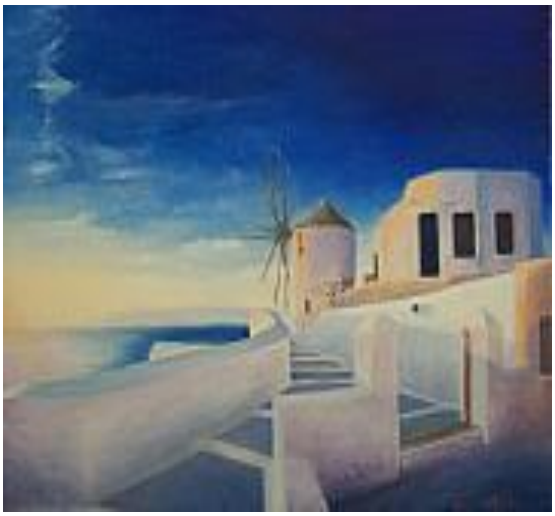
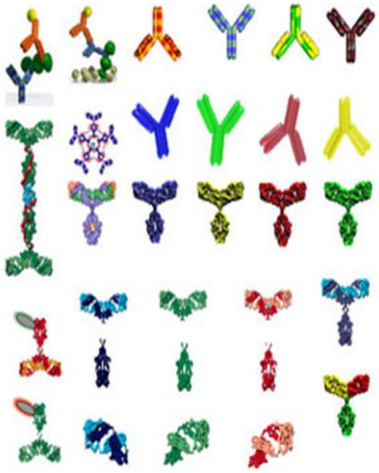
33rd International Conference

Advances in the Applications of Monoclonal Antibodies in Clinical Oncology and Symposium on Cancer Stem Cells

Santa Marina Hotel, Mykonos, Greece

13th- 15th June 2016





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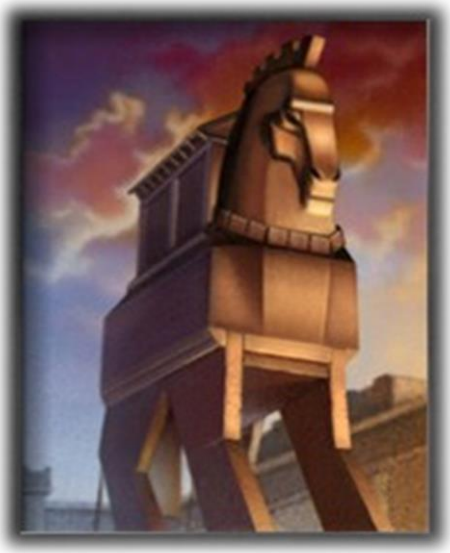

Trojantec

Programme

Monday 13th June 2016

9.00-9.30 **Registration**

9.30-9.35 Welcome **Agamemnon Epenetos**

SESSION 1- Chairman: Sir Walter F Bodmer

9.35-9.55 Klaus Bosslet, TheraPharm GmbH, Germany

Immune check point inhibitors: the path ahead

During their development, most solid tumors have created an immunosuppressive tumor microenvironment. This immunosuppressive environment hinders the immune system to eliminate the aberrantly modified tumor cells.

Especially the T-cell response within the tumor mass is significantly suppressed and not able to kill the tumor cells.

With the advent of the immune check point molecules and their selective modulation by inhibitory antibodies, a new therapeutic approach has been introduced in oncology.

Antibodies directed towards CTLA4, PD1 and PDL1 have entered and successfully concluded clinical studies resulting in marketing authorizations for a variety of these antibody drugs in various solid tumor settings.

I will discuss the clinical signals observed with some of the approved immune check point inhibitors and will give some suggestions how to further improve patient treament by combining immune check point inhibitors with other drugs potentially optimizing the therapeutic outcome to the benefit of patients with cancer.

9.55-10.15 Sir Walter Bodmer, Weatherall Institute of Molecular Medicine and Department of Oncology, Oxford University

Myofibroblast characterisation

Pericryptal myofibroblasts are major cellular components of the colorectal crypt and the colorectal cancer stromal environment. They play an important role in controlling epithelial cell growth and differentiation and are also thought to play some role in aspects of the immune response to cancer. Myofibroblasts were, until recently, only distinguished from skin fibroblasts by the expression of α smooth muscle actin. By characterising the target of the monoclonal antibody we developed nearly 30 years ago, by which the pericryptal cells were identified as myofibroblasts, we have established a new characterisation of these important cells. The proper characterisation of myofibroblasts should enable more targeted approaches to the development of cancer therapies based on blocking the interaction between cancer epithelial cells and their associated myofibroblasts.

10.15-10.35 Mahendra Deonarain, Antikor Biopharma Ltd, Stevenage Bioscience Catalyst, Gunnels Wood Road, Stevenage, Herts, SG12FX, UK. Dept. of Chemistry, Imperial College London, Exhibition Road, London, SW72AZ

Antibody Drug Conjugates: The next wave

It is a great time to be involved in ADC research and development. Two approved products have re-invigorated the field but nothing new has been approved since 2013. Many of the headlines have been grabbed by advances in immuno-oncology but don't be fooled into thinking that ADCs have gone quiet. There has been a phenomenal amount of innovation in payload-linker chemistry, antibody engineering and mechanistic biology understanding and a new wave of product approvals is envisaged over the next 10 years. This overview lecture will summarise recent advances in ADCs and look forward to the next products expected to be approved. There will be a focus on the next-generation of full-length immunoglobulin ADCs and how other formats are sizing up alongside them. With greater clinical experience now available with ADCs, future treatments will involve combinations of ADCs as well as other therapeutic modalities

10.35-11.30 Coffee Break

SESSION 2- Chairman: Mahendra Deonarain

11.30-11.50 Kim Orchard[1], Jon Langford[2], Stephen MacKinnon[3], Ronjon Chakraverty[3], Deborah Richardson[1], Matthew Guy[4], Matthew Jenner[1], James Thom[4], Paul Lloyd-Evans[5], Tim Maishman[6], Ann-Marie Quigley[7], Pei-San Chan[7], Casper Wickham[7], Peter Johnson[8] and Klaus Bosslet[9*]
1 Department of Haematology, University Hospital Southampton, UK,
2 Targeted Radiotherapy Group, University of Southampton and UHS
3 Department of Haematology, Royal Free Hospital, London, UK
4 Depts. of Medical Physics, Radiopharmacy UHS
5 NHSBT Bristol
6 CRUK CTU Southampton
7 Depts. of Medical Physics, Nuclear Medicine and Radiopharmacy, RFH London, UK
8 Cancer Sciences University of Southampton, UK
9 *TheraPharm GmbH, Germany and presenting author

Preclinical and clinical development of a CD66 selective antibody targeted radiotherapeutic (ATRT) for the side effect free induction of complete remissions in Multiple Myeloma (MM)

The efficiency to target cytotoxics, toxins, radio-isotopes or immune activators preferentially to tumours using antibody derived targeting moieties is limited due to the massive accumulation of the respective constructs to the liver or the kidneys (depending on the molecular size) as well as to target expressing normal tissues. Unfortunately, only a marginal part of the injected dose reaches the solid tumour mass: (Average: 0.01% of ID/g, Contrib Oncol. Basel, Karger, 1992, vol 43, pp 1-145. Antibodies as Carriers of Cytotoxicity H.-H Sedlacek, G. Seemann, D. Hoffmann, J. Czech, P. Lorenz, C. Kolar, K. Bosslet).

This limitation is the major reason for many unsuccessful clinical investigations in the targeted antibody field, in which dose limiting toxicity did not allow the generation of a meaningful clinical anti-cancer signal.

To circumvent these limitations, we selected an anti CD66 antibody for the treatment of MM which is neither accumulating in liver nor in kidney but targets bone marrow and spleen. (Both tissues are the only normal tissues which express the CD66 antigen in an easily accessible form and contain the vast majority of the MM cells)

In a first step, dosimetry studies with In-111 labelled anti CD66 were performed to select patients suitable for therapy.

Those patients who showed a favourable dosimetry (more than 90%), were conditioned with Y90 labelled anti CD66. (Stepwise from 5 MBq/kg up to doses of 45 MBq/kg).

It was found that ATRT with anti-CD66 antibody was side effect free up to doses of 45 MBq/kg.

After this conditioning step, which resulted in a complete elimination of bone marrow hemotopoetic cells, patients received HD Melphalan followed by autologous hematopoietic stem cell transplantation (aHSCT).

Results from a randomized clinical phase II study show that anti CD66 ATRT followed by HD Melphalan and aHSCT (Arm A) in comparison to HD Melphalan and aHSCT (Arm B) show a CR rate from 50% whereas Arm B had a CR rate of 25 % only.
The side effect profiles of both treatment Arms were comparable suggesting that ATRT + HD Melphalan is a highly efficacious and side effect free conditioning modatlity for the treatment of patients with Multiple Myeloma.

The approach warrants pivotal studies in MM and other haematological malignancies which can be treated with HSCT.

11.50-12.10 Marianna Prokopi[1, 2], Christina A. Kousparou[1] and **Agamemnon A. Epenetos[1, 3*]**

1 Trojantec Ltd, the Bank of Cyprus Oncology Centre, Nicosia, Cyprus
2 Department of Mechanical Engineering and Materials Science & Engineering, Cyprus University of Technology, Limassol, Cyprus
3 Imperial College London, St Bartholomew's Hospital and the Harley Street Oncology Clinic, London, UK

Delivery of selectively cytotoxic proteins, RNA, DNA and other drugs against mutated cancers, using as carrier, umbilical cord derived mesenchymal cells microparticles

Current cancer therapies are only partially effective in achieving tumor eradication, due to the intrinsic drug resistance of the complex cancer growth process as well as due to extrinsic failure of therapeutic agents reaching the tumor site.
The proposed approach provides for a potentially more efficient way to deliver therapeutic miRNAs and proteins to tumors via the engineering of a novel mesenchymal stem cell (MSC)-derived membrane vehicle that can be enriched with specific miRNAs and membrane proteins. The rationale for using MSCs for delivering therapeutic agents to tumors is based on the concept and observation that MSCs have the ability to home to sites of injury such as inflammation and cancer. As the microenvironment of solid tumors exhibits similarities to that of inflammation, exogenously given MSCs should migrate and localize within tumor sites. MSCs have also been found to promote apoptosis of tumor cells through the expression of IFNα or IFNγ. While, MSCs are primarily known for their anti-inflammatory properties, there is also evidence that they can promote adaptive immunity under certain settings thus serving as an unconventional but innovative, vaccine platform in the prevention and inhibition of cancer and metastasis.

We have developed microparticles (MPs) from umbilical cord derived MSCs due to ease of production and their ability to be expanded and modified ex vivo (e.g. uploaded with miRNAs) as well as retain

their chemokine profile, allowing them to home to tumor cells. MPs generated from the cell membrane of MSCs are intact vesicles with heterogeneous density and relatively uniform size (0.1-1.0 μm).

MPs were shown to have the potential to deliver therapeutic miRNAs affecting multiple pathways involved in cancer development. Specific miRNAs have already been identified, which regulate gene expression in cancer cells both through reduction or deletion of oncogenic miRNA and through amplification or overexpression of tumor suppressing miRNA. Thus, compared to earlier approaches targeting single genes, the miRNA approach may present opportunities to target multiple molecules in cancer cells, and thus offer multiple and simultaneous avenues for tumor reduction with a single approach.

We are currently exploring the preclinical performance of such therapeutics to guide early clinical trials.

12.10-12.30 Mahendra Deonarain, Ioanna Stamati, Savvas Saouros, Antony Constantinou, Prashant Kapadnis, Jared Marklew, Kasia Falenta & Gokhan Yahioglu

Antikor Biopharma Ltd, Stevenage Bioscience Catalyst, Gunnels Wood Road, Stevenage, Herts, SG12FX, UK. Dept. of Chemistry, Imperial College London, Exhibition Road, London, SW72AZ

Antikor Fragment Drug Conjugates: One size does not fit all

Antibody Drug Conjugates (ADCs) are a tried and tested modality for cancer therapy with multiple waves of innovation leading to the current clinical and marketed products. Next-generation technologies in early development are addressing current ADC limitations such as potency, poor penetration, off-target toxicities due to payload exposure to normal tissues and manufacturing. Antikor Biopharma is addressing all of these issues by employing its proprietary OptiLink-FDC platform where recombinant antibody fragments are optimised to possess a high drug-to-antibody ratio (DAR) whilst retaining effective binding, rapid tumour penetration and fast clearance from the body. High DAR antibody fragment drug conjugates (FDCs) promise to be a new class of therapeutics where one size does not fit all applications. Using clinically-validated payloads such as MMAF, MMAE and Maytansine against a benchmark target (HER2), we will show that OptiLinked-FDCs have a favourable pharmacokinetic profile, reproducible manufacturing properties, excellent uptake kinetics and potent efficacy in human tumour xenograft models. These benefits are demonstrated alongside superior tolerability compared to full-length immunoglobulin ADCs and highlight that smaller format ADCs have a potential role in the treatment of solid tumours.

12.30-2.30 Lunch Break

2.30-3.30 Open Air Workshop:
Cancer Immunotherapy– Antibodies and Vaccines
Klaus Bosslet, David Scheinberg

7.00-10.00 Welcome Reception Cocktail

Tuesday 14th June 2016

SESSION 3- Chairperson: Christina Kousparou

9.00-9.30 Evangeli S. Lampri, Anna C. Goussia and **Niki J. Agnantis**

Department of Pathology, School of Medical Sciences, University of Ioannina, Ioannina, Greece

Angiogenesis and Neoplasia: more than Friends

Blood vessels nourish organs with vital nutrients and oxygen and, thus, new vessels form when the embryo needs to grow or wounds are to heal. A widely accepted view is that blood vessels arise through two mechanisms during development, vasculogenesis and angiogenesis. New vessels in the adult arise mainly through angiogenesis, although vasculogenesis may also occur. The existence of a postnatal vasculogenesis is also supported by the evidence that both endothelial cells and endothelial precursor cells co-exist in the circulation. Angiogenesis is a biological process by which new capillaries are formed and it occurs in many physiological and pathological conditions, such as cancer. Malignant neoplasms are based on angiogenesis to spread to adjacent organs, making them life threatening.

Proliferation and metastatic potential of neoplastic cells depends on new growth in the vascular network, in order to reassure adequate supply of oxygen and nutrients, as well as the removal of waste products. New blood vessels inside a tumor are formed through the process of angiogenesis, which is controlled by the net balance between molecules that have positive and negative regulatory activity. This concept had led to the notion of the “angiogenic switch”, depending on an increased production of one or more of the positive regulators of angiogenesis. A plenitude of different proteins, including cell adhesion molecules, extracellular matrix components, transcription factors, angiogenic growth factors and their receptors orchestrate blood vessel differentiation and growth. Levels of expression of angiogenic factors reflect the aggressiveness of tumor cells.

The concept that tumor progression could be regulated by pharmacological and/or genetic suppression of blood vessel growth has engendered a long-standing interest in the identification of molecules or synthetic compounds that block angiogenesis. Among recognized angiogenesis inhibitors are: platelet factor 4 (PF4), thrombospondin-1 (TSP-1) and 2 (TSP-2), angiostatin, endostatin and proteolytic fragments of type IV collagen. Interference in the signaling pathways of specific stimulators, such as vascular endothelial growth factor (VEGF) has proven effective in blocking blood vessel growth. In addition, blockage of integrin binding, in particular αvß3, has been shown to suppress angiogenesis in several tumor types. Moreover, when VEGF levels are low, angiogenin (Ang-2) marks regressing vessels and has been proposed to cause vessel regression, whilst interferons are angiostatic by lowering the expression of basic fibroblast growth factor (bFGF) and VEGF. Additional inhibitors include chemokines binding chemokine (C-X-C motif) receptor 3 (CXCR3.), clotting antagonists and others. Several studies reported that soluble receptors (VEGFR-1, Tie2) efficiently block tumor angiogenesis and growth.

Proteinases may inhibit vessel growth by generating cleavage products of extracellular matrix/basement membrane components (e.g. arresten, canstatin and tumstatin from collagen IV; vastatin from collagen VIII; restin from collagen XV; endostatin from collagen XVIII), proteinases or enzymes (e.g. PEX from metalloproteinase 2; Mini- TrpRS from tryptophanyl-tRNA synthetase) or plasma proteins (e.g. angiostatin from plasminogen; 16K prolactin from prolactin; fragments of several serpins). Although the endogenous role of many of these cleavage products in physiological and pathological angiogenesis remains enigmatic, they offer novel opportunities to suppress tumor angiogenesis and growth, when administered.

Angiogenesis does not initiate malignancy but promotes tumor progression and metastasis. Unlike tumor cells, Endothelial cells (ECs) are genomically stable and were therefore originally considered to be ideal therapeutic targets that would not become resistant to anti-angiogenic therapy. Most previous efforts have thus been focused on developing anti-angiogenic agents that primarily target ECs. Anti-angiogenesis has been appealing for cancer therapy for three main reasons: (a) it is likely that most tumors dependent on angiogenesis, thereby providing a common target in the treatment of widely heterogeneous disease; (b) endothelial cells are considered to be less likely to develop adaptations to bypass drug effects (drug-resistant phenotype, as seen in some tumors); (c) it is anticipated tumor vessels are proliferative providing a differential target than the quiescent vessels present in normal tissues.

In conclusion, after all these years of intensive research, antiangiogenic therapy, especially when combined with chemotherapy, proved to increase survival in patients suffering from advanced solid tumors. Moreover, the benefits may be possibly enhanced if antiangiogenic therapy would be applied in earlier stages of malignancy or in an adjuvant setting or even as a long-term treatment for minimal residual disease, preventing tumor recurrence.

9.30.00-10.00 Felix Hart, Johanna Rühmann, Beate Habel, Ulf Harnack, Renate Stahn, Steffen Goletz,Glycotope GmbH, Berlin

Sweet delivery of the bitter – Using carbohydrate-targeting antibodies for tumor-specific delivery of cytotoxic drugs

Antibody-drug conjugates (ADCs) have great potential to specifically deliver cytotoxic agents to cancer cells. As shown for three novel glyco-optimized antibodies, carbohydrates on the surface of cancer cells represent promising targets for the specific delivery of cytotoxic drugs for cancer therapy. Tumor specificity and Fc-mediated effector functions were shown by immunohistochemistry and antibody-dependent cellular cytotoxicity, respectively. Next, as a prerequisite for intracellular drug delivery, target internalization upon antibody binding and lysosomal localization was confirmed. Moreover, surrogate ADCs using different cytotoxic agents inhibited proliferation of antigen-positive cancer cell lines.

10.00-10.30 David A. Scheinberg, Memorial Sloan Kettering Cancer Center, NY

Targeting undruggable intracellular targets with antibodies

Many important mutated or oncogenic proteins are not expressed on the cell surface, nor are these proteins druggable by small molecules. Therapeutic solutions directed to such proteins may be achieved by vaccines to peptides that are processed and presented by MHC molecules for recognition by the TCR on T cells, or by construction of TCR mimic mAb (TCRm). TCRm can bind to peptides from intracellular targets in the context of HLA on the cell surface, even at extremely low density. The Wilms' tumor oncogene protein (WT1) is an intracellular, transcription factor, expressed in a wide range of human cancers and in leukemias. The preferentially expressed antigen of melanoma (PRAME) is an intracellular oncogenic retinoic acid receptor binding protein that is expressed in leukemias and in a wide range of human cancers. Neither protein is appreciably found in most normal tissues; both PRAME and WT1 are expressed on progenitor cells, and may be involved in the oncogenic process. A peptide based vaccine to WT1 is showing promising results in phase 2 clinical studies in hematopoietic and solid cancers. TCRm mAb have also been developed for WT1 and PRAME peptides. Such TCRm mAb are effective in preclinical models of cancer and leukemias. BiTE forms of TCRm have vaccinal effects. Issues related to efficacy, pharmacology, toxicity, and resistance to these approaches will be discussed.

10.30– 11.30 Coffee Break

Session 4- Chairman: Klaus Bosslet

11.30–12.00 Philip Savage MD PhD FRCP, Consultant Medical Oncologist
Brighton and Sussex University Hospital, Brighton, UK

Improving the clinical applicability of tumour targeting with antibody HLA class I delivery systems

The use of the cellular immune system to kill cancer cells is now an area of intensive clinical development.

One of the systems being explored is to target recombinant HLA class I molecules to the surface of tumour cells via an antibody delivery system. The result is that virus T cells will recognise the targeted HLA complexes and kill the tumour cells.

This system was originally described in 2000 and with the intervening technical development is now being commercially developed.

However the T cell/HLA interaction is specific for both the HLA class I allele and also the antigenic peptide. As result only a small proportion of T cells in vivo will interact with the molecule, so potentially limiting the efficacy and a range of differing constructs will be need for patients of differing HLA types.

Recently we have been working on various approaches to increase the utility of the antibody-HLA system and updated data will be presented.

12.00-12.30 David A. Scheinberg, Peter Maslak, Marjorie G Zauderer, Tao Dao T, Lee Krug, Memorial Sloan Kettering Cancer Center, NY

Phase 2 trials of a WT1 analog peptide vaccine in adults with acute myeloid leukemia and mesothelioma

We previously reported on the safety, immunogenicity, and prolonged survival following vaccination of patients with AML and mesothelioma in pilot studies with a multivalent WT1 peptide vaccine, SLS-001. The vaccine consists of two native and two heteroclitIc WT1 peptides

with adjuvant designed to activate CD4+ and CD8+T cells. We conducted two additional Phase II studies in these two diseases.

The first trial was in 22 adults with AML in CR1 with RT-PCR measurable WT1 transcript levels. Patients received 6 vaccinations administered with adjuvants Montanide and GM-CSF over 10 weeks plus 6 additional monthly doses if they remained in CR. The vaccine was well tolerated with the most common side effects being Grade I/II injection site reaction, fatigue and skin induration. Median leukemia free survival (LFS) from time of diagnosis was 23.5m while the overall survival was 45.5 m. nine of 14 tested patients had a documented immunologic response. Patients that did not make an immune response had shorter LFS and OS than those who made a response.

The second trial in mesothelioma was a randomized, double blind, placebo controlled study with vaccination within 12 weeks of completing multimodality therapy. 40 patients were randomized from two institutions. Patient characteristics were balanced. There were no serious treatment related adverse events. Median PFS from randomization was 11.4 months in the vaccine arm v. 5.7 months in the control arm (HR 0.69, p=0.3). Similarly, median overall survival (OS) from randomization was 21.4 months in the vaccine arm v. 16.6 months in the control arm (HR 0.52, p=0.14). In the subgroup with R0 resection, median OS was 39.3 months in the vaccine arm and 24.8 in the control arm (p=0.04).

These II trials demonstrated that administration of the analog WT1 peptide vaccine was safe, well-tolerated and immunogenic. In AML, OS and LFS were prolonged. In mesothelioma vaccination was associated with a trend toward improved PFS and OS. Pivotal, randomized multicenter studies in both diseases are planned for 2016**.**

12.30–2.30 Lunch Break

2.30-3.30 Open Air Workshop: *Novel Targets for Antibodies and Vaccines*
Sir Walter Bodmer and Toru Kondo

8.00 pm until late: Conference Dinner

<u>Wednesday 15th June 2016</u>

Cancer Stem Cells Symposium

Chairman: Agamemnon A Epenetos

9.30-10.00 Sir Walter Bodmer, *Cancer stem cells and EMT*

LATE ABSTRACT

Department of Oncology, Cancer and Immunogenetics Laboratory, Weatherall Institute of Molecular Medicine, Oxford, UK

10.00-10.30 Christina Kousparou [1, 2], Mahendra Deonarain [2], Aleksandra Filipovic2, Andres A Gutierrez 3, Angelos Stergiou3, Agamemnon A Epenetos [1, 2, 4]

[1] Trojantec Ltd, Nicosia, Cyprus[2] Imperial College London, London, UK,3 Sellas Life Sciences, Switzerland,4Harley Street Oncology Clinic, London, UK

Generation of a selectively cytotoxic fusion protein against P53 mutated cancer

The most common genetic alteration in human cancer involves the p53 tumor suppressor gene resulting in defective control of cell cycle arrest and death.

The p53 protein induces a cyclin-dependent kinase (cdk) inhibitor, p21 which occupies a central position in cell cycle regulation. Cdk inhibition by p21 results in a lack of progression from the G1 to the S-phase due to the prevention of retinoblastoma (Rb) phosphorylation and subsequent inhibition of transcription factors that regulate the genes involved in DNA replication and cell-cycle progression.

It is hypothesized that the re-introduction of p21 into tumor cells will regenerate the pathway to apoptosis (programmed cell death) and inhibit proliferation since it has been suggested that overexpression of p21 results in suppression of tumor growth *in vitro* and *in vivo*. Unfortunately, p21 protein alone is unable to be administered directly *in vivo* and progress to the cell nuclei of cancer cells since there is no active mechanism to transport the protein. However, a number of proteins are known which can translocate across the cytoplasmic membrane of mammalian cells and into the nuclei, carrying additional “cargoes” with them. One of these translocating proteins is a 60 amino acid peptide corresponding to the homeodomain of the *Drosophilia* protein Antennapedia [ANTP].

A fusion protein (TR1) has been developed where the full-length p21 protein is attached to the antennapedia protein with a view to delivering the p21 protein into cancer cells to restore cell cycle control.

TR1 penetrated and killed cancer cells that do not express wild-type p53 or p21. This included cells that were matched to cogenic parental cell lines. Antp-p21 killed cancer cells selectively that were malignant as a result of mutations or

nuclear exclusion of the p53 and p21 genes and over-expression of MDM2. Non-specific toxicity was excluded by showing that TR1 penetrated but did not kill p53- p21- wild-type cells. TR1 was not immunogenic in normal New Zealand White rabbits. Recombinant Antp peptide alone was not cytotoxic, indicating that killing was due to the transduction of the p21 component of TR1. TR1 was shown to penetrate cancer cells engrafted *in vivo* and resulted in tumour eradication when administered with chemotherapy.

TR1 may represent a new and promising targeted therapy for patients with p53-associated cancers supporting the concept that rational design of therapies directed against specific cancer mutations will play a part in the future of cancer therapeutics.

Product is now in clinical development, with GMP, toxicology, Phase I/II study design, disease type and clinical centre selection.

We acknowledge the support from Sellas Life Sciences for this work.

10.30–11.00 Toru Kondo, Division of Stem Cell Biology, Institute for Genetic Medicine, Hokkaido University

Characterization of novel transmembrane proteins that are prominently expressed on glioblastoma-initiating cells

Glioblastoma (GBM)-initiating cells (GICs) are a tumorigenic subpopulation that are resistant to radio/chemotherapies and are the source of recurrence. Although it has been shown many factors that regulate GIC characteristics, the molecular mechanisms by which GICs communicate with their surrounding cells (niche cells) have not yet been elucidated in detail. We identified two transmembrane proteins, Ceacam1 and Eva1, which act as crucial factors in GIC maintenance and tumorigenesis through the activation of STAT3 and non-canonical NF-κB signaling, respectively. These membrane proteins have been also shown to be expressed on immune cells, including microglia/mactrophage. Together, these data suggest that GICs exploit the association with

immune cells through the Ceacam1- and Eva1-dependent intercellular binding for their survival and tumorigenesis. I will present our recent data and discuss about Ceacam1 and Eva1 as the intercellular communication factors in GIC tumorigenesis.

11.00-11.45 Coffee Break

11.45-12.15 Michael Monrad Grandal*, Thomas Tuxen Poulsen*, Klaus Koefoed, Karsten Wessel Eriksen, Anna Dahlman, Gunther Roland Galler, Trine Lindsted, Paolo Conrotto, Thomas Bouquin, Helle Jacobsen, Ivan David Horak, Johan Lantto, Michael Kragh, Mikkel Wandahl Pedersen
*Contributed equally to this work

Sym015, a novel antibody mixture targeting non-overlapping epitopes of MET, effectively inhibits MET amplified tumors through multiple mechanisms of action

The receptor tyrosine kinase MET (Hepatocyte Growth Factor Receptor, HGFR) has been associated with development and progression of a range of human tumors due to its regulation of cell proliferation, migration, invasion, and angiogenesis.

Sym015 is a mixture of two humanized IgG1 monoclonal antibodies against non-overlapping epitopes on the SEMA domain of MET. The specific pair of antibodies was identified in a high-throughput cell based screen searching for antibody mixtures with superior growth inhibitory activity against MET-dependent gastric and lung cancer cell lines. Synergistic anti-proliferative activity of Sym015 compared to its individual antibody constituents was observed in several MET-amplified cell lines and confirmed in cell line xenograft models. Sym015 effectively inhibited growth of multiple patient- and cell line-derived tumor models and was superior to an analogue of emibetuzumab (LY2875358), a monoclonal IgG4 antibody against MET currently in clinical development. Furthermore, Sym015 retained efficacy in models resistant to emibetuzumab.

Sym015 was found to exert its activity through multiple mechanisms of action. At the receptor level, Sym015 blocked HGF binding to MET and induced MET degradation effectively inhibiting MET oncogenic signaling. At the cellular level, Sym015 induced cell cycle arrest and apoptosis and inhibited HGF-induced proliferation, scattering and angiogenesis.

Sym015 also induced higher levels of complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) compared with its individual antibody constituents. The contribution of the secondary effector functions of Sym015 was confirmed in vivo using Fc effector muted variants of the two antibodies. Emibetuzumab did not induce ADCC in vitro, which may partially explain why emibetuzumab demonstrated more limited anti-tumor activity in vivo.

Molecular analysis of models responsive to Sym015 treatment showed a positive correlation between treatment response and MET amplification, pointing to MET amplification as a predictive biomarker for efficacy.

In conclusion, Sym015, a novel monoclonal antibody mixture against MET, shows strong inhibitory activity against MET amplified cell lines and xenografts due to a combined effect of multiple mechanisms. These results warrant the ongoing clinical development of Sym015 in patients with MET-amplified tumors.

12.15- 12.45 Philip Savage MD PhD FRCP, Consultant Medical Oncologist, Brighton and Sussex University Hospital, UK

Biological observations on the Chemotherapy Curable Malignancies; A review exploring their unique genetic events, frozen development, natural apoptosis and absent cancer stem cells

Despite over 40 years of the 'War on Cancer' the list of metastatic malignancies that can be cured with chemotherapy, trophoblast tumours, germ cell tumours, acute leukaemia, high grade lymphoma, and the rare childhood malignancies, is unchanged from the 1970s.

This lack of progress in curing other metastatic cancers with chemotherapy presents a number of major clinical and scientific challenges.

Whilst the paradigm of cancer cells being sensitive to chemotherapy as a result of rapid growth and then developing chemotherapy resistance and hence avoiding being killed is well established, we would like to present an alternate interpretation of the data and a new hypothesis.

The new hypothesis relates to the biological properties of the cancer cells, specifically the observation that each of the chemotherapy curable malignancies arise from normal cells that undergo natural DNA manipulations that are intrinsically associated with high levels of natural apoptosis.

Trophoblast tumours arise from the cells of conception, which have just undergone nuclear fusion. This process is intricately linked with apoptosis and healthy trophoblast cells are very sensitive to chemotherapy.

Germ cell tumours arise from pre-malignant precursor cells that are subject to pressures to undergo meiosis and mitosis and again are inherently linked to apoptosis as part of their natural life cycle.

In the B cell malignancies, acute leukaemia that arises from cells linked to VDJ rearrangement of the immunoglobulin genes is routinely curable as is diffuse large B cell lymphoma which is closely linked to somatic hypermutation. The B cell malignancies that arise at other points in the B cell

development pathway, such as acute undifferentiated leukaemia, CLL, follicular lymphoma and myeloma are not chemotherapy curable.

The other key biological difference the chemotherapy curable malignancies have is that their unusual developmental pathway means that they are not linked to any conventional hierarchical cancer stem cells. The cell biology of different types of cancer cells may be key to their curability with chemotherapy treatment.

In this study we have noted the association for each of the chemotherapy curable malignancies with the Apoptosis linked unique genetic events and also the absence of hierarchical cancer stem cells in these diagnoses.

Further pathway based research may be interesting and lead to novel therapeutic avenues

12.45-12.55 Agamemnon Epenetos - Adjourn to 2017