Nanoparticle Markers for High-Efficiency Non-linear Microscopy: Combining Cancer Imaging and Treatment

Our group has invented a unique method for creating nanoparticles with extraordinarily high second order optical non-linearities. These particles can either be used on their own, as in this proposal, or integrated into a bulk material. The nanoparticles consist of one or more noble metal particles coated by an ionic self-assembled multilayer (ISAM) film. The ISAM film is designed to have a large second-order non-linear optical (NLO) susceptibility, which means it can efficiently up-convert light through second harmonic generation (SHG), the optical process underlying SHIM.

For their part, the metal nanoparticles are designed with a surface plasmon resonance that concentrates the incident light into a very small volume next to the particle where the ISAM film is deposited. Because SHG is a non-linear process, it becomes more efficient when the light's intensity is increased. The addition of the metal particle can, therefore, dramatically increase the SHG efficiency if it is done properly. The metal + ISAM nanoparticle combination is especially powerful since the ISAM film naturally assembles on the surface of the metal, which is precisely where the light intensity concentration is the greatest. This makes the particles simple to fabricate using standard techniques. A first incarnation of this idea has already delivered an increase in SHG efficiency of 1600 times.

The particles can be used as an extremely efficient contrast agent for SHIM. SHIM is an emerging microscopic technique with diverse biomedical applications such as membrane imaging, muscle tissue imaging, imaging of living cells, tumor imaging, neuron activity measurements, and ophthalmological imaging, among others. It has a unique combination of strengths, such as the ability to create three-dimensional visible light images of structures deep inside opaque tissue, the ability to infer local structure below the resolution limit of ordinary microscopy, and a complete absence of photobleaching. It is however hobbled by very low signal levels, which limits its use. The research we propose will remedy this problem and transform SHIM into a standard tool of biomedical imaging.

As mentioned, the nanoparticles are also suitable for hyperthermic therapy. The switch from imaging to treatment is accomplished by simply increasing the incident laser power by a factor of a few hundred, which will cause the nanoparticles to dissipate some of the radiation into heat, sufficient to kill diseased cells. In other words, if the nanoparticles are conjugated with ligands targeted to cancer cells, they can be used both for diagnosis and treatment of cancer.

We propose to develop and characterize a new class of nanoparticles designed to operate as ultra-bright markers for non-linear optical microscopies such as second harmonic imaging microscopy (SHIM). This will radically extend the range of applications for SHIM, transforming this unique microscopy into a standard tool of biomedicine. In addition, the nanoparticles can be used in hyperthermic treatment of cancers and other disease states. This makes for a particularly powerful combination, where the same nanoparticles can serve both to diagnose and to treat disease. This project is highly interdisciplinary (involving Physics, Chemistry, and the Life Sciences), and is geared towards promoting human health.