



SMARTANALYST
INTELLIGENT INSIGHTS. SMART RESULTS.

ONCOLOGY

Newsletter

Bimonthly Oncology News Update

www.smartanalyst.com

Volume 1, Issue 2

January 15, 2008

In This Issue.....

Clinical Development Pg-2

- ASCO/ASH Guidelines for ESAs
- Phase I/II Results of Amplimexon(R) in Melanoma
- Phase 2 Study of Zybrestat (TM) in Ovarian Cancer



Research Highlights Pg-2

- FAK Targeting Ovarian Cancer
- Targeting MET in Gefitinib or Erlotinib Resistant Lung Cancer
- 14-3-3 ζ Is Critical for Lung Cancer Cells
- Tamoxifen-Stimulated Growth of Breast Cancer Due to P21 Loss



Biomarkers Pg-3

- High-Resolution Mapping of DNA in Lung Cancer
- A Biomarker for CNS Lymphoma
- Micro RNA Signature as a Predictor in Lung Cancer



Regulatory Focus Pg-3

- Fast-Track Designation for CDX-110
- Xanthus Receives Orphan Drug Designation for Oral Fludarabine
- Millennium Submits NDA for Velcade (R) (bortezomib)
- Introgen plans to file BLA and MAA for Advexin in Advanced Head and Neck Cancer



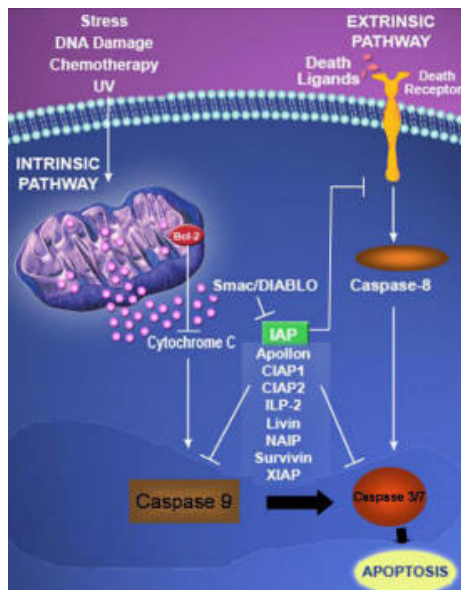
Business News Pg-4

- Galapagos Enters Into Oncology Target Discovery Collaboration with Janssen Pharmaceuticals
- Immunogen, Inc. Expands Pipeline of Targeted Anticancer Compounds
- Oxford Genome Sciences and Amgen to Discover Novel Therapeutic Antibodies in Cancer



SMACKing Cancer Cells

Cancer cells have developed mechanisms to evade cell death by suppressing apoptotic pathways. One such mechanism is by over expression of anti-apoptotic genes such as members of the inhibitors of apoptosis (IAP) family. SMAC (second mitochondria-derived activator of caspase), an endogenous inhibitor of IAPs is released from mitochondria during apoptosis. Inhibiting IAPs through small molecule mimetics of endogenous inhibitors of IAPs is an attractive approach to unleash cell death in cancer cells.



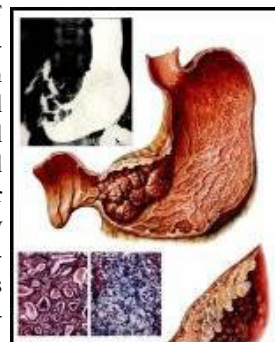
Small molecule mimetics of SMAC were designed by three groups independently, on the basis of crystal structure of SMAC bound with a domain of x-linked IAP. These mimetics, as expected, induced apoptosis in several cancer cell lines even when used alone. Studies from these three investigators have now shown that SMAC mimetics induce cell death by promoting degradation of IAPs, which culminates in TNF- α mediated cell death.

Tumor cells that did not secrete TNF α were sensitive to a combination of both the SMAC mimetic and exogenous TNF α . Reporting in Cancer Cell, Xiaodang Wang and colleagues showed that SMAC mimetic, as a single agent, induced regression of sensitive human lung cancer xenografts, with 40% of treated animals remaining free of tumors without any signs of toxicity. These studies hold promise that SMAC mimetics are attractive candidates for novel anticancer strategies.

Source: *Cancer Cell* 12,2007; *Cell* 2007; *Cell* 131, 2007

Capecitabine and Oxaliplatin for Esophagogastric Cancer

Gastric and Esophageal cancers are currently treated with a regimen containing epirubicin, cisplatin and fluorouracil (ECF). The fluorouracil in ECF regimen is continuously infused which is inconvenient and can be associated with infection and thrombosis. Cancer patients generally prefer oral alternatives to intravenous therapy. Capecitabine is an established oral alternative to fluorouracil. In a report published in New England Journal of Medicine, Cunningham and colleagues described a randomized phase III study of triplet cytotoxic therapy for advanced esophagogastric cancer, which showed that oral capecitabine is at least as effective as infused fluorouracil and that oxaliplatin (which does not require hydration) is as effective as cisplatin with respect to overall survival.



Source: *NEJM*

Human Genome Sciences and Aegera Therapeutics announce licensing and collaboration agreement on novel anti-cancer drugs

Human Genome Sciences, Inc. and Aegera Therapeutics Inc. announced an agreement under which HGS has acquired exclusive worldwide rights (excluding Japan) to develop and commercialize AEG40826, a potent small-molecule inhibitor of multiple IAP (inhibitor of apoptosis) protein family members.

...more on Pg-5

Pharmacyclics receives Non-Approvable letter from the FDA for Xcytrin for the treatment of Lung cancer with brain metastases

Pharmacyclics, Inc. announced that it has received a non-approvable letter from the U.S. FDA for the company's NDA(filed in April 2007) for Xcytrin® (motexafin gadolinium) injection for the treatment of non-small cell lung cancer (NSCLC) patients with brain metastases.

...more on Pg-3

Clinical Development

ASCO/ASH Guidelines for Clinical Use of Erythropoiesis-Stimulating Agents

Guidelines on the use of Epoetin and Darbepoetin were published in the recent issue of *Journal of Clinical Oncology*, after a committee reviewed and analyzed the data published since 2002 through 2007 on the thromboembolic risks associated with these agents. For patients with chemotherapy-associated anemia or ones with low risk myelodysplasia, use of erythropoiesis stimulating agents (ESA) is recommended, as hemoglobin level approaches or falls below 10 g/dL. Continuing beyond 6 to 8 weeks in the absence of response is not recommended as there was no evidence for beneficial effect. The committee also cautioned against ESA use in cancer patients who are not receiving chemotherapy, due to increased thromboembolic risks and decreased survival.

Source: [JCO](#)

Promising 1-Year Survival Data from Phase I/II Study of Amplimexon(R) In Metastatic Malignant Melanoma

AmpliMed reported one year survival results from a Phase I/II trial of its lead drug candidate, Amplimexon(R) (imexon for injection) in combination with dacarbazine in patients with unresectable stage III or stage IV metastatic malignant melanoma. Amplimexon is a small molecule drug that increases oxidative stress in tumor cells leading to mitochondrial damage and apoptosis. A total of 68 patients were enrolled at 13 U.S. centers in the Phase I and Phase II of the study. The drug combination of Amplimexon and dacarbazine was well tolerated, with only 10.8 % of patients showing myelosuppression and only 7 patients having serious adverse events. The median overall survival of all patients was 11.7 months compared to approximately 8 months for dacarbazine treated historical controls. Metastatic melanoma is the most deadly form of skin cancer, afflicting approximately 8,000 patients annually in the U.S.

Source: [PR Newswire](#)

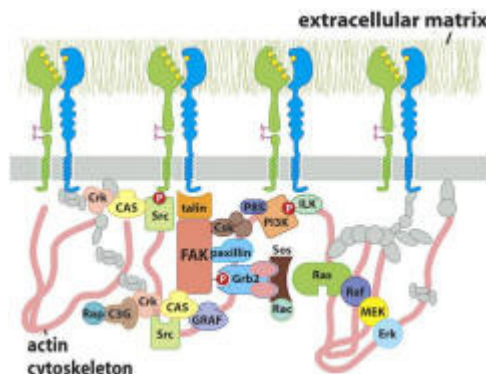
Oxigene Reports Positive Results in Phase 2 Study of Zybrestat(TM) in Platinum-Resistant Ovarian Cancer

Oxigene, announced that its lead product candidate, Zybrestat(TM) (combretastatin-A4 phosphate / CA4P), has achieved the pre-specified primary efficacy endpoint for Stage 1 of an ongoing Phase 2 ovarian cancer clinical trial. The trial utilizes an open-label, Simon two-stage design to evaluate the combination of Zybrestat, carboplatin and paclitaxel in patients with advanced, platinum-resistant ovarian cancer, a refractory form of ovarian cancer for which therapeutic options are limited. Response was determined based upon tumor imaging (Recist) and/or ovarian cancer response biomarker (CA-125) criteria. 18 patients were treated with the Zybrestat-chemotherapy combination. In addition to the three patients with confirmed partial responses, stable disease was observed in seven of the first 11 evaluable subjects in the clinical trial. The combination regimen appeared to be well-tolerated, with no observations of colon perforations that had been reported previously with anti-VEGF therapy in this patient population. Zybrestat(TM) is currently being evaluated in a pivotal registration study in anaplastic thyroid cancer (ATC). Through interaction with vascular endothelial cell cytoskeletal proteins, Zybrestat selectively targets and collapses tumor vasculature, thereby depriving the tumor of oxygen and causing death of tumor cells.

Source: [Oxigene](#)

Research Highlights

A Novel Tyrosine Kinase Target for Ovarian Cancer



The focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that localizes to the

points of cell contact with the extracellular matrix, called focal adhesions. FAK expression was shown to be elevated in a number of human cancers and increased FAK expression and activity are correlated with malignant phenotype and poor prognosis in patients. In a study published in *Cancer Research*, Anil Sood and colleagues demonstrated that a small molecule FAK inhibitor, TAE226 is effective in ovarian cancer mouse models, even those that are resistant to docetaxel. However, the greatest efficacy was observed with concomitant administration of TAE226 and docetaxel (85–97% reduction, all *P* values <0.01). In addition, TAE226 alone and in combination with chemotherapy significantly prolonged survival in tumor-bearing mice. Even in larger tumors, combination therapy with TAE226 and docetaxel resulted in tumor regression. These studies suggest that FAK is an attractive therapeutic target in ovarian cancer.

Source: [Cancer Research](#)

Targeting Met Tyrosine Kinase in Lung Cancers With Acquired Resistance to Gefitinib or Erlotinib

Somatic mutations in exons encoding the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) are found in a proportion of lung adenocarcinomas. Mutations that substitute methionine for threonine at position 790 in the EGFR kinase domain have been found in 50% of lung adenocarcinomas from patients with acquired resistance to the EGFR inhibitors, gefitinib and erlotinib. Using array-based comparative genomic hybridization of EGFR mutant tumor samples before and after treatment, James Bean, and colleagues observed MET proto-oncogene amplification in a significant number of samples. *In vitro* data demonstrated that the MET inhibitor, XL880, is more effective at inhibiting the viability of lung adenocarcinoma cells with EGFR T790M and MET amplification than either reversible (erlotinib) or irreversible (CL-387,785) EGFR inhibitors. These findings suggest that compounds like XL880 could play a significant role in the treatment of patients whose EGFR mutant lung adenocarcinomas have developed acquired resistance to existing EGFR inhibitors as a result of MET gene amplification.

Source: [PNAS](#)

14-3-3 ζ is Critical for Anchorage-Independent Growth of Lung Cancer Cells

The family of 14-3-3 proteins has emerged as critical regulators of diverse cellular responses under both physiological and pathological conditions. 14-3-3 family of proteins control diverse cellular responses through regulated interactions with key signaling molecules. Unlike normal cells, which are anchorage dependent and activate a process of cell death known as anoikis after loss of adhesion to extracellular matrix, cancer cells have developed mechanisms to gain resistance to anoikis. 14-3-3 ζ plays an important role in tumorigenesis through a mechanism by which cancer cells gain resistance to anoikis. In a study published in PNAS, Li and colleagues demonstrated that knockdown (KD) of a single ζ isoform of 14-3-3 is sufficient to impair the anchorage independent growth of A549 cells and restore their sensitivity to anoikis. This study demonstrates a critical role of 14-3-3 ζ in suppression of anoikis in lung cancer cells and, importantly, identifies a novel target for anticancer therapeutic intervention.

Source: [PNAS](#)

Tamoxifen-Stimulated Growth of Breast Cancer Due to p21 Loss

Tamoxifen is widely used for the treatment of hormonally responsive breast cancers. However, some resistant breast cancers develop a growth proliferative response to this drug, as evidenced by tumor regression upon its withdrawal. To elucidate the molecular mediators of this paradox, tissue samples from a patient with tamoxifen-stimulated breast cancer were analyzed. Results demonstrated that loss of CDK inhibition mediated by p21 leads to hyperphosphorylation of ER at serine 118, which in turn leads to the increased expression of known ER-regulated genes. Furthermore, mutation of ER serine 118 to alanine abrogates the tamoxifen growth-stimulatory phenotype. Finally, a tamoxifen-resistant clone derived from the ER positive breast cancer cell line MCF-7 demonstrated a similar ER serine 118 hyperphosphorylation upon tamoxifen exposure. This study demonstrates how loss of p21 function can lead to aberrant ER phosphorylation resulting in an estrogenic growth response to tamoxifen. Therefore, the development of therapies directed against phosphorylated ER

may prove beneficial in the prevention and treatment of tamoxifen resistance.

Source: [PNAS](#)

Biomarkers

High-Resolution Mapping of DNA Hypermethylation and Hypomethylation in Lung Cancer

Changes in DNA methylation patterns are an important characteristic of human cancer. Tumors have reduced levels of genomic DNA methylation and contain hypermethylated CpG islands. Methylated CpG island recovery assay-assisted high-resolution genomic tiling and CpG island arrays were used to analyze methylation patterns in lung squamous cell carcinomas and matched normal lung tissue. Each tumor contained several hundred hypermethylated CpG islands. It was found that the CpG islands of the *OTX1*, *PAX6*, *IRX2*, *OC2*, *TFAP2A*, and *EVX2* genes are tumor-specifically methylated with very little methylation found in normal lung tissue or in blood DNA. Methylation of the *OTX1*, *IRX2*, *OC2*, and *EVX2* genes has not yet been reported in human cancers. Importantly, the methylation frequency of these markers is much higher than methylation frequencies of other lung cancer DNA methylation markers reported previously. Such markers are excellent candidates for clinical or diagnostic applications aimed at either detection of early disease in body fluids such as blood or sputum or at disease management and follow-up by using molecular diagnostic testing.

Source: [PNAS](#)

A Biomarker for CNS Lymphoma

Roy and colleagues used liquid chromatography/mass spectrometry methods to quantify and identify several CSF proteins in CNS lymphoma patients and control patients. From a group of 80 identified proteins, they focused on the expression of one candidate biomarker, antithrombin III (ATIII). Measurement of CSF ATIII level by ELISA method was found to potentially enhance the ability to diagnose and predict outcome in CNS lymphoma patients.

Source: [JCO](#)

Micro RNA Signature as a Predictor of Survival and Relapse in Lung Cancer

Micro RNAs are a class of small non-protein coding RNAs that can post-transcriptionally regulate the expression of several target genes, thereby controlling a wide range of biological functions. Lung cancer is the most common cause of cancer deaths worldwide. Current pathological staging method has limited success in predicting patient survival. In a study published in Cancer Cell, micro RNA expression profiles were investigated, using real-time PCR method, in 112 non small cell lung cancer (NSCL) patients. A micro RNA signature was identified for predicting treatment outcome of patients from 56 patients and validated by testing on the other 56 patients. An independent cohort of 62 patients from a different hospital was used to reconfirm the effectiveness of this signature. Patients with high-risk scores in their micro RNA signatures had poor overall survival compared to the low risk patients. This micro RNA signature can serve as an independent predictor of the cancer relapse and survival of NSCLC patients. This may also have therapeutic implications for the management of NSCLC patients.

Source: [Cancer Cell](#)

Regulatory Focus

Pharmacyclics Receives Non-Approvable Letter from the FDA for Xcytrin for the Treatment of Lung Cancer with Brain Metastases

Contd. from Pg 1

"We are disappointed that brain metastases patients with limited options and serious neurologic problems will not have access to Xcytrin, which we believe has shown important clinical activity in this indication," said Richard A. Miller, M.D., president and CEO of Pharmacyclics. Xcytrin's novel mechanism enables it to selectively concentrate in tumors and induce apoptosis. Its multifunctional mode of action, including its magnetic resonance imaging detectability and its non-overlapping toxicity, make Xcytrin an appealing agent to use in combination with standard chemotherapy regimens, potentially across a broad range of cancers.

Source: [Pharmacyclics](#)

Celldex Therapeutics Receives Fast-Track Designation for CDX-110, a Novel EGFRvIII Vaccine for Glioblastoma

Celldex Therapeutics announced that the FDA has granted Fast Track designation to CDX-110 for the treatment of EGFRvIII expressing Glioblastoma Multiforme (GBM). GBM is the most common and aggressive form of primary brain cancer and carries a very poor prognosis with current therapy.

CDX-110 is an immunotherapy that targets the tumor-specific growth promoter EGFRvIII that can be expressed by GBM. In the ACTIVATE Phase 2a study, GBM patients treated with CDX-110 showed more than a 100% increase in survival, compared to historical control's. Preliminary progression free survival (PFS) and overall survival (OS) data, in an extension study, ACT II, which combines CDX-110 with chemotherapy in a similar patient population, suggest that chemotherapy and CDX-110 can be administered concurrently while still maintaining strong immune responses. Fast Track status acknowledges CDX-110's potential to fill an unmet need for glioblastoma patients and gives it priority within the FDA," said Thomas Davis, M.D., Chief Medical Officer of Celldex Therapeutics.

Source: [PR Newswire](#)

Xanthus Receives Orphan Drug Designation for Oral Fludarabine for the Treatment of CLL

Xanthus Pharmaceuticals, Inc., a privately-held oncology and autoimmune disease drug development company, announced that the FDA has granted Orphan Drug Designation to fludarabine phosphate oral tablets for the treatment of B-cell CLL. Xanthus licensed the exclusive right to develop and commercialize oral fludarabine in the US from Schering AG (now Bayer Schering Pharma AG) in October 2006.

"With the convenience of oral dosing and a strong body of clinical efficacy and tolerability data already behind it, we believe oral fludarabine represents an exciting opportunity for Xanthus." said Richard Dean, Ph.D., CEO of Xanthus. According to the American Cancer Society, approximately 15,300 new CLL cases were diagnosed in the US in 2007. Oral fludarabine is currently marketed by Bayer Schering Pharma AG in

the European Union and Canada for the treatment of relapsed B-cell CLL. Intravenous (IV) fludarabine has been widely available for a number of years in the US and other countries as a treatment for patients with CLL.

Source: [Xanthus](#)

Millennium Submits NDA for VELCADE(R) (Bortezomib) for Injection for the Treatment of Front-Line Multiple Myeloma

Millennium Pharmaceuticals, Inc. (Nasdaq: MLNM) announced the submission of a supplemental new drug application (sNDA) with the U.S. FDA for Velcade in the treatment of patients with previously untreated multiple myeloma (MM) as on December 21st, 2007. The filing is based on data from the 682 patient Phase III VISTA(1) trial, one of the largest, international, randomized clinical trials for patients in this treatment setting. Janssen-Cilag International NV also submitted a Marketing Authorization Application to the European Medicines Evaluations Agency. The VISTA trial compared Velcade, melphalan and prednisone (VcMP) to the standard regimen of melphalan and prednisone (MP) alone. For the VcMP treatment, there was a statistically significant improvement in all efficacy endpoints, including complete remission (CR) rates, time-to-disease progression (TTP) and survival. Velcade is being co-developed by Millennium Pharmaceuticals, Inc. and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Source: [Millennium](#)

Introgen Plans to File BLA and MAA for Advexin in Advanced Head and Neck cancer in First Half of 2008

Introgen Therapeutics, Inc. expects to announce top-line Phase 3 data and submit its Biologics Licensing Application (BLA) and Marketing Authorization Application (MAA) for Advexin for head and neck cancer in the first half of 2008. The Company will include additional patient tissue samples from its Phase 3 trials for p53 biomarker analyses to predict Advexin efficacy to strengthen its U.S. and European regulatory filings.

The Company's MAA for Advexin for the potential treatment of Li-Fraumeni Syndrome, a genetically inherited cancer, was accepted for filing by the European Medicines Agency (EMA) in Nov. 2007 under the EMA's Exceptional Circumstances rules. Advexin is a targeted molecular therapy with the potential to be broadly applicable across a wide range of tumor types and clinical settings because it targets one of the most fundamental and common molecular defects, abnormal or blocked p53 tumor suppressor function, associated with cancer initiation, progression and treatment resistance. Advexin has demonstrated increased survival and tumor growth control in recurrent head and neck cancer.

Source: [Introgen](#)

Business News

Galapagos Enters Into Oncology Target Discovery Collaboration with Janssen Pharmaceutica

Galapagos NV announced two-year target discovery collaboration between Janssen Pharmaceuticals and BioFocus DPI, (service division of Galapagos) in the field of oncology. BioFocus DPI will apply Galapagos' proprietary adenoviral platform to identify novel drug targets for the development of cancer therapies.

Target discovery in cutting edge in vitro assays may provide novel drug targets for cancer areas with an unmet medical need. BioFocus DPI received an upfront payment of €2.9 million. In total, BioFocus DPI may receive additional research, acceptance, license and development fees of up to €7.6 million should certain predetermined criteria be achieved. "This marks BioFocus DPI's first target discovery agreement in oncology, as well as the largest target discovery agreement to date for the service division," said Onno van de Stolpe, Chief Executive Officer of Galapagos.

Source: [Galapagos](#)

ImmunoGen, Inc. Expands Pipeline of Targeted Anticancer Compounds

ImmunoGen, Inc. a biopharmaceutical company that develops targeted anticancer

therapeutics using its Tumor-Activated Prodrug (TAP) technology, announced that it has licensed the exclusive right to develop and commercialize a TAP compound to a novel target using an antibody created by Centocor. Under the terms of the agreement, ImmunoGen gains the exclusive right to develop and commercialize a TAP compound that consists of an integrin-targeting antibody developed by Centocor and ImmunoGen's maytansinoid TAP technology. ImmunoGen expects to file an Investigational New Drug (IND) application for this TAP compound, IMG388, in the second quarter of 2008. Both companies would contribute to the costs of developing the compound. The two companies would share equally any profits on the sales of the compound in the USA, and ImmunoGen would receive royalties on any international sales.

Source: [ImmunoGen](#)

Oxford Genome Sciences and Amgen to Jointly Discover Novel Therapeutic Antibodies in Cancer

Oxford Genome Sciences announced a collaborative agreement with Amgen to develop fully human monoclonal antibodies for the treatment of cancer. The collaboration will generate antibodies using Amgen's XenoMouse technology, against targets identified by Oxford Genome Sciences through its Oxford Genome Anatomy Project (OGAP) database.

The agreement covers up to six oncology programs. Amgen has the right to select up to three programs and Oxford Genome Sciences retains rights to the remaining programs. No financial details of the agreement were disclosed.

Source: [Oxford Genome Sciences](#)

Human Genome Sciences and Aegera Therapeutics announce licensing and collaboration agreement on novel anti-cancer drugs

Contd. from Pg 1

Under the agreement, HGS has paid Aegera an upfront license fee of \$15 million and has made an equity investment of C\$5 million. Aegera will be entitled to receive up to \$295 million in future development and commercial milestone payments, including a \$5 million milestone payment upon FDA clearance of an IND. "Our company has pioneered development of antibody therapies based on the TRAIL receptor apoptotic pathway, and we will now have the opportunity to develop and commercialize exciting small-molecule drugs that also enhance apoptosis in cancer cells," said H. Thomas Watkins, President and CEO, HGS.

Source: [HGS](#)

Editorial Team: Dr. Chandra Kumar, Ms. Meenu Grover, Dr. Anuradha Dhingra
Analysts: Ms. Bhawani Bhatnagar, Dr. Neetu Singhal