

# Nanomedicines to tackle myocardial infarction: where are we now and where are we going?

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## ABSTRACT

Cardiovascular diseases (CVD) are responsible for the highest mortality rates globally. About one-third of the CVD-related casualties derive from ischemic heart diseases, which cause an irreversible injury to the myocardium. As a result of the very limited capacity of the heart tissue to recover from the ischemic insult, this usually leads to remodeling and scarring of the cardiac tissue, eventually progressing to irreversible heart failure. Currently, there is no major discovery of an effective cure to restore the function of an injured heart. Therefore, there is an unmet need to find a permanent solution for patients suffering from ischemic heart disease (IHD) and heart failure. In this regard, nanoparticles made of biomaterials called the attention of the scientific community as potential platform to deliver different therapeutics to the injured heart. Particulate nanomedicines, currently at the pre-clinical stage, are arising as a promising tool to provide minimally invasive treatment, an important aspect to take into account for clinical translation and patient compliance, and specifically deliver therapeutics to the injured myocardium. Here, we discuss about the current knowledge on the nanomedicines investigated for myocardial infarction, and how we see they can help and support medical doctors in shaping the future of IHD treatments.

**Key words:** heart diseases, myocardial infarction, nanomedicines, targeting

## HEART DISEASES AND NANOMEDICINES: CURRENT STATE

### Ischemic heart disease (IHD): statistics and facts

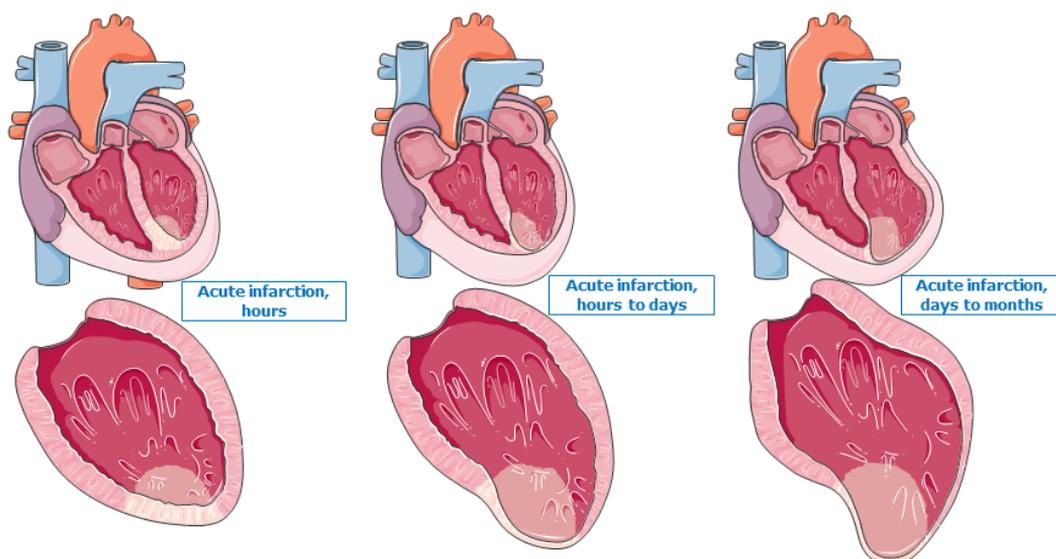
The world has seen tremendous development in the medical field, significantly impacting the health of the global society over the past few decades. Recent examples include the Human Genome Project (Lander *et al.* 2001) targeted therapies for cancer (Tran *et al.* 2017), as well as the development of primary preventive (e.g. control and treatment of hypertension, hypercholesterolemia, diabetes, and smoking decline), symptom-management therapies (e.g. timely use of thrombolysis therapy and percutaneous coronary intervention (PCI)), as well as secondary prevention therapies (statins, beta-blockers, ACE-inhibitors, angiotensin receptor blockers, aspirin and diuretics) for patients with established cardiovascular diseases (CVD) (Reddy *et al.* 2015, Arnett *et al.* 2019). Particularly, therapies for ischemic heart disease (IHD) have dramatically decreased the world mortality by 40% (Mensah *et al.* 2017). However, an astonishing 17 million people still die of CVD globally, particularly from heart attacks and strokes. This accounts

to approximately 31% of all deaths worldwide (WHO, 2017). In Europe, the impact of CVD on loss of productivity, combined with hospitalization and health-care costs amounts to a total of €210 billion per year (EHN, 2017).

IHD are the main cause of death among Finns. Although the same trend in decrease of mortality is verified in Finland (Salomaa *et al.* 1996), and men's and women's age-standardized mortality has decreased by over 40%, IHD still causes one in five deaths in men and one in six deaths in women, with almost 10,000 casualties reported in 2017 (Official Statistics of Finland, 2017). Due to an aging population and sedentary life-style, in addition to the increase in incidence of comorbidities, such as obesity, hypercholesterolemia, diabetes and hypertension, growing incidences of CVD are major drivers for the global myocardial infarction (MI) treatment market, expected to reach \$1.7 billion by end of 2022 (Zion Market Research, 2017).

### Nanomedicines for cardiovascular diseases

Myocardial Infarction (MI), commonly known as heart attack and inserted in the category of IHD,



**Figure 1. Schematic representation of post-myocardial infarction left ventricular remodeling. The acute phase encompasses thinning and elongation of the fibrous scar within the infarcted zone. Subsequent left ventricular dilation is caused by diffuse myocyte hypertrophy associated with increased apoptotic cell death (not shown) and increase in interstitial collagen. This image was constructed using Medical Servier Art (Servier Medical Art, 2019).**

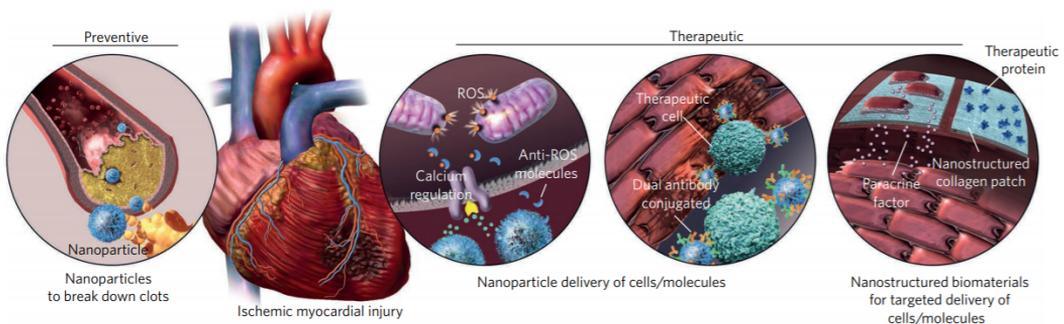
leads to death of the area of cardiac tissue upon blockage of a coronary artery, ultimately developing to an irreversible ischemic cardiomyopathy and heart failure, compromising severely cardiac function (**Figure 1**). Due to the poor turnover of cardiomyocytes and the inability of the heart to recover or regenerate from a cardiac insult, it is important to devise novel solutions to tackle the problem of irreversible heart failure.

Current therapeutic approaches to treat IHD, and more specifically MI, include secondary prevention pharmacological therapy stated above which decreases blood pressure, cardiac overload and risk of arrhythmia, as well as invasive procedures for restoration of reperfusion and aid blood systemic distribution with pacemaker and ventricular assist devices. These mainly manage the patient's symptomatology rather than restoring cardiac function, decreasing mortality and morbidity, and prevent to some extent the development of heart failure (Ibanez *et al.* 2018). Apart from heart transplantation (with its associated complications), despite continuous efforts put in the search for a cure for MI and heart failure, to date this has not been found.

The fundamentals of heart development and MI pathological processes at the cellular and molecular levels have been deeply investigated (Xin *et al.* 2013) in order to develop therapeutic solutions to restore cardiac function after MI. Nanotechnology, and the development of nanomedicines for repair/protection/regeneration of the heart upon an ischemic event, took off only a few decades ago, being at the pre-clinical stage of research for therapy of IHD. In fact, according to the European Medicines Agency, nano-

medicines are designed systems for clinical applications with at least one component at nanoscale size, which renders definable specific properties and characteristics to this kind of therapeutic platform. The purposes of nanomedicines are to: (1) tackle unmet medical needs, e.g. integrating efficacious molecules that otherwise could not be used because of their high toxicity and by exploiting multiple mechanisms of action; and (2) to maximize efficacy and reduce dose and toxicity, by allowing drug targeting, control the specific drug release, improve transport across biological barriers, and regulate preferential distribution within the body (*e.g.*, in the ischemic myocardial injury or in cancer lesion areas) (European Medicines Agency, 2019). Such therapeutic approach differs from the conventional drug therapy as it allows targeted delivery of therapeutics to the tissue of interest (in this case, the ischemic heart). The use of nanoparticles opens up a panoply of opportunities for new drug molecules that are very potent but possess poor physicochemical properties such as low solubility, easy degradation and enhanced toxicity: engineered nanoparticles protect labile cargos from degradation, as well as protecting the body from toxic effects of cargos with narrow therapeutic window that otherwise would distribute throughout the entire body.

It all started with simple liposomes, the most primitive forms of nanomedicines developed primarily for cancer, but later applied to MI (Levchenko *et al.* 2012). As bare nanocarriers are quite unspecific and are rapidly captured by the liver and reticuloendothelial system for clearance upon systemic administration, incorporation of stabilizers like poly-



**Figure 2. Nanomedicine-based strategies developed to tackle ischemic cardiomyopathy. (ROS = reactive oxygen species). Reprinted with permission from reference (Mahmoudi *et al.* 2017).**

ethylene glycol (PEG) to increase circulation time, and targeting moieties to direct the nanocarriers towards the ischemic cardiac tissue took place as early as 1995 (Khaw *et al.* 1995) in order to deliver more efficiently therapeutic drugs. From this point onwards, several nanomedicines have been developed for targeted drug delivery for therapy of MI, by using the most varied (bio)materials and targeting strategies (Ferreira *et al.* 2017, Ferreira *et al.* 2018). As a fast advancing field, nanoplatforms have been developed with mechanisms of action such that they can: (1) target and break down coronary artery plaques and prevent injuries caused by stenosis or occlusion of arteries – preventive nanomedicines; and (2) reduce adverse effects of reperfusion injuries and promote cardiac repair/salvage/regeneration after MI, through sustained and targeted delivery of cells, biomolecules and paracrine factors – therapeutic nanomedicines (Figure 2) (Mahmoudi *et al.* 2017). Our focus in this short commentary is mainly on the therapeutic nanomedicines for MI.

Different materials and different targeting strategies are employed to achieve a higher nanoparticle accumulation in the heart and higher therapeutic efficacy in different animal models (Ferreira *et al.* 2015, Mahmoudi *et al.* 2017). For example, SOMag5 magnetic nanoparticles are being used to aid the engraftment of embryonic and induced-cardiomyocyte cells to ischemic myocardium using a strong magnetic field, improving heart repair processes (Ottersbach *et al.* 2018). Liposomes have been functionalized with antibodies targeting the overexpressed angiotensin II type I receptor in the heart upon MI (Dvir *et al.* 2011). Due to advantages such as high drug encapsulation efficiency, polymeric multifunctional poly(glycidyl methacrylate) nanoparticles were developed for the transport of a combination of two therapeutics with antioxidant and anti-hypertrophic properties (Hardy *et al.* 2015). To tackle the invasive route of administration, calcium phosphate nanoparticles of very small size (50 nm) were developed for administration via inhalation route, for rapid translocation from the pulmonary tree to the bloodstream, and direct transport to the myocardium and targeted release of their therapeutic cargos (Miragoli *et al.* 2018). These are a few examples of the efforts put to develop nanomedicines, at the moment in the preclinical stage, to improve the quality of life of patients suffering from IHD in the future.

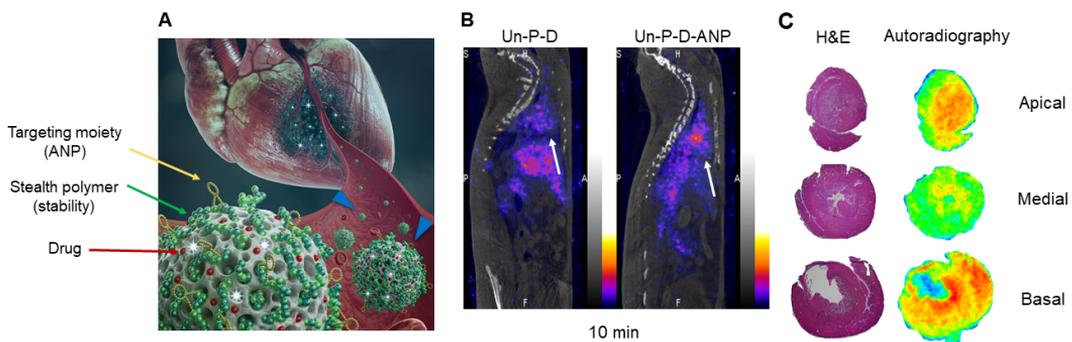
In Finland, and particularly at the University of Helsinki, such work has also been developed. At the

group of Nanomedicines and Biomedical Engineering ([www.3iregeneration.com](http://www.3iregeneration.com)), we have used porous silicon (PSi) and spermine-acetalated dextran to formulate nanomedicines for targeted drug delivery for therapy and imaging of cardiac ischemic injury, work that culminated in a recent Ph.D. thesis (Figure 3) (Ferreira, 2017). These materials were chosen due to their intrinsic properties, such as biocompatibility, biodegradability, customized particle preparation, surface functionalization, efficient drug loading and encapsulation, and tunable release of the therapeutic cargos. Both PSi and dextran-based nanoparticles were stabilized for higher circulation time in the bloodstream, and further decorated with atrial natriuretic peptide (ANP) for targeting purposes because the release of natriuretic peptides and the intrinsic increase in expression of their receptors is one of the markers for cardiac injury. Both PSi and dextran nanoparticles showed good cytocompatibility in cardiac cell cultures and biocompatibility (Tölli *et al.* 2014, Ferreira *et al.* 2016, Ferreira *et al.* 2017). We have also demonstrated specific cardiac cell–nanoparticle interactions through natriuretic peptide receptors, in the presence of ANP in the nanoparticles' surface, showing the successful development of targeted nanomedicines to the heart (Ferreira *et al.* 2016, Ferreira *et al.* 2018). Upon labeling the nanoparticles with radioisotope Indium-111, the nanoparticles displayed a preferential accumulation and selectivity towards the endocardial layer of the ischemic (but not normal) heart in a rat MI model (Figures 3A and 3B). *In vivo* delivery of a cardioprotective small drug molecule (Kinnunen *et al.* 2018) by the developed PSi-nanoplatform showed attenuation of the extracellular signal-regulated kinase pathway that is involved in the hypertrophic signaling of the injured heart (Ferreira *et al.* 2017). In addition, the development of bifunctionalized and dual-loaded dextran-based nanoparticles for potential application in heart cellular reprogramming was proven successful, by utilizing acidic pH-triggered drug delivery of the two poorly water-soluble cargos. Subsequent treatment of cardiac non-myocytes showed therapeutic modulation of key signaling pathways involved in the direct fibroblast reprogramming into cardiomyocytes (Ferreira *et al.* 2018). Thus, the works described here provide insights that may be useful for the future development of nanomedicines with cardioprotection and cardiac regeneration therapeutic purposes for application in the clinic.

## CONCLUSIONS

Overall, although the advancement of nanomedicines field for therapy of IHD is still in the pre-clinical stage, it definitely shows therapeutic potential for promoting repair and/or regeneration of the injured heart tissue, especially in the acute stage of MI. However, translation to the clinical setting remains elusive, where limitations like the ability to overcome biological barriers, time-consuming and complex preparation of the nanomedicines, their reproducibility and scalability, are factors that are yet challenging to be addressed in the clinical development and commercialization. Furthermore, new cardiac markers that would allow a more efficient targeting are still to be discovered, being that some of the research

focus in this field is shifting towards other nanoparticle-related therapeutic strategies, such as the utilization of extracellular vesicles, due to their discovered intrinsic cargos and roles in cellular processes that possess potential to improve cardiac function (Bollini *et al.* 2018). We believe that with the technological advancements where novel and more advanced nanomedicines are being developed, there is an increased hope that these could be translated to the clinic in the near future. As more and more proof-of-concept nanomedicines emerge for MI therapy, new insights on the nanomedicines' particularities, versatility, and advantages offer a wide range of opportunities for the development of adaptable tools to fight MI and heart failure.



**Figure 3. Targeting strategy with imaging modality of nanomedicines to the MI. (A) Heart-targeted nanomedicines in the blood stream (blue triangle), ANP targeting moiety (yellow arrow), stabilizing polymer coat (green arrow) and nanocarrier-loaded drug (red arrow). (B) Representative sagittal single-photon emission computed tomography (SPECT) images, showing the biodistribution of the nanoparticles at 10 min after intravenous administration in a MI rat model. White arrows indicate the location of the heart. Undecylenic acid modified thermally hydrocarbonized porous silicon NPs without (Un-P-D) and with (Un-P-D-ANP) targeting atrial natriuretic peptide. (C) Representative hematoxylin and eosin (H&E) stainings and autoradiograms of apical, basal and medial rat heart sections treated with the targeted nanomedicines. Red areas demonstrate higher regional nanoparticle accumulation. Reprinted and modified with permission from reference (Ferreira *et al.* 2017).**

## TIIVISTELMÄ

### Nanolääkkeet sydäninfarktin hoidossa: missä mennään nyt ja mihin suuntaan kehitys vie?

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Sydän- ja verisuonitaudit ovat maailmanlaajuisesti kaikkein yleisin kuolinsyy. Noin kolmasosa näistä kuolemantapauksista liittyy iskeemisiin sydänsairauksiin, jotka voivat aiheuttaa palautumattomia muutoksia sydänlihakseen. Yleensä sydänlihas toipuu huonosti iskemiasta ja seurauksena voi olla arkipudoksen muodostuminen ja sydämen vajaatoiminnan kehittyminen. Tällä hetkellä ei ole olemassa tehokasta hoitokeinoa vaurioituneen sydämen toiminnan palauttamiseksi, minkä vuoksi tällaisille korjaaville hoidoille on suuri tarve. Viime vuosikymmeninä tutkijat ovat kehittäneet erilaisia biomateriaaleihin perustuvia nanopartikkeleita lääkeaineiden kuljettamiseksi vaurioituneeseen sydämeen. Näitä prekliinisissä tutkimuksissa olevia nanokokoisia lääkehiukkasia pidetään lupaavina työkaluina. Niiden avulla voidaan kohdennetusti kuljettaa lääkeainetta sydänlihakseen käyttäen mahdollisimman vähän potilaaseen kajoavia toimenpiteitä, mikä on tärkeää hoitomyöntyvyyden kannalta. Tässä tieteellisessä kommentissa käydään läpi mikä on tämänhetkinen tilanne sydäninfarktin hoitoon tarkoitettujen nanolääkkeiden kehittämisessä ja miten tulevaisuudessa em. lääkkeet voivat olla hyödyllisiä iskeemisten sydänsairauksien hoidossa.

**Avainsanat:** sydänsairaus, sydäninfarkti, nanolääkkeet, kohdentaminen

#### **Conflict of interest:**

No announced conflict of interests.

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