MRC Stratified Medicine Call
Outline Applications invited to Full Stage

Following the outline meeting of the Stratified Medicine Expert Review Panel (Annex 1) on 6th February, we have invited 15 applications to apply to our Full Stage meeting, which will take place on 2nd November 2017. The deadline for the Full Stage Applications is the 22nd June 2017.

Lead Applicant	Institution	Consortium Title
Professor Christian Ottensmeier	University of Southampton	Developing immune stratification for cancer (DISCovery)
Dr Damian Mole	University of Edinburgh	APPreSci Consortium: Acute Pancreatitis Precision Science
Professor Colin Berry	University of Glasgow	STRATified MEDicine of patients with chest pain due to disorders of Coronary vascular function (STRAT-MED-C)
Professor Martin Wilkins	Imperial College London	Exploiting Molecular PATHwaYs of Pulmonary Arterial Hypertension (EMPATHY-PAH)
Professor Moin Saleem	Bristol University	NURTuRE – changing the landscape of renal medicine to foster a unified approach to stratified medicine
Professor Julia Newton-Bishop	University of Leeds	Circulating (blood) and tumour derived predictive biomarkers for immunotherapies in melanoma
Professor Robert Brown	Imperial College London	Stratification based precision of Treatment for Ovarian Cancer (StraTrOC)
Professor Mark Emberton	University College London	Re-IMAGINE: correcting five decades of error through enabling image-based risk stratification of localised prostate cancer
Professor David Cunningham	Institute of Cancer Research	Therapy stratification in early stage and advanced Gastro-Oesophageal Adenocarcinoma (GOA-Consortium)
Professor David Jones	Newcastle University	Precision Medicine in Autoimmune Liver Disease (UK-AILD)
Professor Adilia Warris	University of Aberdeen	Stratification of Aspergillus disease in paediatric and adult CF patients to enable targeted treatment and improve clinical outcomes (ASperCF)
Professor Anthony Schapira	University College London	Glucocerebrosidase mutations define a subgroup of Parkinson disease for therapeutic targeting to slow disease progression
Professor Tonia Vincent	University of Oxford	Synovial fluid to define molecular Endotypes by Unbiased Proteomics in OA (STEp-UP OA)
Professor Mark Thursz	Imperial College London	Minimising mortality from alcoholic hepatitis
Professor Lucy Wedderburn	University College London	Childhood arthritis and its associated uveitis: stratification through endotypes and mechanism to deliver benefit; the CLUSTER consortium

Successful applicants are now in a consortium building phase to allow them to bring together the community (academic, industry, clinical, patient) in order to build and strengthen the team. Groups with aligned research interests can find abstracts and contact details at Annex 2.

Annex 1 – Stratified Medicine Expert Review Panel Membership

Chair – Professor Andrew Morris, University of Edinburgh

Professor Nick Lemoine, Queen Mary University of London
Professor Richard Kennedy, Queen's University Belfast (and Almac)
Dr Mike Barnes, Queen Mary University of London
Professor Moira Whyte, University of Edinburgh
Professor Ellie Barnes, University of Oxford
Professor Sadaf Farooqi, University of Cambridge
Professor Chris Griffiths, University of Manchester
Professor Elaine Holmes, Imperial College London
Professor Chris Holmes, University of Oxford
Dr Rosemary Barber, University of Sheffield
Dr Duncan McHale, UCB
Professor Andrew Mellor, Newcastle University
Professor Sir Munir Pirmohamed, University of Liverpool
Professor Simon Hollingsworth, AstraZeneca
Professor Anne Barton, University of Manchester
Professor Caroline Savage, GlaxoSmithKline
Professor Richard Coward, University of Bristol
Professor Sir Nilesh Samani, University of Leicester and British Heart Foundation
Professor Thomas Jaki, University of Lancaster
Professor Edward Holmes, The Agency for Science, Technology and Research (A*STAR), Singapore
Professor Max Parmar, University College London
Professor Kim Graham, Cardiff University

Annex 2 – Successful Outline Abstracts and Contact Details

Professor Christian Ottensmeier
Developing immune stratification for cancer (DISCovery)

Abstract

Immunotherapies targeting PD1/PDL1 and CTLA4 offer unprecedented long-term survival in in up to 50% of cancer patients. These drugs boost a pre-existing anti-tumour immune response by awakening paralyzed T-cells. The immunohistochemical confirmation of this response is presence of tumour infiltrating T-cells (TIL). These predict for outcome across cancer types, emphasizing the link between anti-tumour immunity and survival even in patients receiving standard-of-care therapies.

We hypothesise that stratifying patients by defining the features of immune attack and immune escape - in the cancer tissue - will predict clinical outcome. This will shape patient-specific treatment by directing choice of immuno- and other therapies.

In 2014 we formed a consortium to develop prognostic and predictive immune stratifiers in head and neck squamous cell carcinomas (HNSCC) and non-small cell lung cancers (NSCLC). In newly presenting disease, prior to any intervention, we linked gene expression to microscopic and clinical data. Compared to CD8 T-cells in non-cancerous tissue, CD8 Tumour infiltrating lymphocytes (CD8-TIL) use a set of ~1400 distinct genes which link to patient survival. While patients with TILhigh tumours have a good outlook, we refined stratification by showing that tissue resident memory cells, TRM (CD103+), are critical: patients with TRMhigh lung cancer have excellent survival (60% reduction in mortality) compared to those with TRMlow tumours.

In TILlow cancers immune evasion through abundant cancer-associated fibroblasts or upregulated glucose metabolism predict for poor outcome consistently in both HNSCC and NSCLC. Intriguingly, in an animal preclinical model of cancer (HPV+ TC1 model) TILlow tumours can become TILhigh after vaccination, and at a molecular level these converted tumors now look like TILhigh human cancers. Vaccination may therefore offer a solution for activating immune attack in TILlow cancers.

We are now in a unique position to stratify patients with HNSCC and NSCLC according to molecular immune characteristics. By extending the transcriptomic characterization to banked, frozen tissue from 595 patients (200 HNSCC, 300 early, 95 advanced NSCLC in 2 NIHR portfolio studies) we will confirm and refine our stratification in cohorts, where we have full access to clinical annotations and formalin-fixed, paraffin-embedded (FFPE) tissue for immunohistochemical or in situ hybridisation studies.

To develop a molecular test that is deliverable within the NHS, we will collaborate with Affymetrix to assess which aspects of the predictive RNA signatures are retained in FFPE material and, as we have shown for CD103, S100 and GLUT1, aim to reduce complex predictors to immunohistochemical or in situ hybridization assays. We will validate emerging biomarkers in large unselected cohorts (~1000 HNSCC, ~1000 NSCLC).

We will apply our tools prospectively to two funded HNSCC multicenter trials, testing how immune signatures at baseline predict for treatment outcome of conventional therapy (240 patients in 'Pathos' HNSCC, Jones, Evans) or following the addition of immunotherapy with anti-PD1 (120 patients; Sacko, Forster & Bristol Myers Squibb).

In NSCLC, where adjuvant immunotherapy is not yet standard, we will vaccinate against tumour antigens using a state-of-the-art RNA vaccine (BionNtech). By randomizing to vaccination early, vs vaccination at recurrence, we will test whether a) vaccination in high risk (CD103 TILlow) patients delays recurrence, b) vaccination at recurrence leads to clinical benefit c) vaccination turns immunologically 'cold' tumours into immune-cell rich cancers. We will map responses onto the different molecular 'cold' subgroups.

In summary, having identified shared features of immune attack and escape in two common solid cancers, we will use molecular stratification to predict outcome and build the tools for making rational treatment choices in cancer immunotherapy.

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Dr Damian Mole
APPreSci Consortium: Acute Pancreatitis Precision Science

Abstract

We are doing this research to improve the health of people who get a disease called acute pancreatitis. Acute pancreatitis is sudden, painful inflammation of an organ in the body called the pancreas. The pancreas is part of the digestive system, and its main job is to control digestion of food that we eat, so that the body can make full use of the nutrients. When the pancreas goes wrong it can be disastrous for that person and their family. For reasons that we don't entirely understand, the damaged pancreas triggers the immune system to become harmful, and that may result in damage to other organs, for example the lungs and kidneys. If that happens (which occurs about 1 in 4 attacks of pancreatitis), that person can need treatment in intensive care. At the moment, we don't have any specific treatments for acute pancreatitis.

We have put together a team of world experts across lots of difference areas of science to try and understand how the pancreas can cause so much damage. Using high-powered computing, and advanced scientific techniques, we are going to look at how all the genes and the proteins and the various chemicals in the body are working together to cause organ damage. An important part of what we are doing is measuring how people with acute pancreatitis pass through the different stages of their illness, from getting worse to getting better again, and then seeing if we can predict those patterns using a single blood test. Another part of our team is made up from scientists from the pharmaceutical industry, who will be able to make better and safer medicines for pancreatitis and design better clinical trials based on our work together.

If our research is successful, we will have taken a major leap forward to improve the lives of people with acute pancreatitis.

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Professor Colin Berry
STRATified MEDicine of patients with chest pain due to disorders of Coronary vascular function (STRAT-MED-C)

Abstract

According to the British Heart Foundation, more than 2.3 million people in the UK have ischaemic heart disease. Each year, 188,000 people experience a heart attack (1 every 3 mins), and more than 240,000 invasive coronary procedures are performed in NHS hospitals. Angina is a form of chest pain that is due to a lack of blood to the heart muscle. Angina is typically triggered by stress and exertion. The diagnosis of angina is usually focused on imaging blockages in the heart arteries, with linked treatments including drugs, stents or bypass surgery. However, nearly half of all invasive coronary angiograms that are performed in patients with angina do not reveal any blockages, leaving health problems in thousands of patients unexplained, mis-diagnosed and under-treated. Many of these patients may have symptoms due to narrowings in the very small micro vessels (too small to be seen on an angiogram).

This research aims to determine whether routine tests of small vessel function in the heart might help detect sub-groups of patients with angina. This stratified and personalised approach will get the right drug to the right patient at the right time. Our research will investigate the mechanisms of small vessel disease in the heart and related systemic disorders e.g. hypertension. A candidate disease mechanism is dysregulation of endothelin which is a hormone that causes blood vessels to tighten (the most potent constrictor hormone in humans). An increase in endothelin in the heart arteries will cause micro/macrovessel spasm, reducing the supply of blood to the heart muscle, leading to chest pain, heart attack and even death.

RATIONALE: To diagnose and stratify sub-groups of patients with known or suspected ischaemic heart disease, an important public health problem of unmet need, and use underpinning state-of-the-art interdisciplinary research for stratified medicine (diagnosis and treatment) in order to bring health and economic benefits to patients, the NHS, and society as a whole.

STRAT-MED-C: 5 distinct but inter-related workpackages are proposed in one multidisciplinary consortium. The workstrands will be led by international experts in academia, industry and the NHS. Patient groups will have key roles in design, oversight and public engagement. We will secure additional future funding to expand the deliverables and extend the lifetime of partnerships beyond 5 years.

Our stratified medicine goals are the outcomes from the 5 workpackages, including (1) results from the CorMicA phase 2 multicentre trial & Cor-Med cohort study; (2) new mechanisms in small blood vessel disease; (3) optimisation and validation of novel imaging tests for small vessel disease in the heart. We will also exploit mathematics for computed heart modelling with imaging in order to predict responses to drug therapy (www.softmech.org); (4) novel blood tests for molecular 'signatures' in patients with stable chest pain, and (5) new therapies including repurposing of existing medicines and new drugs. The health economic analysis is a prioritised objective. We are leading the DalGenE trial in the UK. This trial involves gene-testing patients who have had a recent heart attack in order to identify sub-groups who might benefit from a novel cholesterol modifying drug, dalcetrapib, as compared with placebo. The genotype-based stratification may avoid hypertension and related adverse events associated with dalcetrapib. DalGenE is the first clinical trial of gene-testing to stratify medicine in patients with vascular disease.

STRAT-MED-C will enable major advances in the understanding of the mechanisms of small blood disease in the heart, leading to new, clinically useful, stratified approaches for patients with ischaemic heart disease. STRAT-MED-C will deliver underpinning science, new diagnostics (imaging & molecular pathology), and novel therapies that will bring direct benefits to patients and the NHS, informed by health economic evaluations.

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Professor Martin Wilkins
Exploiting Molecular PATHwaYs of Pulmonary Arterial Hypertension (EMPATHY-PAH)

Abstract

Pulmonary arterial hypertension (PAH) is a rare disease that affects the blood vessels of the lungs. The vessels that take blood from the right side of the heart to the left side become narrow and stiff, putting an increased pressure on the heart. Patients die prematurely of heart failure. The disease has a silent onset until it is well advanced and so patients present to doctors late with advanced disease. They present with breathlessness and fainting. It can occur at any age but the most common age of presentation is in middle age. Women are more often affected than men. It can present as an isolated disease or as a complication of other diseases, such as rheumatic diseases. The options for treatment are limited to 4 types of drugs which try to relax blood vessels to take the pressure off the heart. They help but they do not stop the disease and about a third of patients die within 5 years of diagnosis.

All patients with PAH are treated the same way, but not all patients are alike. This programme of work will look at the different genes and types of molecules, such as circulating proteins, which are associated with PAH in great detail. The aim is to find groups of people that are more alike and see what types of genes and molecules these smaller patient groups have in common. We will then use this 'signature' to identify particular patients for specific treatments.

We have put together a consortium that includes all the specialist centres for the treatment of pulmonary hypertension in the UK. These centres have spoken to a large group of patients who have already volunteered to take part and, working with the Pulmonary Hypertension Patients Association, we are keen to recruit more. Patients volunteer to have their medical details recorded on an electronic database, to give blood for DNA sequencing and detailed biochemical studies, and be willing to be called if further research questions arise or there is a clinical trial that they might like to participate in. Their DNA is analysed for gene variation and their blood for differences in levels of proteins and other molecules. All this information is then put together with the details of the disease as described by patients and their physicians. We have already found some genes that are associated with the disease and we intend to work with the pharmaceutical industry to develop and trial medicines specifically for patients with PAH with those genes. We expect to find more genes and more ways of telling patients apart. We will also use measurements of proteins in blood to help develop a blood test that allows doctors to work out how unwell a patient is and how well they are responding to treatment, and reduce the need for more intrusive tests such as cardiac catheterisation and heart scans.

We expect this research to change the way patients with PAH are treated. Instead of selecting one or in some cases two or three drugs on the basis of "try and see", we expect to be able to work out what type of PAH a patient has and prescribe the right drug at the right dose for them. This will help patients get better more quickly and reduce the need for hospital visits and admission.

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Professor Moin Saleem
NURTuRE – changing the landscape of renal medicine to foster a unified approach to stratified medicine

Abstract

Renal disease is complex and chronic with variable phases of activity, resulting in advances in therapies being slow and difficult to introduce systematically. We have implemented a sustainable national infrastructure, NURTuRE (National Unified Renal Translational Research Enterprise), kick-start funded by an industry consortium partnership (£2.05M) to ultimately allow comprehensive recruitment of any patient with kidney disease to participate in research lifelong. This establishes a national network of research nurses to recruit patients into two pilot cohorts of kidney disease (1) a common renal condition (chronic kidney disease, CKD) and (2) a rarer disease (idiopathic nephrotic syndrome, INS); held within a comprehensive registry. We will recruit 3000 CKD and 1000 INS patients over 2 years. This proposal will establish a unique analyzed dataset from those cohorts, combining detailed temporal clinical and routine biochemical data, together with meticulous biosample analysis to achieve a paradigm shift in mechanism-based stratification.

Chronic kidney disease (CKD). There are currently no robust methods to identify patients most likey to respond to a particular therapy or accurate predictors of CKD progression. We hypothesize that we can characterise the dominant mechanism of progressive loss of function across a broad range of CKD aetiologies using known and newly discovered biomarkers, and align these to rates of progression: AIM CKD1: Identifying patients with progressive versus stable CKD across a broad range of aetiologies. GFR slopes will be calculated using a minimum of 5 values obtained within 12 months before and after recruitment. Plasma proteomic signatures will be assessed in relation to rate of progression. AIM CKD2: stratifying patients into endotypes according to the dominant mechanisms of progression, based upon deep quantitative analysis of kidney biopsies (in 20% of patients) and a panel of serum, plasma and urinary biomarkers of fibrosis and inflammation. This biopsy sub-group will also have a comprehensive 'omic' signature developed that will provide mechanistic insights via a systems biology approach. AIM CKD3: Determining whether the biomarker and 'omic' signatures of progression can be applied to predict progression in non-biopsied patients within NURTuRE CKD. AIM CKD4: The prognostic value of the above signatures will be validated in a historic single centre cohort of CKD patients (Salford Kidney Study) that has extensive clinical follow-up. AIM CKD 5: The datasets, progression signatures and biorepository will be made available for industry and academic collaboration to help develop new renoprotective drugs and establish focused and appropriately stratified clinical trials.

Idiopathic Nephrotic Syndrome (INS) is a rare chronic disease frequently with poor outcomes, currently classified according to observational response to steroids, with no mechanistic insight. We will exploit exciting biological advances in understanding of the target cell, the podocyte, to re-classify the disease into monogenic and 'circulating factor' disease (CFD), and further sub-group the latter by genomic and transcriptomic approaches on circulating immune cells and their effect on cultured podocytes. The cohort is established and will be substantially expanded in this project.

AIM INS1: Genotyping/Bioinformatics: Via the NIHR BRIDGE consortium whole genome sequencing will be carried out on the cohort to allow seamless bioinformatic analysis of the complete disease spectrum. AIM INS2: Stratify for CFD by (i) transcriptomics analysis on circulating immune cells at different stages of disease, (ii) in vitro podocyte based biomarker assays, utilising patient plasma at relapse/remission disease stages. AIM INS3: Trial Design. Establish staged stratification by genetics, clinical phenotype and key pathway biomarkers, initially to identify patients for 2 trials of monoclonal antibody drugs for mechanistic pathway targeting.

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Professor Julia Newton-Bishop
Circulating (blood) and tumour derived predictive biomarkers for immunotherapies in melanoma

Abstract

Melanoma continues to increase in incidence but considerable progress has been made in extending life for people with advanced melanoma using drugs which boost the patient's immune responses to cancer. These drugs are known as checkpoint therapies. They are currently believed to be very effective in securing long term benefit in about 30% of people with advanced melanoma. They do however have many side effects and it is hoped that in the future we will find tests which predict which people would benefit from the drugs so that we can avoid side effects in those who might benefit more from another type of treatment. Even in those people who do very well on the checkpoint therapies we need a means of testing to determine whether one or two drugs are needed. At the moment most patients are given two drugs, and if we could predict which patients do not need both then severe drug reactions could be prevented in 39% of that group.

Response to these drugs which block "checkpoint molecules" is reported to be better in those people whose cancer cells have more DNA damage, and make a particular protein called PDL1. Two additional blood tests are also being explored in order to better predict benefit from these drugs so that the choice of drug can be best tailored to the patient. These measure a number of proteins in the blood and the range of immune cells in the blood respectively. The consortium we have formed to work on finding efficient tests, predicts that no one test is likely to predict responses sufficiently well: that a combination of tests will be necessary. This application therefore describes an assessment of the two blood tests described above and an examination of the stored melanoma samples to see if there is the protein PDL1, as predictors of response to checkpoint therapies. We will look at the tests individually and then combine to see if a combination proves to predict response better.

We will also explore novel tests: looking at a blood test to measure the damage in DNA circulating in the blood, and we will also look at the genes expressed in the blood and tumour cells. For the person undergoing treatment with checkpoint therapies this would mean blood tests but the test on the tumour would use tissue already stored in the NHS. We will use sophisticated genetic tests which look at the expression of thousands of genes and we will use computer analysis to work out what the gene expression tells us about the tumour and the immune responses occurring against that tumour. The consortium argues that checkpoint therapies are evolving very quickly and in 5 years there may be more drugs available so that complex tests based upon gene expression are more likely to predict response than the more simple tests that have been tried so far.

Although it has so far proved difficult to identify effective tests to predict benefit from drugs generally, the consortium is confident that the study design for this project will be successful. The study is large, uses multiple tests to accommodate failure of some. It uses optimal technologies and the tests are based upon biological knowledge. Identifying the tests which predict response is a critical step towards enabling patients to access the best treatment for themselves.

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Professor Robert Brown
Stratification based precision of Treatment for Ovarian Cancer (StraTrOC)

Abstract

Epithelial ovarian cancer (EOC) is a heterogeneous disease, with different histological, phenotypic and molecular subtypes associated with different clinical outcomes. Patients frequently present with advanced disease associated with a five-year survival of less than 20%. Surgery followed by platinum-based chemotherapy is the cornerstone of treatment. Although over 80% of patients respond to treatment, the majority relapse with disease that will eventually acquire resistance to chemotherapy. Despite an increasing range of molecularly targeted therapies showing clinical activity, survival of ovarian cancer patients has shown limited improvement over the last 40 years.

Consortium members have identified key prognostic mechanisms associated with response to treatment in EOC. These include gene amplification of cell cycle genes, DNA methylation including at WNT and, DNA repair pathway genes, metabolites associated with ketone/organic-acid production and immune checkpoint molecules including PD1/PD-L1. With the exception of BRCA mutations for PARP inhibitors, there are few actionable mutations in EOC.

The vision of the STRATROC consortium is to further integrate, using a systems oncology approach, these function and mechanism related pathways into stratification biomarkers, together with cutting edge imaging, innovation in surgical technology and molecularly targeted/immunological therapies to deliver stratified clinical trials of EOC.

There are no reliable pre-surgical methods for diagnosis or prognosis of EOC. This results in many women undergoing unnecessary surgery for benign disease, with both patient risk and health economic implications. In addition, many women with ovarian cancer present with extensive disease that cannot be completely removed surgically and therefore are more suitable for neo-adjuvant chemotherapy. Even for patients who have complete resection of disease and adjuvant chemotherapy, 20% will recur within 12 months of treatment. This poor prognosis group are important to target with innovative novel treatment strategies. Improved early diagnosis, accurate assessment of the tumour and prediction of prognosis in patients pre-surgery and through treatment would allow personalised surgical management and treatment stratification.

We will evaluate highly sensitive and specific biomarker technologies from academic and commercial collaborators, computational approaches to data integration and emerging mechanistic discoveries to improve early diagnosis, prognosis and surgical/chemotherapy outcomes of EOC linked to ongoing NIHR clinical trials evaluating novel imaging approaches and NCRI/SGCTG cohort studies with mature, high quality survival data. We will focus on copy number variation (CNV), DNA methylation, and immunological markers. Further, through the MRC/NIHR National Phenome Centre potential diagnostic and prognostic metabolites in serum from EOC patients have been identified.

Changes in circulating tumour DNA, metabolites and proteins in plasma/serum provide accessible surrogates for changes in tumour and source of biomarkers for patient stratification following chemotherapy and throughout the patient journey. Indeed, for some biomarkers it is the post-treatment level that is clinically informative. As well as analysing tumours at presentation, sampling of blood longitudinally through treatment and during remission will be examined for association with the primary tumour, imaging endpoints, and treatment outcomes.

Earlier and more accurate diagnosis of EOC patients will lead to more timely treatment choices and improved survival: less extensive surgery for those women with benign/borderline conditions and better planned surgery, as well as targeted treatments, for those with malignant disease. An integrated systems oncology approach that can be readily visualised by clinicians and patients will improve the stratification and precision of treatment for ovarian cancer patients.

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Professor Mark Emberton

Re-IMAGINE: correcting five decades of error through enabling image-based risk stratification of localised prostate cancer

Abstract

Risk stratification for early prostate cancer (PCa) has failed, badly: For the last 50 years we have been applying PSA-Biopsy risk-stratification (PSA triage; prostate biopsy verification) to men at risk of PCa and we now know that it is unfit for purpose. It results in the following stratification errors: unnecessary biopsies, over-diagnosis, over-treatment, and at least 50% of clinically significant cancers are missed (Esserman 2014; Ahmed 2016; Shaw 2014).

The implications are widespread: This systematic error has biased our tissue archives, skewed our risk calculators, rendered our trials un-representative and will have undermined policy-making. The perfect risk-stratification tool for PCa would identify a stratum of men that, if left untreated, would likely experience a negative impact on their quality or quantity of life. The ProtecT trial recently reported an optimal application of PSA-Biopsy in the UK. The result was a stratum of such low overall risk (1% risk of PCa death at 10 years) that active treatment failed to show benefit over conservative management (Hamdy 2016). In contrast, the pre-PSA SPCG-4 trial reported a 20% chance of PCa death if untreated, and treatment conferred both a disease-specific and overall survival benefit (Bill-Axelson 2014).

A solution based on imaging: Our PROMIS trial has shown that magnetic resonance imaging (MRI) provides almost complete correction for each error associated with PSA-Biopsy by identifying a distinct stratum from the wider population at risk that is closely correlated to the two strongest progression predictors - grade and volume (Ahmed 2016). This suggests that imaging, more specifically an MRI of the prostate can derive a novel, clinically meaningful disease prediction model that exhibits little overlap with the stratum derived by PSA-Biopsy.

Due to the error associated with PSA-Biopsy, mathematical models to predict PCa risk from existing data won't solve the problem, as about 50% of clinically important disease is not represented. The findings would be biased due to the poor reliability of PSA-Biopsy.

Our aim is
To establish a novel, image-based, measurable-disease prediction model and to use it to risk stratify men with PCa.

Our objectives
1. To create a UK network of hospitals that will establish the world's first selection of patients who are identified through a measurable, MRI-derived characteristic. This cohort will be evaluated in high detail using information from tissue, blood, urine, semen and clinical follow-up.

2. To use sequential imaging of men with cancers of indeterminate risk to discriminate a sub-group of men with image-based progression from those who do not.

3. To determine risk stratification errors conferred by PSA alone as an initial triage test by inviting a randomly selected, population-based group of men to MRI risk stratification, who have not been exposed to PSA testing previously

4. To derive the image-based signature through machine learning on the best-characterised cohort to date [PROMIS (n=573)] to develop and apply non-invasive, automated, risk-stratification tools.

5. To link formally with advanced PCa cohorts (e.g STRATOSPHERE Consortium) to determine the shared genetics between two disease entities (low risk versus metastatic PCa) that have traditionally been studied in isolation.

6. To work with patient groups/representatives through ecancer to inform design, conduct and communication of all aspects of our work.

Impact
The result will be a complete re-conceptualisation of the way we describe, stratify, understand and communicate early PCa risk to our patients. Our new stratification tool will correct nearly all errors of current standard of care and prepare the way for future comparative effectiveness studies.

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Professor David Cunningham
Therapy stratification in early stage and advanced Gastro-Oesophageal Adenocarcinoma (GOA-Consortium)

Abstract

Gastro-oesophageal carcinoma is the 2nd commonest cause of cancer related death worldwide (>1.1 Mio deaths/y). Most tumours are adenocarcinomas (gastro-oesophageal adenocarcinoma:GOA) and their prevalence is increasing in Western countries. Early stage GOAs are treated using surgery with chemo- or chemoradiotherapy. This is associated with major complications and reduced quality of life but 50-60% of patients still die of their disease. Treatment options for advanced GOAs are confined to chemotherapy combined with a limited number of targeted drugs and 5 year survival remains <5%. The lack of treatment stratification biomarkers leads to overtreatment with ineffective therapies, unnecessary toxicities and costs. Failure to understand the molecular basis of therapeutic resistance hinders the development of more effective drugs. Genomic analyses undertaken by us and others identified distinct GOA endotypes, including chromosomally unstable, microsatellite unstable and genomically stable subtypes, mutagenic tumours and those displaying DNA damage and repair deficiencies. Pre-clinical analyses suggest that several endotypes confer distinct treatment sensitivities. Immunogenic GOA subtypes are suspected based on recent trials showing responses to PD1/PDL1 immune checkpoint targeting antibodies in ~15% of GOAs. We have identified mutation/neoantigen loads as candidate markers of immunogenicity and this requires validation in immunotherapy trials.

Taken together, GOA is a cancer type of major unmet clinical need and the discovery of genetic endotypes with distinct therapeutic vulnerabilities suggests major potential to improve treatment success through genomic stratification. Several trials of targeted drugs recently failed to improve outcomes and intratumour heterogeneity (ITH) and the use of single genetic biomarker assays in these tumours, which are characterized by complex genomes, contributed to these failures. For example, we showed that FGFR inhibitors only achieved high response rates in GOAs with clonally dominant FGFR2 amplifications but not in tumours with subclonal amplifications. Thus, ITH and broad assessment of genotypes need to be central considerations in stratification efforts.

To address these challenges, we assembled a multi-disciplinary consortium, building on the outstanding UK GOA research network and the infrastructure of our internationally leading efforts to characterize GOA genomes. Our consortium will demonstrate the clinical relevance of genomic strata in large trials of standard therapies and in innovative trials using immunotherapy and targeted drugs. Yet undiscovered GOA subtypes will be identified in parallel through genome sequencing and will also be validated in these trials. Our coordinated effort will define predictive endotype markers to rationally allocate established treatments (chemotherapy, radiotherapy and surgery), immunotherapy and novel drugs identified through our work. In collaboration with biotechs, we will apply circulating tumour DNA, heterogeneity metrics and single cell sequencing to develop approaches that mitigate the impact of ITH. Concurrently, we will assess the potential of proteomic and multiparametric immune cell profiling to complement genetic analyses.

These data will inform the design of focused next generation sequencing and complementary molecular stratifiers that can be applied to diagnostic samples in the NHS. Discovery of new therapeutics for strata that do not benefit from existing therapies will be driven through big data approaches and functional analyses in patient derived organoid cultures. The initiation of clinical trials that validate our stratification technology and the benefit of targeting identified therapeutic vulnerabilities in partnership with pharma is integral to the proposal. Finally, we will define the health economic impact and optimal integration of molecular stratifiers into routine care to assure pull through into clinical practice.

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Professor David Jones
Precision Medicine in Autoimmune Liver Disease (UK-AILD)

Abstract

The autoimmune liver diseases (AILD) are a family of liver conditions that cause progressive liver injury culminating in cirrhosis, liver failure and death, as well as symptoms such as fatigue. AILD therefore both shortens life and reduces its quality. Conventionally, AILD is classified into 3 conditions: primary biliary cholangitis (PBC), autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC). "Overlap" or "Cross-Over" syndromes are also recognised, in which immunologic, histologic and radiologic features of two conditions are seen. Treatment for AILD in general remains inadequate: there is no effective pharmacotherapy for PSC and although AIH may respond to conventional immunesuppression many young patients have disease which is either treatment unresponsive or requires a high dose of steroids which they may find unacceptable. Furthermore, there is no established approach to the treatment of the overlap/crossover syndromes. The exception to this picture is PBC where, over the last 5 years, there has been a substantial improvement in risk-stratification of the disease, introduction of novel, second-line therapy for high-risk PBC into practice, and emergence of a robust pipeline of other agents. This has been driven in large part by the UK-PBC programme, precursor to the current proposal and funded by an MRC Stratified Medicine award, which was centred round a mechanistic re-classification of high-risk disease. Our vision is to now extend this transformation in treatment to all AILD.

Drug development for AILD is hampered by inadequate fundamental mechanistic understanding of disease, attributable in part to the current system of disease classification. Emerging data suggest that AILD in fact represents a spectrum of innumerable, overlapping phenotypes, with 'pure' PBC, 'pure' PSC and 'pure' AIH being points along this spectrum rather than distinct diseases. Our hypothesis is that each overlapping phenotype is determined by the relative activity of limited pathological mechanisms, the expression of which is a composite of genetic, epigenetic and environmental forces. Our vision is to characterise the dominant pathological mechanisms that underpin the AILD spectrum. This will enable: (1) mechanistic re-classification of pure as well as intermediate phenotypes; (2) development of specific therapies targeting each pathological mechanism; (3) mechanistic stratification of patients with AILD, and (4) treatment regimens that are based on personalised mechanistic stratification.

To deliver this vision we will recruit treatment-naïve patients from across the spectrum of AILD who will undergo detailed clinical characterisation and provide biofluid and liver biopsy samples for deep phenotyping, including metabonomic and proteomic analysis; immunophenotyping; single-cell transcriptional profiling of circulating immune cells as well as liver parenchymal and non-parenchymal cells. We will also undertake a systematic study of symptom impact across the disease spectrum, focusing on fatigue and itch, exploring the potential mechanisms underpinning the symptoms and their interrelationship with other aspects of the disease phenotype. Using approaches from systems biology, we will look for patterns across datasets and extract latent factors that define key phenotypic features, from which disease mechanisms may be inferred.

Our programme is ultimately aimed at improving the lives of patients whose needs are not being met at present. This requires better therapies which are delivered in practice in better ways. Our approach will also need a radical rethink as to how we assess effectiveness (we are moving away from the historic model of treating a disease towards treating its components). We will work with patients, industry and regulators to develop a new way to address treatments in AILD in novel therapy trial models.

We believe that we can deliver a revolution in the treatment of all AILD.

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Professor Adilia Warris

Stratification of Aspergillus disease in paediatric and adult CF patients to enable targeted treatment and improve clinical outcomes (ASperCF)

Abstract

The fungus Aspergillus fumigatus is frequently cultured from the sputum of patients with cystic fibrosis (CF). Yet clinicians face great uncertainty as to whether Aspergillus is detrimental and if so, how to identify those patients requiring specific treatment. An improved diagnostic stratification of Aspergillus disease phenotypes in CF patients is urgently needed to understand the clinical manifestations and prognosis of these syndromes and to enable stratified targeted treatment based on a better understanding of the diverse immuno-pathology in the CF lung in the presence of A. fumigatus.

CF is the most common fatal genetically inherited disease in humans of North European extraction (~1:2,500 UK births) affecting over 10,000 people in the UK. Progressive lung damage caused by infection and inflammation is the major determinant of survival, median age of death is 28 years. Approximately 60% of all CF patients are infected with A.fumigatus and its presence is associated with reduced lung function and increased hospitalisation. Vulnerability to A.fumigatus infections persists even after lung transplantation (incidence 23%).

Estimates show that half of the patients infected with Aspergillus are < 18 years of age. Time of acquisition of this fungus and the patterns of Aspergillus disease progression from childhood to adulthood and its influence on lung function are unknown. Aspergillus disease in CF patients ranges from fungal sensitization to invasive aspergillosis. Allergic bronchopulmonary aspergillosis (ABPA) is probably the best characterized Aspergillus disease, but is only present in a minority of CF patients infected with A. fumigatus. Although clinical guidelines exist for ABPA, major knowledge gaps persist and the guidelines are criticized because of inconsistency and difficulties in defining ABPA. Treatment with corticosteroids can do more harm than good and inappropriate treatment with potentially toxic azole antifungals promotes development of azole-resistance. The proposed classification of Aspergillus disease in CF patients serves a first step to stratify CF patients but lacks an immuno-pathological underpinning.

To revolutionise management strategies for CF-related Aspergillus diseases we aim:

- To define disease-specific physiological, biometric, pathological and immunological markers of disease progression and outcome in a consortium-based detailed analysis of 250 paediatric and 500 adult CF patients
- To develop, validate, and implement, a stratification algorithm against which the differential efficacy of treatment regimens can be evaluated, thereby identifying best-practice diagnostics and therapies for improved management
- To prevent inappropriate use of antifungals and steroids, improve lung function and quality of life and reduce hospital admissions.

Our objectives are:

1. Stratification of Aspergillus disease in paediatric and adult CF patients using existing fungal diagnostic tools and correlate these with lung function and pulmonary exacerbations to identify which of the Aspergillus disease phenotypes is associated with progressive decline in lung function. The influence of environmental, genetic and patient-related factors will be determined as well.
2. Immune-profiling of paediatric and adult CF patients with and without Aspergillus disease to obtain complementary data on host-microbe interactions needed for improved stratification, identification of biomarkers for diagnostic purposes and disease severity, and discovery of new (immune)therapeutic targets.
3. Deliver molecular insight in the underlying immunopathology of Aspergillus disease in the absence of a functional CFTR protein in both immune and epithelial cells by undertaking patient-specific ex vivo immune-profiling approaches.
4. Perform stratified intervention studies with antifungals and/or immunotherapy based on specific Aspergillus disease phenotypes.

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Professor Anthony Schapira

Glucocerebrosidase mutations define a subgroup of Parkinson disease for therapeutic targeting to slow disease progression

Abstract

The lifetime risk for Parkinson disease (PD) in the UK is currently 3-4%. A delay of only 3 months in PD progression is calculated to be sufficient to cover the individual's drug treatment for their lifetime. In the EU and N. America, 10-15% of PD patients carry mutations of the glucocerebrosidase (GBA) gene. GBA mutations increase the risk for PD by 20-30 fold.

This application follows our 2013 MRC Experimental Medicine Pathfinder award entitled Glucocerebrosidase mutations in PD: molecular pathogenesis, and the basis for personalised therapy with small molecule chaperones. The outcomes of that award form the basis to the current application to provide further insight into the pathogenesis of GBA-PD and design drugs to slow PD progression. There is no overlap in resources requested between the start of this grant and the Pathfinder award.

From an asymptomatic baseline (n=100), we have shown that GBA mutation carriers exhibit clinical prodromal features that are expressed >2-3 years before the onset of the diagnosis of PD, and these can be used to define a subgroup of fast progressors towards clinical PD, constituting approximately 25% of our GBA carrier population. These individuals also express low blood glucocerebrosidase enzyme (GCase) activity and elevation of peripheral biomarkers including IL-6 and -8, IgG kappa and high alpha-synuclein levels (A-SYN).

A-SYN accumulation and aggregation are considered critical steps in the pathogenesis of PD.

In vitro cell, in vivo animal and post mortem human studies consistently demonstrate a reciprocal relationship between GCase activity and A-SYN levels; low GCase activity causes increased A-SYN, increased A-SYN causes reduced GCase activity.

Using patient-derived dopaminergic stem cells and specific mouse models of GBA mutations /A-SYN expression, this project will integrate molecular biochemical studies to define the molecular basis for the GBA-A-SYN interaction, lysosomal dysfunction and dopaminergic neurodegeneration to evaluate current, and develop novel small molecule GCase chaperones/modulators to lower A-SYN levels. In 2014 we established a partnership program with Eisai to develop and test GCase modulators.Current Eisai investment is significant,with 2 post-docs in the host laboratory.

In parallel, we will leverage a UK-wide web-based effort to recruit an additional >1000 GBA carriers for longitudinal stratification using the clinical and biochemical biomarkers defined above to establish their risk profile for PD onset. This cohort will be followed alongside the 100-member longitudinal now in the 6th year of follow up. These cohorts will provide the basis for refining the clinical and biochemical biomarker profile and form the basis for clinical trials using GCase chaperone/modulators in the GBA stratified pre-PD and PD populations.

This combined basic science and clinical approach is designed to stratify a subgroup of individuals at high risk of PD (GBA carriers) and those with PD and GBA mutations. These groups will be suitable for the clinical evaluation of novel GCase drugs that will be developed in collaboration with Eisai.The purpose of such drugs will be to modulate GCase activity and reduce A-SYN in the brain to slow the progression and spread of pathology and so modify disease progression. The clinical and biochemical markers of disease progression we have defined above can be incorporated alongside established clinical endpoints to determine efficacy.

We have demonstrated that PD patients without GBA mutations have reduced brain GCase activity, probably a consequence of A-SYN accumulation (as opposed to GBA gene mutations). We have shown that increasing GCase activity in dopaminergic stem (iPS) cells from wt-GBA PD subjects results in a decrease in A-SYN levels. Therefore we hypothesise that GCase drugs will prevent the onset of PD in those at risk and also slow the disease in patients with PD but without GBA mutations.

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Professor Tonia Vincent
Synovial fluid to define molecular Endotypes by Unbiased Proteomics in OA (STEp-UP OA)

Abstract

Osteoarthritis (OA) is the most common joint disease. The lifetime risk of developing symptomatic knee and hip OA is 45% and 25% respectively; it accounts for over 90% of knee and hip arthroplasties with a lifetime risk of 10.8% and 11.6% respectively. Its associated costs account for 1-3% of GDP. It has recently been shown to be associated with an increased risk of premature mortality. Development of disease modifying drugs in OA has been very challenging; variable rates of disease progression and variable treatment responses in patients, likely accounts for recent limited industry investment in this area. Although specific clinical features contribute to the ability to predict progression this is likely to be substantially improved by recognition of distinct molecular subtypes (endotypes) of disease.

The NIH foundation funded biomarkers study using Osteoarthritis Initiative (OAI) data has invested significantly in identifying biomarkers from systemic fluids (serum/urine) in 600 persons with and without OA with limited success. To date, no large-scale unbiased approach has been performed using synovial fluid, the tissue that is in direct contact with the damaged joint surfaces. The paucity of studies using synovial fluid is mainly due to the relative difficulty in acquiring samples. Candidate synovial fluid proteins show only weak correlation with serum levels so synovial fluid analysis is likely to be more informative.

Our consortium has a unique resource of synovial fluid from 2000 cross-sectional samples from normal individuals and OA patients. The molecular analysis will be performed by SomaLogic, using an aptamer-based platform to measure up to 4000 proteins in each sample. Their technology has been validated in synovial fluid. Data will be analysed in an agnostic manner to identify clusters based upon molecular signatures.

The principal outcome from this core work package (WS1&2) will be to discover whether different molecular endotypes exist in a heterogeneous population of individuals with established (early and late) OA.

Stratification by molecular endotype will feed into a number of other work strands to assess whether the identified molecular endotypes are measurable in serum and urine (WS3) and whether they are associated with important clinical OA phenotypes such as structural joint damage (WS4), joint inflammation (WS5) and pain (WS6). Molecular endotypes will then be validated in a large number of existing prospective cohorts and clinical trials to identify their value as predictive stratifiers of both progression and response to treatment (WS7). These studies already have outcome data so the molecular endotypes will be used to see if they add significant value to predicting outcome and perhaps identify subgroups of individuals who do particularly well or badly with a given treatment. Molecular endotypes will also be used in a number of new small prospective 'experimental medicine' style trials to test the utility of stratification by molecular endotype with new treatments (WS8a).

Finally, we will collect an early OA validation cohort with prospective synovial fluid and detailed imaging in which to check stability of molecular endotype over time and to validate their use in individuals with early stage disease (WS8b). Individuals within this cohort would join a patient-interested list for potential clinical trials.

The data arising from this initiative will be made accessible to the OA stakeholder community in full and will, we believe, be of great value to clinical, academic and industry colleagues alike.

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Professor Mark Thursz
Minimising mortality from alcoholic hepatitis

Abstract

Liver disease is the fifth most common cause of death in the UK but unlike the top four causes mortality rates are increasing and deaths from liver diseases occur at younger ages. Alcohol-related liver disease (ALD) accounts for the majority of hospital admissions and deaths. Alcoholic hepatitis (AH), which is a florid presentation characterised by jaundice and liver failure, occurs in approximately 20% of patients with ALD. We recently conducted a large multicentre trial (STOPAH) to evaluate the exiting treatments (prednisolone or pentoxifylline) for patients with AH but the results show that no specific therapy reduces mortality in AH. As a result, the James Lind Alliance, part of the National Institute for Health Research, have identified alcoholic hepatitis as a priority research area.

Patients admitted to hospital with AH are classified according to the severity of their disease using a scoring system, Maddrey's discriminant function (DF), based on simple blood tests which was devised 40 years ago. A DF score greater than 31 identified a group of patients where the risk of death is over 20% over the four weeks after admission. In the past these patients were selected for treatment whilst those a DF score less than 31 were offered no specific treatment despite the fact that the mortality was still around 6%. A new prognostic test (Lille score) has recently been developed which takes into account blood test results from the time of admission along with the initial response to prednisolone therapy. The Lille score has been used to select patients who might benefit from liver transplantation. However, patients with a bad Lille score still have a 50% chance of surviving up to 6 months which is not helpful in transplant selection. This research programme aims to improve the survival of patients with AH by 1. Increasing the accuracy of prognostic scores and risk of infection. 2. Maximising the efficacy and safety of the existing treatment, prednisolone, 3. Evaluating the efficacy of existing drugs which are currently used for other diseases, 4. Dissecting the biological processes which make inflammation persist and regeneration fail in order to find new treatment targets, 5. Stimulate further investment by pharmaceutical companies.

We need more accurate systems to select patients for treatment, for intensive care and for transplantation. In addition we need to identify patients at high risk of infection which is a devastating complication for patients with AH. In this programme of research we propose to collect data and blood samples from a large group of patients with AH. Using data from the STOPAH trial and from the new cohort of patients we will develop more accurate systems to provide prognostic information to guide patient management. We will also analyse blood and urine samples to identify DNA, proteins, metabolites or other substances which act as biomarkers to improve prognostic accuracy. Accurate tests for prognosis will encourage pharmaceutical companies to invest in AH because it will make it easier for them to design and run their clinical trials. The results of the STOPAH trial suggest that a subgroup of patients might benefit from treatment with prednisolone but in some the benefit is lost because the drug increases the risk of infection. Identification of high risk patients could make the use of prednisolone safer and more effective. For example high risk patients could be given antibiotics to prevent infection.

Research on the biological processes underlying AH suggest that two existing drugs: Canakinumab, which blocks an inflammation pathway, and Obeticholic acid, which modulates bile and lipid metabolism should potentially improve AH. These drugs will be tested in early clinical trials.

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Professor Lucy Wedderburn

Childhood arthritis and its associated uveitis: stratification through endotypes and mechanism to deliver benefit; the CLUSTER consortium

Abstract

Childhood arthritis, currently classified under an umbrella term juvenile idiopathic arthritis JIA, is the most common immune mediated paediatric rheumatological condition, prevalence 1 in 1000. Childhood arthritis, and its associated eye inflammation, JIA-uveitis, can be devastating for both child and family, and impose significant longterm economic burden on society. Despite improvements in the management of inflammatory arthritis, and increasing availability of biologic drugs, many children still undergo prolonged treatment with multiple drugs that may be ineffective, leaving them exposed to uncontrolled inflammation, treatment side effects, and long-term sequelae of disease. These include significant disability, permanent vision loss, lower quality of life and reduced chance of employment. Early control of childhood arthritis translates to better long-term outcomes and economic benefit. However, current JIA classification does not inform choice of therapy for most children, and there are no validated clinical or biological tools with which to predict disease course or outcome, select treatment or predict response. Effective strategies enabling accurate treatment stratification and mechanism-driven drug choices, would increase early remission rates, reduce suffering, improve long-term outcomes and generate economic benefit, avoiding many years of treatment with ineffective drugs.

To start to address these unmet needs, we established an MRC-funded partnership between 4 large UK JIA cohort studies, the Childhood Arthritis Response to Treatment (CHART) Consortium, representing >4800 cases of JIA, with clinical data, biological samples, and significant 'omics' data. We have aligned and harmonised these data, and leveraged support from international collaborators and Pharma partners. Building on this success, and strengthened by important new cohorts and investigators, we now propose an ambitious consortium, CLUSTER, bringing together internationally recognised leaders in childhood arthritis and JIA-uveitis to deliver stratified medicine approaches. CLUSTER will include multidisciplinary expertise in clinical, molecular, genetic, and immunological deep phenotyping, statistics, bioinformatics, and stratified medicine, UK leaders in paediatric rheumatology and ophthalmology, and those designing and delivering clinical trials in JIA and its associated uveitis.

The overall goal of CLUSTER is to define 'endotypes' (or endophenotypes) of childhood arthritis and JIA-uveitis, with associated prognostic biomarkers of treatment response and disease course, and integrate these to generate stratification algorithms to facilitate targeted treatment decisions, leading to earlier effective control of inflammation, improved outcomes, reduced exposure to side effects from ineffective therapy and longterm health care savings.

The key scientific aims of CLUSTER are to:

1. Apply novel data-driven approaches to our existing clinical and genotype data, to define endotypes, and stratify children with inflammatory arthritis (WP1);
2. Explore all available CLUSTER 'multi-omic' data, and publically available data where informative, to define and power an optimal deep-phenotyping strategy (WP2);
3. Undertake high-density molecular phenotyping, (immunome, transcriptome proteome), using biospecimens from both blood and inflamed synovial site, and those from clinical trials of biologics in uveitis, to characterise molecular mechanisms determining therapeutic response and outcomes (WP2, 3);
4. Integrate and explore all CLUSTER data to define prognostic and treatment response endotypes in arthritis and JIA-uveitis, and 'pathotypes' where a specific pathway suggests a novel treatment (WP5);
5. Establish collaborative agreements and pathways with Industry and international partners for facilitating high-quality
6. biospecimen collection and stratification design in all trials of childhood arthritis and uveitis (WP6).

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