The Metaplex Technology: A solution to the development of poorly soluble metal-binding small molecules

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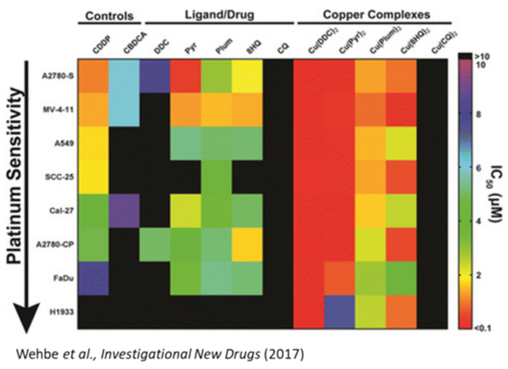
Introduction

- Metal complexes such as copper complexes are useful in treating platinum-resistant cancers



Wehbe *et al., Investigational New Drugs* (2017)

Clinical Limitations

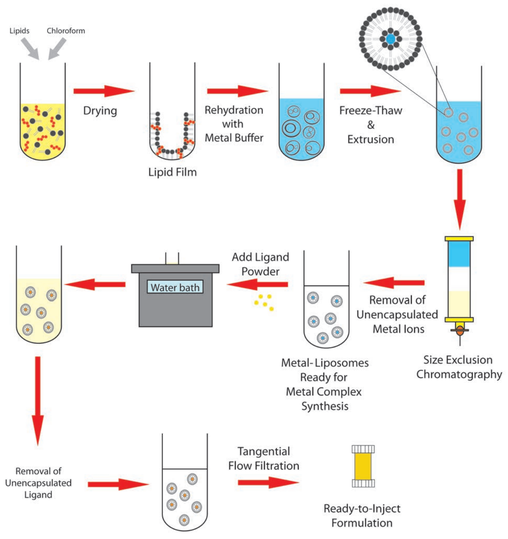
- 70% of compounds that are potent in vitro never translate in vivo due to insolubility
- Many therapeutically active metal complexes are essentially insoluble

Hypothesis

Metal complexes (Metaplex) can be synthesized within lipid vesicles and the resulting formulation will be suitable for parenteral administration and will be therapeutically active.

Experimental Design & Methods

Formulation Preparation



Results

The Metaplex platform improves solubility and Flavopiridol fully demonstrates the robustness of Metaplex

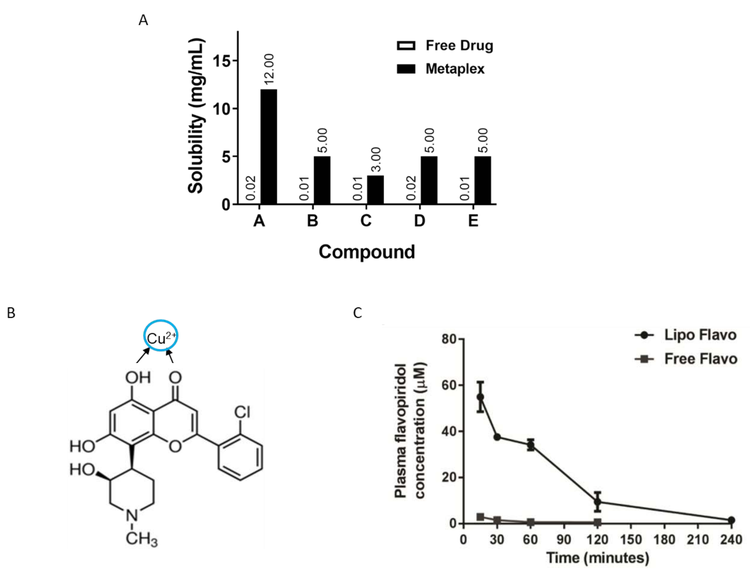


Figure 1. The Metaplex platform improves the apparent solubility of drugs by magnitude of folds (A). Flavopiridol is a semi-synthetic flavonoid that is capable of forming complexes with copper ions (B). The liposomal Metaplex formulation of Flavopiridol showed significantly higher blood levels (C). All data points are plotted as means ± SEM.

The Metaplex Flavopiridol formulation demonstrated improved efficacy in tumour-bearing murine models

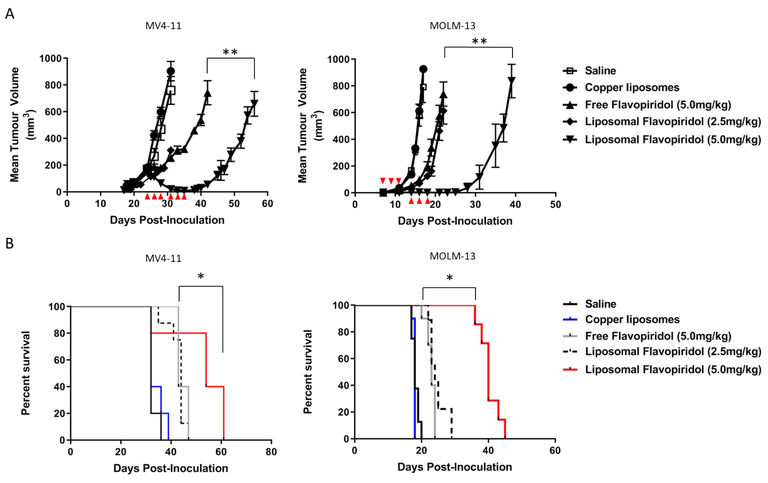
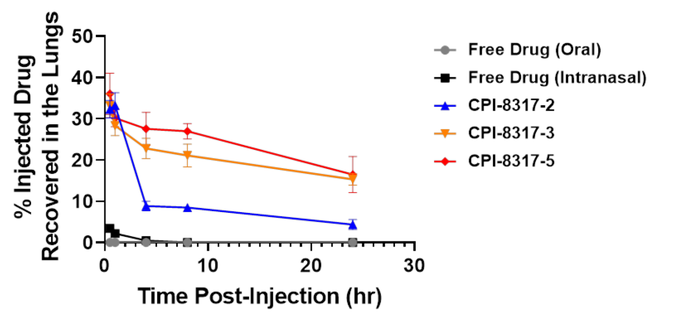


Figure 2. Female NRG mice were inoculated subcutaneously with MV4-11 (left panels) and MOLM-13 (right panels) acute myeloid leukemia cells with 50μL of 1x106 cells/mL and 0.5x106 cells/mL, respectively. Tumour-bearing mice were then injected intravenously with liposomal and free flavopiridol formulations (Free flavopiridol - 5mg/kg; Liposomal flavopiridol – 2.5mg/kg, and 5mg/kg) every Monday, Wednesday, and Friday for two weeks. Liposomal flavopiridol was at least two times more potent than free flavopiridol formulation, leading to delayed tumour growth at half the drug dose (A). At 5mg/kg, liposomal flavopiridol resulted in significantly improved overall survival compared to free flavopiridol formulation (B).

Results

The utility of the Metaplex platform extends to inhalable formulations to treat respiratory infections such as Covid-19

A



B

	Oral	Aerosolized	Aerosolized Nanoparticle
Rapid delivery to the lungs	X	✓	✓
High local concentration	X	✓	✓
Low systemic exposure (safety)	X	✓	✓
Controlled release of drug over time	X	X	✓

Figure 3. Metaplex formulations of CPI-8317 demonstrated >500 fold increase in total drug exposure in the lungs compared to "free" drug when injected intranasally into mice (A). Compared to oral formulations, aerosolized nanoparticles allow for rapid delivery to the lungs, with high local concentration and low systemic exposure, as well as controlled drug release over time (B).

Conclusions

- The Metaplex technology uses metal chemistry and nanotechnology to enable small molecules (even poorly soluble ones) for clinical development.
- Metaplex formulations show improved solubility, improved drug exposure, decreased toxicities, and enhanced therapeutic activity.
- The Metaplex platform is versatile beyond parenteral applications and can be used to formulate aerosolized or inhaled therapeutics.

Acknowledgements

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