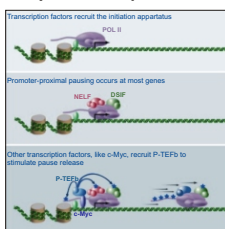


INTELLIGENT INSIGHTS. SMART RESULTS

**C-Myc stimulates pause release**



Cell, 141, April 30, 2010

## In the Spotlight:

### c-Myc Regulates Transcriptional Pause Release

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 Infinity and Intellikine to Develop Therapies Targeting PI3K Isoforms  
 Sanofi-aventis to Acquire TargeGen  
 MorphoSys and Xencor Collaborate for Clinical Antibody Program

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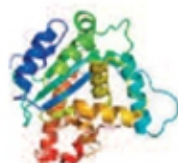
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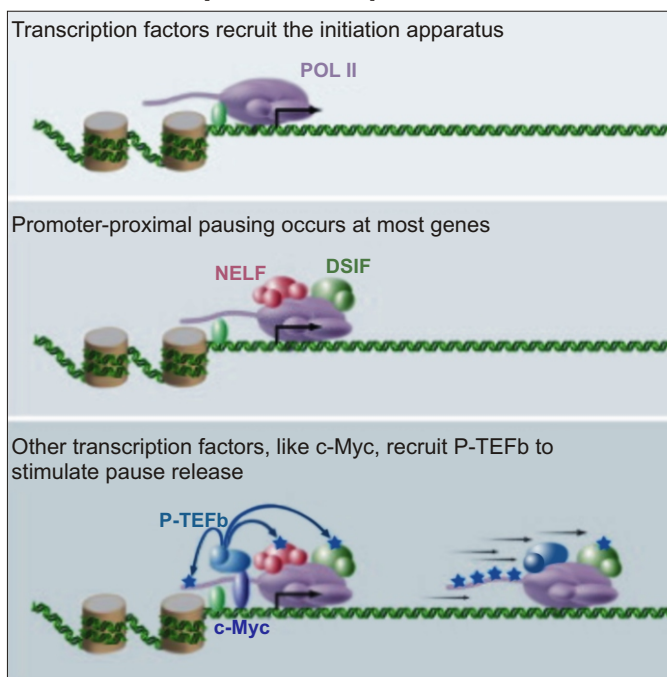


## Spotlight Report

### c-Myc Regulates Transcriptional Pause Release

The Myc family of transcription factors are well-known oncoproteins, and the c-Myc oncogene is expressed in both embryonic stem cells and cancer cells. It is also a key regulator of cellular proliferation. A new study published in *Cell* contributes important insights to the mechanisms of MYC regulation. Rahl and colleagues demonstrate that MYC plays a key role in regulating transcriptional elongation by RNA polymerase II (Pol II). RNA polymerase II is detected in the promoter-proximal region of most genes, and the recruitment of the Pol II transcription initiation apparatus to promoters by specific DNA-binding transcription factors is well recognized as a key regulatory step in gene expression. MYC participates in positive elongation factor b (P-TEFb)-dependent release of paused Pol II, as MYC can bind P-TEFb and stimulate transcriptional elongation in cancer cells.

#### C-Myc stimulates pause release



Cell, 141, April 30, 2010

Rahl and co-workers found that MYC and its heterodimer partner MAX bind to P-TEFb in embryonic stem (ES) cells. To directly test whether MYC regulates pause release, they treated ES cells with an inhibitor of MYC-MAX dimerization, 10058-F4. This decreased the expression of most MYC target genes and reduced the levels of the Pol II form associated with elongation, but the levels of the form of Pol II associated with transcriptional initiation were unaffected. Moreover, reduction of MYC activity by 10058-F4 or by short hairpin RNA knockdown reduced the levels of Pol II across transcribed regions of MYC target genes, but had little effect on the levels of promoter-proximal Pol II. The researchers suggest that combined targeting of MYC and P-TEFb could be an effective therapeutic strategy in tumor cells that overexpress MYC.

Source: *Cell*



## Business News

### **Celgene to Acquire Abraxis BioScience**

Celgene and Abraxis BioScience jointly announced the signing of a definitive merger agreement, under which Celgene has agreed to acquire Abraxis BioScience. The acquisition of Abraxis BioScience accelerates Celgene's strategy to become a global leader in oncology. The transaction adds Abraxane (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) to the company's existing portfolio of leading cancer products. The FDA approved Abraxane in January 2005 for the treatment of breast cancer after the failure of a combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy. It was approved by the EMEA in January 2008 for a similar indication.

Under the terms of the merger agreement, each share of Abraxis BioScience's common stock will be converted into the right to receive an upfront payment of \$58.00 in cash and 0.2617 shares of Celgene's common stock. The upfront payment values Abraxis BioScience at ~\$2.9B, net of cash. Each share will also receive one tradeable contingent value right (CVR), which entitles its holder to receive payments for future regulatory milestones and commercial royalties.

*Source: Celgene*

### **Infinity and Intellikine to Develop Therapies Targeting PI3K Isoforms**

Infinity Pharmaceuticals and Intellikine announced an agreement, under which Infinity obtained global development and commercialization rights to Intellikine's portfolio of inhibitors of the delta and gamma isoforms of phosphoinositide-3-kinase (PI3K). PI3Ks are a family of enzymes involved in cellular functions, including cell proliferation and survival, cell differentiation, intracellular trafficking, and immunity. Among these inhibitors is INK1197, an orally available dual delta/gamma-specific inhibitor of PI3K, for which clinical development in inflammatory diseases is expected to commence in 2011.

Under the terms of the agreement, Intellikine will receive \$13.5M in initial license payments; committed research funding over the first two years of the relationship to identify additional novel delta, gamma, and dual delta/gamma-specific inhibitors of PI3K for future development; up to \$25M in success-based milestones for the development of two distinct product candidates; and up to \$450M in success-based milestones for the approval and commercialization of two distinct products. In addition, Intellikine will be entitled to receive royalties upon successful commercialization of products licensed to Infinity. For products directed primarily at oncology indications, Intellikine will have the option - at the end of Phase II clinical development and upon payment of an option fee - to convert its royalty interest in US sales into the right to share 50% of the profits and losses on US development and commercialization, and to participate in up to 30% of the detailing effort for these products in the US.

*Source: Infinity Pharmaceuticals*



**Business  
News**  
(Cont'd)

**Sanofi-aventis to Acquire TargeGen**

TargeGen has agreed to be acquired by Sanofi-aventis. Formed in 2001, TargeGen's most advanced drug candidate is TG101348, an internally discovered, oral, potent, and highly selective JAK2 kinase inhibitor, being developed for the treatment of patients with myeloproliferative diseases, including primary and secondary myelofibrosis (MF) and polycythemia vera (PV). There are currently no approved drugs to treat MF or PV.

Preliminary data from a 59-patient trial involving the treatment of MF patients with TG101348 was presented at the American Society of Hematology (ASH) Conference in New Orleans, in December 2009. Other pre-clinical data presented at the ASH suggested that in addition to the treatment of certain myeloproliferative disorders, TG101348 may also have potential utility in the treatment of certain forms of leukemia, lymphoma, other hematological malignancies, and blood disorders. Under the agreement, the ultimate purchase price will depend on the achievement of certain future milestones events and will total \$560M if such milestones are fully realized.

*Source: TargeGen*

**MorphoSys and Xencor Collaborate for Clinical Antibody Program**

MorphoSys and Xencor announced the signing of a worldwide exclusive license and collaboration agreement for an antibody in Phase I clinical development. The agreement provides MorphoSys with an exclusive worldwide license to XmAb5574, a high potency monoclonal antibody developed by Xencor for the treatment of B-cell malignancies. XmAb5574 will be renamed MOR208; it is a humanized anti-CD19 monoclonal antibody for the treatment of B-cell malignancies.

As part of the agreement, the companies will collaborate on the Phase I trial in patients with chronic lymphocytic leukemia (CLL) in the US, for which Xencor will continue to carry the costs under its development plan. MorphoSys will be solely responsible for further clinical development. Xencor will receive an upfront payment of \$13M, and will be eligible to receive development-, regulatory- and commercialization-related milestone payments and tiered royalties based on product sales. Further financial terms were not disclosed.

*Source: MorphoSys*



## Research Highlights

### Insulin Receptor Conveys Intrinsic Resistance to IGF-1R Targeted Therapy

Increased signaling through the insulin-like growth factor (IGF) pathway has been implicated in the progression of several types of human cancers. The type 1 insulin-like growth factor receptor (IGF-1R) tyrosine kinase is an important mediator of the protumorigenic effects of IGF-I/II, and inhibitors of IGF-1R signaling are currently being tested in clinical cancer trials aiming to assess the utility of this receptor as a therapeutic target. Despite mounting evidence that the highly homologous insulin receptor (IR) can also convey protumorigenic signals, its direct role in cancer progression has not been genetically defined *in vivo*, and it remains unclear whether such a role for IR signaling could compromise the efficacy of selective IGF-1R targeting strategies.

Studies of Ulanet *et al.* published in *PNAS* in the prototypical IGF-II-driven RIP1-Tag2 mouse model of multistage carcinogenesis demonstrate, *in vivo*, a role of IR in tumor progression and, importantly, in eliciting intrinsic resistance to IGF-1R targeting therapy. The researchers assessed the potential therapeutic efficacy of the IGF1R-specific monoclonal antibody A12 in these mice. Surprisingly, A12 had no significant impact on PNET growth or invasiveness, despite successfully reducing IGF1R levels. The researchers found that INSR isoforms, *Insra* and *Insr*, as well as *Igf1r*, are expressed during PNET development. Moreover, IGF1R and INSR are post-transcriptionally upregulated, and IGF2 stimulation of tumor-derived  $\beta$ -cells resulted in the activation of both receptors. Targeted deletion of *Insr* in  $\beta$ -cells ( $\beta$ -IRKO) of RIP1-Tag2 mice led to decreased tumor burden and increased apoptosis. The workers also assessed the therapeutic efficacy of A12 and found that A12-treated RIP1-Tag2;  $\beta$ -IRKO mice showed significant inhibition of tumor growth, indicating that the loss of INSR can sensitize these tumors to anti-IGF1R therapy. Extending their findings from the PNET mouse model to human cancer, the researchers found that the INSR loss may similarly sensitize breast cancer cells to the inhibitory effects of A12. Cell lines with a high INSR/IGF1R ratio, such as MDA-MB-231, were insensitive to inhibition of IGF signaling by A12, in contrast to cell lines with a low ratio, such as MCF-7. Knocking down INSR expression by small interfering RNA sensitized both MCF-7 and the previously resistant MDA-MB-231 cells to A12 inhibition. These results suggest a functional role of INSR in tumor progression, and implicate increased INSR signaling in intrinsic resistance to anti-IGF1R therapy in an IGF2-driven PNET model.

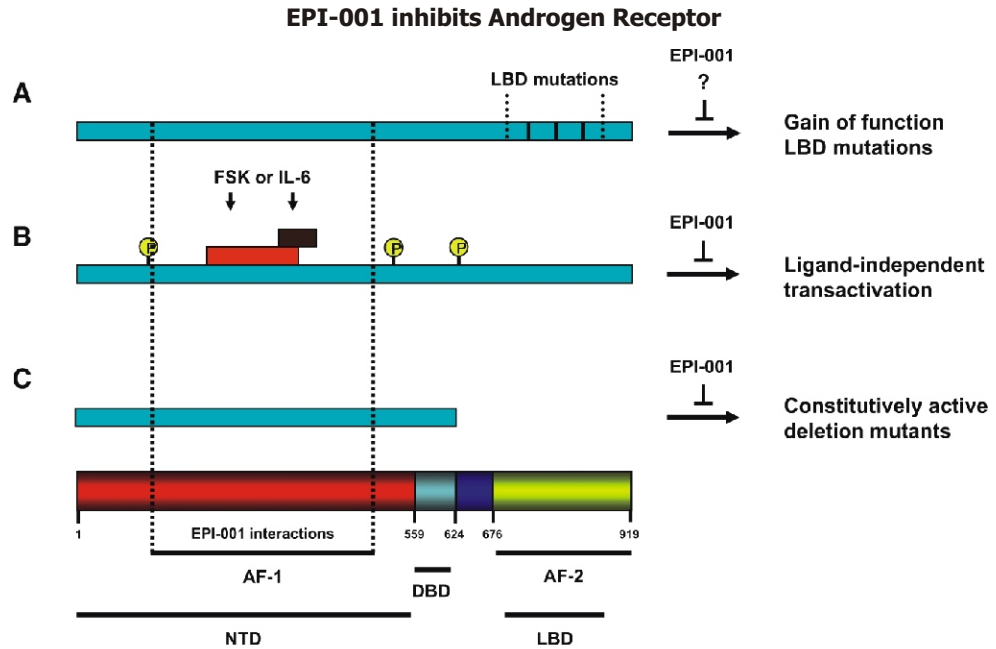
Source: *PNAS*



**Research Highlight**  
(Cont'd)

**Regression of CRPC by a Small-molecule Inhibitor of Androgen Receptor**

Androgen ablation therapy causes a temporary reduction in prostate cancer tumor burden. Unfortunately, prostate cancer will begin to grow again in the absence of androgens to form castrate-recurrent disease (CRPC) and most patients succumb within 2 years. CRPC is believed to emerge after genetic and/or epigenetic changes in prostate cancer cells that render them insensitive to ADT. CRPC is characterized partly by overexpression of AR. In addition, the use of antiandrogens that target the ligand binding domain (LBD) can lead to the selection of prostate cancer cells that harbor AR mutations in the LBD.



Cancer Cell, 17, June 15, 2010

Androgen receptor (AR) is a transcription factor and the AF region in the amino-terminal domain (NTD) of AR contains most, if not all, of the transcriptional activity. Andersen *et al.* in *Cancer Cell* recently reported a small molecule EPI-001 that interacts with and blocks transactivation of the androgen receptor amino-terminal domain. EPI-001 is a BADGE (bisphenol A diglycidic ether) analog, which is specific for inhibition of AR without attenuating transcriptional activities of related steroid receptors. Unlike antiandrogens that target the C-terminal LBD and fail presumably due to gain-of-function mutations in the LBD, or expression of constitutively active splice variants, EPI-001 interacted with the AF-1 region. It inhibited protein-protein interactions with AR, and reduced AR interaction with androgen-response elements on target genes. The workers also showed that EPI-001 can block transactivation of a constitutively active AR deletion mutant containing the NTD, DNA-binding domain, and hinge region, but not the LBD. Importantly, EPI-001 blocked androgen-induced proliferation and caused cytorreduction of CRPC in xenografts dependent on AR for growth and survival without causing toxicity. Currently, there are no curative treatment options for CRPC and this agent can overcome the shortcomings of clinically used antiandrogens. The findings of this study suggest that the AR NTD is a promising target to develop therapeutics for the treatment of CRPC.

Source: *Cancer Cell*



## Research Highlight (Cont'd)

### Integrative Genomic and Proteomic Analyses Identify Targets for Lkb1-deficient Metastatic Lung Tumors

Genetic analyses and gene expression profiling of primary human lung tumors have identified several aberrant signaling pathways involved in the initiation of non-small cell lung cancer (NSCLC). Although large-scale genomic analyses of NSCLC have yielded a better understanding of lung cancer genetic alterations, studies defining the pathways deregulated in tumor progression and metastases are limited.

In a recent study published in *Cancer Cell*, Carretero *et al.* showed that in mice, Lkb1 deletion and activation of KrasG12D resulted in lung tumors with a high penetrance of lymph node and distant metastases. They analyzed these primary and metastatic *de novo* lung cancers with integrated genomic and proteomic profiles, and identified gene and phosphoprotein signatures associated with Lkb1 loss and progression to invasive and metastatic lung tumors. It was seen that Kras/Lkb1 primary and metastatic tumors have upregulated expression of markers and inducers of EMT. Furthermore, they determined that two key modulators of focal adhesion dynamics, SRC and FAK, are upregulated by Lkb1 loss during NSCLC progression. Similarly, LKB1 loss *in vitro* also resulted in SRC activation, increased motility, and SRC-dependent adhesion. In fact, migration was selectively abrogated by SRC and FAK inhibition in LKB1-deficient cells. Finally, whereas Kras mutant lung tumors were sensitive to the combined inhibition of the PI3K and MEK pathways, the workers found that Kras/Lkb1 tumors were resistant to these inhibitors, and that sensitivity could be restored by additional targeting of SRC. It is also important to note that the addition of Dasatinib to combined PI3K/MEK inhibition induced tumor shrinkage in LKB1-deficient tumors, revealing an important role of SFKs in tumor growth and promoting resistance to combined PI3K/MEK inhibition. It was somewhat surprising that single-agent Dasatinib led to increased volume of Kras/Lkb1 tumors and persisting Akt and EMT signatures. Lastly, Kras/Lkb1 mice treated with Dasatinib alone did not show any evidence of metastasis, further reinforcing the data that the Src family members are important mediators of metastatic progression in Kras/Lkb1-driven lung cancer. In conclusion, these results imply that despite the complex transcriptional and signaling changes that occur in the setting of LKB1 loss and progression of NSCLC, these tumors may still be addicted to isolated oncogenic events that can be successfully therapeutically targeted. These studies also demonstrate that integrated genomic and proteomic analyses can be used to identify signaling pathways that may be targeted for treatment.

Source: *Cancer Cell*



## Clinical Development

### Avastin Meets Primary Endpoint in a Second Phase III Study in Ovarian Cancer

Genentech announced that a second large, Phase III, international study showed that the combination of Avastin (bevacizumab) and chemotherapy, followed by the continued use of Avastin alone, increased PFS, compared to chemotherapy alone. Adverse events were consistent with those observed in pivotal trials of Avastin across tumor types for approved indications. Data from the study, ICON7, will be submitted for presentation at an upcoming medical meeting.

The ICON7 study sponsored by the Medical Research Council (MRC) and conducted by an international network of researchers in the Gynecologic Cancer Inter Group (GCIG) enrolled 1,528 women with newly diagnosed ovarian cancer who had already undergone surgery. Another Phase III study of Avastin (GOG 0218) in women with previously untreated advanced ovarian cancer presented in June at the Annual Meeting of the American Society of Clinical Oncology (ASCO) also met its primary endpoint of PFS. The GOG 0218 study used an Avastin dose of 15mg/kg (every three weeks) in combination with carboplatin and paclitaxel, followed by the continued use of Avastin alone, for a total duration of up to 15 months. In ICON7, majority of patients had advanced stage ovarian cancer; however, the trial also included patients with early stage disease. The ICON7 study used an Avastin dose of 7.5mg/kg (every three weeks) in combination with the same chemotherapy regimen, followed by the continued use of Avastin alone, for a total duration of up to 12 months.

*Source: Genentech*

### Afinitor More than Doubles PFS in Advanced Pancreatic NET

Novartis announced the results of a Phase III study, which showed that Afinitor (everolimus) tablets plus best supportive care (BSC) more than doubled PFS, versus placebo plus BSC in patients with advanced pancreatic neuroendocrine tumors (NET). Pancreatic NET can grow aggressively and at the time of diagnosis, nearly 60% of all patients have advanced disease, meaning the cancer has spread to other parts of the body and has become more difficult to treat. The median OS for patients with advanced pancreatic NET is 24 months. Currently, surgery and chemotherapy are the only available treatment options for patients with advanced pancreatic NET.

Findings from the RADIANT-3 (RAD001 In Advanced Neuroendocrine Tumors) study demonstrated that everolimus extended the PFS from 4.6 months to 11.0 months when compared with placebo. Additionally, the data showed everolimus reduced the risk of cancer progression by 65%. The study was presented at the 12<sup>th</sup> World Congress on Gastrointestinal Cancer, and is part of the largest clinical trial program in patients with advanced NET. Worldwide regulatory filings are planned for everolimus as the first mTOR inhibitor treatment for patients with advanced pancreatic NET. Afinitor is approved for the treatment of patients with advanced renal cell carcinoma (RCC), whose disease has progressed on or after treatment with the vascular endothelial growth factor (VEGF)-targeted therapy.

*Source: Novartis*



## Clinical Development (Cont'd)

### **Eisai Announces Results of Phase III Study of Dacogen in AML**

Eisai announced preliminary results from a randomized Phase III clinical trial of Dacogen (decitabine) for injection versus either a low-dose chemotherapy agent or supportive care in elderly patients with acute myeloid leukemia (AML).

OS was the primary endpoint of this study. Although Dacogen did not reach statistically significant superiority over the control arm, a trend was evident. The most frequently reported adverse events included neutropenia, anemia, thrombocytopenia, fever, and pneumonia. Sepsis and febrile neutropenia were reported as serious adverse events. Eisai is further examining the data to better understand the full implications of the study. Based on the primary analysis and supporting secondary data from additional endpoints, Eisai plans to submit a supplemental new drug application (sNDA) to the FDA for Dacogen for the treatment of elderly patients with AML and poor- or intermediate-risk cytogenetics. The submission of an application is planned by March 31, 2011. Recently, a five-day dosing regimen for Dacogen was approved by the FDA for the treatment of MDS (Myelodysplastic syndromes).

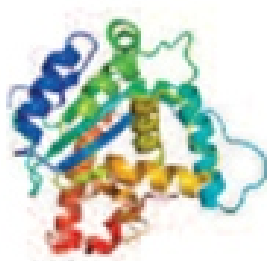
*Source: Eisai*

### **GDC-0449 does not Meet Primary Endpoint in 1<sup>st</sup> Line mCRC**

Curis announced top line results from a Phase II clinical trial conducted by Roche and Genentech of GDC-0449, a first-in-class Hedgehog pathway inhibitor. The Hedgehog pathway is normally active during embryonic development and plays a central role in cell differentiation and proliferation. Inappropriate activation or dysregulation of the Hedgehog pathway is believed to play a critical role in the proliferation and survival of certain cancer cells, including in basal cell carcinoma and medulloblastoma, as well as in colorectal, ovarian, pancreatic, small cell lung, and breast cancers.

GDC-0449 was tested in combination with Avastin and FOLFOX or FOLFIRI chemotherapy in first-line metastatic colorectal cancer (mCRC) patients. Of the 199 patients enrolled in this study, 195 patients received either a FOLFOX chemotherapy or FOLFIRI chemotherapy regimen in combination with bevacizumab every 14 days and were randomized to receive either a 150 mg daily dose of GDC-0449 or a placebo. The primary objective of the trial was to measure the period of PFS from randomization to disease progression or death. Secondary outcome measures included the measurement of Hedgehog protein expression in archival tissue and tracking of adverse events. The trial did not meet its primary endpoint of extending the time from randomization to disease progression or death in study patients who received GDC-0449 in addition to the current SOC of bevacizumab and chemotherapy when compared to those patients who received only the current SOC treatment. GDC-0449 is being developed by Roche and Genentech under a collaboration agreement between Curis and Genentech. It is expected that data from the study will be submitted for presentation in a future medical meeting.

*Source: Curis*



## Biomarkers

### pAkt at Ser473 Predicts Benefit of Paclitaxel Therapy in Breast Cancer

Akt is a serine/threonine protein kinase that has been implicated in the pathogenesis of cancer. The role of Akt phosphorylation (pAkt) at Ser-473 on the outcome of patients with breast cancer who receive taxane-based chemotherapy has not been examined in clinical settings, including adjuvant chemotherapy. In a study published in *JCO*, Yang *et al.* hypothesized that pAkt predicts benefit from the sequential addition of paclitaxel to adjuvant doxorubicin plus cyclophosphamide (AC) chemotherapy in patients with node-positive breast cancer, participating in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28 trial.

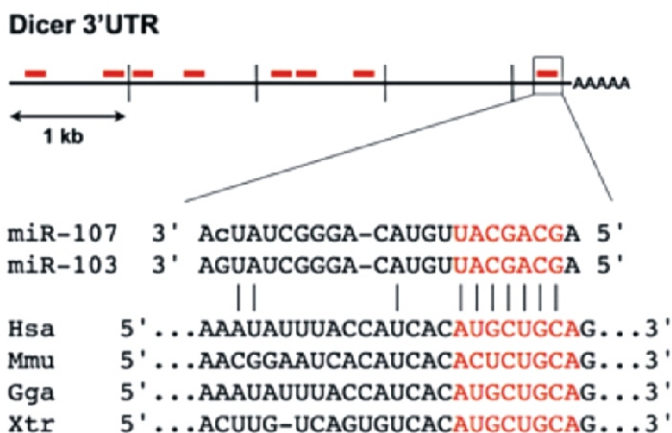
Primary tumors from the NSABP B-28 trial tissue microarray were available from 1,581 patients who were randomly assigned to receive either 4 cycles of AC alone, or followed by 4 cycles of paclitaxel. With a median follow-up of 9.1 years, there were no differences in disease-free survival (DFS) or overall survival (OS) with and without receiving paclitaxel among 975 patients with pAkt-negative tumors. In 606 patients with pAkt-positive tumors, the sequential addition of paclitaxel resulted in a 26% improvement in DFS or a 20% improvement in OS, which did not reach statistical significance. The study concluded that pAkt significantly predicts disease-free benefit from the sequential addition of paclitaxel to AC chemotherapy in patients with node-positive breast cancer. However, patients with pAkt-negative breast tumors do not appear to benefit from the addition of paclitaxel.

Source: *JCO*

### A MicroRNA Targeting Dicer for Metastasis Control

Although specific microRNAs (miRNAs) can be upregulated in cancer, global miRNA downregulation is a common trait of human malignancies. The mechanisms of this phenomenon and the advantages it affords remain poorly understood. The findings published in *Cell* by Martello *et al.* provide evidence that cancer cells use global downregulation of the miRNA network to induce epithelial plasticity and foster invasive and metastatic behaviors. The authors identified a miRNA family, miR-103/107, targeting Dicer, a key component of the miRNA processing machinery that plays a causal role in these events.

#### Schematic representation of the 3' UTR of Dicer



Cell, 141, June 25, 2010



## Biomarkers (Cont'd)

The researchers found that in metastatic cells, high levels of miR-103/107 attenuate Dicer expression: this empowers invasive and metastatic properties without major impact on primary tumor growth. Thus, it appears that distinct cellular functions are differentially sensitive to Dicer fluctuations. miR-103/107 keep Dicer below a threshold required for metastasis protection. Conversely, the miRNA network sustaining tumor growth operates safely at lower Dicer levels. miR-103/107 are both generated by, and are regulators of, Dicer; this mutual feedback relationship allows to scale down Dicer levels, but is also intrinsically incompatible with complete depletion, maintaining sufficient Dicer for growth control and, likely, other cellular functions. Another significant finding was the association of the miR-103/107-Dicer pair with EMT (epithelial-to-mesenchymal transition). This suggests a new pathway by which Dicer inhibition drifts epithelial cancer toward a less differentiated, mesenchymal fate to foster metastasis. The positive effects of antagomiR-103/107 at least suggest that modulation of miR-103/107 by RNA-based therapeutics may prove clinically useful for the treatment of breast cancer.

*Source: Cell*

### RT and Endpoint PCR Assays for Detecting Mutations in PI3K Oncogene

The PI3K pathway plays a significant role in colorectal, gastric, breast, and endometrial tumors, therefore, drugs inhibiting PI3K are a significant focus of current cancer drug development. Multiple scientific papers have shown that PI3K has the potential to be a clinically relevant biomarker for the prediction of individual response to specific cancer therapies. Diagnostic assays that detect mutations in PI3K will be an essential component of cancer drug development and personalized healthcare.

Roche has an ongoing program to develop a RT (real-time) PCR assay that detects mutations in the PI3K oncogene. The assay will run on Roche's cobas 4800 System, easy-to-use software that integrates sample preparation, amplification and detection, and results management. Roche has obtained a worldwide co-exclusive license for the biomarker PI3K from QIAGEN to develop these assays. Roche intends to make the PI3K PCR assay available to internal and external pharmaceutical partners for use in clinical drug trials.

*Source: Roche*

### Monitoring Cancer Therapy Using RECAF Blood Test

BioCurex announced its first set of results supporting the use of RECAF blood test to monitor cancer therapy. RECAF is a receptor for AFP (Alpha-fetoprotein). It is normally expressed by developing cells during fetal and embryonic life, but not expressed in most adult normal cells, which makes this marker an oncofetal antigen (AFP and CEA, two commonly used cancer markers, are also oncofetal antigens). RECAF is found on most cancer cells, including breast, colon, prostate, and lung cancers, and therefore it may be applicable to a much larger patient population. RECAF can be used in blood tests to determine whether a patient has cancer.

The test included samples from 27 human patients with early stages of breast cancer, who were tested before and after surgery. As a control, 15 samples from healthy individuals were also tested. The RECAF blood test detected 26 of the 27 patients as positive for breast cancer (sensitivity = 96%) and 14 of the 15 healthy individuals (93% specificity) were negative at the standard 4,700 RECAF Units cutoff. At a cutoff of 5,500 Units, there were no false positives (all healthy individuals were negative, thus the specificity of the test was 100%). These results indicate that the RECAF test can detect 9 out of 10 women with early stages of breast cancer while being negative in all healthy individuals. While RECAF's potential for cancer screening is important, the use of this marker for follow-up and monitoring of therapy is its most immediate application.

*Source: BioCurex*



## Regulatory



### FDA Rejects Roche's Avastin for Breast Cancer

A FDA panel dealt a blow to Roche's multibillion-dollar cancer drug Avastin on July 20, 2010 urging US officials to revoke the medicine's approval for breast cancer after concluding studies showed insufficient benefit for patients. Members of the FDA were not convinced with Avastin benefits in advanced breast cancer. The drug did not extend patients' lives but delayed cancer growth by up to three months. That improvement was not enough to justify serious complications, panelists said. They voted 12-1 to urge the FDA to remove the breast cancer approval.

Avastin, which is given intravenously, delayed the growth of cancer by 5.5 months in the initial study. In the two later studies, the time ranged from about one month to three months. Avastin, which works by starving tumors of the blood vessels they need to grow, did not extend overall survival (OS) in any of the studies. Advanced breast cancer patients generally live about 18 to 24 months, the FDA said. The FDA usually follows panel recommendations. A decision is due by September 17, 2010.

*Source: Reuters*

### FDA Approves Tasigna for Newly Diagnosed CML Patients

Following a priority review, the FDA has approved Tasigna (nilotinib) for the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase. With this approval, Tasigna becomes the first new therapeutic option for newly diagnosed patients since the introduction of Glivec (imatinib), providing a major advance for patients with this blood cancer.

The US approval was based on results of the pivotal ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+ CML Patients) Phase III clinical trial. Tasigna is a potent and selective inhibitor of the Bcr-Abl protein that causes the production of cancer cells in Ph+ CML. It is also active against a broad spectrum of Bcr-Abl mutations associated with resistance to Glivec. The randomized, open-label, multicenter ENESTnd trial compared the efficacy and safety of Tasigna with Glivec in adult patients with newly diagnosed Ph+ CML in chronic phase. It is the largest global randomized head-to-head comparison of two oral therapies ever conducted in newly diagnosed Ph+ CML patients in chronic phase. Tasigna surpassed Glivec in key measures of treatment efficacy, as has been previously reported. Tasigna eliminated Bcr-Abl faster than Glivec, resulting in lower rates of cancer progression even as early as 12 months. Treatment with Tasigna led to higher rates of both major molecular response and complete cytogenetic response than with Glivec.

*Source: Novartis*



## Regulatory (Cont'd)

### **Cabazitaxel Injection Approved by FDA after Priority Review**

Sanofi-aventis announced that the FDA has granted marketing authorization for Jevtana (cabazitaxel) injection in combination with prednisone for the treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC), previously treated with a docetaxel-containing treatment regimen.

Cabazitaxel, a microtubule inhibitor, in combination with prednisone was approved based on results from the Phase III TROPIC clinical study involving 755 patients with mHRPC, previously treated with a docetaxel-containing treatment regimen. The trial results demonstrated a statistically significant 30% reduction in the risk of death from mHRPC among patients taking Jevtana in combination with prednisone, compared with an active chemotherapy regimen consisting of a standard dose of mitoxantrone and prednisone. Investigator-assessed tumor response rates using Response Evaluation Criteria in Solid Tumors (RECIST) were 14.4% and 4.4% for cabazitaxel-treated and mitoxantrone-treated patients, respectively. Jevtana in combination with prednisone is the only FDA-approved regimen to significantly improve OS in patients previously treated with a docetaxel-based chemotherapy regimen.

*Source: Sanofi-aventis*

### **Pfizer Announces Voluntary Withdrawal of Mylotarg for AML from US Market**

Pfizer will discontinue the commercial availability of Mylotarg (gemtuzumab ozogamicin for injection (used for the treatment of relapsed acute myeloid leukemia (AML)) in the US, based on discussions with the FDA. The company will voluntarily withdraw the new drug application (NDA) for Mylotarg, effective October 15, 2010.

The approval of single-agent Mylotarg in the US was granted under the FDA's accelerated approval regulations based on the overall response rate (ORR) in three non-comparative studies, and required the submission of additional data to confirm clinical benefit. The required post-approval study (SWOG S0106) combining chemotherapy and Mylotarg did not demonstrate improved survival compared with chemotherapy alone in patients with previously untreated AML. Additionally, among all patients evaluable for early toxicity, the fatal induction toxicity rate was significantly higher in subjects given the combination of standard induction chemotherapy and Mylotarg than in those treated with chemotherapy alone. Mylotarg was approved in the US as a single agent for patients with CD33 positive AML in first relapse, who are 60 years of age or older and are not considered candidates for other cytotoxic chemotherapy.

*Source: Pfizer*