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# Evolution of Drug Resistance in Cancer: The Emergence of Unique Mechanisms and Novel Techniques

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## Evolution of Drug Resistance in Cancer: The Emergence of Unique Mechanisms and Novel Techniques

**D**ramatic decreases in the mortality rates due to both cardiovascular and cerebrovascular diseases have been reported over the last fifty years. Despite the age of molecular characterization of disease and the discovery of novel druggable targets leading to pharmaceutical breakthroughs, the mortality trends due to cancer in this time frame have not changed. The evolution of drug resistance to each of these new pharmaceutical entities has formed a nearly impassable barrier to successful drug treatment in cancer.

The overexpression of ATP-binding cassette (ABC) drug transporters has been considered the predominant mechanism responsible for multidrug resistance (MDR). ABC transporters have been studied *in vitro* for decades; nevertheless, significant clinical advancement has been lacking possibly due to the multifactorial nature of resistance. This lack of clinical success has spurred investigators to uncover various other mechanisms of resistance and to generate new tools to illustrate the evolution of drug resistance at the molecular level and to better understand gene regulation in the presence of drug. Not so surprisingly, the use of evolutionary theory to investigate the dynamics of somatic evolution has emerged, giving rise to transdisciplinary programs to champion the application of evolutionary theory to understand the mechanisms involved in MDR.

This issue will highlight the recent work of investigators, both within the cancer community and in the scientific community at large, as they apply evolutionary principles to MDR to illuminate alternate mechanisms of MDR and to establish tools to both elucidate the evolution of MDR and to circumvent it. One such work reviews therapeutics recently devised to alter the epigenetics of tumors by inhibiting histone deacetylase. Robey et al. discusses how mechanisms of resistance to histone deacetylase inhibitors have already surfaced and how they range from the overexpression of ABCB1 to NF $\kappa$ B activation. As in evolutionary biology, selection pressure plays a critical role in the development of MDR, and the Gillies laboratory describes the cellular adaptation that results from the extracellular acidosis within the tumor microenvironment. Advancements in technologies that probe the genome have provided unique opportunities for clinicians and researchers to study MDR. For instance, investigators have created molecular tumor clocks derived from passenger DNA methylation changes as well as a clinical gene signature utilizing TaqMan low density arrays and miRNA expression profiles for cells with increasing levels of MDR. Each of these tools is showcased in papers in this issue. Moreover, the use of evolutionary theory to bypass MDR is also considered. Getzenberg and Coffey look at the use of thermal energy to alter the tumor microenvironment to improve therapeutic response while Cunningham et al. focus on the double bind evolutionary approach to deal with MDR.

As a whole, these works exemplify the severity of MDR in cancer pathogenesis and should spur investigators and pharmaceutical companies alike to pursue forward-looking,

out of the box strategies to make much needed progress in addressing MDR and therefore in cancer research and treatment.

Anna Maria Calcagno, Guest Editor

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