Discovery of IMU-856, a Selective Sirtuin 6 Modulator with Novel Binding Characteristics for Gastrointestinal Disease Treatment

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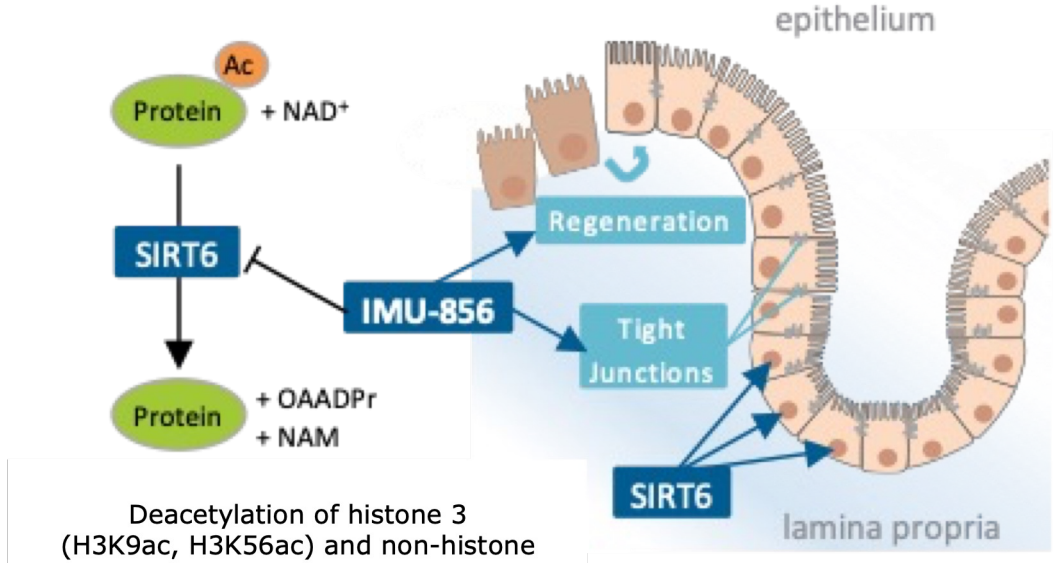
SIRT6 Modulation – Rationale for Gut Barrier Therapeutics

Sirtuins are NAD⁺-dependent enzymes
regulating histone and non-histone protein modification

SIRT6 controls transcription, genome stability, inflammation, metabolism and epithelial homeostasis through deacetylase/deacylase and ADP-ribosyltransferase activities

SIRT6 is highly expressed in **small intestine and colon, with predominant localization in intestinal epithelial cells**

Barrier dysfunction is central to **celiac disease, IBD and other enteropathies**



Deacetylation of histone 3 (H3K9ac, H3K56ac) and non-histone proteins (e.g. transcription factors, other epigenetic proteins)

→ **Key MedChem challenge is to identify potent, selective and drug-like SIRT6 modulators suitable for oral GI disease therapy**

Hit Identification Strategy for SIRT6 Modulators

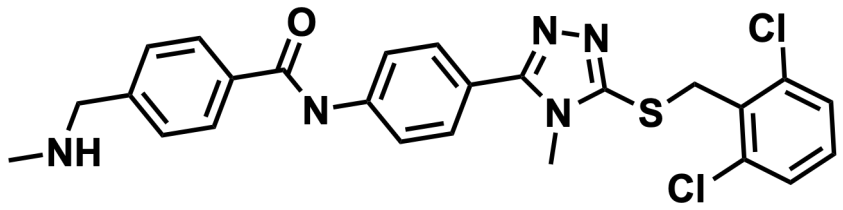
Broad screening via HTS campaign of ~500000 compounds from the in-house library of Daiichi Sankyo

- Thermal shift assay (TSA) used as primary screen
- Goal: identify compounds that bind and stabilize human SIRT6

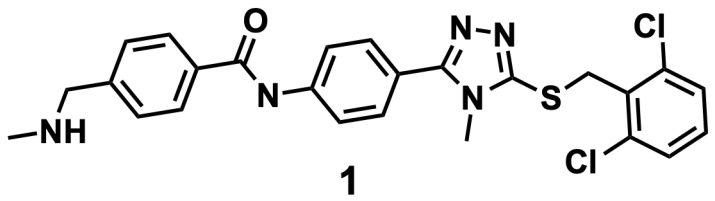
Functional validation

- AlphaLISA-based deacetylase assay as enzymatic inhibition assay
- Prioritized compounds with strong potency and reproducible target engagement

→ Initial hit identified:



Hit Characterization



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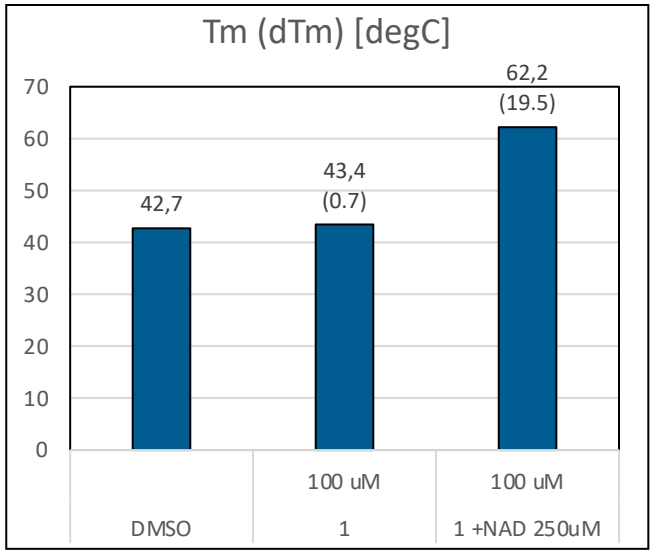
- TSA: addition of NAD^+ resulted in a substantially more pronounced **thermal shift (19.5°C)**
- Deacetylase activity assay (AlphaLISA): IC_{50} = 37 nM for SIRT6
- Surface plasmon resonance (SPR) showed strong binding responses in the presence of NAD^+

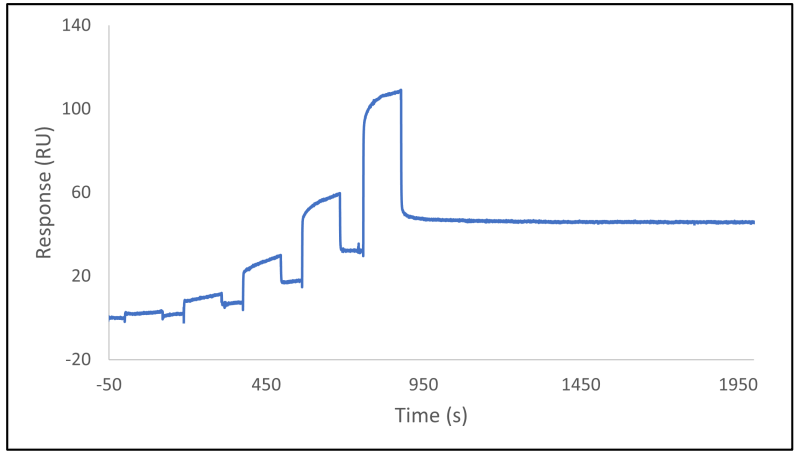
→ Observed markedly slow dissociation kinetics suggest formation of highly stable complexes with SIRT6

- **Drawbacks:** low metabolic stability human liver microsomes, high protein binding and low permeability

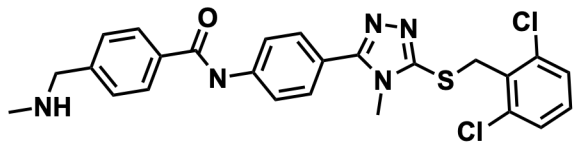
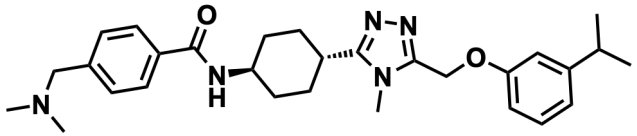
TSA



SPR



Hit Optimization I

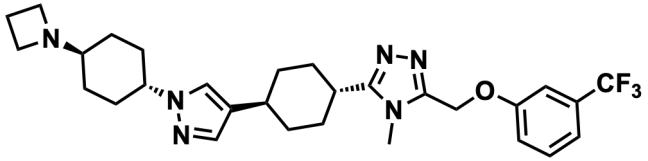
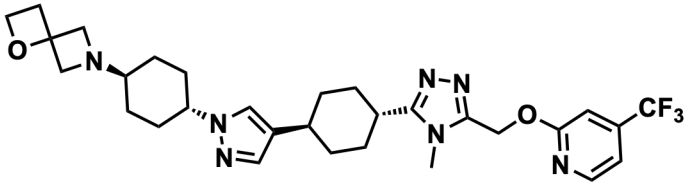
ID	structure	IC_{50} [a] (SIRT6)	metabolic stability human/mouse[b] (% remaining)	cLogP[c]	Protein binding[d] (%unbound)	Pe[e] (x10^{-6} cm/s)
HTS hit		37 nM	1/44	4.97	<0.2	0.1
2 [1]		15 nM	75/72	4.20	14.9	9.4

[a] IC_{50} values were calculated from duplicate experiments by the least-squares method.
[b] Proportion of test compounds (1.0 µM) remaining after incubation for 30 min with liver microsomes (0.1 mg/mL).
[c] Consensus cLogPo/w from www.swissadme.ch/index.php.
[d] Protein binding was tested using BALB/c mouse serum samples.
[e] Permeability (Pe, at pH 7.4, 10^{-6} cm/s) was determined using PAMPA Evolution FP software (Pion).

→ **Thioether replacement and increased sp^3 character retained SIRT6 potency while improving key developability properties: microsomal stability, free fraction and permeability**

[1] WO2019/054430 (Daiichi Sankyo)

Hit Optimization II

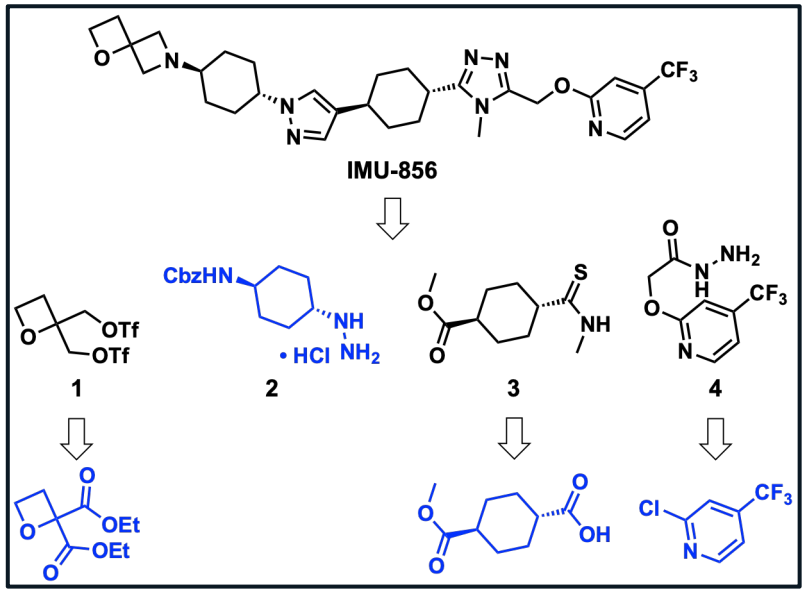
ID	structure	IC_{50} [a] (SIRT6)	metab. stability human/mouse [b] (% remaining)	pK_a cLogP [c]	Protein binding [d] (%unbound)	Pe [e] (x10^{-6} cm/s)	CL [f] (mL/min/kg)	AUC_{all} [g] (µg·h/mL)
3		4.0 nM	54 / 90	9.4 4.90	9.2	35	10.8	19.6
IMU-856		44 nM	56 /71	7.6 4.18	18.5	29	1.69	49.0

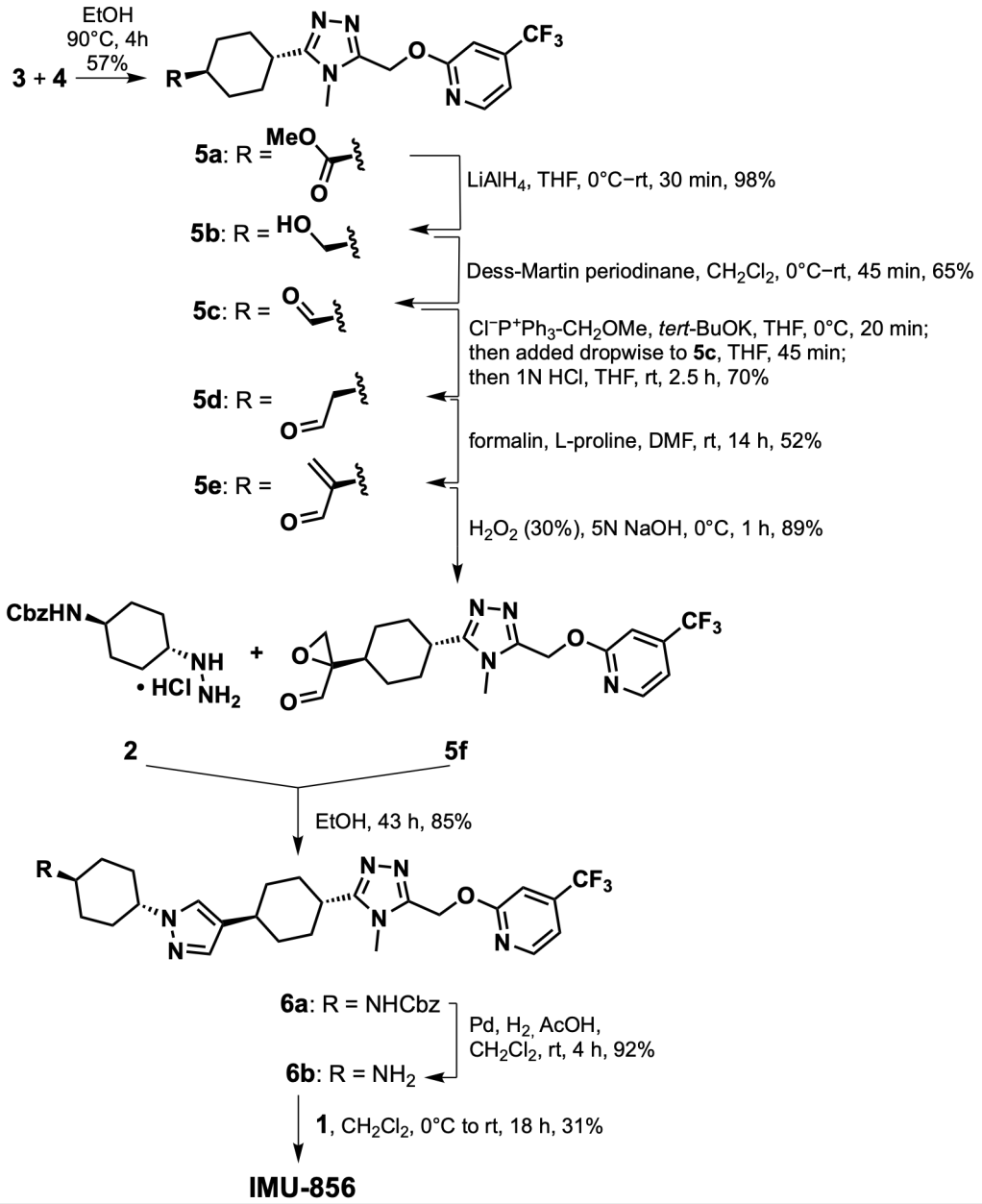
[a] IC_{50} values were calculated from duplicate experiments by the least-squares method.
[b] Proportion of test compounds (1.0 µM) remaining after incubation for 30 min with liver microsomes (0.5 mg/mL).
[c] Consensus cLogPo/w from www.swissadme.ch/index.php.
[d] Protein binding was tested using BALB/c mouse serum samples.
[e] Permeability (Pe, at pH 7.4, 10^{-6} cm/s) was determined using PAMPA Evolution FP software (Pion).
[f] Compounds were dosed iv at 1 mg/kg to mice.
[g] Compounds were dosed po at 10 mg/kg to mice.

- **2** → **3**: Amide-to-pyrazole exchange rigidified the linker and boosted SIRT6 potency
- **3** → **IMU-856**: Spiro-oxetane introduction lowered basicity, improving clearance and oral exposure

→ **MedChem optimization balanced potency and developability through thioether replacement, increased sp^3 character, linker rigidification and basicity tuning**

Synthesis – MedChem Route

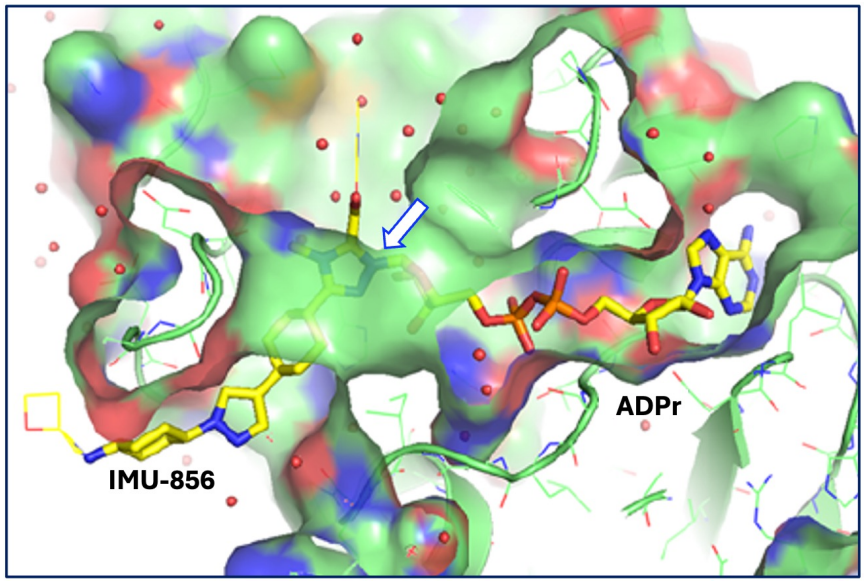


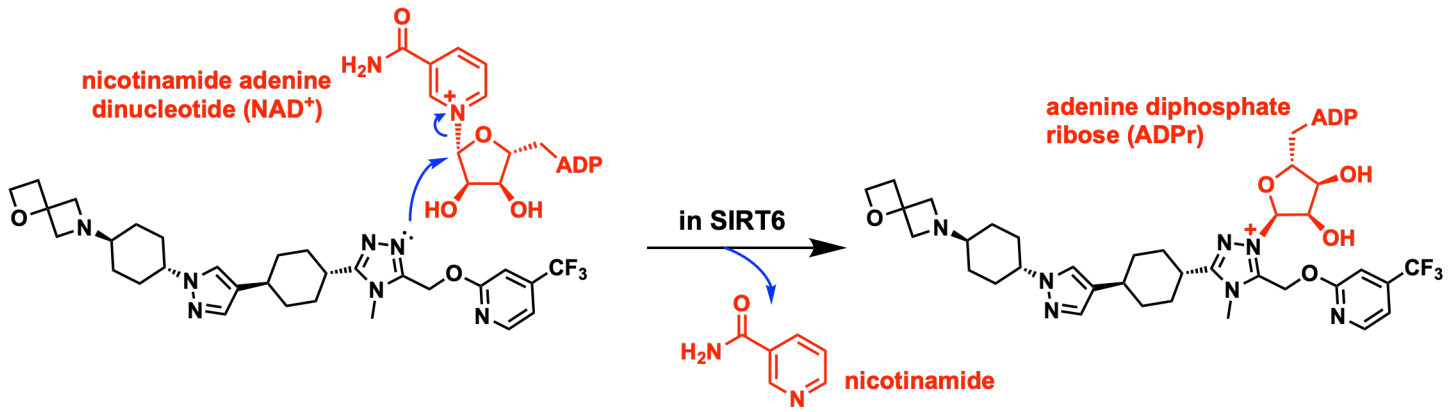


- The IMU-856 route uses a convergent synthesis strategy, preparing three key building blocks that are assembled through triazole-core formation and late-stage pyrazole construction[2]
- Stable epoxyaldehyde **5f** served as a key intermediate, enabling efficient pyrazole formation (while retaining stereochemical integrity) and convergent assembly of the IMU-856 scaffold

[2] WO2019/054427 (Daiichi Sankyo)

Binding Characteristics (X-ray)





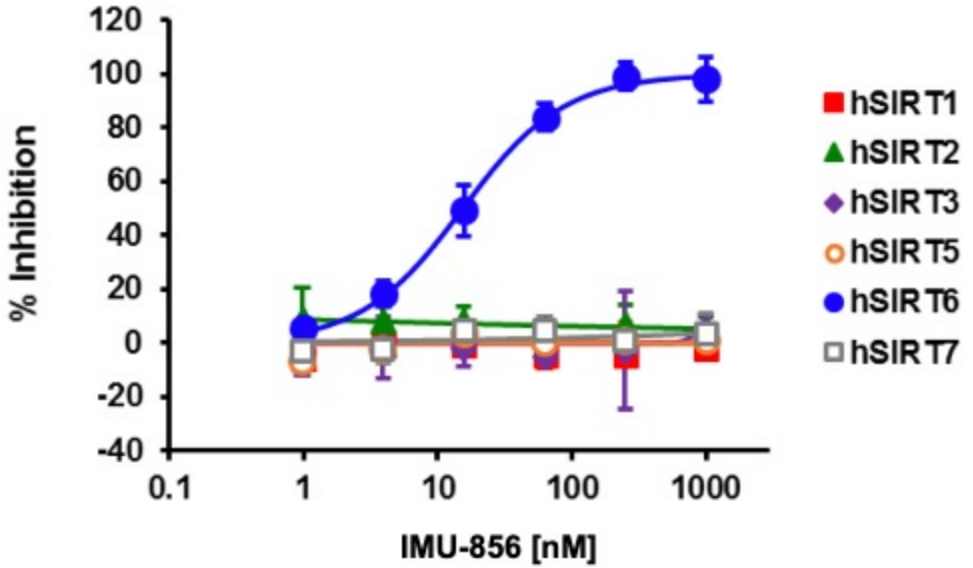
- X-ray structure confirmed NAD⁺-dependent SIRT6 target engagement
- IMU-856 forms a covalent ADP-ribose conjugate in the active site
- The adduct spans the NAD⁺ and substrate-binding pockets, explaining tight binding and stabilization

→ **The X-ray structure supports an emerging mechanism-based sirtuin inhibition concept in which precisely positioned triazoles hijack NAD⁺ chemistry to form stalled ligand-ADP-ribose adducts, consistent with recently described "Sirtuin Trapping Ligands"**[3]

[3] Friedrich et al., *Angew. Chem. Int. Ed.* **2025**, 64, e16782 (Univ. Freiburg)

SIRT6 Selectivity

Enzyme	Assay	IMU-856
SIRT6 (h, m, r, cyno)	*in vitro* histone deacetylase activity assay	IC_{50} = 15/41/28/31 nM
SIRT1/2/3/5/7 (h)	*in vitro* deacetylase activity assay	IC_{50} >1000 nM; <10% inh. @1 µM
SIRT6 (h)	*in vitro* histone deacetylase and demyristoylase activity assay	IC_{50} = 55 and 41 nM
SIRT6 (h)	cellular histone deacetylase activity assay in HT-29 cells	EC_{50} = 4.3 nM



- IMU-856 potently inhibits SIRT6 across species while sparing other human sirtuins, with no meaningful inhibition of SIRT1/2/3/5/7 at 1 µM
- Selectivity extends beyond the sirtuin family, with no inhibition of HDAC1-9 and -11, or nuclear extract at 1 µM, supporting a differentiated SIRT6-focused profile

→ IMU-856 is a selective inhibitor of the deacetylase activity and stabilizer of the SIRT6 protein

In vitro Pharmacology Profiling

Assays	IMU-856
ADME properties	
Thermodynamic solubility (mg/mL)	pH 1.2 (HCl): 39 pH 6.8: 0.09 FaSSIF [a]: 0.24 FeSSIF [a]: 3.1
Microsomal stability $t_{½}$ (min)	>60 (h/m/r)
Hepatocyte stability $CL_{int,u}$ (µL/min/million cells)/$t_{½}$ (min)	<1.76/>395 (all species)
Plasma protein binding (%)	human: 95.5 mouse: 95.4 rat: 91.7 dog: 91.1 cyno: 92.9
Intestinal permeability Caco-2 (pH 7.4) P_{app} A→B (×10^{-6} cm/s)/ER	21.5/0.9

Assays	IMU-856
Target selectivity and toxicity profiling	
CEREP SafetyScreen (10 µM, 87 targets)	No hits
hERG channel (HEK293 cells) IC_{50}	>10 µM
human efflux transporter IC_{50} (µM)	MDR1: 14 BCRP: 8.5 BSEP: no inh. @ 10 µM
human SLC transporter IC_{50} (µM)	OCT2: 6.3 MATE1: 2.0 MATE2-K: 5.7 >30 µM for OATP1B1*1a and OATP1B3 no inh. @ 30 µM for OAT1, OAT3 and OCT1
CYP450 inhibition IC_{50} in HLMs	>10 µM for 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4
Ames and micronucleus assay	negative

- Favorable ADME profile: high metabolic stability, high Caco-2 permeability, and minimal efflux
- Clean safety pharmacology: no CEREP off-target hits and no hERG inhibition up to 10 µM
- Low DDI/genotox risk: weak CYP/transporter liability and negative Ames/micronucleus assay

→ Overall, the favorable ADME, clean off-target profile, and low *in vitro* safety/DDI liability support IMU-856 as a developable oral SIRT6 modulator for clinical translation

Pharmacokinetic Properties

		mouse	rat	dog	monkey
Gender/strain/condition		male, C57BL/6J, fed	male, SD, fed	male, beagle, fasted [b]	male, cyno, fasted
Doses (mg/kg)		1 iv/3 po	1 iv/3 po	0.5 iv/3 po	0.5 iv/3 po
CL (mL/min/kg)	iv	1.69	22.9	5.47	3.00
V_d (L/kg)	iv	0.690	7.61	5.19	1.71
$t_{½}$ (h)	iv	5.42	5.36	11.4	7.63
AUC_{all} (μg·h/mL)	po	19.9	1.44	8.45	17.7
C_{max} (μg/mL)	po	1.60	0.132	0.527	1.37
t_{max} (h)	po	3.00	3.33	5.33	2.67
F (%)	po	67	66	92	106

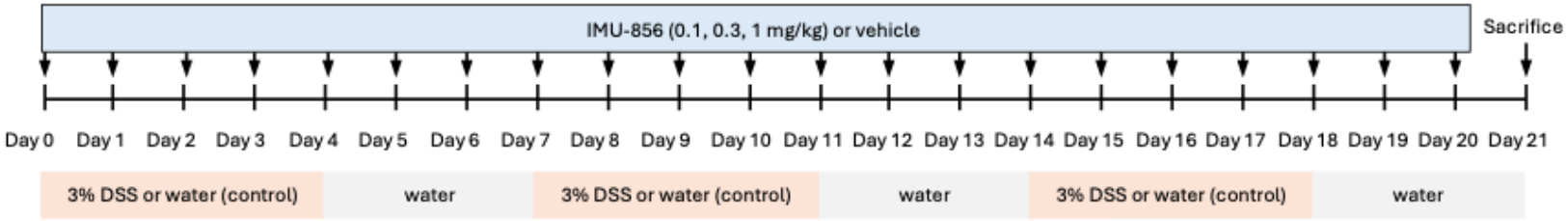
[a] Mean values; dosing formulation: suspension in 0.5% methyl cellulose (MC) for po, DMA/Tween80/saline = 10/10/80 (mouse, rat) and DMSO/PEG400/saline = 10/10/80 (dog, monkey) for iv;

[b] Pentagastrin treated at 60 μg/0.4 mL/body at 30 minutes, right before and 30 min after po administration of **IMU-856**.

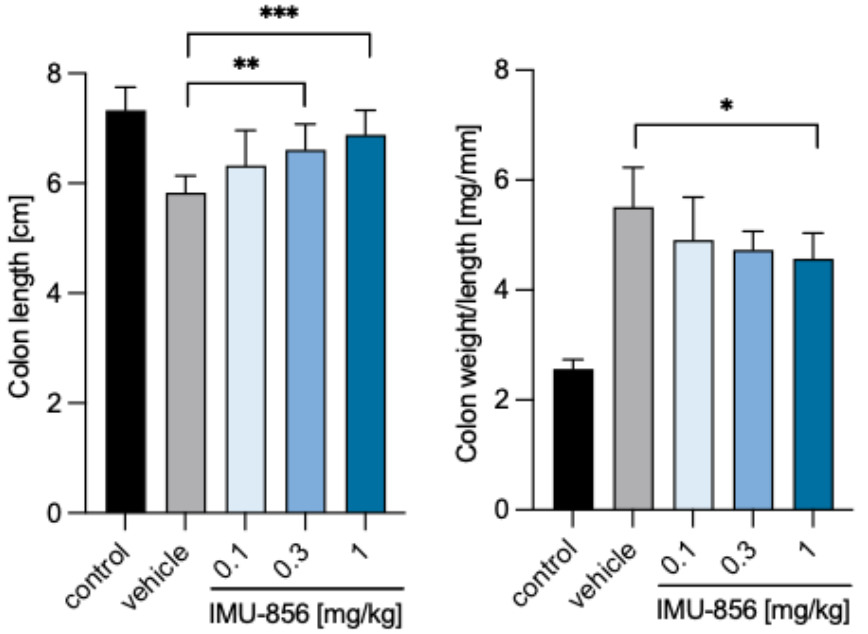
- Low-to-moderate clearance and sustained half-lives across species support durable systemic exposure
- Oral dosing achieved quantifiable exposure with moderate-to-high bioavailability across mouse, rat, dog, and cynomolgus monkey

→ **Cross-species PK supports sustained oral exposure and once-daily dosing potential for IMU-856**

In vivo Efficacy in Chronic Murine DSS-Induced Colitis Models



- **Oral IMU-856 reduced DSS-induced colitis severity**, preserving colon length in acute and chronic mouse models
- **Dose-dependent efficacy was observed during injury and recovery phases**, supporting effects on mucosal protection and regeneration
- **Combination with tacrolimus further attenuated colon shortening**, suggesting complementary benefit with anti-inflammatory therapy

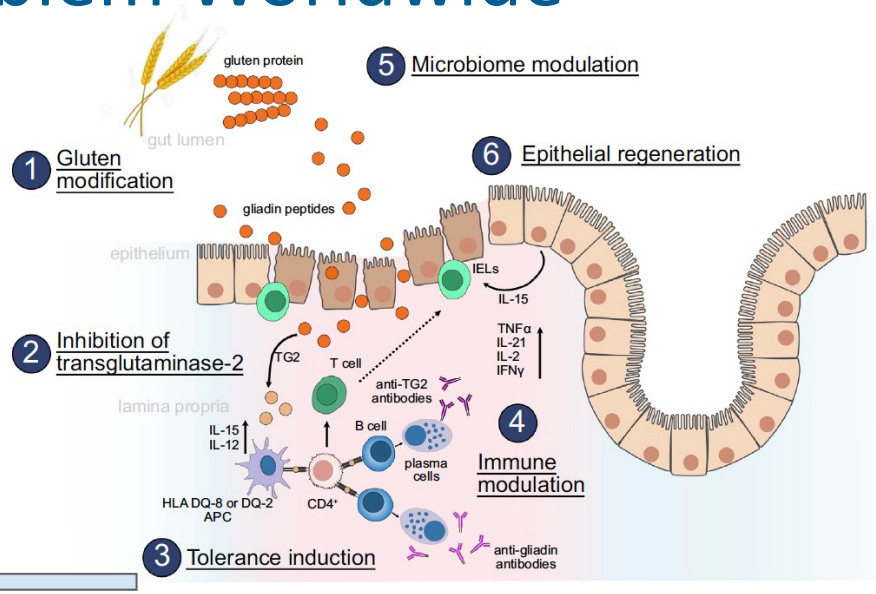


The colon length and colon weight were measured on day 21 following euthanasia. The left panel shows mean colon length ± S.D (n = 10 per group), while the panel on the right shows the colon weight per length ratio ± S.D (n = 10 per group). Statistical analysis using Dunnett's test (comparison to DSS-vehicle group) * P < 0.05, ** P < 0.01, *** P < 0.001.

→ **Overall, oral IMU-856 showed reproducible efficacy across acute, recovery and chronic DSS colitis models, supporting SIRT6 modulation as a barrier-restoring strategy in intestinal inflammation**

Celiac Disease is a Major Public Health Problem Worldwide

- ~1% prevalence; major global health burden
- Rising incidence and substantial underdiagnosis worldwide
- Many patients symptomatic despite gluten-free diet
- Gluten-free diet insufficient and difficult to maintain
- No approved drug therapies available today
- Several development programs ongoing:[4]



	Specific to celiac disease				Can go beyond celiac disease			
Company	ZymagenX™	TOPAS THERAPEUTICS	Takeda	Takeda	teva	sanofi	First Tracks BIOTHERAPEUTICS	Immunic THERAPEUTICS
Program	latiglutenase	TPM-502	TAK-101	TAK-227	TEV-53408	amlitelimab	ANB033	IMU-856
Approach	Gluten modification	Immune tolerance	Immune tolerance	TG2 inhibition	Immuno-modulation	Immuno-modulation	Immuno-modulation	Barrier regeneration
Delivery	Oral	Intravenous	Intravenous	Oral	Intravenous	Subcutaneous injection	Subcutaneous/ intravenous	Oral
Stage	Phase 3 ready	Phase 2a completed	Phase 2 completed	Phase 2b ongoing	Phase 2 ongoing	Phase 2 ongoing	Phase 1b ongoing	Phase 2 ready

[4] Buriánek *et al.*, *Drug Discov. Today* **2024**, 29, 104113

Clinical Phase 1 Results

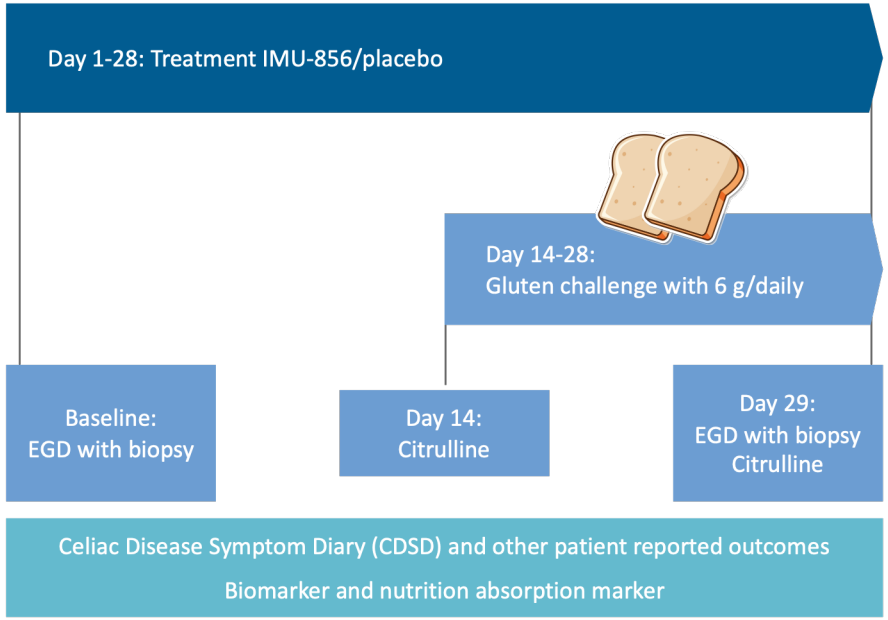
- Proof-of-concept Phase 1b study in celiac disease patients (80/160 mg once-daily) looking for histological changes, blood biomarkers, nutrient uptake and patient-reported symptoms

→ well-tolerated, dose-linear PK and steady-state trough levels achieved within first week of dosing

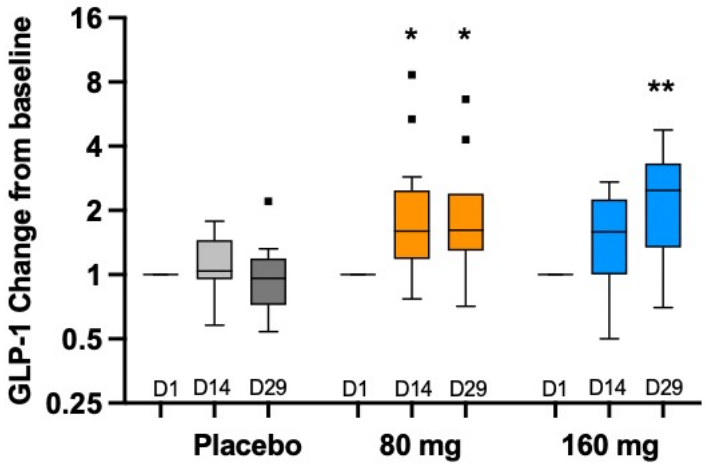
→ consistent signals across 4 outcome domains:[5]

- **Gut architecture:** reduced gluten-induced villous damage vs. placebo (p = 0.04)
- **Biomarker response:** dose-dependent increased citrulline levels (despite gluten challenge)
- **Nutrient absorption:** increased Vitamin B12 and zinc blood levels
- **Symptoms:** reduced gluten-induced symptom scores
- **No immune suppression observed**
- **Increased plasma GLP-1 concentrations[6]**

Flow Chart of Phase 1b Clinical Trial in Celiac Disease



GLP-1 plasma concentration
D14 and D29 change from baseline

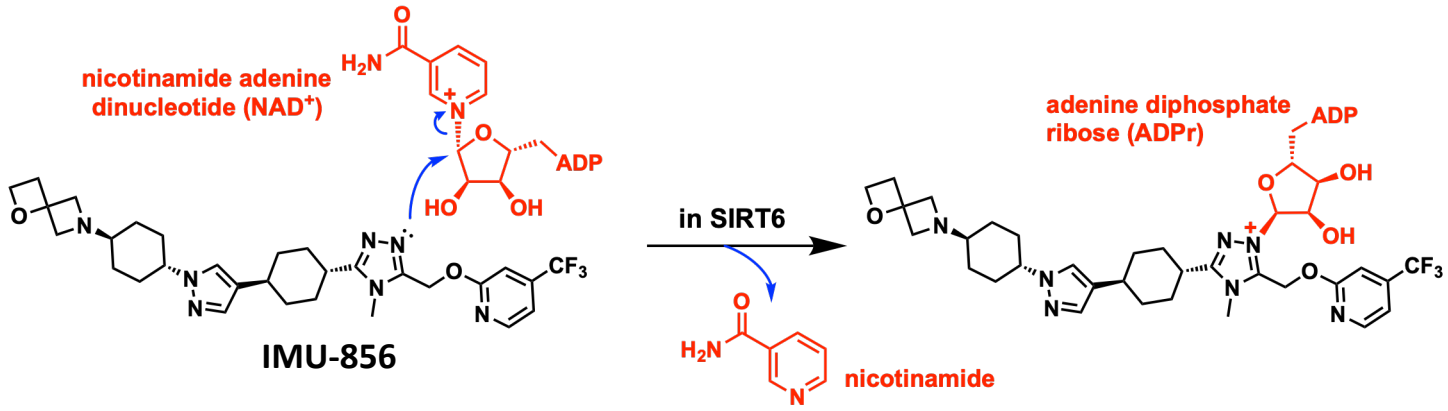


Statistics: two-sided Mann-Whitney U - treatment vs. placebo at Day 14 and Day 29, * P < 0.05, ** P < 0.01

[5] Daveson *et al.*, *Lancet Gastroenterol. Hepatol.* **2025**, 10, 44; [6] WO2025/252661 (Immunic AG)

Summary and Outlook

- **IMU-856: first-in-class, orally available SIRT6 modulator with a novel binding mode driving epithelial regeneration and barrier restoration**



- **Clinical PoC in Phase 1b (celiac disease): improvements observed in villous structure, symptoms, biomarkers and nutrient absorption**
- **Favorable safety and tolerability profile to date, with no evidence of immune suppression**
- **Beyond celiac disease,[7] the approach has potential applicability across GI diseases with barrier dysfunction, e.g. inflammatory bowel disease,[7] graft-versus-host disease[8] or bile acid diarrhea[9]**

[7] WO2024/227956 (Immunic AG); [8] WO2026/017806 (Immunic AG); [9] WO2026/093429 (Immunic AG)

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Thank you for your attention!

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