# Digital mice

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Researchers have produced three-dimensional (3D) magnetic resonance (MR) microscopy images of mice at resolutions that are >250,000 times higher than the resolution achieved with clinical MR imaging techniques. This technology could provide scientists with a new tool to explore the morphologic phenotype of transgenic or knockout mice.

## MR microscopy

MR microscopy has its roots in clinical MR imaging. Scientists at the Center for *In Vivo* Microscopy (Duke University Medical Center, Durham, NC, USA) have been trying to improve the technology and to achieve resolutions that enable the imaging of small animals. More than 15 years of work are now bearing fruits. The Duke scientists have recently reported that they can now view whole mice at a resolution of 110 microns [1]. With single organs they achieve even higher resolutions of up to 25 microns. A technical description of the new technology, MR microscopy, will appear in June 2002 in the *Journal of Magnetic Resonance Imaging*.

MR microscopy provides a perfect complement to other conventional imaging methods used to evaluate the morphologic phenotype of mice, says G. Allan Johnson, who is leading the Duke team. He points out that MR microscopy offers the following advantages over conventional optical histology, which is the current gold standard for examining the morphologic phenotype of mice:

- It is non-destructive, whereas conventional histology distorts the tissue. Researchers can view an entire animal and, therefore, could detect unexpected pathologies. Conventional histology methods can also be applied to explore a particular area of the body in more detail.
- It provides information on how water is bound in tissue, which is of important diagnostic value. By contrast, the chemical stains used in conventional histology leave tissues dehydrated.
- It is 3D; therefore, scientists can view the whole animal or single organs in any orientation (Fig. 1) and can make 3D measurements to determine the total volume of an organ or lesions.
- It is digital, so the scans can be transmitted over the Internet, enabling scientists at multiple sites to 'share' a specimen and to videoconference while simultaneously viewing the same dataset.

The Duke group has called their project the 'Visible Mouse', a term that alludes to the Visible Human Project® (http://www.nlm.nih.gov/research/visible/visible_human.html), which includes digital MR images of a representative male and female cadaver and serves as a common reference point for the study of human anatomy [27]. In similar fashion, Johnson and colleagues are building extensive Internet-based archives to make it easier for scientists to compare morphologic differences between mouse models.

## Potential applications

However, being able to image mice at a high resolution is of little value in itself. Investigators have to learn how to interpret what they see on their desktop. To standardize image acquisition and interpretation, the Duke group has drawn on the expertise of Robert R. Maronpot, Chief of the Laboratory of Experimental Pathology at the National Institute of Environmental Health Sciences (NIEHS; Research Triangle Park, NC, USA).

Maronpot has been working with Johnson and his team for more than 15 years. He has been waiting for the technology to finally come to a point where it could be applied in a practical way to toxicologic and pathologic problems, and he is excited that it is finally there: 'The patience has paid off.' Maronpot is now conducting a series of pilot studies to demonstrate the value of MR

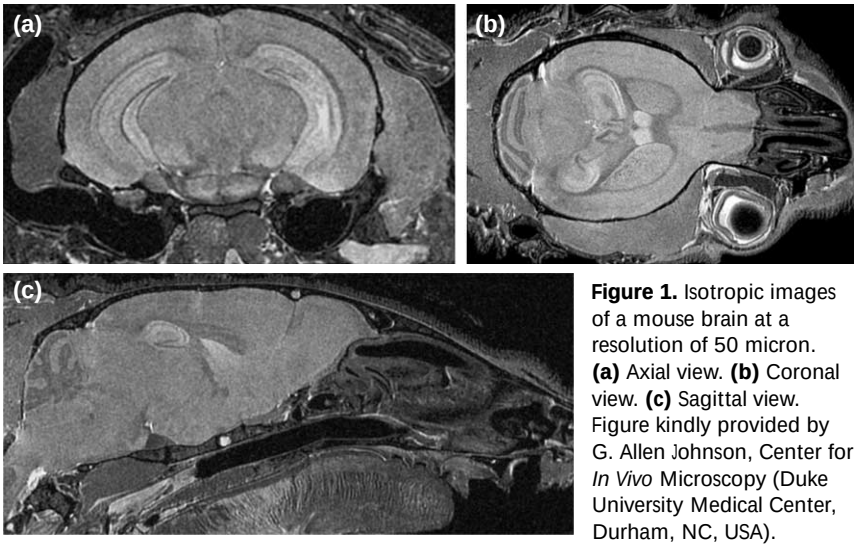


**Figure 1.** Isotropic images of a mouse brain at a resolution of 50 micron. **(a)** Axial view. **(b)** Coronal view. **(c)** Sagittal view. Figure kindly provided by G. Allen Johnson, Center for *In Vivo* Microscopy (Duke University Medical Center, Durham, NC, USA).

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microscopy as an adjunct to conventional toxicology and pathology.

With the sequencing of the human genome and the explosive growth in the use of mouse models – it is estimated that in 2001, >6 million transgenic and knockout mice were bred for research purposes [1] – it became obvious that the Duke team had something that would be of value not only to pathologists but also to scientists working with genetically altered animals. John C. Waterton, who is Associate Director in Enabling Science and Technology at AstraZeneca (Macclesfield, UK) and looks after the company's global imaging capabilities, believes that MR microscopy will be of great use for the field of drug discovery. 'I think it is particularly valuable to understand the phenotype of knockouts and other transgenics in order to support target validation. I can think of many examples where our view on the validity of a target has been changed by the phenotype of a knockout.'

## Limitations and solutions

However, Waterton stresses that it is important to realize that the approach described by the Duke group has been optimized for post-mortem specimens and that its exquisite resolution is not readily applicable to *in vivo* experiments.

He is also concerned that interpretation of the data is still time-consuming because of unsolved informatics problems. 'There is a risk that in taking that approach, you might do very elegant experiments that deliver too late, the company has already made the decision to proceed or not to proceed with a drug discovery project aimed at a given target.' Johnson agrees that this is an issue but says, 'There are many bioinformatics solutions coming from out of the clinical arena and we are adapting those.'

These problems can hopefully be solved over time. Meanwhile, Johnson has founded a company, MRPath (Durham, NC, USA), to offer MR microscopy scanning services and viewing software to the wider research community. The price for a whole-mouse study is currently not set but they expect to push the price down to less than US$200 per animal in the next year. Johnson says, 'Our vision is, you send us the animals, we fixperfuse and scan them immediately and within 24 hours you find your MR microscopy data on your desktop.'

## References


1 Johnson, G.A. *et al.* (2002) Morphologic phenotyping with MR microscopy: the visible mouse. *Radiology* 222, 789–793

2 Ackerman, M.J. (1998) The Visible Human Project: a resource for anatomical visualization. *Medinfo.* 9 (pt 2), 1030–1032


# CNS-targeted sexual dysfunction drug for men and women

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A novel drug has been developed for the treatment of erectile and sexual dysfunction that works through the CNS and could potentially avoid the side effects associated with the traditional phosphodiesterase (PDE) inhibitors. Moreover, because of its different mode-of-action, this drug could have potential for the treatment of female sexual dysfunction (FSD).

Most erectile dysfunction (ED) drugs work through the vascular system but PT141, from Palatin Technologies (Princeton, NJ, USA; http://www.palatin.com), targets receptors in the CNS and could offer therapy for those previously unresponsive to conventional vascular treatments.

The occurrence of sexual dysfunction is widespread: one-third of men aged 40–70 years reported some form of ED [1] and researchers believe that ~40% of women also suffer from a sexual problem at some point in their lives [2].

## Current treatments

The market was, until recently, dominated by sildenafil citrate (Viagra™; Pfizer, Sandwich, UK) [3]. Recently, drugs such as vardenafil (Bayer, Leverkusen, Germany) [4] and Cialis™ (Lilly, Indianapolis, IN, USA) [5], were thought to be more potent and produce fewer side effects than sildenafil. However, these drugs are PDE inhibitors, which target the vascular system and stop the breakdown of cGMP, produced by nitric oxide (NO), which is released upon sexual stimulation, thus resulting in an erection. Alternative treatments include Y27632 (Welfide Corporation, Osaka, Japan) [6], which blocks Rho-kinase activity, inducing erections in a NO-independent manner, and Uprima® (TAP Pharmaceuticals, Lake Forest, IN, USA)

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