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# BIOENGINEERING

PRESENTS

## Advanced Molecular Tracking Microscopes and Few-Atom Silver Cluster-Based Biosensing

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### ABSTRACT:


Molecular trafficking within cells, tissues, and engineered three-dimensional multicellular models is critical to the understanding of the development and treatment of various diseases including cancer. However, current tracking methods are either confined to two dimensions or limited to an interrogation depth of ~15 µm. We have developed a new 3D tracking method capable of quantifying rapid molecular transport dynamics in highly scattering environments at depths up to 200 µm. The system has a response time of 1 ms with a temporal resolution down to 50 µs in high signal-to-noise conditions, and a spatial localization precision as good as 35 nm. Built upon spatiotemporally multiplexed two-photon excitation, this approach requires only one detector for 3D particle tracking and allows for two-photon, multi-color imaging. 3D tracking of epidermal growth factor receptor (EGFR) complexes at a depth of ~100 µm in tumor spheroids is demonstrated. We have coined this technique **TSUNAMI** (**T**racking **S**ingle particles **U**sing **N**onlinear **A**nd **M**ultiplexed **I**llumination; *Nature Communications* 2015).

Other than tracking microscopes, our lab is also exploring a new class of biolabels termed few-atom noble metal nanoclusters. Noble metal nanoclusters are collections of small numbers of gold or silver atoms (2-30 atoms) with physical sizes close to the Fermi wavelength of an electron (~0.5 nm for gold and silver). Providing the missing link between atomic and nanoparticle behavior in noble metals, these nanoclusters exhibit optical, electronic, and chemical properties dramatically different from those of much larger nanoparticles or bulk materials. Among those water-soluble noble metal nanoclusters newly developed, DNA-templated silver nanoclusters (DNA/Ag NCs) have attracted great interest in biosensing owing to a number of useful photophysical and photochemical properties. For instance, controlled conversion of DNA/Ag NCs between bright and dark states by guanine proximity has led to the invention of a new molecular probe, termed a NanoCluster Beacon (NCB), that "lights up" upon binding with a DNA target. Not relying on Förster energy transfer as the fluorescence on/off switching mechanism, NCBs have the potential to reach an ultrahigh signal-to-background (S/B) ratio in molecular sensing. Since the fluorescence enhancement is caused by intrinsic nucleobases, NCB detection is simple, inexpensive, and compatible with commercial DNA synthesizers. We have achieved SNP and DNA methylation detection using NCBs (*ACS Nano* 2014 and *JACS* 2015).


### BIOGRAPHY:

**Dr. Tim Yeh** obtained his BS degree from National Taiwan University, MS degree from University of California, Los Angeles, and PhD degree from Johns Hopkins University. He worked at Optical Micro Machines Inc. in San Diego from 98-03 as an R&D engineer, developing MEMS-based photonic switches for telecommunications. At Johns Hopkins, his research focused on single-molecule spectroscopy, BioMEMS and nanobiosensors. Dr. Yeh received his postdoctoral training at Los Alamos National Laboratory from 09-12, in the Center for Integrated Nanotechnologies. While at LANL, he won a 2011 R&D 100 Award and a 2013 Postdoctoral Publication Prize in Experimental Sciences. Dr. Yeh joined the Biomedical Engineering Department at the University of Texas at Austin in 2012 as an assistant professor. His research interests include 3D molecular tracking and nanobiosensor development.