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 AIRI member institutes that is bringing research discoveries into clinical practice and the marketplace, AIRI has compiled the following examples of basic research successfully moved toward translation. In celebration of AIRI’s 50th Anniversary, this document reflects the tremendous contributions and advances in translational research at independent research institutes.

Below are success stories of research supported by AIRI member institutes and the drug, therapy, diagnostic, company or prevention method that resulted from it, as well as 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 translational research. The AIRI Washington Office continues to accept success stories at airi@lewis-burke.com.

If you have any questions about AIRI, please feel free to contact David Issing, AIRI Executive Director, at hq@airi.org or 410-751-8900.

**Table of Contents**

<table>
<thead>
<tr>
<th>BUCK INSTITUTE FOR RESEARCH ON AGING</th>
<th>.............................................................. 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutics for Alzheimer’s Disease</td>
<td>........................................................................ 4</td>
</tr>
<tr>
<td>CHILDREN’S HOSPITAL OAKLAND RESEARCH INSTITUTE</td>
<td>............................................................ 5</td>
</tr>
<tr>
<td>Cure for Hemoglobin Disorders</td>
<td>........................................................................ 5</td>
</tr>
<tr>
<td>COLD SPRING HARBOR LABORATORY</td>
<td>........................................................................ 6</td>
</tr>
<tr>
<td>Antisense Therapy for Spinal Muscular Atrophy</td>
<td>........................................................................ 6</td>
</tr>
<tr>
<td>CORIELL INSTITUTE FOR MEDICAL RESEARCH</td>
<td>........................................................................ 7</td>
</tr>
<tr>
<td>Infection Control: The Role of Laminar Flow</td>
<td>........................................................................ 7</td>
</tr>
<tr>
<td>Biobanking: Preserving Cells for Future Research</td>
<td>........................................................................ 7</td>
</tr>
<tr>
<td>THE FORSYTH INSTITUTE</td>
<td>........................................................................ 8</td>
</tr>
<tr>
<td>Oral Health Breakthroughs</td>
<td>........................................................................ 8</td>
</tr>
<tr>
<td>FOUNDATION FOR BLOOD RESEARCH</td>
<td>........................................................................ 9</td>
</tr>
<tr>
<td>Immunonephelometry</td>
<td>........................................................................ 9</td>
</tr>
</tbody>
</table>
Immunofixation ........................................................................................................ 9
FRED HUTCHINSON CANCER RESEARCH CENTER ................................................. 10
Tumor Paint ............................................................................................................. 10
Radioantibodies ...................................................................................................... 10
Melanoma Immunotherapy ..................................................................................... 10
H. LEE MOFFITT CANCER CENTER AND RESEARCH INSTITUTE ....................... 11
ERCC1 Assay for Lung Cancer Patients ................................................................. 11
Designer Lymph Nodes ......................................................................................... 11
Molecular Test for Predicting Response to Radiation Therapy ......................... 11
HOWARD HUGHES MEDICAL INSTITUTE ............................................................. 12
Dasatinib/Sprycel: New Cancer Treatment ............................................................ 12
Ipilimumab/Yervoy: Treatment for Late-Stage Melanoma .................................... 12
Genetic Test for Hypertrophic Cardiomyopathy ................................................... 12
THE J. DAVID GLADSTONE INSTITUTES ............................................................... 14
JM6: Potential Treatment for Neurodegenerative Diseases .................................. 14
Induced Pluripotent Stem (iPS) Cell Technology ................................................ 14
iPrEx and Truvada: Treatment for HIV/AIDS .................................................... 15
THE JACKSON LABORATORY ................................................................................ 16
Genetic Chemotherapy ......................................................................................... 16
Glaucoma Breakthroughs .................................................................................... 16
One-Two Punch for Lethal Cancer ..................................................................... 17
LA JOLLA INSTITUTE FOR ALLERGY AND IMMUNOLOGY ................................. 18
Lexiscan Uses for Sickle Cell Disease .................................................................. 18
New Therapy for Asthma ..................................................................................... 18
LOVELACE RESPIRATORY RESEARCH INSTITUTE ................................................ 19
Treatments for Respiratory Diseases .................................................................... 19
LUDWIG INSTITUTE FOR CANCER RESEARCH ..................................................... 20
G250: Therapy for Metastatic Renal Cell Carcinoma ............................................ 20
PI3K: Discovery to Clinic ..................................................................................... 20
Antibody 806: New Treatment for Glioblastoma ............................................... 21
MARINE BIOLOGICAL LABORATORY ................................................................... 22
Oosight Imaging System ...................................................................................... 22
Limulus Amebocyte Lysate (LAL) Test ................................................................. 22
Green Fluorescent Protein (GFP) ......................................................................... 22
MASONIC MEDICAL RESEARCH LABORATORY .................................................... 24
Novel Therapies for Atrial Fibrillation................................................................. 24

MONELL CHEMICAL SENSES CENTER ................................................................. 25
Salt Reduction .................................................................................................... 25
First Acceptance of Fruits and Vegetables ................................................... 25
Smell Loss in First Responders ..................................................................... 26

OKLAHOMA MEDICAL RESEARCH FOUNDATION ......................................... 27
Xigris: Treating Sepsis .................................................................................. 27
Soliris: Tackling a Rare Blood Disease ......................................................... 27

RESEARCH INSTITUTE AT NATIONWIDE CHILDREN’S HOSPITAL .................. 28
Feeding Strategies in Premature Infants ......................................................... 28

THE SALK INSTITUTE FOR BIOLOGICAL STUDIES ...................................... 29
Gleevec: Breakthrough Cancer Drug ............................................................ 29
Nuclear Receptors and the Treatment of Leukemia ...................................... 29

SANFORD-BURNHAM MEDICAL RESEARCH INSTITUTE ............................ 30
ENB-0040: Treatment for Hypophosphatemia ............................................. 30

THE SCRIPPS RESEARCH INSTITUTE ............................................................... 31
Cladribine: Breakthrough Leukemia Drug .................................................... 31
Combinatorial Antibody Library Technology for Rheumatoid Arthritis, Lupus and More... 31

TEXAS BIOMEDICAL RESEARCH INSTITUTE ................................................ 32
Mechanical Ventilation for Respiratory Distress ........................................... 32
Hepatitis B Vaccine ....................................................................................... 32

VAN ANDEL INSTITUTE .................................................................................. 33
Genomic-Based Clinical Trials for Pediatric Neuroblastoma ......................... 33

VETERANS MEDICAL RESEARCH FOUNDATION ....................................... 34
Clinical Trials for Complicated Grief ............................................................ 34
Sequenced Treatment Alternatives to Relieve Depression (STAR*D) ............ 34

THE WISTAR INSTITUTE .................................................................................. 35
RotaTeq®: Rotavirus Vaccine ......................................................................... 35
Antibody 19-9: Monitoring Pancreatic Cancer .......................................... 35
Interleukin-12: Treatments for Inflammatory Diseases ................................. 35

WOOD HUDSON CANCER RESEARCH LABORATORY ................................. 36
eIF4E ASO: Cancer Therapeutic ................................................................. 36
Int7G24A: Potential Diagnostic Tool to Determine Risk of Ovarian Cancer .... 36
Identification of Carcinogenic Chemicals in Drinking Water ........................ 37
Therapeutics for Alzheimer’s Disease

Alzheimer’s Disease (AD) is arguably one of the largest unmet healthcare needs in the developed world. The failure of several large AD clinical trials in recent years has shed light on the dearth of knowledge in neurodegeneration. Hopefully, by allowing us to see better into alternative mechanisms of this disease, scientists will begin to understand how best to treat the symptoms of AD and its causes.

The Bredesen Laboratory at the Buck Institute for Research on Aging has been very active in the field of AD pathophysiology and has uncovered some interesting biology as to the amyloid precursor protein (APP) gene’s function as well as methods to control its processing. Through various foundation grants, the Bredesen Lab has identified several compounds, including some currently registered in territories around the globe. These compounds control APP processing and lead to neuronal and synaptic preservation and maintenance, rather than retraction and eventual death. To that end, the Bredesen Lab has teamed up with a local venture philanthropist to develop this currently approved drug through pre-clinical and phase II trials. The first trial, a phase IIA trial, is scheduled for 2012 outside of the United States. Only in a unique setting like the Buck Institute, which lacks shareholders and hierarchy, could such novel research have been pursued.
Cure for Hemoglobin Disorders

Children’s Hospital Oakland Research Institute’s (CHORI’s) Center for Sickle Cell Disease and Thalassemia (SCT) hosts the nationally and internationally recognized Northern California Comprehensive Hemoglobin Disorders Center. CHORI receives ongoing National Institutes of Health (NIH) funding and other grant support to conduct basic, translational, and clinical research for these disorders. In addition, the program provides the highest standard of excellence in care for children and young adults by offering cures in a clinical setting. SCT offers not only unique tools for research and treatment, it also hosts the internationally recognized Blood and Marrow Transplant Program (BMT), which provided the first cure of alpha thalassemia major in North America in 2000.

Since 2000, over 125 children have received cures for various cancers and deadly blood disorders under the direction of BMT founder, Mark Walters, MD, who continues to pioneer transplant research in these diseases. His most recent focus is on transplant protocols to treat sickle cell and thalassemia patients by mismatched family member and unrelated donor transplantation. Dr. Walters also plans to extend this curative treatment to young adults as part of a larger strategy by the BMT program to enhance access to treatment.
Antisense Therapy for Spinal Muscular Atrophy

Tucked into a list of several dozen neuromuscular disorders is a killer of a disease called Spinal Muscular Atrophy (SMA), the leading genetic cause of death among children under the age of two. At Cold Spring Harbor Laboratory, Professor Adrian Krainer, Ph.D., has been working steadily for the last five years to wipe SMA off this list. SMA is the result of mutations in the Survival of Motor Neuron 1 (SMN1) gene. These mutations lead to abnormally low levels of SMN protein in motor nerve cells of the spinal cord. Without the protein, the nerve cells and the muscles they control slowly waste away. Hence babies born with SMA progressively lose their ability to move, breathe and swallow.

Dr. Krainer is an expert in alternative splicing, a cellular process for editing RNA — the chemical cousin of DNA. Using his insights into this process, Dr. Krainer has successfully corrected the splicing defect that causes SMA in systems of increasing complexity — first in test tubes, then in cells taken from SMA patients and grown in the lab, and most recently, in genetically engineered mouse models of SMA.

In 2009, Dr. Krainer and colleagues identified a compound that stimulates SMN production by altering RNA splicing. In 2010, they carried the work an important step further: by introducing chemically modified pieces of RNA called antisense oligonucleotides (ASOs) into the spinal cords of mice, they succeeded in reversing symptoms of Type III SMA. Dr. Krainer’s team has also made great progress in overcoming barriers to delivering ASOs directly into the fluid that surrounds the brain and spinal cord — a key requirement for the ASO’s success as a therapeutic. The treatment’s beneficial effect in mice persisted for half a year after it was discontinued, indicating the ASO is very stable, and did not trigger toxic side effects or inflammation. Dr. Krainer’s team is now working on the few key steps that remain before the Food and Drug Administration can be petitioned for SMA clinical trials.
Infection Control: The Role of Laminar Flow

Lewis L. Coriell, M.D., Ph.D., virologist, pediatrician, and founder of the Coriell Institute for Medical Research, understood the importance of infection control. He played a key role in optimizing cell culture techniques to sustain living human cells in culture, free from contamination. This breakthrough allowed scientists to grow the polio virus and work toward the first vaccine.

While surgical procedures advanced with incredible speed in the 1950s and 1960s, including the heart-lung machine and the development of coronary angiography, infection remained a post-surgical challenge. Expanding on his understanding of creating sterile environments, Dr. Coriell was thrilled to win a grant from the John A. Hartford Foundation for the study of dust-free biomedical environments. Dr. Coriell and his team looked to the concept of laminar flow: the process by which an entire body of air moves at uniform velocity along parallel lines with minimum disruption between the layers. By creating laminar flow systems that filter air and extract any bacteria, viruses or dust particles before it enters an area, they allow a lab space or an operating room to be completely isolated, effectively preventing any contamination by bacteria or virus-laden air. Today, laminar flow technology is a fundamental component of laboratories and operating rooms around the world.

Biobanking: Preserving Cells for Future Research

In 1959, Dr. Coriell recognized the value of collecting and preserving biospecimens in the present in anticipation of advanced research discovery techniques. He called for the establishment of a central tissue culture bank and cell registry to certify and store cell cultures. In 1960, the United States Public Health Service pledged a $100,000 research facilities grant toward construction of house cell bank operations. In 1964, the National Institutes of Health (NIH), via the National Cancer Institute, partnered with Coriell Institute to create the first standardized cell repository. By 1967, Coriell Institute had characterized, standardized, preserved, and placed a total of 35 pure cell lines into the national cell bank. In 2006, the NIH National Human Genome Research Institute Sample Repository for Human Genetic Research was established at Coriell to support the HapMap Program, and it currently supports the International 1000 Genome Project.

Today, the Coriell Biobank, sponsored significantly by the NIH, is the world’s most diverse repository of cells and DNA samples. Hundreds of thousands of biospecimens from the Coriell biobank have been distributed to researchers in 64 countries; more than 7,000 peer-reviewed papers have been published citing almost 12,000 biospecimens from the Coriell Biobank. These biospecimens have allowed researchers to identify the gene for Huntington’s disease, apply advanced cytogenetics techniques to identify chromosomal abnormalities, and begin to understand neurodevelopment disorders like autism and age-related diseases like Alzheimer’s disease.
Oral Health Breakthroughs
The Forsyth Institute has made seminal contributions to the field of oral health and wellness. Through the integration of clinical studies and laboratory analysis, the Institute has facilitated the movement of ideas from the bench into dental and medical practice. These include the development of localized anti-microbial drug delivery products for periodontal and endodontic therapy, evaluation of systemic antibiotics in periodontal treatment, improved diagnostic techniques for oral disease, introduction of visible light as a therapeutic modality, improvement of local anesthetics and the evaluation of agents that stimulate bone growth.

The first local drug delivery device for the treatment of periodontal (gum) disease was developed at Forsyth by Dr. J. Max Goodson, and led to the first Food and Drug Administration-approved local antibiotic delivery system ActiSite™. Forsyth was also integral to discoveries to treat a wide range of inflammatory diseases. Dr. Thomas Van Dyke, Vice President of Clinical and Translational Research at Forsyth, was part of the team that discovered the technology now utilized by Resolvyx Pharmaceuticals. The company is developing an entirely new class of therapeutics called Resolvins: naturally-occurring, small molecule lipid mediators that actively terminate inflammation.
Immunonephelometry
More than 40 years ago, scientists at the Foundation for Blood Research, led by its founder, Robert Ritchie, M.D., made a major contribution to the practice of laboratory medicine by applying a method known as nephelometry to the measurement of proteins in blood, urine, and cerebrospinal fluid. This technique, now known as immunonephelometry has made it possible to detect and quantify a wide variety of biological agents in a specific, precise and sensitive manner. Over several decades, the technique has undergone a variety of enhancements and has replaced qualitative or semi-quantitative tests with quantitative measurements that have greatly improved their clinical utility and correlation with various disease states.

Immunofixation
This technique was first applied by Foundation for Blood Research scientists for the identification of protein abnormalities associated with immune system disorders such as multiple myeloma, a form of bone cancer. Today, this test is considered by many to be the “gold standard” for identifying and typing monoclonal immunoglobulins and is routinely offered by clinical laboratories throughout the world. Collectively, immunofixation and immunonephelometry have dramatically changed the way laboratory medicine is practiced, reshaping the delivery of patient care.
Tumor Paint
Scorpions are rarely considered in medical research, but for Dr. James Olson of the Fred Hutchinson Cancer Research Center and his colleagues, the scorpion offers a solution to a challenging problem for surgeons: differentiating normal cells from cancer cells. Tumor Paint consists of chlorotoxin, a component of scorpion venom, coupled with Cy5.5, a fluorescent dye. Using magnetic resonance imaging, Tumor Paint lights up brain-cancer cells during surgery, allowing surgeons to spare the maximum amount of normal tissue. Tumor Paint was developed in collaboration with researchers at the University of Washington School of Medicine and Seattle Children’s Research Institute with support from the National Institutes of Health and the Hutchinson Center Synergy Fund. Dr. Olson’s research has required the convergence of disparate disciplines, such as chemistry, biology, physics and radiology, and the combined work of neurosurgeons, engineers and biologists. Independent research institutes like the Hutchinson Center foster a collaborative spirit that breaks down barriers between disciplines and accelerates the development of innovative tools for medicine like Tumor Paint.

Radioantibodies
At the Fred Hutchinson Cancer Research Center, Drs. Oliver Press and John Pagel are undertaking the first-ever human clinical trial of pretargeted radioimmunotherapy (PRIT), an approach that uses antibodies to target radiation directly to tumor cells, sparing healthy cells from damage and patients from harmful side effects. Drs. Press and Pagel, who pioneered this strategy, intend to treat 50 leukemia patients over the next five years to demonstrate the safety and feasibility of PRIT, which has the potential to be the next landmark advance in immunotherapy for blood cancers. This work has been supported by grants from the National Institutes of Health and through the private philanthropy of the Hutchinson Center’s Program in Immunotherapy. By uniting immunotherapy researchers in a common effort, the Program in Immunotherapy is an excellent example of collaboration between the researchers and the cooperative spirit fostered by an independent research institution.

Melanoma Immunotherapy
In 2008, Dr. Cassian Yee of the Fred Hutchinson Cancer Research Center published a landmark paper in the New England Journal of Medicine describing how he and his colleagues had eradicated one patient’s stage 4 melanoma – advanced skin cancer that had spread to a lymph node and a lung – using the patient’s own T-cells as the sole therapy. Dr. Yee is refining these results in ongoing clinical trials, combining T-cell therapy with IL-2 and chemotherapy to expand the power of T-cells. Early results indicate that this combination can cause the T-cells’ lifespan to increase, significantly increasing the chances that they will be effective in eliminating the patient’s cancer. For translational researchers, progress depends on a symbiotic partnership between clinical and laboratory studies, a partnership that is encouraged and fostered at independent research institutes. This work is sponsored by the National Institutes of Health and through private donations to the Hutchinson Center’s Program in Immunotherapy.
ERCC1 Assay for Lung Cancer Patients
Scientists at Moffitt Cancer Center discovered and validated an ERCC1 assay, the first test developed for selecting chemotherapy for non-small lung cancer patients. Each year more than 200,000 Americans are diagnosed with lung cancer. The ERCC1 assay measures ERCC1 levels in cells to predict response to cisplatin-based chemotherapy. Numerous studies have been conducted at Moffitt Cancer Center showing clinical utility of the ERCC1 assay including a clinical study published in the New England Journal of Medicine showing the association between low levels of ERCC1 and survival benefit from adjuvant cisplatin-based chemotherapy. Moffitt Cancer Center licensed this ERCC1 assay to Genzyme Corporation in November 2007 and the product was launched on May 1, 2009. To date, physicians have ordered hundreds of these ERCC1 assays to aid them in selecting appropriate chemotherapy for their patients. The research that led to the ERCC1 assay was funded in part by the National Institutes of Health.

Designer Lymph Nodes
Supported by the National Institutes of Health and private foundation grants, Moffitt scientists have developed fully-functioning designer lymph nodes. Using laboratory platform technology, these lymph nodes can move "at will" anywhere in the body, and can directly incorporate or combine with therapeutic cancer vaccines to producing a "tailored" immune response in combating cancer. The technology can instruct a patient's own immune system organ(s) to combat cancer with fewer side effects, more efficacy and specificity. A Phase I, proof-of-concept clinical trial in advanced melanoma patients is near completion.

The potential benefit from these designer lymph nodes is the possibility they will provide an enhanced, unified, or diversified immune system to fight cancer. In addition, the patented technology extends into the area of gene profiling and personalized medicine. Molecular gene signatures have been identified that predict the presence of certain lymph nodes in human solid tumor masses associated with better patient prognosis (survival). The signatures may be used for preselecting cancer patients for immunotherapy interventions by identifying the presence of tumor-localized, lymph nodes without any supervision.

Molecular Test for Predicting Response to Radiation Therapy
Several years ago, researchers at Moffitt Cancer Center developed a unique molecular diagnostic assay that identifies differences in tumor radiosensitivity, thereby pre-selecting those patients most likely to benefit from radiation therapy. Radiation therapy is the single most common agent used in cancer therapeutics and up to 60 percent of individuals diagnosed with cancer receive radiation therapy. However, clinicians are unable to distinguish differences in radiosensitivity across tumors when prescribing radiation therapy. This molecular test utilizes a proprietary algorithm to generate a radiosensitivity index derived from the expression of 10 specific genes. Importantly, it has been clinically-validated in four different disease sites (head and neck, esophageal, breast and rectal cancer) in hundreds of patient samples. A National Cancer Institute-sponsored trial is currently underway to prospectively validate the assay, while CvergenX, a faculty startup, has further developed this diagnostic assay. The research that led to this molecular test was funded in part by the National Institute of Health.
Dasatinib/Sprycel: New Cancer Treatment
Howard Hughes Medical Institute (HHMI) investigator Charles Sawyers has conceived of new ways to halt the growth of cancer cells that no longer succumb to Gleevec, a drug that has long been considered the "gold standard" in treatment of chronic myelogenous leukemia (CML). Sawyers began working with scientists at Bristol-Myers Squibb to develop a second-line drug that could help patients overcome resistance to Gleevec. In clinical trials led by Sawyers, who is at Memorial Sloan-Kettering Cancer Center, and collaborators at MD Anderson Cancer Center, Sprycel was shown to be effective against all but one of the commonly occurring gene mutations responsible for Gleevec resistance. As a result of this research, the Food and Drug Administration approved Sprycel for the treatment of CML in patients whose cancer does not respond to Gleevec.

Ipilimumab/Yervoy: Treatment for Late-Stage Melanoma
James P. Allison identified a protein, CTLA-4, which stops activated T cells from killing antigen-presenting cells. When Dr. Allison, a HHMI investigator at Memorial Sloan-Kettering Cancer Center, deleted the molecule in mice, the animals’ T cells divided uncontrollably. Dr. Allison hypothesized that the immune system may fail to detect tumor cells because CTLA-4 prevents T cells from eradicating tumors. Dr. Allison hypothesized that shutting CTLA-4 off and allowing T cells to remain activated might stimulate killing of cancer cells.

To test his theory, Dr. Allison made a monoclonal antibody against CTLA-4 that would prevent the protein from functioning properly. When he injected the antibody in mice with different cancers, the least aggressive tumors cleared away. Dr. Allison then collaborated with a biotech company to develop an antibody to human CTLA-4 and conduct clinical trials in a variety of types of cancer. Since then, thousands of people have been treated with this antibody, ipilimumab, and objective responses have been observed in advanced skin, renal, lung, prostate, and ovarian cancer. The results of a large randomized phase III trial of ipilimumab in metastatic melanoma was reported in June 2010. The research showed a remarkable survival benefit to patients receiving the antibody, with 25 percent alive four years after treatment. In March 2011, ipilimumab (now marketed as Yervoy by Bristol-Myers Squibb) was approved by the Food and Drug Administration for treatment of late-stage melanoma.
Genetic Test for Hypertrophic Cardiomyopathy
Sudden cardiac death kills as many as 300 young athletes each year. The root cause is often genetic. For more than 20 years, HHMI investigator Christine Seidman has been studying disorders of heart muscle. Dr. Seidman’s work began with familial hypertrophic cardiomyopathy (HCM), which increases heart thickness, leading to the development of heart failure and sudden death. While HCM is the most common cause of sudden death on the athletic field, it also affects many more people than originally thought. Dr. Seidman, whose laboratory is at Brigham and Women’s Hospital in Boston, used genetic approaches to discover mutations that altered proteins involved in heart muscle contraction. This work enabled the development of models that can help researchers understand the mechanisms by which mutations cause disease.

If HCM is detected in time, doctors can manage the condition with surveillance, lifestyle changes, and, sometimes, an implantable defibrillator. But young adults are not universally screened for heart conditions, and early HCM symptoms—such as shortness of breath—may easily be mistaken for more common conditions such as asthma. Dr. Seidman, her husband Jonathan G. Seidman at Harvard Medical School, and their research teams have developed a genetic test that may allow early identification and diagnosis of those at greatest risk for developing HCM. The test can confirm an HCM diagnosis in patients who show clinical symptoms of the disease and can provide further information for individuals at risk for the condition.
JM6: Potential Treatment for Neurodegenerative Diseases

Scientists at The J. David Gladstone Institutes have identified a drug candidate that diminishes the effects of both Alzheimer’s disease and Huntington’s disease in animal models, offering new hope for patients who currently lack any medications to halt the progression of these two debilitating illnesses. According to the Alzheimer’s Association, Alzheimer’s disease afflicts an estimated 5.4 million people in the United States alone, at an annual cost of $183 billion, without a therapeutic breakthrough, the number of Americans with Alzheimer’s disease is expected to double by 2050. Huntington’s disease, meanwhile, is the most common inherited neurodegenerative brain disorder, diminishing the ability of some 30,000 Americans to walk, talk and reason.

Gladstone experiments, done in collaboration with an international team of researchers, have shown that a new drug candidate, JM6, blocks kynurenine 3-monooxygenase (KMO), an enzyme long speculated to play a role in neurodegenerative diseases. In mice modeling Alzheimer’s, the novel compound prevented memory deficits and the loss of synaptic connections between brain cells—both of which are key features of the human disease. In mice modeling Huntington’s disease, JM6 prevented brain inflammation and the loss of synaptic connections between brain cells, while also extending lifespan. Gladstone, together with the University of Maryland School of Medicine, is currently considering a variety of ways to get JM6 into Phase 1 safety trials in humans—hopefully sometime in 2013—including the spinout of a venture-capital-backed startup or collaboration with a large pharmaceutical company.

Induced Pluripotent Stem (iPS) Cell Technology

Embryonic stem cells—called “pluripotent” because they can develop into any type of cell in the human body—hold tremendous promise for regenerative medicine, in which damaged organs and tissues can be replaced or repaired. Many in science consider the use of stem cells key to the future treatment and eradication of a number of diseases, such as heart disease and diabetes. But the use of embryonic stem cells is controversial—which is one reason why Dr. Shinya Yamanaka’s discovery of an alternate way to obtain human stem cells is so important. Five years ago, Dr. Yamanaka discovered that by altering the genes of skin cells in adult mice, he was able to induce the cells into becoming like embryonic stem cells. He called them induced pluripotent stem cells, or iPS cells. In 2007, Dr. Yamanaka, a
senior investigator at the Gladstone Institutes, announced he had done the same with human adult skin cells.

The use of iPS cell technology represents an entirely new platform for fundamental studies of human disease. Rather than using models made in yeast, flies or mice for disease research, iPS technology allows human stem cells to be created from the skin cells of patients with a specific disease. As a result, the iPS cells contain a complete set of the genes that resulted in that disease—representing the potential for a far-superior human model for studying disease development, new drugs and treatments. At the Gladstone Institutes, iPS cells are being used for customized drug-safety and efficacy testing in individual patients. Gladstone has partnered with a biotechnology company, iPierian Inc., to commercialize this technology for drug-discovery. Gladstone investigators have taken the reprogramming technology one step further, with Dr. Deepak Srivastava, who leads the Gladstone Stem Cell Program and all of Gladstone’s cardiovascular research, showing that non-muscle cells in an adult heart can be directly reprogrammed into beating cardiac muscle cells, and Dr. Sheng Ding demonstrating that skin cells can be turned directly into neural stem cells.

**iPrEX and Truvada: Treatment for HIV/AIDS**

HIV, the virus that causes AIDS, has infected more than 60 million people worldwide—nearly half of them girls and women no older than 24. In the United States alone, more than one million people live with HIV/AIDS at an annual cost of $34 billion. But a recent Gladstone Institutes-led study of men who have sex with men made headlines around the world and was ranked by *Time* magazine as the number one medical breakthrough of 2010. There’s little wonder why: the global iPrEx study showed that participants who received a comprehensive package of prevention services, along with a daily tablet containing two widely used HIV medications, experienced 44% fewer HIV infections than those taking a placebo pill. Further, those who took the pill (called Truvada®) consistently were 90% less likely to become infected than those who did not. This study could fundamentally change strategies to slow the global HIV epidemic and offers new hope for preventing a disease that has killed more than 25 million people around the world since first being identified some 30 years ago.
**Genetic Chemotherapy**

Jackson Laboratory Associate Professor Kevin Mills, Ph.D., with support from the National Cancer Institute and other sources, studies the mechanisms that govern genome stability, and how failure of these mechanisms leads to diseases, including cancer. His laboratory is pioneering a new concept, "genetic chemotherapy," to develop targeted cancer treatments based on selectively inducing cancer cell self-destruction. In August 2010, Mills and his laboratory published a paper in *Nature Immunology* revealing new details about DNA breakdown and repair mechanisms, research that could steer future strategies for treating cancer and other diseases. In December 2009, Dr. Mills and a Jackson colleague, Associate Professor Joel Graber, Ph.D., reported their discovery of telltale variations in mRNA processing—the cell's protein-building function—that correspond to cancer. The team showed that they could distinguish among similar tumor subtypes with at least 74 percent accuracy; the current standard in molecular diagnostics is about 10 percent. Dr. Mills and his laboratory are also developing a new drug discovery tool for leukemia, lymphoma and multiple myeloma. They will identify candidate drugs using a fast, high-throughput approach, initially screening about 1,000 compounds.

**Glaucoma Breakthroughs**

With support from the National Eye Institute and other sources, Jackson Laboratory Professor and Howard Hughes Medical Investigator Simon John, Ph.D., and collaborators have reported three major discoveries in glaucoma, a leading cause of blindness, in 2011. In the *Journal of Clinical Investigation*, the researchers reported on their new analysis technique that detects early stages of glaucoma in mice, and on their success in blocking the disease by targeting some of the molecular events in those early stages. A paper in *Science* demonstrated their findings that RNA granules—key players in messenger RNA (mRNA) processing—can affect eye development, leading to juvenile cataracts and glaucoma in humans and mice. Most recently, they discovered a gene implicated in an acute and severe form of glaucoma known as angle-closure glaucoma (ACG), reporting their findings in *Nature Genetics*. The gene's activity points to previously unsuspected mechanisms involved in both ACG and infant eye development.
One-Two Punch for Lethal Cancer

In 2009, while working at The Jackson Laboratory with National Cancer Institute funding, Shaoguang Li, M.D., Ph.D., led a research team that identified a gene involved with the inflammatory response that could hold the key to treating or even preventing chronic myeloid leukemia (CML), a lethal cancer. In research published in the journal *Nature Genetics*, the researchers identified a new role of the gene *Alox5*, which is known to process essential fatty acids to leukotrienes, important agents in the inflammatory response. According to the researchers, *Alox5* has a more sinister side. It is vital to the development and maintenance of cancer stem cells. Cancer stem cells are slow-dividing cells that are thought to give rise to a variety of cancers, including leukemia, and to be critical for maintaining them. Researchers theorize that cancer stem cells must be targeted for effective treatment of many cancers, but direct evidence is still lacking.

The researchers found that CML did not develop in mice without *Alox5* because of impaired function of leukemia stem cells. Also, *Alox5* deficiency did not affect normal stem cell function, providing the first clear differentiation between normal and cancer stem cells. Dr. Li also treated mice with CML with Zileuton, an asthma medication that inhibits the *Alox5* inflammation pathway, as well imatinib, commonly known as Gleevec, the most effective current leukemia medication. Imatinib effectively treated CML, but Zileuton was more effective. The two drugs combined provided an even better therapeutic effect. The findings provide a new focus of study into how leukemia stem cells are distinct from normal stem cells and how they can be targeted in cancer therapies. It appears likely that other cancer stem cells will have specific pathways that also differentiate them from their normal stem cell counterparts. A future clinical trial targeting *Alox5* will provide the first anti-stem cell strategy in cancer therapy.
Lexiscan Uses for Sickle Cell Disease
For people with sickle cell disease, life’s prospects are harsh. Most sufferers will experience episodes of severe pain, difficulty breathing and, ultimately, a shortened lifespan. The body’s red blood cells become sticky and misshapen or “sickled” in appearance, leading to poor blood flow that deprives tissues of oxygen. More than 70,000 Americans and millions around the world suffer from this genetic disease, which strikes hardest in persons of African descent.

Fortunately, La Jolla scientist Joel Linden, Ph.D., a world expert on adenosine molecules, was struck one day with a novel thought. Could adenosine, known to act as a brake on inflammation – which worsens sickle cell disease – help people with this disorder? Dr. Linden successfully tested his theory in animal models and isolated a good adenosine therapeutic candidate. To his delight, he found that an existing Food and Drug Administration-approved drug, Lexiscan™ used in cardiac stress testing, contained a similar molecule as its active ingredient. It didn’t take long for Dr. Linden to find David G. Nathan, M.D., President Emeritus of the Dana-Farber Cancer Institute and one of the world’s top sickle-cell experts. The pair, with funding from the National Institutes of Health, launched Phase I clinical trials of Lexiscan in Boston and St. Louis in 2010. Early results are promising.

New Therapy for Asthma
Asthma accounts for one-quarter of all emergency room visits in the U.S. each year, and it is the third-ranking cause of hospitalization for U.S. children under age 15. The National Institutes of Health (NIH) estimates asthma-related health care costs in the U.S. at $14 billion annually. La Jolla Institute researcher Michael Croft, Ph.D., understands well the seriousness of this condition, and his discovery is the basis for a new asthma treatment now in Phase II clinical trials. Recognized as a major milestone in asthma research, Dr. Croft’s finding is particularly exciting because it offers the potential to control asthma for longer periods of time and with much more specificity than current therapies. That’s good news for the 20 million Americans, including nine million children, who suffer from this terrible disorder. An NIH grant provided major funding for Dr. Croft’s work.
Treatments for Respiratory Diseases
The Lovelace Respiratory Research Institute focuses its research agenda on the prevention, treatment and cure of respiratory disease. Recent advances include the identification of genes, gene variants and silenced genes that predispose people to developing chronic obstructive pulmonary disease (COPD) and lung cancer. This has lead to the development of diagnostic tests using sputum to identify these diseases in time for intervention, cure or prevention. Further studies have identified Hispanic smokers as an unusual cohort in regards to their risk profiles which may lead to a better understanding of the molecular mechanisms of smoking-induced disease. In addition, the Institute has played a pivotal role in the development of vaccines, antiviral drugs, antibiotics and other countermeasures to Anthrax, SARS, Tularemia, Avian influenza, and inhaled radionuclides. The latter advances are particularly relevant in light of the nuclear disaster in Japan and point to new treatments for people exposed to ingested radionuclides.
G250: Therapy for Metastatic Renal Cell Carcinoma
The five year survival rate of approximately 30 percent for patients with metastatic renal cell carcinoma (RCC) underscores the critical need for diagnostic and therapeutic advances. Laboratory and clinical research sponsored by the Ludwig Institute for Cancer Research led to the discovery that the antibody, G250, binds to a molecule present on the surface of more than 85 percent of RCC cells, but not on normal kidney cells. A pilot clinical trial assessing the use of G250 as a non-invasive diagnostic tool for clear cell RCC, the most aggressive subtype of RCC, produced highly encouraging initial results. This success will make a substantial difference to the care and welfare of anyone suspected of having RCC as they may no longer have to undergo surgery for a diagnosis. Subsequently the biopharmaceutical company Wilex AG, conducted a confirmatory pivotal phase III trial with the radiolabeled G250 antibody (Redectane®) to determine whether with positron emission tomography (PET) and computer tomography (CT) – versus the standard use of CT alone – will improve the diagnosis of renal masses. Wilex is also conducting the Phase III ARISER Study to assess the potential of the G250 antibody (Rencarex®) as an adjuvant therapy after surgical removal of the tumor in patients who have non-metastatic RCC. Recruitment of patients for this clinical trial has been completed.

PI3K: Discovery to Clinic
Phosphatidylinositol 3-kinase (PI3K) is an enzyme that controls several vital cell processes such as cell growth and survival as well physiological processes like inflammation and immunology. It is also involved in human diseases, including solid tumors and leukemias, arthritis, obesity and diabetes. Research conducted by the Ludwig Institute for Cancer Research identified several species of PI3K and identified it as a potential target for targeted drug therapies. In collaboration with a number of pharmaceutical companies and researchers from other institutes around the world, multiple lead compounds were generated and licensed for development. Subsequently, Roche developed a drug currently in Phase I clinical trials as a potential cancer therapy in patients with metastatic breast cancer and metastatic non-small cell lung cancer.
Antibody 806: New Treatment for Glioblastoma

Anti-cancer antibodies are among the most promising of cancer therapies under research and development. If an antibody can recognize and bind to specific receptors on a cancer cell, it will destroy the cell. And while several antibodies have been approved for cancer patients, many cannot discriminate between cancer cells and healthy cells. This deficit is the apparent cause of the toxic side-effects associated with many of these drugs. Ludwig Institute for Cancer Research (LICR) researchers and others discovered that the majority of the most deadly and malignant cases of brain cancer, glioblastoma, are caused by a particular mutation of the epidermal growth factor receptor (EGFR). LICR investigators in several parts of the world set out to generate an antibody that specifically targets the mutated EGFR in the hope of developing an effective therapy for a disease that is intractable to all conventional treatments. They discovered an antibody, 806, which targets the mutation found in glioblastoma but not the normal receptor in non-cancerous tissues. LICR clinical research also showed that 806 does not cause the side-effects observed with other EGFR-targeting therapies. The 806 antibody formed the basis of an LICR spin-off company, Life Sciences Pharmaceuticals. In 2009 the antibody was licensed to the pharmaceutical company, Abbott, for clinical development and is currently in Phase I clinical trials. Some of the mechanistic and pre-clinical analyses were performed with National Institutes of Health funding by LICR investigators in the United States.
Oosight Imaging System

The Oosight microscope and imaging system, which is used in fertility clinics to assess the health of eggs and embryos, is the result of decades of research conducted by the Marine Biological Laboratory (MBL) in polarized light microscopy. The Oosight allows clinicians to improve pregnancy rates by assessing eggs for maturity and viability prior to procedures like in vitro fertilization and cryopreservation. The system resulted from collaboration in the mid-1990s between MBL scientists Rudolf Oldenbourg and Shinya Inoué, physician David Keefe, and Cambridge Research and Instrumentation (CRi), a company which licenses the patented technology from MBL. The Oosight allows clinicians to perform noninvasive quantitative analysis of vital cell structures, such as the meiotic spindle and zona pellucida in human eggs or embryos, without the need for dyes and molecular labels.

The basic technology for the Oosight was developed at the MBL with National Institutes of Health (NIH) support to the laboratory of Rudolf Oldenbourg. Additional NIH grants awarded to CRi, with subcontracts to MBL, supported the commercialization of the technology and its adaptation for use in routine tests performed in clinical laboratories.

Limulus Amebocyte Lysate (LAL) Test

The LAL test is used in clinical settings worldwide to insure that injectable drugs, intravenous fluids, and medical devices are free of gram-negative bacterial endotoxins. These endotoxins, which are present in some pathogens such as *E. coli*, can cause harmful infections if they enter the bloodstream. The LAL test has its roots at the Marine Biological Laboratory (MBL) in the mid-1950s, when Frederik Bang discovered that the blood of the horseshoe crab will clot if the crab is injected with the *Vibrio* bacteria. A decade later, Jack Levin at the MBL showed that the rate that the blood clots depends upon the concentration of bacterial endotoxin present. This led to the development of the LAL test, which uses an extract of the blood cells from the horseshoe crab to detect the presence of endotoxin. LAL is manufactured by several companies in the United States and Japan. This research was supported initially by the Atomic Energy Commission and subsequently by the National Institutes of Health.

Green Fluorescent Protein (GFP)

In 1961, Marine Biological Laboratory (MBL) Distinguished Scientist Osamu Shimomura discovered that the jellyfish has a protein which, when exposed to blue light, fluoresces bright green. It was “a beautiful protein” but it had no practical use, remarked Dr. Shimomura in 2008. The situation changed dramatically in the early 1990s, when Martin Chalfie of Columbia University realized that Dr. Shimomura’s jellyfish protein, now called green fluorescent protein (GFP), could be a powerful tool in microscopy to illuminate the inner workings of cells. Dr. Chalfie devised a way to have his experimental animal, the
worm *C. elegans*, express GFP inside its cells, which then glowed when hit with blue light. This was the beginning of a revolution in microscopy that has allowed scientists to see parts and processes in living cells that were never visible before, such as protein folding, protein transport, and RNA dynamics. Drs. Shimomura, Chalfie and Roger Tsien were awarded the 2008 Nobel Prize in Chemistry for their discovery and development of the green fluorescent protein. Dr. Tsien, of University of California-San Diego, developed a way to make GFP glow brighter, and he also extended the palette of the technology to a rainbow of colors.

Prior to 1982, when Dr. Shimomura joined the MBL, his GFP research was conducted at Princeton University and at the University of Washington’s Friday Harbor Laboratories. This research was supported by the National Science Foundation and the National Institutes of Health as a part of Shimomura’s study of *Aequorea* bioluminescence.
Novel Therapies for Atrial Fibrillation

The Masonic Medical Research Laboratory (MMRL), with the support of the National Heart, Lung, and Blood Institute and Gilead Sciences, has contributed to the development of novel therapies for pharmacologic management of atrial fibrillation (AF), one of the greatest unmet medical needs facing our society today. Drugs available for the treatment of AF have a predisposition to promote ventricular arrhythmias while exerting their action to suppress AF. This has prompted the search for atrial-selective drugs to treat AF.

In 2007, Dr. Antzelevitch and his team at the MMRL discovered that sodium channels in the atria differ from those in the ventricles of the heart. In seeking out drugs that can take advantage of this electrophysiologic distinction, they discovered that ranolazine was such an agent. Ranolazine is an anti-ischemic agent approved by the Food and Drug Administration in 2006 for the treatment of chronic angina. In experimental models of AF tested at MMRL, ranolazine proved to be very effective in terminating and preventing the induction of AF at relatively high concentrations. These actions of the drug are consistent with its high efficacy in terminating AF when used as a “pill-in-the-pocket” approach in investigational studies in patients with recent onset AF. More recently, MMRL scientists have discovered that ranolazine and dronedarone, a safer analog of amiodarone, when combined show potent synergism in producing atrial-selective depression of sodium channel activity and suppression of AF.
Salt Reduction
Excess sodium consumption is strongly linked to increased incidence of hypertension, cardiovascular disease and stroke. As a consequence, virtually all authoritative health organizations tell us that salt is being consumed by the U.S. population in amounts that are detrimental to our health and urge the population to lower their sodium intake. To accomplish this, we need to identify acceptable ways for individuals to reduce their consumption of sodium.

In 2010, the Institute of Medicine recommended mandating that food manufacturers and restaurants reduce the amount of salt in foods so that consumers would adjust and come to prefer the lower levels. This recommendation was strongly based on studies first carried out at the Monell Center in the 1980s. These influential studies demonstrated experimentally that lowering the salt levels in a person’s diet for several months was associated with a parallel decline in the preferred level of salt in food. Funded by the National Institutes of Health, these studies are just one part of a long-standing and comprehensive program at Monell to understand the basis for salt detection and acceptance. Ongoing research will identify additional strategies to successfully reduce sodium consumption in the U.S. population and as such, prevent as many as 100,000 deaths annually.

First Acceptance of Fruits and Vegetables
In the Unites States, obesity is the most prevalent nutritional disease of childhood. Nutritional interventions, viewed as critical, have brought global initiatives promoting a healthier diet and increased fruit and vegetable consumption. However, children can be emotional eaters who eat what they like and reject what they don’t. Research at Monell has shown that the basic taste biology of the child favors sweet, salty, and high-fat foods and spurns bitter ones. Indeed, one in four toddlers does not consume a single vegetable in a given day.

To help direct these responses towards healthy foods, Monell scientists have identified factors that contribute to the first acceptance of fruits and vegetables. Research funded by the National Institutes of Health has shown that flavor preferences begin to develop in the womb, with the unborn infant sampling tastes and odors of the mother’s diet through amniotic fluid. After birth, the introduction to flavor continues through transmission in breast milk. At weaning, this early exposure influences how an infant responds to a flavor when it first is presented as a solid food. For example, infants enjoy carrot-flavored cereal more if their mothers have consumed carrot juice during the last trimester of pregnancy or
during the first months of breastfeeding. Ongoing Monell studies that explore the flavor world of the child will continue to help identify strategies to maximize intake of healthy foods.

**Smell Loss in First Responders**

One of the most important functions of the sense of smell is to warn of danger, including smoke, spoiled food, and cooking gas. These signals are detected by receptors located deep inside the nasal cavity that are sensitive to odors and irritants such as smoke and other powerful irritating chemicals. To protect these important olfactory and irritant receptors from damage, first responders typically are required to wear respirators. However, individuals sometimes choose not to do so or simply do not have the opportunity to don their gear.

A recent Monell study found that two years after exposure to the dust cloud at the World Trade Center site, responders had decreased sensitivity, perhaps permanent, to odors and irritants. Significantly, almost none of the individuals tested recognized their ability to detect odors and irritants was compromised. The loss of sensory function presents a critical safety concern, especially for individuals who are likely to encounter dangerous environmental chemicals in the air. This research, funded by the National Institutes of Health and conducted as a collaborative effort between Monell and the Mount Sinai School of Medicine, provides the basis for occupational health organizations to recommend evaluation of the ability to smell and detect irritants on a regular basis in these individuals, as well as others who are exposed to potent environmental pollutants.
Xigris: Treating Sepsis
Dr. Jeanne Morgan works in a hospital, is married to a physician and, as a clinical psychologist, understands how the human mind and body work. But the tired feeling that kept her at home one weekend in October 2003 was much more sinister than a simple cold or flu. Within hours, Morgan’s lungs, heart, liver and kidneys began to shut down. Unbeknownst to her, she had severe sepsis, a life-threatening blood infection caused by bacteria, viruses or other infectious microorganisms.

Fortunately, her life was saved when doctors gave her Xigris, a drug that has its roots at the Oklahoma Medical Research Foundation (OMRF) in the laboratories of Drs. Charles Esmon and Fletcher Taylor. Developed with funding from the National Institutes of Health, Xigris was the only treatment available for severe sepsis. Although it was new at the time, doctors knew it was Morgan’s only hope. After one dose, her vital signs started going back up. Xigris worked. “In my profession, I know a lot about research,” says Morgan. “And I also know that many times, scientists get little or no feedback. Or they remain low-profile, and the drug company gets all the attention. But Xigris saved my life. And I’m here because of what Drs. Esmon and Taylor do and have done. If we didn’t have breakthroughs like those being developed at OMRF, we wouldn’t have miracle drugs like Xigris. And without it, I wouldn’t be here. You’re saving lives.”

Soliris: Tackling a Rare Blood Disease
Every April 20, Greg Watkins celebrates his birthday. It’s not the day he was born, but it’s the day he got his life back. Greg considered himself a “running addict” and always kept himself in top shape. But 12 years ago, he came face to face with a disease that stopped him in his tracks. His symptoms began when he noticed blood in his urine, and before long chest pains made him think he was headed for a heart attack. Instead, his doctor told him he was having esophageal spasms due to paroxysmal nocturnal hemoglobinuria, or PNH, a rare blood disease with no cure.

Greg’s life changed completely. He was unable to work. The steroids he took caused his weight to balloon to 250 pounds. But on April 20, 2007, his doctors began treating his PNH with Soliris—a drug born in the labs of the Oklahoma Medical Research Foundation (OMRF), and soon, he was on the road to recovery. Collaboration between scientists at OMRF and Yale University funded by the National Institutes of Health led to the drug’s discovery. Watkins’s energy has returned and he no longer needs steroids. His blood pressure is back to normal, as is his weight. He has returned to working out regularly, and his professional life—once decimated by PNH—is back on track. In short, says Watkins, “I feel like I have a whole new life.”
Feeding Strategies in Premature Infants

At Nationwide Children’s Hospital, Dr. Sudarshan Jadcherla has pioneered testing protocols for infants with feeding problems who are at risk for needing long-term feeding tubes. An infant-sized manometry catheter and manometry system is used to test peristaltic reflexes, capturing the rhythm of muscular contractions throughout the digestive tract. These signals are translated into graphic form that shows how these rhythms change as the baby is fed. After the studies are completed, a multidisciplinary team of specialists led by Dr. Jadcherla develop an individualized feeding strategy based on the infant’s neurophysiology of swallowing, gut motility, feeding behaviors and neurodevelopmental status.

A 2009 study showed that these novel diagnostic methods and multidisciplinary feeding strategies were able to transform 75 percent of babies with swallowing difficulties into oral feeders, 50 percent of whom didn’t need any feeding tubes beyond discharge from the hospital. As a result of this study alone, an estimated $1.8 million in healthcare costs related to g-tubes was avoided. Dr. Jadcherla’s research is supported in part by the National Institutes of Health.
**Gleevec: Breakthrough Cancer Drug**

While studying a cancer-causing virus, Drs. Tony Hunter and Bartholomew Sefton discovered a new group of enzymes called tyrosine kinases that are involved in the regulation of various vital aspects of cellular function such as cell growth and development. More than two decades later, Dr. Hunter’s original discovery has led to the development of a new generation of cancer drugs that specifically block the action of wayward tyrosine kinases. These include Gleevec™, used for the treatment of leukemia and gastrointestinal cancer, as well as Iressa™ and Tarceva™ used for the treatment of lung cancer. These drugs revolutionized cancer treatment—rather than carpet bombing the body with indiscriminate chemotherapeutic drugs, Gleevec and related drugs target cancer-specific molecular abnormalities. Since Gleevec was approved in 2001, eight other drugs based on this discovery have been approved for treatment of different types of cancer and more than 40 others are currently in clinical trials. The research was funded in part by the National Institutes of Health.

**Nuclear Receptors and the Treatment of Leukemia**

Dr. Ron Evans’ work discovered how a diverse group of hormones and vitamins – steroid hormones, thyroid hormones, and fat-soluble molecules such as vitamins A and D – control the body’s metabolism, development and reproduction. He has turned up close to 50 different nuclear receptors, two of which – the receptor for vitamin A and its side-kick, the so-called retinoid X receptor – are defective in certain cancers. Today, the resulting leukemia, Karposi sarcoma and a rare type of lymphoma, are routinely treated with vitamin A derivatives. Developed by Ligand Pharmaceuticals Inc, these drugs are sold as Pancretin, Tretinoid, and Targretin. Dr. Evans' technology has been used to discover more than a half a dozen drugs for cancer, diabetes and heart disease with many more on the way. His worked also opened up the possibility of "exercise in a pill." The research was funded in part by the National Institutes of Health and the Howard Hughes Medical Institute.
ENB-0040: Treatment for Hypophosphatasia
Three year-old Corinna was born with hypophosphatasia (HPP), a rare inherited disease that affects bone development, leaving most young patients fragile and unable to walk. Corinna participated in a clinical trial to test ENB-0040, an enzyme replacement therapy developed by Sanford-Burnham Medical Research Institute’s Dr. José Luis Millán, Enobia Pharma and Dr. Michael P. Whyte of Shriner’s Hospital for Children in St. Louis. ENB-0040 is currently the only treatment option for HPP in development. ENB-0040 was awarded orphan designation in the United States in 2008, fast-track designation in 2009 and is currently in Phase II clinical development.

After eight weeks on ENB-0040, Corinna is walking and jumping. Corinna’s mother sent Dr. Millán a video of Corinna that would seem unremarkable if you didn’t know Corinna’s story. Sanford Children’s Health Research Center at Sanford-Burnham includes researchers working on a number of rare diseases. The independent not-for-profit medical research institute combines world-class scientific talent with state-of-the art technology to conquer childhood diseases. Dr. Millán’s research is funded by grants from the National Institutes of Health.
Cladribine: Breakthrough Leukemia Drug
Research by investigators at The Scripps Research Institute in the 1980s and 1990s led to a drug that today cures or produces years of freedom from a rare, potentially fatal form of chronic leukemia. Each year, some 600 people in the United States are diagnosed with hairy cell leukemia, a slow-growing cancer that disrupts normal blood cell production. (The abnormally shaped white blood cells of this disorder are characterized by tiny, hair-like projections.) The drug, 2-chlorodeoxyadenosine or 2CdA, was identified and developed by Dennis Carson, a Scripps Research scientist working in collaboration with Ernest Beutler, then chair of the institute’s Department of Molecular and Experimental Medicine.

An intravenous medication delivered in a seven-day treatment course with remarkably few side effects, 2CdA interferes with a cancer cell’s ability to grow and divide normally, leading to the cell’s death. Marketed under the name cladribine (Leustatin™) by Ortho Biotech Inc., an affiliate of Johnson & Johnson, 2CdA was licensed as an orphan drug in 1994 and is undergoing study for treatment of other blood-based cancers. Carson’s initial research was funded in part by the National Institutes of Health and donations from the William Black family and Stein Endowment Fund.

Combinatorial Antibody Library Technology for Rheumatoid Arthritis, Lupus and More
Harnessing the potential power of human antibodies – which make up part of the body’s natural defense mechanism – to fight the debilitating effects of diseases like rheumatoid arthritis, was long hampered by technological obstacles. Research developed by Dr. Richard A. Lerner’s lab at The Scripps Research Institute provided critical elements in devising a more efficient and accurate method to identify human antibodies for use in therapeutic treatments. Dr. Lerner’s work with combinatorial antibody library technology helped lead to the development of the drug adalimumab (marketed by Abbott Laboratories as Humira®), now widely used to treat millions of adults and children suffering from rheumatoid, juvenile idiopathic, or psoriatic arthritis, Crohn’s disease, ankylosing spondylitis, and plaque psoriasis. The technology also laid the foundation for the drug Benlysta® (belimumab), developed by GlaxoSmithKline and Human Genome Sciences to treat systemic lupus erythematosus. When Benlysta® was approved by the Food and Drug Administration in March 2011, it was the first new drug available to treat lupus in more than 50 years. More potential therapies from combinatorial antibody library technology are currently under investigation.
Mechanical Ventilation for Respiratory Distress
Scientists at the Texas Biomedical Research Institute (Texas Biomed) made major contributions to improving care by establishing the baboon as a model for lung disease in premature infants and refining high frequency oscillatory ventilation (HFOV), which has become standard therapy in treating the disease. Prior to research conducted at Texas Biomedical in 1997, infant respiratory distress syndrome (RSD) was the second-ranking cause of death in infants. Due to progress in prenatal care, by 2007 it had dropped to eighth place, according to the Centers for Disease Control and Prevention. Neonates today receive continuous positive airway pressure, or CPAP therapy, a ventilatory method that avoids the lung damage that even HFOV can cause. Texas Biomed scientists also conducted extensive research with baboons that helped bring about refinements to CPAP therapy. This research was funded in part by the National Institutes of Health.

Hepatitis B Vaccine
Texas Biomed played a key role in establishing the safety and efficacy of a hepatitis B vaccine through tests in chimpanzees. Testing of the first hepatitis B vaccine was conducted during the 1980s at Texas Biomed. An improved, safer vaccine has since been developed, its efficacy also established in research with chimpanzees. The vaccine is now administered in 116 countries, annually saving millions from a life-threatening liver infection that often leads to chronic liver disease and increases the risk of death from cirrhosis of the liver and liver cancer.
Genomic-Based Clinical Trials for Pediatric Neuroblastoma
On May 31, 2011, the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC), a first-of-its-kind genomic-based clinical trial to treat and study pediatric relapsed and refractory neuroblastoma, was launched. The 11-member NMTRC, housed at Van Andel Research Institute, is a nationwide network of pediatric cancer clinical trial sites including the National Cancer Institute (NCI), universities and children’s hospitals, that have begun patient enrollment in the Food and Drug Administration- approved trial.

“This trial offers new hope to those children facing the worst of all pediatric cancers,” said NMTRC Chair Giselle Sholler, M.D. “We are confident the genomic-based personalized medicine approach, often defined as ‘the right treatment for the right patient at the right time,’ will provide the necessary data to validate this approach as the new standard of care in the 21st century.” Genomic-guided therapy leverages next generation sequencing and gene expression technologies to identify subtle differences in an individual’s genetic makeup that provides a clearer picture of the disease state. This analysis involves important collaborative efforts including Grand Rapids-based Intervention Insights and the Pediatric Oncology Branch at NCI.
Clinical Trials for Complicated Grief
Scientists at the Veterans Medical Research Foundation are involved in the first randomized, controlled clinical trial of medications and/or therapy for the treatment of complicated grief. Complicated grief is a debilitating condition that is estimated to affect millions of people in the United States alone, but may be unrecognized and untreated. This study is led locally by bereavement expert Sidney Zisook, M.D., in collaboration with researchers from Columbia University, Massachusetts General Hospital, and the University of Pittsburgh. The trial is sponsored by the National Institute of Mental Health and the American Foundation for Suicide Prevention and conducted at the VA San Diego Health Care System. The results of this study will help inform physicians and therapists alike on the most effective treatment for complicated grief – a condition that affects a significant proportion of the general population, as well as veterans and patients already being seen for other mental health conditions.

Administered through the Veterans Medical Research Foundation in San Diego, this study is notable for its inclusion of veterans. In addition, the alarmingly high suicide rates among active duty military personnel and young veterans create an even larger circle of surviving friends and family who are at high risk for intense and prolonged grief. The affiliation with Veterans Medical Research Foundation facilitates reaching out to these survivors and developing effective strategies to assist their healing processes.

Sequenced Treatment Alternatives to Relieve Depression (STAR*D)
Treatment-resistant depression is common and often associated with enormous individual, familial and societal suffering, substantial morbidity, and increased mortality. Yet until the STAR*D study, there were no large, systematic research trials to inform clinicians of evidence-based treatments for this serious condition.

STAR*D has introduced innovative breakthroughs in study design and outcome measures that already have impacted psychiatric research and drug development. STAR*D helped identify various features of depression associated with treatment response and relapse and that require “non-standard” treatments. The treatment helped define what to expect in real world conditions with respect to remission, time to remission, relapse, and proclivity for suicide and function– all of which have helped inform the field and influence treatment paradigms. STAR*D also helped to define relative advantages and disadvantages of “next-step” treatments for patients who fail to achieve an adequate initial or subsequent response and dispel myths regarding the relationships between pharmacologic properties of medications and differential treatment effectiveness. STAR*D reinforced the importance of perseverance, of achieving remission to improve long term outcomes and the need for intensive long term follow up and attention to enhancing adherence.

This study of over 4,100 outpatients with Major Depression was conducted at 18 primary and 23 psychiatric care settings across the United States. Key regional centers included University of Texas-Southwestern, University of Pittsburgh, Harvard University, UCLA and Columbia University. The research was supported in part by the National Institute of Mental Health.
RotaTeq®: Rotavirus Vaccine
Developed in the 1980s in collaboration with researchers at the Children’s Hospital of Philadelphia, Merck, and The Wistar Institute, the rotavirus vaccine saves American children 250,000 emergency room visits and 70,000 hospitalizations annually. This translates to an estimated $61 million annual savings for our healthcare system. In the developing world, where medical facilities are limited, rotavirus infection – which causes severe dehydration illness – kills 600,000 infants and children each year. Added to the recommended vaccine schedule for all U.S. babies in 2006, the vaccine has been launched in 47 other countries where it has the potential to save millions of young lives annually. RotaTeq® was developed in part with funding from the National Institutes of Health.

Antibody 19-9: Monitoring Pancreatic Cancer
The laboratories of The Wistar Institute have a rich history of discovery of monoclonal antibodies to diagnose and treat various cancers, a set of technologies which continue to have major clinical impact today. Antibody 19-9 is the basis of a simple blood test that enables physicians to monitor pancreatic cancer patients and the effectiveness of treatment; it was the first blood test cleared by the Food and Drug Administration for use in treating the 38,000 Americans diagnosed with the disease each year. Another antibody, discovered at Wistar in the 1980s, mAb-425 today shows promise for treatment of brain cancer, killing cancer cells that remain behind following surgery. Wistar patents for the use of monoclonal antibodies to diagnose and treat cancer was the founding technology for the biotech company Centocor. This research was funded in part by the National Institutes of Health.

Interleukin-12: Treatments for Inflammatory Diseases
Twenty years ago, Wistar scientists co-discovered interleukin-12 (IL-12), a protein that regulates the body’s immune responses. Today, treatments to reduce IL-12 activity show great promise for the treatment of inflammatory diseases, such as psoriasis and Crohn’s disease. Centocor Research & Development, Inc. has developed an antibody that neutralizes the proteins IL-12 and IL-23; this antibody was recently approved as a new treatment for moderate to severe plaque psoriasis, and is marketed under the product name Stelara®. This research was funded in part by the National Institutes of Health.
eIF4E ASO: Cancer Therapeutic
Elevation of eukaryotic translation initiation factor 4E (eIF4E) in experimental cancers selectively enhances translation of growth factors important in cancer growth. In 1998, with the support of Eli Lilly and Company, Dr. Harry Carter, Director of Pathology at Wood Hudson Cancer Research Laboratory, in a study of tumor specimens archived in the Wood Hudson Biospecimen Repository, discovered that expression of eIF4E increased dramatically with increasing grade of human prostate cancers. Further research at Wood Hudson revealed that eIF4E not only increased in advanced prostate cancer but was also associated with poor patient survival. Dr. Jeremy Graff, in collaboration with scientists from Eli Lilly and ISIS Pharmaceuticals, developed an antisense oligonucleotide (ASO) to specifically target the eIF4E mRNA for destruction. Evaluation of preclinical models at Wood Hudson Cancer Research Laboratory and Lilly Research Laboratories revealed that the eIF4E ASO reduced tumor levels of eIF4E without causing toxicity to the tumor-bearing animal. These findings demonstrated the plausibility of therapeutically targeting eIF4E and resulted in the advancement of the first eIF4E-specific therapy to clinical trials. The eIF4E ASO is currently in Phase II clinical trials for cancer therapy.

Int7G24A: Potential Diagnostic Tool to Determine Risk of Ovarian Cancer
Too frequently, ovarian cancer patients are diagnosed at advanced stages of disease. Late-stage diagnosis is a principal factor contributing to the high death rate for ovarian cancer patients. Markers that could reliably identify, before disease onset or at early disease stages, women at risk for the most lethal forms of ovarian cancer could dramatically improve disease management and reduce ovarian cancer death rates. In 2001, Dr. Taiping Chen, then a Senior Staff Scientist at Wood Hudson Cancer Research Laboratory, reported his discovery that germline variations in the gene for transforming growth factor beta receptor 1 were frequent in human ovarian cancer patients. One of these germline variants, Int7G24A, was subsequently found to be highly associated with patients who developed kidney, bladder, and breast cancer. Dr. Jim Schaeper went on to develop an improved method to detect this genetic variant in archived clinical specimens from the Wood Hudson Biospecimen Repository.

Most recently, Wood Hudson scientists reported at the American Association for Cancer Research 2011 Annual Meeting and submitted for publication in Cancer Research, that Int7G24A is specifically associated with patients who develop the most frequent and most lethal forms of ovarian cancer. Moreover, those ovarian cancer patients who are carriers of this genetic variation do not survive their disease. The implication is that a one-time, non-invasive, test for Int7G24A could indicate women at risk for this unusually lethal form of ovarian cancer and lead to prevention of death through early detection or before the disease
Identification of Carcinogenic Chemicals in Drinking Water
Dr. Tony DeAngelo, along with scientists at the Wood Hudson Cancer Research Laboratory and the US Environmental Protection Agency (EPA), has researched the carcinogenic risk of chemicals present in finished drinking water. Funded in accordance to the Safe Drinking Water Act, Wood Hudson scientists have obtained data on the carcinogenic potential of phthalate esters and by-products of water disinfection such as dichloroacetic acid and chloroform. This EPA-funded research at Wood Hudson Cancer Research Laboratory has helped the Agency to extrapolate carcinogenic risk from high dose, two-year exposures in animal bioassays to low dose chronic human exposures to these ubiquitous environmental chemicals. The research has defined pathologic pathways in tumor development and revealed mechanisms by which non-genotoxic carcinogens, which large human populations are chronically exposed to, induce cancer in laboratory animals, and helped to determine the relevancy of these carcinogenic mechanisms between animals and humans. Thus, Wood Hudson Cancer Research Laboratory has assisted EPA in regulatory decision-making. Since 90 percent of human cancers result from interaction between an individual’s environmental exposures and the individual’s genetic make-up, this research is vital to future cancer prevention as well as to the economic health and well-being of our nation, as cancer costs the U.S. economy approximately $260 billion annually.