

Peter M. Howley
Visiting Vallee Professor
Oxford University
July-August 2009

I am pleased to provide a short summary detailing the meetings and interactions during my 4-week term as a Visiting Vallee Professor during July and August of 2009.

My first week was spent as a guest at St. Catherine's College at Oxford at the DNA Tumour Virus Meeting that was hosted by Professor Alan Storey of the Weatherall Institute of Molecular Medicine at Oxford University. Professor Storey is an expert in the area of skin cancer with an interest in melanoma as well as a subgroup of the human papillomaviruses that are associated with squamous cell carcinomas of the skin in humans. These beta genera HPVs have not been extensively studied and the mechanisms by which this group of viruses contribute to skin cancer remain largely unexplored. In the past year I have become interested in this group of understudied viruses and I have written a grant with Wade Harper to explore the proteins and pathways that are targeted by this group of viruses. At this intense meeting at St. Catherine's, I had the opportunity to discuss the molecular mechanisms by which the HPVs contribute to cervical cancer with Denise Galloway (University of Washington), Robert Garcea (University of Colorado), Richard Schlegel (Georgetown University), Cheng-Ming Chiang (Southwestern Medical School), Alison McBride (NIH), among others.

Following the meeting at St. Catherine's I spent 5 days en Provence at a meeting organized by the Fondation des Treilles which sponsors meetings in the areas of the arts and the sciences. This meeting entitled "Cancer: from fundamental research to therapy" had been organized by Moshe Yaniv (Pasteur Institute), a previous Vallee Visiting Professor at Harvard. The meeting format limits invitations to only 20 scientists (half from the United States and half from Europe and Israel). The meeting was a terrific success with in depth discussions of the genomic approaches now being used to study human cancer and determine the genes and pathways that drive malignant progression. I gave a one-hour talk entitled "Mechanisms of HPV carcinogenesis" focusing on my recent work identifying the pathways engaged by HPV to regulate the expression of its E6 and E7 oncogenes. This is unpublished work from my laboratory based on a whole genome siRNA screen that identified a series of genes required for viral E2-dependent and viral-independent mechanisms of oncogene repression. Other scientists at the meeting with whom I discussed potential interactions and collaborations included David Livingston (DFCI, Harvard), Karen Vousden (Beatson Cancer Institute, Glasgow), Moshe Oren (Weizman Institute, Israel), Mike Stanton, (Sanger Labs, Cambridge), Anne Dejean (Pasteur Institute), among others.

I then returned to Oxford and joined Dame Louise Johnson in the beautiful New Biochemistry Building. My stay there was co-hosted by Allen Hill. I was provided an office adjacent to that of the current department chair, Kim Nasmyth. While back in Oxford, I gave two seminars, one in the Biochemistry Department on July 29. The title of my talk was "Regulation of HPV Viral Oncogene Expression" during which I

discussed the results from our recent whole-genome siRNA screen, the pluses and minuses of the current HPV VLP vaccine, and the need for the development of specific anti-viral therapies for HPV infections and for the cancers they cause. On August 5, I visited the branch of the Ludwig Institute for Cancer Research in Oxford that is headed by Professor Xin Liu and located in newly constructed laboratories in the Old Road Campus Research Building. I gave a seminar there entitled "The role of Ubiquitylation and Cancer". I spent the day meeting with Dr. Liu and the other faculty who are members of the Ludwig institute, including Professors Colin Gooding, John Christianson and Gareth Bond.

Dr. Liu's research focuses on the functions of p53 and its related homologs p63 and p73. She is exploring the role of some of these proteins in cervical cancer. We discussed the potential implications of her work in cervical cancer and also in the context of the normal differentiation program of cervical squamous epithelial cells.

I had a number of meetings with the faculty in the Biochemistry Department at Oxford during my term as a VVP. Louise Johnson's group and I have a common interest in a cellular bromodomain protein called Brd4. In 2004 my laboratory identified Brd4 as a major cellular interacting partner of the papillomavirus E2 protein and have shown that Brd4 mediates a number of critical E2 viral functions necessary for the papillomavirus life cycle. Subsequent work has shown that Brd4 interacts with the cellular transcription machinery and binds P-TEFb, a complex involved in transcription elongation that consists of CDK9 and cyclin T1. In 2008, Louise Johnson and her group determined the structure of CDK9 and cyclin T1. We have entered a collaboration with Louise Johnson and her colleagues, namely Sonja Baumli, Jane Endicott, Martin Noble, and Alison Hole, to examine the effect of HPV E2 on this complex and specifically to ask whether E2 competes the binding of P-TEFb to Brd4. The complementary skills of the structural group at Oxford and the molecular biology skills in my laboratory make this a powerful collaboration. Neither Louise nor I were aware of this major interface between our research interests before my visit to Oxford. We have already sent a number of reagents to Jane Endicott's laboratory to facilitate their in vitro and structure studies.

Other individuals I met with in Oxford Biochemistry included the chair, Kim Nasmyth, with whom I discussed his studies on cohesin and chromosome separation during mitosis. I also met with John Sinclair to discuss his ground-breaking work on developing new scaffolds that might enhance structural biology capabilities. I suggested his technology might also be applicable to the development of novel vaccine strategies. I also met with Jane Endicott and her group working on ubiquitylation. They are studying the structure of ubl and uba domain containing proteins, an interest also of my laboratory. We discussed the potential of some additional collaborative studies in the area of ubiquitylation.

In Oxford I also participated in a meeting of the Vallee Foundation that had been organized by Sheila Ohlund on August 3 at the Old Bank Hotel. Other participants in Oxford included Alan Hill, Jesper Haeggström, and Gerard W. Canters, along with Bert Vallee and other in the U.S. by phone. This was an important meeting at which a number

of issues relating to the foundation, and strategies for the future were discussed. Sheila chaired the meeting and did a terrific job keeping us to our agenda. Strong interest was expressed in a science meeting for the foundation sometime next year for which potential venues will be explored.

Ann and I departed Oxford for Boston on August 8, having had a very productive and stimulating mini-sabbatical. I should not fail to mention the generosity and graciousness of both Allen Hill and Louise Johnson in hosting my visit. They looked after Ann and I while we were there. One highlight was an extraordinary evening at Le Manoir aux Quatre Saisons, and a meal that was simply fantastic. I am very grateful to the Vallee Foundation and specifically, Bert and Kugie for providing me the opportunity to spend this time in Oxford. Time was too short to accomplish all that I might have hoped. In future trips to Europe I hope to visit with Jesper Haeggstrom at the Karolinska, Philip Cohen in Dundee, and Alan Ferscht in Cambridge.