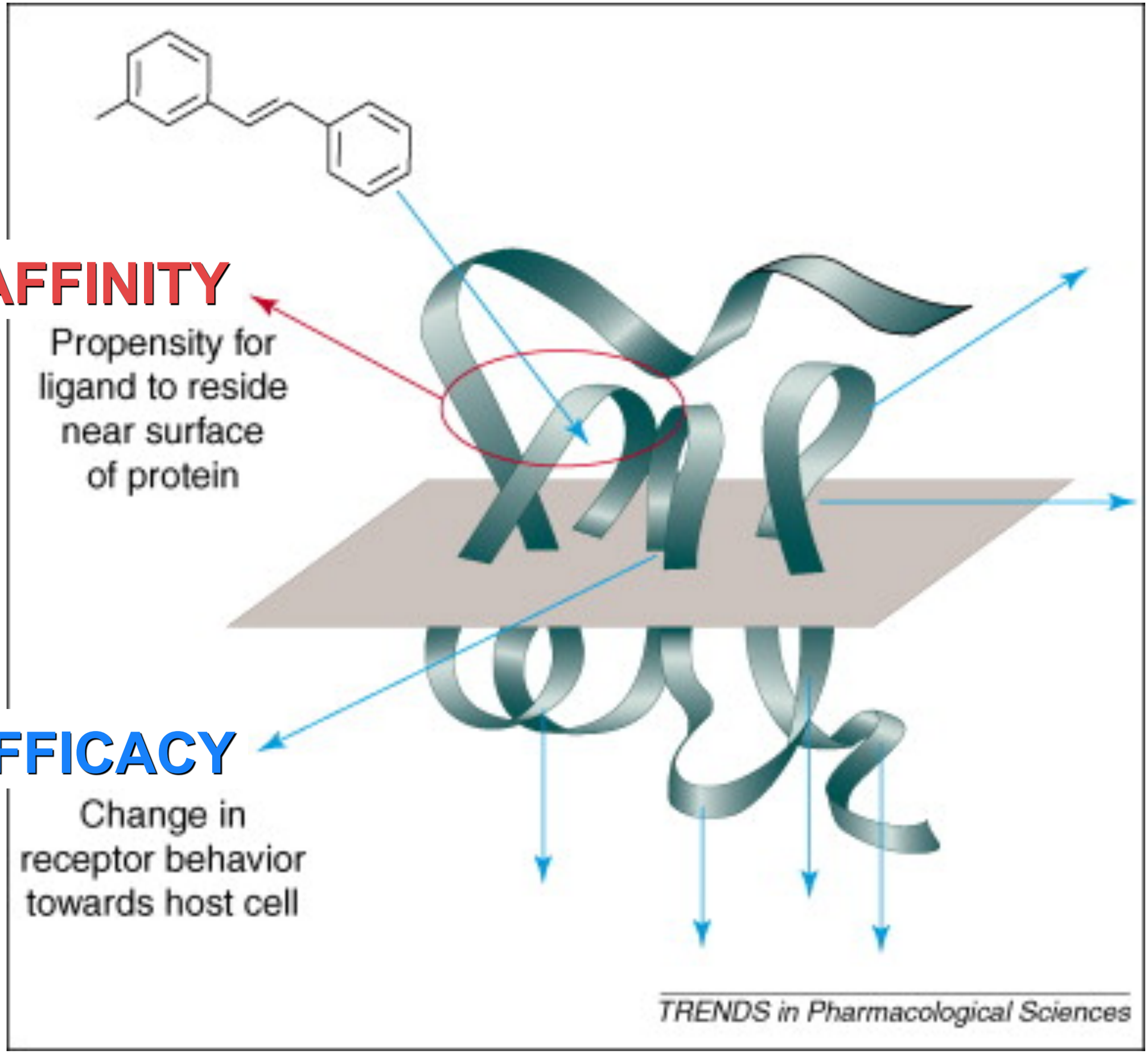
PHARMACODINAMIC

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

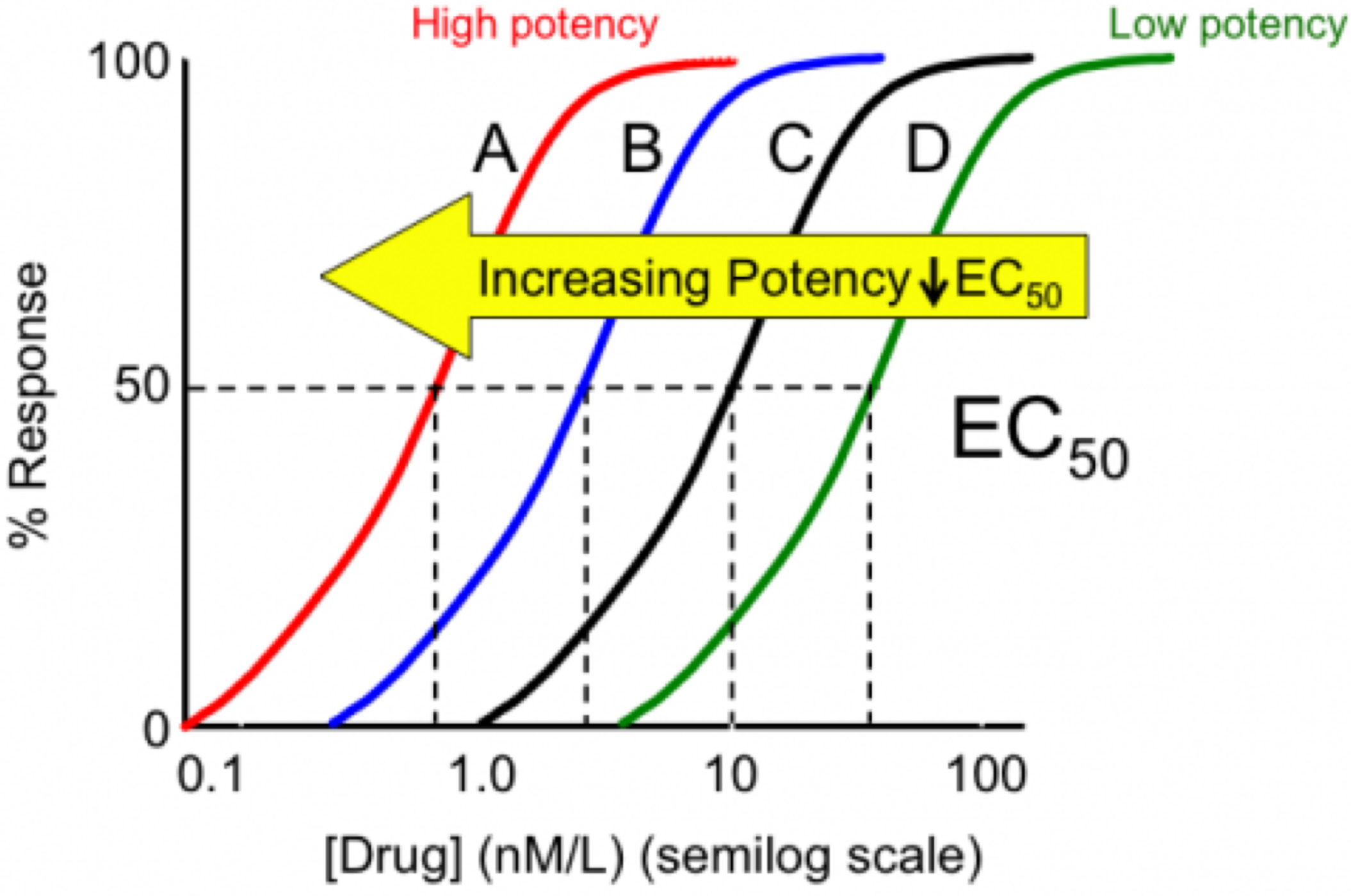
DRUG-RECEPTOR THEORY

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: EC_{50} 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**

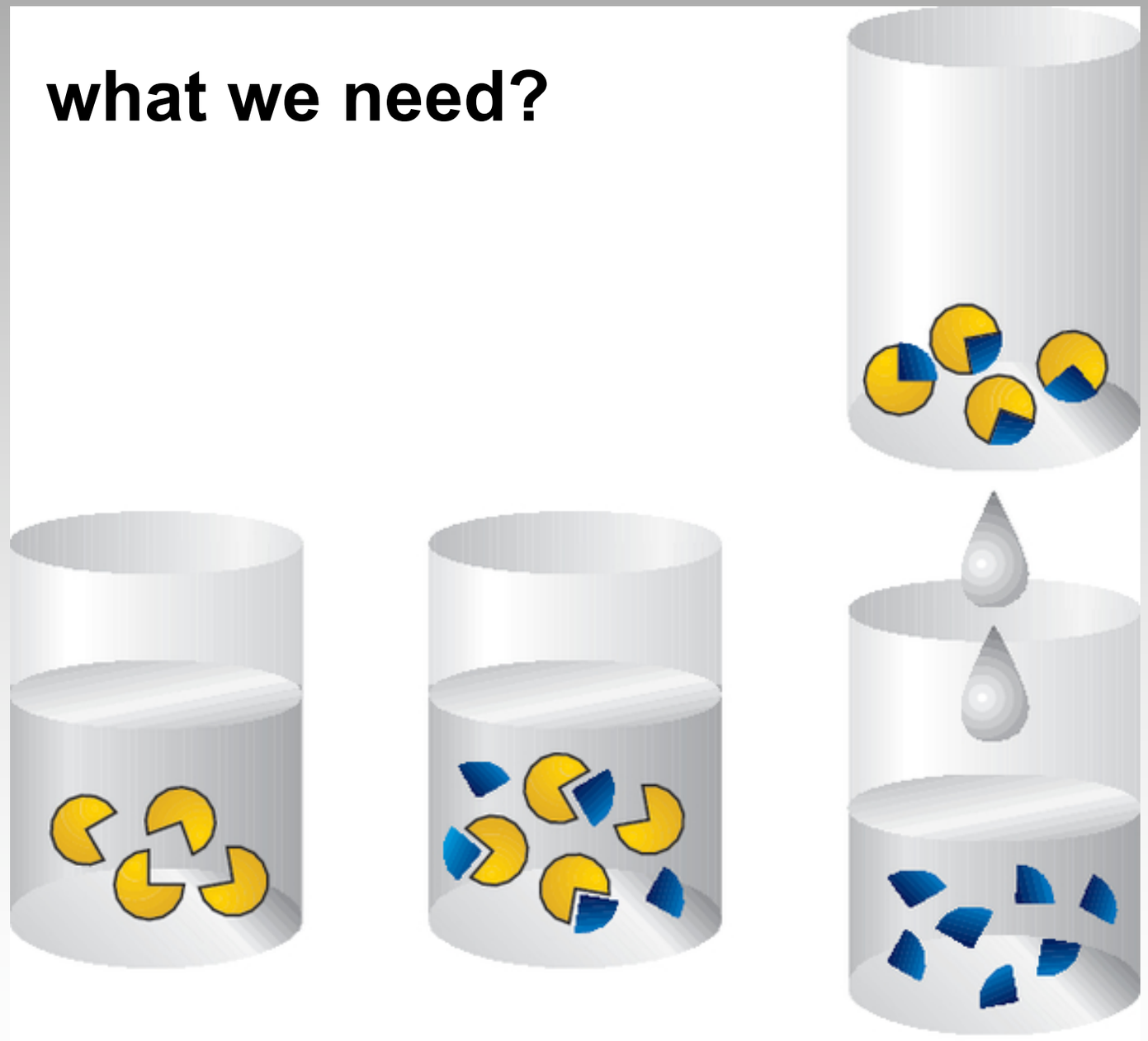
THE RADIOLIGAND BINDING TECHNIQUE TO INVESTIGATE DRUG-RECEPTOR INTERACTION

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

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

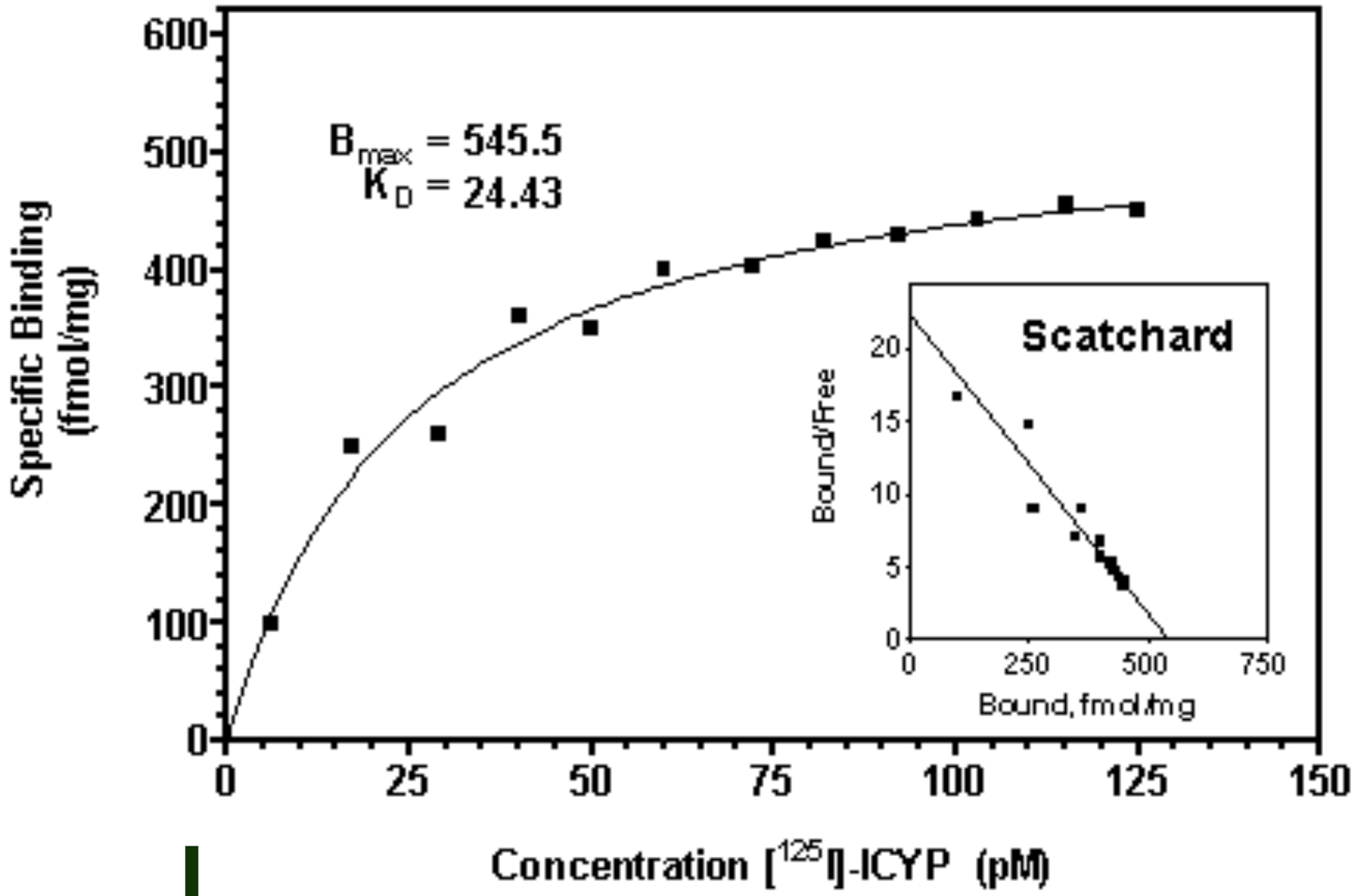
2. Quantify the drug-receptor complex (drug labelled with ^{3}H or ^{125}I)

what we need?

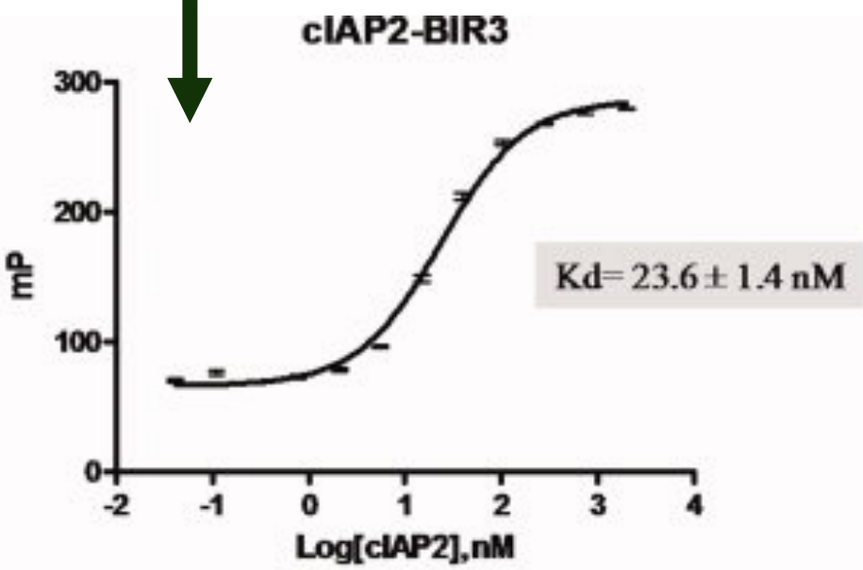


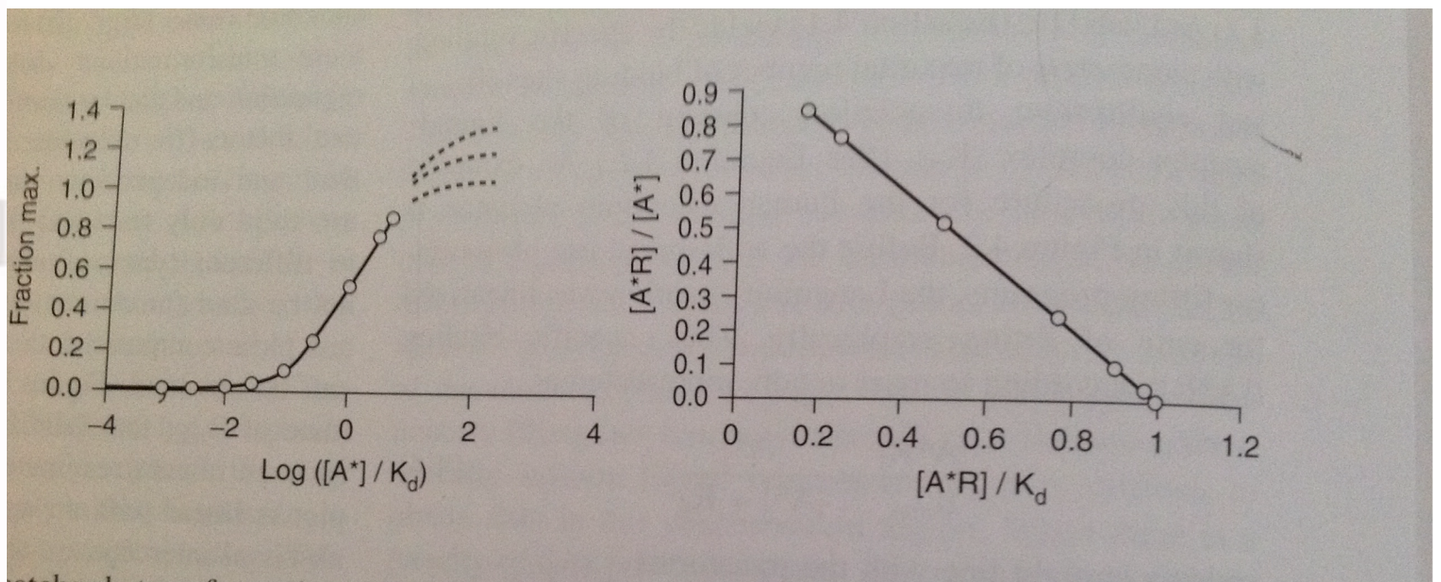
1. **Receptor** 2. **Ligand** 3. **Separation and Quantification**

SATURATION EXPERIMENT

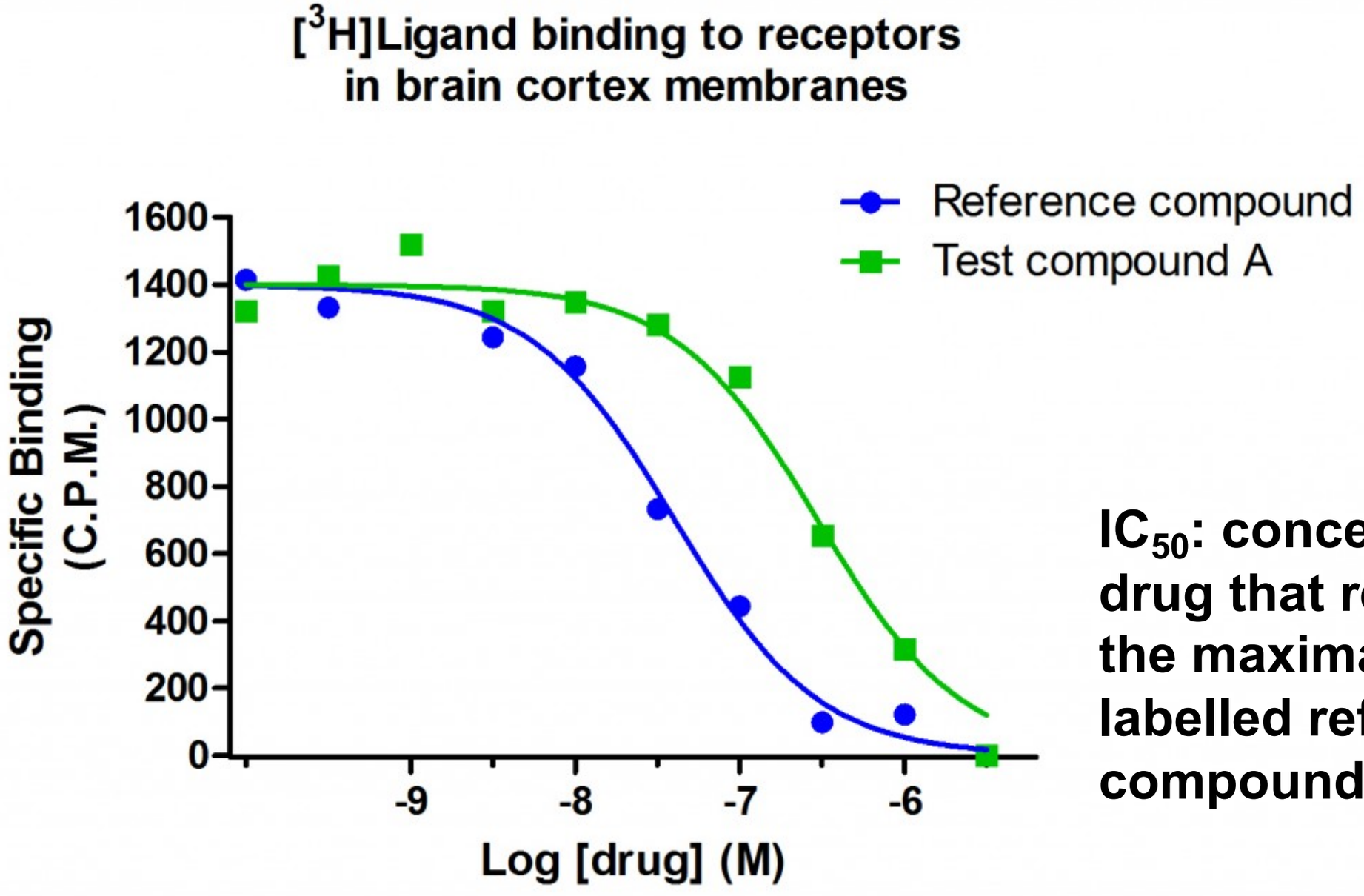


- **Bmax is the maximal binding capacity of a preparation (membranes, cells) containing receptors**
- **Kd is the drug concentration that occupies 50% of receptors at the equilibrium**
- **Erroneous estimation of Bmax with Scatchard plot**





COMPETITION EXPERIMENT



IC_{50}: concentration of a drug that reduces by 50% the maximal binding of a labelled reference compound (relative value)

The Kd value can be calculated adjusting the IC_{50} value for the ligand concentration against which the IC_{50} is determined (Cheng-Prusoff equation)

Efficacy (Intrinsic activity)

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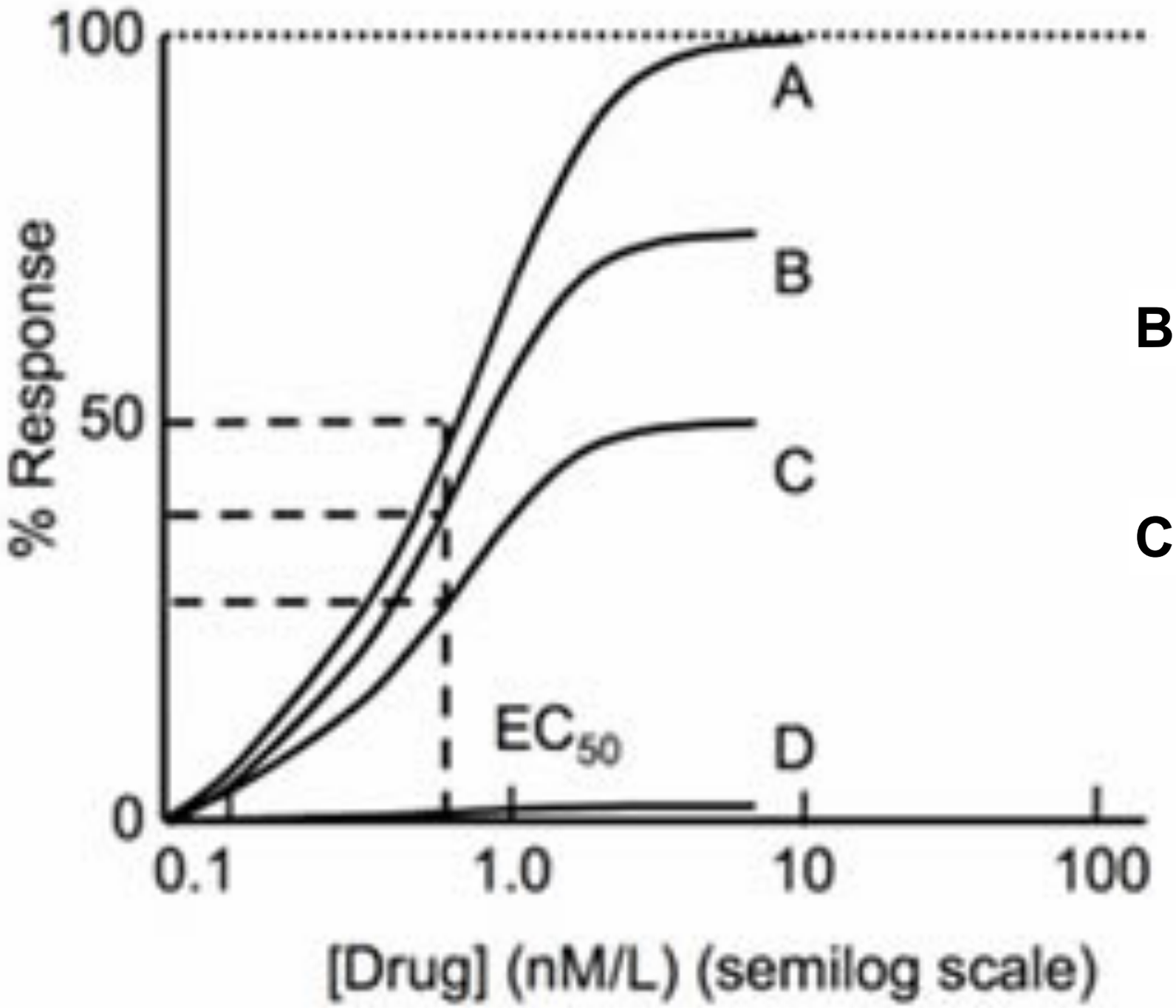
Efficacy (Intrinsic activity)



A: FULL AGONIST

B: PARTIAL AGONIST

C: PARTIAL AGONIST

D: ANTAGONIST

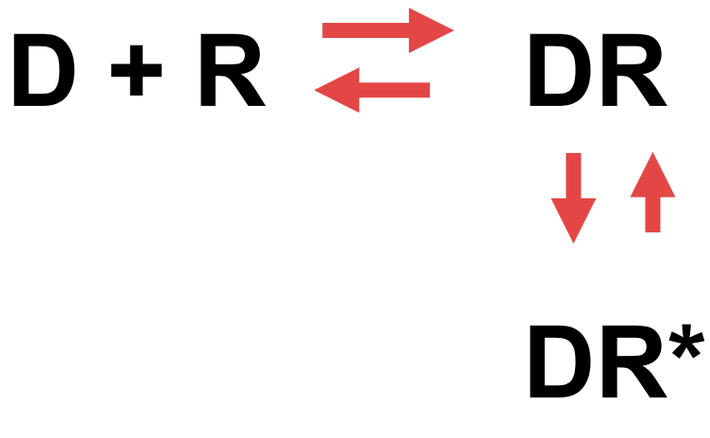
Efficacy (Intrinsic activity)

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

- **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)**

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

Partial agonism and antagonism

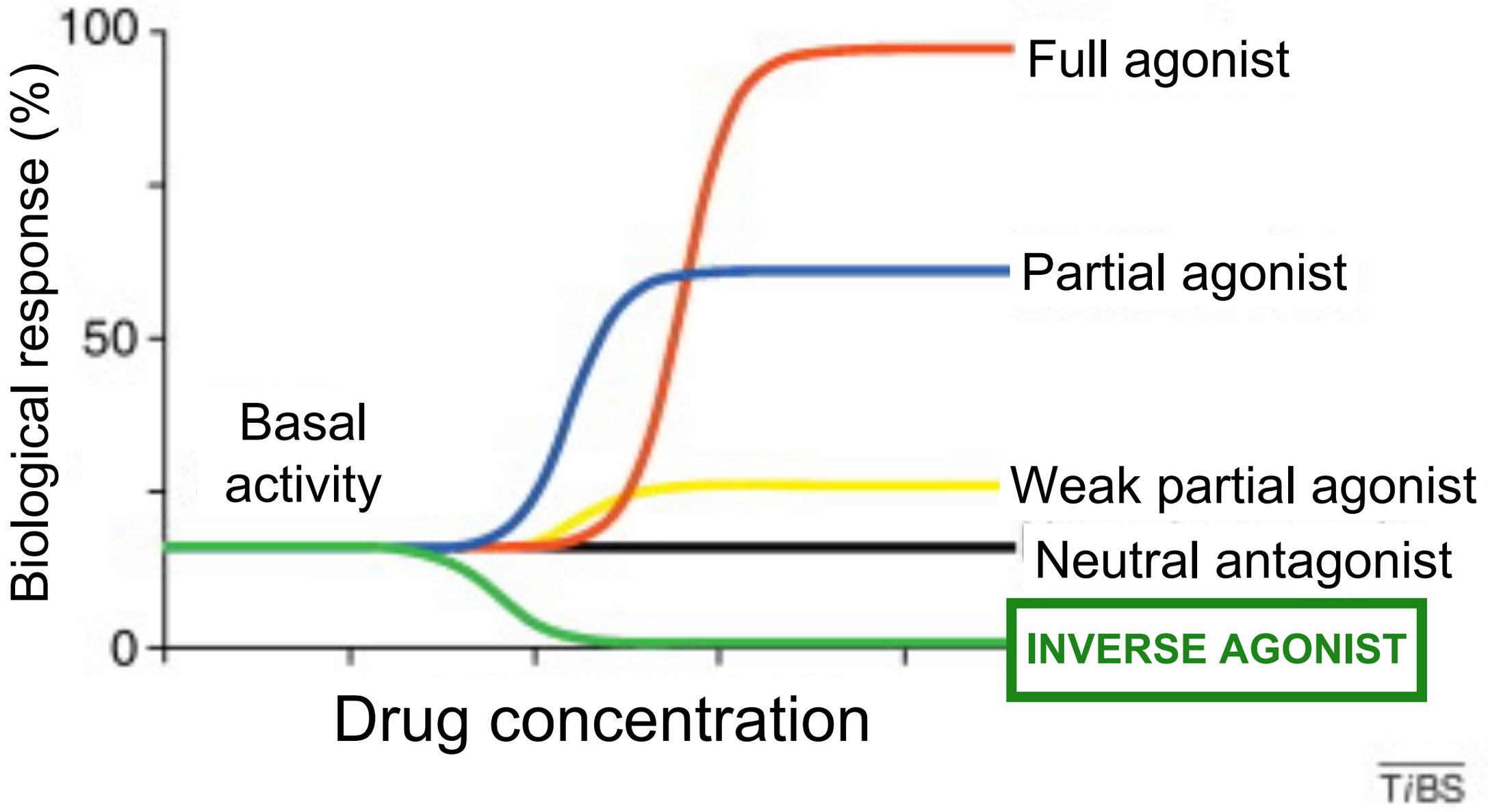


Full agonist: a ligand that produces the maximal response in that tissue

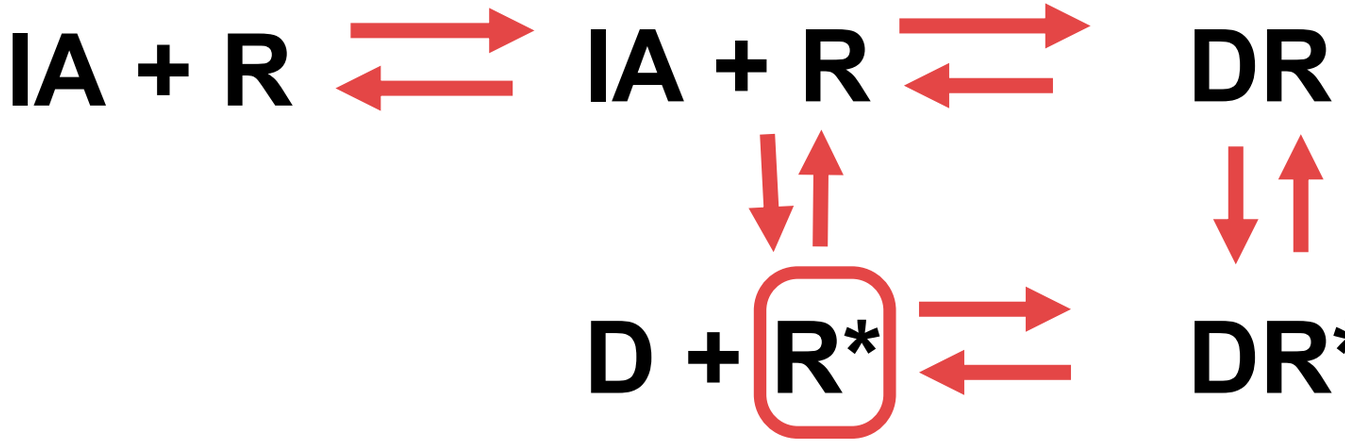
Partial agonist: a ligand that produces a submaximal response in that tissue

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

Inverse agonism



Inverse agonism

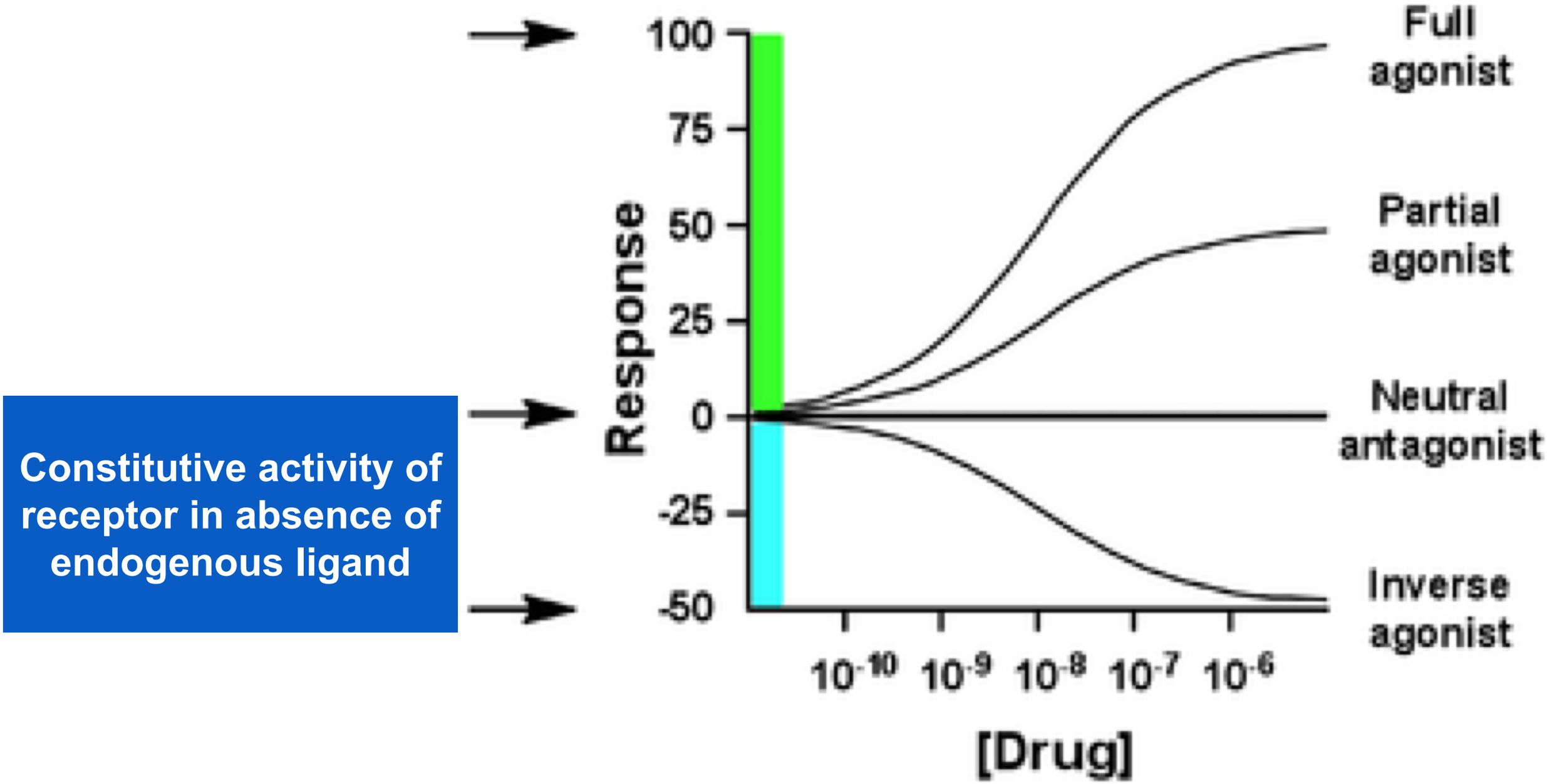


The constitutively active receptor R* is active in absence of endogenous ligand

Inverse agonist IA: a ligand that reduces constitutive receptor activity R* (have higher affinity for the receptor R conformation)

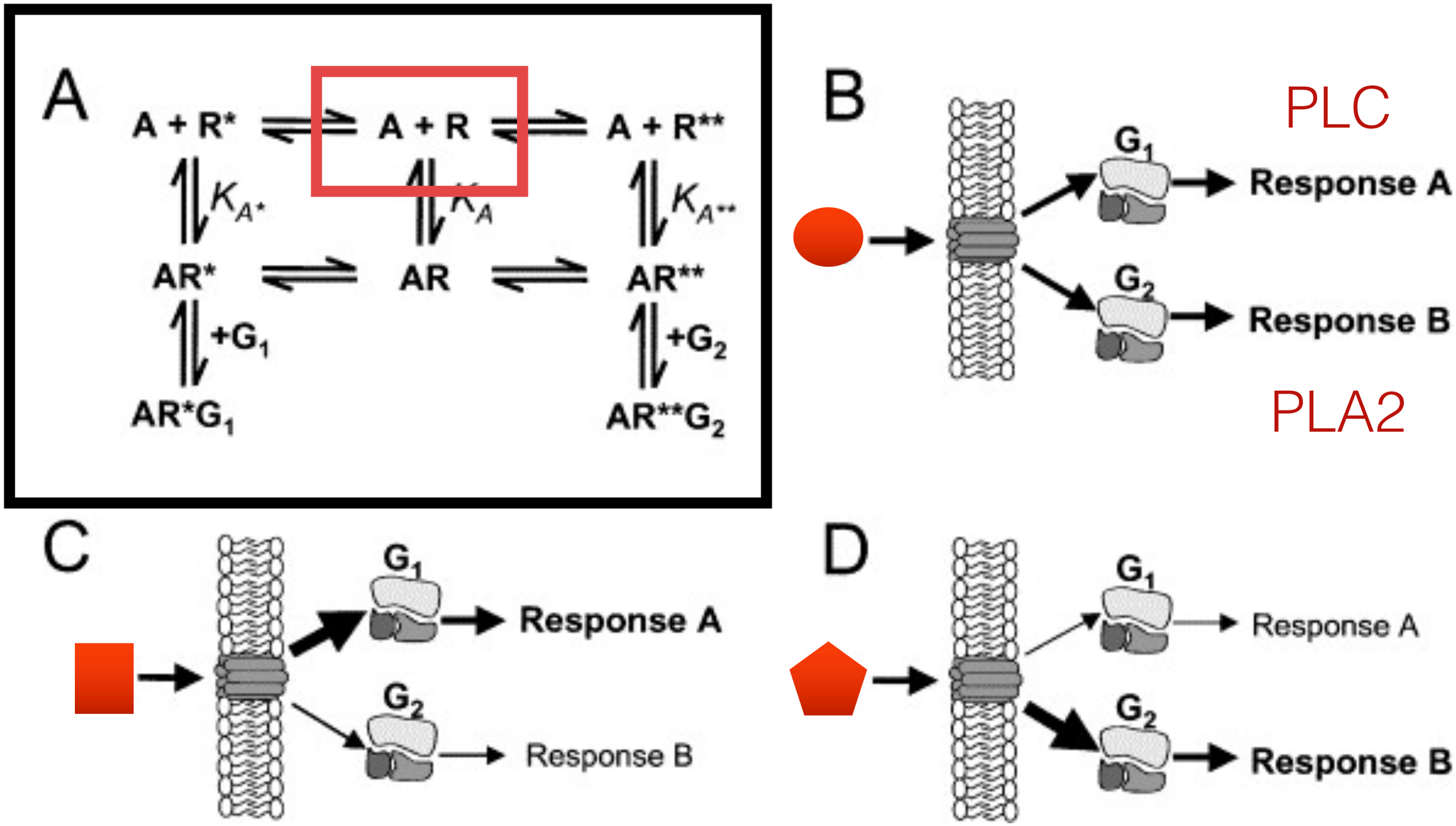
Inverse agonist binds preferentially to R altering the equilibrium R - R*

Inverse agonism



Inverse agonists have Affinity and Efficacy (negative alpha)

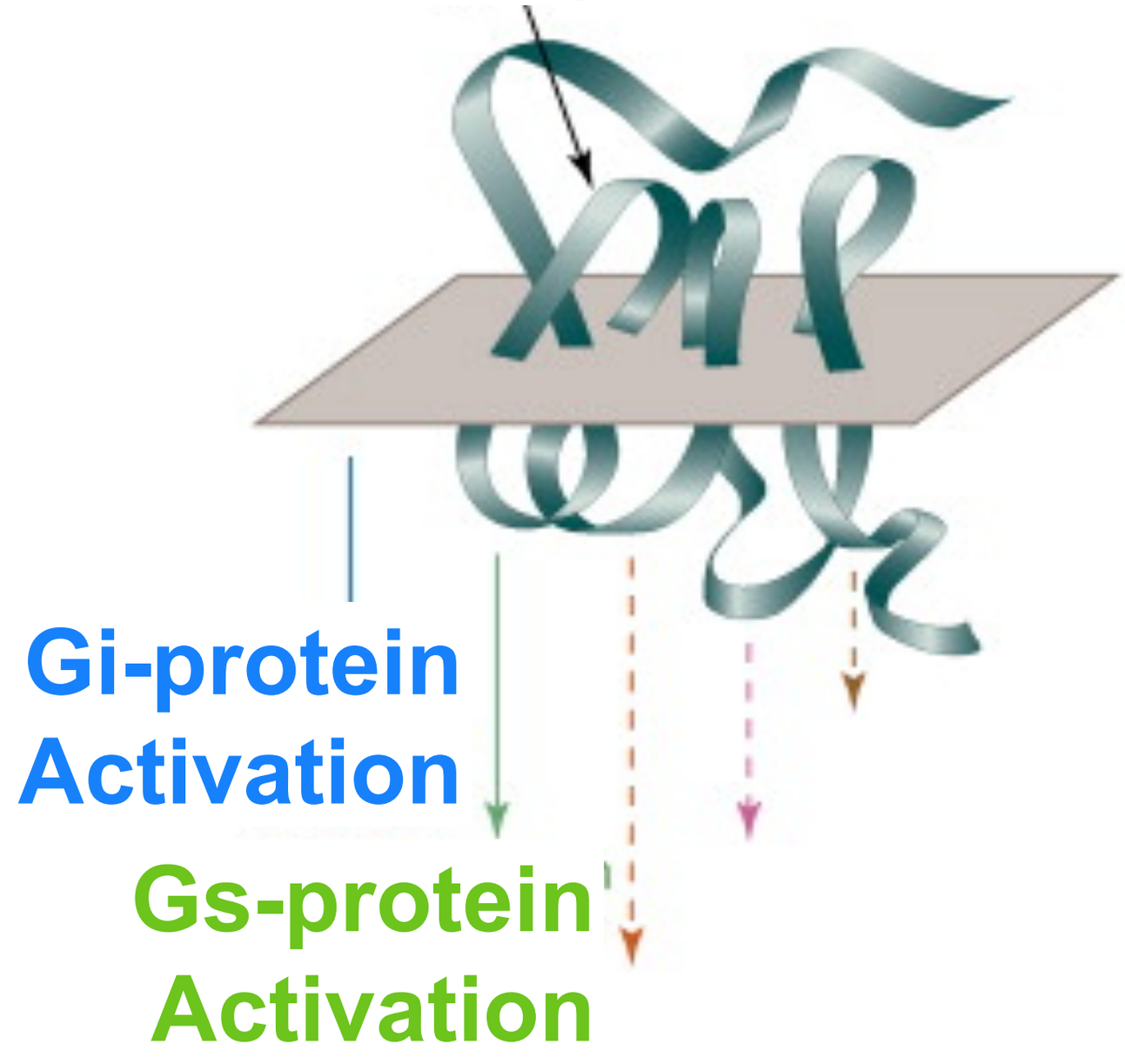
BIASED AGONISM
(LIGAND-SELECTIVE FUNCTIONAL AGONISM)



The ability of ligands acting at the same GPCR to elicit distinct cellular response by preferentially stabilizing different active conformational states of the receptor

BIASED AGONISM

Biased agonist A



Biased agonist B