

Regulation of MYST HAT Activity by Autoacetylation

Hua Yuan

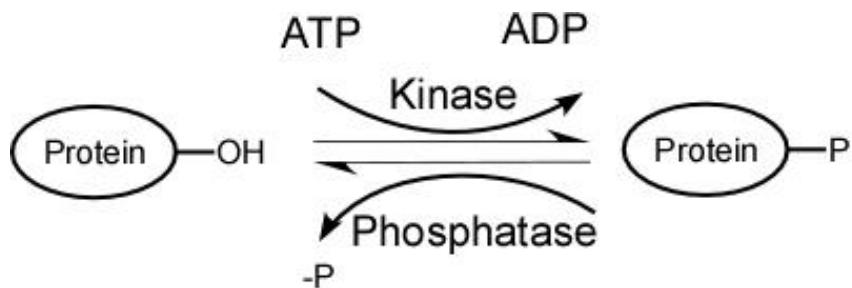
Marmorstein Lab

The Wistar Institute

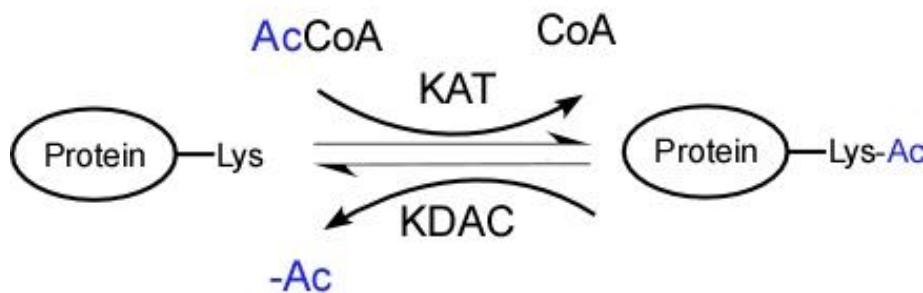
X6A SAC, Feb 10, 2012



Phosphorylation vs. Acetylation

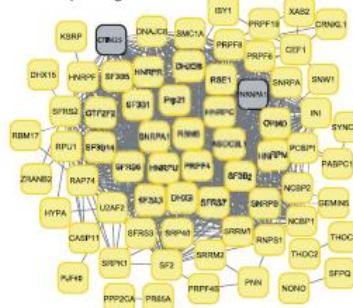


Diverse substrates
Drug targets
Regulatory domains
Auto regulation

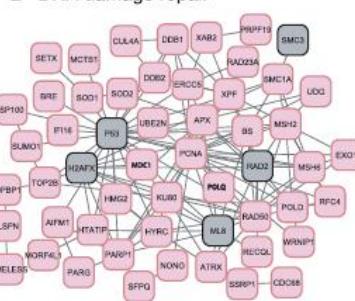


Acetylome

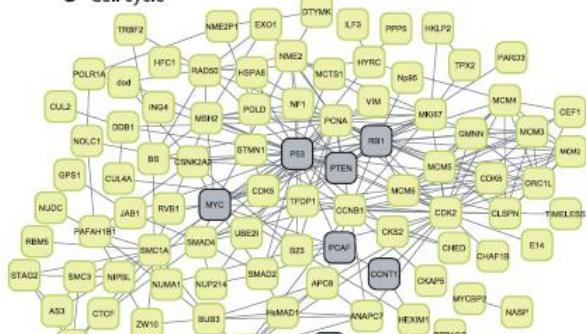
A RNA Splicing



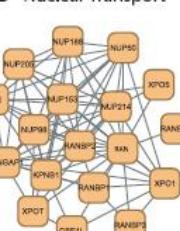
B DNA damage repair



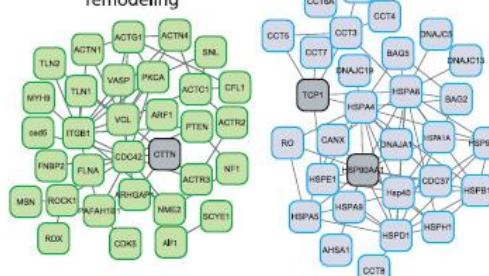
C Cell cycle



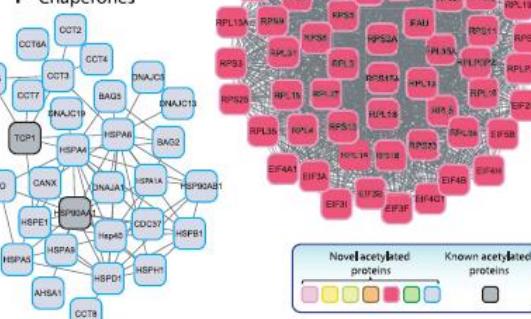
D Nuclear Transport



E Actin cytoskeleton remodeling



F Chaperones

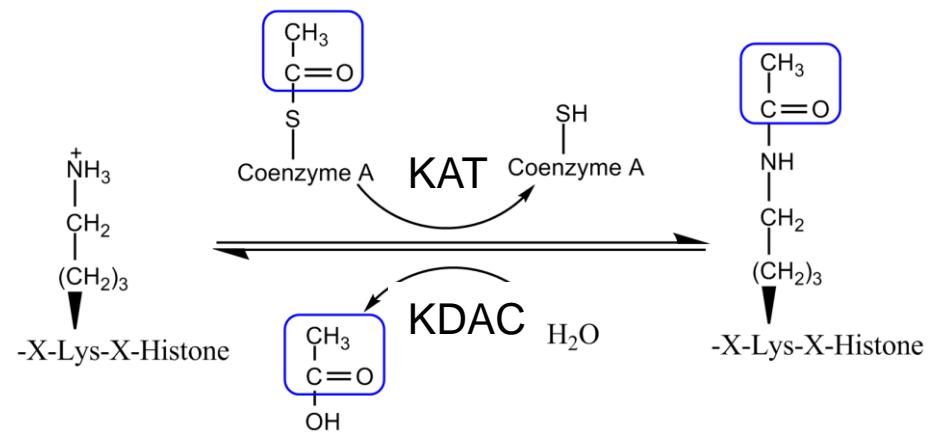
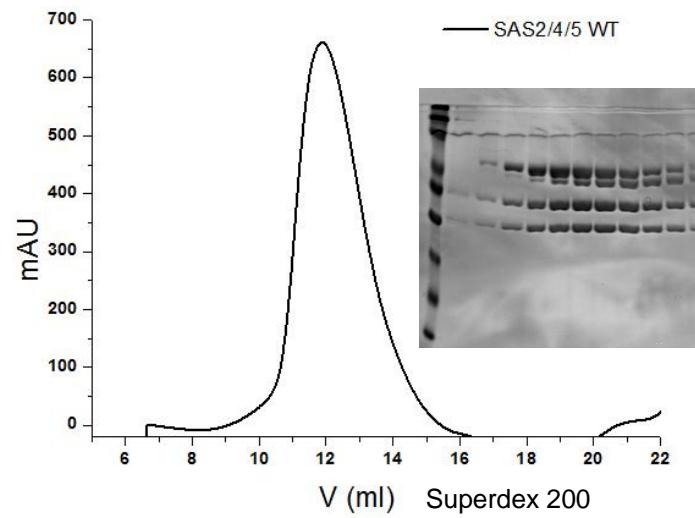
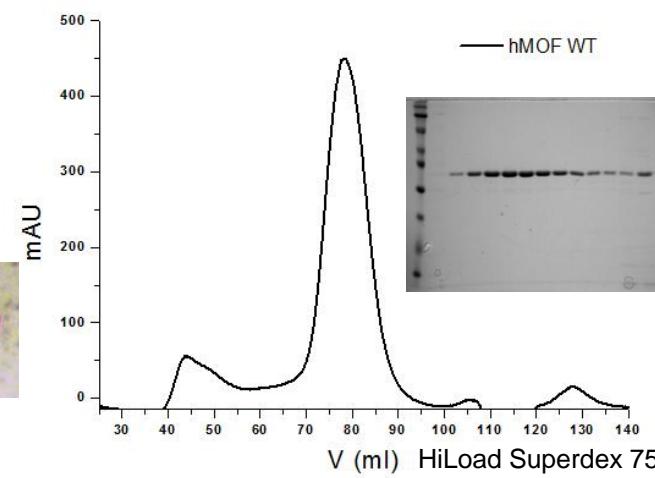
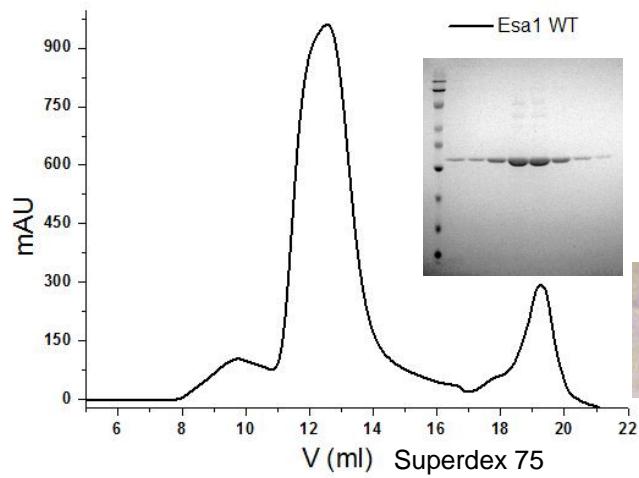


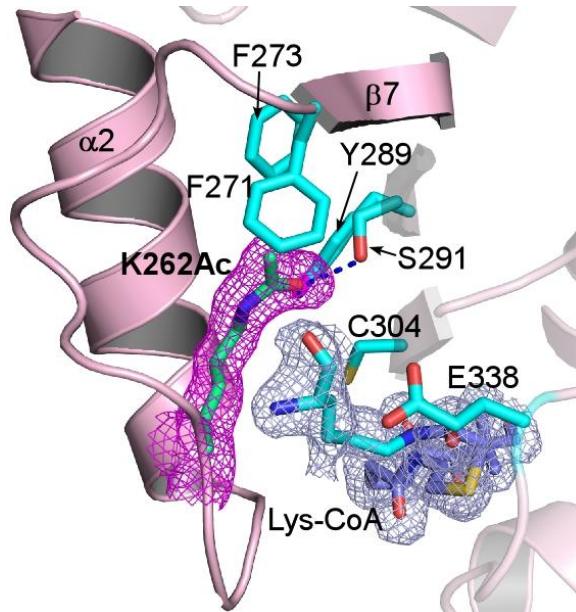
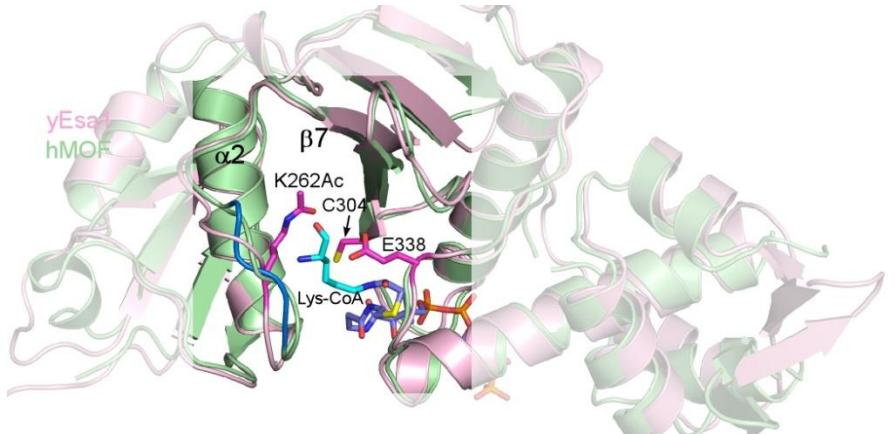
Choudhary, C., C. Kumar, et al. (2009). *Science* **325**(5942): 834-840.

MYST (MOZ/MOF, Ybf2/Sas3, Sas2 and Tip60)

Table 2 MYST acetyltransferases in major model organisms

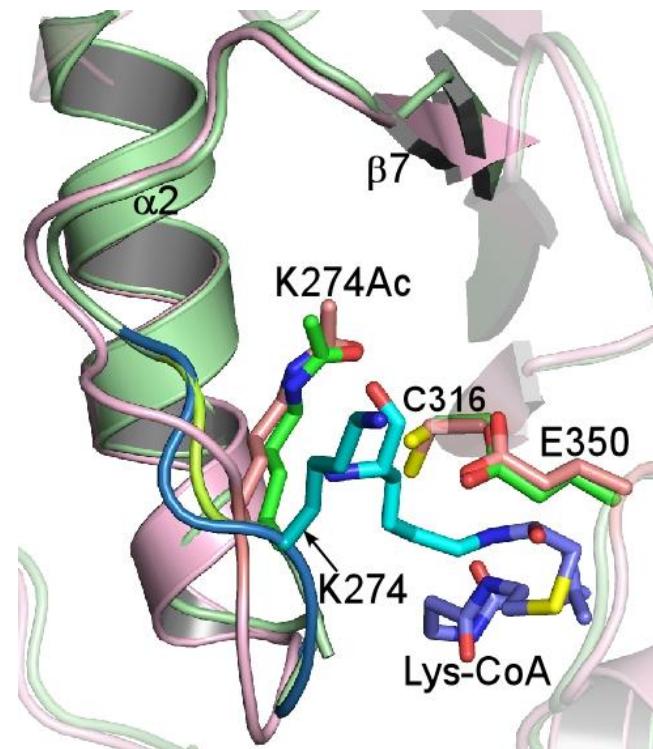
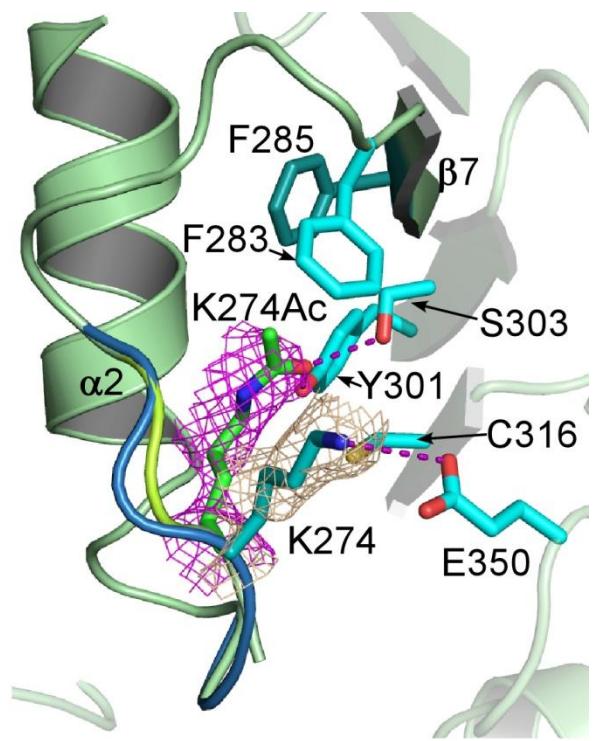
MYST proteins	KAT5	KAT6	KAT7	KAT8
<i>S. cerevisiae</i>	Esal	Sas3		Sas2
<i>S. pombe</i>	Mst1	Mst2		
<i>C. elegans</i>	mys-1	mys-3 mys-4		mys-2
<i>D. melanogaster</i>	dTIP60	ENOK CG1894	CHM	MOF
<i>M. musculus</i>	TIP60	KAT6A/MOZ/MYST3 KAT6B/Qkf/MORF/ MYST4	HBO1/MYST2	MOF/MYST1
<i>H. sapiens</i>	TIP60/PLIP	KAT6A/MOZ/MYST3 KAT6B/MORF/MYST4	HBO1/MYST2	MOF/MYST1
Associated domains	Chromodomain	PHD fingers	Zn finger	Chromodomain
Histone specificity	H4/H2A	H3	H4 > H3	H4K16
Roles	Gene regulation, DNA damage repair/response, development/stem cell renewal, essential for cell viability	Gene regulation, development/stem cell renewal	Gene regulation, DNA replication, chromatin boundary, development	Gene regulation, DNA damage response, dosage compensation, chromatin boundary, early development



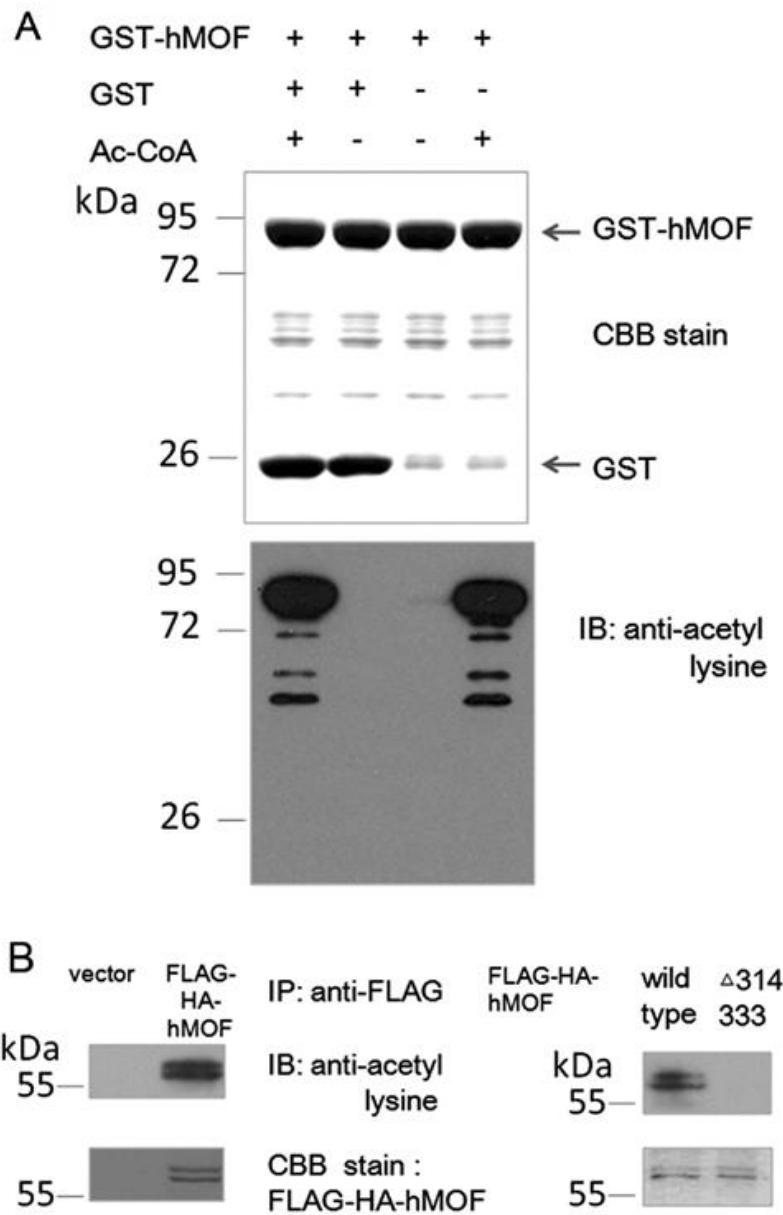
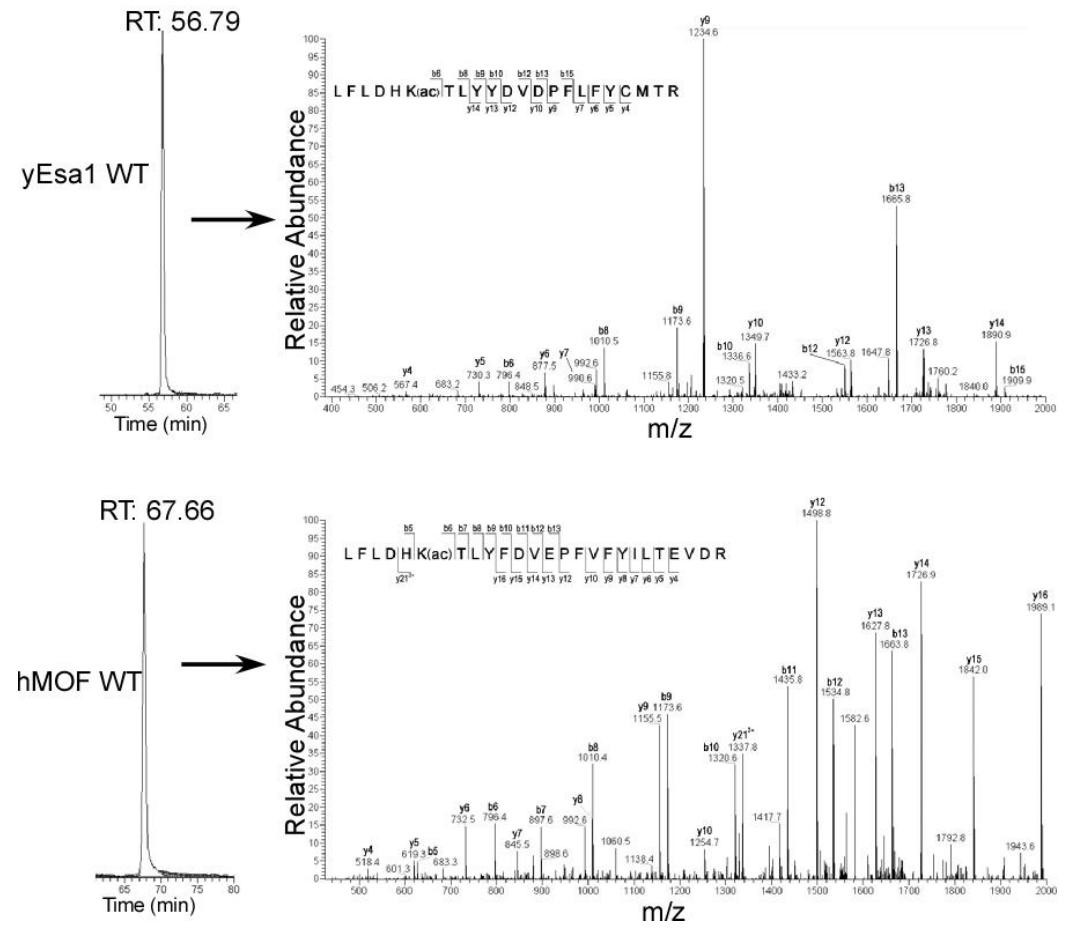


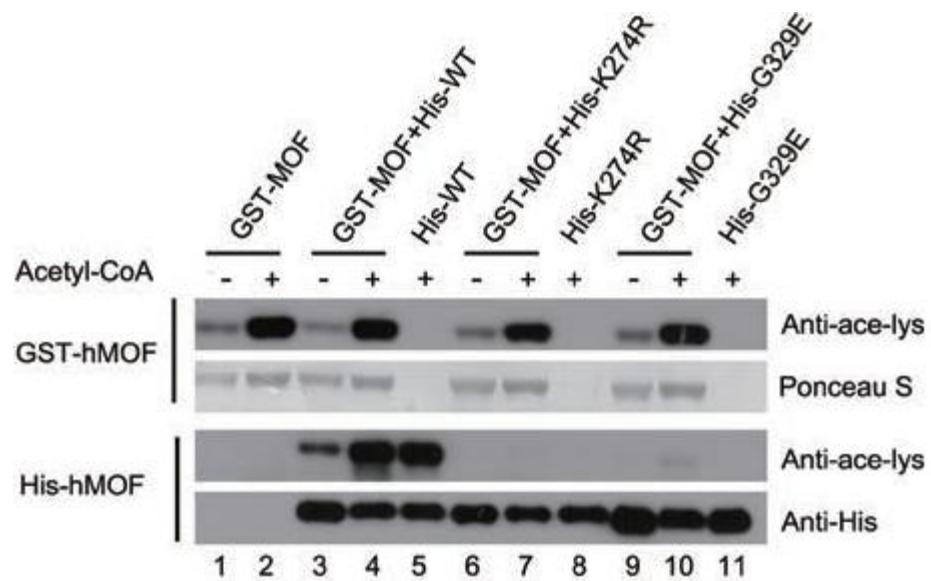
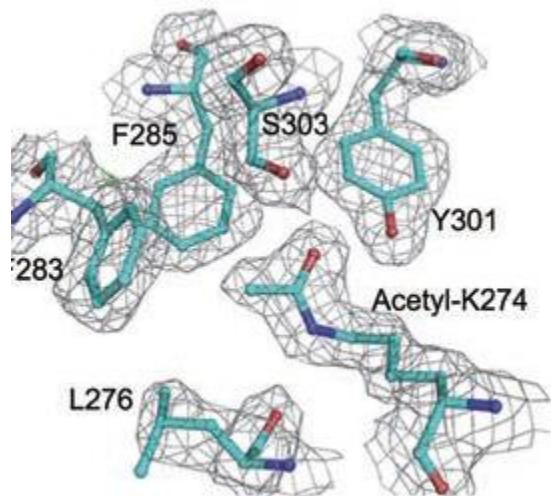
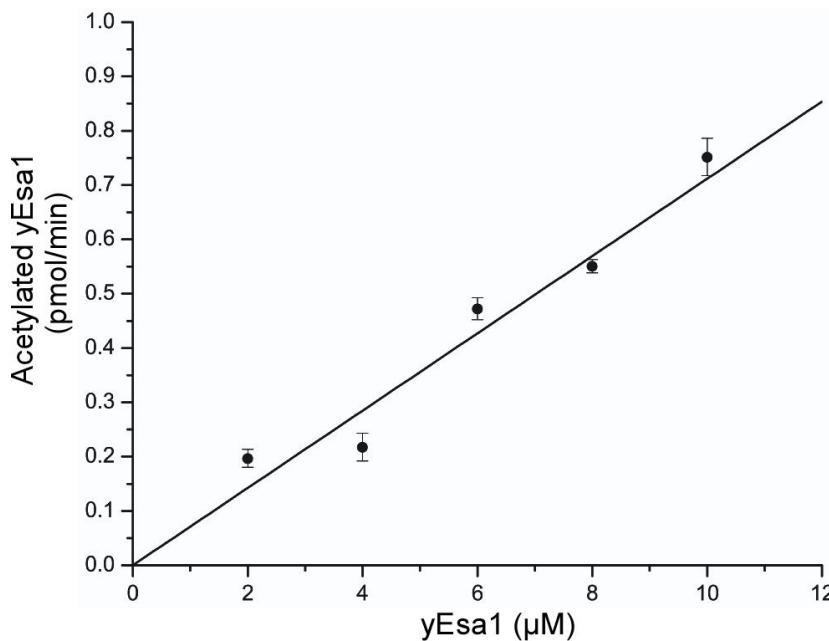
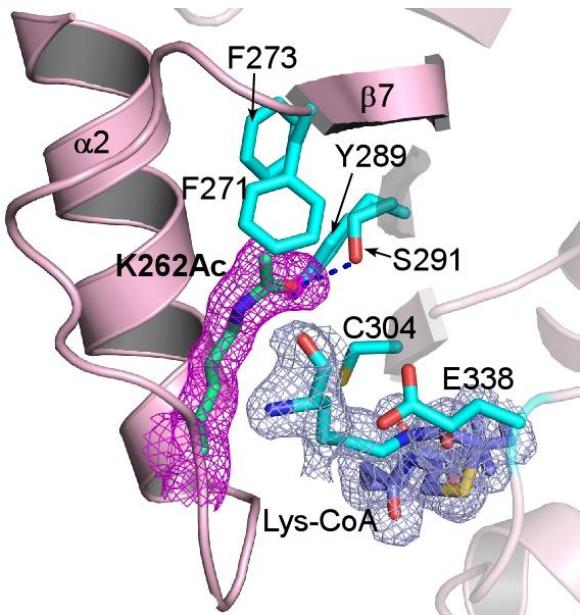
Sequence alignment of the yEsa1-hMOF interaction interface across various proteins. The alignment highlights conserved residues in red and blue boxes. Secondary structure elements are indicated above the sequence: α2 (wavy line), β7 (black arrow), β8 (black arrow), β9 (black arrow), β10 (black arrow), and η2 (wavy line). Residues 250, 260, 270, 280, 290, 300, and 310 are marked along the sequence.

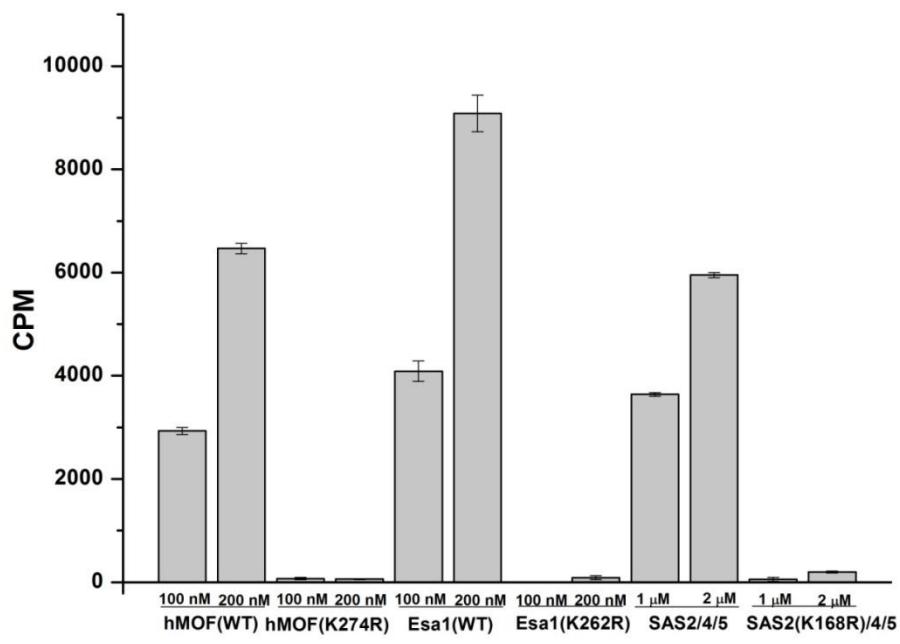
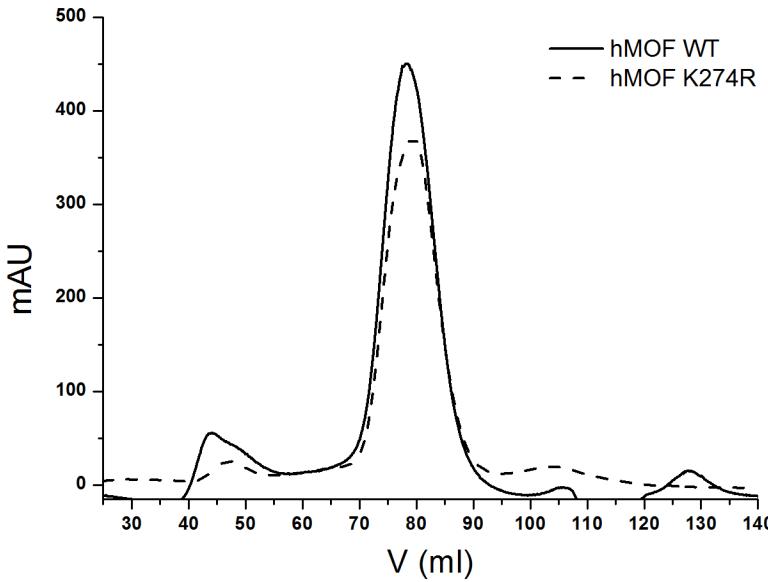
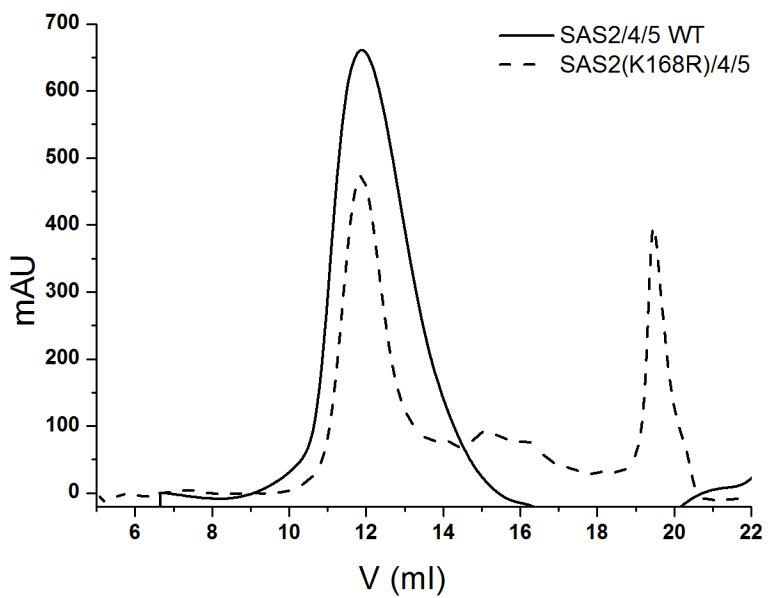
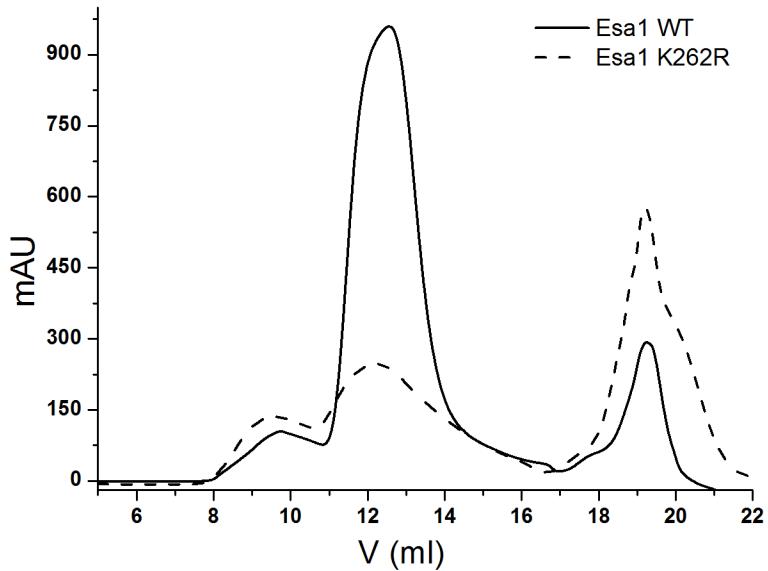
	α2	β7	β8	β9	β10	η2			
250	W C R N	L C L I S K L	F I D H K T I Y Y D V D P	F L F Y C M T R	R D E L G H (0) H I	V G Y F S K E K	E S A D G Y N V A C I L T L P Q Y Q R R M G	316	
yEsa1	247	L C L I S K L	F I D H K T I Y Y D V D P	F L F Y C M T R	R D E L G H (0) H I	V G Y F S K E K	E S A D G Y N V A C I L T L P Q Y Q R R M G	316	
hMOF/MYST1	259	Y C Q N	L C L I L A K L	F I D H K T I Y F D V E P	F V F Y I L T E	E V D R Q G A (0) H I	V G Y F S K E K	E S P D G N N V A C I L T L P P Y Q R R G	328
ySas2	153	F C Q C	L C L I F T K L	Y Y L D N K S M Y	F K V D H Y E F Y I	V Y E T G S T K P (0) .	M G F F S K D L	V S Y Q Q N N L A C I L I F P P Y Q R R G	220
dMOF	590	Y C Q L	L C L I M A K L	F I D H K V I Y F D M D P	F L F Y I L C E	T D K E G S (0) H I	V G Y F S K E K	K S L E N Y N V A C I L V L P P H Q R R K G	659
hMOZ/MYST3	589	Y C Q N	L C L I L A K L	F I D H K T I Y Y D V E P	F L F Y V V L T Q	N D V K G C (0) H I	V G Y F S K E K	H C Q Q K Y N V S C I M I L P Q Y Q R K G	658
hHBO1/MYST2	417	Y C Q N	L C L I L A K L	F I D H K T I Y Y D V E P	F L F Y V M T E	A D N T G C (0) H I	I G Y F S K E K	N S F L N Y N V S C I L T M P Q Y M R Q G	486
hTIP60/PLIP	312	Y S Q N	L C L I L A K C	F I D H K T I Y Y D T D P	F L F Y V M T E	Y D C K G F (0) H I	V G Y F S K E K	E S T E D Y N V A C I L T L P P Y Q R R G	381
ySas3	352	Y C Q N	L C L I L A K C	F I N S K T I Y Y D V E P	F I F Y I L T E	R E D T E N (9) H F	V G Y F S K E K	F N S N D Y N L S C I L T L P I Y Q R K G	430

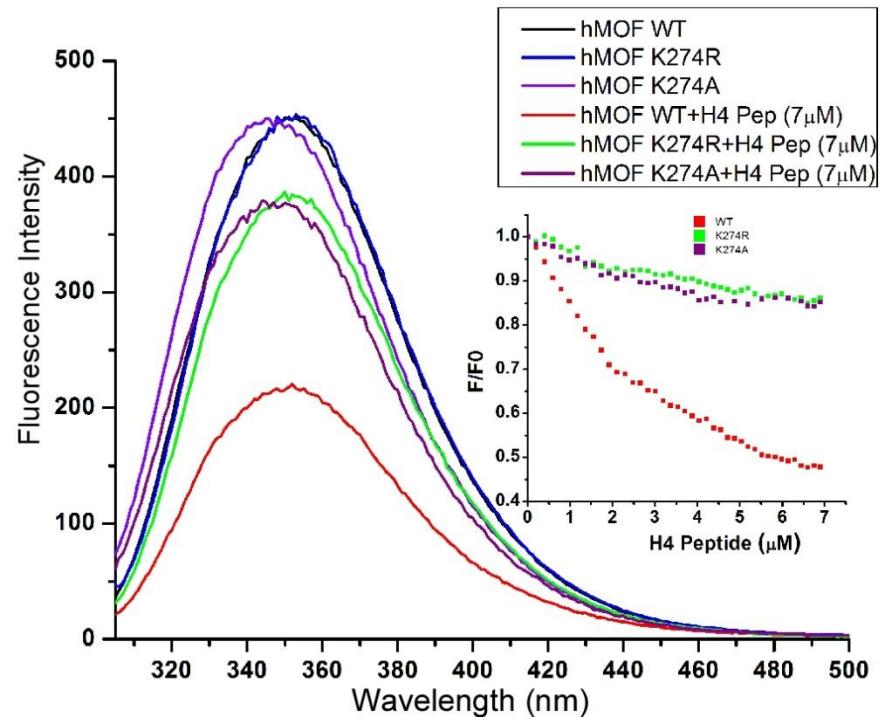
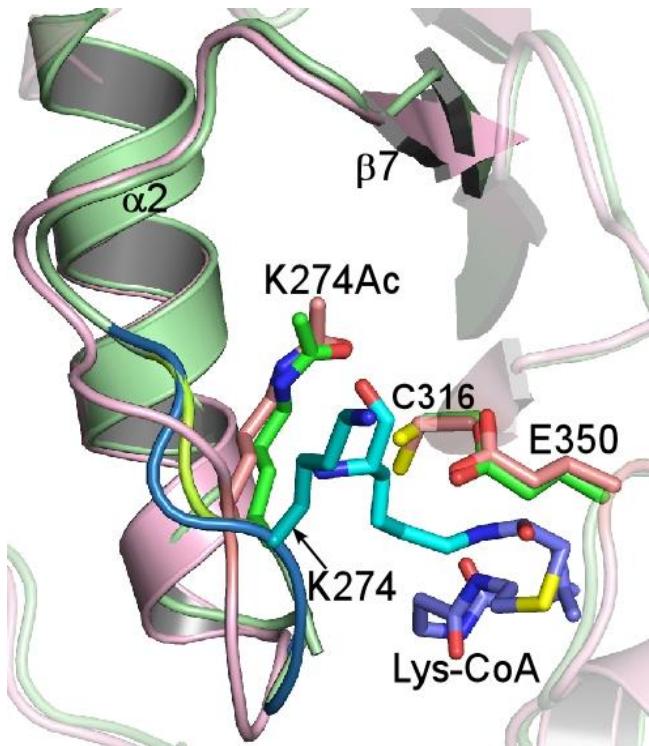


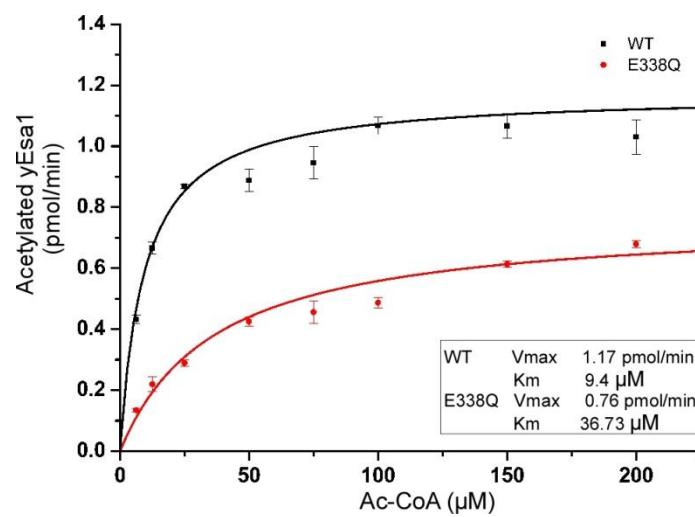
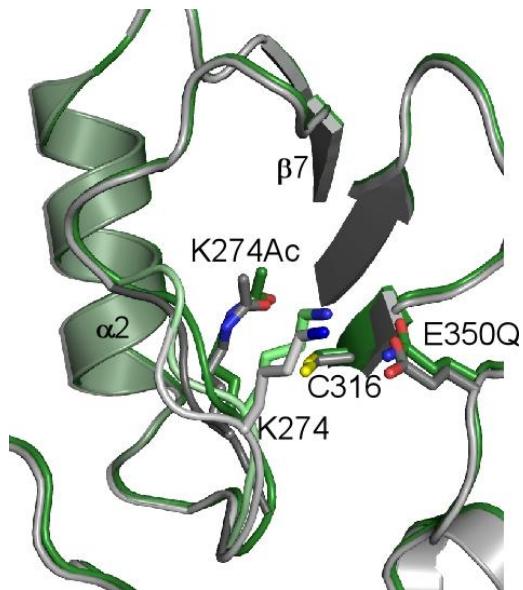
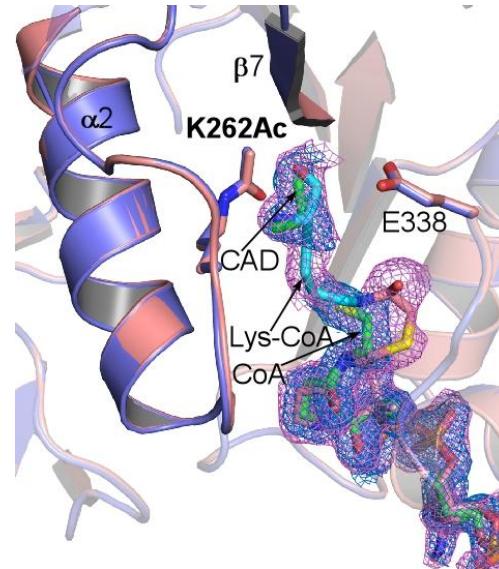
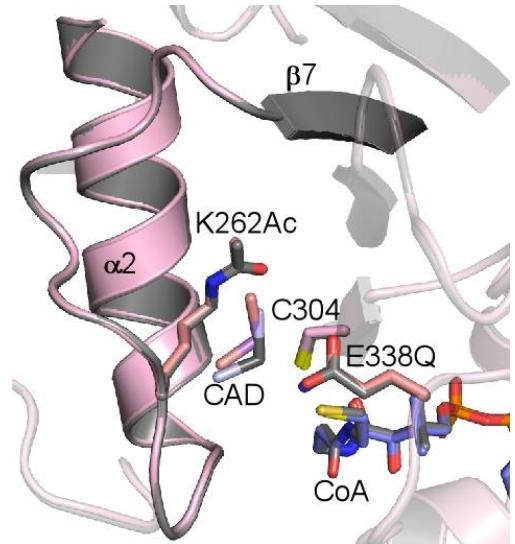
- Is the autoacetylation real?
 - Autoacetylation?
 - *In vitro* and *In vivo*?
 - Intermolecular vs. Intramolecular

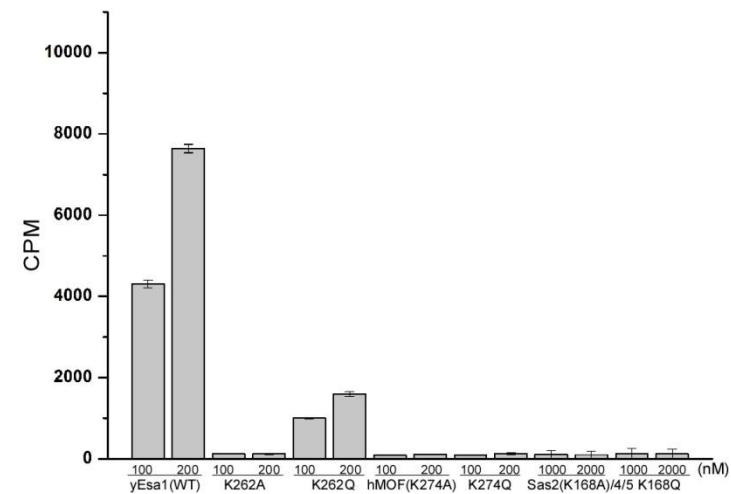
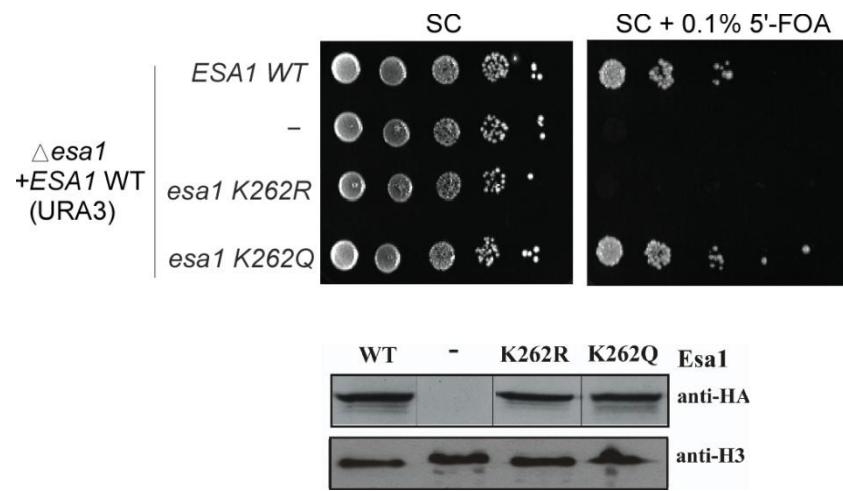


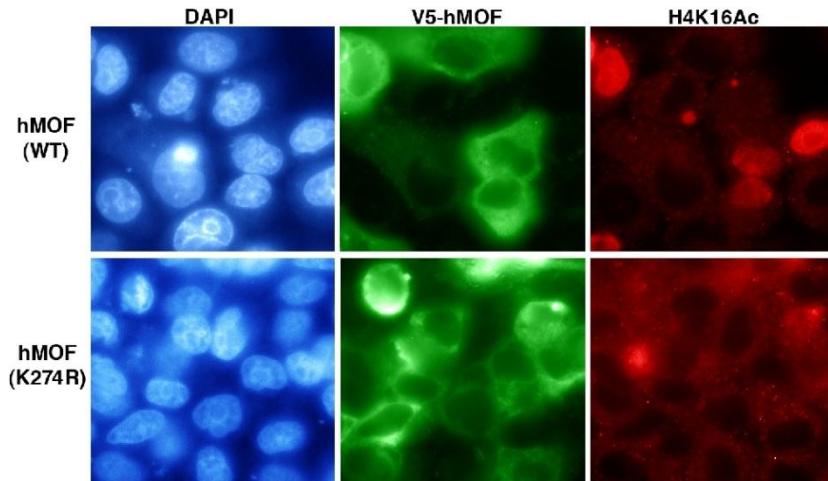
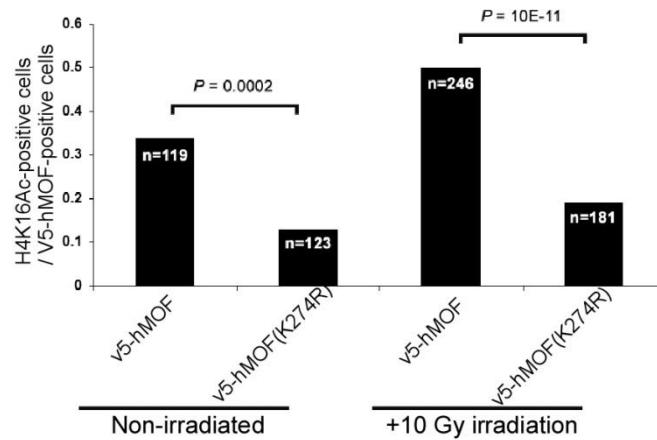
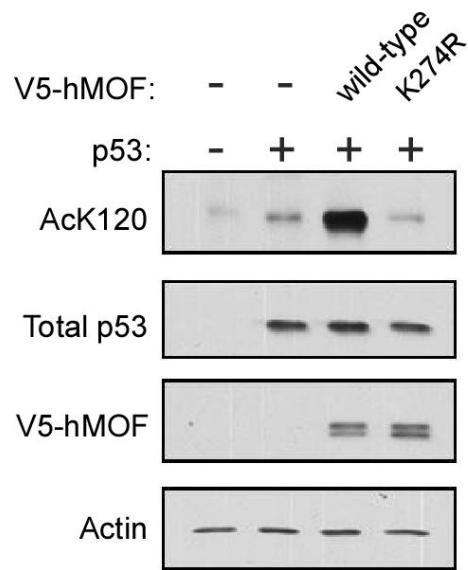


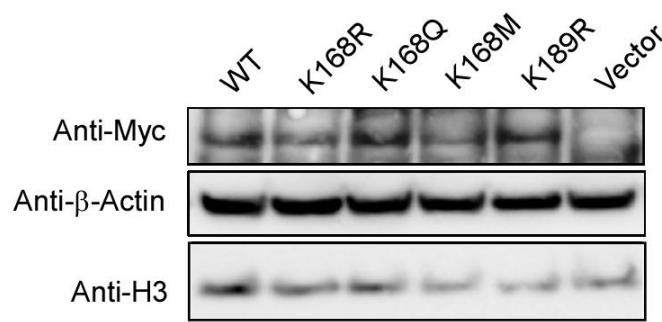
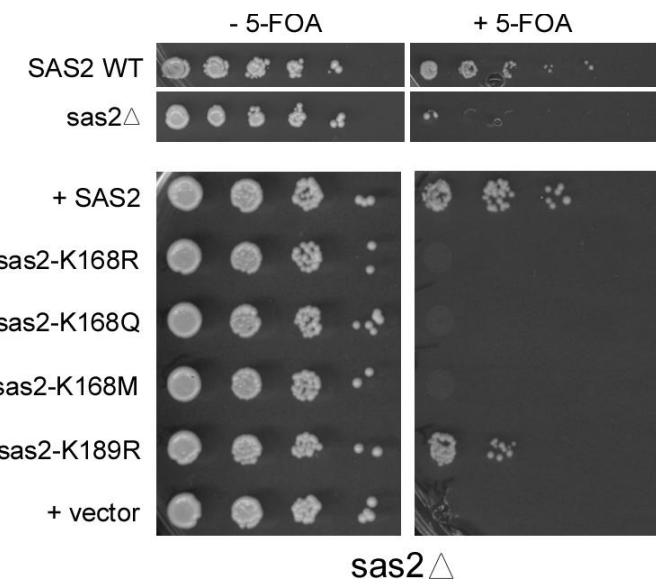


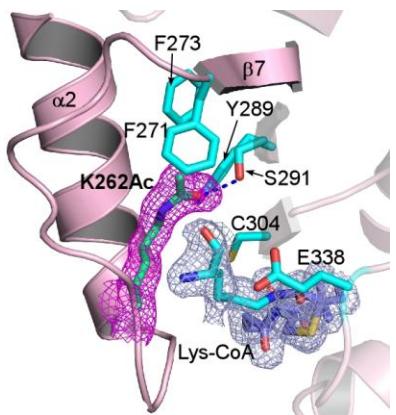






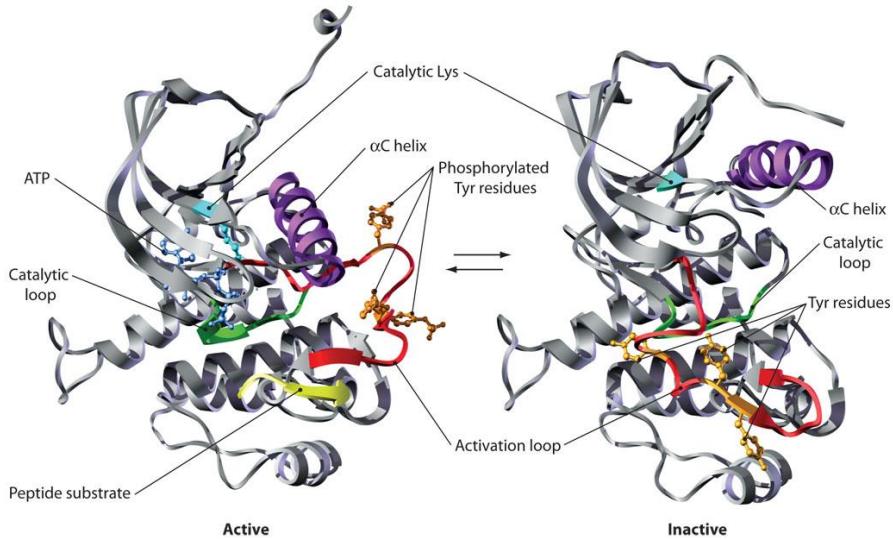
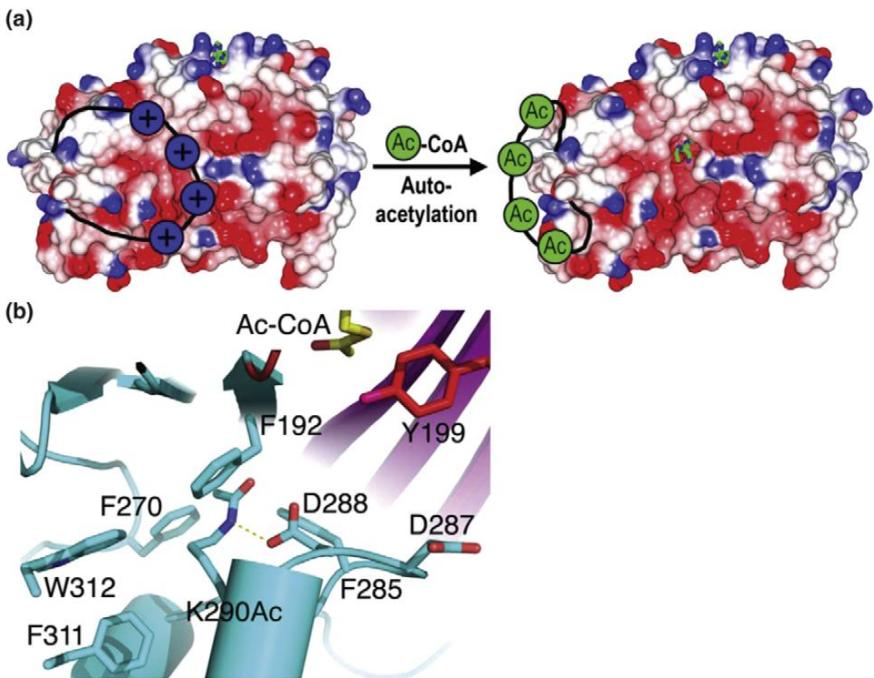






Autoacetylation

- Intramolecularly
- Both *in vitro* and *in vivo*
- Critical for the activity and its function
- Facilitates substrate binding



Acknowledgement

Dr. Ronen Marmorstein
– Emily C. Ding
Dr. Shelley Berger
Dr. Jacques Cote
Dr. David Speicher
Dr. Brad Johnson
Dr. Steve McMahon
Dr. Rolf Stern glanz
Dr. Alain Verreault
Dr. Pierre Thibault
Dr. George Zheng