# NANOPARTICLES-BASED BIOSENSORS FOR CANCER DIAGNOSTICS AND DRUG SCREENING: A STUDY ON TUMOR SUPPRESSOR PROTEIN-DNA INTERACTIONS

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Key Words: Protein-DNA, Metal Nanoparticles, Plasmonics, Diagnostics, Drug Screening

The p53 protein, dubbed “The guardian of the Genome”, is a tumor suppressor protein that plays a central role in cancer biology. It regulates the gene expression through binding with specific DNA response elements (RE), thereby enabling many important biological functions such as DNA repair and apoptosis. About 50% of human cancers can be associated with mutated p53 proteins that do not bind with the RE. This makes mutant p53 an attractive target for reactivation (i.e., restoration of normal function) by drugs. In this study, we have developed versatile metallic nanobiosensors to detect p53-DNA binding interactions and screen reactivation compounds for mutant p53 proteins. These nanobiosensors exploit the unique light absorption and strong scattering properties of gold nanoparticles (AuNPs), which allow unprecedented sensitivity (pM) detection of sequence-specific and/or drug activated protein-DNA binding in complex biological samples. A simple colorimetric biosensor is designed based on the specific binding of wildtype p53 protein to the RE sequence in the DNA-AuNPs, which alters the interparticle-distance of RE-AuNPs, resulting in a distinct change in solution color (red-to-blue) as well as UV-vis absorption spectra. Competition assay with different free RE sequences enables the evaluation of the binding affinity of wildtype p53 to various promoter sequences. Control experiments with the mutated p53 showed no distinct color change of the DNA-AuNPs (remain red and well dispersed) in the binding buffer. The second nanobiosensor is capitalized on the large scattering dimension of AuNPs (106-fold larger than fluorescent probes) due to the LSPR effect. It involved the use of AuNP dimers assembled by DNA (p53 RE), and coupled with Dynamic Light Scattering (DLS) readout system to achieve a much lower detection limit than the colorimetric method. This unique ‘mix-and-test’ DLS-based AuNPs probes not only can allow real-time monitoring of the p53-DNA binding events, but also effectively suppress the signals arising from non-binding substances in the complex cell medium. We have successfully applied these probes for high-throughput screening of the reactivation compounds of mutant p53 proteins in cancer cell lysates. These features will expedite research in the areas of drug discovery, clinical diagnostics and fundamental cell biology.