Longevity Market Intelligence Unit

LongevityTechnology

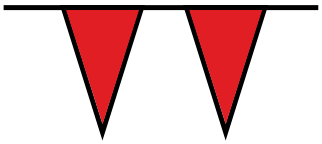
Understanding the reality behind the blood plasma hype:

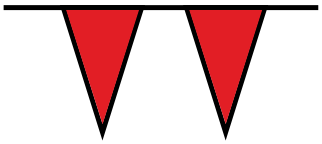
Young blood

This report is written in two sections.

- **Part 1 is a deep dive for scientists into the pathways and interventions that could deepen knowledge for a start-up or scientist interested in the space and looking for an overall view into young blood;**

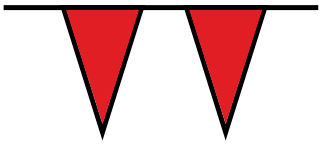
- **Part 2 is for potential investors explaining the investment opportunities in young blood.**





Executive summary

- Using blood as an “elixir of youth” has been explored throughout history as tales of blood’s restorative powers captured the human imagination. Hysteria and criticisms associated with “blood transfer” for aging have been propagated by mainstream media without proper assessment of the benefits that could be found in the blood;
- The circulatory system (blood) carries a rich density of information that can be distributed throughout the body and represents a powerful mode of communication; emerging evidence suggests that the body co-opts the circulatory system to coordinate aging via the secretion of factors called chronokines;
- Chronokines can be “progeronic factors” or “youth factors” that accelerate aging or rejuvenate, respectively. Most companies developing therapeutics are looking for chronokines in the plasma of the blood;
- Aging is driven by an imbalance in plasma chronokines and a dysfunctional communicome. There are several different plasma-based therapeutics that can be used to restore balance, each with their own strengths and weaknesses;
- In many ways, the potential of plasma-based therapeutics stretches far beyond that of other candidate longevity therapeutics. Plasma based therapeutics have the potential of cutting across various aging mechanisms, modulating several at once;
- By addressing the very signals that synchronise aging across the body, plasma-based therapeutics have massive potential for addressing a nearly endless range of acute and chronic pathologies. Targeting neurodegenerative disorders may be the “path of least resistance” for plasma-based therapeutics to enter the longevity market;
- Hematopoietic stem cells and thymus are resistant to the rejuvenative effects of plasma-based therapeutics. Combining plasma-based therapeutics with therapeutics that rejuvenate these tissues may offer the most comprehensive systemic rejuvenation protocol to date;
- Plasma-based therapeutics show promise for rapidly navigating the rigors of the clinical trial process;
- Currently, plasma-based therapeutics are quite expensive, but prices will drop as technologies mature and more data is collected, incentivising healthcare providers to cover costs and making it more accessible to the general public;
- Although there are still misconceptions about the ethical issues surrounding “young blood” there are a number of companies that are going through the clinical trial phases to ensure the efficacy and safety of their plasma-based therapeutics.



An introduction to Young Blood and the potential of plasma therapeutics

- Using blood as an “elixir of youth” has been explored throughout history as tales of blood’s restorative powers captured the human imagination;
- Hysteria and criticisms associated with “blood transfer” for aging have been propagated by mainstream media without proper assessment of the benefits that could be found in the blood;
- There is a growing body of preclinical and clinical evidence, initiating with discoveries in murine models, that the circulatory system could be a key to full body regeneration;
- Despite the growing evidence, scientists and ethicists are still fearful about applying these therapeutics, before thorough clinical trials, due to the safety risks and the ease of unlicensed transfusion of young blood;
- Harnessing the potential of young blood and its plasma derivatives offers the opportunity for developing a whole new paradigm for treating age-related disorders;
- Influencing the factors that cells routinely secrete into the bloodstream to communicate – called the body’s “communicome” – could be a worthwhile focus for rejuvenation and disease reversal.

“This report sets out the role for young blood plasma as a valid and scalable therapy for mitigating diseases of aging through medically valid rejuvenation techniques.”

Young Blood: from vampire mythology to verified therapeutics.

Ancient mythology or practical science?

From Ancient Greek mythology to stories of vampires, tales of blood's restorative powers have captured the human imagination for millennia. Pliny the Elder (AD 23-79), one of the great natural historians of the Roman Empire, described the mad rush of spectators into arenas to drink the blood of fallen gladiators. Hundreds of years later, Italian philosopher Marsilio Ficino (1433-1499) similarly promoted drinking young blood as a means for the elderly to regain their youthful vigour (Dolgin, 2021).

But in the past two decades, the idea of blood as an elixir of youth has leapt from the realm of mythology into the medical mainstream, with several high-profile papers demonstrating the regenerative capacity of young blood in aged mice. This research has led to the emergence of several new biotechnology companies that aim to harness our most essential bodily fluids to combat several age-related pathologies including Alzheimer's, stroke and inflammatory diseases. This has also caught the attention of wealthy seniors invested in preserving their own health, from billionaire investors such as Peter Thiel to North Korean dictator Kim Il-Sung (De Graaf, 2018).

In an ironic twist of historical and scientific fate, for decades clinics, hospitals and research institutes around the world have exchanged blood and blood components, such as plasma, platelets, red blood cells and white blood cells, performing approximately 1.2 million procedures per year (Young Blood Institute, 2017). All this without realising that the fountain of youth may be just skin-deep, coursing within their veins.

True hysteria did not kick in until this idea seeped into mainstream pop culture. This is exemplified by

In the past two decades, the idea of blood as an elixir of youth has leapt from the realm of mythology into the medical mainstream, with several high-profile papers demonstrating the regenerative capacity of young blood in aged mice.

Heterochronic Parabiosis: Vital connections to evolve blood/plasma therapeutics

Surprisingly, the answer to this question emerged from Frankenstein's monster-like studies involving a procedure called heterochronic parabiosis. Parabiosis is a 150-year-old surgical technique that unites the vasculature of two living animals. The word comes from the Greek para, meaning 'alongside', and bios, meaning 'life'.

In heterochronic parabiosis researchers suture together the circulatory systems of young and old animals that remain attached together for the rest of their lives. This grotesque procedure enables researchers to ask whether circulating factors in the blood of one animal affects the health of the other. This presents an invaluable tool to study the mechanisms that drive the process of aging and a seemingly endless number of diseases.

Clive McCay, a biochemist and gerontologist at Cornell University in Ithaca, New York, was the first to apply parabiosis to the study of aging with the astounding results – it extended lifespan of older mice by 4-5 months. This seminal study was followed by breakthroughs in oncology, immunology and endocrinology before it fell out of favour after the 1970s. However, at the beginning of the 21st century, members within Irving Weissman and Thomas A Rando lab at Stanford University brought parabiosis back to life to answer a fundamental question of our existence (Conboy, 2013). What impairs our body's ability to regenerate as we get older, leading to frailty and disease? Is it due to the accumulation of damage within our cells or due to changes in the surrounding environment that are not permissive to regeneration? In other words, is the plant too sick to grow or is the soil not fertile?

To answer this question, these researchers surgically conjoined the circulatory systems of a young and an old animal. If impaired regeneration is due to damage accumulation within the cells, then the old animal should continue in its decline, resistant to youthful factors circulating in the young animal's blood. What they observed was absolutely remarkable. Multiple organ systems – including muscles, stem cells and vasculature – in the older animal were rejuvenated to a youthful state. Not only that, the young animals became functionally older (Conboy, 2005). In other words, factors from within the young animals were rejuvenating the old animals and factors from within the old animals were making the young animals age faster. But what are these factors and how are they mediating rejuvenation (or accelerating aging) within the body? This is the fundamental question that is the prime focus of researchers within this field, the answers to which could carve a path straight to the coveted fountain of youth.

Factors from within the young animals were rejuvenating the old animals and factors from within the old animals were making the young animals age faster.

In order to find and harness these vital factors for clinical use, we would need a more practical approach. The pivotal heterochronic parabiosis experiments opened the door to a world of possibilities in terms of the way we target and address aging; but it was flawed for two reasons:

- Firstly, blood isn't the only factor being shared when two bodies are connected – animals also share organs, immune system, activity level, etc – and it is hard to distinguish the influence of young blood from other confounding variables.

- Secondly, it is not feasible or ethical to perform this procedure in humans. This challenge led to the creation of a small animal device that could gradually remove and exchange blood between young and old mice without the need for physically attaching their circulatory system. Low and behold, it mimicked many of the rejuvenative aspects of heterochronic parabiosis experiments (Rebo, 2016).

At this point, several labs (and even a few companies) were competing to distil the rejuvenate aspects of parabiosis into more practical approaches for clinical use. The ingenuity of the human mind never ceases to surprise as several therapeutic modalities emerged (discussed in section 2), seemingly overnight. This marked the birth of modern-day blood and plasma-based therapeutics.

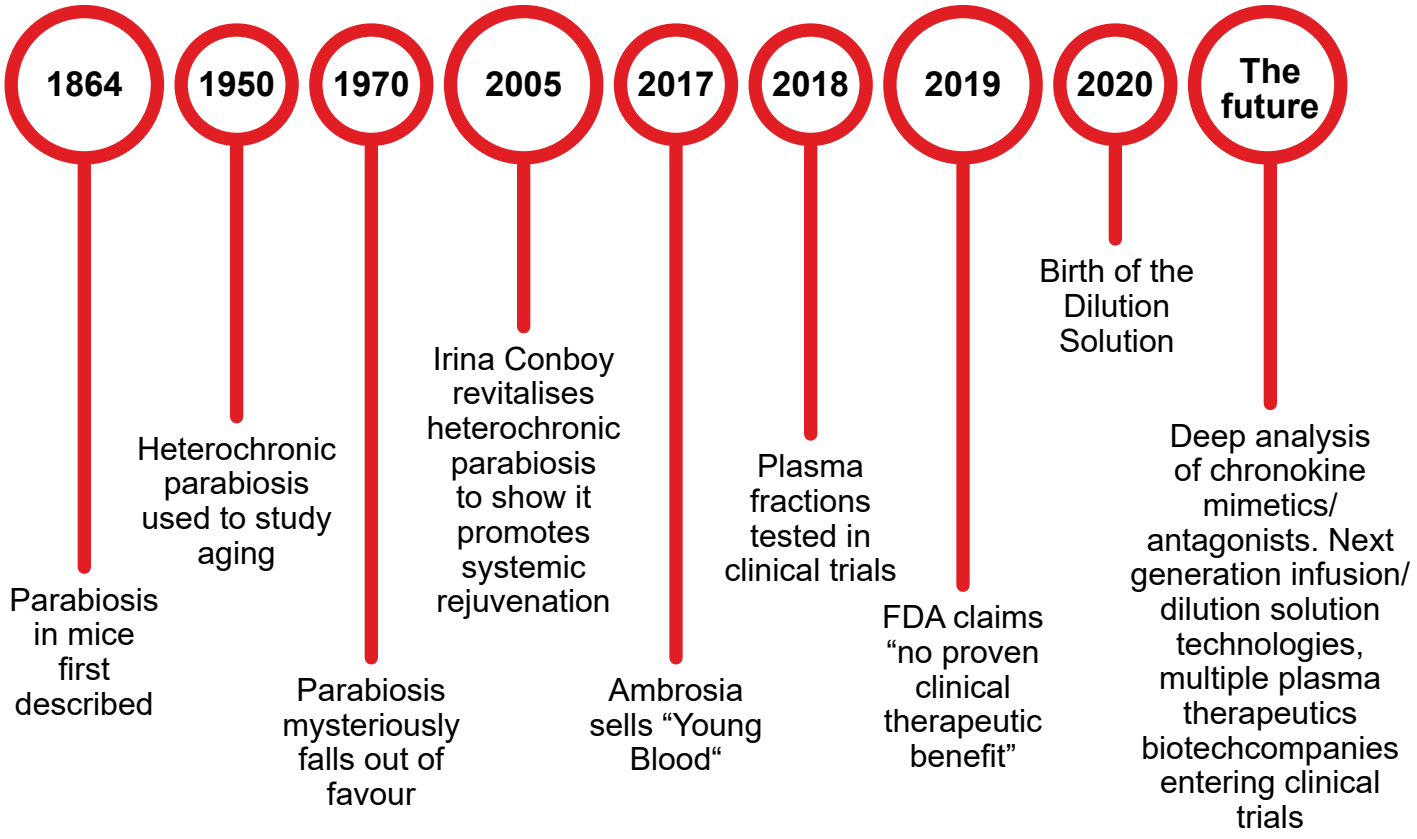


Figure 1. Graphic timeline of tech evolution. The power of young blood has had ancient allure for centuries, but plasma-based therapeutics have only experienced a rapid revolution since the 21st century.

Tapping into the communicome: a new rejuvenation paradigm

- The body's organs and tissues can communicate with one another, but how is this information propagated? The circulatory system (blood) carries a rich density of information that can be distributed throughout the body and represents a powerful mode of communication;
- Emerging evidence suggests that the body co-opts the circulatory system to coordinate aging via the secretion of factors called chronokines;
- Chronokines can be "progeronic factors" or "youth factors" that accelerate aging or rejuvenate, respectively;
- Most companies developing therapeutics are looking for chronokines in the plasma of the blood.

Findings in the last few decades have made it impossible to ignore the integrative nature of human physiology and disease. Organs and tissues once thought to act and behave largely independent of one another (for example, the brain and the gut) are now known to be in constant communication with one another and co-dependent in nature. Similarly, pathologies that were once thought to be separate are now understood to be intimately connected. This is exemplified by the rapid accumulation of comorbidities after an initial disease arises (Rando, 2021). This leads to the questions: "What is the source of biological information that is being propagated across the body leading to "things going to hell in a handbasket" and "how is this information being propagated?"

The obvious place to start such a mining expedition is in the blood. The circulatory system is the largest organ in our body and irrigates and connects all the cells, tissues and organs within our body. Factors within the blood are responsible for healing wounds, defence against microorganisms, maintenance of body temperature and pH, as well as transport of nutrients, oxygen and waste. Perhaps most importantly for the purposes of longevity and rejuvenation, these factors are also responsible for communication. The blood coursing through our circulatory system carries a rich density of information that is distributed from the tips of our toes all the way up to our brain. There are ten to twenty thousand molecules, represented in tiny concentrations, in circulation at any given moment (Matthew, 2021). These molecules reflect the health status of the various cells and tissues in our body and clinicians monitor and use this information to make decisions about disease diagnosis and therapeutic action. Scientific evidence suggests that clinicians aren't the only ones using this information to make decisions. The various organs and tissues in our body are doing the same, every moment of every day (Rando, 2021).

Factors within the blood are a circulating representation of all the cells in our body and represent a powerful mode of communication that can be used to coordinate various responses to our environment, stressors and energy distribution across the body. Examples of this include the secretion of hormones that influence the behaviour and health of distant tissues and the inflammatory response that recruits cells and energetic resources from across the body to a given location. Emerging evidence suggests that the body co-opts the circulatory system to coordinate aging via the secretion of factors called chronokines (Sullivan, 2019).

Chronokines are broadly defined as molecules that increase or decrease with age. Of these molecules, a meaningful percentage influences the rate at which we age. Those that are found to increase as we age and accelerate the pace of cellular aging are called “progeronic factors’’. Those that are critical mediators of cellular rejuvenation and tend to decrease with age are called “youth factors’’ (Figure 2). Together, the ratios of – and interactions between – progeronic and youth factors synchronise aging across the organs and tissues of our body (Hunt, 2020). Thus, identifying chronokines and characterising how they influence the aging process opens the possibility of “changing the conversation” within the aging communicome to one of rejuvenation.

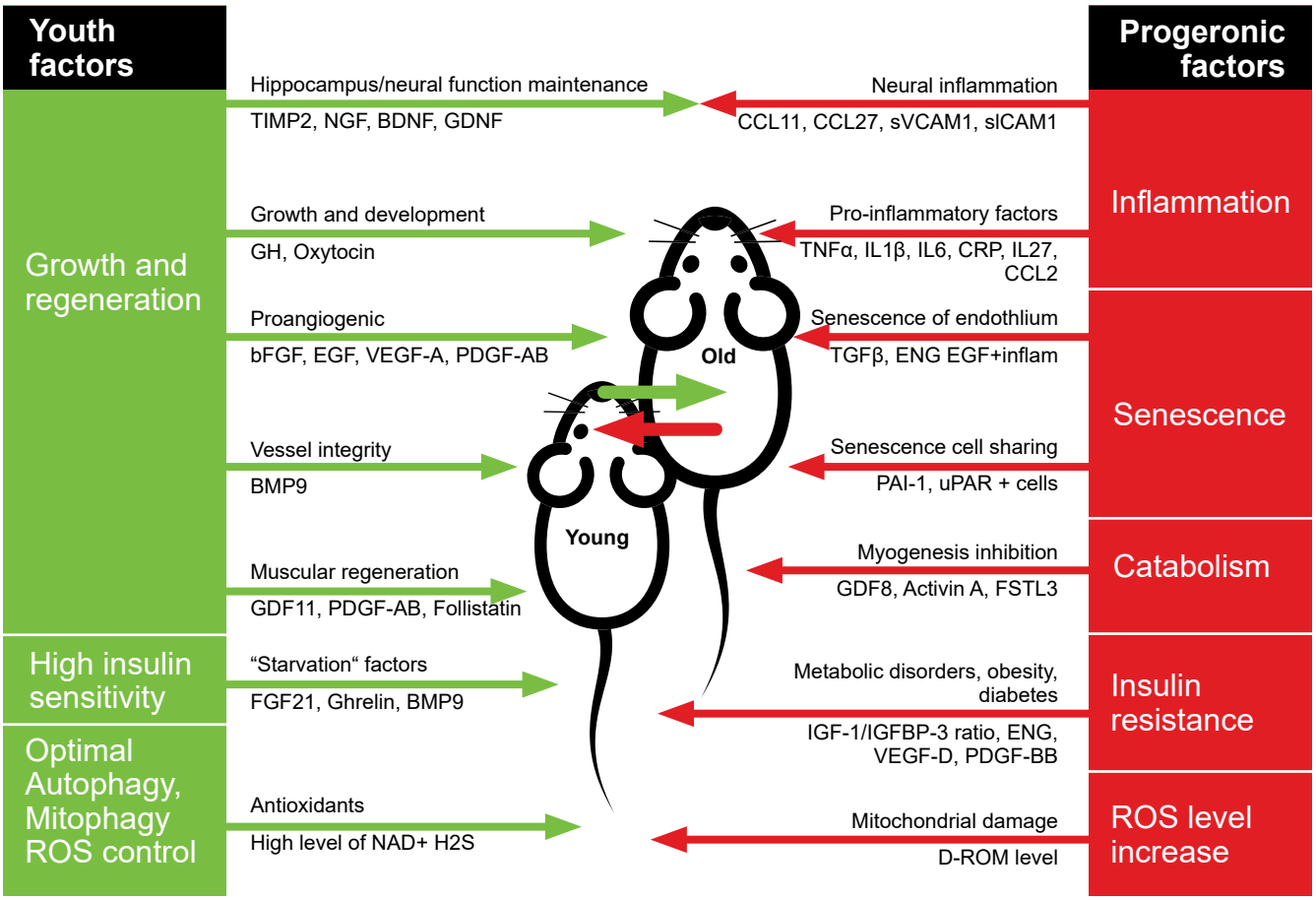


Figure 2. Chronokine factors in the plasma and their function. Chronokine factors play critical roles in growth, regeneration, inflammation, autophagy, senescence and mitochondrial health. Progeronic factors play roles in inflammation, senescence and metabolism. Adapted from Rybtsova et al., 2020.

Most companies developing therapeutics within this space are focused on studying and harnessing the plasma component of blood. Consequently, this is what we will focus on for the rest of the report. Believe it or not, our plasma is mostly made up of water with less than 10% of its composition being solids (Matthew, 2021). And it is within this tiny percent of mass where our "fountain of youth" resides (Figure 3). Harnessing the plasma within blood is quite simple. We can extract plasma, filter, or replace it, and return it back to the patient quite easily. Due to the ease of the process, companies can analyse plasma from many individuals with AI and bioinformatic approaches to identify relevant chronokines and manufacture drugs that mimic or block them.

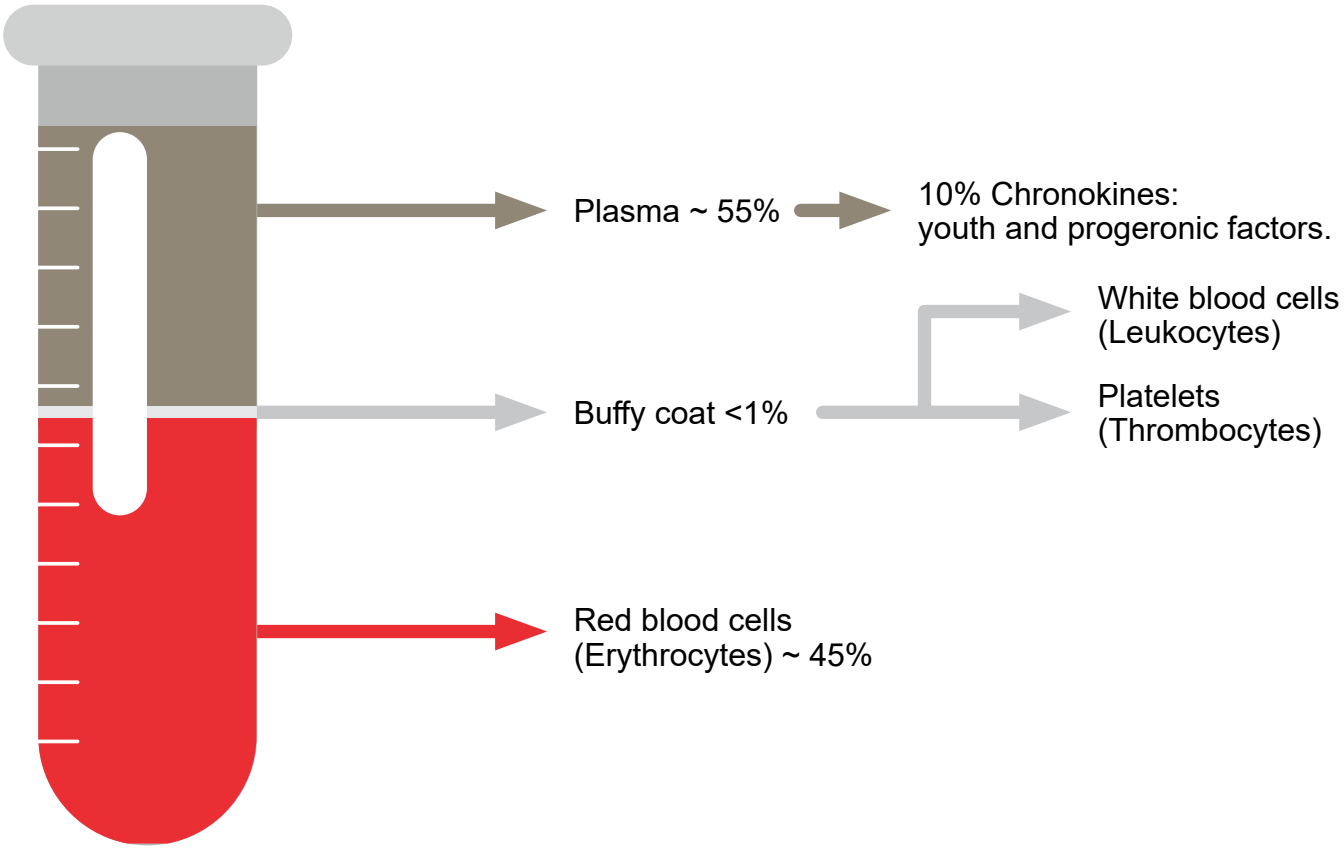
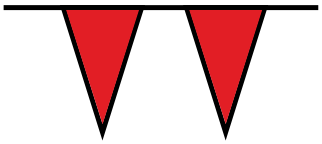


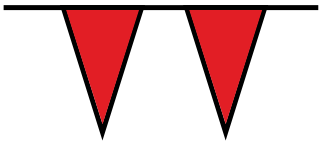
Figure 3. The blood and its components. Our blood consists of red blood cells, white blood cells, platelets and plasma. Plasma is the "liquid base" of the blood and makes up 55% of its total composition, the rest being made up of cells. The plasma is where chronokines reside and these factors have been identified as powerful modulators of the aging process. Adapted from Cornell, 2021.

Part 1: For the scientist looking to deepen their knowledge into the modalities of young blood and plasma therapeutics and their relation to longevity.



For the scientist looking to deepen their knowledge into the modalities of young blood and plasma therapeutics and their relation to longevity

- Technologies have been pivotal in illustrating how proteins within the plasma portion of blood change as we get older;
- Manipulating the plasma proteome could have powerful implications for the future of longevity;
- There are many questions to address when optimising plasma-based therapeutics;
- You can “put in the good” with: therapeutic plasma exchange, plasma fractions and chronokine mimetics;
- You can “get rid of the bad” with: neutral plasma exchange, extracorporeal filtration and chronokine antagonists;
- Aging is driven by an imbalance in plasma chronokines and dysfunctional communicome. There are several different plasma-based therapeutics that can be used to restore balance, each with their own strengths and weaknesses;
- Young blood is appealing as it contains a natural cocktail of youth factors. Young blood transfusion is the quick and dirty approach to plasma transfusion as it carries multiple safety risks;
- Therapeutic plasma exchange with fresh frozen plasma retains many of the benefits of whole blood transfusion but with fewer safety risks. Challenges include significant variability between plasma samples and several “unknowns” with regards to what factors are being infused into the body;
- Technological advances have helped facilitate identification of specific chronokines that modulate aging and disease progression, thereby cutting down on the number of “unknowns” significantly. But in doing so, we lose the value of a polypharmacy approach;
- The risks of plasma transfusion and the challenges of focusing on single factors may be greatly mitigated by the use of refined plasma fractions consisting of sets of chronokines;



- The field of plasma-based therapeutics went through a massive transformation when researchers discovered that removing the influence of toxic factors could be just as effective as introducing youth factors;

- Neutral plasma exchange utilises transfusion of neutral fluids (saline and 5% albumin) to dilute away progeronic factors and activate a powerful “molecular reset” of the communicome that promotes rejuvenation;

- Extracorporeal filters and chronokine antagonists can selectively remove progeronic factors to alter disease progression. But it may not have as wide-ranging benefits as diluting whole plasma; and

- The plasma-based therapeutics field is very much divided into “camps”, but it is likely that the most effective longevity solution will involve a combination of supplementing youth factor and inhibiting progeronic factors.

“The evolution of plasma-based therapeutics is happening at light speed due to emerging technologies”

All the plasma-based therapeutics discussed in this report are derivatives of the seminal, yet primitive, heterochronic parabiosis experiments. From these studies, we discovered the world of chronokines and how they act in concert to drive diseases or systemic rejuvenation. As is often the case, technologies such as artificial intelligence, bioinformatic systems,and high throughput screens help us explore this world of chronokines and harness them to improve our health. This has facilitated the development of next generation approaches that help narrow down the most impactful chronokines that influence the rate of aging. These chronokines often play fundamental roles in regulating tissue repair, stem cell regeneration, inflammation and metabolism (Kang, 2020).

A provocative paper out of the Wyss-Coray lab illustrates how impactful these technologies can be in fuelling the evolution of plasma-based therapeutics. His research used a novel bioinformatic approach to analyse the plasma proteome of over 4,000 adults (18-95 years old) across time and determined that the proteome changes with age in a relatively defined and programmatic fashion. Through this analysis, they determined that undulating levels of clusters of plasma proteins, moving in distinct patterns, culminate in the emergence of three waves of aging that occur in the 4th, 7th and 8th decade of life (Figure 4). These three waves of aging also coincide with the incidence of several chronic diseases of aging. In other words, according to this plasma proteomic clock, our rate of aging accelerates (in a coordinated fashion) at three distinct time points in life (Lehallier, 2019). If our plasma chronokine profile indeed serves as an integrative signal that coordinates aging across the human body, understanding and influencing the behaviour of this profile has powerful implications for the future of longevity. Several critical questions arise from this finding that must be addressed to optimise the efficacy of plasma-based therapeutics.

The three peaks of aging proteins

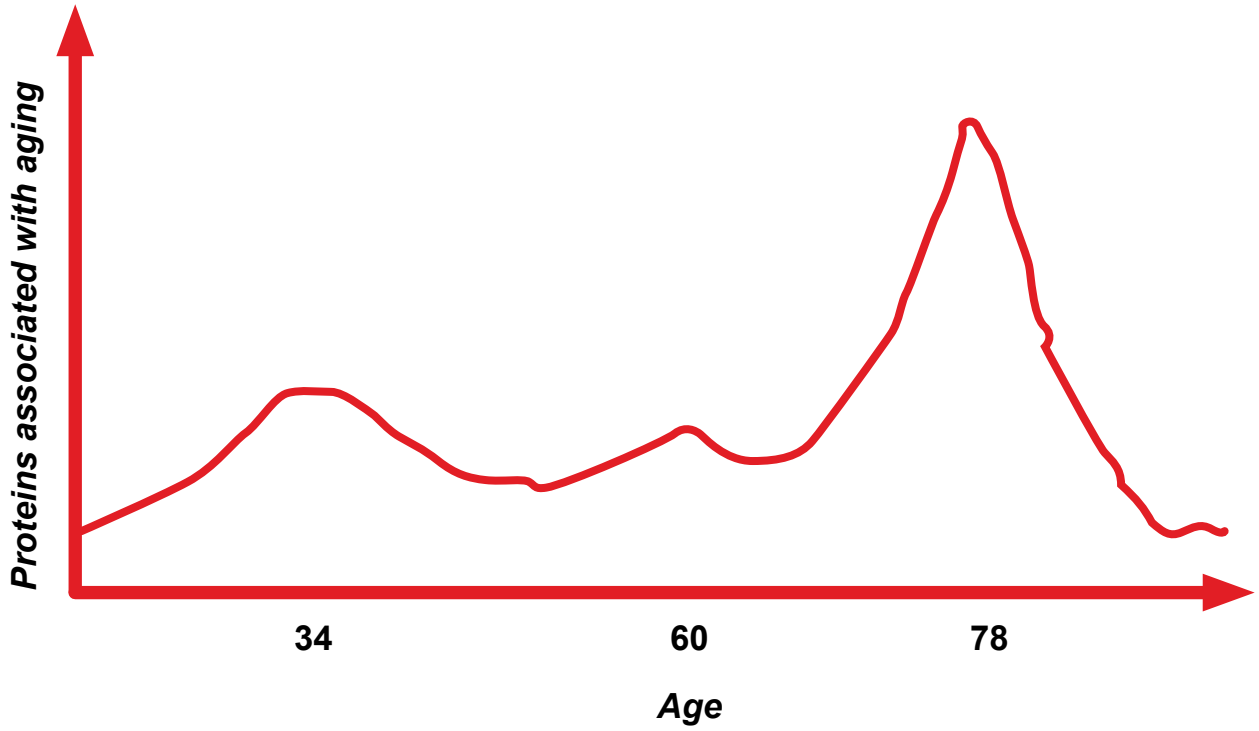


Figure 4. Plasma proteome clock: 3 waves of aging. The process of aging seems to accelerate at three distinct time points (34, 60, and 78 years old) in life that correlate with aberrant levels of progeronic factors in the blood. Adapted from Eric Topel, 2019.

Optimising the efficacy of plasma-based therapeutics

Infusion and dilution solution for systemic rejuvenation

There are two strategies that emerge from our understanding of chronokines and how they influence aging: the infusion solution and the dilution solution. These strategies are conceptually simple but filled with technological challenges. Having this framework in place gives us a map to help make sense of the longevity potential of the rapidly emerging technologies within this space. This map can help guide us in terms of how we engage with, invest in and develop these technologies moving forward; so, what are the infusion and dilution solutions?

Infuse the good

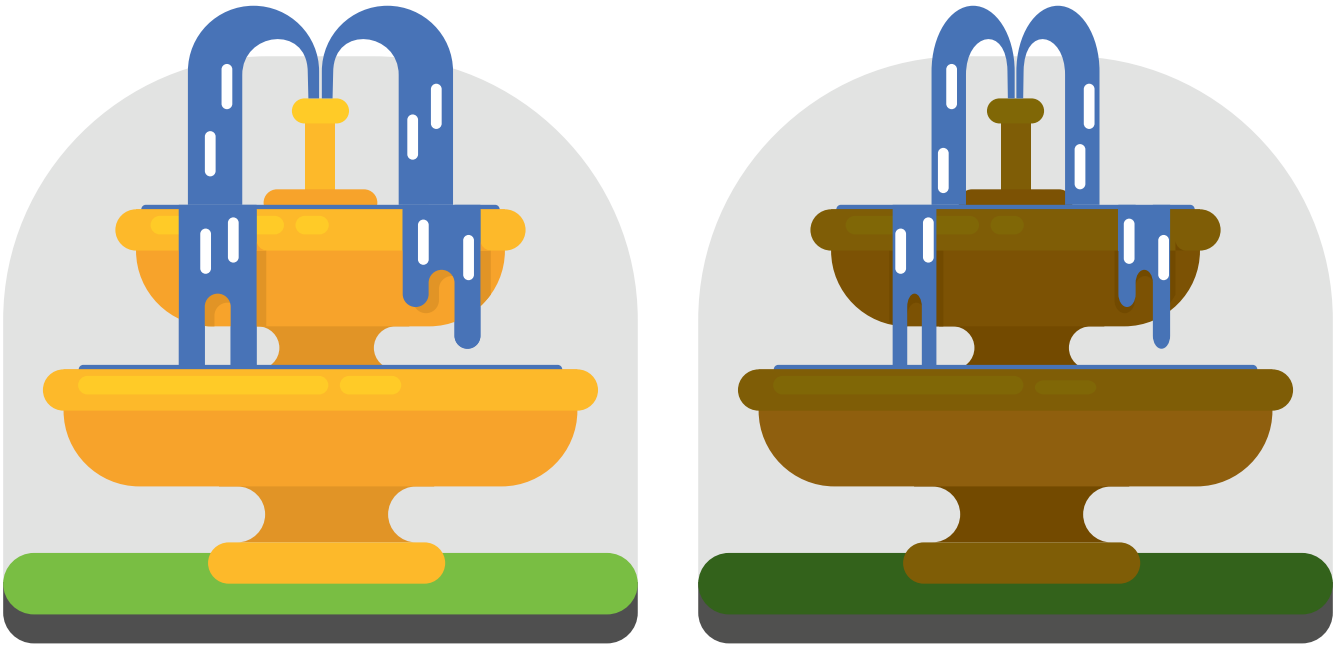
Therapeutics that fall under the category of infusion solution focus on replenishing youth factors within the blood that are critical for our body's ability to regenerate and repair (Rae, 2021). These technologies include: fresh frozen plasma exchange (FFP), plasma fractions and chronokine mimetics. In some ways, the infusion solution is the more tantalising explanation, and for a long time, the most popular one, as it suggests that we all possess an intrinsic fountain of youth that dries up over time. If scientists could just identify these key "youth promoting" factors, then companies could package and deliver them to revive our aging fountain (Figure 5).

Therapeutics that fall under the category of infusion solution focus on replenishing youth factors within the blood that are critical for our body's ability to regenerate and repair.

Dilute the bad

Therapeutics that fall under the category of dilution solution focus on removing or inactivating progeronic factors within the blood that accelerate the process of cellular aging. The release of progeronic factors over time are thought to serve a dual role – like a one-two punch in boxing – that accelerates damage accumulation within the body and, at the same time, suppresses the release of youth factors necessary

for regeneration and repair (Mehdipour, 2021). In our “fountain of youth” metaphor, progeronic factors are the rust that builds up over time and clogs the pipes, effectively drying up our fountain and aging it at the same time. Diluting these factors is like performing an internal cleanse of our fountain that creates the right environment so that the waters of youth can run again (Figure 5). Technologies that adopt the dilution solution include: neutral plasma exchange (NPE), extracorporeal filtration devices and chronokine antagonists.longevity potential of the rapidly emerging technologies within this space. This map can help guide us in terms of how we engage with, invest in and develop these technologies moving forward; so, what are the infusion and dilution solutions?



Young fountain
Strong flow of youth factors

Old fountain
As the fountain ages, progeronic factors clog the pipes, stemming the flow of youth factors and creating rust

Figure 5. The fountain of youth. The “young” fountain is represented by a strong flow of water (youth factors) that promotes rejuvenation. The “old” fountain has developed rust (progeronic factors) that clog the pipes of our fountain, drying up the flow of water (youth factors) and aging it at the same time. The infusion solution strategy involves adding more water (youth factors) to the pipes of our fountain. The dilution solution strategy involves cleaning the rust from the fountain so that the water can run freely once more.

Let's recap. We all possess an intrinsic fountain of youth within our plasma which is represented by a favourable ratio of chronokine youth factors. Our fountain dries up as this ratio tips in favour of progeronic factors. This imbalance of chronokine factors is what ultimately drives the aging process. We can correct this ratio via two simple strategies. Adding more youth factors (infusion solution) or removing progeronic factors (dilution solution). This in turn restores the flow to our fountain of youth and provides the necessary current for rejuvenation (Figure 6).

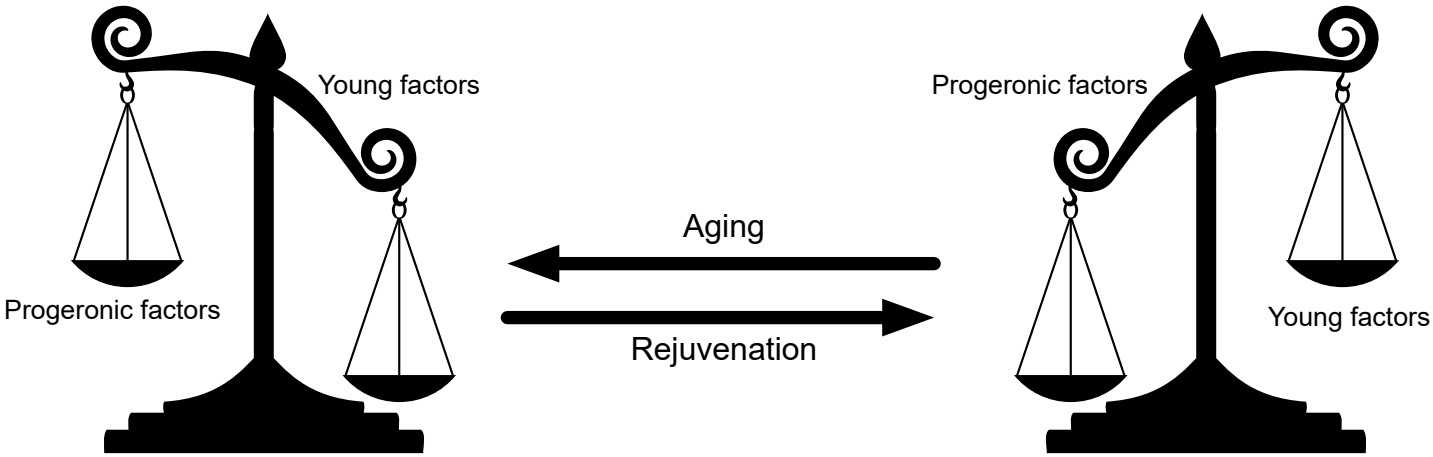


Figure 6. Chronokine balancing act. When we're young, youth factors within the plasma outweigh progeronic factors and this creates a permissive environment for rejuvenation. As we age this balance is tipped in favor of progeronic factors, aging our fountain and preventing rejuvenation. We can correct this ratio via adding more youth factors or removing progeronic factors.

So, what are the specific technologies we can use to renovate our fountain and what are their strengths and weaknesses as a therapeutic modality?

The evolution and optimisation of plasma-based therapeutics

The evolution of blood-based therapeutics is driven by the pursuit to strip away layers of complexity from heterochronic parabiosis, the foundational intervention, and extract (or distill) the most potent features that can practically be applied in humans to mediate systemic rejuvenation. Figure 7 demonstrates the evolution of plasma-based therapeutics into the different infusion and dilution technologies. For simplicity, a "cheat sheet" that summarises each can be found at the end of this section. However, we will deep-dive into each of the infusion and dilution solutions to look at the process and the advantages/disadvantages of each.

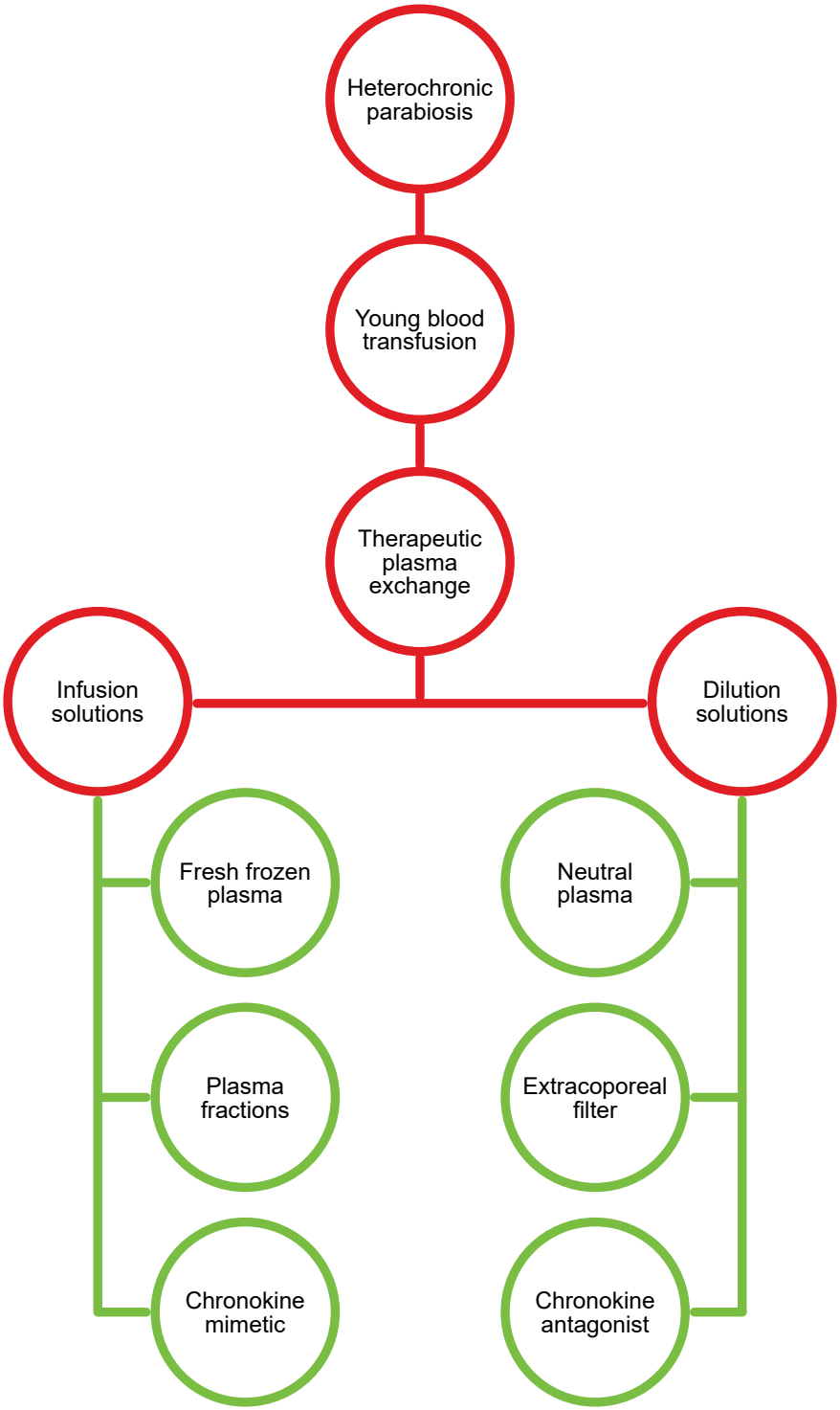


Figure 7. The evolution and optimisation of plasma-based therapeutics

Infusion solutions: Fresh frozen plasma, plasma fractions and chronokine mimetics

The proof is in the plasma: therapeutic plasma exchange with Fresh Frozen Plasma

Within the longevity field, there remains a primal urge to find the single "magic bullet" that can address all of our health issues. But the more we learn about the drivers of various pathologies the more convincing it becomes that no single drug can assuage this need. The presence of a single molecular target hub that underlies all the mechanisms that drive aging and disease is highly unlikely and, therefore, a polypharmacy approach would be the most effective solution. This polypharmacy approach came in the form of harnessing young blood for systemic rejuvenation, and it is heavily supported by preclinical data (Kheifets, 2019). But the many complications of young blood transfusion forced scientists to pause and reflect on the best approach for harnessing the rejuvenative power of the blood. Enter scene: plasma-based therapeutics.

Multiple studies (both on model organisms and humans) have shown that therapeutic plasma exchange with young plasma captures many of the rejuvenative aspects of whole blood but without as high risk for adverse effects.

Our plasma consists of a natural mixture of components (notably chronokines) that have the ability to act multimodally, modulating diverse mechanisms that can converge to change the trajectory of age-related diseases (Conese, 2017). Fresh frozen plasma (FFP) is readily available as the blood donation system is well established worldwide. Further, plasma can be frozen within 8 hours of collection and reliably preserved for up to one year. Multiple studies (both on model organisms and humans) have shown that therapeutic plasma exchange with young plasma captures many of the rejuvenative aspects of whole blood but without as high risk for adverse effects (Basu, 2014).

One issue with FFP exchange is the potential for simultaneously transferring factors that counteract and limit the rejuvenating potential of more potent, purified

youth factors. Given the association of youth factors with growth and developmental processes, the possibility also exists for transferring factors that increase the risk of cancer and other diseases. Other safety risks include significant potential for cross-reactions and transfer of pathogens that lead to undesired immunogenicity. Other non-infectious complications of concern include transfusion-related acute lung injury (TRALI) and transfusion-associated coronary overload (TACO), as well as allergic reactions (Kiprov, 2020).

Finding "the goldilocks zone": plasma fractions

The risks of whole blood/plasma transfusion and the challenges of focusing on single factors may be greatly mitigated using refined plasma fractions consisting of sets of chronokines. The blood product industry has developed methodologies to take source plasma donations (from thousands of donors) and fractionate pooled plasma (based on specific chemistries) into more defined components to provide a series of plasma-derived therapeutic products. This gives the advantage of industrial processes that can scale, introduces additional safety measures and filtering steps that reduce immunogenic properties and minimise the potential for pathogen transmission, as well as provides multiple therapeutics from each donation that act in synergy to rejuvenate the body (Castellano, 2019).

Harnessing and targeting specific chronokines: chronokine mimetic

Fresh frozen plasma exchange is a broad approach that can be used to infuse multiple different

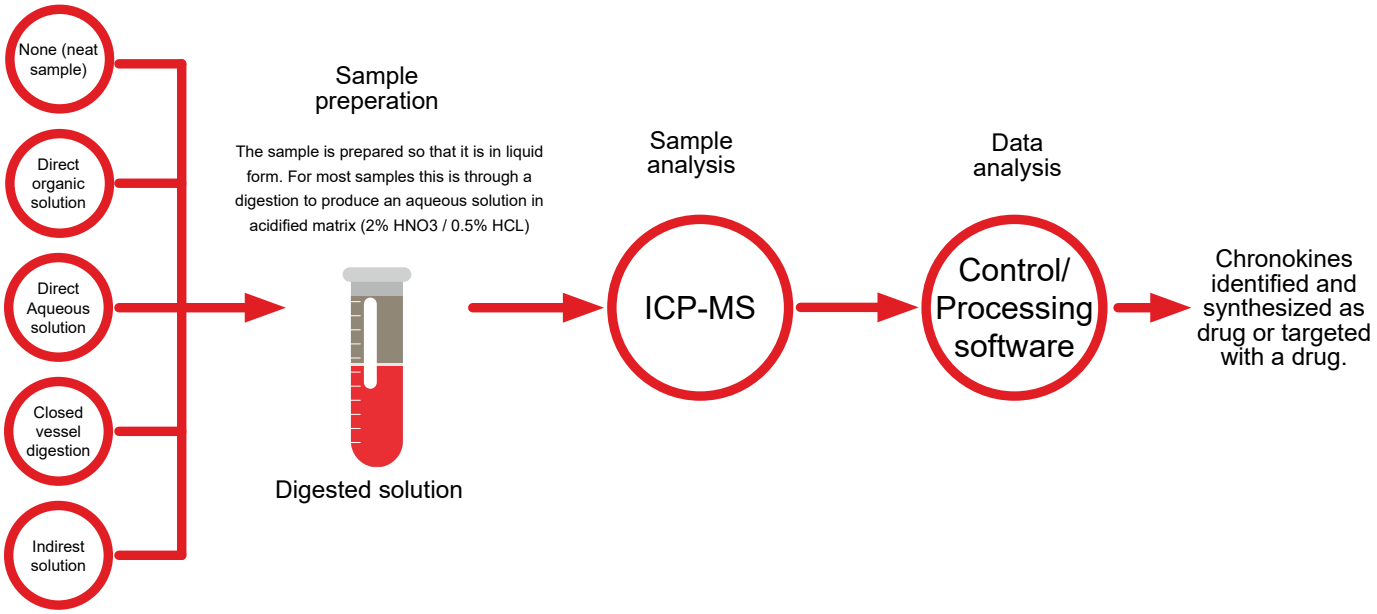
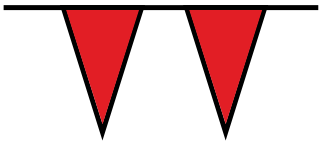


Figure 8. The plasma of many individuals can be extracted and analysed to identify progeronic and youth chronokines



chronokines at once. But the fact remains, it is neither a targeted approach nor one that is amenable to personalisation because effects are mediated by a variable set of chronokines in another individual's body. Some factors being acted upon may be beneficial, some may be detrimental. There are many factors in the plasma that are still uncharacterised and so it is hard to know long term health consequences. Further, conflicting influences of factors on different tissues may complicate rejuvenation-related treatment (Castellano, 2019). This sent scientists on a hunt to find specific plasma youth factors that are most impactful in conferring rejuvenative benefits for a given disease.

Technological advances within the last 5 years have given us tools that we can use to extract valuable insights from large quantities of data. These technologies have been extremely valuable for parsing the complexity of different chronokines and their interactions within the plasma. Identifying specific chronokines that modulate aging and disease progression may yield practical and personalised treatments more quickly, and with fewer ethical and safety concerns, than plasma exchange. Further, this approach may be better suited for our current regulatory system in which therapeutics are developed and positioned to target specific diseases.

However, it must be considered that the functional roles, complexity and sheer quantity of potential candidate factors within the plasma are still far from being understood. The communicome consists of tens of thousands of factors, all interacting with one another in a context-dependent manner within our plasma. It could be that chronokines do not act directly but depend on other factors (that are yet to be discovered) to compound their rejuvenative effects (Rebo, 2015). Regardless, tremendous progress is being made every day in shining a light on what is really going on within the microscopic depths of our plasma that regulate the aging process.

Whether the focus is on plasma transfusion, plasma fractions or specific chronokines, it has become clear from preclinical data that no single factor is responsible for the benefits of young blood, as none of these individual factors is as powerful in reversing aging as parabiosis itself. In these early days, investing in R&D to study the composition of young blood and how it changes over time can help us understand the molecular mechanisms that underlie aging and rejuvenation.

One of the great things about the world we live in today is that technology is advancing at an unprecedented rate and being integrated across fields and disciplines. Biotech companies that aren't taking advantage of the rising tide of technological advancements are quickly left behind. One consequence of this technological boom is that it is becoming a lot cheaper and easier to measure molecules in the blood, paving the way for more studies (and larger studies) that elucidate molecular mechanisms of aging and rejuvenation. There is a vast sea of plasma proteins and other constituents yet to explore, many of which may be involved in driving health and disease. Technologies that help us navigate and explore the complexities of plasma dynamics and its contents across time hold great promise to lead us straight to the fountain of youth.

Dilution solutions: neutral plasma exchange, extracorporeal filters and chronokine antagonists

Neutral plasma exchange

Neutral plasma exchange (NPE) is an FDA approved treatment that involves gradually removing plasma (up to 100%) and replacing it with neutral physiological fluid (typically serum with 5% albumin). Plasma is typically exchanged in volumes of 1-1.5 L at a time (consider we have a total of ~5 L of blood in our body). This process effectively dilutes factors in the plasma that are associated with or causative of certain disease states. Like plasma infusion, the dilution of plasma also converges on multiple mechanisms that drive aging. This procedure has been used within the clinic to “cleanse” the plasma of various pathological metabolites including antibodies, immune complexes, and pro-inflammatory molecules that lead to autoimmunity (Malchesky, 2018).

Leading edge research is revealing the power of utilising NPE to dilute progeronic factors and mitigate the progression of several age-related diseases. Several recent studies have shown that plasma exchange using age-neutral saline as a replacement fluid achieves or exceeds the rejuvenation effects observed in the original parabiosis models. This includes enhanced muscle repair (following injury), reduced liver fibrosis and fat accumulation, and increased neurogenesis in the “memory” region of the brain called the hippocampus. In fact, effects on the hippocampus were 8x more potent than those observed in parabiosis experiments (Mehdipour, 2020). NPE has been shown to dilute other toxic factors more commonly associated with age-related diseases such as protein aggregates, senescence associated secretory peptides (SASP), as well as regulatory proteins and RNAs that suppress the expression of youth factors (Malchesky, 2018).

The post-NPE serum rejuvenated the health of these stem cells and they regained their proliferative potential.

The dilution solution has introduced an entirely new scientific paradigm to the longevity field which reveals that improving the health and function of multiple aged organs doesn’t require complex approaches to design, synthesise and infuse rejuvenative molecules into the body. Rather, all that may be needed is a drop of saline to dilute away the progeronic molecules created by our own aging tissues. This in turn clears

the toxic chemicals within the soils of our internal environment and transforms it to one that is conducive of regeneration and repair. In this way, NPE may be the closest thing to a “magic bullet” longevity intervention being developed today as it holds promise to be broadly effective across several types of cellular dysfunction, pathogenic molecules in the blood and, ultimately, diseases.

NPE is effective at diluting away progeronic factors and stymying the flow of damage accumulation to delay the rate of aging. But what confers its long-lasting benefits and systemic rejuvenation? In other words, what prevents the progeronic factors from building right back up in the plasma and driving the aging process forward once again? Exciting data from the Conboy lab helps piece together the mechanism.

Within these experiments, researchers took some mouse stem cells and grew them within serum taken from old mice to observe how it affected their health and behaviour. They found that the aged serum adversely affected the health of the cells and inhibited their proliferation (the ability to divide and thrive). Interesting, but not entirely surprising. Next, the scientists took the same stem cells (that were grown in the aged serum) and grew them in the serum of old mice that were treated with a single NPE. What they observed next was mind-blowing. The post-NPE serum rejuvenated the health of these stem cells and they regained their proliferative potential.

What is even more intriguing is that these results were replicated with human serum.

Specifically, researchers observed the same adverse effects on mouse stem cells that were grown in the aged serum of four volunteers (aged 65 to 70). Amazingly, the patient’s serum after a single NPE restored the health of the stem cells. When the scientists dug a little deeper to find out exactly what mechanisms were restoring the health of the cells, they found that the post-NPE serum effectively “reset the signalling environment” to one enriched in chronokine “youth factors”, many of which are well known anti-inflammatory factors that create a permissive environment for stem cell proliferation (Mehdipour, 2021).

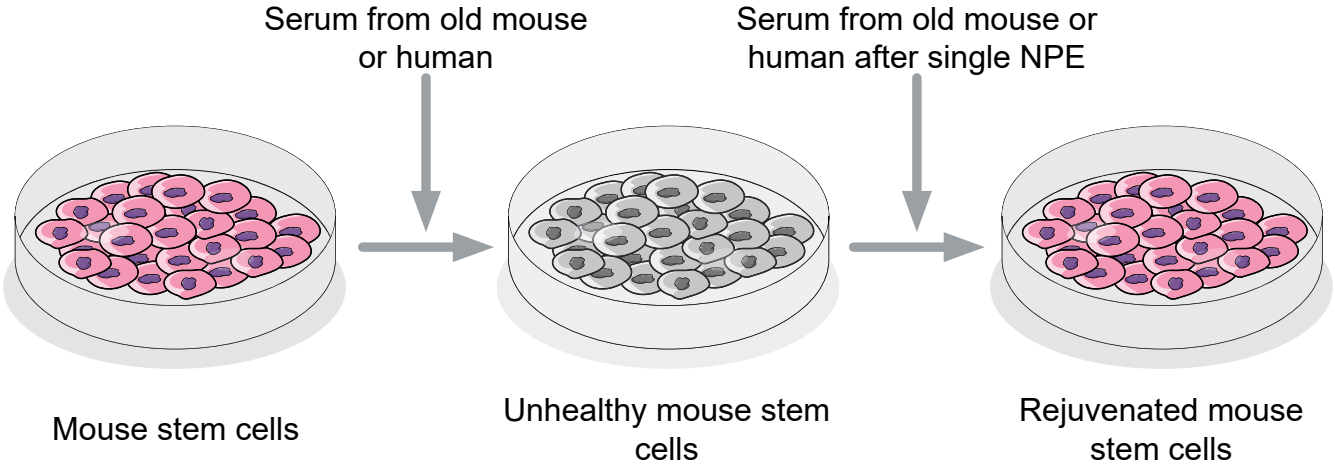
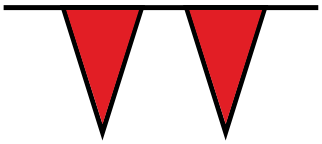


Figure 9. A powerful molecular reset of the communicome. Mouse stem cells grown in serum from old mice and humans ages them considerably. The same mouse stem cells are rejuvenated when grown in the serum of old mice and humans that have undergone a single neutral plasma exchange (NPE) procedure. NPE rejuvenates the body by simultaneously diluting progeronic factors which in turn induces epigenetic changes that “de-suppress” youth factors.



Extracorporeal Filters and (5c) Chronokine Antagonists

Another more targeted variation of the dilution solution involves using an extracorporeal filter or specifically designed chronokine antagonist to selectively remove progeronic factors from the body. Extracorporeal filters allow for the removal of precise amounts of excess progeronic factors (such as TGF-Beta) in the plasma.

Dialysis is one well known example of the utility of extracorporeal filters and is used to compensate for the decline in kidney function in individuals who have end-stage renal disease. A major distinction between the utility of extracorporeal filters in the case of kidney dialysis compared to the dilution solution is that the former is used as a life-sustaining technology to extend lifespan during late-stage pathology and the latter is a rejuvenative technology used to improve healthspan and for disease reversal (Wei, 2019).

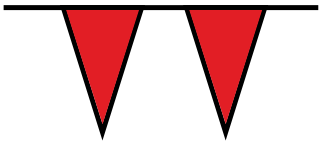
Despite the ultimate differences in application and overall goals, there are many things to learn from decades of academic research and clinical use of dialysis that can be used to optimise extracorporeal filter technologies for longevity. This includes optimizing how the technology operates, regimen, efficacy in various demographics, specific chronokine targets of interest, and other related issues. Regardless, optimisation will require careful analysis and characterisation of physiological vs pathological concentrations of progeronic factors in the blood across time and disease demographics.

The promise of combinatorial therapeutics for longevity

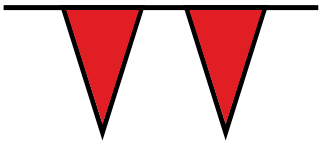
The plasma-based therapeutics field is very much divided into “camps” based on bias towards infusion vs dilution solution, proprietary technologies that companies have developed, and differing opinions on the most relevant chronokine targets of interest. Despite these biases, it is likely that the most effective longevity solution will incorporate a cocktail of multiple factors and a combination of supplementing youth factors and inhibiting one or more progeronic factors. Combinatorial approaches such as these have potential to take advantage of synergies between therapeutic modalities to increase efficacy and improve the overall safety profile of individual plasma based therapeutic technologies. Systemic rejuvenation requires a multi-dimensional approach that complements plasma-based therapeutics with other therapeutic modalities and healthy lifestyle change. Collaborations within the field that unite under the umbrella of this therapeutic strategy will likely be most effective for addressing age-related diseases and possibly even achieving multi-organ rejuvenation in humans.

Table 1. Young blood and plasma modalities

Modality	Infusion/ dilution	Description	Advantages/disadvantages
Heterochronic parabiosis	Both	Connects the circulatory systems of two animals and has shown profound rejuvenative effects in preclinical studies.	Presents a wonderful proof of concept and research and development (R&D) framework for the rejuvenative effects of blood and plasma factors, this approach is not technically or ethically feasible for application in humans.
Young Blood transfusion	Both	Involves direct extraction and administration of blood containing all its components.	It is the crudest of practical approaches for humans and there are multiple safety concerns associated with this procedure such as the risk of pathogen exposure and immune rejection. Significant variability in the quality of blood.
Therapeutic plasma exchange (TPE)	Both	Replaces only the plasma component of blood, volume for volume, with a physiological substitute.	Replacing plasma is a much safer option than whole blood because it eliminates many of the concerns about adverse reactions mediated by the patient's immune system and potential transfer of pathogens in the donor's blood. TPE is the most common of the plasma based therapeutic approaches and is an FDA approved procedure that is commonly used to address many different diseases.
Fresh Frozen Plasma exchange	Infusion	The patient's plasma is replaced with a (typically young and healthy) donor's plasma. This approach is based on harnessing youth factors within the donor's plasma.	Potential to simultaneously transfer factors that counteract and limit the rejuvenating potential of purified youth factors. Could have multiple safety risks including; immunogenicity, increased risk of cancer, non-infectious complications.
Neutral plasma exchange	Dilution	Plasma is replaced with a neutral fluid, typically saline with 5% albumin, that serves to dilute the patient's plasma. In doing so, it dilutes many of the progeronic factors that drive aging and disease.	All that may be needed is a bit of saline to dilute away the progeronic molecules created by our own aging tissues. Could be a "magic bullet" longevity intervention being developed today as it holds promise to be broadly effective across several types of cellular dysfunction, pathogenic molecules in the blood.
Plasma fractions	Infusion	Specific sets of plasma factors that are filtered, extracted, and pooled together from whole plasma. They can consist of hundreds of different chronokine youth factors present in the plasma and represent the broadest approach that can be utilized without removal and replacement of any blood components from the patient	Plasma fractions typically have increased specificity and safety since they are a refined product



Modality	Infusion/ dilution	Description	Advantages/disadvantages
Extracorporeal Filter	Dilution	Used to remove progeronic factors from a patient's plasma. During this process, an individual's blood is temporarily extracted, the plasma passes through the device, and the filtered plasma (and unfiltered blood components) is transfused back into the patient.	Optimisation will require careful analysis and characterization of physiological vs pathological concentrations of progeronic factors in the blood across time and disease demographics.
Chronokine mimetic	Infusion	Mimic the function of natural youth factors in the body that decline with age.	Identifying specific chronokines that modulate aging and disease progression may yield practical and personalised treatments more quickly, and with fewer ethical and safety concerns, than plasma exchange.
Chronokine antagonist	Dilution	Specifically designed chronokine antagonist to selectively remove progeronic factors from the body.	Identifying specific chronokines that modulate aging and disease progression may yield practical and personalised treatments more quickly, and with fewer ethical and safety concerns, than plasma exchange.



Longevity impact: infuse the good, dilute the bad and live healthier for longer

- In many ways, the potential of plasma-based therapeutics stretches far beyond that of other candidate longevity therapeutics;
- Plasma based therapeutics have the potential of cutting across various aging mechanisms, modulating several at once;
- Two of the most impactful hallmarks addressed are stem cell signalling and intercellular signalling (i.e. chronic inflammation);
- By addressing the very signals that synchronize aging across the body, plasma-based therapeutics have massive potential for addressing a nearly endless range of acute and chronic pathologies;
- Hematopoietic stem cells and thymus are resistant to the rejuvenative effects of plasma-based therapeutics. Combining plasma-based therapeutics with therapeutics that rejuvenate these tissues may offer the most comprehensive systemic rejuvenation protocol to date;
- Targeting neurodegenerative disorders may be the “path of least resistance” for plasma-based therapeutics to enter the longevity market.

Plasma based therapeutics have the potential to truly disrupt our healthcare system. In many ways, its potential stretches beyond that of other candidate longevity therapeutics. There are several factors that make it unique as a therapeutic:

- Preclinical and clinical data reveals that it can address several pathogenic processes including inflammation, fibrosis, degeneration and metabolic dysfunction;
- The very nature of plasma-based therapeutics makes it an excellent candidate for inducing systemic rejuvenation as it targets factors that travel across the body and influence aging of multiple tissues;
- Studies in model organisms and humans show that a single TPE is sufficient to induce rapid – within a few days – changes that are sustained for several months. This means that effects can be observed rapidly within clinical trials and it may not need to be administered more than a few times a year, minimising invasiveness and the risk of side effects (Mittledorf, 2020);
- Several plasma-based modalities are built off of existing technologies with proven safety and efficacy.

With the number of different plasma-based modalities and their efficacy across multiple tissues and organ systems, it will be important not to conflate the impact of one particular modality with another. Instead, progress within the field will require careful stratification of each modality based on which diseases or pathological processes it is most suitable to target. The hallmarks of aging provide an excellent guide to assess the impact of various plasma-based therapeutics on the body.

Plasma based therapeutics: Systemic rejuvenation and the hallmarks of aging

The hallmarks of aging are a conceptual framework that encompass the different types of damage and dysfunction that accumulate in the body as we age that eventually lead to the emergence of chronic diseases. The geroscience hypothesis posits that if we methodically target and remedy these damages before they accumulate past a certain threshold, we can prevent the onset, or mitigate the severity, of multiple chronic diseases.

Research on the various hallmarks of aging has revealed the hierarchical and networked relationship through which the hallmarks interact with one another. Such that addressing one hallmark influences the progression of others (van der Rijt, 2020). This finding is particularly noteworthy as it implies that the most effective longevity interventions are optimised to address the most impactful hallmarks, at the right time and in a manner that fundamentally changes the propagation of damage across cells and tissues in the body to slow the rate of systemic aging. Theoretically, each effective iteration on this process takes us one step closer to systemic rejuvenation. This is the goal of geroscience.

Blood has the potential advantage of cutting across various aging mechanisms, allowing several of them to be modulated at once. Further, targeting plasma chronokines has the added advantage of addressing the very signals that synchronise aging across tissues. The preclinical data amassed on plasma-based therapeutics suggests it directly influences epigenetic alterations and autophagy (primary hallmarks), cellular senescence and deregulated nutrient signalling (antagonistic hallmark), as well as stem cell signalling and intercellular communication (integrative hallmark). The exact sequence of events and factors that play a role in this process are still being experimentally elucidated, but there are many viable theories that have emerged from such studies. This has led to the development of next generation plasma therapeutics that are a product of high through-put screens, biological simulations, and bioinformatic computations based on these theories. (Figure 10)

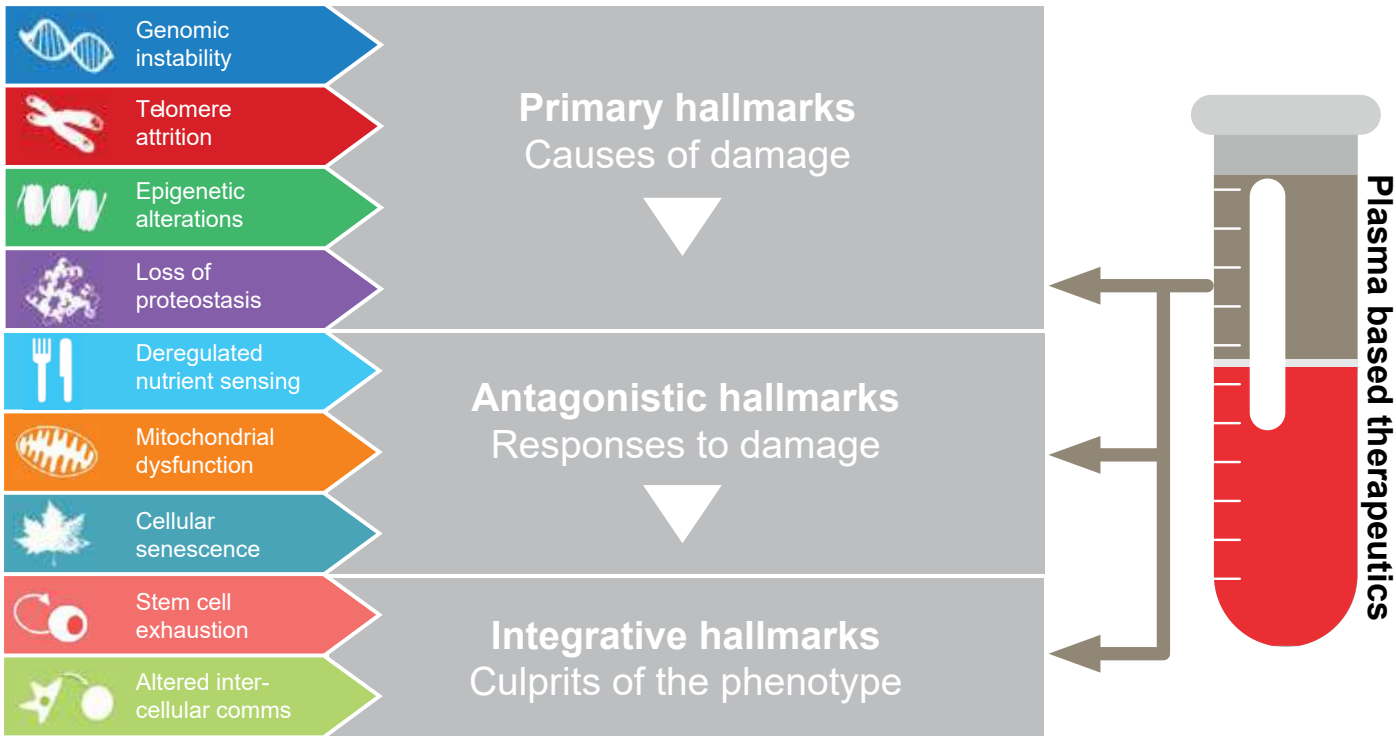
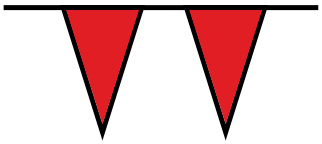


Figure 10. Plasma based therapeutics and the hallmarks of aging. Plasma based therapeutics address multiple hallmarks (primary, antagonistic, and integrative) of aging, making it a prime candidate for systemic rejuvenation. Adapted from Lopez-otin et al., 2013.



We will discuss two of the most impactful hallmarks addressed by plasma therapeutics below:

Stem cell signalling: even an old body remembers how to be young

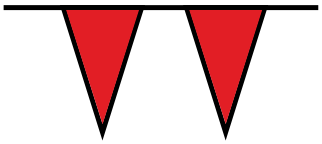
One mechanism through which many plasma-based therapeutics operate is by modulating the signalling milieu of stem cell niches in such a way that promotes a more regenerative state. This seminal finding emerged in 2005 from work performed by Irina Conboy in which heterochronic parabiosis restored molecular signalling that rejuvenated stem cell niches in aged liver and muscle, promoting rejuvenation to a youthful state (Conboy, 2005).

This prompted the idea that the systemic environment of a young animal is one that promotes successful regeneration, whereas that of an older animal either fails to promote, or actively inhibits, successful tissue regeneration. It also revealed a fundamental and empowering truth: the inherent regenerative capabilities of the body are not lost with aging. Even an old body remembers how to be young, if it gets the message in the appropriate biochemical language. In other words, rejuvenation is possible – provided the correct signalling environment is present. This means that stem cells in older individuals retain their youthful capacity but are inhibited by factors secreted by aged and senescent cells in their surrounding niche. Studies reveal that an “aged environment” likely consists of an abundance of pro-inflammatory molecules that drive chronic inflammation as well as a lack of critical growth factors and hormones. Due to this hostile environment, tissues can’t recruit the necessary stem cells when they get damaged and need to regenerate. This leads to further senescence, fibrosis, fat accumulation, and chronic inflammation within tissues (Mehdipour, 2021).

There are now several studies that have linked TPE, plasma fractions and specific plasma factors to the rejuvenation of multiple stem cell niches in the body (brain, blood, muscle, bone, liver, etc). The study and development of plasma-based therapeutics holds promise to address multiple chronic diseases of aging by reactivating unresponsive (yet inherently capable) stem cells to regenerate aging tissues.

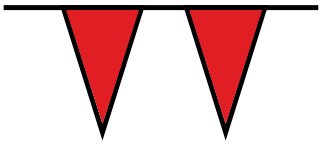
Intercellular signalling: chronic inflammation, senescence and inflammaging

Our immune system plays a central role in healthy physiological functioning. From fighting pathogens to clearing senescent and cancer cells, to wound healing and repair, and even cultivating a healthy microbiome. Hence, it is no major surprise that immune system dysfunction is an absolutely critical factor that drives the aging process. In fact, nearly every chronic disease of aging can be linked, on some level, to a failure of the immune system. So much so that one of the most consistent hallmarks of elderly individuals is persistent levels of low grade, chronic inflammation (known as inflammaging) leading to autoimmunity (attack of one’s own body cells) and immunosenescence (decline of immune system function) (Fullop, 2018).



The rate of progression of inflammaging is currently recognised as the main force driving aging and one of the main risk factors for clinical morbidity and mortality in the elderly (Fullop, 2018). This is because changes in signalling milieu caused by the presence of chronic, sterile low-grade inflammation can lead to damage accumulation, metabolic dysfunction, and a “vicious cycle” of cellular dysfunction and degeneration. A declining immune system drives the secretion of several progeronic factors including autoantibodies that attack healthy tissues, pro-inflammatory factors that drive chronic inflammation, and SASP factors that induce T-cell dysfunction which in turn compromises surveillance and clearance of pathogenic microbes and cells (Young Blood Institute, 2017). NPE has been shown to directly modify our innate immune system and restore functionality of NK cells and macrophages by clearing these progeronic factors and resetting the chronokine milieu to that of a more youthful profile in both aged mice and humans. These effects have been shown to persist for several months after a single procedure (Rybtsova, 2020). This is an extremely powerful finding as the effects on the clearance of SASP molecules alone has been implicated in disease mitigation (and even reversal) in several preclinical studies.

Plasma based therapeutics have also been shown to rejuvenate multiple aspects of the adaptive immune system. One critical way through which it does this is by influencing the relative ratio of CD4 to CD8 T cells. CD4 “helper” T cells are responsible for activating antibody producing B cells that kill foreign invaders, cancer and senescent cells. CD8 “suppressor” T cells are responsible for suppressing the immune system once a pathogen is dealt with; this function is critical for preventing inflammaging. The relative ratio of these cells gets dysregulated (typically increases) as we age and bears closer resemblance to the imbalanced ratios characteristic of autoimmune diseases and immunosenescence than “youthful” ratios. As a marker and predictor of the combined effects of inflammation and immunological changes, the CD4:CD8 ratio has been linked to continuing immune dysfunction, aging and acts as a predictor of mortality in the general population. The CD4:CD8 ratio in both elderly individuals as well as those with autoimmune disorders can be drastically improved (reduced) by TPE (Kiprov, 2020).



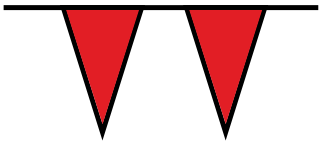
What about the tissues that are resistant to the rejuvenate effects of TPE?

Plasma based therapeutics (PBTs) have profound effects on multiple tissues and organ systems in the body. Hence, they have excellent prospects as longevity therapeutics that address multiple disease comorbidities at the same time. Interestingly, there are two tissue types that seem to be resistant to the rejuvenative effects of PBTs: the aging thymus and hematopoietic stem cells (HSCs). This finding has drawn special attention to the unique mechanisms that drive aging in these tissues and is being studied further to provide insights as to how they might differ from the mechanisms acted upon by PBTs to rejuvenate tissues in the rest of the body (Ho, 2021).

For instance, research has shown that declining levels of the hormone insulin-like growth factor 1 (IGF-1) plays a role in HSC aging. Notably, restoration of IGF-1 levels can slow/reverse decline and this in turn rejuvenates immune system health and slows systemic aging (Young, 2021). Further, the TRIMM trials have combined growth hormone, metformin and dehydroepiandrosterone (DHEA) as a rejuvenative therapeutic for thymus regeneration (Lin, 2015). This begs the question: how are these factors and underlying mechanisms influenced during PBT regimens and how may they be harnessed to enhance the benefits of PBTs? Combining PBTs with therapeutics that rejuvenate the thymus and HSCs has the potential to synergise to create the most complete systemic rejuvenation intervention being developed.

Combining PBTs with therapeutics that rejuvenate the thymus and HSCs has the potential to synergise to create the most complete systemic rejuvenation intervention being developed.

Part 2: For the investor looking to understand Young Blood as an opportunity.



For the investor looking to understand Young Blood as an opportunity

- Due to plasma's regenerative capacity, plasma therapies have a lot of potential to target multiple diseases of aging;
- The easiest "path" to take with plasma could possibly be neurodegenerative disease, due to the fact that multiple studies using various plasma based therapeutic modalities support the finding that reduction in peripheral and neuroinflammation has profound rejuvenative effects on the brain;
- Plasma-based therapeutics show promise for rapidly navigating the rigors of the clinical trial process;
- It will be important to properly bin data generated from preclinical, human non-clinical, and clinical trial approaches before drawing conclusions about the potential of plasma-based therapeutics in addressing chronic disease in humans;
- Currently, plasma-based therapeutics are quite expensive, but prices will drop as technologies mature and more data is collected, incentivising healthcare providers to cover costs and making it more accessible to the general public;
- Although there are still misconceptions about the ethical issues surrounding "young blood" there are a number of companies that are going through the clinical trial phases to ensure the efficacy and safety of their plasma-based therapeutics.

How do we translate the regenerative capacity of young blood and its plasma derivatives into the diseases of aging?

There are approximately 200,000 plasma exchange procedures performed worldwide each year, and it is currently approved to treat more than 50 relatively uncommon diseases (Borfitz, 2020). Biotechnology companies are unearthing the massive potential of therapeutic plasma exchange and other plasma-based therapeutics for addressing a nearly endless range of acute and chronic pathologies. The list is sustantial and continues to grow at a rapid pace. (Please refer to Table 1 in the following link https://onlinelibrary.wiley.com/doi/10.1111/1744-9987.12353).

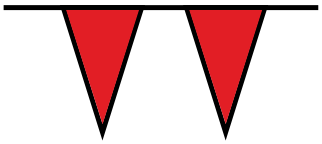
We have highlighted three of the most impactful disease markets in detail below where plasma-based therapeutics show promise based on both preclinical and clinical data:

Liver disease/fibrosis

Liver disease accounts for approximately 2 million deaths per year, which represents 3.5% of all deaths worldwide. What these statistics fail to encompass is the profound effect of liver dysfunction in driving type II diabetes, immune dysfunction and even neurodegeneration (Asrani, 2018). Both TPE and NPE have been shown to reverse hepatic aging (reduced fibrosis, fatty liver, senescence). For example, TPE with young blood has been shown to reverse hepatic aging in mice through the restoration of autophagy, a critical cellular mechanism required for disposal and recycling of damaged cells and molecular machinery. Plasma based therapeutics to address liver disease shows particular promise as there is clinical data within humans revealing that key markers of liver damage are reversed upon NPE (Eggel, 2014). The global liver disease market size is predicted to grow USD 22.46 billion by 2026 from USD 12.9 billion in 2021. This represents a CAGR of 11.72% during the forecast period.

Chronic kidney disease

With the possible exception of the lung, the changes in kidney structure function with aging are the most dramatic of any human organ or organ system – nearly 25% of mass lost. Further, patients older than 65 years have a nearly 28% risk of failing to recover kidney function when suffering from acute kidney injury. A large percentage of these individuals ultimately progress to end stage renal disease (ESRD) within a year. The rapid progression to ESRD after acute kidney injury is likely due to the accumulation of senescent cells and concomitant release of SASP factors. Few therapeutic options are available for even marginally slowing the progression of disease and there are no drugs to date for disease reversal (Wei, 2019). Multiple preclinical studies have found that young blood transfusion in mice confers enhanced autophagy, reduced senescence burden and improved inflammation of aged kidneys (Wei, 2019). Accordingly, several biotech companies in the plasma-based therapeutics space are implementing the infusion or dilution solution to rejuvenate kidney function. For example, Alkahest is using an extracorporeal filter to remove a progeronic chronokine (B2M) from the body as it is thought to be a major driver of progression of ESRD. It is possible



that a combination of infusion and dilution approaches will be most effective for addressing not only chronic kidney diseases, but multiple chronic diseases of aging. The global chronic kidney disease market was valued at 74.5 billion in 2020 and is expected to expand at a CAGR of 12.7% from 2021 to 2028. According to the national kidney foundation, approximately 10% of the global population suffers from chronic kidney disease and millions die each year.

COVID-19

COVID-19 is especially dangerous to the elderly and those with comorbidities, so much so, that many are classifying it as an age-related disease. The most concerning effects of COVID include cytokine storm and so called “long COVID”. Multiple clinical trials are underway to see if TPE can be used in the treatment of the overwhelming inflammatory response, or cytokine storm, seen in severe cases of COVID-19 (Borfitz, 2020).

Efforts to harness TPE to address COVID-19 aren’t coming from nowhere. TPE has been successfully used to treat cytokine storm in other medical conditions, including sepsis and cancer patients being treated with chimeric antigen receptor T (CAR-T) cell therapy. Early data suggests that the use of TPE is associated with superior overall survival, early resolution of cytokine release syndrome (CRS) and reduced time to discharge as compared to standard therapy for COVID-19 triggered CRS. Encouragingly, data suggests that early diagnosis of CRS and initiation of TPE results in dramatically better clinical outcomes (Kamran, 2020). Further, TPE with 5 % albumin replacement has been shown to upregulate innate and adaptive immune factors that are critical mediators of the immune responses to viral particles.

These findings provide further evidence that TPE, especially along with convalescent plasma infusion at the end of the procedure, can be an effective treatment for COVID-19 (Kamran, 2020). TPE is also being tested in the treatment of COVID related long lasting effects, such as long COVID, and vaccine related side effects. Further, the utilization of extracorporeal filters to remove autoantibodies for neurotransmitter receptors may provide a promising therapeutic option for patients with the cognitive impairment that is a hallmark of post-COVID-19 syndrome.

The utility of multiple plasma based therapeutic modalities in addressing different aspects of COVID-19 is an example “case study” of the merit in carefully tailoring this technology towards specific pathological mechanisms. Careful consideration of each technology’s strengths and weaknesses for addressing a specific disease state is essential for clinical trial success. For example, TPE could remove critical anti-SARS-coV-2 antibodies required to combat the virus, whereas more selective filtering with extracorporeal filters may be a more efficacious and safer modality for some COVID-19 related symptoms (Kiprov, 2020). The global infectious disease market is expected to grow at a CAGR of around 5.7% from 2020 to 2027 and reach a market value of over 24.5 billion by 2027. This is in large part driven by the COVID-19 pandemic. Further, COVID-19 not only dominates the infectious disease market but it also drives the expansion of several other disease markets as well. Therefore, targeting this market holds promise to have exponential impact based on its influence on several other disease markets.

Path of least resistance: targeting neurodegenerative disease

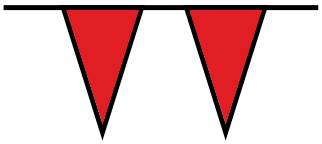
Despite billions of dollars invested each year in addressing Alzheimer's disease (AD), the causal mechanisms are still poorly understood. As such, new drug development is very slow and suffers a high attrition rate. To date, there are no known disease modifying treatments that have been shown to significantly impact the progression of neurodegeneration in humans. This has profound socioeconomic and health consequences. Medicare costs for an older person with AD (or other forms of dementia) are nearly three times higher than for seniors without dementia – and Medicaid payments are nearly 20 times higher (Kiprov, 2020). Beyond the economic costs, dementia has immeasurable effects on the physical and emotional well-being of both those afflicted and their loved ones. The complexity of AD may preclude a "magic bullet" drug that targets a single mechanism to slow or halt disease progression. This is where a systemic therapeutic that addresses multiple pathological mechanisms, like TPE or plasma fractions, really can shine.

The brain-body connection is a fascinating realm of discovery, and the circulatory system serves as a major communication highway between our peripheral system and the brain. There are many variables originating outside of the brain that have been implicated in driving neurodegeneration, including: peripheral inflammation, oxidative stress, gut dysbiosis, cardiovascular health and insulin resistance. Together, the genetic, proteomic and epidemiological evidence within the scientific literature suggests that changes in inflammation and intercellular communication (reflected in plasma profiles) represent chief drivers of normal brain aging and neurodegeneration (Wyss-Coray, 2016)

One perplexing observation is that the brains of many individuals show characteristic changes that are linked to neurodegeneration but do not ultimately end up developing the cognitive decline and loss of function that comes along with such pathologies. A growing body of evidence suggests that the interaction between conventional brain hallmarks of neurodegeneration and progeronic factors may represent the tipping point that drives neurodegenerative pathologies. Several longitudinal studies have revealed an association between increased circulating levels of progeronic inflammatory factors (such as TNF-α levels) and the rate and severity of AD progression as well as decline in cognitive performance (Smith, 2018). Various plasma based therapeutic strategies can be used to mitigate the progression of neurodegenerative disease (Figure 10)

The brain-body connection is a fascinating realm of discovery, and the circulatory system serves as a major communication highway between our peripheral system and the brain.

For instance, evidence is building to support the strategy of targeting peripheral inflammation with NPE to mitigate AD progression. A single round of NPE was able to reduce the level of overactive immune cell activity and inflammation in the aging brain. Further, it completely wiped out the difference between



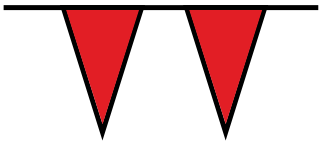
young and old animals' ability to discriminate novel objects by appearance or by texture (assessment of cognitive health). Finally, NPE has been shown to perform better as a senolytic and anti-inflammatory in the brain compared to navitoclax (a first generation senolytic). This indicates that NPE is operating mechanistically beyond just diluting peripheral SASP factors (Mehdipour, 2020).

Another component of NPE that may contribute to its effects on cognitive health is the addition of 5% albumin. Although there is conflicting evidence about whether albumin plays a role in mediating rejuvenative benefits in the brain, the evidence in its favour is compelling. Albumin is a powerful antioxidant and anti-inflammatory protein that binds toxic aggregates (such as amyloid beta) and clears them from the body.

Low levels of plasma albumin bound to amyloid beta is correlated with a higher prevalence of AD and several of its molecular pathologies and biomarkers, prompting investigation into the effects of intermittent therapeutic albumin replacement. Multiple studies (including clinical trials run by Grifols and Alkahest) show that removing albumin with saturated binding sites and infusing fresh albumin with multiple unoccupied binding sites may mediate beneficial effects on the brain (Loeffler, 2020). Emerging clinical research will clarify the extent of its effects on brain aging and health.

Multiple studies using various plasma based therapeutic modalities support the finding that reduction in peripheral and neuroinflammation has profound rejuvenative effects on the brain. Currently, there are multiple clinical studies (> 6) applying TPE in AD patients that show disease modifying effects. Efficacy is dependent on demographics, stage in disease progression and therapeutic regimen, among other clinical design considerations. It will be important to understand whether circulating progeronic factors cross the blood–brain barrier and act directly on neurons, or act indirectly by regulating the production of other factors in the periphery. Pathogenic factors produced in the periphery would likely be easier to target than factors produced in the brain (Imbimbo, 2020).

Further studies, such as the ones mentioned above, will provide mechanistic insights to design precision drugs that can be manufactured at scale and provide increased safety and efficacy in individuals with neurodegenerative pathologies.



Regulatory

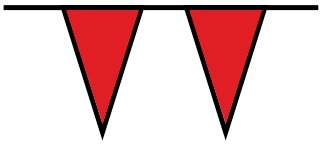
Within the longevity market, plasma-based therapeutics are in rare company in terms of the promise of preclinical data, safety profile in humans, and prospects of deftly traversing the regulatory landscape. This has not escaped the notice of investors as multiple longevity venture firms (such as Apollo Health Ventures, Kizoo, Formic Ventures and Prime Movers Labs) are investing in companies within this space. Plasma-based therapeutics have shown clear rejuvenating effects in aging mice and rats, but the fundamental fact remains, time and time again, that the outcome of clinical trials have shown that humans are not laboratory rats. The challenge within the field is how to translate promising preclinical results into a clinical product that is effective in humans.

Therapeutic plasma exchange shows promise within the longevity realm. Especially as it pertains to navigating the painstaking regulatory environment for therapeutic approval. TPE can be expanded to address many different diseases rapidly because the safety and efficacy of the procedure itself has been validated extensively. This is evidenced by the number of different indications targeted by companies developing their drug pipelines. A recent review highlighted the fact that there are over 100 diseases (affecting various organ systems) that are associated with abnormal or high concentrations of factors in the plasma that have the potential to be remedied by plasma-based therapeutics. In fact, there are already several diseases that can definitively be treated, and are indeed lifesaving, with therapeutic plasma exchange as a first line therapy. Clearly, dozens more have potential to be addressed but have yet to be tested as therapeutic plasma exchange has mainly been used as a last resort measure (Malchesky, 2015).

Making sense of the data: preclinical, clinical trial and non-clinical trial studies

Several clinical trials – initiated by companies such as Alkahest, Grifols and IMYu – are already demonstrating safety and efficacy of plasma factors, plasma fractions and therapeutic plasmapheresis in healthy and diseased populations. This rigorous data is further supported by a significant, but rather tenuous, pool of data collected by licensed clinicians performing therapeutic plasma exchange to address a range of different diseases, as well as biological aging itself. For example, The Young blood Institute is a physician network that administers plasma therapeutics based on American Society for Apheresis guidelines. Of particular note, a recent study on a few volunteers from Russia who underwent plasma dilution followed by assessment of physiological function found improved naive T cell number, reduced oxidised LDL, improved liver markers and myelocyte/lymphocyte ratio. All critical markers for healthy aging (Reason, 2020).

But every coin has two sides, a major challenge that has stymied the flow of investment into the field is a wall of “bad press” generated from unregulated and misinformed practitioners within this space that make false claims, operate on false beliefs and target disease demographics prematurely. In other words, they go to market without the proper data for support. There are still conditions for which TPE is used as a treatment without a good, evidence-based understanding of why or how it works, or even if it provides benefits. The American Society for Apheresis (ASFA) publishes regular updates to its guidelines



and in its most recent issue highlighted 157 indications that can be addressed by TPE. Many of these indications were categorised as “optimum role not established” (Lawrence, 2021). It will be important to carefully distinguish and properly bin data generated from preclinical, human non-clinical trial and clinical trial approaches before drawing any conclusions as to the true therapeutic potential of plasma-based therapeutics in addressing disease conditions. In general, technologies still need to be refined based on robust clinical trial data and continued optimisation within research and development (R&D). This should in turn catalyse a shift in diseases transitioning from category III to category II or I.

Based on the available evidence, the ASFA has categorised conditions treated with apheresis into four groups (Schwartz, 2016):

- Category I – disorders for which plasmapheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
- Category II – disorders for which plasmapheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
- Category III – optimum role of plasmapheresis therapy is not established. Decision making should be individualised.
- Category IV – disorders in which published evidence demonstrates or suggests plasmapheresis to be ineffective or harmful. IRB approval is desirable if plasmapheresis treatment is undertaken in these circumstances.

Can we put a price-tag on our fountain of youth?

The cost of therapeutic plasma exchange is prohibitive to widespread adoption unless covered by health insurance companies and/or healthcare providers. In European and Asian countries, governments have approved reimbursement of plasmapheresis for select diseases and the US is just starting to catch on. For example, in the United States, Medicare has approved payment for a group of 18 disease states. Private insurance programmes, at least in the United States, approve a broader range of disease states that they recognise as medically necessary, likely because of the cost-effectiveness that therapeutic plasma exchange can provide as a treatment for chronic diseases (Schwartz, 2016). As with all technologies, the price will go down with time, technological advancements and increased amounts of data. In regard to this last point, as more data is collected in regard to the prophylactic and disease modifying potential of plasma-based therapeutics, insurance companies will likely have more incentive to cover costs to make it more accessible and affordable to a larger population.

Are we ready to administer young blood?

Despite the growing body of preclinical and clinical evidence, scientists and ethicists were still fearful about applications in humans before therapeutics had traversed the rigors of the clinical trial process. These fears are not in vain as blood and plasma transfusions are approved for use by any licensed professional and are fairly straightforward for even unlicensed individuals to perform. Unlicensed stem-cell transplants are already a booming industry, and unlicensed transfusion of young blood would be even easier (Corbyn, 2020).

These fears were brought to life in 2017, when biotech company Ambrosia started selling young plasma (from 16–25-year-olds) to anyone with the desire to regain their youthful health and had the money to pay for it. Ambrosia's "elixir of youth" costs $8,000 per litre (or $12,000 / 2L), despite no evidence of positive results having been published (Dolgin, 2021).

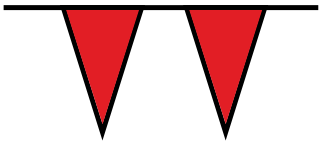
Concerned about the premature and ominous wave of enthusiasts, the US Food and Drug Administration issued a statement in Feb 2019 that transfusions of plasma from young donors have "no proven clinical therapeutic benefit" for diseases in humans and threatened disciplinary action on anyone that claimed otherwise.

There is no question that preclinical research demonstrating the efficacy of plasma-based therapeutics has exploded in recent years, but are they ready for prime time? Several companies are racing to optimize safety and efficacy within clinical trials to make sure they are the first to open the flood gates to a multibillion-dollar market (Robbins, 2019).

The history of blood and plasma-based therapeutics has been plagued with dire consequences, particularly in times preceding the understanding of blood groups and infective agents, with death from adverse reactions or acquired infection being not uncommon.

But now is the time to revisit the potential of young blood therapeutics with a true scientific basis, while considering both safety and ethical considerations. Studying and harnessing the potential of young blood and its plasma derivatives offers the opportunity for developing a wholly new paradigm for treating age-related disorders. This would be a paradigm that focuses on rejuvenation and disease reversal by influencing the factors that cells routinely secrete into the bloodstream to communicate, what is known as the body's "communicome" (Wyss-Coray, 2016).

Now is the time to revisit the potential of young blood therapeutics with a true scientific basis, while considering both safety and ethical considerations.



Companies

There are many emerging companies that are ready to harness the potential of young blood and its plasma derivatives. Figures 10 and 11 show where each company is at in its clinical trial pipeline and what modality it is using. If you need a reminder of the strengths and weaknesses of each infusion/dilution modality, please refer to Table 1 in section 2.

Alkahest

Alkahest is conducting multiple ongoing phase 2 clinical trials. Lead assets target proteins that inhibit the negative “progenic” chronokines that increase with age and their proprietary plasma fractions replenish the “youth” chornokines that decrease with age. Specifically, these include:

1. AKSST4290, targeting “Eotaxin, in phase 2 for WetAMD and Parkinsons disease and phase 1 for inflammatory disease,

2. ASKT/GRF6019/6021, in phase 2 for Alzheimer’s disease (mild-severe), Parkinson’s disease with cognitive impairment and postoperative recovery,

3. ASKT1210, in stage 2 for end stage renal disease related cognitive impairment

4. Novel factors, in research stages for undisclosed indications.

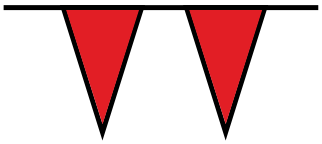
Alhakest was acquired by Grifols in 2019.

Elevian

Elevian is developing a number of therapeutics that regulate growth differentiation factor (GDF11) and other circulating factors, in order to restore the body’s natural regenerative capacity, which it believes addresses a root cause of age-associated diseases. Its product, rGDF11, is in preclinical stages for stroke recovery, obesity, type 2 diabetes and intracerebral haemorrhage.

Grifols

Grifols’ commitment to Alzheimer’s disease research began more than 15 years ago, when the company decided to explore the potential of plasma therapies to treat this devastating neurodegenerative disease. Preclinical trials began in 2004, with two pilot preclinical studies and a phase II clinical trial before starting the AMBAR® (Alzheimer’s Management by Albumin Replacement) study. The AMBAR trials use neutral plasma exchange using a proprietary albumin and immunoglobin formulation for the treatment of Alzheimer’s disease. It is currently in phase 2b clinical trials in the US and phase 3 clinical trials in Europe.



IMYu

IMYu uses neutral blood exchange to rejuvenate tissues. It was founded in 2019 by Irina and Michael Conboy. The company is still in stealth mode, however, it has been implied it is in preclinical stages for neurodegenerative disease and systemic rejuvenation and has reached phase 2 for inflammatory disease.

Rejenevie Therapeutics

Rejenevie's lead product, AR-100, is an autologous mobilised peripheral blood cell therapy using the Rejenevie™ proprietary immune restoration technology. This therapy is currently in phase 2. Rejenevie is also in early development of an immune restoration therapy using a combination of factors isolated from young blood stem and immune cells (RJV-117, RJV-122). In parallel, the company is developing an aged stromal vascular fraction (SVF) restoration therapy using either young, mobilised blood (RJV-200) or the restorative factors that it has have isolated (RJV-217, RJV-222).

Yuvan

Yuvan Research is a pre-clinical stage biotech company developing a plasma fraction called E5 which is based on young blood plasma. The company is still in stealth mode, however, it has been implied that it is finishing conducting preclinical studies in rats targeting sarcopenia, chronic kidney disease and systemic rejuvenation. Yuvan research is in the process of initiating trials with E5 in dogs, non-human primates, as well as humans.

Ambrosia

Ambrosia has not gone through the clinical trials process. Its fresh frozen plasma is already on the market in the US.

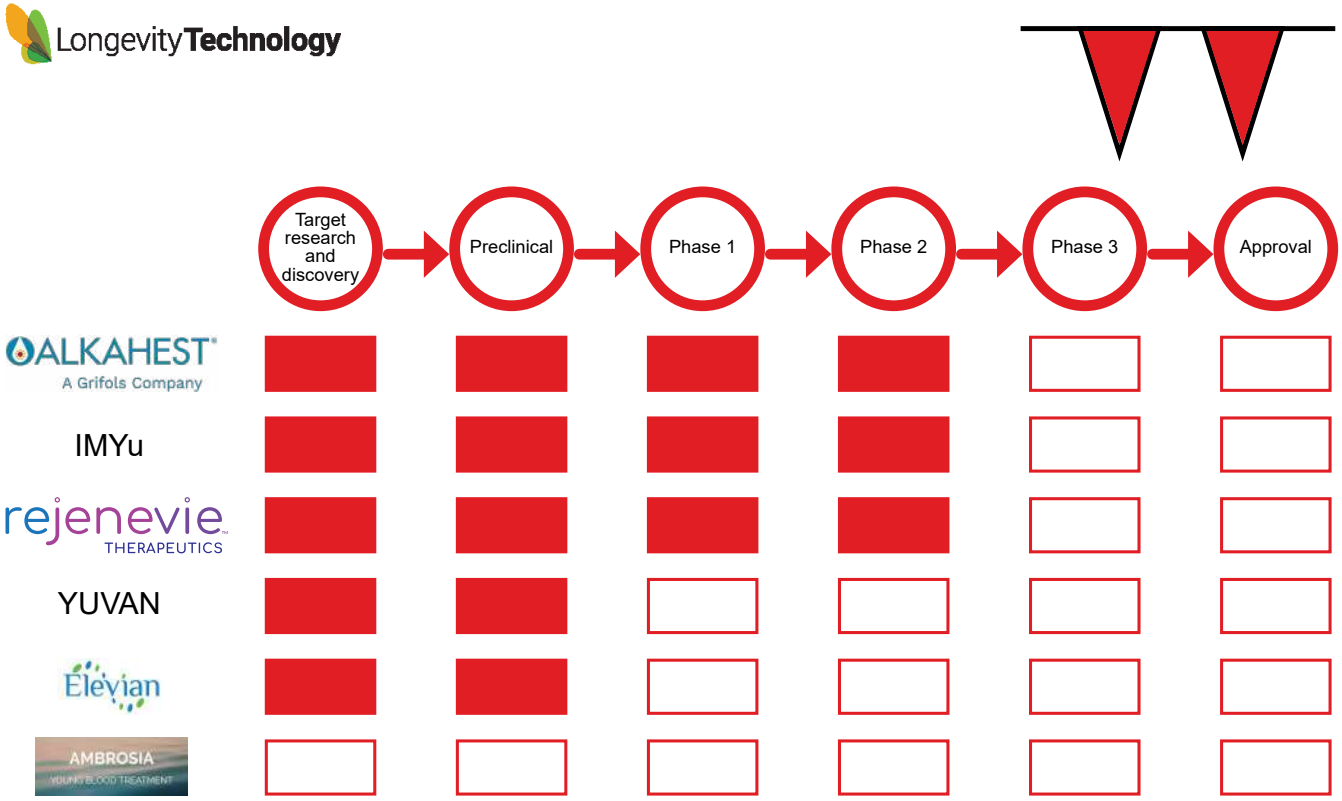


Figure 11 Companies in young blood plasma therapeutics development and their current clinical trial status.

Figure 12 Companies grouped by infusion and dilution solution technologies

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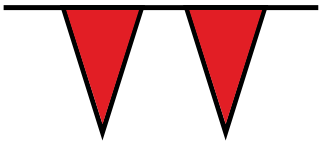

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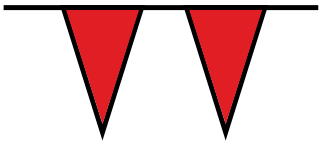

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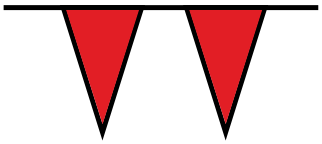

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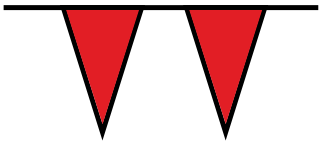

LongevityTechnology

We bring together innovators and investors to commercialise the companies that will form the longevity economy.