



# Prostate Cancer

## The Big Question

For such a common cancer, we still know remarkably little about the basic features of prostate cancer. Every year in the reports to the Orchid Scientific Advisory Board we see detailed accounts of experiments describing, for example, the activity of cancer-related genes and improved treatments, but as scientists we need to be constantly reminded of what we still need to learn.

*So what are some of the big questions as applied to prostate cancer?*

Perhaps first and most importantly, we have no idea what *causes* the tumour. There is clearly a familial involvement: the sons of fathers who died of early age onset prostate cancer (i.e. in their 50s) commonly develop cancer at an even earlier age. Diet is also important. The anecdotal tales of Japanese and Chinese moving to the USA and acquiring American disease patterns with prostate cancer are too common to be ignored. However, many of the international dietary epidemiological studies have failed to reach statistical significance, despite very large numbers of participants. I first got interested in prostate cancer because of a potential viral cause (in 1988), but current thinking associates the cancer with inflammation, which has a number of causes in the prostate, including infection.

The second big question concerns diagnosis. At present we have the PSA test, which could shortly be augmented by a test for the PCA3 gene. While PCA3 requires some further validation, we may soon have the new complementary set of tests which will overcome the acknowledged false

positives with PSA, whose bloodstream levels are raised by much more common diseases such as benign disease, prostatic infection and inflammation.

The real challenge for the future is to identify genuinely novel serum-based markers for diagnosis. There are many studies in tissue biopsies trying to differentiate, between the potentially fatal prostate cancer and the large number of tumours whose progress could be monitored without resorting to radical treatment. There is no doubt that the current trend away from such radical intervention in favour of an *active monitoring* is appealing to both clinicians and patients alike, given the known side-effects of a more radical intervention.

But the output from studies such as the current Transatlantic Co-operation Study on tissue samples (with Orchid supported involvement) should determine the best markers for disease outcome. As this study is biopsy based, it has one major drawback: the biopsy procedure can miss small areas of tumour. There is also the complication of the presence of multiple independent cancers in some prostates: how can we be sure to treat the 'dangerous' tumour?

Hence why non-invasive monitoring through the measurement of serum proteins is an important priority. The ability to detect exfoliated tumour cells in bodily fluids is an even more attractive procedure. Considerable effort is being put into the search for so-called 'circulating tumour cells'.



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Equally the use of prostatic massage (albeit painful) to release cells from the prostate, would provide a potential competing source of tumour cells. The presence of tumour in the blood stream is largely dependent on the access of the tumour to the bloodstream where a highly vascularised tumour is much more likely to have spread outside of the prostate, and such circulating tumour cell studies are generally (at the current levels of detection) more likely to be successful as a means of monitoring patients with metastatic disease.

The next big question which we must address is optimisation of treatment for this extra prostatic disease. Since the 1940s, manipulation of male sex hormone levels is an accepted treatment for prostate cancer. Initially, responses are quite remarkable: decrease in pain indices and eventual shrinkage of the tumour to almost undetectable levels, accompanied by a decrease in serum PSA levels.

However, relapse from such treatments are almost inevitable and the survival time for a patient with hormone refractory disease is embarrassingly stable at around 24 months. With the advent of new 'smart' therapies, based on a better knowledge of hormones responses within the tumour (there is good evidence to suggest that the tumour generates its own hormones) leading to the reactivation of an old drug (abiraterone) for such cases.

However, I think there is more to understanding hormone response than just cleverer ways and more knowledge of the response itself. The method of application of the therapy and the development of hormone refractory disease should be considered on a more biochemical basis. Orchid should take pride in the fact that their

founder Professor Tim Oliver advocated this for many years: the use of intermittent therapy rather than one-dose-fits-all high-level dosage until resistance develops.

This is part and parcel of an increasing realization that the historical need to develop tumour therapy which fits the *majority* of patients, is being replaced by a knowledge of the genetics of disease. Only by fingerprinting individual genetic variations or polymorphisms will we be able to tailor increasingly sophisticated cancer therapies to individual patients' tumours.

There are of course more questions to answer in prostate cancer. It remains very rare to see a true or instant 'breakthrough'.

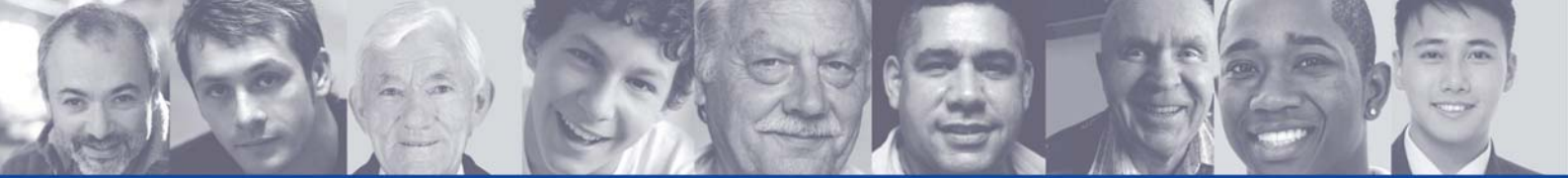
The main task of the Orchid's Scientific Advisory Board must remain to see that the charity's funding is directed towards answering the *important* questions for the ultimate benefit of men with cancer.

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*February 2009*

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