

Drug repurposing

Rare diseases

Question

In your opinion, are we in a favourable context for pharmaceutical research?

The strange decline of pharmaceutical R&D efficiency

Features of a favourable context in R&D

Combinatorial Chemistry

DNA sequencing

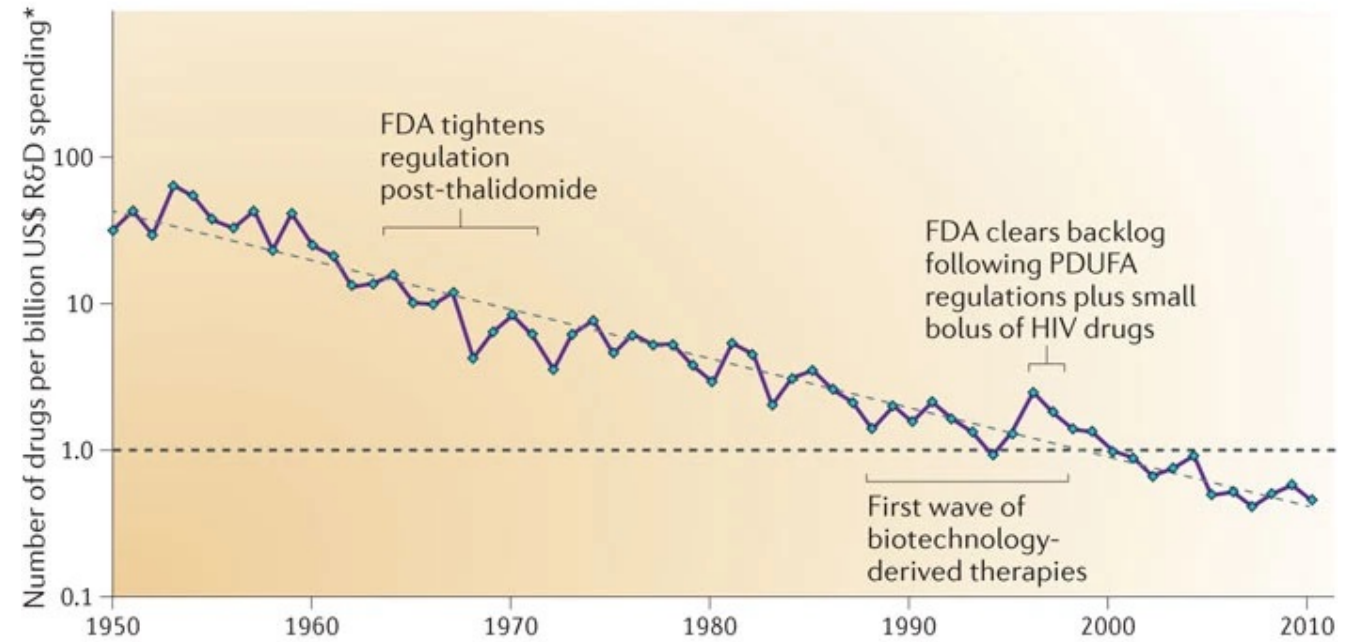
X Ray Crystallography

Databases entries number

High throughput screening

Marketing experience

...



Adapted from Jack W. Scannell et al, Nature, 2012.

Primary causes : “Better than the Beatles”



“We have experience and good outcomes with this one ...”



“... so why should we go with this new one ?”



Primary causes : “The cautious regulator”



Thalidomide

Distilbène

“Really?”

Yes... **desPLEX®**
to prevent ABORTION, MISCARRIAGE and
PREMATURE LABOR

*recommended for routine prophylaxis
in ALL pregnancies...*

96 per cent live delivery with **desPLEX**
in one series of 1200 patients*—
— bigger and stronger babies, too.^{†,1}

No gastric or other side effects with **desPLEX**
— in either high or low dosage^{3,4,5}

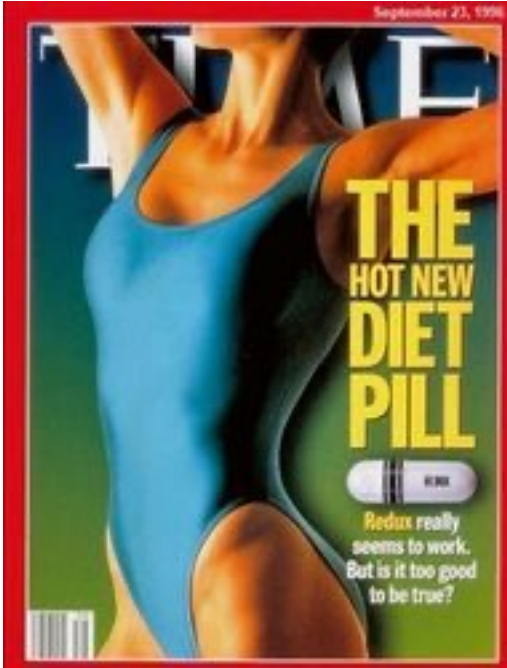
(Each **desPLEX** tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicrotonized to smooth and accelerate absorption and activity. A portion of this ultramicrotonized diethylstilbestrol is even included in the tablet coating to assure prompt help in emergencies. **desPLEX** tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectuation of estrogen.)

For further data and a generous trial supply of **desPLEX**, write to:
Medical Director

REFERENCES

1. Canario, E. M., et al.: Am. J. Obst. & Gynec. 65:1298, 1953.
2. Gilman, L., and Kopolowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
3. Karnaky, K. J., South, M. J. 45:1168, 1952.
4. Patis, E. F.: Med. Times 82:951, 1954; Am. J. Surg. 87:95, 1954.
5. Ross, J. W.: J. Natl. M. A. 43:70, 1951; 45:223, 1953.

GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.



Isomeride



Mediator

Primary causes : “Throw money at it”



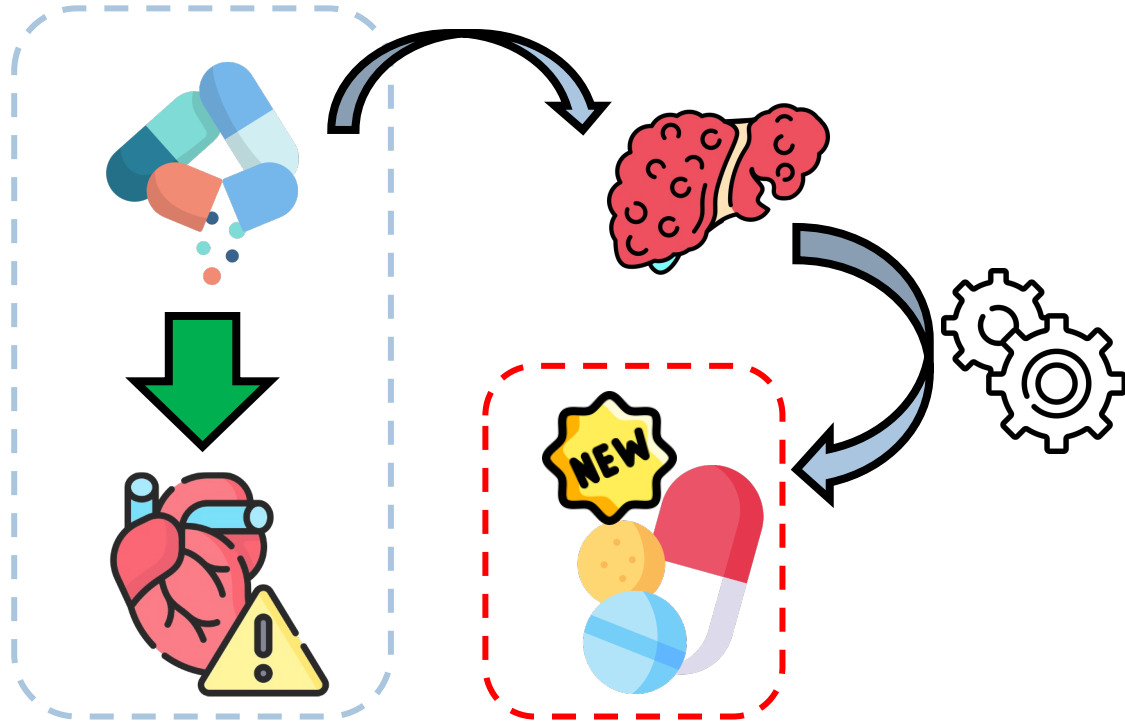
**“We shall now commence
throwing money at the problem.”**

*Indiscriminate spending of human
ressources and money*

Competition to be the first to launch

*Large companies bias :
More budget = more success*

A new opportunity : Drug repurposing



Advantages

Lower risk of failure

Reduced development time frame

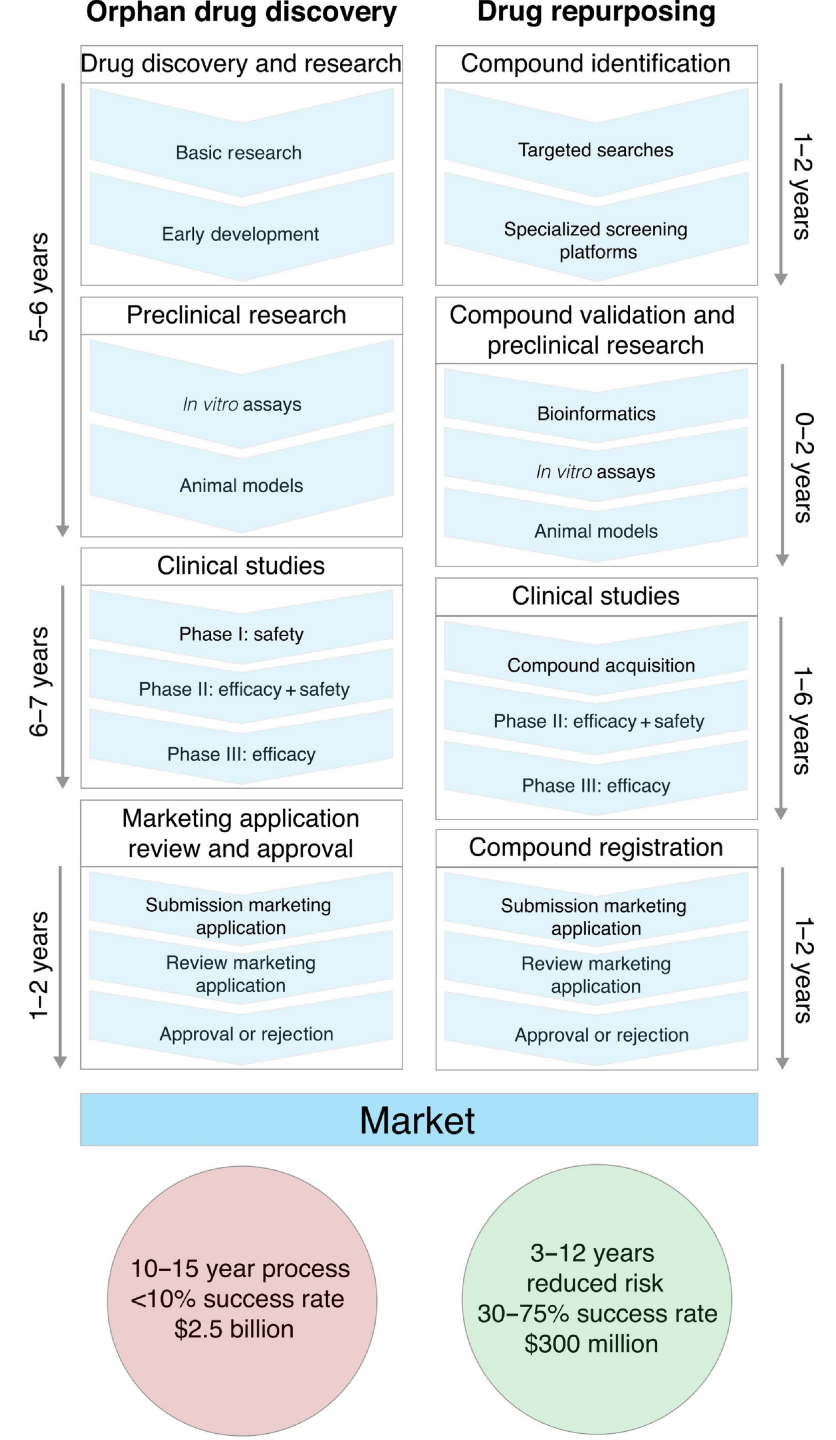
Less investments needed

Approches

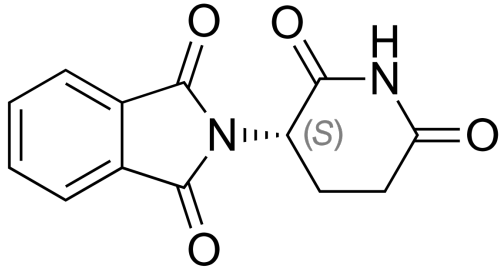
1. Identification of a candidate

2. Mechanistic assessments (pre-clinical)

3. Efficacy assessment in phase II clinical trials



Thalidomide



*First marketed in 1957 as “over the counter” medication to treat anxiety and **nausea***

***Inhibits angiogenesis**, DNA intercalating agent, that affects foetal development*

Removed from the market in 1961

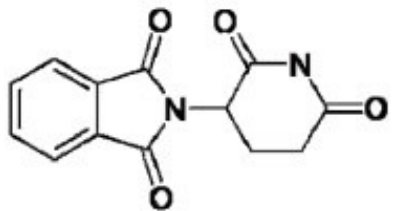


Estimated : 15 000 fetus affected, 12 000 borned with congenital defects, only 8 000 survived over a year of age

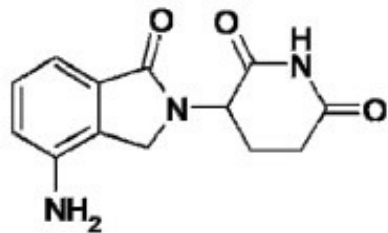
Thalidomide : Repurposing

*Multiple Myeloma :
Incurable malignant disorder of mature B-cells*

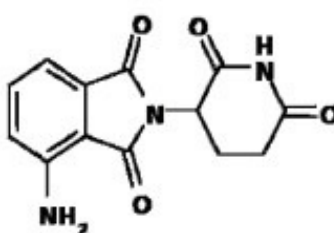
*Make use of Thalidomide **angiogenesis inhibitor and immunoregulator properties (IMiDs)***



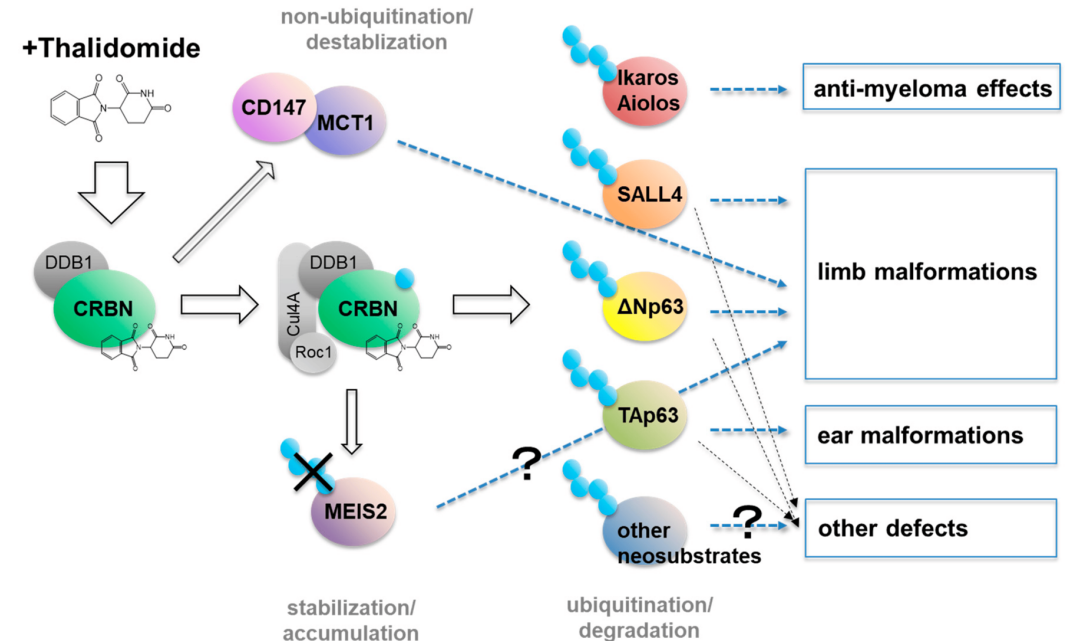
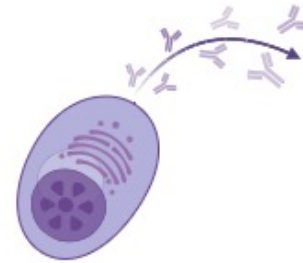
Thalidomide



Lenalidomide



Pomalidomide



Repurposing : problematic for ones, opportunity for others

Patent considerations

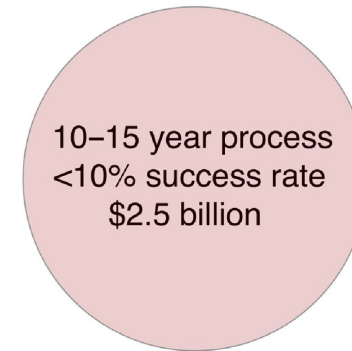
Regulatory considerations

Organizational hurdles in industry

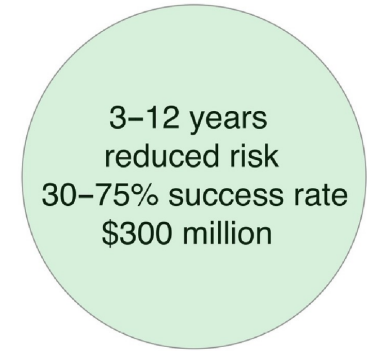
Repurposing is not so appealing for Industry...

...But it is for biomedical research in orphan diseases

7000 rare diseases identified affecting 300 million people



Orphan drug discovery

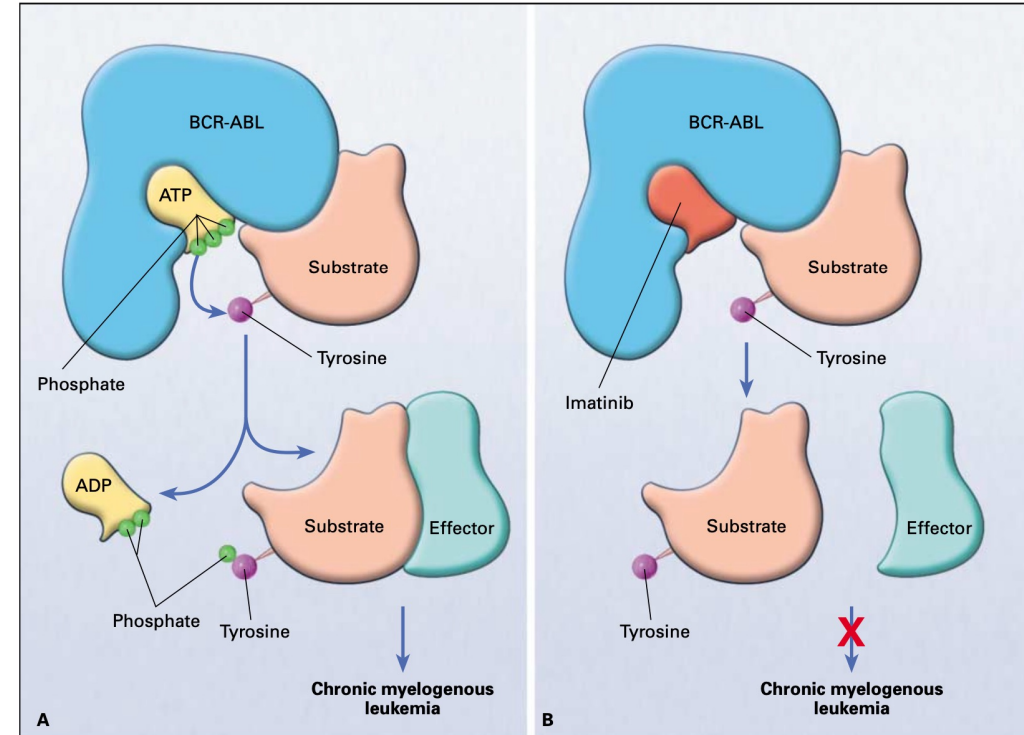
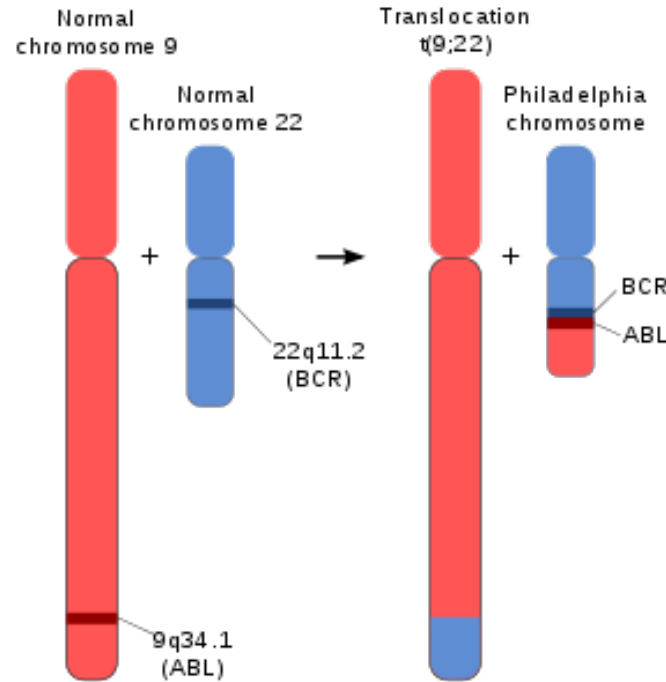


Drug repurposing

BCR-ABL Chronic Myelogenous Leukemia (CML)

10% of new cases of leukemia are CML

Caused by a genetic abnormality, few treatments options were available



*In the late 90's Novartis developed Imatinib (Gleevec) a **tyrosine kinase inhibitor***

- **Highly expensive**
- **Development of resistances**

Drug repurposing identifies a synergistic combination therapy with imatinib mesylate for gastrointestinal stromal tumor