[Subject strapline – one or two words to define the general subject area]

Materials science

Main Title: no more than roughly 40 characters, including spaces]

To bind, or not to bind

Draft standfirst:

Finding a way to control how particles bind to cells could open up opportunities for biomedical research. The discovery of a method for directing the orientation of particle–cell interactions is therefore a cause for excitement.

Andrea J. O'Connor & Frank Caruso

The ways in which small particles interact with cells are crucial in nature, such as when the immune cells in our bodies remove dirt and bacteria to stop infection. These interactions also have many potential applications in promising medical therapies, and have fuelled the growing field of nanomedicine. Writing in *Advanced Materials*, Gilbert *et al.*¹ report a significant contribution to this field: tube-shaped particles that attach to cells in different ways depending on the tubes' surface properties. This could lead to new ways to deliver drugs into target cells and to create cellular constructs.

Small particles (nanometres to micrometres in size) can interact with cells in many different ways, depending on the type of cell, the local environment and, significantly, on the physicochemical properties of the particles. Scientists and

engineers are therefore working on approaches to tailor both the physical and chemical properties of particles to develop control over their interactions with cells and tissues.

The size, stiffness, shape and chemical makeup of small particles all strongly influence how such particles interact with cells — they may bind to the outside of a cell, be taken up by the cell and trafficked through different pathways within it, and ultimately even change aspects of the cell's functions. Gilbert *et al.* have designed and made hollow, tubular, polymeric particles that can have non-uniform chemical properties.

The authors made the microtubes by assembling layers of oppositely charged polymers — polyelectrolytes — in the pores of a special type of filtration membrane that has straight pores. They then chemically cross-linked the polyelectrolytes to stabilize them and dissolved away the membrane. A benefit of this method is that it can be used to make millions of microtubes at a time, and that it could be scaled up by using multiple membranes. The dimensions of the microtubes could also be easily changed by altering the pore size or the thickness of the templating membrane.

The authors prepared microtubes that are either cell-resistant or cell-adhesive by changing the polymers used to make them. In a smart variation, they also made microtubes that are cell-resistant along their length on the outside but cell-adhesive inside. Because cells cannot fit inside the tubes, they can only bind to

the ends of the microtubes where the adhesive molecules are exposed. The researchers therefore observed that these particles tend to bind to cells end-on — that is, the particles' chemical properties control the orientation of their interactions with the cells. Conversely, microtubes were also made with adhesive molecules along their outer length but not on the ends and these tend to bind to cells side-on.

Much of our knowledge about particle interactions with cells originates from studies of spherical particles that have uniform surface chemistry. However, it has become clear that particle shape plays a major role in these interactions. For example, two particles made of the same polymer may have different rates of uptake by cells, solely because of differences in their shape and in their orientation relative to the cells². Furthermore, different surface patterns on particles can have distinctively different effects on the fate of the particles' interactions with cells³. These effects are important for many potential medical applications of nano- and micro-particles, particularly drug delivery.

Particles that have tuneable orientations for cell attachment, like those developed by Gilbert *et al.*, might provide a new level of control over drug delivery into targeted cells. Cell-binding 'patches' on particles could regulate how those particles bind to cells, and even which cells they bind to, if biochemical molecules that target particular proteins or receptors are added to the patches. Furthermore, the other key properties of such particles including their size, aspect ratio (the ratio of width to length) and stiffness could be used to influence rates of particle binding and uptake into the cells.

It can also be envisaged that new biomaterial–cell constructs could be created by using such particles to connect cells into a network that has highly tuneable properties, for example, by changing the numbers, dimensions and cell-binding tendencies of the particles. This could facilitate the formation of biomimetic or tissue-like hybrid materials that contain living cells in an environment that is more like their native milieu than commonly used *in vitro* supports for cells. Furthermore, regulation of cellular microenvironments can alter cellular functions, such as differentiation of stem cells, cell-growth rates and gene expression⁴. So, if cells bind particles in a selective orientation, the particles could potentially also shape how those cells are organized in three dimensions. Such orientation-specific interactions could be valuable for generating scaffold-free tissue engineering constructs. In the future, it might also be possible to form cell-based polymers, using microtubes with engineered regions to link cells to form different architectures, including linear and branched systems.

To achieve therapeutic applications of the microtube particles, several challenges need to be overcome. These include the formation of microtubes that are biocompatible and which can respond to, and degrade in, cellular or physiological conditions. It is likely that Gilbert and colleagues' work will trigger research into optimizing the efficiency with which such particles can be produced and attached to cells, and into what happens to the particles and cells when they interact over extended times *in vitro* and *in vivo*. This is well worth it, because the

prospect of being able to design particles to deliver payloads of drugs and organize cells in new ways is exciting.

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Figure 1 | Surface properties control interactions of polymer tubes with cells.

Gilbert *et al.*¹ have prepared polymeric, micrometre-scale tubes from cell-resistant (orange) and cell-adhesive (green) polymers. **a**, When incubated with mouse cells, the microtubes made from only the cell-resistant polymer did not bind to the cells. **b**, Microtubes that were cell-adhesive along the sides but cell-resistant on the ends bound to cells side-on. **c**, Microtubes that were cell-resistant along the sides, but cell-adhesive at the ends bound to the cells end-on.

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Title:

MATERIALS SCIENCE To bind or not to bind

Date:

2013-10-17

Citation:

O'Connor, A. J. & Caruso, F. (2013). MATERIALS SCIENCE To bind or not to bind. NATURE, 502 (7471), pp.313-314. <https://doi.org/10.1038/502313a>.

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