Interview

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Biomarkers in Medicine

Development of NuQ® nucleosome blood tests for the detection of colon cancer

Dr Jake Micallef speaks to Hannah L Wilson, Commissioning Editor: Dr Micallef has 20 years of experience in research and development and in the management of early-stage biotechnical companies, including the manufacture of biotechnology products and the establishment of manufacturing operations. Dr Micallef gained this experience while working for WHO over a 10-year period from 1985. While working for WHO, Dr Micallef developed new diagnostic products in the areas of reproductive health and cancer. In 1990 he commenced development of a new diagnostic technology platform for WHO that was launched in 1992 and supported 13 tests. Dr Micallef also initiated and implemented in-house manufacture (previously outsourced to Abbott Diagnostics Inc., Dartford, UK) and worldwide distribution of these products for WHO. In 1990, he started a 'not-for-profit' WHO company, Immunometrics Ltd (London, UK), which marketed and distributed those diagnostic products worldwide. In 1999 Dr Micallef studied for an MBA and went on to co-found Gene Expression Technologies Ltd (London, UK) in 2001 where he successfully lead the development of the chemistry of the GeneICE technology and implemented the manufacture of GeneICE molecules. He also played a major role in business development and procured a GeneICE contract with Bayer Pharmaceuticals (Leverkusen, Germany). From 2004 to 2007, he taught 'science and enterprise' to science research workers from four universities at CASS Business School (London, UK) before joining Cronos Therapeutics (London, UK) in 2004. In 2006 Cronos was listed in the UK on AIM, becoming ValiRx. Dr Micallef continued to work as Technical Officer for ValiRx, where he in-licensed the Hypergenomics and Nucleosomics technologies and co-founded ValiBio SA (Namur, Belgium), which is now Belgian Volition SA, a subsidiary of Singapore Volition. Dr Micallef was educated at King's College London (UK; BSc, Biology and Chemistry, 1977; PhD Physical Chemistry, 1981), St Thomas' Hospital Medical School, London (UK; MSc Chemical Pathology, 1985) and Imperial College Management School (UK; MBA, 2000).

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Keywords: cancer • colon • diagnostics • nucleosome

Q Please could you give us an overview of your professional background to date?

I was originally educated as a physical chemist, but have dedicated almost my entire career to the development of ELISA-type blood tests in all sorts of diseases including cancer. I started my career with the NHS during the 1980s where I developed, produced and distributed tests for reproductive steroids that were used in hospitals all over the UK. I then worked for the WHO for more than a decade where I led the development and manufacture of tests in reproductive health, cancer, thyroid disease and other indications that were used globally. Following a year out to study for an MBA I worked in a small drug development company before joining VolitionRX (Namur, Belgium) in 2010.

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Q What would you say was the most important thing you learned during your time working in diagnostics at WHO?

I learnt so much working with WHO about so many aspects of diagnostics that this is a very difficult question. I will go with the very practical experience: that while you may develop a diagnostic test that works well in your laboratory, in the real world any diagnostic product you make will only work as well as its worst component part in the hands of its least experienced and competent user.

Q What do you think has been the biggest achievement of your career to date?

While I've been lucky enough to work on a variety of interesting projects, I think my biggest achievement so far had been my work in developing the nucleosomics technology at VolitionRx.

Q Could you tell us some more about the background & aims of VolitionRx?

Based in Belgium, VolitionRx is a life sciences company working towards creating blood diagnostic tests for a variety of cancers. Currently, there is a lack of accurate and inexpensive tests in the field of cancer diagnostics. Right now the only common blood test for cancer diagnosis in clinical use is the PSA for prostate cancer. VolitionRx is working to address this issue by creating a simple, yet accurate noninvasive blood test for common use.

Q Please could you briefly explain the science behind your NuQ® tests?

NuQ is short for nucleosome quantification. Our cells contain the chromosomes that contain our DNA and genes. These chromosomes are made up of nucleosomes (in the same way that starch is made of glucose).

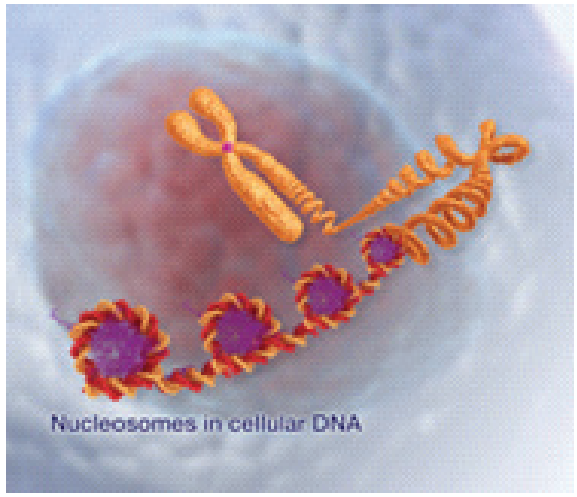

Figure 1. Chromosome and nucleosome structure.

Each of our 46 chromosomes is essentially a coiled up string of about half a million nucleosomes arranged like beads on a string where the string is the DNA, as shown in Figure 1.

Volition's NuQ assays represent a combination of two independent lines of cancer research that have each been going on since the year 2000. The first line has shown that the chromosomes and nucleosomes in cancer cells have different chemical structures to those in healthy people. The second has shown that nucleosomes from dead cancer cells are present in the blood of cancer patients. Our NuQ tests detect these altered nucleosomes in the blood of cancer patients to detect the cancer.

Q You have recently presented some new study results regarding the use of NuQ tests, please tell us about these latest findings.

Our early pilot studies on a small number of patients in Belgium have shown that NuQ assays are able to detect colon cancer and discriminate between people with colon cancer and healthy people. NuQ assays can also distinguish between people with colon cancer and people with other colon diseases such as Crohn's disease, colitis and diverticulosis, to name a few.

Our early Belgian studies have also shown that NuQ assays are able to detect prostate cancer and – most exciting of all – distinguish between people with prostate cancer and colon cancer. The data show that with the right panel combination, NuQ assays can distinguish between different types of cancer as well as healthy samples. This is a really exciting result for us and just what we've been working towards. Colorectal and prostate cancers may be just the start.

These findings are a significant step forward, but there is still a lot of work to do. For example, an ideal prostate cancer test would detect only aggressive prostate cancer cases that require treatment. The current PSA test detects many cancers that do not require treatment leading to many unnecessary painful prostate biopsies.

Q What are the next steps for NuQ tests?

The next steps for NuQ assays are further trials, in both prostate and colorectal cancers to confirm the results we have. We are currently part way through a blind clinical study in a much larger number of patients – 4800 symptomatic patients referred for colonoscopy with Hvidovre Hospital (Copenhagen, Denmark). With the right results, this could provide further evidence of the clinical use of NuQ assays as an initial screening tool for colorectal cancer. We'd hope to use

the results as supporting data for regulatory approval for the assays in Europe.

Q Could you also tell us about VolitionRx's HyperGenomics & its potential clinical applications?

In simple terms HyperGenomics is a rapid high-throughput technology that identifies which genes on the chromosomes are 'open for business'. This produces a unique signature for all cell types (e.g., the genes for muscle proteins are 'open' in muscle cells but 'closed' in brain cells). HyperGenomics signatures have many uses, but one diagnostic application is in oncology. In cancer cells the open/closed signature of the cell changes and the wrong genes for the cell type become open or closed; for example tumor suppressor genes may be wrongly closed or oncogenes may be wrongly open. This altered signature may be useful for a variety of personalized medicine purposes including diagnosis, prognosis and treatment selection.

Q What do you hope to work on next?

We are currently focused primarily on colorectal cancer. We will then move on to developing products to detect other major organ cancers starting with prostate cancer.

Q Where do you envisage the diagnostic field progressing in the next 5–10 years & what do you see as VolitionRx's role?

I see a strong emerging role for epigenetic diagnostics in general. This is something we are already beginning to see come to market. For example, in America the US FDA advisory panel's recent approval of Epigenomics (Berlin, Germany) blood test for colorectal cancer is an indication that epigenetic diagnostics has now left the research stage and moved onto the consumer arena.

I see VolitionRx as having a valuable role in moving diagnostic blood tests for cancer forward. If the results from the larger trials of NuQ assays support our primary data we could see this test coming to market. A test like this could mean a significant change clinically. Early detection is key to successful treatment of cancers and a blood test that could improve detection rate could improve patient outcomes.

Disclaimer

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Future Medicine Ltd.

Financial & competing interests disclosure

J Micallef is a consultant to, and holds stock in, VolitionRX. J Micallef has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.