

生体分子の分子シミュレーションと創薬応用

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池口 満徳

横浜市立大学—理化学研究所連携による高度タンパク質解析拠点

横浜市大鶴見キャンパス 共用計算機

950 MHz (22.3 T) 800 MHz, 700 MHz



600 MHz

国内最高レベルの
NMR研究施設

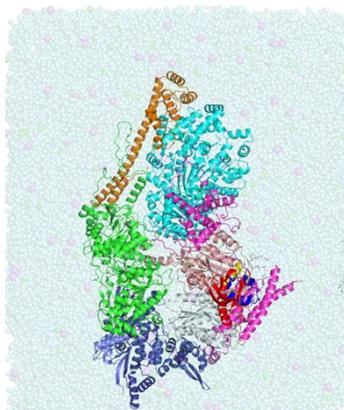
- ✓ 高感度
- ✓ 高分解能
- ✓ 自動測定



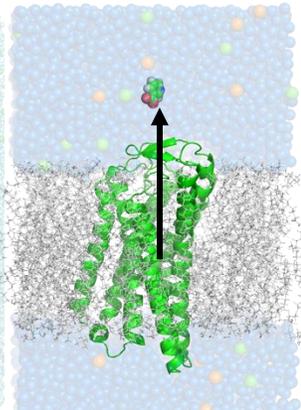
質量分析装置



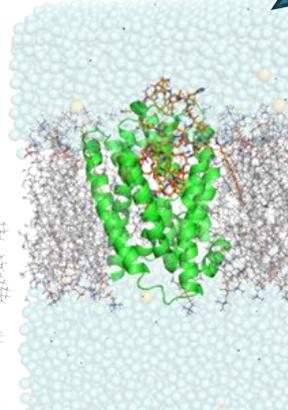
分子シミュレーション/AIによるデータ解析



Full-length of TFIIH
(NAR 2021)



GPCR (HCAR2)
(Nature Comm 2023)

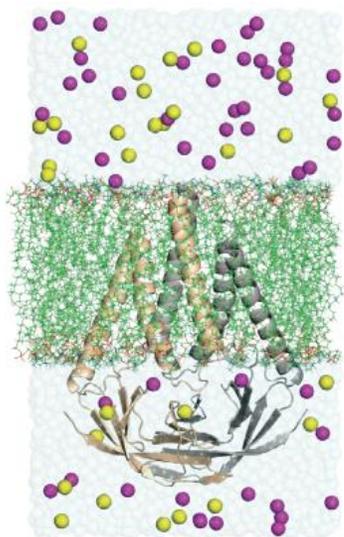


HBV NTCP
(Nature Comm 2024)

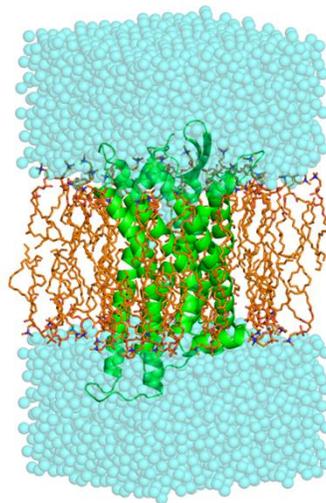
X線発生装置



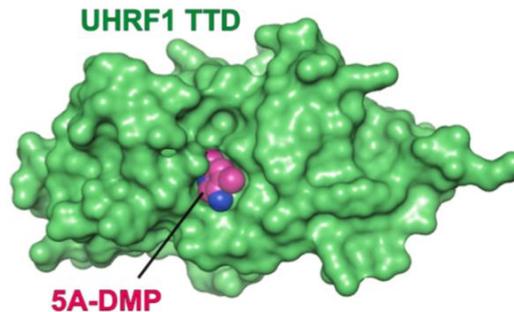
Our Recent Applications for MD Simulations (- 2023)



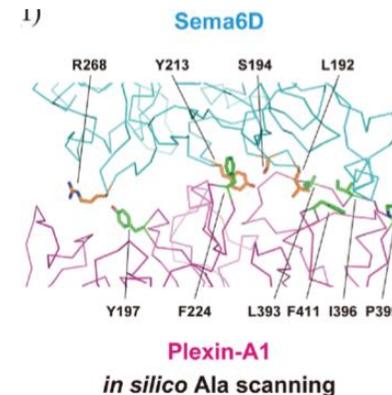
SARS-CoV-2 M protein
(Nature Comm 2022)



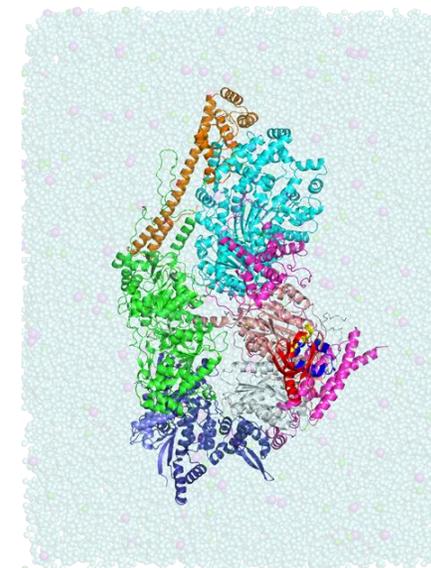
GPCR (ET_AR) mutations
(J. Clin. Invest. 2023)



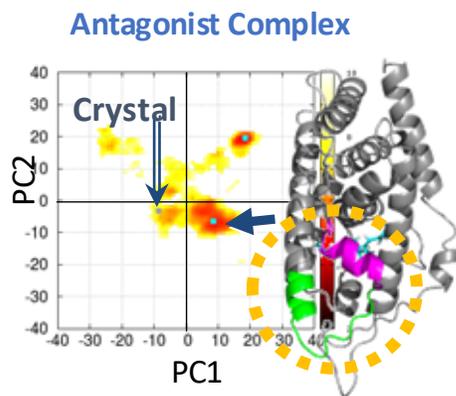
in silico screening UHRF1
(Bioorg. Med. Chem. 2021)



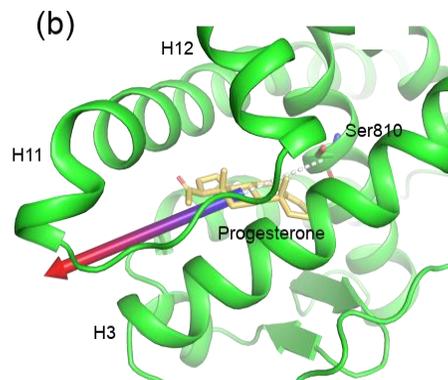
PPI (Semaphorin-Prexin)
(Prot. Sci. 2022)



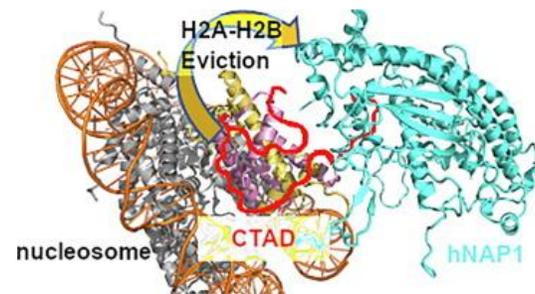
Full-length of TFIIH
(Nucl. Acids Res. 2021)



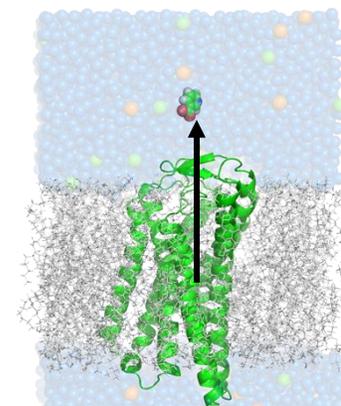
VDR agonism/antagonism
gREST (J. Chem. Inf. Model 2021)



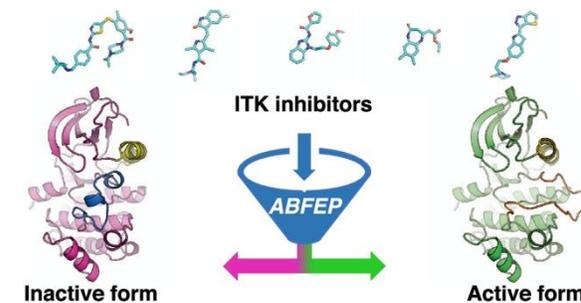
Mutant of
mineralocorticoid receptor
(J. Chem. Inf. Model 2021)



NAP1 – H2A/H2B
(J Mol Biol 2023)



GPCR (HCAR2) ligand binding
(Nature Comm. 2023)



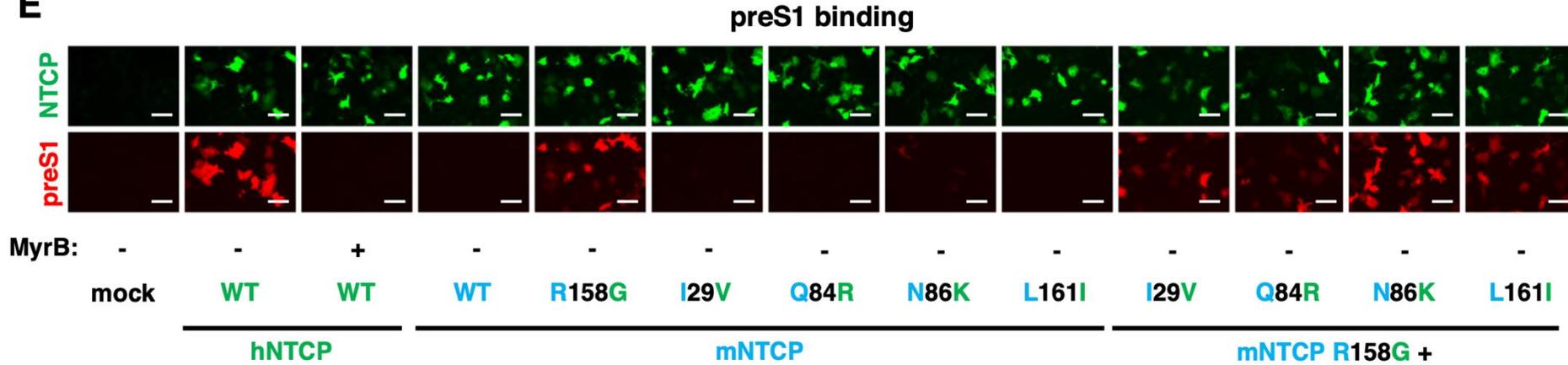
ITK Inhibitors
(J. Chem. Inf. Model 2023)

B型肝炎ウイルスはなぜヒトに感染してサルに感染しないのか

Kaho Shionoya, ..., Toru Ekimoto, ..., Mitsunori Ikeguchi, Sam-Yong Park & Koichi Watashi

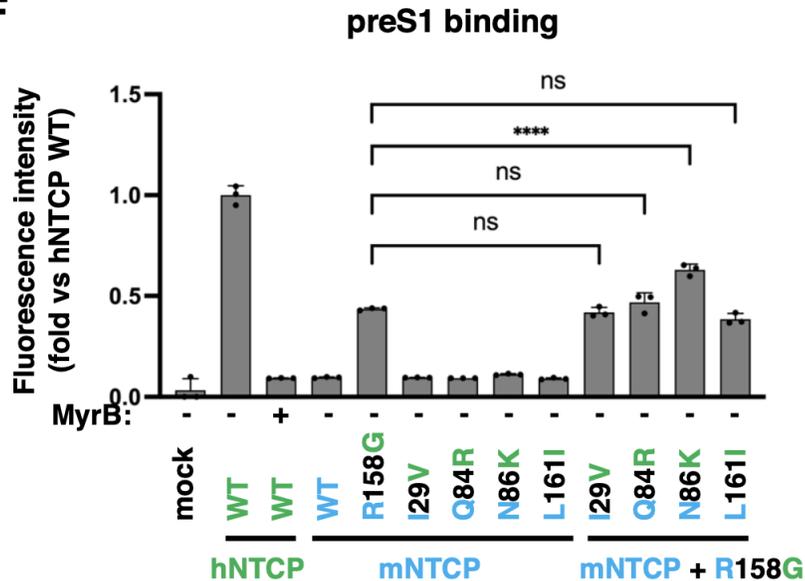
Structural basis for hepatitis B virus restriction by a viral receptor homologue, Nat Comm. 15:9241 (2024)

E

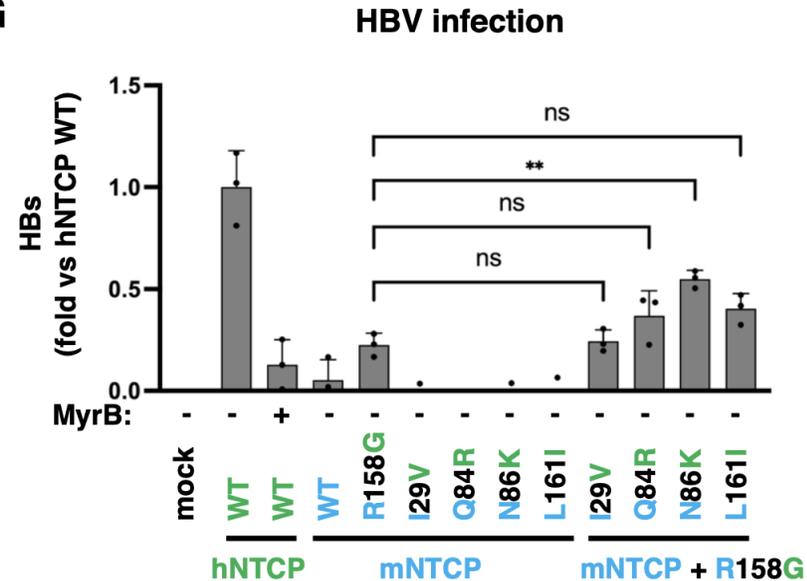


① R158G
② N86K
が重要

F



G

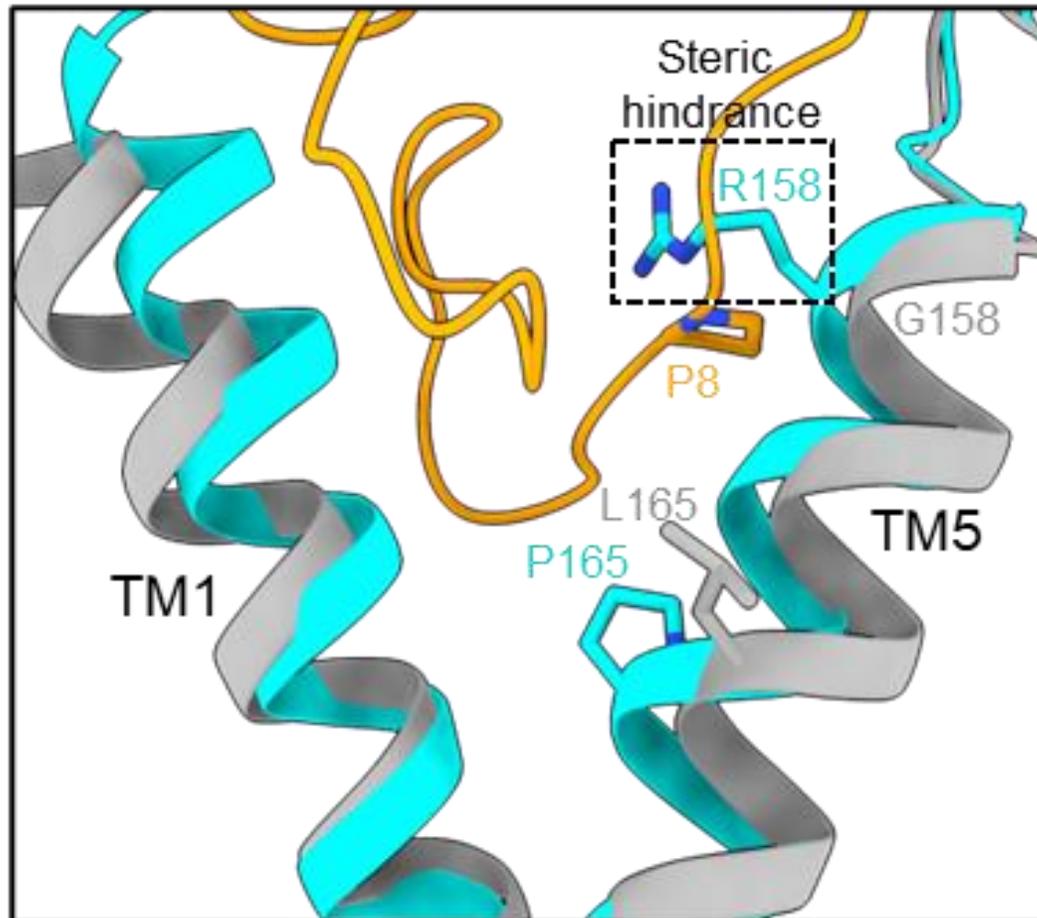


B型肝炎ウイルスはなぜヒトに感染してサルに感染しないのか

Kaho Shionoya, ..., Toru Ekimoto, ..., Mitsunori Ikeguchi, Sam-Yong Park & Koichi Watashi

Structural basis for hepatitis B virus restriction by a viral receptor homologue, Nat Comm. 15:9241 (2024)

(感染する/preS1結合) hNTCP > N86K/R158G mNTCP > R158G mNTCP > WT mNTCP (感染しない/結合しない)

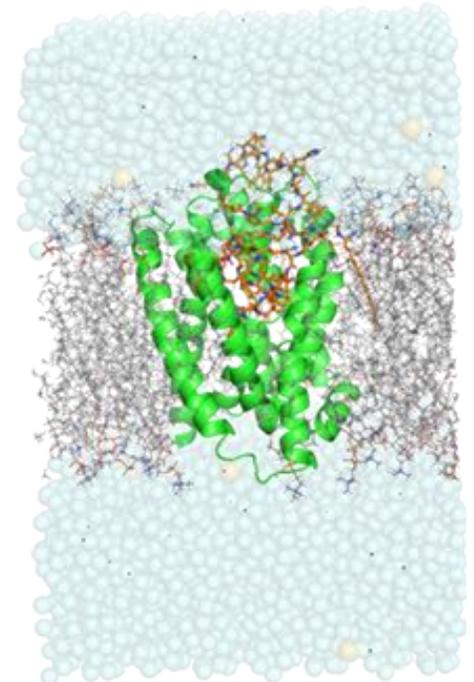


R158の阻害の原因は、立体障害

N86の阻害の原因は？



MDの実施



B型肝炎ウイルスはなぜヒトに感染してサルに感染しないのか

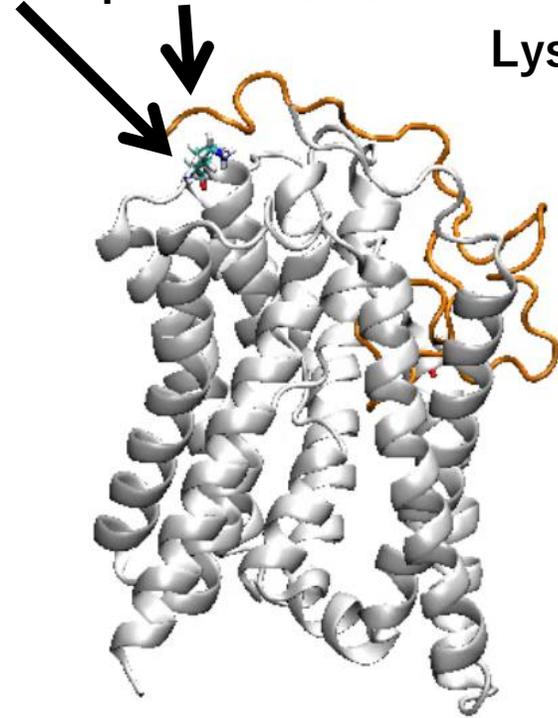
Kaho Shionoya, ..., Toru Ekimoto, ..., Mitsunori Ikeguchi, Sam-Yong Park & Koichi Watashi

Structural basis for hepatitis B virus restriction by a viral receptor homologue, Nat Comm. 15:9241 (2024)

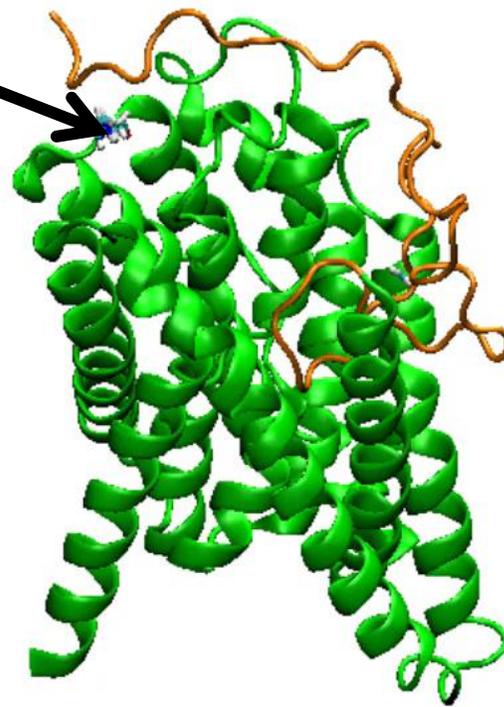
1 μ s MDを3本ずつ実施 ムービーは3本のMDを連続再生 (途中で2回初期ポーズに戻る)

hNTCP(gray)-preS1(orange) **N86K/R158G mNTCP(green)-preS1(orange)** **R158G mNTCP(green)-preS1(orange)**

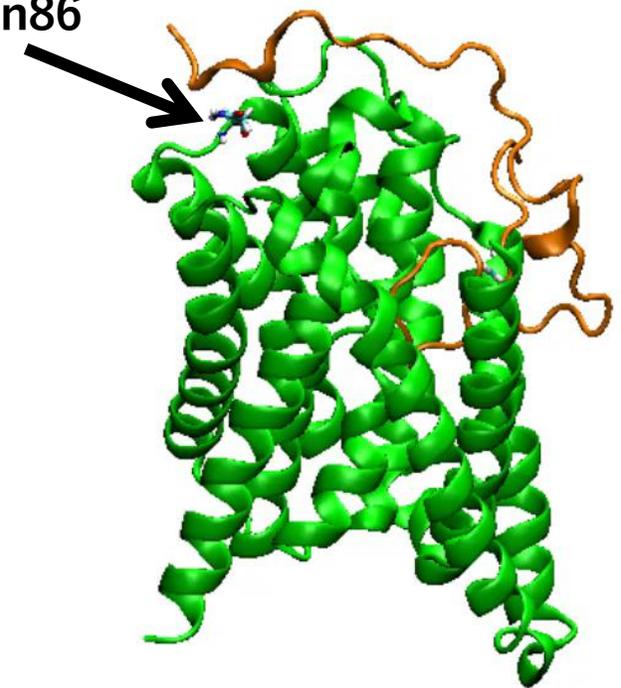
Lys86 preS1 C末端



Lys86



Asn86



感染(結合)の順番

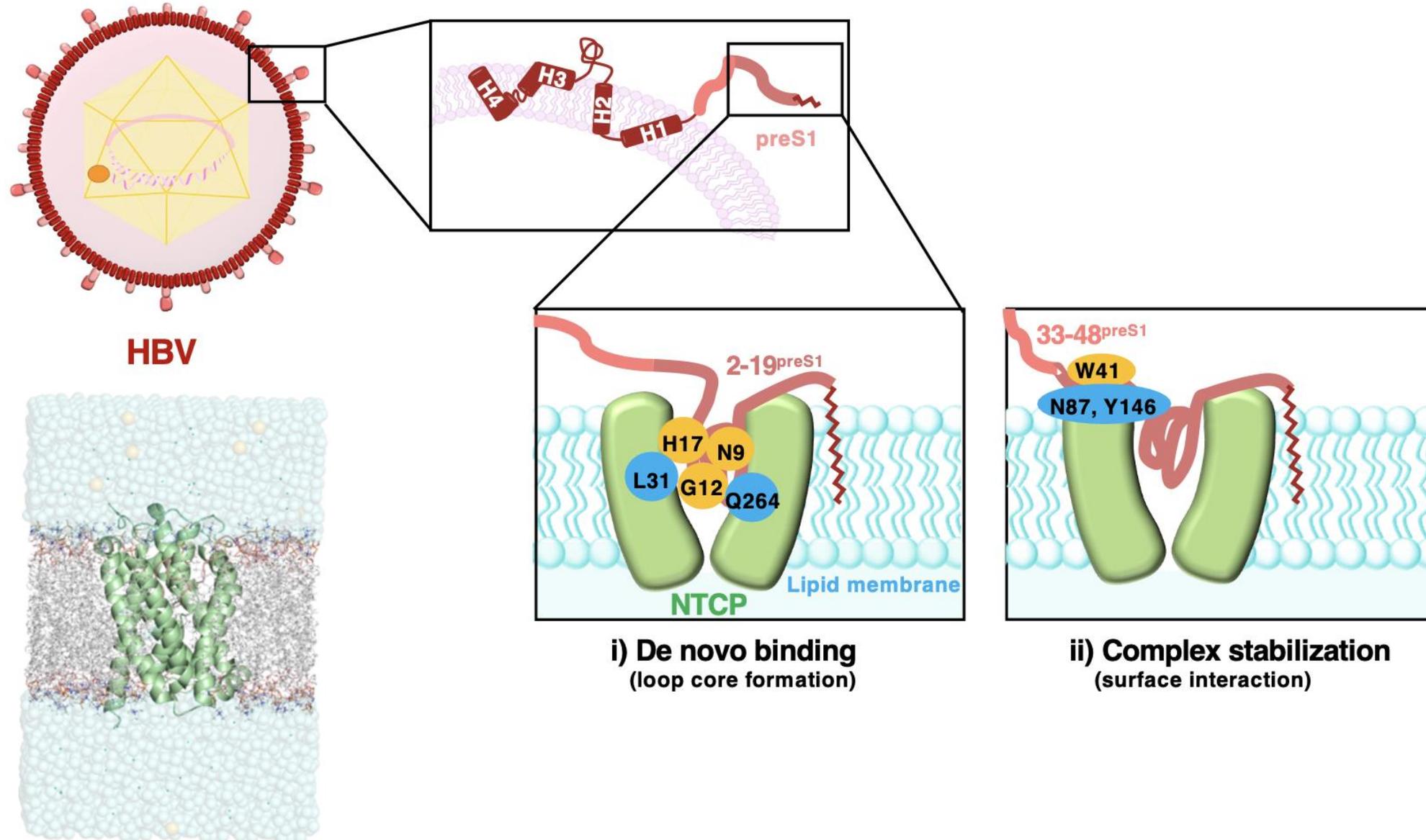
hNTCP > N86K/R158G mNTCP > R158 mNTCP

preS1C末端 (N86K領域と接する部分) の揺らぎの大きさは感染(結合)の順番と対応している

Multistep receptor binding of the hepatitis B virus preS1 domain

Nature Comm. Accepted

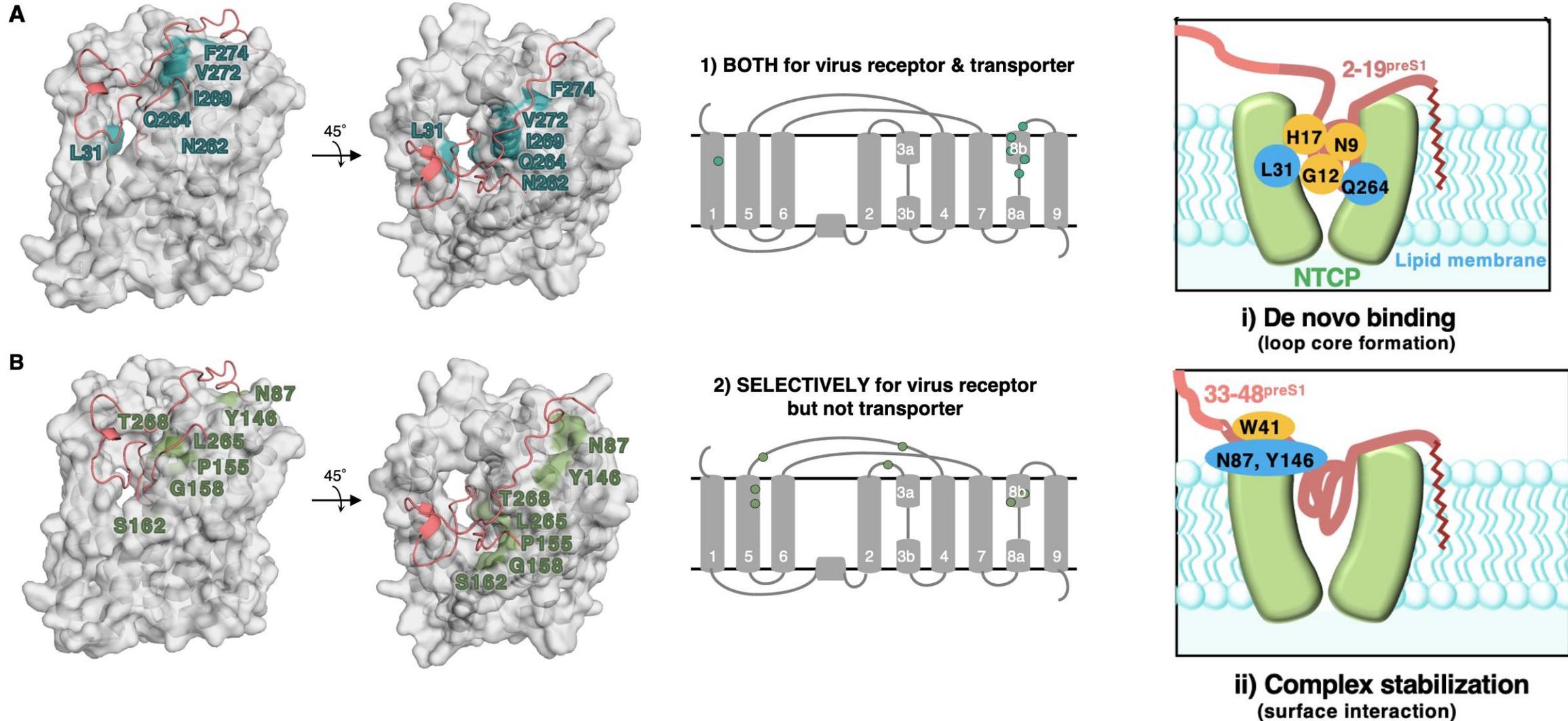
Chisa Kobayashi, Toru Ekimoto, ..., Sam-Yong Park, ..., Mitsunori Ikeguchi, Koichi Watashi



Structural mapping of NTCP distinguishes its dual functionality as a hepatitis B virus receptor and bile acid transporter

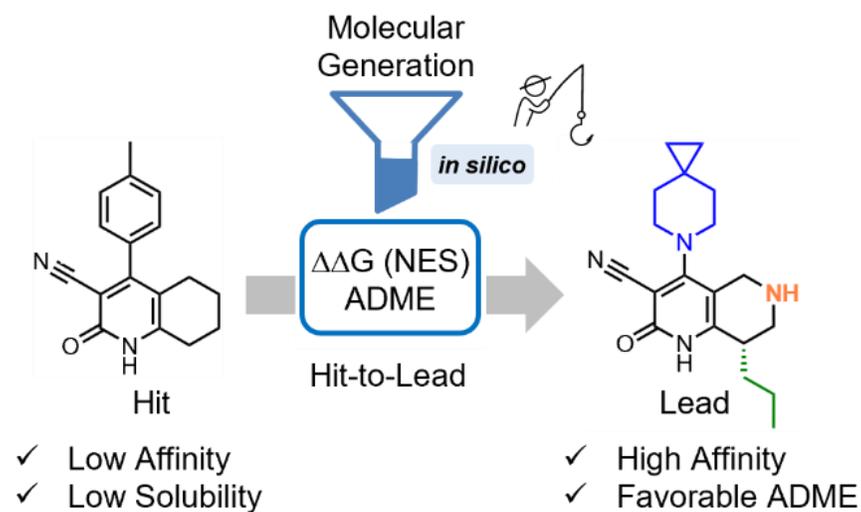
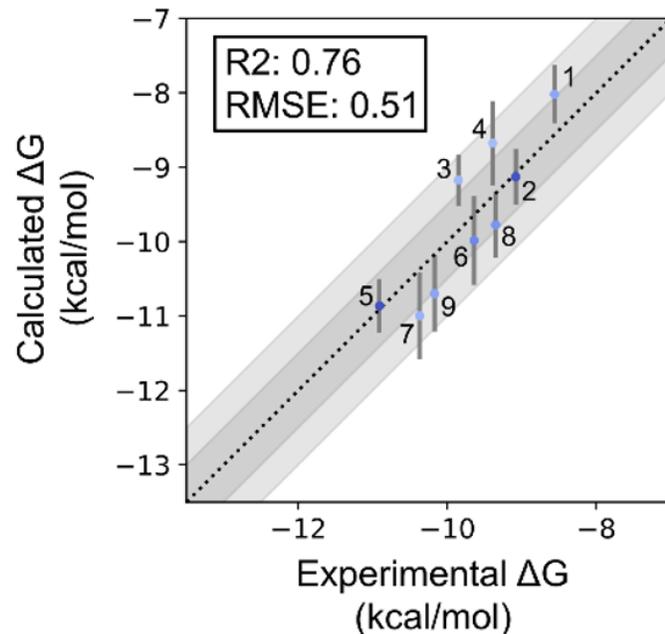
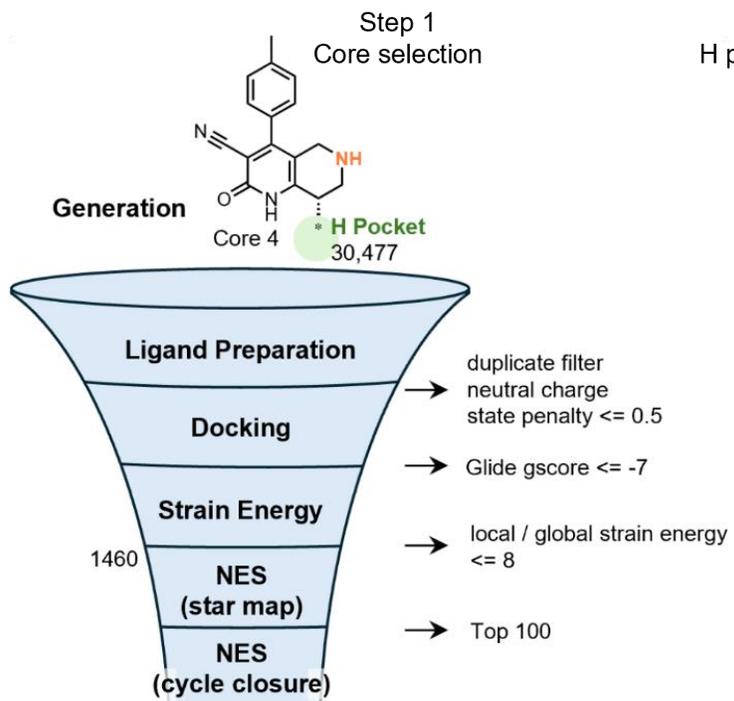
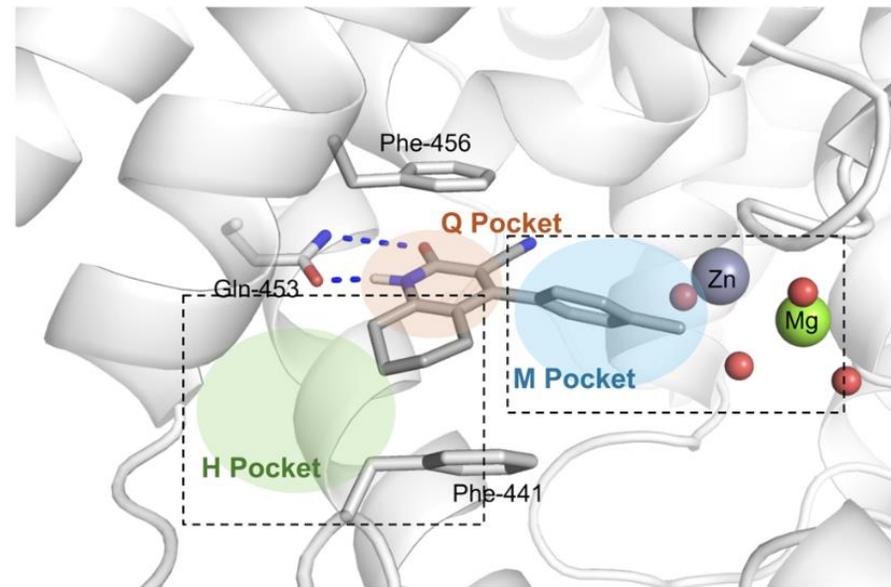
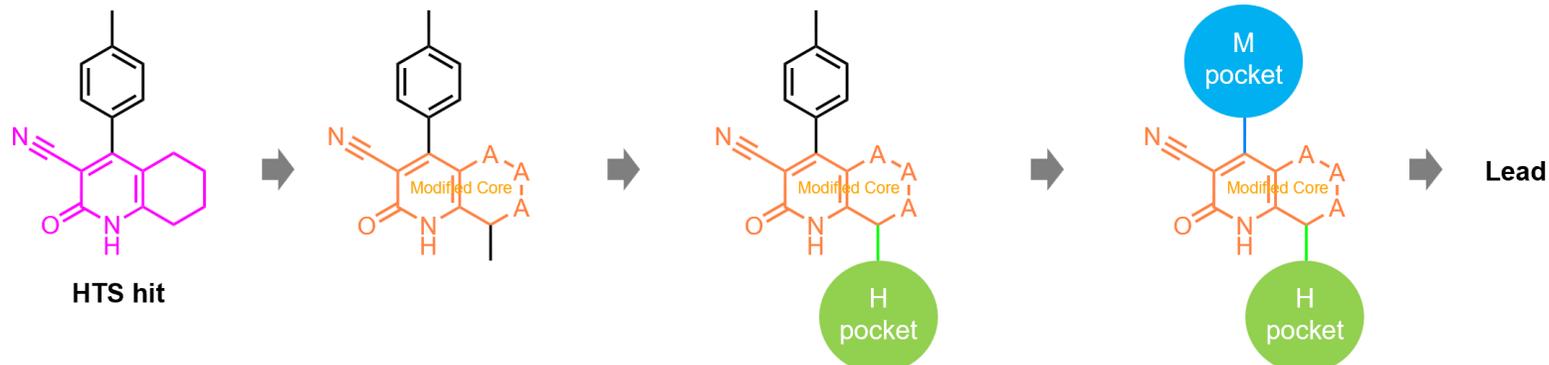
PLOS Pathogen Accepted

Kayo Matsuzawa, Toru Ekimoto, ..., Sam-Yong Park, Mitsunori Ikeguchi, ..., Koichi Watashi



In silico-driven protocol for hit-to-lead optimization: a case study on PDE9A inhibitors

Hiroyuki Ogawa, Masateru Ohta & Mitsunori Ikeguchi *J Comput Aided Mol Des* **40**, 24 (2026).



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Koichi Watashi

Kaho Shionoya

Chisa Kobayashi

Kayo Matsuzawa

Funds

AMED BINDS, Supercomputer

“K” and “Fugaku”, KAKENHI