Revolutionary laser technology could provide a novel approach to painless diagnosis of serious diseases such as cancer and diabetes, and in vivo analysis of drug efficacy – for a fraction of the price of current laser equipment. **Dr Róbert Szipöcs,** research fellow at the Research Institute for Solid State Physics at the Hungarian Academy of Sciences in Budapest, and his colleague, biologist **Dr Attila Kolonics,** explain that the FIBERSC2 project is actually two intriguing projects in one.

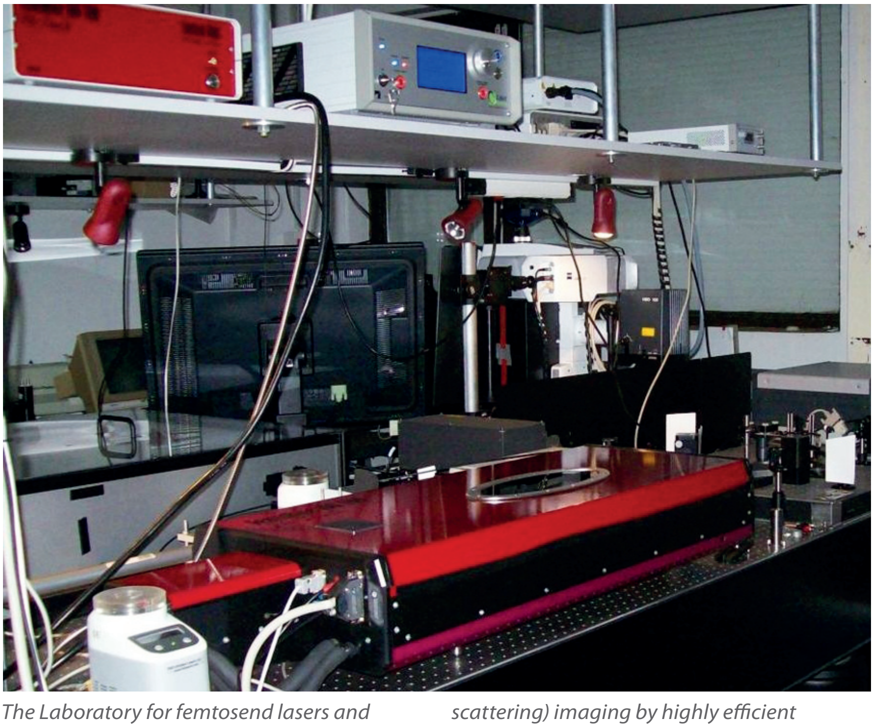
# Optical fiber laser technology delivers the right medicine

Lasers, once the stuff of science-fiction, have become part of everyday industrial life, employed in an array of incredibly detailed applications from guiding mechanisms and cutting tools, to high-speed telecommunications, photo-chemical processing, scientific research and medicine.

Yet despite their apparent ubiquity, current lasers are actually limited by their performance properties – which in turn limits their effective use in medical research and practice, as Dr Szipöcs explains. "Unfortunately, conventional pulsed lasers do not routinely operate below a certain pulse duration and the fibre optics used to transmit them suffer from dispersion and nonlinear effects so that the light pulse is dispersed when reaching the study object. For in vivo 3D microscopy work, a shorter pulse, at a lower thermal load, is required to avoid damaging the study tissue, while dispersion is undesirable because reduces the signal level on the subject area."

Standard laser technology is also very costly. "Broadly tuneable femtosecond pulse solid state lasers such as Ti:sapphire cost hundreds of thousands of Euros – as do the 3D microscopes and micro-endoscopes they go in to – making them prohibitively expensive for widespread research and clinical use," adds Dr Szipöcs. "But if our research is successful, we'll be able to provide effective lasers for approximately quarter of the price of current models."

FIBERSC2 (Femtosecond fibres and fibre-lasers for nonlinear microscopy and micro-endoscopy) is researching both issues in tandem, as two separate but related projects. "The OTKA project aims to develop new fiber optics designs that reduce or prevent the temporal and spectral spreading of the laser's pulses during transmission," says Dr Szipöcs. "The NTP project looks to develop ultra-short-pulse, non-linear laser technologies suitable for micro-endoscopy, for the diagnosis of illnesses including cancer and diabetes, and to monitor the efficacy of drugs in vivo, that are used for treatment.



*The Laboratory for femtosend lasers and nonlinear microscopy at the Research Institute for Solid State Physics and Optics of the Hungarian Academy of Sciences.*

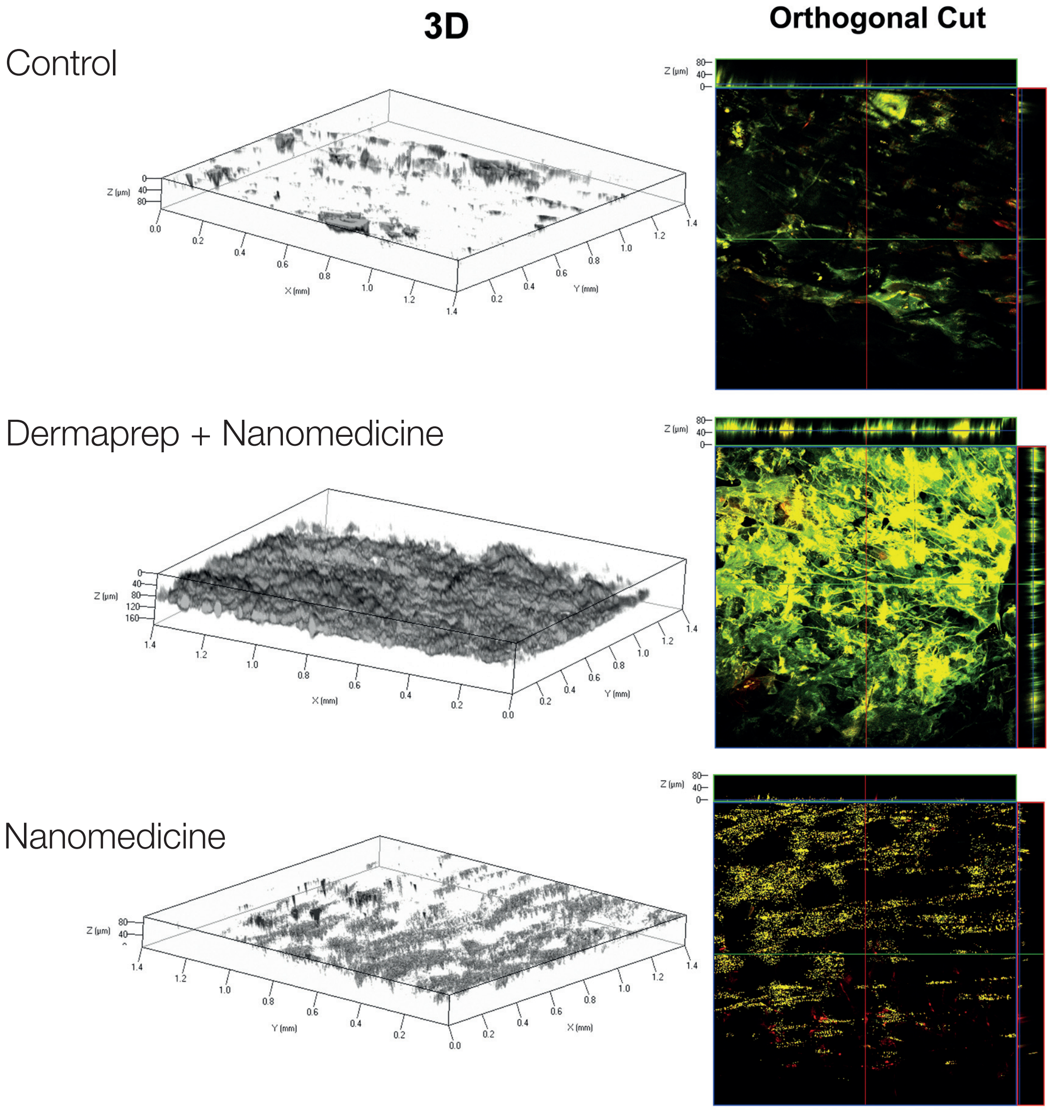
*Bottom left: FemtoRose 100 TUN NoTouch™ broadly tunable Ti:sapphire laser comprising ion-beam sputtered ultrabroadband chirped mirrors for broad tuneability.*

*Bottom right: FemtoFiber™ femtosecond pulse Yb-fiber laser.*
*The FemtoFiber laser is inherently sincronized to the FemtoRose 100 TUN NoTouch laser for CARS (coherent anti-Stokes Raman scattering) imaging by highly efficient nonlinear wavelength conversion in a special photonic crystal fiber.*

*Left (in gray box): the prototype of the broadly tuneable, low (~20 MHz) repetition rate Ti:sapphire laser.*

*Right: the LSM 7 MP Axio Examiner™ nonlinear microscope used for 3D imaging. (The FemtoRose 100 TUN NoTouch™ and FemtoFiber™ are the trademarks of R&D Ultrafast Lasers Ltd, LSM 7 MP Axio Examiner™ is the registered trademark of Carl Zeiss.)*

Dr Kolonics, who heads up the medical and pharmacological application of the




*Nanoparticle penetration into mouse dorsal skin by Low Repetition Rate Ti:Sapphire laser after 2 hours. The data suggested that nanoparticles penetrated far better in case physical trigger reaching 60-80 um depth after 2 hours.*

***Control section was to inform about the basal state of skin autofluorescence after in vivo two-photon fluorescence imaging.***

***In case of Dermaprep + Nanomedicine special rubbing was applied to trigger optimal activation of dentritic Langerhans cell that collect fluorescently labbeled nanoparticles.***

***This special pretreatment was ignored in case of Nanomedicine section, where only nanoparticles suspension was dropped onto the skin surface.***

technology, says if successful, it will offer significant improvements for biological research. "It has always been a dream of biologists to have detailed, high quality 3D microscopy for in vivo imaging, so we can see what is happening, in the body, in real time. By two-photon microscopy tissues show minimal light absorption at so called optical window (650 nm-1300 nm), only endogeneous molecules excitable at these range.

This dynamically developing new method besides revealing the structural alterations provides extreme wealth of information about the chemical composition of the target tissue and the structure of the cells in vivo. In addition it happens without pain by a simple skin readout at the depth of 200 microns.

The obtainable information of target tissue indirectly may offer information about the metabolic condition of the whole body, which maybe exploitable for diagnostic purposes." The NTP project has enjoyed some notable success already, with Dr Szipöcs having already marketed ultrashort-pulse (femtosecond) solid state and fiber lasers in his parallel role as Managing Director of R&D Ultrafast Lasers Ltd, a company that is now one of the partners on the current research project. The solid state lasers make use of what are termed 'chirped' dielectric laser mirrors, invented and developed by Dr Szipöcs in the 1990s, to produce tuneable pulses of just a 80 to 150 femtoseconds (a femtosecond, or fs, being a one million billionth of a second, 1 fs = 10 -15 sec). Whereas standard dielectric mirrors reflect a narrow spectrum of light wavelengths, Dr Szipöcs's invention uses mirrors with 'chirped' structures to reflect a much wider range of wavelengths (typically from 670 nm to 1060 nm).

Chirped-mirror lasers are certainly ahead of the pack – a Ti-Sapphire laser, a model developed for nonlinear microscopy because it is broadly tunable to a range of different wavelengths. A similar laser comprising a chirped mirror compressor held the world record for the shortest pulse – an impressive 4.5fs – set in 1997, which marks a significant achievement for laser technology.

The OTKA project is working with the latest materials to produce more sustainable fibre optics with low nonlinearity and tailored dispersion properties. "Unlike traditional fibre optics, where light travels via a glass core, we're looking at photonic crystal fibre optics where light propagates in an air core, often referred to as hollow-core fibers" says Dr Szipöcs. "This means the short, intense laser pulses don't cause nonlinear effects in the fibres."

Much of the laser research for 3D microscopy has involved imaging skin samples, a readily available source material but also one, as Dr Kolonics explains, that

> “It has always been a dream of biologists to have detailed, high quality 3D microscopy for in vivo imaging, so we can see what is happening, in the body, in real time.”

requires precision lasers for accurate imaging. “In case of success further development of the microendoscope could broaden the area of application: other organs become examinable, like brain, bladder, uterus, esophagus, upper and lower gastro-intestinal tract. Someday it could be an important supplemental tool in the hand of medical doctor to reliable diagnose tissue alterations at several points in real-time without delay and costs of histological sampling.”

So how do Dr Szipöcs and Dr Kolonics view progress so far, in a three-year dual research project due to complete next year? “Well, we have a safe fiber laser source, with a working laser already on the market, and we’ve managed to combine a short laser pulse with a lower repetition rate to give higher quality images without having any damage in the sample,’ says Dr Szipöcs. “We’ve got nice optical fibre designs, too, so progress is very pleasing, but there is still much work to be done.”

Dr Kolonics agrees that, from a medical perspective, there is further painstaking work ahead to achieve the project’s ultimate aim of a marketable, integrated fibre optic laser and nonlinear microendoscope. “If we’re at the clinical trial stage with the laser microendoscope and there is a lot of testing ahead. As always with lasers, its safety first. So we’re trialing them at similar wavelengths where endogenous fluorophores (NADH, flavonoids) are excited, to ensure that the process is no more harmful than sunlight. Then we need to evaluate a range of different wavelengths to see which are safe to use on the human body. We have 2 year left for clinical trial results and would hope at the end of that period to have produced effective prototypes of 3D nonlinear micro - endoscopes. But there’s a big jump from a prototype to a version that can be accurately and affordably mass produced for the market, so that will take a further three years.”

While the team sees the technology largely being used in medical diagnosis, treatment and research, there are potential wider applications too. “The lasers could prove useful in the cosmetics industry or pharmacology and there are obvious possibilities for laser-eye surgery too,” says Dr Szipöcs. “There are also separate research projects in Hungary looking at laser technology for brain imaging. And the optical fibres developed in this project could be used in other industries, such as telecommunications. But for now, we’re just focusing on making a safe, reliable and affordable fibre optic laser for medical use.

It’s the collaboration of the project partners, from theoretical optical fibre designers to laser and pharmacological companies and the Semmelweis University of Budapest, the Department of Dermatology, that has brought the project this far, says Dr Szipöcs. “We are extremely grateful for the efforts of all our partners in helping to make the aims of this project a reality,” he concludes. “And I think it provides a lesson for research at the wider level too. We need to collaborate on a world scale across Europe, the US and elsewhere, to find solutions to the scientific problems of our age.” ★

**Róbert Szipöcs, PhD**

Education:

1982-87 MSc in Electrical Engineering, Technical University (TU) of Budapest

1987-90 University Doctoral Degree in Technical Physics, TU Budapest

2001 PhD in Physics, University of Szeged

## At a glance

*Project Information*

**Project Title:**
FIBERSCN: Femtosecond fibres and fibre-lasers for nonlinear microscopy and micro-endoscopy

**Project Objective:**
OTKA:
The aim our research is modelling, design, test and application of such special photonic crystal fibres in the field of femtosecond pulse laser physics, in which light propagation, in contrast to the well known total internal reflection phenomenon, is based on the multiple interference phenomenon of light.

NTP:
The aim of the research is to develop a new type of micro-endscope based on fiber-integrated non-linear fiber laser technologies. The device is a novel medical approach to diagnose cancer, diabetes and other illnesses painlessly and in real-time, beside characterizing the efficacy of drug in vivo.

**Project Duration and Timing:**
OTKA (2009-2012)
National Technology Program (2009-2012)

**Project Funding:**
OTKA: 30 kEUR/year
NTP: 900 kEUR (2010)

**Project Partners:**
Research Institute for Solid State Physics and Optics
R&D Ultrafast Lasers Ltd.
Genetic Immunity Ltd.
Semmelweis University, Department of Pharmacology
Szeged University, Department of Optics and Quantumelectronics
Biological Research Center, Szeged

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