Probing intraneuronal transport *in vivo* with optically active photostable nanocrystals

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Neurodegenerative disorders such as Alzheimer's disease involve a large network of genes displaying subtle changes in their expression. Abnormalities in intraneuronal transport have been linked to genetic risk factors found in patients, suggesting the relevance of measuring this key biological process. However, current techniques are not sensitive enough to detect minor abnormalities.

In 2017, we reported a method able to measure changes in intraneuronal endosomal transport induced by brain disease-related genetic risk factors mimicked in transgenic mice (*1*). It relied on tracking fluorescent nanodiamonds (FNDs) after their spontaneous endocytosis by hippocampal neuron in culture, and takes advantage of FND.

Here we report the extension of this nanoparticle tracking based-approach to multiphoton microscopy (MPM), opening the possibility of intracellular transport measurement *in vivo* thanks to tissue transparency in MPM excitation wavelength range. To this aim we have tracked sized≈100 nm $KTiOPO_4$ (KTP) nonlinear nanocrystals endocytosed in axons of the periventricular neurons after microinjection in the optical tectum of living zebrafish larvae. NanoKTP large nonlinear second order optical response (*2*) allowed us to maintain the same 20 frames/s rate as in widefield imaging with FND, despite the need for raster-scanning. We showed that we can detect slight endosomal transport impairment due either to knock-out of molecular motor-related genes.

1. S. Haziza *et al.*, *Nat. Nanotechnol.* **12**, 322–328 (2017).
2. L. Mayer *et al.*, *Nanoscale*. **5**, 8466–71 (2013).