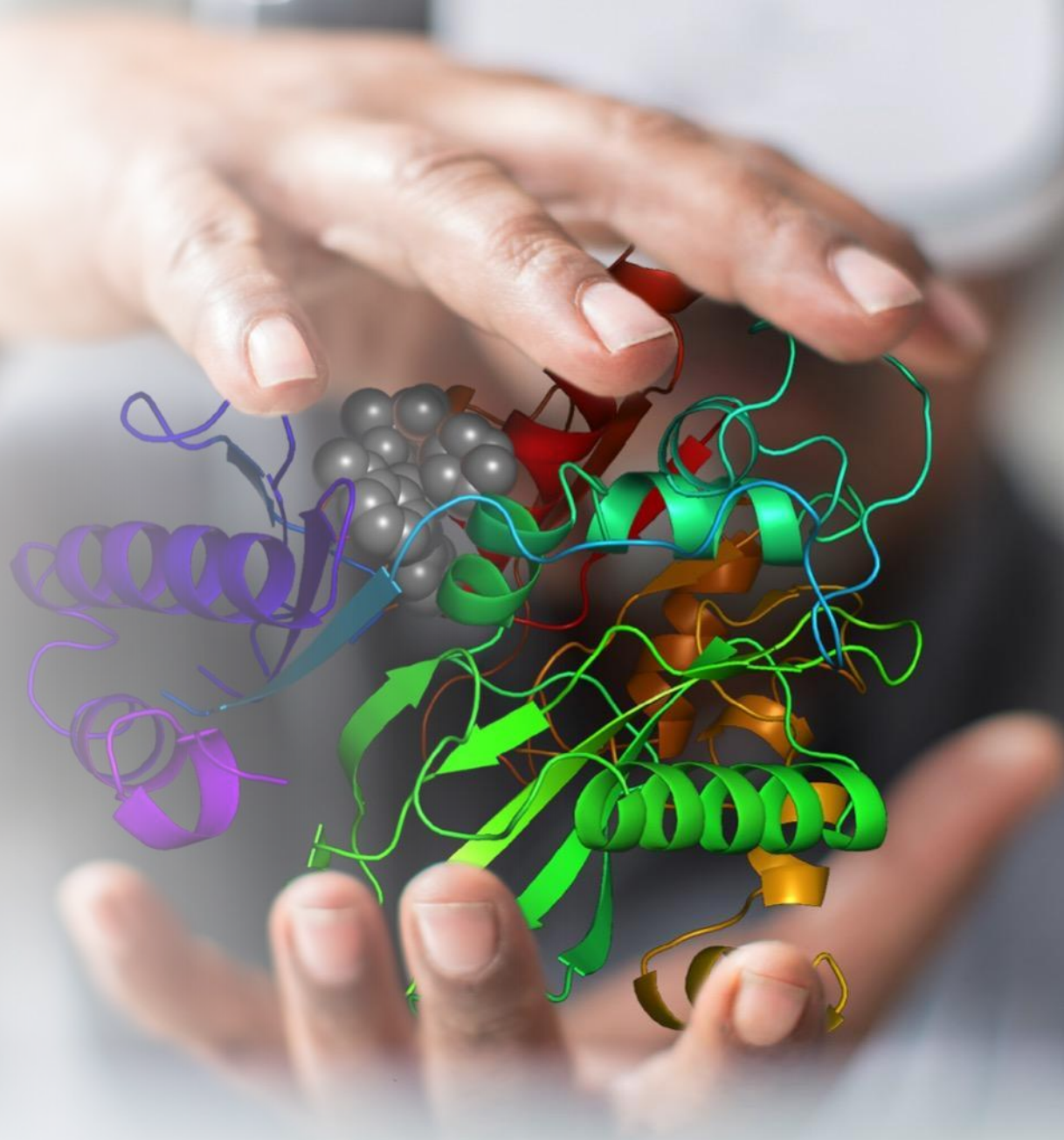
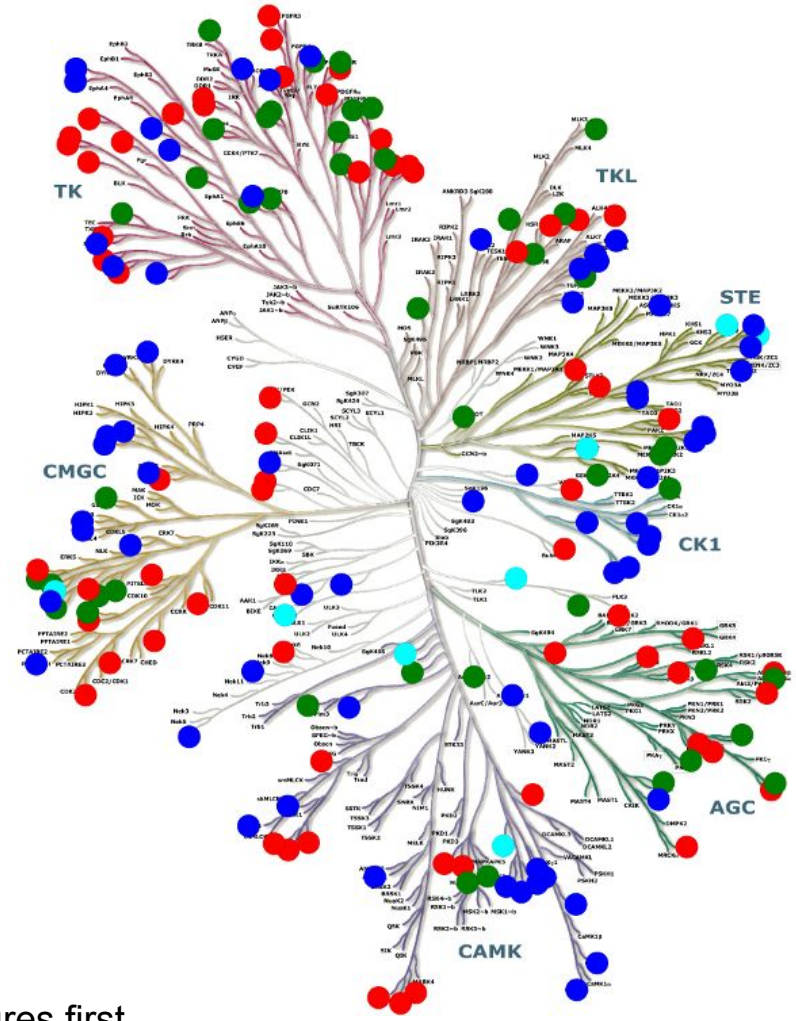
SCHRÖDINGER®

Background on Kinase Structure and Activity



How will this module help you in your work?

- Kinases have been called the most important drug targets of the 21st century
- This module will familiarize you with kinase structural biology and the history of drug discovery on VEGFR kinases

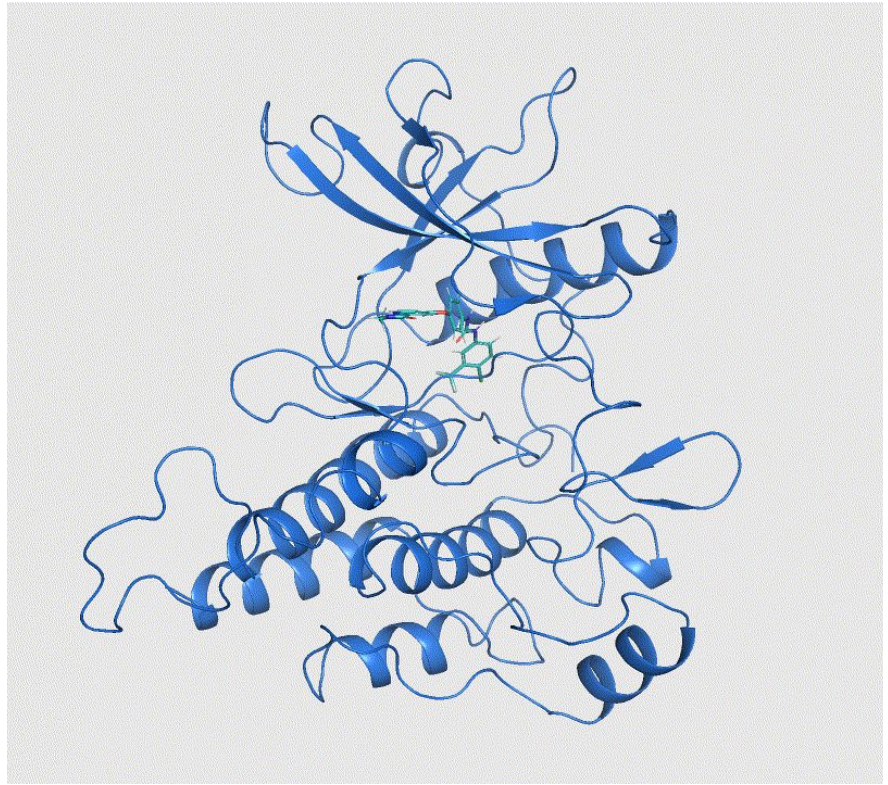


Cohen P., *Nature Reviews Drug Discovery* 1, 309–315 (2002)
https://www.thesgc.org/scientists/resources/kinases

Case Study for completion of the course

Task:

- VEGFR-2 is a potential target for glioblastoma multiforme
- In this case study we are trying to maintain or even improve potency of hit molecules against VEGFR-2 while improving physicochemical properties



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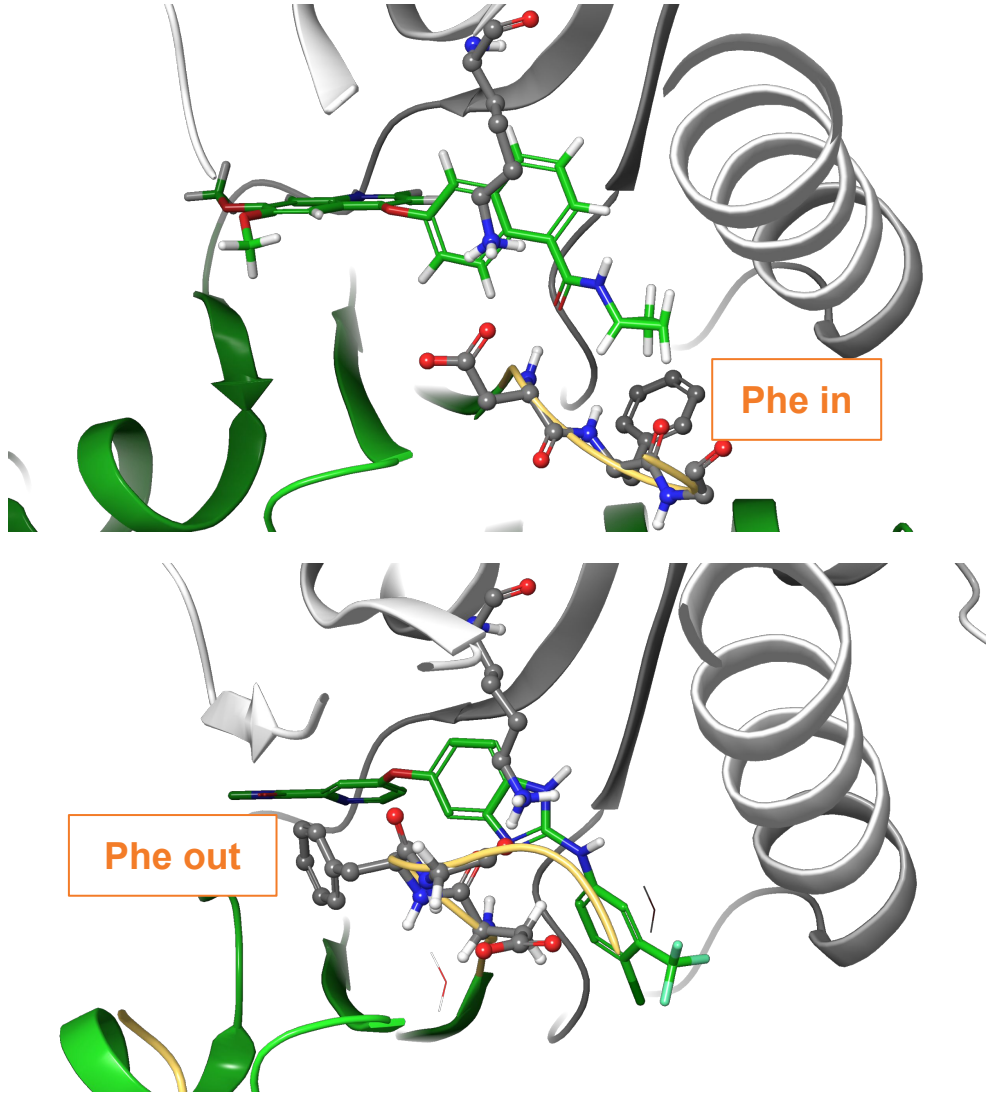
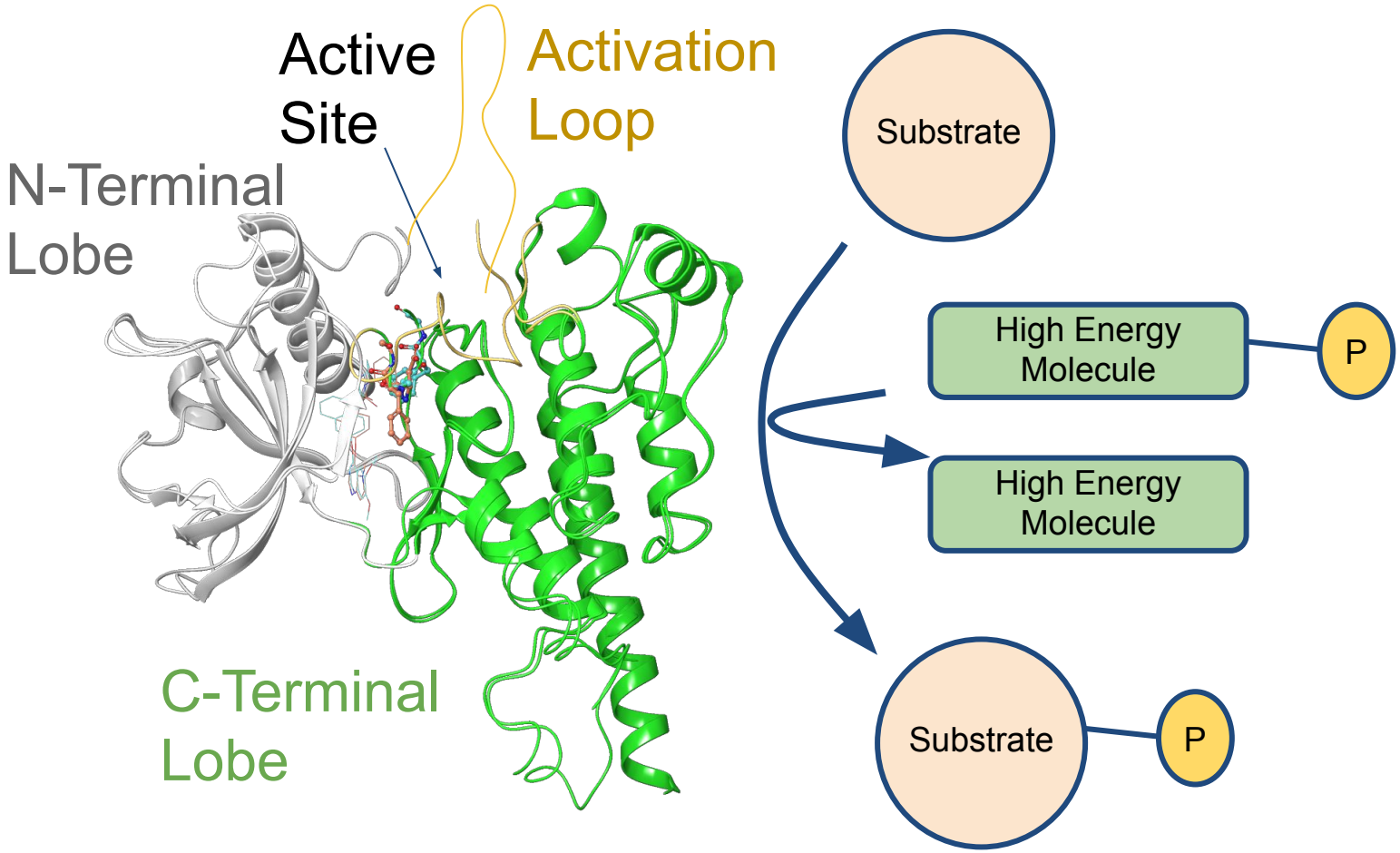
By the end of this module you should be able to:

- **Describe** what kinases do and what their targets are
- **Identify** the activation loop, C-terminal domain, N-terminal domain, DFG motif, and gatekeeper residues in VEGFR kinase
- **Describe** what the structural differences are between **DFG-in** versus **DFG-out** conformations



What do kinases do and what are their targets?



Protein Kinases

Lipid Kinases

Carbohydrate Kinases

Small Molecule Kinases

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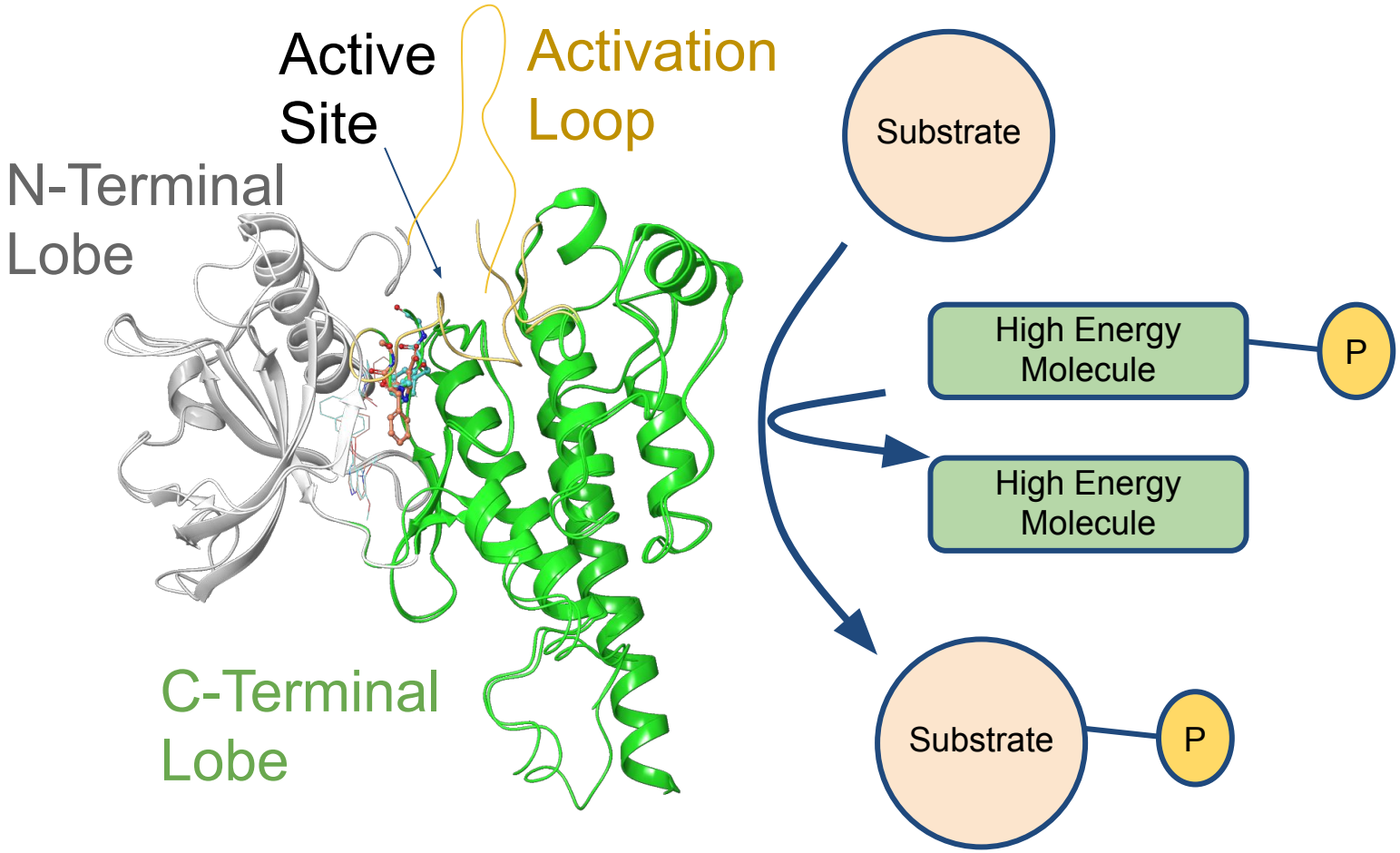


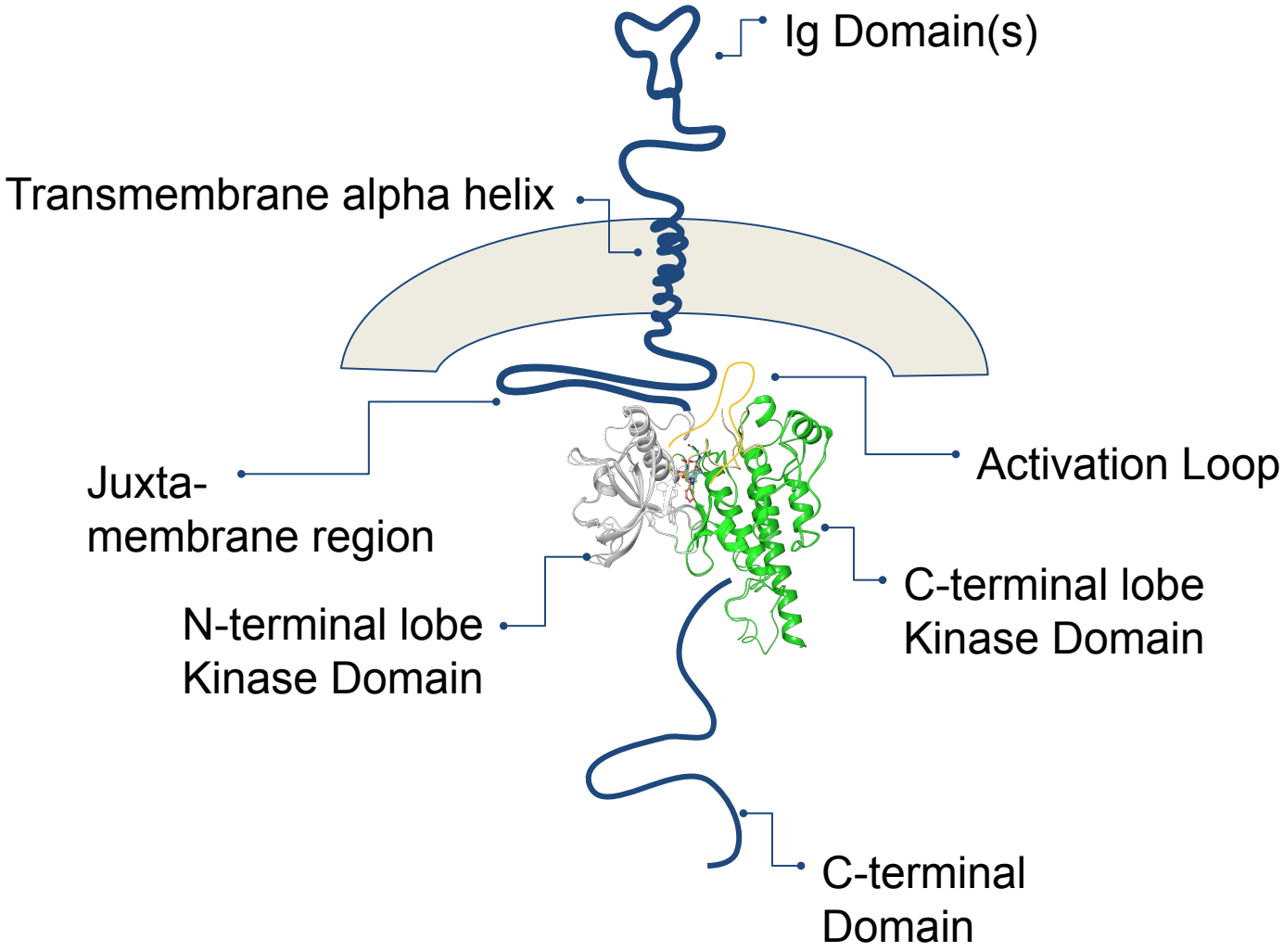
Protein Kinases
- tyrosine, serine, threonine

Lipid Kinases

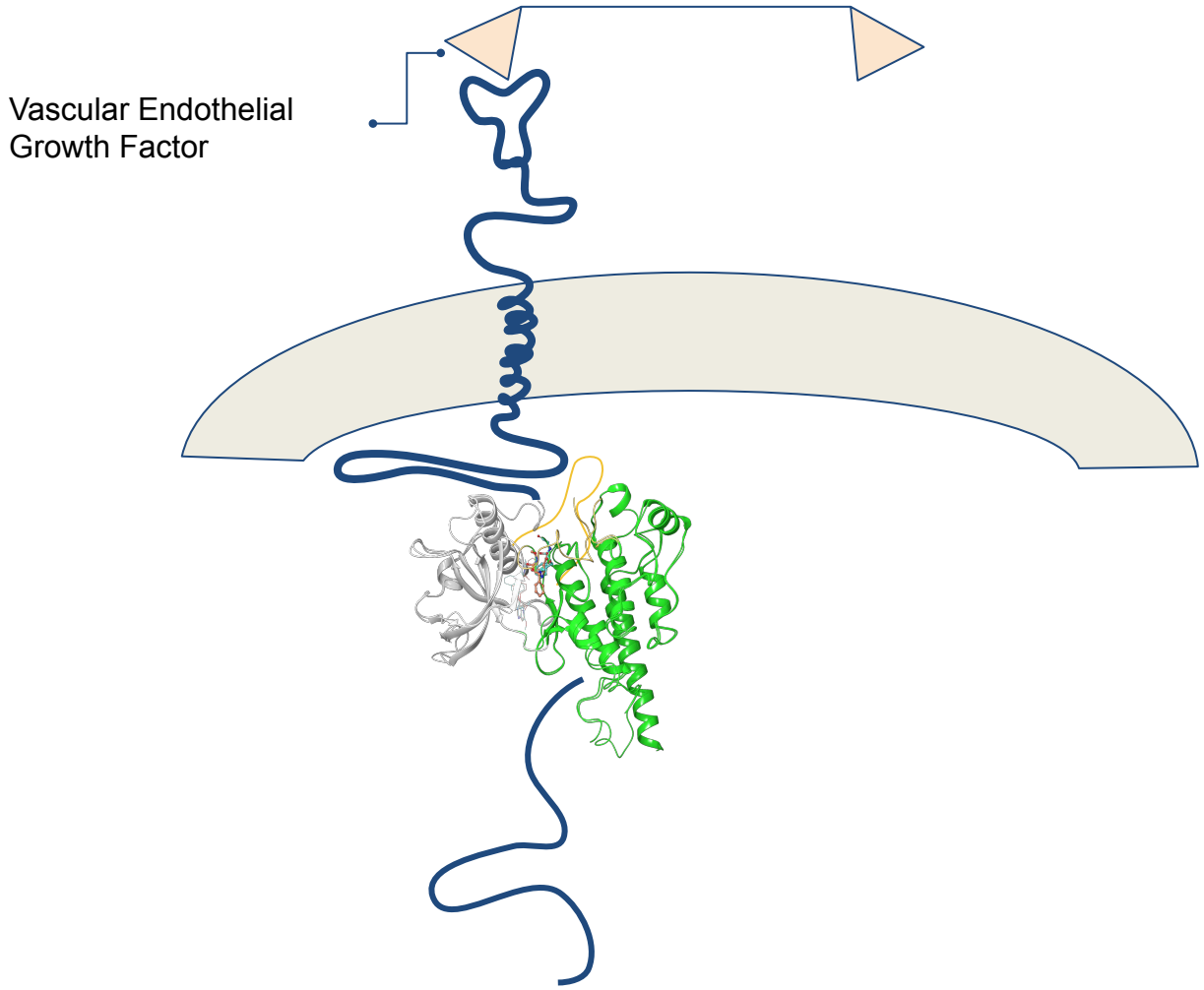
Carbohydrate Kinases

Small Molecule Kinases

What do receptor protein kinases do and what are their targets?



Vascular Endothelial Growth Factor Receptor 2 is a receptor tyrosine kinase



Coulpier, M. et al. *JBC*, 277, 3, 1991-1999 (2002)
Rahimi, Exp Eye Res. 83, 5, 1005-1016 (2006)

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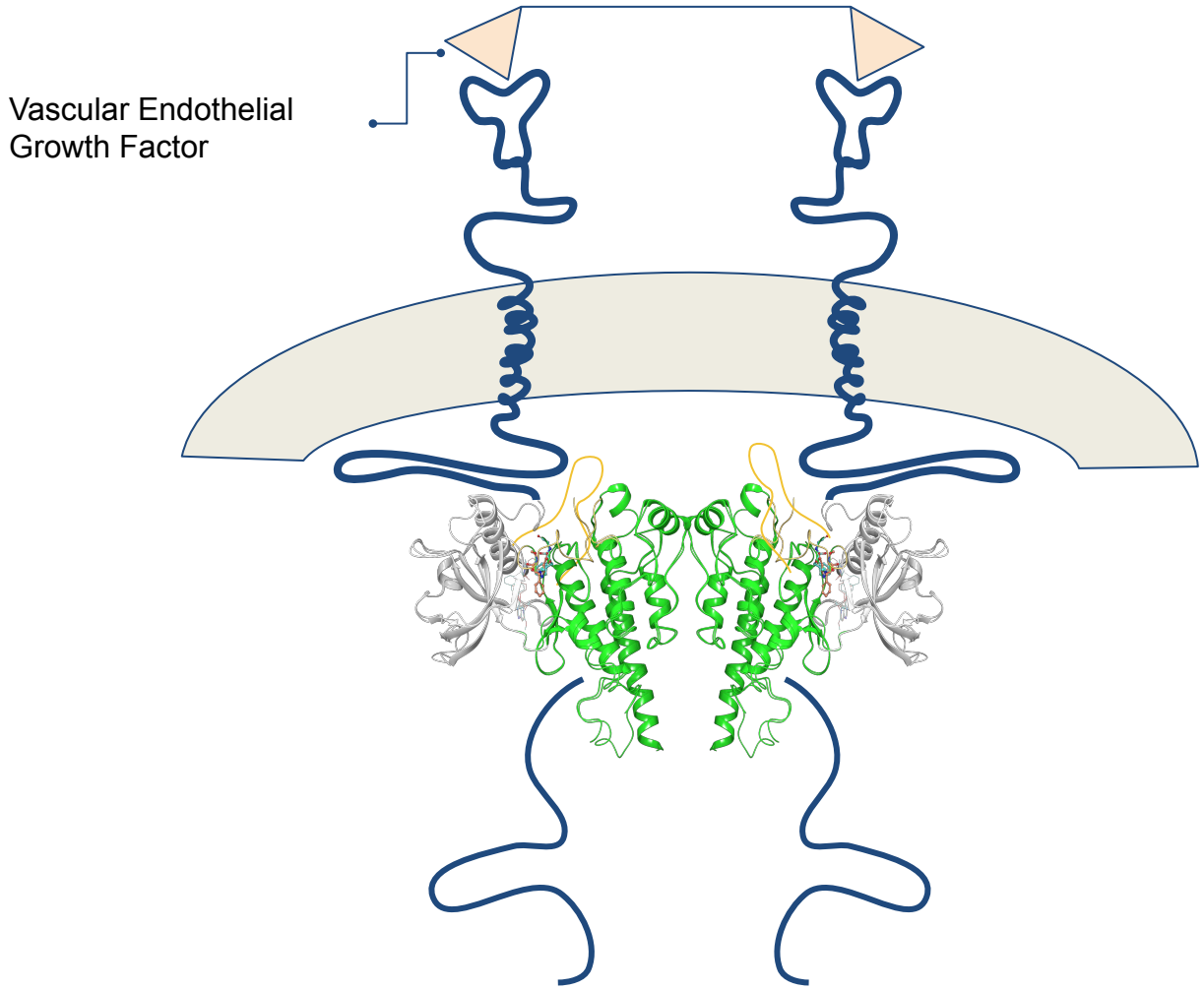

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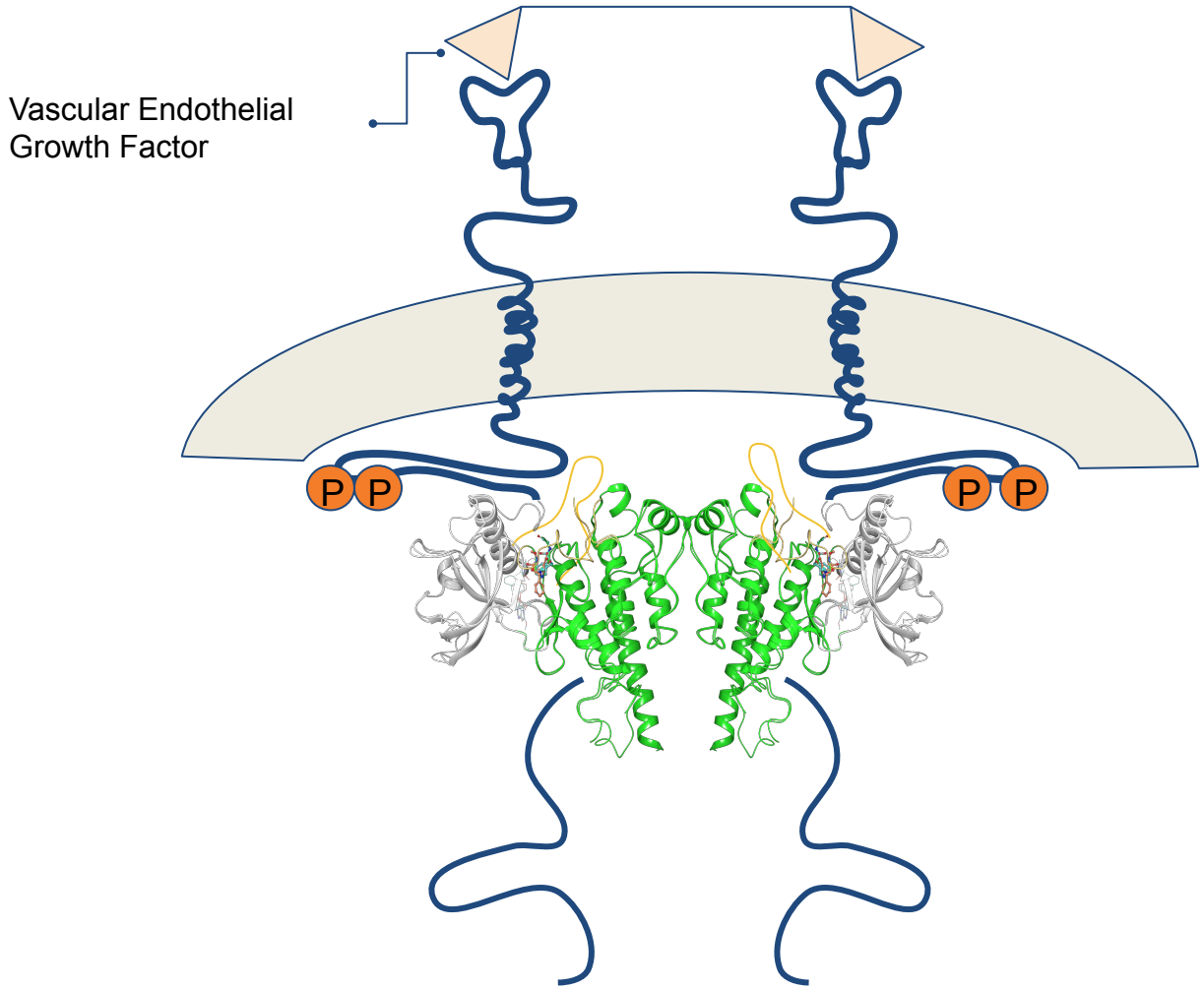

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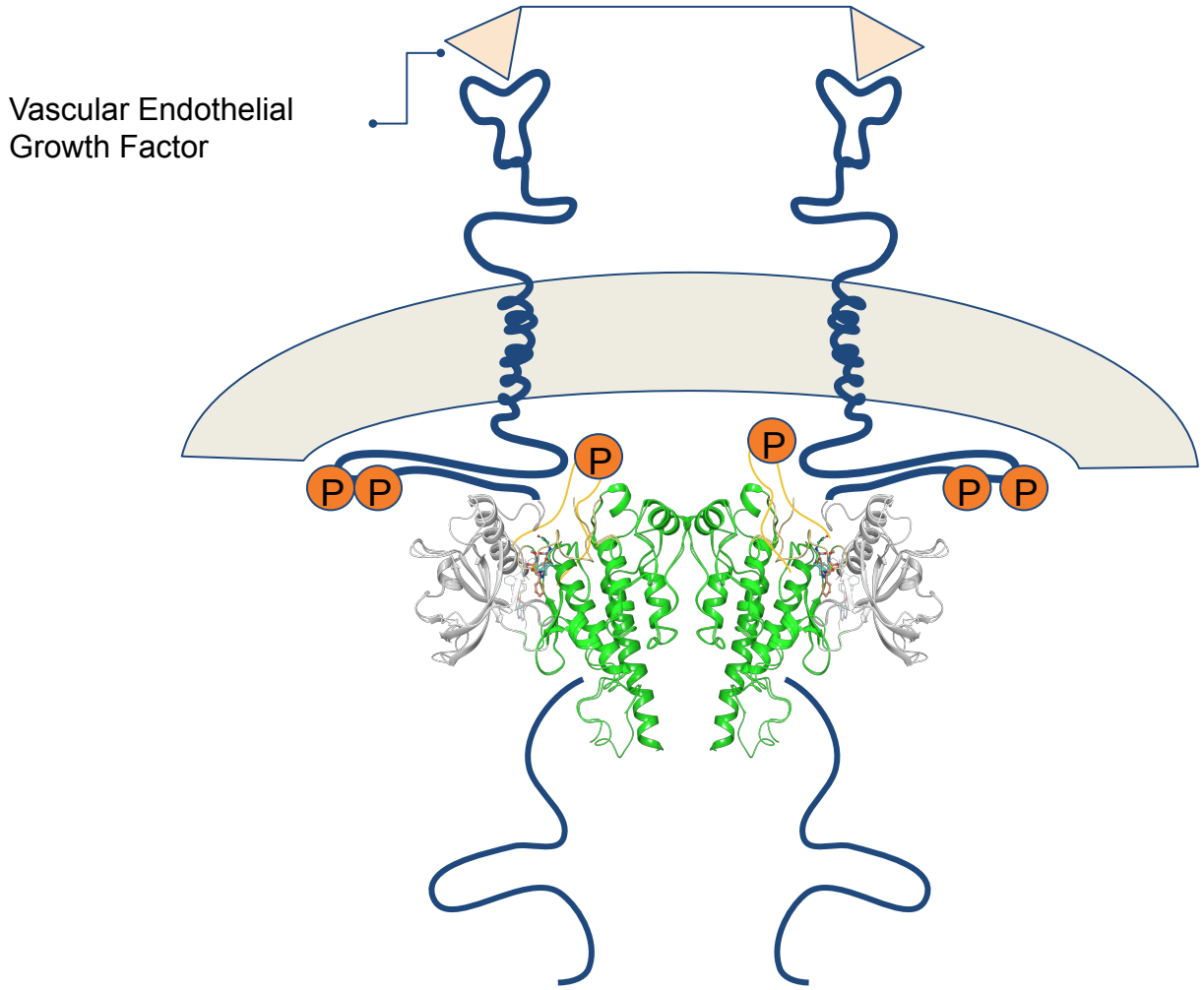

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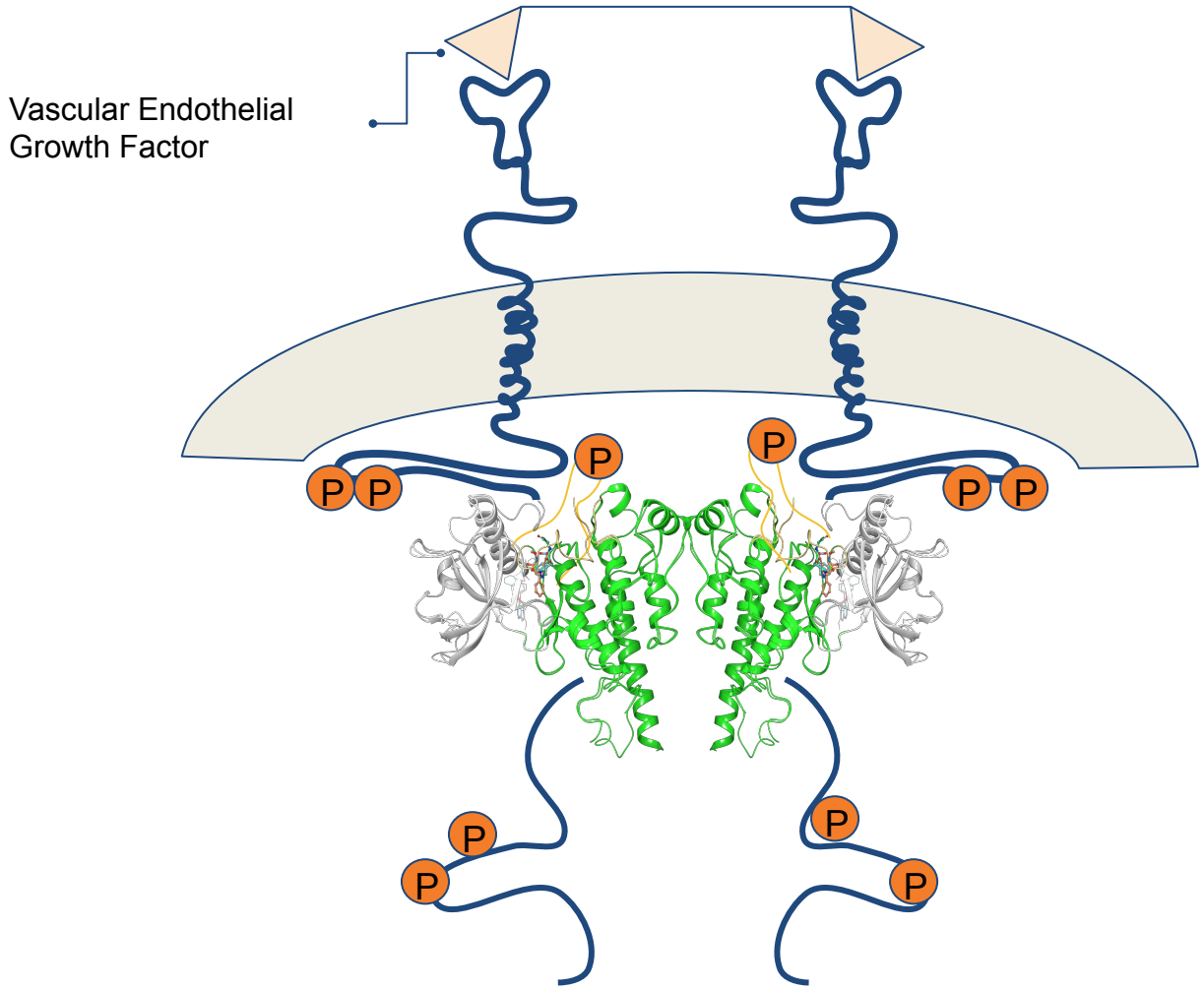

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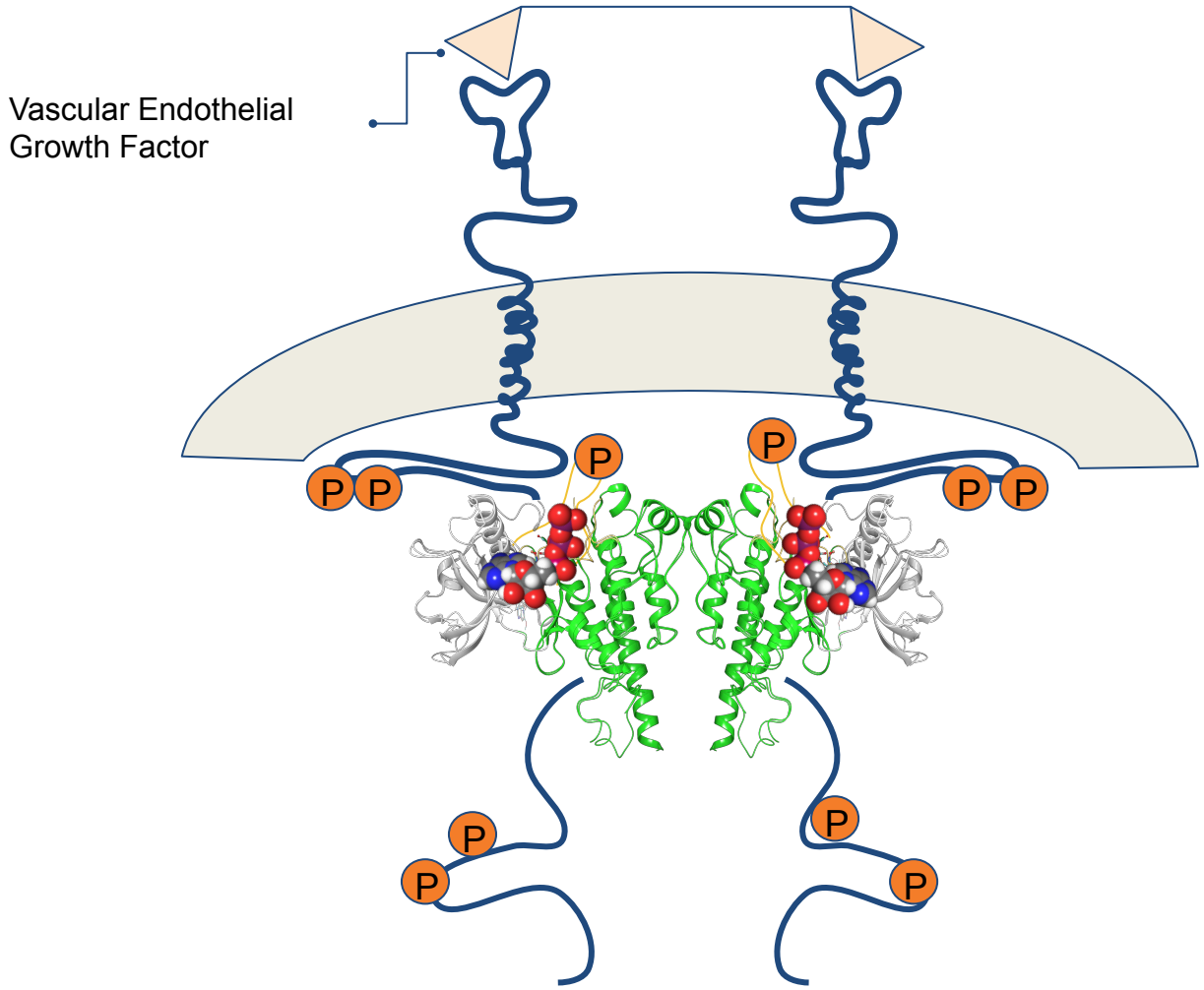

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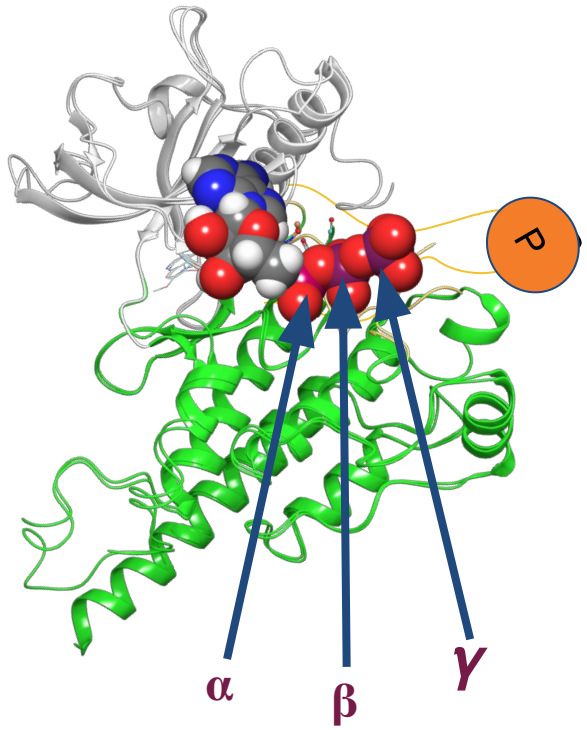

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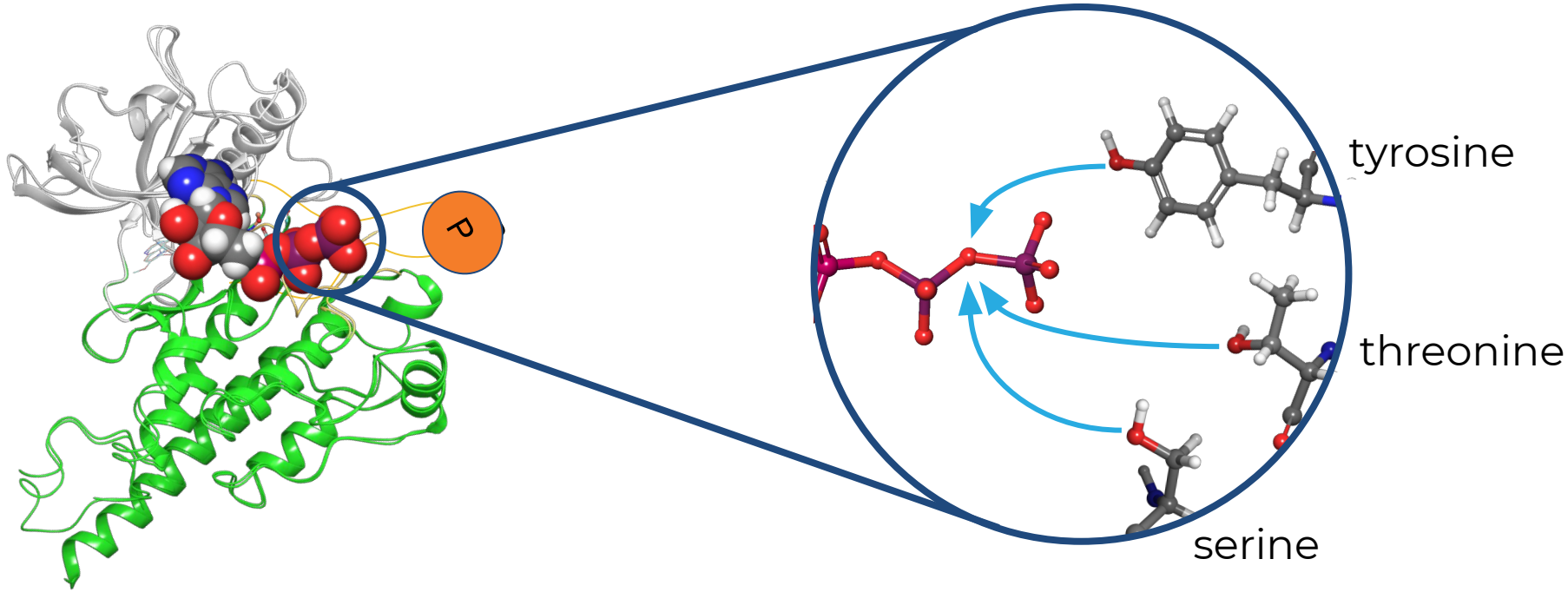

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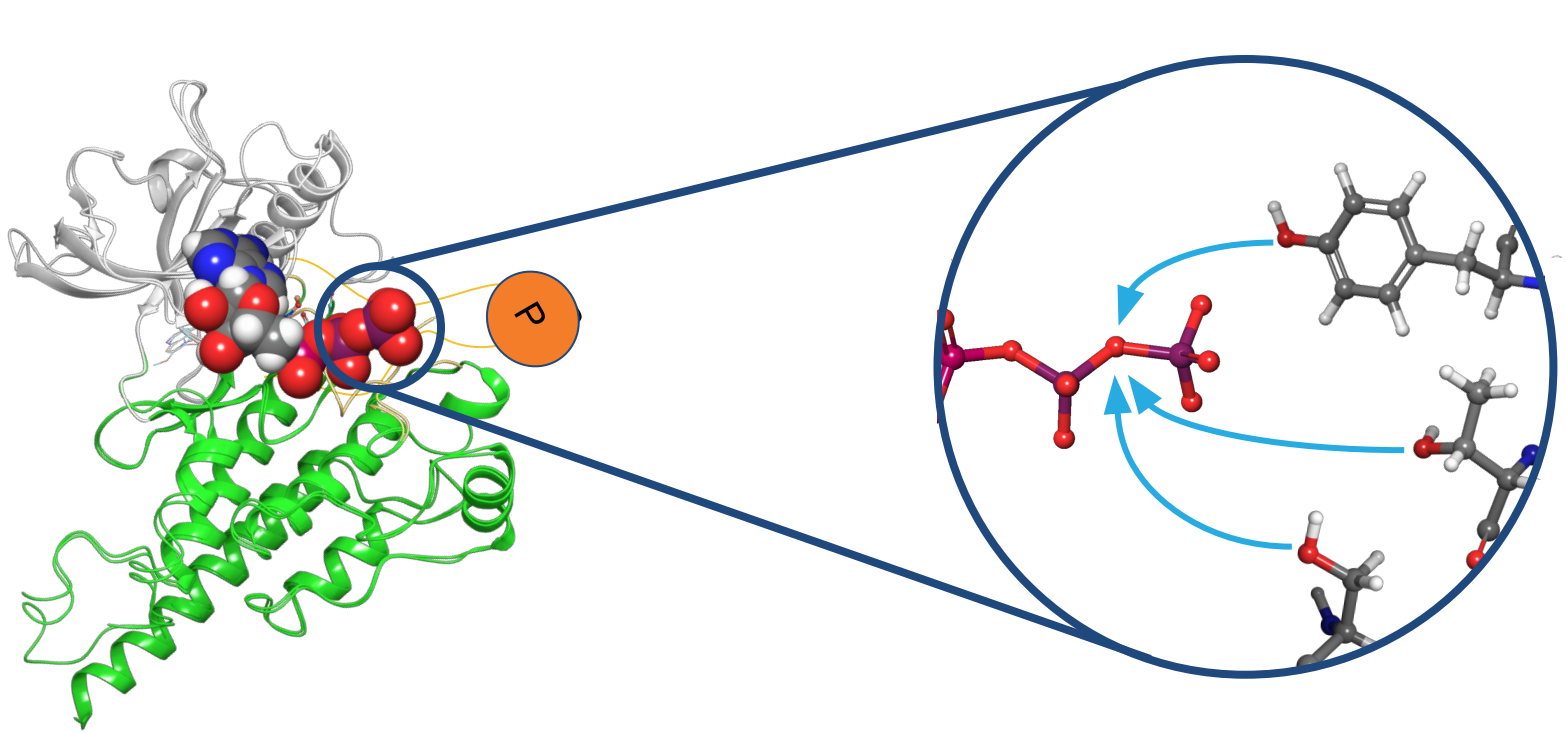

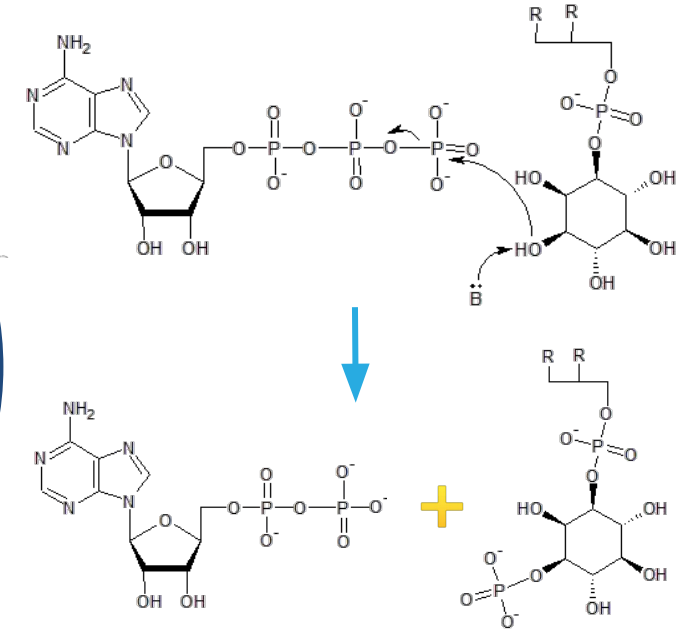

Open web-based Maestro

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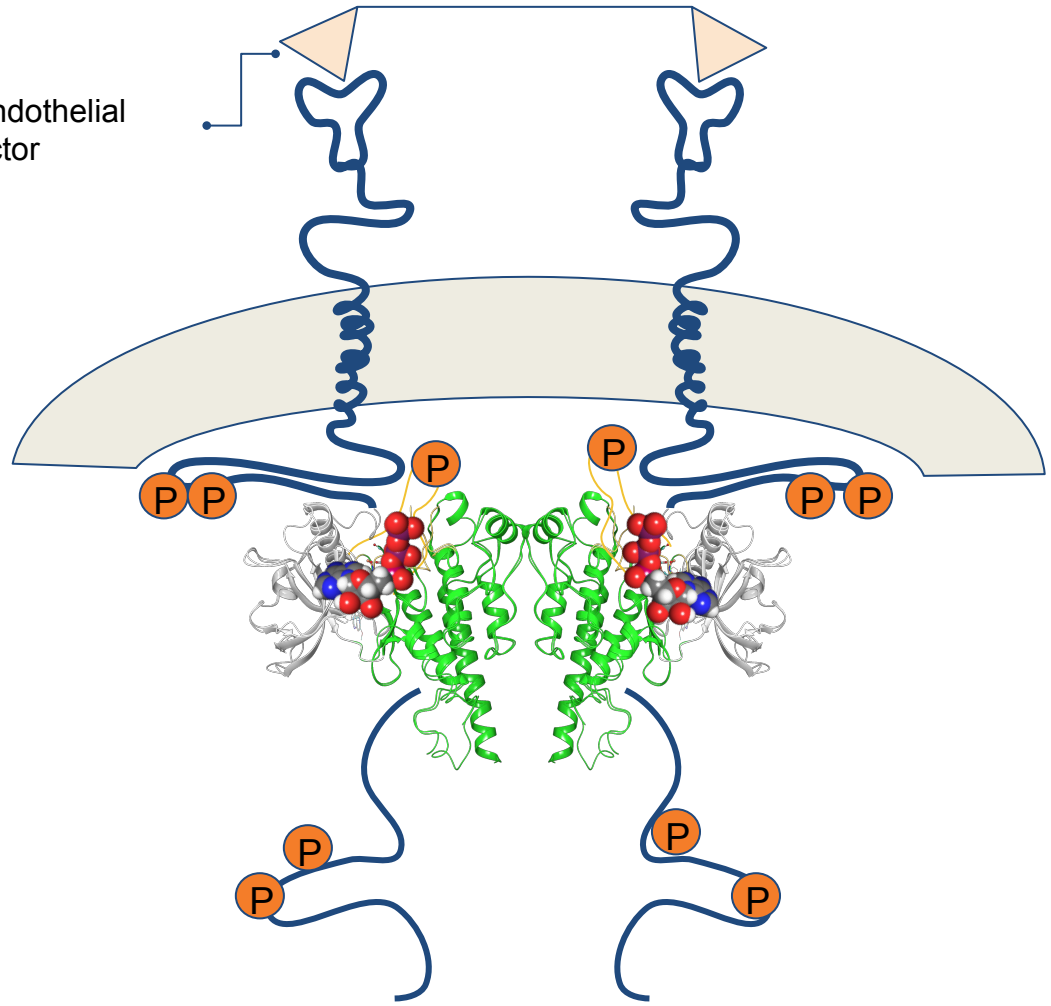

- different categories of kinases
- mechanisms of kinases
- key structural motifs in the target

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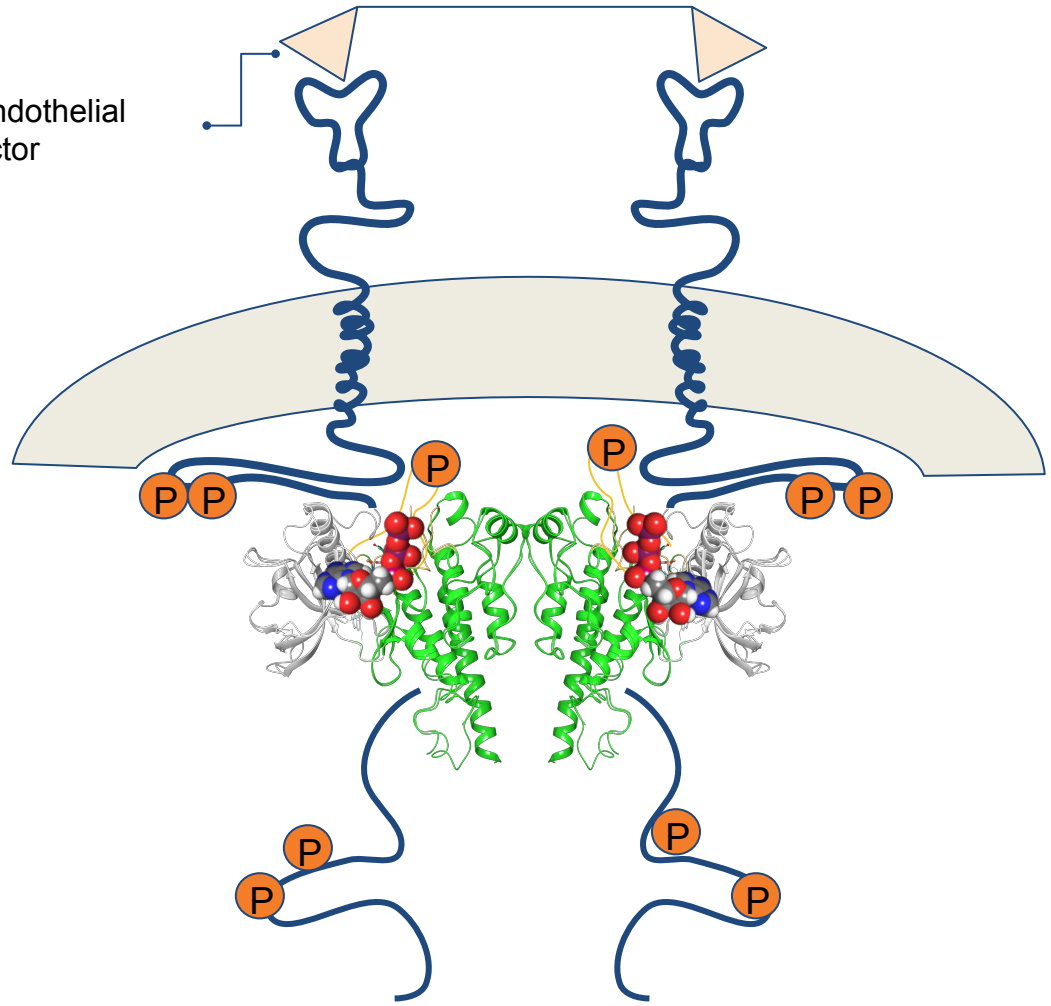

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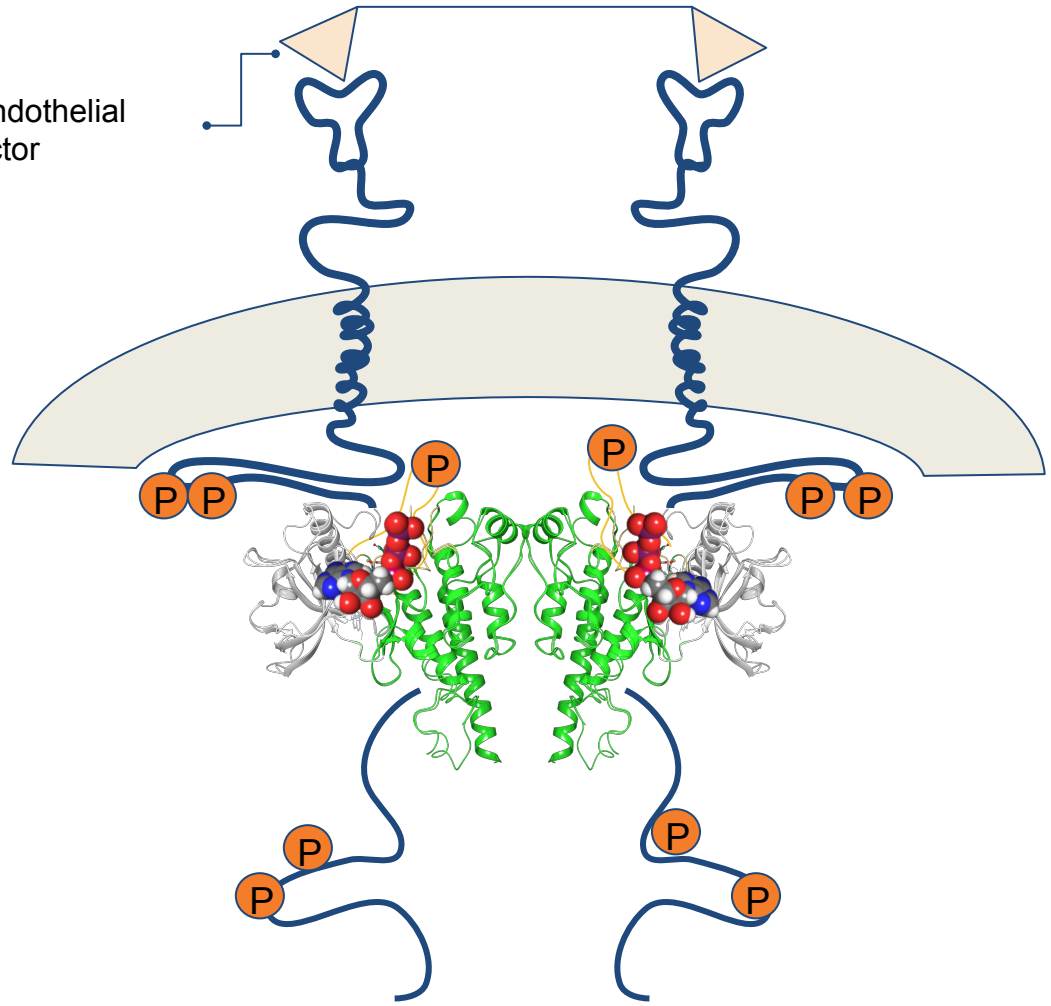

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