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Critical parameters in targeted drug development: the pharmacological audit trail

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ABSTRACT

The Pharmacological Audit Trail (PhAT) comprises a set of critical questions that need to be asked during discovery and development of an anticancer drug. Key aspects include: (1) defining a patient population; (2) establishing pharmacokinetic characteristics; (3) providing evidence of target engagement, pathway modulation, and biological effect with proof of concept pharmacodynamic biomarkers; (4) determining intermediate biomarkers of response; (5) assessing tumor response; and (6) determining how to overcome resistance by combination or sequential therapy and new target/drug discovery. The questions asked in the PhAT should be viewed as a continuum and not used in isolation. Different drug development programmes derive different types of benefit from these questions. The PhAT is critical in making go-no-go decisions in the development of currently studied drugs and will continue to be relevant to discovery and development of future generations of anticancer agents.

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1. Introduction

Molecularly targeted drugs have become an integral component of the treatment of cancer patients over the last three decades and their importance continues to increase. There have been successes where targeted agents have shown benefit in disease subtypes such as melanoma (vemurafenib [1]) and renal cancer (sorafenib [2]) where conventional chemotherapy had close to no efficacy. Molecular therapeutics have also added incremental patient benefit for diseases such as diffuse B-cell lymphoma (rituximab [3]) where chemotherapy was already of proven benefit. However, despite successes, there have been many failures and there is a distinct feeling in the oncology research community that the full potential of molecularly targeted approaches has not yet been realised. Many failures of novel anticancer drugs to meet endpoints in phase III studies have led to an economic model of drug discovery and development that is unsustainable to the pharmaceutical companies [4–6] and to pricing of drugs that will often be out of reach for healthcare systems and cancer patients [7].

The Pharmacological Audit Trail (PhAT) is based on addressing essential questions relating to biomarkers (Fig. 1A) at the appropriate stages of drug development, aiming to maximize our chances of success [8–10]. It is designed to help researchers in evidence-based decision-making at various points in the life cycle of drug discovery and development (Fig. 1B).

2. Population identification for targeted drugs

Many drug discovery campaigns target protein products of specific genetic alterations linked to a tumor type or a subset of patients with poor prognosis within a cancer type. Thus, before the initiation of a first-in-human clinical trial there is often a biologically defined patient population. Clear examples include *BRAF* mutations in melanoma [11] or *HER-2* amplifications in breast cancer [12]. An extension to this is to include the drugs that target an aberrant pathway downstream of a pre-specified genetic alteration, such as MEK inhibitors used in the setting of melanoma driven by *BRAF* mutations [13]. However, this approach does not always lead to finding populations of patients with mutant oncogenes that are likely to respond to treatment; for example, *PIK3CA* mutations do not exclusively predict response to mammalian target of rapamycin (mTOR) inhibitors [14]. Nevertheless, mutation and amplification status of tumors are increasingly being seen as critical to regulatory approval (Table 1).

The availability of affordable hotspot mutation [15,16] and next-generation sequencing platforms [17] have made clinical testing of specific target-based hypotheses possible even in early-stage clinical

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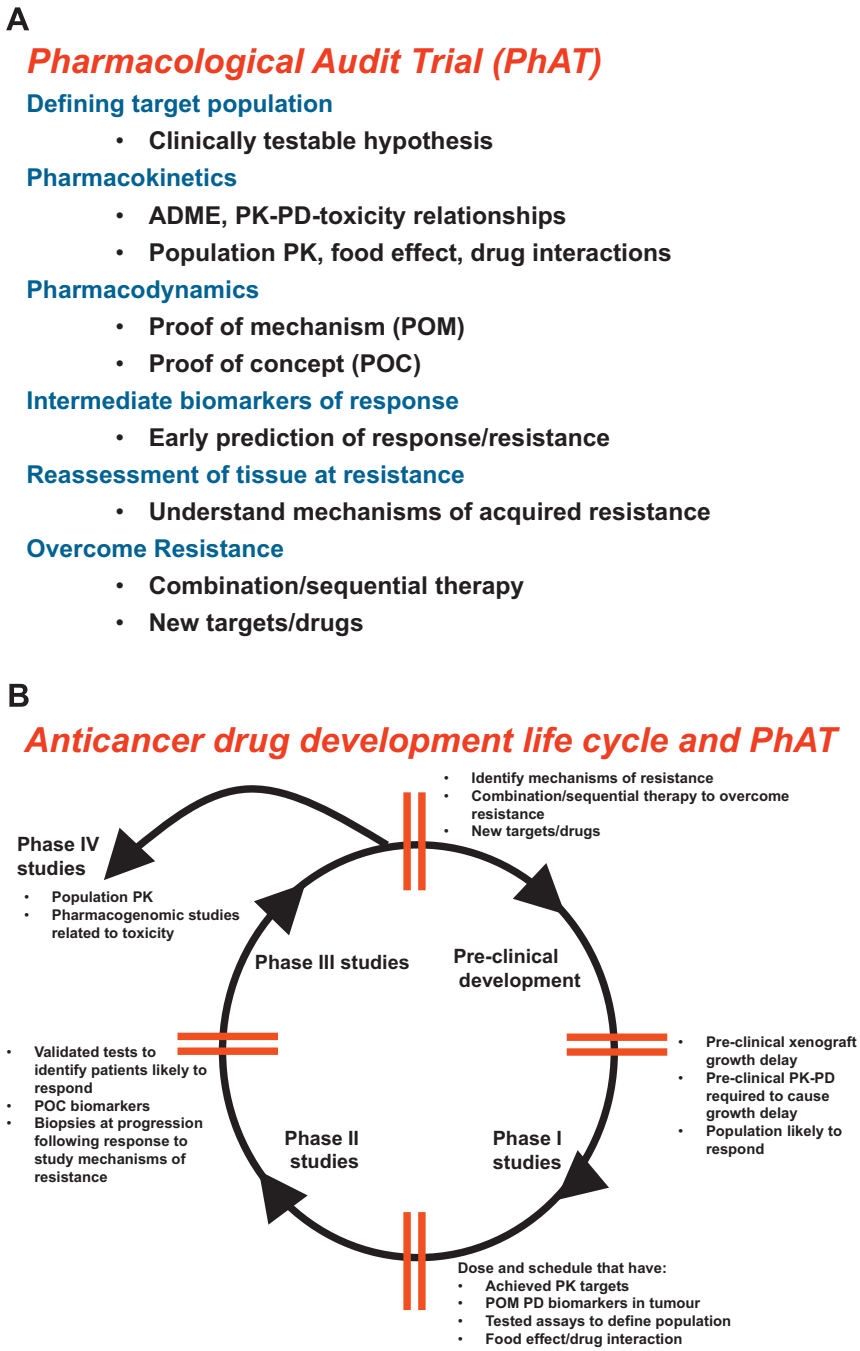

Fig. 1. The pharmacological audit trail (PhAT). (A) The six crucial aspects of the pharmacological audit trail. (B) The relationship of the PhAT to the various phases of the life cycle of an anticancer drug. The red lines indicate 'checkpoints' between different phases of drug development where go-no-go decisions are made.

trials. This has led to the possibility of conducting 'basket' clinical trials where subpopulations of patients with a specific mutation can be tested irrespective of their tumor type [18]. In addition to DNA mutations, protein expression can also be used to define tumor subtypes likely to respond to treatment. As previously noted, *HER-2* amplification has been used to define patients likely to respond to HER-2–targeting therapy and this can be detected by overexpression of the protein in cancer cells.

Immunotherapy has made huge advances in the last decade and more recently programmed death receptor ligand-1 (*PDL-1*) expression [19] is currently being used to stratify patient groups entering clinical trials of anti–PDL-1 antibodies [20]. Of recent interest, the evaluation of unexpected responders in early phase clinical trials (sometimes called n=1 studies) has led to the retrospective study of determinants of sensitivity to targeted anticancer drugs [21].

To help define and validate a patient population biomarker before the start of a first-in-human clinical trial, various approaches have been tried. The use of large (> 500) cancer cell line panels is now feasible. This approach has been retrospectively validated by identifying patient populations with, for example, *BRAF* or *EGFR* mutations that are predictive for the activity of BRAF or EGFR inhibitors, respectively, and remains a promising approach. However, prospective validation of new subgroups of patients suggested by this approach is needed [22]. Other methodologies include use of mRNA gene expression signatures; examples include RAF or RAS-like signatures [23,24], which have been proposed and are currently being used in clinical trials [25]. The use of established cancer cell

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