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Review

Molecular pathology – The value of an integrative approach

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ABSTRACT

Molecular Pathology (MP) is at the heart of modern diagnostics and translational research, but the controversy on how MP is best developed has not abated. The lack of a proper model or trained pathologists to support the diagnostic and research missions makes MP a rare commodity overall.

Here we analyse the scientific and technology areas, in research and diagnostics, which are encompassed by MP of solid tumours; we highlight the broad overlap of technologies and analytical capabilities in tissue research and diagnostics; and we describe an integrated model that rationalizes technical know-how and pathology talent for both. The model is based on a single, accredited laboratory providing a single standard of high-quality for biomarker discovery, biomarker validation and molecular diagnostics.

1. Introduction

The future of modern medicine is likely to be dictated by two main pillars: molecular medicine and technical advances. A key component of the former is personalised medicine and therapeutic pathology, i.e. the development of a new generation of drugs targeting specific genes and pathways, coupled with biomarkers that predict the individual patient's response to those drugs (Ozdemir et al., 2006). In this context, the discovery, validation and clinical application of novel biomarkers become a cornerstone of medical advancement. At the heart of biomarker-related work is molecular pathology (MP) (Harris and McCormick, 2010).

It has become evident that, to advance in the translation of biomarker discovery into diagnostic and therapeutic application (depicted in Figure 1), the interface between basic research and diagnostics is the weakest link. This is the area that MP should be addressing. This cliché is usually accompanied by another truism, namely that MP is one of the most important, and yet less structured and developed areas in translational and clinical research.

The purpose of this article is to review all the different components of what we call MP. By doing so, we would like to suggest an integrated model of provision of MP at all levels, from biomarker discovery to molecular diagnostics. To focus further on this exercise, we will concentrate on tissue molecular

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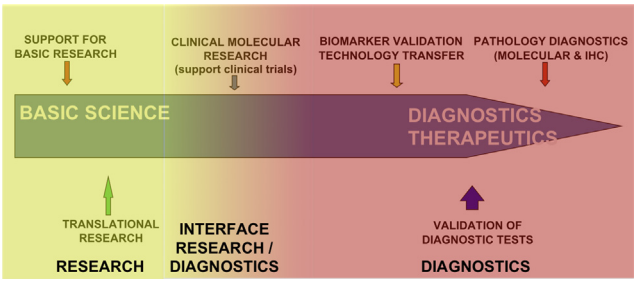

Figure 1 – Pipeline to deliver basic science discoveries into diagnostic and therapeutic end-points.

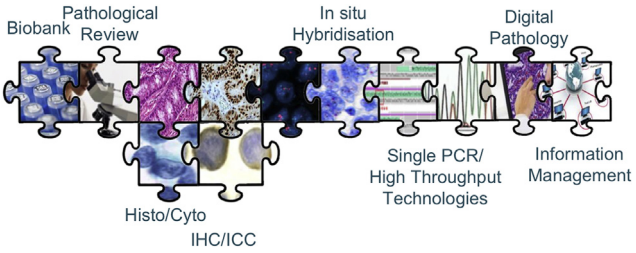

Figure 2 – The integrated puzzle of pathology activities and technologies.

pathology of solid tumours and, hence, on the area of molecular onco-pathology. This analysis of MP will illustrate the transition from traditional tissue-based interpretation of morphology to advanced high-throughput molecular technologies, and from biomarker discovery to molecular diagnostics (Dietel et al., 2013). It is our view that the integration of traditional and molecular pathology within a single laboratory management and delivery infrastructure is essential and that the perception of translational research and diagnostics is a continuum rather than two distinct entities. These facts are basic requirements for the future rationalisation and improvement of pathology services within the context of academic medicine.

2. Molecular pathology – translational research & molecular diagnostics

Why are pathologists needed in translational research, patient stratification and the delivery of personalized medicine? What can pathologists contribute as members of comprehensive, multidisciplinary research teams? There are indeed some aspects in research that can only be provided by pathologists who can interpret tissue phenotype underpinned by a deep understanding of the biological basis of disease, and have the inclination to be involved in research/academic duties. These capabilities can be presented as an integrated pipeline that would take the human tissue sample through different levels of traditional and molecular pathological interrogation (see Figure 2). These activities can be translated into specific techniques and technologies (see Table 1). While other scientists could fulfil some of these needs, it is perceived that only those able to integrate the morphological, clinical and molecular dimensions of the disease would be able to deliver them in an optimal fashion. These subspeciality areas with Molecular Pathology are discussed below.

2.1. *Molecular pathology and molecular diagnostics in the context of clinical trials*

Clinical trials are at the true interface between science and clinical care. While they represent a research exercise strictly speaking, they also provide potential healthcare to patients and thus need to be carried-out with strict clinical and diagnostic rigour (Simon and Roychowdhury, 2013). Typically, there are 2 levels of biomarker analysis in clinical trials, namely a) specific biomarker analysis to decide the stratification of patients within the trial, i.e. *a priori* testing, and b) general biomarker analysis to identify a biomarker (single or multiple) to predict patient response, i.e. a *posteriori* testing. Both are equally important. The biomarkers used in *a priori* testing may already be standard-of-care (for instance, a clinical trial aiming to provide alternative therapeutic avenues to cetuximab for *KRAS* mutant patients would need *KRAS* mutation analysis upfront), while others may represent a more experimental endeavour (such as detecting cMET status in trials using cMET inhibitors). In general, the predominant view is that these tests should be performed by practising diagnostic pathologists in accredited laboratories. *A posteriori* testing is increasingly performed with high-throughput technologies (Simon and Roychowdhury, 2013). Again, although it is a discovery exercise, there is increasing consensus that this analysis should be driven by molecular pathologists, in accredited laboratories for that purpose (CAP, CPA, CLIA, etc) (Wheler et al., 2013), and with patterns of test validation, quality control and quality assurance (QA/QC) as close as possible to fully established clinical testing. Only then will any piece of discovery work be reliable for future use in the clinical context, should the trial lead to positive results.

2.2. *Analysis of tissues ahead of molecular testing*

Despite the predictions that molecular biology would substitute traditional microscopic morphological assessment of the disease, the reality is that genotype and phenotype are not mutually exclusive, but complementary (Muley et al., 2012). It would appear that high-quality microscopy is a *condition sine qua non* for high-quality molecular diagnostics. Indeed, the accurate morphological analysis ahead of the testing itself is essential to confirm that a) the sample is of

Table 1 – Pathology-centred activities in the research endeavour.

Molecular diagnostics in the context of clinical trials
Analysis of tissues ahead of molecular analyses
Tissue biobanking
Digital pathology
Pathology informatics
Data manager
Biomarker validation
Integration of validated biomarkers into routine diagnostics