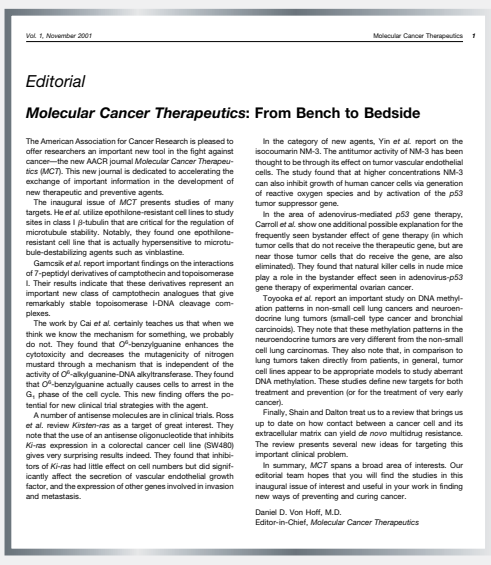
2001

New AACR Journal Focuses on Targeted Therapies: *Molecular Cancer Therapeutics*

DANIEL D. VON HOFF, MD, FOUNDING EDITOR-IN-CHIEF, 2001-2012

In a career devoted to discovering targeted therapies for many different cancers, Dr. Von Hoff is also a consummate physician, literally moving between the bench and the bedside. His research is responsible for developing hundreds of drugs, including gemcitabine, the first effective therapy for pancreatic cancer. He has launched a global network for pancreatic cancer research and heads one of AACR's Dream Teams. A Past President of the AACR, Dr. Von Hoff is presently physician-in-chief and director of translational research at the Translational Genomics Research Institute in Phoenix, AZ, and holds academic appointments at several institutions in Arizona.



Vol. 1, November 2001 — *Molecular Cancer Therapeutics* 1

Editorial

***Molecular Cancer Therapeutics*: From Bench to Bedside**

The American Association for Cancer Research is pleased to offer researchers an important new tool in the fight against cancer—the new AACR journal *Molecular Cancer Therapeutics* (*MCT*). This new journal is dedicated to accelerating the exchange of important information in the development of new therapeutic and preventive agents.

The inaugural issue of *MCT* presents studies of many targets. He *et al.* utilize epothilone-resistant cell lines to study sites in class I β-tubulin that are critical for the regulation of microtubule stability. Notably, they found one epothilone-resistant cell line that is actually hypersensitive to microtubule-destabilizing agents such as vinblastine.

Gamcsik *et al.* report important findings on the interactions of 7-peptidyl derivatives of camptothecin and topoisomerase I. Their results indicate that these derivatives represent an important new class of camptothecin analogues that give remarkably stable topoisomerase I-DNA cleavage complexes.

The work by Cai *et al.* certainly teaches us that when we think we know the mechanism for something, we probably do not. They found that O^6-benzylguanine enhances the cytotoxicity and decreases the mutagenicity of nitrogen mustard through a mechanism that is independent of the activity of O^6-alkylguanine-DNA alkyltransferase. They found that O^6-benzylguanine actually causes cells to arrest in the G_1 phase of the cell cycle. This new finding offers the potential for new clinical trial strategies with the agent.

A number of antisense molecules are in clinical trials. Ross *et al.* review *Kirsten-ras* as a target of great interest. They note that the use of an antisense oligonucleotide that inhibits *Ki-ras* expression in a colorectal cancer cell line (SW480) gives very surprising results indeed. They found that inhibitors of *Ki-ras* had little effect on cell numbers but did significantly affect the secretion of vascular endothelial growth factor, and the expression of other genes involved in invasion and metastasis.

In the category of new agents, Yin *et al.* report on the isocoumarin NM-3. The antitumor activity of NM-3 has been thought to be through its effect on tumor vascular endothelial cells. The study found that at higher concentrations NM-3 can also inhibit growth of human cancer cells via generation of reactive oxygen species and by activation of the *p53* tumor suppressor gene.

In the area of adenovirus-mediated *p53* gene therapy, Carroll *et al.* show one additional possible explanation for the frequently seen bystander effect of gene therapy (in which tumor cells that do not receive the therapeutic gene, but are near those tumor cells that do receive the gene, are also eliminated). They found that natural killer cells in nude mice play a role in the bystander effect seen in adenovirus-*p53* gene therapy of experimental ovarian cancer.

Toyooka *et al.* report an important study on DNA methylation patterns in non-small cell lung cancers and neuroendocrine lung tumors (small-cell type cancer and bronchial carcinoids). They note that these methylation patterns in the neuroendocrine tumors are very different from the non-small cell lung carcinomas. They also note that, in comparison to lung tumors taken directly from patients, in general, tumor cell lines appear to be appropriate models to study aberrant DNA methylation. These studies define new targets for both treatment and prevention (or for the treatment of very early cancer).

Finally, Shain and Dalton treat us to a review that brings us up to date on how contact between a cancer cell and its extracellular matrix can yield *de novo* multidrug resistance. The review presents several new ideas for targeting this important clinical problem.

In summary, *MCT* spans a broad area of interests. Our editorial team hopes that you will find the studies in this inaugural issue of interest and useful in your work in finding new ways of preventing and curing cancer.

Daniel D. Von Hoff, M.D.
Editor-in-Chief, *Molecular Cancer Therapeutics*

First Table of Contents

Inaugural Editorial

Publication of GW2016 (Approved as Lapatinib in 2007)

HIGHLY CITED ARTICLE

The Effects of the Novel, Reversible Epidermal Growth Factor Receptor/ErbB-2 Tyrosine Kinase Inhibitor, GW2016, on the Growth of Human Normal and Tumor-derived Cell Lines *in Vitro* and *in Vivo*

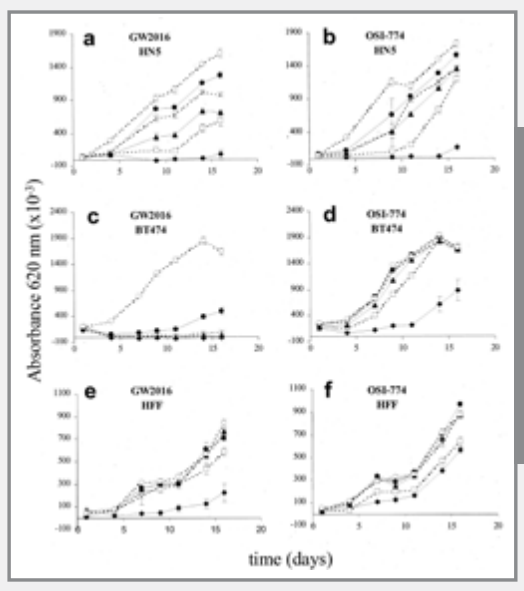


FIGURE 4. Growth arrest or cell death in EGFR- or ErbB-2-overexpressing cells caused by treatment with GW2016. Cells were treated for 3 days with GW2016 or OSI-774 (an EGFR-selective inhibitor, used as a positive control), beginning on day 1. GW2016 (or OSI-774) was removed on day 4 and replaced with fresh growth medium. Cells were fed weekly for the duration of the assay. Methylene blue staining was performed at the time points indicated on the graph. Doses of GW2016 resulting in inhibition outgrowth after 3 days of drug exposure were achieved cells that overexpress EGFR (HN5) and ErbB-2 (BT474). Vehicle -○-, 0.37 μm -○-, 1.1 μm -*-, 3.3 μm -▲-, 10 μm -□-, and 30 μm -◆-.

2003

First Impact Factor: 3.201

Report of SU11248 (Approved as Sunitinib in 2006) in Preclinical Models of Small Cell Lung Cancer

HIGHLY CITED ARTICLE

SU11248 Inhibits KIT and Platelet-derived Growth Factor Receptor β in Preclinical Models of Human Small Cell Lung Cancer

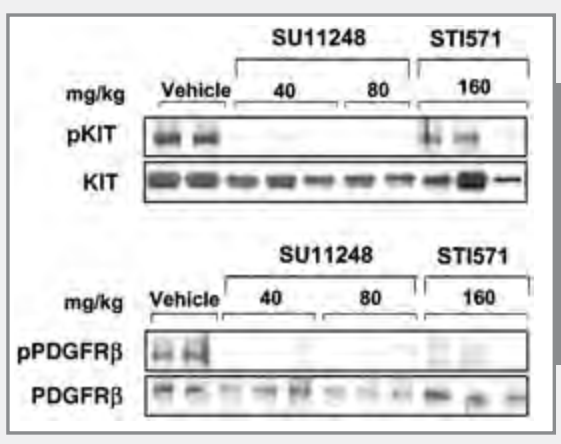


FIGURE 5. SU11248 inhibits KIT and PDGFRβ phosphorylation in vivo. From the end of the efficacy studies, athymic mice bearing NCI-H526 SCLC s.c. tumors were given a single oral dose of SU11248 at 40 or 80 mg/kg, STI571 at 160 mg/kg, or vehicle control. Tumors were resected and lysed at the expected Cmax for each compound (4 h post-dose for SU11248 and 2 h post-dose for STI571). Lysates were immunoprecipitated with an anti-KIT or anti-PDGFRβ antibody. Phosphotyrosine and total KIT and PDGFRβ levels were determined by Western blotting.

SCIENTIFIC PUBLISHING CENTENNIAL
1916-2016
AACR American Association for Cancer Research

2004

Discovery of PD 0332991 (Approved as Palbociclib in 2015)


HIGHLY CITED ARTICLE

Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts

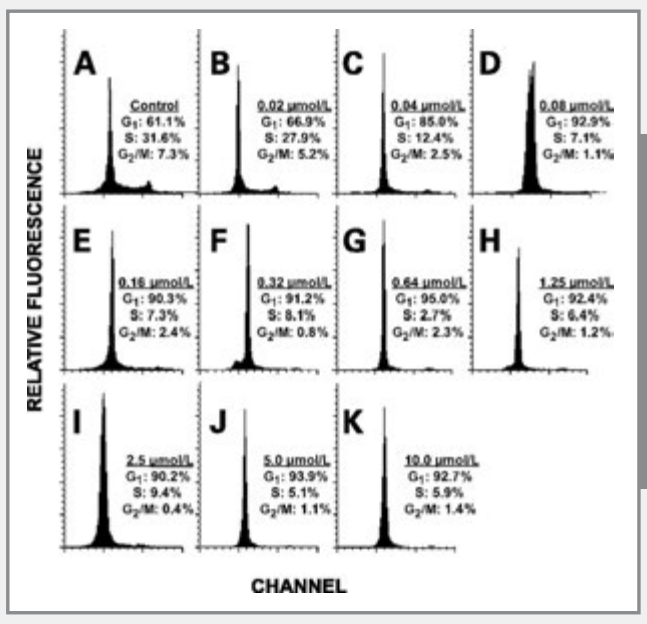


FIGURE 3. PD 0332991 causes an exclusive G1 arrest. MDA-MB-453 human breast carcinoma cells were exposed to varying concentrations of PD 0332991 for 24 hours. Cells were harvested and fixed as described in Materials and Methods. The DNA histograms were generated by flow cytometry and the percentage of cells in each phase of the cell cycle was determined using ModFit. Additional details are given in Materials and Methods.

2008

First publication of NVP-BEZ235 (dactolisib); most-cited paper

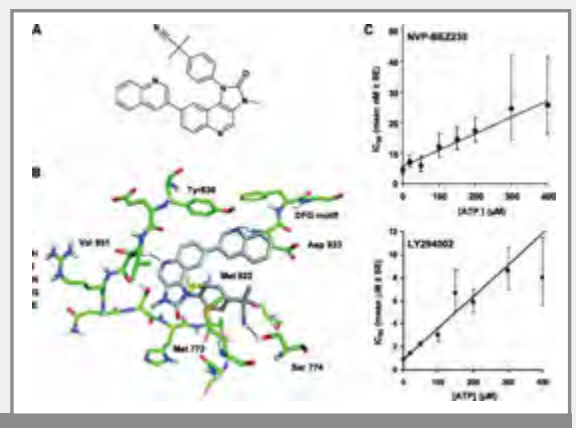


FIGURE 1. Enzymatic characterization of NVP-BEZ235. A, structure of NVP-BEZ235. B, binding mode of NVP-BEZ235 docked in the catalytic site of PI3Kα. The model was generated using the coordinates of known PI3Kγ crystal structures, particularly those of the complex with staurosporine (PDB code 1E8Z), based on a standard sequence alignment. This binding mode hypothesis was the result of systematic docking (followed by energy minimization) of the compound in the ATP cleft. All possible orientations were considered to determine which one was the most consistent with the available structure-activity relationship, particularly with regard to the importance of the H-bond acceptor nitrogen atoms present in the chemical structure of the inhibitor for high potency. C, NVP-BEZ235 is an ATP competitive inhibitor. IC50 values determined using the MaxiSorp assay were plotted against the ATP concentrations used in the presence of either NVP-BEZ235 or LY294002. The large error bars at high ATP concentrations are due to isotopic dilution (lower counts). Data were fitted by linear curve fitting with weights (1 / SE2). The positive slope of the straight line indicates a competitive effect ($P < 0.01$) for both inhibitors. Note that this analysis does not exclude the presence of a noncompetitive component (mixed inhibition).


HIGHLY CITED ARTICLE

Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent *in vivo* antitumor activity

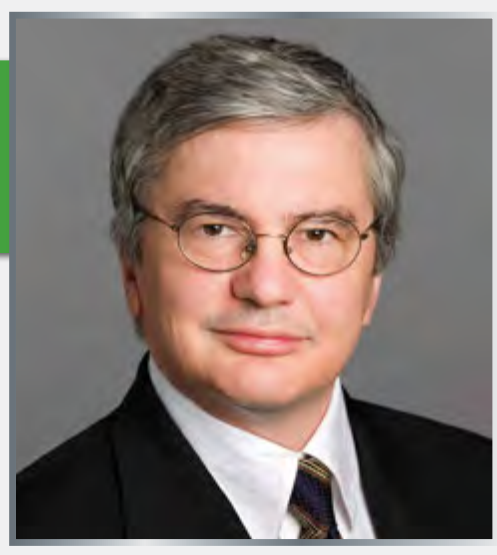
2012

CEO of Research Institute Appointed Editor-in-Chief

JOHN C. REED, MD, PHD,
EDITOR-IN-CHIEF, 2012-2013

2013

Angiogenesis Expert Named Editor-in-Chief



NAPOLEONE FERRARA, MD,
EDITOR-IN-CHIEF, 2013-PRESENT

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