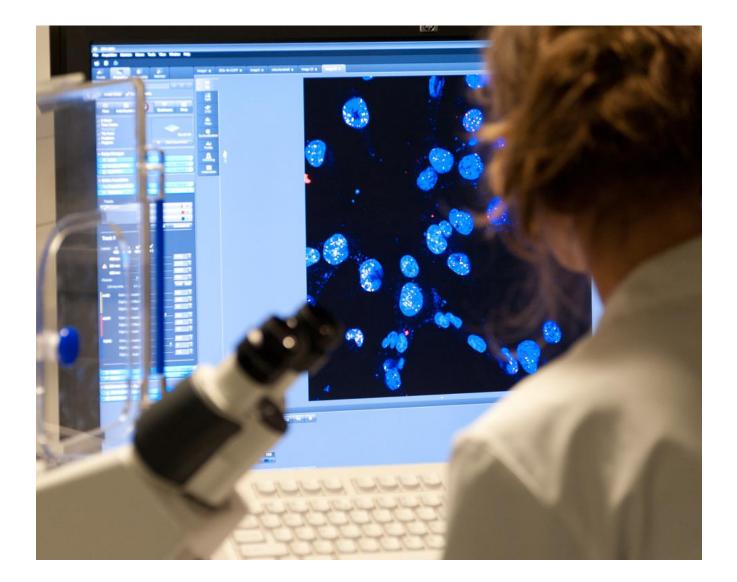# Opportunities and challenges with emerging biomarker technologies and their application in early phase trials

Conference hosted by The Institute of Cancer Research, London
20 March 2017

Contents

Welcome

On behalf of the Translational Science subgroup of the ECMC Quality Assurance and Translational Science Network Group (QATS), I would like to welcome you to the first QATS one day conference "Opportunities and challenges with emerging biomarker technologies and their application in early phase trials".

The QATS Network Group mission is to support and enable ECMCs to conduct translational research to the appropriate levels of quality and regulatory compliance utilising validated cutting-edge technologies. The aims of this conference are to enable delegates to learn about novel technologies being used for translational science across the network, to discuss the challenges of application of novel biomarker analysis in early phase oncology trials and to network with other QATS members.

The conference will showcase the use of novel technologies in translational science through seminars with guest speakers, the ECMC breaking news session, and the poster session. The interactive workshops and panel discussion are intended to provide an opportunity to discuss the challenges of validation of novel technologies to GCP standards, and the future directions of translational science within the network.

The committee ultimately hope that bringing together ECMC members performing translational science plus other interested parties will encourage sharing of knowledge and best practice within the network group.

On behalf of The Institute of Cancer Research, I would like to welcome you to the ICR at Sutton. The ICR recognises that high quality biomarker research is essential in making the discoveries to defeat cancer. We are delighted to host this conference.

I thank you all for showing your support to this event and hope that you find the day useful and enjoyable.

My warmest welcome to you all,

Dr Karen Swales

QATS Network Group, Translational Science sub-committee chair

Agenda

09:00	**Welcome and introduction**	
09:10-10:10	ECMC Translational Science Breaking News *Featuring speakers selected from submitted abstracts*	
09:10-09:30	Use of rare circulating haematopoietic cell phenotypes for pharmacodynamic biomarker assays in early phase clinical trials	**Dr David Jamieson**
09:30-09:50	The TARGET trial: molecular profiling of circulating tumour DNA to stratify patients to early phase clinical trials	**Dr Mahmood Ayub**
09:50-10:10	A Basophil Activiation Test to Monitor Hypersensitivity to a Novel IgE Immunotherapy undergoing First-in-Class, First-In-Man Clinical Trial	**Dr Heather Bax**
10:10-10:30	NCRI Cellular & Molecular Pathology Initiative (CM-Path): developing pathology research in clinical trials	**Professor Gareth Thomas**
10:30-11:00	**Coffee break, poster and exhibitors**	
11:00-11:45	Working in collaboration with a trial sponsor; successes, challenges and opportunities	**Dr Sidath Katugampola & Dr Stephanie Traub**
11:45-12:05	Mass cytometry in clinical settings	**Dr Susanne Heck**
12:05-12:25	Digital pathology and multispectral immunofluorescence approaches to dissect the tumour microenvironment	**Professor Benjamin Willcox & Chris Bagnell**
12:25-13:25	**Lunch, posters and exhibitors**	
13:25-14:10	NanoString Multiplexed Assays for Precision Oncology with extension to high-plex digital spatial profiling for Immuno-Oncology	**Dr Joseph M. Beechem**
14:10-14:30	Analytical reproducibility and longitudinal stability of endogenous small molecules in biofluids: implications for use as biomarker	**Dr Hector Keun**

14:30-15:00	**Coffee break, posters and exhibitors**
15:00-16:30	Parallel workshops
15:00-16:30	The future of translational science in early stage oncology trials: How will the ECMC Network continue to deliver high quality biomarker research? **Dr Fiona Thomson** • What are the current challenging areas of drug discovery in need of biomarker solutions? How might we address these challenges? • How will the role of translational science in clinical trials evolve in the future? What are the strategies for managing multiple markers and tests for precision treatment of cancer? • How will the ECMC Network deliver these future needs?
15:00-16:30	Challenges for translational science analytical validation in early phase oncology trials. **Dr Ruth Challis** • In your ECMC, do you apply the same QA across all assays, irrespective of whether they are primary endpoint or not? • Should primary, secondary, or tertiary endpoints have the same or differing quality assurance requirements? Why? What are benefits/drawbacks? • What are the challenges in implementation of assay validation to complex or novel translational science techniques? Can the ECMC Network be leveraged to help to address these challenges? If so, how?
16:30-17:30	Panel discussion *Featuring selected speakers from the day and QATS committee members*

Speaker abstracts

Dr Gareth Thomas: NCRI Cellular & Molecular Pathology Initiative (CM-Path): developing pathology research in clinical trials

Cellular molecular pathology is the science of understanding disease at the level of cells, genes and molecular pathways. Over the past 15 years, research in pathology in the UK has severely declined; this is best illustrated by a substantial decrease in the academic pathology workforce affecting all grades, from Lecturers to Professors.

Precision medicine is founded on the diagnostic, prognostic and predictive information provided by cellular and molecular pathology. There is an escalating need to reinvigorate academic pathology and research in this specialty so that it continues to support the rapidly developing precision medicine approaches, particularly tissue-based biomarker discovery within clinical trials. The CM-Path initiative is a new National Cancer Research Institute (NCRI) programme, which aims to achieve the change needed to support academic cellular molecular pathology in the UK and make the resulting benefits available to the wider research community.

CM-Path is setting up a new advisory group; the clinical trials pathology advisory group (CT-PAG). The aim of this group is to improve pathology protocols in clinical trials, from tissue collection, fixation and storage to biomarker discovery and validation.

Dr Sidath Katugampola & Dr Stephanie Traub: Digital pathology and multispectral immunofluorescence approaches to dissect the tumour microenvironment

In early phase oncology clinical development, biomarkers are increasingly being used to identify the right drug for the right patient, at the right dose and schedule in order to clearly demonstrate proof of mechanism and proof of principle. This is fundamentally important as often in early phase oncology trials, demonstrating proof of concept in terms of efficacy is very limited and later stage development is performed at risk. Within the Centre for Drug Development (CDD) at Cancer Research UK, it is our aim, as a trial sponsor, to meet these objectives. We work with numerous experimental cancer medicine (ECMC) funded labs with evolving technologies, methods, assays and quality standards to deliver trial end points that enable successful go/no-go decision for further development. The presentation will focus on some the following:

- Role of the sponsor
- Case study on how to put an idea on a potential biomarker in to practice
- Success stories on clinical application of biomarker assays
- Opportunities that a sponsor can provide
- Challenges faced by a sponsor working across the network

Dr Susanne Heck: Mass cytometry in clinical settings

The introduction of high-dimensional mass Cytometry in 2010 has ushered in a new era of single-cell analysis. While traditional cytometers using fluorescent probes now allow confidently the analysis of 16-parameters, with novel instrumentation and reagents pushing this boundary to the mid-twenties, Mass Cytometery is now routinely used for 38+ parameter experiments on single cells with barcoding approaches allowing further multiplexing.

The latest addition to the high dimensional tool box is Imaging Mass Cytometry promising to equally revolutionize the field of histology. These technological advances have given us the tools for true systems biology. Combining comprehensive panels of phenotypic surface markers with equally comprehensive marker panels for functional cell states is allowing us to disentangle complex signalling networks in heterogeneous tissues such as blood, bone marrow, and tumours in ways that were previously impossible. High dimensional Cytometry tools were key to many transformative studies in diverse disciplines including hematopoiesis, immunology, and drug profiling.

The rapid increase in dimensionality brought on by mass cytometry has in parallel necessitated the development and maturation of novel high dimensional data analysis tools allowing researchers to probe and visualize high parameter, single-cell datasets. Today's talk will give an overview of the current state of available high dimensional Cytometry technologies and highlight their use on examples of clinical importance.

Professor Benjamin Willcox & Chris Bagnell: Digital pathology and multispectral immunofluorescence approaches to dissect the tumour microenvironment

The presentation will outline how research in the CRUK Birmingham Centre is using automated IHC and multispectral immunofluorescence approaches, combined with digital pathology analyses, to assess the complexity of the tumour microenvironment. Such methods allow robust quantitative assessments of phenotypic signatures such as intratumoural immunity; analysis of combinations of actionable targets; identification, quantitation and functional characterisation of specific cellular subsets; and delineation of patient subgroups for novel clinical trials

Dr Joseph M. Beechem: NanoString Multiplexed Assays for Precision Oncology with extension to high-plex digital spatial profiling for Immuno-Oncology

The ability of mutated cells to give rise to pathological cancer relies upon the capability of these cells to interact with the immune system and ultimately evade immune recognition, suppress immune activity, and persist in a chronically inflamed environment. There is a clear need for new technologies capable of monitoring these crucial tumor ó immune-system interactions. The importance of measuring non-DNA markers (e.g., mRNA, proteins, protein-phosphorylation) becomes crucial in immuno-oncology (IO), since transcriptional reprogramming, cell-signaling, tumor microenvironment, and protein-protein interactions dominate the immune response. Combining multiple data types together into a single correlated analysis, however, is very difficult, due to the drastically different methodologies utilized for measurement.

New developments in multiple biomarker-class optical barcode counting significantly reduce this problem, allowing the simultaneous (up to 800-plex) measurements of Single-Nucleotide Variants (SNVs), mRNAs, gene fusions, proteins, and protein-PTMs in a single-assay (aka 3-D Biology). The 3D-Biology technology has been further expanded with the development of a High-Plex Microscope (the Digital Spatial Profiler, DSP) that allows for the multiplexed (up to 800-plex) digital counting of proteins and mRNAs using 5um formalin-fixed paraffin-embedded tissue-slices. DSP has now been shown to have single-cell spatially resolved sensitivity and is quantitative over 5-Logs (base-10) of dynamic range. This expanded 3D Biology technology has the potential to usher-in a new era of ultra-high-information content biomarker signatures and greatly extend our understanding of fundamental biological processes.

Dr Hector Keun: Analytical reproducibility and longitudinal stability of endogenous small molecules in biofluids: implications for use as biomarkers

A critical question facing the use of metabolomics is whether data obtained from different centres can be effectively compared and combined. An important aspect of this is the inter-laboratory precision (reproducibility) of the analytical protocols used. We analysed human samples in six laboratories using different instrumentation

but a common widely-used, targeted metabolomics assay (the AbsoluteIDQTM p180 Kit). For typical biological samples (serum and plasma from healthy individuals) the median inter-laboratory CV was 7.6%, with 85% of metabolites exhibiting a median inter-laboratory CV of <20%. Precision was largely independent of the type of sample (serum or plasma) or the anticoagulant used but was reduced in a sample from a patient with dyslipidaemia.

These data compare well to other metabolomics platforms such as NMR spectroscopy that are inherently quantitative and robust, and are favourable compared to longitudinal variability in metabolite levels in biofluids. Despite this, diurnal and other sources of pre-analytical variability continue to present challenges to the interpretation of metabolomics data, particularly in acute studies, and the field has yet to routinely comply with criteria by which metabolomic data can be consistently interpreted and integrated across clinical studies.

Speaker biographies

Dr Gareth Thomas

Gareth Thomas was appointed to the Chair of Experimental Pathology at the University of Southampton in 2009. His research focuses on the role of the microenvironment in promoting tumour progression. The work has a strong translational component, identifying potential prognostic biomarkers, therapeutic targets and molecular classifiers in cancer tissues, including the characterisation of cancer-associated fibroblasts and intratumoral immune cells, and development of immunotherapy clinical trials in squamous carcinoma of the head and neck. He leads the *Discovery* workstream of the NCRI Cellular & Molecular Pathology Initiative (CM-Path).

Dr Sid Katugampola

Sid Katugampola completed his Ph.D in the Clinical Pharmacology Unit at University of Cambridge. Following that, in 2001 he joined Pfizer R&D and worked across multiple departments spanning 10 years. During his last 6 years at Pfizer, Sid led projects in biomarkers and translational medicine across multiple therapeutic areas and targets with a key focus on demonstrating proof of pharmacology in early phase clinical trials. He joined the Centre for Drug Development at Cancer Research UK in 2011 where he has been responsible for the delivery of pharmacodynamic biomarkers and patient enrichment strategies for early phase oncology clinical development. He has worked across multiple modalities and cancer types, majority of therapeutic agents being first in class with a major emphasis on demonstrating target pharmacology.

Dr Stephanie Traub

Stephanie Traub is a Biomarker Development Specialist at the Centre for Drug Development at Cancer Research UK. She is a fellow of the University of Konstanz and has completed her PhD in Immunology. Stephanie has held academic positions as Postdoc in France and at Imperial College for 6 years. She worked after this time in industry at Medimmune in Cambridge UK, then Quotient Bioresearch (LGC group), leading project in Biomarker assay development across multiple therapeutic areas. In the current time at the Centre for Drug Development she is responsible for designing the Biomarker- and patient enrichment strategies for early phase oncology trials.

Dr Susanne Heck

Susanne Heck received her PhD in molecular biology at the University of Bremen, Germany, in 1997. After a postdoc in molecular and cellular biology at Albert Einstein College in New York, Dr Heck took up a position in at Cellular Genomics Inc., USA, to work on preclinical models for small molecule kinase inhibitors. In 2004 she moved to the Lindsey F. Kimball Research Centre to build up and run the research Flow Cytometry Core of the New York Blood Centre. Dr Heck has been appointed as head of the NIHR BRC Flow Cytometry Core for Guys and St Thomas Hospital and King's College London in 2009 and has established a successful human immune monitoring core of international reputation.

Professor Ben Willcox

Professor Ben Willcox is chair of Molecular Immunology at the University of Birmingham, and a Wellcome Trust Investigator. In addition to leading the Cancer Immunology and Immunotherapy Centre at the University of Birmingham, he is a member of the CRUK BioTherapeutic Expert Review Panel, the CRUK-MedImmune Target Selection Committee, and is the designated Scientific Director of the CRUK Birmingham Centre. He has a strong interest in colorectal cancer immunobiology, and in unconventional T cell function. He also works closely with Chris Bagnall, the Queen Elizabeth Hospital Charity Cancer Immunotherapeutics Support Officer, to develop digital pathology and multispectral immunofluorescence approaches, an area in which Birmingham has a Key Opinion Leader agreement with Perkin Elmer relating to the Vectra Automated Quantitative Pathology Imaging System.

Dr Joseph Beechem

Joseph M. Beechem, Ph.D. has served as Senior Vice President of Research and Development, since April 2012. Prior to joining our company, Dr. Beechem held various positions at Life Technologies, a publicly-traded biotechnology tools company, most recently as Vice President, Head of Advanced Sequencing and Head of Global Sequencing Chemistry, Biochemistry and Biophysics from January 2010 to April 2012. From December 2007 to December 2012, he served as Chief Technology Officer of Life Technologies. During his career at Life Technologies, he led the design and development of multiple genetic analysis technologies, the latest advanced SOLiD sequencing technology and the single molecule nano-DNA sequencing technology.

Prior to joining Life Technologies, Dr. Beechem was Chief Scientific Officer at Invitrogen, a publicly-traded biotechnology company that acquired Applied

Biosystems in November 2008 to form Life Technologies, from August 2003 to December 2007 and Director of Biosciences at Molecular Probes, a biotechnology company acquired by Invitrogen in 2003, from August 2000 to August 2003. Prior to his industry experience, Dr. Beechem led an NIH-funded research laboratory for 11 years as a tenured associate professor at Vanderbilt University. He has authored or co-authored more than 100 peer-reviewed papers in diverse fields such as biomathematics, physics, chemistry, physiology, spectroscopy, diagnostics and biology. Dr. Beechem is also named on nearly 30 U.S. patents or patent applications and has served on a number of editorial and scientific advisory boards. He received a B.S. in Chemistry and Biology from Northern Kentucky University and a Ph.D. in Biophysics from The Johns Hopkins University.

Dr Hector Keun

Dr Keun is a Reader in Metabolic Biochemistry in the Division of Cancer at Imperial College London and leader of the Cancer Metabolism and Systems Toxicology group. He joined Imperial in 2001 after completing his undergraduate degree in Chemistry at New College, Oxford University and postgraduate degree in Structural Biology from the Department of Biochemistry, Oxford University in the laboratory of Prof Iain Campbell. With expertise in NMR spectroscopy, bioinformatics, metabolic biochemistry and biomarkers his research programme centres on the application of metabolic profiling (metabonomics/ metabolomics) to problems in toxicology and oncology. In 2009 he was awarded the CEFIC LRI European Chemical Industries Council (Long Range Initiative) Innovative Science Award for *Using Metabonomic Biomarkers To Bridge The Gap Between Environmental Exposures And Human Health*. Dr Keun is author of over 100 publications which have received over 5000 citations. Dr Keun's research is supported by a number of FP7 consortia, CRUK, Ovarian Cancer Action, Prostate Cancer UK, AstraZeneca and MRC.

Dr Fiona Thomson

Fiona joined the Institute of Cancer Sciences, University of Glasgow, in early November of 2014 as Director of the ECMC translational sciences laboratory. Her current research is focused on the discovery and development of novel 'non-invasive' biomarkers to aid early cancer diagnosis, prognosis and to support the development of novel cancer therapies through clinical trials. Fiona is a pharmacologist who has spent the last 15 years in the pharmaceutical industry, latterly at Merck (MSD), discovering and developing novel therapeutics.

Opportunities and challenges with emerging biomarker technologies and their application in early phase trials

Dr Ruth Challis

Ruth Challis received a PhD from King's College London in Cardiovascular Biology and Medicine following an undergraduate degree and Masters of Biochemistry at the University of Oxford. Since 2015 Ruth has been the Laboratory Operations Manager of research laboratories within the Southampton Centre for Biomedical Research and Wellcome Trust NIHR Clinical Research Facility, based in the University Hospital Southampton NHS Foundation Trust.

Included within this remit is operational management of the Wessex Investigational Sciences Hub (WISH) Laboratory, opened in 2014, which specialises in regulatory analytical assays compliant with MHRA / EMA regulations and standards, and also hosts the translational scientists of the Southampton ECMC. Prior to her current role, Ruth was a senior postdoctoral scientist within the ECMC Southampton translational sciences group for over 7 years, although she has also a diverse career background including secondary science teaching qualifications and experience.

Abstracts

ECMC Translational Science Breaking News session

01: Use of rare circulating haematopoietic cell phenotypes for pharmacodynamic biomarker assays in early phase clinical trials.

Suriyon Uitrakul[1], Huw Thomas[1], Claire Hutton[1], Gareth Veal[1], **David Jamieson[1]**.
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The need for data on the mechanism of action (MOA) of novel anticancer drugs in early phase clinical trials needs to be balanced against the inconvenience and risk to the patient of taking multiple biopsy samples. There is potential for circulating tumour cells (CTCs) to serve as a source of tumour cells for the serial measurement of MOA targets during therapy but this will be limited by the sensitivity of CTC detection methods with a proportion of study participants not having any evaluable CTCs.

During our development of CTC characterisation methods by imaging flow cytometry it became apparent that as well as a remarkable degree of inter- and intra-patient heterogeneity in the phenotype of CTCs, heterogeneity was also seen in haematopoietic cell populations with rare populations expressing antigens for putative CTC or pharmacodynamic markers. For example, staining of CTC and control samples with a Ki67 antibody revealed a population of lymphocytes in both patients with HCC and healthy volunteers (mean of 0.44% and 0.24% respectively; P = 0.007). Further investigations into rare blood cell populations have resulted in the development of an imaging flow cytometry assay measuring changes in the proportion of neutrophils positive for acetylated histone H4 following administration of the HDAC inhibitor valproate in childhood ependymoma patients. A second assay measuring modulation of pMCM2 as a MOA marker of CDC7 inhibition is currently undergoing validation.

02: The TARGET trial: molecular profiling of circulating tumour DNA to stratify patients into early phase clinical trials

Mahmood Ayub[1,2], Dominic G. Rothwell[1,2], Sakshi Gulati[1,2], Nigel Smith[1,2], Bedirhan Kilerci[1,2], John Brognard[3], Andrew Wallace[4], Crispin Miller[5], Emma J. Dean[1,6,7], Natalie Cook[1,6,7], Fiona Thistlethwaite[1,6,7], Hui-Sun Leong[5], Helen Eaton[4], Emma Howard[4], Andrew Hudson[3], Carla Siswick[4], Joanne Dransfield[7], Marianna Christodolou[7], Louise Carter[1,6,7], Robert Metcalf[1,2,7], Sreeja Aruketty[7], Jaseela Chiramel[7], Andrew M. Hughes[1,6,7*], Richard Marais[1,8*], Matthew G. Krebs[1,6,7*], Caroline Dive[1,2*], Ged Brady[1,2*]

[1]Manchester ECMC, [2]Clinical Experimental Pharmacology Group, CRUK Manchester Institute, Manchester Centre for Cancer Biomarker Sciences, University of Manchester; [3] Signalling Networks in Cancer Group, CRUK Manchester Institute, [4]North West Centre for Genomic Medicine, [5]Computational Biology Support and RNA Biology Group, CR-UK Manchester Institute, [6]Division of Molecular and Clinical Sciences, University of Manchester, [7]Christie NHS Foundation Trust, Institute of Cancer Sciences, University of Manchester, M20 4BX, UK; [8]Molecular Oncology Group, CRUK Manchester Institute.

The Tumour characterisation to Guide Experimental Targeted Therapy Trial (TARGET) tests the hypothesis that molecular profiling of both archival/fresh tumour and circulating tumour DNA (ctDNA) can be used to stratify patients to early phase trials of targeted therapies to maximise patient benefit. Patients were consented for molecular analysis of tumour and blood. Tumour was analysed by Sequenom OncoCarta using a 19 gene panel. ctDNA was subjected to next generation sequencing (NGS) and bioinformatic analysis of a panel of >600 genes known to be frequently mutated in cancer. Clinical reports from tumour and blood were discussed in a monthly Molecular Tumour Board (MTB)

to identify possible driver aberrations and to aid clinicians in selection of relevant experimental medicine trials.

The initial stages of the trial have focused on process development, optimisation of ctDNA sequencing, bioinformatics analysis and establishing the MTB. The current ctDNA pipeline identified at least one mutation within ctDNA from 87.5% (35/40) samples. For the first 20 samples concordance between tumour and ctDNA was 90%. Eight patients had clinically relevant mutations, confirmed in ctDNA by droplet digital PCR and/or repeat NGS. The MTB has been optimized to review and interpret tumour and ctDNA reports within 3-4 weeks of consent and has identified relevant clinical trials for individual patients.

Our results support the use of ctDNA for routine molecular characterisation. The success of the overall approach has led to scale up of patient recruitment to ~350 patients over the next 2-3 years. The focus of on-going work will be to validate the process to GCP compliance, allocate patients to clinical trials based on ctDNA and/or tumour profiling and facilitate monitoring of treatment response and emerging resistance mechanisms using serial blood samples. Outcome measures will include numbers of patients allocated and recruited to matched experimental medicines, response rates and survival outcomes.

03: A Basophil Activation Test to Monitor Hypersensitivity to a Novel IgE Immunotherapy undergoing First-in-Class, First-in-Man Clinical Trial

Heather J Bax[1,2,3], Debra H Josephs[1,2,3], Sidath Katugampola[4], Paul Jones[4], Claire Barton[4], Heike Lentfer[5], Giulia Pellizzari,[1,3], Hannah J Gould[2,6,7], Chris Corrigan[7], Ana Montes[8], James F Spicer[3], Sophia N Karagiannis[1,2].

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[7] Division of Asthma, Allergy and Lung Biology, MRC and Asthma UK Centre for Allergic Mechanisms of Asthma, King's College London, London, UK.
[8] Department of Medical Oncology, Guy's and St Thomas' NHS Foundation Trust, London, UK.

Nearly all therapeutic antibodies used against solid tumours are of one antibody class, namely IgG. However, efficacy may be improved by the development of tumour antigen-specific IgE antibodies, due to the higher affinity of this antibody class for its effector cell receptors and the longer immune surveillance in tissues exerted by IgE compared to IgG. MOv18 IgE, specific for folate receptor-α (FRα), a surface antigen expressed by up to 90% of epithelial ovarian carcinomas as well as other tumours, is the first IgE immunotherapy to be evaluated in man. Bespoke functional and biomarker assays have therefore been developed to evaluate the mechanism of action, and most importantly, the safety of this novel immunotherapy throughout the first-in-class, first-in-man clinical trial.

The basophil activation test (BAT) is used for *ex vivo* detection of indicators of immediate type I allergic reactions and hypersensitivity to suspected agents (such as allergens) and has been utilised in numerous studies of allergy. We have optimised and validated a BAT assay to monitor hypersensitivity of basophils from patients with cancer receiving MOv18 IgE treatment.

In this *ex vivo* flow cytometric assay, human basophils in whole blood are evaluated for their activation status by measuring expression of the cell-surface marker CD63. Using healthy volunteer blood samples, we optimised the duration and efficiency of incubation with stimulants and we

investigated the robustness of the assay, gaining an understanding of the time constraint for acquisition following blood sample collection. We determined a positive basophil activation response cut-off in order to provide clear criteria for the detection of any activation of basophils by chimeric MOv18 IgE alone, or in combination with its target antigen, FRα and anti-FRα IgG autoantibodies that may be present in patient whole blood.

Furthermore, we validated the use of this fit-for-purpose assay using blood samples from patients with ovarian carcinoma. Results to date indicate that MOv18 IgE does not activate basophils *ex vivo*. We are now utilising the BAT assay to support clinical safety observations during the Phase 1 study of MOv18 IgE.

Poster session

04: Preclinical evidence in patient CTC derived explant models for the combination of topotecan and AZD1775 for the treatment of small cell lung carcinoma

Alice Lallo[1,2], Melanie Galvin[1,2], Lynsey Priest[1,2], Matt Carter[1,2], Mark O Connor[3], Rajesh Odedra[3], Kris Frese[1,2], Fiona Blackhall[1,,4,5] and Caroline Dive[1,2,4,5]

[1]Manchester ECMC, [2]Clinical and Experimental Pharmacology Group, CRUK Manchester Institute and Manchester Centre for Cancer Biomarker Sciences, University of Manchester, [3]AstraZeneca Pharmaceuticals, Cambridge, UK, [4]Division of Molecular and Clinical Cancer Sciences, University of Manchester, [4]Christie NHS Foundation Trust, [5]CRUK Lung Cancer Centre of Excellence at Manchester and University College London.

Despite the rise of genome-based precision medicine and the investigation of multiple targeted agents, platinum-based chemotherapy regimens have remained the standard of care for the treatment of SCLC for over three decades. We have generated a panel of SCLC Circulating tumour cell Derived eXplant (CDX) models that faithfully recapitulate multiple aspects of patient disease, including response to platinum/etoposide. Here we investigated the efficacy of topotecan, the only agent approved for second line treatment, in CDX models that were derived from chemosensitive patients as well as those displaying both innate and acquired chemoresistance. Although topotecan elicited a robust anti-tumour response in all models tested, including those that were resistant to platinum/etoposide, responses were transient suggesting that it should be used in combination with another agent.

Wee1, a protein kinase that phosphorylates and regulates cyclin-dependent kinase 1, is a critical mediator of both the intra-S and G2/M cell cycle checkpoints. AZD1775 is an orally bioavailable small molecule Wee1 inhibitor that has been shown to abrogate these checkpoints and cooperate with various DNA damaging agents. The combination of AZD1775 and topotecan elicited a more sustained anti-tumour response than topotecan alone (median event-free survival of 55 vs 37 days), demonstrating remarkable efficacy against a model that is completely refractory to cisplatin/etoposide. These data suggest that AZD1775/topotecan may be a viable therapeutic option for patients that progress on platinum-based regimens, and provide a preclinical rational for the examination of this combination in clinical trials.

05: Modelling of plasma cytokine networks during therapy in advanced gastro-oesophageal adenocarcinoma

Alan E. Bilsland[1], Sofie Degerman[2], Carol McCormick[1], Jennifer Walker[1], Sharon Burns[1], Liz-Anne Lewsley[1], Martin MacLeod[1], Göran Roos[2], James Paul[1], Fiona Thomson, T.R. Jeffry Evans[1], and W. Nicol Keith[1].

1 – Institute of Cancer Sciences, University of Glasgow; 2 – Department of Medical Biosciences, Umea University

There is emerging interest in developing senescence-inducing therapies for cancer. To successfully translate such agents, validated biomarkers of senescence and immortality are needed. Currently, the "senectome" is poorly defined, though it comprises genes involved in epigenetic control, energy metabolism, inflammatory signalling, and other processes. We initiated 2 multi-centre longitudinal trials to prospectively analyse telomere length (TL) in serial PBMCs of patients with either operable or advanced gastro-oesophageal adenocarcinoma over the duration of therapy in relation to clinical outcomes (n>300, each study). Eligible patients with advanced disease are treated with palliative fluoropyrimidine and platinum–containing chemotherapy regimens (ECX/ECF or EOX/EOF).

Those with operable disease receive perioperative chemotherapy with ECF/EOF or ECX/EOX. Additional to the primary endpoint of TL, exploratory endpoints include analysis of multiple candidate metabolic and inflammatory markers of senescence followed over the patients' clinical course. We have performed baseline (cycle 1) profiling and computational analysis of plasma cytokine networks comprising IFN☐, IL1☐, IL2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13 and TNF☐ in 194 patients with advanced disease and targeted sequencing of telomere, DNA damage, and a range of cancer-associated genes in 35 patients. We have identified baseline cytokine correlation networks and developed graph-clustering methods to allow us to track inflammatory network evolution during therapy for subgroup selection to identify correlates to clinical outcome. Our preliminary sequencing results also indicate widespread associations between SNPs in telomere-associated genes and inflammatory signalling.

06: Validating cell free circulating tumour DNA testing for clinical and research use

Rebecca Bastock and Angela Cox
Department for Oncology and Metabolism, University of Sheffield
Sheffield Diagnostic Genetics, Sheffield Children's Hospital

Testing that uses circulating cell free tumour DNA (cfDNA) has recently been introduced to the NHS to look for EGFR mutations in Non Small-Cell Lung Cancer (NSCLC) patients. In addition to this there are many clinical trials, including the TracerX trial, that have incorporated this type of testing into their protocols. However, a gold-standard methodology and quality guidelines for mutation detection in cfDNA have yet to be established. As a collaboration between a research group and a NHS diagnostic lab we have been working to find and validate the best method for use locally and to establish Standard Operating Procedures for use in both clinical diagnostic testing and translational research.

The two methods we have evaluated are digital droplet PCR and an NGS panel (SwiftBio) run on an Illumina MiSeq. We have used plasma samples from 17 NSCLC patients known to have EGFR mutation positive tumours at diagnosis. All samples were collected as part of the Resolucent study and all patients had previously received at least one round of treatment. All samples were tested by ddPCR for their original mutation and, where possible, for additional common EGFR mutations. The original mutation was detected by ddPCR in 5 out of 17 samples, with allele fractions that varied from 68% to 0.3%. There was a striking correlation between initial cfDNA concentration in the plasma sample (ng/ml) and mutation detection. There were no false positives. Eleven samples had sufficient cfDNA to also be tested by NGS using an EGFR panel and analysis of these results is underway.

We will present our results and a comparison of the two methods from both a practical and technical perspective. We will also discuss the further work required to fully validate these tests.

07: Detecting tumour cell-derived exosomes in liquid biopsies

Prevosto C[1], Spicer J[1,2], Katugampola S[3], Heck S[2].

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In healthy tissues expression of the αvβ6 integrin is limited to epithelial cells undergoing tissue remodeling or wound healing and to hair follicles. Overexpression of αvβ6 was found in a variety of carcinomas, including pancreas, breast and colon, and correlated with tumour progression and poor clinical prognosis. Because of its exclusive expression pattern and its role as a critical upstream regulator of TGFβ signaling, αvβ6 represents an ideal potential drug target.

Given that αvβ6 is not expressed on blood cells, we considered circulating exosomes as potential surrogate biomarkers to monitor directly linked effects of αvβ6 blockade on tumour cells. Exosomes are nanovesicles derived from endosomal membranes that can carry proteins, nucleic acids, lipids and microRNA; exosomes are considered important players in cell-to-cell communication thanks to their specific cargo. Virtually any cell type can release exosomes, including cancer cells, and many biofluids contain them, such as blood or urine. In order to develop a novel assay to monitor anti-αvβ6 therapies in liquid biopsies, we investigated whether cancer-derived exosomes could be detected in peripheral blood. Total exosomes were isolated from either serum or plasma of healthy individuals or from cancer cell lines using commercial kits. After loading exosomes with tracking dye CFSE, surface markers were analysed by imaging flow cytometry. We were able to detect intact *bona fide* exosomes, that were expressing tetraspanins CD63, CD9 and CD81, specific exosome markers, together with other proteins, including CD41, CD235a and CD45, typical for exosomes secreted by platelets, red blood cells and lymphocytes, respectively. Baseline levels of EpCAM and αvβ6 expressing exosomes were found to be negligible or very low in healthy donor serum/plasma.

Known positive (CAPAN-1) and negative (MCF-7) cancer cell lines were next used as controls to successfully and specifically detect αvβ6 expression on exosomes isolated from tissue culture supernatant with EpCAM expressed by both. When spiking serum samples with cancer cell line-derived exosomes, we were able to enrich EpCAM-expressing cell line-derived nanovesicles using immune-magnetic beads coated with EpCAM antibodies.

In summary, we have developed a new method to measure cancer-specific exosomes in peripheral blood; we will implement this assay by including pancreatic cancer patients to provide data on specificity and sensitivity.

08: Clinical utility and associated challenges of circulating tumour cells (CTCs) as biomarkers in early clinical trials

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CTCs provide a minimally invasive biopsy with potential utility as biomarkers to aid treatment decision-making and disease monitoring during therapy. In addition to investigating changes in CTC number during treatment, assessment of protein expression in CTCs (such as DNA damage markers and immune check point modulators) allow study of proof of mechanism and concept pharmacodynamic (POM/POC PD) biomarkers for experimental therapies. We describe the development of POC/POM PD biomarkers in CTCs enriched by marker-dependant (CellSearch) and marker independent (Parsortix) CTC platforms and the challenges encountered.

The CellSearch system is a marker dependant CTC enrichment platform that enumerates CTCs using specific antibodies for CTC capture (EpCAM) and identification, (pan-Cytokeratin, CD45 and DAPI) with automatic staining and in built imaging with manual scoring on the CellSearch gallery. Analysis of an additional protein biomarker is available using a 4th analysis channel. The Parsortix system is a marker-independent cell size/deformability based CTC enrichment platform where enriched CTC samples are stained and imaged on multiple downstream imaging platforms. These include ImageStream imaging cytometry which combines the advantages of multi-parameter Flow Cytometry and fluorescent microscopy and an Opera Phenix platform, a scanning confocal plate reader capable of imaging in 4 fluorescent channels.

Validation of gH2AX in CTCs as a POC PD biomarker of impaired DNA damage repair comparing CellSearch and Parsortix CTC enrichment will be presented contrasting the ease of CellSearch limited by poor CTC image resolution and the challenges of marker independent CTC analysis with the advantage of high resolution CTC imaging which allows accurate DNA damage foci quantitation.

Marker-independent platforms enrich heterogeneous CTC subsets and are valuable complementary tools to CellSearch for isolation beyond dependence on surface epitopes. (Chudziak et al 2016 Jan 21;141(2):669-78). However, such methods present the translational scientist with significant challenges in terms of qualifying the instrumentation and protocols for clinical use.

09: Quantitative proteomic analysis to identify novel circulating biomarkers in serum samples collected from Axi-STS, a national multi-centre single-arm phase II study of Axitinib for advanced soft tissue sarcoma

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Isobaric tag for relative and absolute quantification (iTRAQ) with tandem mass spectrometry, is a proteomic method for identifying and quantifying proteins in complex biological samples. Axitinib is an oral vascular endothelial growth factor receptor inhibitor. We conducted a histologically stratified, multi-centre, ECMC supported, single arm, phase II clinical trial of axitinib for 145 patients with advanced soft tissue sarcoma. Serum samples were collected from patients pre-treatment and every four weeks whilst on study therapy. We performed an exploratory analysis of these samples to identify novel circulating biomarkers associated with response to treatment.

We established a training set of serum samples collected from four leiomyosarcoma patients designated as good responders, and four sex and age-matched leiomyosarcoma patients judged to be poor responders, pre-treatment and after four weeks of therapy. The serum samples were pooled into the four groups and then depleted of twelve high-abundant proteins using Pierce Top 12 Abundant Protein Depletion Spin Columns according to manufacturer's instructions. The 4 groups were compared using a quantitative proteomic workflow to determine differences in protein level between sample groups. The relative expression of identified proteins was compared between patient groups and between pre and post 4 weeks of treatment with axitinib.

Candidate biomarkers were ranked by fold change between groups. Many of these markers included acute phase response proteins such as fibronectin, haptoglobin, antithrombin III, alpha-I-antitrypsin and apolipoprotein A-IV. We selected actin-gamma (ACTG1), a cell junction assembly protein involved in the ephrin receptor signalling pathway, as a candidate biomarker and are currently validating the expression of this protein in the wider patient sample set using ELISAs for ACTG1.

10: Validation of Flow Cytometry Assays for Cancer Immunotherapy Trials

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Flow cytometry is a versatile technique that is widely used in the field of immunotherapy treatment in cancer. It not only allows phenotypic analysis of cell populations but further functional analysis of specifically identified cells. In order to utilise this technique for clinical trial endpoints, validation is required to ensure high integrity of the data generated.

Southampton ECMC have set up and validated multiple assays using flow cytometry. Phenotypic assays using up to 8 fluorochromes have been designed to measure a wide range of immune cells including, T cell subsets, Tregs, B cells, NK cells, dendritic cells, MDSC's along with activation status of these cell types. Functional assays including receptor occupancy and pAkt signalling have also been validated for use as clinical trial endpoints.

We have experience in validating FACS panels and assays. This process comprises optimisation of the protocol by titrating the antibodies, defining the staining protocol, followed by assessment of

relevant parameters such as precision (intra-, inter- assay, inter-operator), assay range and LLOQ (lower limit of quantification), sample stability (shipping temperature and time to analysis), robustness (setting up a second machine). Here we illustrate the validation process as performed in our centre. Example gating analyses for some populations are shown with example data from validation to highlight the process and parameters of validation.

11: A Phase I Study of Olaparib in combination with Chemo-radiation in Locally Advanced Pancreatic Cancer.

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PIONEER is a phase I, open-label, non-randomised, multi-centre, dose escalation study of the Poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib, administered in combination with standard capecitabine-based chemo-radiation therapy in patients with locally advanced, inoperable pancreatic ductal adenocarcinoma. The primary objective is to determine the Maximum Tolerated Dose (MTD) of olaparib when administered in the combination. Pharmacodynamic endpoints include investigation of the effects of the combination in peripheral blood mononuclear cells (PBMCs) and hair follicles.

Analysis of PARP activity using a 96 well ELISA assay for levels of poly-(ADP-ribose) in PBMCs will be used to demonstrate that olaparib intended mode of action is being achieved (Kinders, *et al.*, Clin Cancer Res 14(21): 6877-85). In our hands, sensitivity and reproducibility of a 7-point calibration curve (0 to 1000pg/mL) showed a cubic nonlinear regression with $r^2 > 0.99$. The assay is specific and no false negatives were detected within 9 replicates derived from patients' samples and had a %CV < 15%. Back-calculated values for specific quality control samples (QC) showed intra-run accuracy and precision with %CV <10%, as well as inter-run accuracy and precision with %CV < 15%. In addition, we determined an olaparib-concentration dependent inhibition of PAR production with an IC50 in the low nanomolar.

Following dose-escalation, an expansion cohort will be recruited for treatment at phase II dose. Immunofluorescent analysis of phosphorylated H2AX levels in hair follicles is to be conducted in these patients to provide evidence of DNA damage signalling. These assays are currently being validated using X-irradiated plucked healthy donor follicles. A connected-component approach to segmentation of DAPI-stained nuclei allowed H2AX-channel signals to be extracted from microscopy images. Pre-validation studies indicate that higher H2AX levels are detected in irradiated follicles as expected, suggesting detection is specific.

12: Circulating cell-free DNA analysis in limited and extensive stage small cell lung cancer

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Clinical management of patients with cancer is becoming increasingly dependent on serial monitoring to chart complex tumour dynamics. 'Liquid biopsies', both circulating tumour cells (CTCs) and circulating cell-free DNA (cfDNA) measured in a patient's peripheral blood sample allow the detection of tumour associated alterations and allows serial sampling as compared to the current practice of tumour tissue genotyping. Here we use cfDNA next-generation sequencing (NGS) analysis to compare limited stage (LS, confined to 1 hemithorax) and extensive stage (ES, with distant metastases) small cell lung cancer (SCLC) in order to establish the feasibility and sensitivity of our approach and to determine whether differences are detectable according to the stage of disease.

NGS libraries were prepared from cfDNA and whole genome sequencing was carried out at a low depth (0.1-0.2x) to establish genome wide copy number aberrations (CNA) from 25 LS SCLC patients and 25 ES SCLC patients. From the same NGS libraries, targeted enrichment of 110 SCLC associated genes was performed and subsequently sequenced at a higher depth (500x). Our results demonstrate the characteristic SCLC associated mutations (*RB1*, *TP53*, *TP73*, Notch and Fanconi Anaemia genes) along with canonical SCLC copy number changes (3p, 17p and chromosome 20) in the majority (>90%) of samples. Initial analysis indicates potential differences in cfDNA CNA and mutational profiles between patients with ES and LS disease with more pronounced changes in CNA seen in patients with ES and more somatic mutations detected in patients with LS. These results confirm the feasibility of cfDNA analysis with NGS in blood samples from patients with SCLC and the potential to detect genetic alterations according to stage of disease.

13: Development and validation of an assay to detect SSTR2 and SSTR5 expression in Circulating Tumour Cells

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University College London Cancer Institute ECMC Centre

Somatostatin receptors (SSTR) are often over-expressed in neuroendocrine tumours, providing a target for therapy with somatostatin analogues (SA) or radionuclide treatment. Using the CELLSEARCH platform, circulating tumour cells (CTCs) can be isolated and enumerated, however expression of SSTR in CTCs has not previously been demonstrated. Here we report the development and validation of an assay to assess SSTR2 and 5 expression in CTCs detected by the CELLSEARCH system. Human breast ductal carcinoma MCF7 cells were transfected with plasmid DNA carrying full length human SSTR2 or SSTR5. Transfected MCF7 cells were spiked into healthy donor blood for testing in the CELLSEARCH system using AF488-conjugated SSTR antibodies. Optimum antibody concentration and exposure times were determined using the transfected MCF7 cells with mock transfected MCF7 cells acting as negative controls. Following optimisation, the

method was validated for clinical use and the sensitivity of the assay confirmed by FACS. Direct immunofluorescence microscopy and visual assessment confirmed SSTR2 and SSTR5 expression in transfected cell lines with a transfection efficiency of approximately 16% and 14% respectively. For SSTR2 transfected cells, 12.4% recovered by CELLSEARCH showed SSTR2 staining at an optimum antibody concentration of 50ug/ml and exposure time of 0.8 seconds on the CELLTRACKS Analyzer II. For SSTR5 transfected cells, 13.8% were marker positive at optimum antibody concentration of 10ug/ml and exposure time of 0.8 seconds.

Marker validation was then performed over three subsequent runs, demonstrating specificity, accuracy and reproducibility of the method. In order to assess the sensitivity of this method, transfected MCF7 cells were run concurrently on CELLSEARCH and FACS, showing comparable detection rates of positive cells (37.2% by FACS vs 36.1% by CELLSEARCH for SSTR2, 26.7% and 27.7% respectively for SSTR5). In conclusion, we have developed a valid assay for the detection of SSTR2 and SSTR5 expression on CTCs which can be applied to clinical studies. Demonstration of reliable SSTR2/5 expression on CTCs in patients could lead to an effective "liquid biopsy" approach to determining treatment. (Reference: Childs, A., Vesely, C., Ensell, L., Lowe, H., Luong, T. V., Caplin, M. E., Meyer, T. (2016). Expression of somatostatin receptors 2 and 5 in circulating tumour cells from patients with neuroendocrine tumours. *British Journal of Cancer*. **115**, 1540–1547).

14: Pharmacodynamic biomarker monitoring of novel cancer therapeutics in Phase I clinical trials at the ICR

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Pharmacodynamic (PD) biomarkers, molecular indicators of drug effect on the target in the body, are essential tools in decision making during Phase I clinical trials. The ICR Clinical PD Biomarker Group develops, validates and implements fit-for-purpose assays for evaluation of PD Biomarkers in early clinical trials of new oncology agents. The group specialises in measuring PD Biomarkers in less invasive surrogate tissues such as platelets, PBMCs and hair follicles, plus tumour biopsies, using immunoassays including ELISA, MSD®, Luminex®, Wes™ and immunofluorescence, validated to MHRA Good Clinical Practice (GCP) for clinical laboratories standards. Validated assays include AKT/PI3K/MTOR, PKA, HSP90, ROCK, MEK and IGF signalling, histone deacetylase biomarkers, cell cycle checkpoints and DNA damage response. Assays under validation include Rb, soluble alpha folate receptor and proliferation biomarkers.

We are currently expanding our portfolio to include PD monitoring at a transcriptional as well as translational level utilising a Nanostring technologies® nCounter® system. The Group's PD monitoring has proved highly valuable in over 30 early clinical trials. Surrogate patient tissues combined with robust, quantifiable assays have measured the extent and duration of on-target effects, evaluated downstream biological effects and provided proof of drug mechanism of action. The group is a crucial member of the multidisciplinary clinical trial team, liaising with project teams to develop and optimise assays prior to trial initiate.

15: Trial Endpoints and Biomarker Analysis: A Stratified Approach to Method Validation and GCP Oversight?

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The conduct of translational research to required levels of quality and regulatory compliance, using cutting-edge techniques, necessitates the application of validation to provide assurance of that technique's ability to generate reproducible and reliable data. Nonetheless, there is currently lack of clarity in the regulatory guidance available to translational researchers on pharmacodynamic and patient selection biomarker assays, as most guidance tends to focus on method validation for animal toxicokinetic or pharmacokinetic endpoints.

Further confounding factors are the clinical trial endpoint (Primary, Secondary and Tertiary/Exploratory); the complexity of the analytical method (Definitive/Relative/Quasi Quantitative or Qualitative), where the research is to be reported, the type of decisions to be made based on the data generated (affecting patient treatment or advisory to drug development), available funding, resources/expertise and any contractual sponsor requirements. What this means for the laboratory, with regard to the scope of subsequent analytical method validation, requires interpretation. Is full characterisation and validation of the method required? Does the work have to be conducted within the confines of a quality management system?

This poster considers these factors and puts forward a proposal to stratify subsequent validation and regulatory oversight efforts to provide a standardised, appropriate and justified level of rigour to be applied within the research or GCP regulated laboratory.

16: Southampton Experimental Cancer Medicine Centre: the translational laboratory

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The translational laboratory of Southampton ECMC works in close collaboration with the Centre for Drug Development (CDD), the Southampton Clinical Trial Unit (SCTU) but also with commercial partners to run first-in-human to phase I/II clinical trials. Based in the Wessex Investigational Science Hub (WISH) Laboratory, our roles involve setting up the laboratory side of clinical trials which include multi-centre trial setup, assay validation and endpoint assays under a QA management system.

With years of experience running clinical trials in immunotherapy, we offer a wide range of validated immunomonitoring assays. These include ELISA based assays such as pharmacokinetics assays, anti-drug antibody assays (HAHA, HACA ELISAs); T-cell ELISPOT; flow cytometry based assays such as phenotyping, tetramer assays, intra-cellular staining, cell sorting for downstream –omics applications; and multianalyte assays (for example Luminex).

We also have pathology expertise in characterising immune response compartments in paraffin-embedded and fresh tumour tissue. We use cytometry, multicolour immunochemistry, RNA *in situ hybridisation*, and gene arrays, to translate complex transcriptomic molecular signatures into simpler tests for immune cell phenotyping, and identification of immune escape pathways. As a centre in

CRUKs Digital Pathology Accelerator Network we use digital pathology and image analysis morphometry approaches to map the immune response within tumour tissue.

We develop, validate and then run specific assays required for a given clinical trial. Here we present some examples of what the Southampton ECMC translational laboratory can offer.

17: The UCL ECMC GCLP Facility

Leah Ensell, Helen Lowe, Nasir G Mahmoud, Yashma Pathak, Victoria J Spanswick, Arran Speirs and John Hartley
University College London Cancer Institute ECMC Centre

The UCL ECMC GCLP Facility is a standalone facility with restricted access, located on the ground floor of the UCL Cancer Institute, specifically designed for the purpose of clinical trial sample analysis. The Facility operates to the principles of GCLP in order to ensure sample analysis for clinical trials is carried out in accordance with the current regulations, from translational experiments, through method development and validation, to clinical trial sample analysis.

The Facility is aligned with a large sample processing laboratory in the UCL Clinical Research Facility and with a smaller sample processing laboratory within the UCLH Macmillan Cancer Centre, enabling ease of transfer of clinical trial samples between laboratories. The GCLP Facility comprises several laboratories, including a sample handling laboratory for the receipt and processing of patient samples obtained externally to UCL, a dedicated PCR laboratory, a microscopy darkroom, a laboratory for handling samples containing radioisotopes, and the main analytical laboratory. The GCLP Facility also has a dedicated sample storage area consisting of -80^0C freezers, -20^0C freezers, $2 - 8^0$C fridges and storage for FFPE tissue blocks, megablocks and slides, all of which are temperature monitored and managed by the Freezerworks sample management software.

We perform pharmacokinetic and pharmacodynamic analyses and the UCL ECMC specialises in the analysis of DNA damage and repair mechanisms and DNA damage response, including the single cell gel electrophoresis assay (comet), and gamma H2AX and RAD51 foci induction. Another ECMC research focus is circulating tumour cell (CTC) analysis, for which purpose we have a dedicated CELLSEARCH® system in the Facility. Additionally, the UCL Cancer Institute Single Cell Research Laboratory is situated adjacent to the GCLP Facility, and is equipped with DEPArray™, Parsortix and Nanowire technologies for further analysis of CTCs.

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ANGLE's Parsortix system uses microfluidic technology to capture circulating tumor cells (CTCs) from blood. CTCs are considered to represent the solid malignancy at the primary or the secondary sites and, therefore, have the potential to provide an easily accessible substitute for a solid biopsy. This "liquid biopsy" enables genetic and protein analysis of the patient's cancer and has the potential to direct optimal therapy – an important step towards personalised cancer care.

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