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Cardiovascular Research in France

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France has a long tradition of excellence in cardiovascular medicine, starting with André Cournand, 1956 Nobel Prize for the development of cardiac catheterization, followed by the first coronary stent in man by Jacques Puel in 1986.[1] In 2002, Alain Cribier implanted the first human transcatheter aortic valve implantation.[2] Alain Carpentier received the 2007 Lasker Prize for developing prosthetic mitral and aortic valves and also conceived the first fully implantable artificial heart CARMAT in 2008. More recently, Philippe Menasché initiated the first stem cell–based approach for heart failure using transplantation of human myoblast or human embryonic stem cell.[3] Over the past 50 years, French cardiovascular research has also developed around prominent scientists, including Edouard Coraboeuf (cardiac electrophysiology),[4] Margareth Buckingham (cardiac development),[5] Ketty Schwartz (cardiogenetics),[6] Pierre Corvol and Michel Safar (hypertension),[7,8] and Michel Haissaguerre (rythmology).[9]

Organization of Cardiovascular Research

The complex research organization in France is often described as a *millefeuille*, referring to the many-layered pastry one can admire in French bakeries. This organization results from political decisions, which have led to successive addition of structural administrative layers without removal of redundant ones. For the sake of clarity, this article will summarize the major traits of research organization in the cardiovascular field.

Around 70 laboratories had cardiovascular or hematology research activities in 2016, corresponding to one fifth of those in physiology and pathology. Most of them are either affiliated to the *Institut National de la Santé et de la Recherche Médicale* (INSERM), the *Centre National de la Recherche Scientifique* (CNRS), or Universities. These laboratories are spread throughout the national territory, and unsurprisingly, the highest concentration is found in the Paris area. They are up for competitive renewal every 5 years after independent evaluation by the *Haut Conseil à l'Evaluation de la Recherche et de l'Enseignement Supérieur*. Laboratory size varies from 10 to ≤50 staff members. Universities, INSERM, and CNRS provide permanent positions for scientists, professors, technical or administrative staff, as well as yearly financial support for research activities and laboratory housing. However, a large part of staff members have short-term contracts, which are renewable only under strict administrative rules. On top of that, one should mention the worldwide unchallenged limitation of postdoctoral fellowships to 3 years.

Because INSERM supports research in health sciences and in the medical field, it represents a major actor in cardiovascular research in France. INSERM laboratories are often located next to medical schools or hospitals. In recent years, INSERM has regrouped its teams in either research units or in large centers to optimize resources, technical platforms, and administrative support. Several cardiovascular research centers were created in the past decade, including the *Thorax Institute* in Nantes (also supported by CNRS), the *Institute for Metabolic and Cardiovascular Diseases* in Toulouse, the *Cardiovascular and Nutrition Research Center* in Marseille, and the *Paris-Cardiovascular Research Center*. All are closely associated with the nearby Universities, and each one is composed of 5 to 14 research teams and ≈120 to 280 staff members. French research in cardiovascular sciences also include 36 INSERM Clinical Investigation Centers, which conduct clinical and epidemiological studies, technological innovation, and biotherapies in several domains, including cardiovascular diseases.

Funding of Cardiovascular Research

Academic Funding

While technological revolutions are constantly accelerating on a global scale, the research and development effort in the French economy remains insufficient and is not progressing (http://www.lecese.fr/travaux-publies/rapport-annuel-sur-letat-de-la-france-reconcilier-la-france). In fact, it accounted for only ≈2.2% of GDP in the early 1990s and has remained steady through the next 25 years (2.23% in 2015, of which 0.78% is for academic research).

Therefore, France has not managed to significantly increase its research effort in the last 25 years,[10] despite its 2020 objective to reach 3% of GDP (1% for the public effort) according to its European commitments (Lisbon strategy, March 2000). Because of this delay, the research effort in the French economy is now below the average of the OECD countries (2.38%) and below that of the main industrial countries such as Germany (2,9%), Japan (3.6%), and the United States (2.7%). France, which ranked fifth worldwide in terms of research effort in 1990, is now at the eighth place.

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(*Circ Res*. 2018;122:657-660. DOI: 10.1161/CIRCRESAHA.117.310841.)

***Circulation Research* is available at http://circres.ahajournals.org** **DOI: 10.1161/CIRCRESAHA.117.310841**

Funding for Cardiovascular Research

National Research Institutes such as INSERM or CNRS and local Universities provide basal support in terms of permanent research or staff positions, laboratories, and 5-year recurrent funding, which represents on average 30% of total research laboratory funding. The remaining 70% come from competitive grant applications such as the European community, Charities, or the French Agency for National Research (ANR).

After an initial growth between 2006 and 2010, the total budget for ANR in Health Sciences and Biology dropped by 33% between 2010 and 2013. This decrease in funding, associated with an increase of the number of submission, led to a sharp decrease of success rate, down to 11% to 13%, which we have to compare to the 20% to 30% acceptance rate of the DFG in Germany over the same period.[11] In 2016, the total ANR support for physiopathology was €16.2 million, with €13.5 and €2.7 million devoted to national and European (ERANETs) calls, respectively. Overall, the 2016 ANR budget for national grants in Health Sciences and Biology is still lower than the corresponding one in 2010 (€131 versus €156 million, respectively). Moreover, the 2016 average 3-year funding of €163 000 per research laboratory seems insufficient with respect to the challenges to face. Clearly, the financial capacity of the French ANR seems underpowered in view of the number of research laboratories to support, despite efforts in optimizing its running costs. This must also be seen in the context of restriction of national research institutes–based recurrent funding.

Two major French charities also support cardiovascular research in France: each year, the *Fondation de France* and *Fondation pour la Recherche Médicale* provide €4.8 million in competitive grants, which represents 20-fold less than the British Heart Foundation. In 2016, the *Fondation pour la Recherche Médicale* support to cardiovascular sciences amounted 6.6% of its global budget, which is significantly lower than the amount given to neurosciences (29%), infectious diseases (19%), or cancer (13%). Since 2004, Fondation Leducq has also given substantial support to 41 French cardiovascular laboratories through the 57 transatlantic networks funded.

In 2010, the French government introduced the new program "Investing for the Future" with €22 000 million dedicated to scientific research and higher education. This program created 6 *Instituts Hospitalo-Universitaires* to foster biomedical innovation and improve patient care and treatment, with a financial support of ≈€50 million each for 10 years. Two of these Institutes are dedicated to cardiovascular sciences, in particular cardiac arrhythmias (Lyric, Bordeaux) and cardiometabolic diseases (ICAN, Paris). The program also funded 171 *Laboratoires d'Excellence* with a yearly support of ≈€1 million each on average; one of them (LERMIT, Paris-Saclay) aims to fight 3 major classes of diseases, including cardiovascular pathologies.

Unfortunately, quantitative data on the overall cardiovascular research funding by national Institutes and Universities are not available, and we could not estimate the respective contribution of each of the institutional partners and charities involved.

Funding of Young Investigators

Since 2008, several funding programs specifically support the research activities of young investigators who have obtained their PhD degree within the last 10 years.

First, the *Atip-Avenir* program (jointly driven by INSERM and CNRS) awards each year ≈20 young investigators in health sciences and biology since 2009. These young investigators receive a 5-year starting package and laboratory space, in addition to their salary and that of one postdoctoral fellow. In the past 5 years, this program has selected each year one project in the cardiovascular field, except for 2017.

ANR also developed in 2012 a specific program devoted to young investigators, with a steady increase in the number of awarded grants. Applications in the cardiovascular field have also been increasingly successful from 6% in 2014 to 10% in 2017 (Figure [A]).

French young investigators in cardiovascular sciences are also competitive for European applications, with 2 starting ERC grants awarded each year since 2014 (€1.5 million for 5 years). During the same period, 1 advanced and 2 consolidator ERCs were granted to senior investigators.

Scientific Production in Cardiovascular Sciences

Cardiovascular scientific production has been increasing steadily since 2000, both for clinical and basic or translational studies (Figure [B]). Citations average 77 774 and 459 936 for clinical and basic translational studies over this period. Scientific production by cardiovascular investigators stands out as it represents 34% of French publications in clinical medicine (7000 out of 20 500) and 39% of the top 1% in France (230 out of 585; Web of Science). Therefore, the cardiovascular field ranks higher in quantity and quality when compared with Neurosciences, Cancer and Infectious Diseases in France, despite the fact that these fields receive more funds, both from major French charities and from the national granting agency ANR.

The contribution of French laboratories to scientific papers published in *Circulation Research* seems stable between 2000 and 2016, France remaining at the third place of European countries, behind England and Germany.[10] However, the authors' own publications in American Heart Journals require today a 3-fold increase in the number of figures when compared with that 15 years ago (Figure [C]). The trend is accompanied with a 2-fold increase in the number of coauthors (from ≈7–15, data not shown). These observations are likely not specific to French cardiovascular research. Several causes might have contributed to this trend, including unrestricted requests from reviewers, the possibility of online supplements after 2001, and the numerous technological progress, providing new equipment and biological tools or kits. It is obvious that publishing today requires producing more data, using more sophisticated equipment, tools, and increasing expertise. However, this has an increasing cost that needs to be taken into account.

It also raises the question how French cardiovascular research will cope with these changes to maintain its scientific production over the coming years, despite recent reductions in competitive national funding and a lower level of cardiovascular funding compared with other research fields. No matter

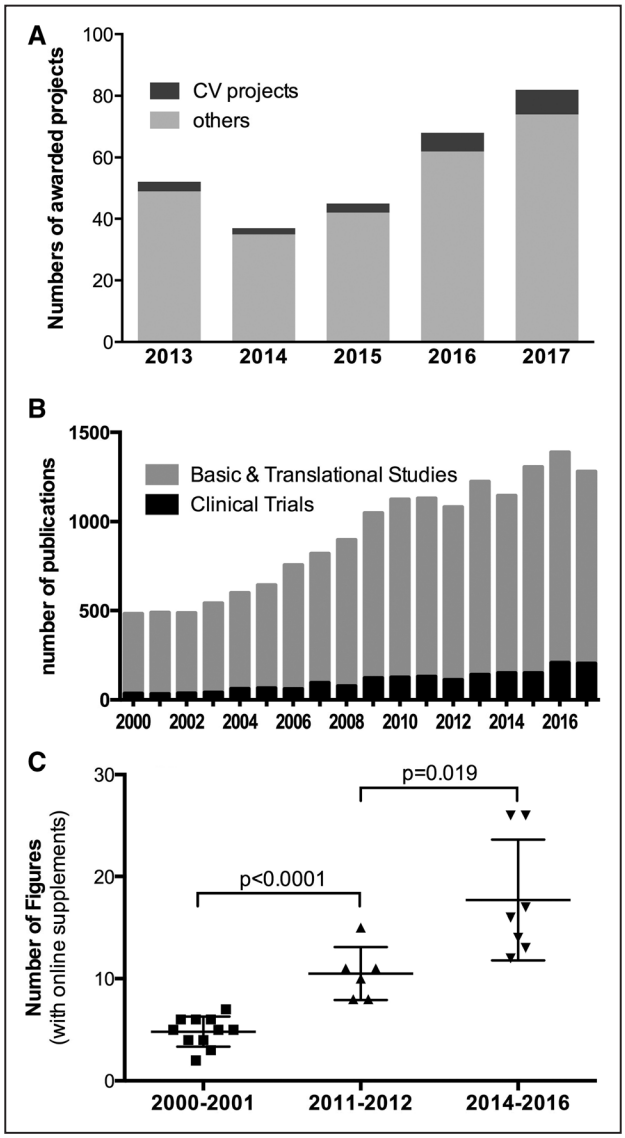

Figure. Cardiovascular research in France. A, Competitive Agency for National Research (ANR) grants for young scientists awarded in health science; cardiovascular (CV) funding is indicated in dark gray. **B**, Scientific production in clinical (dark) and basic translational studies (gray) (Web of science). **C**, Total number of figures, including supplement, in the authors' publications in 3 American Heart Association (AHA) journals (*Circulation*, n=6; *Circulation Research*, n=12; *Arteriosclerosis, Thrombosis, and Vascular Biology*; n=6). Online figures appeared after 2000 to 2001. Statistical analysis was performed using one-way analysis of variance (ANOVA; $P<0.0001$) and post-tests using unpaired *t* tests (GraphPad Prism).

how resourceful French cardiovascular scientists are, there may come a time when they will be unable to keep pace. Unless public policies change regarding investment in academic research, in the long term, such reductions will not only affect the quality of publication, but also new patents and France's ability to compete for European and international grants.

Perspectives and Challenges of Cardiovascular Research in France

Cardiovascular diseases remain the number one killer in France, as in other European countries, but cancer, neurodegenerative and infectious diseases seem as greater threats to the general population. For this reason, public policy makers have set aside specific funding for cancer (the National Cancer Institute, since 2004), neurodegenerative diseases (*Plan Alzheimer* 2008–2012 and 2014–2019), and infectious diseases (the French Agency for Research on Aids and Viral Hepatitis, since 1988). A similar *National Institute for Cardiovascular Diseases* is unfortunately lacking, and cardiovascular research must compete with other domains for financial support. Increasing the public awareness of cardiovascular scientific advances by French research teams may help change the perception of the general population and, in turn, public policies. In this regard, gathering cardiovascular research laboratories in large and visible centers certainly helps, in addition to improving scientific collaboration and production and decreasing running costs.

Taking into account the respective level of funding in specific domains, the quality of cardiovascular research scientific production is far better than that of cancer or neurodegenerative diseases in France. However, our international competitiveness might decline in the future, as other countries increase their research investment.[10,11] It is reassuring to see that recent measures have been taken to specifically support young investigators with *Atip/Avenir* 5-year programs, and increasing number of national grants were awarded to young scientists in the cardiovascular field, attesting their growing competitiveness. To keep this momentum, we must attract our most talented young undergraduate students into cardiovascular research. For this, specific actions need to be taken at the undergraduate level, where teaching programs give priority to neurosciences or immunoinfectious diseases, in turn dragging students away from cardiovascular science.

Acknowledgments

We thank INSERM evaluation department, the thematic Institute for physiopathology (ITMO-PMN), and Agency for National Research (ANR) for their help.

Disclosures

The authors are INSERM research directors. C.M. Boulanger is a member of INSERM Scientific Council and ITMO-PMN Scientific Advisory Board. She is supported by *Fondation pour la Recherche Médicale* (FRM) and Agency for National Research (ANR) grants. J.-S. Silvestre is scientific adviser for the French National Research Agency and supported by grants from ANR, FRM, and Fondation de France. A. Tedgui is past president of the INSERM Scientific Council and a member of the Scientific Advisory Committee of the Fondation Leducq. He is supported by FRM and ANR grants. He is Director of the Paris-Cardiovascular Research Center.

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KEY WORDS: education ■ France ■ heart failure ■ hypertension ■ research