SNAP-tagging gives scientists a glimpse of nerve function

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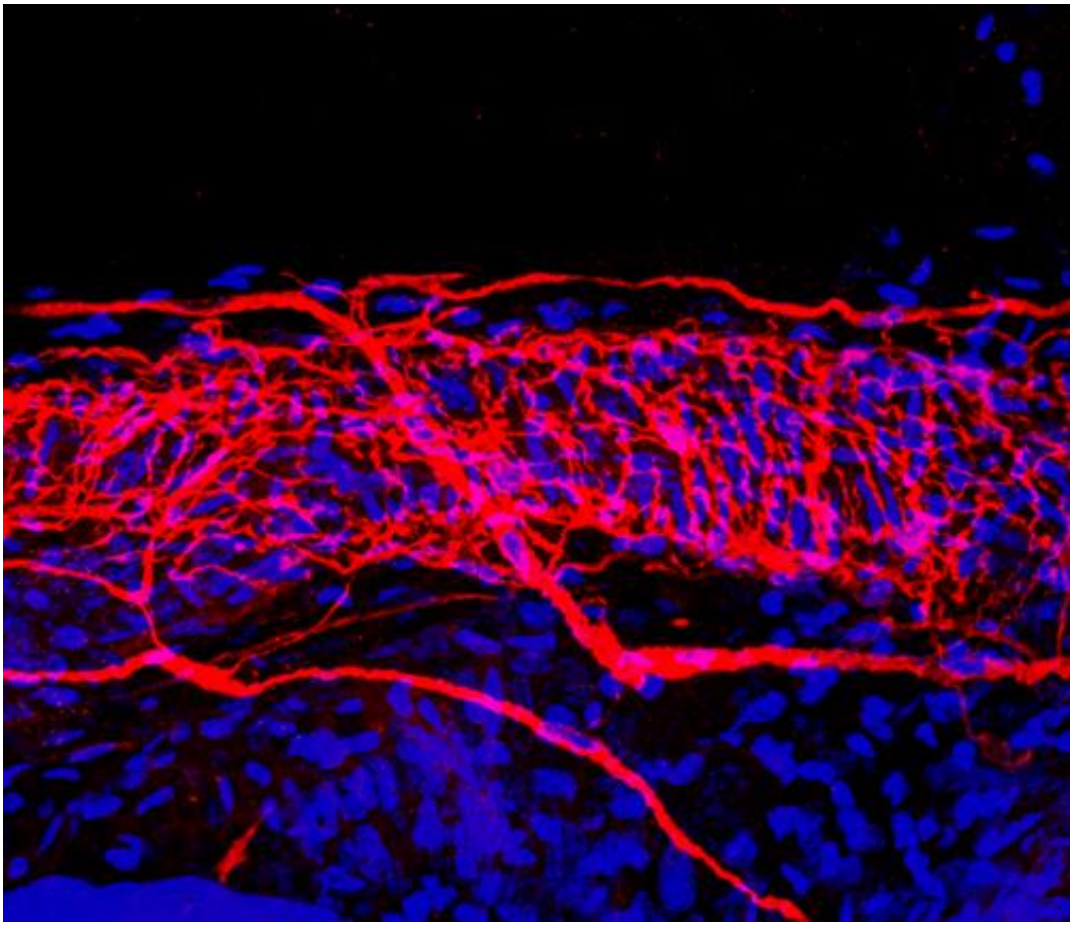


“This is my favorite image – we'd never seen anything like this until we used this technique,” says Heppenstall. “It shows that free nerve endings [red] in the skin split into an incredible number of branches.” Labelled in blue are the nuclei of the skin’s cells. Credit: EMBL/S. Morley

Scientists can now explore nerves in mice in much greater detail than ever before, thanks to an approach developed by scientists at the European Molecular Biology Laboratory (EMBL) in Monterotondo, Italy. The work, published online today in *Nature Methods*, enables researchers to easily use artificial tags, broadening the range of what they can study and vastly increasing image resolution.

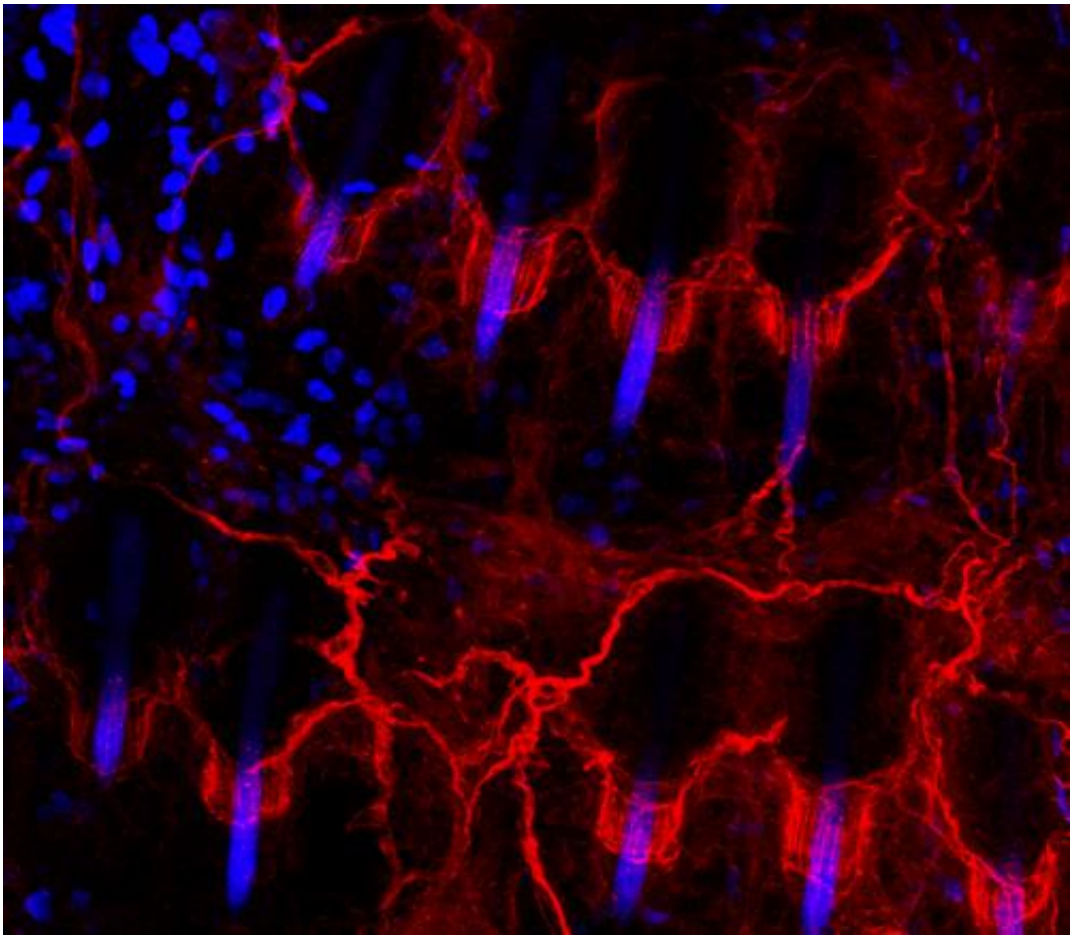
"Already we've been able to see things that we couldn't see before," says Paul Heppenstall from EMBL, who led the research. "Structures such as nerves arranged around a hair on the skin; we can now see them under the microscope, just as they were presumed to be."

The technique, called SNAP-tagging, had been used for about a decade in studies using cell cultures – cells grown in a lab dish – but Heppenstall's group is the first to apply it to neurons in living mice. It allows researchers to use virtually any labels they want, making it easier to overcome the challenges that often come with studying complex tissues and animals. To study nerves in the skin, for instance, Heppenstall's lab can employ artificial dies that are small enough to cross the barrier posed by the skin itself, and stand out better from the skin's natural fluorescence. And because these are artificial, custom-made tags, they can be designed to do more than just highlight particular structures. Scientists can produce tags that destroy certain structures or cells, for instance.

SNAP-tagging relies on a small protein that binds to a specific small chemical structure – and once bound, it won't let go. The EMBL scientists genetically engineered mice so that their cells would produce that SNAP protein. They then used fluorescent probes that contain the small chemical that SNAP binds to, and injected them into the mice. SNAP acts like an anchor, glueing the tags in place for researchers to follow under the microscope.

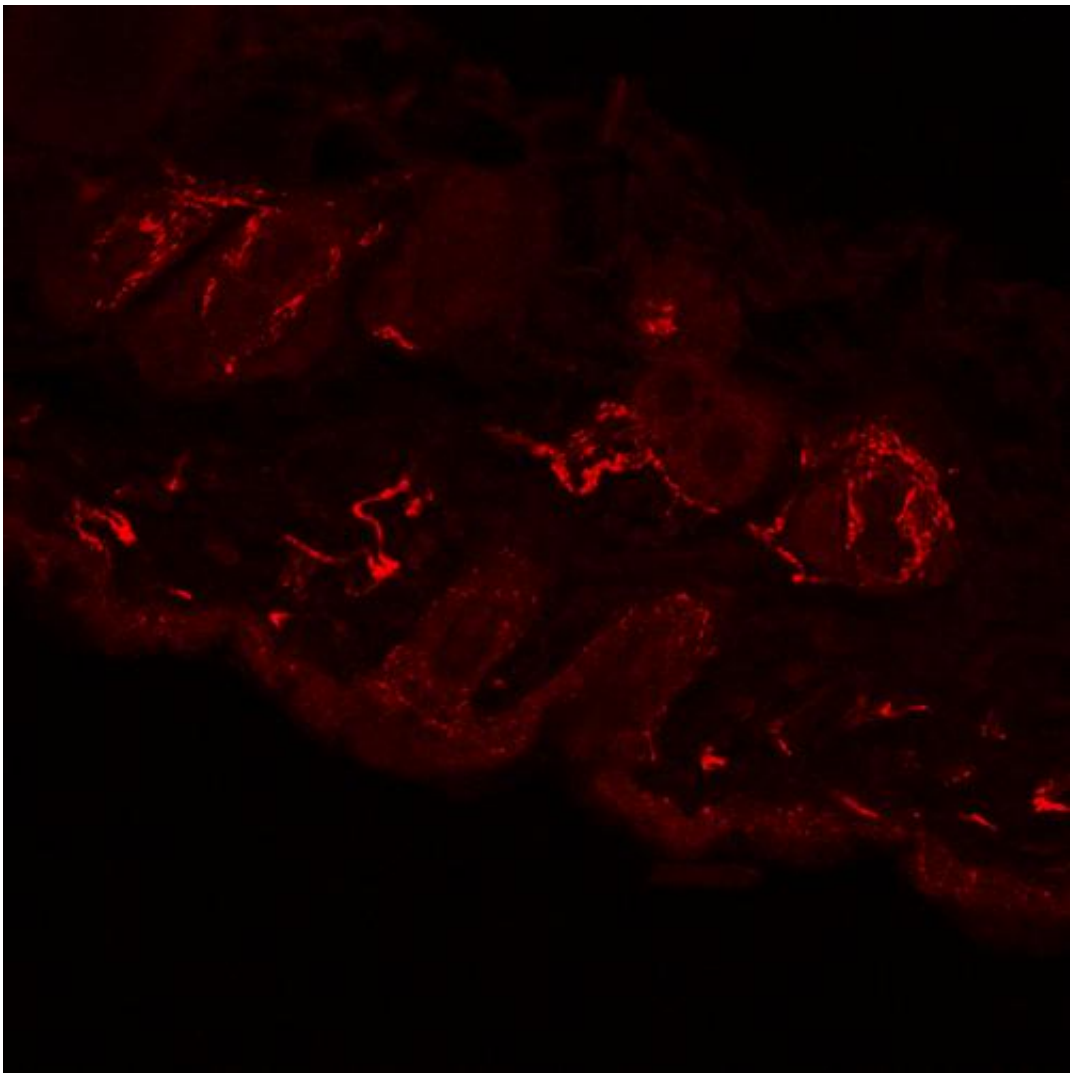
Ultimately, Heppenstall aims to employ this approach to record activity in individual neurons. For instance, he'd like to mechanically stimulate the skin, or change its temperature, and watch that information flow through the nerve, to the next nerve, tracking it throughout the whole network. In principle, he speculates, you could do this in a whole brain. It would be like a taking a scan and zooming in to see what's happening inside each nerve cell.

The work was carried out in collaboration with Kai Johnsson's lab at the École Polytechnique Fédérale de Lausanne, in Switzerland, which helped to develop the tag.

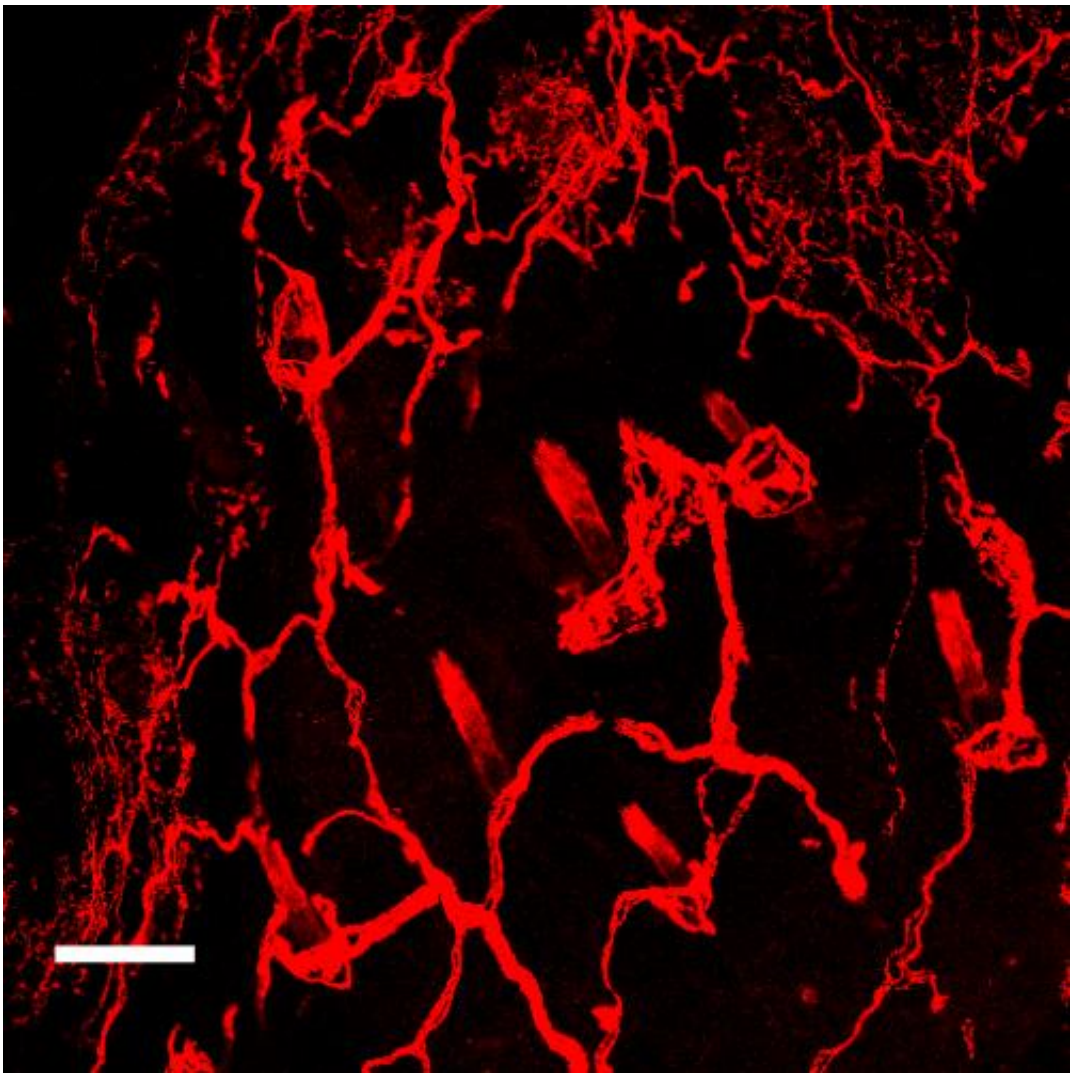


With a new technique, called SNAP-tagging, the EMBL scientists have been able

to see the nerves (red) that branch into a ‘basket’ of endings around the base of each hair (thick blue line) with unprecedented detail. Credit: EMBL/L. Castaldi



The skin’s natural properties create substantial challenges for scientists wanting to study its nerves under the microscope. Labels that relied on large molecules such as the antibody used here, for instance, had difficulty penetrating the skin. Credit: EMBL/R. Dhandapani



With the new technique, researchers can use custom-made artificial labels designed to overcome the challenges posed by skin's natural properties, obtaining much more detailed images of the skin's nerves. Credit: EMBL/F.C. Reis

More information: "Genetic targeting of chemical indicators in vivo." Published online in *Nature Methods* on 8 December 2014. DOI: 10.1038/nmeth.3207.