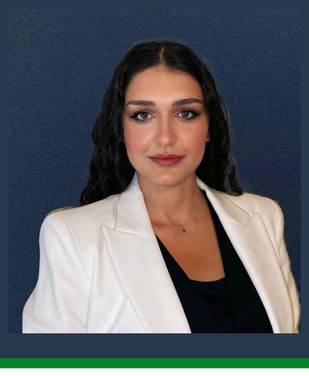
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AI-driven generative peptide design targeting the GC-C dimer for Parkinson's

Generative design and MD screening of cyclic & linear peptides that stabilise the GC-C dimer

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❶ WHY TARGET GC-C? — Parkinson's disease

The fastest-growing neurodegenerative disease in the world

11.8 M people living with Parkinson's (2021)

25.2 M projected cases by 2050

0 No therapy

Neurons die
Progressive loss of dopaminergic neurons in the substantia nigra.

GC-C is expressed there
Guanylyl cyclase C (GC-C) is present in dopaminergic neurons.

GC-C activation protects
Receptor activation raises cGMP and is neuroprotective in PD models.

GOAL

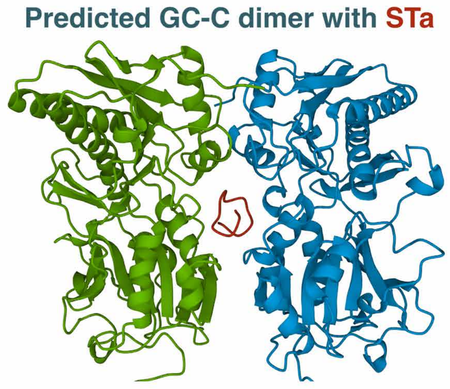
Design peptides that activate GC-C to enhance neuroprotection

GBD Study 2021 · BMJ modelling study 2025 · Cheslow et al., npj Parkinsons Dis 2024 · GUCY2C: Cell Biosci 2024

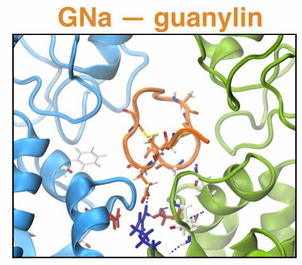
❷ THE TARGET — GC-C dimer interface

GC-C is activated by the endogenous hormones **guanylin** and **uroguanylin,** and by the bacterial **heat-stable enterotoxin** STa.

Predicted GC-C dimer with STa

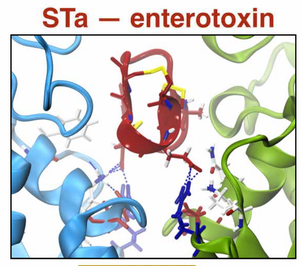


GNa — guanylin

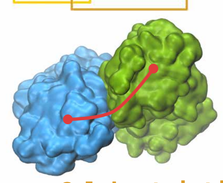


PGTCEICAYAACTGC

STa — enterotoxin



CCELCCNPACAGCY

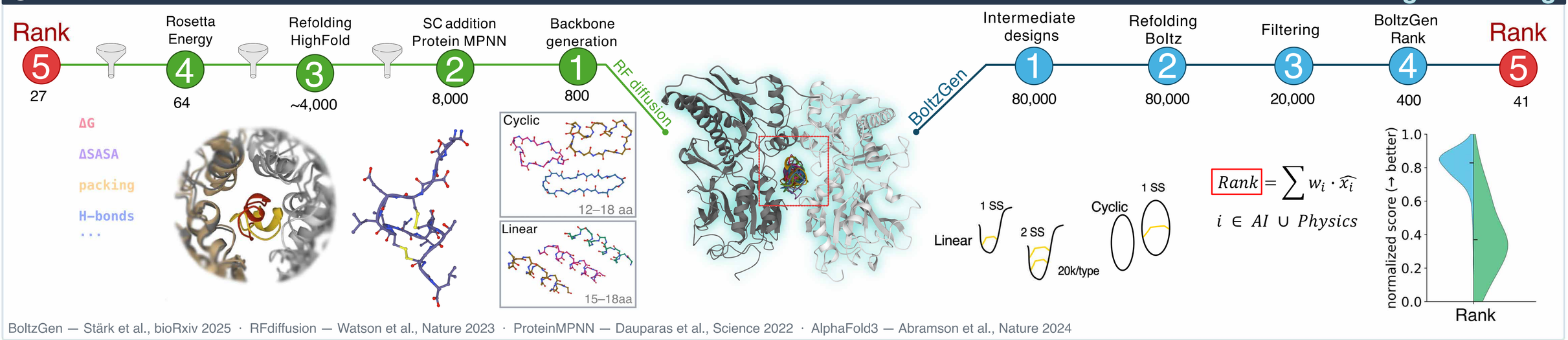


C-lobe twisting

HYPOTHESIS

A peptide that locks the two protomers together should stabilise the active dimer → sustained cGMP signalling.

❸ TWO GENERATIVE TRACKS → 68 CANDIDATES — in silico design & ranking



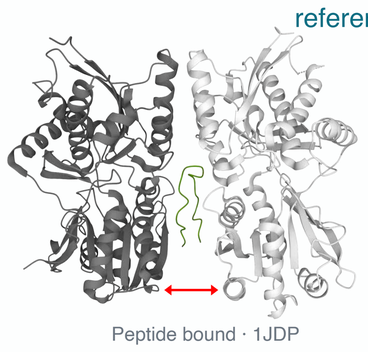
BoltzGen — Stärk et al., bioRxiv 2025 · RFdiffusion — Watson et al., Nature 2023 · ProteinMPNN — Dauparas et al., Science 2022 · AlphaFold3 — Abramson et al., Nature 2024

❹ MD SCREENING — 68 peptides · 100 ns each

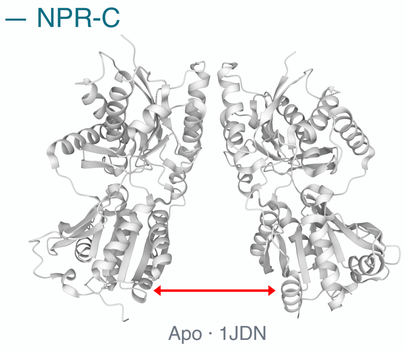
MD → Stability filter → Reject / Accept → Binding free energy

CHARMM36m | TIP3P | 150 mM NaCL | 100 nsl

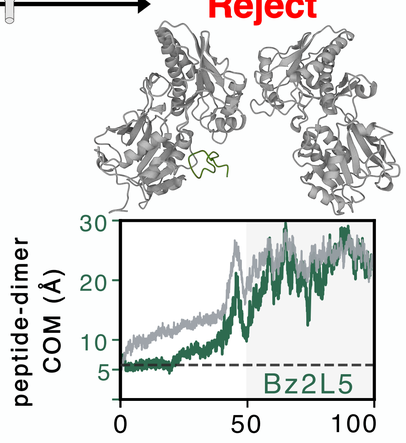
reference — NPR-C

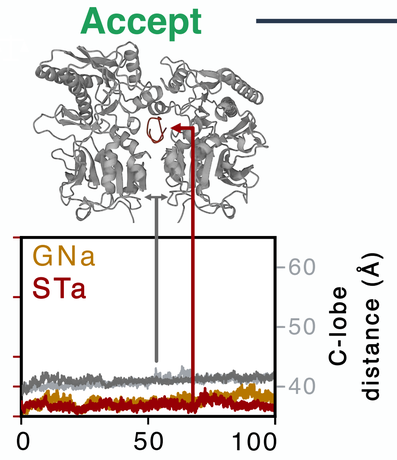


Peptide bound · 1JDP



Apo · 1JDN





Binding free energy

MM-PBSA over the last 50 ns

$$\Delta G_{bind} = \Delta G_{gas} + \Delta G_{solv}^{cpx} - \Delta G_{solv}^{rec} - \Delta G_{solv}^{lig}$$

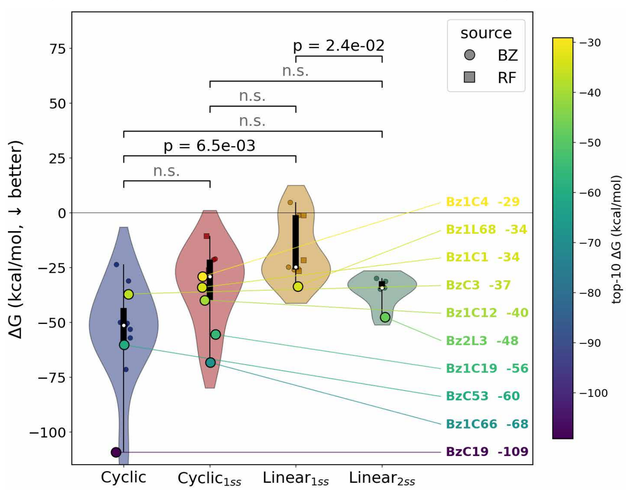
Select & advance

lowest energy + sequence diversity → toxicity, synthesisability

❺ RESULTS — MD-validated designs

Architecture matters

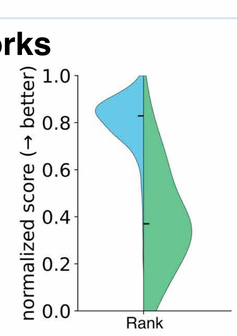
Cyclic peptides bind most favourably



The ranking method works

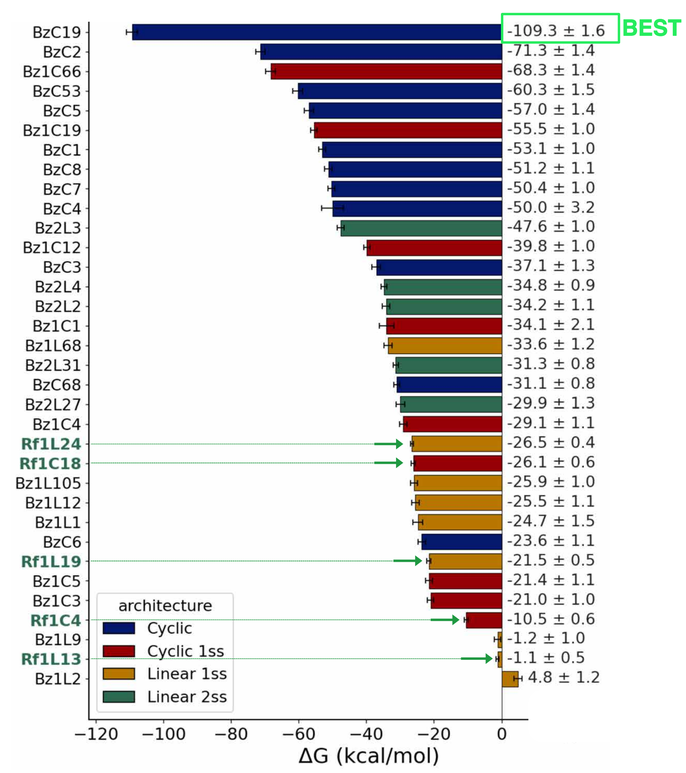
It correctly predicted

BoltzGen > RF diffusion before MD



BoltzGen outperforms RF diffusion

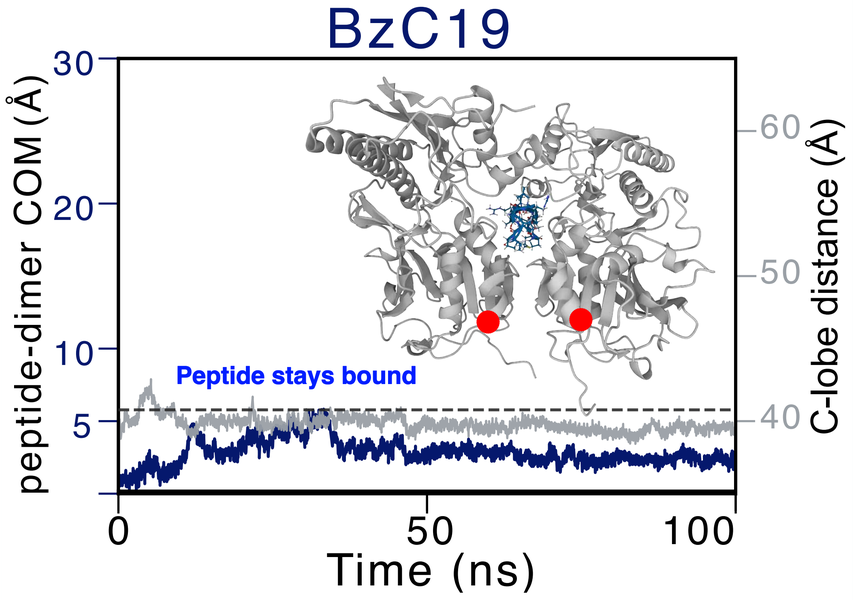
Binding free energy of the 34 designs that kept the dimer intact. BoltzGen (Bz) peptides dominate over RFdiffusion (Rf)



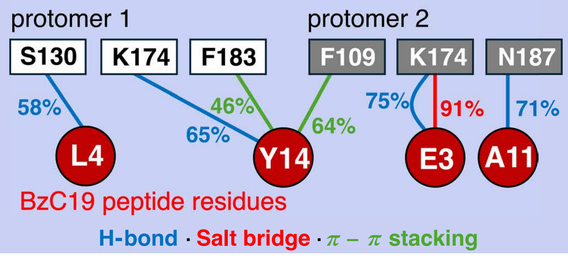
Only 5 RF diffusion peptides were able to hold protomers close & have weaker binding than Boltzgen peptides

Peptides stabilise the dimer interface

BzC19



Persistent contacts over the trajectory



CONCLUSIONS

- First generative peptide-design campaign against the GC-C dimer interface.
- Two complementary generators (BoltzGen + RFdiffusion) gave a large, chemically diverse pool.
- Our ranking predicted BoltzGen > RFdiffusion — confirmed by MD.
- Multi-stage screening: MD dimer-stability → binding free energy → developability.

OUTLOOK

Synthesis

Assay function

Neuroprotection

CONTACT

Happy to discuss collaborations.

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