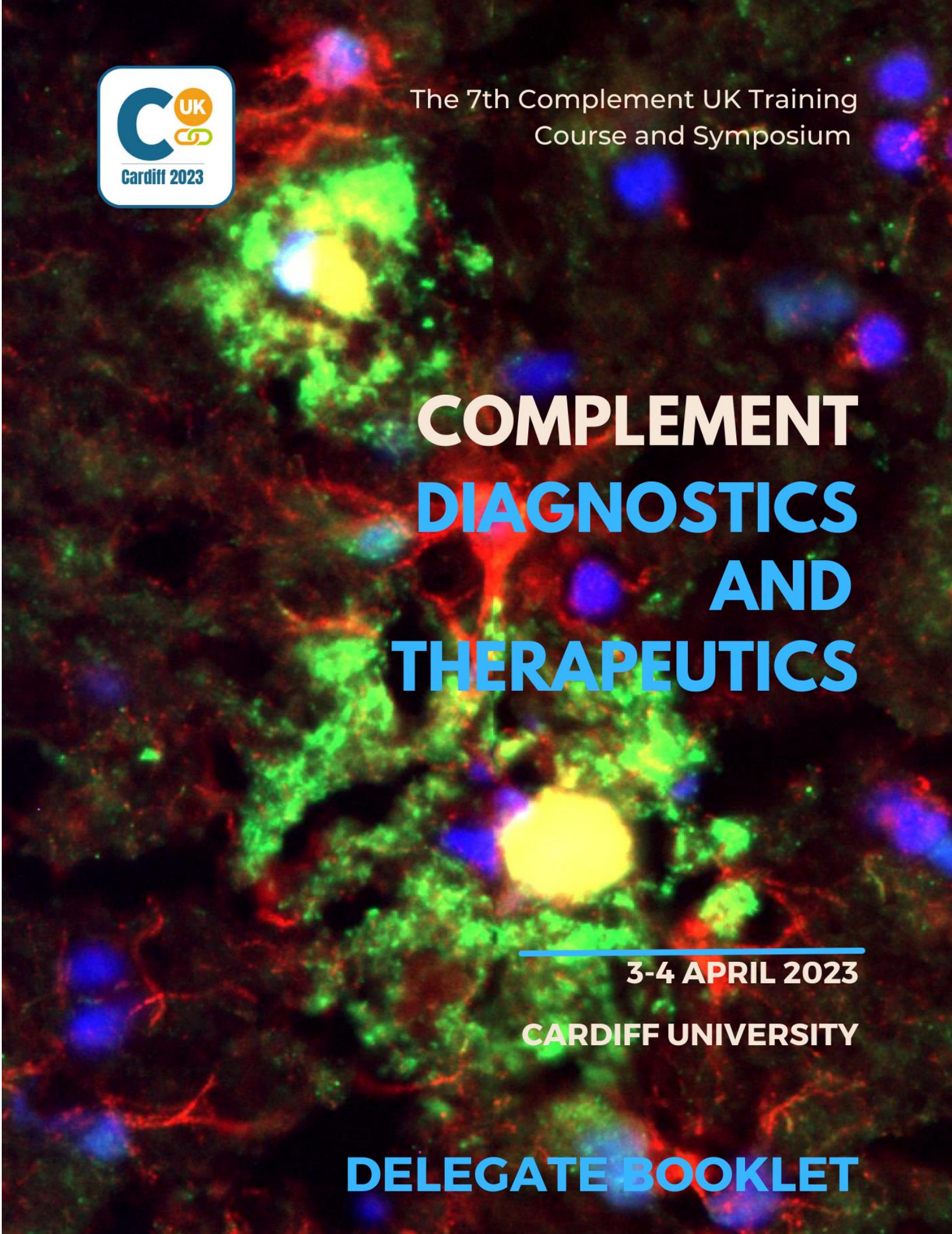
UK
Cardiff 2023
The 7th Complement UK Training Course and Symposium
COMPLEMENT DIAGNOSTICS AND THERAPEUTICS
3-4 APRIL 2023
CARDIFF UNIVERSITY
DELEGATE BOOKLET

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Contents

1. SCIENTIFIC ORGANISERS

Dr Wiola Zelek

Research Fellow,
Division of Infection and Immunity & Dementia Research Institute
School of Medicine
Cardiff University

Professor Paul Morgan

Professor of complement biology,
Division of Infection and Immunity & Dementia Research Institute
School of Medicine
Cardiff University

EVENT MANAGER

Anna Taliadoros

Email: anna.taliadoros@kcl.ac.uk

CONFERENCE WEBSITE: https://complement.org.uk/events/

2. WELCOME NOTE

Croeso i Gaerdydd! Welcome to the unavoidably-delayed Complement UK Meeting in Cardiff, scheduled for March 2020 but then the world went a bit crazy! Great to be finally able to host you all in Cardiff for what we are sure will be an informative, educational and fun meeting. Complement UK exists to raise the profile of complement and provide expertise and training to those new to the field, an increasingly important task as complement drugs progress further into routine clinical practice.

The 2020 meeting would have been the 10th Anniversary of the first meeting of Complement UK so we will pretend it's this year and have a bit of a birthday bash with a special cake for the occasion!

We give our sincere thanks to the Tutors, Speakers, Chairs and Judges who give their time freely to the delivery of this meeting. We thank the Cardiff Complement Group for their help in the organisation and during the meeting (look out for the special T-shirts!), and of course to Anna Taliadoros who has borne the brunt of the work and made this happen. Finally, we thank our generous Sponsors who have supported the costs of staging the meeting, enabling us to keep the registration fees to an absolute minimum – particularly for students!

Have fun and use the opportunity to talk to the experts, network with colleagues and friends and come up with the next great idea for the complement field.

Diolch am ddod i'n gyfarfod.

Paul, Wiola and the local organising team.

3. LOCAL INFORMATION

CONFERENCE WEBSITE

Complement UK: https://complement.org.uk/conference/

The best attractions in and around Cardiff: https://www.visitcardiff.com/see-do/attractions/

CONFERENCE ADDRESS:

Including **Tutorials, Lectures, Wine Reception and Poster Presentations.**
Please note that **Conference Dinner** will be at **Aberdare Hall**.

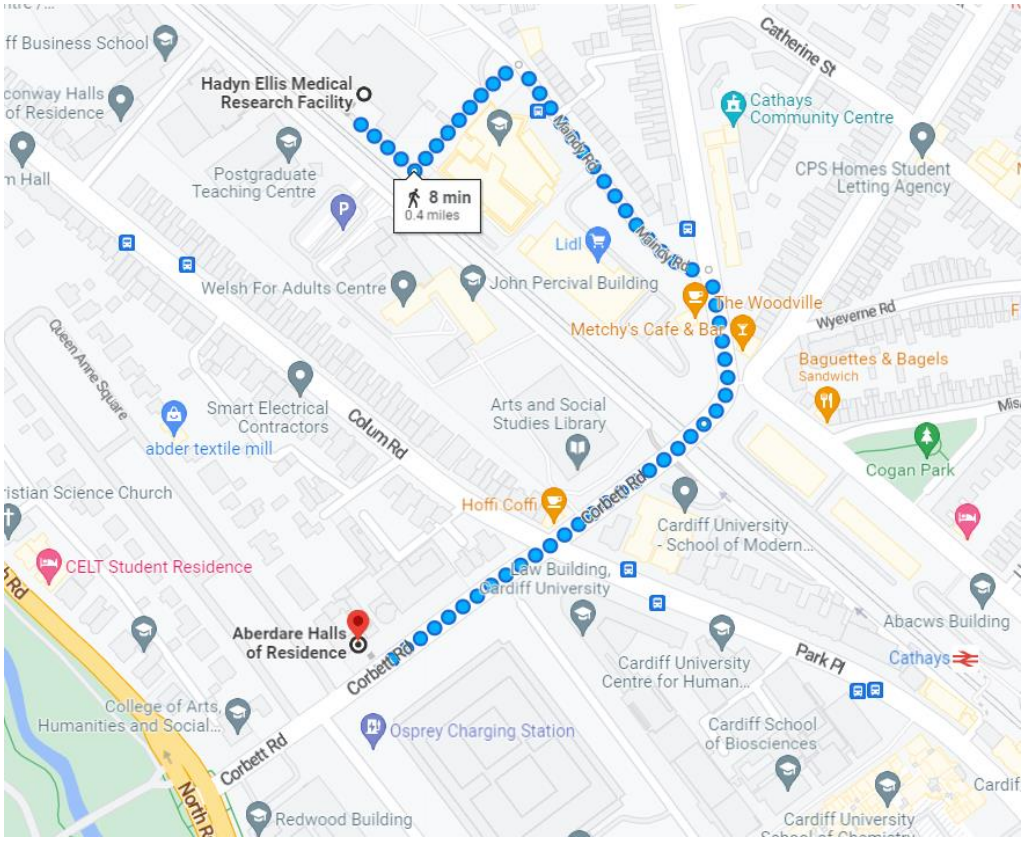
ADDRESS
Cardiff University
Hadyn Ellis Building
Maindy Road,
CF24 4HQ Cardiff

Contact: Anna Taliadoros at 07887522722

CONFERENCE DINNER ON MONDAY, APRIL 3RD

The conference dinner will take place on **Monday, April 3rd at 19:30 at Aberdare Hall.**

ADDRESS:
Cardiff University
Aberdare Hall
Corbett Rd,
Cardiff CF10 3UP



WI-FI Access

Connect to **CU-wireless**

Select the **'conference'** option, then use the details below:

Conference ID: **HEB**

Password: **989019**

4. COMPLEMENT UK

Founded in 2009 by Prof Paul Morgan and Prof Steven Sacks. Complement UK is a collaborative UK network of clinical, research and technological experts with the goal to improve the understanding of complement and related disorders and more rapidly exploit this knowledge for the welfare of patients.

The activities of Complement UK include:

- Host annual meetings to inspire and foster collaborative research in specified areas and deliver a strong training element.
- Build critical mass on collaborative grants from major research organisations.
- Support the development of PhD studentships with charitable and industrial partners.

Complement UK Conferences

Meetings of Complement UK serve two key purposes: to deliver a strong training element; and to foster collaborative research in specified areas. These two-day meetings are for scientists, clinicians and pre- and post-doctoral researchers interested in complement-related disorders. Attendance by industrial partners is also welcomed. A day of core training for research students and other newcomers to the complement field is followed by a day of expert lectures and posters based on an emerging area of research.

Students, clinicians and researchers from different universities, research institutes and industry within the UK have the opportunity to discuss shared interest in complement, in relaxed atmosphere and develop long-term collaborative relationships. These meetings, however, are of confidential nature and any information heard or received is confidential and is treated as such.

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5. MEETING SUMMARY

The 7th "Complement UK Training Course and Symposium" will take place on April, 3rd and 4th 2023, hosted by Cardiff University. This year's event will focus on Complement Diagnostics and Therapeutics.

These meetings are for scientists, clinicians, and pre- and post-doctoral researchers, industrial partners interested in complement biology. We particularly welcome the active participation of early career researchers and have included several slots in our programme for short talks, based on abstract submissions. There will be prizes for best poster and oral presentation.

TUTORIALS

The first day is a teaching day focused on trainees, students and junior Post Docs. There will be introductory lectures on complement, followed by a choice of tutorials covering many aspects of basic complement biology and biochemistry, and the role of complement in disease. Following the tutorials there will be a guest talk by Professor Sir Leszek Borysiewicz.

There is a choice of two tutorials in the morning and two in the afternoon, which are intended to give tutees a grounding in essential basic points which will underpin the rest of the meeting.

SYMPOSIUM

The symposium on the second day will expand on a specific research theme, which this year is the role of complement in diagnostics and therapeutics. The meeting will end with a roundtable discussion on ***Is there a single best target for anti-complement drugs?***.

6. MEETING PROGRAMME

TRAINING DAY,

Monday, 3rd April 2023

09:00 – 09:20 **Registration**

09:20 – 09:30 **Welcome**

09:30 – 11:00 COMPLEMENT TUTORIAL #1

1.1 **Compartmentalisation of complement** – Steven Sacks

1.2 **Complement and break of tolerance** – Marina Botto

2.1 **Complement association with disease** – Simon Clark

2.2 **Complement association with disease** – Meike Heurich-Sevcenco

11:00 – 11:30 Coffee & Posters Viewings

11:30 – 12:15 **Lecture: Complement; the basics** – Paul Morgan

12:15 – 12:45 **Quick-fire poster presentations** (one slide, 60 seconds)
Nikoleta Daskoulidou, Tim Hughes

12:45 – 13:45 Lunch & Posters Viewings

13:45 – 15:15 COMPLEMENT TUTORIAL #2

3.1 **Complement & therapeutics** – Matthew Pickering

3.2 **Complement & therapeutics** – Claire Harris

4.1 **Diagnostics; genetics** – David Kavanagh

4.2 **Diagnostics; biomarkers/assays** –Loek Willems & Erik Toonen

15:15 – 15:45 Coffee

15:45 – 17:05 ABSTRACT PRESENTATIONS

15:45 – 15:50 Introduction by Chairs: Wiola Zelek & Thomas Hallam

1550 – 1605 **Lack of Complement Factor H contributes to endothelial cell injury in Shiga toxin Haemolytic Uraemic Syndrome**, Emily Bowen

1605 – 1620 **Safety, Tolerability and Pharmacodynamic Effects of ARO-C3, a Subcutaneously Administered Investigational RNAi Therapeutic Targeting Complement C3, in Adult Healthy Volunteers,** Hamid Moradi

1620 – 1635 **GWAS of plasma complement protein levels reveals functional effects of Alzheimer's disease risk loci,** Aurora Veteleanu

1635 – 1650 **Complement receptor 1 is expressed on brain cells and impacts roles of microglia relevant to Alzheimer's disease**, Nikoleta Daskoulidou

1650 – 1705 **Complement inhibitors for age-related macular degeneration (AMD): A Cochrane systematic review and meta-analysis**, Nikolaos Tzoumas

17:05 – 18:05 Guest lecture "Cancer and Inflammation" - Prof Sir Leszek Borysiewicz

Introduction: Paul Morgan

18:15 – Poster presentations and Drinks Reception and Cake

19:30 – Dinner (at Aberdare Hall)

Tuesday, 4th April 2023

Symposium: Complement Diagnostics and Therapeutics

08:40 – 08:45 Welcome and introduction to the day

08:45 – 10:45 SESSION 1: THERAPIES

Chairs: Wiola Zelek & Laura Westacott

08:45 – 09:15 **Therapeutic targets – overview** - Claire Harris

09:15 – 09:45 **Anti-complement drugs in disease; Lessons from animal models –** Kevin Marchbank

09:45 – 10:15 **C5 vs. C3 based therapeutic approaches in kidney disease (including eculizumab withdrawal trials -** Neil Sheerin

10:15 – 10:45 **C5 vs. C3 based approaches in PNH -** Richard Kelly

10:45 – 11:15 Refreshment and Poster Viewings

11:15– 11:45 **Targeting complement at the genetic level -** Scott Ellis

11:45 – 12:15 **Designing anti-complement drugs through structural studies** - Jean Van Den Elsen and Alex Macpherson

12:15 – 13:30 Group photo and Lunch and Poster Viewings

13:30 – 16:30 SESSION 2: Mechanisms and Diagnostics

Chairs: Alex Macpherson & Meike Heurich-Sevcenco

13:30 – 14:00 **Complement and genetics -** Santiago Rodriguez de Cordoba

14:00 – 14:30 **Pitfalls in complement analyses** – Erik Toonen

14:30 – 15:00 **New biological insight to complement regulation at the neuronal synapse** – Soyon Hong

15:00 – 15:30 **Lectin Pathway -** Wilhelm Schwaeble

15:30 – 15:45 Coffee

15:45 – 16:30 **Round table discussion:** ***Is there a single best target for anti-complement drugs?***

Neil Sheerin, Richard Kelly, Wilhelm Schwaeble, Simon Clark

16:30 – 1645 **Prizes for best poster / oral presentation / tutor**

16:45 Final remarks and close of the meeting

7. SESSIONS

DAY 1: TUTORIALS

Monday, April 3rd

09:30 – 11:00 COMPLEMENT TUTORIAL #1

Compartmentalisation of complement – Steven Sacks

Complement proteins are produced widely by many cell types in different tissue compartments, each with the potential to initiate and control complement activation in a way that serves local tissue functions of complement. This seminar will explore the functional consequences in terms of inflammation and priming the specific immune response, and the implications for therapeutic targeting and biomarker evaluation, particularly with reference to kidney disease and transplantation.

TUTORIAL ALLOCATION

ROOM: Lecture Theatre (Ground floor)

1	Samuel	**Butler**	Svar Life Science AB
2	Timothy	**Cobb**	Alexion Pharma UK
3	Rebekah	**Cooke**	Cardiff
4	Nikoleta	**Daskoulidou**	UK DRI Cardiff University
5	Anna	**Dreismann**	Alliance Holdco
6	Eric	**Garcia-Medel**	Arrowhead Pharmaceuticals
7	Iasmina	**Gavrilas**	The Binding Site
8	Sebastian	**Hamers**	LUMC
9	Joshua	**Lewis**	Bath University
10	Balaji	**Mahendran**	Newcastle University
11	Jacqui	**Nimmo**	Cardiff University
12	Gemma	**Thompson**	Newcastle University
13	Nikolaos	**Tzoumas**	Newcastle University
14	Juliette	**van den Noort**	Leiden University Medical Centre
15	Lewis	**Watkins**	Cardiff University

Complement and break of tolerance – Marina Botto

The complement system, which consists of three independent but interacting pathways, constitutes a powerful arm of innate immunity. Its major function is to recognize and destroy pathogenic microorganisms as well as eliminate modified self-antigens. Although it is a fine-tuned system with innate capacity to discriminate self from non-self as well as danger from non-danger signals, an unwarranted activation can nonetheless occur and cause tissue destruction. To prevent such activation, specific regulators present both in plasma and on the cell surface tightly control it. Recent data have uncovered novel pathways that link complement-mediated signalling with homeostatic and pathological T cell responses. It is for these reasons that the various activation steps of the complement system have been recently targeted for therapy to treat diseases in which the role of complement is beyond doubt.

TUTORIAL ALLOCATION

ROOM: 0.27B (Ground Floor)

1	Ryan	**Bevan**	Cardiff University
2	Emily	**Bowen**	University of Bristol
3	Chloe	**Connelly**	Newcastle University
4	Eric	**Garcia-Medel**	Arrowhead Pharmaceuticals
5	Emanuela	**Gardenal**	Gyroscope / Novartis
6	Brian	**Golat**	QuidelOrtho
7	Thomas	**Hallam**	Gyroscope / Novartis
8	Mads	**Larsen**	Aarhus University
9	Hanna	**Lemmik**	King's College London
10	Nathan	**Li**	The Binding Site Group
11	Abigail	**Little**	Gyroscope Therapeutics
12	Marie	**LORVELLEC**	CNRS - IBS
13	Ingrid	**Meschede**	Gyroscope Therapeutics
14	Ali	**Quamar**	Svar Life science
15	Daksha	**Ryatt**	Svar Life Science AB
16	Anja	**Schoettler**	Maastricht University

Complement association with disease –Simon Clark

The dysregulation of complement has been associated with a number of different conditions affecting various parts of the body including the brain, kidneys and eyes. Complement acts as a bridge between the innate and adaptive immune systems, stimulating inflammatory responses, and there is much interest in developing therapeutics that can regulate the complement system.

With the help of recent papers and advancements in the field, we will discuss different conditions, affecting different organs but all having a link with complement. Attendees will be asked to consider how complement mediates disease pathogenesis or, in some cases, ameliorates disease phenotype.

Manuscripts to stimulate discussion will be provided in advance and the participants will have the opportunity to put forward any specific questions they may have on this, or any other related, subject.

TUTORIAL ALLOCATION

ROOM: 0.27A (Ground floor)

1	Rotem	**Agmon**	Alexion Pharma UK
2	Dominic	**Alderson**	Newcastle University
3	Anneliza	**Andreadi**	Newcastle University
4	Ahmad	**Ayaz**	Newcastle University
5	Kirsten	**Baillie**	Cardiff University
6	Lauri	**Bloemenkamp**	argenx
7	Eimante	**Bujaite**	Alexion
8	Robert	**Byrne**	UK DRI Cardiff University
9	Sarah	**Carpanini**	Cardiff University
10	Heather	**Clark**	University of Bristol
11	Laura	**Ffrench**	Alexion AstraZeneca Rare Disease
12	Jake	**Fisher**	The Binding Site
13	Sarah	**Hammadi**	Newcastle University
14	Victor	**Iliev**	The Binding Site
15	Samuel	**Keat**	UK DRI Cardiff University
16	Stephanie	**Kelly**	The Binding Site

Complement association with disease – Meike Heurich-Sevcenco

The tutorial will be about the role of complement in psychosis spectrum disorders and in particular complement component C4 associated with Schizophrenia. We will examine recent proteomics studies highlighting differential plasma levels of complement components that are associated with the transition to psychotic disorder. We will have an interactive discussion of what the up-or down-regulation of specific components means for the activity and regulation of complement and overall complement activity. Finally, we will discuss how the differential function of the C4 variants may impact pathophysiological mechanisms.

TUTORIAL ALLOCATION

ROOM: 3.17 (3rd floor)

1	Eleftheria	**Kodosaki**	Cardiff University
2	Alexander	**Marshall**	Cardiff University
3	Claire	**Martin**	CSL Vifor
4	Ana	**Martinez Tormos**	Alexion
5	Saltanat	**Moldakhmetova**	Newcastle University
6	Hamid	**Moradi**	Arrowhead Pharmaceuticals
7	Mollie	**O'Neill**	Kypha Biosensia
8	Martin	**Schmidt**	Kypha Inc.
9	Mark	**Shepherd**	Cardiff University
10	Nathan	**Simpson**	Newcastle University
11	Aitana	**Sogorb Esteve**	University College London
12	Amy	**Tierney**	The University of Manchester
13	Megan	**Torvell**	Cardiff University
14	Katie	**Triantafilou-Wilson**	Anglia Ruskin Medical School
15	Richard	**Unwin**	University of Manchester
16	Aurora	**Veteleanu**	Cardiff University

13:45 – 15:15 COMPLEMENT TUTORIAL #2

Complement and therapeutics – Matthew Pickering

We will discuss existing complement therapies and therapeutic strategies that are under investigation in clinical trials. The applicability of complement inhibition as therapy is broadening since complement-mediated pathways of tissue damage have been identified in many diseases. This is exemplified by the expanded indications for C5 inhibition in the clinic (paroxysmal nocturnal haemoglobinuria, atypical haemolytic uraemia syndrome, myasthenia gravis, neuromyelitis optica) and the recent approval of agents that inhibit C3 (pegcetacoplan for treatment of paroxysmal nocturnal haemoglobinuria); inhibit C1s (sutimlimab for treatment of haemolytic anaemia in cold agglutinin disease) and that block the C5a receptor (avacopan for treatment of ANCA-associated vasculitis. There are many agents in development targeting different aspects of the complement cascade. We will discuss the pros and cons of these approaches based on our understanding of complement biology and the mechanism of disease injury in particular settings.

TUTORIAL ALLOCATION

ROOM: Lecture Theatre (Ground floor)

1	Hanna	**Lemmik**	King's College London
2	Abigail	**Little**	Gyroscope Therapeutics
3	Balaji	**Mahendran**	Newcastle University
4	Alexander	**Marshall**	Cardiff University
5	Ana	**Martinez**	Alexion
6	Ingrid	**Meschede**	Gyroscope Therapeutics
7	Saltanat	**Moldakhmetova**	Newcastle University
8	Ali	**Quamar**	Svar Life science
9	Rebekah	**Cooke**	Cardiff University
10	Daksha	**Ryatt**	Svar Life Science AB
11	Anja	**Schoettler**	Maastricht University
12	Mark	**Shepherd**	Cardiff University
13	Nathan	**Simpson**	Newcastle University
14	Amy	**Tierney**	The University of Manchester
15	Megan	**Torvell**	Cardiff University
16	Katie	**Triantafilou-Wilson**	Anglia Ruskin Medical School
17	Lauri	**Bloemenkamp**	argenx

Complement and therapeutics – Claire Harris

Complement plays a key role in tissue homeostasis, flagging apoptotic cells and debris for removal, guiding immune complexes to the reticuloendothelial system for clearance, and orchestrating crosstalk between adaptive and innate immunity. In health, the system is constantly activating, but that is in perfect balance with control mechanisms which allow sufficient flux through the pathway to recognise appropriate (foreign) targets, but limit 'tick-over' amplification and activation on self surfaces. Unfortunately, this volatile and rapid-acting system can do harm as well as good; various mechanisms disrupt this balance between activation and control resulting in over-activation, tissue damage and disease. The involvement of complement in numerous common (and rare) diseases has driven the development of anti-complement drugs in many large companies and the approval of drugs targeting multiple axes including C1s, C5 and C5aR; other drugs targeting FB and C3 have positive outcomes in phase 3 trials and approved may be on the horizon. Interest has also surged in academia, as evidenced by an abundance of start-up companies and Biotechs focussing specifically on anti-complement therapeutics. In this tutorial, we will explore the different ways in which complement can be blocked or modulated; we will discuss drugs approved or in development, and compare their modes of action, the modalities, their advantages and their pitfalls.

TUTORIAL ALLOCATION

ROOM: 0.27B (Ground floor)

1	Dominic	**Alderson**	Newcastle University
2	Anneliza	**Andreadi**	Newcastle University
3	Ahmad	**Ayaz**	Newcastle University
4	Emily	**Bowen**	University of Bristol
5	Eimante	**Bujaite**	Alexion
6	Samuel	**Butler**	Svar Life Science AB
7	Robert	**Byrne**	UK DRI Cardiff University
8	Heather	**Clark**	University of Bristol
9	Chloe	**Connelly**	Newcastle University
10	Nikoleta	**Daskoulidou**	UK DRI Cardiff University
11	Anna	**Dreismann**	Alliance Holdco
12	Laura	**Ffrench**	Alexion AstraZeneca Rare Disease
13	Emanuela	**Gardenal**	Gyroscope / Novartis
14	Brian	**Golat**	QuidelOrtho
15	Thomas	**Hallam**	Gyroscope / Novartis
16	Sebastian	**Hamers**	LUMC
17	Sarah	**Hammadi**	Newcastle University

Diagnostics; genetics David Kavanagh

Atypical Haemolytic Uraemic Syndrome (aHUS) and Age-related Macular Degeneration are the prototypical genetic diseases of complement activation. Dysregulation of the alternative pathway of complement (AP) is central to the pathogenesis of both. The genetics of disease defines therapeutic targeting strategies and outcomes. This seminar will discuss the genetics of the disease, interpretation of genetic results and the use in personalised management.

TUTORIAL ALLOCATION

ROOM: 3.17 (3rd floor)

1	Rotem	**Agmon**	Alexion Pharma UK
2	Ryan	**Bevan**	Cardiff Unviersity
3	Sarah	**Carpanini**	Cardiff University
4	Timothy	**Cobb**	Alexion Pharma UK
5	Samuel	**Keat**	UK DRI Cardiff University
6	Joshua	**Lewis**	Bath University
7	Nathan	**Li**	The Binding Site Group
8	Marie	**LORVELLEC**	CNRS - IBS
9	Claire	**Martin**	CSL Vifor
10	Hamid	**Moradi**	Arrowhead Pharmaceuticals
11	Nikolaos	**Tzoumas**	Newcastle University
12	Richard	**Unwin**	University of Manchester
13	Lewis	**Watkins**	Cardiff University

Diagnostics; biomarkers/assays – Loek Willems & Erik Toonen

Accurate analysis of complement components and complement activation is of utmost importance for diagnosing disease and/or therapy monitoring. However, reliably determining the complement status of individual patients has proven to be challenging. This tutorial aims to provide general guidelines and practical tips & tricks for assessing complement in a reliable way. What are the main pitfalls in complement analysis? Technical aspects such as pre-analytical sample handling, assay design and selection, determination of assay accuracy/reproducibility and interpretation of results will be part of this workshop. In addition, the importance of proper, standardized complement testing for future clinical implications will be discussed.

TUTORIAL ALLOCATION

ROOM: 0.27A (Ground floor)

1	Miss	Kirsten	**Baillie**	Cardiff University
2	Dr	Jake	**Fisher**	The Binding Site
3	Dr	Eric	**Garcia-Medel**	Arrowhead Pharmaceuticals
4	Dr	Iasmina	**Gavrilas**	The Binding Site
5	Dr	Victor	**Iliev**	The Binding Site
6	Dr	Stephanie	**Kelly**	The Binding Site
7	Dr	Eleftheria	**Kodosaki**	Cardiff University
8	Mr	Mads	**Larsen**	Aarhus University
9	Miss	Jacqui	**Nimmo**	Cardiff University
10	Ms	Mollie	**O'Neill**	Kypha Biosensia
11	Dr	Martin	**Schmidt**	Kypha Inc.
12	Dr	Aitana	**Sogorb Esteve**	University College London
13	Dr	Gemma	**Thompson**	Newcastle University
14	Mrs	Juliette	**van den Noort**	Leiden University Medical Centre
15	Miss	Aurora	**Veteleanu**	Cardiff University

17:05 – 18:05 Guest lecture “Cancer and Inflammation”

- Prof Sir Leszek Borysiewicz

18:15 – Poster presentations and Drinks Reception

19:30 – Dinner at Aber dare Hall

DAY 2: SYMPOSIUM

Tuesday, April 4th

08:45 – 12:15 SESSION 1: THERAPIES

08:45 – 09:15 Therapeutic targets – overview - Claire Harris

During this talk, we take a look back over the checkered past of anti-complement therapeutics and set the scene for the remainder of this morning's session. Soliris™ (eculizumab) was the only marketed complement drug from 2005 until 2021, when Empaveli™ (pegcetacoplan) and Tavneos™ (avacopan) were approved for paroxysmal nocturnal haemoglobinuria (PNH) and anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis respectively; these approvals were swiftly followed by the approval of Enjaymo™ (sutimlimab-jome) for cold agglutinin disease (CAD) in 2022. We will examine the challenges that have been associated over the years with 'drugging the complement system', including the risk of infection and high target concentrations, and discuss how clinical trials and innovative drug designs have revolutionised the field of complement drug discovery.

09:15 – 09:45 Anti-complement drugs in disease; Lessons from animal models – Kevin Marchbank

Animal models, particularly mouse models, have been incredibly useful to define the role of complement and the alternative pathway in health and disease with the development of genetically modified mice such as the FH knockout mouse, arguably, paving the way for the first anti-complement drugs. The development of multiple knockout mice in the complement system established that the AP of mouse and man are highly analogous. Furthermore, the ability of soluble human regulators such as FH to cross the species barrier, has allowed for extensive pre-clinical testing of certain agents. More recently, humanised mouse models (transfer of small changes or whole genes) also greatly extend the ability to test drugs destined for man. In my talk, I will provide background to animal models we have used in the testing of anti-complement drugs, and I will discuss the importance of these approaches in finding the optimal therapy for tackling certain clinical conditions. I will focus on C3G and aHUS models and our testing of a number of novel complement therapeutics.

09:45 – 10:15 C5 vs. C3 based therapeutic approaches in kidney disease (including eculizumab withdrawal trials - Neil Sheerin

In this talk I will discuss how our understanding of disease pathophysiology can help predict whether anti-complement therapies are likely to be effective in patients with kidney disease. I will also discuss this

understanding can inform which treatment strategies are most likely to be effective and how long we will need to continue treatment.

10:15 – 10:45 C5 vs. C3 based approaches in PNH - Richard Kelly

PNH is an ultra rare acquired disorder characterised by haemolysis and an increased tendency to thrombosis. It is caused by somatic mutations of the PIG-A gene. Mutation of the PIG-A gene leads to reduction or absence of the glycophosphatidlyinositol (GPI) anchor which is needed for several proteins to be attached to blood cells. These proteins include complement regulatory proteins. Affected individuals experience symptoms due to chronic intravascular haemolysis due to complement activation. C5 inhibition has been successfully used to treat patients with PNH since 2002 with improvements in both disease mortality and morbidity. Proximal complement inhibitors, blocking at C3 and targeting the alternative pathway are a new way to treat patients with PNH. I will outline the approach to PNH treatment and how this field is changing, comparing the benefits of proximal and terminal complement inhibition.

11:15– 11:45 Targeting complement at the genetic level - Scott Ellis

Complement is a complex but critical part of the innate immune system that represents not only our first line of defence against invading pathogens but also plays an important role in homeostasis through its involvement in several other physiological processes such as tissue regeneration and clearance of immune complexes and dead cells. However, when not properly controlled this system can drive local and systemic inflammation that can lead to disease. There has been success in treating some of these diseases with established treatment modalities such as biologics that target disease at the protein level, and there is huge investment in novel and emerging modalities that target disease at the DNA or RNA level. In this talk I will provide a brief overview of current strategies to target disease at the genetic level, and explain how these are being used to develop potential cures for complement-driven diseases. I will also highlight how these types of medicine can face challenges and opportunities using therapies targeting the eye as an example.

11:45 – 12:15 Designing anti-complement drugs through structural studies - Jean Van Den Elsen and Alex Macpherson

The talk will explore how molecular structures can be used alongside biophysical techniques to aid the discovery and pre-clinical development of complement inhibitors. We will present recent work with a new class of antibody derived peptides, performed at UCB and the University of Bath, which identified a common structural mechanism to enable the allosteric inhibition of complement C5.

13:30 – 16:30 SESSION 2: MECHANISMS AND DIAGNOSTICS

13:30 – 14:00 Complement and genetics - Santiago Rodriguez de Cordoba

I will describe the extension of complement genetic variability in normal populations. I will discuss how genetic variants in components and regulators, determining differences in their activity and concentration, are additive and shape the overall activity of the complement. I will discuss how the complotype (combinations of genetic variants in different complement components and regulators) impact on the disease risk resulting in either increased risk or protection from specific diseases. I will illustrate how the identification of disease-associated genetic variants in complement components and, eventually, their structural and functional characterization has been instrumental to improve our molecular understanding of how complement dysregulation contributes to disease. Finally, I will comment on challenges involved in the identification and classification of the complement genetic variants.

14:00 – 14:30 Pitfalls in complement analyses – Erik Toonen

Assessment of complement activation is critical in monitoring both disease progression and response to therapy. Complement analysis requires accurate and standardized sampling and assay procedures, which has proven to be challenging. We performed a systematic analysis of the current methods used to assess complement components and reviewed whether the identified studies performed their complement measurements according to the recommended practice regarding pre-analytical sample handling and assay technique. A substantial part of the reviewed studies did not use the appropriate sample type for assessing complement activation. Deviations from the standardized procedure may lead to misinterpretation of complement biomarker levels and hampers proper comparison of complement measurements between studies.

14:30 – 15:00 New biological insight to complement regulation at the neuronal synapse – Soyon Hong

Genetic studies in humans as well as functional studies in mice implicate a critical role for microglia in modulating risk for Alzheimer Disease (AD). One crucial function of microglia, as the major brain-resident macrophages, is to eliminate synapses in development and disease, in part via the activation of the classical complement cascade (Bartels et al., Science 2020). In AD, this synapse-engulfment pathway is aberrantly reactivated in a region-specific manner to mediate synapse loss and dysfunction; however, what reactivates the microglial-synapse engulfment pathway in disease remains elusive. Here we use various profiling tools as well as in vivo manipulations of neuronal activity to dissect the triggers of the synapse engulfment pathway in microglia. I also discuss potential consequences of this reactivation in AD mouse models.

15:00 – 15:30 Lectin Pathway - Wilhelm Schwaeble

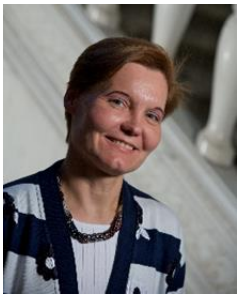
In evolutionary terms, the lectin activation pathway of complement is by far the oldest activation pathway driven by specific recognition subcomponents that bind to pathogen-associated carbohydrate pattern and acetylated surface components and initiate complement activation. It recognises and responds to microbial and viral pathogens and fulfils an important scavenger function by activating complement to facilitate the removal of injured or apoptotic cells. Beside the central role of the Lectin pathway in the innate immune defence uncontrolled and overshooting activation of the lectin pathway critically contributes to severe immune pathology in an ever-increasing list of human diseases, such as stroke, myocardial infarction, renal ischemia and significantly contributes to microangiopathies in a wide spectrum of infectious and non-infectious human pathologies. Since complement can be activated by three independently operating routes, the specific targeting of the lectin activation pathway provides a safe route for therapeutic interventions without the risk of losing the complement-dependant protection against a vast majority of microbial pathogens.

8. SPEAKERS AND TUTORS

Professor Sir Leszek Borysiewicz

MA PhD FRS FRCP FMedSci Chair, Cancer Research UK

Sir Leszek was appointed as a Trustee to Cancer Research UK in July 2016 and as Chair in November 2016. He also serves on the Councils of the Courtauld Institute and Imperial College. Following a distinguished academic and clinical research career and prior to his appointment as ViceChancellor at the University of Cambridge in 2010, Sir Leszek's roles included Chief Executive of the Medical Research Council and Deputy Rector of Imperial College London. He was also a founding Fellow of the Academy of Medical Sciences and elected Fellow of the Royal Society. His work in vaccines included Europe's first trial of a vaccine for human papillomavirus to treat cervical cancer at the University of Cardiff and funded by Cancer Research UK. He was knighted in 2001 for his pioneering work in vaccines



Professor Marina Botto

Head of the Department of Immunology and Inflammation, Professor of Rheumatology and Director of Bioservices at Imperial College London. Consultant Rheumatologist at Imperial Academic Health Science Centre, Hammersmith Hospital Campus.

The focus of Professor Botto's research programme is to understand how Complement deficiency contributes to the autoimmune disease, systemic lupus erythematosus (SLE). Her laboratory is particularly interested in understanding the consequences of inherited complement deficiencies in humans and the role(s) that the complement system plays in the clearance of dying cells as well as immune complexes. Using in vivo models, genetic and cellular approaches and experimental models of inflammation she has demonstrated that i) inherited defects in the pathways for clearance of cellular debris and immune complexes predispose to the development of SLE; ii) there is a link between spontaneous autoimmunity and abnormalities of the physiological clearance of apoptotic cells in humans with complement deficiency; iii) the complement system modulates the adaptive immune system; iv) autoimmunity varies according to the genetic background of the model used and identified lupus susceptibility loci. The laboratory currently aims to delineate the contribution of Complement system in the induction and resolution of inflammation and to define the mechanisms by which the complement system regulates the tolerance to self-antigens.

Professor Simon Clark

Helmut Ecker Endowed Professor of AMD at the Institute of Ophthalmic Research, University of Tübingen, Germany.

Simon is the Helmut Ecker Endowed Professor of AMD at the Institute of Ophthalmic Research, University of Tübingen, Germany, where he leads a research team studying the molecular mechanisms driving age-related macular degeneration (AMD), the third leading cause of blindness worldwide. In particular his work focuses on the role of the complement system, a powerful part of a host's immune system, in the development of this devastating disease and how the modulation of such as response can be harnessed to slow disease progression.

Simon's translational portfolio includes the development of novel complement modifiers that can be used as therapeutics in complement-mediated diseases of the eye, as well as around the body. He also helps develop new diagnostic tools for complement driven disease and methods for patient stratification for future treatment.

In 2015 Simon co-founded the Manchester Eye Tissue Repository (ETR) with Prof. Paul Bishop, where genotyped and phenotyped human eye tissue is collected and stored to act as an international resource for academic research into eye diseases: one of the only such resources in Europe.

Professor Santiago Rodriguez de Cordoba

Department of Molecular Biomedicine, Center for Biological Research, Madrid

Professor Santiago Rodriguez de Cordoba completed his PhD at the Universidad Complutense de Madrid in 1981. He then took a post as visiting Scientist/Associate investigator at the Department of Immunogenetics, New York Blood Center, New York (1981-1989). Following this he became an Associate Professor at his current place of work, Centro de Investigaciones Biologicas, Madrid; and was promoted to Professor in 2000. From 2007 to 2010 he was Head of the Department of Cellular and Molecular Physiopathology. Has served as Vicepresident of the Spanish Human Genetics Society from 2010 to 2014 and as an elected member of the Scientific Boards of the International Complement Society and European Complement Network.

Prof. Rodriguez de Cordoba leads the Complement Genetics and Molecular Pathology laboratory at the Centro de Investigaciones Biologicas. After previous successes in characterizing the molecular bases of various rare diseases (Alkaptonuria, 3-Methylcrotonylglycinuria, Anophthalmia and Lafora Disease), much of his recent work is focused on disorders due to dysregulation of the Complement system, like atypical Hemolytic Uremic Syndrome, C3-glomerulopathy and Age related Macular Degeneration. Research work in his laboratory has produced 270 scientific papers and reviews. His contributions to understanding the molecular bases of rare diseases are internationally recognized. Among various awards, he received in 2009 the Spanish National Genetics Award and in 2019 the Gold Medal of the European Complement Network.

Prof. Rodriguez de Cordoba is a co-founder of Secugen S.L., a company focused on the molecular diagnostic of inherited disorders.

Dr Scott Ellis

Head Of Research and Development, Gyroscope Therapeutics Ltd

I have always had a strong interest in understanding the genetics of human disease. Graduating from University College London with a PhD in Genetics in 1999, I moved to the Brunel Institute for Cancer Genetics and Pharmacogenomics at Brunel University (London) to work on the identification of tumour suppressor genes. In 2002 I moved to the Wellcome Trust Centre for Human Genetics in Oxford to identify genes that were involved in heart disease. However, during this time I realised my real passion was in not just to understand the genetics of human disease but to apply this knowledge to the treatment of disease itself, so in 2006 I joined Oxford Biomedica to start a career in gene and cell therapy Product Development and was ultimately responsible for the research and development of the Company's product pipeline as Head of Early Development. During this time I saw preclinical programmes progress into the clinic for chronic ocular conditions such as wet age-related macular degeneration (AMD), Stargardt disease and Usher syndrome. In 2017 I was recruited to join an exciting start-up gene therapy company targeting the complement system to treat eye disease (Gyroscope Therapeutics), where I am responsible for the development of both the early pipeline programmes and platform technologies as SVP Preclinical Research. We treated our first patient with GT005, our lead programme for dry AMD, at the start of 2019 and this is now under evaluation in two Phase II studies. Developing such complex therapies, taking them from concept through to the clinic, overcoming the many and varied challenges along the way, has been incredibly interesting and extremely rewarding.

Professor Claire Harris, PhD, UK

Executive Director, Complement Translational Research, Gyroscope Therapeutics/Novartis; Honorary Professor, Cardiff University; Visiting Professor, Newcastle University

Claire's interest in complement dates back to her undergraduate days when she was inspired by teaching on innate immunity and was intrigued by the ability of a protein-based, soluble system to punch holes in target cells! Her interest in complement grew while studying complement during her PhD in Cambridge and postdoc in Cardiff. Funding from the Wellcome Trust (2003) enabled her to establish a group at the School of Medicine in Cardiff focused on structure–function relationships in complement activators and regulators with a particular interest in the mechanisms underlying complement dysregulation and disease. Three years spent as Head of Complement at GlaxoSmithKline provided invaluable insight into the process of target and indication validation and drug discovery (2013-2016), and she joined Newcastle University in 2016 to further her work in translational research and experimental medicine. Bitten by the drug discovery bug, in 2020, Claire joined Gyroscope Therapeutics, a Biotech developing gene therapies for AMD. She became an Executive Director at the Novartis Institute for Biomedical Research following Gyroscope's acquisition in 2022, where she heads

Complement Translational Research at the Gyroscope site in London. Her focus remains therapeutic approaches for modulation or inhibition of the complement cascade in ocular and systemic disease with a keen interest in complement biomarkers of disease to determine patient stratification, target engagement and biomarkers of disease.

Dr Meike Heurich

Senior Lecturer, School of Pharmacy and Pharmaceutical Sciences, Cardiff University

Dr Heurich began working in complement research in 2008, focussing on the structure/function analysis of complement proteins and their impact on complement activity and regulation in the Morgan/Harris lab (School of Medicine, Cardiff University) resulting in the establishment of the Complotype.

In 2012, she received an independent career development fellowship funded by the Welsh Government to conduct research into the cross-interactions of complement proteins with the coagulation system. She was appointed Lecturer at the Cardiff School of Pharmacy and Pharmaceutical Sciences in 2017 (and Senior Lecturer in 2022) where she leads the immunology teaching and research into cellular and molecular biochemistry of blood proteins with a particular interest in the molecular interactions of the complement and coagulation system. Her research group is studying protein binding interaction, kinetics and affinity, and protein structure-function relationships using biophysical (SPR/Biacore) and biochemical approaches.

Her clinical research focus is centred on studying altered protein levels in blood plasma and protein dysfunction in disease, where the complement and coagulation pathways have a role in pathophysiology, with a particular focus on the role of these pathways in the development of psychosis. Her other interests are in complement and coagulation biomarker and drug discovery.

Soyon HONG

Group Leader, Immune mechanisms of synaptic function and pathology, UK DRI at UCL

Dr Soyon Hong studies immune mechanisms of synaptic health and function in the central nervous system. In particular, the Hong lab examines how microglia, the brain's principal tissue-resident macrophages, communicate with other immune cells and glia including astrocytes to eliminate synapses in Alzheimer's disease and Parkinson's disease. Soyon received her PhD in Neuroscience from Harvard University and completed her postdoctoral fellowship at Boston Children's Hospital/ Harvard Medical School. Soyon started her independent laboratory in UK Dementia Research Institute at UCL October 2018. She studied microglia biology with Thomas Möller and Michel Kliot (2002-2006), Alzheimer-type synapse pathology with Dennis Selkoe (2007-2012), and microglia-synapse pruning with Beth Stevens (2012-2018), where she identified microglia as synaptic saboteurs. More info.

Professor David Kavanagh

Professor of Complement Therapeutics at the National Renal Complement Therapeutics Centre (NRCTC)

David Kavanagh graduated in Medicine and Immunology from the University of Glasgow in 1998. Following basic medical training he undertook a PhD at Newcastle University elucidating the genetics of atypical Haemolytic Uraemic Syndrome (aHUS). He then undertook a post-doctoral research fellowship in Washington University School of Medicine, St. Louis examining the functional consequences of genetic variants in the complement system in aHUS. He returned to the UK in 2006 to take up a Kidney Research UK Fellowship at the University of Edinburgh Biomolecular NMR unit, examining structure/function relationships in complement factor H. He moved back to Newcastle in 2008 to form his own research group with a Wellcome Trust Fellowship. For his work on aHUS, he was awarded the Renal Association's Young Investigator (Raine) award in 2009. His research group currently investigates complement in renal and retinal diseases and is fully integrated with the NRCTC to provide rapid translational benefits to patients.

Dr Richard Kelly FRCPath, PhD

Consultant Haematologist, Institute of Oncology, St James's University Hospital, Leeds, UK

Dr. Richard Kelly is a Consultant Haematologist at Leeds Teaching Hospitals NHS Trust and Honorary Senior Lecturer at the University of Leeds, UK. He is the Leeds joint lead for the English National Paroxysmal Nocturnal Haemoglobinuria (PNH) Service.

He qualified with honours from the University of St. Andrews and completed his training at the University of Manchester.

He was involved in setting up the English National PNH service in 2007. In 2014 Dr. Kelly received his PhD thesis on "The Pathogenesis of PNH" with an award for research excellence from the University of Leeds and he has published key papers on PNH in peer reviewed journals.

Dr Kelly is a board member of the International PNH Interest Group (IPIG) with responsibility for the design and running of the planned IPIG global PNH registry. He chairs the IPIG registry stakeholder committee and sits on the IPIG registry committee.

He has been a regional lead for the acute lymphoblastic leukaemia (ALL) service since 2014. He is a principal investigator for clinical trials in PNH, ALL, acute myeloid leukaemia and haemolytic anaemias. He also sits on the NCRI ALL subgroup.

Dr Kelly is a Fellow of the Royal College of Pathologists and a member of the British Society for Haematology. He is also an examiner for the Royal College of Pathologists.

Dr Alex Macpherson

Executive Director, the computational chemistry and cheminformatics group at Eli Lilly & Co.

Alex works as an Executive Director within the computational chemistry and cheminformatics group at Eli Lilly & Co. Prior to this, Alex worked as a Senior Principal Scientist at UCB, where he lead the molecular immunopathology research group and various pre-clinical NCE and NBE projects. While at UCB, Alex undertook an industrial PhD with the van den Elsen lab at the University of Bath, which focused on a structurally unique subset of bovine immunoglobulins and isolated the smallest antibody fragments described to date. This work enabled the discovery and structural characterisation of novel allosteric modulators of complement C5.

Professor Kevin Marchbank

Professor of Complement Biology, Newcastle University

Professor Marchbank is a complement biologist and B cell immunologist with a focus on kidney and eye disease. His research group is part of the Complement Therapeutics Research Group which includes the groups of Prof's Neil Sheerin and David Kavanagh. He is also head of autoimmune research and analysis at the National Renal Complement Therapeutics Centre (NRCTC), RVI, Newcastle-upon-Tyne. Professor Marchbanks current interests include the role of anti-complement protein autoantibodies in aHUS and C3G (MPGN) as well as the development of Factor H based therapeutics (including gene therapy), primarily for the treatment of C3G and IgA. His main area of research remain focussed on a variety of small animal models of aHUS, C3G and IgA Nephropathy. With Prof Sheerin, the Marchbank group has also developed a significant interest in control of complement-mediated renal damage caused in transplant.

Professor Paul Morgan

Professor of Immunology, School of Medicine, Cardiff University

Professor Paul Morgan graduated from the Welsh National School of Medicine in 1980. He specialised in Clinical Biochemistry, obtaining his PhD in 1984. Following two years in the US, he returned to Cardiff University to take up a Wellcome Trust Senior Clinical Fellowship; he remained a Fellow for 15 years. He was Dean of Medicine and Head of the School of Medicine in Cardiff University 2009 - 2013. He is a Fellow of the College of Pathologists,

Fellow of the Academy of Medical Sciences, Fellow of the Learned Society of Wales and Fellow of the Academia Europaea. He has created an internationally leading Complement Biology research group at Cardiff and published over 400 research papers exploring basic biology of complement, roles of complement in disease and strategies to inhibit complement for therapy.

He is a PI and former Director of the Systems Immunity Institute and a Programme Lead in the Dementia Research Institute UK, Cardiff. His current research is focussed on roles of complement in neurodegenerative diseases.

Website link(s): https://www.cardiff.ac.uk/people/view/126579-morgan-paul

Professor Matthew Pickering

Wellcome Trust Senior Fellow in Clinical Science and Honorary Consultant Rheumatologist at Imperial College Academic Health Sciences Centre

Prof. Pickering is an established international expert on the complement system and its role in health and disease. He is a Wellcome Trust Senior Fellow in Clinical Science and his research program has been funded by the Wellcome Trust since 2003. His clinical expertise includes systemic lupus erythematous and complement deficiency states. He is a Professor of Rheumatology at Imperial College and Academic Director of the Imperial Lupus Centre. He was Head of Specialty, Rheumatology, Imperial Healthcare NHS Trust between 2014 and 2019. His research has achieved international recognition for elucidating the relationship between uncontrolled complement activation and renal disease. His research program has utilized genetic characterization of families with complement-mediated renal disease, the in vitro studies of complement regulatory proteins and the generation of unique murine models of complement-mediated kidney disease. He is a member of both the International Complement Society and the European Complement Network.

Professor Steven Sacks

Professor of Nephrology, Former Director, MRC Centre for Transplantation, NIHR Emeritus Senior Investigator, King's Health Partners Clinical-Academic Lead in Transplantation & Abdomen, King's College London

Professor Steve Sacks is an academic nephrologist undertaking research on locally made complement components and impact in organ transplantation. This has led to new therapeutic and imaging approaches that are either at or close to clinical evaluation. More recently, his laboratory has identified tissue stress-associated carbohydrate ligands recognised by the complement system, which are being further characterised to enable specific detection and blockade in medical conditions. On-going responsibilities as NIHR Senior Investigator, Fellow of the Academy of Medical Sciences and Executive Committee member/Co-founder of Complement UK allow Professor Sacks to influence research and training policy and build public confidence in research.

Professor Wilhelm Schwaeble

Director of Research, University of Cambridge

Professor Wilhelm Schwaeble is an immunologist at the University of Cambridge. His research focusses on the roles of the complement system in pathophysiology of diseases caused through an overreactive immune response and he developed immune therapeutic reagents targeting early activation events that initiate and maintain inflammatory disease.

His work has been generously funded by the WELLCOME TRUST, the MRC and Royal Society/Wolfson Foundation throughout and he developed and maintained a strong portfolio of patents through the long-term collaboration with an industrial partner, OMEROS Corporation in Seattle. USA. Most recently he received generous support from the NIHR/MRC to analyse the molecular basis of events that initiate and maintain the moderate to severe inflammatory endothelial disease caused in some individuals infected with SARS-CoV-2 now known as COVID-19. This Cambridge based consortium "Humoral Immune Correlates of COVID-19" jointly lead by him with Doctor Helen Baxendale as Clinical Lead and the virologist Professor Jonathan Heeney analyses the immune response profiles in plasma and sera of patients with mild and severe exacerbations of COVID-19 in a longitudinal study. He developed various therapeutic reagents that modulate complement activation for each of the three complement activation pathways which are presently assessed at various stages in clinical trials.

Professor Neil Sheerin

Professor of Nephrology at Newcastle University and a Consultant Nephrologist at the Freeman Hospital, Newcastle upon Tyne.

Professor Sheerin moved to Newcastle in 2007 from Guy's Hospital, London where he was a Senior Lecturer in Renal Medicine and before that a Wellcome Trust Fellow. His laboratory research is focused on immune mediated renal disease, with a specific interest the role of the complement system in native and transplant kidney disease and complement therapeutics. His clinical interests include complement-mediated renal disease, kidney transplantation and the treatment of patients with progressive chronic kidney disease.

Professor Jean van den Elsen

Professor of Biochemistry in the Department of Life Sciences at the University of Bath.

Jean has a particular interest in the molecular aspects of the interactions between pathogenic microbes and the immune system of the host. His group studies the structural and functional aspects of microbial immune evasion proteins that modulate the complement system, with the aim to help design better vaccines and drugs for the treatment of autoimmune diseases. Recent work from his lab involves the development of highly specific antibody fragments, derived from bovine immunoglobulins, as potent allosteric complement inhibitors.

Dr Erik Toonen

Hycult Biotechology (https://www.hycultbiotech.com/) is a world-class manufacturer of antibodies, proteins and immunoassays within the fields of innate immunity and inflammation, in particular related to complement.

Dr. Erik Toonen, PhD has a background in molecular biology, immunology and biomarker discovery. He has extensive knowledge in the fields of (auto)immunity, inflammation and its related diseases and has expertise in all aspects of assay development.

Mr Loek Willems

Hycult Biotechology (https://www.hycultbiotech.com/) is a world-class manufacturer of antibodies, proteins and immunoassays within the fields of innate immunity and inflammation, in particular related to complement.

Mr. Loek Willems, BSc: Expert in business development and intellectual property management and has a background in biochemistry and assay development.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9. POSTER PRESENTATIONS

ROOM: Exhibition area (Ground floor)

P-01 Lack of Complement Factor H contributes to endothelial cell injury in Shiga toxin Haemolytic Uraemic Syndrome, Emily Bowen

P-02 Functional relevance of genetic associations at complement genes with risk of Alzheimer's disease, Samuel Keat

P-03 Characterising complement in amyloid-beta plaques, Lewis Watkins

P-04 GWAS of plasma complement protein levels reveals functional effects of Alzheimer's disease risk loci, Aurora Veteleanu

P-05 Evaluation of minimal Factor H therapy administered to kidneys during ex vivo normothermic perfusion as a treatment to improve ischaemia reperfusion injury, Chloe Connelly

P-06 Performance of a C2 Assay for use with EDTA plasma, Lithium Heparin plasma, and serum on the Binding Site Optilite Analyser, Jake Fisher

P-07 Performance of a C1q Assay for use with Serum, EDTA plasma and Lithium Heparin plasma on the Binding Site Optilite Analyser, Iasmina Gavrilas

P-08 The potent anti-inflammatory product of HMGB1 cleavage by the complement C1s, Marie Lorvellec

P-09 Generation of Novel Antibodies Targeting the Putative Complement Regulatory Domain of CSMD1, Robert Byrne

P-10 Short- and long-term blood and urine storage: implications for complement C5b-9 research and diagnostic development, Martin Schmidt

P-11 Complement dysregulation in Long COVID, Kirstie Baillie

P-12 Roles of complement dysregulation and membrane attack complex formation in developmental synapse loss, Sarah Carpanini

P-13 Complement in clinical trials: the search for human complement challenge models, Juliette van den Noort

P-14 Complement receptor 1 is expressed on brain cells and impacts roles of microglia relevant to Alzheimer's disease, Nikoleta Daskoulidou

P-15 A Novel Functional Properdin Assay – Studying the Positive AP Regulator and Complement Amplification Loop, Samuel Butler

P-16 Differential expression of complement activation markers in the blood of individuals with clinical high-risk for pyschosis, Eleftheria Kodosaki

P-17 Utilising biomarkers to diagnose MS and predict long-term outcomes, Eleftheria Kodosaki

P-18 Measurement of complement deposition at the neuromuscular junction in passive transfer myasthenia gravis in rats, Anja Schöttler

P-19 Complement activation in response to hypoxia and reoxygenation in tubular epithelial cells, Saltanat Moldakhmetova

P-20 Differentiating between activation via the lectin or the classical complement pathway in Systemic Lupus Erythematosus patients, Mads Lamm Larsen

P-21 Safety, Tolerability and Pharmacodynamic Effects of ARO-C3, a Subcutaneously Administered Investigational RNAi Therapeutic Targeting Complement C3, in Adult Healthy Volunteers, Mads Hamid Moradi

P-22 Levels of soluble complement regulators predict severity of COVID-19 symptoms, Anna Tierney

P-23 Complement inhibitors for age-related macular degeneration (AMD): A Cochrane systematic review and meta-analysis, Nikolas Tzoumas

P-24 Complement profiles throughout adolescent development, Laura Westacott

P-25 PET/CT imaging of Blood-Brain Barrier Integrity and inflammatory tracers during Alzheimer's Disease, Basma Alenezi

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10. ABSTRACTS

P-01	
Title:	**Lack of Complement Factor H contributes to endothelial cell injury in Shiga toxin Haemolytic Uraemic Syndrome.**
Author(s):	Emily E. Bowen[1, 2], Jenny Hurcombe[1], Fern Barrington[1], Louise K. Farmer[1], Carolina Ortiz[2], Valentina Bruno[2], Gavin I. Welsh[1], Christoph Licht[2], Moin Saleem[1], Richard Coward[1]
Institute(s):	1. University of Bristol Faculty of Health Sciences, Bristol, Bristol, United Kingdom. 2. SickKids Research Institute, Toronto, ON, Canada.
Presenter:	**Dr Emily Elizabeth Bowen**
Abstract (max 300 words):	**Introduction**: Haemolytic uraemic syndrome (HUS) is a thrombotic microangiopathy that has a predilection for the kidney. In 90% of cases, HUS follows gastroenteritis secondary to infection with Shiga toxin (Stx) producing bacteria such as Escherichia coli. STEC HUS is the leading cause of acute kidney injury in children with a mortality of 5%. We have previously shown endothelial cell complement activation in a PodGb3 mouse model of STEC HUS. Here we build upon these findings to show that a reduction in glomerular endothelial CFH occurs both in our animal model and in-vitro co-culture models. **Methods**: To demonstrate that the podocyte Stx receptor (Gb3) is sufficient to trigger the development of HUS, we used conditional gene targeting to engineer human Gb3 expression specifically in the podocytes of mice (PodGb3). Using an in-vitro human glomerular cell co-culture model we evaluated the effects of Stx on endothelial cell injury, complement activation (C3b, C5b-9) and regulation (CD46, CD55, CFH). **Results**: Following intraperitoneal Stx, PodGb3 mice recapitulate all of the histopathological features of HUS. Further interrogation demonstrated glomerular endothelial cell complement activation, loss of CFH protection and rescue of the HUS phenotype following C5 inhibitor treatment. Interestingly, in co-culture studies Stx caused a reduction in glomerular endothelial (GEnC) CFH that was most significant when GEnCs were co-cultured with podocytes. **Conclusion**: These observations provide compelling evidence for the importance of podocyte-glomerular endothelial cell cross-talk in the development of STEC HUS and suggest a possible therapeutic role for complement inhibition in patients with this devastating disease.

P-02	
Title:	**Functional relevance of genetic associations at complement genes with risk of Alzheimer's disease.**
Author(s):	Samuel Keat, Dr Rebecca Sims, Professor Paul Morgan, Dr Atahualpa Castillo Morales
Institute(s):	Dementia Research Institute, Cardiff University, Department of Psychological Medicine and Clinical Neurosciences, Cardiff University
Presenter:	**Samuel Keat**
Abstract (max 300 words):	**Introduction** Through the presentation of genetic and physiological evidence, the complement system is a strongly hypothesised associated mechanism for AD aetiology. The presence of numerous significant AD Genome Wide Association Study (GWAS) hits tied to complement genes, alongside the evidence that complement activation is a key factor in AD associated synapse loss, has established complement system dysregulation as a well-founded research avenue in potential AD mechanisms and a possible target for future therapeutics. However, whether these relationships between complement gene polymorphisms and biological AD mechanisms are causal or secondary to disease remains poorly understood; complicated further by AD GWAS significant SNPs being found in non-coding regions of complement genes, such as CR1. Single Nucleotide Polymorphisms (SNPs) within in the CLU locus have been demonstrated to increase an individual's risk of developing AD, however the exact mechanism of their effects is unknown. This project will aim to address the paucity of knowledge surrounding complement genes, such as CLU, in AD pathology through a variety of bioinformatic approaches to identify potentially functional genetic variants and then confirming that the variant-linked altered complement levels are involved in AD associated changes using cell culture models. **Methods** From identifying potentially functional variants from AD genotype data, we will then investigate AD chromatin interaction and conformation data (such as ChIP-seq/Hi-C and ATAC-seq), coupled with deeply phenotyped patient data to identify the strongest candidate variants – whilst using available long-read sequencing data to identify rarer variants in long homologous regions and construct a novel genotype imputation panel.

P-03	
Title:	Characterising complement in amyloid-beta plaques.
Author(s):	Lewis Watkins, Megan Torvell, Jacqui Nimmo, Nikoleta Daskoulidou, Sarah Carpanini, Wioleta Zelek, B. Paul Morgan
Institute(s):	Dementia Research Institute at Cardiff University
Presenter:	Lewis Watkins
Abstract (max 300 words):	Introduction Complement is a major component of the innate immune response as it orchestrates immunological and inflammatory processes. Measurements of complement in plasma are highly predictive of Alzheimer's disease (AD) progression and variants in complement genes have been associated with an increased risk of AD in genome-wide association studies. Some animal models also support a role for complement in AD pathogenesis. Amyloid-β (Aβ) plaques are a pathological hallmark of AD in the grey matter with several plaque subtypes being described. Complement activation and plaque formation are mutually promoting mechanisms; aggregated Aβ binds to C1q; further enhancing Aβ aggregation and fibril formation. Previous studies have shown complement bound to Aβ plaques, however, the timing of when complement binds to these plaques and whether different complement components bind different plaque subtypes remains unknown. Methods Using immunohistochemistry, we characterised complement expression and activation on Aβ plaques from post-mortem tissue of five human Braak stage VI AD patients. The tissue was digitally scanned so that a similar area of the tissue was analysed, enabling us to identify plaques from different complement components of the classical, alternative, and terminal pathways. Results Expression of the complement components C1q, C3b/iC3b, and C9neo were present on Aβ (6E10) plaques throughout the cortical grey matter. Complement-positive microglia/astrocytes also were found closely apposed to Aβ plaques. C1q was present on Aβ plaques or peri-plaque cells in 92.1% of Aβ plaques analysed. The proportion of C3b/iC3b-positive Aβ plaques and peri-plaque cells was 88.8%. The proportion of Aβ plaques and peri-plaque cells immunostained for the membrane attack complex (C9neo) was 33.8% and was found on diffuse, dense-core, neuritic, and burnt-out plaques. Discussion Expression of complement activation and recognition fragments of the classical, alternative, and terminal pathway are present on Aβ plaques and indicates that the complement cascade is activated at all stages of Aβ plaque evolution.

P-04	
Title:	**GWAS of plasma complement protein levels reveals functional effects of Alzheimer's disease risk loci.**
Author(s):	Aurora Veteleanu, Joshua Stevenson-Hoare, Samuel Keat, Nikoleta, Daskoulidou, Henrik Zetterberg, Amanda Heslegrave, Valentina Escott-Price, Julie Williams, Rebecca Sims, Sarah Carpanini, Wioleta Zelek, B. Paul Morgan
Institute(s):	UK Dementia Research Institute at Cardiff University UK Dementia Research Institute at UCL
Presenter:	**Aurora Veteleanu**
Abstract (max 300 words):	**Introduction:** Alzheimer's disease (AD) has been associated with immune dysregulation in biomarker and genome-wide association studies (GWAS), which identified the complement genes *CR1* and *CLU* as significant hits. We assessed whether complement proteins are AD biomarkers, and whether AD-associated complement gene variants impact plasma complement levels. **Methods:** Complement proteins, amyloid beta, tau, and neurodegeneration biomarkers were quantified in AD (n=1404) and control (n=504) plasma samples. ROC analyses were used to assess biomarker utility in predicting AD. Effects of SNPs in *CR1*, *CLU, C1S,* and *CFH* on protein concentrations were assessed through GWAS. **Results:** Clusterin and C1q were significantly increased ($p<0.001$) and sCR1 and factor H reduced ($p<0.01$) in AD plasma versus controls. SNPs in *CR1* (rs6656401), *C1S* (rs3919533) and *CFH* (rs6664877) reached genome wide significance and influenced plasma protein levels. SNPs in *CLU* did not influence clusterin levels. ROC analyses identified C1q as the most predictive complement biomarker (AUC 0.68). **Discussion:** Complement dysregulation occurs in AD and may contribute to pathology. Specific SNPs in *CR1*, *C1S,* and *CFH* may influence disease risk through altered plasma protein levels.

P-05	
Title:	Evaluation of minimal Factor H therapy administered to kidneys during ex vivo normothermic perfusion as a treatment to improve ischaemia reperfusion injury.
Author(s):	Chloe M Connelly, Beth Gibson, Balaji Mahendran, Samuel J Tingle, Lucy Bates, Madison Cooper, Emily Thompson, Colin Wilson, Neil Sheerin, Kevin Marchbank
Institute(s):	Newcastle University
Presenter:	Chloe M Connelly
Abstract (max 300 words):	**Introduction:** Complement activation is a key mechanism of Ischaemia reperfusion injury, with the alternative pathway driving damage in particular. The main regulator of the alternative pathway is factor H. We hypothesised that homodimeric mini-factor H (HDM-FH; PMID:29588430) may protect the transplanted kidney from complement mediated damage when administered during normothermic perfusion machine perfusion (NMP). **Methods:** In the first arm of the study, a model of porcine whole blood perfusion was optimised by extending retrieval and static cold storage (SCS) times of porcine kidneys to assess the full efficacy of HDM-FH. Kidneys were retrieved from female white landrace pigs following this optimised protocol. One kidney from each pair was randomised to receive 5mg of HDM-FH (~8µg/mL). Kidneys were perfused at 37°C with autologous blood for 6 hours. HDM-FH binding was measured using ELISA and immunofluorescence. Complement activation was measured by quantifying Bb deposition in tissue. The ability of HDM-FH to inhibit complement in serum was measured using haemolytic assays. **Results:** 25 minutes retrieval time followed by 16hrs SCS led to an increase in complement activation and markers of ischaemic injury. ~4mgs of HDM-FH bound from perfusate during perfusion, with <10% lost in urine suggesting saturation was achieved. HDM-FH binding within the kidneys was confirmed using immunofluorescence. HDM-FH localised to glomeruli with deposition increasing over the time of the perfusion. Alternative pathway activation was reduced in kidneys receiving HDM-FH as demonstrated by reduced Bb deposition. Fibrinogen deposition was also reduced and found to colocalise with C3 in glomeruli. HDM-FH inhibits complement activity in serum in a dose-dependent manner. **Discussion:** Infusion with HDM-FH prior to simulated kidney transplant conditions reduced complement activation and other secondary negative outcomes to the organ. Therefore, organ perfusion with HDM-FH is highly likely to help prolong graft survival after transplant and this will be assessed in future studies.

P-06	
Title:	**Performance of a C2 Assay for use with EDTA plasma, Lithium Heparin plasma, and serum on the Binding Site Optilite Analyser.**
Author(s):	J. Fisher, K. Cappato da Costa, D. Edwards, A. Mulla, P. Showell, M. McCusker, I. Bell, S. Harding
Institute(s):	The Binding Site Group Ltd, Birmingham, United Kingdom
Presenter:	**J. Fisher**
Abstract (max 300 words):	**Introduction** Here we describe the performance testing of a C2 assay for use on the Binding Site's Optilite® analyser. C2 deficiency is the most common inherited complement component deficiency and is associated with a variety of autoimmune diseases including systemic lupus erythematosus (SLE), glomerulonephritis and vasculitis. The C2 assay for the Optilite analyser is programmed to produce a multi-point calibration curve from a single calibrator, with a measuring range of 2.29 - 25.78 mg/L for EDTA plasma, Lithium Heparin plasma, and serum at a standard 1+9 dilution. High samples are automatically re-measured at a dilution of 1+19, with an upper limit of 51.57 mg/L. **Methods and Results** A linearity study was performed as per EP06-ED2:2020 using human EDTA plasma diluted into C2-depleted EDTA plasma. Linearity was demonstrated over a range of 1.94 mg/L – 40.82 mg/L. A precision study was performed following EP05-A3:2014, testing three EDTA plasma levels over 20 days. Between-analyser and between-lot precision were similarly evaluated. Within-run, between-run, between-day and total precision displayed CV% of ≤5.6%. Between-analyser precision was observed at a maximum of 5.5%, and between-lot precision at a maximum of 3.7%. Analytical sensitivity was challenged as per EP17-A2:2012 across three days and two kit lots. A limit of quantitation of 2.29 mg/L was verified, where the maximum CV for this sample type was 8.50%. A reference interval was generated as per EP28-A3C:2010, with 120 EDTA plasma samples from healthy donors and gave a 95th percentile range of 10.6 – 23.9 mg/L. This matched closely with reference ranges produced using C2 radial immunodiffusion (RID) kits of 10-30 mg/L (Sheffield Protein Reference Unit & Immunology Department, UK). **Discussion** In conclusion, the C2 assay for use on the Optilite® provides a reliable and precise method for quantifying C2 in serum, lithium-heparin and EDTA plasma samples and correlates well with existing methods.

P-07	
Title:	**Performance of a C1q Assay for use with Serum, EDTA plasma and Lithium Heparin plasma on the Binding Site Optilite Analyser.**
Author(s):	I. Gavrilas, I. Bell, J.F. Borg, P. Showell, M. McCusker, S. Harding.
Institute(s):	The Binding Site Group Ltd, Birmingham, United Kingdom
Presenter:	**I. Gavrilas**
Abstract (max 300 words):	**Background:** Here we describe the performance testing of the C1q assay for use on the Binding Site's Optilite® analyser. Measurement of C1q provides a useful marker that aids the characterisation of low complement activity in immunological disorders such as complement deficiencies, systemic lupus erythematosus (SLE) and glomerulonephritis. The C1q assay for the Optilite® analyser is programmed to produce a multi-point calibration curve from a single calibrator, with a measuring range of approximately 15-300 mg/L at a standard 1+14 dilution. Low or high samples are automatically re-measured giving the assay a full measuring range of approximately 11-460 mg/L. **Method and Results** A linearity study was performed as per EP06-ED2:2020. Linearity was demonstrated over a range of 7.52 -523 mg/L. A twenty-day precision, as well as between lot and between instrument precision was assessed as per EP5-A3. The precision assessment displayed within-run, between-run, between day and total precision CV% ≤ 3.8%. Between instrument precision was observed at a maximum of 1.5%, and between lot precision at a maximum of 2.1%. Analytical sensitivity was challenged as per EP17-A2:2012 across three days and two kit lots. A limit of quantitation of 10.5 mg/L was verified, where the maximum CV% for this sample type was 5.6%. A reference range generated from 120 serum samples from healthy European donors gave a 95th percentile range of 119 to 195 mg/L. This verifies the reference range quoted by the C1q radial immunodiffusion (RID) predicate device (118-244 mg/L). **Conclusion:** The C1q assay for use on the Optilite® provides a reliable and precise method for quantifying C1q in serum, lithium-heparin and EDTA plasma samples and correlates well with existing methods.

P-08	
Title:	The potent anti-inflammatory product of HMGB1 cleavage by the complement C1s.
Author(s):	Marie Lorvellec, Anne Chouquet, Isabelle Bally, Jonas Koch, Jeanne Vigne, Luca Signor, Nicole Thielens, Thierry Rabilloud, Bastien Dalzon, Véronique Rossi and Christine Gaboriaud
Institute(s):	Institute of Structural Biology (IBS - Grenoble, France) Laboratory of Chemistry and Biology of Metals (LCBM – Grenoble, France)
Presenter:	Marie Lorvellec
Abstract (max 300 words):	Introduction The HMGB1 protein was discovered as a DNA-binding protein regulating chromatin condensation and gene transcription. However, the protein can be released by dying and immune cells. In the extracellular medium, HMGB1 is detected as an alarmin by the immune system, with an interplay with the complement system. Here, the focus is on HMGB1 as a non-canonical target of the complement C1s protease. Methods HMGB1 digestion by the C1s protease was studied at different enzyme/substrate ratios at different times using SDS-PAGE and Western Blot analysis. The identified N-terminal cleavage fragments were produced and purified to test their effects on inflammatory regulation. This was done using RAW264.7 cell lines to analyze pro-inflammatory cytokines IL-6 and TFNα upon stimulation with LPS in complex with HMB1 or its fragments. Results HMGB1 is cleaved into three main N-terminal fragments by the C1s protease. The shorter fragment, F3, includes a large part of the A-box, known as an antagonist of full-length HMGB1 (when not complexed). When complexed with LPS, HMGB1 shows pro-inflammatory effects by enhancing pro-inflammatory cytokines secretion. The same effect is observed with the A-box. Surprisingly, when complexed with LPS, F3 inhibits the LPS-induced secretion of pro-inflammatory cytokines. Discussion According to the literature, it seems that HMGB1 allows TLR4 dimerization through its B-box. We hypothesis that F3 acts as a competitive inhibitor, preventing HMGB1/TLR4 binding. Hence, it would inhibit the receptor dimerization and so, its downstream signaling leading to the secretion of pro-inflammatory cytokines. Furthermore, it was observed that HMGB1's inflammatory effects could be modulated by its post-translational modifications. In the same line, we observed that HMGB1 redox state, its molecular environment, and/or the accessibility of C1s (free or within the complement C1 complex) can modulate the amount of F3 released by C1s cleavage and, thus, indirectly impact the inflammation response.

P-09	
Title:	**Generation of Novel Antibodies Targeting the Putative Complement Regulatory Domain of CSMD1.**
Author(s):	Robert A J Byrne [1, 2], Sarah M Carpanini [2], Lewis Watkins [2], Michael O' Donovan [1, 3], B. Paul Morgan [1, 2]
Institute(s):	[1] Hodge Institute for Neuropsychiatric Immunology, [2] UK DRI at Cardiff University, [3] MRC Centre for Neuropsychiatric Genetics and Genomics
Presenter:	**Robert Byrne**
Abstract (max 300 words):	**Introduction** The CUB and Sushi Multiple Domains 1 (CSMD1) gene encodes a complex transmembrane protein comprising 14 N-terminal C1r/s, uEGF, and BMP1 (CUB) domains interspersed with short consensus repeat (SCR) domains, followed by 15 tandem SCR domains, transmembrane domain, and short cytoplasmic tail. The tandem SCR domains SCR17-21 are structurally comparable to many complement regulatory proteins and allow CSMD1 to inhibit the classical complement pathway. CSMD1 was first identified as a candidate tumour suppressor gene, specifically in head and neck squamous carcinomas. Furthermore, early schizophrenia genome-wide association studies (GWAS) identified CSMD1 as a risk gene - an association that has been robustly replicated in all subsequent GWAS. Despite long established associations with schizophrenia and cancer, reliable tools for studying CSMD1 are scarce. The current panel of commercial CSMD1 antibodies is limited and often function non-specifically in common laboratory techniques, hence only one published study has cited them. **Methods** Mice were immunised with recombinant human CSMD1 SCR17-21, hybridoma were generated via fusion with SP2 mouse myeloma cells, and clones screened via indirect ELISA. Clones expressing CSMD1 monoclonal antibodies (mAbs) were expanded to monoclonality. CSMD1 mAbs were purified and validated in ELISA, western blot, and immunofluorescence. **Results** CSMD1 mAbs were specific to SCR17-21 over SCR23-26 and recognized endogenous CSMD1 in both human and mouse brain via western blot and immunofluorescence. CSMD1 mAbs primarily stained astrocytes in human temporal cortex and whole mouse brain; immunocytochemistry with human induced pluripotent stem cell-derived cortical glutamatergic neurons also resulted in positive CSMD1 staining. **Discussion** We have generated a panel of novel mouse mAbs that specifically target the putative CSMD1 complement regulatory domain SCR17-21. These reagents will be useful tools for researchers investigating CSMD1's roles in schizophrenia and cancer.

P-10	
Title:	**Short- and long-term blood and urine storage: implications for complement C5b-9 research and diagnostic development.**
Author(s):	Ellen Millman[1], Daniel Mills[2], Oksana Shkilnyk[2], Dieudonne Sidi[2], Michelle Elvington[3], Niamh O'Luanaigh[2], Tobin Cammett[1], Martin J. Schmidt[3]
Institute(s):	[1] Biomarker Development, Alexion, AstraZeneca Rare Disease, New Haven, Connecticut, USA [2] R&D, Kypha, Inc., Dublin, Ireland [3] R&D, Kypha, Inc., Saint Louis, Missouri, USA
Presenter:	**Martin J. Schmidt, PhD**
Abstract (max 300 words):	**Introduction** Despite complement-targeted therapeutics' impact, accurate complement analysis remains challenging. Ex-vivo cascade instability is compounded by time, temperature, coagulation, agitation, freeze/thaw, ambient air, storage conditions, etc. Two mitigation strategies make reliable complement analysis available beyond specialized laboratories: #1 standardize myriad unpredictable preanalytical factors into a single micromanaged workflow across clinical sites with varying expertise, or #2 eliminate sources of variability by analyzing fresh samples within hours of collection with point-of-care tests. **Methods** We assessed mitigation strategy #2 using two biological matrices for terminal complement stability in realistic short- and long-term storage scenarios. Healthy donor blood and processed EDTA-plasma (sC5b-9) or urine (uC5b-9) were freshly collected. 20ul plasma mixed in diluent or 100ul undiluted urine was applied to single-use lateral flow test cassettes (Kypha Inc. St. Louis, MO, USA), developed for 30min, and analyzed. In Exp 1, urine samples were collected, tested immediately, and kept at room temp (RT) for 5hr to replicate a common clinical scenario. In Exp 2, EDTA blood samples were collected and tested immediately or processed to plasma, aliquoted and frozen for retesting after 24-96hr, 1mo, 3mo, 6mo, and 12mo. **Results** Mean uC5b-9 dropped ~20% by 5hr (39ng/ml to 32.67ng/ml; $p<0.05$). Compared to fresh blood (139±57.3ng/ml), sC5b-9 was significantly elevated in fresh EDTA plasma (173±92.9)* and further elevated in frozen EDTA plasma (230±90.6)* but decreased after storage time at -80C (1mo 214±92.5*, 3mo 180±92.3, 6mo 125±50.5*, 12mo 98±0). Multiple samples were below the limit of quantitation by 12mo and excluded. *= means ± sem, $p<0.01$ **Discussion** These preliminary results quantify complement protein pre-analytical instability over time in two different biological matrices. Efforts to validate and extend this healthy donor fresh vs. frozen assessment in various diseased patient populations are ongoing and will provide important additional insight on defining best practices for accurate assessment of complement activity in clinical samples.

P-11	
Title:	Complement dysregulation in Long COVID.
Author(s):	Kirsten Baillie, Samuel Keat, Kelly L. Miners, Kristin Ladell, Ermioni Melou, Erik Toonen, Loek Willems, Helen E. Davies, David A. Price, Paul Morgan, Wioleta Zelek.
Institute(s):	Dementia Research Institute Cardiff, School of Medicine, Cardiff University, Cardiff, UK
Presenter:	Kirsten Baillie
Abstract (max 300 words):	**Introduction** Long COVID (LC) is characterised by a heterogeneous set of unresolved symptoms lasting many months after the initial acute phase of SARS-CoV-2 infection. Complement dysregulation is an important contributor to inflammation and tissue damage in COVID-19, driven largely by the alternative pathway. The impacts of complement in LC have yet to be explored. Herein, we sought to investigate if dysregulation of complement is observed in LC, to identify which parts of the complement cascade are dysregulated and whether this could inform therapeutic interventions. **Methods** We undertook a comprehensive study of complement in LC, profiling 21 complement biomarkers. This included key components (C1q, C3, C4, C5, and C9), regulators (C1INH, FH, FD, FI, FB, CR1, FHR4, FHR125, C1INH, properdin, and clusterin), and activation products (TCC, iC3b, Ba), in 166 LC plasma samples and 79 age-matched non-LC controls 2 years post-infection using ELISAs and classical pathway haemolysis assay (CH50). **Results** Compared to controls, levels of the complement activation products Ba, TCC, and iC3b (P=0.0007, <0.0001, and <0.0001, respectively), key complement components C3, C5, and C9 (p=0.0004, 0.0037, 0.0103, respectively), the regulators FD, FH, C1INH, properdin, and clusterin, and the C1s-C1INH complex were significantly higher in LC (p= <0.0001, 0.0079, 0.0011, <0.0001, 0.043, 0.0089, respectively), while C1q levels were significantly reduced (p=<0.0001). Data were subjected to ROC analysis to identify a sub-set of biomarkers predictive of the LC and the disease outcome. **Discussion** Our findings show that complement is dysregulated in LC samples two years post SARS-Cov2 infection. Elevated levels of activation markers (iC3b, Ba, TCC) suggest ongoing complement activation through to the terminal pathway. Increased levels of most components may reflect chronic inflammation; however, low C1q levels may implicate classical pathway as a driver of the dysregulation. The data suggest that complement-blocking therapies may be effective to break the vicious cycle of complement dysregulation and resultant chronic inflammation.

P-12	
Title:	Roles of complement dysregulation and membrane attack complex formation in developmental synapse loss.
Author(s):	Sarah M. Carpanini,[1] Megan Torvell,[1] Lewis Watkins, [1] Robert A. J. Byrne,[1] Timothy R. Hughes,[1] Wioleta M. Zelek,[1] and B. Paul Morgan[1]
Institute(s):	[1]UK Dementia Research Institute Cardiff, and Systems Immunity Research Institute, School of Medicine, Cardiff University, Cardiff, CF24 4HQ, UK;
Presenter:	Sarah Carpanini
Abstract (max 300 words):	**Introduction:** Complement is involved in developmental synaptic pruning and pathological synapse loss in Alzheimer's disease (AD). Our recently published work identified complement dysregulation in AD mice involving the activation (C1q; C3b/iC3b) and terminal membrane attack complex (MAC) pathways. Inhibition or ablation of MAC formation reduced synapse loss in two AD mouse models, demonstrating that MAC formation is a driver of pathological synapse loss; however, the precise mechanism of MAC induced synapse loss and its relevance to developmental synaptic pruning remains to be elucidated. **Methods:** We explored whether complement dysregulation and MAC formation occurred during developmental synaptic pruning and contributed to synapse loss. Novel ELISA methods were used to quantify C1q, C3 fragments and MAC in total brain homogenates from WT and complement deficient (C1q, C3 and C7) mouse brains at 8, 15, 28 and 40 days after birth. **Results:** Complement activation products were present in WT brain homogenates across the developmental period examined, suggesting ongoing complement dysregulation. In each of the complement deficient lines, complement activation product levels were decreased, demonstrating the specificity of the assays. We are currently evaluating the impact of complement deficiencies on developmental synapse loss. **Discussion:** We show that complement dysregulation occurs in the brain during the period of highest synaptic remodelling. Early or late complement component deficiencies reduced complement activation in the brain, implicating complement and the MAC in the process. The impact on synapse loss is under evaluation.

P-13	
Title:	Complement in clinical trials: the search for human complement challenge models.
Author(s):	J.A. van den Noort, T.P. Buters, M.N. Ronner, D. Pereira, J. Damman, N. Klarenbeek, M.A.A. Jansen, M. Moerland
Institute(s):	Centre for Human Drug Research, Leiden University
Presenter:	J.A. van den Noort
Abstract (max 300 words):	**Introduction** Over the past 10 years, complement has played an integrated role in clinical drug development both as a therapeutic target as well as in the mechanistic basis of unexpected drug-induced hypersensitivity reactions. However, well-established methodology to gain a deeper understanding of both the wanted and unwanted effects of complement in clinical development is lacking. We aim to develop serum- and whole blood-based *ex vivo* complement activation models, and *in vivo* human complement challenge models. **Methods** Lipopolysaccharide (LPS) is a well-known challenge agent provoking an innate immune response via activation of toll-like receptor (TLR)-4. *Ex vivo* healthy volunteer serum/whole blood was incubated at 37°C with 2.5-100 µg/mL LPS. SC5b-9 levels were 53nalysed by ELISA. *In vivo*, healthy volunteers were challenged with 5 ng of LPS intradermally. Skin biopsies were taken at 1, 3, 6 and 24h post dose and stained for complement by immunohistochemistry and direct immunofluorescence. Besides LPS, other *in vivo* dermal immune challenges in humans were performed with topical imiquimod (TLR7 agonist; 100 mg, 3 to 7 consecutive days) and UV-B (2x minimal erythema dose). **Results** LPS caused a dose-dependent increase in sC5b-9 levels in whole blood and serum. *In vivo*, a trend of an increased C3d deposition but no C5b-9 was found at 3 and 6 hours post intradermal LPS challenge. No deposition of C3c, or C4d was found post-imiquimod challenge and no deposition of C3c or C3d was found post UV-B. **Discussion** LPS dose-dependently drives complement production in serum/whole blood. However, demonstrating deposition of complement components *in vivo* remains challenging. It is currently unknown whether this is explained by a limited role of complement in these challenge responses or by suboptimal sample timing or endpoint selection. Further research is needed to determine if a dermal LPS, imiquimod or UV-B challenge would be a suitable *in vivo* model for complement activation.

P-14	
Title:	**Complement receptor 1 is expressed on brain cells and impacts roles of microglia relevant to Alzheimer's disease.**
Author(s):	Nikoleta Daskoulidou, Bethany Shaw, Megan Torvell, Lewis Watkins, Sarah M. Carpanini, Nicholas D. Allen, B. Paul Morgan
Institute(s):	UK Dementia Research Institute at Cardiff University, Cardiff, United Kingdom
Presenter:	**Nikoleta Daskoulidou**
Abstract (max 300 words):	**Introduction** Genome-wide association studies (GWAS) in Alzheimer's disease (AD) have highlighted the importance of the complement cascade in pathogenesis. Complement receptor 1 (CR1; CD35) is a top AD-associated GWAS hit; the long variant of CR1 is associated with increased risk. Roles of CR1 in brain health and disease are poorly understood; indeed, CR1 expression in brain is controversial. Our aim was to resolve this controversy by investigating CR1 expression in brain cells and testing whether the AD-associated length polymorphism impacted CR1 expression and function. **Methods** Two well-characterised human microglial cell lines, iPSC-derived microglia from two sources (donor-derived and KOLF2) and post-mortem human brain tissue obtained from AD cases and age- and sex-matched controls were used in this study. Cells and tissue were stained with in-house CR1-specific antibodies and analysed by immunofluorescence. RNA and protein were extracted and subjected to qRT-PCR and western blotting respectively. Functional differences of microglia expressing long and short CR1 variants were tested in phagocytosis assays using diverse targets (E.coli bioparticles, human synaptoneurosomes, amyloid β fibrils) either unopsonised or opsonised with human serum. **Results** CR1 mRNA was detected in microglial lines, iPSC-derived microglia and brain tissue using qRT-PCR. CR1 protein was demonstrated using western blotting and immunofluorescence in cell lines and iPSC-derived microglia expressing long or short variant CR1 and on microglia and astrocytes in situ on brain tissue. Both mRNA and protein expression were significantly increased in the AD samples. Phagocytosis of serum-opsonised targets was significantly different in iPSC-microglia expressing the risk or non-risk variants. **Discussion** CR1 is expressed in the human brain. CR1 expression is an important component of microglial phagocytic activity; expression of the long (risk) variant of CR1 impacts phagocytosis, perhaps explaining its association with AD risk.

P-15	
Title:	A Novel Functional Properdin Assay – Studying the Positive AP Regulator and Complement Amplification Loop.
Author(s):	Samuel Butler, Viktoria Kozma, Cecilia Månsson, Camilla Nilsson, Ali Qamar, Michael Schwenkert
Institute(s):	N/A
Presenter:	Samuel Butler
Abstract (max 300 words):	Complement response is triggered through any out of three complement pathways: the Classical, the Mannose Binding Lectin, or the Alternative pathway (AP). Independent of the trigger, this activation is amplified by the AP amplification loop, the contribution of which accounts for over 80% of terminal complement activity. Dysregulation of the complement system has been implicated in a large number of diseases, emphasising the potential for complement modulating therapeutics to ensure patient homeostasis. Two of the key regulators of the complement amplification loop are Factor H (FH) and Properdin. FH contributes to downregulation of the complement response, through inhibiting C3 convertase formation and increasing its rate of decay. The positive regulator, properdin, stabilises the AP C3 convertase and inhibits FH mediated downregulation, enabling the essential complement amplification of the AP. A high AP function has been linked to increased survivability in critically ill patients, thus, the function of properdin is an interesting target for AP activity modulation. In vivo, properdin assembles into oligomers, P_2, P_3, & P_4 in an approximate 1:2:1 ratio, which exhibit increasing properdin function relative to the degree of oligomerisation. As the only known positive regulator of the AP, properdin's function is imperative to ensure sufficient complement response to pathogen recognition. Imbalances caused by dysregulation of properdin, or opposing regulators, may have severe consequences to the health of a patient, emphasising the need for functional complement assays. The Wieslab Functional Complement ELISAs are an example of such assays, enabling functional studies of all three complement pathways. This study demonstrates how a novel functional properdin assay can help elucidate the integrity of properdin function, as well as provide an increased resolution in research directed toward the complement amplification loop and its key components.

P-16	
Title:	**Differential expression of complement activation markers in the blood of individuals with clinical high-risk for pyschosis.**
Author(s):	Eleftheria Kodosaki (1), John W. Watkins (2), Jonah F. Byrne (3), Melanie Foecking (3), Patrick D. McGorry P (4,5), Diana O. Perkins (6), Paul G. Amminger P (4,5), David Cotter (3), Meike Heurich (1)
Institute(s):	1 School of Pharmacy and Pharmaceutical Sciences, Cardiff University, United Kingdom. 2 Department of Infection and Immunity, School of Medicine, Cardiff University. 3 Department of Psychiatry, RCSI University of Medicine and Health Sciences, Dublin Ireland. 4 Centre for Youth Mental Health, The University of Melbourne, Melbourne, Victoria, Australia. 5 Orygen, 35 Poplar Rd, Parkville, 3052, Australia. 6 Department of Psychiatry, University of North Carolina, Chapel Hill, NC, United States of America
Presenter:	**Eleftheria Kodosaki**
Abstract (max 300 words):	**Introduction:** Psychosis spectrum disorders are severe mental disorders for which identifying the individuals who will develop psychosis and intervening early and effectively can lead to better outcomes. Recent studies showed that altered blood protein levels of the complement and coagulation pathways were able to discriminate between clinically high-risk (CHR) individuals who transition (CHR-T) to psychosis versus those who do not (CHR-NT). However, these studies did not address complement activation markers. Our study quantified the baseline plasma levels of complement activation markers spanning all pathways (C4a, C4d, C3a, iC3b, C5a, sC5b-9 (TCC)) with the aim to identify biomarkers predictive of transition to psychosis, and mechanisms of conversion linked to inflammation by assessing individuals global functioning and clinical symptoms. **Methods:** We analysed plasma samples from from participants of the North American Prodromal Longitudinal Studies (NAPLS) and the NEURAPRO-E study. Quantification of complement C4a, C4d, C3a, iC3b, C5a, sC5b-9 (TCC) in baseline plasma was done using standardised commercial ELISAS. Differential levels were examined comparing CHR and HC, and those individuals who transitioned to a psychotic disorder (CHR-T) vs those who did not (CHR-NT). The relationship of baseline blood marker levels with clinical measures such as glonal functioning, or negative and positive symptoms were measured at baseline, and 6, 12, 18, and 24-months follow up. **Results:** Differential expression of complement C3a, iC3b and Bb was observed comparing HC and CHR (NAPLS2), and iC3b for CHR-T vs CHR-NT (NEURAPRO). A combination of biomarkers resulted in AUC>0.60 for both NEURAPRO and NAPLS2 for differentiating between CHR-T and CHR-NT. Correlation of several markers with general functioning, negative and positive symptoms was observed at baseline and follow up. **Discussion:** Complement activation is evident in those individuals at clinical-high risk of transitioning to psychosis. Altered complement activation marker levels were moderately able to distinguish those who transition to psychosis from those who do not. Intriguingly, several markers were associated with baseline symptoms suggesting a role for complement activation in the development of psychotic disorder.

P-17	
Title:	Utilising biomarkers to diagnose MS and predict long-term outcomes.
Author(s):	[1,2]Kodosaki, E., [2]Watkins, W.J., [3]Loveless, S., [3]Richards, A., [2]Morgan, B.P., [2,4]Zelek, W.M., [3]Tallantyre, E.
Institute(s):	[1]School of Pharmacy and Pharmaceutical Sciences, Cardiff University, [2]Infection and Immunity, School of Medicine, Cardiff University, [3]Division of Psychological Medicine, School of Medicine, Cardiff University, [4] UK DRI at Cardiff University
Presenter:	Eleftheria Kodosaki
Abstract (max 300 words):	**Introduction** Multiple sclerosis (MS) is a severe demyelinating and eventually neurodegenerative disorder, for which there remain challenges in reaching diagnosis and predicting outcomes. Fluid biomarkers capable of facilitating diagnosis or informing treatment choice in MS would be valuable. Several groups have identified single candidate biomarkers (for example Neurofilament light (NfL) and Chitinase 3-like-1 (Ch3L1) that demonstrate potential clinical utility, but few studies have explored whether combinations of biomarkers could improve predictions in MS. Here we aimed to investigate which combination of 28 protein biomarkers, measured in cerebrospinal fluid (CSF) and/or plasma, best predicts diagnosis and likelihood of reaching disability milestones in people with MS. **Methods** ELISAs and SiMoA were used to measure levels of 28 candidate neuronal (e.g. NfL) glial (e.g. Ch3L1, GFAP) and inflammatory (e.g. complement proteins, interleukins, chemokines, osteopontin (OPN)) from 80 people with MS and 80 non-MS controls, in both the CSF and plasma. With MS as a binary outcome variable, logistic regression was employed multiple combinations of biomarkers as explanatory variables in turn to establish to establish the best combination for differentiating MS from controls. The results of the logistic regressions were quantified through the Area Under the Curve (AUC) analysis for MS status (MS vs. control). For people with MS, a survival analysis was used to investigate the relationship between combinations of biomarkers, and the likelihood of developing disability (Expanded Disability Status Scale, EDSS) milestones of 4 and 6. Kaplan-Meier analysis and Cox regression (with and without adjustment for age, sex and use of disease modifying therapy; DMT) were used to this end with the Concordance measure used to compare results. **Results** Compared to controls: i) CSF levels of NfL ,Ch3l1 and CD27 were significantly elevated in MS; ii) plasma levels of NfL and OPN were significantly elevated in MS; iii) The peak AUCs of 0.854 and 0.749 for prediction of MS status using a single marker in plasma and CSF, were achieved using NfL. There was incremental improvement in prediction of MS vs. control status with the addition of up to five further biomarkers in CSF/ blood (combined AUC=0.864 for blood and AUC= 0.938 for CSF). Similarly, incremental improvement in predictions of disability outcomes were seen with combinations of up to six biomarkers in people with MS, when adjusted for sex, DMT and age. In both analyses, the percentage improvement diminished with each added biomarker, effectively plateauing after six were combined. The optimal combination of blood biomarkers for prediction of diagnosis was [FB + Ch3l1 + OPN + CCL27 + MCP1 +

	NfL]. The optimum combination of biomarkers for disability outcome was [CSF(CRP + IL4 + NfL) + plasma(Factor I + Ch3l1 + C1-inh/C1s complex]. Discussion: Complement proteins, cytokines and neuronal markers are known to be elevated in the blood and CSF in MS. Our statistical approach has uncovered a complementary contribution of several markers in improving predictions of diagnosis and disability trajectory. This suggests that we could develop combination panels to measure complement proteins, neurological markers and cytokines, to aid diagnosis and guide management in MS.

P-18

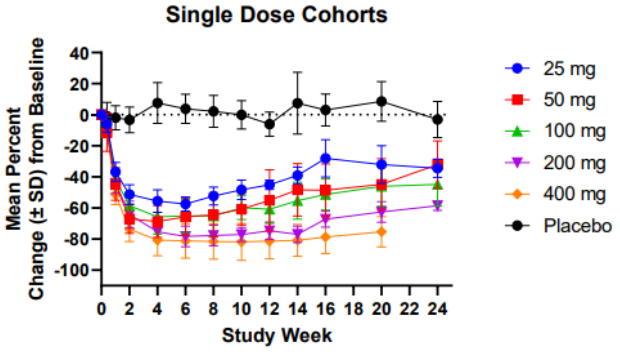
Title:	**Measurement of complement deposition at the neuromuscular junction in passive transfer myasthenia gravis in rats.**
Author(s):	Anja Schöttler[1], Marina Mané-Damas[1], Britt Arets[1], Marc H. De Baets[1], Mario Losen[1], Pilar Martinez-Martinez[1]
Institute(s):	1. Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, The Netherlands
Presenter:	**Anja Schöttler**
Abstract (max 300 words):	**Introduction** Myasthenia Gravis (MG) is an autoimmune disorder, triggered by autoantibodies against proteins in the neuromuscular junction (NMJ), most commonly the acetylcholine receptor (AChR). One of the most relevant mechanisms of action of such antibodies is the activation of the classical pathway of the complement system, leading to membrane attack complex (MAC) formation at the NMJ and muscle cell damage. This results in neuromuscular transmission deficiency, leading to muscle weakness and fatigability. A commonly used rodent model for MG research is the passive transfer MG (PTMG) rat model, directly administrating a monoclonal antibody targeting the rat AChR (mAb35) intravenously to the animals. Disease manifestation occurs approximately 48 hours after induction. We surmise that complement deposition at the NMJ occurs in the acute PTMG model, although no exhaustive analysis has been performed prior to this study. **Methods** 10-weeks-old female Lewis rats were injected with 40 pmol / 100 g mAb35 s.c.; control non-MG animals received the respective volume of saline. 48 hours after disease induction the animals were euthanized and the muscle tibialis anterior was dissected and frozen in melting isopentane. Immunofluorescent staining was performed for complement proteins with anti-MAC and anti-C3 antibodies, as well as markers for AChR and presynaptic proteins as control. **Results** In MG-animals a clear increase in MAC deposition was observed while AChR levels were reduced compared to non-MG animals. **Discussion** The increase of complement proteins at the NMJ in MG-animals and the reduction in AChR indicates that the classical complement pathway is activated in the PTMG rat model. Therefore, we can conclude that the model resembles the human pathophysiology of MG well despite its rapid progression and lacking the period of chronic immune cell activation and antibody production.

P-19	
Title:	Complement activation in response to hypoxia and reoxygenation in tubular epithelial cells.
Author(s):	[1*]Saltanat Moldakhmetova, [1]Simi Ali, [1]Neil S Sheerin
Institute(s):	Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, UK National Renal Complement Therapeutics Centre, Newcastle University, UK
Presenter:	Saltanat Moldakhmetova
Abstract (max 300 words):	**Introduction** Ischemia is the most common cause of complement activation during kidney transplantation. Proximal tubular epithelial protect themselves from complement activation through cellular expression of complement regulatory proteins (CRPs). We investigated whether hypoxia and reoxygenation (H/R) increase local C3 synthesis and alter CRP expression (CD46, CD59 and CD55). **Methods** HKC-8 renal proximal tubular epithelial cells were subjected to 24h of hypoxia (O_2=1%) and reoxygenated for 4h (O_2=21%). qRT-PCR was used to estimate the level C3, CD46, CD59 and CD55 expression. C3 deposition on the cell surface was examined by Immunofluorescence staining, intensity quantified by ImageJ. **Results** H/R led to significantly greater deposition of C3 on hypoxic cells compared with normoxic HKC-8 cells. qRT-PCR analysis of cells in hypoxia revealed the insignificant increase of C3 and CRPs expression following H/R. **Discussion** Preliminary data suggests that H/R significantly increase synthesis of C3 in the proximal tubular cells. The increased C3 deposition is not due to changes in complement regulator expression.

P-20	
Title:	**Differentiating between activation via the lectin or the classical complement pathway in Systemic Lupus Erythematosus patients.**
Author(s):	Mads Lamm Larsen[1,2], Anne Troldborg[1,2,3], Erik J.M. Toonen[4], Lisa Hurler[5], Zoltan Prohaszka[5,6], László Cervenak[5], Annette Gudmann Hansen[2], Steffen Thiel[1]
Institute(s):	1: Department of Biomedicine, Aarhus University, Denmark 2: Department of Rheumatology, Aarhus University Hospital, Denmark 3: Department of Clinical Medicine, Aarhus University, Denmark 4: Hycult Biotech, R&D department, Uden, The Netherlands. 5: Department of Internal Medicine and Haematology, Semmelweis University, Budapest, Hungary. 6: Research Group for Immunology and Haematology, Semmelweis University-Eötvös Loránd Research Network (Office for Supported Research Groups), Budapest, Hungary.
Presenter:	Mads Lamm Larsen
Abstract (max 300 words):	**Introduction** Complement activation is a hallmark of systemic lupus erythematosus (SLE) and can proceed through the classical (CP), lectin (LP), or alternative pathway (AP). When managing SLE patients, pathway-specific complement activation is rarely monitored as clinical assays are unavailable. In this study, we aim to differentiate between CP- or LP-mediated complement activation in SLE patients by quantifying pathway-specific protein complexes, namely C1s/C1-INH (CP-specific activation) and MASP-1/C1-INH (LP-specific activation). **Methods** Levels for both complexes were assessed in 156 SLE patients and 50 controls using two newly developed ELISAs. We investigated whether pathway-specific complement activation was associated with disease activity and lupus nephritis (LN). Disease activity stratification was performed using SLEDAI scores assessed at inclusion. **Results** C1s/C1-INH concentrations were significantly increased in active SLE patients (SLEDAI >6) when compared to SLE patients with low disease activity (SLEDAI <6, $p<0.01$) and correlated with SLEDAI score ($r=0.29$, $p<0.01$). In active LN, MASP-1/C1-INH plasma concentrations were significantly increased compared to non-active LN ($p=0.02$). No differences in MASP-1/C1-INH plasma concentrations were observed between active SLE patients and patients with low disease activity ($p=0.11$), nor did we observe a significant correlation with disease activity ($r=0.12$, $p=0.15$). **Discussion** Our data suggest that the CP and the LP are activated in SLE. The complement system is activated in active SLE disease, whereas activation of the LP might be more specific to disease manifestations like LN. Our results warrant further research into specific complement pathway activation in SLE patients to potentially improve specific targeted and tailored treatment approaches.

P-21	
Title:	**Safety, Tolerability and Pharmacodynamic Effects of ARO-C3, a Subcutaneously Administered Investigational RNAi Therapeutic Targeting Complement C3, in Adult Healthy Volunteers.**
Author(s):	Mark Marshall[1] , Hamid Moradi[2] , Eric Garcia-Medel[2] , Ran Fu[2] , James Hamilton[2]
Institute(s):	1. New Zealand Clinical Research 2. Arrowhead Pharmaceuticals
Presenter:	**Hamid Moradi**
Abstract (max 300 words):	**Introduction**: The complement system is an important part of innate immunity. However, dysregulated complement activity plays a pathogenic role in many diseases. Several therapies targeting the complement cascade are effective in treating these conditions. ARO-C3 is a subcutaneous (SC) investigational RNA interference (RNAi) therapeutic targeting complement component C3 (C3). Methods: AROC3-1001 is an ongoing phase 1/2a double-blind, placebocontrolled, randomized clinical trial evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of ARO-C3 in adult healthy volunteers (HVs) and in patients with complement-mediated diseases. Here we report interim HV safety, tolerability and pharmacodynamic (PD) data. Circulating levels of C3 as well as markers of alternative pathway (AP) complement activity (AH50) were assessed. Results: Five single-ascending-dose (SAD) cohorts enrolled 6 subjects (randomized 2:1) to receive ARO-C3 25, 50, 100, 200 or 400mg or Placebo. Two dose levels (200mg and 400mg) were examined in multiple-ascendingdose (MAD) cohorts, each enrolling 6 subjectsrandomized 2:1 to receive AROC3 or placebo on Day 1 and Day 29. In HVs, ARO-C3 was considered generally well-tolerated with no serious adverse events (SAEs), study discontinuations due to AEs or clinically significant laboratory findings reported. Preliminary data showed consistent reductions in C3 levels across all SAD cohorts with mean C3 reduction of 80.7% achieved on Day 29 in the 400 mg cohort sustained through week 16. The latter was associated with a mean reduction in AH50 of up to 68.8%. In the MAD cohorts, 4 weeks after the last dose, mean C3 reductions of 79.5% and 87.8% were achieved at 200 mg and 400 mg, respectively. This was associated with mean reductions of 67% and 91.3% in AH50. Discussion: Preliminary results demonstrate an encouraging ARO-C3 safety profile, along with significant and durable reductions in C3 and AH50. Findings support further development of ARO-C3 as a potential therapy for complement-mediated diseases

Figure 1: Percent change from baseline in serum Complement C3



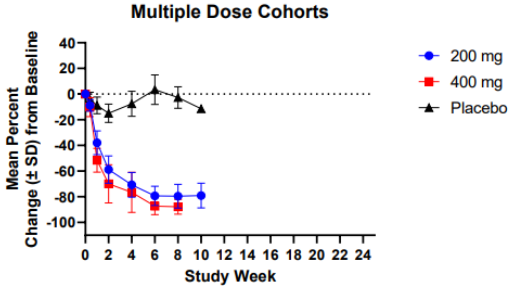
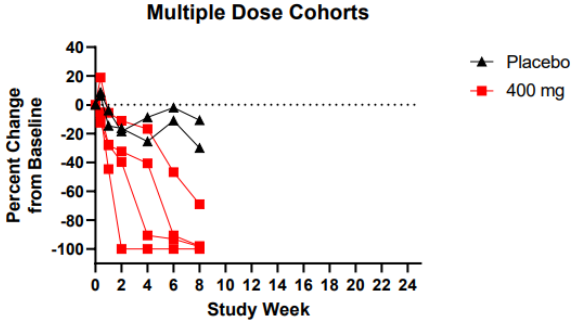


Figure 2: Percent change from baseline in alternative pathway complement activity (AH50) in individual subjects who received 400 mg ARO-C3 or placebo on Day 1 and Day 29.



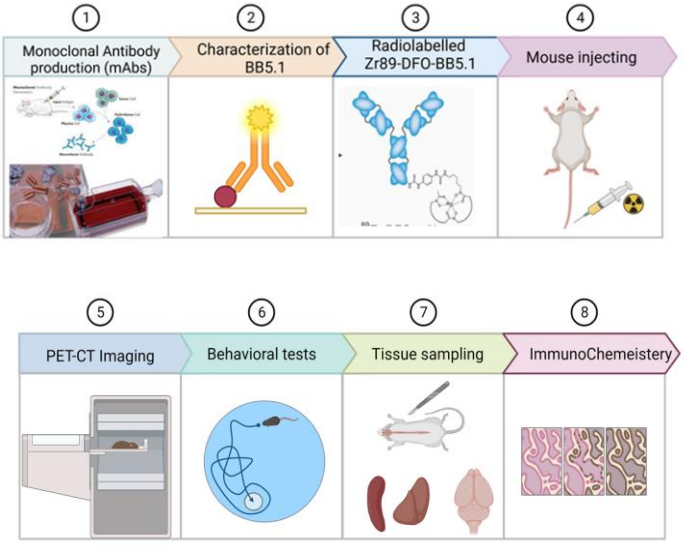
P-22

Title:	Levels of soluble complement regulators predict severity of COVID-19 symptoms.
Author(s):	Anna L. Tierney[1,2], Wajd Mohammed Alali [2†], Thomas Scott[2†], Karen S. Rees-Unwin[2], Simon J. Clark[3,4,5] and Richard D. Unwin[2]
Institute(s):	[1]Division of Cardiovascular Sciences, School of Medicine, Faculty of Biology Medicine and Health, The University of Manchester, Manchester, United Kingdom [2]Stoller Biomarker Discovery Centre and Division of Cancer Sciences, School of Medicine, Faculty of Biology Medicine and Health, The University of Manchester, Manchester, United Kingdom [3]Institute for Opthalmic Research is based at Eberhard Karls University of Tubingen, Tubingen, BW, Germany [4]University Eye Clinic, Eberhard Karls University of Tubingen, Tubingen, BW, Germany [5]Lydia Becker Institute of Immunology and Inflammation, Faculty of Biology, Medicine, and Health, University of Manchester, Manchester, United Kingdom
Presenter:	Anna L. Tierney
Abstract (max 300 words):	Introduction The COVID-19 pandemic caused a significant public health challenge due to high morbidity and mortality. A major hurdle in patient management was the diversity of symptoms, with severe disease requiring hospitalization or proving fatal. To prioritize healthcare resources, it is important to identify patients at risk of adverse outcomes at an early stage. Research has implicated dysregulation of the complement cascade as a contributor to the severity of COVID-19 outcomes. Methods We investigated the involvement of soluble complement regulators including Complement Factor H (FH), its splice variant Factor H-like 1 (FHL-1) and five Factor H-Related proteins (FHR1-5) in COVID-19. We employed targeted mass spectrometry (MS) to quantify these proteins in 188 plasma samples collected at time of diagnosis from individuals with SARS-CoV-2 infection and controls. We further studied 77 individuals who had a second sample taken at ~28d post-diagnosis. Results We demonstrated excellent performance from our MS assay in terms of reproducibility and sensitivity. Analysis of plasma levels of FH, FHL-1 and FHR1-5 demonstrated that all FHRs were elevated in individuals with severe disease. Most striking were elevations of FHR2 and FHR5, which increased 2 and 2.4-fold respectively. This was not the case for FH, which remained unchanged. In comparing matched samples from day 0 vs day ~28, we showed that levels of all regulators remained high in those with severe disease but had fallen to baseline in those who experienced mild or asymptomatic infection.

	Discussion This study supports the hypothesis that elevated complement activation could be a cause, or a result, of severe COVID-19 and that monitoring the levels of complement regulators could provide a useful tool for predicting prognosis. Maintaining momentum in this area is key In this post-pandemic era with the risk of breakout SARS-CoV-2 variants, or to support the management of future pandemics.

P-23	
Title:	**Complement inhibitors for age-related macular degeneration (AMD): A Cochrane systematic review and meta-analysis.**
Author(s):	N Tzoumas,[1] G Riding,[1] MA Williams,[2] DH Steel [1]
Institute(s):	1 - Newcastle University, Newcastle upon Tyne, UK 2 - Queen's University Belfast, Belfast, UK
Presenter:	**Nikolaos Tzoumas**
Abstract (max 300 words):	**Introduction** Complement system overactivity drives AMD, a leading cause of irreversible sight loss. New treatments targeting complement in the eye have recently been developed. **Methods** We searched for and evaluated RCTs on complement inhibition for AMD, focusing on best-corrected visual acuity (BCVA), lesion growth, macular neovascularization (MNV), endophthalmitis, and quality of life at one year. Risk of bias and evidence certainty were evaluated using standard tools. **Results** We analysed 10 RCTs (4052 participants) with foveal/extrafoveal geographic atrophy (GA). Nine studies compared intravitreal administration to sham, one compared an intravenous agent to placebo. Seven studies excluded patients with previous MNV in either eye. Lampalizumab (anti-Factor D Fab) does not affect BCVA or lesion growth, and probably increases the risk of endophthalmitis, and possibly also MNV (three studies, 2010 participants). Pegcetacoplan (anti-C3 peptide) slows lesion growth (19.0% reduction per-monthly; 14.5% every-other-month), but likely does not improve BCVA and probably increases the risk of endophthalmitis, and possibly also MNV (three studies, 1454 participants). Post-hoc analysis suggests possibly greater benefits for extrafoveal GA (26.1% reduction per-monthly; 23.3% every-other-month). Avacincaptad pegol (anti-C5 aptamer) likely slows extrafoveal GA lesion growth (27.4% reduction with 2mg of the agent; 27.8% with 4mg), but probably does not improve BCVA and may increase MNV risk (one study, 286 participants). CLG561 and LFG316 (anti-properdin Fab and anti-C5 mAb) do not improve BCVA or lesion growth, but may increase endophthalmitis risk (two studies, 272 participants). Eculizumab (anti-C5 mAb) may not affect BCVA or lesion growth (one study, 30 participants). **Discussion** Intravitreal complement inhibition can slow GA lesion growth, especially in extrafoveal disease, but most likely does not improve functional endpoints at one year. MNV and endophthalmitis are emergent adverse events. Optimal dosing and cost-effectiveness are unknown.

P-24	
Title:	Complement profiles throughout adolescent development
Author(s):	Laura Westacott, Wioleta Zelek, Maria Elisa Serrano Navacerrada, Ryan Bevan, Eugene Kim, Camila Simmonds, Jeremy Hall, Lawrence Wilkinson & Diana Cash
Institute(s):	Cardiff University, King's College London
Presenter:	Laura Westacott
Abstract (max 300 words):	Introduction There is a gap in our knowledge regarding the influence of complement-mediated synaptic pruning around adolescence, when the peak of pruning is thought to occur. It is also unclear whether other complement pathways may be involved and our previous data indicates that C3aR may mediate physiological synaptic pruning and microglial activation. As part of a larger study characterising adolescent pruning, we measured various complement markers across adolescent development. Methods Serum was collected from male and female WT and C3aR$^{-/-}$ mice at pre-adolescence (P20), puberty (P30-P40) and adulthood (P60). CH50 was measured alongside ELISA for C3b, Terminal complement components (TCC) and TREM2. Results CH50 levels showed changes across development, peaking at puberty (P30). TCC was significantly perturbed in C3aR$^{-/-}$ female mice. C3b and TREM2 levels also varied across development and by genotype. Discussion Complement activation and TREM2 showed sex-specific and temporally variable patterns which were impacted by lack of C3aR. Future work will determine whether peripheral measures reflect central levels.

P-25	
Title:	**PET/CT imaging of Blood-Brain Barrier Integrity and inflammatory tracers during Alzheimer's Disease.**
Author(s):	Basma Alenezi, Stephen J. Paisey, Timothy Hughes
Institute(s):	Cardiff University
Presenter:	**Basma Alenezi**
Abstract (max 300 words):	**Introduction** Alzheimer's Disease (AD) is the most common cause of dementia in elderly people. Although the exact pathogenesis of AD remains unclear, accumulation of β amyloid (Aβ) plaques and neurofibrillary tangles are well established hallmarks of the disease. PET imaging is a powerful non-invasive diagnostic tool that could contribute to the development of therapies by monitoring disease progress. Immuno-PET is an evolution of PET which combines the high sensitivity of PET with the specificity of monoclonal antibodies (mAbs). Zirconium-89 is an ideal radionucleotide to be used as a tracer on monoclonal antibodies because the long half-life of Zr-89 (78.41 hours) matches well with the slow pharmacokinetics of antibodies. **Methods**  **Result** I will present data demonstrating effective labeling of the monoclonal antibody and that the labeled antibody maintains its functional ability to bind to complement C5. Preliminary data will demonstrate use of this labeled antibody in a small animal PET imaging experiment. **Discussion** 89Zr-DFO has been used to successfully radiolabel BB5.1 for the first time in high purity. 89Zr-DFO radiolabelled BB5.1 retains its purity and biological activity as measured by SDS-PAGE electrophoresis and haemolysis assays. Biodistribution of 89Zr-DFO-BB5.1 has been measured in wild type and models mice.

Programme at a glance

DAY 1: Teaching day

9:20 – 9:30	Wellcome
09:30 –11:00	COMPLEMENT TUTORIAL 1
11:00 – 11:30	Coffee & posters
11:30 – 12:15	Lecture: Complement; the basics – Paul Morgan
12:15 – 12:45	Quick-fire poster presentations
12:45 – 13:45	Lunch & posters
13:45 – 15:15	COMPLEMENT TUTORIAL 2
15:15 – 15:45	Coffee
15:45 – 17:05	ABSTRACT PRESENTATIONS
17:05 – 18:05	Guest lecture "Cancer and Inflammation" – Prof Sir Leszek Borysiewicz
18:15 – 19:30	Poster presentations, Drinks Reception & Cake
19:30 Dinner	at Aberdare-Hall

DAY 2: Symposium

8:40 – 8:45	Wellcome
08:45 – 10:45	SESSION 1: THERAPIES
10:45 – 11:15	Coffee & posters
11:15 – 12:15	SESSION 1: THERAPIES continues
12:15 – 13:30	Group photo & Lunch & posters
13:30 – 15:30	SESSION 2: MECHANISMS & DIAGNOSTICS
15:30 – 15:45	Coffee
15:45 – 16:30	Round table discussion
16:30 – 16:45	Prizes
16:45 – 17:00	Final remarks & farewell