Summary

Extracellular signals need to be processed in a correct manner for a cell to function properly. In many cases the signals are internalised via endocytosis and then processed in a specific manner, e.g. by sorting it to a specific destination. My lab not only tries to understand these basic sorting mechanisms but also tries to exploit our understanding of these routes to deliver cargo to specific destinations in the cell.

Our research thus focuses on the visualisation and perturbation of endocytic events both at the light and electron microscopical level by Correlative Light Electron Microscopy (CLEM) and 3-dimensional electron tomography (see Figure and Brown et al., 2012).

Figure: Internalisation of Epidermal Growth Factor (EGF) coupled to a green fluorophore and a gold particle and Transferrin (Tf) coupled to a red fluorophore and 10 nm gold. Using live light microscopy we can follow the fluorophores moving live inside the cell (A, time in seconds). At timepoint 0 both marker segregate and when we trace back the same cell in the electron microscope (B), we can visualise this segregation event in more detail at higher resolution (C, red arrows point to Tf particles and red arrows towards EGF.

In order to be able to perform such experiments we have to develop software and hardware tools suited for the job. As such, our research is of an interdisciplinary nature and we collaborate a lot with chemists and engineers to develop such tools.

Below are some of the topics that we are currently working on:

1. To study the very early steps of endocytosis we are using Total Internal Reflection Fluorescence (TIRF) and aim to combine those with our CLEM approach.
2. The formation of tubular extensions from endosomes and lysosomes (Brown et al., 2012).
3. Development of CLEM probes that are both fluorescent and electron dense for use in intracellular transport studies (Hodgson and Verkade, 2014). In collaboration with Prof. Dek Woolfson, Chemistry, UoB.
4. Targeting and delivery of molecules to specific destinations in cells, either through tagging molecules (Benito et al., 2014) or encapsulating them (Fletcher et al., 2013). This work is done in collaboration with Carmen Galan and Dek Woolfson in Chemistry.
5. Retracing and overlay in light and electron microscopy images. Work done in collaboration with Alin Achim in Engineering (Nam et al., 2014).

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Biography

Dr. Paul Verkade's research focuses on the sorting mechanisms in intracellular transport pathways. His main tools are microscopy techniques, with an emphasis on electron microscopy (EM) in which field he has published over 50 papers. After his post-doc time at EMBL, Heidelberg, Germany and setting up a new EM lab at the Max Planck Institute for Molecular Cell Biology in Dresden, Germany he moved to the University of Bristol, UK in 2006. Here he set up a new EM unit as part of the Wolfson Bioimaging Facility, a fully integrated light and electron microscopy centre. Besides heading the EM unit he also has his own research group.

His current research focus is to develop techniques and tools for the use of Correlative Light Electron Microscopy (CLEM) studying endocytic sorting. Amongst other things he has developed the Rapid Transfer System for the EMPACT2 high-pressure freezer together with Leica Microsystems. This allows for the combination of time-resolved CLEM with optimal preservation of ultrastructure for EM.

Dr. Verkade is currently chair of the Electron Microscopy section of the Royal Microscopy Society and chair of the Cryo Microscopy Group, affiliated to the Royal Microscopy Society. He has also organised and taught on several courses and workshops on subjects such as high-pressure freezing, Correlative Light Electron Microscopy (CLEM), and immune EM, including EMBO practical courses on CLEM.

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