LOOKING BACK TO TRAFFIC FORWARD: REPORT ON A SYMPOSIUM TO HONOR THOMAS KREIS (1952-1998) AND HIS INSPIRATION

Frances M. Brodsky[1] and Franck Perez[2]

[1]Division of Biosciences, University College London, London WC1E 6BT, UK

[2]Institut Curie, PSL Research University, Sorbonne Université, Centre National de la Recherche Scientifique, UMR 144, Paris, France

In September 1998 the membrane traffic community tragically lost our colleague Thomas E. Kreis in a plane crash. In September 2018, we hosted a symposium in Paris to honor the fruits of his legacy from the previous twenty years and to consider where studies of membrane traffic might lead in the next twenty. Thomas was a founding editor of *Traffic* and his enthusiasm was instrumental to its launch (1,2). Therefore, we chose this 20th Anniversary issue of *Traffic* to report on the symposium that celebrated his influence on the community and to share the emerging discussion about cell biology of the future.

Thomas was an outstanding cell biologist who pioneered dynamic analysis of intracellular membrane traffic, contributing seminal research on microtubules and their role in intracellular transport (see for example 3-11). He was a wonderful colleague to members of the cytoskeleton and the membrane traffic communities and was also very active in these communities. At the time of his passing, Thomas was Chair of the Cell Biology Department in Geneva, served on a number of advisory and journal boards and as co-editor of the encyclopedic Guidebook to the Cytoskeletal and Motor Proteins (12). His loss was mourned in obituaries that appeared in the Journal of Cell Biology, Nature

(13) and Trends in Cell Biology (14). In tribute to Thomas the 2018 symposium in his honor was supported by the journal Traffic, the Institut Curie, University College London, the French Society for Cell Biology (SBCF), the LabEx CelTisPhybio and Donna Saint George for the Thomas Kreis Legacy. Participants (Figure 1) included colleagues, collaborators and former lab members from the USA, Europe and Israel, who all supported their own travel and accommodation. PhD students from the Institut Curie, as well as local colleagues from Paris attended. We were especially thrilled to have Donna Saint George (widow) and Eric Saint George-Kreis (son) join us from the USA and Switzerland for the symposium.

The symposium included talks from cell biologist colleagues with particular reference to how their work was inspired by interactions with Thomas, as well as personal reminiscences. What was also special for everyone present was a focus on where the science discussed is going. Thomas foresaw how important dynamic microscopy imaging would become for understanding intracellular transport, which indeed played out over the past twenty years. The participants strove to identify equivalent new developments and challenges for the next twenty, which produced the following predictions and directions.

Molecular cell biology of the past twenty years has realized the definition of basic membrane traffic pathways and identified not only key molecules, but also the intracellular molecular machines involved. Basics of their structure and regulation by signaling have emerged and their dynamics visualized. Much of this work was enabled by genetic studies in yeast and model organisms and biochemical reconstitution of trafficking steps (recognized by the Nobel Prize of 2013 to Rothman, Schekman and Südhof), as well as developments in imaging and structural studies. It is clear that the

next frontier is to integrate this knowledge in multi-scale models to understand how these processes are linked. This challenge includes connecting our understanding of molecular machines with their functions in intracellular pathways, linking two-dimensional studies of cell function to three-dimensional interactions in organs and tissues, and linking cellular pathways to physiological processes dependent on organ and tissue interaction (direct and at a distance). To achieve the latter, it will be necessary to consider how intracellular pathways affect whole body metabolism, immune system and nervous system function, and development of complex organisms. Additionally, the converse must be considered: how physiological and genetic conditions influence cellular processes. For example, how circadian rhythms, gender and aging affect intracellular pathways is only just beginning to be appreciated. The resulting cellular plasticity will of course feed forward to change systemic conditions. Currently the field has linked genetic mutations with cellular and developmental phenotypes in model systems and with diseases in humans. Defects in membrane traffic are associated with cancer, diabetes, cognitive disability, musculoskeletal disease, cystic fibrosis and microbial pathogenesis. However, to truly understand how a single mutation influences disease the problem of multi-scale integration from the molecular to the physiological will need to be addressed. This will also hold true for understanding how pathogens hijack intracellular pathways and, conversely, what we can learn from this about infection and about host cell function.

To meet the multi-scale integration challenge, there are cutting edge approaches that need to become routine, as well as a need for development of new technologies. The contributions of computational data analysis and modeling, as well as chemistry and physics to understanding how intracellular pathways impact biology are opening up new ways of thinking. The need to understand phenomena like mechano-transduction and

the effects of small metabolites underscore the importance of integrating physics and chemistry with cell biology. These cross-disciplinary approaches will also lead to new tools, as physics and computational advances have already expanded imaging capabilities and intracellular chemical modification has enabled local probing of protein interaction. Further developments in chemical biology and ways of measuring physical properties of cells and tissues will be key to multi-scale integration. The community wish list also includes better methods of acute interference in cellular processes to study their influence in real time, as well as live cell imaging at super-resolution. Last, while the use of cell models will continue to dominate the field, in particular thanks to genetic approaches like CRISPR/CAS9 and the progress of high resolution imaging, it is clear that cell biology will move to more complex systems that benefit from the same revolutions. Stem cells, organoids, tissues as well as full organisms will be used in dynamic imaging and functional studies aiming again at better integration.

The cell biology of membrane traffic will also continue to gain from other fields of biology. Studying host-pathogen interactions has revealed specific functions of intracellular pathways by identifying pathways that are exploited for infection and thereby uncovered new regulatory processes. The power of phylogenetic comparison and population genetic analysis has already become apparent and further exploitation of these considerations for intracellular pathways will help understand tissue specialization. This evolving appreciation of diversity will build on decades of reductionist analysis to discover how biological complexity functions in health and disease.

A major concern and challenge is connecting “big data” with strategic “small” science. This is already being confronted as we try to utilize proteomics, metabolomics, genetic diversity and other data sets for analysis of intracellular pathways. With these

approaches, cell biology has, in some ways, returned to old-fashioned data collection. Although the modern Darwin might now use algorithms for analysis, data interpretation still relies on acute observation and search for novel patterns. While the importance of statistics is paramount, need for intuition and thoughtful testing of emerging hypotheses has not disappeared. Here again, gene editing and acute perturbation of cellular functions and pathways will be essential tools in the near future. So, the imagination that inspired Thomas Kreis to take new approaches and open up new avenues remains a key feature of our future enterprise in cell biology. And above all, remembering Thomas, we were reminded of the importance of having fun while pursuing it.

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Figure 1: 20 Years of Cell Biology: A tribute to Thomas Kreis-September 25, 2018

Some of the participants the symposium (clockwise from below the photos of the lecture hall at the Institut Curie: Franck Perez (co-organizer); Frances Brodsky (co-organizer); Philippe Pierre; Genvieve Milon; Isabelle Tardieux; Eric Saint George-Kreis; Donna Saint George; Mark Marsh; Bernhard Dobberstein; Ari Helenius; Martin Lowe; Gisou van der Goot; Jean Gruenberg; Trina Schroer; Philippe Pierre; Holly Goodson; Sandy Schmid; David Stephens; Frank Lafont; Kai Simons