Editorial

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The intersection of bottom-up synthetic cell engineering and nanobiotechnology

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Nanotechnology is intimately intertwined with efforts to bring bottom-up synthetic cell research to the forefront, and only strengthening these bonds will expand the scope of what this might achieve.

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The term 'synthetic biology' made its debut in the 1980s when Barbara Hobom used it to describe genetically modified bacteria created using recombinant DNA technology[1]. Despite being a relatively young scientific discipline, the transformative aspect of synthetic biology has had an unparalleled impact on various research disciplines. Global alliances of synthetic biology-related organizations, such as the SynBio Alliance (https://community.igem.org/synbio-alliance), have been formed to further expand research into their applications and promote technological innovations. These bodies actively encourage collaborative efforts among stakeholders within the synthetic biology landscape worldwide.

While most research efforts in synthetic biology in the traditional sense focused on biotechnology-based approaches (for example, synthetic gene networks for biosensing, metabolic flux engineering, anti-microbial drug discovery, therapeutic antibody developments) in parallel, bottom-up synthetic cell research has picked up significant momentum and aims to tackle outstanding fundamental questions and churn out meaningful applications. To this end, the synthetic cell community has organized itself around the central theme of building artificial cells with its 'Build-a-Cell' initiative (https://www.buildacell.org/). The grand challenge for researchers in the bottom-up synthetic cell community is assembling a minimal, compartmentalized functional unit that is self-sustaining, self-regenerating and stimuli-responsive and may eventually exhibit traits of Darwinian evolution. Additionally, studying these minimally reconstituted systems will offer us a deeper insight into the phenomenon we call 'life'. An advantage of the bottom-up approach is that synthetic cells can be assembled, studied, and tested under controlled conditions against variables and predictive models.

In this direction, researchers have demonstrated various functional biomimetic compartments. These have been put together via self-assembly or programmed routes using modular building blocks with natural and non-natural molecular components, recapitulating some of the essential functional parts and features of a natural cell[2,3]. While looking at almost all these examples, it is evident that these two distinct scientific fields, that is, bottom-up synthetic cell engineering and nanobiotechnology, continue to intersect and converge. This should not come as a surprise since the governing principles that influence bottom-up assembly leading to membrane compartment formation, the chemical reactions occurring within these spaces, selective transport across these barriers and scaffolds that give mechanical stability squarely fit into the 'nano' regime. Some notable examples of recent studies where such an intertwining is apparent are the use of ceria nanozyme for receptor activation in transmembrane signalling[4], DNA origami-based scaffolds as structural cytoskeletons and directional vesicle transport[5], and the motion of a liposome driven by a mechanochemical feedback loop with the help of the MinE protein[6]. Besides these, a recent study discovered that dynamin A, a bacterial GTPase aided by cholesterol-linked DNA nanostructures as synthetic membrane shapers, could be used as a single-component division machine for realizing the complete fission of lipid-membrane-based synthetic cells[7]. Not surprisingly, such a convergence has historically stimulated discussions around epistemology[8].

Efforts into synthetic cell research must have realistic goals in sight. To this end, thought-provoking ideas and opinions have been voiced and discussed in a recent thematic issue on 'Cell mimicry: bottom-up engineering of life' in *Interface Focus* (https://royalsocietypublishing.org/toc/rsfs/2023/13/5). Foreseeable applications that bottom-up approaches to synthetic cells can enable will range from biosensors for diagnostics to nanoreactors for therapeutics, in synthetic immunology for engineering immune cell signalling and adaptive/intelligent biomaterials. Many of these opportunities motivate researchers to venture into unexplored territories, tackling new problems and proposing novel solutions. However, it is early to speculate whether we are at the stage where engineered entities exhibiting emergent life-like functions (or 'Life 2.0') will impact everyday aspects of human life.

At *Nature Nanotechnology*, we share the optimism and excitement of the synthetic biology community for the incredible journey ahead. We hope nanobiotechnology-enabled approaches will continue stimulating research into bottom-up synthetic cells. *Nature Nanotechnology* will always be home to breakthrough research and milestones in the bottom-up synthetic biology field, with the 'nano' aspect at the core of the study. Equally important, we also want to signal our interest in joining the synthetic cell community in their continued efforts to engage with the broader society on the philosophical and ethical aspects of the convergence of fields from synthetic biology and nanobiotechnology for Life 2.0.

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