Efflux Pump Inhibition as a Weapon Against Multidrug-Resistant Bacteria

Hospital-acquired infections caused by multidrug-resistant bacteria, especially Pseudomonas aeruginosa, pose a serious societal challenge. One major cause of resistance is the drug efflux pumps that expel antibiotics from bacterial cells, significantly reducing their effectiveness. We have developed novel compounds that selectively and efficiently inhibit these efflux pumps. These inhibitors lack intrinsic antibacterial activity, minimizing resistance development and offering safety advantages. By targeting multiple efflux pumps, they can address broad-spectrum resistance. Combined with existing antibiotics, these inhibitors have the potential to restore drug efficacy and greatly expand therapeutic options.

SANKEN
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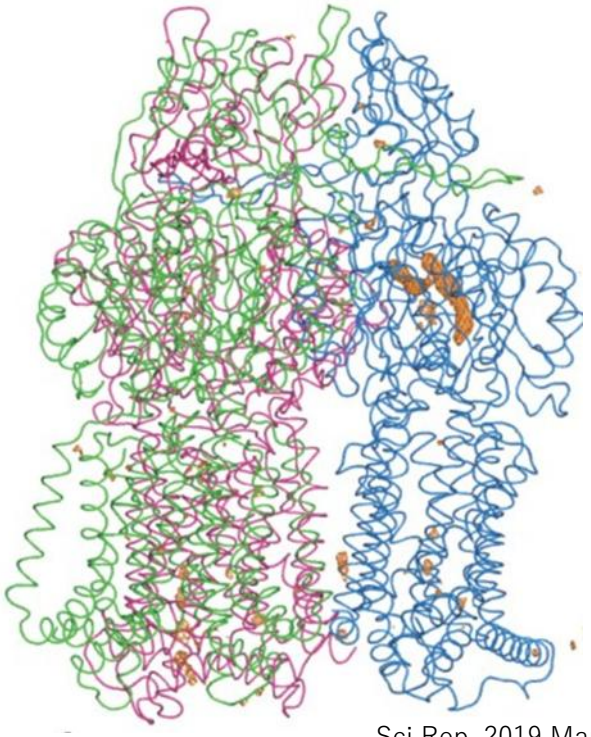
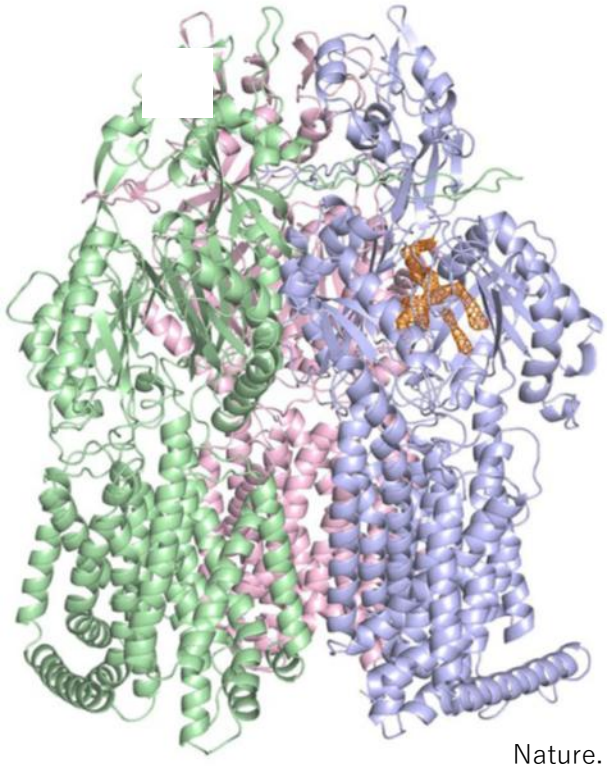
Structural Rationale of MexB-Specificity of PP



Sci Rep. 2019 Mar 13;9(1):4359.

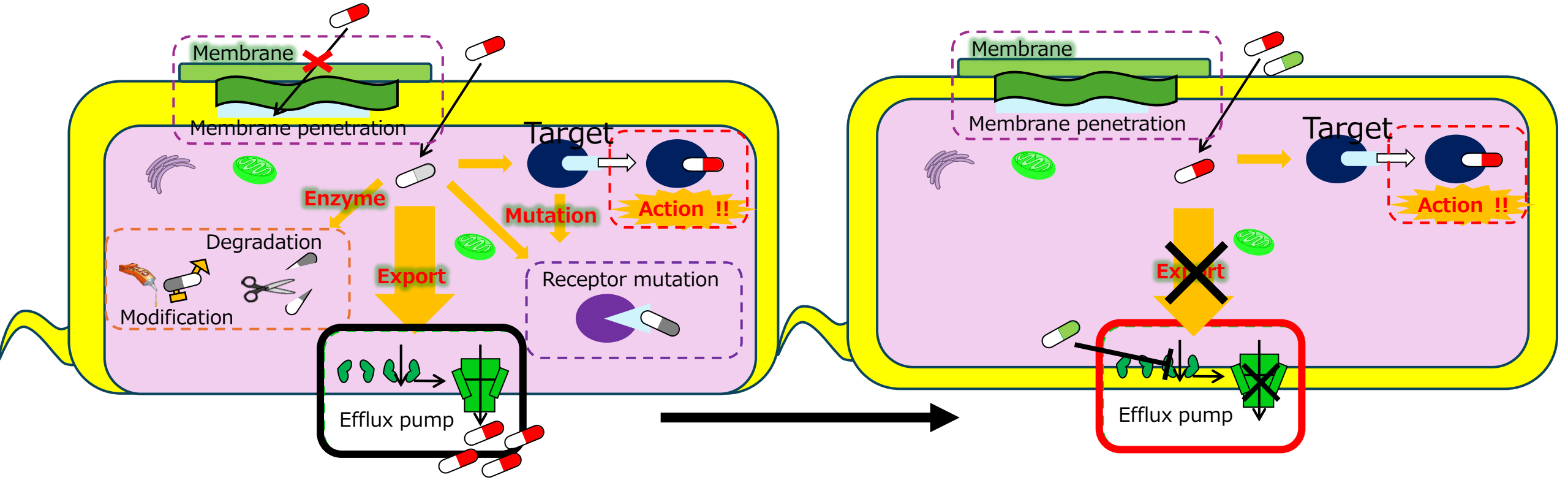


Nature. 2013 Aug 1;500(7460):102-6.

Crystal structure of D13-9001 (efflux pump inhibitor; left) or LMNG (detergent; right)-bound MexB (one of efflux pump of Pseudomonas aeruginosa) is obtained.

In addition the crystal structural analysis of MexB and our compound (efflux pump inhibitor) is successfully performed.

Efflux Pumps: Spotlight in Resistance Mechanisms



Among many resistance mechanisms, efflux pumps play a major role.

Inhibiting efflux pumps offers a powerful approach to reclaim the effectiveness of compromised antibiotics.

Therapeutic Effect of Dual Inhibitor Compound A Targeting MexAB & MexXY[1)]

Antibiotics	Class	Efflux pump	MIC (μg/mL) alone/+EPI	Compound A This Invention	ABI-PP [2)] Prior Inhibitors	Competing Products[3)]
aztreonam	monobactam	MexAB	32/8*	8**	≤4	16
cefepim	cephalosporin	MexAB/MexXY	16/4	8	>64	>64
levofloxacin	FQ	MexAB/MexXY	64/16	16	16	16
amikacin	AG	MexXY	8/2	8	>64	>64
gentamicin	AG	MexXY	4/1	8	>64	>64

*: Restored MIC Value
** : Dose Required to Restore MIC Levels

1) Levofloxacin resistant strain, 2) *Nature,* **2013.** 500. 102. 3) WO2018165611

- **Our EPI significantly restores the antibacterial activity of existing drugs regardless of its class.**
- **Compound A demonstrates the potent and dual inhibition activities against both MexAB and MexXY.**

Therapeutic Effect of Dual Inhibitor Compound B Targeting MexAB & MexXY[1]

Strain No.	MIC (μg/mL) of Gentamicin (GEN)	MIC (μg/mL) of GEN + Compound B 6.25 μM	MIC (μg/mL) of GEN + Compound B 25 μM
No.1	128 (R)	8 (I)	4 (S)
No.2	64 (R)	8 (I)	4 (S)
No.3	64 (R)	8 (I)	4 (S)
No.4	64 (R)	4 (S)	4 (S)
No.5	32 (R)	4 (S)	≤2 (S)
No.6	16 (R)	≤2 (S)	≤2 (S)
No.7	16 (R)	≤2 (S)	≤2 (S)

MICs of Compound B against all tested strains : >50 μM
All tested strains : overexpression of genes MexY (≥10 × PAO1)

Gentamicin & Compound B effectively target gentamicin-resistant P. aeruginosa clinical isolates.

Current Situation and Proposal

- **Material Patent: Granted**
- **Drug Development Stage: Lead Optimization**
- **Currently in Collaboration with Industry; Seeking Early Out-Licensing**