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Rethinking the life sciences

To better serve society, biomedical research has to regain its trust and get organized to tackle larger projects

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Suppose that an international group of scientists presents a 15-year, €750 million research programme to unravel the molecular mechanisms of metabolic syndrome, a disorder implicated in obesity, type 2 diabetes, cardiovascular diseases, cancer and other diseases. The results from this project will neither replace obvious preventive measures—such as reducing food intake or increasing exercise—nor will it magically generate pharmaceutical treatments. Instead, the research aims to gain a systems-level understanding of metabolic syndrome that could lead to more effective prevention schemes, improved food quality, improved early diagnosis of people with higher risk, and better therapies and drugs. From an economic point of view, this is an excellent investment, as the costs of obesity and its co-morbidities in the European Union are estimated to increase to €100 billion per year in 2030 [1]. If the proposed research project helped to lower the costs by only 10%, it would generate a considerable return on investment.

Sadly, such a project would be unlikely to receive funding. The reason is not because it would be scientifically unrealistic or unfeasible, or because society does not want to support expensive research programmes. The Manhattan Project to develop the atomic bomb, the Large Hadron Collider at CERN to identify the Higgs boson and the European Southern Observatory in Chile are all examples of large-scale research programmes that are publicly funded. Rather, the life sciences suffer from a unique set of problems that have developed in the past decades and would prevent such a project receiving popular support and funding. This article explores why this is the case and how modern life sciences could contribute more to society. Specifically, we argue that two areas need rethinking: the embedding of the life sciences in society and the way that research is organized.

There are more than seven billion humans on this planet who need food, energy and health care, and life science research has a huge potential to address these needs. However, critics point out that many of the promises made by life scientists in the past have still not materialized. One example is the promises made to justify the US $3 billion spent on the Human Genome Project. It was supposed to provide a 'blueprint of life' that would quickly lead to new approaches for curing diseases. In the end, however, despite its success at generating new research fields and knowledge, the Human Genome Project has not (yet) lived up to its promises.

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Worse still, some critics perceive the life sciences as a problem that is creating physical and moral hazards. Rather than writing a blank cheque to allow scientists to pursue their research goals, governments are increasingly demanding control over the direction and application of research. This approach tends to reward short-term applications of scientific resources to help solve societal problems. Moreover, the success of projects has to be demonstrated at the application stage, before any of the research has even begun, which is fundamentally incompatible with the trial-and-error processes at the heart of creative research. Long-term, in-depth investments in research have become unpopular. Ironically, this 'short-termism' undermines the potential of the life sciences to be realized. Life sciences and society seem to be in a dead-lock.

The life sciences must therefore regain the trust of society. This cannot be done merely by emphasizing academic freedom and the autonomy of science, or by promoting the so-called 'cornucopia' of science and technology, implying that both bring only precious gifts. It is also not useful to suggest that morals should follow scientific and technological developments rather than shape them. It is equally counterproductive when scientists deny taking responsibility for how their findings are applied after they leave the laboratory. As Ravetz [2] famously remarked: "Scientists claim credit for penicillin, while Society takes the blame for the Bomb". In reality, the definition of ends is always influenced by the available means.

One approach to restore the trust between the life sciences and society is to create platforms that allow for open and symmetrical dialogue. Fortunately, we do not have to start from scratch, as the recent discussions about responsible research and innovation (RRI; [3–5]) have already begun this process. According to René von Schomberg, policy officer at the European Commission, Directorate-General for Research, RRI is "a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products" [5]. An example is the EU 'Code of conduct for responsible nanosciences and nanotechnologies research'. The concept is also expected to have a major role in the upcoming EU Framework Programme for Research and Innovation 'Horizon 2020', and national research councils in the UK, Norway and the Netherlands are supporting initiatives under this heading. The National Nanotechnology Initiative in the USA heralds 'responsible development', and the Presidential Commission on the Study of Bioethical Issues recommends 'responsible stewardship' and 'prudent vigilance' in relation to synthetic biology.

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The starting point of RRI is that society, science, technology and morality comprise a single system. If one component changes, the others are also affected. The traditional division of labour—science provides knowledge and instruments, whilst society determines values and application—therefore does not work anymore. Life scientists have to acknowledge and accept that society is co-shaping their agenda. Scientists should also realise that vice versa they co-shape society, rather than just offering knowledge and tools. In other words, science and society co-evolve [6]. Bringing life sciences and society closer together requires the concerted efforts of life scientists, social scientists, ethicists, legal experts, economists, policy-makers, market parties and laypeople.

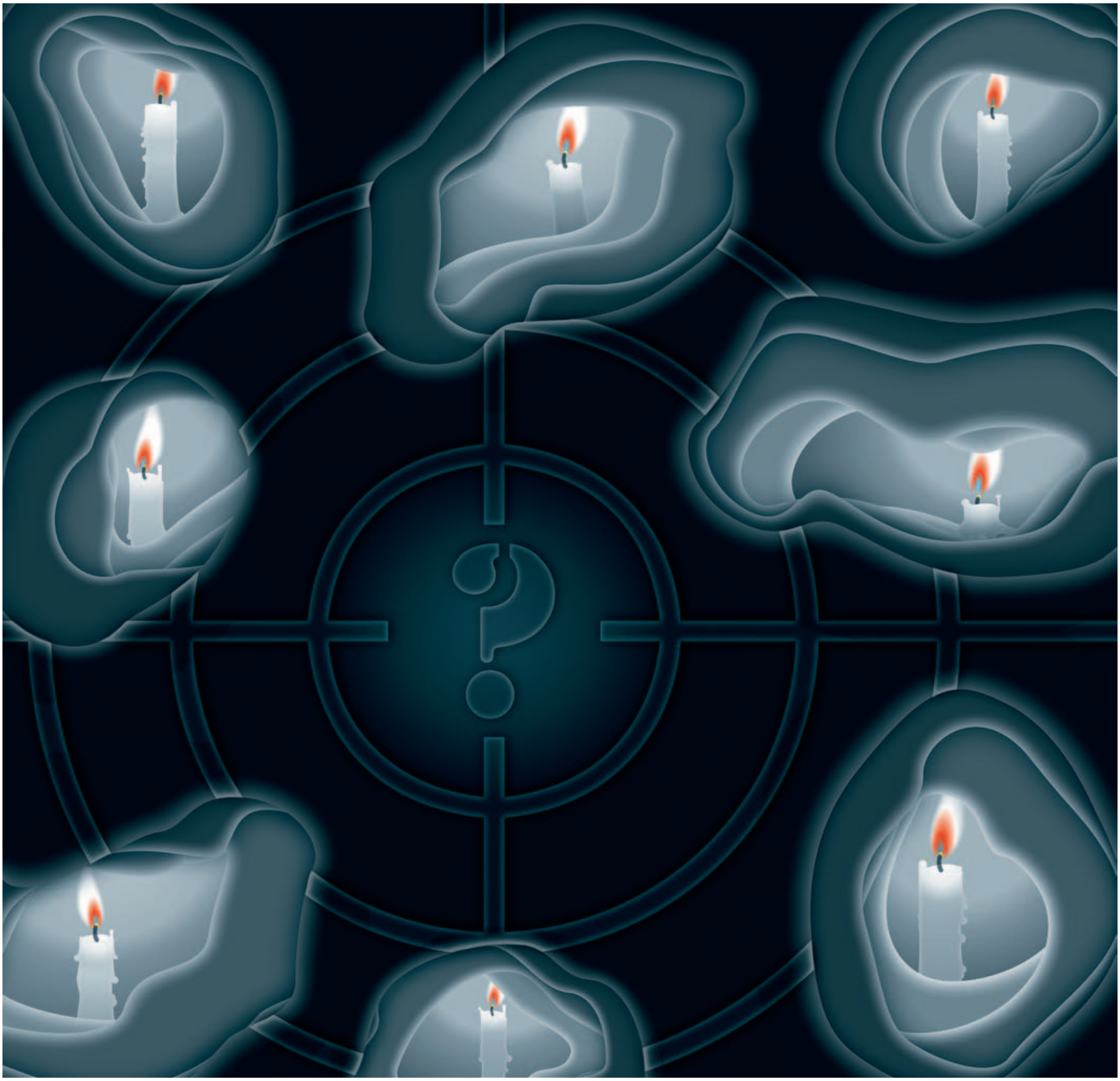
Research and technology are rational activities at the micro level. Science is superior to other methods for creating reliable, testable knowledge, and technology is unmatched in providing solutions to many problems. But both tend to become irrational at higher levels of organization—we drive highly sophisticated cars and still get stuck in traffic jams, nuclear waste remains a huge problem for generations to come, and knowledge and technology have enabled increasingly lethal weaponry. Science and technology therefore need moral guidelines—such as 'the precautionary principle'—to direct what kind of knowledge is worth pursuing and should be applied, why and for whom. This is a one-sided view, however, that ignores the perspective of the scientific method. As science proceeds by trial and error, it must be fundamentally open to pursue any avenue of knowledge. As such, new scientific insight and technological opportunities can often necessitate a reappraisal of established morals. Keeping science, technology and morality in contact with each other requires more than rules and prohibitions that can be ticked off on a form. It needs a culture of attentiveness and reflection to avoid tunnel vision whilst allowing flexibility and improvisation to learn from mistakes and change course if needed.

During the past two decades, many experiments in public understanding, awareness and participation in science and technology have been conducted. In the Netherlands, for instance, this has included science cafes, citizen panels [7], nation-wide public debates about nuclear energy [8], biotechnology and food in 2001 [9], and public participation (http://www.nanopodium.nl). It is yet to be determined how effective these efforts have been. Appreciating that science and technology, as well as society and morality, constitute parts of a larger system demands skills, institutions and procedures that have not as yet been adequately developed. Indeed, many scientists continue to adhere to a 'knowledge deficit' model of public outreach that has scientists 'explaining' scientific developments to an audience that is perceived to be ignorant at best and technophobic at worst. On the other hand, NGOs have sometimes hijacked discussions by simply being 'against', rather than contributing to the debate in an open and constructive manner. Another problem is that the life sciences are poorly organized. They lack an organization that represents the community and can professionalize the relationship between society and life sciences.

What are the requirements for developing responsibly the relationship between society and the life sciences? First, it is important that scientists are explicit about the trial-and-error character of research, and are honest and transparent about the results they expect, rather than inducing unrealistic expectations. Laypeople should be made aware of how the life sciences function and what they might achieve. It is also important that citizens understand that science produces theories that can be corroborated to some degree rather than absolute certainties, and that technology offers solutions that can do both more or less than expected. This should also make clear that the distinction between fundamental science and applied technology is both real and illusionary. It is real because it is important to allow space for unfettered curiosity. It is illusionary because even the most 'fundamental' research is usually embedded in a general normative vision about its possible use. Moreover, even truly applied research can generate new fundamental insight.

Second, it is important to engage societal actors as early as possible in the research enterprise, so that they can determine the research agenda rather than be confronted with final results and products. A specific suggestion would be to attach a 'layman advisory board' to large research programmes. Although the tasks of such boards should be defined carefully to avoid tying them up in minutiae, such boards can help to enhance the involvement of society in the life sciences. Engaging interested individuals and stakeholders early on in the process and offering them an opportunity to influence the research agenda would help to foster a constructive attitude.

These boards should put the definitions, visions and goals of scientific research to the social test and set research priorities accordingly. Research is inevitably conducted with reference to priorities—such as advancing knowledge, improving public health, economic development and military use—but setting these priorities exceeds the authority of science. We need social scientists, philosophers, lawyers, policy-makers, politicians, companies, opinion-makers, NGOs and patient organizations to discuss with life scientists how scientific results can be developed to benefit society. For example, because knowledge can be viewed as an economically valuable resource, we have to consider whether intellectual property laws are adequate to deal with new forms of knowledge. The ongoing debate about the legal and moral problems of intellectual property [10] also highlights issues of fairness and justice. How will science and technology influence prevailing ideas about the meaning of a 'healthy life'? How much do we value physical and mental health, how much are we willing to invest in this value, and how will society react to choices made by individuals? The life sciences are creating enormous data collections about individuals, which raises issues about access, privacy, ownership and consent. Discussing these issues would neither put the life sciences in a strait jacket nor would it curtail curiosity-driven research. On the contrary, we should be more worried about the current situation, in which governments set the agenda by choosing which areas are funded without consulting the life sciences community or other stakeholders.



The sequencing of the human genome and the rapid development of new technologies and research fields—genomics, proteomics, advanced light microscopy, bioinformatics, systems biology and synthetic biology—have not yet paid off in terms of highly visible applications that provide a significant benefit to society. However, there are many examples of progress both scientifically and clinically, such as the ongoing Encyclopaedia of DNA Elements project (ENCODE; http://encodeproject.org), the stratification of patients for anti-cancer therapies based on molecular markers or the creation of genetically modified disease-resistant plants. Notwithstanding, applying the new technologies made scientists realize that biological systems are much more complex than anticipated. The multi-layered and multi-scale complexity of cells, organisms and ecosystems is a huge challenge for research in terms of generating, analysing and integrating enormous amounts of data to gain a better understanding of living systems at all levels of organization.

However, and remarkably, the life sciences have not adapted accordingly to tackle bigger challenges with larger teams comparable with their colleagues in physics and astronomy. Most research is still carried out by small groups or collaborations that are woefully inadequate to address the full complexity of living systems. This type of research is grounded in the history of molecular biology when scientists focused on individual genes, proteins and metabolic pathways. Scientists hope that many small discoveries and advances made by many individual research groups will eventually add up to a more complete picture, an approach that clearly does not work and must change. The new challenge is to systematically acquire and integrate comprehensive data sets on the huge number of components at the cellular level and that of tissues, organs and complete organisms. This requires the life sciences to scale up their research efforts into larger projects.

The putative research programme described at the beginning of this paper could help to reduce the health and economic burden of metabolic syndrome. This multifactorial disorder is an excellent example of the complex interplay between organs, tissues, cells, molecules, lifestyle, genetic factors, age and stress. Unravelling this daunting but finite complexity requires a major and well-coordinated effort. It would have to combine diverse skills and disciplines, including biology, chemistry, medicine, mathematics, physics and engineering. Similar considerations are true for research into areas such as cancer, Alzheimer disease or the development of efficient biofuels. Why, then, are we not making the necessary investments? The answer to this question has four components that we address below: scaling and management of research programmes, the academic culture and funding.

First, one could argue that many national and European research programmes already focus on many aspects of metabolic syndrome. Together, they probably represent an investment of several hundred million Euros. So why spend another €750 million? The problem is that the results from individual research efforts simply do not add up due to a lack of standardization in regard to experiments, the use of model systems and protocols. Given the complexity of the disease, defining standard operation protocols (SOPs) is not a trivial task and requires a considerable research effort. However, experience shows that developing SOPs should be an integral part of larger research programmes. Moreover, SOPs change as our knowledge increases. SOPs can only be effective and stimulate research in the context of a sufficiently large and receptive research community, dedicated to a common well-defined research goal. An example of the successful development and implementation of SOPs in a 'learning-by-doing' setting is the German Virtual Liver Network (VLN) programme (http://www.virtual-liver.de). Obviously, a considerable fraction of the €750 million should come from regrouping and readjusting existing research in the field of metabolic syndrome.

Second, we have remarkably little experience in managing concerted large-scale research efforts in the life sciences in the range of €100–1,000 million. The Human Genome Project cost US $3 billion. However, genomes are just DNA sequences, and it is relatively easy to define SOPs and integrate the contributions of many research groups. In terms of research management it was relatively straightforward compared with, for instance, a metabolic syndrome programme, which would have many more dimensions and components. It would require a highly coordinated approach, as the experiments of the participating research groups from different institutes and countries are strongly interdependent and the results must add up to a larger picture.

To keep such a complex research programme on track, on time and within budget, strategic decisions will inevitably need to be made at a central level, rather than by individual researchers. A serious risk is that scaling-up coordinated research efforts will result in excessive bureaucracy and inflexibility that could kill creativity. Avoiding this problem is a major challenge. The life sciences could learn here from large, long-term projects in other fields, such as high-energy physics, astronomy and ecology. An instructive example is the Census of Marine Life programme [11] that successfully measured the diversity, distribution and abundance of marine life in the oceans over ten years. It involved 80 countries and 640 institutions and had a budget of US $650 million [12]. A recent overview and analysis of large-scale research efforts in the life sciences has been presented and discussed in [13–15].

A third aspect is academic culture, which cherishes freedom, independence and competition and will not necessarily mesh well with the idea of large, tightly managed research programmes. Even so, research institutions will probably compete to participate in goal-oriented, large-scale research programmes. In fact, this is largely similar to the way most research is funded presently, for instance, through the Framework Programmes of the European Commission, except that the total collective effort is scaled up by one to two orders of magnitude. Moreover, as large-scale efforts involve longer timescales of between 10 and 15 years, it would offer a more stable basis of financing research. However, as the cooperation between parties and their interdependency will need to increase, participating research institutes and consortia will be held much more accountable for their contribution to the overall goals. 'Take-the-money-and-run' is no longer an option. This will obviously require explicit agreements between a programme director and participating institutions.

In addition, academic institutions should rethink their criteria for selecting and promoting researchers. The impact factor, *h*-factor and citation scores [16] will have to be abandoned or modified as large-scale research efforts with an increasing number of multi-author publications will decrease their ability to assess individuals. Consequently, less emphasis will be put on first or last authorships, whilst project and team management skills might become more relevant.

Academic freedom and creativity will be just as essential to a collective research enterprise as it is to small projects and collaborations. Large-scale research programmes will create new scientific questions and challenges, but they will not tell investigators how to address these. Academics will be free to choose how to proceed within the programme. Moreover, researchers will benefit from tapping into well-structured, large, knowledge bases, and they will have early access to the relevant data of others. Hence, being part of a large, well-organized research community brings benefits that might compensate for a perceived decrease in independence. Again, all of this depends strongly on how a large-scale programme is organized and managed, including the distribution of responsibilities, data-sharing policies and exchanges of expertise. Competition will probably remain part of the scientific endeavour, but it is important that it does not hamper collaboration and data sharing.

Whilst we stress the need for larger-scale research efforts in the life sciences to have an impact on society, we also want to acknowledge the crucial role of classical curiosity-driven research programmes. It is essential to develop a reasonable and effective balance between different types of research in life sciences.

A fourth issue is the lack of adequate funding mechanisms for international, large-scale research efforts. Given the ambiguous relationship between the life sciences and society—as argued in the first part of this essay—this problem can only be solved if life scientists convince policy-makers, funders and politicians that research can significantly contribute to solving societal problems and at reasonable costs. If not, life sciences will not flourish and society will not profit. As argued above, research efforts should be scaled to the complexity of the systems they intend to investigate. There are only a few problem-focused research programmes with a volume of more than €50 million. The VLN, funded to the tune of €43 million over five years by the German ministry for education and research, comes close. Its aim is to deliver a multi-scale representation of liver physiology, integrating data from the molecular, cellular and organ levels. The VLN involves 69 principal investigators dispersed throughout Germany and is headed by a director who is responsible for keeping the programme on track and on time. Issues such as standardization, division of responsibilities between the director and principal investigators, and decision-making procedures are tackled as the programme develops.

If it is possible to rekindle the trust between society and the life sciences, will society be more willing to fund expensive, large-scale research programmes? Previous examples of publicly funded scientific and technological programmes in the multi-billion Euro range are the Large Hadron Collider, the Apollo programme and the Human Genome Project. Amazingly, none of these contributed directly to human well-being, although the Human Genome Project did make such promises. Hence, a life science programme that targets a crucial societal problem convincingly, such as metabolic syndrome, should have a fair chance of being acceptable and fundable.

The above four issues must be addressed before the life sciences can successfully tackle major societal problems. It will need action from the research community itself, which is painfully lacking an organization to speak on behalf of life scientists and that can take the lead in discussions, internally and between society and science. Any such organization could learn from other areas, such as high-energy physics (CERN), astronomy (European Southern Observatory) and space research (European Space Agency). It would be tremendously helpful if a group of life scientists would get this issue on the agenda. This paper is meant to stimulate that process.

In summary, we argue that if society wants to benefit from what the modern life sciences have to offer, we must act on two parallel tracks. One is to bring the life sciences closer to society and accept that society, science and morality are inseparable. The other is to rethink how we organize research in the life sciences. Both tracks create major challenges that can only be tackled successfully if the life sciences get organized and create a body that can lead the debate. At a more fundamental level, we need to decide what type of knowledge we want to acquire and why. Clearly, the value of generating knowledge for the sake of knowledge itself is important, but it must constantly be balanced with the values of society, which requires a dialogue between researchers and society.

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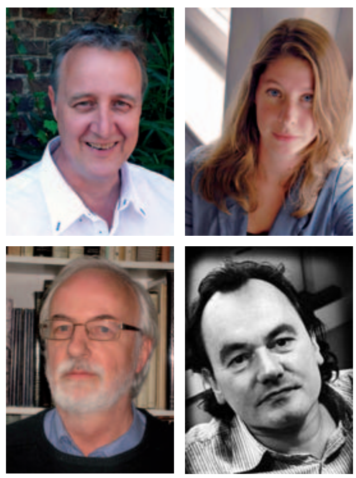
CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

REFERENCES
1. Meijer I, Vullings W, Zuijdam F (eds) (2010) *European Priorities in Health Research, the Dutch Perspective*. Utrecht, the Netherlands: NFU. http://www.nfu.nl/fileadmin/documents/Europeanprioritiesinhealthresearch.pdf
2. Ravetz J (1975) … et augebitur scientia [*… and knowledge will be increased*]. In *Problems of Scientific Revolution: Progress and Obstacles to Progress in the Sciences* (ed Harré R), pp 42–57. Oxford, UK: Clarendon
3. Felt U *et al* (2007) *Taking European Knowledge Society Seriously*. *Report of the Expert Group on Science and Governance to the Science, Economy and Society Directorate, Directorate-General for Research European Commission*. Luxembourg, Belgium: Office for Official Publications of the European Communities
4. Owen R, Heintz M, Bessant J (eds) (2013) *Responsible Innovation*. London, UK: Wiley
5. Von Schomberg R (2012) Prospects for technology assessment in a framework of responsible research and innovation. In *Technikfolgen abschätzen lehren: Bildungspotenziale transdisziplinärer Methoden* [*Teaching Technology Assessment: The Educational Potential of Transdisciplinary Methods*] (eds Dusseldorp M, Beecroft R), pp 39–61. Wiesbaden, Germany: Springer
6. Jasanoff S (ed) (2004) *States of Knowledge: The Co-Production of Science and Social Order*. New York, USA: Routledge
7. Biesboer F (1999) *Clones and Cloning: the Dutch Debate*. The Hague, the Netherlands: Rathenau Institute
8. Gabriëls R (2001) *Intellectuelen in Nederland, Politieke Controverse over Kernenergie, Armoede en Rushdie*. [*Intellectuals in the Netherlands: Political Controversy over Nuclear Energy, Poverty, and Rushdie*]. Amsterdam, the Netherlands: Boom
9. Van Est R, Hanssen L, Crapel O (eds) (2003) *Genes for your Food—Food for your Genes: Societal Issues and Dilemmas in Food Genomics*. The Hague, the Netherlands: Rathenau Institute
10. Agreement on trade-related aspects of intellectual property rights. http://www.wto.org/english/tratop_e/trips_e/t_agm0_e.htm
11. The Census of Marine Life programme. http://www.comlsecretariat.org/
12. Landcare Research (2010) *The Census of Marine Life: Review of Lessons Learned*. New York, USA: Alfred P. Sloan Foundation. http://www.comlsecretariat.org/wp-content/uploads/2010/05/MarineLifeCensusReview.pdf
13. Hampton SE, Parker JN (2011) Collaboration and productivity in scientific synthesis. *BioScience* **61:** 900–910
14. Vermeulen N (2009) *Supersizing Science; On Building Large-scale Research Projects in Biology*. Maastricht, the Netherlands: Maastricht University Press
15. Parker JN, Vermeulen N, Penders B (2010) *Collaboration in the New Life Sciences*. Farnham, UK: Ashgate
16. Preliminary results of Euroscience Survey. http://blogs.sciencemag.org/sciencecareers/2012/07/preliminary-res.html



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