Information from Legacy Research

Legacy Research e-news

LEGACY HEALTH

September 2013

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The mission of Legacy Research is to improve the treatment and prevention of disease by conducting internationally recognized basic, translational, and clinical research.

You can take pride in Legacy's research commitment to improve the lives of people in need.

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Message from Dr. Wackym

Basic and Translational Research: Accelerating the Bench to Bedside Transformation of Healthcare

The Legacy Research Institute (LRI) has a threefold mission: Surgical Education (Legacy Institute for Surgical Education and Innovation [LISEI]); Clinical Research; and Basic and Translational Research. Our agenda for each of these areas is to support Legacy Health's goal of transforming health care and to be a resource for Legacy Health and those physicians dedicated to our entire enterprise's mission. In this edition of the Legacy Research e-news I would like to focus on some of the ways that we are helping to transform healthcare through our basic and translational research efforts.

Prior to my relocation to Portland four years ago to join the Legacy Health leadership team, I devoted 20 years of my career to traditional academic medicine, including serving as the Chair of the Department of Otolaryngology and Communication Sciences at the Medical College of Wisconsin for over a decade. During that time, in addition to my robust clinical practice, the NIH continuously funded me to conduct research related to inner ear function and cochlear implants. Productive scientists at UCLA, the Medical College of Wisconsin, the University of Iowa and the Mount Sinai School of Medicine surrounded me; however, so many productive and functional basic scientists actually having an impact on clinical care have never surrounded me as I am here at the Legacy Research Institute.

Our work here is largely supported by traditional sources such as the NIH, the Department of Defense and private Foundations; however, we are blessed to have significant resources made available to supplement these funds from the Legacy Health Foundations to expand our work in basic eye research and glaucoma, neuroscience, biomechanics, hearing and balance disorders, and diabetes, among other areas. Unlike traditional academic medical centers, who unfortunately are struggling across the country to maintain their mission, we are also not bound by convention and we have forged productive relationships with outside companies to accelerate translational research.

While there is not enough space available to highlight all of our translational research programs, I did want to touch on two major areas. First is our broad neuroscience portfolio that explores a

core supportive molecule of the brain, adenosine, and the relationship to traumatic and neurodegenerative clinical problems such as traumatic brain injury, stroke, Parkinson's disease, epilepsy and schizophrenia. Our team led by Dr. Detlev Boison has used a variety of delivery systems, including gene therapy and engineered stem cells to redirect these systems and reverse the disease or restore function. His team has developed a new nanotechnology system that shows great promise for application in patients. Some of his work is entering the application in patients participating in a new clinical trial at the Cleveland Clinic. You can learn more about this work on the American Association for the Advancement of Science website http://www.scienceupdate.com/2013/08/silk-2/.

Second, I wanted to spend a few minutes introducing a relatively new NIH grant funding mechanism that is designed to accelerate the introduction of new technologies into healthcare. These grants require a collaborative partnership between a small business entity and a research institution. They provide $150,000 to $250,000 for one year in the Phase I studies, depending upon the specific NIH Institute, and $1,000,000 divided over two years for the Phase II studies. During my tenure, we have consciously pursued these grants depending on the close LRI scientist and Legacy Health clinician relationships. We have been flexible and responsive to the intellectual property issues – and not inflexible as many others have been. We have also sought out biotechnology start-up companies who after becoming aware of LRI have selected LRI as their Research Institution when applying for these grants because we offer opportunities and services that others in the region do not and cannot offer. This approach has diversified our research contributions and without question accelerated the ability of companies to develop their biomedical devices and products so that patients can benefit from their innovation.

I want to highlight just one of the many relationships that we have fostered. APEX Biomedical is a Portland company that is led by Dr. Steven Madey, an orthopedic surgeon committed to the clinical care of trauma patients at our Emanuel Medical Center, and Dr. Michael Bottlang, our leading biomedical engineering scientist at LRI. Their company's goal is commercialization of biotechnology products and devices. APEX Biomedical, who shares employment of Dr. Michael Bottlang with Legacy Health, has been extremely productive via these Phase I and Phase II NIH grant mechanisms. These grants and associated research focus on designing new helmet technologies to protect against rotational acceleration injuries of the brain and also tissue engineering technologies. Their work can completely change many of the helmets used for bicycling, football, hockey, and any other helmet application and thereby reduce the sequelae of traumatic brain injury. Their tissue engineering technologies will allow an individual patient's cells to be transformed to create new cartilage for joints and thereby avoid prosthetic joint replacements; among other tissue engineering applications. Their paradigm shifting work is being recognized internationally. I encourage all of you interested in this story to read this article. It is amazing. http://www.bicycling.com/sites/default/files/uploads/BI-June-13-Helmet.pdf

In collaboration with Legacy Health, APEX has successfully introduced two novel trauma care products to the marketplace over the past 5 years: a device for emergent pelvic stabilization that has been licensed to SAM Medical Products, Tigard, OR and is being sold as the "Sam Sling®" at a volume of >38,000 units per year, with international sales in 42 countries; and a locked plating system for stabilization of chest wall fractures that has been licensed to Synthes CMF, West Chester, PA and is being sold as "MatrixRIB™" at >$20 million in 2012 net sales alone. Our translational research efforts are transforming healthcare by radically reducing the mortality and morbidity in trauma – worldwide. We have so many other areas of medicine that are actively working in now and we only want to expand this portfolio so we can impact healthcare in as broad a way that we have resources to accomplish.

The Legacy Research Institute and the investigators across Legacy Health are valuable resources for our organization and it remains our mission to contribute to the transformation of healthcare.

Clinical Vice President of Research

News!

Dr. Boison's Adenosine Research Draws National Attention

Detlev Boison, PhD, Senior Scientist and Director of Basic and Translational Research at the Legacy Research Institute, and his colleagues in the RS Dow Labs and at Tufts University, published a landmark article in the August issue of the *Journal of Clinical Investigation* that attracted national attention. The article summarizes the results of NIH-funded research that provides evidence that increasing the level of adenosine in the brain significantly reduces epileptic seizures.

Adenosine is a naturally-occurring chemical that is an anticonvulsant in the brain, and previous research has suggested that abnormally low levels of adenosine may be linked to epilepsy. In Dr. Boison's studies, adenosine released from implanted silk scaffolds developed by bioengineers at Tufts reduced seizures in rats by a factor of four. Further research is planned that will ultimately lead to clinical trials in humans.

The National Institute of Neurological Disorders and Stroke, funder of this research, issued a press release when the article was published that nicely explains the results in more detail, and that can be viewed here. In addition, the American Association for the Advancement of Science (AAAS), publishers of *Science* and other journals, published a podcast of an interview with Dr. Boison regarding this research on their online blog Science Update, and that can be accessed here. The Oregonian also published a related story on July 30th and a "Legacy in the News" email was distributed by our PR department shortly thereafter.

Dr. Michael Bottlang Featured in *Bicycling* Magazine Article About Helmet Safety

Designing a safer bicycle helmet has long been a research interest of **Michael Bottlang, PhD**, Director of the Legacy Biomechanics Lab, and his colleague, orthopedic surgeon **Dr. Steve Madey**. Helmet designs currently on the market do a good job of preventing fractures, but do little to prevent concussions.

If you fall off your bike and your head hits the ground, your skull absorbs energy from the impact. Wearing a helmet helps, and a thin layer of viscous liquid that separates your brain from your skull dissipates some of the energy from the impact. But the brain also has to contend with rotational acceleration, the shifting action that occurs as the head whips back on the neck, known as shear strain, which can result in a concussion.

After years of experimenting with materials, Bottlang and Madey developed the Angular Impact Mitigation (AIM) design, incorporating an inner and outer shell. In a crash, the outer layer rotates away from the impact, reducing the odds of concussion. Rather than a hard-foam liner, which doesn't offer much protection from slower-speed crashes, an AIM helmet is be made from sliver-thin aluminum strips arranged in a lightweight honeycomb cell structure. On impact, the cells compress against on another like an accordion, to reduce the blow's intensity. On the hardest hits, the structure collapses like a crumple zone in an automobile.

Nate Dau, an engineer in Bottlang's lab, developed the crash testing methods for the new design, began testing prototypes, and collected data for analysis. The data came back strong. Compared with a conventional helmet, the AIM design lowered the likelihood of concussion from greater than 80%t to about 50% in the worst case, and lower in other crashes. Dau's data didn't predict a concussion-proof helmet, but the numbers indicated the AIM design is a solid step forward. Bottlang and Madey hope that their research will lead to new government safety standards for helmets that haven't changed since 1999, and in the meantime will continue with their research fine-tuning the AIM design.
The full text of the article can be accessed here.

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Clinical Trials

Up to date information about new and ongoing clinical trials can be found on Legacy's web site, here.

New Studies Approved by the Legacy IRB (Institutional Review Board)

PI: Michael R Parsons, MD
STUDY: A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneious canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP
Abstract

PI: Lin Wang, MD, PhD
STUDY: Noninvasive assessment of dyamic blood flow autoregulation in human optic nerve head with Laser Speckle techniques..
Abstract

PI: Fawn M Wolf, MD
STUDY: Evaluation of Metabolic Outcomes and Safety of Hylenex recombinant (human hyaluronidase injection) used as a Preadministration Infusion Site Treatment in Subjects with Type 1 Diabetes using Continuous Subcutaneous Insulin Infusion.
Abstract

PI: W. Kenneth Ward, MD
STUDY: Sensor-controlled insulin and glucagon delivery in subjects with Type 1 diabetes: testing of an automated system in a supervised outpatient setting.
Abstract

PI: Harvey Carp, M.D.
STUDY: New Treatment for Drug Resistant, Post-Partum Hemorrhage: Further Studies Using Brief, Low Energy, Electric-Stimulation to Increase Uterine Tone After Cesarean Delivery
Abstract

PI: Daniel Kingsbury, MD
STUDY: A phase 3 multi-center, open-label study to evaluate the pharmacokinetics, efficacy and safety of abatacept administered subcutaneously in children and adolescents with active polyarticular juvenile idiopathic arthritis (pJIA) and inadequate response to biologic or non-biologic disease modifying anti-rheumatic drugs (DMARDS).
Abstract

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Publications

Recent journal articles by Legacy researchers, clinicians and other professional staff.

Bell RB, Markiewicz MR, Dierks EJ, Gregoire CE, Rader A.
Thin serial step sectioning of sentinel lymph node biopsy specimen may not be necessary to accurately stage the neck in oral squamous cell carcinoma.
J Oral Maxillofac Surg. 2013 Jul;71(7):1268-77.

Attending Surgeon, Trauma Service/Oral and Maxillofacial Surgery Service, Legacy Emanuel Medical Center, Portland, OR;
Abstract

Bennett WM.
Images in clinical medicine. Torus palatinus.
N Engl J Med. 2013 Apr 11;368(15):1434.

Legacy Good Samaritan Hospital, Portland, OR, USA.
No abstract

Boison D.
Adenosine kinase: exploitation for therapeutic gain.
Pharmacol Rev. 2013 Apr 16;65(3):906-43.

Legacy Research Institute, 1225 NE 2nd Ave, Portland, OR 97202.
Abstract

Boison D.
Glowing feet control the blood of seizures.
Epilepsy Curr. 2013 May;13(3):122-3.

RS Dow Neurobiology Labs, Legacy Research Institute, Portland, OR
No abstract

Boison D, Sandau US, Ruskin DN, Kawamura M Jr, Masino SA.
Homeostatic control of brain function - new approaches to understand epileptogenesis.
Front Cell Neurosci. 2013 Jul 16;7:109.

Robert Stone Dow Neurobiology Laboratories, Legacy Research Institute Portland, OR, USA.
Abstract

Chandran R, Gardiner SK, Smith SD, Spurgeon SE.
Improved survival in hairy cell leukaemia over three decades: a SEER database analysis of prognostic factors.
Br J Haematol. 2013 Jul 24. doi: 10.1111/bjh.12490. [Epub ahead of print]

Legacy Health, Vancouver, WA, USA.
No abstract

Cull G, Burgoyne CF, Fortune B, Wang L.
Longitudinal Hemodynamic Changes within the Optic Nerve Head in Experimental Glaucoma.
Invest Ophthalmol Vis Sci. 2013 Jun 4. [Epub ahead of print]

Devers Eye Institute, Legacy Research Institute, Portland, OR, United States.
Abstract

Fortune B, Burgoyne CF, Cull G, Reynaud J, Wang L.
Onset and Progression of Peripapillary Retinal Nerve Fiber Layer (RNFL) Retardance Changes Occur Earlier Than RNFL Thickness Changes in Experimental Glaucoma.
Invest Ophthalmol Vis Sci. 2013 Aug 21;54(8):5653-61.

Discoveries in Sight Research Laboratories, Devers Eye Institute and Legacy Research Institute, Legacy Health, Portland, Oregon.
Abstract

Gardiner SK, Demirel S, Gordon MO, Kass MA; Ocular Hypertension Treatment Study Group.
Seasonal changes in visual field sensitivity and intraocular pressure in the ocular hypertension treatment study.
Ophthalmology. 2013 Apr;120(4):724-30.

Discoveries in Sight Laboratories, Devers Eye Institute, Legacy Research Institute, Legacy Health, Portland, Oregon.
Abstract

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Legacy Emanuel Medical Center, 2801 N. Gantenbein Ave. MOB No. 130, Portland, OR 97227, USA.
Abstract

Hegsted D, Gritsiouk Y, Schlesinger P, Gardiner S, Dean Gubler K.
Utility of the risk assessment profile for risk stratification of venous thrombotic events for trauma patients.

Am J Surg. 2013 May;205(5):517-20.

Legacy Emanuel Medical Center Trauma Services, 2801 N Gantenbein Ave, MOB2 130, Portland, OR 97227, USA.
Abstract

Hershman DL, Unger JM, Crew KD, Minasian LM, Awad D, Moinpour CM, **Hansen L**, Lew DL, Greenlee H, Fehrenbacher L, Wade JL 3rd, Wong SF, Hortobagyi GN, Meyskens FL, Albain KS.
Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy.
J Clin Oncol. 2013 Jul 10;31(20):2627-33. doi: 10.1200/JCO.2012.44.8738. Epub 2013 Jun 3.

Legacy Good Samaritan Hospital, Portland, OR
Abstract

Huston RK, Markell AM, McCulley EA, Marcus MJ, Cohen HS.
Computer Programming: Quality and Safety for Neonatal Parenteral Nutrition Orders.
Nutr Clin Pract. 2013 Aug;28(4):515-21.

Randall Children's Hospital at Legacy Emanuel, Portland, Oregon.
Abstract

Lloyd MJ, Mansberger SL, Fortune BA, Nguyen H, Torres R, Demirel S, Gardiner SK, Johnson CA, Cioffi GA.
Features of optic disc progression in patients with ocular hypertension and early glaucoma.
J Glaucoma. 2013 Jun-Jul;22(5):343-8.

Devers Eye Institute, Portland, OR.
Abstract

Metcalf KB, Michaels AJ, Edlich RF, Long WB.
Extracorporeal Membrane Oxygenation Can Provide Cardiopulmonary Support during Bronchoscopic Clearance of Airways after Sand Aspiration.
Emerg Med. 2013 Sep;45(3):380-3.

Legacy Emanuel Shock Trauma Center, Portland, Oregon.
Abstract

Michaels AJ, Hill JG, Long WB, Sperley BP, Young BP, Park PK, Rycus PT, Bartlett RH.
Reducing time on for extra-corporeal membrane oxygenation for adults with H1N1 pneumonia with the use of the Volume Diffusive Respirator.
Am J Surg. 2013 May;205(5):500-4.

Legacy Emanuel Medical Center, Portland, OR, USA;. Electronic address: amichael@lhs.org.
Abstract

Michaels AJ, Hill JG, Long WB, Young BP, Sperley BP, Shanks TR, Morgan LJ.
Adult refractory hypoxemic acute respiratory distress syndrome treated with extracorporeal membrane oxygenation: the role of a regional referral center.
Am J Surg. 2013 May;205(5):492-9.

Legacy Emanuel Medical Center, Portland, OR, USA.
Abstract

Michaels AJ, Hill JG, Bliss D, Sperley BP, Young BP, Quint P, Shanks TR, Dalthorp J, Long WB, Morgan LJ.
Pandemic flu and the sudden demand for ECMO resources: A mature trauma program can provide surge capacity in acute critical care crises.
J Trauma Acute Care Surg. 2013 Jun;74(6):1493-7.

From the ECMO and Trauma Programs at Legacy Emanuel Health Center, Portland Oregon.
Abstract

Pathak M, Demirel S, Gardiner SK.
Nonlinear, multilevel mixed-effects approach for modeling longitudinal standard automated perimetry data in glaucoma.
Invest Ophthalmol Vis Sci. 2013 Aug 15;54(8):5505-13.

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Abstract

Shum J, Markiewicz MR, Park E, Bui T, Lubek J, Bryan Bell R, Dierks EJ.
Low Prealbumin Level Is a Risk Factor for Microvascular Free Flap Failure.
J Oral Maxillofac Surg. 2013 Aug 1. [Epub ahead of print]

Legacy Emanuel Medical Center, Portland, OR.
Abstract

Terry MA, Straiko MD, Goshe JM, Shamie N, Shah A, Alqudah AA, Davis-Boozer D.
Endothelial keratoplasty: prospective, randomized, masked clinical trial comparing an injector with forceps for tissue insertion.
Am J Ophthalmol. 2013 Jul;156(1):61-68.

Devers Eye Institute, Portland, Oregon; Lions VisionGift Research Laboratory, Portland, Oregon.
Abstract

Wackym PA.
Response to "Re: Rapid cVEMP and oVEMP Responses Elicited by a Novel Head Striker and Recording Device".
Otol Neurotol. 2013 Jun;34(4):779-80.

Ear and Skull Base Center, Legacy Research Institute Vice President of Research, Legacy Health Portland, Oregon
No Abstract

Williams-Karnesky RL, Sandau US, Lusardi TA, Lytle NK, Farrell JM, Pritchard EM, Kaplan DL, Boison D.
Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis.
J Clin Invest. 2013 Aug 1;123(8):3552-63. Epub 2013 Jul 25.

RS Dow Neurobiology Labs, Legacy Research Institute, Portland, OR
Abstract

Yee BK, Singer P.
A conceptual and practical guide to the behavioural evaluation of animal models of the symptomatology and therapy of schizophrenia.
Cell Tissue Res. 2013 Apr 12. [Epub ahead of print]

Robert Stone Dow Neurobiology Laboratories, Legacy Research Institute, 1225 NE Second Avenue, Portland, OR 97232, USA.
Abstract

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IRB Approvals (expanded)

PI: Michael R Parsons, MD
STUDY: A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneious canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP
Canakinumab is a human monoclonal antibody targeted at interleukin-1 beta and has been FDA approved for auto-inflammatory syndromes. The purpose of this trial is to test the hypothesis that canakinumab treatment of patients with MI at least one month prior to study entry with elevated hsCRP will prevent recurrent cardiovascular events. A secondary hypothesis, that canakinumab treatment in patients with prior MI and pre-diabetes will prevent new onset diabetes will also be tested. The primary objective of this clinical trial is to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular disease events in a population of clinically post-MI patients with elevated hsCRP receiving standard of care follow-up. There are 1400 centers participating in 36 countries. Total enrollment nationally is 17,200, with 10-15 at Legacy.
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PI: Lin Wang, MD, PhD
STUDY: Noninvasive assessment of dyamic blood flow autoregulation in human optic nerve head with Laser Speckle techniques.
Glaucoma is one of the leading causes of blindness worldwide. One possible reason that glaucoma occurs is that the eye fails to maintain blood flow when blood pressure fluctuates, a loss of 'autoregulation'. In order to test whether this fluctuation fails in glaucoma patients, there needs to be data about how much the blood flow will be altered in a normal person within a given range of blood pressure changes. This study will determine the normal range and begin building a normal range database. Blood flow will be measured by an optically-based device. This study will take place at Legacy Health only with 15 participants expected to be involved.
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PI: Fawn M Wolf, MD
STUDY: Evaluation of Metabolic Outcomes and Safety of Hylenex recombinant (human hyaluronidase injection) used as a Preadministration Infusion Site Treatment in

Subjects with Type 1 Diabetes using Continuous Subcutaneous Insulin Infusion.
Hylenex recombinant is approved by the FDA and helps the body absorb and circulate injectable drugs. In this study, two formulations will be used: the commercial drug as well as a pre-commercial drug that is investigational. Previous clinical studies of insulin co-administered with Hylenex have demonstrated insulin pharmacokinetics that better mimic the natural insulin response to a mean in healthy individuals. Subjects for this study will already be using rapid acting insulin analog for their diabetes delivered by means of a continuous subcutaneous insulin infusion (CSII). The purposed of this study is to gain additional information about the combination of Hylenex and CSII. Approximately 400 subjects will be in the study, with 10-15 subjects from Legacy Health.
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PI: W. Kenneth Ward, MD
STUDY: Sensor-controlled insulin and glucagon delivery in subjects with Type 1 diabetes: testing of an automated system in a supervised outpatient setting.
Good diabetes control decreases the frequency of low blood sugar episodes and reduces the chances of developing diabetes complications. The objectives of this outpatient research study are (1) to assess the ability of this automated system to be operated by a subject with limited professional oversight; (2) to assess whether the new devices will reduce the frequency of hardware and data communication lapses seen in the previous system; and (3) to measure the degree of glucose control achievable with this automated system. The system will adjust blood glucose by administering insulin and glucagon. Each subject will have four devices placed on his/her abdomen: two Omnipod insulin pumps, one for delivering insulin and one for delivering glucagon, and two Dexcom G4 glucose sensors for measuring glucose. The two sensors will feed glucose data into a Motorola smart phone master controller, which will calculate the correct amount of insulin or glucagon to deliver. The system will then send the command to correct the Omnipod. These studies will be carried out in a hotel setting for a 28-hour outpatient study. A study physician and technician will be in the hotel during each study to monitor the study via a cloud-based data communication system. It is anticipated that 22 subjects will participate in this study.
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PI: Harvey Carp, M.D.
STUDY: New Treatment for Drug Resistant, Post-Partum Hemorrhage: Further Studies Using Brief, Low Energy, Electric-Stimulation to Increase Uterine Tone After Cesarean Delivery
After childbirth the uterus must contract to control bleeding. Potent drugs may need to be given to contract the uterus, and these drugs may produce side effects. In some cases bleeding is drug-resistant and emergency surgery is needed to remove the uterus. A previous study showed that an electric muscle stimulator attached to the uterus after caesarean delivery was able to increase uterine tone. The study population will consist of 10 healthy women undergoing elective caesarean delivery and choosing spinal anesthesia. The study will take place in the operating room after caesarean delivery. The obstetrician will place sterile electric muscle stimulator electrodes on the surface of the uterus and insert a pressure monitor into the uterus, through the uterine incision made to deliver the baby. After a one minute baseline period, the stimulator will be activated by the PI and tested for two minutes, for its effect on uterine contraction. This proposal will determine the safety and efficacy of an electric stimulator adjusted to maximally contract the uterus, under normal conditions. These results will form the basis for future studies, designed to test the ability of an electric stimulator to prevent blood

loss after childbirth.
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PI: Daniel Kingsbury, MD
STUDY: A phase 3 multi-center, open-label study to evaluate the pharmacokinetics, efficacy and safety of abatacept administered subcutaneously in children and adolescents with active polyarticular juvenile idiopathic arthritis (pJIA) and inadequate response to biologic or non-biologic disease modifying anti-rheumatic drugs (DMARDS).
The study design will be open-label to assess pharmacokinetics with no formal hypothesis testing. There will be two cohorts of subjects with active pJIA: one will be between the ages of 2-5 (approximately 30) and the other will be between 6-17 (approximately 160). The primary analysis will focus on the 6-17 year old cohort upon completion of an initial 4 month treatment period to evaluate pharmacokinetics, safety, and efficacy. Subjects from both cohorts who complete the short term period will be given the option to enter a 20 month extension period where they continue to receive weekly subcutaneous abatacept injections. Subjects who enter the extension as non-responders will have the opportunity to be treated with subcutaneous abatacept for an additional 3 months.
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Publications (expanded)

Bell RB, Markiewicz MR, Dierks EJ, Gregoire CE, Rader A.
Thin serial step sectioning of sentinel lymph node biopsy specimen may not be necessary to accurately stage the neck in oral squamous cell carcinoma.
J Oral Maxillofac Surg. 2013 Jul;71(7):1268-77.

Attending Surgeon, Trauma Service/Oral and Maxillofacial Surgery Service, Legacy Emanuel Medical Center, Portland, OR;

PURPOSE: The purpose of this study was to assess the predictability of sentinel lymph node biopsy (SNB) for oral squamous cell carcinoma (OSCC) when pathologic processing is performed without serial step sectioning. MATERIALS AND METHODS: We prospectively enrolled 36 patients with T1 or T2 cN0 OSCC into this institutional review board-approved prospective cohort study, and they underwent gamma probe-guided SNB in addition to selective neck dissection. The rate of patients with negative SNB results whose neck dissection was also negative for metastasis (negative predictive value) was the primary endpoint. RESULTS: Of the 28 patients whose sentinel lymph nodes were found to be pathologically and clinically node negative by routine hematoxylin-eosin stain and immunohistochemistry, 27 were found to have no other pathologically positive nodes, corresponding to a negative predictive value of 96%. CONCLUSION: The results of this study suggest that SNB performed without the use of thin serial step sectioning may accurately predict neck stage in OSCC.
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Boison D.
Adenosine kinase: exploitation for therapeutic gain.

Pharmacol Rev. 2013 Apr 16;65(3):906-43.

Legacy Research Institute, 1225 NE 2nd Ave, Portland, OR 97202.

Adenosine kinase (ADK; EC 2.7.1.20) is an evolutionarily conserved phosphotransferase that converts the purine ribonucleoside adenosine into 5'-adenosine-monophosphate. This enzymatic reaction plays a fundamental role in determining the tone of adenosine, which fulfills essential functions as a homeostatic and metabolic regulator in all living systems. Adenosine not only activates specific signaling pathways by activation of four types of adenosine receptors but it is also a primordial metabolite and regulator of biochemical enzyme reactions that couple to bioenergetic and epigenetic functions. By regulating adenosine, ADK can thus be identified as an upstream regulator of complex homeostatic and metabolic networks. Not surprisingly, ADK dysfunction is involved in several pathologies, including diabetes, epilepsy, and cancer. Consequently, ADK emerges as a rational therapeutic target, and adenosine-regulating drugs have been tested extensively. In recent attempts to improve specificity of treatment, localized therapies have been developed to augment adenosine signaling at sites of injury or pathology; those approaches include transplantation of stem cells with deletions of ADK or the use of gene therapy vectors to downregulate ADK expression. More recently, the first human mutations in ADK have been described, and novel findings suggest an unexpected role of ADK in a wider range of pathologies. ADK-regulating strategies thus represent innovative therapeutic opportunities to reconstruct network homeostasis in a multitude of conditions. This review will provide a comprehensive overview of the genetics, biochemistry, and pharmacology of ADK and will then focus on pathologies and therapeutic interventions. Challenges to translate ADK-based therapies into clinical use will be discussed critically.
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Boison D, Sandau US, Ruskin DN, Kawamura M Jr, Masino SA.
Homeostatic control of brain function - new approaches to understand epileptogenesis.
Front Cell Neurosci. 2013 Jul 16;7:109.

Robert Stone Dow Neurobiology Laboratories, Legacy Research Institute Portland, OR, USA.

Neuronal excitability of the brain and ongoing homeostasis depend not only on intrinsic neuronal properties, but also on external environmental factors; together these determine the functionality of neuronal networks. Homeostatic factors become critically important during epileptogenesis, a process that involves complex disruption of self-regulatory mechanisms. Here we focus on the bioenergetic homeostatic network regulator adenosine, a purine nucleoside whose availability is largely regulated by astrocytes. Endogenous adenosine modulates complex network function through multiple mechanisms including adenosine receptor-mediated pathways, mitochondrial bioenergetics, and adenosine receptor-independent changes to the epigenome. Accumulating evidence from our laboratories shows that disruption of adenosine homeostasis plays a major role in epileptogenesis. Conversely, we have found that reconstruction of adenosine's homeostatic functions provides new hope for the prevention of epileptogenesis. We will discuss how adenosine-based therapeutic approaches may interfere with epileptogenesis on an epigenetic level, and how dietary interventions can be used to restore network homeostasis in the brain. We conclude that reconstruction of homeostatic functions in the brain offers a new conceptual advance for the treatment of neurological conditions which goes far beyond current target-centric treatment approaches.
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Cull G, Burgoyne CF, Fortune B, Wang L.
Longitudinal Hemodynamic Changes within the Optic Nerve Head in Experimental Glaucoma.
Invest Ophthalmol Vis Sci. 2013 Jun 4. [Epub ahead of print]

Devers Eye Institute, Legacy Research Institute, Portland, OR, United States.

PURPOSE: To characterize longitudinal changes in basal blood flow (BF) of the optic nerve head (ONH) during progression of structural damage in experimental glaucoma (EG). METHODS: Unilateral elevation of intraocular pressure (IOP) was induced in 15 adult rhesus macaques by laser treatment to the trabecular meshwork. Prior to and after laser, retinal nerve fiber layer thickness (RNFLT) and ONH BF were measured biweekly by spectral-domain optical coherence tomography and a laser speckle flowgraphy device (LSFG), respectively. RESULTS: Average post-laser IOP was 20.2 ± 5.9 mm Hg in EG eyes and 12.3 ± 2.6 mm Hg in control eyes ($P<0.0001$). Longitudinal changes in basal ONH BF were strongly associated with changes in RNFLT as EG progressed from early through moderately advanced stages of damage, with Pearson correlation coefficients ranging from 0.64 to 0.97 (average = 0.81) and an average slope of 1.0. During early-stage EG (RNFLT loss <10%) basal ONH BF was mildly increased (9% ± 10%, $P=0.004$) relative to baseline and compared with fellow controls ($P=0.02$). Basal ONH BF declined continuously throughout subsequent stages in EG eyes reaching 25.0% ± 9.6% ($P<0.0001$) below baseline at the final stage studied (RNFLT loss >40%). In fellow control eyes there was no significant change in basal ONH BF over time ($P=0.27$). CONCLUSIONS: In EG based on chronic mild-to-moderate IOP elevation, a two-phase pattern of ONH BF alteration was observed. ONH BF increased during the earliest stage (while RNFLT was within 10% of baseline) followed by a linear decline that was strongly correlated with loss of RNFLT.
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Fortune B, Burgoyne CF, Cull G, Reynaud J, Wang L.
Onset and Progression of Peripapillary Retinal Nerve Fiber Layer (RNFL) Retardance Changes Occur Earlier Than RNFL Thickness Changes in Experimental Glaucoma.
Invest Ophthalmol Vis Sci. 2013 Aug 21;54(8):5653-61.

Discoveries in Sight Research Laboratories, Devers Eye Institute and Legacy Research Institute, Legacy Health, Portland, Oregon.

PURPOSE: Longitudinal measurements of peripapillary RNFL thickness and retardance were compared in terms of time to reach onset of damage and time to reach a specific progression endpoint. METHODS: A total of 41 rhesus macaques with unilateral experimental glaucoma (EG) each had three or more weekly baseline measurements in both eyes of peripapillary RNFL thickness (RNFLT) and retardance. Laser photocoagulation was then applied to the trabecular meshwork of one eye to induce chronic elevation of intraocular pressure and weekly imaging continued. Pairwise differences between baseline observations were sampled by bootstrapping to determine the 95% confidence limits of each measurement's repeatability. The first two sequential measurements below the lower confidence limit defined the endpoint for each parameter. Segmented linear and exponential decay functions were fit to each RNFL-versus-time series to determine the time to damage onset. RESULTS: In all, 29 (71%) of the EG eyes reached endpoint by RNFL retardance and 25 (61%) reached endpoint by RNFLT. In total, 33 (80%) reached endpoint by at least one of the RNFL parameters and 21 (51%) reached endpoint by both RNFL parameters. Of the 33 EG eyes reaching any endpoint, a larger proportion reached endpoint first by retardance (n = 26, 79%) than did by RNFLT (n = 7, 21%; $P =0.002$). Survival analysis indicated a shorter time to reach endpoint by retardance than by RNFLT ($P < 0.001$). Of the 21 EG eyes that reached endpoint by both measures, the median duration to endpoint was 120 days for retardance and 223 days for RNFLT ($P = 0.003$, Wilcoxon test). The time to onset was faster for retardance than that for RNFLT based on either segmented fits (by 31 days; $P =0.008$, average $R(2) = 0.89$) or exponential fits (by 102 days; $P = 0.01$, average $R(2) = 0.89$).CONCLUSIONS: The onset of progressive loss of RNFL retardance occurs earlier than the onset of RNFL thinning. Endpoints of progressive loss from baseline also occurred more frequently and earlier for RNFL retardance as compared with RNFLT.
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Gardiner SK, Demirel S, Gordon MO, Kass MA; Ocular Hypertension Treatment Study Group.
Seasonal changes in visual field sensitivity and intraocular pressure in the ocular hypertension treatment study.

Ophthalmology. 2013 Apr;120(4):724-30.

Discoveries in Sight Laboratories, Devers Eye Institute, Legacy Research Institute, Legacy Health, Portland, Oregon. Electronic address: sgardiner@deverseye.org.

PURPOSE: Longitudinal testing plays a key role in glaucoma management. Variability between visits hampers the ability to monitor progression. It has previously been shown that average intraocular pressure (IOP) exhibits seasonal fluctuations. This study examines whether visual field sensitivity also exhibits seasonal fluctuations and seeks to determine whether such fluctuations are correlated to seasonal IOP effects. DESIGN: Comparative case series. PARTICIPANTS: A total of 33 873 visits by 1636 participants enrolled in the Ocular Hypertension Treatment Study. Participants were split into 6 geographic zones according to the prevailing climate in their location. TESTING: At each visit, standard automated perimetry was conducted on each eye, and IOP was measured. MAIN OUTCOME MEASURES: Mixed effects regression models were formed to look for sinusoidal periodic effects on the change in perimetric mean deviation since the last visit (ΔMD) and on IOP, both overall and within each zone. RESULTS: When all the data were included, a significant seasonal effect on ΔMD was found with magnitude 0.06 dB, peaking in February ($P < 0.001$). Five of the 6 geographic zones exhibited significant seasonal effects on ΔMD, peaking between January and April, with magnitudes ranging from 0.04 dB ($P = 0.049$) to 0.21 dB ($P < 0.001$). Zones with greater climactic variation showed larger seasonal effects on ΔMD. All 6 zones exhibited a seasonal effect on IOP, peaking in January or February, with magnitudes ranging from 0.14 to 0.39 mmHg ($P \leq 0.02$ in all cases). However, there was no evidence of a significant association between the magnitudes or dates of peaks of the 2 seasonal effects. CONCLUSIONS: The mean deviation was significantly higher in winter than in summer. There is no evidence of an association with seasonal IOP fluctuations. The cause of the seasonal effect on visual field sensitivity is unknown. These findings may help shed light on the glaucomatous disease process and aid efforts to reduce test-retest variability. FINANCIAL DISCLOSURE(S): The author(s) have no proprietary or commercial interest in any materials discussed in this article.
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Gritsiouk Y, Hegsted D, Gardiner S, Merriman L, Dean Gubler K.
Use of volunteer student abstractors for a retrospective cohort analysis: a study of inter-rater reliability.
Am J Surg. 2013 May;205(5):552-6.

Legacy Emanuel Medical Center, 2801 N. Gantenbein Ave. MOB No. 130, Portland, OR 97227, USA.

BACKGROUND: Little is known about the reliability of data collected by abstractors without professional medical training. This investigation sought to determine the level of agreement among untrained volunteer abstractors as part of a study to evaluate the risk assessment of venous thromboembolism in patients who have undergone trauma. METHODS: Forty-nine paper charts were chosen randomly from a volunteer-reviewed cohort of 2,339 and were compared with those of a single experienced abstractor. Inter-rater agreement was assessed using percent agreement, Cohen's kappa, and prevalence-adjusted bias-adjusted kappa (PABAK). RESULTS: Of the 71 data points, 28 had perfect agreement. The average agreement across all charts was 97%. Data with imperfect agreement had kappa values between .27 and .96 (mean, .75), with one additional value at zero even though it was associated with an agreement of 94%. PABAK values ranged from .67 to .98 (mean, .91), an average increase of .17 compared with kappa values. CONCLUSIONS: The performance of volunteers showed outstanding inter-rater reliability; however, limitations of interpretation can influence reliability.
Back

Hegsted D, Gritsiouk Y, Schlesinger P, Gardiner S, Dean Gubler K.
Utility of the risk assessment profile for risk stratification of venous thrombotic events for trauma patients.

Am J Surg. 2013 May;205(5):517-20.

Legacy Emanuel Medical Center Trauma Services, 2801 N Gantenbein Ave, MOB2 130, Portland, OR 97227, USA.

BACKGROUND: Trauma patients are at risk for the development of venous thromboembolism (VTE). The purpose of this study was to validate the Risk Assessment Profile (RAP) as a tool for stratifying the risk of VTE. METHODS: RAP scores were calculated in a retrospective cohort analysis for all trauma patients aged 13 years or older admitted in 2003 and 2006 and hospitalized longer than 48 hours. Association of RAP with VTE, sensitivity, specificity, and receiver operating characteristic curve were included in the analysis. RESULTS: Of 2,281 patients, deep vein thrombosis (DVT) developed in 239 (10.5%) and pulmonary embolism (PE) developed in 34 (1.5%). In moderate- and high-risk patients, the RAP had a sensitivity of .82 and a specificity of .57. Identification of VTE for high-risk patients had a sensitivity .15 and a specificity of .97. The incidence of VTE increased significantly with risk level regardless of mechanism of injury. CONCLUSIONS: The RAP score is highly associated with VTE in trauma patients regardless of mechanism of injury and is a valid risk assessment tool.
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Hershman DL, Unger JM, Crew KD, Minasian LM, Awad D, Moinpour CM, **Hansen L**, Lew DL, Greenlee H, Fehrenbacher L, Wade JL 3rd, Wong SF, Hortobagyi GN, Meyskens FL, Albain KS.
Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy.
J Clin Oncol. 2013 Jul 10;31(20):2627-33. doi: 10.1200/JCO.2012.44.8738. Epub 2013 Jun 3.

Legacy Good Samaritan Hospital, Portland, OR

PURPOSE Chemotherapy-induced peripheral neuropathy (CIPN) is common and leads to suboptimal treatment. Acetyl-L-carnitine (ALC) is a natural compound involved in neuronal protection. Studies have suggested ALC may be effective for the prevention and treatment of CIPN. PATIENTS AND METHODS A 24-week randomized double-blind trial comparing ALC (3,000 mg per day) with placebo in women undergoing adjuvant taxane-based chemotherapy was conducted. The primary objective was to determine if ALC prevents CIPN as measured by the 11-item neurotoxicity (NTX) component of the Functional Assessment of Cancer Therapy (FACT) -Taxane scale at 12 weeks. Secondary objectives included changes in 24-week end points, functional status (FACT-Trial Outcome Index [TOI]), fatigue (Functional Assessment of Chronic Illness Therapy [FACIT] -Fatigue), and NTX grade. Results A total of 409 patients were evaluable (208 received ALC; 201, placebo). In a multivariate linear regression, week-12 scores were 0.9 points lower (more CIPN) with ALC than placebo (95% CI, -2.2 to 0.4; P = .17), whereas week-24 scores were 1.8 points lower with ALC (95% CI, -3.2 to -0.4; P = .01). Patients receiving ALC were more likely to have a > 5-point decrease in FACT-NTX scores (38% v 28%; P = .05), and FACT-TOI scores were 3.5 points lower with ALC (P = .03). Grade 3 to 4 neurotoxicity was more frequent in the ALC arm (eight v one). No differences between arms were observed for FACIT-Fatigue or other toxicities. Serum carnitine level increased with ALC but remained stable with placebo. CONCLUSION There was no evidence that ALC affected CIPN at 12 weeks; however, ALC significantly increased CIPN by 24 weeks. This is the first study to our knowledge showing that a nutritional supplement increased CIPN. Patients should be discouraged from using supplements without proven efficacy.
Back

Huston RK, Markell AM, McCulley EA, Marcus MJ, Cohen HS.
Computer Programming: Quality and Safety for Neonatal Parenteral Nutrition Orders.
Nutr Clin Pract. 2013 Aug;28(4):515-21.

Randall Children's Hospital at Legacy Emanuel, Portland, Oregon.

Background: Computerized software programs reduce errors and increase consistency when ordering parenteral nutrition (PN). The purpose of this study was to evaluate the effectiveness of our computerized neonatal PN calculator ordering program in reducing errors and optimizing nutrient intake. Materials and Methods: This was a retrospective study of infants requiring PN during the first 2-3 weeks of life. Caloric, protein, calcium, and phosphorus intakes; days above and below amino acid (AA) goals; and PN ordering errors were recorded. Infants were divided into 3 groups by birth weight for analysis: ≤1000 g, 1001-1500 g, and >1500 g. Intakes and outcomes of infants before (2007) vs after (2009) implementation of the calculator for each group were compared. Results: There were no differences in caloric, protein, or phosphorus intakes in 2007 vs 2009 in any group. Mean protein intakes were 97%-99% of goal for ≤1000-g and 1001- to 1500-g infants in 2009 vs 87% of goal for each group in 2007. In 2007, 7.6 per 100 orders were above and 11.5 per 100 were below recommended AA intakes. Calcium intakes were higher in 2009 vs 2007 in ≤1000-g (46.6 ± 6.1 vs 39.5 ± 8.0 mg/kg/d, P < .001) and >1500-g infants (50.6 ± 7.4 vs 39.9 ± 8.3 mg/kg/d, P < .001). Ordering errors were reduced from 4.6 per 100 in 2007 to 0.1 per 100 in 2009. Conclusion: Our study reaffirms that computerized ordering systems can increase the quality and safety of neonatal PN orders. Calcium and AA intakes were optimized and ordering errors were minimized using the computer-based ordering program.
Back

Lloyd MJ, Mansberger SL, Fortune BA, Nguyen H, Torres R, Demirel S, Gardiner SK, Johnson CA, Cioffi GA.
Features of optic disc progression in patients with ocular hypertension and early glaucoma.
J Glaucoma. 2013 Jun-Jul;22(5):343-8.

Devers Eye Institute, Portland, OR.

PURPOSE: : To determine the clinical features of optic disc progression in patients with ocular hypertension and early glaucoma. PATIENTS: : A total of 336 eyes of 168 patients with ocular hypertension or early glaucoma. METHODS: : Two glaucoma specialists independently graded the baseline and most recent optic disc photographs for optic disc progression. Optic disc progression was defined as: new or increased neuroretinal rim thinning (2 or more clock hours), notching (1 clock hour or less of thinning of the neuroretinal rim), excavation (undermining of the neuroretinal rim or disc margin), and nerve fiber layer defect(s). They also determined the location of these changes. RESULTS: : Ninety-two of 336 eyes (27.4%) showed optic disc progression after a median of 6.1 years. Of those with progression, excavation occurred in 89% of eyes; rim thinning occurring in 54%; and notching occurring in 16%. Fifty-six percent (56%) had 2 or more features of progression. The inferotemporal quadrant was the most common location for progression, but more than 1 location of progression occurred in at least 30% of eyes with progression. CONCLUSIONS: : Optic disc progression occurred frequently in this cohort of ocular hypertension and early glaucoma patients. When evaluating the optic disc for glaucomatous progression, eye care providers should pay particular attention to increased excavation and neuroretinal rim thinning-especially in the inferotemporal quadrant.
Back

Metcalf KB, Michaels AJ, Edlich RF, Long WB.
Extracorporeal Membrane Oxygenation Can Provide Cardiopulmonary Support during Bronchoscopic Clearance of Airways after Sand Aspiration.
Emerg Med. 2013 Sep;45(3):380-3.

Legacy Emanuel Shock Trauma Center, Portland, Oregon.

BACKGROUND: Sand aspiration occurs in situations of cave-in burial and near-drowning. Sand in the tracheobronchial airways adheres to the mucosa and can cause tracheal and bronchial obstruction, which can be life-threatening even with intensive management. In previous case reports of airway obstruction caused by sand aspiration, fiber optic or rigid bronchoscopy has

been effective in removing loose sand, but removal of sand particles lodged in smaller airways has proven challenging and time-consuming. CASE REPORT: In this case report of sand aspiration with acute pulmonary failure, the use of extracorporeal membrane oxygenation for respiratory support allowed more effective removal of sand particles by rigid bronchoscopy and lavage with less patient compromise. CONCLUSION: Our case of sand aspiration is unique in that the patient presents with complex medical problems (mixed respiratory and metabolic acidosis), hypothermia, hypoxemia, and neoplastic conditions. The fact that she survived the sand aspiration and a long inter-hospital transport time (90 min) with inadequate ventilation and oxygenation without apparent ill effects suggests that the measures we took to resuscitate her and extract the sand from her airways were reasonable and appropriate.
Back

Michaels AJ, Hill JG, Long WB, Sperley BP, Young BP, Park PK, Rycus PT, Bartlett RH.
Reducing time on for extra-corporeal membrane oxygenation for adults with H1N1 pneumonia with the use of the Volume Diffusive Respirator.
Am J Surg. 2013 May;205(5):500-4.

Legacy Emanuel Medical Center, Portland, OR, USA;. Electronic address: amichael@lhs.org.

BACKGROUND: The investigators compared a series of adult survivors of severe H1N1 pneumonia treated with extracorporeal membrane oxygenation (ECMO) with members of the Extracorporeal Life Support Organization registry for patients with H1N1 with regard to ventilator management while on ECMO. METHODS: Adults who survived ECMO were compared regarding time on ECMO for those treated with the Volume Diffusive Respirator (VDR) or with conventional "lung rest." The VDR delivered 500 percussions/min, with tidal pressures of 24/12 cm H2O and a fraction of inspired oxygen of .4 at 15 beats/min. RESULTS: There were no differences between the study patients (n = 7) and the Extracorporeal Life Support Organization cohort (n = 150) regarding age, pre-ECMO ventilator days, pre-ECMO ratio of partial pressure of oxygen to fraction of inspired oxygen, or survival after lung recovery. Patients treated with VDR required ECMO support for a shorter duration (mean, 193.29 ± 35.71 vs 296.63 ± 18.17 hours; P = .029). CONCLUSIONS: These data suggest that the VDR enhanced pulmonary recovery from severe H1N1 pneumonia in adults. Shorter times on ECMO may improve the risk/benefit and cost/benefit ratios associated with ECMO care.
Back

Michaels AJ, Hill JG, Long WB, Young BP, Sperley BP, Shanks TR, Morgan LJ.
Adult refractory hypoxemic acute respiratory distress syndrome treated with extracorporeal membrane oxygenation: the role of a regional referral center.
Am J Surg. 2013 May;205(5):492-9.

Legacy Emanuel Medical Center, Portland, OR, USA. Electronic address: amichael@lhs.org.

BACKGROUND: The investigators present a series of adults with severe acute respiratory distress syndrome (ARDS) who were treated with extracorporeal membrane oxygenation (ECMO) at a regional referral center. METHODS: Patients with refractory hypoxic ARDS received ECMO until they recovered lung function or demonstrated futility. ECMO was initiated at the referring facility if necessary, and aggressive critical care was maintained throughout. RESULTS: ARDS due to multiple etiologies was managed with ECMO in 36 adults. The pre-ECMO ratio of partial pressure of oxygen to fraction of inspired oxygen was 48.3 ± 2.2. Regional facilities referred 89% of these patients, and 69% required ECMO for transport. The mean duration of ECMO was 7.1 ± .9 days for survivors, and the mean post-ECMO ratio of partial pressure of oxygen to fraction of inspired oxygen was 281.2 ± 11. ECMO was successfully weaned in 67% of patients, and 60% survived to discharge. CONCLUSIONS: ECMO provides support that prevents ventilator-induced lung injury while the lungs heal. The investigators present a series of 36 adults with refractory hypoxemic ARDS (ratio of partial pressure of oxygen to fraction of inspired oxygen <50) from 17 different facilities who, treated with ECMO at

a single referral center, had a 60% survival rate.
Back

Michaels AJ, Hill JG, Bliss D, Sperley BP, Young BP, Quint P, Shanks TR, Dalthorp J, Long WB, Morgan LJ.
Pandemic flu and the sudden demand for ECMO resources: A mature trauma program can provide surge capacity in acute critical care crises.
J Trauma Acute Care Surg. 2013 Jun;74(6):1493-7.

From the ECMO and Trauma Programs at Legacy Emanuel Health Center, Portland Oregon.

BACKGROUND: Patients with severe H1N1 pneumonia created a sudden demand for extracorporeal membrane oxygenation (ECMO) capacity. In a single referral center, the established procedures, protocols, and staff of the Level I trauma service were adapted to help manage this nontrauma critical care crisis. METHODS: When airway pressure release ventilation and high-frequency oscillator ventilation failed, we used standard ECMO circuits and the VDR-4 critical care ventilator. We cannulated patients percutaneously in the intensive care unit and transported them on ECMO. Trauma service resources included a mobile surgical transport team, direct to OR resuscitations, massive transfusion protocols, trauma performance improvement processes, trauma resuscitation nurses, in-house attending doctors, and experienced staff familiar with protocol-driven care. RESULTS: During an 84-day period, 15 patients with severe H1N1 pneumonia were treated with ECMO. All patients were referred; 10 were transported on ECMO. Patients were aged 34.4 ± 4.1 years (6-58 years); 47% were male, and they had been ventilated 3.5 ± 0.8 days. Pre-ECMO PaO2/FIO2 ratios were 62.3 ± 6.1; ECMO duration was 9.4 ± 1.3 days for survivors; and post-ECMO PaO2/FIO2 ratio was 295.0 ± 35.1. Recovery occurred in 67% and 60% survived to discharge. No patient died of lung failure. Surviving patients were discharged at their neurologic baseline. CONCLUSION: H1N1 created a severe public health challenge for referral centers with ECMO capability. The resources of our trauma service were adapted to this nontrauma critical care crisis without disruption of other hospital services. These H1N1 patients treated with ECMO had a 67% recovery rate and a 60% survival rate. All survivors were discharged to home. LEVEL OF EVIDENCE: Therapeutic/epidemiologic study, level V.
Back

Pathak M, Demirel S, Gardiner SK.
Nonlinear, multilevel mixed-effects approach for modeling longitudinal standard automated perimetry data in glaucoma.
Invest Ophthalmol Vis Sci. 2013 Aug 15;54(8):5505-13.

Devers Eye Institute, Legacy Research Institute, Legacy Health, Portland, Oregon.

PURPOSE: Ordinary least squares linear regression (OLSLR) analyses are inappropriate for performing trend analysis on repeatedly measured longitudinal data. This study examines multilevel linear mixed-effects (LME) and nonlinear mixed-effects (NLME) methods to model longitudinally collected perimetry data and determines whether NLME methods provide significant improvements over LME methods and OLSLR. METHODS: Models of LME and NLME (exponential, whereby the rate of change in sensitivity worsens over time) were examined with two levels of nesting (subject and eye within subject) to predict the mean deviation. Models were compared using analysis of variance or Akaike's information criterion and Bayesian information criterion, as appropriate. RESULTS: Nonlinear (exponential) models provided significantly better fits than linear models ($P < 0.0001$). Nonlinear fits markedly improved the validity of the model, as evidenced by the lack of significant autocorrelation, residuals that are closer to being normally distributed, and improved homogeneity. From the fitted exponential model, the rate of glaucomatous progression for an average subject of age 70 years was -0.07 decibels (dB) per year. Ten years later, the same eye would be deteriorating at -0.12 dB/y. CONCLUSIONS: Multilevel mixed-effects models provide better fits to the test data than OLSLR

by accounting for group effects and/or within-group correlation. However, the fitted LME model poorly tracks visual field (VF) change over time. An exponential model provides a significant improvement over linear models and more accurately tracks VF change over time in this cohort.
Back

Shum J, Markiewicz MR, Park E, Bui T, Lubek J, Bryan Bell R, Dierks EJ.
Low Prealbumin Level Is a Risk Factor for Microvascular Free Flap Failure.
J Oral Maxillofac Surg. 2013 Aug 1. [Epub ahead of print]

Legacy Emanuel Medical Center, Portland, OR.

PURPOSE: The purposes of this study were 1) to estimate and compare the 1-month survival rates of patients with acute malnutrition (low prealbumin level) and patients who are not malnourished (normal prealbumin level) and 2) to identify risk factors associated with microvascular free flap failure. MATERIALS AND METHODS: To address the research purposes, we designed a retrospective cohort study and enrolled a sample composed of patients who underwent head and neck microvascular reconstruction and had prealbumin levels measured in the perioperative period. The primary predictor variable was nutritional status (low vs normal prealbumin level). The primary outcome variable was flap survival. One-month survival rates were estimated by use of Kaplan-Meier survival analyses. Risk factors for free flap failure were identified by use of multivariate marginal Cox proportional hazards modeling. RESULTS: The sample was composed of 162 patients who underwent microvascular free tissue transfer during the study enrollment period. The 1-month survival estimates for patients who were and were not malnourished were 76.5% (95% confidence interval [CI], 48.8% to 90.5%) and 95.2% (95% CI, 90.1% to 97.7%), respectively (P = .002). In the adjusted Cox hazards proportions model, acute malnutrition was associated with a 4-fold increased risk of failure (P = .04) in comparison with those patients with a normal nutritional status. CONCLUSIONS: Acute malnutrition in patients undergoing microvascular free flap reconstruction in the head and neck region was associated with an increased risk for free flap failure.
Back

Terry MA, Straiko MD, Goshe JM, Shamie N, Shah A, Alqudah AA, Davis-Boozer D.
Endothelial keratoplasty: prospective, randomized, masked clinical trial comparing an injector with forceps for tissue insertion.
Am J Ophthalmol. 2013 Jul;156(1):61-68.

Devers Eye Institute, Portland, Oregon; Lions VisionGift Research Laboratory, Portland, Oregon.

PURPOSE: To compare the complications and outcomes of Descemet stripping automated endothelial keratoplasty (DSAEK) when the tissue is either folded and inserted with a forceps or inserted using a platform injector device without folding. DESIGN: Prospective, randomized, masked clinical trial. METHODS: DSAEK was performed in 100 eyes of 79 patients undergoing DSAEK surgery for Fuchs corneal dystrophy. Fifty eyes were randomized to have the donor tissue inserted with Charlie II insertion forceps (Bausch & Lomb Surgical) and 50 eyes were randomized to have the donor tissue inserted with the Neusidl Corneal Inserter (Fischer Surgical Inc). All other steps of the surgical procedure were exactly the same. Surgical problems, postoperative complications, and central endothelial cell density at 6 months were recorded and then measured by a masked observer. The study's main outcome measures were total central endothelial cell density and percentage of donor endothelial cell loss from before surgery to 6 months after surgery and rate of complications (graft dislocation and primary graft failure). RESULTS: No primary graft failures occurred in either group and only 1 dislocation occurred in the series (Neusidl group). One late failure occurred at 6 months (Neusidl group). There was no difference in the preoperative endothelial cell density between the Neusidl and forceps groups, but there was a higher percentage of cell loss with the Neusidl group (33%) than with the forceps group (25%) at 6 months (P = .017). CONCLUSIONS: The Neusidl Corneal Inserter yielded a low immediate complication rate for DSAEK surgery for novice and experienced surgeons. Although still at an acceptable level, short-term endothelial survival was significantly

worse after Neusidl tissue insertion than that after forceps tissue insertion.
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Williams-Karnesky RL, Sandau US, Lusardi TA, Lytle NK, Farrell JM, Pritchard EM, Kaplan DL, Boison D.
Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis.
J Clin Invest. 2013 Aug 1;123(8):3552-63. Epub 2013 Jul 25.

RS Dow Neurobiology Labs, Legacy Research Institute, Portland, OR

Epigenetic modifications, including changes in DNA methylation, lead to altered gene expression and thus may underlie epileptogenesis via induction of permanent changes in neuronal excitability. Therapies that could inhibit or reverse these changes may be highly effective in halting disease progression. Here we identify an epigenetic function of the brain's endogenous anticonvulsant adenosine, showing that this compound induces hypomethylation of DNA via biochemical interference with the transmethylation pathway. We show that inhibition of DNA methylation inhibited epileptogenesis in multiple seizure models. Using a rat model of temporal lobe epilepsy, we identified an increase in hippocampal DNA methylation, which correlates with increased DNA methyltransferase activity, disruption of adenosine homeostasis, and spontaneous recurrent seizures. Finally, we used bioengineered silk implants to deliver a defined dose of adenosine over 10 days to the brains of epileptic rats. This transient therapeutic intervention reversed the DNA hypermethylation seen in the epileptic brain, inhibited sprouting of mossy fibers in the hippocampus, and prevented the progression of epilepsy for at least 3 months. These data demonstrate that pathological changes in DNA methylation homeostasis may underlie epileptogenesis and reversal of these epigenetic changes with adenosine augmentation therapy may halt disease
progression.
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Yee BK, Singer P.
A conceptual and practical guide to the behavioural evaluation of animal models of the symptomatology and therapy of schizophrenia.
Cell Tissue Res. 2013 Apr 12. [Epub ahead of print]

Robert Stone Dow Neurobiology Laboratories, Legacy Research Institute, 1225 NE Second Avenue, Portland, OR 97232, USA.

Schizophrenia is a chronic debilitating brain disorder characterized by a complex set of perceptual and behavioural symptoms that severely disrupt and undermine the patient's psychological well-being and quality of life. Since the exact disease mechanisms remain essentially unknown, holistic animal models are indispensable tools for any serious investigation into the neurobiology of schizophrenia, including the search for remedies, prevention of the disease and possible biological markers. This review provides some practical advice to those confronted with the task of evaluating their animal models for relevance to schizophrenia, a task that inevitably involves behavioural tests with animals. To a novice, this challenge not only is a technical one but also entails attention to interpretative issues concerning validity and translational power. Here, we attempt to offer some guidance to help overcome these obstacles by drawing on our experience of diverse animal models of schizophrenia based on genetics, strain difference, brain lesions, pharmacological induction and early life developmental manipulations. The review pays equal emphasis to the general (theoretical) considerations of experimental design and the illustration of the problems related to critical test parameters and the data analysis of selected exemplar behavioural tests. Finally, the individual differences of behavioural expression in relevant tests observed in wild-type animals might offer an alternative approach in order to explore the mechanism of schizophrenia-related behavioural dysfunction at the molecular, cellular and structural levels, all of which are of more immediate relevance to cell and tissue research.

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