

CAMBRIA INTERVIEW

HELP FOR ALZHEIMER'S SUFFERERS from THE WELSH NATIONAL FLOWER

"I see no reason why some good, cheap science cannot persuade Wales that in the daffodil it literally has a national treasure and not just an icon."

Prof.J.T. Walker of Alzeim Ltd., Talgarth.

Cambria went to Talgrath in Powys to visit Professor Trevor Walker of the biotech company Alzeim Ltd who are encouraging traditional hill farmers to diversify by growing fields of daffodils. We learned that new (phyto)pharmaceutical drugs, with huge potential, can be extracted from our National flower and that these have exciting potential to help treat some of the most serious illnesses of our age, such as Alzheimer's and Cancer.

Flowers of the genus Narcissus, like the daffodil (gylfinog) and snowdrop, prized for centuries as ornamental garden plants and subject of Wordsworthian poetic inspiration, are now the focus of intense biotechnological research, which is good news for sufferers and the Welsh economy.

Hints that extracts from Narcissi contain beneficial effects, as with most modern drugs (aspirin and digitalis are classic examples), come from traditional Folk Medicine. The earliest account of the medical use of extracts from Narcissus, probably from the snowdrop, is recorded in Homer's Odyssey. The attempts of the Goddess Circe to poison Odysseus and his men causing them memory loss, hallucinations and delusions of being turned into pigs were foiled by Hermes who administered an antidote now thought to be the compound Galanthamine found in snowdrops. Galanthamines have now been identified, by Professor Walker and his team, in commercially viable amounts in certain varieties of Wales-grown daffodil.

Alzheimer's Disease is a very serious illness growing in incidence as the population ages. Anyone who is suffering from this or has a family member with it will understand the enormous strains on care resources that this disease has. Any drug that can help these patients ward off and delay the most debilitating symptoms must be brought into mainstream medicine as soon as possible.

Q. Please can you explain, in layman's terms, the benefits of Galanthamine therapy? How does it work? How is it administered?

Galanthamine is a natural alkaloid found only in the snowdrop and daffodil family. There are also two unrelated and solely synthetic drugs that are used to treat the incurable dementia of Alzheimer's Disease.

Normal brain function is reliant upon the efficient function of a neurotransmitter substance called **acetylcholine**. In the Alzheimic brain this substance is progressively broken down by the mediation of the enzyme **acetylcholinesterase**. Galanthamine inhibits the action of the destructive enzyme and so, along with the other two drugs, is termed an AChE inhibitor. These drugs are not perfect, and do not normally reverse the physical damage appreciably, but Galanthamine does slow down the rate of deterioration. If administered in time there are many instances where patients have been given at least a temporary new lease of active life.

Physically the *post-mortem* Alzheimic brain is characterized by clumps and strings of tissue ('plaques' and 'tangles') and by associated vacant areas. Until cognitive testing (structured memory tests) was sufficiently developed such pathological examination was the only sure diagnosis to differentiate AD from other dementias.

The alkaloids are powerful natural substances made in plants, where they serve such purposes as protection against grazing. Some are of great importance in medicine and, as prescription drugs, are administered in small doses – e.g. morphine, atropine, digitalin. Galanthamine is mainly administered as a water-soluble salt in oral tablet form.

All the logic dictates that the drug Reminyl (and the two other AChE's) be given as early as possible after diagnosis: the need now is for an early-stage chemical (e.g. blood) diagnostic test. Unfortunately, due to its high cost and inability to provide a permanent cure, the UK regulatory body NICE has ruled against such provision in England & Wales. Reminyl is prescribed on the NHS in Scotland for all stages of AD, but in England and Wales it is only thus prescribed for the later, advanced stages of the condition – by which time most of the potential benefit has been lost.

Q. *Can you provide hope for Alzheimer's sufferers?*

Yes we most definitely can! That is what Alzeim is about. We cannot 'cure' them, but we help to slow down the progress of the disease significantly in many cases, giving the patient and his or her carers time to come to terms with it and make provisions for coping.

Q *Do you see Alzeim as mainly a company for producing/farming daffodils for extraction and processing by others or do you foresee a future role in drug development?*

Alzeim is NOT just – or even mainly - a farming company. There are some UK cooperative groups that grow crops (e.g. poppies for codeine) and sell raw material to extraction companies. We have farmer shareholders now, but we manage the crops. All we require from the growers is to open the gate to their fields! Our own agronomists take over, spray off the pasture, plough the land and work it down, then supervise the planting and all subsequent crop care and harvesting.

Thereafter we process the crop yield – at first on-farm - and then process it further in our own buildings to extract the refined alkaloid using our own technology, co-developed with Manchester University, and produce a chemically pure product.

Initially, to survive financially, we will be selling the active pharmaceutical ingredient to the generic drug manufacturers, allowing them to formulate and market the drug as “Galanthamine” tablets as a cheaper, acceptable version of Reminyl. Beyond that, we plan to be deeply involved in other drug delivery systems for Galanthamine, and then also work with other daffodil alkaloids that we have targeted with potential bio-activity.

Q. Do people view/classify you as a farming or a scientific, pharmaceutical or a biotechnological company?

It depends upon the people! Because Alzeim originated (very appropriately) in the old Mid Wales Mental Hospital (in Talgarth) after the latter had been very controversially and unsuccessfully privatized our Company was not taken seriously. Some local, established companies and individuals were quite supercilious about us and our prospects for some time.

It is very hard to do an unsupported start-up, and it seems to be axiomatic now that only big companies with big bucks can succeed in medical matters. But I had been successful in converting the Evening Primrose plant from a garden ornamental and proscribed weed to a significant crop on which the substantial Omega-6 health food and cosmetic business was based. It was done using good science on a shoestring funding.

But there was some moral support, and we were lucky in that the local farming community had associations with the old mental hospital and were sympathetic to the needs of mental patients. So we were afforded land for trials ... and now those people are among our lead farmers.

I don't care how we are perceived. The WDA and some universities saw us, I believe, as having a good idea but assumed that we could not

compete against the big battalions. They did not realize the degree of determination here to make Alzheimer succeed without significant local, EU and Welsh Government money.

The problem with the term "biotechnology" is that it used to have a broad sense, in that brewing, for example, is real biotech with great skills needed. Now most people use the term only for very narrow sectors such as medical, DNA genome work and the genetic engineering of micro-organisms for the manufacture of drugs.

We have the technology to extract other chemicals from daffodils that may have drug potential, but currently do not wish to be distracted from establishing ourselves with Galanthamine. So, for the moment, we are a 'one-trick pony' ... but it is a good trick!

When we have succeeded with that we can proceed with the other daffodil related projects we have "in the pipeline." What we are doing NOW is not very high-tech: when we can implement our wider research programme we shall be doing "real biotech".

Q. *Is it only certain varieties of daffodil that contain reasonable levels of Galanthamine?*

Yes! There are some 30,000 varieties of Narcissus recognized, many of which are still maintained in collections. All make various alkaloids, but only certain botanical classes contain significant Galanthamine, and very few of the constituent varieties in those classes either (a) have enough of the compound to be useful or (b) do not exist in commercial horticultural amounts to be used on a field scale.

Growing and harvesting daffodils for their yield of chemicals is a very skilled process, as levels of alkaloids vary with environmental conditions, with the part of the plant and the stage of growth.

Q *There are a lot of myths and legends attached to the Physicians (Herbalists) of Myddfai, (near Llandovery) do you have a view on this or on herbalism in general?*

Yes. We think it's great that there is a tradition of herbalism in Mid-Wales after the likes of Culpeper, and there are most likely plants surviving in the Myddfai area that were once cultivated for medicines.

60% of all drugs used in the world today originated in plants. Many once natural-only substances such as aspirin from willow bark are now synthesized, but the alkaloids largely defy that option. Galanthamine is

available OTC in some countries and on the internet, and though we do not envisage selling, say, standardized, powdered daffodil in the way that St John's Wort is marketed one might envisage launching a preparation of pure Galanthamine in small doses in combination with various herbal substances as "early stage AD prophylactic" – with proper safety precautions, of course.

Q In what ways have the Assembly Government/WDA helped you?

In general they have been encouraging – in particular the Bioscience sector at Plas Glyndwr. We have been awarded a **SMARTCymru** 'grant' that has been invaluable and we hope to progress further in the scheme.

However, such schemes can be hugely frustrating. It is not the SMART team's fault that the amount of filling in of e-forms and administration involved before an SME draws down money is enormous. Nor that the required 'matching' element of aid is daunting, or that far too much of the money goes to pay outside, adequately-salaried so-called experts and academics. The onerous requirements for multiple quotes for very specialized equipment or services are a great drag. It is almost impossible to get any direct Government help for essentials such as salaries, travel or vehicles. In our opinion the proportion of well-meant assistance money that must be spent by the grant body on policing or auditing the funding of help SME's is far too high.

The best help that we have had came at start-up from a small Powys scheme called **Glasu**, based in Builth Wells. Glasu gave us *de minimis* money to hire young people to help with the sampling of early crops and chemical analysis at IGER, and that proved to be a God-send. Helpful people, minimum fuss!

Q. What do you think about the proposed Biotechnium or the Technium concept in general?

This was a good concept – though geographically they are hopeless! A technium is of no good to mid-Powys if it is sited much further away than Hay on Wye or Brecon. Putting such centres in Aberystwyth, Swansea or the like merely concentrates SME's in the cities, where there are already existing college facilities. They act as black holes for village-based enterprises. Putting a technium in a small town like Brecon would encourage start-ups to undertake some research for their projects.

Q. Have you had dealings with Finance Wales or Xenos?

Yes – initially total disaster! We met both in 2004 and probed to see if we could borrow money for bulbs to increase the acreage, and our judgment

and commitment were questioned. We were told in no uncertain terms that Wales expected inward investment from the English in-comers, and for the founders to continue to take more serious risk (mortgage houses etc) as though we were at the start of our careers. Finance Wales seemed little different from a 'High Street' bank, in terms of taking zero risk via secured loans at standard interest rates.

No private investor from the Xenos network has ever been in touch. However, since the recent (2008) venture equity investment from a Cardiff firm Finance Wales has made an enquiry. The difference between biotech venture investment in USA (wonderful, exciting & rewarding) and UK (pathetic) is huge.

Q. Do you do anything with the National Botanic Garden in Llanarthne? Do you have a view on the biotechnium facility that has been moth-balled for over 3 years there?

As yet, no. However, Sir Roger (Penn) is a great supporter of the NBGW and is interested in Alzeim getting involved. He believes we could have a good, symbiotic relationship. We think that we could make great use of a medicinal substances laboratory based on good science – starting with our daffodil work.

Beyond that, Alzeim has access to a wide range of potent herbal medicines, with more proven bio-activity than most of the vague, herbal products that have received financial assistance. The available drugs come from east and central Europe and need to be assessed under good conditions, the plants possibly multiplied and established here and the products properly standardized and put through western clinical trial procedures.

Q. In general, do you think the Assembly is doing enough to support biotech in Wales? Or even understands it? Or even treats it seriously?

I, despite my given name, am not Welsh born, but I have chosen to come out of retirement to do something really useful and possibly of great economic value to the area around Talgarth. The work is expected to be socially invaluable world-wide. The WAG is helping, so I do not intend to bite any hand that even partially feeds us.

However, as Rhodri Morgan keeps saying, Wales can only make an impact if it concentrates on adding higher technology applications to its natural skills and resources. In biology there is some good blue-sky research, and a lot of run-of-the-mill eco-craft stuff, but not enough recognition that science-based SME's need access to expensive equipment, databases,

consultants etc and should be encouraged and helped much more actively and generously.

In our own case the gearing of reward to investment in Alzeim is expected to be very high, but we foresee that life is still going to be tough and that we are going to have to make and sell product under somewhat inadequate conditions in order to get money to have, eventually, a high quality building and a laboratory.

We want to attract highly qualified staff to what is an area of great natural beauty and offer them a lifestyles as well as hard, rewarding work – but whereas we have managed on a pittance until now such people need salaries and benefits, holidays and pensions. Those have been beyond our dreams while self-funding a project that some in the outside world, judging by technology transfer queries, apparently value more than does Wales.

We hope that the WAG believes in biotech. Our attitude is that Plant Biotechnology should play a big role in the future of Wales – The WAG, like Alzeim, is still learning, and we want to make the journey together.

Alzeim Ltd is based in Talgarth, Powys and more information can be found on their website at: www.alzeim-biotech.co.uk.
Cambria Interview conducted by Chris Jones.