
Monday, February 6, 2017

Re: AACR Annual Meeting 2017 in Washington, D.C.
Abstract Control Number: 5137
Title: Deletion of survivin sensitize human hepatocellular carcinoma cells to low dose of doxorubicin and induce apoptosis

Dear Dr. George:

Your above-referenced abstract has been scheduled for presentation in a Poster Session at the AACR Annual Meeting 2017 in Washington, D.C., and will be published in the 2017 *Proceedings of the AACR*. Presentation information pertaining to your abstract is below:

**Session Category:** Experimental and Molecular Therapeutics
**Session Title:** Targeting p53, Apoptosis, and the Cell Cycle
**Session Date and Time:** Monday Apr 3, 2017 1:00 PM - 5:00 PM
**Location:** Convention Center, Halls A-C, Poster Section 7
**Poster Board Number:** 16

**Permanent Abstract Number:** 2165 [Place this number on your poster board]

Please refer to the online Annual Meeting Itinerary Planner [available in mid-February through the AACR Website at http://www.aacr.org] for complete session information.

Instructions for Presenters in Poster Sessions are provided below. Please check the AACR website for additional information.

Poster presenters at the AACR Annual Meeting must register for the full meeting at the rate appropriate to their membership status and obtain their own hotel accommodations. Registration and housing information are included below:

**Advance Registration Deadline: Sunday, January 29, 2017**
**Online Registration and Letters of Invitation**
http://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=105&DetailItemID=541

**Special Offer for Non-Member Presenters**
Individuals who are interested in joining the AACR and registering at the advance member rate must submit a membership application no later than **5:00 PM ET Wednesday, January 25**. Interested candidates can apply for membership online at http://myaacr.aacr.org/Default.aspx. If you have any questions or need further information on becoming an AACR member, please contact the AACR Member Services Department at (215) 440-9300 or membership@aacr.org.

**Housing Deadline: Friday, February 17, 2017**
**Online Housing System**
http://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=105&DetailItemID=542

**Travel Information**
**[Airline/Train Reservations; Ground Transportation]**
http://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=105&DetailItemID=542

**Discounted Poster Creation/Printing and Delivery Service**
The AACR has selected Call4Posters as its preferred poster printing service partner for the 2017 Annual Meeting. Presenters are encouraged to take advantage of this simple, convenient way to print their posters and pick them up onsite at the meeting in Washington. Delivery is 100% guaranteed; avoid airport hassles and worries about shipping it yourself.

Free PowerPoint™ templates will be available to help you build your poster, or you can simply upload your existing file for this high quality professional printing service. More information about the service—including login information for the poster creation site—will be sent by e-mail in mid-February.

**NEW! Electronic Posters**
Poster presenters at the AACR Annual Meeting 2017 will have the option to make their posters available electronically to meeting attendees. Presenters can include audio, video, or other supporting documents with their electronic poster, and attendees will be able to access the electronic posters at onsite kiosks, on a dedicated poster site, or through the Annual Meeting App. Participation in the electronic posters project is free of charge and is entirely optional for poster presenters. More information about the poster printing service and electronic posters will be sent by e-mail in mid-February. **[PLEASE NOTE: Electronic Posters are not a replacement for onsite presentation. All poster presenters must register to attend the Annual Meeting and accompany their posters in the appropriate sessions.]**

**Session Format**
Presenters will be admitted to the poster area beginning 30 minutes before the start of each session to hang their posters. Poster sessions last for four hours, and posters must remain on the assigned board for this entire period. Presenters must remain at their posters for only the first three hours. During the fourth hour presenters are free to examine the other posters or to attend other sessions. Poster materials must be removed immediately at the end of the session; posters left on the boards after sessions will not be saved.

**Poster Format**
Poster boards have a usable area of 7.75 feet in width and 3.75 feet in height (approximately 2.3 meters wide and 1.1 meters high). Each presentation should contain a top panel listing the abstract number, the title of the abstract and the names of the authors.

For more information, visit the AACR Annual Meeting 2017 home page:
http://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=105

Thank you for your participation in the AACR Annual Meeting 2017.

Sincerely,
Kornelia Polyak, MD, PhD
Program Committee Chairperson

PLEASE NOTE: This document is your official notice of acceptance. No separate letter of acceptance will be mailed.

For all technical questions, please contact OASIS Helpdesk or call (217)398-1792. If you have policy related questions, please contact AACR at (215)440-9300 or (866)423-3965.

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**#2164 BLID is a novel drug-inducible apoptotic molecule: Identification of an integrative mechanism of chemosensitivity in breast cancer cells.** Sivaramakrishna Yadavalli, Rong Hu, Antonina Rait, Xin Li, Esther Chang, Robert Clarke, Usha Kasid. *Georgetown Lombardi Comp. Cancer Ctr., Washington, DC.*

The triple-negative breast cancer (TNBC) is an aggressive form of breast cancer frequently seen in African American women and BRCA1 mutation carriers. The TNBC tumors often relapse with distant metastases following standard chemotherapy. It is now evident that discoveries of new mechanisms and approaches that explain and target breast cancer biology are urgently needed for durable intervention of metastatic disease. Earlier, we have demonstrated that BLID, BH-3 Like motif containing Inducer of cell Death, is a strong prognostic factor in invasive breast cancer. Frequent lack of BLID has been associated with TNBC, African American ethnicity and younger women. Significant correlations exist between BLID negative breast cancer and declines in overall survival, local relapse-free survival and distant metastasis-free survival. Recently, BLID has been shown to inhibit breast cancer cell growth and metastasis. The purpose of this study was to investigate the role of BLID in response of breast cancer cells to chemotherapeutic drugs. In the dose response and time course studies, BLID mRNA expression was found to be induced by chemotherapeutic drugs. Expression of BLID cDNA nanocomplex (scLBLID) resulted in significant increase in chemosensitivity in SKBr3 and MDA-MB-231 cells, and a comparison of BLID with p53 showed that the chemosensitization effect of BLID was significantly greater than that of p53. Consistently, BLID knockdown led to reversal of drug-induced cytotoxicity. In the ChIP-PCR and ChIP-qPCR assays, drug treatment of breast cancer cells resulted in an increased binding of pro-apoptotic transcription factor FOXO3a to the BLID promoter, and the reversal of drug-induced BLID reporter activity was seen in presence of FOXO3a siRNA. Furthermore, siRNA silencing of FOXO3a was found to be associated with decrease in endogenous BLID mRNA expression. Remarkably, we found that expression of central tumor suppressor microRNA miR34a also resulted in increased BLID mRNA expression and drug toxicity in breast cancer cells. Because lack of BLID expression has been associated with poor prognosis in breast cancer patients, we reasoned that the silencing of BLID may reveal as yet unknown changes in gene expression that may drive breast cancer cell proliferation and therapy resistance. In this context, the mRNA array profiling studies showed that BLID knockdown in MDA-MB-231 cells was associated with increased expression of the oncogenic/anti-apoptotic molecules CYP1B1, BIRC3 and CSF1, and decreased expression of the anti-oncogenic/apoptotic molecules AKAP12, DFNA5 and CHRDL1. Our data suggest that chemotherapeutic drugs induce BLID expression via activation of FOXO3a, and the BLID signaling axis downstream of FOXO3a and miR34a is a novel integrative mechanism of breast cancer response to chemotherapy. SY and RH are equal contributors in this study.

**#2165 Deletion of survivin sensitize human hepatocellular carcinoma cells to low dose of doxorubicin and induce apoptosis.** Joseph George, Nobuhiko Hayashi, Takashi Saito, Kazuaki Ozaki, Nobuyuki Toshikuni, Mutsumi Tsuchishima, Mikihiro Tsutsumi. *Kanazawa Medical University, Uchinada, Japan.*

Background and Aims: Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and patients with advanced HCC face a dismal prognosis due to lack of effective therapy. Survivin, a member of the family of inhibitor of apoptosis proteins, is highly upregulated in HCC as well as in experimentally induced intrahepatic tumors. Doxorubicin, the only known chemotherapeutic agent for HCC, is cardiotoxic in addition to several well known side effects. Methods: Survivin gene deletion was established in HepG2, Hep3B, and PLC/PRF/5 human HCC cells using CRISPR/Cas9 system. All the three HCC cells in culture were treated with doxorubicin at various concentrations before and after survivin gene knockout upto 72 hr. TUNEL assay and FACS analysis were performed to demonstrate the induction of apoptosis after doxorubicin treatment. Western blotting was carried out for cleaved fragments of caspase-9 and caspase-3 as well as major apoptotic executioner molecules. Results: Cell viability studies depicted around 20% cell death at 24 h, 50% at 48 h, and 80% at 72 h after treatment with doxorubicin at 1 $\mu$M (final concentration in the media). Among the three cell lines studied, Hep3B cells were more susceptible to doxorubicin compared to HepG2 and PLC/PRF/5 cells. After deletion of survivin gene, the dosage of doxorubicin could reduce to five fold (200 nM, final concentration in the media) with the same cytotoxic effect before the knockout of survivin gene. HCC cells treated with reduced doses of doxorubicin depicted induction of apoptosis that was proved with TUNEL assay and FACS analysis as wells as increased levels of cleaved caspases and major apoptotic executioner molecules. Conclusions: Our studies demonstrated that blocking of survivin molecule with effective methods would be a successful approach to treat primary hepatic tumors with low and safe doses of doxorubicin and other anticancer agents.

**#2166 Arsenic trioxide targets BCL6 oncoprotein for degradation in BCL6-dependent diffuse large B-cell lymphoma.** Lok Man Yue, David Hau Wing Chau, Wenying Piao, (Eric) Wai Choi Tse, Yok Lam Kwong. *The University of Hong Kong, Hong Kong, Hong Kong.*

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma throughout the world. B-cell lymphoma 6 (BCL6) overexpression is frequently observed in DLBCL. Several recent studies have supported that BCL6 is a critical pathogenic oncoprotein in DLBCL. BCL6 represses various downstream genes, including ATR, TP53 and CDKN1A, thereby impairing DNA repair leading to derangement of cellular proliferation. Most importantly, a specific small molecule inhibitor targeting BCL6 successfully suppressed growth of BCL6-dependent DLBCL cell lines and primary human DLBCL cells, further suggesting that BCL6 plays an important pathogenetic role. Arsenic trioxide ($As_2O_3$) has been reported to target various oncogenic proteins, including PML-RARA in acute promyelocytic leukemia, cyclin D1 in mantle cell lymphoma, NPMc+ in acute myeloid leukemia and NPM-ALK in anaplastic large cell lymphoma, for degradation through ubiquitin-proteasome pathway. In this study, we investigated the effects of $As_2O_3$ on BCL6 in DLBCL. $As_2O_3$ was found to inhibit cell proliferation and induce cell death via apoptosis in DLBCL cells. More interestingly, BCL6-dependent DLBCL cells were found to show higher sensitivity towards $As_2O_3$-induced cytotoxicity. BCL6 was found to be degraded by $As_2O_3$ at posttranslational level through the ubiquitin-proteasome pathway. Such degradation led to an upregulation of several downstream targets of BCL6, including PRDM1, CD44 and CD69. Moreover, $As_2O_3$ synergized with cisplatin to inhibit cell proliferation and enhance apoptosis in BCL6-dependent DLBCL cell lines. Concomitant treatment with $As_2O_3$ and cisplatin further enhanced the phosphorylation of Chk1 and γH2AX in these cells. In conclusion, our data suggest that $As_2O_3$ is a potential therapeutic agent for the treatment of BCL6-dependent DLBCL. On top of that, new combination therapies can be developed to expand the therapeutic spectrum of $As_2O_3$ to other neoplasms.

**#2167 Preclinical validation of an Omomyc cell-penetrating peptide as a viable anti-Myc therapy.** Marie-eve Beaulieu,[1] Toni Jauset,[2] Daniel Massó-Vallés,[2] Peter Rahl,[3] Sandra Martinez-Martin,[2] Loika Maltais,[4] Mariano F. Zacarias-Fluck,[2] Silvia Casacuberta,[1] Erika Serrano del Pozo,[2] Christopher Fiore,[3] Laia Foradada,[1] Matthew Guenther,[3] Eduardo Romero Sanz,[5] Marta Oteo Vives,[5] Cynthia Tremblay,[4] Martin Montagne,[4] Miguel Ángel Morcillo Alonso,[5] Jonathan R. Whitfield,[2] Pierre Lavigne,[4] Laura Soucek[2]. *[1]Peptomyc S.L., Barcelona, Spain; [2]Vall d'Hebron Inst. of Oncology (VHIO), Barcelona, Spain; [3]Syros Pharmaceuticals, Cabridge, MA; [4]University of Sherbrooke, Quebec, Canada; [5]Centre de Investigaciones Energeticas, Medioambientes y Tecnologicas (CIEMAT), Madrid, Spain.*

Deregulation of the MYC oncoprotein promotes tumorigenesis in most, if not all, cancers and is often associated with poor prognosis. However, targeting MYC has long been considered impossible based on the assumption that it would cause catastrophic side effects in normal tissues. Despite this general preconceived notion, we showed that MYC inhibition exerts extraordinary therapeutic impact in various genetic mouse models of cancer, and causes only mild, well-tolerated and reversible side effects. For these studies we employed the systemic and conditional expression of a dominant negative of MYC, called Omomyc, which we designed and validated, and that can inhibit MYC transactivation function both in vitro and in vivo. To date, Omomyc has only been considered a proof of principle, with any potential clinical application limited to gene therapy. Here we actually show that the 11 kDa Omomyc polypeptide spontaneously transduces into cancer cells, demonstrating unexpected cell-penetrating ability. Once inside the nuclei, the polypeptide effectively blocks MYC binding to its target DNA sites, interfering with MYC transcriptional regulation and halting cell proliferation. Moreover, intranasal (i.n.) administration of the Omomyc polypeptide in mice results in its rapid and persistent distribution to lungs, as well as to other organs (i.e. intestine, liver, kidneys and brain). Importantly, i.n. treatment of mice bearing either Non-Small-Cell-Lung-Cancer (NSCLC) or glioblastoma (GBM) with the Omomyc cell-penetrating peptide ($Omomyc^{CPP}$) significantly reduces tumor burden compared to their control counterparts. Notably, tumor regression is accompanied by significant reprogramming of the tumor microenvironment and tumor immune response. In summary, our data indicate that this novel generation of polypeptides represents a new opportunity to potentially inhibit MYC pharmacologically in a variety of malignant diseases.