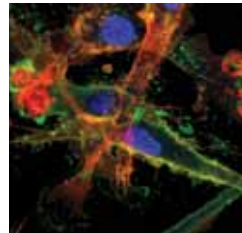


**BAYLOR RESEARCH INSTITUTE**

# INNOVATION FOR EACH PATIENT'S SAKE



 **BAYLOR**  
Research Institute

**BAYLOR RESEARCH INSTITUTE** IS LEADING THE CHARGE TO BRING INNOVATIVE TREATMENTS FROM THE LABORATORY WORKBENCH TO THE PATIENT'S BEDSIDE. **BY DELIVERING THE LATEST IN CLINICAL RESEARCH DIRECTLY TO THE PATIENT, THE INSTITUTE IS ABLE TO IMPROVE THE CARE AND WELL BEING OF ITS COMMUNITY.** BAYLOR RESEARCH INSTITUTE PROMOTES RESEARCH IN THE AREAS OF IMMUNOLOGY, INCLUDING INFECTIOUS DISEASE, ONCOLOGY, AUTOIMMUNE DISEASES AND RHEUMATOLOGY, AS WELL AS GENOMICS, DERMATOLOGY, TRANSPLANTATION, METABOLIC DISEASE AND CARDIOVASCULAR DISEASE.

**AWARD-WINNING SCIENTISTS AND MEDICAL PROFESSIONALS, WHO ARE DEDICATED TO PATIENT CARE, WORK TO UNDERSTAND THE ORIGIN OF A DISEASE, IDENTIFY POTENTIAL TREATMENTS OR PREVENTIVE THERAPIES, AND ENROLL PATIENTS IN RESEARCH TRIALS.** TODAY, THE INSTITUTE IS CONDUCTING MORE THAN 800 ACTIVE RESEARCH PROTOCOLS WITH 350 ACTIVE INVESTIGATORS, SPANNING MORE THAN 20 MEDICAL SPECIALTIES. THE INSTITUTE'S RESEARCH IS ALSO FREQUENTLY PUBLISHED IN MAJOR SCIENTIFIC JOURNALS AND REPORTED AT MEDICAL AND SCIENTIFIC MEETINGS, BOTH NATIONALLY AND INTERNATIONALLY.



### THE BUSINESS OF HEALTH CARE—WHY INVEST IN NORTH TEXAS?

Now tied with California for the most Fortune 500 companies than any other state, Texas provides an excellent climate for conducting business. Now, more than ever, health care is finding a home in pro-business and health-care-friendly North Texas. According to The Health Industry Council of the North Texas Region, the health industry for North Texas alone is greater than the health industries of 31 other states combined. With a central location, mild climate and access to world-class academic resources and technology companies, the Dallas-Fort Worth area continues to gain recognition as a top-tier medical hub and leads the country in pioneering patient care and research.

### LEADERSHIP

Baylor Research Institute is under the leadership and direction of health care professionals adept in driving funding to programs that further research initiatives in medicine. As an affiliate of Baylor Health Care System, the research institute is an integral part of the organization's overall vision of delivering advanced, safe and effective, patient-centered care supported by education and research.

**Michael A.E. Ramsay, MD, FRCA**, leads Baylor Health Care System's clinically relevant research efforts as president of Baylor Research Institute.

In 11 years with the organization, Dr. Ramsay has developed a successful infrastructure that has increased the number of active clinical trials from 250 to more than 800 today. He also has supported and led Baylor Research Institute's investigators in obtaining funding, including more than \$100 million in National Institutes of Health (NIH) grants.



Under Dr. Ramsay's leadership, Baylor Research Institute recently executed a collaborative, yet non-exclusive, agreement with a major pharmaceutical



company to advance early research ideas. This may prove to be a model for the future for many research centers.

In addition to his role at the institute, Dr. Ramsay is a member of the Baylor University Medical Center Board of Trustees and chairman of the hospital's Anesthesiology and Pain Management Department. He is active in liver transplantation anesthesia, having served as president of the International Liver Transplantation Society and authoring many peer-reviewed articles on the specialty. Dr. Ramsay also is recognized internationally for developing the Ramsay Scale, the first sedation scoring system in critical care medicine, and most common sedation scale used worldwide.

**Bernard Brigonnet**, chief operating officer and vice president, leads the strategy and runs the operations for Baylor Research Institute. This includes the management and oversight of the institute's more than \$60 million yearly budget, and leading the continued development of its unique and proprietary research technologies. Brigonnet's guidance is helping take the institute to the next level in its advanced technology and research pursuits.



A native of France, Brigonnet has more than 30 years of experience in the biopharmaceutical industry where he has served in a senior leadership capacity for several international organizations and major companies. Brigonnet holds a post-graduate

degree in marketing from the Paris Business School (ESCP) and an undergraduate economics degree from Besancon, France.

### FROM THE LABORATORY BENCH TO THE PATIENT'S BEDSIDE

Focusing on the patient is the mission of Baylor Research Institute. Transforming lives in numerous areas of medicine, the institute takes an investigative stance to research by considering all aspects of a disease and creating dynamic, therapeutic advancements that improve patient outcomes. Basic science, clinical trials, health care effectiveness and quality of care research are the main areas of study, forming a dual spotlight on research and treatment coupled with providing excellent care.

### ACCREDITATION FOR QUALITY, ETHICAL RESEARCH

Baylor Research Institute is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) for its commitment to quality and ethics in its research



efforts. The association recently reaccredited the institute for five years, rather than the industry standard of three. This accreditation certifies that Baylor Research Institute maintains efficient systems for monitoring research participant safety and embraces ethical standards higher than required by law. Internationally, fewer than 300 out of the thousands of human research protection programs have earned this prestigious distinction.



## ACCELERATING PROGRESS WITH **CANCER VACCINE** RESEARCH

Immunological approaches to the treatment of cancer are particularly attractive because unlike conventional therapies, they are specific, non-toxic and have been shown to generate very few side effects. Despite major advances in the development of cancer immunotherapeutics, cancer vaccines in the form of peptides, proteins and DNA, either alone or with adjuvants, have experienced limited success. However, the recent success of Dendreon's Provenge, an autologous vaccine for prostate cancer, has caused a resurgence of interest and activity in this field. Insight into the role of dendritic cells (DCs) as the pivotal antigen-presenting cells (APCs) has provided the basis for developing more effective immunotherapy regimens.

### ADVANCING RESEARCH AND TECHNOLOGY

Baylor Institute for Immunology Research has been on the forefront of DC immunotherapy since its inception. While the research institute has developed multiple immunological approaches to treat cancer, one area where it has developed particular expertise is using *ex vivo*-generated DCs as cancer vaccines. This approach is based on the rationale that DC vaccines may break the tolerance to the overburdened cancer antigens in the patients and induce strong anti-cancer immunity.

### MAKING AN IMPACT

DC trials led investigators to conclude that:

- DC vaccines are safe
- DC vaccines can induce tumor-specific immunity
- DC vaccines can induce significant clinical responses

Current research and clinical trials are extending the findings from earlier melanoma vaccine trials into other cancers, including pancreatic and breast cancer, and hematological malignancies. A clinical trial to test a therapeutic HIV vaccine also is under way and builds upon learning from the melanoma trials.

### CREATING INNOVATION

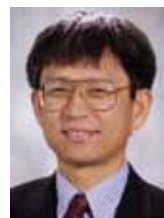
Baylor Research Institute has a broad patent portfolio that includes compositions and methods for producing APCs, use of allogeneic tumor cells to load dendritic cells, and methods to target and load dendritic cells.

### PRINCIPAL INVESTIGATORS: YONG-JUN LIU

Yong-Jun Liu, MD, PhD, is vice president and chief scientific officer for Baylor Research Institute and director of Baylor Institute for Immunology Research.

Dr. Liu joined the institute from a leadership position with Houston's University of Texas M.D. Anderson Cancer Center and is known worldwide as an expert in immunology, particularly the function of immune cells that are central to fighting cancer.

His 25 years of research has focused on human immunology, particularly dendritic cell biology, genomic approaches to the diagnosis of human diseases, the pathophysiology of autoimmune diseases and cancer, and the design of novel vaccines. Dr. Liu has published more than 200 scientific articles during his career, including many in the journals



*Nature, Science, Cell, Immunity, Nature Immunology* and *Journal of Experimental Medicine*, and is among the top cited scientists in immunology.

Dr. Liu also was honored as the George and Barbara Bush Fellow for Innovative Cancer Research in 2004. He earned his medical degree from Norman Bethune University, Chang Chun, Jilin, China, and his doctorate in immunology from the University of Birmingham School of Medicine.

#### KAROLINA PALUCKA

Karolina Palucka, MD, PhD, is an investigator at Baylor Institute for Immunology Research and holds the Michael A.E. Ramsay Chair for Cancer Immunology Research. Dr. Palucka launched the research institute's dendritic cell therapy program together with Joseph Fay, MD, and Jacques Banchereau, PhD, (a founder and former director of Baylor Institute for Immunology Research). Among the key areas of Dr. Palucka's research are improving the efficacy of dendritic cell vaccines, developing a dendritic cell vaccine for breast cancer and metastatic prostate cancer, and targeting human dendritic cells for melanoma therapy. She is an inventor and co-inventor on 14 patents and patent applications in the field of immunology.



Dr. Palucka is author and co-author of more than 100 publications, book chapters and reviews. She earned a medical degree from Warsaw Medical Academy in Poland, where she trained in internal medicine, and completed post-graduate training in medical oncology at the Maria Sklodowska Curie Memorial Oncology Institute in Warsaw, and earned her doctorate in hematology and immunology at the Karolinska Institute in Stockholm, Sweden.

#### JOSEPH FAY

Joseph W. Fay, MD, is the medical director for Immunologic Therapy for Cancer at Baylor Institute for Immunology Research and a Diplomate of the American Board of Internal Medicine with subspecialty certification in hematology and oncology. He specializes in blood and marrow transplantation. Dr. Fay started the bone marrow transplantation program at Duke University in 1977 sponsored in part by the National Cancer Institute. He has been the principal investigator for more than 80 clinical trials and has authored more than 100 peer-reviewed publications. He is currently the principal



investigator for several clinical trials of dendritic cell biology and immunotherapy.

Dr. Fay received his medical degree from The Ohio State University in 1972. His internal medicine internship, residency, and hematology and oncology fellowship were completed at Duke University Medical Center and the National Cancer Institute.

#### PUBLICATIONS

Palucka AK, Dhodapkar MV, Paczesny S, Ueno H, Fay JW, Banchereau J. Boosting vaccinations with peptide-pulsed CD34+ progenitor-derived dendritic cells can expand long-lived melanoma peptide-specific CD8+ T cells in patients with metastatic melanoma. *J Immunother*. 2005 Mar-Apr;28(2):158-68.

Banchereau J, Ueno H, Dhodapkar M, Connolly J, Finholt JP, Klechevsky E, Blanck JP, Johnston DA, Palucka AK, Fay JW. Immune and clinical outcomes in patients with stage IV melanoma vaccinated with peptide-pulsed dendritic cells derived from CD 34+ progenitors and activated with type I interferon. *J Immunother*. 2005 Sep-Oct;28(5):505-16.

Fay JW, Palucka AK, Paczesny S, Dhodapkar M, Johnston DA, Burkeholder S, Ueno H, Banchereau J. Long-term outcomes in patients with metastatic melanoma vaccinated with melanoma peptide-pulsed CD34(+) progenitor-derived dendritic cells. *Cancer Immunol Immunother*. 2006 Oct;55(10):1209-18.

Palucka AK, Ueno H, Connolly J, Kerneis-Norvell F, Blanck JP, Johnston DA, Fay JW, Banchereau J. Dendritic cells loaded with killed allogeneic melanoma cells can induce objective clinical responses and MART -1 specific CD8+ T-cell immunity. *J Immunother*. 2006 Sep-Oct;29(5):545-57.

Wieckowski E, Chatta GS, Mailliard RM, Gooding W, Palucka K, Banchereau J & Kalinski P (2011). Type-1 polarized dendritic cells loaded with apoptotic prostate cancer cells are potent inducers of CD8(+) T cells against prostate cancer cells and defined prostate cancer-specific epitopes. *Prostate* 71, 125-33.

Pedroza-Gonzalez A, Xu K, Wu TC, Asford C, Tindle S, Marches F, Gallegos M, Burton EC, Savino D, Hori T, Tanaka Y, Zurawski S, Zurawski G, Bover L, Liu YJ, Banchereau J & Palucka AK (2011). Thymic stromal lymphopoietin fosters human breast tumor growth by promoting type 2 inflammation. *The Journal of Experimental Medicine* 208, 479-90.

Ni L, Gayet I, Zurawski S, Duluc D, Flamar AL, Li XH, O'Bar A, Clayton S, Palucka AK, Zurawski G, Banchereau J & Oh S (2010). Concomitant activation and antigen uptake via human Dectin-1 results in potent antigen-specific CD8+ T cell responses. *J Immunol* 185, 3504-13.

Klechevsky E, Flamar AL, Cao Y, Blanck JP, Liu M, O'Bar A, Agouna-Deciat O, Klucar P, Thompson-Snipes, L, Zurawski S, Reiter Y, Palucka AK, Zurawski G & Banchereau, J (2010). Cross-priming CD8+ T cells by targeting antigens to human dendritic cells through DCIR. *Blood* 2010 Sep 9;116(10):1685-97. Epub 2010 Jun 7.

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## GENOMIC MEDICINE AND BIOMARKER RESEARCH: THE PROMISE OF INDIVIDUALIZED MEDICINE

The fields of medicine and molecular biology have converged to the extent that the concept of genomic medicine is now being realized. Molecular research on clinical samples is expanding at a furious pace in the post-human-genome era as new enabling technologies are developed and swiftly translated to the clinic. In response, Baylor is forming a precision medicine institute, which encompasses work at Baylor Kimberly H. Courtwright and Joseph W. Summers Institute of Metabolic Disease, Baylor Institute for Immunology Research and Baylor Gastrointestinal Cancer Laboratory to effectively explore the promising future of genomic medicine.

The precision medicine institute will serve as the research engine for basic and translational research while aggregating research and clinical resources around the theme of individualized patient care. Researchers are committed to delivering individualized genomic information for clinical decision support as well as to developing novel biomarkers that deliver powerfully precise diagnoses and treatment.

### ADVANCING RESEARCH AND TECHNOLOGY

The analysis of patients' blood transcriptional profiles offers a means to investigate the immunological mechanisms relevant to human diseases on a genome-wide scale. In addition, such studies provide a basis for the discovery of clinically relevant biomarker signatures (biosignatures). Baylor Research Institute has designed a novel proprietary strategy for microarray analysis based on the identification of transcriptional modules formed by genes coordinately expressed in multiple disease data sets.

Mapping changes in gene expression at the module level generates disease-specific transcriptional fingerprints that provide a stable framework for the visualization and functional interpretation of microarray data. These transcriptional modules are used as a basis for the selection of biomarkers and the development of a multivariate transcriptional indicator (biosignature) of disease status and progression in patients with complex illnesses such as systemic lupus erythematosus (SLE).



Furthermore, the same signature can be used to monitor the patient's response to therapy, thereby enabling the physician to optimize treatment in a personalized manner. The same biosignature approach has been used to identify disease-specific biosignatures for various immunological conditions, including infectious disease, cancer, autoimmune disease and organ transplantation. Importantly, researchers at the institute have developed, validated and implemented a methodology designed to support systems-scale analysis of the human immune system in translational research settings.

### CREATING INNOVATION

Researchers Virginia Pascual, MD, and Damien Chaussabel, PhD, were part of an international coalition of investigators from Great Britain, South Africa and the United States who identified a blood transcriptional signature associated with active tuberculosis. The study also identified a broad range of transcriptional biomarkers that could be useful as the basis for diagnostic and prognostic tests. These tools will be important in developing countries, where more than 90 percent of new tuberculosis cases and deaths occur, as well as in developed countries, as global travel has spread the disease and exacerbated the problem of drug resistance.

Concrete application of this research is already making its way to the bedside and impacting patients' lives. Director of Clinical Rheumatology John J. Cush, MD, and principal investigator Dr. Pascual, recently treated a patient who suffered from acute rheumatoid arthritis (RA). After traditional therapies had failed, Dr. Cush and Dr. Pascual reviewed the patient's blood samples to look for markers that would point toward treatments that had been successful on other patients. Based on the biosignature, as determined by the gene expression pattern in the patient's blood sample, anakinra (an interleukin-1 receptor antagonist, commercially available as Kineret®) was predicted to be an effective treatment. After seven months of treatment with anakinra, the patient's RA continues to be controlled with little or no evidence of inflammation.

Genomic research is a powerful driver for discoveries that will have a dramatic impact on health care. With financial backing for research, the options for tailoring therapy to a patient's genotype and phenotype are limitless. The hope is that one day physicians will be able to take a patient's blood sample and decide the correct course of treatment the first time. This type of approach can translate to treatment options for many different diseases and medical conditions.

### PRINCIPAL INVESTIGATORS: VIRGINIA PASCUAL

Virginia Pascual, MD, is a principal investigator at Baylor Institute for Immunology Research. In 2006, she was selected as the recipient of the Mary Kirkland Scholar Award in Lupus Research. In addition, her research on juvenile arthritis has led to successful treatment for children who did not respond to other therapies.



Dr. Pascual serves on the National Institutes of Health, Arthritis, Musculoskeletal and Skin Diseases Special Grant Review Committee and the Alliance for Lupus Research Scientific Review Committee. She is the author and co-author of more than 80 publications, book chapters and reviews. Dr. Pascual earned her medical degree from Facultad de Medicina, Universidad Complutense in Madrid. She is board certified in pediatrics and pediatric rheumatology.

### LAWRENCE SWEETMAN

Lawrence Sweetman, PhD, is director of the Mass Spectrometry Laboratory in the Kimberly H. Courtwright and Joseph W. Summers Institute of Metabolic Disease within Baylor Research Institute and is board certified in biochemical genetics by the American Board of Medical Genetics. In addition to clinical laboratory diagnostic work with mass spectrometry, Dr. Sweetman's research interests include inherited disorders of amino, organic and fatty acid metabolism with targeted metabolomics.

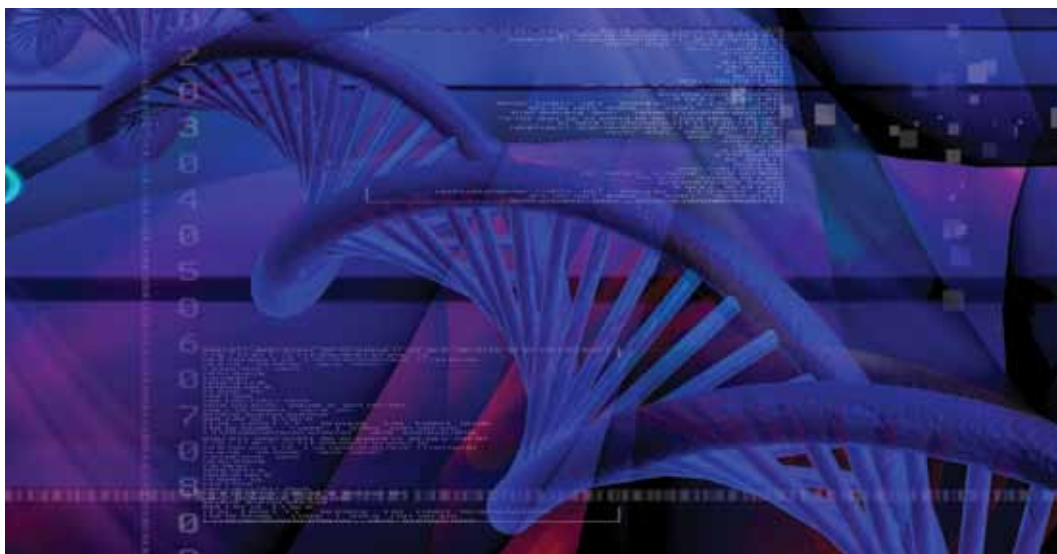


Dr. Sweetman has authored 159 published papers and 18 book chapters on inborn errors of metabolism. His past experience includes serving as director of the biochemical genetics laboratory at Children's Hospital Los Angeles and professor of pediatrics and pathology at the University of Southern California. He received his doctorate in biochemistry from the University of Miami in Florida in 1969.

### AJAY GOEL

Ajay Goel, PhD, is director of epigenetic and cancer prevention at Baylor Research Institute and an investigator at the Gastrointestinal Cancer Research Lab at Baylor University Medical Center. His career spans more than 20 years as a cancer researcher, and his primary





research interest involves cancer epigenetics and cancer prevention. He is currently using advanced genomic and transcriptomic approaches to develop novel DNA- and microRNA-based biomarkers for the early detection of colorectal cancers. In addition, he is researching the prevention of gastrointestinal cancers using integrative and alternative approaches, including botanical products such as curcumin (from turmeric) and boswellia.

Dr. Goel is a member of the American Association for Cancer Research (AACR) and the American Gastroenterology Association (AGA) and is on the international editorial boards of several journals including *World Journal of Gastroenterology*. He has authored or contributed to more than 125 scientific articles published in peer-reviewed international journals as well as several book chapters. His many awards include the Union of European Gastroenterology Federation's Distinguished Researcher Award and multiple Poster of Distinction Awards from the AGA.

#### **RAPHAEL SCHIFFMANN**

Raphael Schiffmann, MD, MHSc, is the director of the Institute of Metabolic Disease. His research primarily focuses on neurometabolic diseases and, in particular, lysosomal diseases and leukodystrophies. He made a significant contribution to understanding the pathogenesis and treatment of Fabry disease, including pivotal studies that lead to the approval of enzyme replacement therapy for this disorder in 45 countries.



Dr. Schiffmann holds a master's of health sciences degree in clinical research from Duke University in North Carolina and completed his medical degree at the University of Liege in Belgium. He has authored 173 peer-reviewed publications, 20 reviews and book chapters and has presented his research in numerous national and international meetings.

#### **TEODORO BOTTIGLIERI**

Teodoro Bottiglieri, PhD, is a principal investigator and director of neuropharmacology at the Baylor Kimberly H. Courtwright and Joseph W. Summers Institute of Metabolic Disease at Baylor Research Institute, where he focuses on understanding the role of B vitamins, methylation and sulfur amino acid metabolism in the central nervous system. The research conducted in Dr. Bottiglieri's laboratory applies to many disease states, including diagnosis of in-born errors of metabolism, Alzheimer's disease, Parkinson's disease, depression and vascular disease.



Additionally, Dr. Bottiglieri serves as an adjunct professor of biomedical studies at Baylor University, Waco. He holds both master's and doctorate degrees in neurochemistry from the University of London and has authored 131 papers in peer-reviewed journals and contributed to 10 book chapters.

#### **ESPERANZA ANGUIANO**

Esperanza Anguiano directs the genomics core laboratory operations at Baylor Institute for Immunology Research. She has attained expertise in molecular biology over the last 14 years in both industry and

academia. Her expertise extends to development, optimization, validation and accreditation of DNA assays, and technology for microsatellite and SNP genotyping. Most recently, she has led the expansion of the genomics core's high throughput platform by implementing advanced technology for application in genomics research, including whole genome and targeted gene expression as well as next-generation sequencing. Her most recent technology development efforts were vital in establishing the reputation of the genomics core laboratory for delivering high quality gene expression data.



#### NICOLE BALDWIN

Nicole Baldwin, PhD, specializes in advanced data analysis at Baylor Institute for Immunology Research. She holds a master's degree in computer science and a doctorate in microbiology and molecular genetics. This unique combination of skills allows her to work closely with researchers to realize their analytical goals. Over the last several years, she has assisted in developing and maintaining various data storage, data visualization and data analysis solutions. One of the most visible of these is the Gene Expression Browser, a web-based tool that allows users to access, search and view genomics expression data institute-wide. On the analysis front, her most notable accomplishment has been the ongoing development and refinement of a modular framework for analyzing genomics expression data derived from whole blood, the first iteration of which was published in *Immunity* in 2008. Currently, she is designing and developing systems to accommodate new technologies implemented at Baylor, including next-generation sequencing.



#### PUBLICATIONS

Ramilo O, Allman W, Chung W, Mejias A, Ardura M, Glaser C, Wittkowski K, Piqueras B, Banchereau J, Palucka K & Chaussabel D. Gene expression patterns in blood leucocytes discriminate patients with acute infections. *Blood* (2007); 109, 2066–2077.

Allantaz F, Chaussabel D, Stichweh D, Bennett L, Allman W, Mejjias A, Ardura M, Chung W, Smith E, Wise C, Palucka K, Ramilo O, Punaro M, Banchereau J & Pascual V. Blood leucocyte microarrays to diagnose systemic onset juvenile idiopathic arthritis and follow the response to IL-1 blockade. *The Journal of Experimental Medicine* (2007); 204, 2131–2144.

Chaussabel D. Translation of genomics research at the bedside: the promise and the challenge. *Clinical Immunology* (2008); 129, 179–181.

Chaussabel D, Quinn C, Shen J, Patel P, Glaser C, Baldwin N, Stichweh D, Blankenship D, Li L, Munagala I, Bennett L, Allantaz F, Mejias A, Ardura M, Kaizer E, Monnet L, Allman W, Randall H, Johnson D, Aimee L, Punaro M, Wittkowski K, White P, Fay J, Klintmalm G, Ramilo O, Palucka K, Banchereau J & Pascual V. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. *Immunity* (2008); 29, 150–164.

Chaussabel D, Ueno H, Banchereau J & Quinn C. Data management: it starts at the bench. *Nature Immunology* (2009); 12, 1225–1227.

Pankla R, Buddhisa S, Berry M, Blankenship D, Bancroft G, Banchereau J, Lertmemongkolchai G & Chaussabel D. Genomic transcriptional profiling identifies a candidate blood biomarker signature for the diagnosis of septicemic melioidosis. *Genome Biology* (2009), 10, R127.

Berry MP, Graham CM, McNab FW, Xu Z, Bloch SA, Oni T, Wilkinson KA, Banchereau R, Skinner J, Wilkinson RJ, Quinn C, Blankenship D, Dhawan R, Cush JJ, Mejias A, Ramilo O, Kon OM, Pascual V, Banchereau J, Chaussabel D, O'Garra A. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature*. 2010 Aug 19;466(7309):973-7.

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## THERAPEUTIC HIV AND HEPATITIS C VACCINE RESEARCH AND CLINICAL TRIALS

Despite decades of research to try to thwart the HIV-1 virus, today more than 33 million people are living with HIV/AIDS worldwide, including approximately 1 million in the United States. Meanwhile, hepatitis C virus (HCV) is growing in prevalence with an estimated 200 million people infected worldwide, including 3 million to 5 million in the US. Of those HCV chronically infected individuals, up to one-third will develop a major liver disorder. Together, these two viruses represent a major global health care burden, both on a personal and societal level. Developing therapeutic vaccines for one or both of these major diseases would be a tremendous breakthrough for health care, both in the US and worldwide.

In 2007, INSERM, the medical research organization of the French state, awarded \$6.8 million to Baylor Research Institute from Agence Nationale de Recherches sur le SIDA (ANRS), to develop and test HIV vaccines, with additional funding for an HCV vaccine program. With this funding, Baylor Institute for Immunology Research became the first INSERM unit in the US and is conducting a clinical trial to test a new therapeutic vaccine for HIV using dendritic cell-based vaccine strategies. These dendritic cells are developed in the laboratory from the patient's own white blood cells. The white blood cells are loaded

with HIV protein antigens and injected back into the patient, becoming, in essence, personalized vaccines to treat each patient's disease in an individualized manner.

Investigators at Baylor Institute for Immunology Research, led by Karolina Palucka, MD, PhD, in collaboration with researchers at ANRS and Louis Sloan, MD, at North Texas Infectious Diseases Consultants, are using this dendritic cell vaccine strategy in a clinical trial that has enrolled 19 local HIV patients who have been controlling their infections with multiple drug therapy. The aim of the trial is to show that this approach can boost the patients' immune systems against the virus and allow them to control the infection without the drugs.

A team led by Gerard Zurawski, PhD, in collaboration with ANRS researchers, is developing advanced versions of similar dendritic cell vaccines for direct injection to prevent and treat HIV and HCV infections.



## ADVANCING RESEARCH AND TECHNOLOGY

Investigators are close to completing a Phase I clinical trial to test their dendritic cell-based therapeutic HIV vaccine. The primary objective of the trial is to test the safety of the vaccine.

Secondarily, investigators are looking at areas of immunity, including:

- Strength of HIV-specific CD4/CD8 responses
- Proportion of responders
- Breadth of T-cell responses

## CREATING INNOVATION

Baylor Institute for Immunology Research investigators are pursuing other vaccine avenues using antibodies directed against antigen-presenting cell (APC) receptors to deliver antigens more efficiently. This receptor-targeting vaccine system facilitates the uptake, processing and presentation of extracellular antigens. In this approach, an antibody against an APC receptor is fused to HIV antigens and these prototype vaccines are being tested for their capacity to stimulate the expansion of HIV-specific memory T cells.

## PRINCIPAL INVESTIGATORS: YONG-JUN LIU

Yong-Jun Liu, MD, PhD, is vice president and chief scientific officer for Baylor Research Institute and director of Baylor Institute for Immunology Research. Dr. Liu joined the institute from a leadership position with Houston's University of Texas M.D. Anderson Cancer Center and is known worldwide as an expert in immunology, particularly the function of immune cells that are central to causing allergies and sustaining some cancers.



During his 25 years of research, Dr. Liu has made many seminal contributions to the field of immunology. He developed the first technology for the detection of antigen-specific B cells in situ, which allows the determination of extrafollicular and germinal center reactions, two critical stages of antigen-specific B cell responses in the secondary lymphoid tissues. His laboratory also discovered the human plasmacytoid dendritic cells (pDCs), a novel cell type in the immune system that is specialized in anti-viral immune responses and implicated in the development of autoimmune diseases. In addition, his laboratory discovered the function of a cytokine TSLP in the generation of inflammatory TH2 responses in human allergic diseases.

## KAROLINA PALUCKA

Karolina Palucka, MD, PhD, an investigator and director of the Center for Cancer Immunology at Baylor Institute for Immunology Research, holds the Michael A.E. Ramsay Chair for Cancer Immunology Research. Among the key areas of Dr. Palucka's work are improving the efficacy of dendritic cell vaccines, developing dendritic cell vaccines for breast cancer and metastatic prostate cancer, and targeting human dendritic cells for melanoma therapy.



Dr. Palucka has been an inventor/co-inventor on 14 patents and patent applications in the field of immunology. She has published more than 100 papers, book chapters and reviews. Dr. Palucka completed post-graduate training in medical oncology at the Maria Skłodowska Curie Memorial Oncology Institute in Warsaw and earned her doctorate in hematology and immunology at the Karolinska Institute in Stockholm, Sweden.

## GERARD ZURAWSKI

Gerard Zurawski, PhD, is an investigator and the Director of the Center for Biotechnology at Baylor Institute for Immunology Research. He has 24 years of experience in cytokine discovery, receptor biology and protein engineering, including the expression and purification of recombinant proteins. His studies at the institute focus on designing and expressing novel vaccines, including fusion proteins consisting of antibodies that target antigens to dendritic cell surface molecules.



Dr. Zurawski has co-authored more than 70 peer-reviewed publications in the fields of microbiology, genetics and immunology. He earned his doctorate in the Department of Genetics, School of Biology, at the University of Sydney in Australia and completed his post-doctoral work in biological sciences at Stanford University in California.

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## PROGRESSIVE APPROACHES TO **SYSTEMIC ONSET JUVENILE IDIOPATHIC ARTHRITIS (SoJIA)** AND **LUPUS** RESEARCH

Approximately 250,000 children in the United States suffer from juvenile arthritis, and systemic onset juvenile idiopathic arthritis (SoJIA) accounts for approximately 10 percent to 20 percent of these cases. Depending on the duration and severity of the disease, long-term disabilities may develop. Moreover, many patients suffer from debilitating side effects from conventional medications. As a result, there is an unmet need for better therapeutic options and for treating the patient in a manner that befits each unique situation.

Another chronic autoimmune disorder, systemic lupus erythematosus (lupus), affects an estimated 1.5 million Americans. Lupus affects the skin, joints, heart, kidneys and other vital organs, with up to 20 percent of all cases beginning in childhood.

Researchers at Baylor Institute for Immunology Research are leading the way in finding treatments for these and other autoimmune disorders using

progressive approaches, both on the therapeutic front as well as the personalized medicine front through diagnosis, prognosis and monitoring treatment.

### **ADVANCING RESEARCH, TECHNOLOGY FOR SoJIA**

In collaboration with a local children's hospital, the team at Baylor Institute for Immunology Research identified children with SoJIA who had not responded to other treatment regimens. They discovered that white blood cells from these SoJIA patients expressed higher levels of certain immune system genes relative to white blood cells from healthy individuals. They also found that blood sera from the SoJIA patients caused healthy white blood cells to start overexpressing these genes and to secrete higher levels of interleukin-1 beta (IL-1 beta), a key regulatory molecule.

Researchers at the institute suspected that oversecretion of IL-1 beta might play a significant role in SoJIA and that inhibiting IL-1b activity could be beneficial. To test this hypothesis, nine SoJIA patients received a drug called anakinra, which inactivates IL-1.



Notably, all nine patients responded to the therapy. In eight of the nine patients, the researchers observed decreases in the arthritic symptoms in the joints as well as improvement in other arthritis indicators. They found that the therapy completely restored the function of six of the eight patients and lessened the symptoms of the remaining two.

### ADVANCING RESEARCH, TECHNOLOGY FOR LUPUS

Virginia Pascual, MD, principal investigator at Baylor Institute for Immunology Research, along with her colleagues, garnered national media attention from a landmark paper detailing one of two new studies that identified a cycle of cell death and chronic inflammation involving blood cells called neutrophils.

The results of this study could help in the discovery of a cure for the disease down the line.

### CREATING INNOVATION

Baylor Research Institute has two issued US patents that cover the treatment of SoJIA patients with at least one active agent that reduces or blocks the interaction between IL-1 beta and an IL-1 receptor.

The Center for Lupus Research, a federally funded center at Baylor Institute for Immunology Research headed by Dr. Pascual, is investigating the role played by different immune system cells in contributing to the disease process in lupus. Additional work addressing the diagnosis and treatment of autoimmune diseases is being conducted with research funding awarded to the Autoimmunity Center of Excellence at Baylor Institute for Immunology Research. This center, also headed by Dr. Pascual, is one of only nine such centers in the country. It was funded in 2009 by the National Institute of Allergy and Infectious Diseases for an initial period of five years.

### PRINCIPAL INVESTIGATOR: VIRGINIA PASCUAL

Virginia Pascual, MD, is an investigator at Baylor Institute for Immunology Research. In 2006, she was selected as the recipient of the Mary Kirkland Scholar Award in Lupus Research. In addition, her research on juvenile arthritis has led to successful treatment for children who did not respond to other therapies.



Dr. Pascual serves on the National Institutes of Health, Arthritis, Musculoskeletal and Skin Diseases Special Grant Review Committee and the Alliance for Lupus Research Scientific Review Committee. She is

the author and co-author of more than 80 publications, book chapters and reviews. Dr. Pascual earned her medical degree from Facultad de Medicina, Universidad Complutense in Madrid. She is board certified in pediatrics and pediatric rheumatology.

### PUBLICATIONS

Allantaz F, Chaussabel D, Stichweh D, Bennett L, Allman W, Mejias A, Ardura M, Chung W, Smith E, Wise C, Palucka K, Ramilo O, Punaro M, Banchereau J, Pascual V. Blood leukocyte microarrays to diagnose systemic onset juvenile idiopathic arthritis and follow the response to IL-1 blockade. *J Exp Med*. 2007 Sep 3; 204(9):2131-44. Epub 2007 Aug 27. Erratum in: *J Exp Med*. 2009 Sep 28; 206(10):2299. Smith, Elisabeth [added].

Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med*. 2005 May 2;201(9):1479-86.

Morita R, Schmitt N, Benteibibel SE, Ranganathan R, Bourdery L, Zurawski G, Foucat E, Dullaers M, Oh S, Sabzghabaei N, Lavecchio EM, Punaro M, Pascual V, Banchereau J & Ueno H (2011). Human Blood CXCR5(+)CD4(+) T Cells Are Counterparts of T Follicular Cells and Contain Specific Subsets that Differentially Support Antibody Secretion. *Immunity* 34, 108-21.

Mathian A, Gallegos M, Pascual V, Banchereau J & Koutouzov S (2011). Interferon-alpha induces unabated production of short-lived plasma cells in pre-autoimmune lupus-prone (NZBxNZW)F1 mice but not in BALB/c mice. *Eur J Immunol*.

Garcia-Romo GS, Caielli S, Vega B, Connolly J, Allantaz F, Xu Z, Punaro M, Baisch J, Guiducci C, Coffman RL, Barrat FJ, Banchereau J & Pascual V (2011). Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Science Translational Medicine* 3, 73ra20.

Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, Bossuyt X, Boutten A, Bienvenu J, Duquesne A, Richer O, Chaussabel D, Mogenet A, Banchereau J, Treliuyer JM, Landais P & Pascual V (2010). A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis*.

Guiducci C, Gong M, Xu Z, Gill M, Chaussabel D, Meeker T, Chan JH, Wright T, Punaro M, Bolland S, Soumelis V, Banchereau J, Coffman RL, Pascual V & Barrat FJ (2010). TLR recognition of self nucleic acids hampers glucocorticoid activity in lupus. *Nature* 465, 937-41.

Chaussabel D, Pascual V & Banchereau J (2010). Assessing the human immune system through blood transcriptomics. *BMC Biol* 8, 84.

Berry MP, Graham CM, McNab FW, Xu Z, Bloch SA, Oni T, Wilkinson KA, Banchereau R, Skinner J, Wilkinson RJ, Quinn C, Blankenship D, Dhawan R, Cush JJ, Mejias A, Ramilo O, Kon OM, Pascual V, Banchereau J, Chaussabel D & O'Garra A (2010). An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature* 466, 973-7.

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## BAYLOR INSTITUTE FOR IMMUNOLOGY RESEARCH: A LEADER IN IMMUNOTHERAPY

Established in 1996 as the immunology research component of Baylor Research Institute, Baylor Institute for Immunology Research brings together research scientists and clinicians in an effort to increase understanding of how the human immune system works. Led by internationally renowned immunologist Yong-Jun Liu, MD, PhD, the institute is devoted to rapidly translating basic laboratory discoveries pertaining to the immune system into effective treatments for patients. Baylor Institute for Immunology Research's interdisciplinary program focuses on developing new therapies, such as using the patient's own blood-derived dendritic cells to modulate immune responses in beneficial ways. The institute has been a pioneer and leader in developing ways to understand and harness the class of white blood cells that play a key role in initiating and controlling the body's immune response.

### ADVANCING RESEARCH AND TECHNOLOGY

Focused on developing new therapies, Baylor Institute for Immunology Research is tackling several areas of dendritic cell research including:

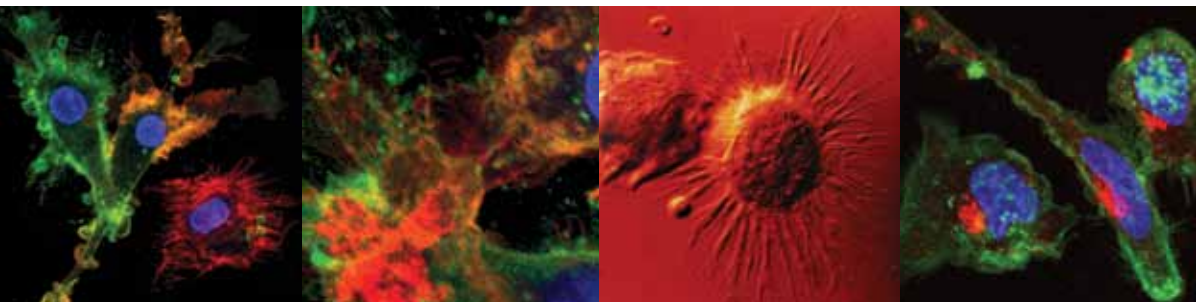
**Metastatic Melanoma** Joseph W. Fay, MD, and Karolina Palucka, MD, PhD, have established more than 500 personalized dendritic cell vaccines that have been used to treat more than 90 patients diagnosed with late-stage metastatic melanoma in Phase I and Phase II clinical trials.

**Breast Cancer** Researchers at Baylor Institute for Immunology Research are investigating the development of a personalized vaccine for breast cancer patients using dendritic cells.

**Lymphoma** Lymphoma is a group of cancers that affect the cells that play a role in the immune system and primarily represents cells involved in the lymphatic system of the body. Baylor Institute for Immunology Research investigators are studying therapies using the patient's own dendritic cells injected into the patient's tumor to combat its growth.

**Lupus** Systemic lupus erythematosus (lupus) is an aggressive autoimmune disease. This disease can damage kidneys, skin, heart and other organs and can be fatal without early therapeutic intervention. Researchers at Baylor Institute for Immunology Research, under the leadership of Virginia Pascual, MD, a principal investigator and practicing pediatric rheumatologist, have linked abnormal secretion of interferon alpha (a naturally produced anti-viral protein) to the malfunctioning immune systems of young patients with lupus. This finding is a major step toward explaining how lupus deceives the body's immune system into destroying healthy cells and suggests new therapeutic approaches.

In the same area of study, Baylor Research Institute was awarded a \$6.2 million grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) in 2006 to establish a Center for Lupus Research, also led by Dr. Pascual.



**Juvenile Arthritis** Dr. Pascual and her collaborators also have reported the successful treatment of children with systemic onset juvenile idiopathic arthritis (SoJIA) and have been granted two US patents that cover the treatment of SoJIA patients with at least one active agent, which reduces or blocks the interaction between interleukin-1 beta (IL-1 beta) and an interleukin-1 (IL-1) receptor.

**Transplant Immunology** Scientists at the research institute also are studying ways to turn off an organ transplant recipient's immune response against a "foreign" donor organ to allow the organ to be accepted without the need for immunosuppressive drugs, thereby avoiding their debilitating side effects. To recognize which patients have developed immunotolerance, Baylor scientists are using proprietary expression analysis technologies developed at the institute. By screening patients through blood analysis, physicians will be able to treat organ rejection or a flare-up of disease before any clinical symptoms appear, or before any organ damage occurs.

**Biodefense Center** In 2003, Baylor Research Institute received a \$14.6 million grant from the National Institute of Allergy and Infectious Diseases (NIAID) to create the Baylor/NIAID Center for Translational Research on Human Immunology and Biodefense. With this funding, investigators are studying the human immune system's response to emerging pathogens and other virulent agents and are seeking to develop more effective vaccines against these threats. This award was renewed in 2009 and three supplementary grants totaling \$6.9 million were funded by the American Recovery and Reinvestment Act (ARRA). The institute also received a National Institutes of Health (NIH) award to study Category B pathogens (bacteria and viruses that cause serious human diseases). This five-year, \$6.3 million grant will support collaborations between Baylor Institute for Immunology Research scientists and researchers from within the United States and around the world.

**Infectious Diseases** Baylor Institute for Immunology Research is actively pursuing the development of vaccines against human immunodeficiency virus (HIV), hepatitis C (HCV) and human papilloma virus (HPV) based on the institute's work in dendritic cell biology. These investigators are conducting a clinical trial to test a novel therapeutic vaccine for HIV, in addition to pre-clinical research that will enable clinical trials for HCV and HPV vaccines. Investigators have developed a technique using dendritic cells from the body's own immune system to fight the diseases. In 2007, INSERM, the medical research organization of the

French state, awarded \$6.8 million to Baylor Research Institute from ANRS (the French AIDS agency) to develop and test HIV therapeutic vaccines. Additional funding has been awarded for an HCV program. Notably, this grant helped the research institute become the first INSERM unit in the United States. Baylor Institute for Immunology Research also received a federal stimulus package grant from NIH to develop a therapeutic vaccine for HPV.

## MAKING AN IMPACT

A critical element of success in this challenging area of improving human health is the ability to develop large-scale collaborative efforts both nationally and internationally. Since Baylor Institute for Immunology Research's launch, Baylor Research Institute has collaborated with more than 40 research organizations worldwide and has been awarded more than \$100 million in outside or competitive grants to fund continued research in the area of dendritic cell technology.

## PRINCIPAL INVESTIGATOR: YONG-JUN LIU

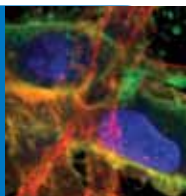
Yong-Jun Liu, MD, PhD, is vice president and chief scientific officer for Baylor Research Institute and director of Baylor Institute for Immunology Research.



Dr. Liu joined the institute from a leadership position with Houston's University of Texas M.D. Anderson Cancer Center and is known worldwide as an expert in immunology, particularly the function of immune cells that are central to fighting cancer.

His 25 years of research has focused on human immunology, particularly dendritic cell biology, genomic approaches to the diagnosis of human diseases, the pathophysiology of autoimmune diseases and cancer, and the design of novel vaccines. Dr. Liu has published more than 200 scientific articles during his career, including many in the journals *Nature*, *Science*, *Cell*, *Immunity*, *Nature Immunology* and *Journal of Experimental Medicine*, and is among the top cited scientists in immunology.

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## TARGETED MICROBUBBLE GENE THERAPY ADVANCES TYPE 1 DIABETES TREATMENT

Diabetes is a disease in which the body does not properly produce or control insulin, and its cause is not fully understood. If left unregulated, abnormally high glucose levels can result in organ damage, involving the nervous system, kidneys, eyes and cardiovascular system, and can eventually lead to death.

Nearly 26 million Americans have been diagnosed with diabetes, with 5 percent to 10 percent of those diagnosed as type 1. This type of diabetes reflects a state of absolute insulin deficiency stemming from autoimmune destruction of the insulin-producing cells in the pancreas. Patients with type 1 diabetes produce little or no insulin and are dependent on injections of insulin for survival, which is currently the mainstay of diabetes treatment.

### ADVANCING RESEARCH AND TECHNOLOGY

Paul Grayburn, MD, has focused his research on the use of Ultrasound Targeted MicroBubble Destruction (UTMD) technology to deliver genes to the pancreas in a novel therapeutic approach that can impact the degenerative symptoms of diabetes. The method uses gas-filled microscopic bubbles to inject “good” genes into the blood-

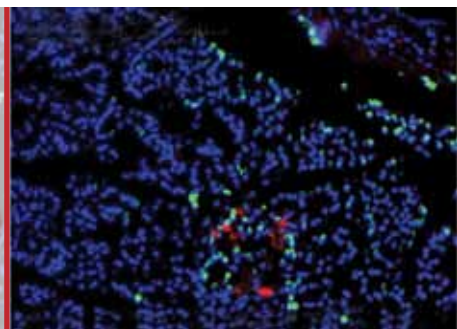
stream and the pancreas. An ultrasound beam is then used to burst the bubbles, allowing the genes to escape and gain access to the membranes of pancreatic cells for internalization.

Dr. Grayburn's UTMD work addresses three key research areas. The first looks at *in vivo* non-viral gene delivery of human vascular endothelial growth factor to improve human islet survival and function after transplantation. The second is the method of gene delivery to pancreatic islets of adult, living animals by UTMD. Finally, Dr. Grayburn's team explores regeneration of pancreatic islets and reversal of diabetes by UTMD.

### MAKING AN IMPACT

Conclusions from *in vivo* non-viral gene delivery showed that plasmid-encoded gene delivery to the host liver using UTMD promoted revascularization of engrafted human islets, improved function of engrafted human islets and improved cure rate after human islet transplantation.

Conclusions from the method of gene delivery to pancreatic islets of adult, living animals using UTMD showed that delivery of a gene-encoding construct resulted in clear increases in circulating human C-peptide and decreased blood glucose levels. Delivery of a second construct resulted in a clear increase in hexokinase I protein expression in islets, increased





insulin levels in blood and decreased circulating glucose levels. Importantly, UTMD allowed relatively noninvasive delivery of genes to pancreatic islets with efficiency sufficient to modulate beta cell function in adult animals.

Dr. Grayburn's studies on the regeneration of pancreatic islets and reversal of diabetes by UTMD concluded that UTMD allows *in vivo* islet regeneration and cures diabetes in rats without viruses.

Research at Baylor is uncovering additional advantages to and for UTMD:

- Targeted gene therapy
- Ultrasound to target specific organ or tissue
- Promoter can further target specific cell type
- Transient or prolonged expression of transgene
- Potential to deliver imaging agents, drugs, etc.
- Potential investigative tool
- Understanding gene function in adult animals without confounding effects of embryogenesis/development
- Targeted microbubbles to identify disease processes
- Drug discovery

### CREATING INNOVATION

Dr. Grayburn and his team have already begun working on using UTMD to transport drugs and genes into other tissues, including the heart, kidney and brain, and they have successfully validated their approach to treating diabetes in rodent models. They are now extending the work to baboons to validate these findings in a non-human primate, which is the next step before human trials. Pending patent applications for a gene and drug delivery system includes modification/regeneration of pancreatic cells with application in diabetes.

### PRINCIPAL INVESTIGATOR:

#### PAUL A. GRAYBURN

Paul A. Grayburn, MD, serves as medical director of cardiology research and education at Baylor University Medical Center and as medical director of the Non-invasive Cardiac Lab at Baylor Heart and Vascular Institute.



He also is the principle investigator of Ultrasound Targeted MicroBubble Destruction (UTMD), a technology focused on delivering genes for patients with type 1 diabetes.

Dr. Grayburn, who is board certified in both internal medicine and cardiovascular disease and specializes in clinical cardiology and echocardiography, has numerous accolades in the field. He has authored numerous book chapters and served as a co-author on more than 225 peer-reviewed publications.

Dr. Grayburn's achievements also include editorial positions with national medical journals including the *American Journal of Cardiology*. He earned his medical degree at the University of Texas Medical Branch in Galveston, Texas.

### PUBLICATIONS

Chen S, Ding JH, Bekeredjian R, Yang BZ, Shohet RV, Johnston SA, Hohmeier HE, Newgard CB, Grayburn PA. Efficient gene delivery to pancreatic islets with ultrasonic microbubble destruction technology. *Proc Natl Acad Sci USA*. 2006 May 30;103:8469-74. Epub 2006 May 18.

Chai R, Chen S, Ding J, Grayburn PA. Efficient, glucose responsive and islet-specific transgene expression by a modified rat insulin promoter. *Gene Ther*. 2009 Oct;16(10):1202-9. Epub 2009 Sep 3.

Bekeredjian R, Chen S, Grayburn PA, Shohet RV. Augmentation of cardiac protein delivery using ultrasound targeted microbubble destruction. *Ultrasound Med Biol*. 2005 May; 31(5):687-91.

Korpany G, Chen S, Shohet RV, Ding J, Yang B, Frenkel PA, Grayburn PA. Targeting of VEGF-mediated angiogenesis to rat myocardium using ultrasonic destruction of microbubbles. *Gene Ther*. 2005 Sep;12(17):1305-12.

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## AT THE FOREFRONT OF PANCREATIC ISLET TRANSPLANTATION

According to the United Network for Organ Sharing (UNOS), 6,291 liver procurements and transplants were performed in 2010, but only about 20 percent of pancreata were clinically useful. These statistics point to a huge medical need—not only in the number of organs, but also for increasing the number of clinically viable pancreata for islet transplantation—which Baylor Research Institute is striving to address.

### ADVANCING RESEARCH AND TECHNOLOGY

Surgeons on the medical staff at Baylor, which pioneered the first liver transplant program in the Southwest a quarter-century ago, have performed nearly 4,000 liver transplants—placing Baylor in an elite handful of centers in the United States to reach this milestone. The Annette C. and Harold C. Simmons Transplant Institute is the integration of transplant services at Baylor University Medical Center at Dallas and Baylor All Saints Medical Center at Fort Worth. Together, they form one of the largest multi-specialty transplant centers in the country.

Under the direction of Marlon Levy, MD, FACS, and Shinichi Matsumoto, MD, PhD, researchers and clinicians at Baylor Fort Worth have performed more than 100 islet isolations using pancreata procured from deceased human donors. In addition, 12 islet transplantations were utilized in nine type 1 diabetes patients. Six of those patients achieved insulin independence with two or three islet infusions, and three patients did so with just one infusion. Finally, 29 autologous islet transplants have been performed for the treatment of chronic pancreatitis.

### CREATING INNOVATION

Baylor's islet transplant program recently implemented several protocols and techniques, including the introduction of three proprietary technologies. The program introduced a novel immunosuppressive protocol that uses a dual combination of anti-inflammatory drugs and strong immunosuppression after islet infusion, as well as a novel technique known as pancreatic ductal preservation, which has improved the efficiency of isolating healthy islets.

In 2011, Baylor Research Institute received a two-year, \$431,200 grant by the National Institutes of Health (NIH) to continue its work on pancreatic ductal preservation methods.



Additionally, invention of a ductal injection method has also improved the quantity and quality of isolated islets while a “top loading bottle” method—meant to improve the yield of pancreatic beta islet cells upon isolation—has also been well-received. A “keep fresh” storage method to improve the isolation, viability and preservation of pancreatic beta islet cells for transplantation was also invented. These proprietary technologies can be applied to allogenic, autologous or xenogeneic islet transplantation.

The institute’s transplant team has also successfully performed extracorporeal perfusion of transgenic pig livers in patients with fulminant hepatic failure awaiting clinical liver transplantation. Two such patients were successfully bridged to human liver transplantation using this technique.

### MAKING AN IMPACT

Currently, Baylor Research Institute’s transplant team is conducting two ongoing clinical trials:

- **Study 1** “Pancreatic Islet Transplantation—A Novel Approach to Improve Islet Quality and Engraftment”
- **Study 2** “Pancreatic Islet Cell Transplantation After Kidney Transplantation—A Novel Approach to Immunosuppression”

### PRINCIPAL INVESTIGATORS:

#### MARLON LEVY

Marlon F. Levy, MD, FACS, is surgical director of transplantation for Baylor All Saints Medical Center at Fort Worth. He also serves as medical director of the Islet Cell Transplant Program for Baylor Health Care System and medical director for the Southwestern Transplant Alliance in Dallas.

Dr. Levy has been the primary investigator for 16 clinical research protocols, including the ongoing study, “Pancreatic Islet Cell Transplantation.” He also has been a co-investigator for 28 clinical research protocols. In addition to being an editorial board member and a journal reviewer, Dr. Levy has authored more than 229 articles in peer-reviewed publications.



#### SHINICHI MATSUMOTO

Shinichi Matsumoto, MD, PhD, is director of islet cell research at Baylor All Saints Medical Center at Fort Worth and director of islet cell transplantation research at Baylor Institute for Immunology Research at Dallas. Dr. Matsumoto joined Baylor All Saints in 2006 from Fujita Health University, Japan, where he served as a full professor of gastrointestinal surgery and director of the Diabetes Research Institute Japan. Dr. Matsumoto is an international expert in islet cell processing and transplantation. He has developed cutting-edge technologies in this field. He has authored more than 254 articles in peer-reviewed publications.



### PUBLICATIONS

Levy MF, Crippin J, Sutton S, Netto G, McCormack J, Curiel T, Goldstein RM, Newman JT, Gonwa TA, Banchereau J, Diamond LE, Byrne G, Logan J, Klintmalm GB. Liver allotransplantation after extracorporeal hepatic support with transgenic (hCD 55/hCD 59) porcine livers: clinical results and lack of pig-to-human transmission of the porcine endogenous retrovirus. *Transplantation* 69, 69: 272–280, 2000.

Matsumoto S, Noguichi H, Shimoda M, Ikemoto T, Naziruddin B, Jackson A, Tamura Y, Olson G, Fujita Y, Chujo D, Takita M, Kobayashi N, Onaca N, Levy M. Seven consecutive successful clinical islet isolations with pancreatic ductal injection. *Cell Transplantation* 19, 291–297, 2010.

Ikemoto T, Noguchi H, Fujita Y, Takita M, Shimoda M, Sugimoto K, Jackson A, Naziruddin B, Shimoda M, Levy MF, Matsumoto S. New stepwise cooling system for short-term porcine islet preservation *Pancreas* 39, 960–963, 2010.

Shimoda M, Noguchi H, Fujita Y, Takita M, Ikemoto T, Chujo D, Naziruddin B, Levy MF, Kobayashi N, Grayburn PA, Matsumoto S. Islet purification method using large bottle effectively achieves high islet yield from pig pancreas. *Cell Transplantation* (in press).

Matsumoto S, Takita M, Shimoda M, Sugimoto K, Itoh T, Chujo D, SoRelle JA, Tamura Y, Rahman AM, Onaca N, Naziruddin B, Levy MF. Impact of tissue volume and purification on clinical autologous islet transplantation for the treatment of chronic pancreatitis. *Cell Transplantation* (in press).

Matsumoto S, Takita M, Chaussabel D, Noguchi H, Shimoda M, Sugimoto K, Itoh T, Chujo D, Sorelle J, Onaca N, Naziruddin B, Levy MF. Improving efficacy of clinical islet transplantation with iodixanol based islet purification, thymoglobulin induction and blockage of IL-1 beta and TNF-alpha. *Cell Transplantation* (in press).

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## COLLABORATIONS: ACCELERATING THE TRANSFER OF SCIENCE TO PATIENT CARE

Baylor Research Institute is dedicated to moving new treatments from bench to bedside as quickly, safely and ethically as possible. Investigators have been successful in attracting research funding from the National Institutes of Health (NIH) sufficient to support testing of new treatments through Phase I and early Phase II trials.

To take promising research to the next level, the research institute is collaborating with outside institutions, organizations and biopharmaceutical companies to complete the development of new treatments and make them available to patients. Under the direction of Bernard Brigonnet, vice president and chief operating officer, Baylor Research Institute is vigorously pursuing collaborations at several levels: academic associations, out-licensing agreements and a unique type of relationship with industry to jointly develop new programs.

### PARTNERSHIPS AND ASSOCIATIONS

Baylor Research Institute and Mount Sinai School of Medicine are creating therapeutic and preventive vaccines for prostate cancer and hematological malignancies under the direction of Baylor Institute for Immunology Research investigator Karolina Palucka, MD, PhD. While the institute works on vaccine development, Mount Sinai is identifying the patients who stand to benefit from these medical advances, with the ultimate goal of moving approved treatments into standard practice. Baylor Institute for Immunology Research and Mount Sinai teams also will analyze gene patterns in patients with autoimmune diseases to better diagnose and treat them.

In 2007, Baylor Research Institute became the first INSERM unit in the United States, also launching an official partnership with the French AIDS research agency (ANRS). INSERM, the medical research



organization of the French state, awarded \$6.8 million to the research institute to develop and test HIV vaccines, with additional funding for a hepatitis C program.

In August 2010, Baylor Institute for Immunology Research was selected as one of six leading world institutions in immunology to participate in a \$100 million, five-year National Institute of Allergy and Infectious Diseases initiative. The institute will leverage its expertise and technological infrastructure to document changes that occur in the immune system of individuals after vaccination or exposure to an infectious agent, including changes in gene expression and the production of proteins and cytokines. The resulting immune profiles will be compiled in a database, with the ultimate goal of defining immune profiles for normal and dysfunctional immune response.

A strategic alliance also has been formed with Eureka Genomics Corp. to achieve a better understanding of the causes of colorectal cancer, potentially leading to advances in the disease's prevention, management and treatment. The collaboration represents the opportunity to use next-generation DNA sequencing and proprietary data-mining techniques to look for non-human DNA sequences in colorectal tumors.

#### OUT-LICENSING AGREEMENTS

In a typical out-licensing agreement, intellectual property is licensed to outside industry to further develop the asset, providing an income stream for the institute from up-front fees, milestone payments and royalties. Out-licensing agreements reached by Baylor Research Institute include:

- An agreement with SBI Biotech Co., LTD. (Tokyo), to support the development of dendritic cell vaccines for the Japanese, Korean and Taiwanese markets.

- An agreement with Millipore (Massachusetts) to add antibodies developed at the research institute to its catalogue.
- An agreement with eBioscience (San Diego) to add antibodies developed at the research institute to its catalogue.
- An agreement with ImmuRx Inc. (New Hampshire) for anti-CD40 antibodies.

#### INDUSTRY RELATIONSHIPS

Baylor Research Institute has additionally entered into a three-year collaboration with Roche, a company that specializes in the development of *in vitro* diagnostics and therapeutics for cancer and transplantation. Through this agreement, which is the first of its kind for the institute, Roche and Baylor Institute for Immunology Research will jointly develop programs that leverage the institute's leading position in human immunology, with a focus on cancer vaccines, autoimmune disease diagnostics and treatment.

This unique relationship is expected to identify new approaches in areas where current therapies are lacking or unsatisfactory. The partnership with a world leader like Roche will accelerate the translation of the research institute's innovative science in human immunology into the clinic, ultimately resulting in diagnostics and treatments that could benefit patients worldwide.

These strategic collaborations are poised to leverage Baylor Research Institute's technologies and infrastructure to achieve remarkable discoveries in immunology, transplant medicine and oncology, with an eye toward the ultimate goal of developing new treatments for patients that have better outcomes.

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## A LARGE DIFFERENTIATED PORTFOLIO OF BIOMEDICAL INTELLECTUAL PROPERTY

As part of its mission to translate medicine from the bench to the clinic, and ultimately to the medical community at large, Baylor Research Institute actively seeks patent protection for new inventions that are developed by its researchers and clinicians. By working with partners and licensees, Baylor is leveraging its portfolio to help the greatest number of patients through commercialization, while at the same time helping its partners succeed by providing access to proprietary differentiated technologies.

Using the criteria of unmet need and significant commercial opportunity, Baylor Research Institute has evaluated thousands of novel inventions, culminating in a current master portfolio of more than 530 pending and issued patents across 92 patent families. Patent protection is sought in those geographies that are deemed most attractive both commercially and strategically, as determined on a case-by-case basis.

### A PORTFOLIO APPROACH

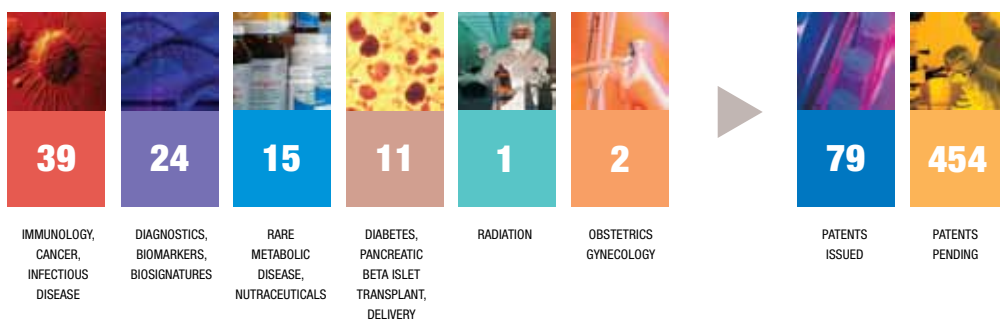
Because of its expertise and activity in key areas of biomedicine, Baylor Research Institute has developed thematic-based patent family series in important strategic areas that span immunology, biomarkers and diagnostics, rare metabolic diseases, nutraceuticals and diabetes. While each patent and patent

application has commercial value in its own right, Baylor's portfolio approach affords the potential to create a proprietary suite of synergistic technologies around potential products.

Within Baylor Research Institute, Baylor Institute of Immunology Research has conducted prolific innovative research and now has a series of 39 patent families with more than 300 pending and issued patents that pertain to the treatment of a wide range of **immune-related disorders**, including cancer, infectious disease, autoimmunity, allergy and transplantation.

Baylor Research Institute also has developed a series of 24 patent families with more than 100 pending and issued patents that encompasses a broad range of **biomarkers, biosignatures and diagnostics**, including a validated biosignature platform that is used to generate novel signatures against various unrelated immune disorders. These biosignatures can be used for diagnosis as well as for monitoring disease progression and response to treatment, and they have been successfully used in the clinic to guide the treatment of patients with serious conditions such as systemic onset juvenile idiopathic arthritis (SoJIA). Notably, many of Baylor Research

### BIOMEDICAL FIELD NUMBER OF PATENT FAMILIES



Institute's proprietary biomarkers and biosignatures were developed concomitantly with the development of the immunological therapeutics, which means that many of these biomarkers and biosignatures can be used in concert with the therapeutics, with potential applications as biomarkers for clinical development as well as companion diagnostics. In addition, the Gastroenterology Cancer Research Institute, which is very active in the field of colorectal cancer, has identified a number of proprietary biomarkers (including methylation and microRNA markers) that show high potential for early diagnosis of gastrointestinal cancer, in addition to monitoring.

The Institute of Metabolic Disease, known for its world class expertise in **rare metabolic diseases**, including Fabry disease, has developed a series of therapeutics and diagnostic biomarkers for these orphan diseases. In addition, Baylor Research Institute has developed a series of **nutraceutical** products with a broad range of applications, including cancer and inflammation. In total, this entire portfolio spans 15 patent families with more than 70 pending and issued patents.

Thanks to the continuum of research efforts in the area of pancreatic beta islet cells, from the preclinical end of the spectrum to the human surgical end, Baylor Research Institute has developed a comprehensive **diabetes** series of 11 patent families with about 50 pending and issued patents focused on developing treatment for diabetes involving transplantation or direct targeting of islet cells.

Importantly, Baylor Research Institute continues to build upon its patent estate, with active filing of new applications in each of these very active areas as they emerge. To help fulfill its mission of helping patients, Baylor Research Institute is actively seeking potential partners and licensees in each of these areas.

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#### ABOUT BAYLOR HEALTH CARE SYSTEM

Baylor Health Care System, unique in the Southwest for its dual role as an educational and commercial health care facility, serves nearly 1.4 million patients each year and recorded \$3.4 billion in total operating revenue, \$3.9 billion in total assets and \$468 million in community benefit in fiscal year 2009. Central to its mission of patient-centered medical research, through Baylor Research Institute, is moving scientific theory from the research bench to clinical trials and, ultimately, to the patient's bedside. This bench-to-bedside focus involves basic science, clinical trials, and health care effectiveness and quality of care research. Among the novel applications developed are customizable cancer vaccines and ultrasound-targeted microbubble transport to deliver genes or drugs to specific tissues including the heart, pancreas, kidneys, skeletal muscle and brain to rejuvenate cells.

#### CONTACT:

Baylor Research Institute  
3310 Live Oak Street  
Suite 501  
Dallas, Texas 75204  
214.820.2687  
BaylorHealth.edu

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#### BAYLOR RESEARCH INSTITUTES, LABORATORIES AND CENTERS:

- Annette C. and Harold C. Simmons Transplant Institute
- Baylor All Saints Medical Center at Fort Worth
- Baylor Charles A. Sammons Cancer Center at Dallas
- Baylor Endocrine Center
- Baylor Heart and Vascular Institute
- Baylor Institute for Immunology Research
- Baylor Institute for Rehabilitation
- Baylor-Kimberly H. Courtwright and Joseph W. Summers Institute of Metabolic Disease
- Baylor Research Institute–Dermatology Research
- Baylor Research Institute–Rheumatology Research
- George Truett James Orthopaedics Institute
- Gastrointestinal Cancer Research Laboratory
- Institute for Health Care Research and Improvement
- Martha Foster Lung Care Center at Baylor University Medical Center at Dallas
- Precision Medicine Institute (future)
- Soltero Cardiovascular Research Center
- THE HEART HOSPITAL Baylor Plano

