IMAGING

# Finding your way

No matter how specific a drug is and how effective it is at killing cancer cells *in vitro*, delivering it to a real tumour is an entirely different challenge. The drug must make its way through the vasculature, cross the vascular wall, and then struggle through the extracellular matrix (ECM) of the tumour. Rakesh Jain and colleagues have adapted and optimized a new technology that allows them to determine the effects of these barriers on diffusion.

Two-photon fluorescence-correlation microscopy (TPFCM) is a three-dimensional microscopy technique that allows *in vivo* measurements of transport parameters in tumours to be made. TPFCM enables researchers to measure the concentration and diffusion of fluorescently labelled molecules within heterogeneous samples, such as tumours, or even within cells.

Using TPFCM, Jain's group made *in vivo* measurements of the diffusion coefficients of fluorescently labelled macromolecules and liposomes. They found that these tracers underwent both a slow and a fast component of diffusion. The tumour interstitial matrix is thought to be composed of two phases — viscous and aqueous. This is the first direct evidence that these two phases affect the transport of molecules within the tumour matrix.

The hyaluronan and collagen components of the ECM are thought to be the main barriers to drug delivery, so some researchers have proposed treating tumours with enzymes that degrade these structures. Jain and colleagues exposed tumours to hyaluronidase and collagenase and found that, predictably, collagenase increased the fraction of the fast-diffusing component. Conversely, hyaluronidase treatment reduced the percentage of fast-diffusing molecules. The authors propose that as hyaluronan forms a cage-like structure that contains water-filled spaces, through which molecules diffuse quickly, collapsing these structures is likely to increase viscous hindrance. Hyaluronidase, therefore, would not facilitate drug delivery.

Jain and colleagues hope to use this system to investigate other barriers to drug delivery *in vivo*.

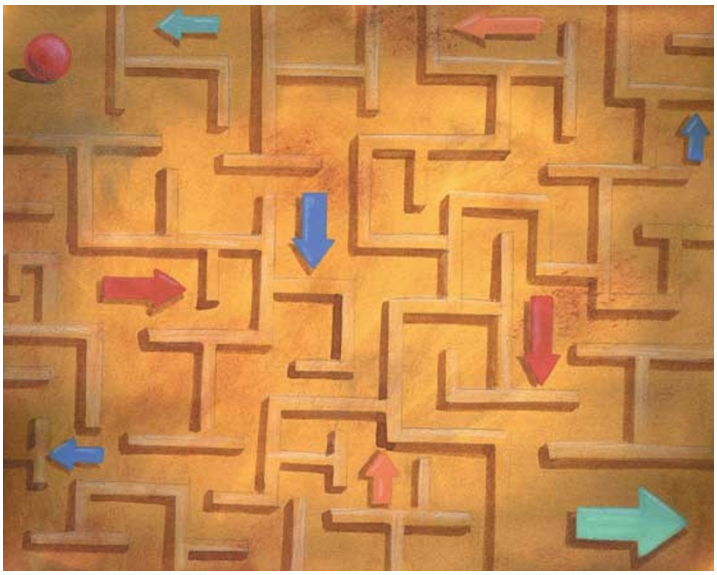
*Kristine Novak*

## References and links

**ORIGINAL RESEARCH PAPER** Alexandrakis, G. *et al*. Two-photon fluorescence correlation microscopy reveals the two-phase nature of transport in tumors. *Nature Med*. **10**, 203–207 (2004)

**WEB SITE**

**Rakesh Jain's lab:**
http://steele.mgh.harvard.edu/cv/rakesh.html



# TRIAL WATCH

## Natural born killers

Although many clinical trials have been developed to induce T-cell- and antibody-mediated antitumour responses, Phase I trial results from Nieda *et al*. show that natural killer T (NKT) cells can also destroy tumours in patients with metastatic cancers.

NKT cells mediate both innate and acquired immunity, and preclinical studies have shown that they can induce effective antitumour immune responses. Nieda *et al*. investigated whether it is possible to induce antitumour responses *in vivo* by activating NKT cells, which are induced to proliferate by dendritic cells (DCs).

The authors administered activated DCs to patients with cancer at 2-week intervals. Peripheral blood NKT cells isolated from the patients were not only also activated, but induced potent secondary immune effects, such as proliferation of T cells and B cells. These results were not observed in control individuals. Most patients experienced temporary inflammatory symptoms, such as enlargement of palpable tumour deposits and lymph nodes in all five patients with nodal metastases, as well as respiratory symptoms in individuals with pulmonary metastases. The therapy resulted in sustained 4–12-month-long decreases in serum tumour markers in two patients with adenocarcinoma. One patient with renal-cell carcinoma developed extensive tumour necrosis, and two patients with hepatic metastases had reduced serum hepatocellular enzyme levels, indicating an antitumour effect.

These preliminary results provide the first clinical evidence that human NKT cells can bridge innate and acquired immunity to induce rapid and vigorous secondary antitumour immune responses.

**ORIGINAL REFERENCE** Nieda, M. *et al*. Therapeutic activation of Vα24$^+$Vβ11$^+$ NKT cells in human subjects results in highly coordinated secondary activation of acquired and innate immunity. *Blood* **103**, 383–389 (2004).

## Obesity and prostate cancer

The findings of two retrospective multi-institutional studies indicate that obese men with prostate cancer are more likely to have aggressive disease that recurs after radical prostatectomy (RP) than non-obese men.

Amling *et al*. analysed the data of 3,162 men who were treated with RP — 19% were obese (defined as body mass index (BMI) ≥ 30 kg/m$^2$) and these patients had higher-grade prostate cancer and a higher risk of recurrence. Freedland *et al*. compared outcome information from 1,106 men who were treated with RP and found that the 22% of patients who were obese had higher-grade tumours. In this study, moderate to severe obesity (BMI ≥ 35 kg/m2) was associated with a higher risk of recurrence by multivariate analysis than mild obesity.

In both studies, higher BMI was also related to black race, but race was only an independent predictor of recurrence in multivariate analysis in the study by Amling and colleagues.

Previous studies have not shown a link between obesity and prostate cancer incidence, so it might be that obesity is a risk factor for prostate tumour progression, but not initiation.

**ORIGINAL REFERENCES** Amling, C. L. *et al*. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. *J. Clin. Oncol.* 22 Dec 2003 (doi: 10.1200/JCO.2004.03.132) | Freedland, S. J. *et al*. Impact of obesity on biochemical control after radical prostatectomy for clinically localized prostate cancer: a report by the Shared Equal Access Regional Cancer Hospital Database Study Group. *J. Clin. Oncol*. 22 Dec 2003 (doi: 10.1200/JCO.2004.04.181)