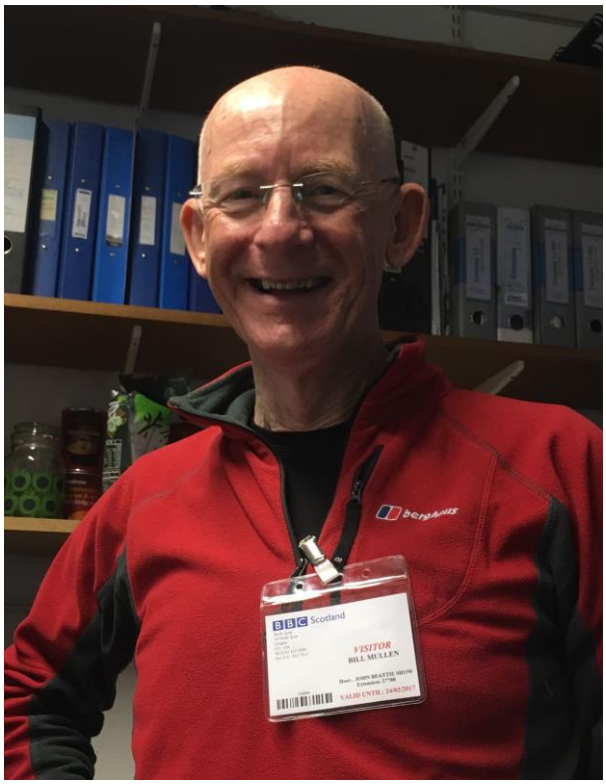
XCVI Wykład JCET, 15.09.2017

Proteomic Biomarkers for clinical applications and basic research



Dr William Mullen

Director of Biomarker Research

University of Glasgow

Glasgow, Szkocja

Proteomics promised a future of new biomarkers for clinical diagnostics, but has so far failed to deliver more than a few disease markers. Like other omics techniques, proteomics has the potential to make significant improvements to the gold standard biomarkers used in clinical applications. This is especially so in chronic diseases that develop over a number of years or even decades. At present by the time these diseases reach a stage where diagnosis is possible it is too late to reverse the adverse effects. We have developed methodologies that allow the development of highly specific disease biomarkers that can provide pre-symptomatic diagnosis of diseases such as coronary artery disease and chronic kidney disease (1,2). This could facilitate earlier intervention, by medication or lifestyle choices, at a stage allowing reversal of affect or at least prevent progression (3).

The core technology is based round capillary electrophoresis coupled with mass spectrometry of urinary peptides (4). This provides a stable, robust and reproducible platform that we have used to build a database of all samples that have been run in a

number of labs over more than 12 years (5) Last check there were over 30,000 samples logged into the database. Disease biomarkers are based on multi-peptide “fingerprints” of diseases as opposed to single compound biomarkers which lack specificity.

In addition to highly specific disease diagnosis, information on the pathophysiology of the disease can be acquired from the identification of the peptides that make up the biomarker (6). However, discovering their sequence is a more difficult task than would at first glance be thought. This is mainly due to a lack of ability to identify post translational modifications of proteins. Existing mass spectrometric proteomic databases are a limiting step in this process. A recent advance in this field has allowed us to gain sequence information on peptides that have undergone glycolysis. I have initial data from this research and what are the next steps in this “work in progress” subject.

1 Delles C,Schiffer E,von Zur Muhlen C et al. Urinary proteomic diagnosis of coronary artery disease: identification and clinical validation in 623 individuals. J Hypertens. 2010 Nov;28(11).

2. Naturally Occurring Human Urinary Peptides for Use in Diagnosis of Chronic Kidney Disease. David M. Good, Petra Zürbig, et al. Mol Cell Proteomics. 2010 Nov; 9(11): 2424–2437.

3. Silva, S., Bronze, M. R., Figueira, M. E., Siwy, J., Mischak, H. , Combet, E. , and Mullen, W. (2014) Impact of a 6-wk olive oil supplementation in healthy adults on urinary proteomic biomarkers of coronary artery disease, chronic kidney disease, and diabetes (types 1 and 2): a randomized, parallel, controlled, double-blind study. American Journal of Clinical Nutrition , 101(4), pp. 44-54. (doi: 10.3945/ajcn.114.094219).

4. Jantos-Siwy, J.; Schiffer, E.; Brand, K.; Schumann, G.; Rossing, K.; Delles, C.; Mischak, H.; Metzger, J., Quantitative urinary proteome analysis for biomarker evaluation in chronic kidney disease. *J Proteome Res* 2009, 8, (1), 268-81.

5. Siwy, J., Mullen, W. , Golovko, I., Franke, J., and Zürbig, P. (2011) Human urinary peptide database for multiple disease biomarker discovery. Proteomics Clinical Applications , 5 (5-6). pp. 367-374. ISSN 1862-8346.

6. Zurbig, P.; Renfrow, M. B.; Schiffer, E.; et al. Biomarker discovery by CE-MS enables sequence analysis via MS/MS with platform-independent separation. *Electrophoresis* 2006, 27, (11), 2111-25.

Short Biography

Dr William Mullen

Employment

2012 – present

Senior Research Fellow, University of Glasgow, Institute CAMS. Director of Biomarker Research. Core funded.

2010 – 2012

Research Fellow, University of Glasgow, Institute CAMS.

Set up a new group to investigate the pre-symptomatic biomarkers of disease. Primary objective of the laboratory was to develop biomarkers of disease for use in diagnostics and to inform clinician of effect of treatment. I have developed this technology to embrace a range of problem from the veterinary diagnostics to exercise and nutrition in health. Core funded.

2007 – 2010

A number of grants obtained, as named researcher and or as joint grant holder, from a range of multinational companies including Mars, Nestle, Coca Cola, Mitsui Norin, POM wonderful, Welchs Purple Grape Juice.

2003 – 2007

Grant position, named researcher, BBSRC grant into the matrix effect of foods on the absorption and metabolism of bioactive plant secondary metabolites. Report on this grant received an Alpha rating.

2003

Position in Institute made permanent. Re-graded to Research Fellow.

1999 – 2003

Research Assistant.

Grant position funded by the Scottish office: Identification and assessment of nutritional relevance of antioxidant compounds from soft fruit species.

1998 – 1999

Research Assistance, Plant products and Human Nutrition Group.

Grant position funded by Scottish Soft Fruit Growers: To investigate the effects of different freezing and storage regimes on the phenolic compounds in raspberries.

Founding Director and General Manager. Reeve Analytical Ltd, Glasgow.

Design, manufacture, sales and service of chromatographic instruments. The first was a post column pumping system for HPLC, the second a HPLC radioactivity detector. These were later produced in the livery of a multi-national company in a million pound plus deal (1985). Progressing from designing instruments from “off the shelf sub-assemblies” to designing the sub-assemblies used. Travelled throughout Europe, America and Canada giving seminars to scientists, service engineers and sales people on the use of radio-chromatography in the investigation of metabolic changes. The company at its peak had a staff of fifteen. Additional products included a chromatographic data system which was a D.T.I. SMART award winner, a fluorimeter sub-system for a glycoprotein analyzer, a temperature controlled luminometer for water quality testing and a nephelometer for PMT10

pollution measurement.

1979 – 1981 Mass Spectroscopist, Syntex Pharmaceuticals, Edinburgh.

1973 – 1979 Research Technician, University of Glasgow, Botany Dept.

Current Grants:

SysVasc EU FP7 A systems biology approach to identify molecular targets for vascular disease treatments.

iMODE-CKD, ITN: Clinical and system-omics for the identification of molecular determinants of established chronic kidney disease.

Urinary proteomics as biomarker for inflammatory arthritis.

Investigation into the effect on the urinary biomarkers of coronary artery disease of an eight week supplement of extra virgin olive oil rich in polyphenolics, with the University of Lisbon and the Sovena Group Olive oil manufacturers.

CSO FFIT in secure institutions, part of Institute of Health and Wellbeing study on improving fitness of staff and detainees.

ISSF Catalyst fund : The Biomarkers in Stroke Programme; Detecting, Understanding, and Predicting Outcome After Stroke.

Investigating the potential of cathepsin-L as a common therapeutic target and biomarker for coronary heart disease and African trypanosomiasis (ISSF Catalyst Fund).

Identification and preliminary validation of urinary proteomic biomarkers for detection of rheumatoid arthritis. Movember,Global Prostate cancer initiative.

NHS-ENDOW, Metabolite and protein profiling in CADASI.

Academy of medical sciences, Urinary proteomic profiles as a biomarker for dementia.

BBSRC manipulating the activity of the gut micobiota with fermentable carbohydrates to maximise the bioavailability of bioactive phenolic acids for health.

BBC, Dietary oils and fatty acid composition impact on cardiovascular and kidney health.

Education

1999 – 2003 MSc, University of Glasgow

2003 – 2008 PhD, University of Glasgow,

Over 130 publications,

H index of 42,

Highly cited research 2014, 2015 and 2016.