Title: Modular peptide nano-carrier design for the discovery of high-drug loaded nanoparticles

While nanoparticles have shown promise in enhancing delivery of drugs to areas of interest to minimize systemic side effects, many have low loading efficiencies. Co-assembly of drugs with carriers is an attractive alternative that can significantly increase loading and encapsulation[1]. However, very little is known about the process of co-assembly, or how it changes with different drugs. Peptides offer the opportunity to probe for motifs that may be important in co-assembly due to their wide chemical space and facile synthesis[2]. To this end, we used an array of 8 pentapeptides and 23 chemically diverse drugs to assess if there was a preference for a particular peptide scaffold. Scaffold design varied in arrangement of aromatic tryptophan moieties, charge, and rigidity. We screened for sub-300nm size and enhanced stability of the particles in aqueous solutions. We identified 7 hits out of 184 formulations. Six of the seven hits that met both criteria contained peptides of alternating aromatic residues. Hits were comprised of up to >98% drug. Molecular dynamics simulations of hits were conducted to further understand interactions between peptides and drugs. Out of the positive candidates from the screen, two peptides were studied in detail for their interaction with the JAK2/FLT3 inhibiter, lestaurtinib, in proof-of-concept studies in models of acute myeloid leukemia. We demonstrate that particles can be engineered from rational peptide design and used for therapeutic applications.

1. Shamay, Y. *et al.* Quantitative self-assembly prediction yields targeted nanomedicines. *Nat Mater* (2018) doi:10.1038/s41563-017-0007-z.
2. Bobo, D., Robinson, K. J., Islam, J., Thurecht, K. J. & Corrie, S. R. Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date. *Pharm Res* **33**, 2373–2387 (2016).