32nd International Conference

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

Santa Marina Hotel, Mykonos, Greece

22- 24, June 2015

WE ARE GRATEFUL TO OUR SPONSORS FOR THEIR SUPPORT

Trojantec

PROGRAMME

Monday 22rd June 2015

8.30-9.30 **Registration**

9.35-9.45 Welcome **Agamemnon Epenetos**

SESSION 1 Chairman: Sir Walter F Bodmer

9.45-10.15 Sergio A. Quezada, Cancer Immunology Unit, UCL Cancer Institute, University College London.

Immune Regulation at the Tumour Site

The continual interplay between the immune system and cancerous cells is thought to result in the establishment of a dynamic state of equilibrium. This equilibrium depends on the balance between subsets of effector and regulatory lymphocytes. Whereas the overall mechanisms underpinning the establishment and maintenance of the intra-tumour balance between Teff and Treg cells remain unknown, in many solid cancers it is characterized by the dominant infiltration of regulatory T cells over effector T cells resulting in a low Teff/Treg ratio. Furthermore, different subtypes of regulatory cells and inhibitory molecules such as CTLA-4 tightly control the few effector T lymphocytes that manage to infiltrate the tumour. The outcome of this balance is critical to survival, and while in a few cases the equilibrium resolves in the elimination of the tumour by the immune system, in many other cases the tumour manages to escape immune control.

Remarkably, antibodies against CTLA-4, a key immune modulatory receptor expressed on T cells, efficiently modify this balance, driving effector T cell expansion and increasing the ratio of Teff/Treg within the tumour. Whilst the high Teff/Treg ratio driven by anti-CTLA-4 directly correlates with tumour destruction in mice and humans, the mechanisms underpinning this phenomenon remain unknown.

By focusing in the study of effector and regulatory tumour-reactive $CD4^+$ T cells my group is interested in the mechanism underpinning the activity of different immune-modulatory antibodies within the tumour microenvironment, and the potential positive and negative impact that the tumour microenvironment may have in the recruitment, survival and function of different T cell subsets. In this context and using a murine model of melanoma we have recently demonstrated that both, the change in the Teff/Treg balance as well as tumour rejection, depend on the selective depletion of tumour-infiltrating Treg cells expressing high levels of surface CTLA-4. Regulatory T cell depletion is mediated by ADCC and completely depends on the expression of FcγRIV on tumour infiltrating $CD11b^+$ myeloid cells. These results reveal novel and unexpected mechanistic insight into the activity of anti-CTLA-4-based cancer immunotherapy, and illustrate the importance of specific features of the tumour microenvironment on the final outcome of antibody-based immune-modulatory therapies.

10.15-10.45 Tariq Ghayur, Ph.D.

Distinguished Research Fellow, Abbvie Bioresearch Center, Abbvie

Worcester MA, USA

Opportunities and challenges of developing the next generation of safe and efficacious bi – and multi – specific biologics

The technical challenges in making bi - & multi – specific antibodies (bsAb) appear to be solved, two bsAbs are now approved and several bsAbs are moving forward through clinical development. The key issue now is how to identify target pairs/combinations to develop the next-generation of safe and highly efficacious bsAb therapeutics. In this talk I will describe: (i) the design, construction and flexibility of our dual-variable-domain (DVD) – Ig format; (ii) How this and related bsAb formats can be used to reveal novel biology and; (iii) How we are applying our learning regarding bsAbs to design “fit-for-purpose” biologics to address specific unmet needs.

10.45-11.45 Coffee Break

SESSION 2 Chairman : Tariq Ghayur

11.45-12.15 David Maussang-Detaille, Senior Scientist, Merus, The Netherlands.

Mechanism of action of MCLA-128, a humanized bispecific IgG1 antibody targeting the HER2:HER3 heterodimer

The receptor tyrosine kinase (RTK) HER2 represents an important therapeutic target in specific breast or gastric cancer subtypes. Its amplification and dimerization with HER3 promotes growth and survival of malignant cells. Signaling of the HER2:HER3 dimer after upregulation of the HER3 ligand heregulin (HRG) has been identified as an important resistance mechanism against HER2-targeted therapies. To improve treatment options for patients with tumors expressing HER2 and HER3, we have developed MCLA-128 for potent inhibition of HRG-induced tumor growth.

MCLA-128 is an ADCC-enhanced humanized common light chain bispecific IgG1 antibody that targets the HER2:HER3 dimer. MCLA-128 binding surpasses that of anti-HER2 or anti-HER3 monoclonal antibodies in a panel of cell lines expressing various HER2 levels. In contrast to anti-HER2 and anti-HER3 monoclonal antibodies, MCLA-128 strongly reduces proliferation and intracellular signaling pathways (e.g. PI3K-Akt and ERK) in HER2-expressing cancer cells cultured with high concentrations of HRG. *In vivo*, MCLA-128 inhibits the growth of the trastuzumab-resistant cell line JIMT-1. This therapeutic efficacy is correlated with reduced HER2:HER3 dimerization and a profound inhibition of the PI3K-Akt signaling pathway. Furthermore, *in vitro* studies showed that MCLA-128 synergistically reduces cellular proliferation when combined with RTK or PI3K-Akt signaling pathway small molecule inhibitors. Besides blocking intracellular signaling, MCLA-128 displays an equivalent ADCC activity compared to trastuzumab on HER2-amplified cell lines, but an enhanced ADCC activity when targeting HER2-low cell lines or when low-affinity FcγRIII-F158 effector cells were used. Finally, in contrast to trastuzumab, MCLA-128 did not show any evidence of cardiotoxicity *in vitro*.

Taken together, these data demonstrate that MCLA-128 is significantly more potent in inhibiting HRG-induced HER2:HER3 signaling and in recruiting immune effector cells than other HER2 or HER3-targeted therapies. A Phase I/II clinical trial is currently ongoing to assess the safety and efficacy of MCLA-128.

12.15-12.45 Ulrich Wuellner; Simon Brack, Michela Silacci; Isabella Attinger-Toller; Julian Bertschinger; Dragan Grabulovski; Covagen AG, Schlieren, Switzerland

Bispecific FynomAbs unlock new biology

Covagen develops bispecific FynomAbs by fusing its Fynomer binding proteins to antibodies resulting in therapeutics with novel modes-of-action and enhanced efficacy. FynomAbs have optimal biophysical and pharmacokinetic properties, making them attractive as drug candidates. We present the discovery and development of COVA322, a clinical-stage bispecific TNF/IL-17A inhibitor for the treatment of inflammatory diseases. In addition, FynomAbs with tailored anti-tumor effects will be presented.

12.45-2.00 Lunch Break

2.00-3.00 Open Air Workshop:
Cancer Immunotherapy and the New World of Bi-specifics –
Sergio Quezada and Tariq Ghayur

7.00-10.00 Welcome Reception Cocktail

Tuesday 23rd June 2015

SESSION 3 Chairperson: Ivan Horak

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

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

Clinico-pathological Study of Angiogenesis in Gastric Cancer

Many models of multistage tumorigenesis have been proposed to explain the conversion of a normal cell into a neoplastic one. In addition to all genetic and epigenetic changes, angiogenesis is necessary for the growth and expansion of tumors. Besides, no neoplastic lesion could not exceed the size of 2 mm if not supported by a rich vascular network.

Angiogenesis is a complex process, depending on a great variety of angiogenic factors, one of the most important being the vascular endothelial growth factor A

(VEGF-A), which acts through its specific receptors (VEGFR-1 and VEGFR-2). Several previous studies showed expression of VEGF-A in tumor cells of gastric carcinomas and correlations of VEGF-A with the micro vessel density (MVD). However, there are contradictory results as far as it concerns the prognostic value of VEGF-A, its receptors and MVD.

Therefore, in the present study we analyzed 145 cases of gastric carcinomas for 1) the immunohistochemical expression of VEGF-A, VEGFR-1, VEGFR-2, p53 and Ki-67 proteins and 2) the estimation of MVD with the immunohistochemical markers CD34 and CD105 (MVD-CD34 and MVD-CD105) to gain further insight on the pathogenesis of this tumor. Moreover, the results were correlated to clinicopathological parameters and clinical outcome of the patients.

Expression of VEGF-A, VEGFR-1, VEGFR-2, p53 and Ki-67 proteins in tumor cells was detected in 123/145 (84.8%), 127/144 (88.2%), 105/143 (73.4%), 104/145 (71.7%) and 143/145 (98.6%) cases, respectively. The MVD-CD34 and the MVD-CD105 were 64.99 and 23.56, respectively. Positive correlations were found between VEGF-A and VEGFR-1, VEGFR-2, p53, Ki-67 and MVD-CD105 ($p=0.002$, $p=0.046$, $p=0,045$, $p<0.001$ and $p=0.024$, respectively) and between MVD-CD105 and MVD-CD34, Ki-67 and p53 ($p<0.001$, $p<0.001$ and $p<0.001$, respectively). Similar correlation was found between VEGFR-1 and VEGFR-2 ($p<0.001$).

Analysis of protein expressions and MVD of the tumor with clinicopathological parameters showed that, VEGF-A expression was correlated with the clinical stage ($p=0.007$), VEGFR-1 expression with the histological grade and histological type of the tumor ($p=0.037$ and $p=0.002$, respectively), VEGFR-2 expression with the vascular invasion ($p=0.045$), and Ki-67 expression with the histological type and the vascular invasion ($p=0.016$ and $p=0.032$, respectively). In addition, the expression of VEGFR-2 and p53 proteins was correlated with prognosis. VEGFR-2 and p53 were found to be independent predictor factors of unfavourable clinical outcome.

The results of the present study suggest an important role of angiogenesis in

the pathogenesis of gastric carcinoma. Expression of pro-angiogenic proteins VEGF-A, VEGFR-1 and VEGFR-2 by tumor cells is a common event. VEGF-A produced by tumour cells may act as paracrine and autocrine growth factor in gastric adenocarcinoma by promoting angiogenesis and tumor cell proliferation through its receptors. Moreover, protein expression of VEGFR-2 and p53 are independent predictor factors of unfavorable clinical outcome in gastric carcinomas.

9.30-10.00 Lars Stöckl, Glycotope GmbH, Berlin

TrasGEX™ and CetuGEX®, glycol-optimized anti-HER2 and anti-EGFR antibodies– Results from phase I/IIa clinical trials

The human epidermal growth factor receptor 2 (HER2) is a validated target in breast cancer and gastric cancer, but also overexpressed in a variety of other cancers. The epithelial growth factor receptor (EGFR) is part of the erbB family of membrane receptors with tyrosine kinase activity.

TrasGEX and CetuGEX are glycooptimized versions of the anti-HER2 antibody Trastuzumab and the anti EGFR antibody Cetuximab engineered using the GlycoExpress™ technology which offers the production of fully human and glycooptimized biotherapeutics. TrasGEX™ is glycooptimized with respect to manifold improvement of anti-cancer activity, optimization of bioavailability and broadening of the patient and indication coverage. In addition CetuGEX is futher optimized by removal of immunogenic glycan structures present on Cetuximab. *In vitro* studies showed a strong improvement of ADCC-mediated anti-tumor activity for both antibodies compared to the non-glyco -optimized counterparts depending on the FcγRIIIa allotype.

TrasGEX: Phase I/IIa, dose-escalation trial in patients progressive with advanced or metastatic cancer for whom no effective standard treatment is available and ErbB2 (HER2) positivity of at least 1+ is observed.
CetuGEX: Phase I/IIa dose-escalating study in patients with EGFR-positive locally advanced and/or metastatic carcinomas who had failed standard therapy or for whom no further standard therapy was available.

TrasGEX™: A total of 37 patients were treated with up to 720 mg TrasGEX IV flat-dose q3w in 5 cohorts of 3 to 6 patients each and an extension group of 16 patients who received 720 mg. No DLT was observed, the MTD was not reached. Infusion-related reactions (IRR) were the most frequently observed drug-related AEs (51.4%) all but two of grade 1 or 2. One patient with salivary duct tumor developed a CR, two patients reached strong PR (breast: 240 mg, FcγRIIIa allotype: FF, prior Trastuzumab non-responder; colon: 480 mg, FV allotype) and 12 (32.4%) showed SD, of which 40% had been exposed to Trastuzumab at earlier therapies.
CetuGEX: Forty-one patients with advanced EGFR-expressing solid tumors refractory to standard therapies received CetuGEX™ weekly up to 1370 mg or two-weekly 990 mg. A maximum tolerated dose was not reached. A high clinical benefit rate was observed including complete and partial responses as well as long lasting stable diseases in Colon, Rectal, NSCLC, Gastric, and Renal Cancer patients incl. patients previously progressive on Cetuximab treatment.

TrasGEX™ and CetuGEX™ were shown to be safe and well tolerated. Strong responses and clinical benefit was seen in patients who had no benefit or were even progressive under prior therapy with the non-glycootimized Trastuzumab or Cetuximab. In many cases these patients carried the FcγRIIIa F allotype and received low dosages of the glycooptimized antibody. All these facts demonstrate the advantages of glycooptimization for cancer therapy using the GlycoExpress™ technology.

10.00-10.30 Victor S. Goldmacher, ImmunoGen Inc, MA, USA

Novel DNA-alkylating agents designed for ADCs

Most ADCs that are currently in the clinic utilize microtubule-targeting cytotoxic small molecules as the payload. We have developed highly cytotoxic indolino-benzodiazepine dimers (denoted below as IGNs) with a novel DNA-alkylating mechanism of action for use in ADCs. IGNs containing a di-imine moiety acted by alkylating and then crosslinking DNA, while mono-imine IGNs induced DNA alkylation only. ADCs containing di-imine IGNs caused delayed mortality in mice, while those with DGN462, a mono-imine IGN conjugated via a disulfide-containing linker, had favorable tolerability in mice (maximally tolerated dose of 700 µg DGN462/kg) without delayed toxicity. DGN462 formed covalent adducts with

double-stranded DNA through alkylation of the C2-amino group of guanine. Consistent with the activity of other DNA alkylating agents, DGN462-treated cells were arrested either in S-phase, or G2/M phase of the cell cycle. DGN462 conjugates with ~3 molecules of DGN462 per antibody were highly cytotoxic and antigen-specific in vitro in killing various cell types, including PgP-expressing cells, with IC_{50} values in the picomolar to low nanomolar range. These conjugates also displayed pronounced bystander cytotoxic activity (killing antigen-negative cells in proximity of the antigen-positive cells), which may provide an advantage in solid tumors expressing antigen heterogeneously. A DGN462-containing ADC targeting CD33 was highly potent in killing acute myeloid leukemia xenografts, with a minimal effective dose (MED) of 0.6 mg conjugate/kg, while a non-targeting control ADC was inactive. An ADC targeting epidermal growth factor receptor, was highly active in an antigen-specific manner against a head and neck squamous cell carcinoma model. The half-life of the intact conjugate in circulation in mice was ~ 90 h, and its bioactivity was retained for 72 h post dosing. In summary, ADCs based on DGN462 exhibit potent, targeted anti-tumor efficacy with the potential for activity in tumors with low sensitivity to tubulin agents, heterogeneous antigen expression, or P-gp-mediated drug resistance.

10.30– 11.30 Coffee Break

Session 4 Chairman Victor S. Goldmacher

11.30–12.00 Charles Conover 7,Rodrigo Dienstmann1,2, Amita Patnaik3, Rocio Garcia-Carbonero4, Andrés Cervantes5, Marta Benavent4, Susana Roselló5, Bastiaan B.J. Tops6, Rachel S. van der Post6, Guillem Argilés1, Niels J.Ø. Skartved7, Ulla H. Hansen7, Rikke Hald7, Mikkel W. Pedersen7, Michael Kragh7, Ivan D. Horak7, Stephan Braun7, Eric Van Cutsem8, Anthony W. Tolcher3 and Josep Tabernero1,

1 Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Universitat Autònoma de Barcelona, Barcelona, Center affiliated to the RTICC (ISCiii), Spain. 2 Sage Bionetworks, Fred Hutchinson Cancer Research Center, Seattle, Washington. 3 START South Texas Accelerated Research Therapeutics, San Antonio, Texas. 4 Hospital Universitario Virgen del Rocío/Instituto de Biomedicina de Sevilla (HUVR, CSIC, Universidad de Sevilla), Center affiliated to the RTICC (ISCiii), Sevilla, Spain. 5 Biomedical Research Institute INCLIVA, University of Valencia, Valencia, Spain.

6 Department of Pathology, Radboud University Medical Center, Nijmegen,the Netherlands. 7 Symphogen A/S, Ballerup, Denmark.

8 Digestive Oncology Department, University Hospitals Leuven and KULeuven, Leuven, Belgium.

Safety and Activity of the First-in-Class Sym004 Anti-EGFR Antibody Mixture in Patients with Refractory Colorectal Cancer

Tumor growth in the context of EGFR inhibitor resistance may remain EGFR-dependent and is mediated by mechanisms including compensatory ligand upregulation and de novo gene alterations. Sym004 is a two-antibody mixture targeting nonoverlapping EGFR epitopes. In preclinical models, Sym004 causes significant EGFR internalization and degradation, which translates into superior growth inhibition in the presence of ligands. In this phase I trial, we observed grade 3 skin toxicity and hypomagnesemia as mechanism-based dose-limiting events during dose escalation. In dose-expansion cohorts of 9 and 12 mg/kg of Sym004 weekly, patients with metastatic colorectal cancer and acquired EGFR inhibitor resistance were enrolled; 17 of 39 patients (44%) had tumor shrinkage, with 5 patients (13%) achieving partial response. Pharmacodynamic studies confirmed marked Sym004-induced EGFR downmodulation. MET gene amplification emerged in 1 patient during Sym004 treatment, and a partial response was seen in a patient with EGFRS492R mutation that is predictive of cetuximab resistance.

12.00-12.30 Gurunadh Chichili , and Research and Development Team, Immunology and Cell Biology, MacroGenics, Inc. Rockville, MD ,USA

CD3-based Bispecific DART® Strategies for Redirecting T-cells Against Liquid or Solid Tumors

Bi-specific antibody technology provides an opportunity to extend the selectivity of monoclonal antibodies to dual targets, heralding opportunity to intervene in disease either through co-engagement of multiple pathways or cell types. Dual Affinity Re-Targeting (DART®) is one such technology which has been successfully designed to overcome limitations of prior bi-specific antibodies in terms of manufacturability, stability and pharmacological properties. Furthermore, DART molecules can be tailored with enhanced pharmacokinetic properties depending on the cancer target population to provide convenient dosing. In this presentation, the development of DART molecules designed to redirect a patient's T-cell response for the elimination of either hematological malignancies or solid tumors

will be presented, showcasing the strategies employed to support and enable clinical development.

1.00–2.30 Lunch

2.30-3.30 Open Air Workshop:
Novel Targets and Enhanced Antibodies-

Sir Walter Bobmer and Victor Goldmacher

8.00 pm until late
Conference Dinner

Wednesday 24th June 2015

Cancer Stem Cells Symposium

Chairman:

9.30-10.00 Dennis Hughes Texas USA

Introduction and Overview to Cancer Stem Cells

10.00 -10.30 Sir Walter F Bodmer ,

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

Colorectal Cancer Stem Cell Differentiation in Cell Lines

Colorectal cancer derived cell lines are good in vitro models for the study of cancer stem cells and their differentiation. We identify stem cells in a subset of cell lines

by their ability to form differentiated lumen structures in 3D gel cultures. This process is largely controlled by the homeobox gene *CDX1.* Recently we have shown that the microRNA, miR-215, is directly controlled by CDX1 and mediates gene expression down stream of *CDX1* and so contributes to enterocyte differentiation .In particular, CDX1 down regulates *BMI1*, which is a key gene for the maintenance stem cells, and so helps prevent reversion from the differentiated state back to a stem cell.

10.30–11.30 Coffee Break

11.30-12.00 Djamila Ouaret [1], Marina Bacac [2] and Walter F. Bodmer [1]

[1]Department of Oncology, Cancer and Immunogenetics Laboratory, Weatherall Institute of Molecular Medicine, Oxford, OX3 9DS, UK
[2]Roche Glycart AG Wagistrasse 18, CH-8952 Schlieren, Switzerland

Surface CEA expression is a strong predictive marker of the anti-tumour activity of CEA TCB, a CEA/CD3 bispecific antibody, in colorectal cancer

CEA TCB (Roche Glycart) is a novel T Cell Bispecific (TCB) antibody that binds carcinoembryonic antigen (CEA) on cancer cells and CD3 on T-cells to induce T-cell mediated killing of cancer cells. To understand the molecular basis of the potency of CEA TCB to mediate T-cell killing, we evaluated its in vitro activity on a panel of 110 colorectal cancer (CRC) cell lines using a lactate dehydrogenase (LDH) release cytotoxicity assay. We achieved this high-throughput immune-mediated screening by plating cells (target cells) directly from LN2 stocks and using frozen peripheral blood mononuclear cells (PBMCs) as effector cells.
Our data showed that there were two major groups of target cells, those displaying less that 10% (non responders) and those with more than 10 % (responders) of tumor lysis. We observed a strong and robust correlation ($p<0.0001$) between the surface level of CEA in the cell line panel, as determined by flow cytometry using the Qifikit method, and the response to CEA TCB. We also found that target cells with expression levels of less than 10,000 CEA binding sites are unlikely to be lysed

by CEA TCB. No significant association was found between CEA TCB activity and any of the major genetic changes described in CRC.

These combined data provide strong evidence that the surface CEA level on cells is strongly predictive of CEA TCB response and may provide a strategy for selecting prospective patients who should benefit from CEA TCB therapy.

12.00-12.30 Piero Pileri[1], Alberto Grandi[1], Susanna Campagnoli[1], Matteo Parri[1], Elena De Camilli[2], Li Fan[4], Luisa Ganfini[1], Hong Wu[4], Chaojun Song[4], Boquan Jin[4], Paolo Sarmientos[1], Guido Grandi[5], Luigi Terracciano[3], Giuseppe Viale[2], Renata Maria Grifantini[1]

[1]Externautics SpA, Siena, Italy; [2]European Institute of Oncology, Milan, Italy; [3]Medical Center -Basel University, Basel, Switzerland; [4]The Fourth Military Medical University, Xi'an, China, [5]Novartis Vaccines & Diagnostics Vaccines, Siena, Italy

Novel targets and monoclonal antibodies discovered by an immune-proteomics approach

The discovery of novel therapeutic targets is an extremely active research field in oncology, both in academia and pharmaceutical companies. In the last few years, we have been applying a "Reverse Proteomics" approach to discover novel tumor markers in different human cancers. In essence, our approach is based on an immuno-histochemical (IHC) screening of tumor tissues using a collection of mouse polyclonal and monoclonal antibodies raised against recombinant human proteins only marginally characterized in the scientific literature. In the course of such high throughput analysis, so far conducted on breast, lung colon ovary and prostate tumors, we discovered a panel of 89 tumor-associated proteins. A molecular and

cellular characterization of the potential markers allowed us to select novel potential therapeutic targets amenable to monoclonal antibody (mAb) treatment. Among others, here we describe the molecular characterization of two surface-exposed proteins (EXN91 and EXN36) associated to different cancer types. EXN91 is an adhesion molecule and it acts as a signaling receptor, cell communication and motility. Prevalence studies showed that the protein is mainly detected in colon cancer (CRC) with high frequency (approximately 90%), both in early and advanced colon cancer stages, with a statistical association for early cancer stages. Moreover, the protein is clearly surface exposed in liver metastasis from colon. Interestingly, EXN91 is over-expressed in KRAS and BRAF mutant CRC with high frequency. Moreover, an expanded IHC analysis revealed that it is also over-expressed and surface exposed in a number of other cancers, including HCC, RCC, bladder and endometrium cancer. EXN36 is mainly over-expressed in ovary and breast cancers, including triple negative breast cancer (frequency of approximately 30%). Moreover, EXN36 is involved in cell proliferation, migration and invasiveness. Murine mAbs towards EXN91 and EXN36 potential for specific therapeutic indications. In particular, a mAb recognizes EXN91 on the surface of colon cancer cells, including KRAS and BRAF mutant CRC. This antibody inhibits growth of colon cancer in xenograft mouse models. Concerning anti-EXN36 antibodies, they are able to bind the surface of different breast and ovary cancer cells. Both EXN36 and EXN91 mAbs show a high number of binding sites on the cell surface of positive cancer cells, with a concomitant limited IHC reactivity in normal tissues. The anti-EXN36 and anti-EXN91 antibodies are efficiently internalized by cancer cells, suggesting that they can be exploited for the development of Antibody-Drug-Conjugate (ADC). In vitro results showed that these antibodies

show significant anti-tumor activity with a specific conjugation chemistry. Moreover, antibody conjugation to Au nanoparticles (NP) showed that the NP-antibodies can be effective targeting vehicles as they improve nanoparticle internalization and promotes the delivery of Au NP in the tumor lesions. Overall, the anti-EXN36 and anti-EXN91 mAbs hold significant potential to improve the treatment of cancer.

12.30-12.35 Marco Loddo[1] and Gareth H Williams[1]
Oncologica UK Ltd, Suite 15, The Science Village, Chesterford Research Park, Cambridge, UK

Companion Diagnostics for Targeted Therapies using Semiconductor Next Generation Sequencing

The linking of specific cancer genetic alterations to molecular targeted therapies is driving a new era of personalised medicine. Here we discuss the implementation of cancer precision medicine into European Cancer Networks using the Next Generation Ion PGM™ System and the Oncomine Comprehensive Panel (OCP) to detect actionable driver mutations in all major tumour types. The OCP is an integrative NGS-based assay used to detect a predefined catalogue of clinically relevant solid tumour somatic genome variants (gain-of-function or loss-of-function mutations, high-level copy number alterations, and gene fusions) coupled to a bioinformatics pipeline to specifically link these variants to a knowledge base of related potential treatments, current practice guidelines, and open clinical trials. Here we will also discuss harnessing this semiconductor "targeted" sequencing technology to develop companion diagnostics for newly developed therapies. The case example presented refers to Oncologica's Cdc7 drug development programme which targets the highly evolutionary conserved DNA replication machinery in somatic cells. The specificity of this intervention strategy is the result of abrogation of a DNA origin activation checkpoint which is dependent on several tumour suppressors, FoxO3a, Dkk3, p53, Hdm2, $p21^{Cip1}$, $p14^{ARF}$ $p15^{INK4B}$, $p27^{Kip1}$ and

Rb. We are now exploring variants of these tumour suppressor genes as predictors of response to Cdc7 targeting agents using the Ion PGM™ System.

1.00-1.05 Agamemnon Epenetos - Adjourn to 2016

POSTER PRESENTATIONS

These will be displayed in the Hall area during the whole period of the conference

Bifunctional PEG-binding antibodies for targeted delivery of PEGylated nanocargos

Yu-Cheng Su[1, 2], Kuo-Hsiang Chuang[3], Bing-Mae Chen[2], Tian-Lu Cheng[4, 5, 6]* and Steve R. Roffler[2]*

[1] Institute of Microbiology and Immunology, National Yang-Ming University, Taipei, 11529, Taiwan

[2] Institute of Biomedical Sciences, Academia Sinica, Taipei, 11529, Taiwan

[3] Institute of Medicine, Kaohsiung Medical University, Kaohsiung, 80708, Taiwan

[4] Department of Biomedical Science and Environmental Biology, MedicoGenomic Research Center, Kaohsiung Medical University, Kaohsiung, 80708, Taiwan.

[5]Institute of Biomedical Sciences, National Sun Yat-Sen University, Kaohsiung, Taiwan.

[6]Center for Biomarkers and Biotech Drugs, Kaohsiung Medical University, Kaohsiung, Taiwan.

Abstract

Modification of small molecules, protein and nanoparticles with poly (ethylene glycol) (PEG) can enhance their *in vivo* stability and pharmacokinetic parameters. However, the therapeutic efficacy of PEGylated nanocargos is mainly governed by the enhanced permeability and retention (EPR) effect. Here, we generated bifunctional antibodies (BiAbs) which are composed of an anti-PEG Fab domain fused to single chain disulfide-stabilized variable fragments (scdsFv) that recognize EGFR or CD19 tumor-associated antigens and facilitate uptake and endocytosis of PEGylated nanocargos in the tumors. The BiAbs preferentially delivered drug-loaded NPs (liposomal doxorubicin) to cancer cells that expressed CD19 or EGFR with improved cancer cell killing. The BiAbs also increased the accumulation of PEGylated liposomes to antigen-positive human tumors in a mouse model. Anti-PEG BiAbs may be useful for tumor-specific targeting of PEGylated nanocargos to improve cancer imaging and anti-tumor therapies.