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# EMERGING GAMUT OF CARDIOVASCULAR NANOMEDICINE: FUTURE IS BRIGHT

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| **Dr Pradeep Kumar Radhakrishnan*** | Prof MS, MCh AIIMS, Postdoctoral Fellow CTVS, Postdoctoral Fellow ECMO, FACC, FIACS, CPDH IISc, Global MBA Lond, Chief Division of Cardiothoracic Surgery GIMSR GITAM University. *Corresponding Author |
| **Gayathri Ananyajyothi Ambat** | Medical Student GIMSR Gitam University, |
| **Syed Ilias Basha** | Msc Pharmacology, Phd NP Research, Associate Professor Pharmacology GIMSR Gitam University. |
| **Dr Nazer Y A** | Prof MS, MCh AIIMS, Chief Division of Cardiothoracic Surgery, THI, TMCH, Kerala. |

**ABSTRACT** The aim of cardiovascular nanomedicine- CVN is to reduce off-target toxicity issues with therapeutic selectivity to the heart .The lipophilic barrier of the cellular membranes should be circumvented to deliver cargo inside the cell. Lipid-based NPs, which show low side effects and greater ability to passively accumulate at tissues with higher vascular permeability (enhanced permeation rate), have been largely used since the earlier times of cardiovascular nanomedicine-CVN. Polymeric NPs, silica NPs, carbon nanotubes, polymeric micelles, quantum dots, nanofibers and nanocrystals represent other examples of nano-formulations for controlled drug delivery. NP-loaded drugs are expected to be protected from systemic degradation, show reduced toxicity and immunogenicity, possess ameliorated pharmacokinetics and increased half-life and exhibit increased bioavailability and precise bio distribution. Nanodrug formulations are expected to enhance selective delivery to the site of interest and benefit from a lower clearance from the body. Nanotechnology represents a convergent discipline in which the margins separating research areas, such as chemistry, biology, physics, mathematics and engineering become blurred with the much needed emergence of integrated science as a new discipline.

**KEYWORDS :** CVN Cardiovascular Nanomedicine, NP Nanoparticle, si RNA, mi NP, Gly-CMNP,VEGF,FET, CLIO: cross-linked iron oxide; PET: positron emission tomography; SPECT: single-photon emission computed tomography; Gd-DTPA: gadolinium chelated with diethylenetriamine pentetic acid; MRI: magnetic resonance imaging; CT: computed tomography; NIRF: near-infrared fluorescence, oxLDL: oxidized low-density lipoprotein; BioMEMS: BIO-micro-electro-mechanical system.

## INTRODUCTION

Impact of cardiovascular disease is huge as revealed by the following statistics on global morbidity and mortality figures. It accounts for 31% of all global deaths [1]. In USA alone 1,055,000 individuals would be affected by coronary events, including 720,000 fresh and 335,000 recurrent coronary events [2].Surface functionalization with cell-specific targeting groups (e.g. peptide, aptamers) may allow for a more direct and selective tuning of NP bio distribution toward the diseased myocardium. Nanoparticles already in use in cardiovascular imaging is listed in Table 1.Neutral and cationic liposomes, HV virus of Japan liposomes, perflurocarbon, polyelectrolyte and lipomeric carriers are already in use.

Agents like miR-199a-3p can trigger cell cycle and induce cardiomyocytes proliferation experimentally. For in vivo applications indigenous methods ought to be developed. One such method is the d polymer-based nanoparticles, with a PFBT core (poly[9,9-dioctylfluorene-alt-benzothiadiazole]), which has a good biocompatibility and stable fluorescence that allows accurate tracking of the particles, and a DSPE-PEG (1,2-distearoyl-sn-glycero3-phosphoethanolamine-poly[ethylene glycol]) shell, which improves stability and protects conjugated si RNA from further degradation. Damaging potential compared with lipofectamine is less for these particles. The miNPs so produced have a hydrodynamic size of approximately 110 nm and a zeta potential of 22 mV. Proposed mechanism of action is by induction of the HIF-1/VEGF pathway. Other methods of delivery of miNPs include suspending in a shear-thinning hydrogel based on elastin-like protein-hyaluronic acid and injection into the affected area shows demonstrable evidence of regeneration and angiogenesis leading to improved cardiac function.

Dual-drug system in the stents with different release profiles promos earlier endothelialization and reduces lumen restenosis [3]. Here paclitaxel (PTX) is incorporated into mesoporous silica nanoparticles, which were mixed into an electrospun poly L-lactic acid fiber membrane. The fibers had a diameter of 1.26 ± 0.64 μm and were evenly distributed in a random arrangement around the stent. VEGF was bound to the surface of the fibers via dopamine, in order to promote the proliferation of vascular ECs. In contrast to PTX, up to 87% of VEGF was rapidly released within the first 3 days. In vivo applications of these are noted in case of intracranial aneurysms. Ma et al. exploited the capability of neuronal stem cells (NSC) engineered to over express CXCR4 by interacting with SDF-1. The levels of this stromal cell-derived factor are significantly increased in ischemic regions 24 h after infarct. Using the genetically modified NSCs, the authors demonstrated their selective accumulation in the ischemic regions in a mouse model of middle cerebral artery occlusion-induced ischemia [4].

Results show improved survival, reduced infarct volumes and improved neurological scores for animals treated with Gly-CMNP. The development of CMNPs could serve as a versatile platform for drug delivery through the BBB into diseased brain tissue. Compound berberine (BBR) serves as an approved nutraceutical substance for the treatment of hyperlipidemia [5].Less efficiently it can lower blood glucose levels also. To increase its accumulation in the liver, the target organ for BBR, Guo et al. developed a drug delivery system consisting of a D-α-tocopheryl hydrophobic core and an on-site detachable cross-linked polyethylene glycol-thiol shell (CTA-Mic) [6]. In mice with a high-fat diet (HFD), BBR-CTA-Mic significantly reduced the levels of plasma and hepatic triglycerides, cholesterol, LDL-c and blood glucose, as compared with the untreated group. Free BBR also reduced lipids and glucose, but with lower efficacy. In line with this, after 16 weeks medication, the body weights of obese mice had been reduced by BBR-CTA-Mic down to healthy levels. Also, their adipocyte size, mesentery and liver weight, epididymal fat, plasma ALT levels and fatty liver had normalized.

Early recognition and treatment of the life-threatening clots that obstruct blood vessels supplying vital organs, is essential to reduce mortality and minimize the massive health deterioration after stroke and MI [7]. Lee et al. described a promising approach using thrombus-targeting aspirin polyconjugate particles (T-APP) as an intravenously injectable agent, which can rapidly target thrombosed vessels and prevent the growth of thrombi. The particles were composed of a copolymer, poly (HEMA-co-MMA), which was covalently

conjugated via a degradable linker with ethyl salicylate (ESA), the major active ingredient of aspirin characterized by a strong antiplatelet activity [8]. Additional functionality was provided by the degradable peroxalate ester linker, which is rapidly oxidized by H2O2, thus scavenging H2O2 molecules responsible for platelet activation, endothelial dysfunction and the expression of pro-inflammatory proteins [9, 10]. The particles were further functionalized with a fibrin-specific pentapeptide, Gly-Pro-Arg-Pro-Pro (GPRPP), acting as a thrombus-targeting ligand and with IR780, as a probe for near-infrared imaging [11].

Targeting experiments with T-APP confirmed its strong ability to specifically bind fibrin-rich clots, as compared with APP. Multifunctional targeted nanoparticles that can scavenge H2O2, inhibit the expression of TNF-α and sCD40L can be utilized to exert the antithrombotic activity of ESA. IL-4, known to induce the macrophage phenotype switch from M1 to M2 can be mobilized on the surface of electrospun polycaprolactone (PCL) nanofibrous scaffold, which is used for production of vascular prostheses. Binding of IL-4 to PCL fibers was done without a linker, but by the plasma immersion ion implantation surface treatment, that facilitates rapid covalent. The bioactive material surface (IL-4 surface) and the controls, including polycaprolactone (PCL) alone, PLC plus IL-4 (passive IL-4), or PLC treated with plasma immersion ion implantation, were generated and characterized. In case of Liprostin (Phase III clinical trial) [12], used for the treatment of peripheral artery disease better drug solubility has also been achieved with dendrimeric formulations in complex with candesartan, a clinically approved angiotensin receptor blocker [13].NP coated with omega fatty acids finds applications in preventive cardiac nanomedicine.

European Commission-funded CUPIDO project (www.cupidoproject.eu), the therapeutic targeting of the heart is tackled via small, biocompatible and inhalable NPs. The first hint for the lung-to-heart phenomenon derives from studies on combustion-derived ultrafine nanoparticles linking air pollution to increased cardiovascular deaths [14].In a mouse model of diabetic cardiomyopathy, inhalation of CaPs loaded with a therapeutic mimetic peptide resulted in restoration of cardiac function [16].

Tunable nanoporous materials have been used to selectively harvest low-molecular-weight proteins, providing a unique opportunity to detect and identify new circulating biomarkers after fractionation of body fluids [17, 18]. Flexible nanoelectrode sensors for $K^+$ were also developed to address the mechanism of ischemic heart disease [19]. In addition, a multi-nanosensor silicon needle was developed *in vitro* for the detection of myocardial ischemia during cardiac surgery by employing field effect transistors (FET) [20, 21]. Details of available senors for in vivo use are listed in Table 2.

The next evolutionary stent advancement may be realized through a combinatory integration of nano-porous stent surfaces for the controlled time release of anti-proliferative agents with nano textured features [22].

## CONCLUSION

Combining a diagnostic imaging moiety with a targeted therapeutic nanoparticle allows for precise, temporal and spatial monitoring of the therapeutic agent as well as treatment outcomes. Nanodrug is intended to prevent adverse side effects and ligand-targeting or receptor-mediated targeting approaches that leads to an additional level of complexity that might be applied to the NP product in CVN. In future stimuli-responsive NPs (e.g., magnetic ones), should provide an additional strategy for enhanced and controlled guidance of NPs to the target site release of the NP-loaded drug. In line with this, despite no clinical trial having yet passed for CVN, the Nano Therm therapy (Mag Force AG) in oncology medicine represents the first magnetic NPs approved for local hyperthermia treatment of solid tumors. Success in these endeavors are thwarted by NP drug loading and release efficiency, biocompatibility and stability in biological environments as well as feasibility of pharmaceutical scale-up. Development of high-performance 'point of care' methods will improve the prognosis for CVD patients by obtaining more sensitive, more specific, and faster assessment of diagnostic markers. Inhalation therapy with nanoparticles is emerging in the horizon as a alluring new treatment modality in heart failure. Emergence of 'click chemistry' or highly controlled cross-linking strategies targeting and 'securing' the plaque may play role in stabilizing the plaque and preventive cardiovascular methodology of future. In GIMSR Gitam the cardio pharmacological research team is looking into drug synergism by novel inhalatation route utilizing nanoparticle based platforms with myocardial localization for treatment of heart failure.

**Table 1 Contrast enhancing nanoparticles in CVN**

| Category | Agent (examples) | Imaging techniques |
|---|---|---|
| Fluorescent | Quantum dots | Fluorescence tomography |
| Radioactive | $^{18}F$ CLIO, $^{111}In$ nanoparticles | PET, SPECT |
| Paramagnetic | Gd-DTPA | MRI |
| Superparamagnetic | Iron oxide nanoparticles | MRI |
| Electron-dense | Gold or I-based nanoparticles | CT |
| Light-scattering | Gold nanoshells | Optical coherent tomography |
| Photoacoustic | Colloidal nanobeacons | Photoacoustic tomography |
| Multimodal | Copper-CLIO | PET, MRI, NIRF |
| | Perfluorocarbon nanoparticles | MRI, Molecular imaging |

CLIO: cross-linked iron oxide; PET: positron emission tomography; SPECT: single-photon emission computed tomography; Gd-DTPA: gadolinium chelated with diethylenetriamine pentetic acid; MRI: magnetic resonance imaging; CT: computed tomography; NIRF: near-infrared fluorescence

**Table 2 CVN Sensors for in vivo approach**

| Sensor targets | Technology | Applications |
|---|---|---|
| $K^+$, $H^+$ ions | Field effect transistor (FET) | Myocardial ischemia |
| $Na^+$ ions | Fluorescent nanosensors | QT syndrome, heart failure |
| $Ca^{2+}$ ions | Boron-doped silicon nanowires (SiNWs) | Multiple CVDs |
| Nitric oxide | Single-walled carbon nanotube (SWNT) | Hypertension<br>Ischemia/reperfusion |
| oxLDL<br>Cholesterol | Porphyrinic nanosensor | Acute heart attack |
| Blood pressure | $In_2O_3$ nanowire-based FET | Pressure monitoring, |
| | Piezoelectric-BioMEMS | Myocardial infarction |
| | Chip-embedded flexible packaging (CEFP) | Stenosis in heart bypass Grafts |
| Blood flow | Piezoelectric-BioMEMS | |

oxLDL: oxidized low-density lipoprotein; BioMEMS: BIO-micro-electro-mechanical system.

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