PHYSICS AND ASTRONOMY COLLOQUIUM

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"Lipids, Drugs and Metals: Ingredients for making therapeutically effective anticancer nanomedicines"

Abstract

One of the research projects that I completed during my PhD concerned the use of safranine, a dye used to assess mitochondrial membrane potentials. When this dye was added to liposomes with a transmembrane potential, the dye redistributed to the inside of the liposomes and under appropriate conditions >98% of the dye became trapped within the liposomes. This observation led to "remote" drug loading methods, where drugs were added to pre-formed liposomes with a transmembrane ion gradient and subsequently redistributed to the liposome interior. This methodology has evolved, with one variation relying on use of encapsulated divalent metal ions that complex candidate drugs bearing appropriate binding ligands. Doxorubicin, as an example, can complex manganese trapped within the liposome. A color change accompanied drug encapsulation as the solution went from an orange to purple. The technology described has provided a versatile method to form metal drug complexes within liposomes. The remote loading technology enabled development of many drug candidate nanomedicines some of which were subsequently developed and approved by regulatory bodies, including MyoCet, Marqibo, and Vyxeos. The latter refers to a fixed ratio drug combination formulations; a formulation of cytarabine and daunorubicin for treatment of AML. The nanomedicines prepared with single drugs or drug combinations that have been developed to date represent successes and illustrate how academic research can lead to translational opportunities with commercial and therapeutic potential. However, these formulations are simply not able to overcome the challenges faced when trying to treat patients with metastatic cancers; the patient population that represent the greatest clinical challenge. The challenges that need to be overcome for these patients include: (i) the heterogeneous microenvironment within tumors that define barriers to optimal drug delivery as well as the genetic heterogeneity that contributes to cancer cells exhibiting differing sensitivities to drugs; (ii) cytoprotective responses that limit the effectiveness of drugs when first used; and (iii) the inability to deliver drugs in a manner that ensure appropriate exposure at all sites where tumors grow. To address these challenges we are now trying to integrate discoveries made in immune mediated cancer cell death with nanomedicine technologies to designed best in class combinations for patients with refractory (insensitive or resistant) metastatic cancers.

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Elliott 226