

## **Nanoscale control by materials of mesenchymal stem cells for identification of bioactive metabolites.**

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Metabolites, or biological small molecules, are usually considered in identification of biomarkers. However, they can be used to drive cellular processes, such as stem cell differentiation. Use of complex media recipes to control stem cell differentiation add artefact to metabolomics experiments and so bioengineering approaches are attractive as they can drive different stem cell fates without changing what the cells are 'fed'. We have developed metabolomics pipelines to identify bioactive metabolites that control mesenchymal stem cell (MSC) self-renewal and differentiation.

We started this research avenue using peptide hydrogels with defined stiffnesses that could control MSC chondrogenesis and osteogenesis, identifying GP18:0 and cholesterol sulphate as bioactive metabolites<sup>1</sup>. Next, using our nanovibrational bioreactor, the Nanokick<sup>2</sup>, along with synthetic chemistry modification of hit metabolites, we focused on refining our putative osteospecific metabolite candidates to tune potency and specificity identifying fludrocortisone acetate. Finally, we have used nanotopography to control MSC self-renewal<sup>3</sup> to identify respiration-link metabolites that drive the immunomodulatory phenotype of MSCs<sup>4</sup>; this is critical if we wish to grow large numbers of high quality MSCs for use as immunosuppressive therapies in transplant procedures.

<sup>1</sup>Alakpa Chem 2016, <sup>2</sup>Tsimbouri Nature BME 2018, <sup>3</sup>McMurray Nature Mat 2011, <sup>4</sup>Ross BioRxiv 2019.