Fundamental behaviour of nanoparticles revealed in zebrafish embryo

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Up to 99% of intravenously administered nanoparticles are cleared by the reticuloendothelial system (RES) cell types in the liver and spleen. The precise biological mechanisms which underpin clearance are not, however, fully understood.

Here, we use the transparent and versatile embryonic zebrafish as animal model to rapidly screen the behavior of nanoparticles *in vivo*. The ability to visualize fluorescent nanoparticles at cellular resolution and across entire living organisms has given us an unprecedented understanding of the fundamental behavior of nanoparticles *in vivo*.

In this presentation, I will demonstrate how key RES cell types of the embryonic zebrafish are genetically and functionally analogous to the mammalian liver sinusoidal endothelium. Furthermore, I will show how we identify *stabilin-1* and *stabilin-2* as the main receptors for scavenging anionic nanoparticles [1] by studying the distribution of various types of nanoparticles in the zebrafish in combination with CRISPR/Cas technology. The ligands that are cleared by zebrafish *stabilin-1* and *-2* receptors include specific (glyco)proteins, polyanionic carbohydrates, endotoxins, viruses and (in)organic nanoparticles -including liposomes used for clinical drug delivery- providing an alternative route to the nanoparticle clearance performed by macrophages.

Importantly, nanoparticle-SEC interactions can be blocked by dextran sulfate, a competitive inhibitor of *stabilin-1, stabilin-2* and other scavenger receptors. The importance of particle size in the nanomedicine field is also highlighted here, showing that small particles are the more convenient to avoid liver sequestration by scavenger receptors and to promote internalization in the cell of interest. Finally, we exploit nanoparticle-SEC interactions to demonstrate targeted intracellular drug delivery resulting in the selective deletion of a single blood vessel.

The identification of *stabilin-1* and *stabilin-2* as mediators in the uptake of anionic nanoparticles, and how to avoid such interaction, is an example of how the zebrafish embryos provides a new and powerful model system to study the mechanism that is required for the role in nanoparticle-mediated drug delivery.

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References

[1] Campbell F, Bos FL, Sieber S., Arias-Alpizar G, Koch BE, Huwyler J, Kros A, Bussmann J. *ACS Nano*20181232138-2150 (2018).

Figure

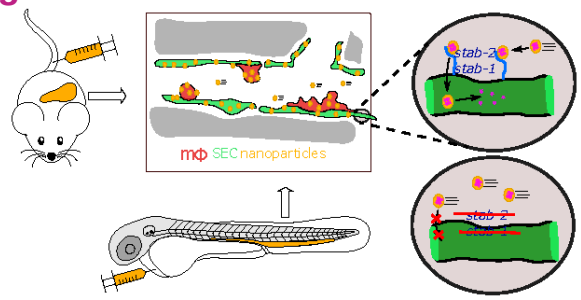

Figure 1. Schematic representation of liver endothelium in mice and zebrafish embryo. Nanoparticles endocytosed by receptor-mediated stab-1 and stab-2 or circulating in the absence/inhibition of stab-1 and stab-2. Modified from [1]