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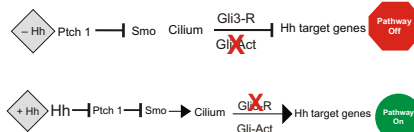
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INTELLIGENT INSIGHTS. SMART RESULT

Primary Cilia can both Mediate and Suppress Hh pathway – dependent Tumorigenesis

Normal Hh signaling



In the Spotlight:

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Clinical Development

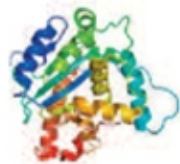
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Biomarkers

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Regulatory

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 FDA Panel Recommends Approval of PEGINTRON for Malignant Melanoma

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Spotlight Report

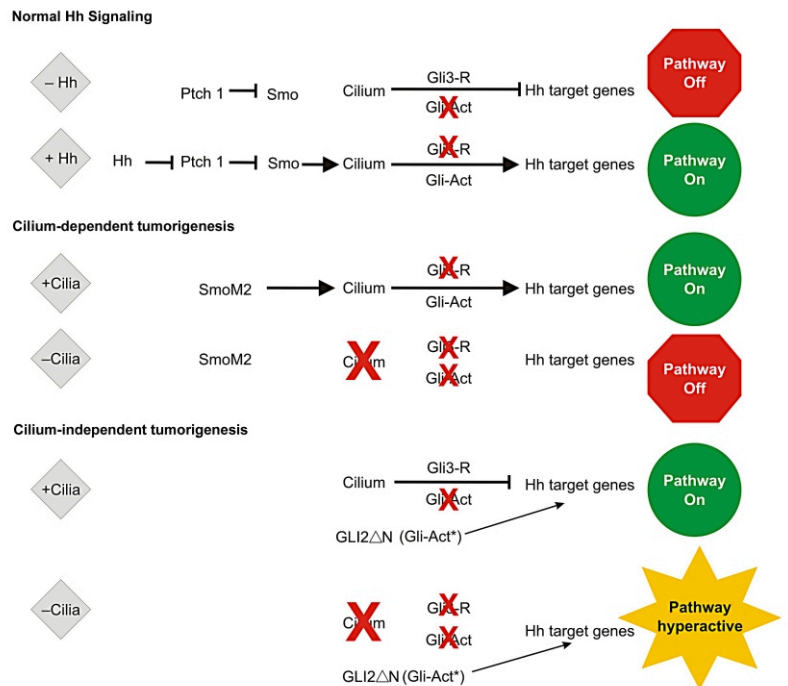
Primary Cilia can both Mediate and Suppress Hh Pathway – dependent Tumorigenesis

Primary cilia are present on most mammalian cells and are sites of regulation of the Hedgehog (Hh) pathway, transducing Hh signals during development. Even though the deregulation of this pathway can cause basal cell carcinoma (BCC) or medulloblastoma, the prevalence of cilia on human tumors remains unclear and their role in cancer has not been examined. A recent study by Wong *et al* in *Nature Medicine* provides evidence that primary cilia have a functional role in modulating oncogenic Hh signaling. Hh binding to its receptor, patched (PTCH1), activates smoothed (SMO), which relocalizes to the primary cilia to activate the transcription factor GLI2. In the absence of HH-PTCH1 binding, proteolytic processing of GLI3 (which is dependent on primary cilia) forms GLI3-R, which represses GLI2-mediated transactivation.

The researchers analyzed 8 human BCCs, using a conditional mouse model of BCC, and found that 5 were extensively ciliated. In this model, tamoxifen treatment induced the expression of a constitutively active SMO mutant (*SmoM2*) and ablated either *Kif3a* or *Ift88*, which are required for ciliogenesis. Loss of cilia suppressed *SmoM2*-induced tumorigenesis, and the Hh target genes *Gli1*, *Gli2* and *Ptch1* were not induced. To clarify whether cilia modulate the activity of GLI2, the authors used mice in which a constitutively active GLI2 mutant (GLI2ΔN) is conditionally expressed and in which *Kif3a* or *Ift88* is conditionally ablated. Loss of cilia significantly accelerated GLI2ΔN-induced tumorigenesis and decreased the levels of GLI3-R, which corresponded to increased expression of some HH target genes. Moreover, inhibition of GLI3 further increased the expression of GLI2, indicating that cilium-mediated formation of GLI3-R is required to suppress GLI2-mediated tumorigenesis, whereas cilia are essential for tumorigenesis when the upstream pathway is activated. These seemingly paradoxical effects are consistent with a dual role for cilia in mediating both the activation and the repression of the Hh signaling pathway. The findings demonstrate that cilia function as unique signaling organelles that can either mediate or suppress tumorigenesis depending on the nature of the oncogenic initiating event. Thus, inhibiting ciliogenesis may be therapeutic in a subset of cancers but may also exacerbate cancer growth in others.

Source: *Nature Medicine*

Primary Cilia can both Mediate and Suppress Hh pathway – dependent Tumorigenesis



Nature Medicine, 15, Aug 23, 2009



Business News

Sanofi-aventis and Merrimack enter into a Licensing Agreement for MM-121

Merrimack Pharmaceuticals and Sanofi-aventis announced the signing of an exclusive worldwide licensing agreement for the development and co-commercialization of MM-121, a first-in-class, fully human monoclonal antibody designed to block signaling of the ErbB3 receptor. MM-121 is currently in Phase I clinical testing.

Under the terms of the agreement, Sanofi-aventis will make an upfront payment of \$60 million and will be responsible for all development costs. Merrimack is eligible for an additional \$470 million in milestone payments as well as tiered double-digit royalties on sales of MM-121. Merrimack will execute the development of MM-121 through Phase II proof of concept for each indication and Sanofi-aventis will be responsible for development thereafter. Merrimack retains the right to co-promote the therapy in the US.

Source: Merrimack Pharmaceuticals

Quest PharmaTech Acquires Late-Stage Immunotherapeutic Antibody Pipeline

Quest PharmaTech announced that it has acquired a pipeline of late-stage immunotherapy product candidates from Paladin Labs. The pipeline of product candidates consists of five monoclonal antibodies targeting certain tumor antigens that are presented in a variety of cancers. The first and most advanced of these product candidates is Oregovomab, an anti-CA125 antibody for the treatment of ovarian cancer patients that Quest will evaluate in combination with front-line chemotherapy.

Quest also acquired anti-MUC1, anti-TAG72, anti-PSA and anti-CA19.9 antibodies that could potentially be used for the treatment of breast, lung, stomach, colorectal, pancreas and prostate cancer. As part of the transaction, Paladin will receive an upfront payment of \$37,500 and 1.5 million common shares of Quest, with an additional 1.5 million common shares to be issued to Paladin on or before December 31, 2010. The agreement also provides single-digit royalty payments to Paladin on future revenues. In addition to the antibodies purchased from Paladin, Quest's oncology pipeline includes small molecule prostate cancer product candidate SL052, which is expected to enter the dosing stage of a Phase I clinical trial in the fourth quarter of 2009.

Source: Quest PharmaTech

Cytopia to Merge into YM Biosciences

YM BioSciences (YM) announced it has proposed to merge Cytopia, a clinical-stage, Melbourne-based drug development company, into YM. Cytopia's lead products are CYT997, a novel vascular disrupting agent currently in Phase II trials, and CYT387, a novel, orally-active JAK2 inhibitor that recently received clearance from the FDA to commence a Phase I trial in myeloproliferative disorders. In the proposal, Cytopia shareholders are being offered 0.0852 common shares of YM in exchange for each common share of Cytopia. The transaction would result in YM issuing approximately 7.2 million new shares.

YM's lead drug, nimotuzumab is launched for head and neck cancer in India and 21 countries have approved it for marketing as of September 2009. As a consequence of YM's acquisition of Cytopia, the company expects to open clinical trials of nimotuzumab in Australia, subject to clearance by the Australian health regulatory authority and to supply nimotuzumab to individual patients in Australia through a Special Access Scheme (SAS) that has already been launched. "After assessing numerous global in-licensing opportunities, we determined that Cytopia's products were an ideal complement to our current portfolio," said David Allan, Chairman and CEO of YM.

Source: YM BioSciences



**Business
News
(Cont'd)**

Amgen Licenses TAP Technology for a Solid Tumor Target to ImmunoGen

ImmunoGen announced that Amgen has licensed the exclusive right to use the company's maytansinoid Targeted Antibody Payload (TAP) technology to develop anticancer therapeutics to an undisclosed target found on solid tumors. This license was taken under an agreement established in 2000 between ImmunoGen and Abgenix, which was later acquired by Amgen. Under the terms of the license, ImmunoGen receives a \$1 million license payment upfront. The company is also entitled to receive milestone payments potentially totaling \$34 million plus royalties on the sales of any resulting products. Amgen is responsible for the development, manufacturing, and marketing of any products resulting from this license.

Source: ImmunoGen

Patrys Acquires Gastric Cancer Antibody Product- SC1 from Debiovision

Patrys announced the acquisition of exclusive rights to commercialize gastric cancer antibody product, SC1. The rights were acquired from Debiovision, a member of the global drug development Debiopharm Group. Patrys has renamed the product PAT-SC1, which has shown survival benefit to gastric cancer patients in a human clinical trial conducted at the University of Wurzburg, Medical Centre in Germany. The acquisition immediately transforms Patrys' internal product pipeline from preclinical to clinical status by adding a product that has already generated positive human clinical trial data.

"Patrys has been considering the acquisition of full commercialization rights for PAT-SC1 for some time, given the promise that PAT-SC1 showed in the human clinical trial, and the fact that we have the internal capabilities to effectively advance natural human antibody based products," said Patrys CEO, Dan Devine. The company expects that it will take approximately 12 months to reach large scale production levels of PAT-SC1, at which time Patrys intends to advance the product into Phase II clinical trials for the treatment of gastric cancer patients.

Source: Patrys



Research Highlight

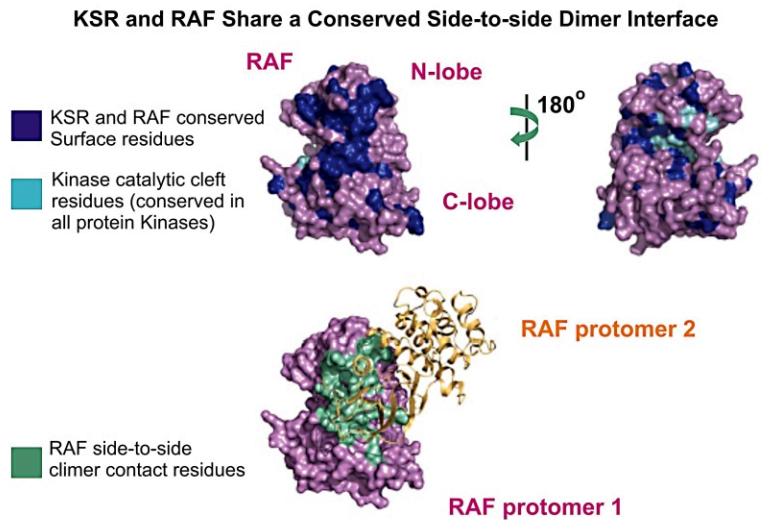
A Dimerization-Dependent Mechanism Drives RAF Catalytic Activation

The RAF family of kinases regulates several cellular processes including cell growth, differentiation, and survival. Activation of the kinase RAF is triggered by growth factors binding to receptor tyrosine kinases, and *raf* is the most frequently mutated oncogene within the kinase superfamily being responsible for more than a quarter of all cancers. A lot of research is focused on understanding the underlying regulation of this family of kinases, especially the process by which the RAF kinase domain becomes activated towards its substrate MEK.

In a recent publication in *Nature*, Rajakulendran *et al.* demonstrate that the dimerization

or combination of two RAF proteins is essential to its activation. The RAF catalytic function is regulated in response to a specific mode of dimerization of its kinase domain (side-to-side dimer) which is relevant for the action of the RAF activator kinase suppressor of Ras (KSR) and certain oncogenic mutations. The authors also discovered that the RAF-related pseudo-kinase KSR also participates in forming side-to-side heterodimers with RAF and can thereby trigger RAF activation. This mechanism not only provides an elegant explanation for RAF catalytic activation, but also explains the capacity of KSR, despite lacking catalytic function, to directly mediate RAF activation. The workers also demonstrated that RAF side-to-side dimer formation is essential for aberrant signaling by oncogenic BRAF mutants, and identified an oncogenic mutation that acts specifically by promoting side-to-side dimerization. The study identifies the side-to-side dimer interface of RAF as a potential therapeutic target for intervention in BRAF-dependent tumorigenesis as inhibiting the dimerization of RAF may block its activation, thus stopping cancer cells from growing. By discovering how to turn off the RAF protein without interfering with other proteins, researchers may be able to design drugs that have unprecedented precision in targeting cancer cells while reducing the toxic side effects for patients.

Source: *Nature*



Nature, 461, Sep 24, 2009



Research Highlight (Cont'd)

p53 Isoforms, $\Delta 133p53$ and p53 β , are Regulators of Replicative Cellular Senescence

Normal human somatic cells undergo a limited number of cell divisions, eventually reaching an irreversible proliferation arrest known as replicative cellular senescence. Whether replicatively induced or prematurely stress-induced, cellular senescence constitutes a critical mechanism for tumor suppression *in vivo* and may contribute to organismal ageing. The p53 signaling pathway has a central role in the regulation of cellular senescence and has been proposed to function as a barrier to tumorigenesis. Kaori Fujita *et al.* in *Nature Cell Biology* present evidence that some p53 isoforms may add a new layer of complexity to p53-regulated senescence. *TP53*, the human gene encoding p53, contains an alternative promoter and produces multiple splice variants, called p53 isoforms. To investigate the roles of two human p53 isoforms, p53 β and $\Delta 133p53$, Fujita *et al.* examined their expression profiles during senescence both *in vitro* and *in vivo*. Replicatively senescent normal human diploid fibroblasts showed increased expression of p53 β but decreased expression of $\Delta 133p53$. Both retroviral p53 β overexpression and RNA interference-mediated knock down of $\Delta 133p53$ were able to induce p53-dependent cellular senescence. Conversely, $\Delta 133p53$ overexpression extended the replicative lifespan of fibroblasts. These results indicate that although p53 β cooperates with full-length p53 to induce senescence, $\Delta 133p53$ negatively regulates senescence-associated functions of p53.

p53 isoform expression was assessed in tissue samples from colon adenomas and carcinomas. Adenomas, premalignant lesions with a high proportion of senescent cells, showed the same pattern of p53 isoform expression as the senescent fibroblasts *in vitro*. By contrast, colon carcinomas displayed the opposite expression pattern, that is, increased $\Delta 133p53$ but decreased p53 β . This suggests that altered p53 isoform expression may facilitate escape from the senescence barrier and subsequent malignant progression from adenoma to carcinoma. Although the mechanisms for the differential expression and degradation of these p53 isoforms await further investigation, the demonstration that a specific p53 isoform expression profile can influence cellular senescence may offer a new approach to p53-based cancer therapy.

Source: Nature Cell Biology

Glucose Deprivation Contributes to the Development of *KRAS* Pathway Mutations

Mutations in oncogenes and tumor suppressor genes allow cancer cells to outgrow their neighboring cells *in situ*. However, little is known about the environmental condition that allows cells with such mutations to clonally expand. In a study published in *Science*, Yun *et al.* examined the transcriptomes of paired colorectal cancer cell lines that differed only in the mutational status of their *KRAS* or *BRAF* genes.

The study results showed that *GLUT1* (Glucose transporter 1) transcript expression was higher, ranging from 3- to 22-fold, in the clones with mutant *KRAS* or *BRAF* alleles compared to the isogenic clones with WT alleles. Investigators hypothesized that the up-regulation of *GLUT1* would result in increased glucose uptake in the clones with mutant *KRAS* or *BRAF* alleles and found that disruption of *GLUT1* substantially inhibited glucose uptake, demonstrating that GLUT1 was the major glucose transporter in these cancer cells. On the other hand, when cells with wild-type *KRAS* alleles were subjected to a low-glucose environment, very few cells survived. Most surviving cells expressed high levels of GLUT1, and 4% of these survivors had acquired *KRAS* mutations not present in their parents. The glycolysis inhibitor, 3-bromopyruvate (3-BrPA), was highly toxic to cell lines with *KRAS* or *BRAF* mutations but was much less toxic to the matched cell lines lacking *KRAS* or *BRAF* mutant alleles. These results provide proof of principle that glycolytic inhibitors can retard tumor growth at doses that are nontoxic to normal tissues *in vivo*. These findings suggest that glucose deprivation can drive the acquisition of *KRAS* pathway mutations in human.

Source: Science



Clinical Development

Herceptin Provides Survival Benefit for HER2-positive Gastric Cancer

A detailed analysis of the Phase III ToGA study revealed an unprecedented survival benefit for patients whose tumors exhibited a particularly high level of HER2 when Herceptin (trastuzumab) was added to standard chemotherapy (capecitabine or intravenous 5-FU and cisplatin). ToGA is the first randomized trial investigating the use of Herceptin in patients with inoperable locally advanced, recurrent and/or metastatic HER2-positive gastric cancer. Approximately 3,800 patients were tested for HER2-positive tumors and 594 patients with HER2-positive disease were enrolled into the study. The analysis evaluated patient benefit according to the level of HER2 identified in their gastric tumor. Overall survival (OS) for patients with high levels of HER2 receiving Herceptin was 16 months on average vs 11.8 months for patients receiving chemotherapy alone. These results were presented at the joint 15th Congress of the European Cancer Organization (ECCO) and 34th Congress of the European Society for Medical Oncology (ESMO) in Berlin, Germany, 20-24 Sept, 2009.

Based on the significant findings of the ToGA study, Roche has submitted a label extension application with the EU Health Authorities for use of Herceptin in HER2-positive advanced gastric cancer.

Source: Roche

Vectibix in Combination with Chemotherapy Improves PFS in 2nd Line mCRC

Amgen announced detailed results from the Phase III '181' trial evaluating Vectibix (panitumumab) in combination with FOLFIRI (irinotecan-based chemotherapy), as a 2nd line treatment for metastatic colorectal cancer (mCRC). In this trial, Vectibix significantly improved median progression-free survival (PFS), co-primary endpoint, in patients with *KRAS* wild-type mCRC. These results were presented at the 15th Congress of the ECCO and 34th Congress of the ESMO in Berlin, Germany, 20-24 Sept, 2009.

Tumor *KRAS* status was ascertained in 91% of the 1,186 patients enrolled in this trial. The addition of Vectibix to FOLFIRI significantly improved median PFS by 2 months (5.9 vs 3.9 months for patients treated with FOLFIRI alone) in patients with *KRAS* wild-type mCRC. However, the improvement in median OS (14.5 months vs 12.5 months, co-primary endpoint) in the Vectibix arm did not achieve statistical significance in the same patient population. Further, the addition of Vectibix to FOLFIRI resulted in greater than a three-fold improvement (35% vs 10%) in response rate in the *KRAS* wild-type patient population as measured by a blinded central review. There were no differences in PFS, OS and response rates among patients with mutated *KRAS* who received Vectibix. Vectibix is currently approved in the US as a monotherapy for the treatment of patients with EGFR expressing mCRC after disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Source: Amgen

Positive Phase II Efficacy Data of Regorafenib in Metastatic RCC

Bayer Schering Pharma announced results from a Phase II trial which demonstrated that treatment with regorafenib, a potent oral multi-kinase inhibitor, resulted in a 31% partial response rate and 50% stabilization rate in patients with metastatic renal cell carcinoma (RCC). This data was presented at the joint 15th Congress of the ECCO and 34th Congress of the ESMO in Berlin, Germany, 20-24 Sept, 2009.

This multicenter, open-label, single-arm study of regorafenib enrolled 49 previously untreated patients with metastatic or unresectable, predominantly clear-cell RCC. At the time of data analysis, 81% of patients in the trial experienced disease stabilization or regression. Specifically, 31% of patients experienced a confirmed partial response (PR), according to the Response Evaluation Criteria in Solid Tumors (RECIST), and 50% of patients experienced stable disease (SD). The data also showed an estimated median PFS of 8.3 months at the time of protocol-defined end of study. Importantly, the time of data analyses, which occurred on May 31, 2009, was prospectively defined in the protocol as when the last patient was treated for at least six months. At the time of analysis, 25 patients remained on treatment and 80% of patients who achieved a PR had an ongoing response. Two additional patients who were classified as having SD achieved a confirmed PR past the data analysis date, bringing the total PR to 35% of patients. Study data continue to be reviewed.

Source: Bayer



Clinical Development (Cont'd)

OPAXIO Produces High Pathologic CR in Advanced Esophageal Cancer

Cell Therapeutics announced that patients with cancer of the lower esophagus demonstrated a high rate of complete remission (CR) when administered OPAXIO (paclitaxel poliglumex), a biologically enhanced paclitaxel, in combination with standard cisplatin and concurrent radiation. These results were presented in the proffered oral session at the Annual Meeting of the International Society of Gastrointestinal Oncology (ISGIO) in Philadelphia, Pennsylvania, October 1-3, 2009.

This Phase II study enrolled 40 patients with pathologically-confirmed, locally-advanced adenocarcinoma or squamous cell carcinoma of the esophagus or gastro-esophageal junction with no evidence of distant metastasis. The patients received weekly paclitaxel poliglumex (50mg/m²) and cisplatin 25mg/m² for 6 weeks with concurrent 50.5Gy of radiation. Of the first 28 patients undergoing surgery, all with adenocarcinoma, 28.5% achieved a pathologic CR. No patients required a feeding tube, in contrast to historical studies using the standard regimen where the large majority of patients require a feeding tube. There were no grade 4 hematologic toxicities; grade 3 hematologic toxicity included neutropenia (n=2) and anemia (n=1). "We look forward to discussing with the Food and Drug Administration a potential Phase III registration strategy for this indication. This would be the first registration study for a radiation sensitizing agent in this indication," said Jack Singer, M.D., Chief Medical Officer at CTI.

Source: Cell Therapeutics

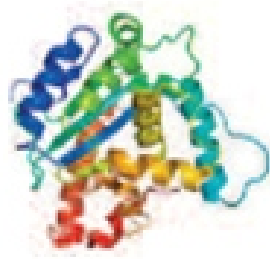
Phase II Trial of RP101 in Late-stage Pancreatic Cancer Discontinued

SciClone Pharmaceuticals announced the discontinuation of the investigational treatments under its randomized, placebo-controlled, double-blind Phase II trial that was evaluating RP101, a nucleoside analog known as BVdU, for the treatment of late-stage pancreatic cancer. This decision followed the recommendation of the Data Safety Monitoring Committee (DSMC) with oversight responsibility for this clinical trial that was based upon the data reviewed at the most recent DSMC meeting. SciClone has notified the study investigators and appropriate regulatory authorities of the decision to discontinue the study. The company expects to conduct a detailed safety and efficacy analysis once the data are unblinded and will then evaluate what effect these data will have on any future RP101 development potential. "We are disappointed with the discontinuation of this study and we will continue to evaluate future opportunities to bring new and effective treatments to these patients," said Friedhelm Blobel, president and CEO of SciClone.

Source: SciClone Pharmaceuticals



Biomarkers

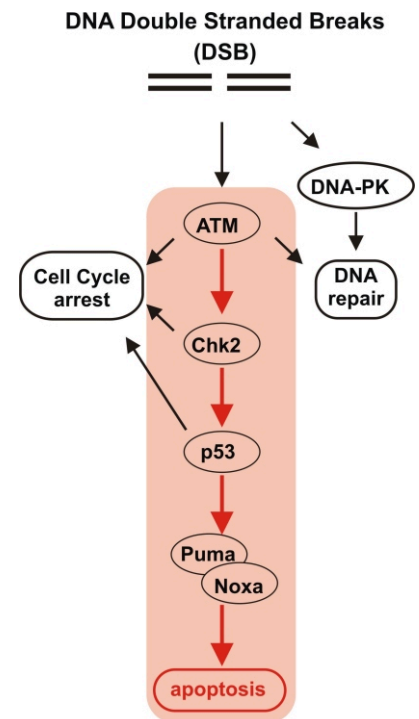


ATM and p53 Link Tumor Development with Therapeutic Response

Following DNA damage, cells activate distinct signaling networks that mediate cell cycle checkpoints, DNA repair, and apoptosis. The selective sensitivity of cancer cells to DNA-damaging chemotherapy suggests that interconnections between cell cycle checkpoint and survival pathways may be altered in tumors. However, it remains unclear how alterations in these networks are integrated to influence the response of tumors to anti-cancer treatments. One of the master regulators of the DNA damage response is the protein kinase - ataxia telangiectasia mutated (ATM), which recruits and phosphorylates a variety of proteins involved in the DNA damage responses.

A paper published by Jiang *et al.* in *Genes and Development* indicates that the status of *p53*, together with one of its regulators *ATM*, can indicate the probable response of a tumor to therapy. The workers showed that in *p53*-deficient settings, suppression of *ATM* dramatically sensitizes tumors to DNA-damaging chemotherapy. Conversely, in the presence of functional *p53*, *ATM* signaling is required specifically for the up-regulation of the proapoptotic *p53* transcriptional target genes, *Puma* and *Noxa*. Both *ATM* and *Chk2* knockdown cells showed significant suppression of *Puma* and *Noxa* at both the mRNA and protein level after doxorubicin treatment, indicating that *ATM* and *Chk2* are required for proper *p53*-mediated activation of an apoptotic program in response to genotoxic chemotherapy. Furthermore, *ATM*-deficient cancer cells display strong non-oncogene addiction to DNA-dependent protein kinase catalytic subunits (DNA-PKcs) *in vivo* resensitizes inherently chemoresistant *ATM*-deficient tumors to genotoxic chemotherapy. Thus, in cells with intact *p53*, *ATM* is required for an effective induction of apoptosis in response to DNA damage, but *ATM* is not required for *p53*-mediated cell cycle arrest. In the absence of *p53*, *ATM* can induce a G2 arrest in response to DNA damage, but this checkpoint is lost in *p53*- and *ATM*-deficient cells, allowing the cells to enter mitosis with damaged DNA, resulting in cell death. The study reveals that mechanisms commonly used by tumors to bypass early neoplastic checkpoints ultimately determine chemotherapeutic response and generate tumor-specific vulnerabilities that can be exploited with targeted therapies.

Source: *Genes & Development*



Genes & Development, 23, 2009



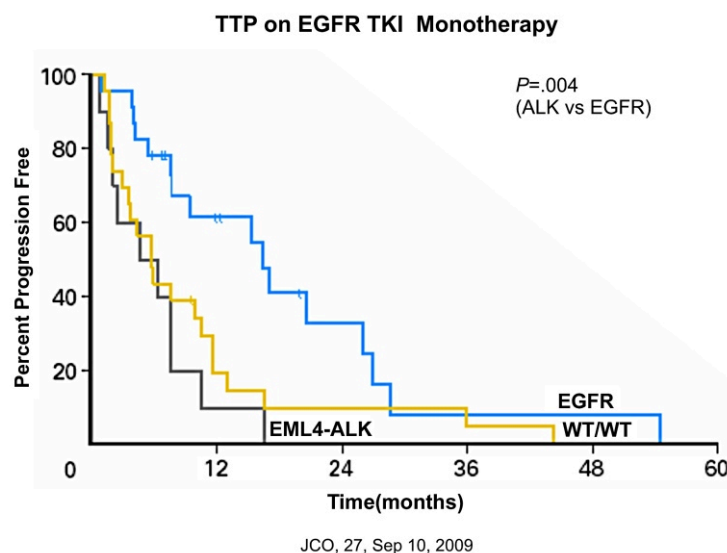
Biomarkers (Cont'd)

Clinical Features and Outcome of Patients with NSCLC who Harbor *EML4-ALK*

The *EML4-ALK* fusion oncogene represents one of the newest molecular targets in NSCLC. The fusion results from a small inversion within chromosome 2p, which leads to expression of a chimeric tyrosine kinase, in which the N-terminal half of echinoderm microtubule-associated protein-like 4 (EML4) is fused to the intracellular kinase domain of anaplastic lymphoma kinase (ALK). In a study published in *JCO*, Shaw et al. describe the clinical and pathologic characteristics of patients with *EML4-ALK*, and also examined treatment response and survival in patients who have metastatic disease with and without *EML4-ALK*. Patients with NSCLC were selected for genetic screening on the basis of two or more of the following characteristics: female sex, Asian ethnicity, never/light smoking history, and adenocarcinoma histology.

Of the 141 tumors screened, 13% harbored the *EML4-ALK* rearrangement, 22% harbored an activating *EGFR* mutation, and 65% were wild-type for both *ALK* and *EGFR* (WT/WT). Compared with patients who had *EGFR* mutant and WT/WT, *EML4-ALK* – positive patients were significantly younger and more likely to be men. Patients with *EML4-ALK* – positive tumors, like patients who harbored *EGFR* mutations, were also more likely to be never/light smokers compared with patients in the WT/WT cohort. Among patients with metastatic disease, *EML4-ALK* positivity was associated with resistance to *EGFR* tyrosine kinase inhibitors (TKIs). For *EML4-ALK* positive patients treated with an *EGFR* TKI, the median TTP was only 5 months, compared with 6 months for WT/WT and 16 months for patients with *EGFR* mutation. In conclusion, *EML4-ALK* defines a new molecular subset of NSCLC with distinct clinical and pathologic features. These findings suggest that patients who harbor this mutation do not benefit from *EGFR* TKIs and should be directed to trials of *ALK*-targeted agents.

Source: *JCO*





Biomarkers (Cont'd)

Polarization of Tumor-Associated Neutrophil Phenotype by TGF- β

The immunosuppressive cytokine, TGF- β , is overexpressed by tumors and plays a significant role in blocking immune responses and affecting tumor progression. The pivotal role of TGF- β in suppressing antitumor immune responses has made it a logical target for the development of antagonists. TGF- β blockers and TGF- β receptor inhibitors have antitumor effects that, in several models, are primarily due to CD8⁺ T cell-dependent immunologic mechanisms. In a study published in *Cancer Cell*, Fridlender *et al.* report that in lung cancer and mesothelioma models, TGF- β blockage is associated with activation of a CD8⁺ T cell-dependent effector arm that involves neutrophils as effectors.

Under conditions of TGF- β -mediated immunosuppression, CD8⁺ T cell activation results in increased recruitment of neutrophils, their "N1" polarization, and antitumor activity. On the other hand, in the presence of TGF- β , depletion of "N2" polarized neutrophils results in retardation of tumor growth. Preliminary data suggest that at least part of the neutrophil-attracting chemokines is derived from tumor-associated macrophages involving T cells, macrophages, and polymorphonuclear leucocytes. Thus, in models of lung cancer, infiltrating neutrophils are driven by TGF- β to acquire a polarized N2 pro-tumor phenotype. After TGF- β inhibition, a shift to N1 occurs with acquisition of antitumor activity *in vitro* and *in vivo*. These findings suggest that tumor-associated neutrophils are a double-edged sword, capable of being pro- or anti-tumorigenic, depending on the tumor microenvironment. The present results call for a reappraisal of prognostic significance of neutrophil in human cancer.

Source: Cancer Cell

ICT-109 Shows Promise in Detecting Pancreatic and Lung Cancer in Serum Test

ImmunoCellular Therapeutics announced results from its pilot study evaluating the cancer detection abilities of one of its lead monoclonal antibody product candidates, ICT-109. Data from this study demonstrated that ICT-109 had a statistically significant ability to discriminate between cancerous and non-cancerous samples, suggesting the potential to detect pancreatic and lung cancer in plasma and serum study sets. The study used reverse phase micro array technology to determine serum and plasma expression levels of glycosylated carcinoembryonic antigen (CEA). Researchers investigated the ability of ICT-109 to detect pancreatic and lung cancer by binding specifically to glycosylated epitopes of CEA-CAM6 and CEA-CAM5, two common markers that are overly expressed in a majority of cancers.

"The results from this study encourage us to believe that ICT-109 could become an important component of future diagnostic technologies for the reliable and early detection of cancers for which early detection is critical for effective treatment," commented Manish Singh, President and CEO of IMUC.

Source: ImmunoCellular Therapeutics



Regulatory



FDA Approves GSK's VOTRIENT for Advanced RCC

GlaxoSmithKline (GSK) announced that the FDA has approved VOTRIENT (pazopanib), an angiogenesis inhibitor, to treat patients with advanced renal cell carcinoma (RCC). The approval of VOTRIENT was supported by a unanimous decision by the FDA's Oncology Drugs Advisory Committee (ODAC) that the benefit-to-risk profile for VOTRIENT is acceptable for patients with advanced kidney cancer.

The ODAC reviewed data from a Phase III clinical trial showing that VOTRIENT reduced the risk of tumor progression or death by 54% compared to placebo, regardless of prior treatment. In this Phase III trial, the overall median PFS was 9.2 months with pazopanib and 4.2 months with placebo. Treatment-naïve patients who received VOTRIENT experienced 11.1 months of median PFS vs 2.8 months with placebo. Additionally, patients who had previously received cytokine-based treatment achieved 7.4 months of median PFS with VOTRIENT vs 4.2 months with placebo.

Source: GSK

FDA Approves FOLOTYN for Relapsed or Refractory PTCL

Allos Therapeutics announced that the FDA granted accelerated approval for FOLOTYN (pralatrexate injection) for use as a single agent for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). FOLOTYN is the first and only drug approved by the FDA for this indication and represents a new treatment option for patients with relapsed or refractory PTCL.

The FOLOTYN approval was based on the results from PROPEL, an open-label, single-arm, multi-center, international clinical trial that enrolled 115 patients with relapsed or refractory PTCL. Out of total patients enrolled, 109 were considered evaluable for efficacy according to the trial protocol. The median number of prior systemic therapies was 3 (range 1-12). The results of the trial demonstrated that 27% of patients responded to FOLOTYN. The median duration of response was 287 days (range 1-503 days). Thirteen of 109 evaluable patients had duration of response greater-than or equal to 14 weeks (range 98-503 days).

Source: Allos Therapeutics

FDA Approves GSK's Cervical Cancer Vaccine, Cervarix

GSK announced that the FDA has approved CERVARIX [Human papillomavirus bivalent (types 16 and 18) vaccine, recombinant] for the prevention of cervical pre-cancers and cervical cancer associated with oncogenic human papillomavirus (HPV) types 16 and 18 for use in girls and young women (aged 10-25). CERVARIX was shown to be 93% efficacious in the prevention of cervical pre-cancers associated with HPV 16 or 18, in women without evidence of current infection with, or prior exposure to, the same HPV type at the time of vaccination.

The FDA's approval of CERVARIX was based on data from clinical trials in more than 30 countries involving a diverse population of nearly 30,000 girls and young women receiving CERVARIX. To date, CERVARIX has been approved in 100 countries around the world, including the 27 member states of the European Union (EU).

Source: GSK

Yondelis Receives CHMP Positive Opinion in Ovarian Cancer

European Union's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for the use of Yondelis (trabectedin) in combination with pegylated liposomal doxorubicin (PLD) for the treatment of patients with relapsed platinum-sensitive ovarian cancer. Zeltia has been developing Yondelis for use in combination with Johnson & Johnson's Doxil for the treatment of ovarian cancer.

Trabectedin is currently being marketed in the EU and has been approved in 12 countries outside the EU for the treatment of soft tissue sarcoma in adults after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. The European decision contrasts with the verdict of the FDA, whose experts were concerned that risks of heart and liver toxicity outweighed the limited ability of Yondelis to keep disease in check.

Source: EMEA



Regulatory

FDA Panel Recommends Approval of PEGINTRON for Stage III Malignant Melanoma

Schering-Plough announced that the FDA Oncologic Drugs Advisory Committee (ODAC) recommended approval by a vote of six to four for PEGINTRON (pegylated interferon alfa-2b) in the adjuvant treatment of patients with Stage III malignant melanoma.

Schering-Plough filed the supplemental Biologics License Application (sBLA) for this indication to the FDA in September 2007. The efficacy and safety of PEGINTRON was assessed in a trial led by the European Organization for the Research and Treatment of Cancer (EORTC) and implemented in 101 sites across Europe. In this randomized, controlled trial of 1,256 melanoma patients, pegylated interferon alfa-2b (N=627) vs. observational arm (N=629) had a significant and sustained impact on relapse-free survival (RFS). Median RFS was 34.8 months in the pegylated interferon alfa-2b arm vs. 25.5 months in the observational arm. Pegylated interferon alfa-2b is marketed in the US for chronic hepatitis C in combination with ribavirin in patients 3 years of age and older with compensated liver disease and as monotherapy for patients who are intolerant to ribavirin with compensated liver disease previously untreated with interferon alpha and who are at least 18 years of age.

Source: Schering-Plough

