”Drug research needs a paradigm shift”

[By Kalle Lötberg]

According to earlier leading researchers, a paradigm shift is necessary that sees pharmaceutical research returning to animal testing in its primary stages.

Top executives of global ”Big Pharma” companies have to realise that pharmaceutical research needs a paradigm shift, moving away from the current practice of early stages protein target testing. A new paradigm is needed in which research returns to experiments based on animal testing models (phenotypic research).

Current models have resulted in far too few products – and new products are the basis of the pharmaceutical industry.

This was the message brought forward at a seminar arranged by the Gothenburg branch of the Swedish Chemical Society on 27 November last year. The main lecture was given by Per Lindberg, PhD, who has previously held leading research positions within AstraZeneca. His opinions were strongly supported by Professor and Nobel Laureate Arvid Carlsson, who was one of many delegates at the meeting.

Photo Kalle Lötberg

Per Lindberg.

”Far too few new drugs have been developed in the last 20 years compared with the period 1970 to 1990,” said Per Lindberg.

This is the result of an almost complete transformation of the research in which biochemical tests are used for the primary selection of substances – so called primary target-based *in vitro* screening (genotypic research) – and an exaggerated emphasis on the necessity to know exactly how the drug works, to see what its inner mechanism looks like.

”People are very biased today,” argued Per Lindberg. ”But medicinal chemists neither can nor have to know exactly how a substance acts. This has always been the case, since organisms are very much more complex than the sum of their receptors, enzymes and ion channels.

For instance, when Losec was developed, researchers used to work as follows, according to Per Lindberg:

- Disease models for animals were often developed in collaboration with hospital-based researchers.
- Newly synthesised substances were tested *in vivo* directly on animals.
- Effects in animals were the all-important driving force.

”This resulted in the selection of just a few drug candidates – but then the desired effect had already been largely proven in animal studies. Hence, there were more new registrations relative to the number of substances – i.e. the output was high.”

”The mechanism was almost always unknown, and it was virtually impossible to predict which substances would prove useful. It was trial and error – and that was precisely how we found Losec, and its pioneering activity principle”, said Per Lindberg.

However, in the 1990s major advances were made in molecular biology and biochemistry. The golden era of the genome had begun, receptors were linked to specific genes, and an *in vitro* technique for measuring a protein’s affinity to synthetic substances was developed.

All this sparked off the current paradigm within pharmaceutical research.

”The animal models were abandoned at the primary stage of testing, and the entire process moved into test tubes. The primary screening was automated and robotised – thousands of tests could be carried out every day, and they could run round the clock,” said Per Lindberg.

The research chain was divided into small steps, which more or less automatically identified substances of varying affinity to different target proteins. It became known as High Throughput Chemistry and High Throughput Screening.

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Automation within the research process was – and is – very attractive to the pharmaceutical industry.

”The process became rational, efficient, simple, elegant and super-fast – and therefore also attractive. The chemists were divided into those who worked at the early and the late testing stages respectively, and their previously acquired competence was often wasted. It was taboo not to know the target and the mechanism already at the start of a new project,” said Per Lindberg.

”The role of the medicinal chemist developed into combinatorial chemistry during the 1990s, and then into parallel chemistry – and very large substance libraries were created.”

A multitude of drug candidates were identified and large project portfolios were created. In the meantime, companies were able to profit from drugs developed during the 1980s and 1990s.

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”Even at the start of the new century, it all seemed very promising. However, setbacks followed – the attrition rate was very high, masses of substances were dropped, in some cases not until Phase 2b, and the number of new registrations declined as well as the number of clinical trials,” said Per Lindberg.

”It might have been difficult to see the problem within each individual company. But already at an early stage, clear warnings were given by Arvid Carlsson, David Horrobin and others.”

More recently (2011), Swinney and Anthony present an analysis of what kind of research had been used in FDA registrations during the ten-year period 1999-2008. In spite of the totally dominating target-based research, more of the registered drugs were based on phenotypic research rather than genotypic.

The researchers themselves were – and are – aware of the unsatisfactory state of things. Many of them have tried to communicate this to their business leaders, but they do not seem to listen.”

The problem with today’s paradigm is that it focuses on individual targets, which means it works according to a method that could be seen as a reductionist approach.

”This method has reached its limits”, wrote Gerald Maggiora in 2011. Biological systems are highly complex and have emergent properties – properties which cannot be explained or predicted through studies of the individual components.

”In order for target-based screening to work, the affinity to the target has to correspond to a clinical effect in patients, the target has to be relevant for the disease and the substance has to be able to produce a desired biological response,” said Per Lindberg.

”All these factors have to work; none of them may go wrong. And yet, almost always something does go wrong, and the result is that the selection of drug candidates is failing, due to an insufficient effect – a new phenomenon within the area.”

There are several reasons for this, according to Per Lindberg. One of the inherent shortcomings is that the affinity to the target often correlates poorly to the effect on the disease. Organisms are robust and adaptable, and they have developed evolutionary systems and functions that help them withstand strong influences.

”Now, a new paradigm is needed, that will utilise the best of previous practices. Most techniques that have evolved during the past 20 years are useful – for instance HTS (High Throughput Screening) and proteomics – but they need to be used in a different manner, and partly in a different order.”

Apart from the use of HTS for the development of “follow-up drugs”, it could be developed for testing the target ideas; lead structures could be screened out and then tested directly on animal models for possible effects. Interesting substances could then be included in the test substance group, and their specific pharmacological profiles added to the emerging database, argues Per Lindberg.

”Proteomics could become particularly important for drug research,” he said. ”Proteins are characteristic to individuals, i.e. phenotypes. Proteomics can for instance identify and follow protein levels in the blood, and these could become valuable biomarkers. *In vivo* screening also allows for direct multivariate studies.”

“Today researchers are identifying biomarkers for human diseases. However, these are then used to find corresponding protein targets instead of being utilised as parameters in direct *in vivo* testing of new compounds.”

According to Per Lindberg, the new paradigm should include the following elements:

- Focus on building disease models – for many years an area neglected in favour of for instance multi-chemistry.
- Use modern integrated multivariate screening directly on animals, including both behaviour and various analyte parameters.
- Synthesise carefully selected substances and test them all on animals.

Fewer animals. “This involves a set of techniques which can be summarised in the term *in vivo* systems response profile-based drug discovery,” said Per Lindberg. ”If a per oral test produces an effect in animals you have already come a long way. This is a methodology that makes the work more interesting, also for the chemists.”

”It is worth noting that this method results in more efficient testing, and probably also in considerably fewer experiments on animals than today’s research requires in the end.”

In conclusion, Per Lindberg quoted an article by Arvid Carlsson published in Göteborgs-Posten (The Gothenburg Post, G-P) in September 2012, in which the author called for ”an inquiry to look into what has gone wrong before more money is being spent. The entire industry and millions of patients are suffering due to a fatal mistake!”. KB

In the late 1990s the entire drug research process moved into test tubes, and the animal models were abandoned.