



PRI Executive Vice President and Chairman Shaker A. Mousa, Ph.D., MBA, FACC, FACB, has demonstrated throughout his distinguished career the ability to bring novel concepts from the bench to the bedside, along with his great vision in selecting the right target. He has exhibited the ability to strategically plan and implement tactical measures in achieving the required goals.

Dr. Mousa came to Albany College of Pharmacy in 2002 following a career of more than 17 years as a principal research scientist at DuPont Pharmaceuticals Co. In addition to his leadership role at PRI, he is a tenured professor at the College, a visiting scholar at The Johns Hopkins University, and is an adjunct professor in the Department of Medicine at Temple University's Sol Sherry Thrombosis Research Center, the Department of Medicine of the State University of New York at Buffalo, and the Department of Pharmacology of the University of Pennsylvania.

In addition, Dr. Mousa serves on the editorial boards and is a reviewer for several scientific and medical journals, including *Cardiovascular Drug Review*, *Atherosclerosis*, *Thrombosis & Vascular Biology*, *Circulation*, *Lab Investigation*, *JCI*, *JBC* and *Current Drugs*.

Dr. Mousa's professional accomplishments include his contributions to several patents – he holds 30 U.S. patents, including six filed in 2004 and 2005, and more than 200 foreign patents. His work has been reported in more than 600 publications. Dr. Mousa has contributed to the discovery and development of novel anti-platelet and anti-thrombotic therapies, and non-invasive myocardial perfusion and thrombus imaging agents. Specifically, he has contributed to the discovery

and development of the following products and clinical candidates:

- **Cardiolite (R)** (Tc99m sestamibi RP30, a non-invasive myocardial perfusion imaging agent)
- **Marluma** (Tc99m sestamibi RP30, for breast cancer detection)
- **DMP444** (Tc99m platelet GPIIb/IIIa antagonist for non-invasive thrombus imaging agent in venous and arterial thromboembolic disorders)
- **Roxifiban** (DMP754, oral anti-platelet/anti-thrombotic agent for the prevention and treatment of coronary, carotid and peripheral artery thromboembolic disorders)

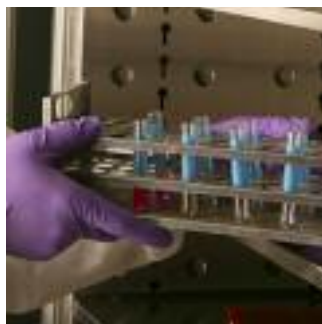
Dr. Mousa was involved in the discovery of novel site-directed anti-alpha v beta 3 tumor radiotherapy and imaging, and in defining novel angiogenesis inhibitors. Also, he contributed to the discovery of novel pharmacological aspects of heparin and low-molecular-weight heparin, and to the advancement of several key concepts, such as the synergistic benefits of GPIIb/IIIa antagonists in combination with thrombolytics, the role of integrin alpha 5 beta 1 in angiogenesis and bacterial invasion of human host cells, and the role of fibrinolytic components such as kininogen in angiogenesis.

Dr. Mousa's current research interests include:

- Adhesion molecules in health and disease
- Novel therapeutic and diagnostic targets
- Treatment and prevention of ischemic and coronary artery diseases
- Angiogenesis modulation, vascular and tissue remodeling, and novel anti-platelet, anti-thrombotic and anti-ischemic therapies

A native of Alexandria, Egypt, Dr. Mousa received his B.Pharm. and M.Sc. degrees from Alexandria University. He received a Ph.D. in Pharmacology from The Ohio State University, completed postdoctoral research in cardiovascular pharmacology at the University of Kentucky, and earned his

MBA from Widener University. He since has been elected a fellow of the American College of Cardiology (FACC) and the National Academy of Clinical Biochemistry (FACB), and is a member of several national and international societies.



An important strategic focus of PRI is the development of state-of-the-art drug formulation and drug delivery units that facilitate drug development for pharmaceutical and biotechnology organizations.

These units function as a resource partner for pharmaceutical and biotech industries operating under the Food and Drug Administration's Good Laboratory Practices (GLP). Through these units, PRI conducts pre-clinical testing and clinical trials to develop drugs for transition to industrial manufacturing, with the potential of discovering new strategies to treat current and emerging diseases. Following is a summary of the products and services PRI provides:

### **Pre-formulation and Stability Testing**

- Novel dosage forms, including sterile products, tablets, capsules, topical preparations and nonconventional products such as semi-solid or sustained-release preparations
- Products to enhance drug solubility and stability, improve bioavailability, target tissue delivery and treat specific patient populations
- In vitro evaluation of stability and release properties for formulations

### **Analytical Chemistry**

- Verification of chemical structure and compound purity
- Development and validation of analytical methods to quantitate drugs in formulations or biological samples
- Conduct drug stability determinations

and other preformulation studies

- Evaluation of pharmaceutical dosage forms following USP requirements

### **Nanotechnology in Preformulation and Stability Studies**

Prior to the development of any dosage form with a drug candidate, it is essential to determine its fundamental physical and chemical properties. Subsequently, this information dictates events and approaches in formulation development. Pharmaceutical preformulation studies encompass this initial assessment of the physico-chemical properties of the drug substance. The Center for NanoPharmaceuticals will be an integral part of PRI's work in this area.

At PRI, we believe that a thorough understanding of drug properties helps minimize problems in the later stages of drug development, reduces the time to market and enhances cost-effectiveness. The goals of preformulation studies are to choose the correct form of the drug substance, evaluate its physical and chemical properties, and assess the stability of the drug under various conditions to provide an optimal drug-delivery system.

PRI offers a wide range of approaches to achieve these goals. We work closely with clients to determine the best approach for their preformulation and stability assessment needs. Our preformulation and stability services include:

- Polymorph screening
- Salt form selection
- Solubility determination
- Stability testing

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We employ the following state-of-the-art techniques for the above-mentioned services:

- X-ray powder diffraction
- Thermal analysis
- Differential Scanning Calorimetry
- Thermogravimetric Analysis
- Fourier Transform Infrared Spectroscopy
- UV-Vis spectrophotometry
- Dynamic Vapor Sorption determination
- Chromatography (HPLC, GC)
- Atomic absorption spectroscopy
- Karl Fischer titrimetry
- Loss on drying
- Optical microscopy

Stability studies provide the first quantitative assessment of the chemical stability of a drug. PRI has state-of-the-art capabilities for stability testing in accordance with ICH guidelines. For example, our stability chambers, equipped with emergency power back-up, are carefully and consistently monitored so that we can provide controlled temperature and humidity conditions as per customer requirements. Furthermore, we offer the following services as part of our stability-testing program:

- Storage of samples for stability studies as per ICH guidelines
- Provision of short-term, long-term and accelerated options for stability testing according to customer needs
- Flexibility in accommodating custom storage conditions

- Development of analytical methods for drug substances and degradation products
- Method development and validation of stability-indicating assay methodology for drug substances and products
- Completion of forced degradation studies, including photostability

### **Formulation Development**

PRI's analysis of drug substances for the development of dosage forms includes:

- Examination of morphology, crystalline or amorphous nature and particle size distribution
- Dissolution testing
- Excipient compatibility
- Flowability, compatibility, bulk and tap density
- Hygroscopicity profile

### **In Vitro Screening for Oral Bioavailability**

The determination of intestinal permeability of drugs intended for oral administration is important in the selection of candidates for drug development. At PRI, we use the established Caco-2 permeability screen as an indicator of in vivo intestinal absorption. Caco-2 cells, which are derived from a human colonic adenocarcinoma, differentiate into a cell monolayer barrier representative of a small intestinal columnar epithelium. The Caco-2 permeability screen offers a way to screen the permeability of drug candidates rapidly and eliminate candidates that would be unable to cross the intestinal barrier.

### **Plasma Protein Binding**

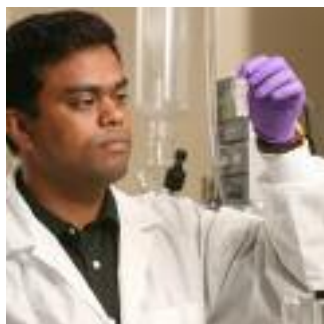
The degree of binding of a compound to plasma proteins can provide important indications about the compound's efficacy and its potential for drug-to-drug interactions. Plasma protein binding (PPB) can have a significant affect on the pharmacokinetic and the pharmacodynamic properties of a drug because an unbound drug can penetrate blood vessel walls, whereas protein-bound drugs cannot.

Determining the amount of drug binding to serum proteins is important in the discovery and clinical phases of drug development. The extent of PPB characteristic of a drug is critical to predicting its pharmacokinetic profile, doses required for the drug and its possible drug-to-drug interactions. PRI is equipped to study the degree of PPB for drugs.

### **Pharmacokinetic Studies**

PRI's preclinical metabolism services provide pharmacokinetic data to prepare for the IND and to define a Phase I clinical study design. PRI is able to conduct pharmacokinetic studies in small and large animals.

In vivo studies elucidate the drug metabolites, as well as the identity and distribution of the drug across tissues and organs. As a result, pharmacokinetic parameters such as AUC, half-life, clearance and volume of distribution can be determined. Furthermore, these studies can help to determine the rate and route of drug elimination.



At the intersection of two of the most exciting emerging technologies in scientific research and development – nanotechnology and biotechnology – a third cutting-edge development that promises breakthroughs that will save and improve lives, while offering dramatic economic benefits.

### **Nanopharmaceuticals**

Albany College of Pharmacy has taken a vital role in this field through the establishment of the Center for NanoPharmaceuticals, which is part of the Pharmaceutical Research Institute. Located at the State University of New York's Gen\*NY\*Sis Center for Excellence in Cancer Genomics in Rensselaer, N.Y, the Center is a state-of-the-art facility that plays a leading role in the development of technologies that will allow the delivery of medicine to specific cellular targets anywhere in the body. Such technologies will greatly increase the efficacy and safety of drug therapies for diseases such as cancer, macular degeneration and vascular disorders.

The Center conducts its own novel inquiries and partners with scientists at other nanotechnology and biotechnology centers to exponentially increase the power of expanding scientific, medical and technical expertise on a global scale. Collaborators include the State University of New York at Albany, Rensselaer Polytechnic Institute, Ordway Research Institute and Albany Medical Center; as well as other national academic and industrial institutes. Interest in this field has increased considerably, especially after the commercial success of

products such as Lupron Depot®, Zoladex®, Norplant® and Gliadel®.

A major focus of PRI is the discovery and development of nanomedicines that can be delivered to specific targets in the body, such as tumors. PRI uses polymer chemistry to enhance the drug molecule to achieve the desired drug-delivery system, and to improve stability, absorption and pharmacokinetics. The key advantages that polymeric drug-delivery systems can offer are localized delivery, sustained release and enhanced stability of a drug.

Nanotechnology is advantageous in drug discovery and development efforts for refinement and enhanced efficiency; it enables scientists to seek drug targets at a submicroscopic level. Therefore, minuscule amounts of a sample can be analyzed quickly to identify targets for drug development. Drug-binding molecules tiny enough to travel through the body's smallest capillaries may provide a way to spare various organs from the toxic effects of drug overdose; evidence suggests that some nanopharmaceuticals markedly reduce the effects of toxic drugs and improve delivery.

This is the tip of the nanotechnology iceberg in terms of how it can be used to modulate drug transport, both for drug uptake and delivery applications. The development of antidote nanopharmaceuticals is very promising in the effort to save the lives of people exposed to severe drug poisoning.

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PRI also is designing nanoparticles, or "nanobullets," that bind to harmful drugs circulating in the body and reduce their free concentration in the bloodstream. Nanoparticles represent a whole new scale of man-made materials that previously only occurred naturally. With modern tools, including the electron microscope, we now can see, characterize and produce materials this minute. For example, particles can be manufactured as small as 5-10 nanometers for delivery, via the blood, to any part of the body.

The ideal nanopharmaceutical agent for detoxification must be safe, biocompatible,

biodegradable and disguised so that the body's immune system will not recognize it as foreign. The ultimate agent will recognize the toxic drug molecules, attract and bind them quickly, and reduce the free drug concentration. Assembling nanoparticles with many components already designated by the U.S. Food and Drug Administration as safe, and applying the various nanoparticle drug-removal agents to life-threatening drug overdoses for which few, if any, therapies currently are available represents a tremendous opportunity. This is an important focus of research at PRI.



Experimental research at PRI focuses on identifying novel therapeutic and diagnostic strategies for unmet medical needs, with the initial focus on advancing the development of key concepts for vascular and cardiovascular diseases.

In this area, initial research is concentrated on in vitro and in vivo models of angiogenesis, thrombosis and vascular biology. Investigation includes a search for new approaches to modulate angiogenesis in oncology, dermatology and ophthalmology.

### **Angiogenesis**

Angiogenesis, the formation of new capillary blood vessels, is dependent upon coordinate production of angiogenesis promoters and suppressors. In pathology, angiogenesis can last for years and be somewhat out of control due to an imbalance between angiogenic and angiostatic factors (overproduction of angiogenic factors and/or deficiency of angiostatic factors).

Regulation of blood vessel growth underlies a wide spectrum of biological processes, including physiological processes such as reproduction, development, repair, wound healing and collateral and pathological processes such as cancer (tumor growth and metastasis), ocular (diabetic retinopathy, macular degeneration), inflammatory arthritis

and cardiovascular disorders (ischemic heart disease and atherosclerotic plaque).

To establish angiogenesis balance, the switch to the angiogenic phenotype involves a change in the local equilibrium between positive and negative regulators of the growth of microvessels. Research at PRI investigates how this imbalance relates to the cause of, and treatment for, these disease states.

### **Thrombosis**

Thrombosis remains the leading cause of morbidity and mortality. Therefore, effective anti-thrombotic strategies remain a critical therapeutic objective.

The past decade has witnessed distinct progress in the development of newer anti-coagulant, anti-platelet and thrombolytics for the prevention and treatment of various thromboembolic disorders. Understanding of the pathogenesis of thrombotic and vascular disorders has greatly facilitated these developments to target blood vessels, platelets and the protease network involving the coagulation, thrombolytic and the fibrinolytic systems.

Improved processing from natural sources, biotechnology and organic chemistry strategies

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played a major role in the development of such drugs as low-molecular-weight heparin (LMWH), oral heparin and anti-thrombin agents. Many of the important drugs, such as LMWH, pentasaccharide, direct anti-thrombin, direct anti-Xa agents and biotechnology-derived therapeutic agents are advancing rapidly.

The need for pharmacokinetic and pharmacodynamic optimization that PRI provides will be critical for the success of these strategies. Additionally, high-throughput screening, drug-drug interactions and clinical monitoring that the Institute provides will be essential to advance the clinical development of these agents.

### **Vascular and Metabolic Disorders**

The search for novel mechanisms that act at the vascular endothelial cell levels in providing vascular protection and, hence, improved vascular patency in the prevention and treatment of cardiovascular and vascular disorders represents a key focus for the next generation medicines.

Experimental research at PRI establishes in vivo animal models of acute arterial and venous thrombosis, and pharmacodynamic (PD) and pharmacokinetic (PK) readouts for various anti-coagulants and anti-platelet agents, and in various combinations with commonly used drugs. PRI also seeks to define novel strategies to improve PD and PK of existing anti-coagulants and anti-platelet agents.



During drug discovery and early clinical development, it is essential to have multiple mechanism-related readouts that predict successful clinical outcomes. This segment of research at PRI provides key information that will help bridge the gap between experimental and clinical results. Additionally, this segment provides surrogates that are linked to clinical outcomes.

Some activities in this process include identifying potent integrin-ligands and other biological targets for therapeutic and diagnostic applications; determining screening strategy, endothelial cell migration, proliferation, tube formation and in vitro neovascularization models; establishing the CAM assay for angiogenesis, tumor growth and metastasis; screening for anti-platelet and anti-coagulant potency; and collaborating with different groups in search of novel strategies.

Biomarker research at PRI includes:

- Endotoxin in humans; this acute model might be useful to evaluate the efficacy of anti-inflammatory agents in Phase IIA
- Deep vein thrombosis and pulmonary embolism
- Congestive heart failure
- Coronary artery diseases
- Interventional procedures for abrupt closure and restenosis

- Inflammatory diseases
- Vascular, ocular, oncological and hematological disorders

Surrogate markers in clinical samples might include:

- Tissue factor (TF)
- C-reactive protein (CRP)
- Soluble P-, E- and L-selectins
- Von Willebrand factor (vWF)
- Soluble vascular cell adhesion molecule-1 (sVCAM-1)
- Soluble intracellular adhesion molecule-1 (sICAM-1)
- F1.2
- D-dimer
- Protein C
- Protein S
- Tumor necrosis factor-alpha (TNF-a)
- TNF-soluble receptors
- Nitric oxide
- Other vascular, inflammatory, angiogenesis and thrombosis biomarkers

Therapeutic and diagnostic opportunities exist to define anti-thrombotic targets to be used in conjunction with standard anti-cancer agents, and to define novel prognostic and diagnostic markers of specific cancer prothrombotic markers.

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The collaborative spirit emerging as the driving force in scientific discovery guides the research environment at the PRI. The Institute strives to form collaborative research efforts as it seeks out new and better ways to solve medical questions. Our research partners include:

### **Academic Institutes in New York State**

- Albany Medical College
- Cornell University
- Department of Health, Wadsworth Center/David Axelrod Institute
- Ordway Research Institute
- Rensselaer Polytechnic Institute
- Roswell Park Cancer Institute
- State University of New York at Albany
- State University of New York at Buffalo
- Veterans Administration – Albany

### **Academic Institutes (National and International)**

- Loyola University
- McMaster University
- Temple University
- The Johns Hopkins University
- University of Frankfurt
- University of Pennsylvania
- University of Toronto

### **Pharmaceutical and Biotechnology Companies**

- Albany Molecular Research Inc.
- AstraZeneca PLC
- Aventis Pharmaceuticals Inc.
- Cytosia Ltd.
- DuPont Pharmaceuticals Co.
- Eli Lilly and Co.
- Emisphere Technologies Inc.
- GlaxoSmithKline Inc.
- Johnson & Johnson
- LEO Pharma
- Merck & Co., Inc.
- Organon Sanofi-Synthelabo LLC
- Othera Pharmaceuticals Inc.
- Pfizer Inc.
- Pharmion Corp.
- SelectX Pharmaceuticals Inc.
- X-Ray Optical Systems Inc.

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