

Introduction

- Osteogenesis imperfecta (OI) is a heterogeneous type 1 collagenopathy that alters either the quantity or quality of type I collagen. It is characterized by bone fragility which often leads to high fracture incidence.
- Bisphosphonates are commonly used to treat children with moderate-to-severe forms of OI, but gaps persist for effective pharmacological treatment in adult patients.
- The *oim/oim* mouse is an established model of moderate-to-severe OI that contains a naturally-occurring *col1a2* variant that leads to *proα2(I)* collagen deficiency [1].
- We previously demonstrated that a monoclonal antibody targeting the sialic acid-binding immunoglobulin-like lectin 15 (Siglec 15) immunoreceptor [2], NP159 (NextCure), improves bone quality and decrease fractures in female *oim* mice.
- We have now extended the study to evaluate efficacy in male *oim* mice.

Methods and Materials

- Eighty male mice (20 wildtype (WT) saline, 20 WT NP159, 20 *oim/oim* saline, and 20 *oim/oim* NP159) were treated from age 14-26 weeks with either NP159 (10mg/kg weekly x1 month then biweekly) or weekly saline.
- Faxitrons at 14 and 26 weeks were taken to evaluate fracture incidence and healing.
- Tibias and femurs were analyzed post-sacrifice for femoral length, microcomputed tomography (micro-CT), biomechanical testing, and Fourier Transform Infrared Spectroscopy (FTIR).
- Statistical analysis was performed using Two-way analysis of variance (ANOVA). A $p \leq 0.05$ was considered significant.
- Results were compared to the previous study using female mice.

Results

- 90% of male *oim/oim* treated with NP159 had no new fractures, versus 85% of females seen earlier (Figure 1).
- Micro-CT (Figures 2, 3, and 4):
 - Both sexes showed decreased trabecular separation with NP159 treatment ($p=0.05$).
 - Treated males had normal cortical porosity, in contrast with females who showed increased porosity.
 - Bone mineral density did not change for either sex.
- Biomechanics (Figure 5): NP159 increased stiffness of the bones in both males and females.
- FTIR:
 - females showed a normalization of mineral:matrix ratio, increased acid phosphate, and decreased collagen maturity, whereas the males showed no similar changes.

Figure 1. Male + Female Fracture Count results

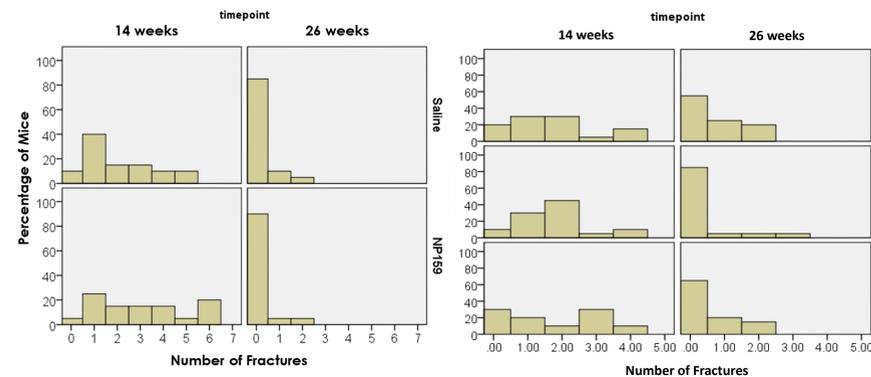


Figure 2. Male Micro-CT results

		Trabecular Bone					
		Number	BVF	TMD (mg/cc)	Trabecular number (1/mm)	Trabecular thickness (mm)	Trabecular Separation (mm)
WT	Saline	20	0.19 ± 0.03	920.06 ± 13.61	4.72 ± 0.56	0.05 ± 0.005	0.21 ± 0.02
	NP159	20	0.22 ± 0.04	937.95 ± 15.29	5.27 ± 0.58	0.05 ± 0.005	0.19 ± 0.02
<i>oim/oim</i>	Saline	20	0.08 ± 0.03	1019.36 ± 74.35	3.53 ± 0.76	0.04 ± 0.004	0.29 ± 0.06
	NP159	20	0.09 ± 0.03	1006.39 ± 67.93	3.91 ± 0.60	0.04 ± 0.004	0.26 ± 0.04

		Cortical Bone					
		Number	BMD	Porosity (%)	TMD (mg/cc)	Cortical thickness (mm)	Minimum inertia
WT	Saline	20	1110.66 ± 13.59	7.6 ± 1.1	1179.32 ± 10.01	0.23 ± 0.03	0.21 ± 0.04
	NP159	20	1116.73 ± 15.08	7.5 ± 0.7	1186.09 ± 14.71	0.23 ± 0.01	0.20 ± 0.04
<i>oim/oim</i>	Saline	20	1223.40 ± 118.20	9.7 ± 1.9	1277.42 ± 104.48	0.21 ± 0.02	0.21 ± 0.03
	NP159	20	1196.92 ± 107.59	8.6 ± 1.5	1265.33 ± 87.71	0.21 ± 0.03	0.21 ± 0.03

Figure 3. Micro-CT 3D images of *oim/oim* trabecular bone

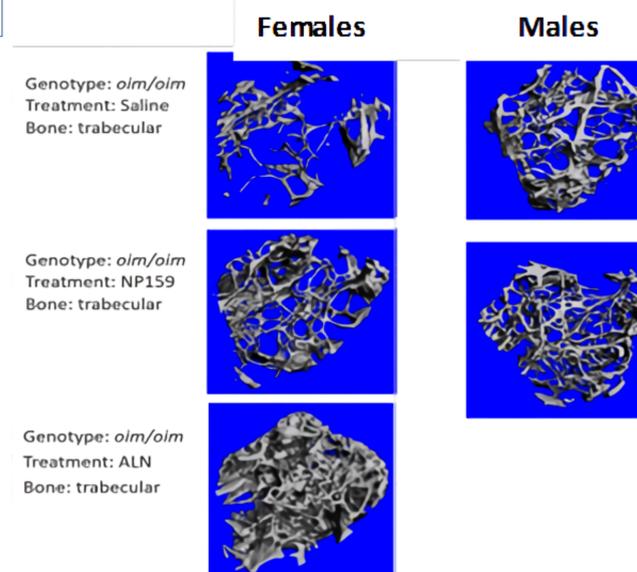
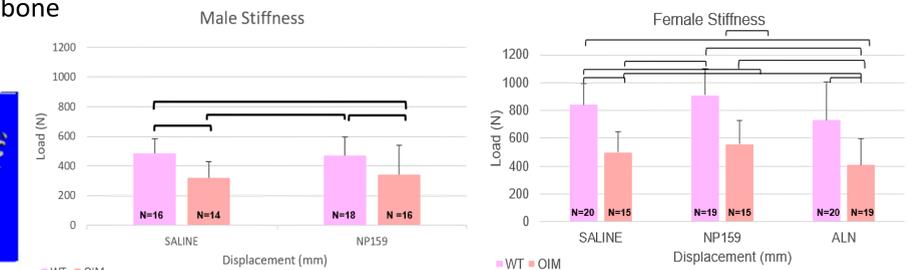


Figure 4. Female Micro-CT results

		Trabecular Bone					
		Number	BVF	TMD (mg/cc)	Trabecular number (1/mm)	Trabecular thickness (mm)	Trabecular Separation (mm)
WT	Saline	4	0.09 ± 0.08	127.68 ± 79.98	3.05 ± 0.76	0.05 ± 0.011	0.34 ± 0.08
	NP159	10	0.13 ± 0.06	121.22 ± 74.11	3.62 ± 0.73	0.049 ± 0.005	0.28 ± 0.06
	ALN	6	0.17 ± 0.06	203.55 ± 83.99	3.92 ± 0.55	0.055 ± 0.010	0.26 ± 0.04
<i>oim/oim</i>	Saline	5	0.02 ± 0.01	39.65 ± 10.46	2.24 ± 0.11	0.040 ± 0.02	0.45 ± 0.005
	NP159	12	0.05 ± 0.02	60.45 ± 37.63	2.61 ± 0.56	0.04 ± 0.006	0.41 ± 0.11
	ALN	5	0.13 ± 0.05	164.67 ± 56.35	3.60 ± 0.66	0.041 ± 0.004	0.29 ± 0.05

		Cortical Bone					
		Number	BVF	Porosity (%)	TMD (mg/cc)	Cortical thickness (mm)	Polar moment of inertia
WT	Saline	4	0.93 ± 0.01	6.7 ± 1	1143.10 ± 32.45	0.25 ± 0.04	0.39 ± 0.05
	NP159	10	0.93 ± 0.007	6.9 ± 0.7	1144.29 ± 15.79	0.24 ± 0.02	0.37 ± 0.06
	ALN	6	0.94 ± 0.005	6.4 ± 0.5	1151.62 ± 19.67	0.26 ± 0.02	0.41 ± 0.11
<i>oim/oim</i>	Saline	5	0.91 ± 0.007	9.1 ± 0.7	1119.84 ± 11.11	0.17 ± 0.01	0.22 ± 0.05
	NP159	12	0.91 ± 0.02	8.8 ± 2	1122.18 ± 53.37	0.19 ± 0.03	0.27 ± 0.10
	ALN	5	0.90 ± 0.003	7.9 ± 0.3	1146.78 ± 10.38	0.20 ± 0.01	0.25 ± 0.05

Figure 5. Male + Female Stiffness results



Conclusions

- These results show promising trends for NP159 treatment in OI.
- Fracture incidence was reduced.
- The observed cortical and trabecular bone changes support the premise that NP159 works as both an antiresorptive and a bone formation agent.
- NP159 seems to be favorable for bone strength in both sexes as indicated by the increased stiffness shown on biomechanical testing.
- Sexual dimorphism is a known phenomenon in both human patients and previously reported treated mice models.
- The sex-specific results seen with NP159 treatment highlights the importance of considering sex when searching for possible therapies for OI.

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Disclosure

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