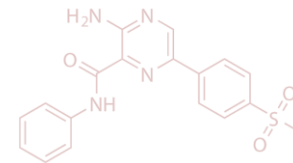
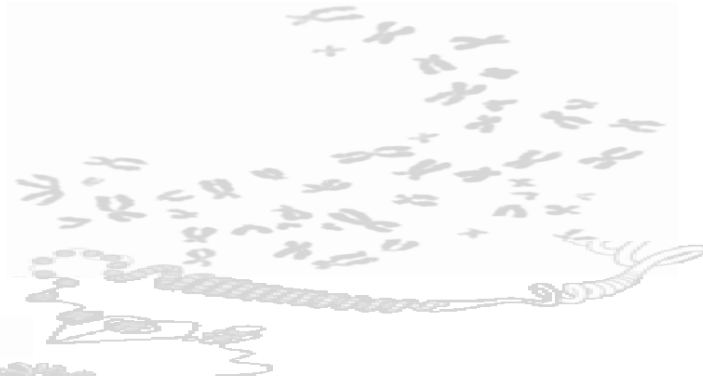
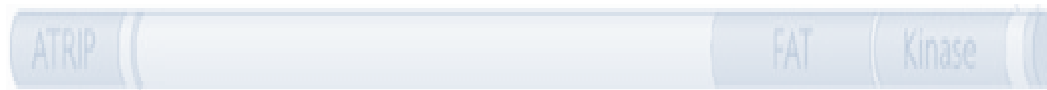


# Probing kinase action and inhibition *in vivo*

Marcus Smolka  
Cornell University

*Fapesp - 2016*



# ATR

(ATM- and Rad3-related)



## Phosphoinositide 3-kinase-related protein kinases (PI3KKs)



from Rivera-Calzada et al. AIMS Biophysics, 2015, 2(2)

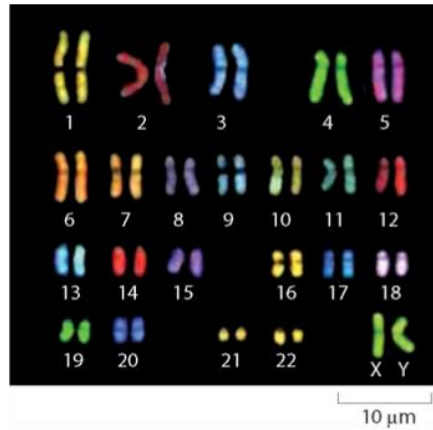
# ATR

(ATM- and Rad3-related)



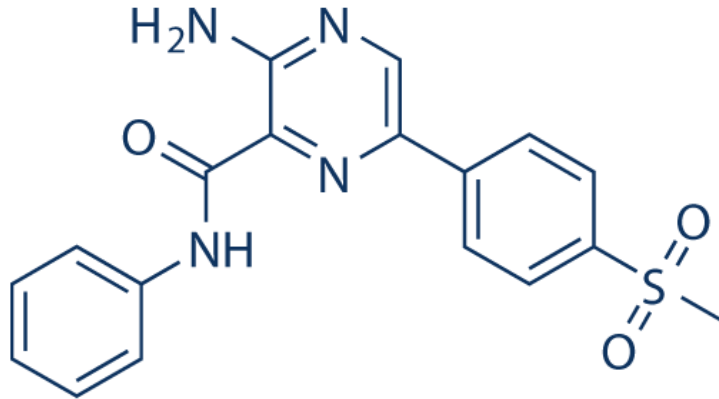
*"Cancer barrier"*

Genomic integrity



# ATR

(ATM- and Rad3-related)



ATP-competitive inhibitor

Vertex Pharmaceuticals

Charrier et al., 2011

## VE-821

Ki: 13nm

Ki (ATM): ~6µm

Ki (DNA-PK): ~3µm

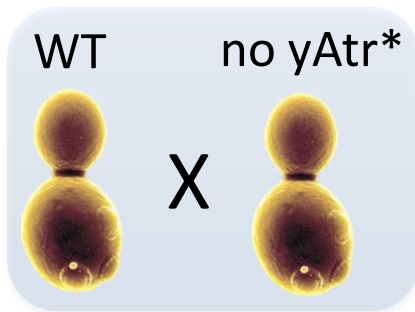
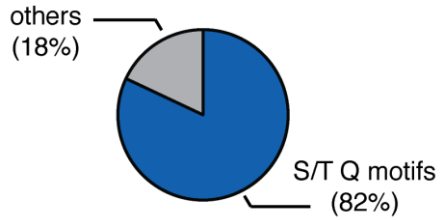
VE-822 and AZD6738 in phase I clinical trials for treatment of pancreatic and lung cancer

**NCT02487095:** Trial of Topotecan With VX-970, an ATR Kinase Inhibitor, in Small Cell Lung Cancer

**NCT02223923:** Phase I Study to Assess Safety of AZD6738 Alone and in Combination With Radiotherapy in Patients With Solid Tumours (Patriot)

# ATR action in yeast

yAtr-dependent  
yChk1-independent  
(117)

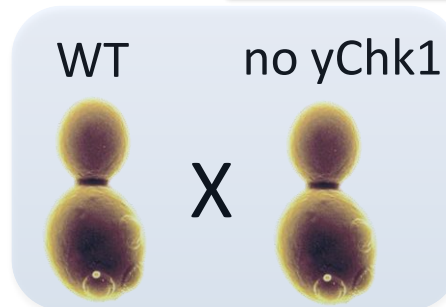
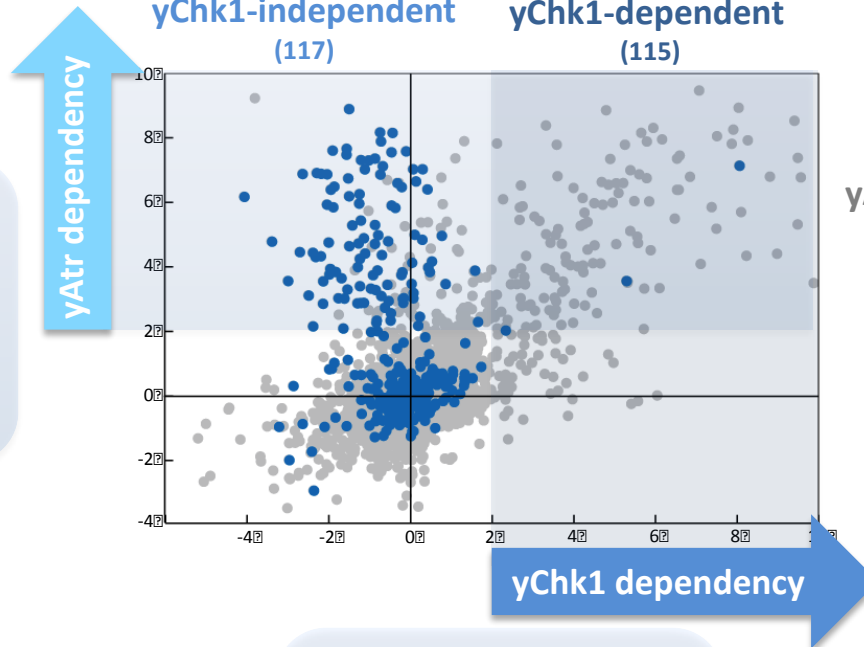


● S/T-Q motifs

Direct yAtr targets?

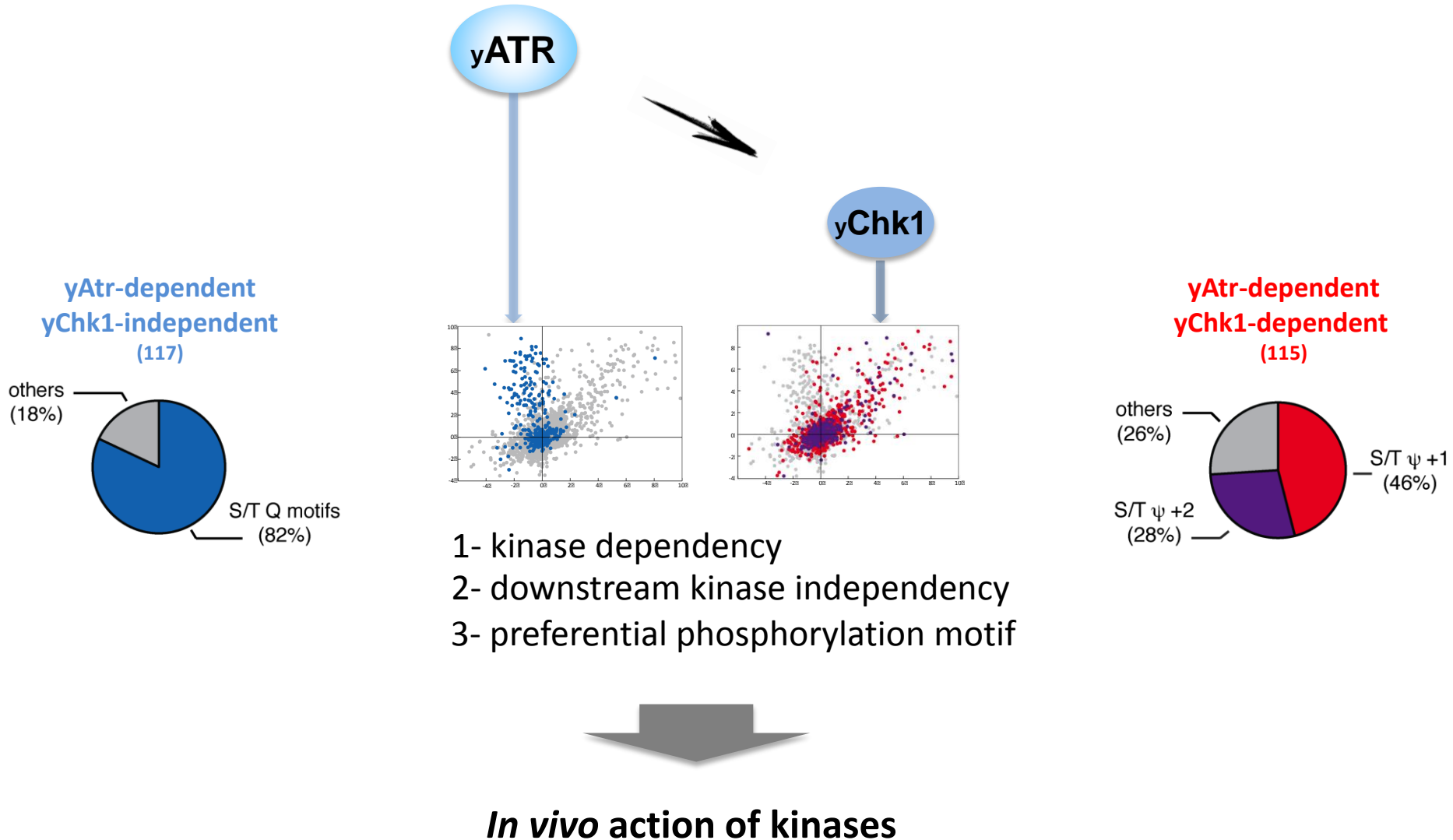
yChk1-independent  
(117)

yChk1-dependent  
(115)

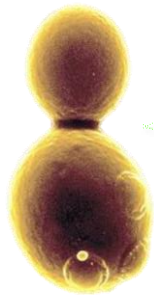
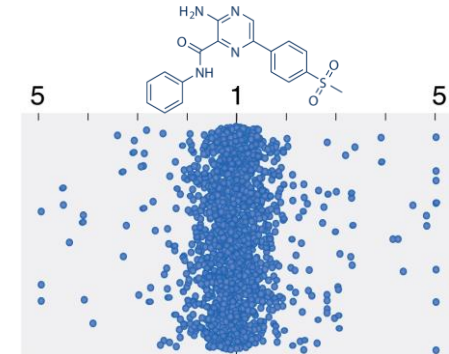
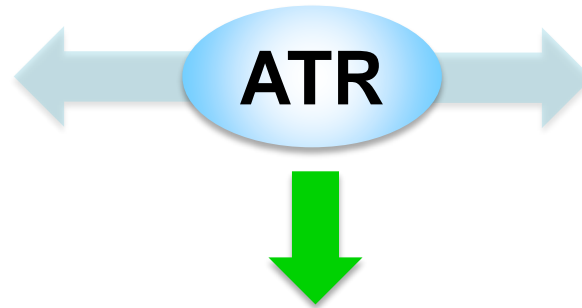
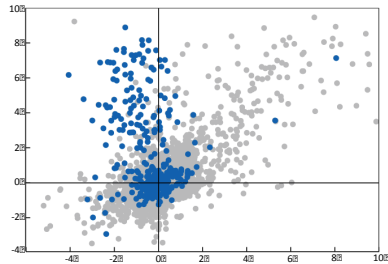


\*yAtm also deleted

# Mapping the ATR signaling network in yeast



# Identifying **functional** ATR targets



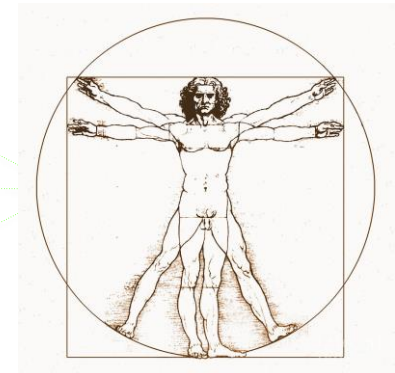
**Slx4**

Orthologs

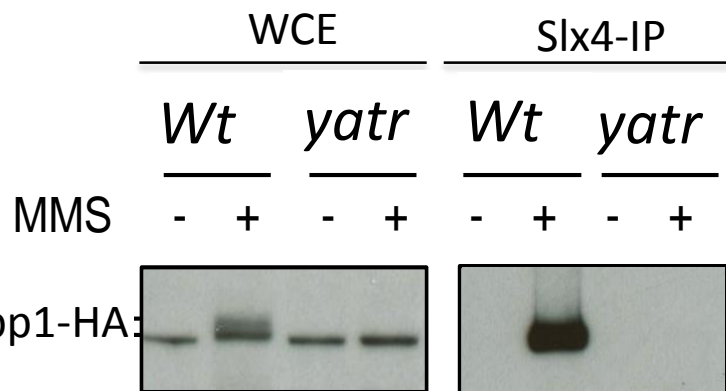
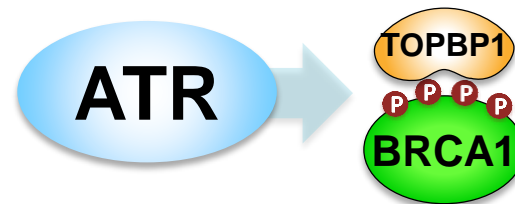
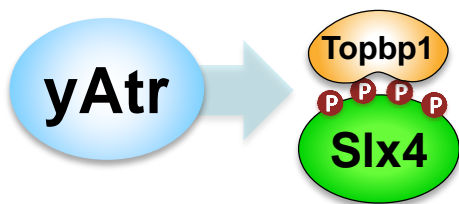
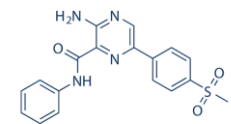
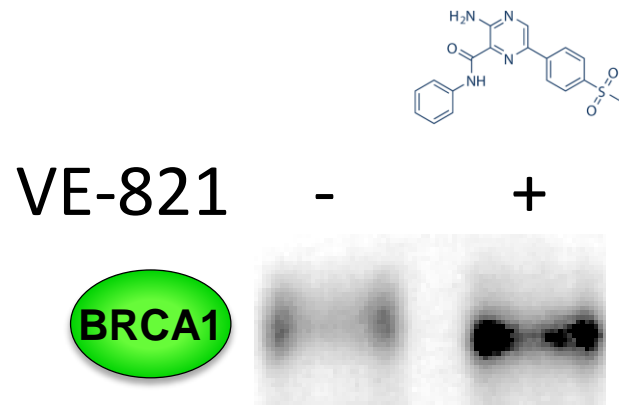
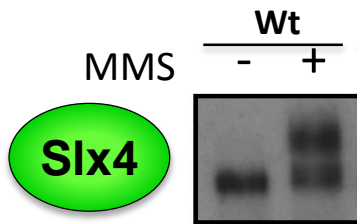
Functional  
analogs

Protein  
interactions

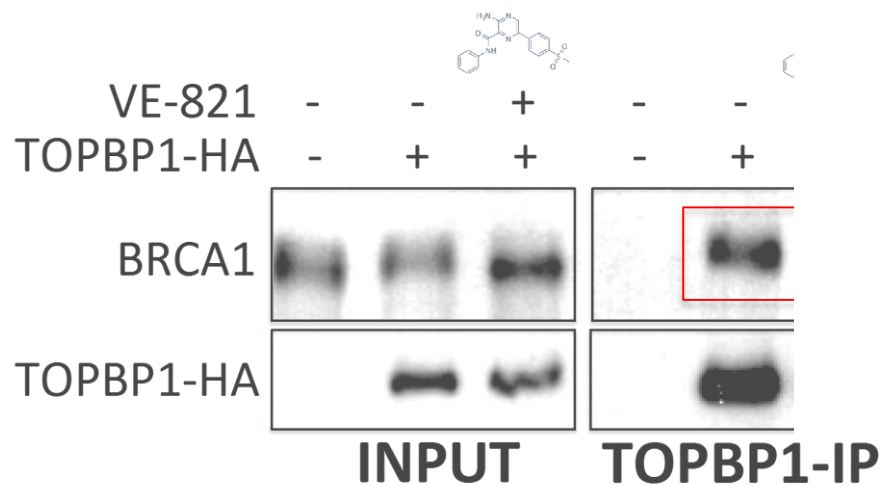
Stoichiometry



**BRCA1**



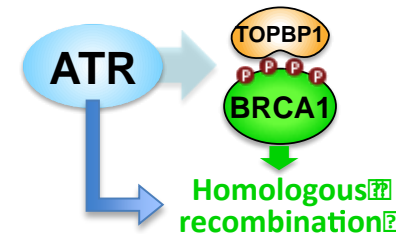
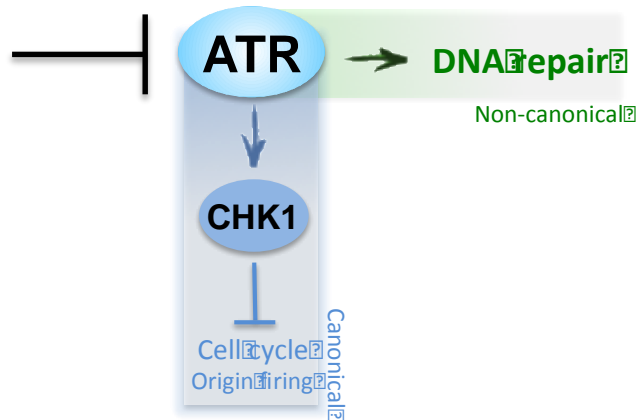
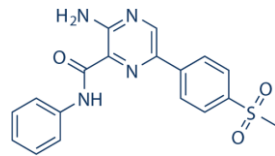
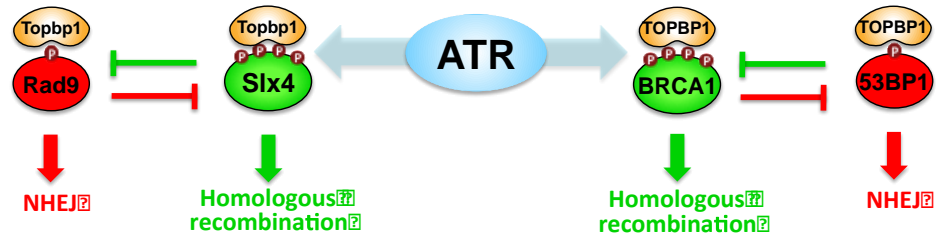
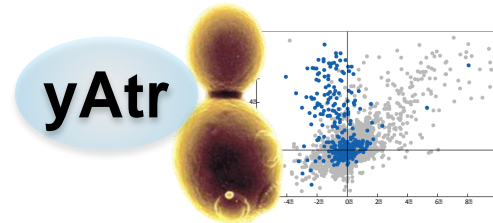
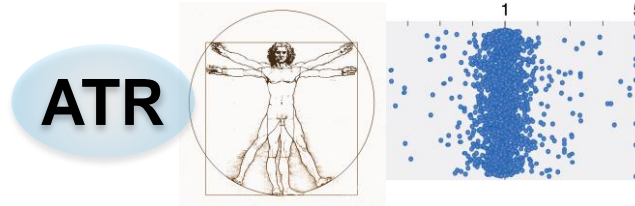
Ohouo et al. Mol. Cell



Liu & Cussiol. Unpublished



# Summary



# Acknowledgments

## Smolka Lab

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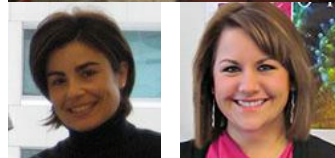
Susannah Oberly

Beatriz Almeida

Jenna

Austin

Kyle Page



### Collaborations:

Haiyuan Yu – Cornell

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**Dr. Francisco  
Oliveira**



**Dr. Patrice  
Ohouo**



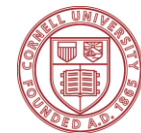
**NIH**

NIGMS P01GM097272



**ACS**

RSG DMC-121517



Cornell University

**VERGE Seed Grant**