Targeted Delivery for Hard-to-Treat Cancers: Progress and Next Steps
16th September 2024
Downing College, Cambridge

AGENDA

12:30 **Poster session and networking lunch**

13:30 **Welcome and introduction**
Prof George Malliaras, IRC Director

13:40 **Clinical translation of dynamic hydrogels for local delivery: challenges and lessons**
Prof Oren Scherman, University of Cambridge

14:00 **Pro-drug nanoparticle loaded supramolecular hydrogels for glioblastoma interstitial delivery**
Prof Ruman Rahman, University of Nottingham

14:20 **Scale-up of Supramolecular Hydrogels for Hard-to-Treat Cancer**
Dr Andrew Howe, Aqdot

14:30 **Translation of Nanomaterials for Hard-to-Treat Cancers**
Prof David Fairen Jimenez, University of Cambridge

15:00 **Q&A session**

15:15 **Coffee break and poster session**

15:45 **Intra-tumoral drug delivery devices**
Prof George Malliaras, University of Cambridge

16:05 **Pre-clinical models of mesothelioma**
Prof Stefan Marciniak, University of Cambridge/Prof Judy Coulson, University of Liverpool

16:25 **Cross-cutting research supporting validation of new technologies for hard-to-treat cancers**
Prof Ronan Daly, University of Cambridge

16:45 **Q&A session**

17:00 **Wrap up and close - Prof George Malliaras, IRC Director**

17:10 **Drinks Reception and Poster session**

SPEAKERS AND TALKS

Clinical translation of dynamic hydrogels for local delivery: Challenges and lessons

Professor Oren A. Scherman, University of Cambridge

Our research efforts in the IRC have focused on the development and translation of hydrogels for local drug delivery primarily aimed at treating Glioblastoma, the most common high grade primary brain tumour in adults.

Over the past 10 years we have pioneered the development of dynamic hydrogels based on CB[8] host-guest interactions between peptide-functionalised hyaluronic acid polymer backbones. We have showcased the use of these biocompatible and biodegradable hydrogels as a platform for local delivery of chemotherapeutics for GB treatment. We have successfully scaled up production of our supramolecular hydrogels to multigram scale, producing enough material at scale to facilitate a first in human trial.

In terms of translation, we have established methodologies that are translatable to clinical settings and through engagement with translational teams and official discussions with the MHRA, we have addressed key regulatory hurdles. We have also achieved a route to sterilise the hydrogel components, which has been a significant obstacle for polymer-based therapeutics to date. External ADME tox studies are planned and MHRA guidance alongside establishing partnerships with manufacturing entities has given us a clear path towards a first in human trial. Despite these advancements, we have found that the funding landscape in the UK remains inadequate for supporting the translation of such innovative local delivery therapies. This lack of proper funding could hinder our progress, particularly as local delivery of therapeutics remains a controversial, yet promising, approach. As other gel systems continue to be developed globally, it is imperative to establish a viable path forward to ensure that we do not fall behind from a field that we were leading prior to facing these funding challenges.

Our collaborative efforts with institutions such as the University of Nottingham and the University of Liverpool have propelled our research forward, exploring controlled release mechanisms utilising gels and nanoparticles. Our broad movement aims to identify and leverage traction points for the local delivery within other areas of clinical need and hard to treat cancers to propel the work into the clinic.

Biography

Oren is a native of Norman, Oklahoma (USA). He graduated from Cornell University in Ithaca, New York, with a BA in Chemistry in 1999. He then moved to Pasadena, California, where he completed a PhD in 2004 in olefin metathesis and controlled polymerisation under the supervision of Professor Robert H. Grubbs at the California Institute of Technology (Caltech). After finishing his PhD, Oren moved to the Netherlands to work on supramolecular polymers with Professors E.W. Meijer and Rint P. Sijbesma at the Eindhoven University of Technology.

In 2006, he moved to the University of Cambridge to take up an academic appointment as a University Lecturer and Next Generation Fellow in the Melville Laboratory for Polymer Synthesis in the Department of Chemistry.
In 2012, he was promoted to Reader in Supramolecular and Polymer Chemistry and in March 2013 he was appointed as the Director of the Melville Laboratory; Oren was promoted to Full Professor in 2015.
During the 2013-2014 academic year, he was on sabbatical at Tsinghua University as the Xuetang Visiting Professor in Chemistry.

Pro-drug nanoparticle loaded supramolecular hydrogels for glioblastoma interstitial delivery

Prof Ruman Rahman, University of Nottingham

Isocitrate dehydrogenase wild-type glioblastoma (GBM) remains one of the most hard-to- treat cancers, with an invariable median overall survival of 14-16 months. There is an urgent clinical need to identify effective chemotherapeutics including synergistic combinations, which are predicated on infiltrative tumour cells as a proxy for residual disease which cannot be safely removed by surgery.

Furthermore, there is an opportunity to directly target residual disease via intraoperative drug delivery systems. We investigated incorporation of drug-loaded polymeric nanoparticles within a hyaluronic acid-based hydrogel with mechanical properties comparable to human brain parenchyma, as an implantable drug delivery vehicle for post-surgical GBM treatment.

We first conducted 3D spheroid drug screening using primary infiltrative GBM cells and identified Doxorubicin (DNA intercalator) in combination with Gemcitabine (nucleoside analogue) as strongly synergistic in a molar-ratio dependent manner, effecting metabolic impairment and cellular apoptosis. Superior hydrogel drug loading was achieved with polymer micelle nanoparticles relative to hyperbranched polymers. Cellular uptake and potency were significantly enhanced by polymer micelles relative to free drug, via dynamin-dependent caveolin and clathrin pathways. Using orthotopic infiltrative GBM xenografts, we have shown both feasibility of intra-operative application of Gemcitabine-loaded hydrogels and determined a maximum tolerated dose to progress to an ongoing therapy study.

Biography

Ruman is Professor of Molecular Neuro-Oncology at the University of Nottingham's Biodiscovery Institute. He currently leads research programmes in neurosurgically-applied drug delivery, brain tumour genomics and tumour metabolomics, with funding from EPSRC, MRC, BBSRC, and the Little Princess Trust. His recent multidisciplinary studies have been published in Nature Nanotechnology, Clinical Cancer Research, Genome Medicine and Small. Key international collaborations include Johns Hopkins University, Mayo Clinic Arizona, and Aix-Marseille University. His affiliation to professional bodies includes membership on the Evaluation Committee for the French National Institute of Health and Medical Research (INSERM) (2019-present), UKRI Interdisciplinary Assessment College Member (2023-2025), Cancer Research UK Early Detection Committee (2024), and Society for Neuro-Oncology Conference Scientific Review Committee (2016-present). He is former Chair for the Children with Cancer UK funded Children's Brain Tumour Drug Delivery Consortium spanning leading institutions across Europe and North America (2020-2023) and former co-Chair of the British Neuro-Oncology Society Research Subcommittee (2021-2023).

Scale-up of Supramolecular Hydrogels for Hard-to-Treat Cancer

Dr Andrew Howe, aqdot

This presentation will give a brief summary of the collaborative work undertaken between Voula Kasapidou of the Scherman Group in the University of Cambridge and scientists and engineers at Aqdot. The work was undertaken in the 6-months from October 2021 when Voula was funded by a BBSRC Flexible Talent Mobility Account postdoctoral placement grant.

The aims were to develop a robust scale-up protocol from small lab scale to grams scale, and to investigate terminal sterilisation methods for the final drug product hydrogel formulation. These aims were achieved with several cost-saving opportunities identified and GMP-accredited manufacturers approached. The development of the work and recommendations were provided in a full “Technology Transfer Pack”.

Biography

Andrew is a colloid / soft matter scientist, with experience in co-optimising material formulation for in-process and end-product performance. The formulations often contain (nano)particles, polymers and / or surfactants and the key measurement technique is often rheology.

Since 2015, Andrew has been a research scientist at Aqdot, a young company that originated in Cambridge University. Andrew has worked on developing applications for the novel macrocyclic chemical, cucurbiturils. "CBs" are extremely effective supramolecular “hosts” that non-covalently bind a wide range of chemical “guests”. Their breadth of application opportunities – and some formulation challenges – arise from the wide range of chemical moieties with which CBs interact. Andrew’s current focus is on the use of CBs in delivery of therapeutics and vaccines.

For 20 years Andrew worked at Kodak in the UK and USA on coating and printing applications then for 5 years at Schlumberger, UK on enhanced oil recovery. Andrew has been active in professional societies, including chairing the RSC/SCI UK Colloid Groups, and he was President of the European Colloid and Interface Society and the British Society of Rheology. Andrew has an H-index of 34 and is co-inventor of 32 filed patents. He gave the RSC/SCI Colloid Group Rideal Lecture in April 2024.

Translation of Nanomaterials for Hard-to-Treat Cancers

Prof David Fairen Jimenez, University of Cambridge

Hard-to-treat cancers demand innovative approaches to enhance the targeting and delivery of various therapeutic modalities, ranging from chemotherapeutics to small molecules and macromolecules.

Our overarching objective within the EPSRC IRC has been to innovate novel materials for drug delivery, focusing on metal-organic frameworks (MOFs) and other high-capacity vehicles. These materials are designed to encapsulate hydrophobic drugs and macromolecules such as peptides, siRNAs, and mRNAs, aiming to boost the efficacy of multiple therapies by increasing their local concentration in the tumours through targeted release.

Over the years, we have progressed from in silico screening of biocompatible MOFs through in vitro and ex vivo assessments, to in vivo studies evaluating efficacy, biodistribution, toxicity, and immune response. A significant part of our pre-clinical work involved developing GMP-compatible methods to transition these materials to clinical applications.

A critical milestone was achieving stable formulations. We accomplished this by modifying MOFs with phosphate-functionalised methoxy polyethylene glycol (mPEG-PO3), which ensured more than a year of colloidal stability, facilitated dry storage, and preserved the material integrity in solutions. With loading capacities as high as 60 wt.%, these modified MOFs exhibited delayed drug-release properties and demonstrated reduced toxicity compared to naked MOFs. Our research has made substantial strides in vitro and in vivo, particularly in addressing pancreatic cancer and mesothelioma — key focus areas of the EPSRC IRC — and also in triple-negative breast cancer.

The research and development undertaken have culminated in the establishment of Vector Bioscience Cambridge, a spin-out that has successfully secured ca. £3 million in seed funding. With 8 current employees, this investment supports the completion of preclinical studies on the material as a drug delivery vehicle, further exploring its toxicity and efficacy through additional in vivo work in preparation for first-in-human studies.

Biography

Dr David Fairen-Jimenez is a Royal Society University Research Fellow (URF) and Reader in Molecular Engineering in the Department of Chemical Engineering & Biotechnology at the University of Cambridge, where he leads the Adsorption & Advanced Material Laboratory (AAML). His research into the application of metal-organic frameworks (MOFs) in energy applications and nanoscale drug delivery is underpinned by fundamental studies into molecular recognition and adsorption processes in nanoporous materials.

He graduated with a PhD in porous materials in chemistry, under the supervision of Prof Carlos Moreno-Castilla, from the University of Granada in 2006. He then worked with Prof. Tina Duren at the University of Edinburgh, studying adsorption in metal-organic frameworks combining advanced experimental techniques molecular and modelling for the design of novel functional materials. He expanded his research at Northwestern University (USA), working with Prof. Randall Snurr and collaborating with Profs. Hupp, Farha and Stoddart, and implementing new computational methods for H2 storage and toxic industrial compounds capture.

David is also a founder and Director at Immaterial Labs Ltd., a MOF manufacturing company for gas storage and air filtration, and Tarsis Technologies Ltd., a company for slower and controlled delivery of drugs using amorphous MOFs. In 2016 he was awarded a European Research Council (ERC) Consolidator Grant (€1.9M) for the “Design of NanoMOFs Capsules for Drug Delivery and Bioimaging” in cancer diagnosis and therapy.

Intra-tumoral drug delivery devices

Prof George Malliaras, University of Cambridge

Localised delivery of chemotherapy directly into a tumour is highly desirable as a means to increase bioavailability and minimise off-target effects. Convection-enhanced delivery, where an implantable catheter delivers a solution of a chemotherapeutic agent into/near the tumour, has been developed for this purpose.

In the case of brain tumours, however, reflux of the supplied solution along the side of the catheter limits the applicability of this technique. Ion pumps utilise electrophoresis to deliver the drug without the solvent and are hence overcome this disadvantage. I will discuss the merits of these devices and show how they can be used to address needs in hard-to-treat cancers.

Biography

George Malliaras is the Prince Philip Professor of Technology at the University of Cambridge. He received a PhD from the University of Groningen and did a postdoc at the IBM Almaden Research Center. Before joining Cambridge, he was a faculty member at Ecole des Mines de St. Etienne and at Cornell University, and served as the Director of the Cornell NanoScale Facility.

His research has been recognized with awards from the European Academy of Sciences (Blaise Pascal Medal), the Materials Research Society (Mid-Career Researcher Award), the New York Academy of Sciences (Blavatnik Award for Young Scientists), the US National Science Foundation (Faculty Early Career Development Award), and DuPont (Young Professor Award). He was awarded an Honorary Doctorate from the University of Linköping (Sweden), elected Fellow of the Materials Research Society and of the Royal Society of Chemistry, and is a member of the Academia Europaea and of the European Academy of Sciences.

Pre-clinical models of mesothelioma

Prof Stefan Marciniak, University of Cambridge/Prof Judy Coulson, University of Liverpool

Mesothelioma is a hard to treat cancer of the lining of the thoracic cavity frequently caused by exposure to asbestos 30 to 40 years previously. Many patients have disease limited to the thoracic cavity and so potentially amenable to local delivery of chemotherapy using high-capacity vehicles and / or gels.

A challenge for the field has been the lack of appropriate pre-clinical models, and so members of the IRC have developed new early passage cell lines, cancer organoids, and chick embryo models for testing drug delivery technologies.

Biographies

Stefan Marciniak studied medicine at the University of Cambridge as part of its MB/PhD Programme. After medical posts in Cambridge, London and Edinburgh, he undertook post-doctoral training in New York funded by the Wellcome Trust and as an MRC Clinician Scientist Fellow back in Cambridge. He established his own group in CIMR as an MRC Senior Clinical Research Fellow in 2012.

He is now Professor of Respiratory Science at the University of Cambridge and an Honorary Consultant Respiratory Physician at Addenbrooke's and Royal Papworth Hospitals. His laboratory research focuses on the role of stress signalling in lung disease. His clinical research focuses on pleural medicine, especially the genetics of pneumothorax. He is Director of the University of Cambridge MB/PhD Programme.

Judy Coulson graduated from the University of Salford in Biological and Biochemical Sciences, and the University of London with a PhD in Biochemistry. She was a post-doctoral researcher at Aston and Nottingham Universities, before joining the University of Liverpool as a lecturer in 2001, and receiving the British Association for Cancer Research/AstraZeneca Young Scientist Award in 2003.

Judy is now the non-clinical Deputy Head of Department in Molecular and Clinical Cancer Medicine and the Academic Lead for the Liverpool Chick Egg Facility. She has served on scientific network and grant awarding committees, including currently for Mesothelioma UK. In 2022, Judy was appointed as Deputy Associate Pro Vice Chancellor for Technology, Infrastructure and Environment in the Faculty of Health and Life Sciences, and the Faculty Lead for Equality Diversity Inclusion and Wellbeing.

She leads an active cancer biology research group interested in deciphering the interplay between cell signalling, transcription and ubiquitylation, to identify potential new therapeutic approaches. A focus on mesothelioma led to the development of new preclinical chick egg models to test therapies for this hard to treat cancer.

Cross-cutting research supporting validation of new technologies for hard-to-treat cancers

Prof Ronan Daly, University of Cambridge

The EPSRC funded IRC in Targeted Delivery for Hard-to-Treat Cancers focused initially on five different emerging technologies that involved innovative gels, implants and nanocarriers.

The cross-cutting theme in Manufacturing was set up to support each of the technology-focused workstreams throughout the lifetime of the project. Here, we present the support from the theme in terms of research planning and creation of validation techniques to support the translation of the technologies.

The project used the Institute for Manufacturing's road mapping approach to create a pathway forward towards clinical trials of the technology. IfM Engage, the knowledge-transfer arm of the Institute for Manufacturing (IfM) at the University of Cambridge, blend consultancy, training and mentoring to help organisations with their strategic and technology innovation planning through road mapping. The IRC team were joined by key stakeholders for a series of workshops on each core technology to develop technology roadmaps and outline a pathway to first-in-human trials and beyond. We brought together stakeholders included researchers, clinicians (who will deploy the technology), potential manufacturers, consultants (who have experience in applications to MHRA for regulatory approvals) and other academics who had already been through the regulatory process for approval for a completely new technology. Over the course of three workshops, the stakeholders reflected on the technology development progress to date; mapped and explored key challenges; and identified the pathway forward towards the clinical trial of the technology.

The manufacturing research team also supported the technology researchers with new validation methods. Here, we will present work carried out to create new quantitative infrastructural technologies, tools that help understand the level of control over drug delivery and targeting. These tools support analysis of innovative gels, nanocarriers and implants, translating the planned clinical use and the physiological environments into accessible and repeatable experiments for rapid iteration of new designs or formulations. The research presented here supports the IRC and aims to accelerate future research by providing new, open access research tools for the broader community.

Biography

Ronan is Professor of Advanced Manufacturing in the Department of Engineering, University of Cambridge. He leads the Fluids in Advanced Manufacturing research group, which tackles a broad range of complex fluid flow and functional material challenges critical to enabling improved design and scale-up in foundation industries, sensors, and medical devices. The team focuses on advanced, digital and distributed manufacturing technologies, looking both at the challenges of new materials in existing manufacturing processes and how to design new manufacturing techniques to more efficiently manufacture a final product. There are three main themes of research.

A. Affordable Healthcare and Sensor Technologies: The group combines research into materials, sensor formats, validation technologies, and innovative manufacturing processes;
B. Advanced Manufacturing: Research is carried out across a wide range of disciplines to create new knowledge around advanced and direct-write additive manufacturing techniques;
C. The Science of Scale-up: Identifying and understanding the interdependencies between the advanced functionality of emerging materials/devices and their manufacturing technologies.