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ILLUMINATING THE DARK KINOME: PRKY MODELING AND VIRTUAL SCREENING

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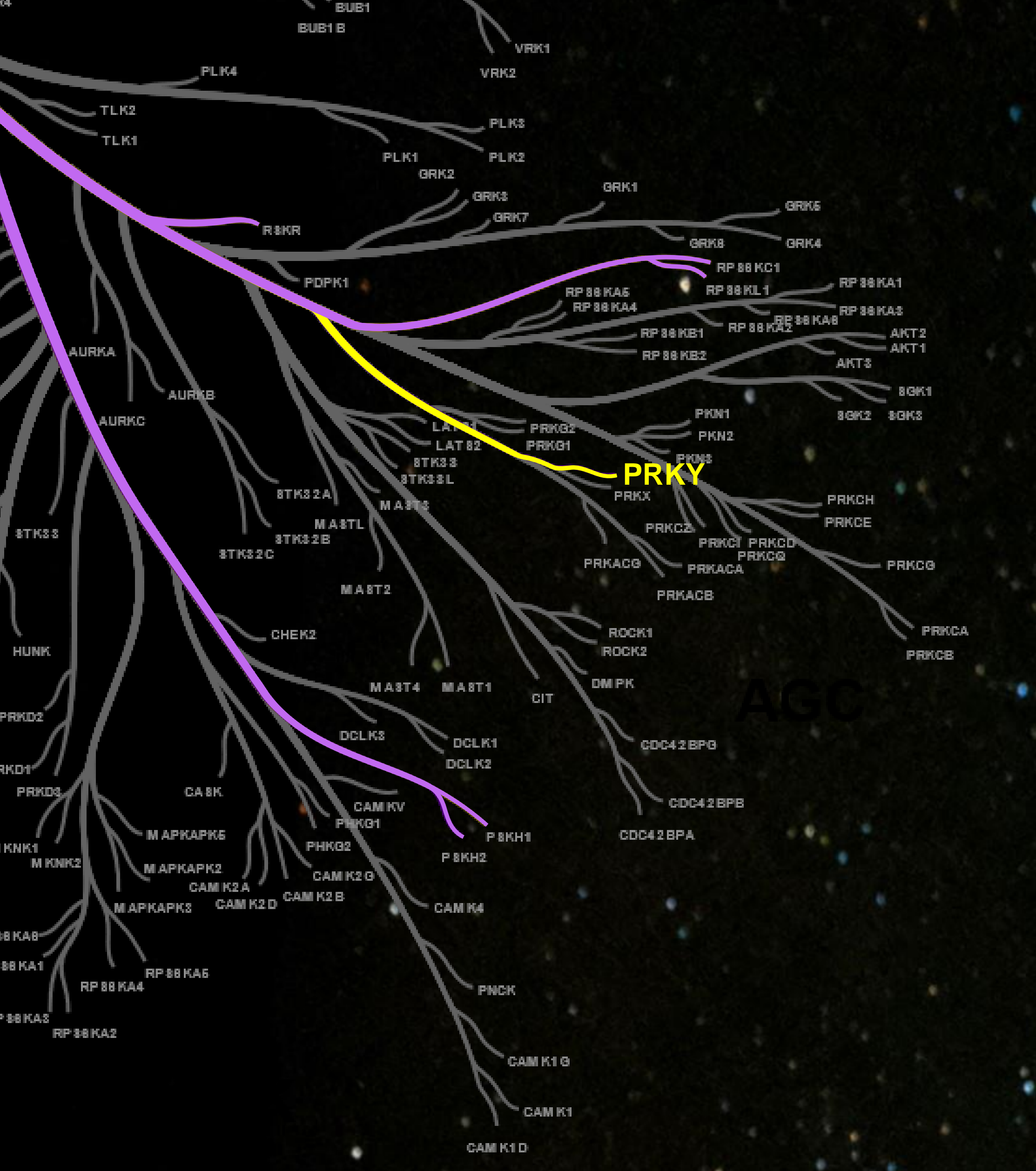
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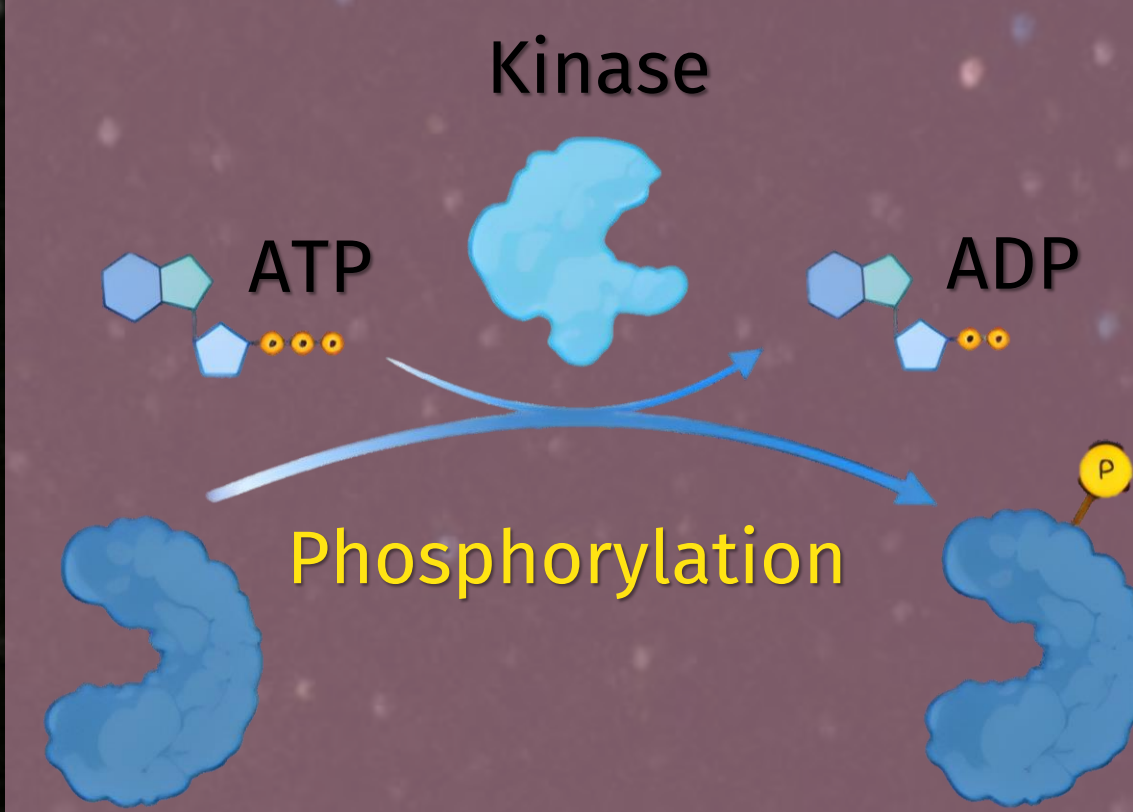
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DARK KINASES: CONTEXT



Kinases are key enzymes catalyzing phosphorylation reactions *via* ATP (adenosine triphosphate), regulating a multitude of biological processes. However, some of these enzymes are still poorly characterized: they are referred to as 'dark' kinases.

Kinases are involved in many cellular aspects (proliferation, metabolism, etc.) and thus have a proven role in many diseases (cancer, metabolic disorders, Alzheimer's disease, etc.).

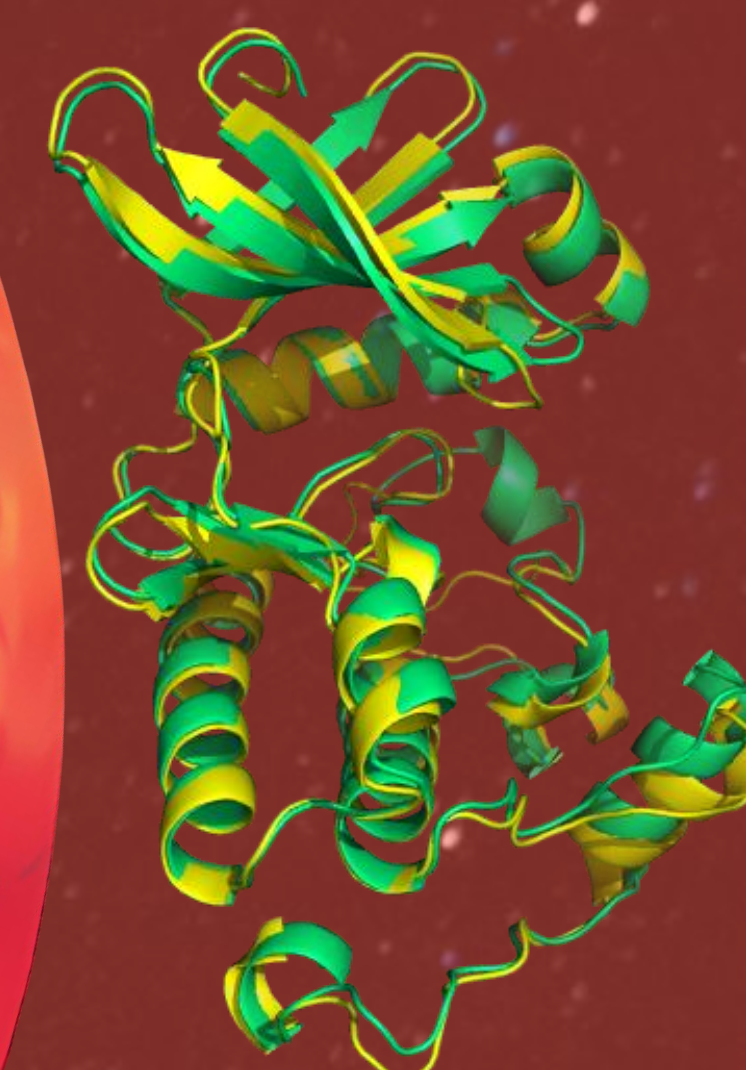
PRKY: PUTATIVE SERINE/THREONINE-PROTEIN KINASE ψ

- Appears to be linked to Nonsense-Mediated Decay (NMD)
- Overexpressed in prostate, testicular and bladder cancer

ALPHAFOLD: AI MODELING



HOMOLOGY MODELING



Green cartoon :
PRKY modeled through AKT1 template (PDB id 3OCB)

Yellow cartoon :
PRKY modeled through PKC θ template (PDB id 2JED)

Criteria for template choice:

- Human kinase templates
- Templates must be co-crystallised with a small molecule
- Geometry (bonds, angles) must be respected
- Templates must be phylogenetically close to PRKY

PRKY MODEL ALIGNMENT

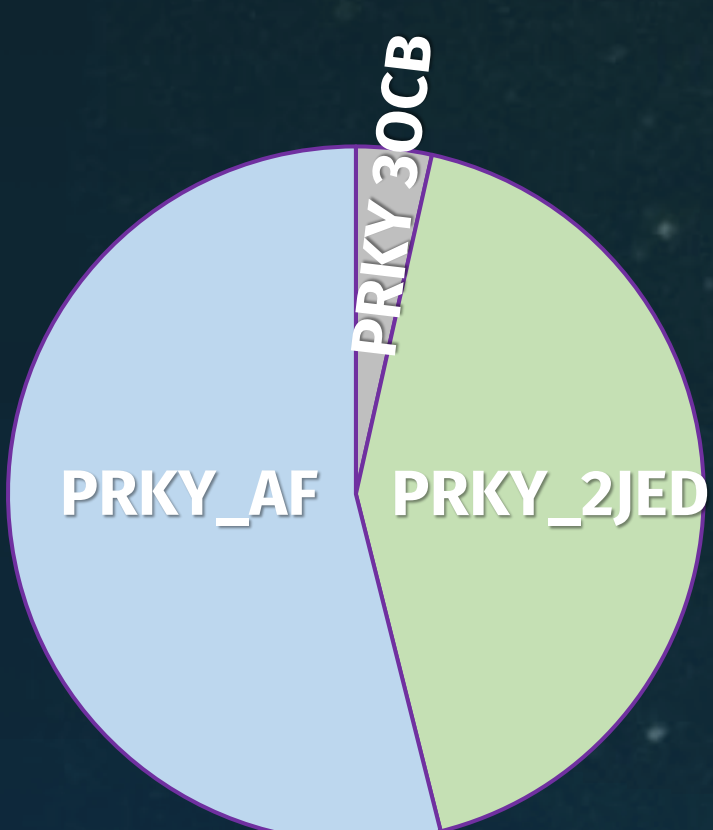
Flexibility in GTFG loop:

PRKY : ⁵⁸GTFG⁶¹
AKT1 (PDB 3OCB) : ²⁰GTFG²⁴
PKC θ (PDB 2JED) : ²⁹GSFG³²

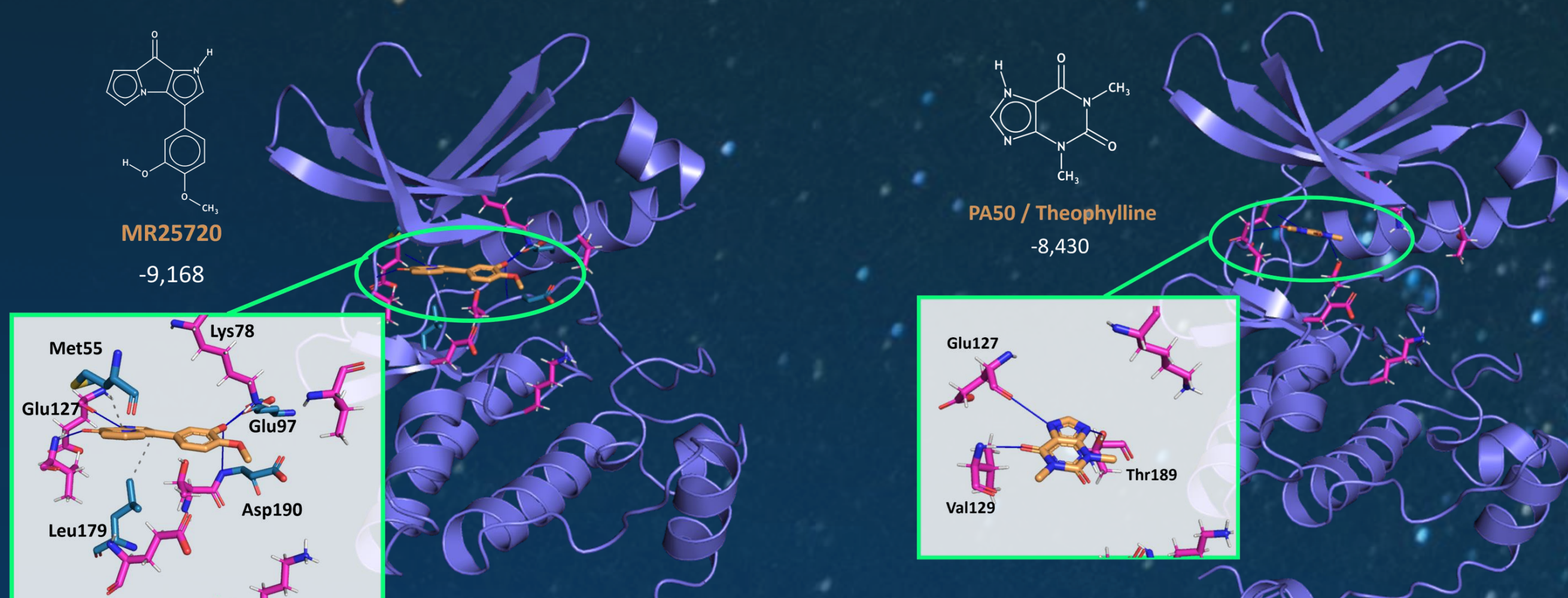
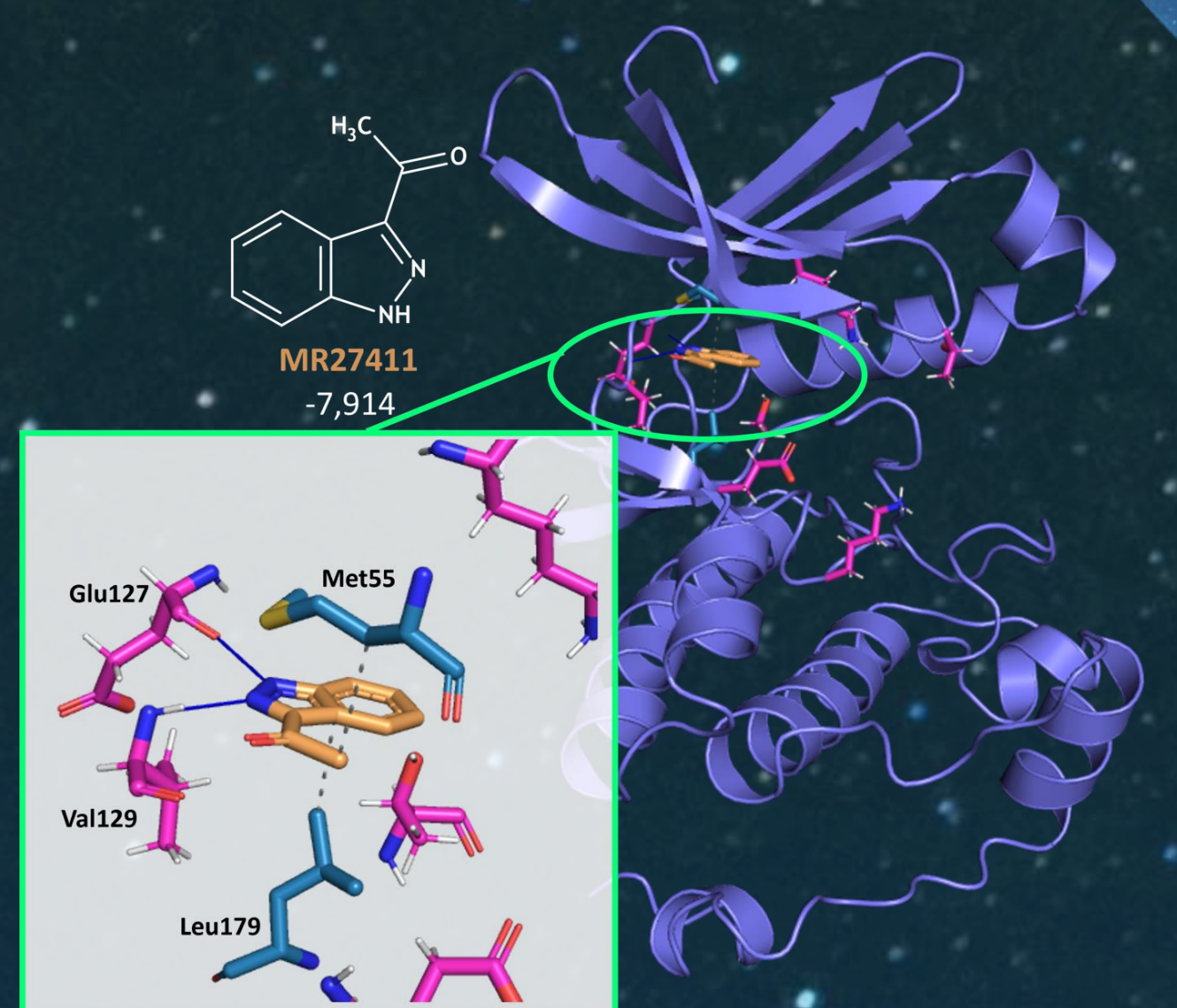
PRKY_2JED (SwM)
PRKY_3OCB (SwM)
PRKY_AF (AlphaFold)

VIRTUAL SCREENING ON PRKY MODELS

Virtual screening of CERMN chemical library was conducted on PRKY models (catalytic site, ensemble docking - Glide Schrödinger, SP, 10,000 compounds).



Ensemble docking:
distribution of compound target



Virtual screening of CERMN chemical library revealed various scaffold as potential *hit* for PRKY inhibition.

2D compound representations were generated with MarvinSketch software by Chemaxon

NEXT STOP: ROSCOFF, FINISTERE, EARTH

This very preliminary hit discovery step will next be conducted through *in vitro* testing for methodology proof of concept and, hopefully, for dark kinome illumination.

The *in vitro* kinase assay is now ready to be used on earth to evaluate the first *in silico* docking hits.