DNA ORIGAMI

TEXT: MARA THOMAS

What is life? How did it emerge? And could it possibly look completely different? At Kerstin Göpfrich's lab at the Max Planck Institute for Medical Research in Heidelberg, scientists are working on answers to the really big questions. Her research group's plan is no less ambitious: to create artificial cells and, by so doing, to discover what is essential for life.

Even the simplest bacterial cell is so complex that disentangling the interplay of its varied components is hugely challenging. It is similarly difficult to determine which of these elements is indispensable for the life of the cell and which is merely a biological "spandrel" – a by-product of the process of evolution. "What I cannot create, I do not understand is a maxim of the physicist Richard Feynman, and for me it holds true: I can only fully understand something if I can create it myself," says Kerstin Göpfrich. This approach is not solely the central theme of her own scientific work, but of an entire field of research: synthetic biology. Some scientists in this field use living cells as a starting point, while others begin with individual cellular components, which they try to reassemble like pieces of a jigsaw puzzle.

And other researchers even go one step further: they plan to design a cell from scratch, using as few building blocks from nature as possible. Because these scientists almost exclusively use new components that have been produced in the laboratory, Göpfrich refers to this approach as "de novo synthetic biology." Proponents of this method are attempting to detach their work from the natural building blocks of life. Are there, for instance, alternatives to cellulose as a material for cell walls? What potential ways are there for a cell to generate energy, and how might it store information?

Components such as the cell membrane, nucleus, or the mitochondria can also be simplistically regarded as systems, respectively, for packaging, information storage, and energy production. These researchers are now looking for alternatives that can accomplish these tasks as well as, or better than their natural counterparts. "Emancipating ourselves from nature provides us with a lot of creative freedom. It allows us to overcome hurdles more quickly," explains Göpfrich. But in any event, laboratory-developed systems like this need to fulfill one condition: they should eventually enable the creation of a new type of cell that possesses all the characteristics of life, in particular, its ability to reproduce and evolve.

Göpfrich's enthusiasm for her field of research is so infectious that it comes as no surprise that she manages to excite non-scientists about her field of specialism as well. Her videos and essays about scientific research are both entertaining and informative. She regularly gives public lectures, presents science talks in schools, and founded the "Ring-a-Scientist" initiative, which links up researchers and teachers to bring science into the classroom via videoconferencing. "Dialog with the public helps me focus on the questions I want to answer through my research: what constitutes life, how might it have arisen, and what other forms of life are possible."

Well packaged in fat molecules

In recent years, Göpfrich's team has been working on the cell membrane, the structure enveloping cells. Life depends on boundaries, at least on a biochemical level. Only by means of boundaries can living systems separate themselves from their environment and create the conditions for their survival within. In nature, the cell membrane consists of a double layer of fat molecules called lipids. →

PHOTO: KATRIN BINNER FOR THE MPG

KNOWLEDGE FROM

BIOLOGY & MEDICINE

Like paper in traditional origami, DNA can be formed into almost any shape. DNA is a long, thread-like molecule, but the technique can be used to fold it into sheets, tubes, boxes, or, if desired, into a cloverleaf.

Scientists already know how to produce such envelope structures in large quantities. Termed "vesicles", they are surrounded by a lipid bilayer and filled with water, just like natural cells. "They are our basic model of a cell," says Göpfrich. "The aim now is to fill the vesicles with life." To accomplish this, the team is utilizing tools from a wide variety of disciplines. One of these is "microfluidics", the targeted maneuvering of tiny amounts of liquid onto microchips the size of a fingernail. This tool allows scientists to sort vesicles by size or content, inject them with substances, and merge two vesicles together. The vesicles are stable enough that researchers can endow them with life-like functions. Reproduction is at the very top of their list. "Regardless of who you ask, the answer to the question of what constitutes a living cell is usually that it must have the ability to divide." The capacity to reproduce is indeed one of the scientific criteria for life.

SUMMARY

To better understand the nature of life, researchers are seeking to develop artificial biological systems. This research involves looking for completely new ways of recreating the properties of cells.

Artificial fat vesicles can mimic the membrane of natural cells. Some can even divide and move around.

Targeted combinations of DNA molecules autonomously fold into a desired shape to form structures that can perform different tasks (DNA origami). Scientists can precisely predict what form multiple DNA molecules will take.

PHOTO: KATRIN BINNER FOR THE MPG

Kerstin Göpfrich is fascinated by the idea of constructing a living cell. She wants to not only make use of prototypes found in nature, but also to completely redesign individual cellular components.

It's a challenge that Göpfrich's team has already surmounted. They can cause vesicles to divide, for instance with the aid of a pulse of light. The light causes a specific type of molecule in the surrounding liquid to decompose and thereby increase the surrounding solute concentration. To counterbalance the resulting osmotic disequilibrium, water flows out of the vesicles. The trick is to make sure the vesicles don't just shrivel but, instead, actually divide. To achieve this, the researchers introduce two different types of lipid molecules into the membrane of the vesicle. These molecule types have a tendency to segregate from each other, and this, together with the shrinking process, causes the vesicle to divide into equally-sized daughter vesicles. There's a catch, though. The daughter vesicles formed in this way cannot continue to divide using the same method, since they now each consist of only one of the two fat molecule types. The researchers therefore allow them to fuse with small globules of fat, each composed of molecules of the other fat type. This allows the daughter vesicles to divide once again.

Cells can assume a wide variety of shapes depending on their type. This is another property that Kerstin Göpfrich has also imbued in her vesicles. It requires an artificial cytoskeleton that, ideally, molds itself in response to a stimulus from the surroundings. To achieve this, the team uses building blocks incorporating a pH-sensitive molecule. These blocks attach themselves to the lipid membrane at a high pH, forcing the membrane to flatten out locally. "The material we use to make our cytoskeleton is nothing really unusual; it's in every one of our cells: DNA," says Göpfrich. The DNA molecule contains a pH-sensitive region and a molecular region that can bind to the lipid envelope, enabling it to deform the vesicles when the pH in the environment changes.

DNA, in general, is a material that Göpfrich has high hopes for – not only as a carrier of inherited information, but also as a versatile biological building block. This technique, in reference to the Japanese art of paper folding, is also referred to as "DNA origami", because, analogous to paper, DNA molecules can also be designed to fold and take on almost any required shape. The technique can be used to construct tunnels, plates, boxes, or connectors between components that are only millionths of a millimeter in size. Along with microfluidics and 3D printing, DNA nanotechnology is one of the key technologies that Göpfrich's team is utilizing. They offer researchers a wide range of possibilities for constructing components for cells and assembling them into a single unit. As part of her doctoral thesis, Göpfrich had already designed and investigated one such component: artificial membrane pores made of DNA to facilitate the exchange of signaling substances.

DNA molecule pair bonding

As Göpfrich explains, the principles underlying DNA folding have been known for a long time: "The secret is chemical interactions between the four different molecular building blocks of DNA, the bases thymine, adenine, cytosine, and guanine. In DNA origami, multiple DNA molecules combine in such a way that as many base pairs as possible are formed. Hence, a long strand of DNA can be shaped by many short DNA snippets until the entire DNA structure attains an energetically favorable state," explains Göpfrich. Using computer software, she can calculate the DNA sequence required for a particular shape. In addition to playful structures such as smileys, stars and other geometric shapes, the technique also makes it possible to produce components for an artificial cell.

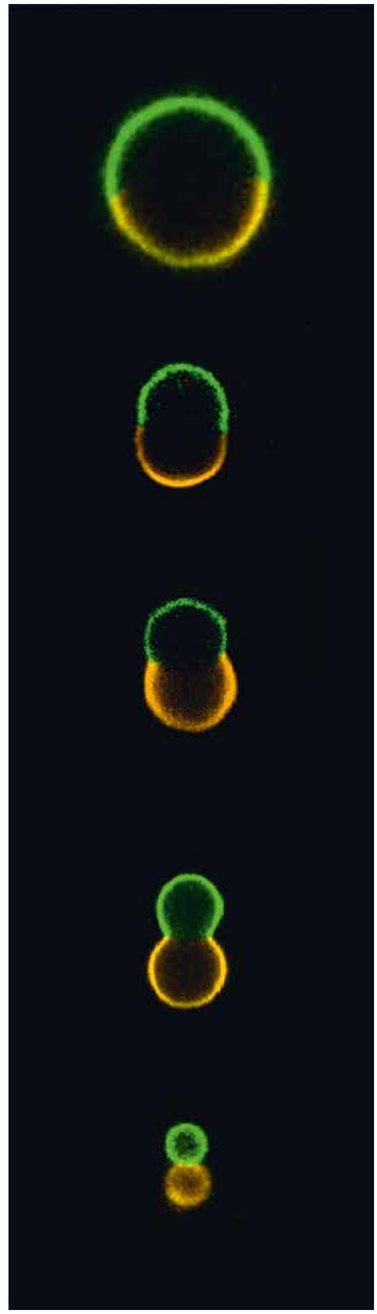

IMAGE: YANNIK DREHER/MPI FOR MEDICAL RESEARCH

When a vesicle's fat molecules (yellow, green) segregate and it simultaneously shrinks, the vesicle starts to divide. Is this a model for artificial cell division?

Equipped with such structures, artificial cells could one day perform a variety of tasks, for example, serve as miniaturized helpers in the human body. "We're still a long way off from creating living systems from scratch," Göpfrich says. But researchers are already making discoveries that are proving useful in other areas of research and in medicine. Göpfrich's self-dividing vesicles, for example, can be used as a sensor to determine solute concentrations, something which, to date, has been very difficult to accomplish during microscopy experiments. This has led Göpfrich to patent some of her findings.

The next big step is to develop a system for encoding information. "In natural cells, the genetic information is in the DNA of the cell nucleus. Right now, we're searching for artificial systems that can encode information. They need to be able to store data permanently and replicate themselves within cells. If we could find a system that can not only produce copies that are accurate but that also occasionally deviate from the originals, we would even have met one of the prerequisites for evolution," explains Göpfrich. It would allow the artificial cells to autonomously evolve. The researchers would then only need to steer this evolution in the desired direction.

Terms like "artificial life" and "artificial organisms" are often used in a misleading way and arouse fear. "Synthetic biology, however, is not in the business of creating monsters like Frankenstein; what primarily interests us are cells. Our research could lead to the development of artificial cells that could one day be programmed to perform medical tasks," says Göpfrich.

At present, the science of building cells is in its infancy. Artificial cells today possess, at most, a small number of characteristics of life, and even then, only in the laboratory. As Kerstin Göpfrich explains: "As yet, our work barely touches on ethically sensitive issues; at this point, artificial cells are little more than molecular aggregates – constructs made of dead matter, no different to those in other areas of materials science and nanotechnology. Nevertheless, it's important that we don't lose sight of the ethical dimension of our research."

www.ring-a-scientist.org