Dear Keck Colleagues,

I am pleased to present the second issue of the Keck Research Quarterly. In this issue, we have highlighted Amy Lee, PhD, one of our most prominent scientists at the Keck School of Medicine. Her groundbreaking research in GRP78 and GRP94 and cloning of GRP78 has provided the impetus for developing and testing therapeutics to treat cancer and other human diseases. We are also featuring one of our Core resources, the Transgenic/Knockout Mouse Core. This article describes two new state-of-the-art services being offered by the core. The Vice Dean of Research Corner discusses Enterprise-Wide Transformation of Clinical Research, a computer-based medical informatics and electronic patient records system spearheaded by the Southern California Clinical and Translational Science Institute at USC and Children’s Hospital Los Angeles.

Tom Buchanan, M.D.
Vice Dean for Research

FACULTY SPOTLIGHT

Amy S. Lee, PhD
Associate Director for Basic Research; Judy and Larry Freeman Cosmetic Chair; USC Norris Comprehensive Cancer Center; Professor of Biochemistry & Molecular Biology; Keck School of Medicine of USC

- BA 1970 Bacteriology & Immunology (Valedictorian) – UC Berkeley
- PhD 1975 Biology – California Institute of Technology (Robert Sinsheimer, PhD)
- Postdoctoral training: 1975-1977; Senior Research Associate: 1977-1979 – California Institute of Technology (Eric Davidson, PhD)

Dr. Lee’s major research focus is in the area of endoplasmic reticulum (ER) stress and, in particular, the ER chaperone proteins GRP78 and GRP94. Dr. Lee was the first to clone human GRP78 and elucidate its regulation and function. The GRPs play essential roles in cellular homeostasis, mammalian development, organ integrity as well as cancer progression and therapeutic resistance. Her laboratory also investigated the regulation and function of GRP94. Currently, she and her collaborators are developing and testing therapeutics targeting GRP78 for application into cancer and other human diseases.

Dr. Lee joined USC in 1979 and was the recipient of the American Cancer Society (ACS) Junior Faculty Research Award from 1980-1983 and the ACS Faculty Research Award from 1983-1988. Dr. Lee received the MERIT Award from the National Cancer Institute in 1988 for her leading research on the GRPs. In recognition of her pioneering work on ER stress and its impact on cell and cancer biology, she was elected Fellow of the American Association for the Advancement of Sciences (AAAS) in 2006. She was the recipient of the Chinese American Faculty Association of Southern California Achievement Award in 2008. Dr. Lee chaired a Major Symposium on the Unfolded Protein Response in Cancer at the American Association for Cancer Research (AACR) Annual Meeting in 2011. In 2012, Dr. Lee was the recipient of the USC Mellon Mentoring Award for mentoring of junior faculty members at USC and her commitment to the training mission of USC.

We asked Dr. Lee to answer a few questions about what influenced her decision to focus on her research area, her thoughts on future research and her role as Associate Director for Basic Research at USC Norris Comprehensive Cancer Center.

Your laboratory was first to clone Glucose Regulated Proteins GRP78 and GRP94. What led you to clone these particular proteins?

When I was a graduate student at Caltech, the ability to clone individual genes from mammalian cells ushered in a new era of molecular biology and I was fascinated by it. Thus, when I was...
What is the significance of these discoveries in cellular biology? It turns out GRP78 is no ordinary protein. In 1980, Hugh Pelham, PhD, of the Medical Research Council, UK, isolated an unusual cDNA clone containing a signal peptide, p78, when he was searching for a cellular heat shock protein family. Strikingly, the mature amino terminal sequence of GRP78 reported by us in 1984 matched the predicted sequence of p78, which Pelham further matched with the immunoglobulin heavy chain binding protein BIP, which functions as a chaperone protein. In 1988, Mary Jane Geering, PhD, and Joe Sambrook, PhD, of the University of Texas Southwestern Medical Center, further demonstrated that malfolded protein induced the synthesis of GRP78 and GRP94. Thus, the two lines of investigation, stress response and chaperone protein merged and in 1990, the term “unfolded protein response” or UPR was born.

The UPR is an intracellular quality control system that senses harmful malfolded protein accumulating in the ER and triggers transcription in the nucleus leading to a number of adaptive pathways for survival or when the stress is too severe, apoptotic death. The protective mechanisms of the UPR include increasing chaperone protein production and degrading the malfolded proteins. The UPR research area is of high significance in both health and disease, as the UPR can protect normal organs against proteotoxic stress, but can also be usurped by cancer cells, enabling them to thrive and overcome resistance to therapy. Now GRP78 is widely recognized as a benchmark of UPR, a multifunctional protein controlling not only the ER stress sensors but also a range of other pathways inside and outside the ER, and plays critical roles in the many facets of human diseases.

You started out looking for a novel gene regulation mechanism. Did you achieve that goal? Yes, and the impact is huge. First, we isolated the promoter of the GRP78 and GRP94 genes from different species and looked for conserved sequence motifs. After much hard work, we finally cracked the genetic code for their stress induction. In 1994, at a meeting in Kyoto, Kaoru Mori, PhD, of the JSPR Research Institute in Japan, and I announced, independently, the discovery of the ER stress inducible promoter element common to mammalian target genes. This was a gratifying moment considering that two laboratories, working continents apart, reached the same conclusion. This was a highly significant advancement in UPR research since this made it possible to work backwards and identify molecular pathways leading to their transcription and then, step by step, find the key players mediating the regulation.

Much of your research is in cancer. How did your influence your decision to focus in this area? As the UPR research field exploded in the 1990s, I decided that while in vitro studies can provide elegant and elegant readouts in a timely manner, the relevance of the UPR in human disease is largely unknown. My interest in cancer was sparked when Brian Henderson, MD, then the director of USC Norris, convinced me to move my laboratory there in 1993. Since the cancer center is interdisciplinary, the cross-fertilization of ideas with immunologists, pathologists, physician scientists and epidemiologists expanded my horizon beyond gene regulation.

What other areas of research have you collaborated and how have these collaborations advanced your own research? I have the good fortune to collaborate with many colleagues both inside and outside of USC to expand our research beyond cancer. Utilizing the traditional and conditional knockout mouse models for GRP78 and GRP94, created in our lab, we and USC colleagues Louis Dubau and David Hinton established an essential role of GRP78 in neuronal protection. Other participants in this collaboration was Richard Thompson on neuro-conditioning, Jeannie Chen on retinal degeneration, Gregor Adams and Si Ye Chen on hematopoietic stem cell biology, Reyhan Zhou and Zea Bork on lung fibrosis and elegant readouts in aging. We have also a long term and fruitful collaboration with Jason Kim, PhD, from the University of Massachusetts on understanding the role of GRP78 in diabetes, obesity and insulin resistance. Work from these collaborations and others in the field illustrate beautifully the yin and yang of GRP78 in human biology. Thus, while GRP78 inhibitors can be anti-cancer, upregulation of GRP78 could confer protection against neurological or metabolic disorders. On that front, we are excited that GRP78 has been recently chosen as a target for drug discovery in a joint effort between USC Norris and the Center for Regenerative Medicine and Stem Cell Research.

What advice would you give to junior faculty about being competitive in getting grant funding? For a grant to be funded in the current climate, you need novelty in the proposed ideas and high impact in your field and beyond. Grants that highlight unusual collaboration of diverse expertise (scientifically and/or technically) to break new ground in the field and can generate excitement. Focus like a laser on your key hypothesis and do not fall into the trap of being over-ambitious by being all over the map.
The core offers expert consultation on vector preparation, developmental biology and approaches to testing gene function in rats and mice. Maxson advises PIs on research strategies and Wu meets with research staff to discuss their orders.

b) BAC Transgenesis: The core offers BAC injection, which entails injecting large (up to several hundred KB) DNA fragments into zygotic nuclei.

c) Production of Gene Targeted Mice/Injection of ES cells into blastocysts: Clones (usually two) that have been demonstrated to have normal karyotypes are injected into blastocysts. If clones are from strain 129/sv ES cells, then they are injected into blastocysts from C57Bl/6 mice. If they are from C3H/He, then they are injected into C3H/He/F1-TyrC-s2/j mice. Pups are assessed for coat color chimera. Those found to be highly chimeric are returned to users for breeding to obtain germ line chimeras.

d) Production of Gene Knockout Rats: This service involves the injection of targeted ES cells into rat blastocysts, implantation of the injected blastocysts into pseudopregnant rats and maintenance of pups up to three weeks in the facility.

e) Genome Editing by means of CRISPR Technology: Type II bacterial clustered, regularly interspaced, palindromic repeats (CRISPR)-associated (Cas) system is a powerful tool for editing genomes. The system consists of the Cas9 nuclease and a single guide RNA (sgRNA). The guide RNA, 20 nucleotides in length, guides the Cas9 nuclease to the target sequence, where it introduces double-stranded breaks. These are repaired imperfectly by the process of non-homologous end joining. The sgRNA together with Cas9 (RNA or protein) are injected into a zygote. Alternatively, Cas9 is supplied by the zygote as the product of a transgene. Injection of a DNA fragment with homology to the sequences flanking the double stranded break can produce mutant alleles with inserts such as loxp sites. The Core injects the Cas9 protein and sgRNA into single-cell zygotes and implants the zygotes into recipient females.

Major Services, Technologies, Equipment and Expertise Provided

Consultation

The core offers expert consultation on vector preparation, developmental biology and approaches to testing gene function in rats and mice. Maxson advises PIs on research strategies and Wu meets with research staff to discuss their orders.

Ancillary Services

a) In Vitro Fertilization: Mouse strains are sometimes preserved as frozen sperm. Thus it is important to have the ability to regenerate such strains by in vitro fertilization. Females are superovulated by hormone injection and unfertilized eggs are collected and combined with sperm, which can be fresh or frozen, in a special buffer. Fertilized eggs are incubated overnight and several 2-cell embryos are implanted in pseudopregnant recipient females.

Clinical Trials Management System (CTMS)

USC and CHLA have purchased the clinical trials management system, OnCore, which is being deployed across USC and CHLA. OnCore will bring together data from multiple sources to help streamline the initiation, management, and financial accounting of clinical research studies. Keck Medicine CIO Joshua Lee is leading the implementation of OnCore, including the integration of multiple existing data sources and numerous business units with disparate and sometimes redundant processes. This team is assisted by the CIO of CHLA, TJ Malseed and by the Director of Sponsored Projects, Samantha Westcott, among others. As part of the project, current processes and workflows related to the life cycle of a clinical trial have been thoroughly examined and evaluated in order to optimize study management processes. In addition, our core team from USC and CHLA participated in immersion training in December. The next phase of training will expand to super users, followed by end-user training in the spring. Pilot studies are scheduled to commence in June and anticipate all new studies to begin enrolling with the new system starting in July 2015. With the addition of OnCore, there are also plans underway to integrate with the EHR systems in order for clinicians and investigators to be able to identify clinical trial opportunities for patients during their clinic visits. When OnCore is fully operational, it will provide a single point of access for managing the business and operational aspects of clinical trials across USC and CHLA.

From the moment of study inception, as feasibility and scientific merit are considered, through the budgeting and calendaring process, the system allows for both facilitated creation of protocols and the centralized tracking of progress of a study towards accrual. With easy-to-use tools to enroll participants and track their completion of the indicated protocol services, the study coordinators and principal investigators will have a more enhanced and at the same time more comprehensive clinical research experience. The ability to centrally monitor the enrollment of various trials will also result in more efficient use of research resources.

VICE DEAN OF RESEARCH CORNER

Enterprise-Wide Transformation of Clinical Research

Computer-based medical informatics and electronic patient records represent an enormous but largely untapped opportunity for research collaboration and coordination. USC and CHLA are implementing a comprehensive electronic infrastructure that will interact with our electronic health record (EHR) systems helping researchers to access clinical data from the EHRs for IRB-approved research. There are two main components to this infrastructure, which is being created with resources from the USC Office of the Provost, Keck Medical Center, Keck School of Medicine, the USC Clinical Trials Office, Children’s Hospital Los Angeles and the Southern California Clinical and Translational Science Institute.

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FACULTY GROWTH AT KECK SCHOOL OF MEDICINE OF USC

Prior to the purchase of the Keck Hospitals of USC, the number of full-time faculty at the Keck School of Medicine had remained fairly stable over the previous 10 years. Since that purchase in July 2009, however, the number of full-time faculty at the Keck School of Medicine has increased by 29%.

MANAGING YOUR RESEARCH FUNDING OPPORTUNITIES?

Are you currently looking for funding opportunities? For a listing of current extramural and intramural funding opportunities, please visit: http://www.usc.edu/schools/medicine/school/offices/research/funding.html

USC Office of Research has implemented a new simpler portal for submission of internal research proposals (http://uscapPLICATIONPORTAL.WEBSITES.COM/) including both external proposals that are institutionally limited and internal funding programs, such as Zumberge and the Collaboration Fund. As in the past, these proposals will be all listed at http://research.usc.edu/funding.html.

KECK CORES

Continued from page 4
b) Rederivation of Transgenic and Knockout Lines: Investigators often wish to import mice that carry pathogens or have been kept in contaminated facilities. USC policies do not permit such mice to be maintained in USC Department of Animal Resources. The core sets up matings, removes fertilized eggs and transfers them into clean pseudopregnant foster mothers.

KSOm FACULTY NUMBERS (JANUARY 2015):

USC Full Time Faculty
Keck full time faculty
Total Keck Clinicians
Total Keck Research and Teaching Faculty
Total Keck Part Time Faculty

Department/Institute/Center     Cumulative Total Since Sept. 2014
Biochemistry and Molecular Biology     11
Cell and Neurobiology     1
Center for Stem Cell Regenerative Medicine     16
Department of Medicine     3
Dermatology     4
Emergency Medicine     2
Family Medicine     5
Institute for Genetic Medicine     5
Institute for Neuroimaging and Informatics     27
Molecular Microbiology and Immunology     33
Neurology & Neurosurgery     9
Norris Comprehensive Cancer Center     18
Ophthalmology     2
Orthopedics     2
Otolaryngology     10
Pathology     6
Physiology and Biophysics     2
Preventive Medicine     96
Psychiatry and Behavioral Science     3
Surgery     5
Urology     2
Zilkha Neurogenetic Institute     25
Grand Total     287

KECK QUARTERLY

Electronic Grant Submissions

On November 3, 2014, the Keck School of Medicine of USC went live with Kuali Coues (KC), the new USC grant and contract proposal submission system. Since the training period in August, the university has successfully logged and submitted 297 proposals through the KC system.

Electronically submitted 287 proposals through the KC system.

b) Rederivation of Transgenic and Knockout Lines: Investigators often wish to import mice that carry pathogens or have been kept in contaminated facilities. USC policies do not permit such mice to be maintained in USC Department of Animal Resources. The core sets up matings, removes fertilized eggs and transfers them into clean pseudopregnant foster mothers.

c) Cryopreservation of Blastocysts: The high cost of maintaining a strain that may be important for long-term research objectives, but is not being used at the present time, sometimes forces the investigator to eliminate mice that would otherwise be maintained. The core obtains 100-300 blastocysts from the strain to be preserved, freezes such blastocysts according to methods in use at the Jackson Laboratory, and stores them in liquid nitrogen. Strains that the core has successfully preserved include C57BL/6J, 129, B6D2F1, as well as mixed strains.

Education

The core is committed to educating and encouraging cancer investigators to use mouse and rat technology in their basic/translational research. It serves as a source of information about mouse husbandry, genotyping, genetics, and histopathology, providing advice to a large number of investigators.

Technology and Major Equipment

Microinjection Facility

The microinjection room consists of a 196 sq. ft. laboratory in the ZNI vivarium. The room has a large number of investigators.

Facility and staff training on grants.gov system-to-system grant proposal submissions.
Should I voluntarily cost share expenses on my grant? Can I charge computing devices? What research faculty should know about OMB A-81?

Effective December 26, 2014, a new federal guidance will go into effect eliminating the Office of Management and Budget’s (OMB) circulars A-21, A-110, and A-133. These circulars will be replaced by A-81, Uniform Administrative Requirements, Cost Principles and Audit Requirements for Federal Awards. The purpose of the guidance is to streamline administrative burdens, and to strengthen oversight of federal funds to reduce fraud, waste and abuse. A-81 applies to all new federal funding (new award, continuation awards, supplements, etc.) and may also apply to unobligated balances and liquidated obligations if specifically stated in the award document.

Where can I find the USC Dunn’s number or employer identification number for my grant application?

Investigators can find most institutional identification information needed for grant application on the following websites, including the address of the USC Department of Contracts and Grants Office, Congressional District and Federal Wide Assurances for Research Subjects. https://research.usc.edu/files/2014/04/General-Information-Page.pdf

SAVE THE DATE: TENURE TRACK FACULTY WORKSHOP

Annual Keck HSC Workshop for tenure track faculty will be held Thursday, February 26 from 3:30 p.m. – 5:00 p.m. in Harkness Seminar Room in the CSC Building (1GM). Tenure track faculty from the Keck School of Medicine, USC School of Pharmacy and Ostrow School of Dentistry are welcome. Senior faculty with experience in appointments and promotions will attend to provide one-on-one mentoring discussions.

OMB A-81 HIGHLIGHTS:

• Voluntary committed cost sharing is not expected and generally cannot be used as a factor during merit review.
• Direct charging of administrative and clerical salaries is appropriate if the salary is integral to the project, the individuals to be charged are specifically identified and included in the budget or have sponsor approval, and the salary is not also recovered as an indirect cost.
• Costs of materials and supplies, including the costs of computing devices, may be directly charged, as long as appropriately allocated.

Read more: http://oc.usc.edu/sites/oc.usc. edu/files/pdfs/Research-Compliance-Newsletter_Summer-2014.pdf

NEED GRANTS SUBMISSION HELP?

If you are looking for help with your budget or assembling grant sections, Janet Stoeckert, Director of Research Advancement, is available to assist you. Contact Janet at (213) 442-3598 or email stoecker@med.usc.edu.

CENTER FOR EXCELLENCE IN RESEARCH

SPRING 2015 WORKSHOPS AND COURSES

February
Mission Agency Funding...OHS, DOD, DOE, ED, EPA, FAA, FHWA, NASA, NDAA, NIST & USDA.

February 19, Noon – 2 p.m. HSC NML E Conference Room

Protecting Your Intellectual Property (SP).

February 25, Noon – 2:30 p.m., HSC NRT LG Room 203/204

Writing Persuasive Proposals...

February 26, March 12.

March

Pathways to Corporate Research Funding...

March 3, Noon – 1 p.m., LIPC CB 309 (Third Floor Conference Room)

April

Developing NIH Grant Applications...

April 2, Noon – 2 p.m., HSC NML E Conference Room

NIH Grants: Strategies to Get Funded...

April 23, Noon – 2 p.m., HSC NML W Conference Room

Funding your Clinical Programs and Projects...

April 24, 11:45 a.m. – 1:30 p.m., CHLA Saban Auditorium

Please check the CER website for workshop descriptions and additional offerings!

https://research.usc.edu/for-investigators/training/

RSVP (required): usccer@usc.edu

VICE DEAN OF RESEARCH CORNER

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Research Data Warehouse

To strengthen the cross-institutional research relationship between USC and CHLA, the SC CTSI is leading the development and implementation of a clinical data warehouse for research. The warehouse will aggregate information on demographics, diagnoses, medications, laboratory values, and imaging results from enterprise-wide EHRs into a single repository to allow the discovery, reuse and sharing of existing clinical data for research. The research data warehouse initiative will take advantage of the common Cerner Millennium EHR used by USC and CHLA and will make patient data accessible to appropriately approved researchers, who can explore the data to determine potential participant cohorts, recruit, and test hypotheses related to clinical care and health outcomes — powerful capabilities that leverage a dataset of this scale. Although full functionality to use re-identified data for recruitment will not be available until the last quarter of 2015, the ability to use de-identified data to project potential study cohorts is targeted for the spring of 2015. As part of the research data warehouse initiative, SC CTSI has created a collaborative working group with representatives from USC Offices of Research and Compliance, Keck Medicine of USC and CHLA. The data sharing agreements created by this group will provide a model to other collaborative ventures seeking to promote maximal inclusion of clinical data while still preserving patient confidentiality. As standards for the reuse of clinical data for research purposes are evolving, SC CTSI and its university compliance partners intend to remain at the forefront of ethical and compliant research conduct. Once the research data warehouse is implemented across USC and CHLA, the SC CTSI plans to expand these capabilities to the Los Angeles County Department of Health Services, which is also implementing a Cerner Millennium EHR. DHS leadership has been actively involved in and supportive of this project, which would greatly expand the ability of our faculty members to conduct clinical, health services, health outcomes and implementation research with the DHS.

These two enterprise-wide initiatives will greatly expand the commitment and capabilities of USC and CHLA in clinical research. Look forward to more information in these pages as the projects progress.
Robert Chow, MD, PhD, Professor of Physiology and Biophysics

Dr. Chow received his MD training at Brown and his PhD degree from the University of Pennsylvania. After postdoctoral training at the Max Planck Institute in Goettingen, Germany, he joined the faculty at the University of Edinburgh Medical School. He was recruited to the University of Southern California in 1999 and joined the faculty of the Department of Physiology and Biophysics as an associate professor on the tenure track with tenure awarded in 2004.

In his early career Dr. Chow became known as an impeccably trained leader in the study of insulin and neurotransmitter secretion. He became internationally known for his development of novel electrophysiology and cell imaging methods that have allowed him to significantly advance the field. For example, he pioneered the use of carbon fiber amperometry in the study of exocytosis from neuroendocrine cells. A series of his papers using this methodology, now considered classics in this area, are cited in every important paper in the field. Subsequent papers on the use of total internal reflection microscopy (TIRFM) are considered equally influential. More recently, his work with the small protein, complexin, has completely altered the understanding of the role of this protein in exocytosis and membrane fusion by clearly demonstrating its positive effect on membrane fusion. Complexin had previously been thought to play an inhibitory role in exocytosis.

David Conti, PhD, Professor of Preventive Medicine

Dr. Conti was recruited to the Keck School of Medicine in 2003 as an Assistant Professor of Preventive Medicine, and was promoted to Associate Professor and awarded tenure in 2009. Dr. Conti, a genetic epidemiologist, is an internationally recognized expert in Bayesian modelling and the integration and application of advanced statistical methods into molecular and genetic epidemiology to solve complex problems. One of the ways in which Dr. Conti has been influential in his field has been on how his work has centered on the improvement of statistical methods used in complex genome wide association studies (GWAS), where he has made important methodological contributions in the study of gene-environment interactions. Much of Dr. Conti’s work involves collaborations with investigators looking at the epidemiology of a number of clinically important problems such as smoking cessation, asthma, psychiatric disorders, lymphoma and cancers of the colon and prostate. Using these hierarchical models he has developed, he is able to more precisely distinguish between the relatively small number of true causal genetic variants and the millions of non-causal variants. Most recently, he has created a Genomics Analysis and Translation Center that along with his expansion of the USC Statistical Consultation and Research Center will make these novel analysis techniques available to investigators in multiple disciplines who are looking at potentially clinically important gene-environment interactions.

Richard Watanabe, PhD, Professor of Preventive Medicine

Dr. Watanabe was appointed as an Assistant Professor of Preventive Medicine at the Keck School of Medicine in 2001, and was promoted to Associate Professor and awarded tenure in 2006. As a statistical biologist with training and expertise in physiology, biostatistics and genetic epidemiology, Dr. Watanabe has been able to utilize this rare combination of skills to become an internationally recognized expert in type 2 diabetes and obesity and a major driving force in the design, conduct and analysis of high profile genome wide association studies (GWAS). As founding members of MAGIC (Meta-Analysis of Glucose and Insulin-related Traits Consortium), Dr. Watanabe’s group has been able to identify loci underlying fasting glucose and insulin, stimulated glucose levels and fasting proinsulin levels. In addition to his prominent role in consortia, Dr. Watanabe has made significant contributions in the understanding of gene-adiposity and gene-gene interactions, including the first demonstration of the role of adiposity in the variation of TCF7L2 and diabetes-related traits and the role of this genetic locus in gestational diabetes. Dr. Watanabe has also made significant contributions in the area of pharmacogenomics by demonstrating the association of several specific genetic variations with changes in diabetes-related traits following treatment with thiazolidinedione medications.
COME EXPERIENCE THE
NEWLY RENOVATED
EDMONDSO N FACULTY
CENTER.

The Edmonson Faculty Center is now open for extended meal periods, including breakfast, lunch and lounge. The center is also offering a hospitality dining card — a convenient payment method that replaces paper internal requisitions and is linked to your specific account. For more information and to sign up, visit the USCard office.

As a reminder, membership is not required to experience The Edmondson Faculty Center. Reservations can be made online at http://www.opentable.com/the-edmondson-faculty-center.