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INTELLIGENT INSIGHTS. SMART RESULTS

In the Spotlight:

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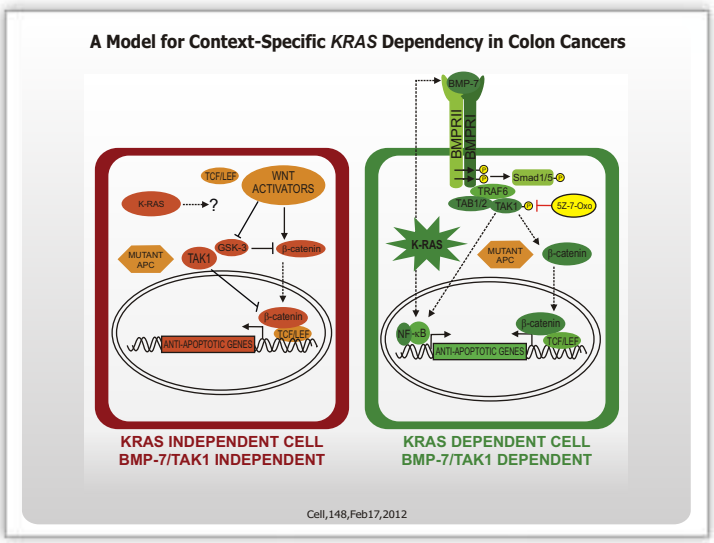

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Tumor of the Month - Colorectal Cancer

Colon cancer is one of the high profile cancers, perhaps in large part to the aggressive educational campaign promoted by Katie Couric, who began her crusade to educate people about colon cancer and colon cancer screening after the death of her husband in 1998.[1] The American Cancer Society estimates that in 2012, there will be 103,170 new cases of colon cancer; 40,290 new cases of rectal cancers; and 51,690 deaths due to colorectal cancer (CRC).[2] The lifetime risk for CRC is ~5.1% with a slightly lower risk for women than for men. If statistics for men and women are combined, CRC is the second leading cause of deaths due to cancer. Despite this sobering statistic, the number of deaths from CRC has declined over the last 20 years, and there are currently more than a million colon cancer survivors in the US alone. Aggressive screening has resulted in diagnosis at earlier stages, when a cure is more likely. Patients diagnosed with stage I disease have a 5-year survival of 76%, whereas those diagnosed with stage IV disease have an expected 5-year survival of 6%.

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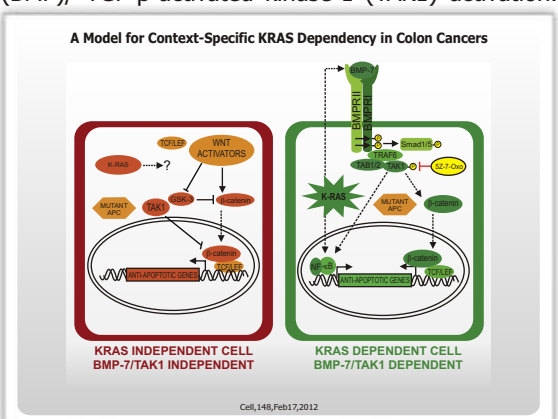
The E-newsletter team: Dr. Shirish Kumar, Sarika Manchanda, Dr. Vinamrata Bhatia, Kimberly Scata, Courtenay Veenis, Monica Tuli.

Spotlight Report

TAK1 Inhibition Promotes Apoptosis in *KRAS*-dependent Colon Cancers

Targeted cancer therapies exploit specific mutations that drive survival signals in subsets of tumors, leading to successful genotype-directed clinical applications of small molecule inhibitors. However, *KRAS*-activating mutations remain a critical therapeutic challenge. These mutations are generally associated with treatment-refractory tumors, and in colon cancer, *KRAS* mutations predict failure of response to antibodies targeting overexpressed wild-type EGFR. Thus, patients with *KRAS*-mutant colon cancers are excluded from targeted EGFR therapies and have only limited therapeutic options.

Colon cancers frequently harbor *KRAS* mutations, yet only a subset of *KRAS*-mutant colon cancer cell lines are dependent on *KRAS* signaling for survival. By analyzing the *KRAS*-dependent subset of *KRAS* mutant colon cancer cells, Singh *et al.* in *Cell* uncovered a pathway by which *KRAS* enhances Wnt activity through bone morphogenetic protein-7 (BMP)/ TGF-β-activated kinase-1 (TAK1) activation.



Researchers compared *KRAS*-dependent and *KRAS*-independent colon cancer cells by using a combination of gene expression and shRNA (small hairpin RNA) knockdown studies, which led to the identification of *MAP3K7*, encoding the TAK1, as a driver of cell survival in *KRAS*-dependent, APC (adenomatous polyposis coli)-deficient cells. In KRAS-dependent cells, but not *KRAS*-independent cells, *KRAS* activates BMP-7 signaling, leading to TAK1 activation, β-catenin nuclear localization, and transcriptional upregulation of Wnt target genes. This is also accompanied by *KRAS*- and TAK1-regulated activation of the NF-κβ pathway. Researchers found that the TAK1 kinase (*MAP3K7*) is required for tumor cell viability. RNAi-mediated depletion or pharmacologic inhibition of TAK1 induced apoptosis via suppression of hyperactivated Wnt signaling, evident in both endogenous and genetically reconstituted cells.

From a clinical perspective, the role of secreted BMP-7 is of particular interest because autocrine or paracrine activation of this pathway could be detectable and targetable in tumors. Importantly, screening for expression of BMP pathway components should help to stratify colon cancer patients into TAK1-inhibitor response groups. This study illustrates that the presence of a *KRAS* mutation does not identify a homogenously drug-resistant tumor type, even within a specific histological type. Instead, degrees of *KRAS* dependency in different cancers are modulated by associated signaling pathways such as the Wnt pathway in colon cancers. Together, these observations point to a potential therapeutic strategy, based on targeting a vulnerable node in an identifiable subset of APC/*KRAS*-mutant colon cancers.

Source: Cell. 2012;148(4):639-650

Tumor of the Month - Colorectal Cancer

Colon cancer is one of the high profile cancers, perhaps in large part to the aggressive educational campaign promoted by Katie Couric, who began her crusade to educate people about colon cancer and colon cancer screening after the death of her husband in 1998.[1] The American Cancer Society estimates that in 2012, there will be 103,170 new cases of colon cancer; 40,290 new cases of rectal cancers; and 51,690 deaths due to colorectal cancer (CRC).[2] The lifetime risk for CRC is ~5.1% with a slightly lower risk for women than for men. If statistics for men and women are combined, CRC is the second leading cause of deaths due to cancer. Despite this sobering statistic, the number of deaths from CRC has declined over the last 20 years, and there are currently more than a million colon cancer survivors in the US alone. Aggressive screening has resulted in diagnosis at earlier stages, when a cure is more likely. Patients diagnosed with stage I disease have a 5-year survival of 76%, whereas those diagnosed with stage IV disease have an expected 5-year survival of 6%. The US Preventive Services Task Force recommends regular screening using colonoscopy, sigmoidoscopy, or fecal occult blood testing (FOBT) beginning at the

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age of 50 years and continuing until the age of 75 years.[3] Hoping to encourage more people to be screened, the American College of Physicians recently issued new screening guidelines for CRC.[4] The guidelines recommend that physicians perform individualized risk assessment on patients, as well as the screening should begin at the age of 50 years unless a patient is at high risk for CRC, in which case the screening should begin at the age of 40 years or 10 years younger than the age at which the youngest affected relative was diagnosed with CRC. Patients with average risk should be screened with a stool-based test, flexible sigmoidoscopy, or optical colonoscopy. High-risk patients, including patients with a previous history of polyps or CRC, should be screened via optical colonoscopy.

CRC screening identifies small precancerous lesions called polyps. Adenomatous polyps (adenomas) form in the inner lining of the colon or rectum and may progress to cancer. In the ascending colon, hyperplastic or inflammatory polyps may have an increased risk of developing into cancerous lesions. Patients with chronic inflammation of the digestive system, such as ulcerative colitis or Crohn's disease, have an increased risk of CRC.[2] Most CRCs are adenocarcinomas (95%), which begin in cells of the mucous producing glands found in the colon and rectum. Other tumor types include carcinoid tumors, which form in the hormone-producing cells of the intestine, and gastrointestinal stromal tumors, which initiate in the interstitial cells of Cajal. Although these tumors are found in the gastrointestinal tract, they rarely form in the colon.

Although numerous putative biomarkers for CRC have been identified, the American Society for Clinical Oncology (ASCO) noted that most CRC biomarkers lack sufficient data to support their clinical use.[5] Despite this assessment, the Oncotype Dx for colon cancer uses the expression levels of seven genes (BGN, FAP, INHBA, GADD45B, Ki-67, C-MYC, and MYBL2) along with five reference genes to predict the likelihood of recurrence of a resected stage II or III tumor.[5] Many clinical trials for CRC stratify patients on the basis of the status of their Ras, as patients with wild-type Ras can be treated with EFGR inhibitors (e.g., cetuximab or panitumumab), whereas patients with a mutant Ras are refractory to such treatment approaches.[6] Chromosomal instability, mutations in Ras and TP53, loss of 18q, and increased expression of CEA (carcinoembryonic antigen) have all been implicated as biomarkers of poor prognosis in CRC.[5]

The current standard of care for stage I and II CRC is surgery. Stage II CRC may or may not be followed by adjuvant chemotherapy, usually FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin). Patients with stage III CRC receive adjuvant chemotherapy, FOLFOX being the most common protocol, but 5-FU and leucovorin or capecitabine alone may be better suited to some patients. Patients with stage IV CRC receive adjuvant or neoadjuvant chemotherapy: FOLFOX, FOLFIRI (leucovorin, 5-FU, and irinotecan) or CapeOx (capecitabine and oxaliplatin) are commonly used. Bevacizumab or cetuximab may also be added to these combinations.[7]

NKTR-102 (Clinical Trial# NCT00856375), is a topoisomerase I inhibitor with a macromolecule to increase stability and decrease toxicity. Nektar Therapeutics is testing the drug in a multicenter, open-label, randomized, Phase II study to evaluate the efficacy and safety of NKTR-102 versus irinotecan in patients with second-line, irinotecan-naïve, KRAS-mutant, metastatic CRC. Both drugs will be dosed every 3 weeks.

Biothera is testing ImPrime PGG, which is derived from naturally occurring b1,3/1,6 glucans. The drug binds to and activates neutrophils in a manner similar to what a pathogen does. Activated neutrophils home to sites of inflammation. Biothera has demonstrated that if the site of inflammation is a tumor, the neutrophils will attack the tumor. To enhance inflammation at a tumor site, the company will combine ImPrime PGG with a therapeutic antibody. NCT01309126 is an open-label, multicenter, randomized trial for *KRAS* wild-type CRC. Patients will be randomized in a 2:1 fashion for ImPrime PGG plus cetuximab versus cetuximab alone. Patients will be dosed until progression or discontinuation for other reasons. The primary outcome is overall survival (OS); secondary outcomes are progression-free survival (PFS) and rates of complete response (CR), partial response (PR), and overall response (OR; CR + PR).

Panitumumab is being tested in several clinical trials, including ASPECCT, which pits panitumumab against cetuximab in *KRAS* wild-type CRC (NCT01001377). The randomized, multicenter, open-label trial of previously treated patients will assess OS in patients with chemo-refractory mCRC. Patients will receive cetuximab (400 mg/m^2 initially, then 250 mg/m^2 IV every 7 days) or panitumumab (6 mg/kg IV every 14 days). Amgen is also testing panitumumab with supportive care against best supportive care for patients with mCRC (NCT01413957).

Eli Lilly and ImClone are conducting a Phase III trial of FOLFIRI ± ramucirumab (NCT01183780), which is a fully human monoclonal antibody against VEGFR2, the major mediator of VEGF signaling in malignant angiogenesis. The study will evaluate OS, PFS, and ORR. The study will be open to all CRC patients, regardless of their KRAS status.

Yttrium-90 microspheres are also being evaluated for CRC. Yttrium-90 is a β-emitter with a half-life of 2.5 days. The spheres are injected into the hepatic artery,

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which has been shown to feed tumors (while the portal vein feeds the liver). The microspheres get trapped in the vascular bed where they irradiate the tumor. Sirtex Medical is testing its SIR-spheres yttrium-90 microspheres in a Phase III trial (NCT00724503) comparing FOLFOX against FOLFOX plus SIR-spheres in patients with liver metastasis from primary CRC. The spheres will be implanted on the third or fourth day of the first week of the first chemotherapy cycle. Primary outcome measure is PFS. Nordion Inc. is testing its version of yttrium-90 microspheres–Therasphere–in patients with mCRC who have failed first-line chemotherapy. Its EPOCH study (NCT01483027), which began recruiting in January 2012, will compare second-line standard of care therapy with or without Theraspheres.

Perifosine is an orally bioavailable, alkyl-phospholipid signal transduction modulator that affects multiple intracellular signaling pathways, including inhibition of PI3K/Akt/mTOR signaling, which is altered in ~40% of CRC cases and has been associated with progression and metastasis of CRC. Perifosine also regulates activation of the proapoptotic c-Jun N-terminal kinase (JNK) cascade and activation of the mitogen-activated protein kinase (MAPK) signaling pathway. Recently, Bendell and colleagues published findings from their placebo-controlled, Phase II trial of capecitabine with or without perifosine[8] and reported that perifosine increased the median time to progression (TTP) from 10.1 weeks to 27.5 weeks and increased the median OS from 7.6 months to 17.7 months. Subset analysis showed that 5-FU–refractory patients also benefited from the addition of perifosine.

In an article published in the *British Journal of Cancer*,[9] Scartozzi and colleagues addressed the relationship between the expression of lactate dehydrogenase (LDH), a glycolytic enzyme induced by HIF1a, and the clinical response to bevacizumab plus first-line therapy for advanced CRC.[9] Patients were treated with a first-line chemotherapy (modified FOLFIRI, FOLFOX-6, or XELOX) with or without bevacizumab; 20% of patients with pre-treatment serum LDH ≥ 588 mg/dL were classified as having high pre-treatment LDH. For patients who did not receive bevacizumab, median OS was 34.9 months for patients with low LDH levels but only 19.6 months for patients with high LDH levels (P = 0.0014). In the bevacizumab group, patients with high LDH level showed a median OS of 26.6 months compared with 22 months in the low LDH group (P = 0.7). Patients with high LDH also benefited from bevacizumab with respect to PFS. In patients with high LDH levels who were not treated with bevacizumab, PFS was 4.2 months, which increased to 8.5 months for patients receiving bevacizumab (P = 0.006). Although the study needs to be confirmed in larger cohorts, results suggest that for patients with high LDH levels, bevacizumab will be an important addition to first-line therapy for controlling advanced CRC.

Business News

Abbott and Merck Partner to Develop Companion Diagnostic Test for Investigational Cancer Therapy

Abbott will collaborate with Merck to evaluate the use of a FISH (fluorescence *in situ* hybridization)-based companion diagnostic test to aid in the development of a Merck's investigational cancer therapy. An Abbott press release noted FISH-based companion diagnostic tests are designed to identify specific DNA sequences to help guide physicians in determining which patients are more or less likely to benefit from a particular therapy.

Under the terms of agreement, Abbott will develop a test based on its proprietary FISH technology, intended to identify deletions of the TP53 gene in cancer patients. The Abbott FISH assay will be evaluated in clinical trials to help identify patients more likely to respond favorably to Merck's investigational cancer therapy.

Abbott's portfolio of companion diagnostic tests includes the PathVysion HER-2 DNA Probe Kit, which represents an example of the developments in the field of personalized medicine. The test is approved for use in selecting breast cancer patients for whom Herceptin therapy is being considered. Furthermore, Abbott's Vysis ALK Break Apart FISH Probe kit was approved in 2011 for use in identifying NSCLC patients for Xalkori treatment.

Source: Abbott

Celgene Completes Acquisition of Avila Therapeutics

Celgene has completed its acquisition of Avila Therapeutics. Celgene acquired Avila Therapeutics for $350 M in cash, plus up to $575 M contingent upon certain milestones related to AVL-292 and candidates from Avila's discovery program.

The transaction provides Celgene with a highly selective Bruton's tyrosine kinase inhibitor, currently in Phase I clinical development, as well as a unique

Business News
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discovery platform, Avilomics, for developing targeted covalent drugs that treat diseases through protein silencing. As disclosed earlier, Celgene expects the acquisition to be neutral to 2012 non-GAAP diluted earnings guidance.

Source: Celgene

ProMetic Finalizes Its Agreement with Celgene Corporation

ProMetic Life Sciences has completed relevant milestones regarding the agreement it entered into in March 2011 with Celgene Corporation for the worldwide rights to a commercial application of ProMetic's protein technologies within a field of use.

As a result, a $10.0 M long-term debt owed to Abraxis BioScience LLC, a wholly owned subsidiary of Celgene, has been completely and irrevocably forgiven. ProMetic recognized revenues of $4 M in the first half of 2011, effectively reducing the said debt by the same amount and leaving $6 M as deferred revenue on ProMetic's balance sheet. The recognition of said remaining $6 M of deferred revenues will effectively reduce ProMetic's current liabilities.

Source: ProMetic

Dainippon Sumitomo Pharma to Acquire Boston Biomedical

Dainippon Sumitomo Pharma (DSP) announced that it has reached an agreement with Boston Biomedical Inc. (BBI) on the acquisition of the later. According to the terms of the agreement, DSP will make an upfront payment of $200 M to the shareholders of BBI and BBI on the closing of the acquisition of its shares; thereafter, DSP will make development milestone payments of up to $540 M related to the compounds (BBI608 and BBI503) currently being developed by BBI. Furthermore, after the launch, DSP will also make milestone payments of up to $1,890 M, based on the achievement of various net sales targets with the last milestone being paid upon net sales of greater than $4 B in any fiscal year. DSP currently aims to commercialize BBI608 and BBI503 in 2015 or later.

BBI is a biotechnology company focusing on the oncology area and possesses two highly promising products in its pipeline – BBI608 and BBI503 – which are oral, small molecular drugs created with the aim to cause an antitumor effect in cancer stem cells (CSCs). Currently, anticancer drugs targeting CSCs are attracting worldwide attention as a potent cancer therapy because they are considered to be effective against refractory, recurrent, and metastatic diseases, which are the current challenges in cancer treatment. To date, the complexity of identifying a target molecule specific to CSCs has prevented the development of such anti-CSC drugs. BBI608 and BBI503 are likely to become the first anticancer drugs in the world targeting CSCs. BBI608 is currently in the preparatory stage for Phase III clinical trial for CRC in North America and in Phase Ib and II clinical trials for various solid tumors. BBI503 is in Phase I clinical trial for various advanced solid tumors in North America.

Source: Dainippon Sumitomo Pharma

Research Highlights

Immune Surveillance and Therapy of Lymphomas Driven by Epstein–Barr Virus Protein LMP1 in a Mouse Model

B cells infected by Epstein–Barr virus (EBV), a transforming virus endemic in humans, are rapidly cleared by the immune system, but some cells harboring the virus persist for life. Under conditions of immunosuppression, the virus can spread from these few cells, resulting in an explosive expansion of infected B cells and their malignant transformation, as seen in pathologies such as post-transplant lymphoproliferative disorder (PTLD) and AIDS-associated B-cell lymphoma. EBV can assume range of latent states: from a highly restricted pattern of viral gene expression in Burkitt lymphoma (latency I) to the expression of just a few EBV genes in Hodgkin's disease (latency II) to the expression of all latent genes in PTLD and AIDS-associated B cell lymphoma (latency III). The EBV-encoded proteins latent membrane proteins 1 and 2A (LMP1 and LMP2A) share functions with receptors on normal B cells. LMP1 expression is essential for the transformation of human B cells by EBV and can, by itself, induce oncogenic transformation.

In a recent article published in *Cell*, Zhang *et al.* described a mouse model of conditional LMP1 expression (mimicking a constitutively active CD40 co-receptor, specifically in B cells) that can be used to study EBV-induced immune surveillance and lymphomagenesis. The expression of LMP1 in B cells is sufficient to induce immune surveillance of the $LMP1^+$ cells by cells of the adaptive immune system, and the weakening of this surveillance mechanism results in rapid generation of LMP1-driven B-cell lymphomas. Like human EBV-infected cells, $LMP1^+$ B cells were efficiently eliminated by T cells, and breaking immune surveillance resulted in rapid, fatal lymphoproliferation and lymphomagenesis. The lymphoma cells expressed ligands for a natural killer (NK) cell receptor, NKG2D, and could be targeted by an NKG2D–Fc fusion protein.

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These experiments indicate a central role for LMP1 in the surveillance and transformation of EBV-infected B cells *in vivo*, establish a preclinical model for B cell lymphomagenesis in immunosuppressed patients, and validate a new therapeutic approach.

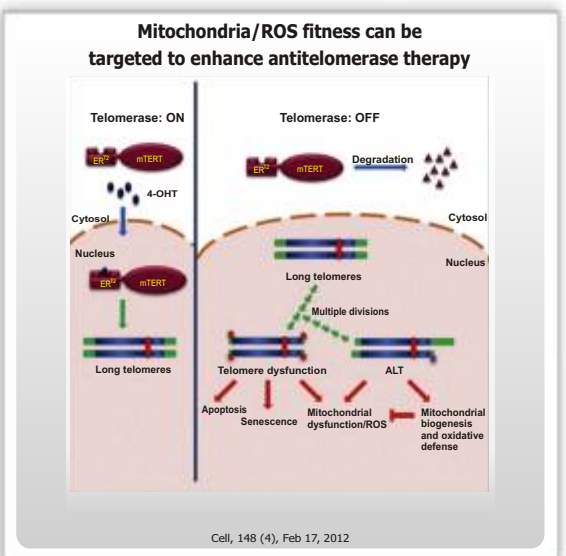
Source: Cell. 2012 Feb 17;148(4):739-51

Anti-telomerase Therapy Provokes ALT and Mitochondrial Adaptive Mechanisms in Cancer

Telomeres are nucleoprotein complexes at chromosome ends that function to maintain chromosomal integrity. The occurrence of telomere erosion and importance of telomerase-mediated telomere maintenance in fully established cancers are evidenced by shortened telomeres relative to normal tissues and robust telomerase activity in most human cancers. Despite the development of telomerase inhibitors in a number of cancer types, it is still uncertain whether anti-telomerase therapy will be hampered by the potential lag time needed for telomere erosion-associated tumor cell killing and/or whether re-entry into telomere-based crisis will engender genomic instability that may allow for emergence of adaptive responses and resistance mechanisms, such as the alternative lengthening of telomeres (ALT) mechanism, which enables telomere maintenance via homologous recombination. One of the hallmarks of cancer cells is the shift from mitochondrial to glycolytic metabolism as the prime source of energy and anabolic support, but multiple lines of evidence suggest that mitochondrial competence is important for cancer cell viability and efficient oncogene-mediated transformation.

In a recent article published in *Cell*, Hu *et al.* studied *in vivo* telomere crisis, telomerase reactivation, and telomerase extinction to assess telomerase as a cancer therapeutic target and to determine adaptive mechanisms to telomerase inhibition. They modeled telomerase reactivation and subsequent extinction in T-cell lymphomas arising in *Atm*$^{-/-}$ mice engineered with an inducible telomerase reverse transcriptase allele. Telomerase reactivation in the setting of telomere dysfunction enabled full malignant progression with alleviation of telomere dysfunction-induced checkpoints. These cancers possessed copy number alterations targeting key loci in human T-cell lymphomagenesis. Upon telomerase extinction, tumor growth eventually slowed with reinstatement of telomere dysfunction induced checkpoints. Growth subsequently resumed as tumors acquired ALT and aberrant transcriptional networks centering on mitochondrial biology and oxidative defense. ALT^{+} tumors acquired amplification/overexpression of PGC-1β, a master regulator of mitochondrial biogenesis and function, and showed marked sensitivity to PGC-1β or SOD2 knockdown.

This study uncovers a critical role for robust mitochondrial function in cancer cells, particularly for those cancer cells with ALT-maintained telomeres. It establishes that ALT^{+} cells strive to maintain adequate mitochondrial and oxidative defense functions and show exquisite sensitivity to loss of such function. On the molecular level, this work also establishes that the intimate PGC-directed link between telomeres and mitochondria is operative in cancer cells. The study highlights that, while ALT^{+} cells suppress apoptosis and senescence as efficiently as telomerase^{+} cells, these cells do not fully restore mitochondrial function, which is speculated to relate to ongoing genotoxic stress partly associated with less efficient telomere capping by ALT-mediated telomere maintenance.



This work provides *in vivo* genetic evidence that telomerase reactivation facilitates the progression of spontaneously arising tumors experiencing telomere dysfunction and, conversely, that telomerase extinction in established cancers activates ALT and other adaptive mechanisms. It illuminates a clinical path hypothesis for utilizing combination regimens targeting telomerase and PGC-mediated adaptive mechanisms in cancer.

Source: Cell. 2012;148(4):651-663

USP15 Stabilizes TGF-β Receptor I and Promotes Oncogenesis through the Activation of TGF-β Signaling in Glioblastoma

Transforming growth factor β (TGF-β) is a cytokine with a key role in cancer. Aggressive tumors tend to acquire high TGF-β activity through diverse mechanisms, including oversecretion of the TGF-β ligand by tumor cells or tumor stroma cells. Glioma is the most common primary tumor of the brain, and glioblastoma (GBM, a grade IV glioma) is one of the most aggressive types of brain tumors. TGF-β is highly

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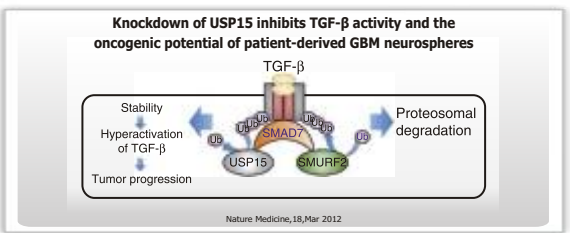
active in high-grade glioma, and elevated TGF-β activity confers poor prognosis. The oncogenic response to TGF-β is pleiotropic and includes the induction, proliferation, invasion, angiogenesis, and immunosuppression.

TGF-β activates a heterodimeric complex formed by TβR-II and TβR-I and initiates an intracellular signaling cascade through phosphorylation of the specific receptor-regulated SMADs (R-SMADs): SMAD2 and SMAD3. The phosphorylation of the R-SMADs facilitates their binding to SMAD4, and the SMAD complex then shuttles to the nucleus, where it regulates gene expression. The TGF-β signaling pathway is tightly regulated through protein ubiquitination. SMAD7 acts as a scaffold protein to recruit SMURF2, an E3 ubiquitin ligase, to the TGF-β receptor complex to facilitate its ubiquitination. This leads to proteasome-mediated degradation of TGF-β receptors and attenuation of TGF-β signaling. Ubiquitination is a reversible process, and ubiquitin moieties can be removed from polypeptides by deubiquitinating enzymes (DUBs). Because of their druggable enzymatic activity, DUBs can be considered therapeutic targets.

In a recent work published in *Nature Medicine*, Eichhorn *et al.* used a functional RNAi screen to identify the DUB ubiquitin-specific peptidase 15 (USP15) as a key regulator of TGF-β activity and TGF-β–dependent oncogenesis in GBM. USP15 binds to the SMAD7-SMAD–specific E3 ubiquitin protein ligase 2 (SMURF2) complex and deubiquitinates and stabilizes type I TGF-β receptor (TβR-I), leading to an enhanced TGF-β signal. High expression of USP15 correlates with high TGF-β activity; the *USP15* gene is amplified in glioblastoma, breast, and ovarian cancers. *USP15* amplification confers poor prognosis in individuals with glioblastoma. Downregulation or inhibition of USP15 in a patient-derived orthotopic mouse model of glioblastoma decreases TGF-β activity. Moreover, depletion of USP15 decreases the oncogenic capacity of patient-derived glioma-initiating cells due to the repression of TGF-β signaling.

TGF-β inhibitory compounds are currently being evaluated as anti-cancer therapeutic agents. These results show that USP15 could be considered as a marker of response to anti-TGF-β molecules. Furthermore, USP15 could be considered a therapeutic target because USP15 downregulation or inhibition leads to a decrease in TGF-β activity and oncogenesis. DUBs have been shown to be targetable through small organic molecules, opening new avenues for therapeutic intervention in glioblastoma multiforme and other aggressive tumors.



Source: Nature Medicine. 2012;18(3):429-435

Clinical Development

Ruxolitinib Improves Survival and Quality of Life in People with Myelofibrosis in a Phase III Study

The *New England Journal of Medicine* (*NEJM*) published results from two Phase III studies (COMFORT-I and COMFORT-II) of Jakafi (ruxolitinib), a JAK1 and JAK2 inhibitor recently approved by the US FDA for the treatment of intermediate or high-risk myelofibrosis (MF).

These data, which were included in the new drug application (NDA) for Jakafi submitted by Incyte, showed that the treatment significantly reduced spleen volume and improved symptoms of MF. Furthermore, in an updated analysis of COMFORT-I, treatment with Jakafi was associated with improved OS compared with placebo. Patients who received Jakafi also experienced relief from the disease's debilitating symptoms, which include fatigue, weight loss, abdominal pain, severe itching, night sweats, and bone pain. The clinical trial enrolled 309 patients at 89 centers in the US, randomizing 155 patients to Jakafi and 154 to placebo.

Source: Incyte

Synta Announces Review of Ganetespib Phase II Results in Lung Cancer

Synta Pharmaceuticals announced that a review of ganetespib Phase II results in non–small cell lung cancer (NSCLC) was presented by Dr. Suresh Ramalingam, Chief of Thoracic Oncology, and Director of Medical Oncology, Emory University, at the International Association for the Study of Lung Cancer (IASLC) 12th Annual Targeted Therapies for the Treatment of Lung Cancer Meeting. Results showed that ganetespib is active in NSCLC; has a favorable safety profile as a monotherapy or in combination with docetaxel; shows evidence of synergy with docetaxel in preclinical models; and has pronounced single-agent clinical activity in ALK+ lung cancer, which is believed to be complementary to, rather than competitive with, direct ALK kinase inhibitors such as crizotinib.

Ganetespib is a potent inhibitor of heat shock protein 90 (Hsp90) that is structurally unrelated to first-generation Hsp90 inhibitors of the ansamycin family.

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Clinical Development (Cont'd)

Ganetespib is being evaluated in more than 20 clinical trials, either ongoing or currently initiating, with the most advanced clinical trial being the Phase IIb/III GALAXY trial evaluating ganetespib with docetaxel versus docetaxel alone in patients with advanced NSCLC who have progressed on first-line therapy. A global trial evaluating single-agent ganetespib in ~100 patients with ALK+ NSCLC who have not been previously treated with an ALK inhibitor is in the process of initiating.

Enrollment of 240 patients in Phase IIb portion of the GALAXY is expected to complete in Q2, 2012. Interim results, including landmark PFS, response rate, and disease control rates are expected in Q2, 2012; final PFS results, as well as OS results, are expected in H2, 2012.

Source: Synta

Active Biotech and Ipsen Report on Tasquinimod (TASQ) Phase II Long-term Safety Data for the First Time at the 27th European Association of Urology Congress

Active Biotech and Ipsen's castrate-resistant prostate cancer (CRPC) project – TASQ – was presented at the 27th Annual EAU Congress held in Paris on February 24-28, 2012. The presentation detailed the analysis of up to 3-year safety data from the TASQ Phase II study in chemotherapy-naïve, metastatic CRPC.

Treatment side effects were mild to moderate (~5% of AEs were grade 3-4), manageable, and less frequent after 2 months of therapy. Observed adverse events were gastrointestinal disorders (primarily observed initially during treatment), fatigue, and musculoskeletal pain. These new data show that tasquinimod has an acceptable long-term safety. Tasquinimod may therefore be a suitable therapy to evaluate at an early stage in the management of CRPC, either as monotherapy or in combination with other effective agents for prostate cancer, as it does not jeopardize the patient's chances to receive additional treatment.

A global, pivotal, randomized, double-blind, placebo-controlled Phase III study of TASQ in patients with metastatic CRPC is ongoing. The aim of the study is to confirm TASQ's effect on the disease, with radiological PFS as the primary endpoint and OS as the secondary endpoint. The study will include ~1,200 patients in more than 250 clinics. The independent Data and Safety Monitoring Board overseeing the ongoing Phase III clinical trial has recommended the study to proceed as per protocol as no safety concerns were identified.

Source: Active Biotech

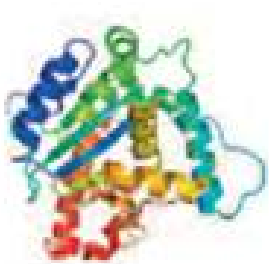
Apogenix's APG101 Meets Primary Endpoint in a Controlled Phase II Trial in Glioblastoma Patients

Apogenix announced that the Phase II clinical efficacy trial with APG101 met its primary endpoint in the second-line treatment of GBM, following a 6-month follow-up of the last patient treated. The company's lead product candidate – APG101 – is a first-in-class, fully human fusion protein combining the extracellular domain of the CD95 receptor and the Fc portion of IgG.

In the controlled, randomized, open-label trial, patients were treated with APG101 and radiotherapy or with radiotherapy alone. The Phase II clinical trial recruited 83 patients in 27 centers throughout Germany, Austria, and Russia. Patients were eligible for inclusion if they had suffered from first or second relapses and if they no longer responded to treatment with temozolomide. Patients were treated until tumor progression. Currently, there are no approved treatment options for second-line GBM patients.

The primary objective of the trial was to increase the percentage of patients reaching PFS6 by 100%. This objective was exceeded substantially. Data on secondary endpoints including OS and QOL are expected within the next few months and will be presented at major cancer conferences in the US and Europe later this year. During treatment with APG101 for up to 2 years, no drug-related adverse effects were observed.

Source: Apogenix



Biomarkers

Activation of p53 by SIRT1 Inhibition Enhances Elimination of CML LSCs in Combination with Imatinib

BCR-ABL kinase inhibitors (TKIs) are effective in the treatment of chronic myelogenous leukemia (CML) but do not eliminate leukemia stem cells (LSC), which remain a potential source of recurrence. The NAD-dependent deacetylase SIRT1 is reported to protect stem cells against stress and functions as a tumor suppressor or tumor promoter, depending on cellular context. A study recently published by Li *et al.* in *Cancer Cell* showed that SIRT1 is overexpressed in CML LSC and that SIRT1 inhibition selectively reduces CML LSC survival and growth through acetylation and activation of the p53 tumor suppressor.

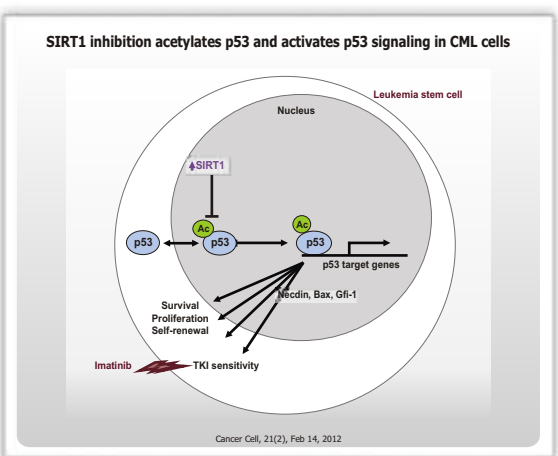
Both BCR-ABL kinase-dependent and kinase-independent mechanisms contribute to increased SIRT1 activity in CML cells, with the latter potentially including epigenetic silencing of HIC1, a negative regulator of SIRT1, through methylation, or altered

Biomarkers (Cont'd)

miRNA regulation of SIRT1 expression. The selectivity of SIRT1 inhibition toward CML stem/progenitor cells is maintained in hypoxic conditions, where SIRT1 plays an important role in supporting normal hematopoiesis.

SIRT1 can deacetylate several lysine residues in the tumor suppressor p53. A variety of post-translational modifications that can regulate p53 activity, including phosphorylation, acetylation, methylation, and sumoylation, have been described. Acetylation is reported to play an important role in stabilization, nuclear localization, and transcriptional activation of p53 and can lead to p53 activation independently of phosphorylation status. Although p53 mutations may occur on progression to the blast crisis (BC-CML) phase, they are rare in chronic phase CML (CP-CML). The results indicate that p53 remains responsive to stress-induced activation in CML progenitors. SIRT1 inhibition increased p53 acetylation and the expression of several p53 target genes, including Bax, Necdin, and Gfi-1, in CD34+ CML cells. Bax is an important proapoptotic gene, and Necdin and Gfi-1 may be important for p53-regulated quiescence of hematopoietic stem cell (HSC). Additional p53 target genes may also contribute to the effects of SIRT1 inhibition. Although p21 expression was reduced in CML progenitors after p53 knockdown, SIRT1 knockdown did not increase expression of p21 in CML progenitors, suggesting that other SIRT1-regulated pathways may counteract the effects of p53 acetylation on p21 induction. BC-CML cells also demonstrated increased p53 acetylation following SIRT1 inhibition, consistent with recent reports that p53 can be activated in BC-CML cells.

Results of the current studies have broader implications in other leukemias, such as acute myeloid leukemia (AML), in which SIRT1 overexpression is observed and p53 mutations are rare.



Source: Cancer Cell. 2012;21(2):266-281

TEM8/ANTXR1 Blockade Inhibits Pathological Angiogenesis and Potentiates Tumoricidal Responses against Multiple Cancer Types

Inhibiting angiogenesis has become an important adjunct to traditional anticancer therapy, but current anti-angiogenic agents, including VEGF/VEGFR2 pathway inhibitors, disrupt normal physiological processes and are associated with an increasing number of adverse side effects. Tumor endothelial marker 8 (TEM8) is a highly conserved single-pass cell-surface glycoprotein that was originally identified on the basis of its overexpression in the endothelial cells (ECs) that line the tumor vasculature of human CRC. Although the understanding of its physiological function is limited, TEM8 has been found to bind to collagens and promote migration of ECs *in vitro*.

A recent study published by Chaudhary *et al.* in *Cancer Cell* demonstrated that TEM8 is critical for promoting pathological angiogenesis evoked by a variety of tumor types and that antibody-mediated targeting of TEM8 provides a rational strategy for combating cancer. In immunocompetent mice, L2 inhibited tumor growth but had no effect on wound healing in the same mice, consistent with earlier studies demonstrating no difference in wound healing between TEM8 wild-type and knockout mice. TEM8 was also dispensable for developmental angiogenesis and normal physiological angiogenesis of the corpus luteum, although a function for TEM8 in these normal physiological processes could potentially be masked through compensation by another molecule. However, CMG2 is the only other protein that shares significant amino acid identities with TEM8 and, aside from misaligned incisors, CMG2/TEM8 double-mutant mice, like TEM8 knockout mice, appear to develop normally.

In summary, it was reported that development of anti-TEM8 antibodies retard tumor growth by inhibiting tumor angiogenesis. Anti-TEM8 antibodies were nontoxic and maintained efficacy in combination with various classes of anticancer agents. Thus, anti-TEM8 antibodies provide a rationally designed tool for selectively inhibiting pathological angiogenesis with important ramifications for the management of angiogenesis-dependent diseases.

Source: Cancer Cell. 2012;21(2):212-226

RET, ROS1, and ALK Fusions in Lung Cancer

Echinoderm microtubule-associated protein-like 4 (EML4)–ALK was the first targetable fusion oncokinase to be identified in NSCLC. This fusion is found in ~4%-6% of lung adenocarcinomas. ROS1 is another receptor tyrosine kinase that forms fusions in NSCLC. Through an integrated molecular- and histopathology-based screening system, Takeuchi *et al.* performed a screening for fusions of anaplastic

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Biomarkers (Cont'd)

lymphoma kinase (ALK) and c-ROS oncogene – receptor tyrosine kinase (ROS1) – in 1,529 lung cancers and identified 44 ALK-fusion–positive and 13 ROS1-fusion–positive adenocarcinomas, including four unidentified fusion partners for ROS1. The study was published in *Nature Medicine*.

In addition, researchers also discovered previously unidentified kinase fusions that may be promising for molecular targeted therapy: kinesin family member 5B (KIF5B)–RET proto-oncogene (RET) and coiled-coil domain containing 6 (CCDC6)–RET, in 14 adenocarcinomas. All 71 kinase-fusion–positive (44 ALK, 13 ROS1, and 14 RET fusions) lung cancers were exclusively adenocarcinomas (6% of all adenocarcinomas in the present study); were positive for antibodies to TTF1, which is regarded as a marker for lung adenocarcinoma, as determined by immunohistochemistry (excluding two ALK-positive tumors); and were negative for *EGFR* and *KRAS* mutations. A multivariate analysis of 1,116 adenocarcinomas containing these 71 kinase-fusion–positive adenocarcinomas identified four independent factors that are indicators of poor prognosis: age ≥50 years, male sex, high pathological stage, and negative kinase-fusion status. Integrated pathology-based screening techniques can also be used for the selection of individuals to receive kinase inhibitors. The results of this study will facilitate the development of a molecular classification of lung adenocarcinomas that is closely related to both the pathogenesis and the treatment of disease.

Source: Nature Medicine. 2012;18(3):378-381

Regulatory

GSK Announces Positive Vote from FDA Panel for Pazopanib in Certain Advanced Soft Tissue Sarcomas

GlaxoSmithKline announced that the Oncologic Drugs Advisory Committee (ODAC) of the US FDA voted 11 to 2 that evidence from clinical studies support a favorable benefit–risk assessment for use of Votrient in treating patients with advanced soft tissue sarcoma who have received prior chemotherapy, noting that those with gastrointestinal stromal tumors and adipocytic sarcomas were not included in the Phase III trial.

The ODAC reviewed findings from one Phase III clinical study and one Phase II study. The ODAC provides the FDA with independent expert advice and recommendations; however, the final decision regarding approval is made by the FDA. Votrient is not approved or licensed in the US or EU for the treatment of advanced soft tissue sarcoma.

Source: GlaxoSmithKline

Merck and Ariad Provide Update on FDA Advisory Committee Vote on Ridaforolimus for the Treatment of Metastatic Soft Tissue or Bone Sarcomas

Merck and Ariad Pharmaceuticals announced that the US FDA's ODAC voted 13 to 1 against the use of the investigational agent ridaforolimus as maintenance therapy for patients with metastatic soft tissue sarcoma or bone sarcoma whose disease has not progressed after at least four cycles of chemotherapy.

The ODAC panel's recommendation will be considered by the FDA when making its decision regarding the NDA for ridaforolimus, an investigational oral mTOR inhibitor under development for the treatment of metastatic soft tissue or bone sarcomas. The FDA is not bound by the committee's guidance but takes its advice into account.

Merck and Ariad had earlier announced that the FDA had accepted for filing and review the NDA for ridaforolimus. As part of an exclusive license agreement with Ariad, Merck is responsible for the development and worldwide commercialization of ridaforolimus in oncology. Ariad intends to co-promote ridaforolimus in the US.

Source: Ariad

Eisai Receives Complete Response Letter from the FDA for Dacogen for Injection sNDA in AML

Astex Pharmaceuticals announced that the US FDA has issued a complete response letter to Astex's partner Eisai for the supplemental NDA (sNDA) for Dacogen (decitabine) injection in AML in adults 65 years or older who are not considered candidates for induction therapy. The FDA declined to approve the application because the pre-specified analysis of the primary endpoint in the study (DACO-016) did not demonstrate statistically significant superiority of Dacogen over the control arm (P = 0.11).

A separate marketing authorization application was submitted to the EMA in May 2011 by Janssen for Dacogen for treatment of AML. It is expected the EMA will issue a decision on this application later this year. Dacogen is currently approved for the treatment of myelodysplastic syndrome (MDS) in ~30 countries. Dacogen is licensed to Eisai, which has licensed rights outside of North America to Janssen-Cilag International NV and other Janssen affiliates. Astex receives royalties on global sales of Dacogen.

Source: Eisai

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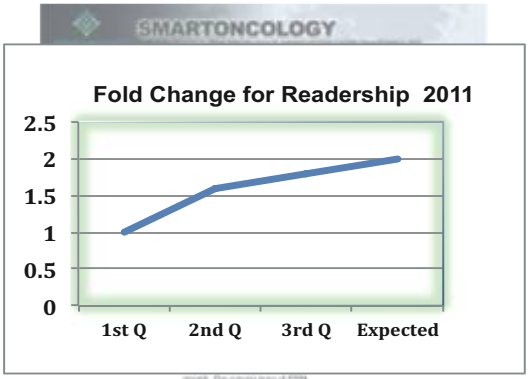

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