

LIPID/POLYMER NANOPARTICLES AS TOOLS TO IMPROVE THE THERAPEUTIC ACTIVITY OF EXISTING AND EMERGING ANTICANCER DRUG COMBINATIONS

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Cancer is a complex disease and virtually all chemotherapy regimens for treating cancer utilize drug combinations selected to affect several targets that contribute to cancer cell survival and disease progression. Although drug combinations are the standard of care for patients with advanced cancer, new anticancer drugs are typically first introduced in patients as single agents and only after many years of clinical trials are these single agents combined with other drugs to determine their optimal role in cancer treatment. This process needs to change if patients are going to receive the full benefit of the arsenal of approved cytotoxic/cytostatic agents and emerging molecularly targeted therapeutics. It is clear that drug delivery systems will play an important role in the development and use of drug combinations for the treatment of cancer and the objective of this discussion is to highlight how existing and emerging drug carriers can be used as an enabling technology to create fixed ratio anticancer drug combination products for the treatment of systemic disease.

The foundation of a drug combination development process has been based on two scientific approaches. Historically, the rationale for selection of agents to be used in a given combination relied on use of different classes of anti-cancer drugs that exhibited proven therapeutic activity as single agents as well as non-overlapping toxicities. Effective drug combinations were subsequently developed on a trial and error basis that took years to optimize, particularly when considering the use of treatment protocols relying on more than two agents. Currently, effective drug combinations are being identified preclinically by means of cell-based screening assays and treatment of animal models of cancer. These assays have, to date, been used to identify whether two (or more) anticancer agents exhibit a therapeutic activity that is greater than that expected based on the combined activity of the individual agents. This is typically referred to as a super-additive or synergistic combination interaction. Careful examination of these *in vitro* and *in vivo* data, however, clearly demonstrate that such combination effects for a given pair of cancer drugs are dependent on the drug-to-drug ratio used in the experimental design as well as the fraction of affected cells. Thus a highly synergistic interaction may be observed at one drug-to-drug ratio, but not another. Also a particular drug combination may prove to be highly synergistic, but this synergy is only observed when the fraction of affected cells is small. Based on these considerations, it is clear that the two approaches outlined above must be integrated in order to identify drug combination products that exhibit the greatest activity (as measured by *in vivo* models), under conditions that insure the combination interacts in a manner where this activity can be achieved with the least amount of each individual drug (the consequence of synergy) and reduced toxicity (reduced drug doses and use of agents with non-overlapping toxic side effects).

In view of the above, it is possible to proactively design drug combinations based on definable and measurable parameters. This design process could take into consideration drug scheduling effects and tumor response data, but for simplicity our research team has chosen to focus on the development of fixed ratio drug formulations, where two or more agents are administered simultaneously. In addition, drug carrier technology has been used in the design of these fixed ratio products in an effort to optimize the simultaneous delivery of the combined agents to the site of action. Examples will be provided to illustrate, using *in vitro* and *in vivo* tumor models, the benefits that can be achieved when using liposomal drug carrier formulations in the development of a fixed ratio product, but the discussion will conclude with a broader conceptual approach as to how nanoparticle technology comprising various materials (lipids, polymers, proteins and peptides) can be used to generate fixed ratio combinations of therapeutic value in the treatment of cancer.