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Human biological sample biobanking to support tissue biomarkers in pharmaceutical research and development

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ABSTRACT

Advances in the understanding of molecular pathology and thereby the mechanisms that could be amenable to therapeutic manipulation are the reason that pharmaceutical research and development is focused increasingly on measurement of molecular biomarkers in human biological samples. Obtaining direct or indirect access to sufficient samples that are fit for research purposes can be a major challenge. A biobanking infrastructure has a significant role in the acquisition, storage and usage of human biological samples and here we review some key requirements for establishing a biobank. These include ensuring; that appropriate governance mechanisms are in place, that samples available are appropriate and fit for the intended research purposes that the infrastructure is sustainable in the future and that use of the biobank assets meets the strategic aims of the host organisation. Finally we present a case study – the STRATUM project which has recently completed and through a collaborative approach involving six industry and public partners drawing on a network of experts, examined biobank policies, public attitudes to biobanking, donor consent, sample and data standards, technical requirements for a register and biobanking financial models, albeit from a UK perspective.

1. Introduction

Human biological samples (HBS) are essential tools supporting research into human disease, particularly using molecular biomarkers. Whilst the collection and use of HBS for diagnostic purposes is widespread and embedded in clinical practice, these collections are not routinely made available for research purposes and many are discarded once diagnostic procedures are complete. Significantly fewer HBS are acquired specifically for research purposes, either from diagnostic archives or prospectively from donors during clinical trials or as part of specific disease or population based collections. Uncomplicated access to sufficient fit for research purpose HBS is widely considered to be a major problem and a major driver for establishment of HBS bio-banks, bio-repositories or bio-libraries. The March 2009 issue of Time magazine included Biobanking as one of the ten ideas changing the world right now [1]. Establishing and maintaining collections of HBS is not straightforward and a recent review highlights the challenges facing biobanking over the next few years [2]. An unpublished AstraZeneca survey of key internal and external clinical decision makers five years ago identified human target expression and disease linkage as the most important problem to be addressed in early cancer drug discovery.

In this paper the authors draw on their combined experiences in both public and private biobanking environments but from the perspective of the UK base of a large pharmaceutical company. The AstraZeneca biobank exists to provide HBS to support pharmaceutical research and development where there is a focus on molecular pathology and biomarkers.

The true research value of HBS is inextricably linked to their associated data whether directly relating to the donor or to the sample itself. However the legal aspects of personal data protection are complex and we have regarded them as out of scope for this review.

2. Relevance of biobanks to the practice of molecular pathology

The main driver for a large pharmaceutical company such as AstraZeneca is discovery and development of personalised or stratified medicines i.e. to deliver the right treatment to the right patient at the right dose and at the right time. In turn this is driven by the molecular segmentation of many diseases leading to hypothesis generation based on molecular pathology platforms. Some examples can be seen in the March 2011 special edition of

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Nature Reviews Clinical Oncology entitled "Focus on personalized medicine" (http://www.nature.com/nrclinonc/focus/personalized-medicine/index.html). Personalised/stratified medicines are not confined to oncology and the 2014 annual review edition of the Journal of Pathology is devoted to "Pathology in Drug Discovery and Development" (http://onlinelibrary.wiley.com/doi/10.1002/path.2014.232.issue-2/issuetoc). Measurement of molecular biomarkers in HBS is then, fundamental to delivering stratified medicines. The scenario is further complicated by the fact that multiple samples (e.g. blood, body fluids, solid tissue) can be collected and used from multiple anatomical sites and in multiple formats (e.g. fresh, frozen, formalin fixed-paraffin embedded).

The original "official" definition of the term "biomarkers" is as follows: Biomarkers have been defined by the Biomarkers Definitions Working Group as being "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [3] but in our everyday, practical working environment, biomarkers are "things that we measure in HBS". A list of biomarker types with brief descriptions is provided in Fig. 1.

Molecular pathology is now firmly established providing technology platforms to deliver biomarker analyses to support drug development and will play an increasing role particularly with new high throughput technologies, particularly so-called "Next Generation Sequencing" or NGS [4].

Increasingly, and particularly in cancer, drug development programmes are accompanied by biomarker development which has the aim of identifying sub groups of patients who are more likely to respond to treatment [5,6]. Personalised or stratified medicines developed to target disease subtypes defined by presence or absence of specific biomarker signatures are intended to deliver multiple benefits: to patients (more effective medicines and more informed choice); to physicians (improved drug response prediction and choice of medicines for each patient); to the pharmaceutical industry (new, innovative treatments and more competitive products) and to those who pay for healthcare systems (optimised healthcare for patients and improved budget management). Interestingly for molecular pathology many of the new technology platforms, for example the genomics based Cancer Research UK Stratified Medicines Programme (http://www.cancerresearchuk.org/science/research/how-we-deliver-our-research/others/by-programme/stratified-medicine-programme/) continue to utilise formalin fixed paraffin embedded (FFPE) HBS, which is still the mainstay for diagnostic histopathology.

A recent report from the Academy of Medical Sciences [7] highlighted that action is required by stakeholders to deliver the potential of stratified medicines. Of particular relevance to biobanking, the report recommended:

"Increased collection of tissues for biomarker research and evaluation, and its organisation in national and international biobanks.

Biomarker type	Description
Pre-disposition	To identify risk of subsequent development of a disease e.g. BRCA mutation and breast cancer
Screening	To identify disease at an early stage where early intervention can lead to improved treatment outcome within a population e.g. Prostate Specific Antigen (PSA) and prostate cancer
Diagnostic	To make a diagnosis of disease e.g. panels of immunohistochemical cytokeratin biomarkers used to define the cancer type and sub-type in tissue samples e.g. "metastatic adenocarcinoma with unknown primary".
Prognostic	To inform disease outcome either as biological progression markers which measure tumour burden or recurrence (e.g. serum CEA in colorectal cancer) and risk biomarkers (e.g Ki 67 activity in some tumours) which usually correspond with disease activity.
Predictive	To select or stratify patients likely to respond to molecularly targeted therapy e.g. overexpression of HER2 in breast cancer and response to trastuzumab. When developed in parallel to the therapy, known as "companion diagnostics"
Pharmacological	To inform drug development, a variety of biomarker types to indicate: - patient reaction to drug (pharmacogenomic), - disease response to drug to inform dosing (pharmacodynamic) - drug mechanism (proof of mechanism) - drug phenotypic effect (proof of principle) - toxicity (safety)
Surrogate	Surrogate response biomarkers can help set the optimal biological dose of a drug e.g. serum PSA during prostate cancer therapy. However, changes in expression do not always reflect disease activity and these markers need to be interpreted with caution.
"Useful" [39]	To inform the risk/benefit ratio when there is a decision to be made To do so in a better/faster/earlier/cheaper way than existing approaches To be generally applicable: sample and technology must be available/accessible.

Fig. 1. A Biomarker Classification (based on E Hitchman, PhD thesis, University of Manchester, December 2011). See Ref. [39].