Institute for Applied Cancer Science

A New Paradigm for High Impact Oncology Drug Development

Executive Summary

The Institute for Applied Cancer Science (IACS) at UT MD Anderson Cancer Center is a unique organizational construct designed to integrate the best attributes of academic science and pharmaceutical drug discovery to identify and validate new cancer targets, convert such targets and the biological insights around them into new and effective cancer drugs and biomarkers, and advance these novel agents into innovative clinical trials. Here we propose to significantly expand our depth, breadth, and value proposition through support from The Cancer Prevention & Research Institute of Texas (CPRIT). By matching MD Anderson's investment of $75 million over the next three years, CPRIT's funding will enable the IACS to:

- Expand current target biology and small molecule drug discovery efforts **from three (3) to five (5) concurrent programs**.

- Expand **depth of current programs** by funding counter-screens against related protein family members, creating a highly leveraged bundle of attractive small molecule assets for new company formation.

- Expand pipeline to include **biologics**, thus capitalizing on significant MD Anderson expertise with immunomodulation and insight into novel antibody-amenable targets through next generation sequencing of human clinical samples.

- Strategically invest in efforts to develop **novel chemistry platforms to address traditionally "undruggable protein targets."**

- Strategically accelerate clinical and value inflection points via **in-licensing of mid- to late-staged assets with composition of matter** for which IACS is uniquely positioned to generate actionable clinical insights.

Such strategic expansion of IACS will substantively increase the impact of IACS on the life science economy of Texas by:

- Reducing the financial pressure to partner or license early, thus enabling IACS to retain ownership/control and internally **prosecute up to four (4) Phase I trials**. This is in comparison to our base case projection (e.g. without CPRIT support) where IACS will partner early and only retain one program for internal Phase I clinical development. Clearing the Phase 1/1b hurdle will increase the value of each asset by 10-fold or greater.

- Creating an attractive portfolio of assets that would be considered strong foundations for successful new company formation. Leveraging CPRIT support will allow IACS to launch at least **three (3) new Texas-based companies**, which could be shepherded by the Rice Incubator program, in comparison to only one such opportunity.

In sum, CPRIT funds will allow the IACS to enhance current efforts while providing strategic areas of expansion to accelerate value creation opportunities. Collectively, CPRIT funding will help IACS build a **self-sustaining**, world-class oncology drug development organization committed to delivering a continuous pipeline of innovative therapeutic candidates while creating assets amenable to seeding a strong new pharmaceutical ecosystem in Texas.

Introduction

In November 2011, The University of Texas MD Anderson Cancer Center launched the Institute for Applied Cancer Science (IACS), a unique organizational construct designed to integrate the best attributes of academic science and pharmaceutical drug discovery to identify and validate new cancer targets, convert such knowledge and insights into new and effective cancer drugs, and advance these novel agents into innovative clinical trials. The Institute is exploiting the enormous opportunities provided by recent truly transformative scientific and technological advances, to improve the appallingly low rate of success in the current cancer drug development system. The institute is designed to convert basic discoveries into effective new drugs and complementary diagnostics for cancer patients via multidisciplinary collaboration using a full range of state-of-the-art technologies. It will enhance and align with many other programs at MD Anderson, spanning basic, translational and clinical research.

We propose here an ambitious business plan to increase the opportunity and probability of IACS to produce assets that can be foundations for new company formation in Texas through support by The Cancer Prevention & Research Institute of Texas (CPRIT). In particular, when combined with MD Anderson's $75 million commitment, a CPRIT matching award of $75 million over three years will enable significant pipeline expansion across new targets and therapeutic modalities. In addition, the support will provide strategic opportunities to bundle a collection of related technologies which could serve as attractive founding assets for the formation of new companies. The Rice Incubator program could serve as an ideal launch pad to mature a business plan, raise venture capital funds, and recruit a professional management team to provide full-time focus on the further development of the IACS therapeutic assets. Together, IACS will have the full resources to rapidly prosecute multiple programs, create a mature portfolio of clinical candidates that will not only allow us to forge co-development deals with the biotechnology and pharmaceutical industry but importantly to strategically spin-off select assets into new Texas-based companies.

IACS Paradigm: Combining Deep Target Biology with Professional Drug Discovery

MD Anderson, like other academic comprehensive cancer centers, is committed to providing patients with optimal care including early access to innovative new treatments via clinical trials. Historically, academia has relied on the pharmaceutical industry R&D to bring revolutionary new drugs to patients. However, the pharmaceutical industry macroenvironment is struggling with the confounding effects of shrinking R&D budgets, poor success rates at translating therapeutic hypotheses into safe and effective new drugs, and challenges with holistically dismantling the traditional (profitable) blockbuster-based business model to deliver personalized oncology medicine. Recognizing the existence of this critical translational gap, MD Anderson has launched the IACS, a new hybrid academia-industry construct to proactively drive our mission to Make Cancer History®. The IACS embraces the best features of both academic and industrial research: its focus will be on scientific excellence, teamwork, and hypothesis-driven goal-oriented research. The IACS has assembled a truly interdisciplinary team of seasoned professionals which enables project teams to ***simultaneously*** discover and validate novel cancer targets, develop assays to discover and optimize small molecule inhibitors or agonists, gain a deep understanding of candidate therapeutic targets, and begin formulating hypotheses around which patient populations would likely best respond (and not respond) to target perturbation.

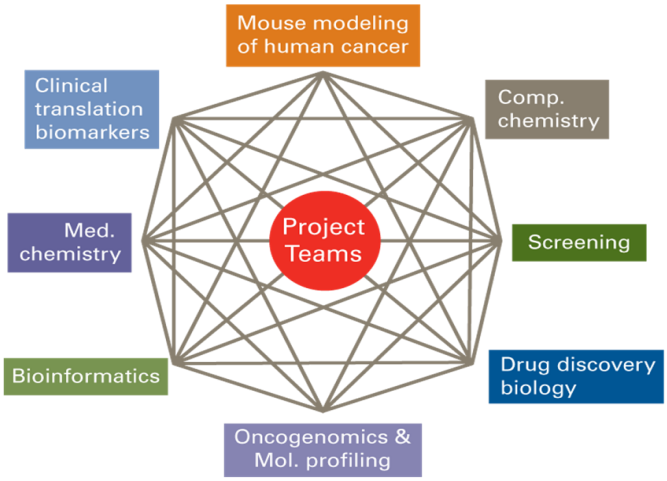


Figure 1. The integrated, multi-disciplinary structure of IACS Project Teams provides all resources necessary to rapidly generate a sophisticated understanding of therapeutic targets and rapid discovery, optimization and evaluation of therapeutic candidates to modulate said targets in specific cancer types and genetic contexts.

IACS Philosophy: Science-driven Drug Discovery

The IACS will succeed by embracing a rigorous, goal-oriented, milestone-driven culture backed by high level cutting-edged science. The team will perform parallel and integrated target and drug discovery biology, with defined **Go/No-Go experiments** designed to rapidly i**) de-risk the program** by demonstrating and establishing robust scientific evidence of the existence of a viable therapeutic approach with a defined clinical path hypothesis, or (ii) **kill the program** by executing with discipline No-Go decisions **early and definitively.** A strict adherence to this philosophy ensures the IACS will remain agile, and able to rapidly make data-driven (re)allocation of resources towards programs with the highest probability of value capture and clinical success. Moreover, IACS will (iii) **build a strong IP portfolio** around each program proactively in order to create and protect the value of its assets for development and commercialization. Further, IACS will (iv) **engage in aggressive and creative business development** strategies to ensure successful exits for its programs with the goal of achieving an "ever-green" situation.

This new academic-industry hybrid model is truly game-changing. IACS blends the best features of academia and industry and eliminates their respective shortcomings. Like other academic institutes, the IACS ensures that scientific excellence is always the top priority. However, by freeing our team from publication or grant application pressure, or any specific allegiance to "my favorite gene," the IACS is free to explore a broad range of science and prosecute the best therapeutic targets and hypotheses in real time. The IACS does not distinguish between targets identified from internal R&D within the IACS (or more broadly at MD Anderson) from equally promising targets identified by other companies/institutions at external meetings or through publications. Conversely, the IACS adopts the best practices found in the biopharma industry, including a strict commitment to goal-oriented timelines, project and program management, R&D expenditure accountability, and a fully integrated team capable of translating chemical probes into valuable clinical candidates. Unlike biopharma, our "investors" are the patients thus our commitment and priorities are unwavering; IACS will define successful programs as those with a strong body of evidence that the candidates fill an unmet clinical need and will positively impact a defined patient population. In short, our biology goal is not to publish our latest and most novel observations in top journals. Instead, it is to generate the most robust and comprehensive biology package around a drug to significantly increase its probability of success in the clinic.

While IACS will differentiate itself from traditional biotech companies in that it will not base programmatic decisions strictly on total available market analysis or reimbursement considerations, IACS will proactively incorporate sound business strategies in its entire decision making process. In other words, IACS will consider business parameters **in addition**, but **never instead** of, scientific rationale in its decisions. It will proactively build and protect intellectual property and have dedicated full-time individuals in areas of IP and business development, advised by a seasoned EAB (see **Appendix**).

In summary, with the best of both worlds, the IACS will translate scientific discoveries into viable therapies by achieving the following:

- Validate novel scientific discoveries having the potential to become cancer therapies;
- Develop efficient means of testing the impact of these discoveries on cancer cells, animal models and human tumor explants using state of the art technologies including molecular imaging;
- Develop an internal drug discovery program to advance unprecedented targets, with particular emphasis on high medical needs and orphan drug indications;
- Conduct pre-clinical trials to enable the rational selection of optimal drug candidates for human testing;
- Work with governmental, biopharmaceutical, and academic collaborators to move viable drug candidates into clinical trials.

A Track Record of Success

Core to the IACS paradigm and its competitive advantages over either industry or academia is its construct that enables truly integrated and complementary R&D. On the research side, it brings the cutting-edged unencumbered academic science to bear on key decision gates along the drug discovery continuum, while on the development side, it brings the same professional dedication and expertise to the process of drug

discovery. Importantly, IACS is not simply an out-of-the-box-idea conceived in theory to address the current gap in oncology drug discovery. It is a construct that has proven successful in driving major alliances with large pharmaceutical companies.

The unique construct of industrialized biology in academia to enable oncology drug discovery was conceived and evolved under leadership of Drs. Chin and DePinho (now President of MD Anderson), later joined by Dr. Draetta, at the Belfer Institute of the Dana-Farber Cancer Institute in Boston, MA. Given its limited initial resources, the Belfer Institute did not build an internal development pipeline on drug discovery; rather it partnered with large pharmaceutical companies that brought the drug discovery capabilities to Belfer.

In its first partnership formed with Merck, the Belfer Institute entered into a co-development structure where both Belfer and Merck jointly participated to identify, validate and develop drug against genomically-altered oncology targets. During Year 2 of the alliance, Merck underwent a merger with Schering-Plough and post-merger portfolio review: all three preclinical programs (at lead-optimization stage) in the Belfer Alliance survived and in fact, remained the only preclinical programs in the Merck pipeline. This speaks directly to the value and quality of target biology being executed in the Belfer. As a definitive validation, Merck renewed its alliance agreement with Belfer Institute for two additional years with an option for a third. With the renewal, Merck increased its R&D support of the Belfer by nearly 50%. In total, the Merck-Belfer alliance brought to Dana-Farber Cancer Institute $7M upfront, $14M in R&D support, and upward of $150 Million in potential downstream milestones and also significant royalties. More importantly, Merck now carries 3 programs in its pipeline on unprecedented targets for oncology that hopefully will benefit patients.

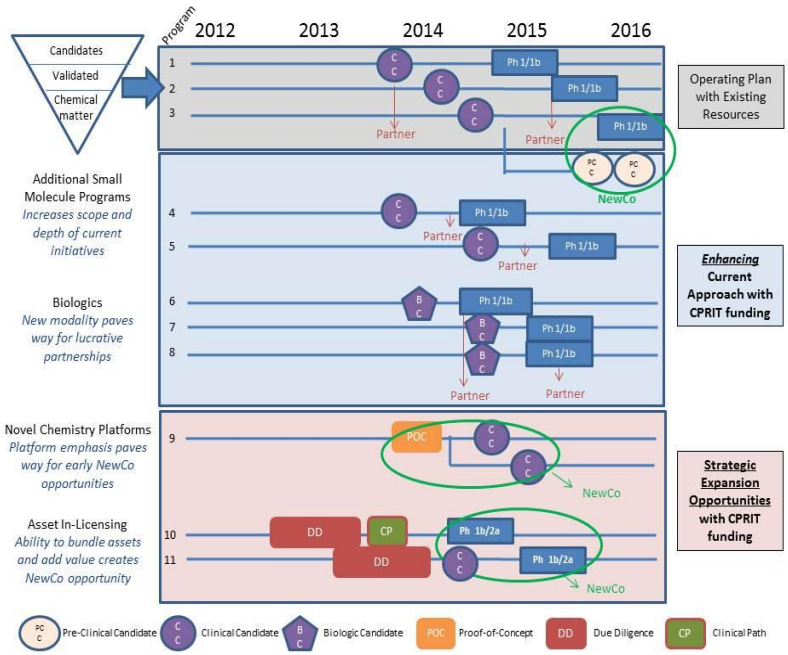
Under Dr. Draetta's leadership, Belfer Institute established a second corporate alliance with Sanofi-Aventis, yet another external validation. This alliance served the role of early target-program pipeline for Sanofi oncology, for which they committed $33M over three years, including $12M up front and $7M per year for three years to support 25 FTEs working at the Belfer Institute, plus $250^{+} Million potential milestones and also significant royalties.

In addition to the upfront and R&D support, both alliances included preclinical and clinical milestones as well as tiered royalties comparable to traditional pharma-biotech deals. Thus, the IACS team has proven itself to be an industry-like professional organization that can execute and deliver, which demonstrates that this construct of industrialized biology in academia is viable. Most importantly, all but one of the leadership team members at the Belfer Institute that supported the two corporate alliances joined MD Anderson and are now in equivalent positions at the IACS (see Appendix for brief bios), along with ~20 key individuals that were selectively recruited to relocate to Houston. In other words, IACS is not a new entity just established under a new paradigm, **it is a proven, functional and successful operation that was transplanted from Boston to Houston.**

What is new in IACS is the establishment of an internal drug discovery capability under the leadership of Dr. Philip Jones (see **Appendix**). The rationale for this is two-fold. First, with drug discovery in the hands of our corporate partners, we learned that we were unable to control our timeline on execution and milestones. An example was the Merck-Schering merger, requiring a portfolio review internal to the corporate partner but resulting in a delay of execution of the Merck-Belfer work plans for almost a year. Second, with MD Anderson's tremendous clinical resources and infrastructure, the IACS now has the ability to proactively drive a program further toward clinical endpoints, thus obviating the need to leave much of the value on the table under the control of a corporate partner. Thus, the IACS has now built a world-class professional drug discovery organization with seasoned industry talent and capabilities (see **Appendix**). The IACS has been able to recruit Dr. Carlo Toniatti as its Head of Research, a truly talented, exceptional scientist, with an outstanding record of achievement. In addition to the experienced professionals that have relocated from Boston, IACS has hired highly talented scientists from biopharma companies including: Pfizer, Sanofi-Aventis, Merck, Array BioPharma, Cephalon, and Lexicon, and we are in the process of offering positions to others. Members of the team in their previous positions have led or been involved in research and development of more than twenty projects that have advanced into the clinic, and supported the clinical development of a further dozen programs including one that has already been FDA approved.

Operating Plan and Value Creation Opportunities

MD Anderson has committed significant capital and physical resource to lay the groundwork for the IACS. To sustain this effort beyond the most generous start-up funds provided by MD Anderson, we are raising funds with public and private granting agencies, seeking philanthropic donations, and preparing to engage biopharma for corporate support. The current funding provides sufficient support to drive three parallel small molecule programs, as well as a funnel of early pipeline activities to identify and prioritize new target candidates. As conceptually illustrated in **Figure 2**, the IACS will engage in a combination of co-development alliances with biopharma and the opportunistic spin-out of new companies. While partnerships will generate the largest opportunity for near-term returns (e.g. upfront and milestone payments), over time the start-up model has the ability to generate a much greater level of overall return, as exemplified by recent acquisitions (e.g. Celgene's $925 million acquisition of Avila Therapeutics, and Daiichi Sankyo's $935 million acquisition of Plexxicon). The leadership team, in consultation with the IACS's external advisory board (EAB, **see Appendix**) will regularly review each asset to discuss the optimal timing and externalization approach. The key analysis parameters will include:



- **Risk/reward profile** for continuing to mature the program internally (to maximize value of eventual partnership) versus forging an earlier partnership (to both minimize risk and generate critical revenues to support other internal initiatives)
- **The most expedient path** to advance promising therapeutic candidates to patients.

As outlined in **Figure 2 above**, the IACS intends to leverage CPRIT funding to capitalize on and accelerate value creation opportunities via four parallel tracks, as described below.

Enhancing Current IACS Approach

(i) Although IACS scientists have identified and prioritized >15 potential therapeutic targets, with existing resources the IACS only possesses the ability to prosecute **three (3)** deep biology and drug discovery initiatives in parallel. In addition to linearly **expanding the number of active programs to five (5),** the IACS plans to expand the depth of these programs. For example, one of our current lead drug discovery programs is against a specific reader of the epigenetic code which is known to be deregulated in a significant percentage (>10%) of different tumor types. Given tremendous enthusiasm for the promise of epigenetics (Constellation Pharmaceuticals recently secured a $95 million upfront payment for a collaboration with Genentech), IACS plans to leverage CPRIT funding to bolster this existing program. Already in the first quarter of 2012 we have established a screening infrastructure to identify novel chemical matter and have identified novel inhibitors of this previously undrugged target, and initial SAR exploration is ongoing. Rather than developing chemical matter against this single target, CPRIT support will enable IACS to perform counter-screens with an expanded panel of family members. By developing a bundle of assets with a related epigenetics theme, we will have a new opportunity to found and **launch a Texas-based new company.** A second active IACS program is addressing the specific ability of cancer cells to survive under conditions of hypoxia, and we are already at an advanced stage of developing inhibitors of HIF-1alpha signaling and are

preparing our first patent application around the lead chemical matter which inhibits the pathway at low nanomolar concentration. Additional opportunities exists in this area include leveraging the research of Dr. Edward Yeh to establish a Newco around tumor hypoxia and metabolism.

(ii) With the initial resources provided by MD Anderson, the IACS has focused on small molecule inhibitors. However, there are multiple justifications to **expand our therapeutic modalities to include Biologics.** First, MD Anderson scientists have significant domain knowledge and intriguing assets in the field of immunomodulation. Given the recent success of ipilimumab, immunomodulation has become an increasingly attractive therapeutic approach for oncology. IACS plans to initiate at least two development programs leveraging MD Anderson expertise in this arena. As a first step, IACS has already evaluated the therapeutic and marketing potential of humanized anti-OX40 agonist antibodies that have been generated and characterized by investigators at MDACC: these antibodies enhance anti-tumor immunity and have a strong therapeutic effect in mouse tumor models. IACS took the lead to engage outside companies to bring these antibodies to the clinic and an agreement with a large pharmaceutical company to partner in the pre-clinical development is expected to be finalized by Q2 2012. The agreement being finalized would bring in approximately $20 million in upfront and research funding as well as significant downstream milestones and royalties. In addition, Next Gen sequencing has identified numerous mutated signaling pathways driving defined tumor sub-populations that would be more appropriately targeted by a biologic agent than a small molecule inhibitor. Thus, rather than focusing on enzymes, the ability to diversify into the mAb arena will allow IACS to target the most disease relevant pathways in any tumor type.

Capitalizing on Strategic Expansion Opportunities

(iii) CPRIT funding will also provide the resources necessary to strategically invest in innovative chemistry platforms to tap into previously **"undruggable" target classes**. Current chemotherapeutic agents target a restricted portfolio of protein targets, including kinases and nuclear hormone receptors. The IACS team has developed a work plan to go beyond this limited repertoire of targets by leveraging inhibitors that are outside classical small molecule physicochemical drug space (including as one example, phosphatases) and leveraging proprietary delivery platforms to bring the therapeutics to the site of action. We plan to execute on our work plan by deploying cross-functional teams of medicinal chemists, pharmacologist and drug metabolism scientists to rapidly advance this proprietary chemistry platform through progressively more challenging hurdles from cell lines, to rodent models, and ultimately to canine and/or non-human primate models in a series of well-defined proof of concept studies. Further opportunities exist through collaborations with investigators such as Dr. Venkitaraman at the University of Cambridge around drugging protein-protein interactions known to be essential for tumor maintenance. By opening up a new druggable space, we believe these platform assets will be optimally advanced through the formation of a Texas-based NewCo and this strategic expansion will provide an opportunity to this entrepreneurial exit at an earlier time point than with other programs.

(iv) Lastly, CPRIT funding will be used to rapidly reach clinical and value inflection points by strategically **in-licensing therapeutic assets** (from Pharma and/or other non-profit institutions, e.g. the Sanford-Burnham Institute or Cancer Research UK). Mining the cancer genome has revealed several new clinical opportunities for modulators of historically targeted signaling pathways. IACS is in a position to capture this value through strategic in licensing clinical or preclinical assets, demonstrating that these agents inhibit the desired activity in preclinical studies, and then conducting a well-defined Phase II study in a specific patient sub-population before looking for a financial partner for Phase III. While we intend to primarily scout more mature clinical assets, as a variation, we may explore in licensing chemical matter at an earlier stage (e.g. hit-to-lead), allowing IACS to develop proprietary chemical matter for clinical validation with no/minimal encumbrances. The IACS leadership is already leveraging our competitive advantage in oncogenomics, and overlaying these genetic alterations onto the IP estate of biopharma companies/academia, and we have already identified a number of "stranded" assets that have been shelved. IACS plans to conducted limited POC studies with tool compounds to demonstrate the feasibility of targeting these genomic alterations in defined sub-populations; CPRIT funding would then allow in-licensing and execution of the clinical study.

Taken together, these opportunities will dramatically broaden our pipeline, increase the number of new company creation opportunities by building compelling "platform stories" necessary to stimulate large scale venture capital investment into Texas-based start-up companies. While recognizing that future partnership structures and valuations will be based on the actual and perceived value of the asset(s), we generated a revenue model for the exits planned in **Figure 2** using an estimate of achievable upfront and near-term (18-month) milestones based on comparable benchmark transactions (**see Appendix**). As illustrated in **Figure 3**, the cumulative near-term partnership-derived revenues in the base case are significant, but not sufficient to fully sustain the IACS. However, when the same models are examined with the expanded scope and additional exit opportunities, the near-term cumulative partnership revenues significantly exceeds expenditures. Importantly, a sustainable IACS model emerges even though three of the planned exits are "Newco" spin-outs, where the therapeutic assets do not generate any significant near-term capital for the IACS. A full 5-year P&L is presented in the **Appendix.**

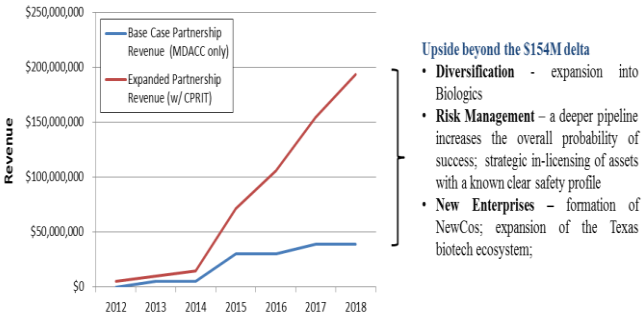


Figure 3. Bringing value to Texas. Diversification and pipeline expansion significantly reduces overall portfolio risk while dramatically improving the near-term partnership opportunities, collectively transforming the IACS into an evergreen Texas institute poised to continually innovate oncology drug discovery and development. Additionally, Texas NewCos can be proactively launched and advised by the entrepreneurial experience of the IACS team. NOTE: revenue figures (y-axis) do not include philanthropic-infusions, which will further support the IACS during the initial years.

Opportunity Summary

In sum, the financial case for support is strong, even before considering the long-term upside of royalties or liquidity events from the Texas-based IACS spin-out companies. Along the way, this opportunity will create numerous Texas jobs and help the State bring an entrepreneurial culture of industry professionals, clinicians, students, corporate partners and seasoned investors together to create an ecosystem capable of supporting the next wave of life science companies. However, the single most important rationale for support is the high probability of helping discover, develop, and commercialize novel targeted therapies to improve and restore the lives of cancer patients in Texas, our nation, and the world.