Come vengono scoperti i nuovi farmaci?

Strategie pre-cliniche per identificare potenziali candidati farmaci:

- Screening basato sul target

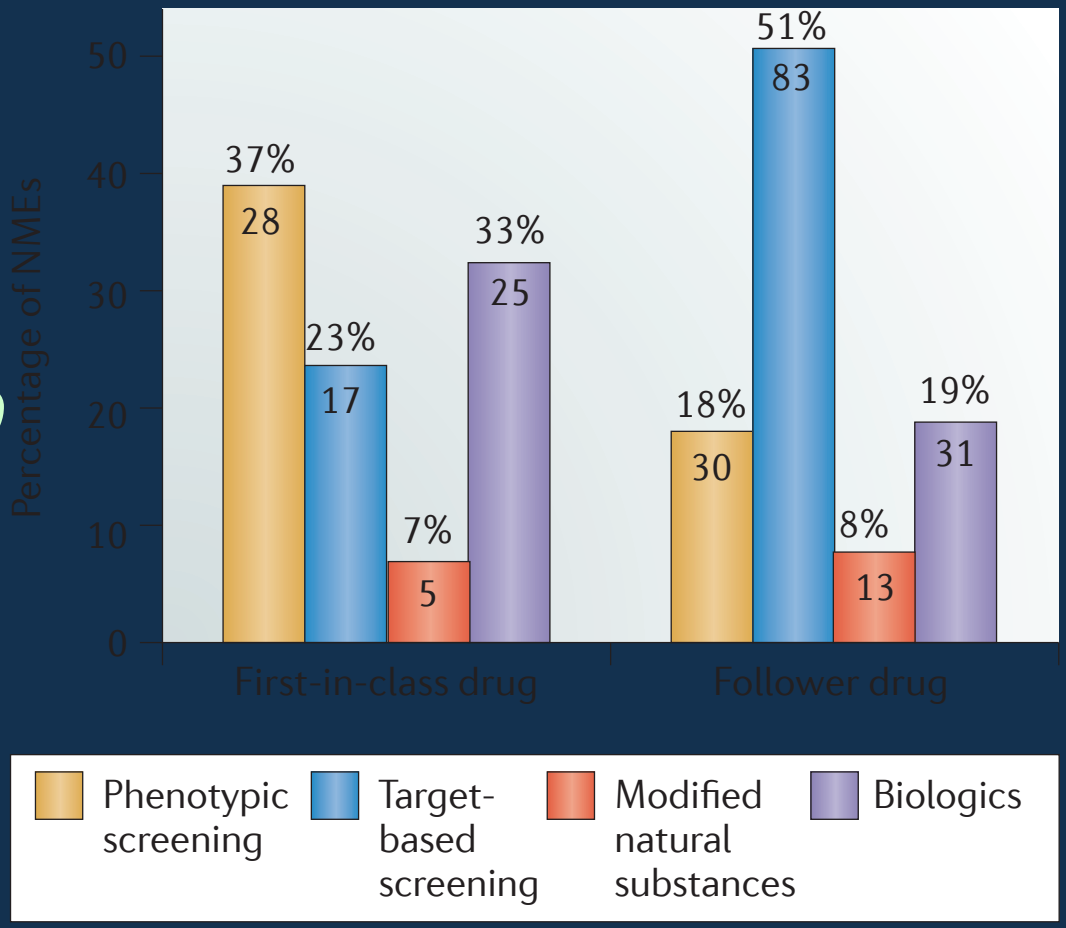
- Screening fenotipico

- Modificazione di sostanze naturali

- Approccio basato sulla biologia

Nuovi farmaci approvati dalla FDA nel periodo 1999-2008

Totale: 259



First-in-class con nuovo MMOA: 75 (50 piccole molecole; 25 biologici)

28 piccole molecole e 17 biologici scoperti con "Screening fenotipico"

MMOA (Molecular Mechanism Of Action)

Meccanismi cinetici

- Equilibrium binding – rapido k_{on} e k_{off}: competizione con substrati/ligandi fisiologici (es.: aliskiren)
- Cinetica lenta – lento k_{on} e k_{off}: non-equilibrio quindi non compettitivo con ligandi/substrati fisiologici (es.: candesartan)

Meccanismi conformazionali

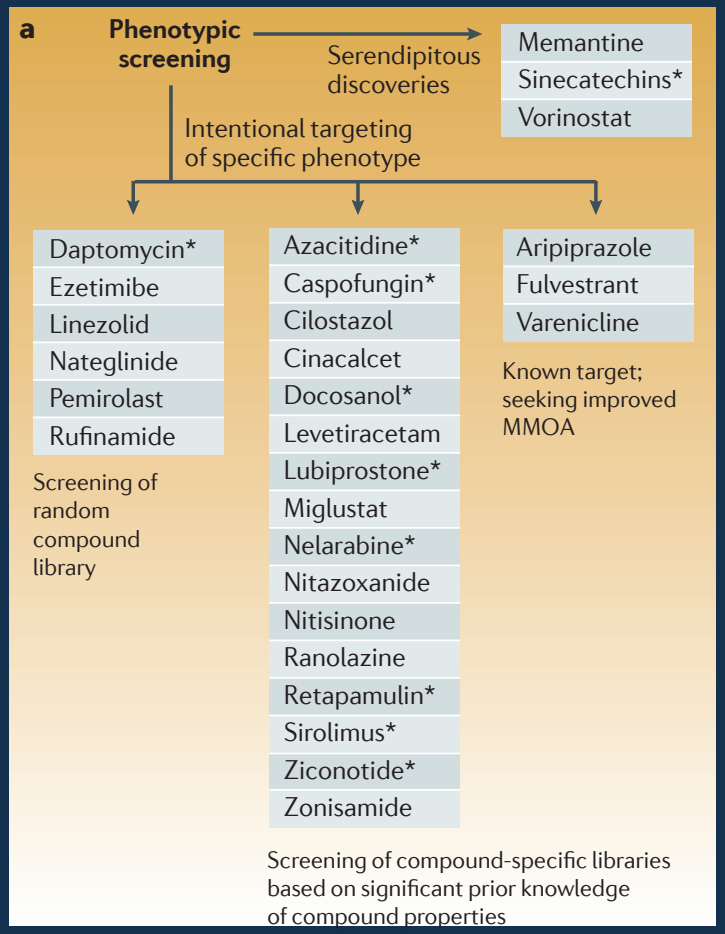
- "Noncompetitive inhibition" e/o antagonismo
- "Uncompetitive inhibition" e/o antagonismo – antagonismo solo dopo attivazione del target e ad alte dosi (es.: memantina e NMDA-glutammato)
- Agonismo pieno (es.: ramelteon agonista recettore di melatonina)
- Agonismo parziale (es.: aripiprazolo agonista parziale D2)
- Modulazione allosterica (es.: cinacalcet allosterico dei recettori per il Ca^{+2})

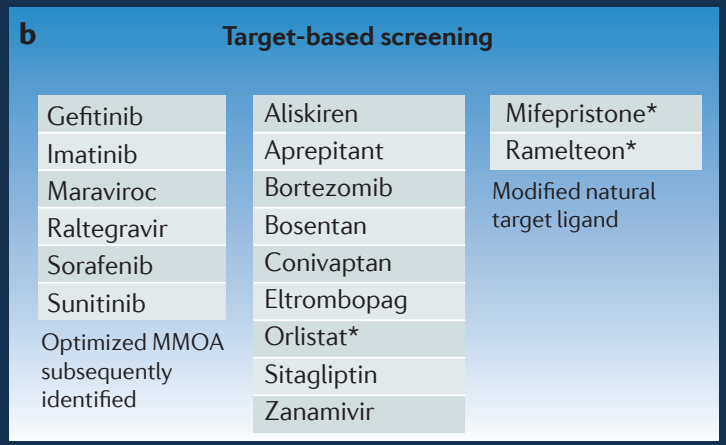
Meccanismi RedOx

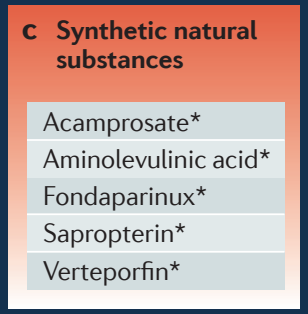
- (es.: nitazoxanide interferisce con piruvato/ferredoxina ossidoreduttasi, essenziale per metabolismo energetico protozoi)

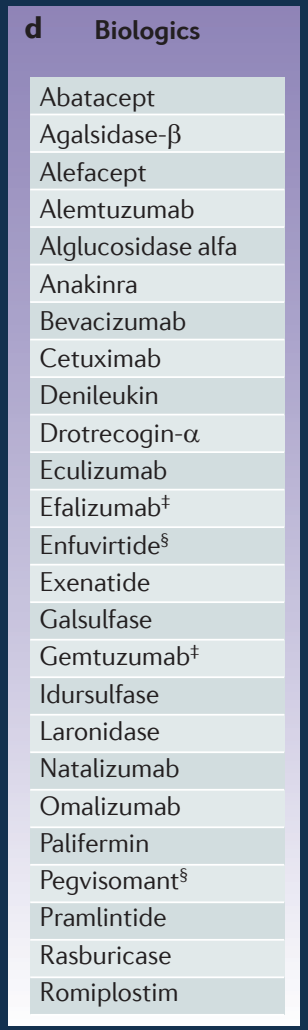
Table 1 | **First-in-class small-molecule new molecular entities approved by the FDA: 1999–2008**

Drug (trade name; company)	Therapeutic area	Target type	Molecular mechanism of action	Refs
Discovered through phenotypic screening				
Aripiprazole (Abilify; Bristol-Myers Squibb/Otsuka Pharmaceutical)	CNS	Receptor	Conformational/partial agonist	74,75, 80–84
Ezetimibe (Zetia; Merck)	Cardiovascular	Transporter	Slow binding kinetics	30
Cinacalcet (Sensipar; Amgen)	Metabolic	Receptor	Allosteric activator	29
Memantine (Namenda; Forest)	CNS	Receptor	Uncompetitive and fast binding kinetics	101–103
Nelarabine (Arranon; GlaxoSmithKline)	Cancer	DNA (nucleoside analogue)	Nucleotide chain termination	109–113
Retapamulin (Altabax; GlaxoSmithKline)	Infectious disease	Enzyme	Allosteric inhibitor	122
Vorinostat (Zolinza; Merck)	Cancer	Enzyme	Equilibrium kinetics	127,128
Discovered through target-based screening				
Aliskiren (Tekturna; Novartis)	Cardiovascular	Enzyme	Equilibrium binding	38,130
Aprepitant (Emend; Merck)	Gastrointestinal	Receptor	Slow binding kinetics	46
Gefitinib (Iressa; AstraZeneca)	Cancer	Enzyme	Stabilize inactive conformation	41,42
Imatinib (Gleevec; Novartis)	Cancer	Enzyme	Stabilizes inactive conformation	49
Sorafenib (Nexavar; Bayer)	Cancer	Enzyme	Conformation state-specific inhibition	44
Sunitinib (Sutent; Pfizer)	Cancer	Enzyme	Conformation state-specific inhibition	147–150
Zanamivir (Relenza; GlaxoSmithKline)	Infectious disease	Enzyme	Equilibrium binding	34,151
Discovered based on natural substrate or natural substance				
Acamprosate (Campral; Merck)	CNS	Ion channel	Conformational channel modulator	152
Aminolevulinic acid (Levulan; Berlex)	Dermatology	NA (photosensitizer)	Redox	153,154
Fondaparinux (Arixtra; Sanofi)	Cardiovascular	Enzyme	Irreversible	155–157
Sapropterin (Kuvan; BioMarin)	Rare diseases	Enzyme	Cofactor	158–161
Verteporfin (Visudyne; QLT)	Ocular	NA (photoreaction)	Redox	77,162



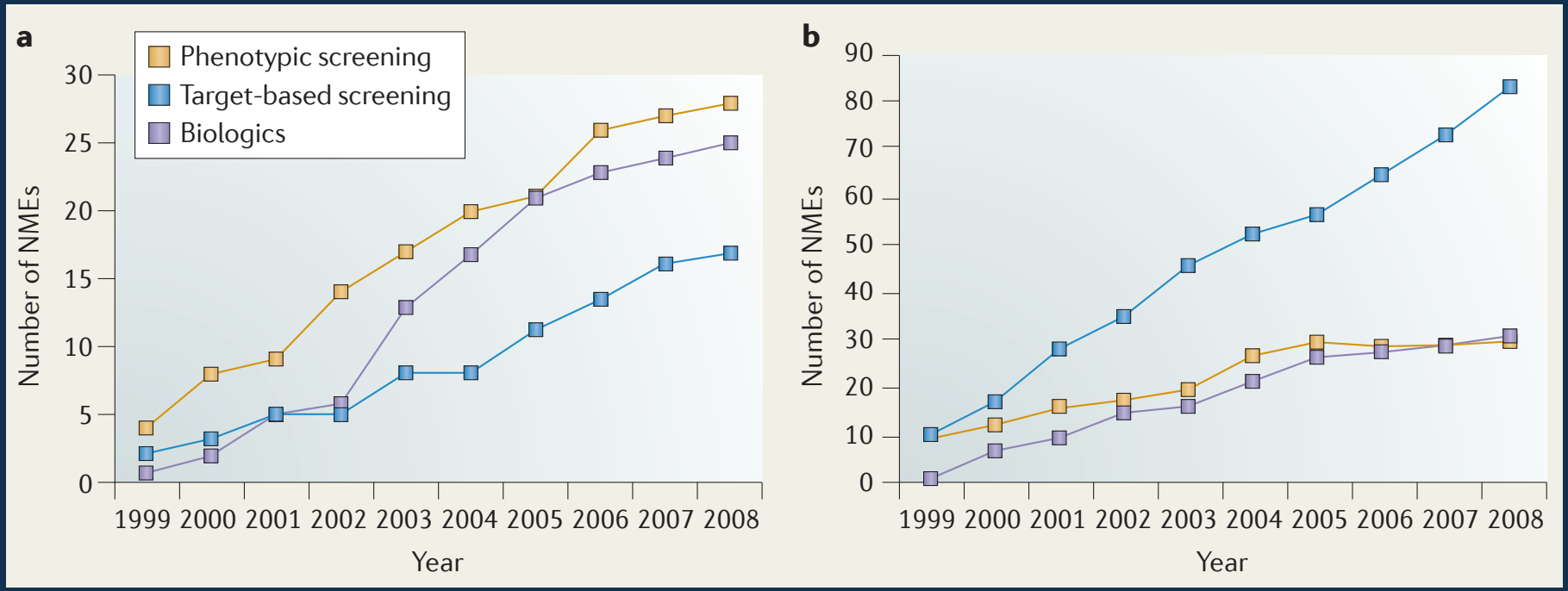






Drugs that were identified through target-based screening that involved optimization of a natural ligand or identification of the optimal MMOA are highlighted. *Drugs that are derived from natural substances. ‡These medicines have been withdrawn from the market. §Although enfuvirtide and pegvisomant were approved as new molecular entities, for the purpose of this analysis they have been treated as biologics, given that they are both much larger than typical small-molecule drugs

Cumulative distribution of new drugs by discovery strategy.



a: first-in-class

b: followers

Efficienza biochimica

The dose of a drug required to achieve the desired physiological response depends on its biochemical efficiency[10,11]. This is defined as 'binding affinity/functional response', which is equivalent to K_i/EC_{50} (effector concentration for half-maximal response). Good biochemical efficiency enables efficacy at lower drug concentrations and increases the therapeutic index. It is a property of many approved medicines[10,11].

There are many factors that can influence the shift in dose–response curves between binding and functional assays, including:

- Pharmacokinetics and ADME (absorption, distribution, metabolism and excretion) properties
- Assay relevance (is the functional assay appropriate for the target? Are the assays technically accurate?)
- The involvement of the target in the functional readout and biology
- The molecular mechanism of action (MMOA)

Although all of these factors can and do contribute to the relationship between binding affinity and the functional response, the role of the MMOA is not always considered. The concept of biochemical efficiency was introduced to quantify this possibility[10,11]. When biochemical efficiency is used as a measure of an optimal MMOA, it is important that the other mitigating factors are eliminated. For example, when evaluating biochemical efficiency, the assays must be run in the absence of serum (or plasma) to eliminate the shift in IC_{50} (half-maximal inhibitory concentration) owing to serum protein binding.