news

'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

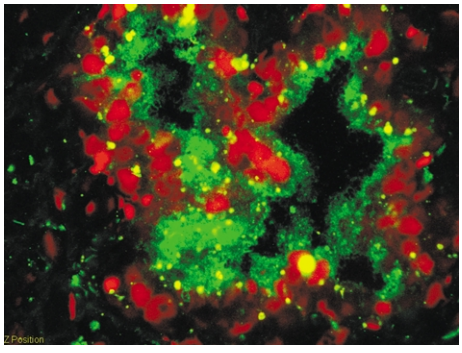

FIGURE 1.

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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interview

research focuses on vascular targeting. 'It needs to be validated *in vivo*.'

A possible addition to immunotherapy

Patients with well-differentiated prostate cancer are most likely to benefit from the combination of anti-PSMA therapy and treatment with microtubule-destabilizing agents. Rajasekaran believes this approach could reach clinical trials within four years, as it is based on 'well established chemotherapeutic agents that are used on a daily basis in cancer clinics.'

As in the laboratory work, where the researchers expressed PSMA in Madin-Darby canine kidney cells as a polarized prostate cell model was not available, 'one of the challenges in the animal model may be to generate tumors that are very well differentiated,' says Rajasekaran.

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interview

John Anson of GE Healthcare

Interviewed by Steve Carney

How do you see the balance of high throughput versus high content screening developing over the next ten years and do you think that companies will adopt a more focused approach to screening with high quality information compared with a mass screening approach?

I think the balance is already changing Steve, and if you look across the industry it is very much company-specific. Clearly, some companies have invested in factory-based approaches to screening and this approach will continue to be an important part of the drug discovery philosophy. That isn't consistent across the industry and we've talked to other companies who are going in a slightly different direction and, as you point out, they are looking at perhaps greater quality within their big compound collections, reducing the number of compounds they want to put through their high throughput screens. Down from where it is today at the multiples of millions in some cases, to the level of, maybe one to two hundred thousand or fewer. Now, at that sort of level, the application of high content screening becomes pretty attractive. As you look across the industry different companies are taking different approaches. If I were to predict where the trend would go, I would see it developing in the direction of high-content at the expense of high speed and high numbers, since from what we're seeing with the quality of data that you can generate in a in a high content screen, it potentially allows you to make better quality decisions in the pre-clinical drug development process.

John Anson

Head of Product Development, Lead Discovery at GE Healthcare

John Anson is Head of Product Development, Lead Discovery at Amersham Biosciences, which is now part of GE Healthcare. He read microbiology at Kent University, obtaining a BSc in 1981. His doctoral studies were at Cranfield University, successfully completed in 1985. Following a period at the PHLS CAMR, Porton Down, John joined Amersham. In his career with Amersham and now GE Healthcare, stretching over 16 years, John has held a number of posts in project and programme management. More recently he has held the positions of Business Development Director, Vice President, Pharmacogenetics and Vice President, Business Development Bioassay Business, before assuming his current role in 2002.

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