EMERGING RESEARCH FRONTS - 2010

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Michael M. Gottesman talks with *ScienceWatch.com* and answers a few questions about this month's Emerging Research Front Paper in the field of Pharmacology & Toxicology.

Article: Predicting drug sensitivity and resistance: Profiling ABC transporter genes in cancer cells
Authors: Szakacs, G;Annereau, JP;Lababidi, S;Shankavaram, U; Arciello, A;Bussey, KJ;Reinhold, W;Guo, YP;Kruh, GD;Reimers, M; Weinstein, JN;**Gottesman, MM**
Journal: CANCER CELL, 6 (2): 129-137 AUG 2004
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SW: Why do you think your paper is highly cited? Does it describe a new discovery, methodology, or synthesis of knowledge?

Resistance of cancers to chemotherapy, either intrinsic or acquired, is the major impediment to the successful treatment of cancer. After over 40 years of study, we are beginning to catalog the major mechanisms of multidrug resistance, and this review summarizes the state of the field, summarizing the work of many researchers over many years, and so represents a synthesis of our current level of understanding of mechanisms of multidrug resistance.

SW: Would you summarize the significance of your paper in layman's terms?

Oncologists won't be able to cure cancers that have spread unless they can use drugs that specifically kill these cancer cells and spare normal cells. Although many cancers are killed by chemotherapy, cancers are quite heterogeneous and some cancer cells are able to survive treatment. These cancer cells can grow and spread and kill our patients. If we can understand why some cancers survive treatment, even very specific, targeted treatment, we can improve the treatment of cancer.

SW: How did you become involved in this research and were any particular problems encountered along the way?

My interest in this problem began in the 1980s when it became clear that there were some very effective anti-cancer drugs, but some cancers didn't respond and others developed resistance. We set about to develop models of multidrug-resistant cancers in cultured cells and use sophisticated molecular techniques to isolate the genes whose expression conferred resistance to the drugs.

Our first discovery, with my colleagues Igor Roninson and Ira Pastan, was that multidrug-resistant cancers overexpressed a gene that encoded an ATP-dependent transporter, termed P-glycoprotein, MDR1 or ABCB1. Although this gene is frequently expressed in drug-resistant cancers, inhibiting it had only minor effects on drug resistance in cancer patients, undoubtedly because there are many other multidrug resistance genes.

"We hope to determine which multidrug-resistance genes are important in clinical drug resistance, and then design approaches to circumventing or overcoming these forms of drug resistance."

In fact, ABCB1 belongs to a family of 48 human ATP-dependent transporters, of which approximately 50% can confer resistance to one or another drug. Plus, there are many other genes whose expression can confer drug resistance. So now we are enumerating all of these genes (at last count, there were at least 400) and trying to determine which play a role in clinical multidrug resistance.

SW: Where do you see your research leading in the future?

We hope to determine which multidrug-resistance genes are important in clinical drug resistance, and then design approaches to circumvent or overcome these forms of drug resistance.

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