Discovery and Development of an Orally Bioavailable Site-selective Covalent STING Inhibitor

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Target Deconvolution with Chemoproteomics Approach

Natural product inspired Drug Discovery and Development:
The Difficulties:

- Discovery
- Diversification
- Development

Bioactive Marine Diterpenoid "*clickable*" probes

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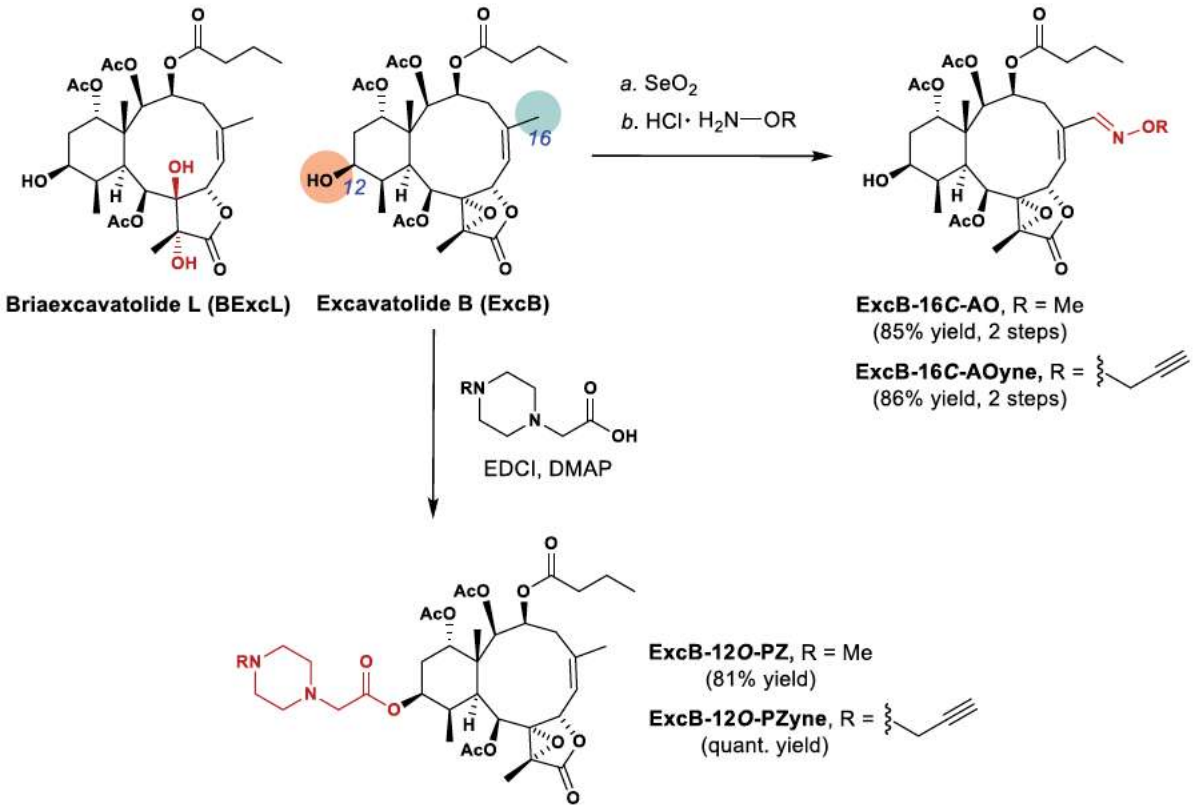
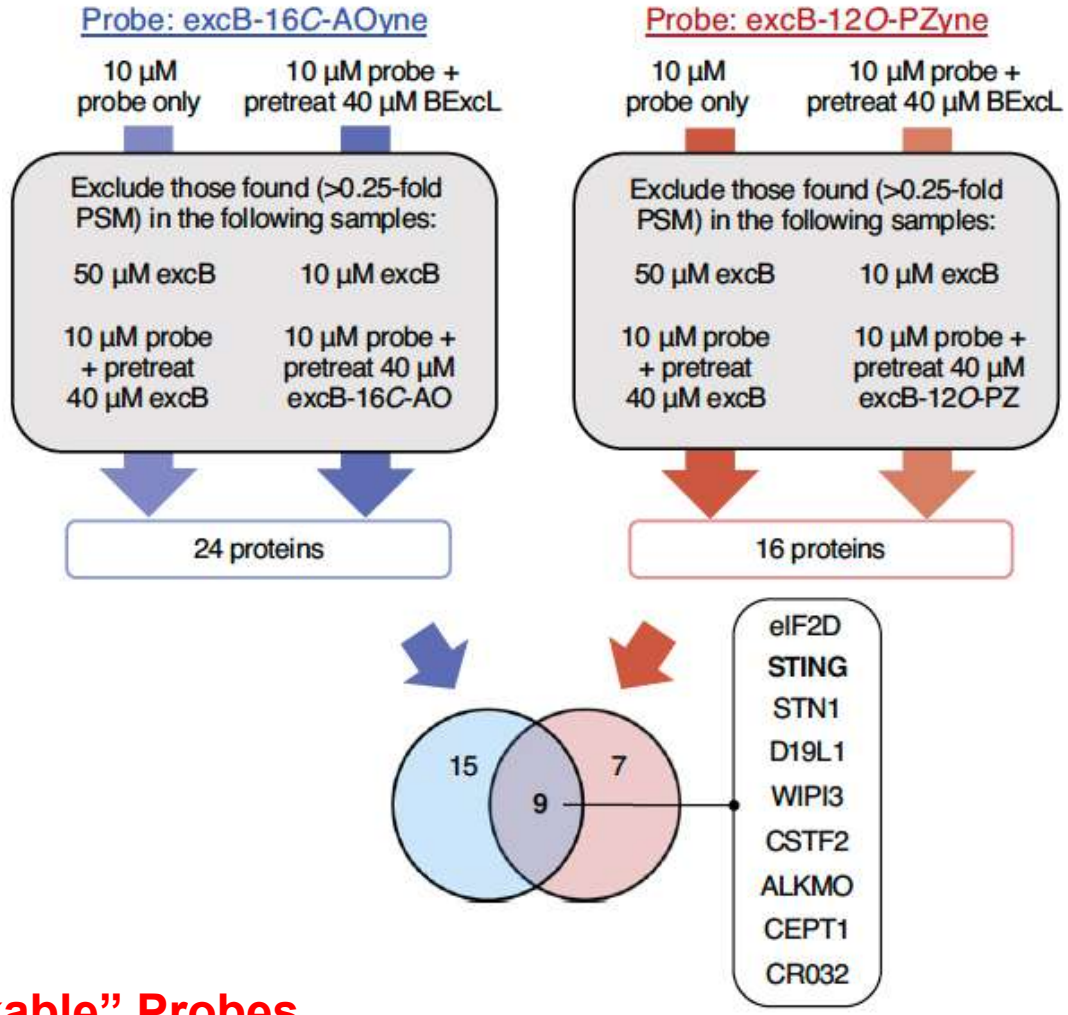
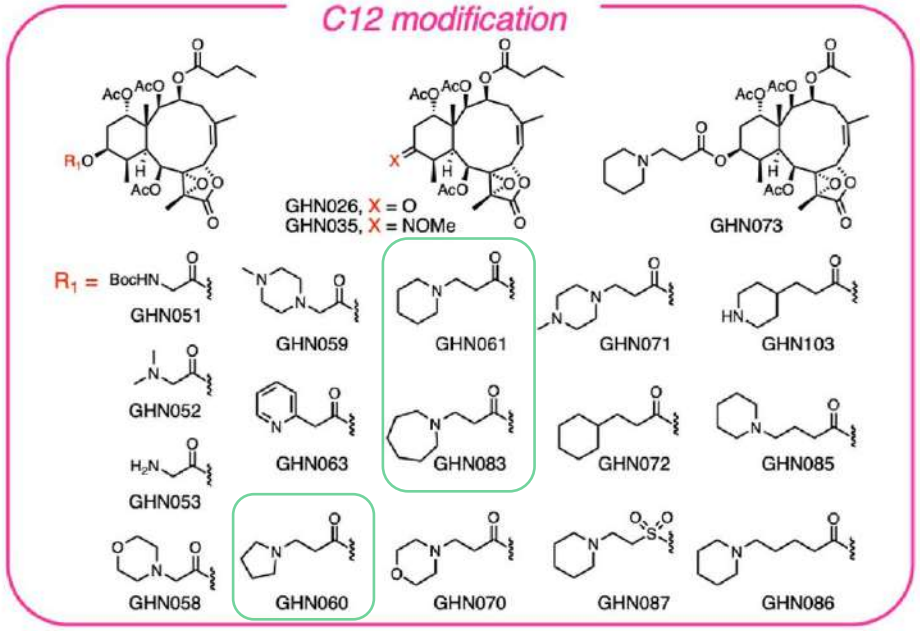
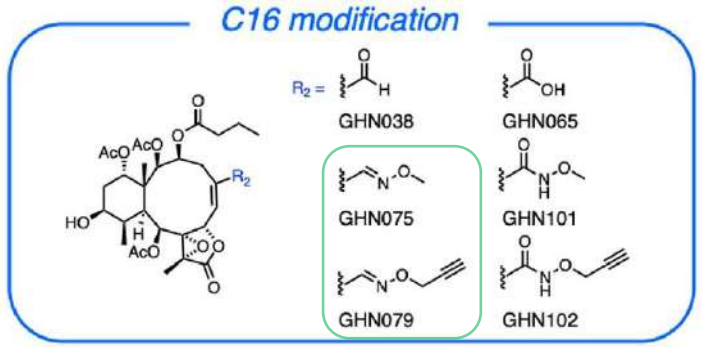


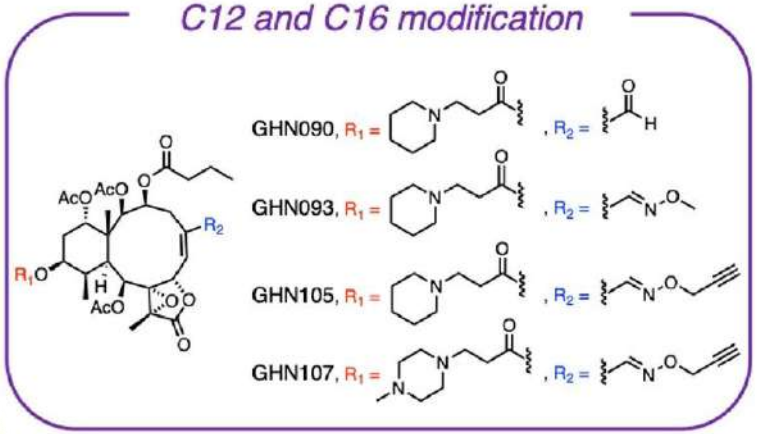


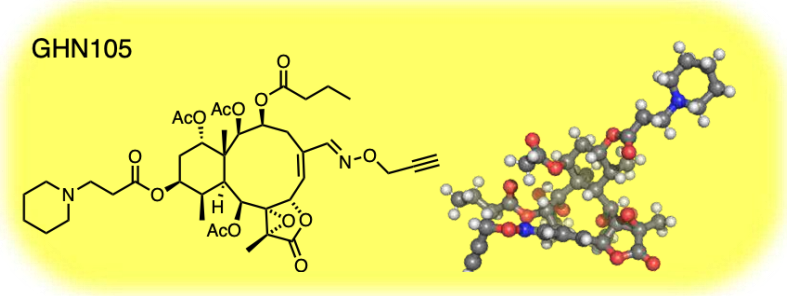
- ✓ **Design and Scalable Synthesis of "Clickable" Probes**
- ✓ **Harnessing *Active probes, compete with Active and Inactive* analogs**
- ✓ **Ranking by enrichment to derive candidate targets**

Hit-to-Lead Optimization

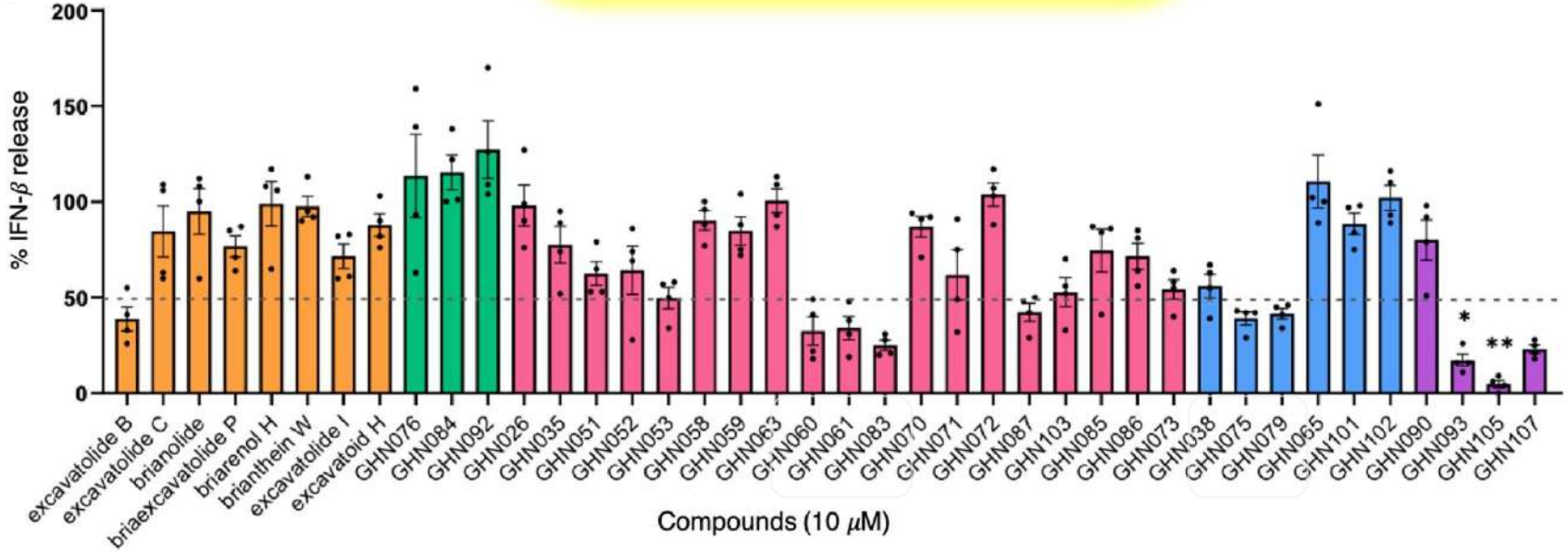








GHN105 (IC_{50} of 4.4 μM) exerted the strongest inhibition of STING-dependent IFN-β secretion in THP1 macrophages among the analogs screened.



90 => 61+38
93 => 61+75
105 => 61+79
107 => 71+79

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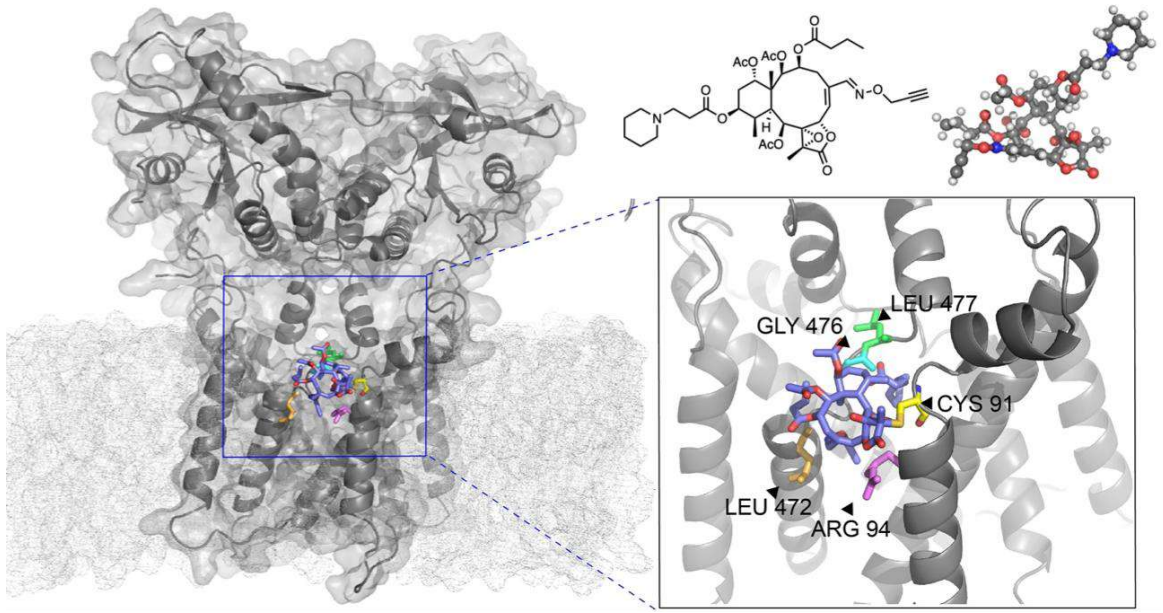
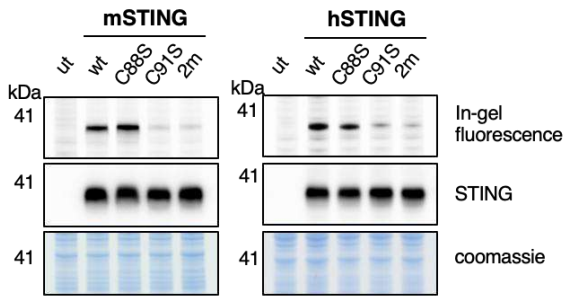
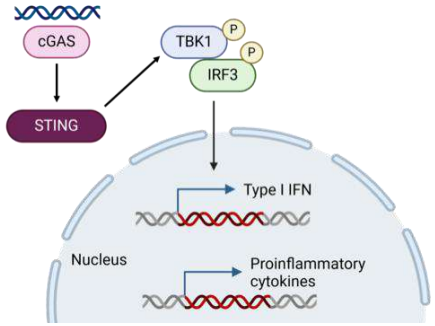
In Vitro Potency/Pharmacology

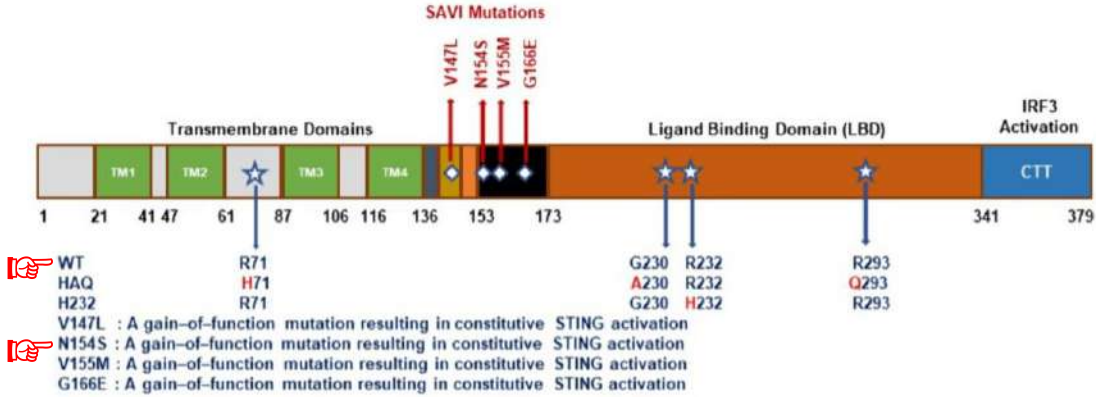
- Covalent engagement of hSTING by **GHN105** at Cys91
- Conserved residue

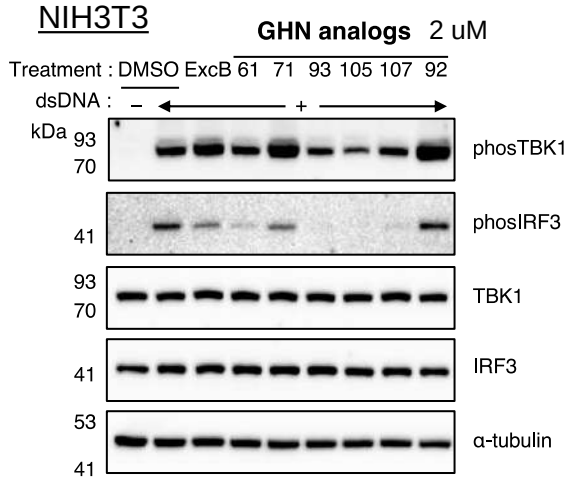


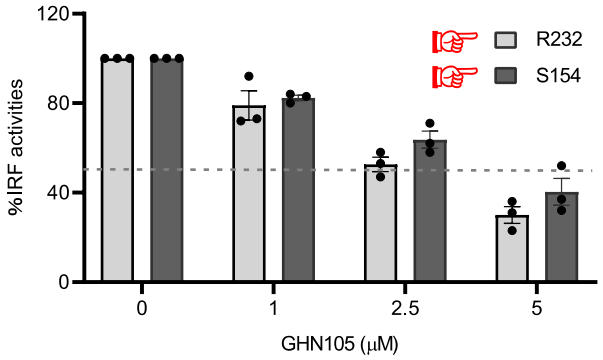




- **GHN105** strongly reduced dsDNA-induced phosphorylation of TANK-binding kinase 1 (TBK1) and IFN regulatory factor 3 (IRF3).
- **GHN105** readily reduced IFN response in wild type (Arg232) and *gain-of-function (Ser154)* hSTING knock-in THP1 reporter cells.

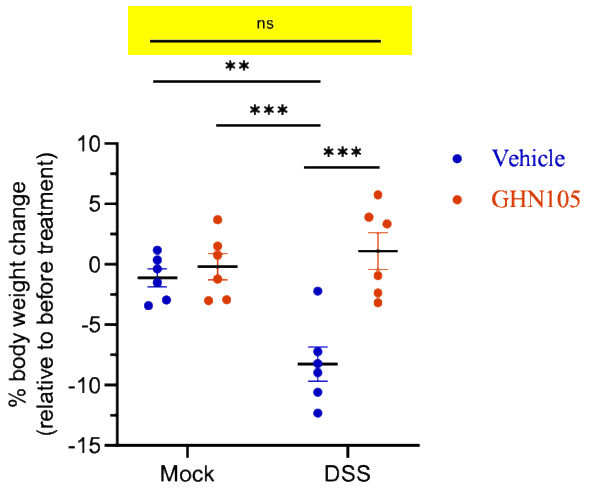




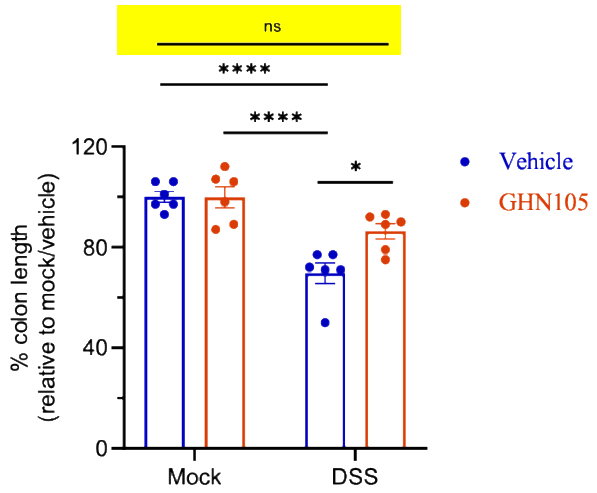


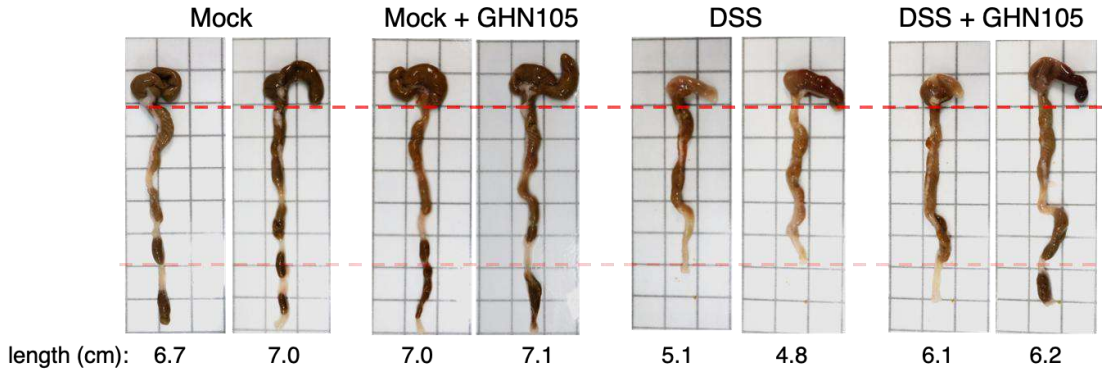
In vivo potency

Recovery in body weight

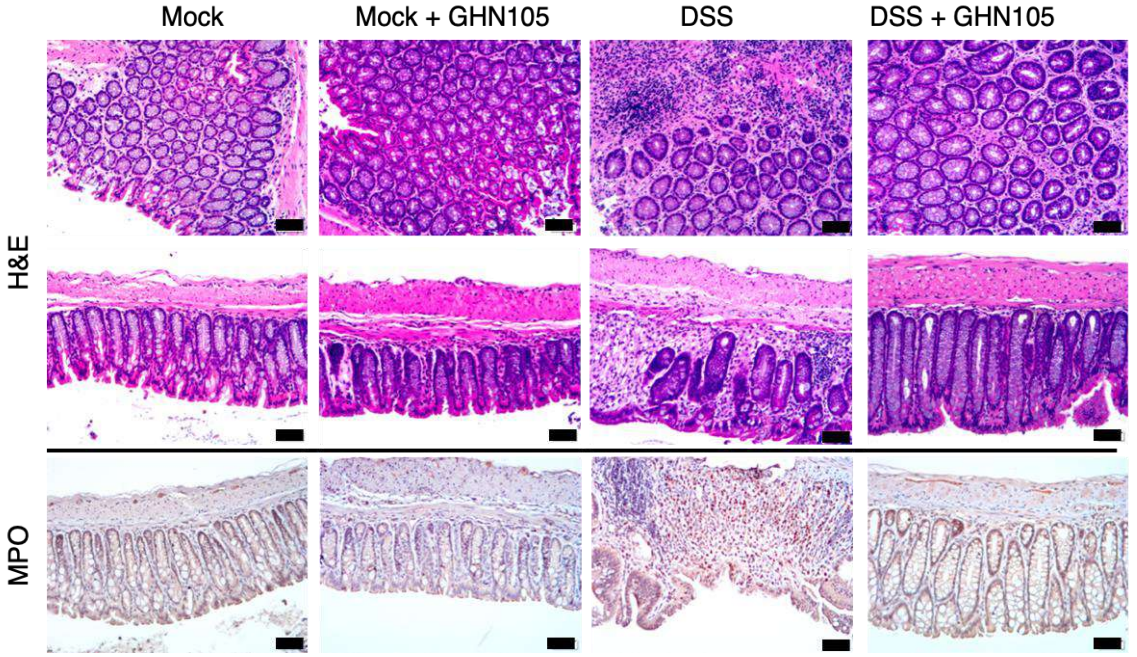


Recovery in colon length





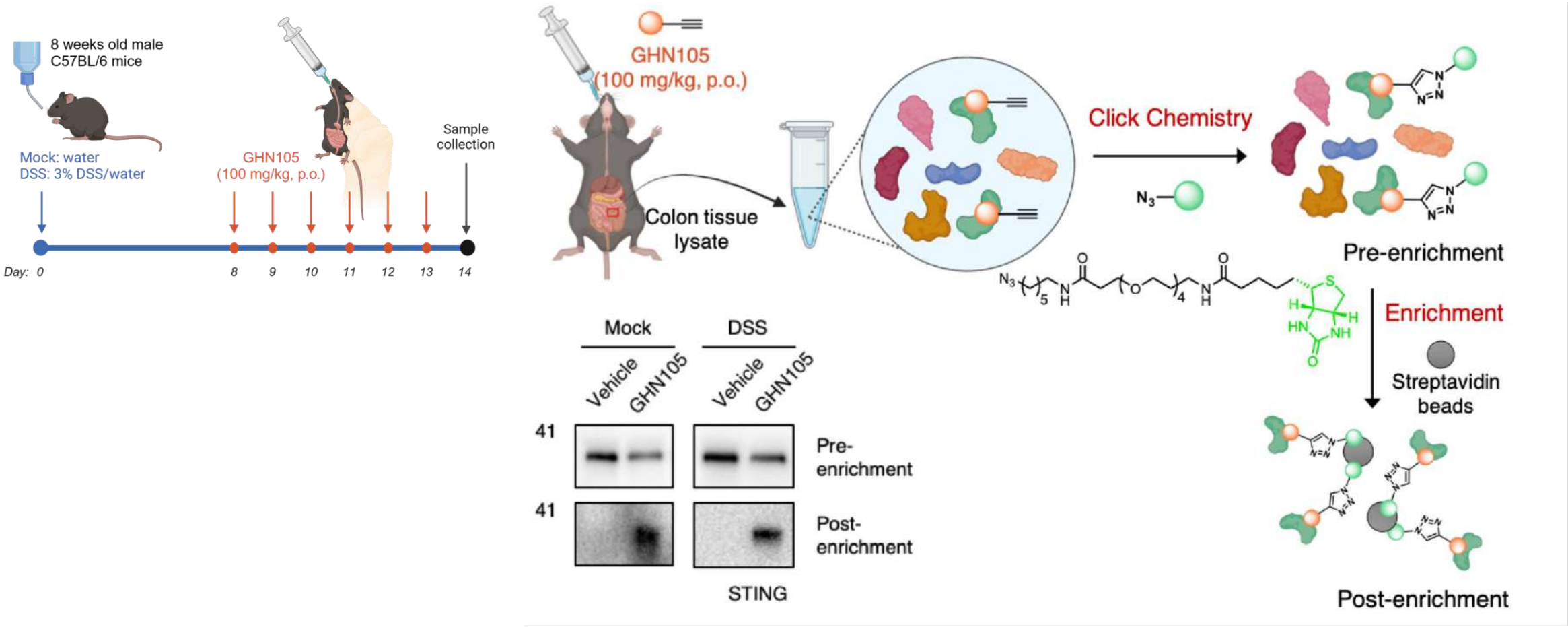
Recovery of epithelial architecture



Marked reduction of neutrophils

- *Orally administered GHN105 **reversed** pathological features in a delayed treatment acute colitis mouse model*

PK/PD Integration Models



- Protein samples were prepared from mock and DSS-treated colon sections and reacted with azide-biotin via CuAAC condition.
- After affinity purification, Western blot analysis of showed the ***in vivo* on-target engagement of STING** by **GHN105** in the colons of mice receiving oral **GHN105** treatment.