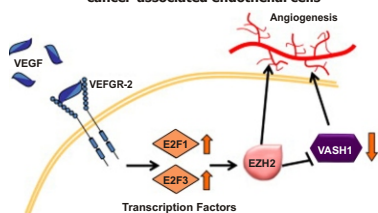


INTELLIGENT INSIGHTS. SMART RESULTS

Analysis of putative ezh2 pathways in cancer-associated endothelial cells



Cancer Cell, 18, Aug 17, 2010

In the Spotlight:

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[Click HERE to read more](#)



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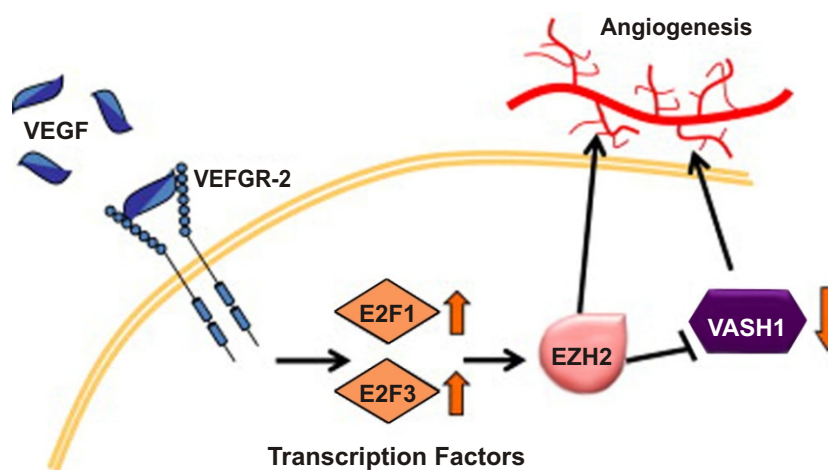


Spotlight Report

Regulation of Tumor Angiogenesis by EZH2

Anti-angiogenic therapeutic strategies are predicted to be meritorious in ovarian cancer patients on the basis of tumor and endothelial VEGF over-expression and response characteristics noted in Phase II clinical trials. However, despite initial responses, most patients eventually experience disease progression. The mechanism for this acquired resistance is not well described but appears to be due in part to expansion or expression of redundant alterations in maturing vasculature and epigenetic mechanisms; therefore, new anti-angiogenesis targets are needed.

Analysis of putative ezh2 pathways in cancer-associated endothelial cells



Cancer Cell, 18, Aug 17, 2010

In a recent study published in *Cancer Cell*, Lu *et al.* identified Zeste homolog 2 (EZH2) as a key regulator of tumor angiogenesis and showed that increased EZH2 expression in either tumor cells or tumor vasculature is predictive of a poor clinical outcome. They developed and characterized a highly effective method of gene silencing in tumor cells and in blood vessels that support their growth. The researchers describe a mechanism by which VEGF increases EZH2 levels in the tumor vasculature. The increase in endothelial EZH2 is a direct result of VEGF stimulation by a paracrine circuit that promotes angiogenesis by methylating and silencing the anti-angiogenic factor vasohibin1 (VASH1). EZH2 silencing in the tumor-associated endothelial cells by using siRNA, packaged in the chitosan delivery system, resulted in significant growth inhibition in an orthotopic ovarian cancer model. EZH2 silencing in the tumor-associated endothelial cells inhibited angiogenesis mediated by reactivation of VASH1 and reduced ovarian cancer growth, which is further enhanced in combination with EZH2 silencing in tumor cells. This work provides a significant conceptual advance in our understanding of the regulation of angiogenesis in ovarian carcinoma and supports the potential for targeting EZH2 as a therapeutic approach. Interfering with EZH2 in the tumor and endothelial cells might represent an important strategy for treatment of ovarian and other cancers.

Source: *Cancer Cell*



Business News

Genmab and Seattle Enter into ADC Research Collaboration

Genmab and Seattle Genetics have entered into an antibody-drug conjugate (ADC) research collaboration agreement. ADCs are monoclonal antibodies that selectively deliver potent anti-cancer agents to tumor cells. Under the agreement, Genmab has rights to utilize Seattle Genetics's ADC technology with its HuMax-TF antibody targeting the tissue factor antigen, which is expressed on numerous types of solid tumors. Seattle Genetics received an undisclosed upfront payment and has the right to exercise a co-development option for any resulting ADC products at the end of Phase I clinical development.

Genmab is responsible for research, manufacturing, pre-clinical development, and conducting Phase I clinical trials of ADCs under this collaboration. Seattle Genetics will receive research support payments for any assistance provided to Genmab. If Seattle Genetics opts into an ADC product at the end of Phase I, the companies would co-develop and share all future costs and profits for the product on a 50:50 basis. If Seattle Genetics does not opt into an ADC product, Genmab will pay Seattle Genetics fees, milestones, and midsingle-digit royalties on worldwide net sales of the product.

Source: Genmab

Sanofi-aventis Announces Non-Binding Offer to Acquire Genzyme

Sanofi-aventis has submitted a non-binding proposal to acquire Genzyme in an all-cash transaction valued at ~\$18.5 billion. Under the terms of the proposed acquisition, Genzyme shareholders will receive \$69 per Genzyme share in cash, representing a 38% premium over Genzyme's unaffected share price of \$49.86 on July 1, 2010. Sanofi-aventis's offer also represents a premium of almost 31% over the 1-month historical average share price through July 22, 2010, the day prior to press speculation that Sanofi-aventis had made an approach to acquire Genzyme.

On the basis of analyst consensus estimates, the offer represents a multiple of 36 times Genzyme's 2010 earnings per share and 20 times 2011 earnings per share. Accordingly, the offer price takes into account the upside potential of the anticipated recovery in Genzyme's performance in 2011. Sanofi-aventis has secured financing for its offer. The combination of both companies will create a global leader in developing and providing novel treatments, giving both companies significant new growth opportunities.

Source: Sanofi-aventis



Business News (Cont'd)

Roche and Aileron Enter Multi-target Alliance to Develop Stapled Peptide Drugs

Roche and Aileron Therapeutics have entered into a collaboration to discover, develop, and commercialize a new class of drugs called "stapled peptide therapeutics." As part of this agreement, Roche will work with Aileron to develop drug candidates against up to five undisclosed targets selected from Roche's key therapeutic areas, which include oncology, virology, inflammation, metabolism, and CNS. Stapled peptide therapeutics are a result of Aileron's breakthrough peptide stabilization technology and are a potential solution to as-yet intractable disease targets, including those originating from long sought-after intracellular protein-protein interactions.

Under the terms of the agreement, Roche will provide Aileron guaranteed funding of at least \$25 million in technology access fees and R&D support. Aileron is eligible to receive up to \$1.1 billion in payments upon the achievement of discovery, development, regulatory, and commercialization milestones, if drug candidates are developed against all five targets. In addition, Aileron will receive royalties on future sales for all marketed products that result from the collaboration. Aileron will have substantial responsibility in collaboration with Roche to develop drug candidates against the selected targets up to clinical development.

Source: Aileron Therapeutics

Onyx and Ono to Develop and Commercialize Carfilzomib and ONX 0912

Onyx Pharmaceuticals has entered into an exclusive agreement with Ono Pharmaceutical to develop and commercialize two compounds from Onyx's proteasome inhibitor development program, carfilzomib and ONX 0912. Carfilzomib, a highly selective proteasome inhibitor, is currently being evaluated in multiple clinical trials for the treatment of patients with multiple myeloma and other cancers. ONX 0912, an oral proteasome inhibitor, is currently in Phase I testing.

Under the terms of the agreement, Ono has exclusive rights to develop and commercialize both compounds for all oncology indications in Japan. Onyx retains commercialization rights in other countries in the Asia-Pacific region and in all other regions of the world, including the US and Europe. The potential value of the transaction, which includes rights to all oncology indications for the two molecules, is estimated to exceed \$300 million, plus royalties. Ono will pay Onyx an upfront payment of ¥5 billion (~\$59 million at current exchange rates). In addition, Onyx will receive development and sales-based payments related to the compounds that could total up to ~\$280 million at current exchange rates. The agreement also calls for royalty payments in double-digit percentages on net sales in Japan, commensurate with a late-stage asset.

Source: Onyx Pharmaceuticals



Research Highlights

HIF-2 α Deletion Promotes Kras-Driven Lung Tumor Development

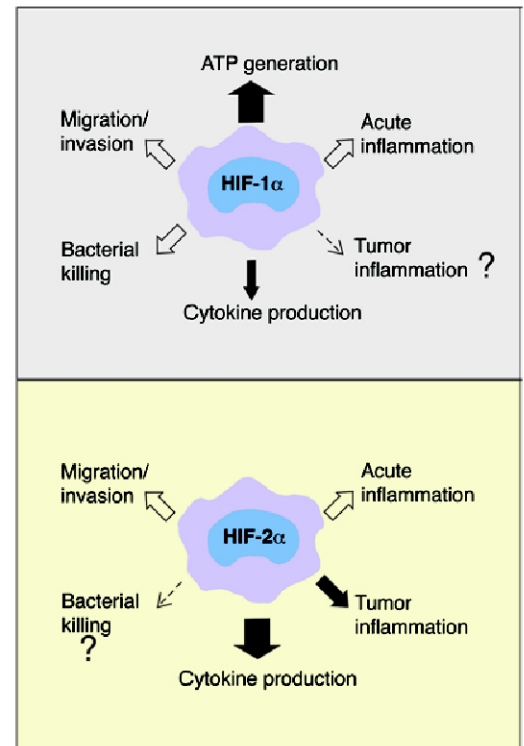
The transcriptional regulators hypoxia-inducible factor 1 α (HIF1 α) and HIF2 α are over-expressed in many cancers, and it has been suggested that the HIFs could be potential anti-cancer therapeutic targets. Two recent studies describe differing roles of HIF2 α in tumor development, indicating that therapeutically targeting this protein may not be straightforward and that context-dependent effects should also be taken into account.

As over-expression of HIF2 α in tumor-associated macrophages (TAMs) has previously been correlated with high tumor grade and poor prognosis, a research published in *J Clin Invest* by Imtiyaz *et al.* examined the effects of myeloid-specific deletion of Hif2 α in mouse models of inflammation-associated hepatocellular carcinoma or colitis-associated cancer. In both models, the authors observed that deletion of Hif2 α in macrophages led to the decreased infiltration of TAMs into tumors, reduced tumor cell mitosis, and delayed tumor growth, suggesting that HIF2 α is needed for efficient TAM recruitment to tumors and that these inflammatory cells have a role in driving cancer progression. This study confirms the earlier findings that have indicated a tumor-promoting role for HIF2 α .

Another study published in *PNAS* by Mazumdar *et al.* also reports that HIF2 α can have a tumor-suppressive role. The authors deleted Hif2 α in a KrasG12D mouse model of lung cancer and found that loss of HIF2 α promoted tumor progression. The authors identified several down-regulated HIF2 α target genes, including the putative tumor suppressor *Scgb3a1*. They extended their studies to human lung adenocarcinoma A549 cells that contain an activating KRAS mutation and observed down-regulation of SCGB3A1 after short hairpin RNA-mediated HIF2 α knockdown and increased growth of these cells as tumor xenografts in immunocompromised mice. Restoration of HIF2 α expression or ectopic expression of SCGB3A1 in the xenografted A549 cells led to the suppression of tumor growth. HIF2 α directly binds to sites in the SCGB3A1 promoter, and levels of bound HIF2 α are increased in hypoxic conditions. The authors suggest that although HIF2 α over-expression can contribute to tumor progression, reduction of HIF2 α below a crucial threshold level might have paradoxical tumor-promoting effects by reducing the expression of tumor suppressor genes such as SCGB3A1, and this might have important consequences for HIF-targeted therapeutic strategies.

Source: *J Clin Invest*, *PNAS*

Models illustrating the roles of HIF-1 α and HIF-2 α in macrophages



J Clin Invest, 120, Aug 2010



**Research
Highlight**
(Cont'd)

DAAP Targets VEGF-A and Angiopoietins in Tumor Progression and Metastasis

The orchestrated actions of multiple growth factors and their receptors, co-receptors, and binding partners are required for tumor angiogenesis. Two vascular growth factor families, VEGF and angiopoietins, play critical and co-ordinated roles in tumor progression and metastasis. Several approaches have been developed to block VEGF-A action, including blocking antibody, decoy receptor, and siRNA against VEGF-A, and clinical applications are currently being tested. So far a single inhibitor targeting both VEGF and angiopoietins is not available.

A recent study published in *Cancer Cell* by Koh *et al.* reports developing a chimeric decoy receptor, namely double anti-angiogenic protein (DAAP), which can simultaneously bind VEGF-A and angiopoietins, thereby blocking their actions. Compared with VEGF-Trap or Tie2-Fc, which blocks either VEGF-A or angiopoietins alone, DAAP is a highly effective molecule for regressing tumor angiogenesis and metastasis in implanted and spontaneous solid tumors; it can also effectively reduce ascites formation and vascular leakage in an ovarian carcinoma model. The binding of VEGF-A or Ang-2 to DAAP enhances its binding of Ang-2 or VEGF-A, respectively, and could be a supplementary benefit of using DAAP to block VEGF-A and Ang-2. DAAP has a relatively higher bioavailability and a longer half-life than VEGF-Trap, thus raising the possibility that DAAP could be a superior therapeutic protein to VEGF-Trap. Indeed, in suppressing tumor growth, angiogenesis, and metastasis, DAAP was superior to the combined therapy of VEGF-Trap plus Tie2-Fc, and DAAP was superior also to VEGF-Trap when in combination with cytotoxic chemotherapy agents. By developing a double decoy receptor, DAAP, which can simultaneously bind VEGF-A and angiopoietins, this study demonstrated that the double blockade of VEGF-A and angiopoietins is highly effective for reducing tumor angiogenesis, metastasis, and vascular leakage, with greater effects over the single blockade of VEGF-A or angiopoietins.

Source: Cancer Cell

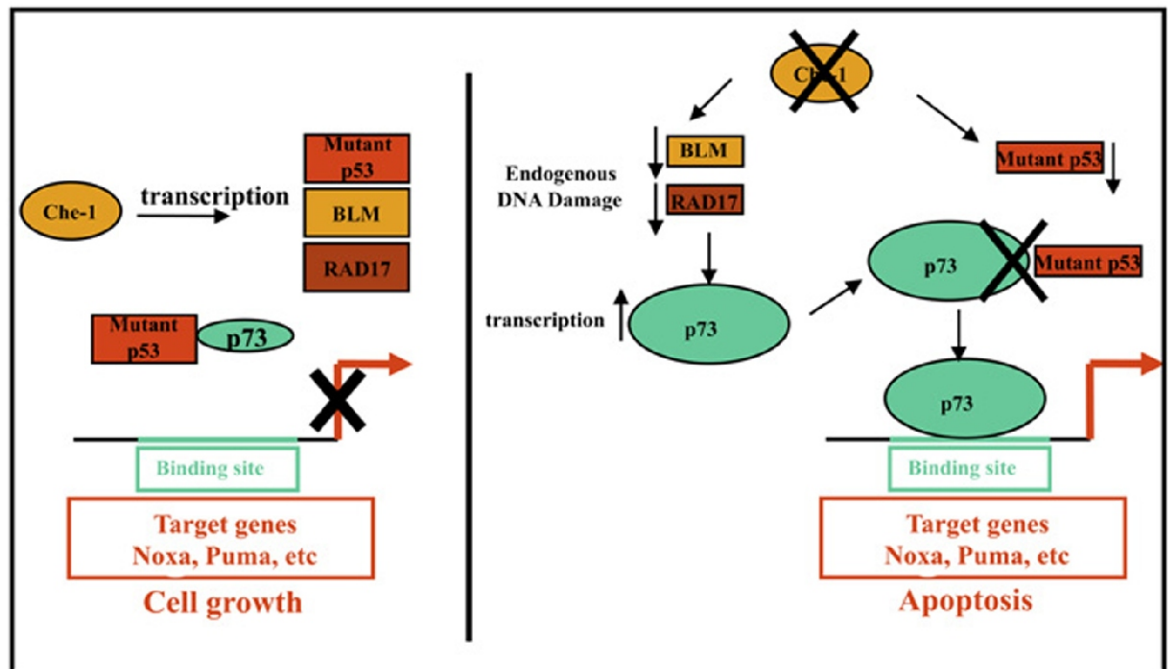


Research Highlight
(Cont'd)

Che-1 Promotes Tumor Cell Survival by Sustaining mtp53 Transcription

Che-1 is an evolutionary conserved RNA polymerase II binding protein involved in the regulation of gene transcription. In response to DNA damage, Che-1 is localized to the p53 promoter, thereby increasing transcription of this gene, and contributes to an increase in p53 protein level after DNA damage. Mutant p53 proteins (mtp53) not only lose wild-type p53 tumor suppressor activity but also gain specific properties contributing to tumor aggressiveness and chemoresistance and are often correlated with poor prognosis. Some mtp53 proteins can interact with and inhibit the transcriptionally active forms of the p53 homologs p73 and p63, leading to reduced apoptotic response and chemoresistance. Therefore, several therapeutic rationales targeting mtp53 activity are currently under investigation, including attempts to inhibit mtp53 expression.

Model to explain the effects of Che-1 depletion in breast cancer cells carrying mutant p53



Cancer Cell, 18, Aug 17, 2010

In a recent study published in *Cancer Cell*, Bruno *et al.* provide evidence that Che-1 is required for mtp53 expression in human cancer cells and that its depletion induces a specific apoptotic program in these cells. The researchers demonstrated that Che-1 is required for mtp53 expression in several human cancer cell lines and, in such a way, it can contribute to mtp53 "gain of function." Furthermore, inhibition of Che-1 leads to DNA damage-dependent p73 activation and apoptosis. They also showed that Che-1 is not only a component of DNA damage response but is also involved in DNA repair mechanisms, regulating the expression of important genes such as BLM and RAD17, suggesting that cancer cells with mtp53 require these proteins to proliferate. Finally, they provide evidence that the constitutive deregulation of Che-1 abolishes the tumorigenicity of cancer cells in an animal model. Their findings suggest that Che-1 is accumulated and recruited onto the p53 promoter in cancer cells but not in primary breast fibroblasts. These findings underline the important role that Che-1 has in survival of cells expressing mutant p53 and suggest a therapeutic approach involving the simultaneous modulation of p73 and mutant p53 levels. This approach could be used to target the large fraction of human tumors harboring p53 mutations.

Source: *Cancer Cell*



Clinical Development



Phase III Trial of Avastin Fails to Meet Primary Endpoint in Adjuvant Colon Cancer

Roche announced the topline results of a second Phase III trial evaluating the use of Avastin plus chemotherapy in the adjuvant treatment (immediately after surgery) of early-stage colon cancer. The trial compared the efficacy and safety of Avastin plus chemotherapy to chemotherapy alone. The study, known as AVANT, did not meet its primary endpoint of improving disease-free survival in stage III colon cancer. Adverse events were consistent with those previously observed in pivotal trials of Avastin across tumor types for approved indications.

In line with the previously reported NSABP C-08 study results that also evaluated Avastin in the early-stage setting, the AVANT study showed that standard chemotherapy plus 1 year of Avastin administration is not effective in reducing the risk of relapses in early-stage colon cancer. Unlike the C-08 results, preliminary efficacy data from AVANT numerically favor chemotherapy alone (the control arm). Roche is evaluating the data from these two studies to help define the next steps for the ongoing Avastin adjuvant program.

Source: Roche

Topline Results from Phase III Trial of Sunitinib in Advanced NSCLC

SUN 1087 trial of sunitinib in combination with erlotinib versus erlotinib alone demonstrated a statistically significant improvement in PFS but not in OS in patients with previously treated advanced non-small cell lung cancer (NSCLC). OS was the primary endpoint of the study, and PFS was a secondary endpoint. No new or unexpected types of adverse events were reported in the study.

Pfizer is continuing to analyze study data, and the results have been submitted to the European Society for Medical Oncology (ESMO) Congress, October 8-12, 2010, in Milan, Italy. Sutent is currently approved for both gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate, and advanced/metastatic renal cell carcinoma on the basis of efficacy and safety data from large, randomized Phase III clinical trials.

Source: Pfizer



Clinical Development (Cont'd)

Zybrestat Improves OS in a Phase II/III Trial of Anaplastic Thyroid Cancer

OXiGENE announced positive results from a randomized, controlled, Phase II/III study of Zybrestat (fosbretabulin, CA4P) at the 14th International Thyroid Congress in Paris. Zybrestat is a vascular disrupting agent and one of a novel class of small-molecule drug candidates. 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.

In this 80-patient FACT study, the median OS time was 5.1 months for patients who received Zybrestat and chemotherapy when compared with a median survival time of 4.1 months for patients receiving chemotherapy alone (HR 0.71), which represents a 29% reduction in the risk of dying for patients receiving Zybrestat and chemotherapy combination. Of patients treated with Zybrestat and chemotherapy, 48% were alive at 6 months, compared with 37% of patients treated with the control arm regimen. At 1 year, 23% of patients treated with Zybrestat and chemotherapy were alive compared with 9% of patients treated with chemotherapy alone. The most common side effects reported with Zybrestat and chemotherapy were neutropenia, transient hypertension, and tumor pain.

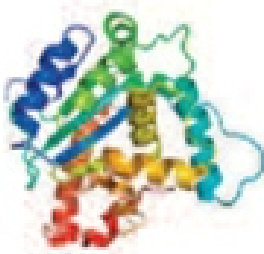
Source: OXiGENE

Phase IIb of Lintuzumab Did Not Meet Primary Endpoint in AML

Phase IIb clinical trial of lintuzumab (SGN-33) in older patients with acute myeloid leukemia (AML) did not meet its primary endpoint of extending the OS. Lintuzumab is a naked monoclonal antibody that targets the CD33 antigen.

The Phase IIb trial was a randomized, double-blind, placebo-controlled, multi-center clinical trial that enrolled 211 previously untreated AML patients 60 years and older who were ineligible for or declined intensive chemotherapy. The study's primary endpoint evaluated whether the combination of lintuzumab and low-dose cytarabine chemotherapy extended OS compared to low-dose cytarabine plus placebo. No statistically significant difference in OS was achieved between treatment arms. The treatment arms were well balanced for multiple demographic and prognostic factors, and the results were consistent across geographies. OS was generally longer in both arms compared with previously published data with low-dose cytarabine. Lintuzumab was well tolerated in combination with cytarabine chemotherapy. As a result of the outcome of this trial, the company will discontinue its development program for lintuzumab.

Source: Seattle Genetics

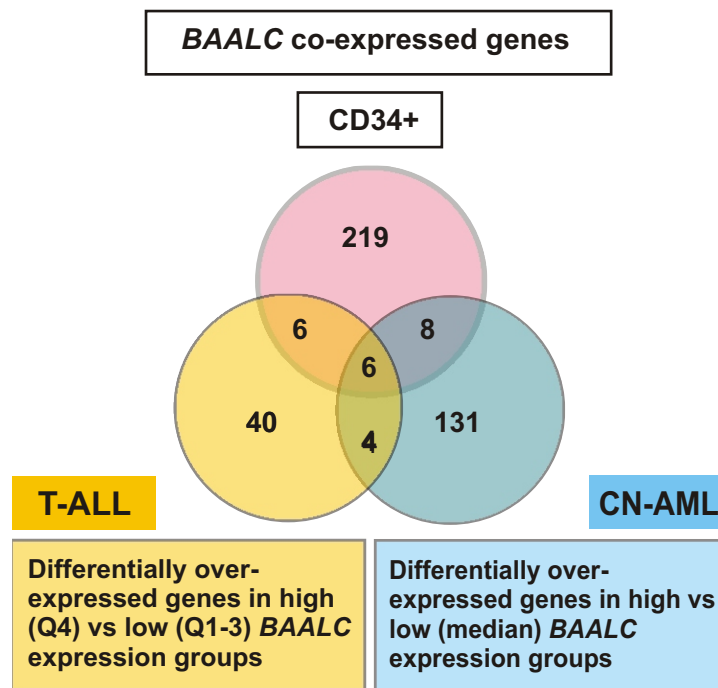


Biomarkers

BAALC Profiles IGFBP7 as a Novel Molecular Marker in Acute Leukemia

It has already been shown that over-expression of BAALC (brain and acute leukemia, cytoplasmic) is associated with an inferior outcome and chemotherapy resistance in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) patients. Recently, a study published in *Leukemia* by Baldus *et al.* has identified a gene correlated with BAALC to gain further insights into the BAALC-associated signaling pathways involved in the chemotherapy-resistant leukemia.

Venn diagram showing the gene overlap among BAALC-associated GEPs in CD34+ progenitors, T-ALL, and CN-AML



Leukemia, 24, 2010

The researchers compared BAALC-associated gene expression profiles (GEP) of normal CD34+ progenitors, T-ALL, and AML blast cells. The insulin-like growth factorbinding protein 7 (*IGFBP7*) was one of the four genes (*CD34*, *CD133*, natriuretic peptide receptor C [*NPR3*], *IGFBP7*) co-expressed with BAALC and was common to the three entities, thus suggesting its role in early hematopoiesis and leukemogenesis. The researchers explored the expression levels of *IGFBP7* during *in vitro* lineage-specific hematopoietic differentiation and observed down-regulation of *IGFBP7* with the onset of maturation. These results suggest that *IGFBP7* might have a role in hematopoietic differentiation and might be a marker of early progenitor cells. Similar to BAALC, increased expression of *IGFBP7* was found to be associated with a lower response rate to induction therapy and an inferior overall survival in ALL patients. Therefore, aberrant *IGFBP7* expression might have a role in drug resistance and may consequently contribute to a poor outcome. Addition of rhIGFBP7 to leukemia cell lines led to a reduction of proliferation; this suggests *IGFBP7* might promote resistance to cell cyclespecific cytotoxic agents by a decrease in replicative activity in these cells.

Source: *Leukemia*



Biomarkers (Cont'd)

Pathway-Based Identification of Biomarkers for Targeted Therapeutics

Patient response to targeted therapy can be predicted by examining the modulation of oncogenic signaling pathways in response to specific drugs, which can also identify new pathway-specific biomarkers. The validity of this approach is illustrated in a new study published in *Sci Trans Med* that uses a proteomics-based strategy to identify novel biomarkers that indicate a response of cancer cells to PI3K pathway inhibitors.

Andersen *et al.* treated differential serine-threonine phosphorylation events with inhibitors of PDK1, AKT, or a dual inhibitor of PI3K and mTOR. They identified "PI3K pathway nodes," the phosphorylation targets that were the most reduced by drug treatment. They also identified several phosphorylation sites that were uniquely down-regulated by each PI3K inhibitor, many of which were novel. These sites could be used as biomarkers for assessing response to PI3K inhibitors, and the researchers also evaluated the newly identified site phospho-Thr246-PRAS40 which was reduced by the AKT inhibitor as a biomarker. The workers generated an antibody against this epitope and found that high levels of PRAS-Thr246 phosphorylation predicted sensitivity to an AKT inhibitor in lung and breast cancer cell lines. Moreover, the phospho-Thr246-PRAS40 epitope is more stable than phospho-Ser473-AKT epitope, which is commonly used in clinical diagnosis of tumors, with AKT pathway activation, thus suggesting a possible application of this new biomarker in clinical evaluation. Therefore, the signaling pathway based strategy allows the discovery of drug-specific biomarkers and has important clinical implications that can be used to guide treatment decisions. Globally analyzing signaling pathways by using a differential phospho-profiling approach could be a way to assess the off-target effects of existing cancer drugs.

Source: *Sci Trans Med*

Clinical and Prognostic Implications of Troponin I Evaluation

The use of trastuzumab in breast cancer over-expressing HER2 receptors has significantly reduced cancer recurrence and has improved survival in women with early-stage and metastatic disease. Its use, however, has resulted in an unexpectedly high incidence of cardiotoxicity in up to 34% of the patients. Clinical studies have shown that troponin I (TNI) is a well-established early marker of myocardial injury, with high diagnostic and high prognostic values in cancer patients treated with high-dose chemotherapy. In a study published in *JCO*, Cardinale *et al.* investigated the usefulness of TNI in the identification of patients at risk for trastuzumab-induced cardiotoxicity (TIC) and prediction of left ventricular ejection fraction (LVEF) recovery.

The study enrolled 251 women. TIC occurred in 17% and was more frequent in patients with TNI elevation (TNI+; 62% vs. 5%; $P < 0.001$). Twenty-five patients (60%) recovered from TIC. LVEF recovery occurred less frequently in TNI+ patients (35% vs. 100%; $P < 0.001$). Multivariate analysis showed that TNI+ was the only independent predictor of both TIC and the lack of LVEF recovery. Thus, treatment of breast cancer with trastuzumab may be complicated by development of asymptomatic and symptomatic cardiotoxicity, particularly in patients previously treated with anthracyclines. Cardiac dysfunction, however, is reversible in 60% of cases, and full LVEF recovery is associated with a striking reduction in long-term major adverse cardiac events. Assessment of TNI during trastuzumab therapy allows for identification of patients at risk of cardiotoxicity and those who, despite heart failure therapy, will not recover from cardiac dysfunction.

Source: *JCO*



Regulatory



FDA Extends Review Period for Avastin in Breast Cancer

Genentech announced that information submitted by the company to the FDA during the review of the supplemental Biologics License Application (sBLA) for Avastin for previously untreated advanced HER2-negative breast cancer has been deemed a major amendment. In accordance with the FDA guidelines, the agency has extended the review period for the sBLA by an additional 90 days. The company now anticipates FDA action on the sBLA by December 17, 2010.

At this time, Avastin remains under accelerated approval in combination with paclitaxel for the 1st-line treatment of HER2-negative metastatic breast cancer. The FDA is currently reviewing two sBLAs that Genentech submitted in November 2009 for Avastin in combination with taxane-based, anthracycline-based, and capecitabine chemotherapies based on the results of the AVADO and RIBBON1 studies. Data from AVADO and RIBBON1 were submitted as part of Genentech's effort to convert the accelerated approval to a full approval. The FDA granted accelerated approval for Avastin in combination with paclitaxel chemotherapy for 1st-line treatment of advanced HER2-negative breast cancer in 2008. The approval was based on an improvement in PFS. Avastin is not approved for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy. There are no data available indicating that Avastin improves disease-related symptoms or survival in advanced HER2-negative breast cancer.

Source: Genentech

Ipilimumab Receives FDA Priority Review Designation for Advanced Melanoma

The FDA has accepted, for filing and review, the BLA for ipilimumab for the treatment of previously treated adult patients with advanced melanoma. The company announced that the FDA has granted priority review designation to ipilimumab. Ipilimumab is a novel T-cell progenitor that specifically blocks the inhibitory signal of CTLA-4 (cytotoxic T-lymphocyte antigen 4). On the basis of the FDA's 6-month goal for completing priority reviews, the projected FDA action date is December 25, 2010.

The filing is based on results from the primary analysis of the pivotal MDX010-020 trial, which were published online in *NEJM* and presented during a plenary session at the 46th Annual Meeting of the ASCO in June 2010. The study compared the OS rate of patients who received ipilimumab plus the gp100 vaccine (3 mg/kg and 1 mg/kg every 3 weeks for four doses; n = 403), ipilimumab alone (3 mg/kg every 3 weeks for four doses; n = 137), and the control therapy of gp100 alone (n = 136). Ipilimumab is also currently under review with the European Medicines Agency and other health authorities for the treatment of adult patients with previously treated advanced melanoma.

Source: Bristol-Myers Squibb



Regulatory (Cont'd)

Genentech Provides Update on FDA Application for T-DM1

Genentech announced that the FDA issued a Refuse to File letter for accelerated approval for the company's trastuzumab-DM1 (T-DM1) BLA. As planned, Genentech will continue with its ongoing Phase III registrational T-DM1 trial, EMILIA. Genentech will continue to work with the FDA, and it expects to submit a new T-DM1 BLA in mid-2012. The BLA submitted in July 2010 requested accelerated approval for T-DM1 based on the results of a single-arm Phase II study, which showed T-DM1 shrank tumors in one-third of women with advanced HER2-positive breast cancer who received, on average, seven prior medicines, including two HER2-targeted medicines.

Consideration by the FDA for accelerated approval requires recognition of a defined patient population of unmet need, for whom a medicine's early safety and efficacy data are reasonably likely to predict clinical benefit. Following the pre-submission meeting with the FDA in March 2010, Genentech concluded it was appropriate to submit a BLA for accelerated approval. In its review of the BLA, the FDA stated that T-DM1 trials did not meet the standard for accelerated approval because all available treatment choices approved for metastatic breast cancer, regardless of HER2 status, had not been exhausted in the study population.

Source: Genentech