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January 16th, 2019

To the Editors of *Journal of Visualized Experiments*,

Enclosed is a manuscript entitled "A uniform shear assay for human platelet and cell surface receptors via cone-plate viscometry", which I have been invited to submit to *JoVE* for publication.

Mechanosensation via cell-surface mechanoreceptors is an important mechanism by which cells can interact with and interpret their physical environment. Some common assays, while efficacious in testing the effects of many biochemical variables on receptor binding and activation, are ill equipped to explore the effects of mechanical force. Many cells that experience shear stress are circulating cells. As such, assays using flow chambers or microfluidics (sometimes paired with imaging) are often used to apply laminar flow. These assays permit specific control over shear time and rate. These assays are often used to interrogate interactions in which either the ligand or receptor is anchored/coating a surface. However, another paradigm in which cells may experience shear is in solution, not tethered to a surface. In this situation the effect of shear may not even be mediated via a specific ligand-receptor pair.

Our manuscript describes the method for a "uniform shear assay" whereby shear force is applied to cells in solution on a cone-plate viscometer. This assay allows for application of shear force to cell suspensions or biological fluids such as blood or plasma with control over specific shear levels and length of shear exposure. The shearing step of this method can be utilized upstream of many different biochemical or imaging readouts. Described herein, we have most recently paired the shearing step with high throughput detection methods like standard and imaging flow cytometry to detect the crosslinking of platelets by human-disease relevant autoantibodies and to reveal specific biophysical requirements for the activation of the platelet mechanoreceptor GPIIb-IX by its ligands in solution.

Thank you for the invitation and for your consideration. I look forward to hearing from you soon

Sincerely,

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