Name	VICTOR TYBULEWICZ
Position	Senior Group Leader Assistant Research Director
Year joined *(Crick or founder institute)*	1991

Career History

EDUCATION
1981: BSc Chemistry and Biochemistry, Imperial College, London
1984: PhD MRC Laboratory of Molecular Biology, Cambridge University

POSTS HELD
1984– 1986: Beit Memorial Fellow, MRC Laboratory of Molecular Biology, Cambridge, UK
1986– 1991: EMBO and Irvington Institute Postdoctoral Fellow, Whitehead Institute for Biomedical Research, Cambridge, MA, USA
1991– 1996: Career Track Scientist, MRC National Institute for Medical Research, The Ridgeway, London, UK
1996– 2001: Senior Scientist, MRC National Institute for Medical Research, The Ridgeway, London, UK
200 – 2015: Head of Division of Immune Cell Biology, MRC National Institute for Medical Research, The Ridgeway, London, UK
2007– 2015: Joint Head of Infections and Immunity Group, MRC National Institute for Medical Research, The Ridgeway, London, UK
2013– present: Professor of Immune Cell Biology, Department of Immunology and Inflammation, Imperial College, London UK
2015– present: Senior Group Leader, Francis Crick Institute, London, UK
2019– present: Assistant Research Director, Francis Crick Institute, London, UK

Major Awards, Honours and Prizes

1979 College Scholarship, Imperial College
1981 Governor's Prize, Imperial College
2007 Member of the European Molecular Biology Organization (EMBO)
2008 Fellow of the Academy of Medical Sciences

Membership of external committees, editorial boards, review panels, SABs etc

2000 – 2019 Member of the Editorial Board of the journal “Immunology”
2002 – 2006 Member of the MRC Molecular and Cellular Medicine Board
2010 – Review Editor for Frontiers in T cell Biology
2011 – Review Editor for Frontiers in B cell Biology
2011 – 2012 Member of Cancer Research UK Biological Sciences Committee
2012 – 2014 Council Member, Academy of Medical Sciences
2012 – 2017 Faculty Member, Faculty of 1000
2016 – Scientific Advisory Board, Centre of Membrane Proteins and Receptors (COMPARE), Universities of Birmingham and Nottingham
2016 – present Wellcome Trust Expert Review Group in Immunity, Member

Lab Name	*Immune Cell Biology and Down Syndrome Laboratory*

Research programme and achievements

Signalling in the Immune System

Major Achievements in the Quinquennium

Our aim is to understand signalling pathways that control the development, survival, migration, activation, and differentiation of lymphocytes. We use a combination of mouse genetics, biochemistry, cell biology and immunology.

We showed that memory B cell (MBC) survival requires the B cell antigen receptor (BCR) and the SYK kinase (Ackermann *et al*, 2015, Müller-Winkler *et al*, 2020). Overturning previous publications, we found that MBC survival is very dependent on BAFF and BAFFR, an important finding because anti-BAFF treatment is a major therapeutic approach for autoimmune diseases.

We previously showed that BAFFR transduces signals in B cells via the BCR and SYK, demonstrating unexpected cooperation between these receptors (Schweighoffer *et al*, 2013). More recently, we extended this to show that the LPS receptor TLR4 also signals via BCR and SYK (Schweighoffer *et al*, 2017).

Using a genetic screen, we discovered that the WNK1 kinase is a negative regulator of CD4+ T cell adhesion and a positive regulator of T cell migration, and acts via the OXSR1 and STK39 kinases and the SLC12A-family of ion co-transporters, implying that movement of ions across the membrane is critical for these processes (Köchl *et al*, 2016).

Future Plans

A major aim of our future work is to understand how BAFFR and BCR transduce survival signals to naïve B cells, and what other receptors may play a role. We will use CRISPR screens, proteomics, transcriptomics, genetics and biochemical analysis. We will investigate how stromal cells provide survival signals to B cells through cell-cell contact.

Secondly, we will investigate how MBC develop, survive and function. Using single cell RNAseq we will establish the differentiation pathways that generate MBC, identifying key transcription factors that control this process.

We will investigate how WNK1 regulates T cell migration and adhesion, focussing on the roles pf the downstream OXSR1 and STK39 kinases and the SLC12A-family of ion co-transporters, aiming to understand how ion and water movement regulate T cell biology.

Genetics of Down Syndrome

Major Achievements in the Quinquennium

Down Syndrome (DS), trisomy of human chromosome 21 (Hsa21), results in learning & memory deficits, congenital heart defects, craniofacial alterations and early-onset Alzheimer's, most likely caused by an extra copy of one or more of the ~230 Hsa21 coding

genes. In collaboration with Elizabeth Fisher (UCL), we aim to identify the genes required in three copies to cause DS phenotypes and to establish their pathological mechanisms.

Hsa21 is orthologous to regions on mouse chromosome 10 (Mmu10), Mmu16 and Mmu17. We generated a mouse strain, Dp1Tyb, with increased dosage of the 148-gene Mmu16 region, as well as 8 other strains with shorter duplications, forming a mapping panel to identify the location of DS genes (Lana-Elola *et al* 2016).

We showed that Dp1Tyb embryos develop congenital heart defects very similar to those seen in DS babies and demonstrated that there must be ≥2 causative genes (Lana-Elola *et al* 2016).

We showed that Dp1Tyb mice have locomotor deficits caused by ≥2 genes, one of which is *Dyrk1a*, a kinase (Watson-Scales *et al*, 2018). Furthermore, we found motor neuron loss in these mice and showed a similar loss in humans with DS.

Finally, we showed that while gene expression is dysregulated in DS in clusters, as previously reported, this clustering is unrelated to DS and occurs whenever gene expression changes (Ahlfors *et al*, 2019).

Future Plans

A major future aim is to identify the genes on Hsa21 that are responsible for learning & memory deficits, congenital heart defects and craniofacial changes, and to establish the mechanisms by which they act.

With Trevor Smart (UCL) we have shown that Dp1Tyb mice have increased GABA-mediated inhibition in the dentate gyrus of the hippocampus. We will identify the genes that cause this.

We have found that one of the genes causing congenital heart defects is *Dyrk1a* and mapped a second causative gene to a 6-gene region. We will identify this second gene and establish the mechanisms by which these genes act and the affected cell types.

We have shown that Dp1Tyb mice have craniofacial defects (Toussaint *et al*, bioRxiv). We will map the location of the causative genes and establish their pathological mechanisms.

Finally, we will investigate whether aneuploidy, i.e. an extra chromosome, contributes to DS phenotypes in addition to the effect of increased gene dosage. We will engineer mouse strains carrying Hsa21 either as a separate chromosome or attached to a mouse chromosome; comparison of these will establish whether an additional chromosome contributes to DS pathology.

Research outputs

Lana-Elola, E, Watson-Scales, S, Slender, A, Gibbins, D, Martineau, A, Douglas, C, Mohun, T, Fisher, EMC, Tybulewicz, VLJ (2016). *Genetic dissection of Down syndrome-associated congenital heart defects using a new mouse mapping panel*. ELife 5:e11614. DOI:10.7554/eLife.11614.001

This paper reported the generation of a mouse mapping panel of mouse strains containing duplications of different regions of the mouse genome that are orthologous to human chromosome 21. This panel can be used to study Down syndrome phenotypes and to identify the location of causative genes. Here we showed that the Dp1Tyb mouse strain has congenital heart defects that are very similar to those seen in DS and demonstrated that there must be at least two causative genes mapping their location to a 39-gene region.

Köchl, R, Thelen, F, Vanes, L, Brazão, TF, Fountain, K, Xie, J, Huang, C-L, Lyck, R, Stein, JV, Tybulewicz, VLJ (2016). ***WNK1 kinase balances T cell adhesion and migration in vivo*****. Nat Immunol, 17, 1075-1083. DOI: 10.1038/ni.3495**
In this study we identified the WNK1 kinase as a negative regulator of CD4+ T cell adhesion and a positive regulator of T cell migration. Furthermore, we showed that WNK1 controls migration through the OXSR1 and STK39 kinases and the SLC12A2 ion co-transporter. This was an unexpected finding since WNK1 had been previously shown to regulate salt homeostasis in the kidney. Our study is the first to have implicated movement of Na+, K+ and Cl- ions in the regulation of T cell migration.

Schweighoffer, E, Nys, J, Vanes, L, Smithers, N, Tybulewicz, VL (2017). ***TLR4 signals in B lymphocytes are transduced via the B cell antigen receptor and SYK*****. J Exp Med, 214, 1269-1280. DOI: 10.1084/jem.20161117**
Here we showed that in B cells, the TLR4 receptor for LPS transduces signals that control B cell activation and proliferation via the BCR and the SYK tyrosine kinase. This was an unexpected finding showing how two distinct receptors signal co-operatively and echoed an earlier finding where we had shown that BAFFR also transduces signals via BCR and SYK.

Watson-Scales, S, Kalmar, B, Lana-Elola, E, Gibbins, D, La Russa, F, Wiseman, F, Williamson, M, Saccon, R, Slender, A, Olerinyova, A, Mahmood, R, Nye, E, Cater, H, Wells, S, Yu, YE, Bennett, DLH, Greensmith, L, Fisher, EMC, Tybulewicz, VLJ (2018). ***Analysis of Motor Dysfunction in Down Syndrome reveals Motor Neuron Degeneration*****. PLoS Genetics, 14:e1007383. DOI: 10.1371/journal.pgen.1007383**
In this study we showed that the Dp1Tyb mouse model of DS has locomotor defects, mapped the causative genes to a 25-gene region and identified that *Dyrk1a* is one of these. Furthermore, we found an unexpected progressive loss of motor neurons in these mice and showed that a similar loss is seen in humans with DS.

Müller-Winkler, J, Mitter, R, Rappe, J, Vanes, L, Schweighoffer, E, Mohammadi, H, Wack, A, Tybulewicz, VLJ (2021). ***Critical requirement for BCR and BAFFR in memory B cell survival*****. J Exp Med 218(2):e20191393. DOI: 10.1084/jem.20191393**
Using conditional genetic ablation, we showed that the survival of memory B cells requires the BCR and its signalling subunit CD79A, as well as BAFF and its receptor BAFFR. Finally, we also showed that memory B cells require IKK2 for their survival. Previous studies had only identified 2 proteins that are required for memory B cell survival – this study identified 5 further proteins, substantially increasing our understanding of how these key memory cells are kept alive.