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Connecting LATS1-regulated epigenetic plasticity with cell metabolism

Prof. Moshe Oren (Weizmann Institute of Science) and Prof. Karen Vousden (The Francis Crick Institute)

Luminal B (LumB) tumors represent a subtype of estrogen receptor-positive (ER+) breast cancer. Compared to the more common luminal A tumors, LumB tumors are more proliferative and more likely to acquire resistance to anti-hormonal therapy. These features are believed to be due, at least in part, to the increased phenotypic plasticity of LumB tumors, which is manifested by transition of the luminal cancer cells into a basal-like state. This is associated with increased tumor aggressiveness, augmented metastasis and reduced efficacy of anti-cancer treatments. Given the strong links between cancer and dysregulation of metabolic processes, and the plastic nature of metabolic flux, we hypothesize that metabolic and phenotypic transitions may be linked. Previously, we demonstrated a functional role of the LATS1 tumor suppressor in modulating epigenetic modifications that dictate cellular plasticity of the cancer cells in a mouse model of LumB breast cancer, and confirmed concordant correlations also in human breast cancer data. We have recently obtained new data supporting the notion that LATS1 may restrict metabolic pathways that could regulate the availability of acetyl-CoA, a metabolite "hub" for histone acetylation. Our collaborative plan is to characterize LATS1-dependent differences in the metabolic landscape, measure the impact of LATS1 on the flux to acetyl-CoA from lipids, glucose and glutamine, and determine the impact of these metabolic processes on the epigeneticallyregulated phenotypic plasticity in LATS1-deficient breast cancer cells. Using targeted knockdown of metabolic genes and/or use of selective inhibitors, we aim to "lock" tumor cells in a luminal phenotype and thus maintain their sensitivity to luminal-specific antihormonal (tamoxifen) treatment. The obtained findings may suggest new ways to reduce breast cancer cell plasticity, paving the road towards potentially more effective therapeutic approaches.

Cross-Modal Generalisation of Fear

Prof. Rony Paz (Weizmann Institute of Science) and Dr Deborah Talmi (University of Cambridge)

Our brain is wired so that once a particular event led to disaster, we respond to similar events as if they are dangerous, too. While generalisation is adaptive, over-generalisation can be maladaptive, and decrease well-being. For example, if survivors of a traffic accident conclude that all vehicles are dangerous, they may become too anxious to leave their home. Events can be similar in many ways, including in how they look and sound, but also in more abstract ways, such as their meaning. We have shown that learning that simple visual and auditory stimuli (line orientations, pure tones) predict aversive outcomes modulates perceptual thresholds and leads to generalization. However, it is not known whether similarity in meaning also facilitates the conclusion that a current event is similar enough to the original disastrous one to be threatening. We propose to test the hypothesis of generalisation based on meaning. First, we teach research volunteers that a set of animal pictures from one semantic category is 'dangerous' (e.g. two pictures of mammals – cow and horse - predict monetary loss) while another set

(e.g. two birds) is safe. We then present them with other exemplars from the same category (pig, sheep) and the vocalisations of these animals. We validate the task by measuring participants' emotional threat response using behaviourally and psychophysiological techniques. We measure perceived similarity to determine whether following aversive learning, participants now perceive exemplars from the conditioned category (the other mammals) and their vocalisation as threatening. Experiments 1-3 do this by taking behavioural measures, explicit judgements of similarity, and objective neural measures of similarity. Evidence that participants generalise threat not only to exemplars from the same category but also to cross-modal stimuli (the vocalisations) suggests that generalisation was based on the meaning of stimuli. For example, a threat response to 'moo' sounds suggests that the concept of cow has become threatening, not merely its visual representation. Such evidence will advance understanding of the circumstances in which people may perceive their environment to be threatening without any previous direct experiences, and suggests novel ways to treat maladaptive overgeneralisation. Moreover, we will use functional MRI to measure correlates of brain activity while subjects perform the task, and hence identify the neural networks that underlie the generalization of fear.

Metabolite mapping using magnetic resonance at ultra-high field for the non-invasive detection of genetic mutations in human brain tumours in vivo

Dr. Rita Schmidt (Weizmann Institute of Science) and Prof. David Porter (University of Glasgow)

The aim of this project is to advance our understanding of biochemistry in tumours, such as gliomas, by developing a novel, non-invasive approach to the diagnosis of genetic mutations in tumour tissue. This research focuses on mapping human brain metabolites using magnetic resonance spectroscopy in vivo at an ultra-high magnetic field strength of 7 T. Previous studies have shown that metabolic signatures associated with specific mutations within tumour tissue can be detected by the non-invasive mapping of brain metabolites, providing a biomarker for tumour characterization and treatment prognosis. This study lies in the interplay of chemical physics and medicine, investigating an optimal fast spectroscopic imaging approach to capturing the metabolic variation in multiple regions in the brain, and providing a sensitive biomarker for better diagnostics. If successful, it will provide a novel framework for rapidly probing brain metabolites in vivo and will advance personalized medicine. As part of the research, a novel ultra-high-field human MRI scanner will be utilized, boosting the sensitivity and the spectral resolution. In this joint project, we will combine the Weizmann Institute and Glasgow university groups' expertise, and state-of-the-art 7-T MR scanners at both sites, to develop a novel approach to high-resolution spectroscopic imaging. The method will be validated with a dedicated 3D-printed, head-shaped phantom, and by scanning healthy human subjects in vivo. Individual datasets of human brain metabolite maps from healthy volunteers will be segmented with the brain structures to characterize regional variation of the metabolite concentrations. Exploring variation in healthy tissue in multiple regions will provide valuable insight into the ability of the technique to detect and characterize pathological changes. Results from the project will be incorporated into clinical studies, which are part of the ongoing cancer research programme at the Universities of Glasgow and Edinburgh.

Understanding the Surface Chemistry of Late 3d-Transition Metal Oxides during Oxygen Evolution Reaction

Dr. Eren Baran (Weizmann Institute of Science) and Dr. Alex Walton (University of Manchester)

This Collaboration has been funded by Denis Raeburn & The Gundle Philanthropic Trust

Water electrolysis is a clean, scalable, and sustainable mean of converting and storing energy. One of the major roadblocks on the way to utilising this technology is the sluggish kinetics during the oxygen evolution reaction (OER). Therefore, optimisation of the OER electrocatalysts is of utmost importance in advancing this technology further. Rational design of new, improved catalysts requires a thorough and molecular-level understanding of the underlying mechanisms by which the catalyst functions. The goal of the proposed research here is to understand the key mechanisms taking place on the surfaces of late 3d-transition metal catalysts (Co, Ni, Fe) under alkaline electrochemical reaction conditions. We aim to identify the chemical state of the catalyst surface, coverage of hydroxyls, geometry of the adsorbed water mocules, and the morphology/structure of the catalyst. Identification of the the chemical state of the surface is especially important. In order to achieve this goal, we will utilise graphene-capped electrochemical micro-reactor cells, which we specially design for performing X-ray photoelectron spectroscopy (XPS) at the solid – electrified liquid interface. Vibrational spectroscopies and electron microscopy will be used as supplementary techniques. XPS is different from the currently prevalent operando spectroscopy techniques used in electrochemistry, as it is element-specific, chemically-sensitive, and most importantly surface-sensitive. We will also associate the chemical sucture to the catalyst performance, e.g., overpotential, in order establish a structure-property-performance relation of a working catalyst. This project builds on our unique expertise in producing and manipulating polymer-free graphene at the Weizmann Institute of Science, and will take advantage of the ambient-pressure (AP)XPS setup at the University of Manchester, as well as the complementary measurement capabilities under electrochemical reaction conditions at the Weizmann Institute of Science.

Advanced X-ray absorption diagnostics and modelling for exploring characteristics of Warm Dense Matter

Prof. Ehud Duchovni (Weizmann Institute of Science) and Dr. Simon Bland (Imperial College London)

Warm dense matter (WDM) describes the crossover between cold, condensed material and hot, lower-density plasmas. It is a state of matter commonly found in high-energy-density (HED) physics research and astrophysical systems, yet is often ill-defined with few directly measured material characteristics. In this proposal we seek to develop a new diagnostic to make quantitative, time resolved measurements of WDM via a collaboration between two laboratories with cutting-edge knowledge and expertise in the field of X-ray spectroscopy. Whilst previous research of WDM using X-ray absorption has relied on a synchrotron or a large laser experiment to provide probing X-ray radiation for such measurements, we will explore the use of a unique, portable, pulsed-power-driven X-pinch already in development at Imperial College. The output from the X-pinch will be optimized to produce an intense, sub-ns pulse of radiation with a relatively flat, broadband spectrum. Spherical-crystal optics will be utilized to focus this

probing radiation through WDM targets formed by a separate pulsed-power driver. The X-ray spectra covering various *K*-shell absorption features will then be examined to determine the material state and bonding as a function of time. Furthermore, this diagnostics will be coupled to density measurements made via radiography with the same X-pinch. Such a unique set of experimental data can be used for benchmarking theoretical WDM models. The Weizmann Institute of Science Plasma Group will apply its well proven capabilities in high spatial and spectral resolution spectrometry and line-shape and plasma-kinetics modelling. The Imperial College Plasma Physics Group, meanwhile, will contribute its skills and prior experience in building novel pulsed-power-driven radiation sources, formation of WDM targets and absorption spectrometry.

2021 – 2022

Reciprocal dynamics and attentional modulation in claustrum-prefrontal interactions

Dr. Ofer Yizhar (Weizmann Institute of Science) and Dr. Adam Packer (University of Oxford)

This project is funded by Bruno Licht

The prefrontal cortex is known to be crucial for goal-directed behavior, orchestrating behavior through its widespread anatomical connectivity with numerous cortical and subcortical circuits. In all mammalian species, PFC dysfunction is tied with behavioral, cognitive and emotional impairment and is strongly linked with psychiatric disorders. The claustrum is a brain region that is strongly connected with the PFC, and has been proposed to mediate attentional processing through brain-wide interactions. Strikingly, both the claustrum and PFC share connections with the amygdala, an important hub for emotional processing and salience detection in the brain. The reciprocal synaptic connectivity among these three brain regions suggest that interactions between them are crucial for cognitive function, but the shared dynamics of these two circuits and their contribution to goal-directed behavior has not been explored. In this proposal, we aim to delineate the functional properties and the behavioral roles of neural connections among this triad of brain circuits. Using advanced optogenetic techniques, we will selectively manipulate individual nodes of this circuit and examine the impact of reversibly severing these connections on the behavior of mice in a rule-learning task that requires attentional control. We will then ask how learning alters the nature of synaptic connections within this tri-synaptic circuit. Using single-cell optogenetics, we will study the structure of synaptic connectivity in local circuits of neurons participating in PFC-claustrum-amygdala interactions. Our findings will shed new light on the contribution of both long-range and local synaptic interactions.

Neural basis of active sensation: fast closed-loop touch

Prof Ehud Ahissar (Weizmann Institute of Science) and Prof Rasmus Petersen (University of Manchester)

Animals actively regulate the position and movement of their sensory systems to boost the quality and quantity of the sensory information they obtain from their surroundings. Rats and mice exhibit active sensation in a particularly clear and experimentally accessible manner. They sweep their facial whiskers back and forth at high speeds in a controlled and feedback-sensitive manner to acquire tactile sensory information through contact with environmental structures. During the last decade the vibrissal system has become a standard model system for studying behavioral and neural mechanisms of active sensing in general and active touch in particular. The findings collected so far indicate that the vibrissal system allows hyper-accurate perception at high resolution via a complex network of neuronal loops connecting the motor and sensory pathways. While many aspects of neural coding and processing in specific stations of the vibrissal system had been clarified, and specific elements of whisking behavior have been documented, we have limited knowledge and understanding of the function of specific neuronal components and on their underlying mechanisms. Here we propose to investigate in depth one intriguing motor-sensory process, which appears to be controlled by tactile attention and still its mechanism and function are not clear. When touch occurs during whisking a fast reflexive response, termed touch-induce pumps (TIP), may be triggered. During a TIP the whisker slightly retracts and protracts again, doubling the number of pressure onsets per contact. In head-fixed rats TIPs occur in ~25% of the contacts. We have recently observed (Ahissar group, WIS) that the occurrence of TIPs depends strongly on attention: when rats intended to explore an object, either after encountering it during exploration or when expecting its existence, the probability of a TIP increased from <20% to >65%. In parallel, we (Petersen group, UM) observed that the sensory neurons are super sensitive to fine mechanical events. Here we propose to join forces and methodologies, and shed light on both the function and mechanism of this fast process. We will apply recently developed methods for electrophysiological recording from the sensory neurons of awake, freely moving mice (UM) and brainstem neurons of closed-loop controlled anesthetized rats (‘rat-machine hybrid’, WIS). Together, the coordinated experiments will provide the required components for understanding and modeling TIP implementation and control and its potential contribution to tactile perception. The proposed study is expected to provide, for the first time, a comprehensive description of the function and mechanism of a basic component of active touch. Moreover, the study will shed light on the way active touch is controlled by higher cognitive functions. We expect that such insights will be valuable for understanding development and use of touch as well as other mammalian sensory

Location, biophysical properties and function of the uncharacterised mitochondrial carrier MTCH1 (SLC25A49)

Prof. Atan Gross (Weizmann Institute of Science) and Prof. Edmund R.S. Kunji (University of Cambridge)

Members of the mitochondrial carrier family (SLC25), which is the largest solute carrier family in humans, transport inorganic ions, nucleotides, amino acids, carboxylic acids, fatty acids and vitamins across the inner membrane of mitochondria. These transport steps are crucial for many important physiological processes, such as the synthesis of ATP from the oxidation of fats and sugars, amino acid metabolism, lipid and steroid synthesis, ion homeostasis, heme synthesis, iron-sulfur cluster synthesis, signaling, macromolecular synthesis, heat production, development, cellular differentiation and cell death. Here we propose to study one of the most divergent carriers of the family, the mitochondrial carrier homolog 1 (MTCH1) or SLC25A49. MTCH1 is phylogenetically related to mitochondrial carrier homolog 2 (MTCH2), but its expression was unable to complement the function of MTCH2, indicating that it has a different and unknown role in cellular physiology. Both proteins are reported to be located in the outer mitochondrial membrane and they are implicated in apoptosis, but their molecular mode of action is unresolved. The aim of the proposed work is to identify the function of MTCH1 by using a combination of different approaches. In the Gross lab, the post-doctoral fellow will apply techniques to confirm the cellular location of the protein using differential solubilization and microscopy analysis. The effect of ablation of MTCH1 on the metabolism and ultrastructure of the cells and mitochondria will also be investigated to obtain clues about its role. In the Kunji lab, MTCH1 will be expressed in bacterial membranes or in yeast or mammalian mitochondria and purified for structural and functional analysis. The purified protein will be used for thermostability assays to establish the binding of small molecules or other proteins to MTCH1, which may form a starting point for its identification. If it is a bona fide transporter, binding and transport studies will be set up to establish the mechanism of MTCH1. This analysis will be supported by computational methods, such as symmetry analysis, which identifies residues important for substrate binding and mechanism, as well as structural modelling. If sufficient material can be obtained, nano-drop robotics will be used for crystal trials and microfocus diffraction and advanced crystallographic methods will be applied to solve its atomic structure

Identifying regulators and executors of peroxisome turnover through pexophagy

Prof. Maya Schuldiner (Weizmann Institute of Science) and Dr. Ewald Hettema (University of Sheffield)

Excessive pexophagy, selective degradation of peroxisomes, is currently thought to be the cause of 65% of peroxisomal disorders; devastating diseases that often lead to premature death. However, the molecular mechanisms that underlay pexophagy are still not fully clear. The goal of this application is to identify proteins that regulate and execute pexophagy. To reach to this goal we wish to initiate a collaboration between the lab of Dr. Hettema, University of Sheffield, experts in pexophagy, and the lab

of Prof. Schuldiner, Weizmann Institute of Science, experts in systems cells biology. As pexophagy is highly conserved through evolution, we will establish and perform two high content screens in yeast. Our screens will identify proteins that are recruited to peroxisomes during pexophagy and genes that regulate the process. We will then further follow up on the proteins and genes that we identify. Receiving the WIS-UK support should enable us, in the course of two years, to get preliminary data that will put us in a position to apply for traditional funding to further study pexophagy in yeast and later, in humans – with the overarching aim to better understand the cause for rare peroxisomal diseases, currently with no diagnosis or cure

Dissecting Melanocortin Receptor's Selectivity - Towards Targeted Drug Design

Dr. Moran Shalev-Benami, (Weizmann Institute of Science and Dr. Trinidad Montero Melendez (Queen Mary University of London)

This project is the recipient of the Bluston Making Connections Award

The superfamily of G-protein coupled receptors (GPCR) make up the largest family of membrane proteins in mammals and represent drug targets for roughly 30% of all drugs currently in the clinic. One of the striking traits of these receptors is the structural similarity across the ~800 members. This similarity makes it particularly challenging to design drugs that are specific to a single receptor. An example of this challenge can be found in the melanocortin family of GPCRs. Two members of this family, MC1R and MC4R are important drug targets for inflammation and obesity respectively, yet drugs for either one of these have side effects due to interaction with the other receptor. This project seeks to combine structural approaches with pharmacology and signaling platforms to compare and contrast these two receptors. The information gleaned from this project will open doors for structure-based drug design for both receptors and provide a blueprint for comparing and contrasting other GPCR families

Investigating Long Non-Coding RNA NORAD Function in Cancer DNA Damage Response

Prof Igor Ulitsky (Weizmann Institute of Science) and Dr Claire Fletcher (Imperial College London)

This project is funded by The Sybil Shine Memorial Trust

It is now well appreciated that the human genome encodes tens of thousands of long noncoding RNAs (lncRNAs), but their functions and modes of action, in particular in the context of human disease remain mostly unknown. Many of the best studied lncRNAs, such as Xist function through cis-acting regulation, influencing only the expression of genes transcribed on the same chromosome as the lncRNAs. However, most lncRNAs localize to the cytoplasm and act in trans. One of the best studied cytoplasmic lncRNAs is NORAD, first described by the Ulitsky and the Mendell labs. NORAD was shown to defend the genome from chromosome instability in both in vitro and in vivo models, and the Fletcher lab has found that its expression is associated with disease outcome in prostate cancer. NORAD functions at least in part through ~20 highly conserved binding sites for the Pumilio RNA binding proteins. Increased NORAD levels

prevent Pumilio proteins from effectively repressing their mRNA targets, which leads to changes in gene expression that ripple through a regulatory network guiding proper cell division and DNA damage response. While the Ulitsky lab and others have focused on proteins binding NORAD and important for its function, the Fletcher lab has recently identified a functionally important interaction between NORAD and the microRNA miR-346, which binds NORAD in multiple cell lines, disrupts its interaction with Pumilio proteins, and has opposing roles in DNA damage response. In the context of this Weizmann-UK proposal, the Ulitsky and Fletcher labs will join forces and use together the rich arsenal of tools they've established for interrogating NORAD as well as new unbiased tools to profile DNA-RNA hybrids and protein-RNA interactions. In the joint project we will: a) characterise the impact of NORAD loss-of-function and miR-346-associated DNA breaks on gene expression b) assess the contribution of R-loops to the NORAD- and miR-346-related DNA damage; c) identify NORAD regions required for its genome-protective effects using novel CRISPR screening approaches; and d) identify NORAD-interacting proteins and NORAD regions required for regulation of the DNA damage response. The proposed research will thus have a substantial impact on understanding the blueprint of NORAD function, miR-346 function, and the DNA damage response pathway they act in. More broadly, the findings will augment our understanding of cytoplasmic functions of lncRNAs and interactions between different RNA classes in the mammalian cell.

2020 – 2021

Circadian rhythms and micro-environmental signals control LT-HSC differentiation and self-renewal: the roles of TNF and melatonin

Prof. Tsvee Lapidot (Weizmann Institute of Science) and Prof. Bertie Gottgens (Wellcome & MRC Cambridge Stem Cell Institute, Cambridge Biomedical Campus)

This project is the recipient of the Bluston Making Connections Award

Blood forming hematopoietic stem and progenitor cells (HSPC) give rise to all mature blood and immune cells, while maintaining the bone marrow (BM) reservoir of undifferentiated HSPC throughout life. We recently demonstrated that mouse BM-retained HSPC are regulated by daily oscillating light- and darkness initiated signals. Light onset signals metabolically program BM HSPC for differentiation and egress in the morning to replenish the blood with new mature immune and blood cells with a finite lifespan. While at night BM HSPC are metabolically reprogrammed by darkness onset signals for their BM retention and self renewal of the undifferentiated stem and progenitor cell reservoir. We identified norepinephrine (NE) and TNF as key players driving these HSPC metabolic programs. The anti-inflammatory darkness hormone melatonin, secreted in the BM in response to NE & TNF signaling, joins to metabolically reprogram HSPC for the night renewal of the undifferentiated BM stem cell reservoir[1,2]. How these daily oscillating proinflammatory signals from the BM microenvironment control HSPC fate orchestrating these opposite directions of differentiation and self-renewal, is still not fully elucidated.

Particularly, we wish to harness transcriptome analyses by RNA sequencing of sorted, primitive HSPC in order to identify what are the transcriptomic modulations that underlie these daily changes in the

metabolic programming/reprogramming of BM HSPC phenotype and function. These studies combined with known stem cell regulating signaling cascades investigated during day light and night darkness will allow us to pinpoint specific HSPC subsets that change their phenotype and function between day and night[3,4]. Alongside the transcriptomic analyses, we will apply metabolic investigations in stem cells and their BM microenvironment in response to NO, TNF and melatonin. These will include metabolic profiling of BM fluids and plasma at different time points to identify modulations in various metabolites and Seahorse metabolic analyses of enriched BM retained HSPC at the different time points for rapid and quantitative measurement of stem and progenitor cells bioenergetics.

Our study will map the daily changes in key factors that determine HSPC function, and their reprograming from differentiation/egress rout to renewal of the BM HSPC reservoir. These identified pathways will provide insight as to potential targets for facilitation of BM engraftment and repopulation with relevance to clinical bone marrow transplantation protocols.

JANET: Joint lab in learning analytics 1 for personalized science teaching

Dr Giora Alexandron (Weizmann Institute of Science) and Prof. Alexandra I. Cristea (Durham University)

Educational technology is a powerful means for preparing students for the knowledge society of the 21 st century. A fundamental educational challenge that technology is especially promising in is Personalisation, namely, addressing the needs of the individual learner. Recent advances in Artificial Intelligence (AI) and Semantic Web Technologies can be used to create Personalised Learning Environments (PLEs). PLEs rely on semantic information that enables AI-agents to make 'intelligent' decisions such as recommending content to students. However, while high-quality digital content is in many cases readily available, it is the semantic information that is usually missing. The conservative approach for generating semantic information relies on experts, but this process suffers from fundamental quality issues, and does not scale. Thus, having scalable processes for generating high quality semantic information is a key barrier to the development of PLEs.

To address this, we propose to *crowdsource semantic information from teachers and learners, and use gamification* mechanisms as means to encourage active, long-lasting user participation. This idea was never applied before in the educational context, and it carries huge promise to the development of PLEs.

The primary experimental setup of our research will be based on a Personalised Teaching and Learning platform named PeTeL that is being developed in the Department of Science Teaching at Weizmann, is already in use by >200 teachers and >7000 learners, and is rapidly growing.
The combined expertise of the groups in personalisation, AI, crowdsourcing and gamification (Durham), as well as in AI and data mining in education (WIS), together with the close collaboration with PeTeL, uniquely position us to conduct this research, which will benefit research and society by providing new strategies for PLEs.

Deciphering ribosome heterogeneity at the protein level and its role in cell physiology

Prof Jeffrey E Gerst (Weizmann Institute of Science) and Prof. Graham Pavitt (University of Manchester)

Textbook illustrations of the process of translational control typically present ribosomes as invariant machines involved in the actual steps of protein synthesis. Yet, it is now known that most eukaryotic cells, including humans, co-express numerous paralogs or isoforms of ribosomal proteins (RPs) that undergo post-translational (phosphorylation, ubiquitination, ufmylation, *etc.*), as well as post-transcriptional modifications (*e.g.* RNA editing), that may alter their function. Cells can also express different ribosomal RNA isoforms, which may also undergo RNA modification, and hundreds of other (non-core) proteins can associate with ribosomes to, potentially, alter function. Altogether, this makes it a huge challenge to understand how and why ribosome heterogeneity comes about and what effects it may have upon cellular translation. In this proposal, we employ a joint collaborative strategy that will help bring coherence towards understanding how the substitution of one RP paralog with another can result in changes in translation and lead to phenotypic changes in cells. Initial studies from both labs using yeast as a model system have independently demonstrated that paralog specificity in yeast controls the translational output and cell physiology (Gerst lab), while defining the ribosome interactome (Pavitt lab). In this synergistic research program, we will employ a high throughput pipeline for the automated analysis of phenotypic responses of yeast cells to RP substitution, perform direct measurements of the translatome, as well as to assess complete ribosome composition under these conditions using mass spectrometry (MS). The expected outcome of this study is to begin defining the ribosomal protein requirements for normal cell physiology and growth under a wide variety of challenging environmental conditions, under which RP paralog specificity evolved.

Machine Learning Through an Information-Theoretic Lens: From Deep-Learning to MetaLearning

Prof. Yonina Eldar (Weizmann Institute of Science) and Prof. Miguel Rodrigues (University College London)

Deep neural networks (DNNs) are complex over-parameterized models, consisting of a series of linear and non-linear transformations, that employ learning algorithms such as stochastic gradient descent to tune their parameters given a dataset composed of a large number of examples. These models have been the focus of very intense study in recent years due to their outstanding performance in a large number of applications such as computer vision, automatic speech recognition, automatic speech translation, natural language processing, artificial intelligence, and many more. However, in spite of these remarkable practical successes, the foundations of deep learning are still poorly understood. This, which is due in part to the fact that conventional learning-theoretic frameworks often do not capture complex interdependences between the various elements associated with the learning process, also prevents one to tackle various outstanding challenges associated with deep learning including dependency on huge training sets, lack of robustness, and lack of interpretability. This research programme aims to explore an information-theoretic foundation to characterize the

performance of deep learning, enabling the design of new learning architectures, models, and algorithms capable of learning robustly from small data. In particular, concrete objectives include:

(1) To develop information-theoretic based characterizations of the generalisation error of supervised deep learning algorithms, along with new supervised deep learning architectures, models & algorithms;
(2) To develop information-theoretic characterizations of the generalisation error of semi-supervised deep learning algorithms, along with new semi-supervised deep learning architectures, models & algorithms;
(3) To generalise the characterizations to emerging learning paradigms, including transfer learning, continuous learning, and meta-learning;
(4) To assess the performance of such new learning architectures, models and algorithms ensuing from our characterizations via a series of case-studies involving relevant datasets.

Life cycle of atmospheric fronts, associated circulation and impact

Dr. Shira Raveh-Rubin (Weizmann Institute of Science) and Dr. Jennifer Catto (University of Exeter)

Extratropical cyclones and atmospheric fronts are the primary systems that govern the variability of weather, and particularly high-impact weather, outside of the tropics. Even though they have been recognised as such for over a century, it is only recently that fronts and their associated circulation have been quantified in global climatological datasets. Such advances allow not only important global quantification of their occurrence, but also crucial understanding of the mechanisms that govern the spatio-temporal variability of the systems, and their impact (e.g., heavy precipitation and strong surface winds). For example, the dry intrusion (DI, the descending air within the cyclone) has been shown by the PIs to be tightly linked to the front characteristics (length, intensity), occurrence frequencies (especially in the subtropics), and precipitation impact. In this context, here we will address four fundamental outstanding questions: (1) how do the lifecycles of extratropical cyclones, fronts and DIs interact? (2) are DIs a necessary ingredient for fronts that develop over strong sea-surface temperature gradients? (3) does the front-DI interaction favour secondary cyclogenesis (4) how do DIs interact with fronts to enhance or suppress convection?

Answering these questions will ultimately lead to better predictability of high impact weather events and how they might change in the future. We will address the questions using novel identification and tracking diagnostic tools using the new reanalysis dataset ERA5, which offers an unprecedented wealth of global atmospheric data in spatial and temporal resolutions that allow for an accurate tracking of the features of interest in time. The tools and datasets resulting from the proposed work will be used further as a basis for studying more complex aspects of the weather systems, and allow an insightful evaluation of climate models that simulate future climate trends. Preliminary results with regard to the link between DIs and fronts are evidence of the successful interaction between the PIs. The proposed project will lay the foundations for an ambitious long-term collaboration, while building the PIs' new groups and fostering the exchange of post-doctoral fellows.

Super-resolved quantitative fluorescence imaging by quantum image scanning microscopy (SuperQMicroscopy)

Prof. Dan Oron (Weizmann Institute of Science) and Prof. Prof. Dirk-Peter Herten (University of Birmingham)

The field of sub-diffraction limited microscopy has seen tremendous advances in the last two decades, with the introduction of revolutionary optical techniques such as STED, structured illumination and single molecule localization microscopy. Yet, when it comes to quantitative microscopy – resolving numbers of active emitters - it is still significantly lagging, especially for more densely labeled samples. Here we propose to combine molecule counting by photon statistics (CoPS) which uses temporal photon correlations, with the recently introduced quantum image scanning microscopy, where super-resolved imaging is obtained by using spatial photon correlations. We anticipate that jointly using the spatio-temporal correlations observable in the photon stream will ameliorate the performance of both methods, enabling quantitative assessment of emitter numbers in denser environments, and, combined with proper algorithms, will lead to an improved spatial resolution beyond what is achievable without exact knowledge of emitter numbers. Moreover, we will demonstrate the suitability of these methods with commonly used organic dyes, and aim for a preliminary demonstration of super-resolved emitter counting in a cell sample. These results will dramatically enhance our ability to study variations in copy numbers or counting of binding sites, tasks which are of utmost importance in current studies of cellular structures and functions on the molecular level.

2019 – 2020

Observing Protein Structural changes in their natural environment – the cell

Prof. Daniella Goldfarb (Weizmann Institute of Science) and Prof. Janet Lovett & Prof. Graham Smith (University of St Andrews)

This project is the recipient of the Bluston Making Connections Award

Currently the great majority of protein structure and dynamic studies are carried out in-vitro on isolated proteins, in environments dictated by the physical method used. These environment, however, differ significantly from that felt by the protein in its native environment, the cell, where it can interact with many other cell components. This in turn can change the protein's conformational equilibrium, which is often closely related to its function. Therefore, major efforts are currently directed towards tracking proteins structure and conformational dynamics inside the cell. As this is a very challenging task we joined forces, the St. Andrews and Weizmann teams, to explore and improve the prospects for using distance measurements electron paramagnetic resonance (EPR) spectroscopy for studying the structure of proteins in their native, by cellular, environment. This collaboration will combine the unique and complementary EPR instrumentation and measurements methodology in each of the lab along with different spin labeling approaches, based on the use of Gd(III), to achieve the high sensitivity required for

such in-cell measurements. The new approach we propose will be developed and tested on small model proteins and then it will be applied to tracking the conformational changes of the human calmodulin protein in eukaryotic cells. Calmodulin is an important calcium sensing protein, which regulates the function of many other proteins and undergoes major conformational changes upon binding Ca2+ and target proteins. These conformational changes are a key factor in its mechanism of action as reported in experiments done in the test tube or in crystals. Now we would like explore this behavior in the cell - does it really happen in a similar manner?

Optimising novel experiments across magnetic resonance using large-scale computational modelling

Prof Lucio Frydman (Weizmann Institute of Science) and Prof Ilya Kuprov (University of Southampton)

Magnetic resonance is an essential tool in analytical chemistry, biochemistry, materials research and clinical practice. Weizmann Institute is a global leader in magnetic resonance instrumentation and experiments: its faculty (Neeman, Vega, Goldfarb, Frydman and others) have, between them, collected every major prize there is in this area. However, as the field evolves towards increasingly sophisticated equipment and techniques, the teams in Rehovot require increasingly sophisticated theoretical and computational frameworks to interpret and optimize their results. This is where the Southampton team comes in – Ilya Kuprov's group is at the forefront of advanced spatio-temporal magnetic resonance simulation methods. The University of Southampton also has a very large supercomputer equipped with the latest GPUs and high- memory nodes. In line with this premise, this project proposes to address a series of theory and simulation challenges that have arose from magnetic resonance research at Weizmann Institute, and that a collaboration with the University of Southampton can help progress further. Specifically, these experiments involve:

1. Three-dimensional diffusion tensor imaging (DTI) projects based on spatiotemporal encoding (SPEN), under active development at Weizmann. DTI is an emerging research and clinical MRI approach, demanding extreme computational requirements at the simulation stage. The formalism recently published by the Southampton team, in combination with their supercomputer can perform such simulations. We propose to adapt these computations to SPEN-based DTI MRI.

2. The Weizmann group has also developed a concatenated cross-polarisation experiment, where the magnetisation of water is transferred, through a complicated quantum mechanical process, to the magnetisation of dissolved biomolecules. This is important because the intrinsic NMR sensitivity of labile groups in proteins and nucleic acids is very short. Still, these experiments are next to impossible to simulate; we propose to develop the framework to overcome this.
3. There is a promise of a massive sensitivity enhancement in solid state nuclear magnetic resonance using exchange saturation transfer techniques. Still, in the Rehovot experiment, only a small fraction of that enhancement could be accessed so far. A theoretical modelling is need to optimise these experiments; these multispin solids NMR simulations will also be tackled.

As soon as the numerical simulations of these complex quantum mechanical and dynamic processes are running, all three problems become viable research projects for further optimisation. Long-term funding for this will be sought from a variety of UK, European, and Israeli funding agencies.

Real-time adaptive quantum sensing

Dr Amit Finkler (Weizmann Institute of Science) and Dr Cristian Bonato (Heriot-Watt University)

Individual spins associated to the nitrogen-vacancy point defect in diamond have shown great promise as nanoscale quantum sensors operating under ambient conditions. Such sensors have been used to map magnetic field of scientific and technological interest at the limits of spectral and spatial resolution. Currently, the main challenge for this system is sensitivity, which is limited to few μT/Hz112 at low frequencies and a few nT/Hz112 at the MHz range. In this Weizmann-UK grant application we address this challenge by investigating the use of adaptive techniques to optimize information collection and processing. The proposed research builds on world-leading capabilities by two young Pis, combining the extensive knowledge and experience in adaptive quantum sensing of the Heriot-Watt University (HWU) team led by Dr Bonato - together with the unique scanning probe capabilities offered by the quantum-enhanced sensing techniques laboratory in the Weizmann Institute of Science (WIS). The latter, led by Dr Amit Finkler, has proven the feasibility of sensing molecules external to the diamond using a single NV centre, and are currently in the final stages of constructing two atomic-force microscopes for single-molecule experiments. The joint work of the HWU and WIS teams will enable a game-changing speed-up of acquisition time, allowing, for the first time, to measure the magnetic resonance from single molecules in a fraction of the time it took in the past. We will combine Bayesian estimation in the standard double-electron-electron resonance protocol to sense paramagnetic electrons of spin-labeled molecules.

Understanding the different calcification mechanisms in coccolithophore life cycle stages

Dr. Assaf Gal (Weizmann Institute of Science) and Dr. Glen Wheeler (The Marine Biological Association of the United Kingdom)

Among marine phytoplankton, coccolithophores are one of the most environmentally important groups. These unicellular algae dominate the global carbon cycle via two distinct cellular processes, photosynthesis and the formation of calcium carbonate platelets, called coccoliths. The inorganic calcification process is under strict biological control. This is exemplified by the very different coccoliths that are produced by the diploid (heterococcoliths) and haploid (holococcoliths) life cycle stages of the organisms. Both life cycle stages form ecologically relevant populations (haplo-diplontic life cycle). Coccolith formation has been almost exclusively investigated in the diploid life cycle stage because the cells are heavily calcified and grow well in laboratory culture. However, many uncertainties remain over the cellular mechanisms of calcification, which hinders our ability to predict how calcification in coccolithophores may respond to future environmental change. In particular, our knowledge of holococcolith formation is extremely limited, as most haploid strains have proven intractable to laboratory culture. In the current proposal, we aim to elucidate the process of coccolith formation in the

haploid life stage in order to identify key mechanistic differences in coccolith production between the life cycle stages. Specifically, we aim to determine the localisation of holococcolith formation and identify associated subcellular structures. This approach is now feasible due to the ability of the UK group to culture and study the physiology of calcifying haploid strains, and the expertise in high-resolution imaging techniques under cryo conditions developed by the WIS group. The findings will provide much needed insight into the biological control over mineral formation and its dependence on cell physiology in both life cycle stages. More broadly, the comparison of distinct life cycle stages will help to inform studies on the ecology and biogeochemical role of this globally abundant phytoplankton lineage.

Characterizing the cell type specific immune response in the Salmonella Typhi human challenge model using single cell RNA-seq

Dr. Roi Avraham (Weizmann Institute of Science) and Prof. Andrew Pollard (University of Oxford)

This Collaboration has been funded by Denis Raeburn & The Gundle Philanthropic Trust

Enteric fever, caused by Salmonella enterica serovar Typhi (S. Typhi), is an important public health problem and, despite decades of research, human responses to the infection are poorly understood. In a recent human challenge model done at the Pollard lab, we have found that after challenge with S. Typhi, marked transcriptional and cytokine responses in blood samples during acute disease were significantly associated with subsequent clinical disease outcomes. This expression analysis represents a measurement of the average response of what are actually multiple cell types that comprise the blood immune compartment. However, the Avraham lab have recently shown that different immune responses are driven by specific cell types and that infection outcome of the entire organism can be, in fact, driven by small subpopulations of cells. Here, by combining the strengths of human in vivo studies at the Pollard lab and emerging single cell RNA-seq approaches at the Avraham lab, we will study the responses of blood immune cell types and subtypes that are associated with the outcome of human S. Typhi infection. Understanding and harnessing these cellular components and pathways that contribute to successful control of the pathogen in human in vivo studies has direct implications to our ability to treat infections.

2018 – 2019

Combinatorial and Algorithmic Primitives for Modern Networks

Prof. Robert Krauthgamer and Dr. Merav Parter (Weizmann Institute of Science) and Dr. Sayan Bhattacharya and Prof. Artur Czumaj (University of Warwick)

Modern-day networks bring along many computational challenges that call for new algorithms, and the proposed work addresses two such challenges, concerning the size of the networks and their dynamics over time, as follows. As large networks can be prohibitive to store (or process) in the big-data era, a common workaround is to employ two fundamental graph structures, called spanners and vertex sparsifiers, which can be viewed as a short summary of the original graph that captures some of its key

properties (e.g., distances). These concepts were thoroughly studied in the literature, and we plan to extend their algorithmic theory to special graph families that are natural and ubiquitous (such as planar graphs or graphs with large minimal degree), in the hope of bypassing existing lower bound constructions towards new and improved algorithms. As most real-world distributed networks undergo repeated and frequent topological changes, such as vertex and edge insertions and deletions, we will also consider the dynamic and distributed setting. Here, the goal is to perform updates in a manner that is distributed and local around the modified part of the network, rather than executing a static global algorithm from scratch following each change. Except for a few instances, so far distributed graph algorithms and dynamic graph algorithms have been developed almost in isolation. Our goal is to bridge this gap by developing dynamic algorithms, mainly for local graph problems, which can be implemented efficiently in the distributed network. This project will establish a new collaboration between four PIs, and more generally between active groups at Weizmann and at Warwick. These groups, and especially the two recently hired PIs, have a great potential to create new ties and cooperation, as the research interests of these teams have a significant overlap but currently there is no such collaboration.

Rapid follow-up of transients

Prof. Eran Ofek (Weizmann Institute of Science) and Prof. Paolo Mazzali (Liverpool John Moores University)

Early spectroscopic and photometric observation of transients (e.g., supernova; NS-NS mergers) are essential for our understanding of supernova progenitors, the latest stages of stellar evolution, the explosion initial conditions, and the heavy nuclei that are generated in the explosion and enrich the interstellar medium. A recent highlight was the discovery of the gravitational wave event by LIGO and the subsequent discovery and study of its electromagnetic counterpart. Here we suggest a synergetic effort between the Weizmann Institute of Science and the Liverpool John Moores University. Specifically, by combining the facilities to which the PIs have access, as well as the diverse technical, and personal capabilities of the PIs, we will launch a program capable of identifying and studying transients soon after their explosion. We suggest using the, under construction, Weizmann Fast Astronomical Survey Telescopes (W-FAST) to search for transients, and to follow up gravitational-wave events, looking for their electromagnetic signature. W-FAST large field of view is optimized for these tasks. The transients will be promptly observed spectroscopically by the Liverpool telescope (at La Palma). The Liverpool telescope is located 35-deg westward of W-FAST which makes it ideal for such a follow-up effort. Our groups bring diverse expertise, in transients observations, transients theory, and transients environments. This project has the potential to initiate a long-term collaboration between the Weizmann Institute and the Liverpool John Moores University. Furthermore, success of these research activities will impact the flagship astronomical facilities of these respective institutions.

Realistic Generation of Quantum States of Light by Single-Atom Cavity-QED

Prof. Barak Dayan (Weizmann Institute of Science) and Prof. Myungshik Kim (Imperial College London)

Light is the backbone of communication, science and technology today, and single photons – the particles of light – will undoubtedly become a center pillar in future quantum communication, information processing and metrology. Yet our ability to control individual optical photons is remarkably limited: even the most elementary tasks such as on-demand generation of single-photon (Fock) states, adding a single photon to a pulse or even just detecting the existence of a photon without destroying it (QND measurement) have so far been demonstrated at very low efficiencies at best. For example, the state-of-the-art probability for on-demand generation of single indistinguishable photons has been limited so far to 15%-33%. The generation of more complicated and powerful quantum states such as higher-number Fock, NOON or Schrodinger Cat states (all of which carry great potential in photonic quantum information processing and quantum metrology) remains extremely challenging. Here we propose to combine the efforts of two of the leading groups in this field, in experiment and theory, to demonstrate efficient, high-fidelity generation of such photonic quantum states. With unique and efficient fibre-based single-atom cavity-QED system designed specifically for photonic quantum state manipulation and generation, Dayan's Weizmann Quantum Optics group has been the first to demonstrate all-optical switching of single photons by single photons, as well as the deterministic extraction of a single photon from an optical pulse and a photon-atom quantum SWAP gate. Professor Myungshik Kim from Imperial College is one of the most influential theoreticians in the field of quantum optics and quantum information processing, with more than 30 years of experience in studying fundamental photonic quantum operations and states. The mutual interests and complementary capabilities have recently (June 2017) sparked the interest of both groups in collaborating on devising schemes for practical generation of quantum states of light. In this proposal we outline our intended collaborative effort for the experimental demonstration of efficient and robust generation of single and multiple photon Fock states, optical Schrodinger Cat states, QND measurements and more – states and tasks that are directly applicable to quantum information processing in photonic circuits, quantum metrology and quantum communication.

New polymer nanocomposites containing inorganic nanotubes

Prof. Reshef Tenne (Weizmann Institute of Science) and Prof. Tony McNally (University of Warwick)

Polymer composites became an essential part of our daily lifestyle from home appliances to cars and airplanes; for encasing mobile phones and much more. Some 20-30 years ago, researchers started to find interest in reinforcing polymer by adding small amounts of different inorganic nanoparticles, which are 2-3 orders of magnitude stronger than the polymer matrix. Few outstanding issues led to slow progress in this field. Among them, are the large-scale synthesis of size-controlled nanoparticles; their tendency to agglomerate and the ability to tune the strength of the nanoparticle-polymer interface in order to optimize the transfer of strain from the polymer matrix to the nanoparticle. In contrast to various graphitic nanoparticles, nanotubes (NT) based on 2D materials, like WS2 disperse very well in polymer matrices showing also very desirable rheological properties in the suspension preform. Furthermore,

they were shown to endow substantial reinforcement to the polymer matrix. The conductivity of WS2 NT and their surface charge can be tuned by the annealing temperature use at the final stage of their synthesis. The higher is the annealing temperature, the higher is the density of negative surface charge (sulfur vacancies) and the better are their *n*-type characteristics. Furthermore, Re-doping of the NT would lead to extra negative surface charge (*n*-type), while Nb doping is expected to produce *p*-type behavior, i.e. NT with positive surface charge. In this collaboration we wish to investigate the influence of the charge and functionalization of the NT surface on the interaction with different polymers, systematically. For this purpose, WS2 NT annealed at different temperatures as well as Nb and Re-doped NT will be synthesized. Furthermore, highly conductive nanotubes from misfit layered compounds, like LaS-TaS2 will be synthesized and used in this study. Surface functionalized and doped NTs will be dispersed in three model polymer systems; i) poly(methyl methacrylate)(PMMA), a polar amorphous polymer, ii) poly(propylene)(PP), a non-polar semi-crystalline polymer and iii) styrene-butadiene-styrene (SBS) block copolymer, an elastomeric material. The interaction between the NT and polymers of different complexities will be studied *via* HRTEM; cryo-TEM and the related analytical techniques, like EDS, ED, EELS and HAADF and micro-Raman. The global structural behavior of the nanocomposite will be studied by XRD/WAXS/SAXS and the UK synchrotron facility (Diamond). Finally, the mechanical and dielectric properties of the nanocomposites will be evaluated in detail. It is not unlikely, that on top of the gained fundamental advances, the present study will produce also new opportunities for technological exploitations of the new nanocomposites.

Surface-sensitive spectroscopies at industrially relevant catalytic reaction conditions

Dr. Baran Eren (Weizmann Institute of Science) and Dr. Robert S. Weatherup (University of Manchester – moved to University of Oxford)

Heterogeneous catalysis is critical to the synthesis and purification of chemicals at the industrial scales demanded by modern society, and in mitigating the impact of harmful pollutants on health and the environment by converting them to more inert products. Much of our existing fundamental understanding of the surfaces involved in heterogeneous catalysis relies on studies of model single crystals using surface-sensitive techniques that typically require rarefied ultra-high vacuum (UHV) conditions, and often cryogenic temperatures. However, to truly understand how catalysts operate under industrial process conditions requires working with more complex materials such as nanoparticles (NPs) and at much higher pressures closer to ambient, respectively referred to as the 'material gap' and 'pressure gap'. In this project, we aim to simultaneously bridge both of these gaps using two specially designed micro-reactors that will enable us to perform surface-sensitive spectroscopies at 1 bar and 200 oC, to reveal the chemical state of NPs, the species absorbed on their surfaces, and the gas phase species. The first reactor will involve the use of graphene membranes as photoelectron transparent windows, that can sustain >1 bar pressure differences, enabling x-ray photoelectron spectroscopy (XPS) and x-ray absorption spectroscopy (XAS) at pressures 3 orders of magnitude higher than widely achievable. Both the catalyst chemical state and the gas phase species can be identified with this approach. The second reactor will be dedicated to polarisation-modulation infrared reflection absorption spectroscopy (PM-IRRAS), which can identify the adsorbed species. We first plan to study the prototypical CO oxidation reaction on Cu NPs. Although catalytic studies show Cu to be more active than

Pt, it is found to suffer a swift deactivation. In contrast to the common hypothesis that CuO formation poisons the surface, our recent ambient pressure XPS (APXPS) experiments have shown that only Cu2O is formed under CO oxidation reaction conditions in the *mbar pressure regime*. To understand if this is related to the forementioned 3 orders of magnitude 'pressure gap' requires direct access to the chemical state of catalyst surface in the *bar pressure regime,* made possible by our unique graphene-cell micro-reactor. We will then progress to study how the chemical state of Cu evolves during related, yet more complex reactions, including partial methanol oxidation, and methanol steam reforming. This project builds on our unique expertise in producing and manipulating graphene, and will take advantage of synchrotron-based XPS at Diamond Light Source (DLS), and complementary PM-IRRAS measurements under atmospheric pressure conditions at the Weizmann Institute of Science (WIS).

Studying the self organizing circuit of actomyosin constriction using advanced optogenetic tools

Prof. Ben-Zion Shilo (Weizmann Institute of Science) and Prof. Jean-Paul Vincent (The Francis Crick Institute)

Non-muscle actomyosin constriction is a highly controlled process important in many aspects of cell biology and tissue morphogenesis. Live cell imaging has been instrumental in advancing the understanding of this process. One critical point that has arisen from a number of studies of various systems is that the actomyosin contractile system has an internal self-organizing circuit. Different factors and conditions modulate this underlying circuit to bring about distinct contextual outcomes. We propose to directly study this basic circuitry, by using advanced optogenetic tools to manipulate it. The *Drosophila* salivary gland is an especially compelling system for such a study. The salivary gland contains many large vesicles that fuse to the apical surface. Secretory vesicles must constrict to excrete their content, in a process dependent on actomyosin activity. Relative to other systems where the actomyosin recruitment takes place in a complex tissue, here constricting vesicles are relatively simple. Each vesicle exhibits of complete cycle of actomyosin assembly and disassembly within a timeframe of about 3 minutes, following its fusion with the apical membrane of the cell. The large size of the vesicles (~ 5 microns in diameter) provides superb imaging conditions. The Shilo lab has established this system and used it to describe the chain of events from fusion to constriction. Based on a number of studies the lab has formulated a model that contains a basic oscillator. The oscillator uses rapid feed forward activation and delayed feedback inhibition. According to the model, fusion brings about recruitment of active Rho that activates diaphanous (Dia), thus inducing actin polymerization. Actin recruits GEF2 that feeds forward back to Rho. Once a certain level of F-actin is formed it will recruit GAP71E that will inactivate Rho, and actin will depolymerize. Depolymerization is essential for constriction and, as expected from the model, blocking constriction will cause repeated waves of actin polymerization and depolymerization. Most of this knowledge was obtained using RNAi and chemical inhibitors with the limitation of compromised temporal control. The Vincent lab has great expertise in genome engineering and has been working on optimizing optogenetic intervention in *Drosophila* development. We therefore propose to join forces on tagging the endogenous loci of the key components RhoGEF2 and RhoGAP71E with traceable fluorescent proteins and produce photo-activatable versions. We then plan to use these tools to manipulate and characterize the secretion process in real time while imaging. The new tools will enable us to gain a deep

insight into the basic temporal order and logic of the actomyosin circuit, that is essential for the selforganized process of tissue morphogenesis.

Elucidating the functional roles of parent-specific IG-DMR methylation dynamics during normal development and in adult tissues

Dr Yonatan Stelzer (Weizmann Institute of Science) and Prof. Anne C Ferguson-Smith (University of Cambridge)

DNA methylation patterns undergo dynamic genome-wide changes during germline differentiation and immediately after fertilization, resulting in cell-type specific epigenetic landscapes. While essential for normal mammalian development, how DNA methylation regulates gene expression programs and cell identity is still largely unknown. One of the most remarkable examples for epigenetic control on genome function is the phenomenon of parental imprinting. Parent-specific DNA methylation marks control the monoallelic expression of imprinted genes and perturbations to these marks, prior to implantation, result in embryonic lethality. We recently established a locus-specific DNA methylation reporter system that allows, for the first time, the monitoring of DNA methylation dynamics, both in vitro and in vivo in single cells. Utilizing the reporter system, we were able to identify striking regulation of parental imprinting in post-implantation embryos and in adult cells. These findings challenge the prevalent belief that following fertilization, parental imprinting is mostly maintained in a passive fashion, further indicating that dynamic epigenetic variations in the adult may be of functional importance. Here, we will utilize cutting-edge DNA methylation reporter system and conditional knockout mice, together with state-of-the-art genome-wide and gene-specific expression analysis methods, to study the functional roles of parent-specific DNA methylation dynamics during mouse development and in adult cells. Specifically, we will determine how parent-specific DNA methylation dynamics regulate normal development, potentially uncovering the contribution of changes in imprinted gene dosage to tissue development and homeostasis. Our combined approach will open new avenues for elucidating the contribution of DNA methylation dynamics to cell fate decisions during development and disease.

A Weizmann and University of London Collaborative Effort to Address Next Generation Metabolomics Resources

Prof. Asaph Aharoni (Weizmann Institute of Science) and Prof. Paul D Fraser (Royal Holloway University of London)

In comparison to other “omics” technologies such as DNA/RNA sequencing, metabolomics has not advanced with the same rapidity to deliver the depth of analysis required. Limiting factors that need addressing are increased metabolite annotation, plus spatial and temporal metabolite resolution. Our aim in the proposed project is to create a collaborative programme that will enable the development and transfer of complementary tools and resources between the UK and Israeli groups. Through this initial investments, resources will be leveraged that will enable the groups to attain their overarching aim of creating a next generation metabolome that can readily be translated across biological kingdoms. In the long-term the approach will enable metabolomics as a discipline to compete with more advanced

"omics" technologies delivering the fundamental knowledge base for specific applications. One of the limitations to our present advancement in metabolomics resides in the limitation of authentic standards, including labelled metabolites facilitating accurate quantification and annotation of profiles from specialised tissues. The proposed project, "METARES" will utilise the specific expertise of the two groups to create a valuable resource of well characterised standards and chromatographic profiles from specific biological matrixes. The focus in 'METARES' will be isoprenoids because these compounds are rarely commercially available, are expensive and complex to prepare, have high commercial value across multiple industrial sectors and abundant in the Solanaceae models and crops used by both groups. The Fraser and Aharoni labs have a unique collection of transgenic/mutant Solanaceae genotypes with perturbed isoprenoid contents in complementary compartmentalised sectors of the biosynthetic pathway. This resource will facilitate an exceptional opportunity to identify and characterise unique metabolite profiles. The activities proposed include vital exchanges of Early Career Scientists (ECR) as well as the PIs. The proposed opportunity will contribute to the leveraging of funds necessary to achieve the long-term goal of creating a next generation metabolome that will enable metabolomics as a discipline to compete with more advanced "omics" technologies.

Dissecting the interrelation between action potential firing rate homeostasis, sensory processing and memory formation

Dr. Ivo Spiegel (Weizmann Institute of Science) and Prof. Tom Mrsic-Flogel (University College London)

Homeostatic control over action potential firing rates in neurons prevents seizure-like activity in neural circuits and is thought be required for proper sensory processing and memory consolidation. However, the molecular mechanisms that dynamically regulate action potential firing rates are poorly understood, and thus the interrelations between firing rate homeostasis, sensory processing and memory consolidation could not be analyzed. We have recently found that the transcription factor Npas4 is experience-induced in somatostatin-expressing inhibitory interneurons (SST neurons) in the adolescent visual cortex where Npas4 promotes excitatory synapses onto SST neurons to maintain the ratio of excitation and inhibition (E/I-ratio) in these neurons. Since E/I-ratio determines the rate of action-potential firing and since Npas4 is experience-induced in SST neurons also in the adult visual cortex, we hypothesise that Npas4 homeostatically controls action potential firing rates in the adult cortex via the regulation of E/I-ratio in SST neurons. Our joint proposal aims to test this hypothesis and to exploit the known wiring-pattern and circuit-function of visual cortex SST neurons to assess the interrelation between firing rate homeostasis, specific forms of visual processing and the consolidation of visually cued memories. To this end, we will: 1. Analyse the cellular and synaptic functions of Npas4 in adult visual cortex SST neurons via electrophysiological recordings in acute brain slices and morphological analyses in vivo. 2. Use calcium imaging and multi-electrode recordings in vivo in the visual cortex of awake mice to longitudinally assess how Npas4 in SST neurons affects action potential firing rates in SST neurons and other neuronal subpopulations. 3. Test how loss of Npas4 in in visual SST neurons affects visual processing and visually cued memory formation. In future studies, we will determine the underlying molecular mechanisms by identifying the target genes of Npas4 in SST neurons. The proposed research we will integrate genomic, morphological, electrophysiological and imaging approaches, thus combining the complementary expertise of the two research groups in molecular and cellular analyses (Spiegel) and

in the functional analyses of cortical circuits in vivo (Mrsic-Flogell). This grant will jump-start our first joint endeavour aimed at dissecting how action
potential firing rates and sensory processing are controlled by experience-induced transcriptional networks. We are confident that the preliminary data acquired within the framework of this grant will be the basis for a full-fledged grant application.

Retrograde Signalling via NOX-dependent oxygen species in axonal regeneration

Prof. Mike Fainzilber (Weizmann Institute of Science) and Prof. Simone Di Giovanni (Imperial College London)

Reactive oxygen species (ROS) contribute to tissue damage and remodelling mediated by the inflammatory response after injury. We have very recently shown that ROS, which are believed to promote axonal dieback and degeneration after injury, are also required for axonal regeneration and functional recovery after peripheral nerve and spinal cord injury. We found that the ROS-producing enzyme NADPH oxidase 2 (NOX2) undergoes retrograde transport in the injured sciatic nerve. Axonal transport of active NOX2 is via endosomes in an importin b1 and dynein dependent mechanism. Endosomal NOX2 inactivates PTEN by oxidization in neuronal cell bodies, thereby stimulating PI3K-pAkt signalling and regenerative outgrowth. These findings challenge the widely held view that ROS are exclusively involved in nerve degeneration; and establish a novel role for retrograde ROS signaling in axonal regeneration. This collaborative research project will investigate the roles of ROS and NOX2 signaling in axonal injury signaling and regeneration. Specifically, we will address how ROS and NOX2 pathways affect proteome dynamics in injured axons and transcriptional responses in neuronal cell bodies. The project will delineate molecular mechanisms mediating the effects of ROS and NOX2 in neuronal repair, providing a firm basis for future comprehensive studies on the roles of these mechanisms in long-lasting regenerative reprogramming and repair.

2017 – 2018

Visualizing Energy Dissipation in Strongly-Interacting Quantum Fluids

Prof. Shahal Ilani and Prof. Eli Zeldov (Weizmann Institute of Science) and Prof. Andre K Geim (University of Manchester)

Dissipation, the process through which an object loses energy to the environment, is a ubiquitous phenomenon, and is well understood for the motion of everyday objects like a bouncing ball. However, for quantum mechanical particles, energy loss remains poorly understood. As modern electronic components such as transistors continue to shrink in size, quantum effects are becoming increasingly important, and thus understanding energy loss in such systems is quickly becoming a problem of both fundamental and technological importance. The Ilani and Zeldov groups at Weizmann have recently developed novel, complimentary techniques that are uniquely capable of creating maps of exactly how energy is dissipated in such microscopic devices. The ideal material for exploring energy dissipation of

quantum particles is graphene, a single layer of carbon atoms that has been pioneered by Andre Geim at the University of Manchester. Now, in collaboration with Andre Geim's group, the Weizmann groups will image how electrons flow through and dissipate energy in nanoscale graphene devices. We anticipate that this new collaboration between the three teams, beyond its broad impact in nanoscale physics, may have significant implications on other fields of physics including high energy-physics and astrophysics, which also have outstanding problems in understanding how energy flows between quantum particles.

Discovering the role of malaria-derived exosomes in modulating parasite transmission through the mosquito vector

Dr Neta Regev-Rudzki (Weizmann Institute of Science) and Dr Jake Baum (Imperial College London)

Malaria disease kills up to half a million people worldwide annually especially young children <5 years of age. The malaria parasite, Plasmodium Falciparum, cycles in a fascinating and complex journey between their human and mosquito hosts. Previously, in a joint study involving the Israeli scientist, Dr Neta Regev-Rudzki and a British colleague, Dr Jake Baum, it was shown that the malaria parasite releases tiny packages, vesicles, which transfer messages between individual parasites allowing them to, remarkably, communicate. Given the abundance of these vehicles produced by parasites within the blood of patients, we would expect there to be a large population of the vesicles carried into the feeding mosquito during a blood meal. However, the effect of parasite-derived vesicles on the mosquito host remains untested and yet to be explored. Specifically, these vesicles may carry signals that affect the immune system of the mosquito to the benefit of parasite transmission.
In this joint-project, combining state-of-the-art skills in parasite and vesicle biology at the Weizmann Institute, Rehovot with unique facilities for studying the parasite journey through the mosquito host at Imperial College London, the aim is to test this hypothesis directly.

Analysis of Ice Nucleating Particles And Their Biological Content In The Eastern Mediterranean Using Microfluidic Devices

Prof. Yinon Rudich (Weizmann Institute of Science) and Prof. Benjamin J. Murray (University of Leeds)

Ice nucleating particles (INP) in the atmosphere can have an impotent role in climate because they affect how some clouds reflect solar light and how they develop precipitation. A multitude of different aerosol types may act as ice nucleating particles. They include some biological materials, desert dusts and sea spray aerosol. However, the relative contributions of these distinct ice nucleating materials to atmospheric processes is poorly understood and there are very few measurements of INP in the Earth's atmosphere. The Eastern Mediterranean is ideal location for studying INP from various regions. This region is influenced by dust storms originating in the Sahara Desert and in the Middle East, marine biogenic aerosols from the Mediterranean Sea, and biogenic particles lofted into the atmosphere from agricultural areas. We intend to take advantage of the unique environment of the Eastern Mediterranean to study the impact of INPs from these sources and to investigate the competition between them and thus their relative importance on a day-to-day basis. To achieve this, we will adapt our state-of-the-art instrument which is based on a device with very small channels (microfluidic technology) in which we can

investigate how atmospheric samples freeze. This cost-effective, portable, automated and integrated device that will provide near-real-time measurement of INPs in the atmosphere. In parallel to the INP measurements we will study the microbial population of desert dust, using deep sequencing analysis, and how it varies between these sources. In this study we will combine analyses of the atmospheric microbiome and microfluidics measurements of INP to identify the effects of biological aerosols, dust loading, dust source regions and composition on the ability of dust to nucleate ice.

Regenerative potential of human pluripotent stem cells and their differentiated progeny revealed through transplantation into mouse embryos

Dr. Yaqub (Jacob) Hanna (Weizmann Institute of Science) and Prof. Roger Pedersen and Dr. Mark Kotter (University of Cambridge)

It has become increasingly evident that the ultimate promise of stem cell research is to create "customized" human pluripotent stem cells with the patient's own DNA that when transplanted, will replace damaged tissues and restore health. We will examine the clinical suitability of these patient derived induced pluripotent stem (iPS) cells by performing a preclinical study in which we will transplant them into a functional mouse model and study their continued developmental potential in a living host organism. This research will help provide the basis for decisions on the future clinical applicability of cells and tissues derived from human iPSCs.

Interplay between senescent cells and stem cells

Dr. Valery Krizanovsky (Weizmann Institute of Science) and Prof. Jesús Gil (Imperial College London)

Research in my laboratory focuses on cellular senescence, the phenomenon in which living cells keep functioning but stop reproducing, losing their ability to divide. It occurs naturally as part of the body's response to stress or injury, and operates as a braking mechanism to limit tumor formation. We study how induction of senescence limits tumor development and how senescent cells influence the progression of ageing. It appears that in both of the above situations senescent cells might be able to influence stem cells, probably due to secretion of molecules that can impact other cells. The collaborative grant with the laboratory of Jesus Gil aims to understand how senescent cells influence stem cells and what are the possible consequences of this impact on cancer initiation and on ageing. During last few years we have developed methods that allow us specifically eliminate senescent cells and Dr. Gil's laboratory developed methods to modify secretion of the molecules from senescent cells. These methods will help us to understand the impact of senescent cells on stem cells in cancer and ageing.

2016 – 2017

Inhibiting Dual-Specificity Tyrosine Phosphatases (DUSPs) as a Method for Preventing Resistance to Herceptin in Her2-Positive Breast Cancer

Prof. Ari Elson (Weizmann Institute of Science), Dr. Lydia Tabernero and Dr. Jean-Marc Schwartz (University of Manchester)

This Collaboration has been funded by Denis Raeburn & The Gundle Philanthropic Trust

The aim of this study to focus on a novel family of molecules (DUSPs) to devise new methods for countering resistance to Herceptin, a major and all too frequent event encountered during state-of-the-art treatment against breast cancer. The approach and results obtained here will impact on the efficacy of cancer treatments and guide future efforts in the design of more efficient and personalized cancer therapies.

Exploring polaronic effects in oxides using range-separated hybrid density functional theory

Prof. Leeor Kronik (Weizmann Institute of Science) and Prof. Alexander Shluger (UCL)

This study, if successful, this will make it possible for researchers to make accurate predictive calculations of polaronic phenomena. This will open the door to understanding, reliably predicting and describing novel polaronic phenomena in technologically relevant materials, notably amorphous ones. This may have a major impact on the understanding and ultimately design of thin-film oxides and the cutting edge of modern electronics.

Decipher how human leukemic cells modify the bone marrow vasculature permeability for their own support and how this impact on chemo-resistance

Prof. Tsvee Lapidot and Dr. Kollet Orit (Weizmann Institute of Science) and Dr. Dominique Bonnet, (The Francis Crick Institute)

The goal of this project is to look at the cross-talk between leukemic cells and their bone marrow microenvironment including bone-forming stem and progenitor cells. The researchers hope to decipher how human leukemic stem cells modify the bone marrow vasculature for their own support and chemo-resistance; and finally see whether modifying or blocking cross-talk could impede leukemic development. The researchers hope the study will shed new light into the role of the bone marrow microenvironment in the maintenance of normal hematopoietic stem and progenitor cells (HSCs) and how this microenvironment might be perturbed during leukemic development. It could also provide some new tools on how to better maintain HSC in their niches and/or how we can intervene to disturb leukemia.

From Flavor & Higgs Precision Physics to LHC Discoveries

Prof. Gilad Perez (Weizmann Institute of Science) and Dr. Sebastian Jaeger (University of Sussex)

This research focuses on the interplay between avor precision measurements, several of which appear in tension with the Standard Model (SM) predictions, and Higgs physics in the context of a new class of natural theoretical models extending the SM. The researchers hope this study will advance understanding of both ends of the luminosity and energy frontiers and that the relationships will pave the path towards dramatic discoveries at the exciting era of the second run of the LHC.

The link between nuclear biomechanics and transcriptional control

Prof. Talila Volk (Weizmann Institute of Science) and Dr. Andrea Brand (Wellcome Trust/Cancer Research UK Gurdon Institute University of Cambridge)

Nuclear morphology and architecture have been suggested to contribute significantly to the epigenetic state of a given cell type. However, the linkage between altered nuclear shape and changes in the DNA occupancy of specific chromatin factors is yet to be elucidated. The collaboration between the groups will be based on combining the application of the TaDa methodology developed by the Brand lab, with the cell biology expertise of the Volk lab. The researchers hope to reveal the contribution of nuclear architecture to the transcriptional output of distinct cell types.

A novel chemical genetics approach to investigate essential yeast enzymes

Dr. Nir London (Weizmann Institute of Science) and Pedro Beltrao (European Molecular Biology Laboratory (EMBL-EBI)

Studies utilizing gene knock-downs have tremendously increased the understanding of cellular biology and protein function. However, the ability to study *essential* genes using such approaches is limited. The researchers expect to generate novel general tools for chemical genomics which should be transferable to investigate signalling in mammalian cells as well.

2014 – 2015

Cellular and molecular control of T-Cell tolerance: Regulation of the thymus medulla

Dr. Jakub Abramson (Weizmann Institute of Science) and Prof. Graham Anderson (University of Birmingham)

In a functional immune system, T cells serve to protect, by attacking foreign invaders (bacteria, viruses etc) whilst tolerating the body's own components. Occasionally, T cells can turn against the body's own organs, which can lead to autoimmune disorders such as type-1 diabetes, IBS, multiple sclerosis and

rheumatoid arthritis. These are called self-reactive T-cells. The collaboration will use expertise from both labs to look at the mechanisms which control mTEC/thymus development which represent a challenging but fundamental aspect of the immune system. mTECs (medullary thymic epithelial cells) are a population of cells in the thymus which play a critical role in purging the body of self-reactive T cells during their development. Understanding how these cells develop may give answers for therapeutic treatment of autoimmune diseases.

Ripk3 as a possible therapeutic target for the devastating infantile disease, Krabbe disease

Prof. Tony Futerman (Weizmann Institute of Science) and Prof. Timothy Cox (University of Cambridge)

Krabbe disease is caused by a defective enzyme called β-galactosylceramidase. Patients normally present in infancy and the disease has a birth frequency of about 1 in 100000. Currently there are no treatments for the disease. The collaboration aims to delinate the precise role of RIPK1 and RIPK2 in Krabbe disease pathology. RipK is a signalling pathway which is involved in the pathology of both Krabbe and Gaucher disease. The joint research will give further understanding about the mechanism that causes the diseases, leading to a new therapeutic target and the development of new drugs to treat the devastating disease.

A systematic genetic and functional analysis to characterize MAGEC1 as a novel melanoma oncogene

Dr Yardena Samuels (Weizmann Institute of Science) and Dr Xin Lu (Ludwig Institute of Cancer Research, University of Oxford)

The collaboration will initiate a new collaborative project between cancer genetics and cancer biology researchers to comprehensively understand the functional effects of a novel melanoma gene. Using a multidisciplinary approach, the researchers aim to reveal the underlying mechanism for the tumorigenic effects of MAGEC1, a cancer/testis antigen which is known to be re-expressed in a number of human tumours and is significantly mutated in several cancer types, most highly in melanoma.

Nanofabrication by combined contact electrochemical and photochemical patterning of self-assembled monolayers

Prof. Jacob Sagiv (Weizmann Institute of Science) and Prof. Graham Leggett (University of Sheffield)

This collaboration will allow both researchers to utilize each other's knowledge in electo- and photo-chemistry to develop the best way of organizing molecules at the nanometer level. This grant enables them to study the way these molecules arrange, which will enable future nanoscale systems to be developed. For example, Prof Leggett's research focuses on studying bacteria and its ability to create and

store energy from sunlight – the physical pathway for which is what he hopes to recreate with the technology developed as part of this collaborative project.

Opening a window onto the final stages of massive star evolution

Dr. Eran Ofek (Weizmann Institute of Science) and Dr Mark Sullivan (University of Southampton)

The researchers are studying data from the Palomar Transient factory which shows that some very massive stars have ‘‘mass ejection’’ episodes on time scales of a few months prior to their terminal supernova. The aim of the collaboration is to strengthen a fledging partnership where the researchers will quantify the frequency and properties of mass-ejection events among all types of supernovae, and to search for the progenitor stars of the supernova explosions themselves. The ultimate goal is to better understand the physics underpinning the supernova explosions themselves.

Infrastructure and instrumentation for discovery of UV and X-ray light from cosmic explosions

Prof. Avishay Gal-Yam (Weizmann Institute of Science) and Prof. Julian Osborne and Prof. Paul O’Brien (University of Leicester)

The researchers will be looking at how the explosion of massive stars gives birth to black holes. These emit high energy γ-ray, X-ray and ultraviolet photons which encode critical information about what drives these events – these can only be studied by space missions which carry sensitive detectors above the blocking effect provided by Earth’s atmosphere. The collaboration will draw upon expertise from both Institutions and by building up preliminary results the research partners will develop new techniques and instruments to study future data sets.

2013-14

Organic-Inorganic Perovskite Semiconductors for Photovoltaic Cells

Prof. Gary Hodes & Prof. David Cahen (WIS) & Dr Henry J. Snaith (University of Oxford)

A novel class of perovskite semiconductors has shown exciting results as the light absorbing semiconductor in nanoporous photovoltaic cells. This collaboration aims to use their combined knowledge of photovoltaic science to understand what determines this exciting behaviour exhibited by these materials with the hope to use this knowledge to create cells with higher open circuit voltages by exploiting their findings.

Probabilistic and Continuum Approaches to Modelling Chemical Transport with Reactions in Geological Formations

Prof. Brian Berkowitz (WIS) & Prof. Sebastian Geiger (Heriot-Watt University, Edinburgh)

Many of society's challenges today, such as the supply of clean drinking water and sustainable energy, require the understanding of the flow of fluids and the transport of chemicals and their reaction products underground. Measuring and modelling the system is very difficult as many different things contribute to the system and therefore standard modelling is not sufficient. This collaboration aims to combining parallel activities from both groups to develop a probabilistic quantification of hierarchical flow and reactive transport in different geological formations.

The Relationship between Optimism and Probabilistic Decision-Making – A Computational Neuroscience Approach

Prof. Yadin Dudai (WIS) & Dr Tali Sharot (University College London)

Humans tend to overestimate the likelihood that positive events will occur in the future and underestimate those of negative events. This 'optimism bias' is maintained by asymmetrical learning in which positive information has more impact on our learning than negative information. The collaboration will investigate possible link between this learning asymmetry and risk preferences at behavioural, pharmacological and neurobiological levels.

Long-range Regulation of Tissue Specific Runx1 Expression

Prof. Yoram Groner (WIS) & Dr Marella de Bruijn (MRC Molecular Haematology Unit, Oxford University)

Runx1 is a critical regulator of important developmental processes, including blood cell development and peripheral nerve growth. The collaboration proposes to use a multipronged approach to identify the distant elements (such as *cis*-regulatory elements) that mediate *Runx1* expression in development. The research will also analyse the *in vivo* function of these regulatory elements.

Roles of Actin Nucleation Factors in Sarcomere Organization and Function

Prof. Ben-Zion Shilo & Dr Eyal Schejter (WIS) & Dr Elisabeth Ehler (King's College London)

The collaborators propose to study the contribution of the actin-based cytoskeleton to two of the major machineries that govern muscle cell function – the membrane systems that couple neural stimulation with the contraction of the sarcomere in the muscle cell and the filament arrays that cause contraction to happen. The research will focus on the forming FHOD/Fhos – a single nucleator which has been identified as a critical element in muscle cell function.

2012-13

Development of Motor-Sensory Strategies for Vibrissal Active Touch

Prof. Ehud Ahissar (WIS) & Prof. Tony Prescott & Prof. Peter Redgrave (University of Sheffield)

The project aims to provide a comprehensive description of the development and maturation of whisking behaviour by investigating the motor-sensory strategies step-by-step of vibrissal active touch, by tracking and analysing the development of such strategies in newborn rodents. They also hope to reveal basic principles of brain control of active touch and factors affecting their development.

Monitoring of Charge Diffusion in Solids by Null-Point Ellipsometry with Lock-In Detection

Ass. Prof. Igor Lubomirsky (WIS) & Dr Peter Slater (University of Birmingham)

The space charge layer (SCL) is a fundamental property of many devices including lithium ion batteries and oxygen sensors. The SCL is responsible for the dependence of electrical properties. The group propose to develop of a technique based on null-ellipsometry to complement impedance spectroscopy and allow real time monitoring of the SCL. The technique will distinguish the contributions of ions, electrons and protons to the overall conductivity.

The Evolution of Protein Foldability

Prof. Dan Tawfik (WIS) & Prof. Jane Clarke (University of Cambridge)

Studying the evolution of foldability in proteins that emerged by duplication and fusion of an elementary sequence unit resulting in a highly symmetrical protein. The group will examine the thermodynamic and kinetic stability effects of the mutations that occur and their effect on the sequence's repetitiveness. They hope to provide unique insights into the evolution of protein folding pathways.

Hierarchical Composites Based on Carbon Nanotube Fibres

Prof. Daniel Wager (WIS), Prof. Milo Shaffer (Imperial College London) & Prof. Alan Windle (University of Cambridge)

This project will measure the mechanical interaction between micron-size fibres made from a large number of carbon nanotubes (CNT) and polymers, to determine the mechanical properties of CNT fibres and their composites, especially the efficiency of stress transfer between CNT fibres and polymers.

Ocean Acidification: Decoupling the Anthropogenic Acidification from the Natural Variability during the Last Millennial in the Eastern Mediterranean

Prof. Aldo Shemesh (WIS) & Dr Gavin Foster (University of Southampton)

Ocean Acidification, changes in the acidity of the ocean through carbon dioxide absorption, has significant impacts on marine biogeochemical cycles. The project will measure the composition of marine biogenic carbonates in well-dated vermetid reefs to obtain the first, high-resolution pH record of the past millennium in the Eastern Mediterranean and therefore, providing data to evaluate the anthropogenic impact on the region.

2011-12

Motor-Driven Transcription Factors In Injured Nerve – How Fast Can They Go?

Prof. Mike Fainzilber (WIS) & Prof. Giampietro Schiavo (Cancer Research UK, London Research Institute)

Retrograde axonal injury signals stimulate regenerative responses by the cell body in lesioned peripheral neurons. The involvement of importins in retrograde transport suggests that transcription factors might be directly involved in axonal injury signaling. This collaboration has previously shown that the transcription factor STAT3 associates with dynein in injured sensory axons. This project will address related questions by monitoring dynein-mediated transport of STAT3 and/or STAT3-derived reporter proteins *in vivo* and *in vitro* in both sensory and motor neurons. The project will provide new insights on fundamental cell biology mechanisms of motor-driven transport, with implications for nerve regeneration and neurodegeneration.

Nuclear Movements and Nuclear Egress of Herpesvirus: Kinetics and Structures

Prof. Michael Elbaum (WIS) & Dr Kay Grunewald (University of Oxford)

Virus-host-interactions must be tightly regulated such that the virus will not drive its host into premature cell death. This project will investigate the role of novel intranuclear structures in more detail by an integrated combination of kinetic and structural imaging approaches. Regarding the virus as a probe, the findings are expected to be of broad relevance to the understanding of basic physiological processes of structure, transport, and communication within the cell nucleus.

Stress-Related Neuropeptides and 'Programming' of the Brain

Prof. Alon Chen (WIS) & Prof. Jonathan Seckl (University of Edinburgh)

Early life environmental factors affect developing systems and may permanently alter organ structure and function throughout life - 'developmental programming'. This proposal aims to explore the involvement of recently identified members of the CRF/Urocortin family of peptides and receptors, in mediating the neurendocrine and behavioral effects of early life stress. Understanding brain 'programming' by focusing on the brain circuits and genes which are associated with, or altered by, prenatal stress will provide important insights into the brain mechanisms by which early life stress affects psychological and neuroendocrine disorders and may improve our ability to design therapeutic interventions for, and thus manage, stress-related disorders.

Switchable Nanomaterials for Catalysis and Sensing

Prof. Rafal Klajn (WIS) & Dr Oren Scherman (University of Cambridge)

Metal nanoparticles (NPs) have attracted tremendous interest in the last decade for their superior optical, electronic, and catalytic properties. Although a number of methods to assemble NPs into macroscopic materials have been developed, these procedures lead to *static* materials – that is, materials whose structure cannot be altered once they have been prepared. We aim to demonstrate how this spectacular behavior can lead to some immediate and important applications in the detection of oxidizing and reducing agents, as well as be applied to systems in which catalysis can be turned on and off using light. Our long-term objective is to integrate our new materials with biological systems for applications such as photoactivated drug release.

Population Dynamics of T Cell Responses Analysed Using High throughput Sequencing of TCR Repertoire

The Late Prof. Nir Friedman (WIS) & Prof. Benjamin Chain (UCL)

Adaptive immunity depends on selective expansion of individual clones of antigen specific lymphocytes, each characterized by an antigen-specific receptor of unique and specific sequence. The rules which determine the selection, expansion and dynamics of the repertoire of clones responding to a particular antigen remain poorly understood. Revealing the TCR repertoire and its dynamics following infection is of basic importance for our understanding of T cell immunity, and has a great applicative potential, for example for better vaccine design and providing new diagnostic markers.

Establishing the Role of Bid in the DNA Damage Response

Prof. Atan Gross (WIS) & Prof. Stephen Jackson (Cancer Research UK, University of Cambridge)

Many cancers of lymphoid origin bear oncogenic chromosomal rearrangements that have arisen as a consequence of defective DNA damage repair. In particular, 10-15% of patients with the genomic instability syndrome ataxia-telangiectasia (A-T), in which the ataxia-telangiectasia mutated (ATM) kinase is absent or inactivated will present a lymphoid malignancy in childhood or early adulthood. Our studies are likely to have important implications for tumor development in the lymphoid lineage, as well as implications for genomic instability syndromes.

2010-11

The Impact of Emotion on Time Perception

Prof. Rony Paz (WIS) & Prof. Marjan Jahanshahi (UCL)

Emotions often affect the precision of our time estimations. However, little is known about the neuronal mechanisms that underlie the interactions between time-estimation and emotions. Using behavioral, neurophysiological and transcranial magnetic stimulation, scientists are exploring the mechanisms that underlie the effect of emotions on time perception in humans

The 'Electrical Double Layer' in Pure Ionic Liquid Next to an Electrified Metal Surface

Prof. Jacob Klein (WIS) & Prof. Susan Perkin (UCL)

Ionic liquids (IL) are a novel class of fluids which are used in applications such as eco-friendly solvents, lubricants, solar cells and even as electrolytes in batteries. Combining techniques by British and Israeli scientists will provide researchers with deep insight of IL at the molecular Level. This is likely to have great implications for the design of batteries, solar cells and other electrochemical applications.

Electromagnetic Induced Transparency with Optically Trapped Atoms

Prof. Nir Davidson (WIS) & Prof. Charles Adams (Durham University)

Electromagnetic induced transparency (EIT) is an intriguing quantum optics effect where a strongly absorptive media becomes transparent over an extremely narrow frequency range due to quantum interference between two or more absorption pathways. By combining techniques developed by both Professors, the two institutions hope to yield unprecedented strong nonlinear effects that may lead to new applications in precision metrology and quantum information science.

The Interplay between Algorithms and Randomness

Prof. Uriel Feige & Prof. Robert Krauthgamer (WIS) & Prof. Amin Coja-Oghlan, Prof. Artur Czumaj & Prof. Harald Räcke (University of Warwick)

Randomness plays a central role in the modern design and analysis of algorithms, a topic that stands in the forefront of research in modern computer science. The scientists' ultimate goal is to advance the theory of algorithm design and analysis as a whole, with a desired long-term impact which is broad and includes developing algorithms that are successful in practice. While the work will focus on basic research and theoretical aspects, its motivation involves, and the results may be relevant to, several application areas, such as databases, computer vision and networking.

A Combined Experimental and Theoretical Study of Dynamics on Surfaces

Prof. Eli Pollak (WIS) & Dr William Allison (University of Cambridge)

The study of surface phenomena is in the forefront of present day research in condensed matter physics. Any real progress in the field has implications for processes ranging from catalysis, to asymmetric synthesis, atmospheric and astrophysical reactions, nanoelectronics and more. The research aims to combine theoretical skills at the Weizmann Institute with new experimental work, performed at the University of Cambridge, in order to understand two major problems in surface dynamics.

2009-10

Brain Substrates of Memory Conformity

Prof. Yadin Dudai (WIS) & Prof. Raymond Dolan & Dr. Tali Sharot (UCL)

Our memories are often inaccurate and social pressure is one reason for false recollection. This leads individuals to change their report of past events to match that reported by others. Scientists are combining a novel behavioral protocol that taxes multiple facets of memory conformity with functional neuroimaging. They hope to understand the brain mechanisms mediating socially-induced memory errors.

Foundations of Dark Energy Research

Prof. Avishay Gal-Yam (WIS) & Dr Mark Sullivan (University of Oxford)

Most of the contents of our Universe are invisible. Understanding the nature of these dark energy components is one of the greatest challenges of contemporary physics. Through critical analysis of

supernovae, researchers hope to identify what stellar systems give rise to these explosions and unravel some of the mysteries of our Universe

Probing the Mechanism of Collagen Degradation

Prof. Irit Sagi (WIS) & Dr Robert Visse (Imperial College)

Collagen turnover is intimately linked with healing of wounds, embryo development and tissue regeneration. By combining biochemical and biophysical tools, scientists will reveal new molecular insights into the complex and important mechanism of collagen degradation.

Cdc42 and the Regulation of Actin Polymerization Dynamics at Cell Membranes: Theoretical Models, Molecular Mechanisms and Developmental Roles

Dr Nir Gov & Prof. Ben-Zion Shilo (WIS) & Dr Buzz Baum (UCL)

Actin cytoskeletal dynamics play a central role in the control of several fundamental cell biological processes in animal cells including cell motility, vesicular trafficking, adhesion and differentiation. Scientists are using a combination of modeling and experiments to reveal the cellular and physiological consequences of activation of the enzyme CDC42 on actin-membrane dynamics.

Self-Assembly of Surface-Confined Functional Materials

Prof. Milko Erik van der Boom (WIS) & Dr Jonathan R. Nitschke (University of Cambridge)

The formation of the assembly of metal-organic systems in solution and their associated studies have had a tremendous impact on many aspects of chemistry, whereas similar well-defined systems on surfaces are relatively rare. Research is being conducted to synthesize a new class of conductive metal-containing self-assembled polymers. Scientists have been developing the techniques that underpin polymer formation in solution, and are continuing to investigate the properties of our products, seeking to optimise their usefulness as surface-confined conductive materials.