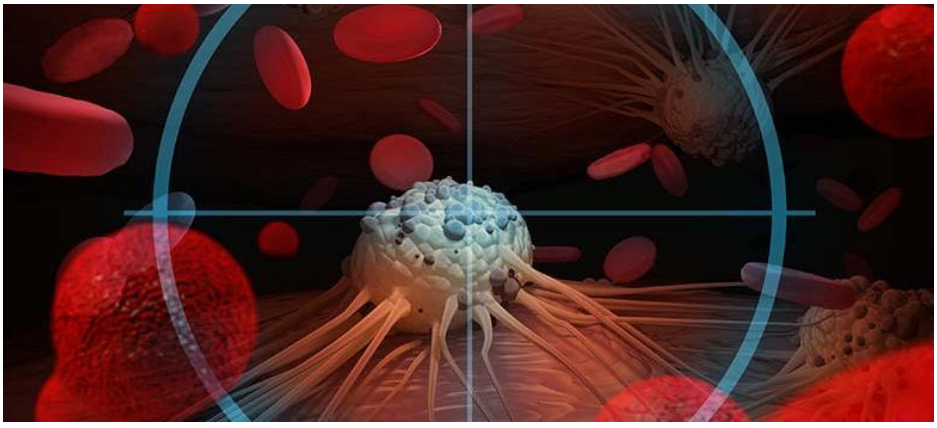
Oxford Centre for Drug Delivery Devices

ONCOLOGICAL DRUG DELIVERY CONFERENCE

Sultan Nazrin Shah Centre, Worcester College, Oxford



Monday 23rd and Tuesday 24th September 2019

EPSRC
Pioneering research and skills

UNIVERSITY OF OXFORD

FOREWORD

Engineering Tomorrow's Cancer Therapies

The greatest challenge in oncological drug delivery is achieving successful penetration and distribution of the therapeutic agent throughout the tumour.

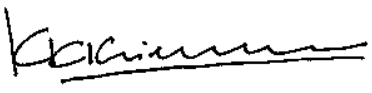
The Oxford Centre for Drug Delivery Devices (OxCD3), which came into being in July 2014, seeks to transform both clinical and industry practice in drug delivery by demonstrating the value and feasibility of engineering approaches, involving a combination of stimulus-responsive nanocarriers and medical devices, for improved tumour uptake and therapeutic outcome. The Centre is based at the University of Oxford and was made possible by a Programme Grant from the Engineering and Physical Sciences Research Council (EPSRC), supplemented by extensive support from Industry and the University of Oxford.

Over the past 5 years, OxCD^3 has enabled the coming together of a cross-disciplinary team of Lead Investigators (**Biomedical Engineering**: C. Coussios, R. Carlisle, R. Cleveland, E. Stride, **Oncology:** L. Seymour, N. Sibson, K. Vallis, **Surgery:** P. Friend, J. Hester, **MRC Weatherall Inst. of Mol. Medicine:** T. Rabbits), post-doctoral researchers, clinical research fellows and passionate doctoral students, and of a broader national and international network of collaborators, to form a multi-disciplinary research and training environment for combinational engineering of biology, chemistry and medical devices.

This extraordinary team of over 40 researchers has been able to make notable inroads in improving the delivery of small molecules, antibodies, viruses and nucleic-acid-based drugs into solid tumours by exploiting physical mechanisms triggered by ultrasound, light, magnetic fields or shock waves. By working closely with the National Health Service (NHS), the National Institute for Health Research (NIHR)and the Oncology Clinical Trials Office at the University of Oxford, we have also taken the most promising approaches into first-in-man clinical trials, demonstrating the safety and clinical feasibility of device-enhanced drug delivery in oncology.

The purpose of this conference in oncological drug delivery is to share these findings with the expert community, but also to identify and re-focus our efforts on those therapeutics, tumour types and indications, which have yet to be conquered.

Leading OxCD^3 has been a privilege and the highlight of my career to date. I would like to take this opportunity to thank every member of the OxCD^3 team, its International Advisory Board, its Steering Committee, and you, the delegates of this expert conference in drug delivery, for your support. We look forward to continuing and extending our collaborative work to ensure that current and emerging cancer therapeutics are able to reach their target and fulfil their curative potential.



Professor Constantin Coussios FREng
Director, Oxford Centre for Drug Delivery Devices
Director, Institute of Biomedical Engineering, University of Oxford

OxCD^3 Oncological Drug Delivery Conference: Programme Overview

Monday, 23 September 2019

8:30-8:50 WELCOME, COFFEE AND REGISTRATION

Opening Session

8:50-09:00 Overview of OxCD3 and aims of the conference
Prof. Constantin Coussios, Univ. of Oxford

9:00-09:30 Getting the Most out of Early Phase Trials in Oncology
Prof. Mark Middleton, Univ. of Oxford and OUH Trust

Session 1: Oncolytic virotherapy

Chairs: Prof. Chae-Ok Yun and Prof. Len Seymour

09:30-10:00 Clinical Trials and Delivery Challenges of Oncolytic Viruses
Prof. Hardev Pandha, Univ. of Surrey

10:00-10:30 Cavitation-Enhanced Virotherapy
Prof. Robert Carlisle, Univ. of Oxford & OxSonics Therapeutics

10:30-11:00 Mini-Presentations and Panel Discussion

11:00-11:30 COFFEE BREAK AND POSTER PRESENTATIONS

Session 2: Antibodies & Antibody-Drug Conjugates

Chairs: Prof. Kate Vallis and Dr Chris Van der Walle

11:30-12:00 Antibody Drug Conjugates - Targeted Toxin Delivery by Antibodies
Dr Phil Howard, Spirogen

12:00-12:30 Ultrasound-Enhanced ADC Delivery to Tumours
Ms Claudia Hill, Univ. of Oxford

12:30-13:00 Mini-Presentations and Panel Discussion

13:00-14:00 LUNCH

Session 3: Immuno-Oncology

Chairs: Dr Joanna Hester and Prof. Mark Middleton

14:00-15:00 **PLENARY KEYNOTE:** Immuno-Oncology in the Clinic: Successes and Challenges
Prof. Jedd Wolchok, Memorial Sloan Kettering

15:00-15:30 Immuno-Oncology: Progress and Future Advances
Dr Robert Wilkinson, AstraZeneca

15:30-16:00 AFTERNOON TEA

16:00-16:30 Can Mechanical and Thermal Effects Help Stimulate Anti-Tumour Immune Responses?
Prof. Elizabeth Repasky, Roswell Park Cancer Center

16:30-17:00 Cavitation-Enhanced Delivery of Checkpoint Inhibitors
Mr Prateek Katti, Univ. of Oxford & NIH

17:00-17:30 Mini-Presentations and Panel Discussion

19:00-22:00 DRINKS AND CONFERENCE DINNER IN WORCESTER COLLEGE HALL

Tuesday, 24 September 2019

08:15-08:45 WELCOME AND COFFEE

Session 4: Nanomedicines for Oncological Drug Delivery

Chairs: Prof. Eleanor Stride and Prof. Tom Matula

08:45-09:15 Towards Clinical Translation of Nanomedicines
Dr Marianne Ashford, AstraZeneca

09:15-09:45 Stimulus-Responsive Polymeric Nanomedicines in Oncology
Prof. Cameron Alexander, Univ. of Nottingham

09:45-10:15 TarDox: First-in-Man Trial of Ultrasound-Triggered Targeted Drug Delivery
Dr Paul Lyon, OUH Trust

10:15-10:45 Mini-Presentations and Panel Discussion

10:45-11:15 COFFEE BREAK AND POSTER PRESENTATIONS

Session 5: Challenging Indications: Brain

Chairs: Prof. Nicola Sibson and Dr. Ruman Rahman

11:15-12:15 **PLENARY KEYNOTE:** First-in-Man Trials of Device-Enhanced Delivery to the Brain
Prof. Alex Carpentier, Neurosurgery, Sorbonne University

12:15-12:40 Targeted Device-Mediated Drug Delivery to Brain Metastases
Mr Oliver Vince, Univ. of Oxford

12:40-13:10 Mini-Presentations and Panel Discussion

13:10-14:00 LUNCH

Session 6: Challenging Indications: Pancreas

Chairs: Dr Laura Spiers and Prof. Robert Carlisle

14:00-14:30 Delivery Challenges & Immunological Targeting of the Pancreas
Dr Shiv Sivakumar, Univ. of Oxford

14:30-15:00 Pulsed Focused Ultrasound and Immune Checkpoint Inhibitors in Pancreatic Cancer
Dr Petros Mouratidis, Institute of Cancer Research

15:00-15:30 Sonodynamic Therapy for Pancreatic Cancer
Prof. Eleanor Stride, Oxford

15:30-16:00 Mini-Presentations and Panel Discussion

16:00-16:30 AFTERNOON TEA

Session 7: Future Directions and Technologies

Chairs: Prof. Brad Wood and Prof. Mo Khan

16:30-16:50 Storz Medical: Transcranial Shock Waves
Dr Pavel Novak, Storz Medical

16:50-17:10 OxSonics Therapeutics: Cavitation-Enhanced Drug Delivery
Dr Christian Coviello, OxSonics

17:10-17:30 IRC in Targeted Delivery for Hard-to-Treat Cancers
Prof. George Malliaras, Univ. of Cambridge

17:30-17:40 CLOSING REMARKS: **Prof. Constantin Coussios, Univ. of Oxford**

17:40-18:30 CLOSING DRINKS RECEPTION

INVITED LECTURE

Getting the Most out of Early Phase Trials in Oncology

Professor Mark Middleton

Head, Department of Oncology, University of Oxford

There are more treatments in development for cancer today than ever before and we have fantastic tools with which to understand their effects on tumours and patients. Despite this very few treatments make it through to become standards of care, and the failure rate in late stage cancer trials remains very high. Early phase trials are used to establish the safety and feasibility of new approaches, and to provide proof of the mechanism of action and/or therapeutic concept in man. Well-designed studies can go beyond this, and provide better data to inform development decisions and to de-risk expensive late phase trials. I will discuss classical trial designs and their weaknesses and consider alternative strategies, using examples from the Oxford unit's portfolio.

NOTES:

SESSION 1: ONCOLYTIC VIROTHERAPY

Chairs: Prof. Chae-Ok Yun and Prof. Len Seymour

INVITED LECTURE

Human Studies of Oncolytic Virotherapy: Key Biological, Delivery and Trial Design Challenges

Professor Hardev Panda

Professor of Medical Oncology, University of Surrey

Oncolytic virotherapy remains an exciting and innovative approach for the treatment of malignant disease. From the original case reports of cancer resolution after concomitant viral infection dating back 100 years, tthrough the FDA licensing of an oncolytic herpes virus (T-VEC , talomigene laherparepvec) for the treatment of malignant melanoma in 2015, to the current day, a large number of wild type and genetically engineered viruses have been evaluated in over 140 human studies. The field has gained momentum through improved understanding of virus biology, virus engineering, tumour dysregulation and the biology of the tumour microenvironment and its fundamental components which limit virus spread. Above all, realisation of the innate and adaptive immune responses resulting from virus cytotoxicity of cancer cells have coincided with the explosion of knowledge, interest and research investment through the development of immune checkpoint inhibitor therapy. Further efforts are needed to consolidate the ability of OVs to activate immune cells against appropriate antigenic tumour targets, improve recruitment and infiltration of immune cells into the tumour microenvironment, and maintain their in situ activity. Virus distribution has to be enhanced despite the hostile physical and immunological barriers around tumours, and notably few human trials have focused on this aspect. Tailoring specific properties of certain types of oncolytic virus to a particular malignancy and cancer biology has to replace current strategies of 'signal seeking' small cohorts of different cancer patients. Combined with strategic applications of oncolytic virotherapy at specific disease stages and in rational sequenced combinations, some of the current barriers to success may be overcome.

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INVITED LECTURE

Cavitation-Enhanced Virotherapy

Professor Robert Carlisle

Professor of Biomedical Engineering, University of Oxford

Oncolytic viruses (OV) demonstrate selectivity, amplification power, capacity to encode therapeutic transgene and non-apoptotic cell kill, which provides them with huge potential for cancer treatment. In indications where direct intratumoural injection is possible, such as head and neck cancer and melanoma, OVs such as adenovirus 'H101' and herpes simplex virus 'Imlygic', have gained approval. However, to broaden the clinical utility of OV, they need to be amenable to intravenous delivery and so their blood stability and their delivery from the bloodstream and into and throughout target tumours must be improved (Grundy *et* al. Exp. Op. Drug Delivery 2016; Hill & Carlisle Exp. Op. Drug Delivery 2019; Hill *et al.* Meth. Mol. Biol. 2019). OXCD3 work to meet these challenges is presented. Specifically, approaches to surface modify OV for extended pharmacokinetics and the combination of intravenous OV dosing with tumour targeted ultrasound-mediated cavitation are described. Crucial studies demonstrated that cavitation does not impact on the structure or activity of adenovirus or vaccinia virus (Myers *et al.* Int. J. Nanomed. 2018) . Experiments with adenovirus or vaccinia virus in tumour bearing mice demonstrated delivery into tumours and anti-tumour efficacy could be dramatically enhanced (Myers et al Mol. Ther. 2016, Mo *et al.* Exp. Op. Drug Delivery 2016). Recent studies have shown that polymer coating vaccinia virus can improve its pharmacokinetic profile and may even permit retargeting of the virus. Remaining studies will define the impact of tumour-targeted cavitation on intravenously delivered polymer coated vaccinia virus.

[Conflict of Interest: Professor Carlisle is a co-founder of, consultant to and has a financial interest in OxSonics Therapeutics Ltd, a company spun out from the University of Oxford to develop cavitation-enhanced drug delivery].

NOTES:

CONTRIBUTED POSTERS AND MINI-LECTURES

#1. Polymer Coating of Vaccinia Virus for Enhanced Bloodstream Stability

Claudia Hill*, Megan Grundy, Luca Bau, Constantin Coussios, Rorbert Carlisle

University of Oxford

Oncolytic Vaccinia Virus is a selective and powerful tool for cancer treatment with natural tumour tropism and the potential for increased selectivity, efficient cell-to-cell spread & rapid replication in cancer cells. It has a well-defined safety profile and is being utilised in many late clinical trials for cancer treatment. However, its clinical utility is currently limited as Vaccinia Virus (VV) is readily neutralised by the immune system and cannot penetrate deep into tumours.

NOTES:

CONTRIBUTED POSTERS AND MINI-LECTURES

#2. Ultrasound-Mediated Cavitation Enhances the Delivery of Enadenotucirev into Tumours

Megan Grundy, Christophoros Mannaris, Claudia Hill, Egon Jacobus, Margaret Duffy, Brian Lyons*, Len Seymour, Constantin Coussios, R. Carlisle
University of Oxford & PsiOxus Therapeutics

Delivery of drugs into and throughout tumours presents a challenge to successful cancer therapy. The physiology of the tumour microenvironment leads to a reduction in convective flow, and thus drug delivery often occurs solely through diffusion-dependent transport. Delivery is further reduced as the size of drugs increases; viruses face a larger delivery challenge than low-molecular weight chemotherapy agents. Externally-applied ultrasound (US) can provide a non-invasive stimulus to increase drug extravasation in solid tumours. to intratumoural injection. Thus, use of US-mediated cavitation will likely have more impact when applied to a virus more amenable to i.v. delivery. Enadenotucirev has demonstrable clinical delivery and virus activity after i.v. administration to patients with colon cancer. Here we present an investigation of the in vitro and in vivo delivery of EnAd, in combination with US and cavitation.

NOTES:

SESSION 2: ANTIBODIES AND ANTIBODY-DRUG CONJUGATES

Chairs: Prof. Kate Vallis and Dr Chris Van der Walle

INVITED LECTURE

Antibody Drug Conjugates - Targeted Toxin Delivery by Antibodies

Dr Phil Howard

CTO, Spirogen

Antibody-drug conjugates (ADCs) offer a new approach to delivering cytotoxic agents to the tumour whilst sparing healthy tissue. ADCs are an attempt to combine the potency of cytotoxic warheads with the selectivity of antibodies. To date, five ADCs Adcetris™, Kadcyla™, Mylotarg™, Besponsa™ and Polivy™ have been approved by the FDA for clinical use in oncology. The presentation aims to introduce the ADC concept, detail the roles of the individual ADC components and review a number of the approved ADCs. The second part of the presentation will focus on the emerging next generation of topoisomerase I and pyrrolobenzodiazepine based ADCs which are currently undergoing clinical and preclinical development..

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SESSION 2: ANTIBODIES AND ANTIBODY-DRUG CONJUGATES

Chairs: Prof. Kate Vallis and Dr Chris Van der Walle

INVITED LECTURE

Antibody Drug Conjugates - Targeted Toxin Delivery by Antibodies

Claudia Hill

OxCD[3] DPhil Student, University of Oxford

Antibody drug conjugates (ADC) offer a means of combining the efficient cell kill provided by cytotoxic drugs with the enhanced pharmacokinetics and target disease selectivity provided by antibodies. This combination has been shown to substantially improve the therapeutic index for several drugs. However, improvements to the percentage of the injected dose which can be deposited within and throughout target tumours would be of benefit in further lowering off target toxicity and further increasing anti-tumour efficacy. Work within OXCD3 has investigated the impact of tumour localised ultrasound-mediated cavitation on a range of antibodies and antibody drug conjugates. Initial work demonstrated that cavitation does not impact on the structure or target (EGF receptor) binding activity of the antibody cetuximab (Myers et al Mol. Ther. 2016, Mo *et al.* Exp. Op. Drug Delivery 2016). Furthermore, the % of injected dose of cetuximab rescued from EGFR positive xenograft tumours in mice could be substantially (up to 4 fold) and significantly ($p<0.001$) enhanced when delivered in combination with tumour targeted cavitation (Grundy *et* al. Exp. Op. Drug Delivery 2016; Hill & Carlisle Exp. Op. Drug Delivery 2019). In work performed in partnership with MedImmune the impact of cavitation assisted delivery on the ADC Trastuzumab-SG3249 was studied. In HER2 positive xenograft tumour models cavitation was shown to provide 2-10 fold enhancements of tumour uptake. In studies of tumour growth control a trend of enhanced efficacy was seen in cavitation but slow and highly variable tumour growth rate prevented definitive conclusions being made.

NOTES:

CONTRIBUTED POSTERS AND MINI-LECTURES

#3. Targeted Delivery in a Colorectal Cancer Model

Ayashe Bouakaz*
Inserm U1253, Université de Tours, Tours France

Sonoporation is an innovative approach based on ultrasound and gas microbubbles, leading to increased permeability of endothelial wall, thus facilitating the passage of molecules. The objective of this study is to optimize the bioavailability of various therapeutic compounds in subcutaneous and orthotopic tumor models. HT29 cells were inoculated subcutaneously with matrigel in nude mice and the tumor growth was monitored every two days using a VEVO2100 imaging system. Sonoporation was applied using three different ultrasound settings. The uptake was assessed at different times post sonoporation and the intratumor distribution was determined by immunohistochemistry. Tumor volume was measured up to 3 weeks post sonoporation. Based on fluorescence data, the results showed a high drug uptake within the tumor depending on the applied US settings and the fluorescence signal persisted significantly longer after sonoporation compared to control. These results indicate that drug accumulated more efficiently and durably in the tumor after sonoporation. This study demonstrates the high efficiency of sonoporation in various animals models and using various drugs, by increasing the bioavailability and improving the delivery therapeutic antibody in the targeted tumor site.

NOTES:

CONTRIBUTED POSTERS AND MINI-LECTURES

#4. Monitoring Cavitation-Enhanced Drug Delivery by Passive Acoustic Mapping with Spatial Exclusion

Cameron A. B. Smith*, Christophoros Mannaris, Luca Bau, Megan Jackson, Prateek Katti, Robert Carlisle and Constantin Coussios
University of Oxford & OxSonics Therapeutics

Ultrasound mediated cavitation can produce a wide range of desirable bioeffects. However, due to the stochastic nature of cavitation and the irregularities in tumor perfusion real time treatment monitoring is essential to allow for reliable, safe therapies. Passive acoustic mapping (PAM) has shown to be capable of localizing and determining the extent of cavitation activity. In this work, a PAM derived cavitation dose metric is related to extravasation of a drug into solid tumors, exploring whether PAM derived cavitation dose can be used to monitor the levels of drug delivery achieved and how cavitation occurring outside the tumor affects this relation. CD-1 nude mice were subcutaneously inoculated with HT-29 tumor cells. Once the tumors reached 90-150 mm3, the mice were intravenously injected with cetuximab and a submicron sized cavitation agent at two different concentrations, and treated with focused ultrasound (0.5 MHz, 50,000 cycle pulses, 0.5 Hz PRF) for 10 minutes. Intratumoral cetuximab concentrations were then assessed via ELISA and compared to PAM derived cavitation dose estimates generated using frequency domain robust Capon beamforming PAM from data recorded using two 90-degree coplanar L11-4v linear arrays. PAM derived cavitation dose showed a strong correlation with the levels of drug delivery achieved regardless of the concentration of the cavitation agent that was used. This correlation could be further improved by spatially excluding cavitation energy that occurred outside of the tumor. Using PAM derived cavitation dose as a predictor of the extent of drug extravasation into solid tumors could allow clinicians to track the progress of ultrasound-enhanced drug delivery in real time.

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SESSION 3: IMMUNO-ONCOLOGY

Chairs: Dr Joanna Hester and Prof. Mark Middleton

P L E N A R Y K E Y N O T E

Checkpoint Blockade: Successes and Challenges

Professor Jedd D. Wolchok

Chief, Melanoma & Immunotherapeutics Service, Memorial Sloan Kettering Cancer Centre, Lloyd J. Old Chair in Clinical Investigation, Director of the Parker Institute for Cancer Immunotherapy, Associate Director of the Ludwig Center for Cancer Immunotherapy.

Given the activity noted with both CTLA-4 or PD-1 blockade, clinical trials are now investigating combination checkpoint blockade. The most mature data with a combination of ipilimumab + nivolumab in melanoma showed a response rate of 60% in the context of increased, yet manageable toxicity. Such responses are generally durable, even when treatment was stopped early for toxicity. Unlike in studies of PD-1 blockade monotherapy, there was no significant difference in clinical activity based on tumor expression of PD-L1. This approach has gained US regulatory approval for metastatic melanoma and is in late stage clinical trials for other malignancies. Attention is being paid to the reasons underlying the efficacy of checkpoint blockade in certain malignancies. One hypothesis has been that cancers having a high mutational load may be more amenable to immune modulation by virtue of the larger number of potential neo-epitopes present, fostering baseline immune recognition that can then be potentiated by checkpoint blockade. We have found that melanoma patients having long term clinical activity with ipilimumab have a significantly greater median number of non-synonymous passenger mutations, compared with patients who do not respond or those who have only short-term regression. Strategies to enhance baseline immune reactivity are therefore necessary to investigate as means to improve the impact of checkpoint blockade on a broad spectrum of cancers. The presence of suppressive myeloid cells and regulatory T cells in the tumor microenvironment is emerging as a mechanism of resistance to the anti-tumor activity for checkpoint blockade. Strategies to overcome this include agonism of GITR and selective suppression of PI3K-γ.

NOTES:

SESSION 3: IMMUNO-ONCOLOGY

Chairs: Dr Joanna Hester and Prof. Mark Middleton

INVITED LECTURE

Immuno-Oncology: Progress and Future Advances

Dr Robert Wilkinson

Senior Director, Oncology R&D, AstraZeneca

Significant advances have been made to identify effective therapies that either restore or generate de novo a patient's immune response to their cancer. Antibody-based therapies targeting the T cell checkpoints CTLA-4 and PD-(L)1, have revolutionised outcomes in several cancer indications including melanoma and lung cancer. However, responses vary and are usually confined to a subset of cancer patients. Our understanding as to why some patients exhibit intrinsic or acquired resistance to IO therapy is evolving and includes the effect of specific mutations in the tumour cells as well as the overall mutational load of the tumour, the level of tumour-infiltration by cytotoxic effector immune cell populations and the balance of this with the prevalence of suppressive immune cell populations that together constitute the tumour microenvironment. There is an unmet need to identify novel IO therapies, as standalones or to enhance the efficacy of immune checkpoints and/or standards-of-care, such as radio- and chemo-therapy. My talk will describe the current landscape of IO, discuss novel therapeutic targets and emerging combinatorial approaches.

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INVITED LECTURE

Device-Enhanced Immunotherapy: Can Mechanical and Thermal Effects Help to Stimulate Anti-Tumor Immune Responses?

Professor Elizabeth Repasky
The Dr William Huebsch Professor in Immunology,
Roswell Park Comprehensive Cancer Center

While remarkable progress has been made toward overcoming barriers to more immunotherapies for patients with cancer, the majority of those treated still do not benefit. One promising area of research is the use effective of various devices that can provide biophysical energies that have the capacity to not only directly kill tumor cells, but also to indirectly influence properties of the tumor microenvironment and strengthen the activities of immune cells. These types of treatments, including ultrasound, photodynamic therapy, hyperthermia and ablative therapies, are being conducted worldwide and there is increasing evidence for their potential efficacy in combination with immunotherapies. For example, while the healing powers of heat have been recognized for hundreds of years, researchers have more recently implicated increased tissue or body temperature in specific aspects of the regulation of the immune system, particularly in the settings of inflammation, autoimmunity and cancer. However, much more research is needed to identify the precise impact that various devices may have on anti-tumor immunity so that we may maximize their use in new clinical trials. This educational session will review selected research published in the last few years highlighting major gaps in the field and critical areas for future research.

NOTES:

SESSION 3: IMMUNO-ONCOLOGY

Chairs: Dr Joanna Hester and Prof. Mark Middleton

INVITED LECTURE

Cavitation-Enhanced Delivery of Checkpoint Inhibitors

Mr Prateek Katti

Interventional Radiology Research Fellow, NIH

NIH Oxford-Cambridge Scholar, University of Oxford

Checkpoint inhibitors (CPIs), antibodies which act to overcome immuno-evasive behavior of tumors, have revolutionized oncology—in fact, over 43% of US cancer patients in 2018 were eligible for CPI therapy across all cancer types. However, despite tremendous excitement, benefits extended to a fraction of those treated, an estimated 12.46% (Haslam & Prasad, JAMA Netw. Open 2019). Drug delivery barriers, including poor, heterogeneous tumor vasculature, elevated interstitial pressures, and cellularity, could play a role in limiting the efficacy of CPIs. We hypothesized that cavitation generated by the sonication of sub-micron sonosensitive particles (SSPs, OxSonics Therapeutics) could be leveraged to improve CPI delivery and efficacy. In whole-tumor imaging studies of bilateral tumor-bearing mice, we observed that cavitation significantly improved drug accumulation 2-3x compared to contralateral, cavitation-naïve tumors. Flow cytometry and microscopy studies extended our findings, revealing that the delivery improvements provided by cavitation could significantly improve the binding and distribution of aPDL1 within tumor microenvironments. In a survival study with PAM-feedback, we observed that the combination of aPDL1 with cavitation significantly improved outcomes compared to mice treated with aPDL1 alone—with the median survival time approximately doubling between the two groups and a cure rate exceeding 40% in mice treated with aPDL1 and cavitation from a base-line cure-rate of 0%. Nanostring characterization of tumor tissue collected 5-days post-therapy revealed that genetic programs consistent with the upregulation of both innate and adaptive anti-tumor programs were uniquely found in tumors of mice treated by aPDL1 with cavitation. Taken together our work reveals that nan cavitation nucleated by tumour-penetrating sub-micron particles can 1) enhance intratumoral delivery of checkpoint inhibitors and 2) induce sustained innate and adaptive changes that, 3) drive tumor control and regression.

NOTES:

CONTRIBUTED POSTERS AND MINI-LECTURES

#5. Patient-derived Malignant Pleural Mesothelioma Cell Lines Could Guide Biomarker-Driven Treatments

Nikolaos Kanellakis[*1,2,3], R. Asciak[1,3], A.M. Hamid[4], X. Yao[4], Y. Peng[4], M.McCole[5], E.O. Bedawi[2], S. Hatch[6], D. Ebner[6], S. Mcgowan[7], GT Stathopoulos[8], T. Dong[4]., I. Psallidas[1,2] and N.M. Rahman[1,2,3]

[1]Laboratory of Pleural and Lung Cancer Translational Research, Nuffield Department of Medicine, University of Oxford, Oxford; [2]Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust; [3]National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford; [4]Centre for Translational Immunology, Chinese Academy of Medical Sciences Oxford Institute, Nuffield Department of Medicine, University of Oxford; [5]Cellular Pathology Unit, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust; [6]Cellular High Throughput Screening, Target Discovery Institute, University of Oxford; [7]Computational Biology Research Group, MRC Weather Institute of Molecular Medicine, University of Oxford; [8]Comprehensive Pneumology Center University and Helmholtz Center, Munich, Germany

Introduction: Malignant pleural mesothelioma (MPM) is an aggressive and incurable malignancy, with increasing global incidence and typically presents with malignant pleural effusion (MPE). Current non-targeted oncological treatments extend survival for only a few weeks, thus MPM is associated with poor prognosis and high mortality rate. We designed and implemented a translational study to assess the feasibility of patient-derived cell lines to serve as an ex vivo MPM model and guide biomarker-driven treatments. Methods: Cell lines were established from MPE specimens of MPM patients and subjected to whole genome sequencing. High-throughput drug screening and co-culture with cancer specific CD8+ T cells assays were performed to profile MPM cells and assess chemotherapy and immunotherapy anticancer agents. Laboratory and clinical data were cross-examined. Results: The patient derived MPM cell lines (n=16) closely resembled native tumours, exhibited stemness features and reflected the intra-tumour and interpatient heterogeneity. High throughout drug screening revealed different response profiles to anticancer agents while co-culture assays with cytotoxic T cells showed diverse immune responses and detected SSX2+ MPM cell lines. Conclusions: Short-term cultured-patient derived MPM cell lines are a faithful ex vivo model of human disease. Multiplatform screening of such cell lines could guide biomarker-driven treatments.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#6. Ultrasound-Induced Inertial Cavitation by Zinc Oxide Nanocrystals

Andrea Ancona*[1], Giancarlo Canavese[1], James Choi[2] and Valentina Cauda[1]
[1]Department of Applied Science and Technology, Politecnico di Torino, Turin, Italy
[2]Noninvasive surgery and Biopsy Laboratory, Imperial College of London, London

Nanoparticles able to promote inertial cavitation when exposed to focused ultrasound have recently gained much attention due to their vast range of possible applications in the biomedical field, such as enhancing drug penetration in tumor, supporting ultrasound contrast imaging or cancer therapy. Due to their nanometric size, these contrast agents could penetrate through the endothelial cells of the vasculature to target tissues, thus enabling more effective therapeutic effects and higher imaging resolutions than commercial gas-filled microbubbles. Herein, biocompatible and bio-degradable Zinc Oxide NanoCrystals (ZnO NCs), opportunely functionalized with amino-propyl groups, are developed as novel nanoscale cavitation-inducing agents. Custom flow-through gel phantoms have been developed to characterize the acoustic response of the nanocrystals flowing in water solutions inside sub-millimiter channels. Passive cavitation detection technique and high-speed camera observations revealed that ZnO NCs are able to induce inertial cavitation when exposed to single 100-cycles pulses with Peak Rarefactional Pressure higher that 1.4 MPa. Bubble dynamics obtained by high-speed camera suggest that gas pockets trapped at the surface of ZnO NCs are able to grow and detach from the NC surface, reaching bubble radii between 4 and 8 µm. Together, these data show great potential for the application of the novel nanoscale agent to the theranostic and drug delivery fields.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#7. Zinc Oxide Nanocrystals and High Energy Shock Waves as Promising Anticancer Agent

Luisa Racca*, Veronica Vighetto[1], Tania Limongi[1], Andrea Ancona[1], Giancarlo Canavese[1,2], Marco Laurenti[1], Marta Canta[1], Bianca Dumontel[1], Nadia Garino[1,2] and Valentina Cauda[1]

[1]Department of Applied Science and Technology, Politecnico di Torino, Torino.

[2] Istituto Italiano di Tecnologia, Center for Sustainable Future Technologies, Torino.

High energy Shock Waves (SW) are mechanical shock waves characterized by a positive pressure, sometimes up than 100 MPa with a phase duration of 0.5-3 ms, and a negative pressure of 10 MPa, whit a duration of 2-20 ms. SW have been clinically exploited for lithotripsy, the treatment of musculoskeletal pathologies, rehabilitative and regenerative purposes. Some authors have proposed SW in combination with sonosensitizers to inhibit tumor growth in in vitro and in vivo studies. In this investigation, we explored the possibility to exploit Zinc Oxide Nanocrystal (ZnO NCs) assisted SW treatment to achieve enhanced cytotoxic effects on cancer cells. The presence of a synergistic effect between ZnO NCs and SW was evaluated performing singular and multiple SW treatments per day (3/day) on cervical carcinoma KB cells pre-incubated with 10 mg/mL ZnO NCs for 24 h. A significant decrease of cell viability was recorded when cells incubated with ZnO NCs were treated 3/day with SW 50 MPa, 500 shots, 4 shots/s. Pilot studies on the mechanism have been performed. The addition of two different reactive oxygen species (ROS) scavengers revealed ROS marginal role in the pathway involved in cell inhibition growth, whereas kinetic evaluation of cell death highlighted the progressive increase of apoptosis and secondary necrosis caused by the combined effect of ZnO NCs and SW.

NOTES:

CONTRIBUTED POSTERS AND MINI-LECTURES

#8. Cavitation Assessment of Extravasated and Passively Accumulated Nanoscale Cavitation Nuclei In Vitro and In Vivo

Catherine Paverd*, Alexander Martin, Jonathan Vince, Luca Bau, Robert Carlisle and Constantin-C. Coussios
University of Oxford

Microbubble cavitation nuclei are routinely used in ultrasound diagnostics; however they are rapidly destroyed in vivo, and their micron scale prevents them moving out of the tumour vasculature into the tumour stroma. The introduction of solid, polymer-based nanoscale cavitation nuclei allows for new possibilities in the field of ultrasound diagnosis and treatment of solid tumours. In particular, it is possible to force nanoscale nuclei through the gaps in tumour vessel walls into the tumour stroma, or to allow the nuclei to passively accumulate within the tumour via the Enhanced Permeability and Retention (EPR) Effect. Nanoscale nuclei lodged in the tumour stroma can then be cavitated under Focussed Ultrasound (FUS), potentially giving an indication of the level of tumour perfusion or vasculature leakiness. Here we demonstrate the re-excitation of cavitation nuclei in vitro, and for the first time show differences in cavitation response in vivo within a tumour region after the clearance of cavitation nuclei from the bloodstream. In particular, different size tumours are evaluated against each other in order to link the probability and energy of recorded cavitation data with different tumour development stages. In future, this method may be applied as a diagnostic tool to assess tumour development and vasculature leakiness in order to inform clinical selection of first-line therapies.

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SESSION 4: NANOMEDICINES

Chairs: Prof. Eleanor Stride and Prof. Tom Matula

INVITED LECTURE

Towards Clinical Translation of Nanomedicines

Dr Marianne Ashford

Senior Scientist, Pharmaceutical Sciences,

Innovative Medicine Biotech Unit, AstraZeneca

There are a huge array of nanomedicines in pre-clinical research for a breadth of applications yet few have progressed to late stage clinical development and commercialisation.

This talk will discuss two different nanoparticles, polymeric nanoparticles and dendrimer conjugates intended for biophysical targeting and changing drug distribution to improve therapeutic index. It will share important considerations in their design and clinical translation; including the importance of understanding the target and disease, formulation and manufacturing and need for advanced analytical characterisation to ensure a robust product.

In addition, it will highlight some of the additional challenges of intracellular delivery systems which are critical for nucleic acid-based drugs. Lipid nanoparticles (LNPs), composed of ionisable lipid, cholesterol, helper lipid and PEG lipid are some of the most widely used and effective nanomedicines for intracellular delivery of nucleic acid drugs in vitro and in pre-clinical models and have recently been approved as a clinical product for siRNA. The talk will describe how we have explored LNPs as a delivery system for mRNA in different tumour cells and will describe work done to understand differences in transfection efficiency through deep endocytic profiling of three tumour cell lines.

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SESSION 4: NANOMEDICINES

Chairs: Prof. Eleanor Stride and Prof. Tom Matula

INVITED LECTURE

Stimulus-Responsive Polymeric Nanomedicines in Oncology

Professor Cameron Alexander

Head of Division of Molecular Therapeutics and Formulation, University of Nottingham

Polymeric materials exhibit many favourable characteristics for oncological drug delivery, including the ability to modify solution properties of drugs, the capacity to carry multiple diagnostic and therapeutic agents simultaneously, and the encoding of functionalities to control drug release. However, the complexity of many investigational polymeric nanomaterials imposes severe barriers to translation. This talk will focus on our studies in developing polymers which can retain these multiple advantageous properties, but which are derived from materials which already have been taken to human clinical trials. The talk will conclude with a consideration of how to couple external stimuli into these materials to enable them to act as probes as well as therapeutic agents in oncological processes.

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SESSION 4: NANOMEDICINES

Chairs: Prof. Eleanor Stride and Prof. Tom Matula

INVITED LECTURE

TARDOX: First-in-man Trial of Ultrasound-Triggered Targeted Drug Delivery in Liver Tumours

Dr Paul Lyon

Department of Radiology,

Oxford University Hospitals NHS Trust

Purpose: To determine the safety & feasibility of targeted delivery of thermosensitive liposomal drug in combination with localised hyperthermia by extracorporeal focused-ultrasound (FUS). Methods and materials: Under ultrasound-guidance a co-axial needle was placed into the target tumour to enable interchange of thermometry device and biopsy needle. FUS parameters were optimised during treatment to achieve bulk intratumoral hyperthermia (40-44°C). Core biopsies were taken for analysis of total intratumoral doxorubicin concentration by HPLC and drug distribution by fluorescence microscopy. Results: Ten patients were treated; optimal hyperthermia was achieved in 5/6 having thermometry and predicted in the remaining 4/4 using a model. Two-to-ten-fold increases in intratumoral doxorubicin concentration were found in 7/10 patients post-FUS (mean 8.56±5.69 μg/g), relative to pre-FUS samples, a mean 3.7-fold increase. 7/8 patients demonstrated nuclear intercalation of doxorubicin post-delivery, indicating release. CT and PET-CT demonstrated partial response in the target tumour alone at 2 weeks in 4/9 by CHOI or PERCIST criteria. Conclusion: We have demonstrated safety, feasibility and enhanced intratumoral drug delivery using a thermosensitive drug delivery system combined with non-invasive FUS for targeted hyperthermia of liver tumours. The study suggests therapeutic benefit in otherwise chemo-refractory liver tumours despite administration of only a single treatment cycle at the conventional dose of doxorubicin.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#9. Normothermic Machine Perfusion: A Novel Platform for Closer-to-Man Measurement of Therapeutic Clearance

Tamsyn Clark*[1,2], Luca Baù[1], Daniel Voyce[1], Robert Carlisle[1], Peter Friend[2] and Constantin Coussios[1]
[1]Institute of Biomedical Engineering, University of Oxford,
[2]Nuffield Department of Surgical Sciences University of Oxford

Less than 4% of developmental cancer therapeutics and nanosized drug delivery systems translate from bench to bedside. Unwarranted toxicity and inadequate therapeutic delivery due to uptake by clearance organs, not predicted by current preclinical testing, contribute towards this high rate of attrition. There is therefore an unmet need for a predictive, closer-to-human model to investigate therapeutic pharmacokinetics and local toxicity. Ex vivo normothermic machine perfusion (NMP) aims to maintain organs in a fully functional haemodynamic, metabolic and synthetic state. We hypothesise that this will provide a physiologically relevant platform to investigate drug clearance and toxicity which, if adequately validated, can help accelerate the translation of novel cancer therapeutics into the clinic, with less risk to patients in early-phase trials. We demonstrate that ex vivo NMP of fresh porcine liver, kidney and spleen provides a stable platform to preserve these organs for 12-24 hours, maintaining metabolic and synthetic function. Model therapeutics (100 nm nanospheres and an antibody) were then delivered to the three organs and detected in biological fluids and tissue over time. To our knowledge, this is the first time that such prolonged, physiological, ex vivo, splenic perfusion has been achieved, and that a physiologically relevant, close-to-man model has been used to successfully investigate the clearance and tissue distribution of model therapeutics. Validation of the model through the delivery of cancer therapies to human organs is the next step.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#10. Metal Organic Frameworks as Drug Delivery Systems

Emily Linnane*
University of Cambridge

Metal-organic frameworks (MOFs), are crystalline porous materials constituting inorganic metal clusters connected by organic linkers to form 2D and 3D structures. With a broad choice of metals and linkers available, there are tens of thousands of different MOFs each with unique properties - making them one of the most exciting developments in recent porous materials science.

MOFs have been proposed as a next-generation drug delivery system, due to their exceptionally high apparent surface areas and substantial storage capacity. They have tuneable chemistry, and can be designed to encapsulate macromolecules such as siRNA, as well as small molecules. MOFs also offer the opportunity to bypass the many undesirable and toxic side effects associated with systemic drug delivery, through controlling drug release and providing targeted delivery. In previous work, we increased the sustained release of drugs by using mechanical amorphization, and temperature treatment to collapse the pores (Teplensky, M.H.et al. J Am Chem Soc. 2017) In vitro characterisation of MOF cellular trafficking has shown uptake through endocytosis mechanisms (Orellana-Tavra, C. et al. ACS Appl Mater Interfaces. 2017, Orellana-Tavra, C. et al. Adv Healthc Mater. 2016). However MOFs can also undergo post-synthesis modifications on their surface, allowing for development of a cell-specific or targeted drug delivery vehicle. Taken together, MOFs have attractive properties which make them exceptional candidates for use as a drug delivery system.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#11. Image-Guided Focused Ultrasound Triggered Drug Delivery

Maya Thanou*, M. Amrahli, P. Cressey, W. Gedroyc, A. Gangi, Michael Wright
King's College London

Localised drug delivery to tumours may be applied using blood compatible nanosized carriers able to respond to an external stimulus with a triggered drug release. Conventional thermo-senstive liposomes (TSLs) or similar delivery systems lack the labels for in vivo tracking or clinical imaging and hence the ability to assess the optimal trigger time post administration. We develop dual labelled thermosensitive liposomal (iTSL) delivery system for localised delivery by Focussed Ultrasound (FUS) triggered release. In addition to labelling for MRI, we introduced a Near- Infrared fluorescence (NIRF) label which greatly assists real time tracking of the carrier in our murine xenograft cancer model. This in turn allows for optimisation of the FUS conditions and timings, required for triggered-release and functional delivery of the therapeutic drugs to the tumours. We synthesise these as lipid attached conjugates to ensure specific and lasting labelling of the carrier liposomes. MRI contrast enhancement ability and NIRF signals are assessed in vitro and in vivo. Nanoparticle (iTSLs) kinetics in murine tumours are assessed with optical imaging and at defined time intervals post intravenous injection, FUS was applied to induce a small increase in temperature to 42-43°C for 3-5 min. Imaging reveals both dramatic nanoparticles accumulation and drug release immediately after FUS treatment. Significant tumour growth inhibition is observed for the FUS treated tumours compared to those that were treated only with the drug nanoparticles. The applications of such multifunctional nanotheranostics with short and repeated FUS applications could have a transformative effect on cancer chemotherapy.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#12. Towards the Synthesis and Delivery of Halogenated MCT1 Substrates

Irini Skaripa-Koukelli*[1], John Walsby-Tickle[2], Joshua Owen[3], Eloise Thomas[1], James McCullagh[2], Robert Carlisle[3] and Katherine Vallis[1]

[1] Gray Institute for Radiation Oncology and Biology, Department of Oncology, Univ. of Oxford

[2] Department of Chemistry, University of Oxford

[3] Institute of Biomedical Engineering, University of Oxford

The monocarboxylate transporter 1 (MCT1), is a potential therapeutic target. A halogenated lactate/pyruvate analogue, 3-bromopyruvate (3BP), may be a toxic substrate for MCT1. Here the effects of 3BP, and the development of a radio-labelled MCT1 substrate for use as a targeted radionuclide therapy agent, are explored. Liposomes were formulated to carry MCT1 targeting agents. Metabolomic studies were undertaken using LC/GC-MS. Radio-iodinated aromatic lactate analogue was synthesized using the Iodogen reaction. Higher 3BP toxicity was observed in BT20(MCT-1 high) cells than MDA-MD-231(MCT1 low) cells. Toxicity was reversed when MCT1 was chemically inhibited or knocked down with siRNA. Accumulation of glycolytic intermediates indicated inhibition of glycolysis. All changes were more evident in MCT1-expressing cells. 3BP was encapsulated in cavitation-sensitive liposomes to allow targeting of its toxic effects. 3BP was released from the liposomes upon exposure to cavitation and was selectively toxic to BT20 cells. Use of MDA-MB-231 cells or (cavitation with empty liposomes) removed toxicity. Furthermore, a lactate analogue, p-hydroxyphenyllactate (HPLA), was radio-iodinated with 123-iodine (123I). Higher uptake was observed in MCT1-expressing BT20 cells following across a range of activities (0.8-1.5 MBq/well). 123I-HPLA was encapsulated into cavitation-labile liposomes. Further experiments for the release of this compound with US are in progress.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#13. Improving Chemoradiation Therapy in Muscle-Invasive Bladder Cancer using Ultrasound-Mediated Gemcitabine Delivery Systems

Jia-Ling Ruan[1], Yesna O. Yildiz*[1] , Richard J. Browning[1], Luca Bau[2], Christophoros Mannaris[2], James Thompson[1], Amy Elliott[1], Sean C. Smart[1], Lisa Folkes[1], Alix Hampson[1], Estelle Beguin[2], Michael Gray[2], Borivoj Vojnovic[1], Eleanor Stride[2] and Anne E. Kiltie[1]

[1] Gray Institute for Radiation Oncology and Biology, Department of Oncology, Univ. of Oxford

[2] Institute of Biomedical Engineering, University of Oxford

Background: Bladder cancer is the fifth most common cancer in the UK with a high incidence rate in the elderly population. Since this population is not suitable for surgery, chemoradiation therapy has become a widely-used bladder preservation method in managing muscle-invasive bladder cancers. Chemotherapeutic drugs like gemcitabine are able to enhance the radiosensitisation of tumours, but most of them still carry systematic side effects to normal tissues. Methods: In this project, we primarily aimed to improve chemoradiation treatment efficacy by developing two novel gemcitabine delivery systems that can be coupled with ultrasound for controlled drug release. In the first system, gemcitabine was incorporated into liposomal nanoparticles and these liposomes were then bio-conjugated to microbubbles. In the second system, gemcitabine was co-delivered with microbubbles. The particle size, concentration, and morphology of both systems were characterised by dynamic light scattering, nanoparticle tracking analysis, and microscopy. The stability of gemcitabine in both systems was also assessed. The ultrasound-mediated delivery efficacy was investigated both in vitro and in vivo. A bioresponsive feedback control system was also developed to improve the ultrasound-mediated drug delivery. Results: Encapsulation of gemcitabine into liposomes demonstrated prolonged gemcitabine retention both in vitro and in vivo compared to free gemcitabine. Investigation into the tumour microenvironment demonstrated the effect of gemcitabine uptake from liposomal conjugated microbubbles was correlated with the vascularity of the tumour. Ultrasound mediated gemcitabine delivery by liposomal conjugated microbubbles using ultrasound pulses with high pulse repetition frequency did not further increase the gemcitabine uptake in the bladder tumour compared to direct liposome administration. However, modulation of the ultrasound treatment regimens toward pulsatile drug perfusion and longer pulse duration improved the delivery of liposome-mimicking fluorescent beads. Conclusions: Our findings indicate that ultrasound-mediated gemcitabine delivery could be a promising new approach for improving chemoradiation therapy in muscle-invasive bladder cancer. However, understanding the local tumour microenvironment would be necessary for efficient delivery.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#22. Effect of Ultrasound on the Vasculature and Extravasation of Nanoscale Particles Imaged in Real Time

Sofie Snipstad*[1,2,3], Petros T. Yemane[1], Andreas Åslund[1,2,4], Astrid Bjørkøy[1], Kristin Grendstad[1], Sigrid Berg[3,5,6], Ýrr Mørch[2], Sverre H. Torp[7,8], Rune Hansen[5,6] and Catharina de Lange Davies[1]

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[2]Department of Biotechnology and Nanomedicine, SINTEF Industry, Trondheim, Norway;
[3]Cancer Clinic, St. Olav's Hospital, Trondheim, Norway;
[4]Stroke unit, St. Olav's Hospital, Trondheim, Norway;
[5]Department of Circulation and Medical imaging, Norwegian University of Science and Technology, Trondheim, Norway;
[6]Department of Health Research, SINTEF Digital, Trondheim, Norway;
[7]Department of Pathology, St. Olav's Hospital, Trondheim, Norway;
[8]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

Ultrasound in combination with microbubbles have been shown to improve the delivery of drugs and nanoparticles to tumor tissue. We have developed a novel microbubble stabilized by polymeric nanoparticles (Ý. Mørch e*t al*., *Contrast Media Mol Imaging* 2015), which has been shown to improve delivery and therapeutic effect of nanoparticles in solid tumors (S. Snipstad *et al.*, Ultrasound Med Biol 2017) and across the blood-brain barrier (A. Åslund *et al.*, J Control Release 2015). In the present study we aimed to understand more of the underlying mechanisms. To obtain new knowledge on the influence of vascular parameters on extravasation and to elucidate the effect of acoustic pressure on extravasation and penetration of nanoscale particles into the extracellular matrix, real-time intravital multiphoton microscopy was performed during sonication of tumors growing in dorsal window chambers (P. Yemane *et al.*, Ultrasound Med Biol 2019). The impact of vessel diameter, vessel structure and blood flow was characterized. Fluorescein isothiocyanate dextran was injected to visualize blood vessels, and the nanoparticle-stabilized microbubbles or SonoVue were injected before ultrasound with various pressures was applied. The rate and extent of penetration into the extracellular matrix increased with increasing pressure. However, to achieve extravasation, smaller vessels required higher pressures than blood vessels with larger diameters. The majority of extravasations occurred at vessel branching points. In addition, ultrasound was observed to change the blood flow rate and direction.

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SESSION 5: CHALLENGING INDICATIONS - BRAIN

Chairs: Prof. Nicola Sibson and Dr. Ruman Rahman

P L E N A R Y K E Y N O T E

First-in-Man Trials of Device-Enhanced Delivery to the Brain

Professeur Alexandre Carpentier

Head of Neurosurgery,

Pitié-Salpêtrière Sorbonne University Hospital

The failure of current brain tumor treatments is in part due to the existence of the blood-brain barrier (BBB), which limits drug delivery to tumors. Transient opening of the BBB with low intensity pulsed ultrasound (US) has emerged in pre-clinical studies in both small and large animal models during the last two decades (Hynynen et al. 2001) as the promising and safe technique for enhancing delivery of therapeutic substances in the brain from small drugs up to antibodies, AAV and immune cells, leading to tumor control and increased survival. This technique entered clinical trials in 2014 (Carpentier at al. 2016) showing tolerance even in eloquent areas and trends for efficacy on recurrent glioblastomas. Interaction between US and injected microbubbles, histological & biological effects of BBB disruption, extracranial (ExAblate®, NaviFUS) versus skull-implanted ultrasound (SonoCloud®) devices, and recent clinical trials will be presented. The great potential of this efficacious and safe BBB opening technique will be discussed.

[**Conflict of Interest:** Pr A.Carpentier is an inventor of the SonoCloud® device patented by Sorbonne University and developed by the university spin-off company CarThera Inc. AC has a financial interest in CarThera Inc and is a paid consultant for CarThera Inc.]

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SESSION 5: CHALLENGING INDICATIONS - BRAIN

Chairs: Prof. Nicola Sibson and Dr. Ruman Rahman

INVITED LECTURE

Targeted Device-Mediated Drug Delivery to Brain Metastases

Oliver Vince

OxCD^3 DPhil Student, University of Oxford

Metastatic tumours in the brain now represent one of the leading causes of death from cancer. Current treatments are largely ineffective due the combination of late diagnosis and poor delivery of chemotherapy across the blood brain barrier (BBB). They are also associated with significant side effects due to lack of specificity. Conjugating MRI contrast agents with a monoclonal antibody for VCAM1 (anti-VCAM1) has been shown to enable detection of metastases two to three orders of magnitude smaller in volume than those currently detectable clinically. The aim of this study was to exploit this targeting approach to enable delivery of chemotherapy to early stage metastases using microbubbles and ultrasound. A new formulation of microbubbles conjugated to anti-VCAM1 was synthesised and shown to bind to VCAM expressing cells in vitro. Selective and reversible opening of the BBB using these targeted microbubbles and unfocussed, low intensity ultrasound was then demonstrated in vivo in a mouse model. This was accompanied by increased uptake of both Evans Blue and Gadolinium-DTPA as model drugs. No adverse effects were observed. Optimisation of the microbubble formulation to increase delivery efficiency has also been demonstrated using lyso-phosphoplipids, enabling a further reduction in the ultrasound intensities required for BBB opening.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#14. Miniaturized Ultrasonic Transducers for Drug Delivery

Menglun Zhang*
University of Cambridge

My work focuses on miniaturized ultrasonic transducers, which size can be as small as 0.1 mm. The small size allows ultrasonic transducers to be implantable or wearable for drug delivery applications with a new regime, for example: 1. implantable transducers in the vicinity of tumors, in which case it may give higher spatial delivery accuracy and higher delivery efficiency without microbubbles; 2. wearable transducers for long-term, on-demand, mobile and smart delivery, e.g. contact lenses with embedded transducers and loaded drugs for ocular drug delivery, and on-skin smart patch with embedded transducers and loaded drugs for transcutaneous drug delivery. Integrated circuit chips can also be integrated with miniaturized transducers to carry out complex tasks, e.g. beam forming and focusing, without greatly increasing the device volume. Besides miniaturized transducers of typical ultrasonic range (kHz to MHz), ultra-high frequency transducers (2000 MHz) have been developed for drug delivery application. Preliminary result of cell-level DOX delivery experiment shows that delivery characteristics and mechanism by ultra-high frequency ultrasound may be quite different from those by KHz ultrasound. Collaborations and new idea of applications are very welcome!

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CONTRIBUTED POSTERS AND MINI-LECTURES

#15. Conductive Elastomer-Based Active Drug Delivery Platform for Targeted Chemotherapy in Glioblastoma Multiforme

Christopher Chapman*
Imperial College London

Glioblastoma multiforme is an aggressive untreatable brain cancer with a 14.6-month median survival time and a 2% 5-year survival rate after diagnosis. The current best practice for treatment is surgical resection followed by radiotherapy and systemic chemotherapy. However, many tumours cannot be removed surgically. Recently, ionic drug delivery has been a subject of increased focus spanning drug eluting electrodes to electronic ion pumps as the delivery vehicle. Because these devices can deliver drug molecules without a liquid carrier (termed 'dry delivery') they are a strong candidate for the targeted delivery of high concentrations of chemotherapeutic agents deep in the brain. Utilizing fully polymeric conductive elastomers fabricated by dispersing a doped conducting polymer poly(3,4-ethylenedioxythiophene):polystyrene-sulfonate (PEDOT:PSS) into polyurethane, a unique platform for the controlled dry release of drug molecules is presented. This elastomer system enables on-demand voltage controlled offloading of drugs through a combination of the elastomer encapsulating small molecule drugs while the conductive polymer enables electronic addressability. This system is shown to actively release both a model drug (fluorescein) and a common chemotherapeutic agent (doxorubicin) in clinically relevant concentrations ranging from 1 µM to 1 mM through the application of electrical potential.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#16. Supramolecular Hydrogels via Curcubit[8]uril Complexation as Local Drug Delivery Systems for Glioblastoma Multiforme

Paraskevi Kasapidou*
University of Cambridge

Glioblastoma multiforme (GBM) is the most aggressive malignant primary brain tumour accounting for approximately 50 % of all brain tumours. Currently, the prognosis of patients with GBM remains poor as the median survival rate is 15-17 months from the time of diagnosis. Its standard clinical treatment includes surgical resection of the tumour mass followed by radiation in the vicinity of the resection cavity and concomitant administration of Temozolomide (TMZ). Despite this multi-therapeutic approach, tumour recurrence occurs in close proximity (1-2 cm) of the initial tumour bed within 5 to 8 months after the standard treatment. Latest advances in the local delivery of chemotherapeutic drugs into the resection cavity through injectable hydrogels represent a major hope for the treatment of GBM. Herein, we propose the use of injectable physically crosslinked hydrogels as drug delivery systems for GBM. We developed injectable hydrogels consisting of hyaluronic acid which are dynamically crosslinked through homoternary host-guest interactions with cucurbit[8]uril. These hydrogels will be designed to match the mechanical properties of the human brain tissue and the release profiles of various therapeutic formulations loaded on these physically crosslinked hydrogels will be further investigated.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#17. Drug Delivery Across the Blood-Brain Barrier using Acoustic Wavelets and Microbubbles for the Treatment of Diffuse Intrinsic Pontine Glioma

Dani Chattenton*[1,2], Matthew Copping[1], Gerard Hernandez Mir[1], Ian Rivens[2], Jessica KR Boult[2], Chris Jones[3], Simon P Robinson[2], Gail ter Haar[2], James Choi[1]

[1]Department of Bioengineering, Imperial College London

[2] Division of Radiotherapy & Imaging , The Institute of Cancer Research, London

[3] Division of Molecular Pathology, The Institute of Cancer Research, London

Diffuse intrinsic pontine glioma (DIPG) is a paediatric brain cancer with a dismal prognosis for which new treatment options are urgently required. Temporary and reversible increases in blood brain barrier (BBB) permeability induced by focused ultrasound and microbubbles enables therapeutic agents to enter the brain. Current standard techniques use long ultrasound pulses (10,000 cycles), but this has caused bleeding and increased BBB permeability lasting for 6-48 hours. Our work has shown that acoustic wavelets – short (≤ 5 cycles), rapid pulses – at a centre frequency of 1-MHz, are able to briefly (<10 minutes) alter BBB permeability, enabling drug delivery. The study presented explored more clinically relevant (lower centre frequency) wavelet sequences that could increase BBB permeability to the pons, where DIPG originates. A regime has been established (centre frequency: 300 kHz, pulse length: 1 cycle, peak-rarefactional pressure: 0.3 MPa) for the efficient delivery of a fluorescent tracer (used as a drug proxy) to the pons of mice (Figure 1). Wavelet parameters will now be further optimised to maximise efficacy and safety of this technique in the pons, and for clinical translation.

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SESSION 6: CHALLENGING INDICATIONS - PANCREAS

Chairs: Dr. Laura Spiers and Prof. Robert Carlisle

INVITED LECTURE

Delivery Challenges & Immunological Targeting of the Pancreas

Dr Shivan Sivakumar

Academic Clinical Lecturer in Medical Oncology,
University of Oxford

Pancreatic cancer has the worst survival of any cancer and this prognosis has not changed in decades. Numerous challenges include the deep-seated location of organ causing late symptomatology and difficult access for diagnosis and intervention, late diagnosis, undruggable oncogene, complex microenvironment causing poor drug penetrance and poor therapeutic efficacy and early metastatic potential. Our work in Oxford is two-fold. Firstly we are testing novel therapeutic and drug delivery strategies in patients with pancreatic cancer and trying to understand the response of various agents to the disease. Secondly, we have started to characterise in detail the complex immune microenvironment of the tumour. The degree of immune infiltration we observe is highly variable between patients, but all patients equivocally show a complex immune microenvironment consistent of macrophages, neutrophils and different lymphocytes. The T-cells infiltrating the tumour, both CD4 and CD8 T-cells, appear to be dysfunctional with hardly any activation signature. A highly suppressive phenotype also characterises the regulatory T-cell population. Our data suggest that the microenvironment of pancreatic cancer is extremely suppressive and could be a major driver of poor prognosis. This work identifies potential therapeutic targets and avenues that should be further investigated and may inspire future clinical trials.

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SESSION 6: CHALLENGING INDICATIONS - PANCREAS

Chairs: Dr. Laura Spiers and Prof. Robert Carlisle

INVITED LECTURE

A Preclinical Study of the Combined Effects of Pulsed Focused Ultrasound and Immune Checkpoint Inhibitors in Pancreatic Cancer

Dr Petros Mouratidis

Postdoctoral Research Fellow,

Institute of Cancer Research

Objectives: No clinical benefit of immunotherapy has yet been realized in pancreatic cancer. In this study, pancreatic tumours have been exposed to pulsed focused ultrasound (FUS) and co-treated with immune checkpoint inhibitors (ICI) to explore whether therapeutic benefit can be achieved. Methods: Orthotopic KPC pancreatic tumours were exposed to pulsed FUS using the small animal Alpinion VIFU 2000 platform. Pulsed FUS exposure parameters were designed to result in cavitation (monitored using a PCD) in the target tissue (power = 200 W, duty cycle = 1 %, pulse repetition frequency = 1 Hz, 25 repeats). A combination of anti-CTLA4 and anti-PD-1 antibodies were administered intraperitoneally 3 days before treatment, and every 3 days thereafter. Tumour growth was estimated using ultrasound imaging. Results: Pulsed FUS exposure of pancreatic tumours resulted in the induction of cavitation in all treated subjects. Combination of a single pulsed FUS exposure with administration of ICIs extended the survival of subjects relative to non-treated animals. Additional results for the systemic and localised abundance of immune cells will be presented. Conclusions: This study provides evidence that focused ultrasound has the potential to be combined with immunotherapy to provide therapeutic benefit in pancreatic cancer.

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SESSION 6: CHALLENGING INDICATIONS - PANCREAS

Chairs: Dr. Laura Spiers and Prof. Robert Carlisle

INVITED LECTURE

Sonodynamic Therapy for Pancreatic Cancer

Professor Eleanor Stride

Statutory Chair of Biomaterials,

University of Oxford

Despite significant improvements in the survival rates for multiple forms of cancer over the past three decades, the prognosis for pancreatic cancer patients has remained extremely poor. This is due to a combination of late diagnosis, reducing treatment options for patients; and the nature of the tumours themselves, typically consisting of dense, poorly vascularised masses that are consequently strongly hypoxic and resistant to most conventional forms of therapy. Sonodynamic therapy (SDT) utilises drugs that can be locally activated using focused ultrasound thereby minimising systemic toxicity. Its effectiveness is however limited in the absence of molecular oxygen. The aim of this study was to conjugate SDT drugs to oxygen carrying microbubbles to address this limitation and to simultaneously exploit the delivery enhancement enabled by exposing microbubbles to focused ultrasound. Significant reductions in tumour volume have been observed in a range of different pancreatic tumour models (both ectopic and orthotopic) in mice, accompanied by corresponding improvements in survival. In addition, an immunostimulatory effect has been observed, manifest in the positive response of untreated secondary tumours. The results indicate that intravenously administered oxygen microbubbles can temporarily reduce tumour hypoxia and facilitate SDT, potentially representing a new treatment option for recalcitrant tumours.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#18. Mouse models of Pancreatic Ductal Adenocarcinoma

Sheena Wallington*[1], Christophoros Mannaris[1], Laura Spiers[1,2], Emma Carter-Biggs[1], Simone Lanfredini[2], Paul Miller[2,3] and Constantin Coussios[1]

[1]OXCD[3], Institute of Biomedical Engineering, University of Oxford

[2]Department of Oncology, University of Oxford

[3] Ludwig Institute, University of Oxford

Background: Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) is treated with chemotherapy although response is poor, with 1-year survival rate 21%. (1) Dense stroma acts as a barrier to drugs and high concentrations of hyaluronic acid raises interstitial pressure. This creates vascular collapse to limit perfusion and drug diffusion. Stroma remodelling involves oncogenic KRas signalling and tumour suppressor TP53. Pdx-1-Cre activates KrasG12D and TP53R172H mutations in the developing mouse pancreas of KPC mice. (2) This phenotype reflects the human clinical picture and morphology, but perfusion has not been fully explored. (3) Methods: PDACs in C57BL/6 mice with surgically implanted KPC cells (orthotopic model) were imaged from four weeks post implantation to maximum permitted tumour growth. Tumours were visualised by Vevo 3100 ultrasound, and 3D volumes generated. Perfusion was assessed using SonoVue. Tumours were then excised and immediately frozen. 10µm sections were stained with H&E and Masson's trichrome to visualise architecture. Results: In the orthotopic model, blood supply increased with tumour volume. This did not translate to perfusion, as tumours were initially twice as perfused as the spleen and kidney, but only a sixth as perfused by the end. This effect is observed despite tumour growth causing reduced individual organ perfusion. Histology from spontaneous KPC mice demonstrates hyperplastic ductal cells surrounded by dense stromal networks. Conclusion: In developing a drug delivery system, a model that accurately reflects PDAC tumour features is important. Both surgical and spontaneous models have characteristics mimicking human PDAC tumours, including perfusion and histological properties. To improve this further we are investigating an image-guided approach to generate an orthotopic model.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#19. Controlled Generation of Reactive Oxygen Species under Ultrasound Exposure of Zinc Oxide Nanocrystals

Veronica Vighetto*[1], Andrea Ancona[1], Luisa Racca[1], Tania Limongi[1], Adriano Troia[2], Giancarlo Canavese[1], Valentina Cauda[1]

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Reactive oxygen species (ROS) are involved in different cell functions and the survival of the cells is related to the ability of maintaining redox homeostasis during all these processes. An instability in this equilibrium results in a variety of possible different diseases. Therefore, controlled generation of ROS can be a promising tool to induce oxidative stress and cell death for cancer therapy applications. Zinc Oxide nanocrystals with a functionalized surface of aminopropyl groups (ZnO-NH2 NCs) have been proved able to produce ROS in a controlled manner, when stimulated by low frequency ultrasound (US) generated by an already approved medical device (LipoZero G39). The generation of hydroxyl radicals is the result of inertial cavitation under the US exposure. Passive Cavitation Detection (PCD) and Electron Paramagnetic Resonance (EPR) spectroscopy were used to evaluate the role of acoustic cavitation on the generation of ROS by the ultrasound irradiation of ZnO-NH2 NCs in water media. Ultrasound B-mode imaging was also applied, proving in respect to pure water, the enhanced ecographic signal generation of the aqueous solution containing ZnO-NH2 NCs when exposed to pulsed ultrasound. Furthermore, to evaluate the applicability of ZnO-NH2 NCs in the biomedical field, the ROS production was studied by interposing different tissue mimicking materials, like phantoms and ex-vivo tissues, between the US transducer and the sample well.

NOTES:

CONTRIBUTED POSTERS AND MINI-LECTURES

#20. Design of Pluronic-Polydopamine Drug-Delivery Vehicles for the Treatment of Pancreatic Cancer

Andrea Bistrovic Popov*
University of Cambridge

Pancreatic cancer is one of the most lethal cancers worldwide with a 5-year relative survival rate of less than 5%. Pancreatic ductal adenocarcinoma (PDA) is one of the most-stroma rich cancers, which is a major contributing factor to the failure of systemic therapies (C. Vennin, et al. Gastroenterology 2018). Design of polymer nanocarriers constituted from natural building blocks (e.g. dopamine and folic acid) has increased in recent years due to their multi-functional properties and biocompatibility. Polydopamine (PDA) is a biopolymer suitable as a carrier for drug delivery due to excellent biocompatibility, stimuli sensitivity and ease of functionalization with a number of targeting and cargo molecules (R.S. Ambekar and B. Kandasurbramanian, Biomater. Sci. 2019). Our research is focused on the design of Pluronic conjugated polydopamine hybrids to be used as drug-delivery vehicles for the treatment of pancreatic cancer modified with anti-stromal agents (e.g. Vitamin A derivatives). Using this polymeric hybrid as a vehicle, our goal is to prepare a stimuli-sensitive carrier with the ability to release anti-stromal agents combined with cytotoxic chemotherapeutics.

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CONTRIBUTED POSTERS AND MINI-LECTURES

#21. Combined Sonodynamic and Chemoradiotherapy for Pancreatic Cancer Treatment

Jia-Ling Ruan*[1], Richard J. Browning[1], Sarah Able[1], Estelle Beguin[2], Heather Nesbitt[3], Sukanta Kamila[3], Eleanor Stride[2], Anthony P. McHale[3], John F. Callan[3] and Katherine A Vallis[1]

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Background: Pancreatic cancer is a treatment resistant, hypoxic tumour with poor prognosis and new treatment therapies are needed. For non-resectable disease, gemcitabine is the cornerstone of control, but only modestly increases survival. It has been shown that release of oxygen (O2) from lipid microbubbles (MBs) can temporarily relieve tumour hypoxia. When combined with gemcitabine (Gem) and sonodynamic therapy (SDT) using ultrasound and Rose Bengal (RB), this led to improved survival and tumour growth delay in a murine model1. As radiotherapy (IR) is also enhanced by O2 and Gem, further combination therapies were investigated to determine additional additive and synergistic effects. Methods: Perfluorobutane biotinylated-lipid MB were prepared by sonication. These were loaded with O2 and avidin-RB to form oxygen MB (O2MB) and RB-loaded oxygen MB (RB-O2MB). Gem and IR toxicity was tested in vitro on BxPC-3 and PSN-1 pancreatic cell lines, with survival determined by clonogenic assays. Subcutaneous xenograft tumours were established in athymic nude mice and treated with combinations of RB-O2MB or O2MB + ultrasound, Gem and IR. Results: In PSN-1 burdened mice, Gem and IR (Gem+IR) was found to be a potent combination, significantly improving survival time and tumour growth delay but the addition of O2MB + ultrasound did not improve either therapy or the combination. When G+IR was combined with sonodynamic therapy – RB-O2MB + ultrasound – it was found that tumour control and survival was improved versus the Gem+IR alone. Conclusions: RB is an already clinically approved drug with known reactive oxygen species generation under ultrasound. The addition of sonodynamic therapy of Rose Bengal loaded on oxygen microbubbles to chemoradiotherapy treatment of pancreatic cancer, could improve tumour control and survival in simple and an inexpensive manner.

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SESSION 7: FUTURE DIRECTIONS AND TECHNOLOGIES

Chairs: Prof. Brad Wood and Prof. Mo Khan

INVITED LECTURE

Storz Medical: Transcranial Shock Waves

Dr Pavel Novak

Director, Product Development

Storz Medical

Acoustic waves and shockwaves have been used in medicine since 1980. Their first application was for extracorporeal kidney stone fragmentation. Meanwhile, low intensity acoustic waves have emerged as beneficial for the treatment of non-union fractures, tendons and muscular pain, wound healing, heart insufficiency, erectile dysfunction, aesthetic applications and most recently neurological indications. In parallel with the continuous increase of medical disorders treated by shockwaves, the initially extensive list of contraindications has decreased steadily, because of an increasing recognition of the limited side effects. Nevertheless, the treatment of brain remained excluded until recently. In order to overcome this limitation, the effect of acoustic pulses on the brain was first tested in-vitro and the safety margins were evaluated in Sprague-Dawley rats. Furthermore, the transmission of shockwaves through the scull cap was evaluated in vitro. Finally, in order to enable the application to a specific area within the brain, sophisticated navigation tools were developed. The first human treatments targeted the possibility of initiating the healing process within brain tissue. Alzheimer's disease or dementia is s multi modal disease resulting from different causes like deposition of dedicated proteins (tau, beta-amyloid), inflammation, reduced blood supply and others. This may in part explain why purely pharmacological solutions have been ineffective until now. On the other hand, Transcranial Pulse Stimulation, or TPS®, with its broad scope of effects promises to be more efficient by addressing different disease causes simultaneously. A multicenter clinical pilot study with 35 patients showed a significant improvement of Alzheimer's disease symptoms of 20% measured with CERAD and a battery of tests. The treatment consisted of 6 sessions in 2 weeks, with 6000 pulses, energy flux density of 0.2 mJ/mm2 at 5Hz. Further RCT studies and the evaluation of new applications, including in the field of drug delivery, are ongoing.

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SESSION 7: FUTURE DIRECTIONS AND TECHNOLOGIES

Chairs: Prof. Brad Wood and Prof. Mo Khan

INVITED LECTURE

OxSonics Therapeutics SonoTran Platform: Ultrasound-Guided Cavitation-Enhanced Drug Delivery

Dr Christian Coviello

Engineering Director & Co-Founder

OxSonics Therapeutics

Penetration of anti-cancer agents into and throughout solid tumours is widely recognized as presenting a major limitation to their effectiveness. With the general trend towards larger, and indeed poorer tumor-penetrating biologic agents such as antibodies, antibody-drug conjugates, bi-specifics and even viruses, an ever-growing clinical need presents itself. OxSonics Therapeutics' proprietary drug delivery platform, SonoTran®, is being developed to address this need by providing a drug-agnostic and purely mechanical means of enhancing delivery into tumours, with the added advantage of not requiring any costly drug reformulation. The ultrasound-based platform comprises infused 'SonoTran Particles' and a mobile ultrasound 'SonoTran System' with handheld probe. The SonoTran System incorporates 'see-as-you-treat' functionality, enabling the user to map and monitor therapy on-screen in real-time with the ease of a conventional sonography exam, but crucially also offers a high-throughput and low-cost approach in an out-patient oncology ward setting. SonoTran is poised to initiate first-in-man clinical trials in 2020, having established a GMP manufacturing process for SonoTran Particles, completed extensive pre-clinical validation in both small- and large-animal models, and GLP-compliant preclinical toxicology testing.

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SESSION 7: FUTURE DIRECTIONS AND TECHNOLOGIES

Chairs: Prof. Brad Wood and Prof. Mo Khan

INVITED LECTURE

EPSRC IRC in Targeted Delivery for Hard-to-Treat Cancers

Professor George Malliaras

Prince Philip Professor of Technology

University of Cambridge

While the survival rate for most cancers has doubled over the last 40 years, hard-to-treat cancers show survival rates below 14%. To combat these cancers, multiple pathways (immune/inflammatory, neoangiogenic, cell replication) need to be targeted and this necessitates a multimodal delivery approach that not only increases the amount but also the range of therapeutic agents that reach the target site. This IRC addresses this challenge by developing (i) delivery vehicles that are based on metal organic frameworks and organic cages and show substantially increased payload capacity, and (ii) implantable/injectable delivery platforms that are based on gels and electrophoretic pumps and enhance drug penetration through e.g. the blood-brain barrier. By combining these two approaches, we can achieve a step change in the amount and range of drugs that reach the tumour site. Two crosscutting translational activities, on material delivery & additive manufacturing and on validation, consider the whole chain from the conception of the delivery system to its clinical application, leading to a holistic approach to the problem of targeted drug delivery. The interdisciplinary team involved in this IRC includes groups from the University of Cambridge, University of Glasgow, University of Birmingham, Imperial College London and UCL with expertise ranging from materials synthesis and characterisation, through device engineering and manufacturing, to pharmacology and cancer. Our research program builds on an institutional-level initiative on therapeutic science and strong links with CRUK and with national labs and industry leaders in drug development.

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“It is hard to look at the tumor and not come away with the feeling that one has encountered a powerful monster in its infancy”

~ Siddhartha Mukherjee

"Cancer is a word, not a sentence."

~John Diamond

"There are no great people in this world, only great challenges which ordinary people rise to meet."

~William Frederick Halsey, Jr.

"There is no medicine like hope,
no incentive so great,
and no tonic so powerful
as expectation of something
tomorrow."

~Orison Swett Marden