Plenary Lectures

PL.1
Interferon responsive genes that link adaptive and innate immunity in human cancer

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Oesophageal cancer is now one of five major disease types now considered a cancer of high unmet clinical need. These form a group of conditions of an increasing global concern due to poor prognosis, late or asymptomatic disease presentation, aggressive growth, and a lack of efficient therapeutics. Current treatment options for oesophageal cancer are primarily non-specific cytotoxic chemotherapeutics with very poor efficacy in patients. Clinical studies with modern molecularly targeted therapies have been disappointing; one trial resulted in a small ~ 3 month survival increase and a second trial, surprisingly, resualted in a *decreased* overall survival. Target directed drug discovery strategies in oesophageal cancer have been hampered by a lack of understanding of the molecular drivers of disease. Our participation in the Oesophageal Cancer Clinical and Molecular Stratification (OCCAMS) consortium applying whole genome sequencing of clinical samples has recently indicated oesophageal cancer is highly heterogeneous, characterized by frequent large scale genomic rearrangements, copy number alterations and co-amplification of multiple receptor tyrosine kinases and mitogenic signaling pathways, with limited numbers of mutations found in actionable oncogenic drivers. Mutational signatures reveal three distinct molecular subtypes of disease, which may help guide future patient stratification, if effective therapeutic classes can be identified. We have focused on developing a proteogenomics target discovery platform in Oesophageal Cancer that aims to identify the expressed mutational landscape and oncogenic driver pathways. Two dominating pro-oncogenic pathways will be reviewed that form our basic research programme that aims to understand fundamental biological pathways of therapeutic relevance.

PL.2
Viral mRNA translation control: linking immune evasion with oncogenesis

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Latent viruses need to proliferate and evade detection by the immune system. Studies on how viruses interfere with these processes have been crucial for understanding the underlying cellular pathways. By suppressing its own synthesis, the Epstein-Barr virus encoded EBNA1, reduces the production of peptides substrates for the major histocompatibility (MHC) class I pathway. This translation interference triggers a cellular stress pathway that induces expression of E2F1 and c-myc. The synthesis of class I peptide substrates takes place on pre-spliced RNAs and is controlled by nucleolin via binding the EBNA1 message and is independently regulated from the canonical translation that governs synthesis of full length proteins. Understanding the molecular mechanisms of EBNA1-mediated translation control in *cis* has provided therapeutic opportunities for stimulating immune recognition of EBV-carrying cancer cells and to rid host cells of the virus. Ongoing works indicate that the concept of *cis*-mediated translation control via RNA sequences within the coding region is not unique for EBV but is also applied by other human cancer-associated viruses.
Future works aims to understand the role and regulation of alternative sources of neoantigens in normal and malignant conditions and the interplay between antigen-producing cells and professional antigen presenting cells. This will be helped by an animal model in which specific CD8 T cells detect intron-derived peptides and will elucidate the source of peptide material for generating CD8 T cell tolerance and for immune detection of tumour cells.

PL.3

Genomics in uncovering our history

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Despite the increase in our knowledge about the factors that shaped the genetic structure of the human population in Europe, the demographic processes that occurred during and after the Early Bronze Age (EBA) in Central Europe remain unclear. One of the issues raising a particularly heated discussion is the origin of the Goths and their early migrations in the Iron Age (IA). To verify the existing hypotheses on these processes, we initiated systematic studies of the populations inhabiting the contemporary territory of Poland during the IA. We sequenced DNA of approximately 100 individuals from cemeteries of the IA Wielbark culture, located in west (Kow-OVIA group) and east (Mas-VBIA group) Poland. The collected data revealed high genetic diversity of both groups, suggesting that they were not small isolated populations. Analyses of all genetically characterized ancient European populations showed that Kow-OVIA and Mas-VBIA were most closely linked to the Jutland Iron Age population. We also found the genetic connection between Mas-VBIA and ancient Pontic-Caspian steppe groups. The picture emerging from our studies seems to be consistent with one of the historical narratives that assumed the Goths migrations through the territory of contemporary Poland towards the Black Sea region, where they mixed with local populations. In general, our findings disclose the mechanisms that could underlie the formation of the local genetic substructures in Central Europe during the IA.

PL.4

Immune microenvironment of glioma

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Malignant gliomas are rapidly progressing brain tumors with a very poor prognosis. Analyses of human and rodent experimental gliomas revealed heterogeneity and complex interactions between tumor and activated astrocytes, endothelial cells and immune cells. Infiltrating innate immune cells are polarized into the immunosuppressive, pro-invasive phenotype. Reprograming of those cells and restoring anti-tumor responses constitute a "holy grail" in tumor immunotherapy. By analyzing tumor secretome we identified tumor-derived signals which are instrumental in shaping the immune microenvironment of gliomas. Osteopontin/SPP1 is upregulated and proteolytically processed in a tumor and when secreted it is essential for immune cell reprogramming. SPP1 knockdown in tumor cells restored anti-tumor functions of infiltrating brain macrophages, reduced Tregs infiltration and re-established antitumor responses of T lymphocytes which results inhibition of tumor growth and prolonged survival. To translate those results into clinically relevant setting, we designed humanized short peptides interfering with binding of tumor-derived factors to cognate receptors. The selected peptides potently inhibit glioma invasion in cell co-cultures and when delivered intra-cranially to human U87 gliomas growing in nude mice, those peptides reduced tumor growth. The results demonstrate identity and molecular mechanisms employed by tumor to modify its microenvironment and host immunity. The presented approach of targeting glioma-microglia interactions with short interfering peptides could be a novel therapeutic strategy.

PL.5

The UDP glycosyltransferase superfamily: its role in signal transduction termination and protection against chemical toxicity

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Our collective exposure to thousands of fat-soluble chemicals necessitates the evolution of enzymes that can convert these chemicals to inactive, water-soluble, excretable derivatives. In most species, this is achieved by attaching a sugar residue to the fat-soluble chemical, in a glycosidation reaction catalyzed by the UDP glycosyltransferase (UGT) superfamily. The human UGT superfamily consists of 9 functional enzymes of the UGT1 family, 10 functional enzymes of the UGT2 family, 2 functional UGT3 enzymes and 1 functional UGT8 enzyme. The UGT1 and 2 families have been well characterized for their capacity to use UDP glucuronic acid to attach glucuronic acid to therapeutic drugs, lipophilic chemicals from the environment and diet, and ligands of nuclear receptors including the androgen and estrogen receptors. In contrast, the UGT3 and UGT8 enzymes use UDP N-acetylglucosamine (UGT3A1), UDP glucose and UDP xylose (UGT3A2) and UDP galactose (UGT8) to add sugars to mainly bile acids and ceramide. The ability of these 22 human UGTs to glycosidate potentially thousands of chemicals resides in their unique kinetic properties and structure, differential splicing and ligand-mediated regulation. Some of these factors that allow expansion of UGT functional diversity will be discussed. Several UGTs are involved in the glycosidation and inactivation of steroid hormones. In particular, UGT2B15 and 2B17 are the major UGTs involved in androgen inactivation in steroid responsive tissues and cancers. Our studies on the importance of these UGTs in androgen signal termination in breast and prostate cells will also be discussed.

PL.6

Clinical Utility rapid whole genome sequencing in pediatric critical care

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The use of rapid genomics in critical care settings is steadily gaining prominence. In addition to diagnostic utility, it is also important to match the timeliness of diagnosis to the clinical need. Moreover, to fully implement genomic medicine in critical care centers across the country, some practical challenges related to scaling remain to be addressed. There are very few genetically trained physicians in hospitals. On the laboratory side, there is a limited supply of board certified genome analysts. Additionally, the burden of re-analysis waiting on constantly evolving literature, poses a real problem to diagnostic labs. To address these critical and practical needs, we have developed a rapid whole genome sequencing (rWGS) based precision medicine framework using artificial-intelligence methods. We will discuss our implementation, challenges and on-going efforts to permeate genomics as an integral part of medical practice.

PL.7

The macrophage-drug conjugate (MDC) as a "Trojan horse" approach in cancer therapy

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Unsatisfactory response of tumours to chemotherapy is mainly related to impaired diffusion of the anticancer drug because of decreased drug uptake due to poor vasculature. Moreover, the drug is not able to penetrate the most hypoxic sites. Cells from these 'untreated' sites are responsible for relapse and metastasis. However, these avascular regions attract macrophages that migrate even to areas far away from blood vessels. Therefore, they might constitute a unique delivery system of drug containing particles to these parts of the tumor mass. A promising example of such particles that could be used are ferritins, whose caged architecture allows for efficient drug encapsulation and whose uptake from macrophage cells has been well demonstrated. Macrophages are also able to specifically and actively transfer these taken up ferritins (loaded with the anticancer drugs) to cancer cells. This is the new mechanisms discovered by our team and named TRAIN (TRAnsfer of Iron-binding proteiN). Thus, there is a possibility to use macrophages to deliver ferritin encapsulated compounds directly to the tumour cells (MDC technology – Macrophage-Drug Conjugate). This is a completely new and modern approach to anticancer therapy and drug delivery. As such we expect to be able to precisely administer drugs to the tumour site (even to the hypoxic regions), decreasing side effects of anticancer therapy.

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PL.8

Stress management in response to mitochondrial dysfunction

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Mitochondria are multifunctional organelle, primarily involved in a fundamental biological process of respiration. The nuclear-encoded proteins make up for the large majority of proteins involved in the formation of mitochondria including the respiratory chain complexes. The efficient functioning of mitochondria depends on the proper transport, sorting and assembly of mitochondrial proteins that originate from the nuclear genome. Two main arms of the cellular response to protein import dysfunction include the inhibition of cytosolic translation and activation of the major protein degradation machinery, the proteasome. The stimulation of the proteasome is driven by its more efficient assembly as a response to the amount of mistargeted proteins. The mechanism is beneficial for cells. Interestingly, activation of the proteasome could be uncoupled from translation effects. The synthesis of cellular proteins is regulated by the signals, which come directly from the dysfunctional mitochondria. To understand translational inhibition, a site-specific redox proteomic analysis to delineate the yeast redoxome was performed. Increased levels of intracellular reactive oxygen species (ROS) caused by the mitochondria serve as a signal to attenuate global protein synthesis. Mapping of redox-active thiols in proteins revealed ROS-sensitive sites in several components of the translation apparatus. Thus, the increased levels of intracellular ROS caused by dysfunctional mitochondria serve as a signal to attenuate global protein synthesis. Thus, several mechanisms exist that link the status of mitochondria with regulation of the cellular protein homeostasis.