AIRI Association of Independent Research Institutes

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AIRI Translational Research Success Stories, Volume 2

The National Institutes of Health (NIH) and other federal research agencies are emphasizing translational research and investing more resources into programs and projects that advance this area. To showcase cutting-edge research conducted at independent research institutes that is bringing research discoveries into clinical practice and the marketplace, AIRI has compiled examples of basic research successfully moved toward translation.

Below is the second set of research success stories supported by AIRI member institutes, including the drug, therapy, diagnostic, company or prevention method that resulted from the research and the impact on health and health care. Many of these examples highlight companies or other research collaborators and the federal funding sources that supported this research. The AIRI Washington Office continues to accept success stories at airi@lewis-burke.com.

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BENAROYA RESEARCH INSTITUTE AT VIRGINIA MASON; Seattle, WA — www.benaroyaresearch.org

Improved Patient Management and Therapeutics Using Biomarkers of Immune Responses

Benaroya Research Institute at Virginia Mason (BRI) serves as an international leader for the production and application of a certain class of biomarkers, known as human MHC class II tetramers, to improve the diagnosis and treatment of a wide variety of diseases. BRI scientists developed MHC class II tetramer technology over the last decade, and now provide these biomarkers to investigators in many fields and locations around the world.

The technology has widespread utility and has been used to study many aspects of disease. For example, the biomarkers have been used to study immune responses to environmental allergens including cat dander, tree and grass pollen, mold, and others. Recent discoveries in this area of research open new horizons for understanding allergic diseases, improving safety and efficacy of current allergy shots, and developing the next generation of improved therapies. The biomarkers can also be used to measure the cellular response and efficacy of other vaccines, including those against several well-known and exotic pathogens including influenza, West Nile, Dengue fever, Japanese encephalitis, anthrax, and yellow fever.

BLOODCENTER OF WISCONSIN; Milwaukee, WI — www.bcw.edu

A Better Blood Supply for Transfusions

Newly developed blood-donor screening tests and improved management techniques have made blood transfusion an extremely safe medical procedure. However, patients receiving transfusions occasionally experience a serious complication designated transfusion-related acute lung injury (TRALI). Most cases of TRALI are caused by specific antibodies present in donor blood that cause lung injury in certain patients through mechanisms that are only partially understood. The incidence of TRALI has been significantly reduced in recent years by screening donor blood for antibodies recognizing human leukocyte (HLA) antigens and transfusing only plasma from male donors, who will not have been immunized against HLA by pregnancy. It was not possible, however, to screen routinely for antibodies recognizing a particular leukocyte antigen system designated human neutrophil antigen (HNA) 3a/3b. Detection of antibodies specific for HNA-3a/3b became a high priority with the recognition that they are much more likely to cause fatal TRALI reactions than antibodies specific for HLA.

Brian Curtis, working in the laboratory of Richard Aster, M.D., at BloodCenter of Wisconsin and its Blood Research Institute, found that HNA-3a is expressed on many different cell types. The researchers also successfully isolated HNA-3a antibodies, identified an antibody binding target, and discovered a genetic variation in humans that corresponds to creation of the HNA-3a and HN-3b antigens. Understanding the molecular structure of the HNA-3a/3b antigens provides a basis for further studies to define the incidence of HNA-3a and HNA-3b antibodies in blood donor populations and to develop practical methods to screen blood donors routinely for these antibodies.

FOX CHASE CANCER CENTER; Philadelphia, PA — www.fccc.edu

New Strategies for Overcoming Drug Resistant Cancer

Molecularly targeted therapies can reduce tumors rapidly. However, not all tumors respond to the drugs, and even those that do often develop resistance over time. Looking for a way to combat the problem of resistance, researchers at Fox Chase Cancer Center hypothesized that hitting already weakened cancer cells with a second targeted agent could kill them—but only if it was the right second agent.

One well-validated molecular target for anti-cancer drugs is the epidermal growth factor receptor, or EGFR. Using a novel screening approach, the scientists identified over 60 additional proteins that are necessary for cells to survive in the presence of an EGFR inhibitor. When they simultaneously inhibited EGFR and any one of these other proteins, more of the cancer cells died. The researchers, Erica A. Golemis, Ph.D., and Igor Astsaturov, M.D., Ph.D., say this screening strategy to identify targets for effective combinations of cancer drugs will open the door for future therapies.

Already, two clinical trials are under way to test innovative drug combinations suggested by the new tactic. The trials focus on two challenging cancers: lung cancer and esophageal cancer. The work of the two scientists is supported by the National Institutes of Health, and their study was published in the journal *Science Signaling*.

A Genetic Link to Mesothelioma

Fox Chase Cancer Center scientist Joseph R. Testa, Ph.D., and colleagues recently discovered that individuals carrying a mutation in a gene called BAP1 are susceptible to developing two forms of cancer—mesothelioma, an aggressive cancer of the lining of the chest and abdomen, and melanoma of the eye. The study also found evidence that some people with BAP1 gene mutations developed breast, ovarian, pancreatic or renal cancers, suggesting the gene mutation may be involved in multiple cancer types.

Mesothelioma tumors are typically associated with asbestos and erionite exposure. Erionite, a naturally occurring mineral fiber similar to asbestos, is found in rock formations and volcanic ash. However, only a small fraction of individuals exposed to erionite or asbestos actually develop mesothelioma, a deadly form of cancer that kills about 3,000 people each year in the United States, with half of those diagnosed dying within one year. The discovery of BAP1 may be a key step to identifying those people at greatest risk for developing mesothelioma, especially those exposed to dangerous levels of asbestos and erionite. Additionally, the discovery offers new information important for understanding the basic biology of this difficult disease. The research, funded by the National Cancer Institute, was published in the journal *Nature Genetics*.

FRED HUTCHINSON CANCER RESEARCH CENTER; Seattle, WA — www.fhcrc.org

Cord Blood Transplants

Colleen Delaney, M.D., M.Sc., a scientist in the Clinical Research Division of Fred Hutchinson Cancer Research Center, has pioneered a method to improve the use of umbilical cord blood for blood stem cell transplants, a technique that is bringing transplants and cures to many of the 16,000 leukemia patients each year who are unable to find a matching bone marrow donor. In related work, Dr. Delaney and her colleague, Michael Boeckh, M.D., developed a strategy to prevent many cases of infection with the virus known as cytomegalovirus, a leading cause of complications and death in cord blood transplant recipients.

Cervical Cancer Vaccine

The fundamental findings of Denise Galloway, Ph.D. and colleagues of Fred Hutchinson Cancer Research Center's Human Biology Division helped lead to the creation of Gardasil®, the vaccine against certain human papillomaviruses (HPVs) that cause cervical cancer and genital warts. Dr. Galloway's group showed that a single HPV protein could assemble into "virus-like particles," which formed the basis for current HPV vaccines and may be extended to other virus vaccines in the future.

Breast Cancer Prevention

The Women's Health Initiative (WHI), one of the nation's largest prevention trials to study the common causes of disease and death in postmenopausal women, was conceived in and continues to be coordinated by researchers in the Public Health Sciences Division of Fred Hutchinson Cancer Research Center. The study has produced numerous findings that have changed the practice of women's health care in the U.S. and have saved many lives. For example, the WHI found that combination estrogen-plus-progestin hormone replacement therapy (HRT), traditionally used for menopause symptoms, significantly increased women's risk of breast cancer and heart disease. This information significantly changed clinical practices in the U.S. regarding hormone therapy use. Two-thirds of the women who were taking HRT stopped and many women since have chosen not to begin this therapy. As a result, rates of breast cancer in the U.S. have declined by about 10 percent, equaling 20,000 fewer cases of breast cancer each year.

ERNEST GALLO CLINIC AND RESEARCH CENTER; San Francisco, CA — www.galloresearch.org

Repurposed Medications for Treatment of Alcoholism

Ernest Gallo Clinic and Research Center researchers have identified a number of medications, already approved for human use by the U.S. Food and Drug Administration, which show promise as potential treatments for alcohol abuse.

Chlorzoxazone, which is commonly prescribed as a muscle relaxant, significantly decreased alcohol consumption in a rat model of heavy drinking, in a study led by Woody Hopf, Ph.D. Dr. Hopf found that chlorzoxazone makes neurons less excitable, which in turn suppresses alcohol consumption. The drug's action takes place in the nucleus accumbens, a key part of the reward system in the brain that affects craving for alcohol and other addictive substances in both rodents and humans. Dr. Hopf sees chlorzoxazone as a possible alcohol-abuse medication among patients for whom currently available drugs do not work, or among patients who do not take those drugs because of adverse or unpleasant side effects.

In another Gallo Center study, a team led by Selena Bartlett, Ph.D., discovered that varenicline, which is currently marketed by Pfizer under the name Chantix® for treatment of nicotine addiction, curbed alcohol dependence in rats. One dose alone cut drinking in half. In addition, varenicline did not kill the rats' appetite for food — a known side effect of the most effective drug currently approved for alcohol dependence. The animals also did not resume drinking in excess after the drug was stopped, a pattern commonly seen in people who stop taking alcohol dependence medications. Eighty-five percent of alcoholics smoke, so if planned clinical trials confirm that varenicline is effective against alcoholism, physicians can prescribe the drug to treat both conditions.

THE HAMNER INSTITUTES FOR HEALTH SCIENCES; Research Triangle Park, NC — www.thehamner.org

Improved Drug Development Using a Liver Injury Model

The Institute for Drug Safety Sciences (IDSS) is a unique partnership between The Hamner Institutes for Health Sciences and the University of North Carolina at Chapel Hill (UNC) Schools of Medicine and Pharmacy. Committed to understanding, predicting, and preventing adverse reactions to drugs, the IDSS is led by Director Paul B. Watkins, M.D., Professor of Medicine, Professor of Toxicology, Professor of Experimental Therapeutics at UNC-Chapel Hill, and an internationally recognized expert with extensive research experience in drug-induced liver injury (DILI). DILI remains the single major adverse drug event that terminates drug development programs and results in regulatory actions leading to failed or stalled drug approvals, market withdrawals, usage restrictions, and warnings to physicians. There is an industry-wide need for predictive tools which will incorporate safety earlier in the drug development process.

The DILI-sim Initiative represents a group of sponsoring organizations combining resources to support the development of the DILIsym™ model – a mechanistic, mathematical model of drug-induced liver injury in mice, rats, humans, and dogs. This validated, predictive model of DILI is capable of evaluating the human toxicity of newly developed compounds based on nonclinical data. In the short term, it is envisioned that this information will be integrated with other key nonclinical data to assess drug safety prior to undertaking nonclinical regulatory studies or administering compounds to humans. In the longer term, it is envisioned that use of the DILIsym™ model will improve human risk assessment and provide enhanced opportunities for customized clinical safety monitoring during all phases of clinical development. Tools like the DILIsym™ model have the potential to reduce drug development timelines and enable real-time decision-making.

HUNTINGTON MEDICAL RESEARCH INSTITUTES; Pasadena, CA — www.hmri.org

Cerebrospinal Fluid Shunt

An early clinical problem addressed by Huntington Medical Research Institute (HMRI) researchers was pediatric hydrocephalus, or water on the brain, for which there was no effective treatment. Usual clinical practice depended on reducing pressure by removing cerebrospinal fluid (CSF) from the body, depleting electrolytes.

HMRI's laboratory work focused on the biology of CSF secretion and resorption. Laboratory studies showed the fluid pressure could be relieved in the brain by draining it to other organs, preserving electrolytes and preventing infection. The researchers developed one-way regulating and clearing valves to maintain normal physiological pressure levels in the brain. An additional challenge of the project was selecting the best material for the implanted tubes and valves running from inside the ventricles of the brain to the chest or abdomen. All initial materials failed until, based on lab biocompatibility studies, HMRI researchers specified a new formulation for silicone rubber, which was well tolerated during long-term implantation. The resulting device, called a hydrocephalus shunt, revolutionized the treatment of pediatric hydrocephalus, as well as normal-pressure hydrocephalus, a treatable form of dementia in adults. In addition, the device is widely used to reduce intracranial pressure in cases of brain hemorrhage or trauma.

No manufacturer or distributor was initially interested in the device, so a new company was formed to launch the system. This company was ultimately sold to a large medical device corporation. After sale, the original physician champion from HMRI joined again with the entrepreneur of HMRI's original spin-out and formed a second company to build additional improved models. That company is now a division of the nation's dominant pacemaker company.

Electronic Neural Stimulators

The successful development of medical devices that electrically stimulate the nervous system depends on understanding how to connect with and transmit signals to the nerves and neural circuits in the brain. Several HMRI studies have led to the understanding of which waveforms, frequencies, pulse sequences, charge densities, and other parameters are safe and effective. Material science studies at HMRI have led to an understanding of systems that are tolerated during movement of the brain, spinal cord, and nerves, and do not suffer mechanical or insulation failure. In addition, research on dynamic mechanical properties of the brain and the nervous system have led to development of new surgical tools to allow accurate placement of electrodes that will then be well-tolerated and move with the brain.

The result of this HMRI research has been a series of new medical devices and new companies. For example, a new nerve stimulation device is effective for some kinds of epilepsy and shows promise for depression. Another device is implanted in the brain's cochlear nucleus, which is important for hearing, and is an effective partial treatment for profound deafness.

THE LANKENAU INSTITUTE FOR MEDICAL RESEARCH; Wynnewood, PA — www.limr.org

Pradaxa® (Dabigatran Exetelate): The First New Blood Thinner in 60 Years

The snake venom toxin warfarin has been used medically as a blood thinner for many years, but its clinical management is costly and difficult for physicians and their patients. One of the more common uses of warfarin is to prevent strokes in patients with atrial fibrillation, but major side effects make its use problematic in many patients. In conducting the largest Phase III trial ever performed in atrial fibrillation patients, involving 5,000 U.S. patients and 18,000 patients worldwide, clinical scientists at the Lankenau Institute for Medical Research (LIMR) demonstrated the superiority of the novel thrombin inhibitor Pradaxa® in preventing strokes in atrial fibrillation patients when compared to warfarin. The new drug application led by the Lankenau team was recommended unanimously by the U.S. Food and Drug Administration (FDA) review board and subsequently approved for use in late 2010, representing the first new blood thinner to be made available to U.S. patients in several decades.

A Generalized Approach to Cancer Treatment

During their development, tumors must evolve strategies to evade the immune system, which can eradicate cancer if stimulated properly. The immune barriers erected by tumors are a chief contributor to mortality, and the mechanisms involved directly contribute to the historical failures of immunotherapy to make significant inroads in cancer treatment. Starting with fundamental research on a genetic pathway that blunts the immune response to cancer, scientists at LIMR pioneered a new type of drug therapy that destroys a key immune barrier and greatly heightens the efficacy of radiotherapy and chemotherapies used to treat most human cancers. Preclinical and genetic validation of the new therapeutic principle was part of a collaborative investigational new drug application to the FDA. The application was sponsored by the National Cancer Institute (NCI) and New Link Genetics Corporation, a now-public company that acquired the technology by purchasing the Lankenau start-up company OncoRx, Inc. On the basis of pioneering proof-of-concept studies at Lankenau, similar inhibitor programs have been started by several pharmaceutical companies. The resulting lead compound has been rated by an NCI workshop as one of the most promising immunotherapeutics in the field, now in Phase Ib/II trials.

Oregon Research Institute; Eugene, OR – www.ori.org

Tai Chi for Falls Prevention

Falls are the leading cause of injury death in older adults and present a significant public health burden. Although there is sufficient evidence from randomized controlled trials to indicate that exercise can prevent falls in older people, few effective community-based fall prevention programs exist in practice. There is wide recognition within public health that proven programs must be translated, implemented and adopted to have widespread effects.

Fuzhong Li, Ph.D., a senior scientist at Oregon Research Institute (ORI) has developed an eight form tai chi program that has proven effective in training and retraining postural control systems for older adults and/or adults with balance and gait impairments. Most recently, the program has shown significant benefits for patients with mild-to-moderate Parkinson's disease, improving postural stability, walking ability, and reducing falls. Li and his team have evaluated how well the exercise program translated into positive results when taught in community centers. Results from this dissemination research showed excellent adoption by community and senior centers, successful program implementation with excellent fidelity, good program maintenance, and strong support in the form of referrals by healthcare professionals. More importantly, participants showed significant improvements in health-related outcomes.

Tai Chi—Moving for Better Balance is a low-cost, scalable, therapeutic balance training program easily implementable in various settings. Tai Chi exercise is recommended by the American Geriatric Society and the British Geriatric Society as a fall prevention exercise program for older adults. Li's program, *Tai Chi—Moving for Better Balance,* has been specifically recommended by the Centers for Disease Control and Prevention (CDC) and the Administration on Aging, and has currently been adopted by several agencies, such as Department of Health, Injury Prevention, Elderly Affairs, Area Agency on Aging, in the states of Oregon, Florida, New Mexico, Connecticut, and Maryland. This evidence-based tai chi program is practical to disseminate and can be effectively implemented and maintained in community settings.

Public Health Institute; Oakland, CA - http://www.ghfp.net/publichealthinstitute.fsp

Network for a Healthy California

Rates of obesity, and corresponding chronic illnesses such as diabetes and heart disease, are major public health concerns. Adequate fruit and vegetable consumption is considered a national public health priority for reducing obesity and other diet-related chronic diseases and maintaining overall good health.

The Public Health Institute partners with the California Department of Public Health to implement the *Network for a Healthy California*, which is supported by the United States Department of Agriculture's (UDSA) Supplemental Nutrition Assistance Program. Since 1997, the *Network* has led a statewide movement of local, state and national partners working to facilitate behavior change and create environments that support fruit and vegetable consumption and physical activity.

Following a decade of *Network* interventions, daily fruit and vegetable consumption among California adults rose 37 percent. The most dramatic improvements were seen among very low-income Californians, who registered a 92 percent increase in consuming five or more servings of fruits and vegetables a day. African-American adults saw a 77 percent increase, while the percentage of Latino men and women consuming five or more servings of fruits and vegetables jumped by 43 percent. More information is available at: http://www.cdph.ca.gov/programs/CPNS/Pages/default.aspx

Regional Asthma Management and Prevention (RAMP)

In California, one in seven children has been diagnosed with asthma. Pediatric asthma is "ground zero" for health disparities. Twenty percent of African-American children in California have been diagnosed, more than any other racial or ethnic group. The costs of asthma are enormous—hospitalizations alone cost $770 million in California in 2007.

The Public Health Institute's Regional Asthma Management and Prevention (RAMP) Program is at the forefront of using policy advocacy to address social and environmental inequities in order to reduce the burden of asthma in the hardest hit communities. RAMP is supported by the Centers for Disease Control and Prevention (CDC) and was designated a CDC Center of Excellence in Eliminating Disparities.

RAMP convened diverse stakeholders (including public health, community-based organizations, schools, clinicians, and environmental health and justice groups) to improve air quality and reduce asthma rates that disproportionally impact low-income African American and Latino communities in California. The group's success led to the passage of state-level diesel emissions regulations that will reduce diesel particulate matter by 43% by 2020 and are projected to:

- prevent 150,000 cases of asthma, 12,000 cases of acute bronchitis and 9,400 premature deaths over 15 years
- result in economic benefits of $48 - $69 billion

More information available at: www.rampasthma.org

The Research Institute at Nationwide Children's Hospital; Columbus, OH – www.nationwidechildrens.org/pediatric-research

Developing a Transcutaneous Vaccine against Middle Ear Infection

The Nationwide Children's Hospital research team led by Lauren Bakaletz, PhD studies the host-pathogen interactions that contribute to otitis media (middle ear infection). Otitis media is the most frequently diagnosed illness in children less than 15 years of age in the United States. More than 80 percent of children will experience at least one ear infection before their third birthday and the annual costs to society are high.

Funded by the National Institute on Deafness and Other Communication Disorders (NIDCD), the Bakaletz Lab is studying nontypeable *Haemophilus influenzae,* the bacterium primarily responsible for this common childhood illness. Dr. Bakaletz's team has effectively used transcutaneous immunization in an animal model of nontypeable *Haemophilus influenzae*-induced otitis media. Not only was transcutaneous immunization able to prevent infection in their model, but also was shown to be able to resolve existing infection when tested in a therapeutic model.

Learning from the now patented chimeric vaccine for *H. influenzae*-induced disease, the team is currently investigating how these findings can be translated to studies in humans in order to develop a therapeutic vaccine for chronic and recurrent ear infections due to this bacterium. Being able to immunize without needles, by harnessing the immune power of the skin, will make this vaccination approach far cheaper and easier to deliver, in addition to increasing compliance and better enabling the vaccine to reach children in the developing world, who bear an enormous burden of this highly prevalent pediatric disease.

Crossing the Blood-Brain Barrier to Reverse Effects of Spinal Muscular Atrophy

Nationwide Children's Hospital scientist Brian K. Kaspar, PhD, has developed an adenoassociated virus 9 (AAV9) vascular delivery method for bypassing the blood brain barrier and delivering genes to the spinal cord and motor neurons. With Ohio State University colleague Arthur Burghes, PHD, Dr. Kaspar is using AAV9 in a gene therapy approach to treat the neurological disease group known as spinal muscular atrophy (SMA). SMA causes progressive muscle degeneration and weakness shortly after birth and leads to mobility and respiratory difficulty and reduced lifespan.

In a study detailed in *Nature Biotechnology*, Dr. Kaspar showed that AAV9-assisted delivery of the survival motor neuron protein corrects motor function, restore nerve signals and improve survival SMA-modeled mice. Within 13 days after the single-injection treatment, 90 percent of the treated mice had the muscle coordination needed to right themselves as quickly as normal animals. By this time, untreated SMA mice already were suffering symptoms that left them unable to right themselves.

Funded by the National Institute of Neurological Disorders and Stroke (NINDS), Dr. Kaspar is working to define the optimal dosage and regulatory safety studies to move toward human clinical trials of this gene therapy technique.

SMITH-KETTLEWELL EYE RESEARCH INSTITUTE; San Francisco, CA – www.ski.org

Optimizing Treatment of Retinopathy of Prematurity (ROP)

Translational Research at the Smith-Kettlewell Eye Research Institute has led to a number of advances that will benefit the health and well-being of children. A recent example is a project funded by the National Eye Institute (NEI) at the National Institutes of Health (NIH) and headquartered at Smith-Kettlewell whose purpose was to optimize treatment for retinopathy of prematurity – a serious blinding disease that still occurs in large numbers of infants.

The study used a complex algorithm developed at the School for Public Health, University of Texas in Houston, to choose infants for treatment for advanced ROP. This project reduced the rate of blindness in afflicted infants and also reduced the rate of unnecessary treatment for children with ROP. The results have provided eye care physicians with greatly improved guidance on when to intervene with early treatment in cases of ROP in order to minimize the vision loss experienced by patients.

An independent research institute was an ideal setting for this type of collaborative translational research study, due to Smith-Kettlewell's unique position in the vision research community where it is well known as a center of expertise in assessment and treatment methods for vision problems affecting infants and young children whose vision cannot be measured by the usual methods requiring reading of letters on an eye chart.

Tactile Map Automated Production (TMAP)

A novel system enabling a blind person to produce custom, on-demand tactile maps for any neighborhood in the United States and Canada has been developed at the Smith-Kettlewell Eye Research Institute. The Tactile Map Automated Production system (TMAP) harnesses Internet technology along with Geographic Information Systems to synthesize a unique tool enabling a blind traveler who intends to visit, explore or attend a meeting anywhere in the country to specify and obtain a simple-to-use tactile map of the area of interest. This provides blind travelers with a hitherto unavailable tool that sighted travelers take for granted.

Previously, tactile maps suitable for navigating and exploring neighborhoods had to be expensively handmade and were virtually unavailable. Now, a blind person can log on to the TMAP website, specify any desired street address or intersection, along with the desired scale and other parameters, and have a unique tactile map generated, downloaded and printed out on his or her Braille Embosser. Individuals who do not have their own embossers can obtain the maps via collaborating agencies such as Touch Graphics Inc of New York, or the San Francisco Lighthouse.

Development of the TMAP system was supported by grants from the US Department of Education, NIH, and Smith-Kettlewell private funds. As an independent research institute with rehabilitation technology as one of its main areas of specialization, Smith-Kettlewell provided a focused environment for such a project through collaboration among its experienced blind and sighted staff who are engaged full time in research.

TEXAS HEART INSTITUTE; Houston, TX – www.texasheartinstitute.org

Novel Alternatives to Heart Transplantation

Cardiovascular disease remains the number one health threat to men and women. Heart failure continues to be one of the most critical problems; yet due to the shortage of donor organs, there have been only about 2,200 heart transplants performed annually across the U.S in the last 15 years or so. The Texas Heart Institute (THI), the site of the world's first artificial heart implantation and many other advances in the treatment of cardiovascular diseases, has been working to address these issues over the last five decades.

During that time, THI physicians and scientists have helped develop succeeding generations of heart pumps and have continued to improve total artificial heart technology. Continuous-flow left ventricular assist devices, which are more durable, have fewer moving parts and are smaller and lighter than traditional pumps, represent a big breakthrough. These pumps now work effectively in patients for up to seven years without mechanical failure. THI physicians have implanted more of these devices than any other institution, improving the lives of hundreds of patients.

In some younger patients, the heart pumps allow their damaged hearts to rest and heal, and after a period of time, the pumps can be removed. Dr. O.H. Bud Frazier, Chief of THI's Center for Cardiac Support, and Dr. William Cohn, THI's Director of Minimally Invasive Surgical Technology, continue to make important advancements toward development of the total artificial heart, employing continuous-flow technology with dual mini-VADs. Current efforts are focused on making such devices increasingly smaller and more durable with improved power sources that are also internalized.

Torrey Pines Institute for Molecular Studies; San Diego, CA – www.tpims.org

Molecular Test for Predicting Chemotherapy Responses

For individuals dealing with cancer, one form of treatment chosen may be chemotherapeutic drugs, such as those that are camptothecin-based. These drugs are among the most potent and widely-used therapies for a variety of solid tumors. However tumor responses are variable and presently unpredictable, thus there is a risk that some patients will not receive optimal treatment for their individual cases.

Dr. Ruth A. Gjerset and her colleagues at Torrey Pines Institute for Molecular Studies have discovered a unique molecular biomarker that identifies tumors most likely to respond to camptothecin-based chemotherapeutic drugs. This research, supported by the National Institutes of Health (NIH), has led to the Gjerset's team's patented technology relevant to the area of personalized medicine. This discovery may eventually enable physicians to tailor chemotherapeutic regiments to ensure better outcomes from available therapeutic drugs.

Biomarker Predicts Type I Diabetes Progression

Patients who are newly diagnosed with type 1 diabetes (TID) are required to take a large dose of insulin to reduce their blood glucose level to normal. However, within weeks of diagnosis, the amount of insulin required is substantially reduced in many patients. This period, called the "honeymoon period", can last from weeks to more than a year. Drug treatment for new onset TID patients is aimed at reversing TID, and is most effective when given during the honeymoon period. Therefore, designing protocols to prolong the honeymoon period might be beneficial to patients by reducing the dose of insulin that they require, and by improving responsiveness to therapy.

In studies funded by NIH and the American Diabetes Association, Dr. Joanna Davies and her research team at the Torrey Pines Institute for Molecular Studies have discovered a new cell subset that is present in significantly greater numbers in TID patients who have a long honeymoon period compared to patients who have a shorter honeymoon period. Additional data from this study suggests that this novel immune cell might delay disease progression in human TID.

Woods Hole Oceanographic Institution**; Woods Hole, MA – www.whoi.edu**

An Economical, Versatile Underwater 'Pickup Truck'

In the mid-1990s, scientists and engineers at Woods Hole Oceanographic Institution pursued a vision of going beyond using ships to explore the ocean. They designed and built free-swimming robotic vehicles that could be programmed to "fly" through the depths, continuously taking a variety of measurements over many hours and large areas. These autonomous underwater vehicles, or AUVs, became known as Remote Environmental Monitoring UnitS (REMUS).

REMUS are relatively lightweight, torpedo-shaped vehicles powered by battery-driven propellers, steered by fins, controlled by a laptop computer, and guided by a navigation system that allows the vehicle and operators to "know" where it is located in the depths. The first REMUS, built in 1995, was developed at WHOI to survey the seafloor in shallow coastal areas, working in concert with a coastal ocean observatory being built at Rutgers University. Original funding came from the National Undersea Research Program and later the Office of Naval Research. The Naval Oceanographic Office has subsequently provided funding to develop other REMUS models to allow the vehicles to go as deep as 6,000 meters and add new capabilities.

In its early deployments, REMUS carried a payload of sensors to measure current velocities and directions and seawater temperature and salinity, as well as sonar to map the seafloor. Since then, REMUS vehicles are commonly referred to as oceanographic pickup trucks because they can be outfitted with a wide range of instruments to detect pollution, search for mines, and study ocean currents and fisheries, for example. REMUS vehicles have been adapted to work underneath sea ice and glaciers and in rivers, estuaries, and lakes. REMUS vehicles were used to inspect New York City's underground water supply tunnels for leaks; to create a detailed sonar map of the *Titanic* wreck site and debris field; to locate the wreck of Air France 447 on the seafloor; and to find the long-lost Pink Terraces, New Zealand's greatest geological landmark, which was submerged in a lake after a volcanic eruption in 1886.

In 2001, the inventors of REMUS founded Hydroid, Inc., in Pocasset, Mass., to manufacture and market REMUS vehicles for marine research, defense, hydrographic, and offshore energy markets. In 2007, Hydroid was purchased by Kongsberg Maritime for $80 million. In 2012, more than 250 REMUS vehicles were being used around the world by many military, scientific, and commercial organizations.