



Growth Differentiation Factor 11 Is a Circulating Factor that Reverses Age-Related Cardiac Hypertrophy

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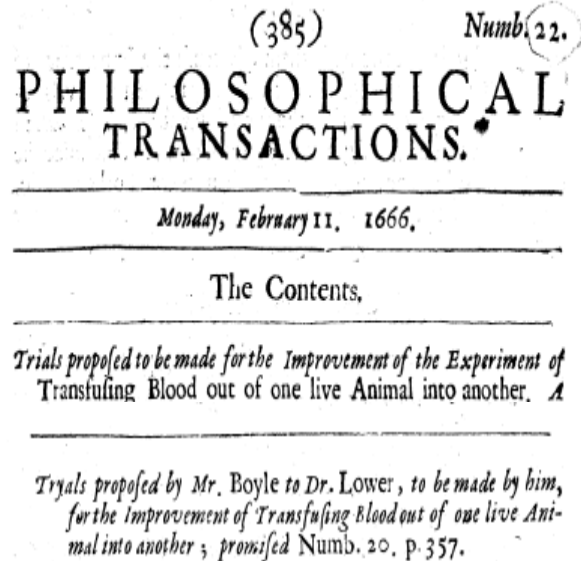
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<http://dx.doi.org/10.1016/j.cell.2013.04.015>

Young Blood has Good Stuff: this concept is also not really that new...



The Queries themselves follow.

1. Whether by this way of Transfusing Blood, the disposition of Individual Animals of the same kind, may not be much altered? (As whether a *fierce* Dog, by being often quite new stocked with the blood of a *cowardly* Dog, may not become more tame; & *vice versa*, &c?)
9. What will be the Operation of frequently stocking (which is feasible enough) an *old* and feeble Dog with the blood of *young* ones, as to liveliness, dulness, drowsiness, squeamishness, &c. *et vice versa*?

Philosophical Transactions started in 1665 and may be the first and longest running science journal.

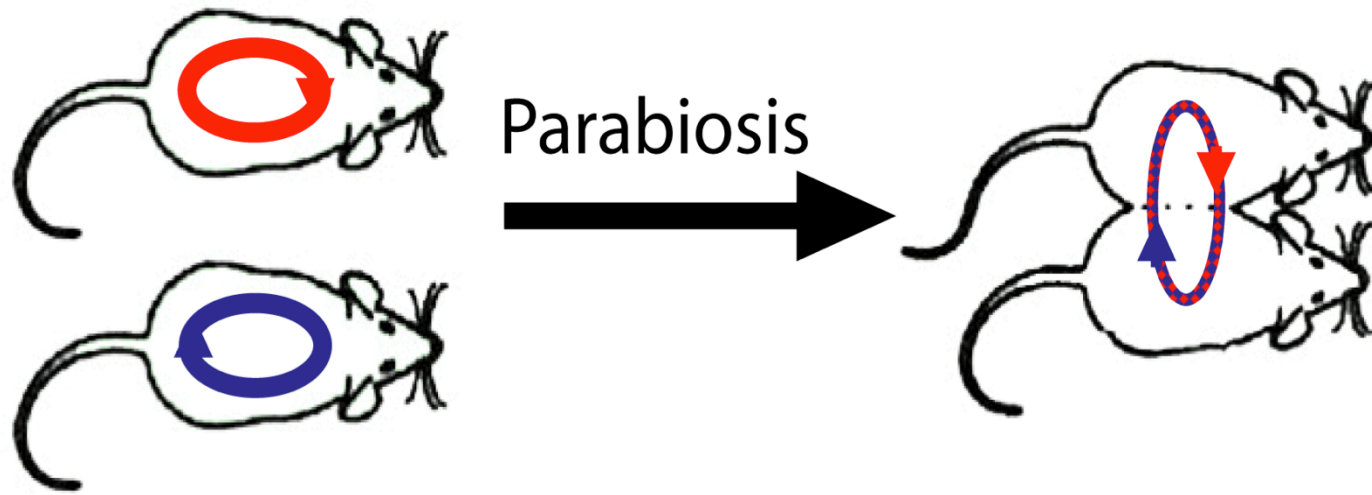
Blood and Rejuvenation



In 1492, Pope Innocent VIII was possibly asked to drink the blood of three young boys to restore his youthful vigor.

“The Story of a Blood Transfusion of a Pope”
Lindeboom GA, Journal of the History of Medicine, 1954

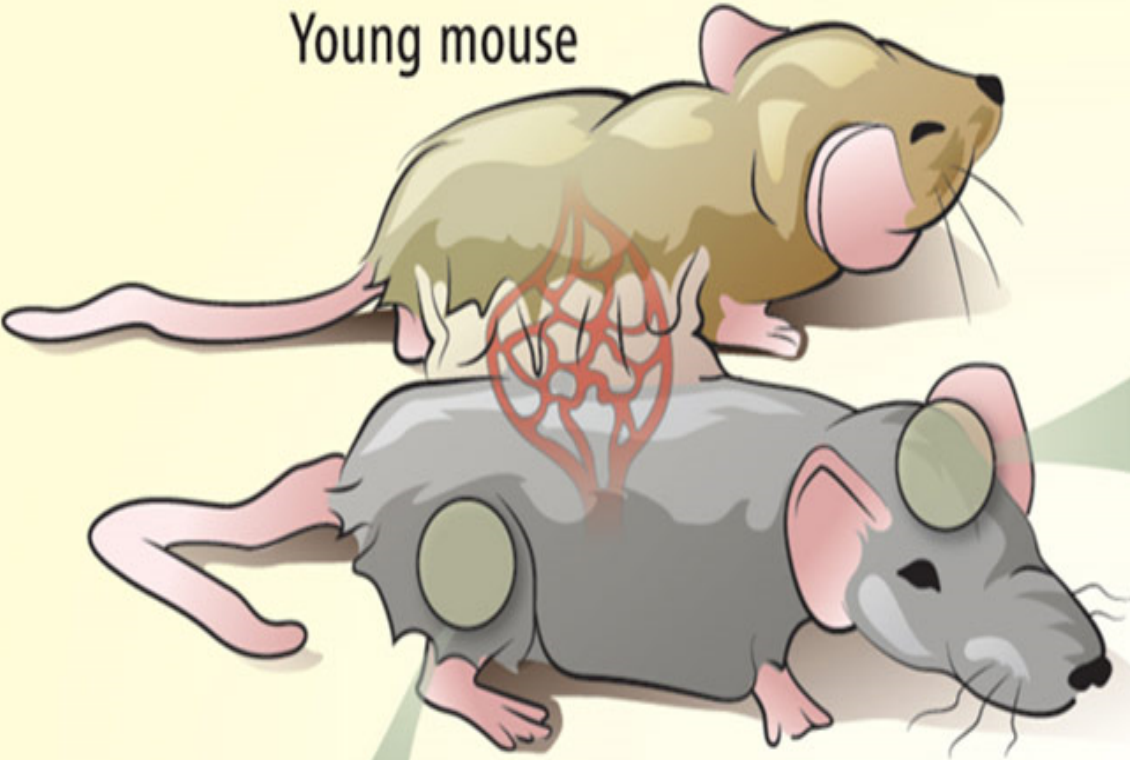
Approach: Parabiosis is the surgical act of artificially creating conjoined twins of two organisms.



- Cross-circulation is established 2-3 days after joining.
- Blood chimerism reaches ~50% by 7-10 days.
- Rapid exchange (~1%/min.) of cells and factors across the vascular junction.

PARABIOSI

Young mouse



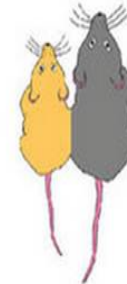
Old mouse



Young-young
(Isochronic)



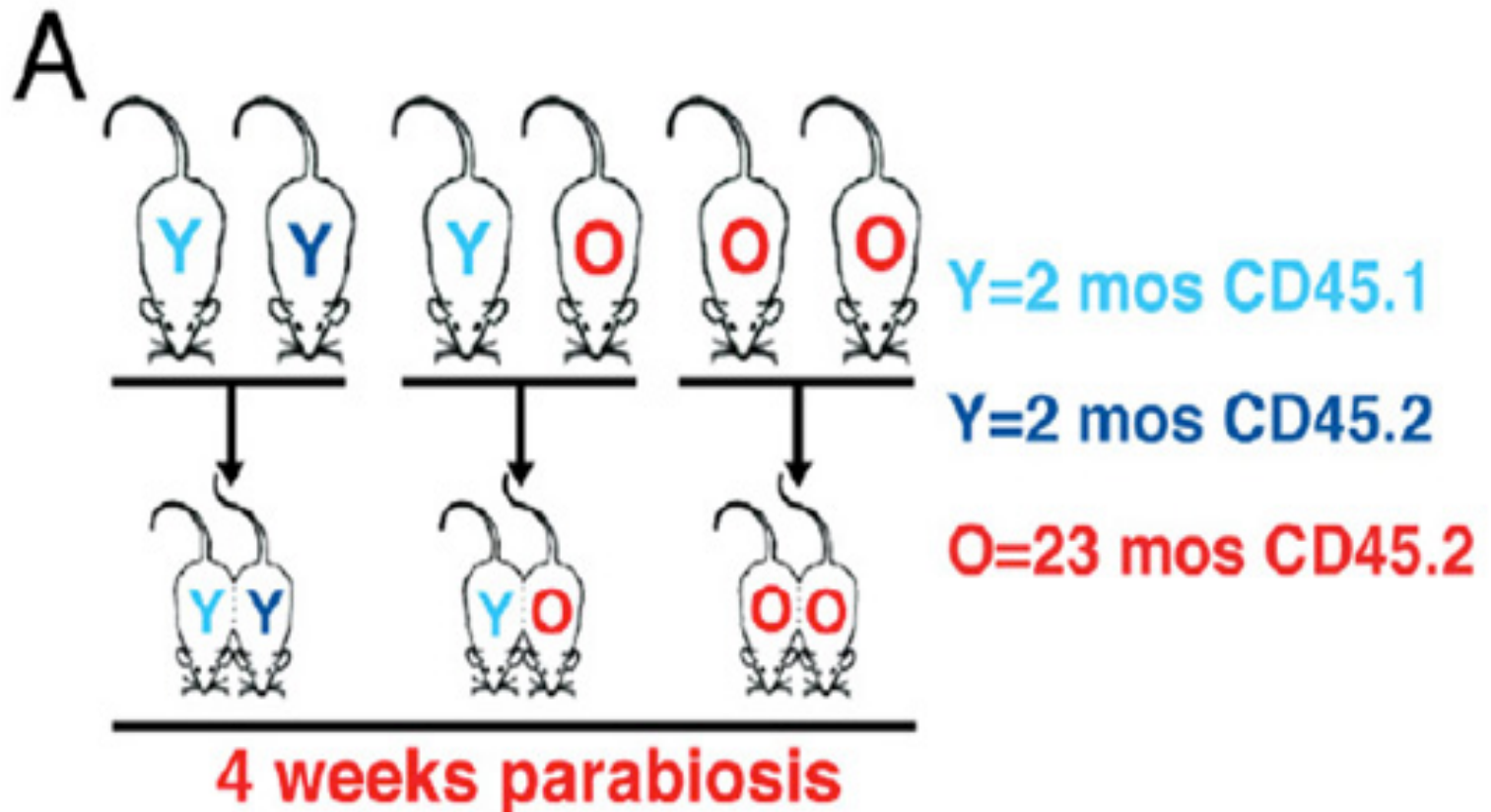
Young-old
(Heterochronic)



Old-old
(Isochronic)



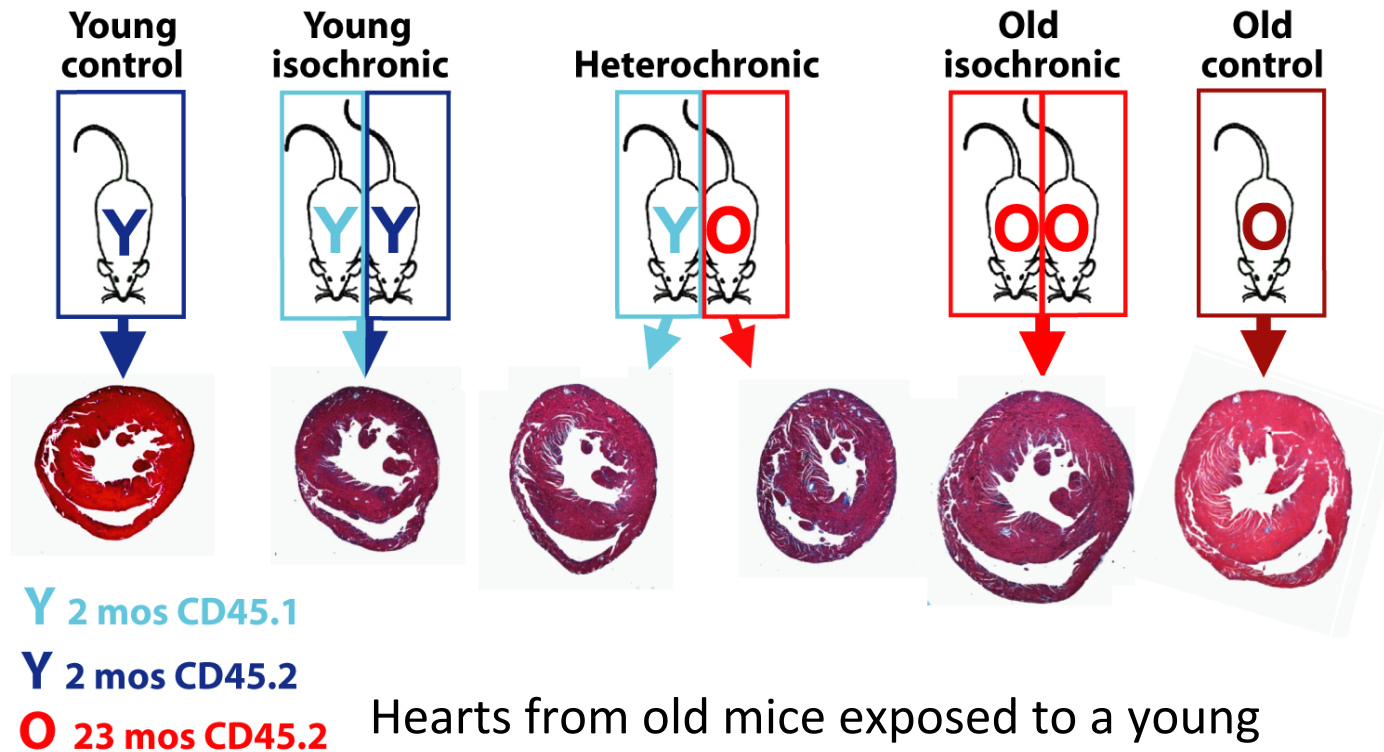
PARABIOSI



Vengono generate coppie isocroniche di topi giovani, anziani e coppie eterocroniche.

Dopo quattro settimane, i topi vengono sacrificati e i tessuti utilizzati per le analisi.

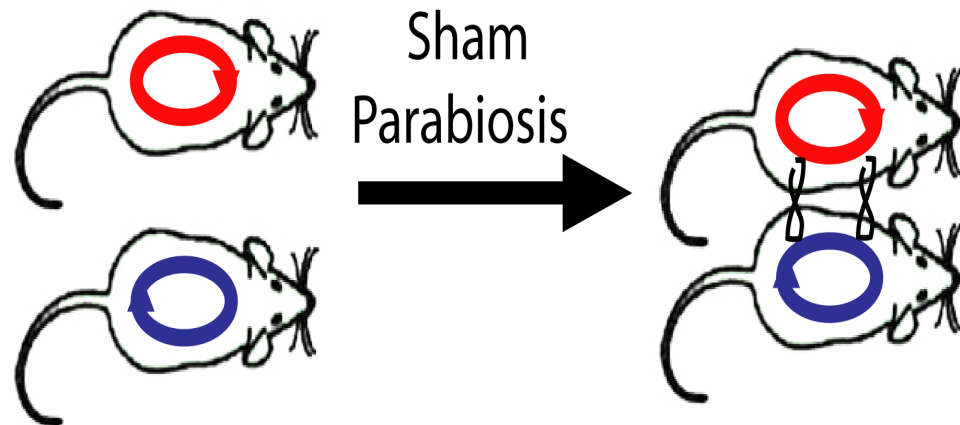
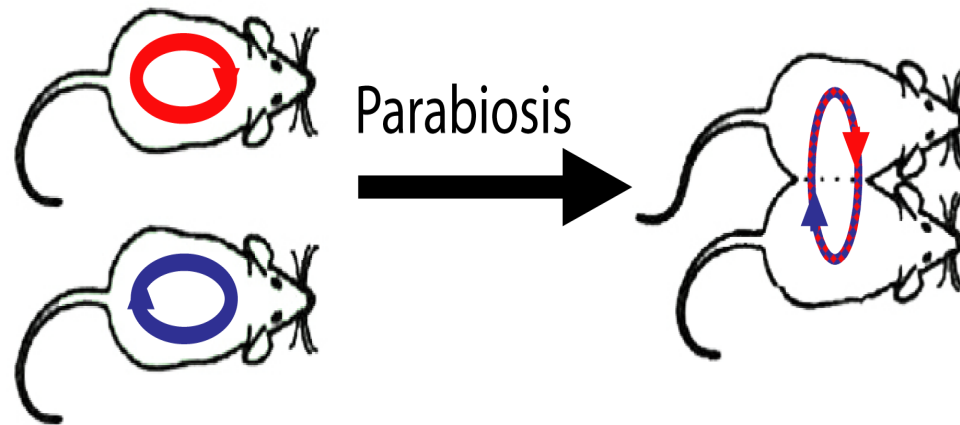
Exposure to a young circulatory system reduces gross cardiac size in aged mice



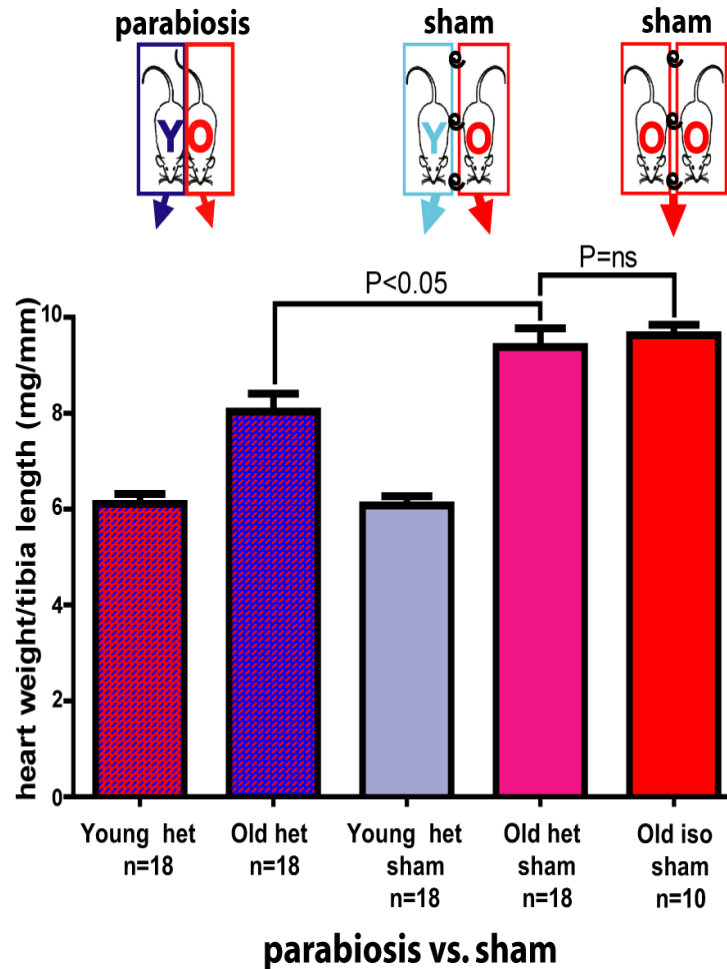
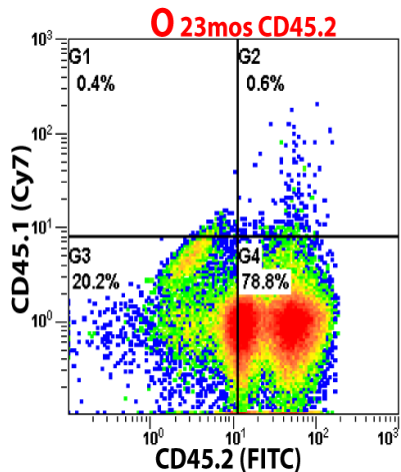
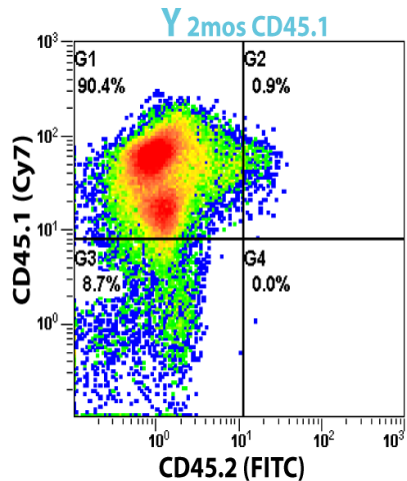
Hearts from old mice exposed to a young circulation for 4 wks were noticeably smaller than hearts from isochronic old mice

The study was conducted in a randomized and blinded fashion.

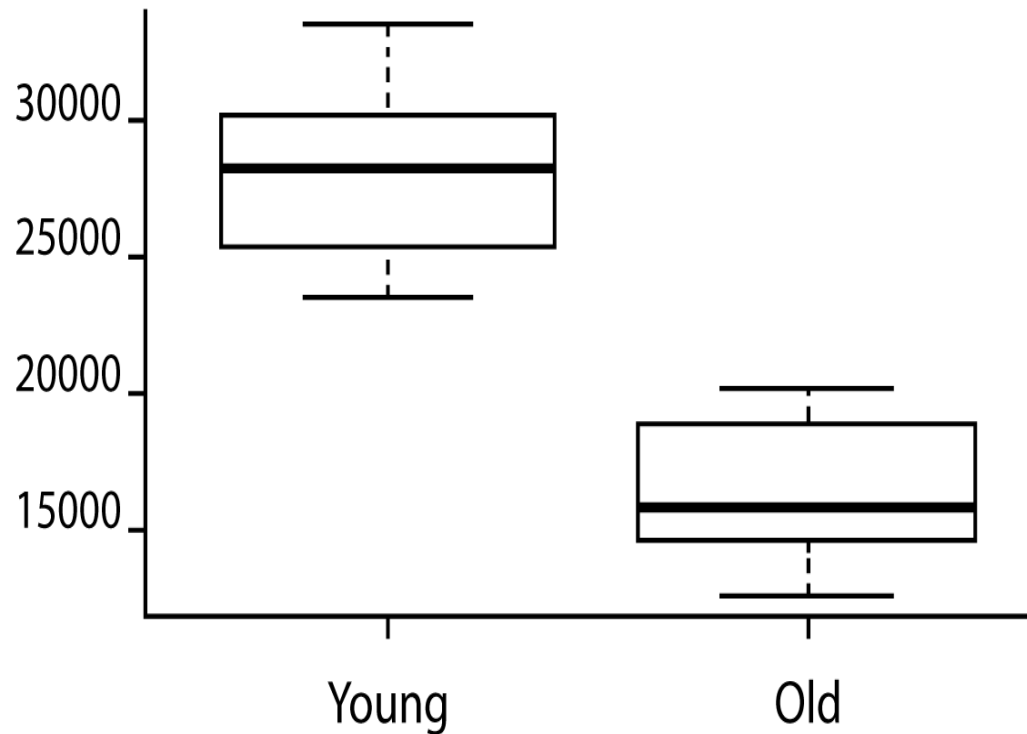
In sham parabiosis, mice are joined by suturing olecranon and knees; there is no contact between internal flaps of the incised skin.



Sham parabiosis does not reverse cardiac hypertrophy in aging mice.



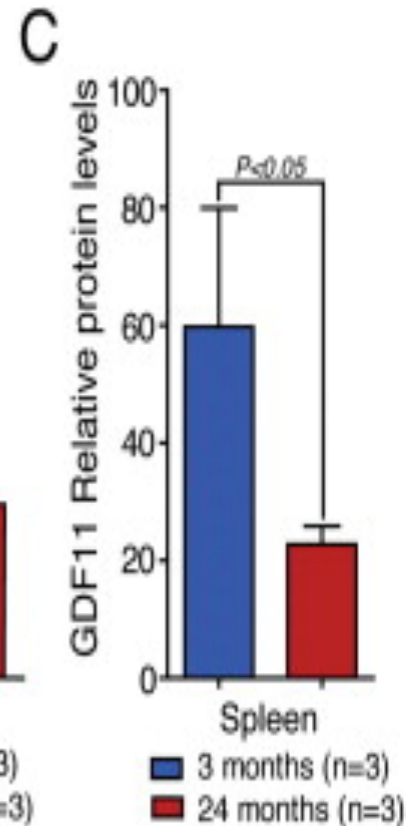
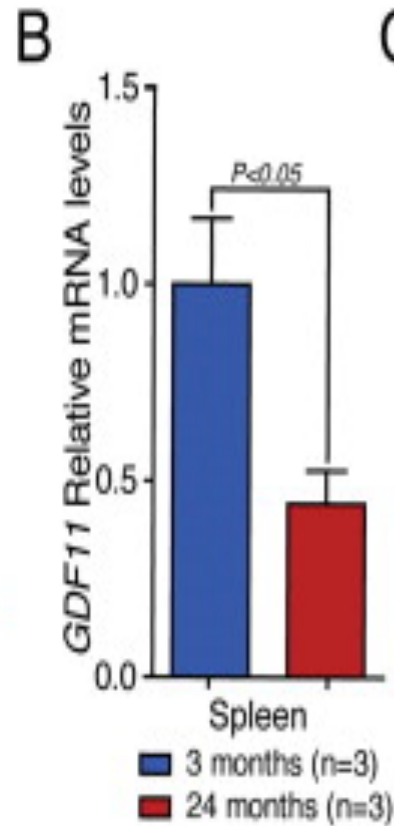
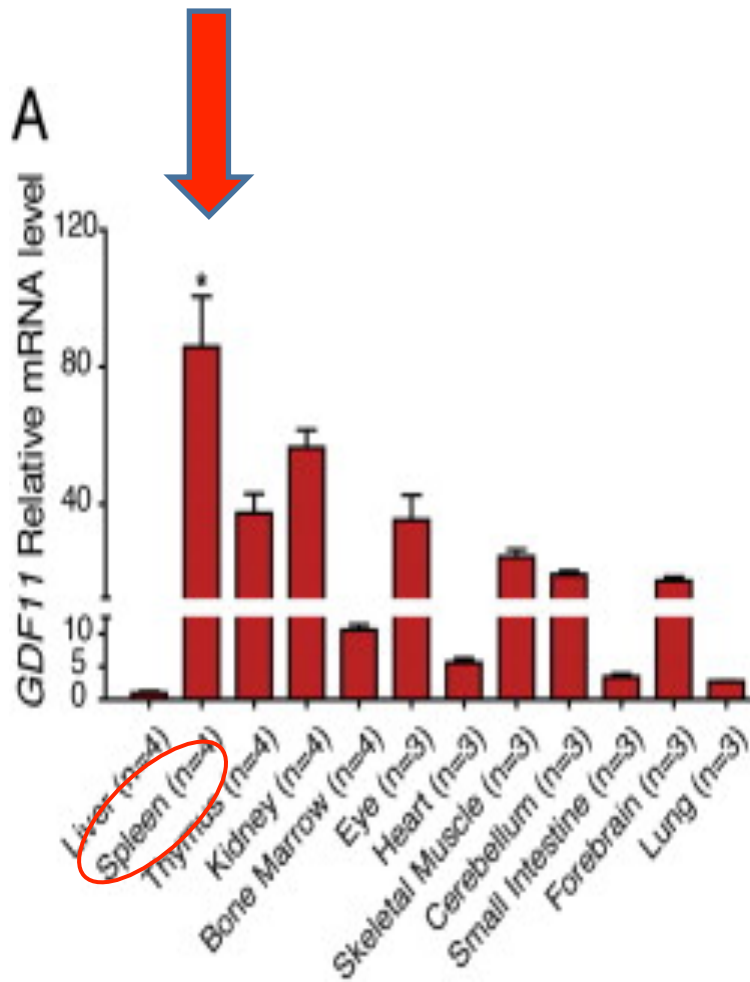
Aptamer based proteomic analysis shows reduced plasmatic levels of Growth differentiation factor 11 (GDF11) in aging mice



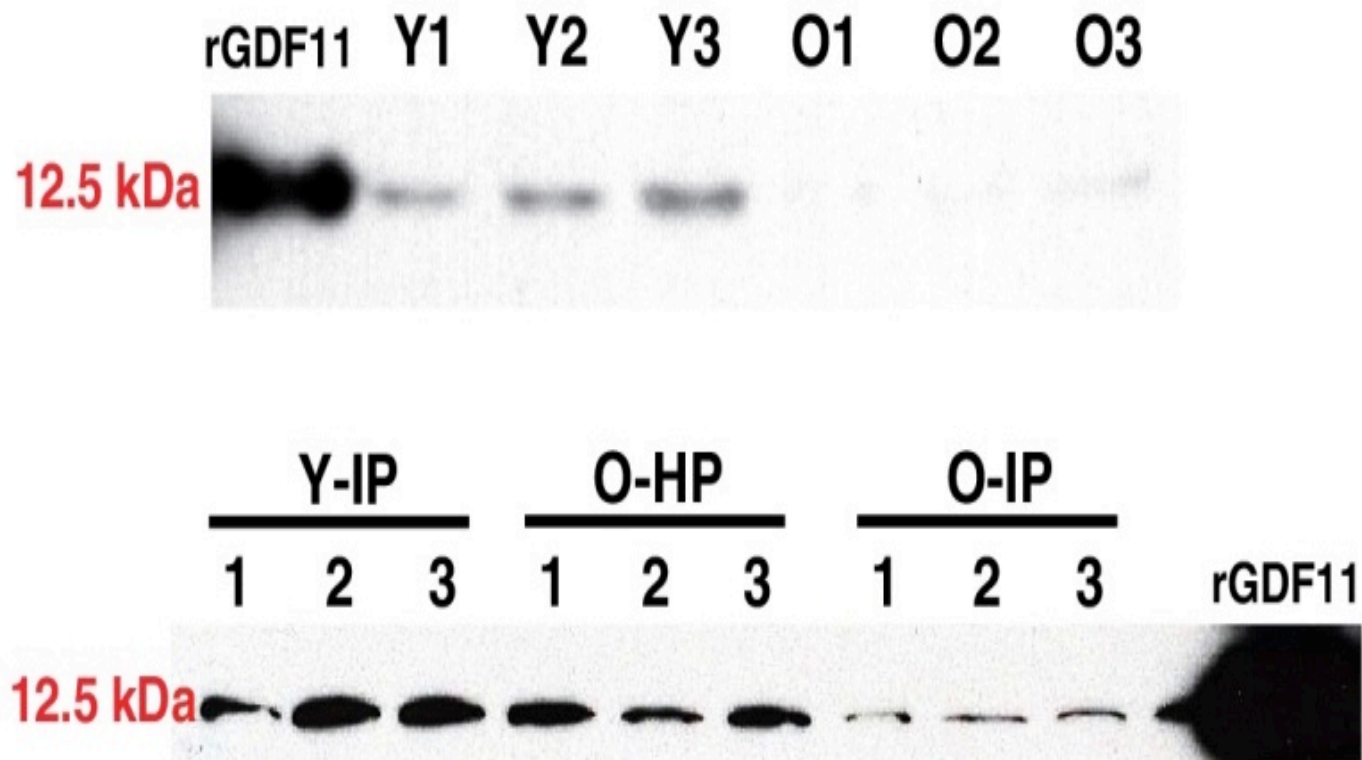
GDF11 controls anterior-posterior patterning during mouse development

- GDF11 also known as bone morphogenetic protein 11 (BMP-11) is a protein that belongs to the transforming growth factor beta superfamily and controls anterior-posterior patterning.
- It is involved in neurogenesis in the spinal cord and olfactory bulb. GDF11 also regulates kidney development and endocrine pancreas development.
- The mature form of GDF11 (12.5 kDa) can bind type I TGF-beta superfamily receptors ACVR1B (ALK4), TGFBR1 (ALK5) and ACVR1C (ALK7), but predominantly uses ALK4 and ALK5 for signal transduction

LIVELLI GDF11

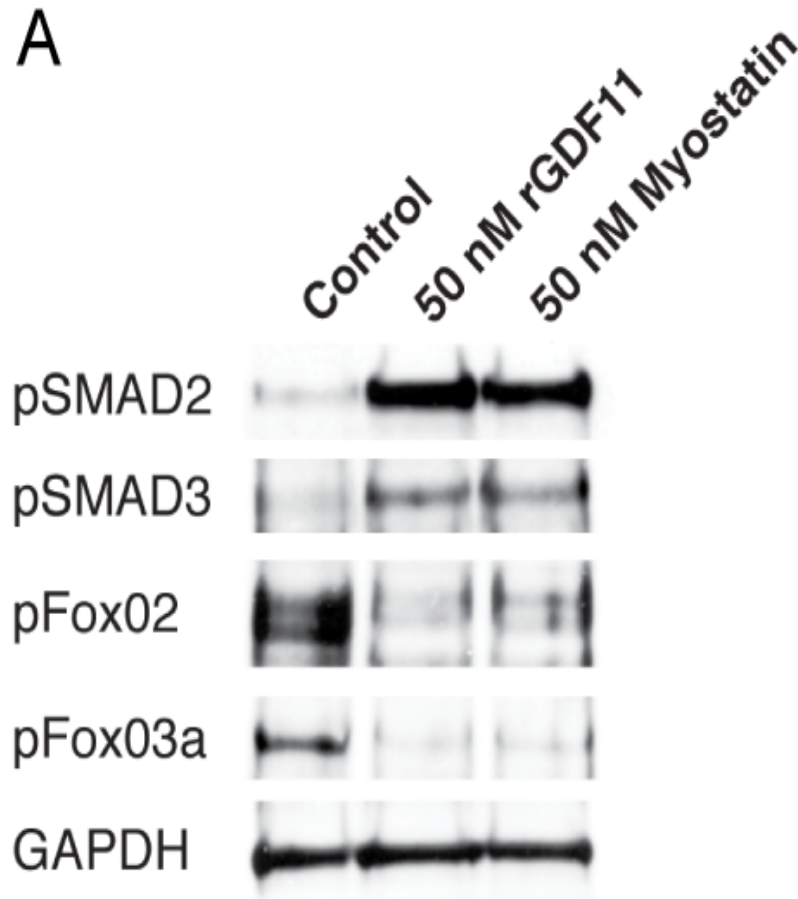


GDF11 is reduced in the circulation of aged mice and “youthful” levels are restored by heterochronic parabiosis.

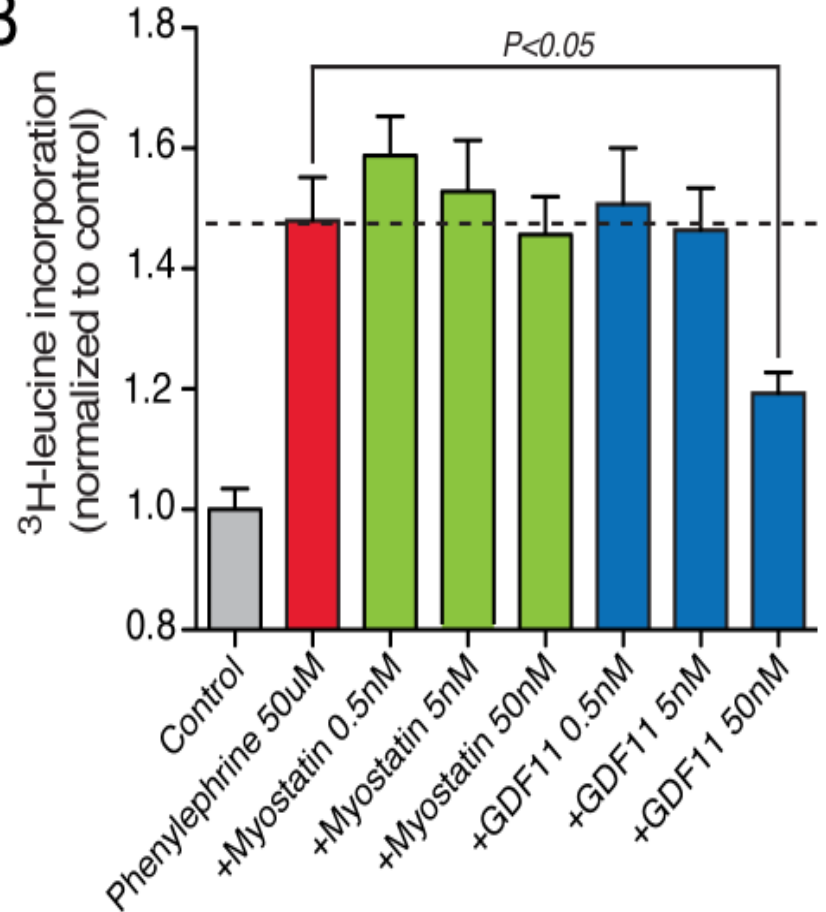


GDF11 stimulate TGF β signaling pathways including anti-hypertrophic FoxO factors

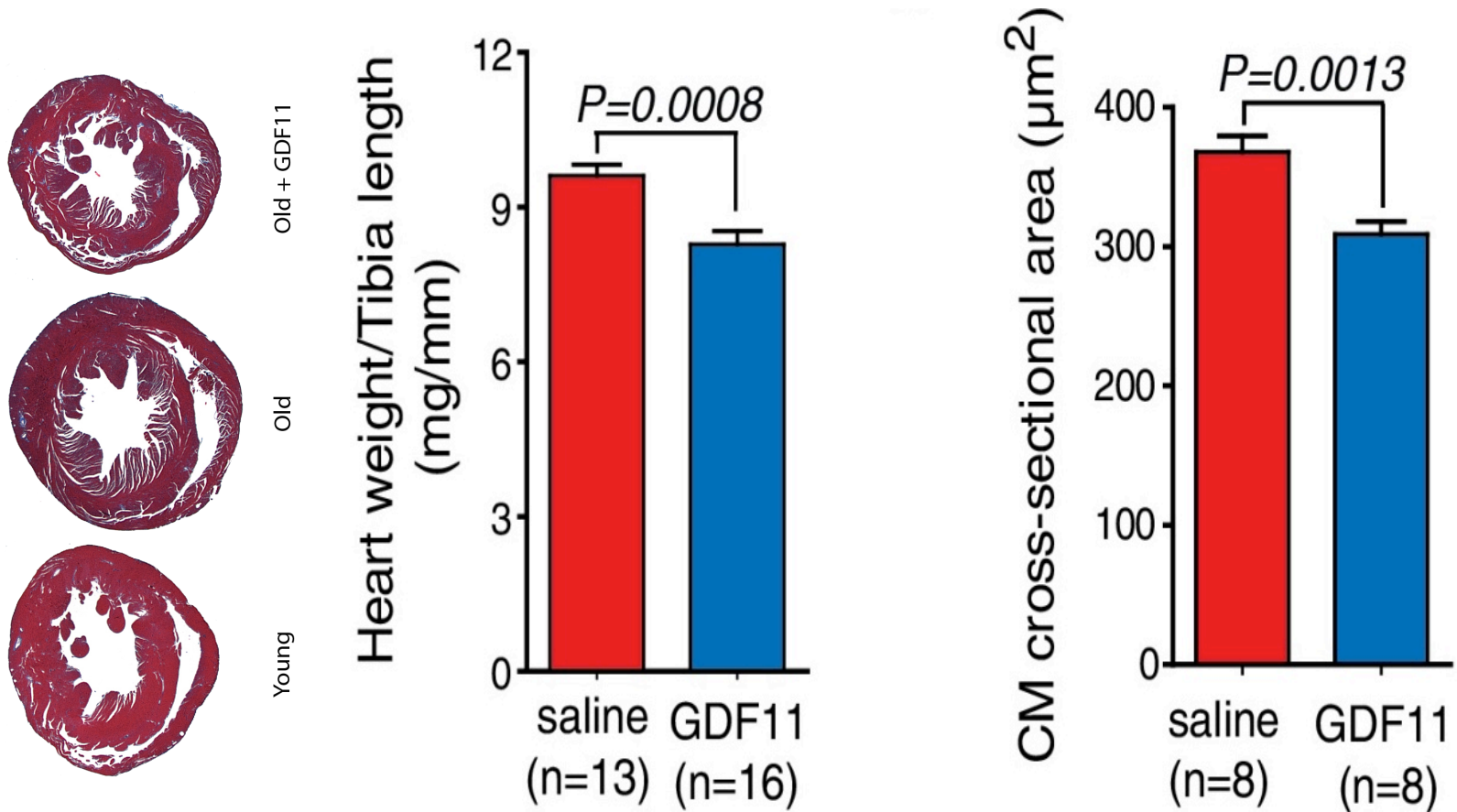
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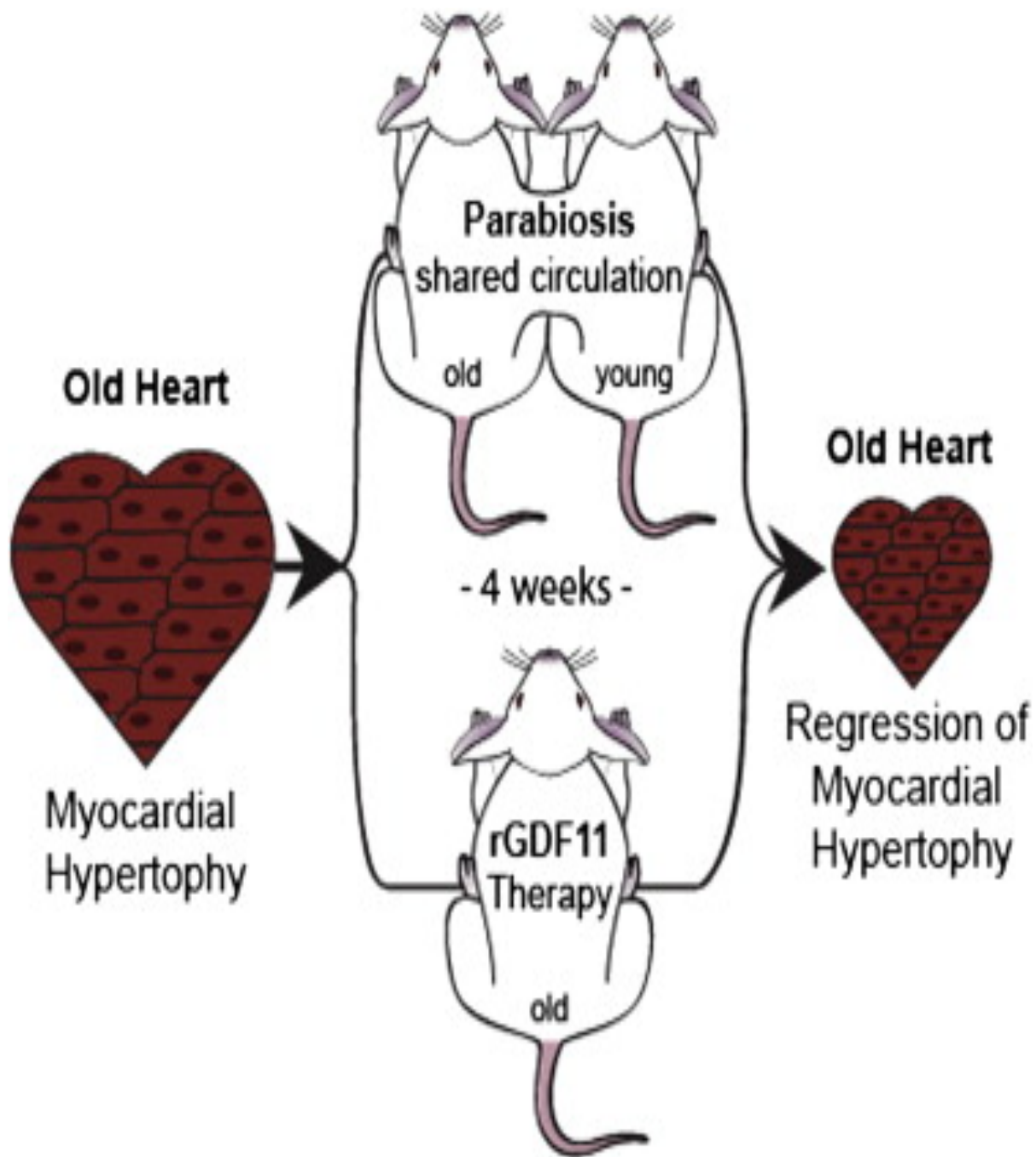


B



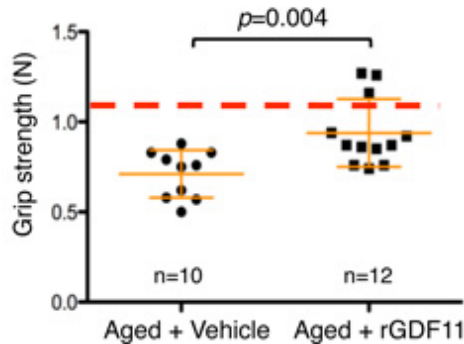
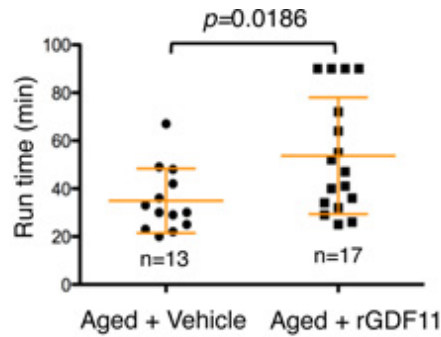
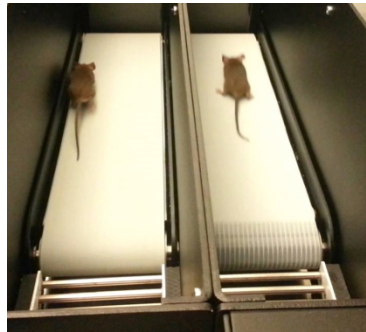
When GDF11 levels of aged mice are restored to “youthful” levels, the hypertrophy of cardiac aging is reversed in 4 weeks.





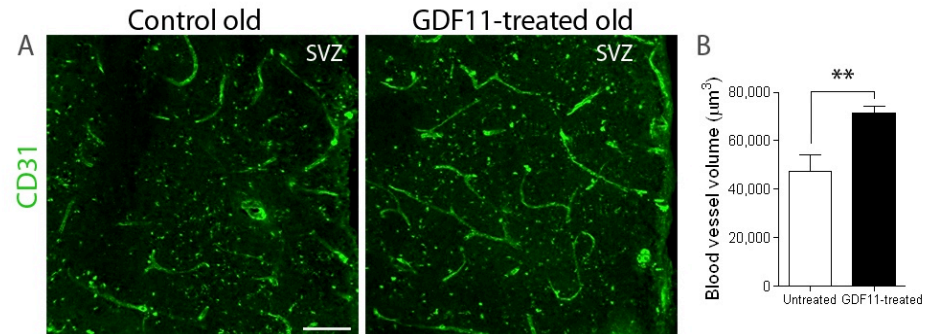
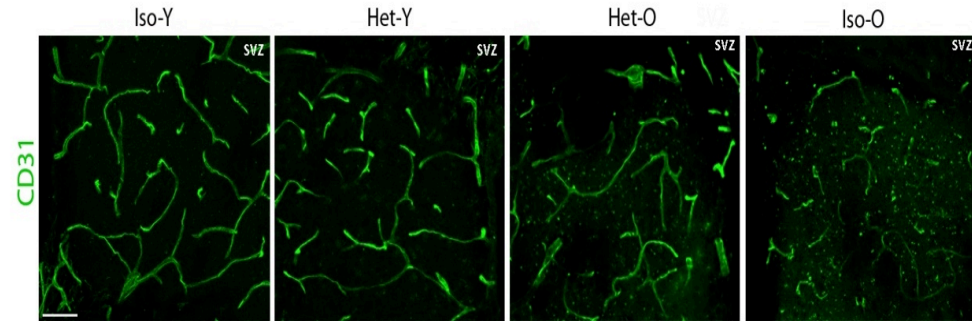
Restoring Systemic GDF11 Levels Reverses Age-Related Dysfunction in Mouse Skeletal Muscle

Manisha Sinha,^{1,2,3,4*} Young C. Jang,^{1,2,4*} Juhyun Oh,^{1,2,4} Danika Khong,^{1,2,4} Elizabeth Y. Wu,^{1,2,4} Rohan Manohar,^{1,2,4} Christine Miller,^{1,2,4} Samuel G. Regalado,^{1,5} Francesco S. Loffredo,^{1,6} James R. Pancoast,^{1,6} Michael F. Hirshman,² Jessica Lebowitz,^{1,2,4} Jennifer L. Shadrach,^{1,2,3} Massimiliano Cerletti,^{1,2,†} Mi-Jeong Kim,² Thomas Serwold,² Laurie J. Goodyear,^{2,7} Bernard Rosner,⁸ Richard T. Lee,^{1,6} Amy J. Wagers^{1,2,3,4,†}



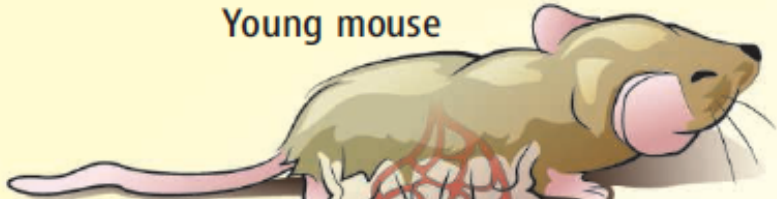
Vascular and Neurogenic Rejuvenation of the Aging Mouse Brain by Young Systemic Factors

Lida Katsimpardi,^{1,2*} Nadia K. Litterman,^{1,2} Pamela A. Schein,^{1,2} Christine M. Miller,^{1,2,3} Francesco S. Loffredo,^{1,2,4} Gregory R. Wojtkiewicz,⁵ John W. Chen,⁵ Richard T. Lee,^{1,2,4} Amy J. Wagers,^{1,2,3} Lee L. Rubin^{1,2*}

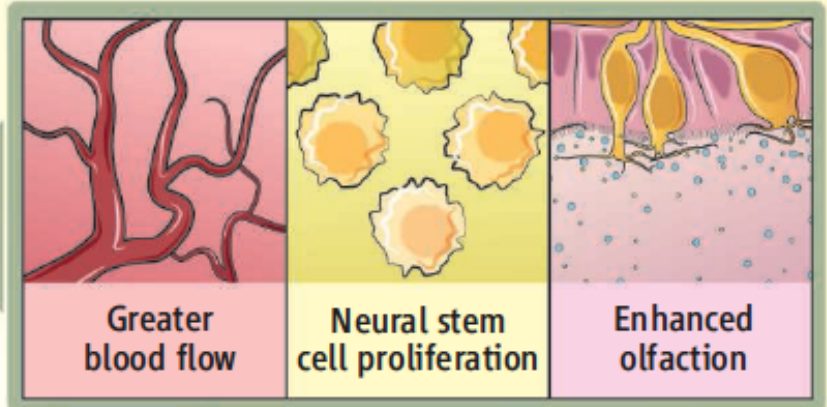


Blood vessels in the brain subventricular zone

Young mouse



Old mouse

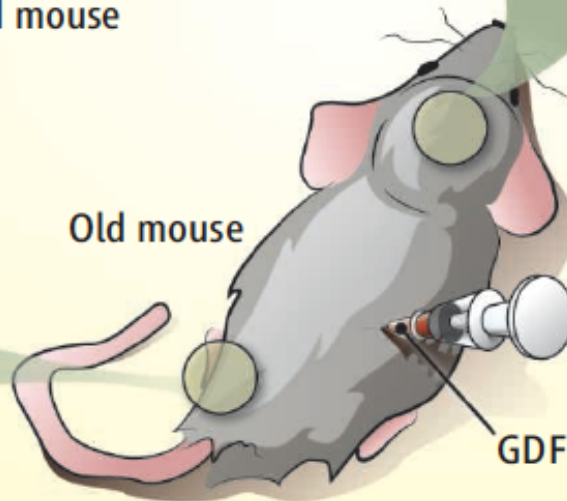


Greater blood flow

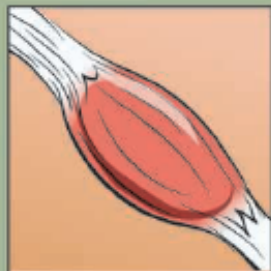
Neural stem cell proliferation

Enhanced olfaction

Old mouse



GDF11



Skeletal muscle rejuvenation

Revitalized. Linking an old mouse to the circulation of a young mouse or injecting the animal with a protein called growth differentiation factor 11 reversed signs of aging in muscle and the brain.

The PLasma for Alzheimer's Symptom Amelioration (PLASMA) Study

A Randomized, Double-Blind, Placebo-Controlled, Cross-Over
Trial of Intravenously Administered Plasma from Young Donors
for Treatment of Mild-to-Moderate Alzheimer's Disease

Details: The PLASMA study is a clinical trial for patients with
mild, moderate, or severe Alzheimer's disease and involves
weekly infusions of "young blood".