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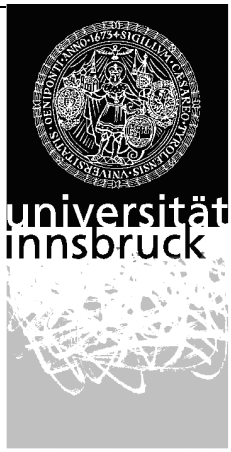

Dr. Zoe Cournia
Biomedical Research Foundation
Academy of Athens
Division of Pharmacology-Pharmacotechnology
Athens, 11527
Greece

June 26, 2012

Dear Zoe,

I am pleased to write this letter to confirm our collaboration on studying nanoparticle (NP)-membrane interactions in order to design nanomaterials with efficient and non-toxic membrane penetration properties. As you know, our current understanding of how nanomaterials interact with the cell membranes in a molecular level is extremely limited. An understanding of the relationship between the physico-chemical properties of nanostructures and their interaction pattern with biomembranes could lead to predictive models for assessing NP toxicity. Our plan is to use computational methods to associate the cell membrane responses with specific types, surface chemistry, size, charge, and shape of nanoparticles, so as to be able to predict the mechanism of nanoparticle internalization inside the cell in a systematic manner.

In my lab, we routinely use computer simulations to describe biomolecular systems and perform computer-aided drug design with a focus on development of nanomaterials as drug carriers as well as small-molecule inhibitors. We work on the understanding and prediction of kinetics and thermodynamics in the course of biomolecular binding processes and reactions. For this purpose we develop new computational methods and perform large scale computer simulations, extensive quantum chemical calculations and combinations of these two techniques (QM/MM).

At the moment, I am participating as a PI in the Initial Training Network NANODRUG (European Commission, Marie Curie Actions, FP7), which aims at the development and characterization of a selected set of novel intelligent nanomaterials to study their suitability as novel drug delivery systems targeting inflammatory skin diseases. For this project we model monomer-drug interactions to aid polymer design using quantum chemical approaches as well as MD simulations. For a given drug, a screening of the best monomers for subsequent co-polymerization is performed with MD simulations of the target with different monomers and prediction of the optimal binding partner for the monomer using the resulting energies and geometries. To evaluate NP-drug interactions we perform simulations of the mixtures of drug, functional monomer and cross-linker in explicit water and use the resulting NP model structures to calculate drug binding energies and drug

loadings. Moreover, we also perform modeling studies of NP-membrane interactions in order to elucidate specific interactions between the NP and the biomembrane and the associated effects such as desolvation as well as the mechanisms of nanoparticle internalization in lipid bilayers. Finally, we study the behavior of nanoparticles loaded with drug molecules in solution in order to study equilibrium properties such as diffusion of drug molecules into the solvent (and vice versa) and monitor structural and transport changes upon modifications of environmental factors such as pH and temperature with computer simulations. Drug release is investigated as a function of polymer structure, network mesh size of the polymer, ordering of water molecules in the solvation shell, polymer-water interactions, drug-polymer interactions and drug-water interactions.

These simulations are being performed in our two cluster systems consisting of 1) 162 compute nodes (total of 1944 cores), connected through an Infiniband 4x QDR high speed interconnect (three of the nodes are equipped with two NVidia Tesla M2090 graphics accellerators each) and 2) 92 compute nodes (1056 cores) with a total of 1176 GB of memory and a common storage system attached by 10 GBit optical network offering a total of 25 TB Raid-6 disk storage. These nodes are interconnected by 3 switched Gigabit networks. We also have access to the University of Innsbruck/Linz supercomputing facility, an SGI Altix UV 1000 system, set up as one maximum sized single system image of 2048 cores (78 two socket nodes, each socket equipped with an 8-core Intel Xeon E78837 CPU). The nodes are connected through SGI's NUMAlink 5 interconnect. The accompanying XFS storage system offers 58 TB of storage space. Both machines are operated within the Research Center High Performance Computing, where I am serving as a member of the Executive Board. For our collaboration, I can provide you with access to all of these machines as well as to the rest of our infrastructure in order to perform part of the simulations mentioned in the "ARISTEIA II" proposal that we are submitting.

Finally, I would like to mention that I would like to embed you and your team into the above-mentioned NANODRUG network. We have the possibility to invite you and one of your students to a future meeting and perform student exchanges between our groups as a NANODRUG activity and accordingly finance it by the network. These activities should then lead to further collaborations.

Our proposed work is of significant biomedical importance given the increasing applications of nanomaterials in medicine and everyday life. Understanding the physicochemical interactions of these engineered materials with biomolecules is central to the advancement of nanotechnology in these applications. I am confident that our studies will at the very least provide the scientific community with a detailed description of the nano-bio interface at molecular detail and at best lead to predictive models of NP internalization through cell membranes according to NP size, shape, and surface attributes. I look forward to continuing our collaboration and to moving forward with the project.

Sincerely,