Considerations on the design of nanoparticles for diagnostic, theranostic and therapeutic purposes.

Fabian Kiessling

Nanoparticles are frequently suggested for medical use. However, often basic considerations on its pharmacokinetic properties are not taken into account and its optimal characteristics have to be very different if they are considered for diagnostic, theranostic of therapeutic purposes.
Nanoparticles larger than 5 nm tend to be removed by the reticulo-endothelial system (RES). Thus, tissues belonging to the RES like liver spleen and lymph nodes can be targeted with such nanoparticles. Furthermore, if phagocyting cells migrate to pathological sites (e.g. an inflammatory lesion or an atherosclerotic plaque), the nanoparticles will also be accumulated, which has been shown for instance for (U)SPIO. Phagocyting cells can also be labelled ex vivo with diagnostic nanoparticles, which opens great perspectives for cell tracking and the imaging of tissue engineered transplants.
Adding stealth properties to the nanoparticles increases their circulation time giving them more time to extravasate in tissue with high vessel permeability. This so called EPR based accumulation is the basis for most tumor targeted nanomedicines. However, the therapeutic benefit over small probes is often only moderate since EPR is variable among patients and even heterogeneous within the same tumor. Here, theranostic agents and companion diagnostics can help to preselect patients and to individualize therapy. In addition, in tumors larger nanoparticles tend to accumulate just outside the vasculature, do hardly penetrate the stroma and thus do not reach the cancer cells. Thus, a refined balance between accumulation and penetration may be therapeutically superior over just maximal accumulation. In this context, active targeting does only marginally help since it does not improve nanoparticle distribution and accumulation but just retention. For example, it was shown for targeted polymers that the overall accumulation can even decrease after adding targeting ligands since increasing recognition of the nanoparticles by the RES lead to faster clearance, lower blood half-life and thus, reduction of EPR based accumulation. Active targeting becomes more evident for small nanoparticles with good penetration and rapid exchange between the tissue compartments but insufficient retention, which mostly are nanoparticles below 5 nm in size. These are the ones that are most suited for molecular imaging purposes as well.
Thus, the intended medical application should route the decisions about design of nanoparticles and all aspects relevant to its in vivo application including the expected superiority over existing clinical gold standards should be considered from beginning on. Following this conduct, many failures in the transition from in vitro to in vivo application can be avoided.