture capital investment in the life sciences in Indiana over the period 2003 to 2013 rose to $349 million across 100 deals and 39 companies. By comparison, over the 1993 to 2002 period, the level of life science venture capital investment was a mere $80 million, across 26 deals and 14 companies (see Table 8).

Indiana's strong rise in life science venture capital investment, albeit from a low level, has raised its visibility on the national scene, with Indiana comprising nearly 1 percent of life science companies receiving venture capital investments. Still, the share of national funding rose only to 0.33 percent

suggesting the total amount of equity going to life science companies in Indiana is well below the national average.

Table 8. Total Investments in Indiana and the U.S., 2003 to2013

Metric	Indiana VC Investment				U.S. VC Investment		
	Life Science	All Industries	Life Science Share of Total	IN Life Science Share of U.S. Biosciences	Life Science	All Industries	Life Science Share of Total
Number of VC Deals	100	232	42.24%	0.72%	13,575	51,687	26.26%
Companies Invested In	39	101	38.61%	1.00%	3,881	18,838	20.60%
Investment Value in $Millions	349	1,369	25.51%	0.35%	99,546	415,170	23.98%

- **Perhaps the biggest change for Indiana in the decade since 2003 was the broader mix of venture capital investors between in-state and out-of-state.** While in the 1993–2002 decade, there were hardly any in-state venture capital investors, the past decade has shown that growing in-state venture capital investors is complementary to generating more out-of-state venture capital investors (see Figure 2).

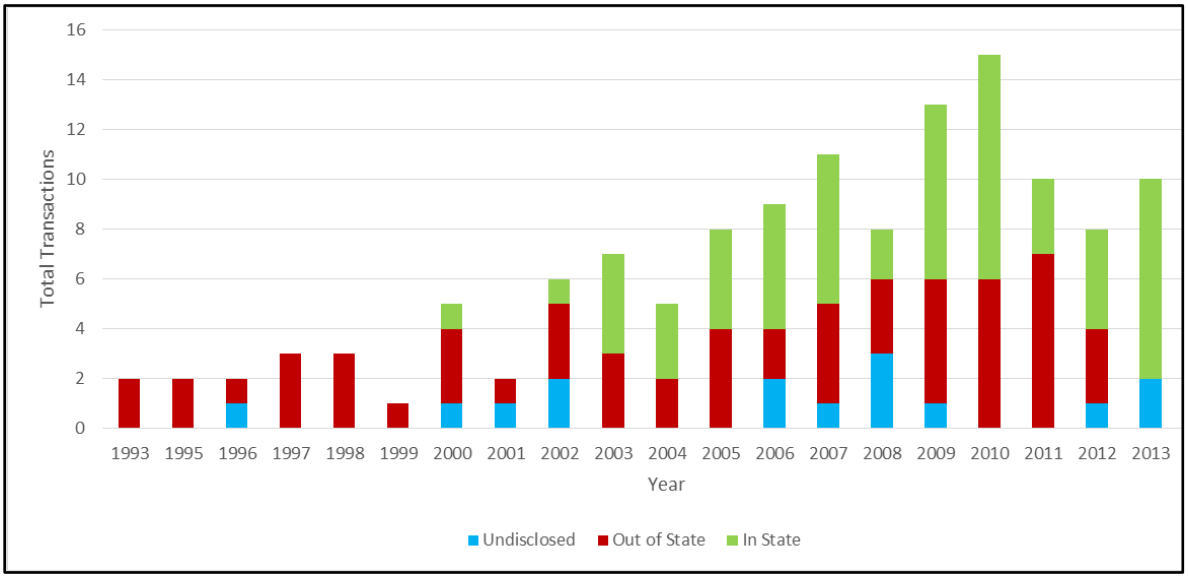

Figure 2. Indiana Life Sciences Venture Capital Investments by In-State and Out-of-State Sources, 1993 to2013

Note: No life science venture capital activity reported in Indiana for 1994.
Source: Thomson Venture One database.

Results/Impact of Life Science Innovation Capital in Indiana

Indiana made substantial gains in total life science patent activities in the 2003 to 2012 decade. Total life science patent activities in Indiana over the 2003 to 2012 decade rose to 7,345, which was 70 percent higher than the number of life science patents generated in Indiana in the earlier decade. The growth in life science patent activities in Indiana also rose in its national share to 3.18 percent in the 2003 to 2012 decade compared to 2.4 percent of the national patents in the prior decade. Still, the generation of life science patents in Indiana was below Indiana's share of national industry life science research funding for the 2003 to 2012 decade – which rose substantially to 6.9 percent – as well as below Indiana's share of national life science industry employment of 3.6 percent in 2012.

In university technology transfer, Indiana's universities continued to outpace the nation in relative performance over the period 2003 to 2012. The share of national activity in technology transfer measures was substantially higher in Indiana than its overall share of national life science research funding of 1.54 percent for the 2003 to 2012 period.

Table 9. University Technology Transfer Performance Metrics, Indiana Universities and U.S. Average for all Universities, per $10 Million Expenditures of Funded Research, 2003 to 2012

Mode of Technology Transfer	Indiana	U.S. Average	Indiana Share of U.S.
Disclosures	4.63	3.84	2.68%
Patent Applications	4.22	3.41	2.75%
Licenses	1.27	1.00	2.82
Start-Ups	0.15	0.11	2.82

Source: Association of University Technology Managers, Annual Reports on University Licensing Activities; Calculations by Battelle

Results for the decade since 2003 suggests that Indiana made substantial gains in the performance of its life science innovation capital in support of emerging life sciences companies:

- **Leverage** – 160 emerging life science companies received $154 million in Indiana sources of life science innovation capital for commercialization and venture funding that generated an additional $323 million, or a leverage ratio of $2.10 for every $1 in assistance.
- **Breadth of Innovation System** – There is a demonstrated connection across the life sciences innovation continuum with 45 of the 160 emerging life sciences companies receiving funding from more than one Indiana-based source of innovation capital. Most companies receiving multiple sources of funding relied on a combination of BioCrossroads seed investments, State of Indiana venture capital investment tax credits, and venture capital investments from Indiana-sponsored Fund of Funds.

Summary of the Decade

The decade since 2003 recorded a marked change and significant improvement in the overall life science innovation capital environment. Among the key highlights raised by Indiana life science stakeholders of the recent decade:

- **BioCrossroads' leadership and activities have helped to create a more vibrant ecosystem for life science innovation capital.** This includes spearheading the two life science fund of funds and the two life science seed-funds that enabled an ecosystem to take hold and evolve today.
- **Development of serial entrepreneurs/talent to provide the human capital for start-up endeavors.** A critical mass of individuals is now found in Indiana whom has been involved in high-growth technology start-ups, exited successfully, and is now moving forward with new ideas/investments either as mentors or as part of a management team. Plus, the level of sophistication/maturity of investment teams active within the Indiana-based funds has increased due to both experience and more national funds being attracted to participate through the Indiana FoF efforts.
- **Universities across the State of Indiana have become much more engaged in technology transfer, commercialization, and industrial partnering—now viewed as a key component of their mission.** The knowledge and understanding of innovation models has greatly deepened and become much more sophisticated at Indiana's research universities. Universities' attitudes towards industrial collaboration have evolved and such collaboration is now viewed as highly valuable by most. Universities have also developed much more of a focus on entrepreneurship and incubation activities, with much higher levels of due diligence and services being provided, which helps to create a pipeline of deal flow throughout the state.
- **The number of life science innovation capital sources has increased over the years through focused activities.** This includes the award and renewal of a NIH Clinical and Translational Science Award (CTSA) – the Indiana Clinical and Translational Sciences Institute (CTSI).
- **The formation of early stage investment vehicles** including organized Angel Networks through VisionTech and Halo Group, IU's Innovate Indiana Fund funded with proceeds from Angel Learning investment, and Purdue's Foundry Fund funded with proceeds from the sale of shares in Cook Biotech.
- **The continued evolution of the partnership between Clarian Health System and the IU School of Medicine, resulting in the formation of IU Health.** This deepening relationship is advancing an integrated academic medical model that allows for better coordination and opportunities in bench-to-bedside clinical and translational research.

Case Studies From the Decade 2003 to 2012

In the decade 2003 to 2012, a key theme that emerges is the continuing engagement of serial entrepreneurs in Indiana to lead life science innovation through new company formation.

Marcadia Biotech

Marcadia was founded in 2006 based on research conducted at Indiana University by Richard DiMarchi, who spent over 20 years with Lilly Research Labs rising to Group Vice President for Biotechnology and Product Development. The company was led by Fritz French, who served as Vice President for Global Marketing for Guidant Corporation's Vascular Intervention Division after more than a decade at Eli Lilly and Co.'s Medical Devices and Diagnostic Division. Marcadia focused on developing therapeutic drugs for the treatment of diabetes and obesity. After raising $16 million in venture capital funding, mostly from California-based 5AM Ventures and Seattle-based Frazier Healthcare, Marcadia was acquired by Roche for $287 million in late 2010 – another success story in advancing Indiana-based life science innovation.

Richard DiMarchi and Fritz French then teamed up in 2012 to create Calibrium, a new life science company focused on developing treatments for diabetes based on research from DiMarchi's Indiana University lab. This effort includes a company-sponsored research agreement with Indiana University to fund further research in DiMarchi's lab. Calibrium also acquired early-stage investment funding from two of the venture capital firms that backed Marcadia – 5AM Ventures and Frazier Healthcare. 5AM Ventures is now part of the second Indiana-based Fund of Funds, INext, investing in life science venture capital firms.

BioStorage Technologies

BioStorage is a home-grown Indiana-based company providing biorepository and sample management solutions for the life science industry with a broad global reach, including strategically located biorepository operations outside the U.S. in Germany, Singapore and China. It was founded in 2002 by Oscar Moralez, who had been recruited to Indiana in 2000 by Covance from Colorado, where he led a start-up venture involving a consortium of hospital laboratories and Mayo Medical Laboratories. In launching BioStorage, Moralez was able to raise more than $11 million in angel investor financing and venture capital financing from 2002 to 2007 and served on its management team through these early formative years.

In 2008, Mr. Moralez choose to stay in Indiana to form his next venture, a management company to facilitate angel investments, now known as VisionTech Partners, LLC. (formerly Stepstone Business Partners). Moralez is now able to share his experience and expertise in starting and funding early stage life science companies across Indiana. Among the emerging life science companies in Indiana that have been served by Moralez include Diagnotes, Fast BioMedical, SonarMed and Orthopediatrics.

Recapping the Differences Between the Decades

The formal life science innovation capital strategies implemented in Indiana have made a considerable difference in the innovation environment and are generating a marked change from the decade before these efforts were undertaken. The evidence suggests just how striking these improvements in Indiana's life science innovation activities have been.

Indiana took a major step forward over the last decade in generating additional sources of life science innovation capital from nationally available sources.

- In the decade before 2003, the vast majority of life science innovation capital in Indiana came from university life science research and industry research. Both technology commercialization funding and venture development funding were quite limited.
- In the decade since 2003, while industry and university research remained quite substantial, there was a substantial rise in technology commercialization and venture development funding.

Table 10. Comparison of Funding Levels for Innovation Capital in Indiana for the Decades 1993 to 2002 and 2003 to 2012/13

Type of Life Science Innovation Capital	Specific Source	Amount of Funding	
		1993 to 2002 Period	2003 to 2012/13 Period
Life Science Research	University Life Science Research Expenditures	$2,218,146,000	$4,852,745,000
	NIH Research Funding	$1,139,816,301	$2,102,108,944
	Industry Life Science Research (estimated)*	$7,680,000,000	$19,766,000,000 (2011)
Technology Commercialization	NIH SBIR	$21,824,934	$66,234,588
Venture Development	Angel Financing**	Not Known	$94,031,825
	Venture Capital Funding	$80, 133,000	$365,339,000

* Industry life science R&D was estimated from annual total R&D using share of life science patents to total patents as a proxy for industry life science activity.

** Based on certified State of Indiana venture capital investment tax credit of 20 percent to life sciences companies of $18,806,365 – which is the equivalent of $94,031,825 in total investment. It is assumed that these are angel investor investments since there are very few Indiana sources of formal venture capital.

The gains made by Indiana in life science innovation capital in the decade since 2003 have generally outpaced the nation. Indiana recorded higher growth than the nation in university life science research, industry life science research and venture capital funding. In particular, the **considerable rise in Indiana of life science innovation capital** for technology commercialization and venture development stands

out. One area of concern, though, is in NIH research funding where Indiana lagged slightly behind the national growth.

Table 11. Comparison of Growth in Innovation Capital from National Sources for Indiana and the U.S., for the Decades 1993 to 2002 and 2003 to 2012/13

Type of Life Science Innovation Capital	Specific Source	Percentage Change from 1993 to 2002 to 2003 to 2012/13 Periods	
		Indiana	U.S.
Life Science Research	University Life Science Research Expenditures	119%	110%
	NIH Research Funding	84%	98%
	Industry Life Science Research (estimated)*	157.4%	48%
Technology Commercialization	NIH SBIR	203%	147%
Venture Development	Venture Capital Funding	336%	98%

*Industry life science R&D was estimated from annual total R&D using share of life science patents to total patents as a proxy for industry life science activity.

The increased engagement of Indiana sources of assistance in technology commercialization and venture investment stands out for the last decade compared to the decade before 2003. In technology commercialization, the last decade has advanced a broad range of funding sources that reached well over $100 million targeted on advancing life sciences innovation through the initial stages of commercialization and support for emerging life science companies. In venture capital investments, significant progress has been made with regard to the level of funding for life sciences companies in Indiana through the efforts of Indiana sources of assistance.

What also stands out over the past decade is the role that the Indiana-based philanthropic foundation community has continued to play as a critical source of life science innovation capital. The Indiana-based philanthropic foundation community has provided an important source of funding both for advancing life science research capabilities as well as in supporting the organizations engaged in technology commercialization.

Indiana's efforts in advancing life science innovation capital in the decade since 2003 have generated measurable results:

- Significant leverage has been achieved for those companies receiving Indiana sources of life science innovation capital, especially when compared to the prior decade. An additional $2.10 for every $1 of funding through Indiana sources of life science innovation capital was achieved over the past decade since 2003 compared to a meager $0.35 of leverage for every $1 of funding in the prior decade.
- Not only are there considerably more companies assisted through Indiana sources of life sciences innovation capital in the decade since 2003 (160 companies compared to five in the

previous decade), but there are increasing linkages across the sources of innovation capital in the most recent decade.

Table 12. Comparison of Life Science Innovation Capital From Indiana Sources, for the Decades 1993 to 2002 and 2003 to 2012/13

Type of Life Science Innovation Capital	Specific Source	Amount of Funding	
		1993–2002 Period	2003–2012/13 Period
Life Science Research	21st Century Funds for University Research	$20,300,000	$4,600,000
	Indiana-based Foundation Support	$155,000,000	$373,000,000
Technology Commercialization	21st Century Fund for Life science to Industry	$8,200,000	$73,200,000
	Public University Sources to Emerging Life Sciences Companies	$0	$2,250,000
	Indiana-based Foundation Support	$52,600,000	$60,750,000
Venture Development	Angel Investor Funding*	Not Known	$18,806,365
	Venture Capital Funding **	$0	$59,750,000

* In the 1993 to 2002 period, there was no State of Indiana venture capital investment tax credit to provide incentives and angel investments are difficult to track. Since 2003, the State of Indiana venture capital investment tax credit to life sciences companies totaled $18,806,365. It is assumed that these are angel investor investments since there are very few Indiana sources of formal venture capital.

** $14.75 million from BioCrossroads seed funds and $45 million from the Indiana Future Fund were invested in Indiana emerging life science companies.

More broadly, the overall performance of Indiana across the continuum in generating innovations appears to be on the rise. Not only has Indiana raised its performance in advancing commercialization across most measures, but its share of national activity in many key measures of commercialization performance has also improved including overall patent generation, venture capital and university technology transfer.

Most importantly, the increase in life science innovation capital has enabled the life science industrial base of Indiana to remain highly concentrated at a time in which the industry sector has experienced significant changes. This is keenly observed in light of the recent impact of the pharmaceutical industry's loss of employment in Indiana. Recognizing that the industry is subject to national and global market pressures and changes in regulations, it is critically important that a state's industrial base remain nimble and flexible to respond to ever mounting pressures and changes—highlighting even further the importance of innovation capital in the decade to come.

Table 13. Indiana Life Science Performance Across Innovation Continuum over the Periods 1993 to 2002 and 2003 to 2012/13

Sources	Measure	1993-2002 Period		2003-2012/2013 Period	
		$ Millions	Share of U.S.	$ Millions	Share of U.S.
Life Science Research	University Disclosures per U.S. $10M*	4.30	1.77%	4.63	2.68%
	University Patent Applications per U.S. $10M	2.35	1.40%	4.22	2.75%
	Total Indiana Life Science Patents	4,323	2.36%	7,345	3.18%
Technology Commercialization	University Licenses per U.S. $10M*	1.78	2.42%	1.27	2.82%
	University Startups per U.S. $10M*	0.12	1.86%	0.15	2.82%
Venture Development	Angel Financing**	n/a	n/a	94.0	n/a
	Total Life Science Venture Investment Equity (not including acquisition deals) ($M)	80.1	0.16%	349	0.35%

* University technology transfer measures encompass all technology areas, though life science research is well over 50 percent of university research activities.

** Based on certified State of Indiana venture capital investment tax credit of 20 percent to life sciences companies of $18,806,365 – which is the equivalent of $94,031,825 in total investment. It is assumed that these are angel investor investments since there are very few Indiana sources of formal venture capital.

FUTURE NEEDS AND EMERGING TRENDS SHAPING LIFE SCIENCE INNOVATION CAPITAL

Indiana has clearly accomplished much with its formal strategies to advance life science innovation capital. The last decade has seen Indiana forge its own unique solutions to the challenges of increasing life science innovation capital needed to fuel the growth of the life science industry. This includes recent initiatives in Indiana to promote collaborations with industry and universities – such as the newly launched Indiana Biosciences Research Institute and the ongoing Indiana Clinical and Translational Sciences Institute. Indiana has also been successful in generating local funding for early stage investment, engaging Indiana's own angel investors, corporate funding arms, the philanthropic community and state government, while also building broader connections and relationships with national venture capital firms for follow-on funding to enable the long-term success of Indiana's high growth-potential, emerging life science companies.

At the same time, however, new challenges to advancing life science innovation are emerging. The convergence of three key challenges is making early stage investments a larger and more critical gap and creating the need for new interventions to further collaborative research and development between universities and industry. These three key challenges are:

- *Increasing pressure on existing large biopharmaceutical and medical device companies to generate greater returns from R&D investments and pursue partnership opportunities to de-risk promising new therapeutics and devices;*
- *The shift in the capital markets to fewer, larger venture capital firms that in turn are making investments in later stage, less risky ventures; and*
- *The decline in federal funding for basic research.*

Thus, it is essential to step back and ask how Indiana can best compete in this new environment.

How Indiana Can Compete for Future Growth in Life Science Development

The analysis of life sciences development in Indiana points to Indiana's existing industrial base as the state's most significant life sciences asset. As noted throughout this report, the one constant over the past 20 years in Indiana's life sciences development has been the size and diversity of the state's life science industry base. This significant industry base is hard for other states to replicate. It provides critical knowledge and access to life science markets, and in itself, is a major driver of innovation investments. Over the past decade, this industry base has increased its focus on innovation as demonstrated by strong growth in industry-led life science research and development and substantial gains in total life science patent activity in Indiana, along with the growing base of innovation-driven emerging life science companies fueled by key new mechanisms such as BioCrossroads' Seed funds, Fund of Funds, and the state's venture capital investment tax credit.

By contrast, Indiana's university and academic medical center activities, while offering many partnership opportunities to work with industry, remain ranked (according to NIH funding statistics) in the middle quintile among life science research institutions in the nation. Indiana will not match the life science, government funded, basic research funding levels of top life science states such as Massachusetts, Maryland, or North Carolina. However, even the leading research institutions across the nation are looking at new strategies for growth in today's fast changing life sciences innovation environment. Growth in the life sciences depends increasingly on the ability of these research universities to pursue more translational research bringing together "bench to bedside" activities and partner with industry to de-risk advances in basic research for commercialization and new product development. Thus, research universities across the nation need to become anchors for new initiatives with industry involving collaborative and multi-disciplinary research centers, proof of concept centers, and more user-inspired research where clinical needs and challenges form the focus of research activities.

Indiana does have a unique advantage in building a more robust "bench to bedside" model due to the strengths of its hospital systems. IU Health works in a highly active partnership for advancing basic, translational, and clinical research with IU School of Medicine and operates a suite of research centers dedicated to advancing biomedical research and development. These include:

- IU Health Arnett Clinical Research
- IU Health Ball Memorial Medical Research
- IU Health Goshen Center for Cancer Care
- IU Health Methodist Research Institute
- IU Health Methodist Cancer Center Research Group
- IU Health Proton Therapy Center Research
- IU Simon Cancer Center.

Beyond the IU School of Medicine/IU Health partnership other Indiana hospitals involved in significant research activities (often in collaboration with IU Health/IU School of Medicine) include the Roudebush VA Medical Center, St. Vincent's Health/Peyton Manning Children's Hospital, and Wishard Memorial Hospital (now part of Eskenazi Health). For example, the Roudebush VA Medical Center was involved in $26 million in research activities in 2012 including $11 million in VA research funding.

Indiana's hospitals are of critical importance to advancing new treatments and technologies through their active participation in clinical trials. Ranging from Phase I, investigator led trials within the IU academic medical system, through participation by hospital staff in multi-center Phase III and IV trials, Indiana's health care providers have shown a desire to provide patients with the latest treatments available. This has resulted in 13 new clinical trials since the start of the year and 30 new trials since June of 2012 bringing the total number of currently active clinical trials at Indiana hospitals to 381.

Indiana has started a number of leading initiatives to advance these new partnerships with industry through the Indiana Biosciences Research Institute and the Indiana Clinical and Translational Sciences Institute. These initiatives must continue to be advanced, while further mechanisms to advance collaboration are fostered.

Indiana's efforts to catalyze sources of innovation capital are modest and targeted at the early stages of commercialization and new firm formation. Indiana is not a money center location with major national investment banks and venture capital firms, such as Boston, San Francisco, New York or Chicago. Rather than leveraging an industry strength in financial services, Indiana must seek to create a targeted focus on ensuring sufficient sources of capital to enable innovation to occur and then facilitate its connection to national sources. Indiana must also ensure continuity of the risk capital sources that it does have, ensuring that the momentum gained to date through the pre-seed funds and the venture capital Fund of Funds continues by capitalizing additional rounds of funds.

Despite the successes of Indiana's efforts in promoting investment by angel investors, seed capital investment and engaging non-state resident venture capital, there is a need to further increase early stage pre-seed and seed investments to advance innovation.

Specific Steps Recommended for Indiana

Based on the global market challenges, analysis of the current state of Indiana's innovation ecosystem, and guidance from Indiana's stakeholders and national innovation capital experts, five broad recommendations emerge regarding the critical steps in a future innovation capital strategy for Indiana:

- **Ensure there is a sufficient level of indigenous early-stage life sciences innovation capital to generate high quality deal flow of emerging life sciences companies in Indiana and facilitate connections to follow-on national venture capital funding.**
- **Improve development of entrepreneurial talent to lead life sciences innovations.**

- **Enhance the commercialization of university research discoveries and technology advances through initial technology and market validation activities.**
- **Enable Indiana to stand out as a global leader in university-industry partnerships to advance translational, "use-inspired" research.**
- **Leverage Indiana's existing life sciences industry strengths to further life sciences innovation within Indiana.**

Each of these recommendations is discussed below. Figure 3 places the recommendations in the context of existing resources to advance life science innovation capital in Indiana. A summary of the specific actions to be considered with each of these five recommendations is set out in Table 14, along with the wide range of stakeholders needed to help in the advancement and implementation of these recommendations.

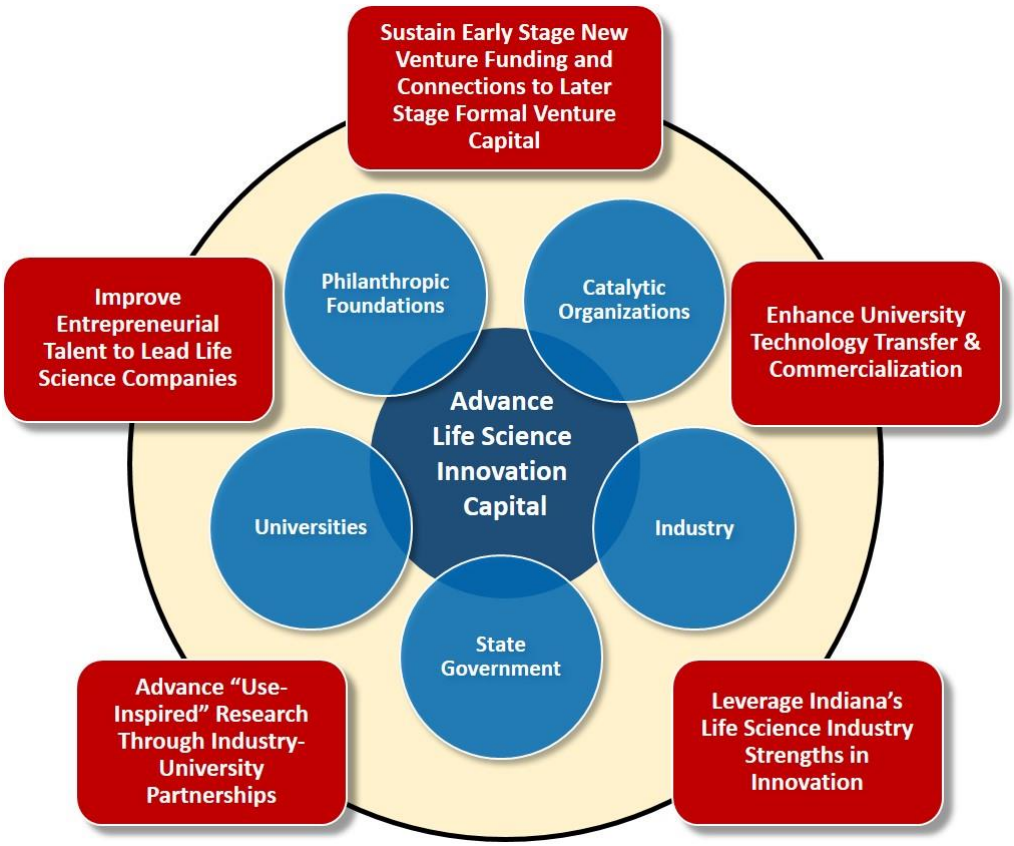

Figure 3. Depiction of Key Recommendations

Table 14. Specific Actions to be Considered and Stakeholder Engagement Needed for Each of the Five Proposed Recommendations

Proposed Recommendations	Specific Actions to be Considered	Key Stakeholders
Sustain sources of indigenous early-stage life sciences innovation capital and connections to follow-on national venture capital funding.	• Continue to provide local seed capital funding in Indiana • Enhance the tax incentives for early stage investment • Support "smart" angel investing • Continue support of University-sponsored Seed Funds • Reinvent the 21st Century Fund to focus on proof-of-concept/prototype development • Capitalize a third Fund-of-Funds for connections to sources of follow-on venture capital investments	• BioCrossroads • State Government • Angel investors • Universities • Indiana institutional investors
Improve Life Sciences Entrepreneurial Talent Development	• Establish a life sciences entrepreneurial development effort involving mentoring by serial entrepreneurs and growing next generation of talent among top graduate students	• BioCrossroads • Universities and Colleges • Philanthropic Foundations • State Government • Industry
Enhance Technology Transfer and Commercialization	• Increase technology and market validation activities at universities • Examine feasibility and benefit of separate technology transfer office at IU School of Medicine • Advance closer alignment to health care system	• Universities • Health Care Systems • State Government
Advance "Use-Inspired" Research	• Advance the ongoing activities of the Indiana Biosciences Research Institute and Indiana Clinical and Translational Sciences Institute/SPARC • Pursue implementation of additional university-industry collaboration opportunities set out in *Advancing Indiana's Life Sciences Competitiveness and Strategic Collaborations* in Health Informatics, Global Health and Plant Improvement	• Industry • Universities • Philanthropic Foundations • State Government • BioCrossroads
Leverage Indiana's Existing Industry Strengths	• Enhance the incentives for industry innovation in Indiana, including modifying the state's R&D tax credit to be refundable for small companies and adding a larger incentive for industry research costs with universities and other Indiana companies.	• State Government • Industry • BioCrossroads

Recommendation: Ensure there is a sufficient level of indigenous early-stage life science innovation capital to generate high quality deal flow of emerging life science companies in Indiana and facilitate connections to follow-on national venture capital funding.

Regional proof-of-concept and seed stage investment approaches have proven to be critical to ensuring the deal flow of high-quality investment opportunities in early-stage companies, by bringing forward promising discoveries and technology advances through the initial technology commercialization and firm formation stages. Indiana is an excellent case study in the importance of these early stage investments in advancing life science innovation. Emerging trends in innovation capital are making it even more imperative for having locally-based funds for technology commercialization and new firm formation. These locally-based funds help in identifying promising discoveries and technology advances, providing the initial funding to validate these opportunities, supporting the formation of new life science ventures and providing the on-the-ground capacity to support these new life science ventures and facilitate their connection to outside venture capital.

While this report clearly shows that a significant level of innovation capital was invested in the last decade, sustained investment is required. Throughout the field and interview-based portions of our research, there was broad consensus on the need for active efforts in Indiana going forward in bridging the funding gap between university research discoveries and the first formal rounds of venture capital funding. Among the efforts that generated broad support were:

- Continue the efforts of BioCrossroads to provide seed capital and find ways to network life science start-ups with national and regional sources of venture capital.
- Create more tax incentives for early stage investment. One step to make the Indiana venture capital investment tax credit more competitive would be to increase the level of the tax credit. Indiana's existing venture capital investment tax credit is at 20 percent, while in Wisconsin it is 25 percent, Arizona 35 percent and Maryland 50 percent. Another feature to consider is to exempt capital gains income earned from investments eligible for the venture capital investment tax credit, which Arizona recently enacted to complement its venture capital investment tax credit.
- Ensure the quality of opportunities for "smart" angel investing through sound due diligence, increased access to mentoring, more rigorous proof-of-concept, etc.
- Continue existing university-sponsored seed funds and faculty engagement initiatives, such as Indiana University's Innovate Indiana Fund and Spin Up program and Purdue University's Foundry, as sources of critical early-stage funding for university-based innovation.
- Reinvent the 21st Century Fund to be more active in advancing life science innovation as an available source for proof of concept/prototype development and other early stage capital.

Complementing the focus on early stage innovation capital, Indiana needs to continue to ensure follow-on venture funding, building on the momentum gained by the FoF model by capitalizing a third Fund of

Funds when INext is almost drawn down. Consideration should be given to continue to evolve the model based on lessons learned from the first two funds. Suggestions would include ensuring that the fund is return-driven and has guidelines in place to help ensure that capital partners have a meaningful local presence. It will also be important to consider the mixture of mid-sized versus larger-sized funds to catalyze the development of indigenous early-stage capital and leverage the relationship that regionally-based funds have with the entrepreneurs, the angel investment community, and the research institutions.

Recommendation: Improve the entrepreneurial talent in Indiana to lead life science innovations.

Indiana has extended significant resources and efforts to raise the level of innovation capital available to emerging life science opportunities. However, the innovation ecosystem is much more than simply access to financial capital. It is equally driven, if not more so, by human capital in the form of the management teams with the requisite talent, experience, business maturity, and sophistication to lead life science innovation as it is advanced by new firm formation. Greater focus and programmatic efforts need to be put in place to mentor entrepreneurial talent, facilitate the connections to seasoned management talent and to grow the next generation of entrepreneurial talent from among top graduate students in the sciences, medical, engineering and management schools in Indiana.

In the current funding environment, the creation of high quality start-ups is of even greater importance for generating life science innovation capital. While the universities are improving, they cannot do it alone. Many high-quality, life science innovation opportunities are falling short as they lack sufficient entrepreneurial management involvement. Continuing to connect Indiana serial entrepreneurs to opportunities in life science innovation, as well as building a stronger talent pool of entrepreneurial talent for the future, is critical.

BioCrossroads should lead the effort, with state, philanthropic, and industrial funding support, to bring more focus, programmatic activity, and funding to build a more robust entrepreneurial network. Best practice across the country points to the importance of having key entrepreneurial development services such as vetting business plans, mentoring by serial entrepreneurs, and establishing strong networks with qualified professional service providers and qualified investors. Typically, states and regions have non-profit organizations take on these critical entrepreneurial development services, as is done in San Diego, Oklahoma, Iowa, Arkansas, and across Ohio through its Entrepreneurial Signature Program network. Profiles of two of the longest standing and most successful entrepreneurial development programs – San Diego CONNECT and Oklahoma's i2E -- - are featured below.

Examples of Leading Entrepreneurial Development Programs: San Diego CONNECT and Oklahoma i2E

San Diego CONNECT was originally founded in 1985 by the University of California (UC) San Diego, the San Diego Economic Development Corporation, and private sector business leaders, to stimulate the commercialization of science and technology discoveries from the local research institutions and facilitate the creation and growth of technology clusters in San Diego. It continues to focus on mentoring entrepreneurs, fostering strategic partnerships between start-ups and established companies, providing in-depth entrepreneurial training, and introducing early-stage companies to the world of venture-capital finance. CONNECT has assisted in the formation and development of more than 2,000 companies since its launch in 1985and has assisted over 1,000 companies in funding their operations. Over 300 companies have graduated from the program and raised more than $700 million in funding.

Another longstanding and successful effort in advancing assistance to technology entrepreneurs can be found in Oklahoma, where a non-profit organization, Innovation to Enterprise (i2E), serves as the outsourced manager of the Oklahoma Technology Commercialization Center. Among its services to entrepreneurs is active vetting of business plans, having on staff serial entrepreneurs to serve as "venture advisors" who collaborate with and mentor entrepreneurs, funding pre-seed and seed investments, offering vouchers to a network of "qualified" professional service providers, advancing strong relationships with angel funders and helping create angel investor funds. The results of i2E have been impressive with over 580 companies served since i2E's formation in 1998. In addition its initial $20.9 million in pre-seed and seed investments has been leveraged in to $478 million in private investment. i2E assisted companies have experienced 31 percent job growth in FY2013 with an average wage of $73,395 compared to 1.3 percent job growth statewide and an average wage of $38,250.

Recommendation: Enhance the commercialization of research discoveries and technology advances through initial technology and market validation activities.

As a result of the uncertainty in the life science market caused by regulation and health care reform, comparative advantage will be found by those who are able to "de-risk" technology to make it more attractive to investors. This will require building stronger public-private collaborations in technology development efforts, preclinical development and initial clinical testing. This approach has been started in Indiana through the Indiana Clinical and Translational Sciences Institute as well as the initiatives of Orthoworx, but an increased focus on these approaches will be important. In addition, over the last decade, both Purdue University and Indiana University have taken important steps to improve their capabilities to commercialize university life science technologies through modest investments combined with management assistance in technology assessment, market analysis and business planning.

The earlier recommendation for reinventing the 21st Century Fund as a source of proof of concept/prototype development funding would be an important step to ensuring funding of these activities. This new orientation for the 21st Century Fund could catalyze additional mechanisms within

the academic community to enhance technology transfer and commercialization efforts, through increased technology and market validation activities.

In enhancing technology transfer, the experience of Battelle Technology Partnership Practice in working with and benchmarking leading U.S. research universities suggests it is also important to continually be refining university technology transfer policies and operations to be more business-friendly in light of changing industry requirements. For the life sciences, what stands out is the growing emphasis that major life science companies are placing on pursuing university collaborations to advance promising life science innovations. These new industry partnerships require more streamlined university technology transfer processes and decision making as well as the ability to leverage university facilities. Among the suggestions offered by Indiana stakeholders to maximize technology transfer is to have a separate technology transfer office at the IU School of Medicine, so it can focus on the specific needs of the life science industry, particularly industries' increasingly important connections to health care, as discussed further below. This idea deserves further study as experience from other large state universities with separate medical campuses is mixed.[12]

Another particular opportunity to lower risk is to ensure closer alignment with the needs and demands of the health care system. With the growing emphasis on proving that new life science innovations are cost effective in order to receive reimbursement from government health programs and private insurance providers, life science innovations require thinking in terms of their connection to "health care delivery systems" and how they impact overall delivery of health care services for the patient. These new developments call for more strategic partnerships with health care systems in advancing life science innovation. Indiana appears to be well-positioned to take advantage of this growing integration of life sciences innovation with health care delivery given the strengths of Indiana's health care systems and their active university collaborations, particularly through the Indiana Clinical and Translational Sciences Institute.

Recommendation: Enable Indiana to stand out as a global leader in university-industry partnerships to advance "use-inspired" research.

Indiana is well-positioned due to its outstanding base of life science industry-driven research and its substantial university life science research base to address the significant changes taking place in how research is being advanced in the 21st century. Through much of the 20th century, a typical university research approach, encouraged by federal funding, focused on supporting either basic or applied research activities, which had very different goals in mind. The objective of basic research was intended to advance fundamental knowledge and the scientific theories in areas such as matter, physical processes, biological function, and human nature without regard to practical applications. In contrast, applied research sought to apply well-understood basic research insights to make something work or to solve a practical problem. This led to the notion of the "ivory-tower" where universities pursue

[12] For instance, the University of Maryland has separated its technology transfer efforts, while the University of Colorado has a single integrated office for its many campuses.

discovery-based research often divorced from industry. As James L. Applegate explains, "It is sometimes said that society has problems, while universities have departments."[13]

A new paradigm of translational or "use-inspired" research is now emerging that bridges the dichotomy between basic and applied research and is being strongly embraced by the life sciences. As the National Research Council explains, in use-inspired research, two questions need to be answered together when evaluating any given research effort: "Does it contribute to fundamental understanding? Can it be expected to be useful?" If the answer is yes to both, the National Research Council says it "warrants special priority."[14]

Perhaps no field of science is more actively embracing this focus on use-inspired research and collapsing the barriers between basic research and their applications within universities than in life sciences research. The fast pace of basic research advances in biotechnology is reshaping all aspects of life sciences development—including the way we study medicine, discover and develop therapeutics, and diagnose and treat diseases and medical conditions for both humans and animals. At the same time, life sciences development has a unique translational research requirement that calls for especially close connections between academic medical centers and industry**.** The connection between life sciences product advancement and clinical care is not simply one of advancing a supplier and buyer relationship. Instead, there is a close and necessary interface of "bench and bedside" for biomedical innovation to move forward. The U.S. National Institutes of Health (NIH) explains that "information flow at this interface is bi-directional, requiring close interaction between clinical and bench scientists."[15] For instance, physician observations often provide insights into unmet medical needs or needs for improved treatments. Those involved in research and product development often find insights for applications from epidemiological studies and conversations with clinical practice professionals. The challenges and needs for life sciences innovation are increasingly shaping new fundamental research activities in the life sciences.

Opportunities exist in Indiana to press its advantage in university-industry life sciences collaborations through use-inspired research in drug discovery and development, orthopedic, surgical and interventional therapy devices, health informatics, global health and plant improvement as detailed in the BioCrossroads 2012 study, *Advancing Indiana's Life Sciences Competitiveness and Strategic Collaborations across Industry, Universities and Academic Health Centers in Targeted Areas of Opportunity*. These industry-university life sciences collaborations in research often need catalytic seed funding from state and philanthropic sources to take hold and then can attract more ongoing industry and federal funding.

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[13] James L. Applegate, "Engaged Graduate Education Seeing with New Eyes," Association of American Colleges and Universities, 2004, page 6.

[14] See Jeff Tollefson, Nature New Blog, May 19, 2010 on National Research Council report calling for fundamental, use-inspired research, http://blogs.nature.com/news/2010/05/us_climate_science_panel_calls_1.html.

[15] National Institutes of Health, Request for Applications for Regional Translational Research Center Planning Grants, page 4, October 2004.

The launching of the Indiana Biosciences Research Institute is an excellent example of Indiana taking a leadership position in advancing use-inspired research where industry, health care and university stakeholders are coming together to focus on a research agenda to address metabolic sciences and disorders common across the major health issues of cardiovascular disease, diabetes, obesity and nutrition, which are a major economic burden and a leading cause of death in the United States. The Indiana Clinical and Translational Sciences Institute, an NIH-funded collaboration among Indiana University, Purdue University and the University of Notre Dame, has also launched an innovative, multi-state collaboration with industry, with initial involvement and financial support by Eli Lilly and Co. and Takeda Pharmaceuticals International Inc., through a newly formed Strategic Pharma-Academic Research Consortium for Translational Medicine, or SPARC. This effort involves a broader consortium of Midwestern universities, including Washington University in St. Louis, Ohio State University and Northwestern University. SPARC will initially focus on advancing research on autoimmune diseases in light of the expertise across the universities as well as the lack of other large-scale consortiums focused on this issue. It is expected that over time additional companies will join the consortium and that the disease focus will broaden.

Recommendation: Leverage Indiana's existing life sciences industry strengths to further life sciences innovation within Indiana.

Indiana should do more to leverage the strength of its existing life sciences industry base for innovation. As mentioned earlier, this significant industry base is hard for other states to replicate. It provides critical knowledge and access to life sciences markets and, in itself, is a major driver of innovation investments. Over the past decade, this industry base has increased its focus on innovation as demonstrated by strong growth in industry-led life sciences research and development and substantial gains in total life sciences patent activity in Indiana.

This existing life sciences industry base is already an active partner in advancing industry-university innovation partnerships in Indiana, including in the Indiana Biosciences Research Institute as well as in the Indiana Clinical and Translational Sciences Institute. It is also notable that a growing number of the successful commercialization efforts of university research in Indiana are acquired as new business units of existing Indiana life sciences companies, as shown in the development of Cook Biotechnology and Roche's acquisition of Marcadia, furthering industry innovation and growth in Indiana.

More can be done in Indiana to create incentives for existing life sciences companies to both invest in new company formation from university research as well as to locate their own innovations and spin-off companies in Indiana.

While Indiana has a wide array of state tax incentives for innovation, including an industry R&D tax credit, a venture capital investment tax credit and a tax credit for production from new innovations, these efforts can be made more competitive. It has already been noted that the venture capital investment tax credit can be made more competitive by increasing the rate and considering new features, such as a capital gains income exclusion. For the R&D tax credit, Indiana should consider making it a refundable tax credit for small companies, as is done in Connecticut, Iowa and Maryland.

Advancing a refundable R&D tax credit is particularly important for emerging life sciences companies, who must undertake a long period of product development and clinical trials before they can generate income and so benefit from the R&D tax credit. Indiana might also want to consider offering a higher level of R&D credit for industry costs related to advancing university research, as is done in Massachusetts, along with research costs undertaken with other Indiana companies. This would encourage more collaborative activities not only between industry and universities, but large and small companies.

By focusing on these recommendations, Indiana can build upon its distinct assets and competitive advantages and address specific weaknesses to grow its life sciences industry through innovation. The specific steps touch upon the complex nature of life sciences innovation capital, recognizing its continuum across research activities, technology commercialization, new firm formation, clinical testing, and new product scale-up and launch. All aspects of the innovation continuum are under-stress in today's changing world of life sciences innovation where open innovation models are being increasingly embraced by industry, the challenge of de-risking new technology is rising in importance, and the funding gaps between research and early rounds of venture capital are growing for new firm formation. The specific recommended steps address these issues in a tailored and measured way for Indiana.

APPENDIX: INNOVATION TRENDS FROM 1993 TO MOST RECENT YEAR

University Life Science Research Trends

As the plot in Figure 4 shows, over the years, Indiana has generally kept pace with the growth in U.S. university life science research.

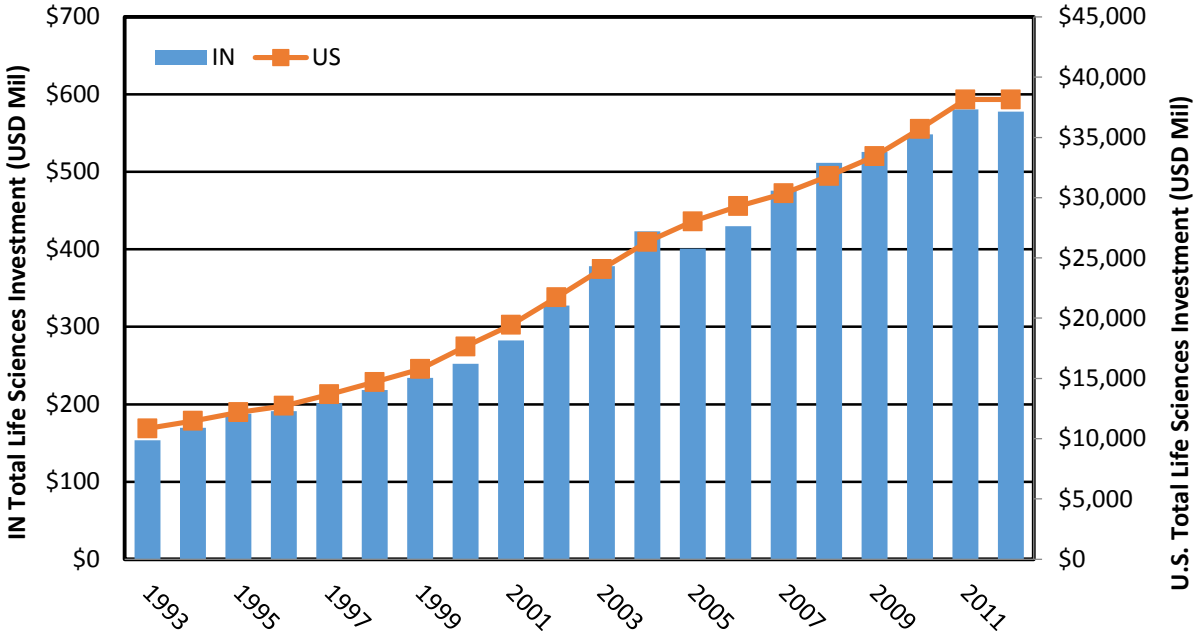

Figure 4. Comparison of Total Life Sciences Investment by Year in Indiana and the U.S.

Source: National Science Foundation.

NIH Research Funding

Figure 5 shows that in NIH research funding, Indiana tracked closely to U.S. growth until 2009.

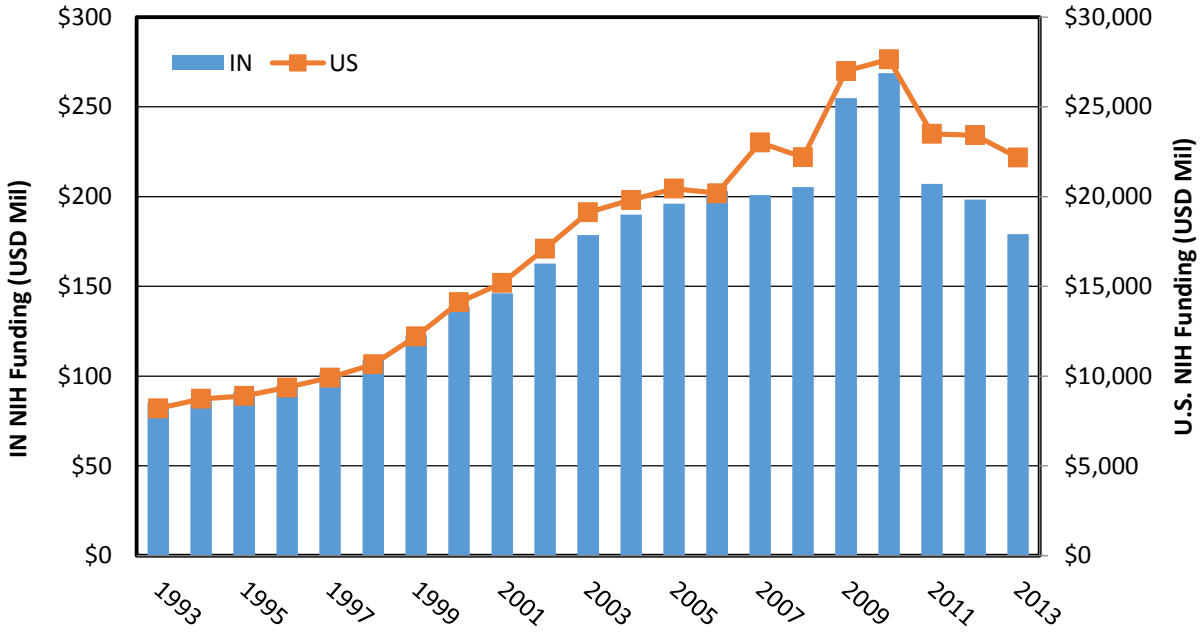

Figure 5. Comparison of NIH Funding by Year in Indiana and the U.S.

Source: National Institutes of Health RePORTER database.

Life Science Patents

Figure 6 shows that Indiana patent numbers have generally followed the national trend, with a dramatic increase since 2009.

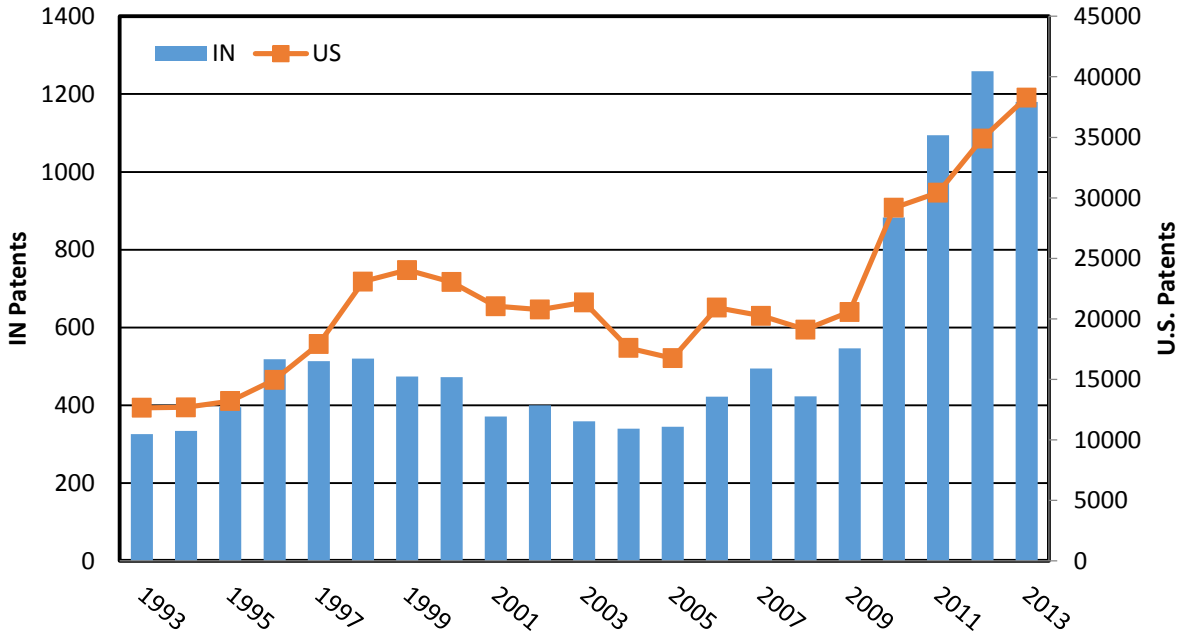

Figure 6. Comparison of Life Science Patent Activity by Year in Indiana and the U.S.

Source: U.S. Patent Trade Office, Delphion database.

NIH SBIR Trends

Figure 7 shows that Indiana's SBIR investment trend, while mostly tracking the national trend, has experienced more variability than that of the U.S.

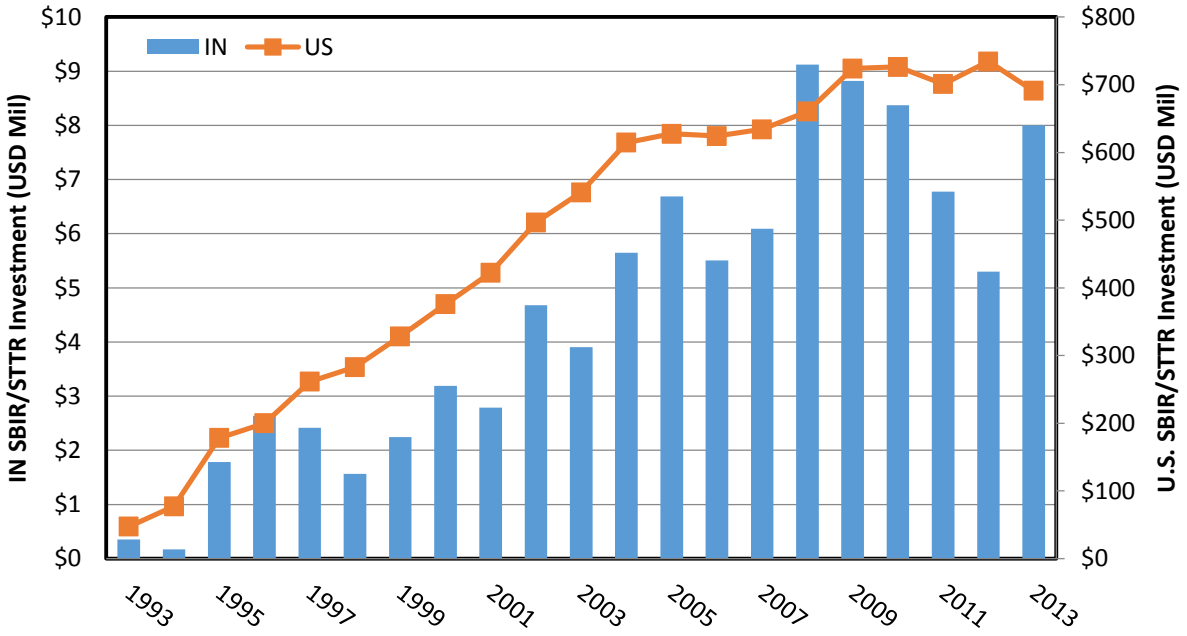

Figure 7. Comparison of SBIR/STTR Investment by Year in Indiana and the U.S.

Source: Small Business Innovation Research awards database.

University Technology Transfer Trends

In Figure 8, Indiana's disclosures trend exaggerates the fluctuations in the national trend over the years.

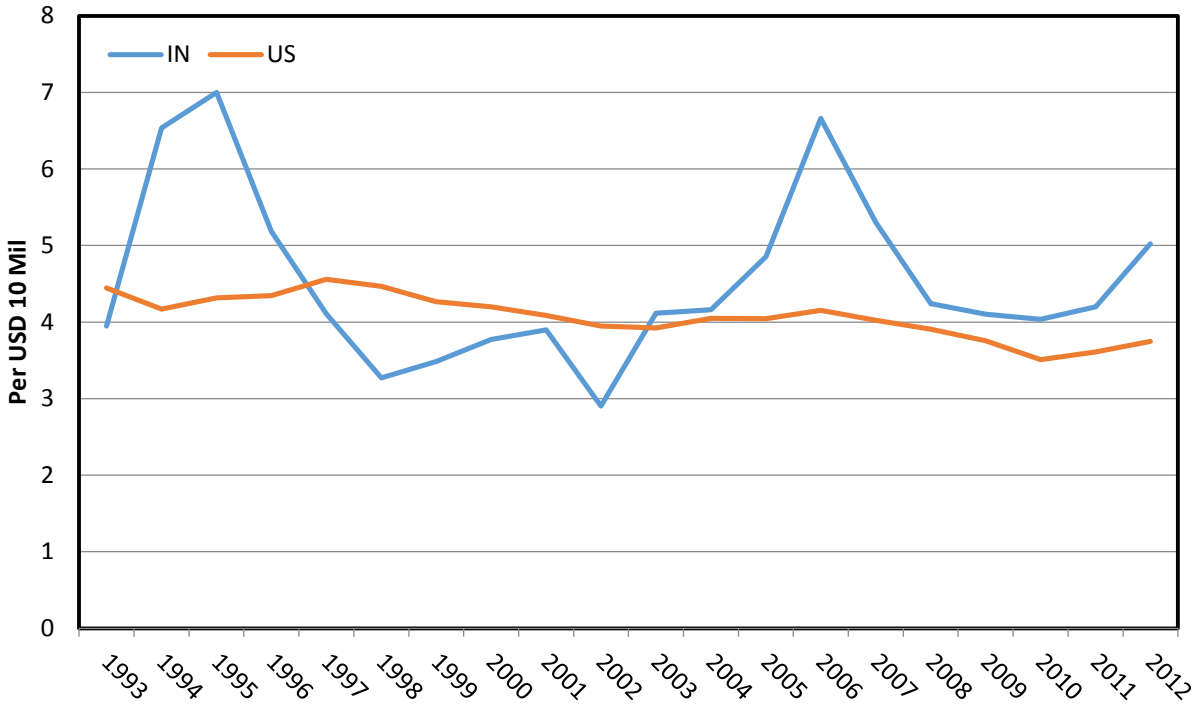

Figure 8. Comparison of Technology Transfer Disclosures by Year in Indiana and the U.S.

Source: Association of University Technology Managers.

Figure 9 shows that Indiana's patent applications trend has experienced more variation than the national trend, with Indiana outpacing the national trend since 2005.

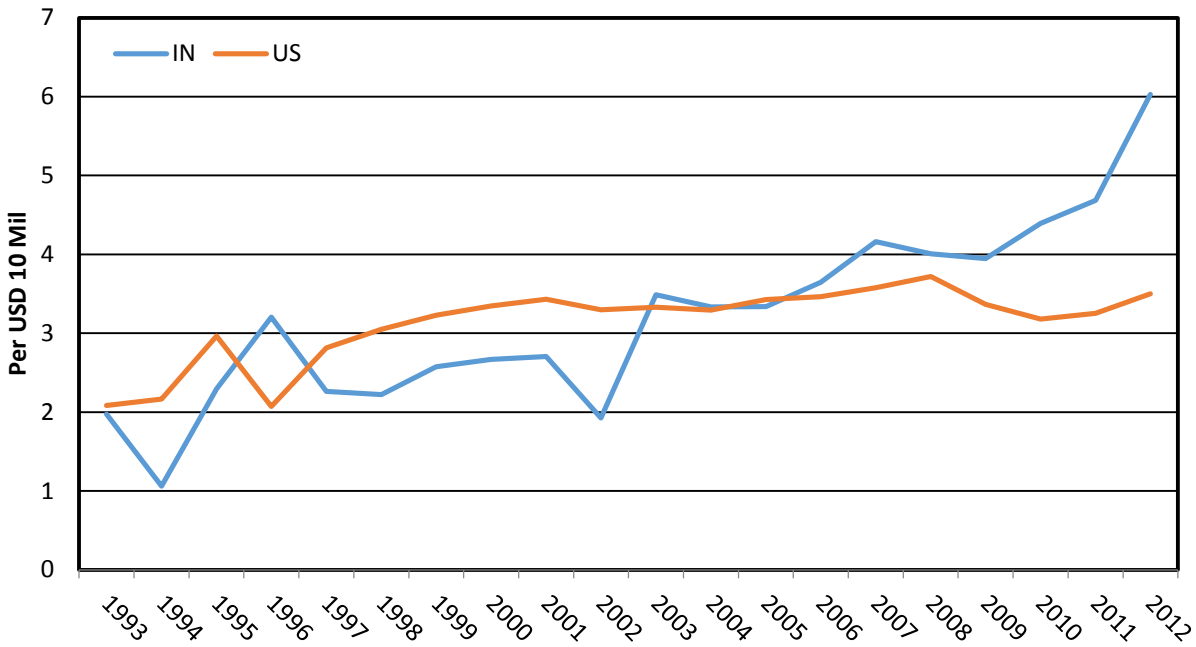

Figure 9. Comparison of Patent Applications by Year in Indiana and the U.S.

Source: Association of University Technology Managers

Figure 10 shows that Indiana licenses have followed the national trend while experiencing more variability than the U.S.

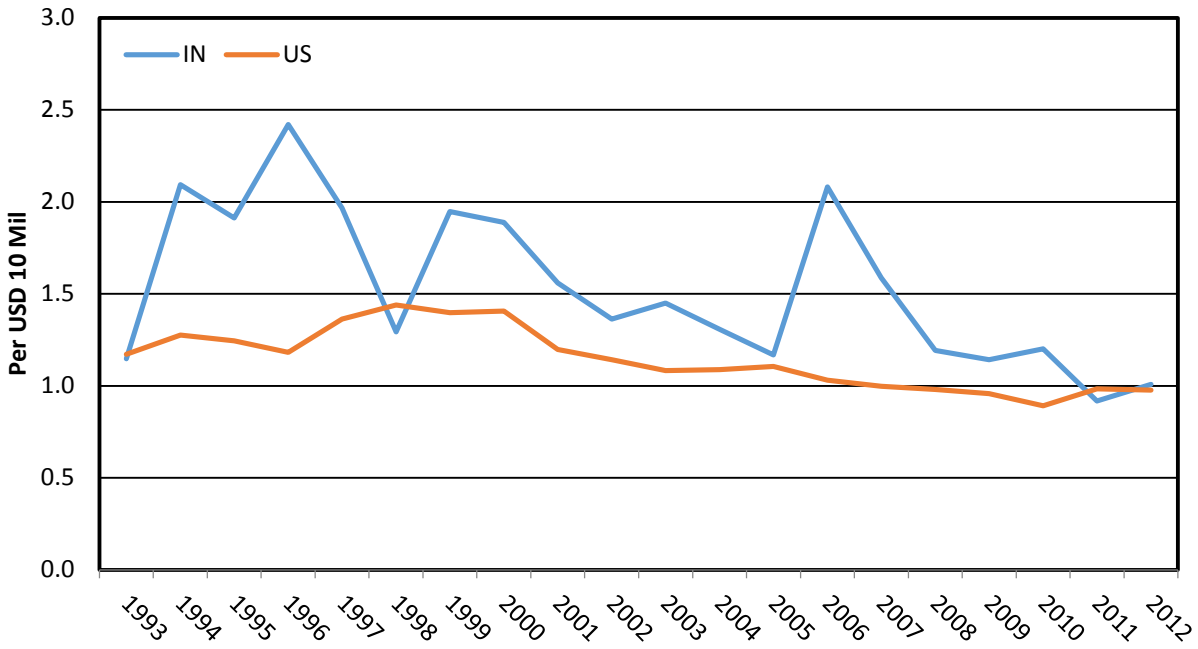

Figure 10. Comparison of License Agreements by Year in Indiana and the U.S.

Source: Association of University Technology Managers.

Figure 11 shows that Indiana start-ups have follwed a general upward trend since 2002.

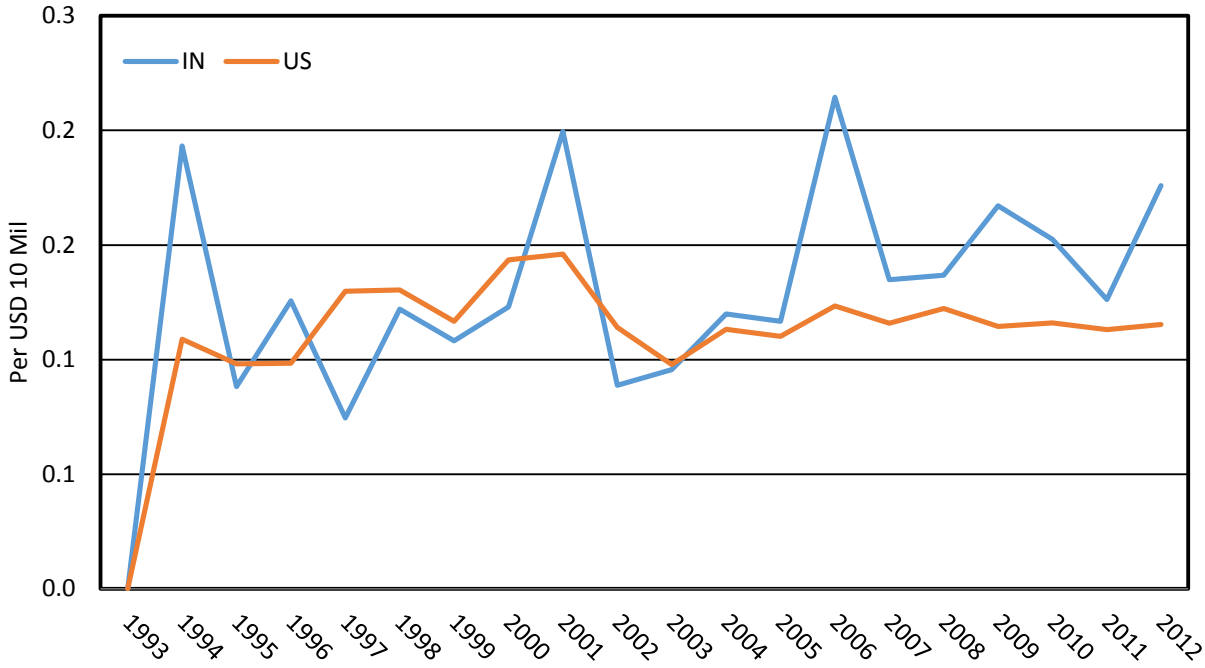

Figure 11. Comparison of Business Start-ups by Year in Indiana and the U.S.

Source: Association of University Technology Managers.

Life Science Venture Capital Trends

As shown in Figure 12, venture capital investment in Indiana has mirrored the national trend in certain years, while breaking away from the U.S. in others, most notably in 2003, 2009, and 2013.

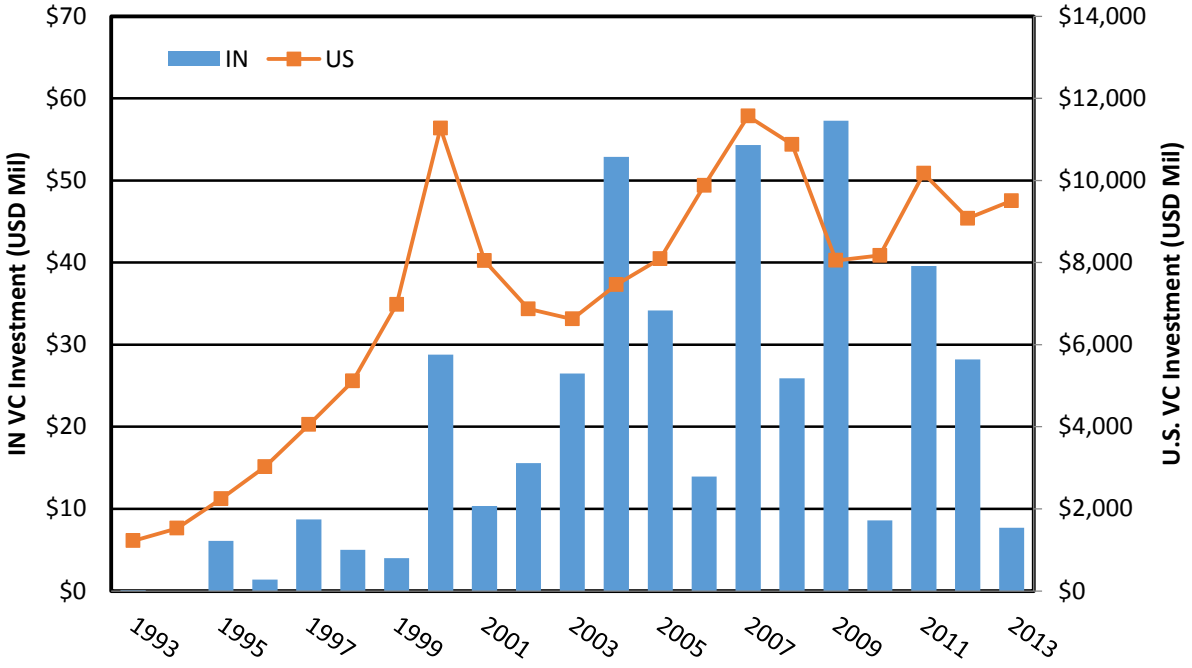

Figure 12. Comparison of Venture Capital Investments Related to Life Science by Year in Indiana and the U.S.

Note: No life science venture capital activity reported in Indiana for 1994.

Source: Thomson Venture One database.

In Figure 13, life science related deals in Indiana began tracking more closely with the national trend around 2003.

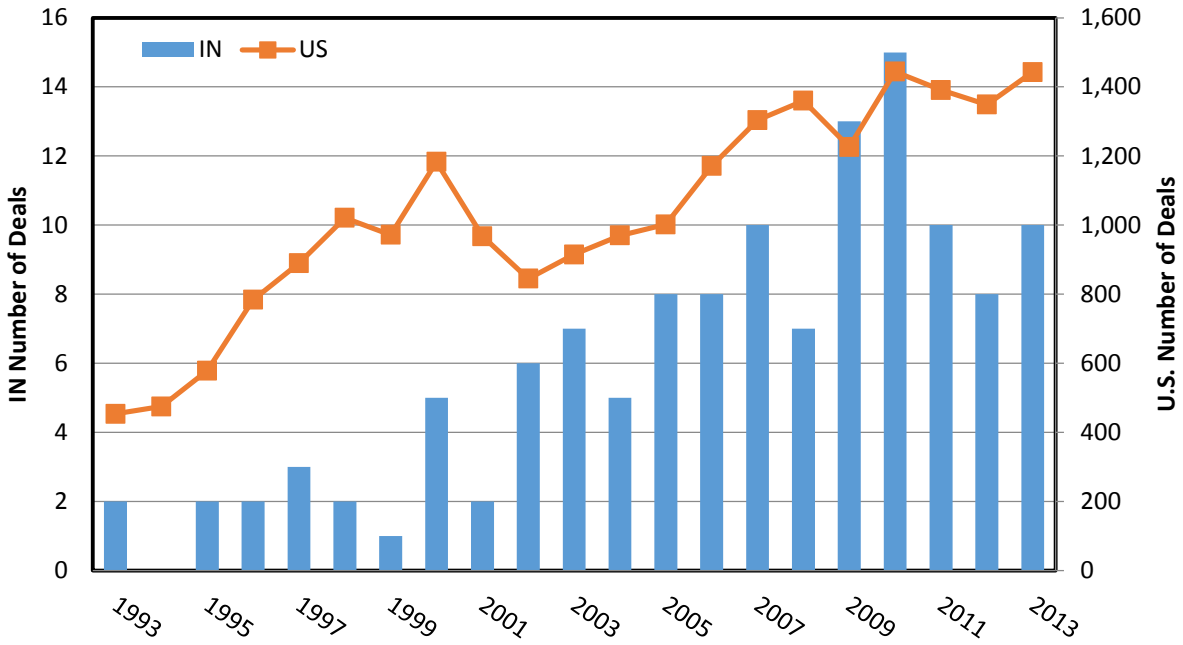

Figure 13. Comparison of Deals Related to Life Science by Year in Indiana and the U.S.

Note: No life science venture capital activity reported in Indiana for 1994.
Source: Thomson Venture One database.