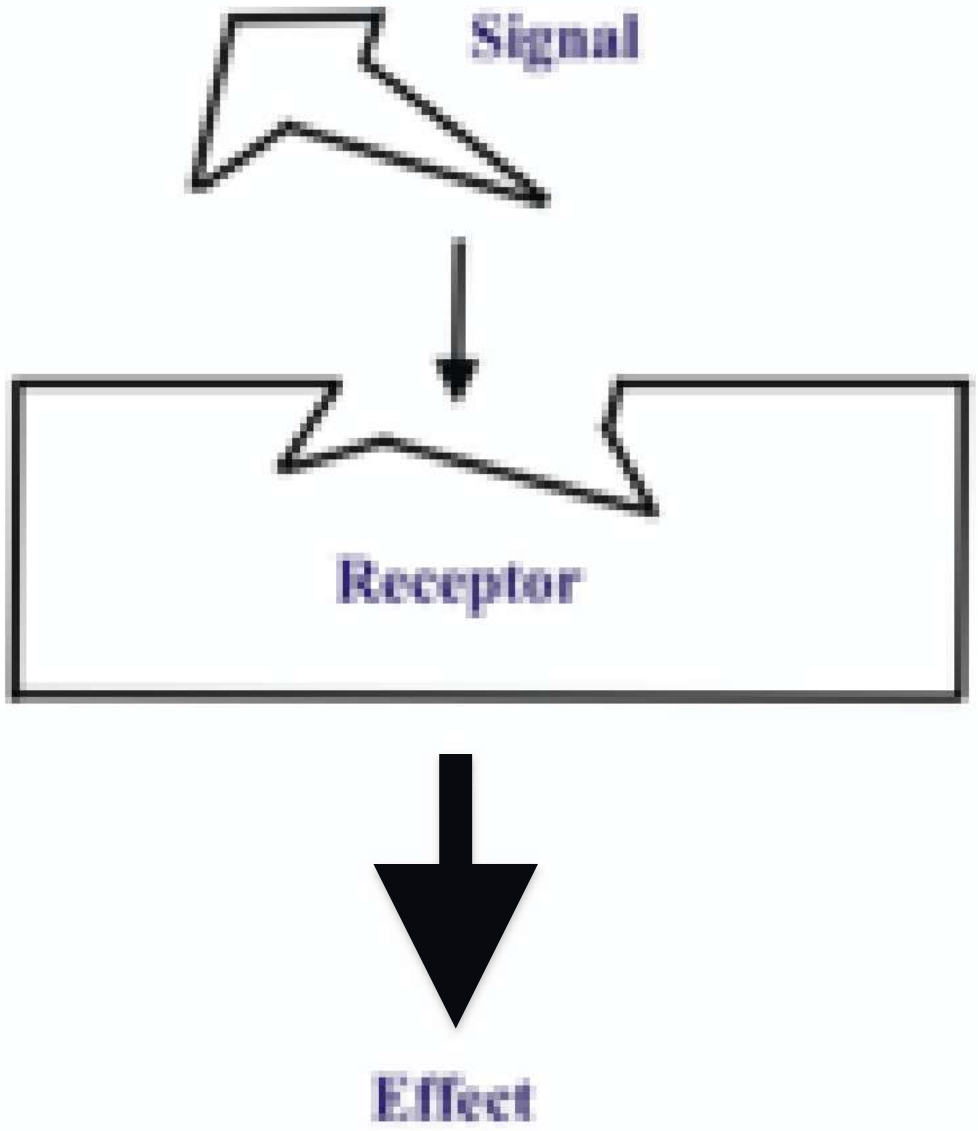
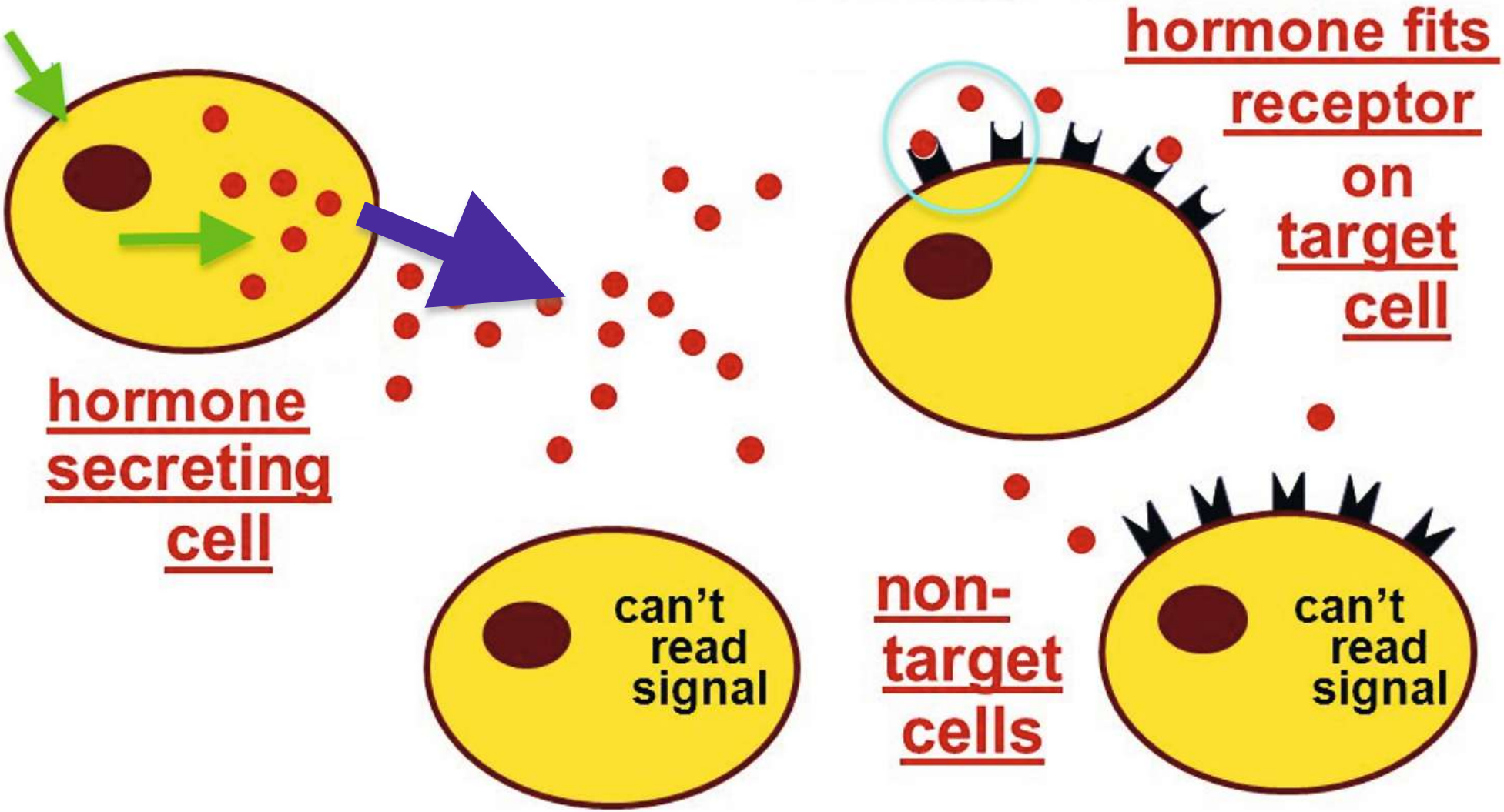
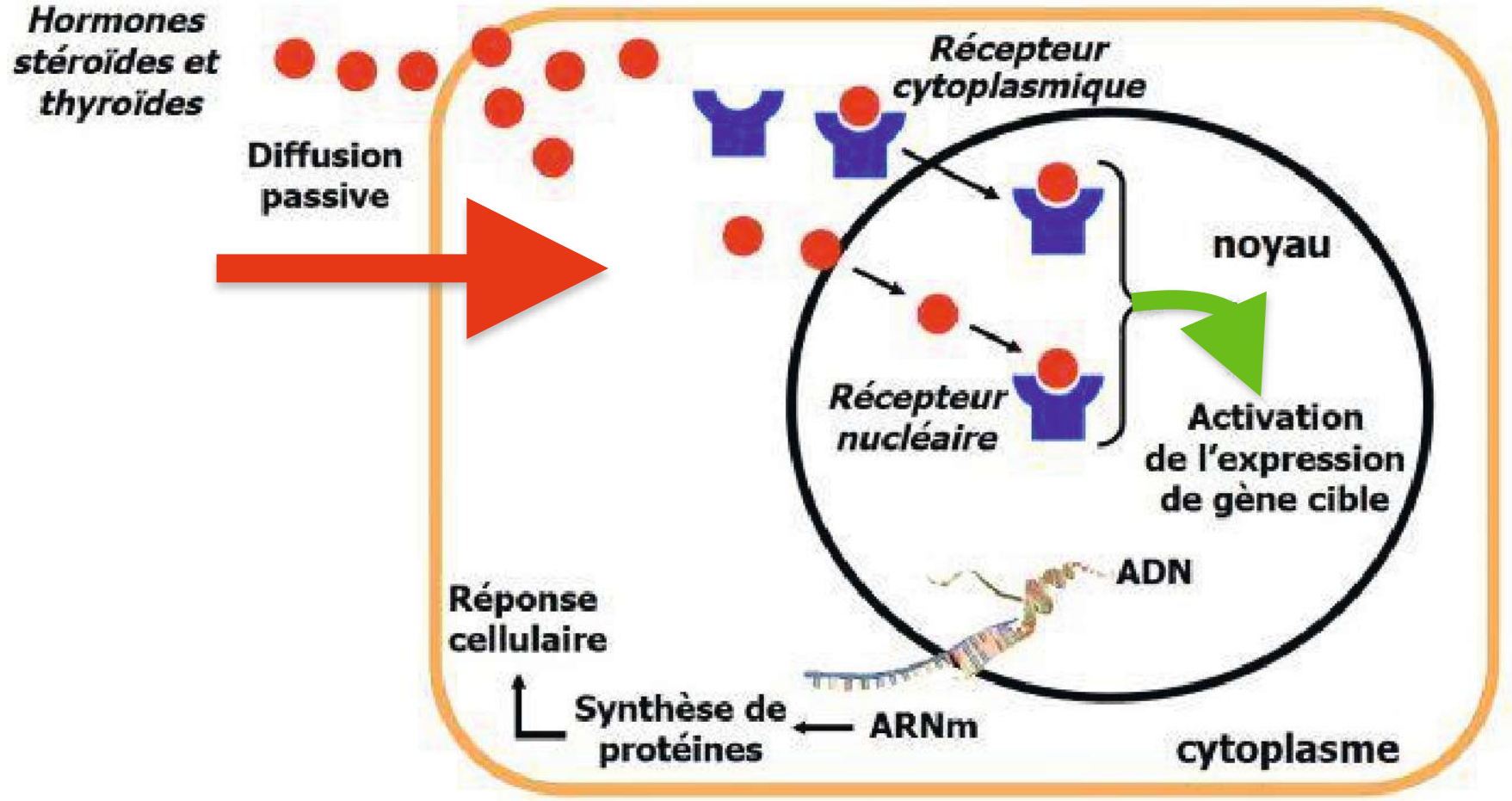
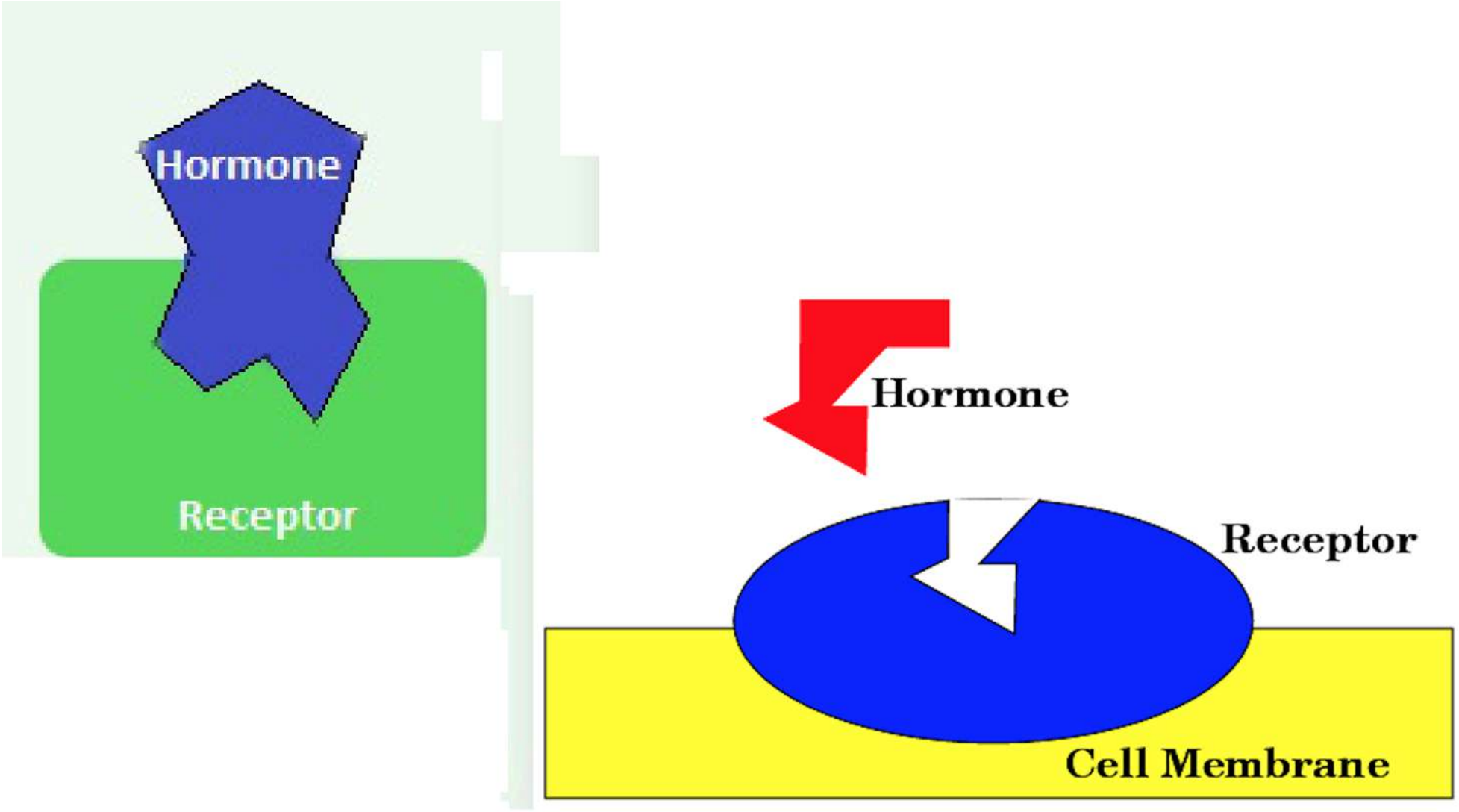

Signal
Receptor
Effect

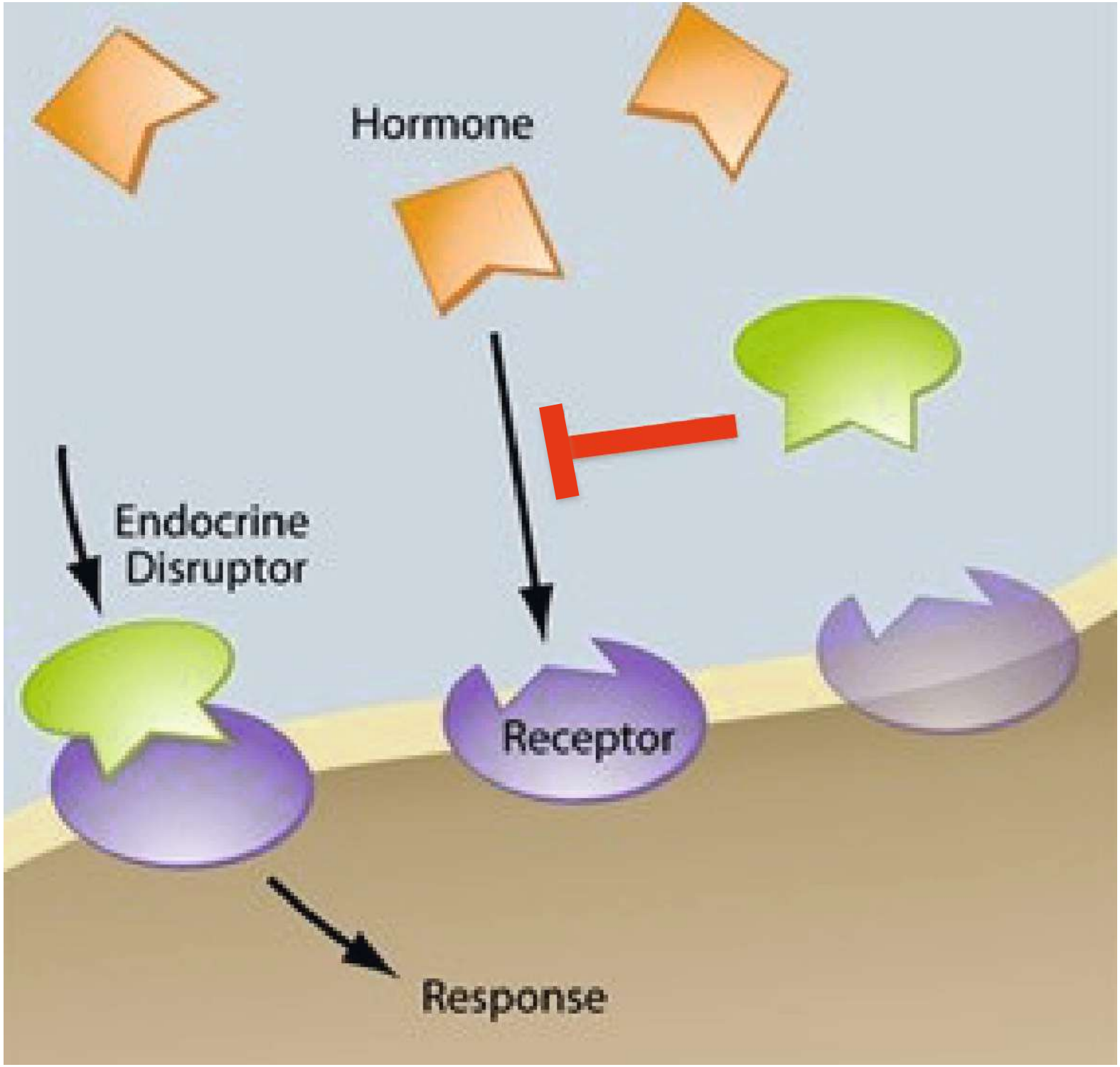
responding to hormones

Lock and key system




Hormones stéroïdes et thyroïdes
Diffusion passive
Récepteur cytoplasmique
noyau
Récepteur nucléaire
Activation de l'expression de gène cible
ADN
Réponse cellulaire
Synthèse de protéines
ARNm
cytoplasme


Hormone
Receptor
Hormone
Receptor
Cell Membrane


Hormone
Endocrine
Disruptor
Receptor
Response

Allosteric regulation of protease activity by small molecules

Department of Pathology, Stanford School of Medicine, 300 Pasteur Drive, Stanford, USA
Aimee Shen*[a]

Abstract

Proteases regulate a plethora of biological processes. Because they irreversibly cleave peptide bonds, the activity of proteases is strictly controlled. While there are many ways to regulate protease activity, an emergent mechanism is the modulation of protease function by small molecules acting at allosteric sites. This mode of regulation holds the potential to allow for the specific and temporal control of a given biological process using small molecules. These compounds also serve as useful tools for studying protein dynamics and function. This review highlights recent advances in identifying and characterizing natural and synthetic small molecule allosteric regulators of proteases and discusses their utility in studies of protease function, drug discovery and protein engineering.

Mol. BioSyst., 2010, **6**, 1431-1443

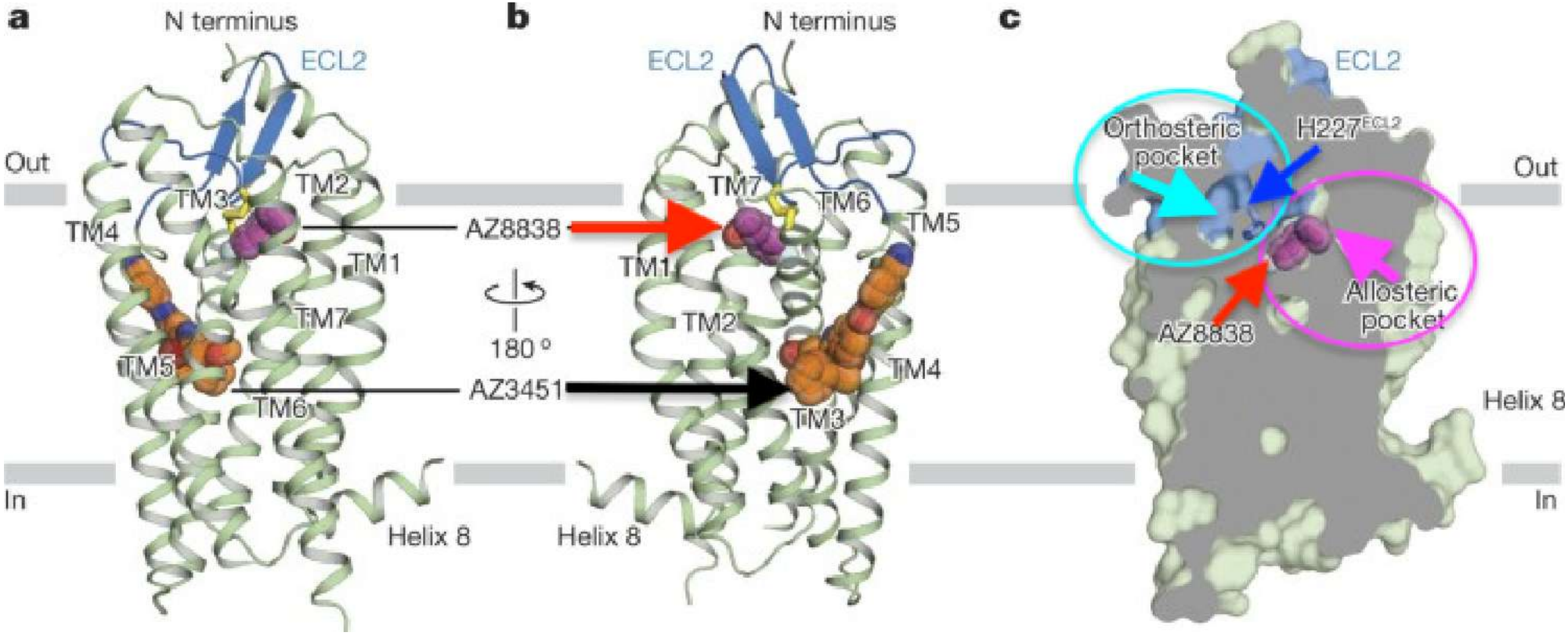
X-ray screening identifies active site and allosteric inhibitors of SARS-CoV-2 main protease

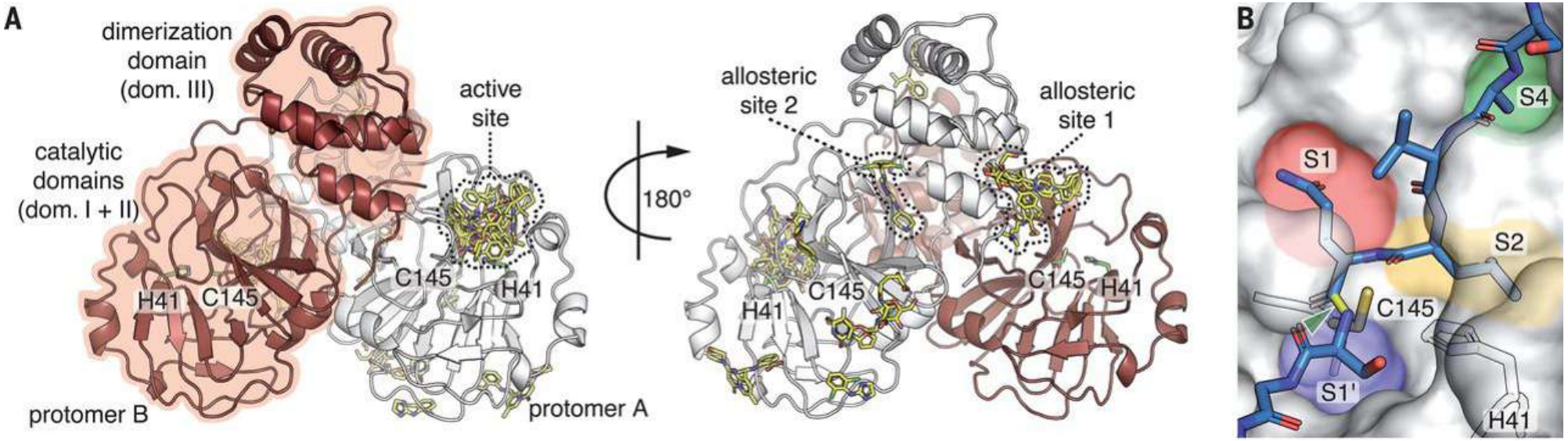
Sebastian Günther[1,*,†], Patrick Y. A. Reinke[1,†], Yaiza Fernández-García[2], Julia Lieske[1], Thomas J. Lane[1], ...

Science 07 May 2021:
Vol. 372, Issue 6542, pp. 642-646
DOI: 10.1126/science.abf7945

A large-scale screen to target SARS-CoV-2

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome is initially expressed as two large polyproteins. Its main protease, M^{pro}, is essential to yield functional viral proteins, making it a key drug target. Günther *et al.* used x-ray crystallography to screen more than 5000 compounds that are either approved drugs or drugs in clinical trials. The screen identified 37 compounds that bind to M^{pro}. High-resolution structures showed that most compounds bind at the active site but also revealed two allosteric sites where binding of a drug causes conformational changes that affect the active site. In cell-based assays, seven compounds had antiviral activity without toxicity. The most potent, calpeptin, binds covalently in the active site, whereas the second most potent, pelitinib, binds at an allosteric site.


a
N terminus
ECL2
Out
TM3
TM2
TM4
TM1
TM7
TM5
TM6
In
Helix 8
AZ8838
AZ3451
180 °
b
N terminus
ECL2
TM7
TM6
TM5
TM1
TM2
TM4
TM3
Helix 8
c
ECL2
Orthosteric pocket
H227ECL2
Out
Allosteric pocket
AZ8838
Helix 8
In


A
dimerization
domain
(dom. III)
catalytic
domains
(dom. I + II)
active
site
H41
C145
C145
H41
protomer B
protomer A
180°
allosteric
site 2
allosteric
site 1
H41
C145
C145
H41
B
S4
S1
S2
C145
S1'
H41

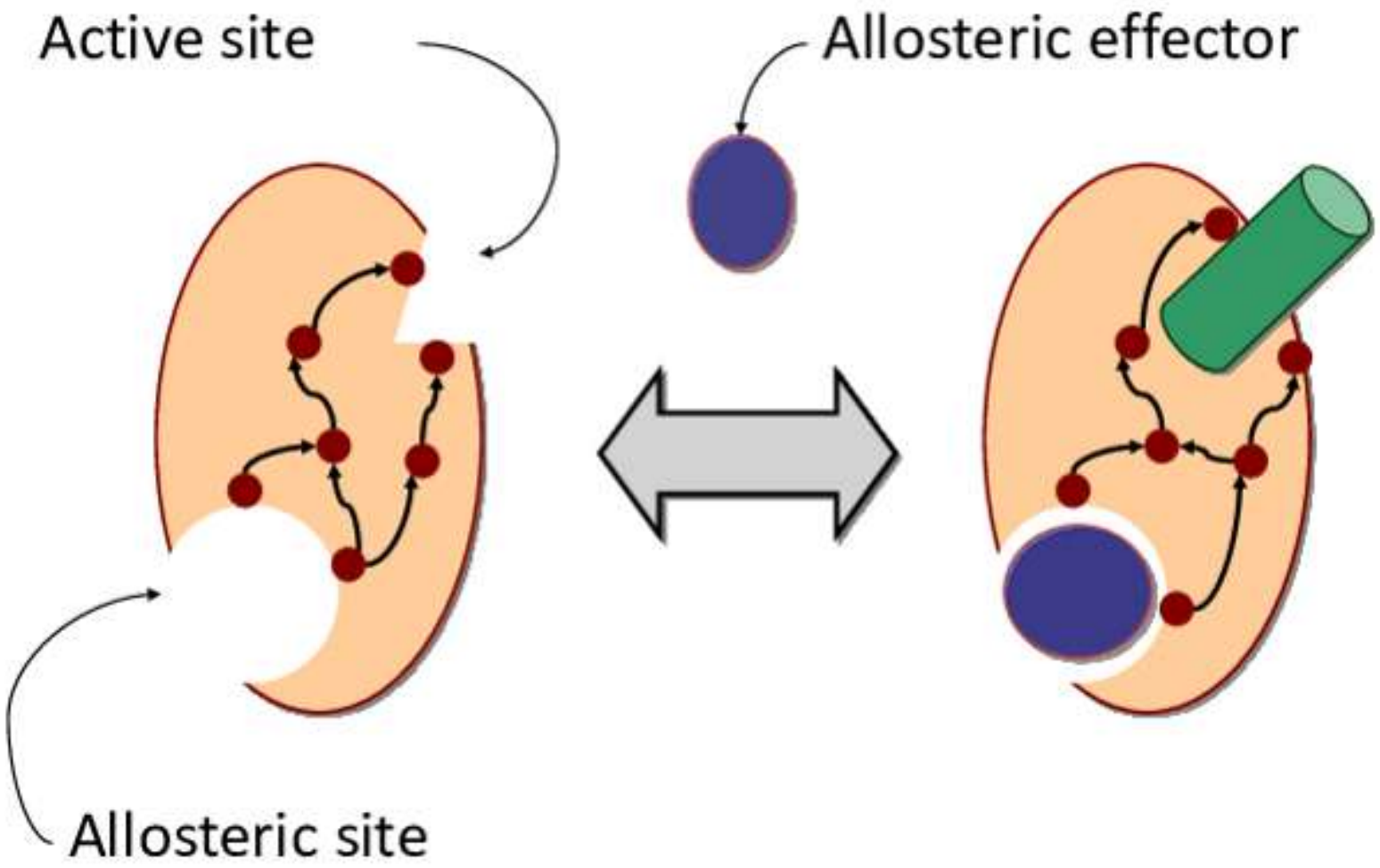
Structural insight into allosteric modulation of protease-activated receptor 2

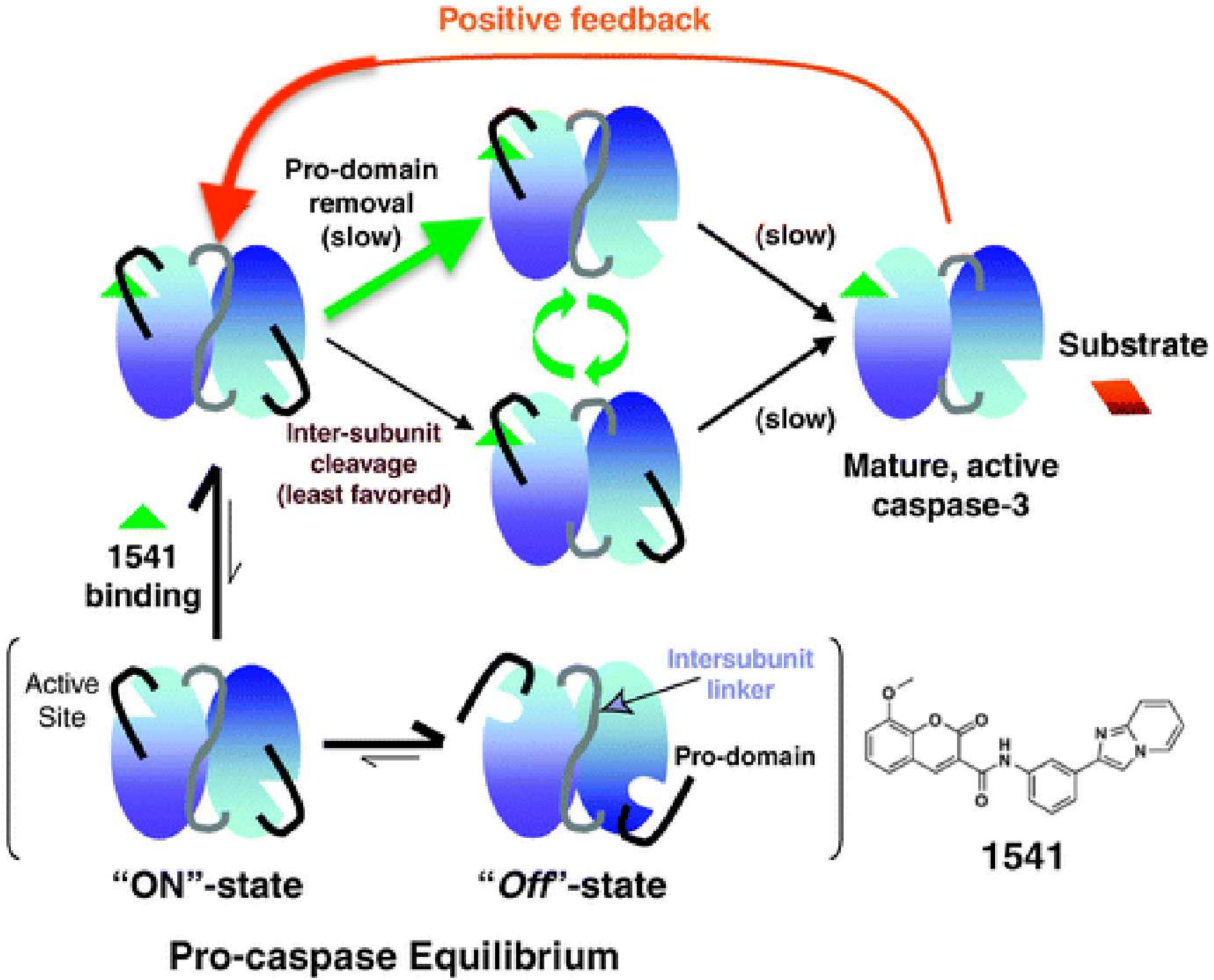
Robert K. Y. Cheng, Cédric Fiez-Vandal, [...]Niek Dekker

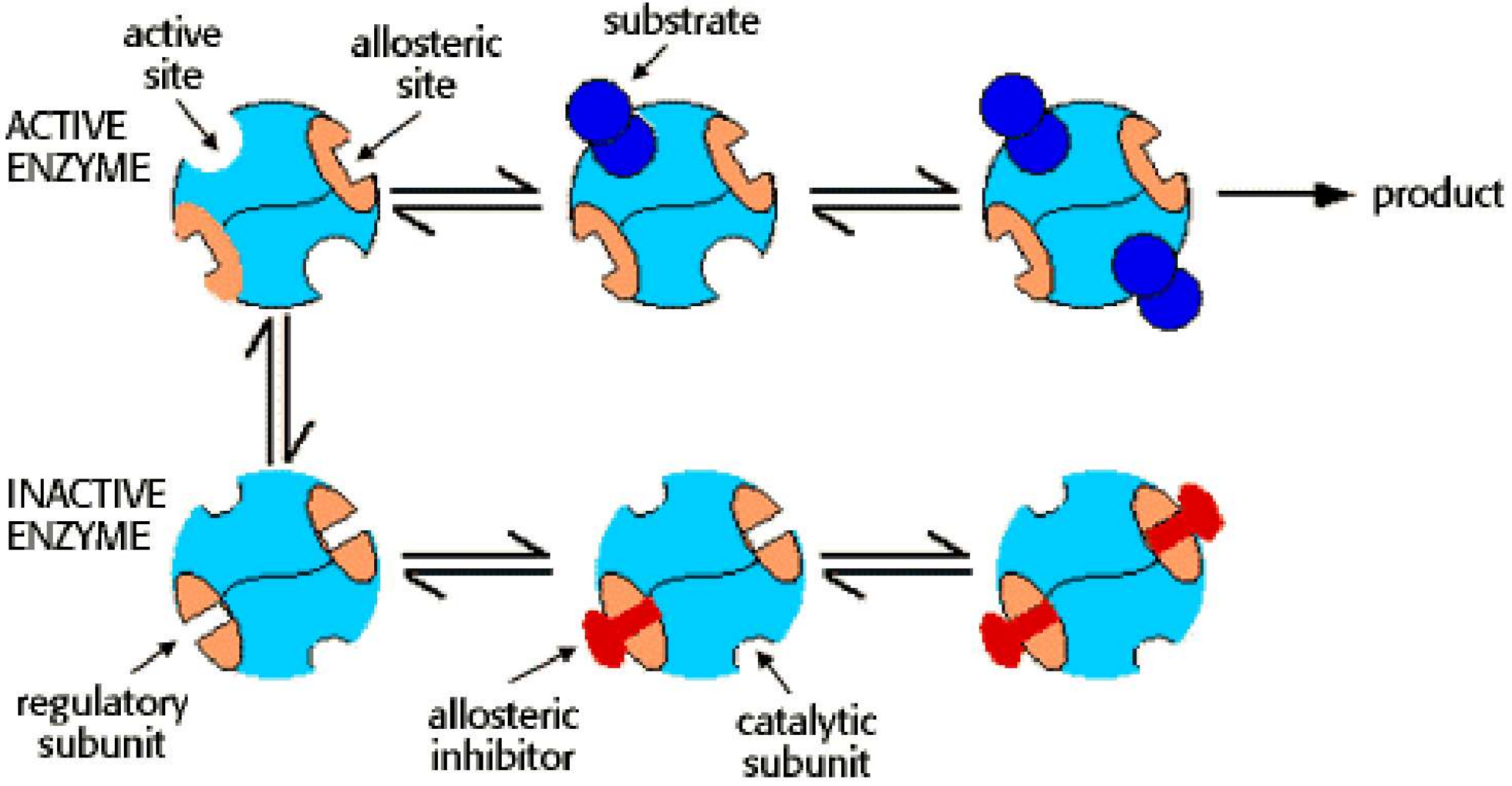
Nature **545**, 112–115 (2017)

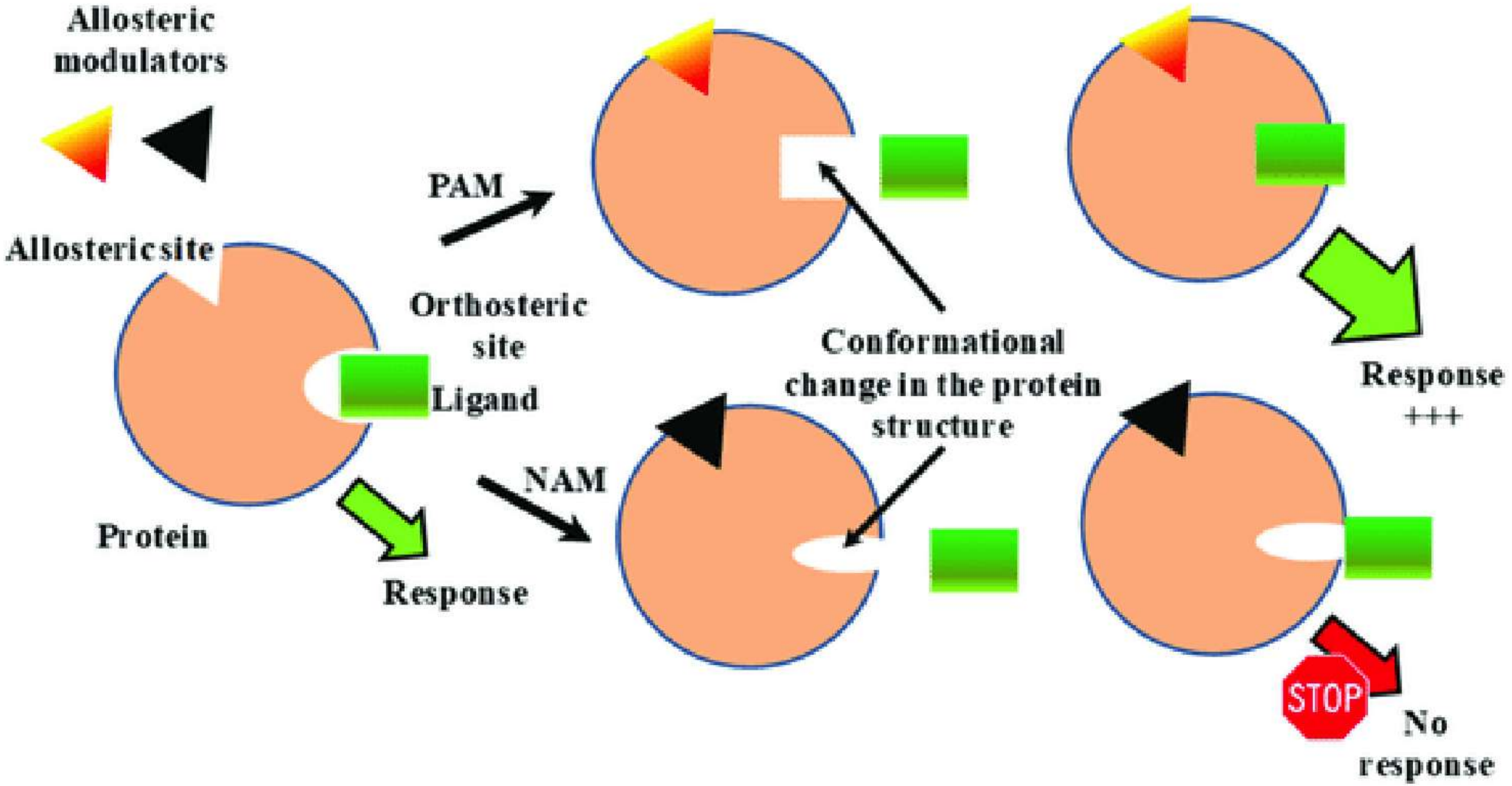
Abstract

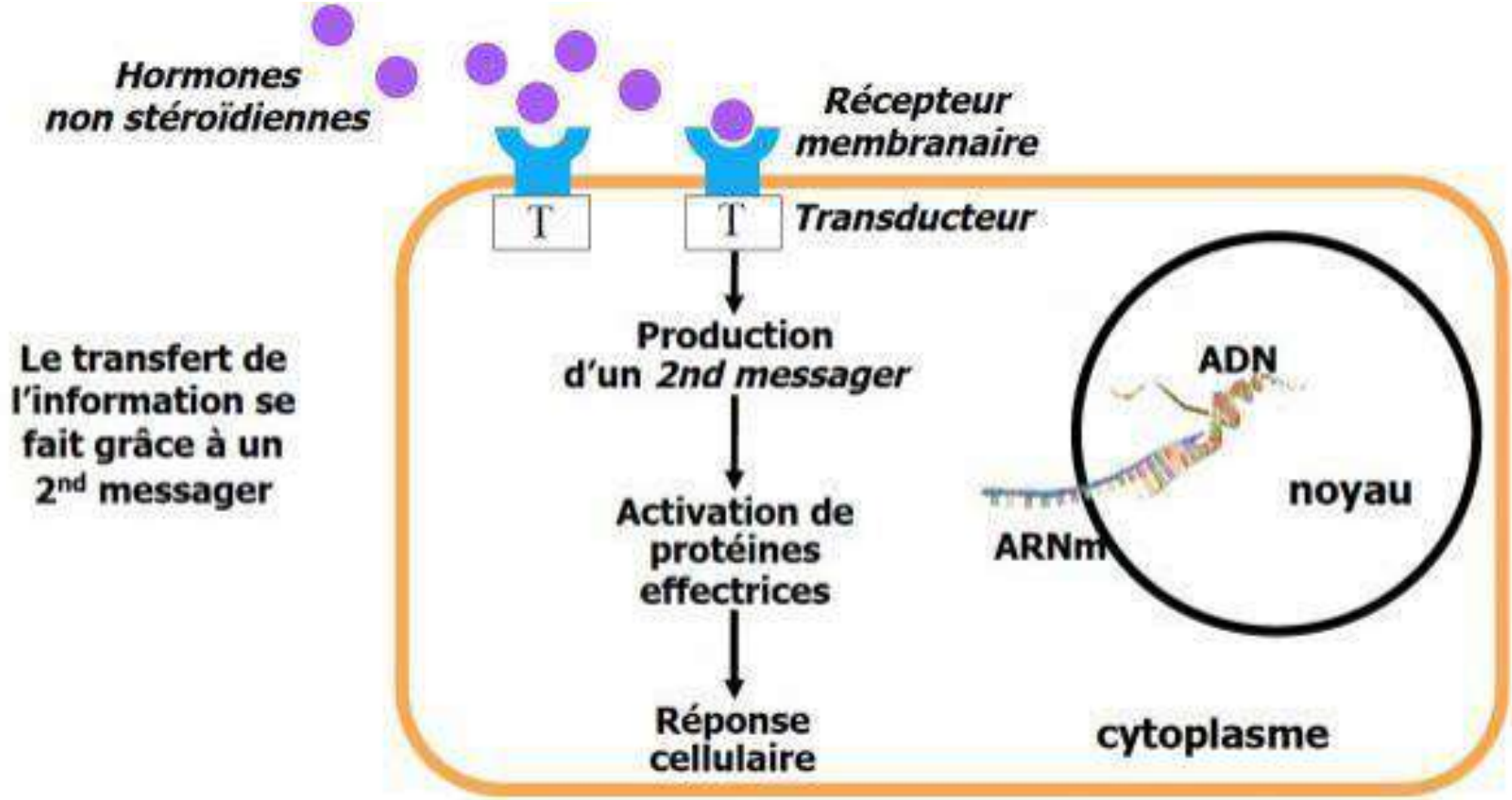
Protease-activated receptors (PARs) are a family of G-protein-coupled receptors (GPCRs) that are irreversibly activated by proteolytic cleavage of the N terminus, which unmasks a tethered peptide ligand that binds and activates the transmembrane receptor domain, eliciting a cellular cascade in response to inflammatory signals and other stimuli. PARs are implicated in a wide range of diseases, such as cancer and inflammation[1,2,3]. PARs have been the subject of major pharmaceutical research efforts[3] but the discovery of small-molecule antagonists that effectively bind them has proved challenging. The only marketed drug targeting a PAR is vorapaxar[4], a selective antagonist of PAR1 used to prevent thrombosis. The structure of PAR1 in complex with vorapaxar has been reported previously[5]. Despite sequence homology across the PAR isoforms, discovery of PAR2 antagonists has been less successful, although GB88 has been described as a weak antagonist[6]. Here we report crystal structures of PAR2 in complex with two distinct antagonists and a blocking antibody. The antagonist AZ8838 binds in a fully occluded pocket near the extracellular surface. Functional and binding studies reveal that AZ8838 exhibits slow binding kinetics.


Active site
Allosteric effector
Allosteric site


Positive feedback
Pro-domain
removal
(slow)
(slow)
Substrate
Inter-subunit
cleavage
(least favored)
(slow)
Mature, active
caspase-3
1541
binding
Active
Site
Intersubunit
linker
Pro-domain
1541
"ON"-state
"Off"-state
Pro-caspase Equilibrium

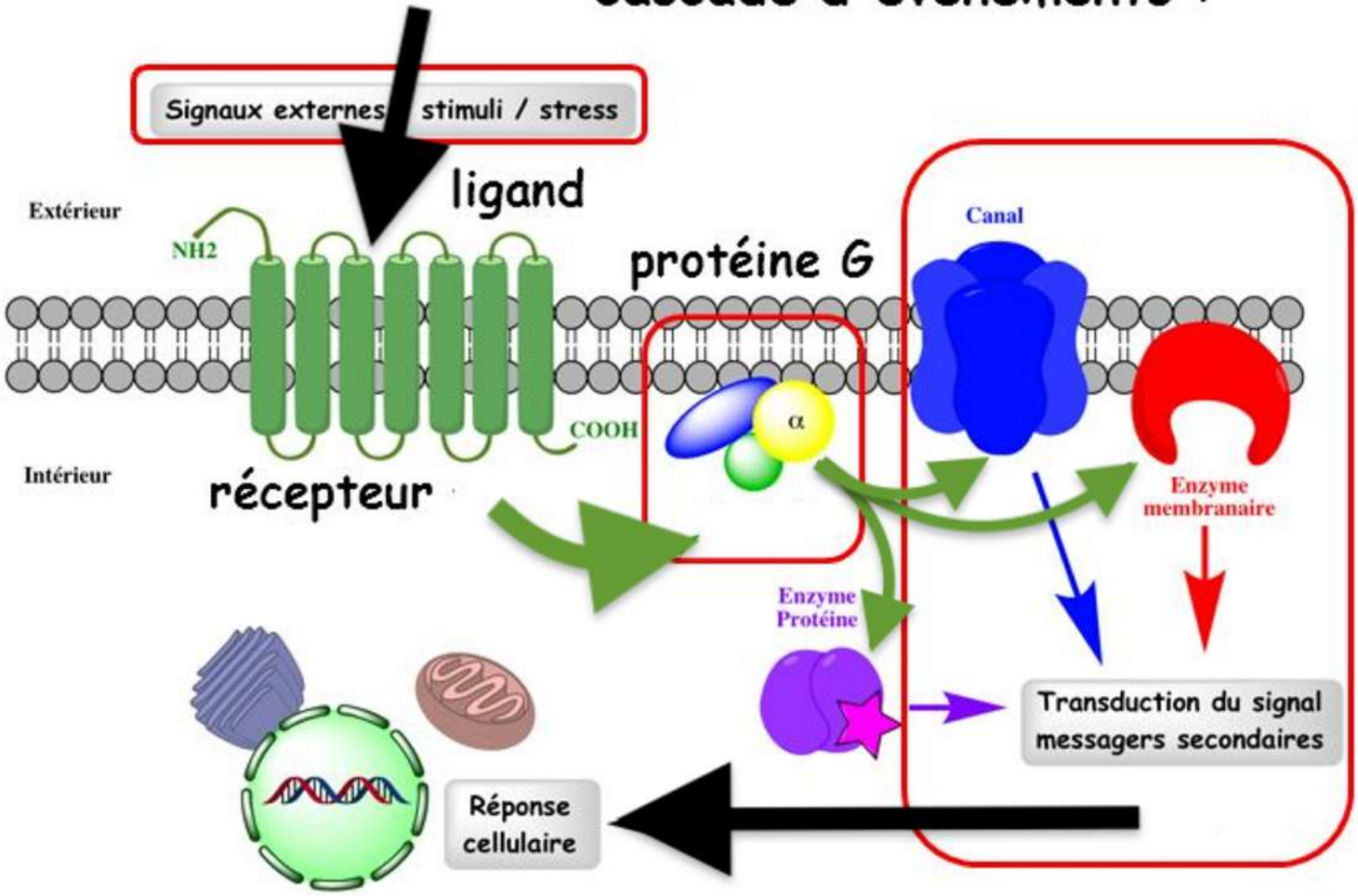

active site
allosteric site
substrate
ACTIVE ENZYME
product
INACTIVE ENZYME
regulatory subunit
allosteric inhibitor
catalytic subunit


Allosteric modulators
PAM
Allosteric site
Orthosteric site
Ligand
Protein
Response
NAM
Conformational change in the protein structure
Response
+++
STOP
No response



Le transfert de l'information se fait grâce à un 2nd messager

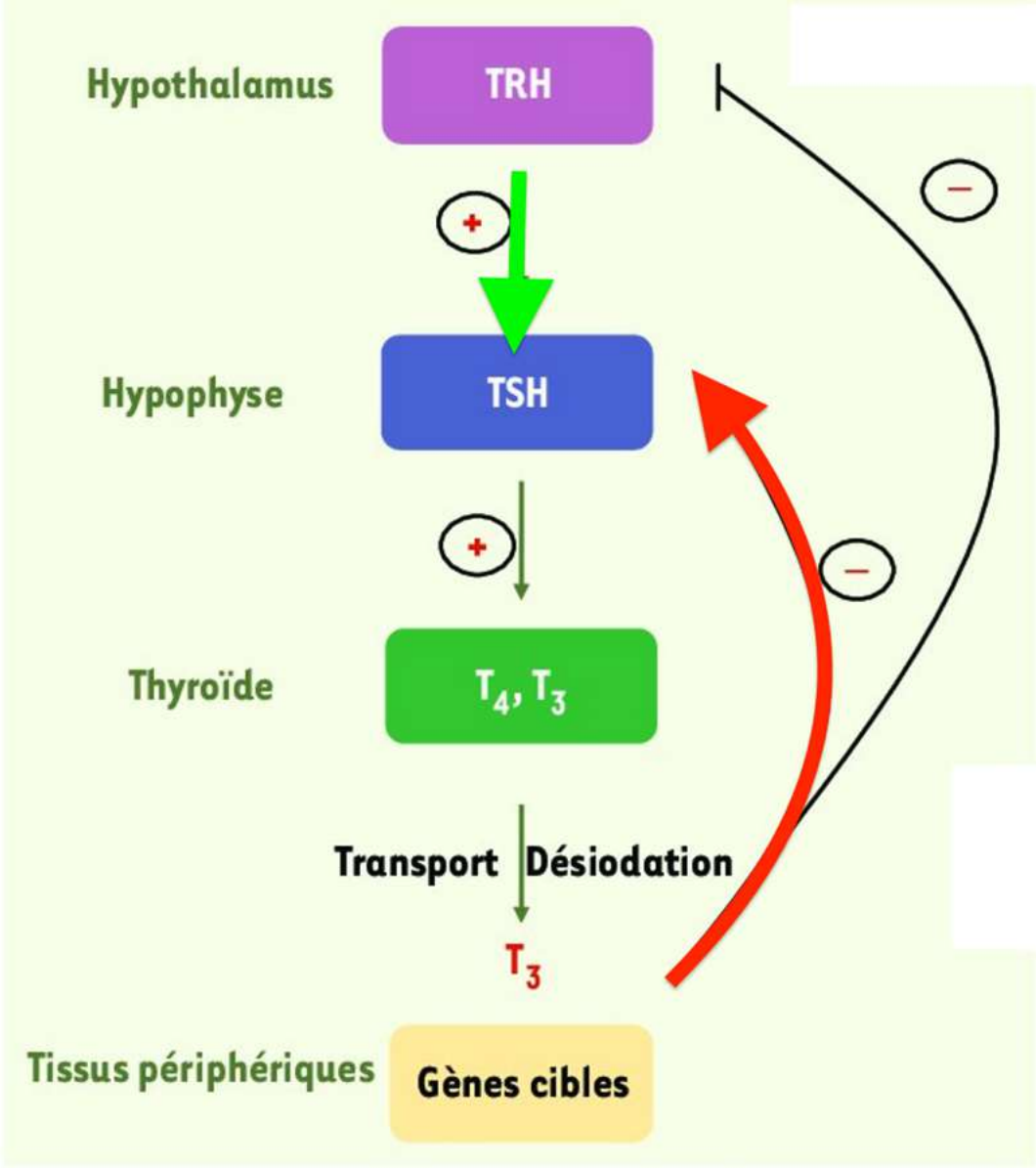
L'activation des récepteurs couplés aux protéines G entraîne une cascade d'événements :



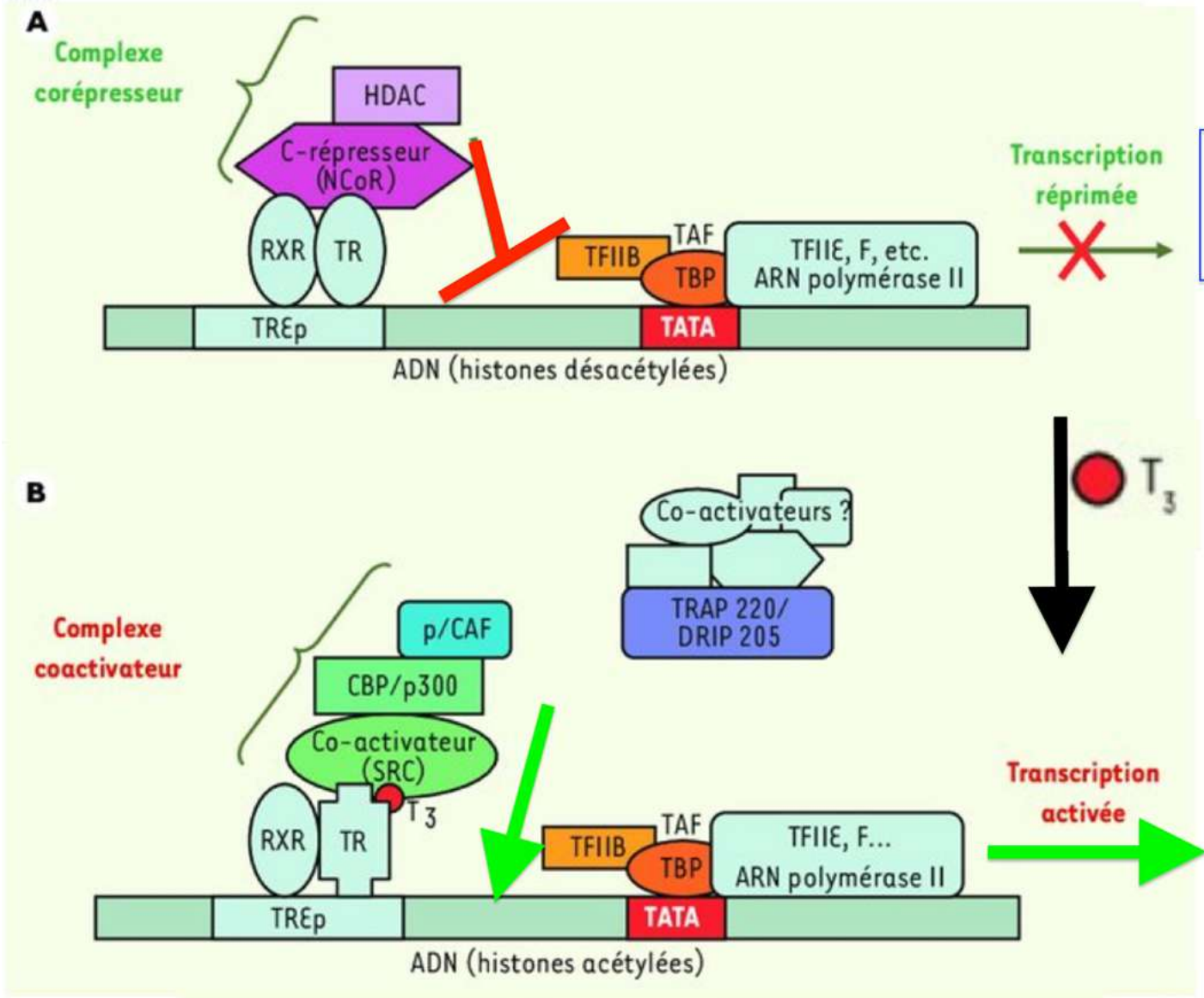
l'activation d'un récepteur par son ligand

l'activation de la protéine G

activation ou inhibition par la protéine G d'une protéine effectrice



Mécanisme de rétrocontrôle négatif de la synthèse des hormones thyroïdiennes. Les hormones thyroïdiennes T 3 et T 4 synthétisées par la thyroïde sont transportées dans le sang par des protéines plasmatiques. La T 4 étant la forme majoritaire produite par la thyroïde, des désiodases vont contribuer à la désiodation de la T 4 en T 3 , forme biologiquement active. Cette dernière agit dans les tissus périphériques en contrôlant la transcription de ses gènes cibles ; de plus, elle contrôle négativement l'expression des gènes codant pour la TSH (thyréostimuline) et la TRH (thyréolibérine), stimulatrices de la sécrétion des hormones thyroïdiennes par la thyroïde.



Activation transcriptionnelle par des récepteurs d'hormones thyroïdiennes fixés sur des TRE positifs (TREp). A. En l'absence de ligand (T 3), les TR (appelés dans ce cas apo-TR) hétérodimérisés avec le facteur RXR recrutent un complexe multiprotéique corépresseur comprenant notamment des histone désacétylases (HDAC), responsables du maintien de la chromatine dans un état condensé peu favorable à la transcription. D'autres protéines interagissent également avec les cofacteurs de la machinerie transcriptionnelle de base, entraînant ainsi une répression de la transcription du gène cible. B. La liaison de la T 3 aux TR (qualifiés dans ce cas d'holo-TR) induit leur changement conformationnel, permettant un relargage du complexe corépresseur au bénéfice de complexes coactivateurs comprenant des enzymes de modification des histones de type HAT (CBP/p300) et des protéines TRAP/DRIP probablement associées à d'autres coactivateurs interagissant avec la machinerie transcriptionnelle (ARNpol II + TAF + TFIIB +TBP), l'ensemble permettant une activation de la transcription (voir texte). CBP : protéine de liaison à CREB ; DRIP : protéine interagissant avec le récepteur de la vitamine D ; GTF : facteur général de transcription ; HDAC : histone désacétylase ; HAT : histone acétyltransférase ; p/CAF : facteur associé à p300/CBP ; RXR : récepteur de l'acide 9-cis-rétinoïque ; NcoR : corépresseur nucléaire ; SRC : coactivateur des récepteurs stéroïdiens ; TAF : facteur associé à TBP ; TBP : protéine de liaison à la boîte TATA ; TF : facteur de transcription ; TR : récepteur des HT ; TRAP : protéine associée aux TE ; TREp : élément de réponse positif aux TR (d'après [11]).

RESEARCH ARTICLE

Science 12 Apr 2019:
Vol. 364, Issue 6436, pp. 148-153
DOI: 10.1126/science.aav7942

Structure and dynamics of the active human parathyroid hormone receptor-1

Li-Hua Zhao[1,*], Shanshan Ma[1,2,*], Ieva Sutkeviciute[3,*], Dan-Dan Shen[4,*], X. Edward Zhou[5],
+ See all authors and affiliations

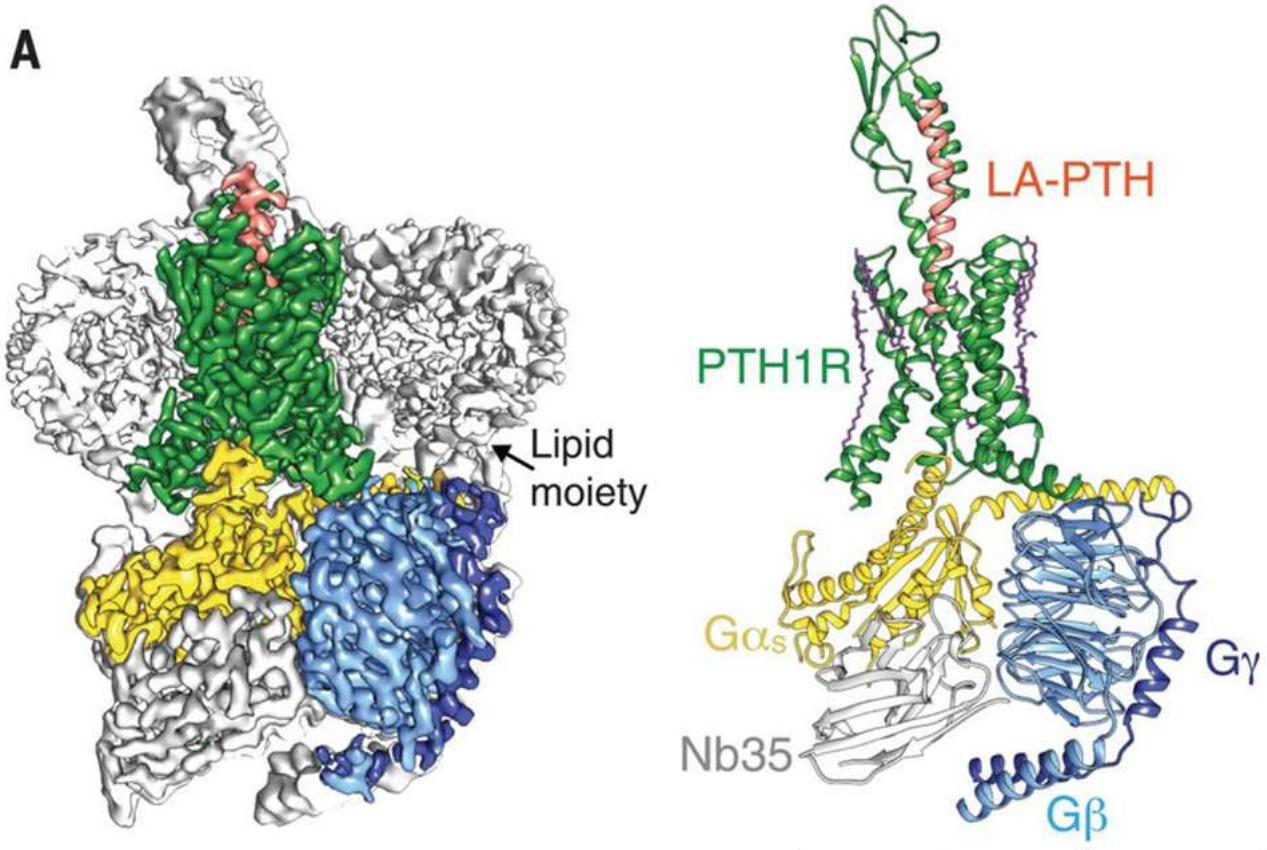
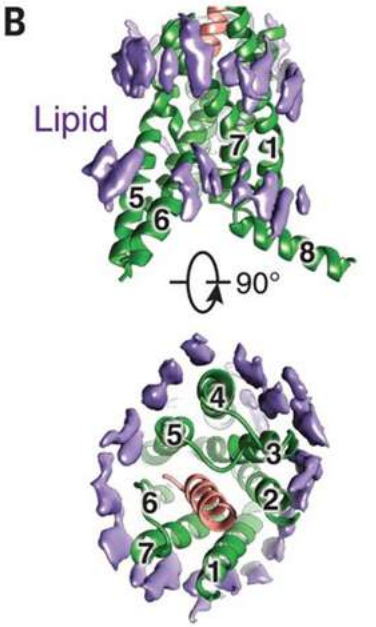


Fig. 1 Cryo-EM structure of LA-PTH–bound human PTH1R in complex with G_s.

(**A**) (Left) Cut-through view of cryo-EM density map that illustrates the LA-PTH–PTH1R–G_s complex and the disc-shaped micelle. The unsharpened cryo-EM density map at the 0.01 threshold shown as light gray surface indicates a micelle diameter of 12 nm. The colored cryo-EM density map is shown at 0.026 threshold. (Right) Cartoon representation of the LA-PTH–PTH1R–G_s complex is shown with annular lipids in purple stick representation. Green, PTH1R; orange, LA-PTH; gold, G_s Ras-like domain; light blue, Gβ; medium blue, Gγ; gray, Nb35. (**B**) Cryo-EM density of the ordered annular lipid layer around the receptor TMD shown in purple; numbers 1 through 7 represent TM1 to TM7; receptor ECD and G protein are omitted.



The high- and low-affinity receptor binding sites of growth hormone are allosterically coupled

Scott T. R. Walsh, Juliesta E. Sylvester, and Anthony A. Kossiakoff

PNAS December 7, 2004 101 (49) 17078-17083; https://doi.org/10.1073/pnas.0403336101

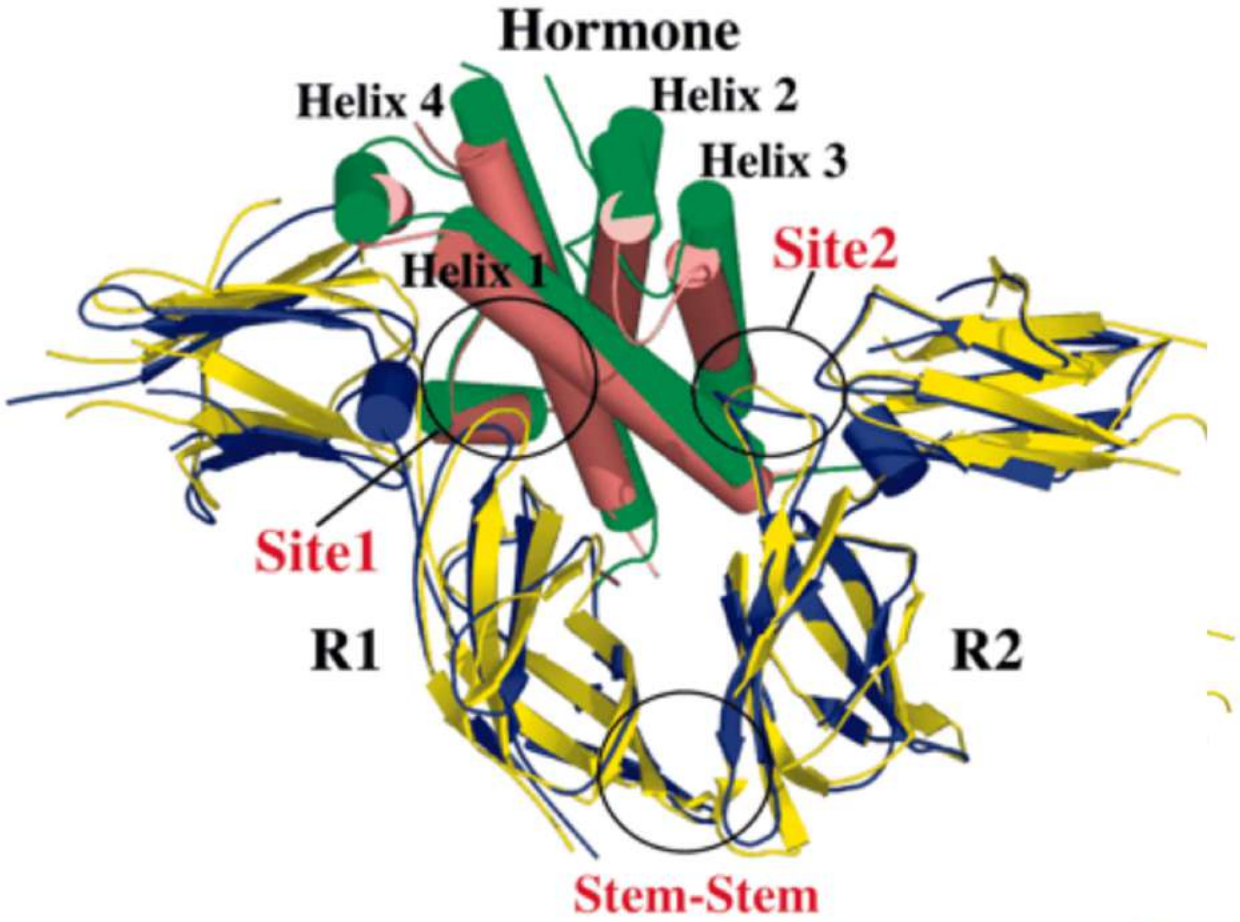
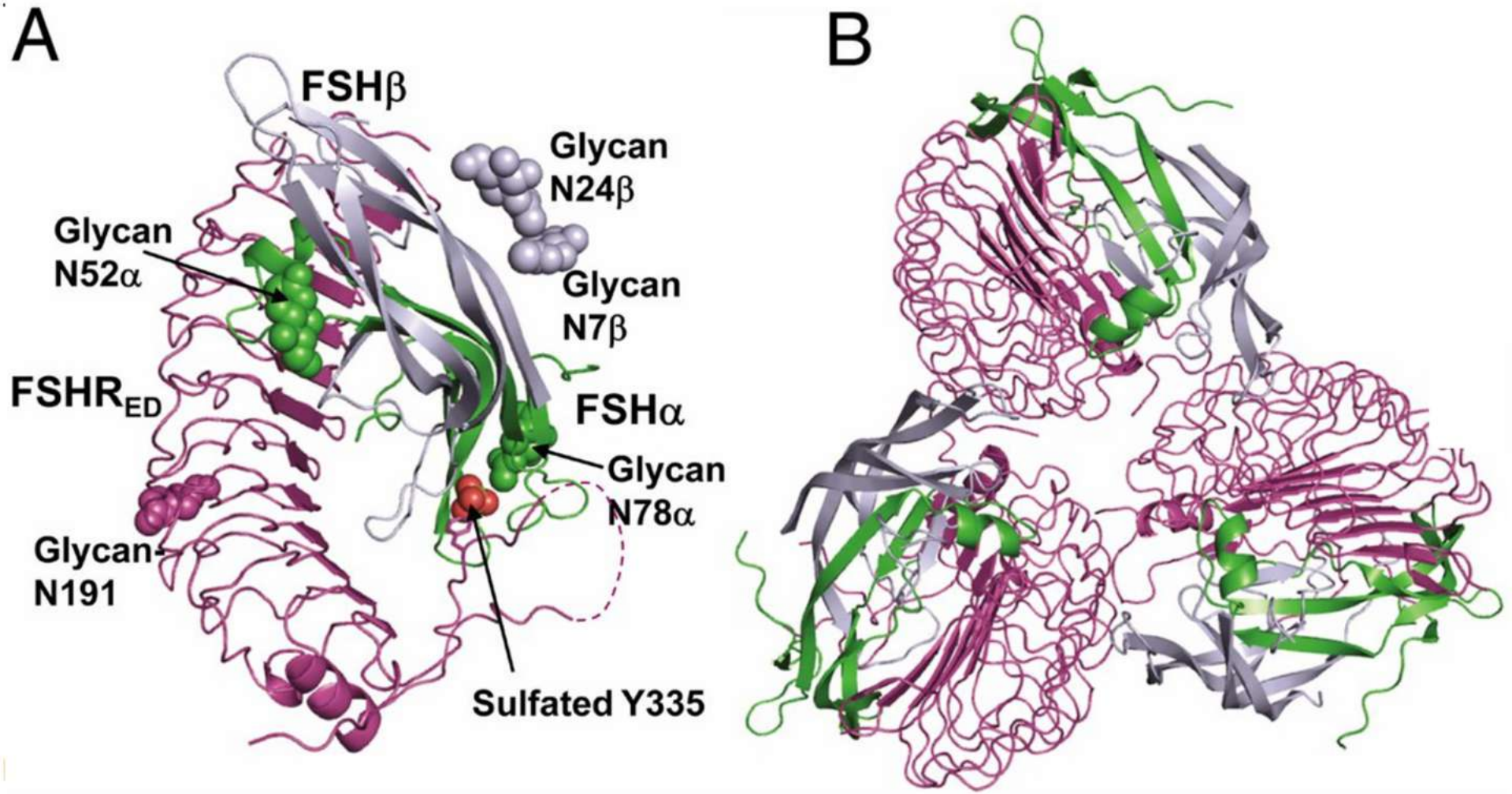


Diagram of the hGHv/R1/R2 receptor (hGHR) ternary complex superimposed onto the WT hGH/R1/R2 complex (6, 16). The hGHv complex is shown in salmon (hormone) and blue (R1/R2), and the WT hGH complex is shown in green (hormone) and yellow (R1/R2). The structures were superimposed by using the β-sheets in both the N- and C-terminal domains of the hGH receptor (hGHR). The Site1, Site2, and Stem–Stem binding interfaces between both hGHv and WT hGH and the hGHR R1 and R2 are circled. All structural figures were generated by using the program PYMOL (DeLano Scientific, San Carlos, CA, www.pymol.org).



Structure of human FSH in complex with human FSHR$_{ED}$. (*A*) Ribbon model of human FSH bound to FSHR$_{ED}$: FSH α-subunit is shown in green, FSH β-subunit is shown in purple, and FSHR$_{ED}$ is shown in magenta. The side chain of sulfated Y335 is depicted as sticks for the tyrosine stem and colored balls for the sulfate group. The carbohydrates are depicted as balls. The disordered residues in the receptors are marked as dashed lines. (*B*) Top view of the trimer observed in the asymmetrical unit.