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Cell-free biotech will make for better products

A new type of biological engineering should speed up innovation

THE stuff of life comes wrapped in tiny bags called cells. Inside are DNA molecules that carry the instructions for how to run the cell, to make it grow, and to cause it, ultimately, to divide into two cells, if that is to be its fate. Messages made of a slightly different molecule, RNA, carry these instructions to molecular machines called ribosomes. A ribosome's job is to read the RNA messages and translate them into proteins, the workhorse molecules of cells. Those proteins then supervise and execute the running, the growing and the dividing.

It is a system that has worked well over the 4bn years that life has existed on Earth. To some biotechnologists, though, the cell is old hat. They approve of the machinery of DNA, RNA, ribosomes and proteins, which can be engineered to make useful chemicals, ranging from drugs to the building-blocks of plastics. But they want to get rid of the bags that contain it, retaining only the part of the protoplasmic "gloop" inside a cell needed to do their bidding.

In this way they hope to control, far more precisely than is possible by conventional genetic engineering (or even by improved methods of gene modification, such as CRISPR-Cas9, that are now being developed) which genes are translated by the ribosomes—and thus what products are churned out. Equally important, cell-free biotechnology of this sort means no biochemical effort is wasted on running, growing or dividing any actual cells. The initial intention is to create a quicker way of finding the best genes for making a particular product. In the end, those working in the field aspire to the idea that cell-free production will equal mass production.

Processing power

A typical recipe for making cell-free protoplasmic gloop is this. Take four litres of culture containing E. coli (a gut bacterium favoured by genetic engineers). Split the bacterial cells open by forcing them through a tiny valve at pressure, thus shredding their membranes and DNA, and liberating the ribosomes. Incubate the resulting mixture at 37°C for an hour, to activate enzymes called exonucleases that will eat up the fragmented DNA. Centrifuge, to separate the scraps of cell membrane and other detritus from the gloop that contains ribosomes. Dialyse to remove unwanted ions. Then stir in amino acids (the building blocks of proteins), sugar and an energy-carrying molecule called adenosine triphosphate (ATP) to power the process. Finally, add a pinch of new DNA to taste, to tell the gloop which proteins it is supposed to produce.

This particular recipe is the one used by Synvitrobio of Berkeley, California, a firm founded by Zachary Sun and Richard Murray of the California Institute of Technology and George Church of Harvard University. Other recipes, with different starting organisms, are possible. Yeast works, as does Streptomyces, another bacterium. Cells from tobacco plants or the ovaries of

Chinese hamsters are also good places to begin. But all such formulae are variations on the theme of isolating a cell's protein-making machinery in a free-floating suspension.

Synvitrobio's engineers have built a robotic system to mix the final stage of their recipe. This robot parcels the purified protoplasm into an array of 384 miniscule test tubes, each with a volume of a few millionths of a litre. It then drops some DNA molecules into each tube and the gloop gets to work on the process of turning the information in those molecules into proteins. Currently, the system can handle eight DNA sequences per test tube, meaning 3,072 proteins can be processed in parallel. The sequences can be up to 10,000 genetic "letters" long—enough to encode almost any protein you care to mention.

At present, Synvitrobio is using its system to test DNA sequences (or, rather, the resulting proteins) to see if they might be worth investigating as antibiotic drugs. Such drugs work by binding to a biologically important molecule and changing that molecule's characteristics in some way that is detrimental to the organism of which it is part. To look for this binding, each mini test tube is also supplied with some of the target molecules, each attached to a "reporter" molecule that emits a flash of light if binding takes place.

Tubes which flash brightly indicate that one or more of the DNA sequences therein are worth a second glance. Synvitrobio's technique is thus able to screen potential drugs at a rate limited only by the availability of new DNA sequences. Since synthesising new sequences on demand is now a routine technology, that means the world's gene libraries can be plundered for likely candidates, and the best of these then tweaked mercilessly until something good enough for the job turns up. Inserting such sequences into the genomes of organisms is far more time-consuming than simply dropping them in some gloop.

At the moment, that is the point when Synvitrobio passes the newly discovered molecule on, for a suitable cut of the proceeds, to someone who can turn it out in bulk by the conventional technique of pasting the relevant gene into appropriate cells, and breeding these cells in fermentation tanks similar to those used for brewing beer. This is because it is expensive to produce cell-free protoplasm in the volumes required to manufacture antibiotics for sale. A few firms are, however, doing so for drugs that can command high prices.

One such is Sutro Biopharma, based near San Francisco. It uses a cell-free system to create antibodies for the treatment of cancer. In April, Sutro announced it had employed its system to make STRO-001, an antibody that inhibits tumour growth. The firm plans to start trials of STRO-001 in 2018. Cell-free production of the antibodies for that trial is about to begin.

Antibodies are specialised proteins, so once Sutro's system has identified the best candidate for the job, all that is required is to seed the gloop with the DNA which encodes that candidate. Other firms, though, hope to go further than this, by devising manufacturing systems that put together entire metabolic pathways for the production of chemicals other than proteins. These, as in a natural metabolic pathway, consist of a series of enzymes (another type of specialised protein) that catalyse a sequence of chemical changes, gradually converting one molecule into another.

Genomatica, an established biotechnology firm based in San Diego, is experimenting with a cell-free system which produces 1,4-butanediol in this way from simple sugars. 1,4-butanediol is a small molecule that is used to make polymers such as Lycra. Generally, it is cheaper to manufacture molecules of this size using chemistry, rather than biology, but 1,4-butanediol is an exception. It is already made for industry with the aid of genetically modified E. coli. Genomatica's system churns out the enzymes involved in this synthesis, creating an entire cell-free metabolic pathway—and one in which all the sugar is devoted to making the target chemical, rather than a percentage of it being creamed off to run a cell's other biochemical processes. The firm has not yet put the system to commercial use, but has high hopes for it.

GreenLight Biosciences, a firm in Medford, Massachusetts, proposes to use its own cell-free system, also based on E. coli, to produce industrial quantities of an undigestible analogue of ribose, a naturally occurring sugar, for use in zero-calorie beverages. The company says it has already got its process to the point where it can make thousands of litres of solution of this sugar at a time. GreenLight is also working on cell-free systems that will generate industrial qualities of specially designed RNA molecules that interfere with the development of insect larvae, and can thus be used as pesticides. Currently, such RNA costs $5,000 per kilogram to produce. GreenLight thinks that by scaling the process up it can reduce this to between $50 and $100.

Whether cell-free biotechnology will be able to displace fermentation by genetically modified organisms as a routine way of making chemicals remains to be seen. Fermentation is a tried and trusted technique, used by humans since the invention of beer around 12,000 years ago. But the idea of stripping molecular biology down to its bare essentials has an efficiency about it which suggests that, for some applications at least, the utility of the biological cell may have run its course.