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Young blood

Young animals' blood holds rejuvenating powers.

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Little Evidence for Developmental Plasticity of Adult Hematopoietic Stem Cells

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To rigorously test the in vivo cell fate specificity of bone marrow (BM) hematopoietic stem cells (HSCs), we generated chimeric animals by transplantation of a single green fluorescent protein (GFP)–marked HSC into lethally irradiated nontransgenic recipients. Single HSCs robustly reconstituted peripheral blood leukocytes in these animals, but did not contribute appreciably to nonhematopoietic tissues, including brain, kidney, gut, liver, and muscle. Similarly, in GFP^+:GFP^- parabiotic mice, we found significant chimerism of hematopoietic but not nonhematopoietic cells. These data indicate that "transdifferentiation" of circulating HSCs and/or their progeny is an extremely rare event, if it occurs at all.

By that time, a national debate was raging over the ethics of studying ES cells. The bearded and burly Weissman became one of the most implacable and articulate scientific voices defending the use of ES cells in research. Working with Weissman, Wagers says, "landed me squarely in the middle of that debate."

A key ethical flashpoint was whether adult stem cells, such as the hematopoietic cells that form blood, could function just as well as embryo-derived cells in potential therapeutic applications. Several prominent groups had claimed that these bone-marrow cells could differentiate into other tissues, including muscle, heart, and brain cells. To

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too negative about potential therapies. Ten years ago, when one of her "negative" studies shot down the notion that bone marrow cells could treat heart attack victims, she got an earful from an outraged heart attack patient: her father. "He was angry at me for publishing that work. That kind of helped me understand the depth, the real power of hope in that way," Wagers recalls.

fute a research claim. The "negative data" papers also marked a turning point in Wagers's career, because some of the work involved pairs of mice with linked circulatory systems. That was her introduction to a curious 19th century laboratory creation that is now playing a starring role in aging research: the parabiotic mouse.

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

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

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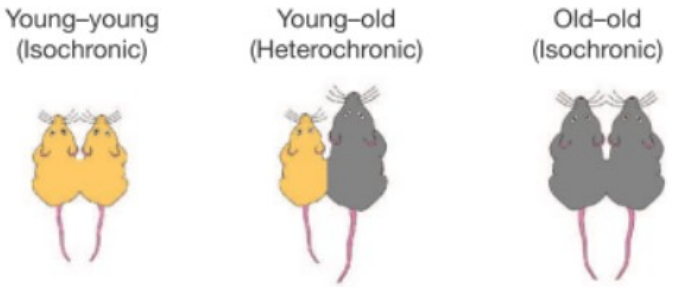
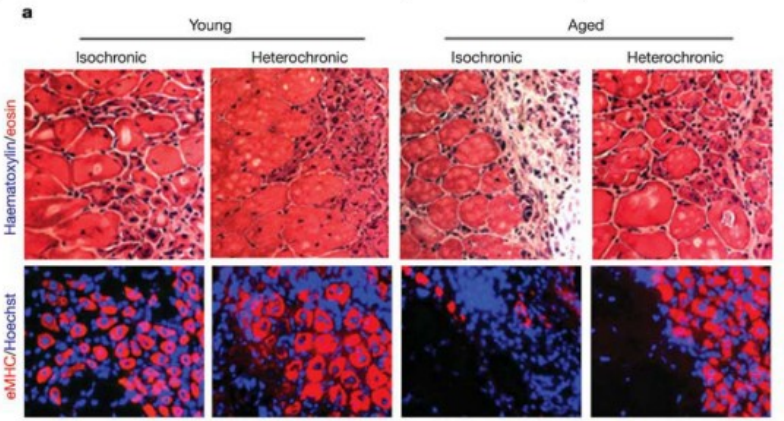
The decline of tissue regenerative potential is a hallmark of ageing and may be due to age-related changes in tissue-specific stem cells[1–5]. A decline in skeletal muscle stem cell (satellite cell) activity due to a loss of Notch signalling results in impair regeneration of aged muscle[1,6]. The decline in hepatic progenit cell proliferation owing to the formation of a complex involvi cEBP-α and the chromatin remodelling factor brahma (Br inhibits the regenerative capacity of aged liver[7]. To examine t influence of systemic factors on aged progenitor cells from the tissues, we established parabiotic pairings (that is, a shar circulatory system) between young and old mice (heterochron parabioses), exposing old mice to factors present in young seru Notably, heterochronic parabiosis restored the activation Notch signalling as well as the proliferation and regenerati capacity of aged satellite cells. The exposure of satellite ce from old mice to young serum enhanced the expression of t Notch ligand (Delta), increased Notch activation, and enhanc proliferation *in vitro*. Furthermore, heterochronic parabio increased aged hepatocyte proliferation and restored the cEB α complex to levels seen in young animals. These results sugg that the age-related decline of progenitor cell activity can 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



IN THE SUMMER OF 2010, Wagers became aware of a potential problem in a figure that had appeared as part of a *Nature* paper published earlier that year. First author Shane Mayack, a postdoc in her lab, had led the study, which claimed that the young blood phenomenon also affected hematopoietic stem cells in old mice, enhancing their blood-forming ability. One illustration in the supplemental material appeared to duplicate data from a 2008 *Blood* paper by Mayack and Wagers.

"old

of spines

The episode left Wagers psychologically bruised and scientifically sobered. "All of the waste in the research dollars; all of the waste in the time and effort of people in our lab and in other labs. And then the enormous amount of waste of the efforts of the people who track it down and document it. It's just horrible." Several online commentators at the

The possibility of impropriety hit Wagers like "a punch to the gut." She alerted Harvard Medical School officials, who launched an inquiry. Without waiting for the outcome, however, Wagers moved immediately to retract the *Nature* paper and contacted editors at *Blood*. "The first thing I thought was: I have to fix this."

conduct"; among the transgressions identified by ORI was the use of a figure from another, unrelated paper "to falsely represent [Mayack's] own experiment" and the use of an illustration from an online source as original data. The ORI report said Mayack also "falsely" relabeled identical flow cytometry plots to represent them as different experimental results.

Despite coverage of the retractions in *The Boston Globe* and *The New York Times*, the episode of misconduct did not dim Wagers's star at Harvard; the university granted her tenure in 2012, and her former mentor Weissman applauded her quick reaction to the incident. "To her credit," he says, "she didn't try to wait the fuss out."

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

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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.

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

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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.

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.

Young blood versus old blood

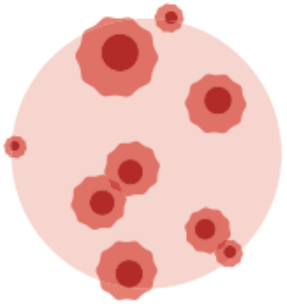
Factors in “young blood” activate stem cells and rejuvenate organs and cells in old mice. Factors in "old blood" appear to inhibit regenerative capacity in young mice.

SKELETAL MUSCLE
Inhibits repair and promotes fibrosis

LIVER
Suppresses cell proliferation

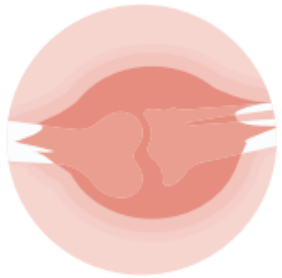
BRAIN
Inhibits

HEART
Reduces wall thickening

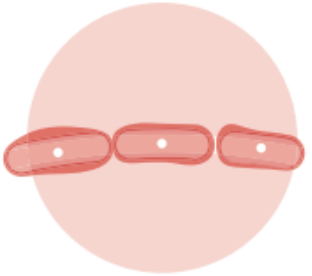


PANCREAS
Reverses ß-cell decline

BRAIN
Improves blood flow



SKELETAL MUSCLE
Increases repair and improves structure



SPINAL CORD
Enhances remyelination following injury

NEURONS
Promotes growth; increases

"vampire therapy"). "It's obviously a fascinating idea that something in the blood can potentially reverse aging," says Toren Finkel, who heads the Center for Molecular Medicine at the National Heart, Lung, and Blood Institute in Bethesda, Maryland. "That's sort of the holy grail for aging research. ... But you'd like to know how these things work, what the mechanism is."

Other researchers caution that the work still needs to be reproduced and note that growth factors have the potential to initiate or accelerate cancers.

Wagers is the first to acknowledge that the biology is far from settled. "This is a complicated and robust system of regulation, so there's likely multiple signals." Indeed, Rando's lab at Stanford has been pursuing blood-borne factors in older mice that seem to suppress stem cell activity and blunt their regenerative capacity. Conboy's lab at UC Berkeley has recently reported that levels of the hormone oxytocin in the blood decline with age, and increased amounts of oxytocin seem to play a major role in activating adult muscle stem cells and improving muscle regeneration. And Wyss-Coray and colleagues reported this past May in *Nature Medicine* that infusions of "young blood plasma" re-

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Cell

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

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SUMMARY

The most common form of heart failure occurs with normal systolic function and often involves cardiac hypertrophy in the elderly. To clarify the biological mechanisms that drive cardiac hypertrophy in aging, we tested the influence of circulating factors using heterochronic parabiosis, a surgical technique in which joining of animals of different ages leads to a shared circulation. After 4 weeks of exposure to the circulation of young mice, cardiac hypertrophy in old mice dramatically regressed, accompanied by reduced cardiomyocyte size and molecular remodeling. Reversal of age-related hypertrophy was not attributable to hemodynamic or behavioral effects of parabiosis, implicating a blood-borne factor. Using modified aptamer-based proteomics, we identified the TGF-β superfamily member GDF11 as a circulating factor in young mice that declines with

Most age-related heart failure occurs in the setting of normal systolic function and is called "diastolic heart failure," in contrast to "systolic heart failure" (Aurigemma, 2006). Although progress has been made in the treatment of systolic heart failure, with substantial improvements in outcome over the past two decades, progress in treating diastolic heart failure has been much more elusive (Hunt et al., 2009). Indeed, one can argue that there are no specific therapies for patients who experience the ventricular "stiffening" associated with the diastolic dysfunction that accompanies aging (Kitzman and Daniel, 2007).

Emerging evidence indicates that systemic factors profoundly influence tissue aging. Some of these data have emerged from the experimental model of parabiosis, which was first developed in the 19th century (Finerty, 1952). In parabiosis, two mice are surgically joined, such that they develop a shared blood circulation with rapid and continuous exchange of cells and soluble factors at physiological levels through their common circulatory system (Wright et al., 2001). The pair of animals may be the same age (isochronic parabionts) or different ages (heterochronic parabionts). Because parabiotic mice are connected

The results were striking. In 2013, Wagers, Lee, and their colleagues reported in *Cell* that injection of GDF11 alone has the same effect on the hearts of old mice as an infusion of young blood: It significantly reversed cardiac enlargement (hypertrophy), which often causes the kind of heart failure commonly seen in older people. And this spring,

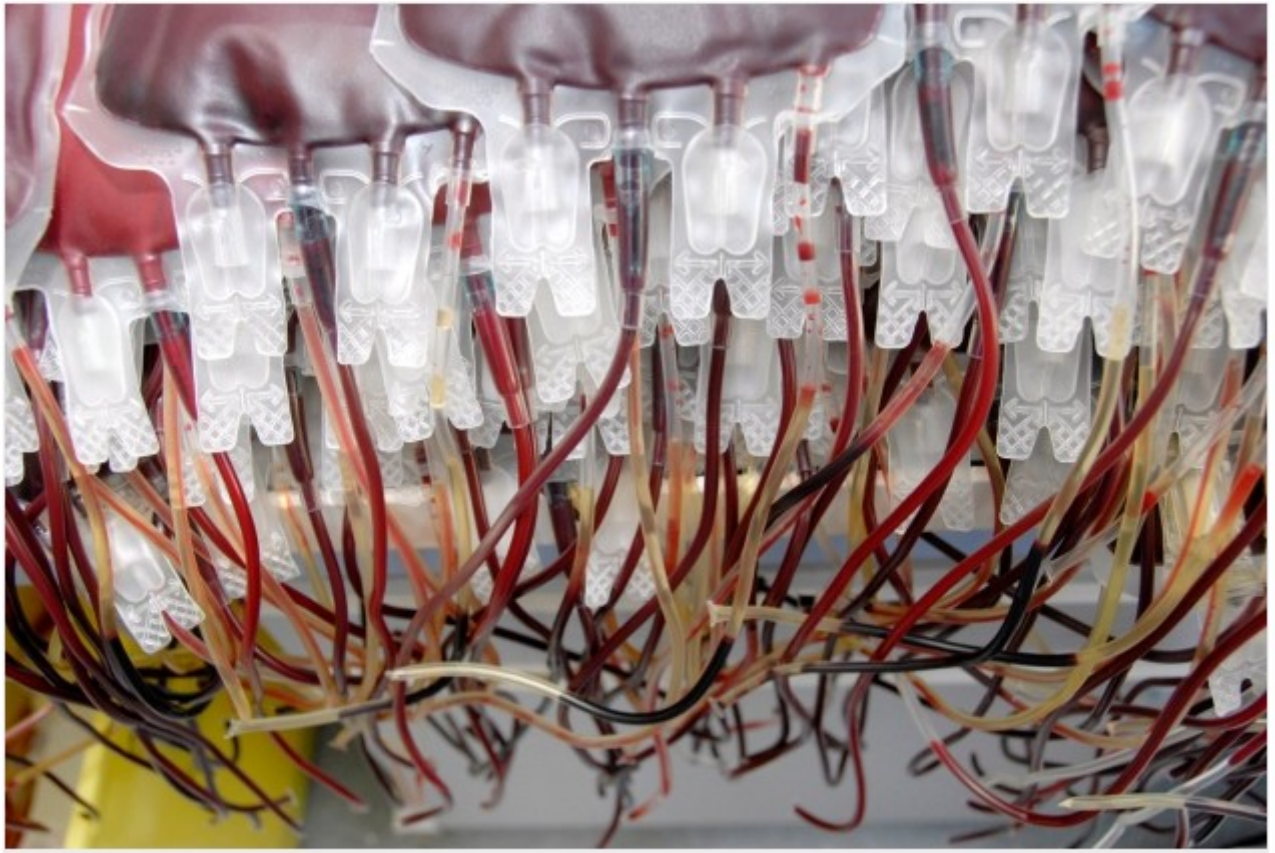
Despite her team's impressive rodent results, Wagers suspects injecting GDF11 directly into patients would be "not ideal," because such an approach would bypass the tight biological regulation governing the molecule and perhaps increase the risk of side effects. "Minimally, we could use it as a biomarker for predicting outcome" and monitoring other treatments for age-related conditions, she says. Citing unpublished data on nearly 2000 elderly heart patients followed for roughly 9 years, for example, Peter Ganz of UC San Francisco and colleagues have reported at meetings that lower levels of GDF11 in the blood predicted higher rates of heart attack, stroke, congestive heart failure, and overall mortality.

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

01 November 2017 | Corrected: 03 November 2017



AJ Photo/SPL

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

Harvard has filed patents on the GDF11 work, and other groups are quickly moving their own young blood findings toward the clinic. Stanford doctors plan to begin transfusing plasma from young blood donors into patients with Alzheimer's disease, and Conboy says clinical testing of oxytocin, already a Food and Drug Administration–approved drug, and other blood-borne factors are under discussion by UC Berkeley scientists.

Wagers is acutely aware of the dangers of going overboard about GDF11's promise. But she has also been chastised, on the most personal level, for being too negative about potential therapies. Ten years ago, when one of her "negative" studies shot down the notion that bone marrow cells could treat heart attack victims, she got an earful from an outraged heart attack patient: her father. "He was angry at me for publishing that work. That kind of helped me understand the depth, the real power of hope in that way," Wagers recalls.

"You want to be enthusiastic about the potential, the real potential of the science," she continues. "On the other hand, you have to turn around and say, 'But not yet.' It's just a really hard message—to be clear that the hope is real, but that it will take time, and we can't tell you the path to get there." ■

pers. And, as an inveterate skeptic who made an early mark by challenging overstated claims by other researchers, she is aiming for balance between scientific enthusiasm about the "rejuvenation factor" and realism about what it might mean for medicine.

Thanks