Stress granules in ascidians: dynamics of formation and role in immune responses.
Contact: Prof. Loriano Ballarin, e-mail: loriano.ballarin@unipd.it

Stress granules (SGs) are cytosolic, non-membrane bound RNA-protein assemblies of silent mRNAs and proteins. They form when translation initiation is limiting, which occurs during many stress responses.

Main aim of the project is to shed light, at cellular and molecular level, on the dynamics of SG formation in ascidians, with particular reference to the solitary species *C. robusta* (where we recently identified the transcripts for the proteins TIAR and TTP, involved in the formation SGs) and the colonial species *Botryllus schlosseri*, easily found in the Lagoon of Venice.

Specific tasks are: 1) Identification of other proteins involved in SGs formation in tunicates, the sister group of vertebrates; 2) Study of the transcription of TIAR, TTP and newly identified proteins under stress conditions; 3) Location of stress protein transcripts through *in situ* hybridisation; 4) Study of the dynamics of SGs formation using anti-TIAR and TTP specific antibodies; 5) Study of the relationships between SGs and immune responses through knockdown, by RNA interference, of genes for TIAR and TTP.

Alpha-synuclein dependent activation of NLRP3 inflammasome in Parkinson's disease.
Contact: Prof. Luigi Bubacco, e-mail: luigi.bubacco@unipd.it

Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons and by the presence of inclusions (Lewy bodies), composed mainly of aggregated alpha synuclein (a-Syn), along with sustained neuroinflammation. Whether a-Syn accumulation is a cause or a consequence of neuroinflammation is still unclear. A crucial component for the development and perpetuation of neuroinflammation is the nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing 3 (NLRP3) inflammasome, a subcellular multiprotein complex highly expressed by microglia, the immune cells of the brain. Aggregated a-Syn has been recognized to induce an inflammatory response through a mechanism that depends at least in vitro on NLRP3 inflammasome assembly and autocatalytic activation of its component protease caspase 1. Besides cleaving pro-forms of interleukins -1 and -18, caspase-1 can also cleave a-Syn, which results in a C-terminally truncated a-Syn with increased propensity to form aggregates, which in turn exacerbate neuroinflammation and may also act as an amplification loop between inflammation and inflammasome activation. We hypothesize that a-Syn and NLRP3 inflammasome may set in motion a self-propagating vicious cycle that promotes a-Syn aggregation and further amplify neuroinflammation through inflammasome activation. To shed light on this outstanding question, in this PhD project we propose to investigate the effect of a-Syn on microglial NLRP3 inflammasome activation both in mouse and adult human microglia in vitro along with in vivo murine disease models, and investigate whether NLRP3 inflammasome activation is essential for the propagation of pathological a-Syn and the associated progression of PD. By addressing the connection between neuroinflammation and a-Syn aggregation we aim at identifying potential modulators of the inflammasome response, the on-site target, to halt or to slow PD progression.

Investigation on the role of CD300e receptor as immune checkpoint.
Contact: Prof. Marina de Bernard, e-mail: marina.debernard@unipd.it

Cancer cells have the ability to activate different immune checkpoint pathways that harbour immunosuppressive functions. Monoclonal antibodies that target immune checkpoints provided an immense breakthrough in cancer therapeutics.
One of the mechanisms adopted by tumours to escape from the immune surveillance consists in silencing the molecules involved in the antigen presentation to effector T cells, by APC cells (i.e. macrophages). These molecules are coded by genes clustered in a locus called *Human Leukocyte Antigen (HLA)*. Recently, we found that the engagement of the immune receptor called CD300e in human macrophages, by an agonistic monoclonal antibody, leads to the downregulation of HLA class II (HLA-II) expression. As result, macrophages are strongly impaired in their ability to activate T cells in an antigen-specific manner. This evidence supports the notion that CD300e might act as an immune checkpoint regulating both physiological and pathological expansion of T cell-mediated responses, and thus, it could become an attractive target for immune therapy.

The PhD project aims at: 1) Identifying the ligand of CD300e and the signalling cascade responsible for HLA-II silencing; 2) Assessing whether CD300e is differentially expressed in the distinct macrophage populations that accumulate in normal and in pathological tissues (including tumors); 3) Determining the pattern of gene expression in macrophages expressing CD300e following the activation of the receptor.

Modeling human mitochondrial diseases in Drosophila melanogaster.
Contact: Dr Cristiano De Pittà, e-mail: cristiano.depitta@unipd.it

Mitochondrial disorders (MD) are a group of mitochondria---related diseases caused by mutations in either nuclear DNA genes, encoding proteins with a role in mitochondrial function, or in mitochondrial DNA protein or tRNA and rRNA encoding sequences. These diseases are among the most frequently inherited neurometabolic disorders, and are characterized by a wide diversity of clinical features making their diagnosis quite challenging. The availability of model organisms, that recapitulate clinical manifestations and molecular aspects of a specific human pathology, provide valuable insights to clarify the relationship between gene mutations and pathogenesis. *D. melanogaster* is a useful tool to investigate the biological and pathological role of mithochondrial disease genes by using behavioral, biochemical, molecular and genomic approaches. Our group has already successfully elucidated the role of some genes involved in MD such as *dTTC19*, *dSurf1*, *dRim1*, *dMpv17* and *dApopt1/Coa8*. Phd student will be involved in the functional and molecular characterization of *D. melganogaster* ortholog of the human MD gene *BCS1L*, associated to GRACILE syndrome with severe CIII deficiency.

Unravelling calcium-mediated signalling pathways in arbuscular mycorrhizal symbiosis.
Contact: Prof. Lorella Navazio, e-mail: lorella.navazio@unipd.it

Arbuscular mycorrhiza is a widespread and ancient symbiosis between most land plants and fungi of the Glomeromycotina subphylum. This symbiotic association improves plant mineral nutrition and decreases the environmental impact of agricultural practices. The project aims to analyze the calcium-based signalling mechanisms activated by plant symbiotic signals in arbuscular mycorrhizal (AM) fungi. Fluorescent Ca^{2+} reporters (GCaMP6) fused to the HIV-1-derived cell-penetrating peptide TAT will be used as new tools to monitor cytosolic and nuclear Ca^{2+} dynamics in the fungal partner during the early stages of AM symbiosis. Moreover, the identity and role of different transcription factor complexes activated in the plant symbiotic signalling pathway and leading to the development of arbuscules (*i.e.* the major site of nutrient exchange) will be investigated. Insights into basic processes underlying mutualistic plant-fungus interactions are essential to develop future strategies to improve plant nutrition and stress resistance.

Role of cellular metabolism in normal and pathological angiogenesis.
Contact: Prof. Massimo Santoro, e-mail: massimo.santoro@unipd.it

Endothelial cells (ECs) and cancer exhibit a remarkable and unique plasticity in terms of redox biology and metabolism. By using advanced redox and metabolic imaging platforms, and innovative molecular and genetic approaches in different in vivo animal models, we aim to shed light on the role of novel metabolic pathways in health and disease. The ultimate objective is to open the way for the development of innovative therapeutic strategies and complement the existing ones based on genetic and pharmacological manipulation of redox and metabolic state in angiogenic processes.

Professor Scorrano project.
Contact: Prof. Luca Scorrano, e-mail: luca.scorrano@unipd.it

The Scorrano lab pioneered the fields of mitochondrial dynamics and interorganellar contact sites (see[1,2] for two recent reviews). We are looking for a potential PhD student to join a well-funded, international group of 20 colleagues (15 postdocs, 4 PhD students, 1 lab manager) coming from 10 different countries from 4 continents. The successful candidate will develop a research program on newly identified modulators of ER-mitochondria contact sites that emerged from a genome wide screening performed in the lab. The

candidate will integrate high content imaging, electron microscopy, superresolution imaging, biochemistry, genetics and metabolomics to unveil how mitochondrial membrane contact sites are maintained.

If you are interested and you did not obtain your MSc in Italy (**this is a strict requisite**), please email luca.scorrano@unipd.it for further details about the project and apply.

1. Giacomello, M., Pyakurel, A., Glytsou, C. & Scorrano, L. The cell biology of mitochondrial membrane dynamics. *Nat Rev Mol Cell Biol* (2020).
2. Scorrano, L. et al. Coming together to define membrane contact sites. *Nat Commun* **10**, 1287 (2019).