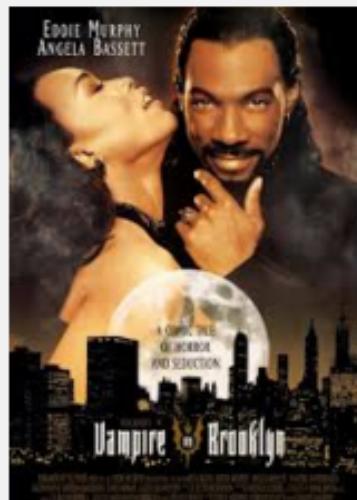
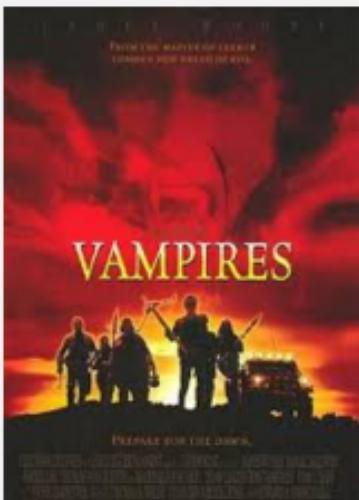


Model organisms and developmental biology

仲寒冰

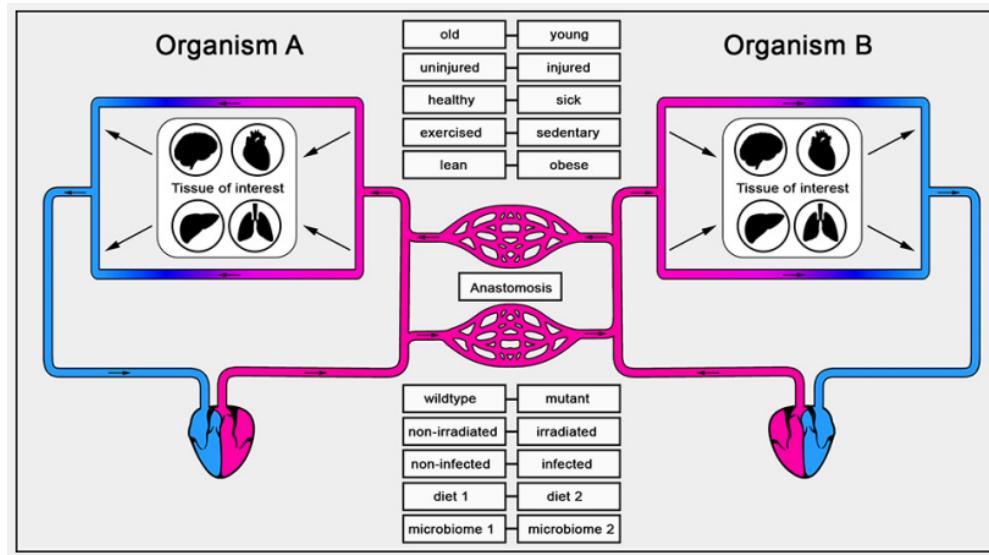
zhong.hb@sustc.edu.cn

The myth between blood and youth

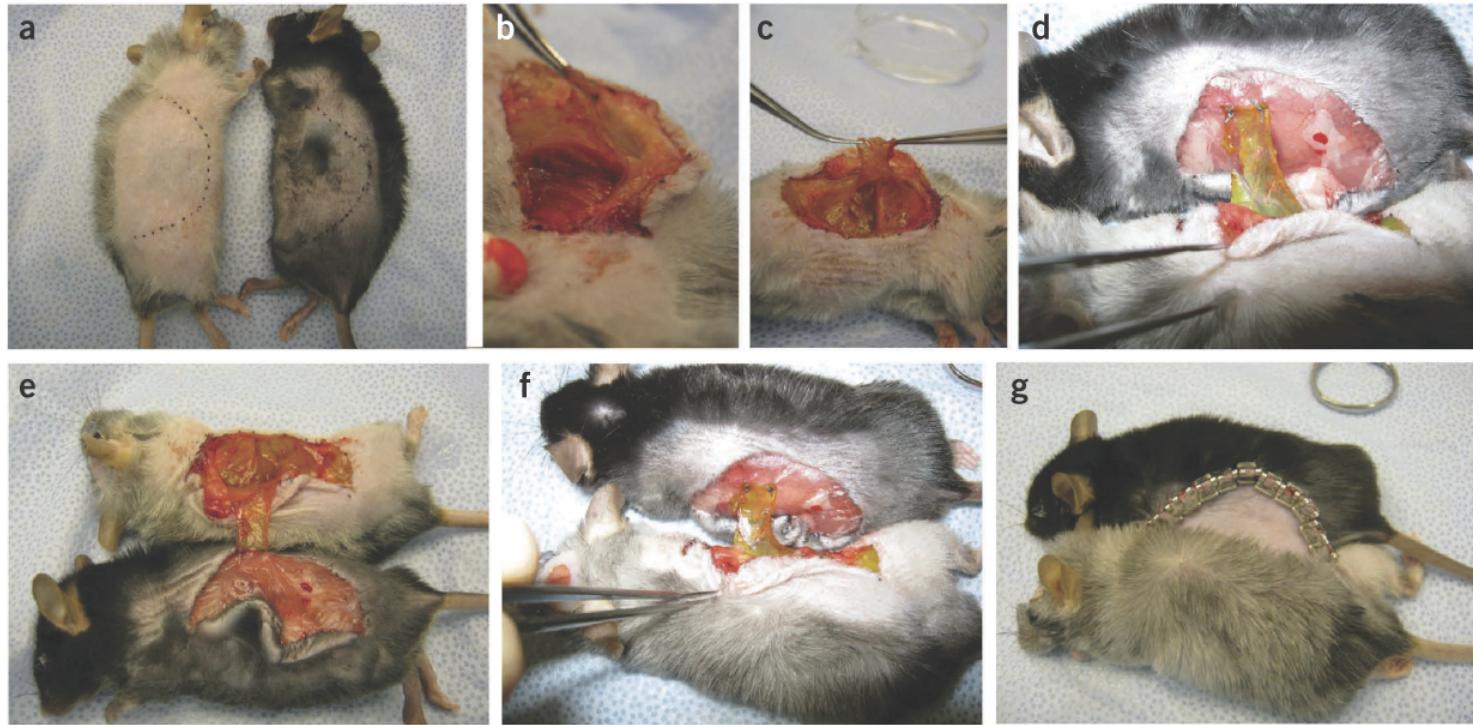


Parabiosis (异种共生 or 并生)

- Parabiosis (from the Greek words, para “alongside” and bios “life”) describes the union between two living organisms that share a common vascular system.

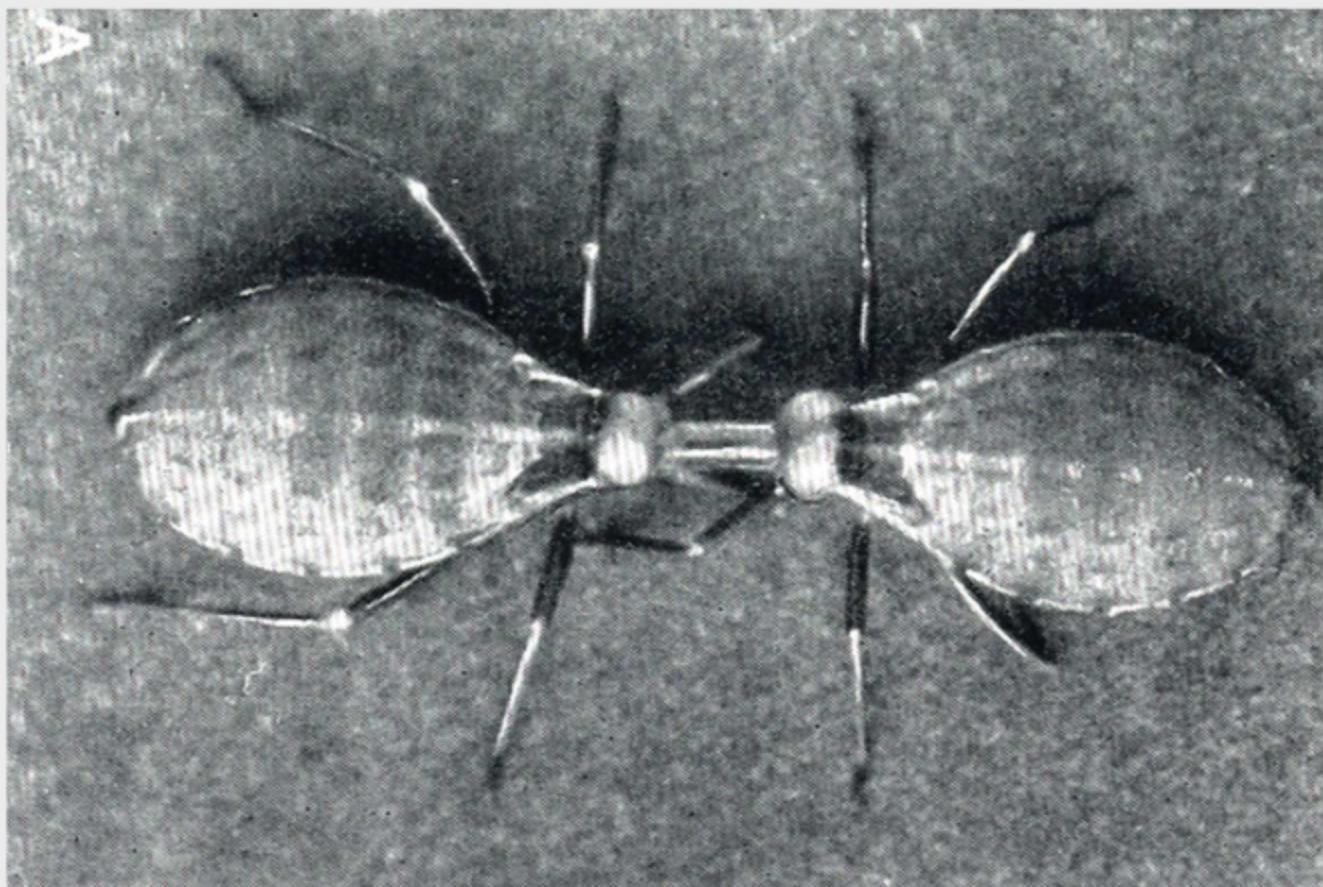


Skin transplantation through parabiosis surgery under general anesthesia



1930 Sir Vincent Wigglesworth

Rhodnius prolixus – Parabiosis experiment



1940 Carroll Williams

Hyalophora cecropia



one month later...

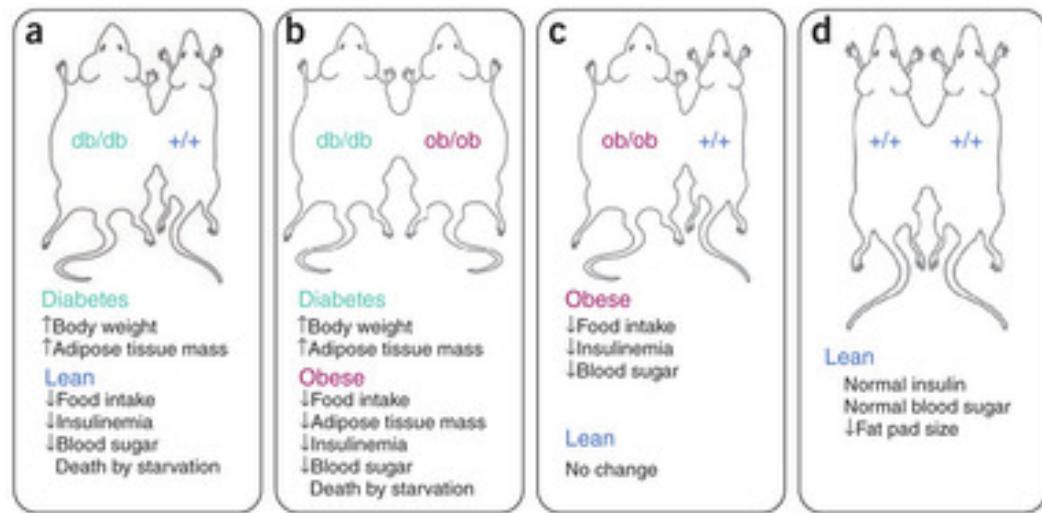
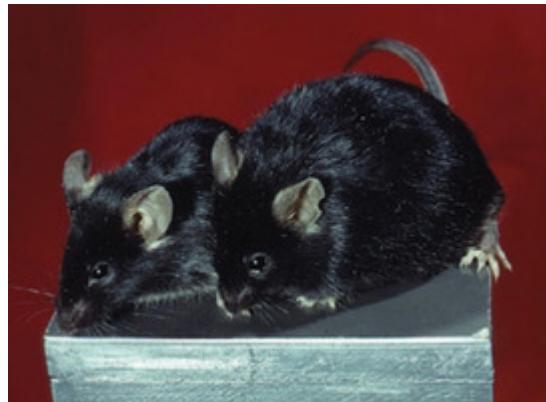


1940 Carroll Williams

Hyalophora cecropia



Effects of parabiosis of normal with genetically diabetic mice



Proved there is a regulatory factor in blood circulation.

IN brief

Mitochondrial medicine

Specialty firm Edison Pharmaceuticals of Mountain View, California, has entered a strategic alliance worth up to \$4.3 billion with Dainippon Sumitomo Pharma (DSP) of Osaka, Japan, to develop drugs for inherited respiratory chain diseases of the mitochondria. Under terms of the deal, the companies will jointly expand Edison's pipeline, bringing ten new compounds targeting redox pathways into clinical development over the next five years. Also in pursuit of mitochondria-related diseases is biotech firm Mitokyne of Boston, which in October 2013 struck a five-year agreement with Astellas Pharma of Tokyo, potentially worth \$730 million, to discover and develop drugs that modulate mitochondrial function. After decades of disinterest from investors, the deals confirm that mitochondrial research is gaining more traction. Douglas Wallace, director of the Center for Mitochondrial and Epigenetic Medicine in Philadelphia, points to a wider acceptance that systemic, cellular-energy metabolism defects caused by mitochondrial mutations can result in organ-specific symptoms and multisystem disorders, such as diabetes and Alzheimer's disease. Wallace, who showed that mitochondrial DNA is inherited exclusively from the mother, says: "I'm hoping we can [persuade other pharmaceutical companies] that mitochondrial bioenergetics is a good target." Hopes of tackling mitochondrial disease were raised on both sides of the Atlantic in February, when the US Food and

Leptin therapy gains FDA approval

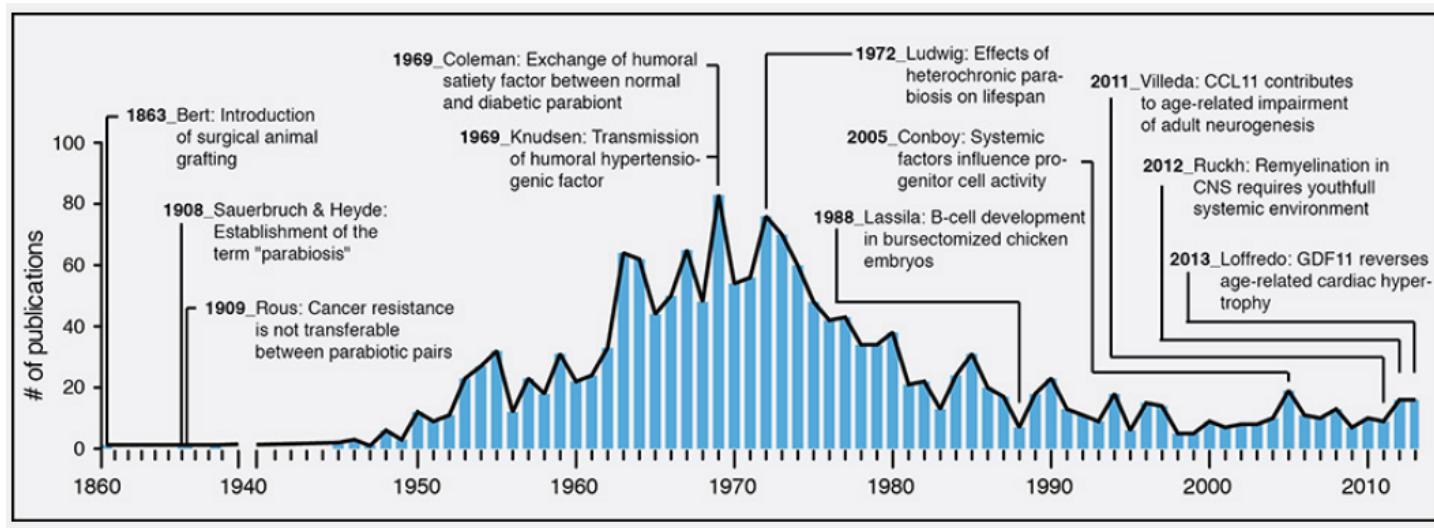
In February, the US Food and Drug Administration (FDA) approved AstraZeneca's Myalept (metreleptin) to treat generalized lipodystrophy—a disorder that affects under 200 people in the US. The approval marks a major milestone in a 20-year odyssey of a drug that almost never was. Myalept is a recombinant form of human leptin, a naturally occurring protein hormone secreted by fat cells. Leptin and its role in controlling satiety, first described in 1994 (*Nature*, **372** 425–432, 1994), ignited a frenzied excitement over the prospect of using leptin replacement therapy to treat obesity. But attempts were abandoned in the late 1990s after studies with obese people failed to show any benefit. It is only thanks to investigator-funded clinical trials and a final push by current sponsor Bristol-Myers Squibb (BMS) of New York that recombinant leptin has wound its way through the FDA to become a lifesaving treatment for a largely neglected indication. "It has been a long and challenging path for metreleptin," says Alex DePaoli, vice president of clinical research at NGM Biopharmaceuticals in San Francisco.

For all the promise once heaped on this hormone, the approval is for a dramatically circumscribed population. Generalized lipodystrophy is a rare disorder characterized by

absence of adipose tissue. With no adipose tissue to secrete the appetite-suppressant leptin, individuals with lipodystrophy eat voraciously. The consequences are catastrophic, says Stephen O'Rahilly, director of the University of Cambridge Metabolic Research Laboratories. Excess calories get stored as fat in liver and muscle cells leading to diabetes, high blood lipid levels and pancreatitis. "It's a totally appalling double whammy of being constantly hungry but of food being your greatest enemy," says O'Rahilly. The disease manifests either as generalized or partial lipodystrophy. Both forms can be inherited or induced by medications or result from autoimmune disease or unknown causes.

The generalized form of lipodystrophy is extremely rare. There are fewer than 200 people in the US and 1,000 at most with partial lipodystrophy of varying severity, says Abhimanyu Garg, chief of the division of nutrition and metabolic diseases at the University of Texas (UT), Southwestern Medical Center. Currently there is no treatment other than managing complications. Myalept treatment yields striking results in people with generalized lipodystrophy. It markedly reduces food intake, improves blood glucose and triglyceride levels, in some cases normalizing levels of both.

Parabiosis history and modern use



The annual number of publications including parabiosis experiments.

Rejuvenation of aged progenitor cells by exposure to a young systemic environment

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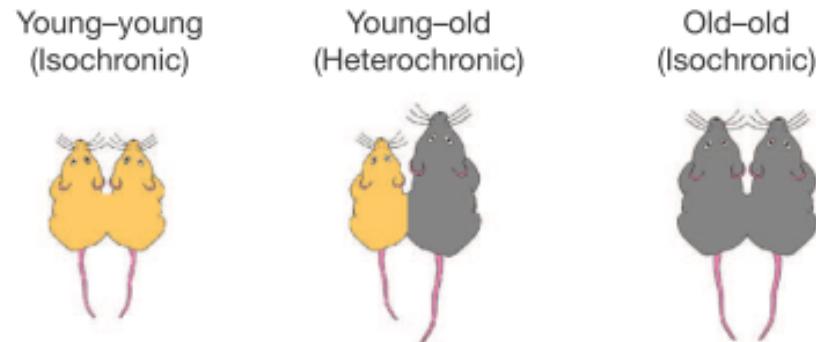
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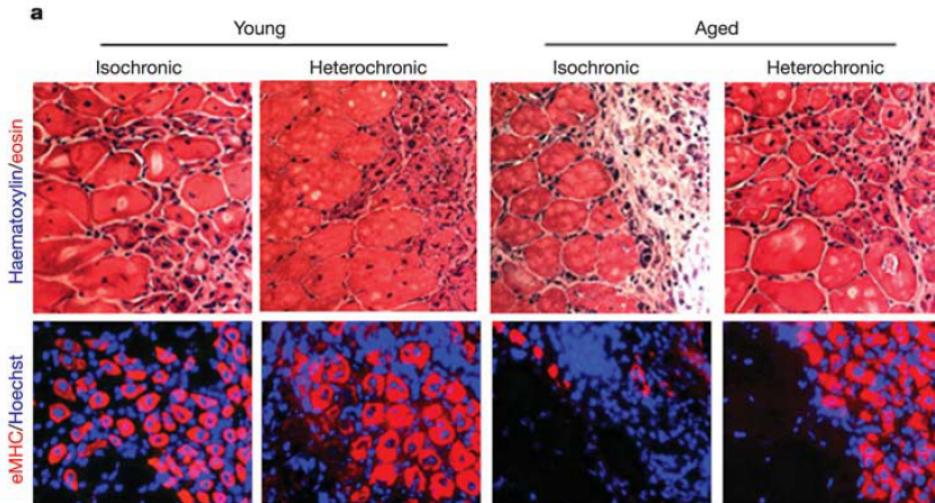
The decline of tissue regenerative potential is a hallmark of ageing and may be due to age-related changes in tissue-specific stem cells^{1–5}. A decline in skeletal muscle stem cell (satellite cell) activity due to a loss of Notch signalling results in impaired regeneration of aged muscle^{1,6}. The decline in hepatic progenitor cell proliferation owing to the formation of a complex involving cEBP- α and the chromatin remodelling factor brahma (Br) inhibits the regenerative capacity of aged liver⁷. To examine the influence of systemic factors on aged progenitor cells from different tissues, we established parabiotic pairings (that is, a shared circulatory system) between young and old mice (heterochronic parabioses), exposing old mice to factors present in young serum. Notably, heterochronic parabiosis restored the activation of Notch signalling as well as the proliferation and regenerative capacity of aged satellite cells. The exposure of satellite cells from old mice to young serum enhanced the expression of the Notch ligand (Delta), increased Notch activation, and enhanced proliferation *in vitro*. Furthermore, heterochronic parabiosis increased aged hepatocyte proliferation and restored the cEBC α complex to levels seen in young animals. These results suggest that the age-related decline of progenitor cell activity can be modulated by systemic factors that change with age.

influences, the molecular pathways could be rejuvenated from an old state to a young state.

To test this hypothesis we set up an experimental system in which—in contrast to transplantation—regenerating tissues in aged animals could be exposed only to the circulating factors of young



tary Fig. S1)¹⁸. The use of GFP-transgenic mice as one member of a pair also allowed us to distinguish the cells from each animal participating in tissue regeneration. After 5 weeks of parabiosis the hindlimb muscles of each mouse were injured and the mice



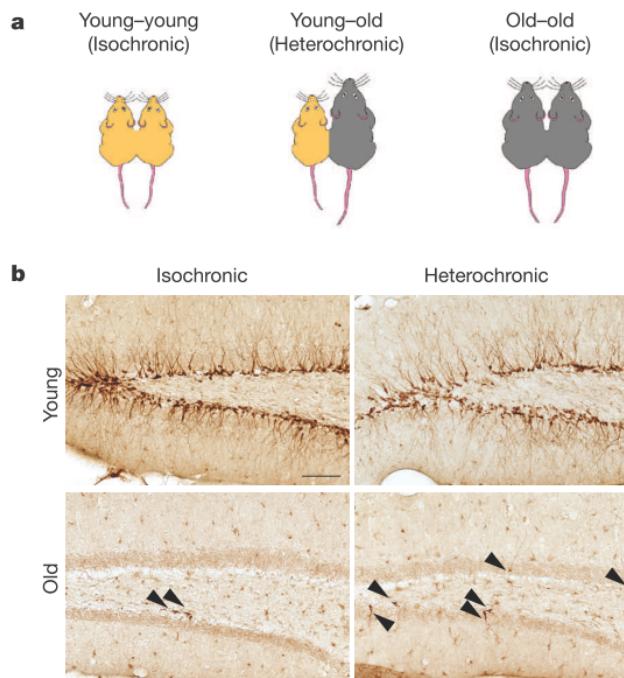
LETTER

doi:10.1038/nature10357

The ageing systemic milieu negatively regulates neurogenesis and cognitive function

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In the central nervous system, ageing results in a precipitous decline in adult neural stem/progenitor cells and neurogenesis, with concomitant impairments in cognitive functions¹. Interestingly, such impairments can be ameliorated through systemic perturbations such as exercise¹. Here, using heterochronic parabiosis we show that blood-borne factors present in the systemic milieu can inhibit or promote adult neurogenesis in an age-dependent fashion in mice. Accordingly, exposing a young mouse to an old systemic environment or to plasma from old mice decreased synaptic plasticity, and impaired contextual fear conditioning and spatial learning and memory. We identify chemokines—including CCL11 (also known as eotaxin)—the plasma levels of which correlate with reduced neurogenesis in heterochronic parabionts and aged mice, and the levels of which are increased in the plasma and cerebrospinal fluid of healthy ageing humans. Lastly, increasing peripheral CCL11 chemokine levels *in vivo* in young mice decreased adult neurogenesis and impaired learning and memory. Together our data indicate that the decline in neurogenesis and cognitive impairments observed during ageing can be in part attributed to changes in blood-borne factors.



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‡}

Parabiosis experiments indicate that impaired regeneration in aged mice is reversible by exposure to a young circulation, suggesting that young blood contains humoral "rejuvenating" factors that can restore regenerative function. Here, we demonstrate that the circulating protein growth differentiation factor 11 (GDF11) is a rejuvenating factor for skeletal muscle. Supplementation of systemic GDF11 levels, which normally decline with age, by heterochronic parabiosis or systemic delivery of recombinant protein, reversed functional impairments and restored genomic integrity in aged muscle stem cells (satellite cells). Increased GDF11 levels in aged mice also improved muscle structural and functional features and increased strength and endurance exercise capacity. These data indicate that GDF11 systemically regulates muscle aging and may be therapeutically useful for reversing age-related skeletal muscle and stem cell dysfunction.

Skeletal muscle is a highly specialized tissue composed predominantly of contractile, multinucleated fibers whose regeneration after injury depends on the activity of a specialized subset of muscle fiber-associated mononuclear stem cells called satellite cells (1, 2). Satellite cells can be isolated by fluorescence-activated cell sorting based on their unique surface marker profile (CD45⁻Sca-1⁺CD11b⁻CXCR4⁺β1-integrin⁺), which effectively distinguishes them from non-myogenic cells and more differentiated myoblasts within the muscle (3, 4).

Aged muscle exhibits decreased satellite cell number, impaired satellite cell function, and reduced regenerative potential (2, 5–9). To evaluate satellite cell function in aged muscle on a per cell basis, we performed clonal myogenesis assays (5, 9) and found that CD45⁻Sca-1⁺CD11b⁻CXCR4⁺β1-Integrin⁺ satellite cells (fig. S1) from aged mice formed fewer colonies by up to a factor of 4 compared with young cells (fig. S2A) (5, 9). To investigate the molecular basis of this reduced satellite cell activity in aged muscle, we examined DNA integrity in young and aged satellite

cells using single-cell gel electrophoresis assays. Freshly sorted satellite cells showed a marked increase in DNA damage with age (fig. S2, B and C), with ~60% of aged cells exhibiting severely compromised DNA integrity (red bars, fig. S2B). Likewise, nearly 60% of satellite cells sorted from aged muscle (fig. S2, D and E) or identified by Pax7 staining on isolated muscle fibers (fig. S3) showed increased immunoreactivity for the phosphorylated form of histone H2AX (pH2AX), a marker of DNA damage (10). In contrast, 40% of freshly isolated young satellite cells were devoid of detectable DNA damage by gel electrophoresis assay (fig. S2, B and C), and young satellite cell nuclei rarely contained more than two pH2AX foci when assayed after cell sorting (fig. S2, D and E) or on single myofibers (fig. S3). Induction of DNA damage by x-irradiation reduced the myogenic function of young satellite cells in transplantation assays (fig. S4), which suggests

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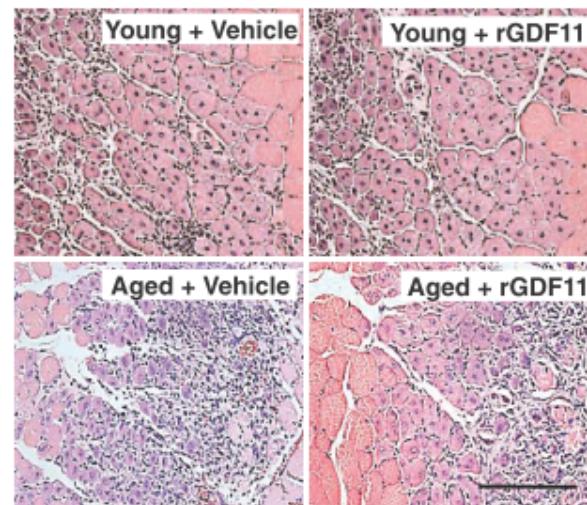
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Vascular and Neurogenic Rejuvenation of the Aging Mouse Brain by Young Systemic Factors

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*}

In the adult central nervous system, the vasculature of the neurogenic niche regulates neural stem cell behavior by providing circulating and secreted factors. Age-related decline of neurogenesis and cognitive function is associated with reduced blood flow and decreased numbers of neural stem cells. Therefore, restoring the functionality of the niche should counteract some of the negative effects of aging. We show that factors found in young blood induce vascular remodeling, culminating in increased neurogenesis and improved olfactory discrimination in aging mice. Further, we show that GDF11 alone can improve the cerebral vasculature and enhance neurogenesis. The identification of factors that slow the age-dependent deterioration of the neurogenic niche in mice may constitute the basis for new methods of treating age-related neurodegenerative and neurovascular diseases.

In the adult brain, neural stem cells reside in a three-dimensional (3D) heterogeneous niche, where they are in direct contact with blood vessels and the cerebrospinal fluid. The vasculature can influence neural stem cell proliferation and differentiation by providing a local source of signaling molecules secreted from endothelial cells (1) as well as by delivering systemic regulatory factors (2). The hormone prolactin (3), dietary restriction (4), and an exercise/enriched

environment (5) positively modulate neurogenesis, whereas increased levels of glucocorticoids associated with stress have the opposite effect (6). In the aging niche, the vasculature deteriorates with a consequent reduction in blood flow (7), and the neurogenic potential of neural stem cells declines, leading to reduced neuroplasticity and cognition (8–10). Systemic factors can also affect these aging-associated events, either positively in which circulating monocytes enhance remyelina-

tion in aged mice (11, 12) or negatively in which the accumulation of chemokines in old blood can reduce neurogenesis and cognition in young mice (10).

To test whether the age-related decline of the neurogenic niche can be restored by extrinsic young signals, we used a mouse heterochronic parabiosis model. Our experiments reveal a remodeling of the aged cerebral vasculature in response to young systemic factors, producing noticeably greater blood flow, as well as activation of subventricular zone (SVZ) neural stem cell proliferation and enhanced olfactory neurogenesis, leading to an improvement in olfactory function. Furthermore, we tested GDF11, a circulating transforming growth factor- β (TGF- β) family member that reverses cardiac hypertrophy in aged mice (13), and found that it can also stimulate vascular remodeling and increase neurogenesis in aging mice. Thus, we have observed that age-dependent remodeling of this niche is reversible by means of systemic intervention.

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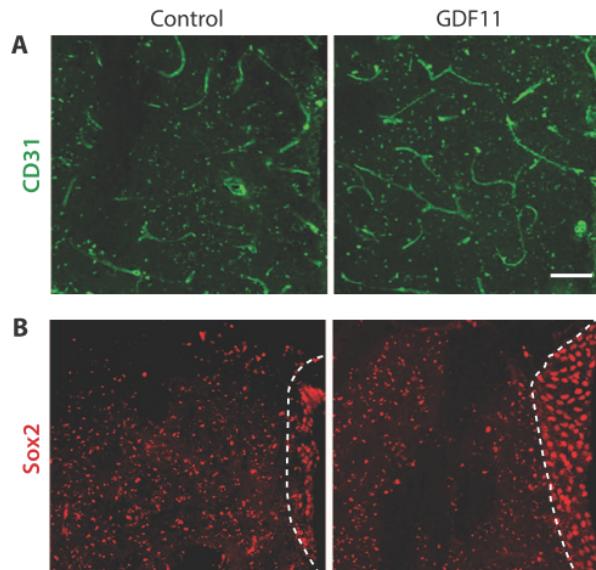
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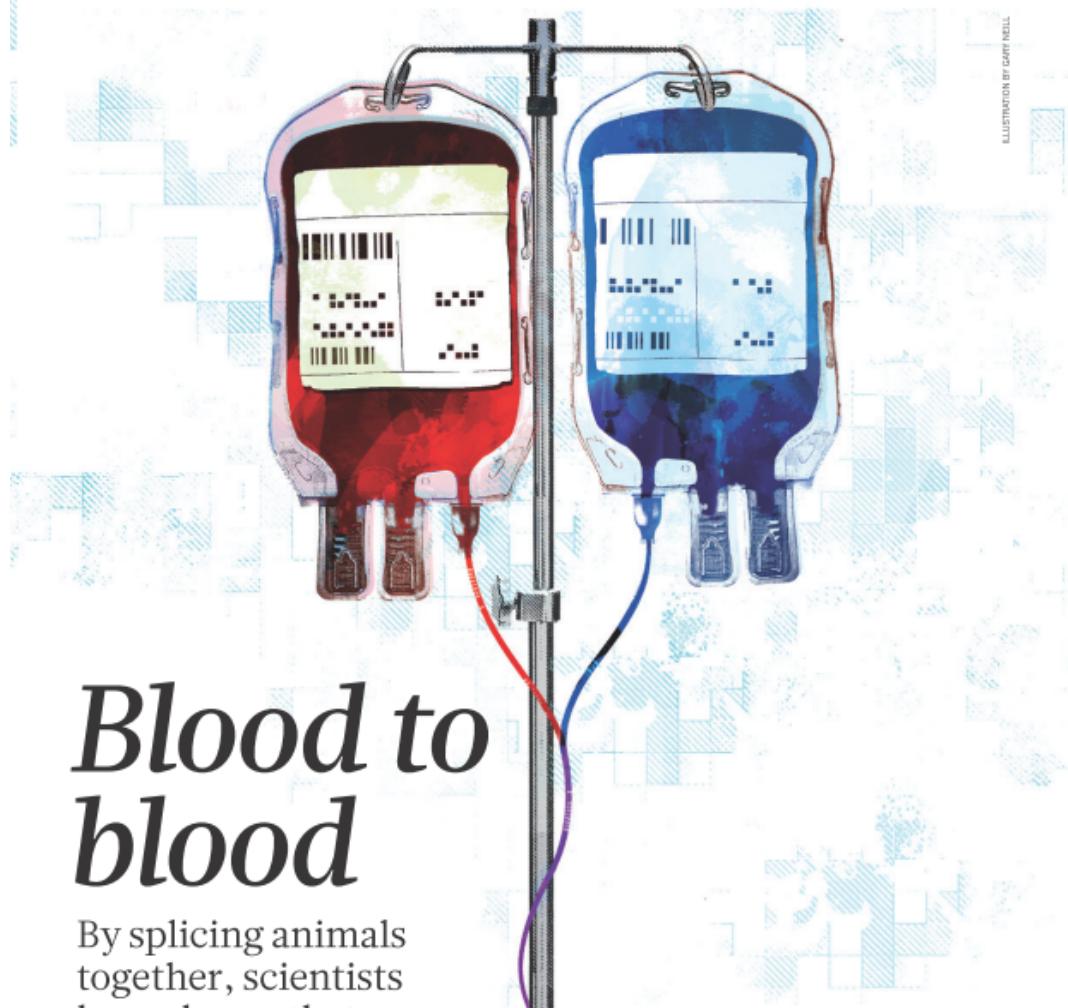
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Blood to blood

By splicing animals together, scientists have shown that young blood rejuvenates old tissues. Now, they are testing whether it works for humans.

BY MEGAN SCUDELLARI

Two mice perch side by side, nibbling a food pellet. As one turns to the left, it becomes clear that food is not all that they share — their front and back legs have been cinched together, and a neat row of sutures runs the length of their bodies, connecting their skin. Under the skin, however, the animals are joined in another, more profound way: they are pumping each other's blood.

Parabiosis is a 150-year-old surgical technique that unites the vasculature of two living animals. (The word comes from the

SHARE

Doubts cast on 'rejuvenating' protein



By Jocelyn Kaiser | May. 19, 2015, 11:00 AM



It was a mind-boggling observation. Hook up the circulatory systems of a young mouse and an old one, and the elderly animal seems to be rejuvenated. Since 2005, a handful of research labs have been hotly pursuing the molecules responsible for this effect, first found in the 1950s, hoping to harness them to slow or reverse aging in people. One in particular stood out: a protein found in young blood known as GDF11. In several high-profile papers, two of them published last year in *Science*, a Harvard University team reported that the protein declines in older animals and that replacing it rebuilds muscles, brain, and the heart. But work described this week by a team at the Novartis research center challenges GDF11's rejuvenating powers.

The Novartis group does not question that young blood renews old mice. But they say the Harvard group's explanation is wrong. Their paper, **published online today in Cell Metabolism**, casts doubt on the assays used in the earlier research and suggests that GDF11 actually inhibits muscle regeneration. "The whole premise is incorrect," says stem cell researcher Michael Rudnicki of the Ottawa Hospital Research Institute, who co-wrote a commentary accompanying the paper. Others are more cautious, but agree that the new work

NATURE | NEWS



'Young blood' anti-ageing mechanism called into question

A protein in the blood of young mice that seemed to rejuvenate older animals may do the opposite.

Sara Reardon

19 May 2015



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GDF11 Increases with Age and Inhibits Skeletal Muscle Regeneration

Marc A. Egerman,¹ Samuel M. Cadena,¹ Jason A. Gilbert,¹ Angelika Meyer,³ Hallie N. Nelson,² Susanne E. Swalley,¹ Carolyn Mallozzi,¹ Carsten Jacobi,³ Lori L. Jennings,¹ Ieuau Clay,³ Gaëlle Laurent,¹ Shenglin Ma,¹ Sophie Brachat,³ Estelle Lach-Trifilieff,³ Tea Shavlakadze,¹ Anne-Ulrike Trendelenburg,¹ Andrew S. Brack,^{2,4} and David J. Glass^{1,*}

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SUMMARY

Age-related frailty may be due to decreased skeletal muscle regeneration. The role of TGF- β molecules myostatin and GDF11 in regeneration is unclear. Recent studies showed an age-related decrease in GDF11 and that GDF11 treatment improves muscle regeneration, which were contrary to prior studies. We now show that these recent claims are not reproducible and the reagents previously used to detect GDF11 are not GDF11 specific. We develop a GDF11-specific immunoassay and show a trend toward increased GDF11 levels in sera of aged rats and humans. GDF11 mRNA increases in rat muscle with age. Mechanistically, GDF11 and myostatin both induce SMAD2/3 phosphorylation, inhibit myoblast differentiation, and regulate identical downstream signaling. GDF11 significantly inhibited muscle regeneration and decreased satellite cell expansion in mice. Given early data in humans showing a trend for an age-related increase, GDF11 could be a target for pharmacologic blockade to treat age-related sarcopenia.

ated with the fibrosis seen in older tissue and as an inhibitor of muscle differentiation (Beggs et al., 2004; Carlson et al., 2009; Massagué et al., 1986). Myostatin, also called growth differentiation factor 8 (GDF8), has also been demonstrated to be an inhibitor of muscle differentiation (McPherron et al., 1997a; Sartori et al., 2009; Trendelenburg et al., 2009). It can also induce atrophy on post-differentiated myotubes (Sartori et al., 2009; Trendelenburg et al., 2009). Myostatin null mice (McPherron et al., 1997a) and cattle demonstrate a doubling in muscle mass (Kambadur et al., 1997; McPherron and Lee, 1997b). This increase in muscularity upon the loss of myostatin has been demonstrated in multiple animals and even in humans (Lee, 2010). It has also been shown that other TGF- β family molecules, distinct from myostatin, play a role in modulating skeletal muscle size, since myostatin^{-/-} mice that are mated with mice that are transgenic for follistatin (TG^{follistatin}), which is capable of inhibiting not only myostatin but also its close relative GDF11 and other TGF- β molecules, such as the activins (Hill et al., 2002; Schneyer et al., 2008; McPherron et al., 2009), resulted in an even greater increase in muscle size (Lee et al., 2010). Myostatin induces cellular signaling by binding either of the type II activin receptors (IIa or IIb), which then allows for activation of type I receptors ALK4 or ALK5 (Tsuchida et al., 2008). The binding of myostatin to these receptor complexes results in the phosphorylation and activation of the transcription

levels induced by myostatin, it is critical to study the role of GDF11 in particular on skeletal muscle both *in vitro* and *in vivo*.

RESULTS

Prior Reagents Used to Detect GDF11 Are Not GDF11 Specific

Previous reports had identified GDF11, through both proteomic and western blot analyses, as a circulating factor in mice whose serum levels decrease with age (Loffredo et al., 2013; Sinha et al., 2014). In the Loffredo study, the SOMAmer technology was used to make an assessment of GDF11 levels. We first sought to test the specificity of the GDF11 SOMAmer used in the prior study by determining whether it might cross-react with myostatin. This seemed possible given the 90% sequence identity between the two proteins in their mature active form. In a direct binding test of GDF11 and myostatin, we observed that the GDF11 SOMAmer does indeed bind both proteins (Figure 1A, apparent K_D for GDF11: 6.6 ± 1.1 nM; for myostatin: 11.8 ± 1.1 nM), while a chemically related control SOMAmer binds neither protein (data not shown). Since the SOMAmer that was previously used to demonstrate a decrease of GDF11 levels in age actually could not distinguish between myostatin and GDF11, we next tried the antibody that was used to demonstrate that GDF11 declines with age (Loffredo et al., 2013; Sinha et al., 2014). This antibody was also first tested for its specificity. By western blot analysis, the antibody was found to recognize both recombinant myostatin and GDF11 to a similar degree, indicating cross-reactivity and a lack of preferential binding to GDF11 (Figure 1B). Importantly, under the reducing conditions used in this study, both the mature dimer (~25 kDa) and reduced monomer (~12.5 kDa) of recombinant myostatin and GDF11 were observed. In addition, some higher molecular weight material was observed, consistent with aggregated GDF11 or myostatin, since the molecular weight of the higher bands are multiples of the monomer.

Loffredo et al., 2013, online ahead of print.

A GDF11-Specific Method Demonstrates a Trend of GDF11 Increasing with Age in Rat and Human Sera

In order to specifically detect the levels of GDF11 in serum samples, an immunoassay was established that was validated to be specific for GDF11 (Figures S2A and S2B). This immunoassay did not detect myostatin (Figures S2A and S2B). The validation work further established that the immunoassay could detect endogenous GDF11 in human sera (Figure S2C, bar graph on left, blue bars) and that it was actually measuring GDF11, since recombinant GDF11 when spiked into human sera was detected (Figure S2C, bar graph on left, red bars). Furthermore, when sera were diluted, GDF11 was recovered in proportion to that dilution, demonstrating that the assay can quantitatively measure GDF11 within a range, even when it is diluted (Figure S2C, graph on right). With this assay, we could not detect endogenous GDF11 in either young or old mice (data not shown), since the levels were below the sensitivity of detection for this immunoassay. We next tried to detect GDF11 in sera from other species. We measured the blood serum concentration of GDF11 in both young and old rats (6 months versus 24 months) and humans (20–30 years versus 60+ years). We found that there was a nearly significant increase of GDF11 (~1.4 fold increase, $p = 0.0534$) in serum from older rats compared to the younger rats (Figure 1E). A similar trend toward an increase in median levels was observed comparing serum from humans over the age of 60 in comparison to sera from humans between 20 and 30 years old (Figure 1F).

GDF11 Expression Increases with Age in Rat Skeletal Muscle

To use a distinct method to detect GDF11 specifically, we performed RNA-seq on skeletal muscle from the rats, using 6-, 12-, 18-, 21-, and 24-month-old animals (Ilbebungo et al., 2013), spanning the lifespan of the animal. This study demonstrated that GDF11 expression increased dramatically as a

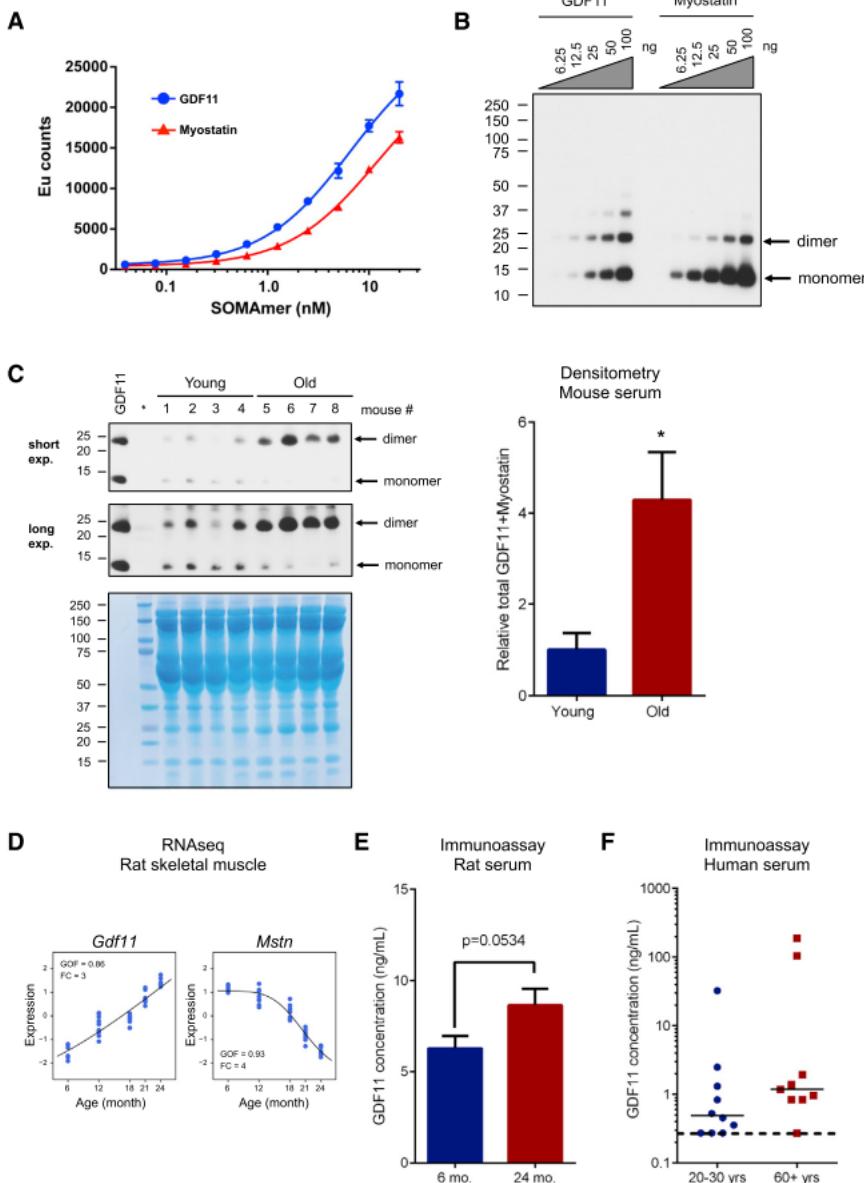


Figure 1. Prior Reagents Used to Measure GDF11 Are Not Specific, but Show that the Combination of GDF11 and Myostatin Increases with Age; Specific Methods show GDF11 Levels Increase with Age

(A) Affinity of GDF11 SOMAmer for recombinant GDF11 and myostatin. Binding of the GDF11 SOMAmer to GDF11 (shown in blue) and myostatin (shown in red) proteins as measured by dissociation-enhanced lanthanide fluorescent immunoassay (DELFIAs). Data represent means \pm SD from three technical replicates.

(B) Western blot analysis to determine specificity of Abcam antibody to GDF11 versus myostatin (GDF8). An anti-GDF11 antibody from Abcam was tested for specificity using a concentration gradient of recombinant GDF11 and myostatin, ranging from 6.25 ng to 100 ng, and was found to cross-react with myostatin. Even though this is a denaturing gel, bands consistent with dimer and even high molecular forms consistent with aggregates of the recombinant material are evident.

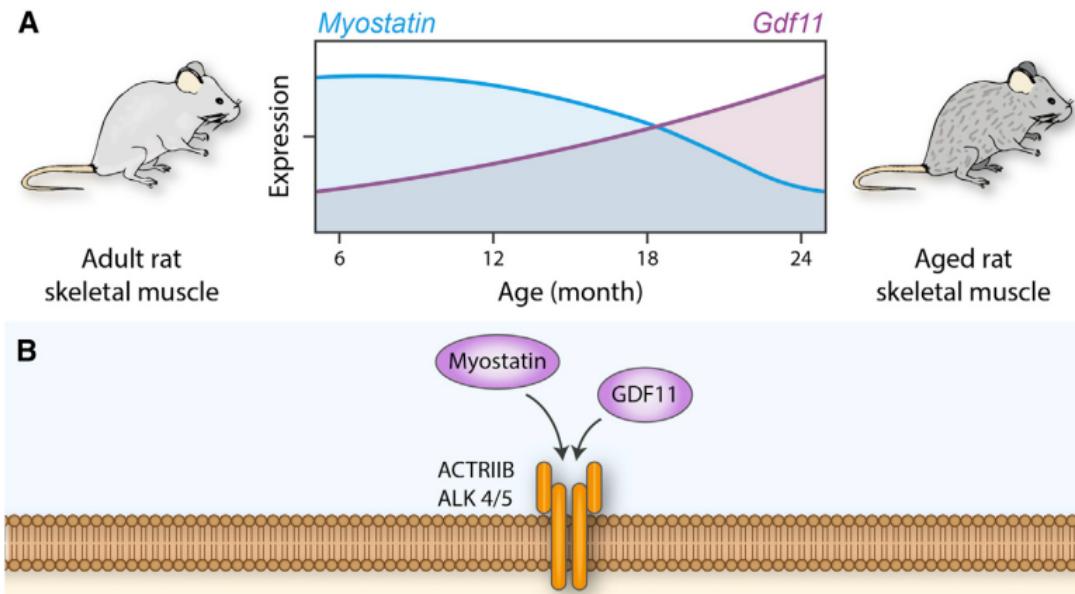
(C) Western analysis on sera from young and old mice. Sera samples from four different young animals (4 months old; 1, 2, 3, 4) and four different old animals (23 months old; 5, 6, 7, 8) were tested by western analysis for myostatin/GDF11 levels (top). Coomassie staining (bottom) demonstrates equivalent loading of each lane. Lane with ladder is indicated. The dimer band was not fully denatured to monomer. There was an increase in GDF11/myostatin dimer levels in the sera from older animals in comparison to young animals. Densitometry of monomer + dimer is provided on the right, indicating an overall increase in myostatin/GDF11 levels in the mouse sera (* $p < 0.05$).

(D) GDF11 and myostatin mRNA content in rat skeletal muscles of Sprague-Dawley male rats aged 6, 12, 18, 21, and 24 months (data derived from the RNA-seq analyses). RNA-seq analysis demonstrates that GDF11 expression increases as a function of age (comparing mRNA obtained from muscles from 6-, 12-, 18-, 21-, and 24-month-old rats). In contrast, myostatin (*MSTN*) expression decreases with age in rats. The y axis is the standardized expression level, with mean of 0 and standard deviation of 1. GOF, goodness of fit to a sigmoidal curve; FC, fold change between 24 m and 6 m.

(E) GDF11 protein levels in sera from young and old rats determined by immunoassay. GDF11 protein content in serum from young (6 months) or old (24 months) rats was measured by immunoassay. Old rats had higher levels of GDF11 compared with young. Data are mean \pm SEM ($p = 0.0534$, Student's t test).

(F) GDF11 protein levels in sera from young and older humans determined by immunoassay. GDF11 protein content was measured in serum samples from nine older (aged >60 years, males, shown in red) or ten young (aged 20-30 years, males, shown in blue). The median GDF11 concentration in serum of older humans was higher than in younger humans, but this did not reach statistical significance. Serum samples from three young and one old subject had GDF11 below a detection limit (less than 0.274 ng/ml), shown with a dotted horizontal line.

GDF11 and Myostatin Expression from Adulthood to Aging



ARTICLE

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OPEN

A single heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood

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Heterochronic parabiosis rejuvenates the performance of old tissue stem cells at some expense to the young, but whether this is through shared circulation or shared organs is unclear. Here we show that heterochronic blood exchange between young and old mice without sharing other organs, affects tissues within a few days, and leads to different outcomes than heterochronic parabiosis. Investigating muscle, liver and brain hippocampus, in the presence or absence of muscle injury, we find that, in many cases, the inhibitory effects of old blood are more pronounced than the benefits of young, and that peripheral tissue injury compounds the negative effects. We also explore mechanistic explanations, including the role of B2M and TGF-beta. We conclude that, compared with heterochronic parabiosis, heterochronic blood exchange in small animals is less invasive and enables better-controlled studies with more immediate translation to therapies for humans.

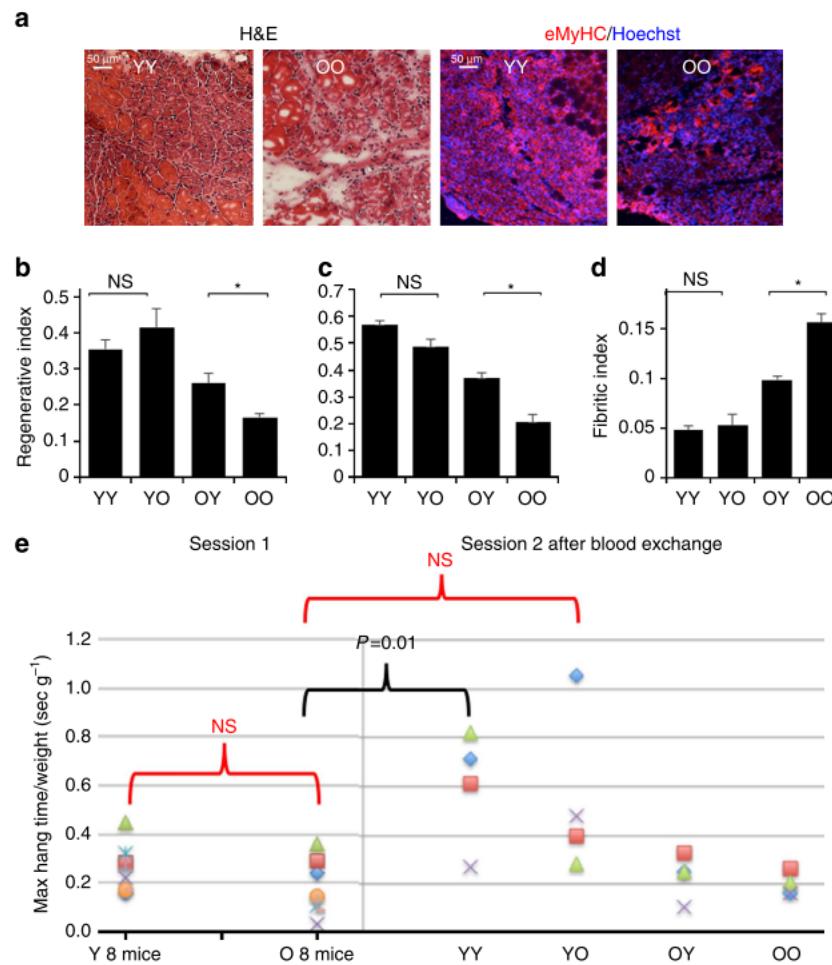


Figure 1 | Heterochronic blood exchange effects on muscle regeneration and performance. One day after blood exchange mice were injured by

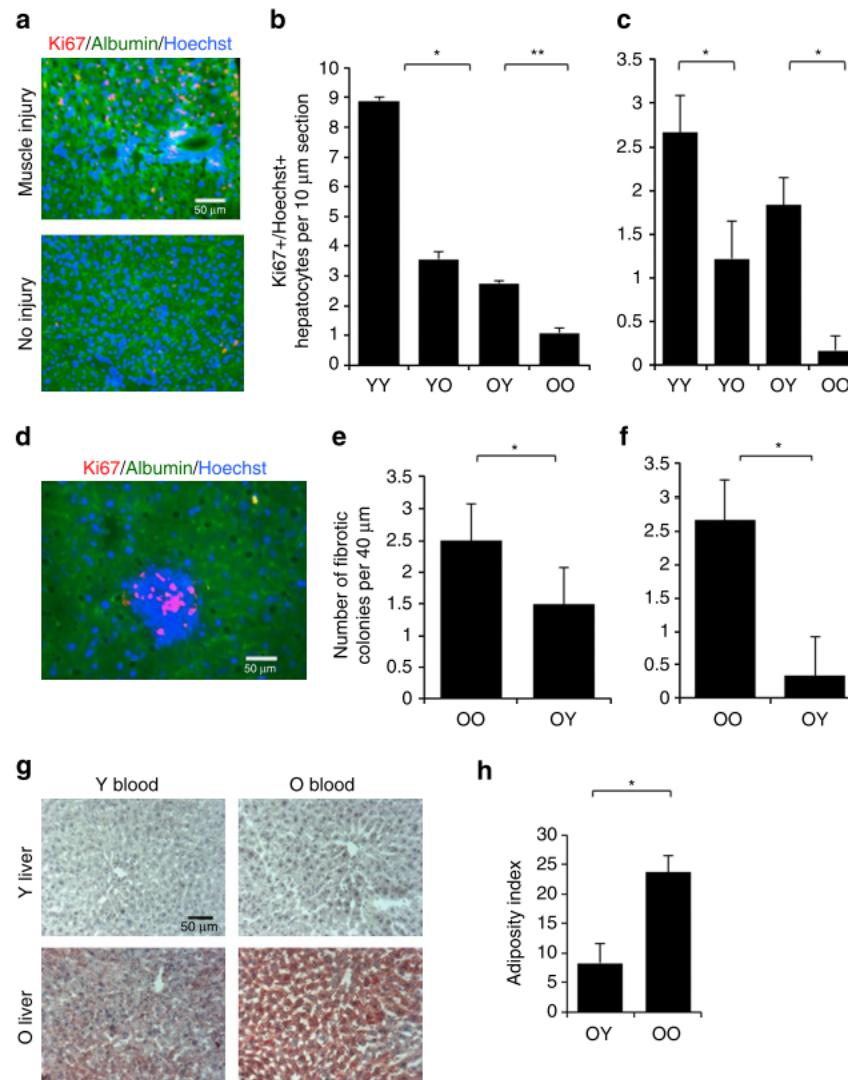


Figure 3 | Heterochronic blood exchange effects on hepatogenesis and liver fibrosis and adiposity. (a) Livers from YY, YO, OY and OO mice with and

Infusions of young blood tested in patients with dementia

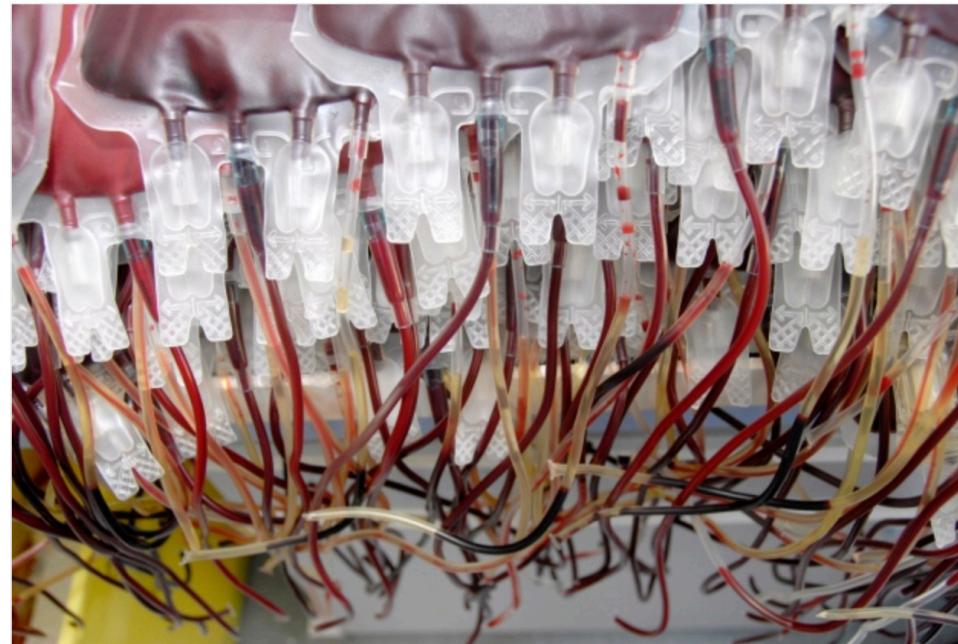
The first controlled human trial of whether blood from young donors rejuvenates old tissue has reported.

Alison Abbott

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Donor blood from young people has been transfused into people with dementia.

Thanks!