



ICGEB Research Grants awarded under the 2020 Call for applications

- Title:** Drug metabolic phenotype and pharmacogenomics of multi-drug resistant and drug susceptible tuberculosis patients
- Principal Investigator:** Dr. Mohammad Khaja Mafij Uddin, International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh
- ICGEB Reference No.** CRP/BGD20-02
- Abstract:** Tuberculosis (TB) is one of the major public health threats worldwide. Countries like India, China and Russia contribute the highest number of tuberculosis cases as well as related deaths. Bangladesh ranks seventh among the top 30 high TB burden countries with 221/100,000 incidence and 45/100,000 mortality rates. The majority of TB patients are cured by the existing treatment methods, but a sub-set of the population fails to respond to existing treatment modalities, or they develop serious treatment-associated adverse events leading to death or to reduced adherence to the treatment regime. These inter-patient differences in treatment response might be influenced by the host genetics, for which limited information is currently available. Therefore, in this project we aim to carry out a pharmacogenomics study of Bangladesh tuberculosis patients at an individual level, and to generate a population-level drug metabolic phenotype (DMP) database to develop future personalised treatment for the elimination of TB.
- Title:** Determination of biochemical and molecular responses of cowpea (*Vigna unguiculata* [L] Walp) genotypes from Burkina Faso under drought stress
- Principal Investigator:** Dr. Pierre Alexandre Éric Djifaby Sombié, Institut de l'Environnement et de Recherches Agricoles (INERA), Ouagadougou, Burkina Faso
- ICGEB Reference No.** CRP/BFA20-01
- Abstract:** Cowpea is a highly important legume crop for both human and animal nutrition; however, drought stress affects the growth and yield of cowpea crops in Burkina Faso. The main research objective of this study will be focused on examining the biochemical and molecular components that may be differentially expressed in drought-tolerant and drought-susceptible cowpea varieties under drought stress conditions, with the aim of identifying some specific cowpea cultivars for potentially enhanced drought tolerance. The results of this project will provide research tools to understand the biochemical mechanisms of cowpea drought tolerance, with a view to screening resistant accessions for cultivation.
- Title:** Fusarium toothpick technology for control of *Striga hermonthica* in cereal crops in smallholders farms in the Sudano Sahelian agroecological zone of Cameroon
- Principal Investigator:** Dr. Christopher Sur, Institute of Agricultural Research for Development, Yaoundé, Cameroon
- ICGEB Reference No.** CRP/CMR20-02
- Abstract:** The parasitic weed *Striga hermonthica* is a major threat to food security in Cameroon's sudano-sahelian agroecological zone. The parasite attacks cereals, the main staple food crops planted annually, and inflicts damage that can cause up to 100% loss in yield. Current *Striga* control methods are not effective alone and require integration with other technologies. An international collaborative effort has developed a biocontrol technology named Foxy, based on native *Fusarium oxysporum* f sp *strigae*, isolated from diseased *Striga* in maize. Coated on toothpicks, Foxy allows smallholder farmers to multiply and apply a fresh vigorous bioagent directly to the seedbed, increasing yield by 35-56%. The objective of this proposal is to select locally-sourced virulence-enhanced *Fusarium* strains, to find alternative substrates, to test these strains in the field, and to develop, evaluate and validate efficient climate-smart delivery systems for Foxy technology for cereals and grain legumes.
- Title:** Identifying host cell factors that control hiv-1 latency in different types of latent reservoirs

- Principal Investigator:** Dr. Chantal Loretto Márquez Badilla, Molecular and Cellular Virology Laboratory, ICBM, Medicine Faculty, Universidad de Chile, Santiago, Chile
- ICGEB Reference No.** CRP/CHL20-05_EC
- Abstract:** HIV/AIDS has caused millions of deaths around the world. Despite the fact that antiretroviral treatment has converted it from a fatal diagnosis to a chronically managed disease, it is still incurable due to the persistence of lifelong latent proviruses in viral reservoirs. Latently-infected cells contain integrated HIV proviruses that are usually silent, but which can produce new virions to infect more cells. The latent reservoir is composed of CD4+T cells, macrophages and microglia, but the molecular regulation of latency establishment and reactivation is still unknown. To investigate this, we will perform a genome-wide CRISPR-based knockout screen to identify novel host genes that confer HIV suppression or reactivation from latency in the three different latent reservoirs. This approach will allow the discovery of key molecular proteins that regulate HIV latency in the different reservoir cell types, providing the scientific foundation for novel opportunities for therapeutic intervention.
- Title:** Catabolism of modified nucleosides from RNA turnover in plants
- Principal Investigator:** Dr. Mingjia Chen, College of Life Sciences, Nanjing Agricultural University, Nanjing, China
- ICGEB Reference No.** CRP/CHN20-04_EC
- Abstract:** RNA post-transcriptional modification, mostly by methylation, is a newly emerging highly dynamic field of research. Upon RNA turnover, the modified nucleosides are released, together with other canonical nucleosides. So far, the metabolic fate of modified nucleosides after RNA degradation has not been elucidated clearly. We have identified and characterised a canonical pyrimidine catabolism pathway, which, surprisingly, degrades both cytidine and 5-methylcytidine in plants. This is the first metabolic pathway discovered to be involved in the degradation of both canonical and modified nucleotides in any organism. We propose to further investigate the relationships between 5-methylcytidine degradation, cytidine catabolism, and RNA modification dynamics in plants. We will extend our research towards establishing methods for the detection of other modified nucleotides derived from mRNA and tRNA, and methods for elucidating their metabolic fate. We envisage that defective removal or end-storage of modified nucleotides may have profound effects on the homeostasis of RNA modification.
- Title:** Understanding *Brucella* phylogeography: a road to specific diagnostic tools
- Principal Investigator:** Dr. Caterina Guzmán-Verri, Tropical Diseases Research Program and Biochemistry Department, Veterinary School, Universidad Nacional, Costa Rica
- ICGEB Reference No.** CRP/CRI20-02
- Abstract:** Brucellosis, one of the world's most widespread zoonoses, is a neglected disease. There are two central questions that have not been answered: (i) what are the bases for the geographical and genomic correlation found among some *Brucella* isolates? (ii) what are the features that induce a *Brucella* species to prefer a particular group of hosts over others?
- Due to the high genomic similarity amongst members of this genus, high-resolution techniques are needed to find differences that may help to address these questions. By analysing the whole genome sequences of the *Brucella* isolates from different bacterial collections in different parts of the world, we aim to identify those elements that induce genomic variability that relates to phylogeography traits. This will help in developing specific molecular tools for detection of *Brucella* and relating it to geographical origin, thereby contributing to the epidemiological tracking of the disease.
- Title:** Redox-sensing and electron transfer at the inner envelope of chloroplasts - the role of the TROL-FNR interaction
- Principal Investigator:** Dr. Lea Vojta, Institute Ruder Boskovic, Division of Molecular Biology, Laboratory of Molecular Plant Biology and Biotechnology, Zagreb, Croatia
- ICGEB Reference No.** CRP/HRV20-03
- Abstract:** Thylakoid rhodanase-like protein (TROL), a photosynthetic membrane component, is a hub at the end of the photosynthetic electron transfer chain that, in vascular plants, influences the preferential electron transfer catalysed by the enzyme ferredoxin:NADPH oxydoreductase (FNR) for the production of sugars. TROL is also located in the inner envelope membrane of chloroplasts, where its function is unknown. Whether it represents just a storage protein for FNR, or is involved in redox sensing and/or in protein import, remains to be revealed in this project. Plants devoid of TROL cope better with oxidative stress by fast elimination of reactive oxygen species. This property will be investigated in more detail, since these plants are good candidates for survivors in the world of aggravated environmental stresses. The advantages of the TROL-FNR interaction can be transferred to agronomically interesting species, such as tomato and other *Solanaceae*, producing stress-tolerant agronomic plants for the future.
- Title:** Microalgae biomass application in broilers as strategy to contain emerging *Salmonella enterica* serovar Infantis in Ecuador
- Principal Investigator:** Dr. Marco Larrea-Álvarez, Yachay-Tech University, School of Biological Sciences and Engineering, Urcuquí-Imbabura, Ecuador
- ICGEB Reference No.** CRP/ECU20-05_EC
- Abstract:** In the Andean region, *Salmonella enterica* serovar Infantis represents an emerging inconvenience for poultry production and public health. This project aims to study the efficacy of algae-produced recombinant proteins as oral vaccines, which will be tested on chickens alone or combined with pro-biotics and algae-derived pre-biotics. Application of synbiotics is expected to stimulate growth performance and the immune response in challenged individuals. The availability of low-cost vaccines appears to be crucial for reducing disease burden, whereas the expensive features of traditional immunization (antigen purification, injectable delivery) can be

avoided using orally-delivered vaccines. The chloroplast of the eukaryotic alga *Chlamydomonas reinhardtii* will be engineered to produce chimeric proteins consisting of epitopes fused to appropriate adjuvants. Administration of synbiotics together with oral vaccination, using freeze-dried algae, is expected to reduce the detrimental effects of *S. Infantis*. Moreover, developing affordable vaccination strategies must be considered as a primary intervention against infectious diseases, particularly in emerging economies.

Title: Examination of the interaction between *Leuconostoc mesenteroides* and *Lactobacillus plantarum* for safe and quality enset (*Ensete ventricosum*) fermentation
Principal Investigator: Dr. Addisu Fekadu Andeta, Arba Minch University, Arba Minch, Ethiopia
ICGEB Reference No. CRP/ETH20-03_EC
Abstract: Enset (*Ensete ventricosum*) is an important food security crop for over 20 million Ethiopian people, after its fermentation into kocho. The fermentation process has hardly been investigated and requires optimisation, as kocho fermented by the conventional method takes a long time and is low in quality. The aim of this project is to examine the interaction between *Leuconostoc mesenteroides* and *Lactobacillus plantarum* as candidates for safe and high-quality enset fermentation. In our previous work, we have already characterised several lactic acid bacteria species, based on their suitability to ferment enset. Three promising lactic acid bacteria species were identified and evaluated in distinct fermentations. However, the interactions between each of these lactic acid bacteria were not examined. Therefore, the focus of this research project will be: (i) to investigate the interaction between *Lactobacillus plantarum* and *Leuconostoc mesenteroides* during enset fermentation; and (ii) to determine the nutrient content and volatile compounds produced during co-culture fermentation.

Title: Broad and efficient gene expression via systemic gene delivery of engineered AAVs in a preclinical species
Principal Investigator: Dr. Daniel Hiller, Research Centre for Natural Sciences (TTK), Budapest, Hungary
ICGEB Reference No. CRP/HUN20-01
Abstract: A large gap exists between the number of therapeutic strategies developed in the lab and those that receive regulatory approval for treating debilitating human diseases. Gene therapy may bring unprecedented precision and efficacy for the treatment of human diseases, but the tools applied in basic research need to be translated for preclinical and, ultimately, for human use. The broad application of gene therapy methods using adeno-associated viruses requires non-invasive, targeted and safe virus delivery strategies. We will develop non-invasive viral gene delivery strategies using synthetic viruses that target various areas and cell types of the brain. The ability to noninvasively deliver these to modulate the activities of different cell types in the brain in preclinical models will provide new avenues for basic research and therapeutic possibilities that have been, so far, unattainable.

Title: Defining the central role of obesity-associated metabolic stress on regulated exocytosis
Principal Investigator: Dr. Bhavani Shankar Sahu, DBT-National Brain Research Center, Manesar, India
ICGEB Reference No. CRP/IND20-05_EC
Abstract: Neuroendocrine cells store neurotransmitters, biomolecules in specialised organelles called secretory granules. Secretory granules store and secrete their contents in response to various stimuli to regulate metabolic/physiological functions, and the process is known as regulated exocytosis. Despite intense research, the mechanistic understanding of neuroendocrine secretion and its subsequent role in metabolic physiology is limited. The proposed research emphasises understanding the role of obesity-associated metabolic stress and the molecular players governing regulated exocytosis in neuroendocrine cell systems. In-depth understanding of these processes will advance our knowledge of fundamental aspects of metabolic physiology, besides offering potential therapeutic solutions for clinical conditions contributed by the neuroendocrine and sympathetic systems, such as diabetes, obesity, common mental health disorders, and hypertension.

Title: Generation of cyanogen free Cassava with reduced post-harvest physiological deterioration through gene specific genome editing
Principal Investigator: Dr. Cecilia Mbithe Mweu, Jomo Kenyatta University of Agriculture and Technology, Institute for Biotechnology Research, Nairobi, Kenya
ICGEB Reference No. CRP/KEN20-03
Abstract: Cassava is the most important staple root crop in the world, playing a significant role as a source of calories for millions of subsistence farmers in sub-Saharan Africa, but is subject to two major problems. Cassava contains toxic levels of the cyanogenic glycoside, linamarin, and its consumption can result in cyanide poisoning; while cassava production is constrained by the short shelf-life of the cassava storage roots, which undergo physiological deterioration very soon after harvest. Thus, elimination of cyanogens and increasing the cassava root shelf-life is of great importance. The clustered regularly interspersed short palindromic repeats (CRISPR)/Cas system has emerged as the most effective sequence-specific nucleases tool for genome editing. This project is designed to generate cyanogen-free cassava with reduced postharvest physiological deterioration through CRISPR/Cas9 genome editing. Improved cassava will provide a more marketable and consistently cyanogen-free food product, potentially providing additional income generation sources for subsistence farmers.

Title: Nanomaterials based-Genosensor (Nano-GS) for improved detection method of SARS-CoV-2 RNA as rRapid COVID-19 diagnosis strategy
Principal Investigator: Dr. Ling Ling Tang, Southeast Asia Disaster Prevention Research Initiative (SEADPRI-UKM), Institute for Environment and Development (LESTARI), Universiti Kebangsaan Malaysia, Selangor Darul Ehsan, Malaysia

ICGEB Reference No.	CRP/MYS20-03
Abstract:	Our research plan is to develop a biosensor, made of a special matrix that holds a G-quadruplex DNA probe, targeting specific a site of the SARS-CoV-2 viral RNA. Binding interaction between the DNA probe and the target sequence on viral RNA produces colour and electrochemical changes that could be visualised and detected by an electronic reader. This biosensor will be adapted as a strip/tube, to be used with a hand-held device that is user-friendly and cheap to manufacture. Prototype units of our biosensor will be tested against an appropriate number of clinical samples to estimate the performance of the device in sensitivity and predictivity. As an immediate effort for developing a diagnosis method during the current COVID19 outbreak, we aim to establish detection tool with a fast turnaround time of 30-45 minutes, from RNA extraction to result interpretation. Later, we plan to integrate the virus isolation and RNA extraction steps in the biosensor system through a microfluidic based-platform to upgrade its versatility as point-of-care testing device in resource-limited settings.
Title:	Enzymatic analysis of the cellulolytic system of ligninolytic <i>Stenotrophomonas</i> sp. and development of bifunctional chimeric enzyme for efficient simultaneous delignification and saccharification of lignocellulosic biomass
Principal Investigator:	Dr. Folasade Mayowa Olajuyigbe, Enzyme Biotechnology and Environmental Health Unit, Department of Biochemistry, Federal University of Technology Akure (FUTA), Akure, Nigeria
ICGEB Reference No.	CRP/NGA20-03
Abstract:	Fuels from agricultural wastes are the most promising and sustainable alternatives to fossil fuels, based on environmental health benefits. However, the plant cell wall has a natural defence substance (lignin), which makes it difficult to access the complex polysaccharide component (i.e., cellulose). Hence, techniques to remove lignin from biomass and break down the cellulose into fermentable sugars are urgently needed.
Recent research led by our group identified a bacterium (<i>Stenotrophomonas</i> sp.), which effectively removes lignin from agro-residues. However the ability of the organism to breakdown cellulose into fermentable sugars has not been investigated.	
This research project, performed in collaboration with Dr. Shams Yazdani from ICGEB New Delhi, seeks to investigate the ability of <i>Stenotrophomonas</i> sp. to break down cellulose in corncob and sugarcane bagasse, and to develop a chimera of biocatalysts for simultaneous removal of lignin and break down of cellulose into fermentable sugars. The expected results will provide a promising and cost-effective approach to efficiently conversion of lignocellulose to fermentable sugars.	
Title:	Development of transgene-free <i>Brassica juncea</i> with low erucic acid and glucosinolate content using CRISPR technology
Principal Investigator:	Dr. Niaz Ahmad, National Institute for Biotechnology and Genetic Engineering (NIBGE), Faisalabad, Pakistan
ICGEB Reference No.	CRP/PAK20-02
Abstract:	<i>Brassica juncea</i> , an important oilseed crop, is more tolerant of various biotic and abiotic stresses compared with other brassicas. However, it contains high amounts of erucic acid and glucosinolates, making its oil unhealthy for humans and its seedcake unsuitable for animal use. In this project we will use CRISPR/Cas9 to generate different <i>B. juncea</i> lines with low erucic acid and glucosinolates by disrupting the functions of the genes involved, in their biosynthesis and transportation, respectively. The CRISPR lines developed with low erucic acid and glucosinolates will be advanced to the T1 generation to identify plants having mutations not linked with the Cas9 locus. The selected plants will then be advanced to the T2 generation to identify plants homozygous for the desired mutations. The individual homozygous transgene-free lines identified will be then crossed to combine both characteristics into one plant line. The lines developed also will be used in the future breeding of <i>Brassica</i> varieties having low erucic acid and glucosinolate contents.
Title:	Role of a metallochaperone in the mechanisms of action and resistance to pyrazinamide a in <i>Mycobacterium tuberculosis</i>
Principal Investigator:	Dr. Mirko Zimic , Universidad Peruana Cayetano Heredia , Lima, Peru
ICGEB Reference No.	CRP/PER20-02
Abstract:	Pyrazinamide (PZA) is the most important drug against the latent stage of <i>Mycobacterium tuberculosis</i> . Despite its importance, its mechanisms of action and mechanisms of resistance to it are not completely understood. The metalloenzyme pyrazinamidase is essential to hydrolyze PZA and convert it to pyrazinoic acid (POA), the active compound. In our previous studies, we found that the Rv2059 <i>M. tuberculosis</i> protein is a true metallochaperone able to facilitate the activation of the metal-depleted/inactivated Pyrazinamidase <i>in-vitro</i> . In this study we want to demonstrate that Rv2059 metallochaperone plays a role and is important in regulating the activity of the pyrazinamidase <i>in-vivo</i> , and participates in the mechanisms of action and resistance to PZA. We plan to inactivate the Rv2059 gene using CRISPRi (alternatively gene knock-out), to explore the effect of replacing Rv2059 with mutated variants by gene-complementation with non-integrative plasmids, integrative plasmids, and the recently standardised ORBIT technique for <i>M. tuberculosis</i> , on the susceptibility to PZA, and in the POA efflux rate of the <i>M. tuberculosis</i> strain.
Title:	Enhancing the therapeutic potential of ribonuclease binase for tumour elimination
Principal Investigator:	Dr. Vladimir Aleksandrovich Mitkevich, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia
ICGEB Reference No.	CRP/RUS20-01
Abstract:	Cytotoxic ribonucleases (RNases) are promising agents in the fight against malignant neoplasms. A fundamental scientific task is to increase the efficiency and selectivity of the toxic effects of RNases in relation to malignant cells. To solve this problem, in this project the toxic effect of RNase binase from <i>Bacillus pumilus</i> is enhanced by combining it with guiding modules, which are modified affibody molecules that are able to efficiently recognise

certain malignant cells. Thus, the cumulative effect of the destruction of tumour cells is achieved. The project is developing an approach for the elimination of a certain type of tumour, which allows one to collect biosimilar therapies from the developed set of modules.

- Title:** Genetic dissection of the enzymatic potential of locally selected *Bacillus* probiotic strains and enzymes adaptation toward higher activity under aquaculture conditions
- Principal Investigator:** Prof. Hichem Chouayekh, Department of Biological Sciences, College of Science, University of Jeddah, Jeddah, Saudi Arabia
- ICGEB Reference No.** CRP/SAU20-01
- Abstract:** Misuse of antibiotics in aquaculture has led to the development of antibiotic-resistant pathogenic bacteria, causing failure of antibiotic treatments and production losses. Many alternatives have been suggested, including feed enzymes and probiotics. In particular, enzymes secreted by *Bacillus*, and *Bacillus* probiotics with the ability to liberate numerous enzymes, are a focus of current interest in aquaculture. Indeed, most *Bacillus* species are generally recognised as safe. They also have the ability to provide extracellular enzymes important for feed digestion, nutrient absorption, and for the lysis of fish microbial pathogens. We had previously selected locally-isolated *Bacillus* probiotic strains, producing extracellular enzymes (such as phytase, xylanase, β -mannanase, etc.) that are intended for future application as DFMs (direct fed microbials) in aquaculture. In the present project we aim to identify and characterise the genes encoding enzymes with the most promising activities. To permit their application as feed supplements in aquaculture, we will perform engineering strategies to adapt the enzymes towards higher activity under aquaculture conditions.
- Title:** Complementary diagnostic approaches for COVID-19
- Principal Investigator:** Dr. Ario de Marco, University of Nova Gorica, Nova Gorica, Slovenia
- ICGEB Reference No.** CRP/SVN20-01
- Abstract:** In recent months everyone has become aware of the danger represented by COVID-19, and has accepted drastic restrictions on her/his freedom of movement. At the same time, we have all followed the daily development of statistics concerning the numbers of detected infections and the explanation of pandemic predictive models. What is unknown to the wider public, and often neglected by several professionals as well, is that the data used to monitor the pandemic are not necessarily as reliable as they could be. There are several technical steps that are difficult to standardise at large scale, such as the time and the modality of sampling, the implementation of uniform protocols for RNA amplification, the lack of independent analyses to use as controls. As a result, there is a high rate of false negatives, and non-comparable results from datasets collected at different checkpoints. This proposal wishes to evaluate alternative diagnostics approaches that should be more reproducible and sensitive.
- Title:** Investigation into the interaction and co-operation between the human papillomavirus oncoproteins E6/E7 with the oncogenic TBX3 transcription factor to promote cervical cancer cell proliferation and migration
- Principal Investigator:** Dr. Sharon Prince, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
- ICGEB Reference No.** CRP/ZAF20-01
- Abstract:** Cervical cancer is a leading cause of death in women globally, with over 80% occurring in low- and middle-income countries. This highlights the need for cheap and effective therapeutics to treat this disease. Most cervical cancer cases are caused by the human papillomavirus (HPV), where its cancer-causing proteins E6 and E7 co-operate with human proteins to drive the cancer. A rapid and cost-effective approach to treating these cases is to identify the human proteins involved and to target them with commercially available non-cancer drugs. We have shown that the cancer-causing factor, TBX3, promotes HPV-positive, but not HPV-negative, cervical cancer and we have identified three commercially available drugs that target TBX3 and exhibit anti-cervical cancer activity. This project aims to determine whether (i) HPV E6/7 and TBX3 interact and co-operate to promote cervical cancer and (ii) if the commercially available drugs target TBX3 as well as HPV E6/7.
- Title:** Investigating the role of Dengue NS1 protein in potentiating Dengue virus infection in uninfected cells by inducing changes in host plasma membrane proteome
- Principal Investigator:** Dr. Kaveesha Jayani Wijesinghe, Department of Biochemistry, Faculty of Medicine, Sabaragamuwa University of Sri Lanka, Belihuloya, Sri Lanka
- ICGEB Reference No.** CRP/LKA20-04_EC
- Abstract:** Dengue infection is caused by four closely related Dengue viruses (DENV 1-4), which are transmitted by mosquito vectors, and which can cause life-threatening conditions, such as Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Dengue viruses produce a protein called NS1, which is secreted from the infected cells into the circulating blood. High levels of NS1 in serum are associated with severe DHF and are known to cause vascular leakage. The Dengue NS1 protein also facilitates Dengue virus infection in uninfected cells. This study is designed to understand how Dengue NS1 protein facilitates Dengue infection in uninfected cells by analysing the changes in protein composition in cells that are exposed to NS1 protein.
- Title:** Is epigenetic regulation of lysosomal sequestration and exocytosis of cisplatin a new target of improving cancer therapy?
- Principal Investigator:** Dr. Ceyda Acilan Ayhan, Koc University, School of Medicine, Istanbul, Turkey
- ICGEB Reference No.** CRP/TUR20-01

Abstract:

A recently recognised strategy, by which cancer cells escape killing, is their absorption of chemotherapeutic drugs by lysosomes, followed by expulsion of the drug by lysosomal exocytosis. We suggest that the lysosomal drug flux is a significant burden on drug discovery and clinical use; therefore suppressing it will be impactful. To identify molecules that play a role in the lysosome flux of cisplatin, we will focus on the "Epigenetics Screening Library", which we have previously used successfully for testing drug resensitisation in taxane-resistant prostate cells. In this project, we will identify epidrugs that either (i) inhibit the lysosomal flux (which will be studied to answer whether they improve the frontline drug/cisplatin efficacy), or that (ii) facilitate the lysosomal flux (which will be used in conjunction with the currently available drugs and/or gene knockdown to reverse the activation of lysosomal flux). Selected drugs, that can resensitise cells to cisplatin, will then be characterised to determine their mechanism of action.