DDT Vol. 7, No. 14 July 2002

Holographic imaging of live tumours

Martina Habeck, freelance writer

Researchers have obtained the worlds first 'visual fly-throughs' of the inside of a tumour, using a technology called optical coherence imaging (OCI). The development could lead to improved diagnostic imaging methods and enable scientists to study the effects of experimental drugs in real time.

Imaging with light

Optical imaging approaches promise imaging at extremely high resolution without exposure to ionizing radiation. A major difficulty with using light to produce an image is that photons are strongly scattered when passing through biological tissue, thus blurring the image. Several strategies can be used to pick out the image-bearing light. The most advanced optical imaging approach, to date – optical coherence tomography (OCT) – exploits the fact that the minimally scattered, image-bearing component of back-reflected light has quasi-coherent properties, that is, the light waves are of the same frequency and are vibrating in phase. By contrast, the diffusely scattered background component of the reflected light is made up of random incoherent light waves. Basically, OCT works in a similar way to ultrasound, except that it measures the echo delay of back-reflected light, rather than sound. A computer then suppresses incoherent background scatter and translates the information into an image.

OCI

OCI, a technology developed by David Nolte and colleagues at Purdue University (West Lafayette, IN, USA), is a variant of OCT. The main difference is that there is no need for computed reconstruction of the image: The Purdue team has found a way to directly capture the image to video. The key to this novel technology is a special holographic film made of 200 alternating layers of two types of semiconductor material, gallium arsenide and aluminum gallium arsenide; each layer is only 8 nm thick. This makes the film highly sensitive for coherent light, whereas the multiple-scattered light is rejected. The film records the information from the reflected light in the form of a hologram. Ping Yu (Purdue University) explains, 'The hologram is background-free. Therefore, we can use a normal charged coupled device (CCD) camera to look at the image; we simply place the holographic film in front of the camera, it acts as a coherence filter.'

Because the holographic film can quickly adapt to changing intensity patterns, it is possible to view the real-time motion of what is happening within the tissue. By using a joystick, the operator can change the delay of the reference light beam and look at different depths.

Adrian Podoleanu, an OCT expert at the University of Kent (Canterbury, UK), believes the film is a 'revolutionary' invention: 'The technology is fast; it eliminates the need for transverse scanning and therefore increases the speed of the data acquisition.'

Proof of concept

The Purdue team, in collaboration with scientists at the Imperial College of Science, Technology and Medicine (London, UK), tested their technology by looking at living tumours. For the experiment, biologist John Turek (Purdue University) grew tumour spheroids derived from rat osteosarcoma in a rotational bioreactor. The tumours were harvested at a diameter of up to 1 mm and then cultured in a petri dish. The Purdue team reported at the Conference on Lasers and Electro-Optics (CLEO 2002) that they successfully recorded video fly-throughs of the *in vitro* tumours [1]. Turek says, 'We achieved good tissue penetration into these spheroids, and we could image most of the internal areas of necrosis.'

Podoleanu finds the results very encouraging: 'The high sensitivity of the film has allowed the authors to already report a tissue penetration that is comparable with what has been obtained in OCT.' In terms of resolution, the technology still has a long way to go. 'It is not what you would expect from high-resolution imaging techniques,' acknowledges Turek. 'At the moment, we achieve a spatial resolution in the range of 10 μm, but that is in non-biological test samples.' However, the scientists believe that any success in OCT can be used in OCI – and investigators are able to look at single cells with OCT.

Future work

Yu reckons that it will take 3–5 years before this technology can be tried in humans. The physicists on the team are currently optimizing the system. Changes might involve replacing the current light source – a pulsed laser shining low-coherent infrared light – with an LED (light-emitting diode), which would make the technology safer. The scientists also want to develop a compact set-up that would be easy to apply in the clinic. Meanwhile, Turek is working out how to interpret the OCI images by comparing them with images obtained by conventional methods, such as confocal microscopy.

Eventually, OCI could improve cancer diagnosis because it would enable clinicians to take 'optical biopsies'. Just as

PII: S1359-6446(02)02373-5

in OCT, endoscopes and fiber-optic catheters could overcome the problem that the penetration depth of the technique is limited to a few mm. OCI could also be of use to scientists involved in drug development. For example, investigators could monitor how a drug penetrates superficial tissue or whether a drug changes diseased tissue.

Gregory Farber at the National Center for Research Resources (Bethesda, MD, USA), which is funding the research, says 'It is probably fair to say that we have not yet worked out all the possible applications. The important thing is that it offers yet another imaging technique.' Turek agrees: 'Because of the nature of how the information is collected, OCI has the potential to give us information from biological tissues that we might not be able to get with other methods.'

Reference

1 Yu, P. *et al*. (2002) Visual fly-throughs of rat osteogenic sarcoma by optical coherence imaging. *Conference on Lasers and Electro-Optics* (CLEO 2002), 19–24 May 2002, Long Beach, CA, USA, Paper no. CthI4

New cannabinoid for multiple sclerosis

Jo Whelan, freelance writer

A new synthetic cannabinoid could provide symptomatic relief from muscle spasticity and tremor in people with multiple sclerosis (MS), without psychoactive side effects. Ajulemic acid (CT-3) has already completed Phase I clinical trials to determine its safety and tolerability, and has recently demonstrated anti-spastic activity in a mouse model of MS.

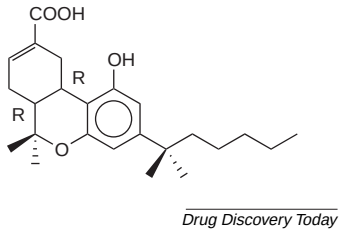
MS and cannabis

Multiple sclerosis is an autoimmune disease in which the myelin sheath surrounding motor and sensory neurones is progressively destroyed. It is the commonest neurological condition in young adults in the developed world. Symptoms result from reduced signal conductivity and vary in type and severity depending on the location and extent of myelin loss. Muscle spasticity affects ~90% of MS patients at some time and can be extremely painful. Debilitating tremor is also common. Controlling these symptoms is difficult: drugs used include baclofen, dantrolene, diazepam and tizanidine, but they are unsatisfactory for many patients because of dose-limiting side-effects.

Many sufferers find that smoking cannabis provides the best relief. Anecdotal evidence for the anti-spastic and anti-tremor effects of cannabinoids has been backed up by experiments with mouse models of MS [1]. These provided strong evidence that cannabinoid (CB) receptors are involved in the control of spasticity where there is neurological damage. CB receptors are thought to have a regulatory role in nerve signal transmission at the synapse. Blocking them makes tremor and spasticity worse, although the mechanism for this is not yet fully understood. Research has thus concentrated on developing selective CB receptor agonists that have therapeutic but not psychoactive effects.

Inhibiting spasticity

Several Phase III clinical trials are under way in the UK using natural cannabis extracts, both in MS and in other indications such a neuropathic pain and appetite enhancement. The main active ingredients in natural cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD). Other researchers are working on synthetic cannabinoids. Atlantic Technology Ventures (ATV; New York, NY, USA) has developed ajulemic acid (CT-3; see Fig. 1), a proprietary synthetic analog of the THC metabolite, THC-11-oic acid. Initially developed as an alternative to non-steroidal anti-inflammatory drugs (NSAIDs), it inhibits prostaglandin synthesis and has shown analgesic and anti-inflammatory activity in animal studies [2]. In a Phase I clinical trial it produced no clinically relevant adverse events, and no cannabis-like psychoactivity at the doses used (ATV, unpublished data). David Baker and colleagues at University College London's Institute of Neurology (London, UK) have now demonstrated that intravenous CT-3 inhibits spasticity in the chronic relapsing experimental allergic encephalomyelitis (CREAE) model of MS in mice (D. Baker, unpublished).



Drug Discovery Today

Figure 1. Ajulemic acid (CT-3), a synthetic analog of the THC metabolite, THC-11-oic acid. R indicates the absolute configuration of the chiral centers.

'CT-3 produced drastic inhibition of spasticity and limb stiffness at microgram doses, with a very rapid onset of action,' said Michael Ferrari of ATV. 'The inhibition was relatively long-lived. The

  PII: S1359-6446(02)02372-3