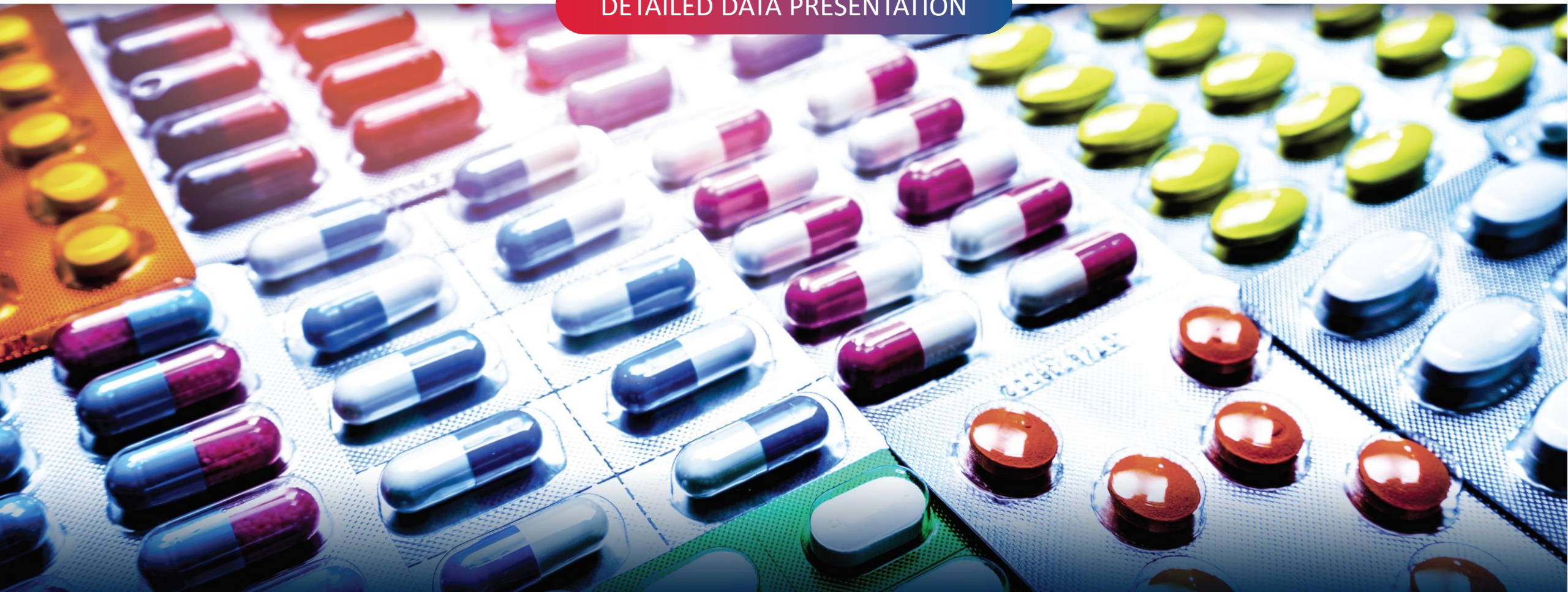
APTORUM

Facilitating Life Science Innovations to Serve Unmet Medical Needs

DETAILED DATA PRESENTATION



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SMART-ACT™: pipeline overview

Current progress of pipeline programs: → Lead Projects → Other Candidates → Projected timeline[1]

Note: all projected timelines refer to the estimated commencement time of the indicated stages

Pillar 1: SMART-ACT™ (SACT series) - Orphan disease drug repurposing platform

Over 7,000 orphan diseases to be screened in the next 5 years

Program	Indication	Computational Discovery	*In vitro* validation	Existing PhI/II clinical safety data[1]	IND 505(b)(2) filing[2] *In vivo* validation	Bridging studies	PhII / III with limited population[3]
SACT-1	Neuroblastoma				Q4 2019		ready for clinical trial by 2H 2020
SACT-2	To be disclosed						
SACT-3	To be disclosed						

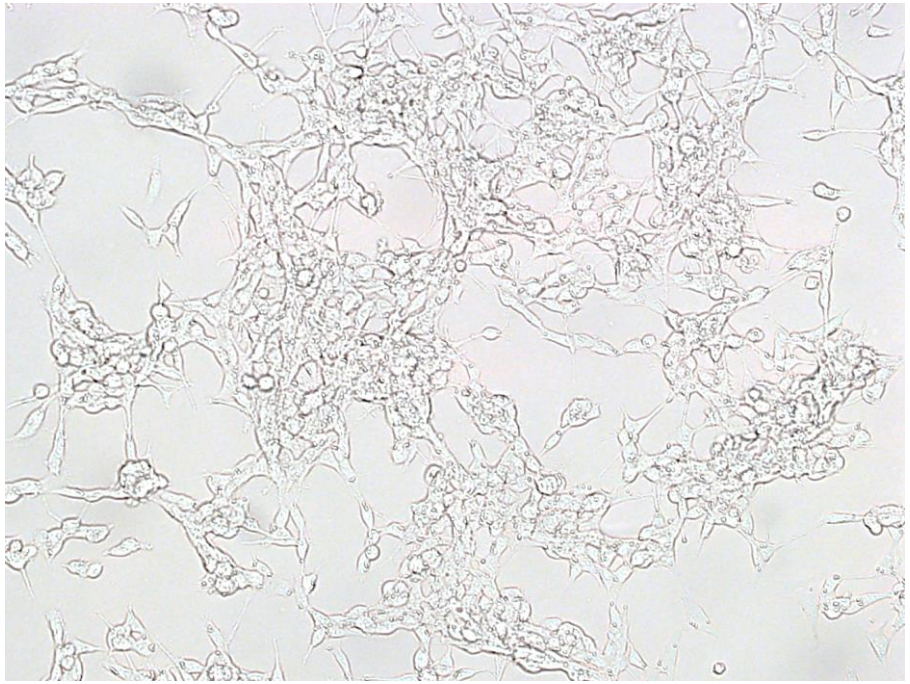
1. All projected timelines refer to the estimated commencement time of the indicated stages 2. Refers to the drug's existing Phase I/II safety data previously conducted by a third party. Does not refer to clinical trials conducted by Aptorum 3. Subject to FDA's approval on a case-by-case basis, a 505(b)(2) can rely in part on existing information from approved products (such as FDA's previous finding on safety and efficacy) or data in the public

- IP rights filed for all 3 programs
- Subject to the FDA's approval, IND-enabling studies and Phase I for repurposing approved drugs may be expedited

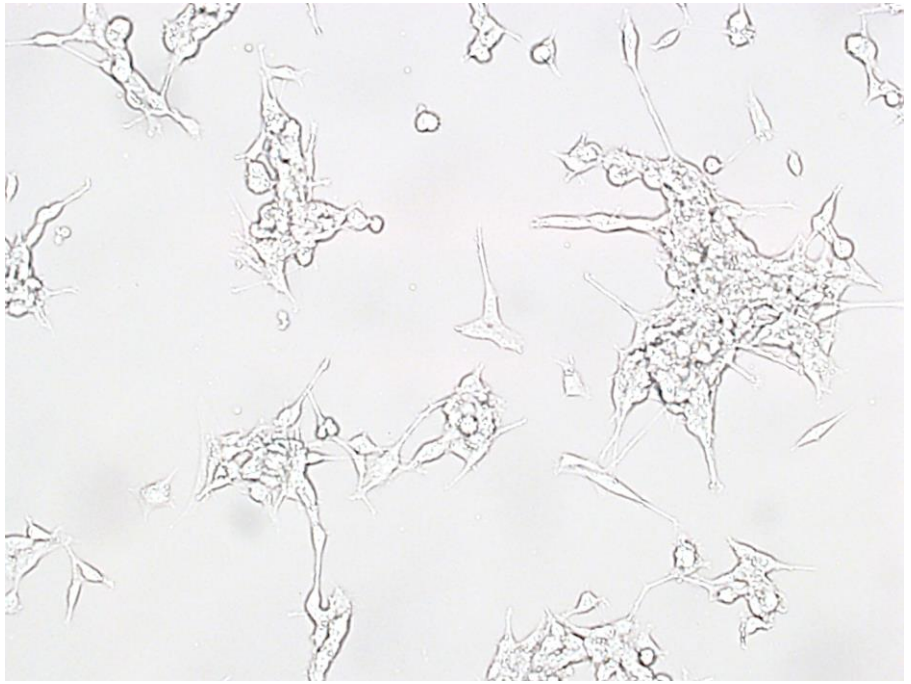
In vitro drug activity against neuroblastoma cell lines

- 48 drug candidate hits from the computational screen were evaluated *in vitro* for activity validation
- 1 candidate, SP055, was found to provide favorable anticancer activities in 4 different neuroblastoma cell lines

Control treatment on neuroblastoma cells



SP055 treatment on neuroblastoma cells

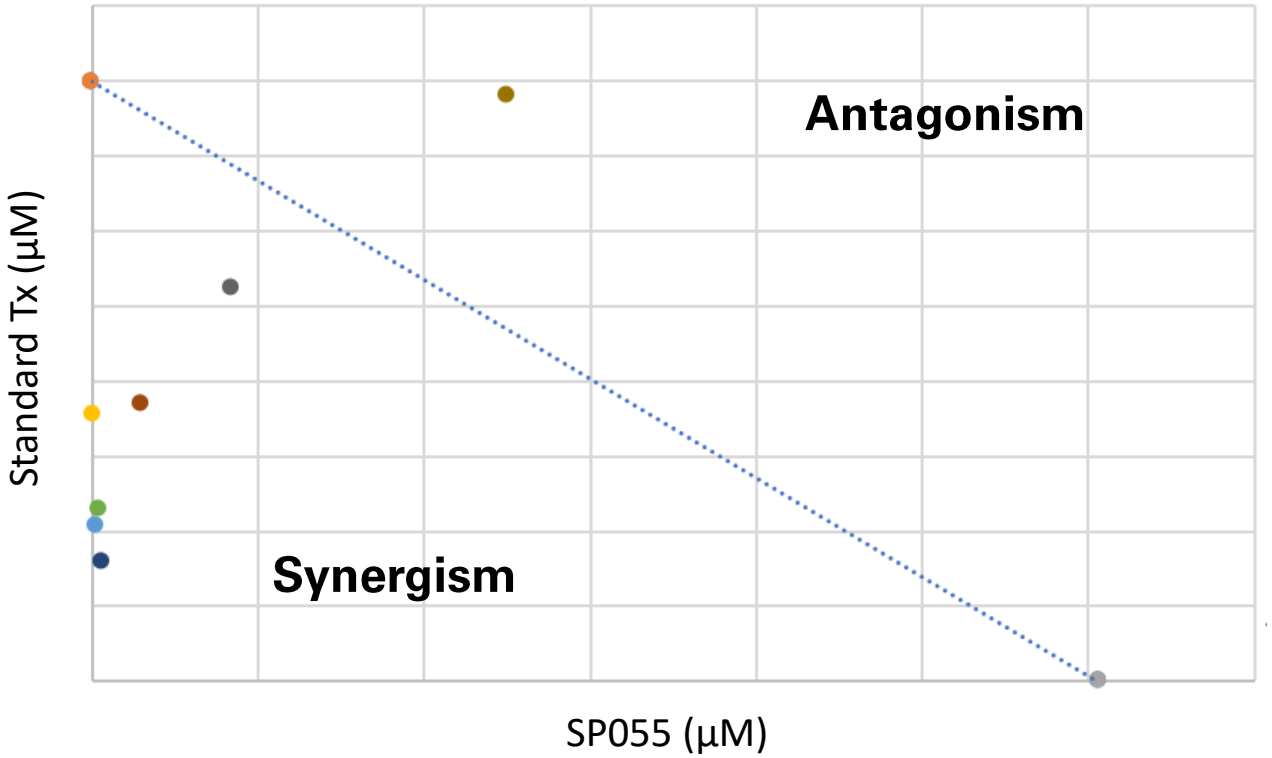


Drug candidates under SACT-1	IC_{50} [µM]
SP055	2.97

The results shown in this slide are based on Aptorum's internal (in vitro/in vivo) tests/experiments that have not been verified in clinical trials and/or third party testing

Synergistic effect of SP055 in combination with standard treatment

- Synergistic effect observed for SP055 in combination with standard treatment in 2 different neuroblastoma cell lines, as seen in the isobologram (left) and the Excess over Bliss (right)



Neuroblastoma cell line #1

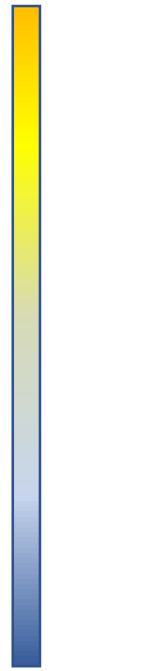
Excess over Bliss

Standard Tx (µM) \ SP055 (µM)	0.37	1.11	3.33	10
0.2	14	13	1	1
0.4	18	21	2	0

Neuroblastoma cell line #2

Excess over Bliss

Standard Tx (µM) \ SP055 (µM)	0.37	1.11	3.33	10
0.2	10	13	5	0
0.4	11	9	2	-7



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SP055: safety & tolerability

FDA approved safety profile

- Did not show genotoxic potential even at the highest feasible concentration dose (*in vitro* and *in vivo*)
- In a phase IIb study over 2 years, all SP055 doses were safe and well tolerated
- No dose relationship between SP055 and adverse events (AE)

SP055	25mg/day (N=93)	75mg/day (N=95)	150mg/day (N=91)
Median treatment duration, weeks	101	100	100
Adverse events (AE)			
Any grade 2-4 AE at least possibly related to SP055	20%	20%	21%
AEs leading to discontinuation	9%	12%	14%
Any serious AE	13%	14%	10%
Deaths	0%	2%	0%

SP055: pharmacokinetics

FDA approved pharmacokinetics profile

- Data package can be potentially accepted by the FDA in our 505(b)(2) new drug application
- Relatively long half-life ($t_{1/2}$ = 43-55h). Frequent dosing may not be required

SP055 pharmacokinetic parameter in humans	(N=19)
t_{max}, h	5
C_{max}, ng/ml	~300
AUC_{last}, ng·h/ml	~10,000
AUC_{inf}, ng·h/ml	~11,000
$t_{1/2,term}$, h	~48

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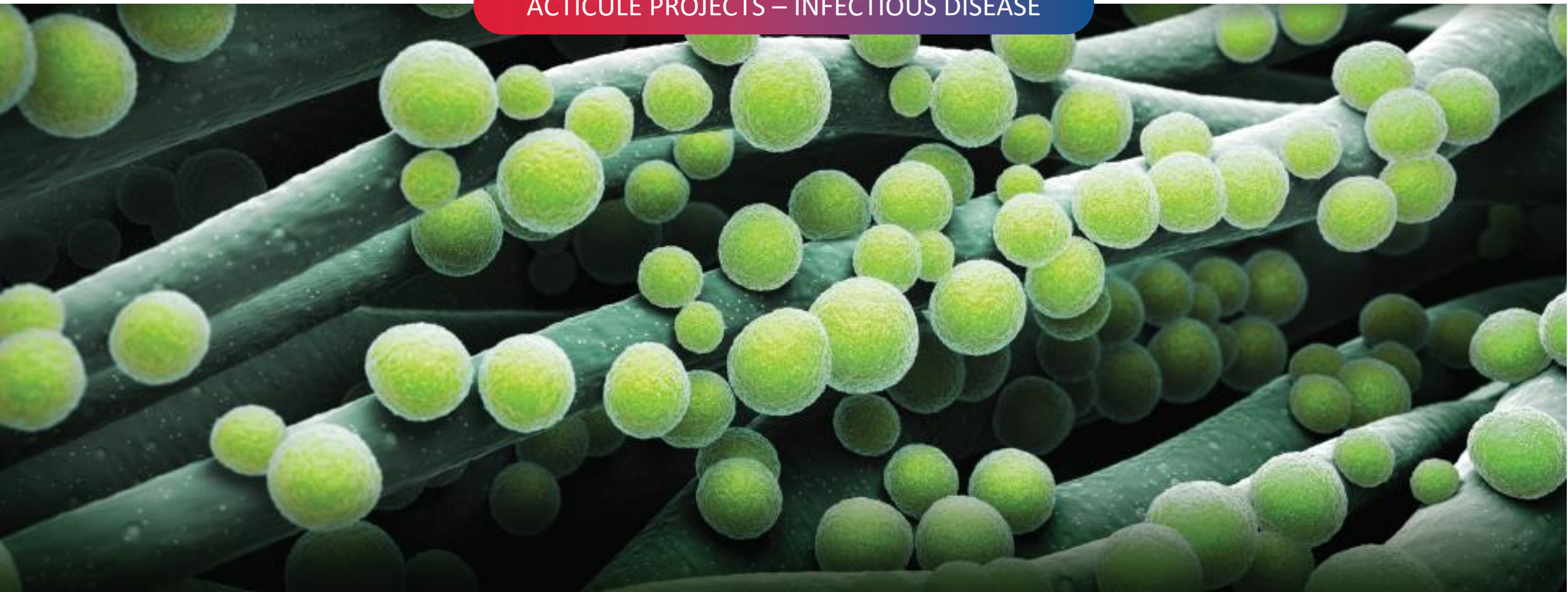
ACTICULE PROJECTS – INFECTIOUS DISEASE



Executive summary: Acticule projects

ALS-4

- Aptorum's lead program ALS-4 is an anti-virulent, non-bactericidal drug candidate for *Staphylococcus aureus* infections including MRSA[1]
- Unlike all major treatments on the market[2], ALS-4 relies on an anti-virulent non-bactericidal approach[1], potentially reducing significant risks of developing *S. aureus* resistance
- IND-enabling studies commenced in Q2 2019, Targeting IND submission by Q1/2 2020
- Upon IND approval, a hybrid Phase I clinical study to commence in 2020 in North America to obtain preliminary efficacy readout
- Targeting to submit written request for approval under the newly established LPAD regulatory pathway (Limited Population Pathway for Antibacterial and Antifungal Drugs), to expedite marketing approval and commercialization

ALS-1

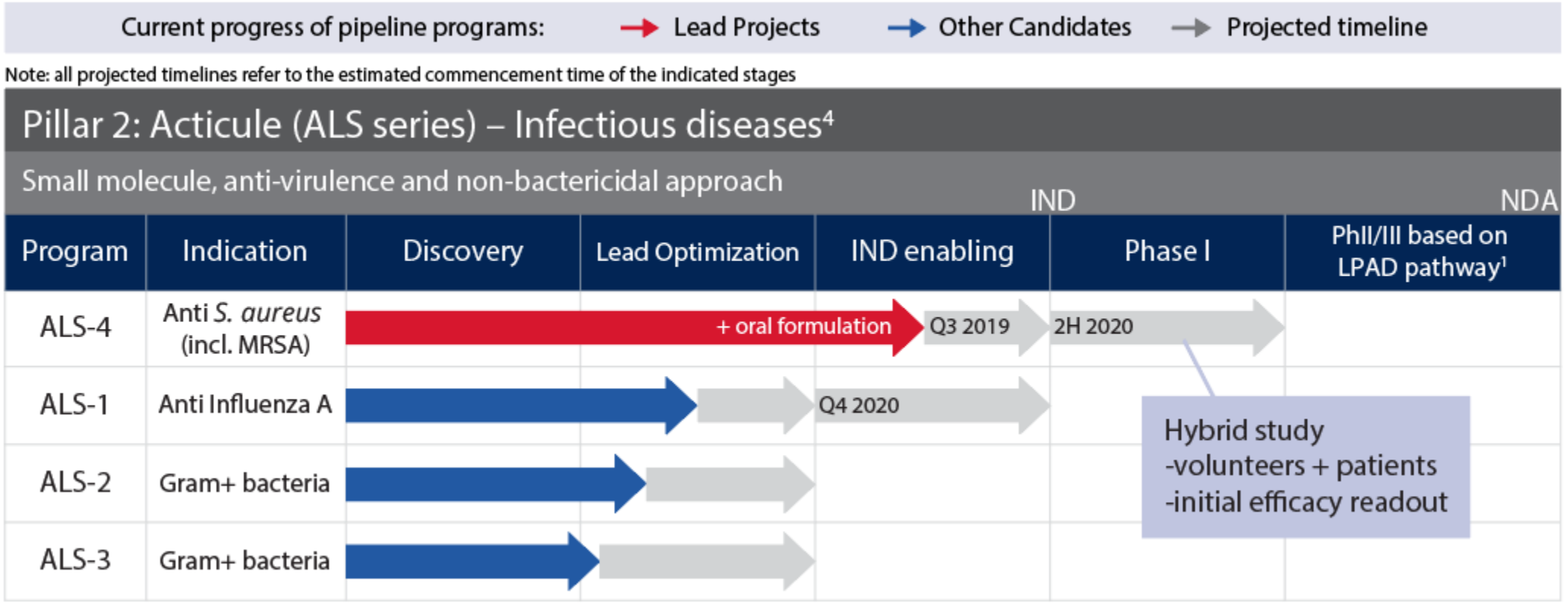
- A unique antiviral therapeutic against Influenza A that has a more upstream target than Tamiflu which is shown to be more effective in vitro[1]
- Viral resistance to Tamiflu and other neuraminidase inhibitors has risen rapidly in recent years[3]
- ALS-1 has a distinct mechanism of action compared with Tamiflu and Xofluza[1,4]

ALS-2/ALS-3

- Additional novel anti-virulent, non-bactericidal approach therapeutics targeting Gram-positive bacteria[1]
- In discovery/lead optimization stage and generating good traction towards doing IND-enabling studies[1]

1. Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing; 2. P T. 2016 Feb; 41(2): 126–128; 3. Influenza Antiviral Medications: Summary for Clinicians. CDC. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm; 4. Nat Biotechnol. 2010 Jun;28(6):600-5

ALS pipeline overview



1. ALS-4's eligibility for the LPAD pathway is subject to the FDA's approval. Targeting other indications in Phase II may affect our valuation. QIDP status can be applied once we identify an indication

ALS-4: mechanism of action

ALS-4

inhibits a key enzyme in the biosynthesis of staphyloxanthin[1]

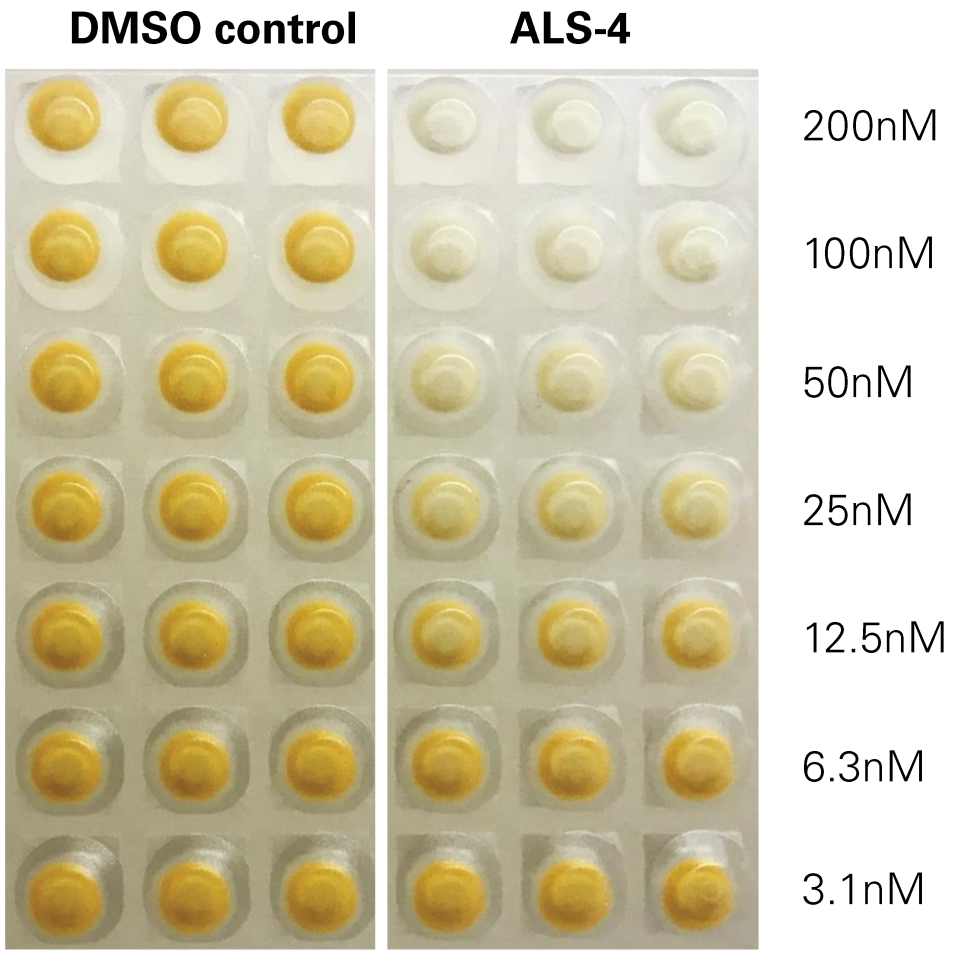
Figure adapted from MBio. 2017 Sep 5;8(5). pii: e01224-17.

The description of ALS-4 and related conclusory statements on ALS-4 on this slide are based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing.

ALS-4: mechanism of action

ALS-4

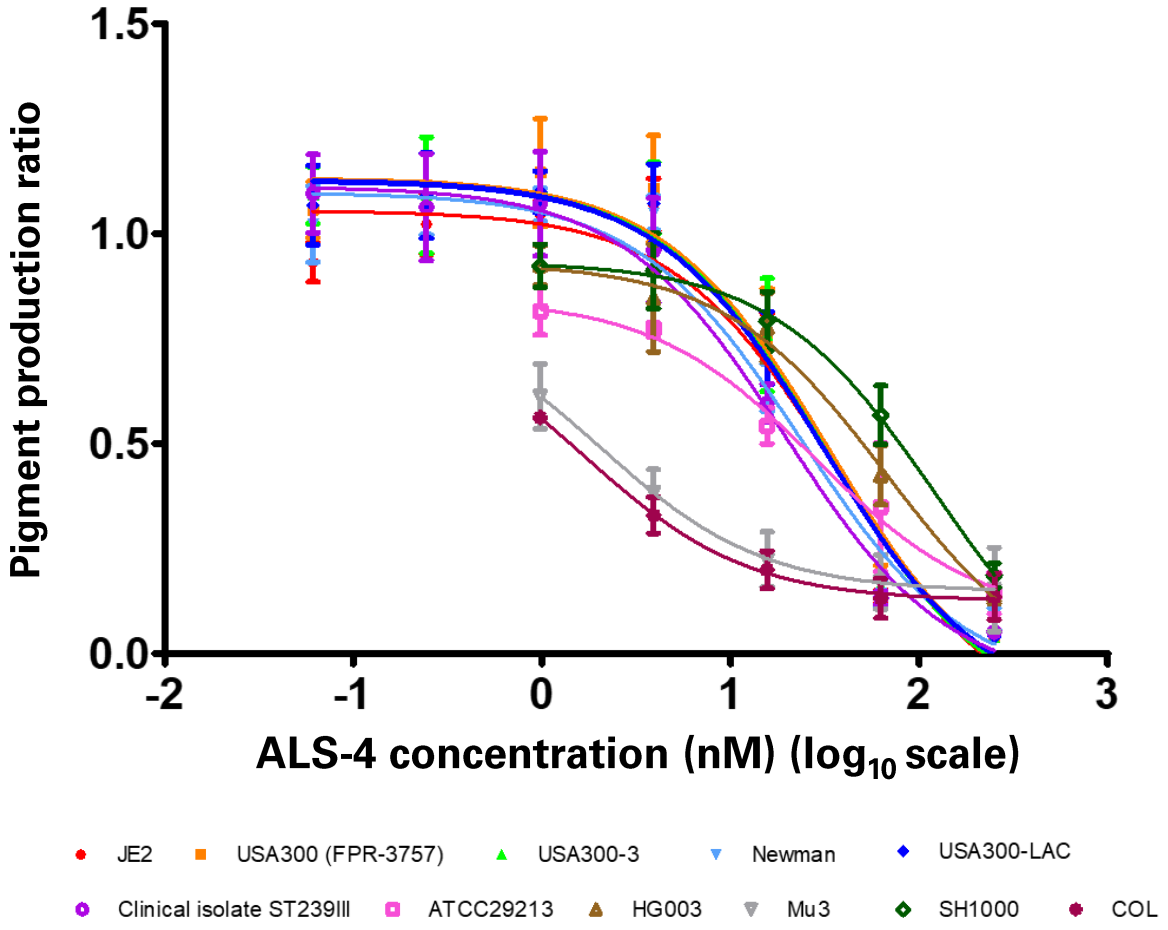
inhibits S. aureus pigment production with an IC_{50} = 20nM



The results shown in this slide are based on Aptorum's internal (in vitro/in vivo) tests/experiments that have not been verified in clinical trials and/or third party testing

ALS-4 is shown to be effective across 11 strains of *S. aureus*

ALS-4 is believed to inhibit the production of staphyloxanthin in 11 strains of *S. aureus in vitro*



Strain	Type	IC_{50} (nM)
SH1000	MSSA	70.5 ± 6
HG003	MSSA	54.4 ± 4
USA300-JE2	MSSA	37.7 ± 4
USA300 (FPR-3757)	CA-MRSA	30.8 ± 5
USA300-3	HA-MRSA	42.8 ± 6
Newman	MSSA	23.7 ± 1
USA300-LAC	MRSA	43.6 ± 5
ATCC29213	MSSA	30.0 ± 5
Clinical isolate ST239III	HA-MRSA	16.3 ± 8
Mu3	VISA	2.6 ± 1
COL	HA-MRSA	0.9 ± 1

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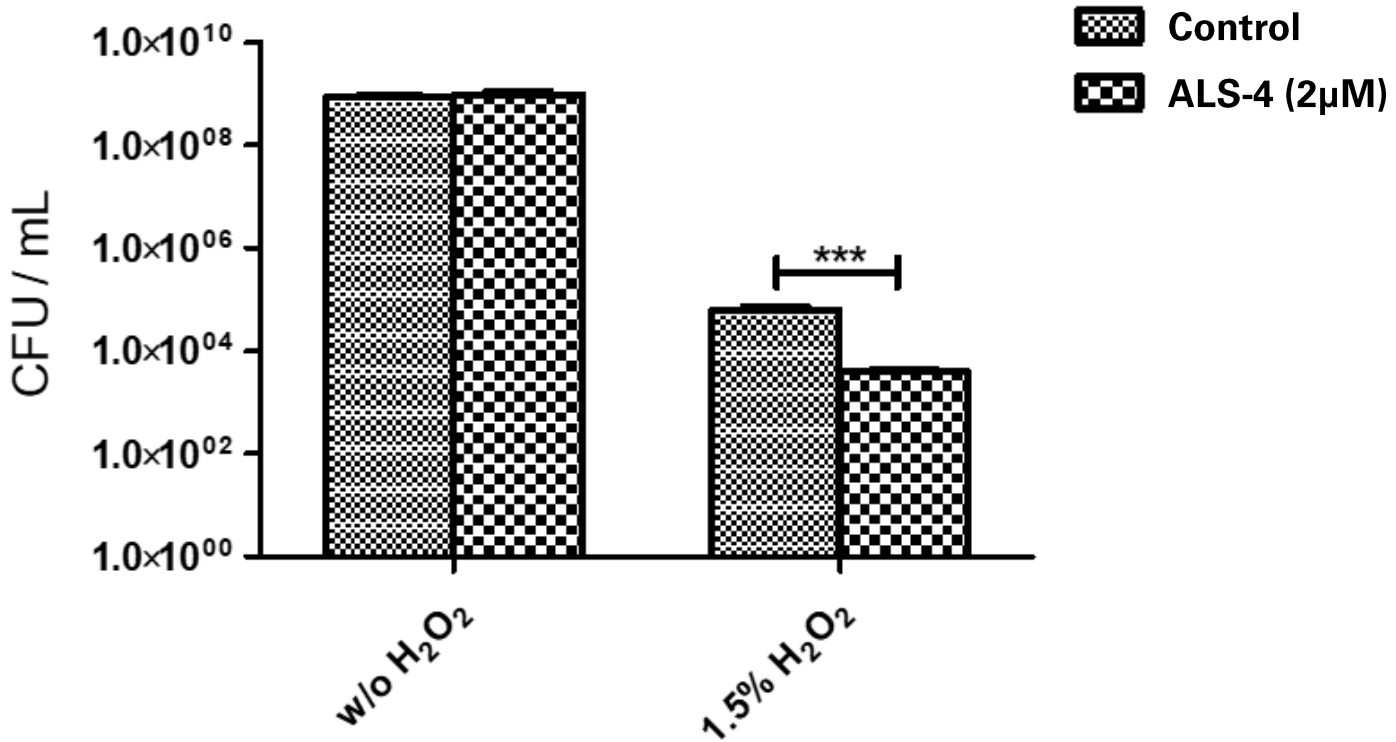
ALS-4 is shown to increase sensitivity of *S. aureus* to oxidative damage

ALS-4 is believed to reduce bacteria number by an additional 10-fold in the presence of hydrogen peroxide



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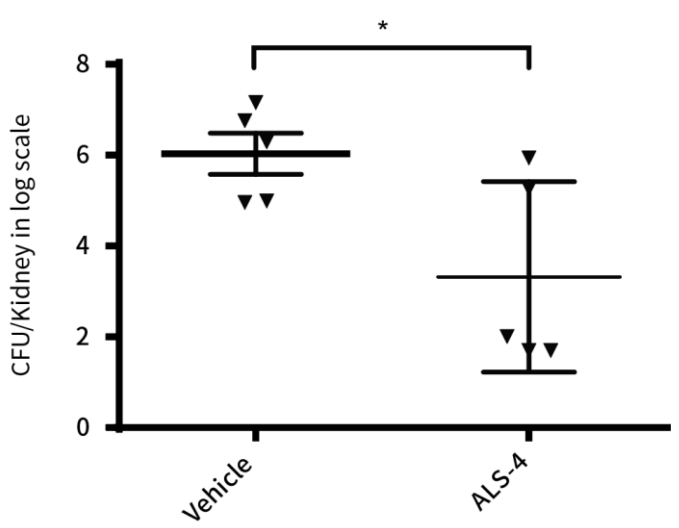
ALS-4: *in vivo* efficacy

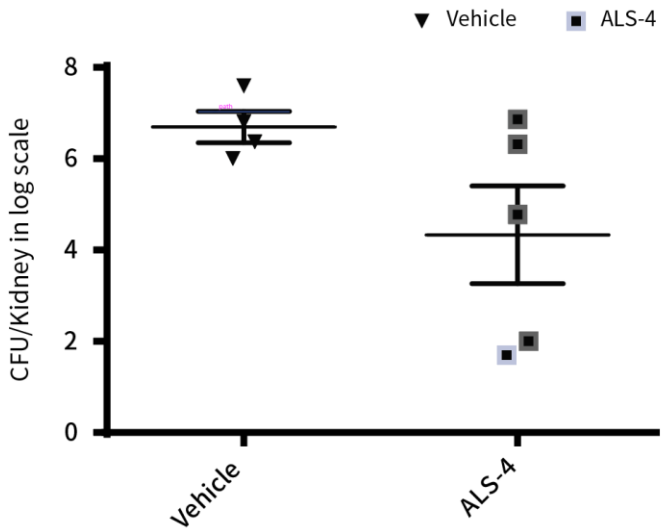
ALS-4 inhibits *S. aureus* pigment production with an IC_{50} = 20nM

Acute treatment



ALS-4 concentration:	1 mM
Inoculum:	5 x 10^6 per mouse
Treatment:	twice for first 7 days
First inject:	30 min after infection

Delayed treatment

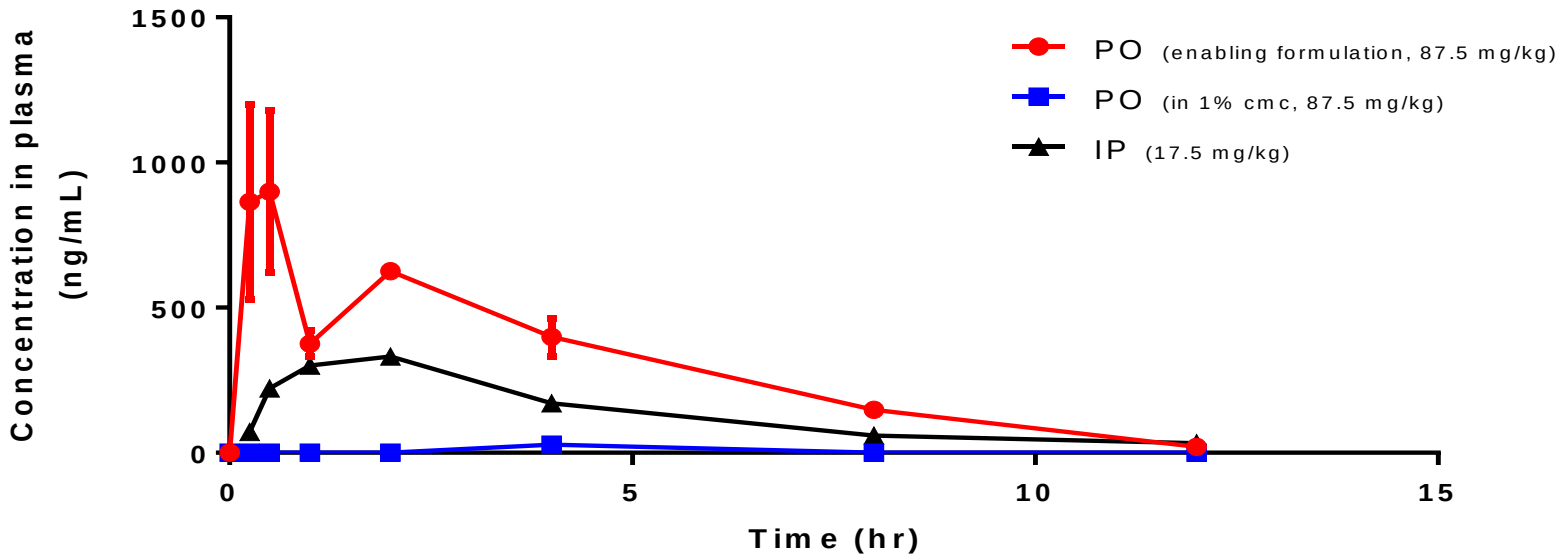


ALS-4 concentration:	1 mM
Inoculum:	2 x 10^7 per mouse
Treatment:	twice for first 7 days
First inject:	11 days after infection

The results shown in this slide are based on Aptorum's internal (in vitro/in vivo) tests/experiments that have not been verified in clinical trials and/or third party testing

ALS-4: oral formulation

Enabling oral formulation (red) vastly improved ALS-4 bioavailability in mice

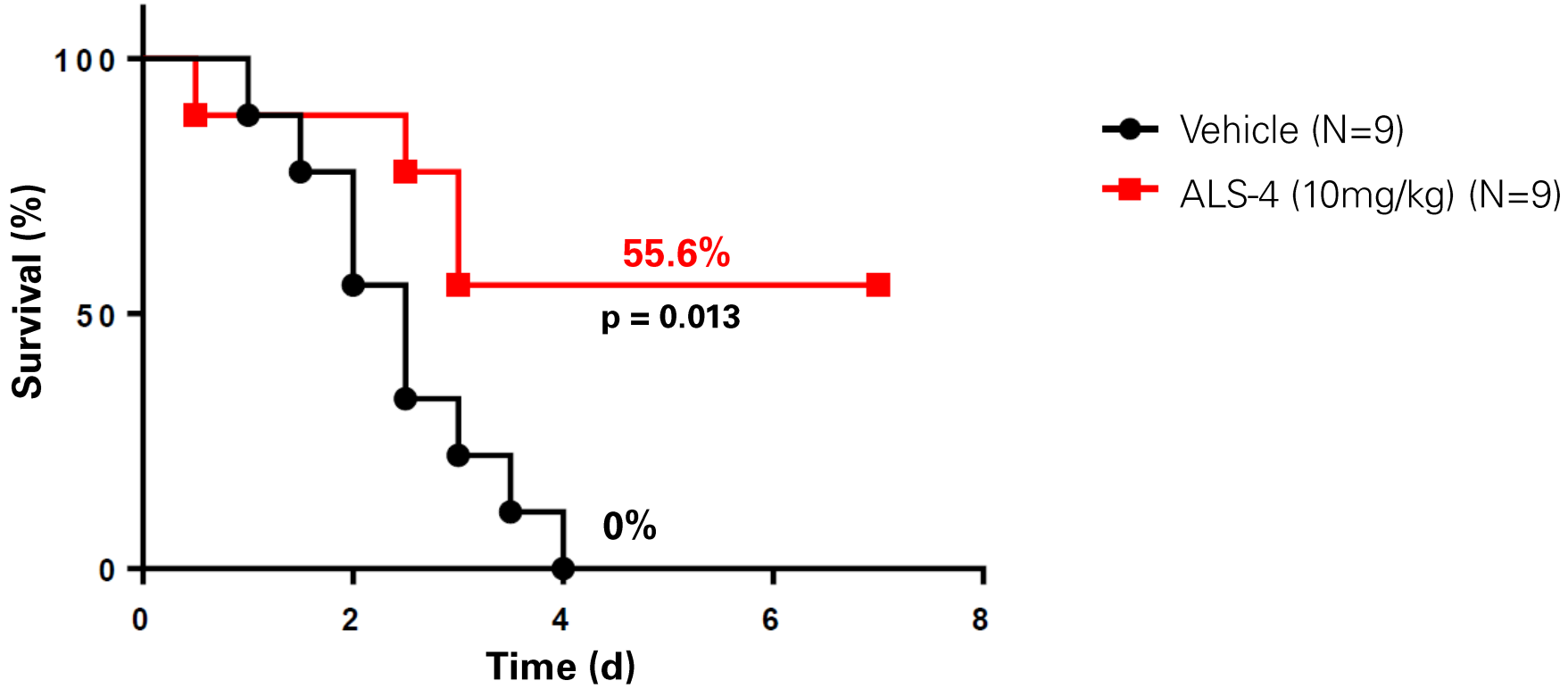


- The enabling oral formulation is being scaled up and stability is being assessed
- GMP manufacturing of the drug product is expected to commence in Q1 2020

The results shown in this slide are based on Aptorum's internal (in vitro/in vivo) tests/experiments that have not been verified in clinical trials and/or third party testing

ALS-4: oral formulation treatment in an MRSA survival study

ALS-4 rescues rats infected with a lethal dose of MRSA USA300 in a bacteremia model

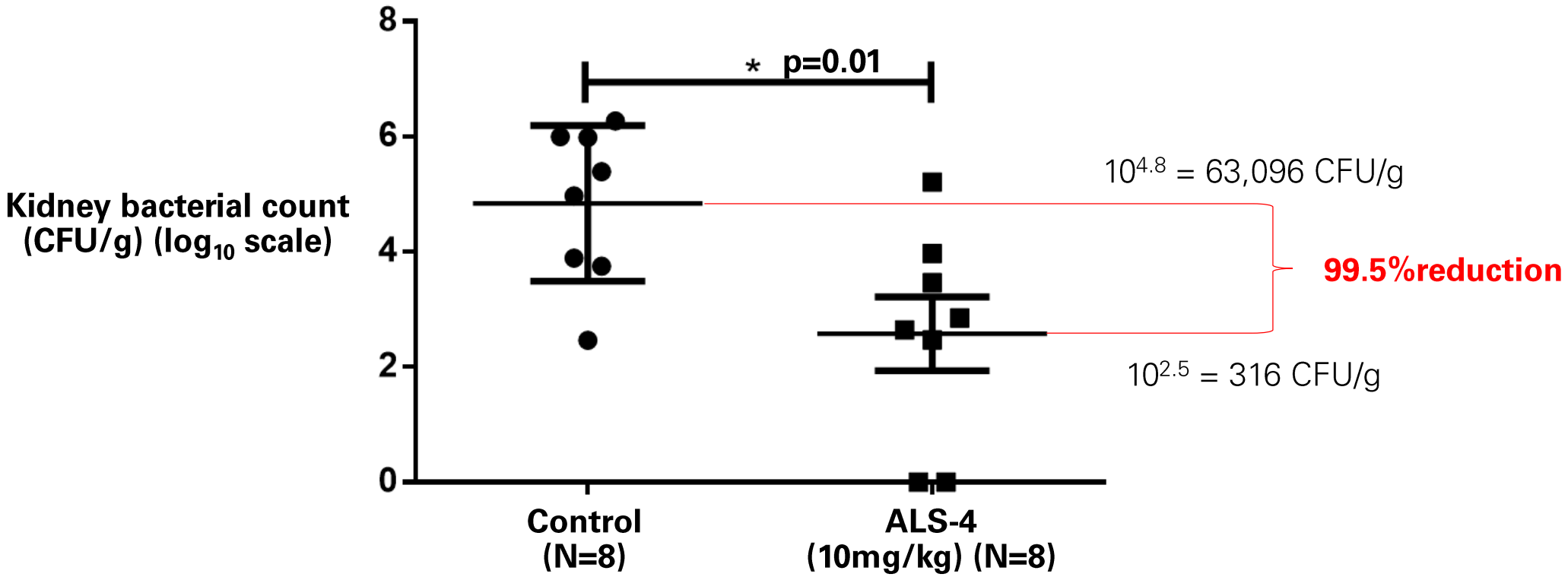


- A lethal dose (10^9 CFU) of MRSA was introduced through the tail vein
- ALS-4 was administered **orally** 30 minutes after infection for twice a day thereafter

The results shown in this slide are based on Aptorum's internal (in vitro/in vivo) tests/experiments that have not been verified in clinical trials and/or third party testing

ALS-4: oral formulation treatment in a non-lethal bacteremia model

ALS-4 is shown to greatly reduce organ bacterial count in a bacteremia animal model



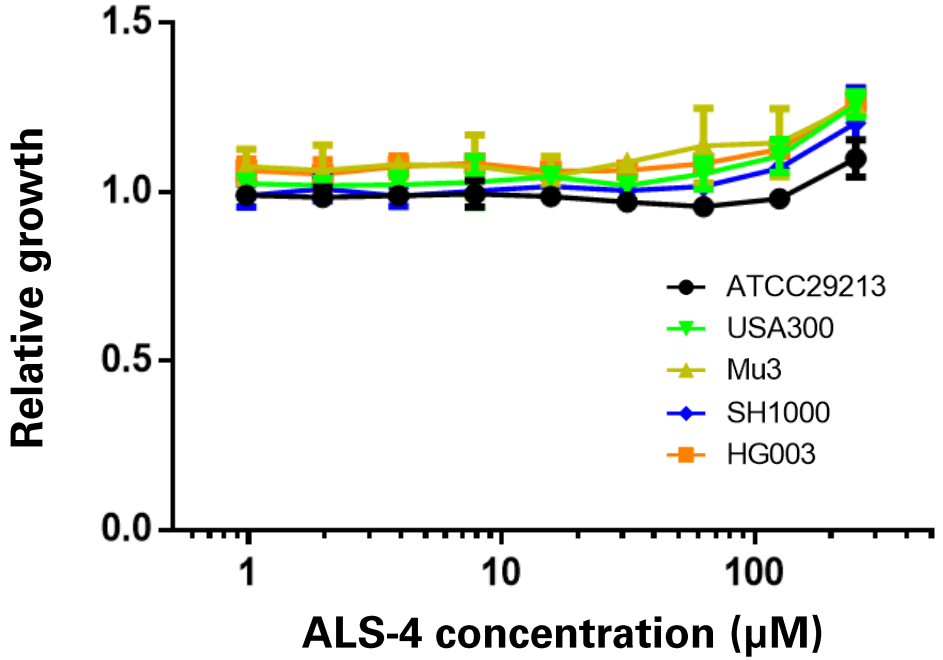
- Rats were challenged with a non-lethal dose (10^7 CFU) of MRSA through the tail vein
- In order to simulate a more realistic clinical scenario, treatment was introduced 14-days after infection, where ALS-4 was administered orally twice a day at 10mg/kg per animal

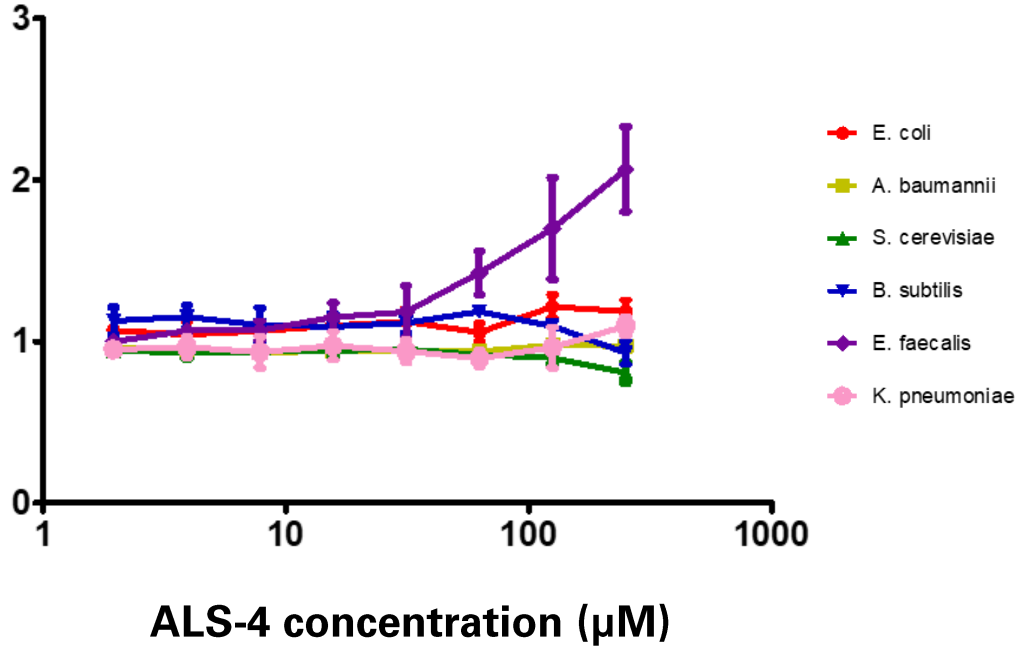
The results shown in this slide are based on Aptorum's internal (in vitro/in vivo) tests/experiments that have not been verified in clinical trials and/or third party testing

ALS-4 is shown not to directly inhibit bacterial growth *in vitro*

Lack of direct selection pressure makes it unlikely for drug resistance to emerge

Does not inhibit in growth in 5 strains of *S. aureus* (left) and 6 different species of bacteria (right)





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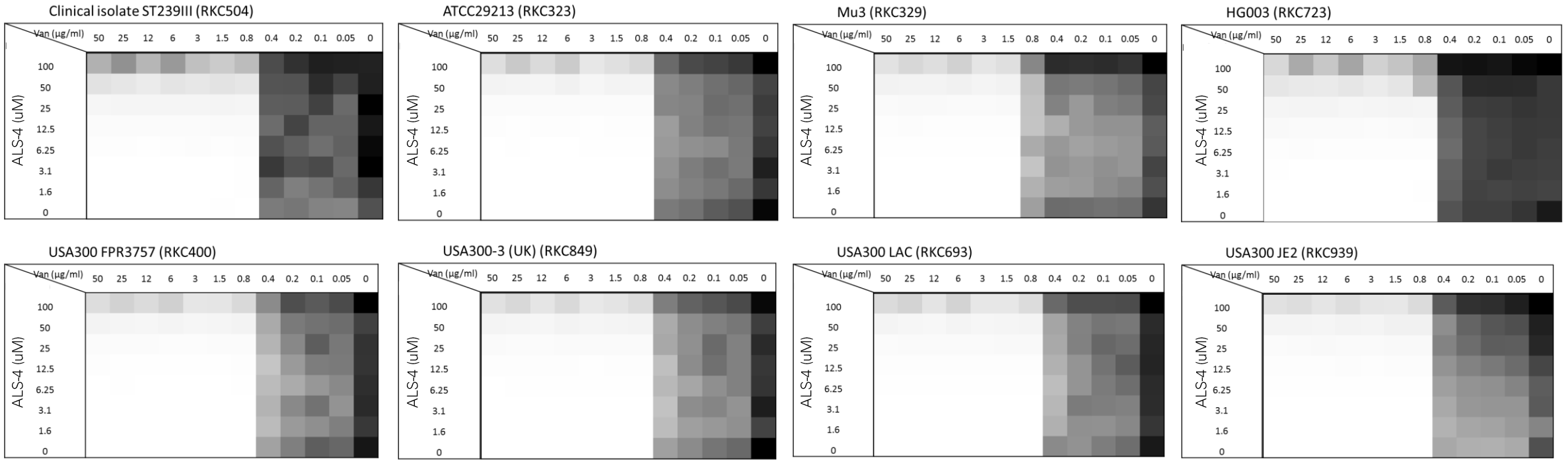
ALS-4 does not interfere with the action of vancomycin

ALS-4 does not affect the minimum inhibitory concentration (MIC) of vancomycin in 8 strains of *S. aureus*



- No effect on the MIC of vancomycin was observed *in vitro* when the concentration of ALS-4 was below 25µM

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ALS-4 resistance raising in MRSA

Protocol

1. Inoculum preparation: USA300-3 (LAC) was cultured overnight in BHI broth at 37˚C, 250 rpm.
2. Subculture preparation: 60 µl overnight culture was added to 6 ml BHI broth with different drugs.

Tubes	Day 1-4	Day 6-10
1	DMSO	DMSO
2	Ery 16 + CLI 0.12 µg/ml	Ery 16
3	ALS-4 1µM	ALS-4 1µM

3. Clindamycin (CLI): 0.12 µg/ml; Erythromycin (Ery): 16 µg/ml; ALS-4: 1 µM. The use of Ery was to ensure no contamination of environmental bacteria as USA 300 (LAC) is resistance Ery.
4. Culturing: during culturing, medium was changed everyday by centrifugation of the bacteria and replacing the supernatant with new medium plus DMSO or antibiotics or compounds as specified.
5. Bacteria collection: on day 11, 1 ml bacteria was centrifuged and resuspended in PBS with 10% DMSO for further testing.
6. MIC testing: in BHI medium in 96-well plate and cultured for 16h
7. Pigment production: in 96 deep-well plate and cultured for 36 h

The results shown in this slide are based on Aptorum's internal (in vitro/in vivo) tests/experiments that have not been verified in clinical trials and/or third party testing

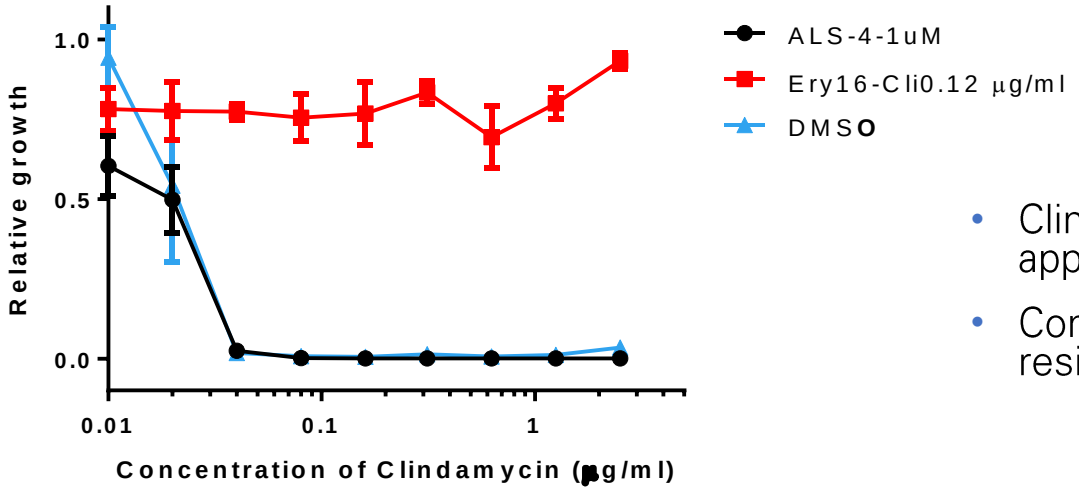
Resistance of *S. aureus* USA 300(lac) to clindamycin after various treatment conditions

Pre-treatment

Tubes	Day 1-4	Day 6-10
1	DMSO	DMSO
2	Ery 16 + CLI 0.12 µg/ml	Ery 16
3	ALS-4 1µM	ALS-4 1µM

(Clindamycin withdrawn between day 5-10)

Clindamycin resistance test after pre-treatment (BHI medium with 5 x 10^4/well bacterial inoculum)



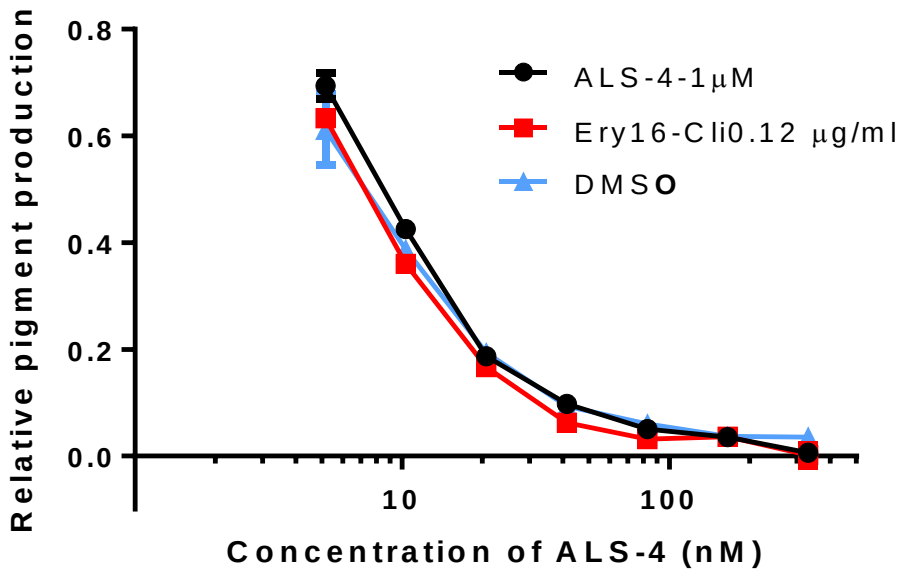
- Clindamycin resistance (MIC from 0.12 µg/ml to >5 µg/ml) appeared rapidly after a 10-day intermittent treatment
- Controls without the addition of antibiotics showed no resistance to clindamycin

Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

Resistance of *S. aureus* USA 300(lac) to clindamycin after various treatment conditions

ALS-4 efficacy test

(Bacterial inoculum: 4 x 10^7/ml)



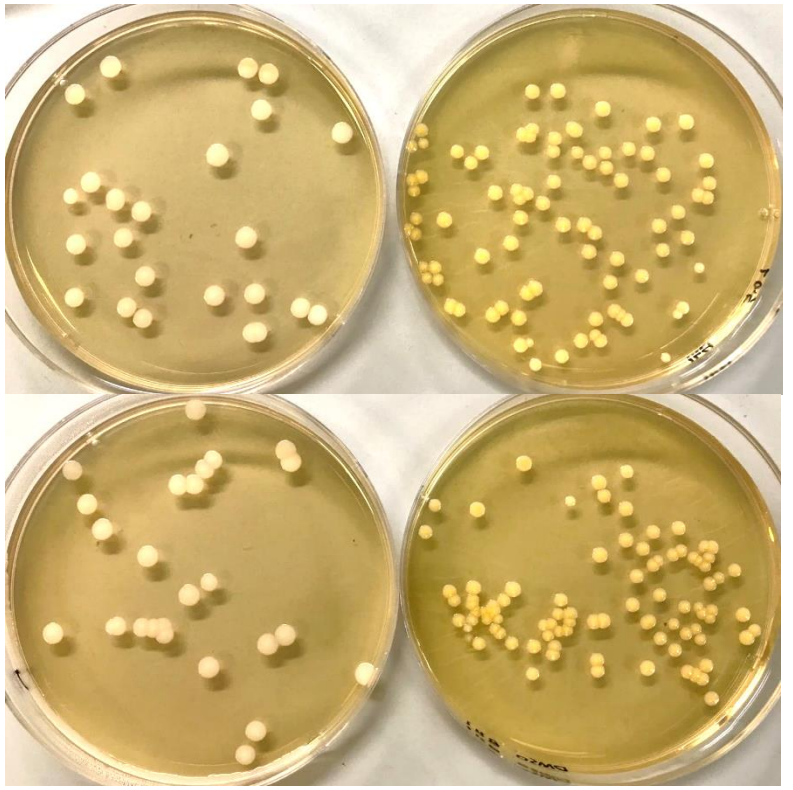
BHI agar plates

Recovered bacteria after 11-day resistance-raising with 1μM ALS-4

Recovered bacteria after 11-day resistance-raising with DMSO as control

100nM ALS-4 (all colonies turned white)

No ALS-4 (all colonies remained yellow)



No bacterial resistance to ALS-4 detected after continuous incubation of the bacteria in the presence of 1μM ALS-4 for 11 days

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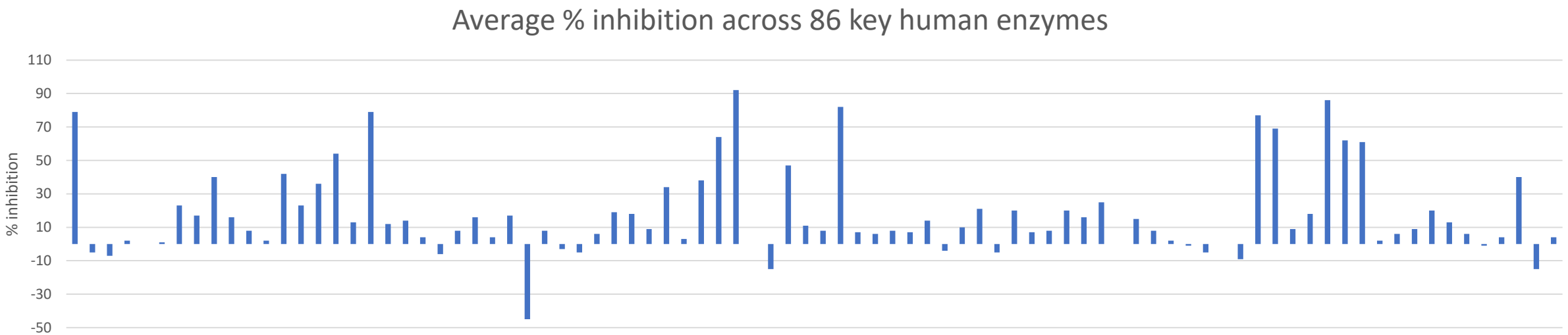
ALS-4: pharmacology & toxicology

In vitro safety screening

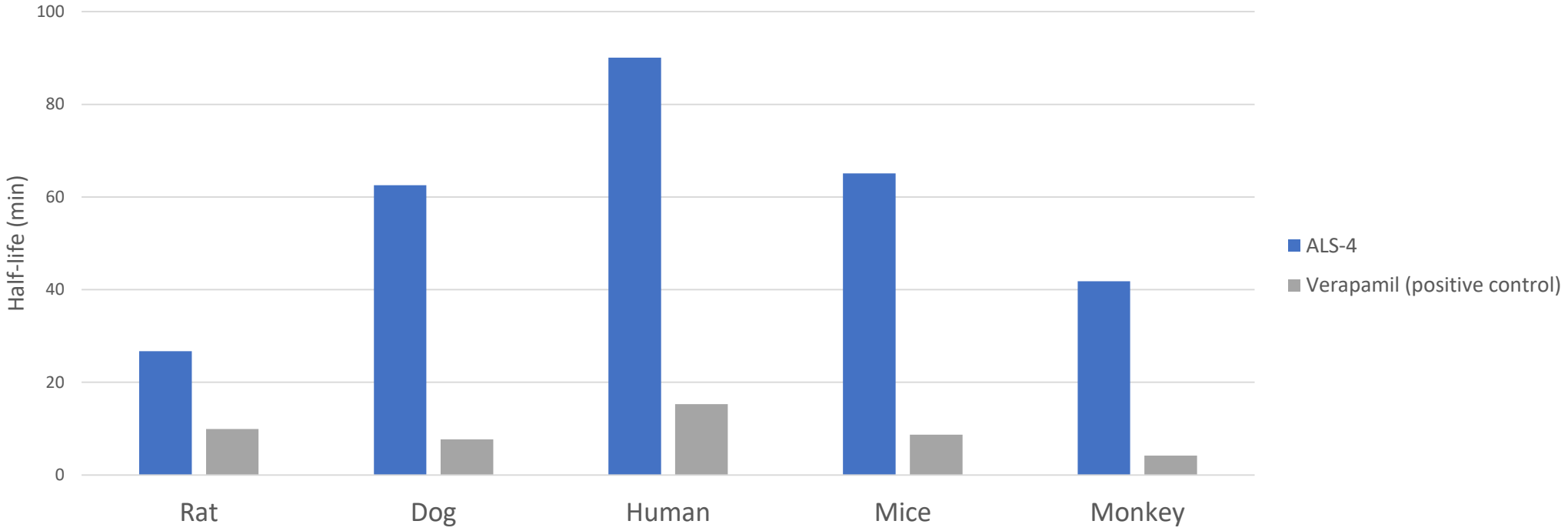


- Average inhibition of 17.5% across 86 key human enzymes
- Enzyme inhibition assay shows that ALS-4 has a clean profile with little off-target inhibition
- Key enzymes including hERG, P450, MAO and UDP are all unaffected

Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

ALS-4: pharmacology & toxicology

In vitro metabolism study using liver microsomes from 5 different species



- Liver microsome studies show low intrinsic clearance in 5 different species, including human. Results suggests indicating slow metabolism

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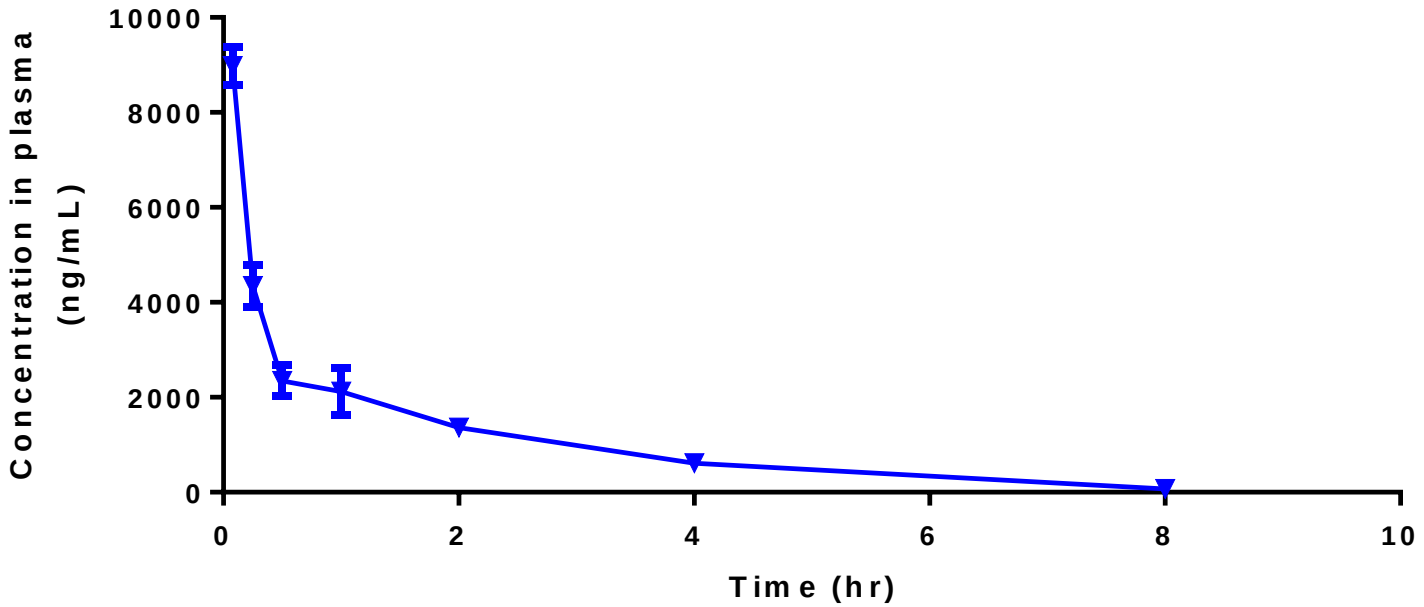
ALS-4: pharmacology & toxicology

Pharmacokinetics

- Biological half-life of ALS-4 is around 2 hours in mice (N=3). Rat pharmacokinetics study ongoing



C_{max} (ng/mL)	12624.55
$AUC_{0\text{-}Tlast}$ (ng*hr/mL)	9732
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	9927
K_{el} (hr^{-1})	0.37
$t_{1/2}$ (hr)	1.87
Extrap AUC (%)	1.97
Vz_{obs} (L/kg)	4.75
Cl_{obs} (L/hr/kg)	1.76
MRT_{obs}(hr)	2.11
Vss_obs (L/kg)	3.71

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ALS-4: pharmacology & toxicology

GLP AMES test for mutagenicity

Results for Plate Incorporation Assay

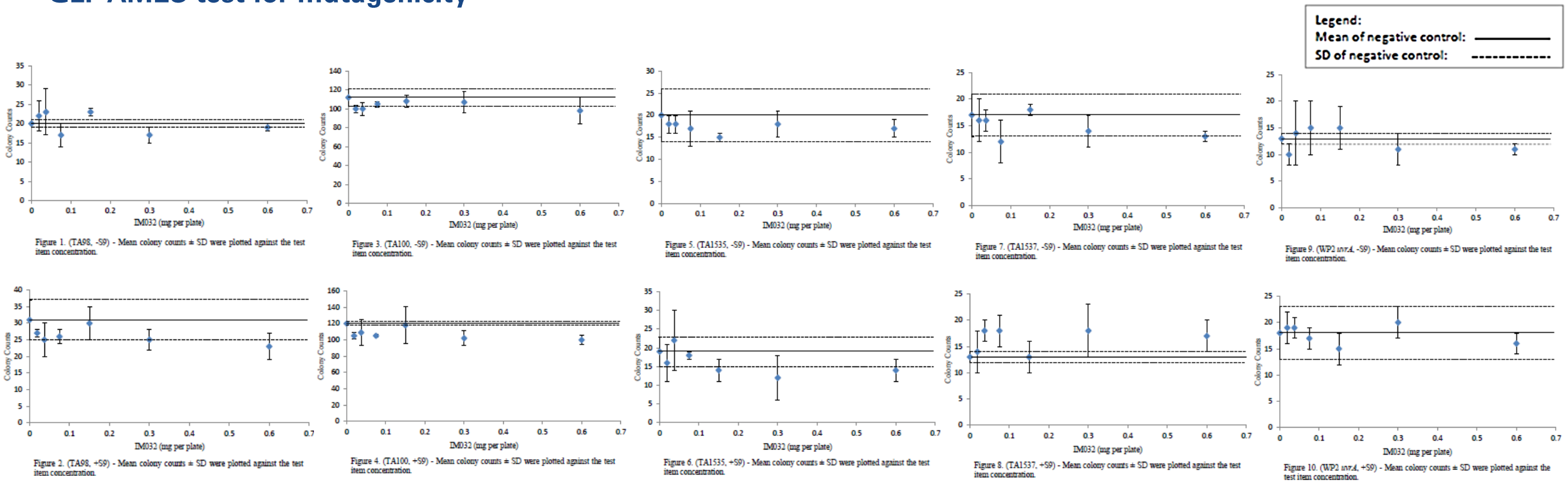


Figure 1. (TA98, -S9) - Mean colony counts ± SD were plotted against the test item concentration.

Figure 3. (TA100, -S9) - Mean colony counts ± SD were plotted against the test item concentration.

Figure 5. (TA1535, -S9) - Mean colony counts ± SD were plotted against the test item concentration.

Figure 7. (TA1537, -S9) - Mean colony counts ± SD were plotted against the test item concentration.

Figure 9. (WP2 *uvrA*, -S9) - Mean colony counts ± SD were plotted against the test item concentration.

Figure 2. (TA98, +S9) - Mean colony counts ± SD were plotted against the test item concentration.

Figure 4. (TA100, +S9) - Mean colony counts ± SD were plotted against the test item concentration.

Figure 6. (TA1535, +S9) - Mean colony counts ± SD were plotted against the test item concentration.

Figure 8. (TA1537, +S9) - Mean colony counts ± SD were plotted against the test item concentration.

Figure 10. (WP2 *uvrA*, +S9) - Mean colony counts ± SD were plotted against the test item concentration.

- AMES mutagenicity study using *Salmonella typhimurium* strain TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2 *uvrA*; with and without the presence of rat liver S9 for metabolic activation
- Negative result in all tested strains

Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

ALS-4: chemistry, manufacturing and controls

ALS-4 properties

Molecular weight (g/mol)	449.36
LogD[1] pH7.4	4.43
pka(s)[1]	14.5
Caco-2 permeability	2.27 x 10^{-4} cm/s (non-pgp substrate)
Permeability (Human jejunum, pH 6.5)	7.39 x 10^{-4} cm/s
In vitro CL (human, monkey, dog, rat, mouse liver microsomes)	94.97, 335.4, 170.92, 145.8, 180 (µL/min/mg)
Plasma protein binding[1]	98.53%
DDI risk (CYP450 reversible inhibition, TDI and induction)	Low

[1]Calculated properties using ACD/Labs (Release 2017.2.1)

Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

ALS-4: chemistry, manufacturing and controls

ALS-4 is an attractive candidate for formulation

- Only 1 physical form identified from polymorph screening
- Physically and chemically stable
- Not hygroscopic

API (active pharmaceutical ingredient) manufacturing

- Successfully scaled up to 200-300g batch
- GLP toxicology batch of API has been synthesized
- GMP manufacturing is expected to commence in Q4 2019

ALS-4 has low solubility in water

- Developed an enabling formulation to improve bioavailability

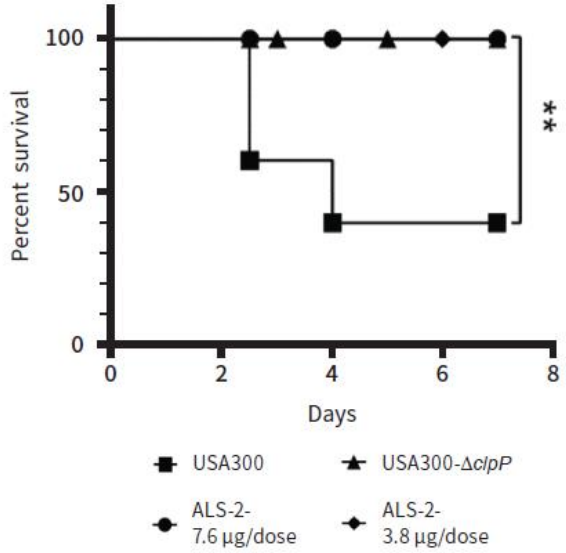
Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

ALS-2 & ALS-3

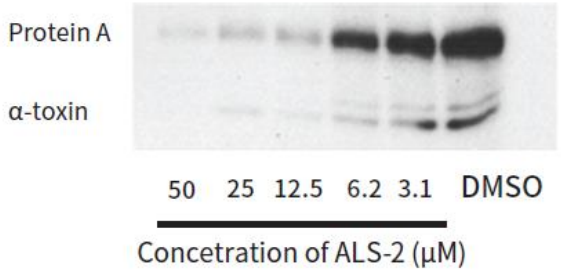
Additional anti-virulence, non-bactericidal therapeutics for the treatment of infections caused by Gram Positive bacteria

ALS-2 Anti-virulence compound that suppresses multiple unrelated virulence factors in *S. aureus*[1]

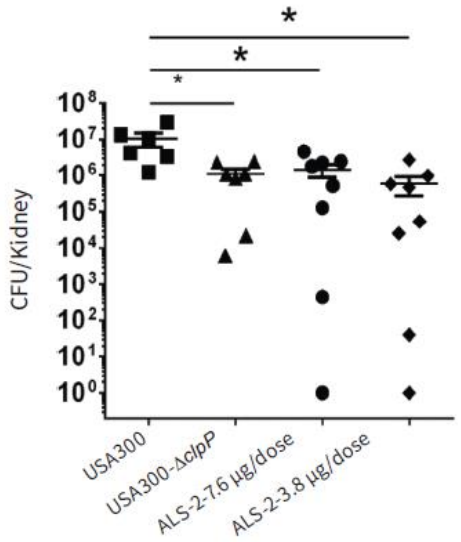
ALS-2 rescues mice from MRSA infection[1]



ALS-2 reduces virulence gene production[1]



ALS-2 reduces bacterial load in mice[1]



ALS-3 Antibiotic-potentiating compound by using a non-bactericidal approach

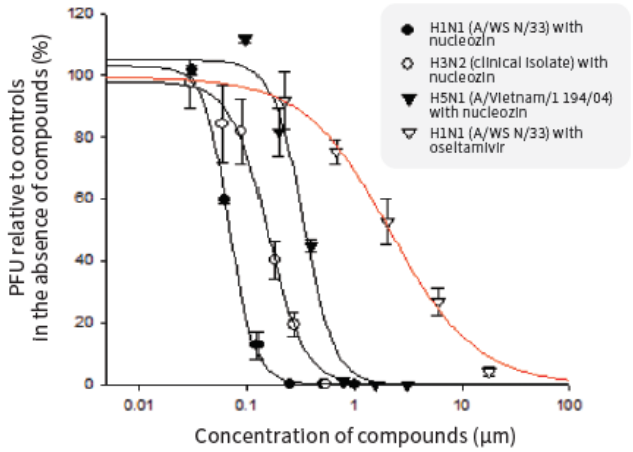
1. Proc Natl Acad Sci U S A. 2018 Jul 31;115(31):8003-8008

ALS-1: targeting a novel druggable target for Influenza A

ALS-1 inhibits influenza A nucleoprotein (NP)

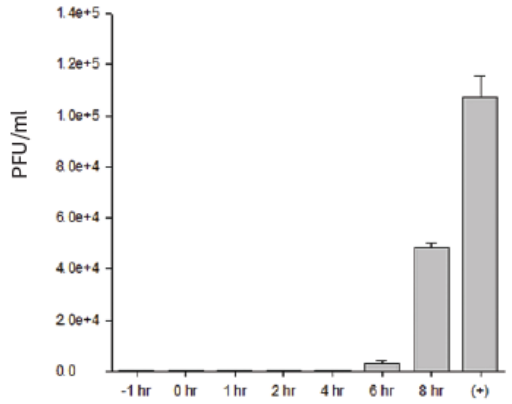
- NP is the most abundantly expressed protein during the course of an infection[1]. Its primary function is to encapsidate the virus genome for RNA transcription, replication and packaging. It is also a key adapter molecule between virus and host processes[1]
- ALS-1, by targeting NPs, acts upstream of Neuraminidase inhibitors such as Tamiflu, which target the last stage (budding) of the viral life cycle[2]. This novel mechanism distinguishes ALS-1 from all other currently marketed antiviral drugs[3]

ALS-1 outperforms Tamiflu® (oseltamivir, in red) in vitro with a lower IC50[2]



This figure shows the concentration dependence of ALS-1 in reducing the plaque-forming unit (pfu, a measure of number of infectious virus particulates) of human H1N1, H3N2 and H5N1 influenza viruses. The IC_{50} for these viruses is between 0.1-1µM

ALS-1 inhibited viral growth up to 6 hours after infection, indicating antiviral activities reside on post-entry and post-nuclear events[2]



This figure shows that MDCK cells were infected and ALS-1 (1 µM) was added before infection (- 1 h), at the time of infection (0 h) and at 1, 2, 4, 6 and 8 hour after infection as indicated. (+) control without ALS-1

1. J Gen Virol. 2002 Apr;83(Pt 4):723-34; 2. Nat Biotechnol. 2010 Jun;28(6):600-5; 3. Refer to the next slide "ALS-1: A Unique Antiviral Therapeutic Against Influenza A".

APTORUM

Facilitating Life Science Innovations to Serve Unmet Medical Needs

CLAVES PROJECTS

Claves pipeline overview

Note: all projected timelines refer to the estimated commencement time of the indicated stages

Pillar 3: Claves (CLS series) - Microbiota

Large molecule approach. Over 70 targets / indications

IND NDA

Program	Indication	Discovery	Lead Optimization	IND enabling	Phase I	Phase II / III
CLS-1	Obesity		Q4 2019	Q2 2020	Q4 2020	
CLS-2	To be disclosed					
CLS-3	To be disclosed					

For illustrative purposes only. There is no guarantee of any project being completed or having a specific outcome

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CLS-1: binding to therapeutic target

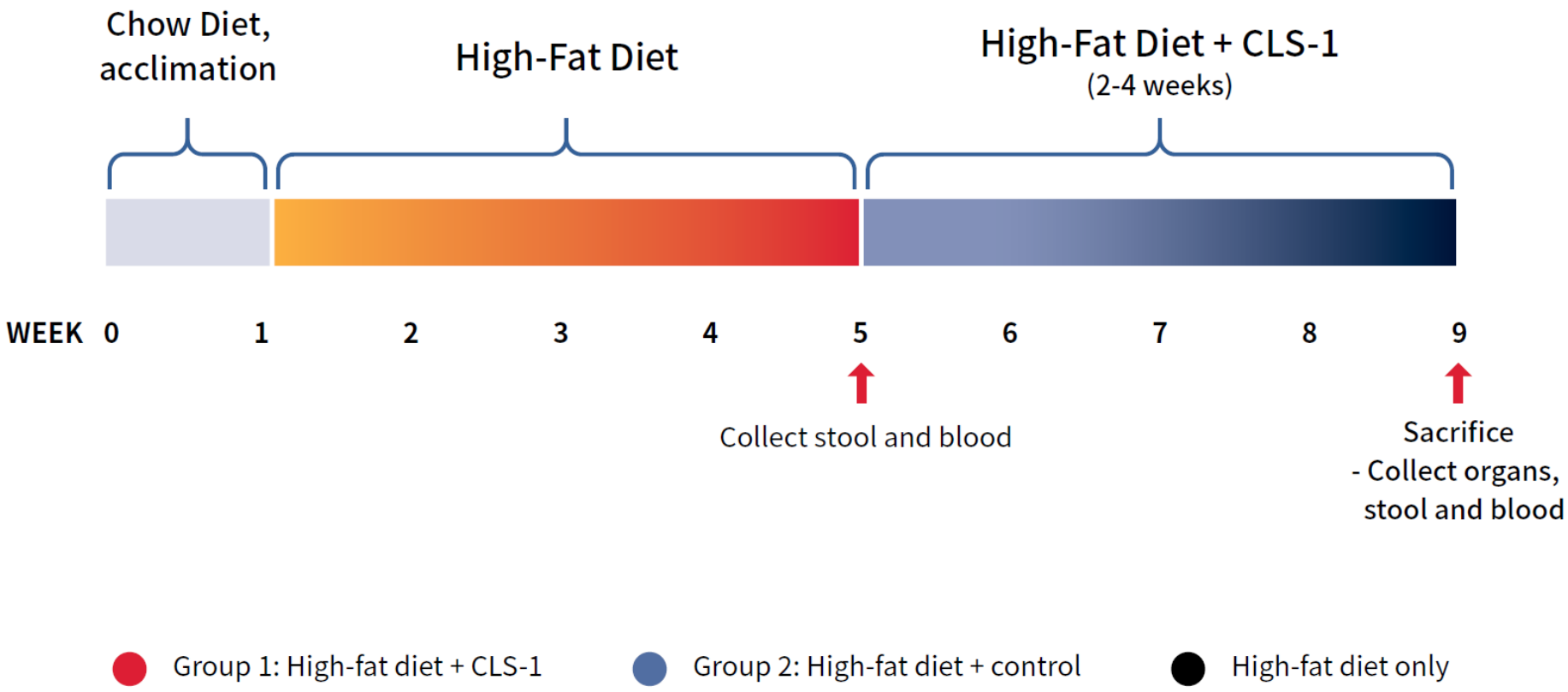
- Identified key microbiota metabolite linked to obesity (therapeutic target)
- Screened different candidates using the Claves platform to target obesity-linked metabolite, by testing the binding capacity of different CLS-1 candidates (with different compositions) to the target metabolites
- A7 was selected for further development

Claves Candidate	Candidate binding of obesity-linked metabolite (mg/g)
A1	2.42
A2	12.32
A3	8.2
A4	7.82
A5	71.9
A6	10.37
A7	33.47

Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

CLS-1: efficacy in a mouse model

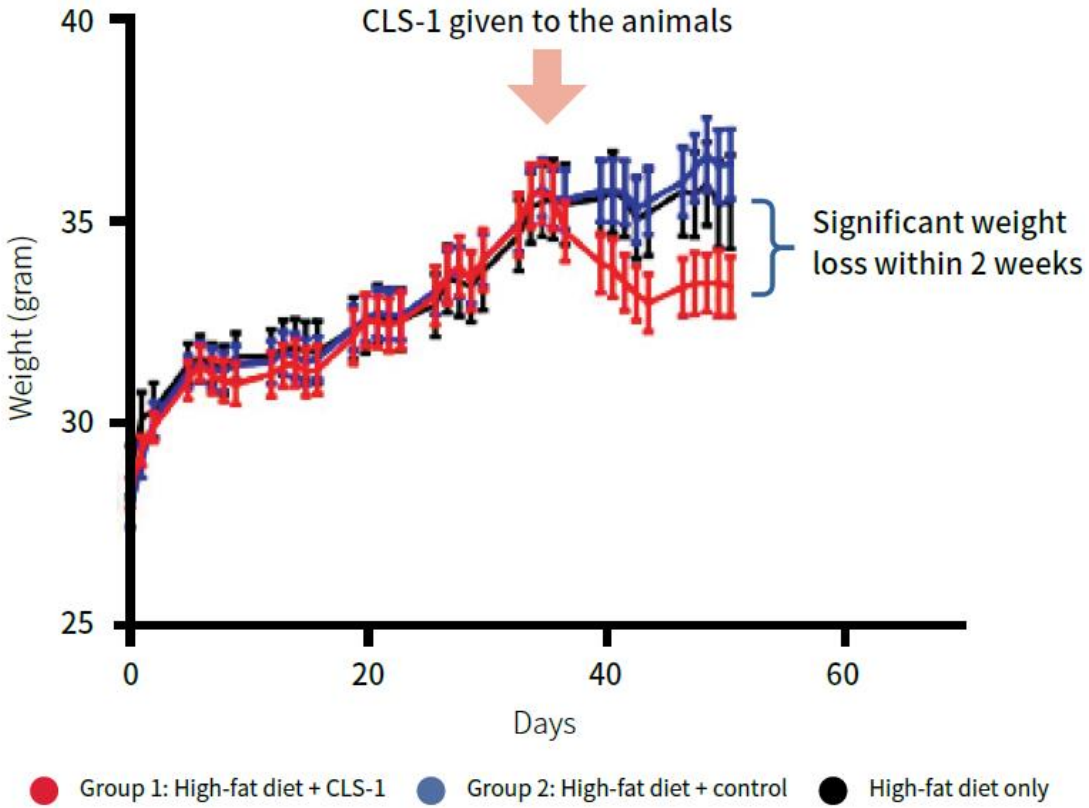
Experimental outline to test efficacy of CLS-1 treatment (orally available, non-absorbable) in mice on a high-fat diet

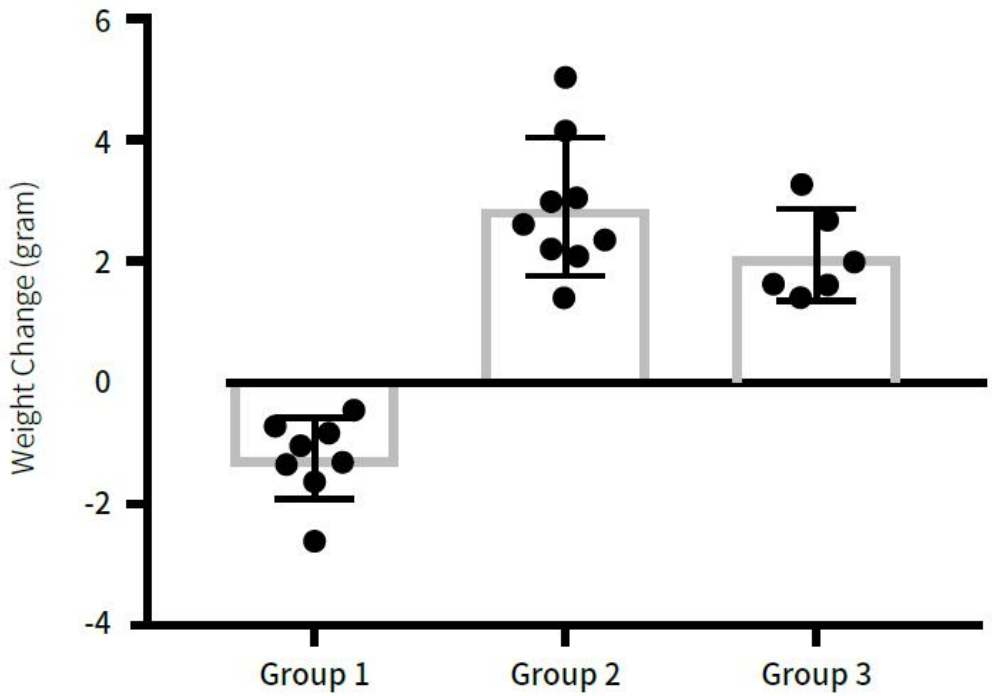


Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

CLS-1: efficacy in a mouse model

CLS-1 treatment significantly reduces body weight in mice

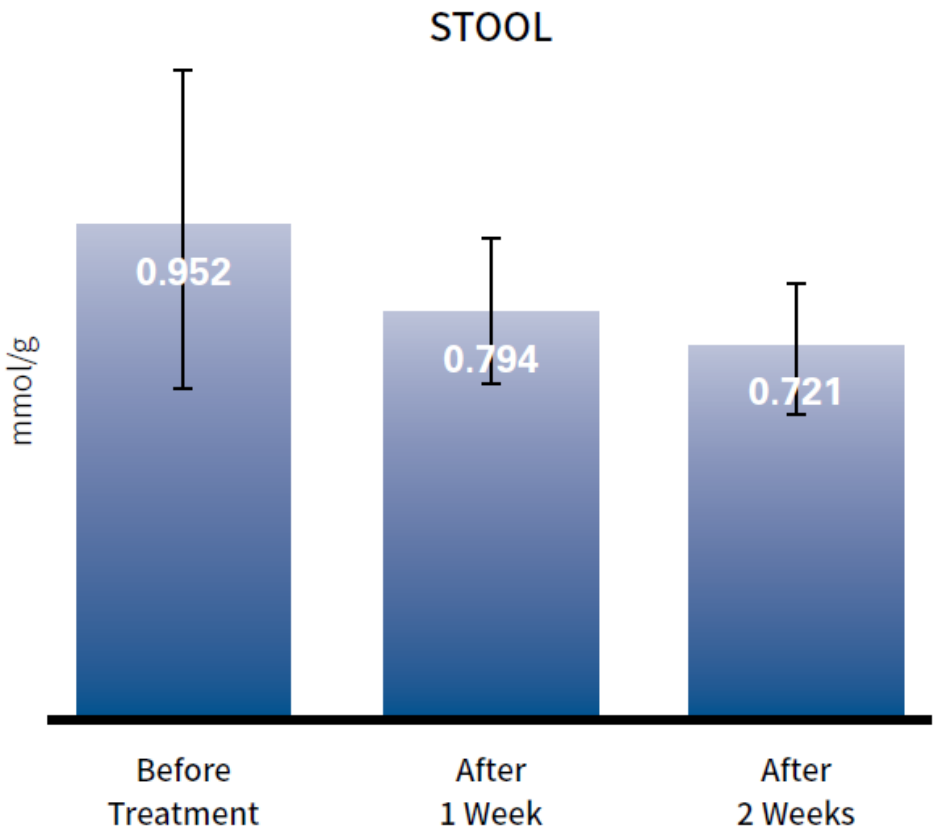


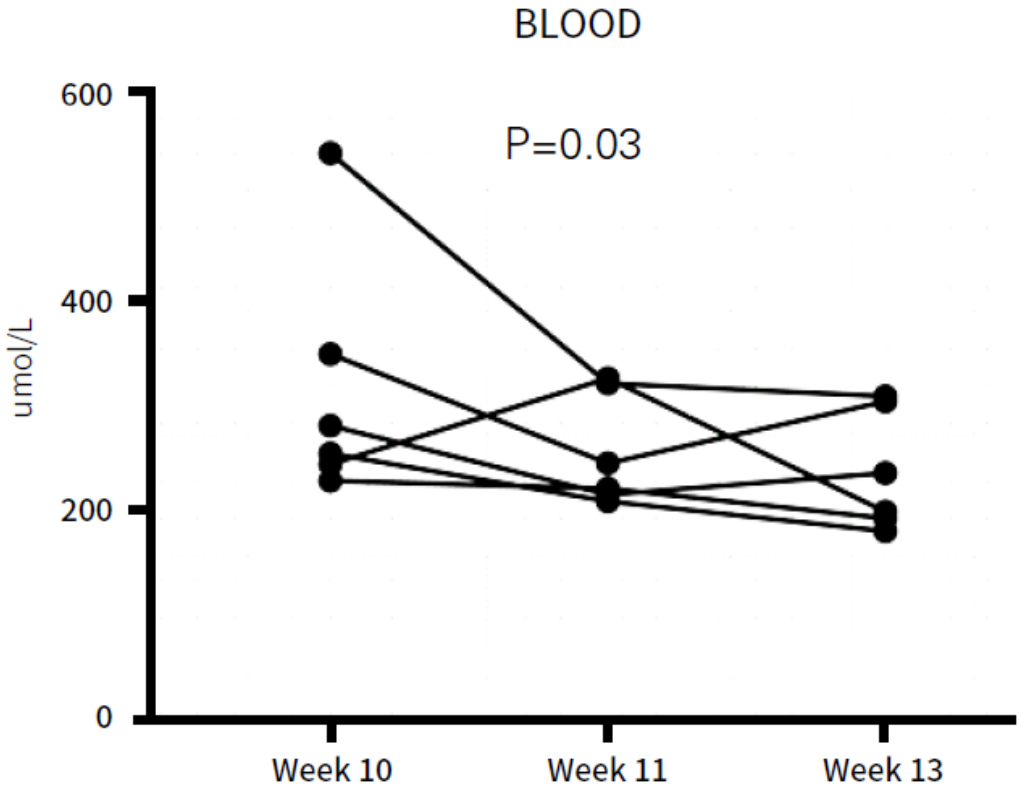


Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

CLS-1: pharmacodynamics

Amount of therapeutic target present in stool and in blood before and after administration of CLS-1





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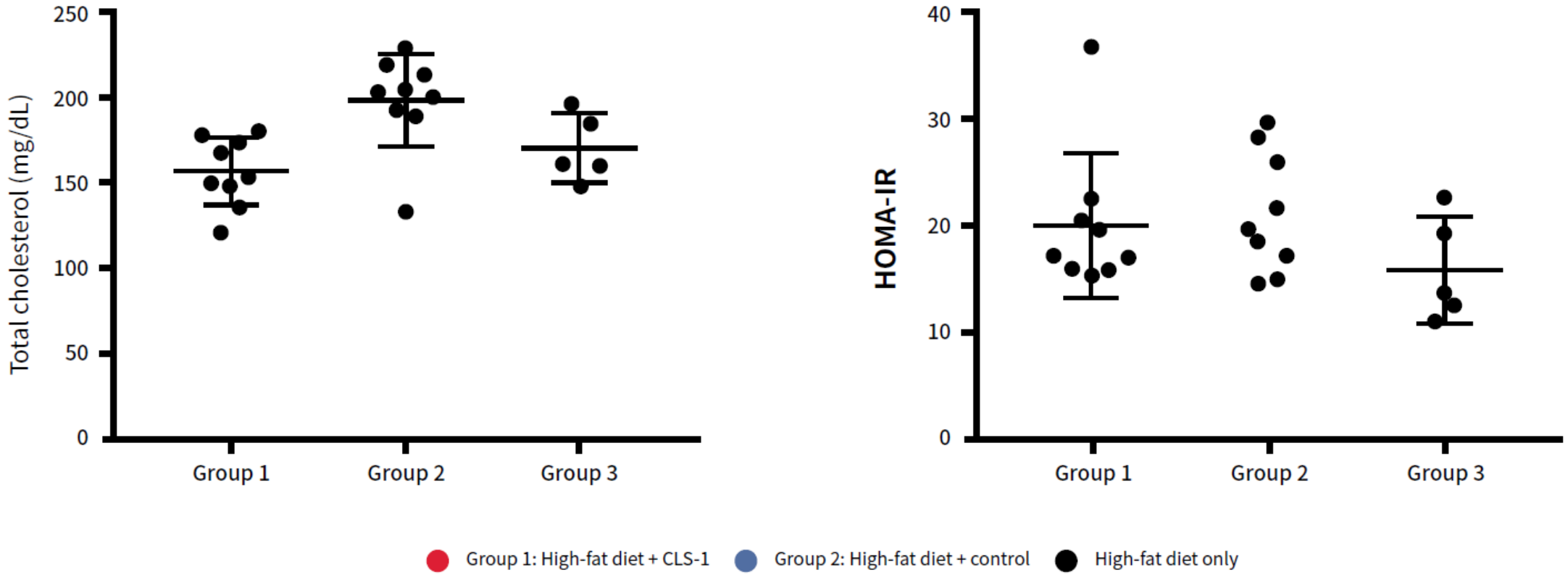
CLS-1: pharmacodynamics

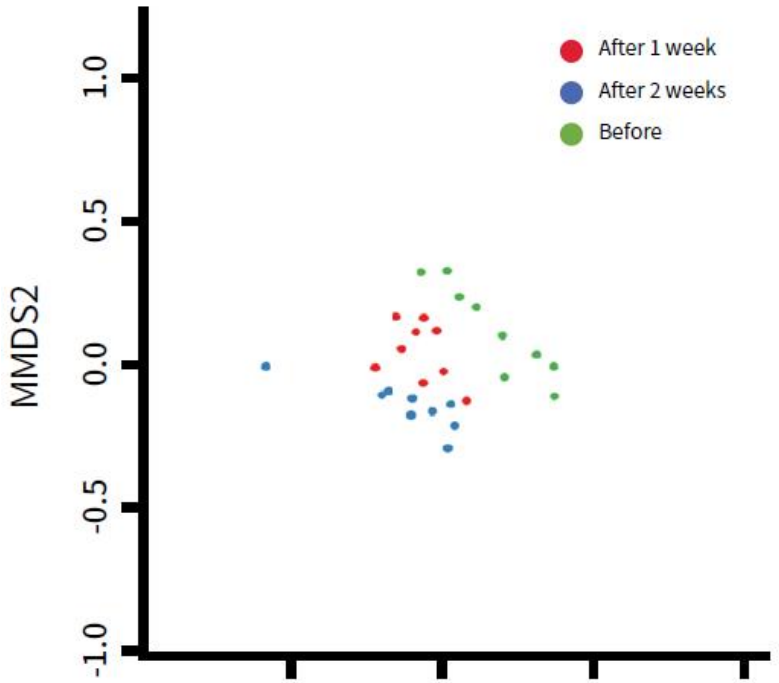
Cholesterol and Insulin Resistance



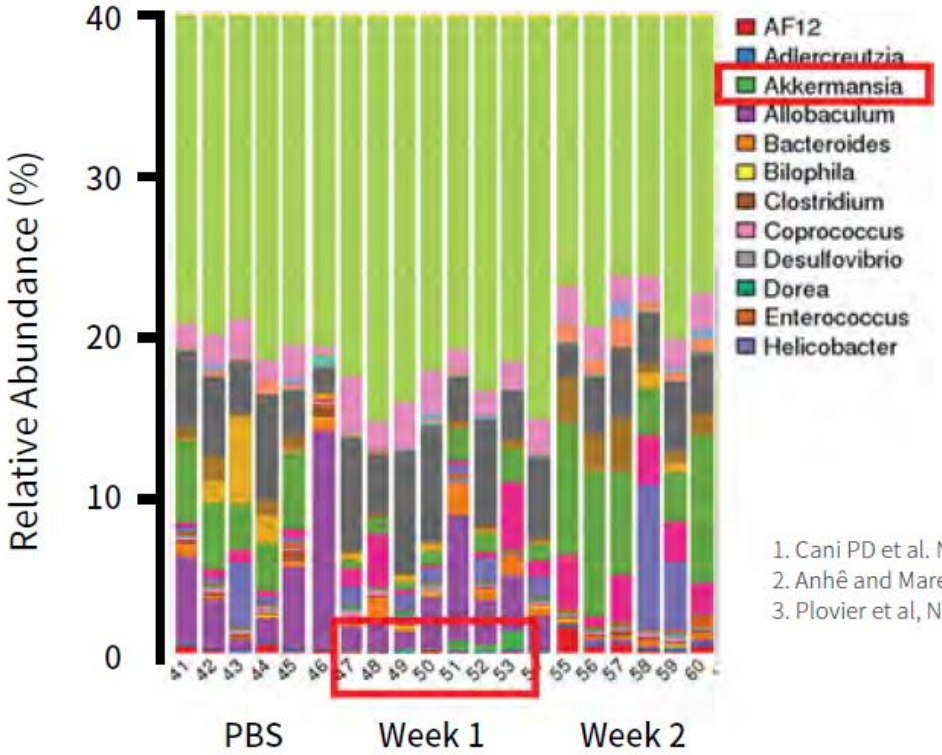
Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

CLS-1: mechanism of action

CLS-1 induced progressive changes in the microbiota



CLS-1 may act by promoting Akkermansia proliferation, a species of beneficial gut bacteria linked to obesity[1,2,3]



1. Cani PD et al. Nat Rev Endocrinol 2014
2. Anhê and Marette. Nat Med 2017
3. Plovier et al, Nat Med 2017

Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

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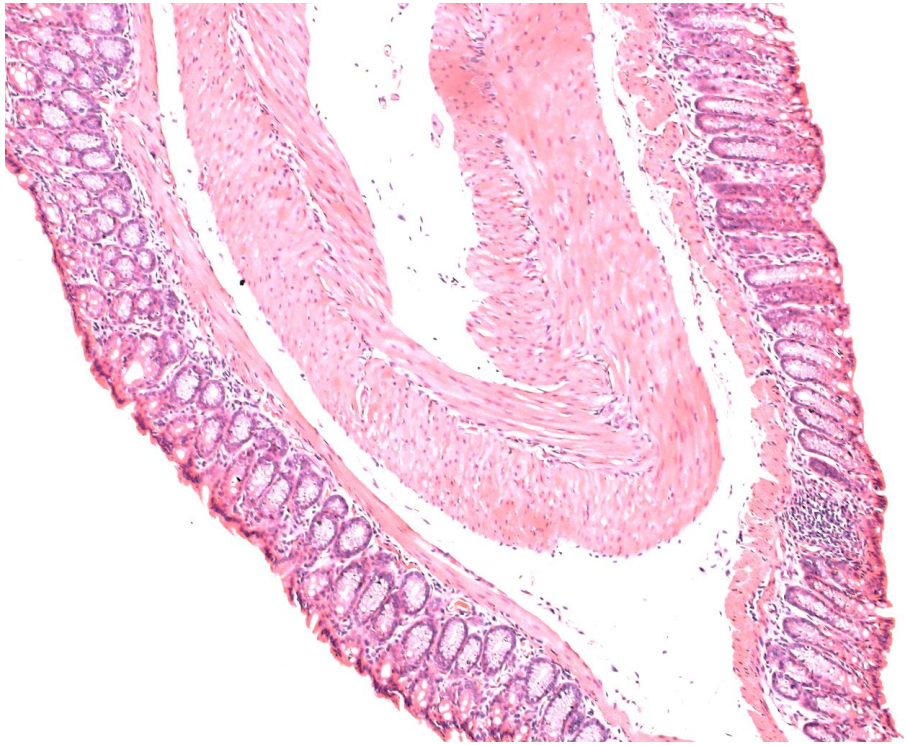
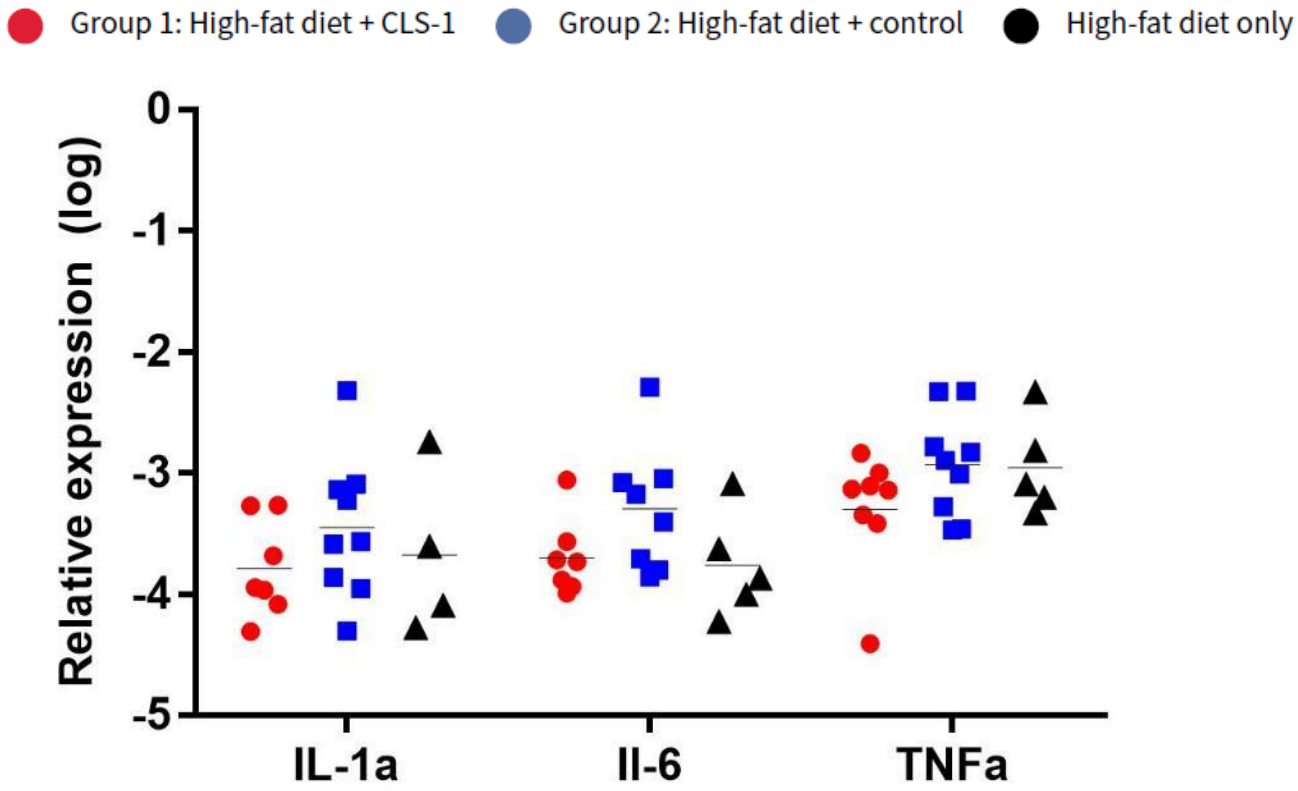
CLS-1: toxicology (gut histology and inflammatory markers)

Mucosa and Inflammatory Markers



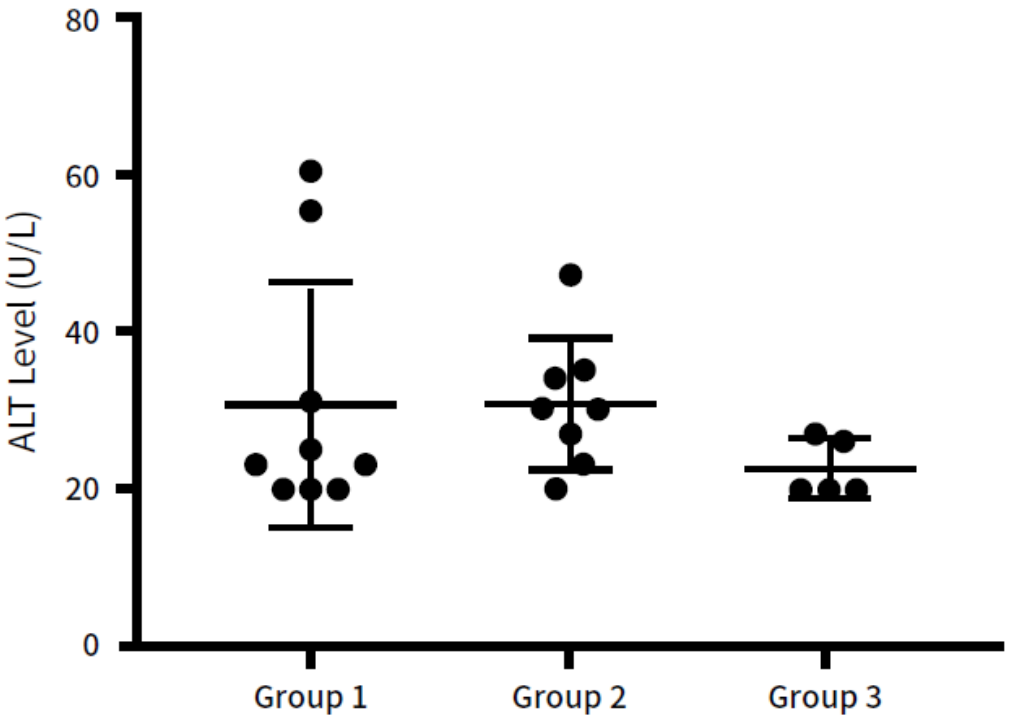


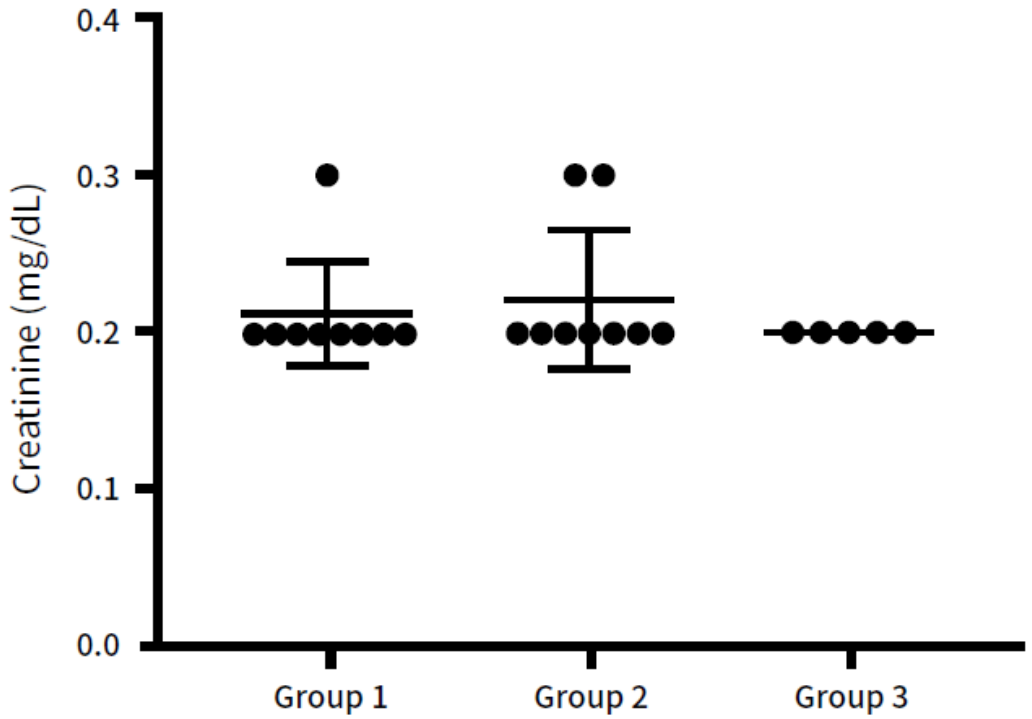
CLS-1 does not upregulate inflammatory markers

Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

CLS-1: toxicology (liver and renal functions)

Liver and Renal Functions





CLS-1 does not interfere with liver and renal functions

Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

CLS-1: Towards Clinical Trials

Pharmacology & Pharmacokinetics

- *In vivo* non-absorbability and mass balance testing is under planning

Toxicology

- Non-GLP Ames test indicates CLS-1 is not mutagenic

Chemistry, Manufacturing & Control

- CLS-1 is likely a non-absorbable macromolecule
- API manufacturing process has been scaled up to 100g, GLP batch manufacturing is under planning
- Process scale-up at a CRO is currently in progress

Clinical Trial Strategy & Protocol

- Plan to conduct a hybrid Phase 1 trial with both healthy volunteers and patients to provide preliminary efficacy readout, subject to a discussion with the FDA in the IND meeting to be conducted
- Targeting unmet need in obesity

Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing. Applies to all content on this slide.

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Facilitating Life Science Innovations to Serve Unmet Medical Needs

DIETARY SUPPLEMENT FOR MENOPAUSAL SYMPTOMS (NLS-2)

NLS-2: Executive Summary

NLS-2[1]

- NLS-2 is a dietary supplement for the relief of menopausal symptoms.
- The bioactive component of NLS-2 is DOI, a novel non-hormonal compound extracted from Chinese Yam
- DOI significantly increased estradiol biosynthesis and aromatase expression in granulosa cells *in vitro* and *in vivo* (rat animal model)
- Osteoporosis is frequently associated with menopause. DOI increases the apparent bone mineral density, bone volume fraction and trabecular thickness in an *in vivo* rat model
- DOI acts in a tissue-specific manner. Upregulation of aromatase, an enzyme involved in the production of estrogen, by DOI was found in ovary but not in other tissue
- DOI does not cause toxicity in vitro based on cell viability in the MTT assay
- Targeting to launch as a dietary supplement in Q1 2020

Timeline

Current progress of pipeline programs → Lead Projects → Other Candidates → Projected timeline

Program	Modality	Indication	Formulation	Commercialization
DOI (NLS – 2)	Supplement	Menopausal symptoms		Q1 2020

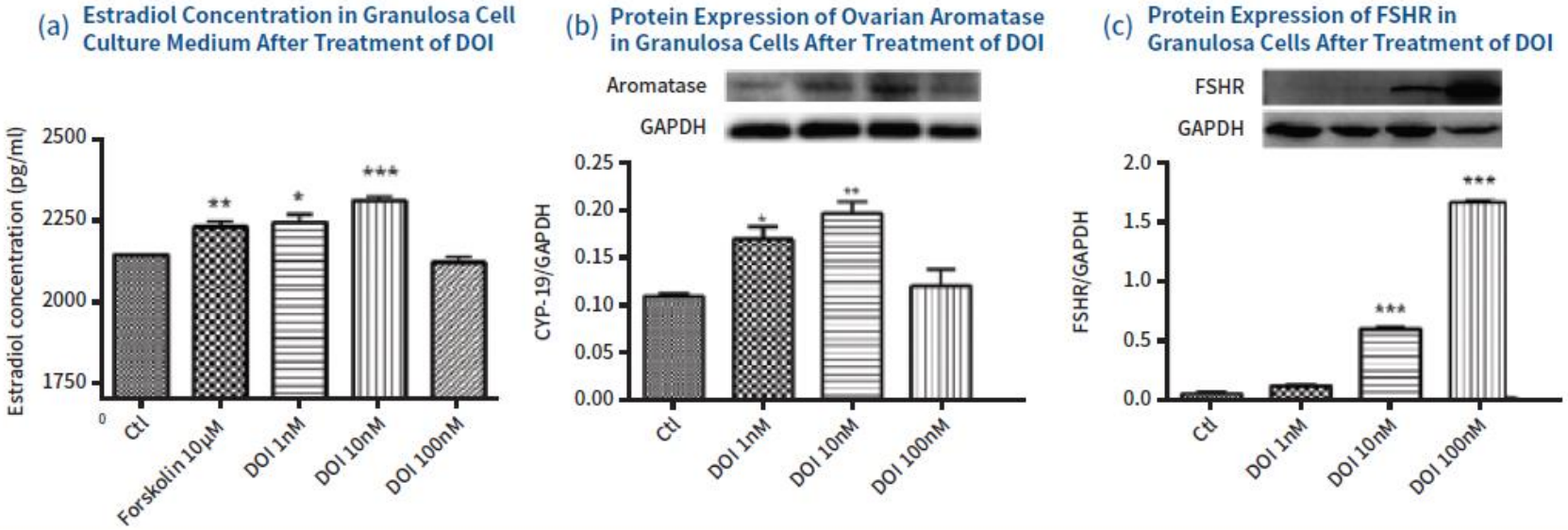
1. Lancet. 2003 Feb 8;361(9356):512-9; 2. Based on Aptorum's internal tests/experimentation and has not yet been verified by clinical trials or third party testing; 3. Data available in this presentation

DOI- a Chinese yam extract to address menopausal syndrome

DOI, a novel bioactive peptide with estrogen-stimulating activity[1]

- Discovered an estrogen-stimulating activity from an extract obtained from the Chinese yam, Dioscorea opposita Thunb
- Identified and isolated a novel bioactive component, DOI, which conferred the estrogen-stimulating activity[1]
- DOI significantly increased estradiol biosynthesis and aromatase expression in granulosa cells
- The upregulation of aromatase, an enzyme involved in the production of estrogen, by DOI was found in ovary but not in other cells/tissues

In vitro **studies show that DOI stimulated estradiol level in rat ovarian granulosa within a specified concentration range.**

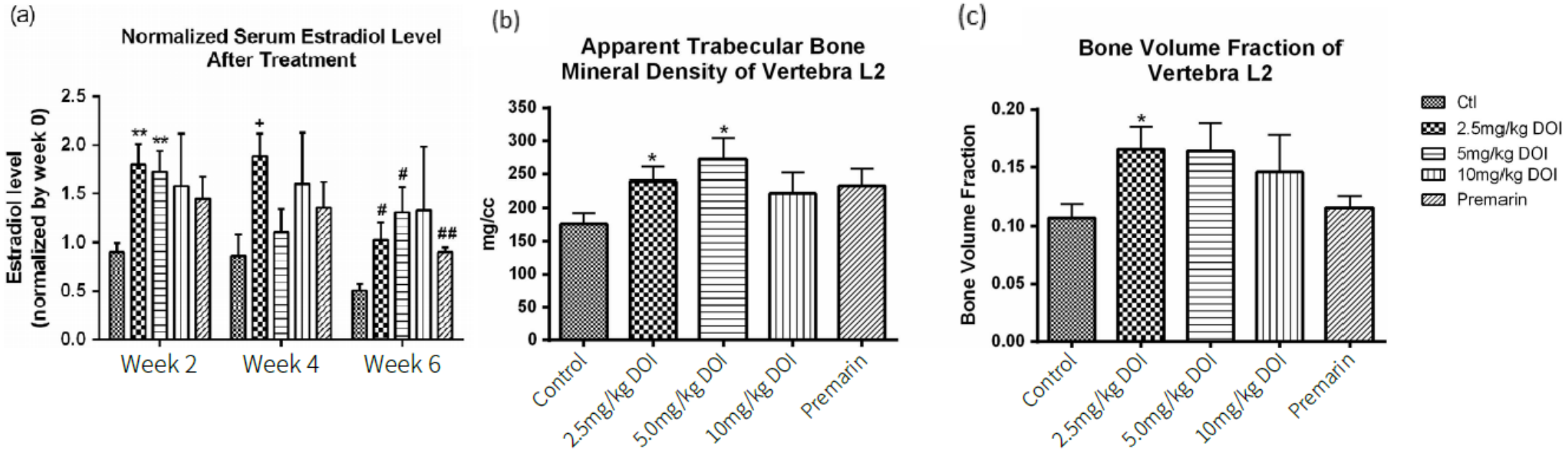


(a) Stimulatory activity of DOI on estrogen biosynthesis in granulosa cells. Protein expression of (b) aromatase and (c) follicle-stimulating hormone receptor (FSHR) in ovarian granulosa cells. Results are expressed as means ± SEM (n = 3). *P < 0.05, **P < 0.01, ***P < 0.001 compared with the control group (unpaired t-test). (Adopted from Science Report (5:10179, 2015))

1. Sci. Rep. 5, 10179; doi: 10.1038/srep10179 (2015). This source applies to all the content on this slide.

DOI- a Chinese yam extract to address menopausal syndrome

In *in vivo* rat models, DOI is shown to stimulate estradiol level and induce estrogen-related gene expressions[1]



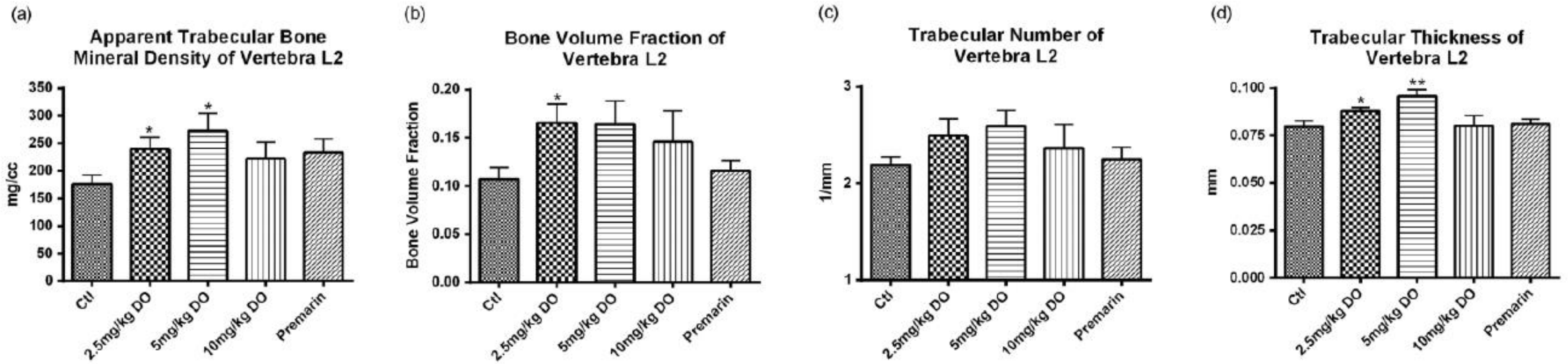
(a) Serum estradiol, (b) apparent trabecular bone mineral density, (c) bone volume fraction of Sprague Dawley rats after treatment with DOI for 2, 4, and 6 weeks. Results are expressed as means ± SEM (n = 6; except Premarin group, where n = 3). *p < 0.05, **p < 0.01 compared with the control group (unpaired t-test).

1. Sci. Rep. 5, 10179; doi: 10.1038/srep10179 (2015). This source applies to all the content on this slide.

DOI- a Chinese yam extract to address menopausal syndrome

DOI and bone density[1]

- DOI in old female SD rats demonstrated an increase in the apparent bone mineral density, bone volume fraction and trabecular thickness by microCT scanning



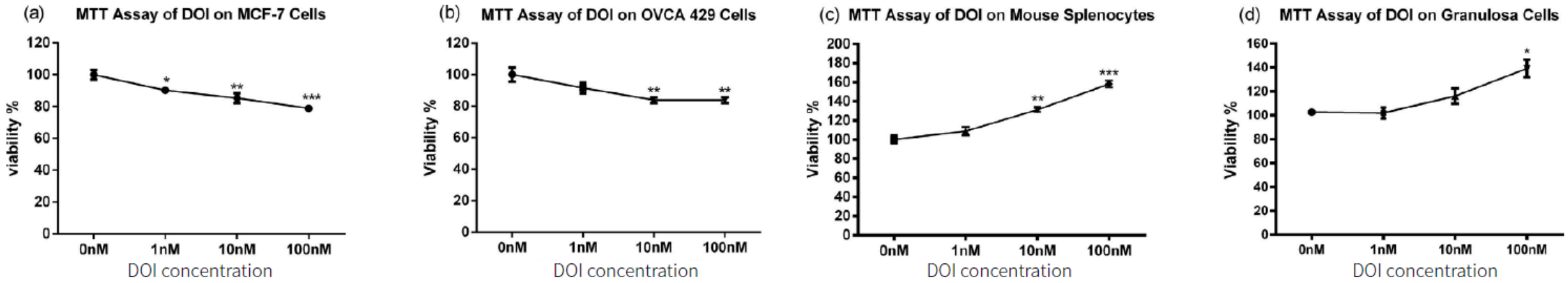
(a) Serum estradiol, (b) apparent trabecular bone mineral density, (c) bone volume fraction of Sprague Dawley rats after treatment with DOI for 2, 4, and 6 weeks. Results are expressed as means ± SEM (n = 6; except Premarin group, where n = 3). *p < 0.05, **p < 0.01 compared with the control group (unpaired t-test).

1. Sci. Rep. 5, 10179; doi: 10.1038/srep10179 (2015). This source applies to all the content on this slide.

DOI- a Chinese yam extract to address menopausal syndrome

DOI does not cause toxicity in vitro based on cell viability in the MTT assay[1]

- DOI demonstrated the decrease in viability of MCF-7 breast cancer cells and OVCA-429 ovarian cancer cells, indicating that DOI is not expected to display any of the side effects of hormone replacement therapy, such as the increase in risk of breast and ovarian cancer



Viability of (a) MCF-7 breast cancer cells, (b) OVCA-429 ovarian cancer cells, (c) mouse splenocytes, and (d) ovarian granulosa cells after treatment with DOI for 48h. Results are expressed as means±SEM (n=3). **p

1. Sci. Rep. 5, 10179; doi: 10.1038/srep10179 (2015). This source applies to all the content on this slide.

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