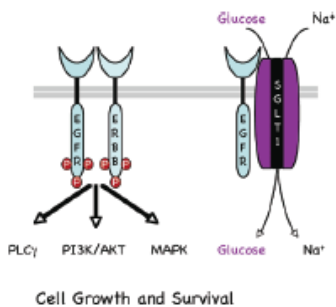


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In the Spotlight:

A New Role for EGFR in Glucose Transport

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Business News

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Protox Therapeutics Collaborates with FDA

BMS to Sell Erbitux in Canada

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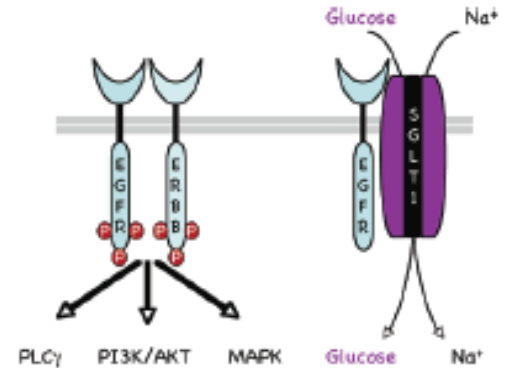
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Spotlight Report

A New Role for EGFR in Glucose Transport

Epidermal growth factor receptor (EGFR), a receptor tyrosine kinase, has been an attractive target for cancer therapies because it is widely expressed in many cancers. Small molecule inhibitors of EGFR have shown impressive activity in a small subset of lung cancers expressing mutant EGFR. However, these drugs do not have clinical activity in majority of cancers that have high expression of EGFR. This raises the question of why EGFR is highly expressed in so many cancers and if it has an important role in these cancers. The first clue that EGFR has a function beyond its tyrosine kinase activity was the finding that in PC-3 prostate cancer cells, down regulation of EGFR with siRNA led to apoptosis but EGFR kinase inhibition did not. EGFR knockout animals die soon after birth, but animals with severely compromised kinase mutant EGFR are completely viable. These studies pointed to the existence of kinase-independent function of EGFR.



Cell Growth and Survival

Cancer Cell, 13, May 2008

In a recent study published in *Cancer Cell*, Weihua and colleagues demonstrated that EGFR physically associates with and stabilizes the sodium/glucose co transporter (SGLT1) to promote glucose uptake into cancer cells. The authors showed that the extracellular domain of EGFR associates with SGLT1 and down regulation of EGFR led to loss of SGLT1 and lowered intracellular glucose levels. This interaction between EGFR and SGLT1 seems to be another adaptation by cells to coordinate cell growth with nutrient uptake. These studies clearly demonstrate that EGFR functions not only as an important regulator of signal transduction cascades, but also as a key component of an active glucose transport system and suggest novel strategies to target EGFR.

Source: *Cancer Cell*



Business

Cytopia Collaborates with CRC for Anti-Cancer Drug

Cytopia Ltd. announced anti-cancer drug discovery and development collaboration with Cancer Therapeutics CRC. Under the terms of the collaboration, Cytopia has out-licensed proprietary technology to Cancer Therapeutics for an undisclosed kinase enzyme target with potential for treating metastatic cancers. Cytopia will retain an option over exclusive commercialization rights for any drug candidates delivered by the collaboration. Both companies will share in any partnering revenues, as well as royalty payments from a marketed drug. Cancer Therapeutics will conduct and fund further development of the Cytopia compounds for at least two years. Cytopia's advanced anti-cancer drug is being tested in four clinical programs covering oral and IV doses in Phase I and Phase II level studies. Trials are in advance stages for both oral and injectable vascular disrupting agents, for multiple myeloma and an aggressive brain tumor glioblastoma multiforme.

Source: *Cytopia*

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Business (cont'd)

ACT Biotech Acquires Oncology Portfolio from Bayer

ACT Biotech Inc., a new company of NGN Capital, dedicated to developing and commercializing targeted oral cancer drugs, entered into a license agreement with Bayer HealthCare LLC., for a portfolio of clinical and early stage oncology assets. Under the terms of the license agreement, ACT Biotech has acquired an anti-angiogenic receptor tyrosine kinase inhibitor entering Phase II clinical studies for colorectal cancer, among other indications. Other additional programs in-licensed in this agreement is a first-in-class multi-targeted kinase inhibitor in late preclinical stage in a variety of cancer types and several other additional preclinical stage programs in oncology. As part of the agreement, Bayer will maintain a minority equity stake in ACT Biotech.

Source: [NGN Capital](#)

Protox Therapeutics Collaborates with FDA

Protox Therapeutics Inc. announced collaboration with the FDA under the terms of a Cooperative Research and Development Agreement (CRADA). The collaboration will focus on characterizing interleukin-4 (IL-4) receptors on various human tumors, the mechanism of their up regulation, and evaluate the safety and efficacy of IL-4 receptor-directed therapeutic agents such as PXR321 either as a monotherapy or in combination with other therapeutic agents. In addition, novel compounds targeting interleukin-4 receptors will be engineered and tested. Under the terms of the CRADA, Protox has an exclusive option to license any future inventions developed under the research program. PXR321 is a novel targeted protein in which a cytokine IL-4 is linked to a Pseudomonas exotoxin, a potent substance that can destroy cancer cells. PXR321 is in clinical development for the treatment of primary brain cancer.

Source: [Protox Therapeutics](#)

BMS to Sell Erbitux in Canada

Erbitux was approved by Health Canada in September 2005. But owing to disagreement over the drug price with the Patented Medicine Prices Review Board (PMPRB), a quasi-judicial body that protects consumers by ensuring that the manufacturers' prices of patented medicines are not excessive, Bristol-Myers Squibb refused to launch Erbitux in Canada. After a two-year wrangle over price, BMS has decided to sell the drug in Canada. According to Marc Osborne, director of public affairs for BMS, the drug's impact on patient survivability and the importance of the drug to Canadian drug market has motivated the company to settle for the drug price set by the PMPRB. The price is confidential for competitive reasons. Erbitux is mainly used to treat colorectal cancer that has metastasized when other drugs have failed.

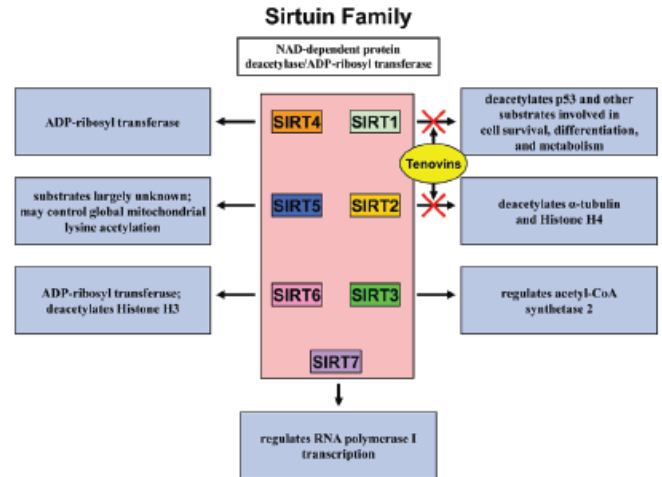
Source: [CBC News](#)



Research Highlights

A Small Molecule Activator of p53

The tumor suppressor p53 functions as a transcription factor controlling cell growth and apoptosis and is inactivated in > 50% of all human cancers. Compounds that activate p53 through direct interaction (RITA) or indirectly through mdm2 inhibition (Nutlins) have shown promising activity in several cancer cell lines. In a recent issue of *Cancer Cell*, Lain et al. have described the identification of a small molecule activator of p53 using a p53-regulated reporter gene as a screening system. Tenovin-6, a small molecule identified using this screen, increased p53 activation and arrested cell growth in a panel of tumor cell lines. Using cell based assays to screen for small molecules offers several advantages. For example, the hit compounds show activity in cultured cells at concentrations that are acceptable for in vivo testing and generally these hits are not cytotoxic. The major drawback to this approach is that identifying the precise mechanism by which these compounds act, is often challenging.



Cancer Cell, 13, May 2008

To identify the target of tenovin-6 the authors screened a collection of *S. cerevisiae* strains containing heterozygous deletions that together covered 94% of protein coding genes and identified SIR-2 as tenovin-6 target. SIR2 is a yeast homolog of mammalian sirtuin family that includes seven SIRT proteins. Tenovin-6 inhibited both SIRT-1 and SIRT-2 in vitro and in cell culture tenovin-6 treatment resulted in an increased acetylation of p53. SIRT1 has been shown to be a direct NAD⁺-dependent deacetylase for p53 and a variety of other proteins. SIRT2 is involved in the direct deacetylation of α -tubulin and histone H4. SIRT1 is a potent negative regulator of p53 function, and the specific activation of p53 seen with tenovin-6 underscores the importance of the SIRT1-p53 interaction. This work demonstrates the versatility of cell-based assays to identify novel compounds with useful mechanisms of action and opens the doors for understanding the biological function of mammalian sirtuins.

Source: *Cancer Cell*



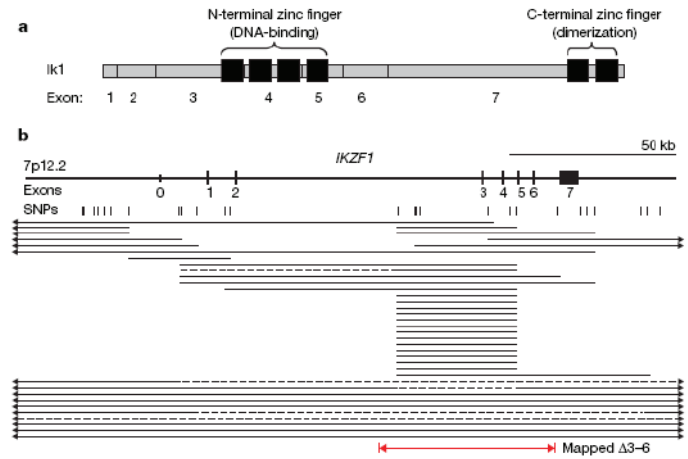
Research Highlights (cont'd)

Deletion of *IKZF1* in BCR-ABL1 Lymphoblastic Leukemia

Chromosomal translocation resulting in BCR-ABL1 fusion protein is the pathological lesion underlying CML and a subset of acute lymphoblastic leukemia (ALL). An ALL subtype with especially poor prognosis is characterized by the presence of the Philadelphia chromosome BCR-ABL1 constituting 5% of pediatric B-progenitor ALL and approximately 40% of adult ALL. However, the specific lesions responsible for the generation of BCR-ABL1 ALL and blastic transformation of CML remain incompletely understood.

To identify cooperating oncogenic lesions in ALL, Charles et al. performed a genome-wide analysis of 304 cases of ALL including 21 pediatric and 22 adult BCR-ABL1 ALL cases, and 23 adult CML cases. They observed that the most frequent somatic copy number alteration was deletion of *IKZF1*, which encodes the transcription factor Ikaros. Ikaros is a member of a family of zinc-finger nuclear proteins that is required for normal lymphoid development. Ikaros has a central DNA-binding domain consisting of four zinc fingers, and a homo- and heterodimerization domain consisting of the two carboxy-terminal zinc fingers. *IKZF1* was deleted in 36 (83.7%) of 43 BCR-ABL1 ALL cases but not in chronic phase CML. This study also demonstrated that, *IKZF1* mutation is a frequent event in the transformation of CML to lymphoid blast crisis. Sequencing of *IKZF1* deletion breakpoints suggested that aberrant RAG-mediated recombination is responsible for the deletions. These results suggest that deletions resulting in loss of Ikaros are an important event in the development of BCR-ABL1 lymphoblastic leukemia. The presence of these genetic lesions can be used to gain a therapeutic advantage against this aggressive leukemia.

Source: [Nature](#)

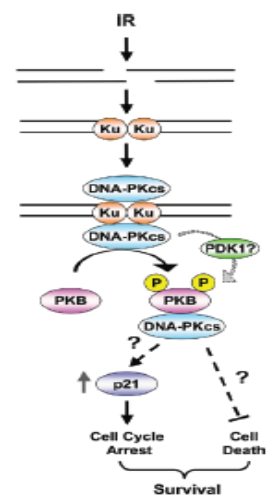


Nature, 453, May 1, 2008

PKB/Akt in the DNA Damage Response

Protein kinase B (PKB) (also called Akt) plays an important role in cell signaling that promote cell survival and growth. DNA-PKcs (the catalytic subunit of the DNA-dependent protein kinase) is required for the repair of ionizing radiation (IR)-induced DNA damage. In a paper published in *Molecular Cell*, Hemmings and colleagues reveal a new potential role for PKB/Akt in the DNA damage response and identify PKB/Akt as a new target for DNA-PKcs. The authors have shown that PKB/Akt is phosphorylated on Threonine 308 and Ser 473 in response to DNA damage. This pathway is distinct from growth factor-induced activation of PKB/Akt since inactivation of DNA-PK abolishes DNA damage-induced activation of PKB/Akt. The findings reported in this study suggest the following model: DNA damage induces double strand breaks (DSBs) which are detected by the Ku70/80 heterodimer. DNA-PKcs is recruited to the DSB via its interaction with Ku, which stimulates the DNA-PKcs activity, promoting the interaction of DNA-PKcs with nuclear PKB/Akt resulting in phosphorylation on threonine 308 and serine 473. Activation of PKB/Akt in turn phosphorylates downstream targets, which results in survival after IR. Whether DNA-PKcs directly phosphorylates PKB/Akt or acts through other kinases is not clear. This study suggests that PKB/Akt and DNA-PK may act together to promote cell survival after DNA damage.

Source: [Molecular Cell](#)



Cancer Cell, 13, May 2008



Research Highlights (cont'd)

Mitochondrial DNA Mutations Regulate Tumor Metastasis

Mitochondrial DNA (mtDNA) mutations occur in many cancers, but their effect on tumor cell behavior or tumor progression is unclear. In a study published in *Science*, Kaori Ishikawa and colleagues have investigated this by replacing the endogenous mtDNA in a mouse tumor cell line that was poorly metastatic with mtDNA from a highly metastatic cell line and vice versa. Using animal models to score for metastasis, they found that the recipient tumor cells acquired the metastatic potential of the transferred mtDNA. The mtDNA with high metastatic potential contained G13997A and 13885insC mutations in the gene encoding NADH (reduced form of nicotinamide adenine dinucleotide) dehydrogenase subunit 6 (ND6) and were associated with overproduction of reactive oxygen species (ROS). The authors also observed that pretreatment of the highly metastatic tumor cells with ROS scavengers suppressed their metastatic potential in mice. This study demonstrates that mtDNA mutations can contribute to tumor progression by increasing the production of ROS in tumor cells, and ROS scavengers might be useful therapeutically to repress metastasis.

Source: [Science](#)



Clinical Development

Lapatinib in Early Breast Cancer Trial

GlaxoSmithKline (GSK) in collaboration with the Breast International Group (BIG), and Spanish Breast Cancer Cooperative Group (SOLTI), announced the start of a global Phase III study that will examine the role of lapatinib (Tykerb®/Tyverb®) in the treatment of early breast cancer (EBC). Neo-ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization) Phase III study will evaluate and compare the rate at which cancer cells disappear in the breast following treatment with lapatinib and/or trastuzumab (Herceptin)/or both, before surgery in women with early-stage HER2-positive primary breast cancer. Surgery will be performed on all patients, after which each patient will receive three courses of chemotherapy followed by the same targeted therapy for 34 weeks. The primary objective of Neo-ALTTO is to compare the rate of pathological complete response (or complete eradication of the tumour) at the time of surgery, as well as understand the biological difference of the three treatment regimens using a neoadjuvant approach. Target enrollment is 450 patients with 130 clinical trial centres planned across 26 different countries. This trial will lead to the identification of new molecular biomarkers that may help to better identify the benefits of lapatinib or trastuzumab.

Source: [GSK](#)



Clinical Development (cont'd)

Interfering with Leukemic Stem Cells by IFN- α

Recombinant interferon- α (IFN- α), an immunomodulatory cytokine, has potent therapeutic activity in *myeloproliferative disorders* (MPDs) like CML, polycythemia vera (PV) and essential thrombocythemia (ET) but has poorly understood mechanism of action. IFN- α was found to induce cytogenetic and molecular remissions in CML. In 2001, the ABL kinase inhibitor, imatinib mesylate substituted IFN- α as front-line therapy for CML. Treatment with imatinib resulted in superior cytogenetic and molecular responses, but showed acquired resistance and inability to eliminate quiescent BCR-ABL⁺ stem cells thus generating the need for treatment strategies that can eradicate leukemic stem cells in CML and other MPDs.

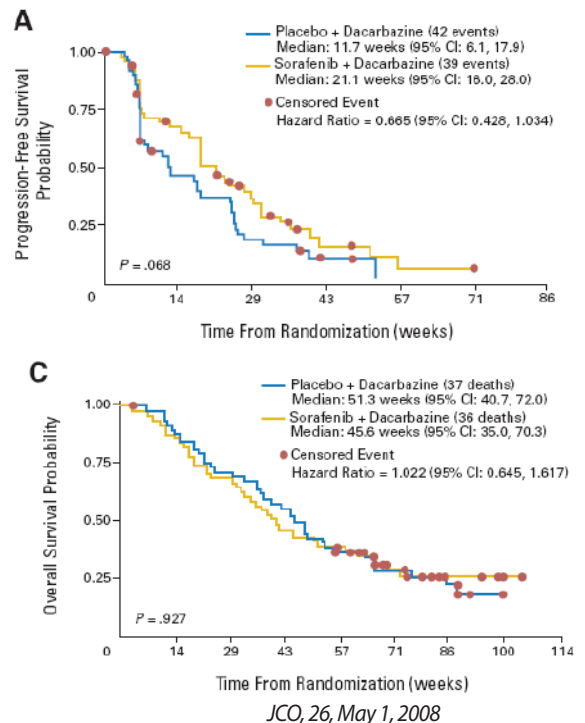
Activating mutation (V617F) in *JAK2* tyrosine kinase was discovered in 2005 in MPDs including PV and ET providing a molecular marker for these diseases that was analogous to PV with a pegylated formulation of IFN- α . They observed complete hematological remission in 83% of subjects accompanied by a decrease in the mutant *JAK2* allele in granulocytes. Similar results were observed in other studies targeting PV and ET patients with IFN- α treatment. A third study reported that CML patients who had received prior IFN- α prior to imatinib treatment achieved molecular remission even after discontinued kinase inhibitor therapy. Collectively, these studies provide strong but indirect evidence that IFN- α targets the mutant clone in MPDs and might act to eliminate the malignant stem cell population in them. Further work at the bench may illuminate the basic mechanisms of IFN- α in CML and offer new approaches to eradicate malignant stem cells in MPDs, resulting in permanent cure.

Source: *Nature Medicine*

Sorafenib and Dacarbazine in Phase II Melanoma

The Ras-Raf-MEK-ERK signaling pathway is activated in the vast majority of melanomas. Sorafenib is an inhibitor of Raf kinase with significant antitumor activity. A randomized, double-blind, placebo-controlled, Phase II study was conducted to evaluate the efficacy and safety of sorafenib plus dacarbazine in patients with chemotherapy-naïve stage III (unresectable) or IV advanced melanoma. A total of 101 patients received placebo plus dacarbazine (n = 50) or sorafenib plus dacarbazine (n = 51). On day 1 of a 21-day cycle, patients received intravenous dacarbazine 1,000 mg/m² for a maximum of 16 cycles. Oral sorafenib 400 mg or placebo was administered twice a day continuously. Median progression free survival in the sorafenib plus dacarbazine arm was 21.1 weeks versus 11.7 weeks in the placebo plus dacarbazine arm. No difference in overall survival was observed (median, 51.3 v 45.6 weeks in the placebo plus dacarbazine and sorafenib plus dacarbazine arms, respectively). The regimen was well tolerated and had a manageable toxicity profile. Given these encouraging results, randomized Phase III trials of sorafenib and dacarbazine are warranted to establish the benefit of this treatment combination.

Source: *JCO*





Clinical Development (cont'd)

Novelos Announces Positive Phase II Results in Breast Cancer

Novelos Therapeutics, Inc. announced positive interim results in an ongoing Phase II trial of neoadjuvant treatment with NOV-002 in combination with chemotherapy in patients with stage II-IIIc HER-2/neu negative invasive breast cancer. The primary objective of this open-label, single-arm trial, is to determine if preoperative administration of NOV-002 in combination with eight cycles of chemotherapy (four of doxorubicin and cyclophosphamide followed by four of docetaxel) results in an appreciably higher pathologic complete response (pCR) rate than expected with this same chemotherapeutic regimen alone. To date, 16 women have been enrolled with four pCRs already demonstrated in the first eight women that have both completed chemotherapy and undergone surgery. NOV-002 was also associated with decreased hematological toxicities and with decreased use of growth factors. Trial conclusion is expected in early 2010.

Source: *Novelos*



Biomarkers

Prognosis in Cytogenetically Normal AML

Somatic mutations affecting cellular growth, proliferation, and differentiation are recognized in 40-50% cases of AML. The reported somatic mutations in AML include partial tandem duplications (PTDs) of the myeloid-lymphoid or mixed-lineage leukemia gene (*MLL*), internal tandem duplications (ITDs) or mutations of the tyrosine kinase domain (TKD) of the *fms*-related tyrosine kinase 3 gene (*FLT3*), and mutations in the nucleophosmin gene (*NPM1*), the CCAAT/enhancer binding protein α gene (*CEBPA*), and the N-RAS (*NRAS*). Mutations in these genes have prognostic relevance. In a study published in *NEJM*, Richard et al. analyzed the frequencies of these mutations and their role in treatment outcomes in 872 patients with cytogenetically normal AML. A total of 53% of patients had *NPM1* mutations, 31% had *FLT3* internal tandem duplications (ITDs), 11% had *FLT3* tyrosine kinase-domain mutations, 13% had *CEBPA* mutations, 7% had *MLL* partial tandem duplications (PTDs), and 13% had *NRAS* mutations. The overall complete-remission rate was 77%. Two genotypes were significantly associated with a complete remission: mutant *CEBPA* and mutant *NPM1* without *FLT3*-ITD. The benefit of the transplant was limited to the subgroup of genotype *FLT3*-ITD or the genotype consisting of wild-type *NPM1* and *CEBPA* without *FLT3*-ITD. The study indicates that identification of mutational status is advisable for evaluating clinical outcomes in patients with newly diagnosed AML.

In another study published in *NEJM*, Guido and his colleagues evaluated the associations of micro RNA in normal AML. They found that expression levels of the microRNA-181 family were inversely correlated with expression levels of predicted target genes encoding proteins involved in pathways of innate immunity mediated by toll-like receptors and interleukin-1 β . This study suggests that miRNA profiling can have prognostic value in patients with cytogenetically normal AML independent of the mutations in *FLT3*.

Source: *NEJM*



Biomarkers (cont'd)

6p22 Locus Associated with Aggressive Neuroblastoma

Neuroblastoma is the most common solid cancer of early childhood, and half of all patients present with widely disseminated disease refractory to intensive chemo radiotherapy. In a study published in *NEJM*, John Maris and colleagues performed a genome wide association study to identify sequence variants associated with susceptibility to the development of neuroblastoma. They compared single-marker allele from 1032 patients with neuroblastoma and 2043 control subjects. They observed significant association between neuroblastoma and the common minor alleles of three consecutive single-nucleotide polymorphisms (SNPs) (rs6939340, rs4712653, and rs9295536) at chromosome band 6p22 and containing the predicted genes *FLJ22536* and *FLJ44180*. Homozygosity for the at-risk G allele of the most significantly associated SNP, rs6939340, resulted in an increased likelihood to have metastatic (stage 4) disease and disease relapse. This study provides proof-of-concept results for a genomewide-association approach to neuroblastoma and shows that the likelihood for malignant transformation of developing neuroblasts is influenced by variants on chromosome 6p22.

Source: *NEJM*

Two Biomarkers for Breast Cancer Treatment

While patients who are ER/PR positive do benefit from endocrine therapy, the therapy fails in approximately 25% of these patients. AviraDx, Inc. announced that combination of two molecular biomarkers improves prediction of disease recurrence and response to therapy in early stage breast cancer patients. The Avira MGI (molecular grade index) is a molecular assay comprising five genes that are involved in invasive tumor growth. This assay assists pathologists and oncologists by improving the accuracy of tumor grading. Avira H/I (HOXB13:IL17BR) is a well-established biomarker that has been shown to predict both recurrence risk and endocrine benefit in more than 2,000 patients in numerous clinical studies. This combination was clinically validated through analyses of 239 ER-positive, lymph-node negative patients. These two markers together should enable oncologists to identify a large subgroup of women with low risk of recurrence who may be spared from toxic chemotherapy regimens. In addition, they may also identify a significant population of patients for whom intensive chemotherapy regimens or new therapeutic agents should be considered.

Source: *AviraDX*



Regulatory

Marketing Application Filed in Europe for Gefitinib

AstraZeneca announced the submission of a marketing authorization application to the European Medicines Agency (EMA) for its oral anti-cancer drug, gefitinib (IRESSA™) as a treatment for locally advanced or metastatic NSCLC in patients who have been pre-treated with platinum-containing chemotherapy. The application is based on data from the Phase III INTEREST study, which showed that patients with pre-treated advanced NSCLC who received gefitinib had non-inferior overall survival to those treated with intravenous chemotherapy (docetaxel). In addition, gefitinib had a more favorable tolerability profile than docetaxel. Gefitinib is currently approved in 36 countries worldwide.

Source: [AstraZeneca](#)

Oncovax Gets License to European Production

Dutch health authorities have licensed Vaccinogen Inc. to manufacture OncoVAX anti-colon cancer vaccine, thus clearing the path to >\$100 million of potential European sales. This license permits the company to commercialize the vaccine, first in Switzerland and then in seven other countries in Eastern Europe. "This manufacturing license being granted by the most stringent and respected biotech manufacturing reviewers in Europe is a major milestone for Vaccinogen as it begins to generate revenues from OncoVAX," said Dr. Hanna, CEO Vaccinogen. OncoVAX immunotherapy transforms the body's immune response and its long-term memory to prevent the return of disease years after surgery. The Dutch approval of the company's facility based in Emmen, Netherlands also paves the way to its pivotal US FDA Phase IIIb clinical trial – the final step before the vaccine can be sold in the United States.

Source: [PRNewswire](#)

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