HOSPITALES

CENTRO INTEGRAL ONCOLÓGICO
CLARA CAMPAL
CIOCC

Nuevas exigencies en la investigación biomédica (en Oncología): Vision de los centros

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Summary

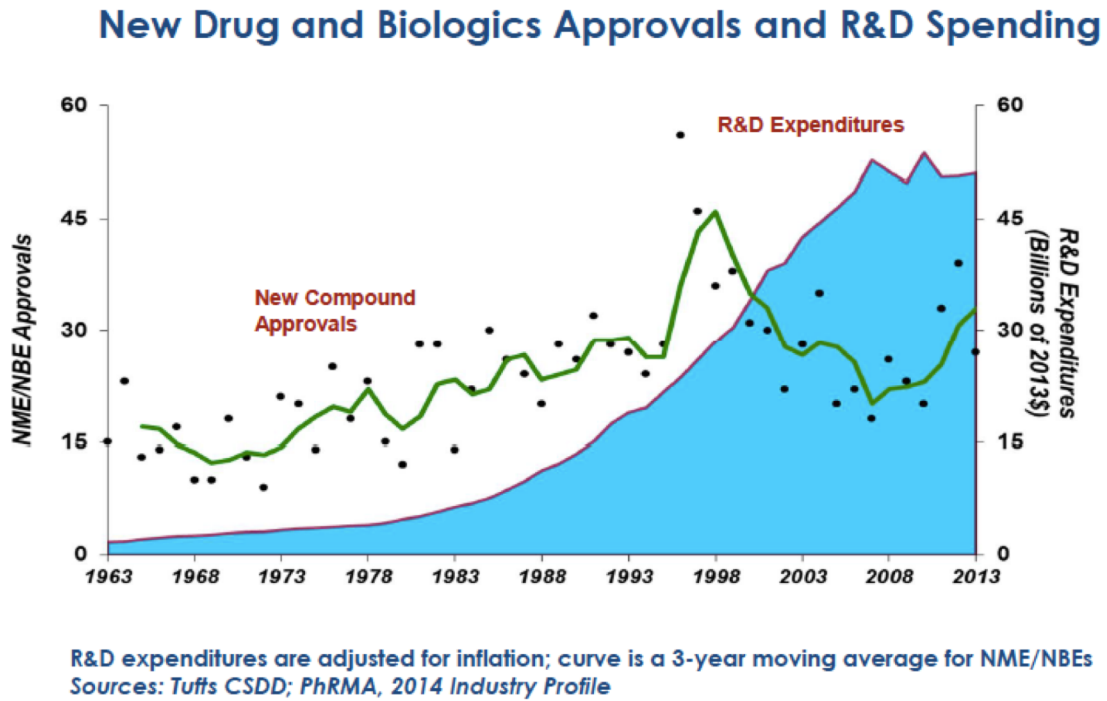
- Inefficient regulatory impulse: *Better drugs, faster and cheaper* for our patients
- Need for Early Phase trials to be more *informative*
- *Adaptation* of study designs and clinical units to the type of drugs in development

Regulatory impulse…

- FDA responsibilites:
  - "advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable"
    - Better drugs, sooner, at lower cost

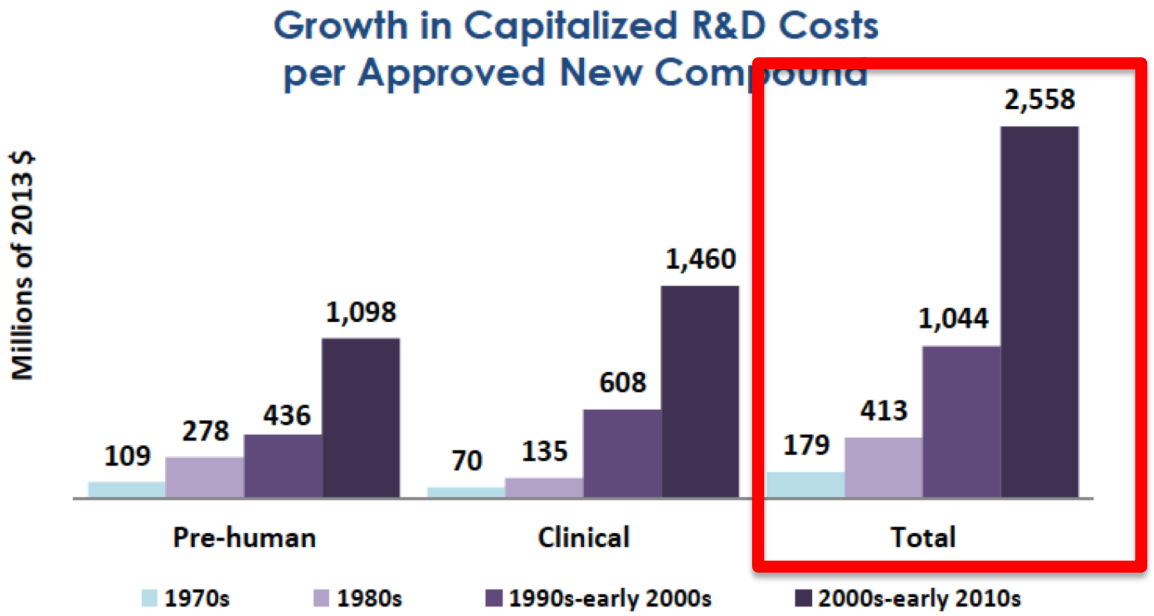
http://www.fda.gov/AboutFDA/WhatWeDo/default.htm

… but few, “bad”, late and expensive drugs



Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

… Unsustainable system: disproportionate R&D expenses…



Sources: 1970s, Hansen (1979); 1980s, DiMasi et al. (1991); 1990s-early 2000s, DiMasi et al. (2003); 2000s-early 2010s, Current Study

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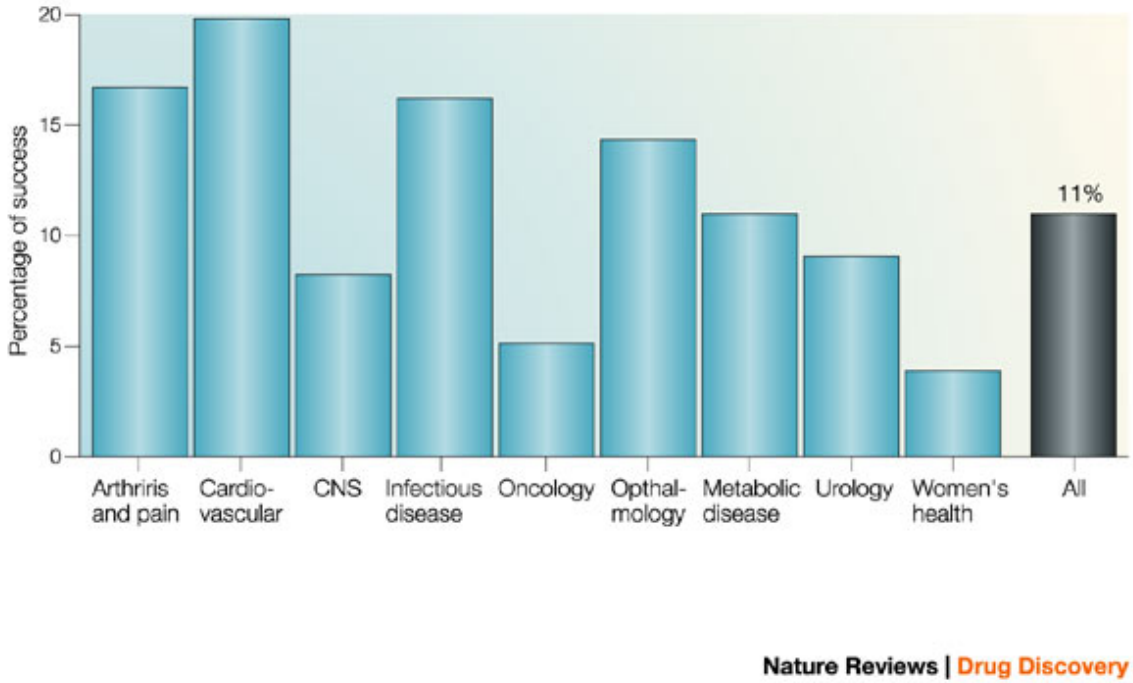
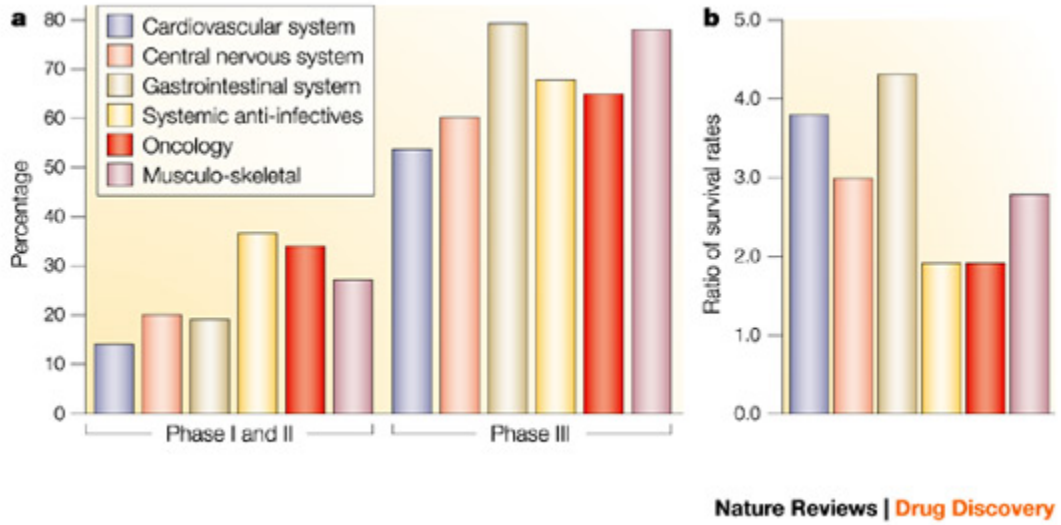
… high attrition rate



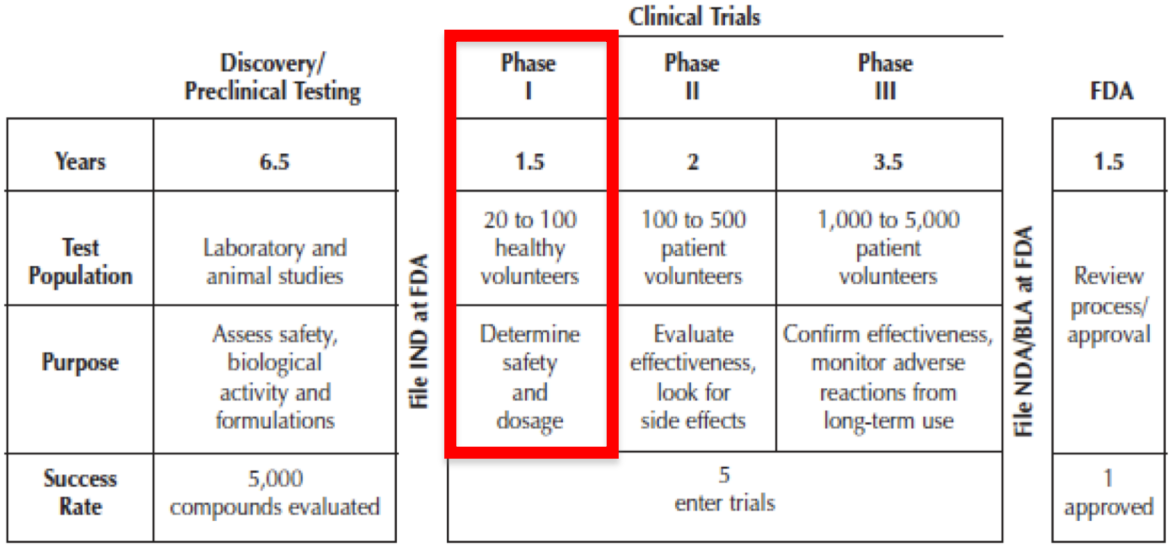
Kola & Landis Nat Rev Drug Discovery 3: 711-715.

… late failure



Nature Reviews Drug Discovery **2**, 609-610 (2003)

Classical Drug-to-patient process



	Discovery/ Preclinical Testing	Clinical Trials: Phase I	Clinical Trials: Phase II	Clinical Trials: Phase III	FDA
Years	6.5	1.5	2	3.5	1.5
Test Population	Laboratory and animal studies	20 to 100 healthy volunteers	100 to 500 patient volunteers	1,000 to 5,000 patient volunteers	Review process/ approval
Purpose	Assess safety, biological activity and formulations	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use	
Success Rate	5,000 compounds evaluated	5 enter trials			1 approved

File IND at FDA

File NDA/BLA at FDA

Better drugs, sooner and cheaper…

Phase 1 studies: "*the most critical step from bench to bedside*"

- Not only first time in humans
  - Unquestionably an exciting event!
- The interface between preclinical testing and the start of human exploration of a new cancer drug
  - Integration of preclinical pharmacokinetics, pharmacodynamics and toxicology
  - Starting point for rational clinical development

Classical Objectives for Ph1 Trials

- Maximum Tolerated Dose
  - Acceptable, manageable, reversible toxicity in a reasonable percentage of patients
  - It assumes dose-dependent activity
- Phase 2 scheme
- Preliminary profile of side effects of the drug

Unmet need in Clinical Drug Development:

Transform Early Phase Clinical Trials to become more informative

Waves of cancer drugs

Darwinian adaptation of clinical trials designs and clinical units to the characteristics of the different families of drugs in early clinical development

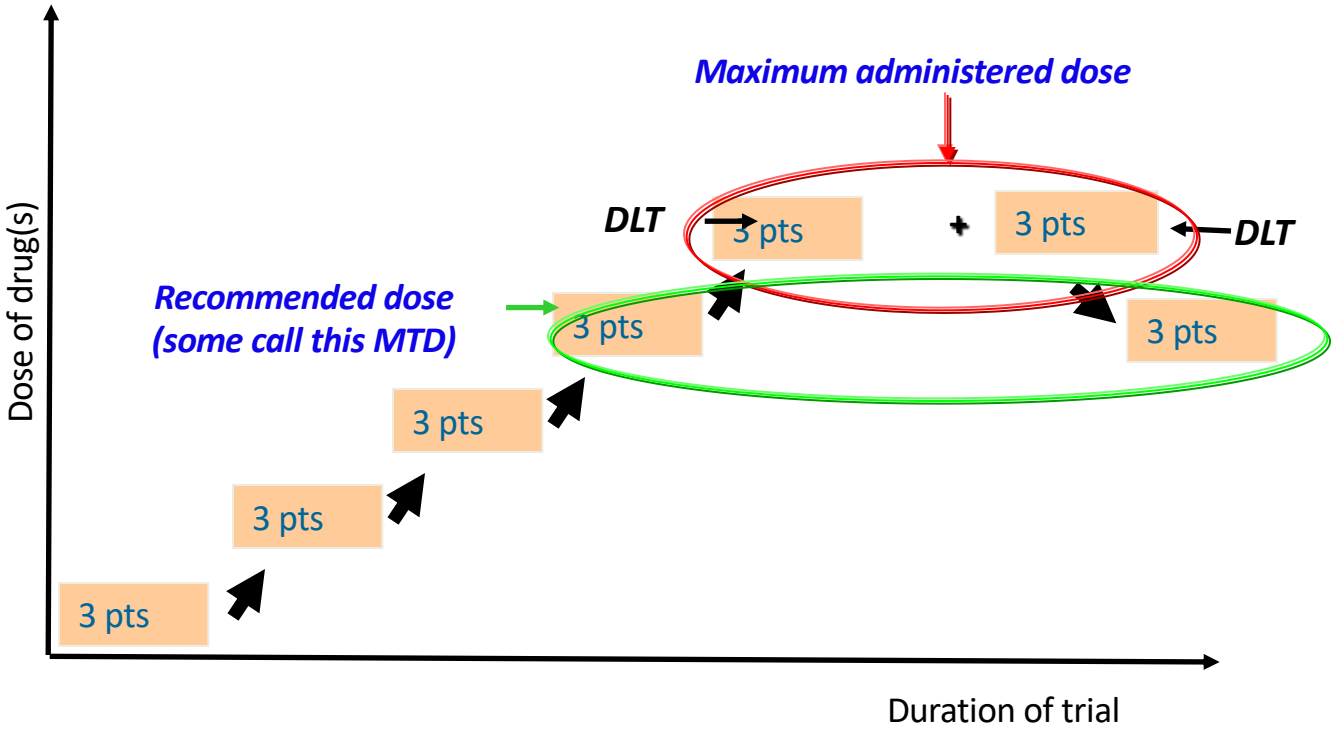
	CYTOTOXICS	TARGETED	IMMUNOTHERAPEUTICS
MoA	Wide spectrum Tumor cell Wide activity	Selective/Specific Tumor cell/stroma Specific activity	Selective/Specific Immune cell Wide actitivy
Clinical effects	Toxic Early	Less toxic Early	Less toxic Late (out of DLT window)
Ph1 objectives	RD Side effects profile	RD Antitumor activity	RD/Feasibility Antitumor activity
Recommended dose	Toxicity based Easy	Tox, Activity, PK/PD Less easy	¿?¿? “Arbitrary” (?)

Three waves of early studies designs

Historical evolution of clinical trials designs: waves and challenges

- 1/ “Classical” designs: the era of cytotoxic drugs
- 2/ “Precision Medicine” designs: the wave of targeted drugs
- 3/ “Seamless designs”: the immunotherapy tsunami.

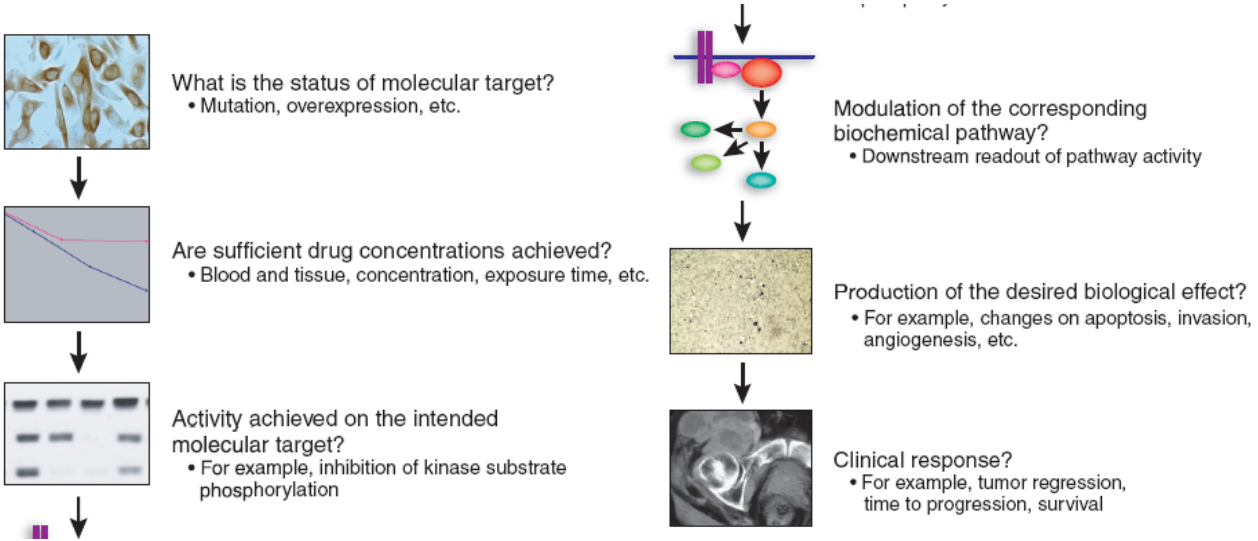
1/ Classical designs: cytotoxics



Phase I trial classical design: standard 3+3 design

More Informative “classical” Early Phase studies

“Pharmacological Audit Trail”



Workman P. Nature Chemical Biology 12, 689-700, 2006

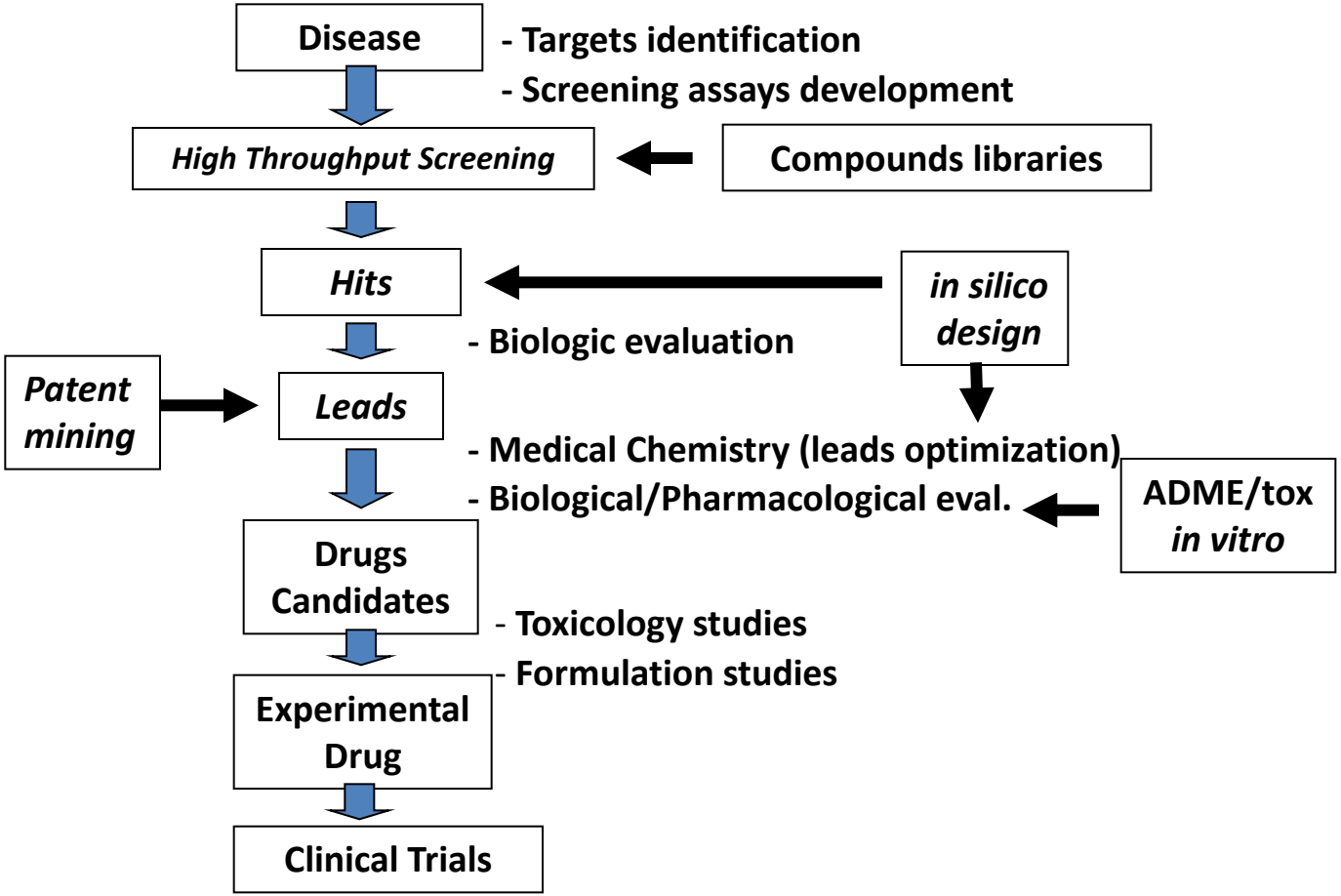
Transform Early Phase Clinical Trials to become more informative:

Biopsies (solid, liquid, basal, on therapy), PKs, activity, toxicity…

Data, data, data

→ Professional multidisciplinary teams, highly specialized, full-time dedicated, perfectly coordinated, of clinical research in Oncology

2/ Precision Medicine designs: What's the target?



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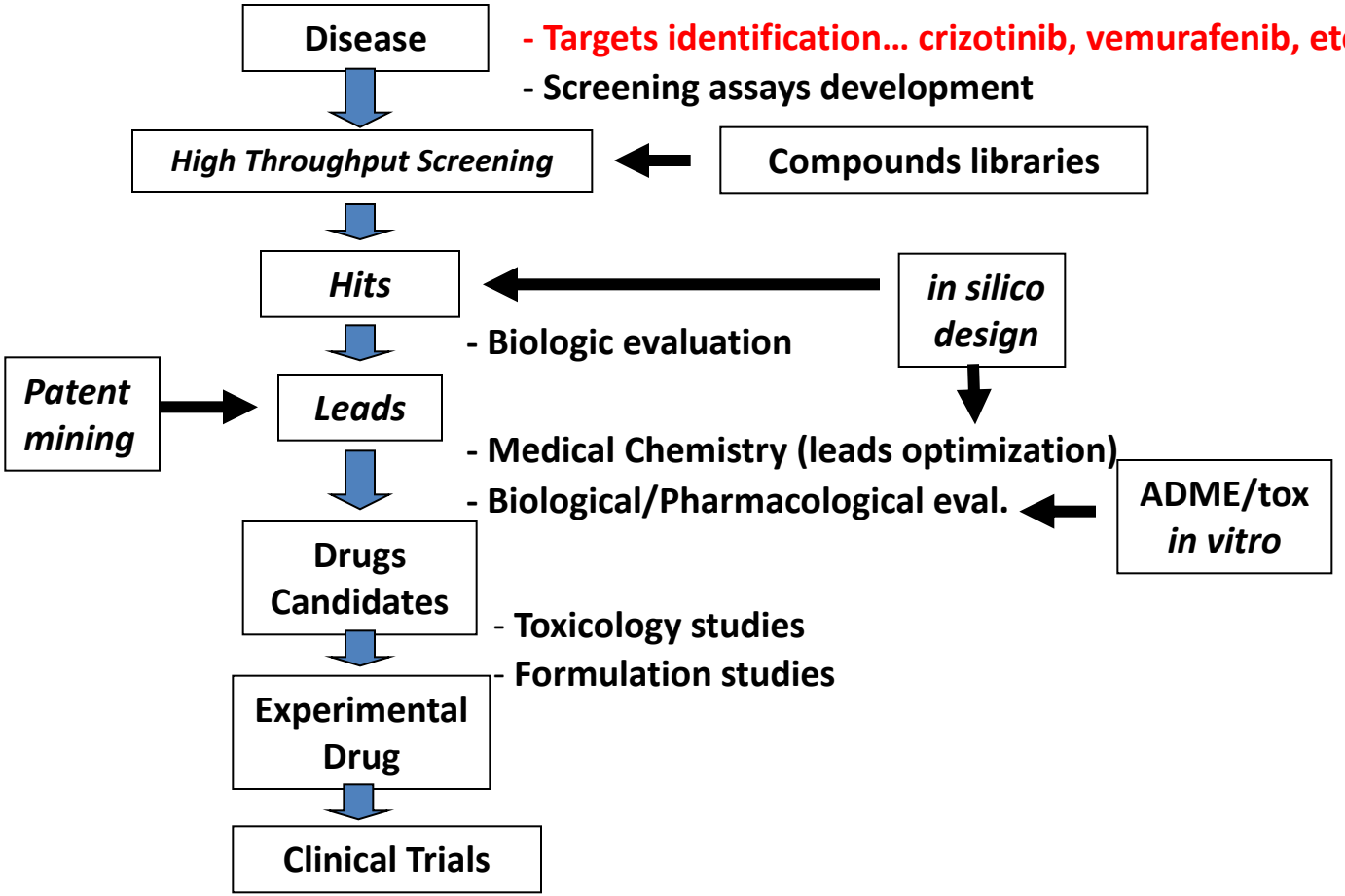


2/ Precision Medicine designs: Targeted agents

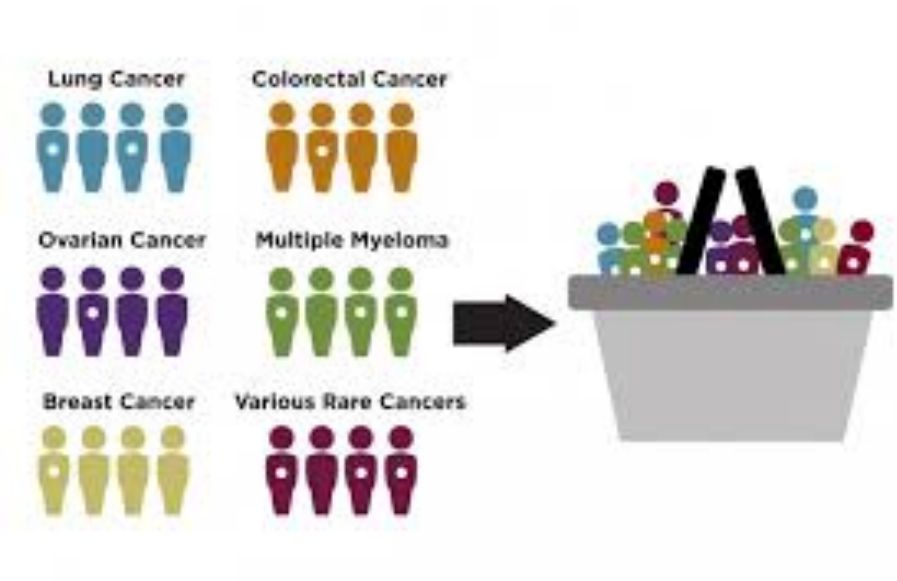
What's the drug doing?

- Sorafenib (Raf kinase inhibitor): VEGFR1–3
- 5-Azacytidine (antimetabolite): DNA Methyltransferase
- Imatinib (PDGFR): bcr-abl, kit
- Crizotinib (MET): EML4/ALK, ROS-1
- Iniparib (PARP): alkylating agent forming adducts with cysteine rich proteins
- Tivantinib (MET): anti-tubulin

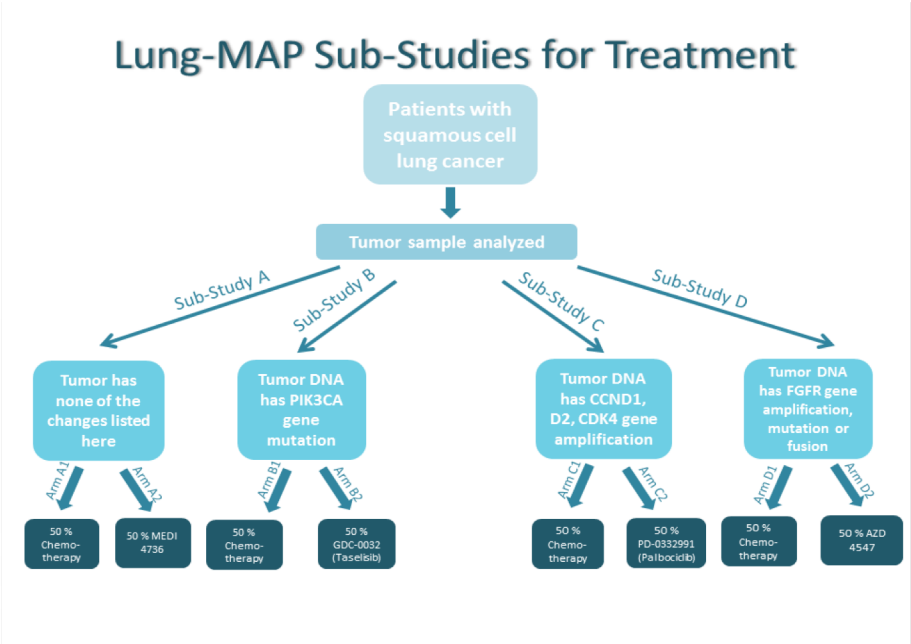
Courtesy of Alex Adjei

Basket/Umbrella studies

Basket



Umbrella



Challenges of targeted studies

Number Needed to Analyze: Biomarker-Driven Clinical Research

$$NNS = \frac{1}{\text{(fraction with biomarker X assay specificity X fraction trial-eligible X fraction giving informed consent)}}$$

	Fraction with biomarker	Assay specificity	fraction trial-eligible	fraction accepting participation	Pt Needed to Analyze
HER2+ in Breast cancer	25%	90%	70%	50%	13
ALK fusion in NSCLC	5%	90%	70%	50%	63
FGFR fusion in GBM (freq 3-8%)	**3%**	90%	70%	50%	105

Courtesy J Rodon

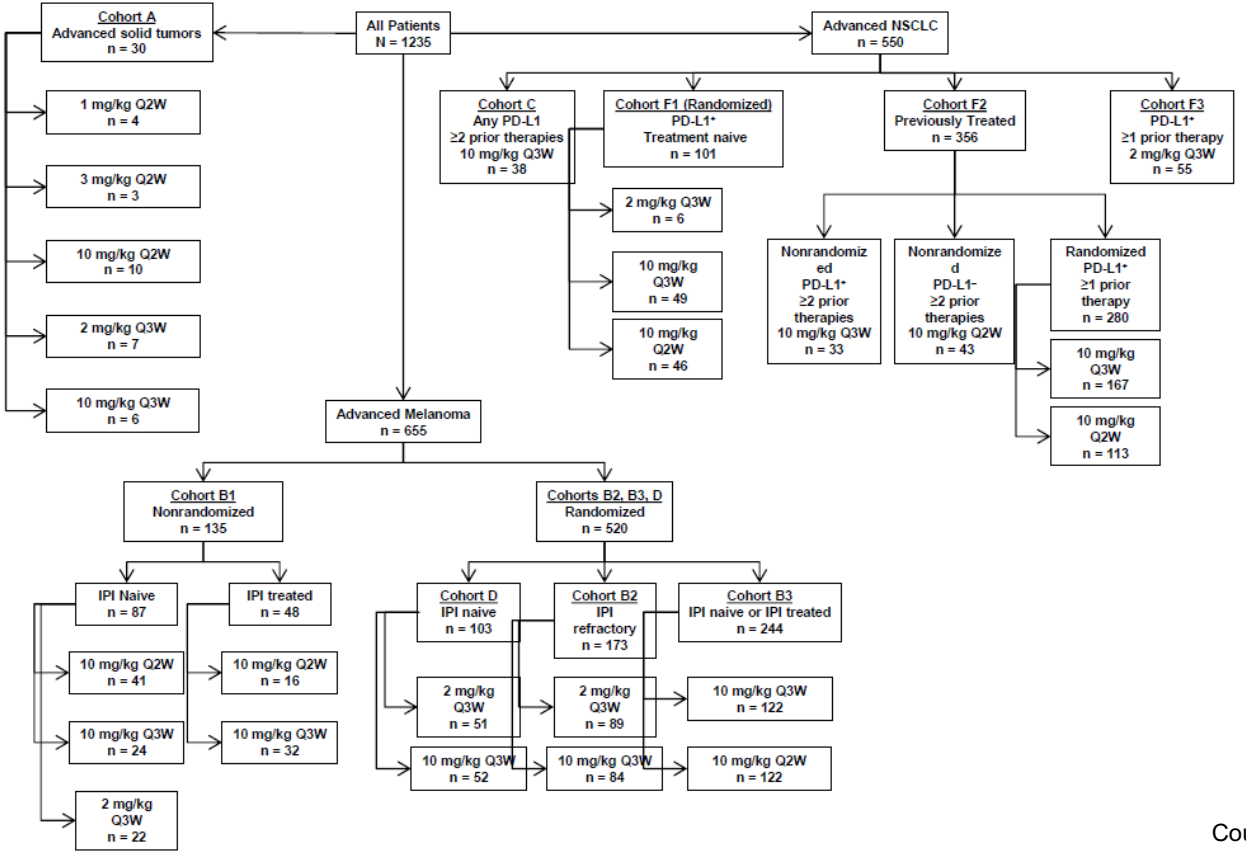
Challenges of Precision Medicine studies

- Rapid evolution of knowledge about targets and drugs
  - Agents found not to be effective against target
  - Evaluation of the wrong molecular aberration (MET amp vs exon 14 skipping mut)
  - Variants of unknown significance
  - Agent found to be efficacious… is there a rationale for continuing study?
- It requires flexible, adaptive design and only a few arms may ultimately be successful -> what to do next?
- Tumor heterogeneity
- Who pays for molecular testing platform?
- Non-biopsiable disease

Precision Medicine studies

- They are here to stay!!:
  - Accessible holistic molecular screening
  - Enthusiasm of patients and physicians for molecular screening
  - Liquid biopsies

3/ Seamless designs: Immunotherapy tsunami



Pembrolizumab development

Courtesy of Alex Adjei

Seamless designs: complexity

Trends in Clinical Trial Protocol Complexity

	2000-2003	2008-2011	Increase in Complexity
Total Procedures per Trial Protocol (median) (eg, bloodwork, routine exams, x-rays, etc)	105.9	166.6	**57%**
Total Investigative Site Work Burden (median units)	28.9	47.5	**64%**
Total Eligibility Criteria	31	46	**48%**
Clinical Trial Treatment Period (median days)*	140	175	**25%**
Number of Case Report Form Pages per Protocol (median)	55	171	**211%**

PhRMA.org

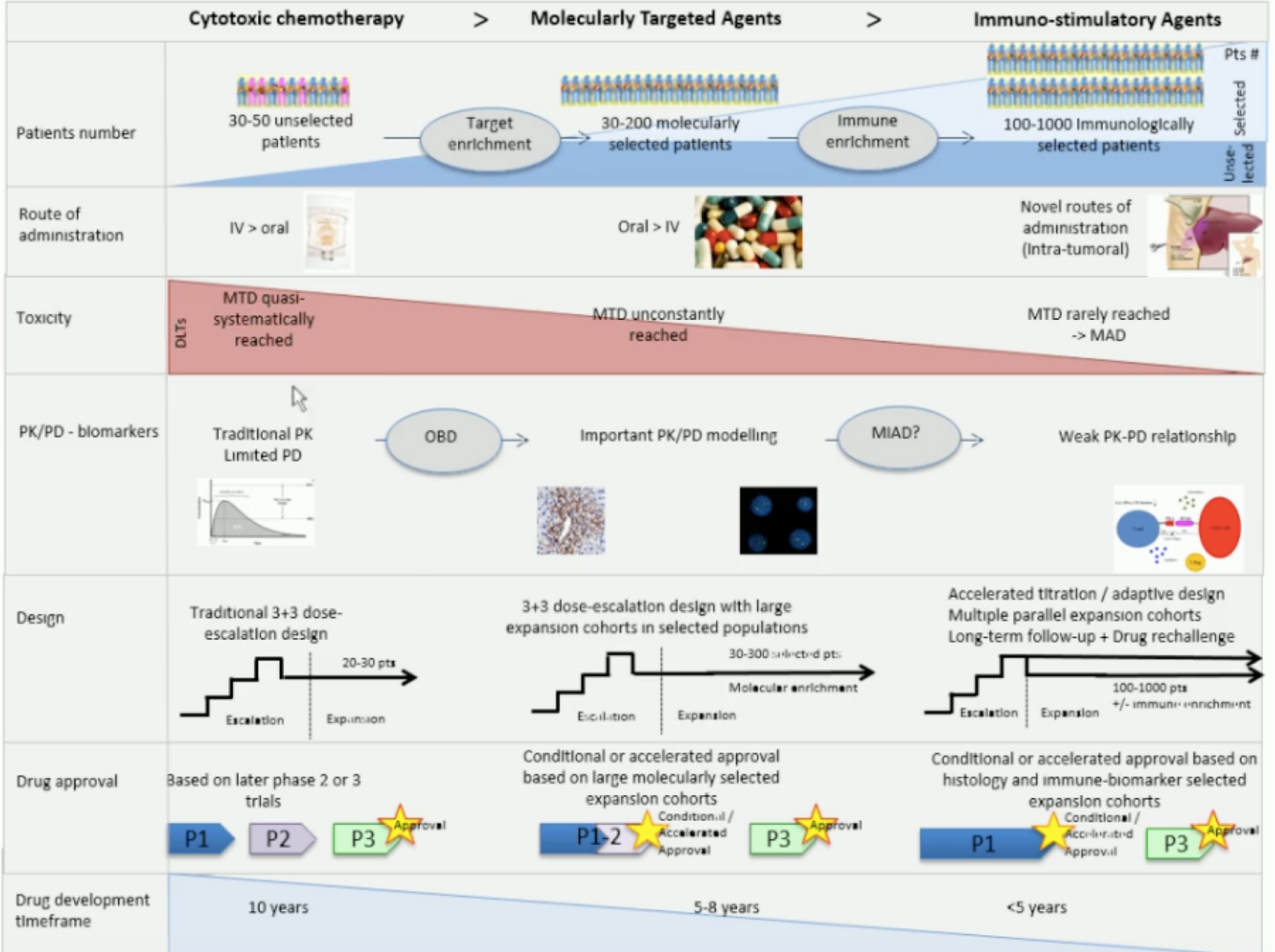
Challenges of seamless studies

- Challenging intellectual complexity
  - Slots updates, dynamic selection criteria, dose/escalation mistakes
- Trials never seem to close to enrollment
  - Higher work load (PIs, RNs…) per study
  - Increasing number of amendments (reconsents, training)
- Competitive/challenging slots: many arms, few slots, many sites

Challenges of seamless studies

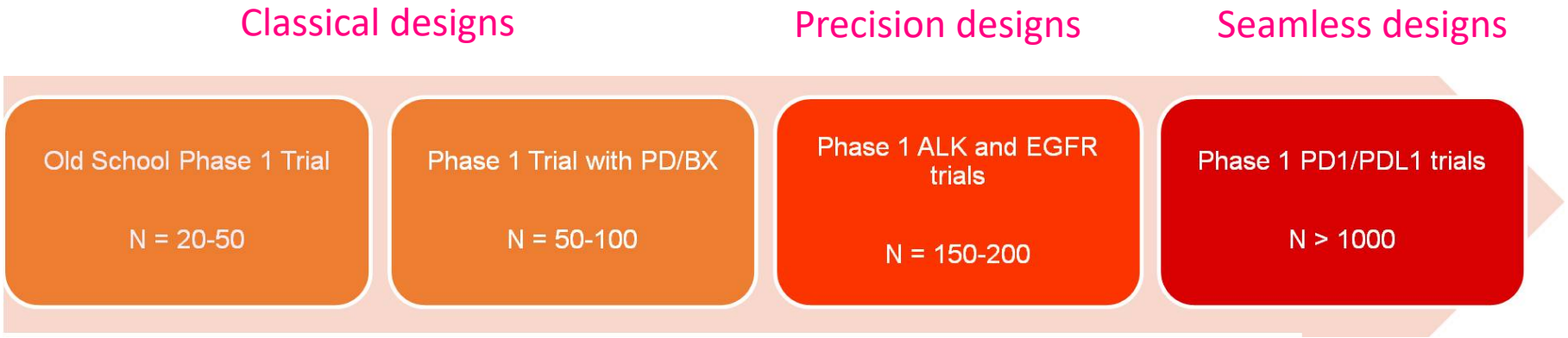
- New endpoints in Early Phase: costs, PROs, efficacy…
- Re-building of Clinical Trials programs
  - Sophisticated low-volume “three-star Michelin” plus very efficient high-volume “McDonalds franchise” in same restaurant!
  - Different tumor type populations
    - Knowledge and expertise needed
    - Synergy early/late phase programs

What's next



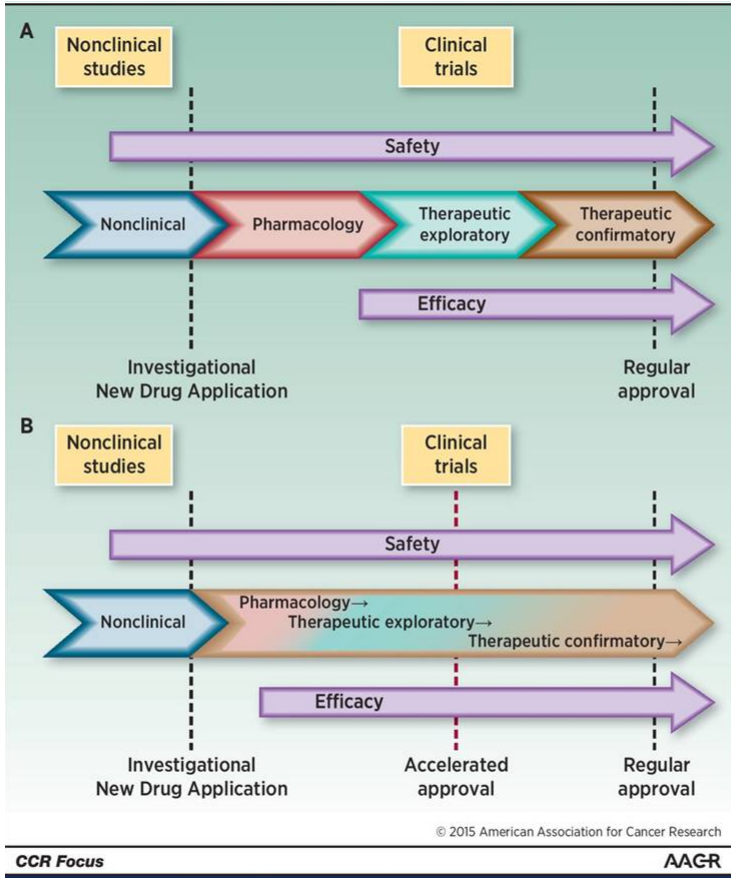
Jean-Charles Soria
at 2015 ECCO meeting

Revolution in clinical studies designs



Fast-track designation or even regulatory approval
might be a potential goal now:
<u>These novel designs allow for good drugs to show early how good they are</u>!

Revolution in clinical trials designs



Will the future provide us with only two types of studies?:

- *Non-randomized Studies* (“old” Ph1/2), for great well-defined drugs
- *Randomized Studies* (”old” Ph 3), for drugs that are not that good or understood

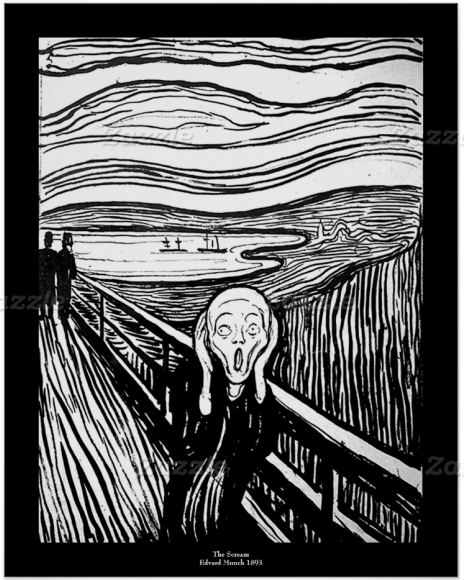
Theoret M,
Clinical Cancer Research, 2015

Regulatory driver impulse

- Regulatory agencies lately allow for quicker access of patients to innovative drugs
  - Outstanding signal of activity in Ph1/2 might be enough for breakthrough designation or conditional approvals
  - Increasing number of approved novel drugs to compete against each others
- However, the real medical value is to be confirmed with randomized studies after fast-track conditional approval
  - Is it ethical? How to do it?
- Still, faster approval does not bring lower prices and wider access to drugs
  - Fixed high prices
  - Disconnection between value and cost

Price and Value

100 million Euros



10 Euros

Drug Access market:

- Highly interventional
- We need a libertarian open-market revolution

"Todo necio confunde valor y precio" (Antonio Machado)

Price and Value

Investigational hospitals

Artificial Intelligence

BIG DATA

“Drugs for patients” instead of ”Patients for drugs”