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Application of microscopy technologies for nanomaterial characterization and biological quantification

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As a research group developing micro- and nano- technologies for critical biomedical applications, the Penn State MINIBio Laboratory has been using various microscopy technologies and analytical methods to investigate biological and non-biological objects at the micro- and nano- scale. In my presentation, I will discuss three examples from our recent studies.

My group has synthesized various nanomaterials and nanomaterial composites, such as iron oxide nanoparticles, iron oxide nanoparticles encapsulated in silica and zinc oxide, titanium oxide nanosheets on graphene, zinc oxide nanowire array, graphene encapsulated in silica, iron oxide nanoparticles decorated graphene with and without metal-organic frameworks (MOF) (Figure 1). When we prepared the porous nanostructures for EM characterization, sometimes it's challenging to obtain sharp images under. For the SEM, the charging effect can be serious for non-conductive materials, and the image shift cannot be addressed through regular tuning. During the synthesis of the materials, we used some surfactants (organic agents) as the templated for generating the nanopores. Thus, in some cases these residual organic surfactants can boost the charging effect. After removing the residuals in the nanopores, we repeated the SEM imaging and successfully obtained much sharper images. In general, the porous structure was observed more clearly under the TEM.

In another case, we observed an interesting phenomena. When we used empty silica nanoparticles to treat cancer cells first, then exposed drug-loaded silica nanoparticles to cancer cells, the therapeutic effect was significantly reduced. The pre-treatment of empty silica nanoparticles seems to reduce the therapeutic efficiency of subsequent drug delivery. To investigate the potential mechanism, we used time-lapsed fluorescence microscopy to investigate the location and intensity of fluorescence-labeled silica nanoparticles inside cells. After applying quantitative imaging process, it becomes clear that the pre-occupation of endo/lysosomes by the empty silica nanoparticles changes the spatial distribution of the subsequently introduced drug-loaded silica nanoparticles, therefore inhibits those drug-loaded silica nanoparticles to access intracellular organelles.

Finally, we developed a microdevice, the flexible micro spring array (FMSA), to enrich circulating tumor cells (CTCs) from peripheral blood samples of cancer patients as a liquid biopsy assay. The CTCs are detected *in situ* by immunofluorescence staining. We would like to scan and save the images from each clinical sample as a digital profile for later study. However, the task becomes challenging due to 3 factors: (1) the effective surface area of FMSA is 7x7 mm^2, (2) three fluorescent channels and 20x objective need to be used for CTC detection; (3) although the FMSA is a planar structure, after mounting on slides, the height can still be uneven for up to 100 μm. We have been using an automatic fluorescence microscope and adopted a scanning protocol to perform the task. We are working on an imaging processing software for automatic detection of CTCs.

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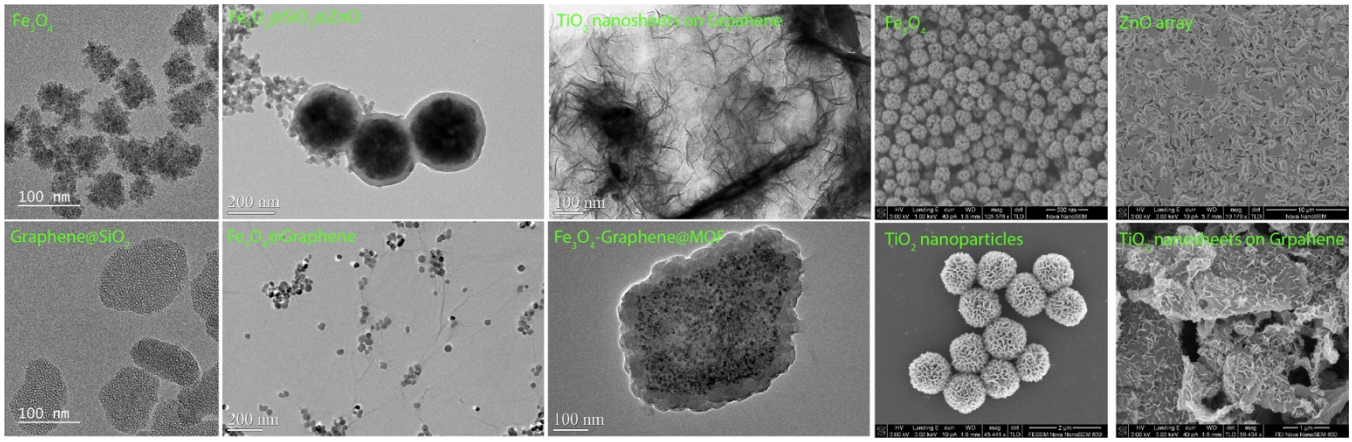

Figure 1. Palette of inorganic nanomaterials imaged with EM.

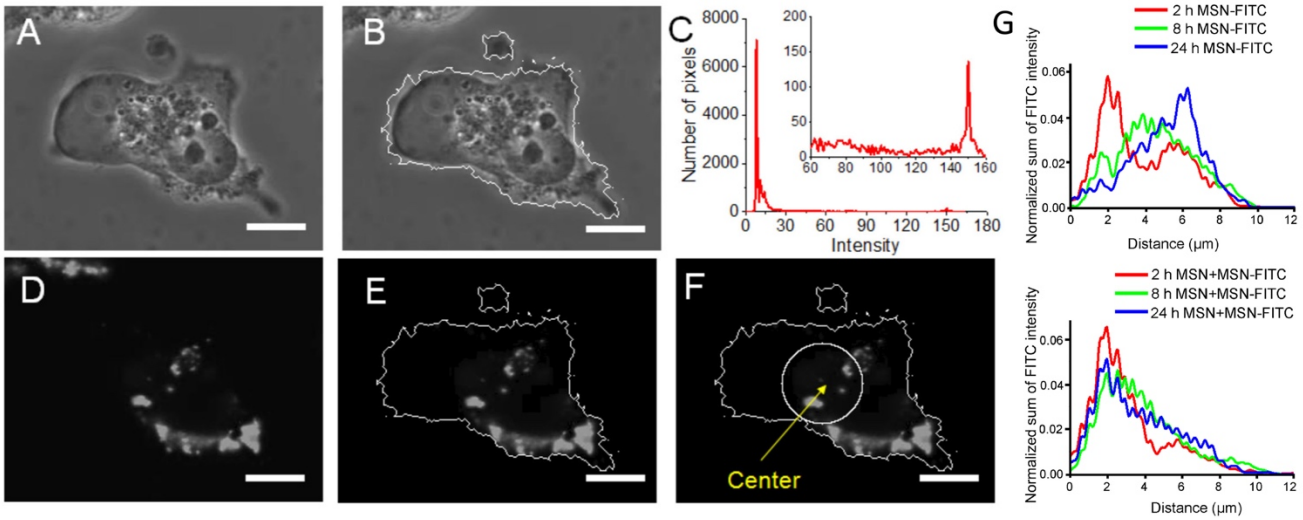

Figure 2. Image processing illuminates the inhibition mechanism of intracellular drug delivery using silica nanoparticles under pre-treatment.

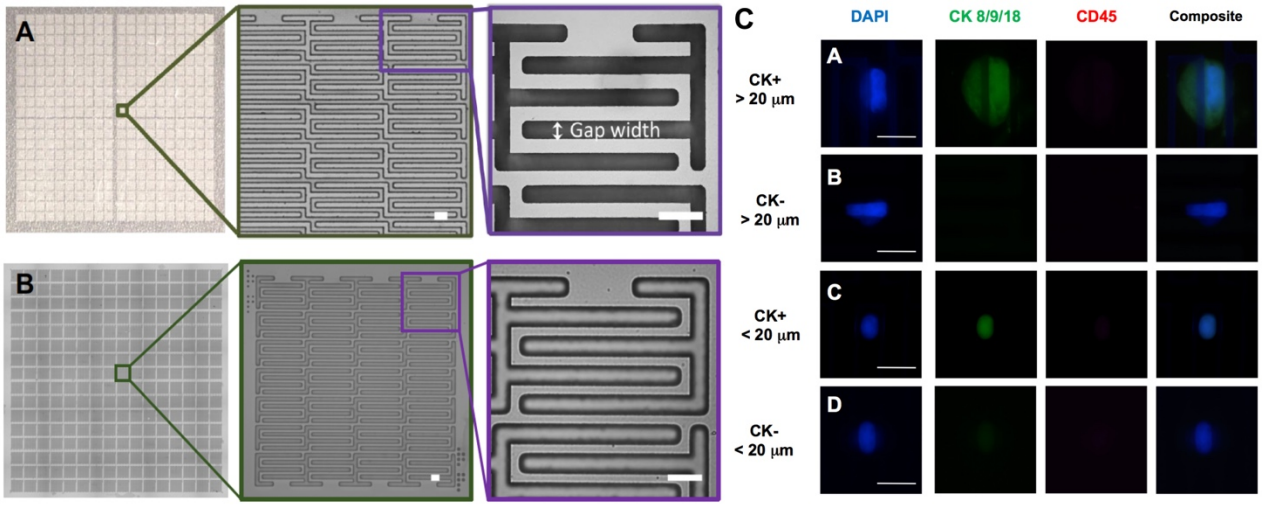

Figure 3. Flexible micro spring array (FMSA) devices (A, B) for circulating tumor cell (CTC) enrichment and immunofluorescence detection (C).

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