

2015

INSERM International Scientific Advisory Panel Report

Evaluation, Advice and
Recommendations



Inserm

Institut national
de la santé et de la recherche médicale

International Scientific Advisory Panel

INSERM

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Acronyms

IRP - International Review Panel

CNRS - Centre National de la Recherche Scientifique

CEA - Centre d'études nucléaires

CHU - Centre Hospitalier Universitaire

CIC - Centre d'investigation clinique

EU - European Union

OECD - Organization for Economic Co-operation and Development

ANR - Agence Nationale de Recherche

INRIA - Institut national de recherche en informatique et en automatique

Letter from the Chair

On behalf of the International Review Panel (IRP), I would like to acknowledge INSERM's excellent and efficient organization of the review process. INSERM displayed great professionalism in handling this review and provided the Panel with a great deal of information and materials which aided with the undertaking. We have appreciated both your support throughout our mandate and your respect for our independence.

I would also like to thank the members of the IRP for devoting their time and expertise to this process. Each member brought thoughtful and incisive perspectives to bear, which were integral to the success of the review. The dedication and commitment of all those involved were greatly appreciated.

Finally, I would like to thank Secretary of State for research and higher education Thierry Mandon, for taking time out of his busy schedule to meet with the IRP and share with us his passion for science and his vision for INSERM.

It has been an honour and a privilege to lead the review of this premier research Institute. Assessment exercises are always great learning experiences and INSERM's evaluation was a particularly enriching one. The IRP hopes that its recommendations will help to strengthen INSERM as it undertakes to advance biomedical research in France and to more efficiently foster the application of research results to the service of patients and society at large.



Alain Beaudet, MD, PhD
President, Canadian Institutes of Health Research
Chair, International Review Panel

Composition



The International Review Panel, or as herein referred to as “IRP”, was comprised of the following members:

Alain Beaudet (Chair), CANADA

President of the Canadian Institutes of Health Research

Pierre Corvol, FRANCE

Former head of INSERM’s Vascular Pathology and Renal Endocrinology Unit

Ruxandra Draglia-Akli, EUROPEAN UNION

Director of the Health Directorate of the Research DG of the European Commission

Richard Frackowiak, SWITZERLAND

Former Head of the Department of Clinical Neurosciences at the Université de Lausanne

Michel Goldman, BELGIUM

Former Executive Director of the Innovative Medicines Initiative Joint Undertaking of the European Union

Yuko Harayama, JAPAN

Executive Member, Council for Science and Technology Policy, Cabinet Office of Japan

Nora D. Volkow, UNITED STATES OF AMERICA

Director, National Institutes of Health’s National Institute of Drug Abuse

Summary of the IRP's Recommendations

Recommendation #1. That INSERM take full advantage of its organizational structure to increase the number and scope of its multidisciplinary UNITS. For this purpose, INSERM should seek out the interest of other research organizations (e.g. CNRS, CEA, INRIA or universities) in co-developing and co-funding mixed UNITS comprised of biomedical researchers, as well as of researchers from the natural sciences, mathematics, engineering, or the social sciences as it has achieved with the information technology sector.

Recommendation #2. That INSERM, taking advantage of the implementation of the Action Plan for translational and clinical research jointly commissioned by the Minister of Research and the Minister of Health, enhance its capacity for translational and clinical research and embrace a more integrated approach to clinical trials. It also encourages INSERM to take a leadership role in international clinical trial networks, such as the European clinical trial networks, and to foster the development of alternative trial methodologies.

Recommendation #3. That INSERM work closely with the universities and CHUs to develop curricula for schools of public health to link research, teaching, and practice and to educate and train the next generation of epidemiologists, health economists and health services researchers.

Recommendation #4. That the French government support INSERM in ensuring better transfer and integration of research results into care, through the development and support of implementation science and health services and policy research.

Recommendation #5. That the Ministry of Health recognize the expertise and the role of INSERM in developing research on the health care system integrated to its network of CICs.

Recommendation #6. That INSERM strengthen its partnerships with the private sector, not only pharmaceutical companies, but also IT companies, telecom companies and the other emerging players in the healthcare sector, as well as take advantage of the opportunities under the European Juncker investment plan, and condition for venture capital investment in new (bio)technologies in Europe.

Recommendation #7. That INSERM continue to work in close partnership with the various other tech transfer entities (regional, universities, hospitals, research institutes)

to clarify roles and responsibilities, to improve system nimbleness, decrease administrative burden for researchers, and avoid dilution of Intellectual Property.

Recommendation #8. That INSERM develop a “toolbox” of performance indicators that go beyond bibliometric data, to assess the health, social and economic impacts of its large cross-cutting initiatives. This would require a specific support from the French authorities, especially the Ministry of Health.

Recommendation #9. That the French government be made aware of the serious consequences of INSERM’s flat-lined budget on the rejuvenation of INSERM’s workforce, and of the need to increase the budget of the organization to ensure the competitiveness of the French health and biomedical research enterprise in the long term.

Recommendation #10. That INSERM work with its university partners to identify alternative recruitment paths that would ensure in the short term a steady intake of outstanding young investigators in health research.

Recommendation #11. That INSERM conduct an environmental scan to determine research needs and gaps, develop strategic recruitment and gender representation policies, including for upper management positions, and rethink the structure of its competition process and composition of its review panels to allow for the recruitment of a workforce adapted to tomorrow’s national and international scientific and social imperatives.

Recommendation #12. That INSERM underscore its role in graduate training, in collaboration with university partners, in order to strengthen training models, emphasize multidisciplinary training, and develop training paths that will foster greater mobility between academia and industry.

Recommendation #13. That universities and CHUs work more closely with INSERM to design research training tailored for health professionals and take into consideration the impact of new technologies and methodologies on medical education.

Recommendation #14. That Aviesan be strengthened through:

- a. a rationalization of partnering organizations, and most particularly a broadened participation of CNRS (that should not be confined to the sector of Life Sciences) and a stronger input from the Research Directorate of the Ministry of Health;
- b. a consolidation of INSERM’s leadership role in Aviesan for the long term;

c. a formalization of Aviesan's role in providing strategic advice to inform both Health Science and Biomedical research policies at the national level.

Recommendation #15. That INSERM continue to ensure a close alignment of these targeted multidisciplinary efforts with the strategic directions of EU's Horizon 2020, to further strengthen its position in the European health research landscape.

Recommendation #16. That INSERM rationalize its international partnership efforts to optimize the socio-economic impacts of its investments by looking at countries and international partners that best align with its mission and priorities.

Recommendation #17. That INSERM continue to enhance the role played by Aviesan Sud in mobilizing national research institutions in global health research (INSERM, CNRS, IRD, Pasteur Institute, Cirad) to develop a concerted approach in international partnership in Global Health.

IRP Mandate

The International Review Panel was established by INSERM with the goal of soliciting an evaluation of its past performance (2011-2015) as well as expert advice and recommendations in relation to its strategic plan (2016-2020) and accompanying implementation plan (objectives-based contract). Specifically, the IRP was asked to address the following four questions:

1. How does it view INSERM's performance in completing its 2011-2015 objectives-based contract?
2. What are the main recommendations of the committee regarding INSERM 2020 strategic priorities?
3. Does the Committee believe that the strategic plan will allow INSERM to conduct its scientific policy in a multi-partner context?
4. Which of the INSERM strengths are the best assets to succeed in its 2020 strategic plan?

The Panel met between November 3 and 5, 2015 and held hearings with both INSERM senior staff and key relevant stakeholders. The presentations and discussion sessions with senior staff from INSERM included, *inter alia*, a presentation on the life sciences landscape in France; on the outcome of INSERM's 2011-2015 activities; on INSERM's three strategic directions for 2016-2020; and on the Institute's internal operational areas of focus.

The Panel had the opportunity to interview key strategic INSERM partners including Alain Fuchs, Chairman and CEO of the Centre National de la Recherche Scientifique (CNRS); Patrick Lévy, President of the University of Grenoble; Manuel Tunon de Lara, President of the University of Bordeaux and member of Aviesan's Executive Board; Liselotte Hojgaard, Chair of the Danish National Research Foundation and member of INSERM's Governing Council; and Martin Hirsch, Director General, Assistance Publique, Hôpitaux de Paris.

The IRP also had the privilege to share their preliminary findings with France's State Secretary for research and higher education, Mr. Thierry Mandon, and to hear his views on INSERM's performance and vision for the future. This meeting also provided an opportunity for the IRP to hear, first hand, how the Government of France sees INSERM within the broader context of its science, technology and innovation landscape.

Contextual Setting

There are a number of social and political factors that have affected INSERM's evolution over the past five years. Most notably, in 2012, President Francois Hollande put in place measures for reforming France's public expenditure system in the attempt of eliminating the country's budget deficit by 2017. This economic challenge has not spared healthcare or health research spending.

On the healthcare front, France has witnessed a decline in public health spending, which has been growing more slowly than average in the Organization for Economic Co-operation and Development (OECD). This decline may be attributed in part to the Government of France's hospital reforms, which are expected to reduce spending (compared to trend) by over € 3 billion in 2015 and about € 10 billion during 2015–17 (about 0.15 percent of GDP each year). This being said, no OECD country dedicates more public spending on health than France, and only the USA spends more on health when private spending is taken into account.

On the research front, INSERM's government grant funding budget line has flattened since 2013 and witnessed a slight decrease in the past two years. However, this stagnation did not affect the whole of the French research enterprise since over the past 10 years, France's gross domestic expenditure on research and development (GERD) has continued to grow. In 2012, France's GERD ranked sixth in the world, after the United States, China, Japan, Germany and South Korea, with an annual R&D spending of € 46.5 billion, equaling 2.23% of its gross domestic product (GDP).

It would therefore appear that INSERM's lack of growth was due in part to a redistribution of governmental research funds through a series of political and structural reforms. Some of these changes of note include, for example, the creation of l'Agence Nationale de Recherche (ANR) in 2005; the adoption of legislation for higher education that sought to increase the autonomy of universities in 2007; and the "Operation Campus", including the "Programme d'Investissements Avenir", in 2008.

However, these reforms indirectly affected INSERM's support in that while its direct government funding was flat lined (despite an apparent increase due to the addition of monies from ANRS and the National Cancer Plan), its total income increased through the doubling of external resources between 2007 and 2015 from competitive grants and research contracts.

Therefore, while INSERM's budgetary situation has become preoccupying, France's global research enterprise continues to perform at a very high level. According to a 2015 Government of France report on the state of higher education and research, the country ranked sixth in terms of scientific publications in the world in 2013 and fourth in terms of patent filings according to the European patent office. In 2012, 259,100 full-time researchers worked in France (second in the European Union after Germany).

INSERM's Overall Performance 2011-2015

INSERM's research base is strong and the organization has made great strides to solidify its reputation as a world leader in health research over the past five years.

INSERM's bedrock continues to be its support of research excellence, particularly in fundamental biomedical sciences. In point of fact, INSERM remains the leading health research institution in Europe in terms of publications, patent filings and participation in European research programs. According to its 2015 situational report, INSERM is ranked second amongst all health research institutes in the world for number of publications (roughly 10,000) following the USA's National Institutes of Health.

INSERM's growth in the past ten years is undeniable: where the growth in terms of publications in France has been roughly 30%, INSERM's has been at 80%. Furthermore, it should be noted that INSERM's production and visibility have been stronger in the last five years, with a 41% increase in the number of publications.

Not only are INSERM's research publications numerous, they are also of high quality, as attested by the growth of the citation index (from 1.5 to 1.9 since 1999). INSERM's scientific output focuses on highly relevant issues that are well aligned with France's and the world's most challenging health priorities. With the exception of pharmacology and toxicology, all other major health fields tackled by INSERM's researchers have performed significantly well. Of note, in the field of clinical medicine, INSERM publishes three times the world's average rate (19.5% versus 5.9%). INSERM's bibliometric indicators for the field of molecular biology, genetics and immunology have also shown tremendous growth. The IRP is of the view that INSERM's successes have played an important role in France's strong research showing.

INSERM is in the unusual situation of being both a *bona fide* Institute, with most of its governmental budgetary allocation being funneled towards the salary support of academic and non-academic research staff, and an "Agence de moyens", akin to a Granting Council, providing operational support to its research staff on a competitive basis. As for other research institutions, the capacity of INSERM's researchers to attract extramural funding from other, governmental or non-governmental sources can be seen as an important performance indicator.

In this context, the IRP was pleased to note an increase in INSERM's capacity to leverage extramural funding, notably from ANR, from which it raised, in 2015, € 45M out of a total of € 325M in external resources. Likewise, competitive funding from

philanthropic/charity partners represented an envelope of € 39M in 2015. Finally, the IRP acknowledges recent efforts to intensify INSERM's competitiveness in Europe, as illustrated by its performance within Horizon 2020 for example, with 75 projects selected and funded by the European commission.

In 2008, a panel led by Elias Zerhouni, the former head of the US National Institutes of Health, called on the Government of France to take action and address the complexity and fragmentation of the life sciences in France. Following the release of this report, a number of policy shifts have opened the door for the emergence of new models of scientific cooperation and functioning aimed at intensifying linkages not only between research organizations, such as between INSERM, CNRS, and ANR, but also between research organizations, universities, teaching hospitals, stakeholder organizations and healthcare providers within France and internationally.

INSERM played a key leadership role in this restructuration as it pertains to ensuring greater alignment and cohesion between health research organizations and funding bodies, to ensure greater uptake and impact of France's investments in the health field.

Former CEO, Professor André Syrota and current CEO, Professor Yves Lévy, both demonstrated strong leadership and made important commitments to ensure the continued success of INSERM in this new environmental context. Under Syrota's guidance, INSERM took on, in 2008, an increased responsibility for the strategic, scientific and operational coordination of biomedical research, which ultimately led to the creation of Aviesan in 2009. The goal of Aviesan is to ensure the harmonization and synergy of France's complex biomedical research system in addressing national policy and research priorities.

Since its creation in 2009, Aviesan's activities and mandate have continued to flourish, in large part thanks to the leadership and vision of Professor Lévy. Aviesan's role include finding solutions to better assist government decision-making processes; defining an authentic public health policy; creating better links with patient associations; improving on the dissemination of scientific culture; and supporting research excellence in a coordinated fashion.

Among Aviesan's successes, the IRP noted the creation in 2013 of REACTing, a multidisciplinary network allowing for a quick response in targeting emerging infectious diseases. REACTing allows for improved research preparedness by defining research priorities, an improved coordination of research, addressing governance issues to link disciplines, address regulatory issues, and more importantly launch institute-based research calls in a timely and most impactful manner.

France's handling of the Ebola outbreak is another example of Aviesan's success in coordinating the health research enterprise towards a specific goal. Aviesan and its partner organizations moved quickly to undertake research on Ebola in West Africa; train African researchers; and set-up seven laboratories in Guinea. Equally important, Aviesan, under the leadership of INSERM, coordinated therapeutic research projects on Ebola virus disease with the first results of the clinical trial of Favipiravir showing great promise.

The IRP also recognized that INSERM had made great efforts to recruit and offer incentives for young researchers through targeted programs such as Atip/Avenir (a joint program with CNRS). In the past four years alone, approximately 140 laureates were supported through these programs. However, as we will see below, the IRP remains concerned with the lack of flexibility that INSERM has in recruiting new investigators due to the restrictive fiscal context.

On the administrative front, the Zerhouni report noted that INSERM's overhead as a percent of its total budget was relatively high as compared to other institutions of its type internationally. The IRP noted with pleasure that overhead spending by the organization has since considerably decreased. Thus, for the administration of its laboratories alone, the overhead has decreased from 11% to 8% since 2010, despite an increase of activities and number of teams supported.

Overall, the IRP lauds INSERM's success in producing high-level scientific outputs, in playing a leadership role in coordinating health research activities in the country, and in maintaining a high profile of scientific excellence and administrative rigor in a fiscally and environmentally challenging context over the past five years.

This being said, the IRP has also noted some areas for improvement as INSERM embarks upon its planning exercise for 2016-2020. These will be discussed in details below.

INSERM's Strategic Plan 2016-2020

The IRP is fully supportive of the priorities and objectives outlined in INSERM's 2016-2020 draft strategic plan. While ambitious, it is the opinion of the IRP that INSERM's three main priorities are achievable and generally well aligned with the societal needs and overarching goals of France and Europe's broader health research community.

The IRP also believes that the proposed plan builds on INSERM's significant progress made in recent years, will help ensure the organization's leadership in France and in the world for the long-term.

This being said, the IRP also felt that the strategic plan would have gained from being more tightly focused around a smaller number of strategic objectives. Indeed, all fourteen objectives are not of equal importance, and their number tends to dilute the organization's top strategic goals.

Priority 1: More integrated research that matches societal needs and expectations as well as public policy

Priority 1 sets the goal for INSERM to foster collaboration between fundamental, translational, and clinical research to establish a tighter relationship between basic and clinical discoveries and societal needs. Specifically, the plan sets an agenda for INSERM to launch additional cross-cutting programs, to develop new structures to speed up the dissemination of state-of-the-art technologies, to better coordinate research infrastructures, and to increase research impacts on human health.

The IRP fully endorses INSERM's proposal to keep focusing on excellence in basic biomedical research. This research field has been historically the organization's strengths and it is only logical that INSERM would want to build on it. Furthermore, basic research fuels the innovation pipeline and any translational research endeavor can only be successful if it rests on a strong knowledge base.

The IRP approves INSERM's proposals for developing large scale cross-cutting strategic programs and commends it for selecting a restricted number of highly strategic themes, based both on its past achievements and research capacity (e.g. human genomics), and on major societal needs (e.g. ageing). The IRP also agrees with INSERM's proposals to better support research activities by reinforcing the coordination and visibility of its research infrastructures, the development of new initiatives to cope with changes in

research using animal models, and a better access and stronger policies with regards to data management. The IRP was particularly impressed with the role that the organization has been called to play with regards to the establishment of a national data system, which could eventually give French investigators access to a unique set of administrative and health databases.

While INSERM is clearly stepping up its efforts to foster translational research activities and cross-cutting strategic initiatives within the life sciences sector, the IRP missed a convincing work plan to ensure that other scientific disciplines, such as mathematics, physics, bioengineering, materials sciences or the social sciences would be integrated with activities in the health field to contribute to new diagnostic or therapeutic approaches.

New knowledge often arises at interfaces between different disciplines. It is therefore particularly important to ensure that leading experts in mathematics, physics, the various engineering disciplines, or the social sciences be integrated within INSERM's portfolio. It appeared to the Panel that the development of multidisciplinary research Units in partnership with other like-minded institutions, for instance with the CNRS with which INSERM already co-funds mixed Units in life sciences, could offer a pragmatic approach to this aim. In fact, INSERM has already used successfully this type of approach with the Institut national de recherche en informatique et en automatique (INRIA) to integrate bioinformatics, medical informatics, and computational biology into the biomedical field.

Recommendation #1. That INSERM take full advantage of its organizational structure to increase the number and scope of its multidisciplinary UNITS. For this purpose, INSERM should seek out the interest of other research organizations (e.g. CNRS, INRIA, CEA, or universities) in co-developing and co-funding mixed UNITS comprised of biomedical researchers, as well as of researchers from the natural sciences, mathematics, engineering, or the social sciences as it has achieved with the information technology sector.

One of INSERM's challenges is to develop a research agenda that includes not only biomedical and clinical research, but also research concerning health systems, health services and the health of populations. While traditionally strong in biomedical and clinical research fields, INSERM is clearly struggling to foster translation between the two sectors, as well as to further ensure uptake of research results by the health care system.

All health research organizations face difficulties in meeting this objective, but they are exacerbated in the case of INSERM by the fact that a significant proportion of France's clinical research activities are funded through budgetary envelopes provided directly to the Centres Hospitaliers Universitaires (CHU) by the Minister of Health, and therefore outside of INSERM's purview.

This being said, INSERM's balance sheet in the field of clinical trials is perfectly honorable. There are currently 36 clinical investigation centers (CIC), with 374 ongoing trials sponsored by INSERM. Efforts have also been made to ensure that the appropriate infrastructure was provided for clinical trials, namely through an € 18M investment from PIA into the French Clinical Research Infrastructure Network (FCRIN) and its connection with the larger European setting through the European Clinical Research Infrastructure Network (ECRIN). Most of these trials, however, are classical double-blind, randomized-controlled studies, and the IRP recommends that INSERM also invest in the development and application of alternative trial methodologies such as Bayesian approaches, registry trials, etc.

INSERM has also developed an impressive number of patient cohorts, which the IRP believes could be more efficiently used as a rallying point for clinical studies and as a major attractive feature for industrial partnerships. Hopefully, this avenue will be explored as INSERM moves with its partners towards the implementation of the Action Plan for translational and clinical research jointly commissioned by the Minister of Research and the Minister of Health. The IRP is also hopeful that this ongoing harmonization process will allow INSERM, not only to improve integration of clinical trials nationally, but also to increase France's participation in large investigator-driven trials that are coordinated through EU sponsored initiatives.

Recommendation #2. That INSERM, taking advantage of the implementation of the Action Plan for translational and clinical research jointly commissioned by the Minister of Research and the Minister of Health, enhance its capacity for translational and clinical research and embrace a more integrated approach to clinical trials. It also encourages INSERM to take a leadership role in international clinical trial networks, such as the European clinical trial networks, and to foster the development of alternative trial methodologies.

Despite its progress on the clinical front, INSERM has been falling behind Anglo-Saxon countries both in the field of population and public health, and in that of health services and policy research. The organization is to be commended for recognizing this fact and for articulating in its strategic plan a strong vision for developing research that sets out

to understand how the health and welfare of populations and the efficiency of the health care system can be improved through interventions and policies based on the best available data, so as to offer society the best possible health care.

The IRP believes that INSERM is heading in the right direction and strongly supports its intent of developing this sector of research in close partnership with the universities. It does also believe, however, that INSERM should go further through the development of implementation science and knowledge translation activities to ensure better translation of health research results into practice and to ensure the scale up of successful interventions and practice into the health care system.

Recommendation #3. That INSERM work closely with the universities and CHUs to develop curricula for schools of public health to link research, teaching, and practice and to educate and train the next generation of epidemiologists, health economists and health services researchers.

Recommendation #4. That the French government support INSERM in ensuring better transfer and integration of research results into care, through the development and support of implementation science and health services and policy research.

Recommendation #5. That the Ministry of Health recognize the expertise and the role of INSERM in developing research on the health care system integrated to its network of CICs.

Like many other research organizations of its type, INSERM has been struggling with the interrelated issues of commercialization of research results and of partnerships with the industrial sector. Its current strategic plan rightfully sets objectives that support opportunities to intensify partnerships with the private sector through mechanisms, which, to name a few, include: (1) the interactions with *ARIIS - Alliance pour la Recherche et l'Innovation des Industries de Santé*; (2) the creation of the *Epidemiology France* portal; (3) the creation of a committee to coordinate tech transfers of Aviesan members (Covalliance); and (4) a successful participation in the European Innovative Medicines Initiative (IMI).

The IRP acknowledges the important work that INSERM has undertaken in terms of partnering with the private sector through the creation and growth of 15-20 new companies with an average investment of € 2M per company over a five-year period. The IRP also welcomes INSERM's commitment to provide operational support for the

proof of concept principle and development for companies, that will result in strengthened business development.

The IRP believes that if INSERM has made great strides in mobilizing the private sector for a better exploitation of research results, it should also be exploring prospects for developing partnerships with industry more upstream, for instance to launch joint funding opportunities on the model used by IMI in Europe. It could look for new opportunities in untapped markets and better utilize those that already exist such as the European Union's *Juncker Investment Plan for Europe* which consists of a series of measures to unlock public and private investments in the real economy with an envelope of approximately € 315 billion until the end of 2017.

While INSERM has increased its capacity for technology transfer through the creation of INSERM Transfer, France is lagging behind in its exploitation of results and commercialization efforts, particularly when compared to the achievements in other countries (e.g. Israel, UK). The IRP also felt that recent national efforts in this area (such as investments in Sociétés d'accélération des transferts de technologies, (SATT)) have led to a complexification of the technology transfer environment which unduly burdens researchers and dilutes intellectual property rights.

Recommendation #6. That INSERM strengthen its partnerships with the private sector, not only pharmaceutical companies, but also IT companies, telecom companies and the other emerging players in the healthcare sector, as well as take advantage of the opportunities under the European Juncker investment plan, and condition for venture capital investment in new (bio)technologies in Europe.

Recommendation #7. That INSERM continue to work in close partnership with the various other tech transfer entities (regional, universities, hospitals, research institutes) to clarify roles and responsibilities, to improve system nimbleness, decrease administrative burden for researchers, and avoid dilution of Intellectual Property.

The IRP took note of how INSERM effectively reported on its scientific outcomes using bibliometric data as its primary source of reporting. However, while useful for measuring scientific activity, publications and citation measurements tell only part of the story. In particular, they do not inform on the clinical, social, or economic impact of the work carried out by INSERM's researchers.

The IRP felt that INSERM would be better served by developing mechanisms to track

the various complex social and economic benefits associated with its large-scale investments. This would allow decision makers to better understand the return on INSERM's investments. To develop a "toolbox" of social and economic impacts, INSERM could work collaboratively with health authorities and decision makers to ensure that the indicators selected can effectively measure the impact of its activities.

Recommendation #8. That INSERM develop a "toolbox" of performance indicators that go beyond bibliometric data, to assess the health, social and economic impacts of its large cross-cutting initiatives. This would require a specific support from the French authorities, especially the Ministry of Health.

Priority 2: Develop, capitalize on, and organize skills to serve strategic ends

Priority two's overarching objective is to attract the best scientists while improving operational policies that will assist with the recruitment of new investigators and a redefinition of how researchers and Research Units will be evaluated. INSERM will reaffirm its commitment to responsible conduct of research in terms of both experimental practices and the management of human resources. Finally, INSERM will work to sustain the significant links established over the past 20 years with patient support groups as it pertains to training, education and partnership for clinical research.

Most of the objectives outlined in this priority area are fully supported by the IRP. The IRP is in full agreement, for example, with INSERM's efforts towards the promotion of responsible conduct of research and with the reaffirmation of its identity, vocation and values for reinforcing its corporate spirit, two objectives on which it has little to add to management's proposals.

However, the IRP had a number of concerns with issues of research recruitment and training, which it felt were central to INSERM's continued success. The IRP also debated INSERM's proposed changes in the peer review process, which is a critical element for all research governing bodies.

Considerable efforts have been made by the French government to support higher education in France, as witnessed by the continued increase of its higher education expenditures on research and development (HERD) over the past five years. INSERM has demonstrated strong leadership in taking advantage of that support to best serve the interests of its workforce. For example, INSERM has strived to better promote staff mobility and develop pathways between different sectors (i.e., engineers and researchers). This is reflected in the commitment to organize partnerships between

INSERM and engineering schools. Another example of positive support is the Atip-Avenir program that aims to attract excellent young researchers and provide them with the necessary support to build a team dedicated to their own research project. The success of this program is evident by the fact that one hundred percent of the Atip-Avenir laureates secured a permanent research position between the period of 2000 and 2008.

However, the IRP was struck by the serious challenges INSERM is facing with regards to the renewal and rejuvenation of its workforce in the face of changing demographics. INSERM is witnessing a serious decline in the number of recruitments (expected to hit a low of 36 by 2017) that coincides with a lower number of retirements (expected to hit a low of 55 in 2016). An indirect result of this recruitment challenge is a significant increase in the number of non-permanent workers at INSERM, rising from approximately 500 to 2,000 over the past ten years.

INSERM's researchers remain internationally competitive and are at the vanguard of the French health research system. However, this competitive advantage may soon be lost if serious corrective measures are not brought to INSERM's recruitment capacity.

At the heart of the problem is the stagnation of INSERM's direct government funding, which constitutes the sole source of salary support for its personnel (INSERM researchers are members of the public service). Indeed, government funding (when excluding the integration of ANRS and the National Cancer Plan) has actually declined since 2007. It can be argued that the end result of this trend, as witnessed in a recent government audit, is that INSERM now has the lowest ratio of government over total funding.

The IRP strongly felt that if these trends were not reversed, INSERM's capacity to attract the best and the brightest to rejuvenate its work force would be put in serious jeopardy. Not only are governmental budgetary increases necessary, but these increases should be planned over several years to give INSERM the opportunity to develop a long term recruitment policy.

As a short term measure, the proposal of INSERM to work closely with universities to jointly support the recruitment of promising young investigators who would otherwise be lost to the system appealed to the IRP. Indeed, in contrast to INSERM, many research-intensive universities have been able to access new positions thanks to the Programme d'Investissements Avenir referred to above. It would be a shame for these universities not to take advantage of INSERM's highly competitive process to recruit on their campuses some of the outstanding talent bred by INSERM. In the long run, this

joint recruitment approach would increase the international competitiveness of universities in research and promote a better integration of INSERM researchers within its academic ranks, rather than breed two unequal parallel streams.

Recommendation #9. That the French government be made aware of the serious consequences of INSERM's flat-lined budget on the rejuvenation of INSERM's workforce, and of the need to increase the budget of the organization to ensure the competitiveness of the French health and biomedical research enterprise in the long term.

Recommendation #10. That INSERM work with its university partners to identify alternative recruitment paths that would ensure in the short term a steady intake of outstanding young investigators in health research.

INSERM is to be commended for bringing changes to its assessment bodies and namely for decreasing the number of its adjudication panels in response to the redistribution of its research themes. This being said, the Panel felt that the structure of INSERM's review panels, while appropriate for maintaining excellence in today's world, is poorly adapted to recruit as a function of the needs of tomorrow, i.e. in a way that is more strategic, ensures better gender balance, and is better geared to face future multidisciplinary environments.

Also, the IRP felt that the panels were too inbred, and that they should include international members not only to help improve INSERM's recruitment practices in light of international evaluation standards, but also to help French researchers adapt to international norms and improve their competitiveness in international funding calls, particularly within the EU.

Finally, the IRP would like to encourage INSERM to systematically include in the performance evaluation of its Research Units, not only partners from the universities and the CHUs, but also patient representatives.

INSERM has been a precursor in engaging patients through the creation of patient support groups and intends to keep on maintaining "the relationship it has established with the patient advocate actors". However, it is unclear how the organization plans to include patients - or representatives from the public - into its strategic planning and funding adjudication structures. The IRP felt that INSERM's patient engagement strategy should be updated, particularly in light of recent data showing that engagement of patients throughout the strategic planning process actually improves research quality in addition to furthering its relevance towards societal needs.

Recommendation #11. That INSERM conduct an environmental scan to determine research needs and gaps, develop strategic recruitment and gender representation policies, including for upper management positions, and rethink the structure of its competition process and composition of its review panels to allow for the recruitment of a workforce adapted to tomorrow's national and international scientific and social imperatives.

The IRP was struck by the fact that INSERM's strategic plan paid little formal attention to issues of training, particularly at the graduate level. Equally striking was the fact that academic informants (from universities or CHUs) did not appear to appreciate at its full value INSERM's educational role.

Yet, the IRP felt strongly that graduate and post-graduate training should be at the heart of INSERM's mission and that the organization should take pride in its educational achievements. Indeed, through its supervision of Masters, Doctorate and post-doctorate students in some of France's best laboratories, INSERM is in a position to profoundly shape the country's future health research profile in a way that responds to societal needs.

This should be better recognized – and taken advantage of – by universities who ought to be working with INSERM to identify gaps and opportunities, to trace novel interdisciplinary training paths, and to ensure France's capacity to respond to future research needs, not only in biomedical and clinical fields, but also in health economics, bioinformatics, and health administration.

INSERM should also be thinking of new ways to bridge the gap between academia and industry, by creating training programs that foster disruptive innovation i.e. innovations that will eventually disrupt existing markets to create new value networks, leaders and alliances.

Recommendation #12. That INSERM underscore its role in graduate training, in collaboration with university partners, in order to strengthen training models, emphasize multidisciplinary training, and develop training paths that will foster greater mobility between academia and industry.

The IRP recognized INSERM's efforts over the last decade to promote research training of medical students, namely through its partnership with the Fondation Bettencourt Schueller. The IRP was therefore highly supportive of INSERM's proposal to further develop this collaboration through new programs which, *inter alia*, will allow physicians in training to spend more time in research. However, the IRP also felt that

INSERM should be working more closely with the Faculties of Medicine and affiliated CHUs to enhance medical students' exposure to new scientific findings and emerging technologies, particularly as it pertains to the use of e-data. Clearly, medical practice is undergoing major shifts with the introduction of more refined imaging techniques, genetic- and proteomic- (and soon microbiomic-) based precision medicine, and the expansion of e-records and big data exploitation potential. A partnership between INSERM and the Faculties of Medicine/CHUs along those lines could go a long way in furthering evidence-based practice in the health care system.

Recommendation #13. That universities and CHUs work more closely with INSERM to design research training tailored for health professionals and take into consideration the impact of new technologies and methodologies on medical education.

Priority 3: Optimized academic and private-sector partnerships, INSERM's leadership role reinforced at European and international levels

Priority 3 establishes the goal for INSERM to consolidate its role as a key protagonist in biomedical research and create a knock-on energizing effect promoting the search for synergies with other organizations affiliated with the Aviesan Alliance and other alliances. This will include reinforcing links between research units and university hospital settings; consolidating its role of initiator and decision-maker in the matter of research and health-care policy with its partners through its activities within Aviesan; and, preserving a place as a major actor in European and international life sciences and health care research.

The IRP believes that the creation of Aviesan was a major policy shift that enabled France's research enterprise to become synergistically aligned both internally and abroad with other research and healthcare organizations. Aviesan, as was explained to the IRP, is an informal, non-legal entity that aims at mobilizing the health research community on large-scale priorities or crises in a nimble and flexible way. Given the growing focus on multidisciplinary research and the need to engage multiple ministries and agencies on health priorities, Aviesan is providing a unique venue for providing coordinated, and at times integrated, global responses.

Thanks to Aviesan, research activities within its nine partner organizations are now much better streamlined. For example, ANR's programming is now poised to better address the strategic priorities established by Aviesan's various ITMOS. Similarly, Aviesan has fostered increased cooperation at the European and international level,

largely due to the creation of concrete working groups that include Europe Aviesan and Aviesan Sud, which not only focus on supporting research coordination, but also innovation and industrial partnerships.

These successes have increased Aviesan's credibility to the point that the French Government is using increasingly frequently the regrouping as an operator for the implementation of some of its national plans or emergency responses. For instance, Aviesan played a critical role in coordinating the French response to the Ebola outbreak. Through the leadership of INSERM and the Institut Pasteur, Aviesan and its members mobilized quickly in the early days of the epidemic in March 2014 and set up a series of coordinated activities which included developing diagnostic and therapeutic approaches, supporting the training of African researchers, helping launch seven Ebola laboratories in Guinea, and working directly with the World Health Organization (WHO) in coordinating global research activities.

INSERM has invested significantly in Aviesan, and in so doing, has taken the risk of trading some of its independence, particularly as pertains to strategic planning, for greater impact. The IRP is of the view that to keep on delegating its authority to Aviesan on an increasingly large number of issues, INSERM will need clarification regarding its leadership role within the Aviesan structure, and to explore best practices to better formalize Aviesan's model for the long term.

The IRP also believes that Aviesan would benefit from a review of its membership, to ensure that the right partners are at the table. For instance, while not denying the importance of having a representation of the Life Sciences Sector of the Centre National de la Recherche Scientifique (CNRS), the IRP would like CNRS's representation to be broader, to allow for more extensive inter-sectoral interactions. The IRP would recommend that INSERM find ways of obtaining more meaningful input from the Research Directorate of the Ministry of Health, to ensure better translational mechanisms towards clinical practice and, more broadly, the health care system.

Recommendation #14. That Aviesan be strengthened through:

- a. a rationalization of partnering organizations, and most particularly a broadened participation of CNRS (that should not be confined to the sector of Life Sciences) and a stronger input from the Research Directorate of the Ministry of Health;**
- b. a consolidation of INSERM's leadership role in Aviesan for the long term;**

c. a formalization of Aviesan's role in providing strategic advice to inform both Health Science and Biomedical research policies at the national level.

The IRP commends INSERM for its long term commitment to international partnerships, and to its increasingly successful integration into Europe's collaborative networks. It is clear that INSERM has international collaboration imbedded within its vision and mission, as reflected in the fact that more than half of its publications are co-authored with one or more foreign institutions and with the fact that it lists more than 6,500 collaborations with international teams.

The IRP also saw very favourably INSERM's efforts to maintain its position within the EU Commission under Horizon 2020, as it had under FP7. Already, since Horizon 2020's launch in 2014, 75 projects involving INSERM have been selected and funded by the European Commission, with € 66M going directly to INSERM investigators and more than € 115M managed by INSERM. The IRP was also impressed with INSERM's involvement in European research strategies, through the development of work programs and of position papers on topics such as personal data protection or the use of animals in research.

INSERM's commitment to global health is also evident through its dedicated focus on issues such as chronic diseases in low-and-middle income countries, and health services delivery in the developing world. INSERM has established a clear vision and agenda that reflects the specific needs of countries most in need, taking into account the changing burden of disease and the evolution of health systems.

Despite INSERM's very engaged and proactive accent on international activities, it was not evident to the IRP that these activities were focused on maximizing strategic alignment with countries and organizations that best complement INSERM's priorities and mission. International partnerships only make sense when struck to meet certain needs, fulfill critical gaps, or achieve specific objectives. For this reason, the IRP felt that the strategic objectives and impact of the organization's international linkages needed clarification and strengthening.

Recommendation #15. That INSERM continue to ensure a close alignment of these targeted multidisciplinary efforts with the strategic directions of EU's Horizon 2020, to further strengthen its position in the European health research landscape.

Recommendation #16. That INSERM rationalize its international partnership efforts to optimize the socio-economic impacts of its investments by looking at

countries and international partners that best align with its mission and priorities.

Recommendation #17. That INSERM continue to enhance the role played by Aviesan Sud in mobilizing national research institutions in global health research (INSERM, CNRS, IRD, Pasteur Institute, Cirad) to develop a concerted approach in international partnership in Global Health.

Conclusion

IRP members were unanimously impressed by INSERM's continued strong showing on the international health research scene, despite the considerable fiscal constraints that it has had to face in recent years. The quality of INSERM's researchers and of their scientific output clearly places INSERM among the top research bodies in the biomedical world today and a fundamental institution in the French science enterprise.

This being said, INSERM faces considerable challenges with regards to the aging demographics of its work force and its decreasing capacity to recruit new talent. It also lags behind some of its OECD competitors in its capacity to translate research results into socioeconomic benefits. In particular, it currently lacks the solid health services and implementation science capacity that is needed to exert transformative effects on clinical practice and France's health care system.

Nonetheless, the IRP was impressed by the clarity of vision and the originality of approaches that INSERM brings to tackling these fundamental issues. There is no question the INSERM's senior management is fully aware of the trends, challenges and opportunities facing the health research world today.

The IRP is fully aware that many of its recommendations cannot be implemented by INSERM alone, but will require the close collaboration of other actors on the political and academic scenes, namely the Ministries of Research and Health to which INSERM reports, but also other research organizations (CNRS, CEA, ANR, INRIA), the universities and the CHUs. The French health research landscape is still fragmented and, despite the considerable structural reforms achieved over the past 10 years, historical fiefdoms are still strong.

Yet, the IRP was struck by the improved collaboration between national research bodies, for instance through informal alliances such as Aviesan, due in part to the increasing influence of the European research framework. The Panel strongly feels that through the broadening of this dialogue to the research-intensive universities and the CHUs, INSERM could contribute to markedly strengthen France's academic competitiveness on the international scene. It is indeed critical that French "Ivy League" universities do not develop in competition, but in complementarity with the country's research organizations.

The IRP can only conclude by wishing that the French Government keep on recognizing, through its financial support, the critical socio-economic impact of

INSERM as well as its contribution to the international repute of the French research system.