Insulin Signaling Pathway

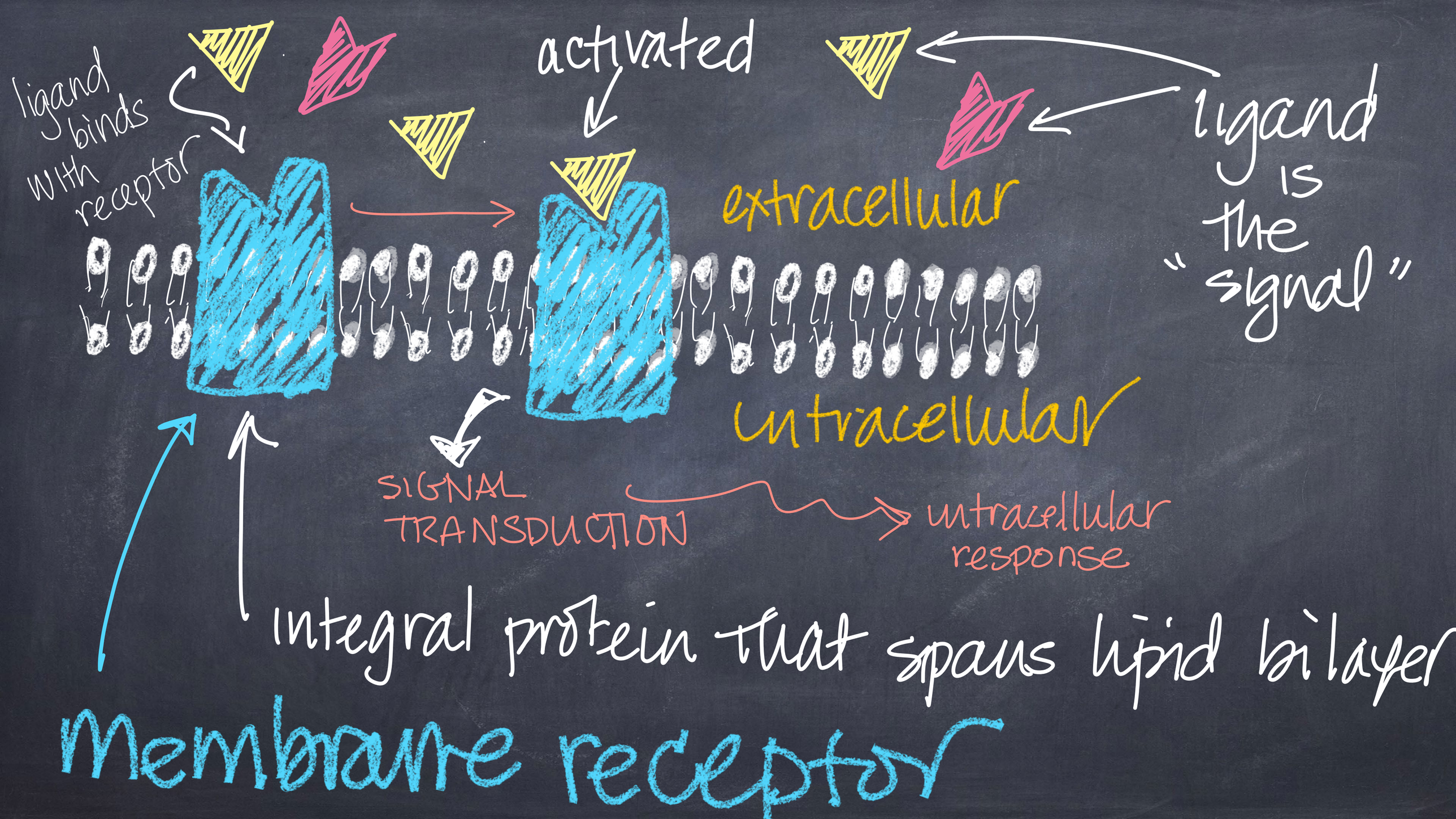
Boyle - Metabolic Brain Disorders

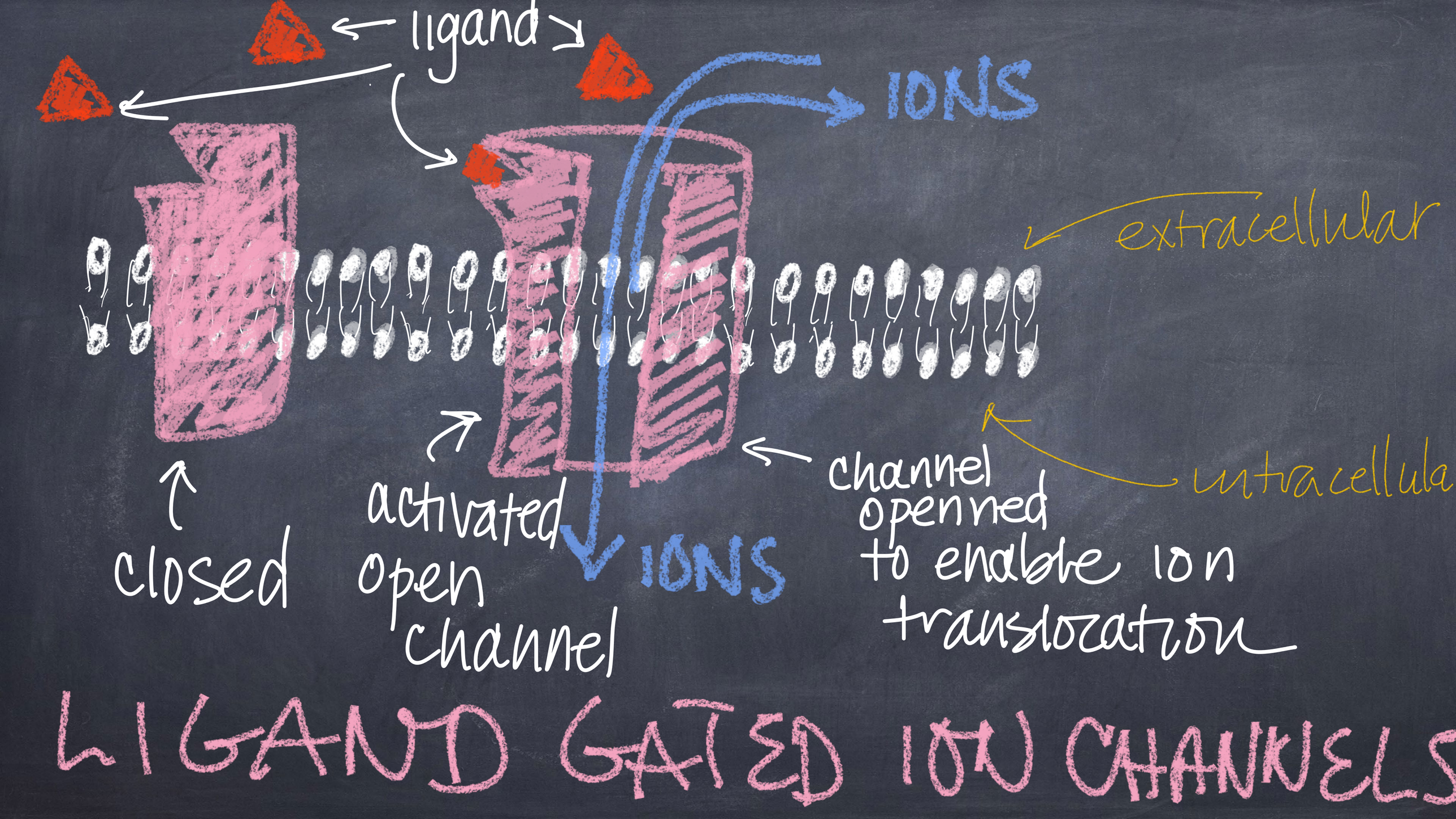
Insulin Signal Transduction Pathway

- Primary messenger: insulin
- The release of insulin is induced by having specific levels of glucose in the blood.
- Insulin binds to the insulin receptor.

The Basics of Signaling

- 1. primary messenger → attaches to a receptor
- 2. receptors are a way to mediate information from the outside of the cell to the inside of the cell
- 3. once information is communicated or transduced into the cell there may be a secondary messenger (for example, cAMP or Ca++).
- 4. There needs to be a mechanism to terminate the signal.

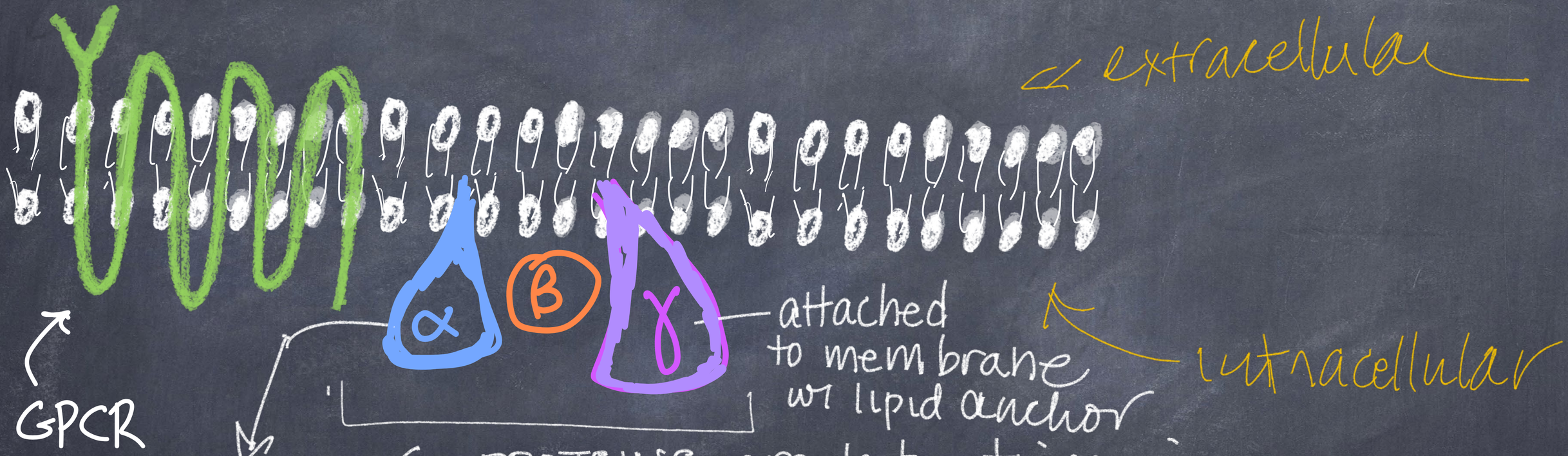

ligand binds with receptor
activated
ligand is the "signal"
extracellular
untracellular
SIGNAL TRANSDUCTION
untracellular response
integral protein that spans lipid bilayer
Membrane receptor



LIGAND GATED ION CHANNELS

G-PROTEINS CAN BIND GTP &/OR GDP

(GPCR)



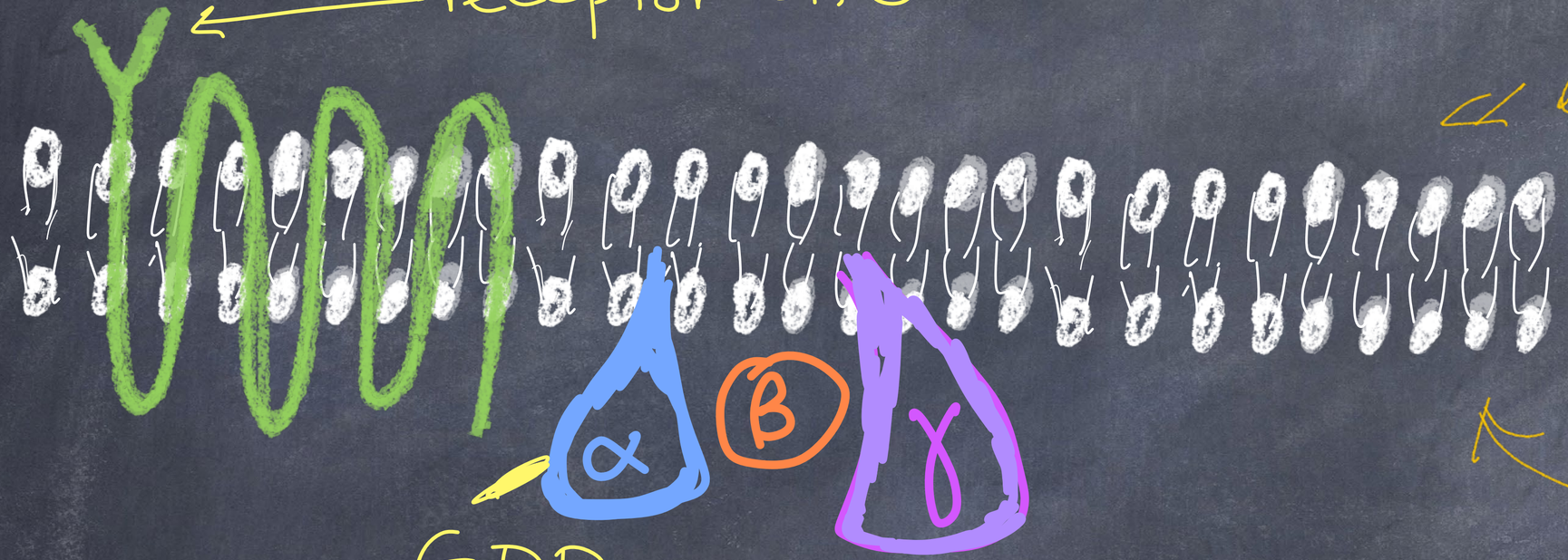
G-PROTEINS are heterotrimeric

attached to membrane with lipid anchors

G-PROTEIN COUPLED RECEPTORS

G-PROTEINS CAN BIND GTP &/OR GDP

(GPCR)



GDP binds to α subunit

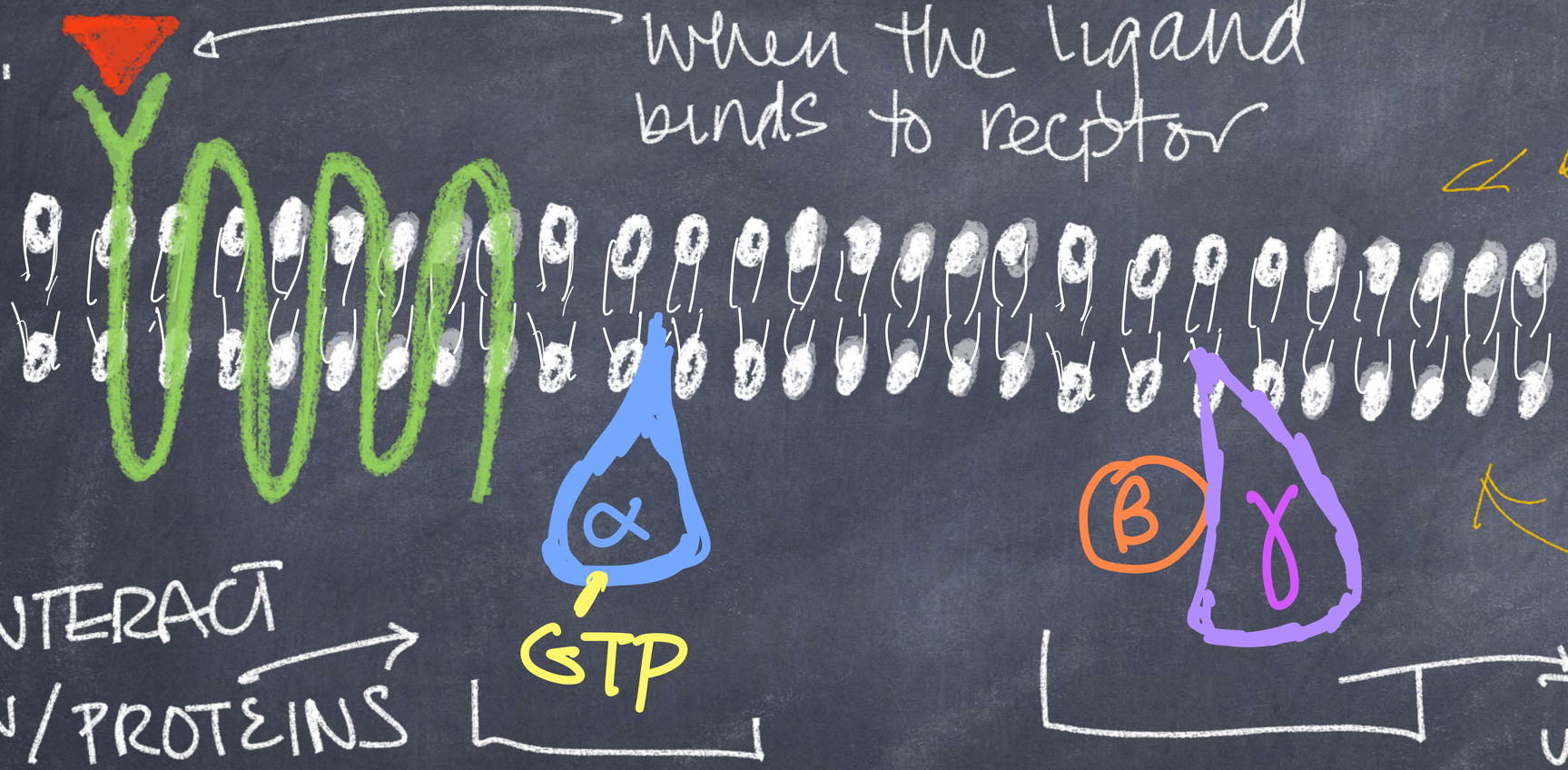
↑

inactive state (GDP)

G-PROTEINS CAN BIND GTP &/OR GDP

(GPCR)

1. when the ligand binds to receptor



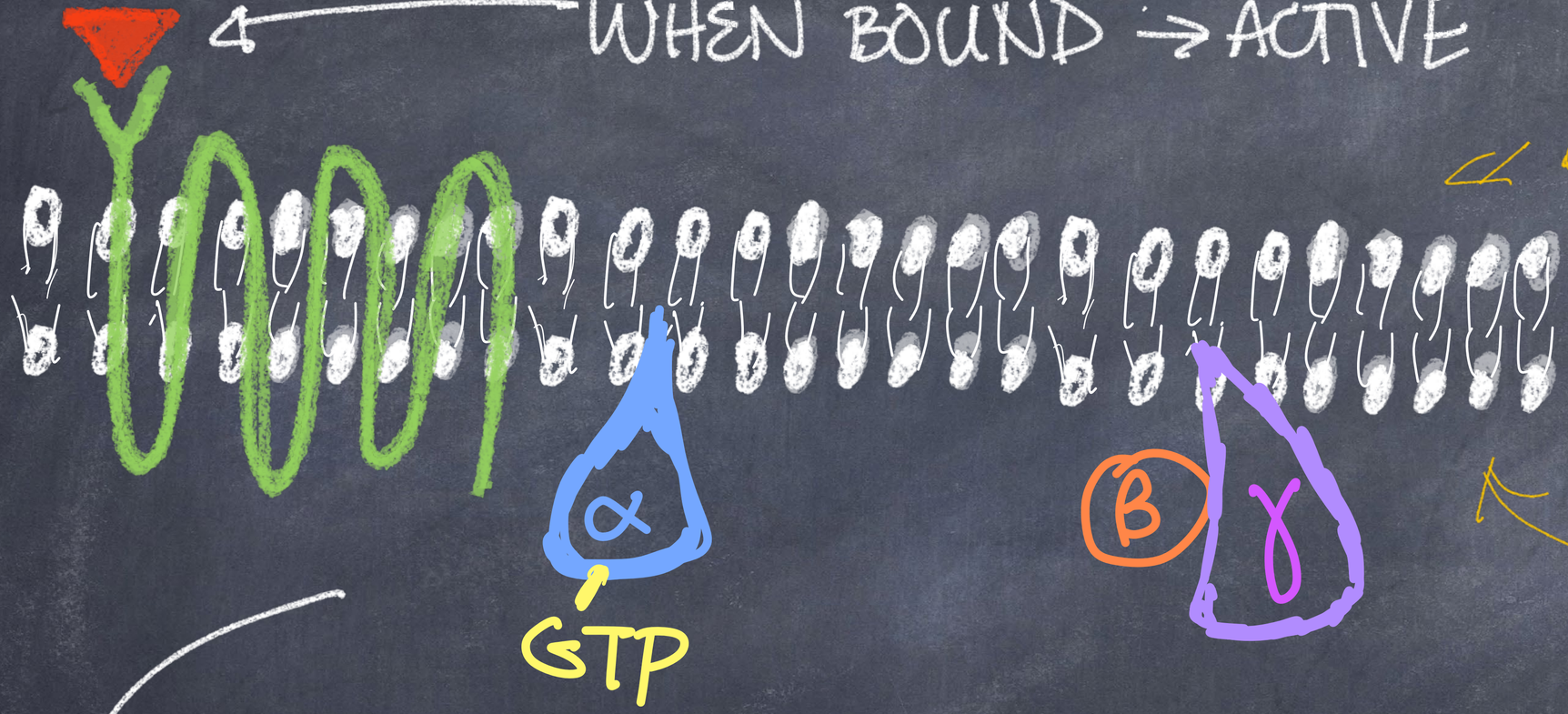
2. CONFORMATIONAL CHANGE → α BINDS GTP

3. βγ SUBUNIT DISASSOCIATE → TARGET PROTEINS

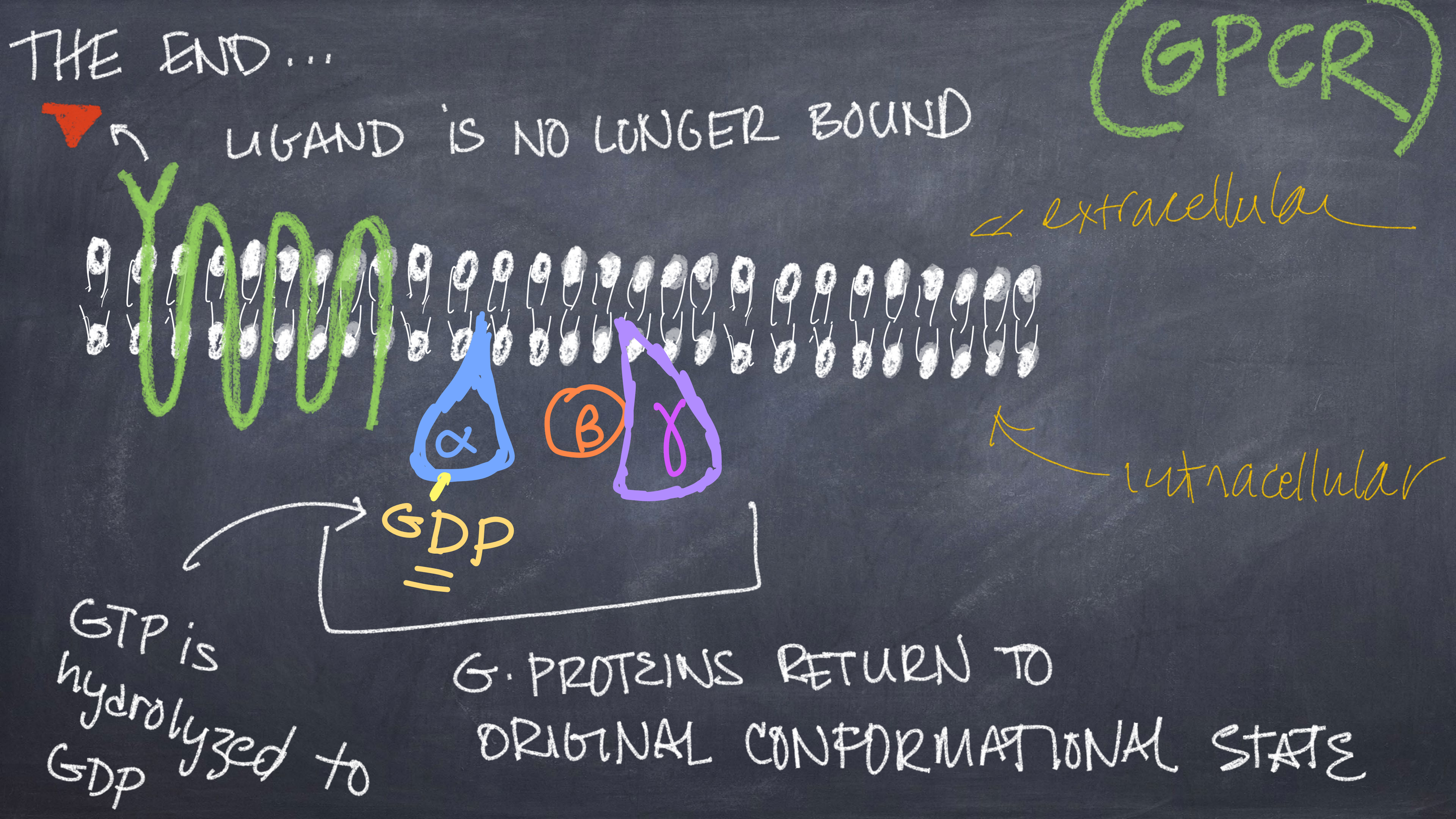
LONG LASTING ....

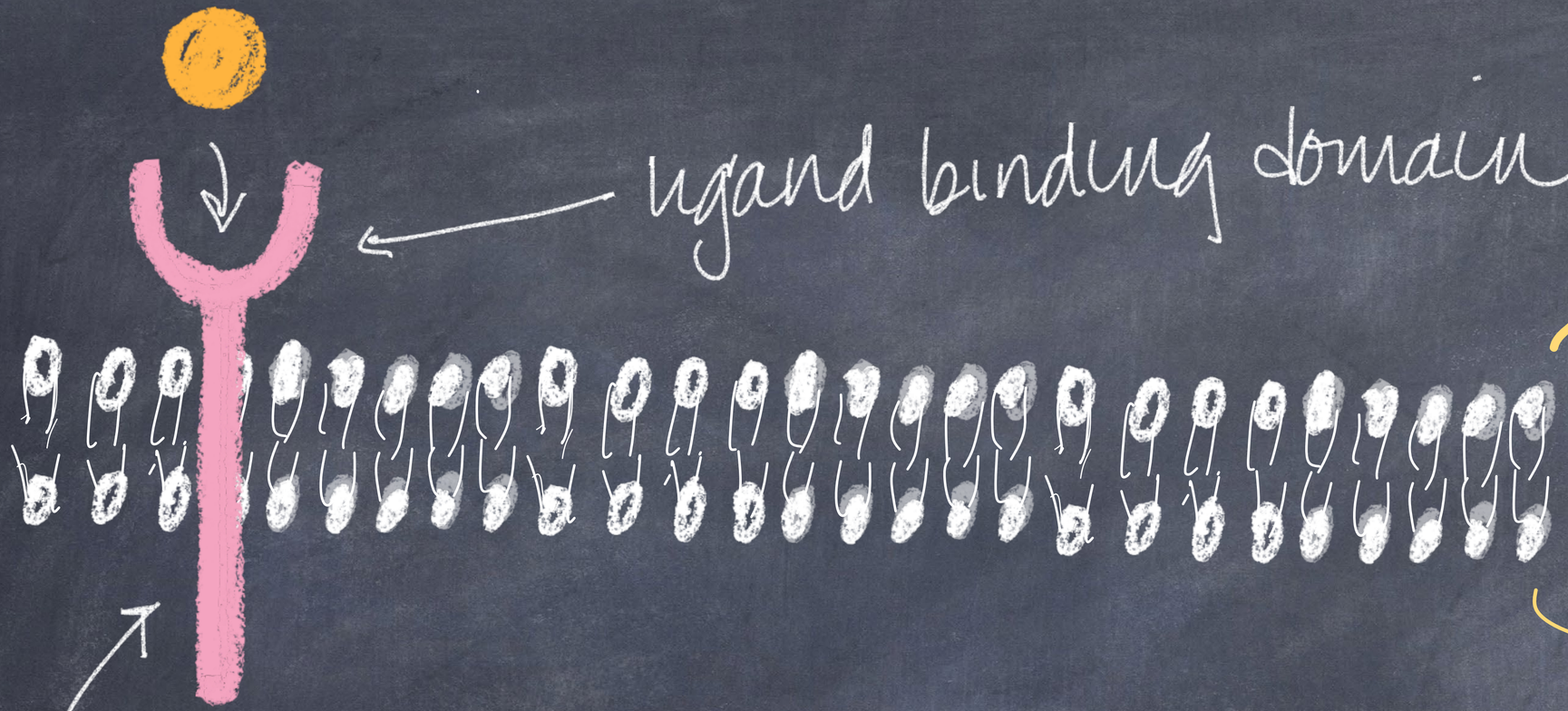
GPCR

← WHEN BOUND ⇒ ACTIVE



→ the signal stays "active" for as long as the ligand is bound to the receptor.


THE END...
LIGAND IS NO LONGER BOUND
GPCR
extracellular
intracellular
α
β
γ
GDP
GTP is hydrolyzed to GDP
G-PROTEINS RETURN TO ORIGINAL CONFORMATIONAL STATE



ligand binding domain

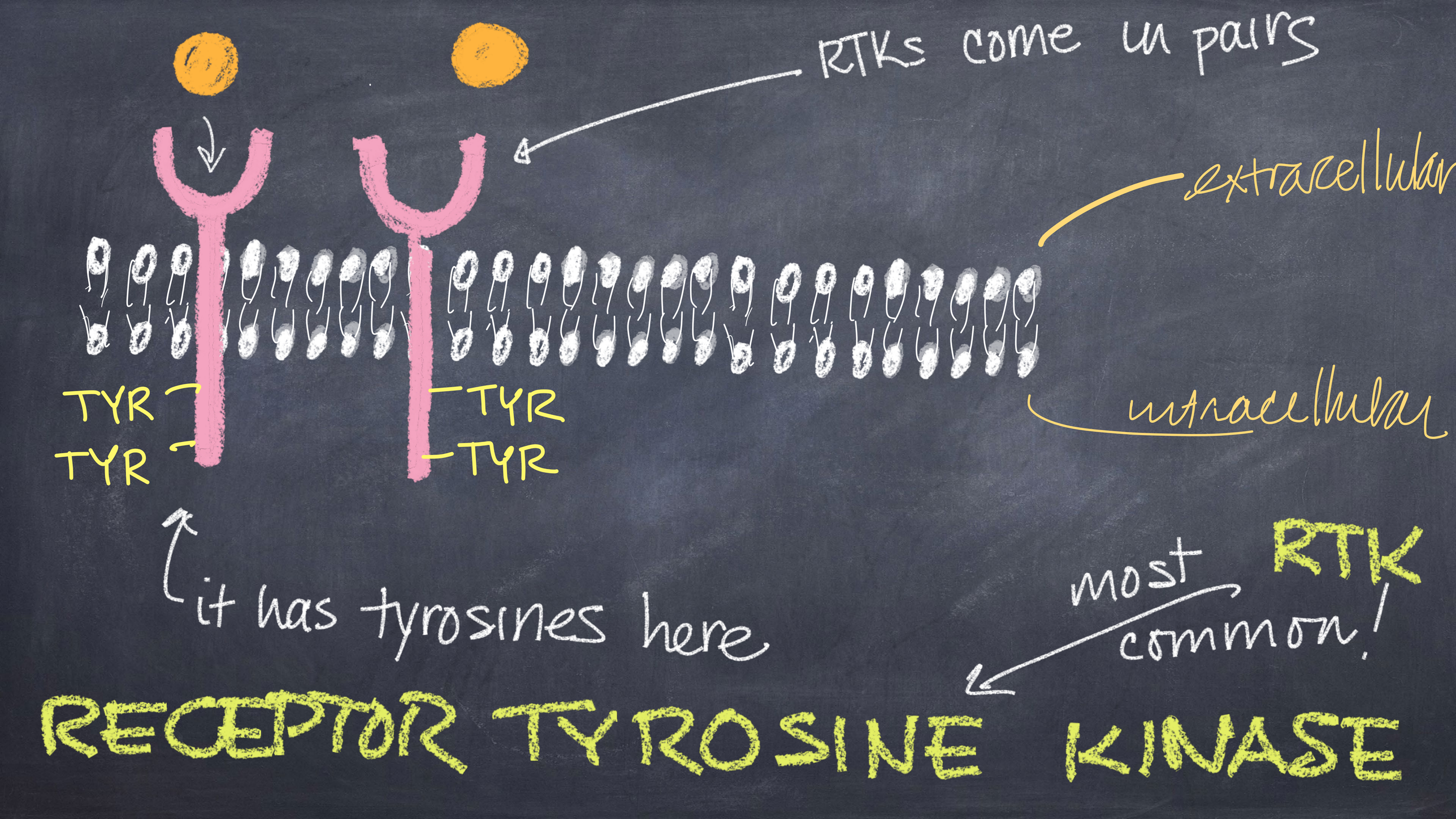
extracellular

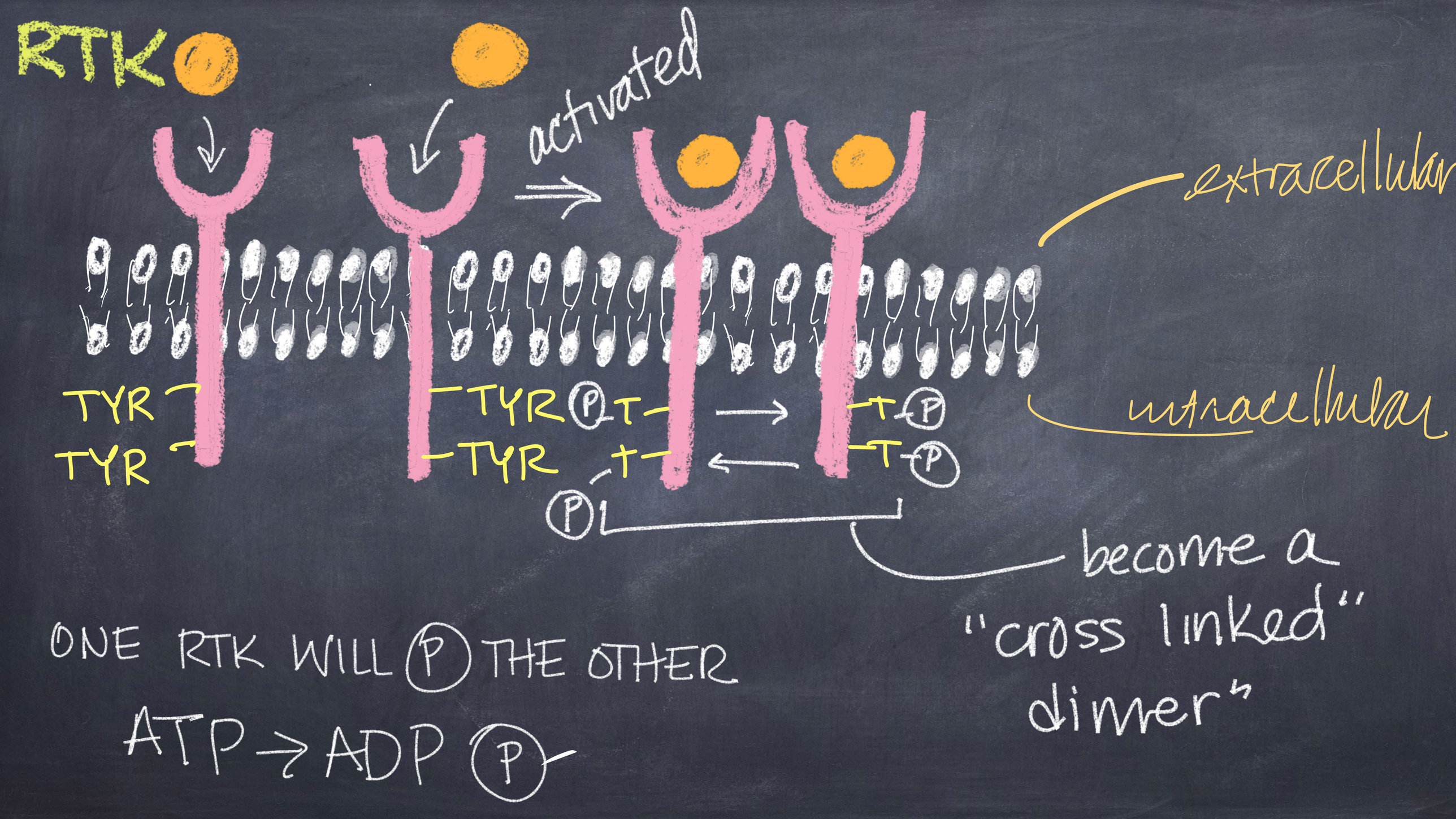
intracellular

functional domain
enzyme

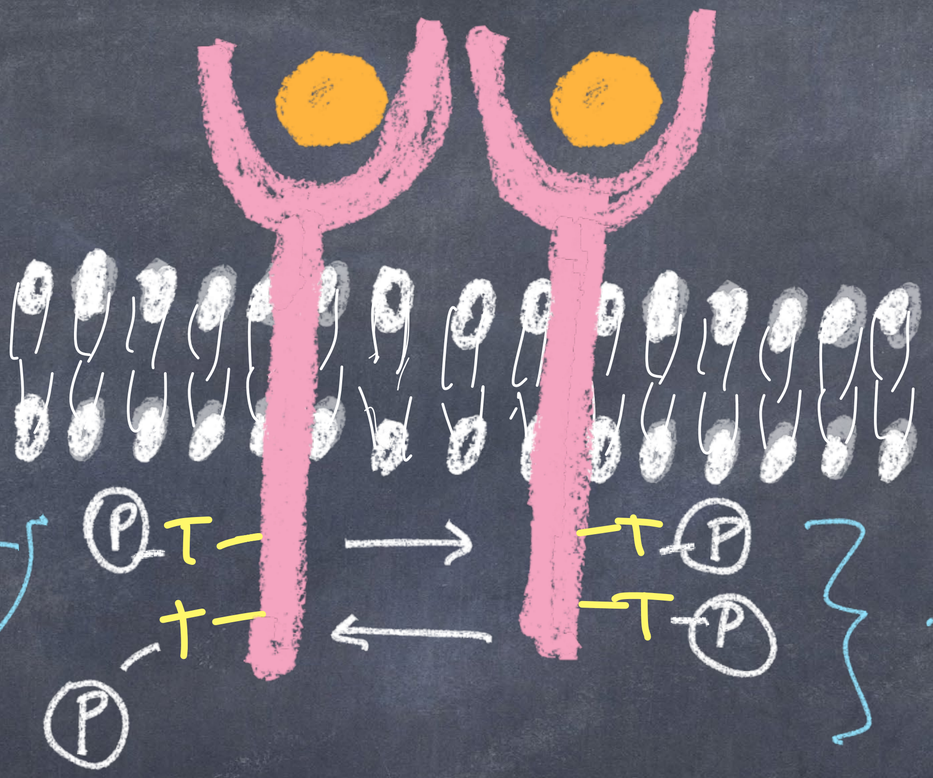
"catalytic"

ENZYME LINKED RECEPTORS


RTKs come in pairs
extracellular
intracellular
TYR
TYR
TYR
TYR
it has tyrosines here
most common!
RTK
RECEPTOR TYROSINE KINASE


RTK
activated
extracellular
intracellular
TYR
TYR
TYR
TYR
P
P
P
P
become a "cross linked" dimer
ONE RTK WILL P THE OTHER
ATP → ADP P

RTK

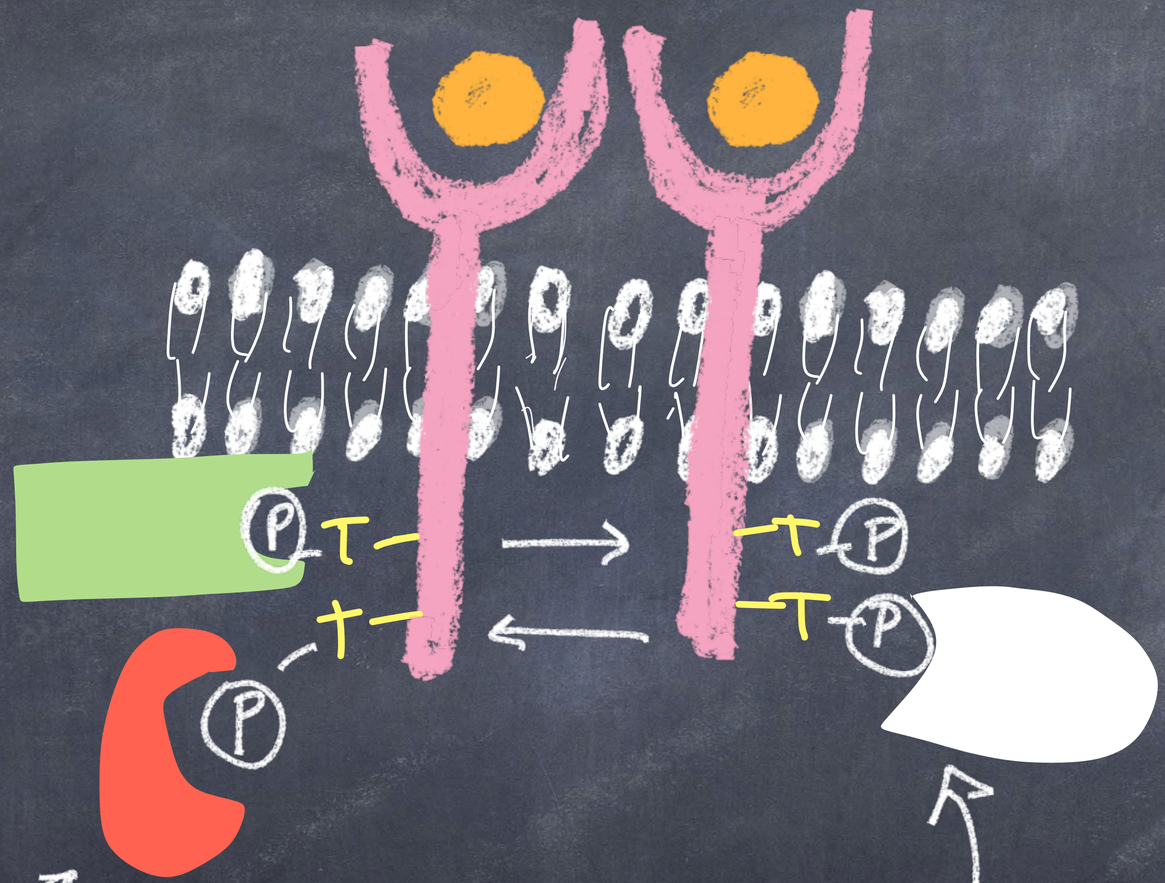


extracellular

intracellular

THESE WILL SERVE AS DOCKING PLATFORMS FOR DIFFERENT INTRACELLULAR PROTEINS

RTK



extracellular

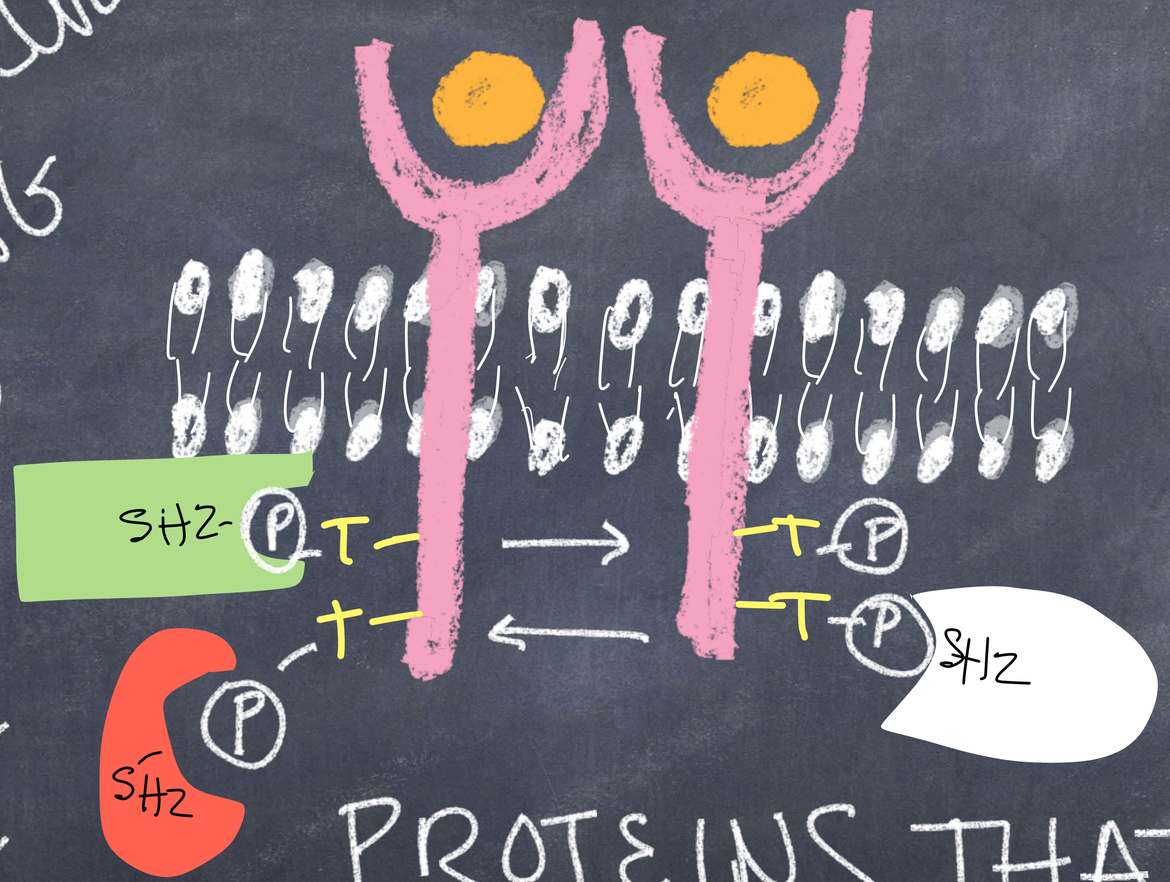
intracellular

PROTEINS CAN DOCK

RTK

MULTIPLE INTRACELLULAR SIGNALING PATHWAYS IN PARALLEL

WOW!!

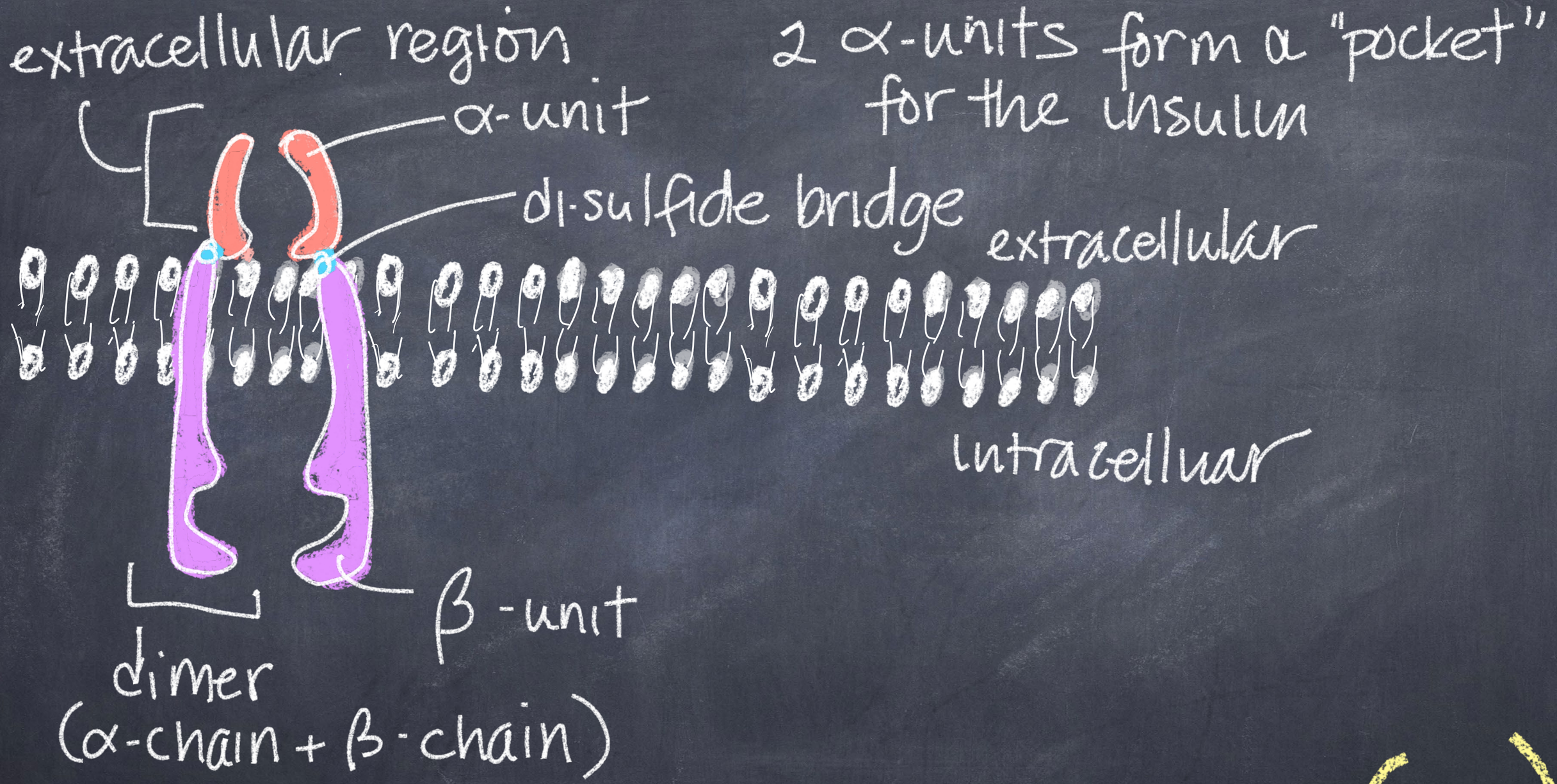


extracellular

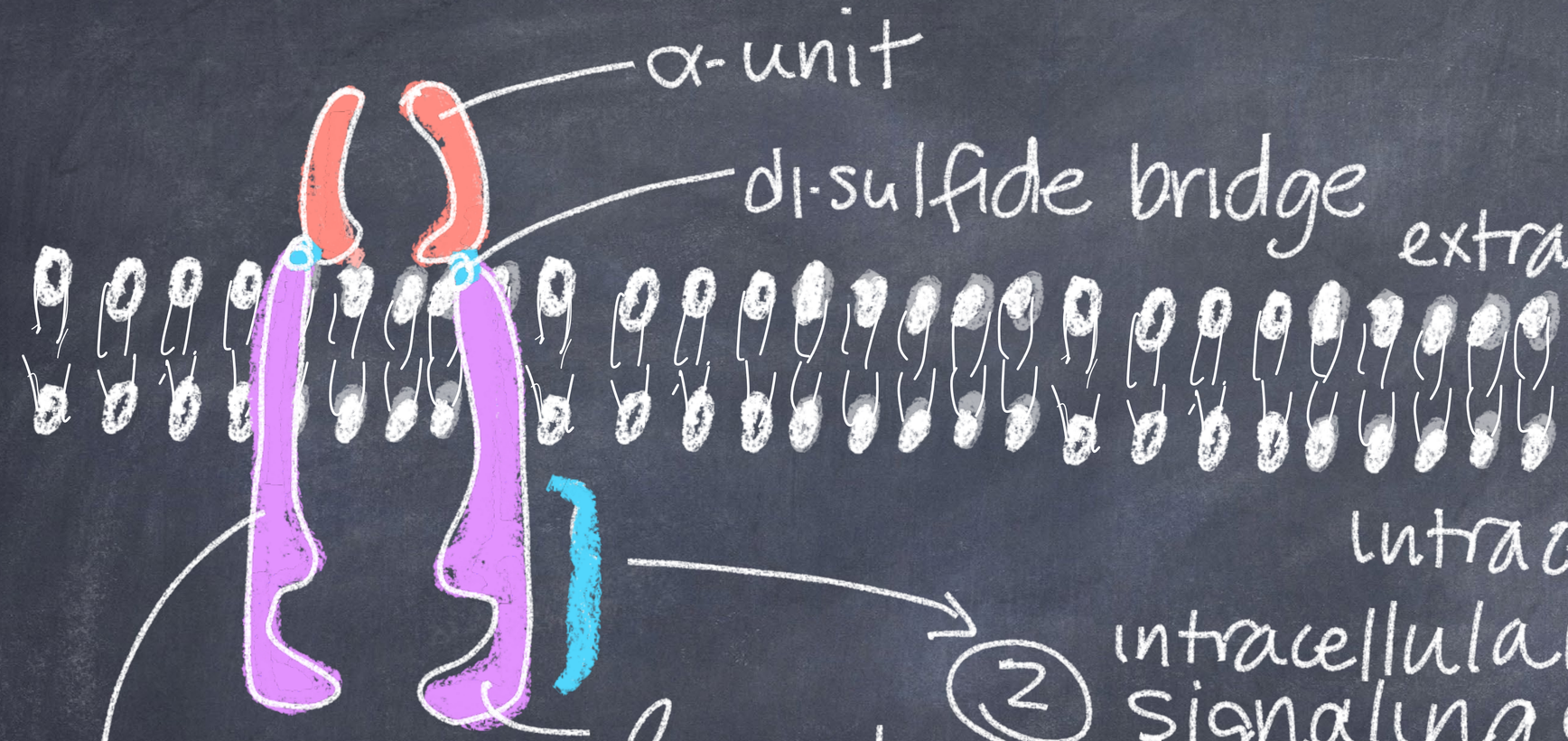
intracellular

PROTEINS THAT HAVE SH2 DOMAINS CAN DOCK ON

T-P



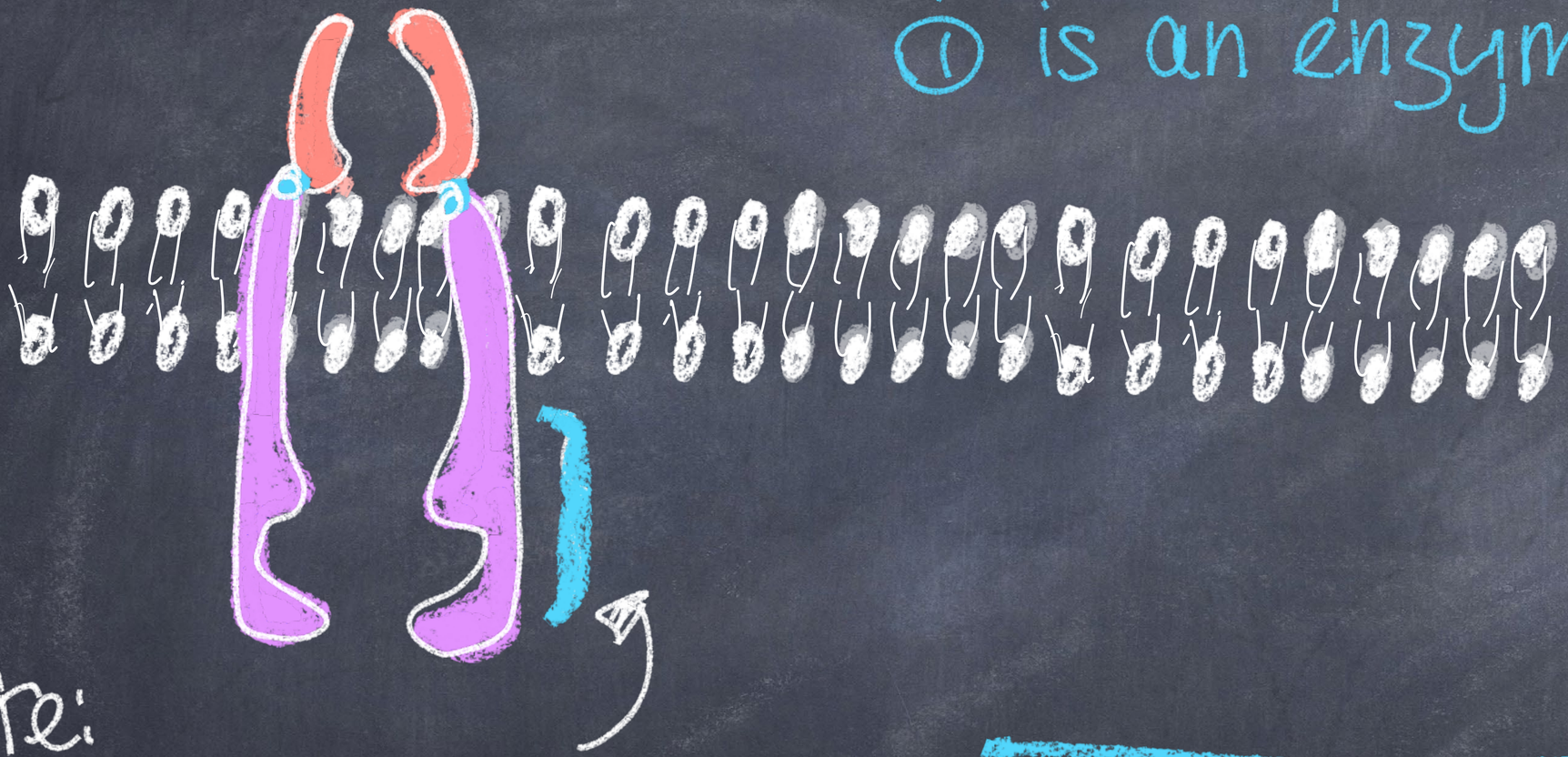
INSULIN RECEPTOR (IR)



* tyrosine protein kinase

Recall: tyrosine protein kinase

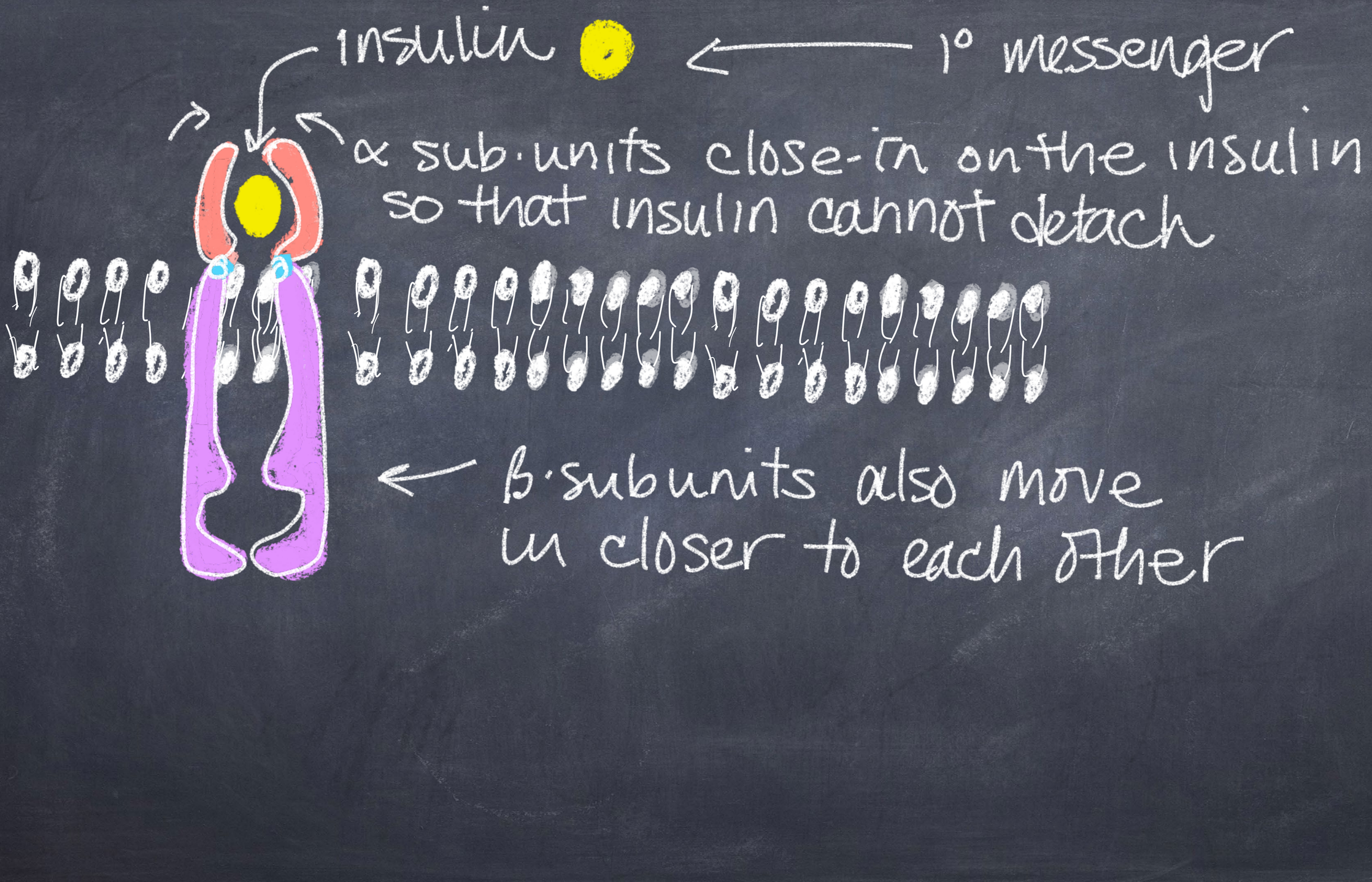
① is an enzyme, the Ⓟ tyrosine amino acids

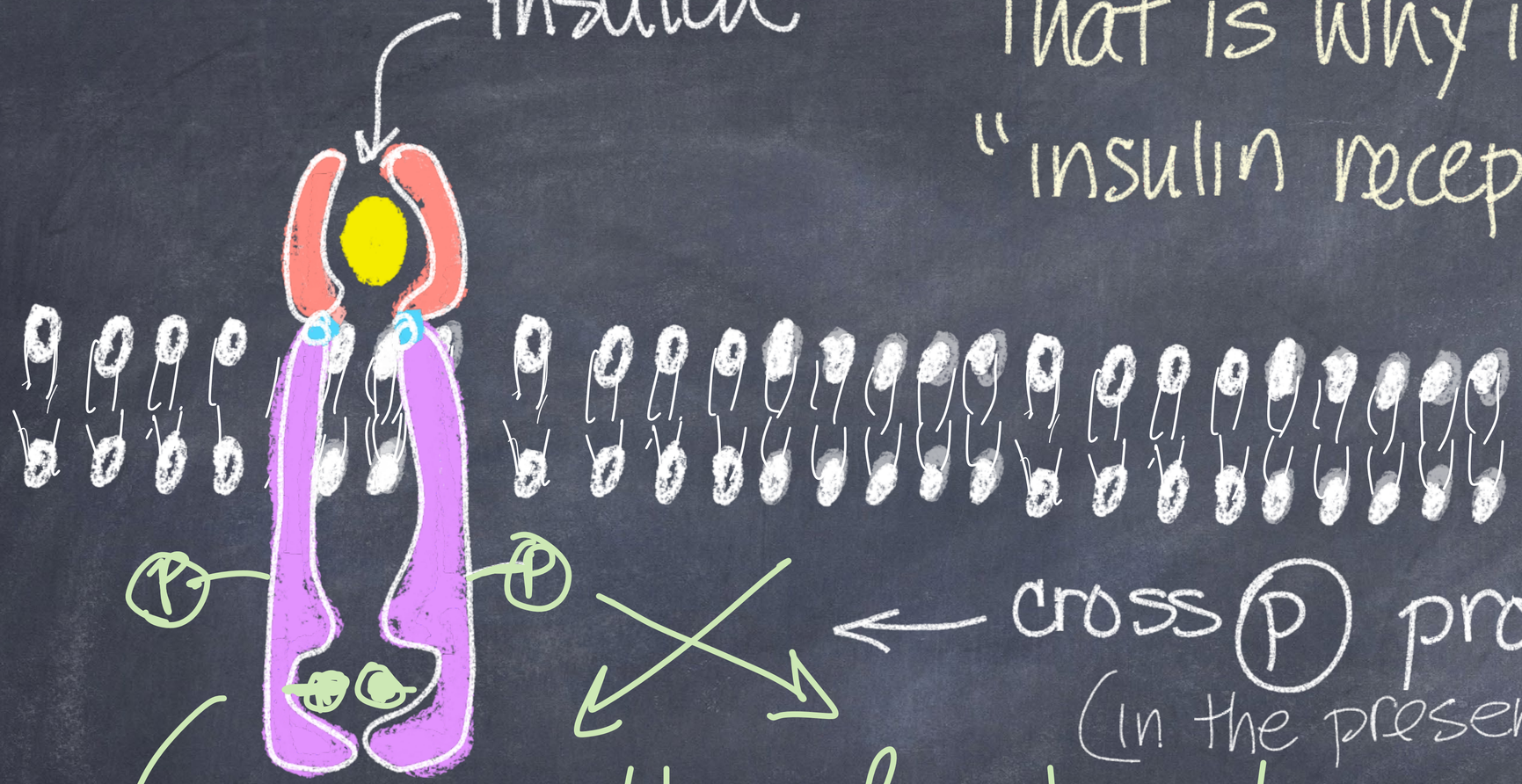


note:

* the protein kinase is found in the structure

* tyrosine protein kinase

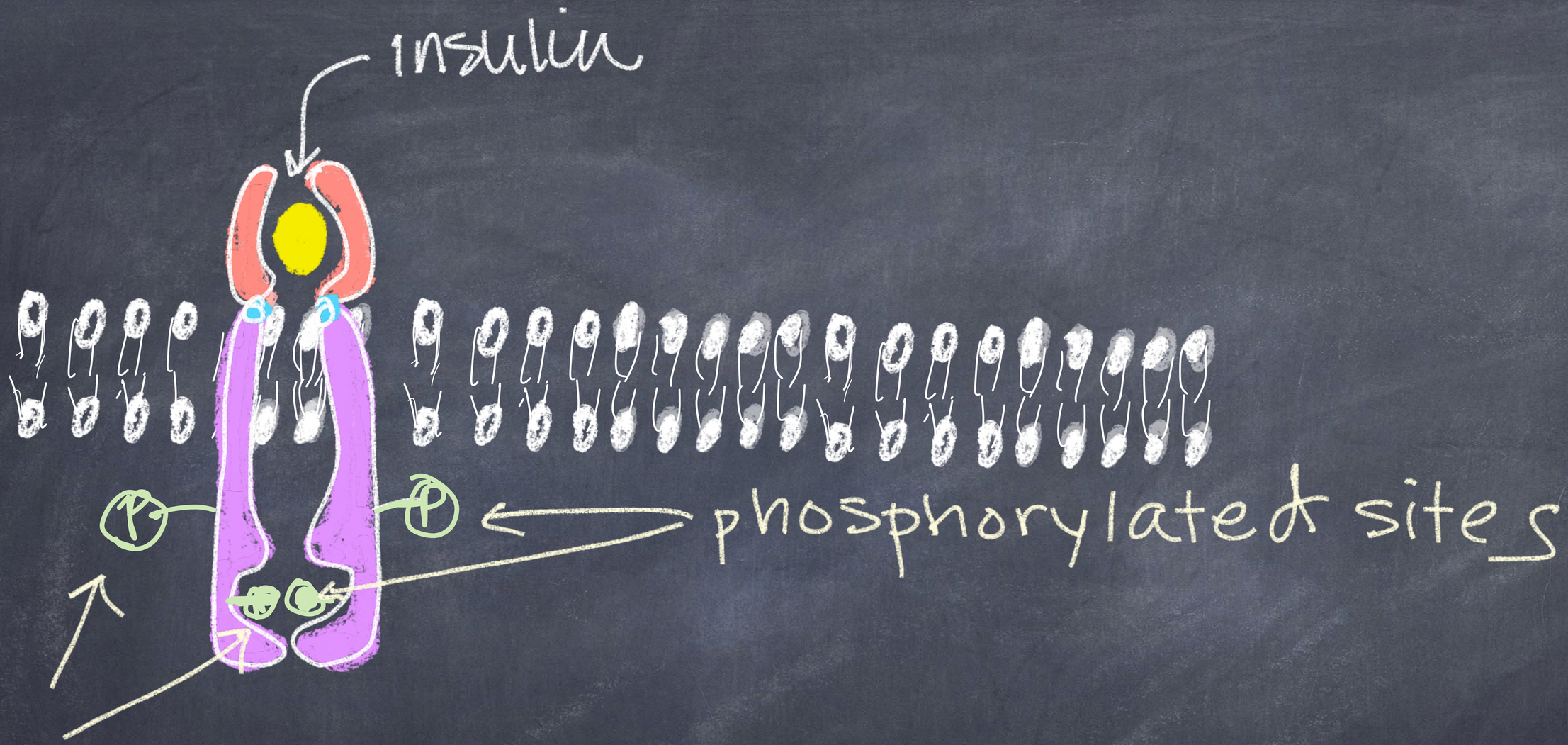

insulin
1° messenger
α sub-units close-in on the insulin so that insulin cannot detach
β-subunits also move in closer to each other

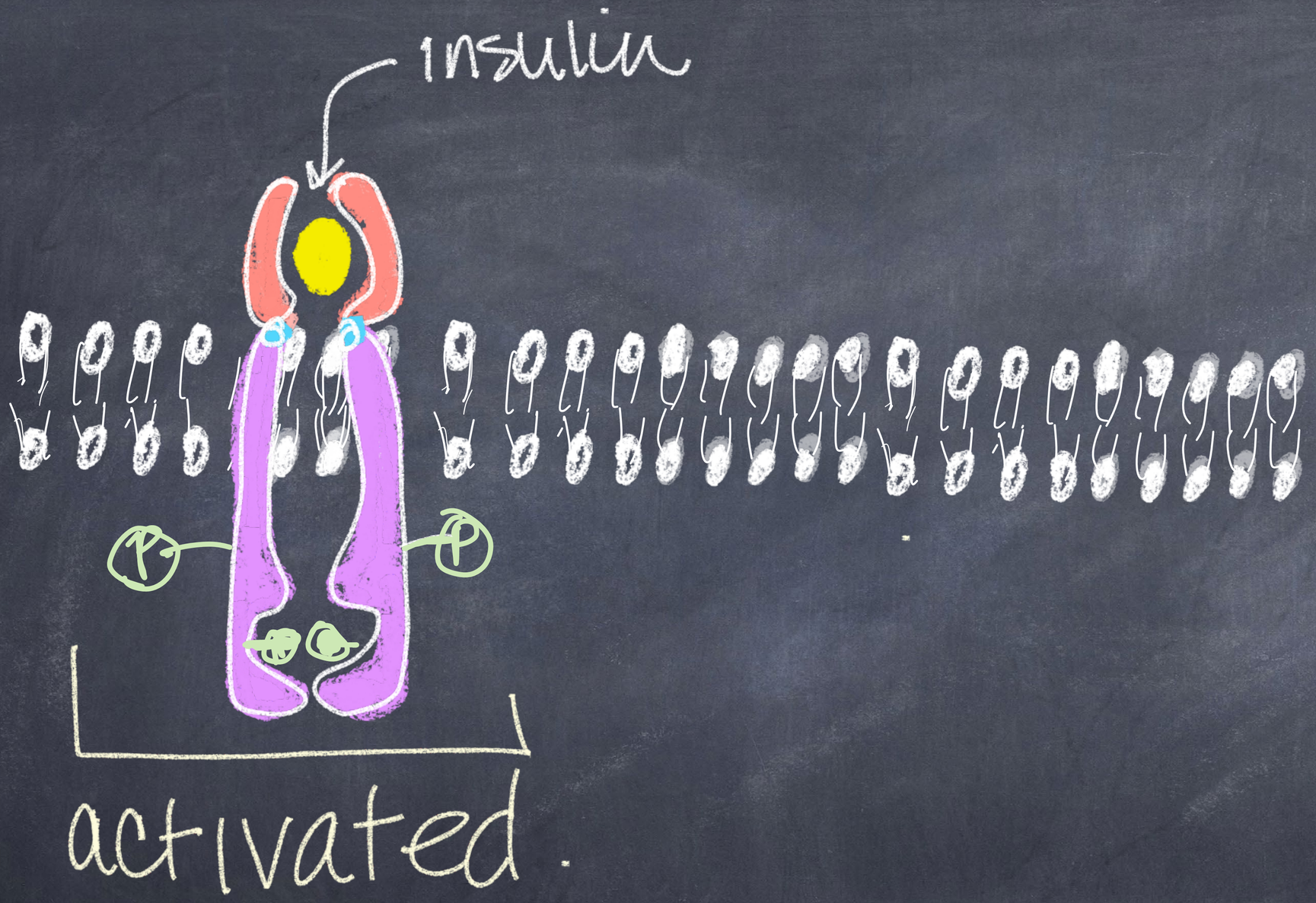


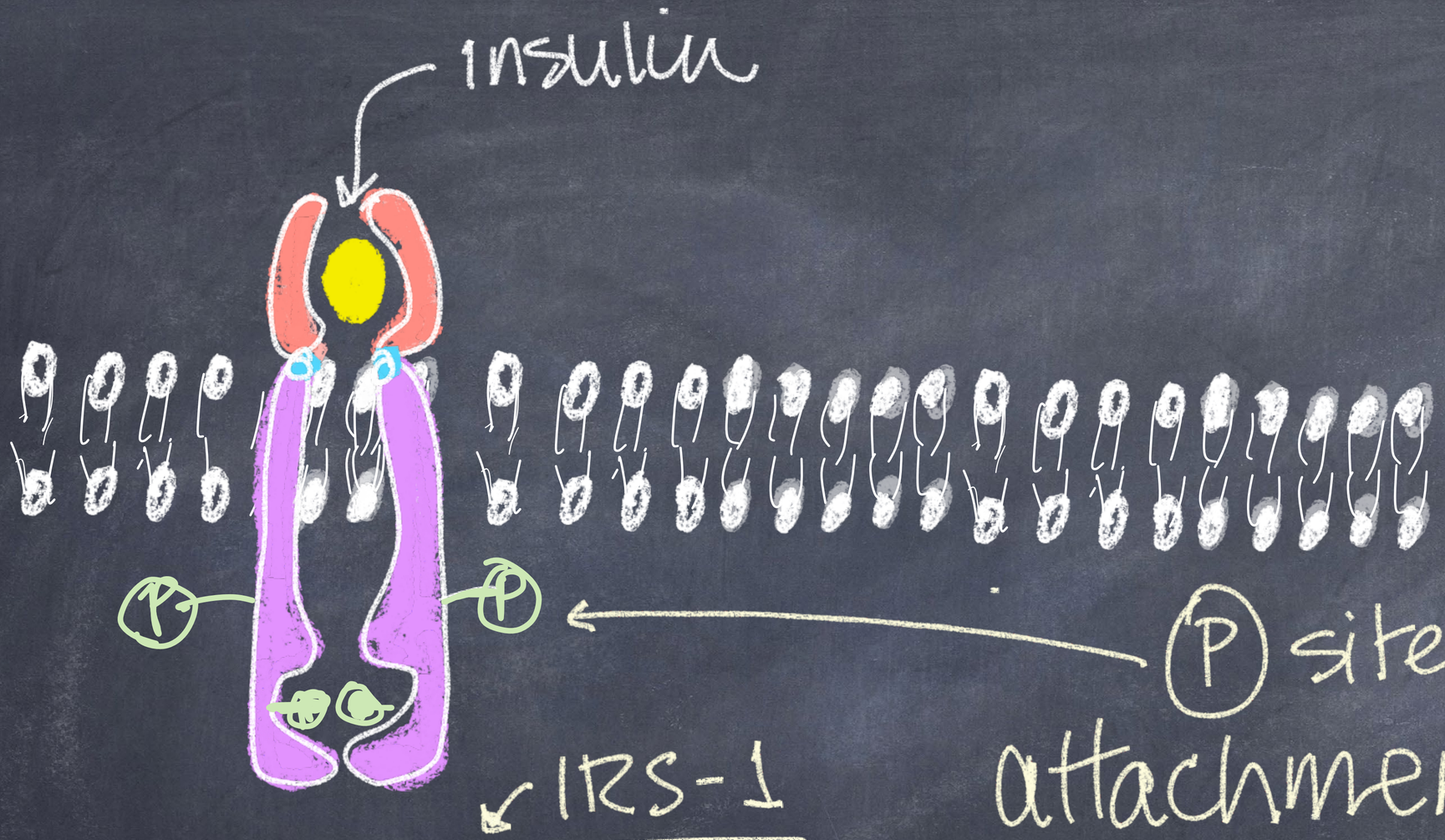
That is why it is called "insulin receptor protein kinase"

← cross (P) process
(in the presence of ATP)

as the β-subunits move closer together one subunit activates the other subunit.

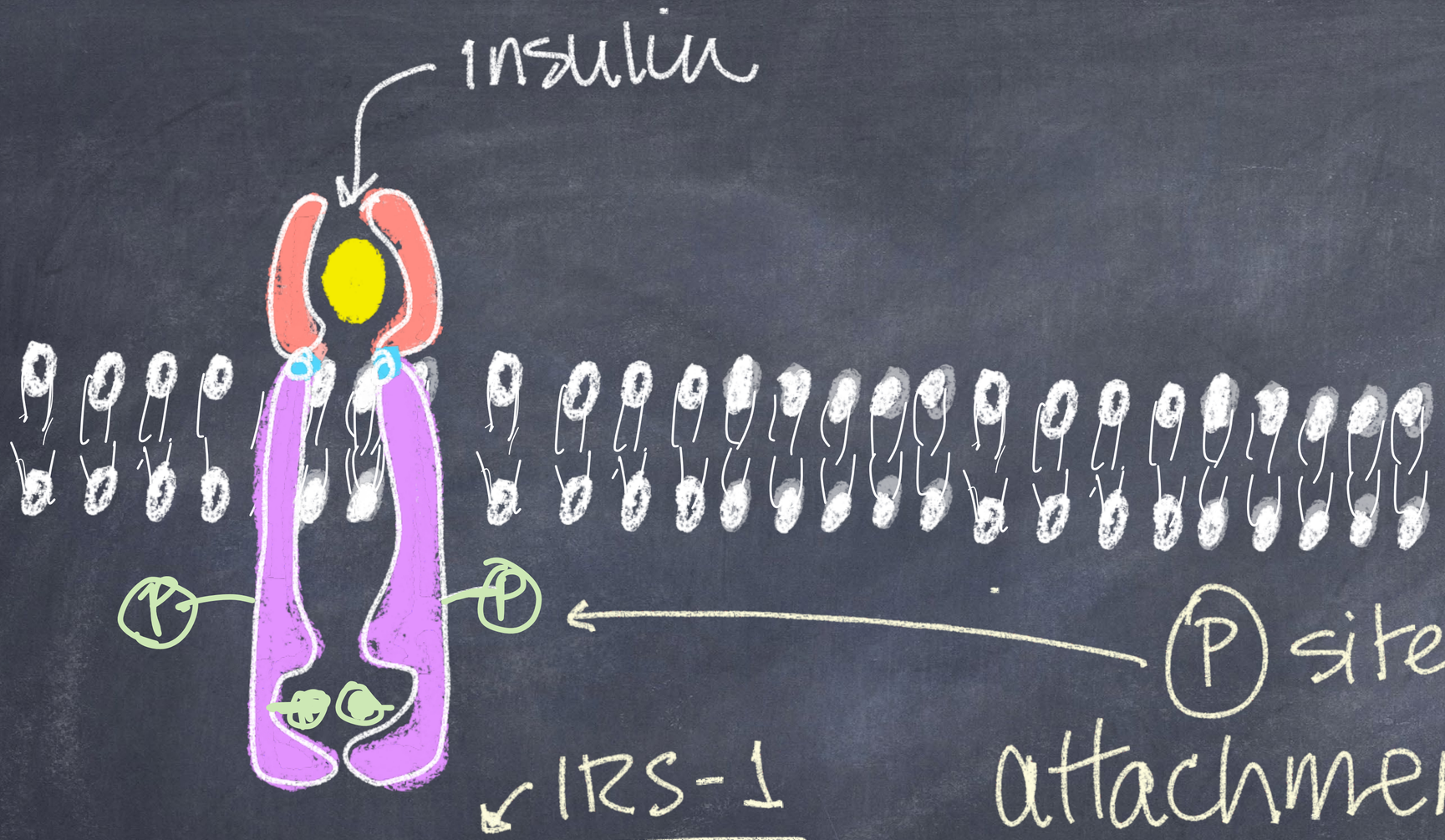

insulin
phosphorylated sites


insulin
P
P
activated.



Insulin Receptor Substrate

(P) sites act as attachment sites for other proteins
→ e.g. IRS-1



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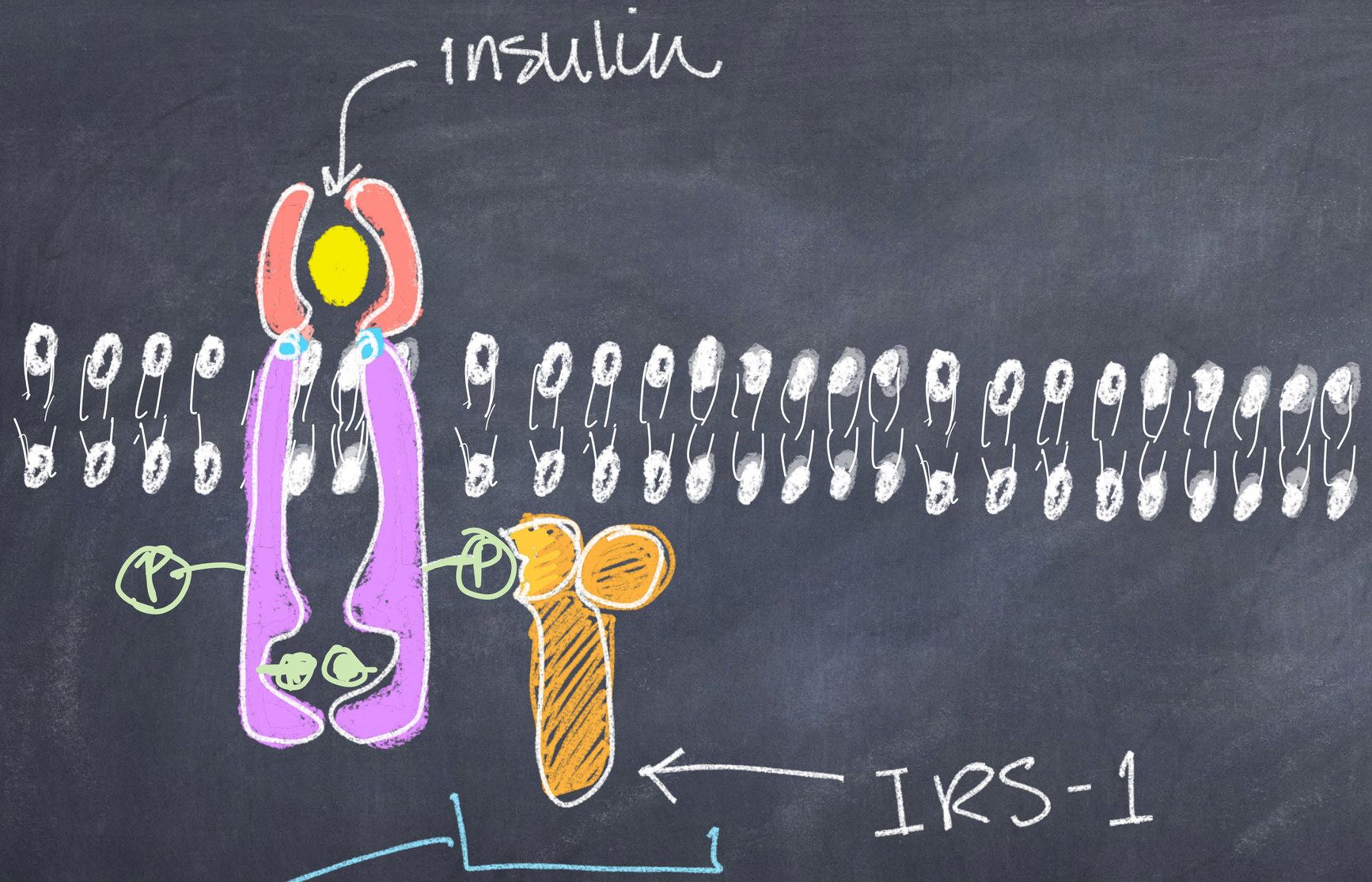
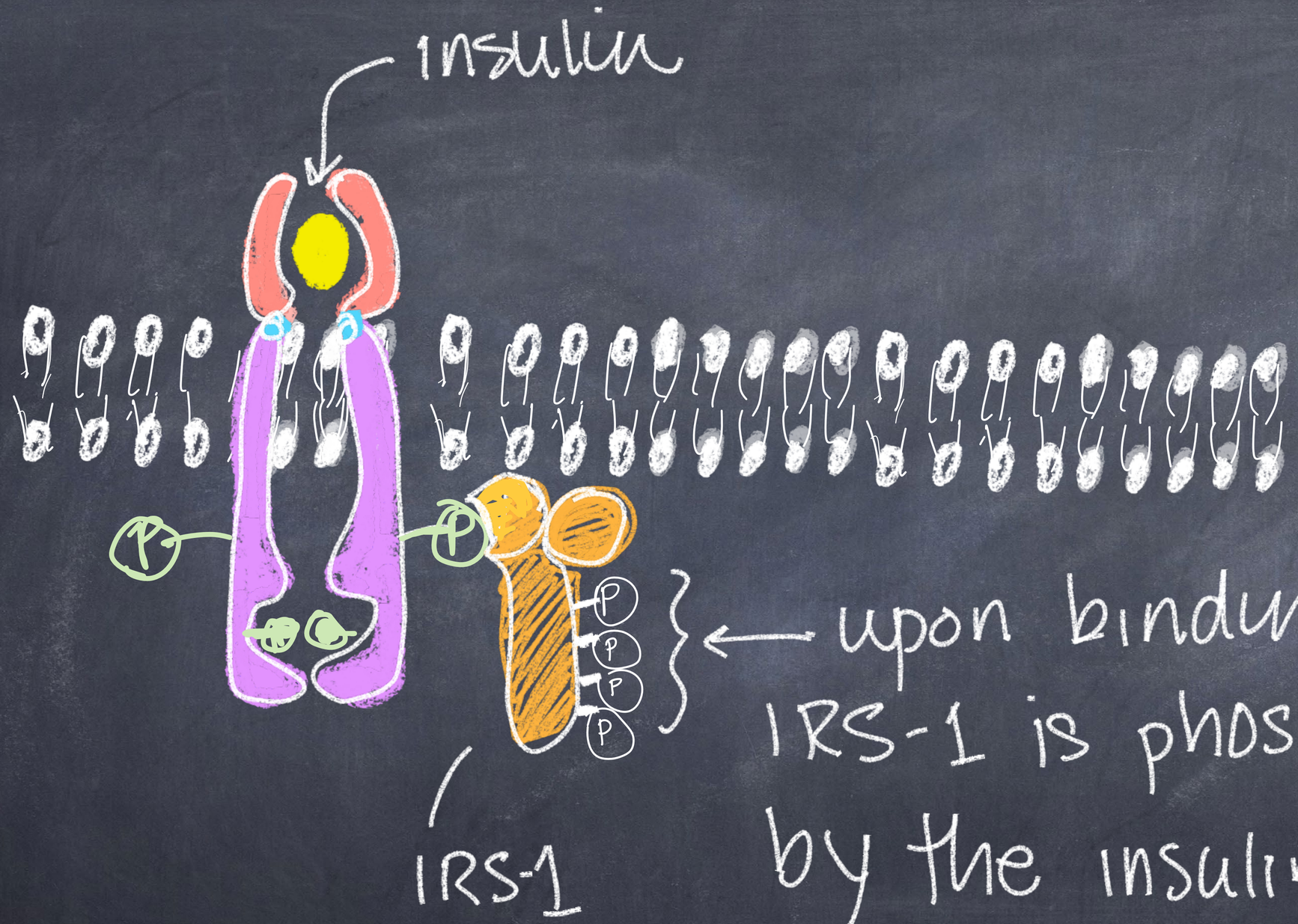


IRS molecules are called adaptor proteins

IRS = insulin receptor substrate



upon binding, IRS-1 is phosphorylated by the insulin receptor kinase