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Signaling Networks Assembled by Oncogenic EGFR and c-MET

Gefitinib and Erlotinib are selective inhibitors of EGFR that have shown significant efficacy in non-small cell lung cancer (NSCLC) patients that carry EGFR activating mutations or EGFR amplifications. Similarly, a subfraction of gastric cancer cell lines known to exhibit c-Met amplification are sensitive to the small molecule inhibitor of c-Met. The reason why activating mutations in EGFR or amplifications of c-Met predict response to targeted kinase inhibitors is not very well understood.

In a study published in PNAS, Ailan Guo and colleagues characterized the phosphotyrosine signaling downstream of the EGFR in EGFR inhibitor-sensitive and resistant cell lines and downstream of c-Met in gastric cancel line. This study identified a large network of receptor tyrosine kinase signaling proteins established in cells expressing mutated and activated EGFR that collapse with drug treatment. As observed for EGFR cell lines, c-Met also assembled a large signaling network that is blocked by treatment with c-Met inhibitor. This network shares many signaling components with the gefitinib sensitive network and consists of a “core network” of ~50 proteins that participate in pathways mediating drug response.

Source: PNAS

MicroRNAs Suppress Breast Cancer Metastasis

The genetic mechanisms by which tumor cells metastasize to various organs are poorly understood. Breast cancer preferentially metastasizes to the bone and lung. Using human breast cancer cell (MDA-MB-231) derivatives that are highly metastatic to bone and lung, Joan Massague and his group identified a set of microRNAs whose expression is lost as these cells develop metastatic potential. Two microRNAs among this set, miR-126 and miR-335, are lost in the majority of primary breast tumors from patients who relapse and their loss correlates with poor metastasis-free survival. Restoration of their expression in malignant cells suppresses lung and bone metastasis. These studies identify miR-126 and miR-335 as candidate metastatic suppressors in human breast cancer and suggest the potential use of these molecules in the prognosis of breast cancer patients in addition to clinical and pathological staging.

Source: Nature

Roche to Buy Ventana for $3.4 billion

Roche, a world-leading healthcare provider of pharmaceuticals and diagnostics, and Ventana Medical Systems, announced the signing of a definitive merger agreement. Under the terms of the agreement, Roche will purchase Ventana common shares at $89.50 per share in cash (or an aggregate of approximately $3.4 billion on a fully diluted basis).

Genzyme Announces License Agreement with Moffitt Cancer Center for Exclusive Rights to Lung Cancer Diagnostic

Genzyme Corp. announced a licensing agreement with Moffitt Cancer Center to obtain exclusive worldwide diagnostic testing rights for the discovery of the relationship of two proteins to patient response to non-small cell lung cancer (NSCLC) treatment. The expression levels of the two proteins, RRM1 and ERCC1, correlates with patient response to platinum drugs and gemcitabine, shown by Dr. Gerold Bepler, M.D., and his team from Moffitt.
Rituximab Improves the Treatment Results of Chemotherapy and ASCT in Relapsed/Progressive Aggressive CD20+ NHL

Chemotherapy, along with autologous stem-cell transplantation (ASCT), is curative in a proportion of patients with relapsed or refractory aggressive non-Hodgkin lymphoma (NHL). The chemotherapy regimens used in this setting include DHAP (cisplatin-cytarabine-dexamethasone), VIM (etoposide-ifosfamide-methotrexate), ICE (isosfamide-carboplatin-etoposide) or combinations. In a study by Edo Vellanga et al, which is a prospective randomized Phase III study conducted by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON), the efficacy of rituximab added to the DHAP-VM-DHAP regimen followed by ASCT was tested. A significant improvement in failure free survival (FFS) and progression free survival (PFS) was observed in favor of the rituximab treatment. The beneficial effects of rituximab were observed both in patients with progression on first-line treatment as well as in relapsed patients. The overall response rate in the DHAP-arm was CR, 35% and PR, 15% versus 46% and 27% in the R-DHAP arm. These results show that the addition of rituximab to the reinduction therapy significantly improves FFS and PFS in relapsed aggressive B-cell NHL.

Source: Blood

Threshold Announces Phase II Results of Glufosfamide

Threshold Pharmaceuticals announced results from two Phase II clinical trials of glufosfamide for the treatment of patients with soft tissue sarcoma and platinum-resistant ovarian cancer. The sarcoma trial evaluated the efficacy and safety of glufosfamide in patients with advanced, soft-tissue sarcoma. Twenty-two patients with metastatic and/or advanced unresectable soft tissue sarcoma previously treated with one or two prior systemic therapies were enrolled in the Phase II, open-label, clinical trial at various sites in the US. Tumor response was evaluated at baseline and every six weeks using the Response Evaluation Criteria in Solid Tumors (RECIST). Eight of 18 (44%) evaluable patients demonstrated clinical benefit by RECIST criteria of stable disease or partial response. The most common severe adverse event was renal failure (5 of 22 patients). The company has decided not pursue clinical investigation of ovarian cancer due to lack of efficacy. Due to a recent shift in the company’s focus to TH-302 and its underlying pipeline of HAP product candidates, it is seeking a partner to continue the development of glufosfamide for these and potentially other indications.

Source: Threshold Pharmaceuticals

Phase II Study of Zevalin® in Patients with Previously Untreated Non-Follicular Indolent Lymphoma

Cell Therapeutics, Inc., announced the results of a Phase II clinical study published in the journal CANCER. This study demonstrated that the addition of radioimmunotherapy (RIT) to chemotherapy for previously untreated patients with non-follicular indolent NHL was both well tolerated and effective. In this single-arm, non-randomized Phase II trial, 26 eligible patients with previously untreated, indolent, non-follicular NHL were treated using a novel regimen that consisted of 6 cycles of fludarabine/mitoxantrone (FM) chemotherapy followed by 6 to 10 weeks of 90Y ibritumomab tiuxetan (Zevalin). After chemotherapy, the overall response rate was 80.5% (20 patients). Of the 20 patients (13CR/7PR) who were evaluated for subsequent Zevalin, 100% obtained a CR at the end of treatment. With a median follow up of 20 months, the estimated three-year progression free survival (PFS) was 89.5%. Zevalin is a form of cancer therapy called RIT, approved by the FDA in February 2002 as the first radioimmunotherapeutic agent for the treatment of NHL.

Source: MGI Pharma

Small Molecule XIAP-Antagonists Induce Apoptosis in Diffuse B cell Lymphoma Cells

X-linked inhibitor of apoptosis (XIAP), a potent inhibitor of apoptosis, is overexpressed in many malignancies, including diffuse B cell lymphoma cells (DLBCL). XIAP suppresses apoptosis by inhibiting caspases-3, 7 and 9. A small molecule inhibitor of XIAP, 1396-12, was shown to relieve the inhibition of caspase-3 and induce apoptosis in lymphoma cells of patients with DLBCL. Sensitivity to XIAP antagonists correlated with the high expression level of XIAP protein, low level of Bel-2 and by constitutive activation of caspase-9. These results suggest the possibility of predefining DLBCL patients most likely to benefit from XIAP therapy.

Source: Blood
Bcl-2/Bcl-X\textsubscript{L} Inhibitor Sensitizes Ovarian Cancer Cells to Carboxplatin

Current treatments for ovarian cancer include a combination of carboplatin and paclitaxel. A majority (~80%) of patients who receive carboplatin and paclitaxel initially respond well to therapy; however, several suffer a relapse. Expression of Bel-X\textsubscript{L}, a member of the Bcl-2 and Bcl-X\textsubscript{L} family of proteins, which function as apoptosis inhibitors, is increased in ovarian cancer patients who relapse following chemotherapy. ABT-737, a small molecule inhibitor of Bel-X\textsubscript{L} and Bcl-2 proteins, binds to a hydrophobic groove in these proteins and prevents them from sequestering proapoptotic proteins such as BAD and BIM. In a study published in Clinical Cancer Research, James Witham and his colleagues reported that ABT-737 does not potently inhibit the growth/survival of several ovarian cancer cells in vitro. However, ABT-737 increased the sensitivity of these cell lines to carboplatin. Combined administration of ABT-737 and carboplatin inhibited the growth of ovarian tumor xenografts in mice more effectively than either agent used alone. These results suggest that small molecule inhibitors of Bel-2 and Bel-X\textsubscript{L} may be useful in the treatment of patients with ovarian cancers.

Source: Clinical Cancer Research

RPS14, Encoding a Ribosomal Protein, Functions as a Tumor Suppressor Gene in 5q-Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) arises from abnormal haematopoietic stem cells leading to inefficient production of blood cells. A subtype of MDS known as 5q- syndrome is characterized by loss of the q31-33 segment of chromosome 5. The specific gene responsible for this disease is not known. Ebert and colleagues described an approach to the identification of genes using the technique of RNA interference. Using this technique, they reduced the expression of each candidate suppressor gene in the 5q31-33 segment and identified RPS14 as a tumor suppressor gene. This gene encodes a component of the 40S subunit of ribosome and is essential for the formation of RNA-protein complexes. Although many cancers arise from deletions of both copies of tumor suppressor genes, in some cancers inactivation of just one copy of selective tumor-suppressor gene promotes tumorigenesis. The authors show that inactivation of one allele of RPS14 is common in 5q- MDS.

Source: Nature

Sirolimus in Treating Tuberous Sclerosis and Lymphangioleiomyomatosis

Sirolimus is an inhibitor of mTOR a serine-threonine kinase involved in the regulation of protein synthesis and cell growth. The tuberous sclerosis complex (TSC), a genetic syndrome characterized by sporadic tumorigenesis in multiorgan systems, is caused by inactivation of TSC1 and TSC2 tumor suppressor genes. Loss of TSC1 or TSC2 leads to increase in mTOR activity. Bissler and colleagues conducted a prospective, 2 year uncontrolled clinical trial to test the effects of sirolimus on angiomyolipomas and lymphangioleiomyomatosis tumors which are associated with mutations in TSC genes. The results published in NEJM showed that angiomyolipomas regressed (30% or more) during sirolimus therapy, but tumors regrew after therapy was stopped. Similarly, some patients with lymphangioleiomyomatosis had an improvement of lung function that persisted after treatment was stopped. These results suggest that mTOR inhibitors may have utility for treating tuberous sclerosis complex. Further trials are needed to confirm these results.

Source: NEJM

Histone H4, a Ubiquitous Protein, is Recognized by Prostate Cancer-Infiltrating T Lymphocytes

Identifying proteins exclusively expressed in tumor cells are valuable for therapeutic targeting and also as tumor-specific antigens. T-lymphocytes can recognize many tumors and identifying the antigens recognized by these cells is critical for the development of immunotherapeutic strategies. Using a mouse model of prostate adenocarcinoma, Savage and his colleagues reported that T cells recognize a fragment of nuclear histone H4 protein expressed in prostate cancer cells and bypassing the normal cells. It is significant that histone H4 is expressed not only by prostate cancer cells but also by all normal cells, yet was recognized only in cancerous tissue by the immune system. These studies demonstrate that tumor-infiltrating T cells can recognize a broad repertoire of antigens than previously recognized.

Source: ScienceMag

Biomakers

Identification of Novel High-Frequency DNA Methylation Changes in Breast Cancer

Molecular biomarkers capable of detecting early-stage disease, recurrence, as well as predicting the progression of the disease are a critical need for the management of breast cancer, which is the second leading cause of cancer-related deaths among women in the US. Over diagnosis, false positives, and false negatives are some of the problems associated with mammography and MRI. A microarray-based strategy was used by Jared Orndway and colleagues for DNA methylation profiling of differentially methylated loci in breast cancer. This approach led to the identification of several differentially methylated loci, a subset of which was validated across a panel of over 230 clinical samples. Significantly, this approach also identified a single locus within the promoter region of the GHSR gene, encoding the G protein-coupled receptor for the peptide hormone Ghrelin, which is hypermethylated in 90% of ductal breast carcinomas. The methylation status of this locus is capable of distinguishing infiltrating ductal carcinoma from normal and benign breast tissue with a high degree of sensitivity and specificity. This represents a highly specific DNA-based biomarker for breast cancer reported to date. The discovery of over 50 novel DNA methylation-based biomarkers of breast cancer may provide new routes for development of DNA...
methylation-based diagnostics and prognostics and identify epigenetic mechanism involved in breast tumorigenesis.

Source: Cancer research

**KRAS Mutation Status is Predictive of Response to Cetuximab Therapy in Colorectal Cancer**

The anti-epidermal growth factor receptor (anti-EGFR) cetuximab has been proven to be efficient in metastatic colorectal cancer though the exact molecular mechanisms underlying the clinical response or resistance to this drug remain unknown. Lièvre and colleagues evaluated genetic alterations of three intracellular effectors (KRAS, BRAF, and PIK3CA) involved in EGFR-related signaling pathways in 30 metastatic colorectal cancer patients treated with cetuximab. The presence of KRAS mutation was significantly associated with the absence of response to cetuximab and a shorter survival in EGFR-positive metastatic colorectal cancer patients. This finding has demonstrated the potential of KRAS mutation status in identifying patients likely to benefit from cetuximab thus avoiding a costly and potentially toxic administration of this treatment in nonresponder patients. Further studies are needed to validate this result.

Source: Cancer research

**Dako Receives FDA Approval of Top2a FISH PharmDx**

Dako, based in Denmark, is a global leader in tissue-based cancer diagnostics. It is the first company to receive FDA approval for a TOP2A diagnostic test for breast-cancer patients. The test, TOP2A FISH pharmDx™, is marketed to assess clinical breast-cancer tissue specimens for changes in the status of the TOP2A. This information aids physicians in evaluating the prognosis for breast-cancer patients, since patients with normal TOP2A status have a better outcome than patients with TOP2A gene amplifications or deletions. TOP2A is a molecular target for the pharmacological action of anthracyclines. “The TOP2A FISH pharmDx™ kit adds a new dimension to the way breast cancer will be treated in the future, giving oncologists and pathologists a reliable tool when assessing the disease prognosis for individual patients,” says Patrik Dahlén, CEO and President of Dako.

Source: Dako

**Regulatory Focus**

**Pharmion Submits European MAA for Vidaza in Patients with Higher-Risk Myelodysplastic Syndromes (MDS)**

Pharmion Corporation announced the submission of a Marketing Authorisation Application (MAA) with EMEA for Vidaza (azacitidine) in the treatment of patients with higher-risk MDS. The application is based on highly compelling data of a Phase III, multi-center, international, randomized study of Vidaza in the treatment of patients with higher-risk MDS. Results showed two-year overall survival rate of 50.8% for Vidaza, compared to 26.2% for conventional care regimens (BSC alone, low-dose cytarabine or standard chemotherapy).

Vidaza has been designated as an Orphan Medicinal Product in the EU for the treatment of MDS and AML, which, if approved, entitles the drug to 10 years of market exclusivity for the approved indication. Vidaza is the first of a new class of anti-cancer compounds known as demethylating agents, a subset of a category of drugs referred to as epigenetic therapies.

Source: Pharmion

**FDA Extends Review of an Appeal for Genasense, a Treatment for Refractory CLL**

FDA has extended its review of Genta's appeal against the non-approvable decision for NDA that proposed the use of Genasense in patients with relapsed or refractory CLL. The FDA gave a thumbs down to Genta's cancer therapy, Genasense, in September 2007, voting seven to three to recommend against approval. The therapy was intended to treat refractory CLL in conjunction with chemotherapy, however, data from a pivotal trial failed to impress a majority of the committee. Genta is currently recruiting patients to the AGENDA Trial, a global Phase III trial of Genasense in patients with advanced melanoma. Genta now expects a final decision on the drug later in the current quarter.

Source: Genta

**Health Canada Approves Eloxatin for the Adjuvant Treatment of Patients with Stage III Colon Cancer**

Health Canada has approved Eloxatin (oxaliplatin for injection), manufactured by Sanofi-Aventis, in combination with infusional 5-fluorouracil (5-FU) and leucovorin (LV) (FOLFOX4), for the adjuvant (post-surgical) treatment of patients with stage III colon cancer, after complete resection of the primary tumor. Survival data at six years show a numerical improvement in overall survival in patients with stage III colon cancer. This approval is based on demonstrated improvement in disease free survival. The safety and efficacy profile of Eloxatin is clinically superior to the previous standard treatment, making this an important advancement in the treatment of the disease.

Source: Sanofi Aventis

**France’s High Council for Public Health Backs the Use Cervical Cancer Vaccine Gardasil over Cervarix**

France’s High Council for Public Health backed the use of Merck & Co’s cervical cancer vaccine Gardasil over GlaxoSmithKline’s rival product Cervarix. It said in a bulletin that girls of 14 years should be vaccinated against cervical cancer using a vaccine that targets four viruses effectively, endorsing Merck’s product. Both Cervarix and Gardasil protect against cancer-causing strains of the sexually transmitted human papillomavirus (HPV) and are designed for girls and young women. But Gardasil targets four strains of HPV – two responsible for cervical cancer and two causing the less serious condition of genital warts. However, Glaxo’s product addresses only two cancer strains. Cervarix is one of Glaxo’s biggest new drug hopes and is already approved in nearly 45 countries, including the 27 member states of the EU. Gardasil is already well established in the US.

Source: Reuters

**Business News**

**Roche to Buy Ventana for $3.4 billion**

Contd. from pg 1

After offering $75 per share for Ventana in June 2007, Roche extended that same offer
five times, before agreeing to pay $89.50 per share, a price that Ventana accepted.

The acquisition of Ventana, a leader in the fast-growing tissue-based diagnostics segment, will allow Roche to broaden its diagnostic offerings and complement its world leadership in both in-vitro diagnostic systems and oncology therapies.

Source: Roche

Genzyme Announces License Agreement with Moffitt Cancer Center for Exclusive Rights to Lung Cancer Diagnostic

Contd. from pg 1

This test may assist physicians in identifying the appropriate first-line therapy for their NSCLC patients and improve patient outcomes. Under the license agreement, Genzyme has agreed to pay Moffitt when various milestones are reached and provide Moffitt with running royalties on the sales of licensed services and products. Genzyme Genetics’ relationship with Moffitt will broaden its lung cancer testing portfolio.

Source: Genzyme

Alfacell Corporation Licenses Onconase US Commercial Rights to Strativa Pharmaceuticals

Alfacell Corporation announced a licensing agreement with Strativa Pharmaceuticals for the commercialization of Onconase (ranpirnase) in the US. Onconase is first-in-class product candidate from Alfacell's proprietary ribonuclease (RNase) technology.

It is currently being evaluated as a treatment for unresectable malignant mesothelioma in a confirmatory Phase IIIb clinical trial. Under the terms of the agreement, Strativa will have exclusive marketing, sales and distribution rights to Onconase in the US and its territories. Alfacell will retain all rights for product manufacturing, clinical development and obtaining regulatory approvals. This agreement could provide Alfacell with up to $225 million in cash milestones. For the commercial production of Onconase, Alfacell has entered into a purchase and supply agreement with Scientific Protein Laboratories LLC.

In South Korea, Taiwan and Hong Kong, Alfacell entered into an agreement with BL&H Co. Ltd., a leading pharmaceutical company in Southeast Asia, for the marketing, sales and distribution of Onconase. Alfacell has received an up-front fee of $100,000 and is eligible for milestone payments based on the achievement of certain regulatory approvals and net sales levels. Alfacell will also receive 50% of all net sales in the territory.

Source: Alfacell

Immupharma Enters Oncology with Novel Potential Blockbuster Drug for Multiple Cancer Indications

Immupharma has taken the rights for the worldwide development and commercialization of a novel drug candidate (IPP-204106) for cancer from its ongoing collaborator, the Centre National de la Recherche Scientifique (CNRS), France's leading scientific research institution.

The molecule, IPP-204106, has a dual mechanism of action, acting both in preventing angiogenesis as well as proliferation. It is a nucleolin antagonist, the lead molecule in a family of pseudopeptides designed to block the activity of a protein called nucleolin. Preclinical data have shown that nucleolin antagonists inhibit the growth of tumors and metastasis in many cancer types. Immupharma is planning to complete the formal preclinical development this year with a Phase I study expected to start by year end.

Source: Immupharma

Morphotek Announces Agreement for the Development of Antibodies to Treat Prostate Cancer

Morphotek Inc., a subsidiary of Eisai Co., Ltd., announced the signing of a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) for the development of therapeutic antibodies to a cancer-associated protein identified by NCI researchers. Prostate-specific protein, referred to as ProCa-1, is a gene product that is expressed on the cell surface in normal prostate and prostate cancer cells, but not in other tissues tested.

As part of this CRADA, Morphotek will apply its antibody discovery technology – Morphodoma – to the development of monoclonal antibodies that can bind the ProCa-1 protein and test lead antibodies for anti-cancer properties in collaboration with NCI researchers.

Source: Morphotek