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INTELLIGENT INSIGHTS. SMART RESULTS.

In the Spotlight:

Antibodies Specifically Targeting Tumor-Associated EGFR

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Business News

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BMS Expands its Strategic Collaboration into Oncology with Otsuka
Bayer and Ardea Biosciences Enter into Global Agreement

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A Mutant-p53/Smad Complex to Empower TGFβ-Induced Metastasis
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Positive Phase II Bavituximab Data from Lung and Breast Cancer Trials

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Regulatory

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NCCN Incorporates FDA Approval of Everolimus
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The E-newsletter team: Dr. Anuradha Dhingra, Ms.Meenu Grover, Ms. Sarika Manchanda.
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Spotlight Report

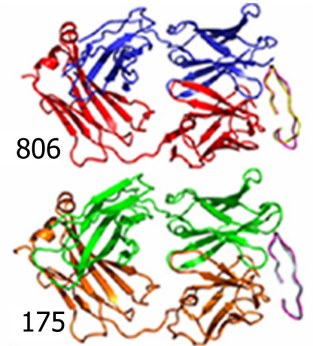
Antibodies Specifically Targeting Tumor-Associated EGFR

Targeting epithelial growth factor receptor (EGFR) is an attractive therapeutic option for cancer treatment but the use of such agents has been limited due to interference with EGFR expressed on normal cells. Successful attempts have been made to generate monoclonal antibodies (mAbs) targeting over-expressed wild-type EGFR (wtEGFR) on cancer cells but not on normal cells. The mechanism underlying this differential binding remained unclear.

A recent study reported in *PNAS*, by Garrett *et al.* suggests that it may be possible to create antibodies that specifically recognize tumor-associated EGFR by targeting a cryptic epitope. The researchers tested the anti-tumor activity of two anti-EGFR antibodies (mAb806 & mAb175) using nude mice xenografted with U87MG cells that express the D2-7EGFR mutant and observed a reduction in tumor volume. Importantly, xenografts from DU145 prostate cells, which contain an amplified transforming growth factor- α (*TGFA*) gene that leads to autocrine stimulation of wtEGFR, showed reduced tumor growth to a greater extent than the U87MG xenografts when treated with these antibodies. The specificity of these anti-EGFRs was due to the molecular interactions between the antibodies and their cryptic EGFR epitope which is a short cysteine loop of the extracellular EGFR domain. Though conformationally similar to wtEGFR, steric hindrance due to a disulphide bond between two cysteine residues preceding the peptide epitope, prevents the anti-EGFRs from binding it. The workers broke this bond thus exposing the cryptic epitope which led to binding of the antibodies. The binding of the anti-EGFRs only to wtEGFR on cancer cells while sparing normal cells is explained by the fact that during EGFR activation, the receptor undergoes a conformational shift that exposes the cryptic epitope. The results of this study indicate that designing antibodies to other misfolded or inappropriately activated receptors may be of benefit in cancer therapy.

Source: *PNAS*

Crystal structures of Fab806 and Fab175



PNAS, 106, March 31, 2009



Business News

Seattle Genetics Collaborates with Millennium for Development of ADC's

Seattle Genetics announced a worldwide collaboration agreement with Millennium, a wholly owned subsidiary of Takeda Pharmaceutical Company, for the development of antibody-drug conjugates (ADCs).

Under the terms of the collaboration, Millennium will pay a \$4 million upfront fee for an exclusive ADC license to an initial antigen expressed on solid tumors. Millennium also can exercise options for exclusive licenses to two other antigens upon payment of additional fees to Seattle Genetics. Millennium is responsible for research, product development, manufacturing and commercialization of all ADC products under the collaboration. Seattle Genetics will receive progress-dependent milestone payments and mid-single digit royalties from Millennium on worldwide net sales of any resulting ADC products.

ADCs are monoclonal antibodies that carry potent, cell-killing drugs through stable linker systems and release the drugs under specific conditions once inside targeted cells. Seattle Genetics is also advancing its own proprietary pipeline of ADC programs, including SGN-35 in a pivotal trial for Hodgkin lymphoma and a planned Phase II trial for systemic anaplastic large cell lymphoma (ALCL). The company is also developing a number of preclinical ADC programs.

Source: Seattle Genetics

BMS Expands its Strategic Collaboration into Oncology with Otsuka

Bristol-Myers Squibb (BMS) established an oncology collaboration for two of its products – Sprycel (dasatinib) and Ixempra (ixabepilone) with Otsuka Pharmaceutical. BMS also extended the US portion of the companies' long-standing agreement for the development and commercialization of Abilify (aripiprazole) from the currently scheduled end date of November 2012 until the expected loss of exclusivity in April 2015.

Under terms of the agreement BMS will pay Otsuka an up-front cash payment of \$400 million. Beginning in 2010, BMS and Otsuka will collaborate on two oncology assets Sprycel and Ixempra as follows: Otsuka will share in commercial expenses for the US, Europe and Japan and co-promote Sprycel with BMS in the US, Japan and major EU markets; BMS will pay Otsuka a collaboration fee on aggregate annual net sales of Sprycel and Ixempra beginning in 2010 on a regressive tiering basis through 2020.

Source: Bristol-Myers Squibb

Bayer and Ardea Biosciences Enter into Global Agreement for Development of MEK Inhibitors

Bayer HealthCare has entered into a global agreement with Ardea Biosciences for the development of small molecule mitogen-activated ERK kinase (MEK) inhibitors for the treatment of solid tumors. These kinases are believed to play an important role in cancer cell proliferation, apoptosis and metastasis, as well as inflammation. The lead compound in this program, RDEA119, is currently being evaluated in advanced cancer patients of different tumor types as a single agent in a Phase I study as well as in combination with sorafenib (Nexavar, Bayer/Onyx Pharmaceuticals) in a Phase I/II study. Preclinical and clinical results suggest that RDEA119 has favorable properties including oral dosing, excellent selectivity, and limited retention in the brain, which, in turn, may result in a reduced risk of central nervous system (CNS) side effects.

Under the terms of the agreement, Ardea will grant Bayer a worldwide, exclusive license to develop and commercialize Ardea's MEK inhibitors for all indications. Potential payments to Ardea under the agreement could total up to \$407 million, not including royalties. This amount includes an upfront cash payment to Ardea of \$35 million, as well as additional cash payments upon achievement of certain development, regulatory and sales-based milestones. In addition, Ardea is also eligible to receive low double-digit royalties on sales of products under the agreement. Ardea will be responsible for the completion of the Phase I and Phase I/II studies currently being conducted for RDEA119. Thereafter, Bayer will be responsible for the further development and commercialization of RDEA119 and any of Ardea's other MEK inhibitors.

Source: Bayer Healthcare AG

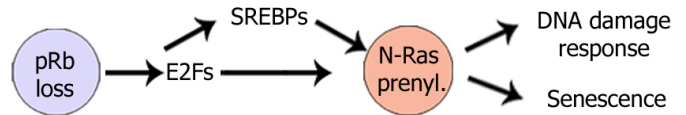


Research Highlights

Ras and pRb: An Intimate Relationship

Oncogene-induced cellular senescence (OIS) is accepted as one of the cellular functions that antagonizes carcinogenesis despite the presence of oncogenic mutation. The *Ras* family of proto-oncogenes and the retinoblastoma tumor suppressor gene, *Rb*, act as key regulators of cellular proliferation and differentiation. Despite their distant locations, the two genes communicate intimately through various signaling channels. pRb acts as a critical effector for *Ras* with *Rb*-deficient cells continuing to proliferate irrespective of *Ras* activity. *Rb* deficiency markedly increases the ability of *Ras* to bind guanine nucleotides, resulting in the activation of the latter. This communication is bidirectional (negative feedback loop) and *Ras* activity is regulated as a function of *pRb*, but the mechanism still remained unclear.

Interactions between N-Ras and pRb in Senescence, and Cancer



Cancer Cell, 15, April 7, 2009

Recently, Shamma *et al.* in *Cancer Cell*, have unraveled the mechanism by which Ras and pRb functionally interact and also showed the relevance of this communication in OIS in the progression of murine *Rb*-deficient C cell adenoma to adenocarcinoma. This study clarified the mechanism by which N-ras loci protect mouse C cells and primary fibroblasts from *Rb* loss-induced carcinogenesis. Inactivation of pRb induces aberrant expression of farnesyl diphosphate synthase, many prenyltransferases, and their upstream regulators sterol regulatory element-binding proteins (SREBPs) in an E2F-dependent manner. This leads to enhanced isoprenylation and activation of N-Ras and the consequent enhanced N-Ras activity induces DNA damage response and p130-dependent cellular senescence in *Rb*-deficient cells. Furthermore, *Rb* heterozygous mice additionally lacking any of *Ink4a*, *Arf*, or *Suv39h1* generated C cell adenocarcinomas, suggesting that cellular senescence antagonizes *Rb*-deficient carcinogenesis. Since Ras proteins promote carcinogenesis in many cell types, these findings may provide a rational basis for the application of prenyltransferase inhibitors to human cancers with aberrations in the RB pathway.

Source: *Cancer Cell*

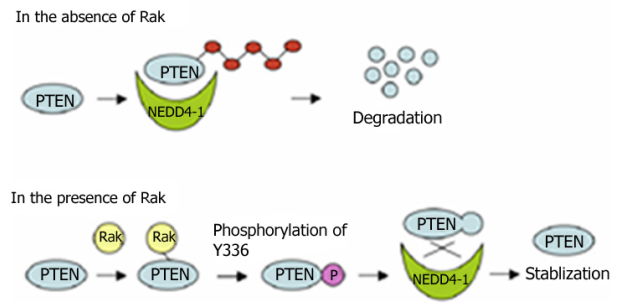


Research Highlights (cont'd.)

Rak Functions as a Tumor Suppressor by Regulating PTEN Protein Stability

The phosphatase and tensin homolog (*PTEN*) tumor suppressor gene is reported to play fundamental roles in the maintenance of chromosomal stability as well as stem cell biology. *PTEN* antagonizes the actions of phosphatidylinositol 3-kinase by dephosphorylating the second messenger phosphatidylinositol 3,4,5-trisphosphate, regulating activation of the kinase Akt as well as the downstream cellular survival and growth responses. The epigenetic regulation of *PTEN* expression has been attributed to transcriptional regulation, microRNA, and/or alteration of *PTEN* protein stability. *PTEN* is frequently mutated in a number of tumors, including glioblastoma, melanoma, and carcinomas of the prostate, breast, and endometrium and expression of the *PTEN* is frequently lost in breast cancer in the absence of mutation or promoter methylation. The mechanism causing *PTEN* protein loss has not been defined.

Rak Phosphorylates PTEN and Protects PTEN from Ubiquitin-Mediated Degradation



Cancer Cell, 15, April 7, 2009

A study by Yim *et al.* from *Cancer Cell*, has demonstrated that Rak, a *PTEN*-interacting protein, strongly correlates with *PTEN* protein levels in breast cancer tissues, and positively regulates *PTEN* protein stability through phosphorylation of *PTEN*, which in turn prevents *PTEN* from ubiquitin-mediated degradation. Knockdown of Rak enhances the binding of *PTEN* to its E3 ligase NEDD4-1 and promotes *PTEN* polyubiquitination, leading to *PTEN* protein degradation. Notably, ectopic expression of Rak effectively suppresses breast cancer cell proliferation, invasion, and colony formation *in vitro* and tumor growth *in vivo*, at least in part through regulating *PTEN* protein stability. Furthermore, Rak knockdown is sufficient to transform normal mammary epithelial cells. *Rak*, thus, acts as a tumor suppressor gene through the mechanism of regulating *PTEN* protein stability and function and further understanding of its function may contribute to effective therapeutic approaches for both Rak- and *PTEN*-defective cancers.

Source: *Cancer Cell*



Research Highlights
(cont'd.)

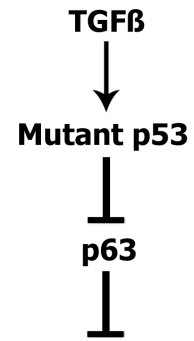
A Mutant-p53/Smad Complex Opposes p63 to Empower TGFβ-Induced Metastasis

TGFβ/Smad signaling plays a central role for tumorigenesis of several epithelia, paradoxically switching from tumor suppressor to promoter of metastasis during cancer progression. In a study reported in *Cell*, Adorno *et al.* present evidence of a TGFβ-initiated intracellular cascade specifically relevant in advanced tumor cells for metastasis. Investigators showed that mutant-p53 expression is required for sustaining TGFβ proinvasive responses and metastatic spread *in vivo*. TGFβ-dependent cell migration, invasion and metastasis are empowered by mutant p53. p63 which is downstream of mutant-p53 opposes TGFβ-induced malignant responses. Ras signaling promotes mutant-p53 phosphorylation and is required for the formation of the mutant-p53/Smad complex. Smads serve as an essential platform for the process.

The functional inactivation of p63 by the TGFβ induced mutant-p53/Smad complex is critical for gain of metastatic proclivity. Mutant-p53 and Smad intercept p63 to form a ternary complex, in which the p63 transcriptional functions are antagonized. Two genes, *Sharp1* and *Cyclin G2*, that are downstream of the TGFβ/mutant-p53/p63 pathway were also identified to be essential mediators of p63-mediated antagonism toward TGFβ responses. Thus, in presence of mutant-p53, TGFβ attains control over p63. This unleashes TGFβ malignant effects. p63 being downstream of mutant-p53, its inactivation transforms non-invasive cells into malignant tumors and rescues metastasis ability in mutant p53-depleted breast cancer cells. Mutation of p53, the levels of Ras and p63, as well as the strength of TGFβ signaling, are critical variables in p63 distribution. Thus, two common oncogenic lesions, mutant-p53 and Ras, selected in early neoplasms to promote growth and survival, also show a tendency to promote metastasis by TGFβ-dependent inhibition of p63 function.

Source: *Cell*

Epistatic Relationships between TGFβ, Mutant-p53 and p63



Migration & Invasion

Cell, 137, April 3, 2009



Research Highlights (cont'd.)

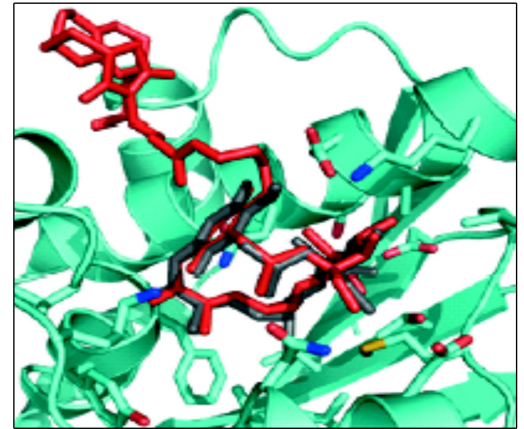
Combinatorial Drug Design Targeting Multiple Cancer Signaling Networks

Therapeutically targeting a single signaling pathway to inhibit tumor progression has not been successful in many cases. Combinatorial drug design, whereby inhibitors of signaling networks are targeted to specific subcellular compartments, may generate effective anticancer drugs with novel mechanisms of actions. Hsp90 is a chaperone protein that controls the folding of proteins in multiple signaling networks which drive tumor development and progression.

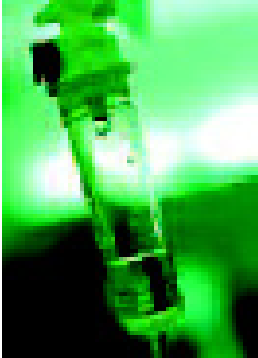
In a study reported in *JCI*, Kang *et al.* reported the impact of network subcellular compartmentalization in dictating the activity of Hsp90 inhibitors such as Gamitrinibs (GA mitochondrial matrix inhibitors) a class of fully synthetic, small molecules engineered to selectively target a compartmentalized Hsp90 network in tumor mitochondria. Gamitrinibs is a combinatorial drug with a benzoquinone ansamycin backbone derived from the Hsp90 inhibitor 17-(allylamino)-17-demethoxygeldanamycin (17-AAG), designed for the first time to target mitochondrial Hsp90. The 17-AAG portion of Gamitrinib is predicted to make contacts with the Hsp90 ATPase pocket. Gamitrinibs efficiently accumulate in mitochondria, trigger sudden and irreversible organelle permeability transition, and induce exceedingly fast (~1 hour) and complete tumor cell killing by apoptosis. In turn this results in inhibition of tumor growth *in vivo*, with no detectable toxicity for normal cells or tissues. Gamitrinibs were shown to accumulate in the mitochondria of human tumor cell lines and inhibit Hsp90 activity by acting as ATPase antagonists. They target a potential upstream step in mitochondrial permeability transition exhibiting mitochondrial toxicity, and do not affect global Hsp90 homeostasis outside of mitochondria. For these combined properties, Gamitrinibs are believed to be novel, attractive anticancer agents, suitable for human testing.

Source: *JCI*

3D Docking Model of Gamitrinib-G1 with Hsp90 N-Domain



JCI, 119, March, 2009



Clinical Development

Avastin Fails Colon Cancer Trial Target

Roche announced the results of the first Phase III trial evaluating the use of Avastin (bevacizumab) plus chemotherapy (FOLFOX) for the treatment of colon cancer immediately following surgery compared to chemotherapy alone. The study, known as NSABP C-08, did not meet its primary endpoint of lowering the risk of the cancer returning (disease-free survival). This is the first trial of Avastin in early-stage cancer and results do not affect approved indications in advanced (metastatic) disease. This trial was initiated based on the improvement in overall survival observed in metastatic colorectal cancer patients treated with Avastin plus chemotherapy and positive results from two other adjuvant colon cancer studies (MOSAIC and NSABP C-07) with an oxaliplatin containing regimen.

"In order to provide patients with the full potential benefit of Avastin in early-stage cancer, we believe the findings of the C-08 trial should be considered for the ongoing adjuvant trial programs. The current studies and indications in advanced disease are not affected," said CEO of Roche's Pharmaceuticals Division William M. Burns.

Source: Roche Pharmaceuticals

Cancer Vaccine Provenge Showed Prolonged Survival

Dendreon Corporation announced that its pivotal Phase III IMPACT study of PROVENGE® (sipuleucel-T) in men with advanced prostate cancer met its primary endpoint of significantly improving overall survival compared to placebo. PROVENGE extended median survival by 4.1 months (25.8 months vs 21.7 months); improved 3-year survival by 38% (31.7% vs 23.0%); reduced the risk of death by 22.5% compared to placebo. IMPACT was conducted under a Special Protocol Assessment (SPA) agreement with the FDA. Because the data meet the criteria and specifications outlined in its SPA agreement, Dendreon intends to file an amendment to its existing Biologic License Application in the fourth quarter of this year to gain licensure of PROVENGE.

Paul Schellhammer, professor of urology and a principal investigator of the IMPACT study said, "The results from this landmark study confirm that PROVENGE prolongs survival with a favorable benefit to risk profile. If approved, PROVENGE has the potential to fill a large unmet medical need and create a new paradigm using immunotherapy for the treatment of men with advanced prostate cancer."

Source: Dendreon Pharmaceuticals

Nexavar Phase III Trial Does Not Meet Primary Endpoint in Advanced Melanoma

Bayer HealthCare and Onyx Pharmaceuticals announced that a Phase III trial evaluating Nexavar® (sorafenib) tablets in patients with unresectable stage III or stage IV melanoma was stopped early following a planned interim analysis by an independent Data Monitoring Committee (DMC). The primary endpoint was overall survival, and secondary endpoints included progression-free survival and response rate. The DMC concluded that the study would not meet the primary endpoint of improved overall survival among patients receiving Nexavar in combination with the chemotherapeutic agents carboplatin and paclitaxel versus patients receiving placebo plus the chemotherapeutic agents. The treatment effect was comparable in each arm. The DMC also reported there were no unexpected serious side effects, though the final analysis of data will occur per protocol and statistical analysis plan. Bayer and Onyx will further review the findings of this analysis and DMC recommendation to determine what, if any, impact these data might have on other ongoing Nexavar melanoma trials.

Source: Onyx Pharmaceuticals



Clinical Development (cont'd.)

Positive Phase II Results of Picoplatin in SCLC

Poniard Pharmaceuticals announced the publication of the results of its Phase II clinical trial of picoplatin in patients with recurrent small cell lung cancer (SCLC) in JCO (April 20, 2009). Picoplatin demonstrated a survival benefit in this open-label, multi-center Phase II trial of SCLC patients who failed prior platinum-containing first-line chemotherapy or who progressed within 6 months of first-line therapy. The median overall survival was 27 weeks and the median one-year survival rate was 17.6% in this patient population of mostly platinum-refractory and -resistant patients. Efficacy endpoints included response rates, progression-free survival, overall survival, improvement in disease-related symptoms and disease control. Poniard is currently evaluating the efficacy and safety of picoplatin in the pivotal Phase III SPEAR (Study of Picoplatin Efficacy After Relapse) SCLC trial, which is being conducted under a Special Protocol Assessment (SPA) agreement with the U.S. Food and Drug Administration (FDA).

"The publication of these clinical findings in JCO represents an important milestone for Poniard. The positive survival results of the Phase II picoplatin trial in this difficult-to-treat disease formed the basis of our decision to initiate the Phase III SPEAR trial for which we recently completed patient enrollment ahead of internal projections," said Robert De Jager, M.D., chief medical officer of Poniard

Source: Poniard Pharmaceuticals

Positive Phase II Baviximab Data from Lung and Breast Cancer Trials

Peregrine Pharmaceuticals announced updated preliminary data from the initial cohort of 21 patients in its Phase II trial evaluating baviximab in combination with carboplatin and paclitaxel in non-small cell lung cancer (NSCLC) and breast cancer patients. This combination showed that 11 of 17 evaluable patients with locally advanced or metastatic NSCLC and nine of 14 evaluable patients in the initial cohort of breast cancer patients achieved an objective tumor response according to RECIST criteria, after completing the maximum 6 treatment cycles. The company also reported that patient dosing is underway in the expansion stage of the trial, which will enroll an additional 31 patients for a total of 46 advanced breast cancer patients overall.

President and CEO of Peregrine Steven W. King said, "We are very pleased to see these additional objective tumor responses in this difficult-to-treat cancer following the full regimen of six treatment cycles of baviximab and chemotherapy. The tumor response data to date from this trial compares favorably to published studies with current standard-of-care lung cancer treatments, and we are looking forward to seeing results from the entire study."

Source: Pregerine Pharmaceuticals^{1,2}



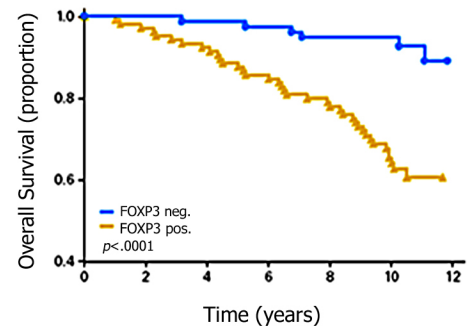
Biomarkers

FOXP3 Expression and Overall Survival in Breast Cancer

Forkhead box P3 (FOXP3) is a member of the forkhead/winged-helix family of transcription regulators. This gene plays a crucial role in the generation of CD4+CD25+ regulatory T cells (Tregs). Loss of FOXP3 function leads to the lack of Tregs, resulting in lethal autoaggressive lymphoproliferation, whereas overexpression of FOXP3 results in severe immunodeficiency.

In a study reported in *JCO*, Merlo *et al.* showed the association of FOXP3 expression with the survival of breast cancer patients. In this study, approximately 57% and 73% of breast tumor specimens in the Milan 3 and 1 trials, respectively, were scored positive for FOXP3 expression by immunohistochemical staining. Univariate analysis indicated that FOXP3 expression in primary breast carcinomas correlated significantly with distant relapse and overall survival, but not with local relapse. Multivariate analysis demonstrated the significant correlation between FOXP3 and decreased overall survival. In both the trials, FOXP3 protein expression was found to correlate with axillary lymph node metastases and MIB1 expression, but not with other clinical parameters such as tumor size, grade, estrogen receptor status, age or other biologic parameters (*HER2*, *p53*, or *ER expression*). The highly significant association between FOXP3 expression and worse prognosis, as well as its independent prognostic value, identify this transcriptional factor as a new prognostic marker for breast carcinoma. Association of FOXP3 expression with survival but not with local relapse suggests that this molecule might be related to metastatic potential rather than to suppression of the immune response. Together, the results suggest the utility of FOXP3 as a novel, independent molecular marker of breast carcinoma outcome, with a significant impact on important outcome measures for breast carcinomas. In conclusion, our data strongly suggest the inclusion of FOXP3 for further exploration as a prognostic marker for breast cancer.

Association between FOXP3 Positive and Negative Staining with Overall Survival



JCO, 27, April 10, 2009

Source: *JCO*

ZNF423, a Marker of Neuroblastoma Outcome

All-trans retinoic acid (all-trans RA), a key biologically active derivative of vitamin A, can be isomerized into 9-*cis*RA and 13-*cis*RA forms (collectively known as retinoids). Retinoids play a key role in differentiation, growth arrest, and apoptosis and are increasingly being used for the treatment of a variety of cancers, including neuroblastoma. The biological actions of retinoids are mediated via retinoic acid receptors (RARs), that act as ligand-regulated transcription factors to modulate the expression of complex gene networks. RARs function as heterodimers formed from one of three RARs and one of three retinoid X, or retinoid, receptors (RXRs). In the absence of agonists, RAR/RXR heterodimers bind to some target genes as corepressor complexes and silence their transcription by histone modification.

In a recent study published in *Cancer Cell*, Huang *et al.* have identified the Krüppel zinc-finger protein ZNF423 (also known as Ebfaz, OAZ, or Zfp423) as a component critically required for retinoic acid (RA)-induced differentiation. Using a large-scale RNA interference-based genetic screen, they demonstrated that ZNF423 interacts with all RAR subtypes as well as RXR and is required, at least in some cells, for effective transcriptional activation induced by RA. ZNF423 associates with the RARa/RXRa nuclear receptor complex and is essential for transactivation in response to retinoids. Down regulation of ZNF423 expression by RNA interference in neuroblastoma cells results in a growth advantage and resistance to RA-induced differentiation, whereas over-expression of ZNF423 leads to growth inhibition and enhanced differentiation. The binding of ZNF423 to RARs and RXRs does not require ligand. They also demonstrated its role as a prognostic biomarker for human neuroblastoma independent of MYCN amplification as high expression of ZNF423 correlates with good outcome of neuroblastoma patients, possibly reflecting enhanced levels of RA signaling. This study leads to the interesting possibilities that ZNF423 may predict responses to RA-based therapies.

Source: *Cancer Cell*



Biomarkers (cont'd.)

Diagnostic Assay Based on hsa-miR-205 Expression in Lung Carcinoma

Lung carcinoma is the leading cause of cancer mortality in the US. There is a need for standardized assays based on biomarkers with high sensitivity and specificity to aid in accurate subclassification of NSCLC. In a study in *JCO*, Lebanony *et al.* hypothesized that specific microRNA biomarkers may exist which could accurately and reliably distinguish squamous from nonsquamous NSCLC, in order to potentially guide clinicians regarding the appropriate therapy for lung cancer patients.

High-throughput microarray was used to measure microRNA expression levels in 122 adenocarcinoma and squamous NSCLC samples. Results demonstrated that hsa-miR-205 was significantly overexpressed in the squamous cell carcinomas. Hsa-miR-21 and the U6 snRNA had high expression levels in both squamous cell carcinomas and adenocarcinomas. Thus, investigators identified hsa-miR-205 as a highly specific marker for squamous cell lung carcinoma. A microRNA-based qRT-PCR assay that measures expression of hsa-miR-205 reached sensitivity of 96% and specificity of 90% in the identification of squamous cell lung carcinomas in an independent blinded validation set. The study concluded that hsa-miR-205 expression levels in NSCLC samples can be reliably quantified, and show a high sensitivity and specificity for distinguishing squamous from nonsquamous NSCLC. A clinical diagnostic assay based on the expression levels of hsa-miR-205 provides a new tool of potential practical value, to aid in differential diagnosis of NSCLC.

Source: JCO

Aberrant Expression of Homeobox Gene CDX2 in ALL patients

Molecular characterization of acute lymphoblastic leukemia (ALL) has greatly improved the ability to categorize and prognostify patients with this disease. Members of the caudal (cdx) family of homeobox proteins are essential regulators of embryonic blood development. Previously it was reported that the murine homologues (Cdx1, Cdx2, and Cdx4) affect formation and differentiation of embryonic stem cell (ESC)-derived hematopoietic progenitor cells.

A study of the proto-oncogene *CDX2* in healthy and leukemic human lymphoid cells reported by Thoene *et al.* and Riedt *et al.* in *Leukemia* and *Blood* respectively showed that a majority of leukemic samples display various degrees of aberrant CDX2 expression. This aberrant expression is seen in specifically those cases with B-lineage ALL and T-ALL. High expression of CDX2 correlated significantly with the ALL subtype pro-B ALL, cALL, Ph⁺ ALL and early T-ALL. Furthermore, high expression of CDX2 was associated with inferior overall survival and showed up as a novel and strong risk factor for ALL in bivariate analysis. Functional analyses showed that overexpression of Cdx2 in murine bone marrow progenitors perturbed genes involved in lymphoid development and that depletion of CDX2 in the human ALL cell line Nalm6 inhibited colony formation. Analysis of a cohort of 37 childhood ALL patients reveals that high CDX2 expression levels at diagnosis correlate with persistence of minimal residual disease (MRD) during the course of treatment. Thus it can be concluded that aberrant CDX2 expression occurs frequently and has adverse prognostic impact in adult as well as pediatric patients with ALL.

Source: Leukemia, Blood



Regulatory



FDA Grants Accelerated Approval of Avastin® for Most Aggressive Form of Brain Cancer

Roche announced that the FDA granted accelerated approval of Avastin® (bevacizumab) for people with glioblastoma with progressive disease following prior therapy. The new indication for Avastin was granted under the FDA's accelerated approval program that allows provisional approval of medicines for cancer or other life-threatening diseases. It follows the unanimous vote by the FDA Oncologic Drugs Advisory Committee (ODAC) on March 31, 2009.

The accelerated approval is based on independently reviewed data from the Phase II, BRAIN study, an open-label, multicenter, non-comparative trial. The study population included 167 patients with glioblastoma that had progressed following initial treatment with temozolomide and radiation. In 26% of patients in whom tumor response was observed, half experienced a response of at least 4.2 months.

Roche has also filed an application with the EMEA in December 2008 for marketing authorisation for Avastin as a therapy for patients with previously treated glioblastoma.

Source: Roche

NCCN Updates Kidney Cancer Guidelines to Incorporate FDA Approval of Everolimus

The National Comprehensive Cancer Network (NCCN) has added everolimus (Afinitor®, Novartis) as category 1 option to the NCCN Clinical Practice Guidelines in Oncology(TM) for Kidney Cancer for advanced renal cell carcinoma in patients whose disease has progressed after treatment with kinase inhibitors such as sunitinib and sorafenib. This recommendation followed March 30, 2009 FDA approval of everolimus based upon results of a clinical trial which showed that the everolimus therapy significantly extended progression-free survival to 4.9 months compared to 1.9 months.

Everolimus targets a protein known as mTOR, which affects tumor cell division, angiogenesis, and cell metabolism. The mTOR pathway integrates signals from nutrients and growth factors and is considered to be a major regulator of cell growth and angiogenesis. By inhibiting the mTOR pathway, everolimus has the potential to block renal cell cancer growth.

Source: NCCN

CHMP Issued Positive Opinion for Iressa for NSCLC with EGFR-TK mutations

Committee for Medicinal Products for Human Use (CHMP), the scientific advisory committee of the European Medicines Agency (EMA), has issued a positive opinion supporting approval of the targeted oral anti-cancer drug, Iressa® (gefitinib) for adults with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK (epidermal growth factor receptor-tyrosine kinase), in all lines of therapy.

The CHMP opinion is based on results of two pivotal Phase III studies, IPASS and INTEREST. The IPASS study demonstrated superior PFS, greater objective response rate (ORR, tumor shrinkage), improved tolerability and significant QOL benefits for Iressa compared to carboplatin/paclitaxel doublet chemotherapy in clinically selected first-line patients in Asia. PFS was significantly longer for IRESSA than doublet chemotherapy in patients with EGFR mutation positive tumours, and vice versa. Pre-planned sub-group analyses in INTEREST study showed a significant improvement in PFS and ORR for Iressa over docetaxel in patients with EGFR mutation positive tumors.

AstraZeneca will be required to conduct a follow-up Measure Study, to generate further data in a Caucasian NSCLC patient population. Iressa is already an established therapy for pre-treated NSCLC in the Asia-Pacific region.

Source: AstraZeneca