However, these CSC populations differ dramatically, making therapeutic approaches illusive.

**Material and methods** Initially, we identified that Wnt and YAP signalling suppressed both mesenchymal and epithelial CSCs in vitro and in vivo using TNBC cell lines, patients’ tumour samples, and a database of 2509 patients with invasive breast cancer. Subsequently, we encapsulated Wnt and YAP inhibitors (PRI-724 and simvastatin respectively) in polyethylene glycol–polyactic acid nanoparticles (NPs) to increase intra-tumoral specificity and accumulation. Mice were implanted with patient derived xenografts (PDX) and were treated with NP-encapsulated PRI-724 and simvastatin. Additionally, NP accumulation within the tumour versus other organs was tracked using NP-conjugated fluorophores followed by flow cytometry and in vivo imaging system analysis (IVIS). To determine CSC and tumorigenesis, secondary transplantation was performed after NP treatment.

**Results and discussions** NP-encapsulated PRI-724 and simvastatin effectively suppressed Wnt and YAP gene expression in vitro. NP-encapsulated inhibitors were tolerable in vivo and accumulated in the TNBC PDX tumours. In contrast to paclitaxel (a commonly employed chemotherapeutic agent), NP-encapsulated PRI-724 and simvastatin markedly reduced the epithelial (ALDH+), and mesenchymal (CD44+/CD24−) CSC subpopulations. Additionally, co-administration of NP-encapsulated inhibitors with paclitaxel potently retarded the growth of TNBC PDX tumours but significantly maintained diminished epithelial (ALDH+) and mesenchymal (CD44+/CD24−) CSC populations.

**Conclusion** We developed a novel, tangible approach for the treatment of TNBC using NP-encapsulated Wnt and YAP inhibitors which accumulated in TNBC PDX tumours and potently retarded tumour growth, and inhibited CSC enrichment and tumorigenicity.

**Results and discussions** Both physical and chemical characterisation of this novel ELR showed that it is able to self-assemble into nanoparticles with a diameter of 68 nm, which are an effective way to deliver the Akt inhibitor into the cytoplasm, where it will bind to its protein target Akt and stop the kinase activity. With a transition temperature of 18°C and a high negatively-charged surface, nanoparticles perfectly met all requirements for its use as biomedical tools. Moreover, nanoparticles showed increased killing ability on cancerous cells compared to non-cancerous cells.

**Conclusion** Thus, we have designed a new system able to enter into the cancerous cells and inhibit Akt signalling pathway. As an interesting advantage, ELRs have the ability to be modified by adding different molecules, such as aptamers or single chain antibodies, in order to be selectively targeted against cancerous cells. Thus, the action of these nanoparticles will be more accurate so as to achieve a new therapeutic tool for colorectal cancer treatment.

**Poster Presentation: Experimental/Molecular Therapeutics, Pharmacogenomics**

**PO-431** **ABSTRACT WITHDRAWN**

**PO-432** **NEW COMBINED NANOPARTICLE THERAPY INHIBITS METASTATIC BREAST TUMOUR GROWTH WITH SUPERIOR EFFICACY AND LOWER SIDE EFFECT PROFILE TO DOCETAXEL**

J González*, A Grotti, JC Rodriguez-Cabello, FJ Arias. University of Valladolid, BIOFORGE group, Valladolid, Spain

10.1136/esmoopen-2018-EACR25.456

**Introduction** With almost 1.4 million new cases each year worldwide, colorectal cancer kills 228,000 Europeans every year. Although new therapies have been discovered, the use of recombinant elastin-based biomaterials could open a new approach in cancer research as polymeric carriers for drug delivery in order to improve the accuracy of the action and reduce the toxicity of chemotherapeutic agents. In this work, we have developed a new elastin-like recombinamer (ELR) fused to a peptide inhibitor of the protein kinase Akt. This polymer self-assembled into nanoparticles, which showed killing ability on colorectal cancer cells (Caco-2).

**Material and methods** Taking advantage of the recombinant DNA technology, the constructs were formed by an amphiphilic backbone and several bioactive sequences, with an Akt inhibitor among others. ELR were produced by E. coli fermentation and, after purification process, were characterised and tested in vitro. Cellular viability assays on cancerous cells were carried out in order to study the killing ability of these nanoparticles.

**Results and discussions** Both physical and chemical characterisation of this novel ELR showed that it is able to self-assemble into nanoparticles with a diameter of 68 nm, which are an effective way to deliver the Akt inhibitor into the cytoplasm, where it will bind to its protein target Akt and stop the kinase activity. With a transition temperature of 18°C and a high negatively-charged surface, nanoparticles perfectly met all requirements for its use as biomedical tools. Moreover, nanoparticles showed increased killing ability on cancerous cells compared to non-cancerous cells.

**Conclusion** Thus, we have designed a new system able to enter into the cancerous cells and inhibit Akt signalling pathway. As an interesting advantage, ELRs have the ability to be modified by adding different molecules, such as aptamers or single chain antibodies, in order to be selectively targeted against cancerous cells. Thus, the action of these nanoparticles will be more accurate so as to achieve a new therapeutic tool for colorectal cancer treatment.

**Poster Presentation: Experimental/Molecular Therapeutics, Pharmacogenomics**

**PO-431** **ABSTRACT WITHDRAWN**

**PO-432** **NEW COMBINED NANOPARTICLE THERAPY INHIBITS METASTATIC BREAST TUMOUR GROWTH WITH SUPERIOR EFFICACY AND LOWER SIDE EFFECT PROFILE TO DOCETAXEL**

J González*, A Grotti, JC Rodriguez-Cabello, FJ Arias. University of Valladolid, BIOFORGE group, Valladolid, Spain

10.1136/esmoopen-2018-EACR25.456

**Introduction** Combining molecular therapies with chemotherapy may offer an improved clinical outcome for chemoresistant tumours. Sphingosine kinase 1 (SK1) is a proto-oncogene that is highly expressed in breast cancer, especially in oestrogen receptor (ER) negative tumours. SK1 inhibitor FTY720 has promising anticancer properties as monotherapy. In this study, we have developed and tested polymer and silicon nanoparticles combining docetaxel and FTY720 for enhanced anticancer effect, targeted tumour delivery and reduced systemic toxicity.

**Material and methods** Docetaxel, FTY720 and glucosamine were embedded or covalently conjugated to poly(lactic-co-glycolic acid) or silicon nanopores. Nanoparticles were characterised by dynamic light scattering and electron microscopy. The cellular uptake, cytotoxicity and in vivo antitumor efficacy of nanoparticles were evaluated.

**Results and discussions** Our data indicate that in ER negative breast cancer cells FTY720 provides chemosensitisation to docetaxel, allowing a four-fold reduction in the effective dose. We have encapsulated both drugs in nanoparticles, with narrow size distribution of ~100 nm and excellent cancer cell uptake providing sequential, sustained release of both drugs. In mouse models of human ER negative breast cancer nanoparticles had superior efficacy to systemic free docetaxel. Both polymer and silicon nanoparticles had significantly lower side effect profile including reduction of chemotherapy-induced weight loss, liver toxicity and neutropenia.
Conclusion Here we have shown for the first time that FTY720 can sensitise ER negative breast cancer to docetaxel. We further demonstrate that encapsulation of free drugs in nanoparticles can improve targeting, provide low off-target toxicity and enhance antitumour efficacy offering potential therapeutic use of FTY720 in clinical breast cancer treatment.

PO-433

THE MODULATION OF REDOX HOMEOSTASIS AND INDUCTION OF FERROPTOTIC CELL DEATH IN HEPATOCELLULAR CARCINOMA AS AN ANTICANCER STRATEGY

1,2,3J Liese*, 4J Lippmann, 2,4SS Fulda. 1University Hospital of Giessen, Department of General- Visceral- Thoracic- Transplant and Pediatric Surgery, Giessen, Germany; 2German Cancer Consortium DKTK, German Cancer Consortium DKTK, Heidelberg, Germany; 3German Cancer Consortium DKTK, German Cancer Research Center DKFZ, Heidelberg, Germany; 4Goethe-University, Institute for Experimental Cancer Research in Pediatrics, Frankfurt, Germany; 5German Cancer Research Center DKFZ, German Cancer Research Center, Heidelberg, Germany

Abstracts

Conclusion By providing new insights into the molecular regulation of ROS and ferroptosis, our study contributes to the development of novel treatment strategies to reprogramme cell death in HCC cells.

PO-434

AT1413 ANTIBODY DERIVED FROM A CURED AML PATIENT RECOGNISES UNIQUE SIALYLATED CD43 EPITOPE SHARED BY AML, MDS AND MELANOMA CELLS

1G De Jong, 2L Bartels, 2M Kedde, 2E Verdegaal, 2E Yasuda, 2P Van Helden*, 2K Wagner, 2R Schotte, 2H Spits, 1M Hazenberg. 1Academic Medical Center, Department of Hematology, Amsterdam, The Netherlands; 2AIMM Therapeutics, AIMM Therapeutics, Amsterdam, The Netherlands; 3LUMC, Department of Medical Oncology, Leiden, The Netherlands

Introduction AT1413 is an antibody derived from B cells of an AML patient who was cured following allogeneic hematopoietic stem cell transplantation. It recognises a sialylated epitope on CD43 (CD43s), which is expressed on myeloid cells but not on B and T cells and is over-expressed on acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) cells. AT1413 kills AML cells in vitro and in vivo via antibody dependent cell-mediated cytotoxicity (ADCC) suggesting that AT1413 played a role in the graft versus leukaemia response of this patient. Because CD43 is broadly expressed in non-hematopoietic cells we explored whether CD43s is present on non-hematopoietic tumours.

Materials and methods AT1413 binding on a panel of tumour cell lines was analysed by flow cytometry. AT1413 was assembled into a bispecific T-cell engaging format (AT1413 bTCE) by linking the full-length AT1413 IgG to two single chain variable fragments against CD3e with a combination of site-specific enzymatic and chemical coupling. Two point mutations in the IgG heavy chain were introduced to prevent interactions between AT1413 bTCE and Fc gamma receptors. The cytotoxicity-inducing activities of naked AT1413 and its bTCE format were tested with PBMCs as effector and tumour cells as target cells using standard cytotoxicity assays.

Results and discussions AT1413 bound to melanoma cell lines but not to pancreas carcinoma, colon carcinoma, or liver carcinoma. Expression on melanoma cells was confirmed by immunoprecipitation and western blot using a mouse anti-human CD43 antibody. AT1413 bound to 14 out of 21 patient-derived primary melanoma samples with varying intensities. AT1413 induced ADCC of melanoma cell lines and patient-derived melanoma cells. The level of ADCC correlated with CD43s expression levels. To increase the cytotoxicity inducing potential of AT1413 we generated a bTCE format and demonstrated that it induced strong cytotoxic T cell activities against melanoma cells in vitro. The efficacy of AT1413 and AT1413-bTCE on human melanoma cells in vivo in a xenograft mouse model is currently tested.

Conclusion The AT1413 antibody recognises a sialylated epitope on CD43 shared by melanoma, AML and MDS cells. Both the non-modified IgG- and the bispecific TCE form of AT1413 induce strong anti-tumour cytotoxic activities in vitro and in vivo. Because of its broad tumour reactivity and functional activities AT1413 has promising therapeutic potential.