

aromatherapy has antioxidant, sedative-hypnotic, anxiolytic, and anti-depressant activities. It also has beneficial effects on the neuroendocrine system.<sup>10</sup>

In conclusion, Avicenna made a great contribution to the field of cardiology and discussed some basic herbal actions in his specific book on cardiovascular medicine. He mentioned the effects of aroma and taste in cardioactive medications. According to his claims, aromatic plants with an astringent taste have strong cardiotonic effects. Current findings show that olfactory and taste receptors are also expressed in several extra-nasal and extra-oral tissues, which are involved in miscellaneous biological processes. These receptors, as common chemoreceptors, may have affect physiological and pathological processes, which may have unwrapped therapeutic potential. To this aim, further evaluations are needed.

**Conflict of interest:** none declared.

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doi:10.1093/eurheartj/ehab076

# How a new drug is born

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Despite the unmet medical needs in the prevention and treatment of cardiovascular disease, the development of new cardiovascular drugs and investments are declining compared with many other therapeutic areas such as oncology.<sup>1</sup> The lagging in drug development is partly due to challenges in pre-clinical discoveries and the high cost in conducting cardiovascular clinical trials.<sup>2</sup>

A critical first step in the drug discovery and development process is the selection, identification, and/or validation of the target itself (Figure 1). This can range from simply new drug 'best in class' profiles for known targets to true de novo target identification. The latter has been helped immeasurably by new high-fidelity technology platforms including next-generation DNA sequencing and tools like CRISPR that allows the precise modulation of gene function by gene deletion or more subtle changes such as point mutations or catalytically dead enzymes. Ideally, a firm understanding of the disease relevance (and even patient subpopulations) and potential therapeutic impact of target inhibition should be at least partly in hand before beginning. These techniques offer opportunities to identify new drug targets for cardiovascular disease and provide a more accurate phenotype of patients with cardiovascular disease, potentially allowing a personalized cardiovascular medicine approach.

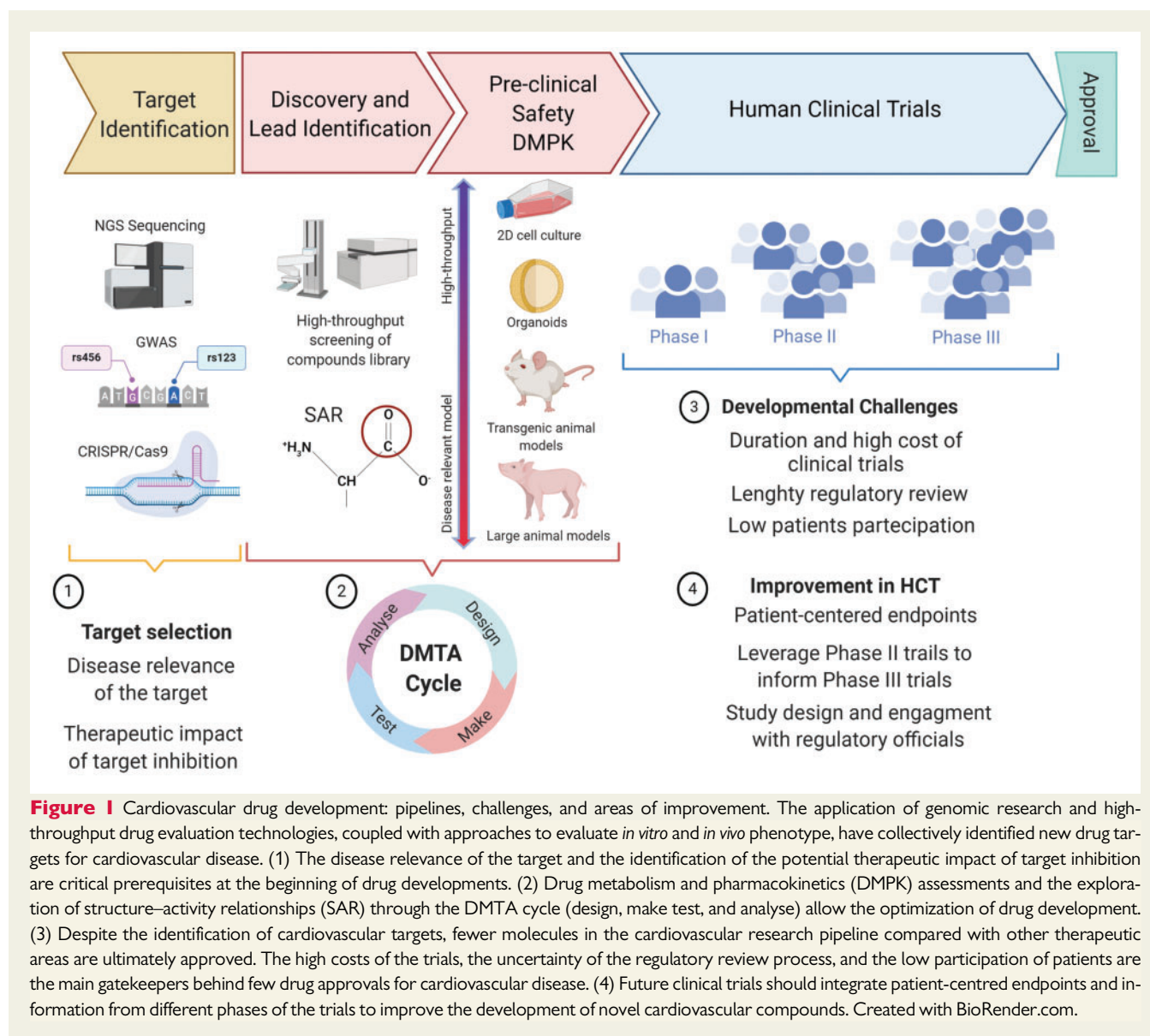
Once a target has been identified, the drug discovery process can begin (Figure 1). This could simply involve generating function modulating monoclonal antibodies or recombinant proteins or for intracellular targets the small molecule screening process. For novel targets, this

typically involves assay development and then high-throughput screening of large compound libraries or DNA-encoded libraries that capture enormous molecular diversity. Hits from these efforts need considerable further optimization to be useful even as probe molecules (the hit to lead process) and yet further optimization still before being of high enough quality for clinical evaluation, referred to as lead optimization. Target specific assays allow the characterization of potency and selectivity as well as activity in appropriate *in vitro* cellular efficacy models. More general assays measure solubility and permeability, compound stability and begin to explore drug metabolism and pharmacokinetics (DMPK) and oral bioavailability across multiple preclinical species (typically mouse, rat, and dog, and with *in vitro* assays to predict human properties. All these assessments and the exploration of structure–activity relationships (SAR) through the DMTA cycle (design, make test, analyse) allow the chemists to juggle often opposing characteristics in search of the optimal balance. Increasing potency often leverages hydrophobic target interactions and comes with decreased solubility, compounds must be soluble enough to dissolve in the GI tract but be permeable enough to escape from the gut and be cell penetrant.

Once compounds of adequate potency and activity are available with enough bioavailability *in vivo* efficacy can be assessed in relevant animal models. Analysis of PK/PD relationship, the relationship between pharmacokinetic drug exposure to pharmacodynamic drug effect and thus to efficacy is then used to understand the

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optimal candidate drug profile needed for humans, and these final considerations feed back into the DMTA cycle now with a view to optimizing and fine-tuning compound features to be fit for purpose in humans. Final considerations include predicted human dose, compound synthetic routes and simplicity and the potential for drug–drug interactions or time-dependent inhibition or induction of metabolizing enzymes (notably CYPs) that could impact co-dosed medications. Finally, as optimization zeros in on the final candidate compound an analysis of drug safety is also begun, culminating in IND enabling GLP studies. There are principles for maximizing the success of this process, from detailed target validation to identifying the safety concerns and margins, patient biomarkers, and consequent selection.

A clear example of this pipeline's potential in cardiovascular drug development is demonstrated in the development of PCSK9 inhibitors.<sup>3</sup> The success of this strategy was also determined by the identification of a highly predictive biomarker (low-density lipoprotein cholesterol) to allow validation and optimization of novel PCSK9 inhibitors.

At this point, the 'best' candidate molecule is chosen for engaging in clinical testing and safety. Usually, this process begins with the so-called 'dose escalation', where a limited group of patients is treated with increasing doses (initially very low) of the drug until the maximal tolerated dose (MTD) is found. A classical dose-escalation design involves groups of three patients on whom adverse events of the drug are studied and reported following a fairly rigid and accepted protocol. Once the MTD is found, a lower, more tolerable (but still active) dose is chosen to conduct phase I trials where the number and typology of patients enrolled will vary upon the type of drug and statistical considerations. As a matter of fact, despite the primary purpose of phase I trials is to assess the safety and tolerability of the investigational drug, there is no doubt that some clinical responses are awaited and expected. These first 'signals' often guide the design and/or patient selection for the following phase II studies, where a higher number of patients with a more uniform disease type/stage is typically enrolled.

Phase II clinical trials are often the moment of truth. A subpopulation of patients with the same disease and/or alterations is treated with

the new drug (experimental arm), and a similar counterpart receives the standard of care known to date (control arm). Many parameters can be considered to evaluate the activity of the new drug. These parameters can vary widely depending on the field of investigation. In cardiovascular clinical trials, the integration of traditional endpoints (such as death and hospitalizations) and patient-centred outcomes may capture patients' most meaningful endpoints.

The next step, if the results from phase II trials are encouraging, is to launch a more prominent study enrolling more patients, usually several hundreds, to test the activity of the new drug, sometimes using different treatment schedules and/or administration routes. These are the studies that FDA (USA), EMA (Europe), and other authorities use the most to base their decision on whether the drug can be approved and commercialized.

However, this is not a strict rule. There are examples of approved drugs in earlier stages of clinical development due to their indisputable efficacy, often in patients with very specific diseases. One example is the rapid approval of LCZ696, a combination of the neprilysin inhibitor sacubitril with the angiotensin-receptor blocker valsartan, currently indicated for treating patients with heart failure with reduced ejection fraction.<sup>4</sup> The in-depth understanding of the two inhibitors' pharmacology allowed to skip the phase II development program for LCZ696, therefore proceeding directly from phase I to be approved for the use in practice.

A parallel and complementary kind of research, called 'translational', can be done when the new drug enters in the clinical setting. These studies are based on analyses of tissue/blood from patients treated with the new compound to identify potential drug resistance

mechanisms and, consequently, investigate new strategies to potentiate or prolong its activity, perhaps by testing its combination with other drugs. Nowadays, strong translational research programs are present in many advanced academic centres and in most of the big pharmaceutical companies.

Leveraging academic research and industry collaborations to identify novel therapeutic targets through pre-clinical development and innovate the study design in clinical trials would provide a positive path forward in cardiovascular drug development.

**Conflict of interest:** A.C. has no conflict of interest. S.F. and M.S. are AstraZeneca employee and hold AstraZeneca equity.

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