# REPURPOSING OF CATIONIC AMPHIPHILIC DRUGS AS NANOPARTICLE ADJUVANTS FOR CELLULAR DELIVERY OF RNA THERAPEUTICS

## Introduction

RNA drugs are an emerging class of therapeutics that address diseases at the genomic and/or transcriptomic level. Following cytosolic delivery, siRNAs activate the RNA interference (RNAi) pathway leading to the sequence-specific silencing of genes. As an advantage over conventional small molecule inhibitors and monoclonal antibodies, RNA drugs can target virtually any human gene, offering a broad spectrum of biomedical applications. However, their widespread clinical translation is hampered by many extra-and intracellular barriers. RNAs are negatively charged macromolecules that cannot cross biological membranes, which makes cellular delivery challenging. As access to the cytosol of target cells is key to their therapeutic effect, efficient intracellular delivery of RNA drugs remains the most important barrier to overcome. Encapsulation of RNA into synthetic nanoparticles (NPs) allows its internalization by cells through endocytosis followed by release of the encapsulated RNA into the cytosol (i.e. endosomal escape), albeit the latter occurs with very low efficiency (typically <1% of the internalized dose).

## Technology

Researchers at Ghent University have identified cationic amphiphilic drugs (CADs) with divergent structure and pharmacology as strong promotors of intracellular nanoparticle-mediated siRNA delivery. CADs are able to induce transient pores in the membrane of endolysosomes, leading to enhanced cytosolic delivery of siRNA and improved target gene silencing.

## Applications

This technology can be used for the treatment of pathologies (both via local and systemic delivery routes) with an unmet medical need, where delivery of siRNA can be of therapeutic benefit. Two pharmacological approaches can be envisioned, i.e. a sequential approach in which the CAD and nanocarrier are administered separately from each other, as well as an integrated approach, in which the CAD and RNA therapeutic are co-encapsulated in the same nanocarrier and administered together.

## Advantages

The presented technology

- ✓ targets (endo)lysosomes, where the majority of the intracellular RNA dose will accumulate
- ✓ improves delivery efficiency, thus enabling dose reduction
- ✓ repurposes clinically approved drugs with a well-documented safety profile
- ✓ uses existing drugs of which the pharmacology can synergize with desired therapeutic outcome
- ✓ is applicable for different CAD, nanocarrier and cargo combinations
- ✓ can be extended to improving cellular delivery of other membrane-impermeable therapeutics

## State of development

*In vitro* proof-of-concept has been obtained for a selection of CADs, showing enhanced siRNA and/or antisense oligonucleotide delivery via a polymeric nanocarrier in different cell types, including non-small cell lung cancer cells. Moreover, combining a CAD antihistamine with a PLK-1 targeting siRNA allowed a 2-log improvement in cell killing in the same (p53 deficient) cell model. Screening of a compound library allowed the identification of >50 cationic amphiphilic drugs that demonstrate an adjuvant effect on siRNA delivery. Finally, it was demonstrated that repeated sequential exposure of transfected cells to an antihistaminic CAD could induce multiple rounds of cellular siRNA delivery, indicating that endolysosomes can indeed be used as intracellular small RNA drug depots.

## Partnership

Ghent University is seeking a licensing partner or a collaboration to explore the CAD adjuvant technology in combination with proprietary (nano)carrier platforms for RNA delivery in the disease of interest and to validate the technology for both local and systemic therapeutic applications.

## Intellectual property

"Molecular adjuvants for enhanced cytosolic delivery of active agents"
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## The Scientists

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## References

Joris F., De Backer L., Van de Vyver T., Bastiancich C., De Smedt S.C., and **Raemdonck K.**, Repurposing cationic amphiphilic drugs as adjuvants to induce lysosomal siRNA escape in nanogel transfected cells. *J. Controlled Release* 2018, 269: 266-276. Impact factor: 7.877, category: PHARMACOLOGY & PHARMACY, rank: 9/261

## Keywords

Nanomedicines, RNA therapeutics, cationic amphiphilic drugs, endosomal escape, intracellular delivery

## Figure

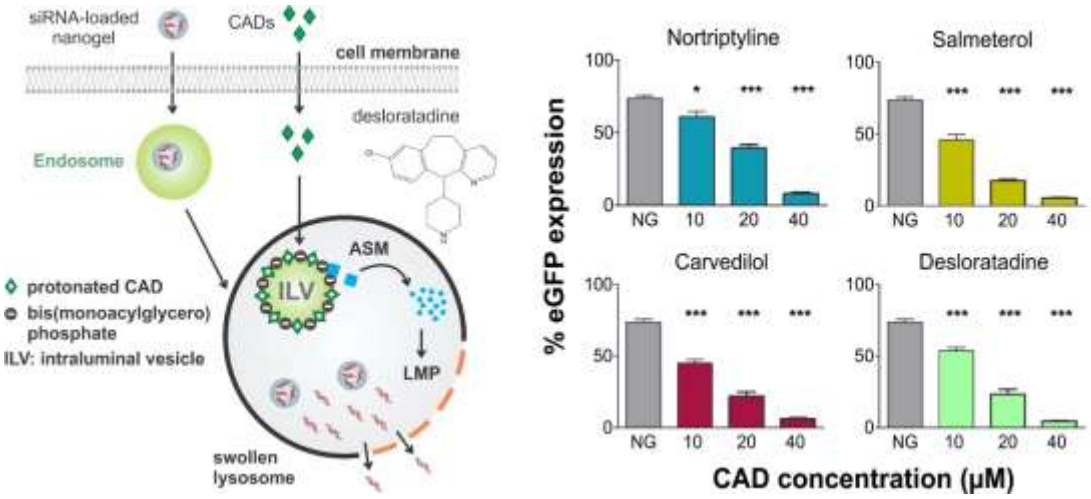


**Figure.** Through functional inhibition of acid sphingomyelinase (ASM), cationic amphiphilic drugs (CADs) induce non-lethal lysosomal membrane permeabilization (LMP), enhancing the cytosolic delivery of siRNA and improving target gene knockdown.

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