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Gardasil performs in protecting against other HPV types. We should be able to show these possibilities in a few months', says Villa.

Because women are at risk of HPV infection for as long as they are sexually active, protection induced by a HPV vaccine must be durable. 'Regarding the durability of the vaccine, we have in our Phase II study a longer follow-up time, but a smaller group of women', says Villa. Merck's vaccine data were indeed followed up until month 36, whereas GSK's stopped at 27 months. 'The current data gives us up to three years now', says Hunter-Ward. 'My understanding is at the time of filing, we expect a good four to five years of protection. We are hoping for a lifetime protection but obviously it has not been tested for this duration', he added.

'Several Phase III clinical trials are ongoing, where up to 25,000 women are vaccinated' says Villa. 'The protocols include not only young women but also mid-age women, because we want to see whether the vaccine could be helpful in already exposed women'.

Studies examining the potential health and economic effects of an HPV vaccine in a setting of screening every two or three years studies are under process. Several reports [3,4] predict that a type-specific HPV vaccine will reduce but not eliminate the risk of cervical cancer. The best balance between costs and benefits appeared to be vaccination at the age of 12, followed by triennial screening starting at age 25 years. It remains to be seen whether these vaccines will be affordable in developing countries.

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Cancer prevention a step nearer

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Cancer remains the most feared of diseases. New research from the University of Dundee, UK, provides an insight into how we might be able to protect ourselves against cancer. Environmental factors play a big role in cancer, particularly oxidants. Much has been said about how diet can protect against oxidants by stimulating the body's natural defences. Foods like broccoli, cauliflower, garlic and onions are all known to cause increases in levels of antioxidant proteins. 'Our cells run lots of processes, held in balance,' said John Hayes, Professor of Molecular Carcinogenesis at Dundee University's Biomedical Research Centre, and leader of the team at Dundee. 'The oxidant:antioxidant balance is regulated – it's a bit like a see-saw', Hayes continued. 'Too many oxidants are harmful, and it is possible to have too much antioxidant in our cells. For example, we know high levels of the antioxidant vitamin E can be harmful.'

Balancing the see-saw

The use of chemicals to protect against cancers has been mooted since the 1970s. Certain chemicals are known to stimulate cells into switching on their complex antioxidant machinery, to remove oxidants. It has been clear for some time that the oxidant:antioxidant balance is held in place by some very complex mechanisms. There are currently >200 proteins recognized to play a part in the process. Surprisingly, recent research has shown that the battery of 200 or so proteins balancing the see-saw is controlled by just a single protein, Nrf2. Shortly after its discovery, it became clear that Nrf2 is very unstable, and is undergoing constant turnover. This instability is a negative feedback system, designed to prevent an excess of antioxidant accumulating in the cell.

'The feedback system is sensitive to Nrf2 accumulation through the protein Keap1,' continued Hayes. 'Oxidants entering the cell inactivate Keap1, allowing Nrf2 to switch on the antioxidant system.' Activating the antioxidant system reduces the oxidant levels in the cell, ultimately allowing Keap1 to regenerate and resume turnover of Nrf2. Looking for a way to increase levels of antioxidant, to protect against cancers, the team looked for a way to stabilise Nrf2.

'The oxidant:/antioxidant balance is regulated – it's a bit like a see-saw'

Of mice and men

Significantly, Hayes' team set out to remove Keap1 from their system, following the logic that, to activate the battery of antioxidant proteins, all that's needed is to remove Keap1. To achieve this they employed a small interfering RNA (siRNA). 'siRNAs trick the cell into thinking they are 'a viral problem,' said Hayes. 'The cell then seeks out all mRNA with similar base-pair sequences and destroys them. Using siRNA designed with a sequence unique to Keap1 effectively removes Keap1 from the cell.'

One other factor of this research is that it shows a mechanism in humans. Virtually all previous work in this field has been through studies in mice and rats. Parallels across species are not always as straightforward as researchers might hope. 'Using siRNA against Keap1 has been critical to identifying which human genes are important in this pathway,' agreed Professor Kensler of John Hopkins University.

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'This helps us understand the similarities and differences between human and rodent models.' Identifying the key factors in human cells will certainly help in understanding how the balancing act is managed in people, and also in the race to develop new and effective cancer-preventing medicines.

Prophylactic drugs

'Prophylactic drugs are becoming popular with pharmaceutical firms,' said Hayes. 'Drugs like statins and tamoxifen are the best examples.' Cancer-preventing drugs would also prove extremely popular. Being something of a niche area, smaller firms are currently the front runners in developing therapeutic agents against Keap1. One such company is German firm Cenix BioScience. Cenix specializes in RNA interference. Indeed, Cenix supplied Hayes' team with the anti-Keap1 siRNA used for this research. Existing compounds are also showing promise for further development. 'We now know that existing drugs – both pharmaceutical and natural – act through this same pathway,' added Kensler. 'For example, we know that isothiocyantes work through the same pathways. A dithiothione used in chemotherapy – oltipraz – has undergone clinical trials for chemoprevention. We now know it also works through this pathway.' Kensler is also aware of the need to develop more specific and potent agents, citing recently studied triterpenoid molecules with potencies greater than existing molecules [3]. To say this simplifies the task for drug developers is something of an understatement. Where previously there over 200 potential drug targets, now there's just one.

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Prostate cancer target 'moveable'

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A blood-based immunotherapy for prostate cancer that is currently in phase II clinical trials might benefit from the relocalization of its target to an accessible site on cell membranes. Researchers at the University of California, LA, USA have found common chemotherapeutic agents can move prostate-specific membrane antigen (PSMA) from the apical to basolateral membranes in polarized cell cultures, increasing its access to the blood supply (Figure 1). It's now up to them to prove the validity of this approach in animal models.

Diagnosis radically changes treatment

Nearly two million men in the USA alone suffer from prostate cancer and about 30,000 of them will die of the disease this year, says Neil H. Bander, Bernard and Josephine Chaus Professor of Urologic Oncology at New York-Presbyterian Hospital and Weill Medical Center/Cornell University.

The diagnosis and treatment of patients with prostate cancer, however, has changed dramatically since the prostate-specific antigen (PSA) blood test was developed in the late 1980s. Once commonly diagnosed based on an abnormal prostate exam or other disease symptoms, prostate cancer patients today typically have localized disease at the time of diagnosis and thus are candidates for surgical treatment or radiation therapy.

Still, prostate cancer remains the second most common cause of cancer death in America. 'There is certainly a need for a second line of therapy to treat patients with bone metastasis and those that have soft tissue disease,' Bander says.

A boost for anti-PSMA therapy?

Targeted therapies need to meet several criteria for success: their receptor must be expressed in the organ and tumor of interest, have the ability to be internalized, and effect survival of the tumor cell, says Wadih Arap, Professor of Medicine and Cancer Biology at The University of Texas M. D. Anderson Cancer Center, USA. 'PSMA falls into this category.' And unlike important biomarkers for other cancers, which often have variable expression in individual patients, all prostate cancers are PSMA positive.

Millennium Pharmaceuticals, a biopharmaceutical company based in Cambridge, MA, USA, has funded two Phase II trials to determine the therapeutic effectiveness of an anti-PSMA antibody conjugated either to a radioactive isotope or chemotherapeutic agents [1,2]. 'The only cells that swallow up the cytotoxic agent and get exposed to the drug or isotope are the cancer cells that express the PSMA receptor,' explains Bander.

> 'There is certainly a need for a second line of therapy to treat patients'

Recent work led by Ayyappan K. Rajasekaran, Associate Professor in the Pathology and Laboratory Medicine Department and Member of the Jonsson Comprehensive Cancer Center at the University of California, LA, USA, found that PSMA is predominantly located on the apical cell membrane and thus inaccessible to the blood stream [3,4]. His group has also demonstrated that treatment with vinblastine, vincristine or vinorelbine – common chemotherapeutic agents that destabilize microtubules – can move PSMA to the basolateral membrane. 'It's an exciting conceptual advance,' says Arap, whose

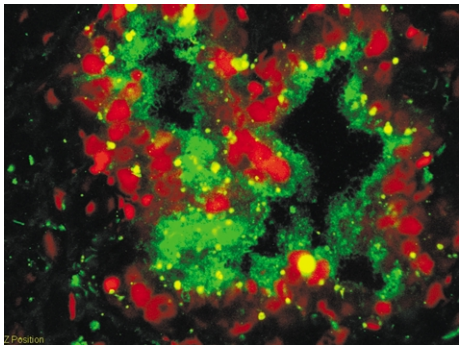

FIGURE 1.

PSMA (green) is localized on the apical membrane, or lumen, of prostate cancer tissues. (Cell nuclei are stained red.) Image courtesy of J. Christiansen and A. K. Rajasekaran of the University of California, Los Angeles, USA.

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