LECTURE INVITATION

**Extracellular Vesicle-mediated RNA Delivery: from Mechanistic Insights towards Therapeutic Applications**

**Prof. Pieter Vader**

**The lecture will take place on Thursday 11th of May 2023 at 14.00h in seminar room -1.4 Frederich Sertürner**

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*Registration not required.*

**Contact**

Prof. Kevin Braeckmans

**Abstract**

Extracellular vesicles (EVs) form an endogenous system for information transfer between cells. Since the recent discovery that EVs are also capable of functionally transferring RNA molecules, they are increasingly being considered as therapeutic RNA delivery systems. Despite extensive research into the engineering of EVs for RNA delivery, our understanding of the pathways and mechanisms regulating EV-mediated RNA delivery and processing is limited. Moreover, little is known about how their intrinsic RNA delivery efficiency compares to current synthetic RNA delivery systems.

To increase our understanding of the biology underlying EV-based intercellular transfer of RNA, we developed a novel CRISPR/Cas9-based reporter system in which eGFP expression is activated upon functional delivery of targeting single guide RNAs (sgRNAs) that allows study of EV-mediated RNA transfer at single-cell resolution. This allowed us to uncover various novel genes that play a regulatory role in functional RNA transfer. Furthermore, we employed this system to compare the delivery efficiency of EVs to clinically approved state-of-the-art DLin‐MC3‐DMA lipid nanoparticles and several in vitro transfection reagents. We found that EVs delivered RNA several orders of magnitude more efficiently than these synthetic systems. This finding supports the continued research into EVs as potential RNA delivery vehicles.

To overcome challenges related to the difficulty of RNA loading into EVs, we prepared EV-liposome hybrid nanoparticles and evaluated them as siRNA delivery systems in terms of cellular uptake, toxicity, and gene-silencing efficacy. We show that hybrids combine benefits of both synthetic and biological drug delivery systems and might serve as future therapeutic carriers of siRNA.

Our data underline the potential of EVs as RNA delivery vehicles and highlight the need to study the mechanisms by which EVs achieve their efficiency. This may in turn contribute to the development of more efficient EV-based RNA delivery systems and accelerate clinical adoption of therapeutic EVs.

**Biography**

**Pieter Vader** graduated in Chemistry (B.Sc., 2005) and Drug Innovation (M.Sc., 2007) from the University of Utrecht. He earned his PhD degree in 2012 from the University of Utrecht on the subject of targeted delivery of siRNA to inhibit tumor angiogenesis. From 2012 to 2014, Pieter was employed as a (senior) postdoctoral fellow at the University of Oxford, UK, in the lab of Prof. Matthew Wood, supported by a NWO Rubicon fellowship. The research topic was development of small RNA-loaded extracellular vesicles for targeted delivery. In 2014 he moved back to The Netherlands to continue his work at the University Medical Center Utrecht. Currently, he is Associate Professor at CDL Research and at the Department of Experimental Cardiology. His main research interests are in the field of therapeutic applications of extracellular vesicles, including unraveling the mechanisms underlying extracellular vesicle-mediated cargo transfer. His research has been supported by a NWO Veni Grant (2014), ERC Starting Grant (2019), Dutch Heart Foundation Dekker Senior Scientist Grant (2019), and NWO Vidi Grant (2020). In 2021, Pieter was awarded the Prix Galien Research Award for his work on drug delivery.