PAMAM and PPI dendrimers as potential anti-cancer drug carriers: A computational investigation

Eric A. Zizzi[1], Lorenzo Pallante[1], Marcello Miceli[1], Krzysztof Sztandera[2], Mateusz Bątal[2], Jack A. Tuszynski[1], Marco A. Deriu[1]*

[1]Department of Mechanical and Aerospace Engineering, PolitoBIOMed Lab, Politecnico di Torino, C.so Duca degli Abruzzi, Torino, Italy
[2]Department of General Biophysics, University of Lodz, Faculty of Biology and Environmental Protection, Pomorska St., Lodz, Poland
**marco.deriu@polito.it, Phone number: +39 0110903394*

OBJECTIVES

Photodynamic therapy (PDT) is a promising technique for several types of anti-cancer therapy, exploiting a photosensitizer, a light source and oxygen. The present work computationally investigates the properties of poly(amidoamine) (PAMAM) and poly(propyleneimine) (PPI) dendrimers of generation 3 and 4 as potential nanoscale drug delivery systems [1] for Rose Bengal (RB), a candidate photosensitizer for PDT.

METHODS

The starting configurations corresponding to neutral pH for G3 and G4 PPI and PAMAM dendrimers were generated using the Dendrimer Builder Toolkit [2]. Protonation of amines was checked and corrected according to the Ising model [3]. 200-ns Molecular Dynamics simulations of neat dendrimers were carried out in GROMACS 2020.4 after equilibration. Final dendrimer configurations were extracted and used as starting structures for further, 200-ns MD simulations with Rose Bengal at 10:1 ratio with respect to the dendrimers in the surrounding solvent. Dendrimer geometry and behaviour was analysed from the neat simulations in terms of radii of gyration (RoG) and Radial Distribution Functions (RDF) of external amines, negative Cl- ions and water. The formation of dendrimer-RB complexes was analysed in the simulations with RB.

RESULTS

Analysis of the RoG over the last 20 ns of neat MD simulations shows stable results, consistent with data from previous literature (Fig. 1). The RDF for negative Cl- ions showed the counterion penetration with peaks between 0.5 and 1.0 nm for both PPI G3 and G4, with more subdued penetration maxing at around 1.5 nm for PAMAM G3 and G4. The RDF for water showed penetration towards the dendrimer core, in agreement with previous computational and experimental results, in the case of PPI G3 and G4, with peaks at 0.5 nm. PAMAM showed comparably less water density, with RDFs gradually increasing from 0.3 nm from the core. Simulations in the presence of Rose Bengal show the formation of a stable dendrimer-drug complex after about 20-50 ns, with all RB molecules remaining bound to the dendrimers, which undergo conformational rearrangements that lock RB into position, as visible in the snapshot in Fig.2.

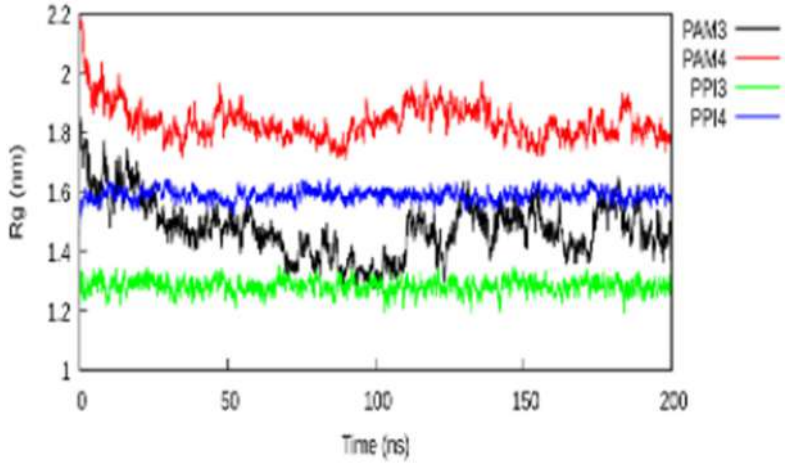

FIGURE 1: RoG of the simulated systems.

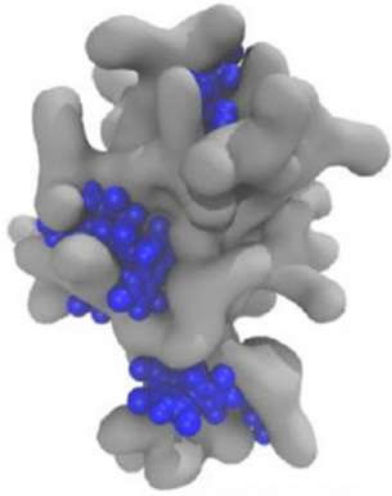

FIGURE 2: PAMAM G4 Dendrimer (grey) in complex with RB (blue).

CONCLUSIONS

MD simulations show that both PPI and PAMAM G3 and G4 dendrimers are promising drug delivery systems for Rose Bengal. Indeed, a single dendrimer is shown to be able to form a stable complex with up to 10 RB molecules, a might as such constitute a valid scaffold for enhanced RB delivery for PDT cancer therapy.

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