Structure-based drug discovery and development using light sources: focused on PPI using examples

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POHANG ACCELERATOR LABORATORY

신약은 다양하다.

돈이 되는 약들
돈이 안되는 약들

도움을 주는 약들
사람을 살리는 약들

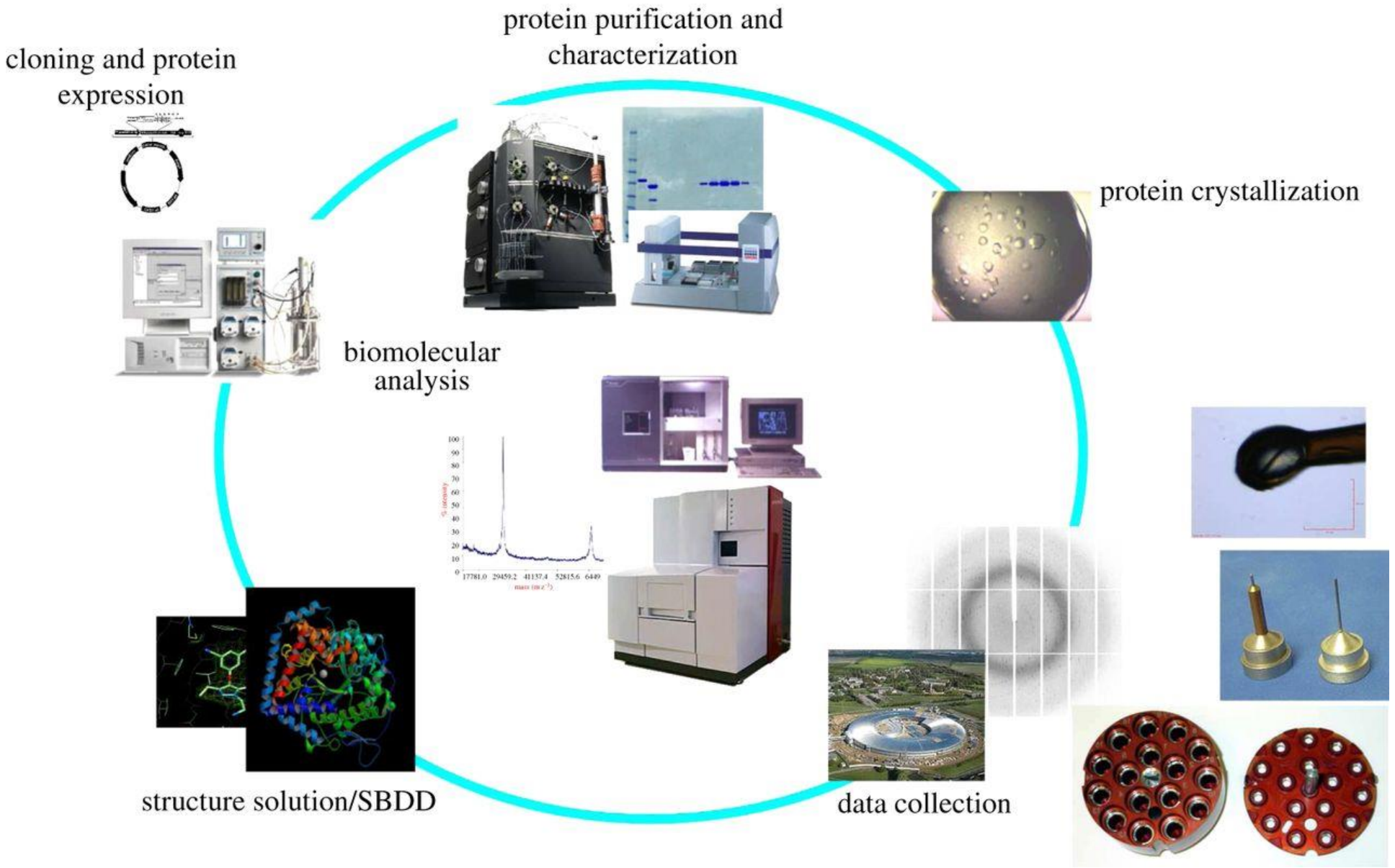
What can we do ?

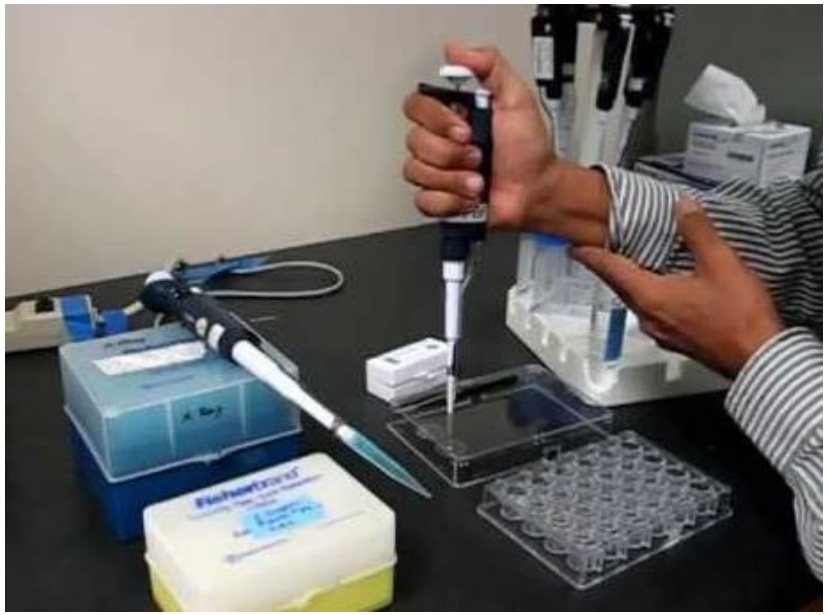
Targeting the intrinsic mechanism of pathogenic bacteria

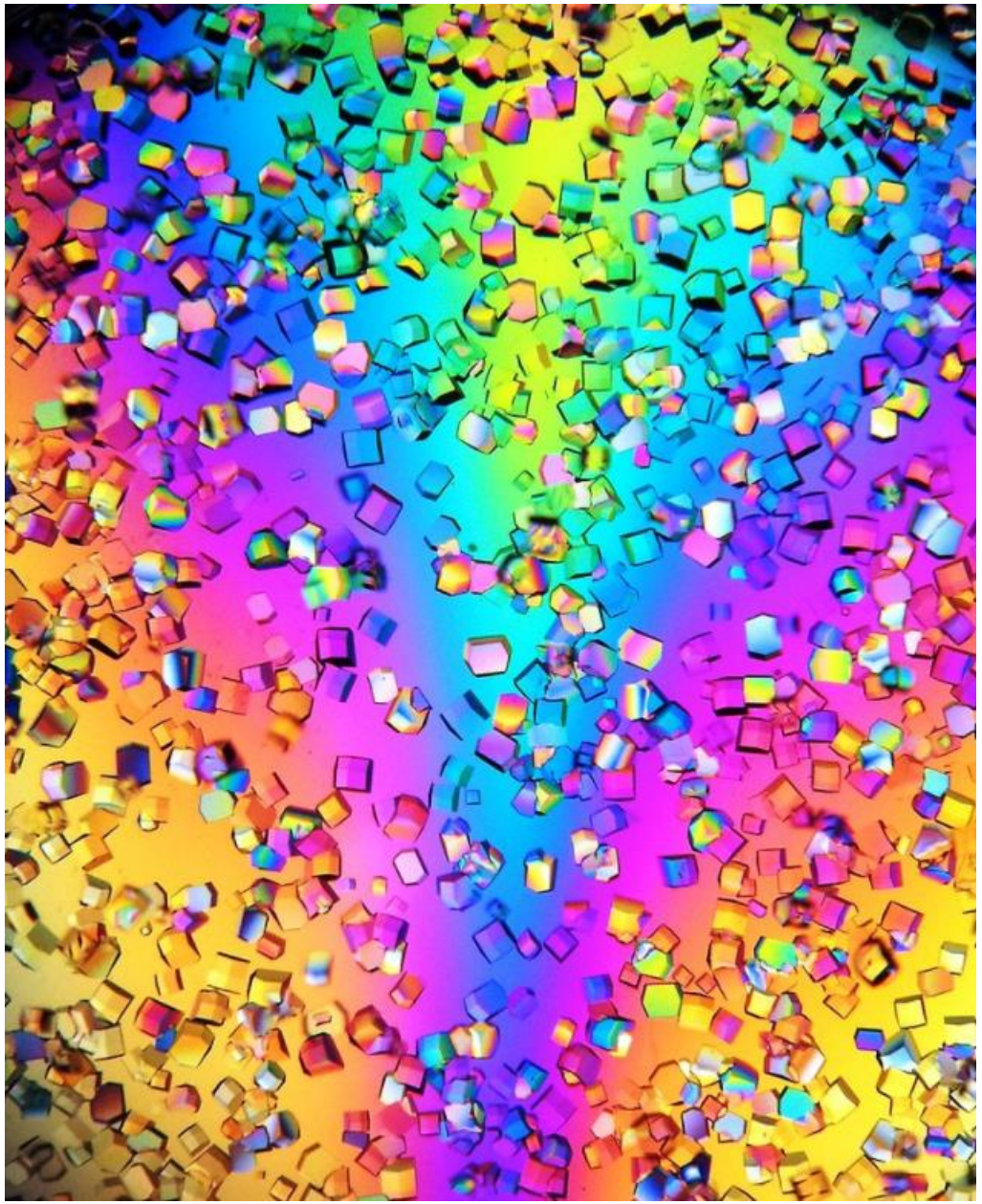
Various strategies are available

New targets

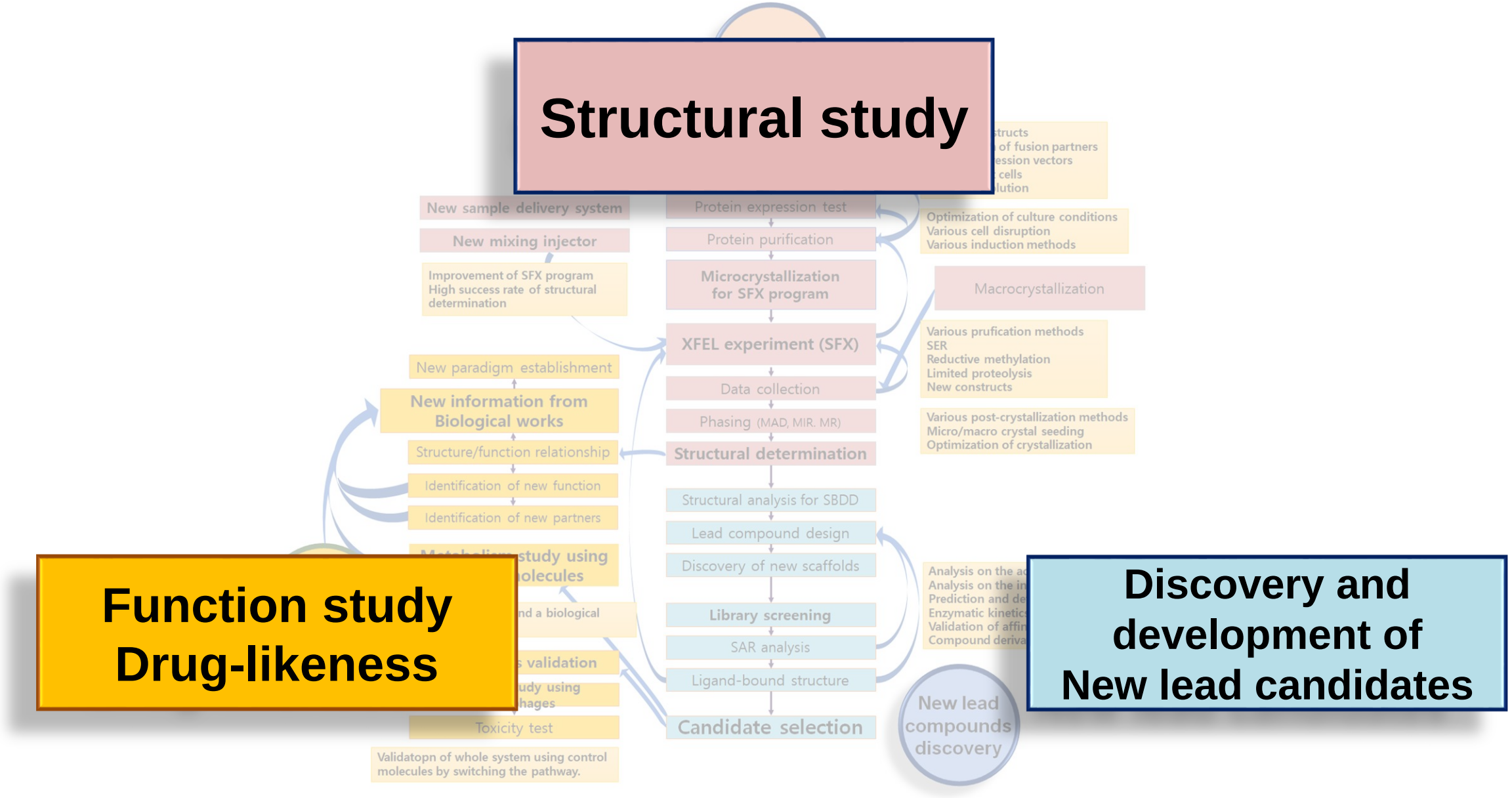
Total procedures







Procedures in detail



단백질구조를 기반한 신약개발

효소활성화 부위
(inc. coenzyme-binding site)

효소활성화 부근
단백질간 결합 부위

단백질구조를 기반한 신약개발

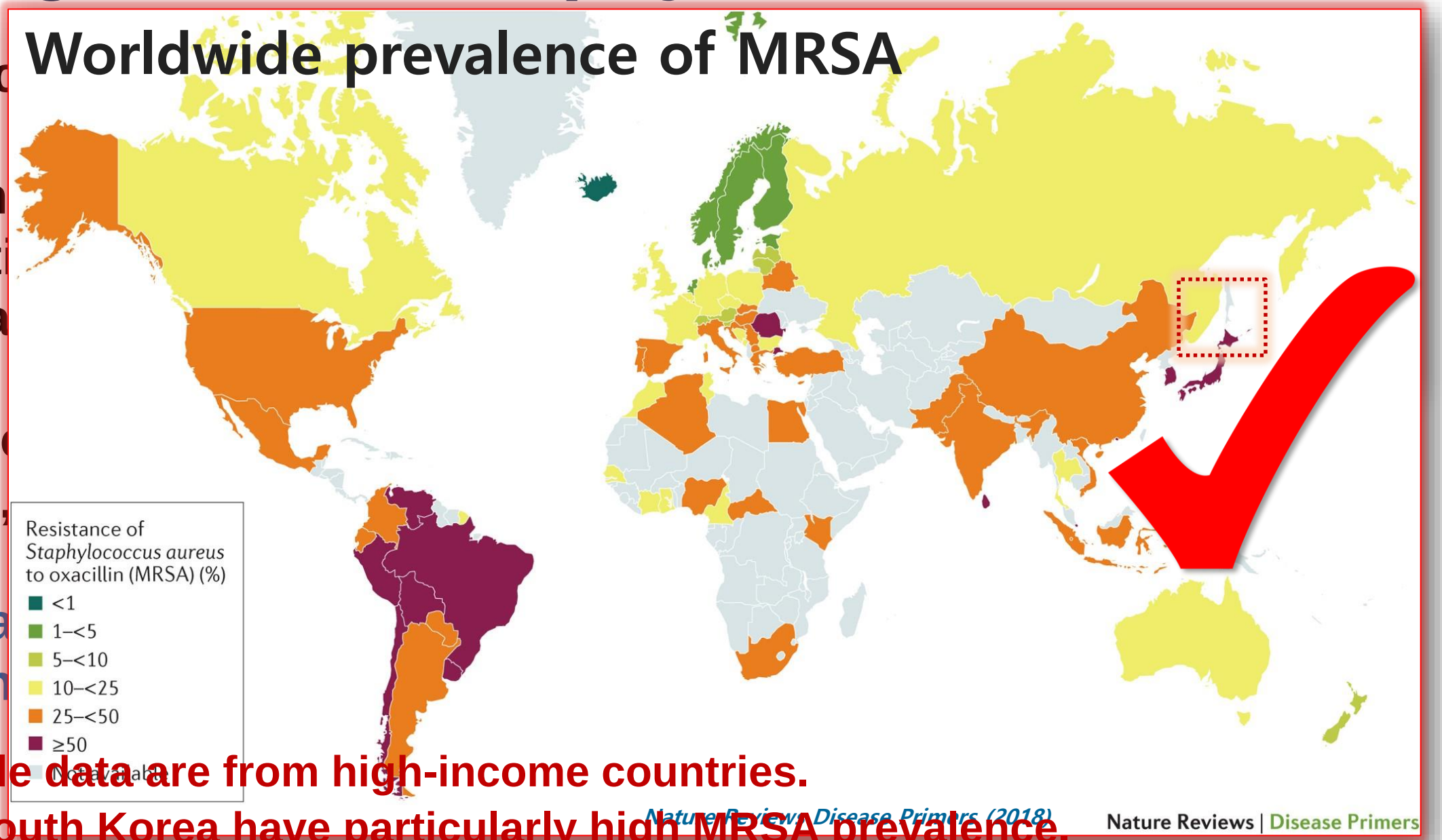
항생제, 두 가지의 전략을 모두 갖는 경우

효소활성화 부위
(inc. coenzyme-binding site)

효소활성화 부근
단백질간 결합 부위

Pathogenesis of *Staphylococcus aureus*

- ***S. aureus* c**
  minor skin
  such as pn
  endocarditi
  bacteremia
- **Its inciden**
  bone, joint,
- **It is the ma**
  acquired in

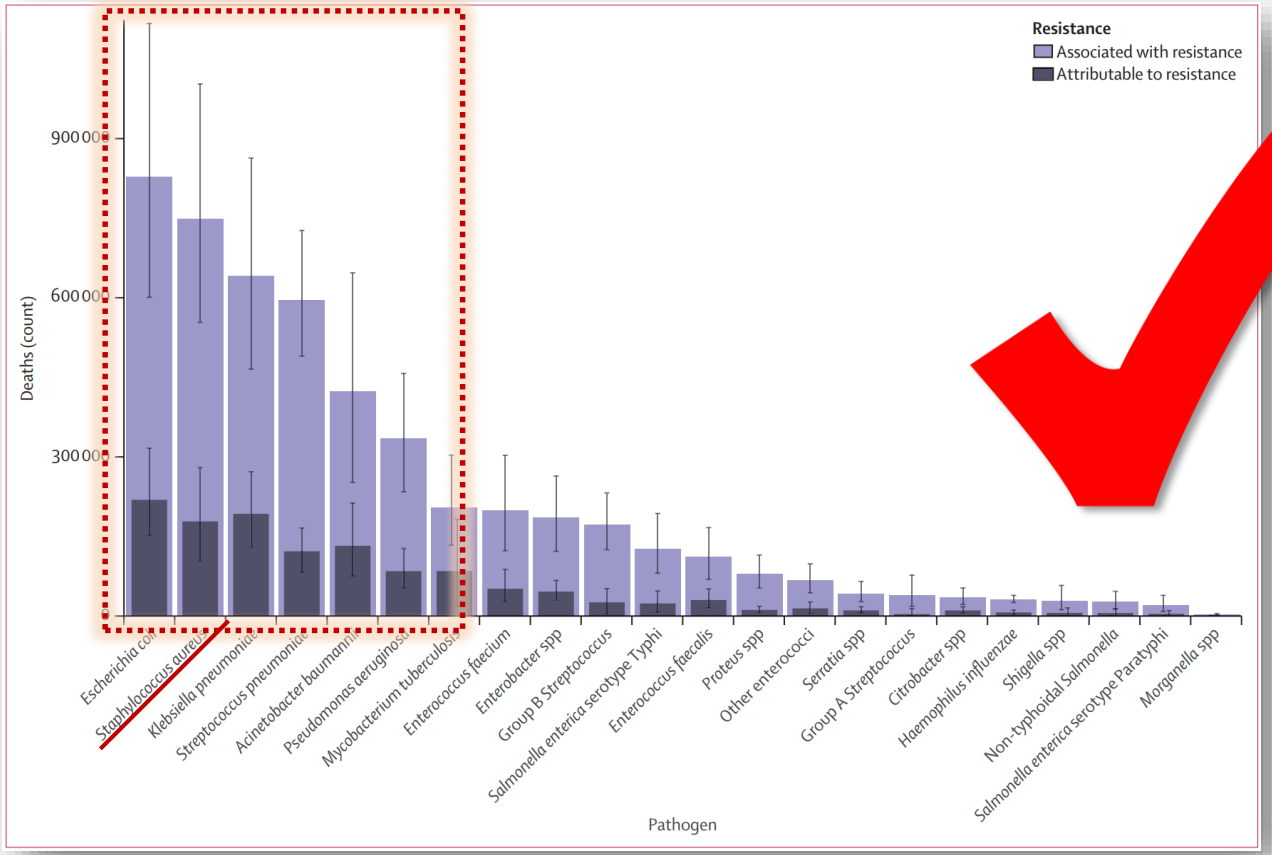


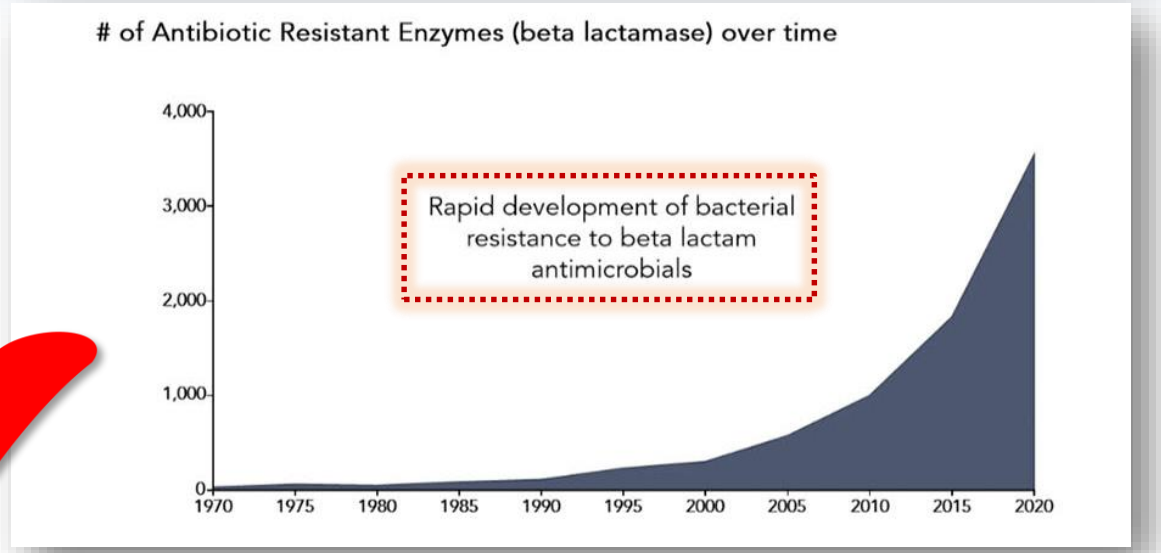
Most available data are from high-income countries.
Japan and South Korea have particularly high MRSA prevalence.

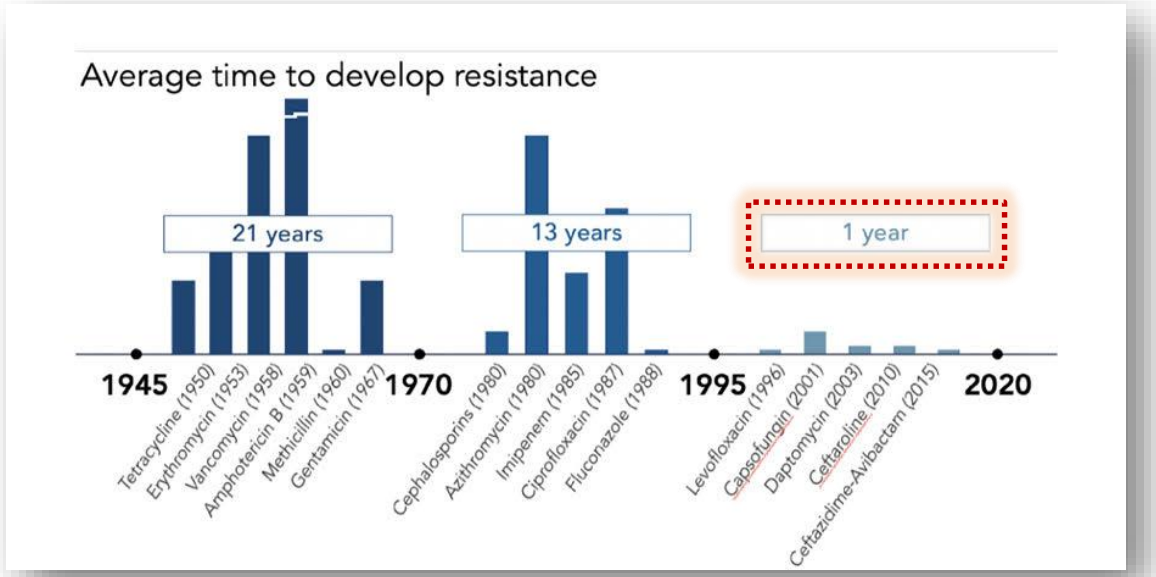
Nature Reviews Disease Primers (2018)

Global burden of bacterial antimicrobial resistance

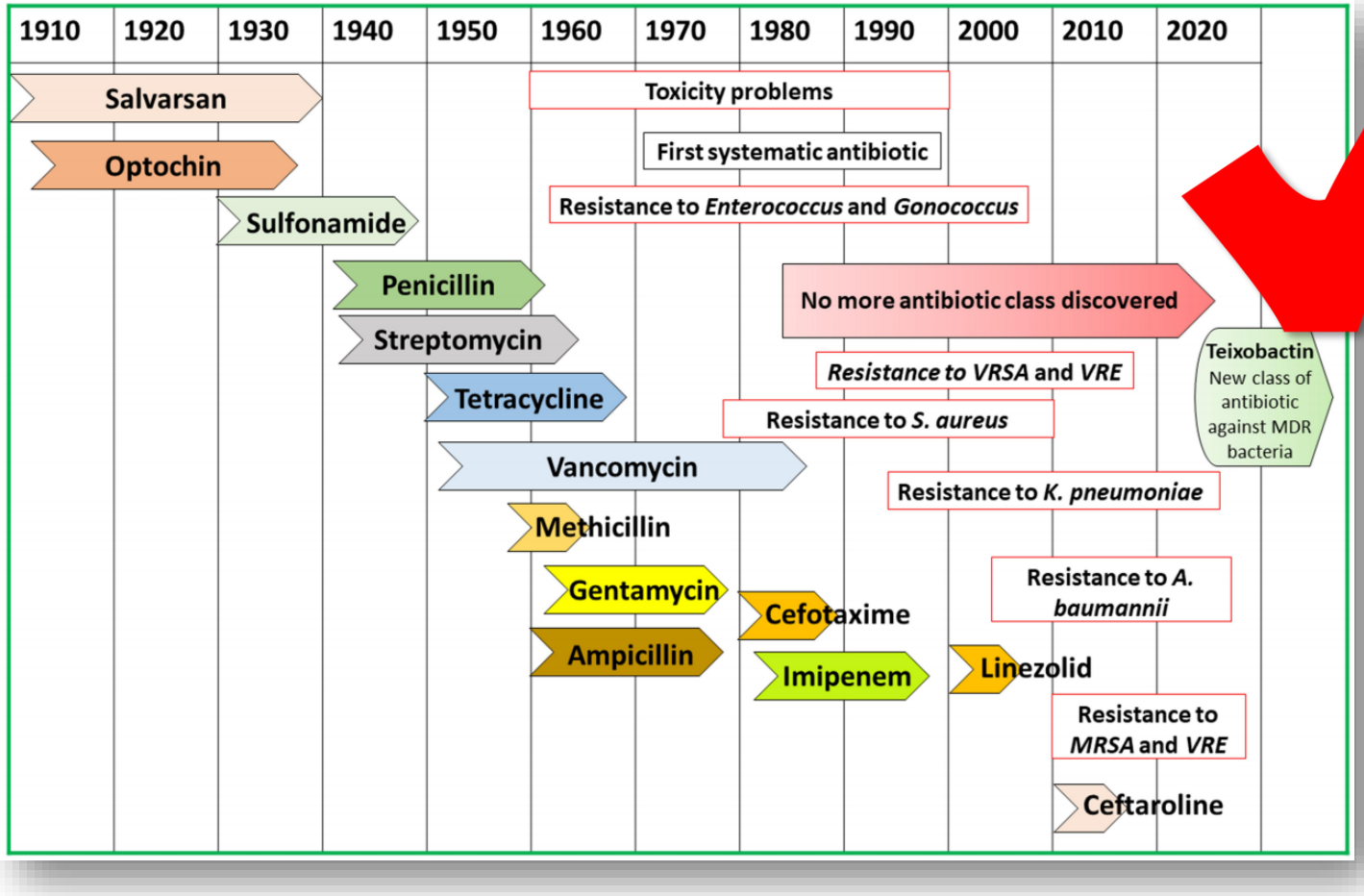
Global deaths attributable to and associated with bacterial antimicrobial resistance by pathogen

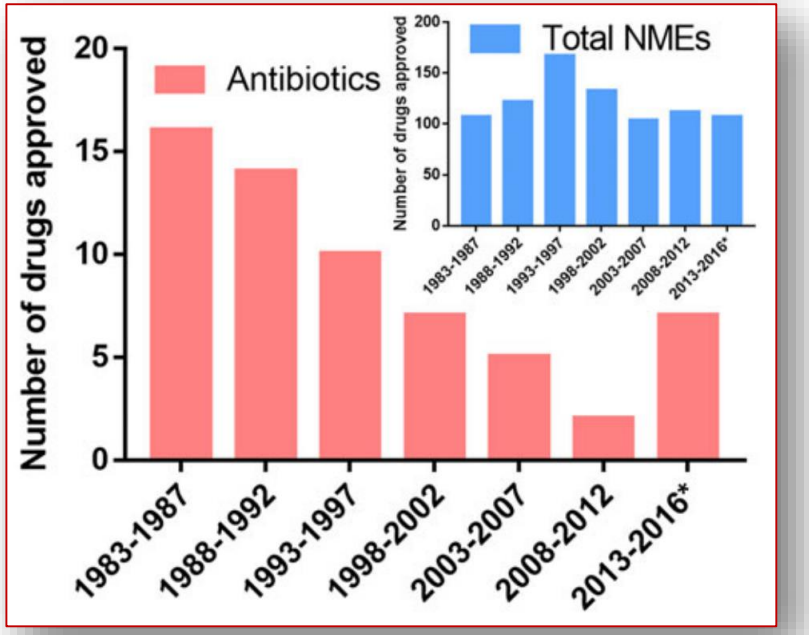






The development of new antibacterial drugs is lagging behind the increasing rate of antibiotic resistance.





We need novel antibiotics against new targets

- **Capitalists are commercial.**

THE BIG ISSUE

- **Many of the currently used antibiotics will sooner or later become ineffective due to the acquisition of resistance mechanisms by pathogenic bacteria.**

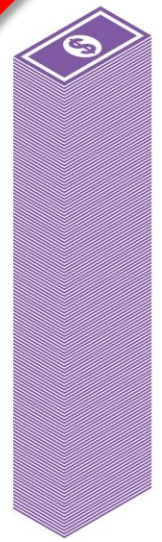
Source: Renwick MJ, Simpkin V, Mossialos E, International and European Initiatives Targeting Innovation in Antibiotic Drug Discovery and Development, The Need for a One Health – One Europe – One World Framework, Report for the 2016 Dutch Presidency of the European Union.

ANTIMICROBIAL R&D IS NOT ATTRACTIVE TO VENTURE CAPITALISTS

Less than 5%

of venture capital investment in pharmaceutical R&D between 2003 and 2013 was for antimicrobial development.

Review on Antimicrobial Resistance



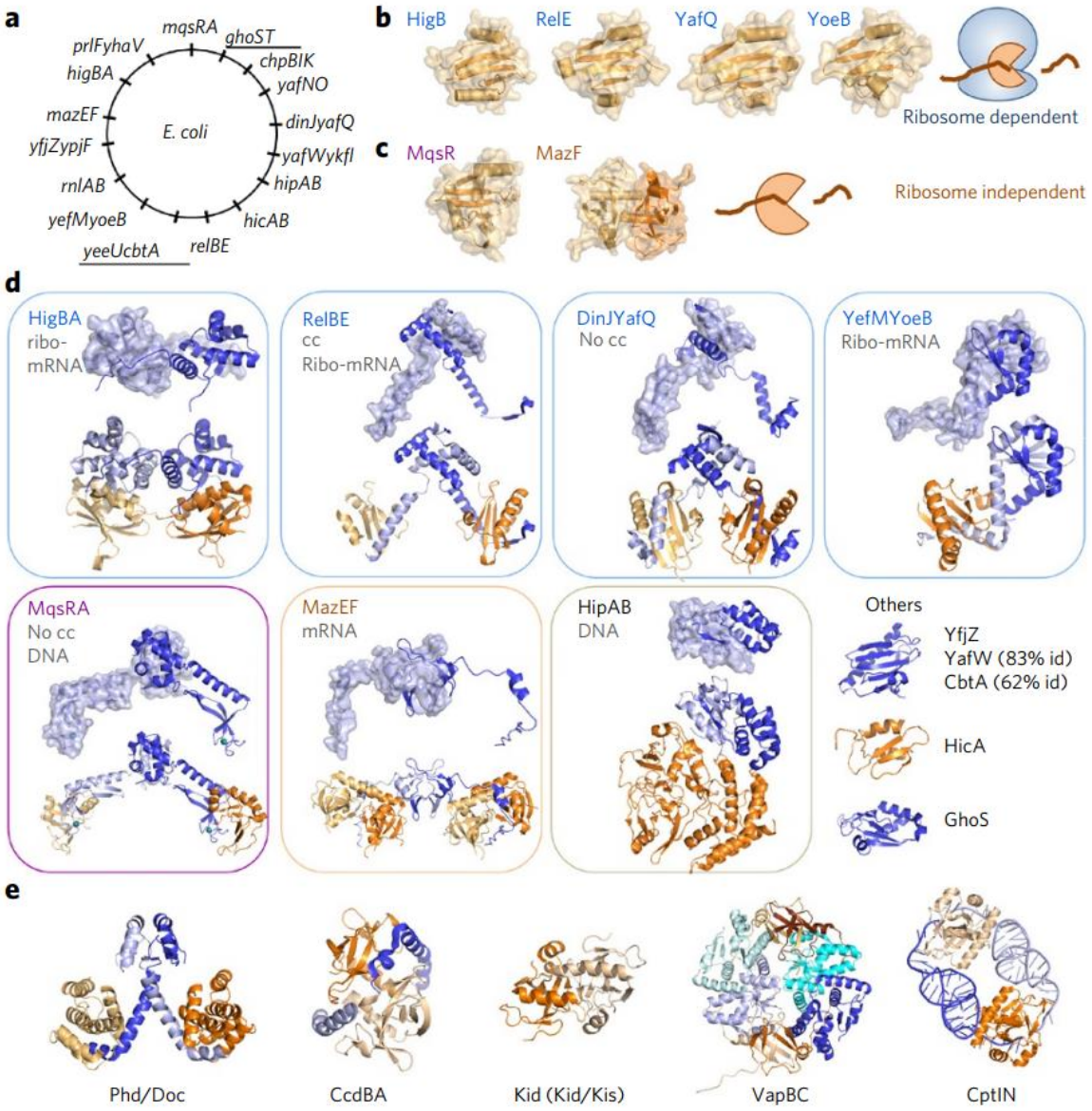
Total venture capital investment

$38bn

Antimicrobial venture capital investment

$1.8bn

Toxin-antitoxin systems in bacteria



TA systems in *E. coli* *Nat Chem Biol* (2016)

Many kinds of toxin-antitoxin systems exist in bacteria.

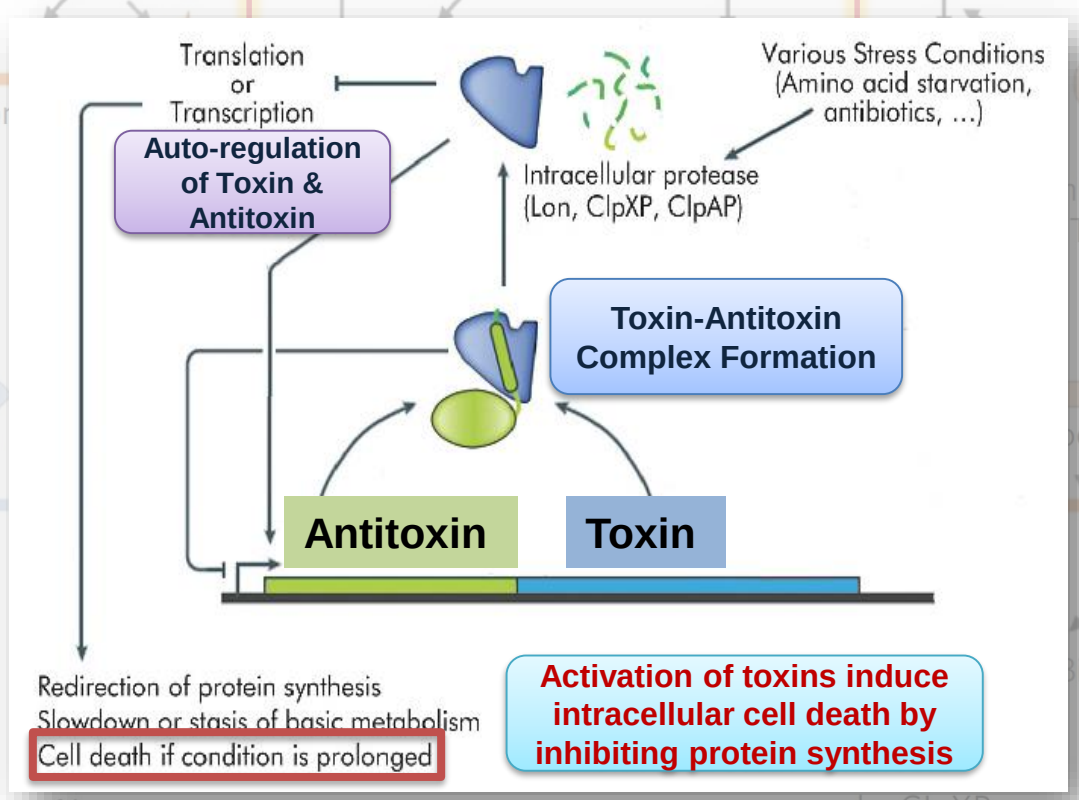
→ No human proteins

→ They are essential to their survival.

High specificities with distinct structural features

Toxin-antitoxin systems in bacteria

Toxin-antitoxin systems



Nat Chem Biol (2016)

Elimination of persisters

→ Reduction of the number of recurrent infections

→ benefit of reducing the number of antibiotic-resistant mutations

Possible approaches

Inhibition of the toxins

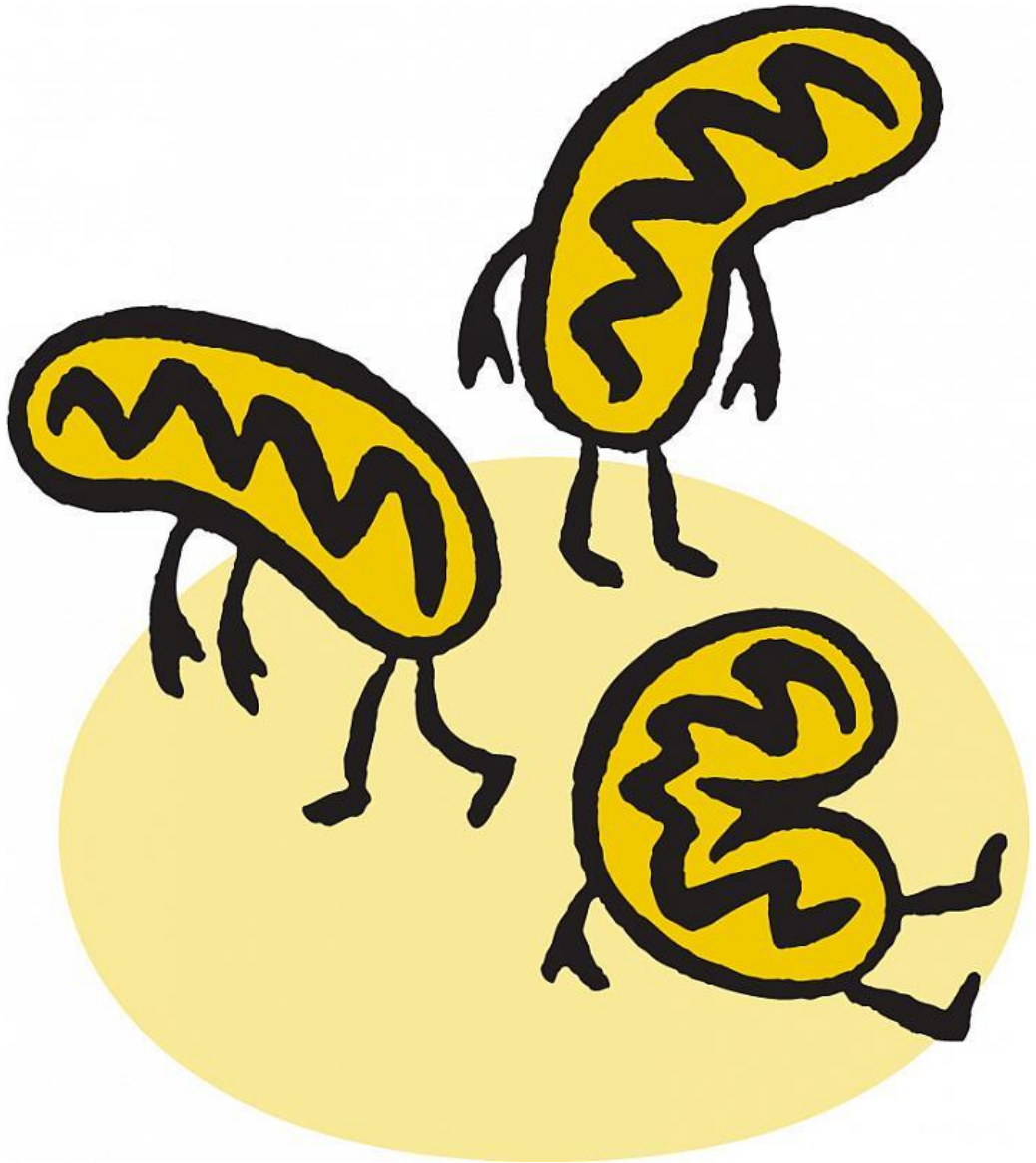
→ inhibiting entry into growth arrest

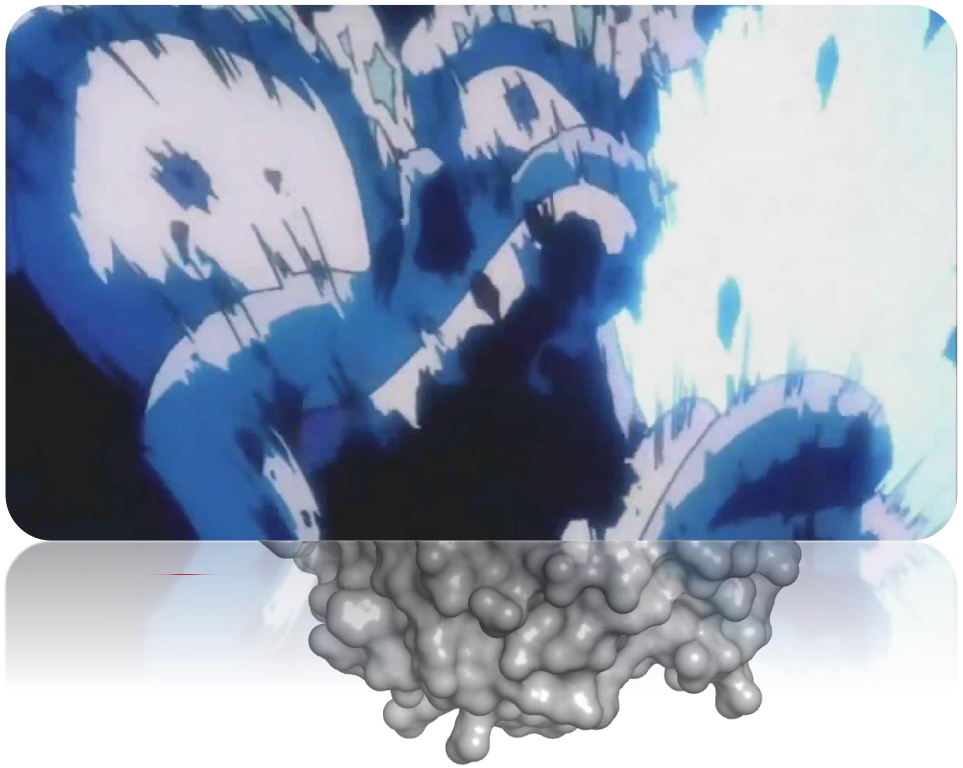
Dissociation of TA complexes

→ Activation of toxins, leading to cell death

PemIK toxin–antitoxin complex from *S. aureus*

- **To dissociate toxin-antitoxin complexes for activation of toxins, leading to cell death**





Nucleic Acids Research (2022) 50(4):2319–2333

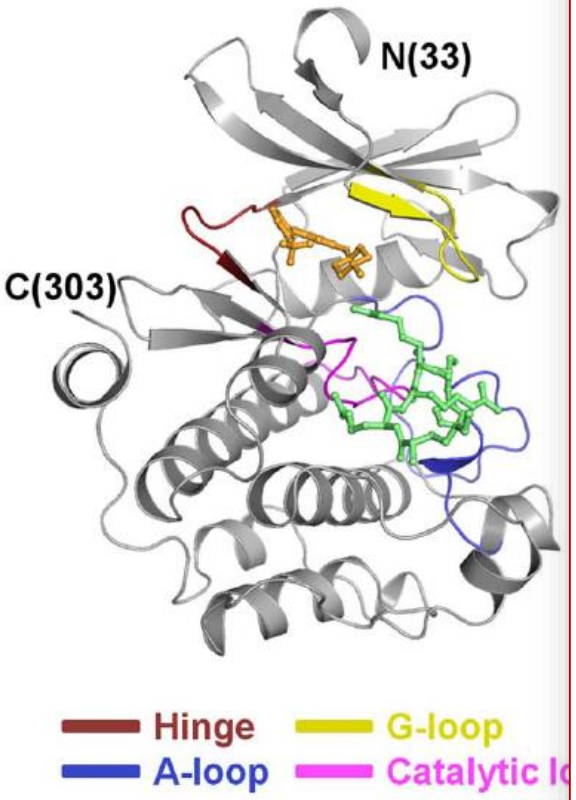
단백질구조를 기반한 신약개발

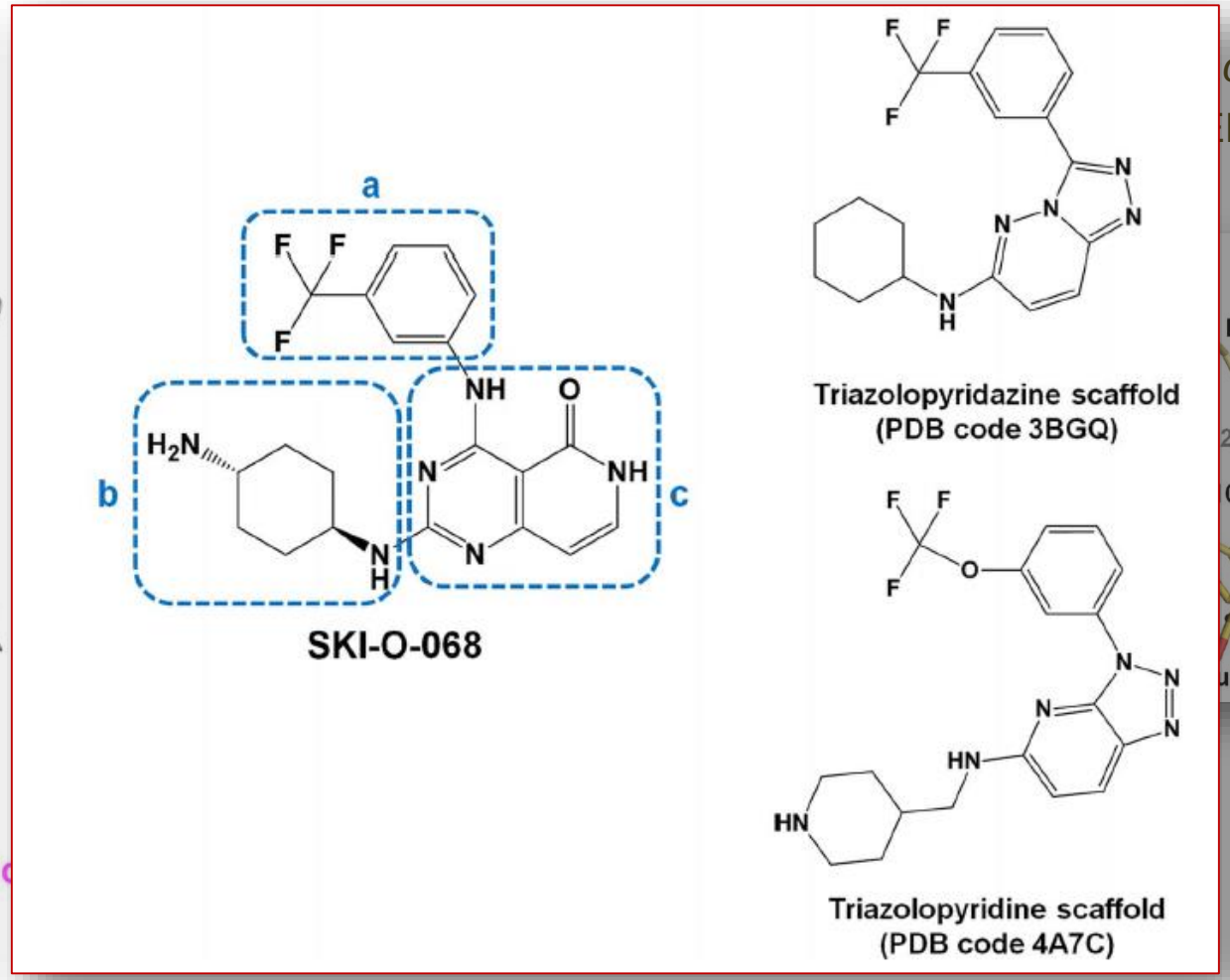
항암제

효소활성화 부위
(inc. coenzyme-binding site)

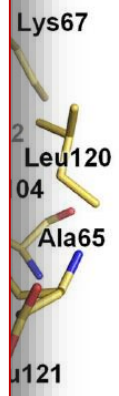
Structure-based drug design (SBDD)

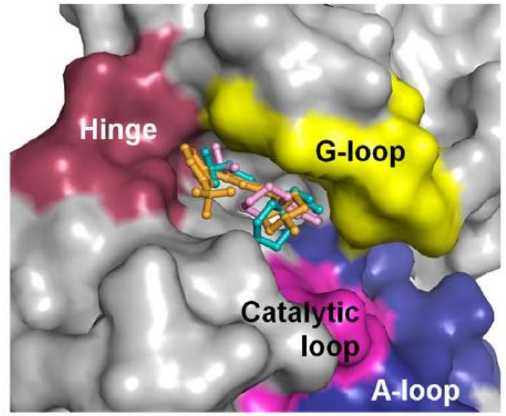
Design of new anti-cancer candidate based upon Human Pim1 kinase structure





oS One (2013) 8(7):e70358
BS Journal (2016) 283:3613–3625





FBDD
(3세대 구비)

단백질구조를 기반한 신약개발

웰빙약물

효소활성화 부위
(inc. coenzyme-binding site)

Human NSDHL

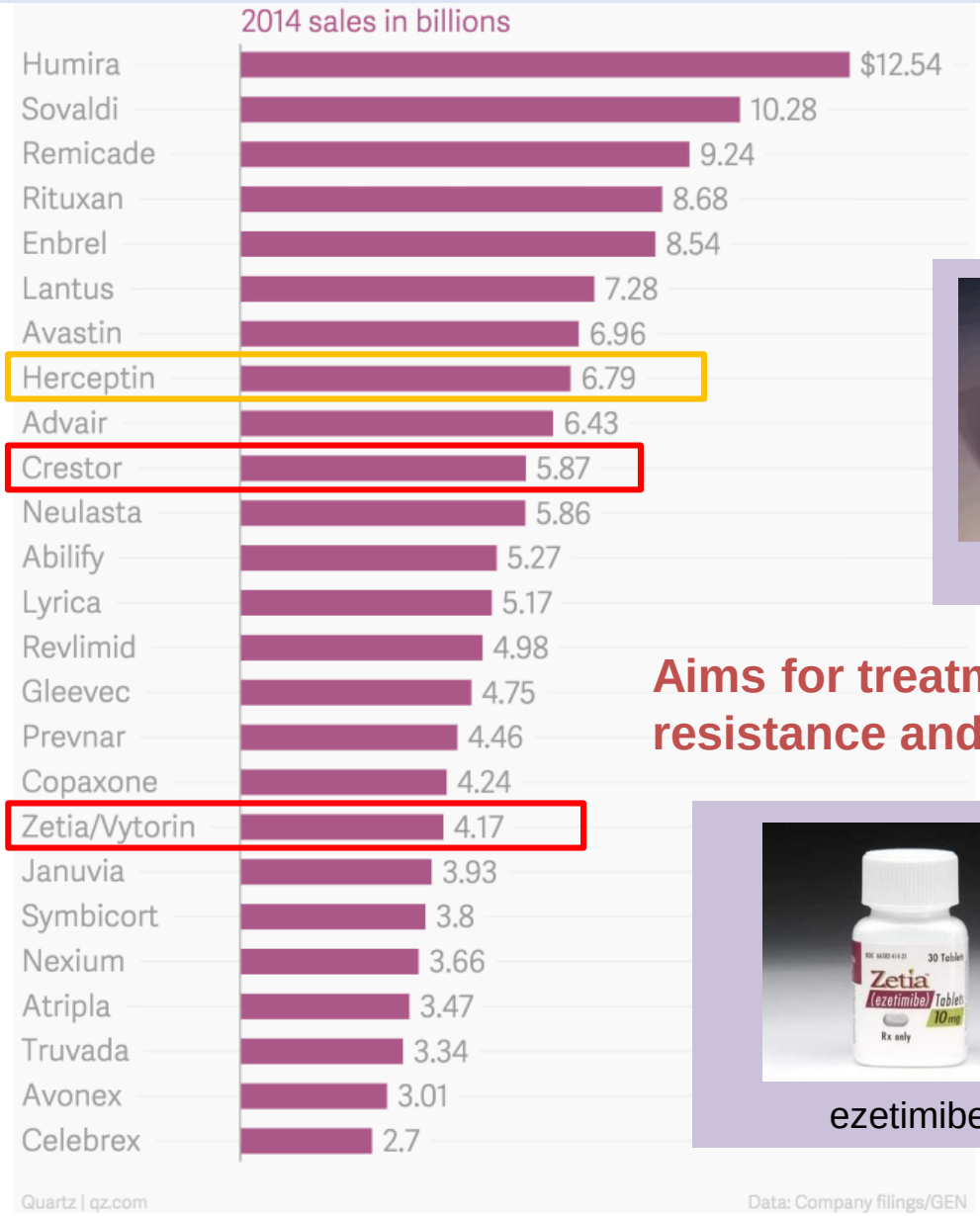
Human cholesterol biosynthesis

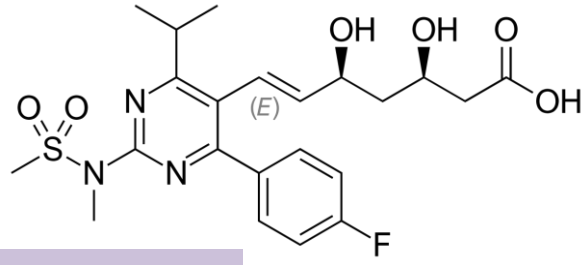
Cancers

Hypercholesterolemia

Human CHILD and CK syndromes

SC4MOL HSD17B7

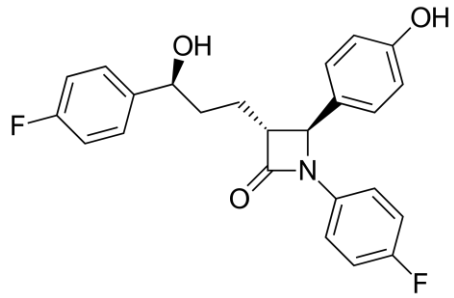




Rosuvastatin

Aims for treatment of EGFR-targeted drugs resistance and hypercholestrolemia

ezetimibe



Human NSDHL

NSDHL

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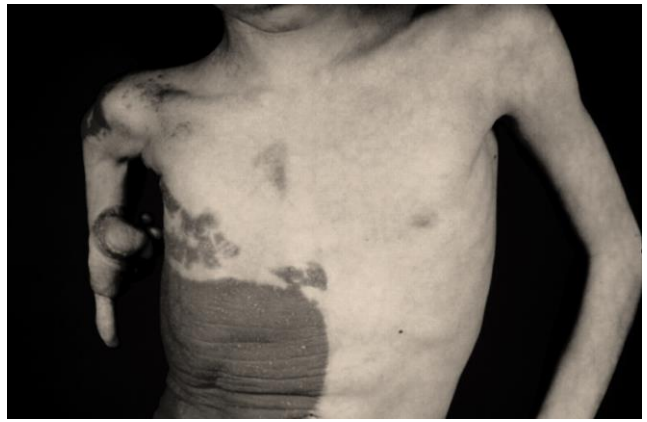

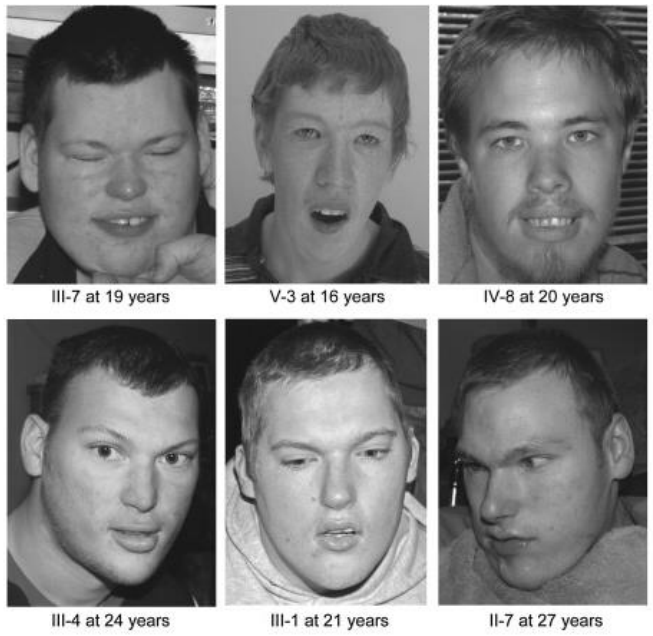

CHILD syndrome

Congenital hemidysplasia with ichthyosiform erythroderma and limb defects
Genetic disorder
Site-mutations in NSDHL
(A105V, A182P, G205S)

CK syndrome

X-linked recessive intellectual disability syndrome
Genetic disorder
Deletion in NSDHL
(K232Δ)

Am J Hum Genet. 2010 Dec 10;87(6):905-14

Human NSDHL

Differential Scanning Fluorimetry study on the mutants

Human cholesterol biosynthesis

Cancers

Hypercholesterolemia

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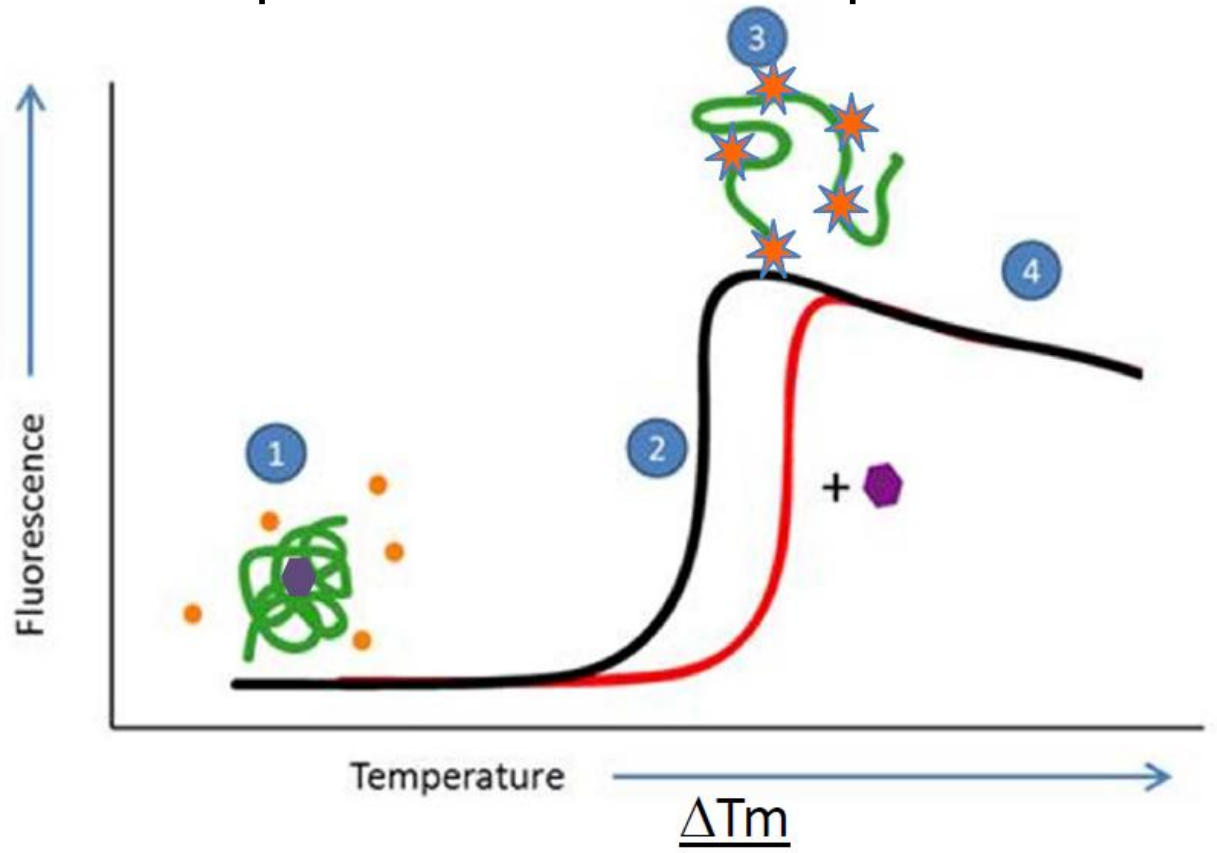
SC4MOL
HSD17B7

The temperature at which a protein unfolds is measured by an increase in the fluorescence of a dye with affinity for hydrophobic parts of the protein, which are exposed as the protein unfolds.



Human NSDHL

Human cholesterol biosynthesis

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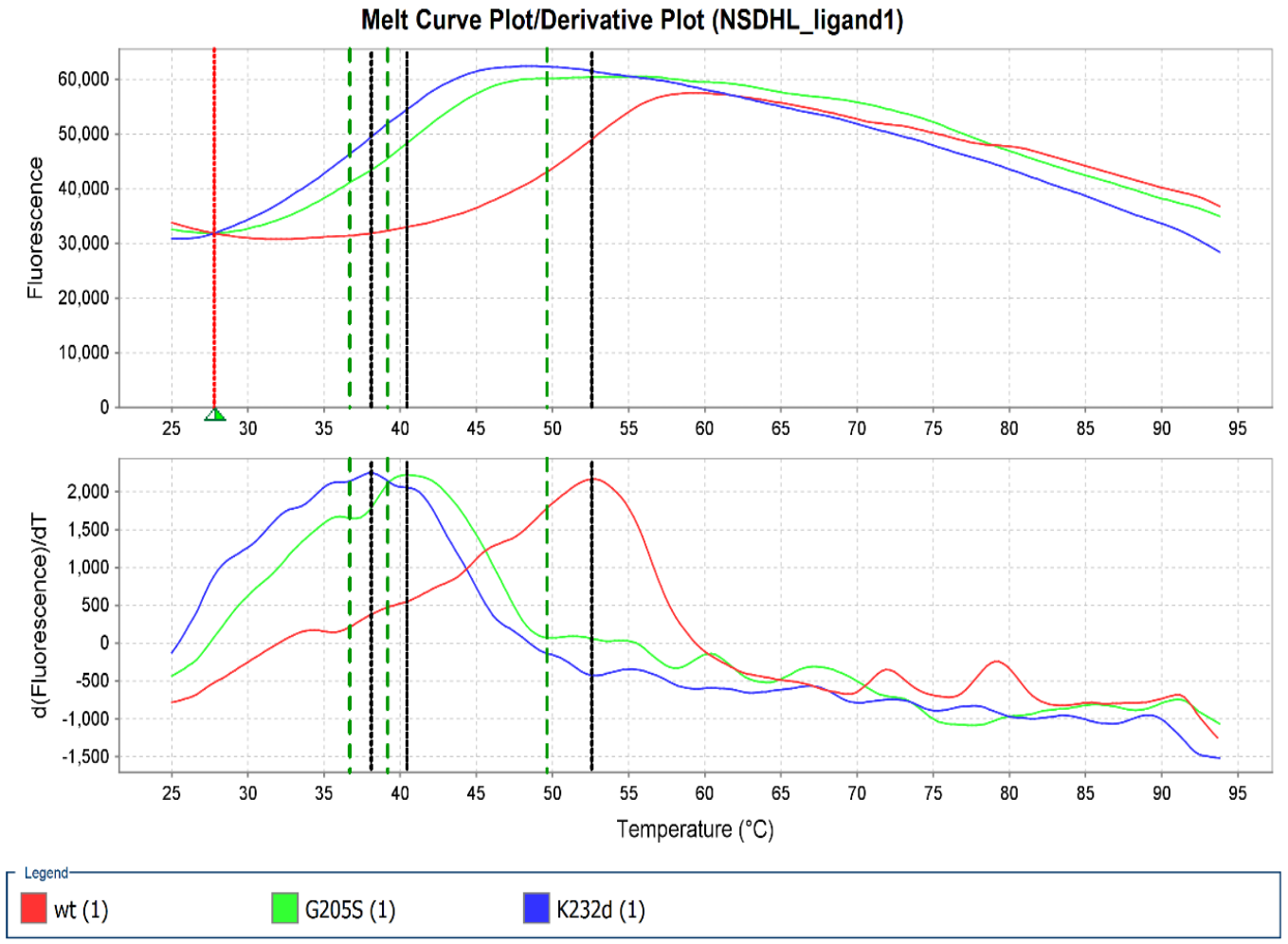


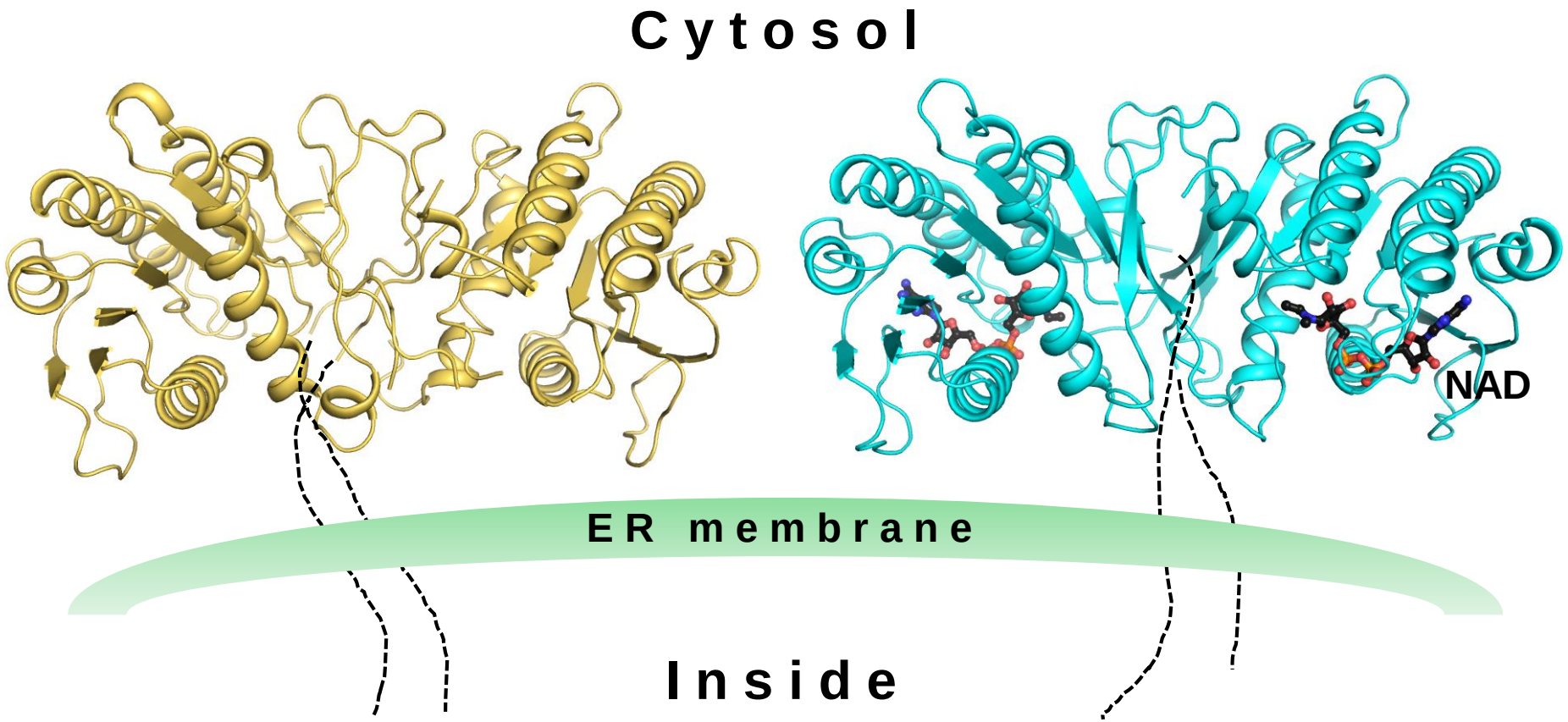
Tm (℃)

Wild type = 50

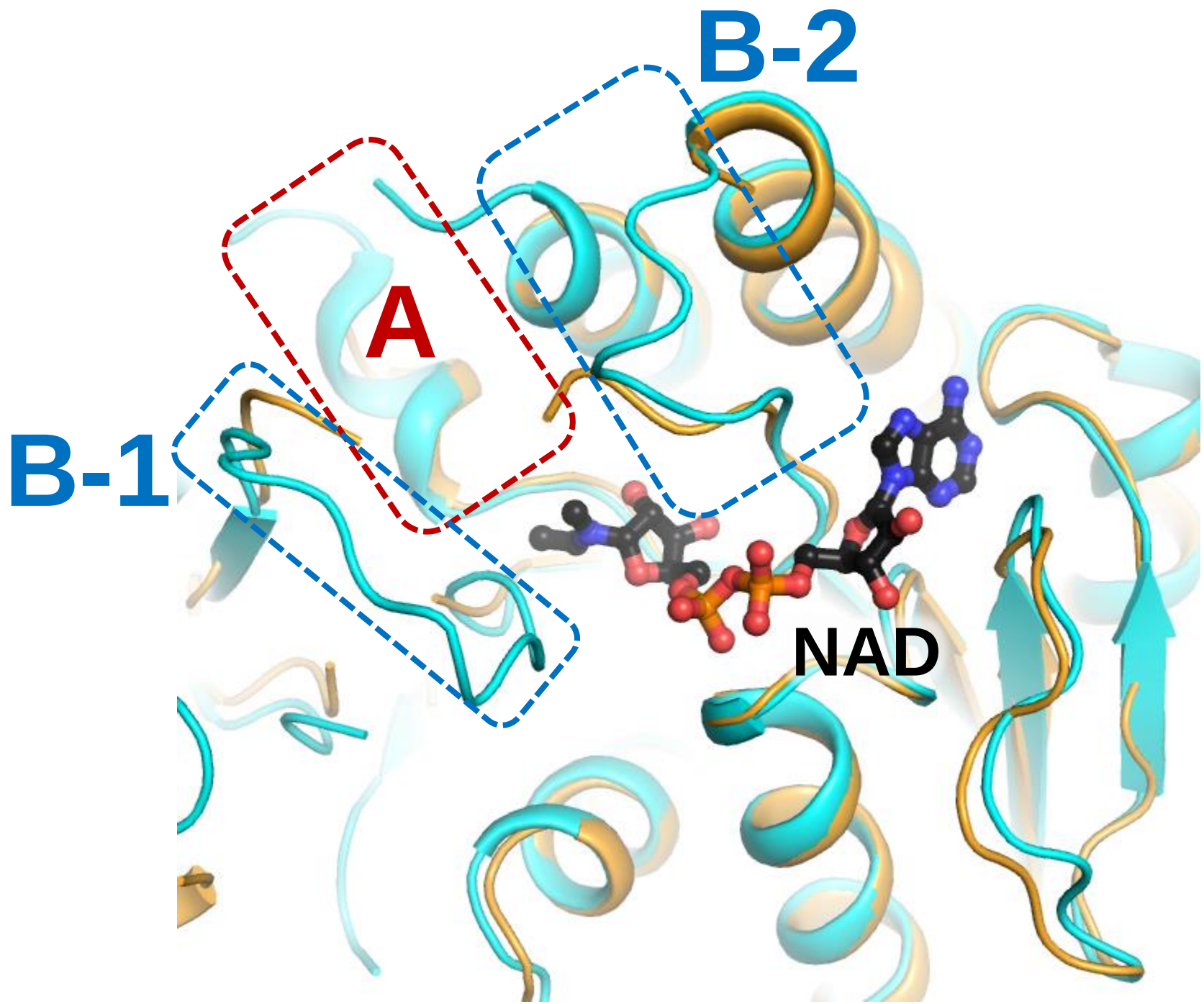
G205S = 39

K232Δ = 38

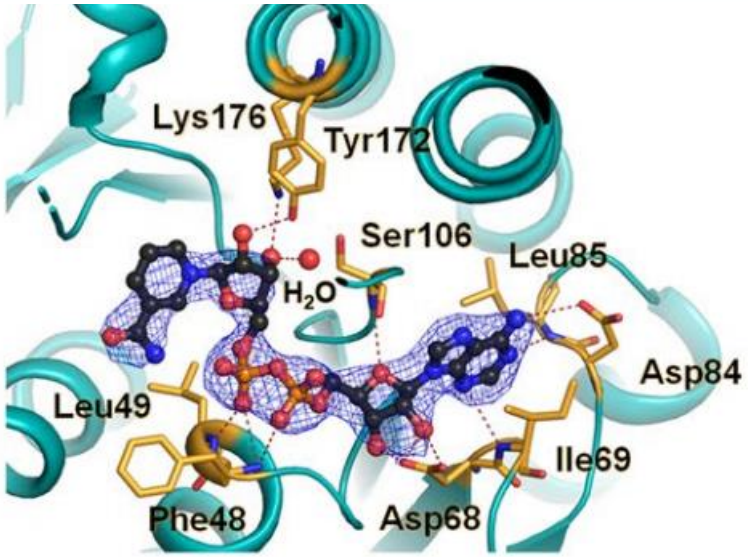
Human NSDHL (related to CHILD syndrom)

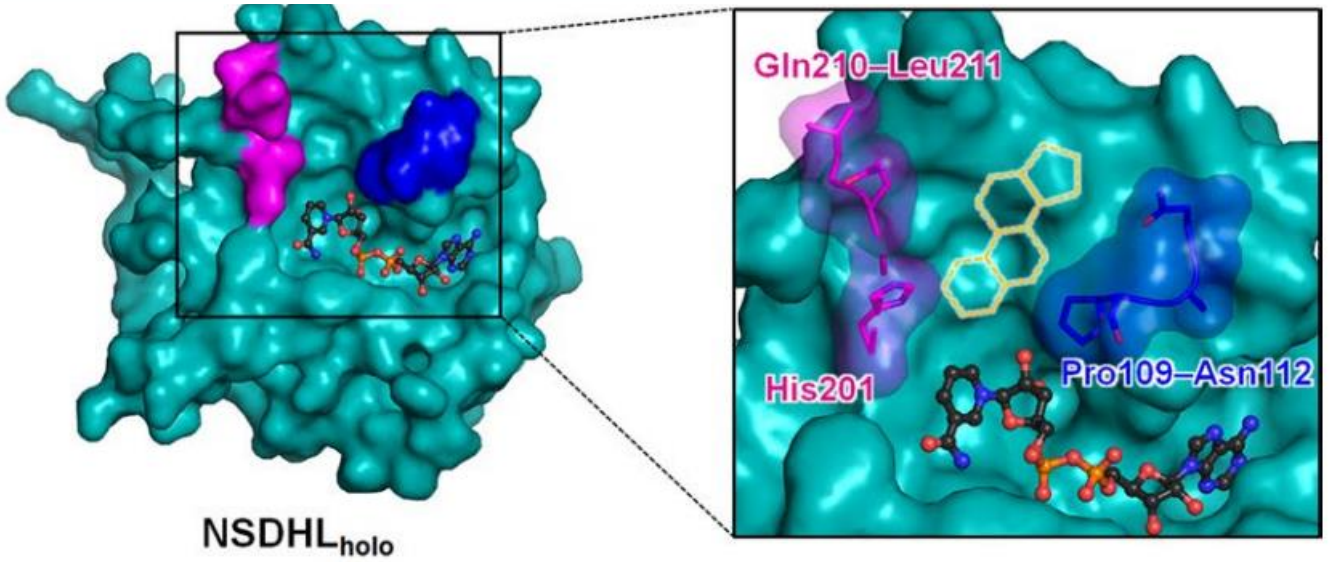


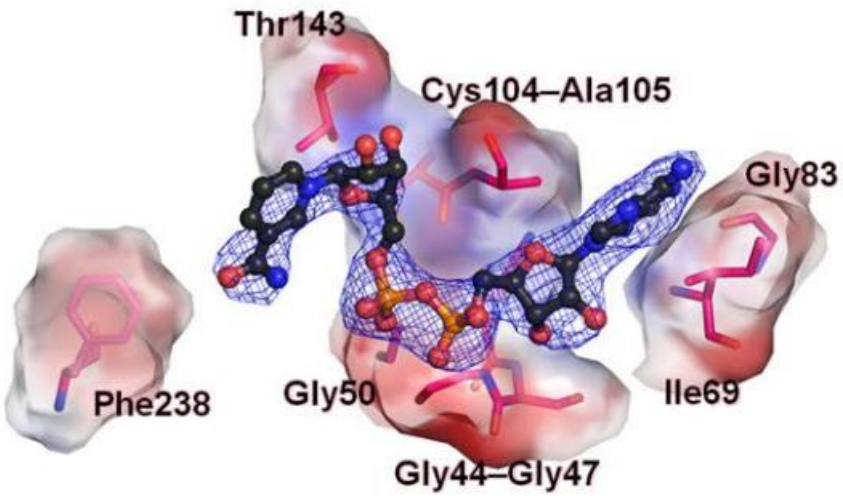
Cellular and Molecular Life Sciences (2021) 78:207–225

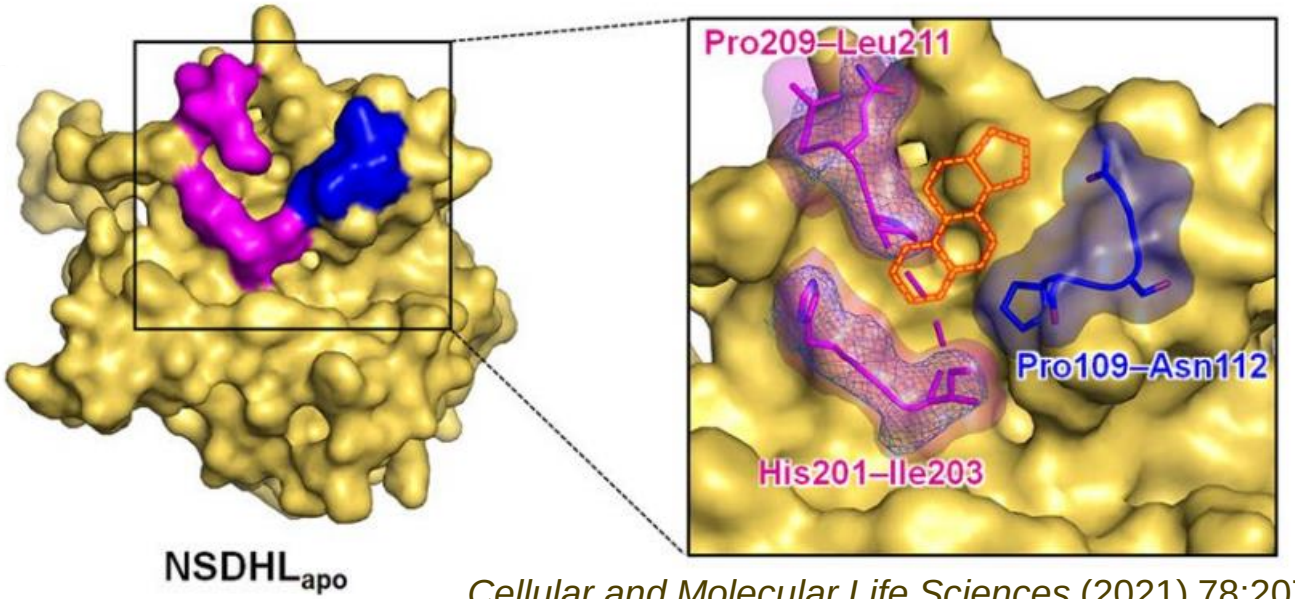

B-2
A
B-1
NAD

Human NSDHL (related to CHILD syndrom)



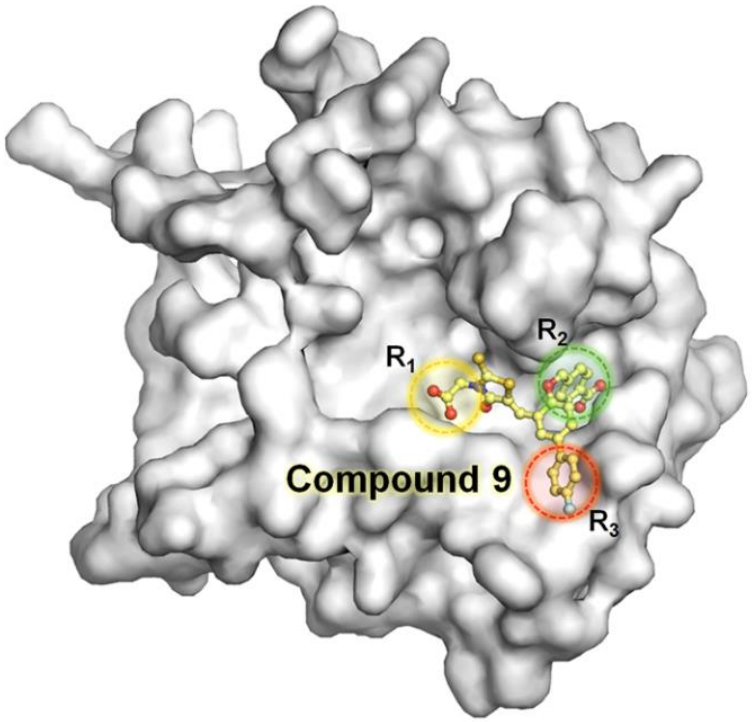


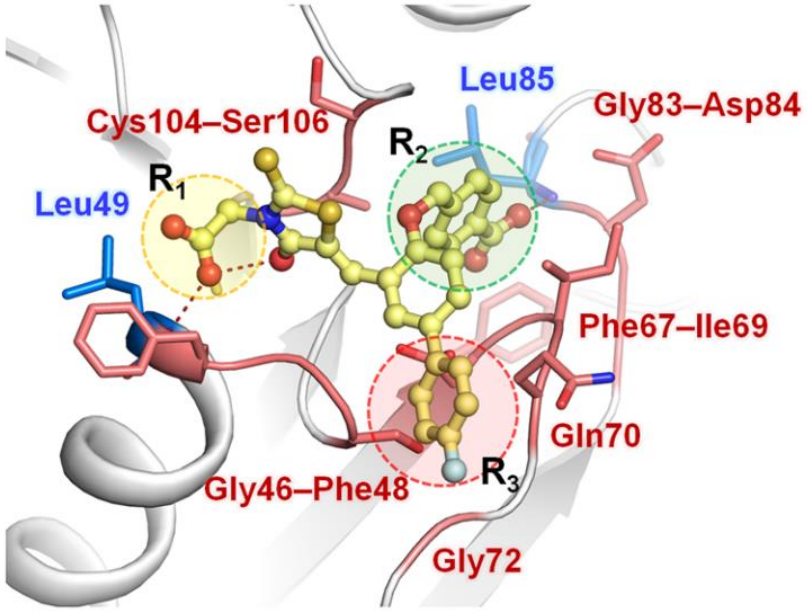


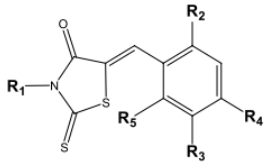


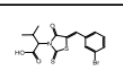
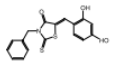
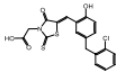
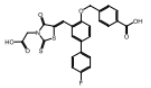
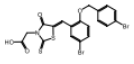
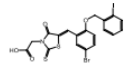
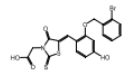
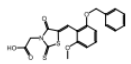
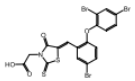
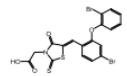
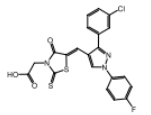
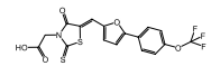
Cellular and Molecular Life Sciences (2021) 78:207–225

Human NSDHL (anti-hypercholesterolemia)







Cpd	Structure	R_1	R_2	R_3	R_4	R_5	IC_{50} (μM)	$LogIC_{50}$ ± S.E. (μM)	K_i (μM)
5			-	Br	-	-	39.33	1.59 ± 0.08	13.70
38			OH	-	OH	-	30.71	1.48 ± 0.03	10.70
6			OH		-	-	70.59	1.85 ± 0.11	24.59
9					-	-	8.42	0. 93 ± 0.10	2.93
12				Br	-	-	20.99	0. 96 ± 0.09	7.31
16				Br	-	-	27.13	1.43 ± 0.03	9.45
17				-	OH	-	20.79	1.32 ± 0.08	7.24
31				-	-		19.85	1.30 ± 0.05	6.91
13				Br	-	-	46.95	1.77 ± 0.07	16.35
14				-	Br	-	36.96	1.57 ± 0.07	12.87
32							11.56	1.11 ± 0.03	4.03
35							24.49	1.39 ± 0.07	8.53

Cellular and Molecular Life Sciences (2021) 78:207–225

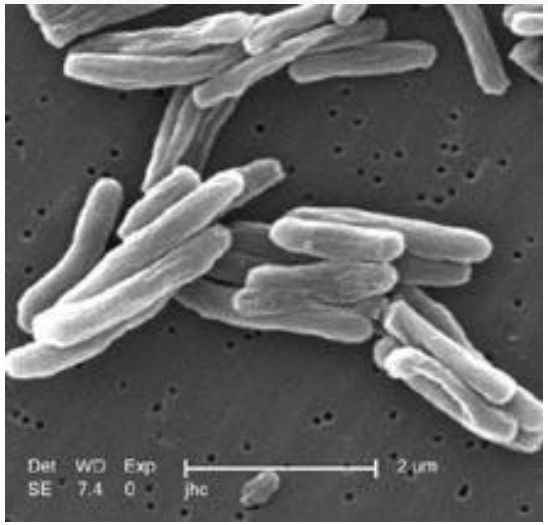
단백질구조를 기반한 신약개발

항생제

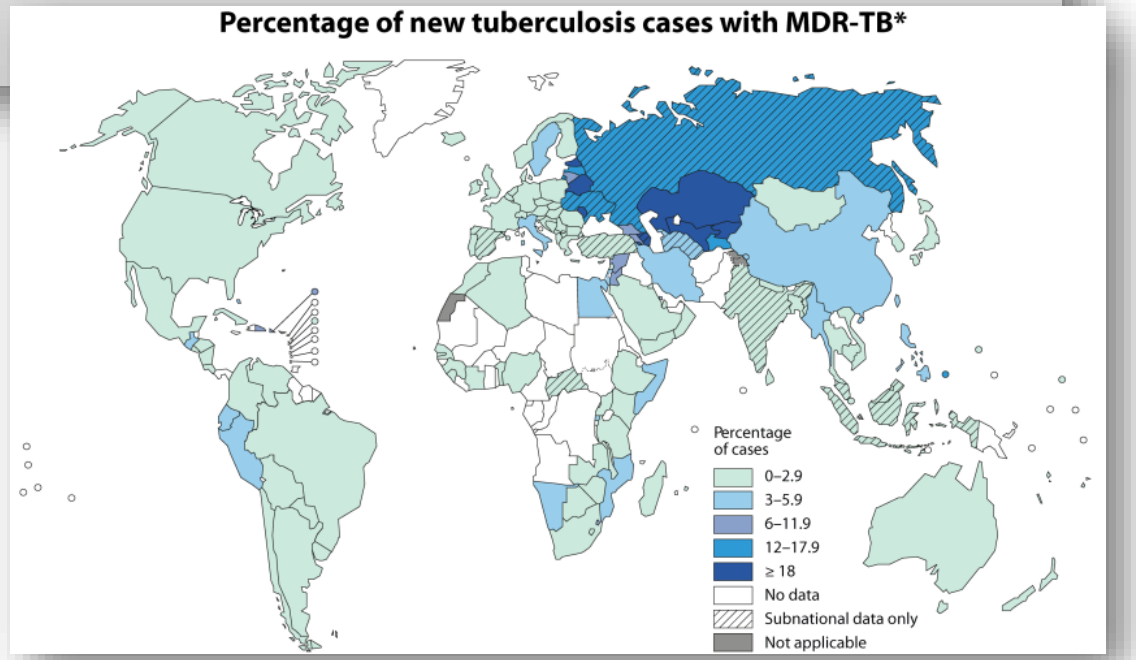
효소활성화 부위
(inc. coenzyme-binding site)

Why *Mycobacterium tuberculosis* (MTB)?

- Pathogen of the respiratory system
- One-quarter of the world's population is infected with MTB
- Tuberculosis (TB) is one of the top 10 causes of death worldwide.
- In 2017, 10 million people fell ill with TB, and 1.6 million died from the disease (including 0.3 million among people with HIV)
- Approximately new 350,000 MDR-TB (Multi-drug resistant tuberculosis) cases occur annually worldwide.



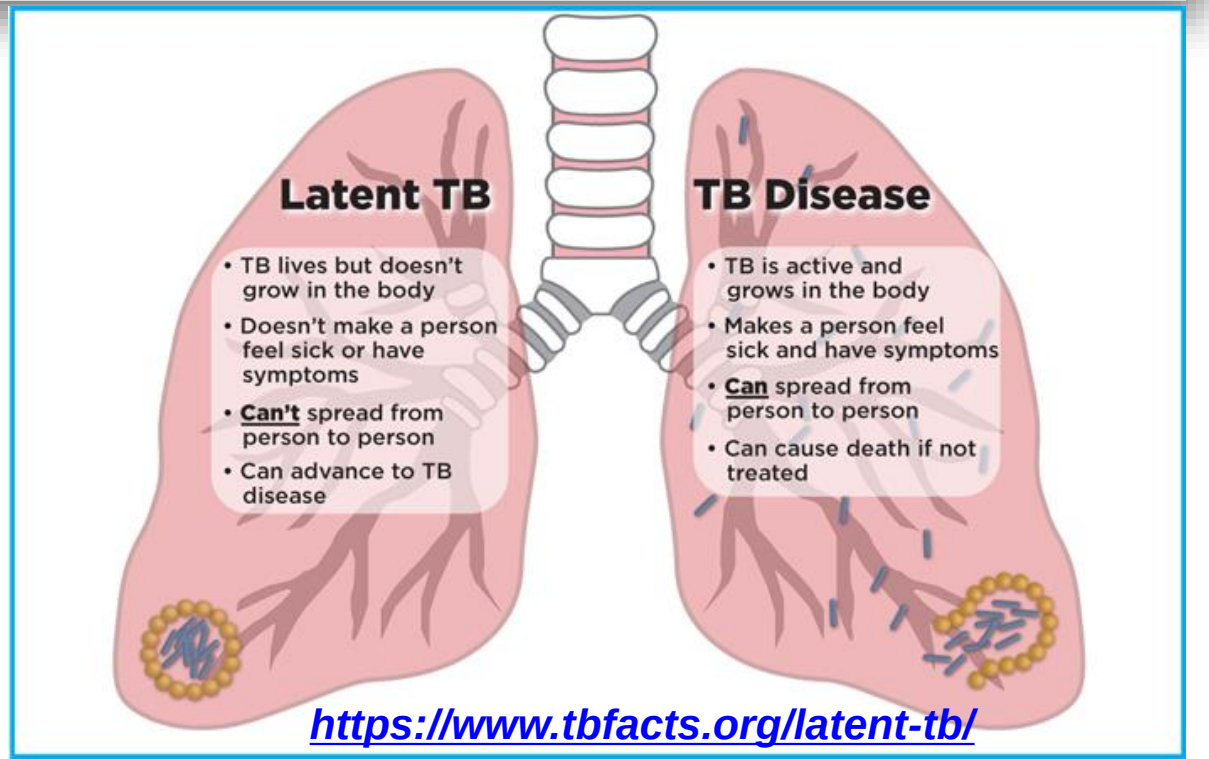
Wikipedia



Global tuberculosis report 2012, WHO

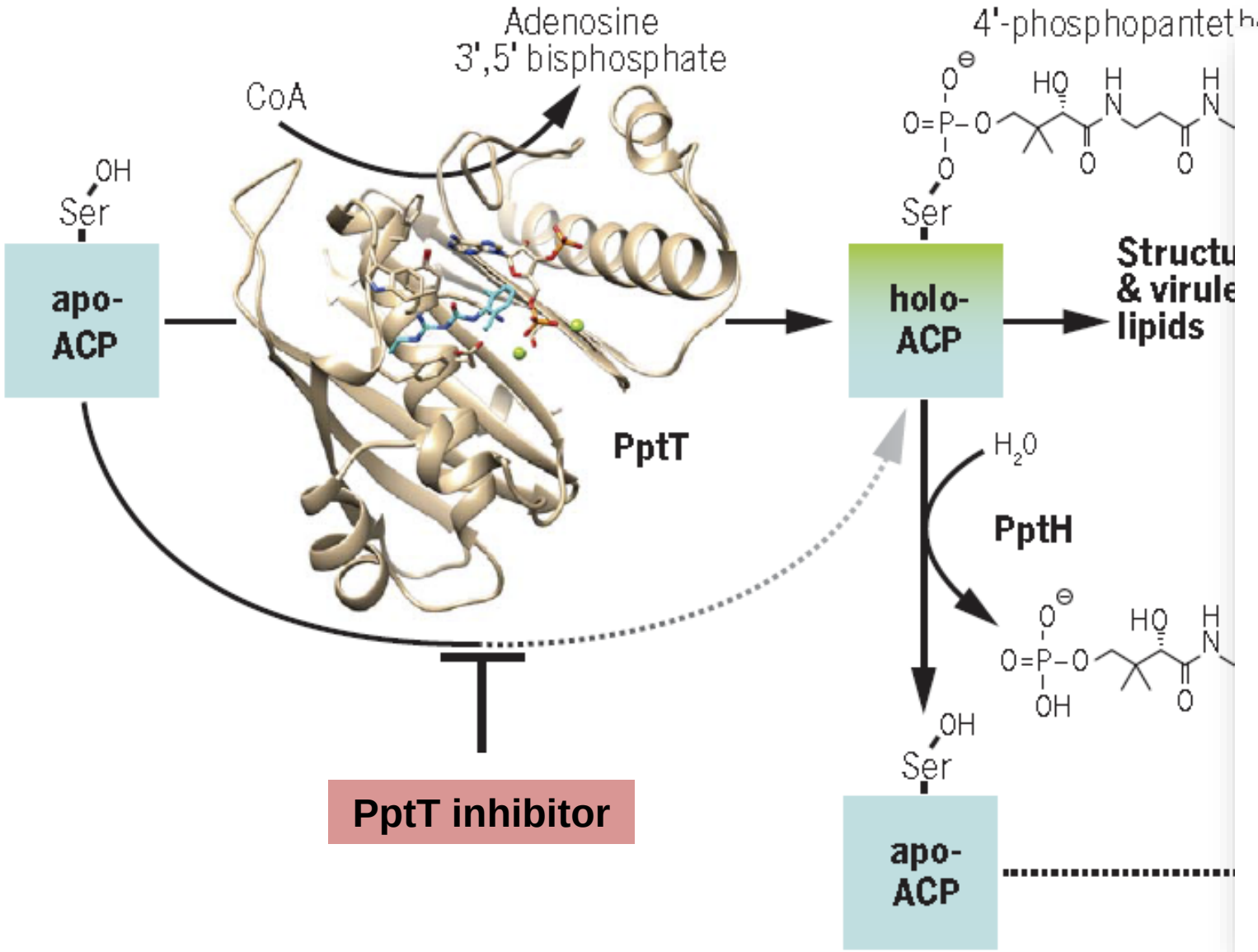
Why *Mycobacterium tuberculosis*?

- **10% of latent infections progress to active disease which, if left untreated, kills about half of those affected.**
- **Bacteria inside the granuloma can become dormant, resulting in latent infection.**
- **Latent TB is treated with either isoniazid alone, or a combination of isoniazid with either rifampicin or rifapentine (at least three months).**



https://www.tbfacts.org/latent-tb/

Why MTB PptT?



PptT leads MTB to possess

Erratum 20 June 2019. See erratum.

RESEARCH

RESEARCH ARTICLE SUMMARY

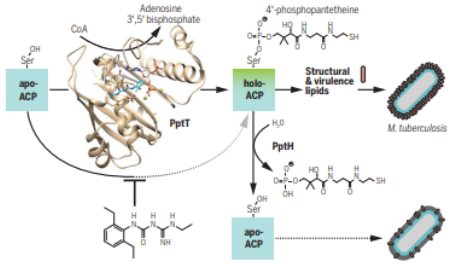
TUBERCULOSIS

Opposing reactions in coenzyme A metabolism sensitize *Mycobacterium tuberculosis* to enzyme inhibition

Elaine Ballinger*, John Mosior*, Travis Hartman, Kristin Burns-Huang, Ben Gold, Roxanne Morris, Laurent Goullieux, Isabelle Blanc, Julien Vaubourgeix, Sophie Lagrange, Laurent Fraisse, Stéphanie Sans, Cedric Couturier, Eric Bacqué, Kyu Rhee, Sarah M. Scarry, Jeffrey Aubé, Guangbin Yang, Ouathek Ouerfelli, Dirk Schnappinger, Thomas R. Ioerger, Curtis A. Engelhart, Jennifer A. McConnell, Kathrine McAulay, Allison Fay, Christine Roubert, James Sacchettini†‡, Carl Nathan†‡

INTRODUCTION: *Mycobacterium tuberculosis* (Mtb) is the leading global cause of lethal infection in humans and accounts for the largest number of drug-resistant infections by a single bacterial pathogen. Resistance is particularly high against the most widely prescribed tuberculosis (TB) drug, isoniazid. Isoniazid blocks synthesis of mycolates, ultralong-chain fatty acids that provide structure to the waxy coat that surrounds Mtb cells and are incorporated into some of its virulence lipids. There is currently no known method to block the synthesis of both mycolates and nonmycolate-containing virulence lipids of Mtb at a single point of control. One such control point is phosphopantetheinyl transferase (PptT). PptT transfers 4′-phosphopantetheine (Ppt) from coenzyme A (CoA) to acyl carrier proteins (ACPs) that synthesize the lipids critical to Mtb structural integrity and virulence.

RATIONALE: TB drug discovery often begins with whole-cell, high-throughput screens that yield compounds that kill Mtb by unknown means. Selection of Mtb mutants resistant to these compounds can indicate candidate targets of the active compound, but experimental validation is required to confirm the functionally relevant target, which is often an enzyme. A suitable target must be essential in vivo, such that its inhibition precludes development of TB in animal models, but also "vulnerable," meaning that a pharmacologically attainable level of inhibition should be lethal to Mtb within a patient. The inhibitor should act only on Mtb, and resistance should be rare.



The enzymes PptT and PptH have been found to perform opposing reactions in Mtb lipid metabolism, an essential process demonstrated to be a target for drug development. PptT transfers 4′-phosphopantetheine (Ppt) from CoA to apo-acyl carrier proteins (Apo-ACP) in Mtb, generating holo-ACPs that help synthesize structural and virulence lipids. Compound 8918 binds to the Ppt binding pocket of PptT, displacing the Ppt arm of CoA and partially inhibiting this enzyme. The Ppt hydrolase PptH can release Ppt, regenerating apo-ACP and thus sensitizing Mtb cells to inhibition of PptT.

RESULTS: Screening a chemical library revealed an amidino-urea compound called "8918" that kills Mtb, including drug-resistant clinical isolates. 8918 inhibits Mtb in mice and spares other bacteria, yeast, and mammalian cells.

Rare Mtb mutants resistant to 8918 bore a point mutation in the PptT gene *rv2794c*, altering an amino acid residue overlying the Ppt-binding pocket of PptT. When Mtb carried the mutant allele as an extra copy of *rv2794c*, the Mtb was protected from 8918. 8918 inhibited recombinant PptT, albeit noncompetitively and incompletely. The impact of 8918 on the Mtb metabolome and lipids was consistent with inhibition of PptT in the intact cell. A crystal structure of the PptT-8918 complex at 1.8-Å resolution confirmed that 8918 binds within the Ppt binding pocket, adjacent to the phosphoadenosine phosphate portion of CoA. Intact CoA remained in the PptT-8918 complex, but the Ppt arm was displaced, decreasing but not abolishing PptT's catalytic activity. Strains of Mtb producing reduced amounts of PptT became hypersensitive to 8918.

ON OUR WEBSITE

Read the full article at http://dx.doi.org/10.1126/science.aau8959

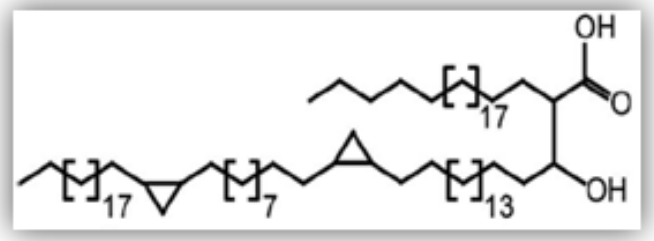
It was puzzling that even partial inhibition of PptT killed Mtb. We observed that mutants with disruption of *rv2795c*, a gene encoding a hypothetical protein, were also highly resistant to 8918. Recombinant Rv2795c protein hydrolyzed Ppt from a mycolate-building holo-ACP that is a substrate for PptT. The action of this Ppt hydrolase (PptH) resembled that of nonhomologous enzymes called ACP hydrolases that remove Ppt from ACPs in vitro but whose physiological function is unknown.

CONCLUSION: We identified a small molecule that kills Mtb by inhibiting PptT, demonstrating that a key enzyme in CoA metabolism is a viable target for TB drug development. Even partial inhibition of PptT is toxic to Mtb, likely because PptH synergizes with the inhibitor by undoing the PptT reaction. PptT and PptH are co-regulated by translation from the same operon, and thus Mtb cannot respond to inhibition of PptT by making more PptT without also generating more PptH. The joint functioning of PptT and PptH suggests that Mtb closely regulates the activation of ACPs. The transcriptional co-regulation and constitutive function of both members of the PptT-PptH couple suggests that a posttranslational signal that impairs PptT more than PptH could allow Mtb to rapidly reverse a prior commitment to synthesis of its metabolically most costly lipids. ■

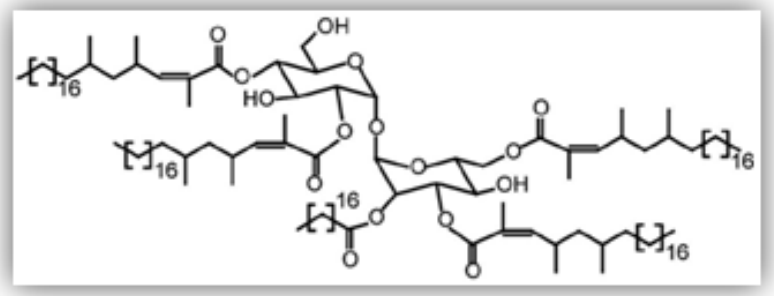
The list of author affiliations is available in the full article online.
*These authors contributed equally to this work.
†These authors contributed equally to this work.
‡Corresponding author. Email: cnathan@med.cornell.edu (C.N.); sacchett@tamu.edu (J.S.)
Cite this article as E. Ballinger *et al.*, *Science* **363**, eaau8959 (2019). DOI: 10.1126/science.aau8959

Why MTB PptT?

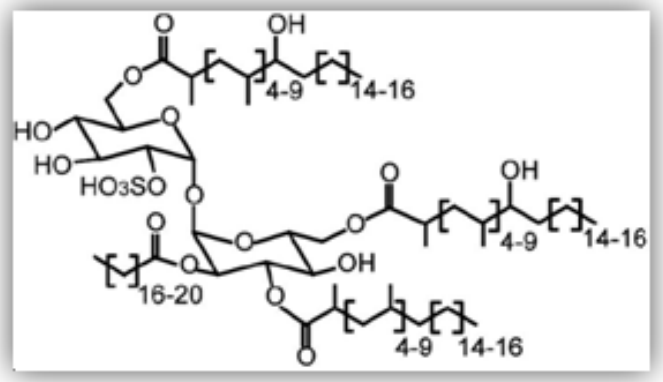
Mycolic acids



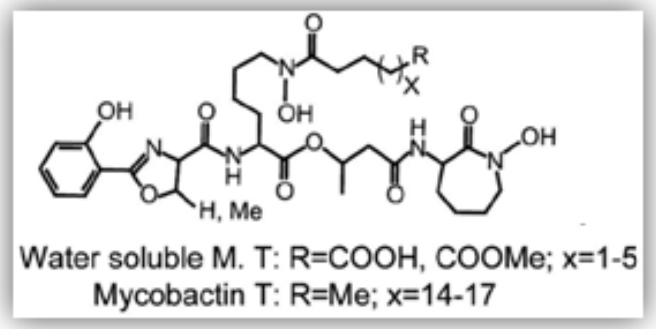
Polyacyltrehaloses



Sulfolipids 1

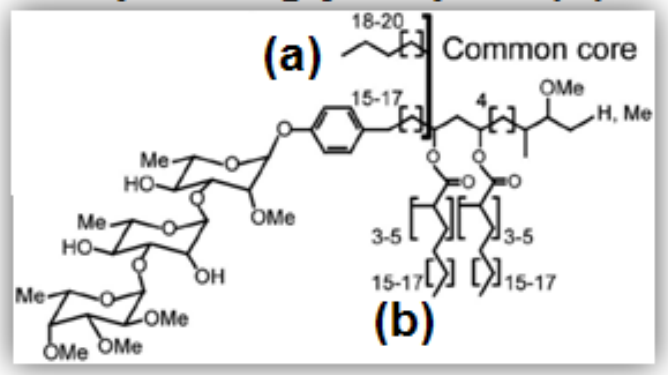


Mycobactins



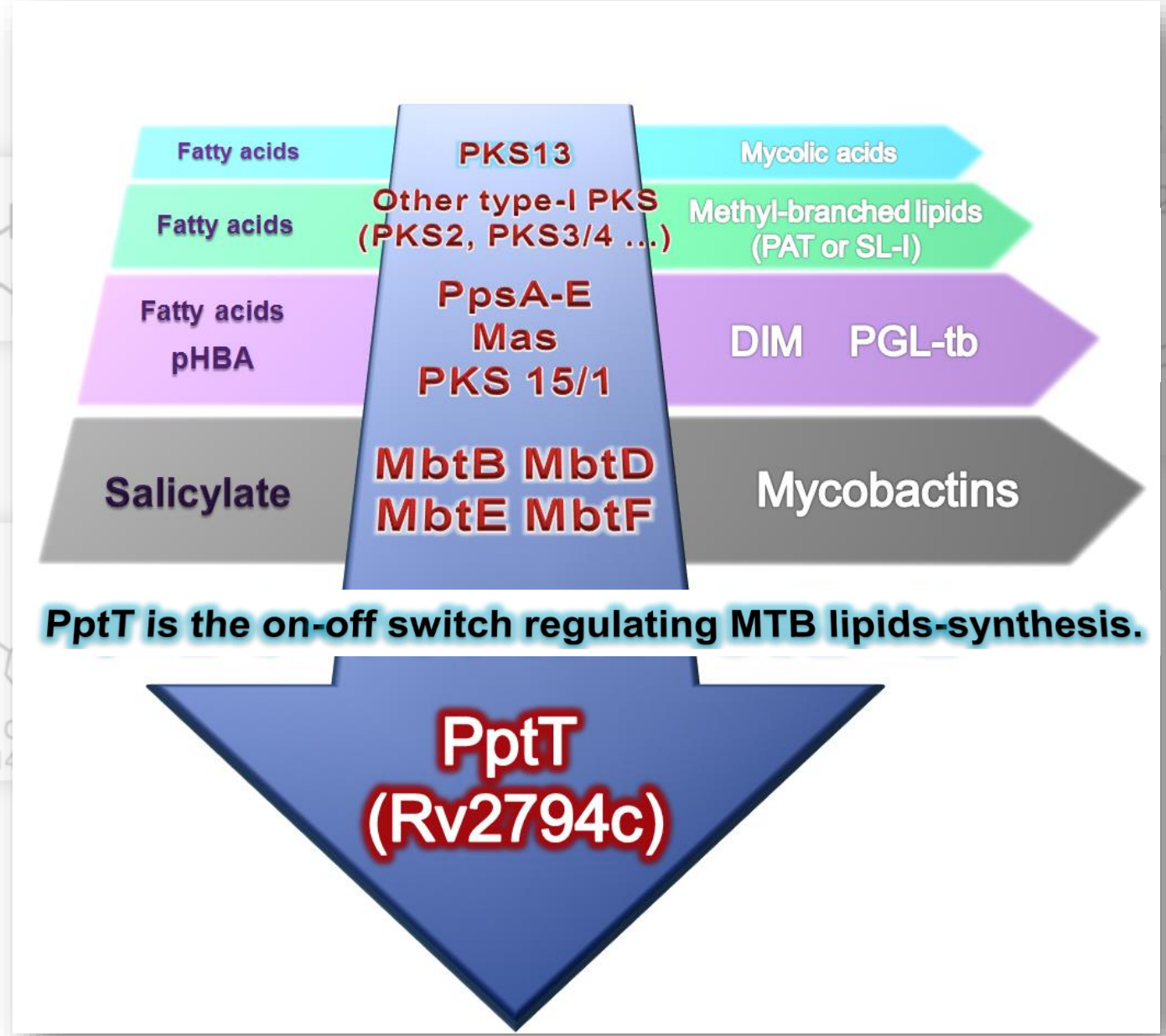
Water soluble M. T: R=COOH, COOMe; x=1-5
Mycobactin T: R=Me; x=14-17

Phthiocerol dimycocerosates (a) and phenolglycolipids (b)



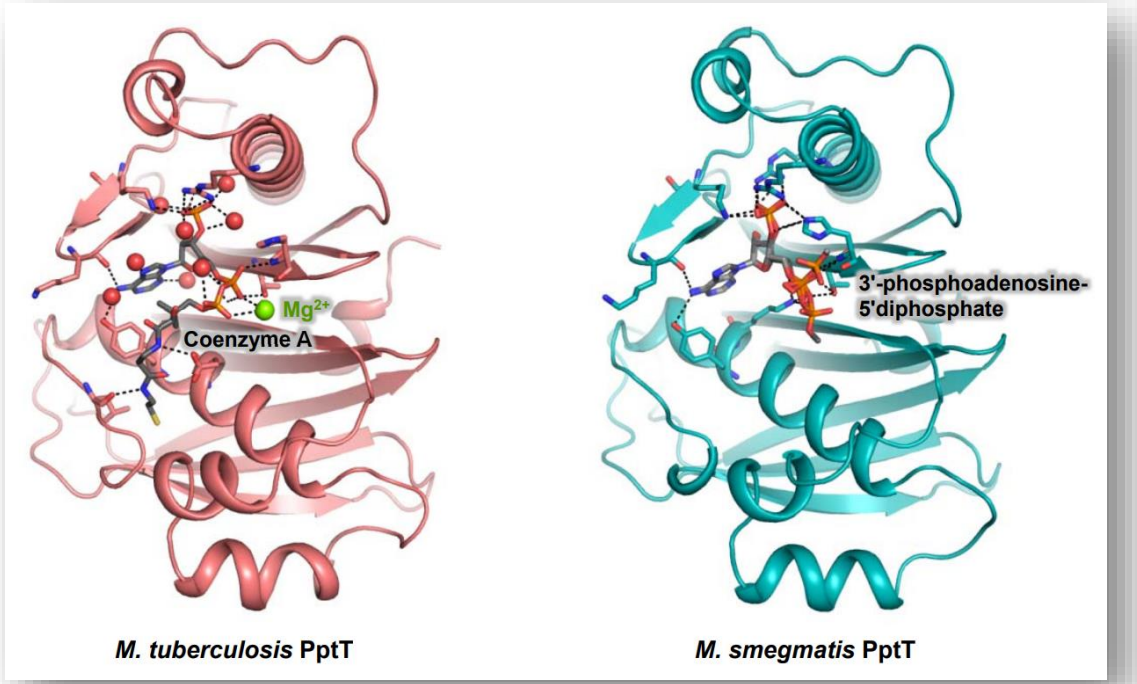
Unique lipids in MTB

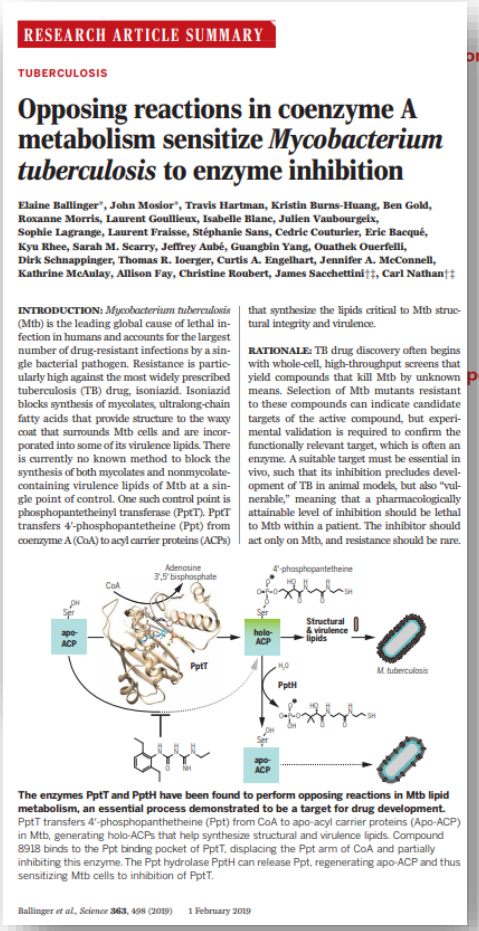
Why MTB PptT?


Fatty acids
PKS13
Mycolic acids
Fatty acids
Other type-I PKS
(PKS2, PKS3/4 ...)
Methyl-branched lipids
(PAT or SL-I)
Fatty acids
pHBA
PpsA-E
Mas
PKS 15/1
DIM
PGL-tb
Salicylate
MbtB MbtD
MbtE MbtF
Mycobactins
PptT is the on-off switch regulating MTB lipids-synthesis.
PptT
(Rv2794c)

New protein structures from bacterial pathogens

Mycobacterium tuberculosis PptT




RESEARCH ARTICLE SUMMARY

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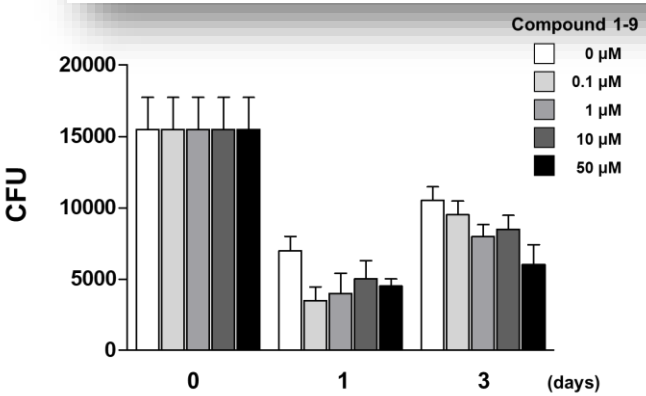
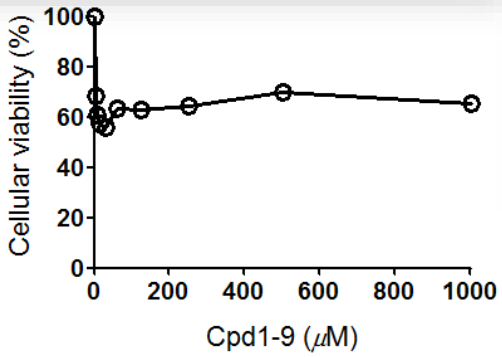
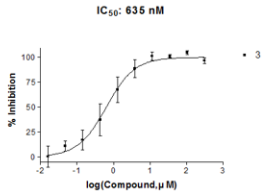
Ballinger *et al.*, *Science* **363**, 498 (2019) 1 February 2019

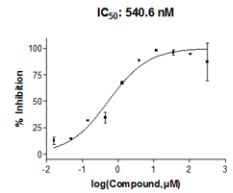




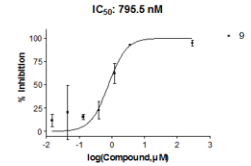
Compound 1st_3번 (IC50 : 635 nM)



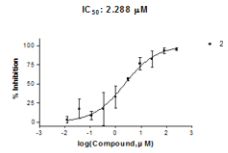
Compound 1st_4번 (IC50 : 540.6 nM)



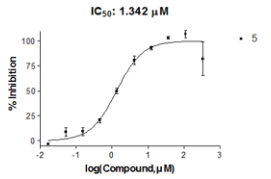
Compound 1st_9번 (IC50 : 795.5 nM)



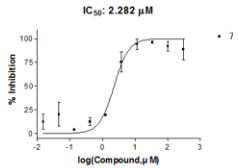
Compound 1st_2번 (IC50 : 2.288 μM)



Compound 1st_5번 (IC50 : 1.342 μM)



Compound 1st_7번 (IC50 : 2.282 μM)



Two papers and one patent are in preparation.

단백질구조를 기반한 신약개발

항생제

효소활성화 부근
단백질간 결합 부위 (PPI)

Mycobacterium tuberculosis AnsA

- ***M. tuberculosis* must acquire its nutrients and adapt to harsh environment in the human body.**
- **AnsA exploits asparagine to assimilate nitrogen and resist acid stress during Infection.**
- **New therapeutic strategies to impair nitrogen acquisition by inhibition of AnsA**

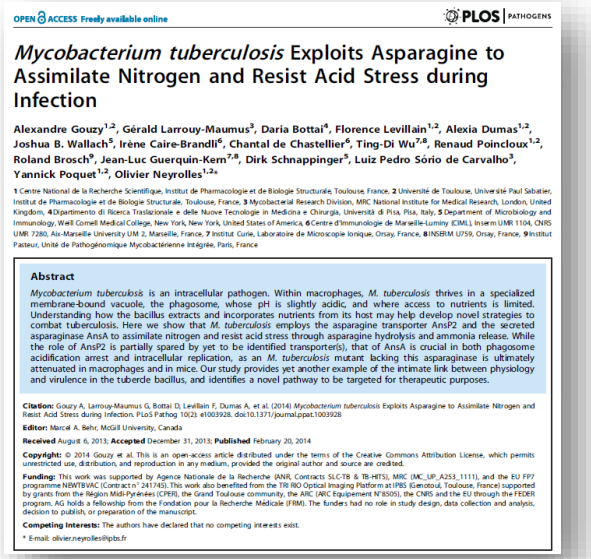
Gouzy A. et al. Nitrogen metabolism in *Mycobacterium tuberculosis* physiology and virulence. (2014) Nat Rev Microbiol. 12(11), 729-737.

PROGRESS

Nitrogen metabolism in *Mycobacterium tuberculosis* physiology and virulence

Alexandre Gouzy, Yannick Poquet and Olivier Neyrolles

Abstract | Several major pathogens, including *Mycobacterium tuberculosis*, parasitize host cells and exploit host-derived nutrients to sustain their own metabolism. Although the carbon sources that are used by *M. tuberculosis* have been extensively studied, the mechanisms by which mycobacteria capture and metabolize nitrogen, which is another essential constituent of biomolecules, have only recently been revisited. In this Progress article, we discuss central nitrogen metabolism in *M. tuberculosis*, the mechanisms that are used by this pathogen to obtain nitrogen from its host and the potential role of nitrogen capture and metabolism in virulence.



OPEN ACCESS Freely available online

PLOS | PATHOGENS

Mycobacterium tuberculosis Exploits Asparagine to Assimilate Nitrogen and Resist Acid Stress during Infection

Alexandre Gouzy[1,2], Gérald Larrouy-Maumus[3], Daria Bottai[4], Florence Levillain[1,2], Alexia Dumas[1,2], Joshua B. Wallach[5], Irène Caire-Brandli[6], Chantal de Chastellier[6], Ting-Di Wu[7,8], Renaud Poincloux[1,2], Roland Brosch[9], Jean-Luc Guerquin-Kern[7,8], Dirk Schnappinger[5], Luiz Pedro Sório de Carvalho[3], Yannick Poquet[1,2], Olivier Neyrolles[1,2]*

1 Centre National de la Recherche Scientifique, Institut de Pharmacologie et de Biologie Structurale, Toulouse, France, 2 Université de Toulouse, Université Paul Sabatier, Institut de Pharmacologie et de Biologie Structurale, Toulouse, France, 3 Mycobacterial Research Division, MRC National Institute for Medical Research, London, United Kingdom, 4 Dipartimento di Ricerca Traslazionale e delle Nuove Tecnologie in Medicina e Chirurgia, Università di Pisa, Pisa, Italy, 5 Department of Microbiology and Immunology, Weill Cornell Medical College, New York, New York, United States of America, 6 Centre d'Immunologie de Marseille-Luminy (CIML), Inserm UMR 1104, CNRS UMR 7280, Aix-Marseille University UM 2, Marseille, France, 7 Institut Curie, Laboratoire de Microscopie Ionique, Orsay, France, 8 INSERM U759, Orsay, France, 9 Institut Pasteur, Unité de Pathogénomique Mycobactérienne Intégrée, Paris, France

Abstract

Mycobacterium tuberculosis is an intracellular pathogen. Within macrophages, *M. tuberculosis* thrives in a specialized membrane-bound vacuole, the phagosome, whose pH is slightly acidic, and where access to nutrients is limited. Understanding how the bacillus extracts and incorporates nutrients from its host may help develop novel strategies to combat tuberculosis. Here we show that *M. tuberculosis* employs the asparagine transporter AnsP2 and the secreted asparaginase AnsA to assimilate nitrogen and resist acid stress through asparagine hydrolysis and ammonia release. While the role of AnsP2 is partially spared by yet to be identified transporter(s), that of AnsA is crucial in both phagosome acidification arrest and intracellular replication, as an *M. tuberculosis* mutant lacking this asparaginase is ultimately attenuated in macrophages and in mice. Our study provides yet another example of the intimate link between physiology and virulence in the tuberde bacillus, and identifies a novel pathway to be targeted for therapeutic purposes.

Citation: Gouzy A, Larrouy-Maumus G, Bottai D, Levillain F, Dumas A, et al. (2014) *Mycobacterium tuberculosis* Exploits Asparagine to Assimilate Nitrogen and Resist Acid Stress during Infection. PLoS Pathog 10(2): e1003928. doi:10.1371/journal.ppat.1003928

Editor: Marcel A. Behr, McGill University, Canada

Received August 6, 2013; **Accepted** December 31, 2013; **Published** February 20, 2014

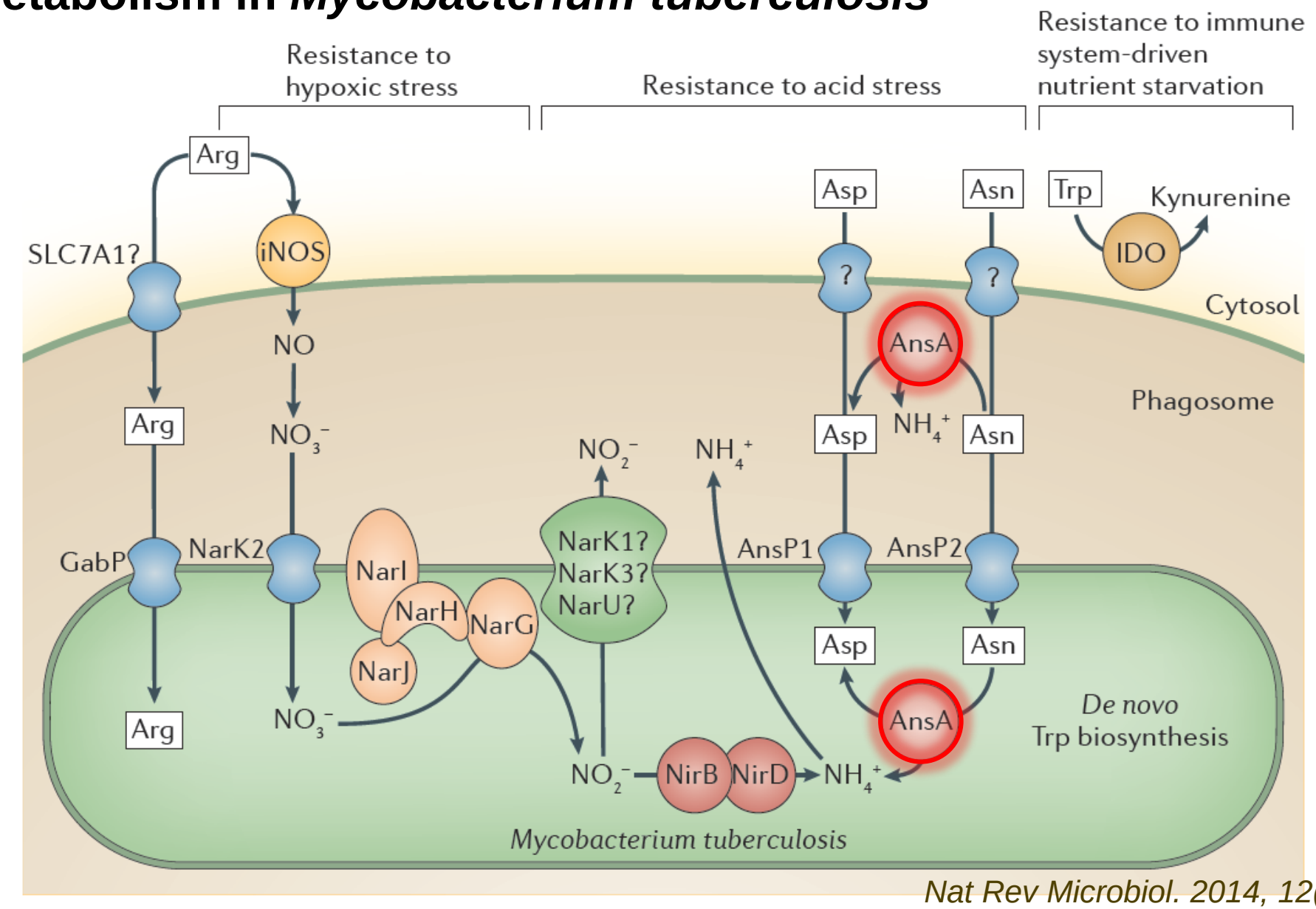
Funding: This work was supported by Agence Nationale de la Recherche (ANR, Contracts SLC-TB & TB-HITS), MRC (MC_UP_A253_1111), and the EU FP7 programme NEWTBVAC (Contract n° 241745). This work also benefited from the TRI RIO Optical Imaging Platform at IPBS (Genotoul, Toulouse, France) supported by grants from the Région Midi-Pyrénées (CPER), the Grand Toulouse community, the ARC (ARC Equipement N°8505), the CNRS and the EU through the FEDER program. AG holds a fellowship from the Fondation pour la Recherche Médicale (FRM). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: olivier.neyrolles@ipbs.fr

Mycobacterium tuberculosis AnsA

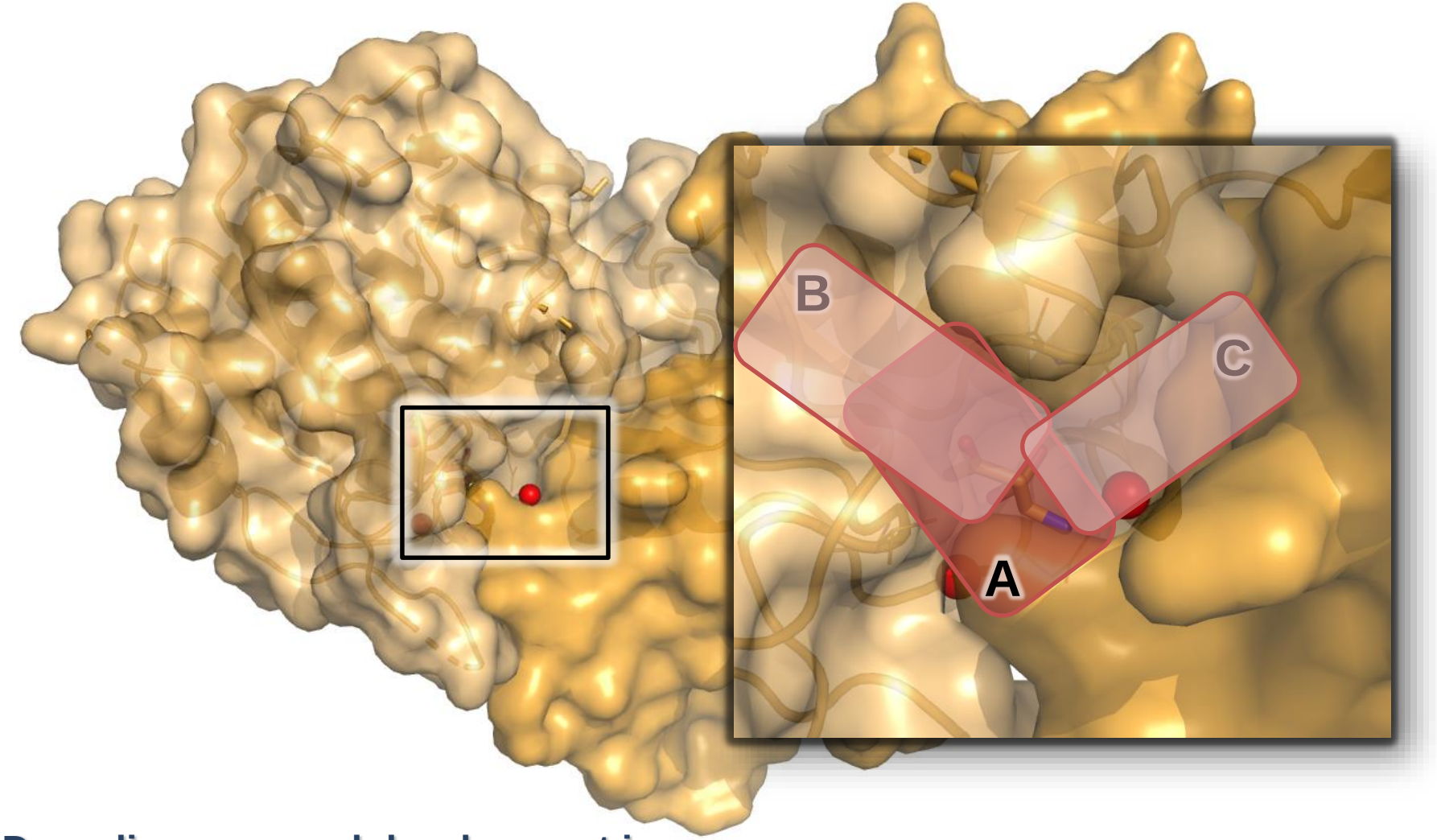
Nitrogen metabolism in *Mycobacterium tuberculosis*



Nat Rev Microbiol. 2014, 12(11), 729-737

New protein structures from bacterial pathogens

AsnA from Mycobacterium tuberculosis



Drug discovery and development in progress.

단백질구조를 기반한 신약개발

100K 또는 얼은 상태의 구조

RT의 구조
XFEL을 이용한 단백질 구조: 중요함
XFEL SFX의 신규기법 이용 보다 범용적인 구조해석을 추구함이 중요함.

SBDD에 있어서 약물개선이 미치는 영향

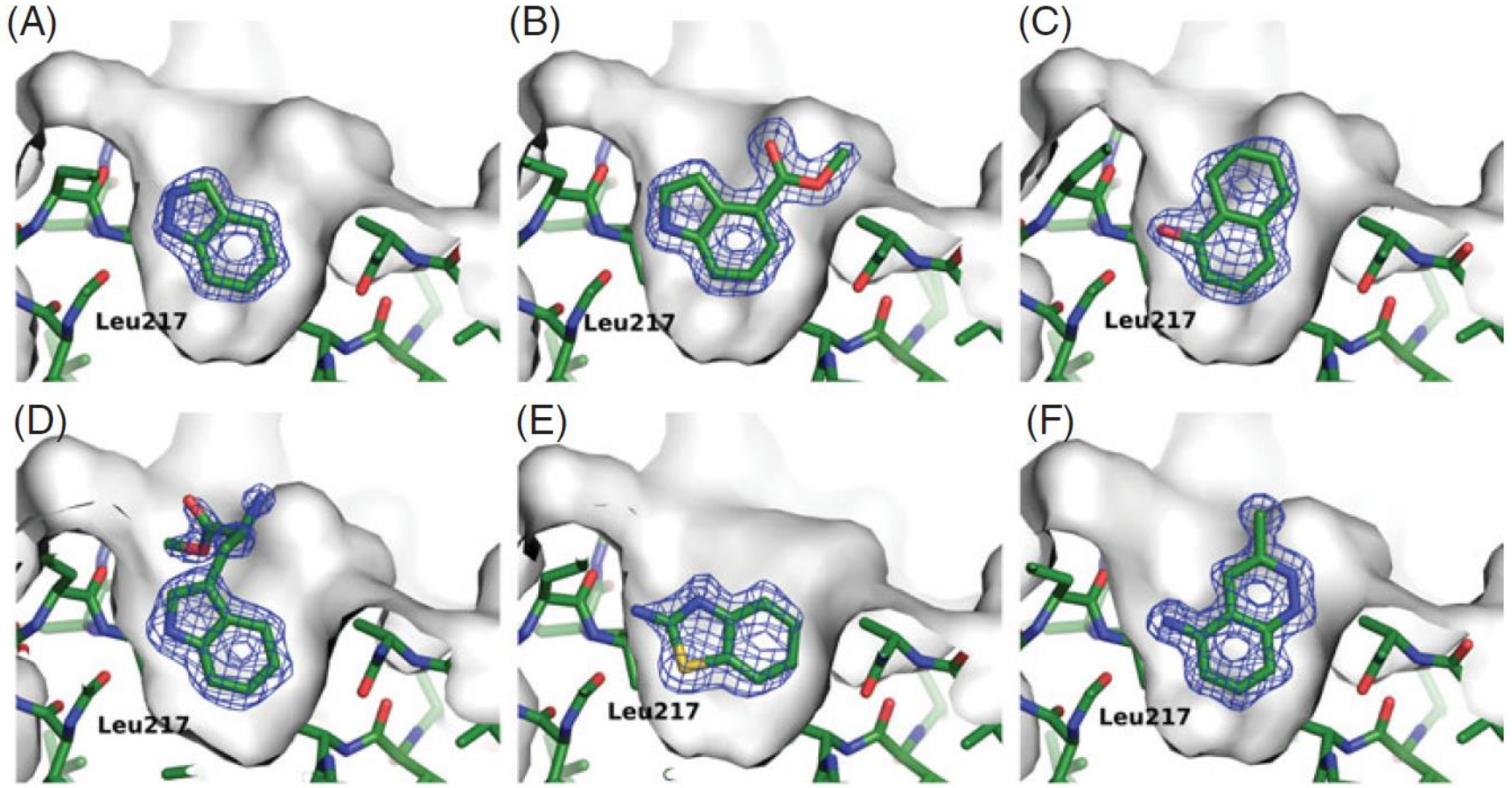


Fig. 5. Fragments binding to the Phe pocket of the RAD51 interface with the BRC4 peptide of BRCA2. The fragments bind with the following K_Ds (A) 540 μM (B) 1000 μM (C) 600 μM (D) 730 μM (E) 430 μM (F) 460 μM (from Scott *et al.* 2012).

단백질구조를 기반한 신약개발

XFEL SFX 활용한 단백질구조 해석

RT의 구조 → 시작 물질의 개선

(단백질구조의 99.9% 이상은 100K하 구조)

In silico 작업의 정확도가 높아짐

합리적인 약물개발을 추구. 성공 가능성 향상

PPI 기반의 약물 개발 추구

보다 합리적 접근. 연구개발비/시간 단축

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Four main mechanisms by which microorganisms exhibit resistance to antimicrobials

Drug inactivation or modification

Enzymatic deactivation of penicillin G in some penicillin-resistant bacteria through the production of β-lactamases.

Alteration of target site

Alteration of PBP in MRSA and other penicillin-resistant bacteria.

Alteration of metabolic pathway

Some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (pABA) like mammalian cells. They turn to using preformed folic acid.

Reduced drug accumulation

By decreasing drug permeability and/or increasing active efflux of the drugs across the cell surface.