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Wohl Virion Centre Annual Report 2013.

The Centre is located in the Cruciform building and comprises five PIs, eight postdoctoral fellows, one research assistant and four PhD students. This year Prof. Paul Kellam with his UCL group joined the Wohl Virion Centre, bringing new expertise in virus genome sequencing and host-pathogens interactions. Grant income comes from the MRC, EPSRC, EU, the Bill & Melinda Gates Foundation, the Wellcome Trust and the Biomedical Research Centre (BRC). Lab meetings are held every Thursday and are attended by all the members of the Centre.

Five Principal Investigators work in the Centre:

Robin A Weiss PhD FRS

As emeritus professor, Robin still works about three days per week in the Wohl Virion Centre. Although he stopped laboratory research in March 2013, he remains active in teaching, training young researchers and acting in an advisory position on several national and international organisations. During 2013 Laura McCoy moved to a position at Scripps Institute, La Jolla California and clinical fellow, Thushan de Silva took up a clinical senior lectureship and NHS consultant post in infectious disease at the University of Sheffield, UK. Until mid-2013, Robin's research was supported by the Bill & Melinda Gates Foundation. He is currently involved in grants awarded by the Engineering & Physical Sciences Research Council, and European Union Framework 7 Programme. The research is collaborative with the London Centre for Nanotechnology and the Universities of Utrecht and KwaZulu-Natal.

Robin's interests have focused on the interface between infection and cancer and on the envelope properties of the AIDS virus, HIV. He has contributed to the development of potential vaccines, microbicides and diagnostic reagents affordable in resource-poor countries. In particular, he has exploited a curiosity of nature, namely that llamas make single chain antibodies, to characterise the 'Achilles heel' of the HIV envelope. His expertise on HIV has allowed him to apply similar techniques to the neutralisation of other highly pathogenic viruses such as SARS, H5N1 influenza and rabies. The incorporation of a high containment laboratory for dangerous viruses in the Wohl Virion Centre made these investigations possible.

During the past year, McCoy and Weiss spoke at the Keystone HIV Vaccines meeting in USA, the International AIDS Vaccine Conference, and the Frontiers of Retrovirology Conference in Cambridge, UK. Weiss was an invited speaker at Cumberland Lodge series on "Ethics and HIV"

and at the International Institute of Genetic Engineering & Biotechnology in New Delhi, India. An invited review article written by McCoy and Weiss entitled “Neutralizing antibodies to HIV-1 induced by immunization” was published in the Journal of Experimental Medicine in 2013. Laura McCoy won a prestigious EU Marie Curie Award commencing in 2014.

Robin Weiss has recently been appointed Chair of the Scientific Advisory Committee of the International AIDS Vaccine Initiative, Reviews Editor of the learned journal, *Retrovirology*, and a member of the Nuffield Council for Bioethics. In 2013, Robin received a rare accolade for a British scientist of being elected a Foreign Associate of the US National Academy of Sciences.

Clare Jolly PhD

Clare Jolly is an MRC Career Development Fellow who joined the Wohl Virion Centre in 2009. Her lab comprises two postdoctoral fellows, Dr Elisabetta Groppelli and Dr Alice Len and a MRC funded PhD student, Shimona Starling. Her work is funded by a MRC Career Development Award and a MRC project grant. The research interests of the Jolly laboratory are directed at understanding the molecular mechanisms that regulate Human Immunodeficiency Virus transmission between CD4+ T cells – the main targets for the virus *in vivo*. This mode of HIV-1 transmission is important because it escapes most antiretroviral drugs developed so far and may be one of the main mechanisms to allow virus spread in lymphoid organs and during reactivation from latency. Clare’s laboratory has recently shown that different classes of antiretroviral drugs vary in their ability to inhibit cell-cell spread of HIV. Specifically, they found that protease inhibitors effectively blocked cell-cell spread whereas reverse transcriptase inhibitors were less effective. This work was published in the journal *Retrovirology*. In addition in collaboration with Robin Weiss’s laboratory she has been evaluating antibody-mediated inhibition of cell-cell spread and this work is being prepared for submission.

Clare’s group is especially interested in how the virus hijacks and possibly modifies existing cellular machinery to promote efficient transmission by direct cell-to-cell spread. Such host factors may represent novel targets for therapeutic development. She has recently shown that HIV infected T cells can respond to contact with an uninfected T cell by polarizing the cellular cytoskeleton and secretory organelles towards the contact site. This work was published in 2011 in the open access journal PloS Pathogens and additional publications are being prepared for submission. Dr Jolly has recently given invited seminars at the Institut Cochin in Paris, King’s College London, Imperial College London and as part of the Bloomsbury Research Institute, a new joint-initiative between UCL and the London School of Hygiene and Tropical Medicine. She was an invited speaker at the 2012 Keystone Symposia meeting on Frontiers in HIV Pathogenesis, Therapy and Eradication in Canada and co-organised the annual UK Recently Independent Virology Researchers (RIVR) in 2013 and 2014.

Yasuhiro Takeuchi PhD

Yasu Takeuchi’s group currently comprises a research associate (Ilaria Nisoli started in December 2013 on a new EU FP7 programme); three PhD students (Sabine Winkler (mainly based at the NIBSC), Khaled Samber (his primary supervisor is Mary Collins) and Kanayo Doi (started in June 2012, awarded a highly-competitive full-studentship from Japan Student Services Organization)); a full-time master project student from University of Milan (Marta Ferraresso). Yasu’s main interests are in gene therapy and in xenotransplantation.

Yasu’s work in gene therapy is in collaboration with Mary Collins in two directions. A project taken on by Khaled and Marta is the development of stable LV packaging cell lines for future clinical

application. This development has extended to vector processing following harvest from producer cells in collaboration with Sabine/NIBSC whose main project is proteomics of vector preparations. Kanayo takes on continuation of our effort in the study of insertional mutagenesis by lentiviral vectors with particular interest in mutagenesis caused by aberrant splicing between a cellular gene and the vector genome.

Takeuchi is a leader in the field of safety in xenotransplantation and he studies the risks associated with potential zoonosis following transplantation of pig organs. Various studies funded by EU FP6 XENOME consortium in which Takeuchi acted as the work package leader on safety (funding duration ended in April 2012) continued to be published (Ref 1-4). One of these (Ref 2), which Yasu corresponded, reported induction of xeno-antibodies against sugars with terminal sialic acid of non-human type Neu5Gc in burn patients treated with vital pigskin. This work inspired him and his European collaborators to form a new EU consortium TRANSLINK under FP7 to define the role of xeno-directed and autoimmune events in patients receiving animal-derived bioprosthetic heart valves. Ilaria started to work on this project recently. With regards of xenotransplantation safety, Yasu will be involved as a subcontractor to Glasgow Caledonian University (Linda Scobie) in another newly formed FP7 consortium XENOISLET which seeks development towards clinical trials of pig islet cell transplantation for diabetes.

Ariberto Fassati MD PhD

Ari Fassati is the Director of the Wohl Virion Centre. His group comprises an MRC funded postdoctoral fellow, Alex Zhyvoloup, an EU FP7 Innovative Medicine-funded postdoctoral fellow, Aksana Labokha, one undergraduate student (Nicole Yim), and Nan-Yu Chen, a paediatrician with expertise in infectious diseases who won a Governmental scholarship from Taiwan and joined the Wohl Virion Centre as a PhD student in 2011. Ari also co-supervises two PhD students mainly based at the London Centre for Nanotechnology: Dino Osmanovic (soon to submit his thesis) and Aizhan Bestembayeva. He collaborates with Bart Hoogenboom (London Centre for Nanotechnology), Stephan Beck (UCL Cancer Institute), Liz Murchison and Michael Stratton (Wellcome Trust Sanger Institute), Peter Cherepanov (CRUK), Ben Berkhout (AMC Amsterdam), Alessandro Marcello (ICGEB Trieste).

The Fassati lab has three main interests: the discovery of new antiviral drug targets, understanding the mechanisms of viral nuclear transport, and understanding the origin and mechanisms of regression of the canine transmissible venereal tumour (CTVT) as a model to understand cancer regression in general.

In 2010 Fassati, with MRC funding, set up a high through put cell based screening facility in the Wohl Virion Centre to perform screenings with live pathogens. In 2012 the first two screening projects were completed and the group made several discoveries; First, Hsp90 is required for HIV-1 gene expression and reactivation during hyperthermia (PLoS Path. 2012). Second, a transcription factor that induces histone acetylation important for HIV-1 gene expression has been identified by chemical genetics. A compound that inhibits the transcription factor has been identified (manuscript in preparation). Third, in collaboration with Robin Weiss and Laura McCoy, a high through put screening was performed and two new llama nanobodies with very broad and potent HIV-1 neutralizing activity have been isolated. Importantly, such nanobodies appear to target the CD4 receptor using the same "angle of approach" of the very broad human neutralizing antibodies recently identified (VCR01, VCR02). A patent has been filed on these new nanobodies and a paper submitted.

In collaboration with Bart Hoogenboom, Fassati is elucidating the biophysical nature of the selective barrier present in nuclear pores using biochemical methods, atomic force microscopy and mathematical modelling. The first paper describing the model was recently published (Phys Rev E 2012) and another experimental paper is currently under review. In addition, with Peter Cherapanov, Ari has contributed the crystal structure of the nuclear transport receptor Transportin 3 and identified critical functional domains for the transport of splicing factors and for HIV-1 infection (PNAS 2014).

In collaboration with Stephan Beck, Liz Murchison and Mike Stratton, the Fassati lab has identified approximately 300 genes that are differentially expressed in progressive or regressive CTVT and mapped epigenetic changes of such genes, which will help to understand the mechanisms leading to its regression (ongoing work). Weiss and Fassati collaborated with the Sanger Centre to elucidate the origins of CTVT (Science 2014).

Ari co-organised the 2013 international meeting "Frontiers of Retrovirology" in Cambridge, which was a significant success http://www.frontiers-of-retrovirology.com/. He was invited speaker at the 6th Nuclear Envelope and Chromatin Organisation" meeting, and at NIMR Mill Hill, London. Ari also joined the CSS2 Basic Science Board of the *ANRS* (Agence Nationale de Recherche sur le Sida et les hépatites).

Paul Kellam PhD

Paul Kellam is the Viral Genomics group leader and Senior Investigator at the Wellcome Trust Sanger Institute and a Professor of Viral Pathogenesis in the Wohl Virion Centre at UCL. Paul's research uses virus and host genetics to understand virus tranmission and disease pathogenesis. Although virus genomes are small they are incredibly diverse and subject to rapid genetic change. This both affords virus adaptation and evolution to but also allows the genetic tracking of viruses as the spread from person to person. Paul's lab used such virus molecular epidemiology to understand more about the emergence of a new human virus, the Middle East Respiratory Syndrome Coronavirus (MERS CoV). In June 2012 MERS CoV caused the first document human fatal case in a man in Saudi Arabia. MERS CoV has since caused over 180 infections with 43% of cases being fatal, mainly in Saudi Arabia. Together with Professor Ali Zumla, the Professor of Infectious Diseases and International Health at UCL and the Professor Ziad Memish of the Saudi Arabian Ministry of Health, Paul's lab showed MERS CoV most likely evolved and diversified in animals and then infected humans, probably on more than one occasion, at which point its was able to spread in a limited way from person to person. This work continues as the MERS CoV infection still occurs in the Middle East.

Paul's lab also continues to investigate virus genome variation during influenza virus infection and how virus diversity within HIV infected patients can predict effective antiviral therapy. The emergence of MERS CoV and pandemic influenza A H1N1/09 virus over the last 4 years shows how little we know about virus diversity and the potential for viruses to jump between animal and humans, so called zoonosis. Therefore, in collaboration with groups in Cambridge and Amsterdam, Paul's lab has used powerful next generation sequencing methods to detect viruses in human and bat samples. Through the Wellcome Trust and Department of Health funded project ICONIC, awarded to UCL, the Sanger Institute and Public Health England, Paul's lab and UCLH virology, will over the next 3 years translate some of these genome scale

methods into clinical virology in the NHS, aiming to sequence and interpret the genomes from 20 000 virus isolates from routine diagnostics.

Paul's lab has continued its work on the human gene Interferon Inducible Transmembrane 3 (IFITM3) which he identified as the first human influenza disease severity determining allele. In collaboration with Oxford University and the Beijing You'an Hospital, we showed that the IFITM3 disease severity genotype was associated with severe influenza in China. We investigated the function of IFITM3 amino acids in preventing influenza and dengue virus infection of cells, showed in a mouse model that IFITM3 seems to only effect the pathogenesis of viruses that enter cells by acidic endosomes and that IFITM antiviral proteins are present and functional in avian species suggesting they maybe important for controlling virus zoonosis. Paul's lab is now continuing to drive the use of virus and host genetic studies in understand the pathogenesis of virus disease and is helping shape the collaborative studies required to do this.

Paper authored by members of the Wohl Virion Centre.

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