Published by
International Centre for Cancer Vaccine Science, University of Gdańsk

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Contents

About International Centre for Cancer Vaccine Science (ICCVS)

PROFILE

A new **multidisciplinary center** for studies on the **molecular mechanisms of cancer immunology** has been launched at the University of Gdańsk (UG) / Poland in partnership with the University of Edinburgh (UoE) / UK in 2017. The ICCVS is supported by the Foundation for Polish Science within the *International Research Agenda Program*.

RESEARCH FOCUS

The ICCVS research program is aimed at **supporting the development of new cancer vaccines therapies by providing a better understanding of oncogenic processes and their effects on immune surveillance and the elimination of transformed cells**. Apart from human cancer immunology we also encourage researchers interested in spontaneous in veterinary tumour models to join new groups.

FACILITIES

The ICCVS is housed in new lab facilities at UG with **state of the art mass spectrometry, virology, protein biochemistry and vaccine technology**. ICCVS researchers will also have access to **infrastructure and strategic platforms for stem cell science, phenotypic drug screening, synthetic biology, informatics, and veterinary medicine** at the UoE. This provides a great opportunity for advanced researchers that to pursue their own independent research and for post-docs and PhD students that are looking for international multidisciplinary research and training programs.

INTERNATIONAL COOPERATION

ICCVS cooperates with strong partners locally in Poland. The main local partners include the Medical University of Gdańsk, the Intercollegiate Faculty of Biotechnology of University of Gdańsk and Medical University of Gdańsk as well as the Faculty of Chemistry of the University of Gdańsk. Moreover, ICCVS provides an international research agenda and the post doc candidates will have opportunities to work in Edinburgh, Paris or other locations best suited for the research. PhD students will be encouraged to spend time in labs in Paris and Edinburgh to get a broad introduction to cancer immunology research.

RECRUITMENT OF RESEARCHERS

The ICCVS provides a generous start-up package to allow the candidates to develop independent and sustainable research programs. We will be looking for team leaders and post-doctoral researchers in the fields of:

- Neoantigen signalling pathways
- Proteogenomics
- Computational Science
- The cancer-immune synapse
- Veterinary medicine
- Vaccinology
- Antibody therapeutics

ICCVS RESEARCH GROUP MEMBERS

Human Cancer Models Research Group
Ted Hupp – Group Leader
Magdalena Pilch – PhD student
Marcos Yebenes Mayordomo – PhD student
Tsabieh Bilal – PhD student

Neoantigen Science Research Group
Robin Fahraeus – Group Leader
Iolanda Alves – PhD student
Ewa Sroka – PhD student
Mikołaj Kocikowski – PhD student

PARTNERS & COLLABORATORS

STRATEGIC PARTNER

LOCAL HOST & PARTNER

REGIONAL & GLOBAL PARTNERS

The project is carried out within the International Research Agenda Programme of the Foundation for Polish Science and funded from the funds of the European Regional Development Fund under the Smart Growth Operational Programme, Priority Axis 4: Increasing the research potential, Measure 4.3: International Research Agendas.

Program of the Workshop

08:15	Pick up from the hotel	
08:30-09:00	Arrival at venue & morning coffee	
09:00-09:20	Robert O'Neill The University of Edinburgh, UK	Proteogenomics for cancer therapies
09:20-09:40	Jakub Faktor RECAMO, Brno, Czech Republic	Detecting mutated peptides in human cancer cells
09:40-10:00	Chandra Verma A*STAR, Singapore, Republic of Singapore	MD of mhc class i peptide complexes
10:00-10:20	break	
10:20-10:40	Fiona Lickiss The University of Edinburgh, UK	Investigating the interaction between MDM2, UbcH5a and ubiquitin.
10:40-11:00	Ted Hupp ICCVS, University of Gdansk, Poland & The University of Edinburgh, UK	Discovering new genes in cancer cells that control MHC Class I production
11:00-11:20	Javier Alfaro University of Toronto, Canada	Protegenomics of cancer mutations
11:20-11:40	break	
11:40-12:00	Robin Fahraeus ICCVS, University of Gdansk, Poland & INSERM, Paris, France)	New biological sources of neoantigens in cancers
12:00-12:20	Stephan Thorgrimsen Immunitrak, Copenhagen, Denmark	Neoepitope identification and validation by MHC based reagents. Assays, tetramers and more
12:20-12:40	Sune Justesen Immunitrak, Copenhagen, Denmark	Affinity and stability measurements of MHC Class I peptide complexes
12:40-13:00	break	
13:00-13:20	Jonathan Heddle Jagiellonian University, Krakow Poland	Synthetic drug delivery vehicles (DNA origami and others)
13:20-13:40	Marc Blondel INSERM, Brest, France	A yeast model for the mechanism of the oncogenic Epstein-Barr virus immune evasion identifies a new therapeutic target to interfere with the virus stealthiness
13:40-14:00	Håkan Axelson Lund University, Sweden	Transcriptional profiling of the nephron and renal tumors

14:00-14:20	break	
14:20-14:40	Zhi Jane Chen Univesity of Turku, Finland	Proteomics of T cells
14:40-15:00	Irena Dapic University of Zagreb, Croatia	Proteomics of cancer
15:00-15:20	Maciej Parys The University of Edinburgh, UK	Veterinary models and cancer
15:20-15:40	break	
15:40-16:00	Laura Bindila University of Mainz, Germany	Immunology active lipids
16:00-16:20	David R. Goodlett University of Maryland, Baltimore USA	Lipidomics and proteomics in infectious diseases
16:20-16:40	Yury Tsybin Spectroswiss, Laussane Switzerland	Data analysis developments
17:00	Transfer to hotel	
18:30	Departure for dinner (meeting point: hotel lobby)	
19:00-23:00	Dinner	
23:00-23:30	Transfer to hotel	

Venue

The Workshop will take place in the building of the Intercollegiate Faculty of Biotechnology University of Gdańsk and Medical University of Gdańsk.
Address: ul. Abrahama 58, 1st floor, room 120

Information on Speakers and Talks

Javier Alfaro (University of Toronto, Canada)

BIOGRAPHY: Dr. Javier Alfaro uses a variety of different molecular profiling strategies to interrogate cancers. Javier believes that while cancer is a disease of the genome, the selection pressures that support the development of cancer hallmarks act on the expressed phenotypic traits of the cancer cell. This means that a comprehensive molecular portrait of the tumour must include the proteome and the metabolome, which are significant endpoints of gene processing. Javier's most recent work has focused on the interrogation of proteomic data to identify mutations within important cancer genes. He uses predictions from genomics about proteome content alongside algorithmic strategies for mass-spectrometry based mutation identification to guide his analysis. He has a PhD in Medical Biophysics (University of Toronto), specializing in computational proteomics, a Masters in Biochemistry specializing in bioinformatics (Dalhousie University) and a double major in Biochemistry and Computer Science (University of Victoria).

ABSTRACT: Detecting protein variants by mass spectrometry

Onco-proteogenomics aims to understand how changes in a cancer's genome influences its proteome. One challenge in integrating these molecular data is the identification of aberrant protein products from mass-spectrometry (MS) datasets, as traditional proteomic analyses only identify proteins from a reference sequence database. We established proteomic workflows to detect peptide variants within MS datasets. We used a combination of publicly available population variants (dbSNP and UniProt) and somatic variations in cancer (COSMIC) along with sample-specific genomic and transcriptomic data to examine proteome variation within and across 59 cancer cell-lines. We developed a set of recommendations for the detection of variants using three search algorithms, a split target-decoy approach for FDR estimation, and multiple post-search filters. We examined 7.3 million unique variant tryptic peptides not found within any reference proteome and identified 4771 mutations corresponding to somatic and germline deviations from reference proteomes in 2200 genes among the NCI60 cell-line proteomes. We discuss in detail the technical and computational challenges in identifying variant peptides by MS and show that uncovering these variants allows the identification of druggable mutations within important cancer genes.

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Alfaro, J. A., Sinha, A., Kislinger, T., & Boutros, P. C. (2014). Onco-proteogenomics: cancer proteomics joins forces with genomics. *Nature methods*, *11*(11), 1107-1113.

Alfaro, J. A., Ignatchenko, A., Ignatchenko, V., Sinha, A., Boutros, P. C., & Kislinger, T. (2017). Detecting protein variants by mass spectrometry: a comprehensive study in cancer cell-lines. *Genome medicine*, *9*(1), 62.

Håkan Axelson (Lund University, Sweden)

BIOGRAPHY: Prof. Axelson has throughout his career been working in the field of basic cancer research, with particular focus on cellular and molecular biology. In particular he has been interested in the role of Notch signaling in cancer. During recent years he has been focusing on renal malignancies. He has been a Professor at the University of Lund since 2008 and the Head of the Division of Translational Cancer Research since 2013.

ABSTRACT: We have been performing in-depth analysis of the transcriptional landscape of the normal human nephron and compared this to the different types of renal neoplasms. We identify a series of gene expression programs along the nephron and use these to define the histological origin for kidney cancer. We show that expression of a hepatocytic nuclear factor (HNF)-regulated program, specific for proximal tubule cells of the nephron, is an integral part of the ccRCC and pRCC transcriptomes. Similarly, expression of forkhead box 1 (FOXI1)-driven genes, strongly enriched in intercalated cells of the distal nephron, is retained in chRCCs. We believe that retention of such segment-specific expression programs provide compelling evidence for the cellular origin of different RCC subtypes and that these expression programs may be used as a framework for understanding the interplay between genomic changes in RCC subtypes and the lineage-defining regulatory machinery of their non-neoplastic counterparts. Using the same platform we also identified a novel unique biomarker for ccRCC, the transporter protein SLC6A3. In contrast, normal kidney does not express appreciable levels of this transporter. Importantly, we demonstrated that the elevated expression of SLC6A3 in ccRCC cells is associated with specific uptake of dopamine. We conclude that the dopamine transporter SLC6A3 constitutes a novel biomarker that is highly specific for ccRCC. We further postulate that the protein can be exploited for diagnostic or therapeutic purposes for detection or treatment of ccRCC and a clinical phase II trial has been instigated based on these observations.

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Laura Bindila (University of Mainz, Germany)

Quantitative lipidomics reveals a role of lipids in immune system

The lipids serve not only a constitutive role in the cell membrane, but also as the source for downstream signaling lipids, such as sphingosine phosphate, ceramide phosphate, endocannabinoids or eicosanoids underscoring many biological processes in neurodegenerative diseases, metabolic and immune diseases, cancer etc. Glycolipids, play a particular important role in cell-cell communication, cell signaling and pathogen recognition and have been shown to serve valuable markers in cancer biology, microbiology. In general, lipids emerge as important candidates for biomarkers, drug targets, but also as therapeutic agents.

To gain a better understanding of their specific functions and to define the signaling networks, especially under pathological conditions, accurate identification and quantification of lipids, as well as profiling of other molecular correlates such as related genes and proteins in one and the same tissue source is essential. In addition, (sub)localization of disease-associated lipid changes within and across tissue regions is essential to expedite the unravelling of disease mechanisms, as well as discovery of lipid-based drug targets and lipid-based therapeutic agents.

We developed advanced lipidomic strategies, combining quantitative mass spectrometric assays with tailored, high-throughput sample preparation for multiplex lipid profiling in minute amounts of biological matrices, that enabled translation of pre(clinical) features of disorders into quantitative lipidomics will be discussed. Here an overview of the findings implicating glycolipids in cancer biology, lipids and lipid-based therapy that modulate immune responses, will be provided.

BIOGRAPHY: Laura Bindila is Head of Lipidomics/Mass Spectrometry Facility at the Institute for Physiological Chemistry, University Medical Center Mainz, where her scientific interest is unravelling the lipid signals involved in various neurobiological processes, and more generally in physiological and pathophysiological states. She is also a member of Research Center for Translational Neuroscience, of the University of Mainz. She has previously worked at Luxembourg Clinical Proteomics, and University of Münster where she has focused on glycoconjugates and (glyco)proteomics in cancer research and rare diseases.

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Session name/ number:
Category: Oral presentation

Marc Blondel (INSERM, Brest France)

BIOGRAPHY: Marc Blondel is Professor of Cell Biology at the University of Brest UBO, France, since 2006. He also leads a research group in INSERM UMR1078 focused on the use of budding yeast *Saccharomyces cerevisiae* to model various human diseases. Based on these yeast models, chemobiological approaches are then developed to isolate both candidate drugs active against these diseases and new pathophysiological actors and mechanisms involved in these disorders. He has published 59 papers in international peer-reviewed journals and holds six patents. He received the CNRS Bronze Medals in 2004 and is Editor for Biotechnology Journal and Microbial Cell.

www.univ-brest.fr/umr1078

TITLE: A yeast model for the mechanism of the oncogenic Epstein-Barr virus immune evasion identifies a new therapeutic target to interfere with the virus stealthiness

ABSTRACT: The oncogenic Epstein-Barr virus (EBV) evades the immune system but has an Achilles heel: its genome maintenance protein EBNA1. Indeed, EBNA1 is essential for viral genome replication and maintenance but also highly antigenic. Hence, EBV evolved a system in which the glycine-alanine repeat (GAr) of EBNA1 limits the translation of its own mRNA at a minimal level to ensure its essential function thereby, at the same time, minimizing immune recognition. Defining intervention points where to interfere with EBNA1 immune evasion is an important step to trigger an immune response against EBV-carrying cancers. Thanks to a yeast-based assay that recapitulates all the aspects of EBNA1 self-limitation of expression, we recently uncovered the role of the host cell nucleolin (NCL) in this process via a direct interaction of this protein with G-quadruplexes (G4) formed in GAr-encoding sequence of EBNA1 mRNA. In addition, the G4 ligand PhenDC3 prevents NCL binding on EBNA1 mRNA and reverses GAr-mediated repression of translation and antigen presentation. This shows that the NCL-EBNA1 mRNA interaction is a relevant therapeutic target to unveil EBV-carrying cancers to the immune system and that the yeast model can be successfully used for uncovering drugs and host factors that interfere with EBV stealthiness.

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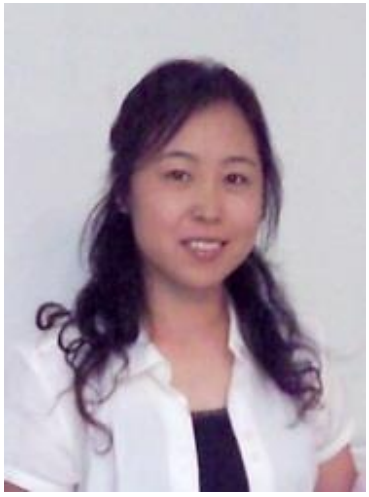
Voisset C, Daskalogianni C, Contesse MA, Mazars A, Arbach H, Le Cann M, Soubigou F, Apcher S, Fåhraeus R, Blondel M (**2014**) ***Disease Models & Mechanisms*** 7: 435-444

Zhi Jane Chen (Univesity of Turku, Finland)



BIOGRAPHY: Zhi Jane Chen graduated from Beijing Medical University (Peking University, Medical School), China. She carried out her Ph.D study at the Turku Centre for Biotechnology, University of Turku, Finland and obtained Ph.D degree in 2004. During 2005-2007, she was a postdoctoral fellow in Dr. John O'Shea's laboratory at the NIH, USA. She received a Postdoctoral Fellowship from the Academy of Finland and worked in the Faculty of Medicine, University of Turku in 2008-2010. From 2012-2017, she was an Academy of Finland Research Fellow and became an independent researcher. In 2014, she obtained docentship (Adjunct professor) in immunology from the Faculty of Medicine, University of Turku. Dr. Chen's research has been focused on signal transduction and regulation of helper T cell subsets differentiation.

ABSTRACT: The goal of cancer vaccine is to stimulate effective tumor specific T cell responses. During the past years, several cutting-edge technologies, such as RNA-seq, proteomics, flow cytometry and mass cytometry have been established or applied in our studies and can be used to monitor T cell responses of cancer vaccines.

In recent years, CD4+ helper T cells have gained much interest in antitumor immunity, immunotherapy and cancer vaccine development (1). CD4+ T cell subsets have distinct cytokine production profiles and functions in tumor immunity. IFN-producing Th1 cells have shown potent antitumor activity through multiple mechanisms (1, 2). Foxp3+ regulatory T (Treg) cells are a subset of CD4+ T cells that play critical roles for the maintenance of immunologic homeostasis and self-tolerance (3, 4). Because of their immunosuppressive function, in many cancers, high levels of Treg cells in the intratumoral microenvironment are associated with increased inhibition of antitumor responses (5). Recently, we performed label-free quantitative proteomics study to profile proteins that are specifically expressed by naïve CD4+ T cells, Th17 and iTreg cells (6). These data provide a valuable resource for further identification of novel potential targets to dampen Treg function in cancer. Developing cancer vaccines can raise Th1 response, on the other hand, the anti-tumor activity can be further enhanced when combined with targeting Treg cells.

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Irena Dapic (University of Zagreb, Croatia)

BIOGRAPHY: Irena Dapic finished her PhD in 2014 at the University of Zagreb with the focus on the development of the analytical methods for determination of the biochemical indicators in the damaged skin barrier (i.e. atopic dermatitis). Through the joined projects during PhD she had several internships in Academic Medical Centre (Amsterdam) and Faculté de Médecine et de Pharmacie (Lyon). After completing PhD she moved for postdoctoral research in Van 't Hoff Institute for Molecular Sciences at University of Amsterdam (2015-2017) where in the group of prof. Garry Corthals she worked on quantitative proteomics of the human tissues. In collaboration with pathology her work involved development and translation of the methods for mass spectrometry based quantitative protein analysis from human biopsy materials and biofluids.

ABSTRACT: Human tissues and biofluids are important source of molecular information for characterizing disease activity and progress. Extensive sample preparation steps and use of large amounts of materials makes many existing protocols difficult to translate for analysis of minute tissue samples. Moreover, many patient samples are limited by number and unique as one-off (invasively obtained) samples, therefore the need for analysis of small amounts of tissues is important. We used small uterine tissue section samples to investigate influence of the tissue preparation protocol on proteomic analysis. Protocols were tested on minimal amount of the tissue needed for reproducible analysis and results were compared in protein distribution and quantity across different samples.

Moreover, while detection of disease related compounds in human tissues is important, their detection in biofluids makes them more accessible and ready to analyze. Therefore, to speed up protein digestion we have developed a cyclic-olefin-copolymer (COC) immobilized enzyme reactor (IMER) which allowed shorter digestion times in the order of seconds to minute. IMER was successfully applied for digestion of the proteins from dried-blood-spots and IMER-facilitated digestion showed comparable number of identified proteins compared to in-solution digestion, while the total workflow was considerably shortened.

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Robin Fahraeus (ICCVS, University of Gdansk, Poland & INSERM, Paris, France)

BIOGRAPHY: Robin Fahraeus is a director of research and works for the Inserm in Paris France. He leads a research group focused on physiological implications of mRNA translation control in cancer.

TITLE: New biological sources of neoantigens in cancers.

ABSTRACT: The detection of non-self antigens on major histocompatibility class (MHC) I molecules allows the immune system to detect and eliminate cells expressing parasite- or cancer-derived neoantigens. The source of these peptides, how they are produced and regulated are important factors for designing new therapeutic approaches to boost the immune response against cancer. This talk will focus on some advances that have been made during the last few years and in particular on the role of alternative mRNA translation events.

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Jakub Faktor (RECAMO, Brno Czech Republic)

BIOGRAPHY: Mr. Faktor has started his career in the field of proteomics. His research is focused on quantitative mass spectrometry in cancer biology. He participated in mass spectrometric part of projects focused on neoantigen identification, protein interactomes, research of cancer molecular markers, and perturbed pathways involved in cancer [1, 2, 3]. He has studied biochemistry Ph.D. programme (2012-until now) at Masaryk University, Brno, Czech Republic and works at Regional Centre for Applied Molecular Oncology (RECAMO) at Masaryk Memorial Cancer Institute, Brno, Czech Republic (2013-until now). RECAMO will be an international partner in the ICCVS.

ABSTRACT: Developing cancer cell models for identifying the source of neoantigens in human cancers. Vaccines directed against tumor specific antigens are nowadays gaining significance as an effective approach for personalized cancer treatment. We built-up a multiplexed proteogenomics platform that identifies expressed oncogenic mutational landscape of human melanoma A375 cell line as a model to study sources of neoantigens. Genomic sequences stratified by the number of sequencing variant reads from DNA-seq or genomic sequences stratified by high levels of variants detected using shotgun RNA-seq were translated to mutant protein sequences enabling their mass spectrometric (MS) identification. MS identification of DNA-seq or RNA-seq derived variants was performed on tryptic digest of A375 cell line lysate in 2D LC-MS/MS proteomic screen. RNAseq derived reference database more accurately identified variants than DNAseq alone. More than 80 neoantigens were identified out of which approximately 52 were high confidence. Successful SRM validation confirming effectivity and validity of our proteogenomics workflow was performed on a set of 10 representative neoantigens. Moreover, an orthogonal SWATH approach detected three neoantigens, allowing ad-libitum post-acquisition quantitative data mining from once acquired data. These proteogenomics pipelines form a methodology for quantitative mutated protein detection to accelerate future neoantigen discovery projects.

ACKNOWLEDGEMENT: The work was supported by the project MEYS - NPS I - LO1413 and by the Grant Agency of the Czech Republic (GAČR 16-07321S).

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David Goodlett (University of Maryland, Baltimore USA)

BIOGRAPHY: Prof Goodlett has spent his career using mass spectrometry to solve biomedical problems via novel technology and software developments. He has been active in a variety of fields including medicine, oceanography, pharmacy, microbiology, proteomics (including clinical applications), lipidomics, and protein & glycolipid structure-function relationships publishing over 240 papers. He has been a Professor at the University of Maryland (2013-present) and the University of Washington (2004-2012) as well as first Director of Proteomcis at the Institute for Systems Biology (2000-2003). From 2012-2016 he was a Finland Distinguished Professor; https://www.youtube.com/watch?v=jfOOMNJivvY. He is an Editor at Rapid Communications in Mass Spectrometry and a co-organizer of www.msbm.org. In 2018 he will join the International Centre for Cancer Vaccine Science (ICCVS) at the University of Gdansk as a Visiting Professor to set up proteomics within the centre.

ABSTRACT: Lipid A is the membrane anchor for Gram-negative bacteria that holds the much larger lipopolysaccharide (LPS) molecule in place in the outer membrane. Importantly in mammals, Toll receptor 4 (TLR4) recognizes lipid A the result of which is activation of a cytokine cascade that can aid the host in clearing the infection or if unchecked lead to a deadly cytokine storm. There are a range of activities from agnostic to antagonistic that are directly related to structure (e.g. Li). To exploit this we are working to better define the lipid A structure activity relationship for use as a vaccine adjuvants and antisepsis therapeutics (e.g. Scott). We are also using lipid A and related Gram-positive molecules to identify bacteria direct from source in under an hour (Leung). At the ICCVS we are interested in investigating the classic use of bacterial extracts as an immunotherapy (i.e. Coley's toxins late 1800s NYC) that have been recently revived (Kim). We are also defining protein antigens that can be used as imaging agents, therapeutics and diagnostics in point of care devices (Freiberg).

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Jonathan Heddle (Jagiellonian University, Krakow Poland)

BIOGRAPHY: Jonathan Heddle studied Pharmaceutical Science at The University of Nottingham, UK before moving to The University of Leicester to work on the antibacterial target DNA gyrase and its inhibitors. He then moved to Japan as a Japan Society for Promotion of Science Special Research Fellow where he first studied structural biology before setting up his own laboratory increasingly researching bionanoscience first at Tokyo Institute of Technology and then at RIKEN. He recently moved back to Europe to head a lab at the Malopolska Centre of Biotechnology, Jagiellonian University, Poland where he continues to research bionanoscience and topoisomerases.

ABSTRACT: Synthetic Structural Biology is an exciting discipline whereby biological molecules (typically proteins and DNA) are used as building blocks for the design and construction of novel shapes and even nano-robots. The techniques and applications involved are very wide and here will consider a general overview of some of the techniques with particular emphasis on our recent work in producing artificial cage proteins with interesting geometrical and biophysical characteristics which may provide a basis for future drug delivery or antigen presentation.

Homepage: www.heddlelab.org

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Ted Hupp (ICCVS, University of Gdańsk, Poland & The University of Edinburgh, UK)

BIOGRAPHY: Ted Hupp was originally educated in microbiology & chemistry in Ohio, USA. Following a PhD in Biochemistry at Michigan State University, enzymology principles were then applied to the cancer research field in the UK to develop the paradigm that the tumour suppressor p53 could be activated by Biologics, such as peptides and antibodies. His current position of Professor is as the Chair of Experimental Cancer Research at the University of Edinburgh and aims to spearhead the formation of novel, interdisciplinary research programmes in cancer biomedicine. Examples of such themed programmes include topics such as (i) Drug Discovery programmes in the Ubiquitin-Proteasome system that target protein-protein interactions; (ii) The development of naïve canine-specific phage antibody libraries as new therapeutic tools to address the paucity of immune-competent preclinical cancer animal models; (iii) A proteomics consortium RASOR-"Radical Solutions for Researching the Proteome" that links proteomics technologies to cancer research problems; and (iv) emerging international efforts to develop new medicines based on natural biodiversity (ffmn.co.uk). It is during these past research activities that Ted met two other key scientists involved in setting up the International Center for Cancer Vaccine Science (ICCVS), Robin Fahraeus and Dave Goodlett. The ICCVS scientific objectives build on existing, long-standing international, collaborative networks. Several inter-disciplinary programme teams will be appointed in themes focused on (i) neoantigen science; (ii) receptors at cancer-immune synapse; (iii) the cancer secretory system; (iv) proteogenomics and computational science; (v) novel preclinical models to develop rules for vaccine and Biologics therapies; and (vi) translational models in human cancers of high unmet clinical need.

ABSTRACT: Genetic ablation of *ifitm1* attenuates interferon-mediated induction of MHC class I molecules. Oesophageal adenocarcinoma is a cancer of high unmet clinical need. Proteomics and genomics have defined the major signalling landscapes that form therapeutic targets in this cancer type. One signalling pathway activated in OAC is the interferon-stimulated DNA damage resistant signature, including the transmembrane receptor, IFITM1. This receptor plays a dual role in restriction of RNA viruses and in oncogenic cancer cell growth. The signal transduction events that are orchestrated by IFITM1 are not well defined. We set out to identify IFITM1 interacting proteins to begin to define its mechanism of action. Affinity purification of SBP-tagged IFITM1 from isotopically labeled cells identified SRSF splicing and mRNA translation factors as associated proteins. Isogenic *ifitm1-ifitm3* null cell panels were generated using CRISPR gRNAs to define signalling events that are linked to these protein-interactions. A cytosolic association of SRSF1:IFITM1 complex was identified in interferon treated cells using proximity ligation assays. Ribosome SWATH-MS profiling using gradient sedimentation identified a reduction in both A254 80S ribosomal fractions and IFITM1:S100P complexes in interferon-treated *ifitm1-ifitm3* null cells. The localization of IFITM1 to ribosomal protein components prompted an analysis of interferon-dependent protein synthesis using pulse SILAC-mass spectrometry. MHC class I molecules were most highly suppressed interferon-responsive proteins in the *ifitm1-ifitm3* double null cells. Transient depletion of IFITM1 using targeted siRNA also depleted MHC class I molecules as well as IFITM3, STAT1, and ISG15. These data have implications for the function of the IFITM1 in mediating interferon-stimulated protein induction as well associated MHC Class I-antigen presentation during oncogenic and anti-viral signalling.

Fiona Lickiss (The University of Edinburgh, UK)

BIOGRAPHY: Fiona's undergraduate degree was in Biochemistry and Biological Chemistry. With funding from the Cancer research UK, a PhD project was centered around structure-function analysis of the MDM2 oncoprotein in order to develop improved strategies for targeted therapeutics. This included integration into the RASOR proteomics consortium which aimed to identify radical solutions for researching the proteome(1). Fiona identified multiple stages in MDM2-catalyzed ubiquitination through allosteric modifications of the E2 ubiquitin conjugating enzyme. Following her PhD, Fiona became interested in developing better preclinical models to validate novel therapeutic targets in human cancer. She is now involved in developing novel canine-scFV phage antibody libraries, setting-up parallel canine and human glioma stem cell models, and developing patient-centered approaches to stratify novel therapeutics from her parallel work on an oncology ward.

ABSTRACT: Novel protein-protein interactions in the MDM2-dependent multi-component ubiquitin conjugation reaction. The MDM2 protein regulates the tumour suppressor protein p53, targeting p53 for degradation(2). The E3 ligase activity of MDM2 is dependent on its C-terminal RING domain(3). E3 ligases containing a RING domain are traditionally thought to catalyse the transfer of ubiquitin from their conjugating enzyme (E2) partner to the target protein((4). Various E2 enzymes have been shown to interact with their partner E3 ligases(5,6), yet evidence for the interaction between MDM2 and its partner E2, UbcH5α has not yet been shown. I demonstrate that UbcH5α and ubiquitin both interact with the RING of MDM2. My results show that both these proteins can bind the RING simultaneously. I highlight specific residues, including tyrosine 489 and arginine 479, important for UbcH5α and ubiquitin binding respectively. Furthermore I show by limited proteolysis and hydrogen deuterium exchange that UbcH5α can be allosterically activated by MDM2. A novel peptide phage display technique linked to next generation sequencing was developed to further confirm an allosteric change and demonstrates that UbcH5α has different binding specificity for peptides when in a free or ligand bound conformation.

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Robert O'Neill (The University of Edinburgh, UK)

Clinical Lecturer Edinburgh University, Honorary Specialty Registrar in General Surgery.

Rob is a surgeon scientist with an interest in the treatment of oesophageal cancer. During a Wellcome Trust-funded PhD studentship in the Hupp lab he established a programme of oesophageal cancer research in Edinburgh. He has developed a high quality oesophageal tissue resource incorporating clinically-annotated, prospectively-collected patient material and fostered collaborations with Prof. Rebecca Fitzgerald's Group (Cambridge) and multiple other UK centres, forming the OCCAMS network.

This collaborative group have recently undertaken the ICGC oesophageal adenocarcinoma (OAC) cancer genome project (Genome Res. 2017;27(6):902-912. Nature Genetics. 2016;48(10):1131-41, Nature Genetics. 2015;47(9):1038-46, Nature Genetics. 2014;46(8):837-43). This body of work has yielded multiple insights into this disease and the OCCAMS collaboration have recently completed the analysis of the OAC cancer genomes from over 300 patients providing a powerful resource.

Rob has previously applied proteomics to uncover candidate therapeutic targets for OAC. He recently identified multiple novel proteins to be highly expressed in OAC compared to surrounding tissues (MCP 2017;16(6):1138-50). Several of these are under active investigation as therapeutic or imaging targets (OPTIMA research programme, Edinburgh and RECAMO programme, Brno).

He is currently developing methods to uncover expressed mutated proteins in OAC by combining whole genome and transcriptome sequencing, and shotgun proteomics and he will discuss this ongoing work in Gdansk.

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Maciej Parys (The University of Edinburgh, UK)

BIOGRAPHY: Maciej Parys received his veterinary degree from University of Warmia and Mazury in Poland. After a year in clinical practice he moved to Michigan State University where he was a graduate assistant and subsequently a research associate. In 2016, he relocated to University of Edinburgh, where he is a clinical lecturer at the Royal (Dick) School of Veterinary Studies and a clinical research associate at the Roslin Institute. His research interests include use of spontaneously developing canine and feline cancer and inflammatory diseases, as models for human diseases and development of novel treatment approaches that would benefit the both worlds. He is a recipient of multiple prestigious awards including Morris Animal Foundation Fellowship for Advanced Study, American Veterinary Medical Association Young Investigator Award as well as Advisory Board on Cat Diseases and Boehringer-Ingelheim Young Scientist Award.

ABSTRACT: Companion animals spontaneously develop various types of cancers that frequently resemble histologically, clinically and genetically human neoplasms as well. It is estimated that approximately 25% of all dogs will die of cancer, while in certain breeds this number increases to almost 50%. Due to spontaneous development, fully functional immune system as well as many shared genetic aberrations that lead to cancer development and progression, companion animal cancers make a promising model for designing of new therapeutic approaches for human disease. Cancers such as lymphoma, glioma, melanoma, osteosarcoma or urothelial carcinoma occur in dogs with similar or higher frequency than in humans. Importantly due to small genetic pool of each breed, certain breeds are predisposed to specific types of cancer. Dogs' proteins are also structurally closer to human proteins than mouse. This makes dogs also an invaluable model for identification of new cancer susceptibility genes as well as gene functions and interactions. Due to intact immune system, canine cancers can make significant impact on development of novel immunotherapies. Although for the dog model to be used to its full potential, several challenges need to be addressed such as lack of comparative studies between human and canine immune cells or limited reagents. With further developments in the field, dogs can potentially fill the gap between mouse and human studies and help in faster development of the novel treatment approaches.

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Yury O. Tsybin (Spectroswiss, Laussane Switzerland)

BIOGRAPHY: Dr. Yury O. Tsybin is a CEO and founder of an innovation-driven mass spectrometry company Spectroswiss located in Lausanne, Switzerland. Tsybin received his PhD degree in ion physics in 2004 from Uppsala University and did his postdoctoral research with Prof. Alan Marshall at the National High Magnetic Field Laboratory. From 2006 to 2014 Tsybin was an assistant professor of physical and bioanalytical chemistry at the Ecole Polytechnique Fédérale de Lausanne (EPFL) in Switzerland where he established and headed the Biomolecular Mass Spectrometry Laboratory and served as a Director of the Mass Spectrometry Service Facility. In 2014 he founded an EPFL spin-off company, Spectroswiss Sàrl, which he is directing since then. Interests of Tsybin and Spectroswiss are around the high-performance mass spectrometry method and technique development with subsequent applications for in-depth analysis of biological and environmental samples. Particular interests are in FTMS fundamentals and instrumentation, including data acquisition and signal processing. Application interests are in structural analysis of monoclonal antibodies, middle-down and top-down proteomics development, as well as in lipidomics and imaging. In 2011 Tsybin received the European Research Council (ERC) Starting Grant to pioneer and develop the super-resolution mass spectrometry, in 2012 the European Young Chemist Award, in 2014 the SGMS award of the Swiss Group for Mass Spectrometry, and in 2016 the Curt Brunnée Award from the International Mass Spectrometry Foundation.

ABSTRACT: Advances in environmental, pharmaceutical and life sciences require improved performance of even the most powerful analytical techniques to target the extreme complexity of modern samples. Due to its high performance, Fourier transform mass spectrometry (FTMS) is the central analytical technique in (bio)molecular analysis. Recent innovations and breakthroughs in FTMS are almost exclusively in the developments of mass analyzers and MS/MS capabilities, increased efficiency of ion sources and ion transfer optics. Contrastingly, FTMS time-domain data acquisition methods and techniques have progressed only incrementally and do not rely on the state-of-the-art electronics. Although FT is a robust and well-characterized method of signal processing, it is inherently slow due to its strict uncertainty principle. We will discuss the possible hardware and software solutions to improve the FTMS data acquisition and processing resulting in the proportional improvements in FTMS performance and applications [1, 2].

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Further Speakers

Justesen Sune (Immunitrak, Copenhagen, Denmark)

Thorgrimsen Stephan (Immunitrak, Copenhagen, Denmark)

Verma Chandra (A*STAR, Singapore, Republic of Singapore)

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