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Title: Customized DNA-based nanocarriers to boost heart healing

Acronym: DNABEATS

Consortium:

UNIVERSITY OF TARTU

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ABSTRACT

Heart disease (HD), particularly myocardial infarction (MI), and its evolution towards heart failure (HF) is a leading cause of death worldwide and in Europe. The project aims to break the ground in the fight against HD and its associated socio-economic burden by creating innovative nanomaterials to promote efficient cardiac regeneration through gene therapy. Precisely, microRNAs (miRs) are promising therapeutics that have robustly proved heart regeneration capacity in vivo after MI, even in large animals. However, advanced delivery strategies are required to boost their clinical applicability by surmounting miRs' biological instability and attaining their selective targeting of the heart without reaching healthy organs. The project's primary goal is to create fully functionalized nanocarriers that deliver cardio-regenerative miRs selectively to the heart. Specifically, cutting-edge DNA nanotechnology is proposed to build DNA-based Nanocarriers (DNCs) that outperform other gene delivery nanocarriers in terms of reproducible production, intrinsic biodegradability, and simplicity to house large amounts of miR cargo. DNCs will be thoroughly customized to address current limitations of gene delivery related to cell targeting, cellular uptake, and endosomal escape. Namely, DNCs will contain DNA aptamers to target miR delivery to human cardiac cells and innovative endosomolytic peptides to enhance intracellular doses. To accomplish this overall goal, our project will address four specific objectives: (1) developing fully functional DNCs, (2) characterizing DNC's biological properties, (3) demonstrating DNCs selectivity and therapeutic efficacy in a clinically relevant model based on human-derived cardiac cells and (4) performing a thorough investigation on DNCs' biocompatibility in vitro and in vivo. Biocompatibility studies will focus on nanotoxicity analysis performed primarily on cells isolated from the blood (in vitro studies) and mouse models (in vivo studies). Additionally, nanomaterials' biodistribution and pharmacokinetics will be determined (in vivo studies on mouse models). The expected results of the project will allow: (i) generating essential knowledge on the interactions between DNCs and cells and living organisms (mice), (ii) attaining a complete physicochemical characterization of the DNCs, and finally, (iii) a complete biocompatibility assessment. Therefore, the project will verify the therapeutic potential of innovative DNC designed to improve heart healing.