A revival of parabiosis in biomedical research

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Summary

Modern medicine wields the power to treat large numbers of diseases and injuries most of us would have died from just a hundred years ago, yet many of the most devastating diseases of our time are still untreatable. Chronic conditions of age such as cardiovascular disease, diabetes, osteoarthritis or Alzheimer's disease turn out to be of a complexity that may require transformative ideas and paradigms to understand and treat them. Parabiosis, which is characterised by a shared blood supply between two surgically connected animals, may just provide such a transformative experimental paradigm. Although forgotten and shunned now in many countries, it has contributed to major breakthroughs in tumour biology, endocrinology and transplantation research in the past century. Interestingly, recent studies from the United States and Britain are reporting stunning advances in stem cell biology and tissue regeneration using parabiosis between young and old mice, indicating a possible revival of this paradigm. We review here briefly the history of parabiosis and discuss its utility to study physiological and pathophysiological processes. We argue that parabiosis is a technique that should enjoy wider acceptance and application, and that policies should be revisited to allow its use in biomedical research.

Key words: parabiosis; aging; stem cells; Alzheimer's disease

Parabiosis – an experimental model inspired by nature

Parabiosis (from the Greek words, para "alongside" and bios "life") describes the union between two living organisms that share a common vascular system. Such pairings are generated experimentally by surgery, although a natural form of parabiosis can occur owing to abnormal development of embryos in monozygotic twins in some mammalian species, resulting in conjoined individuals, also known as Siamese twins in humans. The experimental technique to establish parabiosis in animals was first introduced by the French physiologist Paul Bert in the 1860s using white albino rats in an attempt to understand and facilitate organ transplantation. More than 1,700 articles related to parabiosis have been published by groups around the globe (source: http//www.gopubmed.org) since Bert's original dissertation, with a publication peak between 1960 and 1980 (fig. 1).

Although mice are being used preferentially today, the surgical procedure still follows Bert's initial descriptions, in general by generating skin incisions extending along the adjoining flanks of two mice and suturing adjacent skin flaps between the animals. In current protocols the incisions are longer and typically extend along the whole body flank. Moreover, the peritoneum is incised and sutured together between the animals to form a common peritoneal cavity. In some models the limbs are also sutured at the joints in order to increase stability (see Conboy et al. [1] for a detailed protocol of the procedure). As a result of revascularisation of the injured tissue, blood vessels between the two animals join to form anastomoses and establish a joint vascular system (fig. 2). By using genetically identical animals there is no "tissue" rejection, and survival rates similar to other invasive surgical procedures (>80%) can be attained in mouse parabionts. Once established, pairs of mice or rats can live together for months or years [3]. Besides mice and rats, axolotls [4] have been used for parabiosis studies and, recently, embryonic tissues in amphibians and fish have been joined to study developmental processes [5].
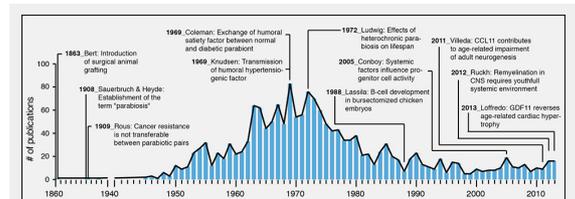

Figure 1

Parabiosis history and modern use.

The annual number of publications including parabiosis experiments is shown from 1860 to 2013. Several studies are highlighted as they provided groundbreaking findings. All values have been extracted from http://www.gopubmed.org.

CCL11 = eotaxin; CNS = central nervous system; GDF11 = growth and differentiation factor 11

Early scientific breakthroughs facilitated by parabiosis

In his doctoral thesis, "la greffe animale," Bert sutured the skin of two albino rats at their flanks and found that intravenously administered fluids passed from the circulation of one animal into the bloodstream of its adjacent partner. He therefore postulated that surgically connected animals spontaneously develop a single, shared circulatory system (fig. 2) [6]. For his pioneering work, Bert was awarded the Prize of Experimental Physiology of the French Academy of Science in the year 1866. Thereafter, very few studies followed up on his approach until the early 20th century.

In 1908, the German surgeons Sauerbruch and Heyde revived the technique and introduced the term parabiosis for the artificially established symbiosis between two animals [7]. Researchers from a variety of different fields (e.g., endocrinology, metabolism, transplantation, nephrology, radiology, allergy and immunology) started to take advantage of the parabiosis model for their own scientific investigations (table 1). A main question at the time was whether transmissible, humoral factors present in one animal have a physiological effect on its adjacent partner. Rous, who won a Noble Prize in 1966 for his discovery of tumour-inducing viruses, used parabiosis to examine whether the presence of circulating anticancer antibodies in tumour-resistant rats would affect tumour susceptibility in attached nonresistant rats. He did not succeed in identifying such protective humoral anticancer factors in these experiments [8], but parabiosis was instrumental in his early studies. By the middle of the last century, parabiosis had become a key research tool for dissecting the function of endocrine factors and growth and sex hormones, and for understanding the communication between the endocrine glands, as detailed in an extensive review on the early successes of parabiosis by Finnerty [9].

In 1969, Coleman grafted mice with the mutation *diabetes (db/db)*, which are prone to become obese and develop type II diabetes, to inbred wild-type mice [10]. He initially hypothesised that the db/db mouse would lose weight upon exposure to a systemic environment of a non-obese mouse. Surprisingly, he observed that the wild-type mouse significantly decreased food intake while the obese mouse continued to gain body weight. Coleman concluded that there must be a satiety factor involved, to which only the wild-type but not the db/db mouse had been able to respond [11]. Almost three decades later, Friedman finally identified this satiety factor and called it leptin [12]. Today, leptin is known as one of the key hormones regulating body weight. Shortly after this remarkable discovery, Friedman and Leibel found that the *db* gene encodes for the leptin receptor and that mutations in this gene result in a nonfunctional molecule [13, 14]. This finding, which earned Coleman and Friedman the 2010 Lasker Award, clearly confirmed Coleman's interpretation of his earlier experiments and underlines the importance of parabiosis models for the identification of new transmissible, humoral factors. In 1969, another remarkable study using parabiotic pairings was performed by Lewis K. Dahl's group [15]. They grafted wild-type rats to partners with constitutional predisposition for hypertension. As a result, they found that renoprival hypertension occurred in both rats at the same frequency. Again, this finding pointed towards a humoral factor inducing hypertension in the wild-type animal. Additionally, they described that nephrectomised rats with a predisposition to develop hypertension did not induce higher blood pressure in the wild-type parabiont, suggesting that the factor is produced in the kidney of hypertensinogenic rats. The presence of this factor has subsequently been confirmed in other studies [16] and, in 1993, Lewanczuk et al. identified it as parathyroid hypertensive factor (PHF) [17]. Parabiosis was not only helpful in the discovery and study of individual humoral factors, but it has also been useful in the assessment of the physiological consequences in an organism after exposure to the systemic environment of its attached partner. Initially, parabiotic surgeries showed highest success rates when using young, sex- and age-matched littermates. Over time, the procedure has improved and, in the early 70s, scientists started to graft animals of different ages to each other. This *heterochronic* parabiosis set the basis for the investigation of effects induced through exposure of an aged organism to a youthful systemic environment. In their studies, Ludwig and Elashoff particularly focused on the extension of lifespan in the old heterochronic parabiont when attached to a young counterpart. Indeed, in 1972 their results provided the first evidence that the old organism in the heterochronic pairing lived longer in response to the young environment than the age-matched *isochronic* control animals [18]. Later, as we will discuss, this model proved critical to study the physiology of aging and stem cells in different tissues and organ systems.
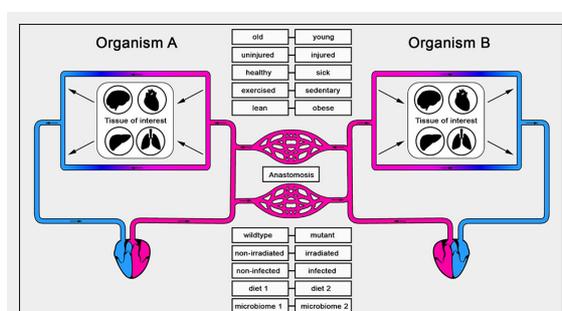
A revival of parabiosis for the study of stem cells and tissue regeneration

In spite of these remarkable findings by the end of the last century, parabiosis had fallen out of favour with the research community and only a handful of papers reported use of the technique (fig. 1). It was at that time when Drs Weissman, Wagers and Rando "rediscovered" parabiosis at Stanford University for the study of stem cell engraftment and trans-differentiation [19, 20], as well as tissue regeneration in the aged organism [21]. Different studies have

Figure 2

Circulatory system in parabiosis.
Organism A and B share a common blood supply, which spontaneously develops through anastomosis after surgery. Organisms with different physiological conditions may be used for parabiosis in order to assess the systemic effect of one organism on a particular tissue of interest in its attached partner.

shown that the regenerative capacities of tissues and organs are dependent on the proliferative activity of progenitor cells derived from tissue-resident stem cells [22–26]. A major hallmark of aging is that the regenerative properties significantly decline in most tissues. This has been partially attributed to impaired stem cell function [27–29]. However, whether these age-related effects were due to cell intrinsic changes or alterations in the microenvironment of stem cells required further investigation. In 2005, Conboy et al. used heterochronic parabiosis experiments to address this question. They showed that factors derived from the young systemic environment are able to activate molecular signalling pathways in hepatic or muscle stem cells of the old parabiont, leading to increased proliferation and tissue regeneration [21]. These findings strongly suggest that the age-associated impairment of stem cell function is induced to a significant extent by the molecular composition of the surrounding niche rather than by cell intrinsic changes alone.

In line with these remarkable findings, in 2011 our group showed that an old systemic environment can be detrimental for neural stem cell function and negatively regulate adult neurogenesis in brains of young heterochronic parabionts. This led to the discovery that factors in old blood are sufficient to decrease synaptic plasticity and impair contextual fear conditioning and spatial memory. Using a systematic proteomic approach (fig. 3), we were able to identify soluble factors that were significantly increased in blood plasma of old mice and humans. One of these factors was the chemokine CCL11 (eotaxin), a chemokine known to attract eosinophils to tissues. Indeed, systemic administration of CCL11 was sufficient to induce impaired adult neurogenesis in young mice [30]. Again, these findings provide evidence that the age-related decline in stem cell function can be attributed to changes in the systemic environment. Three more recent publications using heterochronic parabiosis further support this conclusion. Ruckh et al. reported that recovery from experimentally induced demyelination in the central nervous system (CNS) is enhanced in old mice that were exposed to a young systemic environment [31]. Salpeter and colleagues showed that the decline in pancreatic β-cell proliferation in old mice can be reversed in old parabionts paired with young mice [32]. And most recently, Loffredo et al. demonstrated that age-related loss of normal cardiac function leading to diastolic heart failure is partially due to the lack of certain circulating factors in old mice. Specifically, the authors reported that cardiac hypertrophy was reversible upon exposure of an aged animal to a youthful systemic environment through heterochronic parabiosis, and that growth and differentiation factor 11 (GDF11), which is significantly reduced in the blood plasma of old mice, has a critical role in this process.

The promise of parabiosis for regenerative medicine and the study of age-related diseases

The value of parabiosis as an experimental model is most evident for physiological or pathophysiological studies that affect the organism as a whole or that induce changes in the circulatory system. Naturally, such (patho)physiological studies are most relevant to understanding the complexity of higher organisms and disease processes, but they are also the most challenging to conduct and they cannot be replaced by in-vitro experiments. Indeed, it becomes increasingly evident that many diseases and biological processes, including aging, result in organism-wide, systemic changes contributing to local tissue alterations. Thus, studying an individual organ or cell type in isolation may not lead to a holistic understanding of events. This shift in thinking has been particularly noticeable with respect to the brain, where decades of neuroncentric research has started to give way to include studies on other brain cell types as critical regulators of cognition and disease. Moreover, a growing number of studies document effects of factors outside the brain including gut microbiota, diet and other systemic changes on CNS function [33–37].

Parabiosis is an ideal tool to investigate whether alterations occurring in an organism as a consequence of disease, aging, genetic background, infection, diet, exercise, etc. might result in circulatory changes altering the status of a healthy, young, uninfected or exercised organism (fig. 3). Thus, parabiosis may help in assessing the effects of any number of functional states of one organism on a partner organism through a shared circulatory system. This is, of course, only a first step in linking particular factors or cells

Biological phenomenon	**Involved humoral factor(s)**	**Animal species**	**Year**	**Reference**
Tumour grafting	Unidentified	Rat	1909	[8]
Rejection of skin grafts	Unidentified	Rat	1921	[41]
Regeneration of nerves	Unidentified	Rat	1923	[42]
Control of mammary growth during pregnancy	Unidentified	Rat	1927	[43]
Regulation of gonadal hormone secretion	Folliculin	Rat	1930	[44]
Growth stimulation in genetic dwarfism	Pituitary growth hormones	Mouse	1945	[45]
Amelioration of hyperglycaemia in diabetes mellitus	Insulin	Rat	1947	[46]
Mitotic activity in hepatectomised parabionts	Unidentified	Rat	1951	[47]
Regulation of energy intake and expenditure	Satiety factor (later termed leptin)	Mouse	1969	[10]
Regulation of blood pressure	Rinoprival hypertension factor (later termed PHF)	Rat	1969	[15]
Extension of lifespan after radiation	Multiple undefined factors	Rat	1972	[18]
Regeneration of muscle and liver	Notch ligand (Delta)	Mouse	2005	[21]
Regulation of neurogenesis and cognitive function	Eotaxin (CCL11)	Mouse	2011	[30]
Increased pancreatic β-cell replication	Unidentified humoral factors	Mouse	2013	[48]
Regulation of cardiomyocyte hypertrophy	Growth differentiation factor 11 (GDF11)	Mouse	2013	[38]
Remyelination of central nervous system	Unidentified	Mouse	2013	[31]

Table 1: Selected biological phenomena and humoral factors investigated by parabiosis.

to a newly discovered transmissible effect. But as the above cited reports show, it has indeed been possible to identify cells that regenerate an injured brain [31] or proteins that induce satiety [11], regenerate an aging heart [38] or accelerate aspects of brain aging [30]. A generalised approach to reveal such factors or cells using heterochronic parabiosis is to analyse systemic changes and correlate them with local alterations in a particular tissue of interest (fig. 2). Whether the identified candidates are necessary or sufficient to induce pathophysiology may subsequently be assessed by exogenous application or neutralisation as well as endogenous overexpression or ablation experiments in suitable animal models.

As many of the major untreatable diseases of our time are chiefly dependent on aging, understanding them will require more insight into the systemic changes and the resulting molecular alterations occurring with age. Animal

models can replicate many aspects of chronic diseases including heart disease, stroke, or neurodegeneration, yet we know very little about the contribution of the systemic environment and aging to these conditions. Parabiosis, and heterochronic parabiosis in particular, could help answer some of the fundamental questions in this regard: are circulatory factors or cells in a young organism protective against age-related disease, and *vice versa*, are factors or cells in the old organism predisposing or promoting disease in a younger organism? Parabiosis between mutant mice genetically manipulated to develop disease and age-matched or heterochronic, wild-type littermates or between other genetically engineered mice can help address the importance of systemic factors in the disease process. Variations of this paradigm can help elucidate pathways and mediators in many other conditions (fig. 3).

A revived future for parabiosis

Given the numerous breakthroughs, distant and very recent, it is curious then as to why this model is not being used more widely across different countries. In more recent history, most of the parabiosis studies have been conducted in the United States and in Japan, whereas only a few publications originate from Europe and only one, for example, from Switzerland (fig. 4) [39]. While there may not be laws or rules that would outlaw the procedure in certain places, it is possible that a visceral reaction towards the idea of surgically connected mice has prevented animal care committees from approving studies involving parabiosis. Based on our years of experience with this model, we have observed the well-being of paired mice far exceeds that of mice exposed to many pathogens, cancer, traumatic injuries or debilitating mutations. In fact, once they recover from surgery, mice conjoined by parabiosis regain their presurgical weights, their hormonal and endocrine profiles normalise and they start building intact nests together (our unpublished observations), an indicator of overall well-being in mice [40]. In our hands, such pairs can live together well beyond a year after the surgery although, to our knowledge, no controlled longevity studies have been done in mice. In a large rat study conducted in the mid-70s to assess the effect of whole body radiation on survival, only 1% of the pairs died as a result of the surgeries. Importantly, control pairs of nonirradiated age-matched parabionts survived on average almost 2 years following surgery
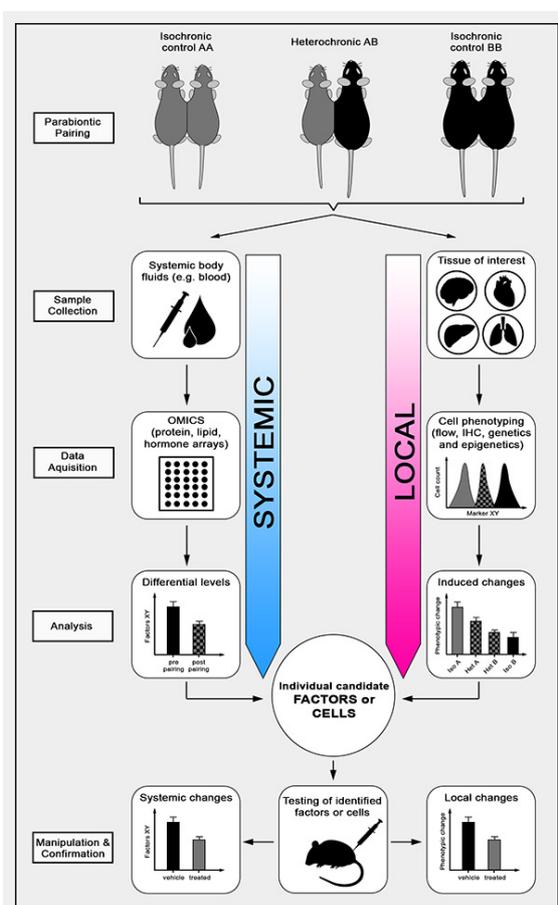

Figure 3

Heterochronic parabiosis.

Using heterochronic pairings of young (A) and old (B) mice allows assessment of the effect of a young systemic environment on a particular local tissue of interest in the aged partner and vice versa. Isochronic pairings (AA or BB) are important controls to exclude surgery-related observations and to determine age-related changes in the systemic environment. Briefly, systemic body fluids such as blood, lymph or cerebrospinal fluid are collected, assessed with omics tools such as protein, lipid or hormone arrays and analysed for differential levels of soluble factors and after parabiosis.

A particular tissue of interest is isolated, phenotypically characterised by flow cytometry, immunohistochemistry (IHC) or epi-/genetic measures and analysed for parabiosis-induced phenotypic changes. The integration of these data leads to the identification of individual candidate factors or cells that can subsequently be tested in a suitable mouse model.
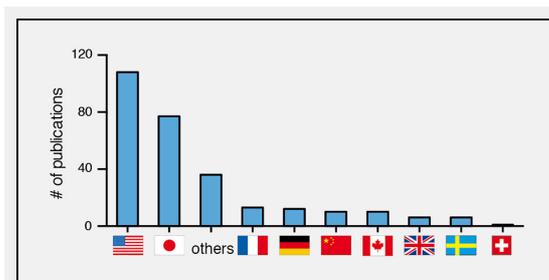

Figure 4

Parabiosis in different countries.

Publications including parabiosis experiments are listed for different countries. All values have been extracted from
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and showed only a 10% reduction in lifespan compared with normal, unpaired rats [3]. This study underlines again that the procedure is very well-tolerated in rodents and has minimal impact on life expectancy. Believing strongly in the benefits careful animal experimentation can provide towards relieving human suffering, while also appreciating the importance and value of oversight in the ethical use of animals, we advocate that parabiosis should once again be considered a viable procedure for the study of some of the most devastating diseases that affect humankind.

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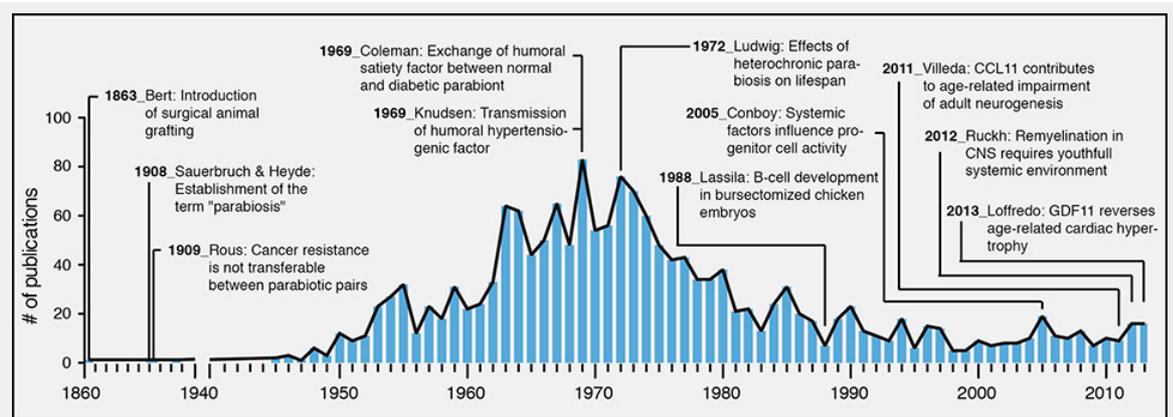
Figures (large format)

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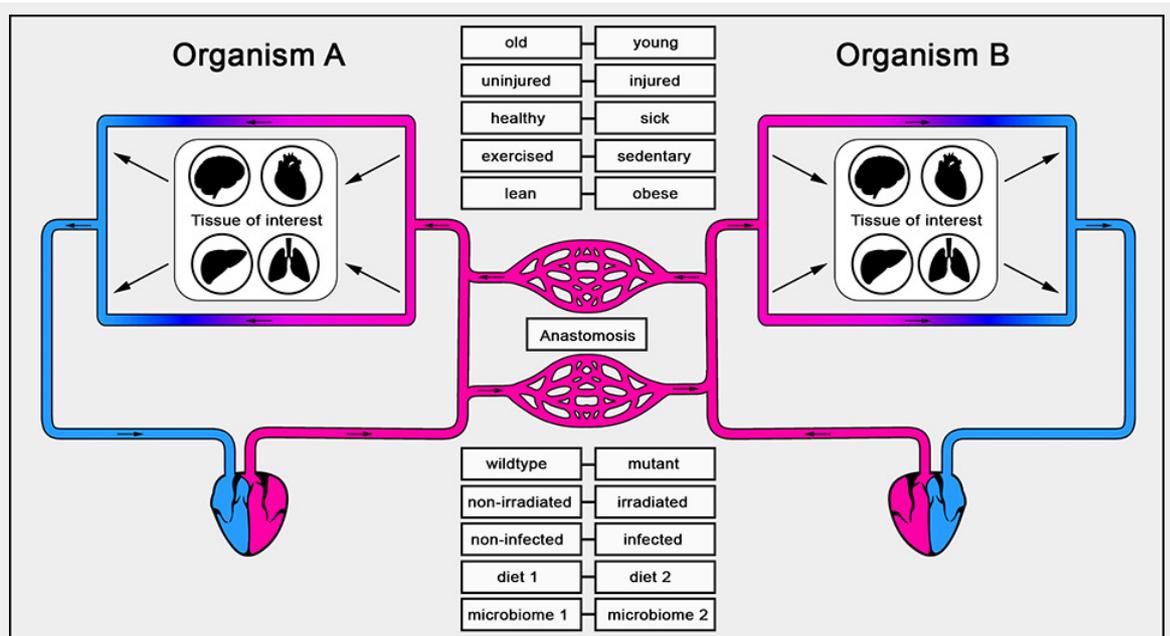
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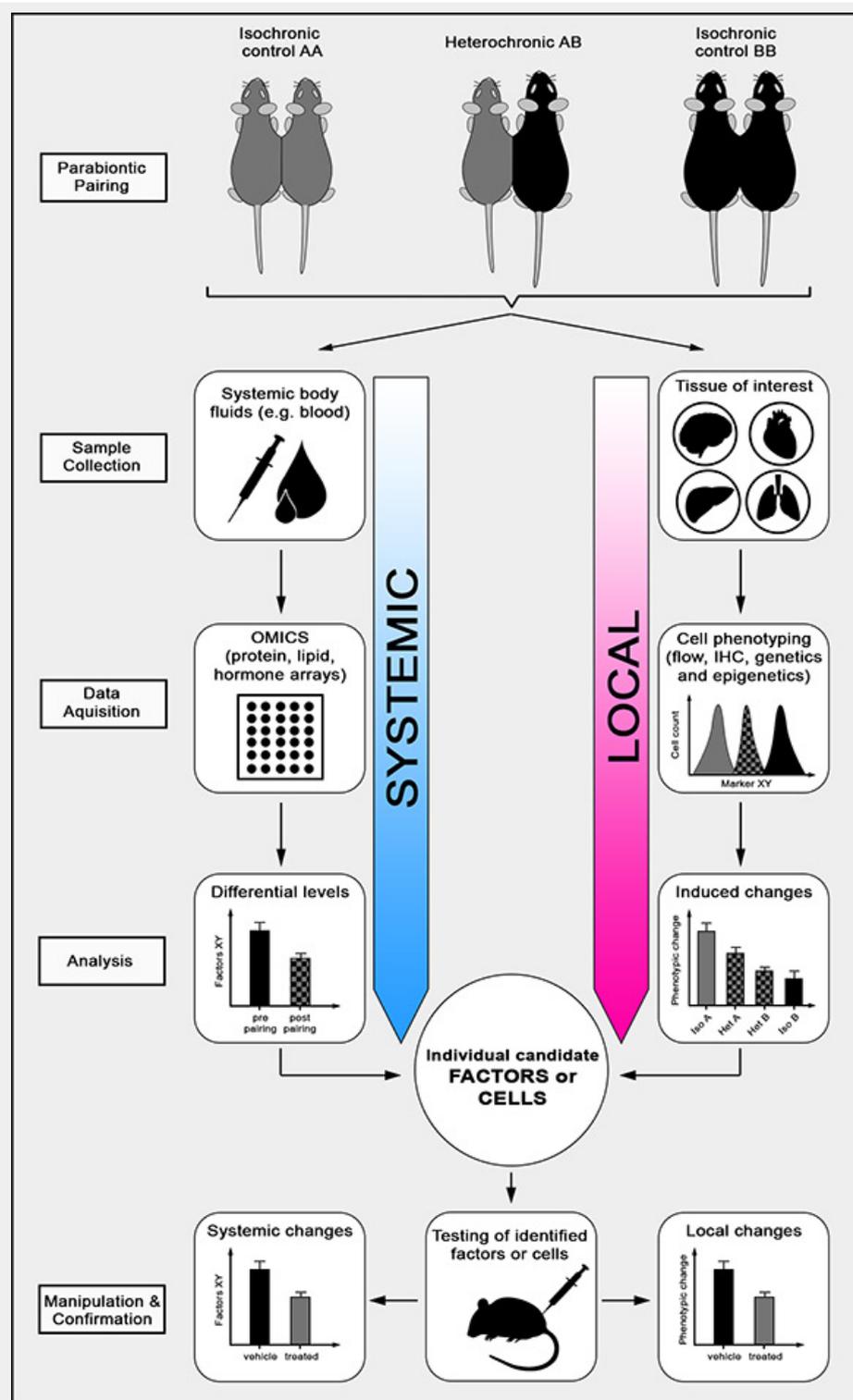
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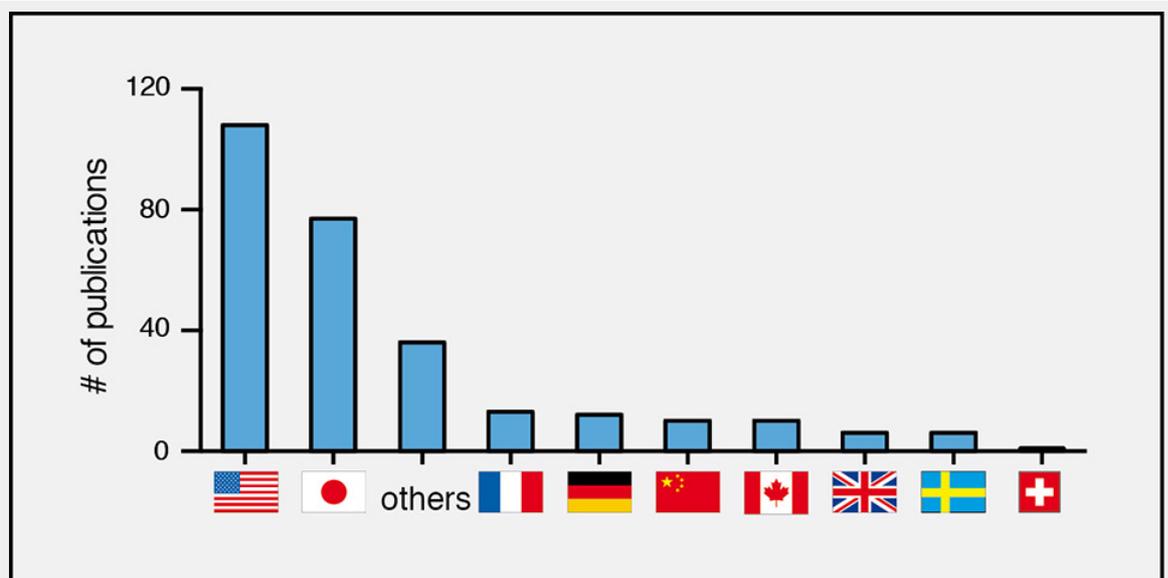
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