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VIDIVitals

this issue

VIDI Vision

A look at post-transplant viral infections with Steve Pergam

CMV, or cytomegalovirus, is a common herpesvirus that rarely causes problems for healthy patients. Between 60 and 70 percent of Americans are CMV positive, and for most, the virus remains latent. But for immunosuppressed individuals, it's a different story—CMV can be dangerous or fatal for post-transplant patients due to their weakened immune systems.

Given that 60 percent of transplant recipients are CMV positive, and those who are CMV negative may receive transplants from CMV positive donors, a majority of transplant patients are at risk for CMV disease, said Dr. Steve Pergam, VIDI senior fellow. Complications can range from CMV reactivation, which is very common in CMV positive recipients and requires a toxic course of IV antiviral therapy, to more severe CMV disease, which occurs in 6 to 9 percent of bone marrow transplant recipients and can be fatal. The problem is that there is no good way to predict which transplant patients will end up with CMV complications. Pergam, who just received a fundable score on an NIH K23 grant and will transition from senior fellow at the Center to acting instructor on July 1, wants to explore genetic variations in patients and donors to make better predictions of CMV risk, hopefully improving outcomes for transplant patients.

To explore new avenues of predicting CMV disease, Pergam is studying genetic variations of natural killer cells, a type of immune cell that targets and kills infected host cells. Specifically, he wants to look at killer cell immunoglobulin-like receptors, or KIR, proteins that reside on the surface of natural killer cells and interact with proteins on other cells. KIR proteins have a complicated biology that is still being unraveled, but are known to influence individual susceptibility to viral infections.

Because bone marrow transplant recipients acquire a complement of KIR genes from their donors, and because natural killer cells are the first immune cells to recover after a transplant, Pergam wants to ask whether genetic variation among KIR proteins affects the potential for post-transplant infection. Working with VIDI member Dr. Michael Boeckh and Clinical Research Division member Dr. Effie Petersdorf, Pergam plans to look at how a patient's or donor's specific KIRs affect the likelihood of CMV reactivation and disease severity.

Pergam's preliminary studies have found that specific KIR genes from the donor affect the patient's chances of CMV reactivation and development of more severe complications. Previous studies have shown an association between KIR and risk of CMV in transplant patients, Pergam said, but he hopes to delve deeper and draw correlations that haven't been possible in prior studies.

The Center is the perfect place to expand this work, he said. "We actually have a really great opportunity, because we have a repository of DNA from previous transplant patients, and incredibly diverse clinical data that allow us to look at all kinds of CMV out

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VIDI senior fellow Steve Pergam grew up in Omaha, Nebraska, and comes by his interest in medical research honestly – his mother is a pediatrician and his father a radiologist. Pergam will be transitioning to VIDI acting instructor on July 1.

FRED HUTCHINSON
CANCER RESEARCH CENTER
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Pergam, cont.

comes: reactivation, disease, even viral kinetics," Pergam said. "I think we're going to have the ability to answer some important questions."

If the researchers are successful in identifying which KIR genes are predictive of better or worse CMV outcomes in transplant patients, those results could change CMV treatment for the better, Pergam said.

"Right now we don't know who will develop CMV. If we had better pre-transplant predictors, we could really tailor our therapies, which are somewhat toxic, to those patients at highest risk," he said.

Pergam, who is now wrapping up his fourth year as a fellow at the Center through an additional year of funding from the Joel Meyers Infectious Diseases Scholarship, came to his current position through a somewhat unusual route. He completed a residency in internal medicine at the University of New Mexico, and accepted an assistant professor position there. Through a research project studying West Nile Virus, Pergam became more interested in infectious disease and, despite being fairly established, eventually made the decision to leave his faculty position to join the infectious diseases fellowship program and pursue research at the Center.

"It was a difficult decision, but the right one," Pergam said. "Meeting with all the people here that I would have the opportunity to work with, I couldn't pass that up."

Pergam also has a unique perspective on his work with post-transplant infection—he was once a transplant patient himself. Due to a viral infection, he suffered chronic kidney disease for years and received a kidney transplant from his mother five years ago—the same day he was accepted into the infectious disease fellowship program. After the transplant, Pergam developed non-Hodgkin's lymphoma, a cancer that infrequently occurs after organ transplants.

"I think I've lived in a really interesting place, because I understand what it's like to be both a transplant recipient and a cancer survivor," Pergam said. "That's part of the reason I've been drawn to the Center and to the research that's done here."

Pergam hopes to continue working in the field of post-transplant infections, using CMV as an entrée into the relationship between immunogenetics and infection.

"I like to think ahead, but in some ways you can never predict where you're going to go," he said. "Five years ago I never would have predicted what I'm doing now."

- Rachel Tompa

Accolades

Congratulations to **Limei Fan** (pictured at right), Chief Admin Officer of the Infectious Disease Science Program, who graduated from Seattle University's Leadership Executive MBA program this month. Fan won the Center's Peggy Means Leadership Development Fund in 2007 and 2008 to pursue her degree.

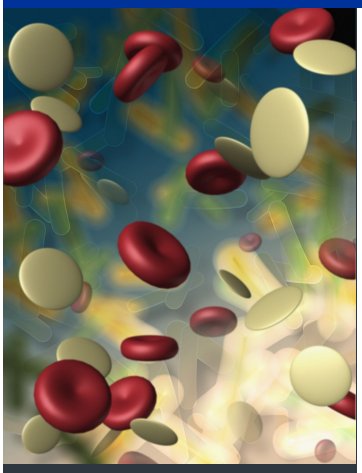
And to **Sam Pine** who completed his Ph.D. at UW under the mentorship of VIDI co-director Julie McElrath. His thesis was entitled "HIV Immunity: Innate Immune Correlate and Vaccine Responses." He finished just in time to welcome his new daughter Estelle Marie, who was born on June 16. Pine will start his post-doctoral work at the Infectious Disease Research Institute this fall.

VIDI welcomes its newest fellows:

- **Jessica Yager**, senior fellow (Corey Casper, mentor). Yager will work with the Uganda Program on Cancer and Infectious Diseases to study how nutritional status influences the natural history of both HIV and human herpesvirus infections, examining the link between under-nutrition and specific micronutrient deficiencies and immune responses in the setting of HIV, and determining how the response to treatment of various infection-associated cancers differs in persons with adequate and inadequate nutrition. She will start her fellowship in July.

- **Alexandre Boudreault**, visiting Canadian fellow (Michael Boeckh, mentor). He will obtain clinical training in transplantation infectious disease and will be part of the consulting service as visiting physician, and will start his fellowship in September.

- **Christian Renaud**, visiting Canadian fellow (Jane Kuypers and Larry Corey, mentors). Renaud will work in the lab on respiratory viruses and will also do patient-oriented investigations, and will start his fellowship in September.



VIDI Progress

Recent Publications

Size matters...and should be accounted for statistically

The size of an outcome variable, a variable that is dependent on other factors, can be a challenging issue in study design because it can be a source of bias. For example, in cross-sectional studies, which collect outcome variables at one time point, larger values are more likely to be observed. This bias, caused by so-called size-biased sampling, should be accounted for when statistically assessing study results. Dr. Ying Qing Chen, VIDI Associate Member, proposed a new regression method (i.e., a statistical method of modeling numerical data) to analyze studies that may have size-biased outcomes. Chen validated this method with analyses of two very different studies, one that estimated the area of vegetation coverage by measuring tree width in a gridded area, and a second that determined the relationship between tumor size and the occurrence of metastasis in lung cancer patients. This new method will provide a powerful regression tool to analyze observational studies involving sized-biased sampling. *-RCI*

Semiparametric Regression in Size-Biased Sampling. Chen YQ. *Biometrics*. 2009 May 4.

Leprosy takes its Toll

Leprosy may not get as much press as some diseases, but it remains a global health concern, with more than 250,000 new cases every year. The Toll-like receptor 2 (TLR2) protein is involved in initiating human immune responses to invading pathogens and influences the clinical presentation of leprosy. Patients with certain polymorphisms (small changes in DNA sequence) in the *TLR2* gene are more likely to develop reversal reactions, which are severe inflammatory reactions that occur after treatment initiation. VIDI affiliate investigator Dr. Pierre-Yves Bochud and his colleagues looked at other TLR genes for genetic interactions with leprosy, and found that two polymorphisms in *TLR4* confer protection against leprosy. These polymorphisms were already known to influence susceptibility to other infectious diseases such as tuberculosis and aspergillosis, indicating that this protein is important for sensing a variety of infectious agents. *-RT*

Polymorphisms in Toll-like receptor 4 (TLR4) are associated with protection against leprosy. Bochud PY et al. *Eur J Clin Microbiol Infect Dis.* 2009 May 9.

Response to a challenge of the tissue matching guidelines

Since cytomegalovirus (CMV) can cause severe clinical complications, current clinical guidelines recommend that CMV-negative leukemia patients undergoing hematopoietic cell transplants (HCT) should receive CMV-negative transplant tissues. However, a recent report indicated that children who had undergone HCT using CMV-negative donor tissues had an increased risk of relapse in the leukemia. Surprised by this finding, VIDI Member Dr. Michael Boeckh and colleagues replicated this study in children undergoing HCT at the Center and the Seattle Children's Hospital. In contrast to the earlier study, they found that CMV-negative patients receiving CMV-negative bone marrow or stem cells were not at higher risk of relapse. Since Boeckh and colleagues could not replicate the study results, they recommended that clinicians should follow the current clinical guidelines on treating CMV-negative recipients with CMV-negative donor tissues, at least until further studies can address these contradictory results. *-RCI*

Donor CMV serostatus not predictive of relapse in D-/R- pediatric HCT. Travi G et al. *Biol Blood Marrow Transplant.* 2009 Jun;15:758-60

Risk of CMV complications in cell transplant patients

Cytomegalovirus (CMV) infections can cause serious complications in cell transplant patients. Early work on a small patient group indicated that patients who received nonmyeloablative hematopoietic cell transplants (NM-HCT, a procedure that does not eliminate all of a patient's immune cells) may contract CMV infections much later than those who received myeloablative hematopoietic cell transplants (M-HCT, which eliminates all immune cells of a certain type). VIDI Member Dr. Michael Boeckh and colleagues tracked CMV infections in a larger group of 3,026 cell transplant patients. When comparing patients who received NM-HCT versus M-HCT, they found that both treatment groups had similar rates of CMV infection and survival after infection, but NM-HCT patients had an increased risk of late CMV disease. Thus, NM-HCT patients may have some residual immunity that prevents CMV progression early after transplantation, but are not protected against serious outcomes caused later by CMV. They also found that survival after CMV disease is

not different between NM-HCT and M-HCT patients. By knowing when CMV infection is likely to occur after transplants, clinicians will be better able to monitor for CMV infection in transplant patients. *–RCI*

Effect of Conditioning Regimen Intensity on CMV Infection in Allogenic Hematopoietic Cell Transplantation. Nakamae H et al. *Biol Blood Marrow Transplant.* 2009 Jun;15:694-703.

A molecular hunt for viruses

Respiratory illnesses in immunocompromised stem cell transplant patients can be dangerous, so early detection of the respiratory viruses is key. VIDI affiliate staff scientist Dr. Jane Kuypers and colleagues developed a new molecular diagnostic tool to track these viruses using PCR. To test the sensitivity of their technique, the scientists compared it to the traditional virus detection methods of culture and microscopy using nasal washes from transplant patients. PCR detected respiratory virus in 34 out of 131 patients, while culture and microscopy found only 15 and 6, respectively. The patients who tested positive by PCR but negative by other methods tended to have lower viral loads and fewer symptoms, indicating that this more sensitive technique could detect viruses earlier, before they do as much damage. *-RT*

Comparison of conventional and molecular detection of respiratory viruses in hematopoietic cell transplant recipients. Kuypers J et al. *Transpl Infect Dis.* 2009 May 8.

Reviews/Editorials

Public health. The cholera crisis in Africa. Bhattacharya S et al. *Science*. 2009 May 324: 885.

Riddle of the Sphinx Revisited: The Role of STDs in HIV Prevention. Barnabas RV, Wasserheit JN. *Sex Transm Dis.* 2009 Jun;36:365-7.

Issues in Using Progression-Free Survival When Evaluating Oncology Products. Fleming TR et al. *J Clin Oncol.* 2009 May 4.

Other articles with VIDI authors

Human papilloma virus infection prior to coitarche. Doerfler D et al. *Am J Obstet Gynecol.* 2009 May;200:487.e1-5.

Infants with late breast milk acquisition of HIV-1 generate interferon-gamma responses more rapidly than infants with early peripartum acquisition. Lohman-Payne B et al. *Clin Exp Immunol.* 2009 Jun;156: 511-7.

Prospective Study of Vaginal Bacterial Flora and Other Risk Factors for Vulvovaginal Candidiasis. McClelland RS et al. *J Infect Dis.* 2009 Jun 199:1883-1890.

Blood and Seminal Plasma HIV-1 RNA Levels Among HIV-1-Infected Injecting Drug Users Participating in the AIDSVAX B/E Efficacy Trial in Bangkok, Thailand. Kittikraisak W et al. *J Acquir Immune Defic Syndr.* 2009 May 6.

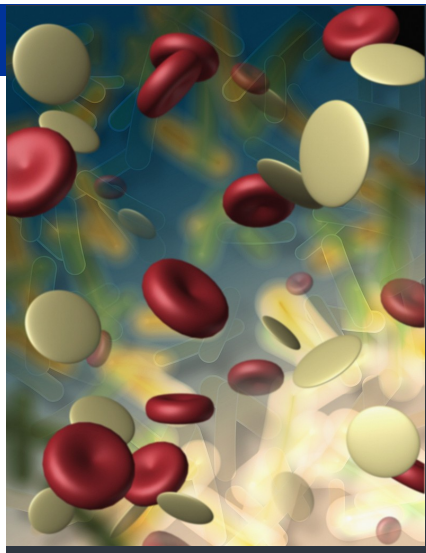
Evaluating nurses' implementation of an infant-feeding counseling protocol for HIV-infected mothers: The Ban Study in Lilongwe, Malawi. Ferguson YO et al. *AIDS Educ Prev.* 2009 Apr 21:141-55.

Gram-negative bloodstream infections in hematopoietic stem cell transplant patients: the roles of needleless device use, bathing practices, and catheter care. Toscano CM et al. *Am J Infect Control.* 2009 May;37:327-34.

Towards a quantitative understanding of the within-host dynamics of influenza A infections. Handel A et al. *J R Soc Interface.* 2009 May 27.

Induction of robust cellular and humoral virus-specific adaptive immune responses in HIV-infected humanized BLT mice. Brainard DM et al. *J Virol.* 2009 May 6.

Note: Each newsletter features original research articles published in the previous month where VIDI scientists are either the primary or last author. The newsletter will also provide links to review articles and other articles by VIDI authors. We want to include all VIDI publications from the previous month, so to ensure your publications are included, please email them to rtompa@fhcrc.org.



Upcoming Events

■ **Special VIDI Seminar**, Thursday, July 2, 10—11 a.m.
Thomas Building, Sze conference room
Dexi Chen, Beijing You An Hospital, Capital Medical University
"Research Projects of Infectious Disease in Beijing You An Hospital, Capital Medical University"

■ **Special VIDI Seminar**, Thursday, July 2, 11 a.m.—12 p.m.
Thomas Building, Sze conference room
Stephen Kent, University of Melbourne
"Viral evasion moves that thwart humoral and cellular HIV vaccination strategies – plotting moves to checkmate HIV"

■ **Special VIDI Seminar**, Monday, July 6, 3:30—4:30 p.m., Arnold Building, M4-A805/A817
Bin Zhang, Rosetta Inpharmatics, Merck Research Lab
"Pathway and gene target identification via weighted gene co-expression network analysis"

■ **IDS/Virology Research Conferences**, Thursdays, Thomas Building, D3-120
July 9, Guest speaker Don Diamond (City of Hope) – 4 p.m., **Pelton Auditorium**
July 16, Amos Mwaka and Maria Lemos – 4 p.m.,
July 23, Jeff Stanaway – 4 p.m.

■ **HIV Immunology 101 Seminar**, Wednesday, July 15, 12—1p.m. Orca conference room (LE-4203, 1616 Eastlake)
Greg Spies
"Adaptive B Cell Immunity"

■ **VIDI faculty grant forum**, Thursday, July 16, 11:30 a.m.—1 p.m. Thomas Building, D3-120

■ **VIDI Journal Club**, Thursday, July 16, 5 – 6:30 p.m., Thomas Building, Room D2-120
Jane Kuypers, Morgan Hakki, moderated by Michael Boeckh

■ **HVTN Data Forum**, Monday, July 20, 12—1 p.m., Orca conference room (LE-4203, 1616 Eastlake)
Peter Gilbert
"Improving vaccine trials with predictors of immunogenicity and outcomes"

VIDIVitals

VIDI Vitals **is published monthly by Rachel Tompa, editor-in-chief, and Renee Ireton, writer and editor, 1616 Eastlake Avenue, Seattle, WA, 98109. Ideas, suggestions, and submissions for future *VIDI Vitals* can be sent to Rachel at rtompa@fhcrc.org.**