COMMENT

ILLUSTRATION BY CHRIS RYAN/*NATURE*

Where is the brain in the Human Brain Project?

Europe's €1-billion science and technology project needs to clarify its goals and establish transparent governance, say **Yves Frégnac** and **Gilles Laurent**.

Launched in October 2013, the Human Brain Project (HBP) was sold by charismatic neurobiologist Henry Markram as a bold new path towards understanding the brain, treating neurological diseases and building information technology. It is one of two 'flagship' proposals funded by the European Commission's Future and Emerging Technologies programme (see go.nature.com/icotmi). Selected after a multiyear competition, the project seemed like an exciting opportunity to bring together neuroscience and IT to generate practical applications for health and medicine (see go.nature.com/2eocv8).

Contrary to public assumptions that the HBP would generate knowledge about how the brain works, the project is turning into an expensive database-management project with a hunt for new computing architectures. In recent months, the HBP executive board revealed plans to drastically reduce its experimental and cognitive neuroscience arm, provoking wrath in the European neuroscience community.

The crisis culminated with an open letter from neuroscientists (including one of us, G.L.) to the European Commission on 7 July 2014 (see www.neurofuture.eu), which has now gathered more than 750 signatures. Many signatories are scientists in experimental and theoretical fields, and the list includes former HBP participants. The letter incorporates a pledge of non-participation in a planned call for 'partnering projects' that must raise about half of the HBP's total funding. This pledge could seriously lower the quality of the project's final output and leave the planned databases empty.

With the initial funding, or 'ramp-up', phase now in full swing, the European Commission is currently evaluating the HBP directors' plan for the larger second part of the project. This offers an opportunity to introduce reforms and reconciliation. ▶

Here, we offer our analysis of how the HBP project strayed off course and how it might be steered back.

THE ROOTS OF CRISIS

The HBP blends two styles. One comes from a history of successful interdisciplinary collaborations in the European Union in brain- and neuron-inspired computation[1]. The second originates from a computational research programme, the Blue Brain Project[2], initiated by Markram in 2005 (see 'Brain activity'). This collaboration between the Swiss Federal Institute of Technology in Lausanne (EPFL) and the IBM computing corporation aimed to build large-scale 'bottom up' numerical simulations of a rat's neocortical column, a set of about 100,000 neurons considered to be a functional unit within the brain.

The crisis results mainly from ambiguities concerning the place of neuroscience in the HBP. From the beginning, neuroscientists pointed out that large-scale simulations make little sense unless constrained by data, and used to test precise hypotheses. In fact, we lack, among other resources, a detailed 'connectome', a map of connections between neurons within and across brain areas[3] that could guide simulations. There is no unified format for building functional databases or for annotating data sets that encompass data collected under varying conditions. Most importantly, there are no formulated biological hypotheses for these simulations to test[4].

Many scientists also feared that the HBP would siphon funds from fundamental research. The European Commission's investment in a large 'brain project' would influence what other research areas it chooses to fund. Nonetheless, such an opportunity seemed unlikely to arise again, and neuroscientists (ourselves included) joined up, even if they did not agree with all aspects of the HBP proposal or with certain promises used to sell it. We put our faith in open and interdisciplinary collaboration, trusting that intellectual and operational details would take shape gradually and collectively.

Preparation of the HBP flagship document (in a pre-project phase funded by the European Commission) lasted several months and took place at the EPFL. Selection criteria for flagship proposals included scientific vision, societal impact and the size of the scientific community involved. We trust that the selection of the HBP by the commission rested on its focus on the relationship between brain structure and function, and on the project's interdisciplinary approach. More than 240 labs were initially pegged to participate. Official descriptions expressed hopes that the project would "gain fundamental insights into what it means to be human, develop new treatments for brain diseases and build revolutionary new information and communications technologies". The exploration of the principles of neural computation through animal studies was considered integral.

Flagship initiatives differ from other European Commission projects because unusually large administrative, scientific and strategic leadership responsibilities fall onto few principal investigators. As the HBP prepares to move into its second phase, the project's executive board has revised its objectives. As well as decreasing the emphasis on experimental neuroscience, it has eliminated non-human-primate research, and restricted the focus of experimentation mainly to human imaging and 'atlases'. These are typically static catalogues of gene expression, neuronal couplings, cell types and other measurements across brain structures, but without experiments to assess function. The board also announced plans to dissolve the cognitive-neuroscience sub-programme, leading to the resignation of that project's 18 principal investigators, including its director.

Neuroscience in the HBP is now limited mainly to simulations and to building a massive infrastructure to process mostly existing data. The revised plan advances a concept in which *in silico* experimentation becomes a "foundational methodology for understanding the brain"[5]. Numerical simulations and 'big data'[6] are essential in modern science, but they do not alone yield understanding. Building a massive database to feed simulations without corrective loops between hypotheses and experimental tests seems, at best, a waste of time and money. The HBP's goals now look like a costly expansion of the Blue Brain Project, without any further evidence that it can produce fundamental insights.

BRAIN WRECK

Neuroscientists who initially supported the HBP feel that they have been taken advantage of. The organizers attracted well-funded neuroscience labs for credibility and, ultimately, for their data. Now those labs are being edged out.

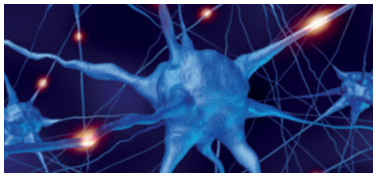
The changes to the HBP are not only disingenuous, they are self-defeating. About €430 million (US$570 million) of the European Commission funding goes to the HBP's 'core team'. The remainder of the €1-billion budget depends mostly on scientists throughout Europe raising partnering funds from sources such as regional governments, and then being selected by the HBP management on the HBP's terms. Why would people want to join the project under such conditions?

Since problems surfaced, the HBP executive board of directors and administrators at the EPFL, the coordinating institution, have been deflecting rather than addressing criticism (see go.nature.com/nenowj). Supporters argue that the Human Genome Project was also initially criticized by the biological community and eventually proved its detractors wrong. But the genome project was different: its goals were well defined, and the associated challenges, mostly technological, were well posed. These descriptions do not apply to the HBP.

In July, HBP co-executive director Richard Frackowiak wrote[7] that the project is "a CERN

BRAIN ACTIVITY

Timeline of the Human Brain Project.



SHUTTERSTOCK

2005 The European Union starts funding research merging computing architecture and neuroscience.

MAY 2005 Neurobiologist Henry Markram launches the Blue Brain Project, led by IBM and the Swiss Federal Institute of Technology in Lausanne (EPFL).

NOVEMBER 2008 US defence department launches programme on brain-inspired electronic systems.

JULY 2009 Markram publicizes his vision to build the brain in a supercomputer.

JULY 2010 The European Commission calls for proposals for 10-year, €1-billion 'flagship' interdisciplinary technology projects.

APRIL 2012 European neuroscientists sign on to a proposal for a brain project.

JANUARY 2013 The Human Brain Project (HBP) is selected as a winning flagship proposal, along with a project on graphene.

APRIL 2013 US President Barack Obama announces the BRAIN initiative.

OCTOBER 2013 The HBP launches, coordinated by Markram at the EPFL.

APRIL 2014 The HBP governance announces plans for the project's larger second phase, radically reducing the role of experimental neuroscience.

JULY 2014 European researchers write an open letter (now with about 750 signatories) to the European Commission, decrying shifting goals and lack of transparent leadership.

for the brain", equating the HBP with Europe's particle-physics laboratory near Geneva, Switzerland. But CERN is a cooperative structure built around large, shared instruments, designed to collect experimental data and test carefully constructed hypotheses. This, again, does not apply to the HBP.

Public grants of even a few tens of thousands of euros are typically subject to rigid oversight. Science projects of the HBP's magnitude and complexity are typically handled by agencies (such as the European Space Agency or CERN) with existing infrastructure and managerial experience. Why, then, did the commission grant nearly all of the design, management and decision power of a huge European public project to one academic institution and three principal investigators, two of whom are faculty members at the institution? The other flagship project, which focuses on graphene and has generated little controversy, opted for a distributed and transparent governance that includes all sub-project leaders on an executive board.

"We cannot feel assured that the HBP is managed cost-effectively."

The tight schedule imposed to prepare the second phase of the HBP, compared with the several years taken to develop the proposal, has also exacerbated problems. How can a single group coordinate tens or hundreds of labs and sub-projects in such a short time, without tried-and-tested structures that facilitate the task and maintain trust?

Given the sizeable fraction of the HBP's core budget devoted to administration, we cannot feel assured that the HBP is managed cost-effectively or adapted for research operations across Europe. We are concerned that not all internal partners have read or had access to the 180-page draft of the next partnership agreement, and few seem aware of plans for a private, Swiss-operated foundation charged with exploiting commercial opportunities that emerge from the HBP.

WHERE DO WE GO FROM HERE?

We see three possible routes forward. All require transparent discussion of the project's goals and profound changes in governance and oversight.

One option would be to explicitly eliminate neuroscience from the HBP. This solution would annihilate the enormous efforts of many HBP partners (neuroscientists and clinicians), and redirect this flagship towards purely technological objectives. Finding a new name would be a small price to pay.

A second option would be to split the technology and neuroscience sections of the HBP. This would group all IT components of the HBP together and create of a new, independent entity to fund collaborative neuroscience to decipher brain function.

The third option is to attempt to put the HBP back on track. This road is probably the most challenging. It would require re-establishing the HBP's experimental-neuroscience component with real funding avenues for biological and hybrid projects combining theory and experiment, under funding, review, award and administration conditions acceptable to the science community. Radical action would be required to revive trust and enthusiasm in an exceptional collective effort to address an enormously exciting challenge. Reunification might even be possible with major theoretical neuroscience institutes — the Gatsby Computational Neuroscience Unit in London, the Bernstein Centers in Germany, the École Normale Supérieure in Paris and the Edmond & Lily Safra Center for Brain Sciences in Jerusalem — at present largely hostile to the HBP. A Europe-wide committee of scientists should be established to organize neuroscience funding in Europe and work with funders to institute borderless, collaborative, curiosity-driven, interdisciplinary, peer-reviewed science. Issues concerning the partnership programme need to be addressed: notably the management and exploitation of data obtained through other funding sources.

The irony of this episode is that the HBP, by giving the impression of exceptional investment from the European Union in brain research, spurred the creation of competing, well-funded neuroscience initiatives in the United States (which focuses on techniques development[8]) and in China (which focuses on brain disease[9]). Now it is not at all clear that Europe has invested in brain science through the HBP. ■

Yves Frégnac *is a CNRS research director and head of the CNRS Unit of Neuroscience, Information and Complexity in Gif-sur-Yvette, France.* **Gilles Laurent** *is director at the Max Planck Institute for Brain Research in Frankfurt, Germany.*
e-mails: fregnac@unic.cnrs-gif.fr; gilles.laurent@brain.mpg.de

1. European Commission. *Future & Emerging Technologies (FET): FP7 Projects Compendium 2007–2013* (European Union, 2013).
2. Markram, H. *Nature Rev. Neurosci.* **7,** 153–160 (2006).
3. Seung, S. *Connectome: How The Brain's Wiring Makes Us Who We Are* (Houghton Mifflin Harcourt, 2012).
4. Frégnac, Y. *Cell* **155,** 265–266 (2013).
5. Markram, H. *et al. Procedia Comp. Sci.* **7,** 39–42 (2011).
6. Kandel, E. R., Markram, H., Matthews, P. M., Yuste, R. & Koch, C. *Nature Rev. Neurosci.* **14,** 659–664 (2013).
7. Frackowiak, R. 'Defending the grand vision of the Human Brain Project' *New Scientist* (16 July 2014).
8. Brain Research through Advancing Innovative Neurotechnologies (BRAIN) working group. *BRAIN 2025: A Scientific Vision* (National Institutes of Health, 2014).
9. Poo, M.-M. *Natl Sci. Rev.* **1,** 12–14 (2014).

For a list of further reading on this topic, see go.nature.com/7jg7zc.

Supplementary Information

(Where is the Brain in the Human Brain Project? Frégnac and Laurent)

A few keywords and definitions

This section is to help—to the extent that we can—readers navigate around the complex EC administrative literature associated with Flagships. The curious reader is encouraged to check (and occasionally decrypt) the suggested official websites.

Horizon 2020: EU research and innovation program providing some €80 billion over the years 2014-2020 (7 years). According to the Horizon 2020 website, "Horizon 2020 is the financial instrument implementing the Innovation Union, a Europe 2020 flagship initiative aimed at securing Europe's global competitiveness."
More information at: http://ec.europa.eu/programmes/horizon2020/

Future Emerging Technologies (FET): FET is the EU's Information and Communication Technologies (ICT) Incubator for long-term research in this area: it supports collaborative research to extend Europe's capacity for advanced innovation in the area of information and communication technologies. Its mission is to foster scientific collaborations across the members of the EU, and across scientific communities and disciplines, on new, high-risk ideas, to accelerate development of the most promising emerging areas of science and technology. FET has three main programs: FET-Open; FET-Proactive; *FET-Flagships*.
More information at: http://cordis.europa.eu/fp7/ict/programme/fet_en.html

FET-Flagships: FET Flagships are "ambitious, large-scale, long-term, science-driven research initiatives tackling grand challenges in Science and Technology that aim to achieve a visionary goal". They correspond to *a joint effort of the EU and national programs to provide a large financial support* (ca. 100 M€/year over 10 years). According to the FET Flagship documents, "the overarching nature and magnitude of these initiatives implies that they can only be realized through a federated effort of the different EC services, along with Member States, regional and other funding agencies, and where appropriate, global partners and industry". This point is key to understand the hybrid nature of the funding scheme for HBP: about one half of the budget originates from the EU; the other must originate from investigators who wish to join HBP, via individual applications to their local funding agencies, plus a vetting by the HBP core team, according to criteria defined by them, to fit the Flagship's overarching goal.
More information at: http://cordis.europa.eu/fp7/ict/programme/fet/flagship/home_en.html

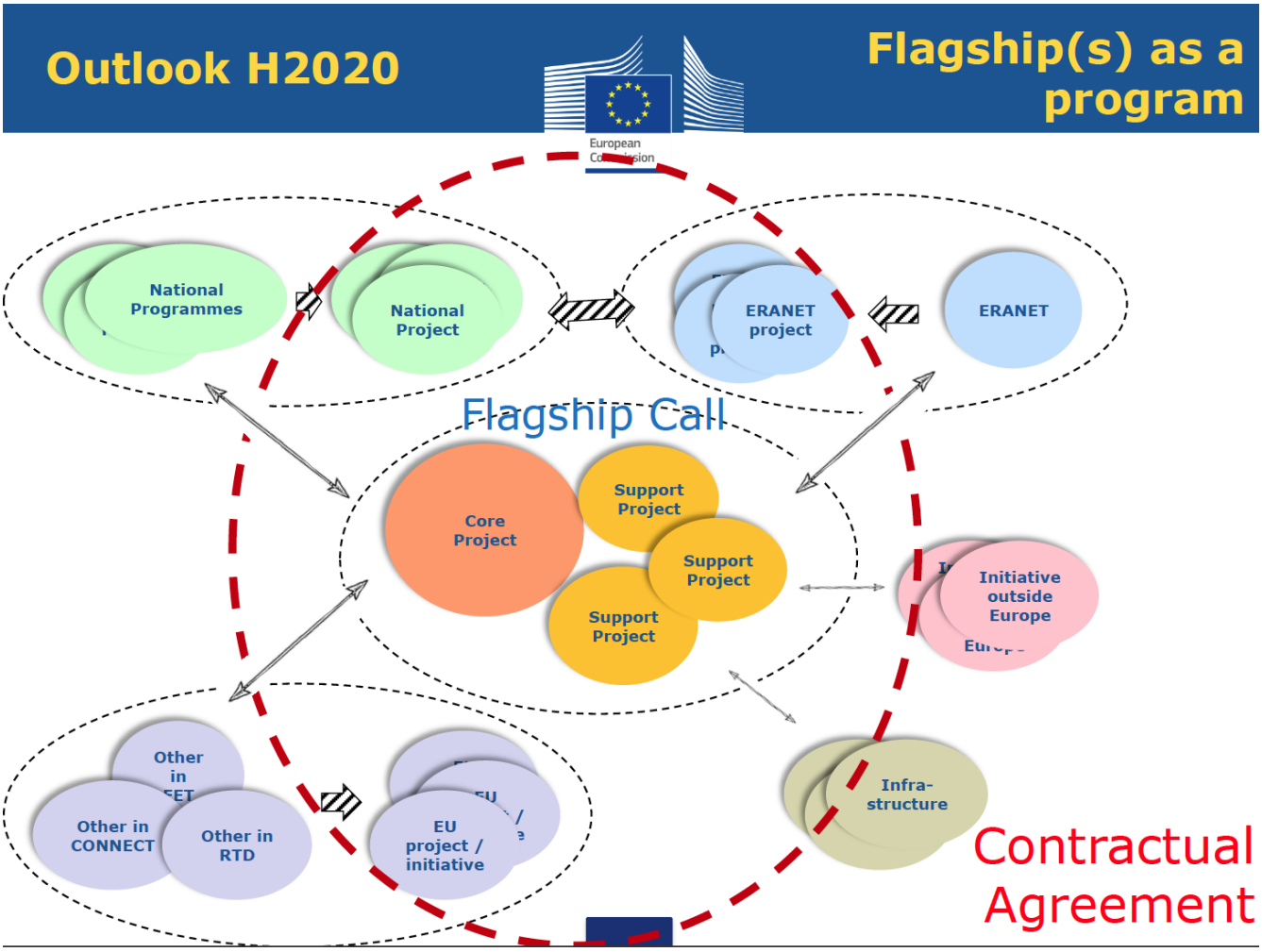
Framework partnership agreement (FPA): The objective of the FPA is to establish, for each one of the two funded FET-Flagships, a "*stable and structured*" partnership between the EC and the institutions/organizations who are committed to "*establishing, maintaining and implementing the strategic research roadmap of the Flagship*". The Framework Partnership Agreement has no budget. It has an overall "roadmap" and sets out most of the contractual conditions. S*pecific grant agreements* (SGA) are also established to execute parts of the roadmap. An SGA exists only within the context of an FPA. *Core projects* (implemented as successive SGAs) will take each FET-Flagship along the 10-year strategic roadmap. *Complementary projects* are foreseen to complement the core project, thus opening it up to the broader scientific community.

ERA-NET schemes: Long-term schemes "to step up the cooperation and coordination of research activities carried out at national or regional level in EU Member and Associated States through the networking of research activities conducted at national or regional level, and the mutual opening of national and regional research programs". These schemes are some of the tools set up to help co-finance European Partnership

Programs.
More information at: http://cordis.europa.eu/coordination/era-net.htm

FLAG-ERA scheme: FLAG-ERA is an ERA-NET scheme set up in Nov 2013, specifically to support the construction of the two FET Flagships Graphene and HBP (and also to help support the four runner-ups of the initial Flagship competition). It involves some 31 national and regional funding organizations from 24 countries.
More information at: http://www.flagera.eu

Diagram illustrating the funding structure of a FET-Flagship



This diagram illustrates the actual complexity of the funding structure of a Flagship project. While a Flagship's overall budget is on the order of €1B, only part of this budget is guaranteed and provided by the EC (core in figure). The remainder must be raised by individual scientists (via "partnering programs") from a variety of local (national, regional etc) sources and be accepted by the executive/decisional structure of the Flagship.

Source: Public presentation by Wolfgang Boch, FET-Flagship information day, Bratislava, SK, 23 May 2013 : "*FET Flagship Initiatives: Concept, Call and Evaluation results* "

Additional Information concerning Funding and HBP:

Over the past ten years, the FET program has financed a number of interdisciplinary initiatives at the interface of neuroscience and information technology (IT) (e.g., Life-like Perception Systems; Bio-inspired intelligent information systems; Bio-ICT Convergence), each funding mid-sized "integrated projects" with up to €12M over 4 years. Examples can be found at:
http://daisy.ini.unizh.ch/24.html,
http://facets.kip.uni-heidelberg.de/
http://brainscales.kip.uni-heidelberg.de/
As indicated in our analysis, these biology-inspired and interdisciplinary projects are historical antecedents (together with the Blue-Brain-Project) to the HBP-Flagship. These projects, however, provided balanced funding to their computer science, physics/microelectronics and neuroscience components.

The funding structure of HBP follows a two-step process. Funding for HBP started less than a year ago with a short "ramp-up" phase (to last 2.5 years), organized as one of the above FET projects, but with a larger budget. The bulk of the funding, however, will come during phase 2. The official statement of the EC is: "*The overall EC contribution to each FET Flagship initiative in Horizon 2020 is expected to be around EUR 50M/year, subject to several factors such as budget availability, quality of proposals and performance of the action*". According to new rules ("Horizon 2020" see above), funding will be split in two shares. One half (430 M€) will originate entirely in the EC (via FET), and will fund what is called the "core team", limited coordination actions (<€5M) and a limited set of trans-national open calls (FLAG-ERA, €3M). The other half is at present entirely hypothetical, and depends on so-called "partnering funds", to be raised by investigators in and across the different nations of the European Community via independent national and regional open calls and private funds. The successful applicants to these calls who wish to join HBP will then undergo selection by HBP—through a process yet to be defined, but presumably requiring promise of data transfer—and given an HBP label. Thus, what appears to most observers as a €1B initiative from the EC will in fact rely on "partnering" investigators and institutions bringing about half of the money.

Extended reading list

1 – FET, Flagship and EC

(1.1). Research EU Focus on "Future Emerging Technologies: Science beyond fiction", N°9, May 2011, ISNN : 1831-1901.

(1.2). Sestini, F. and van der Pyl, T. (2005). Future Emerging Technologies: a vision for tomorrow of EU IST research. ACM SIGCOMM Computer Communication Review. Volume 35, N°2, pp 87-91.

(1.3). Future and Emerging Technologies (FET): FP7 Projects Compendium 2007-2013. Edited by the European Commission. 100 pages.

(1.4). The FET flagship model, key policy and implementation issues: Conclusions from an external consultation workshop, 29 April 2014, Brussels, Digital Agenda for Europe, 75 pages.

(1.5) http://www.7rp.sk/fileadmin/user_upload/infodni/Boch_FET_Flagship_Initiatives.pdf

2. – Selected FET projects at the interface of Neuroscience, Computer Science and Physics

FP6 : Bio-inspired
- http://daisy.ini.unizh.ch/24.html,
- http://facets.kip.uni-heidelberg.de/

FP7 : Bio-ICT convergence
- http://brainscales.kip.uni-heidelberg.de/).

3 – Flagship Pre-projects linked to Neuroscience

(3.1). The Human Brain Project. (April 2012). A report to the European Commission. HBP-PS Consortium, 107 pages.

(3.2). The Robot companions for citizens manifesto: More than future. (2012). FP7-ICT-2011-FET-F 284951, 13 Pages.

4 – The "Blue Brain Project"

(4.1) Markram, H. (2006). The Blue Brain Project. *Nature Reviews Neuroscience* (Perspectives), 7: 153-160.

(4.2) Markram, H. (2009). A Brain in a supercomputer. TED ideas worth spreading.
http://www.ted.com/talks/henry_markram_supercomputing_the_brain_s_secrets

(4.3). Evaluation of the Blue Brain Project and Human Brain Project. (2011). EPF internal Report. Committee chaired by G. Shepherd. 19 pages.
http://www.ethrat.ch/sites/default/files/BBP_HBP_Evaluation2011.pdf

5 - Scientific debate on Big Data and HPC in Neuroscience

(5.1) Seung, S. (2013). Connectome: how the brain's wiring makes us who we are. 359 pages. Houghton Mifflin Harcourt. A dialog between Henry Markram and Sebastian Seung can be watched in the movie "Blue Brain" directed by Noah Huton (2009) (http://bluebrainfilm.com/bb/).

(5.2) Sporns O (2013). Commentary – Focus on brain mapping: Making sense of brain network data. *Nature Methods*. Volume 10, 6: 491-493.

(5.3) Eliasmith, C. and Trujillo, O. (2014). The use and abuse of large-scale brain models. *Current Opinion in Neurobiology* 25: 1-6.

(5.4) Kandel, ER, Markram, H, Matthews PM, Yuste R and Koch C (2013). Neuroscience thinks big (and collaboratively). *Nature Reviews Neuroscience* (Perspectives), 14: 659-664.

(5.5) Einevoll, G. Generosity in Brain Research (in Norwegian). Reply letter in Morgenbladet Journal, July 17, 2014.

(5.6). Markram, H., Meier, K et al. (2011). Introducing the Human Brain Project. *Procedia Computer Science*. Vol.7: 39-42. See also Markram, H (2014). Building electronic brains for in silico Neuroscience. AAAS 2014 Annual Meeting. 13-17 February, Chicago. Meeting global challenges: discovery and innovation.

(5.7). Monard, D., Summary of the conference "perspectives of high power computing in Neurosciences. Conference series "the Big Six-spotlight on the EU-Flagship initiative. In: 2012 Report of the Swiss Academy of Sciences. www.akademien-schweiz.ch/fr/flagshipseries

(5.8). In the Press:
Dessibourg, O. (2012). Le cerveau virtuel qui échauffe les esprits. Le Temps. Rubrique Neurosciences du 01 Février 2012.
Waldrop, M. (2012). Brain in a Box. *Nature*, vol. 482, 456-458

(5.9) Frégnac Y (2013). Big science needs new concepts. *Cell*. In "Voices": Brain initiative and Human Brain Project: Hopes and Reservations. Volume 155, Issue 2, 265-266 DOI: 10.1016/j.cell.2013.09.037

6 – Open letter to the European Community and HBP replies

(6.1) Open letter: Open message to the European Commission concerning the Human Brain Project. July 7, 2014. Collective letter coordinated by Zach Mainen and Alexandre Pouget.
http://www.neurofuture.eu/

(6.2) Frackowiak, R (2014). Defending the grand vision of the Human Brain Project, 16 July 2014. New Scientist Magazine, issue 2978.

(6.3). Aebischer, P. (2014). Interview in http://www.rts.ch/info/sciences-tech/6021226-patrick-aebischer-repond-aux-critiques-sur-le-human-brain-project.html.

(6.3). Official reply of HBP: the vital role of neuroscience in the Human Brain Project. 4 pages. https://www.humanbrainproject.eu/documents/10180/17646/HBP-Statement.090614.pdf

7 – Comparison with other international large-scale initiatives

(7.1) Palca, J (1990). Genome backlash going full force. *Science*. 18 May 1990:Vol. 248 no. 4957 pp. 803-804. DOI:10.1126/science.11642769

(7.2). Brain initiative: Brain 2025, a scientific vision: Brain Research through Advancing Innovative Neurotechnologies (BRAIN) working group report to the advisory committee to the Director, NIH. June 5 2014. 146 pages.

(7.3). Poo, Mu-Ming (2014). Where to the mega brain projects? *National Science Review*. 1: 12-14. Doi: 10. 1093/nsr/nwt019.

(7.4). Qiu, J. (2014). FORUM on China's funding system and research. *National Science Review*. 1: 161–163, doi: 10.1093/nsr/nwt034