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# Editorial

This special issue of Biochemical Pharmacology highlights a series of articles from leading experts at the forefront of understanding the problems associated with preclinical and clinical treatment failures caused by the advent of drug resistance in the management of cancer patients. Different classes of drugs are exemplified. Such aspects of their pharmacology relevant to how resistance arises are detailed. In general, understanding how cells become resistant to a new drug can help in understanding how best to use it in a clinical setting. Moreover, information can also be employed at various stages of the drug discovery and development process. We hope that this information will be of interest to both the general reader and those directly involved directly in cancer drug research.

One of the hallmarks of cancer cells is their genetic instability and accompanying plasticity. Such characteristics convey advantages when cancer cells are subjected to drug treatments since they facilitate cell survival by the allowing the parallel adaptation to the stresses provided by drug exposure. Under either experimental or clinical conditions this gives rise to the acquired drug resistance phenotype. Contingent upon the class of anticancer drug, specific mechanisms of resistance may depend upon the level at which the threat is handled. For example, Fig. 1 shows some of the cellular loci and conceptual mechanisms that have been associated with a variety of drug resistant phenotypes. At one level, adaptations may be extracellular, associated with certain characteristics of the whole animal. In others, acquired resistance may be a function of changes or adaptations at the cellular and sub-cellular levels. In many of these cases adaptations will be multiple and cross- or collateral-resistance to other related or unrelated drugs can be a consequence of modified adaptive traits. This can represent an accelerated evolutionary adaptation to extreme selective conditions. Since many anticancer drugs are derived from natural products, traits that permit survival will likely be an extension or progression of the natural mechanisms by which cells protect themselves against their natural environment.

For a number of decades experimentalists have studied drug resistance by first creating cell lines with acquired drug resistance phenotypes. An example of the sort of experimental flow scheme that can be used to produce resistant cell lines is shown in Fig. 2. Such cell lines have been the mainstay of preclinical models

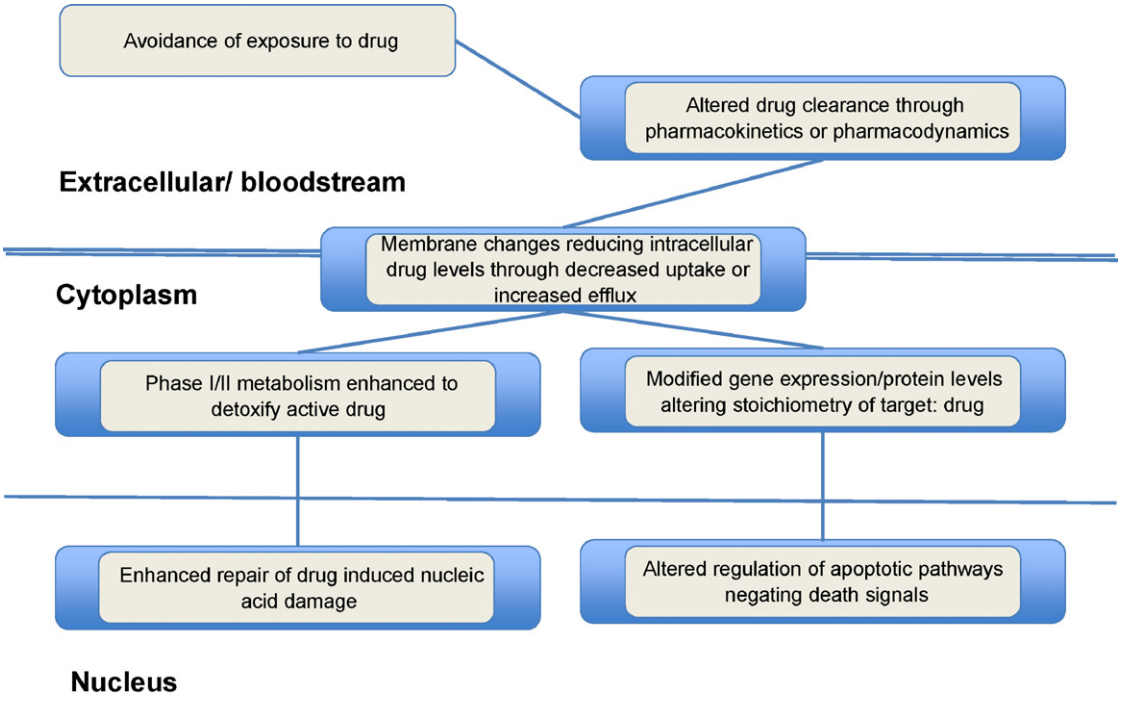


**Fig. 1.** Outline of those factors that may influence the development of acquired drug resistance.

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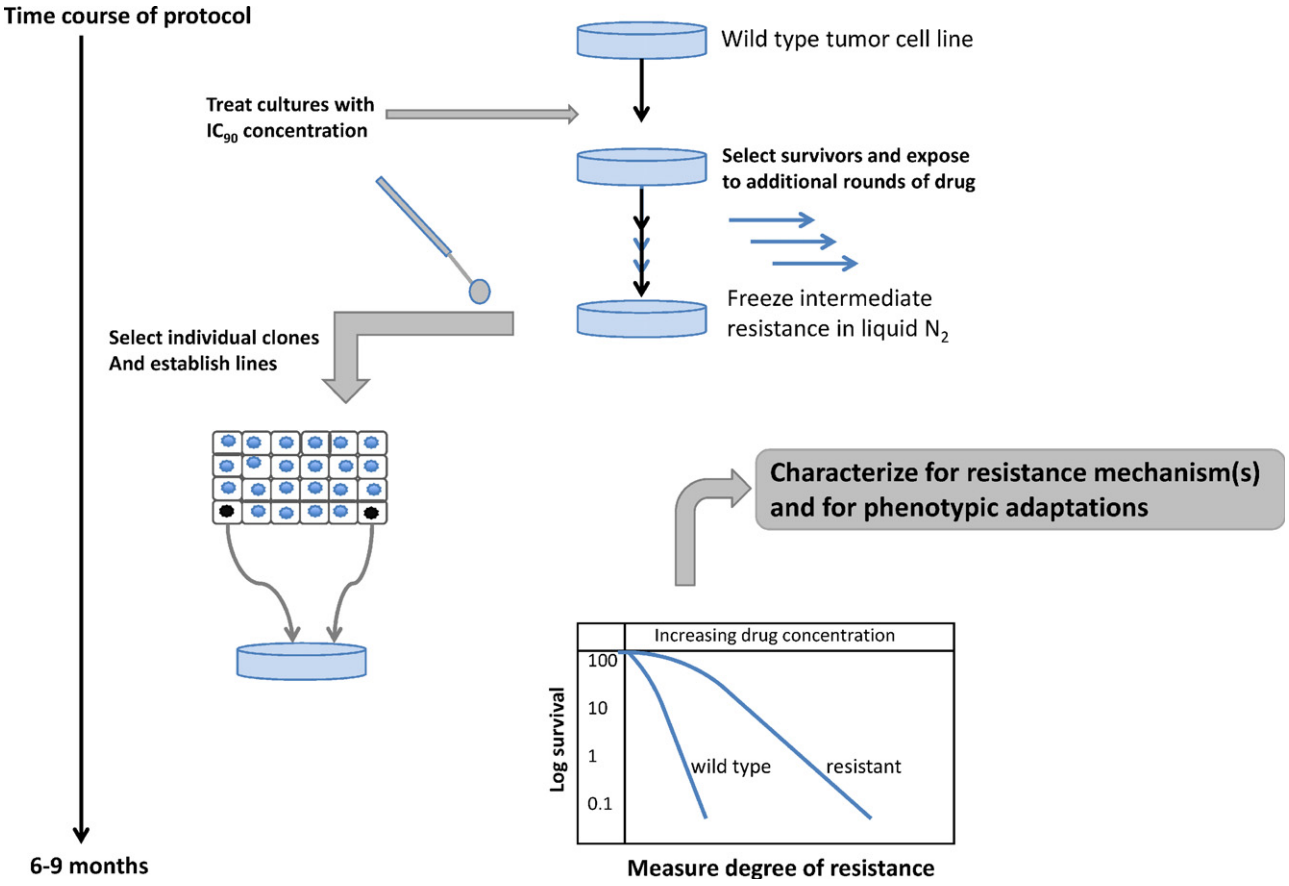


**Fig. 2.** Flow scheme of experimental approaches frequently utilized to select laboratory models of acquired drug resistance.

and regularly lend themselves to growth in murine model systems. The combination of *in vitro* and *in vivo* model systems permits a generally thorough analysis of the properties most responsible for conveying resistance. As a result there has been a consistent literature on how cells adapt to anticancer drugs and this in turn has led to a more complete understanding of the mechanisms of action of such agents. Indeed, the development of novel small molecule drugs is frequently accompanied by resistance studies that can expedite the understanding of how the drug works in cells and what targets may be specifically affected.

In humans, cancer therapies are essentially administered through multiple administration regimens, *i.e.* split doses. Proportional therapeutic effectiveness of a drug is contingent upon which cycle of therapy the patient is receiving. For example, the first line of treatment gains the greatest antitumor effect. Each subsequent cycle reduces the therapeutic benefit by about fifty percent. Clinical prognosis is also influenced by how big tumors are at the onset of therapy. If breast cancers are discovered through early detection, there may still be as many as $10^6$ to $10^7$ cells at the time of diagnosis. Thus even after several rounds of treatment, the cells remaining may establish acquired resistance properties and repopulate, leading to disease relapse. With the advent of focus on targeted therapies, there is an evolving literature on adaptive changes associated with mutations in very specific drug targets. For example, non-small cell lung cancer patient responses to the tyrosine kinase inhibitor gefitinib are frequently short lived. Patient relapse can be a function of the presence of low densities of mutations in the targeted EGFR receptor that gain a greater prevalence following initial drug treatments. Ongoing drug development efforts seek to anticipate this resistance mechanism and use new agents that circumvent this adaptive resistance. This is but one example of how knowledge of resistance is fueling the search for effective therapeutic approaches. More examples follow in the proceeding sections.

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