

ESC Summer School

How big pharma and academia collaborate ?

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Servier

A global pharmaceutical company



A turnover of € 4 billion
Servier's drugs € 2.8 billion
Generic drugs € 1.2 billion



2nd French pharmaceutical company
30th worldwide
3 research centres, including 2 in France,
15 production sites, including 2 in France



25% of turnover excluding generic drugs is invested in R&D



A workforce of 21 000 in 148 countries
(4 800 in France)



64 million patients treated daily
(Servier's drugs + generic drugs)

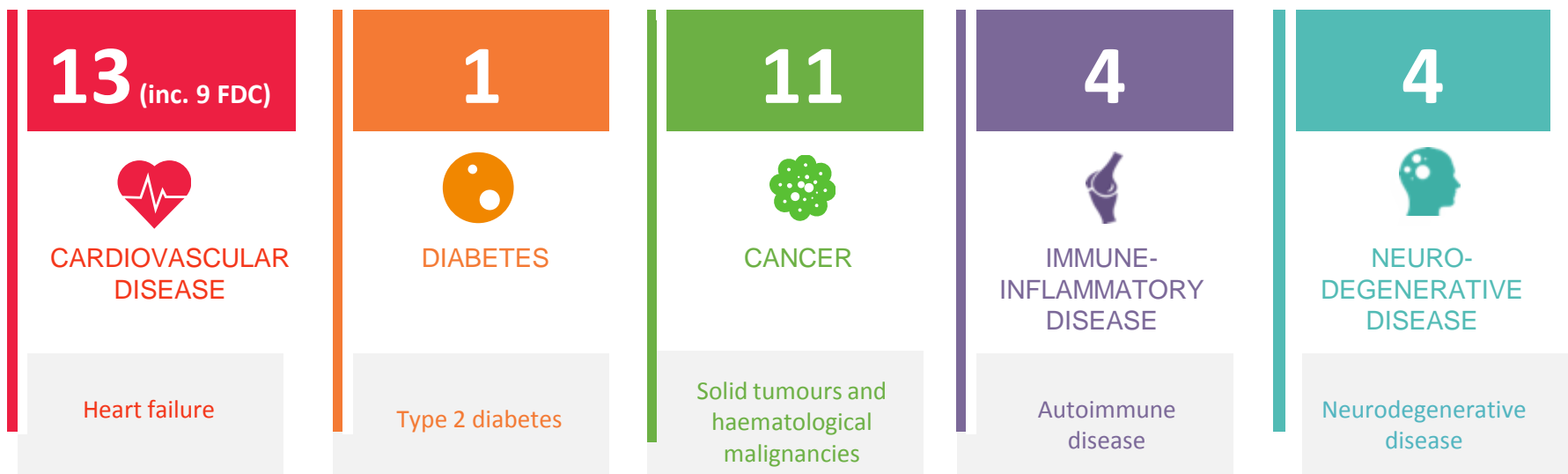


A leader in cardiology
2nd in Europe, 8th worldwide



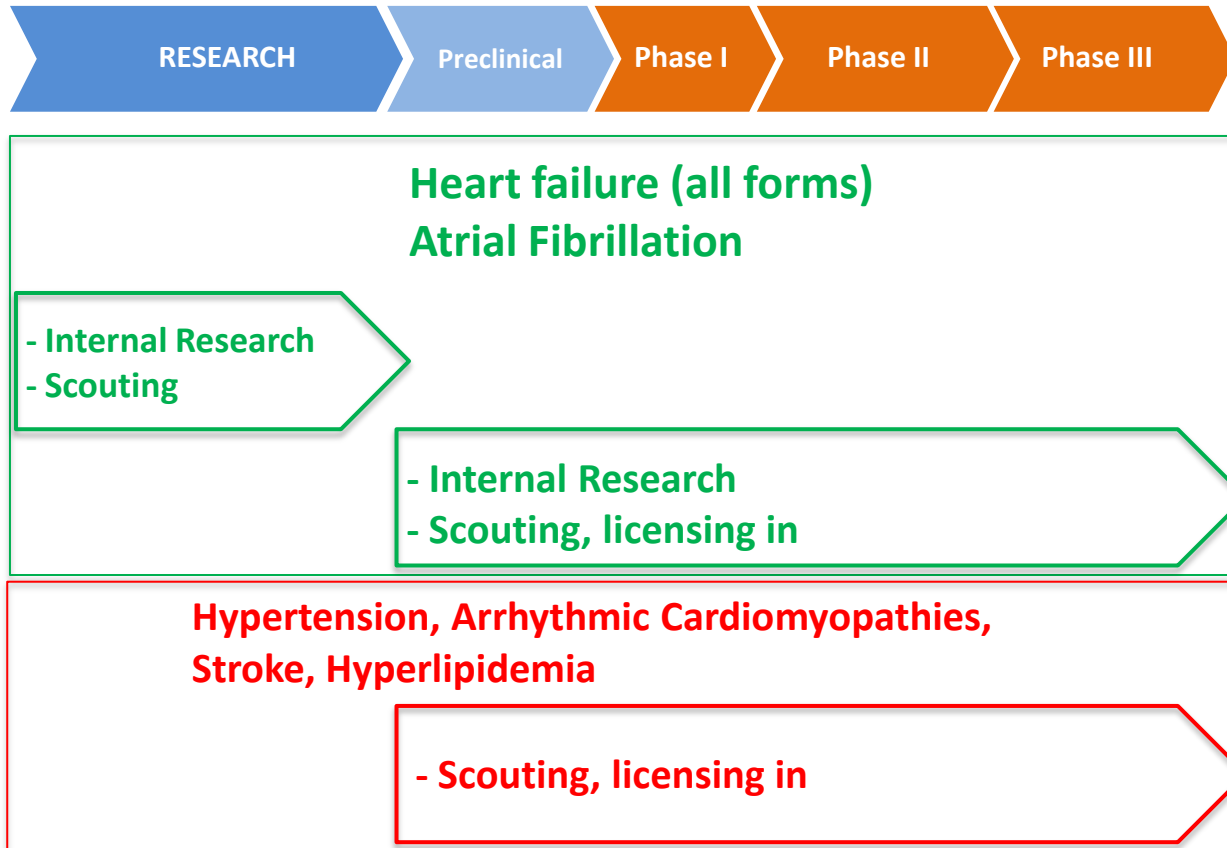
OUR R&D IS SPECIALIZED IN 5 MAJOR AXES

33 drug candidates in clinical development



Including **22 new molecular entities** and 9 Fixed-Dose Combinations (FDC)

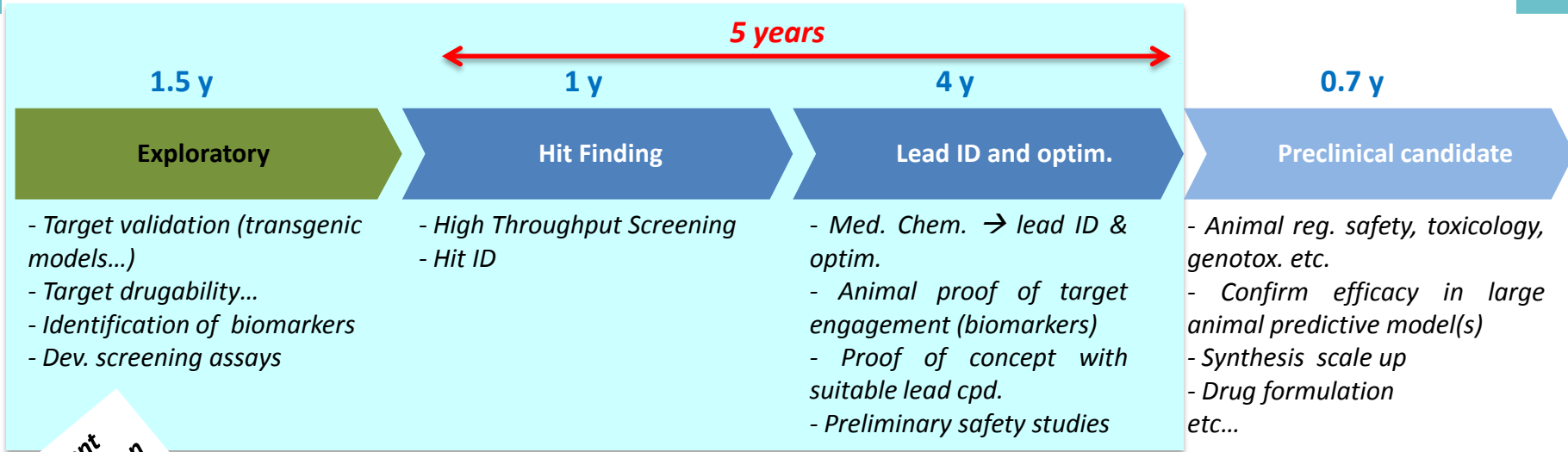
OPPORTUNITY ROADMAP – CARDIOVASCULAR DISEASE



≈ 50% of R&D projects are developed in partnership

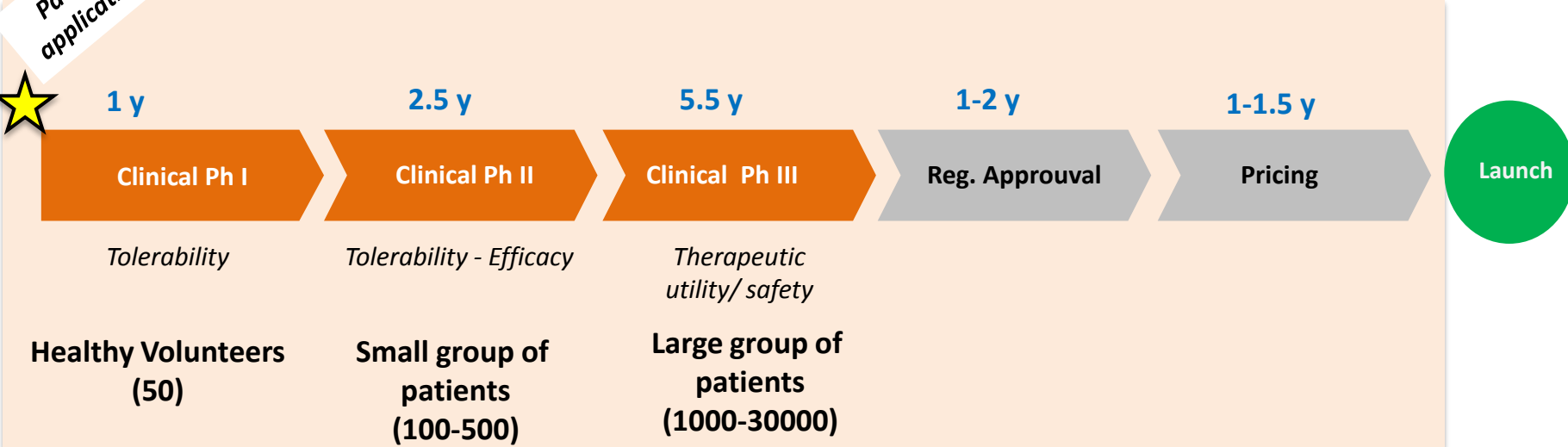
PROJECT LIFE CYCLE (SMALL MOLECULE)

Research



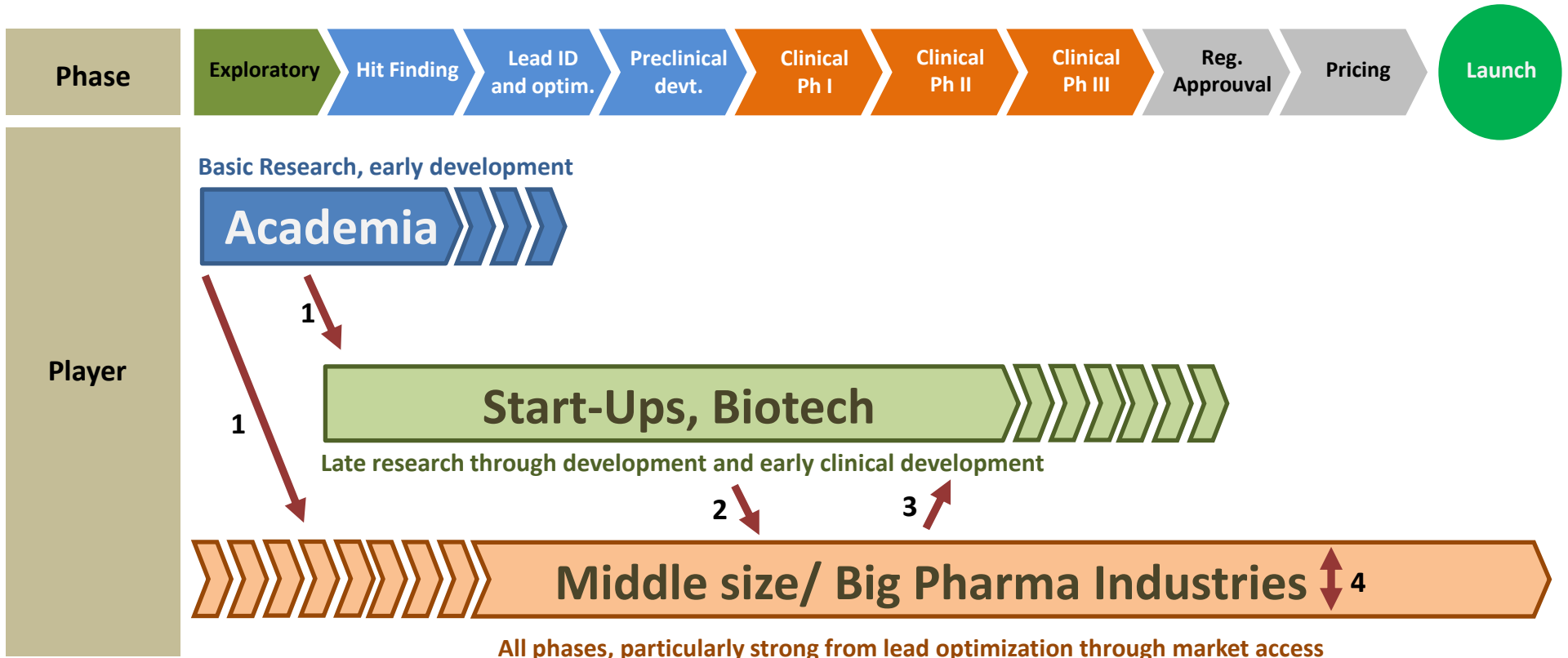
Patent application

Clinical



Partners in the pharma ecosystem

Interaction is the key for success



Interactions/transactions

- 1 Collaboration, Licensing, Startup creation
- 2 Partnering, Licensing to support financial risk at later stages
- 3 Asset transfer of promising project from Pharma following strategic portfolio decision
- 4 Asset transfer due to strategic reasons, mergers, insolvencies etc.

Pharma constraints: to have a sustainable system

➤ Key parameters of cost:

- Attrition rate (*number of project/ drug that failed*)
- Development stage of the drug when it fails: cost at the end of phase III >> cost during early research
- Development duration (Cardiovascular >10 y): cost + patent
- Development cost (requirement of large morbi-mortality trials)

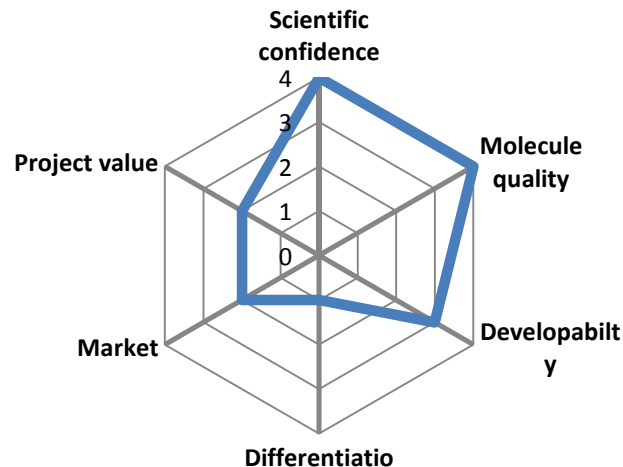
➤ Key parameters of profit:

- Duration of the protection when the drug reaches the market, overall patent duration 20y (EU possibly 5 extra year)
- Market size: incidence/prevalence
- Reimbursement: proportion of patients for which the drug will be reimbursed
- Labeling: limitations/contra-indications/ black box warning
- Penetration: competitors/price/perceived medical need/characteristic of the drug
- Price
- Cost of goods

Evaluation of project value

6-dimension analysis by scoring:

- Scientific confidence (*key external/ internal data (preclinic/ clinic)*)
- Molecule quality (if applicable)
- Developability (*regulatory/development challenges*)
- Differentiation (*versus drugs in development and SoC*)
- Patients (*target population, duration of treatment ...*)
- Project valuation (*medical need, peak sale estimation, PoS, patent life*)



Drug project attrition: How much and why

Research & Preclinical dev.

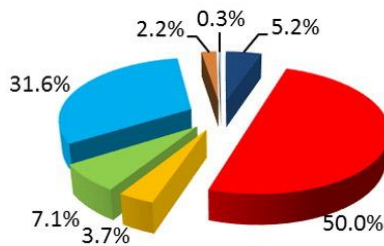
Clinical dev.

Launch

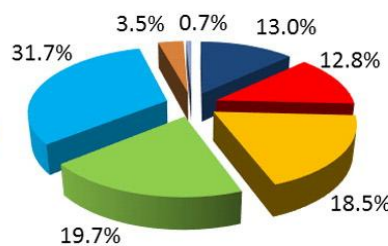
Cumulative cost

0.8-1.2B €

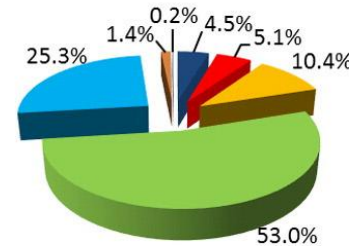
Pre-clinical: **67%** success
n=1106



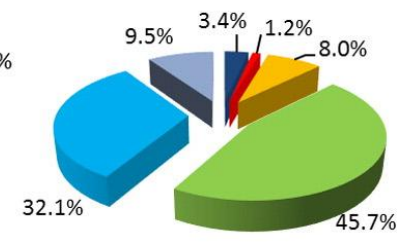
Phase I: **51%** success
n=982



Phase II: **23%** success
n=546



Phase III: **55%** success
n=193



Reasons for failure

- Pharmacokinetics/bioavailability
- Non-clinical toxicology
- Clinical safety
- Efficacy
- Commercial
- Technical
- Regulatory

Bayliss et al., Drug Discovery today, 2016

90% of drugs fail to get to Market due to lack of efficacy (>60%) or safety issues
Likelihood of approval for a pre-clinical candidate: 4%

Drug project attrition: what are the solutions ?

To counteract attrition, a critical mass of projects in Research is needed



Collaboration between Pharma, Academia and Biotech is the key for success



Strength of academic research

12



Basic Research, early development

Academia >>>



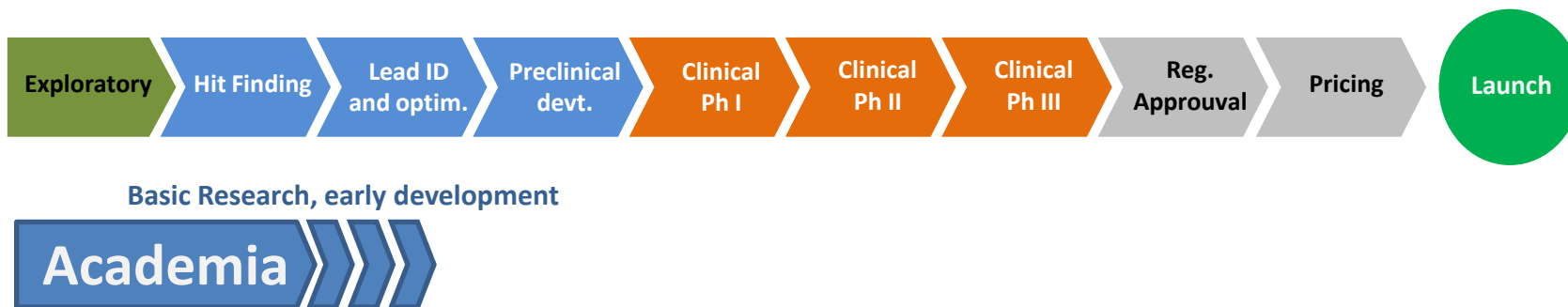
Excellency in basic research

- > innovation for new therapeutic targets/ pathways
- > cutting edge of science in determining specific mechanisms of action
- > technical expertise
- > scientific networks facilitating exchanges

The input of academia for innovative therapeutic target remains indisputable

... but academic research must be in phase with Pharma constraints !

13



Druggability of the target

Duration of a research project : 5 years -> “fast” development of screening assays and hit identification required

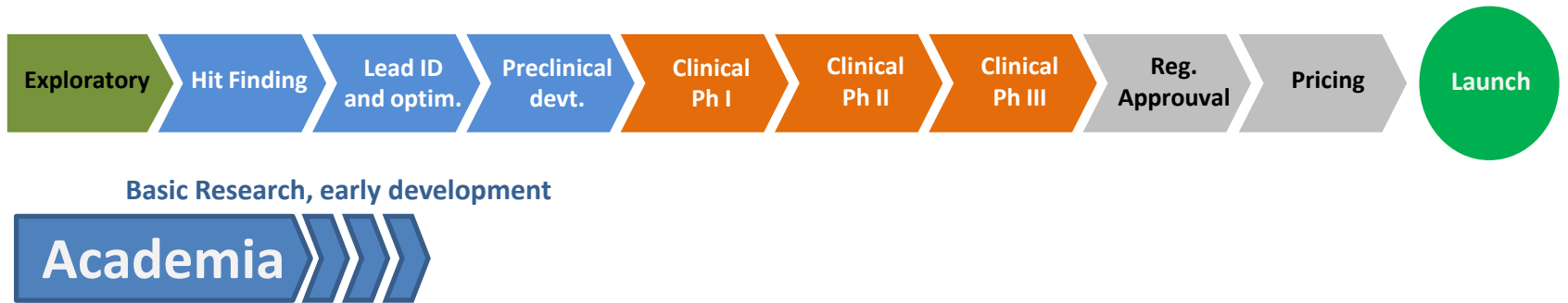
Differentiate a pharmacological tool and a preclinical candidate !

For ex., chronic treatment needs an orally bioavailable compounds, large scale chemical synthesis transposable for industry, etc...

Patent

Patent filing as late as possible ! (just before phase I) allowing a longer duration of the protection when the drug reaches the market

... but academic research must be in phase with Pharma constraints !



Differentiation

A new therapy must differentiate from existing therapies and those in development !
-> *Warning with cross talk pathways for instance ...*

In vivo preclinical model

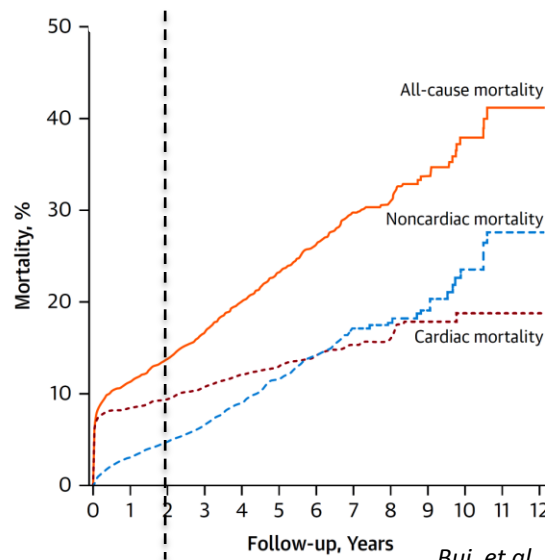
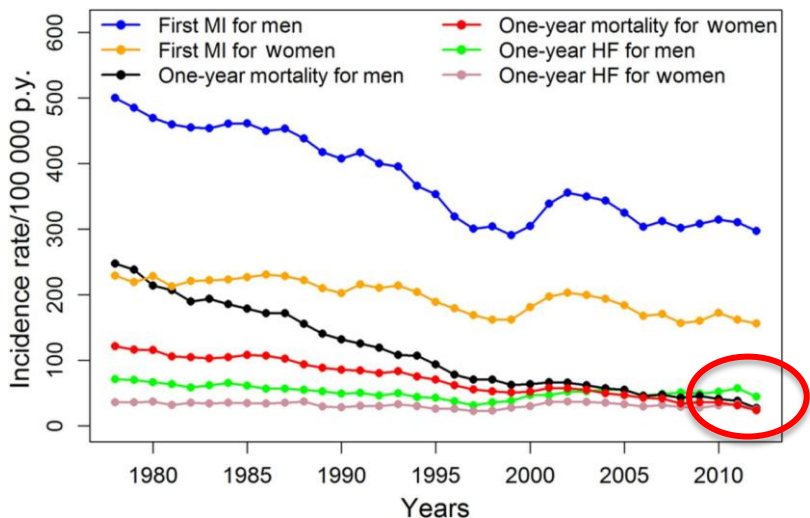
Proof of concept in a predictive and translatable models is the key for success:
limitation of failure in late stage development !

Medical need

A perception of medical need could be erroneous ...

Medical need for cardioprotection post MI: Myth or reality ?

Numerous publications describe new targets for reperfusion lesions in patients undergoing PCI



*Bui, et al., Nat. Rev. Cardiol., 2010
Pedersen et al., JACC, 2014*

Prevalence and mortality of acute MI are decreasing over time

Very early mortality within 3 months (7.9%) – Low number of CV events following this early phase

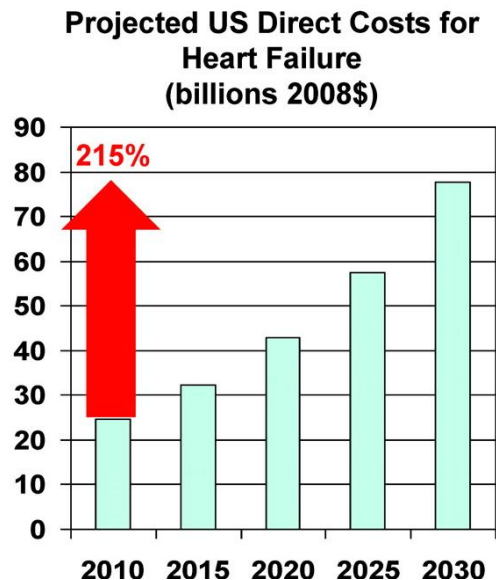
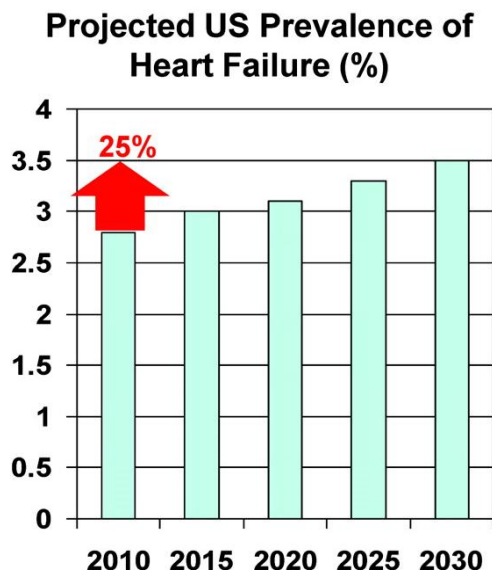
-> **Short term: medical need IS the prevention of cardiogenic shock/ MODS in selected higher risk patients to limit short term mortality**

-> **Long term: Prevention of HF/ mortality at long term (>2 y) is a big challenge for a clinical trial (with a race against time for the patent !)**

Treatment of Heart Failure remains a high medical need

Hospitalization for HF increases and mortality does not decrease substantially

- Despite optimal treatment, HF prevalence is 2.8%
- Annual mortality of 12% → half of HF patients die within 4 years from diagnosis
- Economic and social burden is extremely high



Curative treatment of HF remains a high medical need

Research collaboration between Academia and Pharmas ...to be efficient all together !

What is needed to find new treatments in CV diseases:

- Medical need is mainly in HF (all forms) or atrial fibrillation treatment
- Relevant targets should not be modulated by existing treatment
- Proof of target engagement in predictive therapeutic models and/ or genetic models (and ideally in patients !)
- Druggable target
- When preclinical candidates are available, patent should be recent (or ideally not yet filed !)

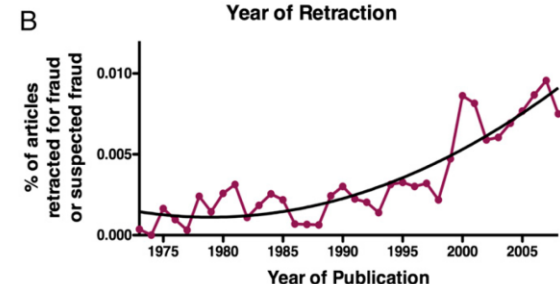
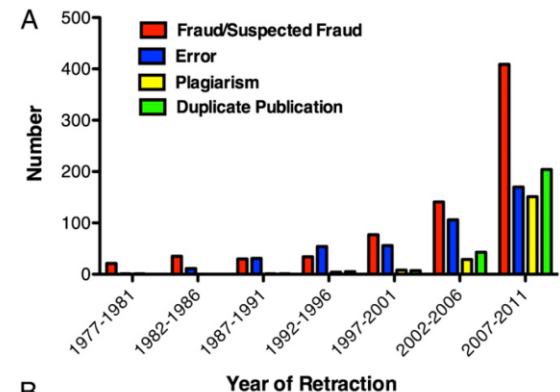
Collaboration Academia/ Pharmas in Research ...to be efficient all together !

What is needed to find new treatments in CV diseases:

- Robust/ rigorous experimental data : increasing number of unreliable scientific publications is a major issue !

- 85% of research resources are wasted
Currently, **many published research findings are false or exaggerated** (Ioannidis, Plos Medicine 2014)
- **90% of 53 studies were not reproducible.**
Amgen scientists could not reproduce the findings of 53 “landmark” articles in cancer research (Begley ex Amgen, Nature, 2012)
- **79% of 67 projects were not reproduced**
by Bayer scientists trying to reproduce the findings of 67 target-validation projects in oncology (Prinz et al., Bayer, Nature Discovery 2011)

Number of retracted articles for specific causes by year of retraction



Conclusion

Collaboration between Academia and Pharmas is central for innovation

Complementarity of expertise allows a higher efficiency

These links will make it possible to find new treatments for the benefit of patients





THANK
YOU!

