Thursday, 18 November 2010 08:00–09:45

PLENARY SESSION 4

Targeting checkpoints/DNA repair in cancer

242 INVITED

The concept of synthetic lethality

H. Calvert. *United Kingdom*

Abstract not received

243 INVITED

Targeting the Chk1/Cdc25A pathway in p53-deficient tumors

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Cancer cells frequently overproduce proteins that positively regulate the cell division cycle in order to maintain their proliferative capacity. The Cdc25A protein phosphatase is an example of a key cell cycle regulator that is overproduced in a wide variety of human cancers. Cdc25A drives the cell cycle forward by activating cyclin-dependent protein kinases. In addition to tightly controlling Cdc25A levels during a normal cell cycle, cells rapidly shunt Cdc25A for ubiquitin-mediated proteolysis when they are exposed to genotoxic stress. By eliminating Cdc25A, cells are able to temporarily arrest the cell division cycle to allow time for DNA repair. The Chk1 protein kinase targets Cdc25A for ubiquitin-mediated proteolysis during the S-and G2-phases of the cell division cycle. Importantly, p53-deficient cells are absolutely dependent on the integrity of this pathway to arrest cell cycle progression in response to DNA damage. This property makes the Chk/Cdc25A pathway a potential therapeutic target in p53$^-$deficient tumors. Results of a phase I clinical trial targeting the Chk1/Cdc25A pathway in resistant solid tumor malignancies will be described. In addition, a preclinical mouse model has been developed to evaluate combination therapies for treating p53$^-$deficient tumors. In this model, fresh tumor biopsies from breast cancer patients are engrafted into humanized mammary fat pads of immunodeficient mice. The initial xenograft tumor is transplanted into additional mice for experimental treatment and pathway studies that parallel our phase I studies. *TP53* is sequenced in each engrafted tumor explant and the integrity of the p53 pathway is determined by monitoring p53 stabilization and p21 induction following DNA damage. Three independent tumor explants, one wild-type and two mutant for *TP53* were analyzed for their response to irinotecan (to induce DNA damage) followed by Chk1 inhibition, with two independent Chk1 inhibitors. Results indicate that p53 status is a significant predictor of response to combination therapies involving DNA damage followed by Chk1 inhibition. Therefore, tumors lacking a functional p53 pathway may be effectively treated using this strategy.

244 INVITED

PARP inhibitors

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This session focuses on Poly(ADP-ribose) polymerase (PARP), which is an attractive antitumor target because of its vital role in DNA repair. The homologous recombination (HR) DNA repair pathway is critical for the repair of DNA double strand breaks and HR deficiency leads to a dependency on error-prone DNA repair mechanisms, with consequent genomic instability and oncogenesis. Tumor-specific HR defects may be exploited through a synthetic lethal approach for the application of anticancer therapeutics, including PARP inhibitors. This theory proposes that targeting genetically defective tumor cells with a specific molecular therapy that inhibits its synthetic lethal gene partner should result in selective tumor cell killing. The demonstration of single agent antitumor activity and the wide therapeutic index of PARP inhibitors in *BRCA1* and *BRCA2* mutation carriers with advanced cancers provide strong evidence for the clinical application of this approach. Emerging data also indicate that PARP inhibitors may be effective in sporadic cancers bearing HR defects, supporting a substantially wider role for PARP inhibitors. Drugs targeting this enzyme are now in pivotal clinical trials in patients with sporadic cancers. We review the evidence supporting this antitumor synthetic lethal strategy with PARP inhibitors, discuss evolving resistance mechanisms and potential molecular predictive biomarker assays and envision the future development of these agents.

245 INVITED

Targeting ATM and p53

M. Kastan[1], K. Guo[1], J. Chen[1], K. Guy[2]. *[1]St Jude Children's Research Hospital, Department of Oncology, Memphis, USA; [2]St Jude Children's Research Hospital, Department of Chemical Biology, Memphis, USA*

Significant progress has been made in recent years in elucidating the molecular controls of cellular responses to DNA damage in mammalian cells. Much of our understanding of the mechanisms involved in cellular DNA damage response pathways have come from studies of human cancer susceptibility syndromes that are altered in DNA damage responses. ATM, the gene mutated in the cancer-prone, radiosensitive disorder, Ataxia-telangiectasia, is a protein kinase that is a central mediator of responses to DNA double strand breaks in cells. Once activated, ATM phosphorylates numerous substrates in the cell that modulate the cell's response to the DNA damage. p53, one of the many targets of the ATM kinase, is a critical mediator of cell cycle changes and cell death signaling following DNA damage and other stresses. Mechanistic insights about these pathways provide us with opportunities to develop new approaches to target the pathway for patient benefit. Small molecule inhibitors of ATM lead to increased sensitivity to ionizing irradiation – I will discuss the development of ATM inhibitors as therapeutic enhancers in the treatment of malignancies. Conversely, inhibition of p53 induction has the potential to protect normal tissues from the ravages of chemotherapy and radiation therapy. Based on recent insights into a novel mechanism involved in regulation of p53 induction, new approaches to protecting normal tissues by blunting p53 induction will be discussed.

Thursday, 18 November 2010 10:15–12:00

PLENARY SESSION 5

New modalities of anticancer treatment

246 INVITED

New platforms of immunoconjugates

M. Sliwkowski. *USA*

Abstract not received

247 INVITED

Dual function BAFF receptor aptamers inhibit ligand induced proliferation and deliver siRNAs to NHL cells

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Non-Hodgkin's Lymphoma (NHL) killed 20,000 people in 2009 and 66,000 new cases were indentified. Currently patients suffering from NHL receive treatment in form of radio-, chemo-, or biological therapy. These interventions rarely cure and relapses within one year are all too common. Many types of NHL feature the constitutive expression of oncogenes such as transcription factors STAT3 or MYC, anti-apoptotic protein Bcl-2 or Cyclin family members such as Cyclin D1 (Monti et al. 2005; Shaffer et al. 2006). Over-expression of these genes causes not only uncontrolled cell proliferation and survival of malignant cells but it also provides protection against ionizing radiation and many commonly used chemotherapeutics (Domen et al. 1998; Makin and Hickman 2000). Hence, knockdown of these genes using RNA interference (RNAi) is a rationale strategy for therapeutic intervention.

We developed bifunctional siRNA duplexes that contain two fully target-complementary antisense strands. This technique can be used to down-regulate two critical B-cell lymphoma oncogenes simultaneously, promoting apoptosis or rendering lymphomas more susceptible to standard chemotherapy.

An algorithm predicts the sequence and efficiency of these bifunctional siRNAs. We tested the efficiency of bifunctional 27mer siRNAs against Cyclin E2, Cyclin D1, C-Myc, BCl2, Survivin, STAT3 and Syk in different combinations by qRT-PCR. We saw efficient target-gene down-regulation in HEK293, PC3 and HCT116 cells. CyclinE2/CyclinD1 bifunctional siRNA showed in all three cell lines approximately 60% down-regulation of both genes simultaneously as the algorithm predicted. No interferon response