Immunomodulation, GvHD and Transplant Dilemmas

Friday 14th September 2018

Manchester Conference Centre
Sackville Street, Manchester M1 3BB

Welcome

In 1981 the American surgeon William Coley, demonstrated that the immune system could be harnessed to attack human malignancies by injecting Coley's toxin. Ever since these seminal observations, clinicians and scientists have endeavoured to elaborate the nature of the immune response to malignant cells and how this could be employed for therapeutic benefit. Although progress has been slow, we now have a much clearer understanding of how both the innate and acquired immune systems work at a molecular, cellular and systemic level and this has facilitated the development of a variety of immune therapies. We now have available a growing array of monoclonal antibodies, bi-specific antibodies, gene modified T lymphocytes and immune checkpoint inhibitors that have all been shown to induce effective anti-tumour immune responses. The challenge we now face is how to optimize these potent immune-therapies and incorporate them alongside conventional treatment strategies for patient benefit.

Today's meeting brings together an eminent panel of speakers who have been involved in the development of immune based therapies. Sessions on donor lymphocyte infusions, CAR T cell therapy, ECP and gene therapy will initiate a discussion of how these potential new initiatives may be employed throughout the region.

We wish you a warm welcome to Manchester and an enjoyable day.

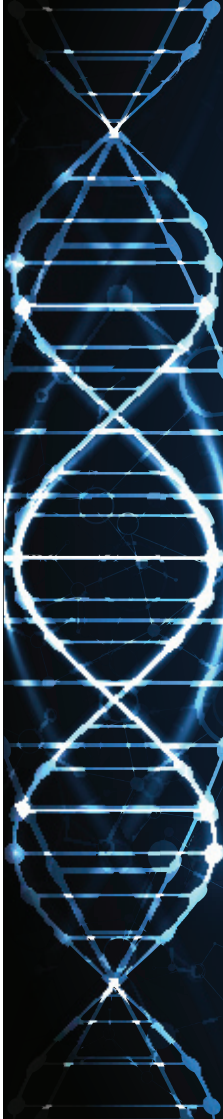
Dr Fiona Dignan
Organiser and Chair

Organiser & Chairman

Dr Fiona Dignan
Clinical Lead for Haematology
Manchester Royal Infirmary

Dr Fiona Dignan is a consultant in haemato-oncology and clinical lead for haematology at Manchester Royal Infirmary. Her main clinical interests are acute leukaemia, chronic myeloid leukaemia and allogeneic transplantation. She is the lead author of national clinical practice guidelines on graft-versus-host disease and veno-occlusive disease following haematopoietic stem cell transplantation. She is also treasurer for the British Society for Blood and Marrow Transplantation and has been a member of the working party for the National Institutes of Health consensus project on chronic graft-versus-host disease.

She undertook her haematology training at The Royal Marsden in London and developed a research interest in post-transplant complications including infection and graft-versus-host disease. She undertook an MD research degree from University College London on novel strategies for managing graft-versus-host disease which has led to a number of national and international presentations and peer-reviewed journal articles.



Programme

Chair: Dr Fiona Dignan *(Manchester)*

09.30	*Arrival and registration*	
10.00	Introduction and keypad voting	**Dr Fiona Dignan** *Manchester Royal Infirmary*
10.10	Gene therapy and SCT	**Professor Rob Wynn** *Royal Manchester Children's Hospital*
10.40	BMT complications:	
	Paediatric cases	**Dr Denise Bonney** *Royal Manchester Children's Hospital*
	Adult case	**Dr Nuria Martinez-Cibrian** *Manchester Royal Infirmary*
11.40	*Coffee*	
12.00	GvHD and ECP cases	**Dr Therese Callaghan, Helen Melia and Alexandra Lehane** *NHSBT Liverpool*
12.30	Improving quality of life for patients with GvHD using ECP earlier	**Dr Arun Alfred** *Rotherham District General*
13.00	*Lunch*	

Parallel Session:

Chairs: Dr Fiona Dignan & Dr Eleni Tholouli
Manchester Royal Infirmary

13.40 Immunomodulation - the science
Dr James Griffin, *University Hospitals Bristol*

14.10 Immunology and GvHD
Dr Mark Williams, *The Christie Hospital*

14.40 Prophylactic DLI in myeloid malignancy
Dr Victoria Potter, *King's College Hospital*

Parallel Session:

Facilitators: Marie Waller, Helen Webster and Angela Leather

- Challenging cases
- Paediatric cases
- Late effects
- CAR T cell therapy
- ITU and advance care planning in BMT

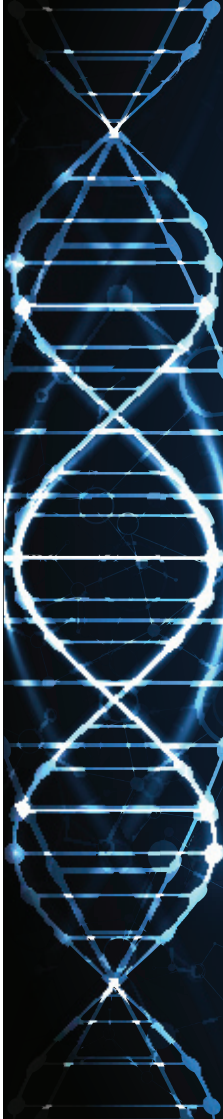
15.10 *Coffee*

Co-Chair: Dr Adrian Bloor, The Christie, Manchester

15.30 Transplantation in the evolving paradigm of lymphoid malignancies
Dr Stephen Robinson
University Hospital Bristol

16.00 CAR T cell set up and patient selection
Dr Reuben Benjamin
King's College Hospital, London

16.30 *Summary and take home points*



Professor Rob Wynn

Professor Rob Wynn
Director of Blood and Marrow Transplant Unit
Royal Manchester Children's Hospital

Rob Wynn is Director of the Blood and Marrow Transplant (BMT) Unit in the Royal Manchester Children's Hospital and Honorary Professor of Clinical Paediatric Haematology and Cellular Therapy. He grew up in Liverpool and undergraduate medical training was undertaken in Cambridge and The London, post graduate training in Newcastle and Edinburgh and Haematology and Transplant training in Manchester and Toronto. He is also an avid Liverpool fan!

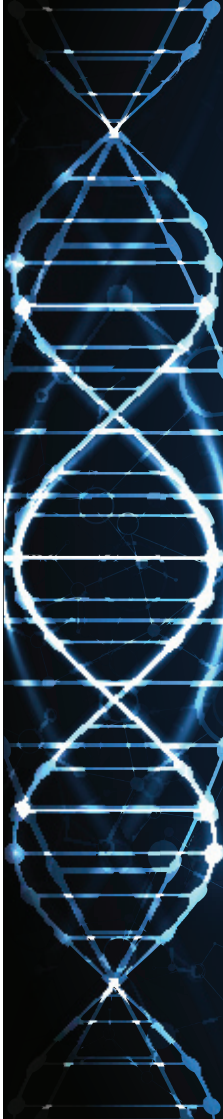
Manchester has a specific interest and expertise in the transplant of children with metabolic disorders. The BMT Unit and its practice and development in this field have been enormously influenced by the late Professor Ed Wraith, a true pioneer in this field. The success of allogeneic cellular therapy in some disorders has recently led to a re-appraisal of gene therapy for currently treatment-refractory disorders. Rob has over 140 papers, has authored several chapters and textbooks in the Haematology and BMT fields and often talks to audiences of different backgrounds on these topics.

Gene Therapy and SCT

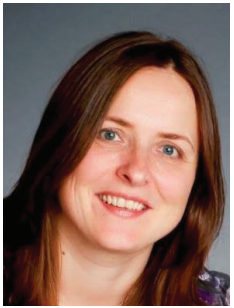
Manchester is a paediatric BMT centre, specialising in the transplant management of children with genetic illness and malignant illness. We have become a centre with a specialist interest in the transplant of children with inherited metabolic illness. I was influenced and helped by Professor Ed Wraith, and Manchester has become a national and international referral centre for children requiring such transplants.

Collaboration is key to development. With collaborators in Europe and USA, we have improved transplant outcomes, with systematic investigations of the causes of graft failure. We have also distinguished patient outcomes and transplant outcomes. We have recognised that age at transplant and the enzyme delivery by that transplant both influence the ability of the transplant to modify disease phenotypes.

The future of BMT builds on its past. Gene therapy (GT) will allow grafts to deliver more enzyme than allografts, and will make BMT safer, more effective in correcting disease and more available to children throughout the world. This is as true for malignant disease as for metabolic and genetic illness. In malignant disease, and CAR-T cell therapy specifically, will allow the “graft-versus-leukaemia” effect which mediates much of the beneficial effect of BMT in malignant disease, without the toxicity of graft-versus-host disease.



Dr Denise Bonney



Dr Denise Bonney
Paediatric Haematology Consultant
Royal Manchester Children's Hospital

Qualifications: MBChB, MRCPCH, PhD, FRCPath

Special Interests: Stem cell transplantation, relapsed leukaemia, aplastic anaemia, CML

Denise trained at Manchester University and qualified in 1997. She then undertook paediatric training at junior and middle grade level in Manchester and attained MRCPCH in 2000. Following this she undertook a research fellowship funded by personal award from Kay Kendall Leukaemia Fund and was awarded PhD in Fetal Stem Cell Biology by Manchester University. She completed postgraduate training in haematology and was appointed as Paediatric Haematology Consultant at RMCH in 2010. Her research interests are BMT, aplastic anaemia and relapsed ALL.

Dr Nuria Martinez-Cibrian

Dr Nuria Martinez-Cibrian
Bone Marrow Transplant Fellow
Manchester Royal Infirmary

Dr Martinez-Cibrian received her medical education at the University of Barcelona graduating in 2009. She did her haematology training between 2010 and 2014 at Hospital Clinic de Barcelona, which is a tertiary centre and a reference centre for malignant disorders and stem cell transplantation. After finishing her training, she worked there as a Locum Consultant for 1.5 years and she then moved to the UK to focus on her career in stem cell transplantation. Since March 2016 she has been a bone marrow transplant fellow at Manchester Royal Infirmary. Her main interests are acute leukaemia and stem cell transplantation.

Dr Therese Callaghan

Dr Therese Callaghan
Consultant Haematologist
NHS Blood and Transplant and Royal Liverpool University Hospital

Therese Callaghan trained in Glasgow and London prior to taking up her current position as Consultant Haematologist at NHS Blood and Transplant (NHSBT) and Royal Liverpool University Hospital. She also holds Honorary Consultant contracts with The Christie NHS Foundation Trust and Central Manchester University Hospitals NHS Foundation Trust. She is the Clinical Lead for NHSBT Therapeutic Apheresis services in the North West; this service includes the provision of extracorporeal photopheresis. Her other main areas of interest are stem cell donation and red cell immunohaematology.

Dr Arun Alfred

Dr Arun Alfred
Consultant Haematologist and Director of ECP Unit
Rotherham NHS Foundation Trust

Dr Arun Alfred is Consultant Haematologist and Director of the ECP Unit based at The Rotherham NHS Foundation Trust, South Yorkshire, UK. His team provide a regional photopheresis service for the treatment of GvHD. Working closely with the referring centers the team are actively involved in managing patents with GvHD, treating both adult and paediatric patients. The unit has a particular research interest in understanding the mechanisms of action of ECP.

Improving quality of life for patients with GvHD using ECP earlier

Haematopoietic stem cell transplantation offers a potentially curative option for treatment of haematopoietic malignancies but is also associated with morbidity which affects quality of life (QoL). GvHD following HSCT causes functional impairment and prolonged duration of immunosupression with a negative impact on QoL and survival (Pidala J, et al. 2009) QoL is an essential measure in the patients' and physicians' evaluation of treatment outcome and should be subjected to the same degree of rigorous study as other relevant treatment outcomes. In this presentation Dr Alfred will be discussing health related QoL measurements post HSCT and their relationship to GvHD with a particular focus on QoL measurements in ECP treated patients.

Dr James Griffin

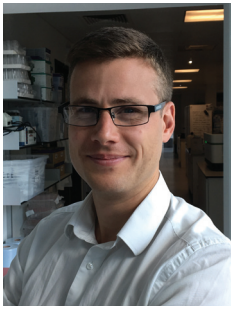
Dr James Griffin
Consultant Haematologist
University Hospitals Bristol

Dr Griffin is a Consultant Haematologist working for NHS Blood and Transplant as the Clinical Director Therapeutics covering Apheresis, Stem Cell and Immunotherapy Laboratories, British Bone Marrow Registry, UK Cord Blood Bank and UK Tissue procurement and delivery. Working as part of the team at University Hospitals Bristol NHS Foundation Trust, he specialises in myeloma and stem cell transplantation and is the lead for the autologous transplant program. Dr Griffin completed his PhD in adoptive immunotherapy at UCL which highlights his longstanding interest in the immune system starting with a BSc in cellular and molecular pathology.

Immunomodulation - The Science

The immune system is a fundamental component of the bodies response to potentially cancerous cells as well as infection. Immune cells are able to clear malignancy, either by being boosted by drugs impacting immune checkpoints or through genetically modified cells. For much longer we have utilised the immune system through bone marrow transplantation, the graft versus leukaemia effect is well established and is required following reduced intensity transplantation. The potentially life-threatening complication of graft versus host disease limits the potential overall benefit of transplantation. In this session we will review the basics science behind the immune response and the development of graft versus host disease and then how we are able to suppress or modulate the immune system either in prophylaxis or treatment.

Dr Mark Williams



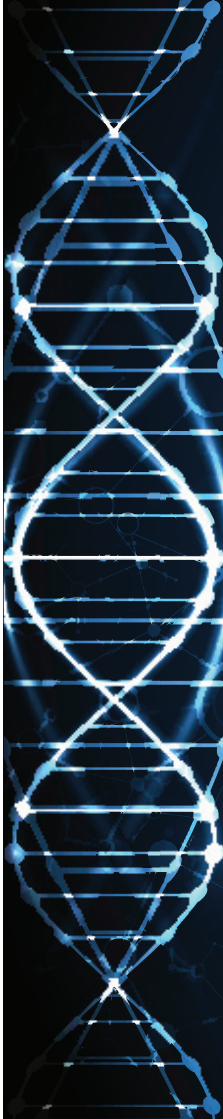
Mark Williams
Clinical Research Fellow
CRUK Manchester Institute & The Christie NHS FT

Dr Williams graduated from the University of Cambridge in 2007 and currently holds a training number in Clinical Haematology in the North West of England. He is working towards a doctorate with Professor Somervaille at the CRUK Manchester Institute, studying mechanisms of chemotherapy resistance in acute myeloid leukaemia. Earlier this year he was chosen to lead a Manchester Cancer Research Centre team science project to develop novel biomarkers for acute graft versus host disease. This project leverages the high volume of clinical transplant activity within Manchester (>190 allografts/year) and the expertise of the Stoller Biomarker Discovery Centre, the world's largest clinical proteomic facility.

Immunology and GvHD

Whilst allogeneic haematopoietic stem cell transplantation (HSCT) remains the only potentially curative intervention for many patients, efficacy is limited by several life-threatening complications. HSCT is therefore a prime candidate for the development of novel biomarkers that predict both the occurrence of complications and their response to therapy. Successful biomarkers could be used to individualise prophylaxis, allow early intervention and target the use of high-risk treatments and novel therapies. The most advanced biomarkers currently under development are for a GvHD with the MAGIC algorithm, a two-factor test (ST2 and REG3α) performed at day seven post-transplant, able to identify patients at high (28%) and low (7%) risk of early non-relapse mortality and GvHD-related death.

This talk will cover key concepts in precision medicine, outline the current state of the field with respect to a GvHD, and describe how Manchester is poised to deliver the next generation of precision medicine for HSCT.



Dr Victoria Potter

Dr Victoria Potter
Consultant Haematologist
King's College Hospital

Dr Victoria Potter is a Consultant Haematologist specialising in stem cell transplantation at King's College Hospital, London. After graduating from the University of Sydney she completed early post-graduate and specialty training in haematology in Sydney, Australia, working at Westmead, Prince of Wales and St Vincent's Hospitals. In 2010 she moved to London to take up a clinical fellowship position at King's before accepting a consultant position in myeloid malignancies and transplantation. During this time she participated in the visiting physicians programme at Fred Hutchinson Cancer Centre Seattle. In November 2017, Victoria was appointed BMT Director at King's College Hospital. She is a member of the CMWP of the EBMT and is committed to the development of clinical trials in transplantation. Her research interests focus on the use of DLI for the prevention of relapse post-transplant.

Prophylactic DLI in Myeloid Malignancy

Allogeneic stem cell transplantation remains the only cure for the majority of myeloid malignancies. The use of reduced intensity transplantation has widened the applicability of this therapeutic intervention to those of older age and with co-morbidities. T-cell depletion has the potential to further improve outcomes and quality of life by decreasing GvHD. In this context relapse is the major cause of treatment failure. In recent years increasing numbers of patients have received donor lymphocyte infusions (DLI) as a strategy to improve the graft versus leukaemia effect and decrease rates of relapse after T-cell depleted transplantation. Despite this widely adopted practice limited high quality evidence exists to determine either the efficacy or best schedule in which to deliver this approach. This presentation will summarise the current evidence for DLI, prospective trials and consider strategies to be used in the future.

Marie Waller, Helen Webster and Angela Leather

Marie Waller
Advanced Nurse Practitioner, Manchester Royal Infirmary

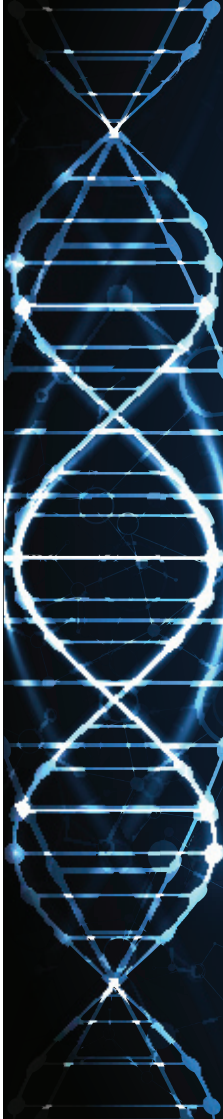
Marie has been working in haematology and stem cell transplant for 18 years. She has worked at Manchester Royal Infirmary since 2006 initially as a Bone Marrow Transplant Coordinator and in her current role as Advanced Nurse Practitioner since 2015. Marie has presented locally and nationally on various topics in haematology and transplant. Marie is also a member of several local and nation committees and is an expert adviser to NICE following involvement in NICE guideline - Haematological cancers: improving outcomes (2016). Marie had the opportunity to author a chapter in a nursing text book which was published earlier this year.

Helen Webster
Lead BMT Coordinator, Royal Manchester Children's Hospital

Helen started her career in paediatric haematology at Alder Hey Children's Hospital in 1991. She took up the newly created post of Bone Marrow Transplant Coordinator in January 2003. Helen then moved to Royal Manchester Children's Hospital as Lead BMT Coordinator. She has presented at many conferences both nationally and internationally. Helen is the chair of the paediatric BMT nurses group and has been involved in many publications the group has produced, both professional literature and patients' information literature.

Angela Leather
Transplant Coordinator, The Christie

Angela is Transplant Coordinator at The Christie in Manchester and has worked in haematology and bone marrow transplant since 1996, responsible for ensuring timely transplants and apheresis as part of her role. Angela also has keen interest in women's health and set up a nurse led clinic for post transplant patients. Angela attends bone marrow transplant conferences where possible and is keen to improve service for her patients, presenting and sharing experiences and knowledge is an important component of her senior nursing practice and contributed to the recently published EBMT nurses text book.



Dr Stephen Robinson

Dr Stephen Robinson
Consultant Haematologist
University Hospital Bristol

Dr Robinson trained in medicine at the Royal Free Hospital, London graduating in 1992. He trained in Haematology between 1995 and 2002 at University College London. He was awarded a PhD for research into developmental aspects of human dendritic cells in 1998. Since 2002 he has worked as a Consultant Haematologist in the Bone Marrow Transplant Unit at University Hospital Bristol with a specialist interest in malignant lymphoma and stem cell transplantation. Since 2014 he has been the Clinical Director of the Bristol Cancer Institute. Dr Robinson is currently conducting research into reduced intensity allogeneic stem cell transplantation in lymphoma and is the Scientific Secretary of the EBMT Lymphoma Working Party.

Transplantation in the Evolving Paradigm of Lymphoid Malignancies

The therapeutic landscape for patients with lymphoma is undergoing a dramatic transformation as a variety of novel therapies are incorporated into routine clinical practice. New monoclonal antibodies, small molecule B cell receptor inhibitors, immune checkpoint inhibitors and CAR T cells all offer alternative strategies to eradicate malignant lymphoid cells. These agents used either alone or in combination with other agents are demonstrating impressive and durable responses in high risk lymphoid malignancies and we are now witnessing there incorporation into earlier stages of the treatment pathway. As a consequence established therapies, including stem cell transplantation, are challenged and their place in the treatment paradigm need to be reappraised. Some of the novel agents may also interact with stem cell transplantation resulting in additional toxicities. I will discuss how some of the novel therapies for lymphoma are now changing the role of stem cell transplantation in lymphoid malignancies and how these agents may also be successfully combined with more traditional treatments.

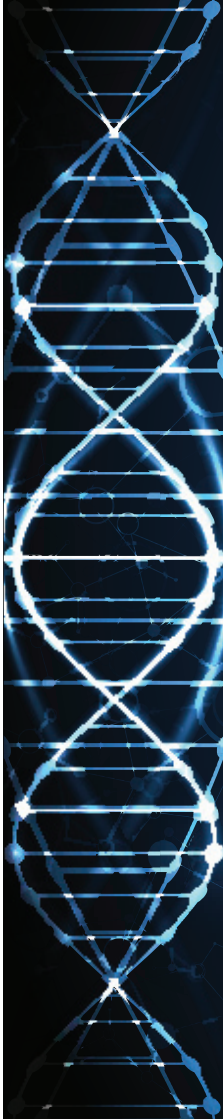
Dr Reuben Benjamin

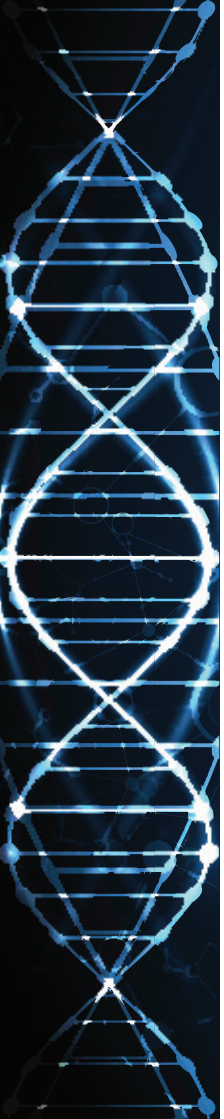
Dr Reuben Benjamin
Consultant Haematologist
King's College Hospital

Reuben Benjamin is a haematologist with an interest in multiple myeloma, stem cell transplantation and cell therapy. He completed his haematology training at University College Hospital, London and then spent a period at Memorial Sloan Kettering Cancer Center, NY undertaking research in CAR-T cell therapy for leukaemia and myeloma. Since 2014 he has been based at King's College Hospital, London where he leads the plasma cell disorder service and CAR-T cell programme. He is currently leading the first allogeneic off-the-shelf CAR-T cell study for relapsed adult B-ALL (CALM Trial).

CAR T Cell Set-up and Patient Selection

Chimeric antigen receptor (CAR) T cells are an exciting new form of therapy that has shown great promise in B-acute lymphoblastic leukaemia, lymphoma and myeloma. The first reports in 2014 of >90% complete response rates in patients with relapsed B-ALL who received CD19 targeted CAR-T cells has led to an explosion of interest in this technology. Subsequent trials in lymphomas and more recently myeloma have confirmed the early promise of this novel therapy. Whilst the response rates to CAR-T cell therapy are impressively high the toxicity has also been considerable. FDA approval in 2017 of Kymriah and Yescarta and more recently by EMA has created an urgent need for centres offering this therapy to develop the expertise for appropriate patient selection and managing the side effects of this novel therapy. In this talk I will briefly summarise some of the key trial CAR-T clinical trial results in ALL, lymphoma and myeloma and discuss the hospital setup required to deliver such a therapy safely.





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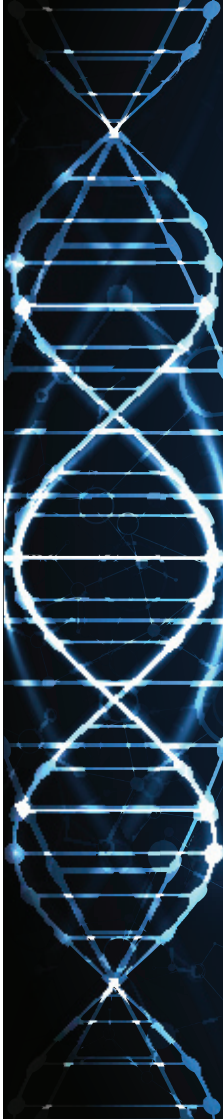

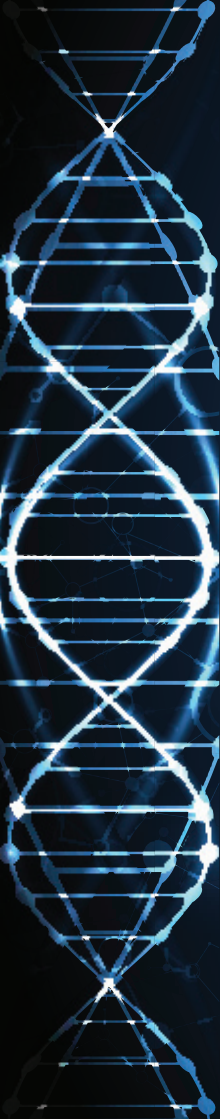

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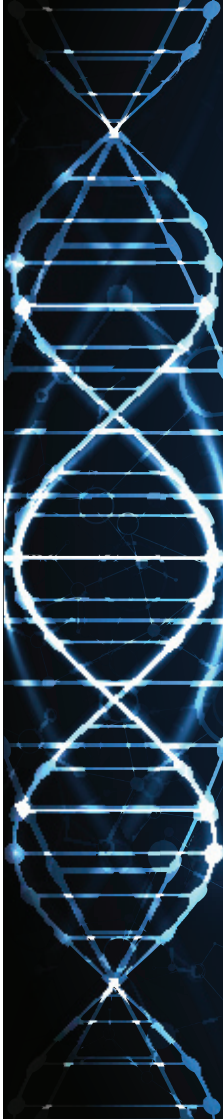

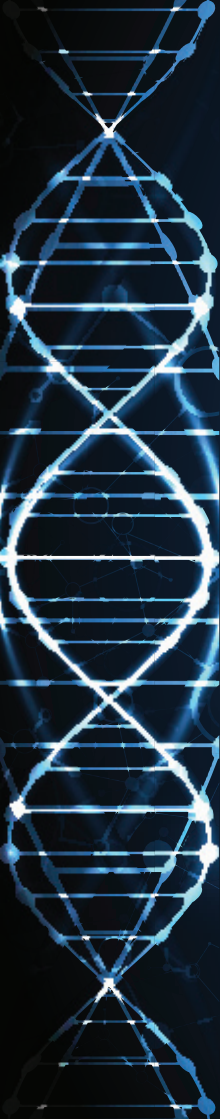

Notes

This meeting is one in a series to be held in the UK during 2017 – 2018.

The programme was designed by the Chairs with an Expert Panel's opinion and organised by Hartley Taylor Ltd. Sponsors have had no input into the agenda or choice of speakers

Sponsorship has been provided by Mallinckrodt.

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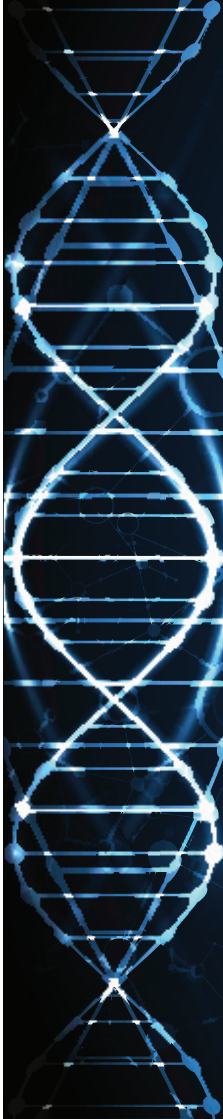

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