Team A.I.N.C.A.D: Development of an Artificial Implantable Nanoparticle Carrying-Defibrillator Device to Treat Forms of Heart Arrhythmia

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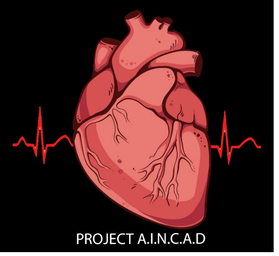

Abstract

- While the majority of heart arrhythmias have been treated through implantable cardioverter defibrillators (ICD) or orally through medication, many of these treatments have not accomplished fast acting relief from an arrhythmia, and have led to malfunctions in sensing of ICD and damage to organs by Amiodarone
- Our goal for our project takes a two pronged approach:
  (1) ICD - consists of a physical treatment of heart arrhythmias
  (2) Drug Delivery - consists of targeted delivery of amiodarone for biochemical treatment of heart arrhythmias using Poly(propylene imine (PPI) dendrimer

What we have accomplished:

- Designed and Developed a 3D model of a prototype Implantable Cardioverter Defibrillator, using CAD software
- Developed procedure to synthesize and characterize PPI Dendrimer Nanoparticles, and Au nanoparticles
- Developed procedure to synthesize and characterize dendrimer-Au nanoparticle (NP) complex
- Developed models for PPI dendrimer using pymol
- Comparative study between effectiveness of drug delivery PPI dendrimer and beta-cyclodextrin nanoparticle

Introduction

ICD

- ICDs use electrodes to send electrical pulses that correct irregularities in heartbeats[1]. Electrodes flex under heart contractions and can fracture causing infection and inflammation[2]. This is solved by placing the electrodes within a flexible silicon
- We developed a model for a more efficient and reliable ICD, but because of online restrictions, no engineered prototype has been made

PPI vs. beta-cyclodextrin

- Another way to treat heart arrhythmias, is through A Beta Blocker drug called Amiodarone. This drug is taken orally, but do not have a localized effect, and leads to serious health risks.
- Using PPI dendrimer nanoparticles, heart arrhythmia drugs such as Amiodarone can be easily encapsulated in hydrophobic cavities within the branching polymer chain structure and delivered. By performing synthesis several times, generation 4 and 5 (G4/G5) nanoparticles can be created and used to deliver larger amounts of medication[3].
- Each jump in generation yields a greater surface area for the encapsulation of Amiodarone[3].
  - PPI Dendrimer Nanoparticles are water soluble and have a narrow pH range that allows for controlled timing of drug release[3]
  - Adhere Au nanoparticles to dendrimer/s surface or core for detection
  - Lots of Intermolecular forces (IMF) interactions with Amiodarone
- Beta-cyclodextrin's surface area cannot be expanded and has a fixed single pore for less efficient drug encapsulation[4]
  - Contains no core so Au nanoparticles can not be adhered
  - IMF interactions with Amiodarone are unsubstantial

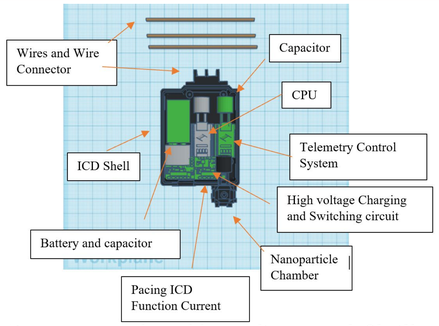

Figure 1. Prototype Implantable cardioverter defibrillator model

Our Methodology/Approach

- Decided to model an Implantable Cardioverter Defibrillator (ICD) using CAD with a drug delivery system housed within, which uses pH and temp. Indicators to eject NPs and targeting ligands to help reload injected NPs
- Developed a solution for ICD lead fracture using Silicon - based flexible electrodes
- Developed a solution for electromagnetic interference of ICD Defibrillation with destructive emf
- Found a better way of getting amiodarone to the body, by embedding amiodarone into the pores of dendrimer nanoparticles.
- Developed the synthesis procedure for dendrimer with coupled Au nanoparticles
- Designed a Comparative study to hypothesize the efficacy of PPI dendrimer nanoparticles in delivery of Amiodarone to Cardiac Myocytes
- Comparative study based on efficacy of drug encapsulation of PPI dendrimer and beta-cyclodextrin, where IMF interactions were dicussed in figures (use of ChemDraw)
- Modeled Au NP (Fusion 360), PPI Dendrimer (open source Pymol); made logo using Photoshop

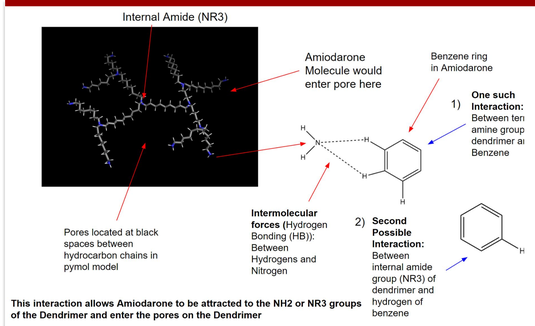

Figure 2. Interactions between Hydrogen atoms of bottom benzene ring (Amiodarone) and terminal amine and internal amide of PPI Dendrimer

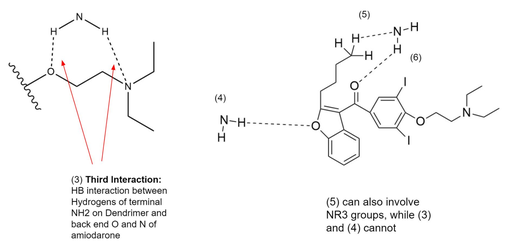

Figure 3. Interactions between atoms of front and back sides (Amiodarone) and amine groups of PPI Dendrimer

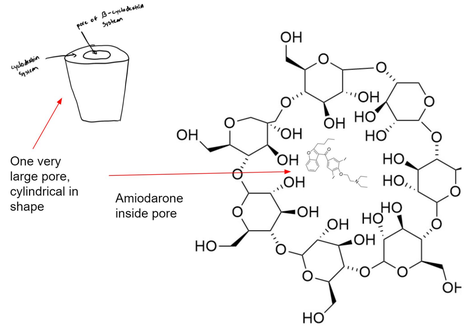

Figure 4. Encapsulation of Amiodarone inside beta-cyclodextrin system

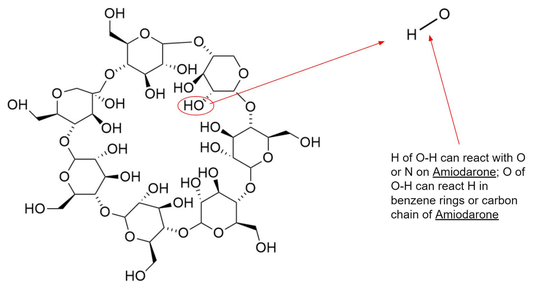

Figure 5. OH groups of beta-cyclodextrin as main contributors to interactions with Hydrogen, Oxygen, and Nitrogen atoms of Amiodarone

Synthesis Procedures

Synthesis of Au nanoparticles (NPs)

- First a 1 mM solution is made from $HAuCl_4$ $3H_2O$, deionized (DI) water, and arginine ligand[6].
- Then a 38.8 mM solution continuing trisodium citrate and deionized water is made[6].
- The first solution is stirred and brought to a rolling boil, and the second solution is added after and boiled while stirring to produce Au NPs[6].

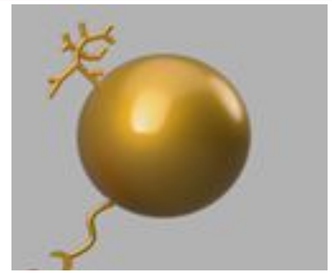

Figure 6. 3D model of Spherical Gold Nanoparticle modeled using Fusion 360 software

Synthesis of PPI Dendrimer (Au NP) core

- Synthesized Au NPs are dispersed in toluene using sonication bath, and mixed with 3-(Aminopropyl)triethoxysilane, and washed/dried with methanol[7].
- Then the solution was mixed with acrylonitrile and acetic acid, and eventually washed with DI water[7].

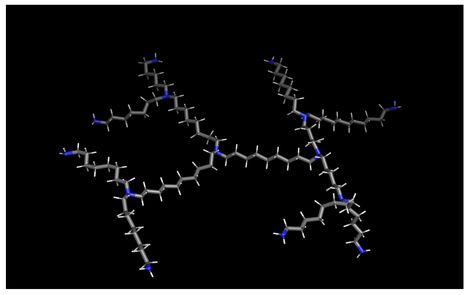

Figure 7. Molecular structure of G1 polypropylene(imine) Dendrimer modeled using pymol software

Future Aplications

- Engineering of our Nanoparticle Carrying Arrhythmic Defibrillator
- Synthesis and Characterization of PPI Dendrimer, Au nanoparticles, and Amiodarone using UV-vis Spectroscopy, Scanning-Electron Microscopy, and X-ray Diffraction
- Testing of Amiodarone drug kinetics in differing pH and temperature environments (in cell of organism)
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- Attaching carbohydrates to PPI Dendrimer to make them more biodegradable and decrease toxicity of terminal amine groups

Conclusion

- We first started our endeavor by attempting to create a new ICD device with non-fracturable leads in order to counteract heart arrhythmias.
- We then transitioned into developing a method to transport amiodarone to target tissues throughout the body as we realized this can be more helpful as well as a more realistic venture to counteract heart arrhythmias.
- This semester we dove deep into pursuing and tackling our idea. We were successful in the creation of a synthesis that can transport amiodarone to target tissues using nanoparticles. However, due to COVID-19 restrictions, we are now sitting on a synthesis proposal that has not been laboratory tested. In the future, we plan on taking this synthesis and testing it out in the lab and possibly testing it on live organisms.

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Citations

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