@고대의대 유광사홀

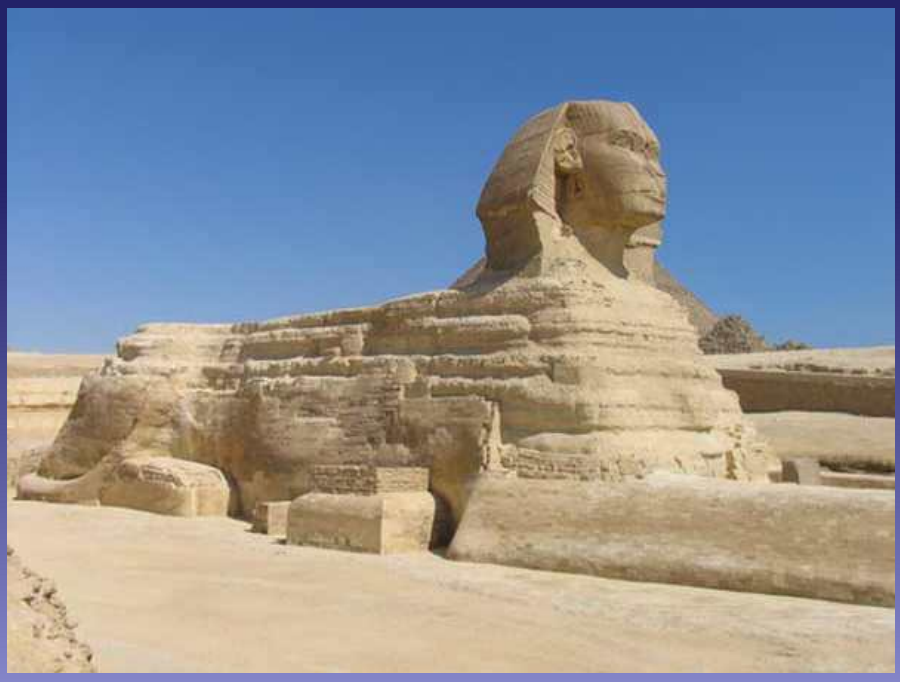
세포 내 단백질 운명

2014. 7. 24

송현규

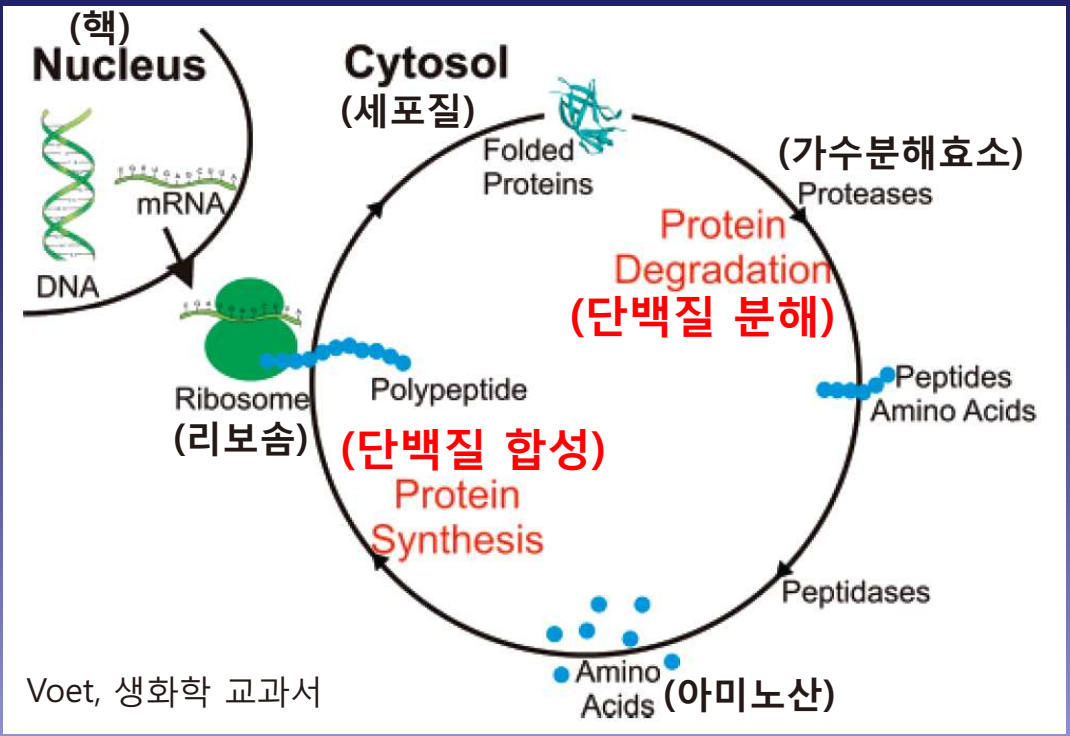
고려대학교 생명과학부

스핑크스의 수수께기



http://www.crystalinks.com/sphinxfacts.html

단백질의 일생

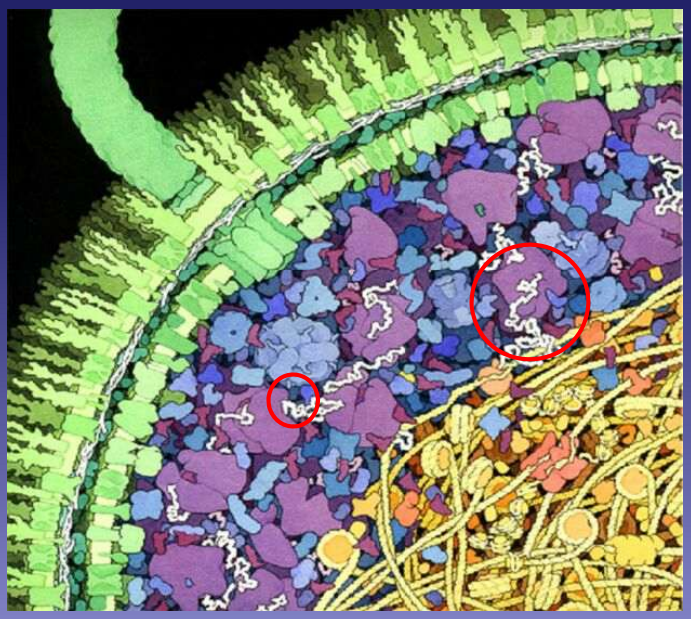


Voet, 생화학 교과서

단백질 우주

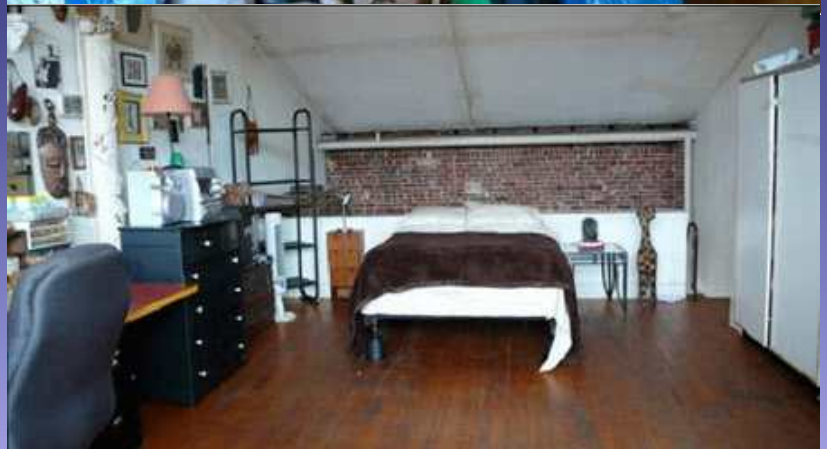
나사 허블 망원경

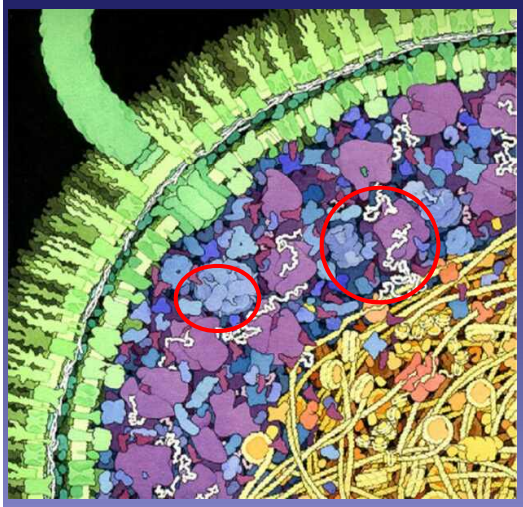
"분해될 단백질 인식 문제"



우리의 일상 생활

청소 전 · 후





기질 선택

타이밍

장소

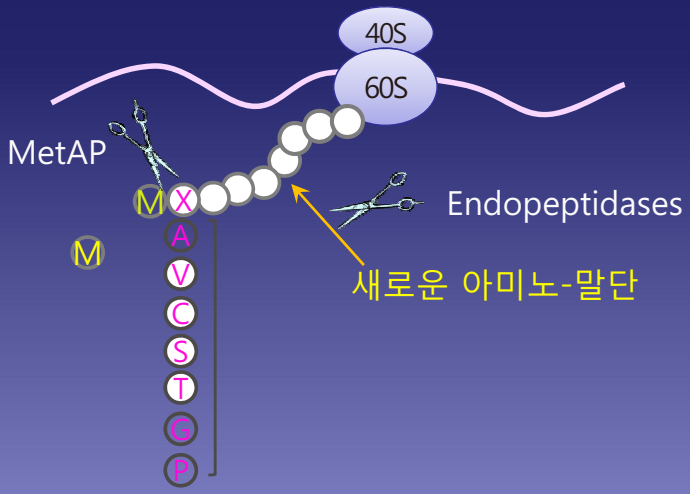
분해

단백질

세포소기관

아미노-말단 규칙 (N-end rule)

생성되는 단백질의 수명이 아미노-말단 아미노산 종류에 따라 정해지는 규칙



모든 생명체에 보존된 규칙

아미노-말단 불안정화 아미노산 잔기

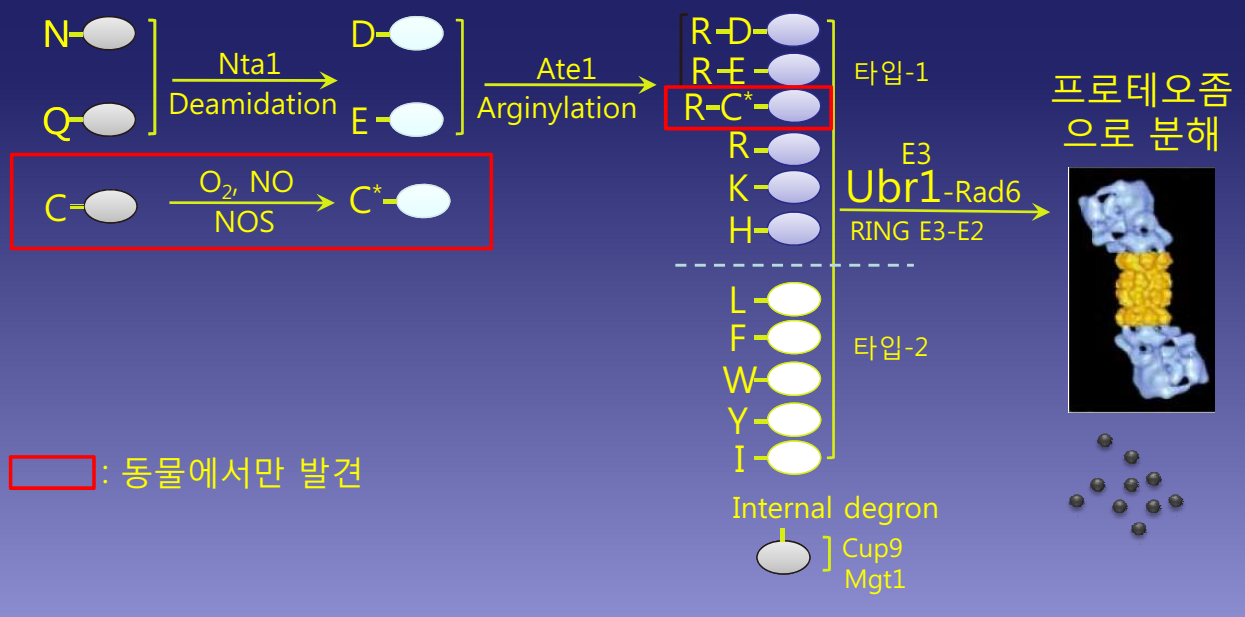
Residue X in ub-X-βgal	Radius of gyration of X (Å)	Deubiquitination of ub-X-βgal	$t_{1/2}$ of X-βgal
Met	1.80	+	
Ser	1.08	+	
Ala	0.77	+	
Thr	1.24	+	>20 hours
Val	1.29	+	
Gly	0	+	
Ile	1.56	+	~30 minutes
Glu	1.77	+	
Tyr	2.13	+	~10 minutes
Gln	1.75	+	
Phe	1.90	+	
Leu	1.54	+	
Asp	1.43	+	~3 minutes
Lys	2.08	+	
Arg	2.38	+	~2 minutes
Pro	1.25	–*	~7 minutes

안정화

불안정화

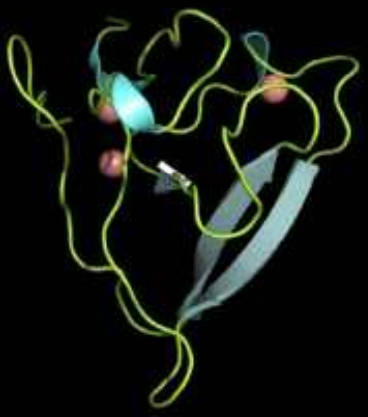
(Bachmair *et al.* Science 1986)

불안정화 아미노산 잔기



(Tasaki & Kwon, Trends Biochem Sci. 2007 - 수정)

Ubr1 단백질의 아미노-말단 기질 인식



세포 주기

고등학교 생물II 교과서 / 도서출판 형설

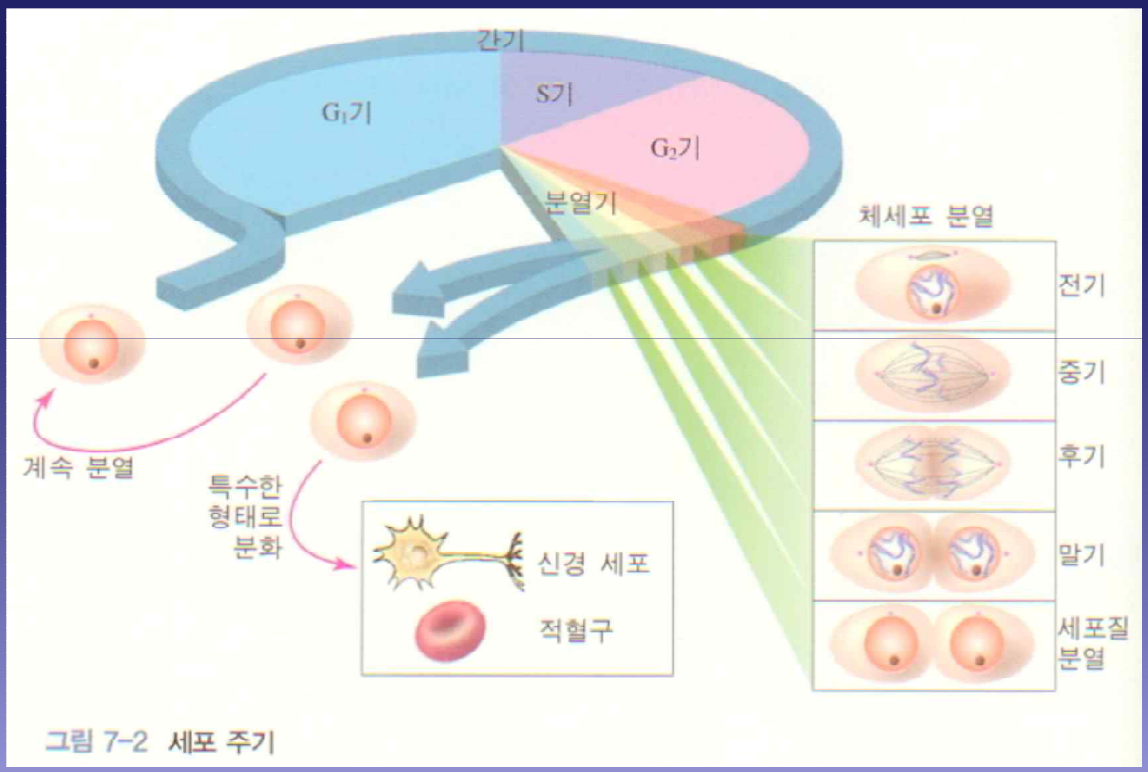
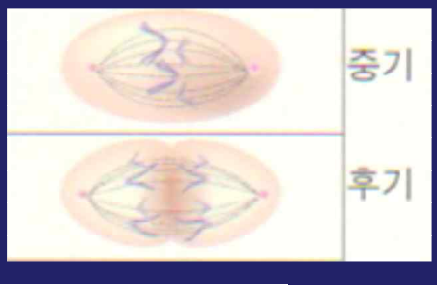
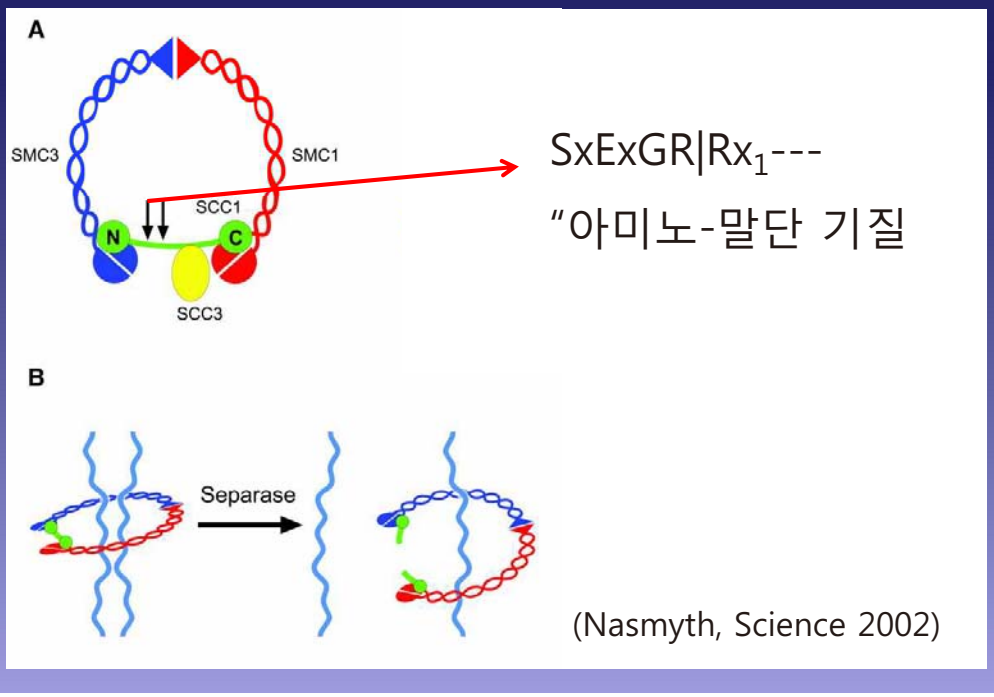


그림 7-2 세포 주기





SxExGR|Rx$_1$---

"아미노-말단 기질

(Nasmyth, Science 2002)

세포 내 소기관

고등학교 생물II 교과서 / 도서출판 형설

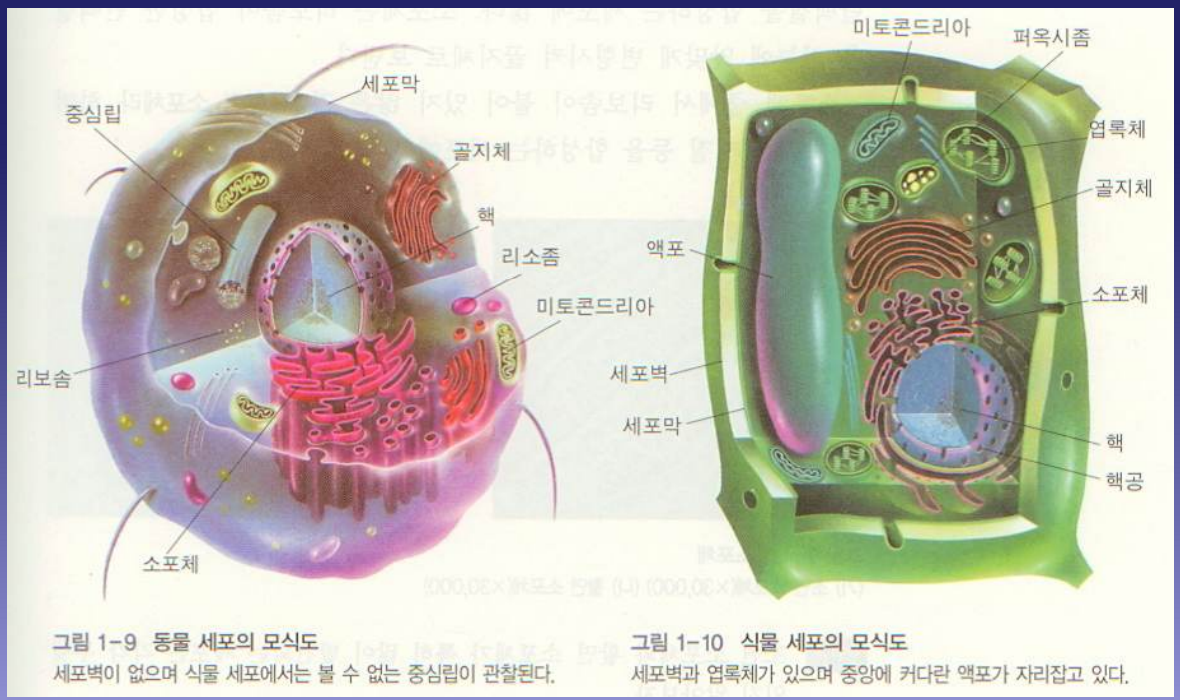


그림 1-9 동물 세포의 모식도
세포벽이 없으며 식물 세포에서는 볼 수 없는 중심립이 관찰된다.

그림 1-10 식물 세포의 모식도
세포벽과 엽록체가 있으며 중앙에 커다란 액포가 자리잡고 있다.

자식작용 (자가포식): Autophagy (*self-eating*)

세포 내 소기관(단백질 응집체, 병원균) 등이 이중막에 의해 둘러 쌓여 자가포식소체(autophagosome)을 형성하고, 리소좀과 융합하여 모두 분해하는 현상

rmBook.org

구획화의 중요성

2013년 고려대학교 자연계논술

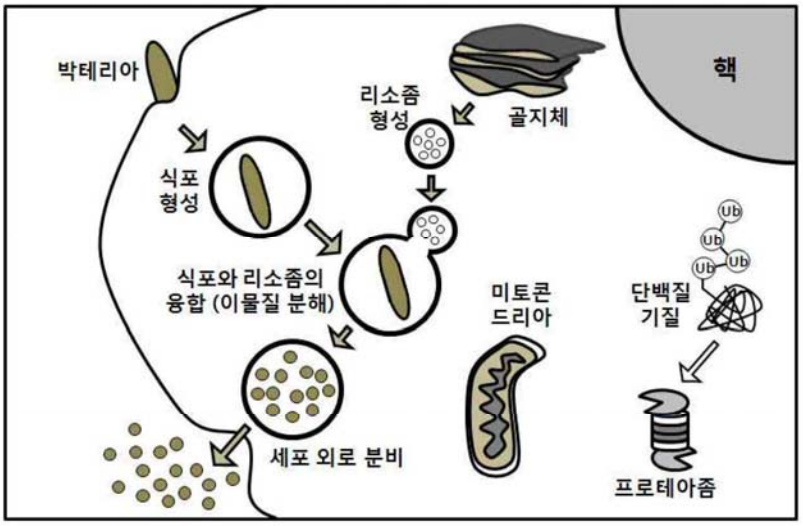


그림 1. 세포 내 구획화 및 리소좀의 작용

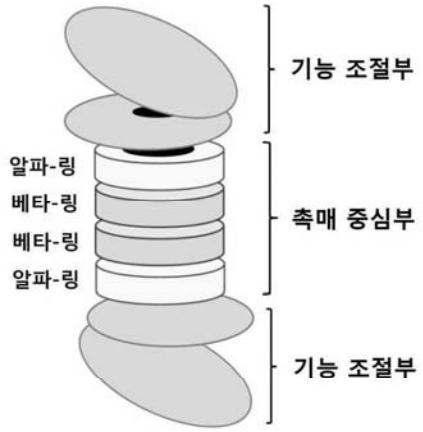
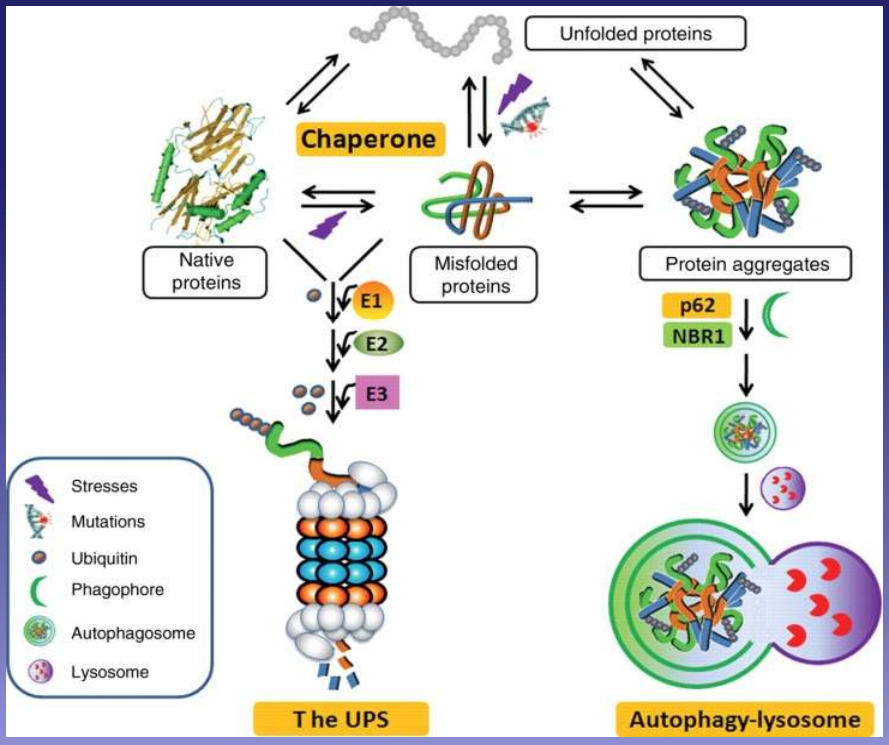


그림 2. 단백질 가수 분해 효소 프로테아좀의 구조

세포 내 단백질 및 소기관 분해

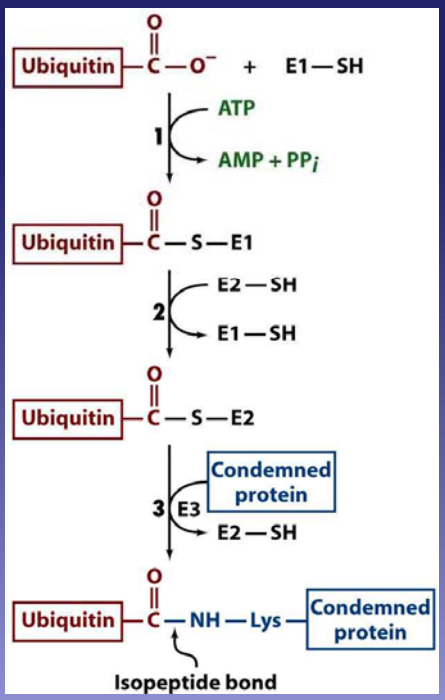
유비퀴틴-프로테오좀 시스템 / 리소조말 분해 (자식작용)



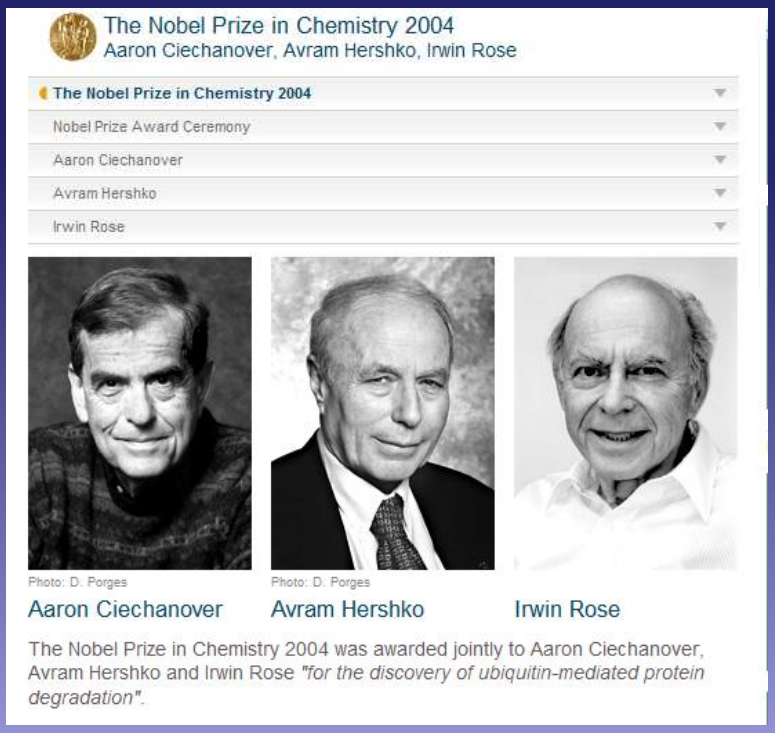
(출처: Huabo 등, Cardiovascular Research, 2009, http://cardiovascres.oxfordjournals.org/content/early/2009/12/04/cvr.cvp287/F1.expansion)

유비퀴틴-프로테오좀 분야의 중요성

기초연구 → 2004년 노벨화학상
응용연구 → 1 approved, 16 clinical trials (2010.11.24)



Voet 등, 생화학 교과서



http://www.nobelprize.org

단백질 분해와 인체 질병의 연관성

Table. **Human Disorders Related to Aberrant Function of the Ubiquitin Proteasome System***

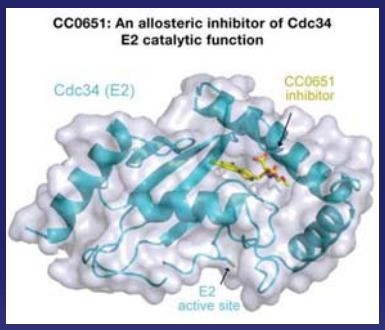
Disorder	Defect
Angelman syndrome	Mutation in E6-AP, an E3 enzyme
Autosomal recessive juvenile parkinsonism	Mutation in Parkin, an E3 enzyme
Liddle syndrome	Mutation in the β/γ subunit of a renal sodium channel, a substrate of the UPS
von Hippel–Lindau protein-associated malignant conditions	Mutations in the von Hippel–Lindau protein, an E3 enzyme
Colon cancer	Mutation in the adenomatous polyposis coli, a regulator of β-catenin, a substrate of the UPS
Fanconi anemia	Mutation in the FANCD2 protein, a substrate of the UPS
Uterine cervical carcinoma	HPV-mediated accelerated degradation of p53 by the UPS
Various malignant conditions	Overexpression of Hdm2 and Skp2 (E3 enzymes) mutations in various oncogenes and tumor suppressor proteins that are UPS substrates
Breast and ovarian cancer	Mutations in BRCA1, an E3 enzyme
Familial cylindromatosis	Mutation in CYLD, a deubiquitinating enzyme

* Not a comprehensive list. HPV = human papillomavirus; UPS = ubiquitin proteasome system.

Reinstein & Ciechanover (2006) Annals of Internal Medicine

유비퀴틴-프로테오좀 분야 신약개발

Soucy *et al.* (2009) Nature
- E1 target



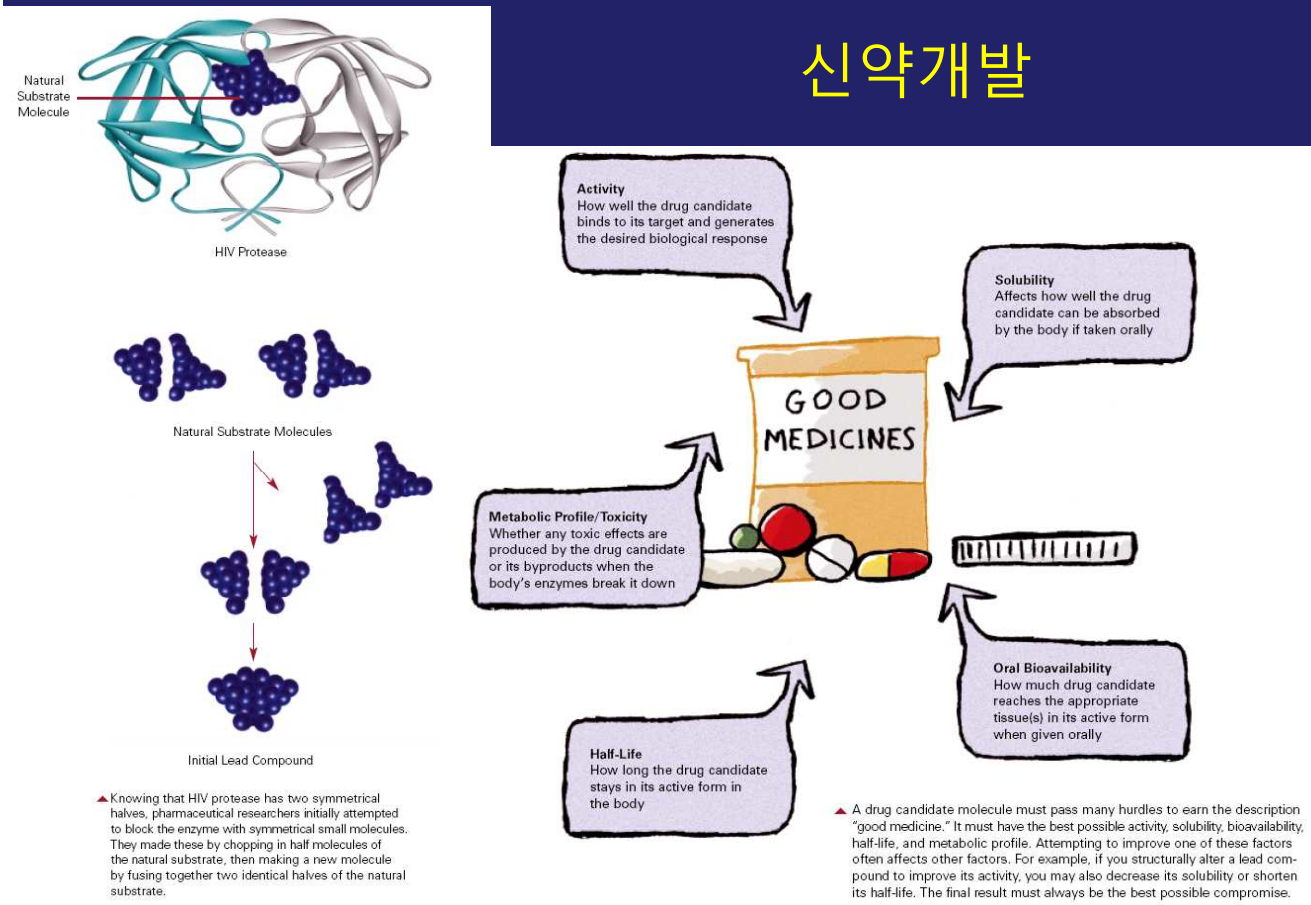
Ceccarelli *et al.* (2011.6.24) Cell
- E2 target

Millennium Pharmaceuticals
- Proteasome target

Company	Inhibitor	Target	Stage	Disease
Millenium/Takeda	MLN4924	NAE-E1[b]	Phase II	Multiple myeloma and Hodgkin's lymphoma
Roche	Nutlin/R7112	E3-Hdm2	Phase I	Blood cancers and solid tumors
Johnson & Johnson	JNJ26854165	E3-Hdm2	Phase I	Multiple myeloma and solid tumors
Genentech/Roche	GDC-0152	E3-IAP	Phase I	Metastatic malignancies
Novartis	LCL161	E3-IAP	Phase I	Solid tumors
Ascenta Therapeutics	AT-406	E3-IAP	Phase I	Solid tumors and lymphoma
Aegera Therapeutics	AEG 35156[a]	E3-IAP	Phase II	AML and liver cancer
Aegera Therapeutics	AEG 40826	E3-IAP	Phase I	Lymphoid tumors
Tetralogics Pharma	TL 32711	E3-IAP	Phase I	Solid tumors and lymphoma
Astellas Pharma	YM155	E3-IAP	Phase II	Lung cancer

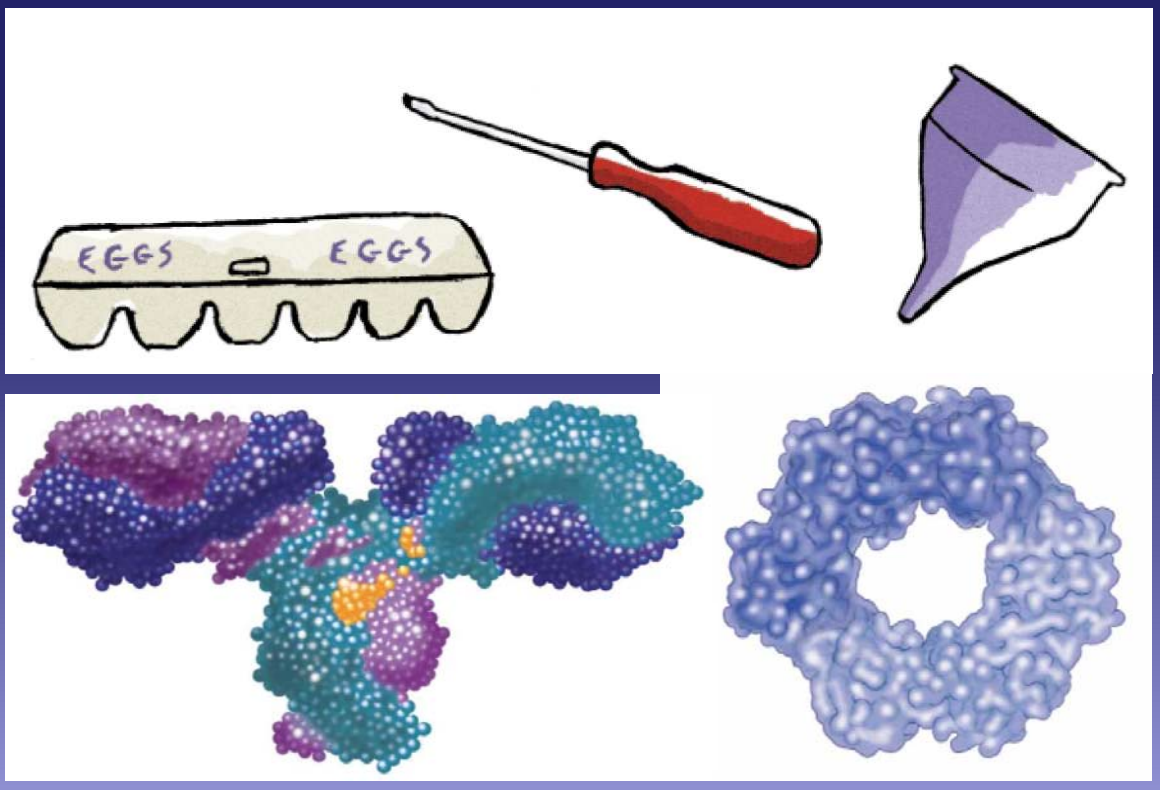
Cohen & Tcherpakov (2010) Cell

신약개발



The Structures of Life, NIH http://publications.nigms.nih.gov/structlife/

구조 생물학 연구



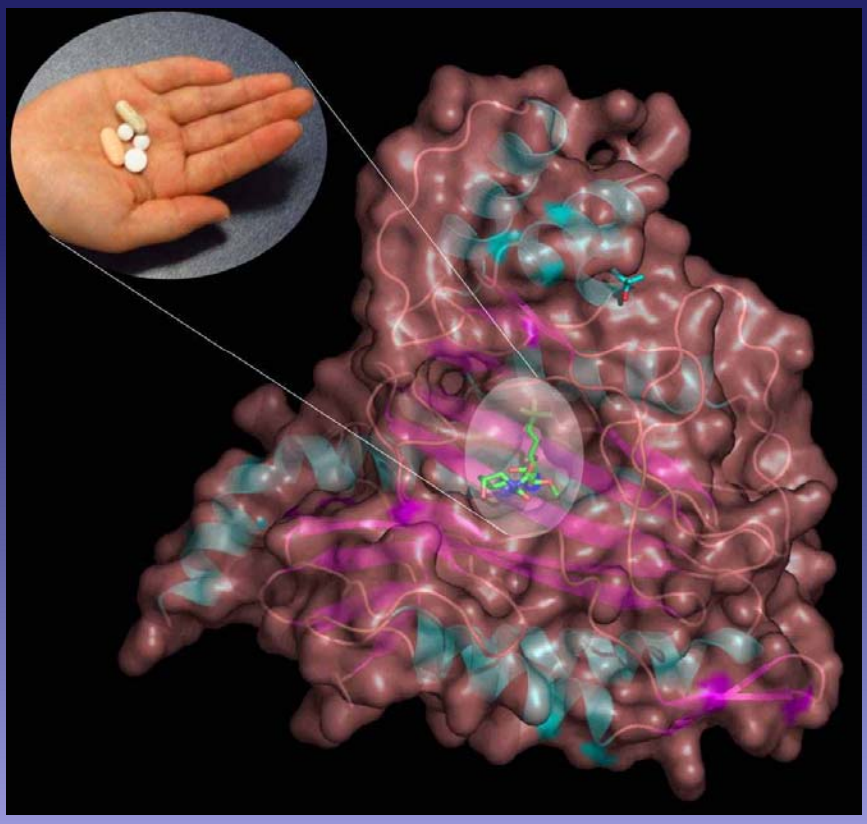
The Structures of Life, NIH http://publications.nigms.nih.gov/structlife/

군맹무상 (群盲撫象)

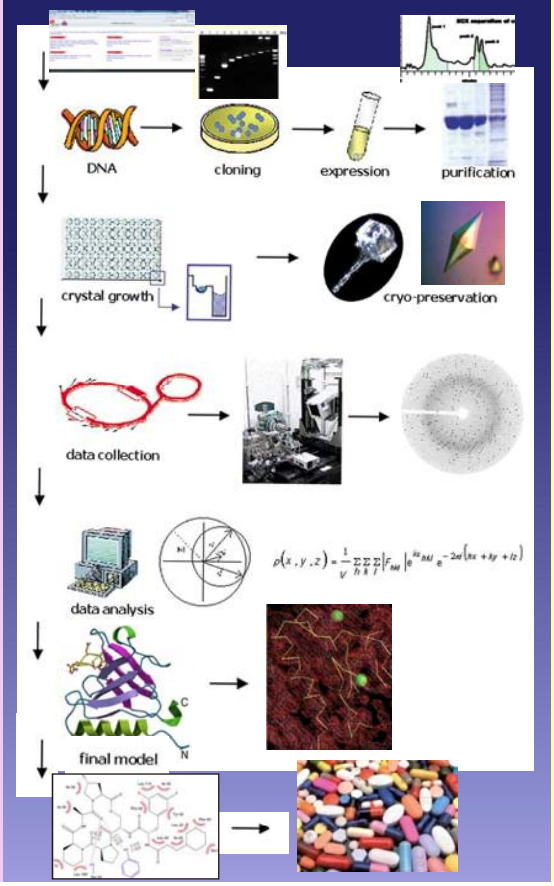
"여러 소경이 코끼리를 어루만진다"

Seeing is Believing – 보는 것이 믿는 것이다

구조기반 신약개발



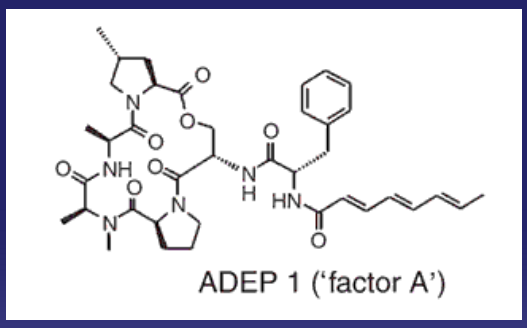
구조기반 신약개발 과정

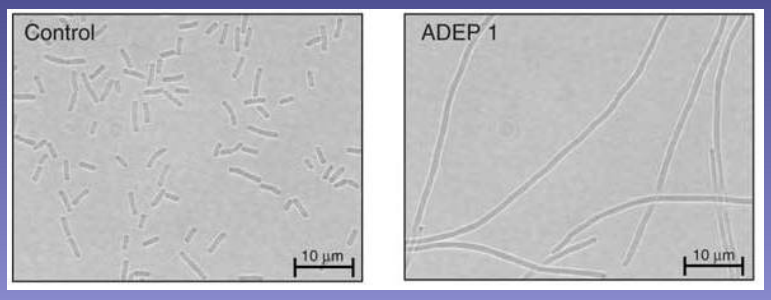
생물정보학		표적분자 선정
분자생물학 및 생화학		클로닝, 발현, 순수분리
예술		결정화
물리학 및 화학 (결정학)		X-선 실험, 방사광 이용
IT (계산)		수학적 계산
컴퓨터 그래픽스		분자모형 및 정밀화
의약학		구조기반 신약개발

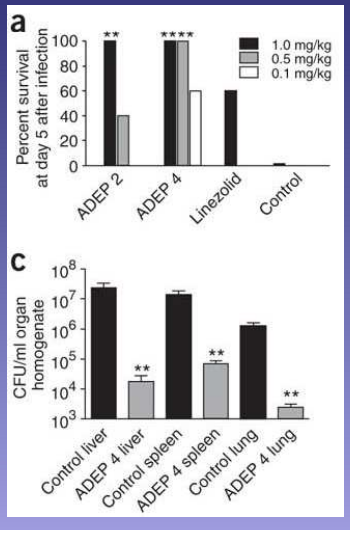
ADEP 계열 항생제 개발 - 연구 배경

ADEP (acyldepsipeptide)

- *Streptomyces*에서 분리한 천연물
- AiCuRis에서 개발 중인 항생제
- 그램(+) 균에 효과적
- ClpP 가수분해효소 활성제 (ClpX의 효과)

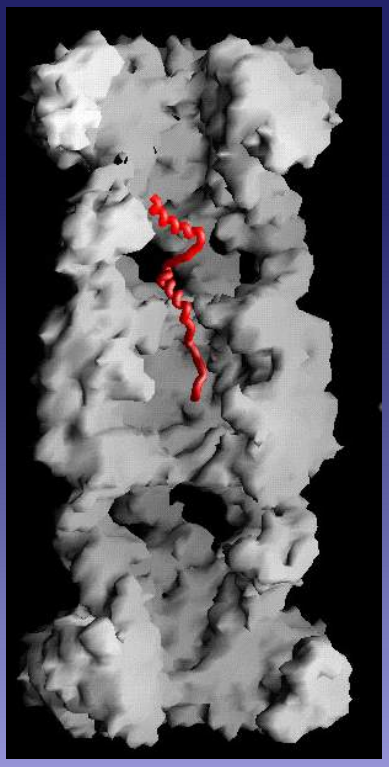




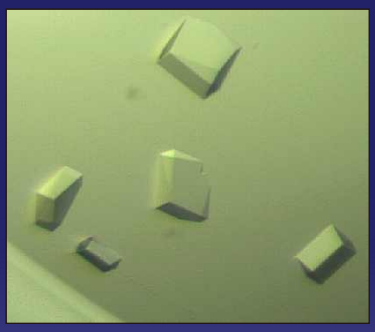


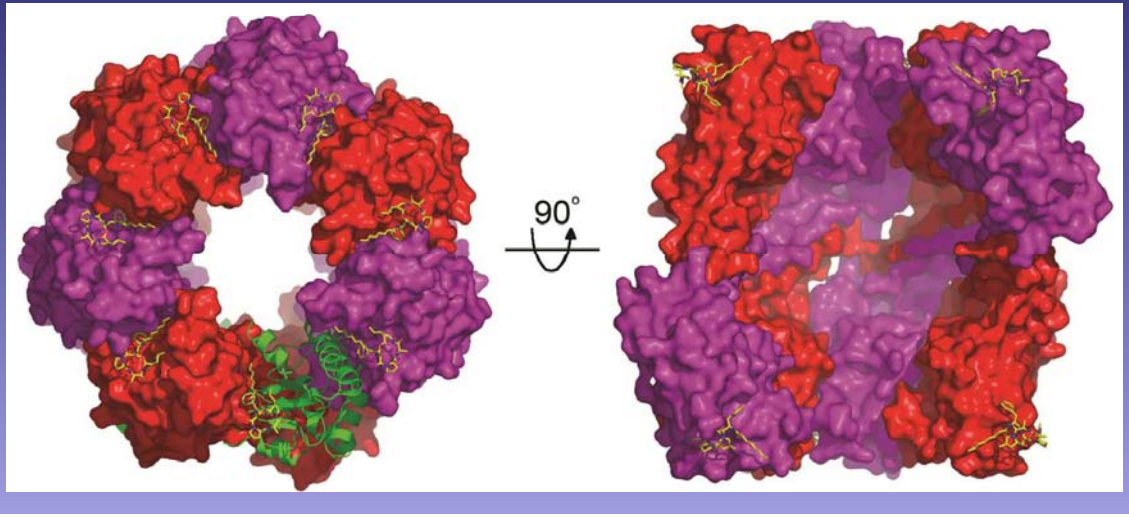
Brötz-Oesterhelt *et al.* (2005) Nature Med.

거대 단백질 분해효소 복합체 (프로테오좀, ClpXP)



가수분해효소-항생제 복합체 전체구조

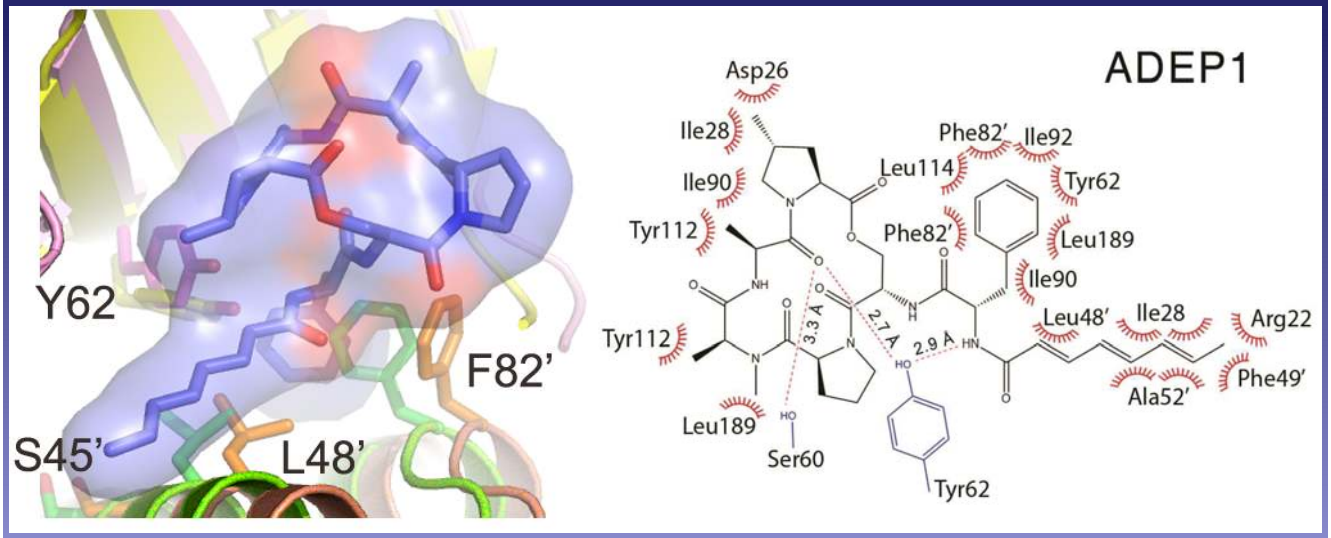


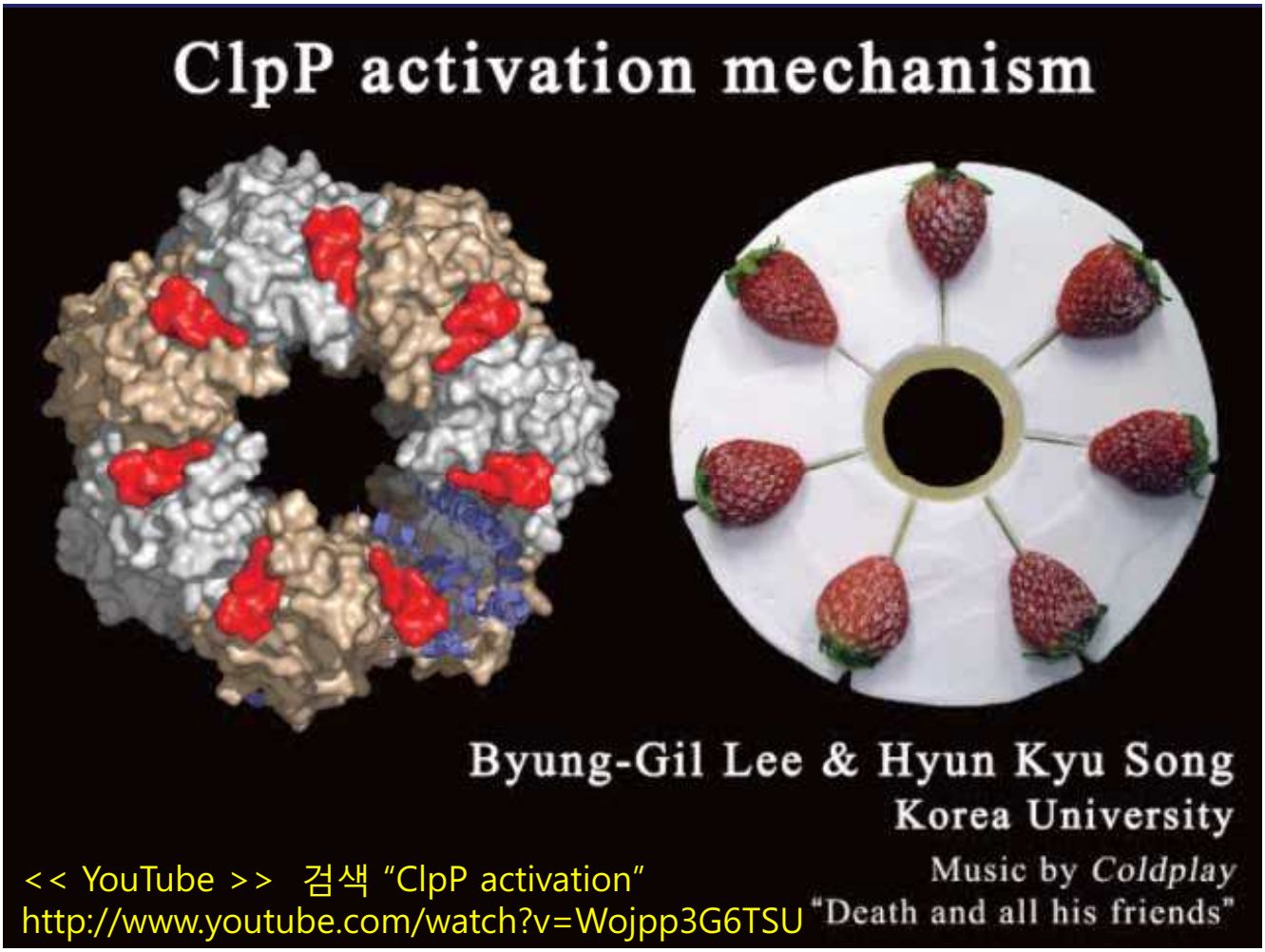


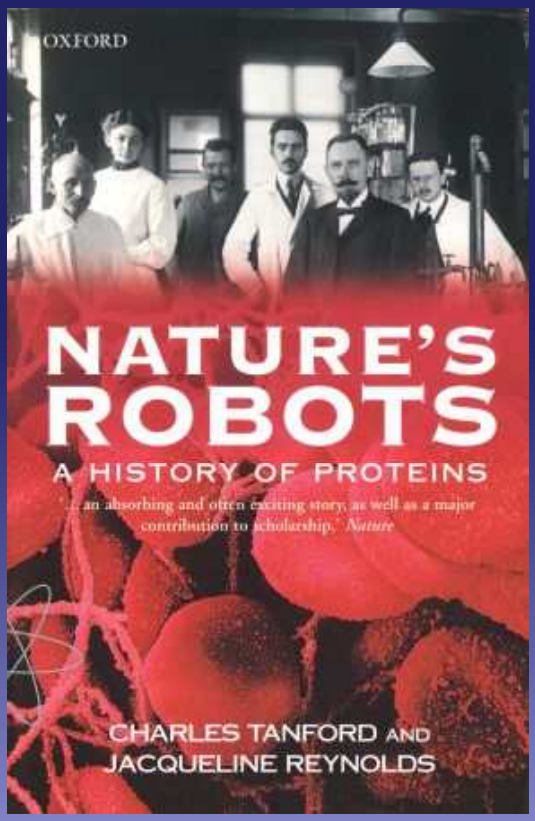
항생물질 결합부위

ADEP 분자와 결합하는 ClpP 부위의 정확한 구조

→ 향상된 신약 개발에 이용







Nature's Robots: A History of Proteins

Charles Tanford and Jacqueline Reynolds

Oxford University Press

경청해 주셔서 감사합니다