PLENARY LECTURES

Tuesday - Friday

PLE-TUE-01

Sponsored by
MONASH MICRO IMAGING, MONASH UNIVERSITY

TOWARDS DIGITAL BIOLOGY

Myers G.
Max Planck Institute of Molecular Cell Biology and Genetics

Our group has been actively pursuing the idea that with great microscopes and great informatics we will be able to truly digitize models of cells, tissues, and organisms through time with information about the genetic and proteomic states of each cell layered there on. The belief is that these atlases combined with optical observations of labeled entities will accelerate the life sciences by allowing us to visualize these systems from any vantage point and as a system, thus leading to many discoveries such as the nature of the genetic control of fly wing development. Since arriving in Dresden three years ago we have made significant progress on hard segmentation and tracking problems with the use of AI techniques developed in the computer vision community. We will present several examples of current projects aimed at digitizing light microscope data sets that exemplify various such techniques and present the quality of the results we obtain with them. Despite these improvements we still find ourselves at the limit of what can be extracted from the images because of limited resolution and contrast. Fortunately, advances in microscope componentry such as adaptive optics, spatial light modulators, and ultra high-speed cameras present opportunities for improving the underlying imagery. We will report on two microscope development projects in our lab, where the aim is to improve resolution by making multiple observations of a volume and from them computing a better reconstruction of the object under observation. We think better microscopy through computation and dynamic onboard control of acquisitions is an emerging trend that we generally call computational optics.

PLE-TUE-02

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RECONSTRUCTING ANCIENT PROTEIN EVOLUTION: THE DIVERSIFICATION OF STEROID HORMONE RECEPTOR SEQUENCE, STRUCTURE AND FUNCTION

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We would all like to understand how a protein's sequence determines its structure and function - and *why* it has each of these properties -- but a protein is such a complex physical object with so many degrees of freedom that this is a very hard problem to solve. I contend that evolutionary analysis of a protein's history through time is the *only* effective way to answer these questions. In this talk, I show how we have retraced in detail the mechanisms by which an essential family of ligand-regulated transcription factors evolved its diverse functions by using ancestral protein reconstruction - phylogenetic inference, synthesis, and expression of ancient protein sequences followed by experimental characterization of their structures and functions and the effects of historical mutations upon them. These studies reveal how just a handful of sequence changes hundreds of millions of years ago - driven by blind chance, natural selection, and the physical architecture of biochemical function - triggered the evolution of biological functions that are now essential to the biology of all vertebrates.

PLE-TUE-03

CELLULAR DYNAMICS OF CELLULOSE AND LIGNIN PRODUCTION IN PLANT SECONDARY CELL WALLS

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Annually, trees deposit billions of tons of cellulose and lignin, macromolecules essential to the strength of the plant vascular system. The dynamic cellular mechanisms underlying cellulose and lignin deposition in secondary walls have remained elusive, as the xylem cells are deep inside developing plant tissues. Using an inducible master transcription factor controlling xylem cell fate, the processes of cell wall synthesis, such as cellulose deposition, can be directly examined in developing xylem cells with live-cell imaging. The high density, rapid velocity, and spatial concentration of cellulose synthase complexes in the cell membrane accounts for the rapid and spatially well defined secondary cell wall production. In addition to polysaccharides such as cellulose, the polyphenolic polymer lignin is essential for maintaining the structural integrity and, therefore, the function of vascular cells. Lignin precursors, monolignols, are made in the cytoplasm and exported by an unknown mechanism to the cell wall, where they are oxidized by enzymes such as laccases and peroxidases, leading to random combinatorial coupling into the lignin polymer. Using plants that overproduce monolignols, we have tested candidate ATP-binding cassette (ABC) transporters in monolignol export, as well as testing the effect of overexpression of laccases. These data challenge current paradigms of active transport, and support a model of monolignol export where laccase-mediated polymerization in the cell wall creates a concentration gradient leading to monolignol export by diffusion.

PLE-TUE-04

DECIPHERING DEVELOPMENTAL CELL DEATH USING *DROSOPHILA* AS A MODEL

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For over a century the little vinegar fly, *Drosophila melanogaster*, has played a major role in scientific discovery by serving as a model for genetic investigations in animal development. Short life cycle, genetic amenability, ready access to reagents and genetically altered fly lines, and a well connected & (mostly) collaborative community make *Drosophila* a system of choice for the study of animal development, complex biological pathways and genetic diseases. In addition, around 60% of the genes affected in various human diseases have counterparts in *Drosophila*. This makes flies a useful tool for biomedical research. Alongside our studies in mammalian cells and mouse models, we have used *Drosophila* for the discovery of several components of the cell death machinery and for characterizing the apoptotic machinery to understand how it is activated and regulated to precisely delete obsolete cells and tissues during development. The use of *Drosophila* has also allowed us to discover a non-apoptotic form of cell death that is independent of caspase activity/ activation. In this lecture I will summarize our studies which are uncovering the intricacies and modalities of cell death using fly as a model.

PLE-TUE-05

microRNAs: MASTER REGULATORS OF LEGUME NODULATION

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Legume plants are able to establish a symbiotic relationship with rhizobia by forming specialized lateral organs—nitrogen-fixing root nodules in which nitrogen fixation takes place. The whole process of symbiotic nitrogen fixation is complex and is regulated by a molecular network involving a multitude of factors and regulatory pathways influencing rhizobia infection and nodule development. Nod factor (NF) signaling pathway has evolved to sense NF released by rhizobia during infection and to regulate rhizobia infection and nodule development. In addition, the NF signaling pathway can be suppressed by a long distance negative feedback loop, autoregulation of nodulation (AON signaling pathway), to prevent overproduction of root nodules that is harmful to legume plants. The regulation of the NF and AON signaling pathways and the integration of these signaling transduction pathways control the nodulation process and the ultimate number of root nodules, which is important for the efficiency of nitrogen fixation. MicroRNAs (miRNAs) are small noncoding RNAs that act as master regulators to modulate various biological processes by post-transcriptionally repressing their target genes. Recently, we reveal that miRNAs, such as miR172 and miR167, are master regulators that regulates soybean nodulation through direct targeting their target genes in soybean. In the presentation, I will describe how miRNAs regulate nodulation with a major focus on miR172 and its role in NF signaling pathway and nodule development, and in integration of NF and AON pathways in nodule number control. miR172 has been shown to primarily regulate the phase transition from vegetative growth to reproductive growth through repressing its target genes encoding AP2/ERF transcription factors in plants. We have unveiled the functions of miR172 and its target gene, NNC1 (Nodule Number Control 1) in rhizobia infection, nodule primordia formation and nodule organogenesis in soybean. I will describe the studies involving morphological, genetic and genomic data uncovering the molecular mechanism through which the miR172-NNC1 module regulates soybean nodulation. I will also discuss our most recent findings on how miR172 and NNC1 regulate attenuation of the AON pathway and integrate the NF and AON signaling pathways for fine tuning nodule number in soybean. The potential application of miR172 and its target genes in genetic improvement of nitrogen fixation efficiency in legumes will also be discussed in the meeting.

PLE-WED-06

TOWARDS A BLUEPRINT FOR BUILDING THE BRAIN

Tole S.
Tata Institute of Fundamental Research.

The cerebral cortex arises from a simple sheet of neuroepithelial tissue in the embryo. How this sheet is patterned to produce distinct cortical structures in a reliable and reproducible manner is a question of both evolution and development. We discovered that the cortical hem, a Wnt-rich signaling center that forms at the telencephalic midline, acts as a secondary organizer in the embryonic brain, and induces the hippocampus. Embryos that were genetically manipulated to form additional ectopic hems displayed multiple ectopic hippocampi. How the hem itself forms and how its position is limited to the telencephalic midline therefore becomes a compelling question, because the position of the hem determines the position of the hippocampus. We explored interactions between three regulators of early patterning, transcription factors Foxg1, Lhx2, and Pax6, and identified mechanisms that regulate the formation and position of the cortical hem. These genetic interactions provide insight into the early steps of patterning of the cortical primordium. Further, we found that hem is itself part of a multi-component “forebrain hem system” that may have arisen as part of an evolutionary mechanism to regulate the formation of the cerebral cortex.. Work in Dr. Tole’s lab has been supported by a Wellcome Trust Senior International Fellowship (056684/Z/99/Z), Swarnajayanti Fellowship (Dept. of Science and Technology, Govt. of India), and grants from the Department of Biotechnology, and the Department of Science and Technology, Govt. of India.

PLE-WED-07

EPIGENETIC REGULATION IN HIGHER PLANTS

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Epigenetics is the study of stable and heritable changes in gene expression without alterations in the DNA sequence, including DNA methylation, histone modifications and variants, chromatin remodeling, and non-coding RNA-mediated regulation of gene expression. Epigenetic control has indispensable functions in multiple aspects of development and cellular processes of multi-cellular organisms. Recent efforts have identified many chromatin modifiers, which play important roles in various biological processes. These chromatin modifiers normally bind a subset of specific genomic loci. Discovering the mechanisms of recruiting these modifiers is essential for understanding their biological function. During the recent decades, enormous progress has been made in dissecting the various epigenetic mechanisms that contribute to important agronomic traits in rice. Yet, varied morphological and adaptive phenotypes conferred by similar genotypes remain to be explained from an epigenetic perspective. Emerging studies have shown that transposable elements (TEs) can be regulated by epigenetic mechanisms to maintain their silenced state, and reactivated and mobilized to produce genetic variation, possibly in response to environmental stress. Here, we will discuss the distinct targeting mechanisms of chromatin modifiers and epigenetic control of TE activity in higher plants. Evolutionary selection through TE-induced epigenetic variation to improve agronomic traits in cultivated rice will also be discussed.

PLE-WED-08

USING THE BREAST EPITHELIAL HIERARCHY TO DECIPHER BREAST CANCER

Visvader J.E.[1, 2, 3]
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Breast cancer is a highly heterogeneous disease at both the molecular and pathological levels. To understand this heterogeneity and 'cells of origin' of breast cancer, it is important to dissect the normal mammary epithelial hierarchy. Over the past decade, we have established master transcriptional and epigenetic regulators that act at specific points along the mammary differentiation hierarchy, including GATA-3 and EZH2. Both transplantation and lineage tracing strategies have proven to be essential for understanding the cell types that reside in breast tissue and their molecular regulators. Lineage tracing is a powerful strategy that enables the fate of stem and progenitor cells to be tracked in situ and their roles established in development, tissue maintenance and cancer. We have combined lineage tracing with a novel three-dimensional imaging strategy to explore the relative contributions of stem and progenitor cells to post-natal mammary gland development and tissue homeostasis. Cell lineage tracing studies also provide the current gold standard for identifying 'cells of origin' in cancer. Towards this end, we are utilising newly generated transgenic strains harbouring lineage-specific gene regulatory regions, to direct the expression of specific mammary oncogenic lesions to distinct epithelial cell types. These include *Pten* and *p53* gene deletion, both of which are frequently inactivated in breast cancer. Interrogation of the molecular expression profiles of the diverse epithelial subsets in human breast tissue has provided insight into potential 'cells of origin' of the different subtypes of cancer. Recently, we have identified a target cell population that is perturbed in precancerous tissue from *BRCA1* mutation carriers, who are highly predisposed to breast and ovarian cancer. Interestingly, the RANK receptor marks a small subset of luminal progenitors and this subset is expanded in precancerous tissue from *BRCA1* mutation carriers (performed in collaboration with Amgen). RANK+ but not RANK- cells were shown to be highly proliferative, prone to DNA damage and exhibited a molecular signature similar to that of aggressive basal-like cancers, thus pinpointing them as a key target population for oncogenesis. Furthermore, inhibition of the RANK ligand (RANKL) could prevent or delay tumorigenesis in *Brca1*-deficient mouse models, thus implicating blockade of the RANK-RANKL signaling axis as a promising breast cancer prevention strategy. Finally, to test new therapies for breast cancer, we have generated an extensive bank of patient-derived xenografts (PDXs) from primary breast cancers that have proven to be valuable preclinical models for exploring new 'druggable' targets.

PLE-WED-09

SECURING GLOBAL FOOD PRODUCTION THROUGH RAPID ISOLATION OF WHEAT RUST DISEASE RESISTANCE GENES

Periyannan S.[1], Steuernagel B.[2, 3], Hernandez Pinzon I.[3], Witek K.[3], Rouse M.[4], Ayliffe M.[1], Bariana H.[5], Jones J.[3], Lagudah E.[1]and Wulff B.[2, 3]
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Wheat is one of the world's most important crops, providing 20% of global calorific intake. A constant threat to production of this cereal crop are rust diseases caused by fungal pathogens of the *Puccinia* genus. Rust diseases are most economically and sustainably managed by breeding resistant wheat crops containing rust resistance genes. However constant evolution of new, aggressive rust pathogen requires new sources of resistance to be identified in unimproved landraces and wild relatives of wheat. Transfer of resistance from wild species into domesticated wheat by conventional breeding is time consuming, expensive and often impeded by linkage drag of undesirable traits linked to resistance genes of interest. Isolation of rust resistance genes enables their direct transfer into elite wheat cultivars by transformation or alternatively these cloned gene sequences can be used as perfect markers to facilitate conventional breeding. By exploiting current advances in DNA sequencing coupled with gene capture technology we have developed a rapid resistance gene cloning methodology called **Mut**agenesis, **R**esistance gene**en**richment and **Seq**uencing (**MutRenSeq**) which was used for isolation of two globally important stem rust resistance genes. This new approach greatly accelerates the isolation of these agronomically important resistance genes from the large and complex hexaploid wheat genome and will enable new biotechnological disease resistance approaches to be undertaken; such as stacking multiple resistance genes at a single locus. This technology is currently being tested in other important crop species.

PLE-THU-10

STRUCTURAL BIOLOGY OF JAK KINASES: INSIGHTS INTO KINASE REGULATION AND RECEPTOR SPECIFICITY

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The Janus kinases, also known as JAKs, are a family of multidomain, non-receptor tyrosine kinases essential for cytokine and interferon signaling through type I and type II cytokine receptors. JAKs are constitutively bound to their cognate transmembrane signaling receptors, and ligand-mediated dimerization of two JAK-bound receptors facilitates activation of the kinase domain leading ultimately to activation of STAT family transcription factors and transcription of target genes. JAK signaling drives processes as diverse as adaptive immune functions, hematopoiesis, metabolism, and cellular growth, and abberant JAK activation can trigger several myeloproliferative and auto-immune disorders. Pharmacological inhibition of JAK kinase activity has been shown to effectively treat several of these indications, and given the promise of these anti-JAK therapies, a complete understanding of the mechanisms of JAK activation has the potential to reveal novel means for therapeutic inhibition. The four JAK family members, JAK1, JAK2, JAK3, and TYK2, share a conserved domain architecture consisting of an N-terminal FERM domain, followed by a SH2-like domain, a pseudokinase domain, and a kinase domain. Through their FERM and SH2-like domains, JAKs constitutively associate with specific peptide motifs (called “box1” and “box2”) present on the intracellular domain of cytokine receptors. We have recently determined crystal structures of the human JAK1 and TYK2 FERM/SH2 domains in complex with box1- and box2-containing peptides, respectively, shedding light on how these kinases interact with their receptors and where these interactions may have evolved from. The structures have also raised some unanticipated questions about how the receptors may influence kinase-kinase interactions inside the cell. JAK kinase regulation has also been an active area of research in our group. For many years it has been understood that the pseudokinase domain plays a role in regulating kinase activity. This work includes the discovery of a large set of myeloproliferative neoplasm (MPN)-associated JAK2 mutations, such as V617F allele, that localize to the pseudokinase domain and result in constitutive kinase activation. We have recently determined the structure of the two domain pseudokinase-kinase fragment of human TYK2, which revealed that the pseudokinase and kinase assume a dimeric conformation. Furthermore, we found that >90% of MPN-associated mutations lie in or near the dimeric interface between the pseudokinase and kinase. This analysis suggests that the pseudokinase-kinase dimer is an autoinhibited conformation common across JAK family members, and reveals a likely cause for the constitutive activity found in MPN-associated mutant JAK alleles.

PLE-THU-11

GENOMES, GENES AND GENOMICS-ASSISTED BREEDING IN CHICKPEA FOR ENSURING NUTRITIONAL AND FOOD SECURITY IN DEVELOPING COUNTRIES

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Chickpea *(Cicer arietinum)* is the second largest cultivated grain food legume globally. Terminal drought stress, Fusarium wilt and Ascochyta blight are serious yield constraints for chickpea production. We are using next generation genomics and genetics approaches to sequence and characterize several thousand chickpea genomes. Comprehensive genome analysis, together with extensive phenotyping data, is providing candidate genes/ QTLs for breeding related traits for both advancing molecular biology research as well as genomics-assisted breeding applications in chickpea. For instance, large-scale genomic resources including draft genome sequence, re-sequencing of ca. 3000 chickpea lines, comprehensive transcriptome assembly, high density genetic and BIN maps, QTL maps as well as physical maps have been developed. By using linkage mapping approach, one “QTL-hotspot” harboring QTLs for several drought tolerance related traits has been identified on linkage group CaLG04. This “QTL-hotspot” has been successfully introgressed in several elite chickpea cultivars using marker-assisted backcrossing (MABC) approach. Several introgression lines have shown higher yield as compared to recurrent parent under rainfed as well as irrigated conditions. Similarly by using MABC approach, several introgression lines with enhanced resistance to FW and AB have also been developed. In brief, above mentioned genomics and molecular breeding approaches are expected to enhance genetic gains in chickpea improvement and deliver superior varieties in sub-Saharan Africa and Asia.

PLE-THU-12

MOLECULAR INSIGHTS INTO MEMBRANE TRAFFICKING AND NEURODEGENERATION

Collins B.M.
The University of Queensland, Institute for Molecular Bioscience.

Compartmentalisation is a defining feature of all eukaryotic cells, and we have evolved highly sophisticated protein machineries to control the flow of transmembrane molecules and membrane lipids between different organelles. Disruption of these processes are linked to numerous diseases including neurodegenerative disorders, pathogen invasion and cancer. We are determining how these trafficking machineries are assembled and regulated at the molecular level through a combination of structural biology, biophysical, and cell biology approaches. This seminar will describe our most recent work on critical protein sorting machineries - the retromer complex and the sorting nexins - regulating endosomal membrane recycling and cellular homoestasis. The role of retromer and its potential as a target in neurodegenerative diseases including Parkinson's and Alzheimer's will also be discussed.

PLE-THU-13

WALKING THE C4 PATHWAY

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2016 marks 50 years since the publication of the seminal paper from Hatch and Slack describing the biochemical pathway we now know as C4 photosynthesis. In my presentation I will provide insight into the initial discovery of this pathway, the clues which led Hatch and Slack and others to these definitive experiments, some of the intrigue which surrounds the international activities leading up to the discovery and give some personal views on the future of this research field. Although the biochemistry of the basic pathways came quickly, the role of the bundle sheath intermediate CO2 pool took a number of years to be elucidated. C4 photosynthesis functioning as a biochemical CO2 concentrating pump was then linked with the unique Kranz anatomy of C4 plants, already known for many years. Decades of “grind and find” biochemistry accompanied by leaf level physiology defined the regulation of the pathway and the differences in physiological response to the environment between C3 and C4 plants. The more recent advent of plant transformation, high throughput RNA and DNA sequencing and synthetic biology has allowed us carry out biochemical experiments and test hypotheses in planta as well as mine large data sets for bioinformatics driven research. With this knowledge, we now better understand the evolution driven molecular and genetic changes which occurred in the genomes of plants in the transition from C3 to C4. These evolutionary changes are now informing attempts to engineer C4 photosynthesis into rice and improve the C4 engine itself for enhanced food security and to provide novel biofuel feedstocks.

PLE-THU-14

THE DETAILED MECHANISM OF TURING PATTERN FORMATION IN THE SKIN OF ZEBRAFISH

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The reaction-diffusion (RD) model presented by Alan Turing in 1952 is a theoretical mechanism to explain how spatial patterns form autonomously in an organism. In his classic paper, Turing examined the behaviour of a system in which two diffusible substances interact with each other, and found that such a system is able to generate a spatially periodic pattern even from a random or almost uniform initial condition. Turing hypothesized that the resulting wavelike patterns are the chemical basis of morphogenesis. The importance of the Turing model is obvious, in that it provided an answer to the fundamental question of morphogenesis: “how is spatial information generated in organisms?” However, most experimental researchers were sceptical until the mid-90s because little convincing evidence had been presented. In 1991, two groups of physicists succeeded in generating the Turing patterns in their artificial systems, which showed for the first time that the Turing wave is not a fantasy but a reality in science. Four years later, we reported that the stripes of colour on the skin of some tropical fishes are dynamically rearranged during development in accordance with Turing model predictions. Soon after, convincing experimental evidence claiming the involvement of a Turing mechanism in development has been reported, and in some cases, the candidate diffusible molecules were suggested. Currently, the Turing model has been accepted as one of the fundamental mechanisms that govern morphogenesis. On the other hand, experimental researchers have pointed out problem that occur when the Turing model or other derivative models (called as LALI models because Local Activation and Long range Inhibition is required) are used as the working hypothesis. For instance, LALI models can exhibit similar properties of pattern formation despite being based on different cellular and molecular functions. Therefore, the simulation of a model rarely helps to identify the detailed molecular mechanism. Even when a pattern-forming phenomenon is successfully reproduced by the simulation of an RD system, it does not guarantee the involvement of diffusion. This problem is quite serious because, in most experimental uses, the key molecular event that governs the phenomenon is unknown when the experimental project begins. In my talk, I will explain the experimental data proving that Turing-like mechanism really functions in the skin of zebrafish, and then, I will propose a new version of the Turing model that might compliment the shortcomings of the present model.

PLE-THU-15

DELINEATING MECHANISMS OF TOBACCO INDUCED CELLULAR TRANSFORMATION USING AN INTEGRATED APPROACH

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Tobacco in its smoking as well as chewing form is known to be a risk factor for a number of cancers. A causal relationship has been established between smoking and cancers of different tissues including lung, oral cavity, esophagus, bladder and pancreas. Mechanism by which cigarette smoke causes cancer is extensively studied and is attributed to several carcinogenic compounds that exist in tobacco and some that are produced during combustion. These studies have been mainly carried out using acute treatment models. However, molecular mechanisms underlying chewing tobacco induced cellular transformation is not well understood. We have developed chronic treatment models by treating non-neoplastic esophageal and oral keratinocyte cell lines with condensed cigarette smoke and aqueous extract of tobacco over a period of 12 months. Both smoke treated and chewing tobacco treated cells acquired oncogenic phenotype in 6-8 months and showed increased proliferation and invasion capability. We carried out quantitative proteomic profiling to evaluate protein expression and phosphorylation pattern to systematically map molecular changes that are influenced by tobacco exposure. We observed distinct changes in cigarette smoke exposed and chewing tobacco exposed cell models. Proteins involved in DNA damage response pathways were found to be elevated in cigarette smoke treated cells. This is in agreement with previous studies where DNA damage has been reported to be one of the major ways in which cigarette smoke induces cellular transformation. On the contrary, chewing tobacco treated cells showed increased expression of proteins involved in β-oxidation, TCA cycle and oxidative phosphorylation and decreased expression of proteins involved in glycolysis. This metabolic reprogramming was further evaluated by mass spectrometry based metabolomics studies. Chewing tobacco treated cells also showed elevated expression of cancer stem cell markers. Our studies provide detailed insights into mechanisms that are associated with tobacco induced cellular transformation. These insights would be valuable to identify biomarkers relevant for risk assessment and to develop therapeutic intervention strategies for cancers associated with tobacco usage.

PLE-THU-16

PERIOD AND PATTERN IN THE DEVELOPING EMBRYO

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The Oates group studies a population of coupled genetic oscillators in the vertebrate embryo termed the segmentation clock. This system drives the rhythmic, sequential, and precise formation of embryonic body segments, exhibiting rich spatial and temporal phenomena spanning from molecular to tissue scales. In this talk I will discuss our recent progress in understanding how the gene expression waves that sweep across the segmentation clock are formed and how their pattern and position of arrest are regulated. We used live imaging of individual cells isolated from the segmentation clock to measure an autonomous program of differentiation that underlies the patterns observed at the tissue level. We find evidence for a slow cell-intrinsic timer that regulates this program and yet can be influenced by extrinsic signals.

PLE-THU-17

PROTEOME CENTRIC PRECISION MEDICINE: DEFINING AND TREATING PATHOLOGICAL DIVERSITY

Van Eyk J.
Advanced Clinical Biosystems Research Institute, Cedar Sinai Medical Center, Los Angeles, USA.

Precision medicine requires success in two intertwined aspects: precision therapy and personalized medicine. Precision therapy is being able to effectively treat the right disease; to have therapies that target for the correct pathological pathways. Personalized medicine requires diagnosing a specific individual's disease based on accurate assessment their complex health and pathological status. Our underlying premise is that an individual's baseline proteome reflects their past and present and thus, will dictate their future health and disease. Thus, the crux of precision medicine will be the identification and precise quantification of proteins and their modified forms. We will present data to support the notion that an individual's baseline proteome dictates the manifestation of their disease, its progression and their response to therapy. Our studies on 100s of individual's samples with different cardiovascular diseases have provided key insights on the effect of biological and pathological variability. This work has led us to consider the need for continuous patent-centric health screening at the population level. We will share our work on developing technical pipelines for health screening that reduces the barriers around sex, age and social economic status. This will/has required development of microsampling device, point of service devices, pathways for client data return and specific clinical grade assays. We have begun down this path with production of system suitability and quality control measures, assays and volumetric sampling device and will discuss the remaining challenges involved and requirement.

PLE-FRI-18

NEW REGULATORS OF STEM CELLS IN PLANT DEVELOPMENT AND CROP YIELDS

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Shoot growth depends upon meristems, pools of stem cells that are maintained in a number of ways, including a negative feedback loop between the CLAVATA pathway and the WUSCHEL homeobox gene. CLAVATA signaling involves a secreted peptide, CLAVATA3 (CLV3), and its perception by cell surface leucine-rich repeat (LRR) receptors, including the CLV1 receptor kinase, and an LRR receptor-like protein, CLV2. We are interested in finding novel players in the CLV-WUS pathway, as well as new regulators that could affect meristem size in parallel pathways. Maize provides a rich source of new information, because there are many clavata- type mutants, and their isolation is becoming routine. We isolated the maize COMPACT PLANT2 (CT2) gene, and it encodes the predicted α subunit (Gα) of a heterotrimeric GTP binding protein. ct2 mutants have CLAVATA-like meristem proliferation phenotypes, and genetic, biochemical and functional assays indicate that CT2/Gα signaling transmits a stem cell restrictive signal from a maize CLAVATA LRR receptor, suggesting a new function for Gα signaling in plants. Recent studies have questioned the idea that plant heterotrimeric G proteins interact with canonical GPCRs, and our findings suggest that single pass LRR receptors act as GPCRs in plants, challenging the dogma that GPCRs are exclusively 7TM proteins. We have also identified new regulators of maize shoot meristem size, including a new CLV- related receptor, FEA3, that appears to function in a different pathway to control meristem size in parallel to CLV-WUS. We believe that FEA3 responds to a CLV3-related ligand that is expressed in differentiating cells, so it could provide a feedback from primordia to the meristem, The roles of these genes will be discussed, as well as their potential use in improvement of maize yields, for example through control of seed yield.

PLE-FRI-19

LYSOSOMAL SIGNALING CONTROLS CELL HOMEOSTASIS

Ballabio A.
Telethon Institute of Genetics and Medicine (TIGEM) and Medical Genetics, Department of Translational Medicine, Federico II University, Naples, Italy, Department of Molecular and Human Genetics, Baylor College of Medicine and Jan and Dan Duncan Neurological Research Institute, Texas Children Hospital, Houston, TX, USA.

In the early 50s, Christian De Duve identified a new cellular structure, the lysosome, defined as the cell's "suicide bag". Sixty years later, it is clear that the lysosome greatly exceeded the expectations of its discoverer. Over 50 different types of lysosomal storage diseases have been identified, each due to the deficiency or malfunction of a specific lysosomal protein. In addition, an important role of the lysosome has been unveiled in several common human diseases, such as cancer, obesity, neurodegenerative diseases, and infection. Recent studies in our lab have led to the identification of a lysosome-to-nucleus signaling pathway and a lysosomal gene network that regulate cellular clearance and energy metabolism. These observations have changed our traditional view of the lysosome from a dead-end organelle and last step of cell catabolism to a signaling hub that controls cellular energy metabolism. An important challenge for the future will be to exploit these discoveries to identify modulators of lysosomal function that may be used to treat human diseases.

PLE-FRI-20

NEW STRATEGIES FOR REGENERATIVE MEDICINE

Elisseeff J.
John Hopkins University, Baltimore, Maryland, USA.

Humans have struggled for eons to replace tissues lost due to trauma, disease or congenital abnormalities, going back to the Ancient Egyptians where broken bones, dental implants, and even artificial toes were found in tombs. Jumping forward to modern medicine and the advent of the device industry in the 1960's, metals and plastics, chosen as stealth materials to interact minimally with the body, served as the basis for structural implants to replace knees, hips, and larger vascular structures. The field of tissue engineering, now frequently termed regenerative medicine, emerged in the late 1980's to create biological tissue replacements. From there arose the concept of designing biomaterial scaffolds to actively engage with surrounding cells and to support tissue morphogenesis. Biomaterial scaffold research further exploded with the discovery of stem cells that required multiple biological signals to induce proliferation and differentiation. Today, biomaterials can be engineered with exquisite control and can present an array of biophysical cues in the form of peptides, sugars, and other biopolymers with varying mechanical and structural paradigms depending on the need. This lecture will discuss examples of biomaterial scaffolds for tissue reconstruction in orthopedics, ophthalmology and plastic surgery. Future perspectives of the field and the newly discovered importance of the immune system and the development of biomaterials-directed regenerative immunology will be presented.