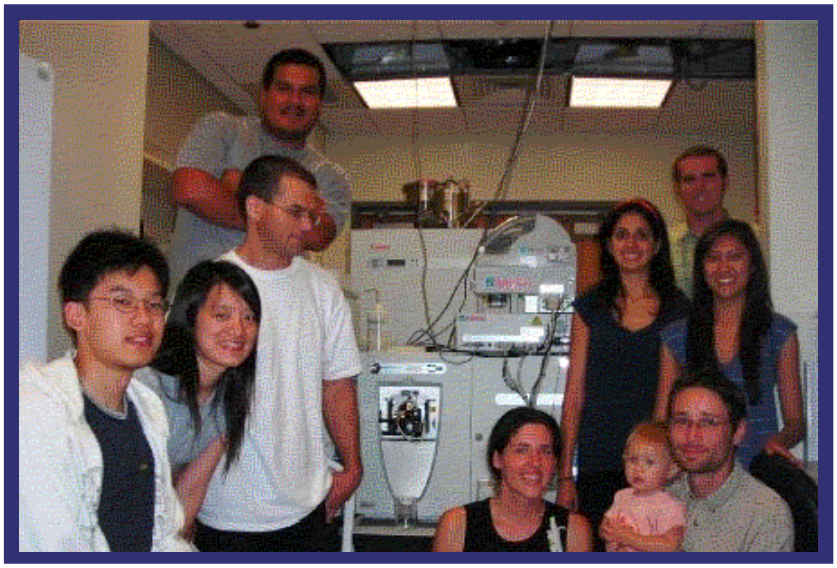
UNIVERSITY of CALIFORNIA, SAN DIEGO
SKAGGS SCHOOL of PHARMACY
and PHARMACEUTICAL SCIENCES

Summer 2007

Welcome Pieter Dorrestein

By Andrina Marshall, MBA

The Skaggs School of Pharmacy and Pharmaceutical Sciences would like to welcome Pieter C. Dorrestein, an Assistant Professor in the Skaggs School of Pharmacy and Pharmaceutical Sciences and the Departments of Pharmacology, Chemistry and Biochemistry at the University of California, San Diego. Pieter came to us from the University of Illinois at Champaign, Department of Chemistry.



Wei Zheng, Elaine Tsang, Dario Meluzzi, David Gonzalez, Kathleen Dorrestein, Tatiana Dorrestein, Pieter Dorrestein, Cindy Wu, Candie Bautista, Scott McDonnell (Sara Weitz not pictured).

He received his Bachelor of Science degree from Northern Arizona University (NAU) in 1998, his masters degree and Ph.D. in chemical biology from Cornell in 2001 and 2004. Following the completion of his Ph.D. program, Pieter became an NIH NRSA Kirschstein fellow at the University of Illinois where he learned protein mass spectrometry with Dr. Neil Kelleher, in a joint effort with the Walsh lab (Harvard Medical School), in order to elucidate biosynthetic aspects of natural products that have therapeutic value.

Pieter's current research projects involve the development of new mass spectrometry and chemical biology based approaches to study the biosynthesis, targets and functions of secondary metabolites. He extensively uses proteomic tools to harvest existing and publicly available genomic information to make new therapeutic discoveries and targets. One such project involves the development of mass spectrometry tools that will allow the mining microbial genome sequences for their ability to make protease inhibitors. In the past such inhibitors have found uses in HIV and cancer treatments and Pieter hopes that any of the newly discovered compounds will reveal additional targets.

Pieter views his research as "creating bridges between genomics, proteomics and natural products for the discovery of future therapeutic agents."

A second project involves joint efforts with Drs. Nizet and Dixon labs where they are looking at a class of gene clusters products

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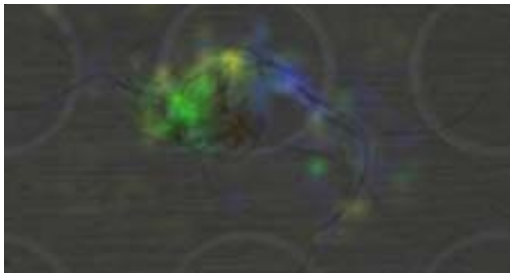


The above image is from the MALDI-imaging system. This image was produced via a joint project with the Gerwick lab in an attempt to localize the production of an anti-cancer agent in a cyanobacterial mat. Each color represent a different molecule produced by this culture.

responsible for the generation of a secondary metabolite required for invasive infections in a variety of bacteria such as Staph. Aureus (leading cause of hospital infections), Group A streptococci (cause of strep throath), and Clostridium botulinum. His primary focus is Clostridium botulinum, a bacteria sometimes present in honey, the bacteria creates a toxin that can cause botulism, the main reason why it is not recommended to give infants honey. He hopes to use mass spectrometry to elucidate the functional roles of a set of genes found on the genomes of these organisms. It is likely that these genes are involved in the biosynthesis of a secondary metabolite required for early on-set infection. In the long-term, together with the Drs. Dixon and Nizet labs they hope to evaluate the immunogenic properties of the secondary metabolites produced by these organisms. Such a response would be the first step towards the development of vaccines against these organisms.

Pieter's research endeavors are supported by graduate students, David Gonzalez, Dario Meluzzi, undergraduate students Candie Bautista, Elaine Tsang, Sara Weitz, Cindy Wu, Wei Zheng, and researcher, Scott McDonnell.. His lab uses two instruments that are "one of a kind" on the UCSD campus. The first is a Linear trap ion cyclotron resonance Fourier-transform mass spectrometer that is used to observe the biosynthesis of secondary metabolites as they are produced by microorganisms. The second is a MALDI-imaging system that localizes molecules in specific regions of tissues or cyanobacterial mats (see figure below). The continued development of a world-class proteomic and mass spectrometry capabilities in the Skaggs School of Pharmacy by the Dorrestein lab will ensure that the school will be at the forefront in the analytical capabilities for therapeutic discovery by creating bridges between genomics, proteomics and natural products for the discovery of future therapeutic agents.

Second-year student pharmacists will have the opportunity to learn from Pieter, who will be teaching this Fall in the Cell Biology/Biochemistry (CBB) course. He will provide instruction in the Biochemistry, Health and Disease section. Then in the future, Pieter plans to provide additional team-teaching support in the Pharmaceutical Chemistry courses taught to first-year student pharmacists.

Faculty News

Applied Pharmacoeconomic and Outcomes Research Forum

By Jan Hirsch, Ph.D.

The third Applied Pharmacoeconomic and Outcomes Research Forum was held May 14th at the UCSD Faculty Club. The event was hosted by the Skaggs School of Pharmacy and Pharmaceutical Sciences and supported by a grant from Biogen Idec.

The topic was **"Quality Adjusted Life Years (QALY's) for Decision Making: Views from Canada and the US"**

A QALY is a way of measuring health outcomes that takes into consideration two priorities of health care simultaneously: quality of life and life expectancy.

Faculty News

The Canadian Experience with QALY's

Decision makers in Canada often use QALY's to help decide if a new drug should be on the provincial formulary. Lesia M. Babiak, Pharm.D., MBA, Director, Federal Affairs & Health Policy, Janssen Ortho Inc. and formerly Associate Director, Drug Programs Branch for the government of Ontario answered some key questions for Forum attendees.

Is using QALY's for selecting pharmaceuticals working for Canada?

- Effectiveness of QALY's in enhancing decision making has not been evaluated retrospectively
- QALY's are specifically useful in chronic pain, oncology and ADHD; They are not as useful for diseases with few symptoms (e.g. hypertension)
- Very limited awareness of the use of QALY's in drug product selection among the public and prescribing community in Canada

Is there a threshold for an acceptable drug cost per QALY gained (cost/QALY) in Canada?

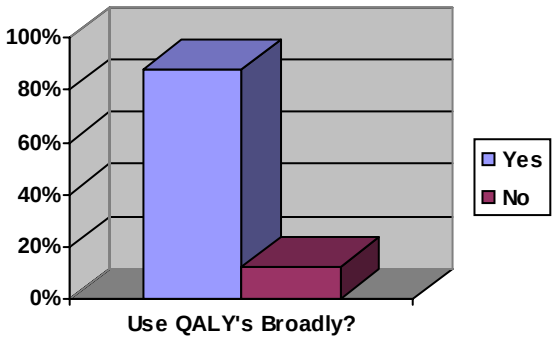
- There is no official threshold – C$50,000/QALY is an arbitrary cut-off often deemed "acceptable" - pharmaceuticals that cost less per QALY are more cost-effective
- A debate exists regarding the need for disease-specific thresholds (e.g. for drugs for rare diseases or oncology)

Future of QALY's in Canada

- Short term: QALY's will be requested and preferred by some decision makers
- Medium term: more active and public debate on the usefulness of QALY's is looming

Using QALY's in the United States - Forum Participant Opinions

Should QALY's be used broadly as a factor in decision making for pharmaceuticals in the US?



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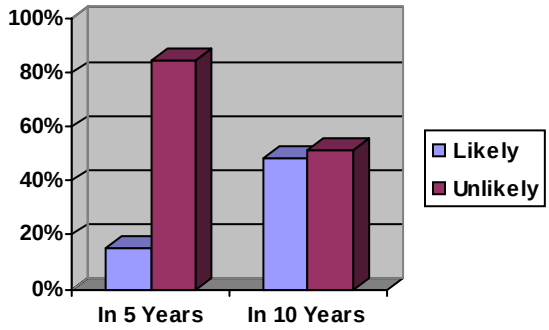
Likelihood of U.S. having broader use of QALY's for decision making among pharmaceuticals?



Forum attendees included managed care, government, medical center, academia, and pharmaceutical and biotech company representatives from Southern California. Attendees were invited because of mutual interest in expanding the practical application of pharmacoeconomic and outcomes research to enhance decision-making. More information and the speaker slides are posted at http://pharmacy.ucsd.edu/news.shtm .

Preceptor News

Jonathan P. Lacro, Pharm.D., FCSHP, FASHP, BCPS, BCPP

By Anthony Morreale, Pharm.D. and Chuck Daniels, Ph.D.

Dr. Lacro was recently named the Director of Pharmacy Education and Training at the VA San Diego Healthcare System where he also serves as Director of Clinical Specialists in Pharmacy and is a Clinical Pharmacy Specialist in Psychiatry. He is also a Research Scientist for the Veterans Medical Research Foundation and Associate Clinical Professor of Psychiatry at the University of California, San Diego. He is a Fellow of the California Society of Health-System Pharmacists and the American Society of Health-System Pharmacists. Additionally, he is the current Chair of the Board of Pharmaceutical Specialties Specialty Council for Psychiatric Pharmacy and is Board Certified as a Pharmacotherapy Specialist and a Psychiatric Pharmacist.

Dr. Lacro earned his Doctor of Pharmacy degree from the University of the Pacific School of Pharmacy in Stockton, California. After graduating, he completed a pharmacy practice residency at the VA San Diego and a fellowship at the University of California, San Diego with an emphasis in Geriatric Psychiatry.

Dr. Lacro's clinical and research interests are primarily devoted to schizophrenia and other psychotic disorders, geriatric psychiatry and the optimal use of psychopharmacologic therapies. His clinical responsibilities include providing medication management services in a Cognitive Disorders Clinic and a Geriatric Psychiatry Clinic as well as provide pharmacologic consultation on the Inpatient Unit at VA San Diego. Dr. Lacro has been actively involved in psychopharmacology studies since 1991. Currently, he is the Principal Investigator of an NIMH-supported grant on "Medication Adherence Therapy in Older Psychotic People" and is a co-investigator of the NIMH-funded Geriatric Psychiatry Center for Community-Based Research in Older People with Psychoses at UCSD. He has previously received federal funding for projects titled "Antipsychotic Treatment in Late-Life Schizophrenia" and "Exploring the Rationality of Co-Medication in Antipsychotic Treatment." He is the author or coauthor of articles published in journals such as *Journal of Clinical Psychiatry, American Journal of Psychiatry, Journal of Clinical Psychopharmacology* and *Journal of the American Geriatrics Society.*

Student News

Annual APhA Auction Benefits All Involved

by Christie Tran, P-4

In May of 2007, the members of the UCSD chapter of APhA-ASP again held their Student Service Auction. The event has been a recently anointed tradition at the young pharmacy school. This year's auction marks the fourth consecutive year that the faculty members and student pharmacists have donated their time and efforts to the student organization for its annual fundraiser.

The UCSD pharmacy community banded together, as one faculty member and 25 students all offered their talents to the highest bidders. The services offered were very diverse and ranged from administrative services and athletic lessons to delectable cuisines and beautiful handmade crafts. The auction was opened up to students, faculty, staff members, and other pharmacists in the San Diego pharmacy community. Bids were then received by email, where bidders would be continuously updated regarding the status of their bid. This silent auction, where bidders could anonymously outbid one another, turned into a friendly bidding war, as particular items were bid on up to 6 times a day by 3 or 4 people at a time. By the end of two weeks, the bidders were notified of their final winnings and advised that their services would be fulfilled before the beginning of the next academic year. Currently, most services have been provided well to the satisfaction of the generous bidders, and the chapter has received warm compliments and encouraging words to continue the tradition next year.

Through the donations of 23 generous supporters, the UCSD APhA-ASP raised $890 that will be used by the organization to promote community outreach and patient education through projects, such as Operation Diabetes, Operation Immunization, Hypertension Awareness, and Heartburn Awareness. With continued interest among generous donors, next year the chapter hopes to raise even more money to serve an even larger student population.

The UCSD APhA-ASP Chapter would like to thank the following generous donors:

Anisa Arjmand

Brookie Best

Lindsey Bowman

Ed Capparelli

Karen Chen

Kim Ciero

Ashley Dalton

Paul Hamrah

Jan Hirsch

Kathy Hollenbach

Doug Humber

Farivar Jahansouz

Shirley Lash

Tuan Mai

Andrina Marshall

Prudy Morris

David Rapaport

Sonny Satanapong

Renu Singh

Pam Tetu

Tom Tozer

Binh Tran

Chris Woo

Student News

Skaggs Students Volunteer at Healthy Neighbors Clinic for "Lost Boys"

by Stephanie Gershgol, P-4

The Sudanese "Lost Boys" are a group of refugees; their families were victims of ethnic cleansing in their home country and are survivors. As children, they ran from their villages in fear as their families were murdered behind them, and walked across the desert seeking safety and rescue. Older children had to care for the younger ones as the Janjaweed a militia group massacred the adult members of their family. Some of the "boys" later gained refugee status here in the US and other countries.

Here in San Diego and other parts of the US and abroad, these "boys," now both men and women are being treated for abdominal parasitic infections indigenous to their region of the world. John and Rebecca Moore and multi-disciplinary health care providers from UCSD, San Diego State University and Children's Hospital are all working to treat this patient population.

Many local volunteers, including myself attended a movie premier on Thursday, March 1, 2007 at the La Jolla Village Cinemas called "God Grew Tired of Us." It was a benefit for the "Lost Boys of Sudan" and those who managed to reserve tickets (as the event sold out) were truly privileged. The film was powerful and personal, and was followed by a question and answer session with 5 of the Sudanese survivors as they discussed what an incredible journey and transition they made as orphans walking hundreds of miles, and later as they learned to live in the US where they first discovered electricity and running water.

The pharmacy part of the clinic was led by Abby Adesanya, Pharm.D., BCPS. William Wong and I recruited colleagues from the UCSD Skaggs School of Pharmacy to volunteer at the clinics. Skaggs volunteers included Daisy Chang, Nina Haste, Kevin Mee, Lina Meng, Rita Patel, Elizabeth Sarles, Cynthia Shin, Angela Tran, William Wong and Ali Yasseri.

Drs. Abby Adesanya, BCPS, Frank Chu, Ashley Dalton, Ashley Feist, Jennifer Freeburg, Jenny Hu, Carolyn Nguyen, Sharon Reed and Nka Sajed served as clinic preceptors to Skaggs student pharmacists.

Volunteers counseled patients on the use of praziquantel (Biltricide®), a drug treating the parasitic infection so many of these individuals suffer from, schistosomiasis. These clinics will continue to benefit those from Sudan, and volunteers continue to be welcome.

Lina Meng (Class of 2009) received the United States Public Health Service Award for Excellence in Public Health Pharmacy from LCDR Ray Ford, Pharmacist, U.S. Public Health Service. The award was given in recognition of the outstanding work Lina has done in the Free Medical Clinics, Operation Immunization and other activities to promote the health of under served communities.

Student News

UCSD SSPPS First Year Student Pharmacists Educate Seniors at the Veterans Home

by Candis M. Morello, Pharm.D., Shirley Tsunoda, Pharm.D., and Teah Stacks

To help seniors better understand the use of Over-the-Counter (OTC) or Non-Prescription medications and supplements, student pharmacists from the Class of 2010 and faculty held a Seniors Health Education Event on Wednesday, May 30th at the Veterans Home of California in Chula Vista. This beautiful facility is where veteran seniors can live independently and receive medical and pharmacy services on site. In addition, they receive their meals and other social services there.

The students and faculty helped attendees promote their general wellness while increasing their awareness and safe use of OTCs and supplements. The class and faculty have focused on public education and service as a goal of their educational process. This community service event allowed the students to combine skills developed during their 3rd quarter experience in Pharmacy Practice including patient counseling, public speaking, disease management with OTC medications, literature evaluation, and dealing with special issues related to an older population.

To prepare for this event, the students worked in groups of 3 or 4 and created educational posters and pamphlets during the Spring Quarter with assistance from volunteer faculty liaisons as part of the requirement for the SPPS 203 Pharmacy Practice course. Students presented topics including Uses of Vitamin E, Acetaminophen and Preventing Toxicity, How to Treat a Cough, Smoking Cessation, OTC's for Red, Dry and Itchy Eyes, Athlete's Foot, How to Evaluate Complimentary/Alternative Medicines, Dry Skin, OTC Prevention of Osteoporosis, Safety Concerns of Non-Steroidal Anti-Inflammatory Agents, Insect Bites, GERD and Heartburn, Zoster Vaccine Live, Oral Health and Dentures, and Prostate Health.

On the outside patio, students set-up their posters, provided educational information, and answered questions from the seniors who attended. The seniors who attended were very appreciative for all of the great non-prescription drug information that they received from the students. The medical director and the pharmacy director were in attendance also and thought that the students did an excellent job presenting themselves and representing UCSD SSPPS.

Development of Novel Viral Vaccines at the Skaggs School of Pharmacy and Pharmaceutical Sciences

By Christopher S. Morello, Ph.D.

Cytomegalovirus (CMV), a herpesvirus that infects the majority of adults worldwide, is the major viral cause of birth defects. Between 0.5% to 2.5% of all newborns are infected with CMV, and of the 5% to 10% that are show symptoms at birth, most will develop deafness, blindness, motor disabilities, or learning impairment. Each year in the United States, an estimated 40,000 children are born with congenital CMV infection, resulting in 400 deaths and leaving approximately 8,000 children with permanent defects. More children are affected by serious CMV-related disabilities than by Down syndrome, fetal alcohol syndrome, and spina bifida. In addition to causing birth defects, CMV also causes serious disease in organ transplant recipients that can lead to organ rejection or death. The need for an effective vaccine against CMV is undeniable, and a study by the Institute of Medicine has placed the development of a CMV vaccine on its high priority list.

Chris S. Morello

CMV has been an elusive target for effective vaccination for over 35 years. Unlike most of the other viruses in which vaccines have been successfully developed, CMV causes a persistent, life-long infection. This is in contrast to influenza virus, in which the infected individual generates an immune response that eradicates the virus from the body. With CMV, the immune responses that are generated against the virus protect against serious disease in people with intact immune systems, but these responses are ultimately unable to eliminate the virus: thus allowing for future reinfection or passing of the virus from mother to fetus. Design of a CMV vaccine is therefore particularly challenging since the vaccine must provide immunity better than the natural infection. The natural immunity to the virus has been found to be subverted by the virus in order to favor its persistence, and several viral proteins function together to help the virus evade the T cells that could otherwise clear the virus from the host. CMV has also been found to misdirect the T cell response by eliciting high numbers of T cells that are ineffective at controlling the virus. Taken together, the current vaccine development paradigm in which vaccines are designed so that the immune responses to the vaccine mimic those that are found against the infection may not apply to CMV and the other persistent viruses, and therefore new vaccine strategies are needed.

For over the last 16 years, one of the goals of the laboratory of Dr. Deborah H. Spector, Professor in SSPPS, has been to design a vaccine that fully protects against CMV infection. When I joined the lab, I used murine CMV (MCMV)—a CMV that only infects mice—to test candidate vaccines for their ability to generate immunity and protection in mice. We found that immunization with DNAs that direct the synthesis of specific MCMV proteins generated virus-specific T cells, reduced the virus load in the spleen after MCMV infection, and protected against lethal infection. However, the viral load in the salivary glands, a key organ for viral transmission, was not significantly reduced. We then gave the DNA immunized mice a boost vaccine consisting of killed virus in order to generate antibodies that could neutralize the virus and could complement

the protective T cell responses. The optimized combination of DNAs and killed virus elicited immune responses in the mice that resulted in the virus being undetectable in both the spleen and the salivary glands, as well as in the other target organs examined, after mice received a high dose of live virus. In contrast, this complete protection was not achieved in mice immunized with only the DNAs or killed virus alone.

Having optimized the prime-boost vaccination strategy in mice, the next question was how to design the DNA arm of the vaccine such that it was applicable to human vaccination. The viral genes encoded by the vaccine DNAs that we used were specific to the mouse virus, and we needed a more universal strategy for choosing which viral proteins for the T cells to target. We decided to test vaccine DNAs that encode genes that are essential for the virus to replicate and that are highly conserved among the herpesviruses. Interestingly, the CMV proteins that these genes encode were found to be recognized by few if any T cells in the natural immune response to the virus. Going against the paradigm of choosing viral proteins that are targeted by high numbers of T cells, we chose instead to test vaccines using these novel targets. We tested 3 DNA vaccines encoding the conserved, essential CMV genes and found that 2 of these generated strong virus-specific T cell responses and could protect against viral challenge. We speculate that the virus may have evolved strategies to prevent the conserved, essential proteins from being strongly targeted by T cells during infection and instead to favor production of nonprotective T cells.

We hope to begin the pre-clinical work for the development of a vaccine for humans, including immunogenicity and safety studies using the human CMV vaccine components. In addition, because the essential genes used in the DNA vaccination are highly conserved among the herpesviruses, our novel vaccine strategy may also protect against infection with other herpesviruses, and we plan to test an analogous vaccine against herpes simplex virus type 2, the cause of genital herpes.

Dr. Christopher S. Morello is an Assistant Project Scientist. Also in the Spector Laboratory, Chuck Clark, Karen Tran, Anokhi Kapasi, and Rebecca Sanders study human CMV gene expression and the interactions of the virus with the host cell.