



北京大學

PEKING UNIVERSITY

ADP/ATP 转位酶ANT1的序列与结构分析

Sequence and Structure Analysis of ADP/ATP Translocase 1 (ANT1)

G08 & G20

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Jiangle Liu 刘江乐

2020.1.4

Outline

1

Background

2

Sequence Alignment

3

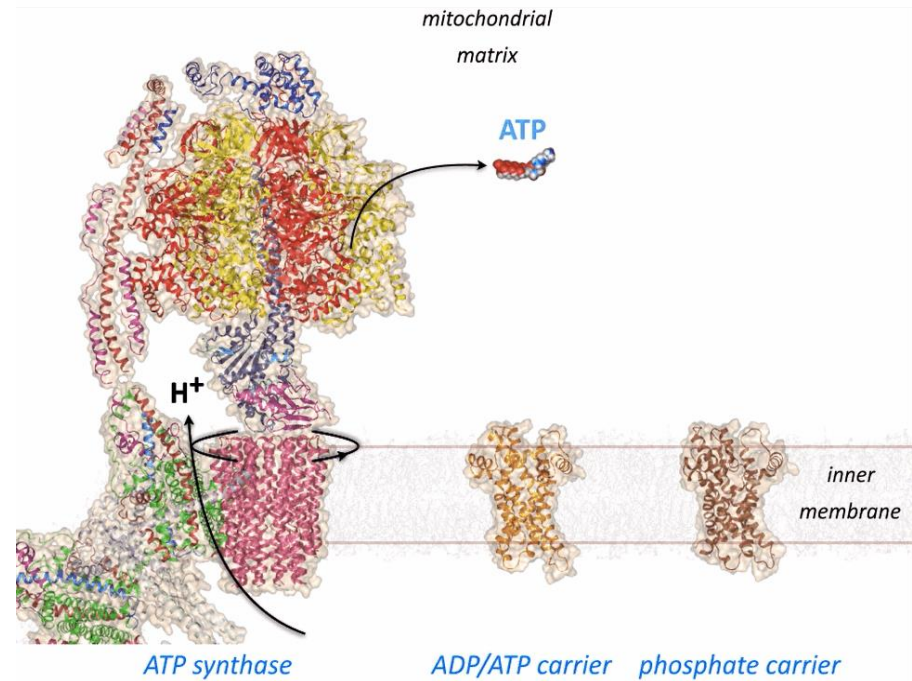
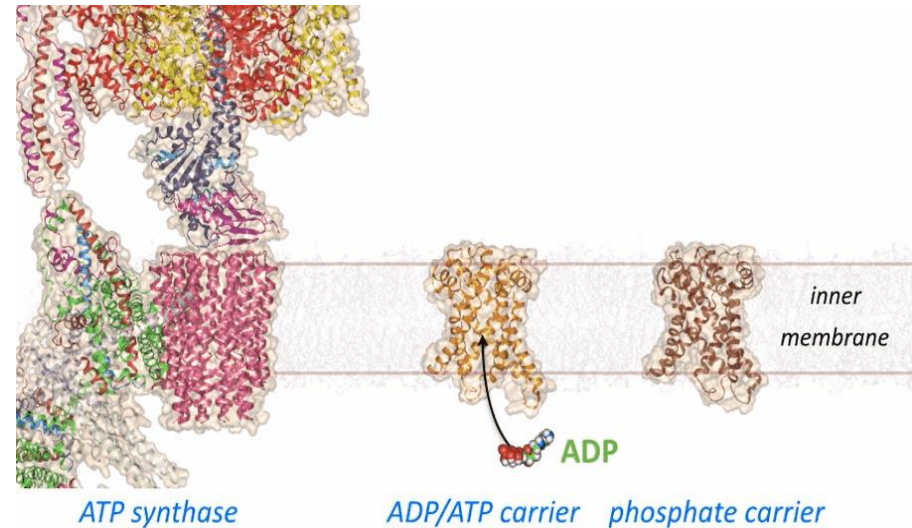
Phylogenetic Tree

4

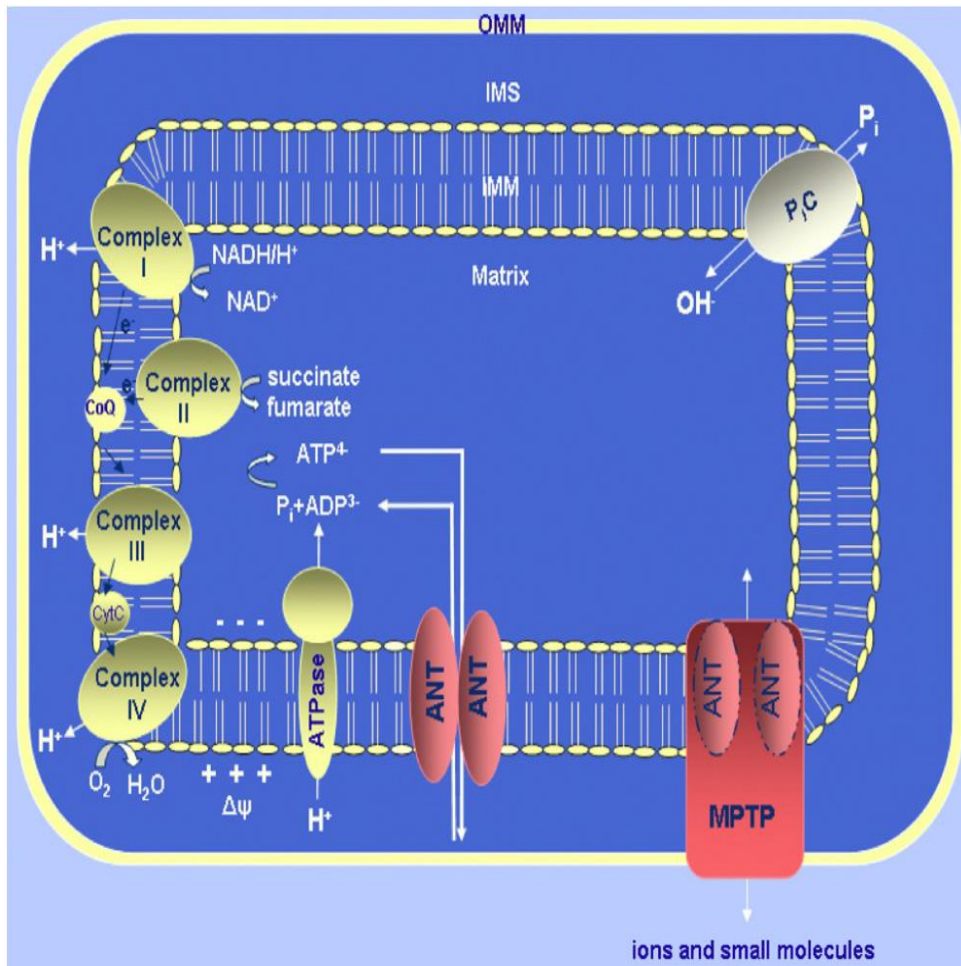
Structure Analysis

1.1 Introduction of ANT: **ADP/ATP carrier**

- **1955年**提出ADP/ATP载体的假说.
- **1964年**苍术昔对大鼠肝脏线粒体氧化磷酸化和ADP结合位点的抑制作用被发现.
- **1982年**测定了牛的cDNA序列,
1989年测定了人的cDNA序列.
- **胞质开放状态和基质开放状态。**
- 占线粒体内膜蛋白的**10%**.
- 自然突变体功能丧失可导致进行性眼外麻痹和心肌病.



1.2 Function of ANT



ANT1的主要功能包括介导线粒体ATP/ADP的转运，介导解偶联和质子泵。作为线粒体转运体家族的一员，ANT1可以介导线粒体内合成的ATP转出至胞浆和胞浆内ADP转入线粒体，这种ATP/ADP的交换是ATP合成过程的重要保证。

此外，ANT1还与位于线粒体外膜的电压依赖性离子通道(VDAC)和亲环蛋白D(CyP—D)等构成线粒体膜通透性转换孔(MPTP)复合体。

1.3 ANT related human diseases

TABLE 1: Ant-associated human diseases.

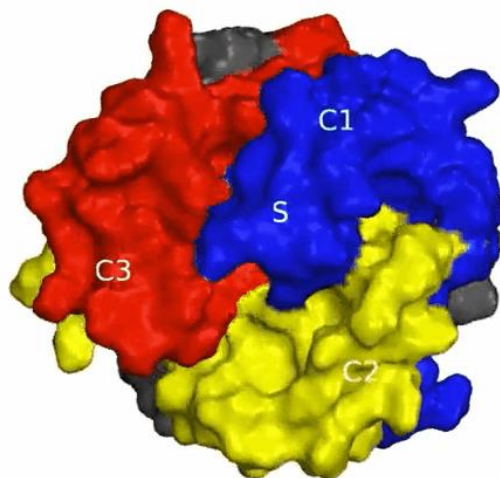
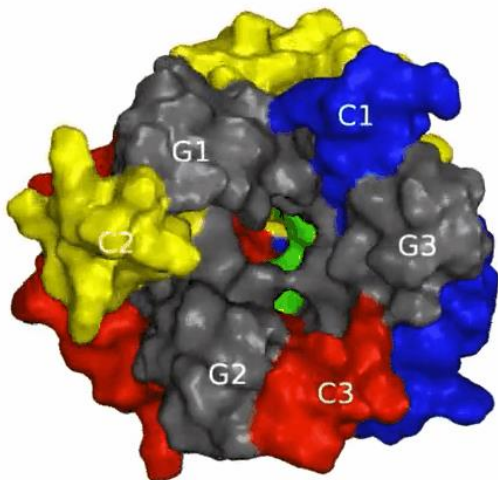
Disease	Mutation	Pathogenic Mechanism	Characteristics	
adPEO	<i>ant1</i> ^{A90D} , <i>ant1</i> ^{L98P} , <i>ant1</i> ^{D104G} , <i>ant1</i> ^{A114P} , <i>ant1</i> ^{V289M}	Membrane stress; altered transport properties	Adult/late-onset, mitochondrial myopathy; muscle weakness (especially in the eyes); sensory ataxia; mtDNA deletions	线粒体肌病 感觉共济失调
Cancer	Overexpression of Ant2	Reversed ADP/ATP exchange by Ant2	The adaption to intratumoral hypoxia of cancer cells	心肌病
FSHD	Deletions of subtelomeric repeats on chromosome IV	<i>DUX4</i> overexpression; possibly <i>ANT1</i> overexpression	Adult-onset disease, muscle weakness in face, shoulders, and hips, oxidative stress	心脏肥大
Mitochondrial myopathy and cardiomyopathy	<i>ANT1</i> null mutations <i>ant1</i> ^{A123D}	Defect in nucleotide transport Defect in nucleotide transport; other mechanisms?	Cardiomyopathy, myopathy, exercise intolerance, and lactic acidosis	白内障
Senger's syndrome	Mutation in AGK affecting Ant biogenesis leads to depletion of Ant1	Defect in nucleotide transport	Cardiac hypertrophy, mitochondrial myopathy, cataracts, lactic acidosis	乳酸性酸中毒

1.4 Recent Progresses on ANT Study

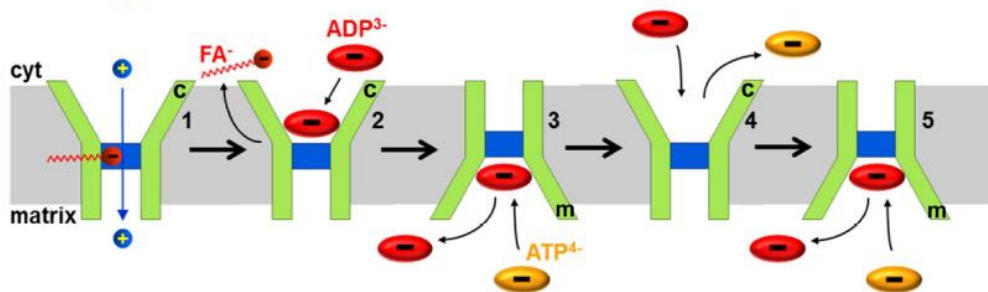
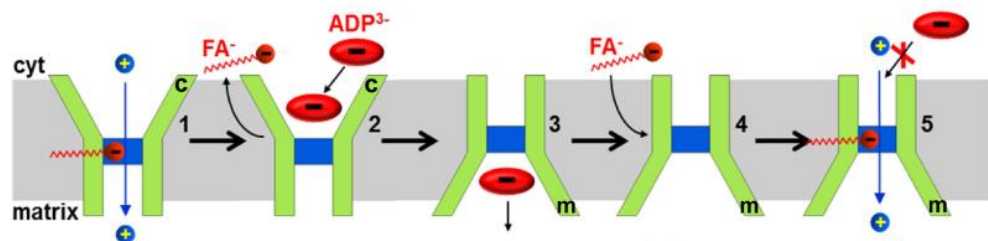
The dynamics of the mitochondrial ADP/ATP carrier

View from the outside

View from the matrix



Kunji *et al*, December 2018, *Cell*

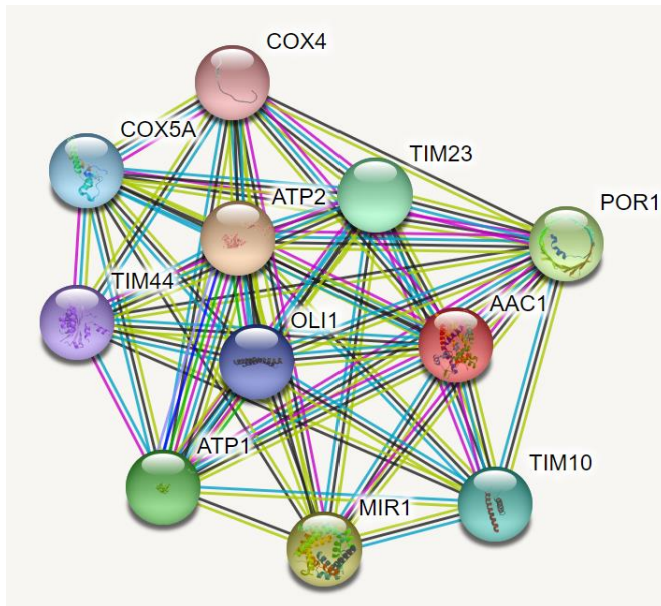
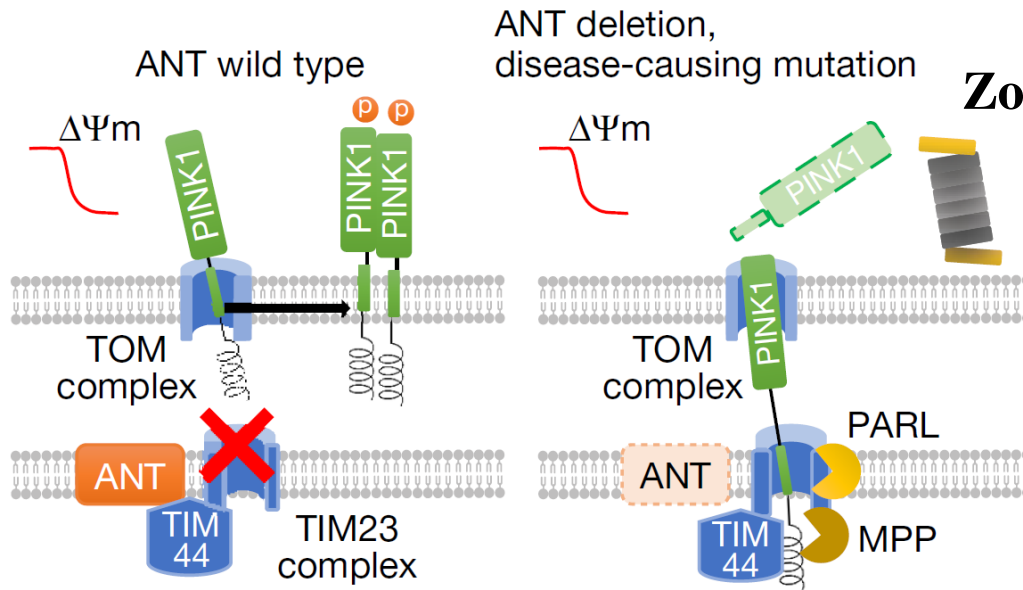


ANT具有H⁺转运功能

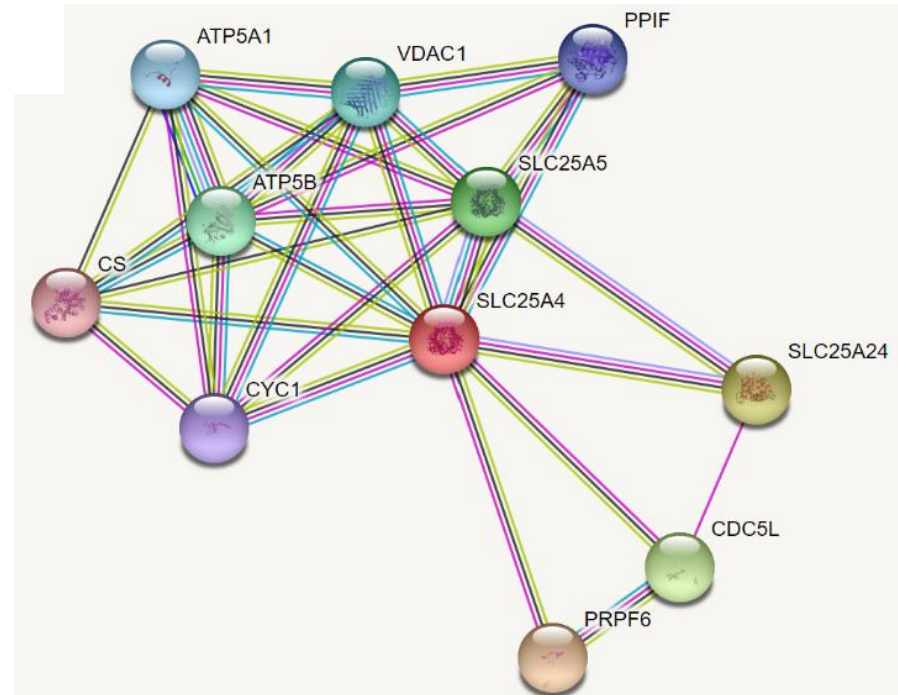
Yuriy Kirichok *et al*, July 2019, *Nature*

1.5 Protein-protein interaction

Zoltan Arany *et al*, October 2019, *Nature*



YEAST(ANT1)



HUMAN(SLC25A4)

2.2 Conservative amino acid analysis

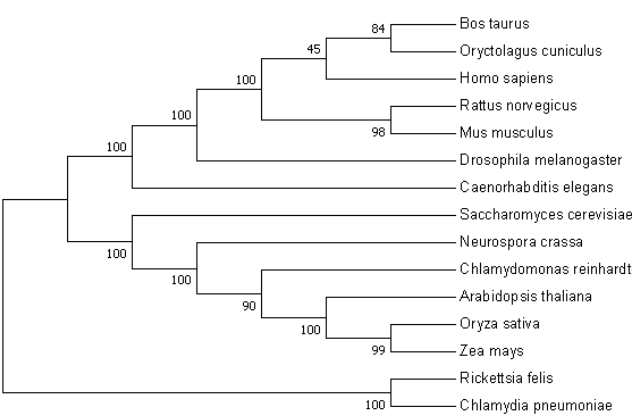
□ Sequence Alignment: Homo sapiens vs Bos taurus

Range 1: 1 to 298 [Graphics](#)

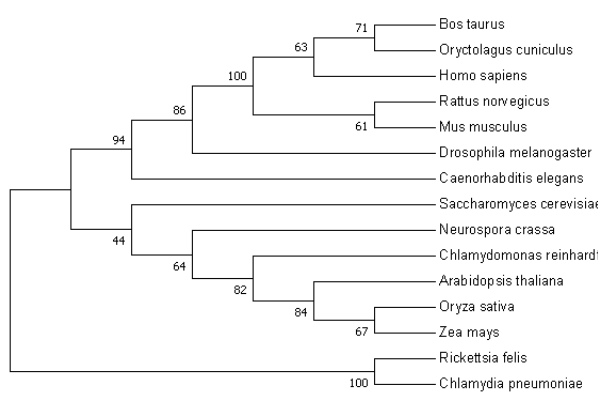
▼ [Next Match](#) ▲ [Prev](#)

Score	Expect	Method	Identities	Positives	Gaps
588 bits(1515)	0.0	Compositional matrix adjust.	286/298(96%)	291/298(97%)	0/298(0%)
Query 1		MSDQALSFLKDFLAGGVAAAISKTA			
Sbjct 1		MGDHAWSFLKDFLAGGVAAAVSKTA			
Query 61		IPKEQGFLSFWRGNLANVIRYFPTQ			
Sbjct 61		IPKEQGFLSFWRGNLANVIRYFPTQ			
Query 121		GAAGATSLCFVYPLDFARTRLAADV			
Sbjct 121		GAAGATSLCFVYPLDFARTRLAADV			
Query 181		VQGIIIYRAAYFGVYDTAKGMLPDP			
Sbjct 181		VQGIIIYRAAYFGVYDTAKGMLPDP			
Query 241		QSGRKGADIMYTGTVDCWRKIAKDE			
Sbjct 241		QSGRKGADIMYTGTVDCWRKIAKDE			

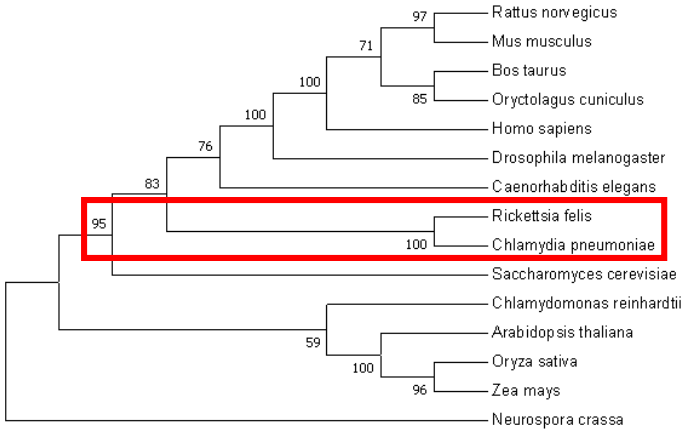
2.3 Phylogenetic Tree



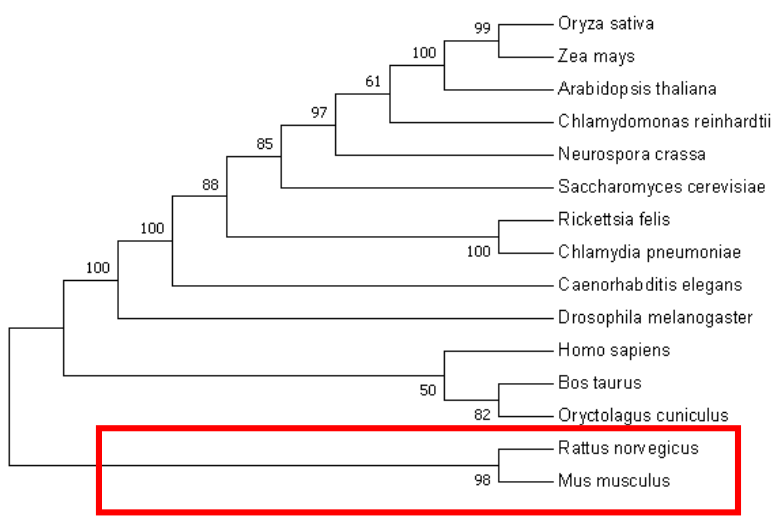
UPGMA



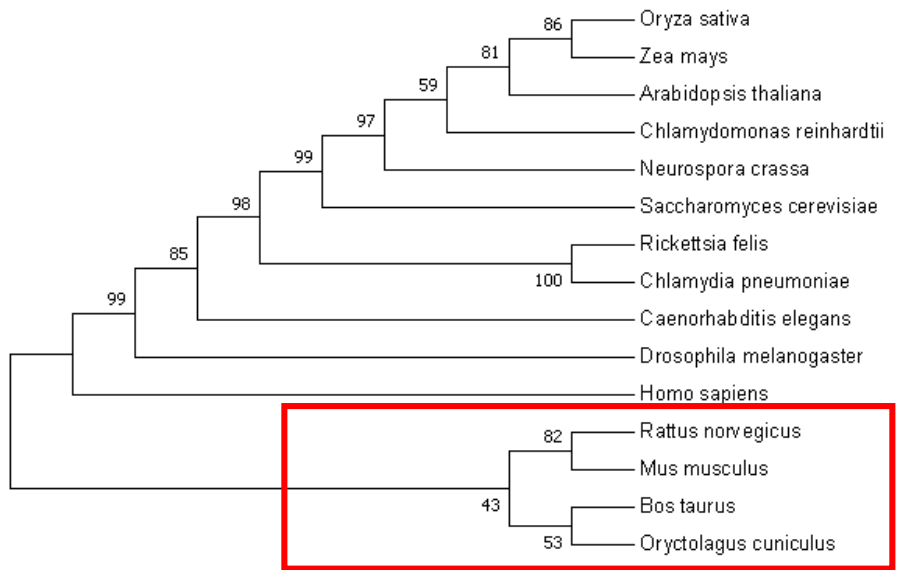
ML



MEM



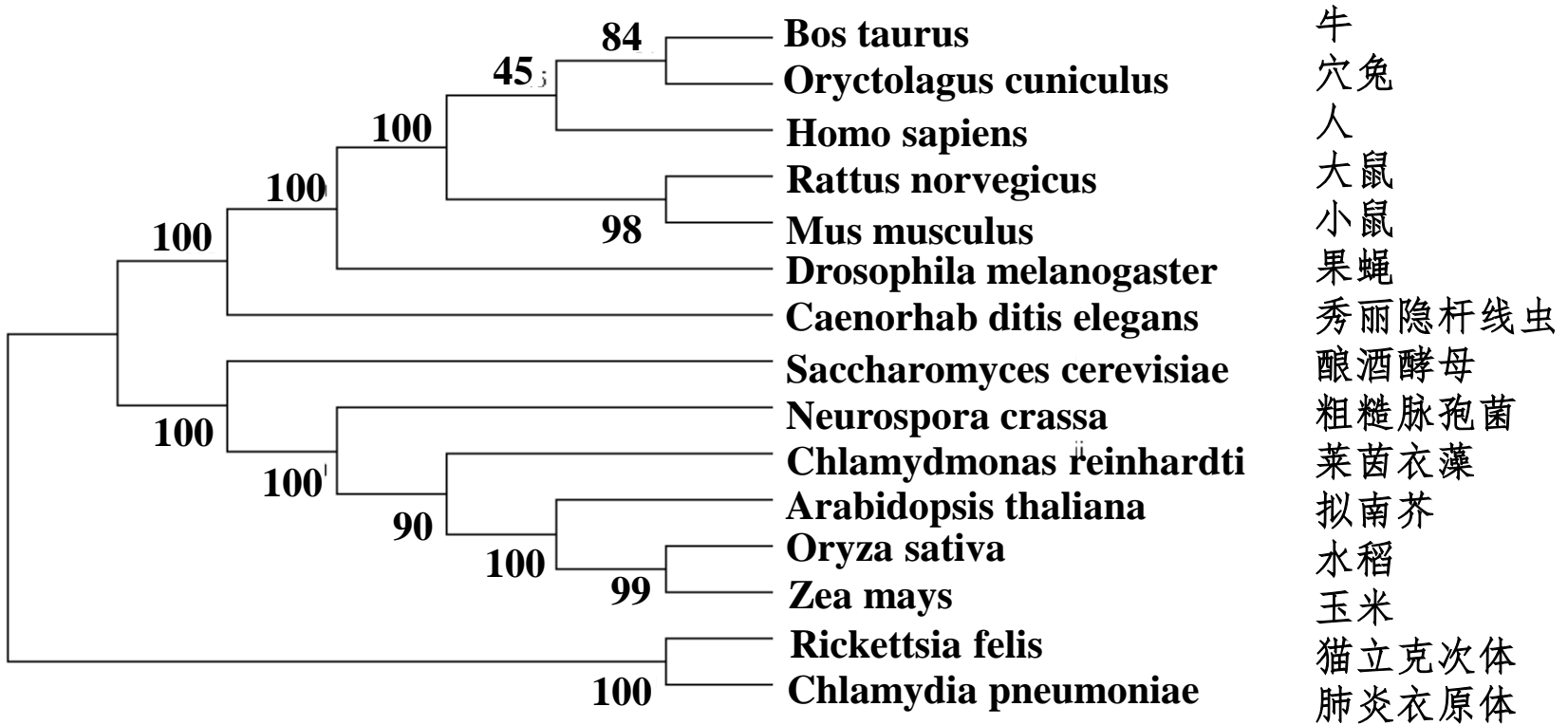
NJ



MP

2.4 Optimization of the ANT tree

✓ UPGMA Method



3.1 Swiss-Prot information of ANT1

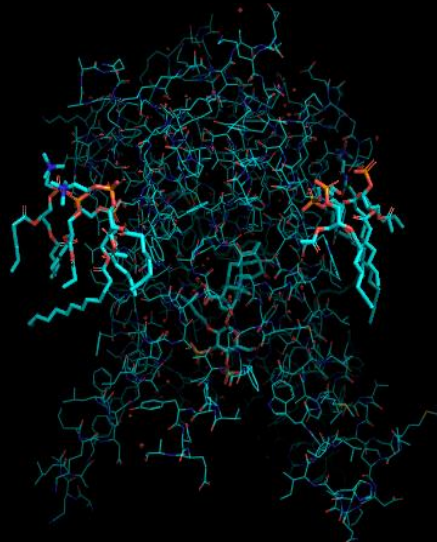
Entry	Entry name	Protein names	Gene names	Organism	Length
Q27238	ADT1_ANOGA	ADP,ATP carrier protein 1	AGAP006782	Anopheles gambiae (African malaria mosquito)	301
P31167	ADT1_ARATH	ADP,ATP carrier protein 1, mitochondr...	AAC1 ANT1, At3g08580, F17O14.5	Arabidopsis thaliana (Mouse-ear cress)	381
P02722	ADT1_BOVIN	ADP/ATP translocase 1	SLC25A4 ANT1	Bos taurus (Bovine)	298
G5ECS8	ADT1_CAEL	A disintegrin and metalloproteinase...	adt-1 C02B4.1	Caenorhabditis elegans	1,461
O22342	ADT1_GOSHI	ADP,ATP carrier protein 1, mitochondr...	ANT1	Gossypium hirsutum (Upland cotton) (Gossypium mexicanum)	386
P12235	ADT1_HUMAN	ADP/ATP translocase 1	SLC25A4 ANT1	Homo sapiens (Human)	298
P04709	ADT1_MAIZE	ADP,ATP carrier protein 1, mitochondr...	ANT1 ANT-G1	Zea mays (Maize)	387
P48962	ADT1_MOUSE	ADP/ATP translocase 1	Slc25a4 Anc1, Ant1	Mus musculus (Mouse)	298
O46373	ADT1_RABIT	ADP/ATP translocase 1	SLC25A4 ANT1	Oryctolagus cuniculus (Rabbit)	298
Q05962	ADT1_RAT	ADP/ATP translocase 1	Slc25a4 Ant1	Rattus norvegicus (Rat)	298
P25083	ADT1_SOLTU	ADP,ATP carrier protein, mitochondr...	ANT	Solanum tuberosum (Potato)	386
Q41629	ADT1_WHEAT	ADP,ATP carrier protein 1, mitochondr...	ANT-G1	Triticum aestivum (Wheat)	331
P04710	ADT1_YEAST	ADP,ATP carrier protein 1	AAC1 YMR056C,	Saccharomyces cerevisiae (strain ATCC	309

激活 Windows
转到“设置”以激活 Windows。

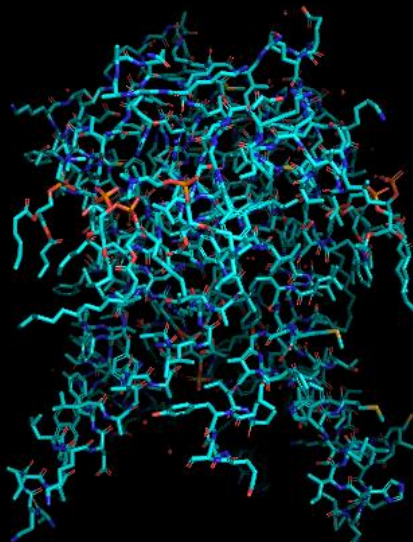
Only P02722 has structure information at experimental level

3.2 Structure representation of ANT1

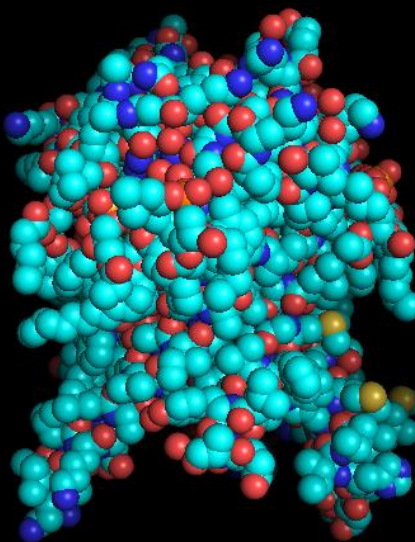
Lines



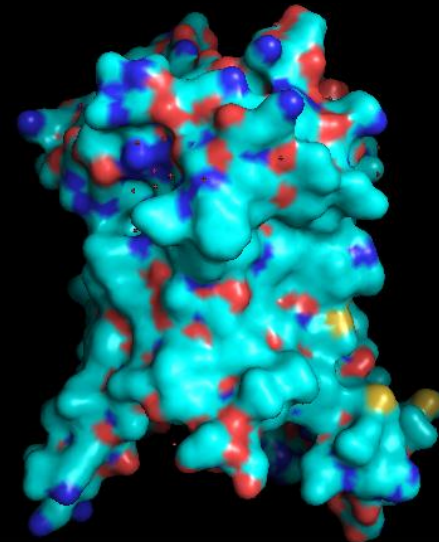
Sticks



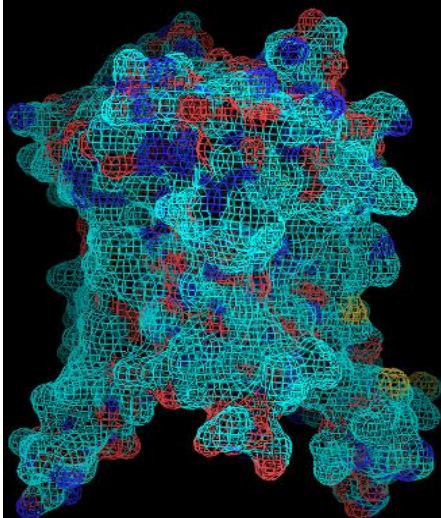
Spheres



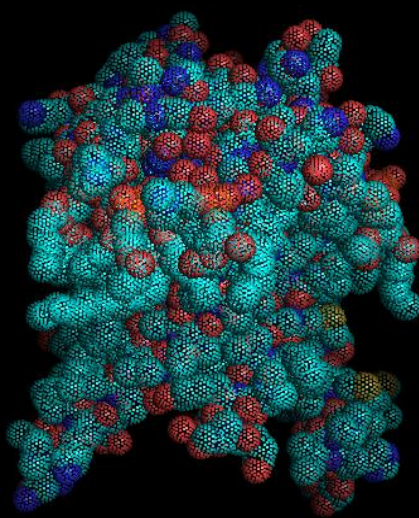
Surface



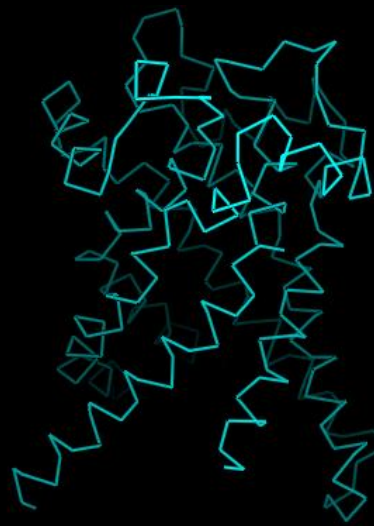
Mesh



Dots



Ribbon



Cartoon

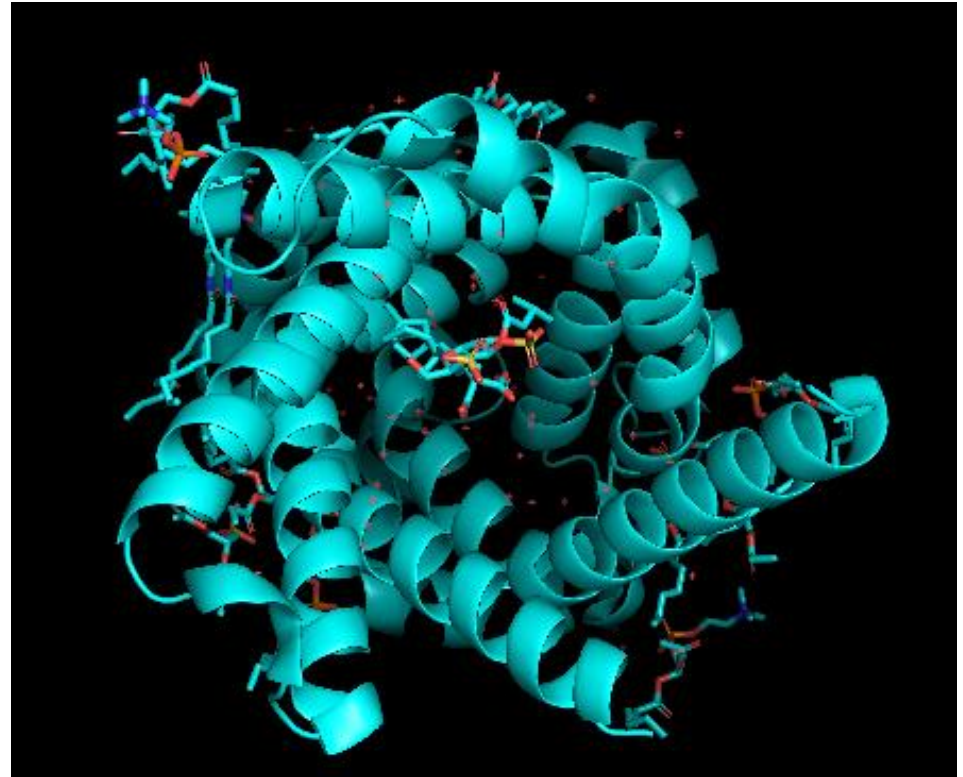


3.3 10KC.pdb

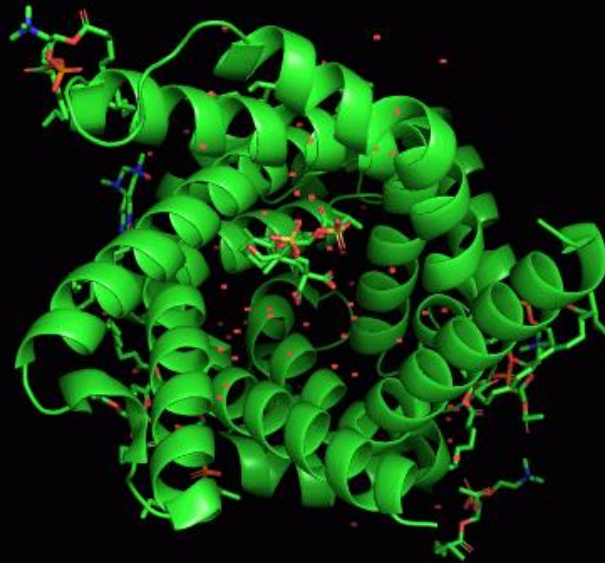
Front view



Bottom view



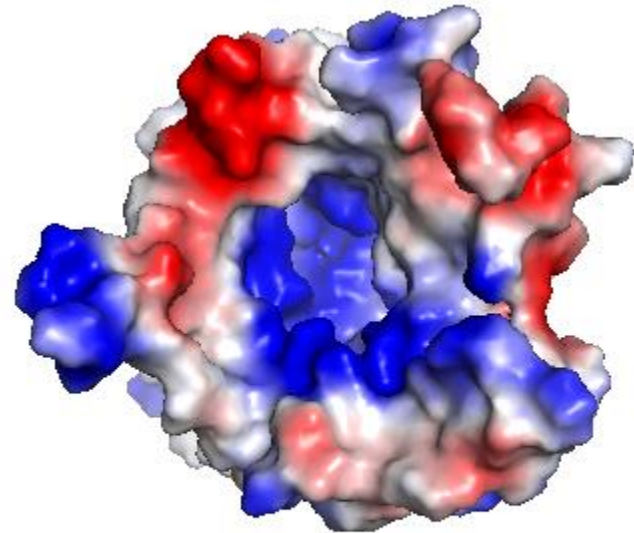
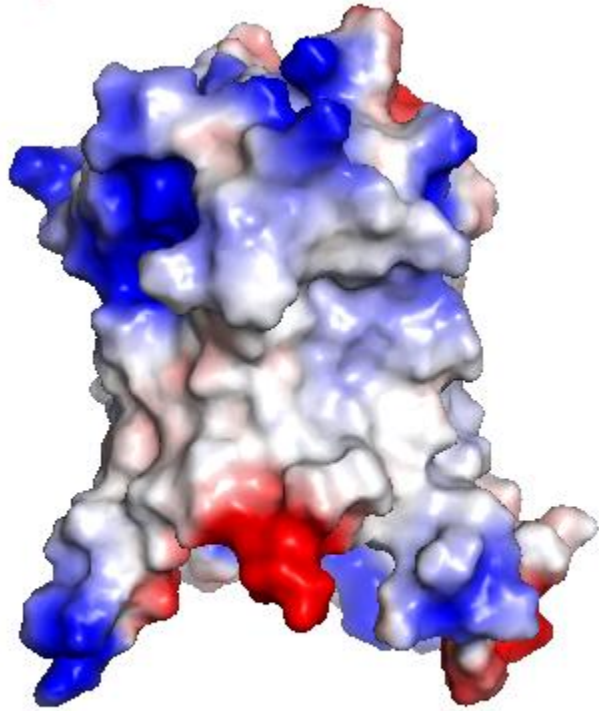
3.4 Structure movie



3.5 Structural composition of 1OKC

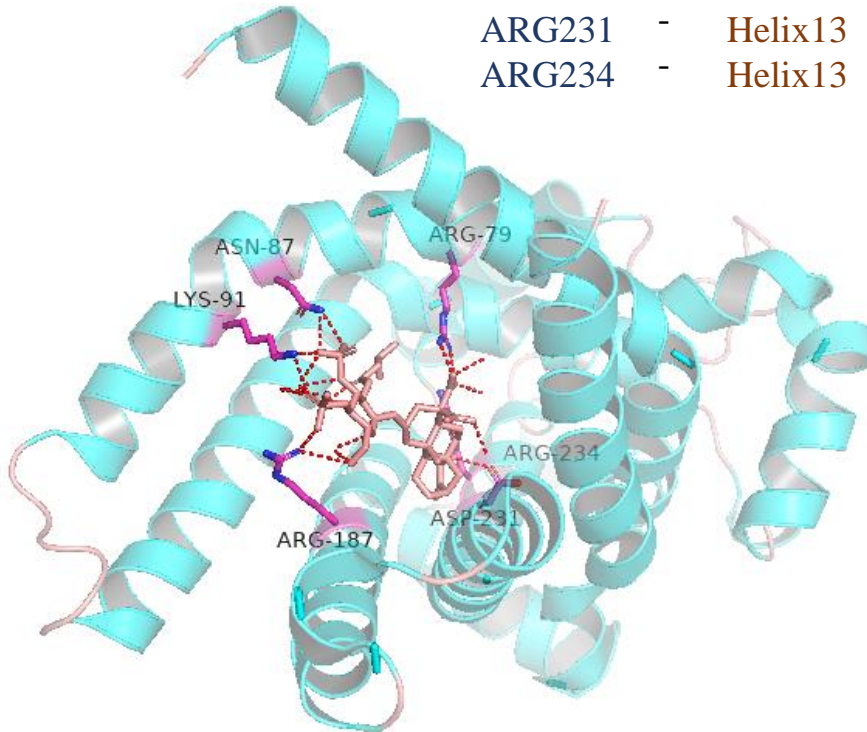
Type	Description	Note
CLASSIFICATION	Transport protein	
CAVEAT	CXT A 401 WRONG CHIRALITY AT ATOM C1	Warning
SOURCE	Cattle (Taxid: 9913) ; Organ: Heart; Tissue: Muscle	
EXPDTA	X-Ray Diffraction	
REVDTA	29-JAN-14; 24-FEB-09; 07-NOV-03	
JRNL	PMID:14603310	
SEQRES	297 residues	No "MET"
HET	1 CXT (C31 H46 O18 S2) 3 CDL (C81 H156 O17 P2 2-) 2 LDM (C17 H36 N2 O2) 4 PC1 (C44 H88 N O8 P) 83 HOH (H2 O)	
HETNAM	CATR: Carboxyatractyloside CDL: Cardiolipin LDM: 3-Laurylamido-N,N'-Dimethylpropylaminoxyde PC1: 1,2-Diacyl-SN-Glycero-3-Phosphocholine	
HELIX	17 Helix	
ATOM	2254 (Protein) + 433 (HET) =2687	

3.6 Protein contact potential

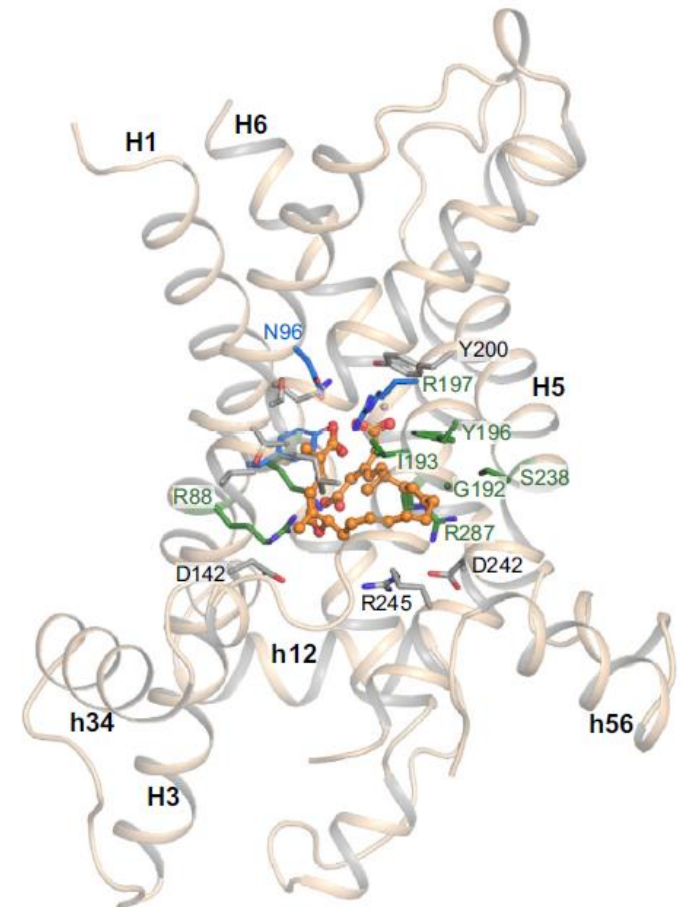


3.7 Protein-ligand interaction

- ARG79 - Helix7
- ASN87 - Helix7
- LYS91 - Helix7
- ARG187 - Helix11
- ARG231 - Helix13
- ARG234 - Helix13

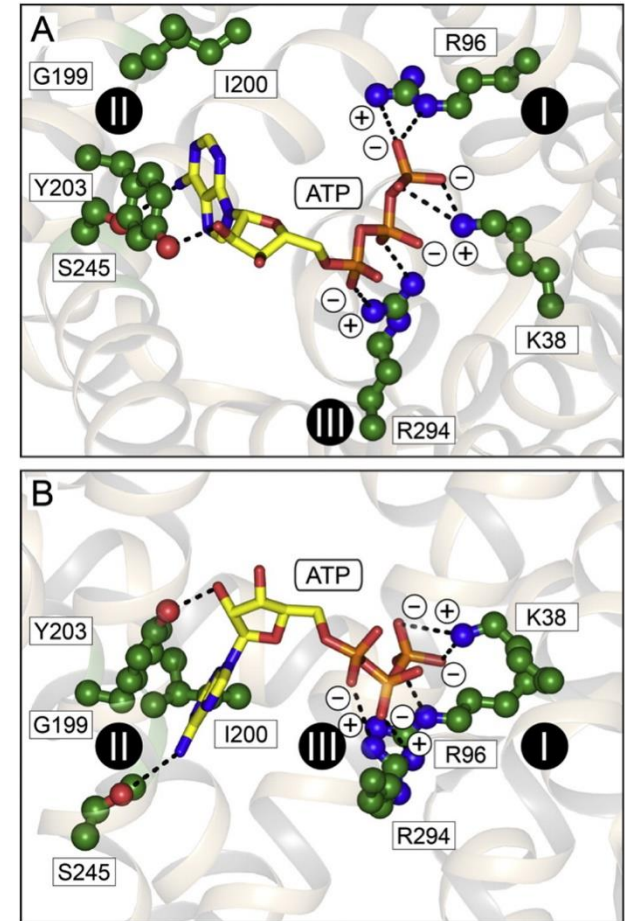
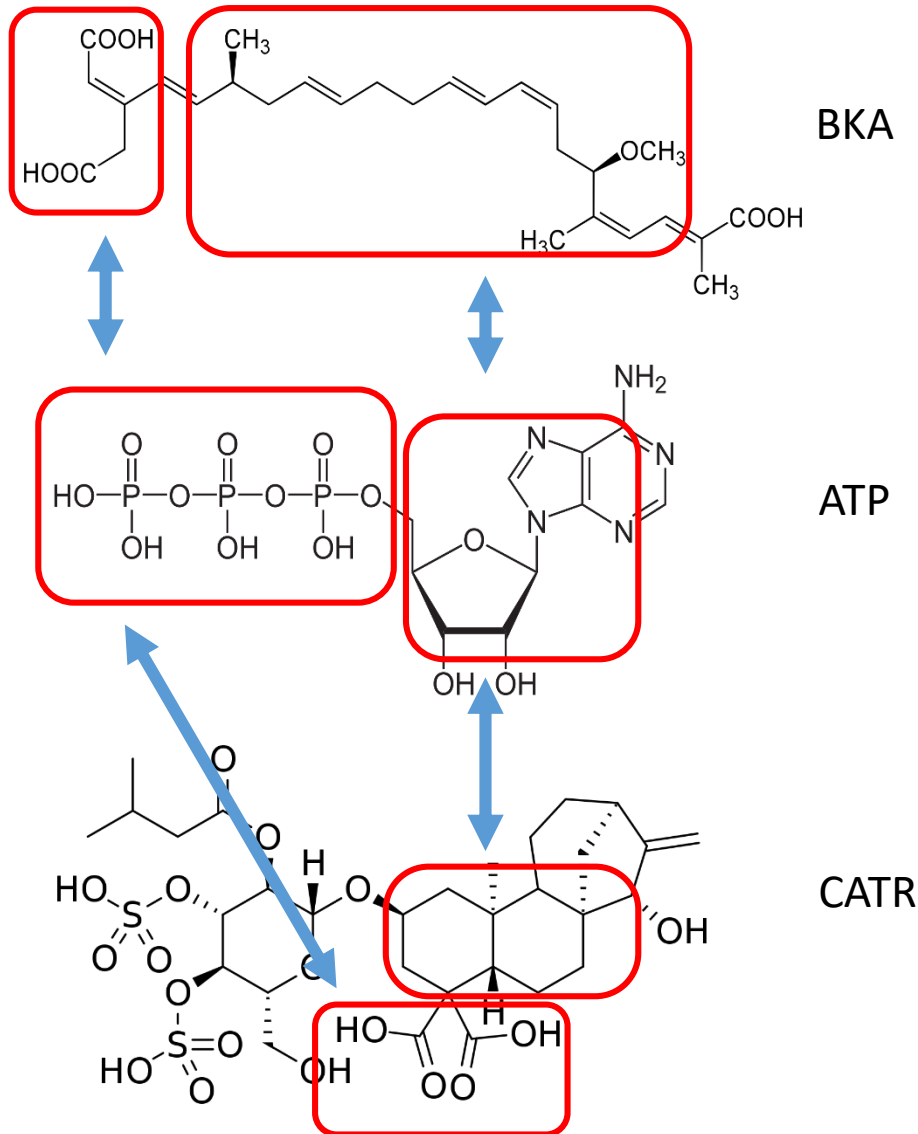


Six residues in ANT1 form hydrogen bonds with ligand CATR

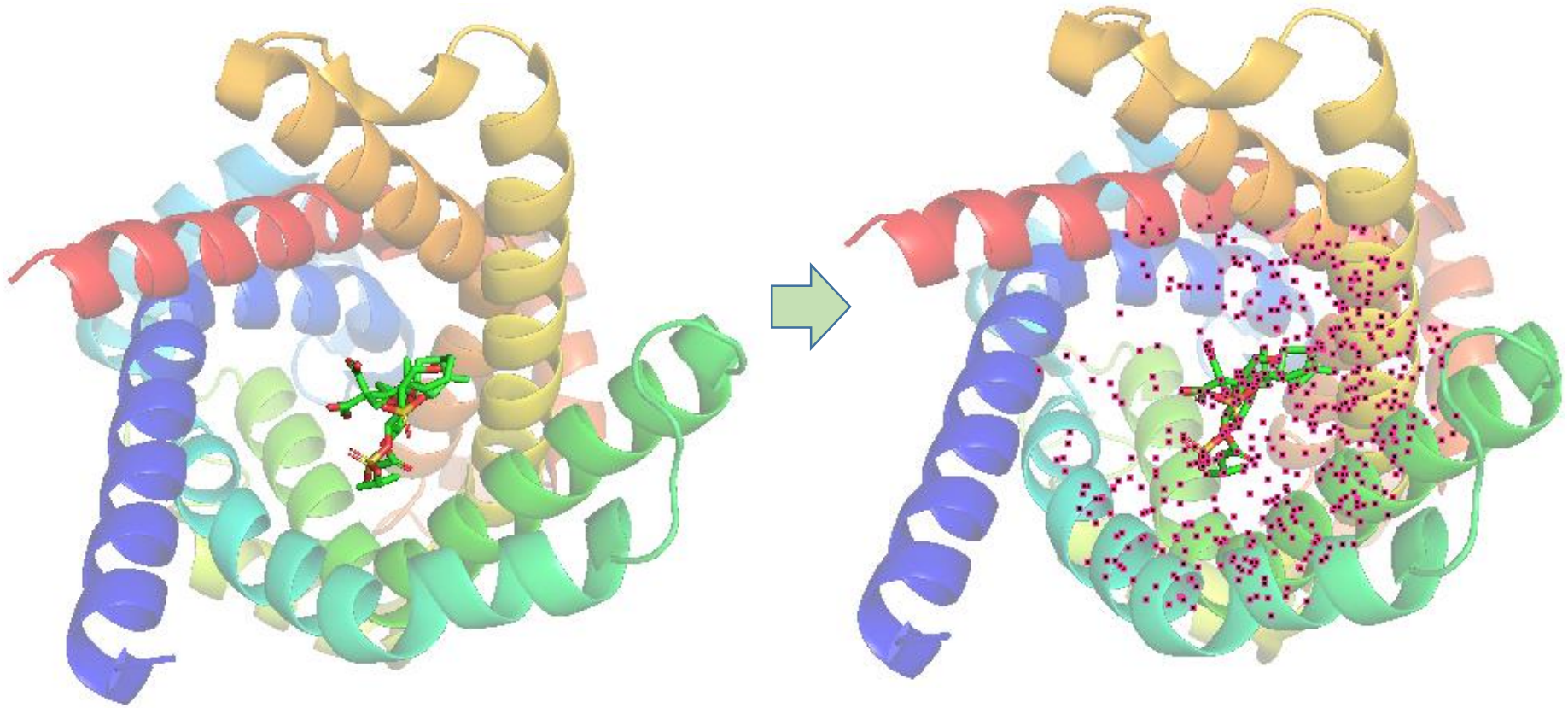


Overview of inhibitory sites of ANT1 with ligand BKA (Bongkrek acid)

3.8 Similarities and differences between ATP and BKA



3.9 5 Å residues around the ligand

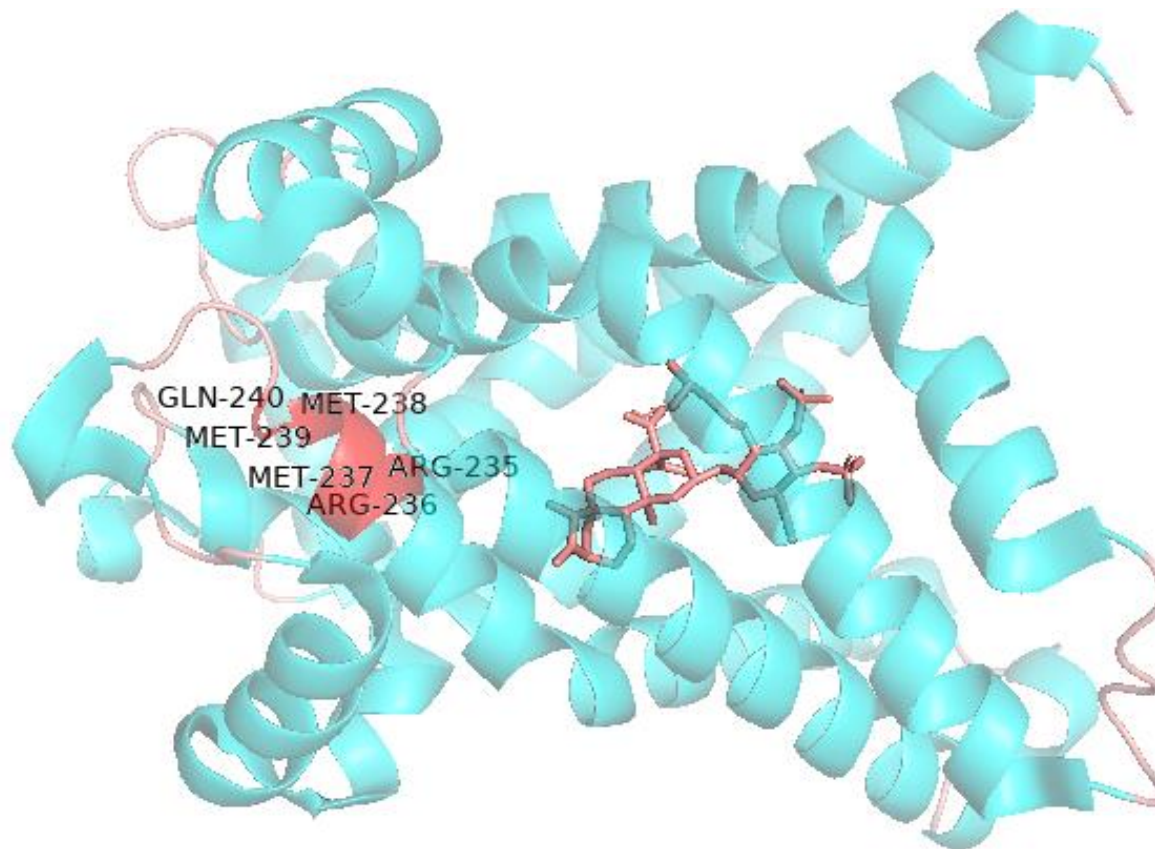


'2 6 11 16 21 26 31 36 41 46 51 56 61 66 71 76 81 86 91 96 101 106
DQALSFLKDFLAGGVA¹AI²S³TAVAPI⁴RV⁵K⁶LL⁷QVQHASKQISA⁸EKQYKGI⁹IDCVVRI¹⁰PKEQGFLS¹¹FWRGNLAN¹²VI¹³RY¹⁴PT¹⁵QALN¹⁶FAFK¹⁷D¹⁸K¹⁹Y²⁰K²¹QIFLGGVDRHKQ²²FI

106 111 116 121 126 131 136 141 146 151 156 161 166 171 176 181 186 191 196 201 206 211 216 :
KQFWRYFAG¹NLASGGAAGAT²SLCFVY³PLDFART⁴RLAADV⁵GKGAQREFTGLGNCITK⁶IFKSDGLRGL⁷YQGFN⁸SVQGI⁹I¹⁰IYRAAY¹¹F¹²GVYDTAKGMLPDPKNVHI¹³IVSWMIAQT¹⁴VT¹⁵

201 206 211 216 221 226 231 236 241 246 251 256 261 266 271 276 281 286 291
GMLPDPKNVHI¹IVSWMIAQT²VT³AV⁴AGLVSYPFD⁵TVRRR⁶MI⁷IQSGRKGADIMYTGTVDC⁸WRKIAKDEGPKAFFKGAWS⁹N¹⁰VL¹¹RG¹²MGGAFVLVLYDEI

3.10 Transport activity-related residues



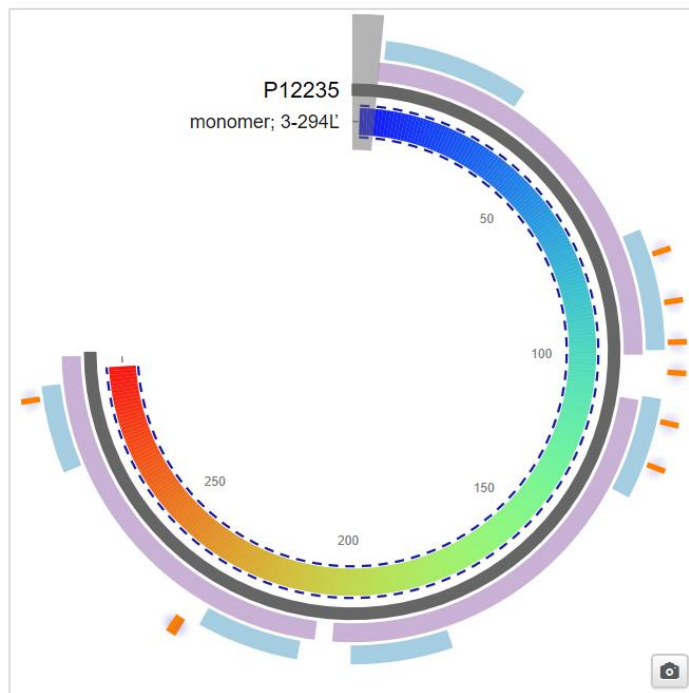
Natural variant ¹ (VAR_078072)	235 R → G in MTDPS12A; severely decreased function in ADP transport. ◆ 1 Publication ▼ Corresponds to variant dbSNP:rs886041082 Ensembl, ClinVar.	
Natural variant ¹ (VAR_078073)	236 R → P in MTDPS12B; loss of function in ADP transport. ◆ 2 Publications ▼ Corresponds to variant dbSNP:rs770816416 Ensembl, ClinVar.	

3.11 ANT1 in human

P12235 (ADT1_HUMAN) *Homo sapiens* (Human)

ADP/ATP translocase 1 ★ UniProtKB [InterPro](#) [STRING](#) [Interactive Modelling](#)

298 aa; Sequence (Fasta) [Identical sequences: *Homo sapiens*: A0A0S2Z3H3; *Pongo abelii*: H2PEV7; *Pan troglodytes*: K7AY97; *Gorilla gorilla gorilla*: A0A2I2YVC0; *Macaca nemestrina*: A0A2K6CBR7; *Macaca mulatta*: F6QA37; *Macaca fascicularis*: \[A0A2K5V3Q3\]\(#\); *Cercocebus atys*: A0A2K5MMJ7; *Rhinopithecus roxellana*: A0A2K6Q1W5; *Rhinopithecus bieti*: A0A2K6L1C9](#)



1okc.1.A ADP, ATP CARRIER PROTEIN HEART ISOFORM T1

Seq Identity 96.28%
Seq Similarity 0.60
2 x CARDIOLIPIN [☐](#)
1 x 1,2-DIACYL-SN-GLYCERO-3-PHOSPHOCHOLINE [☐](#)
1 x CARBOXYATRACTYLOSIDE [☐](#)
1 x 3-LAURYLAMIDO-N,N'-DIMETHYLPROPYLAMINOXYDE [☐](#)
SMTL Version 2019-12-12
Download Model [↓](#)

Model Quality Estimate [▼](#)

QMEAN -2.85
C β -2.51
All Atom 1.36
solvation -0.48



Acknowledgments

- We thank Prof. Jingchu Luo for his work on lectures and interesting stories. We like the stories as well as the knowledge.
- We thank Tao Wang and Yaqi Wang and TAs for their assistance on this course.
- Chenyang Liu, Cuitong He, Xuejiao Song, Yuluan Tang and Wendi Luo have assisted with review of concepts, methods, and consideration of references. Changxing Hu, Jiankun Wang and Jiangle Liu also assisted with review structural and format issues.

References

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3. Ruprecht JJ, King MS, Zogg T, Aleksandrova AA, Pardon E, Crichton PG, et al. The Molecular Mechanism of Transport by the Mitochondrial ADP/ATP Carrier. *Cell*. 2019;176(3):435-47.e15.
4. Pebay-Peyroula E, Dahout-Gonzalez C, Kahn R, Trezeguet V, Lauquin GJ, Brandolin G. Structure of mitochondrial ADP/ATP carrier in complex with carboxyatractyloside. *Nature*. 2003;426(6962):39-44.
5. Kumar S, Stecher G, Tamura K. MEGA7: Molecular Evolutionary Genetics Analysis Version 7.0 for Bigger Datasets. *Mol Biol Evol*. 2016;33(7):1870-4.