Dose finding study of AAV-LSP-MMUT in a mouse model of MMA and efficient suppression of anti-capsid antibody responses by single and multiple administrations of ImmTOR nanoparticles

October 2021

NIH
NHGRI

Dose finding study of AAV-LSP-MMUT in a mouse model of MMA and efficient suppression of anti-capsid antibody responses by single and multiple administrations of ImmTOR nanoparticles

PO Ilyinskii[1], AM Michaud[1], LE Venturoni[2], GL Rizzo[1], RJ Chandler[2], T Capela[1], LPM Johnston[1], SS Leung[1], CP Venditti[2], TK Kishimoto[1]

[1]Selecta Biosciences, 65 Grove Street, Watertown, MA 02472, USA

[2]NHGRI, NIH, Bethesda, MD 20892 USA

Selecta Biosciences

NIH NHGRI

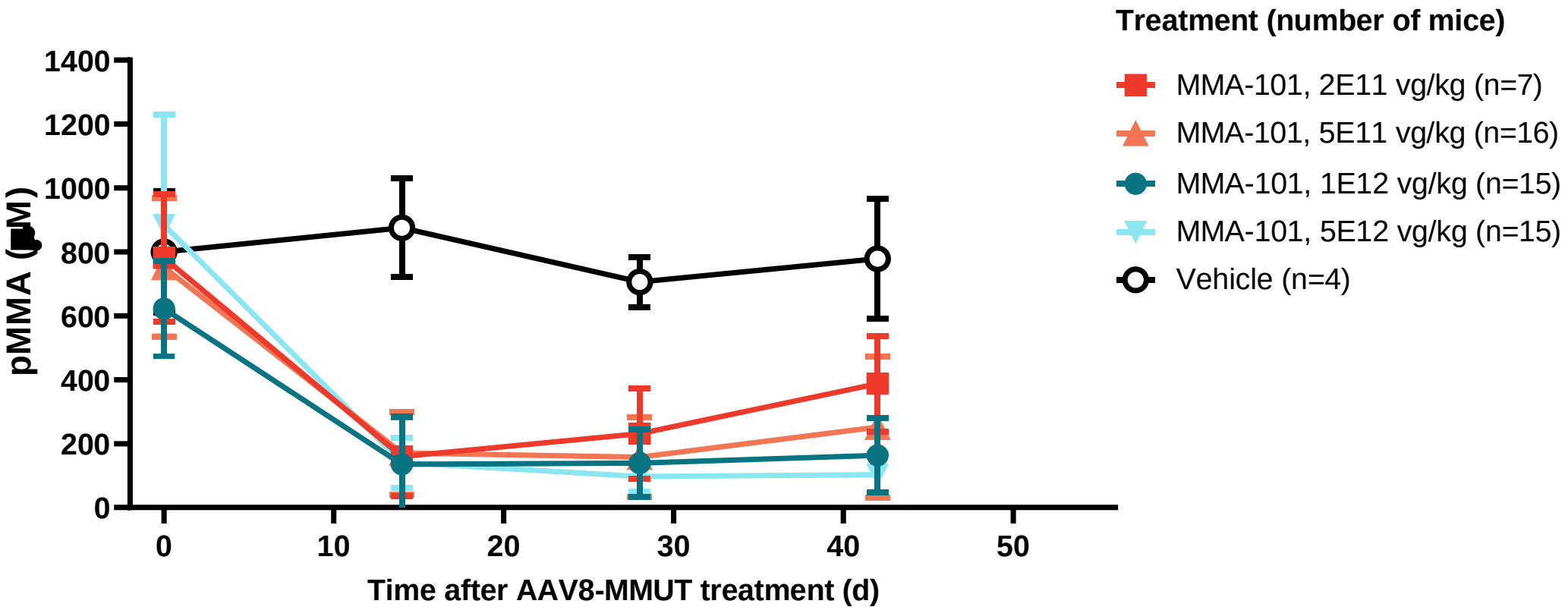
Dose finding study of AAV-LSP-MMUT in a mouse model of MMA and efficient suppression of anti-capsid antibody responses by single and multiple administrations of ImmTOR nanoparticles

A wide dose range of MMA-101, an AAV vector encapsidating the methylmalonyl-CoA mutase (MMUT) gene under control of a liver-specific promoter, was tested in juvenile (14 and 28-day old) *Mmut*-/-;$Tg^{INS\text{-}MCK\text{-}Mmut}$ (MCK-MMUT) mice, a model of methylmalonic acidemia. A rapid and dose-dependent decrease of plasma methylmalonic acid (pMMA), a key disease-associated metabolite, was seen at doses ranging from 2E11 to 5E12 vg/kg in 28-day old mice maintained on a low protein diet. Similar efficacy was observed in 14-day old mice at MMA-101 doses of 1E12 vg/kg to 1E14 vg/kg, although pMMA partially rebounded at 1E12 vg/kg. ImmTOR, nanoparticle-encapsulated rapamycin, combined with 1E13 vg/kg of MMA-101 reduced anti-capsid IgG antibody responses. Additional monthly doses of ImmTOR doses led to further and more durable IgG suppression at high vector dose. No adverse effects were seen after AAV-MMUT +/- ImmTOR administration. Histological analysis of key target organs showed improvement in MMA-related vacuolization in the liver with MMA-101 +/- ImmTOR treatment, and, in addition, 1-C-13 propionate oxidation was improved in the treated MMA mice. Thus, MMA-101 +/- ImmTOR corrected the metabolic defect in MCK-MMUT mice and showed no adverse effects in MCK-MMUT model. Repeated administration of ImmTOR provided more durable suppression of antibodies against AAV capsid. Monthly dosing of ImmTOR has been shown to be well tolerated and effective in mitigating immunogenicity of a fungal-derived uricase therapy in Phase 2 clinical trials in gout patients and is currently in Phase 3 clinical testing.

Selecta Biosciences

NIH NHGRI

Reduction of pMMA in MMut-/-;Tg mice by MMA-101

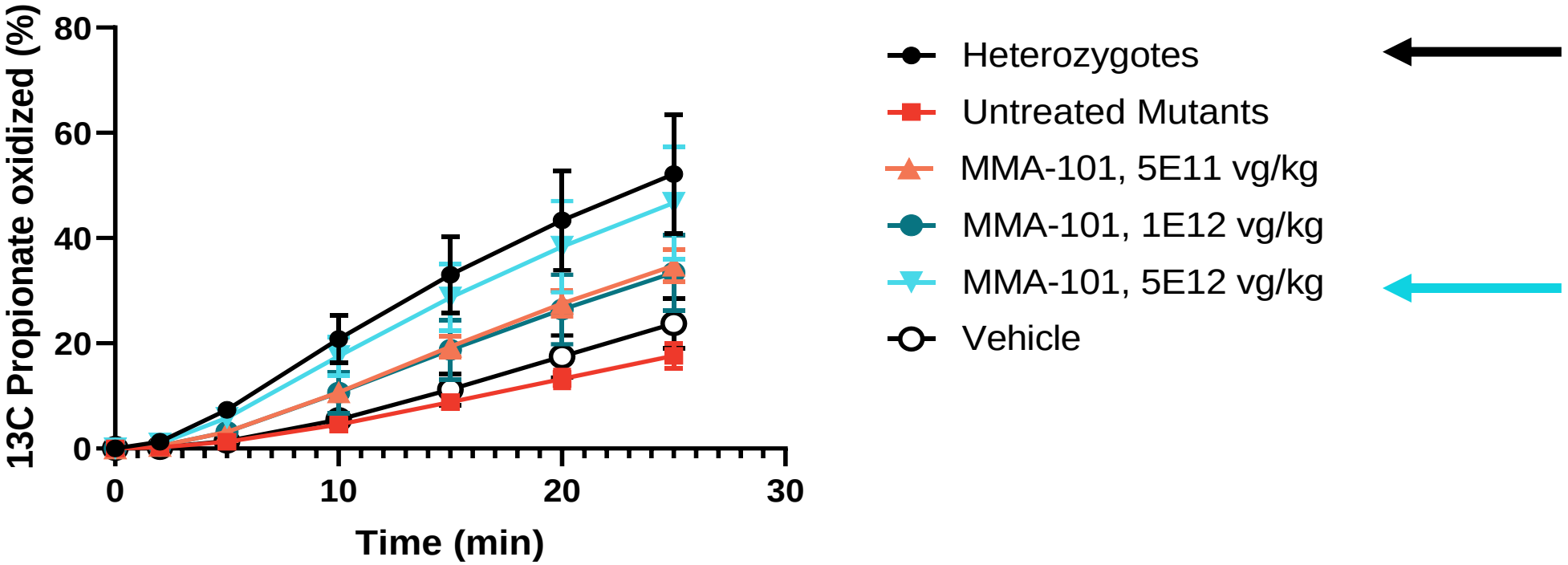


Rapid and dose-dependent decrease of plasma methylmalonic acid (pMMA), a key disease-associated metabolite, at MMA-101 doses ranging from 2E11 to 5E12 vg/kg in 28-day old mice maintained on a low protein diet

Selecta Biosciences

NIH NHGRI

MMA-101 increases 1-13C-propionate oxidation in MMut-/-;Tg mice



Propionate oxidation (PO): a direct biomarker of MMUT enzyme activity in Mmut-/-;Tg mice and MMA patients

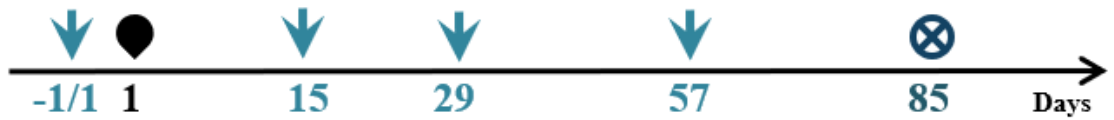
PO levels in mice treated with a single dose of 5E11 vg/kg or 5E12 vg/kg: different from those in vehicle-treated mice at every time-point measured ($p<0.01$ with the exception of 2-min point for 5E11 vg/kg being at $p<0.05$), those treated with 1E12 vg/kg: different vs. vehicle-treated at 15-25 min interval ($p<0.05$; Mann-Whitney test)

Selecta Biosciences

NIH NHGRI

Dose finding study 1 in 14-day old Mmut-/-;Tg mice: MMA-101 alone, 1E12-1E14 vg/kg

Group	Injection	Virus Dose
1	Vehicle Control	N/A
2	MMA-101	1E12 vg/kg
3	MMA-101	1E13 vg/kg
4	MMA-101	1E14 vg/kg



MMA-101 +/- ImmTOR (RO)

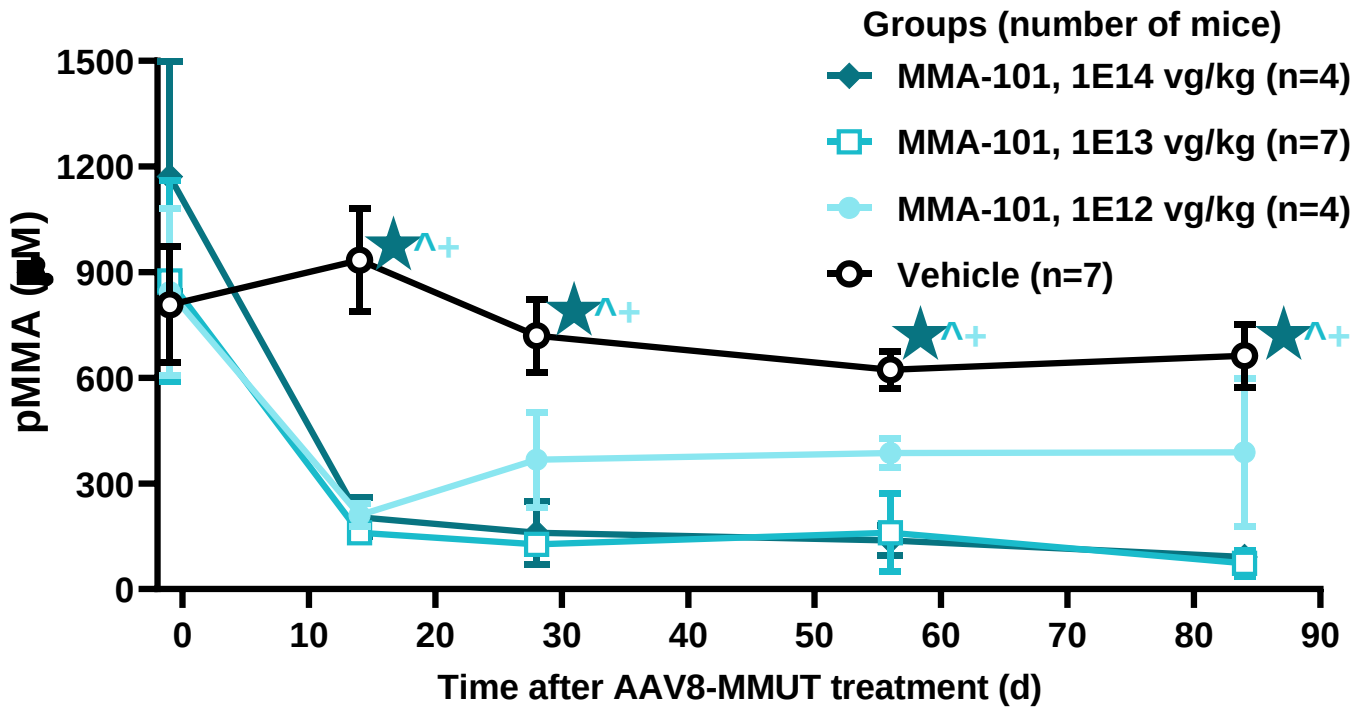
Bleeds (RO)

Terminal

Selecta Biosciences

NIH NHGRI

All dose levels of MMA-101 reduced pMMA in 14d-old mice (DFS #1)



★ - p <.05 compared to MMA-101 1E14 vg/kg
^ - p <.05 compared to MMA-101 1E13 vg/kg
\+ - p <.05 compared to MMA-101 1E12 vg/kg

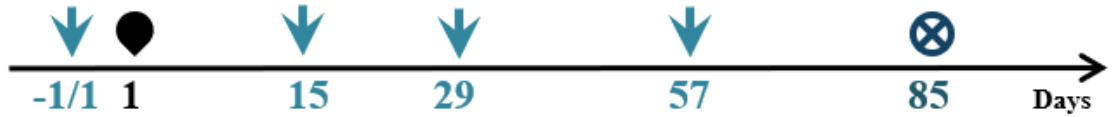
All doses of MMA-101: a reduction in pMMA levels within 14d (~75%; p<0.05 vs. vehicle). Doses of 1E13 & 1E14 vg/kg: reductions of pMMA below 250 µM through the 12-week study endpoint, where they were ~90% vs. baseline/vehicle. Dose of 1E12 vg/kg: a partial d28 rebound, plateaued, remained <500 µM through the end of the study

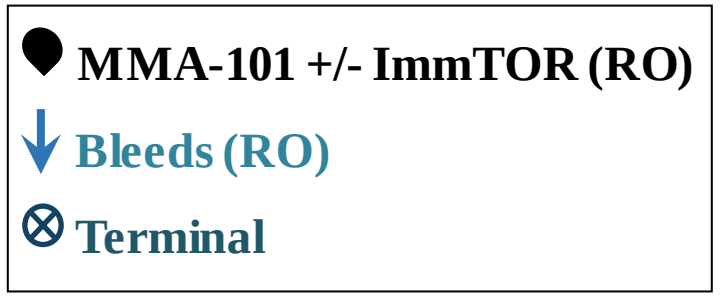
Selecta Biosciences

NIH NHGRI

Dose finding study 2 in 14-day old Mmut-/-;Tg mice: MMA-101 at 1E13 vg/kg combined with ImmTOR

Group	Injection	MMA-101 Dose	SEL-110 Dose
1	**Vehicle Control**	**N/A**	**N/A**
2	**MMA-101**	**1E13 vg/kg**	N/A
3	MMA-101 + **ImmTOR**	**1E13 vg/kg**	**2 mg/kg**
4	MMA-101 + ImmTOR	**1E13 vg/kg**	**6 mg/kg**
5	ImmTOR	**N/A**	6 mg/kg

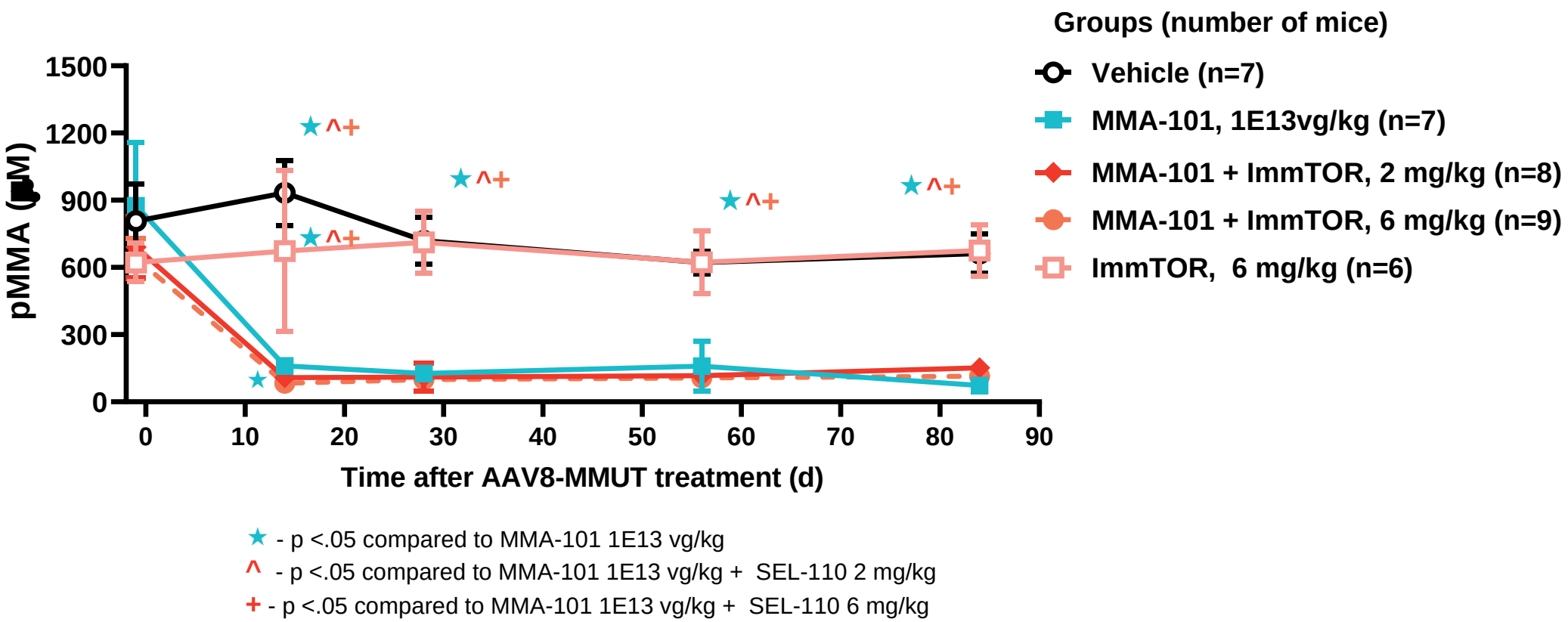




Selecta Biosciences

NIH NHGRI

MMA-101 combined with ImmTOR reduced pMMA (DFS #2)

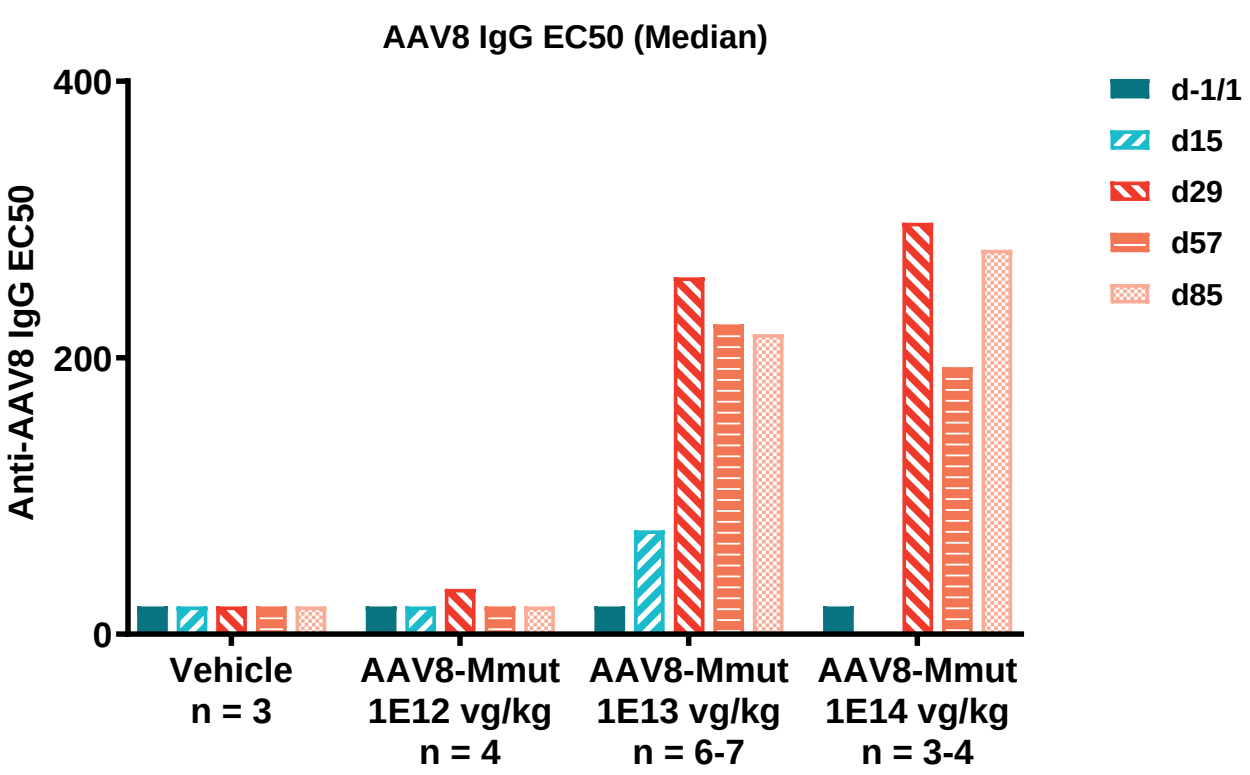


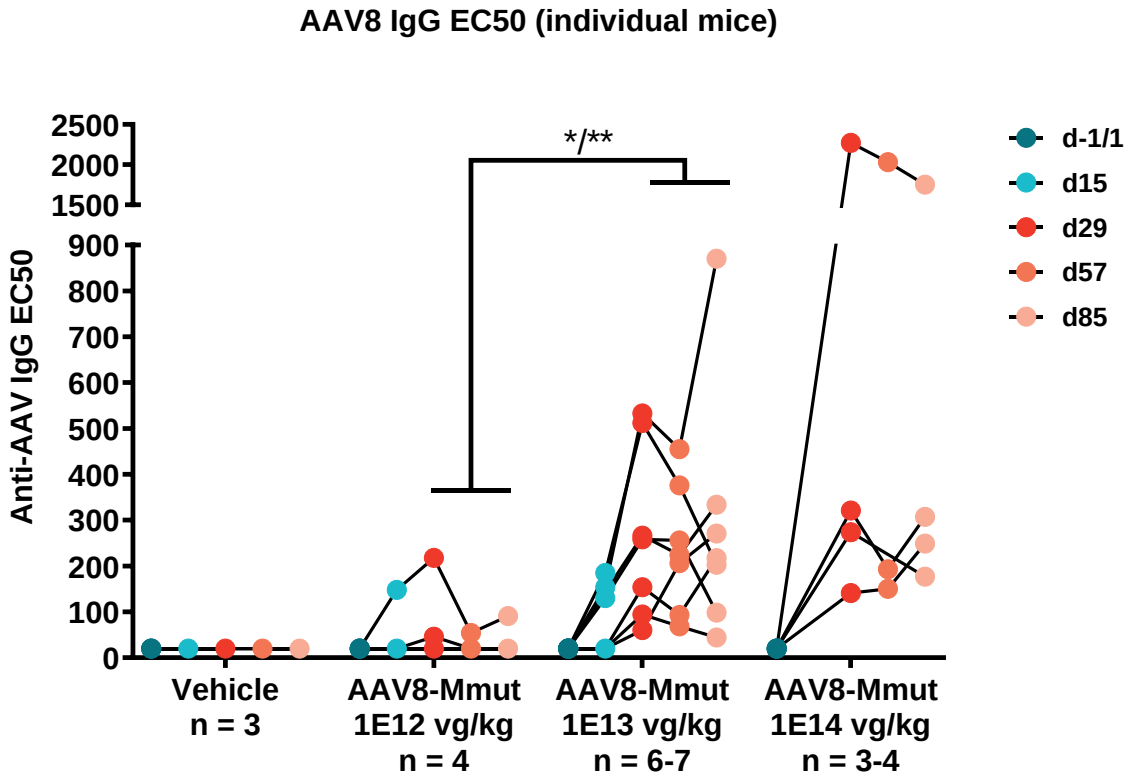
When 2 or 6 mg/kg ImmTOR was combined with 1E13 vg/kg MMA-101, sustained reduction in pMMA was maintained at levels similar to that observed with MMA-101 alone

Selecta Biosciences

NIH NHGRI

MMA-101 induces strong IgG response in a dose-dependent manner (DFS #1)



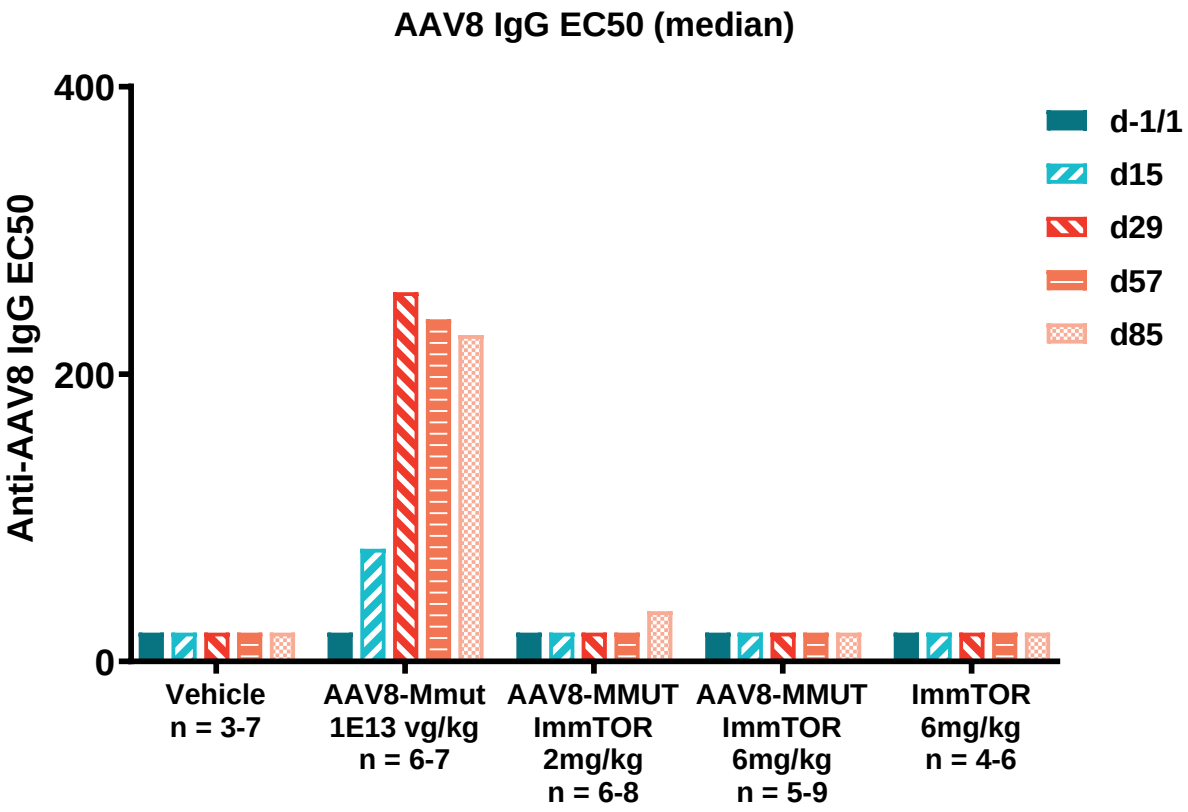


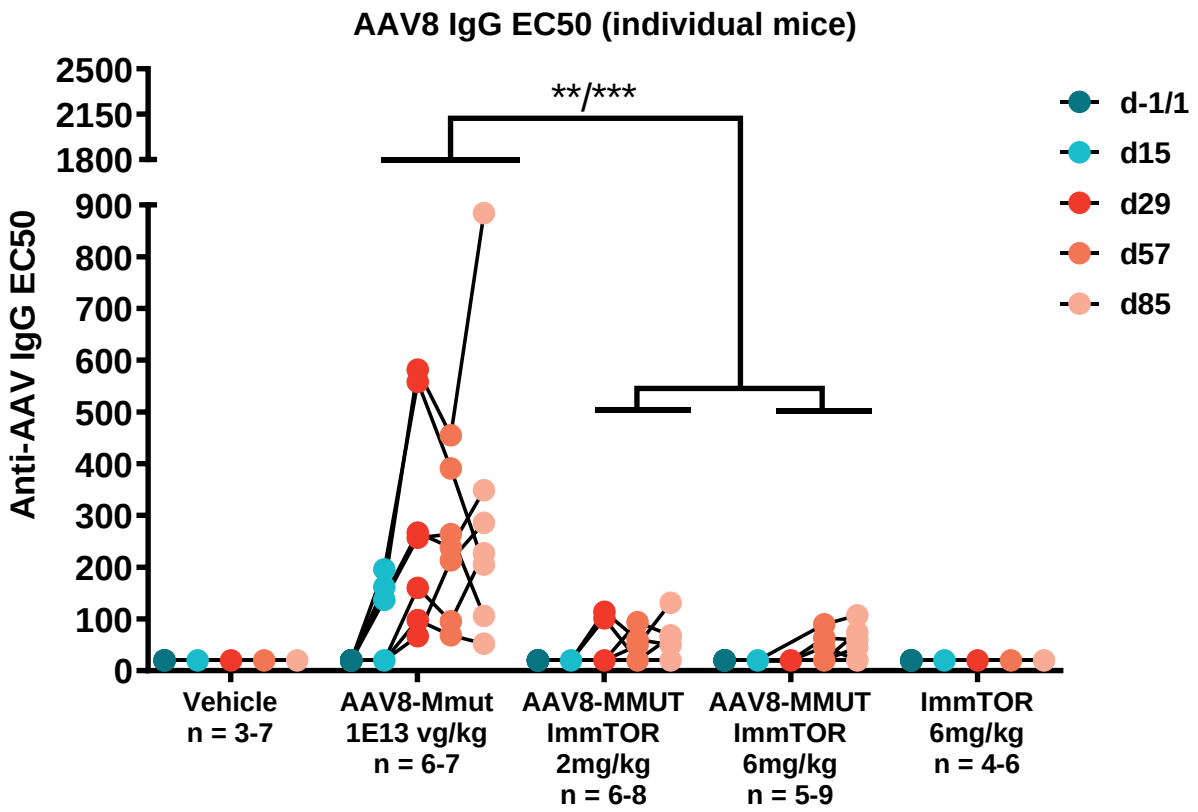
All mice treated with 1E13 vg/kg MMA-101 showed detectable IgG EC50 at the end of the study

Selecta Biosciences

NIH NHGRI

Reduced IgG response to AAV8 if MMA-101 is combined with ImmTOR (DFS #2)



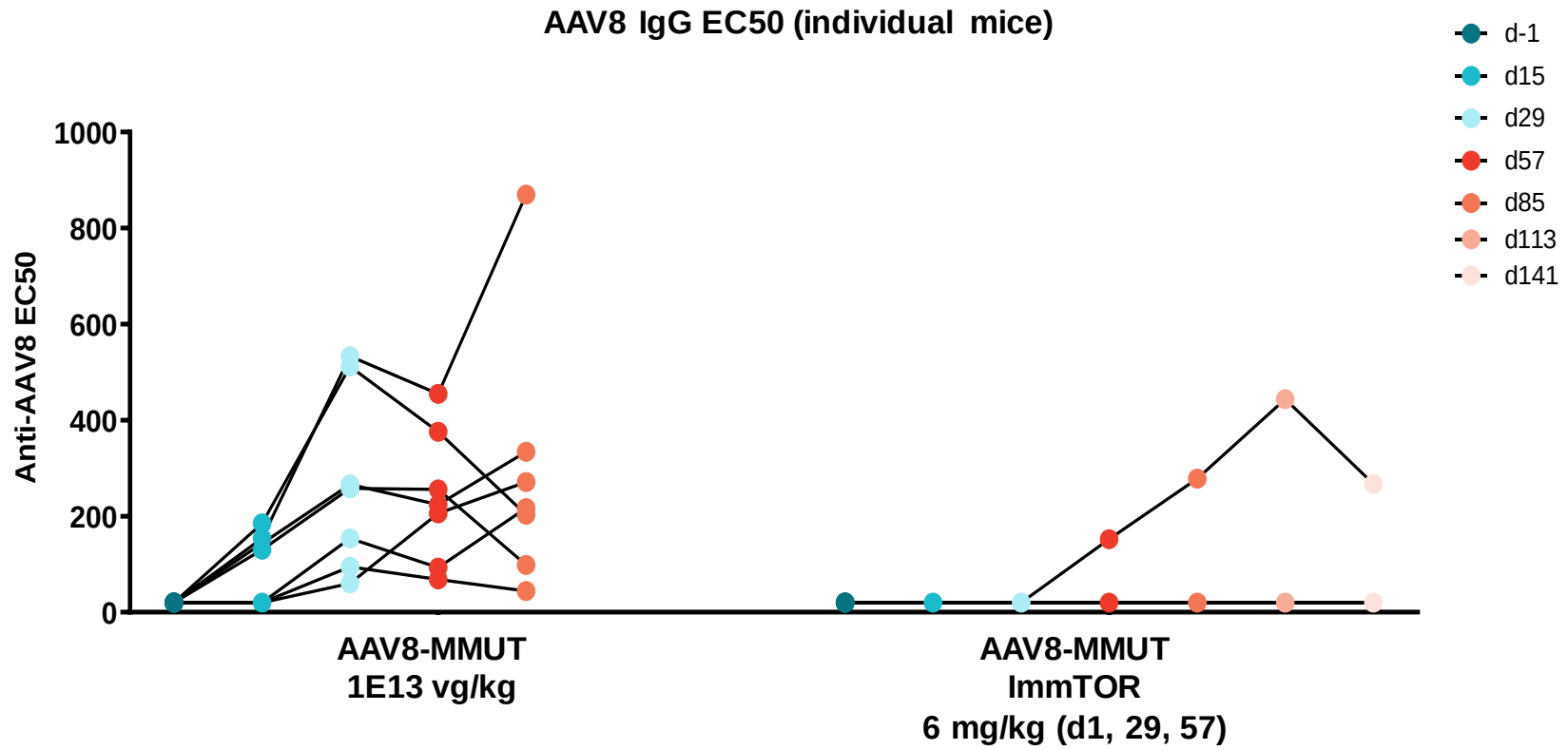


Less than 50% of mice treated with 1E13 vg/kg MMA-101 and 6 mg/kg ImmTOR showed detectable IgG EC50 at the end of the study

Selecta Biosciences

NIH NHGRI

Monthly administration of ImmTOR inhibits the formation of anti-AAV8 IgG antibodies after MMA-101 administration



Treatment	Number of Mice with Detectable EC50 (of total tested)					
	D15	D29	D57	D85	D113	D141
MMA-101 1E13 vg/kg	3/6	7/7	7/7	7/7	N/A	N/A
MMA-101 1E13 vg/kg + ImmTOR 6mg/kg d1, d29, d57	0/6	0/6	1/6	1/6	1/6	1/6

Selecta Biosciences

NIH NHGRI

Conclusions

- MMA-101 (AAV8-LSP-MMUT) corrected metabolic defect in MCK-MMUT mice in a dose-dependent fashion with 5E12 vg/kg providing the highest therapeutic activity in 28-day old mice and 1E13 vg/kg being the minimal effective dose in 14-day old mice
- A single-dose of ImmTOR co-administered with MMA-101 led to the same therapeutic effect as MMA-101 used alone and showed no adverse effects
- A single-dose of ImmTOR co-injected with MMA-101 suppressed IgG to AAV8 in >50% mice
- Repeated monthly administrations of ImmTOR provided more durable suppression of antibodies against AAV capsid than a single administration

Selecta Biosciences

NIH NHGRI