

Advances in personalised medicine in the treatment of tumour patients – the modern pathologist’s role



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‘Personalised’ or ‘precision’ medicine is about getting the right therapy to the right patient at the right time. Pathologists play a vital role in determining which therapies may be effective in each patient, not only by providing specific diagnoses, but by performing extended analyses of tumour phenotypes and genotypes through evaluation of a growing number of specific and relevant tumour biomarkers.

Traditionally viewed as diagnosticians working behind closed doors, today’s pathologists are informational interventionists, essential to guide personalised treatment strategies for oncology patients

Targeted cancer therapies first emerged over two decades ago, with the monoclonal antibody rituximab (Rituxan®) for the treatment of patients with refractory B-cell non-Hodgkin lymphoma being the first FDA approval. Today, dozens more exist, e.g., small molecules such as the tyrosine-kinase inhibitor, gefitinib (Iressa®), which interrupts EGFR signalling in select non-small cell lung cancer (NSCLC) patients and immuno-oncology agents such as the PD-1 inhibitor pembrolizumab (Keytruda®), an immune checkpoint inhibitor that now has several indications.

Recently, more bespoke therapies such as CAR T-cell therapies have come on the scene, bringing cancer therapy even closer to truly personalised medicine. Information from the pathology team – e.g., the presence or absence of specific gene alterations and/or expression of key target proteins – is needed to help guide treatment decisions for targeted therapies. Currently, eligibility for specific targeted therapies may require relevant biomarker assessment with a clinically validated assay, often available as a FDA-approved assay. An example of such a clinically validated assay is the Dako PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay, for which the current purpose is to aid in the identification of NSCLC as well as gastric or

gastroesophageal junction adenocarcinoma patients for potential response to treatment with pembrolizumab. Not only does a targeted approach help to improve patient outcomes, it also reduces financial and resource-based burdens compared with conventional approaches and protects patients who are deemed unlikely to respond, from unnecessary side effects.

Personalised medicine in the treatment of cancers requires a thorough understanding of the unique cancer pathology in each patient. In their quest to fully interrogate each tumour specimen, pathologists may use a wide variety of techniques across different laboratories such as the Immunohistochemistry Laboratory and the Molecular Diagnostics Laboratory. The overwhelming complexity of the techniques lends itself to the misconception that pathologists work across many disciplines, but in simple terms, everything falls within the remit of the central dogma of molecular biology, which describes the flow of genetic information from DNA to RNA through to the protein product.

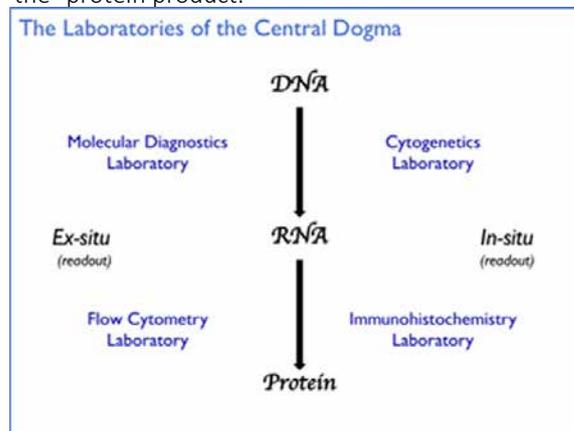


Figure 1: Laboratories of the molecular biology central dogma

Thus, as simplified in Figure 1, the work of a pathologist involves the study of DNA, RNA and/or protein, whether in situ or ex situ. As an example, PD-L1 immunohistochemistry assays (used to determine expression of the transmembrane protein PD-L1 to predict response to select PD-1/PD-L1 checkpoint inhibitors) would fall under the Immunohistochemistry Laboratory situated within the lower-right quadrant of the figure.

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Another example is next-generation sequencing – an umbrella term for different technologies in high-throughput DNA or RNA sequencing – which would be situated in the top-left quadrant. Classic histology techniques such as microscopic evaluation using hematoxylin and eosin staining are still used in every day practice too. After all, morphological assessment is actually the oldest known gene expression profiling methodology because the morphological characteristics of cancer is a snapshot that represents the culmination of the phenotypic expression of many thousands of genes that gives each tumour type its specific “look”. Whilst no longer the sole focus of their work, pathologists are still involved in essential tasks such as diagnosing, classifying and staging each tumour, for which histology still dominates.

Defining the role of a pathologist can be challenging as there are different types of pathologists. The exact role of pathologists also varies both within a laboratory and across different centres. While some may find themselves tightly integrated with the clinical laboratories, working closely with medical laboratory technologists and technicians, many pathologists spend much of their time outside of the laboratory. In some sub-specialties such as hematopathology and cytopathology, pathologists may be involved in obtaining the biopsies themselves (e.g., bone marrow aspirates/biopsies and fine needle aspirates, respectively).

Pathologists are part of multidisciplinary teams and are responsible for requesting appropriate laboratory testing on tissue samples, and then analysing and interpreting the findings. Pathologists collate results of the tissue testing that comes out of the laboratory – whether glass slides, images, protein expression readouts or gene signatures – and use this information to generate insightful and clinically meaningful reports that help guide treatment decisions. Rarely functioning in isolation, pathologists work alongside treating physician colleagues to help advise on the clinical implications of their reports, often attending ‘tumour boards’ alongside oncologists, other pathologists, radiologists, and surgeons to discuss their patients in a

holistic manner. On occasion, pathologists may also interact directly with patients.

Another important aspect of a pathologist’s work is quality assurance. Laboratory directors are often pathologists who essentially have the role of ensuring every test result that comes out of the laboratory is valid for its specific purpose. This comprises initiating, implementing, maintaining and updating countless quality assurance processes. Development of new assays and their maintenance is often challenging especially for laboratory developed tests, which need to be fit-for-purpose and validated for specific intended use by the laboratory. Even already validated FDA-approved instruments and kits require considerable expertise to set up; while specific parts of the workflow are standardised, they are in no way ‘plug and play’ devices. These too require regular monitoring by the laboratory and are also subject to external quality assurance processes (i.e. proficiency testing or interlaboratory comparison). Pathologists, their colleagues and indeed their patients, must be able to rely on laboratory results with confidence as potentially life-changing treatment decisions are made based upon them. Without stringent quality assurance processes, this is simply not possible.

It is an exciting time for pathologists, who – in the field of oncology at least – play a key role in clinical decision-making and may be described as informational interventionists. As medicine and technology advance, we will continue to understand ever more about the pathology of tumours. From this will undoubtedly come the arrival of yet more state-of-the-art targeted therapies and associated biomarkers. Tumour mutational burden – the number of mutations within a tumour genome – is an example of an emerging biomarker with potential predictive value that may well become part of the armamentarium in the new future. Such developments are great news for patients. As new life-saving therapies emerge and new biomarkers are developed, laboratories respond to these new needs by developing new tests, new quality assurance tools, and new types of pathology practices and expertise.

Pathologists are now in more demand than ever before and with numerous targeted therapies in various stages of clinical development; it seems that this demand is unlikely to fade. Targeted therapies are the foundation of the modern approach to fight cancer, the deadliest of all maladies; it

is very likely that we are only at the start of a new era for cancer diagnostics and treatment. For pathologists, the biggest challenges will be to ensure that the most relevant assessments are selected for each patient and, of utmost importance, that time, resource and workload pressures do not ever lead to compromise in terms of accurate, reliable and clinically meaningful results.

For more information on the role of pathologists in personalised cancer medicine see a short film from Agilent:

<https://www.agilent.com/about/newsroom/videos/2017/fight-against-cancer.html>.

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Cancer Hypotheses

This open access journal appeared in early 2016 as a new online publication from BioMedES UK (www.biomedes.biz).

The journal's main purpose is to act as a forum where hypotheses, old and new, can be aired and discussed. Every cancer study, experimental or clinical, should be hypothesis-based, but we could not handle papers on all of them! We will focus on those that are truly original and have some novel data or evidence to support them. Researchers are often reluctant to publish new ideas about cancer, especially if they seem "way-out". However, submissions of this kind are welcome; some may well have an element of truth in them, and we all know that there are no "fundamental" theorems of cancer. "Today's crazy idea can become the received wisdom of tomorrow"...(jumping genes?).

The journal will be based on the author-pays model, but this will not apply to any paper accepted for publication before the end of July 2018. Thereafter a charge will be made, but it will be far less than that currently being levied by most other (cancer) journals. For more information, Google cancer hypotheses and it should come top of the search: www.cancerhypotheses.org.uk