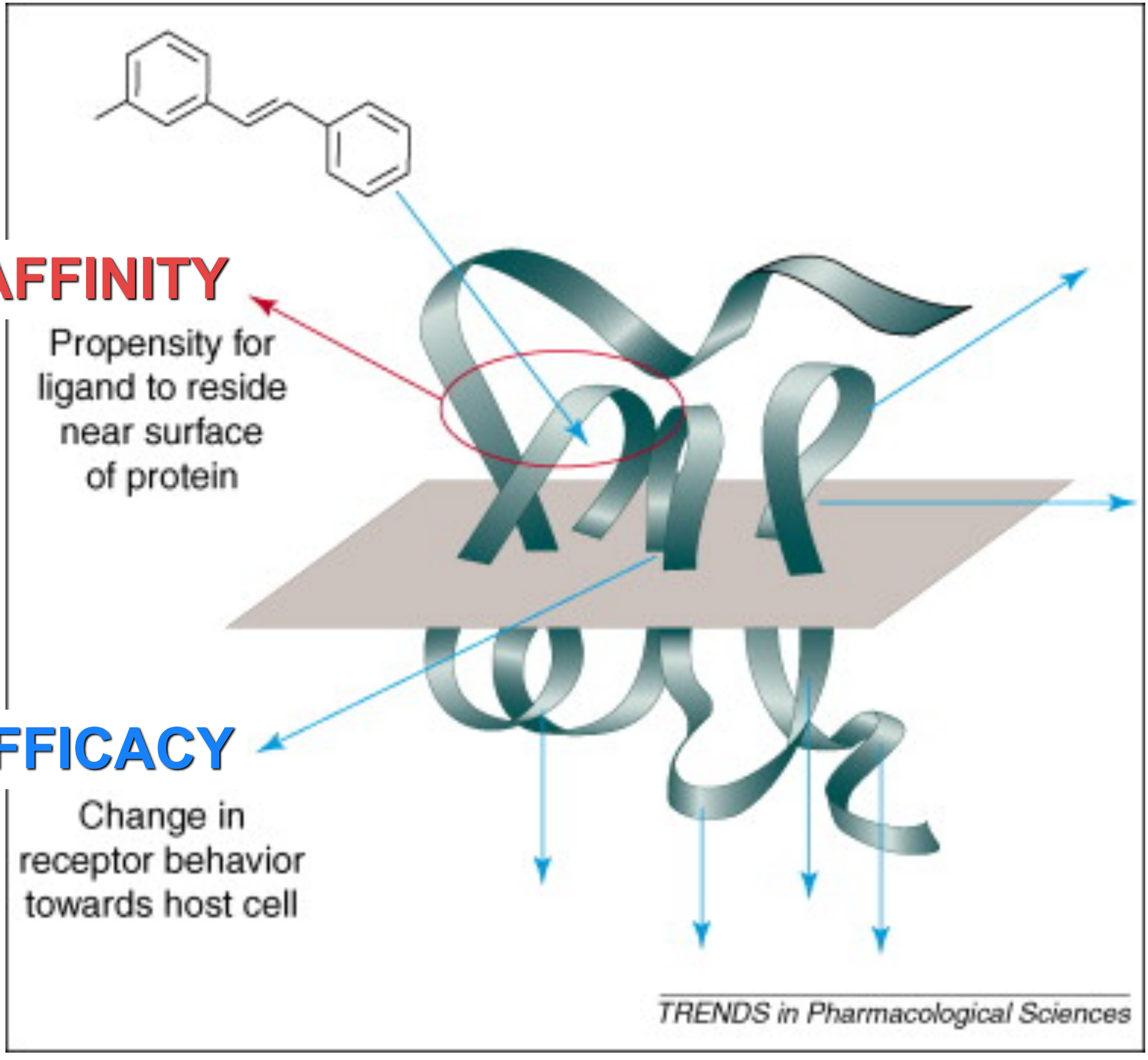
Pharmacodinamic

AFFINITY

the strength of interaction between a drug and its binding site

EFFICACY

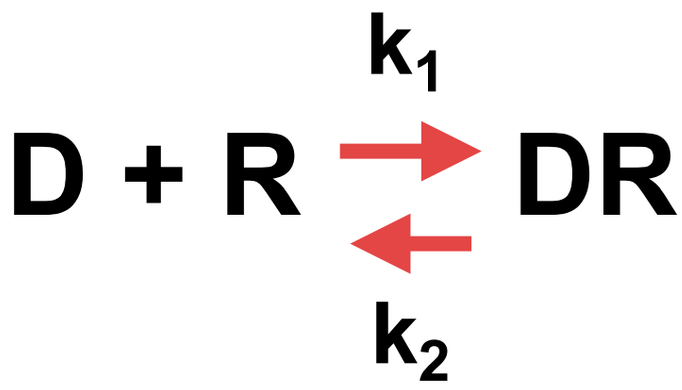
the ability of a drug to change receptor conformation to produce a cellular response


AFFINITY
Propensity for ligand to reside near surface of protein
EFFICACY
Change in receptor behavior towards host cell
TRENDS in Pharmacological Sciences

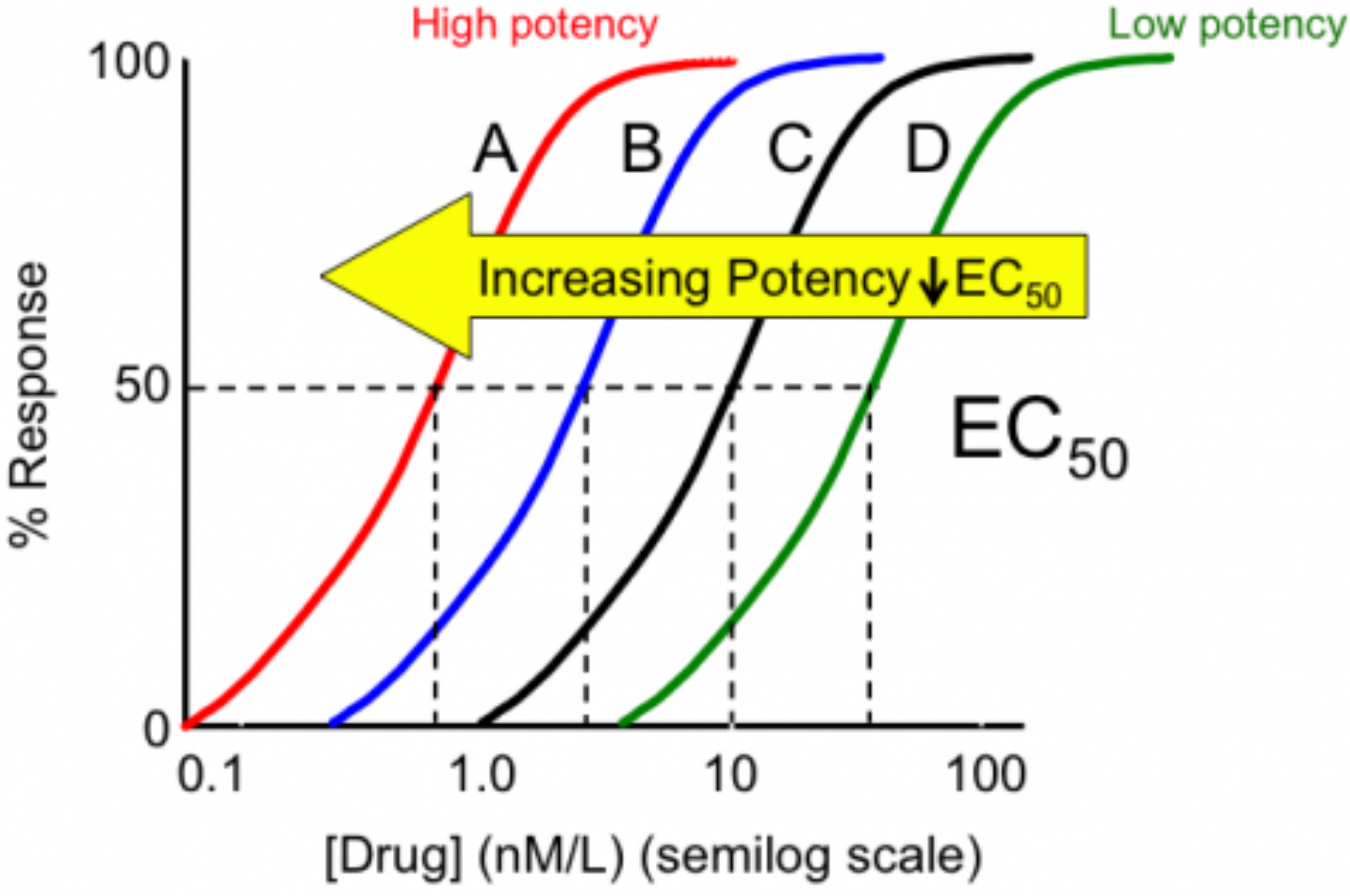
DRUG-RECEPTOR THEORY

The effect of a drug D is the consequence of its binding to the receptor R

The intensity of the effect is proportional to the complex [DR]



Concentration-Response Curves: EC50 and Order of Potency



The true AFFINITY of a drug for its receptor is given by the Dissociation Constant Kd

- **Kd is the drug concentration that occupies 50% of receptors at the equilibrium**

- **Unit: molar concentration**

- **Kd value is determined by radioligand binding experiments**

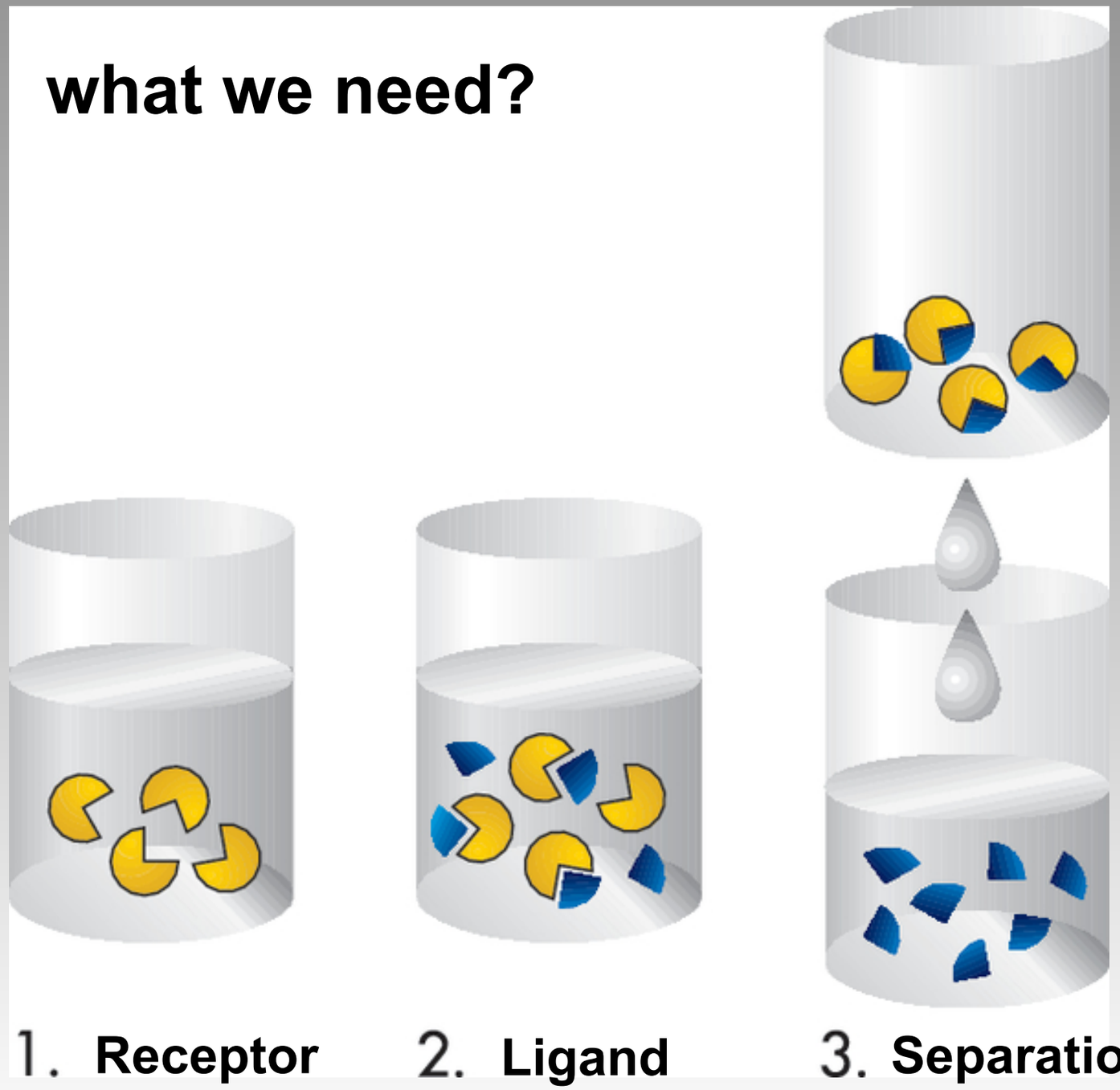
THE RADIOLIGAND BINDING TECHNIQUE TO INVESTIGATE DRUG-RECEPTOR INTERACTION

A direct measurement of the binding of a molecule to its receptor can be obtained if it is possible to:

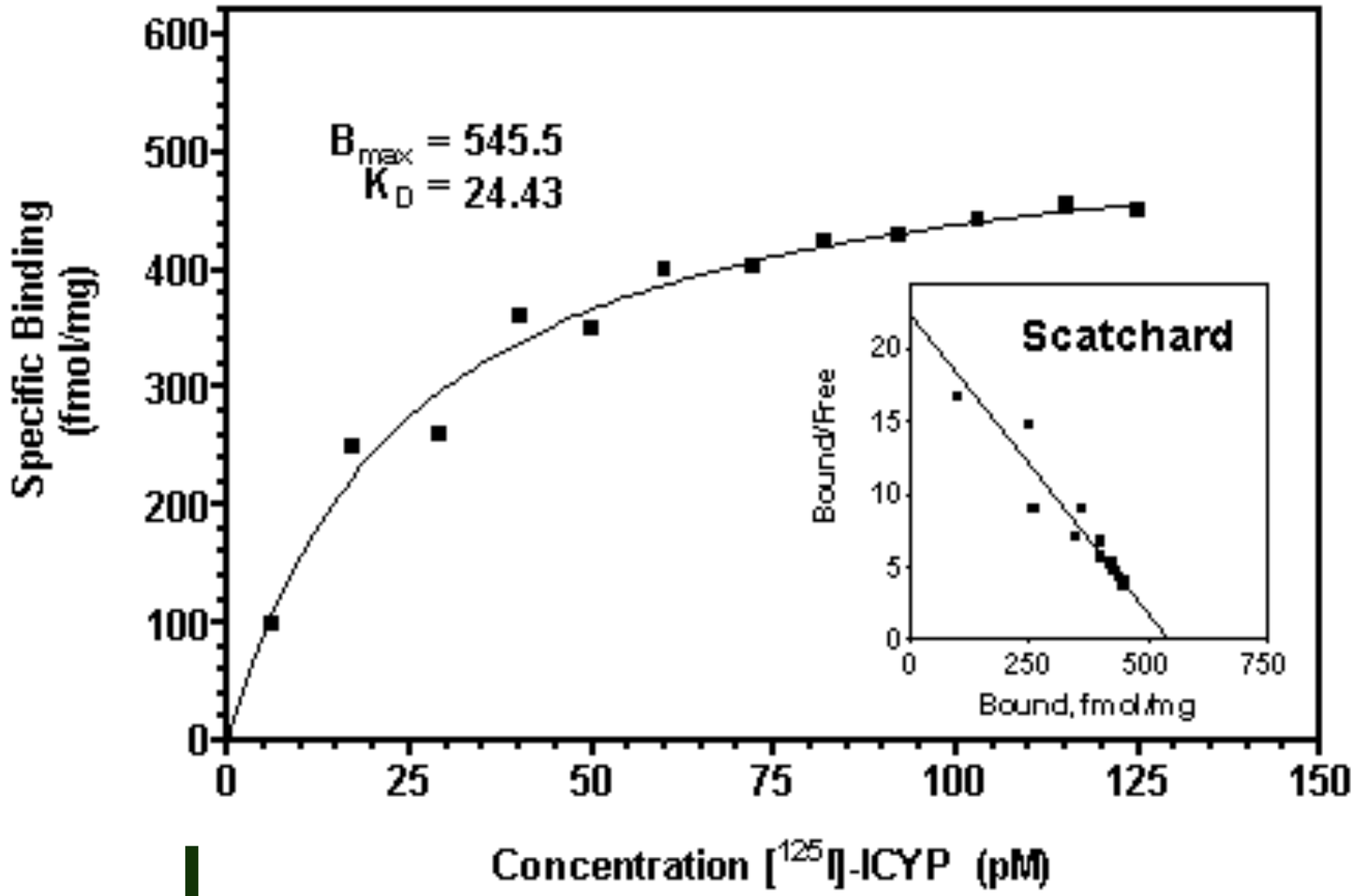
1. Distinguish the drug bound from the unbound (free)

2. Quantify the bound (labelled with ^{3}H or ^{125}I)

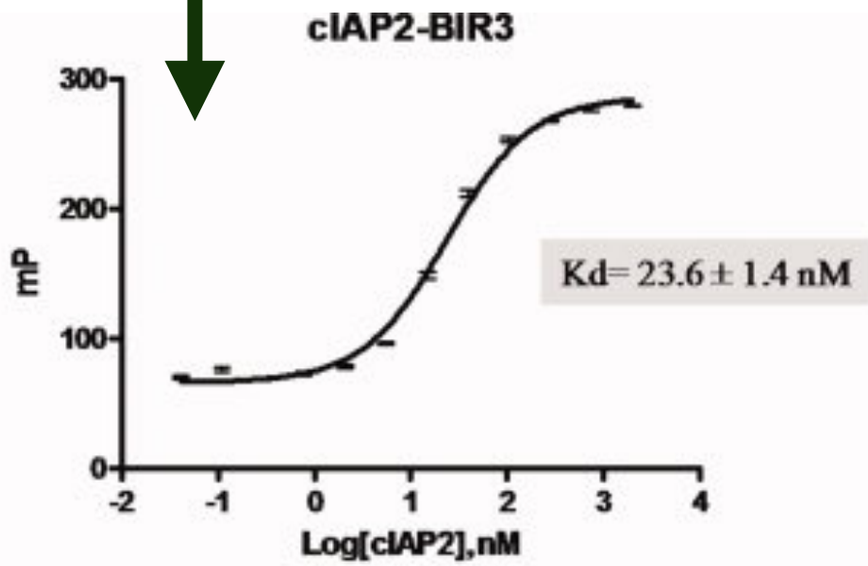
what we need?

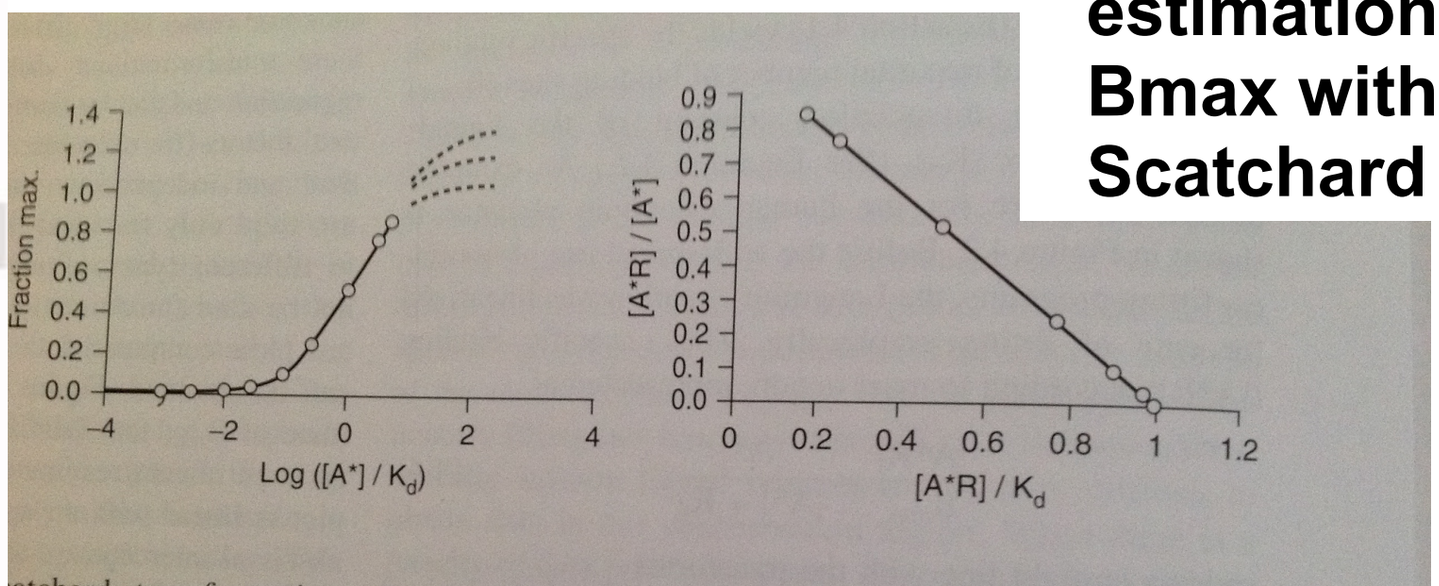


SATURATION EXPERIMENT



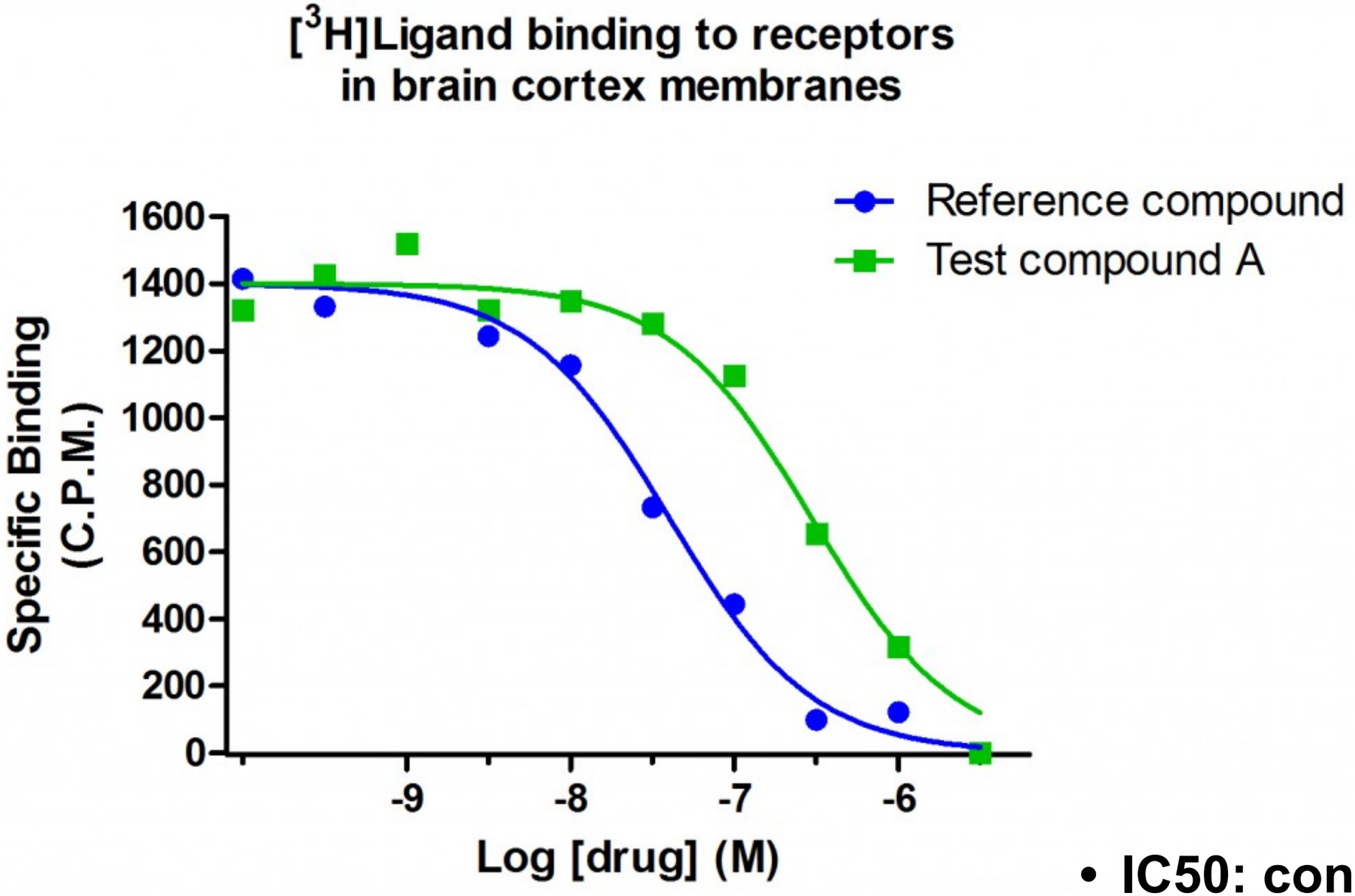
- **Bmax is the maximal binding capacity of a preparation (membranes, cells) containing receptors**





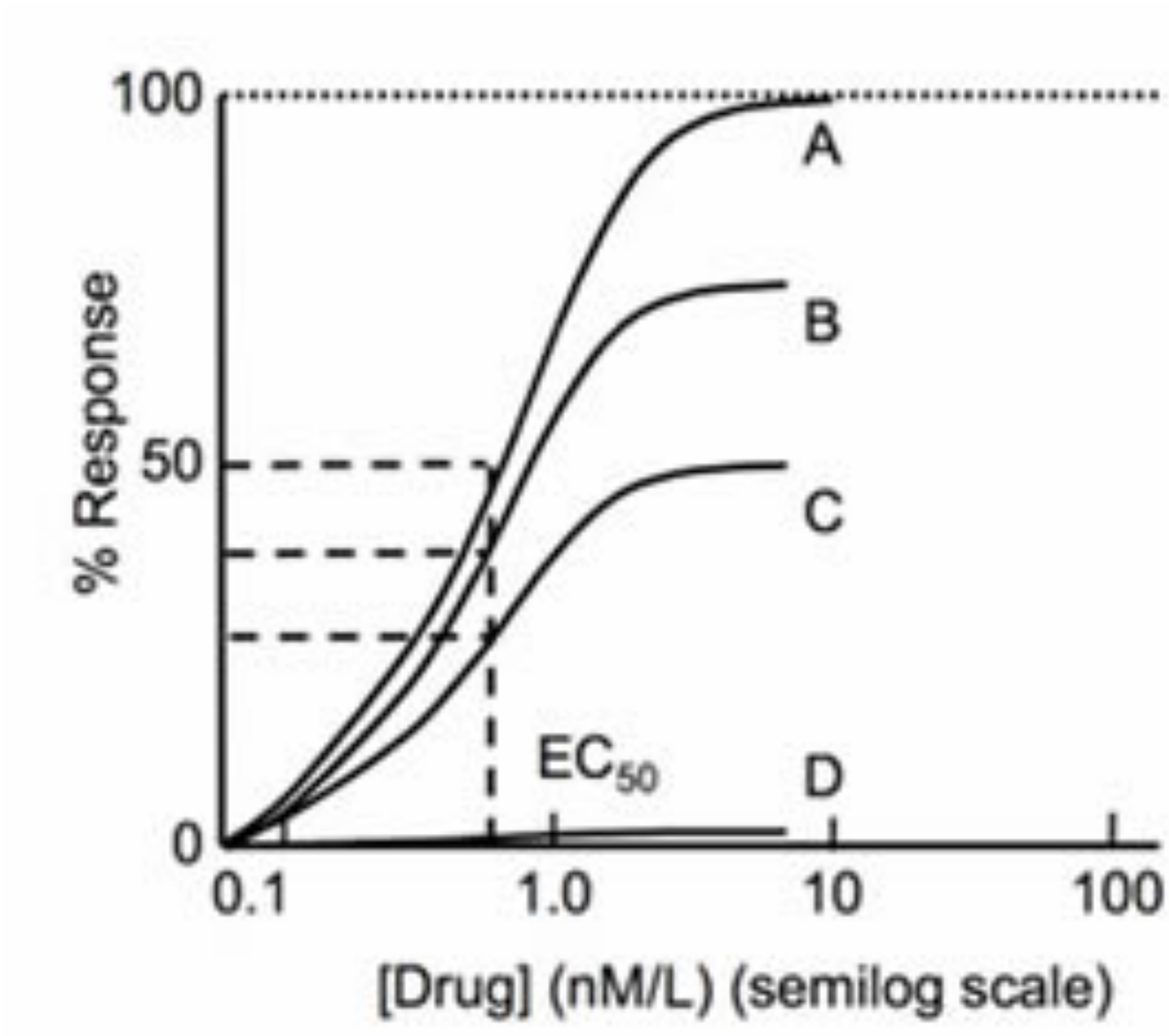
- **Erroneous estimation of Bmax with Scatchard plot**

COMPETITION EXPERIMENT



- **IC50: concentration of a drug that reduces by 50% the maximal binding of a labelled reference compound (relative value)**

Concentration-Response Curves: EFFICACY



A: FULL AGONIST

B: PARTIAL AGONIST

C: PARTIAL AGONIST

D: ANTAGONIST

DRUG-RECEPTOR THEORY

The effect of a drug D is the consequence of its binding to the receptor R

The intensity of the effect is proportional to the complex [DR]

$$D + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR$$

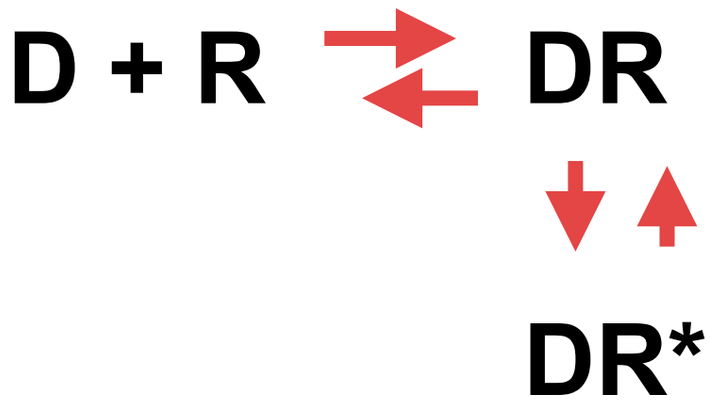
Effect = α [DR] with α a constant named intrinsic activity or efficacy

Efficacy or Intrinsic activity

- **efficacy α is a measure of the response that can be obtained in a tissue with a drug**
- **Increase of drug concentrations does not Increase drug effect**
- **α value ranges from 1 to 0 (is the percentage between the maximal effect of the drug and the maximal effect that can be obtained in that tissue)**

$$\frac{\text{\% effect of partial agonist}}{\text{\% effect of full agonist}} \qquad \frac{80\%}{100\%} = 0{,}8$$

Partial agonism and antagonism

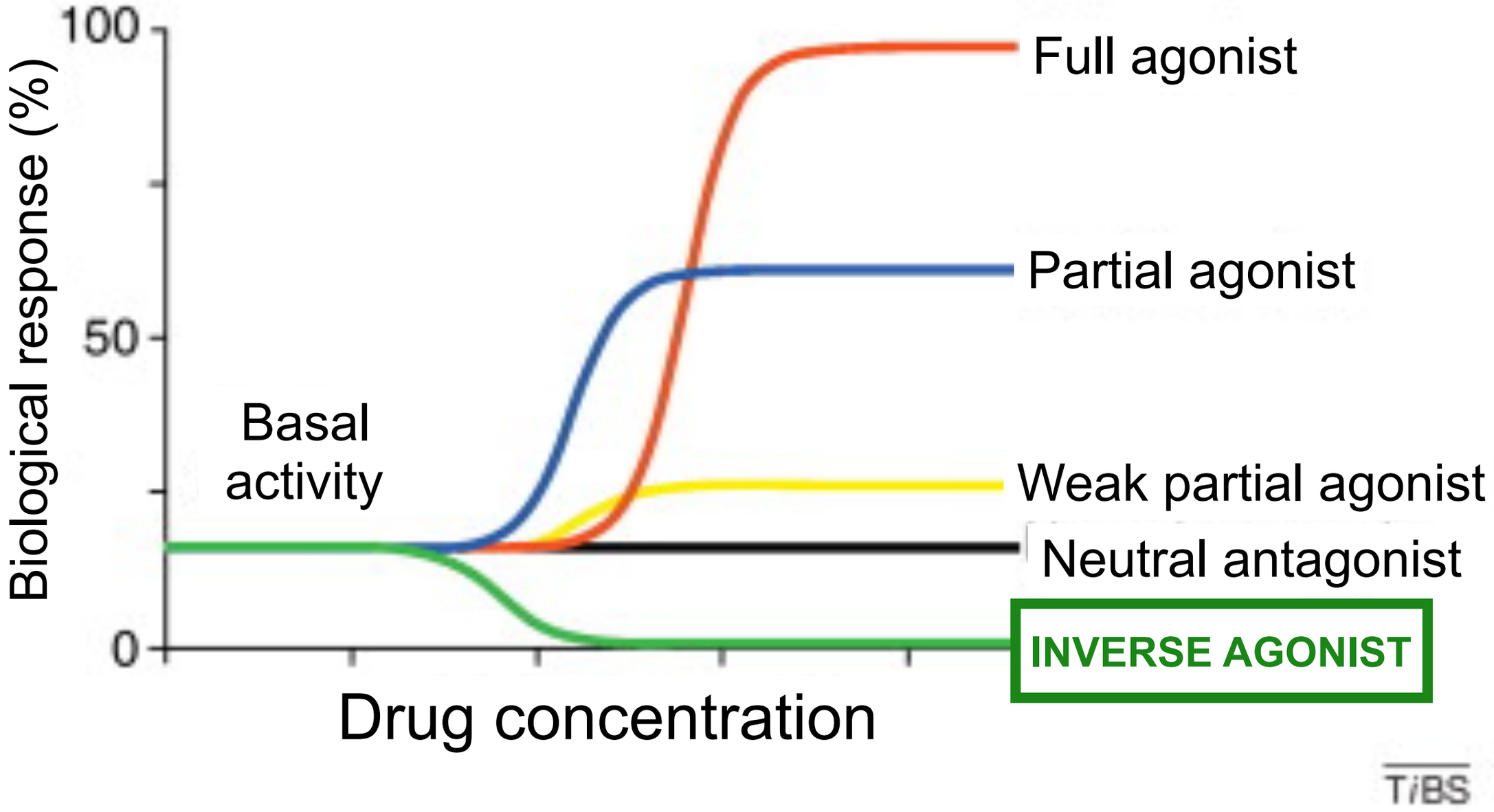


Full agonist: a ligand that produces the maximal response in that tissue

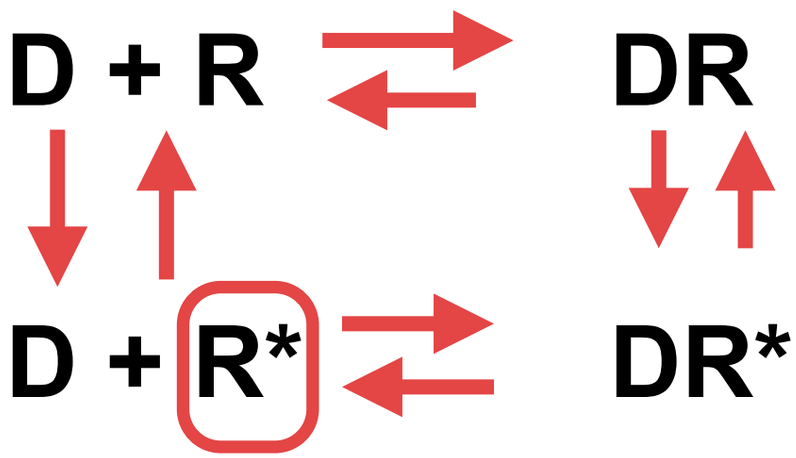
Partial agonist: a ligand that produces a submaximal response in that tissue

Antagonist: a drug that binds to the receptor but produces no response

Inverse agonism



Inverse agonism



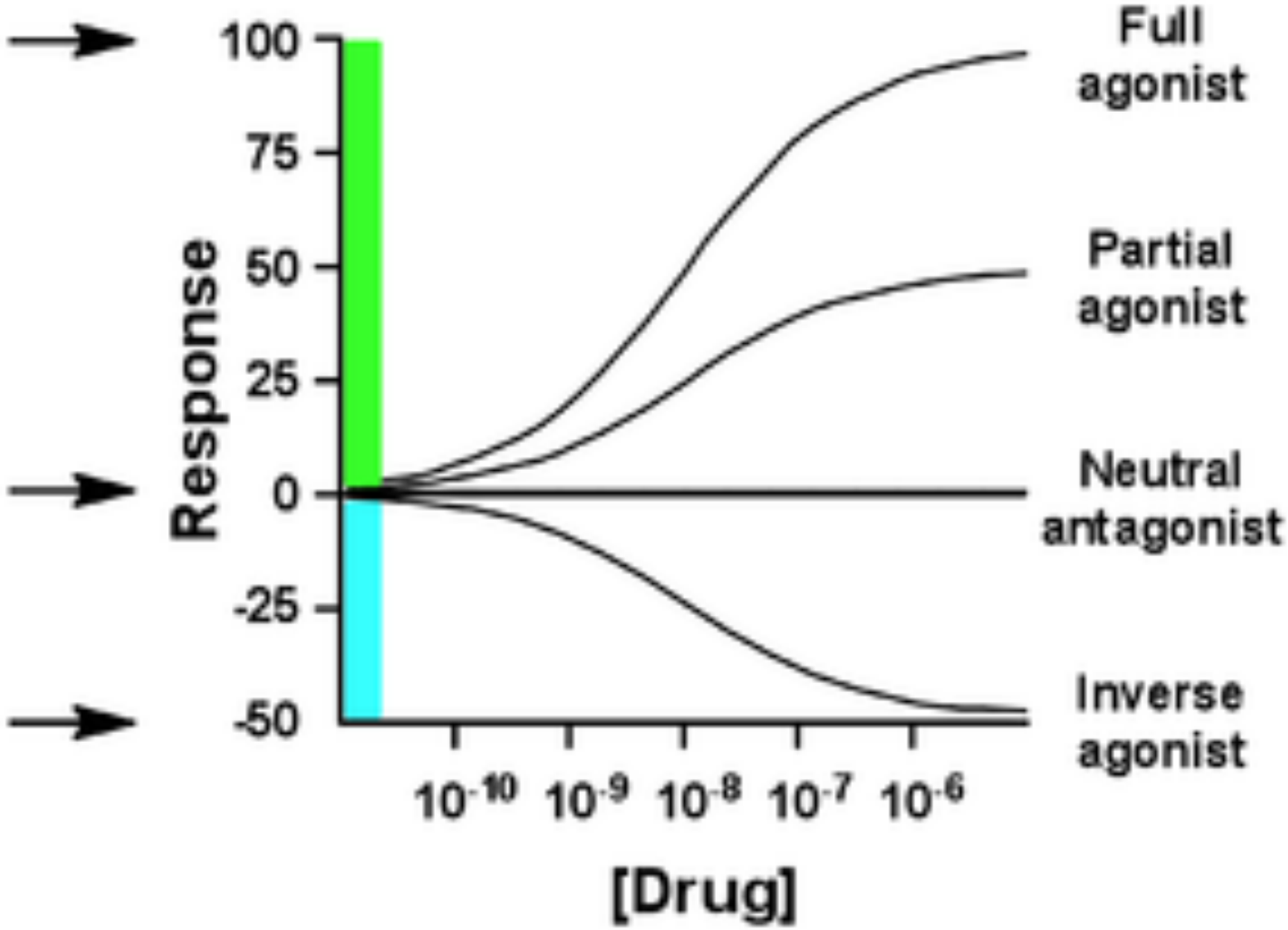
The constitutively active receptor R* is active in absence of endogenous ligand

Inverse agonist: a ligand that reverses constitutive receptor activity R*

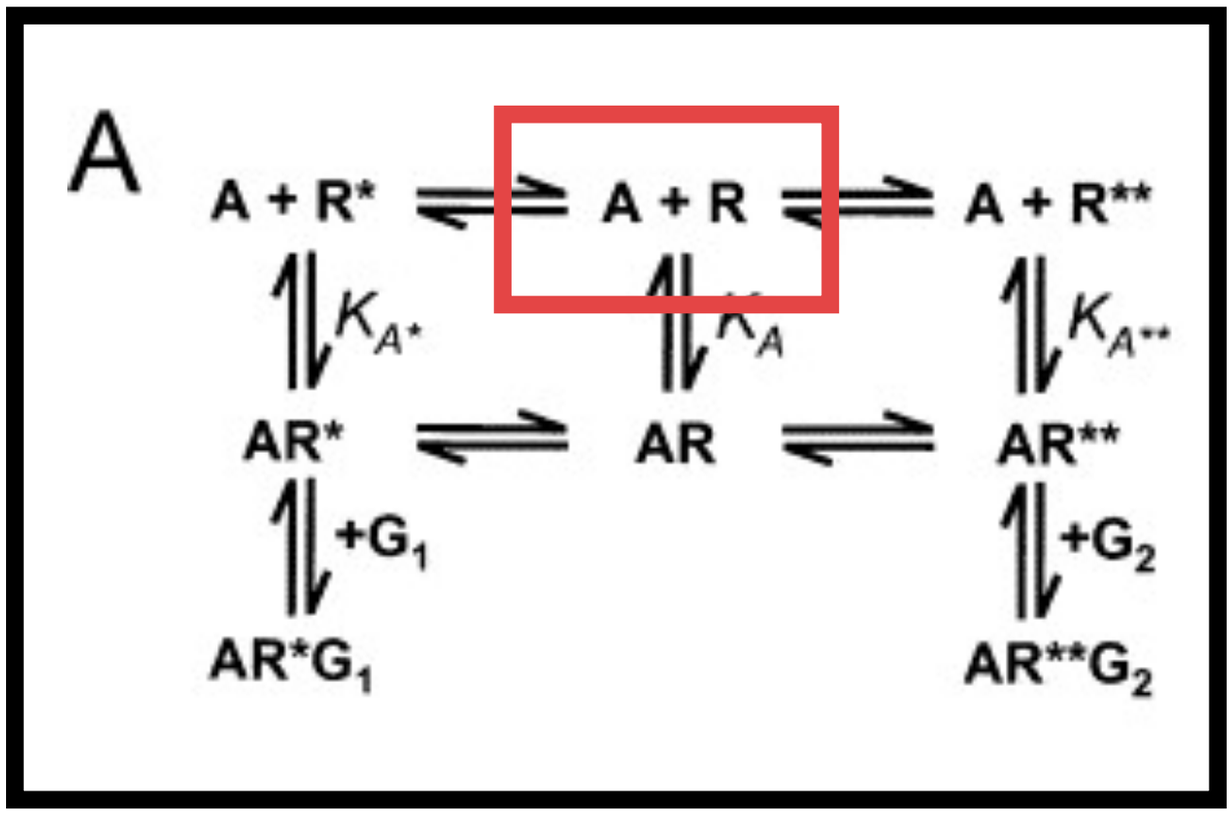
Inverse agonist binds preferentially to R altering the equilibrium R - R*

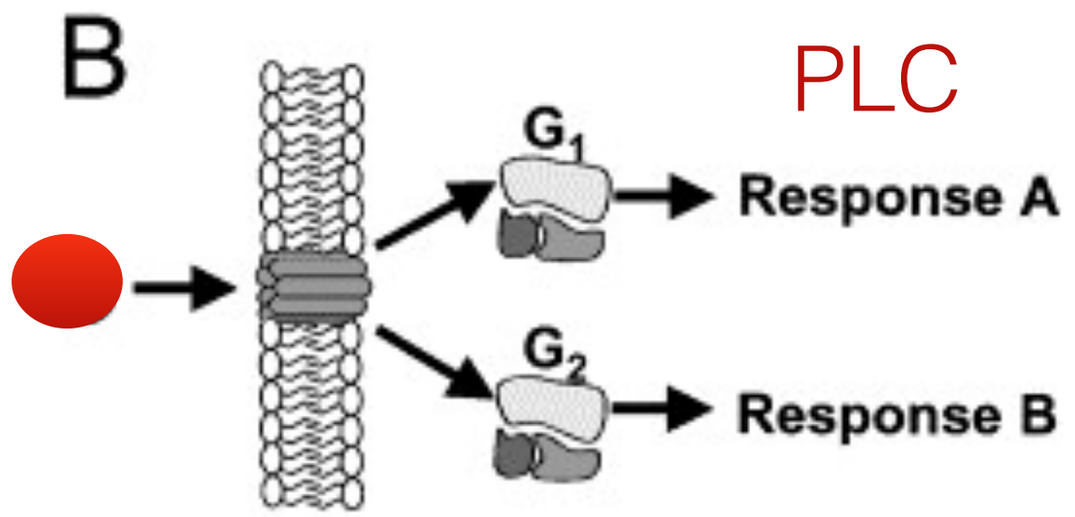
Inverse agonism

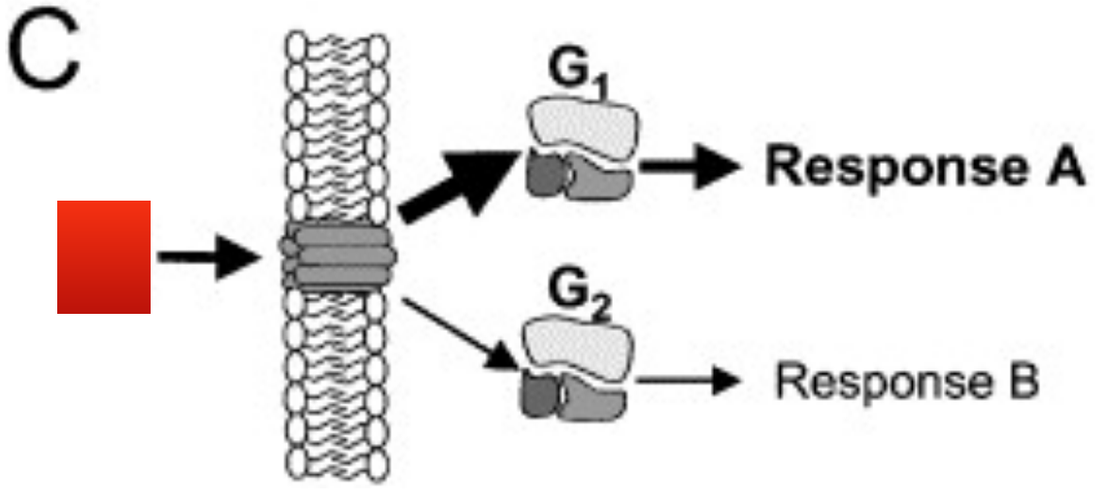
Constitutive activity of receptor in absence of endogenous ligand

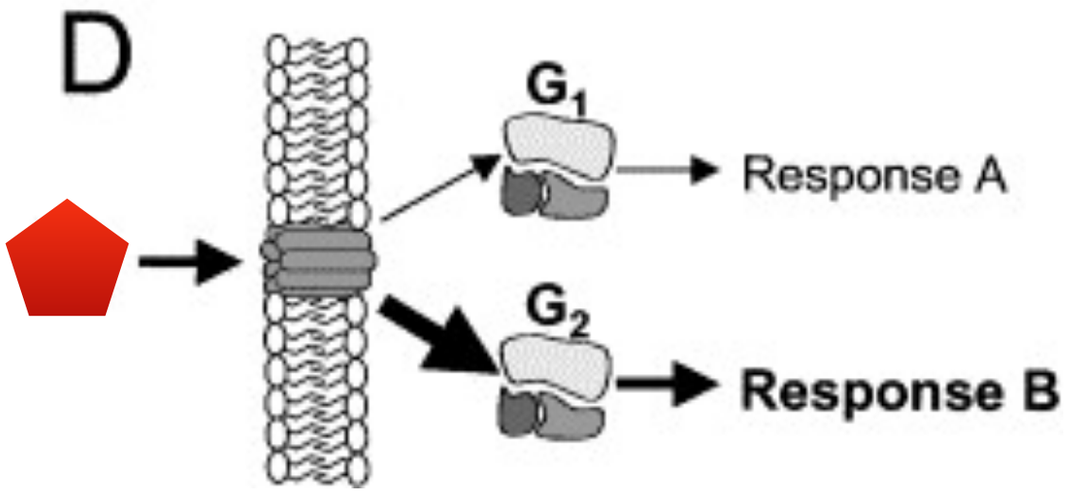


BIASED AGONISM
or
LIGAND-SELECTIVE FUNCTIONAL AGONISM



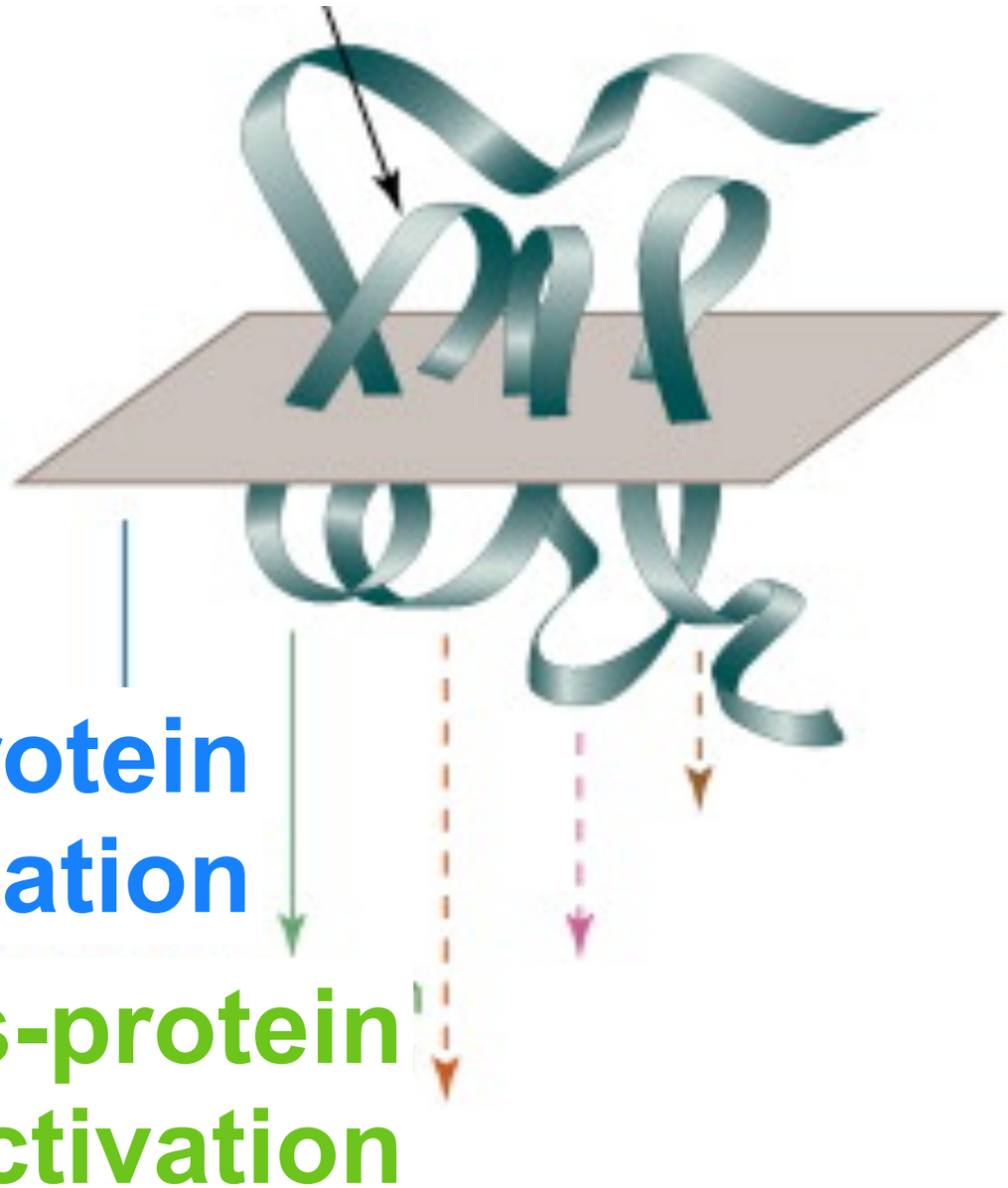






BIASED AGONISM

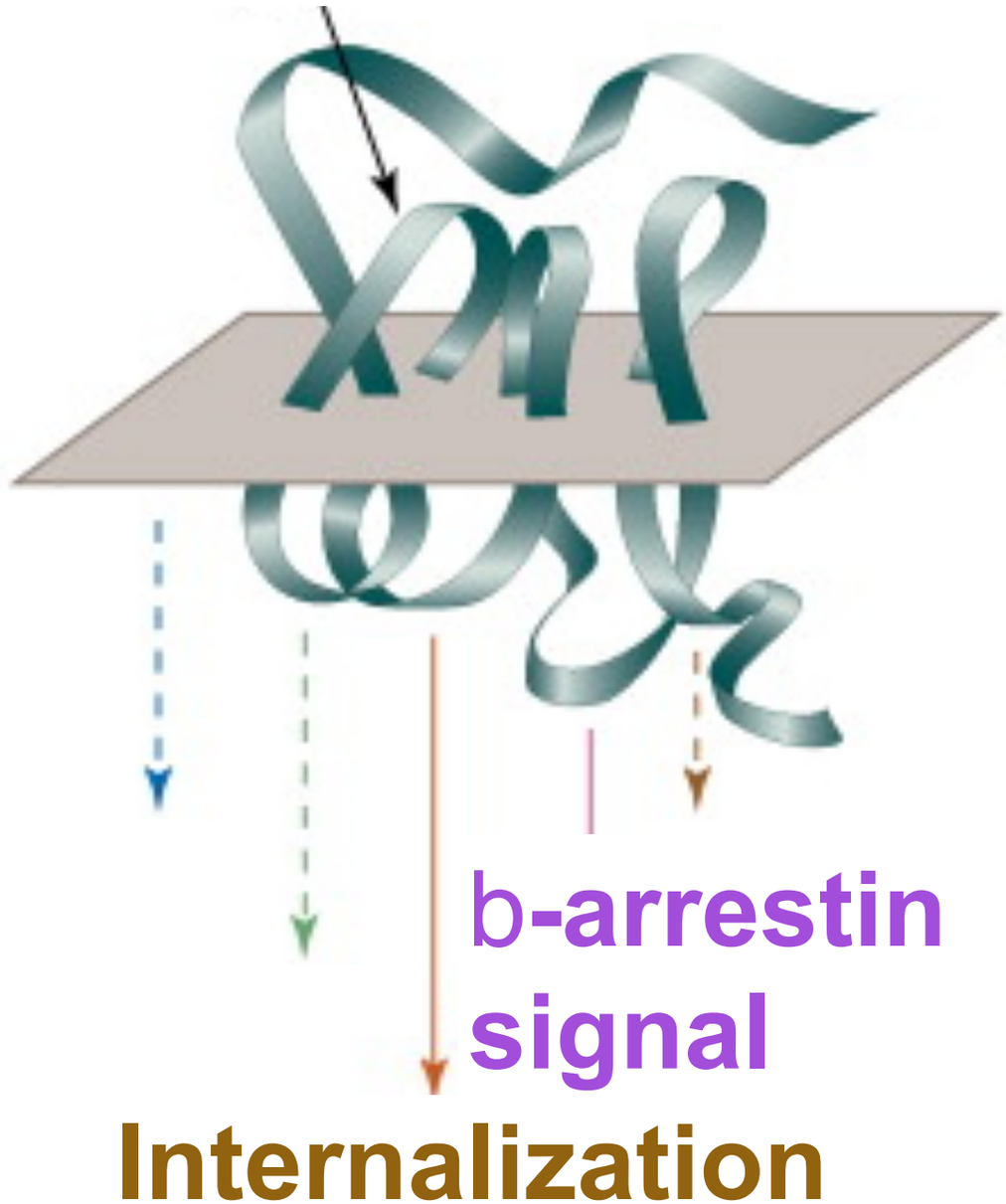
Biased agonist A



Gi-protein Activation

Gs-protein Activation

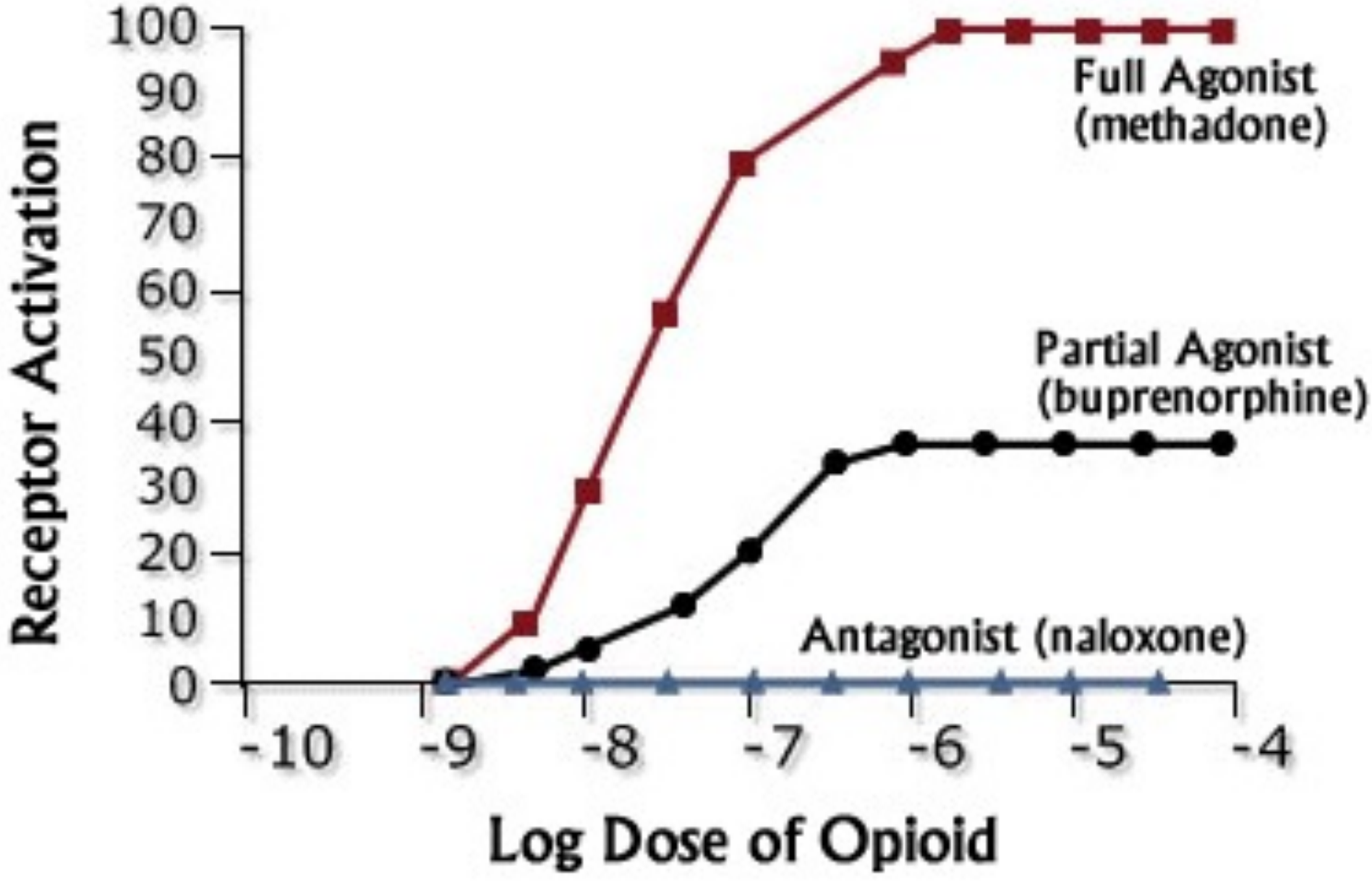
Biased agonist B

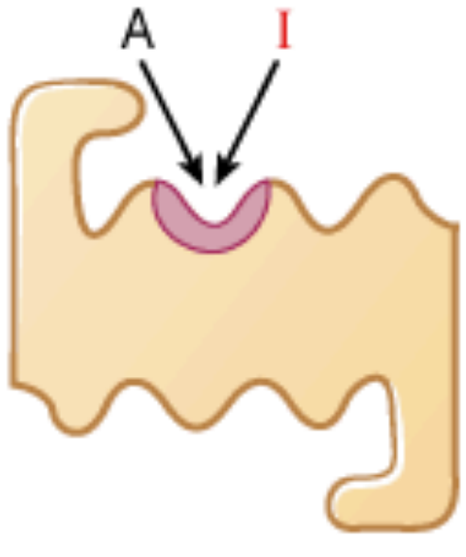


b-arrestin signal

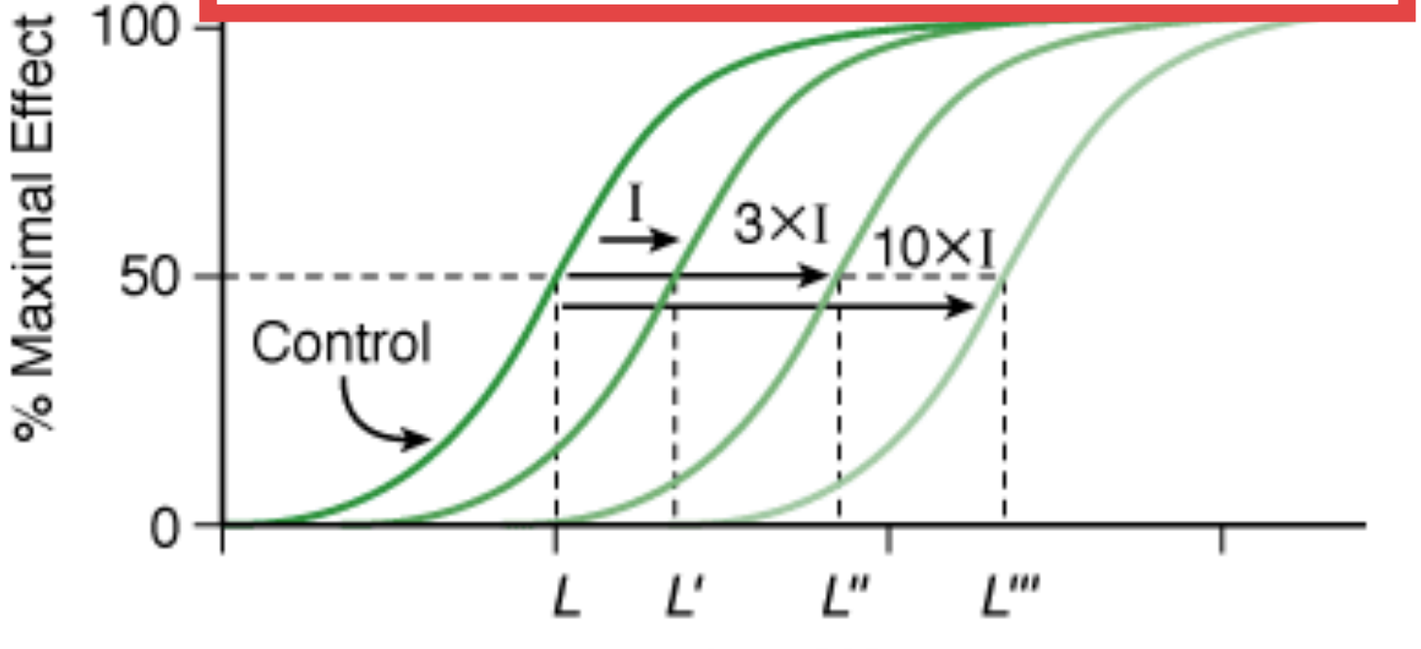
Internalization

Receptor Activation:
Full Agonist, Partial Agonist, Antagonist

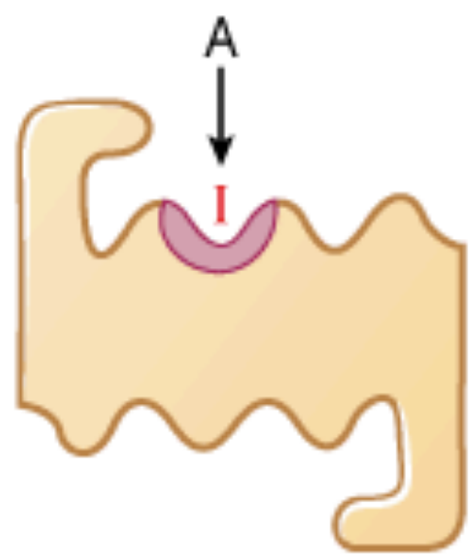


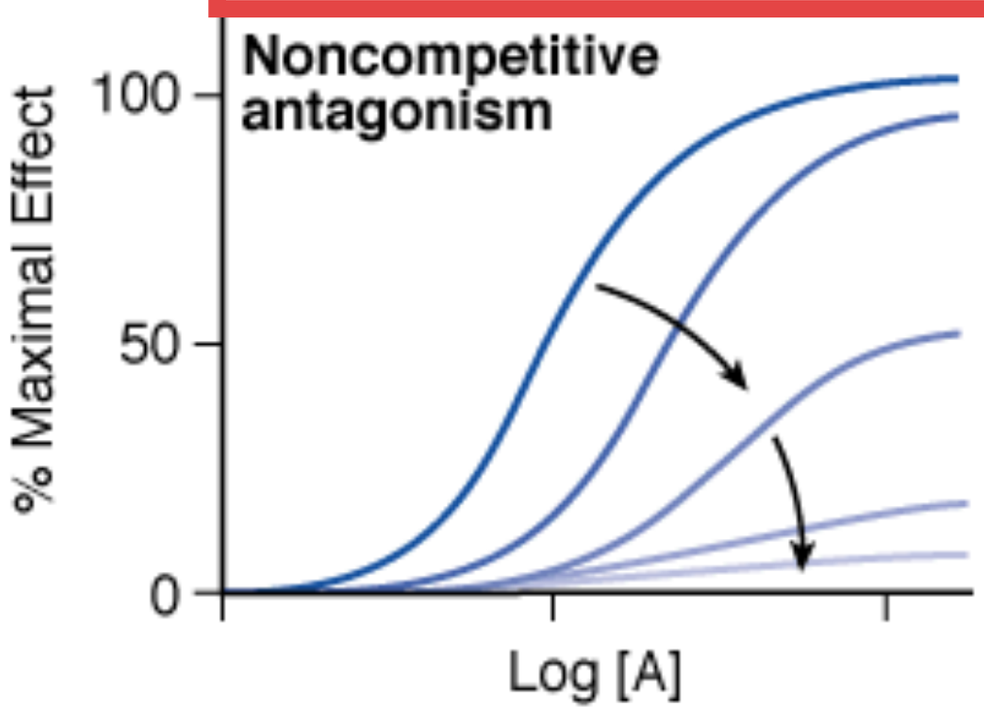


Competitive antagonism

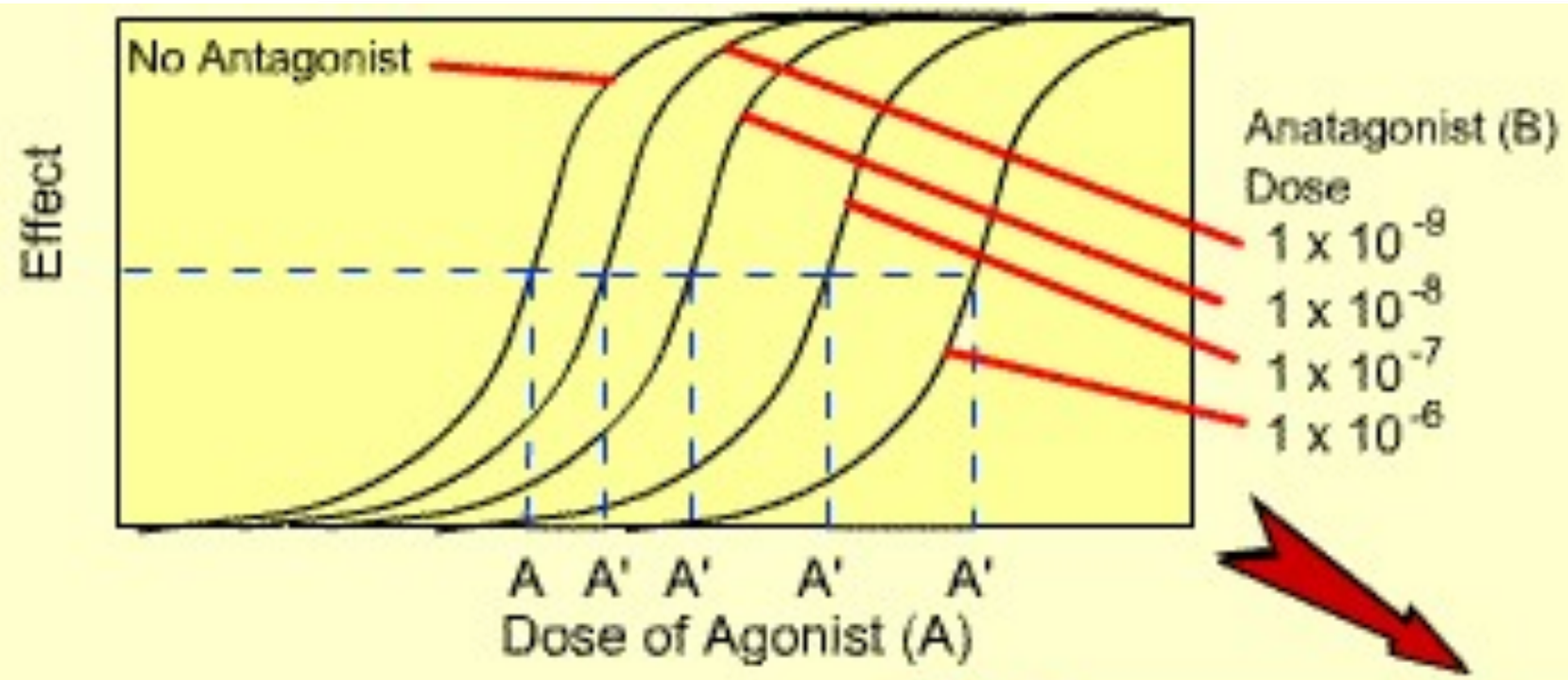


Irreversible antagonism

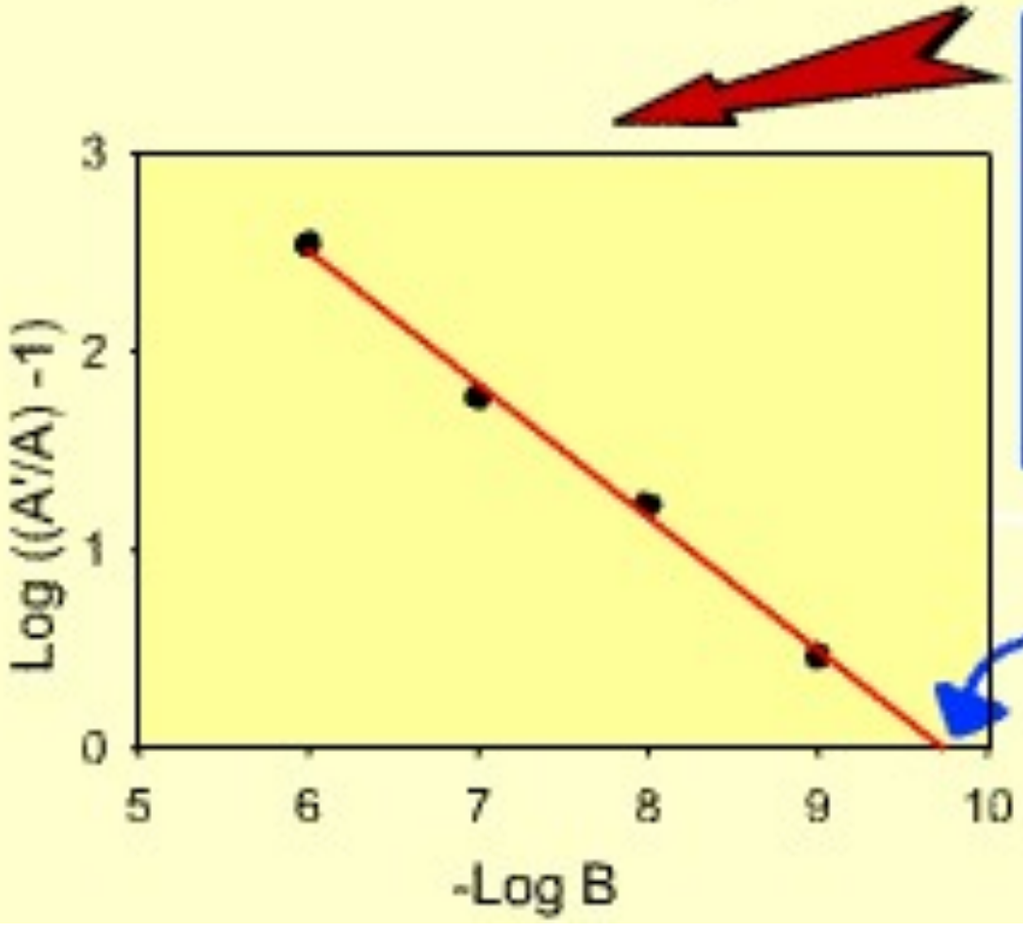




Schild Plot for pA2 determination



pA2 is the measure of the affinity of a reversible competitive antagonist for a specific receptor

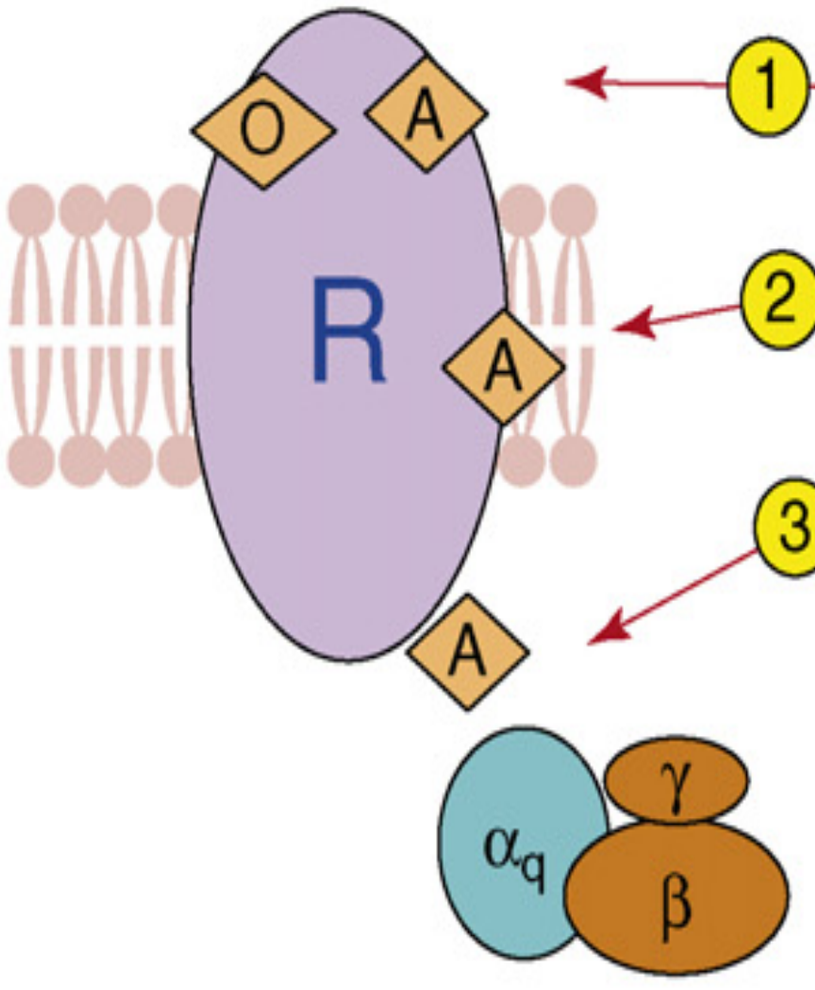


Antagonist Dose	A'/A	-logB	log((A'/A-1)
1 x 10 -9	4	9	0.47
1 x 10 -8	18	8	1.23
1 x 10 -7	60	7	1.77
1 x 10 -6	350	6	2.54

pA2 is the negative log of molar concentration of the antagonist which will reduce the effect of double dose of the agonist drug to that of a single dose

Allosteric ligands

Orthosteric site = O Allosteric site = A



1 — Modulate orthosteric ligand binding

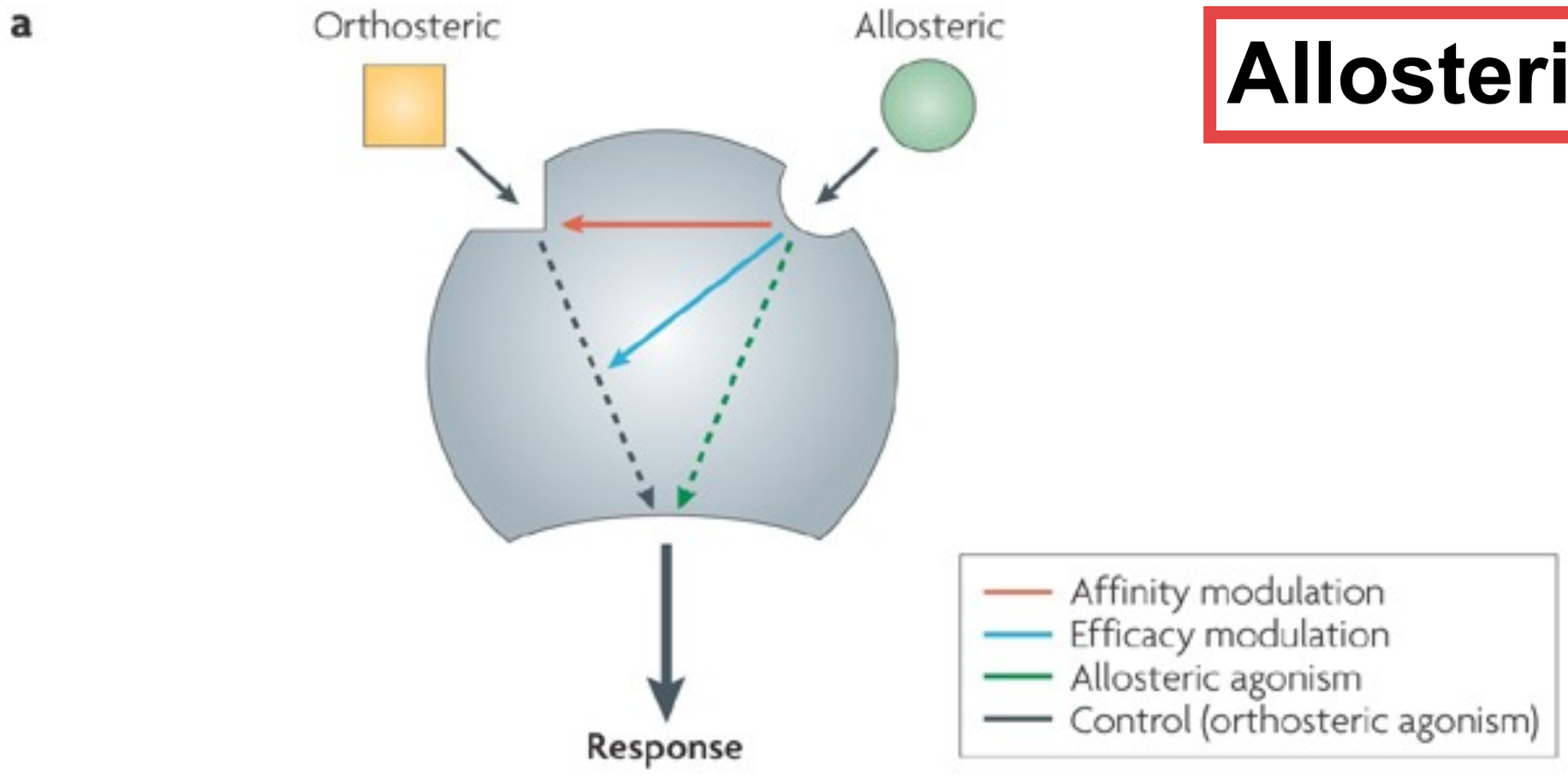
2 — Modulate orthosteric ligand efficacy independent of orthosteric ligand binding or G protein coupling sites

3 — Modulate G protein binding

Allosteric modulators work only in the presence of orthosteric ligand, but don't necessarily alter orthosteric ligand binding

TRENDS in Pharmacological Sciences

Allosteric ligands



Allosteric modulation: effect on affinity and efficacy