From the sand to the operating room: a medical revolution is underway for organ transplantation

It was by observing the sand on the Breton beaches that Dr Franck Zal, then a CNRS biologist, discovered a nugget: the extracellular haemoglobin secreted by the lugworm, 250 times smaller than the human haemoglobin, was able to carry 40 times more oxygen! An unsuspected medical revolution that had been hidden under the sand of the foreshore for millions of years. It was necessary to know how to detect, with a simple observation and a simple question, the deposit of major innovations for medicine on which everyone was walking. It was through an approach linked to what's now called biomimicry that HEM02life® was born.

It was by using this approach that Leonardo da Vinci imagined several flying machines inspired by bats and left us with this famous phrase that resonates as the legacy of a visionary that we still struggle to apply today but that's so important for future generations " Learn your lessons in nature, that is where our future lies". Life was forged by 4 billion years of evolution, by a long trial-and-error process from which came the different organisms that are brought together under the term biodiversity. Da Vinci understood that Nature was a library of innovations that gave birth or caused to disappear, like an immense research and development laboratory, the biological processes that allows life to evolve like a limitless continuum.

At the origin of this discovery, a simple question asked by a Doctor of Marine Biology, eager to understand and explain how a marine worm, known under the scientific name of Arenicola marina, better known by Breton fishermen under the name of "buzuk", was able to breathe both under water and in air. In order to answer this basic research question which intrigued him, but didn't really interest anyone else, he focused on the blood of this invertebrate. Why? simply because the blood of an organism, especially the haemoglobin it contains, creates the link between the environment in which it lives and its own physiology. It shows that the lugworm breathes when it is underwater thanks to a giant macromolecule consisting of more than 150 globins, and at low tide it stops breathing and lives on the stock of dissolved oxygen fixed on this molecule. This haemoglobin plays the role of an oxygen bottle and makes the lugworm the world champion in apnea.

He discovered in this 450 million years old marine worm, the ancestor of the haemoglobin contained in our red blood cells. The haemoglobin molecule he described is extracellular, it's not contained in anucleate cells like red blood cells but is dissolved in the animal's blood. It also shows that the basic globins that make up this macromolecule are very similar to those of vertebrates and that this molecule is neither immunogenic nor allergenic. All these elements lead him to think that this molecule could be interesting to use in medical applications, but which ones? He then made the link between the environment of this invertebrate and a well-known physiological phenomenon in medicine, source of major problems in many pathologies, called ischemia/reperfusion (hypoxia linked to a blood circulation problem/hyperoxia and oxidative stress linked to reperfusion).

Although oxygen is essential for life and in particular for tissue and cellular respiration, it must be delivered in a physiological way and this is one of the reasons for the existence of oxygen transporters and in particular haemoglobins within living organisms. The link was then made in his mind: what if, for millions of years, the lugworm already had the answer to the ischemia/reperfusion phenomenon thanks to his haemoglobin? For the lugworm, ischemia is low tide, and reperfusion is high tide.

Franck Zal then made the connection with organ transplantation knowing that when an organ is removed from a donor, there is a race against the clock to reconnect it to a recipient (ischemia problem), another problem then follows, after the reconnection, there is an excessive

supply of oxygen within the graft, a source of oxidative stress (reperfusion problem). He then demonstrated an intrinsic antioxidant activity on the haemoglobin molecule of the lugworm, which further sharpened his growing interest in using it in graft preservation applications. Tests were then carried out on kidney transplants, initially on animal models in collaboration with a team from INSERM in Poitiers led by Pr. Thierry Hauet, with remarkable results which immediately aroused the interest of nephrologists and surgeons.

simplement.

In 2007, he decided to resign from his position as an academic researcher at the CNRS to take on a new challenge and embark on the long path that awaited him, saving thousands of lives thanks to this discovery, and providing suffering patients and their families a solution to the problem of ischemia/reperfusion. He then created the HEMARINA company and set up complex processes to extract and purify this precious molecule to turn it into a universal oxygen carrier, a real pipeline of therapeutic applications, in response to unmet medical needs. All ischemic pathologies are in the line of fire. In the shorter term, applications target blood diseases, war trauma, complex wounds, periodontitis... The molecule also raises hopes for a universal oxygen carrier for blood transfusions. But, for the time being, it's in organ transplantation that HEMARINA's technology has taken the biggest step forward after a 15 years long journey built on patience, perseverance, resilience and self-sacrifice. What made it last? The newfound smiles on patients faces.

To give the transplant more time

In France, more than 26,000 patients were waiting for an organ in 2020 and more than 250,000 worldwide. Over 900 died for lack of a viable graft in France and over 8000 in the USA, i.e. nearly 20 patients per day. Deprived of blood supply and therefore of oxygen, the organ removed from a donor is damaged. It therefore risks malfunctioning or even being rejected by the recipient's body. This is where HEMARINA's technology comes into play: it provides an unprecedented oxygenation solution that makes it possible to prolong the preservation time of the graft after its collection from the donor: one week on kidney cells depending on the concentration of haemoglobin molecules instead of a day with conventional techniques, 48 hours instead of 4 to 6 hours for a lung... A revolution recognized by the greatest specialists who've mentioned that HEMARINA's technology is as important as the immunosuppressants which have enabled the rise of transplantations.

To preserve an organ is to save a life. HEMARINA supports this ambition, with the potential to bring transplantation into a new era: increasing the chances of successful transplants, no longer losing a graft and turning an emergency procedure into a procedure that can be better planned, for the benefit of the safety and serenity of all.

au monde.

CE marking: the recognition of a collective adventure

The story seems almost too good to be true. However, it is now real. From sand to the laboratory bench, from the laboratory to the operating room, HEMARINA's innovation now has a name in transplantation, HEMO2life®, an innovation designed by nature. After 20 years of research (a thousandth of a second on the scale of evolution) and clinical studies that have demonstrated its safety and effectiveness, the technology is ready to take off worldwide. All it needed was regulatory validation for it to benefit patients and healthcare professionals around the world. After a process delayed by the ongoing revision of European regulations on medical devices, HEMARINA has obtained CE marking for its organ preservation solution. This event

recognized the hard work of a team of women and men who, alongside Franck Zal, had never given up on the dream to create a healthcare company unique in the world.

HEMO2life® technology optimizes the storage time of kidney grafts and their quality in order to accelerate post-transplant function recovery (DGF: Delay Graft Function). The improvement of these essential parameters translates into a marked improvement in patient survival. This technology can now be a preferred solution in transplantation. Several clinical studies, and 4-year follow-up of transplanted patients, have been carried out, making it possible today to demonstrate, for a transplanted patient with HEMO2life®:

- *A decrease in ischemia-reperfusion damage thus allowing accelerated recovery of the graft after transplantation: decrease in the DGF marker by 6.9% (HEMO2life® arm) vs. 26.1% (Control arm).*
- *A survival rate of 98.3% after 4 years compared to 86% under conventional preservation conditions.*

Gone are the days where we simply imitate nature, now we do so to save lives!

ZAL Franck

Cofounder of HEMARINA SA