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Nanopore quantitation of cancer BRAF driver mutation facilitated by a DNA interstrand MercuLock

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Driver mutations are a special type of genetic alterations that are causally correlated with oncogenesis. Accurate detection of the presence of driver mutations is extremely useful for early cancer diagnosis. BRAF (serine/threonine-protein kinase B-raf) has a predominant driver mutation V600E, which occurs with the highest incidence mainly in melanoma, colorectal and thyroid cancers, and in other cancers. Currently the BRAF pathway has become a drug target for molecular therapy. Here we devise a novel nanopore single-molecule assay to accurately detect this driver mutation. We designed such a probe that its hybridization with the target (mutant antisense strand) forms a T-T mismatch. The nanopore single-molecule sensor can be used to visually discriminate a single T-T mismatch bound with a mercury ion (Hg^{2+}), due to that the Hg^{2+} binding creates a reversible interstrand lock, called MercuLock, which enhances the hybridization strength by two orders of magnitude. Such MercuLock cannot be identified in the A-T base-pair between the same probe and the wild type BRAF gene. Counting the frequency of MercuLock blocking events in the nanopore allows quantizing trace amount of mutation gene in the mixture. This approach can be adapted to detect any thymine-involved driver mutations and single nucleotide polymorphisms (SNPs) for cancer detection.

Biography

Li-Qun Gu, an Associate Professor of Bioengineering at the University of Missouri, is leading an interdisciplinary laboratory that has a long term vision: Integrating biomolecular engineering with nanobiotechnology to explore life science problems and to develop sophisticated molecular diagnostic tools for personalized medicine. He received the NSF CAREER award the NIH grant to develop ultrasensitive single-molecule technology for disease biomarker detection. He has published over 40 peer-reviewed papers in high tier journals including *Nature, Nature Nanotechnology, Science and PNAS*. The nanopore-nanosensor he developed can detect circulating microRNAs in cancer patient plasma, offering a non-invasive approach to screening and disease diagnose.

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