Top Photo: David Wang, MD, PhD, studies biochemical and genetic mechanisms of hepatic and biliary lipid metabolism as part of his research efforts in the Division of Gastroenterology and Hepatology.

Bottom Photo: In the Division of Geriatric Medicine, Susan Farr, PhD, researches learning and memory changes associated with aging and conditions such as Alzheimer’s disease.
Systemic lupus erythematosus (SLE, or more simply Lupus) is a disabling and often deadly autoimmune disease that disproportionately affects women and African Americans. Researchers in the Division of Rheumatology have helped to develop effective treatments for this condition and continue to obtain insights into how lupus is caused and how it damages target organs.

The Saint Louis University Liver Center has made progress on several fronts. Most notably in research on hepatitis C, with studies that have sought to understand the fundamentals mechanisms of how the hepatitis C virus attacks the liver and causes cirrhosis and liver cancer. Members of the Saint Louis University Liver Center have also been at the forefront of efforts to develop effective treatments against chronic hepatitis C, a battle that now seems largely won and may lead to the saving of hundreds of thousands of lives around the world. The next challenge the Liver Center will face is fatty liver disease, an epidemic sweeping our nation. Many patients with these two chronic diseases will also develop progressive liver fibrosis which may result in cirrhosis and be complicated by primary liver cancer.

The ECG Core Lab has provided an essential core function to dozens of major clinical trials in cardiac disease, aimed at preventing and treating coronary artery disease. Almost all of these clinical trials use changes in electrocardiography as a major outcome variable. The Core Lab provides an expert and standardized interpretation of these electrocardiograms, placing the Lab and its researchers at the center of many major developments in cardiology which have resulted in the dramatic reduction in mortality rates from cardiac disease which we have seen in developed western countries.

Research related to kidney disease is varied and achievements have been made on several fronts. Thus, some researchers in the Division of Nephrology have become experts in understanding the mechanism by which secondary hyperparathyroidism occurs in patients with chronic renal failure while others have studied the role of growth genes such as the SALL family in renal growth and development. Another area of achievement has included the discovery of the CLIC family of proteins and the demonstration that they can function as ion channels. Finally researchers in the Division of Nephrology have become national leaders in finding ways to increase the number of kidney transplants done each year, including the safe use of kidneys donated by liver donors.

Faculty in the Division of Geriatric Medicine have been national leaders in teaching people about aging successfully. They have studied and developed approaches to managing delirium, frailty and even Alzheimer’s Disease. Researchers in Geriatric Medicine have pioneered the use of a unique mouse model, the SAMP8, to study mechanisms of Alzheimer’s and, more recently, to develop a novel therapeutic approach to this common disease of aging through the use of antisense RNA that blocks the conversion of amyloid precursor protein to beta amyloid, thus developing a therapeutic approach to the basic problem in Alzheimer’s rather than simply trying to manage its complications.

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Over the last 5 years, 14 researchers in the Department of Internal Medicine have received funding from the National Institutes of Health, totaling $41,942,705. This funding has led to significant new discoveries and inventions that have already had a major impact on the health of Americans and I fully expect that we will go on to make new impactful discoveries to keep up this long tradition of accomplishment by faculty in the Department of Internal Medicine at Saint Louis University.

I AM PROUD to have served as Chairman of the Department of Internal Medicine since 2006 — nearly a decade — and I have been a researcher and faculty member in this department for 20 years. I have been privileged to see extraordinary achievements by faculty in this department, particularly impressive during the recent lean years. We have chosen to highlight eight areas of accomplishment — this does not mean these are the only productive areas but they are some of the most important and meaningful. The Vaccine Center has long been the best funded center within the Department of Internal Medicine. It has played a key role in the development of vaccines that have saved lives and protected the public from important diseases, such as influenza and herpes virus infection. It has played a role in our national response to terrorism with its rapid testing of potential vaccines against smallpox and it looks to the future hoping to develop strategies to prevent infection with or reactivation of tuberculosis, a major killer worldwide.

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THE CENTER FOR VACCINE DEVELOPMENT (CVD) has been a pioneer in the development of vaccines to protect global health for more than 25 years. In September 2013, the Center received the largest research grant in the University’s history when it was among nine Vaccine and Treatment Evaluation Units (VTEUs) selected by the National Institutes of Health to bid on almost $1 billion in projects focused on vaccine development. The scope of research — both in the laboratory and in clinical studies — covers a wide range of diseases, including tuberculosis, hepatitis C, influenza, pneumonia, meningitis, small pox, dengue fever, and others. Over the past 25 years, the center has received more than $150 million in funding from the NIH, foundations, and other organizations. It continues to receive $5-6 million in total extramural funding per year with independent NIH grants and NIH contracts as equal sharings, comprising ~90% of this total. Among its current research activities:

**INFLUENZA** — This year, the center is beginning the first human clinical trials of a universal vaccine targeting new influenza A viruses that have pandemic potential. Researchers are focused on key pieces of the virus that do not undergo rapid mutational change located in the highly conserved stalk domain of the hemagglutinin (HA) protein. Current vaccines targeting the head domain of the HA protein must be re-configured annually because that region of the virus continuously and rapidly mutates. Long-term collaborators of Robert Belshe, MD, founder of the Center for Vaccine Development, created two chimeric HA vaccines that have novel heads but a common stalk. In a prime/boost vaccination scheme, these chimeric HA vaccines induced broadly protective antibodies in animal models. Key research conducted in collaboration with Dr. Belshe, provided proof-of-concept that broadly protective antibodies directed against the HA stalk can be induced in humans. The SLU VTEU was selected as the site to conduct the first-in-human clinical trial of this chimeric HA vaccine strategy. In yet another strategy, Daniel Hoft, MD, PhD, current Director of the Division of Infectious Diseases, Allergy & Immunology and PI of the new VTEU contract, and colleagues researchers have found highly conserved epitopes within internal viral proteins that can trigger immune responses in T-cells and block influenza viral replication in human microphages. These epitopes are present in virtually all influenza A strains and therefore could induce immunity protective against...
any future influenza pandemic. The research is ongoing and the team is optimistic that effective vaccines for a broad spectrum of influenza A viruses could be developed within the next 5–10 years. In the meantime, over the past 2 years, researchers have built upon Dr. Belshe’s key role in developing work in developing the intranasal live attenuated influenza vaccine. They currently are advocating for the use of quadrivalent vaccines that target two influenza A and two influenza B strains, resulting in the virtual elimination of influenza B. Geoffrey Gorse, MD, from the SLU CVD team also showed that the use of higher doses of quadrivalent vaccines in the elderly (four times higher) was safe and resulted in significantly better protection rates. Sharon Frey, MD, from the SLU CVD team, played a key role in testing vaccines that were used to protect the US public from the 2009 H1N1 influenza pandemic. Additional studies by the SLU CVD team have tested new vaccines that could protect against future pandemics with H5 and H7 avian influenza strains.

SMALLPOX AND NATIONAL PREPAREDNESS — Just over a year ago, the CDC unexpectedly found several small vials containing the deadly smallpox virus. The discovery renewed concerns that a disease once eradicated through effective vaccination could arise again, either as a pandemic or an agent of bioterrorism. At SLU, research into smallpox has been ongoing for more than 15 years. Sharon Frey, MD, discovered that the supply of smallpox vaccine held in the National Strategic stockpile could be used at 1/10th of its standard dose and remain effective, thereby dramatically increasing the amount of vaccine doses available in case of an outbreak. Further research has led to the development of second and third generation smallpox vaccines that are safer and more reliable. Two have been added to the strategic stockpile. Ongoing studies are honing in on the most effective route of vaccine needed as well as optimal vaccination schedules for these newer vaccines.

TUBERCULOSIS — With one-third of the world’s population infected with TB, Daniel Hoft, Director of the Division of Infectious Diseases, Allergy & Immunology has conducted 15 vaccine trials focused on the development of a new and more effective vaccine against Mycobacterium tuberculosis (Mtb). These trials have explored the strengths and weaknesses of the current TB vaccines and compared new recombinant vaccines, prime/boost TB vaccine combinations and explored TB vaccines designed to induce mucosal protection against initial TB infection. Dr. Hoft has found that an oral version of the currently available BCG vaccine induced mucosal immune responses not induced by the standard intradermal administration of BCG, and uniquely prompted a five-fold increase in protective TB-specific T cells in the lungs. Studies are ongoing to evaluate if a two-pronged approach using both oral and intradermal BCG builds upon that result and if an intranasal BCG vaccine could be more effective. Another approach, first reported by Dr. Hoft and his colleagues, targets a subset of T-cells, expressing T cell receptors (TCR) composed of variable (V) gamma 9 and V delta 2 proteins. His group further demonstrated that these cells use a novel mechanism to inhibit intracellular Mtb growth. Current animal studies are focused on an antigen designed to induce Vgamma9/Vdelta2 T-cell response, leading researchers into new directions in efforts to produce a better TB vaccine. This gamma/ delta T cell work has been funded by the VTEU and NIH R01 and other awards for the last 20 years, and in April of 2015, the Bill and Melinda Gates Foundation approved a new $2.89 million award to Dr. Hoft’s laboratory to help complete final pre-clinical testing of this Vgamma9/Vdelta2 T cell TB vaccine strategy.

DENGUE VIRUS — This virus, common in tropical and subtropical areas, has been increasingly diagnosed in the United States over the past six years. In the CVD, researchers are homing in on the correlates of protective immunity to dengue disease. The center was part of the first human clinical trials of promising recombinant and live attenuated dengue vaccines. Using samples from one of the trials (DENVax), Sarah George, MD, and her colleagues have identified a unique gene signature that is highly predictive of a multivalent immune response. This, along with the identification of specific T helper cells that arise after vaccination could better define and predict dengue immune responses and lead to new targets that trigger immune protection.

HERPES SIMPLEX AND SEXUALLY TRANSMITTED DISEASES — NIH-funded research at SLU has resulted in a paradigm-changing observation as scientists work to develop an effective vaccine to combat herpes simplex viruses. Over the past 6 years, clinical trials have focused on the development of a vaccine that would prevent genital herpes from being transmitted to an infant at delivery. Recent research has identified the specific types of antibody responses that are much more effective for virus suppression. This finding is re-directing vaccine development into novel areas.
Hepatitis and Other Liver Diseases

THE SAINT LOUIS UNIVERSITY LIVER CENTER is the largest treatment and research center for liver disease in Missouri and one of the largest in the United States. It is housed in the Department of Internal Medicine and staffed by its physicians, all of whom are leading clinical trials. Physicians in the department’s Gastroenterology/Hepatology Clinical Studies Unit see more than 200 patients a month involved in industry sponsored research protocols for such diseases as hepatitis B and C, primary biliary cirrhosis, liver transplantation and fatty liver disease. The NIH Clinical Studies Unit supports adult and pediatric research that is funded by federal or foundation supporting research in the areas of hepatitis, pancreatitis and liver cancer. We highlight some of the most recent breakthroughs.

Viral hepatitis is the leading cause of liver cancer and the most common reason for liver transplantation. At Saint Louis University, several groundbreaking research efforts and clinical trials have resulted in new, highly effective treatments that point towards cures:

HEPATITIS C

The Department of Internal Medicine and the Saint Louis University Liver Center has led the nation in enrollment for several pivotal, multi-center clinical trials that have resulted in breakthrough treatment regimens for hepatitis C. Between 2013 and 2014, the Food and Drug Administration (FDA) approved three treatment protocols with 90 percent or better cure rates:

- **Olysio and Sovaldi** an oral antiviral combination 90% + cure rate
- **Harvoni** a once-daily single tablet 95% + cure rate
- **VieKira Pak** a combination of three oral antivirals 95% + cure rate

Research nurses Debra King, RN, and Jacqueline Cerkoski, RN, work in the SLU Liver Center.

GI clinical research members Rebecca Miller, RN, and research assistant Brooke Higginbotham
SLU Liver Center researchers wrote or co-wrote major published papers describing results from the clinical trials. In addition, center physicians have served as consultants to pharmaceutical companies developing the new drugs. Tests of the new medications demonstrate substantial improvement over previous regimens that included the protease inhibitors, telaprevir and boceprevir, along with ribavirin and peginterferon. These regimens had side effects so intolerable that some patients discontinued treatment. The newer medications have virtually no side effects and also can be given to patients who cannot tolerate the interferon-based treatment regimens, who are awaiting liver transplantation or who are co-infected with HIV.

Because there are still some patients who have less than optimal responses to the new regimens, including patients with advanced liver disease and those infected with the genotype 3 strain of hepatitis C, SLU researchers continue to work to optimize treatment for these individuals.

Department researchers also played a key role in the NIH-funded Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) multi-center trial. Researchers enrolled more than 1,000 patients with CHC and advanced fibrosis or cirrhosis to assess the long-term benefits of IFN-α therapy in patients who were non-responders or only partial responders to optimal pegylated IFN/RBV–based therapy. Long-term, low-dose IFN therapy was found to be ineffective in improving important clinical outcomes of CHC but the HALT-C Trial fostered an enormous amount of clinically useful information and new hypotheses regarding the natural history and complications of CHC.

HEPATITIS B

The Department of Internal Medicine is home to one of only 13 NIH-funded centers that form the Hepatitis B Research Network. The network’s mission is to study the hepatitis B virus (HBV) as it occurs in the United States. HBV is much more common in Eastern Asia and Sub-Saharan Africa than it is in this country therefore the burden of the virus is on immigrant populations.

In one of two studies the network is undertaking, the Department of Internal Medicine has been recruiting patients for a prospective study of patients with HBV to identify factors that may have caused the virus to activate or worsen. The department has recruited more than 100 patients for the study, including many from the large and vibrant Vietnamese community in St. Louis. Working with the Asian Pacific American Medical Student Association, the department has screened more than 1,500 Vietnamese Americans living in St. Louis for HBV.

What researchers have learned thus far is that the HBV genotype is very different in Africans than it is in African-Americans. HBV in Africa is transmitted most commonly from mother to child, but in the United States, HBV is spread through sexual contact and intravenous drug use. Scientists are using this epidemiological knowledge to track how the virus migrated throughout the globe.

In another study under the Hepatitis B Research Network umbrella, the department is conducting clinical trials with two FDA-approved drugs prescribed to manage HBV. Department researchers are exploring whether combining two medications — tenofovir and interferon — can cure the virus. The clinical study includes both adult and pediatric patients.

Because collaboration is an integral aspect of the department’s research philosophy, it has used some of its network grant dollars to award sub-contracts to other Saint Louis University researchers working to cure hepatitis B, including a team in the Department of Molecular Microbiology and Immunology that studies how complex patterns in the viral genes effect the way the HBV works and how it causes disease.

Bruce Bacon, MD, Co-Director of the SLU Liver Center, is a past president of the American Association for the Study of Liver Diseases and currently has several ongoing clinical studies at Saint Louis University focused on viral hepatitis.

“To go from discovery of a virus to a cure in 95 percent of patients is an amazing thing to happen during the course of one’s career.”

Bruce R. Bacon, MD
Co-director,
Saint Louis University Liver Center
FATTY LIVER DISEASE

Nonalcoholic steatohepatitis (fatty liver disease) is the third most common reason for liver transplantation and a substantial risk factor for death from end-stage liver disease.

THE DEPARTMENT OF INTERNAL MEDICINE’S NASH CLINICAL RESEARCH NETWORK is one of eight centers across the United States conducting research trials to better understand nonalcoholic steatohepatitis (NASH). Supported by NIH grant dollars, the department’s researchers are leading research initiatives to advance potential therapies for the disease.

SLU has conducted numerous large-scale NASH clinical trials, including the FLINT trial that revealed promising results of an experimental drug called obeticholic acid. The drug helped improve liver function in nearly half of the NASH patients who used it. Previous research with vitamin E and the diabetes medication pioglitazone has generated positive results as well.

SLU also is conducting early-stage research into promising drug candidates using animal models. In one study, SLU researchers fed mice a special high trans-fat, high fructose diet designed by a Department of Internal Medicine scientist to mimic the liver disease that people develop. These mice then were treated with SR9238, a liver-specific LXR inverse agonist that reduces the liver’s ability to produce fat. The drug, developed by a team in the School of Medicine’s Department of Pharmacological and Physiological Science, will now progress to clinical trials to determine its safety and effectiveness in people.
A cure for nonalcoholic steatohepatitis (fatty liver disease)

Research Investment Pays Dividends
Friends of the Saint Louis University Liver Center

In 2005, the Saint Louis University Liver Center established a seed grant program to provide bridge funding to Center scientists while they develop their investigations, gather preliminary data, submit NIH grant applications and publish findings. The program is funded by donations to the center from the Friends of the Saint Louis University Liver Center, which over the past 15 years has donated more than $3 million to the center to further the study of liver disease.

To date, the seed grant program has awarded more than $800,000 to liver investigators. The current return on investment is 16:1, meaning that for every dollar invested in seed grant funding, liver center investigators have succeeded in securing an additional $16 from external funding sources such as the NIH.

“Our hope is that we can develop an effective treatment for fatty liver disease that will prevent ongoing damage to the liver and allow scar tissue to gradually recede, even if someone has already developed cirrhosis.”
Brent Tetri, M.D., Director of the Division of Gastroenterology and Hepatology.

Regulation of gene expression by FXR

Regulation of liver bile acids:
- Bile acid synthesis
- Bile acid uptake by hepatocytes
- Bile acid secretion by hepatocytes

Regulation of fat metabolism:
- FGF15/19 → ↓SREBP1c → ↓Fatty acid synthesis
- SHP1 → ↓SREBP1c → ↓Fatty acid synthesis
- FGF21 → ↑PGC1α → ↑Fatty acid oxidation

Arrows point to liver cancer in a yellowish fatty mouse liver with NASH.

SLU Liver Center investigators: Xiaofeng Fan, MD (gastroenterology & hepatology); John Tavis, PhD; Brent Tetri, MD; Jeffrey Teckman, MD (pediatrics); Ranjit Ray, PhD (infectious diseases); and Ratna Ray, PhD (pathology).

Adrian Di Bisceglie, MD, Chairman, Department of Internal Medicine and Co-Director of SLU Liver Center, with Leisa Duff, Executive Director of Friends of the SLU Liver Center, and Brent Tetri, MD, Director, Division of Gastroenterology & Hepatology.
The principal investigator, Bernard Chaitman, MD, is part of global efforts to develop a universal and standardized definition for heart attacks and to develop standardized definitions for adverse cardiovascular events such as cardiac death and stroke. Standardized definitions reduce variability when multiple researchers report cardiovascular end-points as part of safety and efficacy in large, multinational clinical trials.

“You have to have core labs to standardize the process and tighten the margins of variability for these studies. The quality of work that we do in the Core ECG Lab and the rigor in which it’s performed is respected internationally.”

Bernard Chaitman, MD, FACC
Professor of Internal Medicine
Medical Director & Founder,
SLU Core ECG Lab

By assisting in the physician assessment of cardiovascular event classification and creating universal definitions for data interpretation, the Core ECG Lab is an integral component for a wide range of clinical trial efforts, including pharmaceutical and government-sponsored clinical studies examining the safety of new drugs and vaccines. One major trial underway is the ISCHEMIA Trial, an eight-year NIH study that involves 8,000 patients enrolled at 400 medical centers around the world. The trial aims to identify the best way to manage stable ischemic heart disease, the leading cause of death and disability worldwide. With so many patients and researchers involved, any new treatment recommendations rest upon the standardization and quality of data collected as well as its analysis. The SLU Core ECG Lab serves as one of several international “gatekeepers” to verify patient inclusion in the study.

The Core ECG Lab is one of just a handful of academic ECG core labs in the country. On average, the lab participates in 20 major multicenter clinical trials annually.

**SLU ECG CORE LAB CLINICAL TRIAL PARTICIPATION**

**TIMI 2,3** – Evaluation of tPA effectiveness in patients with ST-elevation myocardial infarction.

**ACIP** – Assessment of the role of suppression of myocardial ischemia and reduction in cardiac events.

**AIM-HIGH** – Evaluation of niacin in raising HDL-C to reduce cardiovascular events in patients with coronary heart disease and optimally treated LDL-C.

**COURAGE** – Comparison of medical therapy with and without percutaneous coronary intervention on patients with stable coronary artery disease.

**BARI** – Comparison of coronary artery bypass grafting versus transluminal coronary balloon angioplasty in patients with multi-vessel coronary artery disease.

**BARI 2D** – Comparison of treatment strategies for patients with Type II diabetes and stable coronary heart disease.

**FOCUS** – Liberal or Restrictive Transfusion in High Risk Patients After Hip Surgery

**IMPACT**

- Establishing international clinical definitions for heart attacks
- Evaluating optimal cardiac treatment strategies worldwide
- Improving the cardiac safety of new drugs or vaccines
A HEALTHIER IMMUNE SYSTEM requires an appropriate balancing act by activating and inhibitory Fc-receptors (FcRs) expressed by myeloid and lymphoid cells. However, over past three decades it is suggested that CD4\(^+\) T lymphocytes do not express these receptors; hence these receptors do not play a role in adaptive immunity.

The researchers were the first to identify the presence of FcRs on activated peripheral naïve CD4\(^+\) T-cells and showed that when bound to immune complexes (ICs) these receptors triggered a distinct signaling, which led to the generation of pathogenic T cells i.e. Th1 and Th17 cells, observed in many autoimmune pathologies. Both these cell types are known to drive SLE pathology. The cytokines IFN-\(\gamma\) and IL17A produced from this new activation pathway are therapeutic targets for several autoimmune diseases.

The expression of FcRs by cells of adaptive immunity in response to innate and humoral stimuli suggests a coordinated role of these immune pathways in autoimmune pathology. Recently the antigens on CD4\(^+\) T-cells have seen successful development of drugs. Findings of these researcher opens and an avenue to further enhance the efficacy of such drugs such as Orencia and Ipilimumab. Blocking FcR mediated signaling on CD4\(^+\) T-cells using bi-specific antibodies could provide a powerful approach for developing new therapies that will have fewer side effects than the handful of current medications available. A broader view is that these discoveries will benefit lupus patients and will potentially lead to treatments for other autoimmune diseases and, perhaps, even cancer. These findings will be very useful in developing new generation of vaccines by modulating helper T-cell responses.

The significance of their work can be found in the numbers. Lupus is the most common systemic illness of young females between the ages of 10 and 40 in the United States. Lumped together, more than 2.35 million Americans are affected by autoimmune diseases. Despite their prevalence, however, there are only a handful of effective treatments for some autoimmune diseases such as lupus.

The expression of FcRs by cells of adaptive immunity in response to innate and humoral stimuli suggests a coordinated role of these immune pathways in autoimmune pathology. Recently the antigens on CD4\(^+\) T-cells

**“Finding Fc receptors on activated CD4\(^+\) T-cells was innovative because the current paradigm denies their presence on CD4\(^+\) T-cells. Establishing a role of these receptors in T-cell physiology will propel development of T-cell based therapies for not only autoimmunity but also for malignancies. Identifying their role in lupus is innovative and it is the result of the fact that we’re stepping into new areas of research that haven’t been ventured into before.”**

Terry L. Moore, MD
Professor of Internal Medicine, Pediatrics, and Molecular Biology and Immunology, Director, Division of Adult and Pediatric Rheumatology

Rheumatologist Terry Moore, MD, and his colleague, Anil Chauhan, PhD, Director of Rheumatology Research, have collaborated for more than a decade to identify the role these receptors play in the pathogenesis of connective tissue diseases such as systemic lupus and arthritis.

IMPACT

- Modulating T-cell responses by targeting FcRs provides a new therapeutic approach for lupus, connective tissue diseases, graft vs. host disease and cancers
- Better understanding of FcR signaling in CD4\(^+\) T-cells can improve current biological therapies to mitigate undesired immunogenic responses
THE NUMBER OF PEOPLE over the age of 65 in the United States is climbing rapidly, with some estimates saying there could be 72.1 million older adults in this country by 2030. The Department of Internal Medicine has focused on issues related to aging for more than 2 decades, establishing a Division of Geriatric Medicine in 1988. The Division has a robust research program, focused on major conditions and diseases affecting the elderly. Significant contributions in the past several years focus on:

ALZHEIMER’S DISEASE – Laboratory research that has identified key antisense compounds that can reverse memory loss in Alzheimer’s disease now is on the cusp of being translated into a search for treatments to restore memory loss in patients diagnosed with traumatic brain injuries (TBIs) and concussions.

New research by Susan Farr, MD and her research colleagues in the Division of Geriatric Medicine has found that an antisense to a specific enzyme, glycogen synthase kinase beta (GSK3B), can help restore memory after TBI. The Department of Defense now is funding more research because of the promising hope that it will lead to effective treatments for war-related traumatic brain injuries.

The latest effort builds upon longstanding research here to identify potential mechanisms by which memory loss can be reversed. For the past 27 years, the Division of Geriatric Medicine has utilized a unique mouse model not available anywhere else in the world, SAMP8, to search for the triggers of memory loss in Alzheimer’s disease. Laboratory studies here identified the first antisense to the amyloid precursor protein (APP) that actually blocks the conversion of APP to beta amyloid (amyloid-β). It was a critical finding because when beta amyloid clumps together in the brain, it leads to the build-up of amyloid plaques, a hallmark of Alzheimer’s disease. Further studies have found that the antisense actually reverses the cognitive deficits and oxidative damage caused by beta amyloid actions and brings the level of beta amyloid back to normal levels in the body. The antisense, by working like a micro RNA, normalizes the function of the beta amyloid.

Now that these antisense models are proven in the laboratory, the focus turns toward efforts to translate the basic research findings into clinical trials. With an estimated 5 million Americans over the age of 65 estimated to have Alzheimer’s disease and another 5.3 million Americans living with disabilities as a result of TBI, results in the clinical trials that mirror what’s shown in the lab could have profound implications.

As the research continues, the team also remains focused on patient care. A screening tool developed here, called the Saint Louis University Mental Status Examination, has become one of the premier screening tools for persons with Alzheimer’s disease. A shorter version of that tool, called the Rapid Cognitive Screen (RCS) also has been created and is ideal for use in a busy physician’s office. The RCS tool has proven so successful for its ease of use, it is now available globally in 24 languages.

APP Antisense
• Antisense molecules alter the expression of genes by interacting with complementary strands of nucleic acids.
• Antisense RNA sequences interact with mRNA to form a duplex which blocks mRNA translation.
• Antisense had no effect on mRNA, but decreased protein levels.
• The end result was a decrease in Ab.

IMPACT
• Reversal of memory loss
• Novel treatment pathways identified for Alzheimer’s disease, traumatic brain injury and concussions
• Easy screening tools for initial Alzheimer’s disease assessments
DELIRIUM — In a significant advancement in the treatment of hospitalized older adults diagnosed with delirium, geriatric medicine researchers are the first to develop a successful and cost-effective care model that significantly reduces length of stay and improves patient functional status. At the same time, the care model, called the Delirium Room model, has been shown to significantly reduce the number of medications needed and eliminate the need to restrain patients.

Current care practices often utilize restraints and require a high level of staffing (1:1 ratio) as well as numerous medications. The Delirium Room model changes nursing and medical management protocols through the creation of a small restraint-free inpatient unit with 24-hour nurse observation. At its core, the model incorporates the principles of “tolerate, anticipate and don’t agitate” (TADA), which enables nurses to better understand and then respond to behaviors that may cause acute confusion. It also focuses on educating nursing staff on nonpharmacologic ways to manage agitation, thereby reducing the number of medications taken by patients.

A just completed multi-center NIH study has found that the new care model can help significantly reduce post-operative delirium in older adults undergoing elective surgery. The finding is significant because up to 20 percent of elderly adults develop post-operative delirium. Other research has shown that delirium impacts almost 80 percent of older patients admitted to intensive care units. All totaled, more than seven million Americans will be diagnosed with delirium each year. Many of these patients subsequently experience persistent delirium after discharge and have a significantly higher probability for developing dementia or dying.

The Delirium Room care model, the result of a lifelong effort by researcher Joseph Flaherty, MD to find better ways to take care of delirium patients, has already been replicated in Australia, Hong Kong and Singapore. Building upon the model’s success, researchers are identifying more clinical models that can enhance care practices further. They also are delving into the pathophysiology of delirium in the hopes of identifying the specific triggers that contribute to delirium development.

IMPACT

- Improved care of delirium patients
- Reduced hospital length of stay
- Lower healthcare costs

FRAILTY — In less than 2 years, a 15-second screening tool developed at Saint Louis University has become a global standard for the identification of early signs of frailty in adults over the age of 70. Called FRAIL, it focuses on five key questions that must be screened for in older adults.

Fatigue: Are you fatigued?
Resistance: Do you have difficulty in walking up one flight of steps?
Aerobic: Are you unable to walk at least one block?
Illnesses: Do you have more than five illnesses?
Loss of weight: Have you lost 5+ percent of your weight in the past six months

In 2013, six major international and national societies endorsed the significance of frailty as a key medical condition that must be screened for in older adults. Among screening tools, FRAIL was noted as both simple and highly effective, resulting in rapid worldwide adoption of its use.

The screening tool, one of more than a dozen developed by John Morley, MB, BCh, Chief of the Division of Geriatric Medicine proves that simple, rapid questionnaires can assist clinicians in identifying key preventive measures that may help ward off some of the negative consequences of aging. Over the years, several simple screens have been developed, including for sarcopenia (SARC-F) as well as for early dementia and Alzheimer’s disease.

Frailty, characterized as a loss of strength, energy and weight loss, can lead to a cascading number of problems, including falls and other more serious disabilities as well as death. Sarcopenia, the decline in muscle mass and function, is one of the signposts for frailty. Because fairly simple preventive measures such as exercise, protein consumption and Vitamin D supplements as well as hormonal therapy can offset some of the deleterious effects of frailty and sarcopenia, easier assessment tools such as FRAIL will encourage more doctors to screen patients and start interventions early.

For hormonal interventions, researchers here have confirmed in multiple studies — from the cellular level to clinical trials — that older adults who lose muscle mass can improve overall muscle strength when given high doses of testosterone. The benefit of that finding was another screening tool developed in 2000 to detect Androgen Deficiency in the Aging Male (ADAM), which also has been adopted worldwide.

The team is now strongly advocating for physicians to reduce the number of medications that older adults often take. The number, which can be as high as 15-20 different medications, puts older adults at higher risk for adverse drug interactions, hospitalizations, and numerous side effects. By reducing the number of medications, they have found better patient medical management and quality of life.

IMPACT

- Breakthroughs in Alzheimer’s Disease research
- New international model for care of delirium patients
- Global screening tools for aging concerns
Kidney Development and Complications of Kidney Disease

CHRONIC KIDNEY DISEASE affects 26 million Americans. The disease almost always results in disturbances in bone and mineral metabolism and the development of secondary hyperparathyroidism, both significant contributors to bone fractures, vascular calcification and mortality in patients with CKD. At Saint Louis University, innovative basic and clinical research aims to improve the care of patients and advance understanding of the disease.

HYPERPARATHYROIDISM IN KIDNEY DISEASE

Basic research has led to the development of a unique liquid chromatography tandem mass spectrometry (LC-MS/MS) assay that now is being used to accurately measure and assess the development of secondary hyperparathyroidism throughout the stages of chronic kidney disease. The assay, which was presented at a meeting of the American Society of Nephrology, has been found to accurately measure the level of parathyroid hormone. Lead researcher Kevin J. Martin, MB, BCh, Director of the Division of Nephrology, now is part of an international work group that aims to harmonize a variety of assays for parathyroid hormone in use globally and set worldwide measurement standards for various stages of CKD.

Martin also is focused on a novel peptide calcimimetic that can be injected during dialysis treatments to target and activate a calcium-sensing receptor so that the parathyroid gland shuts down secretion of parathyroid hormone. In phase I and II trials, this calcimimetic was found to lower the level of parathyroid hormone (and calcium) with very little side effects and can be used in combination with a vitamin D analog, paricalcitol. The strategy currently is undergoing phase III clinical trials.

GENETIC EXPLORATION OF KIDNEY DISEASE

To better understand the genetic basis of kidney development and renal disease, Michael Rauchman, MD, is targeting signaling pathways that regulate progenitor cells responsible for making nephrons, the filtering units in kidneys. In premature infants, all of the filtering units don’t fully develop, putting these children at risk for kidney disease and hypertension later in life. Rauchman is looking for the on/off triggers in progenitor cells so that he can stimulate and re-program differentiated cells and prompt them to make new nephrons. He and colleagues have identified molecules in the SALL family of proteins that repress gene expression by recruiting the nucleosome remodeling and deacetylase co-repressor complex (NuRD). By looking at a laboratory model of a rare birth defect, Townes-Brock Syndrome, which can lead to kidney abnormalities, early research has found that SALL1 promotes self-renewal of progenitor cells in the developing kidney, and dramatically protects adult kidneys from acute injury. More investigation into the function of SALL1 and its-cofactors could lead to strategies that create new nephrons in diseased kidneys.

In more innovative research, Rauchman is collaborating with clinicians at the St. Louis Fetal Care Institute. The Institute, a joint effort by SSM Cardinal Glennon Children’s Medical Center, SSM St. Mary’s Health Center and Saint Louis University, is the only comprehensive fetal care program in the Midwest to offer open and minimally invasive fetal surgery for a wide range of medical complications. Rauchman and others are gearing up to obtain parental and fetal DNA samples from pregnancies with renal anomalies to do whole exome sequencing looking for mutations in novel genes. The hope is that the identification of genes important in renal health will eventually lead to better anticipatory guidance for families regarding prognosis in these pregnancies as well as the possibility of improved in-utero treatments that could prevent the development of chronic kidney disease later in life. Rauchman already is a principal site investigator of a similar DNA research project at the St. Louis Veterans Medical Center that aims to expand the knowledge of the genetic triggers of disease.

ION CHANNELS IN KIDNEY FUNCTION AND DISEASE

Ion channel proteins have long been recognized as essential to kidney function by serving as the pathways through which the kidney moves some salts in and out of the urine, thus regulating the composition of the body. John Edwards, MD, PhD has been
Whole mount view of developing embryonic mouse kidney (left) showing green fluorescent protein expressed in nephron progenitor cells. High power view of a single nephron stem cell niche (right). The green Sall1 progenitors form a cap around the tip of the ureter bud (unstained). The two early differentiating nephron structures below the ureteric bud co-express Sall1 (green) and Lef1 (red) and appear yellow.

studying channels which specifically allow chloride to move across cell membranes and is contributing to a growing awareness of roles of ion channels in kidney development and function well beyond simply controlling the ionic composition of the urine. Dr. Edwards and his group were instrumental in the initial discovery of the CLIC family of proteins and the demonstration that they in fact can function as channels. These proteins are examples of atypical ion channels, which are more like some bacterial toxins rather than usual mammalian ion channels. Analysis of the family member, CLIC4, revealed that this protein is abundant in the kidney where it is highly expressed in both the proximal tubule brush border and in the endothelial cells of glomerular and peritubular capillaries. Mice which fail to express CLIC4 have impaired ability to generate new blood vessels, have fewer glomeruli, leak albumin into the urine, and are more susceptible to acute kidney injury. The failure of endothelial cells to form new capillaries is correlated with the inability of these cells to acidify the intracellular vesicles which lead to capillary tube formation, suggesting a specific role for an ion channel in this process which is essential to kidney development as well as in many disease states.

More recently, Dr. Edwards has shifted his work to focus on another atypical ion channel, ApoL1, which has been recognized to play a critical role in the high rate of progressive kidney disease among people of African ancestry. ApoL1, like the CLIC channels, is a bacterial-toxin like molecule that can post-translationally insert directly into membranes where it can function as a channel. Abundant genetic evidence has shown that variants in ApoL1 which are uniquely present in Africans are responsible for the high rate of progressive kidney disease, particularly that associated with hypertension and focal segmental glomerulosclerosis. Understanding the fundamental biochemistry of ApoL1 should lead to insight into how this protein exacerbates disease with the ultimate hope of leading to treatments to fight the epidemic of kidney disease among African Americans.

Mouse kidney section stained for CLIC4 (red), endothelial cells (blue), proximal tubule brush border (green), and nuclei (cyan). CLIC4 co-localizing with the glomerular and peritubular endothelial marker appears purple; CLIC4 co-localizing with the brush border marker appears yellow.

IMPROVING TRANSPLANT OUTCOMES

Kidney transplantation, especially from a living donor, is the best therapeutic option for patients with end-stage kidney failure. Saint Louis University has garnered several NIH grants examining long-term health outcomes related to live kidney donation and kidney transplantation. Krista Lentine, MD, PhD, Medical Director of the Living Kidney Donation Program at Saint Louis University, is co-chair of a global work group focused on setting standards related to live kidney donor evaluation and care. In a study published in the New England Journal of Medicine late last year, Lentine reported that women who donated kidneys were at higher risk of developing hypertension during a subsequent pregnancy than non-donors, but importantly, most women had uncomplicated pregnancies after donation. Because of these findings, new living donor informed consent policies and clinical practice guidelines may include counseling women about the risk of possible pregnancy complications such as preeclampsia. Lentine and her colleagues also have focused their research on racial and geographic disparities in kidney donation and transplantation. New R01 grant subcontracts focus on defining health outcomes in African American live kidney donors and tailoring immunosuppression regimens for patient characteristics.

IMPACT

- Worldwide standards for staging chronic kidney disease
- New treatments for hyperparathyroidism
- Identification of new signaling pathways in kidney development
- Global standards for living kidney donation
- Tailored counseling and care of organ donors and recipients.
TARGET: BONE MARROW TRANSPLANTATION AND LEUKEMIA

Researchers in the Division of Hematology, Oncology and Bone Marrow Transplantation are participating in a pivotal multicenter study (Study 1101) comparing the utility of stem cells coming from cord blood to those from half matched family members (haplo-identical donors). These types of transplants, called “alternative donor” procedures, are considered higher risk and are done when a patient does not have a perfectly matched donor. The trial is being conducted through the Clinical Trials Network for Bone Marrow Transplant (CTN-BMT), a national research consortium. Many BMT programs have a strong local bias for either cord blood or haplo-identical stem cell sources, so a true randomized controlled trial has not been done prior to this latest effort. Over the last year, nearly 30% of allogeneic transplants at Saint Louis University have been from alternative sources, and the program has experience with both types of stem cell sources.

In addition to clinical research, Jack Lionberger, MD, PhD is focused on better understanding the effects of aging on stem cells and stem cell kinetics. Using normal elderly bone marrow and high definition genotyping, he is identifying intrinsic somatic genetic markers that allow modeling of recruitment, expansion and senescence of adult hematopoietic stem cells during normal aging and in stress situations such as leukemogenic chemotherapy, radiation, and transplantation. Normal and stress response stem cell kinetics are not well understood in vivo, but these innovations have allowed novel approaches to determining stem cell dynamics, which is a prelude to understanding age-related stem cell disorders like leukemia or myelodysplastic syndrome.

TARGET: HIV/AIDS AND HEMOPHILIA A

Induced pluripotent stem (iPS) cells hold promise for studying diseases in a dish, drug screening of patient-specific cells, and the possibility of cellular therapy using autologous cells following differentiation of patient-derived iPS cells. Researchers Srinivas Kumar, MBBS, MD, PhD, and Michail Zaboikin, PhD, are working to genetically engineer an HIV-1 resistant phenotype in T-cells and macrophages (known natural targets for HIV-1 replication). Other research seeks to derive iPS cells from hemophilia A patients, introduce a functional FVIII cDNA downstream of its natural promoter by genome engineering, and then differentiate the cells into endothelial progenitor cells for eventual cell therapy. The approach may lead to a universal solution to overcome the myriad of debilitating mutations in hemophilia A genetic locus. Already, researchers have successfully introduced the Δ32 mutation in the CCR5 gene (a co-receptor for HIV-1) in a cultured cell line using TALENs. They now are working to extend their promising studies to iPS cells and CD3-positive T-cells.

A novel approach to cancer treatment involving alteration of membrane lipid components as a lethal, or growth inhibitory

Jack Lionberger, MD, PhD

Chunfa Huang, PhD, and Carl Freter, MD, PhD
target in cancer cells is being used to search for new, more effective drugs to combat cancer. Exciting research by Carl Freter, MD, PhD, director of the division of hematology and oncology, and his research associate Chunfa Huang, PhD, has led to the identification of several useful agents, now patented, that have been found to reduce or completely reverse cancer drug resistance. Because this approach involves repurposing a drug already in use, researchers now are anticipating the start of phase 1 clinical trials in the near future.

Researchers also are collaborating with other scientists in St. Louis and India in a novel approach to design new enzymatic inhibitors. They currently are synthesizing promising compounds that may work as an anti-cancer treatment either alone or in conjunction with conventional chemotherapy.

**TARGET: NEW HEPATITIS VIRUSES**

Since the introduction of next-generation sequencing (NGS), the exceptional sequencing power has quickly been adopted to the discovery of new viruses that are potentially associated with human diseases. This power, however, has not brought much success in the field of viral discovery, a historically laborious, expensive and difficult endeavor. The sequencing power might be counteracted by low efficiency from steps in the entire pipeline of NGS-based viral discovery, notably sample preparation and data analysis, respectively prior and after NGS. Researcher Xiaofeng Fan, MD, PhD, and Adrian Di Bisceglie, MD, chairman of the Department of Internal Medicine, have invented a novel method for nucleic acid amplification. Called template-dependent multiple displacement amplification, this method, now patented, allows full recovery of genome information from biological specimens containing as little as $10^{-14}$ grams of nucleic acid templates. An enrichment strategy also has been developed to eliminate false signal for viral categorization and detection.

Equipped with this new technology, the team’s first target is new hepatitis viruses. Multiple large-scale epidemiological studies reveal the lack of etiological factors in nearly thirty percent of patients across various types of liver diseases, including acute liver failure, chronic hepatitis, cirrhosis and hepatocellular carcinoma. Through national and international collaborations, researchers have obtained clinical specimens from these types of patients. Within a few years they hope to have a clear answer if there are novel hepatitis viruses beyond the current five hepatitis A through E viruses.

**TARGET: OBESITY AND SLEEP DISORDERS**

Researchers and clinicians are working to prevent and cure multiple obesity-related diseases through therapies that target metabolic determinants of sleep and circadian rhythm. Prevalence of chronic, preventable, metabolic disorders, such as type 2 diabetes mellitus, non-alcoholic steatohepatitis and sarcopenia, has rapidly increased worldwide. Economic analysis by the McKinsey Global Institute estimates the yearly cost of obesity alone is $2 trillion. Concomitant with and likely causative to the increase in obesity-related metabolic disease is an increase in disorders of sleep and circadian rhythm. Disorders of sleep and circadian rhythm that associate with metabolic disease include short sleep duration, sleep fragmentation, periodic limb movement disorder, menopause, use of stimulants, and irregular sleep-wake cycles.

Department scientists such as Raymond Bourey, MD, are working with researchers across campus and around the country to explore the neuromodulation of metabolism, sleep and activity in obese mice. Bourey also provides translational assistance to the Department of Physiology and Pharmacology as members treat models of obesity and steatohepatitis with clock gene analogues.

At the epidemiological level, department investigators and medical center colleagues study mid-sleep phase differences between work/school days and free days (“social jet lag”); obesity; and physical activity.

Clinical studies are also underway to quantify the high rate of sarcopenia and frailty among middle-aged, obese patients with sleep disturbance. Dr. Bourey and colleagues also plan to evaluate the effects of caffeine and other stimulants on sleep quality, and effects of weight loss on sleep and, conversely, the impact of improved sleep on weight loss.

**Viral Categorization using Mapping Enrichment Strategy**

SLU researchers are part of a national effort to better understand obesity-related diseases.
RESEARCH IN THE DEPARTMENT of Internal Medicine is funded not only by the National Institutes of Health (14 faculty in the department currently serve as principal investigator on an NIH grant or contract), but also through interactions with industry in at least two ways.

First, research performed in this department has led to numerous patents, highlighted on the facing page, with the potential for commercialization in partnership with industry. Second, clinical trials funded by industry sources continue to be an important research activity. There were more than 100 active clinical trials in the Department during the 2014 fiscal year.

“Basic science research typically funded by the NIH can generate fundamental new insights into human biology leading to new disease diagnosis and treatment; but it is in clinical trials, often funded by industry, that the best ways to apply this knowledge in the care of people is determined.”

John Edwards, MD, PhD, Professor of Medicine, Division of Nephrology

Clinical Trials
Fiscal Year 2014

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Ranjit Ray, PhD, has researched respiratory and hepatitis viruses for more than 30 years.
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**FY 2014 TOTAL RESEARCH EXPENDITURES (Federal and Foundations) ($ in thousands)**

- Cardiology / ECG Core Lab: 102
- Infectious Diseases: 5139
- Endocrinology: 243
- Gastroenterology and Hepatology: 651
- Geriatric Medicine: 785
- Other Divisions: 1436

**TOTAL RESEARCH EXPENDITURES (Federal and Foundations) ($ in thousands)**

- **FISCAL YEAR 2014**: $7,404,287
- **FISCAL YEAR 2013**: $8,443,938
- **FISCAL YEAR 2012**: $9,491,857
- **FISCAL YEAR 2011**: $10,772,678
- **FISCAL YEAR 2010**: $10,159,136

**Total Federal and Foundations Expenditures for FY 2014**: $10,640,518

**Total Federal and Foundations Expenditures for FY 2013**: $12,399,592

**Total Federal and Foundations Expenditures for FY 2012**: $12,697,884

**Total Federal and Foundations Expenditures for FY 2011**: $15,097,097

**Total Federal and Foundations Expenditures for FY 2010**: $15,594,992
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<td>Adrian Di Bisceglie</td>
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<td>John Edwards</td>
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<td>Role of Gamma/Delta T Cells in Vaccine Induced Immunity (R01)</td>
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<td>Molecular Mechanisms of Host-Derived CCL5 Mediated Mammary Tumor Growth (K22)</td>
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<td>The Role of Tristetraprolin in Control of Breast Cancer Progression (R01)</td>
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<td>Brent Neuschwander-Tetri</td>
<td>The Saint Louis University Component of the NASH Clinical Research Network (U01)</td>
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<td>Role of GPR30 In Hepatic Lipid Metabolism (R56)</td>
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### Type of Contracts and Grants

- **Contract:** Consortium of Individual Contracts
- **K22:** Career Transition Award
- **R01:** NIH Research Project Grant Program
- **R03:** NIH Small Grant Program
- **R21:** NIH Exploratory/Developmental Research Grant Award
- **R56:** NIH High Priority, Short-Term Project Award
- **U01:** Research Project Cooperative Agreement


