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Abstracts

Speaker Abstracts for the 2nd International Meeting on Molecular Staging of Cancer, 22–26 June 2006, Heidelberg, Germany

S1. CELL SIGNALING BY RECEPTOR TYROSINE KINASES: FROM BASIC CONCEPTS TO CLINICAL APPLICATIONS

Joseph Schlessinger. *Yale University School of Medicine, Department of Pharmacology, P.O. Box 208066 New Haven, CT 06520, USA.*

Receptor tyrosine kinases (RTKs) comprise a large family of cell surface receptors that control many critical cellular processes. The intrinsic protein kinase activity of RTKs is stimulated following growth factor binding to the extracellular ligand-binding domain which stimulates receptor dimerization, tyrosine autophosphorylation and enhancement of enzymatic activity leading to the recruitment and activation of multiple intracellular signaling pathways. It is now well established that various human diseases and pathologies are caused by dysfunction in RTKs or in the intracellular signaling pathways that they activate. These include many cancers, developmental abnormalities, sever bone disorders, immune diseases, arteriosclerosis and angiogenesis among others.

We have used mass spectrometry and X-ray crystallography to demonstrate that tyrosine autophosphorylation of the catalytic tyrosine kinase domain of FGF-receptor-1 (FGFR1) is mediated by a sequential and precisely ordered reaction. We also demonstrate that the rate of catalysis of two FGFR substrates is enhanced by 50–100-fold following autophosphorylation of the first site in the activation loop while autophosphorylation of the second site in the activation loop results in 500–1000-fold increase in the rate of substrate phosphorylation. We propose that FGFR1 is activated by a two-step mechanism mediated by strictly ordered and regulated autophosphorylation suggesting that distinct phosphorylation states may provide both temporal and spatial resolution to receptor signaling. Genetic models in mice provide new opportunities for exploring and developing new treatments for diseases caused by dysfunctions in RTKs and in their intracellular signaling pathways. Inhibitors of tyrosine kinases have been successfully applied for the treatment of cancers driven by activated tyrosine kinases. Sutent/SU11248 is a new drug that blocks the actions of several tyrosine kinases including c-Kit, PDGFR and VEGFR. Sutent has been approved by the FDA for the treatment of gastrointestinal stromal tumors (GIST), Gleevec resistant GIST, advanced kidney cancers as well as other cancers. The approval marks the first time the FDA has approved a new oncology product for two indications simultaneously. Finally, a novel scaffold-based drug discovery approach will be described that enables the development of many new families of inhibitors for protein kinases and other enzymes that play a role in cell signaling.

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S2. Src-FROM ONCOGENE TO CLINICAL TARGET

Justin M. Summy, Michael J. Gray, Gary E. Gallick. *Department of Cancer Biology, University of Texas, M.D. Anderson Cancer Center, TX, United States.*

The protein tyrosine kinase, Src, is the founding member of a nine-gene family that regulates such diverse processes as proliferation, migration, invasion, cell survival and angiogenesis. Aberrantly high Src activity is seen in numerous human tumors, with increases in Src activity associated with progressive stages of disease and poor prognosis. In mouse models for several types of human tumors, we demonstrate that Src activation increases metastatic potential with limited effects on primary tumor growth. In these models, pharmacologic inhibitors of Src retard growth of large tumors and inhibit the development of metastases. Therefore, small molecule Src-selective inhibitors are now in clinical trial in advanced stages of a number of solid tumors. However, given its diverse modifications, Src itself may not represent the best marker for effectiveness of these therapeutic agents. Therefore, we have examined Src signaling pathways that promote tumor progression, with an emphasis on pro-angiogenic pathways. Src regulates expression of vascular endothelial growth factor (VEGF) by activating Akt, p38 and STAT3. In addition, Src regulates IL-8 expression in a pathway requiring

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p38 and STAT3 activation that is NFκB-independent. We demonstrate further that Src activation contributes to the expression of the transcriptional repressor, Id2 (Inhibitor of differentiation 2), expressed in pancreatic (and some other) tumor cells but not in normal adult cells. Expression of Id-2 is regulated transcriptionally by Hif-1α, and, in turn, Id-2 regulates Hif-1α stability, thereby contributing to increased expression of VEGF in tumor cells. These results suggest that Src activation deregulates multiple pro-angiogenic programs that may provide markers as well as targets for novel therapies.

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S3. AP-1-DEPENDENT GENE EXPRESSION DURING SKIN TUMOURIGENESIS

Peter Angel. *Deutsches Krebsforschungszentrum, Division Signal Transduction and Growth Control, Heidelberg, Germany.*

The transcription factor AP-1, which is composed of members of the Fos, Jun and ATF protein families participates in physiological and pathophysiological processes due to its central role as a cellular switch of genetic programs in response to extracellular signals. The distinct expression pattern of AP-1 subunits in the skin, the loss of chemically induced carcinogenesis in AP-1 compromised mice, and the large number of putative AP-1 target genes in epidermal cells, indicate that AP-1 members play a pivotal role in epidermal organisation, skin homeostasis and tumourigenesis. To define AP-1-dependent genetic programs associated with distinct stages of tumourigenesis in vivo we have combined the well-established chemically induced mouse model of epithelial skin tumours and comprehensive expression profiling. A series of novel tumour-associated genes could be identified including previously unrecognized molecules involved in protein trafficking and novel serine and aspartic proteases, which are expressed depending on the differentiation and progression state of the tumours. Moreover, four members of the S100 family of Ca^{2+} binding proteins, S100A3, A6 and A8, A9 were identified, which are differentially expressed in murine and human epithelial tumours of the skin and other organs. These molecules are part of a novel signalling pathway controlling AP-1 and NFκB-dependent genetic programs, which are likely to play an important role in tumour formation, progression and metastasis.

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S4. ENZASTAURIN – FROM BENCH TO BEDSIDE, AND BACK

Manfred Lehnert. *Eli Lilly and Company, Oncology Platform Team, Indianapolis, IN, USA.*

Enzastaurin is an oral serine-threonine kinase inhibitor of the PI3K signaling pathway and PKCβ. In preclinical in vitro and in vivo tumor models, enzastaurin promotes apoptosis, inhibits tumor cell proliferation and blocks tumor-induced angiogenesis. Phase II studies showed encouraging efficacy in heavily pretreated patients with glioblastoma multiforme and diffuse large B cell lymphomas, respectively. Prospective randomized phase III trials are about to commence in these two tumor types. Phase II trials are in progress or development in a variety of cancers, including breast, ovarian, colon, prostate, non-small cell lung cancer, chronic lymphocytic leukemia and follicular lymphomas. The available safety data show good tolerance of enzastaurin when used as a single agent. Phase I studies in combination with various cancer agents, cytotoxic as well as biologically targeted, are in progress. Most enzastaurin trials include tumor tissue collection for correlative analysis of candidate biomarkers and clinical outcome. We hope this will allow selection of those cancer patients in the future who gain most benefit from enzastaurin treatment.

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S5. SURVIVING AND TRANSFORMING GROWTH FACTOR BETA (TGF-β) AS DRUG TARGETS IN CANCER

Michael Lahn. *Oncology Therapeutic Area, Lilly Research Laboratories, Indianapolis, IN, USA.*

The molecular heterogeneity of malignant cells and their interaction with the surrounding microenvironment is one of the most challenging aspects of drug development in oncology. Developing successful drug intervention strategies requires the identification of molecular targets that show high impact on either tumor cell growth or the supporting microenvironment. In recent years, several such targets have been proposed, including Survivin and TGF-β. Survivin is uniquely upregulated in most cancer cells, while in non-malignant cells it is generally not expressed. Thus, an inhibition of Survivin could lead to a selective treatment of malignant cells without affecting normal tissue cells. Because of its structure, selective small molecule inhibitors are difficult to identify.

In collaboration with Isis Pharmaceuticals (Carlsbad, CA, USA) Eli Lilly and Company (Indianapolis, IN, USA) (Lilly) developed a second generation antisense oligonucleotide (ASO) that is specific for the inhibition of Survivin in cells. This ASO against Survivin has been evaluated in various non-clinical in vitro and in vivo models confirming its specificity. Based on this information, a phase I clinical trial was started to evaluate its safety and pharmacokinetic profile in cancer patients. In contrast to a target in cancer cells, inhibiting TGF-β signaling is designed to modulate the microenvironment of cancer cells. Lilly developed various small molecule inhibitors for the TGF-β receptor type I (TGF-βRI) kinase. From this series of molecules, one inhibitor has been selected for clinical investigation. The compound LY2157299 has demonstrated anti-tumor activity in various non-clinical in vitro and in vivo models, supporting its evaluation in a phase I clinical trial of patients with cancer. In summary, Lilly has a comprehensive program to develop inhibitors of tumor cells and their supporting microenvironment, such as Survivin and TGF-β.

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