## IN THE NEWS

Gardasil — the perfect guard? **Merck & Co. have announced that their new vaccine against cervical cancer, Gardasil, was 100% effective in a phase III clinical trial.**

**Gardasil is directed against the two forms of human papilloma virus — HPV16 and HPV18 — that between them cause 70% of the 290,000 deaths worldwide from cervical cancer each year. The study followed 12,167 women aged 16–23 years. Among those who were given the vaccine, there were no cases of cancer caused by HPV16 or HPV18; in the controls, there were 21 cases. Margaret Stanley, of Cambridge University, said that "The results … are so exciting because of the sheer size of the trial and the fact that it demonstrated 100% efficacy" (http://news.bbc.co.uk, 7 October 2005).**

**Merck hopes to get regulatory clearance for the drug in 2006, after which the vaccine could be widely given to adolescent women. Eliav Barr, of Merck, said that they were "… popping out the champagne corks" (http://www.timesonline.co.uk, 7 October 2005).**

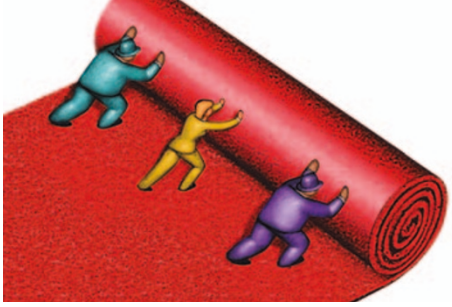
**However, there are other cancer-causing strains of HPV against which Gardasil does not protect, causing Allan Hildesheim, of the National Cancer Institute, to warn that "This is not a panacea" (http://www.nytimes.com, 7 October 2005). Indeed, Merck have not disclosed how many vaccinated women in the trial developed forms of cervical cancer that were caused by other HPV strains.**

**Meanwhile, GlaxoSmithKline continues to work on its own cervical cancer vaccine, Cervarix.**

*Patrick Goymer*

TUMOUR HOMEOSTASIS

# Newton's third law



For every action there is an equal and opposite reaction — if you push a wall it pushes back with the same force. So, does it follow that in tumours, which are more rigid than normal tissues, cells are under more tensional stress than their normal counterparts owing to the force that is exerted by the surrounding matrix? New findings from Valerie Weaver's group show this to be the case, and because of this tumour cells have an increased activation of growth factor signalling pathways, which promotes their malignant phenotype.

Tumours are often identified as a hard mass within a normal tissue — a characteristic that is exploited for breast cancer screening. But the molecular relationship between tissue rigidity and tumour behaviour is not clear. To address this, Valerie Weaver and colleagues analysed non-malignant human mammary epithelial cells grown in three-dimensional gels of a defined rigidity. Cells grown in gels with a comparable stiffness to normal mammary tissue produced mammary acini as expected, with polarized cells and evident adherens junctions between the cells. However, when these cells were plated out on gels of increasing rigidity they lost the capacity to form these structures and demonstrated increased growth, similar to malignant breast cancer cells plated out in a normal 3D matrix.

What then, in molecular terms, changes in cells that are subjected to an increased exogenous force? Weaver and colleagues found that although cells adhered with the same force to all the gels that were analysed regardless of their rigidity, the nature of the adhesion complexes differed. Integrins that are expressed at the points of cellular adhesion to an underlying matrix function as mechanotransductors, relating the nature and force of the matrix interaction to intracellular signalling pathways. Integrin adhesions formed in fibroblasts that were plated out on all types of gels, but only in the stiffer gels did these adhesions result in the induction of focal adhesions with the recruitment and activation of both focal adhesion kinase (FAK) and vinculin. It was only in the cells with focal adhesions that increased activation of the extracellular regulated kinase (ERK) signalling pathway was seen. Moreover, because integrins were activated by a stiffer matrix, levels of Rho GTPase activity and its downstream effector Rho-associated, coiled-coil containing protein kinase 1 (ROCK1) were increased, which in turn further increased focal adhesion formation, cytoskeletal tension, cell spreading and cell growth.

Why are the links between Newton's third law and signalling pathways of interest to tumour biologists? Changes in the nature of the matrix are known to occur early on in tumour development. So, a greater understanding of how exogenous force and cytoskeletal tension are integrated and how they influence integrin adhesions and activation of ERK offers a fresh perspective on the molecular basis of tumour formation.

*Nicola McCarthy*

### References and links

**ORIGINAL RESEARCH PAPER** Paszek, M. J. *et al.* Tensional homeostasis and the malignant phenotype. *Cancer Cell* **8**, 241–254 (2005)

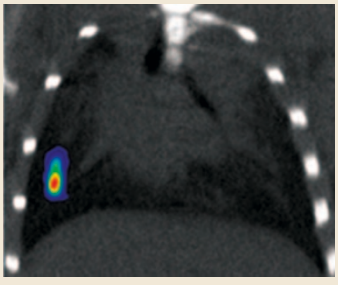
**WEB SITE**

**Valerie Weaver's homepage:** http://www.med.upenn.edu/camb/faculty/cgc/weaver.html

IMAGING

# Seeing the light

**New technologies are needed to detect tumours at early stages and also to non-invasively monitor tumour progression or the response to therapy. Ralph Weissleder and colleagues have created an *in vivo* molecular imaging method to identify and track lung tumours in mice, which might eventually be developed to do the same in patients.**



**Through gene-expression-profiling analysis, Weissleder's group, with colleagues in Tyler Jack's laboratory, found that cathepsin cysteine proteases are overexpressed in a mouse model of lung adenocarcinoma. In this model, lung tumorigenesis is induced by the overexpression of KRAS specifically in the respiratory epithelia, and the resulting adenocarcinomas resemble human tumours at the molecular and histological level. Using an optical probe that is selectively activated by cathepsin proteases and a new tomographic imaging modality, the authors were able to detect lung tumours as small as 1 mm in diameter in live mice (see image). Three-dimensional maps of the fluorescence signal, fused with computed tomography images, showed a close correlation between fluorescence signal and tumour burden. Importantly, the group was able to follow tumour progression over time by serial imaging of the same mouse.**

**Cathepsin proteases are also overexpressed by human lung adenocarcinomas, as well as colorectal cancers, pancreatic adenocarcinoma and oral squamous cell carcinoma. So, this technology might eventually be developed to identify various types of tumours and to track their progression in patients.**

*Kristine Novak*

### References and links

**ORIGINAL RESEARCH PAPER** Grimm, J. *et al.* Use of gene expression profiling to direct *in vivo* molecular imaging of lung cancer. *Proc. Natl Acad. Sci. USA* **102**, 14404–14409 (2005)