P5.01

SIRNA-MEDIATED TARGETING OF HER2 AS A Viable APPROACH FOR TREATING TRASTUZUMAB-RESISTANT BREAST CANCER CELLS

Shenda Gu, Shaun Goodyear, Worapol Ngamcherdtrakul, Jingga Morry, Thanapon Sangvanich, David Castro, Wassana Yantasee

Oregon Health and Science University, Portland, OR, USA

The human epidermal growth receptor type 2 (HER2) is overexpressed and amplified in 15-20% of breast cancers and contributes to poor survival. Current chemotherapeutics such as lapatinib and trastuzumab are only effective in a fraction of patients and a significant number of them develop resistance and relapse within a year of treatment. We investigated siRNA silencing of Her2 gene expression as an alternative method to treating trastuzumab-resistant breast cancer cells. Our results indicate that siRNA-mediated silencing of HER2 is effective in reducing cell viability and growth of BT474, HCC1954 and JIMT1 breast cancer cell lines in vitro. Moreover, long-term, repeated transfection of these cells with HER2 siRNA over a course of three months did not alter their sensitivity to HER2 gene silencing. Notably, their response to trastuzumab was also unaltered. Our findings suggest that while breast cancer cells incur resistance to trastuzumab, the cells remain dependent on HER2 expression. These findings support a siRNA therapeutic approach towards silencing HER2 as a viable method of overcoming trastuzumab resistance. We are currently developing a nanoparticle based siRNA delivery system for targeting HER2 positive tumor in vivo.

Response to HER2 siRNA and trastuzumab after long term repeated transfection.
HER2 signaling pathway after long term repeated transfection.
HEPATOCYTE GROWTH FACTOR-INDUCED MET ACTIVATION LEADS TO NVP-AEW541 RESISTANCE IN GASTROINTESTINAL CANCER CELLS

Jin Li, Rujiao Liu
Fudan University Shanghai Cancer Center, Shanghai, China

**Background:** Although several early phase clinical trials of insulin-like growth factor 1 receptor (IGF-1R)-specific antibodies for cancer treatment are impressive, initial phase III results in unselected patients have been disappointing. Our research aims at revealing that hepatocyte growth factor (HGF)-induced MET activation is a novel mechanism for IGF-1R tyrosine kinase inhibitor NVP-AEW541 resistance in gastrointestinal cancer cells, and inhibition of MET improves response to IGF-1R inhibitors, which may benefit further clinical studies.

**Methods:** NCI-N87 and HCT-116 cells were treated with varying concentrations and combinations of NVP-AEW541, HGF and crizotinib. Biological end points included proliferation and cell apoptosis. Receptor activation and downstream signaling pathway were examined to explore the resistance mechanism.

**Results:** MET-overexpressed MKN-45 cell showed the most unresponsiveness to NVP-AEW541. HGF-induced MET activation leads to NVP-AEW541 resistance in gastrointestinal cancer cells (Fig 1) by activating shared downstream AKT pathways, and inhibition of MET using crizotinib prevents MET-dependent activation of AKT and MAPK. Furthermore, combination therapy of NVP-AEW541 and crizotinib shows synergistic anti-tumor effect in vitro (Fig 2).

**Conclusions:** HGF-induced MET activation leads to NVP-AEW541 resistance in gastrointestinal cancer cells. A rational combination of tyrosine kinase inhibitors which raises hope for overcoming resistance to mono-agent therapy merits further investigation.
COMBINED 2-DEOXYGLUCOSE AND METFORMIN IMPROVES THERAPEUTIC EFFICACY OF RADIOIODINE TREATMENT IN SODIUM IODIDE SYMPORTER EXPRESSING BREAST CANCER CELLS

Sushmita Chatterjee¹, Abhijit De², Asawari Patil¹, Sudeep Gupta², Vani Parmar¹

¹TATA MEMORIAL CENTER, Navi Mumbai, India
²ACTREC, Navi Mumbai, India

Sodium Iodide Symporter (NIS) is known for its potential to uptake iodine in normal and malignant thyroid tissue. It facilitates successful therapeutic targeting of primary as well as metastatic thyroid cancer via radioiodine. In the past few years, several studies including studies by our group reported NIS over-expression in breast malignancies. In the present study, we have analyzed NIS expression in 42 breast cancer patient samples at the transcript level across the 4 major subtypes of breast cancer and observed high expression of NIS in ER positive samples as compared to ER-negative samples (p=0.0021, CI=95%). For the first time, NIS expression was analyzed by immunohistochemistry in 45 paired (primary and lymph node metastatic) breast tissue samples and 86% of samples showed either higher or equal expression of NIS in metastatic node as compared to the respective primary tumor tissue. Further to mimic the clinical scenario in an experimental model, a breast cancer cell line, MCF-7, was transfected by designing an attB integrase based bi-cistronic plasmid vector expressing human NIS and firefly luciferase (Fl2) linked via IRES. Stable cells were screened for correlated NIS and Fl2 expression and 4 such cell clones with varied expression of NIS and Fl2 were chosen for the model development. The correlation coefficient for NIS and Fl2 gene expression in this model was 0.9081. NIS expressing stable cells were further evaluated for their iodine uptake ability using I-125, and blocking with KClO4 showed complete inhibition of iodine uptake. Treatment of NIS-expressing cells with I-131 showed reduction in cell viability which was further reduced by the application of the two radiosensitizers, namely 2-deoxyglucose (2-DG) and metformin as a combination (p=0.0084, CI=95%). The combination therapy of I-131 with 2-DG and metformin also demonstrated elongation in S-phase of the cell cycle which was retained even after 48 hrs of treatment whereas in case of any of the therapies alone this elongation of S-phase was relieved after 48 hrs. The results open up a new possibility of enhanced radioiodine treatment efficacy in breast cancer cells overexpressing NIS protein.

Acknowledgement: ACTREC research fellowship to SC and ICMR, New Delhi research funding to AD is gratefully acknowledged.
ESTABLISHMENT AND CHARACTERIZATION OF MULTI-REGIONAL PATIENT-DERIVED RENAL CELL CARCINOMA XENOGRAFTS FOR TRANSLATIONAL RESEARCH

Iduna Fichtner1, Susanne Flechsig2, Burkhard Jandrig3, Charles Swanton4, Christian Schmees5, Jens Bedke6, Jens Hoffmann6, Jörg Hennenlotter6, Marco Gerlinger4, Annika Wulf-Goldenberg2, Zoltan Szallasi7

1 Max Delbrück Center for Molecular Medicine, Berlin, Germany
2 Experimental Pharmacology and Oncology GmbH, Berlin, Germany
3 University Medical Center, Berlin, Germany
4 Institute of Cancer Research, London, United Kingdom
5 Natural and Medical Science Institute, Tübingen, Germany
6 University Clinics, Tübingen, Germany
7 Boston Childrens Hospital, Boston, MA, USA

Objective: Patients with advanced kidney cancer have a poor prognosis. The majority of patients develops treatment resistance towards Standard of Care (SoC) drugs within months. The successful development of novel personalized therapies depends on the availability of preclinical models with high clinical relevance. Our aim was to establish a panel of patient-derived renal carcinoma xenografts (PDX) for translational research. We especially focused on potential differences in engraftment, response and mutation pattern in PDX established from multiple regions of the same patient tumour.

Methods: Specimens from primary and metastatic renal cell carcinomas (RCC) from consenting patients were collected after surgery and transplanted subcutaneously to immunodeficient mice. Tumor engraftment was followed for an initial period of up to 4 months. Successfully engrafted PDX were subsequently passaged. HE stained tumor sections were histopathologically examined to assess concordance between patient tumor and PDX model. RCC marker expression was determined by immunohistochemistry. Stably growing xenografts were tested for sensitivity towards bevacizumab, sunitinib, sorafenib and everolimus. Primary tumors as well as the derived xenografts were characterized for common oncogene mutations using the Illumina TruSeq Amplicon Cancer Panel.

Results: 189 tumor samples were transplanted since 2011. To date, 23% were successfully engrafted in immunodeficient mice, among them PDX from multiple regions of 6 patient tumors. Engraftment rates of samples from pT3 and pT4 tumors were higher (34%) than those from pT1 and pT2 tumors (12%). Two tumor samples which were pre-treated before surgery engrafted so far (11%). We show that specific tumor histology and renal cell carcinoma marker expression remained preserved over the passages. The drug sensitivity testings revealed a heterogeneous response to SoC treatments with sunitinib (25% responding PDX) and everolimus (20% responder). Bevacizumab showed a significant growth inhibition in 57% of PDX whereas sorafenib was effective in 36% of the RCC models. We are furthermore presenting the individual gene mutation status of each RCC model and of several multi-region derived PDX.

Background: Single targets are not effective in the clinic due to activation of collateral pathways, thus, combinatory treatments may abrogate the induction of pro-survival feedback loops. This research was undertaken with the aim to evaluate the anti-cancer action of combinations, which include chemotherapeutics used in clinics now with newly developed compounds.

Methods: Solution and solid phase methods for the synthesis of peptide and non-peptide compounds, cell cultures, MTT-based cell proliferation assay, western blot analysis.

Results: Several bradykinin antagonists (BA) and thiazolidinone derivatives (TD) were screened for their anti-proliferative effect on different glioma and mantle cell lymphoma (MCL) cells. Among all BA under investigation, BA1 appeared to be the most effective with LC50 4 μM and 3.3 μM in rat glioma C6 and human glioblastoma U373 cell lines, respectively. ERK1/2 and AKT1 phosphorylation was suppressed in U373 cells after treatment by this compound, thus, the growth-repression effect of BA1 could be mediated by the modulation of MAPK- and PI3K-signaling cascades. Temozolomide (TMZ), a first-line anti-gliomic drug, used in the clinic at 100 µM concentration has only temporary positive effect and severe side effects in GB patients. However, combination of 1 µM BA1 with only 10 µM temozolomide (TMZ), led to about 80% growth reduction of C6 and U373 cells, compared to temozolomide used alone. Moreover, screening of thiazolidinones revealed TD1 to be the potent suppressor of C6 and U373 cells growth (LC50 4 μM and 15 μM, correspondingly). TD2 demonstrated the highest activity in C6 cells with LC50 0.13 μM. Treatment of MCL cells by this compound and its chemical analogs showed also good results: LC50 values for TRS3 (0.27 μM) and TRS4 (0.16 μM) are even better than for doxorubicin, the conventional chemotherapeutic drug (0.37 μM).

Conclusions: We showed a strong synergistic growth inhibiting effect after combination of TMZ with BA1. Substantial suppression of human and rat glioma, as well as MCL cell growth was obtained by TD treatment. In vivo experiments are going on for the evaluation of these compounds in the pre-clinical setting.
TARGETED DELIVERY OF A MICRORNA MIMIC AS A NOVEL APPROACH TO THERAPY FOR MALIGNANT PLEURAL MESOTHELIOMA

Glen Reid¹, Casey Wright¹, Himanshu Brahmbhatt², Jennifer MacDiarmid², Jocelyn Weiss², Marcella Pel³, Marissa Williams¹, Michaela Kirschner¹, Nico van Zandwijk¹, Nancy Mugridge², Sonja Klebe⁴, Yuen Yee Cheng¹

¹ADRI, University of Sydney, Sydney, Australia
²EnGeneIC Ltd, Sydney, Australia
³University of Amsterdam, Amsterdam, Netherlands
⁴Flinders University, Adelaide, Australia

Background: Malignant pleural mesothelioma (MPM) is recalcitrant to treatment and new approaches are needed. MicroRNAs in the miR-15/16 family have been implicated as tumor suppressors in a range of cancer types, and restoration of microRNA expression has been shown to inhibit tumor cell proliferation. The miR-15/16 status in MPM is largely unknown.

Methods: MicroRNA expression was analysed by RT-qPCR in 10 MPM cell lines and 60 tumour specimens consisting of archival blocks from patients undergoing surgery. MicroRNA expression was restored in vitro using synthetic mimics, and effects on proliferation and target genes were assessed with standard methods. Human xenograft-bearing mice were treated with miR-16 mimic, or a novel miR-15/16-based consensus mimic, packaged in minicells targeted with EGFR-specific antibodies.

Results: Expression of the miR-15/16 family was consistently down-regulated in MPM cell lines and MPM tumor specimens. A 2- to 5-fold decrease in the expression of miR-16 and the co-expressed miR-15a and miR-15b was found in MPM cell lines compared with the normal mesothelial cell line MeT-5A. Comparing tumor specimens with normal pleura, the down-regulation of these microRNAs was in the order of 10-fold. Using synthetic mimics with sequence identical to miR-15a, 15b or 16 to restore expression led to time- and dose-dependent growth inhibition in a MPM cell lines but did not affect MeT-5A. Growth inhibition correlated with cell cycle arrest and concordant down-regulation of miR-15/16 target genes including Bcl-2 and CCND1. In a series of experiments with nude mice bearing (MSTO-H211) xenografts, intravenous administration of a minicell-packaged mimic (either miR-16 or a mimic based on the miR-15/16 family consensus sequence) led to consistent and dose-dependent inhibition of tumor growth.

Conclusions: Restoring expression of the miR-15/16 family represents a novel approach to treatment for MPM. Preparations are being made to test the miR-15/16 family consensus mimic packaged in minicells as a new treatment approach for patients with recurrent MPM and NSCLC.

References & acknowledgements: This work was supported by grants from the Asbestos Research Fund, the Workers’ Compensation Dust diseases Board NSW (GR), and the Cancer Institute NSW (GR and NvZ).
PATIENT-DERIVED CHILDHOOD LIVER CANCER XENOGRAFTS TO IMPROVE KNOWLEDGE ON PEDIATRIC LIVER TUMOR BIOLOGY

Stefano Cairo¹, Aurore Gorse¹, Charlotte Mussini², Christophe Chardot³, Delphine Nicolle⁴, Elie Fade⁵, Laurence Brugères⁵, Louise Galmiche-Rolland⁶, Monique Fabre⁵, Maria Rosa Ghigna⁶, Sophie Branchereau⁷

¹Xentech, Evry, France
²Centre Hospitalier de Bicêtre, Le Kremlin Bicêtre, France
³Hôpital Necker - Enfants malades, Paris, France
⁴Xentech, Evry, France
⁵Institut Gustave Roussy, Villejuif, France
⁶Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France

Despite being the predominant type of pediatric liver malignancies, hepatoblastoma (HB), with a worldwide incidence of 1 case per million persons per year, is a rare tumor. Liver tumors in children and adolescents occur on apparently normal liver. The high rate (> 60 %) of β-catenin activating mutations places HB as the human tumor most tightly associated with activation of the Wnt/β-catenin pathway. Evidence for an (epi)genetic origin of HB is provided by its association with congenital anomalies, Beckwith-Wiedemann syndrome, and familial adenomatous polyposis, a disorder caused by germline mutation of APC, involved in β-catenin degradation. HCC, fibrolamellar carcinoma (FLC), and transitional liver cell tumors (TLCT) also arise in children and adolescents, at a lower extent though. Sporadically, very rare forms of liver tumor of non-epithelial origin such as rhabdoid tumor or hepatic sarcoma also occur. Rare cancers are particular challenging due to their low incidence, particularly for the identification of novel therapies. The rarity and the heterogeneity of childhood liver cancers hamper the development of reliable research tools that recapitulate each disease.

To tackle this issue, we have launched a program aimed at the constitution of liver cancer patient-derived xenografts (PDXs). At present, 12 HBs, 2 TLCTs and 1 rhabdoid tumor have been successfully grown in immunocompromised mice. HB, TLCT and rhabdoid PDXs maintain the histological features of primary human tumors, and upon treatment with different chemotherapy agents, these models show unique profiles of response, indicating a tumor-specific sensitivity. Like for their parental tumors, HB and TLCT PDXs secrete alpha-fetoprotein (AFP), and the heterogeneity of AFP levels in mouse blood correlate with that observed in patients. Screen of a panel of 73 genes among the most frequently mutated in cancer by next-generation sequencing show identical mutation profile between PDX and tumor of origin. When put in culture, cells from PDXs grow and get immortalized more easily than they do with tumors from patients, and once injected back in mice, these cells develop tumors with the same characteristics of parental PDX. This property makes PDX-derived cells a useful tool to perform high-throughput ex-vivo studies. As the 14 HB/TLCT models have been obtained out of 47 tumors grafted, comparative analysis of the clinical parameters associated to tumors from which PDX could or could not be established has been performed. This analysis shows that tumor take is associated with high AFP level post-chemotherapy, with low percentage of treatment-induced necrotic/fibrotic area in the resected tumor, and, most important, with poor prognosis. RNA-sequencing and array-CGH analysis is currently ongoing for all these models. Development of a panel of childhood liver tumor PDXs will endow the scientific community with an innovative and versatile research tool that will decisively contribute to improve our understandings on pediatric liver malignancies. These models constitute an unperishable reservoir of biological samples that strongly recapitulate the human tumor biology, and they can be used in several research domains such as functional genomics, cancer stem cell biology and pharmacogenomics, notably for the identification of Wnt/β-catenin inhibitors. In the long run, improved knowledge in all these research fields will be translated in improved cures for kids.
Schematic representation of the rationale for development of a preclinical panel of rare cancers.
IMPAIRMENT OF PLATELET ACTIVITY IN METASTASIS PREVENTION. PERSPECTIVES FOR CHEMOTHERAPY APPLICATION, EFFICACY AND SIDE EFFECTS ANALYSIS.

Agnieszka Blazejczyk¹, Marcin Nowak², Stefan Chlopicki³, Marta Switalska¹, Joanna Wietrzyk¹

¹Institute of Immunology and Experimental Therapy, Wroclaw, Poland
²Wroclaw University of Environmental and Life Sciences, Wroclaw, Poland
³Jagiellonian University, Medical College, Krakow, Poland

Background: Efficiency of metastasis, a phenomenon that remains of a major interest among clinical oncologists, depends mostly on events occurring while cancer cells migrate through the unfavorable environment of flowing blood. We believe that enhanced exposure on a detrimental influence of vascular microenvironment, which can be achieved through an interference with cancer cell and platelets interactions, may lead to decreased survival of migrating cells and consequently to lower number of developed metastases.

Materials and methods: Mice bearing metastatic prostate, breast or colon tumors were treated with 1,4-dimethylpyridinium chloride (1,4-DMP) that modulates a process of prostacyclin synthesis, antiplatelet drug (clopidogrel) and a relevant chemotherapeutic. Antitumour and antimetastatic activity together with a systemic toxicity of the proposed treatment regimes, were assessed.

Results: Results of the presented studies indicate that, regardless the tumor type, both 1,4-DMP and clopidogrel did not influence the growth of primary lesions. However, when applied with 5-fluorouracil, cyclophosphamide or docetaxel, 1,4-DMP increased their activity in 20-30% (TGI value of 70%, 55%, and 80% , respectively, P < 0.05 vs. control). When aforementioned chemotherapeutic agents were administrated with clopidogrel the observed tumor growth inhibition was slightly reduced, however, animals in the groups receiving such a combined treatment developed lower number of lung metastases (80% less metastases in case of mice bearing mammary gland tumors, P < 0.05 vs. control).

Furthermore, we have noticed that 1,4-DMP diminished elevated blood concentrations of alanine and aspartate aminotransferases, induced by chemotherapy, which may suggest its potential liver protective function.

Conclusions: Presented studies indicate that a vascular-oriented treatment, supplemented with drugs with an anti-platelet activity, may beneficially influence overall anticancer effectiveness and alleviate side effects of selected chemotherapeutic drugs, applied in tumors of commonly occurring types.

Acknowledgments: This study was supported by European Union from the resources of the European Regional Development Fund under the Innovative Economy Program (grant coordinated by JCET-UJ, No POIG.01.01.02-00-069/09).
ROLE OF FOXP3 IN IMMUNE PRIVILEGE OF PRIMARY GLIOBLASTOMA CELLS

Shao-Chih Chiu¹, Der-Yang Cho¹, Ming-Chao Liu¹, Hao-Yu Chung²

¹China Medical University Hospital, Taichung, China, Taiwan
²Tainan Municipal An-Nan Hospital-China Medical University, Tainan, China, Taiwan

Glioblastoma multiforme (GBM) is the most frequent and malignant high-grade glioma (WHO grade IV). Despite substantial progress in treatment protocols, only 15% of patients undergoing radical surgery and chemotherapy with temozolomide are still alive within a median survival at about 14.6 months. Our positive outcome of phase II clinical trial in China Medical University Hospital (CMUH) has shown that immunotherapy of autologous dendritic cell/tumor antigen (ADCTA) could significantly prolong the median survival period to 28 months with a 5-year survival rate of 18%. Recently, glioblastoma stem cell (GSC) was characterized for distinctive proneural (PN) and mesenchymal (MES) subtypes according to different signatures of gene expression. GSC has been shown to contribute to tumor evasion of the immunosurveillance and determine the niche of GBM for modulating responses of immune cells. In our present studies, high level of FOXP3 expression in GBM tissues was observed a trend of decreasing survival in patients. We had characterized primary GSCs which were separated into two subtypes, PN-GSC (CD133+) and MES-GSC (CD133-). In tumor sphere cultures, FOXP3 was induced and expressed higher in PN-GSC than in MES-GSC. It resulted in different morphology of two subtypes of primary glioma cells after sphere culture for 24 hours. In the meanwhile, tumor-related immunosuppressors, IDO and TGF-beta were induced in cultured PN-GSC. Furthermore, PN-GSC was detected the activity of endothelial-to-mesenchymal transition. Our findings were comparable to recent studies in tumor-produced FOXP3 transcript and protein. Foxp3 thus acts as a multifaceted factor in the tumor microenvironment. FOXP3 might play a critical role in stemness and immune privilege of glioblastoma cells.
NK CELLS FROM GLIOMA-BEARING MICE TREATED WITH TEMOZOLOMIDE ARE ENRICHED FOR GENES RELATED TO MULTIDRUG RESISTANCE AND HOMING ABILITY

Serena Pellegatta, Barbara Galbardi, Dimos Kapetis, Emanuela Cazzato, Gabriele Cantini, Gaetano Finocchiaro, Sara Pessina

Fondazione IRCCS Istituto Neurologico C. Besta, Milan, Italy

**Background:** Chemotherapy influences the immune response by inducing immunogenic death of tumor cells or modulating tumor microenvironment (Galluzzi L, 2012). The limitations of chemotherapy and immunotherapy as single therapeutic modalities have generated considerable interest in combinatorial strategies (Zitvogel L, 2008). Here we focused on understanding the molecular mechanisms directly induced by temozolomide (TMZ), the standard chemotherapeutic agent for glioblastoma, that can activate immune cells.

**Methods:** We studied the in vivo effects of TMZ on immune cells by treating mice 9 days after intracranial implantation of GL261 gliomas with intraperitoneal injections of TMZ (5 mg/kg) or vehicle (control mice) for 5 days. Gliomas and peripheral blood were harvested and analyzed by flow cytometry at different time points.

**Results:** Trafficking of NK1.1+ CD3- NK cells in blood and their homing ability into the brain significantly increased in TMZ-treated mice on day 12, after the second administration of TMZ. At this early time point TMZ led to a significant enrichment of CD11b(low) CD27(high) and CD11b(high) CD27(high) subsets. Microarray analysis revealed differentially expressed genes represented in different clusters of which chemotaxis, multidrug resistance and anti-apoptosis were predominantly up-regulated in blood-derived NK cells isolated from TMZ-treated compared to control mice. We focused validation experiments on genes related to chemotaxis and multidrug resistance. Chemotaxis was assayed using the in vitro transwell system confirming that the migration ability of NK cells from treated mice significantly increased by 3-fold compared with controls. Increased expression of three ATP transporter genes was confirmed by real time PCR (3.2-fold higher than controls, P=0.006). Five days after the end of the treatment we found an enrichment of CD11b(high) CD27(low) NK cells. IFN-gamma production evaluated by flow cytometry and the in vitro cytotoxic activity of NK cells from TMZ-treated mice were higher than that of NK cells from control mice.

**Conclusions:** Our results support the idea that NK cells can be resistant to chemotherapy (Lowdell MW, 2003). In particular at early time points TMZ leads to an enrichment of NK cells with migratory function, in the later phase TMZ leads to an increase of NK cells promoting cytotoxic ability.
P5.11

THE ROLE OF CENTROSMAL PROTEIN TAX1BP2 IN LIVER CANCER CELL CHEMOSENSITIVITY

Yick Pang Ching, Wai Lung Lai

The University of Hong Kong, Hong Kong, Hong Kong

Supernumerary centrosome is one of the major factors that drive chromosomal instability and is a common phenotype in cancer cells. Recently, we have identified a novel cellular centrosomal protein, called TAX1BP2, which is able to suppress centrosome over-amplification. Since aneuploidy is frequently observed in human liver cancer, our previous data showed that TAX1BP2 acts as a putative tumor suppressor in hepatocellular carcinoma (HCC). Using quantitative RT-PCR, we showed that TAX1BP2 was frequently under-expressed in human HCC. The under-expression of TAX1BP2 transcript was significantly associated with a poorer prognosis of HCC patients. Furthermore, we demonstrates that TAX1BP2 regulates tumor suppressor, p53 level in a p38 MAPK dependent manner. Interestingly, we also observed that TAX1BP2 was significantly accumulated in HCC cells under the treatment of chemotherapeutic drug, cisplatin and etoposide. In this presentation, we will demonstrate that TAX1BP2 is a novel substrate of ATM kinase and phosphorylation of TAX1BP2 by ATM modulates the protein level of TAX1BP2 via ubiquitination proteasomal degradation. Taken together, our data suggest that TAX1BP2 can be a potential target for the enhancement of HCC cell chemo-sensitivity.
A PRECLINICAL STUDY COMBINING THE DNA REPAIR INHIBITOR DBAIT WITH RADIOTHERAPY FOR THE TREATMENT OF MELANOMA

Marie Dutreix¹, Julian Biau², Pierre Verrelle², Jian-Sheng Sun³, Flavien Devun³

¹Institut Curie, Orsay, France
²Centre Jean Perrin, Clermont-Ferrand, France
³DNA Therapeutics, Evry, France

Background and purpose: Melanoma is radioresistant. The cytotoxicity of radiotherapy (RT) is mainly due to DNA double-strand breaks (DSB). Dbait are innovative molecules which mimic DSB that trap DNA repair proteins and prevent their recruitment thereby inhibiting repair of RT-induced DNA damage. We assessed the efficacy and safety of combining RT with Dbait in a model of human melanoma.

Material and Methods: Initially, the cytotoxic efficacy of Dbait in combination with RT was evaluated in vitro. We further assayed the capacity of DT01 (clinical form of Dbait) to enhance radiotherapy efficiency on a radioresistant human melanoma xenografted model (SK28). For this we monitored tumour growth and survival of nude mice subcutaneously engrafted with SK28 after treatment with Dbait, “palliative” (10x3Gy) or “radical” (20x3Gy) RT, or a combination of Dbait and RT.

Results: In vitro, Dbait enhanced RT-induced cytotoxicity independently of RT doses (p<0.05). In Dbait and RT treated cells, initially the level of DNA damage was not greater than in RT treated cells, but damage persisted for longer (p<0.05) indicating a defect in their repair. Mice treated with DT01 and RT combination had significantly better tumor growth control and longer survival compared to RT alone with the “palliative” protocol or the “radical” protocol (p<0.001). Only animals that received the combined treatment showed complete responses. No additional toxicity was observed in any DT01-treated group.

Conclusions: This preclinical study provides encouraging results for a combination of a new DNA repair inhibitor, DT01, with RT, with no added toxicity. A first-in-human phase I study is currently underway in the palliative management of melanoma in-transit metastases (DRIIM trial).

Acknowledgements
This study was supported by Curie Institute, CNRS, INSERM, ANR, and DNA Therapeutics.

References:
Radiosensitization of SK28 tumors by DT01 with a “palliative” and “radical” RT protocol. (A) Treatment schedule. Each 3-Gy fraction is represented by a black triangle and each 4 mg DT01 administration by a gray triangle (B) Tumor growth (Vₜ: Tumoral Volume/ Vᵢ: Initial Volume) and (C) Survival of nude mice bearing subcutaneous SK28 melanoma tumor xenografts.

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| **B**                           |                              |
| Tumor growth (Vₜ/Vᵢ)            |                              |
| Time (days)                     |                              |

| **C**                           |                              |
| % of survival                   |                              |
| Time (days)                     |                              |

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MAGNETIC-BASED ENGINEERED NANOSTRUCTURES FOR TUMOR ABLATION AND DRUG DELIVERY

Teresa Pellegrino

Istituto Italiano di Tecnologia, Genova, Italy

The field of nanoscience is providing new nanomaterials that have the potential to find application in medicine. Superparamagnetic nanoparticles are particularly interesting as heat mediators in magnetic induced hyperthermia for tumour ablation. The preparation of superparamagnetic nanoparticles has been reported in the early 80's. The recent advances in the synthesis of magnetic inorganic nanomaterials of varying size, shape, composition and magnetic performances, have renewed the interest in those materials and have made available new types of nano-heater probes which are less invasive and more appealing as heat foci and drug delivery carriers. The aim of this poster/presentation is to provide examples of iron oxide based nanoparticles with enhanced performance as heat mediators. Moreover, nanoparticles can also act as cargo systems for drug molecules. Their advantages as shuttle for drug does not only reside in their small size (which results a higher surface to volume ratio and thus a higher drug loading capacity together with the ability to escape the reticulum endothelial system) but also to their intrinsic magnetic properties. Nanoparticles can be only activated under the exposure to an alternative magnetic field, therefore local heat is generated only under specific conditions. In this regard, the heat stimulus could be the trigger mechanism to release cargos with spatial and temporal control release. To such aim, proper thermo-sensitive coatings at the nanoparticle surface have been designed by us. To activate some of them the macroscopically temperature of the system needs to overcome 42°C. We will also provide latest concepts on the temperature gradient effects at the magnetic nanoparticle surface. In this latter case, the delivery can be still achieved via an external source, the radiofrequency, but without the need to macroscopically increase the temperature above the body temperature. Finally, an example developed by us of molecular targeting of magnetic nanoparticles towards ovarian cancer cells in vitro and in vivo we be also provided.