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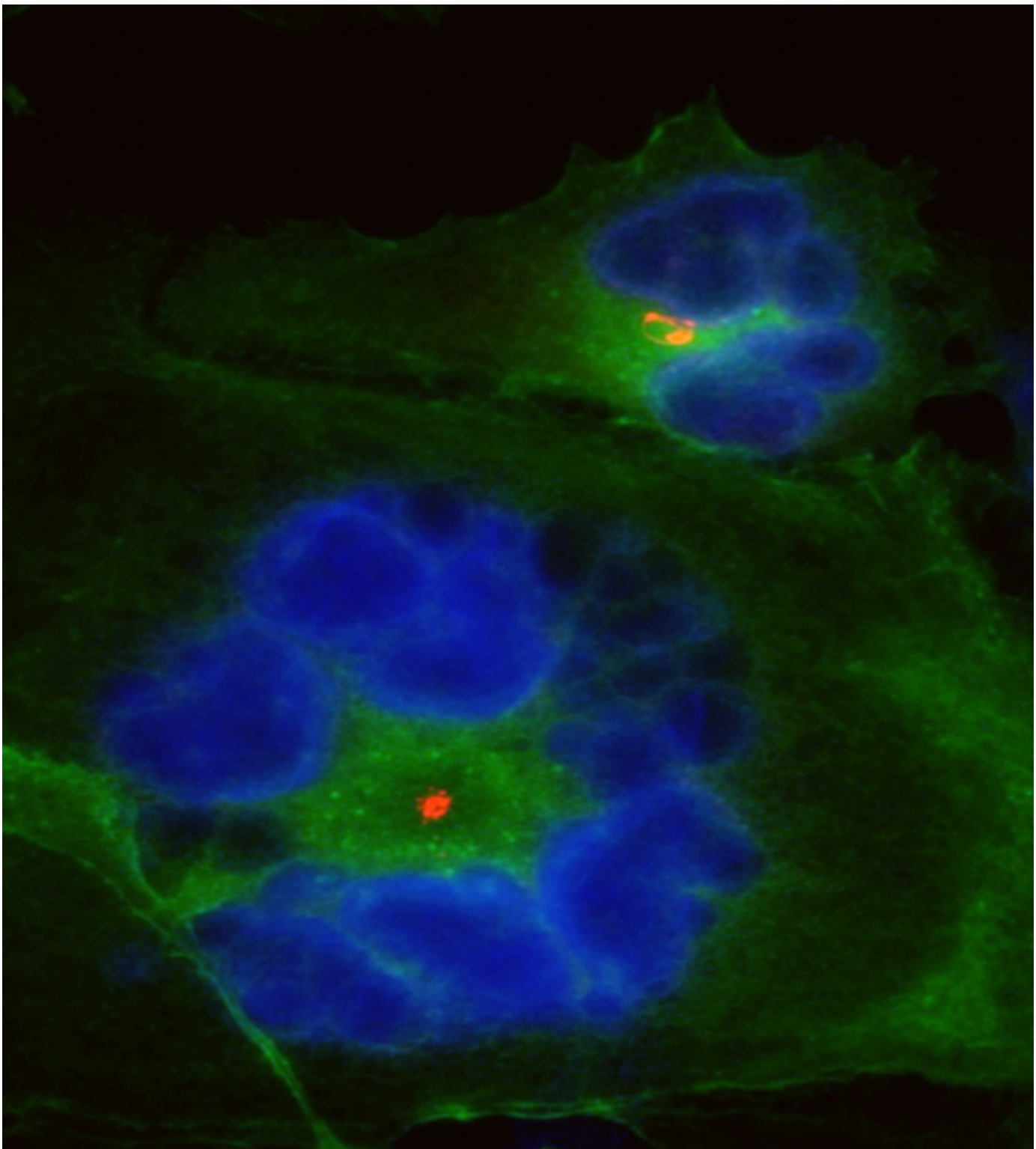

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Cover page: The Synthetic Lethal Rosette

Aberrant mitotic phenotype found in BRCA1-deficient cells treated with the PLK1 inhibitor Volasertib. Cells become giant and multinucleated and acquire a flower shape, with nuclei arranging in a circular disposition around a cluster of centrosomes. Blue (DAPI: nuclei), Green (FITC-phalloidin: actin cytoskeleton), Red (γ-Tubulin: centrosomes).

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detergent micelles or lipid bilayers, mechanistic insights into the detection of these processes in vacuum are still not clear. By combining nMS on membrane transporters, such as EmrE and Sav1866, and molecular dynamics simulations, we have been able to characterize the phosphatidylethanolamine and cardiolipin binding to specific regions of the transporters. In addition, via nanomechanical simulations of the collision events between lipid-transporter complexed to detergent micelles and gas molecules in vacuum, we can propose the interaction energy pattern associated with detection of the lipid-transporter complexes. Taken together, these data lead to a molecular mechanism of the release of lipid-membrane proteins in the gas phase and highlights the role of lipid binding to control protein stability. *Funded by Millennium Science Initiative P10-035F and Wellcome Trust Programme #088150/Z/09/Z grants.*

LI-03
REGULATION OF SPHINGOSINE-1-PHOSPHATE AND ITS ROLE FOR CHRONIC INFLAMMATION AND CARCINOGENESIS

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For the last 15 years, sphingolipids (SphL) have been the focus of the research in my group. SphL enzymes generating sphingosine-1-phosphate (S1P), dephosphorylating and degrading it, as well as S1P receptors have been analyzed mainly in immune cells *in vitro*. The understanding of the *in vitro* function of S1P but moreover its role *in vivo* in chronic inflammation has been boosted by the success but also adverse effects of fingolimod (FTY720-phosphate) a modulator of 4/5 S1P receptors. SphL and its main representative S1P are basic lipid mediators ascribed to cellular functions like survival, proliferation, and migration, with a most prominent role as immune modulators and targets of clinical relevance in autoimmunity and chronic inflammation. Currently, new functions of S1P in basic cellular energy metabolism and carcinogenesis start to be addressed. Initially, the S1P receptor 1 (S1PR1) was the dominant therapeutic target. Meanwhile, more detailed knowledge gathered recently about the other four S1P receptors 2-5 (S1PR2-5) by us and others unraveled a vastly more complex picture of S1Ps actions and possibly, new therapeutic immune-modulatory applications. In this presentation, these newly defined actions will be covered in some detail rather than the "S1PR1-dependent lymphocyte sequestering effect". In addition, new findings of immune relevance regarding sphingolipid enzymes and transporters will be included and are briefly mentioned. New concepts of the spatial organization of adaptive immune cells, central memory versus local, tissue-resident memory lymphocytes, are arising in the field of immunology and clearly challenging the textbook concepts. Their meaning for the concepts of SphL and S1P immune function and subsequent possible new therapeutic targets will be discussed. In conclusion, the immune cell type- and their differentiation status-dependent expression of S1P receptors, the regulation and the activity of SphL enzymes, and transporters of the SphL pathway, vastly extend the scope of therapeutic options of SphL-targeting modulators in chronic inflammation, fibrotic diseases, and carcinogenesis.

LI-04
BIOSYNTHESIS OF SPHINGOLIPIDS WITH VERY-LONG-CHAIN PUFA: A HALLMARK OF DIFFERENTIATING MALE GERM CELLS

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The sphingomyelins (SM) and ceramides (Cer) of rodent spermatogenic cells contain very-long-chain (C28-C32) polyenoic fatty acids (VLCPUFA), in non-hydroxy (n-V) and 2-hydroxy (h-V) forms. The SM and Cer species with n-V, present in meiotic spermatocytes, become in part h-V species in post-meiotic spermatids. In each of these cells, the mentioned species are located in the non-raft fraction of the plasma membrane. The enzymes required for PUFA elongation to n-V, Elovl5, Elovl2 and Elovl4, and the fatty acid 2-hydroxylase (Fa2h) that converts n-V to h-V, are expressed in germ cells, with Elovl4 and Fa2h protein levels being highest in spermatocytes and spermatids, respectively. The Cer and SM species with n-V and h-V are biosynthesized *de novo* in a germ cell type-specific and steroid hormone-dependent manner. CerS3, which specifically N-acylates VLCPUFA to sphinganine, is highly expressed in meiotic cells. The Elovl4 and CerS3 protein expression prevails in spermatocytes, is seminiferous stage-specific, and is mostly concomitant. In spermatids, the Fa2h protein appears concentrated in late stages, especially when they elongate and their heads change shape. The unique sphingolipid species with n-V and h-V, as well as the enzymes involved in their biosynthesis, are useful biomarkers for investigating normal and pathological aspects of germ and sperm cell functions. *Supported by SGCyT UNS-PGI-UNS (24/B272 to GMO and 24/B218 to MIA), FONCyT (PICT2017-2535 to GMO).*

PL-01
MEMBRANE REMODELING DURING ENDOSOMAL SORTING

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Endocytosis and endosomal trafficking control the turnover of plasma membrane proteins, a critical process for cell survival, development, and physiological responses. Ubiquitylated plasma membrane proteins are internalized by endocytosis and delivered to endosomes, where they are sorted by the ESCRT (Endosomal Sorting Complex Required for Transport) machinery into endosome intraluminal vesicles for their final degradation in the vacuole. Besides their role in endosomal sorting, ESCRT proteins play other essential functions, by remodeling cellular membranes during cytokinesis, plasma membrane wound repair, nuclear envelope reformation after mitosis, and autophagy. I will discuss the diversification and functional specialization of plant ESCRT proteins and a novel membrane remodeling mechanism operating in plant endosomes.