

UA FRONTLINE RESEARCH DOMAINS – DRUG DISCOVERY AND DEVELOPMENT

Introduction

Despite a substantial increase in the availability of therapeutic approaches over the past decades, appropriate curative medicines and/or vaccines are still lacking for a considerable number of diseases, as such necessitating continued efforts of both academia and industry in developing effective therapies. This need is further emphasized by the fact that existing drugs often induce unwanted side effects, that a specific drug will not always be effective for the entire patient population and that the incidence of antimicrobial resistance to antibiotics is increasing.

The University of Antwerp has gathered considerable expertise in all phases of drug discovery and development, with research teams involved in highly multidisciplinary projects ranging from more fundamental research to understand the molecular mechanisms involved in different pathologies to identify potential targets, over the pharmacological and pharmacokinetic characterization of candidate drugs, up to the performance of clinical trials. In these projects, the research teams often rely on close collaborations with various university hospitals and international research and/or industrial partners.

Research Interests and Expertise

The search for new therapeutics involves two major phases: In the preclinical phase, new therapeutic approaches are developed and validated in *in vitro* and *in vivo* models of human diseases. In the subsequent clinical phase, promising preclinical drug candidates are further optimized and validated in clinical trials.

Preclinical drug discovery and development

Preclinical drug discovery and development is characterized by three consecutive steps: target discovery, Lead discovery and preclinical drug development. To guarantee a truly integrated approach from 'hit' generation to 'lead' optimization, the expertise at the University of Antwerp has been bundled into a preclinical drug discovery platform: the Antwerp Drug Discovery Network (ADDN, www.addn.be).

Over the past years, considerable expertise has been developed in enzymological targets, including both reversible and irreversible modifiers of enzymatic activity. Furthermore, the platform has already proven useful in the design and development of several protease inhibitors, which are important targets in different disease areas, such as diabetes, cardiology, oncology, tropical diseases (e.g., malaria, Leishmaniasis) and HIV, but which may be equally important as probe molecules in chemical biology and biomarker research.

Target Discovery

Target discovery focuses on the identification of potential targets, which requires detailed knowledge of the molecular mechanisms underlying specific pathologies and/or influencing the action of potential therapeutics. It involves target isolation and purification, *in vitro* and *in vivo* assay development and testing of compounds. To this end, several recent advanced techniques are applied at the University of Antwerp, including genomics, proteomics, knock-out and transgenic animals, gene silencing, crystallography and bioinformatics. Concomitant access to human material allows extrapolation and validation of the data obtained in the animal experiments.

Drug Discovery

Drug discovery involves the design or identification of compounds that are capable of influencing the actions of a target. In this respect, the University of Antwerp not only focuses on the design and synthesis of small molecules, but also performs pharmacological, chemotherapeutic and biochemical evaluation and standardisation of traditional plant medicines to find new 'lead' compounds with new chemical structures and/or new mechanisms, and to improve the efficacy and safety of these traditional plant medicines. In both cases, structures are revealed and structure-activity/structure-property relationships are established, using a combination of advanced techniques such as bioassay-guided fractionation, 3D molecular modelling and crystallography. Furthermore, dedicated tools are used to screen both synthetic and natural compound libraries for a range of microbial pathogens and parasites.

Preclinical Drug Development

In this phase, the toxicity and pharmacokinetic behaviour of the preclinical candidates are investigated in depth, using integrated *in vitro* and *in vivo* screening and selectivity assessment. In this context, biomarker research has become important, since biomarkers can be used as early indicators of efficacy and/or toxicity, which could accelerate clinical development or identify specific patient populations for which the proposed drug candidate shows the most optimal efficacy. Bio-imaging, which is another frontline research domain of the University of Antwerp, can be particularly valuable for this type of research. State-of-art *in vivo* and *in vitro* imaging techniques, as well as in situ and quantitative analysis of the target are employed to perform drug binding, efficacy and mechanism of action.

Additionally, the formulation of the drug candidate is investigated at this stage. Both optimization of the more standard oral dosage forms and dedicated research on new and innovative non-oral dosage forms is performed using a wide range of techniques.

Clinical drug discovery and development

As far as clinical drug discovery and development is concerned, the University of Antwerp is involved in performing clinical trials (stage 1-4), including clinical vaccine trials. Our teams not only deal with the design and evaluation of clinical trials, but are also involved in screening of samples for specific metabolites and/or unwanted by-products of the drug under investigation. Additionally, combined expertise in medicine, epidemiology, biostatistics, sociology and economics allows in-depth investigations of the determinants of health and disease and economic evaluations of health programmes.

Key Infrastructure and Techniques

The University of Antwerp boasts several fully equipped research laboratories for drug development research, including the following infrastructure and techniques:

- **(Bio)chemistry:** HPLC, GC (FID and MS), UV spectrophotometry, IR and melting point determination, TLC densitometry, IASYS (Biospecific Interaction Analysis), protein purification and analysis techniques, immunohistochemistry
 - o Laboratory accredited by Beltest according to the European standards NBN-EN 45001
- **Models:** cell culture facilities, rodent and rabbit models, animal housing facilities
- **Libraries:** both synthetic and natural compound libraries for screening purposes
- **Imaging facilities:** multimodal imaging platform for *in vitro* and *in vivo* imaging

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