The Prospects for a Single Cell Secretome: Using a Nanopore for Both Analyte Detection and Cell Transfection

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The promise of using a nanometer-diameter pore as a non-optical, molecular sensor relies on the distinctive electrical signal that develops when a single molecule, immersed in electrolyte, translocates across a membrane through the pore. The molecular configuration and the pore geometry determine how the electrolytic ions passing through the pore come into contact with the potential presented by the molecule. Differences in the potential associated with each molecule should have a substantial effect on the current-voltage relationship and facilitate discrimination against the complex chemical background found both inside and outside cells. However, to control the electric field and the forces in a pore, the geometry has to be defined with sub-nanometer precision due to the molecular size. Ideally, optimal signal-to-noise for detection would result if the occluded pore volume, electrolytic resistance and parasitic membrane capacitance were all stringently controlled at the same time. Concomitantly, these stringent specifications offer the prospect for electroporation and transfection of single cells with the same device. In particular, control of the electric field in and beyond the pore lumen enables transfection via electroporation.

We will show that it is now possible to produce pores with a sub-nanometer diameter in a solid-state dielectric membrane embedded in a microfluidic device. We show that control of the electric field and forces in a pore facilitates discrimination between different proteins and nucleic acids, and enables the transfection of single cells via electroporation. While single cell transfection along with non-optical single molecule detection offers the prospect of a paradigm shift for detecting the sectretome associated with a single cell, it also demands precise registration of the cell relative to the pore. We accomplish this registration using microfluidics to convey cells to the membrane and optical tweezers to control the position of the cell over the pore.