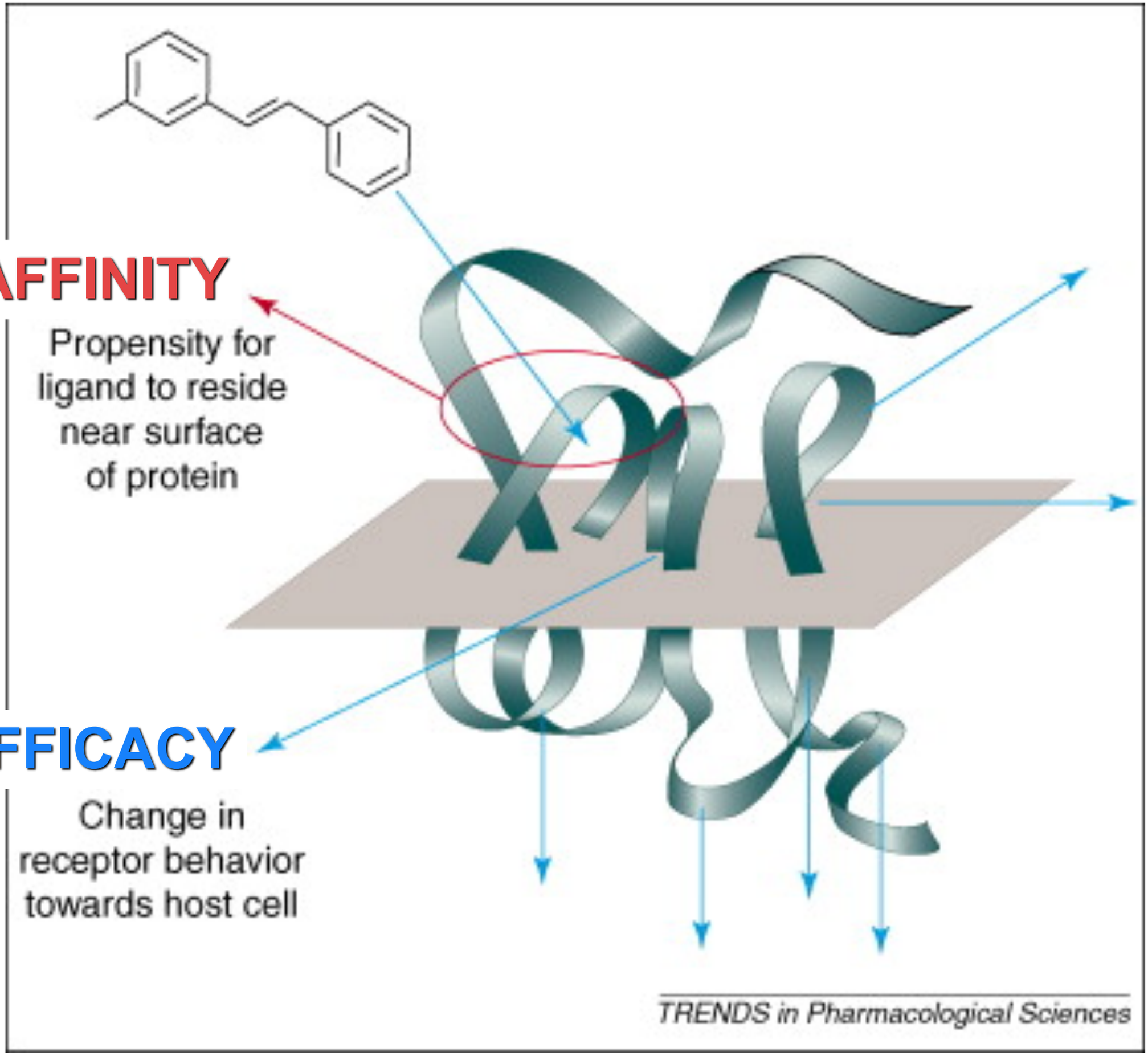
# Pharmacodinamic

## 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

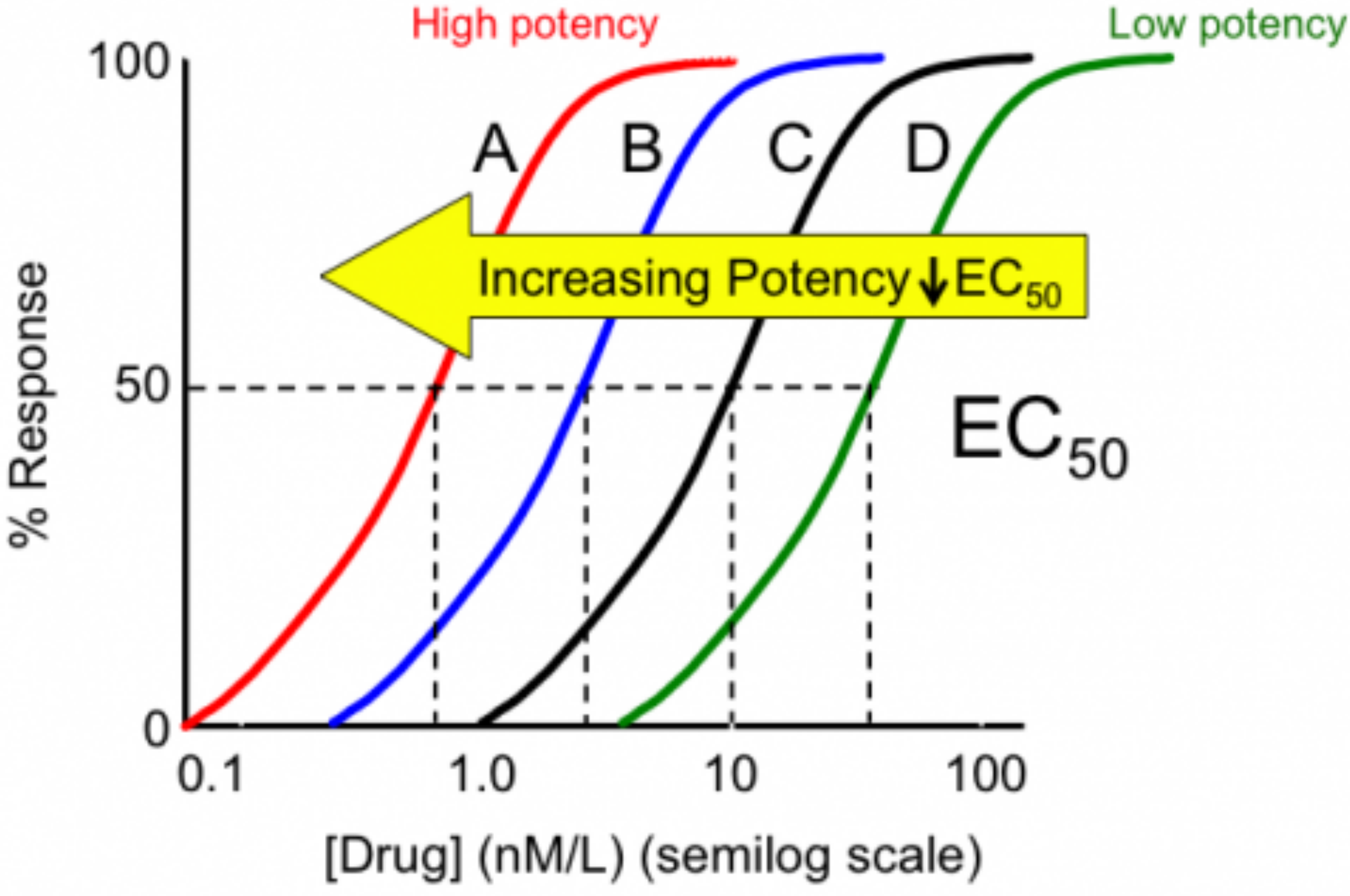
# DRUG-RECEPTOR THEORY

**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]**

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

# 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**

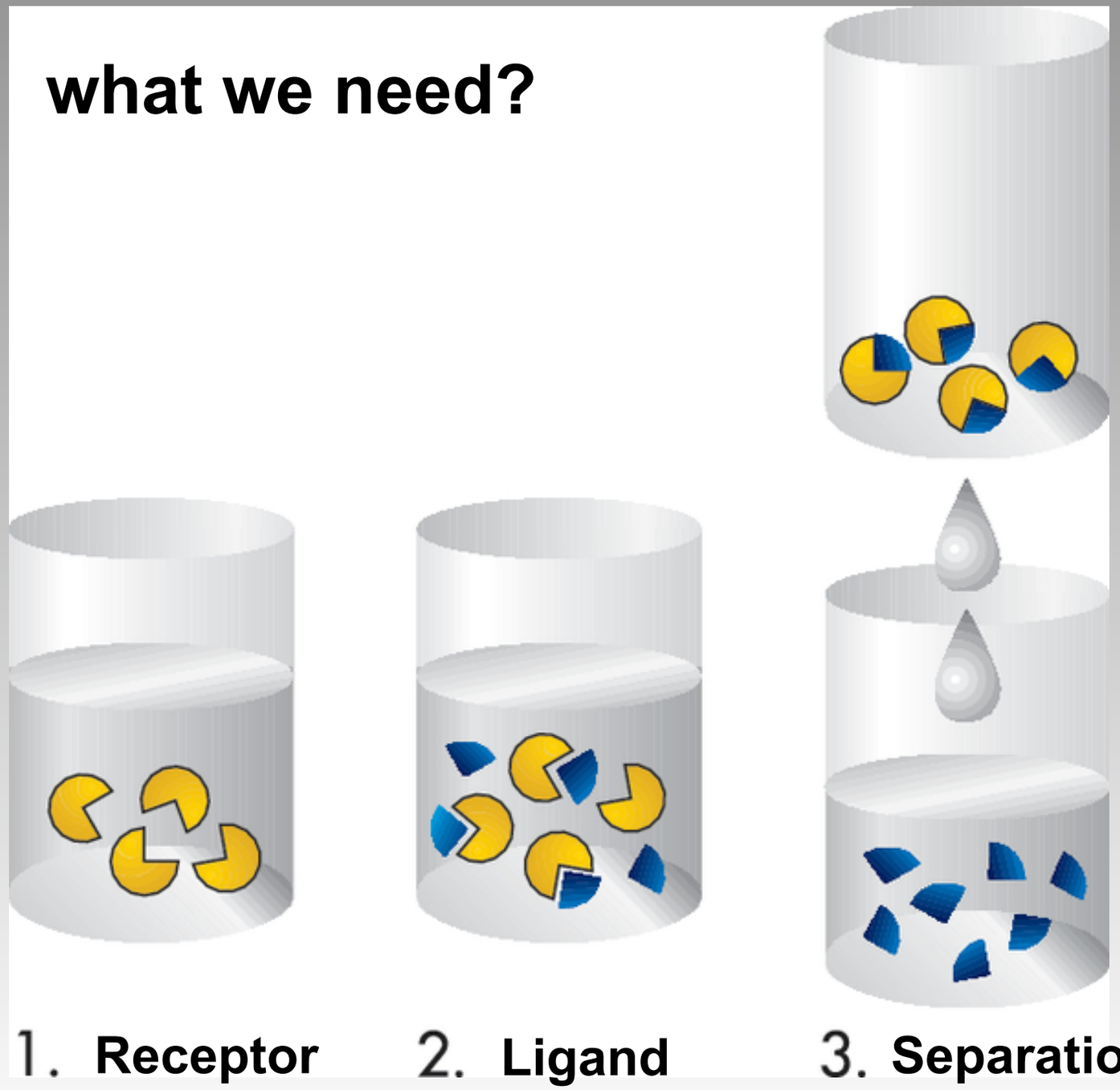
# THE RADIOLIGAND BINDING TECHNIQUE TO INVESTIGATE DRUG-RECEPTOR INTERACTION

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

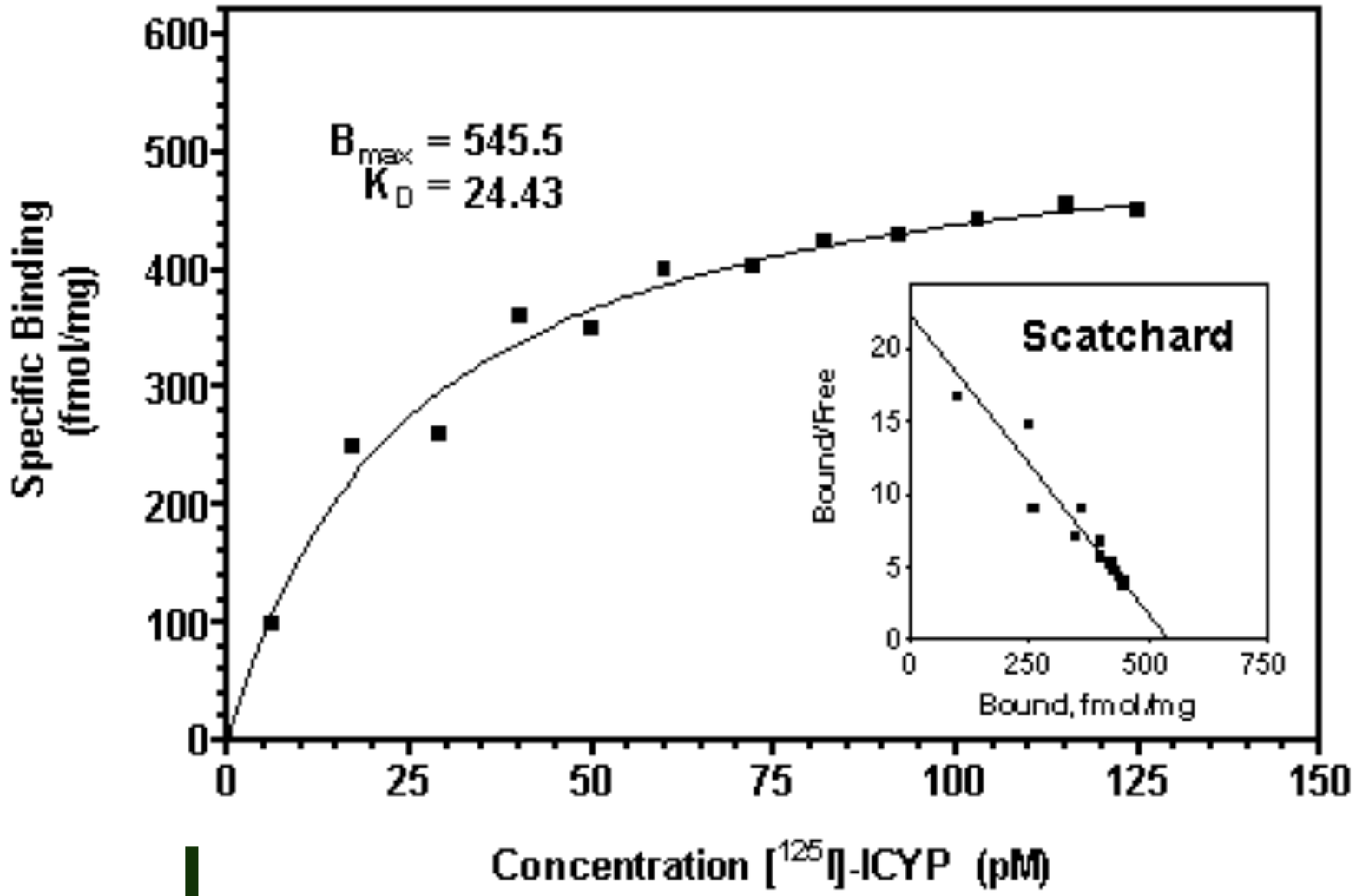
1. Distinguish the drug bound from the unbound (free)

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

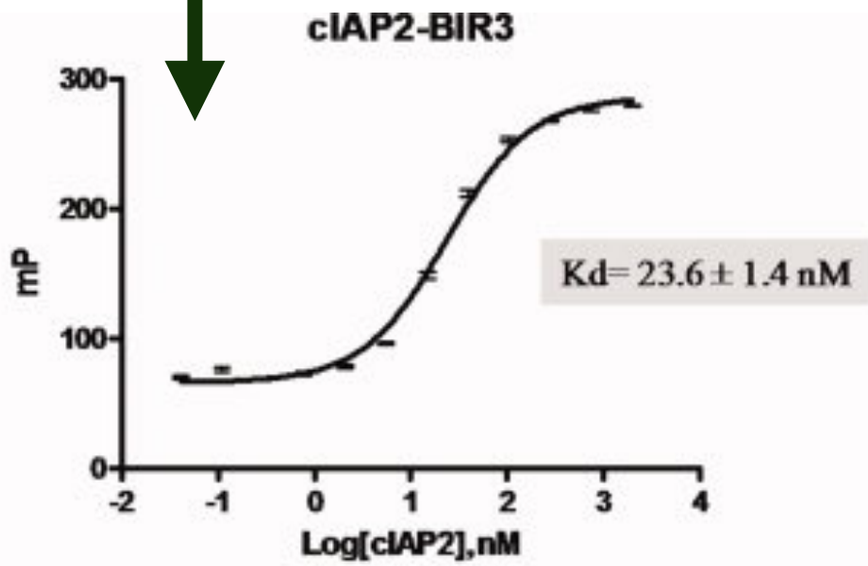
**what we need?**

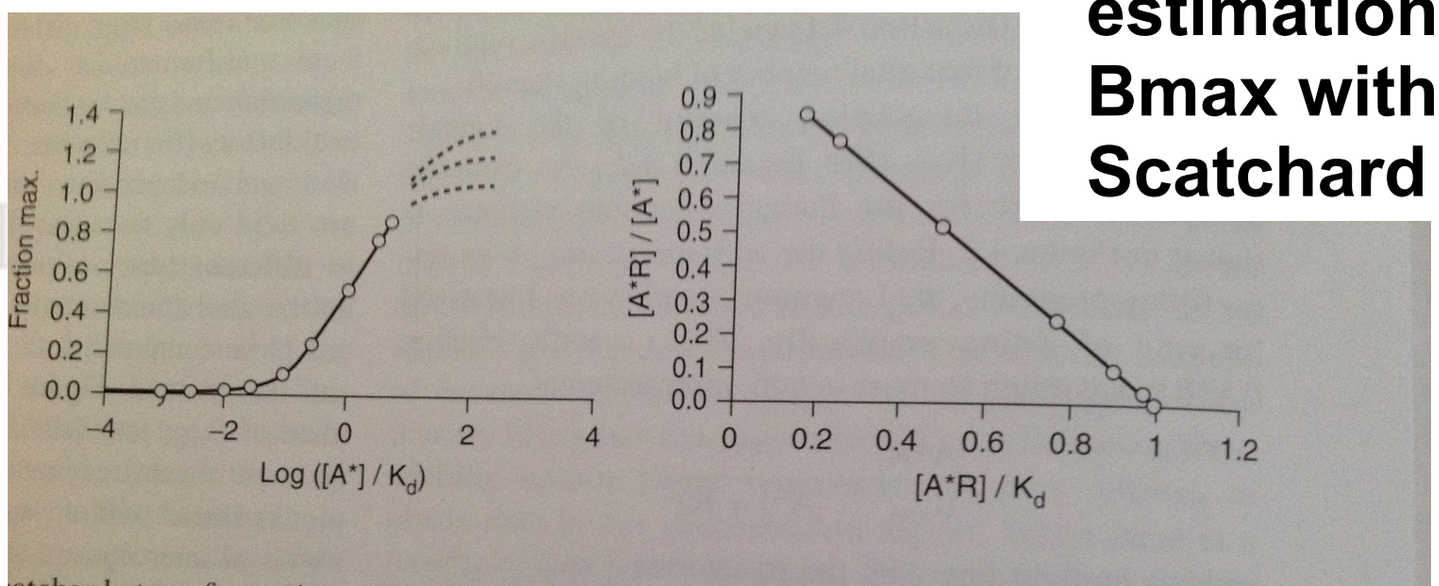


# SATURATION EXPERIMENT



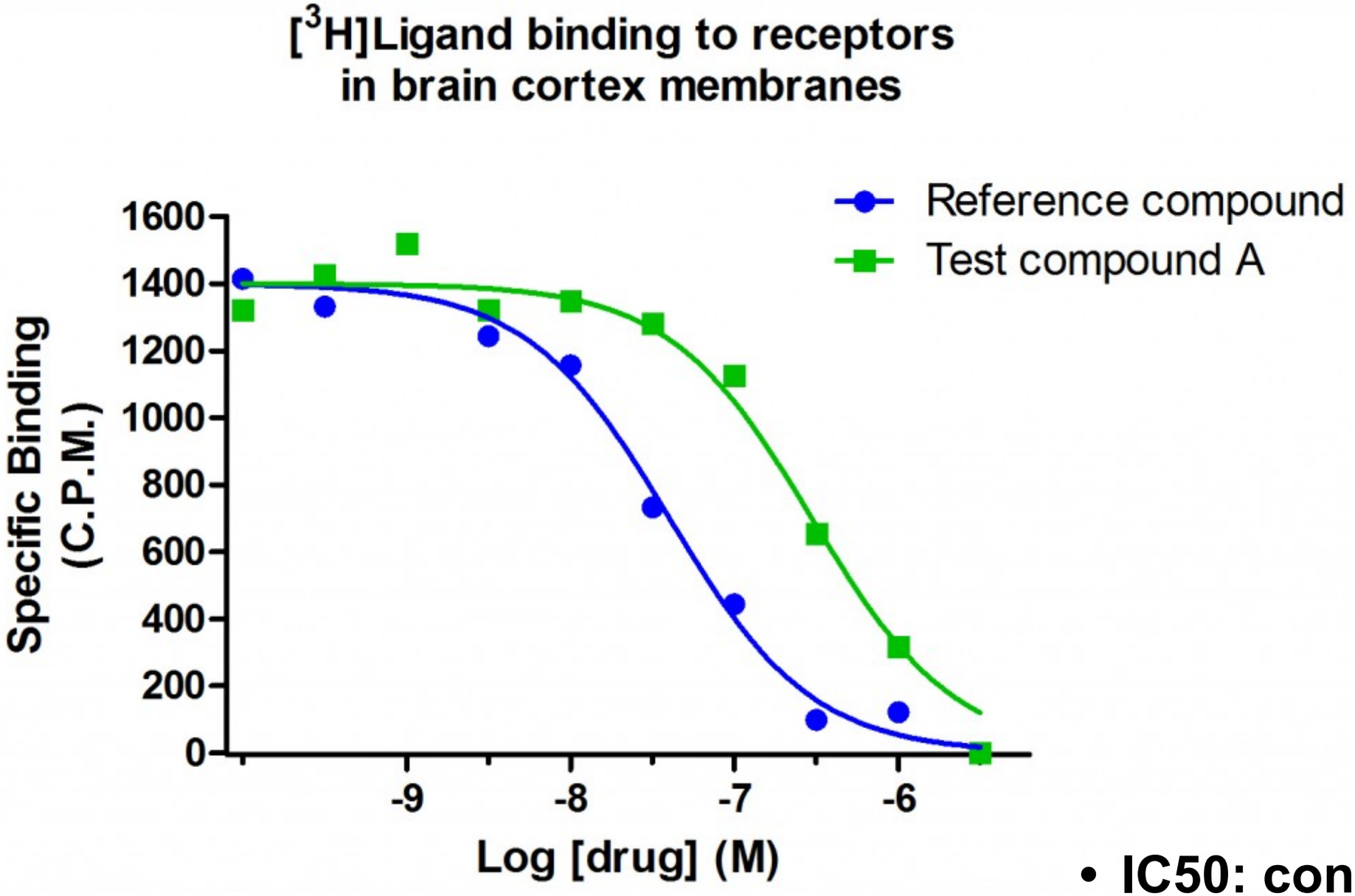

- **Bmax is the maximal binding capacity of a preparation (membranes, cells) containing receptors**



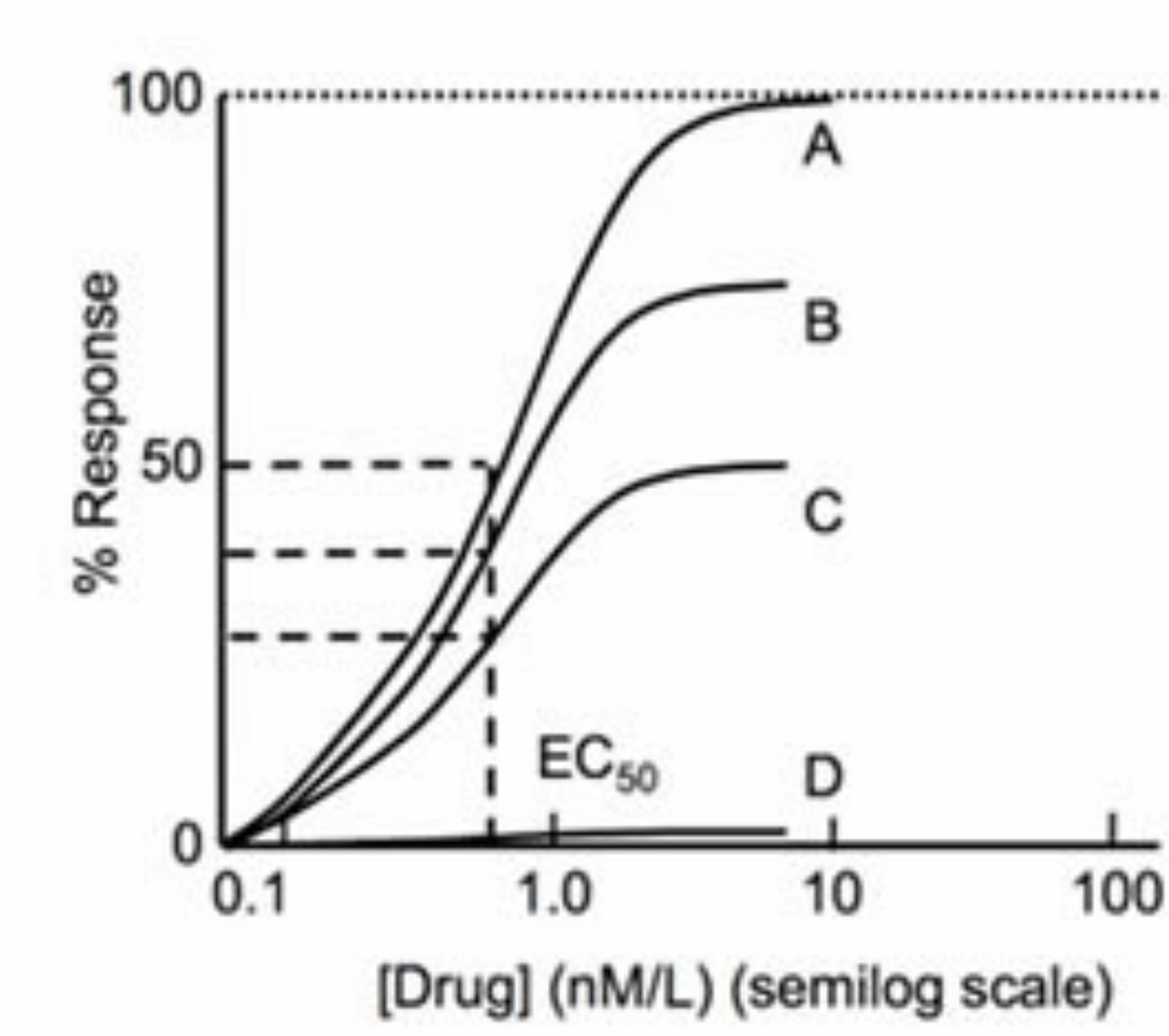

- **Erroneous estimation of Bmax with Scatchard plot**

# 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]**

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

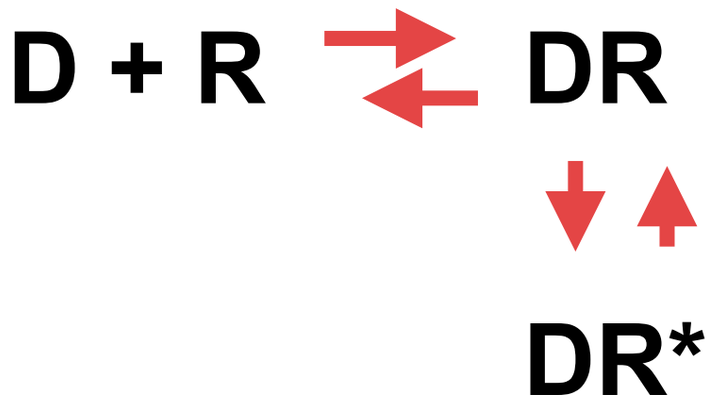
**Effect = α [DR] with α a constant named intrinsic activity or efficacy**

# 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

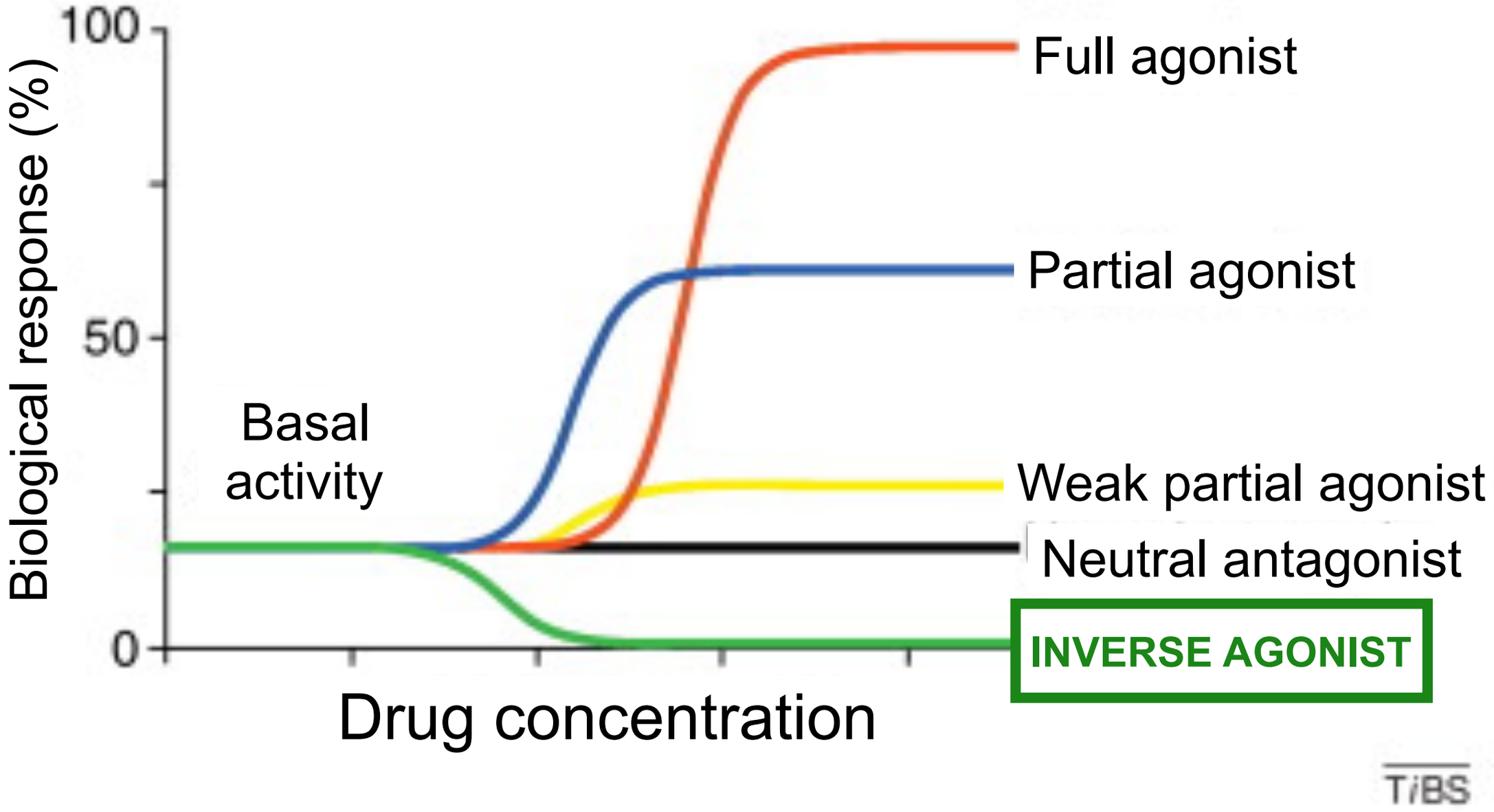



**Full agonist**: a ligand that produces the maximal response in that tissue

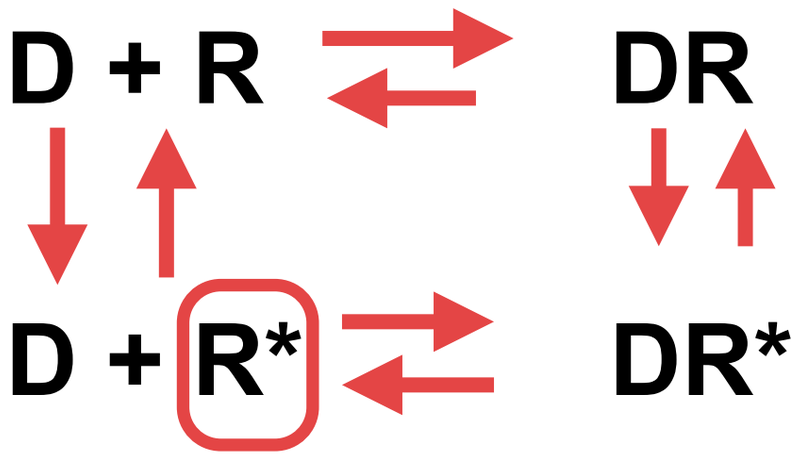
**Partial agonist**: a ligand that produces a submaximal response in that tissue

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

# Inverse agonism



# Inverse agonism

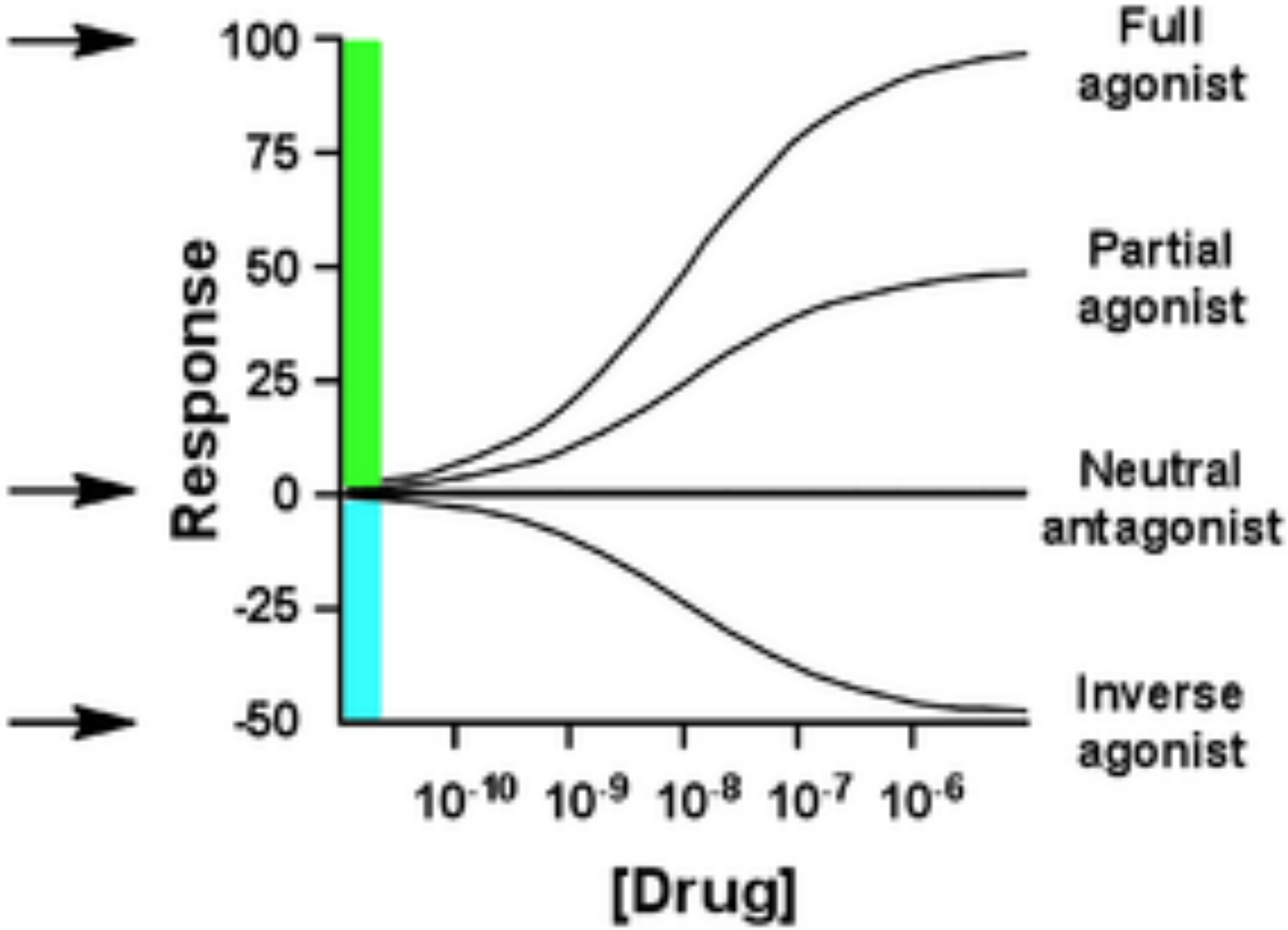



Inverse agonist: a ligand that reverses constitutive receptor activity R*

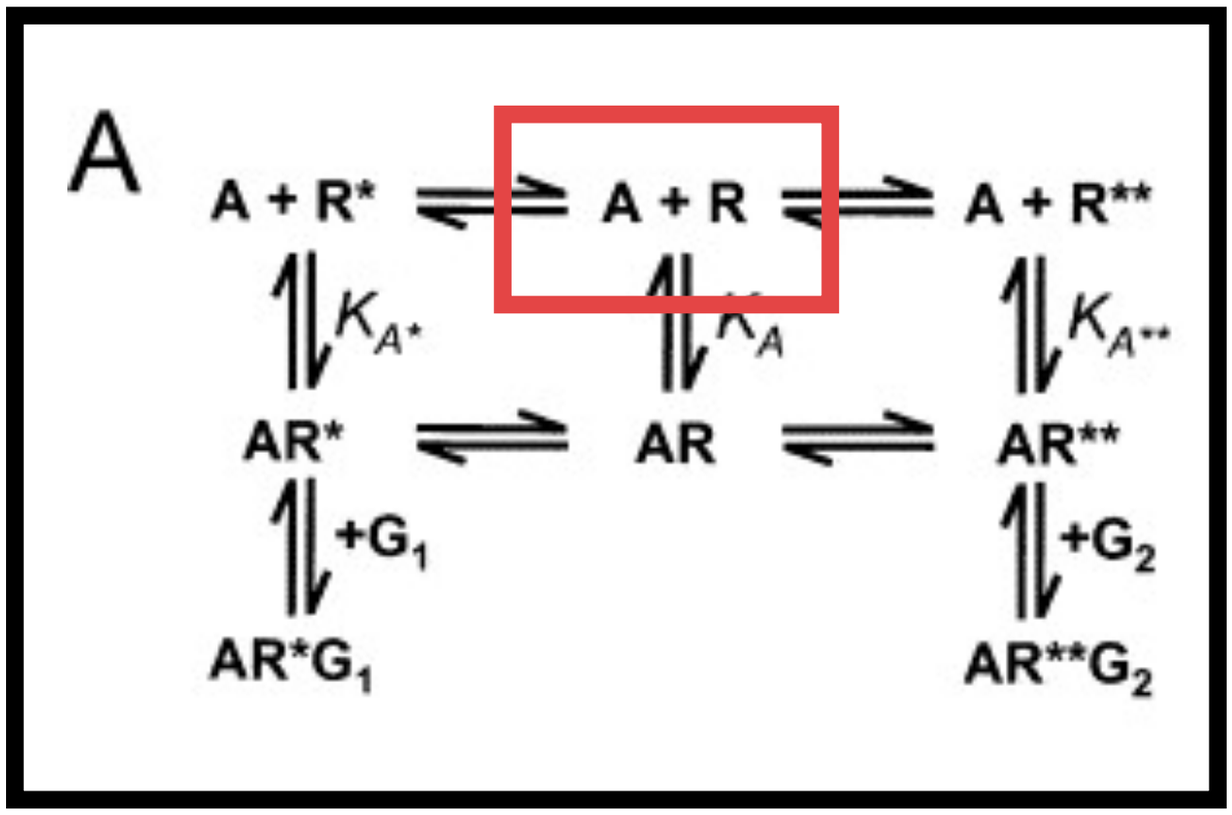
The constitutively active receptor R* is active in absence of endogenous ligand

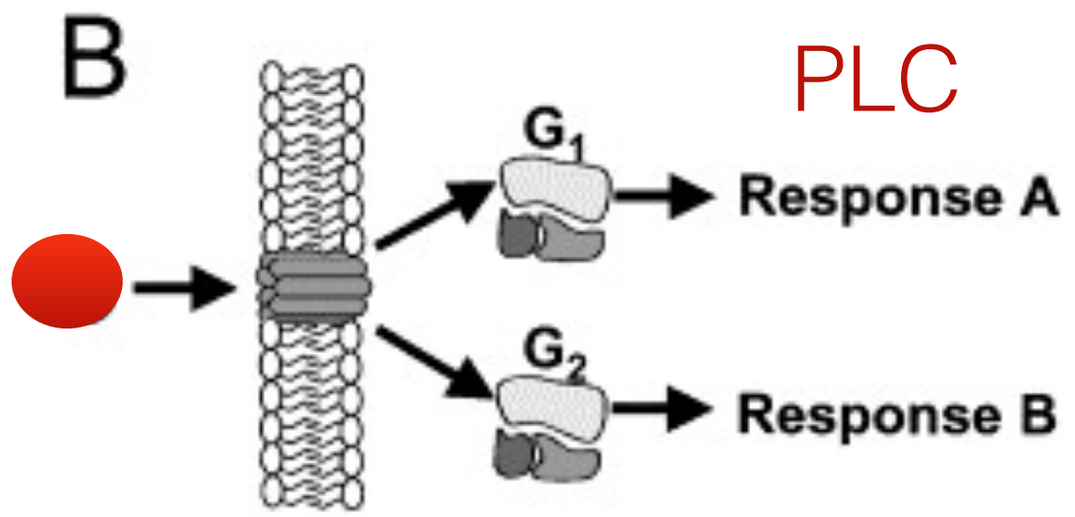
# Inverse agonism

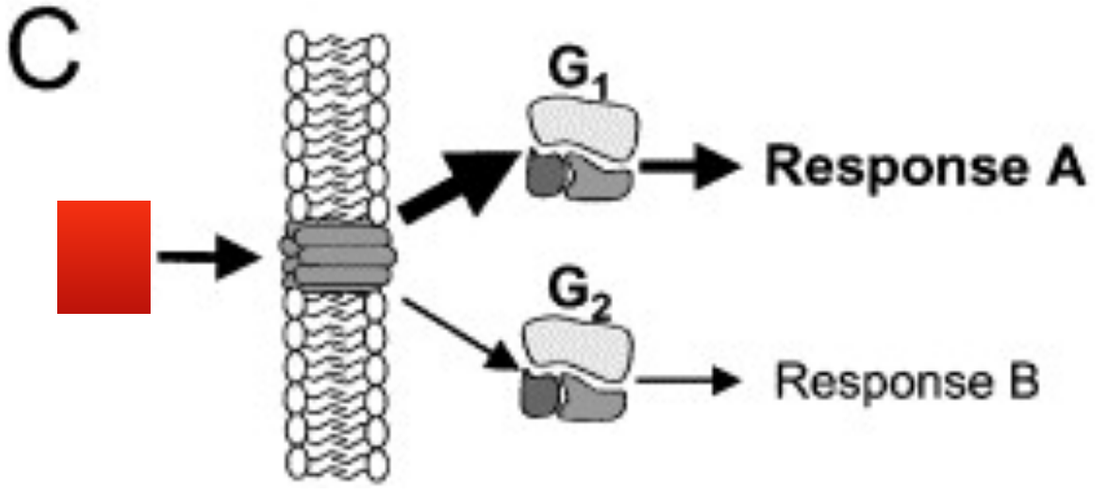
**Constitutive activity of receptor in absence of endogenous ligand**

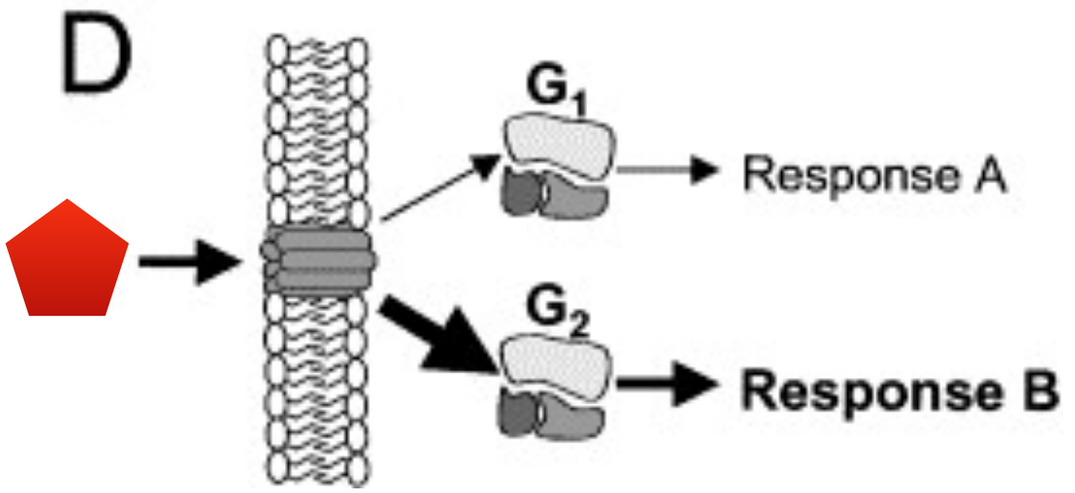


# BIASED AGONISM
# or
# LIGAND-SELECTIVE FUNCTIONAL AGONISM



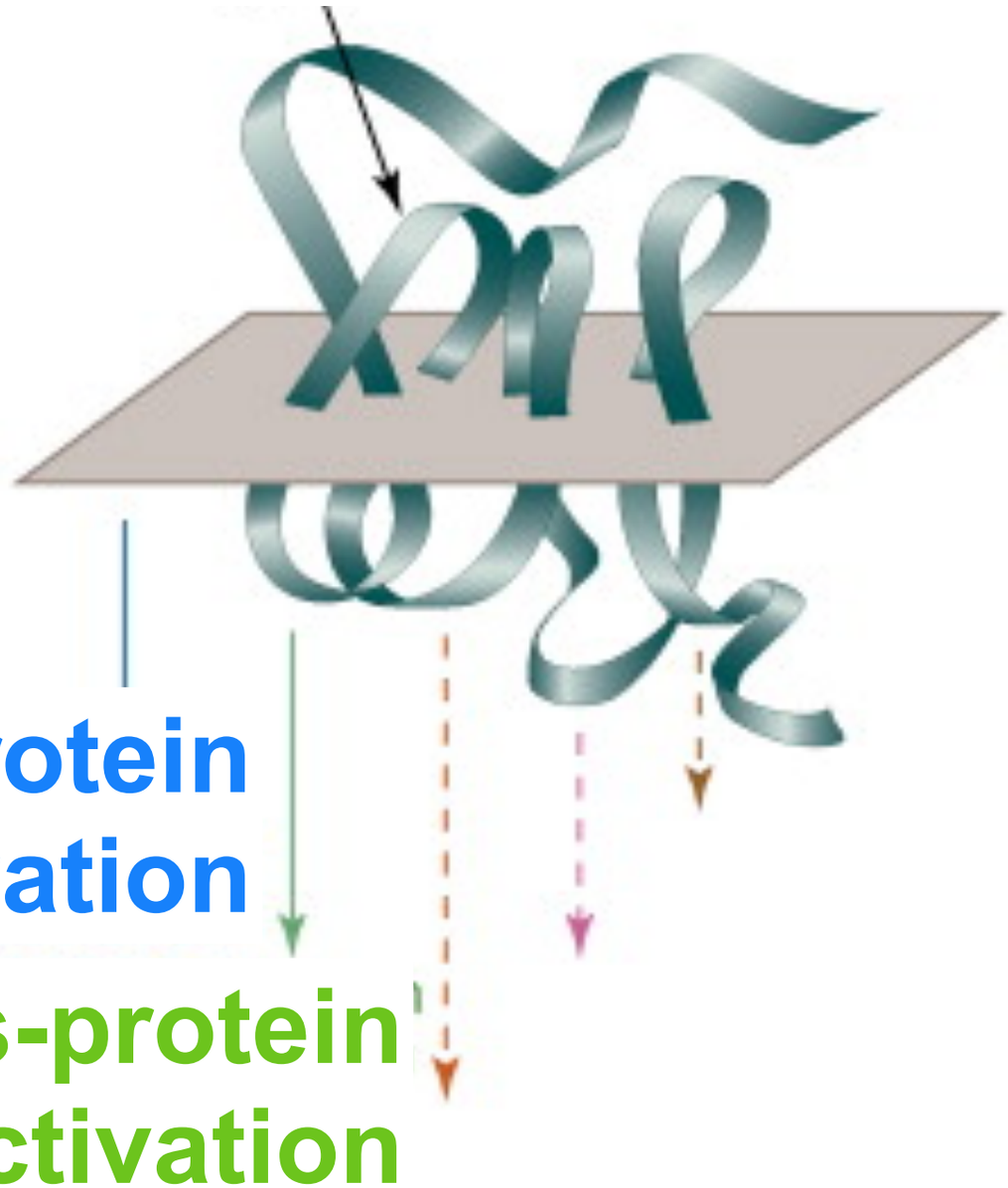



# BIASED AGONISM

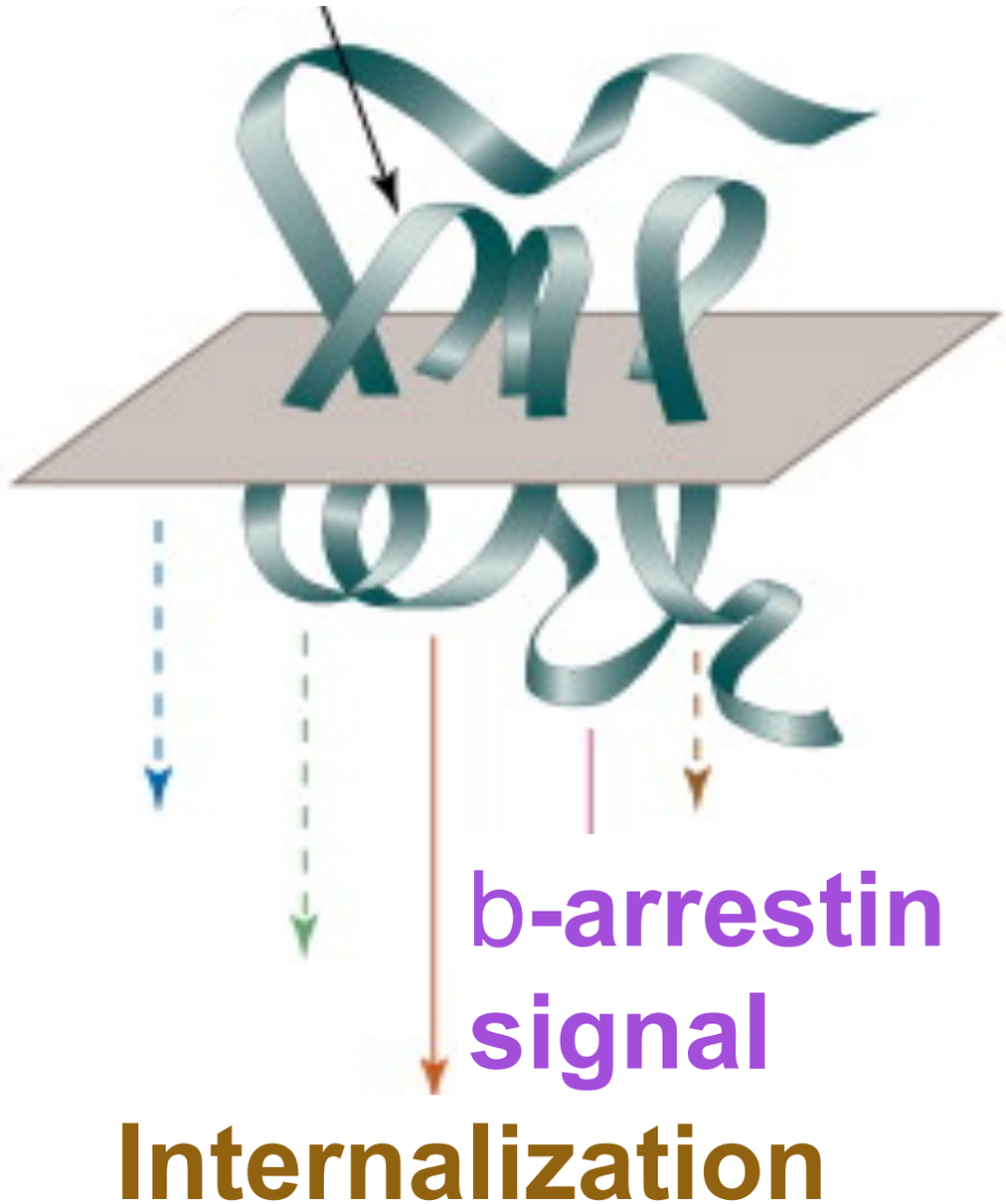
## Biased agonist A



Gi-protein Activation

Gs-protein Activation

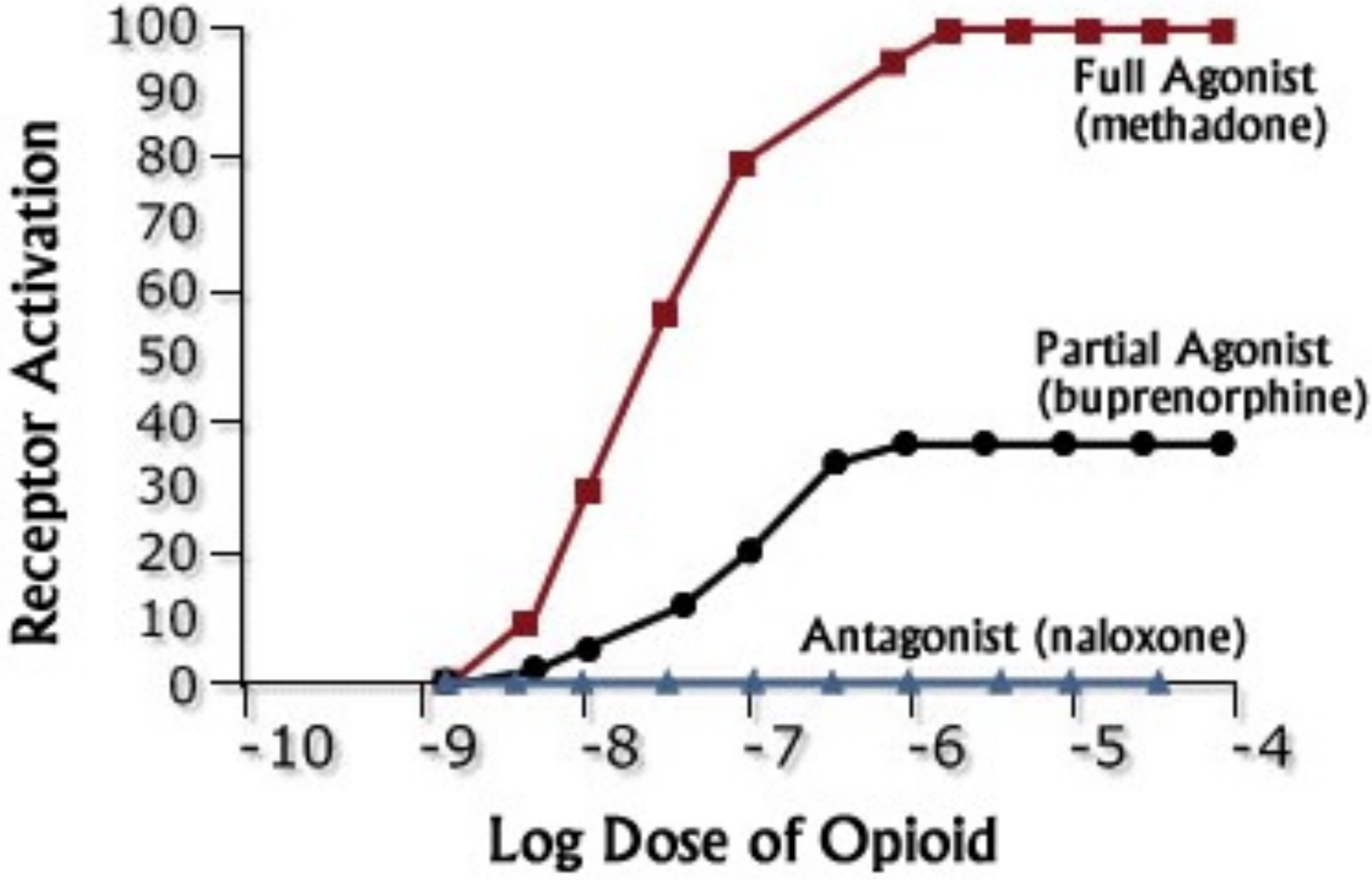
## Biased agonist B

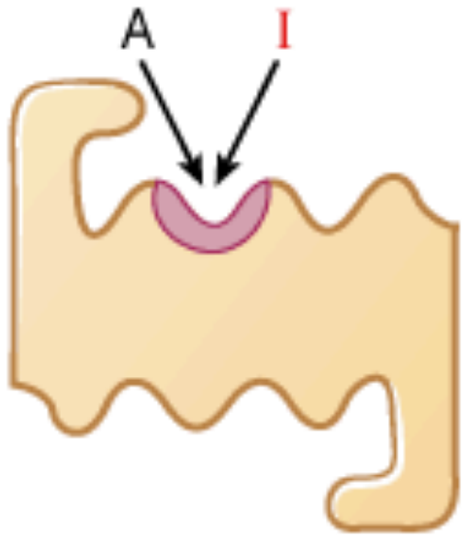


b-arrestin signal

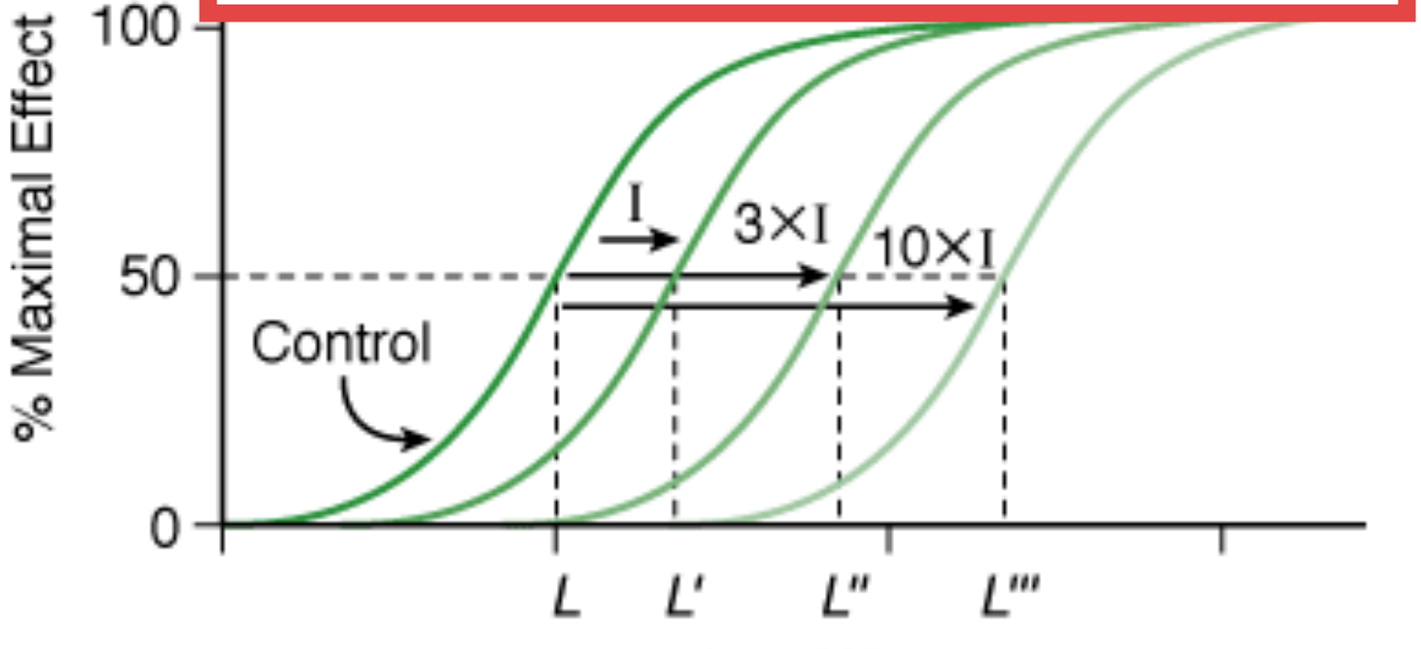
Internalization

# Receptor Activation:
## Full Agonist, Partial Agonist, Antagonist

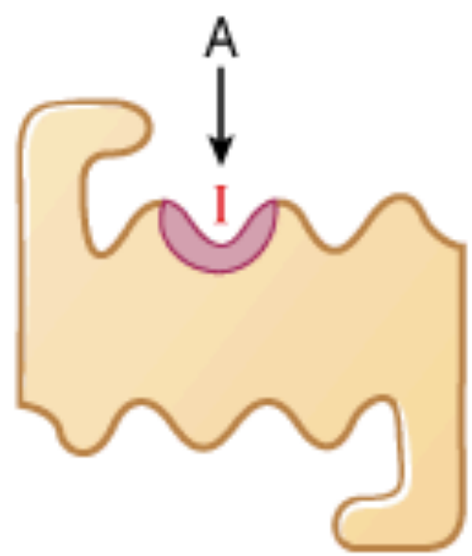


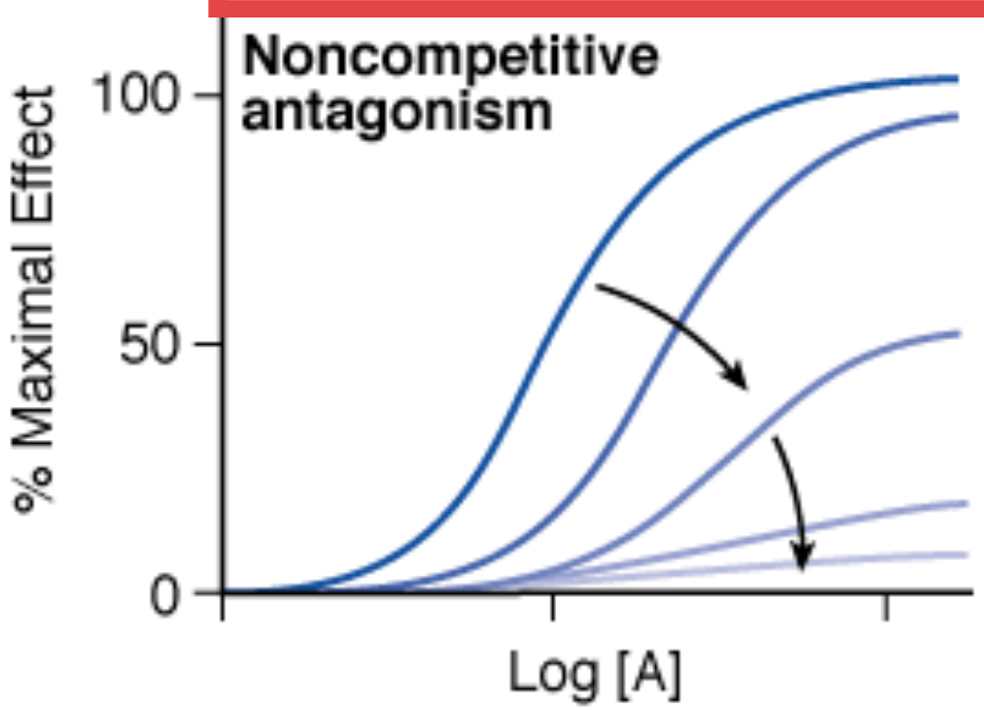



## Competitive antagonism

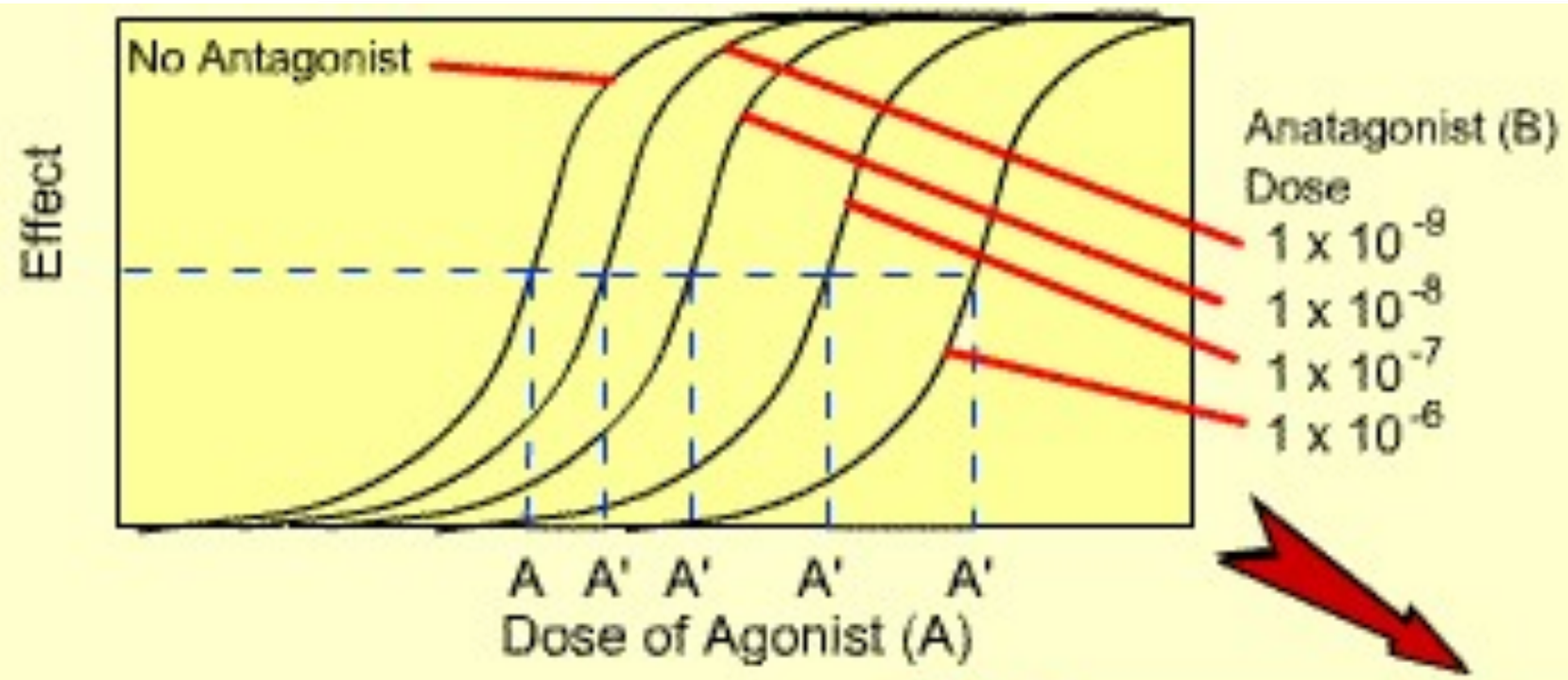



## Irreversible antagonism

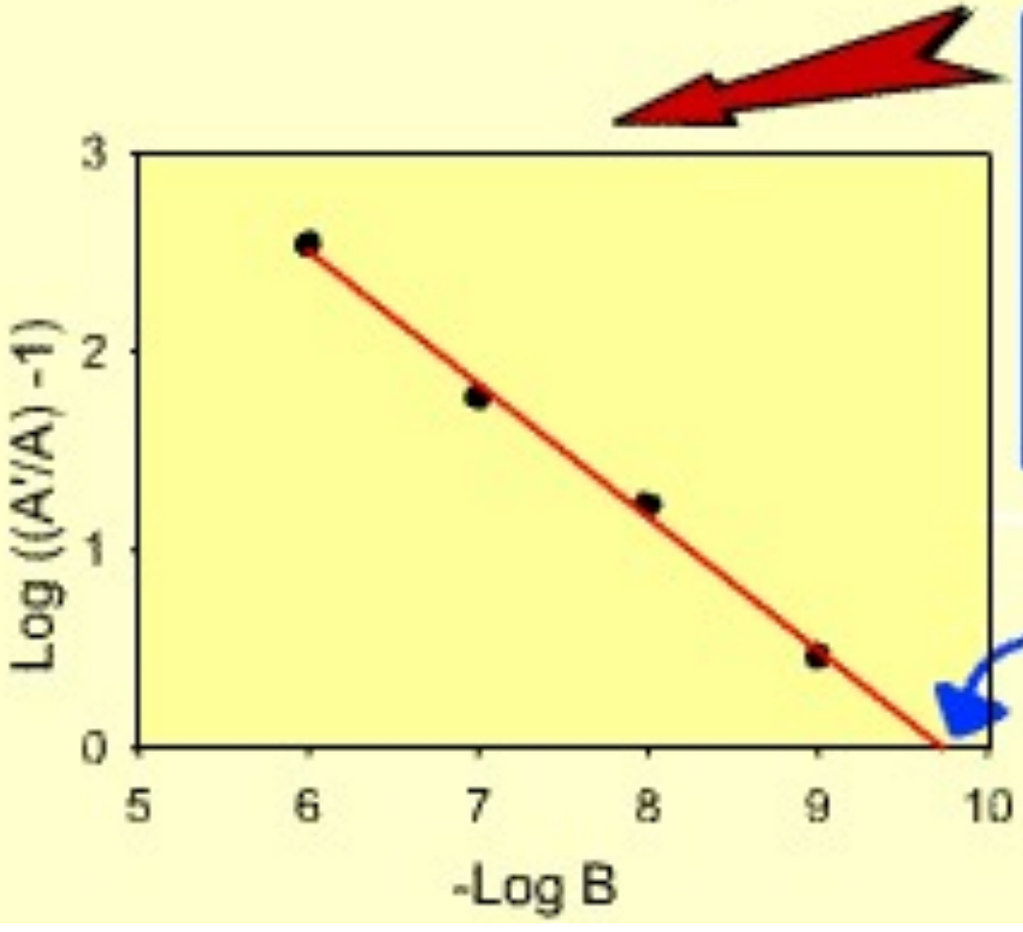


# Schild Plot for pA2 determination



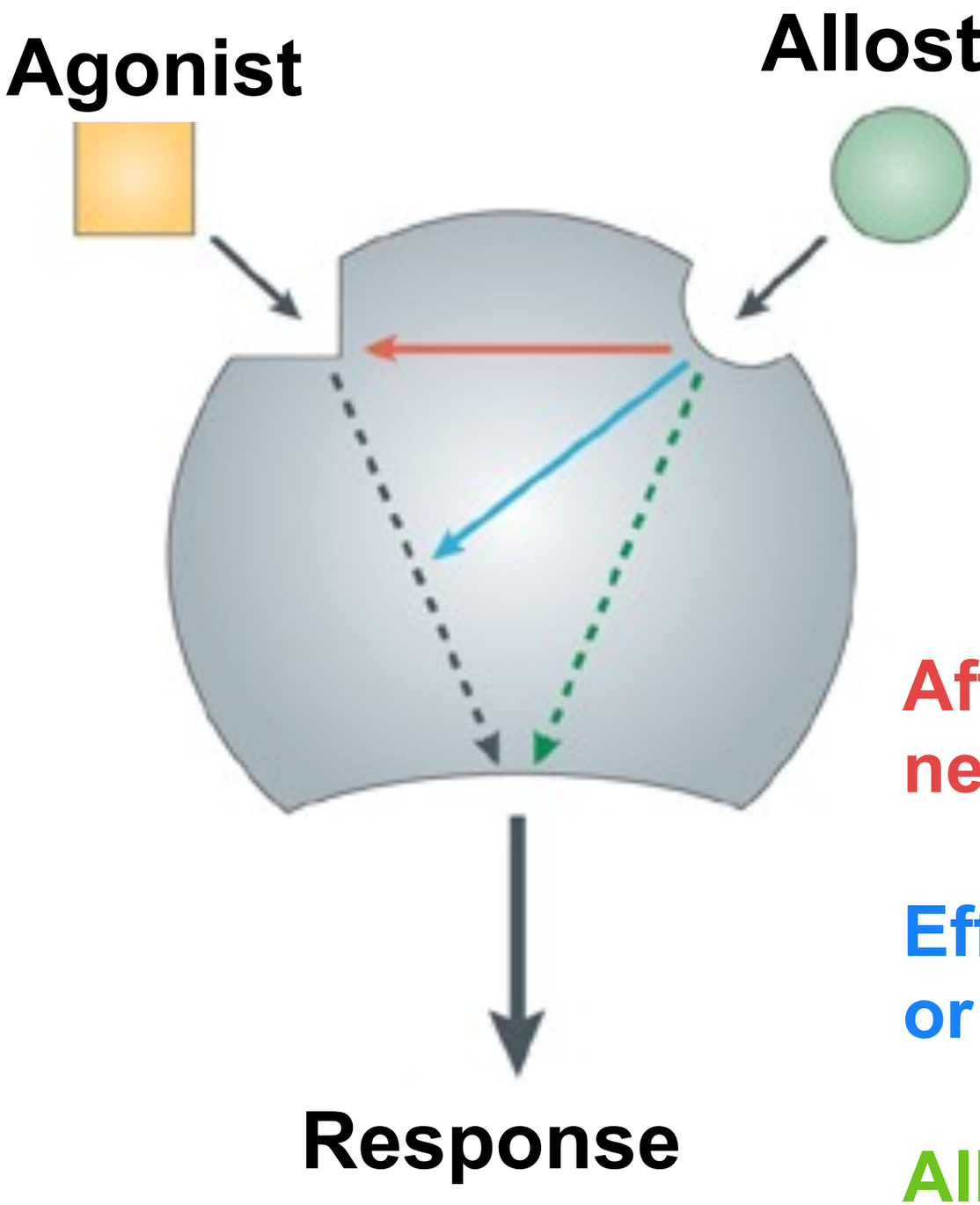

**pA2 is the measure of the affinity of a reversible competitive antagonist for a specific receptor**




| 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




**Affinity modulation (positive or negative)**

**Efficacy modulation (positive or negative)**

**Allosteric agonism (or antagonism)**

# Allosteric modulation: effect on affinity and efficacy