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Review

Bench to bedside molecular functional imaging in translational cancer medicine: to image or to imagine?

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Ongoing research on malignant and normal cell biology has substantially enhanced the understanding of the biology of cancer and carcinogenesis. This has led to the development of methods to image the evolution of cancer, target specific biological molecules, and study the anti-tumour effects of novel therapeutic agents. At the same time, there has been a paradigm shift in the field of oncological imaging from purely structural or functional imaging to combined multimodal structure–function approaches that enable the assessment of malignancy from all aspects (including molecular and functional level) in a single examination. The evolving molecular functional imaging using specific molecular targets (especially with combined positron-emission tomography [PET] computed tomography [CT] using 2- [^{18}F]-fluoro-2-deoxy-D-glucose [FDG] and other novel PET tracers) has great potential in translational research, giving specific quantitative information with regard to tumour activity, and has been of pivotal importance in diagnoses and therapy tailoring. Furthermore, molecular functional imaging has taken a key place in the present era of translational cancer research, producing an important tool to study and evolve newer receptor-targeted therapies, gene therapies, and in cancer stem cell research, which could form the basis to translate these agents into clinical practice, popularly termed "theranostics". Targeted molecular imaging needs to be developed in close association with biotechnology, information technology, and basic translational scientists for its best utility. This article reviews the current role of molecular functional imaging as one of the main pillars of translational research.

Introduction

One in eight deaths worldwide is due to cancer, with approximately 12 million new cases diagnosed every year. Despite aggressive treatment strategies, the mortality is still

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high with a need to focus research on developing novel approaches to cancer management.[1–3] Ongoing research in the field of cancer biology has resulted in a greater understanding of the molecular pathology of cancer and carcinogenesis. This has led to the development of methods to image the evolution of cancer, target specific biological molecules, and study the anti-tumour effects of novel therapeutic agents.[3–5]

A question remains as to whether these research-based molecular and functional imaging techniques can be translated into clinical practice and integrated into clinical radiology.[6,7] There is now greater focus on developing imaging methods that probe putative physiological and molecular targets, such as angiogenesis, apoptosis, signal transduction, and functional metabolic pathways.[7,8] It is anticipated that molecular imaging will eventually provide biologically relevant information, aiding patient stratification, better therapeutic management, and on-treatment monitoring.[8,9] This article reviews the current molecular and functional imaging techniques performed in translational research, which may aid and improve comprehensive cancer management in the future.

Present status of cancer imaging in translational cancer medicine using molecular imaging endpoints

Translational research bridges basic science to clinical applications that in turn provide meaningful health outcomes[3,10,11] (Fig 1). Imaging is already being used widely in the management of patients with cancer for diagnosis, staging, therapy planning, monitoring, and surveillance, making imaging an indispensable part of clinical cancer protocols[7,8]; however, there are recognised limitations to current clinical imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) for studying *in vivo* biological changes related to carcinogenesis, prognosis, and response to therapy.[5,7,8] Techniques in clinical practice include combined positron emission tomography (PET)/CT, single photon emission CT (SPECT)/CT, and PET/MRI. PET/MRI, now available in a few centres worldwide, confers the possibility of high-resolution anatomical information from MRI (related to better soft-tissue contrast compared to CT) together with the ability to simultaneously study physiological MRI and molecular PET data; thus, improving the understanding of tumour biology on a multiparametric scale with the advantage of lower radiation doses compared to PET/CT.[12,13]

Integration of non-invasive molecular imaging into molecular medicine by way of feature extraction and analysis of quantitative imaging features from a variety of conventional imaging techniques and correlation with tumour biology, i.e., genomics, proteomics, and metabolomics, is called "radiomics".[14–16] One such example is radiogenomics with phenotype analysis of multiparametric MRI in glioblastoma multiforme (GBM), which is a non-invasive technique to investigate the molecular pathology and intratumoural heterogeneity in glioblastomas[17–19] (Fig 2).

A variety of preclinical imaging methods, such as optical-based molecular imaging techniques, are being used in preclinical research to characterise and understand tumour biology; however, they have the inherent limitations of imaging deeper tissues.[20,21] Preclinical images can be correlated with histological images to aid validation of functional imaging markers[22,23] (Fig 3). Some of these imaging techniques have potential for clinical translation for *in vivo* imaging of skin, oesophageal, urinary bladder, and colon cancers.[21–24] Thus molecular functional imaging (MFI), which allows detection of molecular events and interactions of cancer cells *in vitro* and *in vivo*, is gaining ground in comprehensive cancer care[24,25] (Table 1; Fig 4).

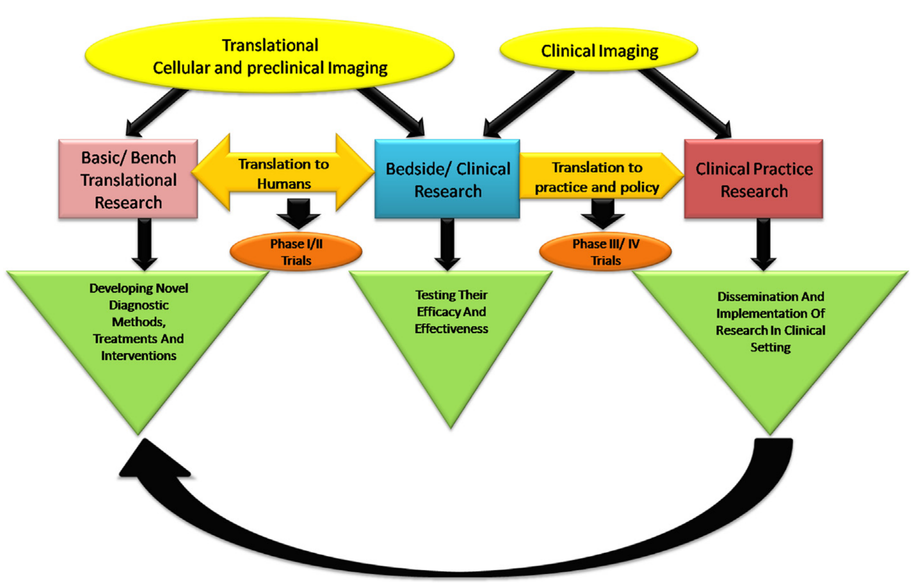

Figure 1 Road map to practice-based translational research. This schematic diagram depicts the working model of bench-to-bedside translational research. Imaging is the main cornerstone of this chain that helps translation of molecular discoveries into clinical application (forward translation). Scientific questions that arise from relevant clinical findings in turn triggers advances in research (reverse translation).