Inside This Issue:

Message from the Director............................1
McArdle News................................................2
Research Snapshot: Bill Sugden and the Epstein Barr Virus.............................................3
Alumni Updates: Where are they Now?......5
Recent Graduates............................................6
Your Gift Matters............................................7
Message from the Director

Dear McArdle Alumni and Friends:

Greetings from all of us in Madison! This academic year is off to a busy start with all the usual activities, including submission of grant applications, teaching, helping our new graduate students find laboratories and preparing for the rapidly approaching move to the WIMR.

I am pleased to report that we have been successful in renewing several of our long standing grants and in securing new funding, in spite of a challenging funding climate. Examples of renewed grants include our long standing program project grant in tumor virology (Paul Lambert, PI) and our pre-doctoral training grant in Cancer Biology, which is one of the longest funded training grants on the UW campus (Bill Sugden, PI). New grants include an R01 to Eric Johannsen and Shannon Kenney to fund studies on epigenetic determinants of Epstein-Barr virus and cellular DNA in oral diseases; an R01 to Paul Lambert to support research on molecular and therapeutic studies on HPV-associated anal cancer; and an R01 to Jing Zhang to study activation of the MEK/ERK pathway in hematopoiesis.

McArdle faculty members continue to serve leadership roles in the UW Carbone Cancer Center (UWCCC) and contributed significant time and effort to the recent renewal of the Cancer Center Support Grant from the NCI. Four of the eight research programs in the UWCCC are led by McArdle faculty: Caroline Alexander and Shigeki Miyamoto, Cell Signaling; Paul Ahlquist and Shannon Kenney, Cancer Virology; Michael Hoffmann, Experimental Therapeutics; and Michael Gould, Cancer Genetics. Mike Hoffmann also directs the Small Molecule Screening and Synthesis Shared Resource, and I continue to serve as Associate Director for Laboratory Research.

We are excited to announce the upcoming UW-Madison Stem Cell Symposium, which will be held at the Promega campus on April 30, 2014. Organized by Jing Zhang and Emery Bresnick (Department of Cell and Regenerative Biology), the focus will be on the normal and malignant development of blood cells from stem and progenitor cells. In addition, Wei Xu and Elaine Alarid are organizing a Nuclear Receptor Meeting to be held in Madison next fall. We would be delighted if you are able to attend these conferences and visit us in our new home.

Finally, I wish to take the opportunity to recognize and thank the McArdle Animal Care Team, who earlier this year received a letter of commendation from the UW School of Medicine and Public Health’s Animal Care and Use Committee (ACUC) for their outstanding work in maintaining first-rate animal use areas. These staff members include our facility supervisor Jim Taubel (2010), lead technicians Terry Fritter (1992) and Lori Theobald (1995), and technicians Chuck Rolfsmeyer (1981), Dale Peterson (2001), Satya Miranpuri (2006), Vicki Krasel (2007), and Ramona Hennessey (1964). We greatly appreciate the effort these individuals devote to our research by providing a superior quality of care for our research animals.

As always, we welcome hearing from you. Please send us news regarding your activities (alumni@oncology.wisc.edu). Best wishes for a productive and happy year.

Sincerely,

James D. Shull
Director, McArdle Laboratory
Dr. Jing Zhang receives Scholar Award from Leukemia & Lymphoma Society
Dr. Zhang's research interests include hematopoietic and leukemic stem cells, mouse models for hematopoietic malignancies and cytokine signaling.

Dr. Dick Burgess receives Entrepreneurial Achievement Award
Dr. Burgess was honored for his work through the UW Biotechnology Center to encourage entrepreneurship and new biotech company formation in Wisconsin.

Dr. William Dove receives 2013 Emeritus Faculty Award in Basic Sciences
Dr. Dove was honored for his long and effective service to the UW School of Medicine and Public Health in research.

Dr. Elaine Alarid receives Vilas Associates Award
Dr. Alarid’s research is focused on elucidating the mechanisms through which estrogens contribute to breast cancer.

Dr. Wei Xu awarded 2013 Society of Toxicology Achievement Award
Dr. Xu’s research interests include epigenetic transcriptional control in breast cancer.

Jordan Becker and Jaye Gardiner (Sherer Lab) receive 2013 NSF Graduate Research Fellowships
Jaye’s and Jordan’s research interests include HIV-1 trafficking and cell to cell spread.

Amy Irving (Dove Lab) awarded Graduate Student Peer Mentor Award
This award recognized Amy for her outstanding mentorship and overall support to fellow graduate students.

Shawn Jackson (Miyamoto Lab) receives F30 from NCI
Shawn’s research focuses on defining NEMO interactions to selectively inhibit NF-kB activation by DNA damage.

Taryn James (Xu Lab) receives Postdoctoral Fellowship from PhRMA Foundation
Taryn studies mechanisms and molecular targets of phytoestrogens in breast cancer.

Saja Fakhraldeen (Alexander Lab) receives Graduate Research Award from Kuwait Foundation for the Advancement of Sciences
Saja is researching the functional significance of IGF2BP1 expression in breast cancer.

Dr. Paul Ahlquist elected to Association for the Advancement of Science
Dr. Ahlquist was honored for his contributions to the area of molecular virology, viral evolution, and pathogenesis.

Dr. Waclaw Szybalski is awarded the doctorate honoris causa from Jagiellonian University
Jagiellonian University is among the oldest universities in the world (established in 1364). This is Dr. Szybalski’s fifth degree honoris causa received since 1980.
Did you know that almost a fifth of all new cases of human cancers every year are caused by an infectious agent, such as bacteria or viruses? Epstein Barr Virus or Human Herpesvirus 4, commonly called EBV, is one such virus, and in fact was the first human virus to be associated with cancer. EBV causes the common, benign disease infectious mononucleosis, but can also cause lymphomas such as Burkitt’s lymphoma and other B-cell lymphomas, as well as carcinomas such as nasopharyngeal and gastric carcinomas. Burkitt’s lymphoma is the most common childhood and adolescence cancer in equatorial Africa.

Dr. Bill Sugden – who prefers to go by Bill – has been studying the Epstein Barr Virus for more than forty years. He recalls that “it was 1973 when I went to Stockholm to study EBV. It seemed likely even then that EBV was a human tumor virus, and I wanted to study a human tumor virus.”

Over the years Bill and the people in his laboratory have worked to understand how EBV infects and persists within cells in our bodies and what role the virus plays in causing and sustaining the cancers it is associated with. Understanding how the virus contributes to the survival of the tumors it causes can lead to the development of therapies for these cancers. Recently, Bill and his colleagues have found that microRNAs (miRNAs) expressed by EBV sustain several EBV-induced lymphomas.

EBV is a peculiar virus in that it maintains its DNA as a plasmid – i.e. as a piece of DNA that is physically distinct from cellular DNA – in infected cells, such as tumor cells.

One infected cell may contain multiple copies of EBV DNA. The viral plasmids are replicated along with cellular DNA during the S-phase of the cell cycle, and when the infected cells divide, the plasmids are partitioned equally and non-randomly to the daughter cells. This process allows EBV to maintain itself in infected cells.

But, surprisingly, research by Dr. Asuka Nanbo, a post-doctoral fellow in Bill’s lab, has shown that not all the EBV plasmids in a cell are replicated every cell cycle, which implies that over time EBV plasmids should be lost from a population of dividing cells (See Image 1).

Image 1: This is a cartoon picture of a tumor cell, shown in blue, harboring EBV DNA. The EBV DNA, which is present as plasmids in this cell is represented by the black circles labeled A, B, C or D. These plasmids are present in the nucleus of the cell, represented by the enclosed purple area, along with the cell’s own DNA (not shown). In Figure (I) this cell has not yet gone through the DNA-replication phase of the cell cycle and four EBV plasmids are present. In Figure (II) the cell has undergone DNA replication and 3 out of 4 EBV plasmids (A, C, and D, but not B) have been replicated; there are now 7 plasmids in the cell. By Figure (III) the cell has divided into two daughter cells. One daughter cell has four plasmids, but the other one only has three because plasmid B was not replicated. You can imagine that as this process is repeated it will give rise to some cells with no EBV plasmids.

However, this is not the case in cancer cells, which continue to harbor EBV DNA even while proliferating. Therefore, EBV must be providing a selective advantage to infected cells, which allows these cells to outgrow the cells that have lost the viral DNA. Dr. Dave Vereide, a former graduate student in Bill’s lab, engineered certain EBV-positive cancer cell lines to express a mutated version of the viral protein EBNA1. When cells containing EBV plasmids expressed this mutant EBNA1 protein, they lost the viral plasmids and died by apoptosis. This finding – that forcing the loss of EBV genomes from infected cells, such as lymphoma cells, leads to their death – confirmed the hypothesis that EBV provides survival factors to infected cancer cells. But what are these survival factors provided by EBV?
miRNAs are small RNAs expressed by many organisms, from humans to viruses. They play a role in regulating protein levels by binding to messenger RNAs (mRNAs) and either inhibiting their translation into proteins or causing their degradation. Dr. Ya-Fang Chiu, a post-doctoral fellow in Bill’s lab, says, “The only viral genes expressed in a number of EBV-derived lymphomas are the protein EBNA1, a couple of small RNAs called EBERs and a set of viral microRNAs called BARTs. We were very curious whether these EBV miRNAs contributed to tumor cell survival.” Along with Dr. Vereide and Mitch Hayes, a research specialist in the lab, Dr. Chiu found that if they expressed EBV miRNAs in EBV-positive cells and then forced the loss of EBV DNA from these cells, they did not die, but continued to proliferate (see Image 2). Thus, the death of infected cells caused by forcing the loss of EBV DNA could be rescued by expressing the EBV BART microRNAs in those cells.

These findings by Bill’s laboratory have opened the possibility of developing therapies for EBV-induced cancers. Understanding how tumor cells depend upon EBV for their survival makes it possible to plan potential treatment for cancers sustained by EBV. For example, since the viral protein EBNA1 is absolutely essential for the viral DNA to persist in infected cells, inhibiting the functions of this protein could be a way to disrupt the maintenance of EBV DNA in tumor cells and lead to the destruction of the tumor. The intrinsic advantage of targeting an EBV protein is that cellular functions need not be affected by the therapeutic strategies. “I began my career in cancer research in 1965 with the goal of developing a treatment for some form of cancer,” says Bill, “and it is encouraging to be at a point where we have learned enough about EBV to identify possible treatments so that we can now try to bring them into practice.”

Image 2: This figure graphs the number of times cells doubled across a given number of days for 1. An EBV-positive tumor cell line (shown by the solid green line); 2. The same cell line expressing mutant EBNA1 protein and therefore losing EBV plasmids over time (shown by the dashed red line); 3. The same cell line expressing mutant EBNA1 protein AND also the EBV miRNAs (shown by the dashed blue line). We can see that as these tumor cells lose EBV their doubling rate starts to slow (see red line), but when they also express the viral miRNAs - in addition to losing EBV genomes - they are able to maintain a doubling rate much closer to that of tumor cells not losing the viral genomes (the blue line is much closer to the green line, compared to the red one).
I arrived at the University of Wisconsin with the incoming class of 2004. What had attracted me was a keen interest in molecular biology and the desire to study how viruses cause disease. As a point of pride, I believe Madison is one of the most vibrant hubs for molecular virology research in the world. McArdle, in particular, can claim many exceptional faculty in this area. I trained under the auspices of Dr. Dan Loeb, a highly esteemed Hepadnavirologist, from the years of 2004-2010.

Dr. Loeb’s lab works on Hepatitis B virus (HBV), which is linked with increased risk for hepatocellular carcinoma, among other hepadnaviruses. My studies focused on the mechanism through which this virus regulates amplification of its genome within a cell, a process that may be involved in persistence of HBV in patients. I fondly remember the many fruitful discussions this project generated at lab meetings, seminars, and the McArdle symposium. Over the course of my project I believe I interacted with most McArdle faculty at some level. This community approach to science was prolific and is part of what made McArdle such a special place.

Since leaving Dan’s Lab, I have applied my expertise in molecular virology toward an approach to treating disease that has always piqued my curiosity, gene therapy. I began a postdoc with Dr. R. Jude Samulski at the University of North Carolina gene therapy center in 2011. Dr. Samulski has been at the forefront in developing virus-based, particularly adeno-associated virus-based, vectors for therapeutic gene delivery. In this new frontier, I have sought a balance of both basic and applied research. With the support from the Lineberger Cancer Center (UNC), I have been investigating how viruses and derived vectors are sensed by the cellular DNA damage response pathways. I have also begun work, supported by the Alpha-1 foundation, to use enhancer elements from HBV to improve the efficiency of liver-targeted vectors for treating alpha-1 antitrypsin deficiency. And as a welcomed surprise, my work has even led me back to McArdle. Dan and I have collaborated with Adam Zlotnick (University of Indiana) to develop vectors for delivery of inhibitors of HBV replication. Much of the success in these new pursuits I owe to my growth and development as a scientist at McArdle Lab.

Though it has been only a few years since I walked the streets of McArdle’s 7th floor, I find that I already miss many things about my time there. Of course there was happy-hour at the terrace, the great time I had living in Madison, and all of the friends that I hope to stay in contact with. But also, I miss the colleagues and the community that made McArdle and UW-Madison such an invigorating place to do science. As my career moves forward and I am faced with the task of teaching the next generation of budding scientists, I hope I can draw from my experiences in Madison. At least I was thoughtful enough to bring a piece of Wisconsin with me. My wife Becky (a Wisconsin native and UW alum) and I were married in September 2012. We met in Madison and I’m sure she will see to it that I never forget my roots. Go Badgers!
Peter Angeletti, Ph.D.

My wife, Anisa, and I were postdocs at McArdle from 1998-2003. I worked in Paul Lambert’s lab and Anisa worked in Jeff Ross’ lab. We certainly feel that these were some of the most important and formative years of training for us. The emphasis on key questions and on quality science is what sets McArdle apart. While I was in Lambert lab, we developed a yeast-based system to study HPV functions, in particular, viral genome maintenance. This work became the basis for my Howard Temin grant (K01), which helped me launch my independent career. I am forever grateful to Paul for allowing me to take this creative venture and to Bette Sheehan who helped put together the budget for that grant.

I began my faculty position at the Nebraska Center for Virology (NCV) in 2003 and was promoted to Associate Professor in 2009. Over the years, my lab has continued to focus on mechanisms of HPV genome maintenance, as well as newer topics, such as regulation of HPV DNA packaging. Another project we have begun investigates the influence of HIV status on HPV genotype distribution among Zambian women.

It’s nice to see the McArdle traditions carry on and I feel fortunate to have been a part of those traditions. To students and postdocs who are in McArdle now, I say, absorb all the knowledge you can.

Recent Graduates

Fall 2012-present

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<thead>
<tr>
<th>Name</th>
<th>Program</th>
<th>Advisor</th>
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<tbody>
<tr>
<td>Geonyoung Ahn, MS</td>
<td>Cellular &amp; Molecular Biology</td>
<td>Elaine Alarid</td>
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<tr>
<td>Catherine Albright, MS</td>
<td>Cellular &amp; Molecular Biology</td>
<td>Bill Sugden</td>
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<tr>
<td>Eric Hilton, MS</td>
<td>Cancer Biology</td>
<td>Bill Sugden</td>
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<tr>
<td>Jung Wook Park, PhD</td>
<td>Cellular &amp; Molecular Biology</td>
<td>Paul Lambert</td>
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<tr>
<td>Prashant Rajbhandari, PhD</td>
<td>Molecular Pharmacology</td>
<td>Elaine Alarid</td>
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<tr>
<td>Ryan Raver, PhD</td>
<td>Cellular &amp; Molecular Pathology</td>
<td>Shannon Kenney</td>
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<td>Erin Shanle, PhD</td>
<td>Molecular &amp; Environmental Toxicology</td>
<td>Wei Xu</td>
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<td>Vitali Stanevich, PhD</td>
<td>Biophysics</td>
<td>Yongna Xing</td>
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<td>Brian Johnson, PhD</td>
<td>Molecular &amp; Environmental Toxicology</td>
<td>Chris Bradfield</td>
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<tr>
<td>Shawn Jackson, PhD</td>
<td>Cellular &amp; Molecular Biology</td>
<td>Shigeki Miyamoto</td>
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