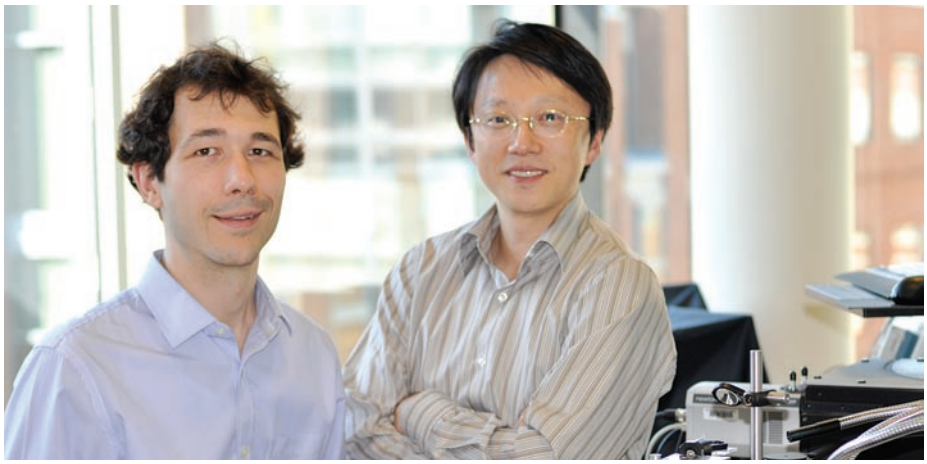
Cellular lasers

Researchers have now shown that lasers — usually thought of as being inanimate optoelectronic instruments — can also be made from certain biological gain media. *Nature Photonics* spoke to Malte C. Gather and Seok Hyun Yun about their realization of a living single-cell laser.

How did this idea start?

Certain organisms in nature — mostly marine species — can synthesize fluorescent proteins. One example is the jelly fish *Aequorea victoria*, which produces green fluorescent protein (GFP) and uses it to generate bright green bioluminescence. Biologists have shown that GFP can be a very interesting tool for cell biology because it allows you to clearly see where and when the protein is formed inside a cell. Almost any organism from bacteria to higher mammalians can be programmed to synthesize such luminescent proteins, so we wondered if GFP could be used to amplify light and build biological lasers. If we could do that, we knew it might even be possible to generate laser light from a single cell.



GIULIANO SCARCELLI

Malte C. Gather (left) and Seok Hyun Yun (right) have developed the first single-cell biological laser.

How did you make your single-cell laser?

We started by genetically programming cells to produce GFP. We placed these GFP-expressing cells into a microcavity, which in our case was formed by two parallel dielectric mirrors spaced 20 μm apart — only one cell can fit in this width. We then used a customized microscope to homogeneously expose an individual cell to short (~5 ns) pulses of blue light. Normally the cell would just fluoresce, but in this case cavity feedback caused the stimulated emission of green light. The energy levels of GFP form a quasi-four-level laser system that is similar to the four-level systems described in laser physics textbooks. We observed clear threshold behaviour in the output intensity and shape of the emission spectrum. A unique characteristic of this laser is that the gain medium is comprised solely of biological materials. The fluorescent proteins are produced and reabsorbed by the cell in a very dynamic process. This means that the laser can self-heal; if we photobleach or damage some of the emitters, the cell can make new ones.

Are the cells damaged by the lasing?

The lasing threshold is very low — around 1 nJ per pulse. You would have to pump the cells far above this threshold to induce any thermal damage. Of course we were able to kill the cell, but this required a pump power that was orders of magnitude higher than the normal operating range. We also saw some dynamic changes related to photobleaching as the pump power was varied. However, the cells were alive before and after laser operation, which suggests that they can function normally for a long period afterwards.

What were the main challenges?

Both of us have physics backgrounds, but making the single-cell laser required an interdisciplinary approach combining biology and photonics — bringing these aspects together was a challenge. Also, we realized early on that we would need a lot of fluorescent protein for trial experiments. Fortunately, we were able to obtain purified proteins produced by *Escherichia coli* bacteria in large quantities. Another challenge was that we were limited by the pump sources available to us. Initially we employed a green 532 nm *Q*-switched laser that forced us to use different proteins such as red fluorescent protein, which was quite expensive to purchase in large quantities. But then we found an old tunable optical parametric oscillator system in a storage room that allowed us to generate blue pump light and switch to using GFP. Now that we understand the system more, we can work with tiny quantities of GFP-producing cells and, in principle, could use a compact diode-pumped solid-state laser.

What does the future hold for this technique?

We are currently working on several projects, including the realization of stand-alone cellular lasers by integrating the cavity with the cell using nanostructures. We also have a prototype of the cellular laser in a microfluidic platform. In terms of applications, laser sources at the cellular level may be useful for biological imaging; compared with regular fluorescence, the emission from a cellular laser is intense, directional, narrowband and has characteristic temporal and spectral modes. We can think about new applications by harnessing these properties. For example, in cellular sensing we may be able to detect intracellular processes with unprecedented sensitivity. For light-based therapeutics, diagnosis and imaging, people think about how to deliver emission from an external laser source deep into tissue. Now we can approach this problem in another way: by amplifying light in the tissue *in situ*.

INTERVIEW BY DAVID PILE

Malte C. Gather and Seok Hyun Yun have a letter on single-cell biological lasers on page 406 of this issue.