Inborn errors of metabolism as an example of RDs: Biopharmaceutical industry perspective

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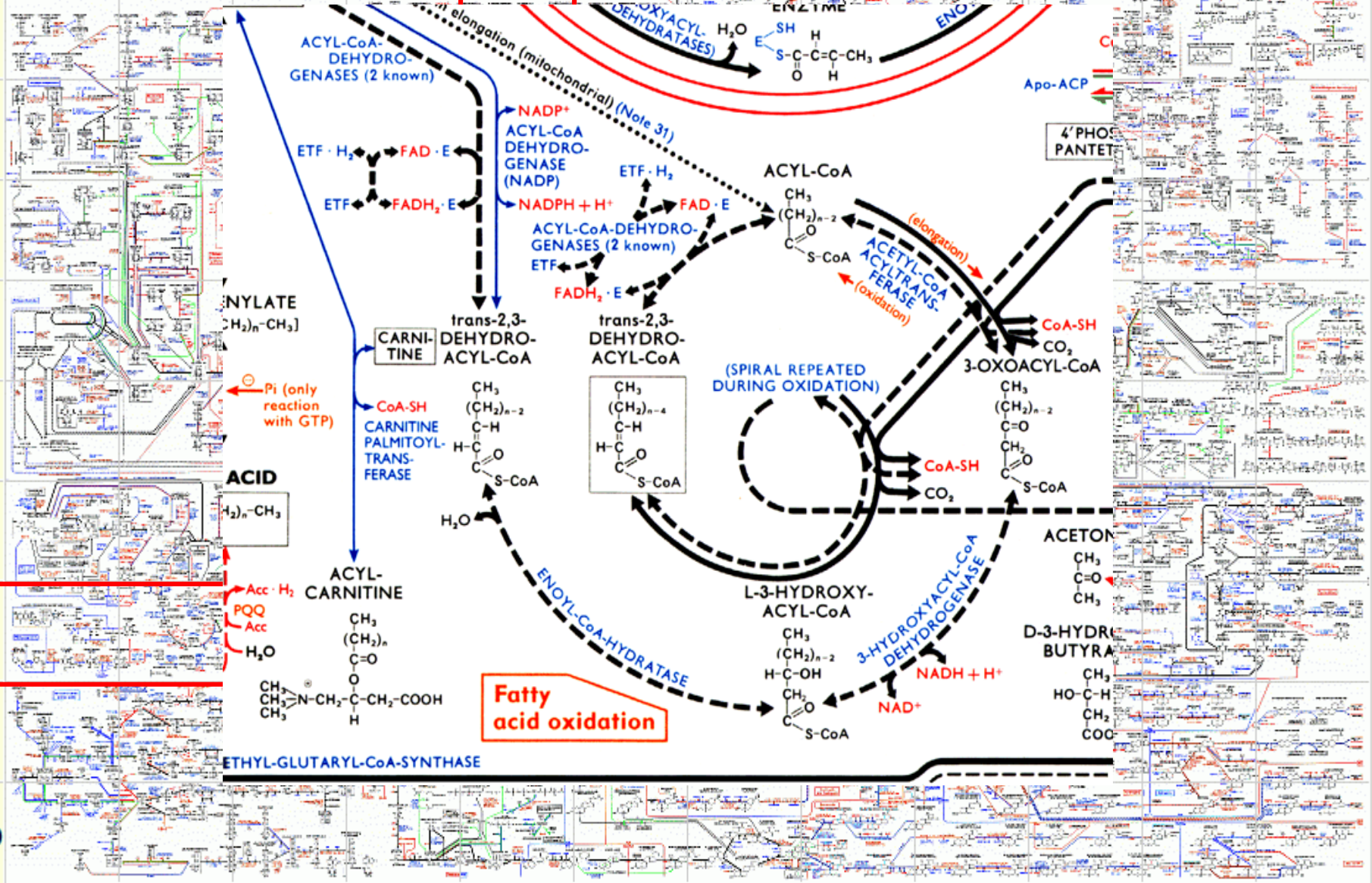
Conflicts of Interest / Disclaimer

I am currently employed by Genzyme, now a Sanofi Company, and have been since 1993

The views and opinions expressed in this presentation are solely my own and do not necessarily represent the official policy or position of Genzyme, Sanofi or any of its affiliated companies

Metabolic Pathways



Metabolism: the "essence" of LIFE

…but also a mind-boggling puzzle

With such level of complexity, it's not surprising that *somewhere, something* **goes wrong**, leading to one of several thousand rare diseases

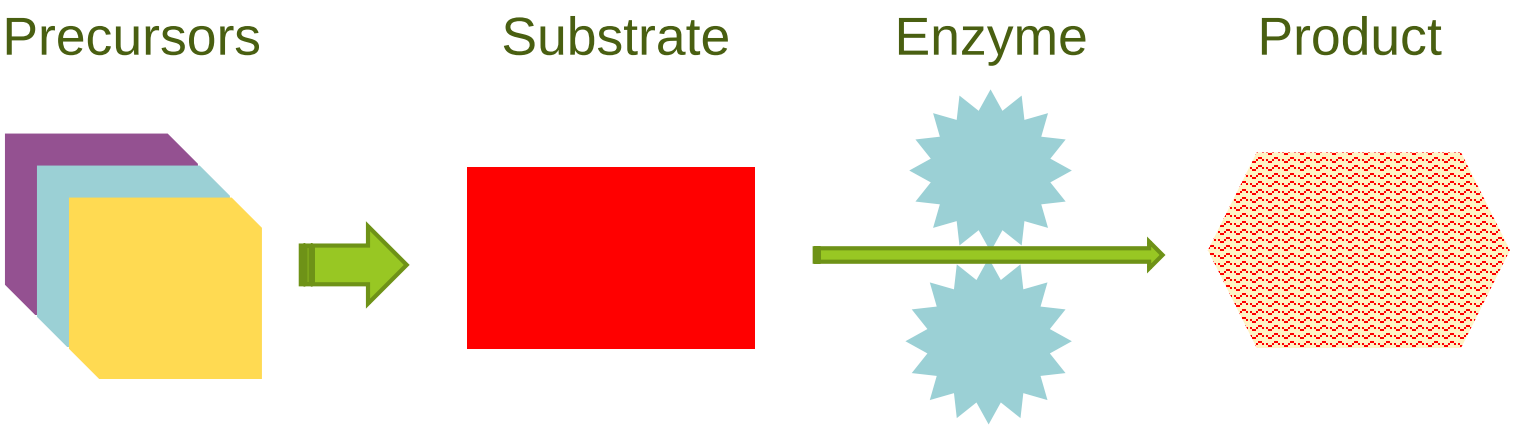
In fact, inborn errors of metabolism are the area which has triggered more therapeutic R&D initiatives, and successfully lead to new "orphan drugs"

They are also the area where the broadest range of therapeutic approaches has been proposed and successfully developed

With permission from biochemists and molecular biologists, let's try to represent things in a somewhat simpler way

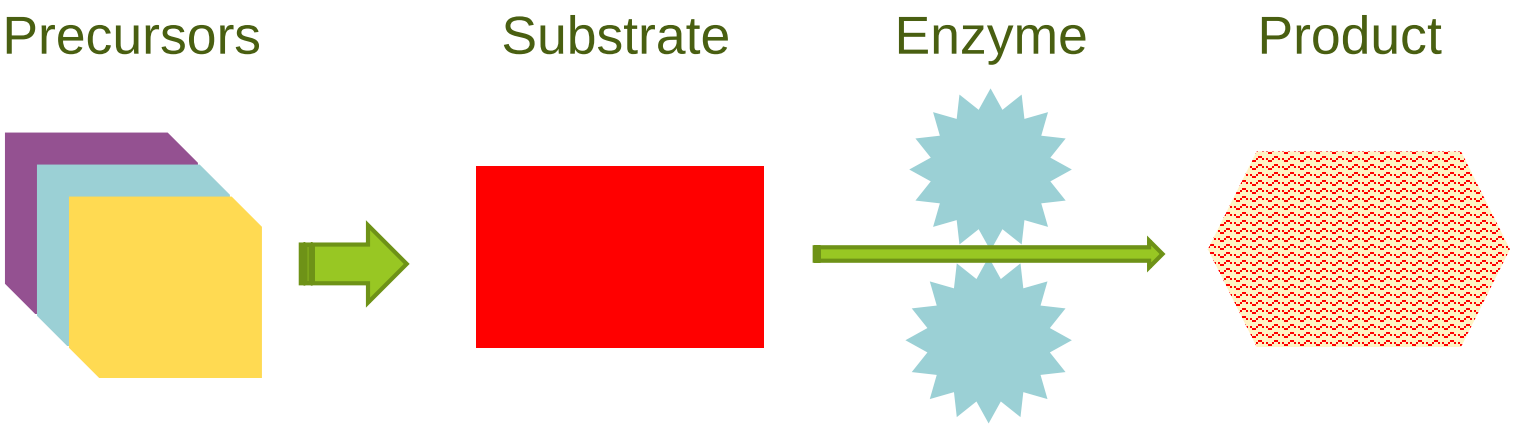
Metabolism: the "essence" of LIFE

Basically, every metabolic reaction consists of a sort of "*production chain*":



What can go wrong and how can we try to fix it?

If we want to **reduce the amount of end-product**, we can, for example:



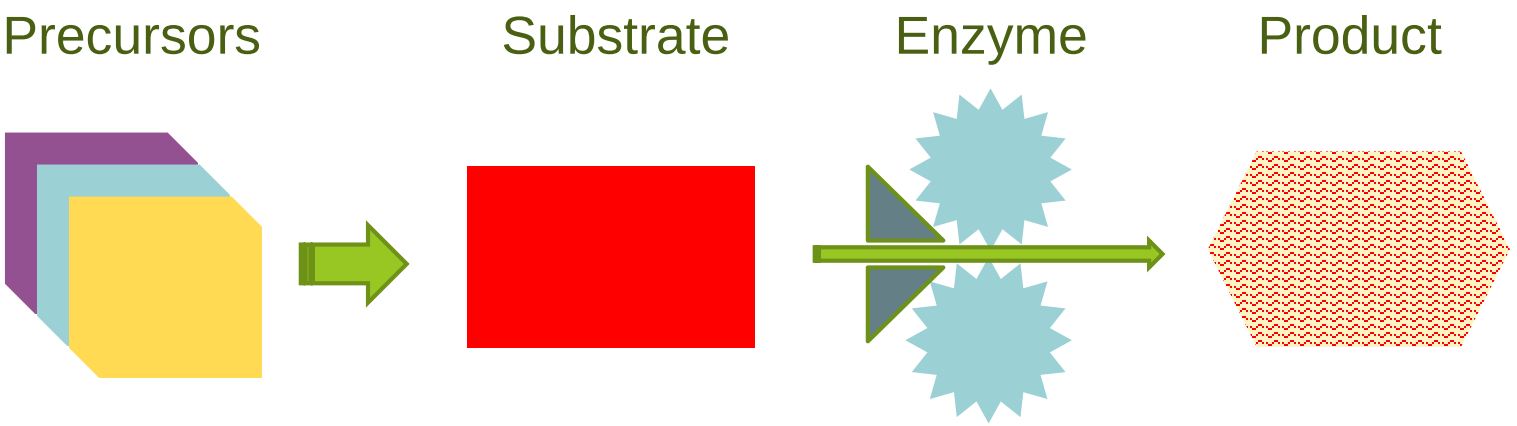
Reduce/eliminate the intake of one or several precursors in diet

This strategy has been long and successfully applied in RDs like phenylketonuria, galactosemia, maple syrup urine disease, organic acidemias and urea cycle disorders

Similarly, substrate levels can also down-regulated by adding interfering dietary precursors, pharmacological “chelators” that modify intestinal absorption or “substrate synthesis inhibitors”

What can go wrong and how can we try to fix it?

Things start to get more complex if we want to “regulate” the enzyme activity



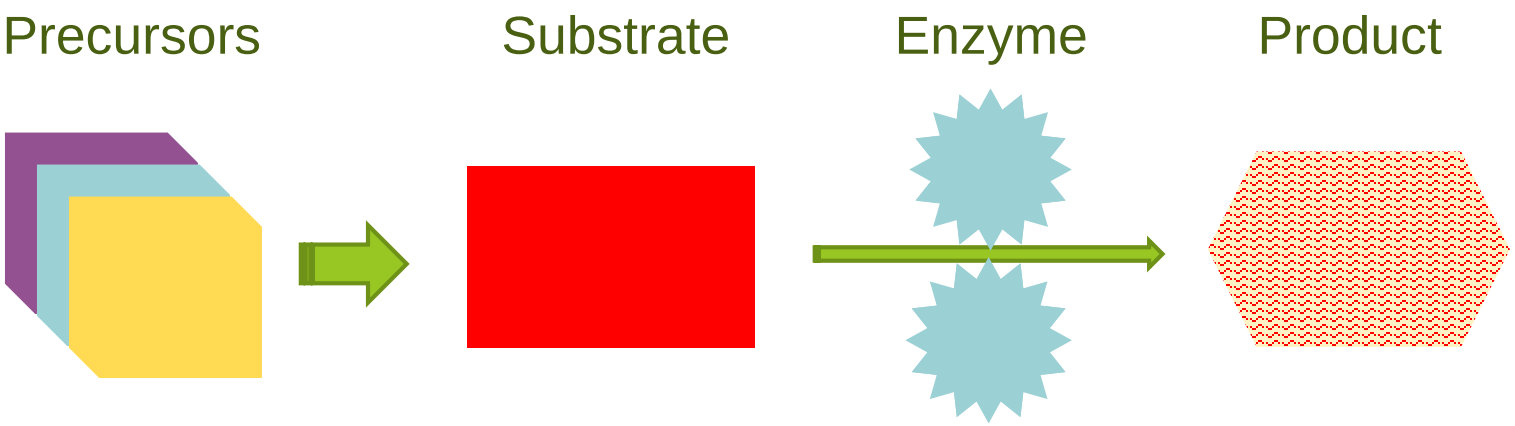
It’s relatively easy to “slow down” an enzyme with drugs (“blockers”)

However, this strategy often leads to substrate accumulation, which in turn usually “re-accelerates” the enzyme, and product soon returns to undesired levels

Instead, apart from increasing substrate levels, there are almost no conventional pharmacological ways to increase the activity of a “slow” enzyme

What can go wrong and how can we try to fix it?

In many RD's, the problem is a defective enzyme, leading to substrate accumulation and scarce product

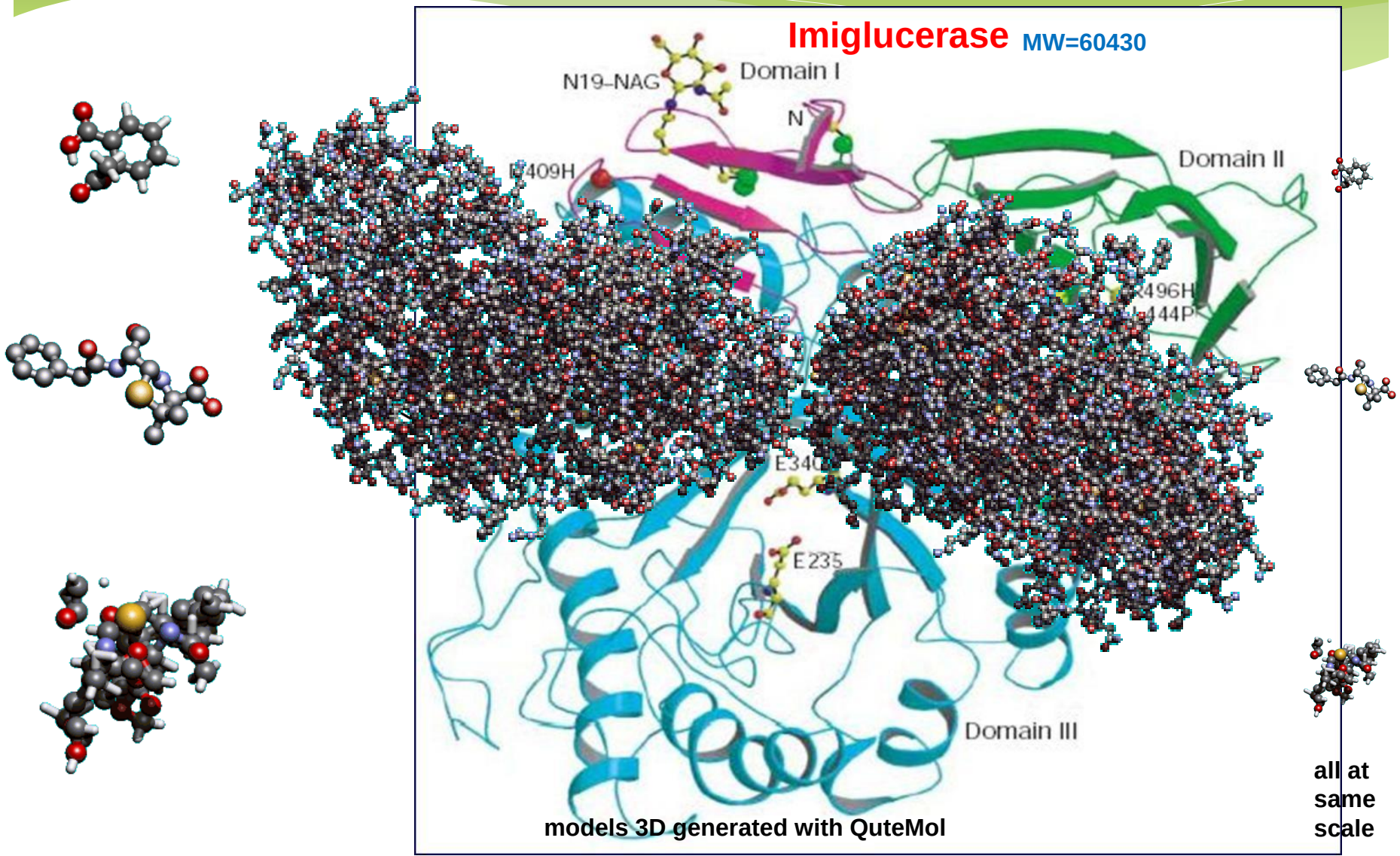


The most direct strategy is to "replace" it with a correct version

This strategy has been successfully applied, for example in many lysosomal storage diseases (Gaucher, Fabry, Pompe, MPS I, II, IV A and VI)

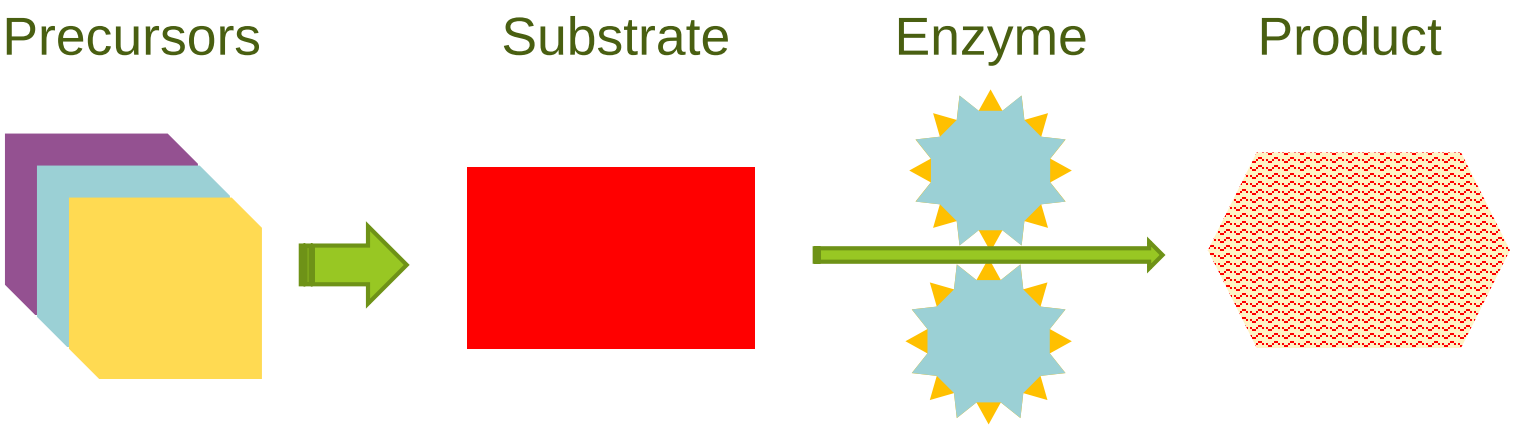
However, this is much easier said than achieved…

Enzymes are HUGE proteins, and much more complex than standard drugs ("small molecules")



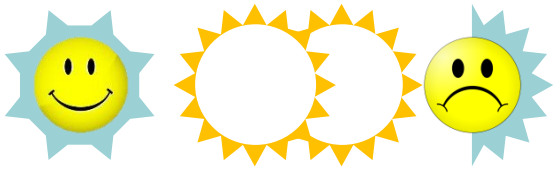
What can go wrong and how can we try to fix it?

Therefore, other ways to correct defective enzymes have been explored



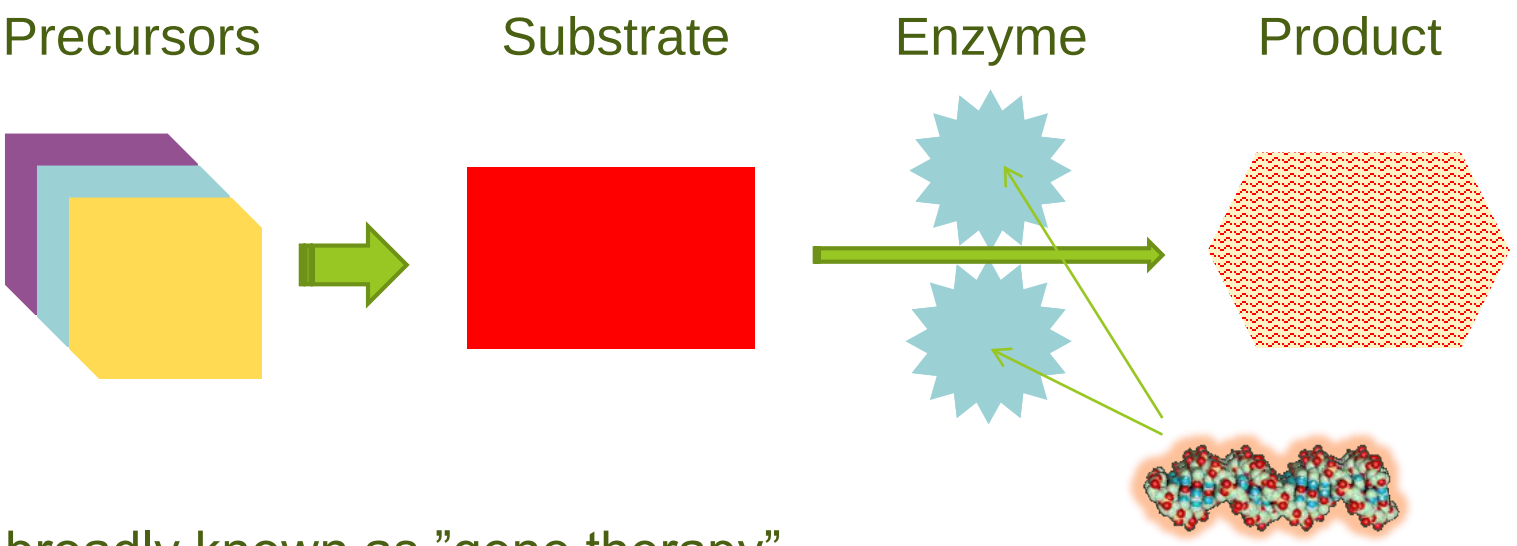
One is to “stabilize/re-activate” it with pharmacological “chaperones”

However, the effectiveness of this strategy largely depends on the underlying defect in **each individual patient**:



What can go wrong and how can we try to fix it?

One step further is to correct the “instructions” leading to a defective enzyme



This is broadly known as ”gene therapy”

Other advanced therapies target mRNA or incomplete transcription, replace whole cells with “cured” or normal ones, or even employ a combination of these techniques

Diverse therapies, diverse access issues

RD patients' accessibility to these treatments is equally diverse, depending not only on strictly medical, but also on societal and economic factors

For many of the new, most innovative drugs, its high price is a growing concern for healthcare administrators, in emerging as well as in some of the most developed economies

Given the extreme rarity of many of the targeted RDs, the economical issues are often more linked to local, immediate **affordability** than to the overall **sustainability** of healthcare systems, and therefore amenable to joint cooperative approaches and innovative pricing and reimbursement schemes

I hope I didn’t bore you too much…!

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Thank you for your attention!