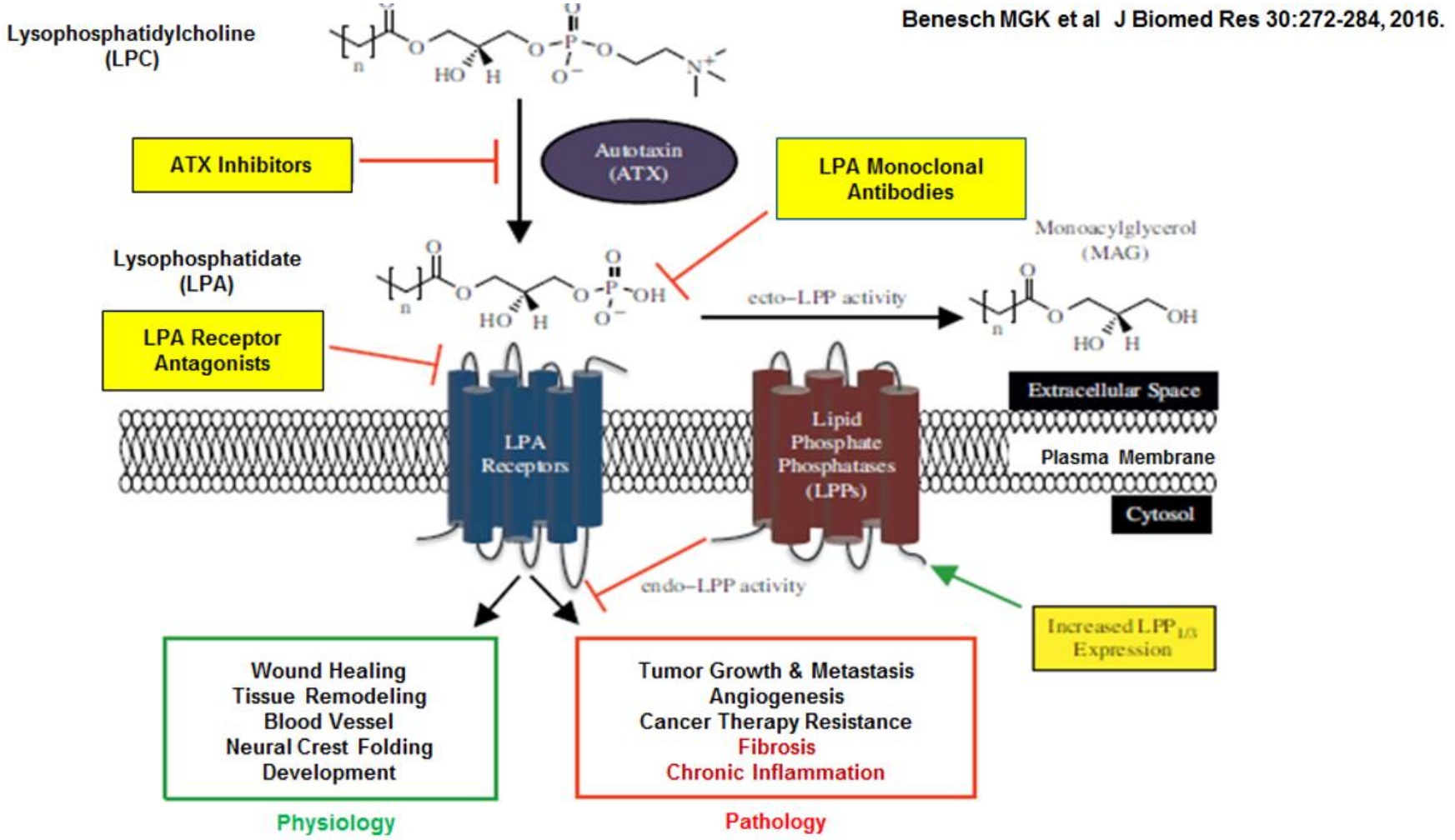
GEMSEKI

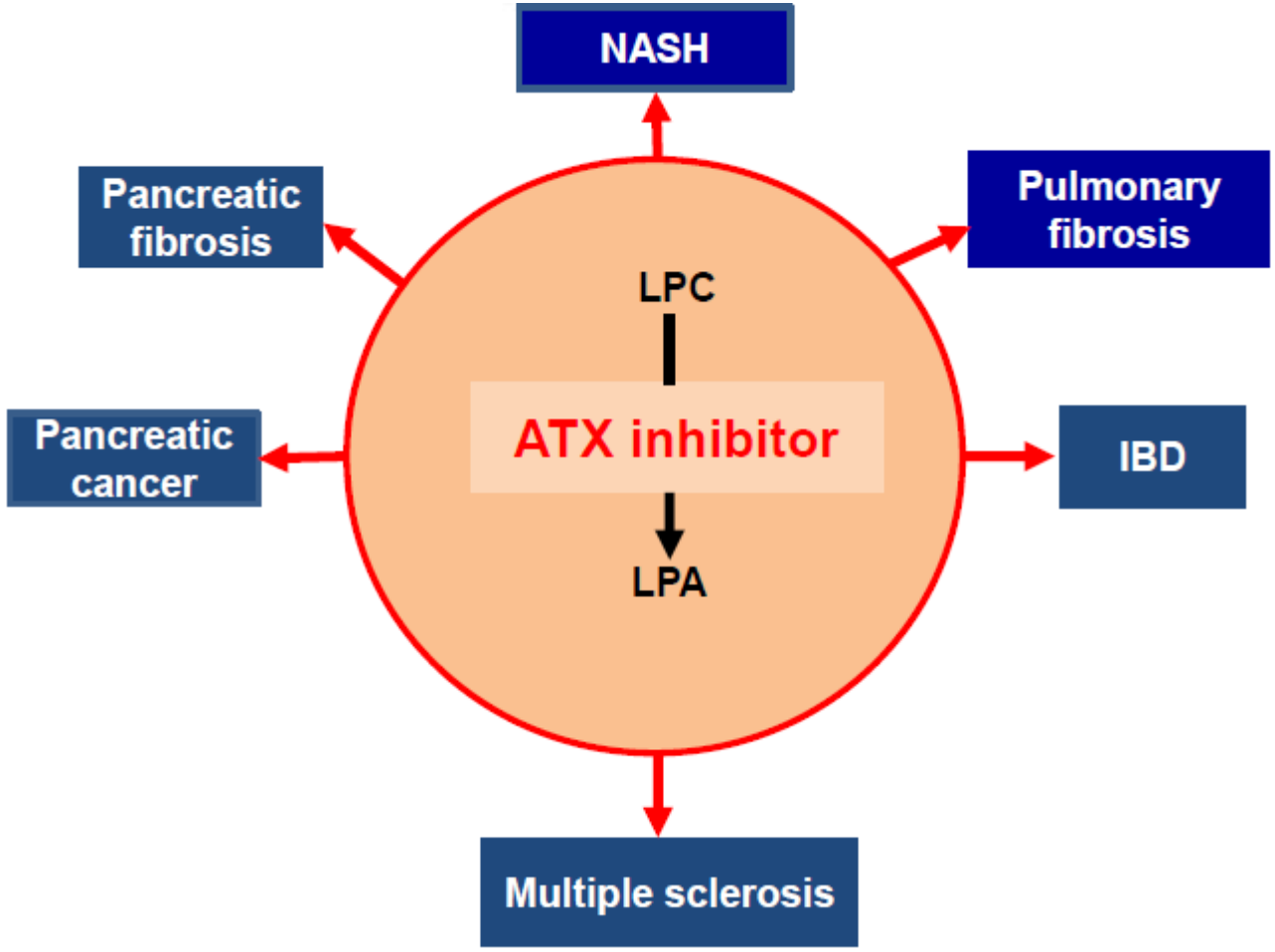
GEM045　Overview

Gemseki Inc.

Background of Autotaxin

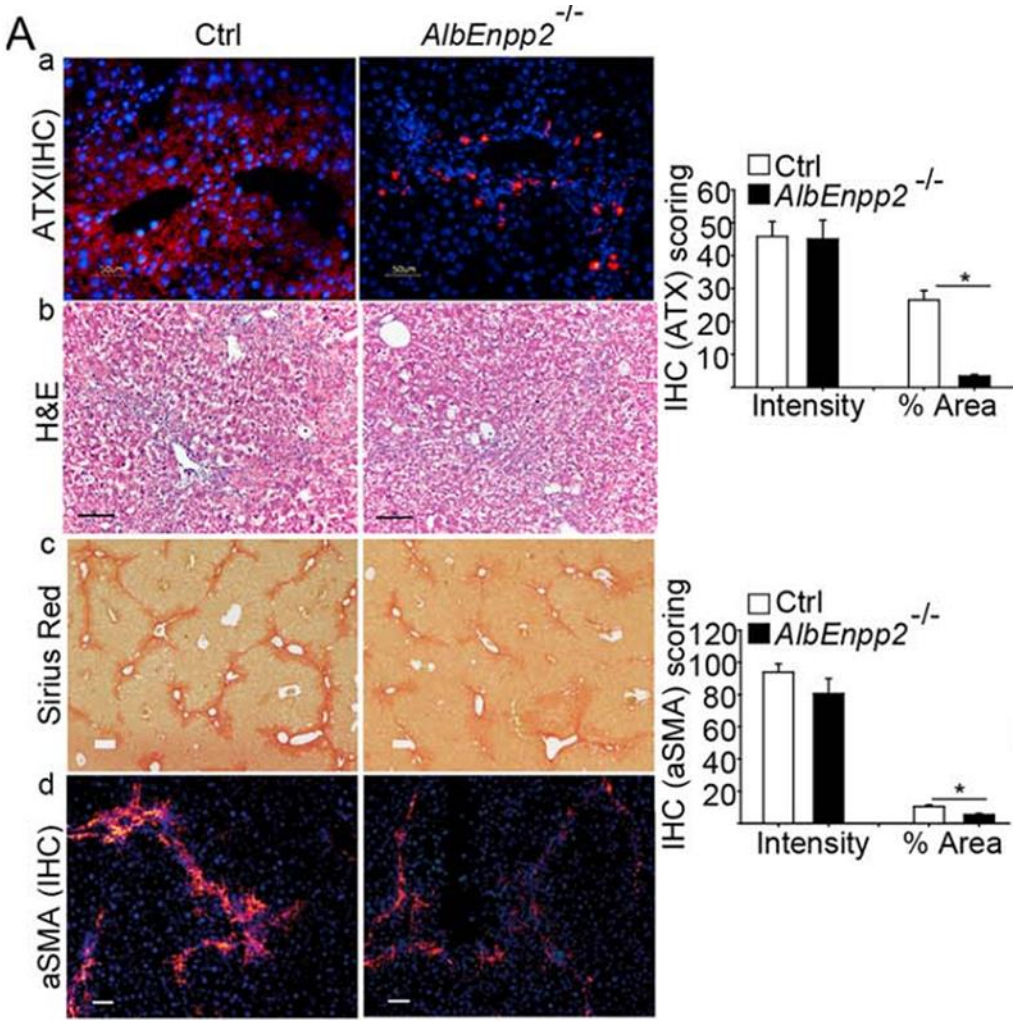


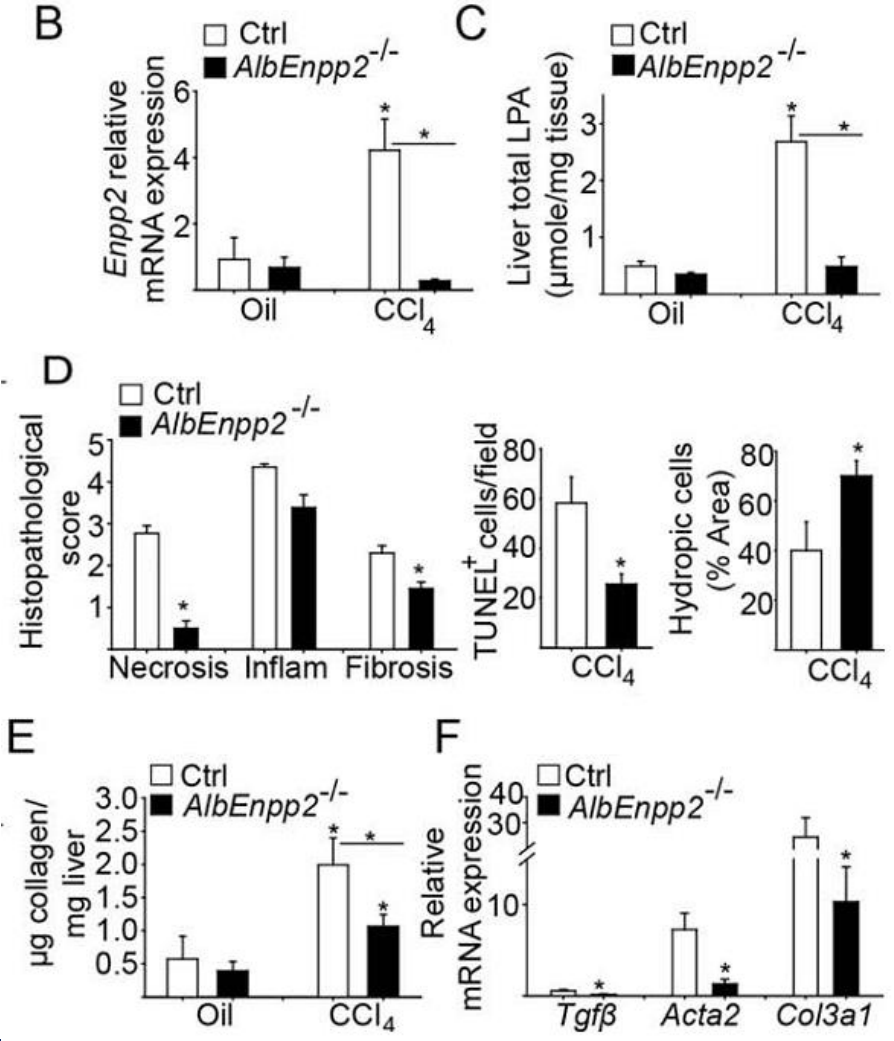
Potential Utility of ATXi in Various Therapeutic Areas



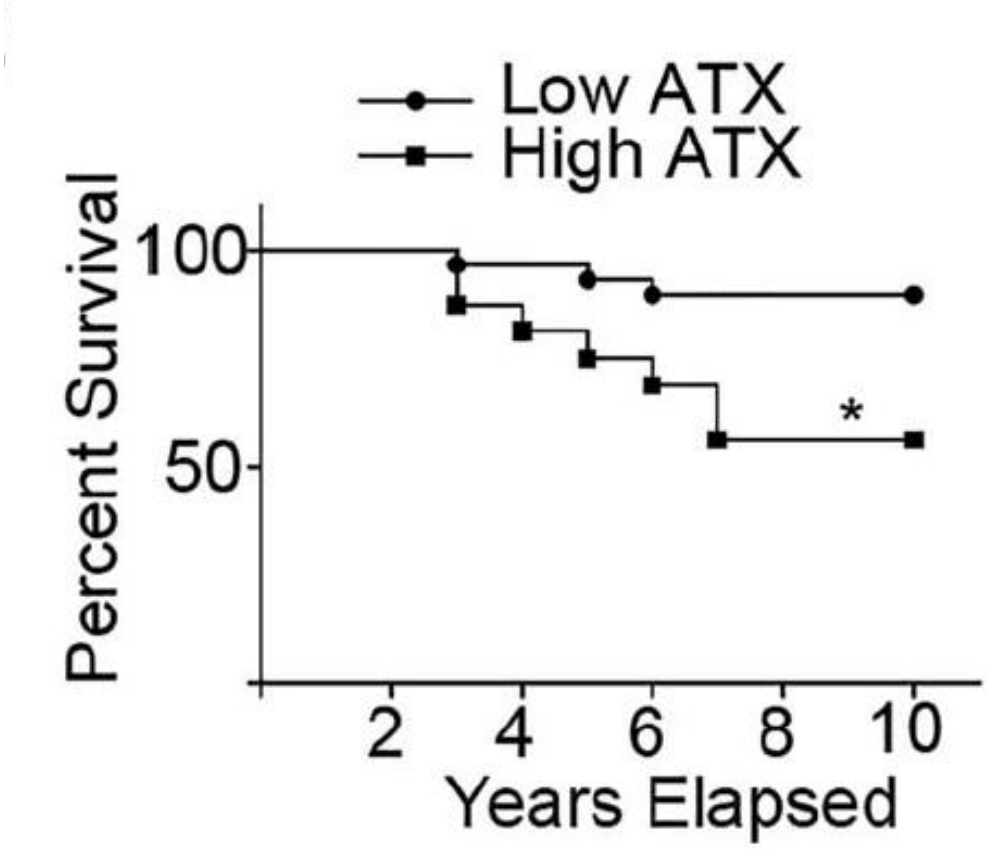
Autotaxin Deletion Ameliorates Liver Fibrosis

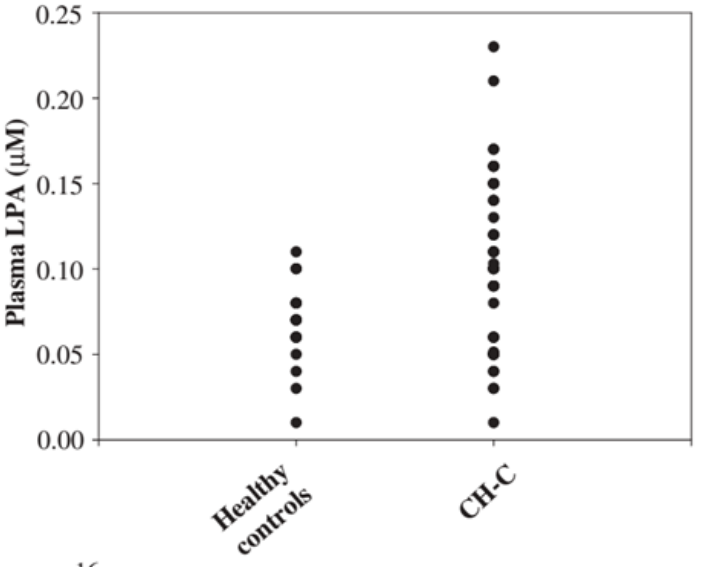
- **Abrogation of liver ATX/LPA production resulted in diminished necrosis, apoptosis, and proliferation**

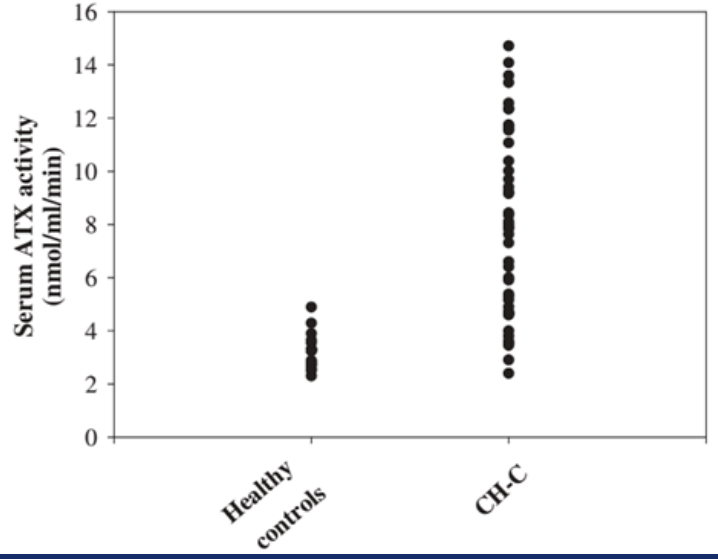




Increased Serum ATX Levels in CLD Patients of Different Etiologies, correlating with Poor Survival





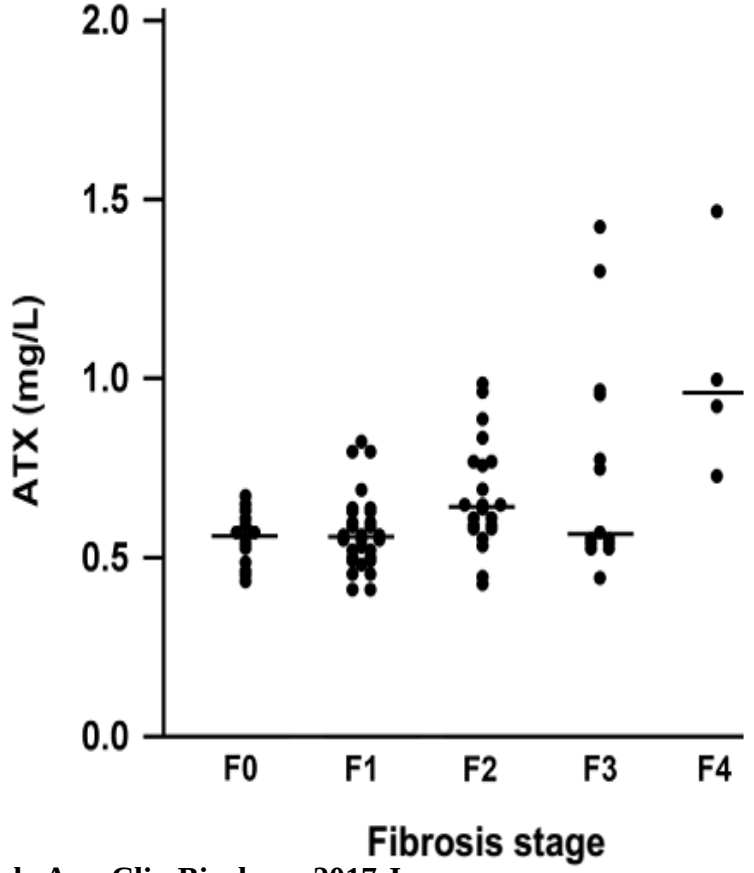


CH-C, chronic hepatitis C

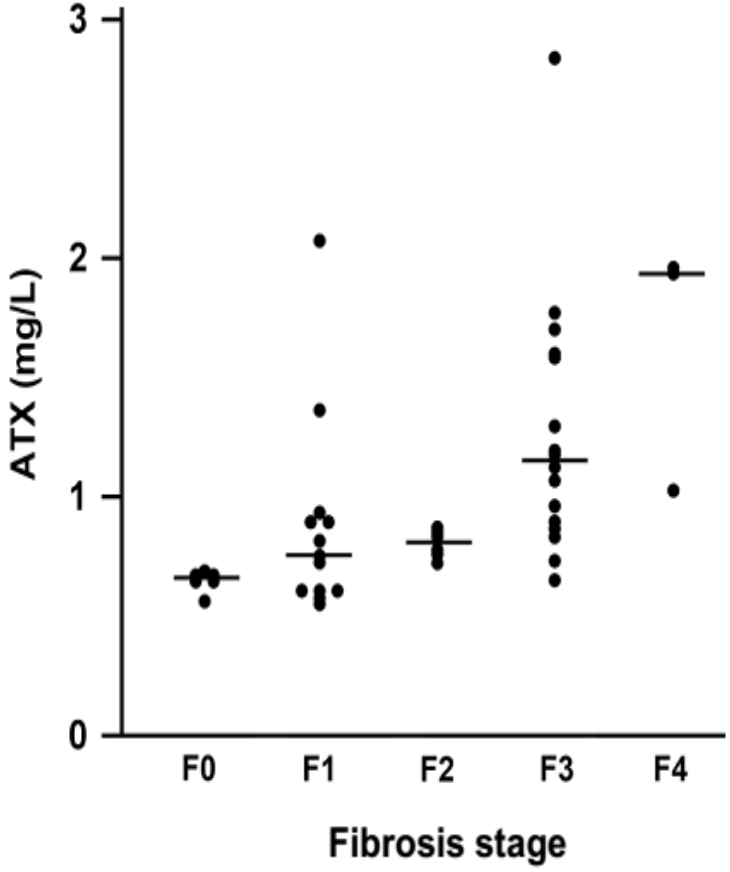
Hepatology (2017) v65, p1369; J Clin Gastroenterol (2007) v41, p616

Relationships between Serum Levels of ATX and the Liver Fibrosis Stage with NAFLD

Male



Female



Ikeda et al. Ann Clin Biochem. 2017 Jan 1:4563217741509.

Autotaxin Inhibitors -- Series 1

- GEM045 bNPP IC_{50} = 58 nM; LPC-CR IC_{50} = 330±72 nM.

	LPC-CR (in-vitro) IC_{50} (nM)	LPA Reduction (rat plasma) (ex-vivo) IC_{50} (nM)	LPA Reduction % (PD in mice) at 24 hr. (same dosage estimate)	Dog PK	hERG IC_{50} (μM)	CYPs IC_{50} (μM)
GEM045	330	1	Maintained ~80%	$T_{1/2}$ (iv) 7.6 h F% 49.6	>10	>10
GLPG-1690 (Finished Phase II for IPF)	231	100	Dropped to ~30%	$T_{1/2}$ (iv) 3.5 h F% 63	>10	>10

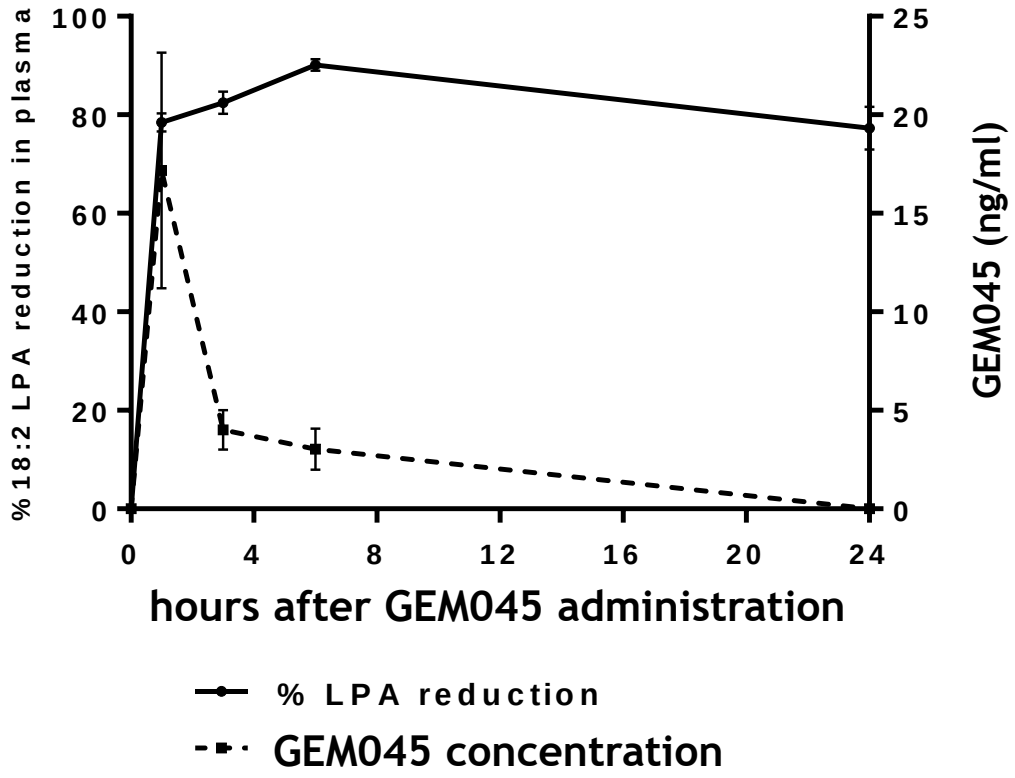
- GEM045 showed significant effects in chronic pancreatitis (Histology Score 11.0 → 7.4); MCD (NAS 6.4 → 0.9, Fibrosis 1.9 → 0.0); Stelic-STAM (NAS 4.5 → 3.3); CDA-HFD (NAS+Fibrosis Score 8.5 → 5.4); IPF (Pulmonary Inflammation 3.1 → 2.1, Pulmonary Fibrosis 4.3 → 2.7); paw edema (edema volume ↓ 67%); and A549 Xenograft (anticancer) animal studies.

- Only one reduced metabolite (M+2) by liver hepatocytes in all species (rat, dog, monkey, human). The metabolite has the same LPA reduction activity as the mother species GEM045.

- MTD of GEM045: no findings up to 900 mg/kg, po, b.i.d. for 5 days in mice.

Autotaxin Inhibitors (PK/PD)

GEM045 Mouse PK/PD Properties
Reduction of plasma LPA 18:2 as a PD biomarker



1. Compound: GEM045
2. Dose: PO= 20 mg/kg
3. Formulation:
   5% DMSO + 20% Cremophor EL®+ PBS
4. Time point (hour): PO= 0, 1, 3, 6 and 24
5. Analysis: GEM045 and LPA 18:2
   by LC-MS/MS

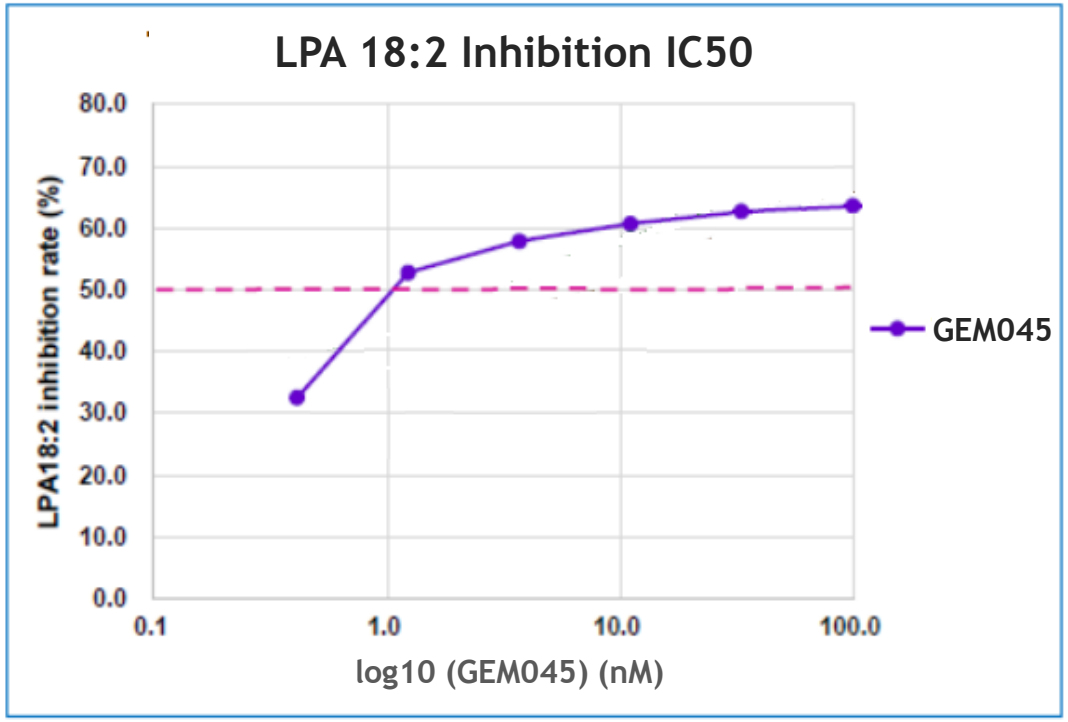
- **GEM045 showed transient half life but with sustained inhibition of plasma LPA, indicating ATX inhibition dissociated from PK**

LPA Plasma Inhibition

LPA 18:2 Inhibition in Rat Plasma of GEM045

Setting:

1. Compound: GEM045
2. Test system : SD rat plasma
3. Concentration (nM): 0, 0.4, 1.2, 3.7, 11.1, 33.3, 100 nM
4. Time point (min): 0, 2h at 37℃



	IC_{50} (nM) in rat plasma
GEM045	1.1

Autotaxin Inhibitors (MCD)

Effect of GEM045 on Methionine-Choline-Deficient Model

ITRI (B6 mice) — Methionine-choline deficient (MCD) diet Treatment initiation — Finished and sacrificed

Naïve	Sham control	n=4
Vehicle	(V po., bid)	n=9
GEM045	(Low dose, po., bid)	n=8
GEM045	(High dose, po., bid)	n=8

TJC0265 formulation 5%DMSO+10%CrEL+H_2O

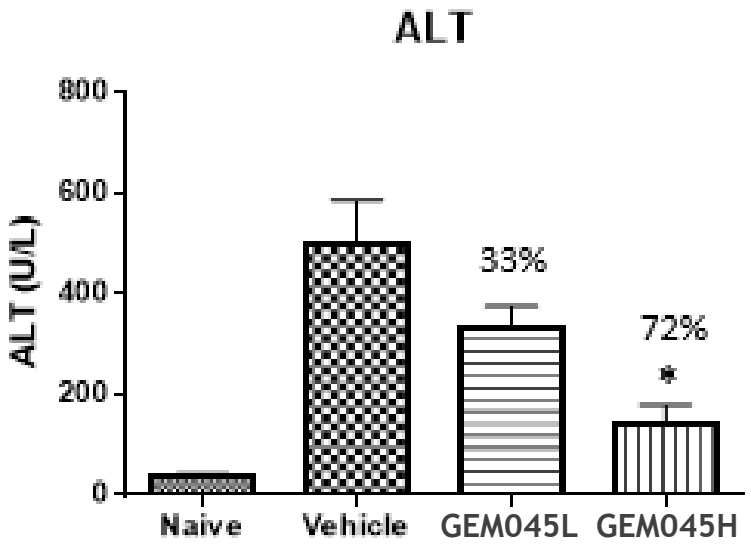
- Body weight is recorded twice per week, just before compound administration at each time point.
- When sacrificed, serum samples will be collected and liver samples will be fixed using formalin and then wax embedded.
- Liver samples will also be collected for frozen storage.

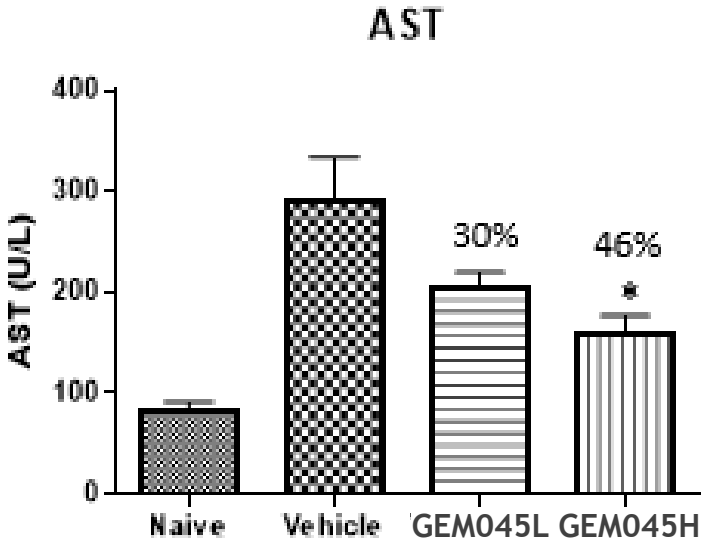
Autotaxin Inhibitors (MCD)

Effect of GEM045 on Methionine-Choline-Deficient Model (8 wks.)

GEM045L = Low Dose. **GEM045H = High Dose**

- Naïve (N=4)
- Vehicle (N=9)
- GEM045L X mg/kg, po, bid (N=7)
- GEM045H Y mg/kg, po, bid (N=7)





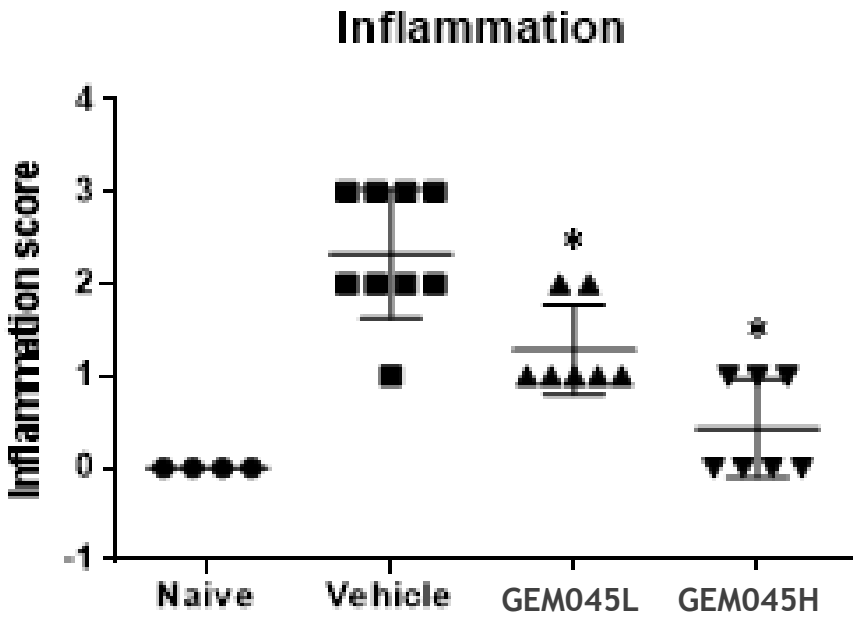
GEM045 po bid x 8 weeks

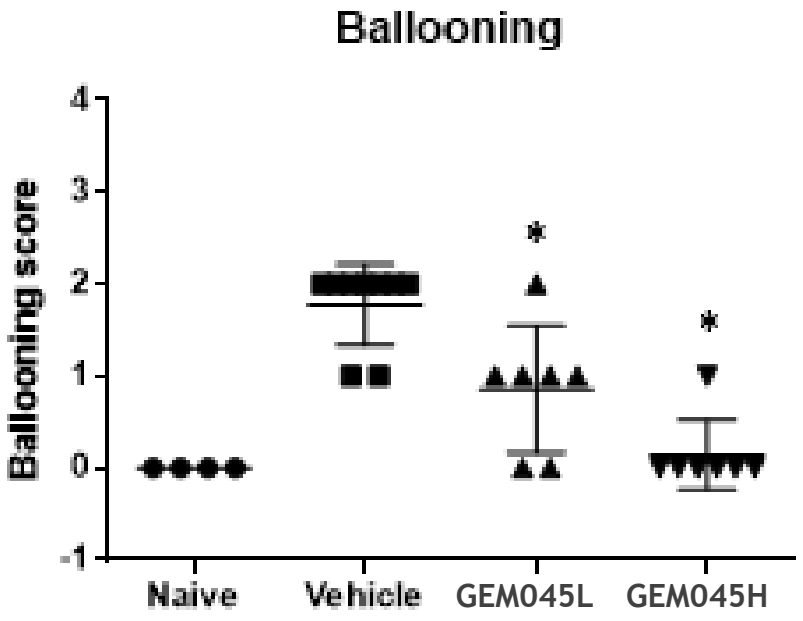
* P<0.05, vs Vehicle; One-way ANOVA

Autotaxin Inhibitors (MCD)

Effect of GEM045 on Methionine-Choline-Deficient Model

GEM045L = Low Dose. GEM045H = High Dose



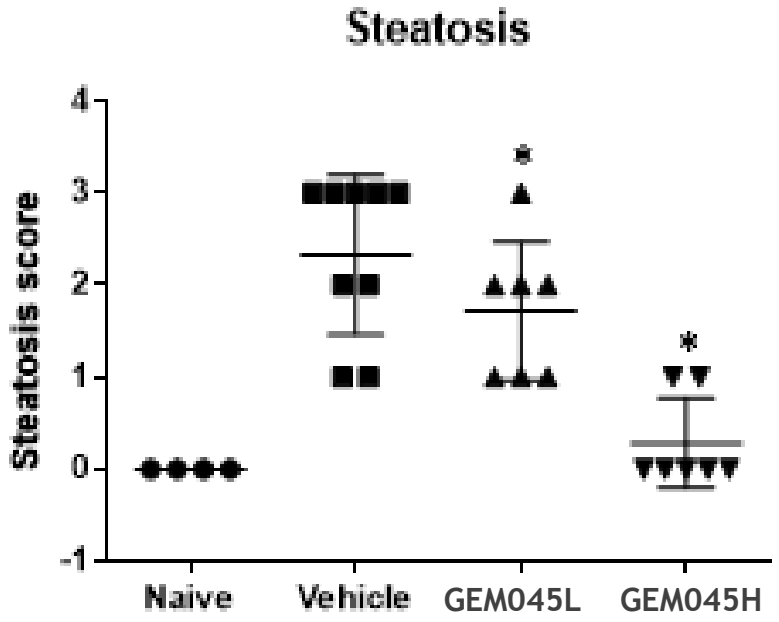


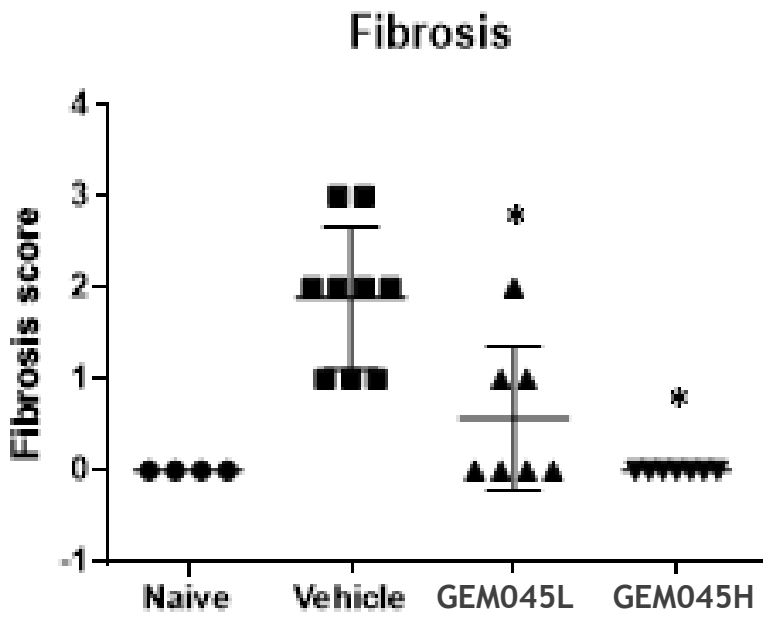
***P<0.05 vs Vehicle**

Autotaxin Inhibitors (MCD)

Effect of GEM045 on Methionine-Choline-Deficient Model

GEM045L = Low Dose. GEM045H = High Dose

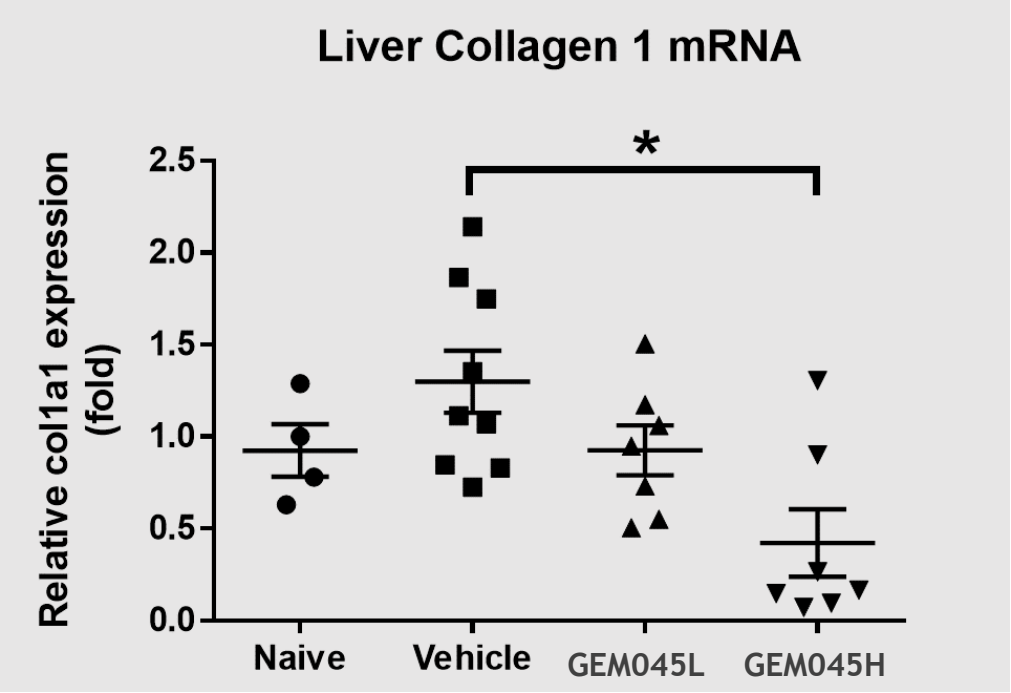




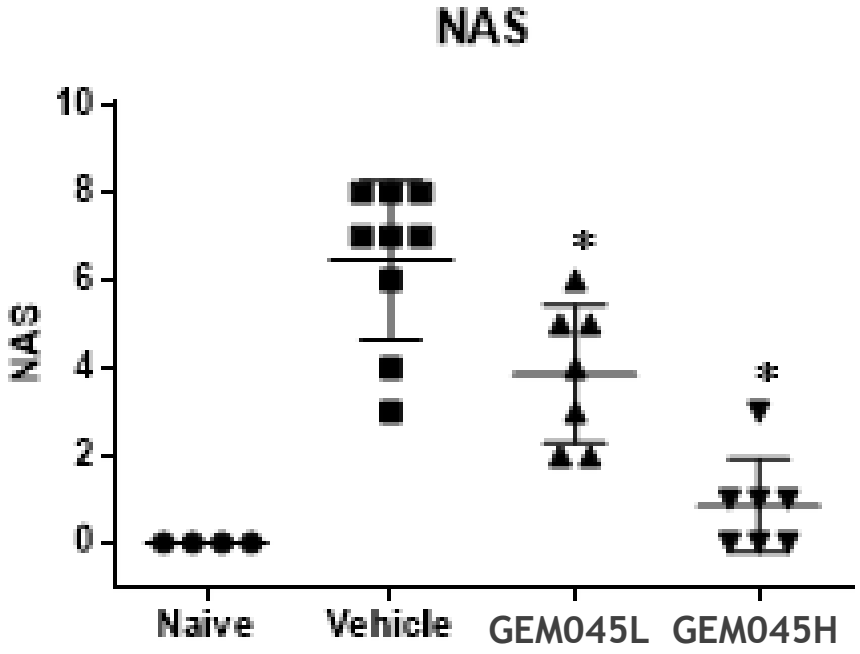
***P<0.05 vs Vehicle**

Autotaxin Inhibitors (MCD)

Effect of GEM045 on Methionine-Choline-Deficient Model



*P<0.05 vs Vehicle



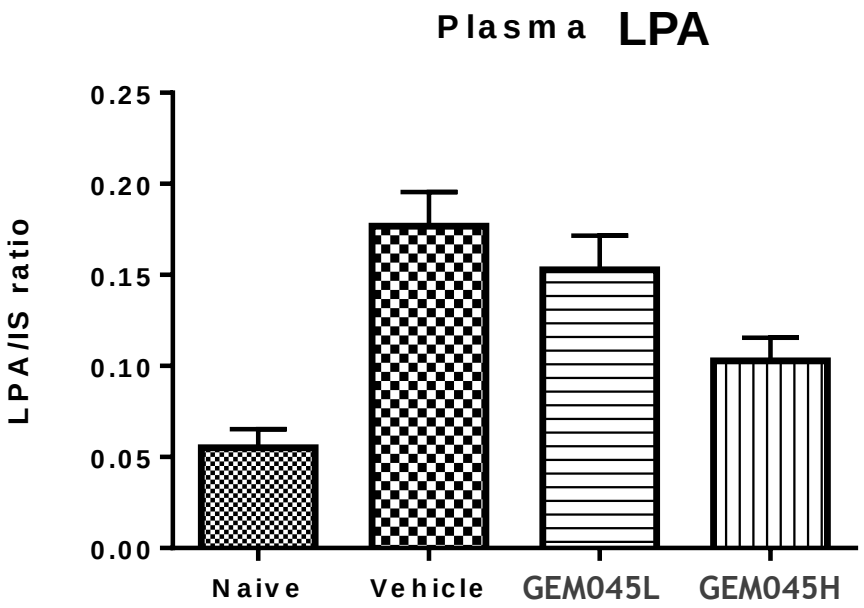
*P<0.05 vs Vehicle

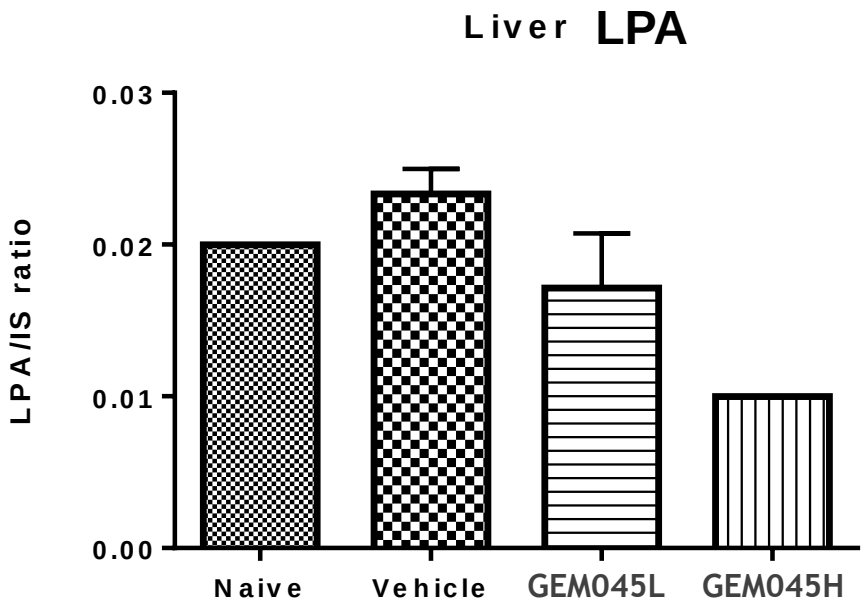
GEM045L = Low Dose. GEM045H = High Dose

Autotaxin Inhibitors (MCD)

Effect of GEM045 on Methionine-Choline-Deficient Model

GEM045L = Low Dose. GEM045H = High Dose





IS: internal standard

GEMSEKI

Autotaxin Inhibitors (MCD)

Effect of GEM045 on Methionine-Choline-Deficient Model

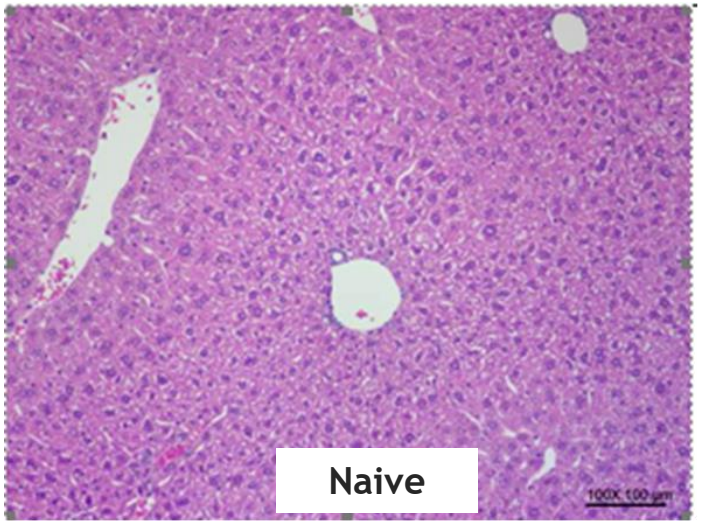
GEM045L = Low Dose. GEM045H = High Dose

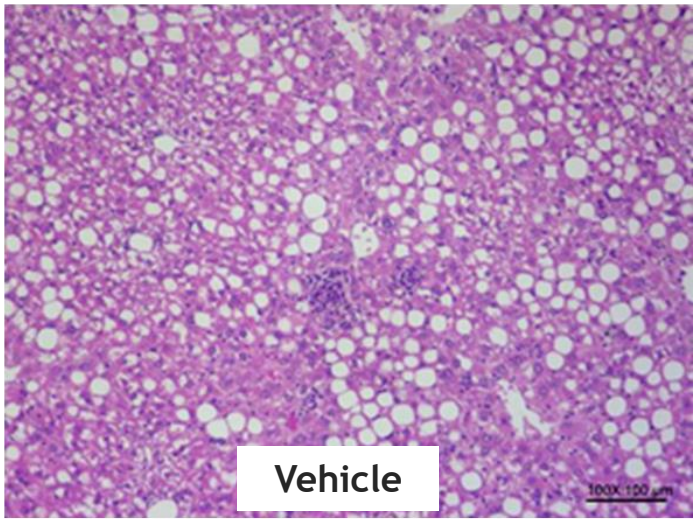
	Treatment Group			
Measurements	**Naive**	**Vehicle**	**GEM045L X mg/kg**	**GEM045H Y mg/kg**
Steatosis	0.00±0.00	2.33±0.87	1.71±0.76	0.29±0.49*
Inflammation	0.00±0.00	2.33±0.71	1.29±0.49*	0.43±0.53*
Ballooning	0.00±0.00	1.78±0.44	0.86±0.69*	0.14±0.38*
NAS	0.00±0.00	6.44±1.81	3.86±1.57*	0.85±1.07*
Fibrosis	0.00±0.00	1.89±0.78	0.57±0.79*	0.00±0.00*

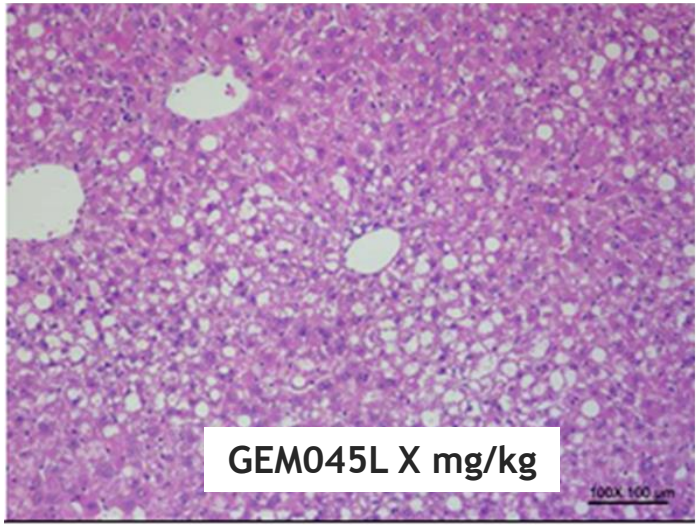
Autotaxin Inhibitors (MCD)

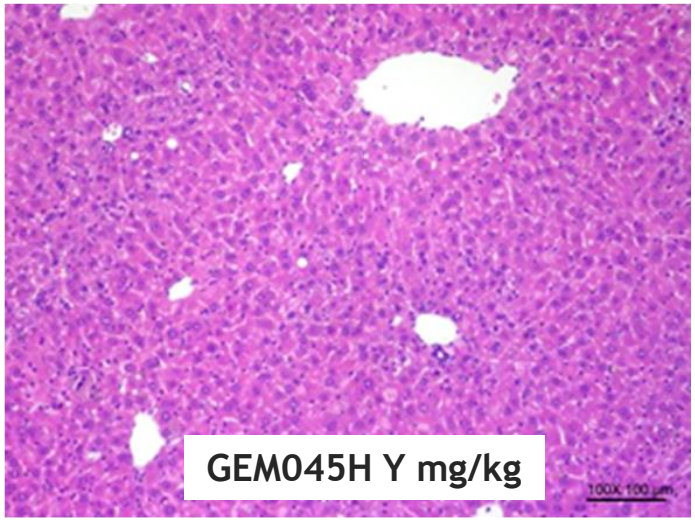
Effect of GEM045 on Methionine-Choline-Deficient Model

H&E 100X





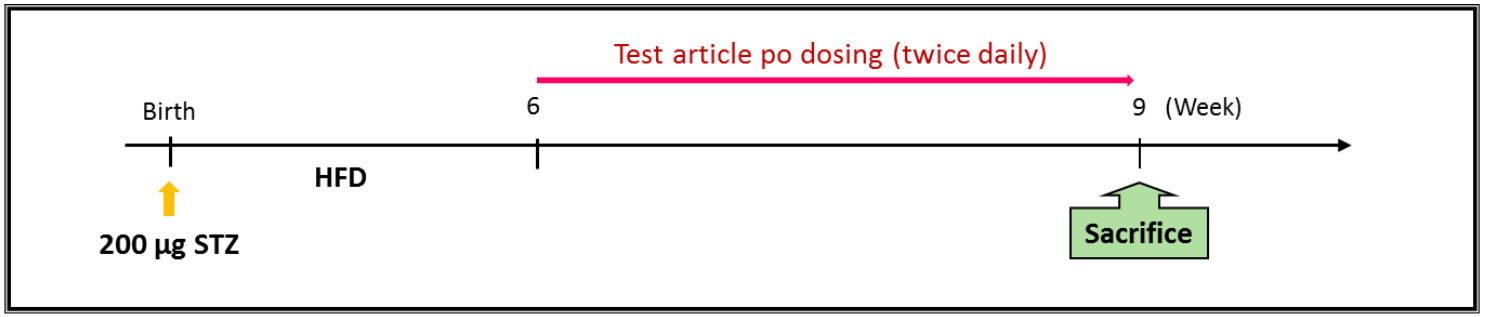




Autotaxin Inhibitors (STAM)

Effect of GEM045 on Stelic-STAM Model

1. Vehicle po (5% DMSO/10% CrEl in saline)
2. GEM045 Low dose po bid x **3 weeks**
3. GEM045 High dose po bid x **3 weeks**

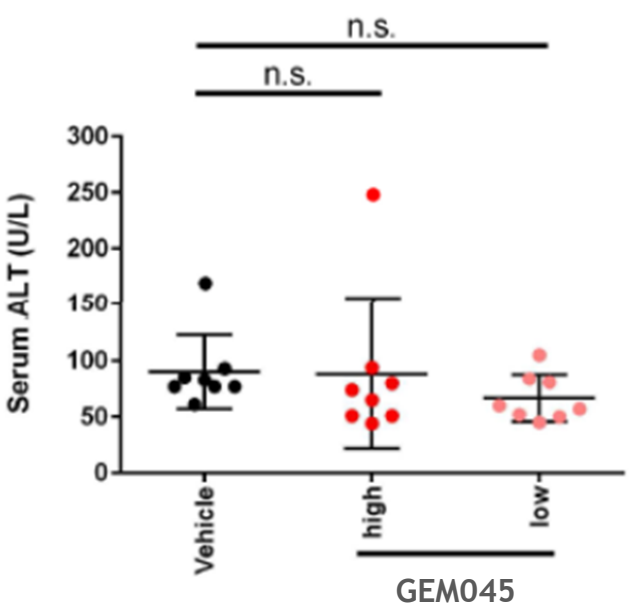


Group	No. mice	Mice	Test substance	Dose (mg/kg)	Volume (mL/kg)	Regimen	Sacrifice (wks)
1	8	STAM	Vehicle	-	10	PO, BID, 6 - 9 wks	9
2	8	STAM	GEM045	High	10	PO, BID, 6 - 9 wks	9
3	8	STAM	GEM045	Low	10	PO, BID, 6 - 9 wks	9

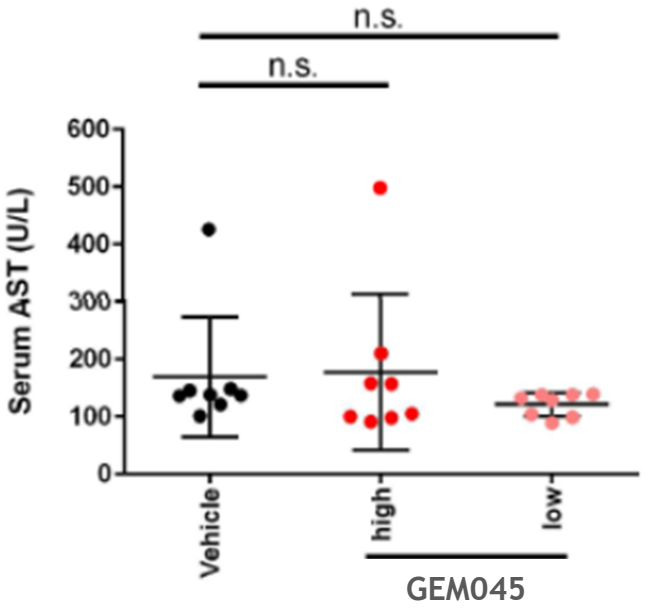
Autotaxin Inhibitors (STAM)

Effect of GEM045 on Stelic-STAM Model (po, bid, 9 wks.)

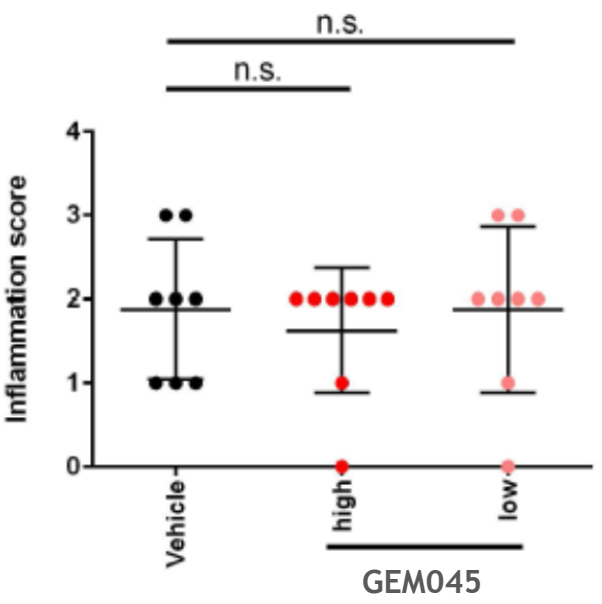
ALT



AST



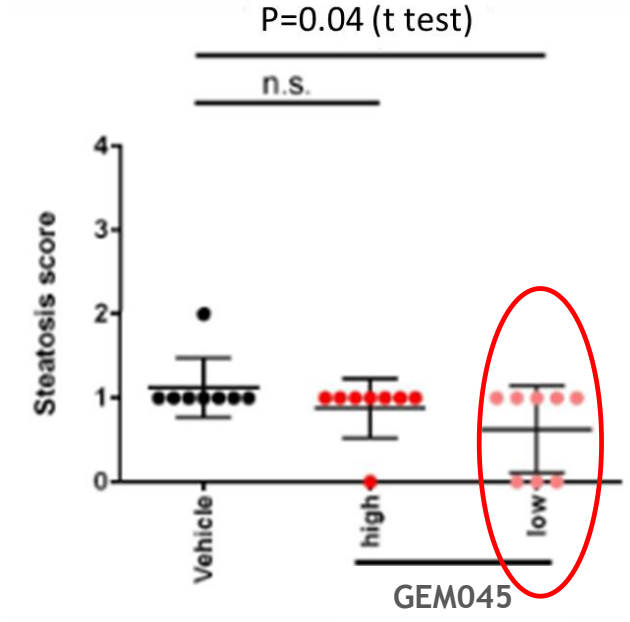
Inflammation



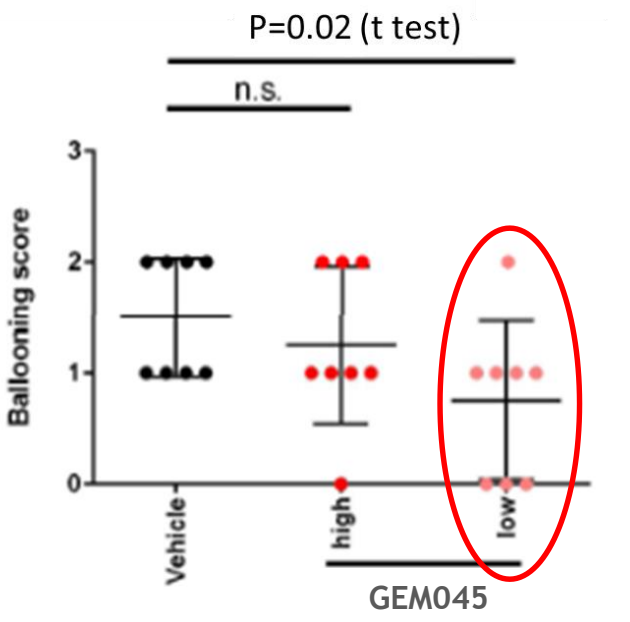
Autotaxin Inhibitors (STAM)

Effect of GEM045 on Stelic-STAM Model

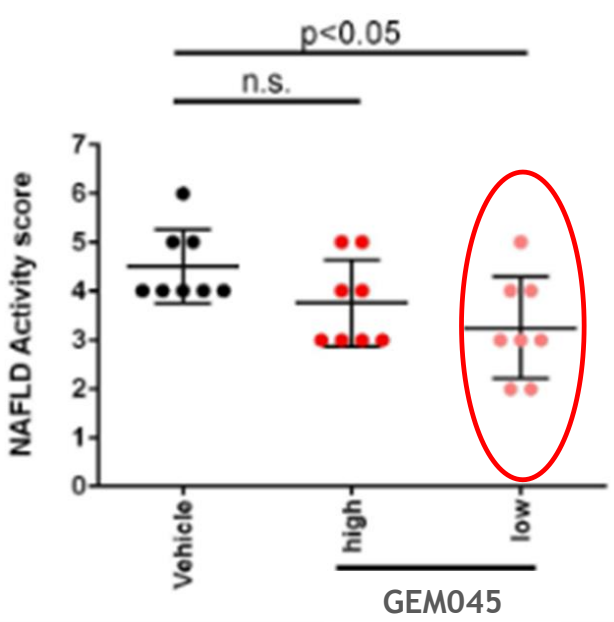
Steatosis



Ballooning

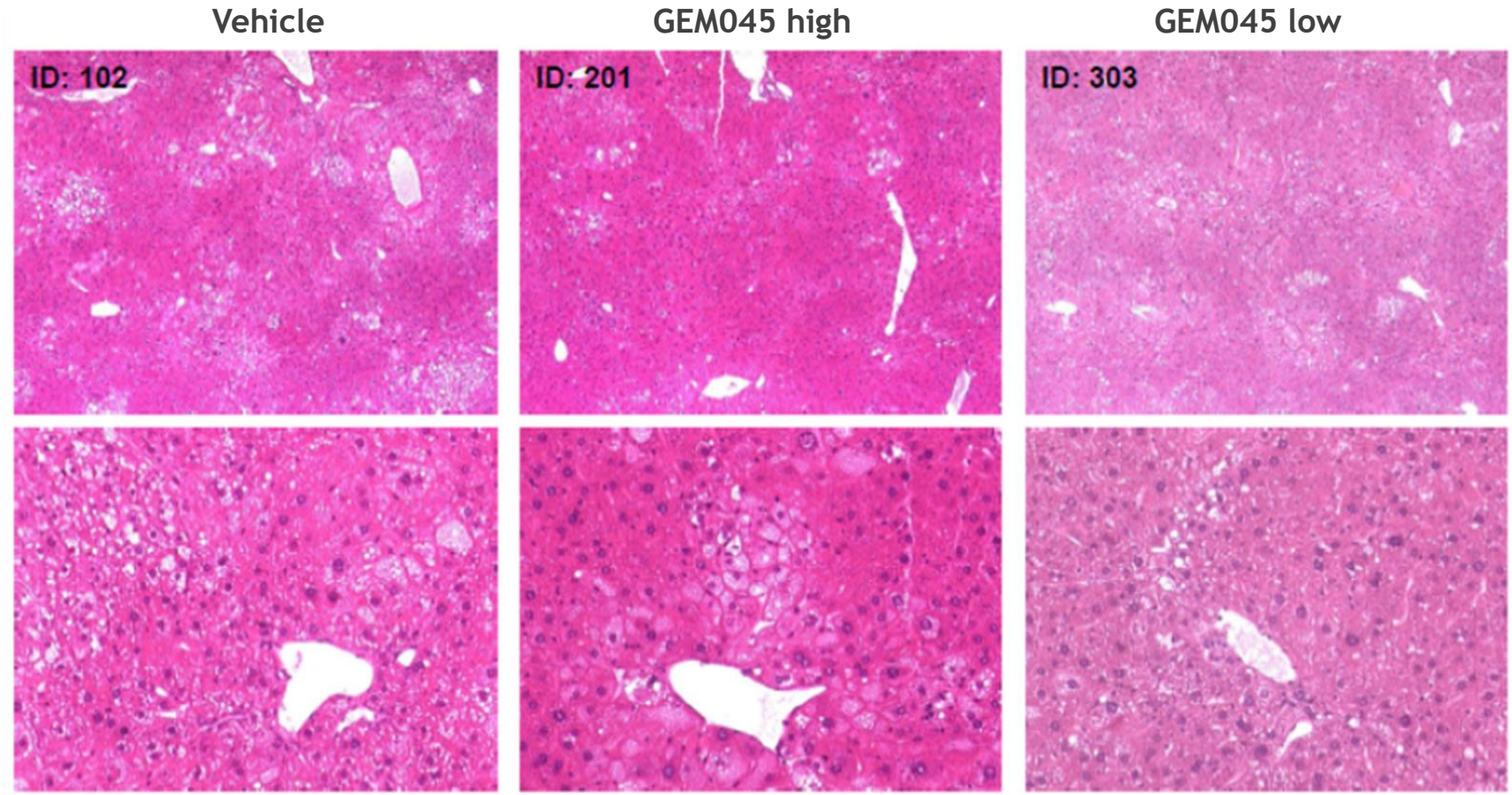


NAS



Autotaxin Inhibitors (STAM)

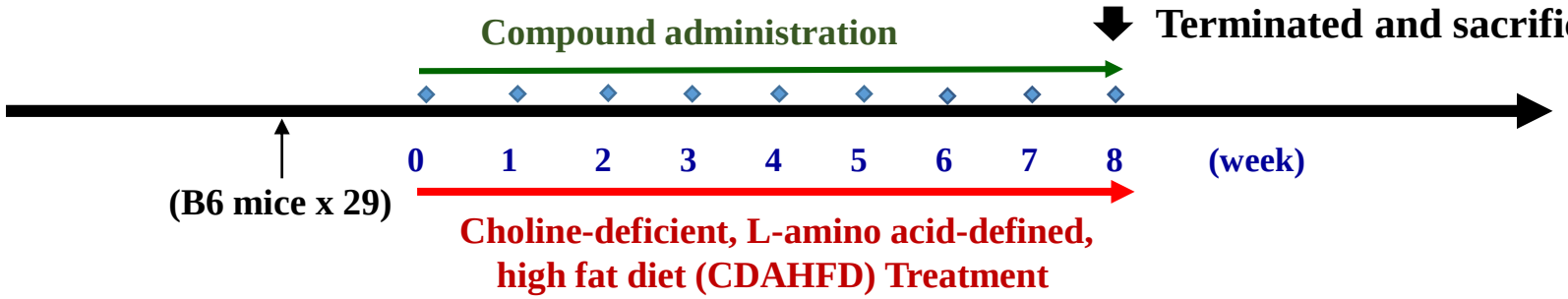
Effect of GEM045 on Stelic-STAM Model



Original magnifications,
Upper panels, x50.
Lower panels, x200.

Autotaxin Inhibitors (CDA-HFD)

Effect of GEM045(M) on Choline-Deficient Amino acid-Defined High Fat Diet Model



Chow diet

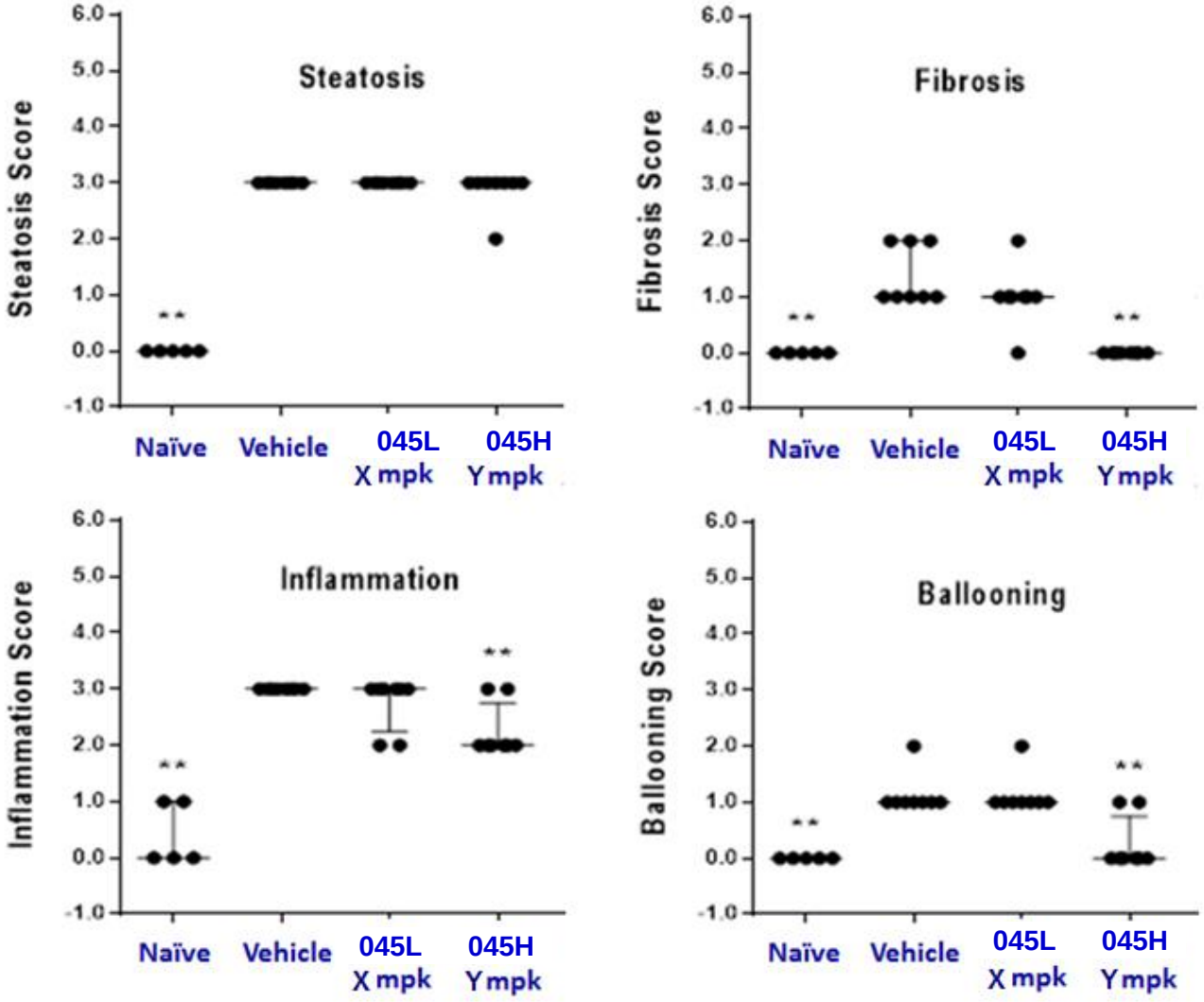
CDAHFD

Group	Treatment	Group Size
Naïve	Normal chow diet	5
Vehicle	feeding with CDAHFD for 8 wks	8
GEM045(M) X mg/kg	Low Dose, po, bid	8
GEM045(M) Y mg/kg	High Dose, po, bid	8

Autotaxin Inhibitors (CDA-HFD)

Effect of GEM045(M) on Choline-Deficient Amino acid-Defined High Fat Diet Model

Histopathology



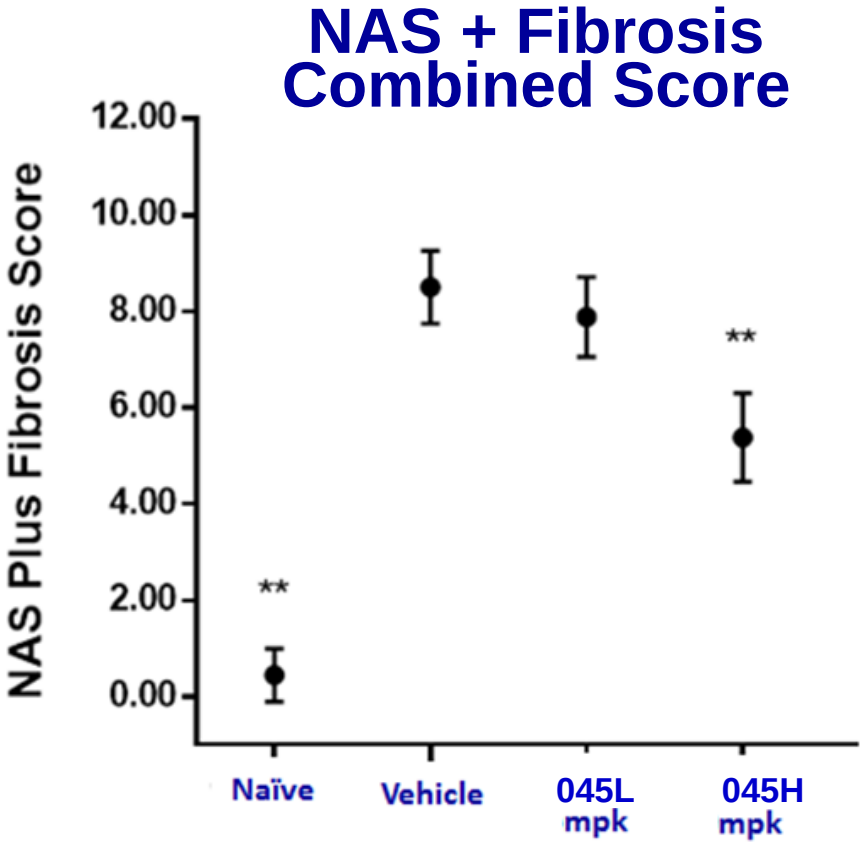
**, One-way ANOVA, $p<0.01$.

Autotaxin Inhibitors (CDA-HFD)

Effect of GEM045(M) on Choline-Deficient Amino acid-Defined High Fat Diet Model

	Treatment Group [a]			
Measurements	Naïve	Vehicle	**045L** mpk	**045H** mpk
Steatosis	0.00±0.00	3.00±0.00	3.00±0.00	2.88±0.35
Fibrosis	0.00±0.00	1.38±0.52	1.00±0.53	0.00±0.00 **
Inflammation	0.45±0.55	3.00±0.00	2.75±0.46	2.25±0.46 **
Ballooning	0.00±0.00	1.13±0.35	1.13±0.35	0.25±0.46 **
NAS + Fibrosis [b]	0.45±0.55	8.50±0.76	7.88±0.83	5.38±0.92 **

[a] Data are presented as Mean ± SD
[b] One-way ANOVA. (P<0.01)

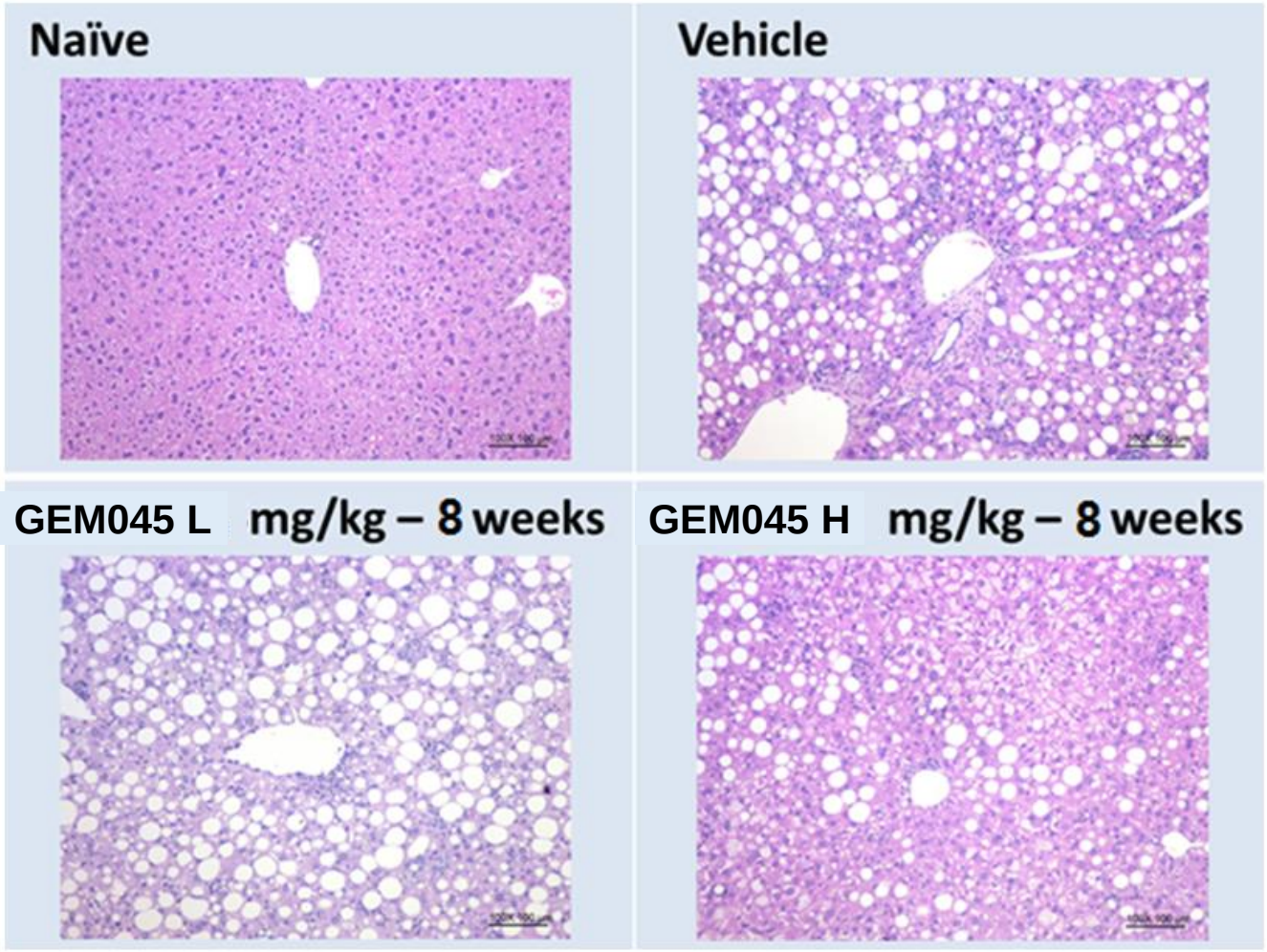


Autotaxin Inhibitors (CDA-HFD)

Effect of GEM045(M) on Choline-Deficient Amino acid-Defined High Fat Diet Model

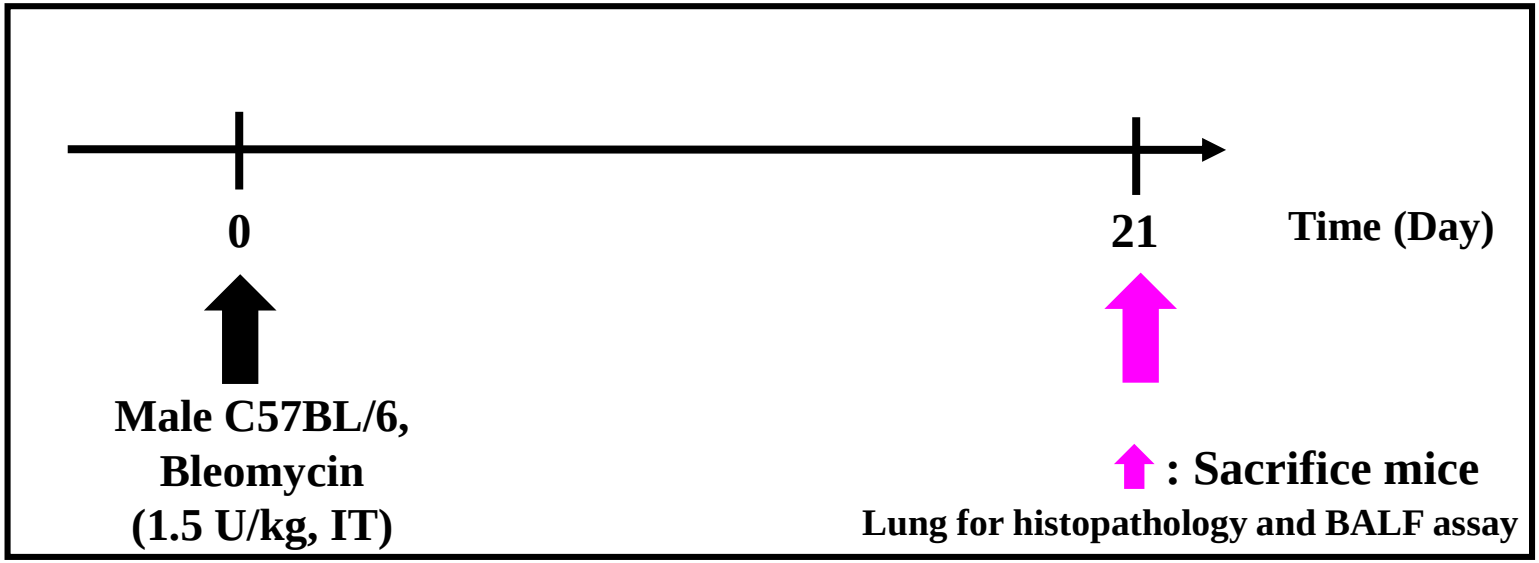
Histopathology

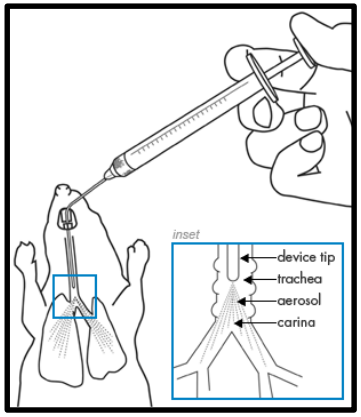
H&E
100X



Autotaxin Inhibitors (IPF - Mice)

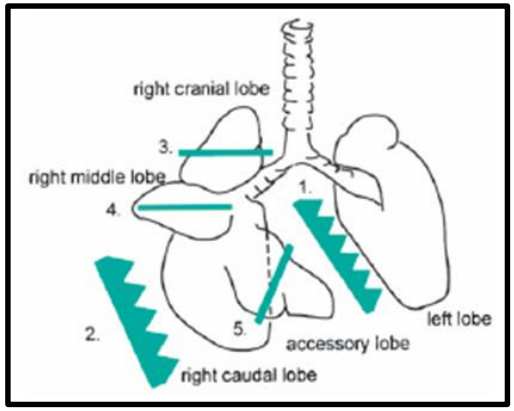
Bleomycin-Induced Pulmonary Fibrosis in Mice





Intra-tracheal (i.t.)

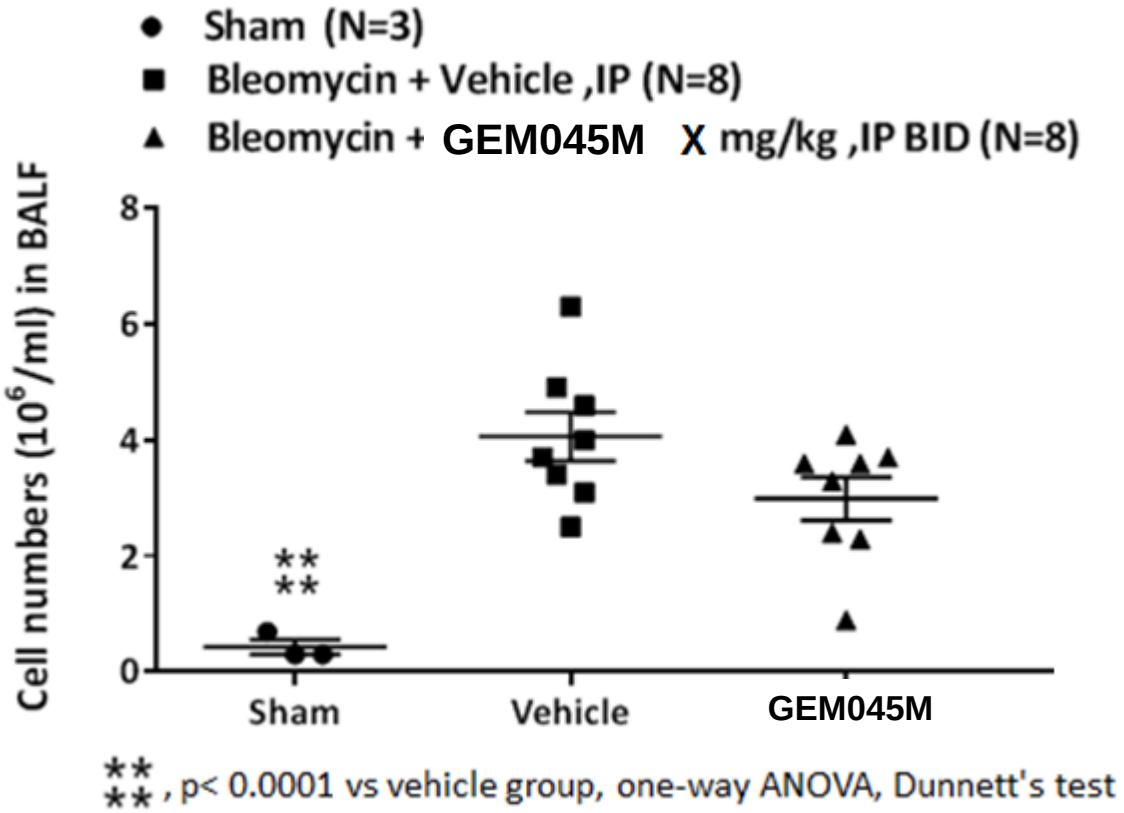
Group	Dosage & route	N value
Sham	Saline	3
Vehicle	1.5U/kg BLM	8
GEM045M	X mg/kg ip bid	8



Autotaxin Inhibitors (IPF - Mice) - Total Cells

Bleomycin-Induced Pulmonary Fibrosis in Mice

Total WBC, GEM045M at X mg/kg ip, bid × 21



- **The Sham group was significantly different from the vehicle (P< 0.0001).**
- **Cell numbers in BALF trended to decrease in GEM045M (new salt of GEM045) group (27% inhibition)**

Autotaxin Inhibitors (IPF - Mice)

Bleomycin-Induced Pulmonary Fibrosis in Mice

Criteria of Histopathology

Some commonly used severity grading schemes

Shackelford *et al*. (Toxicologic Pathology 30: 93-96, 2002).
1 = minimal (< 1%)
2 = slight (1-25%)
3 = moderate (26-50%)
4 = moderately severe (51-75%)
5 = severe/high (76-100%).

Criteria for grading lung fibrosis

Ashcroft *et al*. (J Clin Pathol 1988; 41:467-470).

0: Normal lung
1: Minimal fibrous thickening of alveolar or bronchiolar walls
2-3: Moderate thickening of walls without obvious damage to lung architecture
4-5: Increased fibrosis with definite damage to lung structure and formation of fibrous bands or small fibrous masses
6-7: Severe distortion of structure and large fibrous areas; "honeycomb lung" is placed in this category
8: Total fibrous obliteration of the field

Autotaxin Inhibitors (IPF - Mice) – Histopathology

Bleomycin-Induced Pulmonary Fibrosis in Mice

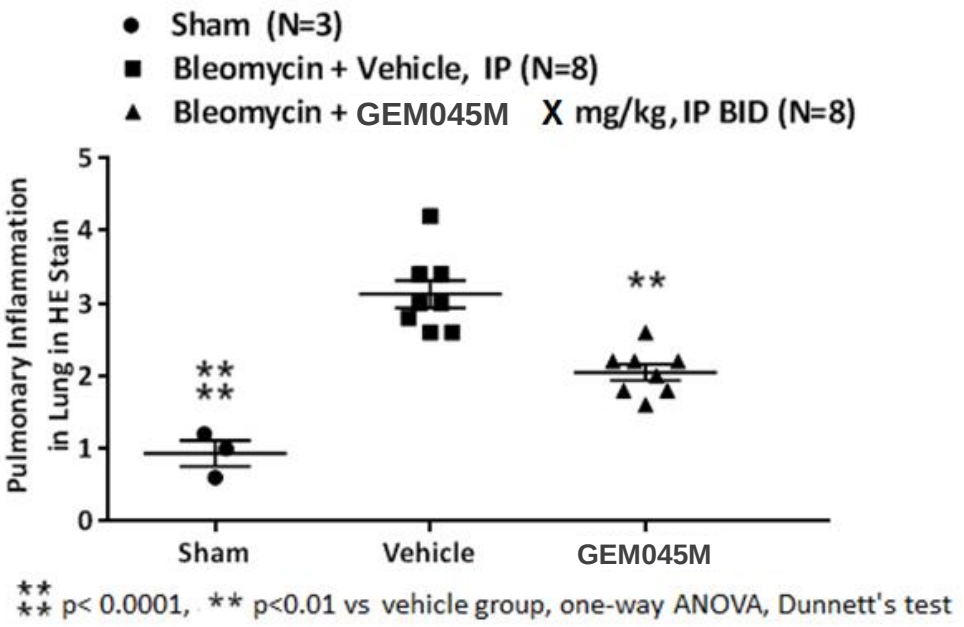
	Treatment Group [a]		
Measurements	**Sham**	**Vehicle**	**GEM045M X mg/kg ip bid**
Inflammation	0.93±0.31 ** **	3.13±0.53	2.05±0.32 **

[a] Data are presented as Mean ± SD.

	Treatment Group [a]		
Measurements	**Sham**	**Vehicle**	**GEM045M X mg/kg ip bid**
Fibrosis	0.00±0.00 ** **	4.30±1.14	2.70±0.50 **

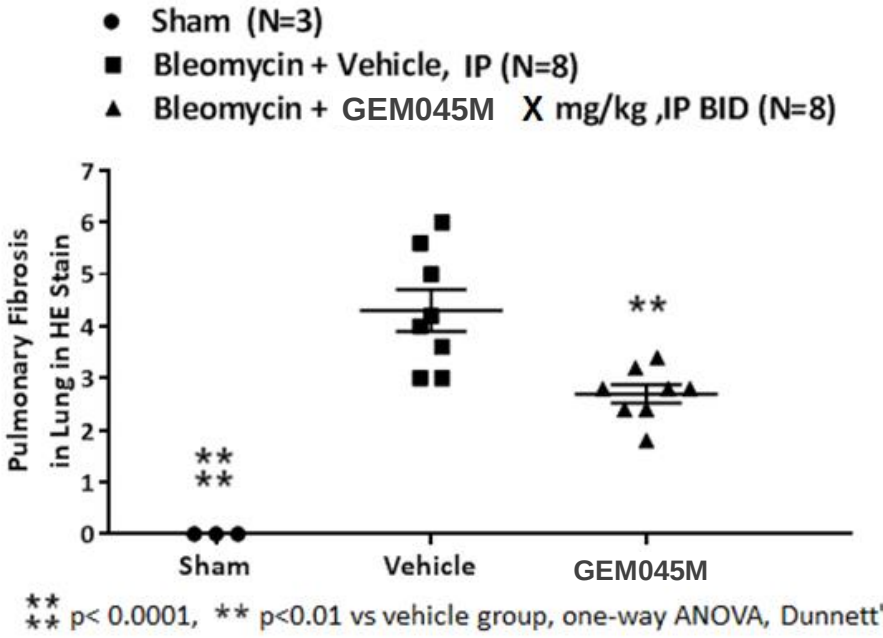
[a] Data are presented as Mean ± SD.

Pulmonary Inflammation



** ** p< 0.0001, ** p<0.01 vs vehicle group, one-way ANOVA, Dunnett's test

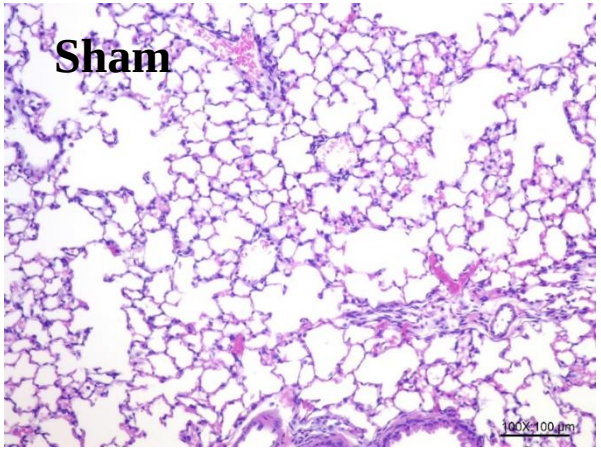
Pulmonary Fibrosis

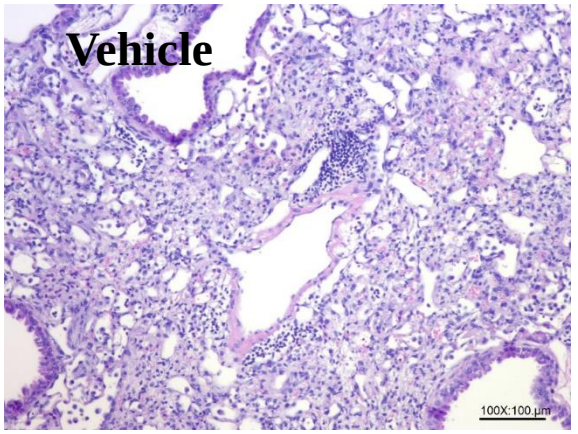


** ** p< 0.0001, ** p<0.01 vs vehicle group, one-way ANOVA, Dunnett's test

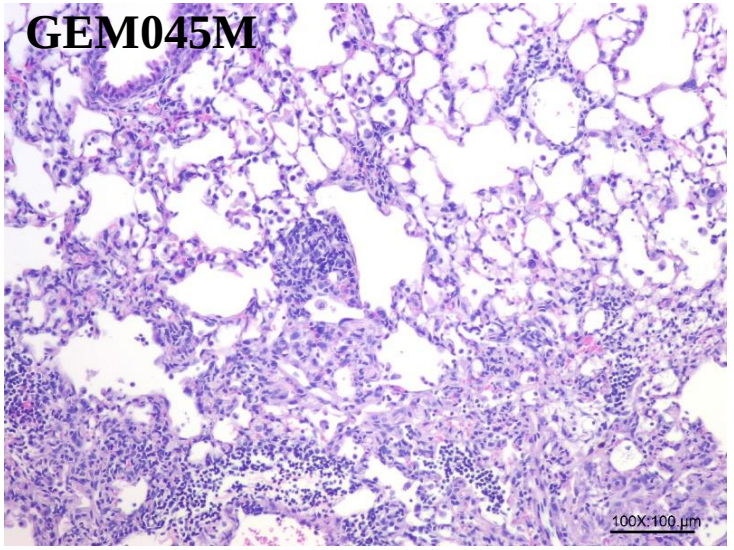
Autotaxin Inhibitors (IPF - Mice) - Histopathology

Bleomycin-Induced Pulmonary Fibrosis in Mice



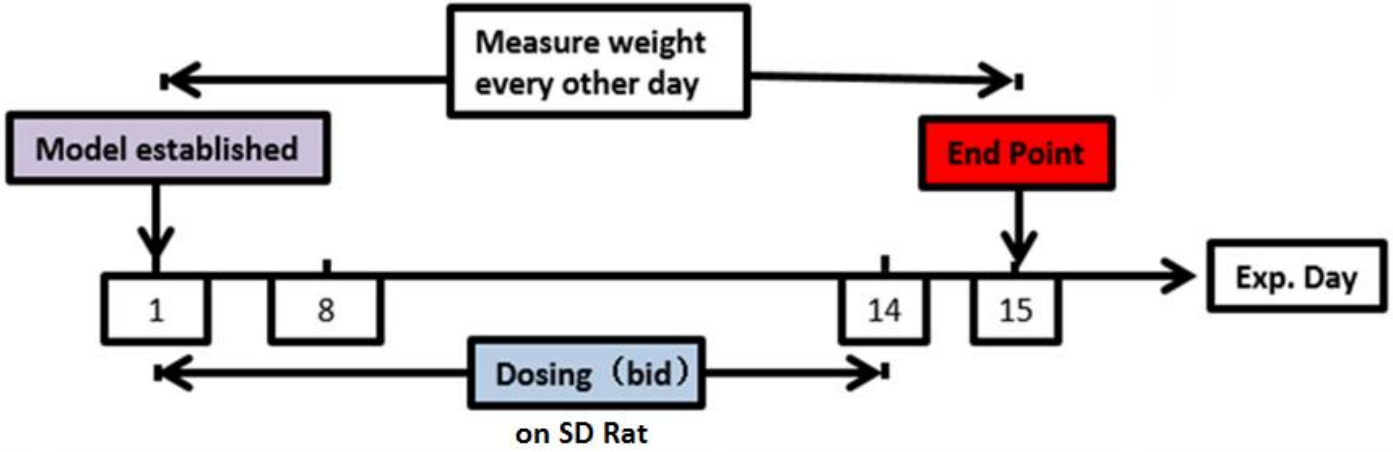


The lesions of the GEM045M group (X mg/kg ip, bid) showed significantly decrease focal pulmonary fibrosis and multifocal inflammatory cell infiltration as compared to the vehicle group.



Autotaxin Inhibitors (IPF - Rat)

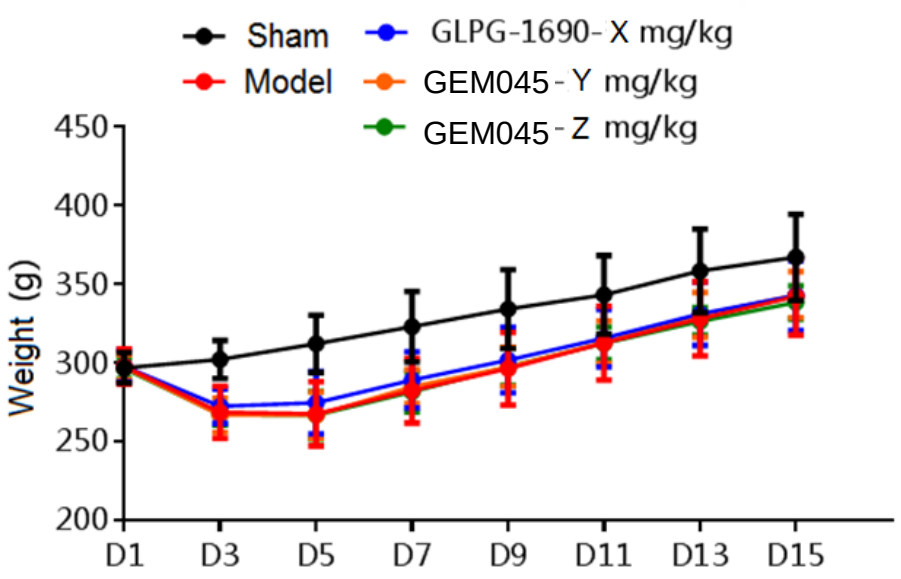
Bleomycin-Induced Pulmonary Fibrosis in Rat

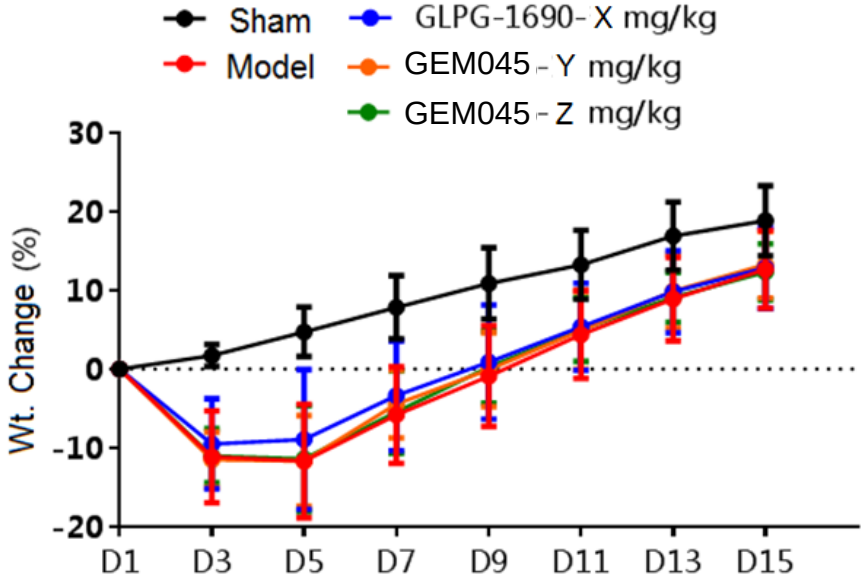


Group	Compound	Animal#	Bleomycin (3.0 mg/kg)	Dose & Freq.
1	Vehicle-Sham	8	NO	10ml/kg/d,po,bid
2	Vehicle-Model	8	YES	10ml/kg/d,po, bid
3	GLPG-1690	8	YES	X mg/kg/d,po,bid
4	**GEM045**	8	YES	Y mg/kg/d,po,bid
5	**GEM045**	8	YES	Z mg/kg/d,po, bid

Autotaxin Inhibitors (IPF - Rat)

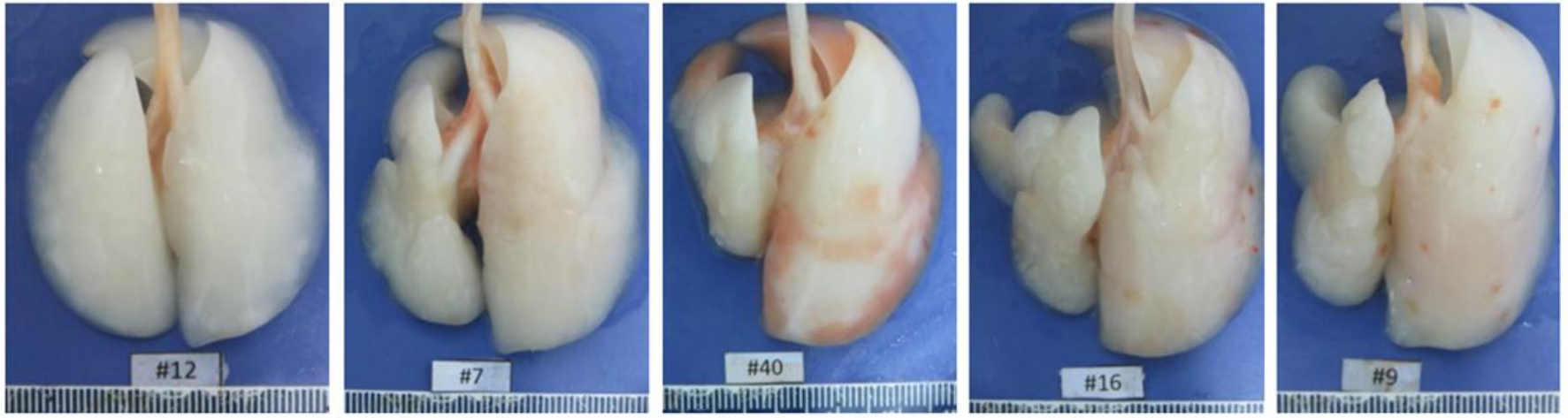
Bleomycin-Induced Pulmonary Fibrosis in Rat





Autotaxin Inhibitors (IPF - Rat)

Bleomycin-Induced Pulmonary Fibrosis in Rat



Autotaxin Inhibitors (IPF - Rat)

Bleomycin-Induced Pulmonary Fibrosis in Rat

Pathological Changes of the Bronchiole & Arteriole (in the core zone of the lung fibrosis)

Pathological analysis parameters

Score	Bronchiole wall damages
0	Normal structure without inflammatory cell infiltration
1	Normal structure damage within 1/2 of the wall including epithelial cell damage, regeneration, bronchiole wall edema, muscle degeneration, regeneration
2	Normal structure damage over half of the wall including epithelial cell damage, regeneration, bronchiole wall edema, muscle degeneration, regeneration
3	EC damage + media damage + adventitia granulation, fibrosis

Score	Arteriole wall damages
0	Normal arteriol structure
1	Endothelial cell damage showing EC denudation partially or all
2	Endothelial cell denudation plus media damage showing SMC degeneration and necrosis focally
3	EC damage + media damage + adventitia granulation, fibrosis

Score	Inflammatory cell infiltration in the wall
0	Normal structure without inflammatory cell infiltration
1	There are several inflammatory cells in the wall, within 10 cells
2	Inflammatory cell infiltration as foci in the wall.
3	Inflammatory cell infiltration in the wall diffusely over half of the wall area

Score	Inflammatory cell infiltration in the arteriole
0	Normal structure without inflammatory cell infiltration
1	There are several inflammatory cells in the arteriol wall especially in the adventitia area, within 10 cells
2	Inflammatory cell infiltration in the arteriol wall as foci in the wall, especially in the adventitia area.
3	Inflammatory cell infiltration in the wall diffusely over half of the wall area especially the tansmural wall inflammatory cell infiltration

Autotaxin Inhibitors (IPF - Rat)

Bleomycin-Induced Pulmonary Fibrosis in Rat

Pathological Changes of the Bronchiole & Arteriole (in the Border zone of the lung fibrosis)

Pathological analysis parameters

Score	Bronchiole wall damages
0	Normal structure without inflammatory cell infiltration
1	Normal structure damage within 1/2 of the wall including epithelial cell damage, regeneration, bronchiole wall edemia,muscle degeneration, regeneration
2	Normal structure damage over half of the wall including epithelial cell damage, regeneration, bronchiole wall edema, muscle degeneration, regeneration
3	EC damage + media damage + adventitia granulation, fibrosis

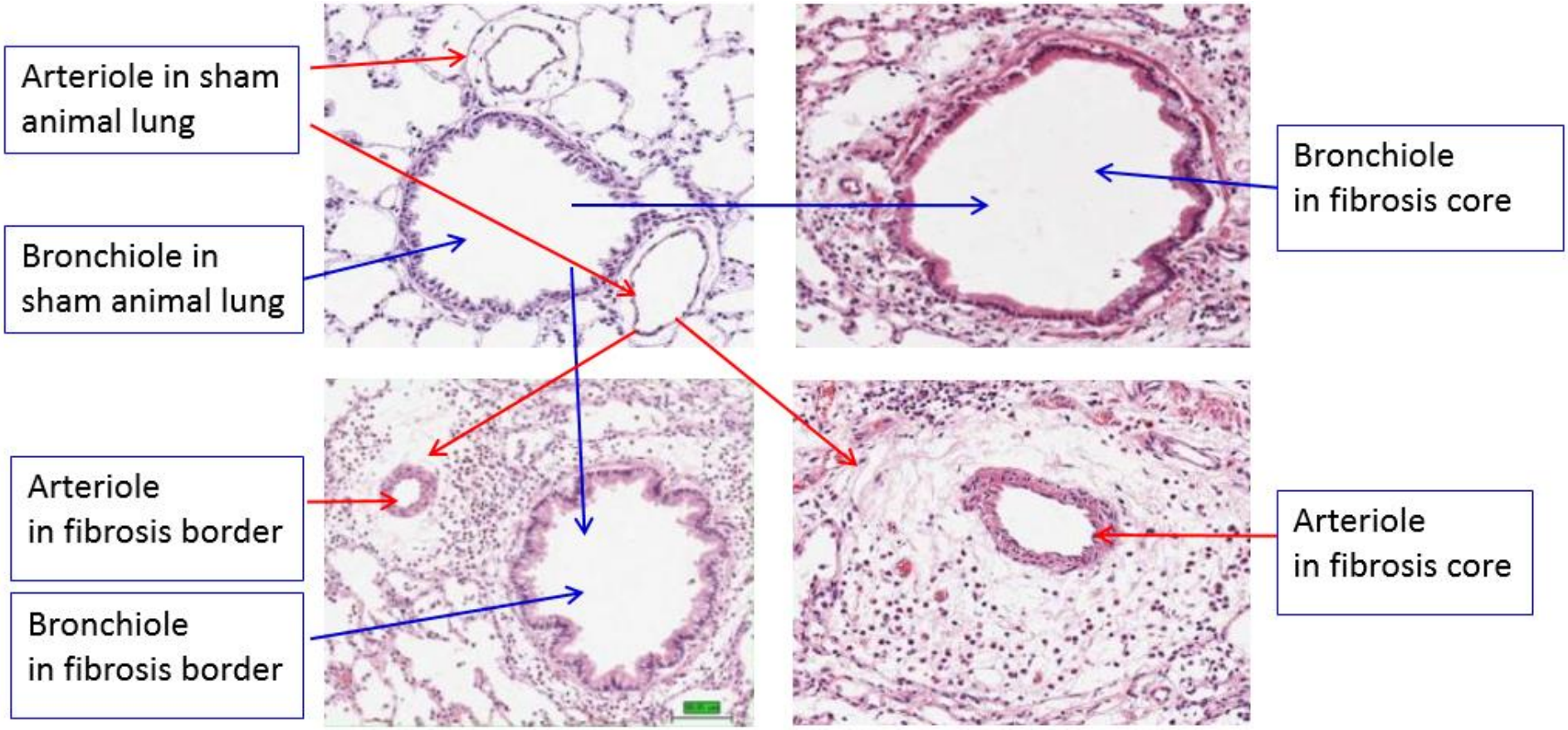
Score	Arteriole wall damages
0	Normal arteriol structure
1	Endothelial cell damage showing EC denudation partially or all
2	Endothelial cell denudation plus media damage showing SMC degeneration and necrosis focally
3	EC damage + media damage + adventitia granulation, fibrosis

Score	Inflammatory cell infiltration in the wall
0	Normal structure without inflammatory cell infiltration
1	There are several inflammatory cells in the wall, within 10 cells
2	Inflammatory cell infiltration as foci in the wall.
3	Inflammatory cell infiltration in the wall diffusely over half of the wall area

Score	Inflammatory cell infiltration in the arteriole
0	Normal structure without inflammatory cell infiltration
1	There are several inflammatory cells in the arteriol wall especially in the adventitia area, within 10 cells
2	Inflammatory cell infiltration in the arteriol wall as foci in the wall, especially in the adventitia area.
3	Inflammatory cell infiltration in the wall diffusely over half of the wall area especially the tansmural wall inflammatory cell infiltration

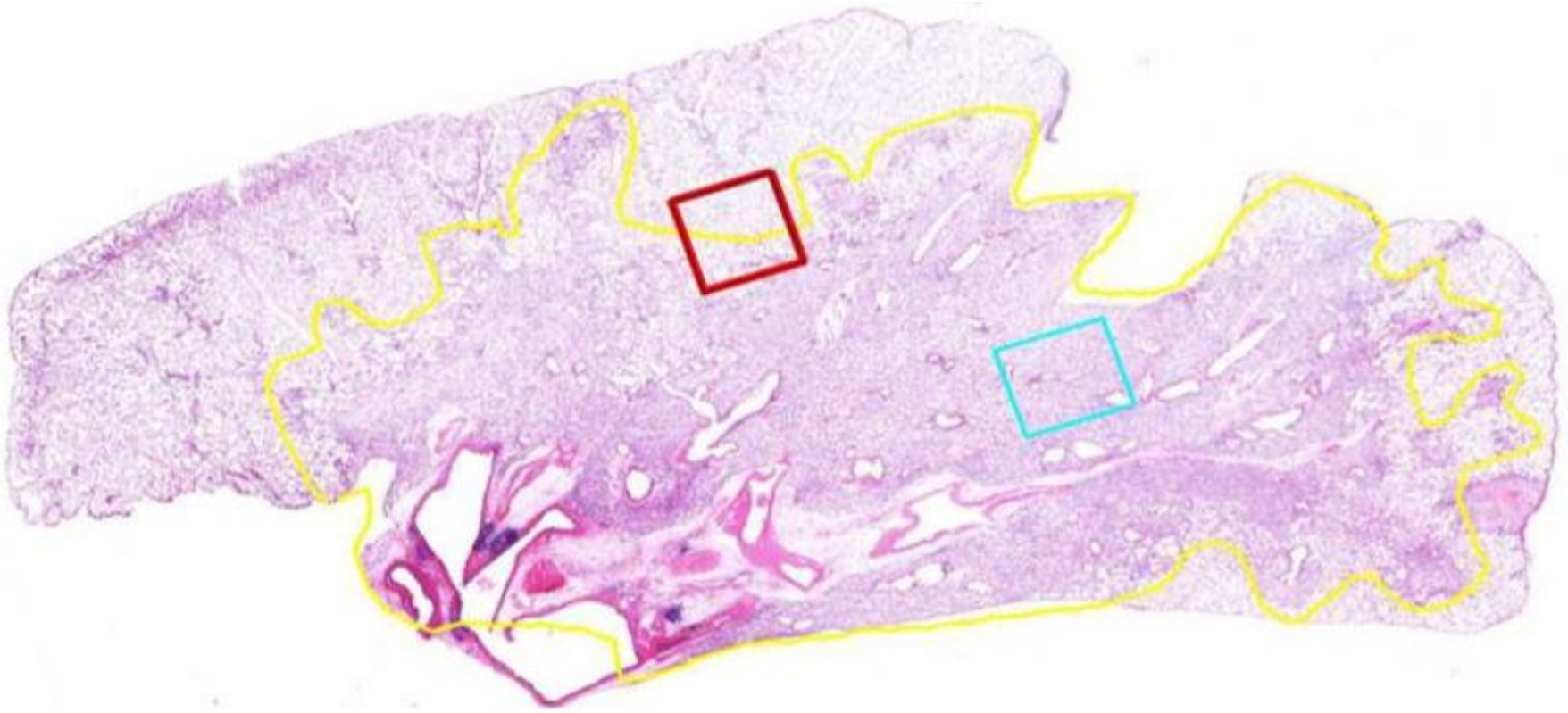
Autotaxin Inhibitors (IPF - Rat)

Bleomycin-Induced Pulmonary Fibrosis in Rat



Autotaxin Inhibitors (IPF - Rat)

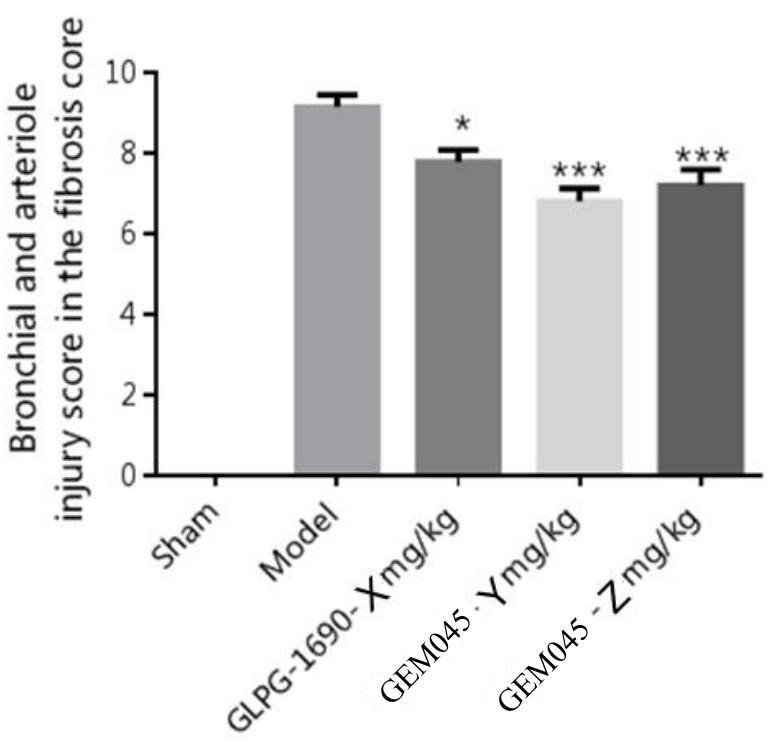
Bleomycin-Induced Pulmonary Fibrosis in Rat

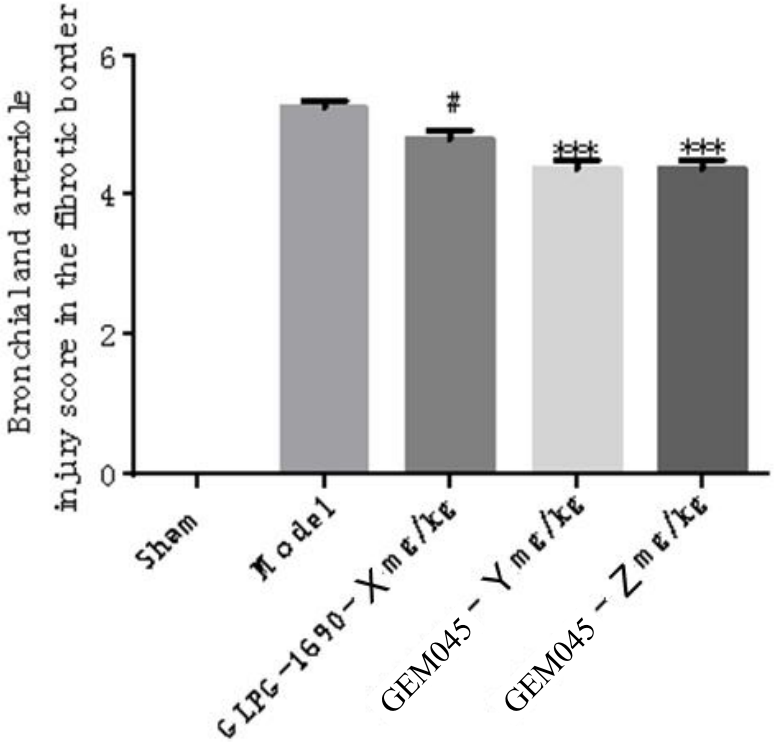


Damage in the fibrosis core: Blue
Damage in the border: Red
Fibrosis area: Inline of yellow

Autotaxin Inhibitors (IPF - Rat)

Bleomycin-Induced Pulmonary Fibrosis in Rat



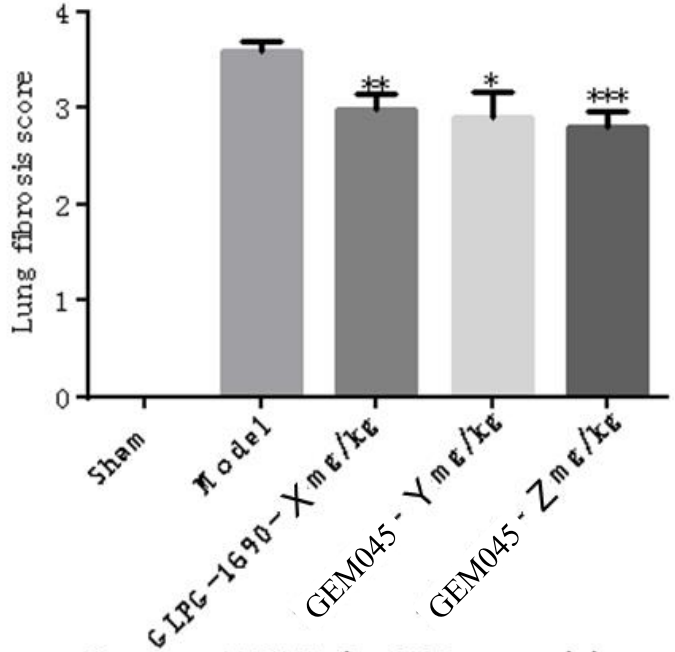


One-way ANOVA: *p<0.05 vs. model; ***p<0.001 vs. model. T-test: #p<0.05 vs. model

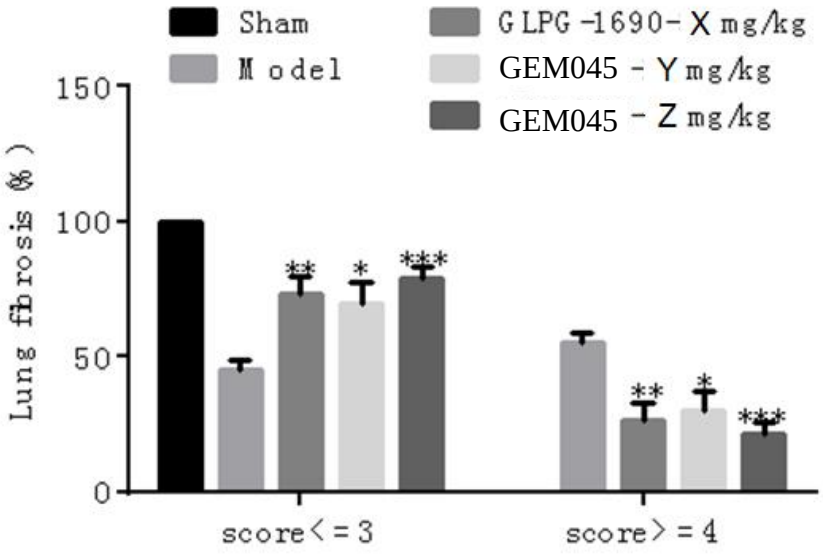
- Bronchiole and arteriole damages in fibrosis core were scored and summarized together.

Autotaxin Inhibitors (IPF - Rat)

Bleomycin-Induced Pulmonary Fibrosis in Rat



One-way ANOVA: *p<0.05 vs. model;
***p<0.001 vs. model



Two-way ANOVA: *p<0.05 vs. model; **p<0.01 vs. model;
***p<0.001 vs. model

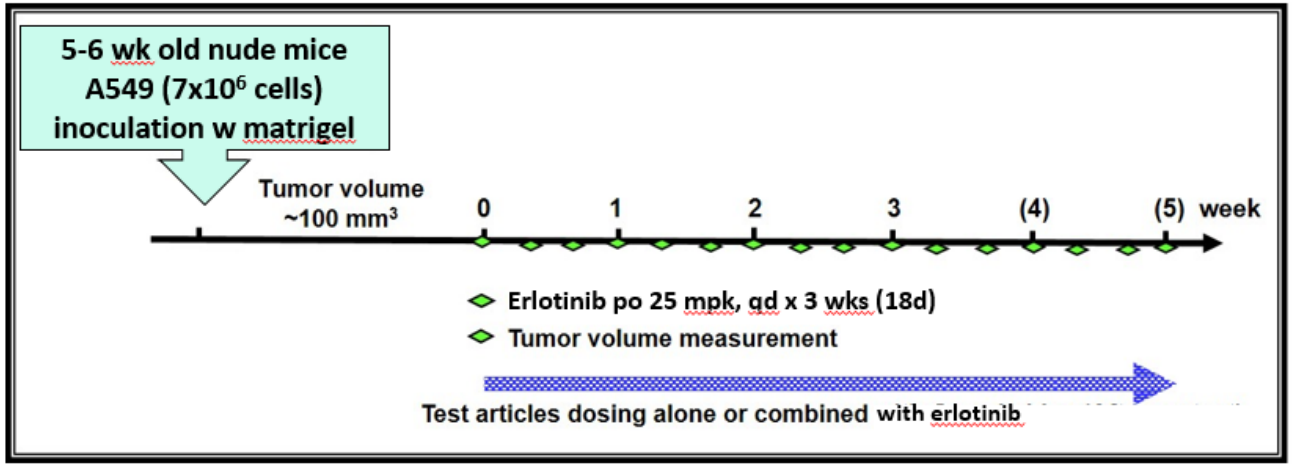
- Left lung fibrosis are scored under Ashcroft score methods
- Left lung fibrosis scores are divided as two groups based on the alveolar damage (Ashcroft score); score 1-3 indicate alveolar structure preserved well, score 4-8 indicate alveolar structure broken or disappeared.

Autotaxin Inhibitors (Anti-Cancer Effect)

- **GEM045 showed additive anticancer effect in combo use with Erlotinib on A549 (lung cancer) xenograft animal model.**
- **Shrank A549 cancer cell volume by 35.8% after 3 wks. (18 days) treatment.**
- **Will further test in BxPC-3 (pancreatic cancer) and PC-3 (prostate cancer) xenograft models.**

Autotaxin Inhibitors (Anti-Cancer Effect)

Effect of GEM045 on A549 Xenograft Model

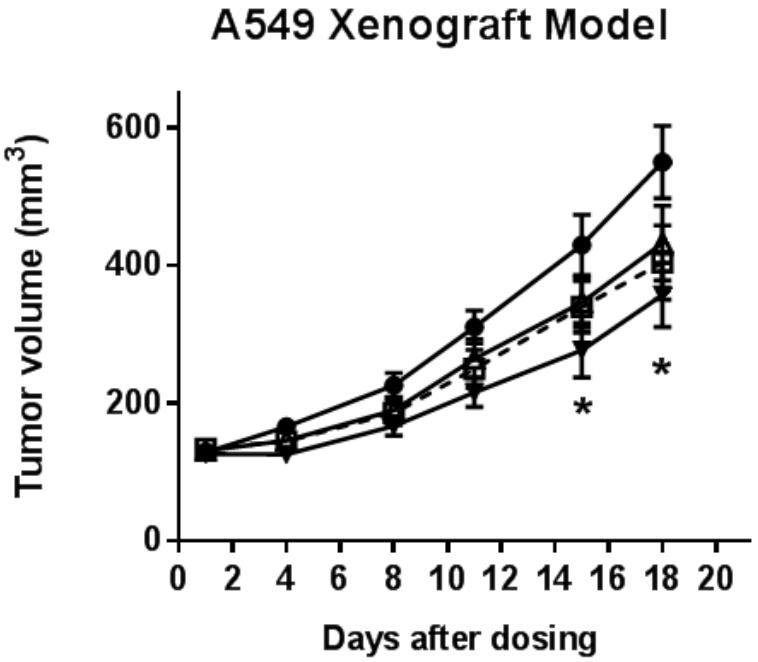


Group	Test Article	Dose	Route	N
1	Vehicle (5% DMSO, 0.5% HPMC)	NA	po	9
2	Erlotinib	25 mg/kg, QD x 3 wks (18d)	po	9
3	**GEM045**	**X** mg/kg, BID x 3 wks (18d)	po	9
4	Combined therapy	Erlotinib 25 mg/kg, QD x 3 wks (18d) **+ GEM045 X** mg/kg, BID x 3 wks (18d)	po	8

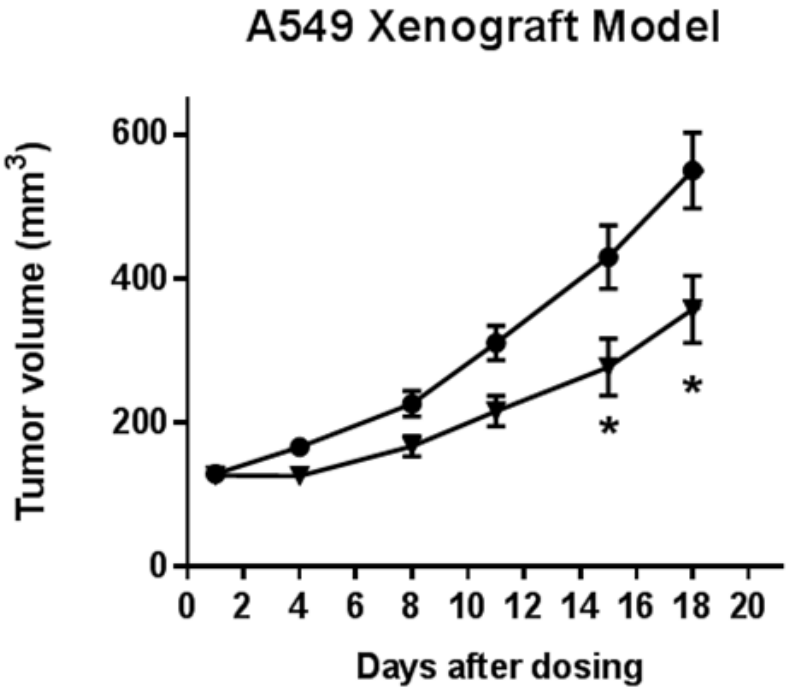
Autotaxin Inhibitors (Anti-Cancer Effect)

Effect of GEM045 on A549 Xenograft Model

- Vehicle (N=9)
- Erlotinib 25 mg/kg, qd (N=9)
- GEM045 X mg/kg, bid (N=9)
- Erlotinib 25 mg/kg + GEM045 X mg/kg (N=8)



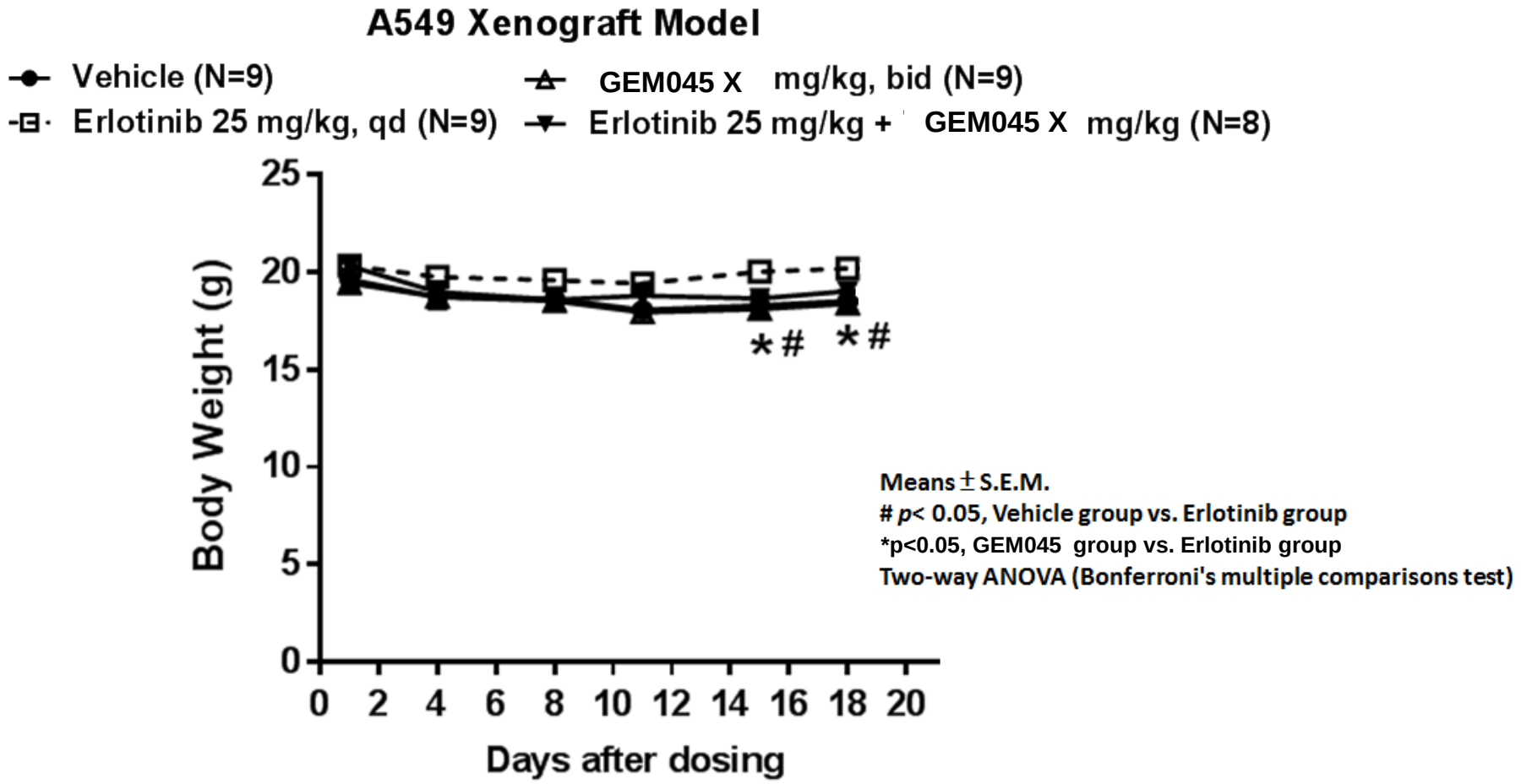
- Vehicle (N=9)
- Erlotinib 25 mg/kg + GEM045 X mg/kg (N=8)



Means ± S.E.M.
*,# $p < 0.05$ vs. Vehicle group
Two-way ANOVA (Bonferroni's multiple comparisons test)

Autotaxin Inhibitors (Anti-Cancer Effect)

Effect of GEM045 on A549 Xenograft Model



Autotaxin Inhibitors (ADME)

in-vitro ADME of GEM045

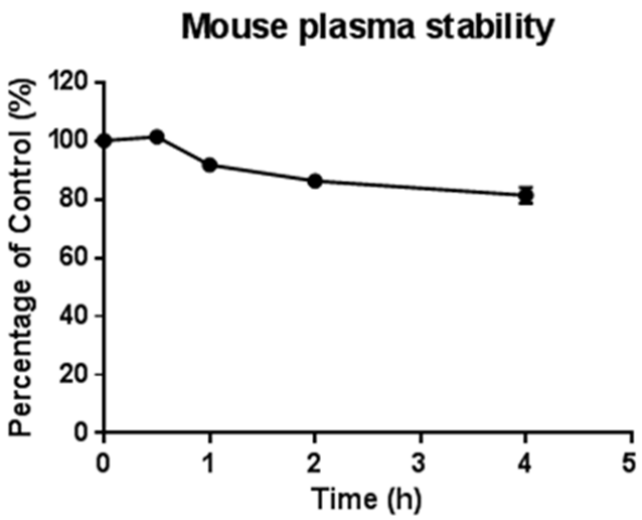
CRITERIA	GEM045
LogD	3.23
Solubility (phosphate buffer, pH 7.4)	0.47 µM
Stability in PBS (@ 2h)	> 100%
Plasma Stability (@ 2h)	> 100% (Ms, Rt, Dg, Mk, Hu)
Microsomal Stability (@ 30min)	> 86% (Hu) > 85% (Dg) > 87% (Rt)
Plasma Protein Binding	> 99.5% (Ms, Rt, Dg, Mk, Hu)
CYPs IC_{50} (3A, 1A2, 2C9, 2C19, 2D6)	> 50 µM
hERG IC_{50}	> 10 µM
MDR1-MDCK (P-gp substrate/inhibition)	Negative/Negative
Metabolite Profiling	One Putative Metabolite

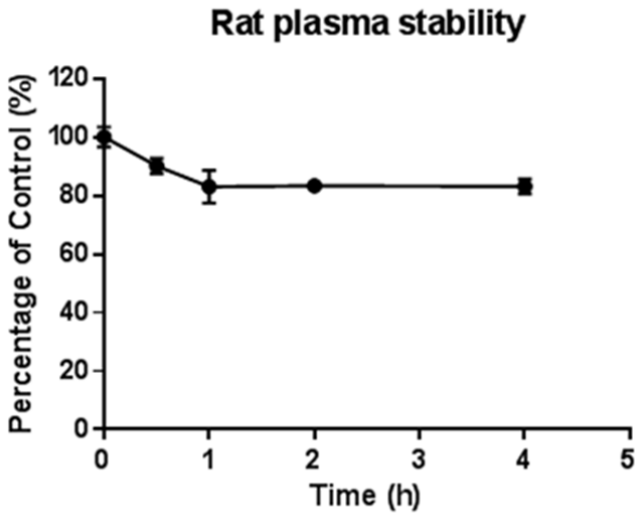
Autotaxin Inhibitors (Plasma Stability)

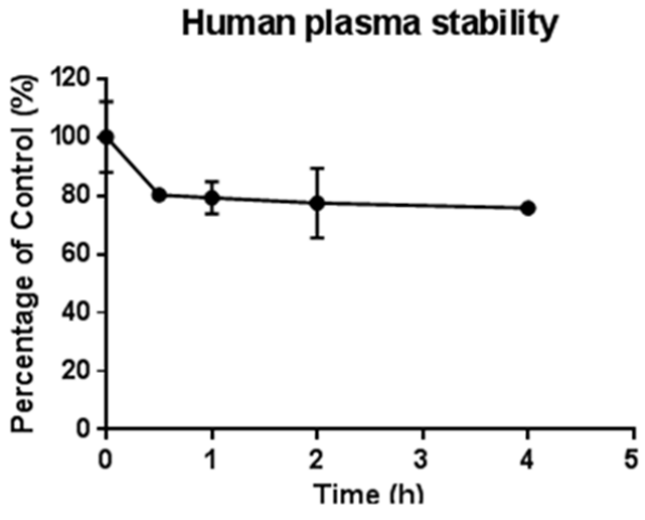
Plasma Stability of GEM045

Setting:

1. Compound: GEM045
2. Time point (min): 0, 0.5, 1, 2, 4h
3. Analysis: GEM045 by LC-MS/MS







Autotaxin Inhibitors (Metabolite)

Metabolite Study of GEM045

Results of Partial Characterization of Putative Metabolite M1 and Relative Quantification of the TA and M1 in Pooled Human and Animal Hepatocyte Incubation Samples

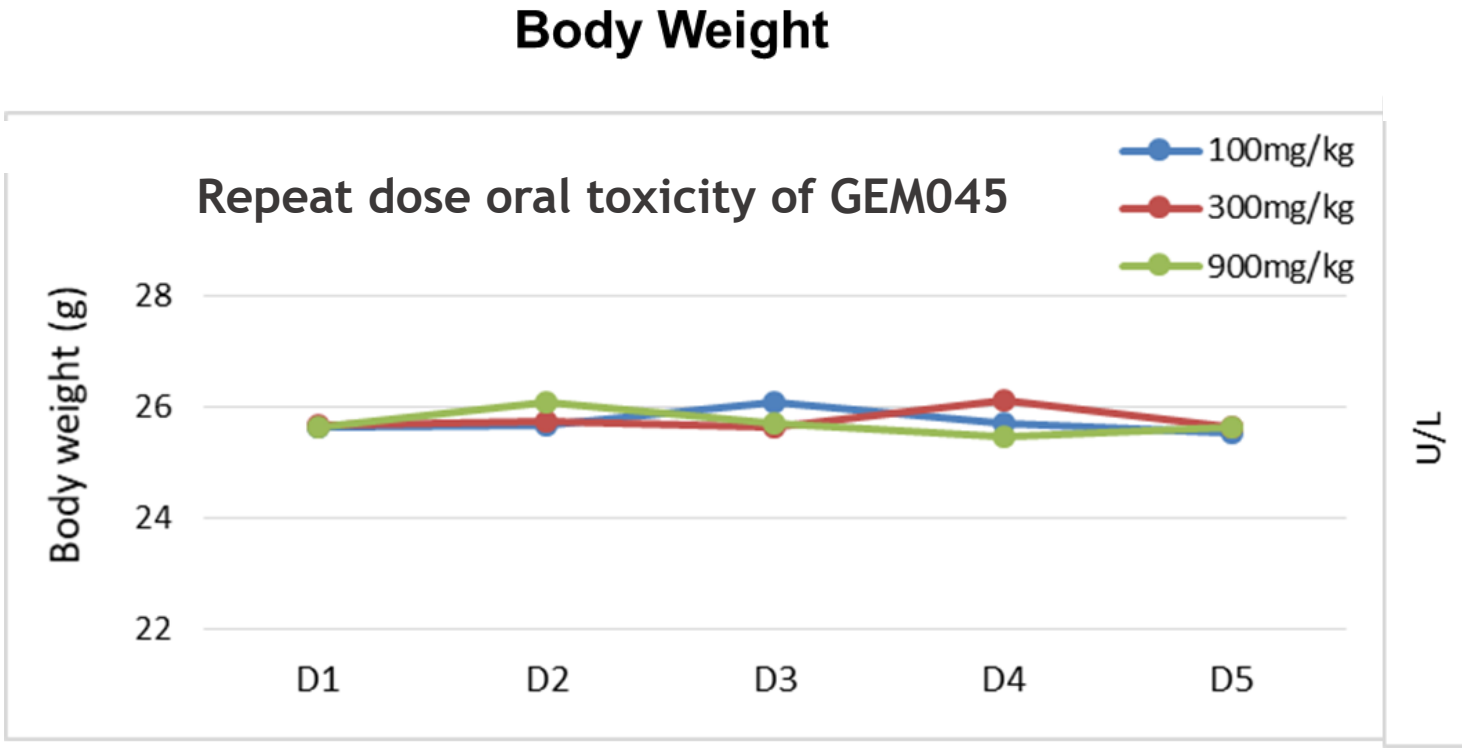
Species	Sample	GEM045	M1 (+2H)
Human	T=0 min	100.0	3.4
	Pooled	69.5	181.5
Monkey	T=0 min	100.0	1.5
	Pooled	87.6	24.9
Dog	T=0 min	100.0	2.0
	Pooled	52.0	59.6
Rat	T=0 min	100.0	0.6
	Pooled	74.6	62.1

Relative amounts expressed as a percentage of the amount of the TA in the T=0 minute sample

Autotaxin Inhibitors (Safety)

MTD of GEM045 in Mice

GEM045 at 900 mg/kg po bid (repeat dose) was well tolerated in terms of autonomic effects.



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Autotaxin Inhibitors (Comparison)

	PF-8380	GLPG1690	PAT-409	GEM045
LPC IC_{50}	1.7±0.6	231±62 nM	4 nM	330±73 nM
Plasma IC_{50}	101±0.036 (human)	221 nM (human)	50 nM (human)	10 nM (rat)
NAS • Inflammation • Steatosis • Ballooning	Not available	Not available	-2 • 0 • ≈-1.5 • Not available	-6 • -2 • -2 • -2
Fibrosis	Not available	Not available	-1	-2
Status	Discontinued	Phase 2 (IPF)	Phase 1 ready	IND enabling

Autotaxin Inhibitors - Series 2 (Back-up)

- **Discovered lead GEM045A**
  - **LPC-CR IC_{50} = 36 nM (vs. 234 nM for GLPG-1690 tested in parallel)**
  - **LPA reduction (rat plasma) IC_{50} = 3 nM (vs. 100 nM for GLPG-1690 tested in parallel)**
- **More potent compounds discovered**
  - **GEM045B IC_{50} = 29 nM**
  - **GEM045C IC_{50} = 10 nM**
  - **GEM045D IC_{50} = 26 nM**
  - **GEM045E IC_{50} = 9 nM**
  - **GEM045F IC_{50} = 25 nM**
- **Selected compounds are currently under PK study.**
- **Lead optimizations ongoing.**

GEMSEKI

Autotaxin Inhibitors (GEM045 Property Improvement)

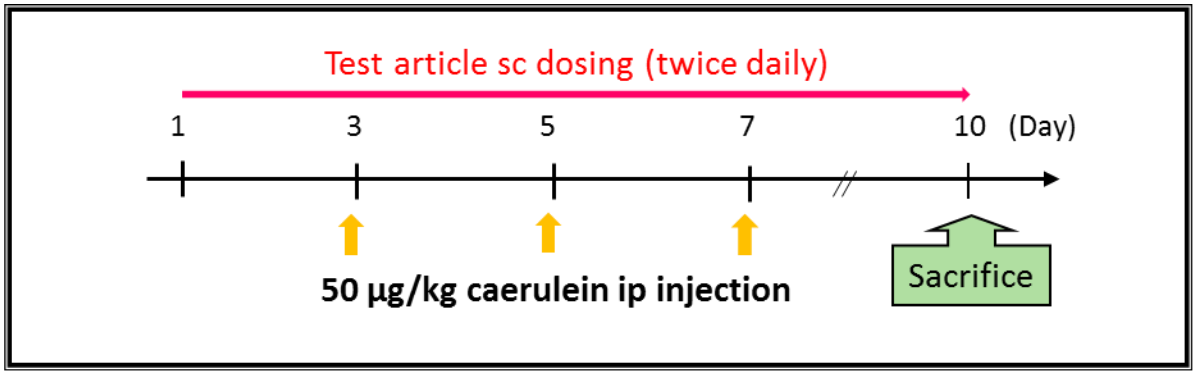
- **The solubility of GEM045 is not so good in most vehicle solutions for many animal efficacy studies.**
- **Various organic and inorganic salts have been attempted.**
- **A good salt form of GEM045 (M) is finally available right now.**
- **PK study on GEM045 (M) showed only one in-vivo metabolite (M+2); LPA reduction plasma assay showed this metabolite has same activity as GEM045.**
- **GEM045 (M) (new salt) showed significant efficacy in CDAA-HFD, MCD (new test), IPF models.**

Autotaxin Inhibitors GEM045 Summary

- **GEM045M showed dose-dependent efficacy by oral route for both preventive & therapeutic CDA-HFD models (separate experiments).**
- **GEM045 showed obvious efficacy in both preventive & therapeutic MCD models (separate experiments).**
- **GEM045 has demonstrated repeated efficacy in NASH animal models of MCD, STAM, and CDA-HFD.**
- **Hit-profiling of GEM045 does not have "show-stopper" enzyme inhibitions (e.g. hERG, CYP450, metal-ion channel, etc.).**
- **No observations at high MTD dose limit (900 mpk).**
- **GEM045 is a very promising agent for NASH drug development.**

Supplement

Effect of GEM045 on Caerulein-Induced Chronic Pancreatitis



- Caerulein: 50 µg/kg ip injection per hour, 6 times / day on Day 3, 5, 7
- Strain: C57BL/6 male
- Weekend: double dose, qd administration

Main study:

Group 1: Naïve, n=3

Group 2: Vehicle, n=8

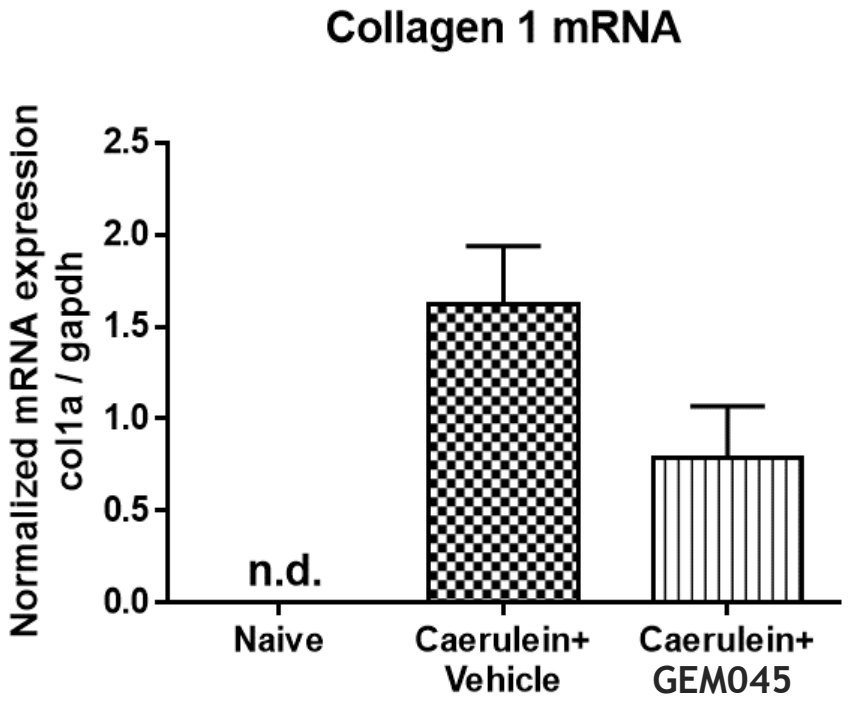
Group 3: GEM045 10 mg/kg (sc, bid), n=8

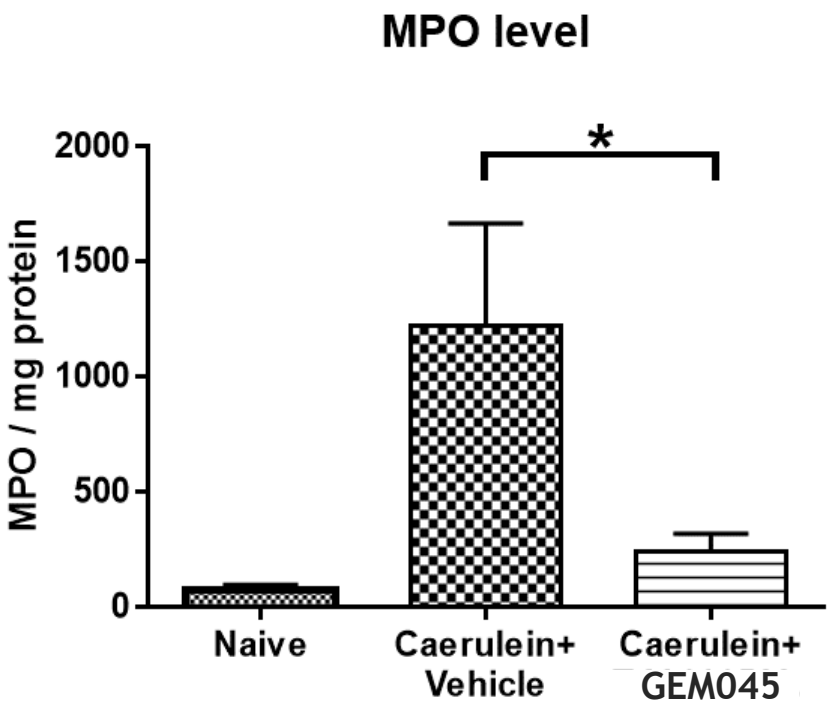
Items of analysis:

- Blood amylase assay
- Pancreas weight
- MPO assay
- Histology scoring (inflammation & Fibrosis)
- Collagen I mRNA

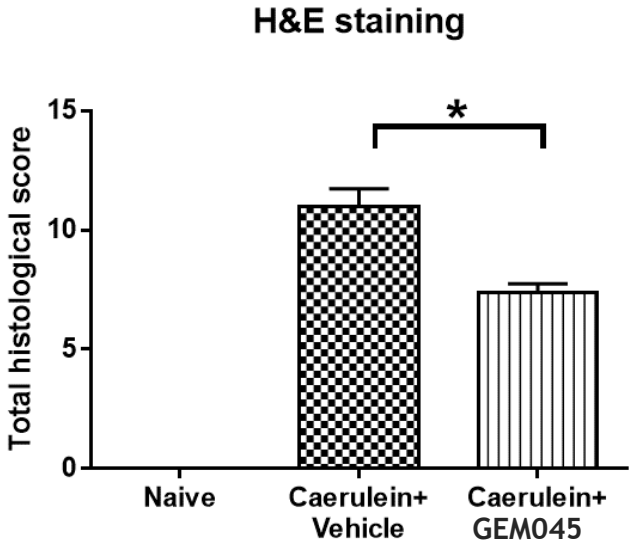
Effect of GEM045 on Caerulein-Induced Chronic Pancreatitis

(10 mg/kg, sc, bid, 10 days)





Effect of GEM045 on Caerulein-Induced Chronic Pancreatitis



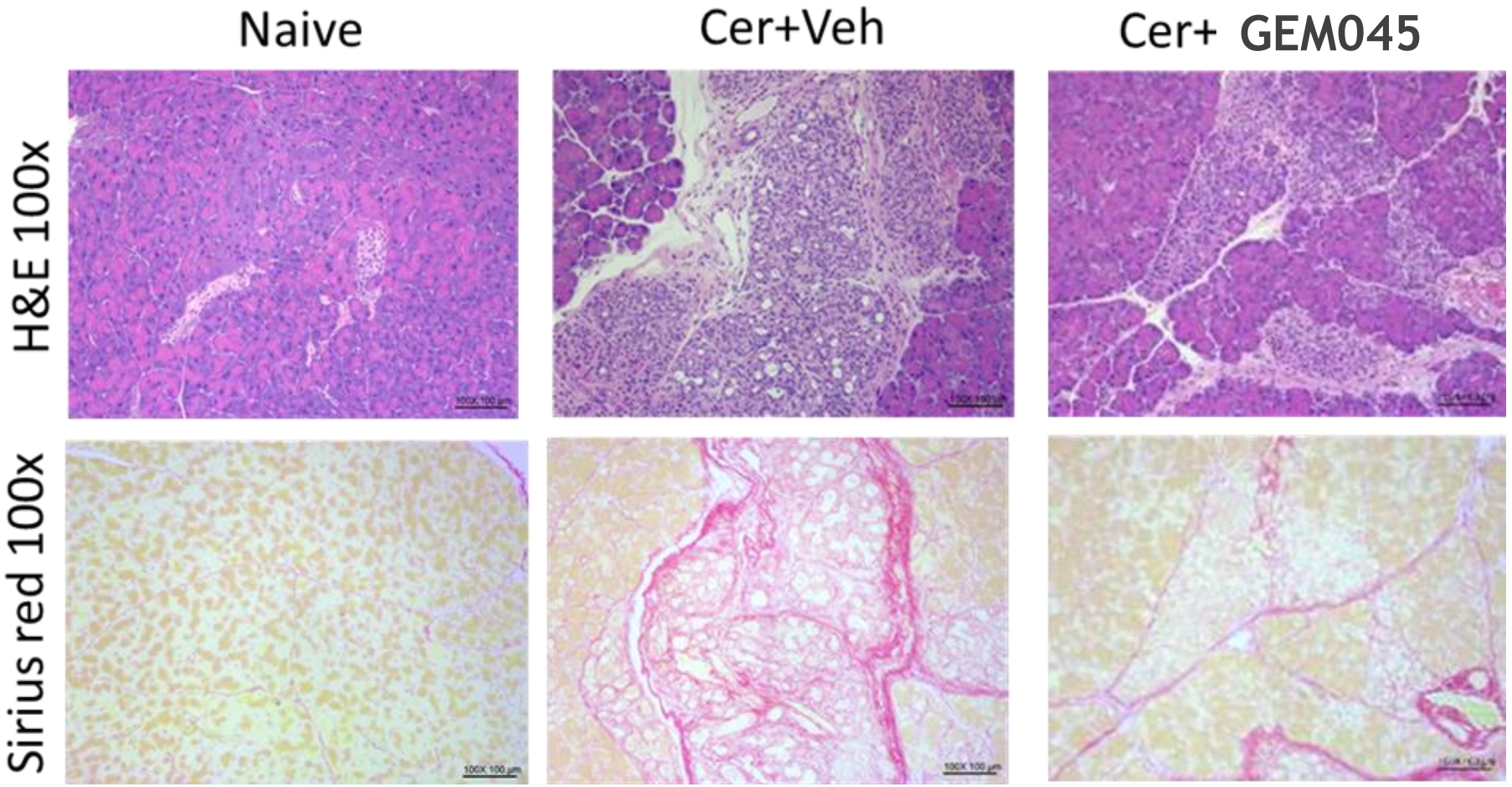
	Treatment		
Lesions	**Naïve**	**Caerulein+ Vehicle**	**Caerulein+GEM045**
Atrophy	0.00±0.00	1.63±0.92	1.50±0.53
Intralobular fibrosis	0.00±0.00	2.13±0.64	1.25±0.46 *
Perilobular fibrosis	0.00±0.00	1.75±0.71	1.25±0.46
Interlobular fibrosis	0.00±0.00	2.25±0.46	1.38±0.52 *
Inflammation	0.00±0.00	3.25±0.71	2.00±0.00 *
Total histological score	0.00±0.00	11.00±4.36	7.38±2.91 *

All values represent mean ± standard deviation.

* P <0.05 vs Caerulein+Vehicle

GEMSEKI

Effect of GEM045 on Caerulein-Induced Chronic Pancreatitis



Effect of GEM045 on Carrageenan Paw Model

- **Animal**

  BALB/c, male, 8 weeks old

- **Material**

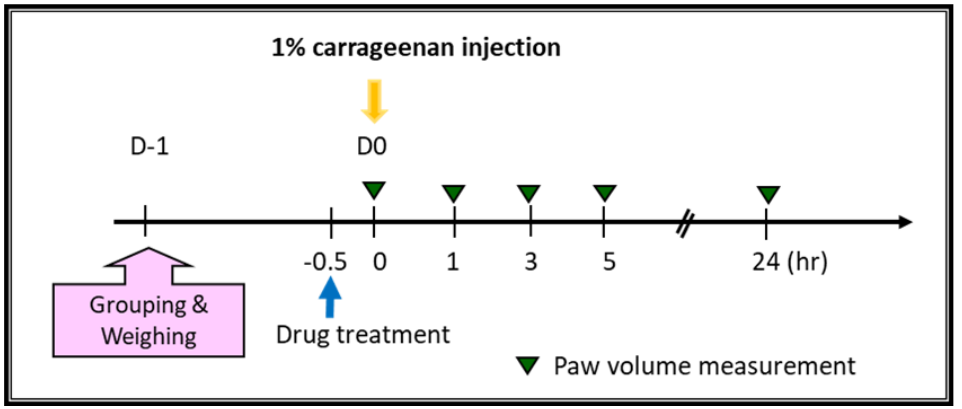
  λ-Carrageenan, 30 μL of 1% suspension intraplantar

- **Method**

  1. Animals are fasted overnight.
  2. Paw volume of 0hr are measured before carrageenan intraplantar injection in the left hind paw.
  3. Vehicle and test article are administrated at 0.5hr prior to carrageenan injection.
  4. Paw volume are measured at 1, 3, 5 and 24 hr post to carrageenan injection.

- **Group**

  1. Vehicle, n=5
  2. GEM045 15mg/kg (po, -0.5hr), n=5
  3. Naïve , n=3



Effect of GEM045 on Carrageenan Paw Model