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Top Ten Clinical Research Achievement Awards
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Clinical Research Forum Top Ten Clinical Research Achievement Awards Ceremony

Tuesday, April 18, 2017
National Press Club, Washington, DC

Masters of Ceremonies

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2017 Top Ten Clinical Research Achievement Awards

- Baricitinib in Patients with Refractory Rheumatoid Arthritis
- Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders
- Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease
- Helmet Ventilation Reduces the Need for Endotracheal Ventilation in ARDS
- How Environmental Exposures Protect Against Asthma
- HSD3B1 and Resistance to Androgen-Deprivation Therapy in Prostate Cancer: A Retrospective Multicohort Study
- Life Expectancy After Myocardial Infarction, According to Hospital Performance
- A Randomized Trial Comparing Skin Antiseptic Agents at Cesarean Delivery
- Reengineering Chimeric Antigen Receptor T Cells for Targeted Therapy of Autoimmunity
- The Use of Focused Ultrasound for Essential Tremor
Project Title: Baricitinib in Patients with Refractory Rheumatoid Arthritis


Summary: Rheumatoid arthritis (RA) is an inflammatory disease that can affect the entire body. While the initial triggers of the disease remain unknown, it is acknowledged that both environmental and genetic factors contribute to cause the immune system to function in an abnormal fashion. The hallmark features of RA are the development of stiffness, pain, swelling, and loss of function in many of the small and larger joints of the body. The ongoing inflammation often results in destruction of the joints leading to significant disability. There have been a number of advances in the treatment of autoimmune diseases in the past 20 years. Improvements in the treatment of RA have come from better use of traditional medications designed to suppress the immune system (immunosuppressants) as well as from the advent of new protein based injectable or infused medications (biologic agents). Despite these improvements in treatment, many of the 2 million Americans (the majority being women) who suffer from this disease remain refractory to treatment.

This clinical trial sought to study a new drug (baricitinib) that modulates an enzyme pathway known as the Janus associated kinase pathway that is responsible for many inflammatory signals inside of immune cells. Importantly we sought to study this new therapy in patients who had tried and failed both traditional immunosuppressants as well as the newer injectable and infused biologic agents that have become commercially available in the past two decades. Despite the refractory nature of the disease in the over 500 patients studied in this trial, baricitinib was safe and effective at significantly improving the disease in over 50% of the subjects by 12 weeks. This improvement was seen independent of how long the patients had suffered with the disease, or the number or nature of the therapies the patients had previously tried.

Authors: Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, Beattie SD, Koch AE, Cardillo TE, Rooney TP, Macias WL, de Bono S, Schlichting DE, Smolen JS

Institutions: Stanford University; Albany Medical College; Rheumazentrum Favoriten (AT); East Penn Rheumatology; Rheumatology Clinic MAK-MED (PL); Eli Lilly; and Medical University of Vienna (AT)

Funding: Funded by Eli Lilly and Incyte.
Project Title: Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders


Summary: The U.S. is currently experiencing an unprecedented epidemic of opioid addiction, with over 30,000 deaths per year from opioid overdoses. Most addiction patients are treated by daily doses of opioid agonists such as methadone or buprenorphine. These medications prevent withdrawal symptoms and enable the patient to function as long as the medication is continued. However, these agonist medications produce dependence and inability to stop the medication. Further, the agonist medication produces well-known opioid effects desired by abusers, tempting patients to sell their meds or share them with friends.

This paper describes a completely different pharmacological strategy using monthly injections of an opioid receptor antagonist instead of an agonist. If the patient takes an opioid, the euphoric effects are blocked with no negative consequences – there is no punishment if the patient uses an opioid, only absence of reward. The study involved 308 patients with a history of opioid addiction who were recently released from criminal justice restrictions. Participation was completely voluntary. Participants were treated at 5 different sites and were assigned to treatment on a random basis; 153 received 6 monthly injections of extended-release naltrexone and 155 received standard treatment with methadone or buprenorphine (Suboxone) if they wished.

During the 24-week treatment phase, participants assigned to naltrexone experienced significant advantages – a longer median time to relapse than those assigned to usual treatment (10.5 vs. 5.0 weeks, P<0.001), a lower rate of relapse (43% vs. 64% of participants, P<0.001); and a higher rate of opioid-negative urine samples (74% vs. 56%, P<0.001). At week 78, rates of opioid-negative urine samples were equal (46% in each group, P=0.91). The rates of other pre-specified secondary outcome measures – self-reported cocaine, alcohol, and intravenous drug use, unsafe sex, and re-incarceration – were not significantly lower with naltrexone than with usual treatment. Over the 78 weeks observed, there were no overdose events in the extended-release naltrexone group compared to 7 in the usual treatment group (P=0.02) with two deaths.


Institutions: New York University; Rhode Island Hospital; Brown University; University of Baltimore; Friends Research Institute; New York State Psychiatric Institute; Columbia University; University of Pennsylvania; Maryland Treatment Centers; University of Virginia School of Law; Philadelphia Veterans Affairs Medical Center; and Washington State University, Spokane

Funding: Dana Foundation, National Institutes of Health-National Institute on Drug Abuse.
Project Title: Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease


**Summary:** The study derives data from more than 55,000 people, showing that by living right – by not smoking, by exercising moderately, and by eating a healthy diet heavy in fruits, vegetables, and grains – people can reduce and mitigate even the worst genetic risk. As the author said in an interview with the New York Times, “DNA is not destiny; it is not deterministic for this disease,” “You do have control over the problem, even if you have been dealt a bad genetic hand.” The research conducted by Dr. Kathiresan and his colleagues is the first attempt to use large data sets to discriminate the effects of genes and lifestyle in heart disease. About 365,000 people die of coronary heart disease – the most common type – annually in the United States, and 17.3 million worldwide, making it one of the biggest killers. The researchers found that genes can double the risk of heart disease, but a good lifestyle cuts that risk in half. Just as critical, they found that an unhealthy lifestyle erases about half of the benefits of good genetics.

**Authors:** Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, Fuster V, Boerwinkle E, Melander O, Orho-Melander M, Ridker PM, Kathiresan S

**Institutions:** Massachusetts General Hospital; Brigham and Women’s Hospital, Broad Institute; Lund University (SE); Icahn School of Medicine at Mount Sinai; University of Pennsylvania; and University of Texas Health Science School of Public Health

**Funding:** National Heart, Lung, and Blood Institute, National Institutes of Health, Massachusetts General Hospital Research Scholar Award
Project Title: Helmet Ventilation Reduces the Need for Endotracheal Ventilation in ARDS

Publication: Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients with Acute Respiratory Distress Syndrome. JAMA 2016; 315[22]: 2435-41.

Summary: Acute respiratory distress syndrome (ARDS) is a condition where the lungs fill with fluid, preventing oxygen from being absorbed into the body. As a result, internal organs are deprived of oxygen and many patients do not survive. The mainstay of treatment for ARDS mechanically ventilating patients through a tube placed into the windpipe, which is extremely uncomfortable and often requires sedation and even paralysis. Consequently, these patients often suffer from muscle weakness, memory problems, and functional impairment, if they survive. A special breathing mask was previously developed to support breathing and deliver oxygen without the tube so that patients might avoid these complications.

Unfortunately, that mask covered the nose and mouth, was uncomfortable, and leaked substantially under the high pressures needed to support the breathing of patients with ARDS. In fact, about half the patients treated with standard mask for ARDS end up requiring tube ventilation, and thus are subjected to its inherent complications. The authors were aware of an alternative to the mask – a helmet – that seemed well tolerated by patients who needed breathing support for other conditions. (The helmet is a pressurized, transparent hood that encompasses the entire head and provides oxygen.) So, they tested the helmet in patients with ARDS in a clinical trial comparing it against the standard mask.

Remarkably, helmet ventilation reduced the chances of needing a tube ventilator from 60% to 20%. Even more importantly, patients who wore the helmet were 20% more likely to survive their ARDS. Indeed, this study was stopped early because these results so dramatically favored helmet over mask breathing support. Helmet ventilation may provide a new approach to breathing support for ARDS that substantially reduces the need for the tube ventilator and improves survival.


Institutions: University of Chicago

Funding: Funded by the Daniel Edelman Grant, a gift of the Edelman Family; T32 NIH/NHLBI – supported the salary of BK Patel and KS Wolfe.
Project Title: How Environmental Exposures Protect Against Asthma


**Summary:** Over the past half century, the prevalence of asthma has been increasing at an alarming rate especially in children. The reason for this increase is unknown, but interestingly children raised on traditional farms remain relatively protected from developing asthma. In this study, the authors compared Amish farm children, who have very low prevalence of asthma, to Hutterite farm children, who have high prevalence of asthma. The lifestyles of the Amish and Hutterites are similar with respect to many factors known to influence the risk of asthma, but there are major differences in their farming practices. While Hutterites have embraced modern highly industrialized farming techniques and farm communally, Amish continue to farm traditionally on single family farms. Importantly, Hutterite children have limited exposure to the barns and livestock, while Amish children have near daily exposure.

The investigators found that the two groups were highly similar genetically arguing against a role for genetic susceptibility, and instead for a role of environment, in the disparate asthma rates. Asthma is a disease mediated by the immune system, yet how the environment affects the immune dysfunction that leads to asthma is unknown. This study established that specific components of the children’s immune system, called the innate immune response, dramatically differed between the Amish and Hutterites. Furthermore, while mice that breathed dust from Amish homes were protected from developing asthma, mice with defective innate immune responses were not protected from asthma. Thus, this study demonstrated that dust from the environment of Amish children changes their innate immune responses, and these changes may protect them from the development of asthma and allergies. Identifying the components in the dust that stimulate and change the innate immune response may ultimately pave the way for the development of effective strategies for the prevention of asthma.


**Institutions:** University of Chicago; University of Arizona; Arizona Respiratory Center and Bio5 Institute; Argonne National Laboratory; Allergy and Asthma Consultants; University of Iowa; and Ludwig-Maximilians-Universität in Munich (DE)

**Funding:** This work was supported by the National Institutes of Health, St. Vincent Foundation (Indianapolis), and the American Academy of Allergy, Asthma, and Immunology Foundation Inc (AAAAI Foundation), formerly the ARTrust™.
Project Title: HSD3B1 and Resistance to Androgen-Deprivation Therapy in Prostate Cancer: A Retrospective Multicohort Study


Summary: Prostate cancer progression is profoundly dependent on androgens (male hormones). Since the 1940’s, the standard upfront treatment for metastatic prostate cancer has been androgen deprivation therapy (ADT) by way of medical or surgical castration. Although 80-90% of tumors initially shrink, all eventually progress to a form termed castration-resistant prostate cancer (CRPC). Interestingly, in spite of medical or surgical castration, multiple clinical studies have established that high levels of tumor androgens are present in CRPC. It is now clearly established that CRPC makes its own androgens from non-testicular sources, enabling tumors to progress to this lethal form. However, how tumors develop the capacity to regenerate their own androgens and which patients have tumors that do this quickly has been a mystery. Sharifi’s group identified the first example of a “gain-of-function” genetic alteration in an enzyme that allows tumors to rapidly increase the synthesis of potent androgens and to develop CRPC (Chang, et al. Cell. 2013).

This genetic alteration is also a common germline variant – in other words may be inherited from one’s mother and/or father. The current study asked the question whether patients with advanced prostate cancer who inherit the germline variant of the androgen synthesizing enzyme develop more rapid resistance to ADT compared with other patients. The findings clearly show that patients in 3 independent cohorts (1 from Cleveland Clinic and 2 from Mayo Clinic) who inherit the variant androgen synthesizing enzyme develop CRPC more rapidly and die more quickly. Furthermore, patients who inherit 2 copies of this variant appear to have profoundly worse outcomes, probably because their prostate tumors are capable of making their own potent androgens even more rapidly. These findings establish the clinical relevance of the first example of a genetic variant in an androgen synthesizing enzyme for lethal prostate cancer (CRPC) and overall survival.


Institutions: Cleveland Clinic and Mayo Clinic

Funding: NIH, Prostate Cancer Foundation, Howard Hughes Medical Institute, American Cancer Society, Department of Defense Prostate Cancer Research Program.
Project Title: Life Expectancy After Myocardial Infarction, According to Hospital Performance


Summary: Use of life expectancy as a metric to evaluate hospital performance provides an intuitive and quantitative way to portray the impact of variation of quality in different institutions. However, this had not been previously done because of limitations in data and statistical modeling, and lack of appreciation of the approach’s utility. We hypothesized that using life expectancy could provide a perspective on why which hospital you use matters – and the consequence of having poor quality hospitals. We accessed the largest, most comprehensive evaluation of hospital quality, the Cooperative Cardiovascular Project. This effort, conducted by the US government, evaluated all Medicare enrollees who suffered heart attacks during ~9 months in 1994-5.

We extended the follow-up on these people almost 20 years to evaluate long-term outcomes. We further developed statistical methods, building on existing techniques, to estimate life expectancy for these individuals after their heart attacks – and compared life expectancy for people hospitalized at different places. We found that patients treated at high-performing hospitals lived, on average, between 9-14 months longer than those treated at low performing hospitals. These findings resulted from quality differences between hospitals and not differences in the types of patients seen at particular hospitals. We also found that the survival advantage for patients treated at high-performing hospitals occurred largely in the first 30 days after hospitalization and persisted over their lifespan. In other words, the initial survival advantage from being treated at a high-performing hospital was retained over time. The article stimulated national conversation about the lifespan cost of poor quality care and the potential to save years by improving quality. It also indicated that the longer life expectancy in patients treated at higher performing hospitals was realized by good early care – and that once the dangerous period passed, these people were not at heightened risk over their lifetime.

Authors: Bucholz EM, Butala NM, Ma S, Normand ST, Krumholz HM

Institutions: Yale University and Yale-New Haven Hospital

Funding: Emily Bucholz was supported by Training Grant F30HL120498-01A1 from the National Heart, Lung, and Blood Institute and by the National Institute of General Medical Sciences Medical Scientist Training Program Grant T32GM07205. Harlan Krumholz was supported by grant U01 HL105270 (Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute.
Project Title: A Randomized Trial Comparing Skin Antiseptic Agents at Cesarean Delivery


Summary: In the U.S., more women (1.3 million per year) undergo a cesarean section than any other major surgical procedure, accounting for about 33% of all deliveries. Despite preventive measures, up to one in eight patients (12%) have a surgical-site infection, the most common complication after cesarean. These infections cause patient suffering and even death, increase hospital stays and healthcare costs, and impair women’s abilities to care for their newborns.

The skin is a major source of germs that cause surgical-site infections, so optimal skin cleansing before surgery could reduce infections. However, the best antiseptic to use to cleanse the skin before surgery was unknown. The investigators conducted a randomized, controlled trial comparing the two common antiseptics for cleansing the skin before cesarean section (ClinicalTrials.gov#NCT01472549). Women who agreed to be part of the study were randomly assigned by a computer to be cleansed with either chlorhexidine-alcohol or iodine-alcohol. They were then followed for up to 30 days after surgery to identify those who developed surgical-site infection and other wound complications.

A total of 1147 patients were enrolled between September 2011 and June 2015; 572 were assigned to receive chlorhexidine-alcohol and 575 to iodine-alcohol. Surgical-site infection was diagnosed in 23 patients (4.0%) in the chlorhexidine-alcohol group and 42 patients (7.3%) in the iodine-alcohol group. This meant that patients who were cleansed with chlorhexidine-alcohol had nearly half the risk of surgical-site infection as those cleansed with iodine-alcohol. Patients cleansed with chlorhexidine-alcohol were also less likely than those cleansed with iodine-alcohol to visit their physician’s office for wound complications (7.9% versus 12.5%). The frequency of adverse skin reactions was similar in the two groups.

The investigators concluded that chlorhexidine-alcohol is a better antiseptic than iodine-alcohol for cleansing the skin before cesarean section because it reduces the risk of surgical-site infections.

Authors: Tuuli MG, Liu J, Stout MJ, Martin S, Cahill AG, Odibo AO, Colditz GA, Macones GA

Institutions: Washington University School of Medicine in St. Louis and University of South Florida

Funding: 1. National Institutes of Health: Women’s Reproductive Health Research Career Development grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development; 1K12HD063086-01 – PI (Macones), Scholar (Tuuli) 2. Washington University School of Medicine in St. Louis: Department of Obstetrics and Gynecology (Chair-Macones)
**Project Title**: Reengineering Chimeric Antigen Receptor T Cells for Targeted Therapy of Autoimmunity


**Summary**: Autoimmunity occurs when the body’s immune system, which normally defends against infections and cancer, mistakenly attacks the body’s own tissues. Pemphigus vulgaris is an autoimmune disease that results when B cells produce antibodies that attack the skin protein desmoglein 3, causing potentially fatal blistering of the skin and mucous membranes. Current therapy for pemphigus vulgaris, as with most autoimmune diseases, globally suppresses the body’s defense system, although deadly infections and secondary cancers can result from such an approach. Thus, the ideal for autoimmune disease therapy is to target only the disease-causing autoimmune cells while sparing the beneficial cells that provide protection.

Using desmoglein 3, the target of autoimmune attack in pemphigus vulgaris, as a decoy on the surface of genetically engineered T cells to lure in and kill B cells that react to desmoglein 3, this study demonstrated potent and specific elimination of anti-desmoglein 3 B cells by “chimeric autoantibody receptor” or CAAR T cells in pemphigus vulgaris mouse models. Desmoglein 3 CAAR T cells were effective even in the presence of circulating anti-desmoglein 3 antibodies, which can either neutralize or help stimulate CAAR T activity. Additionally, CAAR T cells showed no detectable collateral damage in other tissues, indicating their high degree of specificity for only autoimmune B cells. Because CAAR T cells have the potential to persist for the lifetime of an individual to provide continuous protection against disease recurrence, CAAR T cells represent a novel strategy for targeted therapy of autoimmunity that aims for a safe and lasting cure of disease.


**Institutions**: University of Pennsylvania; Istituto Dermopatico dell’Immacolata (IT); and Institute for Research in Biomedicine (CH)

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Project Title: The Use of Focused Ultrasound for Essential Tremor


Summary: These investigators developed and implemented a new treatment for essential tremor consisting of using focused ultrasound applied to the brain to create a lesion in a part of the brain that regulates movement. By creating a lesion in the thalamus, a part of the brain that controls movement, ultrasound can noninvasively diminish severe tremor.

Based on work in this paper, focused ultrasound (FUS) is now an FDA approved technology for the treatment of essential tremor, for which previously there was no treatment. FUS is now being investigated for use in Parkinson’s disease and other movement disorders. It completely changes the treatment paradigm for patients with severe tremor and offers hope to literally thousands of patients with tremor.


Institutions: University of Virginia; Toronto Western Hospital (CA); Sunnybrook Health Sciences Centre (CA); Stanford University; Yonsei University (KR); Swedish Neuroscience Institute; University of Maryland; University of Miami; Nicklaus Children’s Hospital; Brigham and Women’s Hospital; Shin-yurigaoka General Hospital (JP); and Tokyo Women’s Medical University (JP)

Funding: Focused Ultrasound Foundation, BIRD Foundation and Insightec.
About the Top Ten Clinical Research Achievement Awards
Recognizing the need to celebrate our nation's clinical research accomplishments that involve both innovation and impact on human disease, the Clinical Research Forum conducts an annual competition to determine the ten outstanding research accomplishments in the United States. These major research advances represent a portion of the annual return on the nation's investment in the health and future welfare of its citizens.

The Distinguished Clinical Research Achievement Awards are presented to the top two studies that demonstrate creativity, innovation, or a novel approach to improving the health and well-being of patients. The awards come with a cash prize of $3,500.

The Herbert Pardes Clinical Research Excellence Award is the Clinical Research Forum’s highest honor. It is awarded to the research study that best exemplifies the spirit of the awards in that it shows a collaborative, innovative and creative approach to advancing an area of science with a measurable and significant impact upon human health and disease. The award comes with a cash prize of $5,000.

About the Clinical Research Forum
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