## Democratizing Mechanobiology with Force Sensing Nucleic Acids

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Cells are highly dynamic structures that are constantly pulling and pushing on one another and on their surroundings. These pulls and pushes are mediated by molecular complexes that experience forces at the scale of piconewtons (pN). For context, 7 pN applied a distance of 1 nm is ~1 kcal/mol and most biomolecular forces are in the range of 1-50 pN. Despite the small magnitudes of these forces, they can have profound biochemical consequences. For example, the rapidly fluctuating forces between immune cells and their targets can drastically tune immune response and function. Unfortunately, there are limited methods to study forces at the molecular scale and particularly within forces generated by living cells.

In this talk, I will discuss my group's efforts at addressing this gap in knowledge by developing nucleic acid sensors to map the molecular forces applied by cells (1,2) . The talk will focus on DNA probes that respond to specific magnitudes of molecular forces by undergoing conformational changes and reactions (3). These conformational changes are then designed to trigger biochemical and catalytic reactions that can enhance the sensitivity of the probe. I will discuss a mechanically-triggered hybridization chain reaction (mechano-HCR) that allows chemical amplification of mechanical events (4). The amplification is triggered when a cell receptor mechanically denatures a duplex revealing a cryptic initiator to activate the HCR reaction in situ, leading to a 10-fold enhancement in signal. Importantly, the mechano-HCR amplification enables direct readout of pN forces using a plate reader. We leverage this capability to measure the forces generated by platelets during activation. We report mechano-$IC_{50}$ (concentration of a drug that leads to 50% inhibition of receptor force) for platelets treated with aspirin, ROCK inhibitor, and eptifibatide (an FDA approved anti-coagulant). Given that cell and platelet mechanical phenotypes are of clinical importance and predict bleeding risk, mechano-HCR offers a convenient route for drug discovery, personalized medicine, and disease diagnosis.

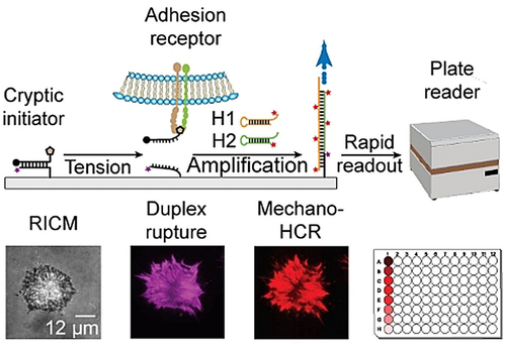


Fig. 1. Schematic and data showing the mechano-HCR reaction used to detect the molecular forces applied by cells using a conventional plate reader.

[1] "Emerging uses of DNA mechanical devices" Aaron Blanchard & Khalid Salaita Science, 2019

[2] "DNA Nanotechnology as an Emerging Tool to Study Mechanotransduction in Living Systems" Victor Pui-Yan Ma & Khalid Salaita, *Small*, 2019

[3] "DNA Probes that Store Mechanical Information Reveal Transient Piconewton Forces Applied by T Cells" Rong Ma, Khalid Salaita, et al. *Proceedings of the National Academy of Sciences,* 2019

[4] "Mechanically-triggered Hybridization Chain Reaction", Yuxin Duan, Khalid Salaita, et al. *Angewandte Chemie*, 2021