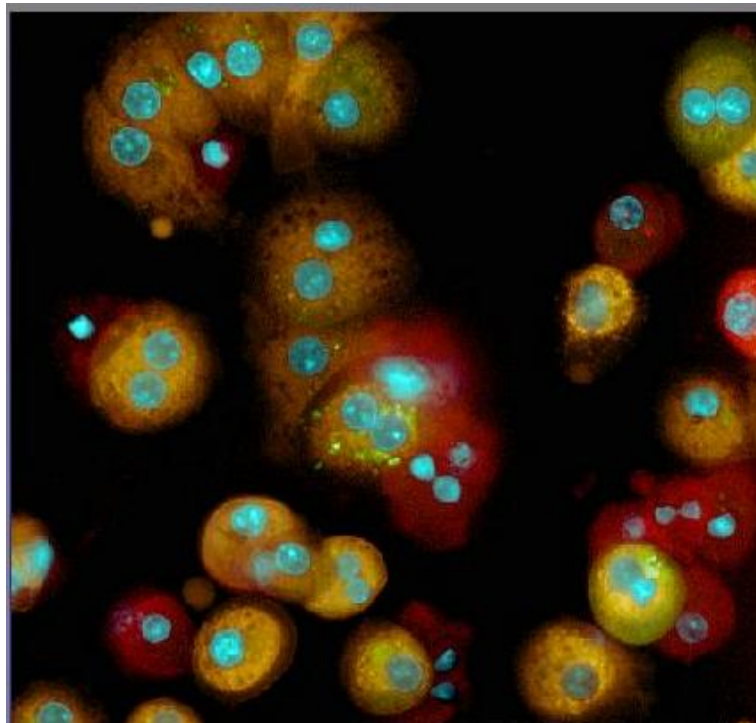




**MICHIGAN TECHNOLOGY
& RESEARCH INSTITUTE**

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SCIENTIFIC AND TECHNICAL CAPABILITIES

Expediting pharmaceutical decision making through
biomarkers, enhanced clinical trial designs,
and unique drug research and development strategies

MICHIGAN TECHNOLOGY AND RESEARCH INSTITUTE, LLC

INTRODUCTION

The INSTITUTE is organized to provide services which facilitate research and development activities in the pharmaceutical and biotechnology industry sectors including:

- Clinical and pre-clinical pharmaceutical research groups
- Contract research organizations
- Biotechnology companies
- Independent clinical and hospital laboratories
- Academic health research institutions
- Academic groups interested in optimizing intellectual property value of new discoveries.

The INSTITUTE is comprised of two centers of expertise, a Laboratory Center providing biomarker and specialized genetic testing, and a Technical Center offering drug-development consulting, project management, preclinical safety program strategy and testing, and integrated clinical trial design.

THE PHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

Traditionally, drug development and discovery followed structured paradigms under regulatory guidance which only rarely covered all eventualities encountered in the very complex process of drug development. This is particularly true in an era of rising development costs and a regulatory climate becoming increasingly risk averse. These factors have forced pharmaceutical companies, large and small, to seek means of cutting costs and accelerating the process of moving promising drug candidates through pivotal stages of

development to critical decision points. In many instances costing pressure has forced companies to scale back investigative laboratory research to focus activities and resources on conventional testing of a larger number of molecules to ensure a steady flow of drug candidates. Tests that were not part of routine drug screening are now being performed by external laboratories which specialize in these assays and increase flexibility and contribute innovation to the new drug development process. Outsourcing expertise has become a common approach in the increasingly challenging pharmaceutical world. This is a service provided by the INSTITUTE.

Regardless of the high hurdles in regulatory approval, the exceptional revenues generated by successful drugs have attracted a heterogeneous contingent of new players into the pharmaceutical arena. These groups often have advanced discovery research expertise and specialize in early stage activities, but very limited laboratory capabilities and/or insufficient hands-on experience in shepherding new chemical entities through the various stages of development to proof of concept clinical testing. Also, these new companies generally do not have sufficient resources or capitalization to fully fund the estimated \$950 million now required to get a promising drug to market. Increasingly, new molecules for the various large corporate pipelines are generated from smaller organizations specializing in early-stage drug development, with the more expensive Phase II and III clinical trials being the purview of the large pharmaceutical segment. It is in the best interests of the early-development stage companies to advance their discovery ideas and develop compounds as far as

possible, and as fast as possible, through the drug-development protocols to optimize return for founders, shareholders, and investors. As an expediting research organization this is a service provided by the INSTITUTE.

Biomarkers of pharmacological or therapeutic activity and safety can be critical indicators of a compound's potential and attractiveness to big pharmaceutical companies. When the biomarker is a routine test widely available in reference laboratories (i.e. troponins, cholesterol, blood cell counts), the path is clear and costs are relatively modest. However, that is rarely the case for drugs with new mechanisms of action or targeting chronic diseases such as diabetes, arthritis, or dementia. In most instances new drugs do not emerge with a validated biomarker that can enable decision making or allow safe progression. Laboratories capable of developing, validating, performing, and assessing biomarkers are relatively rare, representing a strategic opportunity in an area that promises increased diagnostic and research tools. The INSTITUTE provides the capability to develop and validate novel biomarkers and genetic tests to facilitate pharmaceutical decision-making.

PHARMACEUTICAL EXPEDITING ORGANIZATION

The INSTITUTE is an integrated pharmaceutical expediting organization with laboratory, research, and expert consulting capabilities. The INSTITUTE services are targeted at accelerated decision making and optimization of strategies that allow identification of high-potential drug molecules. The laboratory techniques and expert consulting ensure compound characteristics, both efficacy and safety, are identified as early as possible for decision-making and timely attrition as warranted. The latter consideration being of particular importance in that failure during later stage development can be crippling. If non-

viable molecules can be identified in Phase I human testing or during pre-clinical testing, the potential savings can be \$75 million to \$130 million per program versus a program that progresses through Phase II and fails.

The INSTITUTE provides tools, ideas, and laboratory support to help clients select the most promising drug candidates and determine as early as possible their potential. The Institute offers expertise in Good Laboratory Practices (GLP) and Good Clinical Practices (GCP) compliant high-complexity testing.

BIOMARKER DEVELOPMENT

Biomarkers are the most promising tools for reducing the cost of developing drugs and ensuring that the appropriate patient populations are treated. The goals of biomarker use are identification, at the earliest possible stage, of the best projects to devote scarce resources. This allows shortening of timelines to critical decisions and enhanced productivity by increasing the number of new drugs eventually achieving approval. Proper use of these tests improves the quality and quantity of mechanistic information obtained at each step of the drug development process, allows better understanding of other results and the factors relevant to their interpretation, and provides clearer indications of a molecule's activity or potential safety liabilities. Biomarkers also differentiate a new drug from products already on the market. There is a wide spectrum of new technologies encompassing biomarkers. While biomarker development and use have been featured at many specialized scientific meetings and the field has received extensive media coverage, the number of individuals with true experience in answering relevant drug-development questions and "hands-on" application of tests is quite limited. This is especially true for scientists with experience in both pre-clinical animal testing and support of human clinical trials. The INSTITUTE scientists

are experienced in a broad range of biomarker applications encompassing activity and safety.

CLINICAL AND PRE-CLINICAL RESEARCH

The INSTITUTE also brings value to clients through clinical protocol development, project management, development of pre-clinical programs, medical writing, and pre-clinical to clinical bridging strategies. These services are available to complement a company's existing capabilities or to handle all aspects of drug development stages for organizations without clinical resources or internal laboratories. Specific options, including strategic program opportunities, testing protocols, assembly of research and global registration documentation, peer review, and study logistics also can be provided.

THE INSTITUTE provides this rare combination of comparative experience and a proven history of determining the relevance of unexpected or species-specific findings. These approaches offer expertise learned from previous successful experiences encompassing compounds in multiple therapeutic areas (i.e. cancer, anti-infective, anxiety, anti-psychotic, pain, oncology, cardiovascular, diabetes) for small molecules and biologics. Additional value resides in the expertise and interpretation of biomarker data generated from the INSTITUTE laboratories, the client's laboratory, or an external CRO. Distinguished expert consultants in this area are tangible assets in providing quality service to the clinical trials community.

THE LABORATORY CENTER

The Laboratory Center provides genotyping and biomarker support for both pre-clinical and clinical studies. This aspect of the INSTITUTE involves development of new tests specific to a client's need and monitoring other biomarkers from established tests that cover a broader range of physiologic and pharmacologic assessment. The INSTITUTE specializes in high-complexity

testing involving methods that necessitate specialized levels of technical expertise. The majority of these procedures utilize molecular biology, ELISA, cell biology, and chemiluminescence approaches.

THE TECHNICAL CENTER

The Technical Center is structured to serve as a base of expert consultants specialized in different medical and technical disciplines. In addition to its internal personnel, the INSTITUTE has established alliances with complementary groups for specialized services. Thus, the operating model effectively accomplishes excellent client service with the flexibility to address a broad range of strategic situations.

The Technical Center specializes in planning, design, implementation, and interpretation of preclinical safety programs. These services include expert nonclinical safety assessment, pharmacokinetics and toxicokinetics, compliance with Good Laboratory Practices, and international regulatory support. The medical specialists also provide expertise in Good Clinical Practice compliance, and clinical research protocols. The knowledge base provides excellent study management and evaluation, including report preparation in compliance with FDA and ICH guidelines. This group is involved in clinical trial deployment including protocol preparation, amendments, Investigators' Brochures, and ongoing medical management of studies.

MANAGEMENT STRUCTURE

THE INSTITUTE management has many years of experience in drug development, biomarkers, mechanistic solutions for late-stage drugs experiencing safety issues, regulatory filings, toxicology methods, incorporation of genomic applications into clinical trials, pre-clinical to clinical translation, regulatory affairs, and project management. Through their more than

85 combined years of experience in corporate drug development, the INSTITUTE'S Executive Team has participated actively in the development of more than a dozen major new drugs, including Accupril, Quinaprilat, Lopid, Nipent, Tacrine, Fempatch, Rezulin, Neurontin, Lyrica, Celebrex, Bextra, Cerebyx, Dilantin, Omnicef, Dilantin, Detrol, Camptosar, Viracept, and Lipitor.

Michael R. Bleavins, Ph.D., DABT

Dr. Bleavins is the President of the Laboratory Center in the Institute. Dr. Bleavins retired from Pfizer in 2006 and has more than 21 years of experience in biomarkers, translational medicine, collaborations in Pharmaceutical Research and Development, and application of new technologies to facilitate pharmaceutical decision making. He has a Ph.D. in Environmental Toxicology and Animal Science from Michigan State University, with postdoctoral fellowships at the University of Wisconsin-Madison and the General Motors Biomedical Sciences Research Laboratories. He is a Diplomat of the American Board of Toxicology and a member of several scientific societies. He holds adjunct appointments at the University of Michigan and Wayne State University. Dr. Bleavins was responsible for extensive laboratory operations including biomarkers, clinical pathology, cell biology, molecular biology, immunotoxicology, live-cell imaging, genetic toxicology, investigative pathology, pharmacogenomics, genomics, metabonomics, proteomics, and biochemistry when at Pfizer. He has 66 publications in these areas and multi-species effects of toxic agents. He is internationally recognized as an expert in biomarker development, validation, and translation, as well as drug development, with invited lectures across the United States, United Kingdom, Europe, and Japan. Dr. Bleavins' has significant experience in multidisciplinary collaborations, bridging pre-clinical and clinical

safety testing, clinical trial support, academic collaborations, and application of emerging technologies.

David G. Pegg, PhD, DABT

Dr. Pegg is President of the Technical Center in the Institute. He retired from Pfizer in 2007 and has 25 years serving in managerial and scientific positions leading drug development, investigative research, regulatory and scientific/regulatory policy initiatives. He holds a PhD in Pharmacology and Toxicology from Michigan State University with postdoctoral training in inhalation toxicology research at Dow Chemical Research Laboratories. He was employed for 7 years at General Motors Biomedical Sciences Research Laboratories in environmental toxicology research before joining the Parke-Davis Pharmaceutical Research Division of Warner-Lambert which was acquired by Pfizer. Dr. Pegg is a Diplomat of the American Board of Toxicology and a member of the Society of Toxicology. He holds an appointment as adjunct professor of pharmacology/toxicology at Michigan State University. He has extensive experience in drug development decision-making, and is a strong proponent of investigative research in pharmaceutical risk management. He led the investigative research team at Pfizer resulting in eventual approval of Lyrica®. He also was the nonclinical lead for licensing/acquisition and due diligence assessment of candidate compounds. He is internationally recognized as a principal architect of the exploratory IND concept through his work within the Pharmaceutical Research and Manufacturers Association and has lectured extensively in the US and Europe on design and development of rapid first-in-human trials for key pharmaceutical decision-making. He has over 30 publications in toxicology research

