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The Biochemistry Department of the University of Geneva: Understanding the Molecular Basis and Function of Intracellular Organization

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Abstract: The Biochemistry Department at the University of Geneva currently has four full professors, a professor emeritus, one assistant professor, two MER (*Maître d'enseignement et de Recherche*) and a permanent scientific collaborator. The research interests of the members of the Biochemistry Department are described.

Keywords: Animal cells · Cell division · Dictyostelium · Drosophila · Endocytosis · Lipids · Organelles · Secretion · Signaling · Yeast · Zebra fish

Introduction

The Biochemistry Department at the University of Geneva currently has four full professors, a professor emeritus, one assistant professor, two MER (*Maître d'enseignement et de Recherche*) and a permanent scientific collaborator (Fig. 1). Two of the professors have joint appointments with the Department of Molecular Biology, *Thanos Halazonetis* has his laboratories in Molecular Biology and *Marcos González-Gaitán* has his laboratories in Biochemistry. The director is chosen yearly by consensus and is currently *Howard Riezman*. The department teaches informatics for chemists and biochemists, as well as biochemistry at all levels. The research in the department is highly focused on membrane biology and cellular organization, however the systems used and the questions addressed are highly diversified (Fig. 2). Most of the topics of research concern the biosynthesis, function and trafficking of membranes. The groups of González-Gaitán, *Gruenberg*, Riezman and *Soldati* have all worked on the pathway of endocytosis, especially concerning the roles of endocytosis in fly development, the formation of multivesicular bodies in animal cells, the internalization step in yeast, and phagocytosis in *Dictyostelium discoideum*, respectively. The *Watanabe* and Riezman groups have worked on membrane trafficking from the endoplasmic reticulum. The *Laemmli* group works on nuclear organization and how it regulates gene expression. The *Matter* group works on developmental neurobiology and his laboratories are housed in the department of Animal Biology. *Olivier Schaad* has specialized in bioinformatics and has been involved in data analysis of transcription and lipidomics. In this short article the research accomplishments of the different groups are exposed.

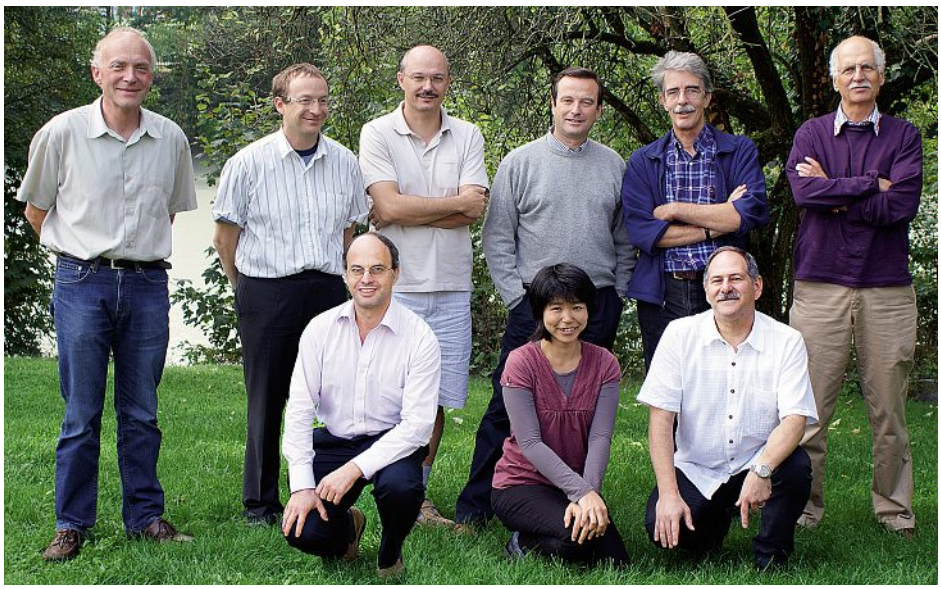

Fig. 1. Current members of the Biochemistry department at the University of Geneva (October 2009). Top row, left to right, Jean-Marc Matter, Olivier Schaad, Thierry Soldati, Marcos González-Gaitán, Jean Gruenberg, Ulrich Laemmli, bottom row, left to right, Thanos Halazonetis, Reika Watanabe, Howard Riezman

In and Around the Nucleus

Linking the regulation of gene expression to ontogenesis remains a major issue in developmental neurobiology. The *Matter* group is interested in defining how the interplay between regulatory factors and key transcriptional targets coordinates the complex processes of neuron specifica-

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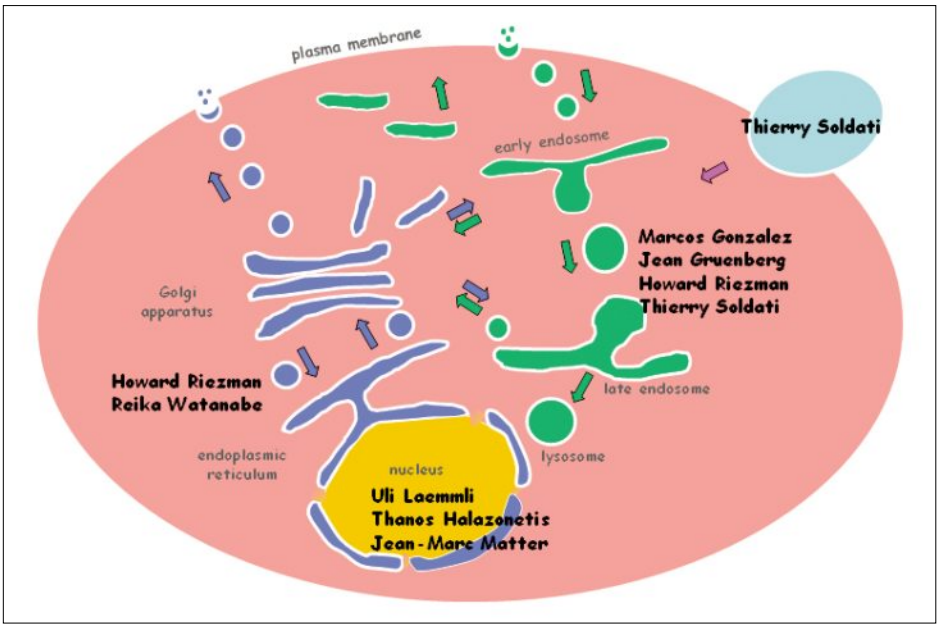

Fig. 2. A schematic representation of the cell with the names of the groups and the cellular structures on which they work.

tion and morphogenesis of the retina.[1] Although retina development relies on the whole on regulatory proteins widely expressed in the developing nervous system, Atonal homolog 5 (Ath5) expression is a specific feature of retina ontogenesis.[2] The group focuses on the regulation and function of Ath5 as a key determinant of the retina cell fate and as an important regulator of neuronal patterning. They ask how Ath5 interconnects a cell fate decision with the genetic pathways that regulate cell cycle exit, cell polarity and cell migration.

The characterization of interspecies differences in gene regulation is crucial to understanding the molecular bases of phenotypic diversity and evolution. Ath5 participates in the ontogenesis of the vertebrate retina. Their study reveals how evolutionarily conserved, non-coding DNA sequences mediate both the conserved and the species-specific transcriptional features of the Ath5 gene.[3,4] In the mouse and chick retinas, species-related variations in the chromatin-binding profiles of bHLH transcription factors correlate with distinct features of the Ath5 promoters and underlie variations in the transcriptional rates of the Ath5 genes.[5–7] The different expression kinetics of Ath5 generate differences in the expression patterns of a set of genes regulated by Ath5 in dose-dependent manner, including those involved in neurite outgrowth and growth cone migration. In sum, they show how highly conserved regulatory elements are put to use mediating non-conserved functions and creating interspecies neuronal diversity (Skowronska-Krawczyk *et al.* in press).

Prof. *Thanos D. Halazonetis* began his career investigating the control of transcription[8,9] where he made important contributions before shifting his attention to oncogenesis, in particular the role of DNA damage in cancer. He has become a world leader in this field in which he has investigated the mechanism whereby cells detect and respond to DNA damage, in particular double strand DNA breaks.[10–20] These studies have important implications for the understanding of the origins of cancer, in particular, because DNA damage and the way a cell deals with it seem to be early predictive parameters for oncogenesis.

In recent years, *Olivier Schaad* has focused on the analysis of microarray data. He was concerned with the subsequent management of the huge amounts of computer data, and development of software to analyse microarray data.[21–29] He approached the analysis of microarray data in a quantitative manner starting by the developing of software for the automation the analysis of microarray data.

A recent focus of his work has been the study of microarray data for the analysis of circadian gene expression.[25] The discovery of circadian transcripts is a challenging task. There are two major difficulties: the lack of high temporal resolution in the levels of expression of the transcripts of interest and the large number of probesets (>45,000) to analyze. He developed an automatic and robust procedure that addresses these challenges. The algorithm combines Fourier analysis, random permutation, and least square optimization.

Prof. *Ulrich K. Laemmli* has been a pioneer in the fields of biochemistry and molecular biology. His early work was on the biogenesis of bacteriophage particles and among these classic papers in the field of molecular genetics is one of the most highly cited studies in the history of science.[30–36] The bacteriophage work was done before Prof. Laemmli moved to Geneva. When he arrived in Geneva he devoted most of his efforts towards the study of how eukaryotic chromosomes are organized and has published numerous articles in this field in the most prestigious journals.[37–45] His work revealed the presence of a nuclear scaffold to which the DNA is attached. This creates chromosomal DNA loop structures. These structures are important features, not only to explain how the DNA is organized in the nucleus, but also how gene regulation is controlled. More recently he has shown that nuclear pores interact with the promoter regions of genes influencing their expression[46] and he has introduced novel technology to rapidly inactivate proteins by sequestering them away from their site of action.[47]

Intracellular Trafficking and Membrane Biogenesis

The major aim of the *Soldati* group is to understand the integration, the cooperation of signalling, cytoskeleton and membrane trafficking in phagocytosis and its relevance to host–pathogen interactions. To this end, they use the social amoeba Dictyostelium as a model organism as it is a professional phagocyte very similar to mammalian phagocytes of the innate immune system in morphology and behaviour, but it is genetically and biochemically tractable.[48] In the recent past, their work has concentrated on the lipidomic and proteomic characterisation of phagosomal components[49] (Dieckmann and Soldati, in press), as well as on the molecular dissection of the role of actin and class I myosins in the formation and closure of the phagocytic cup, and in the flux of membrane during maturation and recycling from endosomes/phagosomes.[50] The projects are being extended to include other major regulators of the specificity and efficiency of membrane transport such as the Rab GTPases and the exocyst tethering complex.

Crucially, the group has established Dictyostelium as a model host to study infection and dissemination of pathogenic mycobacteria.[51] Interestingly, pathogenic mycobacteria such as *M. tuberculosis*, *M. marinum* and *M. leprae* use common strategies to invade phagocytes of the innate immune system, manipulate their otherwise bactericidal phagocytic apparatus and increase the success of cell-to-cell transmission. *M. marinum*, a fish pathogen, is the closest relative to the tuberculosis group of mycobacteria and provides a powerful model to study the pathogenesis of tuberculosis in genetically tractable model organ-

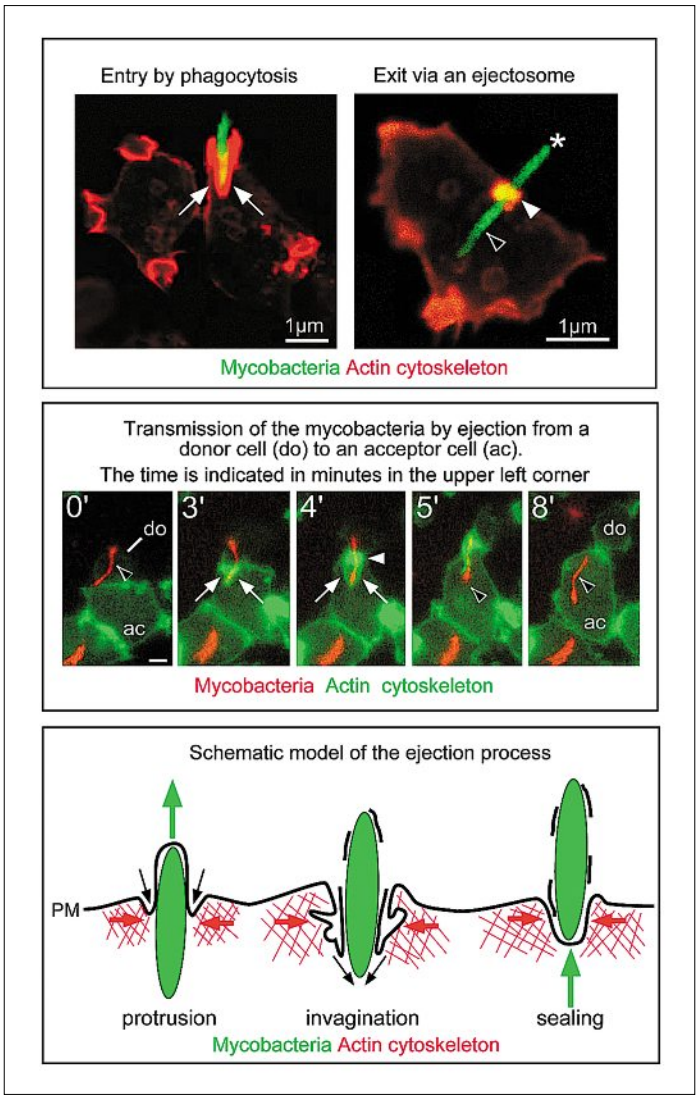

Fig. 3. Entry and exit of Mycobacteria into and out of *Dicytostelium discoideum*. The entry and exit of Mycobacteria into Dictyostelium requires action and the co-localization of actin with the bacterium is shown in the top panels. The middle panels illustrate the transfer of Mycobacteria from one cell to another. The lower panel presents a schematic model of the process.

isms, such as Drosophila and zebrafish.[51] In particular, the Soldati group discovered that both *M. marinum* and *M. tuberculosis* can escape from their vacuole into the cytosol, and are then ejected from the cell through an F-actin structure, they named the ejectosome.[51] Ejection is crucial for the maintenance of an infection and is a concerted process that requires both host and pathogen factors. They propose that this specific strategy evolved as a necessity for the release of a cytosolic pathogen in a mutually beneficial manner, and discuss its evolutionary origin and relevance for dissemination of a mycobacterial infection (Fig. 3).

Most cells, including single cell organisms such as bacteria and multicellular organisms such as vertebrate, show particular shape and cell polarity. Especially when individual cells come together to form complex multicellular tissues, the cells establish polarity to localize different proteins and lipids in the distinct regions of cells. Protein and lipid traffic is important in cell polarity formation and maintenance. The *Watanabe* group is studying the role of membrane traffic in cell polarity in mammalian cells. The glycosylphosphatidylinositol-anchored proteins (GPI-APs) are a group of lipid-anchored proteins expressed on the cell surface of all eukaryotic cells. It has been shown that most GPI-APs are localized in the apical domain of polarized epithelial cells. In yeast, it has been shown that GPI-APs are already sorted from other secretory proteins in the ER before arrival at the Golgi apparatus where proteins of the different localization within the cells are sorted.[52] Furthermore, they found evidence that GPI-APs and sphingolipids, lipids known to have a preferential localization in apical domain of epithelial cells, are co-transported from ER in yeast.[53,54]

Recently, Prof. Watanabe has focused on studies in mammalian cells and found that GPI-APs and transmembrane proteins are only partially segregated upon ER exit in contrast to the remarkable segregation seen in yeast. They also found differential requirements for GPI-APs ER exit in yeast and mammalian cells. The different mechanisms explain the different behaviors regarding their segregation from non GPI-APs upon ER exit (manuscripts under preparation). Now they are investigating how GPI-APs are sorted at the Golgi apparatus in mammalian cells using biochemical, morphological and genetic approaches. They also investigate the role of GPI-APs in lipid transport and cell polarity formation in mammalian polarized epithelial cells using the three-dimensional cell culture system, where one can reconstitute epithelial cyst and tubule formation derived from single cell.

Prof. *González-Gaitán* is a pioneer in using cell biological techniques to study the role of membrane trafficking in developmental biology. Before coming to Geneva he made important discoveries concerning the endocytic pathway in Drosophila development,[55,56] in particular the role of endocytosis in the creation and dynamics of a morphogen, TGF-β gradient. Several subsequent articles on morphogen gradients appeared from the lab[57–62] and they have successfully combined the use of physics with cell biology to carefully describe the different parameters that contribute to the formation of the TGF-β gradient.

Since coming to Geneva the laboratory has investigated the relationship between the endocytic pathway and intracellular signaling, mainly in Drosophila,[63–67] but more recently in zebrafish as well. They have focused on Notch signaling, a pathway that has important implications for control of cell division, cancer and development. His recent contributions, in particular his use of quantitative approaches to study development, have made him a leading figure in this field internationally.

The long-term interest of Prof. *Jean Gruenberg* has been to investigate the mechanisms that control the movement and the sorting of proteins and lipids within the cell, especially the pathway of endocytosis and more particularly endosomes. More specifically, higher eukaryotic cells contain a complex system of intracellular organelles or compartments (the vacuolar apparatus) that are interconnected by membrane flow (intracellular traffic).[68–70] They have designed novel biochemical assays that reconstitute individual steps of membrane traffic *in vitro*, so that complex molecular events can be analyzed in a highly quantitative manner and manipulated in the test tube.[71,72] Using this strategy, they have for example investigated the role of small GTPase in membrane docking and fusion.[73–75] Such biochemical experiments complement biochemistry with cell and molecular biology strategies *in vivo*, including electron microscopy and video microscopy – and *vice versa*. Using this approach, combined with cell and molecular biology strategies *in vivo* including electron microscopy and video microscopy,[76] they have studied membrane trans-

port along the endosomal pathway leading to lysosomes.

The Gruenberg laboratory was the first to describe the presence of a unique lipid, lysobisphosphatidic acid, in endosomes[77] and they have shown that this lipid is important for endosome architecture[78] as well as handling of cholesterol.[79] They have also made crucial discoveries on the role of the endocytic pathway in virus infection.[80–82] One of their main interests today is to study mechanisms that drive organelle biogenesis and maintenance – how organelle architecture controls functions. One of their recent observations shows that during endosome biogenesis, membrane transport is coupled to membrane deformation *via* the cytoskeleton, ensuring that the organelle growth and maturation are coordinated.[83,84] They continue to investigate the mechanisms and molecular machineries that control the architecture and functions of endosomes and the onset of the degradation pathway. They wish to characterize how membrane dynamics and protein sorting is controlled in time and space, and thus how membrane homeostasis is regulated at the organellar level.

The interests of Prof. *Howard Riezman* also concern the structure, function and biogenesis of biological membranes. His initial studies as an independent group leader pioneered the use of *Saccharomyces cerevisiae* as a model system to study the endocytic pathway.[85,86] After moving to the Biozentrum they published on mutants in endocytosis[87–89] and showed that actin,[90] calmodulin,[91] type I myosins,[92] ubiquitination of cell surface receptors,[93,94] and specific lipids[95–98] are required for endocytosis. Initially, it was thought that these requirements might be specific to yeast, but more recent studies show that the basic endocytic mechanisms are conserved.[99]

A second major interest has been the synthesis and transport of a specific class of plasma membrane proteins, linked to the membrane by a glycolipid, called GPI. Together with Prof. *Andreas Conzelmann* (University of Fribourg) they identified and cloned the first GPI-anchored protein genes in yeast.[100,101] The Riezman lab used a screening technique to identify chemicals that affect the synthesis[102] and transport[103] of GPI-anchored proteins. They were also among the first to identify genes required for GPI synthesis[104–106] and anchor attachment.[107,108] Following the intracellular transport of GPI-anchored proteins, they found several specific requirements for exit from the endoplasmic reticulum[103,109–112] and have shown that GPI-anchored proteins are sorted from other secretory proteins upon ER exit, both by biochemical reconstitution techniques[53,113–115] and by microscopy.[52,116]

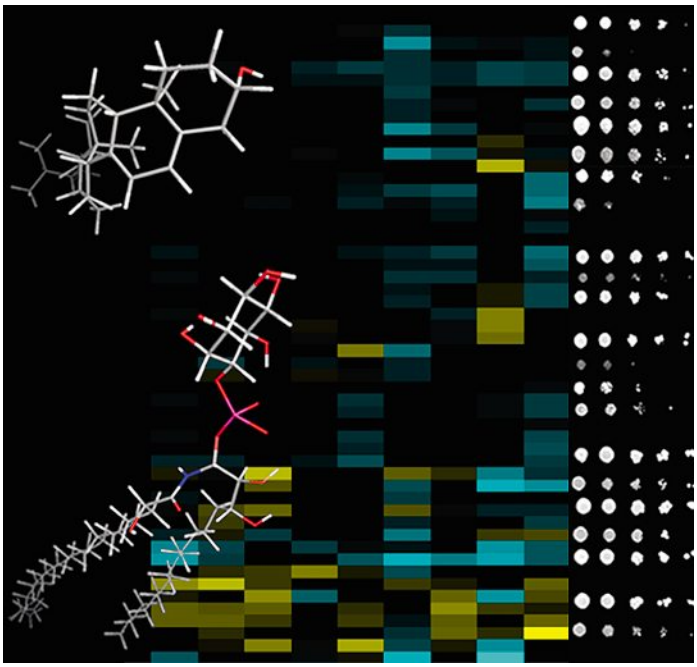

Fig. 4. Representation of the novel approaches used by the Riezman lab in collaboration with the Wenk lab to investigate sterol and sphingolipid functions in yeast. Shown is an example of how quantities of different individual lipid species in various yeast strains can be displayed and the corresponding growth of the yeast measured under different conditions. The major yeast sterol and sphingolipid structures are shown.

The most recent studies from the Riezman laboratory focus on the role of lipids in cell biology and physiology. They have taken on the challenge to address, in a general and unbiased way, the role of sterols and sphingolipids in biology. The initial results look very promising with implications of sphingoid bases in endocytosis[97] and protein translation after heat shock,[117,118] convincing evidence that sterols and sphingolipids interact in biological membranes,[22] roles for sphingolipids in GPI-anchored protein transport,[103,109,113] and most recently in determining the capacity of the worm, *C. elegans*, to respond to anoxic conditions.[119] The latter work has depended upon recent advances in mass spectrometry of lipids (Fig. 4) which the laboratory is using to address the genetic control of lipid metabolism and function.

The year 2009 has been already been particularly remarkable with no less than three articles appearing in the leading journals *Science* and *Nature*,[51,65,119] as well as other quite notable publications including a paper selected as *Molecular Biology of the Cell* paper of the year.[21–23,83,120–122]

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