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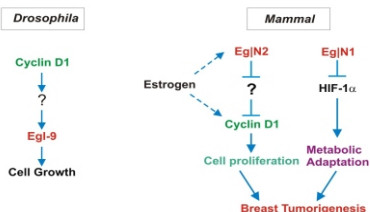
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INTELLIGENT INSIGHTS. SMART RESULT

Links between EglNs and Cyclin D1 in Drosophila and Mammals



Cancer Cell, 16, Nov 2009

In the Spotlight:

Control of Cyclin D1 and Breast Tumorigenesis by the EglN2 Prolyl Hydroxylase

Most successful drugs are small organic molecules that inhibit specific cellular proteins, especially enzymes. Establishing additional classes of enzymes that can be manipulated with small organic molecules opens new avenues... [Read more](#)



Business News

Astellas and Medivation to Co-Develop and Co-Commercialize MDV3100

Micromet and Sanofi-aventis Sign Collaboration Agreement for BiTE Antibody

SuperGen and GSK to Collaborate on Novel Epigenetic Therapeutics

Spectrum and Nippon Kayaku Enter Collaboration Agreement for Apaziquone

Quintiles Announces Strategic Alliance to Advance Eisai's Oncology Pipeline

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Research Highlights

Polyhomeotic has a Tumor Suppressor Activity Mediated by Repression of Notch Signaling

Requirement for NF-κB Signaling in a Mouse Model of Lung Adenocarcinoma

Smoothed Drug Resistance to a Hedgehog Inhibitor in Medulloblastoma

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Clinical Development

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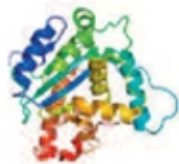
New Phase II Data for XL184 in Patients with GBM

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Biomarkers

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Regulatory

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Antigenics Announces a Negative Vote from the CHMP on Oncophage

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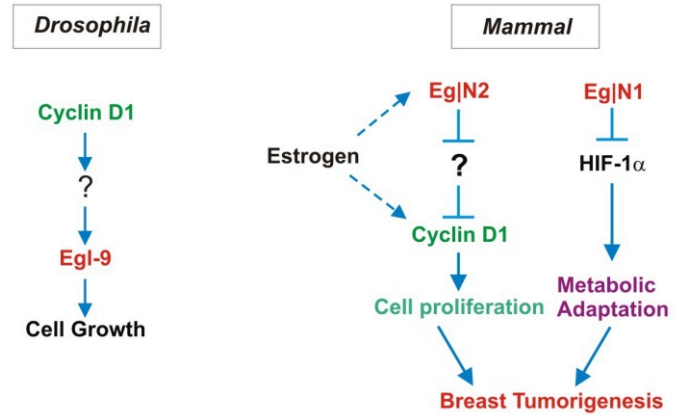
The E-newsletter team: Dr. Anuradha Dhingra, Ms.Meenu Grover, Ms. Sarika Manchanda. Copyright©2009 SMARTANALYST INDIA PVT LTD,



Spotlight Report

Most successful drugs are small organic molecules that inhibit specific cellular proteins, especially enzymes. Establishing additional classes of enzymes that can be manipulated with small organic molecules opens new avenues for drug discovery. EglN prolyl hydroxylases, members of the 2-oxoglutarate and iron-dependent dioxygenase superfamily, that regulate hypoxia inducible factor 1 α (HIF-1 α), can be inhibited with drug-like molecules. HIF-1 α is a ubiquitous transcription factor mediating cellular genomic responses to hypoxia. The Cyclin D1 protein is an important regulator of cell division and plays an important role in many cancers, including breast cancer. The Cyclin D1 gene is frequently amplified in breast cancer and induced by estrogen, and its loss of function results in delayed mammary tumorigenesis in the mouse.

Links between EglNs and Cyclin D1 in Drosophila and Mammals



Cancer Cell, 16, Nov 2009

Zhang *et al.* in recent issue of *Cancer Cell* have documented that EglN2 activity positively influences the level of Cyclin D1, independent of HIF. EglN2 is estrogen inducible in breast carcinoma cells and interacts genetically with Cyclin D1. Although EglN2 is a nonessential gene, the authors found that EglN2 inactivation decreases Cyclin D1 levels in cancer cells and suppresses mammary gland proliferation *in vivo*. Regulation of Cyclin D1 is a specific attribute of EglN2 among the EglN proteins and is HIF independent. Loss of EglN2 catalytic activity inhibits estrogen-dependent breast cancer tumorigenesis and can be rescued by exogenous Cyclin D1. EglN2 depletion also impairs the fitness of lung, brain, and hematopoietic cancer lines. This relationship between EglN2 and Cyclin D1 might be especially relevant in hormone-sensitive breast cancer, in which new therapies are needed for women who become refractory to estrogen antagonists. EglN2 appears to be an attractive drug target because EglN2 is not essential in mammals and it has already been established that enzymes of this class can be inhibited with drug-like small organic molecules. These findings support the exploration of EglN2 inhibitors as therapeutics for estrogen-dependent breast cancer and other malignancies.

Source: *Cancer Cell*



Business News

Astellas and Medivation to Co-Develop and Co-Commercialize MDV3100

Astellas Pharma and Medivation announced that they have entered into a global agreement to develop and commercialize MDV3100, Medivation's investigational drug for the treatment of prostate cancer. MDV3100, a new generation of oral anti-androgen, is currently being evaluated in the Phase III AFFIRM clinical trial in men with castration-resistant prostate cancer, who were previously treated with docetaxel-based chemotherapy.

Under the terms of the agreement, Medivation will receive an up-front cash payment of \$110 million. Medivation is also eligible to receive payments of up to \$335 million upon the attainment of development and regulatory milestones plus up to an additional \$320 million in commercial milestone payments. The companies will collaborate on a comprehensive development program that will include additional studies to develop MDV3100 for both late- and early-stage prostate cancer. Subject to receipt of regulatory approval, the companies will jointly commercialize MDV3100 in the US, Astellas will have responsibility for developing and commercializing MDV3100 outside the US and will pay Medivation tiered double-digit royalties on ex-US sales.

Source: Astellas

Micromet and Sanofi-aventis Sign Global Collaboration Agreement for BiTE Antibody

Micromet and Sanofi-aventis announced a global collaboration and license agreement to develop a BiTE antibody against an antigen present at the surface of carcinoma cells. BiTE antibodies are designed to direct the body's cytotoxic, or cell-destroying, T cells against tumor cells, and represent a new therapeutic approach to cancer therapy. Under this agreement, Micromet will be responsible for the discovery, research and development of the BiTE antibody through the completion of Phase 1 clinical trials under the supervision of a Joint Steering Committee. Sanofi-aventis will then have full responsibility for further development, as well as for the worldwide commercialization of the BiTE antibody.

Under the terms of the agreement, Sanofi-aventis agreed to pay Micromet an up-front cash payment of €8 million following signing of the agreement. Micromet is eligible for development and regulatory milestone payments of up to €162 million, plus performance-based sales milestones of up to €150 million euros and royalties on worldwide product sales.

Source: Micromet

SuperGen and GSK to Collaborate on Novel Epigenetic Therapeutics

SuperGen and GlaxoSmithKline (GSK) have entered into a multi-year collaboration to discover and develop cancer therapeutics based on epigenetic targets. Epigenetics refers to the regulation of genes with mechanisms other than changes to the underlying DNA sequence. Epigenetic processes are widely believed to play a central role in the development and progression of almost all cancers.

Under the terms of the deal, SuperGen will progress candidate compounds through to early clinical proof of concept. GSK will then have the right to exercise an option to develop further and commercialize resulting products on a global basis. In connection with the transaction, SuperGen will receive \$5 million up-front, inclusive of a \$3 million common stock investment, priced at a premium to market. Total potential development and commercialization milestones payable to SuperGen could exceed \$375 million, in addition to the potential for tiered royalties into double-digit magnitudes, payable on net sales of any resulting products.

Source: SuperGen



Business News (Cont'd)

Spectrum and Nippon Kayaku Enter Collaboration Agreement for Apaziquone

Spectrum Pharmaceuticals and Nippon Kayaku announced an exclusive collaboration for the development and commercialization of apaziquone in Asia. Apaziquone, an antineoplastic agent, is being investigated for the treatment of non-muscle invasive bladder cancer by intravesical instillation. Spectrum Pharmaceuticals has previously entered into a strategic collaboration with Allergan for North America, Europe, and other key markets. These two collaborations are representative of the company's stated objective of achieving solid strategic partnerships that are aimed at fully exploiting developmental goals for apaziquone on a worldwide basis.

Under the terms of the agreement, Nippon Kayaku will pay Spectrum an up-front payment of \$15 million and will make additional payments of up to \$136 million based on the achievement of certain regulatory and commercialization milestones. Nippon Kayaku received exclusive rights to apaziquone for the treatment of non-muscle invasive bladder cancer in Asia, including Japan and China. Nippon Kayaku will conduct the apaziquone clinical trials pursuant to a development plan. Nippon Kayaku will be responsible for all expenses related to the development and commercialization of apaziquone in the Nippon Kayaku territory. Spectrum is currently conducting two Phase III trials to investigate apaziquone's safety and efficacy in non-muscle invasive bladder cancer.

Source: Spectrum Pharmaceuticals

Quintiles Announces Strategic Alliance to Advance Eisai's Oncology Pipeline

Quintiles announced a strategic alliance with Eisai to develop 6 potential oncology products in Eisai's R&D pipeline. Under the terms of the agreement, Quintiles' oncology experts will conduct Phase II proof-of-concept studies for 11 solid tumor indications. A key goal of the alliance is to determine the efficacy of the products in the shortest possible time in order to bring therapies to market faster for the benefit of cancer patients worldwide.

The strategic alliance will be structured on a risk-sharing basis, with Quintiles funding, in part, the design and conduct of the clinical studies in exchange for success milestone payments. The agreement is designed to enable Eisai to extend its oncology program, increasing the number of indications investigated for the 6 potential products, including eribulin (E7389), E7080, Ontak (denileukin diftitox), E7820, E6201 and E7050. These assets will remain the property of Eisai, with Quintiles having development accountability through the Phase II proof-of-concept stage. In addition to projects covered under the agreement with Quintiles, Eisai will continue ongoing development of 18 additional indications for the same 6 compounds.

Source: Quintiles



Research Highlight

Polyhomeotic has a Tumor Suppressor Activity Mediated by Repression of Notch Signaling

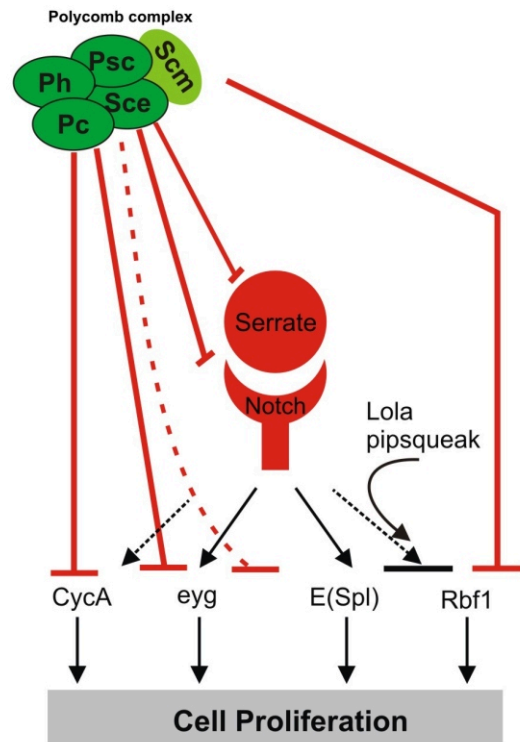
Coordination between cellular proliferation and differentiation controls and maintains homeostasis in multicellular organisms. Appropriate numbers of undifferentiated cells must be generated at specific developmental stages and these cells must exit the cell cycle in a tightly regulated manner to ensure proper cell fate specification and pattern formation. Polycomb group (PcG) proteins silence critical differentiation genes during development, modulate cell proliferation, and are thought to have a primarily oncogenic role in human cancer.

However, a recent study by Martinez *et al.* in *Nature Genetics*, using the *Drosophila melanogaster* eye as a model system, shows that PcG proteins can also function as tumor suppressors by repressing key oncogenic signaling pathways. The authors demonstrate that cells with mutations in the gene locus (*ph*) that encodes the PcG protein Polyhomeotic (PH) over proliferate and lose both the ability to differentiate and their normal polarity. The cells invade neighboring tissues and, when combined with an activated form of the *Ras* proto-oncogene, can trigger the formation of metastases. PcG proteins bind to multiple genes in the Notch pathway and control their transcription as well as Notch signaling. The massive cell-autonomous over proliferation of *ph* mutant cell clones can be rescued by ectopic expression of a dominant negative form of Notch or by RNA interference (RNAi)-mediated repression of Notch. Conversely, over expression of *ph* induces a

small-eye phenotype that is rescued by activation of Notch signaling. These findings thus reveal that *ph* is a tumor suppressor locus that controls cellular proliferation by silencing multiple Notch signaling components. The identification of the PcG proteins as tumor suppressors in flies challenges our view of the role of PcG proteins in cancer. It will be of interest to study the link between PcG-mediated gene silencing and Notch signaling regulatory pathways in normal and cancerous human cells and determine the contexts in which PcG proteins have oncogenic and tumor suppressor roles.

Source: *Nature Genetics*

A Model for PcG-dependent Control of the Notch Signaling Pathway



Nature genetics, 41, October 2009



Research Highlight (Cont'd)

Requirement for NF- κ B Signaling in a Mouse Model of Lung Adenocarcinoma

Lung cancer is the leading cause of cancer death in the world with NSCLC accounting for 80% of all lung cancer cases, with adenocarcinoma being the major subtype. Oncogenic *Kras* mutations occur in approximately 20-30% of patients with lung adenocarcinoma, whereas inactivating mutations in the tumor suppressor protein p53 are found in at least 50% of NSCLC cases. NF- κ B transcription factors function as crucial regulators of inflammatory and immune responses as well as of cell survival. They have also been implicated in cellular transformation and tumorigenesis. The overexpression of oncogenic forms of Ras has been reported to result in NF- κ B activation whereas wild-type p53 has been shown to antagonize NF- κ B activity. However, despite extensive biochemical characterization of NF- κ B signaling during the past twenty years, the requirement for NF- κ B in tumor development *in vivo*, particularly in solid tumors, is not completely understood.

A recent study by Meylan *et al.* in *Nature* shows that the NF- κ B pathway is required for the development of tumors in a mouse model of lung adenocarcinoma. This pathway plays a critical role in lung cancer cells containing mutations in the commonly mutated genes *Kras* and p53. Concomitant loss of p53 and expression of oncogenic *Kras* resulted in NF- κ B activation in primary mouse embryonic fibroblasts. Conversely, in lung tumor cell lines expressing *Kras* and lacking p53, p53 restoration led to NF- κ B inhibition. Furthermore, the inhibition of NF- κ B signaling induced apoptosis in p53-null lung cancer cell lines. Inhibition of the pathway in lung tumors *in vivo* resulted in significantly reduced tumor development. These results indicate a critical function for NF- κ B signaling in lung tumor development and, further, that this requirement depends on p53 status. This study provides a basis to consider the pharmacological inhibition of the NF- κ B pathway in the treatment of lung cancer and provides support for the development of NF- κ B inhibitory drugs as targeted therapies for the treatment of patients with defined mutations in *Kras* and p53.

Source: *Nature*

Smoothened Drug Resistance to a Hedgehog Inhibitor in Medulloblastoma

The Hedgehog (Hh) signaling pathway has emerged as a key contributor to the growth of medulloblastoma, an aggressive brain tumor. GDC-0449, a drug that inhibits Hh signaling by targeting the serpentine receptor Smoothened (SMO), was recently shown to induce rapid and dramatic tumor regression in a patient with metastatic medulloblastoma, but the tumor eventually developed resistance to the drug. Yauch *et al.* show that resistance arose because the tumor acquired a mutation in Smoothened that disrupts binding of the drug. To evaluate the mechanism of resistance, the mutational status of Hh signaling genes was determined in the tumor after disease progression. An amino acid substitution at a conserved aspartic acid residue of SMO was identified. The corresponding mutation had no effect on Hh signaling but disrupted the ability of GDC-0449 to bind SMO and therefore suppressed the pathway. A mutation altering the same amino acid also arose in a GDC-0449resistant mouse model of medulloblastoma.

These findings show that acquired mutations in a serpentine receptor with features of a G protein-coupled receptor can serve as a mechanism of drug resistance in human cancer. Furthermore, the demonstration that these mutations do not impact Hh signaling continues to support the rationale for targeting this pathway. These findings also highlight the need to either identify second-generation SMO inhibitors capable of overcoming acquired resistance, or identify inhibitors targeting downstream signaling molecules.

Source: *Science*



Clinical Development

Pivotal Phase III Trial of Picoplatin in SCLC Did Not Meet Primary Endpoint

Poniard Pharmaceuticals announced that its pivotal Phase III SPEAR (Study of Picoplatin Efficacy After Relapse) trial of picoplatin in the 2nd line treatment of small cell lung cancer (SCLC) did not meet its primary endpoint of overall survival. The analysis, based on 320 evaluable events (patient deaths), showed a hazard ratio of 0.82 with a p value of 0.089. In addition to the SPEAR Phase III trial in SCLC, Poniard is evaluating intravenous picoplatin in a Phase II clinical trial in patients with colorectal cancer, in a Phase II clinical trial in patients with castration-resistant prostate cancer, and in a Phase I cardiac safety assessment

"We are disappointed that the trial did not meet the primary endpoint. The data indicates that more patients on the best supportive care arm received chemotherapy following progression than those on the picoplatin arm, and we believe that this may have been a significant factor contributing to the trial outcome, as picoplatin appeared to demonstrate a trend toward a survival advantage. Based on these findings and other analyses, we are contacting the FDA today to request a meeting to discuss a regulatory path forward," said Jerry McMahon, CEO of Poniard

Source: Poniard Pharmaceuticals

Overall Survival Results for Vectibix in 1st Line mCRC

Amgen announced that the Phase III PRIME "203" trial evaluating Vectibix (panitumumab) administered in combination with FOLFOX as a 1st line treatment of metastatic colorectal cancer (mCRC) failed to meet a secondary endpoint of overall survival (OS). Earlier this year, the trial met its primary endpoint by significantly prolonging progression-free survival (PFS) in the first-line treatment of patients with *KRAS* wild-type mCRC. The prospective analysis of the 203 study showed that Vectibix, when added to a FOLFOX chemotherapy regimen in patients with *KRAS* wild-type mCRC, resulted in a median OS of 23.9 months compared to 19.7 months for patients treated with FOLFOX alone. The median OS difference of 4.2 months in the Vectibix arm did not reach statistical significance. Originally designed to compare the treatment effect in the overall population, the study was amended to analyze outcomes with respect to the presence or absence of activating mutations in *KRAS* in the tumor itself. Tumor *KRAS* status was ascertained in over 90% of the 1,183 patients enrolled in the trial.

Vectibix is the first fully human anti-EGFR antibody approved by the FDA in September 2006 as a monotherapy for the treatment of patients with EGFR expressing mCRC after disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. In December 2007, the EMEA granted a conditional marketing authorization for Vectibix as monotherapy for the treatment of patients with EGFR-expressing mCRC with wild-type *KRAS* genes after failure of standard chemotherapy regimens.

Source: Amgen

Eribulin Meets Primary Endpoint of OS

Eisai announced preliminary results from a recently completed Phase III study with eribulin mesylate (E7389), a tubulin polymerization inhibitor, in patients with locally advanced or metastatic breast cancer. This global Phase III study, EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389), was an open-label, randomized, parallel two-arm, multi-center study of 762 women with locally recurrent or metastatic breast cancer. Subjects enrolled in the study were previously treated with at least 2 and a maximum of 5 prior chemotherapy regimens, including an anthracycline and a taxane. The patients were treated either with eribulin or with treatment of physician's choice.

Preliminary results from the study demonstrated a statistically significant improvement in OS, the primary endpoint, in eribulin-treated patients compared with the physician's choice of therapy. The safety profile of eribulin in this Phase III study was consistent with the adverse events seen in previous Phase II clinical studies. The most common adverse event reported was myelosuppression. Eisai will complete a more detailed analysis of the data prior to submitting marketing authorization applications for eribulin to health authorities in Japan, the US, and Europe for locally advanced and metastatic breast cancer by the end of the fiscal year 2009.

Source: Eisai



Clinical Development (Cont'd)

Tasigna Meets Primary Endpoint as 1st Line Treatment in CML against Glivec

Novartis announced that Tasigna (nilotinib) met its primary endpoint in the first head-to-head comparison with Glivec (imatinib). Tasigna produced faster and deeper responses than Glivec when given as 1st line therapy for adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Tasigna was well-tolerated in the study. The Phase III clinical trial, Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients (ENESTnd), enrolled 846 patients. Patients were randomized to receive Tasigna 400 mg twice daily (n = 281), Tasigna 300 mg twice daily (n = 282) or Glivec 400 mg daily (n = 283). The primary endpoint was Major Molecular Response (MMR) at 12 months; the secondary endpoint was complete cytogenetic response (CCyR) by 12 months. Planned follow-up is for five years. It is also the first registration study in which molecular traces of a key biomarker specific to Ph+ CML have been used as a primary endpoint for regulatory review. The comparison study also met its secondary endpoint, a difference in CCyR in favor of Tasigna.

Tasigna has been approved for the treatment of chronic phase and accelerated phase Ph+ CML in adult patients resistant or intolerant to at least one prior therapy, including Glivec.

Source: Novartis

YM Biosciences Reports Positive Nimotuzumab Four-Year Survival Data

YM BioSciences announced that an oral presentation at the American Society for Therapeutic Radiology and Oncology (ASTRO) 2009 Annual Meeting reported positive 48-month survival data for its EGFR-targeting antibody, nimotuzumab. The "BEST" trial was a randomized 4-arm study treating patients with inoperable, locoregionally-advanced, stage III/IVa head and neck cancer with radiation alone (RT), chemoradiation alone (CRT), or radiation or chemoradiation in combination with nimotuzumab. A total of 92 patients were enrolled in the BEST trial, of which 76 were considered evaluable. These data were a follow-up to 30-month survival data presented at the 2009 ASCO Annual Meeting and demonstrate that the benefit of adding nimotuzumab to radiation and chemoradiation is durable and persists for several years.

At 48 months, 41% of the patients in the nimotuzumab + CRT arm were alive compared to 21% in CRT-alone arm, and 34.7% in the nimotuzumab + RT arm were alive compared to 13% in the RT-alone arm. The difference at 48 months between CRT and nimotuzumab + CRT arms reached statistical significance. Kaplan-Meier curves for survival maintained a consistent separation at the 48-month update, demonstrating that the benefit of adding a fixed course of nimotuzumab to RT and CRT persists for an extended period. The combination of nimotuzumab with radiotherapy and chemoradiotherapy was safe and nimotuzumab did not potentiate radiation dermatitis.

Source: YM BioSciences

New Phase II Data for XL184 in Patients with GBM

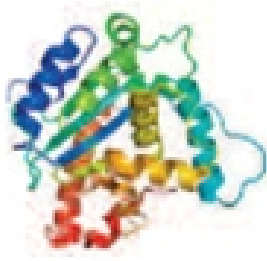
Exelixis and Bristol-Myers Squibb Company (BMS) reported updated Phase II clinical data of XL184, an investigational oral inhibitor of MET, VEGFR2, and RET, demonstrating activity in patients with glioblastoma multiforme (GBM). The data from the study XL184-201 were presented during a poster session at the 2009 Joint Meeting of the Society for Neuro-Oncology and the American Association of Neurological Surgeons. The study evaluates the safety, tolerability, and clinical activity of XL184 in patients with previously treated GBM, including some patients who had received prior antiangiogenic therapy. A total of 46 patients in first or second relapse were enrolled and dosed with 175 mg of XL184 administered daily. Due to frequent dose interruptions and reductions, the study was amended earlier this year to initiate a new cohort of 38 patients receiving 125mg.

As of September 25, 2009, the overall rate of confirmed partial response in the intent-to-treat population of all patients treated at 175 mg was 17%. Among patients without prior antiangiogenic therapy, 7 of 34 (21%) achieved confirmed responses. In patients who had received prior antiangiogenic therapy, 1 of 12 (8%), a patient who had progressed on vandetinib achieved a confirmed partial response. Of the 46 patients treated at the 175 mg dose level, 21% attained 6-month progression-free survival (PFS) rate with 35% patients censored for PFS at the time of analysis. The median duration of response was 5.9 months. The median PFS interval was 3.7 months. Follow up for the patients receiving 125 mg is relatively short, with the first patient enrolled in late June 2009. Of the 38 patients enrolled at the 125 mg dose level as of October 12, 2009, 18 patients had at least one post-baseline scan available that had undergone independent and blinded radiology facility (IRF) evaluation. Of these 18 patients, 7 have discontinued treatment, 4 due to progressive disease/clinical deterioration per investigator and 3 due to adverse events. Of 14 antiangiogenic naïve patients enrolled at this dose level, 8 have had tumor shrinkage of more than 50% as determined by IRF, including two confirmed partial responses by IRF.

Source: Exelixis



Biomarkers

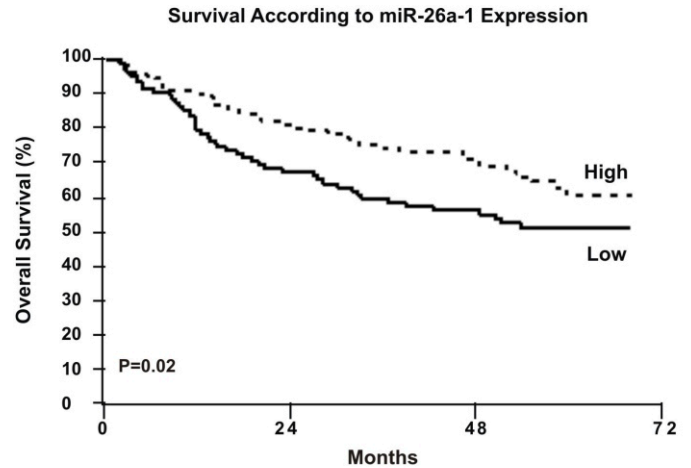


MicroRNA Expression, Survival, and Response to Interferon in Liver Cancer

Hepatocellular carcinoma (HCC) is a common and aggressive cancer with higher incidence in men as compared to women. Clinical studies have shown that microRNAs are excellent biomarkers for cancer diagnosis and prognosis. Given the therapeutic and prognostic potential of microRNAs as biomarkers in HCC, Ji *et al.* in a study published in *NEJM*, examined microRNA expression patterns, survival, and response to interferon alfa in both men and women with the disease. The analyses involved 3 separate cohorts of patients. Cohort 1 consisted of 241 patients with HCC (test cohort) for whom microRNA microarray data were available. Data from these patients were analyzed to search for microRNAs that were associated with sex and survival. Investigators were able to analyze miR-26 expression in 224 patients and survival in 217 patients. Cohorts 2 and 3 consisted of 214 patients from prospective, randomized, controlled trials of adjuvant therapy with interferon alfa in patients with HCC.

The study results showed that the expression of miR-26a and miR-26b in non-tumor hepatic tissues was higher in women than in men, but the expression was significantly down-regulated in tumor samples, as compared with paired samples of non-cancerous tissues, regardless of sex. Tumors with reduced miR-26 expression had a distinct gene-expression profile, and patients whose tumors had low miR-26 expression had shorter survival but were more likely to have a response to interferon alfa, as compared with patients whose tumors had high miR-26 expression. The results suggest that miR-26 may be a tumor suppressor and that miR-26 silencing in hepatocytes may contribute to the development of a more aggressive form of hepatocellular carcinoma in men.

Source: *NEJM*



NEJM, 361, Oct 8, 2009



Biomarkers (Cont'd)

MicroRNA Dynamics in the Stages of Tumorigenesis

Altered expression of microRNAs (miRs) in tumors has been well documented, however, it remains unclear how the miR transcriptome intersects neoplastic progression. In this backdrop, in a study published in *Genes and Development*, Douglas Hanahan and colleagues analyzed the miRNA transcriptome in distinct stages of tumorigenesis in the RIP1-Tag2 mouse model of pancreatic neuroendocrine tumors (PNETs).

Normal, hyperplastic and angiogenic islets, primary tumors and liver metastases from RIP1-Tag2 mice were profiled for expression of all known mouse miRNAs, which revealed that each stage had specific differences in miRNA expression.

By comparing primary tumors and liver metastases, the authors discovered that a small subset of primary tumors had miRNA signature that was similar to metastases rather than to other primary tumors. It is possible that these 'metastasis-like' primary PNETs represent tumors that are more likely to metastasize, and therefore the propensity to metastasize might be determined early in tumorigenesis. Decreased expression of the miR-200 family of miRNAs, leading to the loss of E-cadherin expression through the increased expression of the transcriptional repressor ZEB1, was substantial in both metastasis-like primary tumors and metastases. Treatment of RIP1-Tag2 mice with approved angiogenesis inhibitor, sunitinib, reduced the expression of miRNAs upregulated in the angiogenic signature. The authors found that changes in miRNA expression levels reflected a decrease in the relative proportions of endothelial cells, pericytes and inflammatory cells present in tumors following treatment. In response to treatment with sunitinib, many tumors acquired miRNA profile similar to that of metastases, supporting previous studies suggesting that adaptive resistance to angiogenesis inhibitors may involve increased metastasis. This study begins to segregate the functions of previously identified miRs that are altered in human cancers according to the stage of their initial alteration and the hallmark capability with which they are associated.

Source: Genes and Development

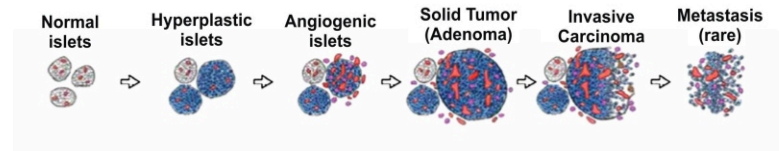
GE and Lilly Develop Technology to Visualize and Map Complex Biomarker Networks

Scientists at GE Global Research and researchers at Eli Lilly announced a significant advancement in cancer research resulting from the two companies' collaboration formed in October 2007. Working together, the research teams have developed tissue-based biomarker technology that for the first time that can simultaneously map more than 25 proteins in tumors at the sub-cellular level, an important step in the development of personalized and more effective cancer treatments. With this new molecular pathology technology, researchers can now look at a visual map of the tissue sample, seeing a cancer cell's comprehensive biomarker signaling pathway, and the interplay of signaling networks inside the tumor. To date, the new technology has been tested successfully on colon and prostate cancer tissue samples and is believed to be applicable to all types of cancer.

Mapping a tumor's complex biomarker network could allow researchers involved in drug discovery and the clinicians making treatment decisions to identify the most effective cancer therapies for patients. GE researchers with specialties in biology, bioinformatics, optics, fluidics, chemistry and mechanical engineering have built a prototype system capable of staining, washing and re-staining tissue samples for study under a digital microscope. The system combines image analysis of cancerous cells and structures with GE's patented visualization tools to provide a color map of protein concentrations within the sample.

Source: Lilly

Differential expression of the miR transcriptome in the distinctive stages of multistep tumorigenesis



Genes Dev, 23, 2009



Regulatory



FDA Approves ISTODAX for Patients with CTCL

Gloucester Pharmaceuticals announced that the FDA-approved ISTODAX (romidepsin) for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. The ISTODAX approval was based upon two prospective multicenter, single-arm clinical studies in patients with CTCL.

Study 1 included 96 patients with confirmed CTCL after failure of at least 1 prior systemic therapy. Study 2 included 71 patients with a primary diagnosis of CTCL who received at least 2 prior skin directed therapies or one or more systemic therapies. The primary efficacy endpoint, objective disease response rates (ORRs), in these two trials were similar (34% and 35% in Study 1 and Study 2, respectively) and complete response (CR) rates were the same (6%). The median response duration was 15 months in Study 1 and 11 months in Study 2. Median time to first response was 2 months in both studies. Median time to CR was 6 months in Study 1 and 4 months in Study 2.

Source: Gloucester Pharmaceuticals

GSK and Genmab Receive Accelerated Approval for Arzerra

GSK and Genmab announced the accelerated approval of Arzerra (ofatumumab) from the FDA for use in patients with chronic lymphocytic leukemia (CLL) that is refractory to fludarabine and alemtuzumab. The approval is based on results from a pivotal study in which 42% of patients with CLL who were refractory to both fludarabine and alemtuzumab responded to treatment with Arzerra. These patients had a median duration of response of 6.5 months.

The approval of Arzerra was supported by a positive recommendation by the FDA's Oncologic Drugs Advisory Committee (ODAC) at ASCO on May 29, 2009, in which the panel voted, 10-3, that the Arzerra data were likely to predict clinical benefit for patients with CLL whose disease is refractory to fludarabine and alemtuzumab. Arzerra is anticipated to be available for prescription use in the coming weeks.

Source: Genmab

AstraZeneca Withdraws Regulatory Submissions for Zactima

AstraZeneca announced that it has withdrawn the regulatory submissions for the use of Zactima (vandetanib) 100mg in combination with chemotherapy in patients with advanced NSCLC from the FDA and the EMEA. The applications were submitted to regulatory agencies in June 2009. The decision to withdraw these submissions was based on an updated analysis that demonstrated no overall survival advantage when vandetanib was added to chemotherapy as well as preliminary feedback from regulatory agencies that the current package with progression-free survival (PFS) as the primary endpoint may not be sufficient for approval.

AstraZeneca will complete the ongoing Phase III trial programme which will give a more complete view of vandetanib efficacy in different clinical settings. Results from the ZEPHYR (300mg vandetanib monotherapy study in patients with advanced NSCLC who have previously received an EGFR inhibitor) and ZETA (300 mg vandetanib monotherapy in advanced medullary thyroid cancer) studies are expected in late 2009 or early 2010.

Source: AstraZeneca



Antigenics Announces a Negative Vote from the CHMP on Oncophage

Antigenics announced that the Committee for Medicinal Products for Human Use (CHMP), of the EMEA, has verbally informed the company at an oral meeting to anticipate a negative opinion on the marketing authorization application (MAA) for Oncophage (vitespen) in early-stage, localized renal cell carcinoma.

Antigenics will evaluate its options, including an appeal of this decision, after the CHMP has formally adopted an opinion at the November 2009 plenary meeting. The patient population for which approval is being sought represents a major unmet medical need. There are no approved drugs in Europe or the US for the post-surgical treatment of adjuvant kidney cancer, a disease characterized by a high risk of recurrence. Antigenics believes clinically relevant benefits were demonstrated with Oncophage in recurrence-free survival and overall survival endpoints and that this benefit has persisted for nearly five years. "With the considerable support of the urology and oncology communities, we will continue to evaluate our options for making Oncophage available to kidney cancer patients in the EU," said Garo Armen, Chairman and CEO of Antigenics.

Source: Antigenics