Hydrophobic Drug Aggregates: Structure and Biology

Yulia Volovik Frenkel[a], Kalyan Das[a], Arthur D. Clark[a], Paul J. Lewi[b], Eddy Arnold[a], [a]*Center for Advanced Biotechnology and Medicine, and Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ, USA.* [b]*Janssen Pharmaceutica NV, Vosselaar, Belgium.* E-mail: yuliav@cabm.rutgers.edu

Using a variety of physicochemical approaches, we have determined that some highly hydrophobic drugs with great promise for the clinical treatment of AIDS form aggregated structures in simple aqueous solutions mimicking gastrointestinal conditions [1]. Aggregate size and oral bioavailability are correlated; compounds forming aggregate structures with 30-100 nm in radii had good bioavailability and those with aggregate sizes exceeding 250 nm in radii had poor bioavailability. The aggregates contain on the order of 10^6 drug molecules, with size depending on the structure of the compound and the solution conditions.

In the current study we have been exploring the structure and mechanisms of formation of NNRTI aggregates using diffraction, spectroscopic, and computational simulation approaches. The aggregates appear to represent an intermediate state between monomeric and precipitated forms of the hydrophobic compounds. X-ray powder diffraction measurements from the aggregates using synchrotron radiation at CHESS provided evidence for the presence of micro-crystalline domains. From our findings we are hoping to deduce an explanation of the unique biological behavior of these compounds.

[1] Frenkel Y.V., Clark A.D., Das K. Jr., Wang Y.-H., Lewi P.J., Janssen P.A.J., Arnold E., *J. Med. Chem*., 2005, *in press*.

Keywords: nanoparticles, pharmacology, microcrystalline domains