

Repairing the Heart: Cell Therapy, a Promising Avenue?

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ABSTRACT

Given the shortage of grafts and the limits of the medical device paradigm (assisting the heart) for advanced heart failure, the challenges of innovation are more than obvious. Through an analysis of the dynamics and geography of publications and patent filings on cell therapy applied to heart failure, this article analyzes the potential paradigm shift towards biotechnologies (repairing the heart) in this sector. The analysis of the actors positioning on this technology shows that if the transition is not yet completed, the trend tends to be confirmed: the exploration of the sector by private actors (startups and big pharma) next to universities and public institutions allows us to conclude that there is a progressive technology transfer and a promising future for market application.

Keywords: Cell Therapy; Advanced Heart Failure; Innovation Management; Technological Intelligence; Inventive Dynamics

Introduction

Vital par excellence, the heart's main function is to provide the necessary blood flow to supply all the cells in the body with the oxygen and energy substrates they need. Heart failure (HF) occurs when this flow is too low or is achieved at the expense of an abnormal increase in the filling pressure of the heart. This results in a range of particularly disabling clinical symptoms and signs. HF affects about 2% of the population in developed countries (Roger, et al. [1, 2]). As the population ages, the prevalence is expected to increase further in the coming years (Savarese, et al. [3]). Its mortality rate at 5 years is estimated to be around 67% (Tsao, et al. [4]), rising to 90% at 10 years (Bowen, et al. [5]). This is linked to the fact that heart failure is a long-term progressive syndrome (Ramirault et al., 2010). Because of the progressive course of heart failure, patients require frequent hospitalisations (approximately 150,000 hospitalisations per year in France). Above all, there is no cure for heart failure. About 50% of patients die within three years of diagnosis. Given this major health problem, the challenge of innovation is important in order to improve the care and treatment

of affected patients. Developments in cellular therapies for heart failure (HF) have allowed a new paradigm to emerge over the past decade, with therapies aimed at repairing the heart (Iglesias, et al. [6]) rather than assisting or replacing it.

This trajectory of innovation for the treatment of heart failure can be illustrated by the very recent announcement (July 2022) by the American company Genzyme Biosurgery of the launch of a large randomized study involving 300 patients in Europe and the United States in order to validate the efficacy of muscle cell autotransplantation for the treatment of ischemic heart failure. In France, the start-up CellProthera also announced that it would enter the clinical trial phase in 2021. The recomposition of the chemistry paradigm under the impulse of biotechnologies is not new in the health field, as shown by studies conducted since the end of the 1980s (Orsenigo, et al. [7-10]). Hence the questions that we propose to answer with our tools: What is the state of development of this technology? Who are the main players in this sector?. Using tools from innovation management, we propose to position the per-

spectives opened by cell therapy in comparison to other existing or developing treatments for advanced heart failure.

The Context of Heart Failure as a Progressive Syndrome: A Need for Innovation Facing the Lack of Treatment

When heart failure reaches an advanced stage (AHF; classes 1, 2 and 3 of the Intermacs classification and III and IV of the NYHA classification, see (Figure 1), drug and resynchronisation treatments (pacemakers) fail. There is an urgent need to act as the patient's vital prognosis is at risk within a year (25 to 75% mortality at one year, [Ammar, et al. [11-12]]). At this stage of the disease, the only solution is heart transplantation, the results of which are considered satisfactory: survival at one year after surgery is about 90%, life expectancy after transplantation averages 10-15 years (Hsieh, et al. [13]), and patients' quality of life is significantly improved (Khush, et al. [14-16]). Unfortunately, there are many limitations to the possibility of offering a heart transplant. The most important of these is the shortage of grafts. In France, for example, according to data from the French biomedicine agency, 15% of patients die within a year due to a lack of grafts. Other important limitations are comorbidities: certain lung diseases, morbid obesity or severe damage to other organs such as the liver or kidney. This increases the risk of transplant failure or incompatibility with the immunosuppressive treatment that the transplant recipient must take. Overcoming these limitations and keeping patients alive while waiting for a transplant has been the driving force behind research to develop medical devices. When transplantation is not possible (or is put on hold), a long-term mechanical circulatory support device may be considered. This is one of the driving forces to develop new solutions within the technoeconomic paradigm of mechanical medical devices. These solutions aim at assisting the heart (Figure 2), mainly through LVAD devices (for left ventricular assist device; ESC Guidelines, 2021). Currently, the track of assist devices is the

most successful. We are at the third generation of devices actually implanted in Destination Therapy (DT; Mehra, et al. [16]). However, numerous technical limitations (limited hemocompatibility of materials, lack of bi-ventricular configuration, transcutaneous cable, continuous flow of turbines, and large device volume) are the cause of many complications such as bleeding (especially gastrointestinal), strokes, right heart failure, or infections. The volume of the pumps has an impact on the complexity of the surgery and the eligibility of the patients. These technical limitations raise innovation issues, particularly with regard to materials, the elimination of the transcutaneous cable (fully implantable devices), the possible biventricular configuration of devices (total artificial heart), the development of a physiological pump flow and the miniaturization of pumps (Rodriguez, et al. [17,18]). For the moment, LVAD is only a palliative solution. In addition to this possibility, the idea of replacing the failing heart with a total artificial heart (TAH) is one of the most promising avenues of research. However, and even though TAH could serve patients with right ventricular failure as well, no marketing authorization has been granted for Destination Therapy (DT; long term implantation) because of numerous limitations (Vis, et al, [19]) remain major barriers to market entry as long-term devices. As an example, Carmat is still facing many uncertainties regarding its market launch, despite the recent restart of clinical trial. We focus here on another track, that of cell therapy (biotechnology paradigm) which aims to repair the heart. In order to question the inventive dynamics in the sector, the following tools are mainly used: collecting and processing data on patents (Orbit) and scientific publications (articles and conferences, Scopus). Through an interdisciplinary work between economics and cardiology, queries have been constructed (presented in appendix 1; see also the definition of IPC codes in this appendix). Our queries allow us to identify 33197 academic productions (since 1941) and 1461 patent families (since 1969) in order to characterize the main actors in time and space [20-21].

1. Philippe Menasché, Ottavio Alfieri, Stefan Janssens, William McKenna, Hermann Reichenspurner et al. (2008) MAGIC Study (Myoblast Autologous Grafting in Ischemic Cardiomyopathy) 117(9): 1189-1200.
2. In France, the clinical trial will be conducted in partnership with several hospitals. It will involve 80 patients at a total cost of €1.4 million, of which €400,000 will be financed by a ministerial programme (hospital clinical research programme) and €1 million by Genzyme (whose president did not wish to reveal the overall cost of the study for Genzyme when the collaboration was announced).
3. Source (in French): <https://www.agence-biomedecine.fr/annexes/bilan2017/donnees/organes/03-coeur/synthese.htm>.
4. To our knowledge, the only device with a BTT marketing authorization from the US Food and Drug Administration (FDA) is the CardioWest TAH from the US company Syncardia (Gerosa et al., 2014). In France, the Aeson TAH developed by Carmat has a CE mark authorizing implantation in BTT in affiliated countries and an FDA authorization to conduct a feasibility study in the US (Han, 2021).
5. Carmat has stopped its clinical trials at the end of 2021 due to quality problems with several components. The company has announced that the study will restart on 26 October 2022.

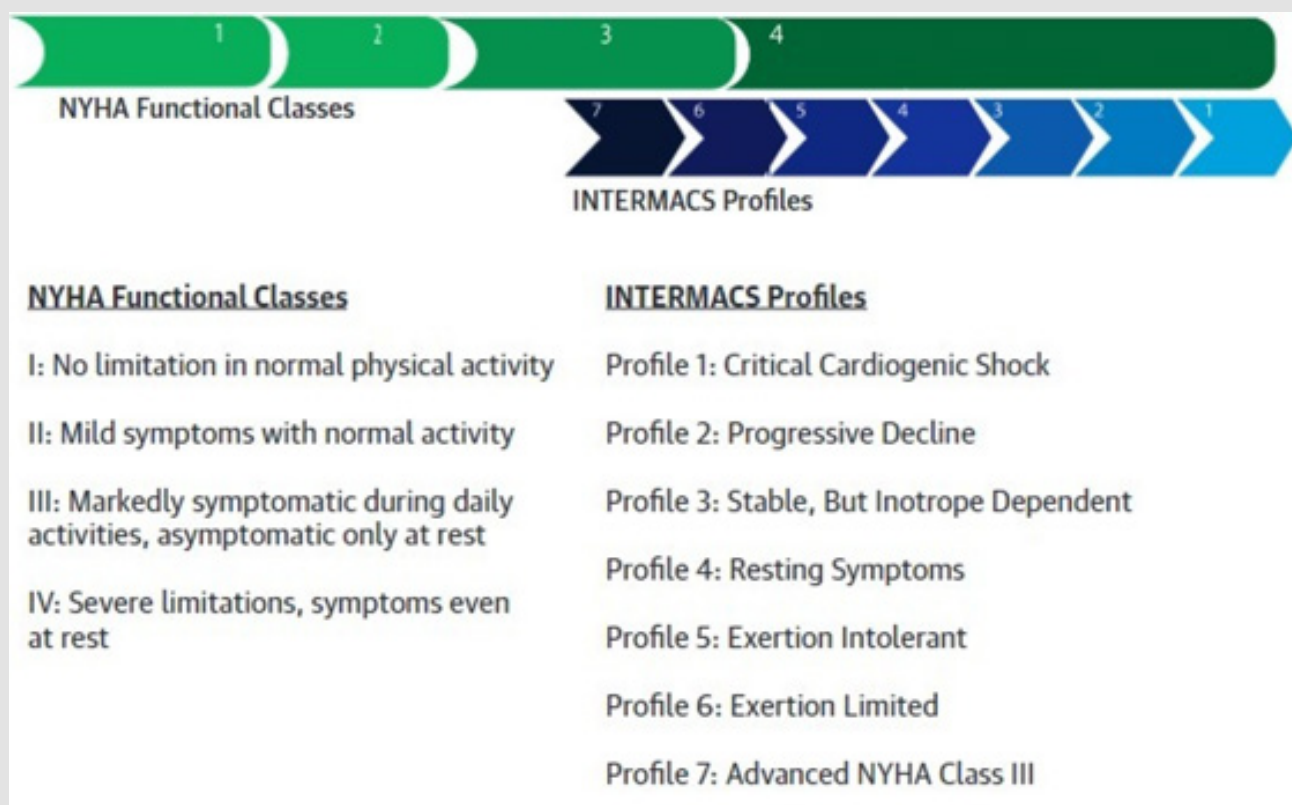


Figure 1: Classifications of heart failure.

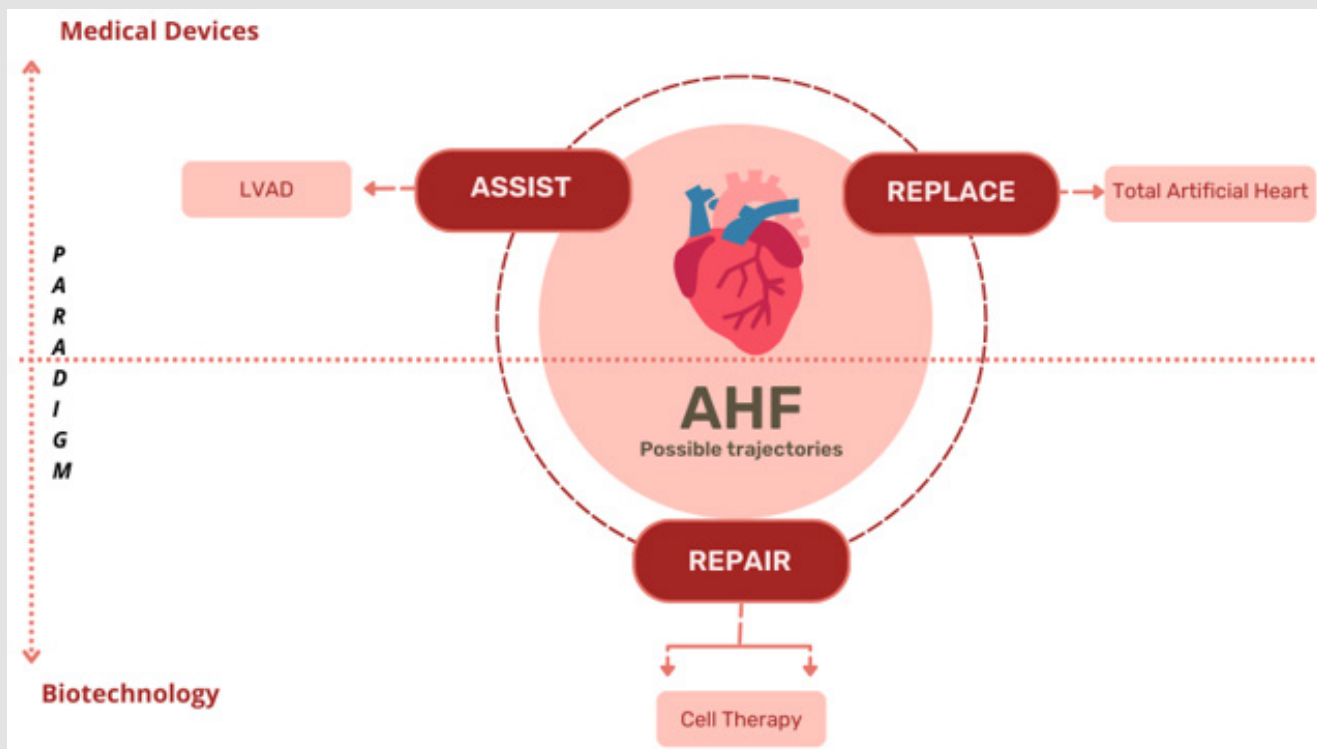


Figure 2: Possible innovation trajectories for heart failure treatment.

The Trend: Research that Accelerated at the Turn of the Century

The dynamics of academic production and patent applications follow the same trend (Figures 3 & 4): an initial period, prior to 2000, when activity is relatively low, then production which be-

comes significant and increases from the turn of the century. In terms of academic production, there has been a very clear acceleration in recent years. On the patent side, after a rapid acceleration (perhaps due to the introduction of Chinese patents) the situation seems to be stabilizing. There were two peaks, around 2010 and in 2018.

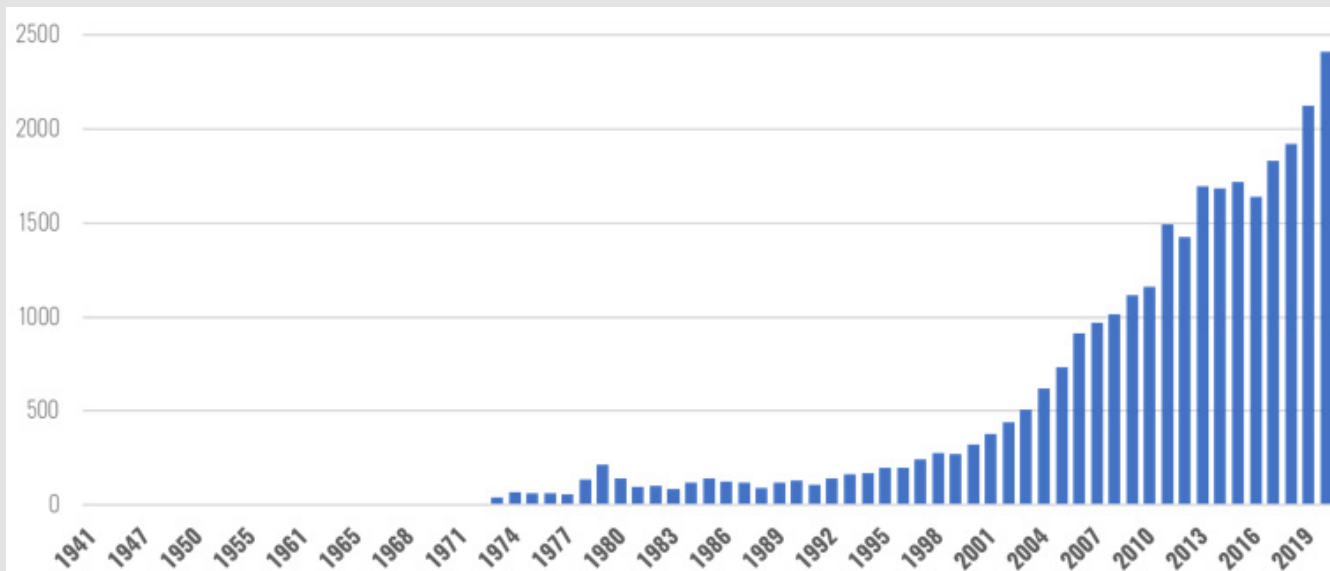


Figure 3: Cell therapy for heart failure: number of scientific publications per year (1941-2021).

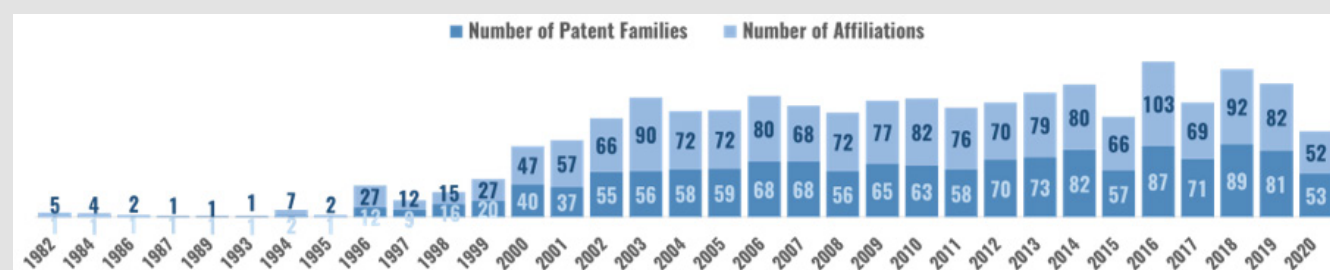


Figure 4: Cell therapy for heart failure: number of patents family per year (1969-2021).

Clear Dominance by the US, Japan and China

Whether in terms of academic production (Figure 5) or patent filings (Figure 6), American, Japanese and Chinese domination is very clear. This is not surprising, given the well-known positioning and dominance of the US in the field of biotechnology for health,

which the recent race for the anti-covid vaccine clearly reminded us of. China is also clearly positioning itself in the biotech field, another well-known observation. Japan has an interesting position with a mix of well-positioned public and private players in the multiple rankings we established (Figures 5-10).

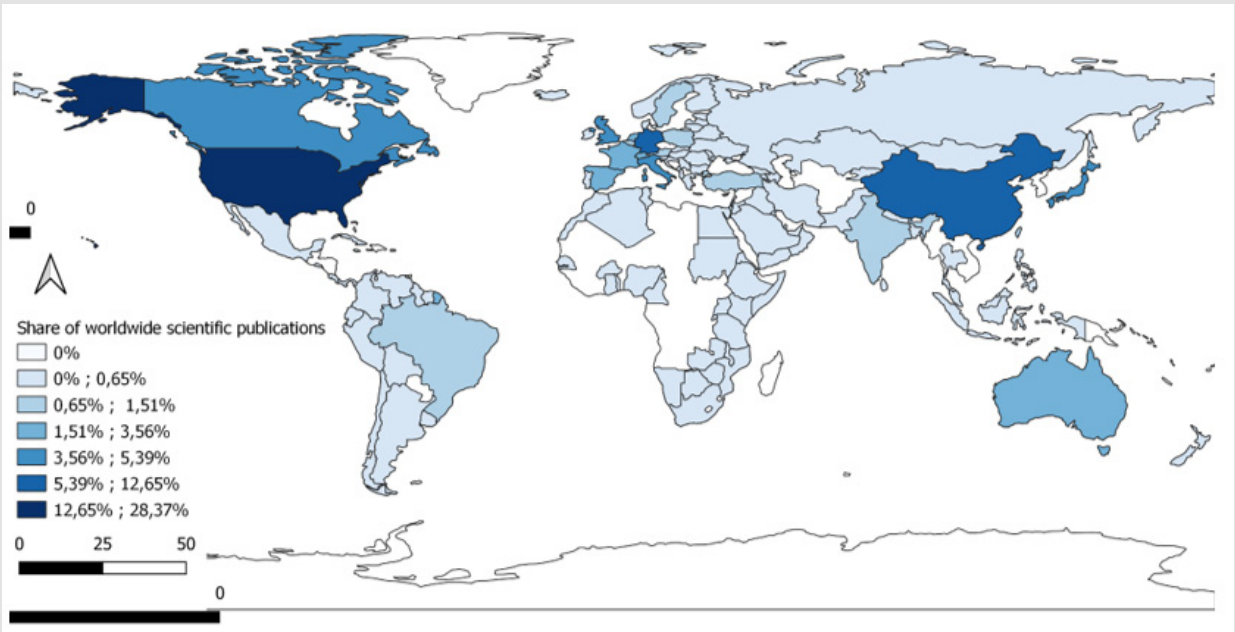


Figure 5: Mapping of scientific productions on cell therapy for heart failure.

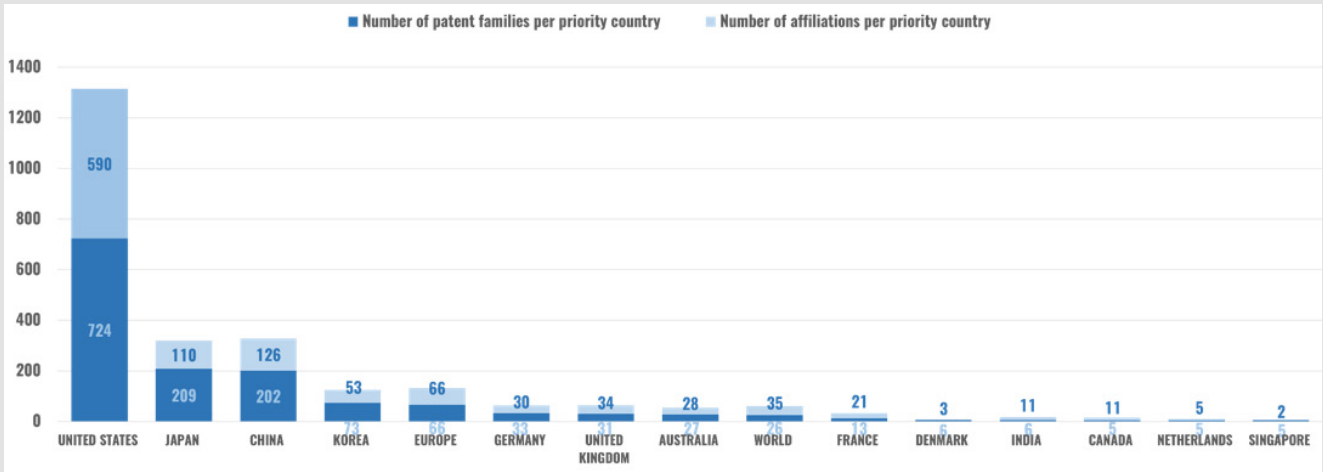


Figure 6: Main priority countries.

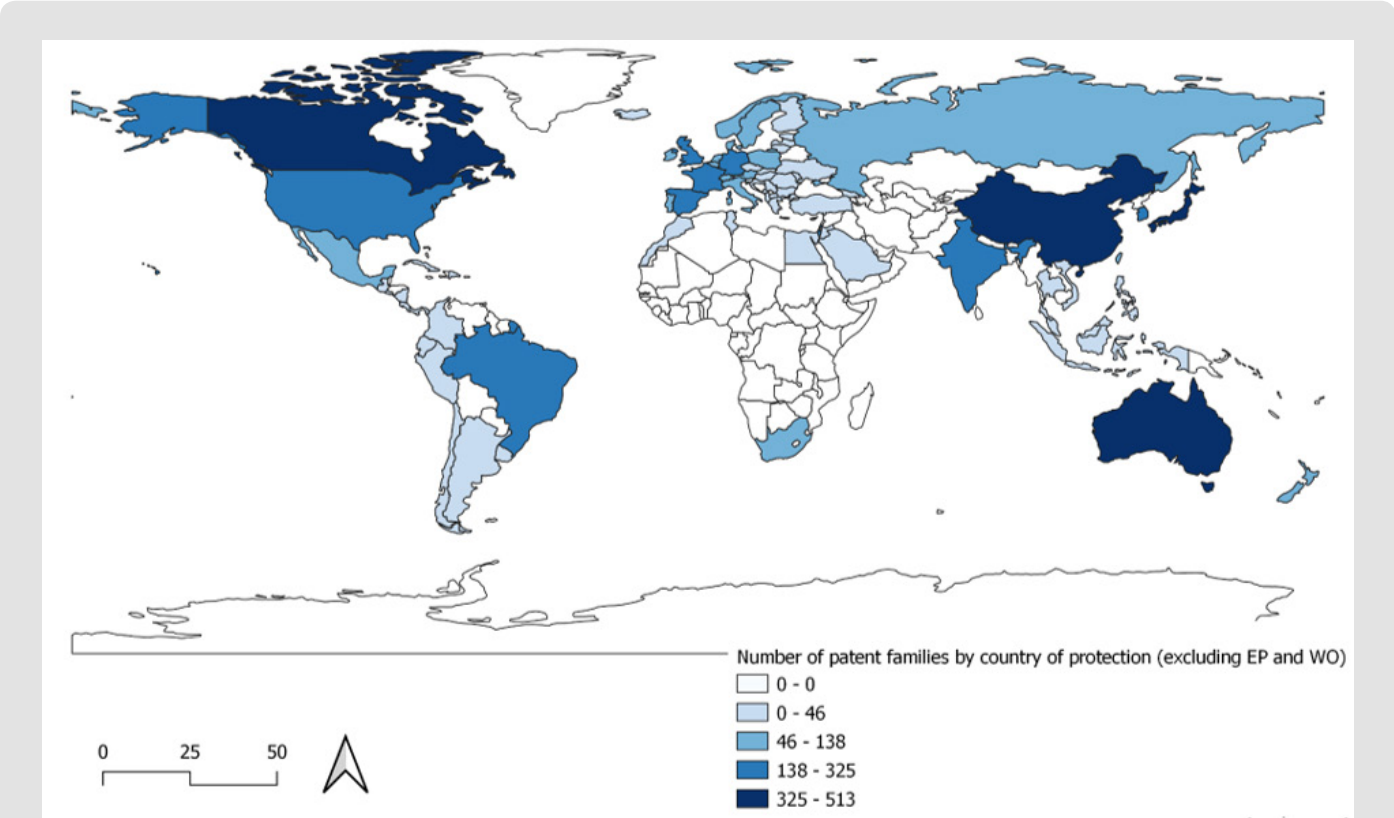


Figure 7: Mapping of patent extensions on cell therapy for heart failure.

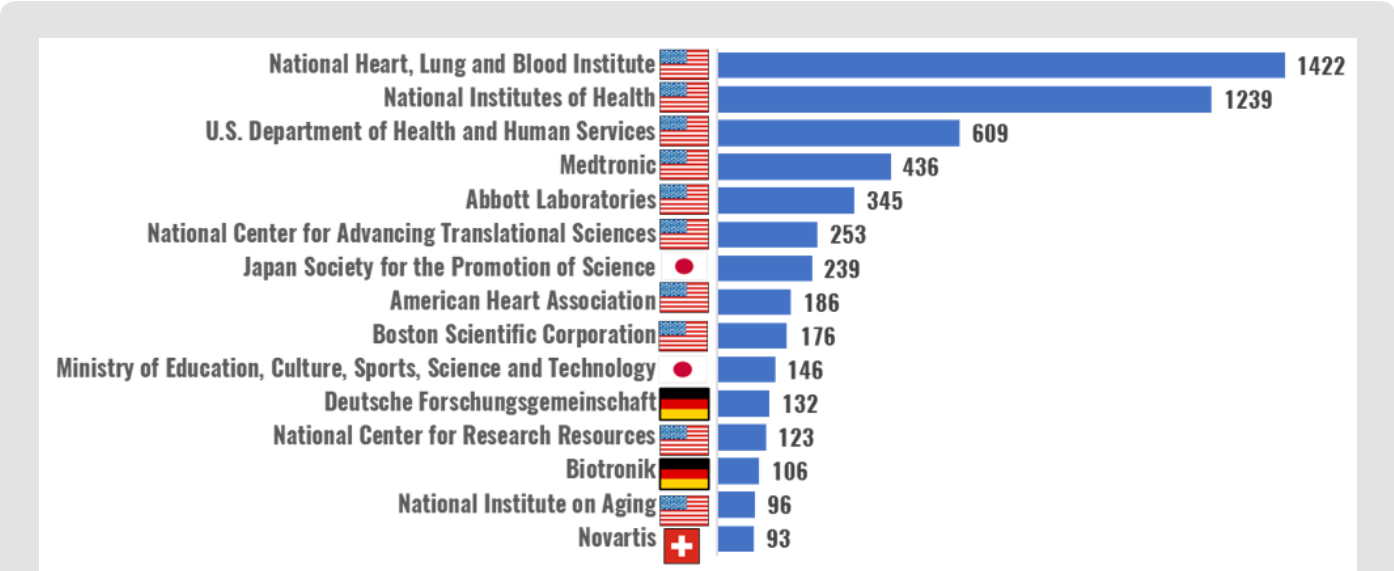


Figure 8: Cell therapy for heart failure: publications by researchers affiliated with public research organizations (top 15 publishers by affiliation).

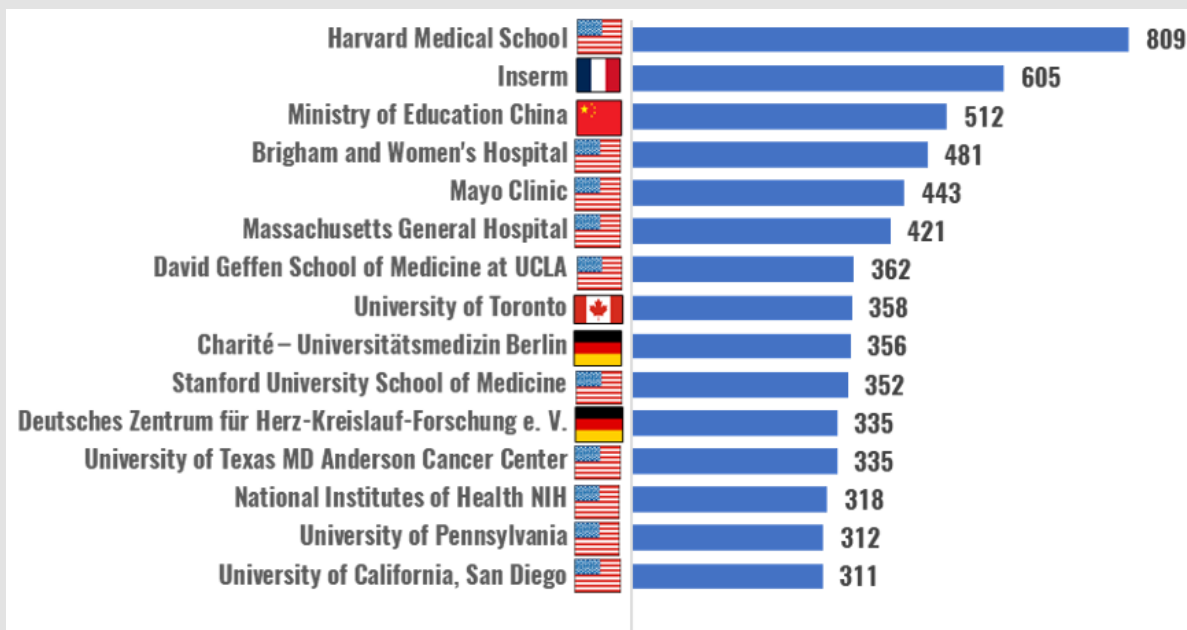


Figure 9: Shows that despite the fundamental aspect of research, private players are already positioning themselves to explore the paradigm. At the top of this ranking is Terumo, already identified among the medical device players.

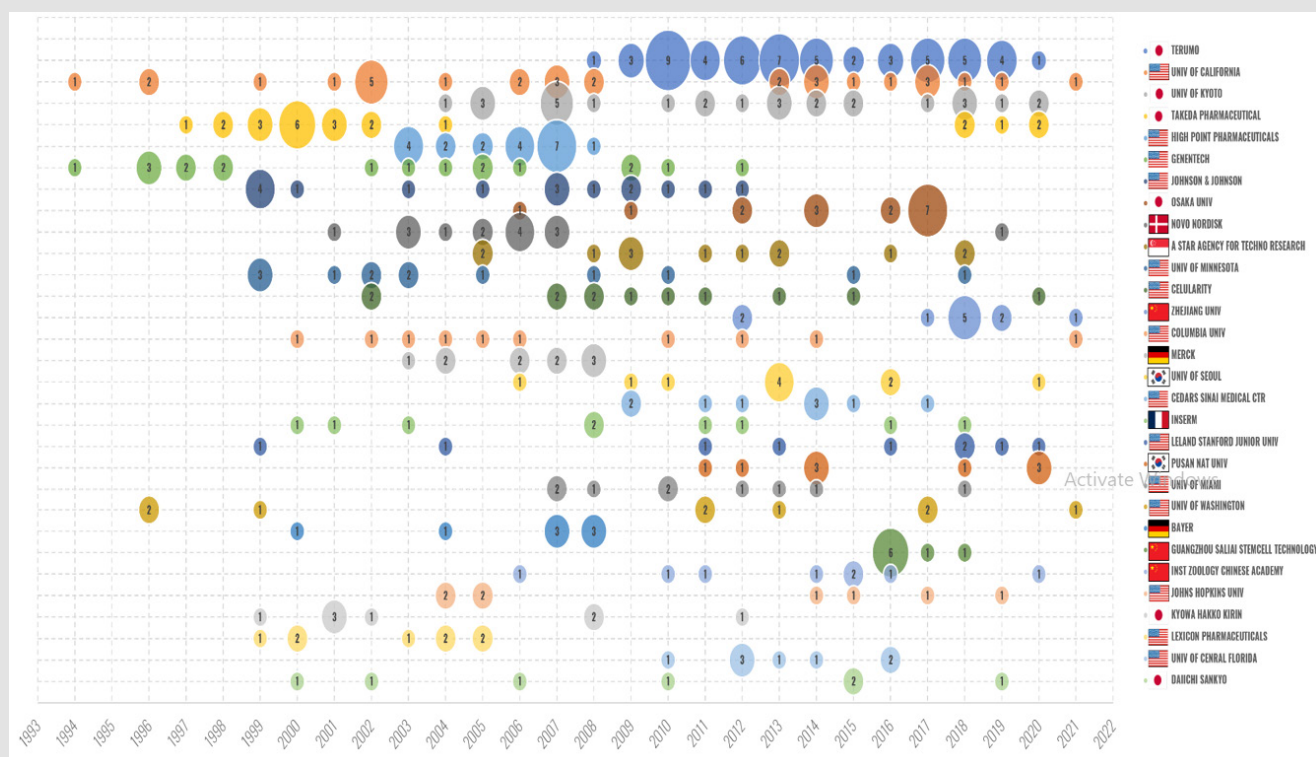


Figure 10: Temporal dynamics of the main applicants of cell therapy for heart failure patents (see appendix 2 for more visibility).

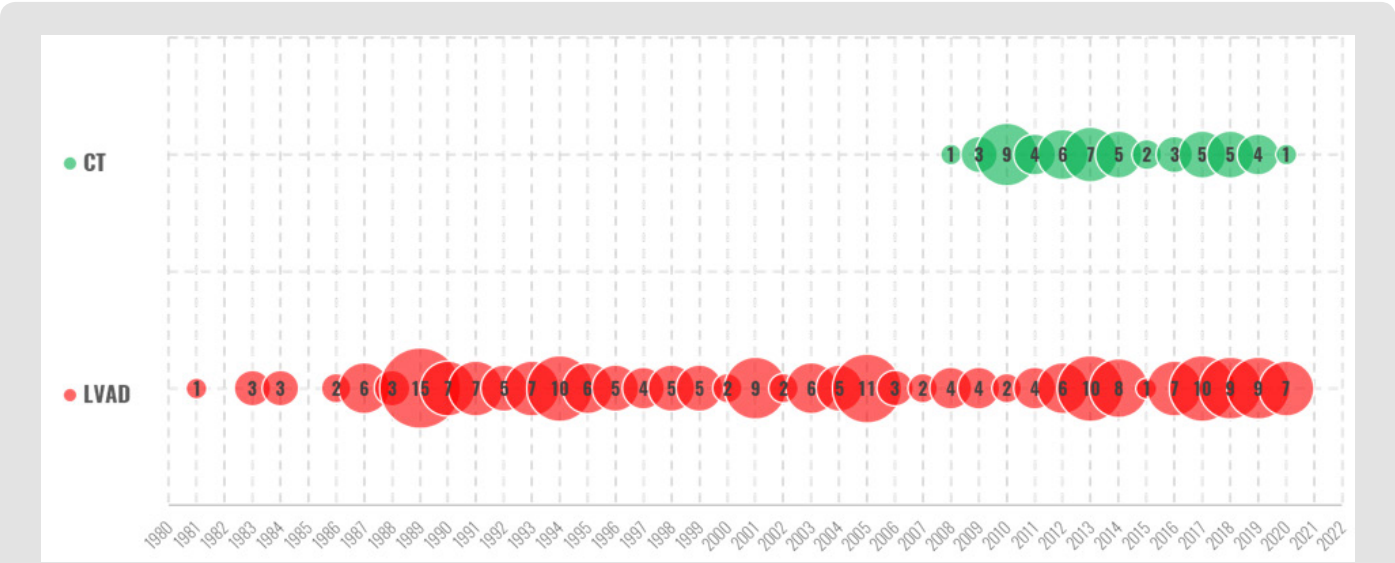


Figure 11: Temporal dynamics of Terumo’s patent filings on LVAD and cell therapy (CT) technologies.

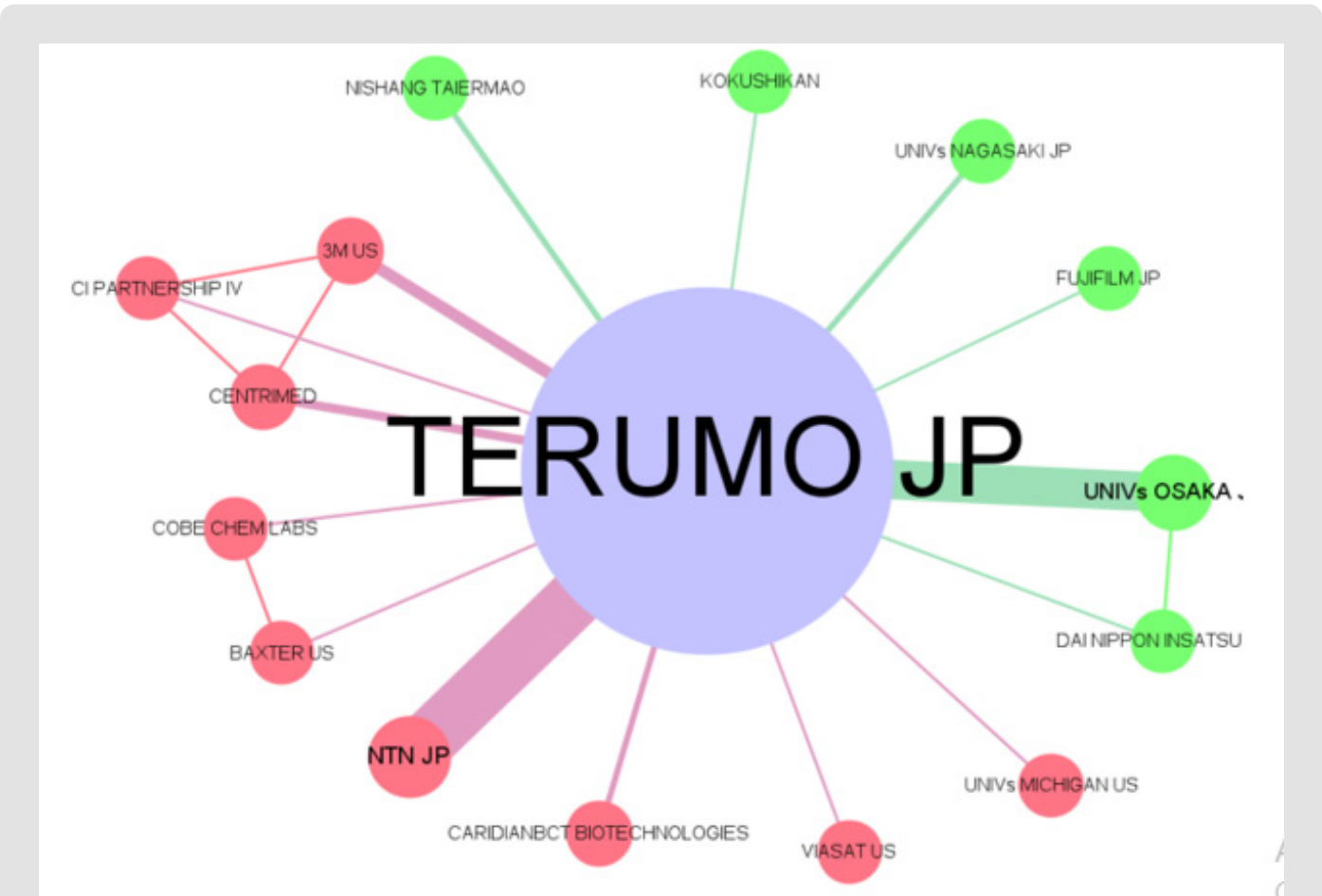


Figure 12: Terumo Patent Collaboration Network (for CT and LVAD).

A Near Absence of Private Actors

What is particularly notable in terms of inventive activity and innovation in the field of cell therapy for the treatment of heart failure is the near absence of private players. The financiers of scientific production are mainly public funds (Figure 8). The high uncertainty of financial returns could explain the absence of private actors among the main investors. In terms of author affiliation, the domination of members of public research laboratories is also very clear (Figure 9), mainly from American, German and Chinese universities. The same observation can be made about patent applicants. This characteristic, linked to the fundamental nature of the research, seems to attest that cell therapy for the treatment of HF is still far from being completed (i.e. the marketing authorisation of a drug product).

The Very Special Case of the Japanese Company Terumo

According to this data, the Japanese company Terumo (Figure 10) is the top applicant for this technology. Terumo is a highly diversified medical device marketing company. The group has sales of more than €2 billion, of which €230 million is generated by its cardiology subsidiary (source: Orbis, 17/11/2022). In terms of intellectual property, the group holds a portfolio of 13,656 patents, including 215 for LVADs and 55 for cell therapy for heart failure (source: Orbit, 17/11/2022). The presence of this player in cell therapy is of particular interest to us because Terumo has also been very active in the development of LVADs since the 1980s, as can be seen from its temporal dynamics of patent filing (Figure 11), in particular in the Japanese domestic market niche, but in collaboration with Abbott, with its DuraHeart II device. Terumo's inventive activity in cell therapy for heart failure is more recent. Terumo is therefore positioned on two technologies that are apparently in competition. It can be assumed that it maintains an activity of exploitation of the medical device paradigm (Terumo has sold the DuraHeart technology to Thoratec, a subsidiary of Abbott, but keeps an exclusive right to distribution in Japan and South-East Asia) while maintaining an activity of exploration with cell therapy. This example of organizational ambidexterity (Duncan, 1976) raises questions about the positioning of cell therapy in relation to LVADs. Is cell therapy meant to replace LVADs in the longer term? Terumo's strategy here would therefore be to ensure short-term profits by exploiting the current paradigm while anticipating a long-term paradigm shift. Another interpretation could be that of hybridization of the two paradigms as evidenced by one of Terumo's patents which reports a bridge-to-recovery LVAD implanted with a stem cell trans-

plantation system to repair the failing heart. While the heart is vulnerable, it is mechanically assisted until the heart is repaired with cell therapy. One thing is certain, this transition or hybridization is still uncertain: while the majority of co-patents on LVAD technology are with private partners (Figures 12 & 13), in red), those for cell therapy are more likely to come from public partnerships and suggest that this is more of an emerging technology based on basic research.

Conclusion

Research on cell therapy as a treatment for heart failure is still recent and at an early stage. The transition to the biotechnology paradigm in this sector is not yet a reality, in the sense that there are no drug products on the market today, but the trend is very much in evidence, following the evolution of the health industries towards the biotechnology paradigm. The purpose of this paper is to present the complex work of understanding the evolution of treatments in this sector, made possible by a collaboration of more than a year with cardiologists of the IHU of Bordeaux (professor-researcher and practitioners). This work opens up prospects for interdisciplinary collaborations between economics and medicine. It appears to us that the tools of innovation management, by intervening more upstream of research in medical sciences (before the medico-economic evaluation) will certainly lead to a greater success rate of projects. We think that it would be interesting to deploy these tools more widely to facilitate technological applications of medical research.

Appendices

Appendix

Orbit and Scopus Queries

Orbit and Scopus are structured databases used in innovation economics and management. They allow the analysis of data on patents (Orbit) and multidisciplinary bibliographic data (Scopus). The following two queries were set up as part of an interdisciplinary dialogue to collect the information that allowed the analysis presented in the article.

Scopus

The Scopus query presented below combines keywords on heart failure and cell therapy in order to isolate publications on both topics. The search for identified keywords is carried out on the titles, abstracts and keywords of the articles. We limited the analysis to scientific articles and conference papers. The corpus consists of 35,379 publications (as of 12/11/2022).

6. Terumo announced entering a strategic alliance with Thoratec (an Abbott subsidiary) on June 30, 2013. The agreement included the sale of certain assets and licenses on the DuraHeart II to Thoratec. In exchange, Terumo will remain the distributor of the device in Japan and Asia.

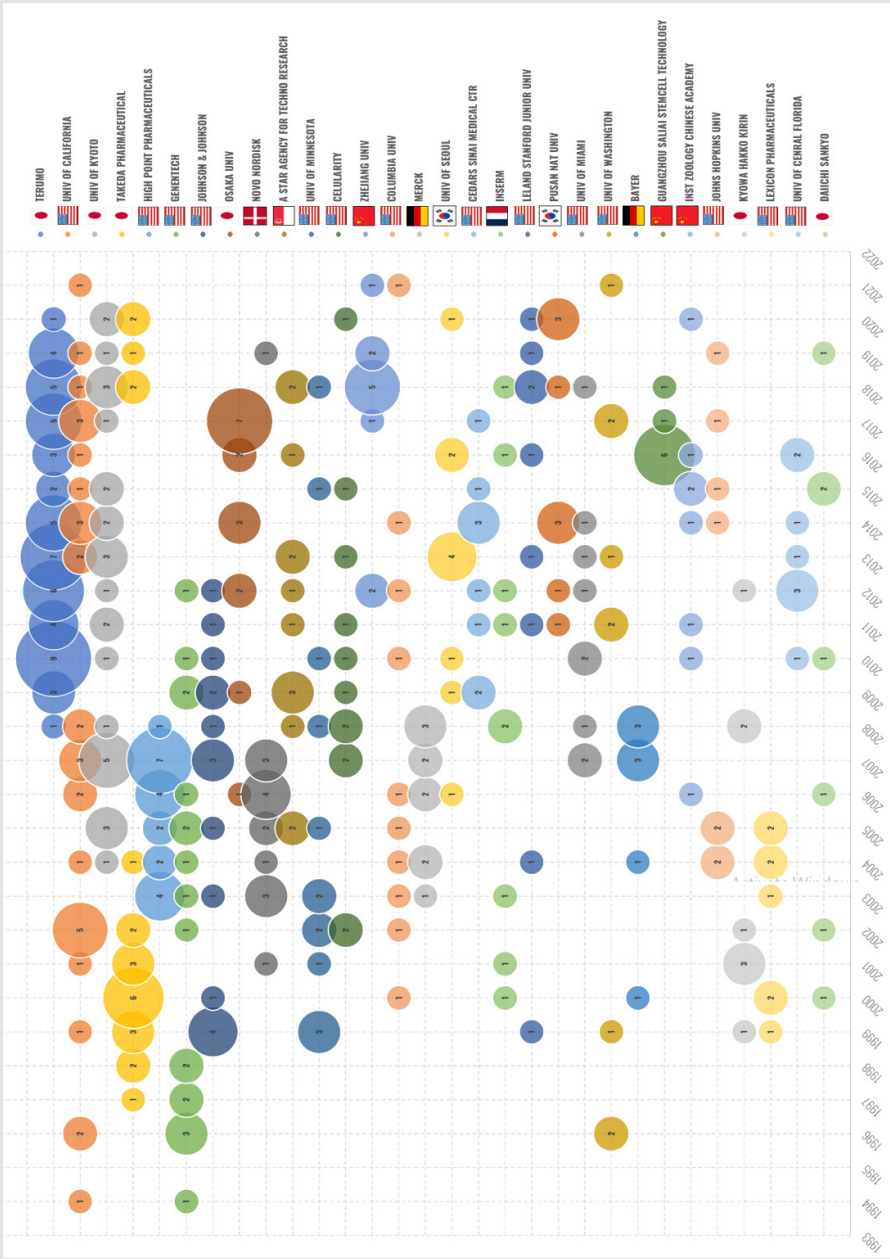
TITLE-ABS-KEY ((((left PRE/2 ventric*) OR heart OR cardiac) AND ((failure) OR (function))) AND (cell* AND (therap*))) AND (LIMIT-TO (DOCTYPE , «ar») OR LIMIT-TO (DOCTYPE , «cp»))).

Orbit

The query below is used to collect data on patents with Orbit. It is a combination of keywords and IPC codes. The International Patent Classification (or IPC) is a hierarchical system for classifying patents according to the different fields of technology to which they belong. These codes allow for greater precision in the results

(details of the codes in the table below). The search for identified keywords is carried out on the titles, abstracts, claims, subject matter of the invention and on independent claims of the patents. The corpus studied consists of 1461 patents (as of 15/12/2022).

((((STEM W CELL+) OR (CELL+ W THERAP+) OR (CELL+ TRANSPLANT+))) AND (((LEFT W VENTRIC+ FAILURE) OR (LEFT W VENTRIC+ FUNCTION) OR (HEART FAILURE) OR (ADVANCED HEART FAILURE) OR (HF) OR (CHD) OR (CHRONIC HEART DISEASE) OR (HEART DISEASE) OR (HEART))))/TI/AB/CLMS/OBJ/ICLM AND (A61K OR A61P OR C12M OR C12N)/IPC/CPC (Appendix Table 1 and Appendix Figure 1).



Appendix Figure 1: Temporal dynamics in terms of patent filings by actors.

Appendix Table 1.

IPC Code	Description
A61K	PREPARATIONS FOR MEDICAL, DENTAL, OR TOILET PURPOSES
A61P	SPECIFIC THERAPEUTIC ACTIVITY OF CHEMICAL COMPOUNDS OR MEDICINAL PREPARATIONS
C12M	APPARATUS FOR ENZYMOLOGY OR MICROBIOLOGY
C12N	MI CROORGANISMS OR ENZYMES; COMPOSITIONS THEREOF; PROPAGATING, PRESERVING, OR MAINTAINING MICROORGANISMS; MUTATION OR GENETIC ENGINEERING; CULTURE MEDIA

References

- Philippe Menasché, Ottavio Alfieri, Stefan Janssens, William McKenna, Hermann Reichenspurner et al. (2008) MAGIC Study (Myoblast Autologous Grafting in Ischemic Cardiomyopathy) 117(9): 1189-1200.
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- Roger, VL (2013) 'Epidemiology of heart failure', *Circulation Research*, 113(6): 646-659.
- Benjamin, EJ, Michael J Blaha, Stephanie E Chiuve, Mary Cushman, Sandeep R Das, et al. (2017) Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 135(10): e146-e603.
- Savarese G, Lund, LH (2017) Global Public Health Burden of Heart Failure. *Cardiac Failure Review* 3(1): 7-11.
- Tsao, CW, Asya Lyass, Danielle Enserro, Martin G Larson, Jennifer E Ho, et al. (2018) Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. *JACC Heart failure* 6(8): 678-685.
- Bowen RES (2020) Statistics of heart failure and mechanical circulatory support in 2020. *Annals of Translational Medicine* 8(13): 827.
- Iglesias JFM Tapponnier, R Hullin, G Vassalli, E Eeckhout, P Vogt, et al. (2012) Thérapie cellulaire régénérative en cardiologie: le futur au présent ?. *Revue Médicale Suisse Urologie* 365(8): 2364-2369.
- Orsenigo L (1989) The emergence of biotechnology. Institutions and markets in industrial innovation. St Martin Press, NewYork.
- Gambardella A (1992) Competitive advantages from in-house scientific research : the US pharmaceutical industry in the 1980s. *Research Policy* 21(5): 391-407.
- Balmer B, Sharp M (1993) The battle for biotechnology: Scientific and technological paradigms and the management of biotechnology in Britain in the 1980s. *Research Policy* 22(5-6): 463-478.
- Bottazzi G, Dosi G, Lippi M, Pammolli F, Riccaboni M (2001) Innovation and corporate growth in the evolution of the drug industry. *International Journal of Industrial Organization* 19(7): 1161-1187.
- Ammar KA, Steven J Jacobsen, Douglas W Mahoney, Jan A Kors, Margaret M Redfield, et al. (2007) Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation* 115(12): 1563-1570.
- Xanthakis, V, Danielle M Enserro, Martin G Larson, Kai C Wollert, James L Januzzi, et al. (2016) Prevalence, Neurohormonal Correlates, and Prognosis of Heart Failure Stages in the Community. *JACC. Heart failure* 4(10): 808-815.
- Hsich EM (2016) Matching the Market for Heart Transplantation, *Circulation. Heart failure* 9(4): e002679.
- Khush KK, Wida S Cherikh, Daniel C Chambers, Michael O Harhay, Don Hayes, et al. (2019) The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report- 2019; focus theme: Donor and recipient size match. *The Journal of Heart and Lung Transplantation* 38(10): 1056-1066.
- Lund LH, Leah B Edwards, Anna Y Kucheryavaya, Anne I Dipchand, Christian Benden, et al. (2013) The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report--2013; focus theme: age. *The Journal of Heart and Lung Transplantation* 32(10): 951-964.
- Mehra MR, Charles E Canter, Margaret M Hannan, Marc J Semigran, Patricia A Uber, et al. (2016) The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update, *The Journal of Heart and Lung Transplantation*: 35(1): 1-23.
- Rodriguez LE (2013) Ventricular Assist Devices (VAD) Therapy: New Technology, New Hope?. *Methodist DeBakey Cardiovascular Journal* 9(1): 32-37.
- Sidhu K, Lam PH, Mehra MR (2020) Evolving trends in mechanical circulatory support: Clinical development of a fully magnetically levitated durable ventricular assist device. *Trends in Cardiovascular Medicine* 30(4): 223-229.
- Annemijn Vis, Maziar Arfaee, Husain Khambati, Mark S Slaughter, Jan F Gummert, et al. (2022) The ongoing quest for the first total artificial heart as destination therapy. *Nature Reviews. Cardiology* 19(12): 813-828.
- Han JJ (2021) Aeson-The Carmat total artificial heart is approved for enrollment in the United States. *Artificial Organs* 45(5): 445-446.
- Truby LK, Rogers JG (2020) Advanced Heart Failure: Epidemiology, Diagnosis, and Therapeutic Approaches. *JACC: Heart Failure* 8(7): 523-536.

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