

# ACTELION'S DRUG DISCOVERY

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## INTRODUCTION

Scientists at Actelion use an inquisitive drug hunting approach to discover and develop novel medicines to improve patients' lives.

From the outset, Actelion's founders wanted to create a company with a bold, pioneering spirit, one that understands the true nature of innovation. The founders understood that innovation could not be taught, but the right environment to allow innovation can be fostered. Actelion's productivity is evidence that from creative freedom, innovative ideas flourish.

By removing the barriers to innovation, such as bureaucracy and hierarchy, the founders set out to empower "their" people. In turn, Actelion's people take ownership of their projects and grasp opportunities.

There are many barriers to overcome when guiding a compound that addresses an unmet medical need from the bench to the market. To maximize success, the Research and Development teams must know which projects are most promising, which compounds should be promoted, and where to focus their efforts.

The only way to make the correct choices is to base these decisions on all facts available. This means open, effective communication within teams and across functions in an integrated approach.

This sharing of knowledge stimulates and builds scientific intuition. By using this approach, innovation can be translated into evidence-based medicine.

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## DRUG DISCOVERY PROCESS

To maximize output from its focus on target families, Actelion implements appropriate state-of-the-art technologies. The Drug Discovery group, comprising of more than 400 professionals at the end of 2011, combines technology with human expertise and teamwork in a single research center based in Allschwil to make the best use of Actelion's toolbox.

Actelion has over 120 medicinal and process chemists creating low molecular weight compounds which go through a cyclic drug discovery process for optimization.

These innovative compounds are then characterized by molecular biologists and biochemists in relation to the chosen molecular drug targets. The characterization includes the development of a variety of assays and execution of activity screens. The vast quantities of assay result data generated, are managed and analyzed by data-management programs developed in-house.

A lead compound is then passed to our pharmacologists, neurobiologists, immunologists and electrophysiologists to further characterize the compounds. These lead compounds are then passed back through this cycle until an optimized compound is available for preclinical development by our pharmacokineticists, formulation specialists, and toxicologists.

At the end of 2011, the platform approach, combined with our technological capabilities and in-house expertise, resulted in six novel compound progressing into clinical development and an additional compound undergoing preclinical investigation, with the potential selection of several other preclinical candidates during 2012. The final outcome is a robust clinical development pipeline of compounds discovered and optimized in Actelion's laboratories.

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## DRUG DISCOVERY PLATFORMS

Actelion's efforts in drug discovery have focused on developing platforms of expertise based on its core capabilities. This focus allows high productivity in the generation of innovative compounds potentially addressing a wide range of highly unmet medical needs.

The first focus is the design, synthesis and optimization of low molecular weight drug-like molecules. The productivity of Actelion's drug discovery endeavors is demonstrated by the more than 2,300 pending patent applications and/or granted patents currently in Actelion's portfolio.

Actelion also focuses on the choice of its molecular target families. Initially, the company looked solely at G-protein coupled receptors (GPCRs) and a specific enzyme family known as aspartic proteinases. As the company's capabilities have expanded, so too have the target platforms to include anti-infectives, ion channels and a broad range of soluble enzymes.

### NEW CHEMICAL ENTITIES (NCE)

Actelion's research focuses on the design and synthesis of novel low molecular weight drug-like molecules. Experience has shown that small molecules generally lend themselves to easier formulation, have a broader array of dosage forms, have greater potential for bioavailability, in particular after oral administration, and are more efficiently manufactured. While Actelion's medicinal chemistry and high-throughput chemistry groups synthesize smaller quantities of structurally diverse molecules, process research chemists prepare the quantities of selected compounds needed for further studies.

### G-PROTEIN COUPLED RECEPTORS

G-Protein coupled receptors (GPCRs), also known as seven transmembrane domain receptors (7TMs), are integral membrane proteins. They can be activated by external signals, such as hormones, neurotransmitters, or odors. This activation induces a conformational change of the receptor which in turn causes activation of G-proteins and the subsequent transmission of biochemical signals within the cell.

There are more than a hundred known GPCRs in humans, and many of them are involved in a broad range of diseases. Some of these receptors are the subject of our development programs, such as the endothelin receptors ETA and ETB, orexin receptors OX1 and OX2, or the sphingosine-1-phosphate receptor S1P<sub>1</sub>.

### ENZYMES

Enzymes are proteins that catalyze chemical reactions and are involved in almost all metabolic pathways in a living cell. They speed up the conversion of a substrate into a new product. Enzymes are specific for a given molecular substrate and are classified by the mechanism by which they act on the substrate. Actelion currently works on several different enzyme targets in its research programs, most of them being soluble intracellular proteins.

One such class is the aspartic proteinases. This class of enzyme promotes chemical reactions inside and outside cells. There are more than 50 known aspartic proteinases, of which at least nine are currently known to exist in humans. Although knowledge of their precise physiological roles is still emerging, they have been implicated in cancer, as well as in inflammatory, degenerative, and cardiovascular diseases. In addition, aspartic proteinases play a vital role in organisms that cause infections, including parasites, fungi, and retroviruses such as HIV.

### ANTI-INFECTIVES

Due to the development of resistance to currently available antibiotics and the emergence of new pathogens, the medical need for new antibiotic compounds is high. In order to address this high unmet medical need, Actelion initiated, in 2004, a research program in the field of antibiotics.

Actelion's focus is on the discovery of novel classes of antibiotics that may offer improved properties, such as increased potency, coverage of multi-resistant pathogens, and a decreased inherent liability for resistance development. A portfolio of projects has been established focusing on both antibiotics for intravenous treatment of severe hospital infections, and oral antibiotics for community acquired infections.

## ION CHANNELS

Ion channels are transmembrane pores that allow the passage of ions (charged molecules) into or out of a cell. There are hundreds of different ion channels, distinguished by ion selectivity, opening mechanism, and protein sequence. Ion channels can be opened by chemical ligands, voltage fluctuations, acidity changes, temperature variations, or mechanical stimuli (e.g. touch or sound).

Initially, Actelion established an in-house in-vitro electrophysiology group to provide internal support for early pre-clinical evaluation of drug safety in the area of cardiac electrophysiology. Since the scientific knowledge and technical capabilities required in this area are very similar to those in the area of cardiovascular ion channel therapies, research programs were soon initiated looking for modulators of selected ion channels to treat cardiovascular diseases.

Expansion of the electrophysiology group and integration of new expertise and technologies led to the initiation of research projects targeting ion channels to treat neurological and immunological diseases.

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## PROJECT SELECTION

Actelion selects its molecular drug targets on the basis of the established platforms of expertise, capabilities, technologies and the professionals at its research center. Actelion's inquisitive researchers all have the opportunity to suggest a new target and follow the evaluation process. Additional selection criteria which the proposed projects are required to demonstrate include:

- medical need
- therapeutic novelty
- predictive animal models
- clinical feasibility

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## THERAPEUTIC AREAS

We use our expertise to address a variety of therapeutic areas including cardiovascular disorders, central nervous system disorders, infectious diseases, cancer, and immunological disorders. In addition, during 2010, two new areas of focus - fibrosis and neurodegeneration - were integrated.

We aim to tackle diseases through multiple mechanisms, delivering novel therapies to patients, with maximum impact on the selected diseases.

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**Actelion Pharmaceuticals Ltd** is a global biopharmaceutical company headquartered in Allschwil/Basel, Switzerland. Actelion concentrates on discovering, developing and marketing innovative drugs for high unmet medical needs. The company is quoted on the SIX Swiss Exchange (tickersymbol: ATLN).

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