Collaboration shapes extracellular vesicle retention strategy

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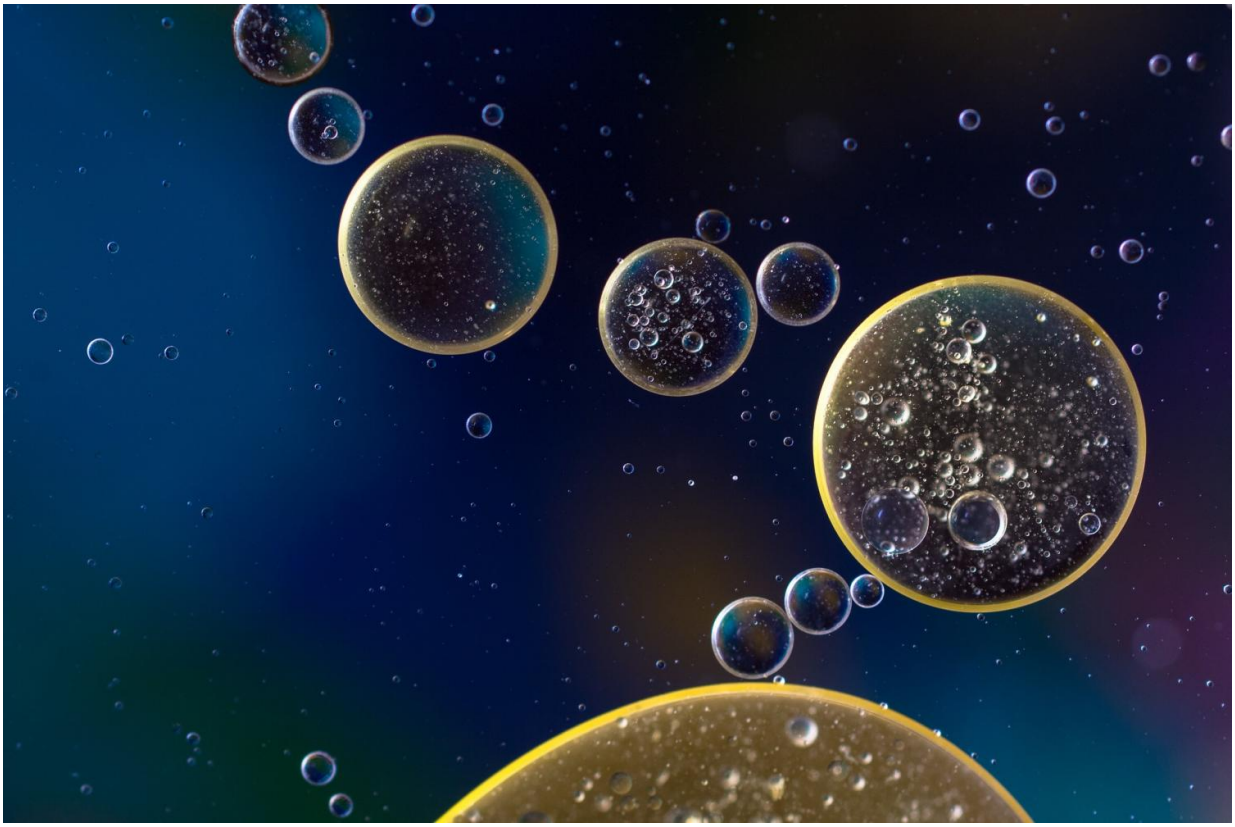

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Leveraging unique expertise in the spirit of collaboration is one of Carnegie Mellon University's formulas for success. Over the past three years, Phil Campbell and Xi (Charlie) Ren partnered on research related

to spatial control of extracellular vesicles (EVs). Their efforts have yielded a novel strategy that enables long-term EV spatial retention, a key variable to enable future tissue engineering and regenerative medicine applications.

"EVs can be thought of as the universal communicators—not only in the body, but in all living things," explained Campbell, research professor of biomedical engineering. "They occur naturally, are biocompatible, and can be used to deliver messages between cells at a nanoscale level."

Studies have shown that EV-based therapeutics are less likely to trigger adverse immune responses and do not pose the same logistical and regulatory concerns as therapies based on living cells. However, while rich in potential, EVs delivered in their natural form are usually prone to rapid clearance and typically lack controlled targeted delivery. In some applications, repeated extended dosing is required, which presents challenges with both overall effectiveness and efficacy.

"Our work stemmed from a very simple question," said Ren, assistant professor of biomedical engineering. "There are many aspects of controlling the biologic function of EVs, but if we can provide retention (of EVs), can we do something great? One of the best ways to advance research is to talk to other faculty who have different expertise. We have taken the chemistry aspects and tools from my lab and coupled them with the EV platform developed by Phil's lab to present innovative new technology."

In recent research published in *Biomaterials*, the group described a method for immobilizing mesenchymal stem cell (MSC)-derived EVs in collagen hydrogels to augment angiogenesis, or the formation of new blood vessels, which is a critical step for most reparative and regenerative applications. Practically speaking, diabetic patients who suffer from vascular disease, where arteries are hardened throughout

their bodies, could benefit from pro-angiogenic biomaterials like these.

To accomplish this, the researchers incorporated a selective chemical tag onto EV's exterior surface, which does not affect its morphological or functional properties. Through this chemical tag, EVs can be effectively rooted within hydrogel implants and elicit more robust host cell infiltration. In the study, angiogenic and immunoregulatory responses compared to 10 times the higher dose required by using conventional, non-immobilized EVs.

"In a nutshell, what we now have the ability to do is to spatially control where we put EVs and keep them there under controlled conditions," summarized Campbell. "We specifically looked at promoting angiogenesis for this paper, but broader than that, this technique could lead to increased therapeutic applications for wound healing and other regenerative and reparative therapies."

Efforts to apply this EV platform to bone tissue engineering as an alternative to titanium is also under way. The group is designing scaffolding and exploring functionalization to overcome the current challenges titanium presents as a limited regenerative when implanted within the body.

"We hope that we can design a way to infuse non-biological materials, such as a metal implant, with this hydrogel, with EV loaded, that could encourage the body to take the foreign implant amongst the body parts," said Ren.

More information: Yunhui Xing et al, Engineering pro-angiogenic biomaterials via chemoselective extracellular vesicle immobilization, *Biomaterials* (2021). DOI: 10.1016/j.biomaterials.2021.121357