Institution: The University of Chester

Unit of Assessment: Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Identification of vitamin B12 as a treatment for Alzheimer's Disease

1. Summary of the impact

John Williams and colleagues found that serum homocysteine predicted cognitive decline and predicted the potential for vitamin B_{12} in treatment of dementia, including Alzheimer's Disease. This finding has led to the production of 2 novel cobalamin compounds, glutathionyl cobalamin (GSCbl) and N-acetyl cysteinyl cobalamin (NACCbl), in collaboration with Kent State University (USA), the use of which were patented in USA. We have also identified a novel anti-oxidant activity of vitamin B_{12}. This work has led to the production of Betrinac sold by the Chester company, Cobalz Ltd, in the UK and PamLab Llc, USA.

2. Underpinning research

This case study is based upon the work of Williams as key researcher (Senior Lecturer then Professor, University of Chester, 1998 - present).
In 2001, Williams and the group published the first prospective study looking at the link between serum homocysteine and cognitive decline in a group of healthy aged individuals (none of whom at the start of study had any symptoms of Alzheimer's Disease) over a period of 5 years (1). Blood samples were taken at the start of the study and then 5 years later from a group of 40 healthy individuals aged 65 or over, and cognitive function assessed at the 2 time points by two well-validated measures the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale (ADAS-Cog) (1). The study demonstrated for the first time that serum homocysteine predicted cognitive decline and suggested that it might have a causative role in Alzheimer's Disease – in support of the data on correlative associations. It was further proposed that the serum homocysteine could be reduced, and therefore cognition improved, by manipulating one-carbon metabolism through increased intake of folate or vitamin B_{12} (1). This work was followed by a demonstration of the importance of Vitamin B_{12} transport in the development of Alzhemier's Disease (2) and that manipulation of one-carbon metabolism could be used to reduce serum homocysteine levels(3). McCaddon later demonstrated that this manipulation could successfully reverse cognitive decline in Alzhemier's Disease (4). We further demonstrated that vitamin B_{12} and the modified thio-latocobalamins GSCbl and NACCbl were protective against oxidative stress in cell models (5). Our data suggested that vitamin B_{12} had direct anti-oxidant properties as well as its traditional cofactor role (5). We were able to confirm this anti-oxidant activity of vitamin B_{12} in collaboration with Dr Nicola Brasch of Kent State University (6).

3. References to the research

References to the research, all of which have appeared in peer reviewed journals:

1. McCaddon, A., Hudson, P., Davies, G., Hughes, A., Williams, J. H. H. and Wilkinson, C. (2001). Homocysteine and cognitive decline in healthy elderly. Dementia and Geriatric Cognitive Disorders **12**(5): 309-313.
2. McCaddon, A., Blennow, K., Hudson, P., Hughes, A., Barber, J., Gray, R., Davies, G., Williams, J. H. H., Duguid, J., Lloyd, A., Tandy, S., Everall, M., Cattell, H., McCaddon, A., Ellis, D., Palmer, M., Bogdanovic, N., Gottfries, C. G., Zetterberg, H., Rymo, L. and Regland, B. (2004). Transcobalamin polymorphism and serum holo-transcobalamin in relation to Alzheimer's disease. Dementia and Geriatric Cognitive Disorders **17**(3): 215-221. DOI: 10.1159/000076359.
3. Hunter-Lavin, C., Hudson, P. R., Mukherjee, S., Davies, G. K., Williams, C. P., Harvey, J. N., Child, D. F. and Williams, J. H. H. (2004). Folate supplementation reduces serum Hsp70 levels in patients with type 2 diabetes. Cell Stress & Chaperones **9**(4): 344-349.
4. McCaddon, A. (2006) Homocysteine and cognitive impairment; a case series in a General

Practice setting. *Nutrition Journal* 2006, **5**:6 doi:10.1186/1475-2891-5-6.
5. Birch, C. S., Brasch, N. E., McCaddon, A. and Williams, J. H. H. (2009). A novel role for vitamin B_{12}: Cobalamins are intracellular antioxidants in vitro. Free Radical Biology and Medicine **47**: 184-188. DOI: 10.1016/j.freeradbiomed.2009.04.023.
6. Suarez-Moreira, E., J. Yun, C.S. Birch, J.H.H. Williams, A. McCaddon, and N.E. Brasch, (2009).Vitamin B12 and Redox Homeostasis: Cob(II)alamin Reacts with Superoxide at Rates Approaching Superoxide Dismutase (SOD). Journal of the American Chemical Society, **131** (42): 15078-15079. DOI: 10.1021/ja904670x.

4. Details of the impact

As a part of this work described in section 2 we hypothesised that:

1. Reducing homocysteine with combinations of folic acid, vitamin B_{12} and anti-oxidants such as glutathione or N-acetyl cysteine would reverse the cognitive decline seen in Alzheimer's patients and the aging population in general.
   Since our work, a number of clinical trials have been carried out and the resulting data is conflicting. However, the use of combined therapy has been more successful than use of single agents – and the result locally is the formation of a new company – Cobalz Ltd (1). The aim of this company is to focus on research and treatments for Alzheimer's Disease and other dementias – focusing principally on B vitamins and homocysteine (1). Cobalz Ltd have successfully applied for patents for the use of vitamin B_{12} as a medication for Alzheimer's Disease (e.g. 2) and have also recently been awarded a patent for their formulation – Betrinac which contains vitamin B_6, vitamin B_{12}, folic acid and N-acetyl cysteine (3). Cobalz Ltd present £100 to the best MSc Biomedical Science student annually.

2. Chemically linking glutathione or N-acetyl cysteine to cobalamin to form thiolatocobalamins would be more effective against oxidative stress than either of the compounds or cobalmin in isolation.
   In a collaboration with Dr Nicola Brasch, Kent State University, USA, we designed the synthesis of the novel thiolato cobalamins GSCbl and NACCbl. These compounds proved to be superior to other anti-oxidants in a cell model of oxidative stress (4) and as a result we jointly applied for patents on the compounds (5, 6). PamLab Llc then took a licence on these patents with the intention of going to pre-clinical trials (7). Work is continuing on these compounds with plans to synthesise further novel cobalamin derivatives.

3. Vitamin B_{12} has a multiple effects – indirect due to its effect on one carbon metabolism, direct due to a previously unknown anti-oxidative action, and direct due to a previously unknown effect on signalling pathways.
   We were able to confirm that vitamin B12 has anti-oxidative activity (4, 8) also that the compound influenced signalling pathways in particular Akt phosphorylation (9) which has later been confirmed by other workers (10).

5. Sources to corroborate the impact

1. Home page for Cobalz Ltd. http://www.cobalz.co.uk/ corroborates section 4 paragraph 1.
2. McCaddon, A. Method for treating or preventing a functional vitamin B12 deficiency in an individual and medical compositions for use in said method. Cobalz May, 4 2010: US 07709460 corroborates section 4 paragraph 1.
3. Home page for Betrinac Sales http://www.betrinac.com/ corroborates section 4 paragraph 1.
4. Birch, C. S., Brasch, N. E., McCaddon, A. and Williams, J. H. H. (2009). A novel role for vitamin B_{12}: Cobalamins are intracellular antioxidants in vitro. Free Radical Biology and Medicine **47**: 184-188. DOI: 10.1016/j.freeradbiomed.2009.04.023. Corroborates section 4 paragraph 2.
5. Brasch, N. E., Birch, C. S. and Williams, J. H. H. (2008). Pharmaceutical compositions and

therapeutic applications for the use of a novel vitamin B_{12} derivative, N-acetyl-L-cysteinylcobalamin. US Trade and Patent Office, Application No. 20080076733. Corroborates section 4 paragraph 2.

6. Brasch, N. E., Birch, C. S. and Williams, J. H. H. (2008). Pharmaceutical compositions and therapeutic applications for the use of a synthetic vitamin B_{12} derivative, glutathionylcobalamin. US Trade and Patent Office, Application No. 2008011390. Corroborates section 4 paragraph 2.
7. Pamlab Licence corroborates section 4 paragraph 2.
8. Suarez-Moreira, E., J. Yun, C.S. Birch, J.H.H. Williams, A. McCaddon, and N.E. Brasch, (2009).Vitamin B12 and Redox Homeostasis: Cob(II)alamin Reacts with Superoxide at Rates Approaching Superoxide Dismutase (SOD). Journal of the American Chemical Society, **131** (42): 15078-15079. DOI: 10.1021/ja904670x. Corroborates section 4 paragraph 3.
9. Altiae, O. PhD thesis Unversity of Liverpool. Corroborates section 4 paragraph 3.
10. Albertosa et al. (2009) Vitamin B12 deficiency reduces proliferation and promotes differentiation of neuroblastoma cells and up-regulates PP2A, proNGF, and TACE. PNAS 106: 21930–21935. Corroborates section 4 paragraph 3.