MEDICINE OF THE FUTURE

Discovering the Cure to Cancer

SPLASH 2018

Matthew Yarnall

What is Cancer?

- Uncontrollable Cell Growth

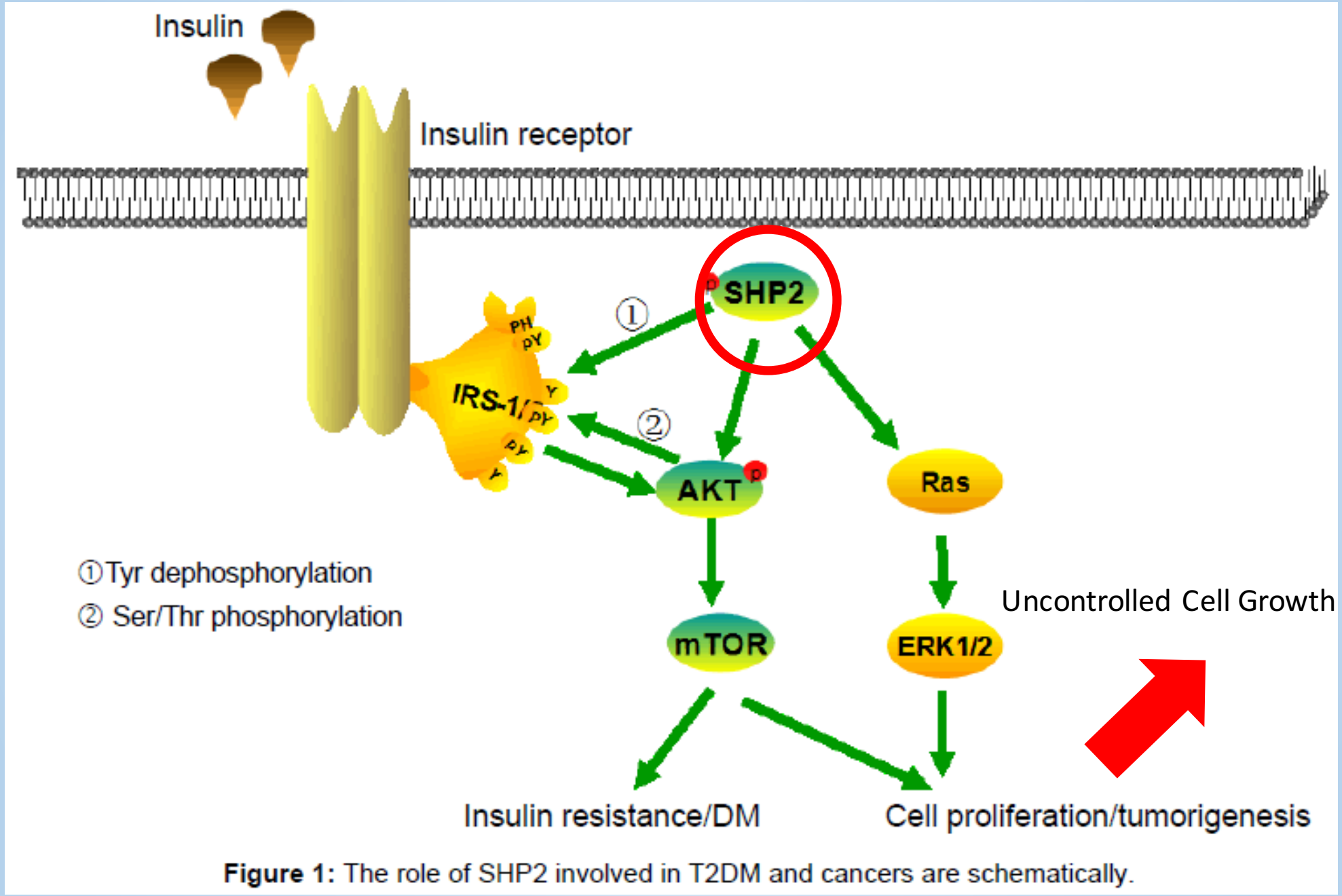
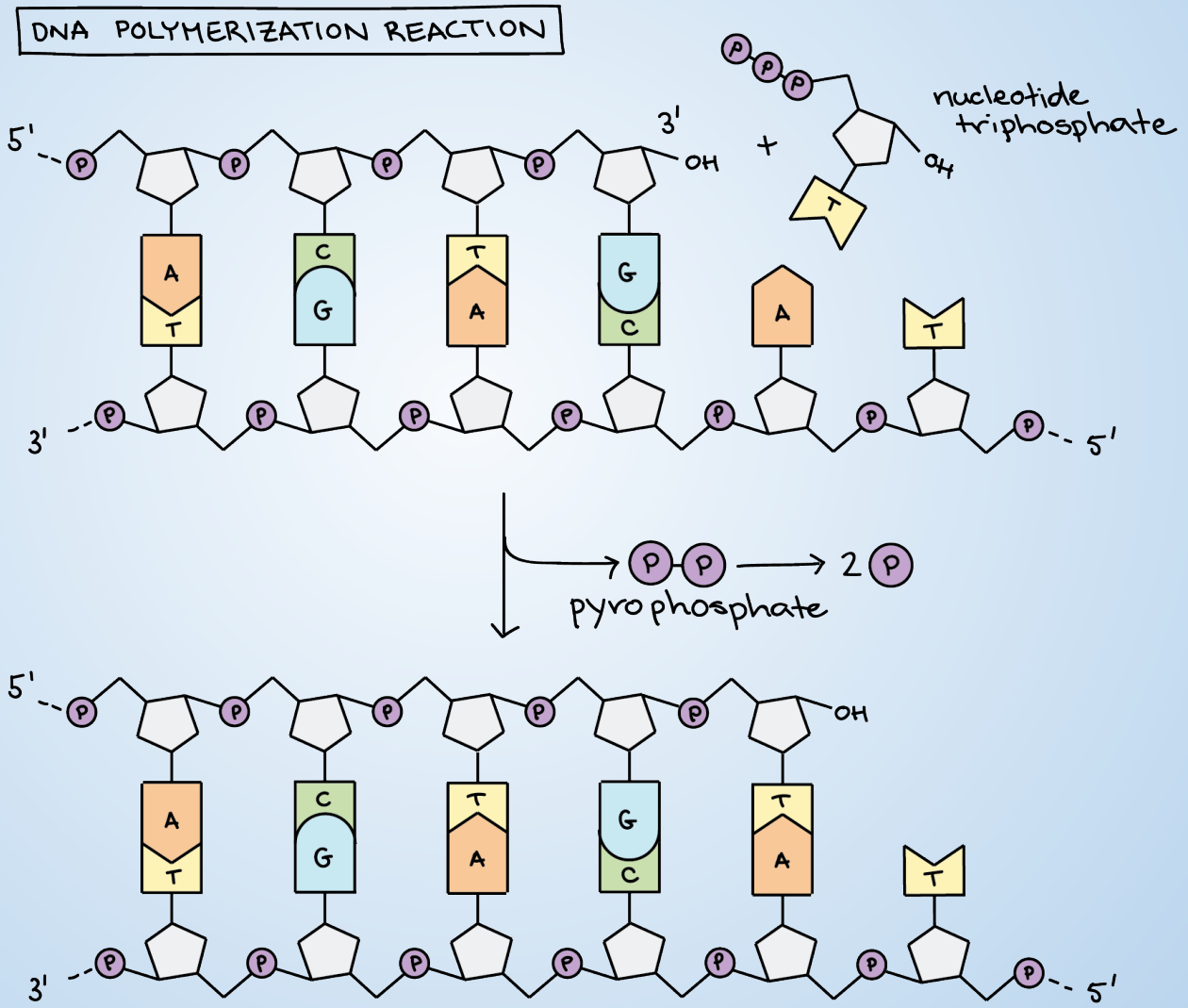
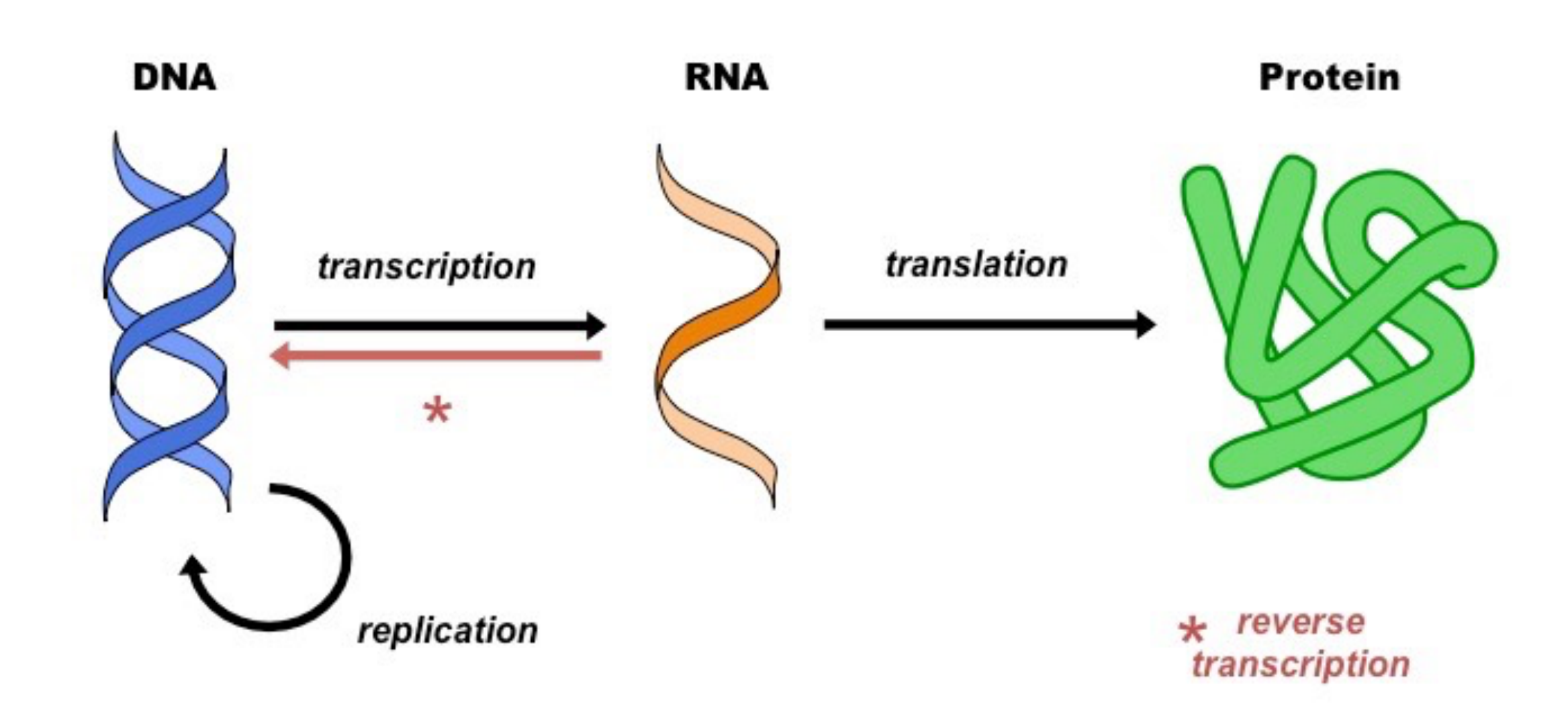


Figure 1: The role of SHP2 involved in T2DM and cancers are schematically.

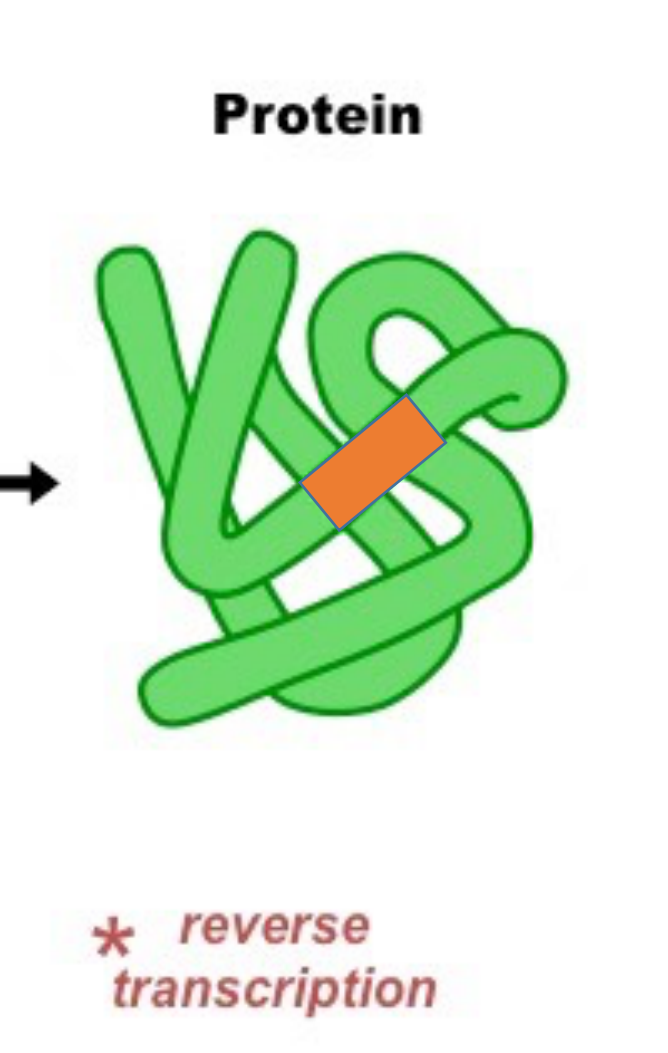
What Causes Mutations?



Central Dogma



Protein Mutation:



- May lead to new biochemical properties
- May loose ability for regulation

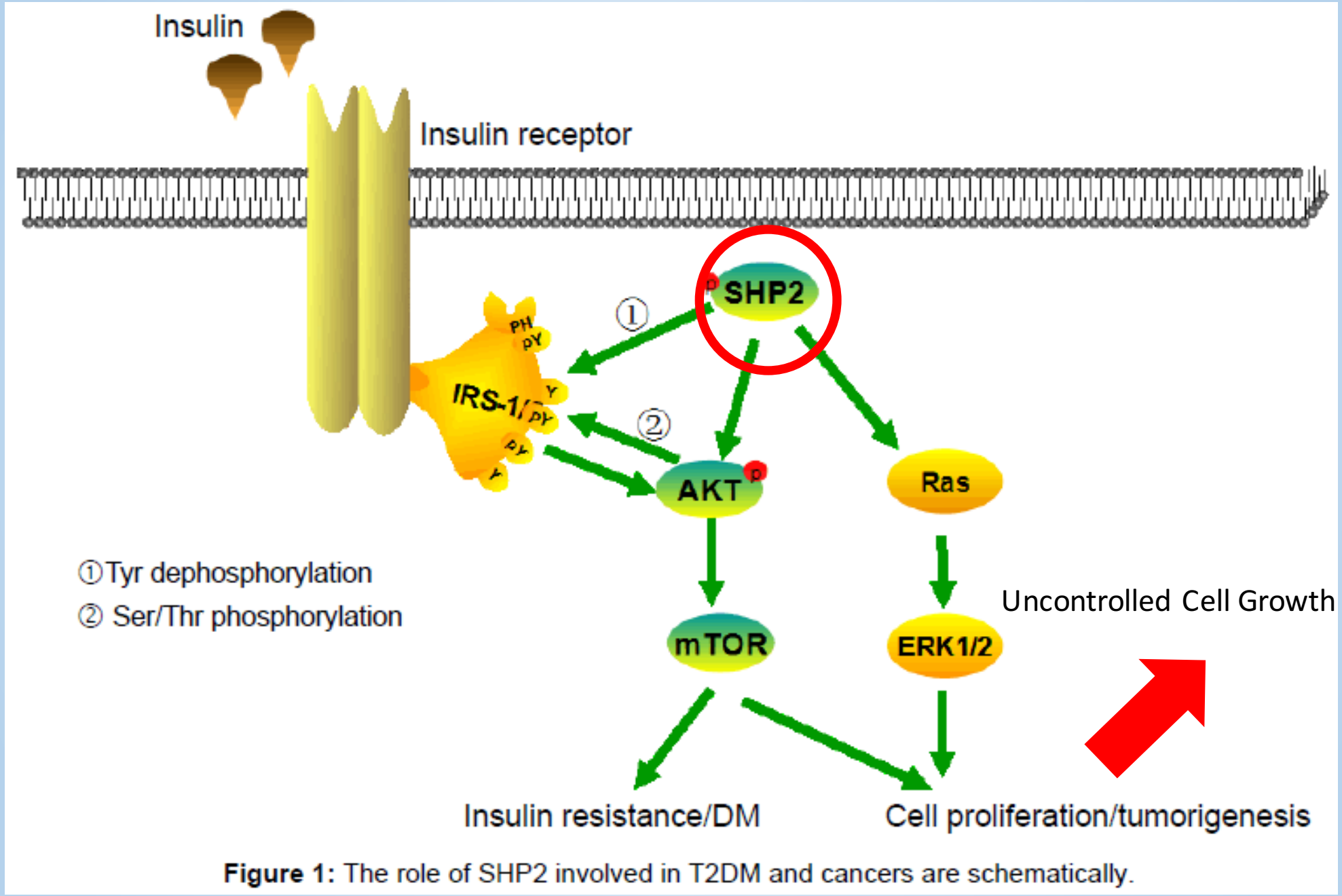
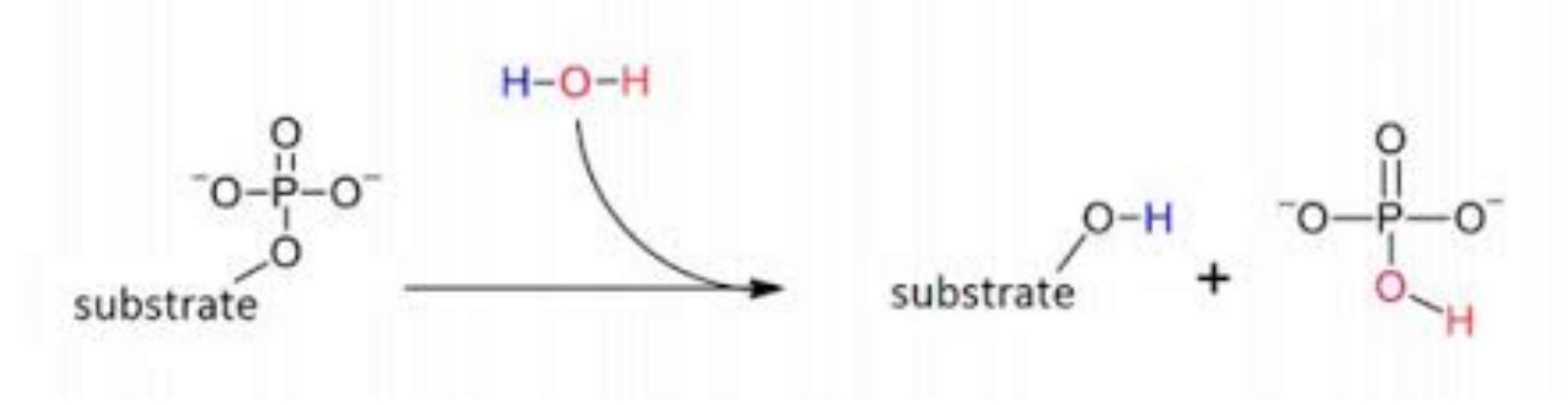
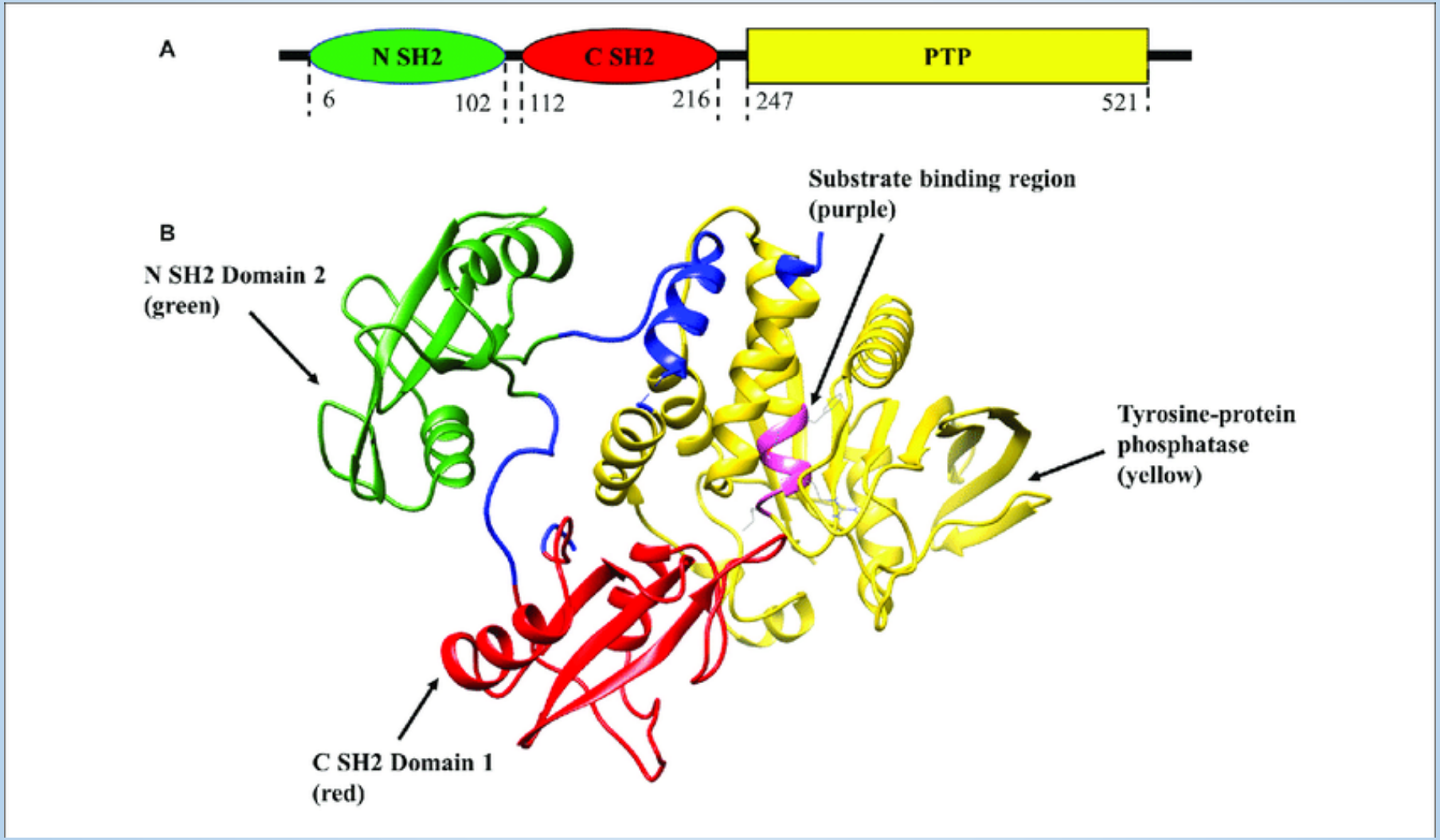


Figure 1: The role of SHP2 involved in T2DM and cancers are schematically.

What's Happening at the Chemical Level?



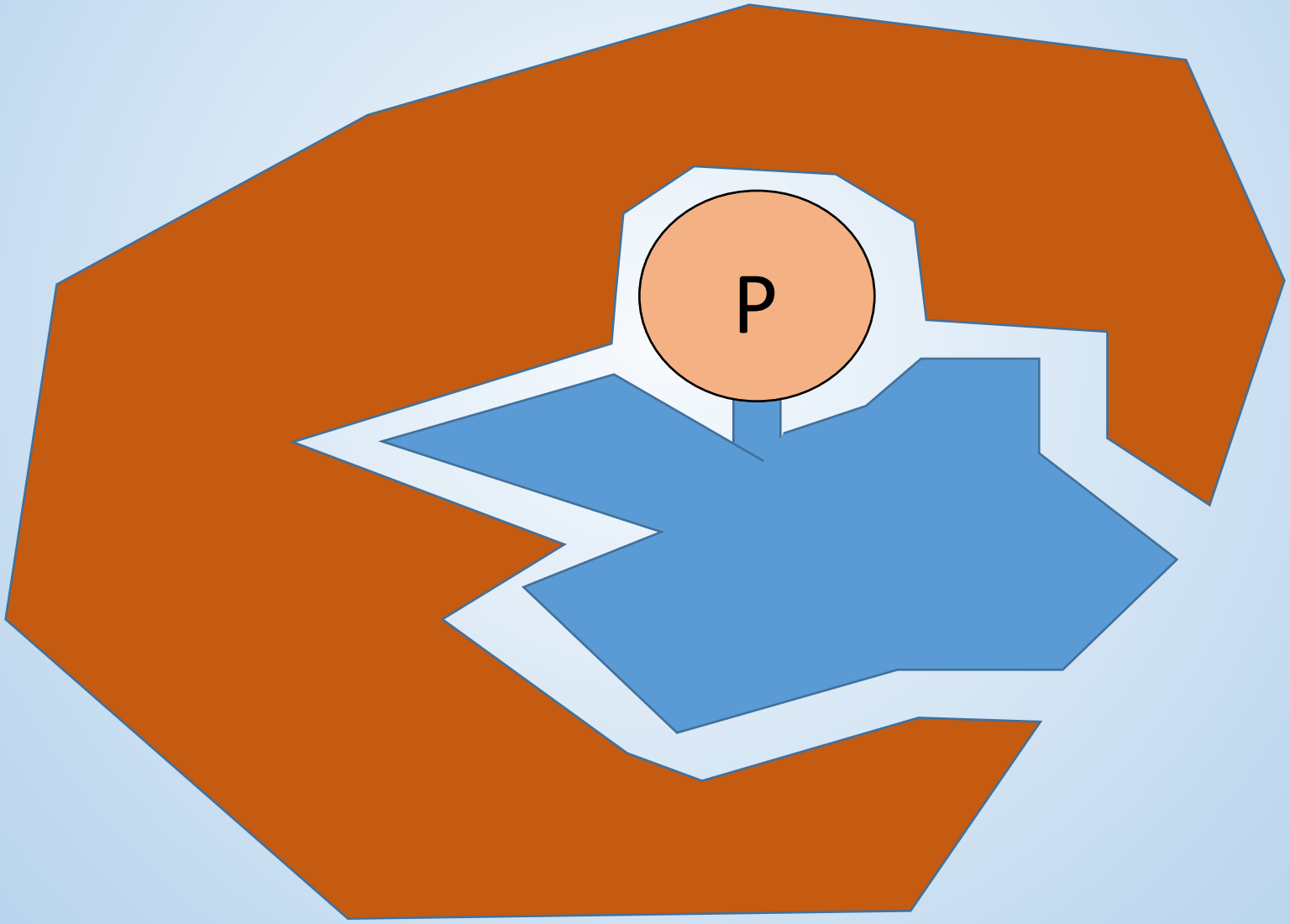
Regulation in Phosphatases



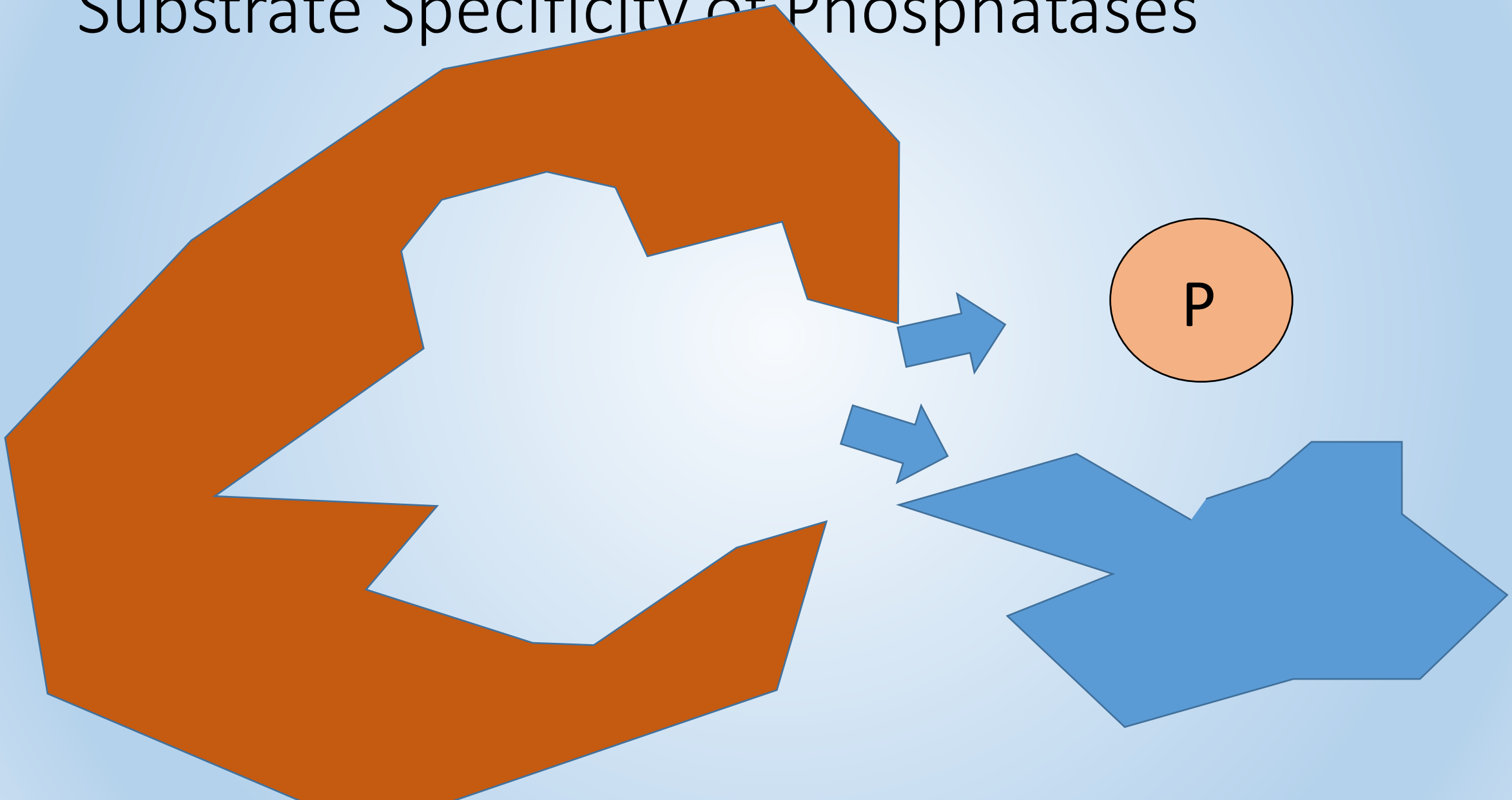
How do we stop constitutive activation?

Drugs!

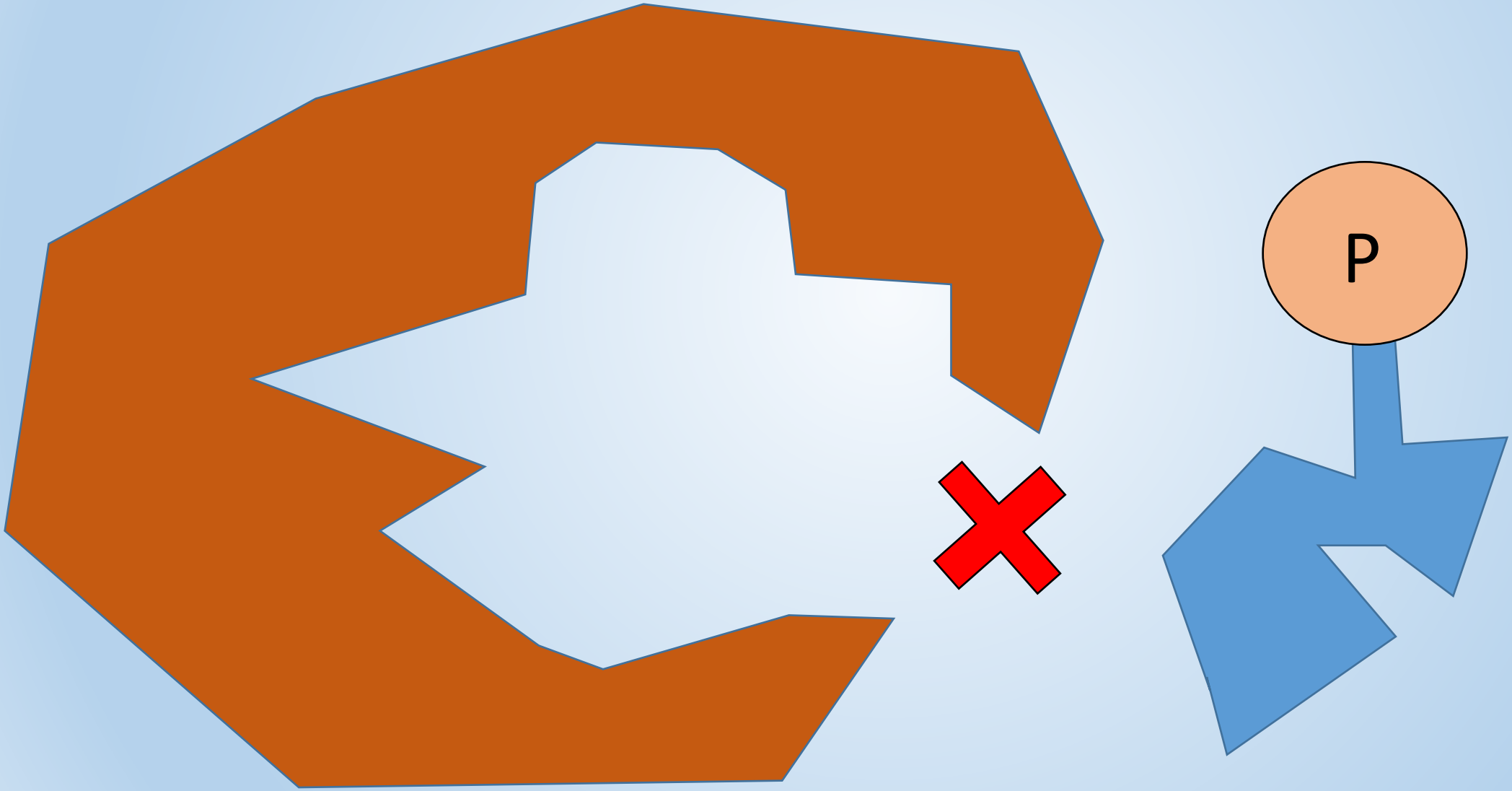
Substrate Specificity of Phosphatases



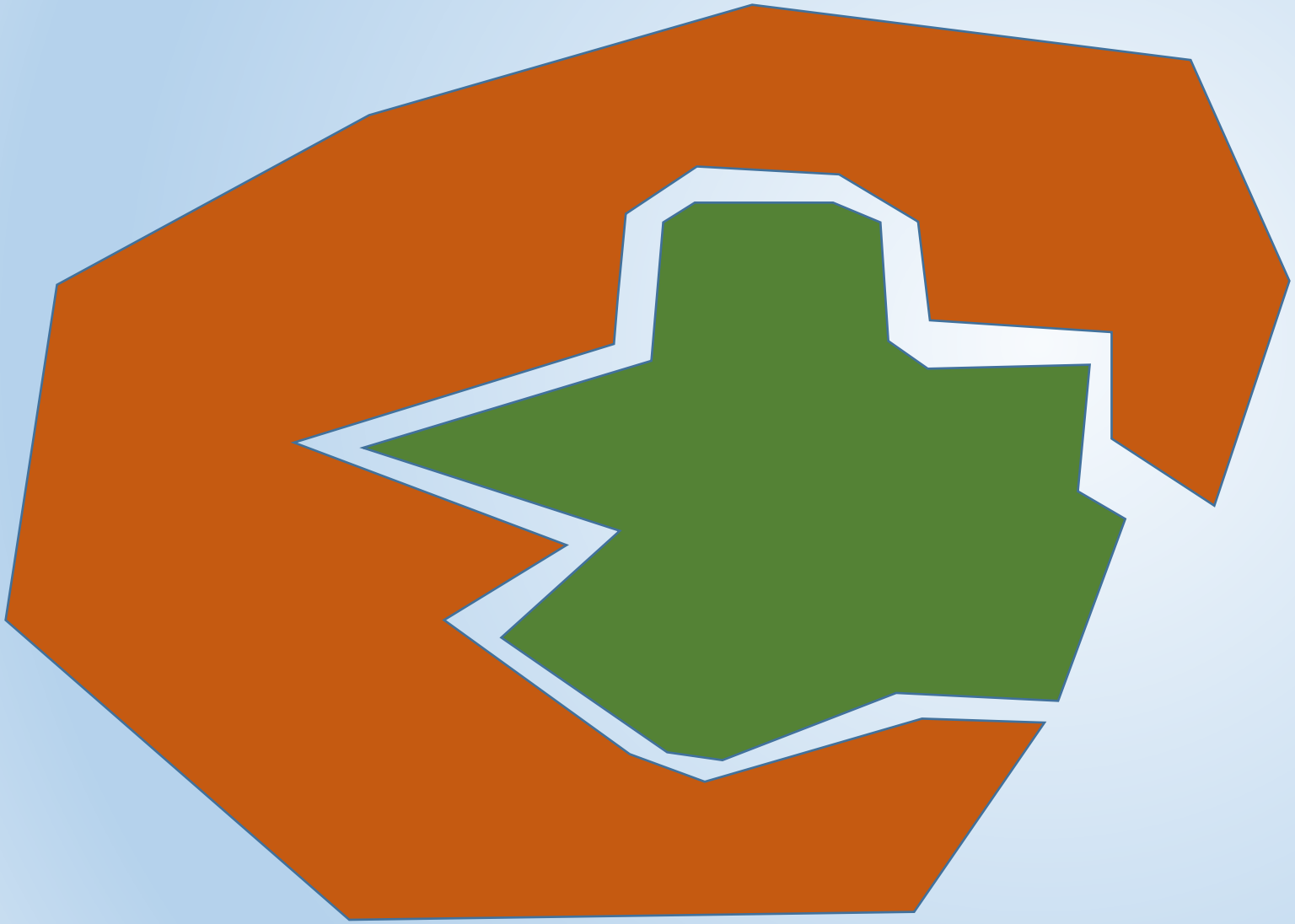
Substrate Specificity of Phosphatases



Substrate Specificity of Phosphatases

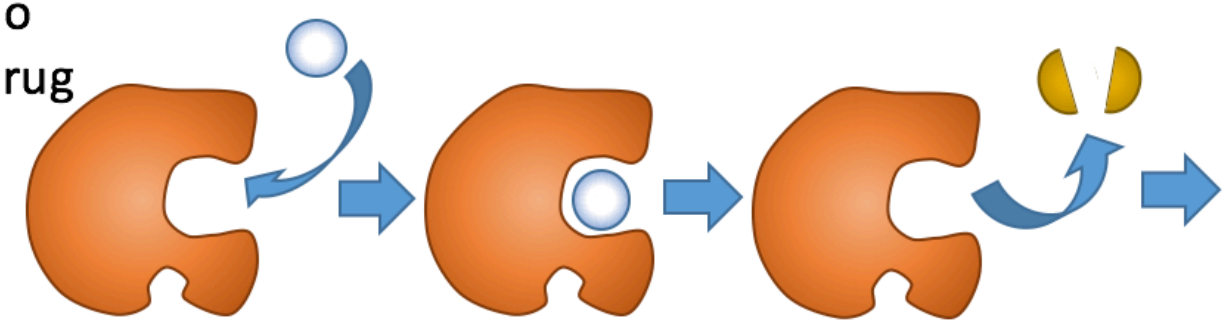


Making a Drug!



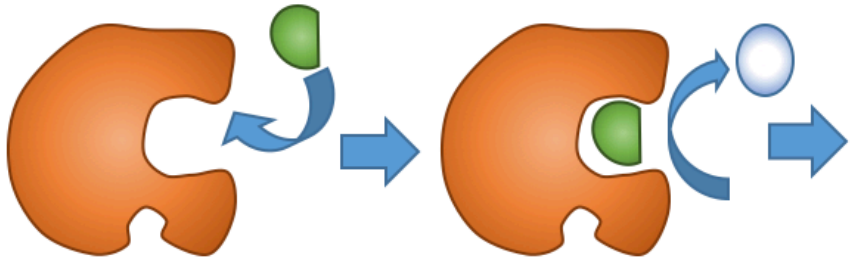
1A: Traditional Active Site Targeting

No Drug



Excessive tyrosine phosphorylation: **Uncontrolled cell growth**

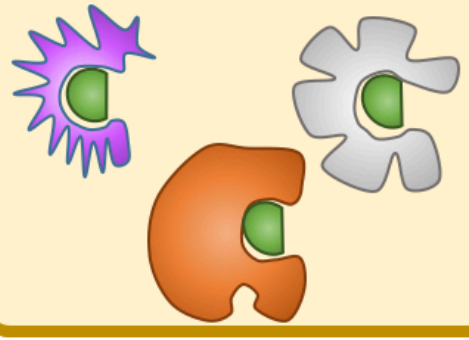
With Traditional Drug



Tyrosine blocked from PTP binding,
No phosphorylation,
No uncontrolled growth

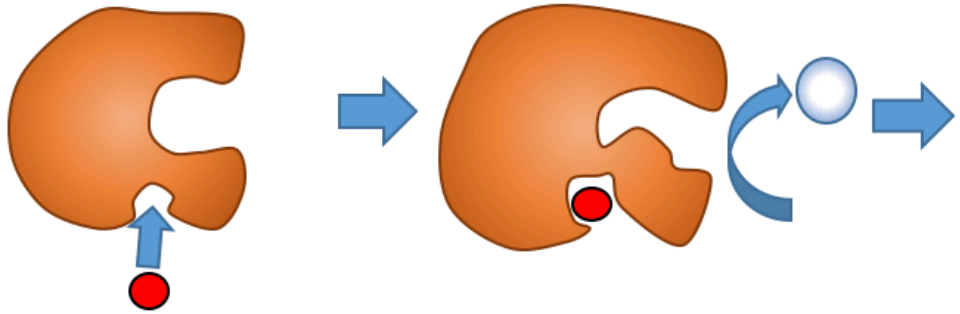
The Problem With Active Site Targeting:

PTP active sites cannot be targeted with specificity!



1B: Allosteric Site Targeting

With Allosteric Inhibitor



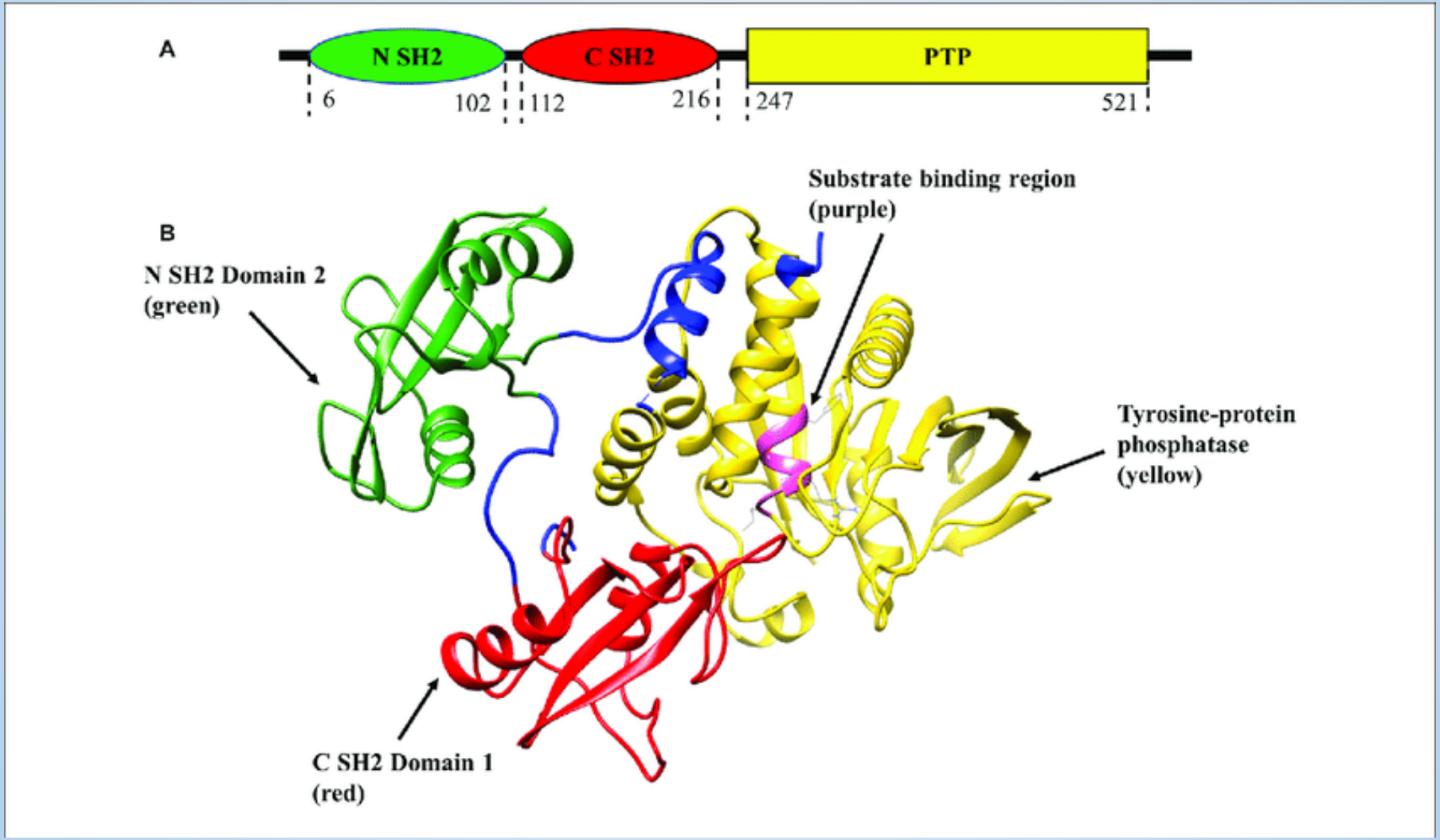
PTP active site unable to bind tyrosine,
No phosphorylation,
No uncontrolled growth
Other PTPs unaffected

Targeting a Cryptic Allosteric Site for Selective Inhibition of the Oncogenic Protein Tyrosine Phosphatase Shp2

Cynthia M. Chio, Christopher S. Lim, and Anthony C. Bishop*

Protein tyrosine phosphatases (PTPs) have been the subject of considerable pharmaceutical-design efforts because of the ubiquitous connections between misregulation of PTP activity and human disease. PTP-inhibitor discovery has been hampered, however, by the difficulty in identifying cell-permeable compounds that can selectively target PTP active sites, and no PTP inhibitors have progressed to the clinic. The identification of allosteric sites on target PTPs therefore represents a potentially attractive solution to the druggability problem of PTPs. Here we report that the oncogenic PTP Shp2 contains an allosteric-inhibition site that renders the enzyme sensitive to potent and selective inhibition by cell-permeable biarsenical compounds. Because Shp2 contains no canonical tetracysteine biarsenical-binding motif, the enzyme's inhibitor-binding site is not readily predictable from its primary or three-dimensional structure. Intriguingly, however, Shp2's PTP domain does contain a cysteine residue (C333) at a position that is removed from the active site and is occupied by proline in other classical PTPs. We show that Shp2's unusual cysteine residue constitutes part of a Shp2-specific allosteric-inhibition site, and that Shp2's sensitivity to biarsenicals is dependent on the presence of the naturally occurring C333. The determinative

Regulation in Phosphatases



For Research Confidentiality Reasons I Can't Share the Experimental data with you.

- Below is link to paper I talked about in class:

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4303306/

Allosteric Site-Directed Drugs are the Future

Thank You