



## **Backgrounder**

### **Depleted Pharmaceutical Pipelines: Why the Drug Failure Rate is Rising**

The U.S. Food and Drug Administration's (FDA) approval in 2007 of only 19 new drugs and gene-based therapeutics – the fewest since 1983 – is the most recent evidence that the existing drug development model is in need of a drastic overhaul. Meanwhile, drug development costs have soared 1,244% from \$3.2 billion to \$43 billion during the same period.<sup>1</sup>

The high rate of drugs failing in late-stage clinical trials is a major contributing factor to the spiraling cost of drug development.<sup>2</sup> Drugs which may have shown promise in proof-of-concept and early-stage clinical trials fail to achieve endpoints in later-stage studies, or they exhibit toxicities and side effects that force companies to terminate the development program entirely.

The reasons for these costly missteps are multi-faceted, though much of the cause has been attributed to the widening gap between basic research discoveries and the understanding of disease mechanisms required to effectively apply these discoveries to drug development. While there has been increasing recognition of the need to provide resources for translational medicine – moving discoveries from concept to clinical evaluation – there has been a lack of adequate attention to furthering critical path research - science directed toward improving the process of product development itself by establishing new evaluation tools.

Mindful of the impact of these deficiencies, the FDA developed its Critical Path Initiative<sup>3</sup> (<http://www.fda.gov/oc/initiatives/criticalpath>) to stimulate and facilitate a national effort to modernize the scientific process through which potential drugs, biological products, and medical devices are transformed from a discovery or "proof-of-concept" into a medical product.

An invigorated product development science enterprise could generate new methods to investigate the biological mechanisms of disease and more accurately predict the clinical efficacy and safety of emerging therapeutics. However, while applauded by industry and academia, the Critical Path Initiative alone has not yet generated the on-the-ground momentum needed to accelerate progress in bringing new medical products to patients<sup>4</sup>.

### **Bench to Bedside: Limitations of the Academic Research Model**

Academic institutions are the engines that generate basic discoveries. However, academia is not optimally suited to cost-effectively mount successful clinical research programs to translate its own discoveries into new medical products.

To create a more effective model for academic clinical research, the Immune Tolerance Network (ITN) was established eight years ago as a collaborative research effort which partners with both industry and academia to define the mechanisms of immune function in disease pathogenesis, identify new biomarkers of tolerance in immune system related diseases, and develop new immune tolerance therapeutics. Funded by the National Institutes of Health (NIH) and the Juvenile Diabetes Research Foundation (JDRF), ITN has created a robust infrastructure that performs world-class, mechanism-based clinical research fully integrated with high-quality clinical trials. ITN-conducted clinical trials evaluate the safety and efficacy of emerging therapeutics, while at the same time performing a comprehensive set of cellular, molecular and immunological assays on clinical specimens obtained during the trial. The results of these assays are analyzed together with clinical efficacy and safety data to identify biomarkers that determine whether the drug being tested causes an appropriate biological response or conversely, any potentially detrimental responses. This mechanism-based science, pioneered by ITN, facilitates development of new immune therapeutics and therapeutic approaches. Working

with both industry and academia, ITN has supported the design and implementation of more than 25 clinical trials since its founding in 1999.

While highly productive in generating new knowledge, insights from ITN's experience have shown that consortium-driven clinical efforts often lack the dedicated infrastructure needed to most effectively convert discoveries into new medical products. For example, single-investigator studies can lack robustness and scalability. Furthermore, inefficient, costly, and outmoded manual processing of patient samples from clinical trials has also lacked quality control, as well as industrial reproducibility and standardization. The decentralized structures and shortage of standards for data sharing in such multi-institutional partnerships – including those involving both academia and industry – have further limited the productivity of these collaborations.

### **The Immune Tolerance Institute (ITI): Creating a New Corporate Model for Critical Path Research**

ITI's founders have realized that the next-generation clinical research paradigm requires a dedicated organization that:

- 1) **CENTRALIZES** resources and expertise and provides scale as well as quality assurance and control;
- 2) **STANDARDIZES** and links data (basic and clinical) in clinical trial design to maximize interpretive power; and
- 3) **COORDINATES** data sharing and intellectual property (IP) generation to allow efficient transition to the marketplace.

Recognizing the limitations of the academic discovery model and the potential of the Critical Path Initiative, ITI was founded together with the University of California San Francisco (UCSF) as a non-profit 501(c)(3) corporation to bring industrial rigor and economies of scale to translational and critical path science, foster new partnerships with the pharmaceutical and biotech industries, and accelerate the successful development of new immune-based therapeutic compounds.

Establishing a new paradigm in critical path research, ITI will bridge the gap that has existed between academia and industry, making the discovery-to-development process more cost-efficient and more successful at generating new effective and safe drugs for immune-related diseases.

ITI core capabilities and services will include:

- **Assay development:** Working with academic and corporate partners, ITI performs assays that support mechanism-based clinical studies
- **Biomarker discovery:** ITI will identify novel, relevant biomarkers of disease activity and therapeutic effect
- **Product development:** ITI validates biomarkers in clinical studies, partnering with industry to out-license diagnostic products generated by its research or spin-out new companies based on ITI discoveries
- **Bioinformatics,** the management and analysis of biological data using advanced computing techniques; bioinformatics is particularly important in biomarker and diagnostics research, which generate large amounts of complex data
- **Linkage and standardization of basic and clinical data,** to increase the interpretive power of clinical trial data
- **Data sharing and Intellectual Property,** to facilitate speedy and efficient transition of discoveries to the marketplace
- **Economies of scale** through centralized resources and expertise

By integrating and industrializing multiple emerging technologies at its research facility, the Center for Critical Path Immunology, ITI can more rapidly and efficiently discover and validate disease biomarkers and diagnostics that reveal the mechanisms of action of new therapeutic compounds, and help predict drug safety and efficacy with greater speed and precision.

### **Targeted Diseases**

The immune system plays a critical pathogenic role across a range of diverse disorders. Excessive immune activation is central to the progression of allergies, asthma, cardiovascular disease, organ transplant rejection and autoimmune disorders such as type 1 diabetes, rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus. An insufficient immune response often prevents

effective patient responses in cancer and infectious diseases, such HIV, tuberculosis and malaria.

While two decades of groundbreaking basic research have advanced the scientific understanding of the nature and mechanisms of immune function, current available therapies still act predominantly either through global suppression or stimulation of the immune response, rather than through antigen or tissue-specific regulation. Translating important basic research discoveries into targeted therapeutics that specifically modulate the immune system in disease (without harming its disease-fighting capabilities) has the potential to transform the lives of millions.

### **ITI Technology Platforms**

ITI will accelerate the pace of drug development by performing assays for academic and pharmaceutical industry partners, utilizing the following integrated technology platforms:

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#### **Cellular Analysis**

Flow cytometry is a powerful quantitative method for characterizing single cells from blood and other fluids and tissues. Cells are labeled with fluorescently tagged reagents which bind to specific cell surface and intracellular molecules and then passed through a laser beam for analysis. Through the use of multi-color flow cytometry, phenotypically distinct subsets of leukocytes in peripheral blood can be defined and characterized. Such specific leukocyte populations are identified and characterized based on the combinations of molecules they express. ITI will use state-of-the art multi-laser instruments to enable fine phenotyping of cells of the immune system. Recently the development of new fluorochromes and quantum dots has provided the means to progress from current standard flow cytometry in five to six colors to nine-color, and then ultimately even higher parameter flow cytometry (the potential for up to 19-colors with current instrumentation). A highly polychromatic flow platform provides a robust assessment immune function based on differences in cell numbers, cell types and expression of cell-associated molecules related to disease or response to treatment. Quantitative measures of distinct cell types can be correlated to levels of gene expression and used to help normalize gene expression profiles of

hundreds to thousands of genes determined by multiplex real-time PCR or microarray based techniques.

**Flow cytometry assays that will be performed by ITI include:**

- cell surface phenotyping from peripheral blood
- intracellular staining
- cytokine production in whole blood or from *in vitro* cultured cells
- phosphoprotein assessment of whole blood or *in vitro* cultured cells
- cellular proliferative responses following *in vitro* culture
- tetramer analysis for antigen-specific T cells
- apoptotic responses following *in vitro* culture

**Immune cell function.** Most of the phenotypically distinct subsets defined by flow parameters also have unique functional profiles, as determined by cytokine production, proliferative capacity, or apoptotic potential. By examining the distinct functional responses, including antigen-specific responses, among these subsets, the roles of each of these subsets in immune system function can be understood. Additionally, the function of immune system cells can be altered by disease or treatment. Ex vivo response to stimuli, such as specific antigens or drugs, will be used to evaluate the immune cell function. Evaluation of cytokines, which can stimulate or inhibit the growth and activity of various immune cells and mediate inflammatory responses, is of particular utility. Cytokines are essential for a coordinated immune response and, when properly regulated, have the potential to fight infection by organisms such as viruses and bacteria. However, some immune conditions are characterized by overproduction of cytokines that cause inflammation and pathology. Similarly, non-specific immunostimulatory therapies can also trigger cytokine overproduction which can be toxic. ITI will use multiple platforms, including multi-parameter flow cytometry, cell specific ELISPOT assays and bulk immunoassays, for the assessment of immune cell function.

**ITI will employ technology platforms as required to:**

- Enumerate frequencies of cytokine-producing cells using *in vitro* culture system

- Determine concentrations of multiple cytokines from *in vitro* cell culture supernatants
- Determine concentrations of multiple cytokines *in vivo* (serum)

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### **Protein Analysis**

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Protein analysis will focus on specific analytes in serum or secreted in cultured stimulation assays that are relevant to immune system monitoring. This includes: molecules which are involved in immune and inflammatory processes such as cytokines, chemokines and acute phase reactants; antigen-specific antibodies, including autoantibodies, pathogen specific antibodies and antibodies specific to therapeutic agents; and, markers for specific organ damage that can be caused by immune system dysfunction. Specific immunoassays will be developed on platforms with multiplex capabilities with the goal of minimize sample needed and maximizing throughput.

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### **Genomic Analysis**

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Genomic analysis will focus on gene expression with two approaches:

**Gene expression microarrays:** Microarrays permit the study and comparison of thousands of genes simultaneously in order to obtain measures of all the expressed genes from blood or tissue samples and then make comparisons with other samples to identify differentially expressed genes. Expressed gene profiles from blood or tissue will be generated from samples collected longitudinally over the course of a clinical trial or in natural history studies for disease staging. With this technology, researchers can study which genes are turned on or off by either disease or treatment and formulate a detailed picture of the genetic profile of a specific disease and its treatment on patient groups or individuals over the course of a clinical trial. Differential gene expression profiles representative of individual disease or treatment groups can then be determined. Individual patient profiles can be generated by comparing and contrasting samples in a longitudinal series over the course of a clinical trial.

**Quantitative gene expression:** Validation of expressed gene markers requires the use of a quantitative method in order to determine a more precise level of gene expression not possible from microarrays. This quantitation is often the second step in developing a validated expressed gene marker for clinical monitoring or diagnostics. However, single quantitative real-time PCR reactions have proven to be quite laborious and expensive, thereby limiting the number of genes able to be examined simultaneously. Recent advances in the multiplexing of real-time PCR reactions are circumventing this problem, allowing quantitative real-time PCR to be used to examine hundreds of genes at once. Unlike traditional approaches, ITI will employ newer technologies that will examine precise levels of expression of hundreds of genes at once, providing a more in-depth genetic profile of disease progression and treatment effects.

ITI will utilize these methodologies for:

- Quantitation of mRNA transcripts of hundreds of genes
- Profiling of microRNA
- Epigenetics-such as DNA methylation

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## **Bioinformatics**

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ITI will optimize new statistical approaches for interpretation of multi-parameter flow data and gene expression data, as well as for exploring cross platform data normalization. In addition, ITI will implement sophisticated informatics platforms in sample tracking and data visualization.

Advanced robotics will be utilized to facilitate large-scale and efficient immunophenotyping, which identifies cell subsets based on their surface antigens. Enhancing the scale and throughput of immunophenotyping will make it possible to integrate cellular analyses with high-throughput genotyping and proteomics, providing a more unified approach to immune biomarker development than currently available. ITI's platforms are standardized so that phenotypic data can be linked bioinformatically to genomic and clinical data. Such standardization will further enable the study of individual patient responses over the course of a clinical trial.

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## **Automation**

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## **References**

1. FDA Approves 19 New U.S. Drugs, Fewest Since '83; Glaxo Leads. Bloomberg.com, January 9, 2008. Available at: <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=a2MOCNVDHucs>
2. Schachter, A.D. and Ramoni, M.F. Clinical forecasting in drug development. *Nature Rev. Drug Discov.* 6, 107-108, 2007
3. Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Products. U.S. Department of Health and Human Services, Food and Drug Administration, 2004
4. Agres, T. Condition: Critical. FDA's critical path initiative reaches its third birthday, and its time for a report card. *Drug Discov. And Dev.* 10, 41-44, 2007.