Super-selective nanomedicines

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We have also advanced our ability to deliver drugs combining the high selectivity of active molecules with molecularly engineered carriers equipped with the necessary attributes to navigate biological environments. A critical element of such a nanomedicinal effort is the introduction of ligands that enable targeting and selectivity to guide carriers across biological barriers. This is now allowing to extend drug discovery to target biological macromolecules that are not accessible via simple passive diffusion such as the inside of cells or the central nervous system. However, tight control on the selectivity of drugs and nanomedicines' interaction with biological systems is paramount for the development of targeted therapies. The large number of synthetically tuneable parameters makes it difficult to identify optimal design "sweet spots" without rational guiding principles. Here I address this problem combining super-selectivity theory (SST) with analytical models from soft matter and polymer physics into a unified theoretical framework. Starting from an archetypal system, a polymer-stabilized nanoparticle functionalised with targeting ligands, we use our model to identify the most selective combination of parameters in terms of particle size, brush polymerisation degree and grafting density, as well as tether length, binding affinity and ligands number. I further discuss how to combine multivalent interactions into multiplexed systems which act holistically as a function of the density of more than one receptor type, so as to achieve binding only when multiple receptors are expressed above a threshold density. I christen this as "phenotypic" targeting and I propose its use for drugging unique cell populations enabling personalised therapies. I will show few examples of phenotypic targeting in both blood brain barrier crossing, cancer targeting and immune cell recognition. Finally I will combine phenotypic targeting with chemotaxis in all effect amplifying molecular interaction to create organotropic diffusion profile. I will show this with a fully synthetic, organic, nanoscopic system that ex- hibits attractive chemotaxis driven by enzymatic conversion of glucose. I will finally demonstrate that the chemotactic behaviour of these nano- swimmers, in combination with LRP-1 (low-density lipoprotein receptor–related protein 1) targeting, enables a fourfold increase in penetration to the brain compared to non-chemotactic systems.

References

1. Battaglia et al ***ChemRxiv***. 2018 DOI: 10.26434/chemrxiv.5647969.v1;
2. Joseph et al. ***Science Adv.*** 2017, 3, 8, e1700362;
3. Tian et al. ***Sci. Rep.*** 2015, 5, 11990