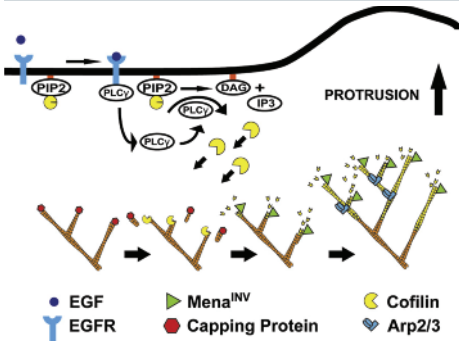


INTELLIGENT INSIGHTS. SMART RESULTS.



In the Spotlight:

MENA^{INV}, a Cytoskeletal Protein Plays A Crucial Role in Metastasis

Metastasis is the process by which cancer cells migrate from the primary tumor to establish in a new tissue. Actin cytoskeleton which provides structural integrity to the cell is also known to play a critical role in cell motility. However, very little is known about how actin cytoskeleton influences metastasis of cancer cells. In a study published in *Development Cell*, Phillippar and colleagues show that the Enabled (*Ena*)/vasodilator-stimulated... [Read more...](#)



Business News

BMS and Exelixis Enter into Global Collaboration

Drais and Diatos Partner to Develop DTS-108

Paladin Labs Acquires ViRexx Medical Corp

Morphotek Signs Research Agreement

Cytokinetics Retains Development and Commercialization

[Click HERE to read more](#)



Research Highlights

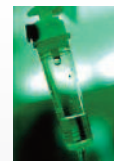
Molecular Basis for Resistance to Tamoxifen in Breast Cancer

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Blockade of mTOR Potentiates Growth Arrest by HDAC inhibitor

PI3K and MEK Inhibitors in Treatment of Lung Cancer

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Clinical Development

Efficacy of DOXIL[®] Combination Therapy in MBC

Improved Survival with ASA404 in Lung Cancer

Vorinostat plus Bortezomib for Relapsed/Refractory MM

Sequential Therapy with FCR in CLL

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Regulatory

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EC Grants VIDAZA[®] Full Marketing Authorization

Antisoma Receives FDA Approval for Oral Fludarabine

Roche Wins Final UK Okay for Discounted Tarceva[®]

Roche Seeks European Drug Approval for Glioblastoma

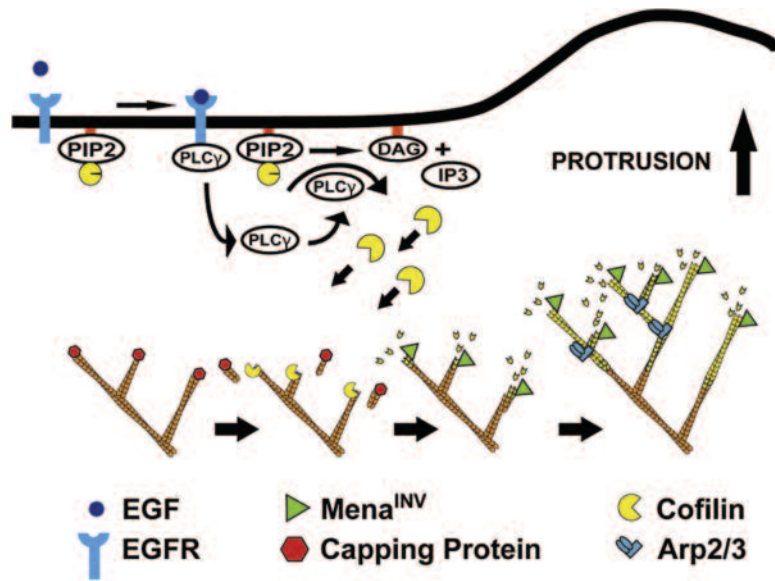
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Spotlight Report

MENA^{INV}, a Cytoskeletal Protein Plays a Crucial Role in Metastasis

A Model of the Function of Mena^{INV} Downstream of EGF Signaling



Developmental Cell, 15, Dec 9, 2008

and MENA^{INV} show enhanced motility leading to increased metastasis to the lungs. The authors proposed a model in which MENA and MENA^{INV} are recruited to the free barbed ends leading to enhanced stability of invadopodia thus allowing increased matrix degradation by local activation of proteases.

Further studies have shown that expression of MENA^{INV}, allowed cells to invade in response to only a small concentration of epidermal growth factor (EGF). This increased sensitivity to EGF by MENA^{INV} expressing tumor cells accounts for why metastatic cancer cells are resistant to EGFR drugs. Over expression of MENA^{INV} could enable tumor cells to invade in the absence of EGF and escape from the action of EGFR inhibitors.

Source: [Development Cell](#)





Business

BMS and Exelixis Enter Global Collaboration on Novel Cancer Programs

Bristol-Myers Squibb (BMS) and Exelixis announced a global collaboration covering two novel molecules for cancer: Exelixis' XL184, a small molecule inhibitor of c-MET, vascular endothelial growth factor receptor (VEGFR)-2 and RET, which is currently in Phase III development for medullary thyroid cancer; and Exelixis' XL281, a small molecule inhibitor of RAF kinase, which is currently in Phase I development for the treatment of patients with advanced solid tumor malignancies.

Under the terms of the collaboration, BMS agreed to pay Exelixis an upfront cash payment of \$195 million for the development and commercialization rights to both programs and to make additional license payments of \$45 million in 2009. The companies will share worldwide development costs and commercial profits on XL184 in the US. BMS will receive an exclusive worldwide license to develop and commercialize XL281 and will be responsible for funding all future development. Exelixis is eligible for development and regulatory milestones of up to \$315 million, sales performance milestones of up to \$150 million and double-digit royalties on worldwide sales of XL281.

Source: [Exelixis](#)

Drais and Diatos Partner to Develop and Commercialize DTS-108

Drais Pharmaceuticals and Diatos S.A. announced that they have entered into a global agreement to develop and commercialize DTS-108, a pro-drug of SN38, the active metabolite of the widely-used anti-cancer chemotherapy drug irinotecan, for the treatment of solid tumors. DTS-108 is currently ready to begin Phase I clinical trials in Europe for the treatment of patients with advanced or metastatic solid tumors.

Under the terms of the agreement, the license grants exclusive rights to Drais to develop and commercialize DTS-108 worldwide. In return, Diatos will receive an upfront payment, development milestones and sales milestones, plus royalties. The total value of the non-royalty portion of the partnership is valued at \$46.9 million.

Source: [Drais](#)

Paladin Labs Acquires ViRexx Medical Corp

Paladin Labs, a Canadian pharmaceutical company, announced that it has acquired all the outstanding shares of ViRexx Medical Corp. ViRexx is a Canadian-based development-stage biotech company focused on developing innovative-targeted therapeutic products. ViRexx has three proprietary technology platforms, Chimigen™ Vaccine Platform, T-ACT™ Platform and the AIT™ Platform. The T-ACT™ Platform technology is designed to interrupt blood supply to tumors, leading to tumor starvation and death. The lead product candidate of this platform is Occlusin™ 50 Injection, a treatment for primary cancer of the liver. The second product candidate of this Platform is Occulsin™ 500 AED, an embolic agent designed to treat hypervascular tumors including uterine fibroids. The lead product candidates for the AIT™ Platform include OvaRex® MAb for ovarian cancer and BrevaRex® MAb for breast cancer.

Paladin paid \$1.25 million payable to existing ViRexx creditors. "ViRexx spent over \$30 million in developing its promising, innovative technology. Unfortunately, ViRexx got caught in this financial storm without the protection of cash. We intend to continue ViRexx's stated strategy of focusing resources on the Chimigen™ Platform while seeking outside partnerships for the T-ACT™ and AIT™ Platforms," said Jonathan Ross Goodman, President and CEO of Paladin Labs.

Source: [Paladin](#)



Business (cont'd)

Morphotek Signs Research Agreement with the University of Pennsylvania

Morphotek®, a subsidiary of Eisai Corporation of North America, announced that it has signed a Sponsored Research Agreement with the University of Pennsylvania to fund research for the development of therapeutic antibody candidates targeting an antigen associated with hypoxic regions in tumors. Tumor hypoxic regions are considered to be a potential therapeutic problem, leading to increased resistance of tumors to radiation and chemotherapeutic drugs.

"We are very interested in and looking forward to this collaboration, as targeting the hypoxic tumor microenvironment is a high priority in our ongoing efforts to develop more effective cancer therapies," said Dr. Wafik S. El-Deiry, Professor of Medicine, Genetics and Pharmacology at the University of Pennsylvania School of Medicine.

Source: [Morphotek](#)

Cytokinetics Retains Development and Commercialization Rights to Ispinesib and SB-743921

GSK has informed Cytokinetics that it will not exercise its option to license ispinesib and SB-743921 as provided under the Collaboration and License Agreement entered into by the Companies in 2001. All rights to ispinesib and SB-743921, novel inhibitors of kinesin spindle protein (KSP), will revert to Cytokinetics. The collaboration between Cytokinetics and GSK will continue, and will be focused on the development of GSK-923295, an inhibitor of centromere-associated protein-E (CENP-E).

"The decision by GSK to not exercise options on ispinesib and SB-743921 was the result of a shift in portfolio direction for GSK. "We continue to believe that the novel mechanism of anti-mitotics may bring hope to cancer patients, reflected in GSK's ongoing development of GSK-923295 under its collaboration with Cytokinetics," said Paolo Paoletti, MD Senior Vice President of GSK Oncology R&D.

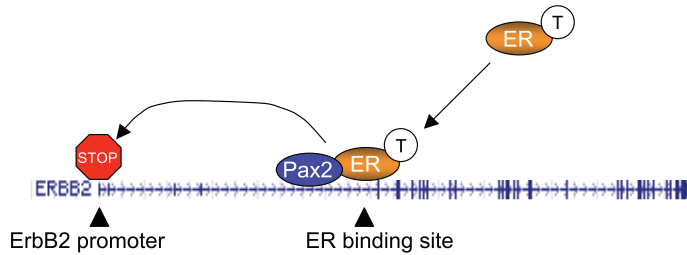
Source: [GSK](#)



Research Highlights

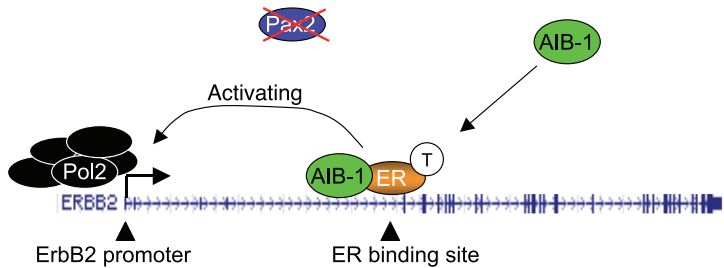
Molecular Basis for Resistance to Tamoxifen in Breast Cancer

Tamoxifen-ER repression of ErbB2



Breast cancer is the most common cancer among American women. A significant percentage of breast cancers are dependent on estrogen for their growth. Tamoxifen prevents the binding of estrogen to its receptor (ER) and inhibits the growth of ER+ breast cancers. Tamoxifen is one of the most effective therapies for breast cancer, but resistance to tamoxifen is common.

Tamoxifen resistance



Nature, 456, Dec 4, 2008

Jason Carroll's group at Cancer Research UK and collaborators have used Affymetrix technology to discover the molecular basis for tamoxifen response in breast cancer cells. Their studies are published in the December 2008 issue of *Nature*. The authors used genome-wide ER chromatin immunoprecipitation (ChIP) analysis to identify ER binding sites within genes and discovered an ER binding site within the intron of the ERBB2/HER2 gene. Further studies

demonstrated that estrogen-ER and tamoxifen-ER complexes directly repress ErbB2 transcription by binding to this ER binding site and this repression is mediated by a paired box 2 gene product (PAX2).

The role of PAX2 as a repressor of ERBB2 was a surprise since it is a general transcriptional activator and was shown to be a tamoxifen regulated gene that can induce endometrial cancer. Since tamoxifen has antiproliferative effects in the breast and agonistic effects on in the endometrium, it is hypothesized that PAX2 may possess tissue-specific effects. PAX2 and ER co-activator AIB-1/SRC-3 compete for binding and regulation of ERBB2 transcription, the outcome of which determines response to tamoxifen. Tamoxifen resistant breast cancers develop by circumventing the PAX2-mediated repression and upregulating ERBB2 transcription. This is supported by the finding that Tamoxifen-resistant breast cancers are characterized by elevated ERBB2 levels and ER+ve breast cell lines overexpressing ERBB2 acquire resistance to tamoxifen. This study provides a molecular basis for endocrine resistance in breast cancer.

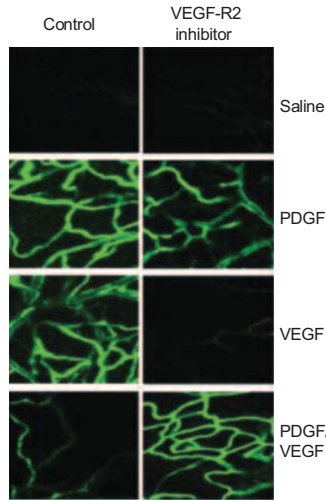
Source: *Nature*



Research Highlights (cont'd)

Complex Nature of VEGF Signaling in Angiogenesis

VEGF Inhibits PDGF-mediated Angiogenesis through VEGF-R2



Nature, 456, Dec 11, 2008

Angiogenesis and the development of a vascular network are required for tumor progression. Infiltration by cells of the myeloid lineage is a hallmark of many tumors, and in many cases the macrophages in these infiltrates express vascular endothelial growth factor (VEGF). Angiogenesis also requires pericyte coverage of vascular sprouts for vessel stabilization. This is coordinated by VEGF and platelet-derived growth factor (PDGF) through their cognate receptors on endothelial cells and vascular smooth muscle cells (VSMCs) respectively. Although VEGF directly stimulates endothelial cell proliferation and migration, its role in pericyte biology is less clear.

In a study published in *Nature*, Stockmann *et al.*¹ examined the role of myeloid cell-derived VEGFA in angiogenesis and tumor progression by deleting *Vegfa* in mouse myeloid cells. Deletion of myeloid VEGFA resulted in decreased vascular density, shorter and less tortuous vessels and increased pericyte coverage. Furthermore, Lewis lung carcinoma tumors in mice lacking myeloid cell-derived VEGFA were more susceptible to chemotherapy with either cyclophosphamide or cisplatin, which may partially explain the efficacy of anti-VEGF therapy in combination with chemotherapy in some cancers. In another study published in *Nature*, Greenberg *et al.*² define a role for VEGF as an inhibitor of neovascularization on the basis of its capacity to disrupt VSMC function. VEGFA or PDGF-induced

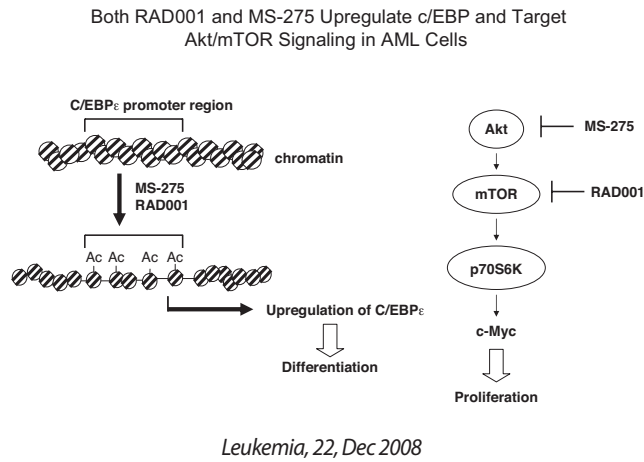
neovascularization in mouse models but, surprisingly, the combination of the two factors suppressed angiogenesis completely. VEGF inhibits PDGF-mediated angiogenesis through VEGF-R2. It was shown by martigel assay that, VEGF-mediated activation of VEGF-R2 suppresses PDGF-R β signaling in VSMCs. This is brought about by assembly of a receptor complex consisting of PDGF-R β and VEGF-R2. Inhibition of VEGF-R2 not only prevents assembly of this receptor complex but also restores angiogenesis in tissues exposed to both VEGF and PDGF. The reduced neovascularization appeared to be a result of reduced VSMC activation and reduced pericyte coverage of vessels leading to vessel destabilization. The complex nature of VEGF signaling in angiogenesis helps to explain the mechanisms underlying the blood vessel normalization that is induced by VEGF inhibitors in cancer patients.

Source: [Nature](#)^{1,2}



Research Highlights (cont'd)

Blockade of mTOR Potentiates Growth Arrest by HDAC Inhibitor

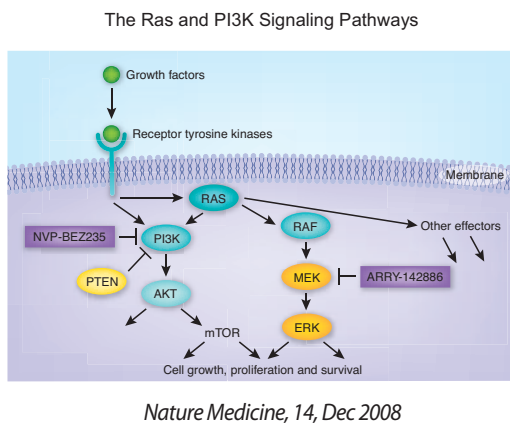


Acute myelogenous leukemia (AML) is a lethal disease, resulting from the clonal expansion and accumulation of hematopoietic stem cells arrested at various stages of development. Intensification of chemotherapy has led to remissions in 70–85% of individuals with AML and postremission relapses occur frequently. Histone deacetylase inhibitors (HDACIs) have emerged as a potentially promising new class of anticancer drugs. They induce growth arrest and apoptosis of cancer cells by manipulating the transcription of genes, modify chromatin structure and increase promoter accessibility leading to transcriptional activation. The mammalian target of rapamycin (mTOR) is a serine/threonine kinase, activated by PI3K/Akt signaling and regulates cell proliferation.

In a study reported in *Leukemia* by Nishioka et al., a novel synthetic benzamide HDACI, MS-275, was shown to block Akt/mammalian target of rapamycin (mTOR) signaling in AML- HL60 and acute promyelocytic leukemia (APL)- NB4 cells. Inhibition of mTOR by rapamycin analog RAD001 (everolimus) significantly enhanced MS-275-mediated growth inhibition and apoptosis of these cells in parallel with enhanced upregulation of p27^{kip1} and downregulation of c-Myc. In addition, RAD001 improved the ability of MS-275 to induce differentiation of cells. Also it significantly enhanced MS-275-induced growth inhibition of HL60 tumor xenografts in nude mice without adverse effects. MS-275 in combination with RAD001 upregulated levels of p27^{kip1} and down-regulated the levels of c-Myc proteins. This study, for the first time, showed that inhibition of mTOR dramatically potentiated the ability of HDACI in turn to cause acetylation of histone H3 in leukemia cells. These observations suggested that Akt signal pathway may be a common target of HDACI. Taken together, the combination of MS-275 and RAD001 may be useful for treatment of individuals with a subset of AML.

Source: *Leukemia*

PI3K and MEK Inhibitors in Treatment of Lung Cancer



Phosphoinositide 3-kinase (PI3K) and RAF signaling pathways have received enormous attention as targets for tumor therapy. Both these pathways are regulated by RAS proteins. PI3K inhibitors have entered into early clinical trials on the basis of large bodies of preclinical data with these agents. Somatic mutations are most frequently observed in the kinase domain (H1047R) of p110- α catalytic subunit of PI3K.

In a study published in *Nature Medicine*, Engelman et al. explored the oncogenic potential of p110- α mutants as targets for treatment of lung tumors. In this study, the clinical efficacy of a potent dual pan-PI3K-mTOR inhibitor, NVP-BE235 was evaluated in p110- α H1047R-induced mouse lung tumors. At most of the dose levels examined, NVP-BE235 induced suppression of PI3K signaling

was seen by a decrease in phosphorylated Akt (P-Akt) at both Ser473 and Thr308. There was substantial reduction in the ¹⁸F-fluorodeoxyglucose (¹⁸FDG) avidity of the tumor, as measured by PET imaging and also a marked decrease in their size. Although this drug by itself is ineffective against Kras-induced mouse lung tumors, treatment with a combination of PI3K and MEK inhibitors showed a marked down-regulation of PI3K and extracellular signal-related kinase signaling. The findings are certainly very encouraging and prove that the drug can block PI3K pathway within established tumors and further show that the combination of PI3K and MEK inhibitors may be very potent for such cancers.

Source: *Nature Medicine*



Clinical Development

DOXIL® Combination Therapy Delays Disease Progression for MBC Patients

Results from a Phase III study presented at the 31st Annual San Antonio Breast Cancer Symposium (SABCS) showed that patients with metastatic breast cancer (MBC) who were treated previously with an anthracycline in the adjuvant setting experienced a significant improvement in time to disease progression (TTP) and overall response rates after receiving a combination of DOXIL® (doxorubicin HCl liposome injection) and docetaxel as compared to docetaxel alone. The study enrolled 751 patients who were randomly assigned to receive either docetaxel 75 mg/m² (N=373) or Doxil 30 mg/m² followed by docetaxel 60 mg/m² (N=378) on Day 1 every 21 days.

The study found that patients treated with the DOXIL and docetaxel combination had a 35% risk reduction for developing disease progression compared with docetaxel alone. There was an almost 3-month improvement in median TTP for patients treated with the combination compared with docetaxel monotherapy (9.8 versus 7.0 months, respectively). ORR was also significantly improved for the combination compared with docetaxel monotherapy (35% vs. 26%, respectively). The safety profile was consistent with known toxicities of the two agents. "The study suggests that the combination of DOXIL and docetaxel may be an effective treatment for patients with metastatic breast cancer who have relapsed after prior adjuvant anthracycline therapy," said Dr. Joseph Sparano, the lead investigator of the study.

Source: [SABCS](#)

Phase II Trial Shows Improved Survival with ASA404 in Lung Cancer

Antisoma plc announced that the British Journal of Cancer has published the results of a randomized Phase II trial of ASA404 in non-small cell lung cancer (NSCLC). ASA404 (5,6-dimethylxanthenone-4-acetic acid or DMXAA) is a small-molecule tumor-vascular disrupting agent. This randomized study evaluated ASA404 plus standard therapy of carboplatin and paclitaxel in patients with histologically confirmed stage IIIb or IV NSCLC not previously treated with chemotherapy. Patients were randomized to receive 6 cycles of carboplatin and paclitaxel (CP, n=36) or standard therapy plus ASA404 (ASA404-CP, n=37).

Tumor response rate (31 vs 22%), median time to tumor progression (5.4 vs 4.4 months) and median survival (14.0 vs 8.8 months) were improved in the ASA404 combination group compared with the standard therapy group. This study established the feasibility of combining ASA404 with carboplatin and paclitaxel in patients with previously untreated, advanced NSCLC. Positive data from this trial supported the progress of ASA404 into Phase III development.

Source: [British Journal of Cancer, Antisoma](#)



Clinical Development (cont'd)

Vorinostat plus Bortezomib for the Treatment of Relapsed/Refractory MM

Vorinostat is a potent inhibitor of histone deacetylase enzymes, and has been shown to affect growth of various cell lines, including multiple myeloma (MM), in a variety of *in vitro* preclinical studies. Furthermore, the combination of bortezomib and vorinostat has demonstrated synergy in several *in vitro* and murine models. Subsequently, 2 multicenter, open-label, Phase I clinical trials have been conducted to investigate the combination of vorinostat with bortezomib in patients with MM.

In the first trial, 34 patients with relapsed/refractory MM were enrolled. Patients received escalating doses of vorinostat (200 mg bid or 300-400 mg daily for 14 days) and bortezomib (0.7, 0.9, 1.1, or 1.3 mg/m² on days 1, 4, 8, and 11); cycles were repeated every 21 days for ≤8 cycles or until progressive disease (PD) or intolerable toxicity. Among 34 evaluable patients, the best response to vorinostat plus bortezomib was a partial response (PR) in 9 patients, minimal response (MR) in 7 patients, and stable disease (SD) in 18 patients. Mean duration of SD was 89 days. Of the 13 evaluable patients who had previously been treated with bortezomib, 5 achieved a PR, 1 had a MR, and 7 had SD.

The second trial enrolled 23 patients who received vorinostat (100-500 mg on days 4-11) and bortezomib (1-1.3 mg/m² on days 1, 4, 8, and 11). Maximum tolerated dose was identified as vorinostat 400 mg plus bortezomib 1.3 mg/m². Twenty-one patients were evaluable for response (2 achieved very good PR, 7 PR, 10 SD, 2 progressive PD). Of the 9 patients who were refractory to bortezomib, 3 had PR, 4 had SD, 1 had PD, and 1 was non-evaluable. Co-administration of bortezomib did not alter the pharmacokinetics of vorinostat. The findings from two studies suggest that the combination of vorinostat plus bortezomib is active for treatment of MM, even among some patients with prior exposure to bortezomib.

"Based on these data, Merck has moved rapidly into late-stage clinical development to further evaluate Vorinostat (Zolinza®) in combination with bortezomib for advanced multiple myeloma," said Jose Garcia-Vargas, M.D., senior director, Clinical Oncology, Merck Research Laboratories

Source: [ASH](#)

Sequential Therapy with FCR in Previously Untreated Patients with CLL

Combination strategies used in chronic lymphocytic leukemia (CLL) can have significant myelosuppression and immunosuppression that may require dose attenuation for safety. Previously, Weiss et al have studied sequential therapy with fludarabine followed by cyclophosphamide (FC) and showed that cyclophosphamide consolidation improved the frequency of complete response (CR) four-fold. Given those encouraging results, in a recent study published in *JCO*, investigators added rituximab as a non-cross-resistant second consolidation to create the sequential fludarabine, cyclophosphamide, and rituximab regimen (F3C3R).

Thirty-six previously untreated CLL patients received therapy with fludarabine 25 mg/m² on days 1 through 5 every 4 weeks for six cycles, followed by consolidation with cyclophosphamide 3,000 mg/m² administered every 3 weeks for three cycles, followed by consolidation with weekly rituximab 375 mg/m² for four cycles. Evaluation for minimal residual disease included flow cytometry and a highly sensitive clonotypic polymerase chain reaction (PCR). There were 32 responses (89%), including 22 CRs (61%). Consolidation with cyclophosphamide improved responses in 13 patients (36%); 9 patients (25%) further improved their response with rituximab. Twenty patients (56%) achieved flow cytometric CRs, and 12 patients (33%) achieved a molecular CR (PCR negative). Patients achieving molecular CRs had an excellent prognosis with a plateau in the response duration curve, and 90% remained in clinical CR at 5 years. For the entire group, 5-year survival rate was 71% compared with a rate of 48% with prior FC regimen. The study concluded that sequential therapy with FCR yields improvement in quality of response, with many patients achieving a PCR-negative state.

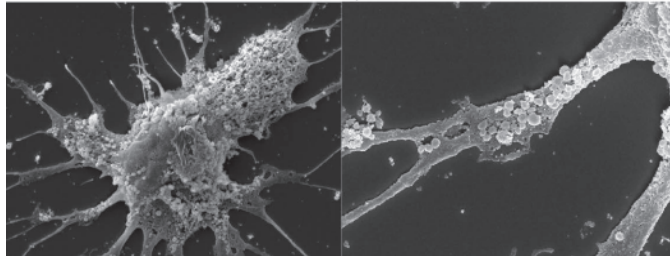
Source: [JCO](#)



Biomarkers

Tumor-derived Microvesicles as Diagnostic Biomarkers

Glioblastoma Cells Produce Microvesicles containing RNA



Nature Cell Biology, 10, Dec 2008

Microvesicles are formed through inward budding of endosomal membranes that later fuse with the plasma membrane releasing them to the outside. These vesicles are shed from many different cell types and act as a multicomponent delivery vehicles for mRNA, miRNA and proteins to recipient cells in the tumor microenvironment.

In a study published in *Nature Cell Biology*, Skog and co-workers have used microvesicles (exosomes) formed through inward budding of endosomal membranes, as an aid of diagnostic information for glioblastoma patients, through a blood test. Bioanalysis of RNA from microvesicles and their donor cells revealed that the microvesicles contain a broad range of RNA sizes, consistent with a variety of mRNAs (approximately 4,700 different mRNAs) and miRNAs. Incubation of glioblastoma microvesicles labeled with the fluorescent dye PKH67 with human brain microvascular endothelial cells showed their internalization into endosome like structures by the later. Epidermal growth factor receptor (*EGFR*) mRNA was used as a biomarker for glioblastoma tumors as the expression of the *EGFRvIII* mutant/variant is specific to a clinical subtype of glioma. Moreover, *EGFRvIII* mRNA was not detected in serum samples taken 2 weeks after resection of *EGFRvIII*+ tumors, suggesting that this less invasive method of assessing the *EGFRvIII* status of tumors may have clinical utility.

These studies suggest that microvesicles may provide diagnostic information and aid in therapeutic decisions for cancer patients through non-invasive methods. Finally, these microvesicles may prove useful as delivery vesicles for therapeutic proteins and RNAs.

Source: *Nature Cell Biology*

Serum S100B Protein as a Prognostic Marker in Melanoma Patients

High-risk melanoma is a disease that after surgery, is associated with a recurrence and/or mortality risk higher than 35% to 50%; as formulated by the most recent 6th edition American Joint Committee on Cancer (AJCC) system. Serum S100B (isoforms S100AB and S100BB) protein, shed by melanoma cells, in the peripheral blood, has shown promise as a prognostic marker for melanoma relapse and mortality risk. The mean serum concentration of S100B protein has been reported to be significantly related to the clinical stage in melanoma and to have a high sensitivity and specificity for the detection of metastatic melanoma.

In a study reported by Tarhini *et al.* in *JCO*, sera from 670 patients enrolled in adjuvant trial E1694 were analyzed for S100B levels. The results of this study demonstrated that higher serum S100B levels were associated with poorer prognosis in terms of relapse and survival. The median baseline serum S100B value was 0.08 µg/L. At baseline, 582 patients (87%) had an S100B level less than 1.54µg/L (normal) and 88 patients (13%) had ≥ 1.54µg/L (high). In univariate analysis, a baseline S100B level significantly correlated with overall survival (OS), and less significantly with relapse free survival. In the multivariate analysis, treatment was not significant for OS; however, patients with a high baseline S100B level treated with high-dose interferon alfa-2b (HD) experienced a longer survival. Lower S100B values at baseline and during follow-up were associated with longer survival. These results indicate that baseline S100B is a significant prognostic marker for mortality. Since no serum biomarkers have reliably demonstrated the capacity to predict disease outcome in the adjuvant setting of high-risk melanoma, S100B is a valuable prognostic biomarker correlated with mortality risk.

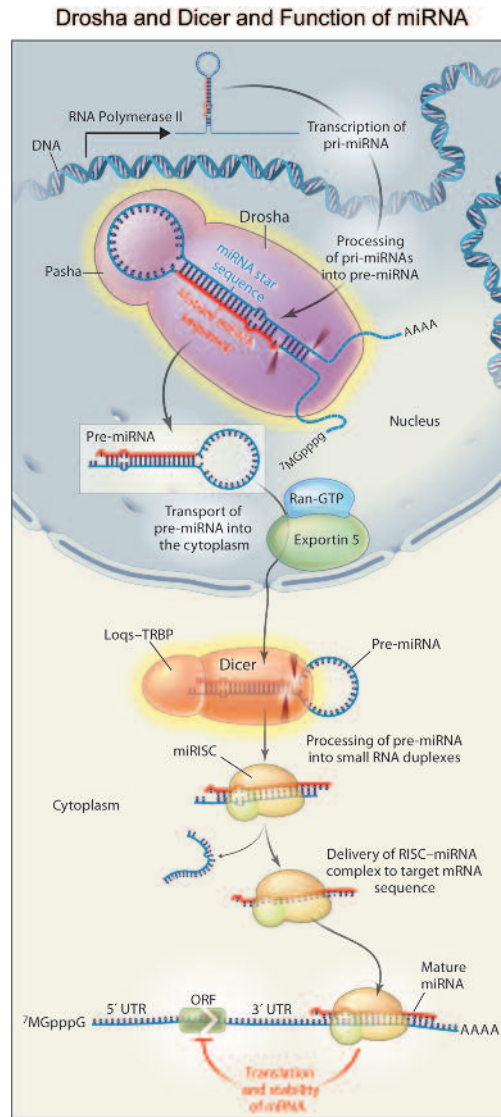
Source: *JCO*

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Biomarkers (cont'd)

Dicer, Drosha and Outcomes in Patients with Ovarian Cancer



NEJM, 25, Dec 18, 2008

The micro-RNAs (miRNAs) are a class of small, regulatory noncoding RNAs that inhibit gene expression by binding to imperfect complementary sites within the 3' untranslated regions of their target mRNA transcripts. These miRNAs regulate processes essential to cell growth, differentiation, apoptosis, and adhesion, and for this reason they have provided insight into the mechanisms of human cancer. Studies indicate that proteins involved in miRNA biogenesis are likely to play important roles in cancer.

In a study reported in *NEJM*, Merritt et al. demonstrated that levels of the miRNA processing enzymes Drosha and Dicer (both RNase III enzymes), are prognostic indicators in patients with ovarian cancer. They found that low levels of Dicer are associated with advanced tumor stage whereas low levels of Drosha are associated with suboptimal surgical cytoreduction, both known to be poor prognostic factors. High levels of Dicer and Drosha identified a subgroup of patients with ovarian cancer with significantly better survival. Analysis of previously published microarray data in patients with ovarian, breast and lung cancer validated the potential of low dicer levels to serve as a biomarker for poor outcome. Also the cells with low Dicer expression could not effectively silence genes when synthetic short hairpin RNA constructs were transfected. The findings indicate that levels of Dicer and Drosha mRNA in ovarian-cancer cells can serve as useful prognostic markers.

Source: *NEJM*

Wild-Type BRAF is Required for Response to EGFR-Targeted Therapies

Presence of mutated *KRAS* alleles is an independent predictive marker of resistance to epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAb) like cetuximab and panitumumab. However, the occurrence of *KRAS* mutations only accounts for approximately 30% to 40% of non-responsive patients. Therefore, the identification of additional genetic determinants of primary

resistance to EGFR-targeted therapies in colorectal cancers (CRCs) is important. The serine-threonine kinase BRAF is the principal effector of *KRAS*. In a recent study published in *JCO*, Di Nicolantonio et al. evaluated the role of BRAF mutations as prognostic or predictive factors for response to cetuximab or panitumumab.

A retrospective analysis of 113 patients treated with either cetuximab or panitumumab was conducted. The presence of *KRAS* mutations in this population was 30%. Twenty-eight percent of wild type *KRAS* patients responded to either cetuximab or panitumumab. *BRAF* mutations (*BRAF V600E allele*) were identified in 11 patients (10% of the population evaluated; 14% of wild type *KRAS* patients). The presence of *BRAF* mutations was inversely associated with response to therapy. *BRAF*-mutated patients had significantly shorter progression-free survival and overall survival than wild-type patients. *BRAF V600E allele* impaired the response of CRC cells to cetuximab or panitumumab. Treatment with the *BRAF* inhibitor sorafenib restored sensitivity to panitumumab or cetuximab of CRC cells carrying the *BRAF V600E allele*. The study concluded that wild-type *BRAF* is required for response to EGFR targeted MoAb therapies. Multiple therapies with EGFR and BRAF inhibitors should be explored in CRC patients in whom the *KRAS/BRAF* pathway is oncogenically activated.

Source: *JCO*



Regulatory

FDA Approves Degarelix for Advanced Prostate Cancer

Ferring Pharmaceuticals received approval from the FDA for degarelix, a new injectable gonadotropin-releasing hormone (GnRH) receptor antagonist, indicated for patients with advanced prostate cancer. On December 18, 2008, the Committee for Medicinal Products for Human Use (CHMP), part of the European Medicines Agency (EMA), recommended granting a marketing authorization for degarelix in Europe.

Phase III studies showed that degarelix is at least as effective as leuprolide (Lupron Depot®) in sustaining castrate levels or lower testosterone, and had a statistically significant faster reduction of testosterone. At day 3 of treatment, 96% of degarelix patients achieved castrate levels of testosterone, compared with 0% receiving leuprolide. By day 14, 99% of degarelix patients achieved castrate levels of testosterone, compared with 18% receiving leuprolide. In the clinical trial, prostate specific antigen (PSA) levels were also monitored as a secondary endpoint. PSA levels were lowered by 64% two weeks after administration of degarelix, 85% after one month, 95% after three months, and remained suppressed throughout the one year of treatment.

Source: *Ferring Pharmaceuticals*

EC Grants VIDAZA® Full Marketing Authorization

Celgene International announced that its cancer drug, VIDAZA® (azacitidine), has been granted full marketing authorization by the European Commission (EC) for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

- Intermediate-2 and high-risk myelodysplastic syndromes (MDS), according to the International Prognostic Scoring System, or
- Chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts without myeloproliferative disorder, or
- AML with 20-30% blasts and multi-lineage dysplasia, according to WHO classification

The approval was based upon efficacy and safety data from clinical studies evaluating VIDAZA in MDS and refractory anemia with excess blasts in transformation patients within the AML category as defined by the WHO classification system. These pivotal efficacy and safety data were primarily provided from the VIDAZA survival trial (AZA-001), the largest, international randomized Phase III controlled study in higher-risk MDS and WHO AML patients. The results demonstrated a clinically relevant increase in median survival of 9.4 months (24.4 vs. 15 months) as compared to conventional care regimens. VIDAZA has received orphan drug designation for the treatment of MDS and AML in the European Union.

Source: *Celgene*



Regulatory (cont'd)

Antisoma Receives FDA Approval for Oral Fludarabine

Antisoma plc announced that the FDA has approved fludarabine phosphate film-coated tablets as a single agent for the second-line treatment of adult patients with B-cell chronic lymphocytic leukaemia (CLL). Antisoma plans to make the drug available to US patients through a commercialization deal. Antisoma expects to conclude a deal early in 2009. The marketing authorization has been granted under the FDA's accelerated approval provisions (21 CFR 314 subpart H ('accelerated approval')). Under these provisions, the sponsoring company is required to perform an additional clinical trial.

Antisoma's rights to market fludarabine are specific to the oral (tablet) form of the drug and to the US market, where Antisoma has an exclusive license from Bayer Schering Pharma AG. Oral fludarabine has US orphan drug status for treatment of CLL, providing seven years' exclusivity from approval. Antisoma has an exclusive license to US patents covering the oral formulation of fludarabine phosphate. Oral fludarabine was added to the Antisoma pipeline through the acquisition of Xanthus Pharmaceuticals, in June 2008.

Source: [Antisoma](#)

Roche Wins Final Approval for Discounted Tarceva® in UK

Roche Holding AG's lung cancer drug, Tarceva® (erlotinib), has won final approval for use by Britain's state health service after the Swiss drugmaker agreed to discount the price of the medicine. The National Institute for Health and Clinical Excellence (NICE) now recommends Tarceva as an alternative to Sanofi-Aventis SA's Taxotere for people who have already tried one chemotherapy regime without success in NSCLC.

But NICE, which decides which treatments should be funded by the state in England and Wales, said Roche's drug should only be used if its overall treatment cost did not exceed that of Taxotere. The new price for a 125-day course of Tarceva treatment is £6,128 (\$9,265), compared with a previous typical cost of 6,800 pounds. NICE had originally recommended against Tarceva, arguing that buying the costly drug, was not a good use of National Health Service (NHS) resources. It was licensed and launched in Britain in 2005 but Roche has since been fighting to get it paid for by the NHS. Roche had already announced in October 2007 that it was cutting the British price of Tarceva as an interim measure.

Source: [Reuters](#)

Roche Seeks European Drug Approval for Glioblastoma

Swiss drugmaker Roche Holding AG announced that it has filed for European approval of Avastin® (bevacizumab) for the treatment of patients with previously treated glioblastoma, the most aggressive type of brain cancer. The application is supported by data from the Phase II BRAIN study in glioblastoma patients that evaluated Avastin as a single agent or in combination with irinotecan chemotherapy. Roche said the study showed 43% of patients treated with Avastin on its own lived without their disease advancing at 6 months, increasing to 50% when the drug was used in combination with irinotecan. Avastin also decreased tumor size by at least half in 28% of patients, rising to 38% together with irinotecan. Patients receiving Avastin alone had a median overall survival of 9.3 months compared to 8.8 months for those receiving Avastin in combination with irinotecan, which was a secondary endpoint in the study. Based on this data, Genentech has already filed in the US in November of this year.

Source: [Roche](#)