

On the Disregarded Effects of Biological Fluids in the Delivery of Nanomedicines & how Lessons in Simplicity Should Shape the Future of Drug Delivery

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In the drug delivery field, interest goes to developing 'intelligent' nanoscopic particles that are capable of efficiently delivering biopharmaceuticals to target cells. These nanoparticle formulations should fulfill several requirements. Besides efficiently encapsulating the biopharmaceuticals, they also have to provide protection against degradation during the entire delivery process. Furthermore, the nanoparticles should not aggregate e.g. after intravenous injection. Nor should they release the therapeutic cargo while being suspended in the blood circulation or when traversing the extracellular space. Release of the biopharmaceuticals in many cases should only occur after being internalized in the target cells. Obtaining a better insight into the physicochemical and biophysical behaviour of the nanoparticles during the various phases of the delivery process is required to achieve efficient optimization of their structure and composition. For more than 10 years, our group has been exploring the use of advanced fluorescence microscopy methods for this purpose. This lecture will overview what we learnt regarding the use of light based methods (like fluorescence recovery after photobleaching-FRAP, fluorescence correlation spectroscopy-FCS, fluorescence Single Particle Tracking-fSPT) for the characterization of the behavior of nanomaterials in complex biological fluids like blood, sera, eye vitreous, lung mucus,.... Special emphasis will be on a recently developed light based method which seems successful in a challenging application for which no alternative technique is currently available, namely the determination of the extent of vascular permeability which is an important parameter in the extravasation of nanomaterials from blood into the tissues.

Besides the use of *light to measure* critical steps in the delivery of drugs from nanomaterials we got a recent interest in the use of *light to deliver* biologically active compounds. Laser-induced photoporation, especially in combination with gold nanoparticles, is a physical method that is receiving increasing attention for delivering macromolecules in cells. By allowing gold nanoparticles to bind to the cell membrane, nanosized membrane pores can be created upon pulsed laser illumination. Depending on the laser energy, pores are created through either direct heating of the AuNPs or by vapour nanobubbles (VNBs) that can emerge around the AuNPs. In our hands photoporation seems to be very useful for efficient high-throughput macromolecular delivery in live cells.

Although we should always be on the lookout for novel yet unambiguous concepts and ideas that might shape the next generation of breakthrough technologies in drug delivery, the last part of this lecture will try to convince the audience that, in the end, simple materials and simple drug delivery concepts are urgently needed to make significant steps forward in drug delivery.

Stefaan C. De Smedt (°1967) graduated from Ghent University in 1995 and joined Janssen Research Foundation. He has been a post-doctoral fellow at the universities of Ghent and Utrecht. In 1999 he became Professor in Physical Pharmacy and Biopharmacy at Ghent University where he founded the Ghent Research Group on Nanomedicines. He served as dean of his Faculty from 2010 till 2014. He is a member of the Board of Directors of Ghent University. Since 2004 Dr. De Smedt serves as the European Associate Editor of the Journal of Controlled Release; In 2015 he became Editor of JCR. His research is at the interface between drug delivery, biophysics, material sciences and advanced optical imaging. Dr. S.C. De Smedt received the Scott Blair Biorheology Award, the Controlled Release Society Young Investigator Award 2006 and the APV Research Award 2010 for Outstanding Research Achievements in Pharmaceutical Sciences. Dr. Stefaan De Smedt holds patents on carriers for drug delivery and diagnostics. He is a scientific founder of Memobead Technologies, a spin-off from Ghent University, whose technology is currently under further development by **Biocartis** (Lausanne and Mechelen) and Mycartis (Gent).