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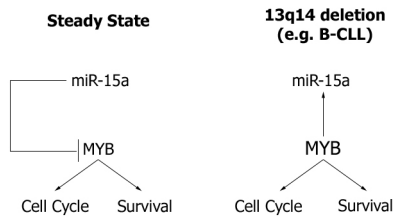
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INTELLIGENT INSIGHTS. SMARTRESULTS.

## Myb/miR-15a Regulatory Loop



Blood, 113, Jan 15, 2009

## In the Spotlight:

### c-Myb–miR-15a, an Autoregulatory Feedback Loop in Human Hematopoiesis

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GPC Biotech and Agennix Announce Proposed Merger

Novelos and Mundipharma Sign Collaboration Agreement

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UCB and WILEX to Enter into Strategic Alliance

Micromet Enters into Agreement with Bayer Schering Pharma AG

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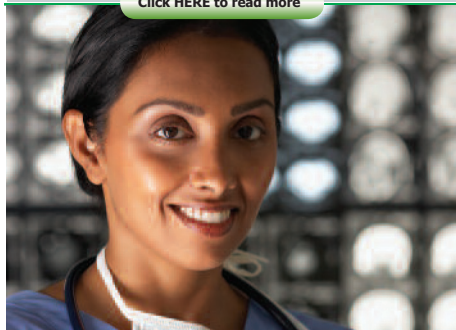
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Longer Survival with TG4010 in Phase IIb NSCLC Trial

Bavituximab Achieves Primary Endpoint in Lung & Breast Cancer Trials

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## Biomarkers

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Rel A as a Biomarker of Clinical Outcome in CLL

Deletion of *IKZF1* and Poor Prognosis in ALL

TP53 Mutations Predicts Rapid Disease Progression in CLL

MACC1 Predicts Colon Cancer Metastasis

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## Regulatory

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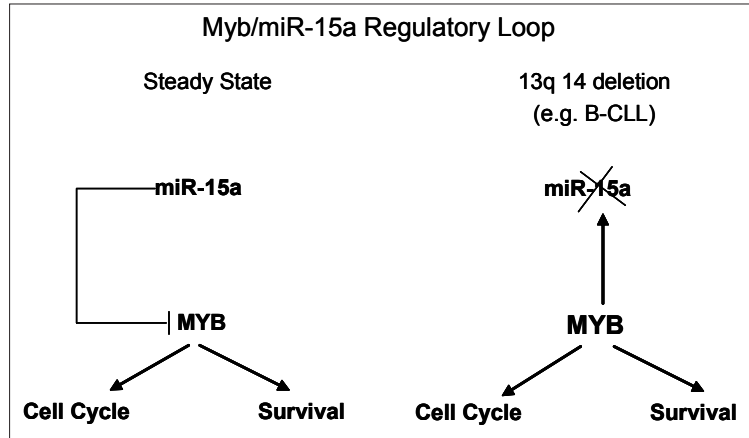
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# Spotlight Report

## c-Myb–miR-15a, an Autoregulatory Feedback Loop in Human Hematopoiesis



*Blood, 13, Jan 15, 2009*

The c-myb proto-oncogene, described nearly three decades back, is the founding member of a family of genes, A-myb (MYBL1), B-myb (MYBL2), and c-myb (MYB). These encode obligate hematopoietic transcription factors that regulate genes responsible for self-renewal, lineage commitment, and differentiation. Its aberrant expression is implicated in a variety of human malignancies ranging from solid tumors like colon and breast carcinoma to leukemia. The gene deregulation can occur due to several mechanisms that include structural changes, genomic rearrangements, gene amplification

or its inappropriate or over-expression. The regulatory factors and control mechanism of c-myb have been an area of intense study.

In a recent issue of *Blood*, Zhao et al demonstrate that post-transcriptional regulation of c-myb expression is governed by a micro RNA, specifically miR-15a; and that c-Myb–miR-15a autoregulatory feedback loop is of potential importance in human hematopoiesis. Non-coding microRNAs are important post-translational regulators of gene expression and target transcription factors. They exert this effect by suppressing mRNA translation, or by promoting mRNA physical destruction. Myb in fact, acts a transcription factor for its own inhibitor, the miR-15a precursor gene, which, after maturation, interferes with Myb mRNA translation. miR-15a promoter was shown to contain several potential c-myb protein binding sites. In vitro studies using human CD34 cells, the researchers found that the expression of c-Myb and miR-15a were inversely correlated in cells undergoing erythroid differentiation and the over-expression of miR-15a blocked both erythroid and myeloid colony formation. The effects of miR-15a are dependent on the stage of development of the cell with colony-forming unit–erythroid being more susceptible to inhibition than burst forming unit-erythroid. In addition to its role as a regulator, miR-15a may also play a possible role as a tumor suppressor. Earlier studies have also shown that deregulated expression of miR-15a induces apoptosis by targeting the antiapoptotic protein BCL2. The authors finally hypothesize that mutations in miR-15a precursors or miR-15a binding sites in the c-myb might play a role in the pathogenesis of human hematopoietic malignancies.

*Source: Blood*



## Business News

### GPC Biotech and Agennix Announce Proposed Merger

GPC Biotech and Agennix announced that the two oncology-focused biotechnology companies have signed a Business Combination Agreement under which they propose to merge their businesses. In the transaction, GPC Biotech is to be merged onto a new German company, which will hold all of the shares of Agennix and a €15 million cash contribution by dievini Hopp BioTech holding GmbH & Co KG, one of the largest shareholders of GPC Biotech. The merger combines GPC Biotech's and Agennix's oncology pipelines, with the clinical development and financial resources of GPC Biotech and dievini Hopp BioTech holding.

The new company will focus on the development of new anti-cancer therapies. GPC Biotech currently has two oncology programs in clinical development: satraplatin, an oral platinum compound and RGB-286638, a multi-targeted protein kinase inhibitor. The lead compound will be Agennix's talactoferrin, a novel dendritic cell recruiter and activator, being developed for lung, kidney and other cancers, as well as for severe sepsis. Talactoferrin has recently entered Phase III clinical testing for non-small cell lung cancer (NSCLC).

*Source: Agennix*

### Novelos Therapeutics and Mundipharma Sign Exclusive Collaboration Agreement

Novelos Therapeutics has signed an exclusive collaboration agreement with Mundipharma International Corporation Limited to commercialize in Europe and Asia / Pacific (excluding China) Novelos' lead compound, NOV-002, which is in a pivotal Phase III trial for NSCLC under a Special Protocol Assessment (SPA) and Fast Track.

Under the terms of the collaboration agreement, Novelos may receive up to \$25 million of launch milestones and \$60 million of fixed sales-based payments. Novelos will receive a double-digit royalty, which increases as the annual sales increase in the licensed territories. Mundipharma will be responsible for certain development activities, regulatory submissions and commercialization of NOV-002 in the licensed territories. Novelos retains all rights and responsibilities in the US and the rest of the Americas.

*Source: Novelos*

### Tragara to Jointly Develop S\*BIO's Novel Multi-kinase Inhibitor

S\*BIO has granted a worldwide exclusive license to Tragara to develop and commercialize its novel multi-kinase inhibitor, SB1317. Under the terms of the agreement, S\*BIO is eligible to receive up to \$112.5 million in payments. This includes an upfront fee, development and sales milestone payments and up to double-digit royalties. Additionally, S\*BIO will perform certain preclinical activities for Tragara under a defined workplan in return for research fees. Tragara is responsible for all IND enabling, development and commercialization activities under the agreement.

SB1317 is a novel orally-available, multi-kinase inhibitor with excellent pharmacological and pharmaceutical properties. SB1317 development will be initially focused on the treatment of hematologic malignancies and Tragara will also explore the therapeutic potential of the compound's activity in solid tumors.

*Source: Tragara*



## **Business** (cont'd.)

### **UCB and WILEX to Enter into Strategic Alliance**

UCB Pharma and WILEX announced that they have agreed to enter into a strategic partnership. WILEX will acquire world-wide rights to develop UCB's entire preclinical oncology portfolio, comprising two small-molecule programmes and three antibody programmes. UCB retains exclusive rights to re-purchase each of the five programmes, following completion of initial clinical feasibility studies for each programme. Furthermore, UCB assumes the responsibility for further development and commercialization of each product. In this case, WILEX will receive development and commercialization milestone payments and royalty payments from UCB.

Alternatively, in the event UCB does not exercise its re-purchase right for each programme, WILEX will retain rights to develop as well as commercialize each programme and UCB will receive milestone and royalty payments from WILEX. As a strategic investor, UCB will invest €10 million in WILEX upon closing. WILEX will also make milestone payments of €10 million in total upon application of clinical Phase I trial and first dose in man, expected within approximately 12 months upon closing.

*Source: UCB*

### **Micromet Enters into Agreement with Bayer Schering Pharma AG**

Micromet announced the signing of an option, collaboration and license agreement with Bayer Schering Pharma AG, Germany, under which Bayer Schering Pharma has the exclusive option to obtain a license to one of Micromet's preclinical BiTE® antibodies against an undisclosed oncology target. 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.

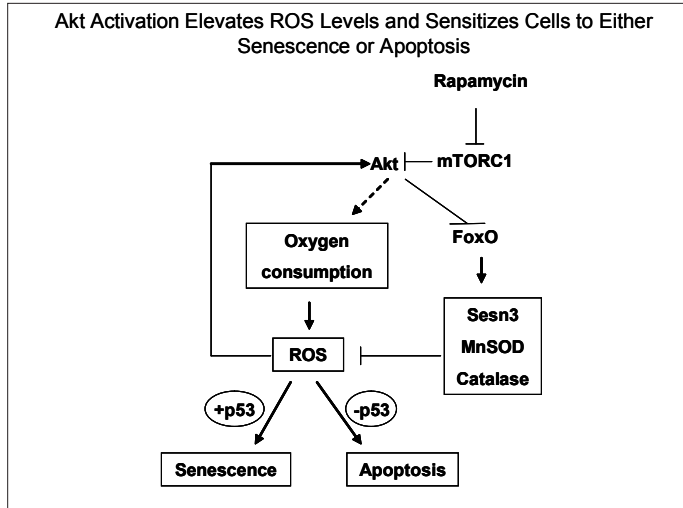
Under the terms of the agreement, Bayer Schering Pharma will pay Micromet a €4.5 million fee to secure a one year option on a specific BiTE antibody. Bayer Schering Pharma may exercise this option prior to January 5, 2010 through the additional payment of an option exercise fee. The exercise of the option would trigger a formal collaboration between Micromet and Bayer Schering Pharma on the development of the BiTE antibody through the completion of Phase I clinical trials. Micromet would be eligible for an option exercise fee and milestone payments of up to €290 million in total and up to double digit royalties based on tiered net sales of the product. In addition, Micromet would be reimbursed for its R&D expenses incurred in connection with the development of the BiTE antibody in the collaboration with Bayer Schering Pharma.

*Source: Micromet*



# Research Highlights

## Akt Sensitizes Cells to Oxidative Apoptosis



*Cancer Cell, 14, Dec 9, 2008*

The thrust in current oncology research is to characterize the molecular changes that govern the initiation and progression of cancer so that more efficient targeted therapies can be designed. It is now evident that cell regulation mechanisms are highly dependent on cell type and cellular context and signals that normally lead to progression of cancer can, in contrast, contribute to tumor suppression early in transformation by triggering senescence or cell cycle arrest. The PI3K/Akt signaling pathway is implicated in the initiation and maintenance of cancer with the hyperactivated serine/threonine kinase Akt playing a pro-tumorigenic role by promoting cell resistance to cytotoxic agents that induce apoptosis. It is also well known that oncogenic and oxidative stress-induced senescence acts as a barrier to cell transformation.

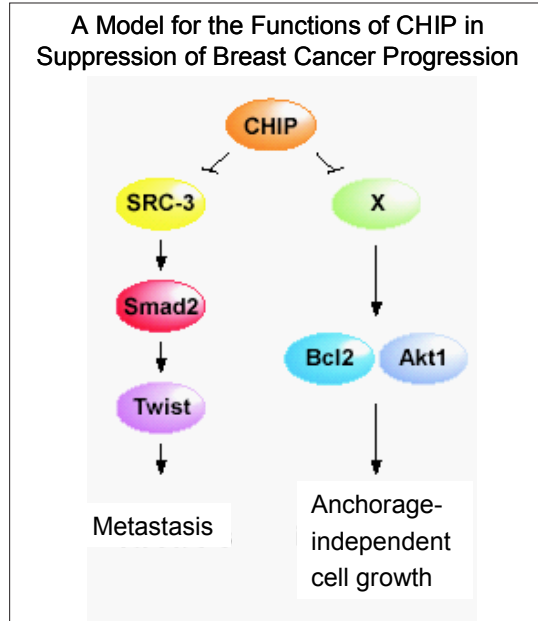
In a recent publication in *Cancer Cell*, Nogueira et al. show that Akt can induce the accumulation of oxygen radicals in murine fibroblasts and human cancer cells derived from glioblastoma and ovarian tumors, and this can be exploited to selectively target such sensitized cells. The mechanism for this is the induction of intracellular reactive oxygen species (ROS) by the PI3K/Akt pathway through increased oxygen consumption and impairing ROS scavenging downstream by inhibiting FoxO transcription factors, particularly sestrin 3. The elevation of ROS then sensitizes cells to either senescence or apoptosis depending on p53 status. Rapamycin, which inhibits mTORC1, further activates Akt as consequence of the negative regulatory loop inhibition. Thus, a strategy to selectively eradicate cancer cells with hyperactivated Akt by oxidative stress might be beneficial for treating tumors containing high levels of ROS, especially if combined with drugs that modulate specific signal transduction pathways.

*Source: Cancer Cell*



**Research Highlights**  
(cont'd.)

**CHIP Suppresses Tumor Progression in Breast Cancer**



**Nature Cell Biology, Feb 8, 2009,  
Advance Online Publication**

Twist, marker protein of the epithelial-mesenchymal transition were also upregulated. This regulation may account for the enhanced migration and invasion of shCHIP cells. A proteomic analysis was carried out that identified transcriptional co-activator SRC-3 as a direct target for ubiquitylation and degradation by CHIP. However knocking down, SRC-3 in shCHIP cells reduced the expression of Smad and Twist, and suppressed tumor metastasis in vivo. In contrast, SRC-3 co-expression prevented CHIP-induced suppression of metastasis formation. The study demonstrated that CHIP inhibits anchorage-independent cell growth and metastatic potential by degrading oncogenic proteins including SRC-3.

*Source: Nature Cell Biology*

CHIP (carboxyl terminus of Hsc70-interacting protein), a U-box-type ubiquitin ligase induces ubiquitylation and degradation of its substrates, which include several oncogenic proteins. However, the association between CHIP and tumor progression has not been elucidated. In a study published in Nature Cell Biology, Masashi Kajiro and colleagues showed that CHIP suppresses tumor progression in human breast cancer by inhibiting oncogenic pathways. A study was conducted on samples of breast cancer tumors and normal tissue from 27 breast cancer patients and the expression levels of CHIP mRNA were examined. The study showed significant negative correlation between CHIP mRNA levels and tumor malignancy in human breast cancer tissues.

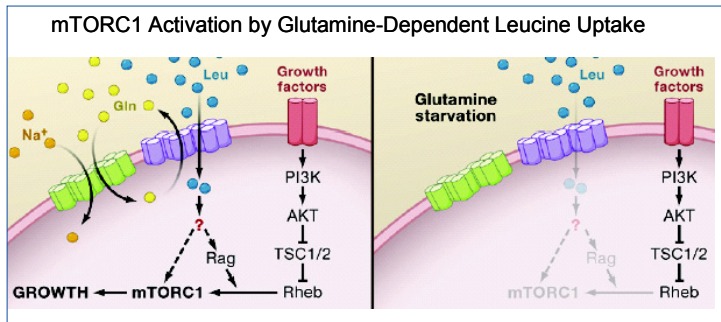
In a nude mouse Xenograft model, CHIP significantly suppressed tumor growth and metastasis. However, knockdown of CHIP (shCHIP) in breast cancer cells resulted in rapid tumor growth and metastatic phenotypes in mice. In cell based experiments, the levels of anti-apoptotic proteins, such as Bcl2 and Akt1, were higher in the shCHIP cells.

In addition, expression levels of Smad2, a signal transducer in the TGF- $\beta$  signaling pathway, as well as



## Research Highlights (cont'd.)

### An Amino Acid Shuffle Activates mTORC1



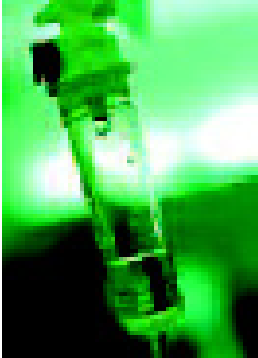
*Cell 136, Feb 6, 2009*

The target of rapamycin complex 1 (TORC1) serine/ threonine kinase activates cell growth in response to nutrients (amino acids), growth factors, and cellular energy status (ATP). Growth factors activate mTORC1 by inhibiting the tuberous sclerosis complex (TSC1-TSC2) downstream of AKT. TSC1-TSC2 is a GTPase-activating protein (GAP) for the small GTPase Rheb, the direct activator of mTORC1. Although the signaling cascades leading from growth factors and energy to mTORC1 activation are known, the pathway that leads from

amino acids to mTORC1 activation is less clear. It has been recently shown that amino acids signal to mTORC1 through heterodimers of Rag GTPases, which deliver mTORC1 to GTP loaded Rheb.

In a study published in *Cell*, Nicklin et al. show that cellular uptake of L-glutamine and its subsequent rapid efflux in the presence of essential amino acids (EAA) is the rate-limiting step that activates mTOR. Using S6K1 and 4EBP phosphorylation as a readout for mTORC1 activity, investigators demonstrated that mTORC1 activation in response to L-leucine requires preloading of cells with L-glutamine. Using pharmacological inhibitors and short-interfering RNAs (siRNAs) the authors show that L-glutamine uptake requires SLC1A5, a high-affinity transporter for neutral amino acids that lack branched side chains. Loss of SLC1A5 function inhibits cell growth and activates autophagy. The molecular basis for L-glutamine sensitivity is due to SLC7A5/SLC3A2, a bidirectional transporter that regulates the simultaneous efflux of L-glutamine out of cells and transport of L-leucine/EAA into cells. These findings may also have implications for cancer. Although activation of mTORC1 does not require glutamine metabolism, the results suggest that glutamine could also drive tumor growth through activation of mTORC1.

*Source: Cell*



# Clinical Development

## Combination of Tarceva® and Avastin® Improves PFS in Advanced NSCLC

Genentech announced that a Phase III study (ATLAS) of Tarceva® (erlotinib) in combination with Avastin® (bevacizumab) as maintenance therapy following initial treatment with Avastin plus chemotherapy in advanced NSCLC met its primary endpoint. ATLAS is a global, multicenter, randomized, double-blind, placebo-controlled study that enrolled 1,157 patients with locally advanced, recurrent or metastatic NSCLC. The study was stopped early on the recommendation of an independent data safety monitoring board after a pre-planned interim analysis. Analysis showed the combination of Tarceva and Avastin significantly extended the progression-free survival (PFS), compared to Avastin plus placebo. A preliminary safety analysis showed adverse events were consistent with previous Avastin or Tarceva studies, as well as trials evaluating the two drugs together. No new safety signals were observed.

"We plan to discuss these data with the FDA to determine next steps. Tumors use different pathways to grow and these results showed that combining medicines targeting two of these pathways instead of one delayed disease progression", said Hal Barron, Genentech's senior vice president, Development and Chief Medical Officer.

*Source: Genentech*

## Pfizer Discontinues Phase III Trial of Axitinib in Advanced Pancreatic Cancer

Pfizer announced the discontinuation of a Phase III study of its investigational agent axitinib, an oral and selective inhibitor of VEGF receptors 1, 2 and 3, for the treatment of advanced pancreatic cancer. Based on an interim analysis, an independent Data Safety Monitoring Board found no evidence of improvement in the primary endpoint of survival in patients treated with axitinib and gemcitabine, compared to gemcitabine alone. The full data set from this study is being analyzed and more details will be presented at an upcoming medical meeting.

"These results were disappointing, given the trend towards prolonged survival seen in a Phase II study of axitinib in this extremely difficult-to-treat patient population. However, we remain steadfastly committed to continued investigation of axitinib in renal cell carcinoma where it is currently in Phase III for 2nd line treatment. We also are continuing to evaluate axitinib in Phase II trials in other tumor types, including advanced NSCLC and colorectal cancer." said Mace L. Rothenberg, M.D., Senior vice president, Clinical development and medical affairs, Pfizer's Oncology Business Unit.

*Source: Pfizer*



## Clinical Development (cont'd.)

### **Pixantrone Increases PFS in Relapsed Aggressive NHL**

Cell Therapeutics (CTI) announced preliminary PFS results from its pivotal Phase III EXTEND (PIX301) trial of pixantrone, a DNA intercalating antitumor agent, in patients with relapsed, aggressive non-Hodgkin's lymphoma (NHL) who received two or more prior therapies and who were sensitive to treatment with anthracyclines. Results demonstrate statistically significant improvement in median PFS with pixantrone compared to standard chemotherapy (4.7 months vs. 2.6 months). PFS was a prospectively defined secondary endpoint in the study.

The Company had previously announced that this pivotal Phase III trial had achieved its primary endpoint demonstrating a significantly higher rate of confirmed and unconfirmed complete remissions with pixantrone compared to patients treated with standard chemotherapy (20.0% vs. 5.7%). "Pixantrone is the first agent in this patient population to demonstrate a significant and meaningful PFS advantage. We believe these data will support a priority review designation on our New Drug Application once we share them with the FDA," stated James A. Bianco, Chief Executive Officer of CTI.

*Source: Cell Therapeutics*

### **Longer Survival for Patients Treated with TG4010 in Phase IIb NSCLC Trial**

Transgene announced additional data from the ongoing, randomized, open label, controlled Phase IIb clinical study of its therapeutic vaccine TG4010 (MVA-MUC1-IL2) as an adjunct to first line chemotherapy in patients with advanced NSCLC. The study enrolled 148 patients to assess the efficacy of TG4010 in combination with cisplatin and gemcitabine (experimental arm) compared to the chemotherapy regimen alone (control arm). The data at 21 months of median follow-up confirms a statistically-significant 6-month increase in median survival (17.1 months in the experimental arm vs. 11.3 months in the control arm) in patients with normal levels of activated Natural Killer cells at baseline, a sub-population identified by Transgene's biomarker programme. The measurement of this biomarker is based on flow cytometry, a technique routinely used in hospital laboratories.

The results are consistent with previous reported data on the efficacy of the drug after 17 months of median follow-up, which were released at ESMO in September 2008. The company plans to have meetings with the FDA and the European Medicines Agency during the second quarter of 2009 in preparation of a Phase III programme in metastatic NSCLC.

*Source: Transgene*

### **Bavituximab Achieves Primary Endpoint in Lung and Breast Cancer Trials**

Peregrine reported that bavituximab, a monoclonal antibody, achieved the primary efficacy endpoint in the first stage of its ongoing Phase II clinical trial in patients with NSCLC and advanced breast cancer. The open-label, Simon two-stage study is designed to evaluate the safety and efficacy of the combination of bavituximab with the chemotherapy drugs carboplatin and paclitaxel in locally advanced or metastatic breast cancer and NSCLC. The primary objective of the trial is to assess the overall tumor response rate. Secondary objectives include measuring time to tumor progression, duration of response, overall patient survival and safety parameters.

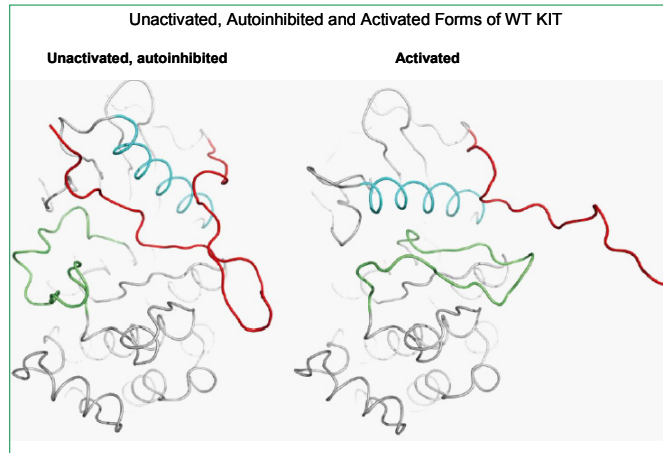
Fourteen of the 15 patients with advanced breast cancer enrolled in first stage of the trial were deemed evaluable for tumor response, with 7 patients achieving an objective response by approximately 8 weeks, after completing two treatment cycles. Six of the patients achieved partial tumor responses and 1 patient achieved a complete tumor response, according to RECIST criteria. In NSCLC trial of bavituximab, 17 of the 21 patients enrolled in first stage were deemed evaluable for tumor response by the end of 4 treatment cycles, with 6 patients achieving partial tumor responses and 1 patient achieving a complete tumor response, according to RECIST criteria.

*Source: Peregrine<sup>1,2</sup>*



# Biomarkers

## KIT Kinase Mutants Show Resistance to Imatinib and Sunitinib in GIST



**PNAS, 106, Feb 3, 2009**

Acquired resistance to systemic therapy is a critical problem in treating metastatic cancers. Such resistance is seen in the secondary mutants of KIT identified in gastrointestinal stromal tumors (GIST). Most GISTs have primary activating mutations in the genes encoding the Receptor Tyrosine Kinases (RTK) KIT. The majority of KIT mutations affect the juxtamembrane (JM) region of the protein encoded by exon 11 of the gene. The efficacy of the inhibitors imatinib mesylate and sunitinib malate in GIST patients has been linked to their inhibition of the mutant KIT proteins.

In a report published in PNAS, Gajiwala et al. investigated the mechanism using structural biological and functional enzymology studies of wild type (WT) and mutated KIT proteins

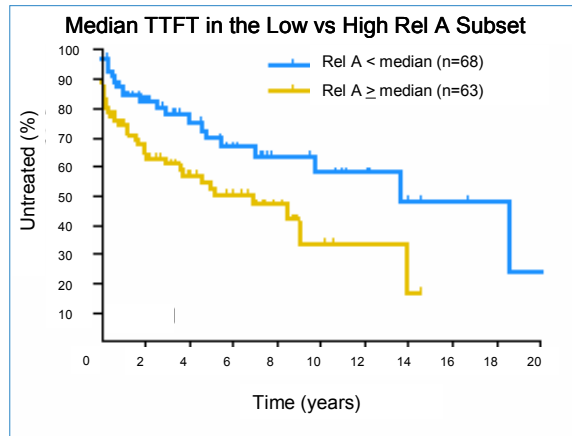
comprising the JM and kinase domains. The results show that sunitinib and imatinib prevent KIT activation by targeting the unactivated conformation of KIT. They are more potent inhibitors of unactivated WT KIT than fully activated, phosphorylated KIT. Imatinib has been shown to target the unactivated state of the enzyme where as sunitinib binds to the unactivated conformation of KIT at the ATP-binding pocket, thus blocking autoactivation. Sunitinib has shown efficacy against certain imatinib-resistant mutants, although a subset that resides in the activation loop, including D816H/V, remains resistant. Biochemical and structural data presented in this report provide an explanation for the different drug sensitivities of GISTs to sunitinib and imatinib observed in patients. These findings suggest that successful cancer treatment regimens may require a mixture of kinase inhibitors that block various conformations of the target protein.

Source: PNAS



## Biomarkers (cont'd.)

### Rel A as a Biomarker of Clinical Outcome in CLL



**JCO, 27 Feb 10, 2009**

IgVH mutation status, CD38 expression, and ZAP-70 expression although Rel A was markedly elevated in patients with advanced disease and in those who had previously received treatment. Elevated Rel A DNA binding was predictive of significantly shorter time to first treatment (TTFT) as well as time to subsequent treatment. The median TTFT in the low Rel A subset was 13.6 years vs 6.8 years in the high Rel A subset. Moreover, Rel A was the most predictive marker of survival both from date of diagnosis and date of entry into the study and retained prognostic significance in multivariate analysis for both time to first treatment and overall survival in the presence of Binet stage, IgV<sub>H</sub> mutation status, CD38, and ZAP-70. In conclusion, this study identifies Rel A as a superior prognostic marker for survival in CLL and crucially demonstrates that Rel A has the potential to predict the duration of response to therapy.

Source: JCO

Clinical studies have shown that unmutated immunoglobulin VH (*IgV<sub>H</sub>*) genes, high zeta-chain-associated protein kinase 70 (ZAP-70) expression, high CD38 expression and cytogenetic abnormalities are all associated with a poor prognosis in chronic lymphocytic leukemia (CLL). Nevertheless, search for better markers is required to predict the clinical course of patients more accurately. Nuclear factor kappa B (NF-κB) proteins have been known to be key regulators of cell survival, cell growth, immune response, and inflammation, and have been shown to be elevated in CLL cells.

In a study reported in JCO, Hewamana et al. analyzed Rel A (a subunit of NF-κB) DNA binding in 131 patients and correlated the results with the established markers of prognosis and clinical outcome. Rel A DNA binding was independent of

### Deletion of IKZF1 and Poor Prognosis in ALL

Acute lymphoblastic leukemia (ALL), common among children, has a cure rate of more than 80%. Treatment failure is seen in BCR-ABL1–rearranged and MLL (mixed-lineage leukemia)–rearranged ALL and relapse occurs in up to 20% of patients. Deletion of IKZF1, which encodes the lymphoid transcription factor IKAROS, is a very frequent event in BCR-ABL1–positive ALL, suggesting that perturbation of IKAROS is a key event in the pathogenesis and progression of BCR-ABL1 leukemia.

In a recent NEJM issue, Mullighan et al. reported a study conducted on copy-number abnormalities driven by the deletion or mutation of IKZF1 in 221 children with high-risk ALL, which was further validated in an independent cohort of 258 patients with B-cell–progenitor ALL. Results show a mean of 8.36 copy-number abnormalities per patient in the original cohort. The most common deletions involved CDKN2A/B (45.7%), the lymphoid transcription-factor genes PAX5 (31.7%), IKZF1 (28.6%), ETV6 (12.7%), RB1 (11.3%), and BTG1 (10.4%). Among the 221 patients, the entire IKZF1 locus was deleted in 16 patients, and in 47 patients, a subgroup of exons or the genomic region immediately upstream of IKZF1 was deleted. In 20 of these 47 patients, there was a deletion of coding exons 3 through 6, which results in expression of a dominant-negative form of IKAROS, Ik6, which lacks all N-terminal, DNA-binding zinc fingers. Since BCR-ABL1 ALL has a poor prognosis, these findings suggest that the mutation of IKZF1 is a key determinant of a poor outcome both in patients with BCR-ABL1–positive and negative patients. These results provide a rationale for the integration of IKZF1 status in the evaluation of patients with ALL.

Source: NEJM



## **Biomarkers** (cont'd.)

### **TP53 Mutations Predicts Rapid Disease Progression in CLL**

The clinical course of CLL patients is highly variable. CLL patients with deletions of the long arm of chromosome 13 (del (13q)) show good prognosis whereas patients with deletions of the short arm of chromosome 17 (del (17p)) show poor prognosis. The tumor suppressor gene TP53 is located at 17p13. It regulates a network that senses extracellular stress, oncogene activation and DNA damage.

In a study reported in *Leukemia*, Dicker et al. hypothesized loss of TP53 function to be partially responsible for the poor prognosis of del (17p) CLL patients. Investigators analyzed a large cohort of CLL patients (n=193) for TP53 mutations by two independent methods and correlated the results to cytogenetics and clinical outcome data. Denaturing high performance liquid chromatography (DHPLC) analysis detected 24 mutations in 20 different patients (10.4%), which were further confirmed by DNA sequencing. The Amplichip identified a total of 30 mutations in 25 different patients (13%). The time from diagnosis to initial treatment (TTT) was used as the primary study end point for evaluation of the clinical significance of TP53 aberrations. The clinical courses of patients with del (17p) and with isolated TP53 mutations were unfavorable with a median TTT of 21.3 and 2 months, respectively, compared to 64.9 months in patients without aberrations. In the absence of del (17p), CLL patients with TP53 mutation alone require early treatment, which was not found to be significantly different from patients with del (17p). Screening for TP53 mutations adds prognostic information for individual CLL patients and might help to identify patient not eligible for therapy which target the p53 pathway in tumor cells.

*Source: Leukemia*

### **MACC1, a Key Regulator of HGF-MET Signaling, Predicts Colon Cancer Metastasis**

The hepatocyte growth factor HGF-MET pathway plays a key part in cellular growth, angiogenesis, cell motility, invasiveness and metastasis. In a study published in *Nature Medicine*, Stein et al. report the identification and characterization of a previously undescribed gene associated with colon cancer, MACC1 (metastasis-associated in colon cancer-1) in primary and metastatic carcinomas. MACC1 mRNA expression in primary tumors directly correlates with metastasis formation and metastasis-free survival. These features qualify MACC1 as a gene that can be used to predict the risk of metastasis and guide further diagnostic and therapeutic decisions. Investigators also characterized key cellular aspects of MACC1 function, identifying a gene encoding the HGF receptor, MET, as one of its transcriptional targets. MACC1-induced cell motility, proliferation, HGF-dependent scattering in vitro and, in vivo metastasis were blocked by siRNAs targeting MACC1 or MET. The detailed cellular and molecular studies indicate that MACC1 acts as a key regulator of the HGF-MET pathway and could represent a major target for intervention in metastasis formation. For clinical practice, MACC1 will be useful for the identification of poor prognosis subjects with colorectal cancer.

*Source: Nature Medicine*



# Regulatory



## **NICE Recommends Use of Sutent as First-Line Treatment for mRCC**

Pfizer said that the UK's National Institute for Health and Clinical Excellence (NICE) has issued its final appraisal document (FAD) recommending the use of Sutent® (sunitinib malate) as a first-line treatment for patients with metastatic renal cell carcinoma mRCC (advanced kidney cancer). According to NICE, "Sutent provided a step-change in the first-line treatment of advanced and/or metastatic RCC and more than 20% of the public and patients that responded in consultation highlighted this impressive benefit from sunitinib."

In September 2008, NICE had issued an appraisal consultation document (ACD) which advised against the use of all four medicines for the treatment of mRCC. Today's announcement reverses their previous recommendation regarding the coverage of Sutent, and makes Sutent the only one of the four medicines, under review, that is recommended for coverage to date.

*Source: Pfizer*

## **EC Grants Approval to FIRMAGON® for Treatment of Prostate Cancer**

Ferring Pharmaceuticals announced that it has received marketing authorization from the European Commission (EC), for FIRMAGON® (degarelix), a new GnRH receptor antagonist indicated for patients with advanced, hormone-dependent prostate cancer.

In Phase III studies degarelix produced a significant reduction in levels of testosterone, within 3 days in more than 96% of study patients. The data show that degarelix provided an extremely fast effect on testosterone levels, close to the immediate effect achieved with surgery (orchidectomy). The EC approval for FIRMAGON® follows FDA approval in December 2008.

*Source: Ferring Pharmaceuticals*

## **MabThera Receives Positive Opinion in Europe for First-line Treatment for CLL**

Roche announced that the European Union's Committee on Human Medicinal Products (CHMP) has issued a positive recommendation for the use of MabThera (Rituximab®) with any chemotherapy combination as a first-line treatment for chronic lymphocytic leukaemia (CLL). The label extension is based on the results of the international CLL8 study which showed that the median PFS was 42.8 months in the MabThera plus chemotherapy (fludarabine and cyclophosphamide) treatment arm compared to 32.3 months in the chemotherapy arm. MabThera is already licensed for the treatment of non-Hodgkin's lymphoma (NHL).

Genentech and Biogen Idec co-market MabThera in the US, and Roche markets MabThera in the rest of the world, except Japan, where MabThera is co-marketed by Chugai and Zenyaku Kogyo Co. Ltd.

*Source: Roche*