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Establishing a Drug Discovery Platform to Progress Compounds into the Clinic

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Abstract : The requirements for progressing a compound to clinical trials is well established and relies on the results from in-vitro and in-vivo animal tests to indicate that it is likely to be safe and efficacious when testing in humans. The typical data package required will include demonstrating compound safety, toxicity, bioavailability, pharmacodynamics (potential effects of the compound on body systems) and pharmacokinetics (how the compound is potentially absorbed, distributed, metabolised and eliminated after dosing in humans). If the desired criteria are met and the compound meets the clinical Candidate criteria and is deemed worthy of further development, a submission to regulatory bodies such as the US Food & Drug Administration for an exploratory Investigational New Drug Study can be made. The purpose of this study is to collect data to establish that the compound will not expose humans to unreasonable risks when used in limited, early-stage clinical studies in patients or normal volunteer subjects (Phase I). These studies are also designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on their effectiveness. In order to reach the above goals, we have developed a pre-clinical high throughput Absorption, Distribution, Metabolism and Excretion–Toxicity (ADME–Toxicity) panel of assays to identify compounds that are likely to meet the Lead and Candidate compound acceptance criteria. This panel includes solubility studies in a range of biological fluids, cell viability studies in cancer and primary cell-lines, mitochondrial toxicity, off-target effects (across the kinase, protease, histone deacetylase, phosphodiesterase and GPCR protein families), CYP450 inhibition (5 different CYP450 enzymes), CYP450 induction, cardio-toxicity (hERG) and gene-toxicity. This panel of assays has been applied to multiple compound series developed in a number of projects delivering Lead and clinical Candidates and examples from these will be presented.

Keywords : absorption, distribution, metabolism and excretion–toxicity , drug discovery, food and drug administration , pharmacodynamics
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