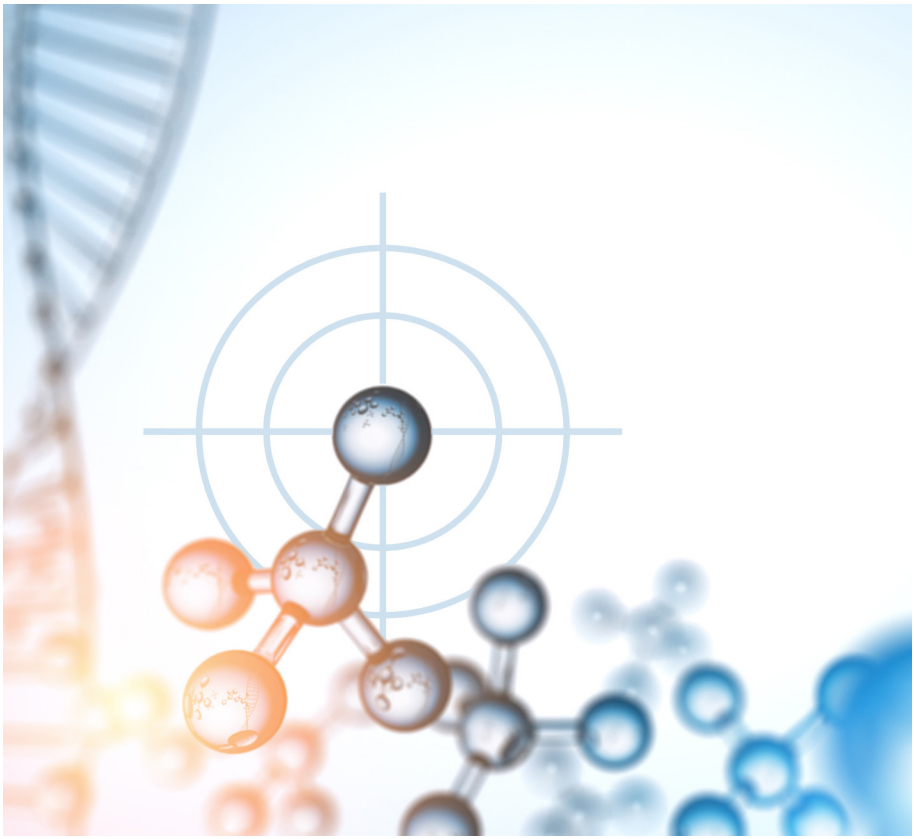
Targeted Medicine: from molecules to therapies

Chowen Lecture Theatre and Foyer, Medical Teaching Building
Brighton and Sussex Medical School
9:30am-6:30pm, Wednesday 13 March 2024



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Contents

Welcome

Welcome to the Symposium on “Targeted Medicine: from molecules to therapies”.

The purpose of this Symposium is to showcase the research being carried out at BSMS and collaborating institutions in the area of Precision Medicine. The programme comprises a wide variety of talks, ranging from life-style choices to genomics, all with the common theme of tailoring treatments to specific groups of patients. We are pleased to have talks from New Investigators as well as established Principal Investigators and have encouraged scientists as well as clinicians to give presentations. Targeted Medicine research will also be presented as posters, which can be viewed throughout the meeting. The Symposium is part of our BSMS20 Research Symposia series, celebrating 20 years of Brighton and Sussex Medical School (BSMS), and is a hybrid event.

A key aim of this meeting is to foster networking and collaborations between institutions and also between scientists and clinicians. By exchanging ideas and finding out about new techniques, we hope the meeting will facilitate collaborations plus future grant applications and publications. To promote networking, we have provided ample time during the lunch and refreshment breaks for research discussions. We have also encouraged participants to name the “molecules” as well as the “diseases/syndromes” they are researching to encourage future collaborations. This list of research topics is presented at the end of the abstract book and is striking in the diversity of molecules, diseases and syndromes covered. The event is funded by BSMS as well as our company sponsors, Brand and New England Biolabs. Please visit their trade stands for information on their products.

We hope that you enjoy the meeting!

Meeting organisers

Prof Sarah Newbury
Prof Somnath Mukhopadhyay
Ms Erika Cummings
Ms Olivia Cottingham
Ms Jemma Jones

IT support

Dr Oliver Rogoyski

Programme

Wednesday 13 March 2024: Chowen Lecture Theatre, Medical Research Building, Brighton and Sussex Medical School, University of Sussex.

9:30 - 10:00 **Registration and tea/coffee/spring cookies served in the foyer**

Session 1 Chaired by Professor Sarah Newbury

10:00-10:10 **Professor Malcolm Reed (Dean, BSMS)**
Introduction to Symposium

10:10-10:35 **Professor Alan Lehmann (Genome Damage and Stability Centre)**
Multidisciplinary clinics for DNA repair disorders: Molecular analysis directs the prognosis, management and treatment of patients with xeroderma pigmentosum (page 8)

10:35-11:00 **Professor Florian Kern (BSMS)**
The MHC Locus in Targeted Medicine (page 9)

11:00-11:25 **Dr James Price (BSMS)**
Is personalised infection prevention achievable? (page 10)

11:25-11:50 **Professor Melanie Flint (University of Brighton)**
The role of stress and glucocorticoids on the risk of breast cancer (page 11)

11:50-13:00 **Lunch and poster viewing**

Session 2 Chaired by Professor Melanie Flint

13:00-13:25 **Dr Ekow Mensah (BSMS and University Hospitals Sussex NHS Trust)**
The use of biomarkers in assessing frailty – findings from a pilot study (FRAXI) (page 12)

13:25-13:50 **Dr Elaney Youssef and Dr Tom Ruffles (BSMS and Brighton and Sussex University Hospitals NHS Trust)**
Onesizefits1 - a new way to practise children's medicine? (page 13)

13:50-14:15 **Dr Jessica Eccles (BSMS)**
Joint hypermobility: Insights from bench to bedside (page 14)

14:15-14:40 **Dr Dorina Cadar (BSMS)**
The interplay between genetic risk and lifestyle behaviours in Alzheimer's Disease (page 15)

14:40-15:20 **Tea, coffee and poster viewing**

Session 3 Chaired by Professor Somnath Mukhopadhyay

15:20-15:55 **Professor Nigel Leigh (BSMS) and Professor Majid Hafezparast (Life Sciences, University of Sussex)**
One Diagnosis, Many Diseases: Trials, Biomarkers, and Heterogeneity in Motor Neuron Disease (pages 16 and 17)

15:55-16:20 **Dr Simon Mitchell (BSMS)**
Getting the right drugs into the right patients with computational systems biology (page 18)

16:20-16:45 **Dr Maziar Bonab (Kent and Medway Medical School)**
Emerging Frontiers in Colorectal Cancer Therapy: From Targeted Molecules to Immunomodulatory Breakthroughs and Cell-Based Approaches (pages 19 and 20)

16:45-17:00 **Professor Somnath Mukhopadhyay (BSMS)**
Closing remarks

17:00-18:30 **Networking over drinks and canapes, close of meeting**

Poster presentations

Oral Presentation Abstracts

Session 1

Multidisciplinary clinics for DNA repair disorders: Molecular analysis directs the prognosis, management and treatment of patients with xeroderma pigmentosum

Alan R Lehmann[1,2] and the XP Clinical Team[2]

[1]Genome Damage and Stability Centre, University of Sussex and [2]Rare Disease Centre, Guy's and St. Thomas' NHS Foundation Trust, London

Individuals with xeroderma pigmentosum (XP) are defective in the repair of UV-induced DNA damage, resulting in extreme hypersensitivity to sunlight-induced pigmentation changes and skin cancers. 30-50% of affected individuals have associated progressive neurological abnormalities. We have been carrying out cellular diagnoses for this disorder for several decades. In 2010 a multidisciplinary specialist clinic for XP was established in London and we have now seen over 120 XP patients, representing most of the XP population in the UK. The clinical features of the UK XP cohort are unexpectedly heterogeneous and molecular analysis of the causative mutations is, in many cases, able to explain the clinical phenotypes and provides improved prognosis and management. I will present several examples of this as well as a case of an XP patient with end-stage disease from a very aggressive tumour. Whole genome sequencing of the tumour suggested that immunotherapy would be appropriate, and the patient made a dramatic recovery.

The MHC Locus in Targeted Medicine

Florian Kern, Jak Kostrzanowski and Bernhard Reus

The major histocompatibility complex (MHC) locus, or HLA locus in humans, is the most polymorphic human gene locus. MHC molecules are critical for the recognition of 'self' and 'non-self'-peptides by T-cells. Some 10% of anyone's T-cells recognise 'non-self MHC' (irrespective of the peptide presented). Representing a hurdle to organ transplantation since a recipient's immune system can destroy the transplant if there is no sufficient HLA- between recipient and graft. Stem-cell transplantation carries a double risk since graft may recognise the host's MHC as 'non-self' causing 'graft-versus-host disease'. The MHC locus is also of significant interest in vaccine development. Personalised cancer vaccines use the information obtained from sequencing entire tumours and identifying the mutated peptides most relevant and most suitable for inducing for 'private' cancer mutation-specific T-cells. These therapies target patient-specific mutations in the context of specific MHC-molecules. A topic of significant interest to our own work are HLA-disease associations that are explained by the presence of HLA-molecules (risk-alleles) able to present disease-relevant peptides that will trigger T-cell responses and tissue destruction in a proportion of risk allele carriers. Identifying disease-associated alleles and associated peptides in autoimmunity may be key to developing new targeted therapies aiming to induce T-cell tolerance.

Is Personalised Infection Prevention Achievable?

James R Price[1]

[1]Department of Global Health and Infection, Brighton and Sussex Medical School

Healthcare-associated infections (HCAI) present a persistent challenge worldwide, exacerbated by the rising threat of antimicrobial resistance (AMR). Despite extensive infection prevention and control (IPC) measures employed in healthcare settings the prevalence of HCAI remains high, necessitating a shift towards more personalised approaches to prevention. The potential of innovative technologies such as whole-genome sequencing and mathematical prediction tools maybe the key to addressing this, but clinically translations studies characterising their impact have been lacking. Until now. This session will highlight promising findings of integrating and translating novel approaches to IPC in healthcare settings, emphasising the potential impact of personalised approaches in mitigating the burden of HCAI and AMR.

The role of stress and glucocorticoids on the risk of breast cancer

Melanie S Flint[2]*, Renee L. Flaherty[1], Elizabeth Bancroft[1], Elizabeth Page[1], Rosalind Eeles[1] and Andrew Hesketh[2].

[1]The Institute of Cancer Research, London, UK

[2]School of Applied Sciences, University of Brighton, Moulsecoomb, Brighton, UK

The role of psychological stress on cancer risk is not yet established. We have previously shown that the stress hormone, cortisol can induce DNA damage in breast cancer through an iNOS mediated pathway correlating with tumour progression. To study the effect of stress on cancer risk, we examined cortisol levels and 8-Hydroxy-2-Deoxyguanosine (8-OHDg) a biomarker of oxidative stress, in women with BRCA1/2 mutations at baseline and subsequent years. Study participants with high minimum cortisol levels (above a threshold of 7300 pg/ml) and 8-OHDg levels (above a threshold of 6ng/ml) have a significantly increased risk of a breast cancer diagnosis. Mechanistically, we also show that cortisol can induce phosphorylation of H2AX (an indicator of DNA damage) and BRCA1 in mammary epithelial cells and this is mediated through the glucocorticoid receptor. Moreover, we found that cortisol impairs the cells ability to effectively repair this DNA damage. Following knockdown of BRCA1 in MCF10A cells we found that although cortisol did not increase DNA damage compared to BRCA1 wild type, there was significantly less DNA repair in BRCA1-deficient cells. In summary, our findings suggest a strong mechanistic link between stress markers, DNA damage, and susceptibility to breast cancer initiation in patients with BRCA mutations.

Session 2

The use of biomarkers in assessing frailty – findings from a pilot study (FRAXI)

Ekow Mensah[1,2], Khalid Ali[1,2], Winston Banya[3], Frances Kirkham[1,2], Manuela Mengozzi[4], Pietro Ghezzi[5], Chakravarthi Rajkumar[1,2]

[1]Department of Medicine, University of Sussex, Brighton and Sussex Medical School, Brighton, UK

[2]University Hospitals Sussex NHS Trust, Royal Sussex County Hospital, Brighton, UK
[3]Research Office, Royal Brompton and Harefield Clinical Group, Guy's and St. Thomas' NHS Foundation Trust, London, UK
[4]Department of Experimental Medicine, University of Sussex, Brighton, UK
[5]Università degli Studi di Urbino, Italy

Frailty, which is a clinical state where there is significant decline in the ageing body's physiological reserve, presents with vulnerability leading to inability to cope with acute stressors. Frailty is known to be directly correlated to vascular ageing. There is evidence that both oxidative stress and inflammaging (chronic state of inflammation in ageing) underpin vascular ageing. Although these two are known to be associated with frailty and considered to be underlying vascular ageing, there are no observational studies in humans, on the effects of these on the different grades of frailty. Similarly, there are no studies showing the correlation of vascular ageing with the spectrum of frailty. FRAXI study aimed to examine the relationship between arterial stiffness, oxidative stress and inflammation with the various states of frailty among older adults and assess if biomarkers of inflammation and oxidative stress can be used as an objective measure for frailty. Biomarkers for oxidative stress and for inflammation, were measured in 50 adults ≥ 70years. Frailty status was assessed using clinical markers of frailty. Results of this pilot study and future research ideas will be discussed.

Onesizefits1 - a new way to practise children's medicine?

Tom Ruffles [1,2] Elaney Youssef [1], Somnath Mukhopadhyay [1,2]

[1]Brighton and Sussex Medical School, Brighton, UK

[2]Academic Department of Paediatrics, Royal Alexandra Children's Hospital, University Hospitals Sussex NHS Foundation Trust, Brighton, UK

Asthma is the most common chronic condition affecting children. Whilst many children achieve symptom control with preventer therapies, a significant proportion have poorly controlled disease despite treatment. This is associated with substantial health and quality-of-life burden for the patient and family, as well as significant healthcare expenditure.

There is evidence that inter-individual variation in drug response in asthmatic patients may be partly genetically determined. Children from different populations and ethnic groups respond differently to asthma medications, likely due to genetic variants. A personalised approach, tailored to an individual's genotype is essential for improving asthma outcomes in children. However, before changes to current services are made, it is important to consider the experiences and concerns of patients to ensure services meet their needs. We will aim to review the current pharmacogenomic studies in children's asthma and identify the potential pathway for implementation into clinical practise. We will also discuss ongoing work and visions for future work in this area.

Joint hypermobility: Insights from bench to bedside

Jessica A Eccles [1,2], Lisa Quadt [1] and Hugo D Critchley[1,2]

[1]Department of Clinical Neuroscience, Brighton and Sussex Medical School

[2]Neurodevelopmental Service, Sussex Partnership NHS Foundation Trust

Brain and body are dynamically coupled. Dr Eccles and colleagues believe that the false dichotomy between body and brain hinders our holistic understanding of human experience, holds back clinical practice and research and further perpetuates stigma. They will use the presence of a common bodily variant of connective tissue (joint hypermobility) to demonstrate such brain-body links and how this may relate to a number of conditions including affective disorder, neurodevelopmental conditions, pain and fatigue, and long COVID. They will draw on prize-winning work in the field of hypermobility/EDS that spans bench to bedside. They hope to encourage curiosity and challenge stereotypes.

The interplay between genetic risk and lifestyle behaviours in Alzheimer's Disease

Dorina Cadar[1], Emma R Francis[2], Olesya Ajnakina[2], Andrew Steptoe[2]

[1]Department of Clinical Neuroscience, Brighton and Sussex Medical School, Brighton, UK

[2]Department of Behavioural Science and Health, University College London, UK

The interplay between genetic predisposition for ageing-related traits and Alzheimer's disease (AD) and lifestyle behaviors is crucial for understanding dementia onset and considering tailored personalised medicine. Utilising data from the English Longitudinal Study of Ageing, we applied an accelerated failure time survival model to explore interactions among APOE 4, polygenic scores for AD (AD-PGS), general cognition (GC-PGS), and lifestyle factors like daily fruit and vegetable intake and exercise in relation to dementia diagnosis over a decade. Findings revealed that consuming less than five portions of fruits and vegetables daily correlated with a 37% increased dementia risk, influenced by individual polygenic propensity. A one standard deviation increase in AD-PGS was linked to a 24% higher dementia risk and a 47% higher AD diagnosis risk. Additionally, a notable additive interaction was observed between GC-PGS and inadequate fruit and vegetable intake concerning AD diagnosis. High exercise levels were associated with a 75% reduction in dementia onset risk, while moderate levels reduced the hazard by 52%. These results underscore the significance of a healthy lifestyle, characterised by a diet rich in fruits and vegetables and regular exercise, in mitigating dementia risk, especially in individuals predisposed to AD, highlighting the need for targeted interventions.

Session 3

‘One Diagnosis, Many Diseases’: Trials, Biomarkers, and Heterogeneity in Motor Neuron Disease

Nigel Leigh[1] and Majid Hafezparast[2]

[1]Department of Neuroscience, Brighton and Sussex Medical School and Sussex Neuroscience

[2]School of Life Sciences, Department of Neuroscience, and Sussex Neuroscience, University of Sussex

Motor Neuron Disease (MND; Amyotrophic Lateral Sclerosis, ALS) is a devastating neurodegenerative disease, usually fatal within 3-5 years of onset. To date only one drug- riluzole- has been approved worldwide, despite dozens of subsequent trials. We now realise that MND is a heterogeneous disease both clinically and aetiologically, explaining why many trials have failed.

This clinical and molecular heterogeneity pose major challenges for the design of clinical trials in MND. In the MIROCALS (Modifying Immune responses and Outcomes in ALS; NCT03039673) we designed a randomised controlled trial (RCT) of low-dose interleukin-2 ($IL2_{LD}$) that combined regulatory-compliant clinical outcomes with pre-specified blood and CSF biomarkers to design an ‘experimental medicine’ approach to adjust for disease heterogeneity in relation to treatment. Here we summarise the trial design and key results in relation to existing biomarkers, demonstrating the potential for specific biomarkers (e.g., CSF pNFH) to stratify MND trial populations in relation to disease heterogeneity. However, there is a pressing need for new biomarkers for prognosis, disease mechanisms, and treatment responses.

We have therefore concurrently investigated the potential importance of non-coding RNAs (ncRNAs) as biomarkers in cross-sectional blood serum of ALS patients. Modelling seven differentially expressed ncRNA, we could classify a sample as being from an ALS patient or not with an average cross-validation accuracy of 72% in our sample cohorts. Moreover, we have identified a set of ncRNA that are correlated with prognosis in longitudinal serum samples. Of these, three ncRNA appear to change dependent on the speed of progression of the disease, suggesting that they may be markers of disease pathology. We are currently processing the MIROCALS longitudinal samples in order to identify new potential candidates that are linked to disease progression and to test these newly identified biomarkers using our existing cohorts to not only cross-validate our signature but to ascertain whether they would improve the accuracy of our existing diagnostic signature.

In conclusion, we suggest that integrating biomarkers of prognosis, disease mechanisms, and drug response into clinical trials in MND will help us identify new treatments despite disease heterogeneity, and help to break the current deadlock in the search for more effective disease-modifying treatments.

Acknowledgements: The European Commission H2020 Programme (PNL); The Motor Neurone Disease Association (MH and PNL); MyName'5Doddie Foundation (PNL, MH); Association pour la Recherche contre SLA (ARSLA, France; PNL)

Getting the right drugs into the right patients with computational systems biology

Simon Mitchell[1], Richard Norris[1], Arran Pack[1], Aimilia Varelli[1], Eleanor Jayawant[1], Ielyaas Cloete[1], Andrea Pepper[1], Chris Pepper[1]

[1]Brighton and Sussex Medical School

Despite vast knowledge of the molecular biology of the disease, patient-to-patient variability has blocked advances in treatments for B cell lymphoma. Computational systems biology provides a tool to encode and simulate this knowledge, and potentially overcome the impact of patient-to-patient variability.

We found that, when we added commonly occurring mutations to simulations of B cell signalling, the cell is predicted to misinterpret microenvironmental cues. We tested these computational predictions in the lab and found “crossed wires” withing B cells, as they incorrectly produced a pro-inflammatory response to microenvironmental stimuli.

We created personalised simulations of B cell lymphoma patients, by incorporating the vast mutational heterogeneity found in patient tumours. Analysis of these simulations identified a new subgroup of the disease in which patients have simultaneous pro-apoptotic and anti-proliferative signalling. These patients do not respond to the standard of care and have poor prognosis. To establish whether simulation may also identify alternative treatment approaches for these patients we simulated a heterogeneous library of lymphoma cell lines. We found we could predict each cell line’s response to drugs that target apoptosis revealing a new approach to assign personalised, targeted therapeutic approaches to heterogeneous patient populations.

Emerging Frontiers in Colorectal Cancer Therapy: From Targeted Molecules to Immunomodulatory Breakthroughs and Cell-Based Approaches

Maziar Ashrafian Bonab[8] Nayeralsadat Fatemi[1], Seyedeh Nasim Mirbahari[1,2], Sascha Tierling[3], Fatemeh Sanjabi[4], Shabnam Shahrivari[4], Mandana AmeliMojarad[5], Melika Amelimojarad[5], Meygol Mirzaei Rezaei[6], Parsa Nobaveh[6], Mehdi Totonchi[1,2], Ehsan Nazemalhosseini Mojarad[7].

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Colorectal cancer (CRC) is ranked as the second leading cause of cancer-related deaths globally, necessitating urgent advancements in therapeutic approaches. The incidence is slightly higher in men, and it peaks around the age of 50. Genetics, environmental, and lifestyle risk factors, all have a role in the development and progression of CRC. The emergence of groundbreaking therapies, including chimeric antigen receptor-T (CAR-T) cell therapies, oncolytic viruses, and immune checkpoint inhibitors, marks a transformative era in oncology. These innovative modalities, tailored to individual genetic and molecular profiles, hold the promise of significantly enhancing patient outcomes. Here we explore the latest clinical trials and advancements, encompassing targeted molecular therapies, immunomodulatory agents, and cell-based therapies. By evaluating the strengths, limitations, and potential synergies of these approaches, this presentation aims to discuss the treatment landscape and improvements in clinical outcomes for CRC patients. These advancements offer newfound hopes for those who have exhausted conventional options.

Poster Presentation Abstracts

Determining the role of lncRNAs in the pathogenesis of high risk, gain(1q) positive, Multiple Myeloma

Ben J. Green[1], Benjamin P. Towler[2], Sarah F. Newbury[1] and John R. Jones[1]

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Multiple Myeloma (MM) is a plasma cell malignancy that affects the bone marrow, accounting for 15% of haematological malignancies and 2% of all cancers. MM is a genetically complex, non-curable disease which evolves following therapy, leading to therapeutic resistance and disease progression.

An important genetic abnormality is gain(1q), which is the addition of either part of or the entire q arm of chromosome 1. Gain(1q) occurs in 40% of newly diagnosed MM cases, reduces survival and confers resistance to treatments. We and others have shown that gain(1q) is the most commonly acquired new genetic aberration at relapse and remains preserved throughout the disease course. Therefore, an understanding of how gain(1q) impacts malignant cell survival is required for drug discovery and improved outcomes.

Long non-coding RNAs (lncRNAs) have been shown to drastically affect prognosis in several cancers. LncRNAs make up 27% of the genes encoded on 1q but over 50% are not characterised, making their contribution to MM largely unknown.

Our research aims to establish the functional properties of lncRNAs on 1q and decipher the role they play in myelomagenesis, clonal evolution and therapeutic resistance through transcriptomic, bioinformatic and functional analyses of differentially expressed lncRNAs in patient samples with different gain(1q)-statuses.

Uncovering an allosteric mode of action for a selective inhibitor of human Bloom syndrome protein

Antony W. Oliver[1], Xiangrong Chen[1,2], Yusuf I. Ali[2,3], Charlotte E.L. Fisher[1], Raquel Arribas-Bosacoma[1], Mohan B. Rajasekaran[3], Gareth Williams[3], Sarah Walker[3], Jessica R. Booth[3], Jessica J.R. Hudson[3], S Mark Roe[4], Laurence H. Pearl[1], Simon E. Ward[3], Frances M.G. Pearl[2],

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BLM (Bloom syndrome protein) is a RECQ-family helicase involved in the dissolution of complex DNA structures and repair intermediates. Synthetic lethality analysis implicates BLM as a promising target in a range of cancers with defects in the DNA damage response; however, selective small molecule inhibitors of defined mechanism are currently lacking. Here, we identify and characterise a specific inhibitor of BLM's ATPase-coupled DNA helicase activity, by allosteric trapping of a DNA-bound translocation intermediate. Crystallographic structures of BLM-DNA-ADP-inhibitor complexes identify a hitherto unknown interdomain interface, whose opening and closing are integral to translocation of ssDNA, and which provides a highly selective pocket for drug discovery. Comparison with structures of other RECQ helicases provides a model for branch migration of Holliday junctions by BLM.

Identification of FKBP51 as the link between senile plaques and tau pathology and the Hsp90-FKBP51 complex as the molecular target for LA1011, which cures Alzheimer's Disease in a mouse model

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There is a pressing need to slow the progression of Alzheimer's Disease (AD) to improve patient life span and lower care costs. In AD a 42 kD proteolytic fragment (beta-amyloid) of the amyloid precursor protein forms senile plaques that in turn elicit a cascade leading to tau pathology. This is characterised by tau hyperphosphorylation resulting in the destabilization of microtubules and the formation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau. The latter cause neurotoxic effects on neurones which eventually die. We now identify FKBP51 as a major factor that links senile plaques to tau pathology. It appears that senile plaques cause damage and inflammation to the brain and therefore induce the Hsp90 co-chaperone FKBP51, which leads to dysregulation of tau phosphorylation. We have now identified the molecular target of a small molecule, LA1011, that competes with FKBP51 binding to Hsp90. LA1011 was shown to cure AD in an AD mouse model and we believe that LA1011 normalizes high levels of Hsp90-FKBP51 resulting from the senile-plaque activated heat shock response. LA1011 also shows a co-inducing effect on the heat shock response, eliciting chaperone systems like Hsp70 that aid in reducing the burden of senile plaques and tau NFTs in the brain.

Combined NF-κB and Bcl-2 "fingerprinting" of DLBCL predicts resistance to venetoclax and reveals microenvironment-mediated vulnerabilities that can be exploited by inhibiting non-canonical NF-κB

Aimilia Vareli, Heather Clark, Eleanor Jayawant, Fabio A Simoes, Andrea G S Pepper, Chris Pepper, Simon Mitchell

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Aberrant NF-κB activation, driven by genetic mutations or signals from the tumour microenvironment (TME), is common in DLBCL, leading to overexpression of Bcl-2 proteins and therapy resistance. While global NF-κB inhibitors pose toxicity concerns, the impact of inhibiting the non-canonical NF-κB (RelB) pathway remains unclear. We aimed to characterize NF-κB and Bcl-2 heterogeneity, investigate TME-induced resistance to ABT199 (venetoclax), and assess the efficacy of targeting non-canonical NF-κB with a NIK inhibitor (Amgen16) in overcoming resistance.

DLBCL cell lines exhibited varied sensitivity to ABT199, with some showing resistance. Co-culture with CD40L-expressing cells mimicking TME increased Bcl-2 family protein expression and activated non-canonical NF-κB, inducing ABT199 resistance. This resistance was reversed by Amgen16. "NF-κB fingerprinting" revealed heterogeneity in NF-κB and Bcl-2 levels within cell lines. High Mcl-1 and RelB levels correlated with ABT199 resistance but sensitivity to NIK inhibition.

Overall, our findings suggest a promising treatment strategy for DLBCL involving combined Bcl-2 and non-canonical NF-κB inhibition to overcome therapy resistance. Targeting these pathways based on individual tumour characteristics could enhance treatment efficacy.

Parallel vs serial processing linked to mind wandering: extending the metronome response task

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[2] Orcid 0009-0006-7042-0889

BACKGROUND: Mind wandering (MW) is a ubiquitous activity during consciousness where thoughts drift haphazardly, increasing the risk of performance decrement and catastrophic accidents. During MW, do attentional resources undergo parallel redeployment of some (executive) resources away from the primary task, or serially cycle between complete redeployment and refocusing?

METHODS: In the metronome response task (MRT), participants predict the timing of a regularly occurring tone. During the traditional MRT, MW reduces consistency of responses but not accuracy. We compared the traditional MRT to more difficult versions that increased the inter-trial interval (ITI) from 1.3s to 2.6s and 5.2s. We assessed MW with timed subjective thought probes.

RESULTS: Longer ITIs successfully elicited a less anticipatory strategy. The difficult-to-predict 5.2s version elicited a strategy that either reacts to each tone, or guesses wildly, whereas the borderline-feasible 2.6s version led to a mostly anticipatory strategy when on task, but MW when ITI=2.6s strongly encouraged reactive strategies. MW consistently delayed the thought probe response (the most demanding task), but ITI did not.

CONCLUSIONS: MW usually recruits parallel resources without causing serial attentional vacillation. However, when demanding tasks require extensive attention, MW may monopolise needed attentional resources, causing cycling serially between the task and MW.

With thanks