# Digital Resolution Detection of miRNA with Single Base Selectivity by Photonic Resonator Absorption Microscopy

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**Abstract**

We demonstrate the incorporation of DNA nanotechnology with photonic biosensors to construct a diagnostic approach that demonstrates “digital” resolution of individual miRNA molecules with high signal-to-noise ratio. Gold nanoparticle tags are prepared with thermodynamically optimized nucleic acid toehold probes that, when binding to a target miRNA sequence, displace a probe-protecting oligonucleotide and reveal a capture sequence that is used to selectively pull down the target-probe-nanoparticle complex to a photonic crystal (PC) biosensor surface. By matching the surface plasmon resonant wavelength of the nanoparticle tag to the resonant wavelength of the PC nanostructure, the reflected light intensity from the PC is dramatically and locally quenched by the presence of each individual nanoparticle, enabling a new form of biosensor microscopy that we call Photonic Resonator Absorption Microscopy (PRAM). Dynamic PRAM imaging of nanoparticle tag capture, enables direct 100 aM limit of detection and single-base mismatch selectivity in a 2-hour kinetic discrimination assay. The PRAM assay demonstrates that ultrasensitivity (<1 pM) and high selectivity can be achieved on a direct read-out diagnostic.