Smart Functional GLA—nanoformulation for Fabry disease

THE DRUG DEVELOPMENT PATHWAY

SMART4FABRY project deals with the development of a novel drug formulation for Fabry disease. A strict development pathway has to be followed for any medical innovation, moreover for nanomedicines.

The full development may last approximately up to 10 years, to cover all the subsequent phases from idea to clinical practice. Moreover, around nine out of every ten drug candidates fail to win approval. In any case, these failures may give also valuable knowledge for other developments, other indications for the drug, etc. During early clinical trials of sildenafil, a drug candidate originally intended for angina, male volunteers taking the pills consistently reported unprovoked, long-lasting erections. At the end this candidate is now better known by its trade name Viagra. The main steps of this challenging pathway are the following:

DDR Drug Development & Regulation

SOME FACTS ON DRUG DEVELOPMENT

- Approximately up to 10 years may be needed for a new drug to get to the market
- On average, only 14% of drugs in clinical phases are finally approved
- Nanotechnology based drugs require special attention in their development and regulatory science

PARTNERS

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THE GENERATION OF AN IDEA. THE IMPORTANCE OF BASIC RESEARCH

Long before a new drug can even be imagined, scientists are working to gain a basic understanding of chemistry, biology, disease mechanisms and how to connect all these pieces to solve the puzzle. In the case of S4F, after a deep understanding of the disease and the enzyme replacement therapy, dozens of nanoformulation prototypes have been developed, tested, and prioritized depending on results. The idea has to be validated, as a first proof of concept, using *in vitro* models (i.e. Fabry cell cultures). Computer models also help at this stage, these approaches also known as "*in silico*" trials are gaining importance to reduce experiments and costs.

NONCLINICAL RESEARCH

Once one entity or a reduced number of them have proven their potential, the development pathway enters the next step, the nonclinical research. Some research may be performed *in vitro*, using, for example, cell cultures. S4F has applied this approach. Nanovesicles which offer promising results in *in vitro* will be tested using animal models (*in vivo* tests). Researchers can use healthy, wild type animals to assess drug candidate safety, potential toxicity, maximum tolerated dose, absorption, distribution, metabolism and excretion. More recently, genetically modified animal can be used to test efficacy, reproducing disease models in those mutant animals, as it is the case In S4F. We have tried to rationalize and reduce the use of animals as much as possible light of 3R principles (the replacement, refinement and reduction of animal use in research), while obtaining valuable biodistribution, and efficacy in mutant Fabry mice.

FORMULATION & MANUFACTURING

In parallel to nonclinical research, it is necessary to get a formulation suitable to be administered through the selected route. This may include the use of excipients or even more sophisticated approaches, like the use nanovesicles that has been implemented in S4F to improve efficacy while reducing amount of active principle.

DRUG DEVELOPMENT USING NANOTECH

729 projects in nanomedicine were EU funded under FP7 and H2020 for a total amount of 1.2 B€

3700 NANOMEDICINE RELATED PATENTS FILLED IN 2016

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 720942.

CLINICAL RESEARCH

Once solid nonclinical evidences exist, the drug candidate will be tested in humans. This step includes subsequent phases. Phase 1 clinical trials aim to assess the safety profile of the candidate in a range of doses. Phase 1 clinical trials may involve the inclusion of healthy volunteers or patients depending on the condition, etc. Phase 2 to first demonstrate the efficacy of the drug in a limited number of patients (proof of concept) as well as assess dose/s for subsequent clinical testing (dose finding) and the safety, and, finally, Phase 3 clinical trials involve a bigger number of patients and constitute the confirmatory stage in the development that the drug can be of value for the studied condition. Once the drug is in the market, Phase 4 or post-marketing clinical trials and pharmacovigilance activities are also conducted to monitor potential adverse events which may appear when the drug is applied to the overall patient's population.

REGULATORY AGENCIES REVIEW

The fourth and final step prior to market is the evaluation by the regulatory agencies, during which the agency makes an in-depth examination of the data provided and takes a final decision about the drug's approval based on the benefits and the risks associated with the use of the drug; if approved, it can enter the marketplace. Once in the market, the agency (EMA, FDA, among others) is entitled to review drug-related issues that may have arisen and impose measurements to correct them.

CONCLUSIONS

Drug development is a complicated, time-consuming process were chances to fail are very high. Solid scientific approaches and good regulatory guidance can prevent failures, but many uncertainties could appear along the pathway. In any case, good science will always offer valuable results, even in case the new therapy does not reach patients.

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