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Tissue collection in drug discovery and development research

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ABSTRACT

A major step in targeted cancer drug discovery is demonstrating 'proof of mechanism'. Tissue samples are an integral part of current drug development. At the Biotherapy Development Association Meeting in March 2007, the benefits and problems of tissue related endpoint inclusion in clinical drug development were discussed; Academic, Regulatory Authority and Pharmaceutical Industry representation being present.

It was agreed that the public supports the use of human tissue in research; cooperation and collaboration are essential to ensure that tissue samples are collected and available for research; tissue sampling should be mandatory for clinical trials; and that tissue remaining from diagnostic, surgical and clinical trial based sampling should be made available for research.

Until existing or new technologies provide utility for alternative sampling, access to human tissue samples of consistent quality will underpin the success of cancer drug pipelines in the era of molecular biological biomarkers and personalised medicine.

1. Introduction

Before attempting to show a novel compound has benefit in the clinic, a major step in cancer drug discovery is demonstrating we have hit our target (proof of mechanism). Traditional physician examination and imaging are no longer adequate to confirm a 'hit' in the new molecular era. Despite active research to increase the utility of blood and other body fluids[1,2] identification of biomarkers to assist in the understanding of drug mechanism and effect still relies heavily on tissue samples. In turn, this reflects the fact that, despite being based on technology that is 150-years-old, the microscopic examination of tissue samples – histopathology – remains the 'gold standard' for cancer diagnosis worldwide.[3]

2. Baseline

At the Biotherapy Development Association (BDA) 3rd Alpine Meeting: Strategies for Harmonisation of Next-Generation Oncology Drug Development, 14–16th March 2007, Innsbruck, Austria, it was agreed that:

- Cooperation and collaboration are essential to ensure that tissue samples are collected and available for research: the stakeholders are patients, academics, regulators, industry and payers. The group also agreed that virtual tissue banks should be encouraged. These require central coordination with a greater or lesser emphasis on central physical tissue storage and there are examples in cancer across Europe,[4] as well as in individual countries such as Spain[5] and UK.[6]
- Tissue should be available and mandatory for recruitment into clinical trials.
- Tissue 'left over' from diagnosis, surgery and at the end of clinical trails should be made available for research.

3. Definitions

We each have an understanding of what 'human tissue' is and in some countries this is defined in law, e.g. in England, Wales

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and Northern Ireland tissue is any material containing human cells but there are exceptions (www.hta.gov.uk). However, there is no worldwide consistent definition of 'tissue' in laws and guidelines. This makes a definition of tissue banks that much more difficult. Two quite different examples are:

- 'An intermediary to legally, ethically and safely, acquire, store and distribute human tissue (cell material containing DNA) and body fluids, on a cost recovery/not for profit mechanism, for bone fide research purposes'.[7]
- 'A biospecimen resource is defined as a collection of human specimens and associated data for research purposes, the physical structure where the tissue is stored, and all relevant processes and policies.'[8] This definition recognises that resources can range from informal collections in the freezers of individuals to formal organisations.

4. Infrastructure and coordination

The interrelationships between regulation for tissue, information technology to support high throughput tissue sample research strategies and ethics are shown in Figs. 1 and 2. Tissue-specific legislation including research is currently a European phenomenon and established in Denmark, Norway, Sweden and UK. The separate Scottish Act 2006 (http://www.opsi.gov.uk/legislation/scotland/acts2006/20060004.htm) does not apply to tissue taken from living people. Development of bioinformatics required to support the correlation of tissue sample and clinical data with the results of research from a variety of biomics technologies (e.g. immunohistochemistry, in situ hybridisation, genetic mutational analysis, RNA expression, etc.) is a major challenge as these technology platforms are increasingly high throughput, even immunohistochemistry.[9,10]

There is some harmonisation of ethics in relation to clinical trials and a general worldwide agreement that the human body and its parts shall not, as such, give rise to financial gain, which stems largely from the Council of Europe.[11]

Appropriate informed consent underpins ethical use of human tissue in research. The public supports the use of human tissue in research. In a recent analysis[12] of 30 studies using different methods but involving 33,000 people worldwide, incorporating the views of patients, research participants, family members, religious leaders and public over a 10-year period found that

- 80% would agree to donate if asked. Those who did not agree were concerned about the procedure required to obtain the sample, rather than the use of the sample for research purposes;
- 79–95% are willing to provide 'one-time general consent' and rely on decisions of ethics committees to approve research presently and in the future;
- 83–99% are willing to donate leftover samples for research. This is consistent with the authors' own experience who have also shown that the donors are willing to provide tissue for research in pharmaceutical and biotechnology research.[13] This includes taking tissue after death[14] for which the demand is likely to increase for regulatory cross-reactivity studies in the preclinical development of therapeutic monoclonal antibodies.[15]

Wendler[12] concluded that most respondents wanted to decide whether their samples are used for research pur-

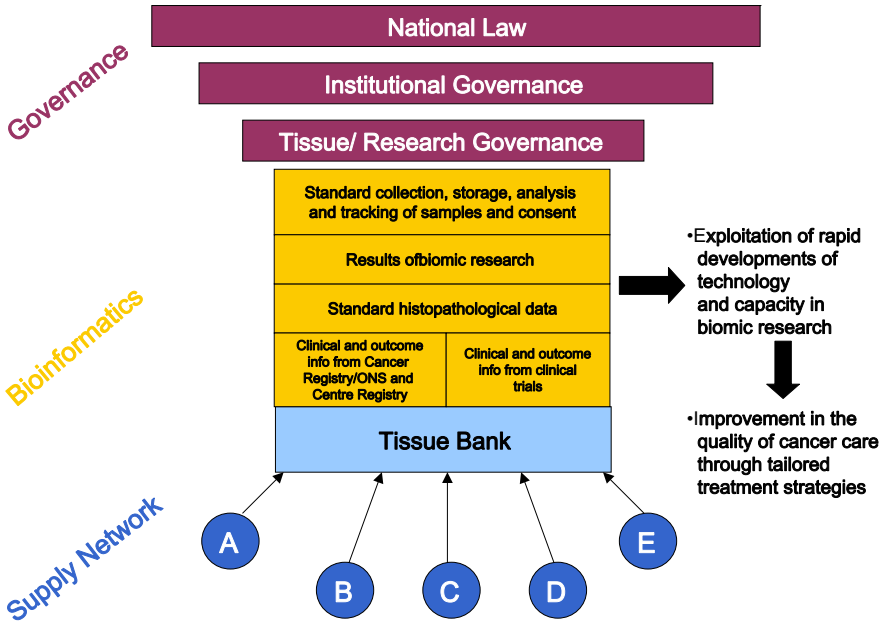

Fig. 1 – Regulation/IT/Collaboration. The interrelationship between governance (high level), centralised tissue collection from a network of sources and bioinformatics in between. The bioinformatics integrates primary clinico-pathological data, secondary follow-up clinical data and results of biomic research. Information technology is critical to the success of the interrelationship.

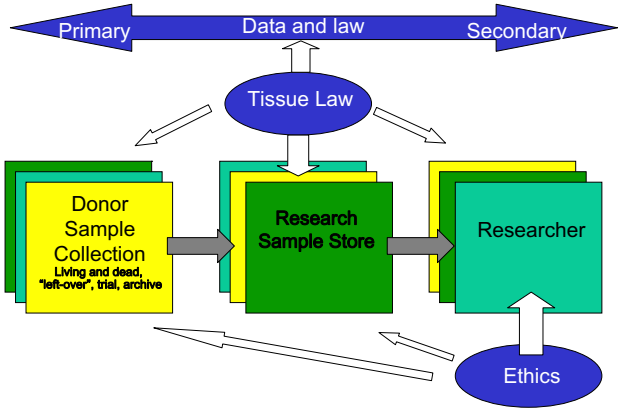

Fig. 2 – Regulation and ethics. The interrelationship between law (data and tissue-specific) and ethics on donor tissue collection, storage and use in research. The multiple boxes indicate that one or multiple donor collection sites can feed one or multiple tissue banks that can feed one or multiple researchers.

poses and that 'one-time general consent' is the best option because it offers people the choice(s) that reasonable people would want to have; it respects the wishes of people to control the use of their samples without mandating that they decide which specific projects they are used for: it protects people from risk provided ethics committees find projects are acceptable with no more than minimal risk, and it is practical.

We need to recognise and respect this international public support and begin to re-align the professional approach. Examples of successful application of one-time general consent for the use of human tissue in research including pharmaceutical research, with no demonstrable risk to patients are published,[16,17] but there are many others unpublished.

5. Tissue banks

However defined, centralised tissue banks offer advantages over individual collections:

- standardised consent;
- standardised collection, preservation, quality control and storage;
- coordinated and systematic tissue collection according to need;
- sharing and coordinated tissue research use (is it ethical for an individual to collect tissue for research and then not use but deny access to others?);
- controlled disposal to avoid wasting and over-collection;
- better institutional governance (whether a legal requirement or not);
- better collaborative opportunities between academia and industry;
- Economies of scale (particularly for staff, freezers and also with supporting technologies, e.g. immunohistochemistry, in situ hybridisation, DNA/RNA extraction).

Advantages of centralised over individual collections are independent of whether the tissue bank is real or virtual. Virtual tissue banks should be encouraged as they encourage tissue resource sharing but allow local tissue collection, storage and expertise to continue which adds to the research potential of the collaborative network created. The challenge is making this happen.

Individual physician versus institutional ownership of human tissue collections has recently been challenged in the US with the courts finding in favour of the institution.[18] There is now recognition that funding is required for meaningful tissue collection for research purposes and funders will be expected to have some degree of control. But these controls for tissue are no different from other research areas. The process of both contribution and access to a tissue bank needs to be transparent and governed by sound ethical and scientific principles so we can assure our patients that their free donations are put to appropriate and as wide a use as possible.

5.1. *Benefits of performing biopsies in oncology clinical trials*

Biopsies taken during the course of clinical trials are used to demonstrate

- Pharmacodynamic effect in tumour (Proof of Mechanism/ Proof of Principle);
- Pharmacokinetic effect in tumour;
- Genomic expression;
- Non-PoM/PoP biomarker expression, e.g. P-glycoprotein;
- Tissue bank (to provide baseline data with history, correlation with other biomarkers for comparison with follow-up biopsies, e.g. at 'failure of therapy' and as tissue resource when the trail is finished).

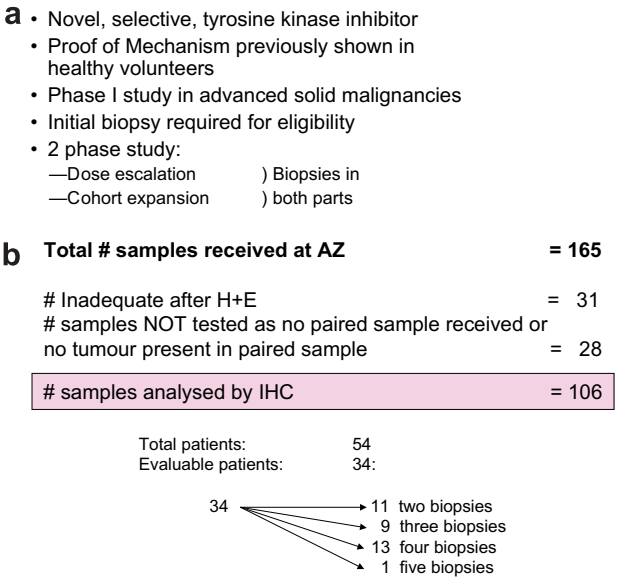

Fig. 3 – The study was carried out in six centres (five Europe and one USA). Biopsy driven 'first into patient' study: (a) an example and (b) metrics.

5.2. *Issues with performing biopsies in oncology clinical trials*

Fig. 3a and b shows an example of the tissue metrics of a recent AstraZeneca phase I clinical trial. In general, biopsy recruitment for phase I trails conducted in a handful of centres will yield a higher proportion of evaluable samples than a multicentre phase II or III trial.

Other difficulties obtaining biopsies from a trial patient population are the perceived detrimental effect that consent for biopsy may have on recruitment timelines: it is generally considered that given the option patients will opt for the no biopsy study. Additional issues in Phase I studies in advanced disease are related to the ethics of additional invasive procedures, the relevance of population to early non-metastatic disease (including disease biology and drug tolerability) and the relevance of biopsying only one lesion.

Biopsy procedure is relatively costly. Careful attention to rapid tissue preservation using formalin or freezing and to tissue processing requires additional logistics to ensure consistency. Resulting tissue samples are often small which limits use both within and outside the individual study and an opportunity to gain knowledge. In the future, less invasive procedures and improvement in existing technologies (e.g. proteomics) and emerging technologies (e.g. circulating tumour cells in blood) may provide validated alternatives to tissue biomarkers). The issue of custodianship of existing samples is not easily resolved but closer working with better collaboration including recognition and understanding of the intellectual property aspects of studies should enable this problem to be addressed.

6. Conclusion

Tissue samples are an integral part of current drug development research and their consistent collection and use presents problems which are not new but which can be addressed. The public (the basis of our patient population) supports the use of human tissue in research. Coordinated and centralised facilities will enable faster and more efficient access to human tissue for research. Until existing or new technologies provide utility for alternative sampling, access to human tissue samples of consistent quality will underpin the success of cancer drug pipelines in the era of molecular biological biomarkers and personalised medicine.

Conflict of interest statement

The two authors of this paper Drs. Christopher Womak and Glen Clack are employees of AstraZeneca and it can be confirmed that there is no conflict of interest involved in this paper, nor in their participation in this entire event.

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