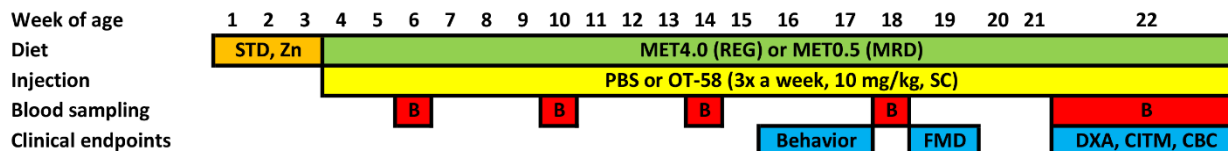


Supplementary Table S1. Study design – groups.

Group	Genotype	Diet	Treatment	Number of mice (males/females)
A	WT (+/+)	REG (Met4.0)	PBS	9M & 9F
B	WT (+/+)	REG (Met4.0)	OT-58	10M & 8F
C	I278T (-/-)	REG (Met4.0)	PBS	10M & 12F
D	I278T (-/-)	REG (Met4.0)	OT-58	8M & 9F
E	WT (+/+)	MRD (Met0.5)	PBS	8M & 8F
F	WT (+/+)	MRD (Met0.5)	OT-58	9M & 8F
G	I278T (-/-)	MRD (Met0.5)	PBS	9M & 9F
H	I278T (-/-)	MRD (Met0.5)	OT-58	8M & 9F

- All raised on standard rodent chow until D24, then switched to amino acid-defined diets, as indicated
- Treated SC with OT-58 (10 mg/kg) or an equal volume of PBS, 3 times per week (Monday, Wednesday, Friday) from W4 through W22.
- Blood collected once every 4 weeks, beginning on W6, for measurements of plasma metabolites
- Behavioral assessment at W16-17
- FMD at W19
- DXA & CITM at W22

Supplementary Figure S1. Study design – timeline. Mice were divided into 8 study groups, as shown in Supplementary Table S1. Mice in the corresponding groups were maintained continuously on one of two diets, with normal (regular diet – REG or Met4.0) or restricted methionine content (Met-restricted diet – MRD or Met0.5). Mice received injections of either 10 mg/kg OT-58 or PBS vehicle three times per week over the same experimental period. The timing of various experimental assessments is indicated in the scheme. B, blood draw; Behavior, behavioral assessment; FMD, endothelium-dependent flow mediated vasodilation; DXA, dual energy x-ray absorptiometry; CITM, carotid artery chemical injury thrombosis model; CBC, complete blood counts.



Supplementary Figure S2. Time course profiles of plasma sulfur metabolites. Time course plasma concentrations of total homocysteine (A), total cysteine (B), cystathionine (C), methionine (D) and SAM/SAH ratio (E) in mice. There were 8 study groups (A-H) as detailed in **Supplementary Table S1** following study design showed in **Supplementary Figure S1**. Briefly, beginning from week 4 of age, mice were maintained on diets with normal (REG) or restricted (MRD) methionine content and received subcutaneous injections of either PBS vehicle or 10 mg/kg OT-58 three times a week until the study end at week 22 of age. Plasma samples were collected via submandibular bleeding at weeks 6, 10, 14 and 18 weeks of age, while the last sample at week 22 of age was collected from inferior vena cava. Embedded legend describes study groups and designates color. The same color scheme is used throughout all the figures.

