Institution: Nottingham Trent University School of Science and Technology

Unit of Assessment: A03: Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Development of bioinformatics techniques leads to biomarker discovery and realisation of commercial potential

1. Summary of the impact (indicative maximum 100 words)

The research led by Professor Graham Ball at Nottingham Trent University has developed new bioinformatics techniques for mining complex post genomic bio-profile data. The approach allows development of predictive models to answer clinical questions using an optimum biomarker panel. The impact of this work is through the filing of four patents associated with algorithms, breast cancer and tuberculosis, subsequently licensed to a spin-out company. To date three clinical trials have been supported with others in the pipeline. Through the spin-out company the approach is being applied to stratify patients in clinical collaborations and to optimise biomarker panels for diagnostics companies.

2. Underpinning research (indicative maximum 500 words)

The underpinning research was led by Professor Graham Ball (Professor of Bioinformatics) in collaboration with Professor Robert Rees (Director of The John van Geest Cancer Research Centre) over the last 12 years, focusing on bioinformatics algorithms for biomarker discovery. Professor Ball has been involved in a number of clinical collaborations leading to publication of 72 papers since 2002, 50 of which have directly utilised the algorithms developed.

The technique consists of algorithms based on artificial neural networks (ANNs) that facilitate analysis of complex biological data, such as mass spectrometry, gene expression arrays and miRNA arrays. One of the problems with analysis of such data is its complexity and dimensionality. This leads to over-fitting and false discovery. The algorithms developed by the Ball group (which included L Lancashire, PhD student and then post-doctoral fellow, 2001-2008) overcome these problems by utilising extensive cross-validation coupled with biomarker selection based on a stepwise additive approach. Numerous publications by the group demonstrate that these limitations have been overcome, (e.g. Lancashire et al, 2009. Briefings in Bioinformatics 10 (3): 315-329; Ref 1). The algorithms have been applied to the analysis of clinical data to identify an optimised subset of markers and incorporate them into a model that best predicts an answer to a given clinical question. These markers and models provide an insight into disease aetiology and can be used from a diagnostic perspective.

The group was one of the first to mine mass spectrometry data using an ANN approach. The initial study identified biomarker ions that accurately differentiated between astrocytoma and glioblastoma (Ref 2). This study showed that it was possible to utilise the non-linear predictive capabilities of ANNs to classify a clinical state using biomarker ions from SELDI-MS data. These approaches were then developed further, and applied to analysis of melanoma data for a larger cohort (Ref 3). Subsequently the methods were refined, developed and validated to improve performance, optimise the biomarker panels identified, overcome limitations associated with high dimensionality and the complexity of the data. These new methods facilitated improved predictive performance for unseen cases from disease populations.

The approach has been applied:

- in a prostate cancer vaccine clinical trial in 2005 (Ref 4). This study demonstrated that a cytokine profile derived using an ANN model could stratify the response of patients on a clinical trial with high sensitivity and specificity (Onyvax Ltd).
- to integrate immuno-histochemical data, pathological data, gene expression and miRNA data (Habashy et al, 2008. European Journal of Cancer, 44:11, 1541-1551. Lowery et al, 2009. Breast Cancer Research 11:R27, DOI:10.1186/bcr2257).
- to the rapid typing of microbial pathogens from mass spectrometry data (Ref 5), in collaboration with Public Health England (PHE) Colindale.
- in the characterisation of breast cancer - contributing to the revision and remodelling of the Nottingham Prognostic Index (Ref 6).

3. References to the research (indicative maximum of six references)
Citations and impact factors below refer information according to http://wok.mimas.ac.uk on 18th October 2013.

1. LANCASHIRE L J, POWE D G, REIS-FILHO J S, RAKHA E, LEMETRE C, WEIGELT B, ABDEL-FATAH TM, GREEN A. R., MUKTA R., BLAMEY R., PAISH E. C., REES R. C, ELLIS I O, BALL G R 2010. A validated gene expression profile for detecting clinical outcome in breast cancer using artificial neural networks. Breast Cancer Research and Treatment Volume 120, Number 1, 83-93, DOI: 10.1007/s10549-009-0378-1. Impact Factor: 4.469, Citations 15.
2. BALL G, MIAN S, HOLDING F, ALLIBONE R O, LOWE J, ALI S, LI G, MCCARDLE S, ELLIS I O, CREASER C and REES R C 2002. An integrated approach utilizing artificial neural networks and SELDI mass spectrometry for the classification of human tumours and rapid identification of potential biomarkers. Bioinformatics vol 18 (3) , pp. 395-404. DOI: 10.1093/bioinformatics/18.3.395. Impact Factor: 5.523, Citations 153.
3. MIAN, S, UGUREL, S, PARKINSON, E, SCHLENZKA, I, DRYDEN, I, LANCASHIRE, L, BALL, G, CREASER C, REES R and SCHADENDORF, D 2005. Serum proteomic fingerprinting discriminates between clinical stages and predicts disease progression in melanoma patients. Journal of Clinical Oncology vol 23 (22) , pp. 5088-5093. DOI:10.1200/JCO.2005.03.164. Impact Factor: 18.038, Citations 68.
4. MICHAEL A, BALL G, QUATAN N, WUSHISHI F, RUSSELL N, WHELAN J, CHAKRABORTY P, LEADER D, WHELAN M and PANDHA H. 2005. Delayed disease progression after allogeneic cell vaccination in hormone-resistant prostate cancer and correlation with immunologic variables. Clinical Cancer Research vol 11 (12), pp. 4469-4478. DOI: 10.1158/1078-0432.CCR-04-2337 Impact Factor: 7.837, Citations 72.
5. LANCASHIRE L, SCHMID O, SHAH H and BALL G, 2005. Classification of bacterial species from proteomic data using combinatorial approaches incorporating artificial neural networks, cluster analysis and principal components analysis. Bioinformatics vol 21 (10), pp. 2191-2199. DOI:10.1093/bioinformatics/bti368. Impact Factor: 5.468, Citations 42.
6. BLAMEY, R W, ELLIS I O, PINDER, S E, LEE, A H S, MACMILLAN, R D, MORGAN, D A L, ROBERTSON J F R, MITCHEL M J, BALL, G R, HAYBITTLE J L and ELSTON C W, 2007. Survival of invasive breast cancer according to the Nottingham Prognostic Index in cases diagnosed in 1990-1999. European Journal of Cancer. vol 43 (10) , pp. 1548-1555. DOI: 10.1016/j.ejca.2007.01.016. Impact Factor: 5.061, Citations: 67.

4. Details of the impact (indicative maximum 750 words)

The area of biomarker discovery has seen significant developments over the last 10 years and the team at NTU continues to offer unique and leading approaches in the field. Novel non-linear approaches have been applied to the identification of biomarkers, from complex genomic data, addressing clinical questions such as prognosis and response to therapy. These biomarkers have subsequently been validated using immuno-histochemical techniques and applied in clinical practice and decision making.

Clinical collaborations with the Ian Ellis group, Nottingham University Hospitals Trust, have identified biomarkers of proliferation and prognosis in breast cancer (Refs 5 and 6). These have been used to re-define the Nottingham Prognostic Index allowing more accurate prediction of prognosis for the individual (Source to corroborate 1). This approach has been used by multi-disciplinary teams in clinical decision making, and to evaluate prognosis in medico-legal cases (Sources to corroborate 2, 3), and has influenced the decisions around patient care and stratification. Collaboration with the Steve Chan group at the Nottingham University Hospital Trust has identified a set of core proliferation related markers in breast cancer. The most influential marker predicts response to Anthracycline and the set has been successfully evaluated as predictive using immunohistochemistry. In addition the approaches developed have been utilised in identifying markers associated with circulating miRNAs in colorectal and breast cancer (Kerin Group, National University Ireland, Galway), Tuberculosis (Public Health England, Porton Down and Colindale (Source to corroborate 4), sepsis (Severnside Alliance for Translational Research,

Cardiff and Public Health England, Porton Down), ovarian cancer (Chan Group, Nottingham University Hospital Trust), prostate cancer (Khan Group, Leicester Royal Infirmary) and Alzheimer's Disease (Morgan Group, University of Nottingham).

This biomarker discovery work has led to the filing of 4 patents (application numbers cited):

1. Data Analysis Method and System – PCT GB/2009/051412, EPO 09796034.8, USA 13/125954 and China 200980143624.4
2. Time to Event Data Analysis Method & System – Divisional application US application No13/230956.
3. TB Marker PCT GB2013/051635
4. SPAG 5 Biomarker (Biomarker response to Anthracyclin) PCT/GB2013/051465v

In 2009 Lachesis funding and BioCity (Mobius) investment (initial funding ca. £300,000) were secured to launch a spin out company utilising the algorithms for biomarker discovery and patient stratification - CompanDX Ltd (http://companDX.com)- which exploits the IP within these patents (Source to corroborate 5). Patents 1 and 2 are currently exclusively licenced to CompanDX Ltd and the remaining patents are currently under negotiation as a part of an exclusive IP pipeline agreement between CompanDX and NTU. Further patents are currently under development for pancreatic cancer, cardiovascular disease and Alzheimer's disease. Professors Ball and Rees are founders and directors of this company.

The company has secured significant contracts (to a value of around £250,000) from large pharmaceutical and diagnostics companies to utilise the bioinformatics technologies in international clinical trials in order to identify biomarkers of response to cancer therapy (Astra Zeneca, Oxford Biomedica, Diagenic). In these instances these approaches have impacted upon trial design and have increased the efficiency of diagnostic development, thus making trials and diagnostics more cost effective. Further contracts on a fee for service model are currently in discussion.

The patents have recently resulted in an investment into CompanDX of 48million RMB (approx. £3.9M) in partnership with New Summit Biopharma Co Ltd, a Chinese Clinical Research Organisation funded by the Shenyang Regional Government (Sources to corroborate 5, 6). As a result of this investment clinical trials are currently being undertaken in China to evaluate the efficacy of diagnostics for time to event in breast cancer, and diagnosis of tuberculosis. These diagnostic tests will be evaluated on 1000 cases. Sino Federal Drug Administration regulatory approval is anticipated in 3 years' time. It is important as it will validate the clinical trial in the context of regulatory approval.

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Nottingham University Hospitals Trust, Breast Cancer Pathologist. Will corroborate the clinical impact of breast cancer biomarkers and the use of such biomarkers within the development of the Nottingham Prognostic Index.
2. Potter Rees Ltd (serious injuries solicitors), letter of agreement available to corroborate support given in medico legal cases where models based on the NPI have been used to predict median survival.
3. Pannone Law Group, letter of agreement available to corroborate support given in medico legal cases where models based on the NPI have been used to predict median survival.
4. Public Health England, Principal Scientist. Will corroborate the impact of biomarker identification in infectious diseases, including those associated with tuberculosis.
5. CompanDX, Chief Executive Officer. Will corroborate the commercial impact of the algorithms and biomarkers, particularly projects running in China.
6. http://www.manufacturingchemist.com/news/article_page/CompanDX_raises_39m_in_China/79920 - demonstrates the funding received from China for clinical work.