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Plasma, the liquid component of blood, could lead to treatments for Alzheimer's disease.

NEUROSCIENCE

The power of plasma

Alzheimer's disease and ageing brains could benefit from therapies based on blood's liquid component.

BY LIAM DREW

Blood plasma seems an unlikely place in which to find a cure for Alzheimer's disease. But neuroscientists increasingly appreciate that the brain and the circulatory system have a more intricate relationship than was previously acknowledged. And with more than 1,000 litres of blood passing through the brain of an adult each day, the plasma — blood's lemon-curd-coloured liquid component — is instrumental in shaping the biochemical environment in which neurons exist.

Currently, two teams, inspired by distinct facets of plasma's nature, are working towards new therapies for Alzheimer's disease.

The first project began with a narrow focus, inspired by a simple interaction between proteins. In 2004, Víctor Grífols Roura was captivated on learning that the plasma protein albumin binds to peptides of amyloid-β — molecules widely thought to be the root cause of Alzheimer's disease. As the then president of Grifols, a health-care company based in Barcelona, Spain, Grífols Roura recognized that his company's expertise in plasma-based medicine might offer a way to treat this debilitating cause of dementia.

The second project could barely have had a more broad foundation, with Tony Wyss-Coray, a neuroscientist at Stanford University in California, conducting — at around the same time as Grífols Roura's realization — an unbiased survey of how the myriad blood-borne substances to which the brain is exposed change with age and Alzheimer's disease. His goal was to study ageing brains not in isolation, but as organs operating in declining bodies.

More than a decade later, the work at Grifols has yielded promising data from clinical trials in which people with Alzheimer's disease underwent a procedure developed for treating diseases of the blood. And Wyss-Coray has led a surge of research showing that brain health is dramatically affected by changes in the array of signalling molecules that circulate in plasma as organisms age.

Now that Grifols has tested one of the main hypotheses to arise from Wyss-Coray's work, the way forward may involve a meeting of the two approaches.

NEW PLASMA

Albumin accounts for more than half of the total protein content of plasma, and it has a crucial role in balancing the water content of the blood. But it is also a sponge-like carrier protein, long understood to bind and inactivate many of the proteins and metabolites that travel in plasma. In 1996, researchers at Harvard Medical School in Boston, Massachusetts, found that amyloid-β was one such compound[1].

Aggregations of amyloid-β underlie the profusion of plaques that form around neurons in brains affected by Alzheimer's disease. Although the exact consequences of plaque formation are under debate, most researchers think that aberrant processing of amyloid-β is fundamental to development of the disease — and that the peptides may even damage neurons directly. A widely proposed hypothesis is that cutting levels of amyloid-β in the brain would therefore slow, or even stop, the progression of Alzheimer's disease.

The Harvard study showed that the interaction between albumin and amyloid-β was the main reason blood contains barely any unbound amyloid-β. Antonio Páez, a clinical haematologist at Grifols, recalls how Grífols Roura circulated the corresponding paper, asking staff scientists to investigate. They soon learnt that amyloid-β levels in the plasma and in the cerebrospinal fluid that percolates through the brain are in equilibrium, meaning that blood amyloid-β levels should directly affect the concentration of amyloid-β in the brain.

The company had extensive experience in plasmapheresis, a procedure in which blood is removed from a patient, the blood cells are separated from the plasma, and the cells are then returned to the patient in a synthetic plasma substitute. Since the 1970s, doctors have used plasmapheresis to treat disorders caused by problematic constituents of plasma, most commonly removing circulating antibodies that underlie autoimmune diseases. The scientists at Grifols reasoned that removing plasma from a person with Alzheimer's disease — with its albumin-bound amyloid-β — and replacing it with a solution of amyloid-β-free albumin would reduce the overall level of amyloid-β in the plasma. Amyloid-β would then move from the brain, through the cerebrospinal fluid and into the plasma, to be bound and inactivated by the fresh albumin. And if plasmapheresis could lower the level of amyloid-β in the brain, then perhaps it could treat Alzheimer's disease.

Subsequent work, in 2012, by John Viles, a biochemist at Queen Mary University of London, supported the model by showing that albumin's affinity for amyloid-β is sufficient to stop the peptides forming new fibrils and plaques[2]. A small study of plasmapheresis in 7 people with Alzheimer's disease, conducted by Páez in collaboration with Mercè Boada at the ACE Foundation in Barcelona, showed that the relatively invasive procedure was well tolerated[3], leading to a phase II trial involving 42 patients[4]. Those who were randomly assigned to the treatment group received up to 18 plasma exchanges using a 5% albumin solution, whereas those in the control group underwent an elaborate sham procedure. Participants' amyloid-β levels and cognitive functioning were monitored throughout the 5-month treatment and over a further 6-month follow-up period.

Those studies confirmed that plasmapheresis changed the amount of amyloid-β in both plasma and the cerebrospinal fluid. However, the nature of these changes wasn't always straightforward to explain. "The concept of clearing amyloid-β from the brain via plasma

is a good one," Viles says, "but some of the data were a bit surprising." If albumin was helping the body to clear amyloid-β, "you might expect to see a decrease in amyloid-β in the brain", as inferred from the level in the cerebrospinal fluid, he says. "But in fact, it increased."

Páez agrees that some of those data are difficult to reconcile with the original Grifols model. He offers that raised levels of amyloid-β in cerebrospinal fluid might reflect soluble peptide leaving neurons and moving to the plasma — an idea that needs further substantiation. Páez also notes that the see-sawing levels of amyloid-β observed in plasma mirror changes seen in trials of other strategies to lower amyloid-β.

"What's more interesting," says Viles, "is some of the cognitive impacts that they're seeing." The results of the phase II trial indicated that participants received clinical benefits. Páez remains cautious, emphasizing that "the trial was a small one, not sufficiently powered to find differences among the two groups in cognition and other neuropsychological variables". But the results of tests for language skills and memory indicated improvements that were strong enough for Grifols and their academic collaborators in Spain and the United States to launch a much larger phase III trial.

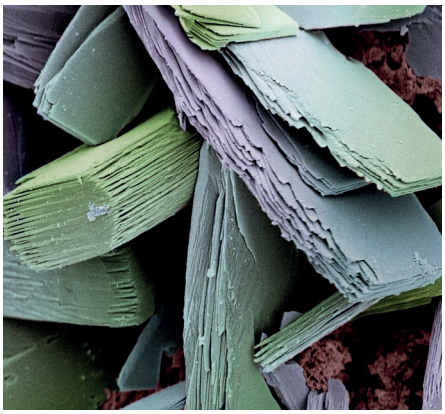
Páez is excited about that ongoing trial, and he provides another perspective on how plasmapheresis might act. "We may be removing other substances, potentially related to Alzheimer's disease and not even known at the moment," he says — an idea that stems directly from the work of Wyss-Coray.

FRESH BLOOD

Wyss-Coray's initial studies of blood and dementia led to a 2007 paper in which he showed that by analysing a panel of 18 plasma proteins, he could predict with almost 90% accuracy whether the plasma came from a person with Alzheimer's disease[5]. This was intriguing, but it only got him so far — an altered blood composition could be contributing to the disease, or merely be a result of it.

The experiment that broke this cause-or-effect conundrum arrived from the laboratory next door at Stanford, where bioengineers Irina and Michael Conboy had been surgically joining pairs of mice — one old and one young. This set-up, resurrected from work published in the 1950s, enabled the circulatory systems of the two mice to be united, exposing the old mouse to young blood and the young mouse to aged blood. After Wyss-Coray's neighbours had shown that this procedure rejuvenated the muscles of old animals[6], Wyss-Coray asked a postdoc in his lab, neuroscientist Saul Villeda, now at the University of California, San Francisco, to conjoin mice and then examine their brains.

Villeda showed that although the brains of old mice were indeed rejuvenated, the brain health of young animals deteriorated[7]. Importantly, simply injecting young mice with plasma from old mice also had negative effects.



STEVE GSCHMEISSNER/SPL

Albumin is the main constituent protein of plasma.

A further study showed that administering plasma from young mice to old animals had the opposite effect[8] — increasing the birth rate of neurons in the brain's hippocampus, boosting neurons' synaptic function and improving the animals' performance in memory tasks. Together, these experiments demonstrated that circulating factors in young plasma benefit the brain, whereas old plasma negatively affects the brain and cognition.

The work has been well publicized, with the early ghoulish experiments lending the reports a vampiric flavour. However, Jonathan Kipnis, a neuroimmunologist at the University of Virginia in Charlottesville, thinks that the attention is merited. "There is no question about the importance of this work," he says, although he suspects that medical applications remain a distant prospect.

Wyss-Coray and Villeda have sought to more fully understand what accounts for the effects that they saw, identifying a number of molecules that partly mimic the effects of either old or young plasma. And in 2016, Wyss-Coray's lab showed that young plasma boosted cognitive function in a mouse model of Alzheimer's disease[9]. But Wyss-Coray and Villeda have also explored the therapeutic possibilities of the approach — including co-founding, in 2014, a company called Alkahest to lead such work.

So far, Alkahest, located in San Carlos, California, has run a small phase I trial to assess the safety and feasibility of giving 4 weekly infusions of plasma from young donors to 18 people with Alzheimer's disease. As secondary outcomes, the patients' cognitive functions were tested. The data are still being analysed, and Wyss-Coray cautions that the trial is probably too small to detect clinical benefits.

CONVERGENCE

The potential restorative effect of young plasma on ageing recipients is, however, only one implication of the work by Wyss-Coray and other researchers. The studies indicating that old plasma negatively affects the brain suggests that older people might benefit by having it replaced. That's an idea championed by the Conboys, now at the University of California, Berkeley, who performed the initial muscle experiments at Stanford. And it's also a possibility that Grifols addressed in its plasmapheresis trials.

Páez says that although Grifols researchers followed the work to conjoin old and young mice, they didn't see it as being directly relevant to their research. However, when Wyss-Coray and Villeda published the beneficial effects of young plasma[8] in 2014, Grifols contacted Alkahest. Within a month, the companies had sat down to talk.

Páez reports that, at the time, Alkahest "didn't know there was someone removing plasma from Alzheimer's patients with a therapeutic intention". Moreover, Wyss-Coray recalls that many Alzheimer's-disease researchers thought that Grifols's approach was a "totally crazy idea", with those researchers believing that Grifols did it simply because it could. But given that plasmapheresis had flushed out the patients' old plasma, Wyss-Coray says, "maybe they actually tested our greater hypothesis".

Such was the apparent synergy between the two approaches that, in March 2015, Grifols acquired 45% of Alkahest for US$37.5 million, and invested a further $12.5 million in the work.

In the long term, neither Grifols nor Alkahest see donated whole plasma from young people as a potential therapy for Alzheimer's disease-related dementia. Instead, Páez says: "We are investigating which substances are responsible for the effects that Alkahest is seeing in mice and we at Grifols are seeing in Alzheimer's."

Although Wyss-Coray seeks to further understand the effects of young plasma, Grifols's phase III albumin-replacement trial has finished recruiting participants and will run final assessments in early 2018. Many promising therapies for Alzheimer's disease have run aground at phase III, including ones aimed at lowering amyloid-β levels. But if the health-giving effects of plasmapheresis are confirmed, its therapeutic value might be further improved by adding plasma proteins that boost brain health.

So far, Alzheimer's disease has resisted all attempts at a cure, and there's no certainty that these plasma-based therapies will succeed. But serendipity has often contributed to the discovery of treatments for brain disorders. Given the prevalence and devastation of Alzheimer's disease, we might again hope that it has nudged research in the right direction. ■

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