ARTICLES
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Senolytics improve physical function and increase lifespan in old age

Ming Xu[1,2*], Tamar Pirtskhalava[1], Joshua N. Farr[1], Bettina M. Weigand[1,3], Allyson K. Palmer[1], Megan M. Weivoda[1], Christina L. Inman[1], Mikolaj B. Ogrodnik[1,3], Christine M. Hachfeld[1], Daniel G. Fraser[1], Jennifer L. Onken[1], Kurt O. Johnson[1], Grace C. Verzosa[1], Larissa G. P. Langhi[1], Moritz Weigl[1], Nino Giorgadze[1], Nathan K. LeBrasseur[1], Jordan D. Miller[1], Diana Jurk[3], Ravinder J. Singh[4], David B. Allison[5,6], Keisuke Ejima[5,6], Gene B. Hubbard[7], Yuji Ikeno[7,8], Hajrunisa Cubro[9], Vesna D. Garovic[9], Xiaonan Hou[10], S. John Weroha[10], Paul D. Robbins[11], Laura J. Niedernhofer[11], Sundeep Khosla[1], Tamara Tchkonia[1*] and James L. Kirkland[1*]

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Katharina Klas, PhD Student

Hypothesis

- Senescent cells might potentially contribute to age-related physical dysfunction

And if so...

- Targeting them therapeutically could improve life- and healthspan

Transplanting small numbers of senescent cells induces physical dysfunction in younger mice

Transplantation of senescent cells

- CON = non-senescent control cells
- SEN = senescent cells
- i.p. transplanted cells: preadipocytes
  - Isolated from luciferase-expressing transgenic mice (LUC^{+})
- Senescence induction:
  - 10Gy radiation (=>85% senescent cells)

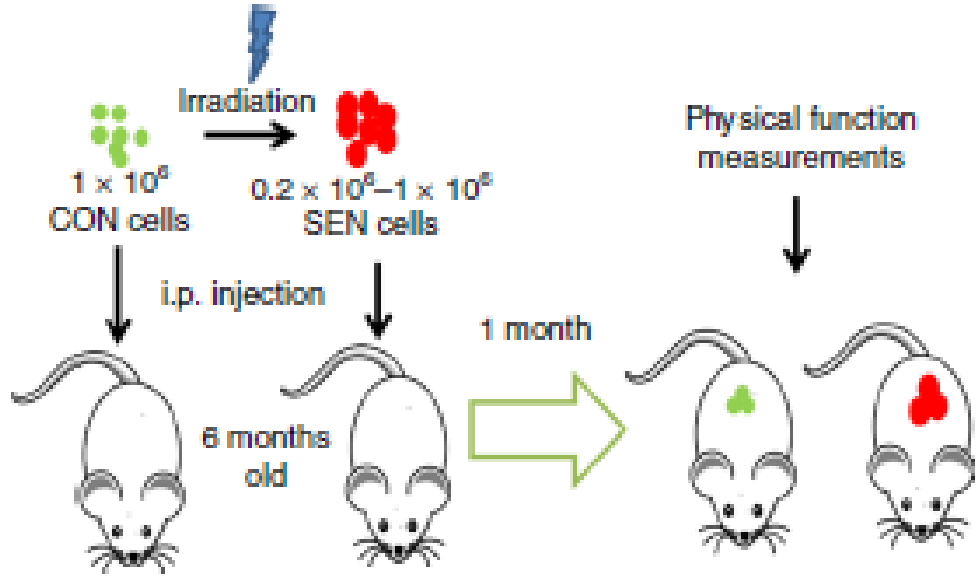

Fig. 1: Transplanting small numbers of senescent cells induces physical dysfunction in younger mice

- Representative image of LUC activity of various organs from LUC$^-$ mice 5days post-transplantation

5 days post- i.p. transplantation

- SEN and CON preadipocytes mainly located in visceral fat

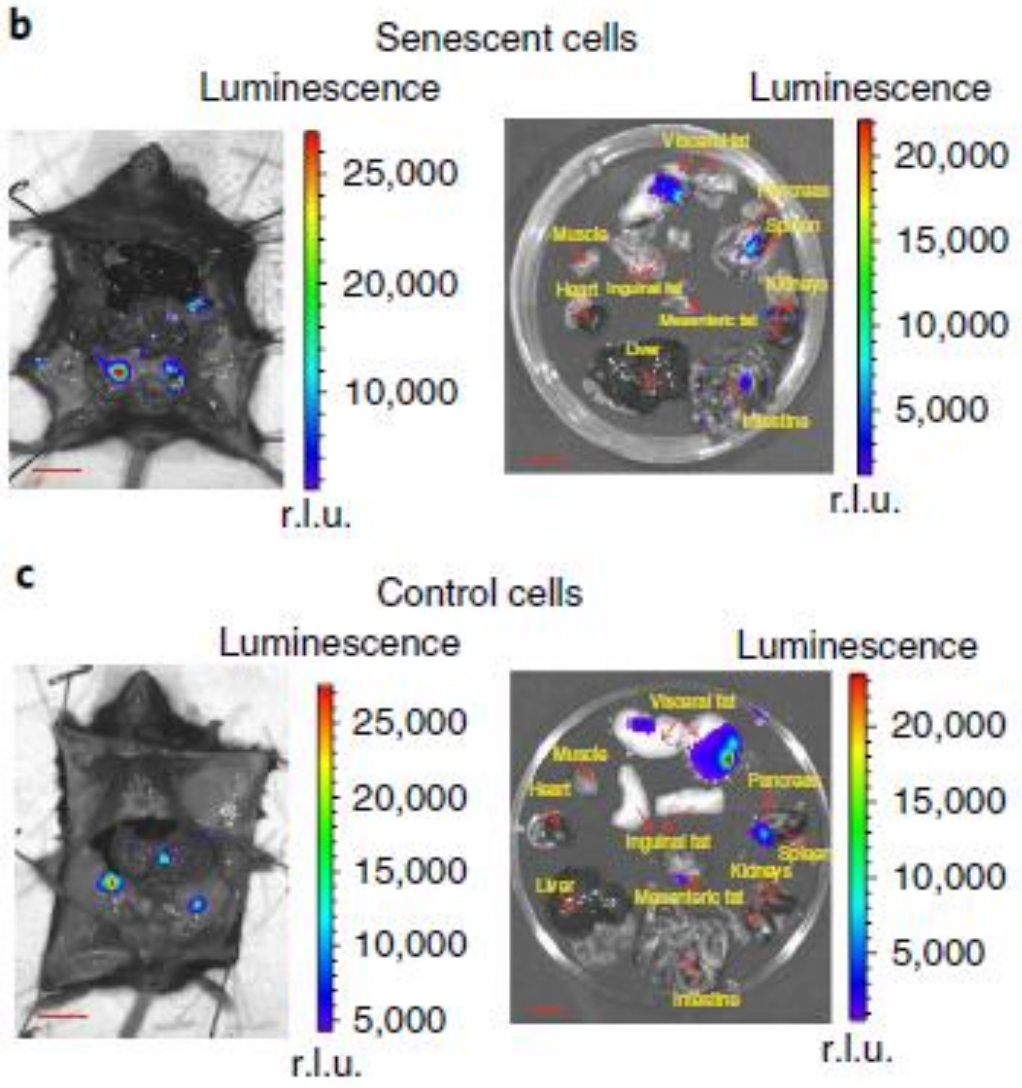

Fig. 1: Transplanting small numbers of senescent cells induces physical dysfunction in younger mice

- Max. walking speed
- Hanging endurance
- Grip strength

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- Daily activity
- Treadmill performance
- Food intake
- Body weight

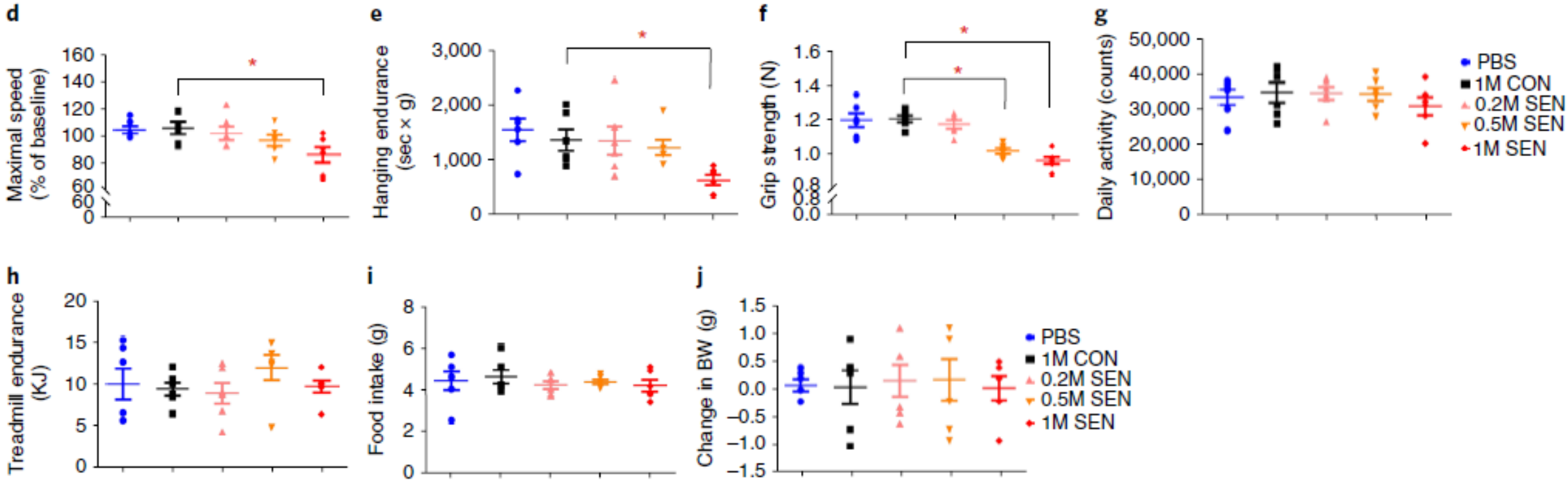
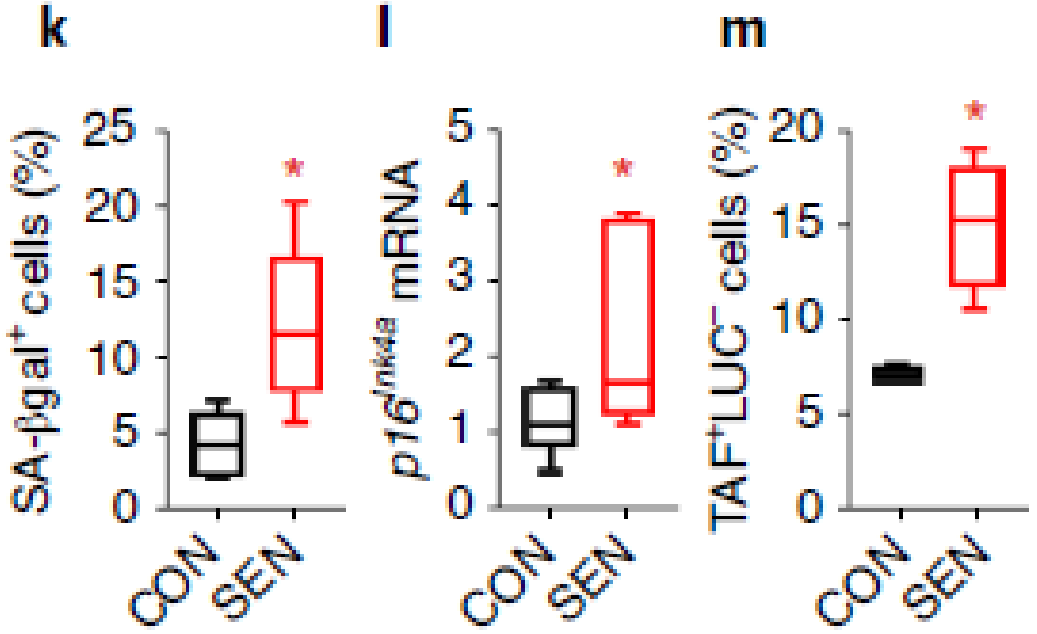


Fig. 1: Transplanting small numbers of senescent cells induces physical dysfunction in younger mice

2 months post transplantation in visceral fat:

- More senescence associated b-galactosidase (SA-bgal)$^+$ cells
- Higher cyclin-dependent kinase inhibitor 2A (p16Ink1a)
- Sign. more Telomere associated foci (TAF)$^+$ cells



Aging exacerbates the effects of senescent cell transplantation

Transplantation of senescent cells

- Same transplantation procedure
- Recipient mice were older → 17 months old

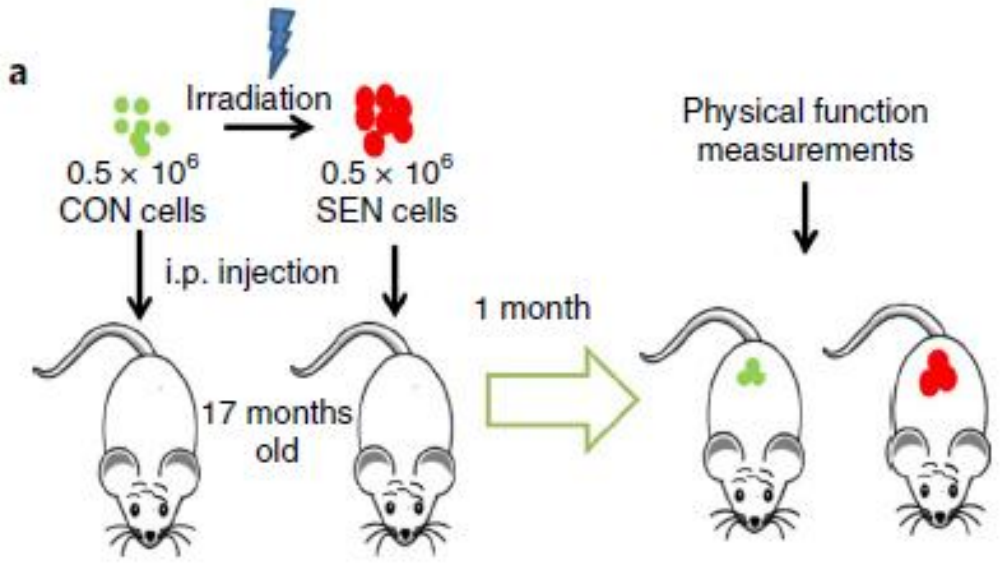


Fig. 2: Aging exacerbates the effects of senescent cell transplantation

- Max. walking speed
- Hanging endurance
- Grip strength

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- Daily activity
- Treadmill performance
- Food intake
- Body weight

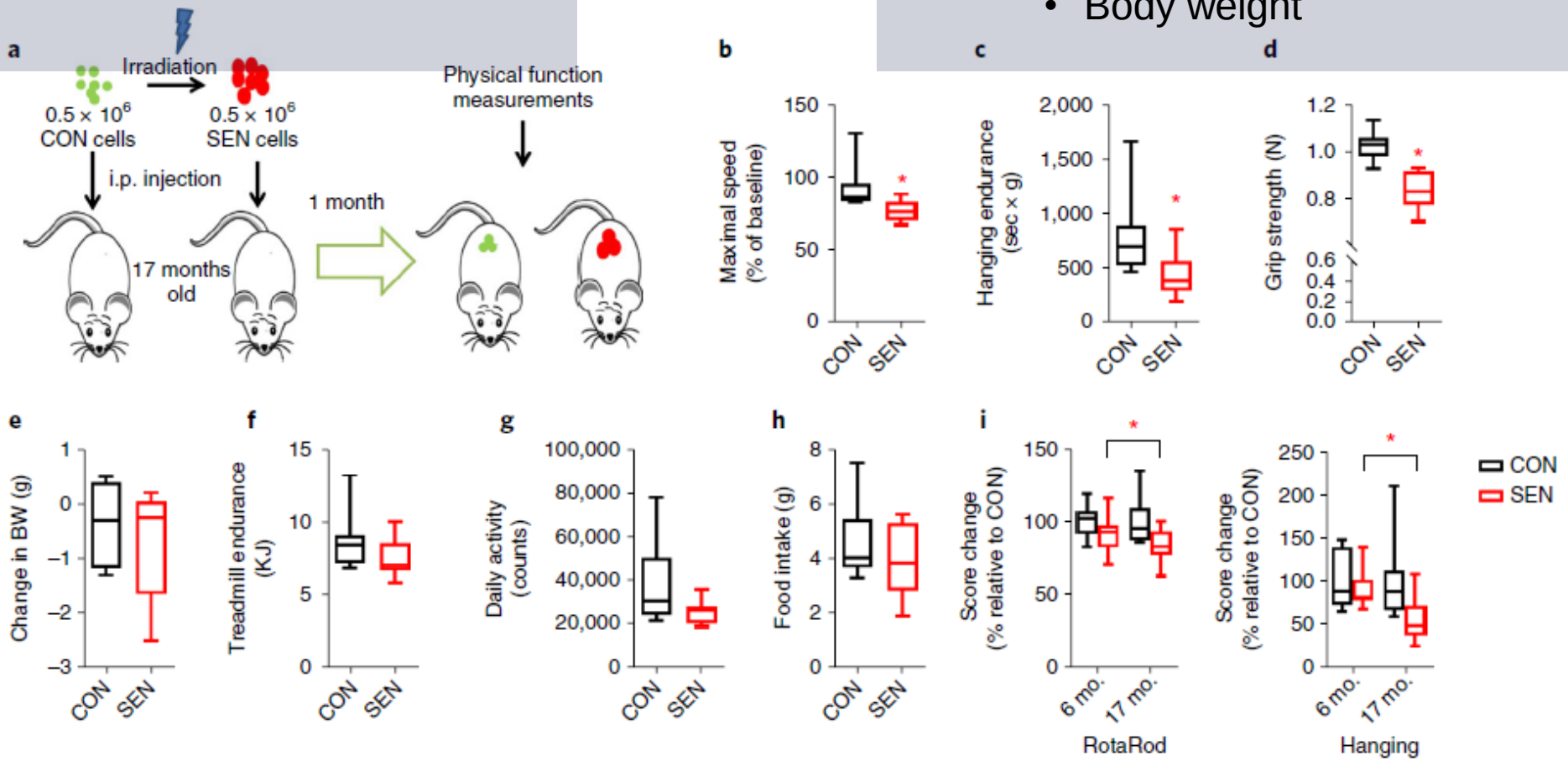
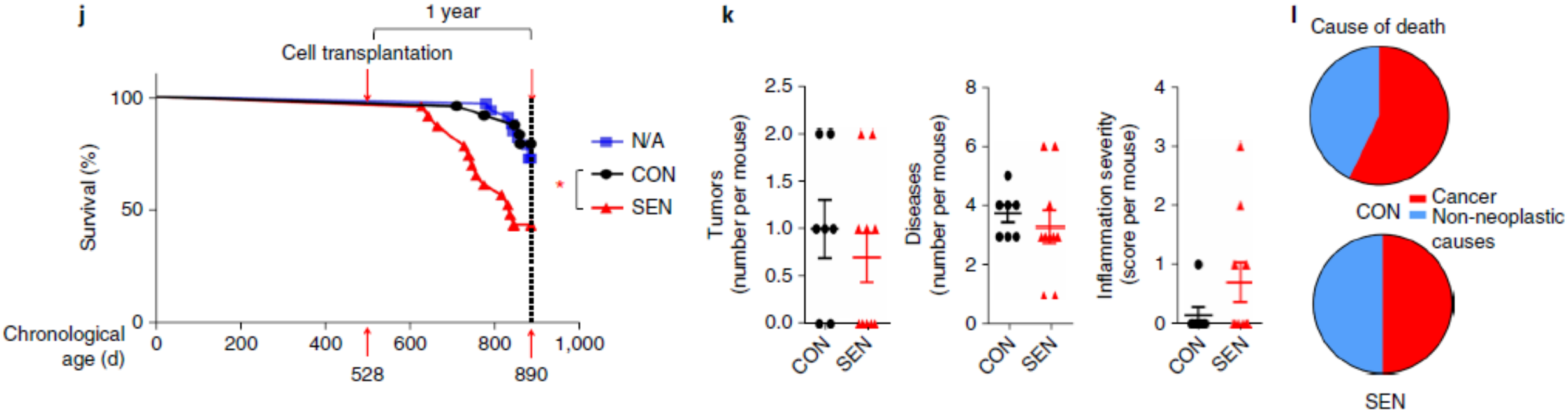


Fig. 2: Aging exacerbates the effects of senescent cell transplantation

- Senescent cell transplant mice:
  survival for the following year was significantly lower

- Tumour burden, disease burden at death, causes of death were not significantly altered



Senescent cells reduce resilience to metabolic stress in mice

Transplantation of senescent cells

- Same transplantation procedure
- Recipient mice (non-obese) were younger → 8 months old
- 1 month high-fat diet

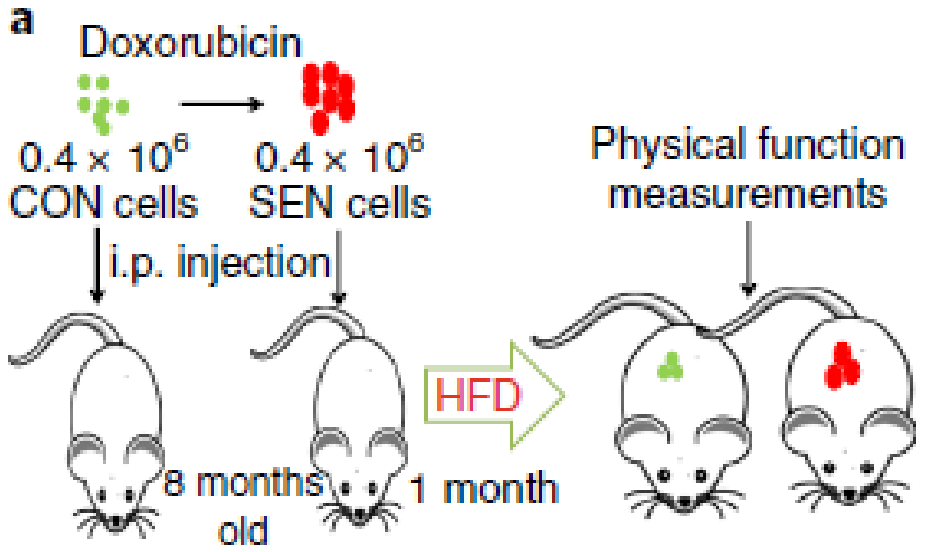


Fig. 3: Senescent cells reduce resilience to metabolic stress in mice

- Max. walking speed
- Hanging endurance
- Grip strength
- Daily activity
- Food intake

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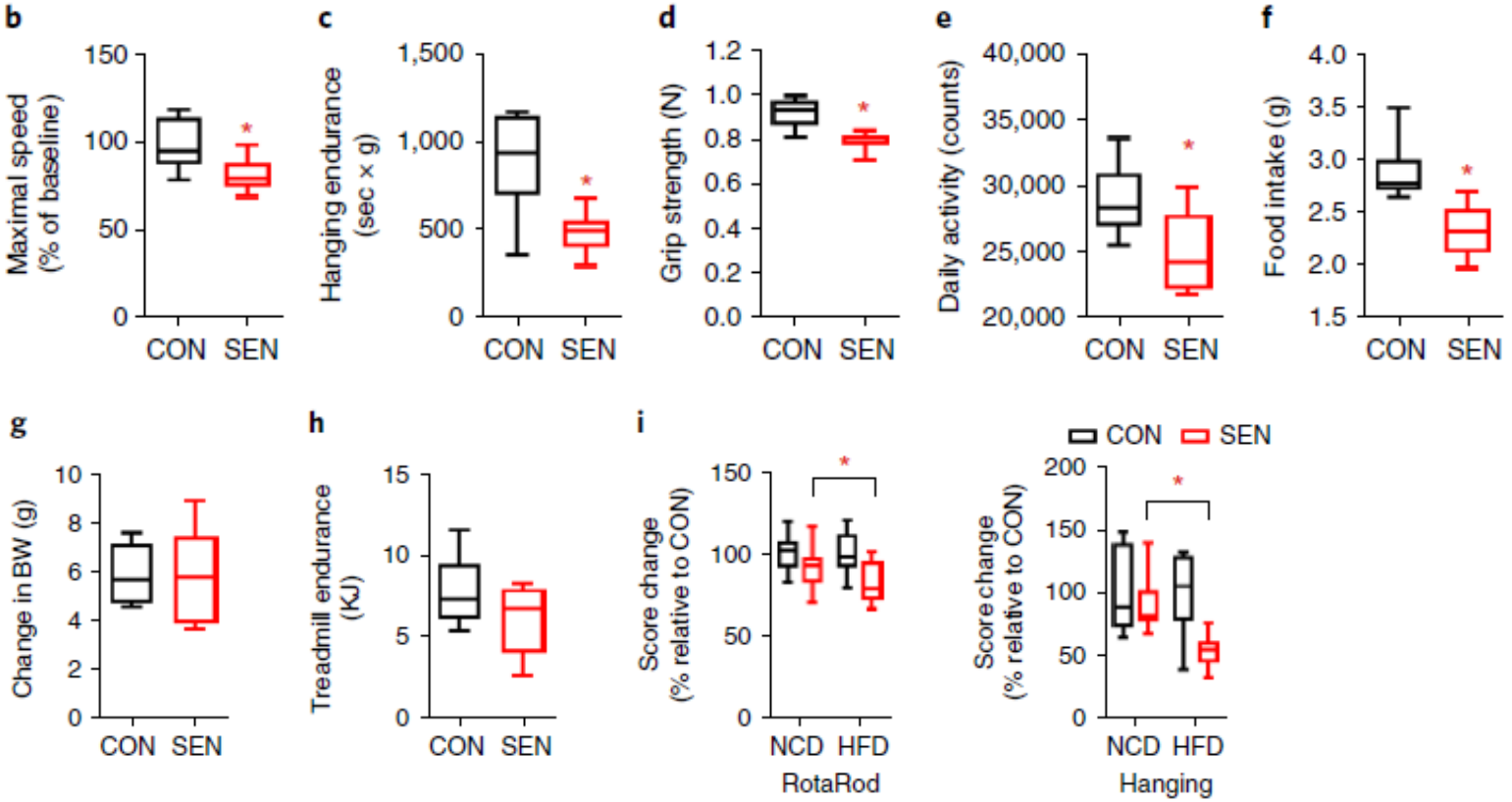
- Treadmill performance
- Body weight



Physical dysfunction did not arise principally as a consequence of transplant immune rejection

Transplantation of senescent cells

- Same transplantation procedure
- Mice received autologous ear fibroblasts
  - Senescence induction: 10Gy radiation

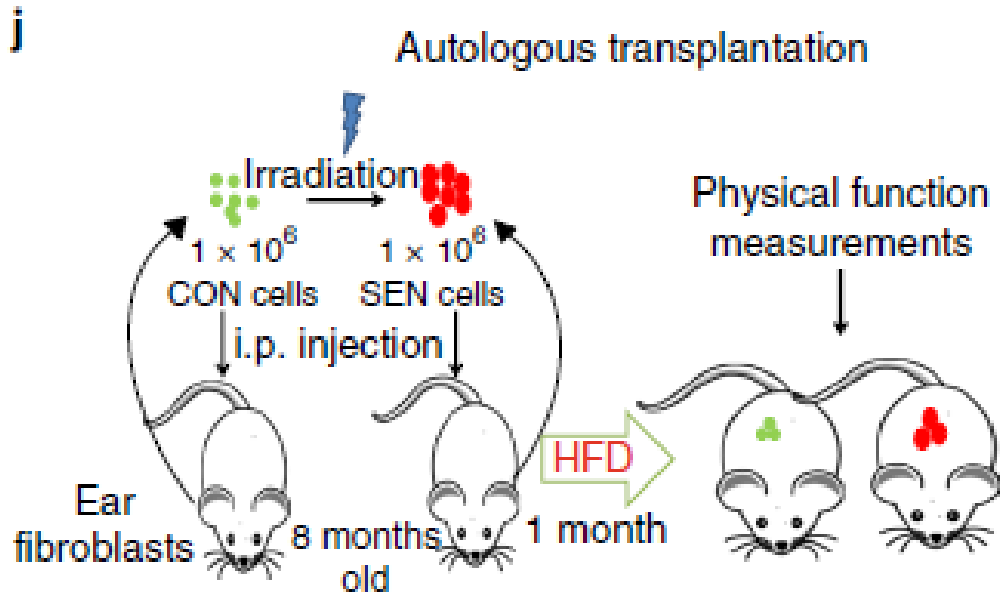


Fig. 3: Physical dysfunction did not arise principally as a consequence of transplant immune rejection

- Max. walking speed
- Hanging endurance
- Grip strength

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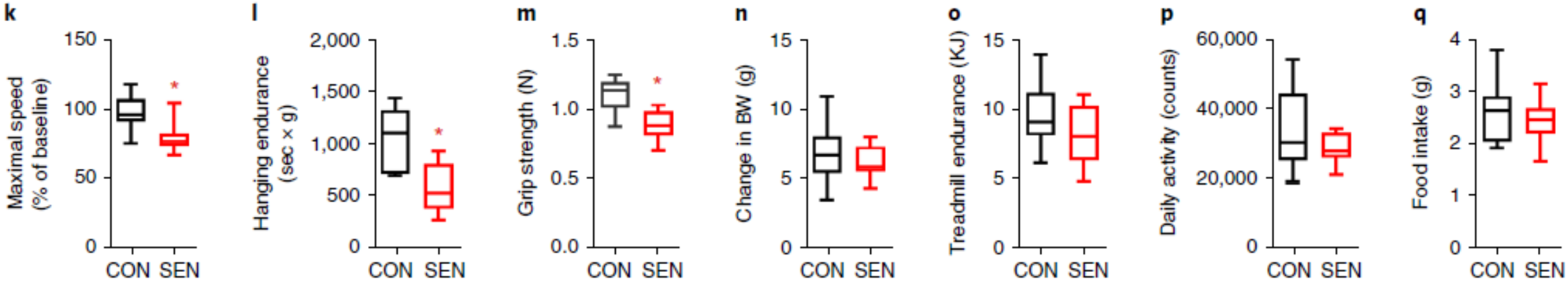
- Daily activity
- Treadmill performance
- Food intake
- Body weight

Similar results as seen after transplanting nonautologous senescent preadipocytes



Dasatinib plus quercetin reduces senescent cell burden and decreases proinflammatory cytokine secretion in human adipose tissue

Transplantation of senescent cells

- Freshly isolated human omental adipose tissue
- Surgically excised explants treated with combination of Dasatinib (D) + Quercetin (Q) (or vehicle) for 48h

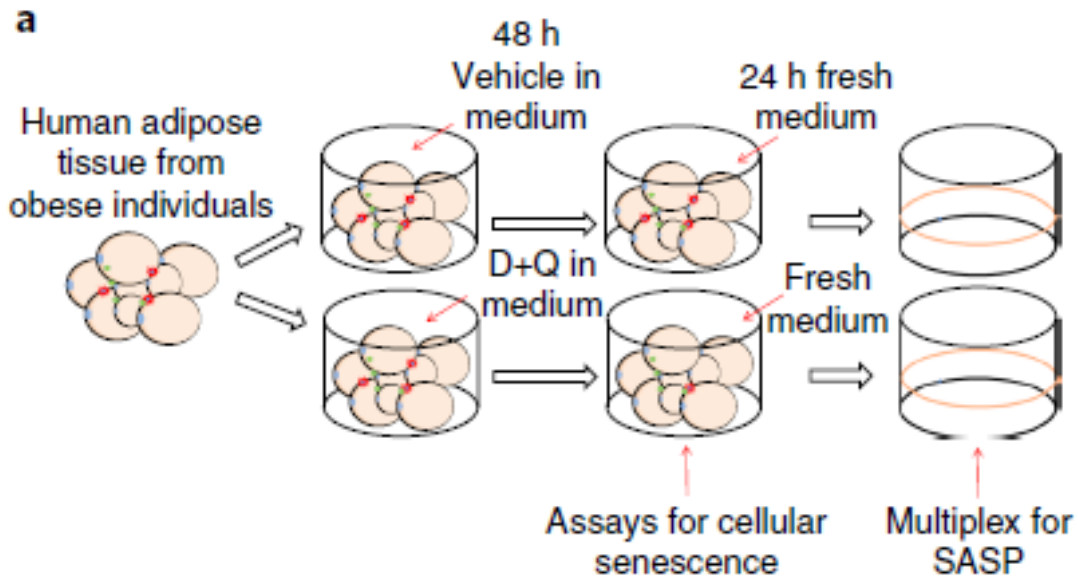


Fig. 4: D + Q reduces senescent cell abundance and decreases proinflammatory cytokine secretion in human adipose tissue

- TAF+
- p16Ink1a
- SA-bgal

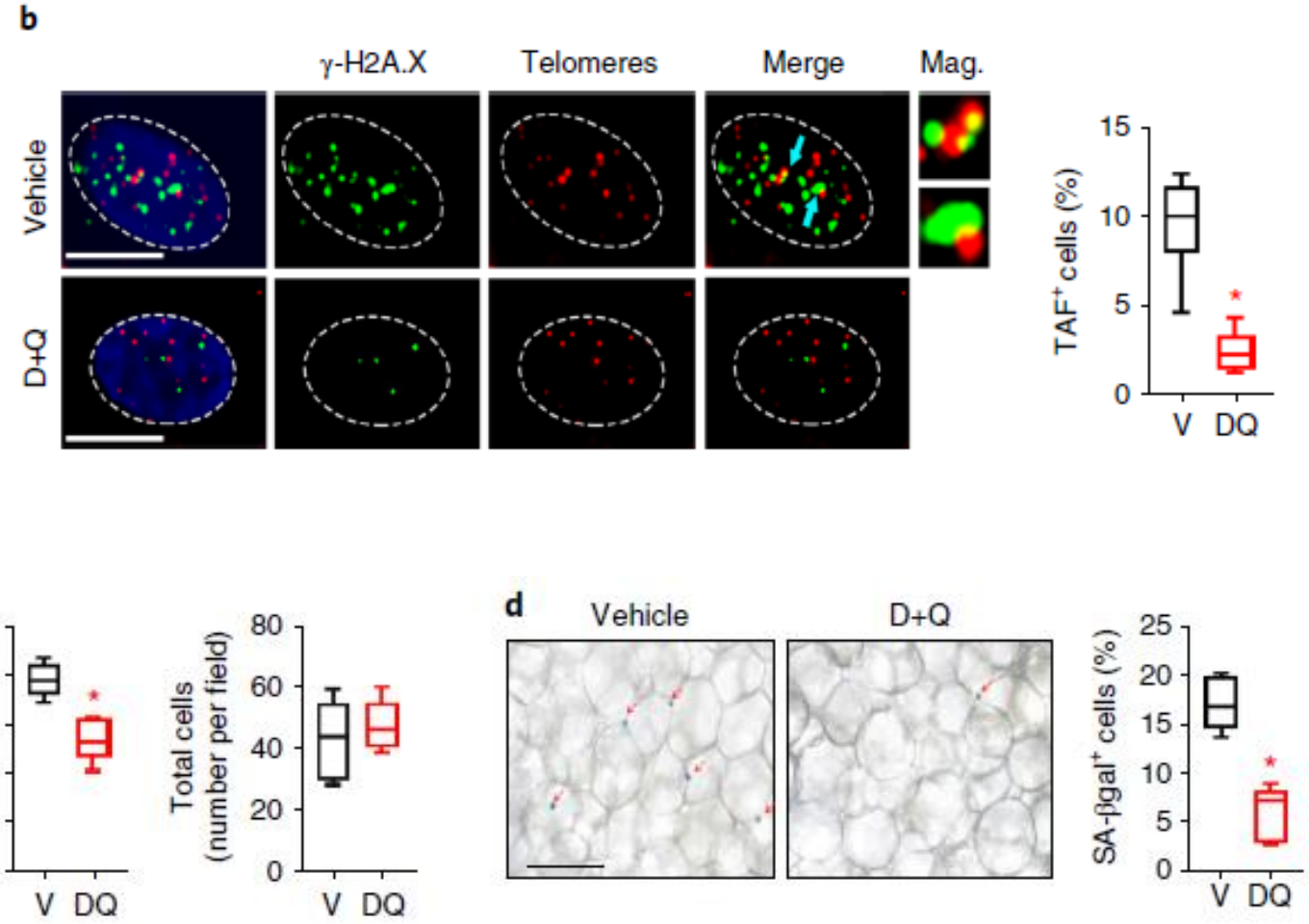


Fig. 4: D + Q reduces senescent cell abundance and decreases proinflammatory cytokine secretion in human adipose tissue

- Cells undergoing apoptosis

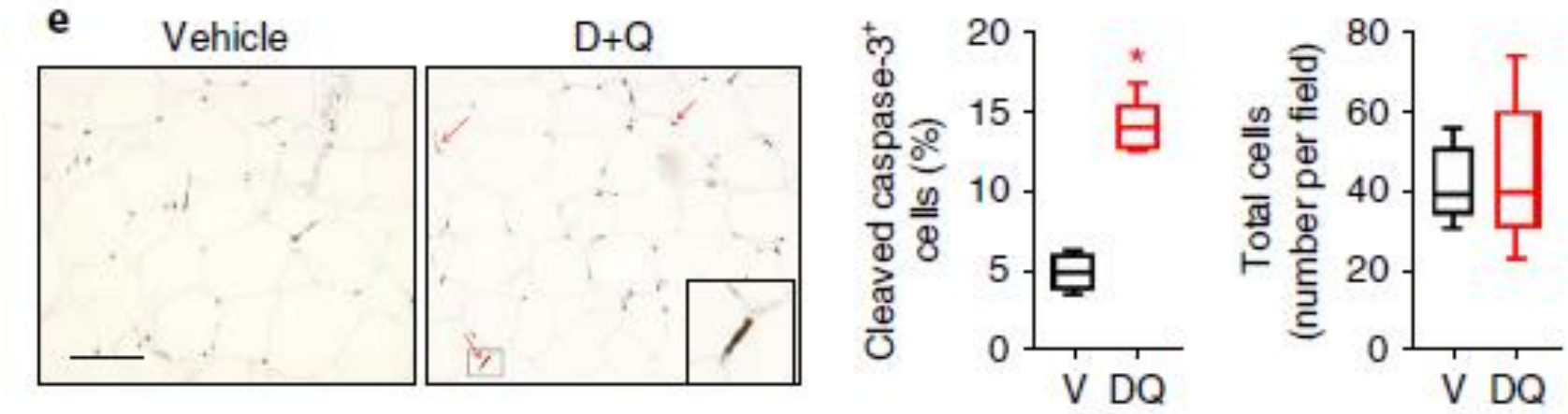


Fig. 4: D + Q reduces senescent cell abundance and decreases proinflammatory cytokine secretion in human adipose tissue

- Less secretion of key SASP components

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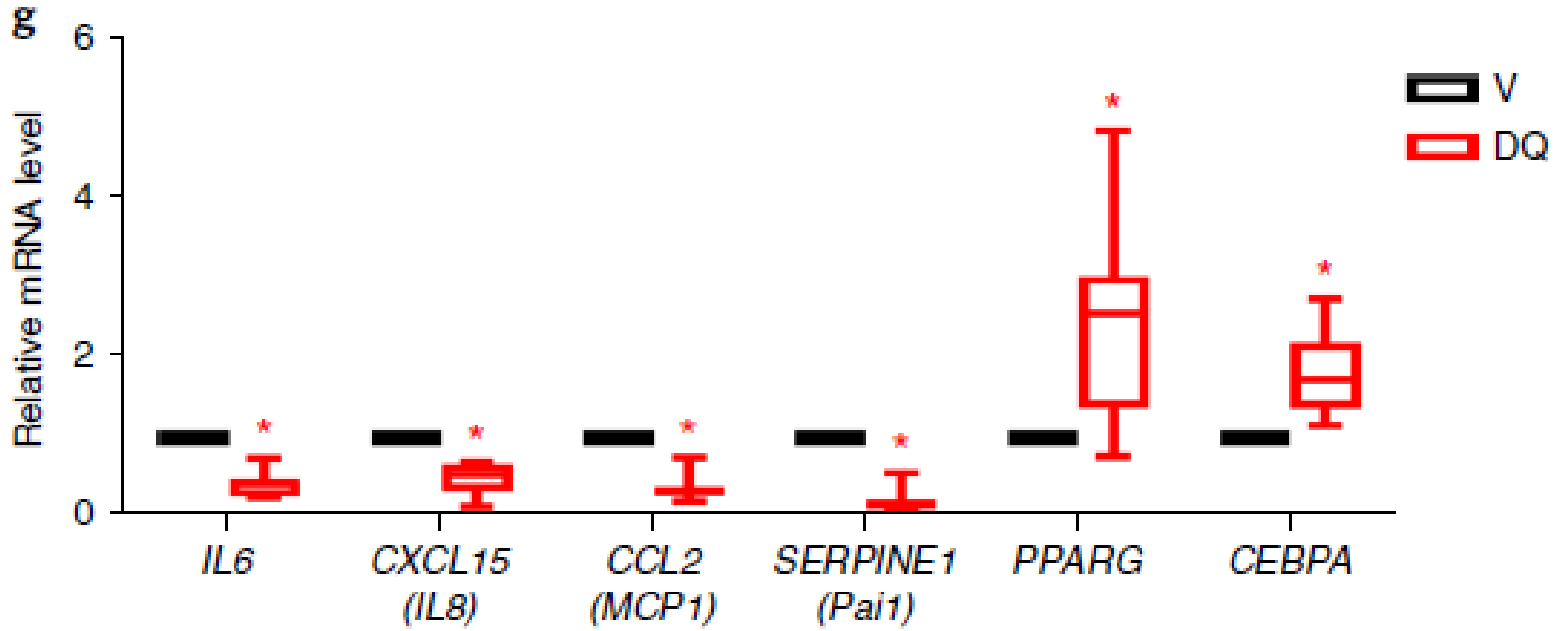
Secreted protein in CM

Protein (pg/mg tissue)	Vehicle	D+Q	*P* (paired)
IL-6	60 ± 14.7	11.6 ± 4.4	0.007
IL-8	220.8 ± 46.2	48 ± 13	0.006
MCP-1	180.2 ± 46.3	32.3 ± 9	0.015
PAI-1	22.8 ± 6.5	6.9 ± 2.5	0.008
GM–CSF	0.2 ± 0.03	0.1 ± 0.01	0.011
IL-10	0.26 ± 0.1	0.43 ± 0.26	0.364
IFN-γ	0.08 ± 0.01	0.06 ± 0.01	0.157
Adiponectin	255.7 ± 23.3	327.6 ± 50.8	0.088
Adipsin	303.5 ± 83.6	530.4 ± 244.3	0.234

Fig. 4: D + Q reduces senescent cell abundance and decreases proinflammatory cytokine secretion in human adipose tissue

- Peroxisome proliferator-activated receptor γ
- CEBPα



Eliminating senescent cells both prevents and alleviates physical dysfunction induced by senescent cell transplantation

Transplantation of senescent cells

- LUC+ SEN preadipocytes
- Recipient mice LUC- WT mice
- Immediate treatment with D+Q for 3 days

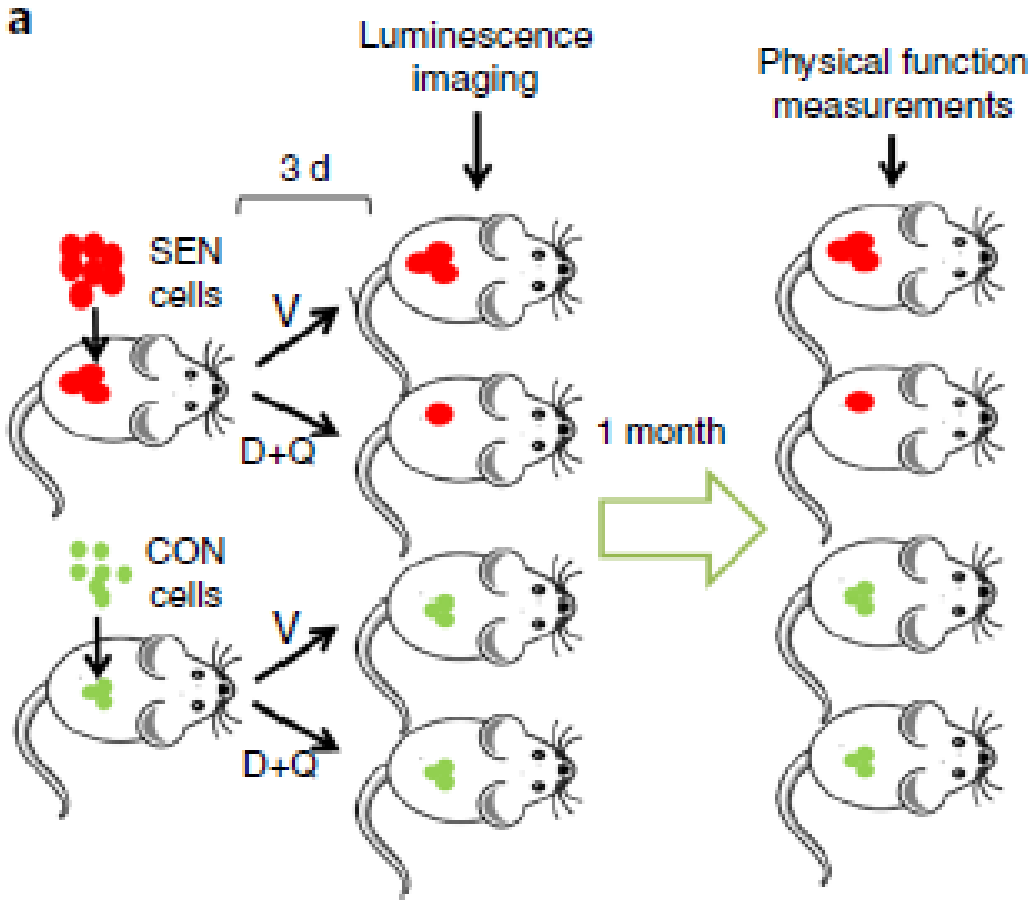


Fig. 5: Eliminating senescent cells both prevents and alleviates physical dysfunction

- Luciferase in senescent cell transplanted mice treated with D+Q

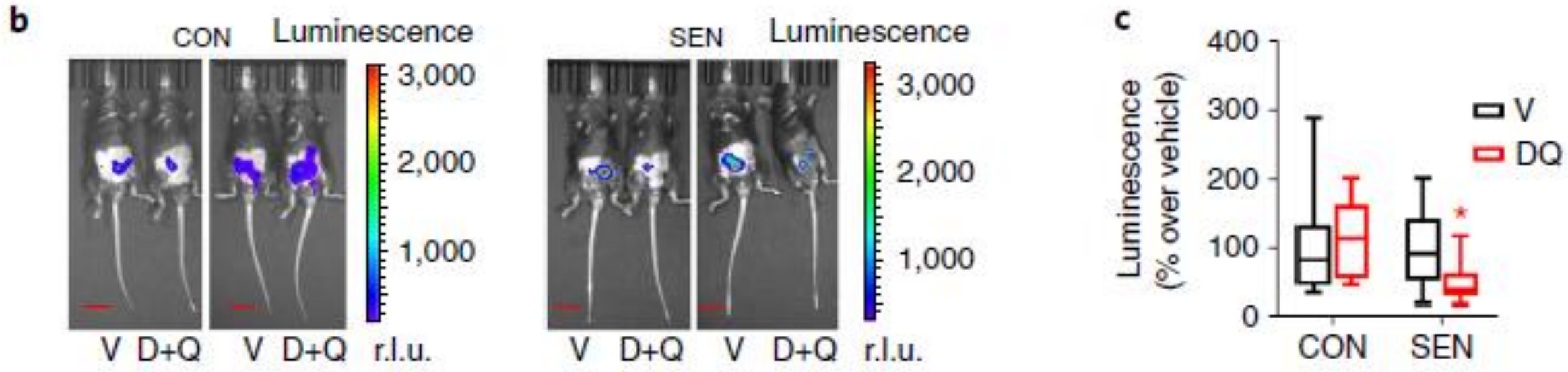


Fig. 5: Eliminating senescent cells both prevents and alleviates physical dysfunction

- D+Q treatment attenuated deteriorations in walking speed, hanging endurance, grip strength (which occurred 1 month later in vehicle treated SEN transplanted mice)

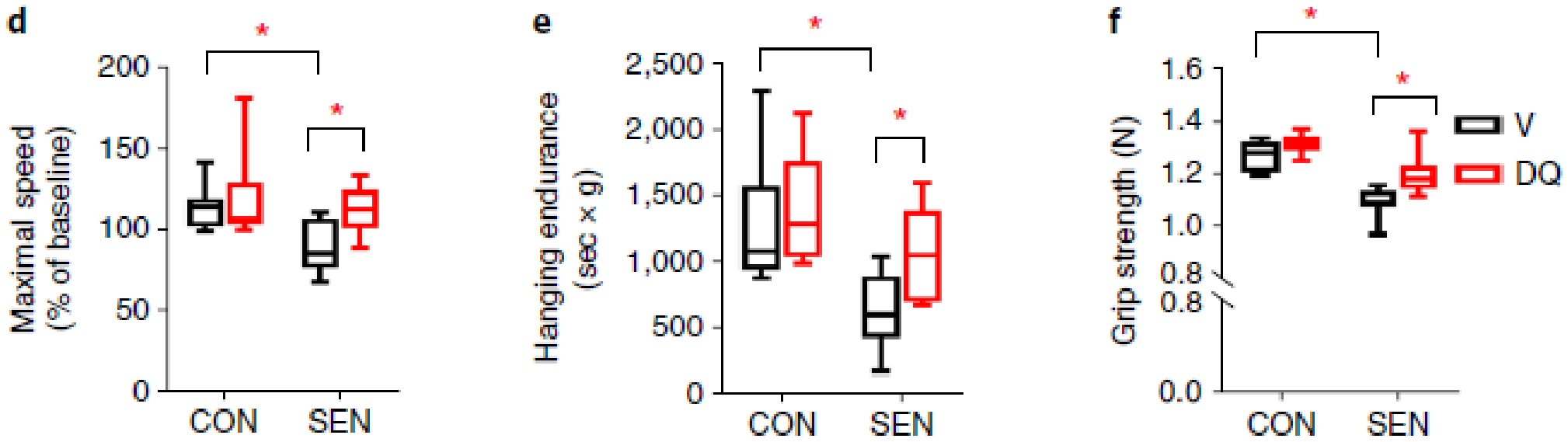
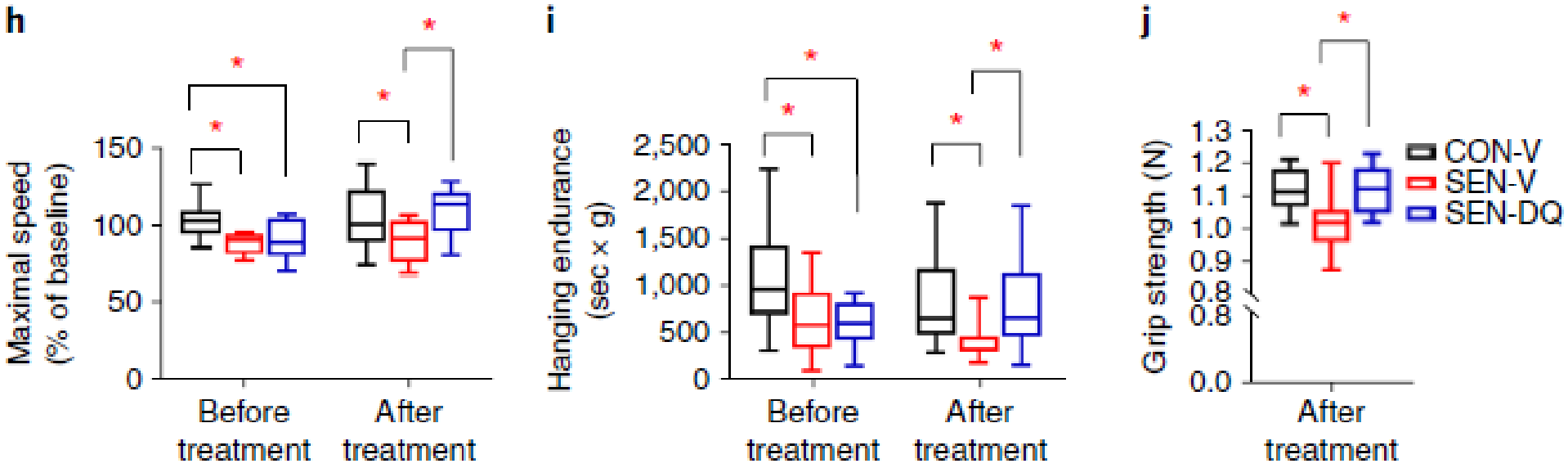


Fig. 5: Eliminating senescent cells both prevents and alleviates physical dysfunction

- A single 5 day course of D+Q treatment improved physical function
- Improvement was evident 2 weeks after treatment & lasted for several months



Clearance of senescent cells alleviates physical dysfunction and increases late-life survival without extending morbidity in aged mice

Fig. 6: Senolytics extend both health- and lifespan in aged mice

- D+Q treatment alleviated physical dysfunction

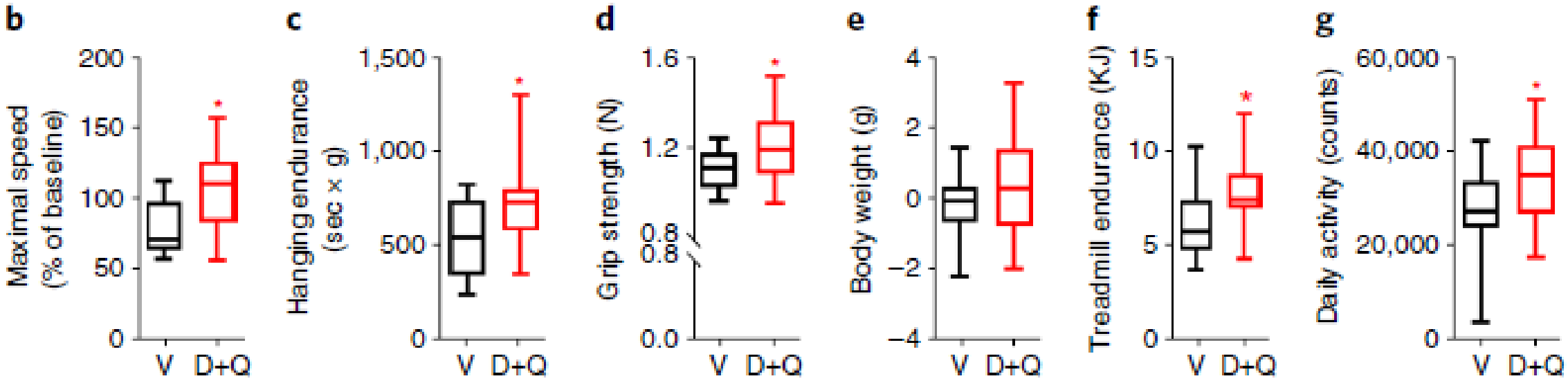


Fig. 6: Senolytics extend both health- and lifespan in aged mice

- Expression of several key SASP components was lower in the visceral adipose tissue from aged mice treated with D+Q

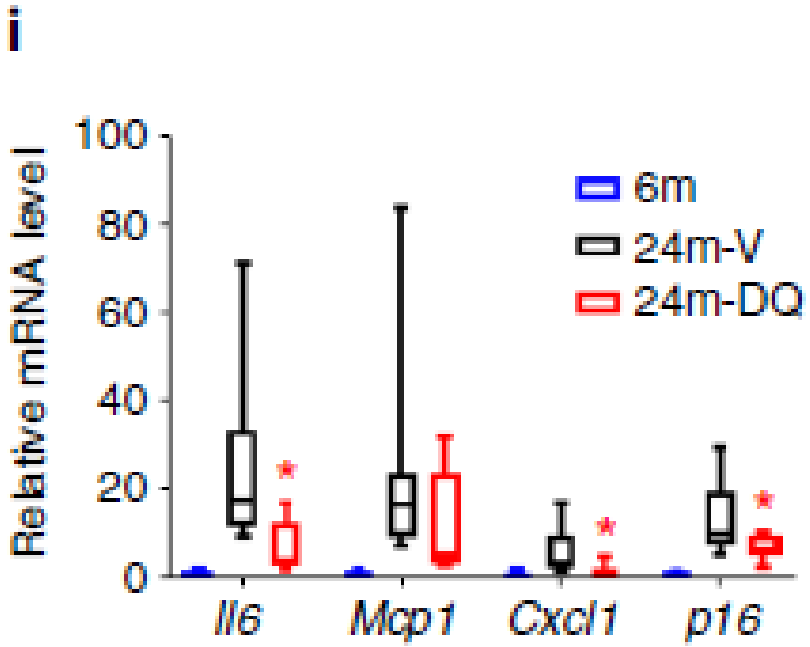
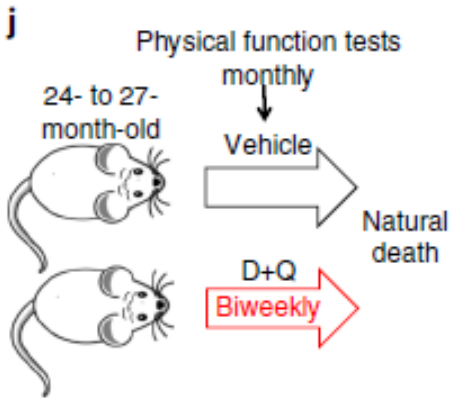
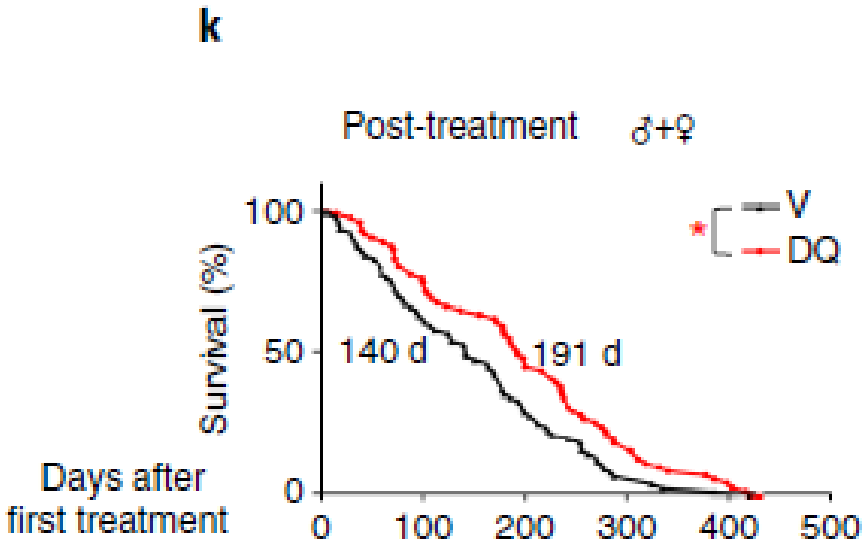


Fig. 6: Senolytics extend both health- and lifespan in aged mice

- Biweekly administration of D+Q yielded 36% higher median post-treatment lifespan and lower mortality hazard





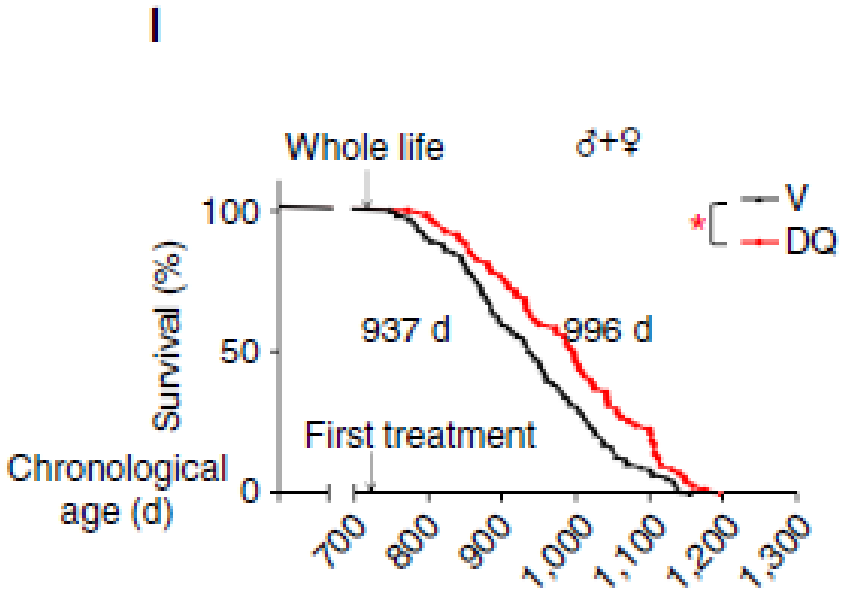


Fig. 6: Senolytics extend both health- and lifespan in aged mice

- Physical function in the last 2 months of life was not lower than that of vehicle-treated mice

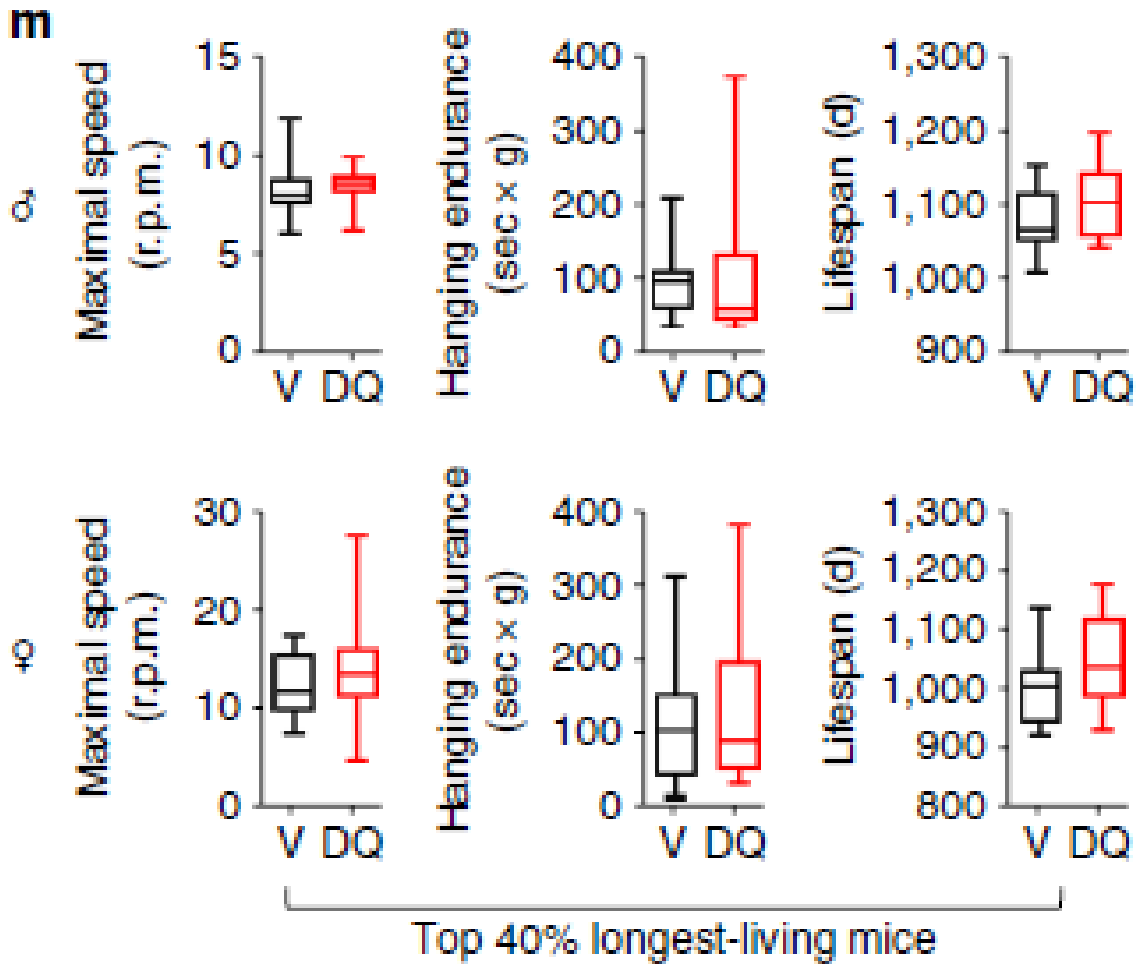


Fig. 6: Senolytics extend both health- and lifespan in aged mice

- At autopsy: prevalence of several age-related diseases, tumour burden, and cause of death were not statistically different between D+Q treatment and vehicle treatment group