

A recent crisis in regenerative medicine: Analyzing governance in order to identify public policy issues

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Abstract

This article focuses upon issues that public policy makers need to address, when trying to stimulate world-leading research into new areas, which are potentially also valuable to solving societal challenges. Our analysis helps contribute to the theoretical discussions about governance of new knowledge. We focus upon the sequence of events surrounding the main actors of a recent crisis of regenerative medicine in Sweden. We define governance theoretically, and use a conceptual model in order to structure the empirical analysis. Regenerative medicine is an interesting setting to explore these topics, not least because both public and private actors are often involved, and because governments struggle with how to promote ‘translational research’, e.g. diffusing scientific research into clinical practice. Our case study helps understand the process that led up to a crisis in regenerative medicine and identifies and discusses four issues that need to be addressed by policy makers.

Key words: innovation policy; governance; medical research and innovation

1. Introduction

Public policy makers face challenges, when trying to stimulate what is in policy terms called world-leading research, and specifically new areas which are also potentially available to solving societal challenges. Governments can invest money, but no one can promise that the scientific research involved will be successful—but the government hopes to both open up new knowledge frontiers as well as capture the reputational and economic returns to potential scientific success in such areas. To some extent, then, what policy makers call world-leading research involves taking risks as compared to known knowledge, because otherwise one could not discover and test new ideas. One stream of research within the innovation systems and policy literature argues that the concept of governance can be used as a way of conceptualizing public policy for innovation, especially involving public–private partnerships (Borrás 2011; Edquist and McKelvey 2000; Nelson 1993), drawing upon traditions in political science about collective action (Ostrom 1990). Governance is an interesting concept, because governance is a theoretical idea about the complexity of how actors interact, when not only responding to markets or hierarchies. Here, governance refers to mechanisms for coordinating and regulating intended interactions related to the development and diffusion of new knowledge. Developing the concept further can help specify what roles that government could take,

as compared to the roles played by the individuals and organizations involved. This article proposes a conceptual framework for understanding how actors interact in ways which create (or fail in creating) collective action and governance, which we then use to analyze a recent crisis in regenerative medicine and identify and discuss issues that policy makers need to address when trying to stimulate world-leading medical research and innovation.

More specifically, from the perspective of science and innovation policy, a key policy challenge is to understand how and why actors and their interactions promote the development and diffusion of new knowledge into society. Public policy makers have been challenged about how to understand, impact, and design governance for specific scientific and technological areas (Borrás and Edler 2014; Gerritsen et al. 2013; Meijer et al. 2012; Salter and Salter 2010). In recent decades, public policy makers have been considering many new policy instruments, such as how to develop networks and facilitate interactions among different types of actors. This theoretical approach is interesting for analyzing regenerative medicine, also because these processes of medical research and medical innovation in turn involve actors from science, market, and the government.

The article uses a detailed historical narrative about the key actors and interactions involved in the building up of scientific and clinical knowledge in regenerative medicine at Karolinska Institute (KI), Sweden, which is an internationally leading university in

medicine. However, the case study is primarily focused around the public outcry and crisis that has become associated with a single clinical-scientist hired by the KI to translate ground-breaking research into clinical practice. The national institutional context involves a strong public policy push to attempt to concentrate research funds into leading fields, such as the fast-moving field of regenerative medicine. We argue that this created a demand for star scientists willing to take the risks needed to move the field, and that this risk taking was made possible due to uncertainties at the interface between medical research and practice and due to a culture of human experimentation in medicine.

Section 2 presents a brief overview of the crisis. Section 3 selectively reviews theories, enabling us to propose a conceptual framework involving the concepts of governance, collective action, and common resource pool. Using this framework, the specific crisis is analyzed, including interactions among the key actors. Section 4 presents details of the case study, in relation to the main actors and interactions, including their governance, while Section 5 provides a more specific analysis of the case.

Section 6 returns to the challenges of public policy, specifically in relation to regenerative medicine, using the theoretical framework of governance. The final section considers conclusions and areas for future research, in relation both to the special case of regenerative medicine as well as in the more general case of public policy designed to stimulate governance for the development and diffusion of knowledge in fast-moving fields.

2. This crisis of regenerative medicine and its main actors

In January 2016, a Swedish television documentary aired on public TV (Lindquist 2016), which tells the story of the thoracic surgeon Paolo Macchiarini at the KI in Stockholm and his attempts to develop a new procedure for replacing parts of the trachea by growing stem cells on a synthetic scaffold, which was subsequently implanted into a patient.

The national institutional context which enabled the hiring of Macchiarini at the KI goes back to earlier Swedish public policy, designed to promote world-leading scientific research. In 2008, the government introduced a new science and innovation policy where only a few, but strategically selected, research areas would receive long-term funding on a scale unprecedented for Sweden. One of these strategic research areas (SRA) was regenerative medicine. Based on this new policy, in 2010 the KI applied for and received a large 5-year government grant for regenerative medicine. KI had a strong incentive to show good performance during these 5 years, because in case of good results, the government indicated that this large-scale funding might become a permanent addition to the university's funding base.

The 5-year grant for regenerative medicine enabled the KI to attract world-renowned scientists, one of which was Paolo Macchiarini—who was considered a pioneer in translating stem cell research into clinical practice. The first operation, performed in 2011 at the Karolinska University Hospital (KUH), was originally presented as a ground-breaking achievement documented in prestigious medical journals and hailed by the press. Macchiarini and his collaborators, using equipment provided by an American company Harvard Apparatus Regenerative Technologies (HART), subsequently performed a number of similar operations.

Five years later, a different picture was painted. The Swedish public television (SVT) aired a 3-hour documentary called *The Experiments* (Experimenten) by Bo Lindquist (2016). Based on

footage from teams from German TV and Swedish TV, the 3-hour series followed Macchiarini over several years, including operations using the synthetic trachea implants at KUH, as well as similar operations in Russia. The documentary showed patients preparing for an experimental implant operation followed by interviews with their close relatives who believed that the operations contributed to the patients' premature deaths. Furthermore, the documentary presented information that suggested that the operations lacked proper scientific support and regulatory approval, and showed leaders of the prestigious KI defending the key scientist's conduct despite mounting evidence of its inappropriateness.

A public outcry followed in Swedish media, where KI was criticized for supporting Macchiarini's conduct. The magnitude of the crisis can be illustrated by the reaction of the Royal Swedish Academy of Science as reported in *The Lancet*:

The resignation of Anders Hamsten as Vice-Chancellor of the Karolinska Institute has accelerated a growing sense of emergency within the Swedish biomedical science community. His departure comes during the same week that the Royal Swedish Academy of Sciences issued an unprecedented statement accusing Paolo Macchiarini of 'ethically indefensible working methods'. The Academy is the body that awards annual Nobel Prizes in Physics, Chemistry, and Economics (the Nobel Prize in Physiology or Medicine is awarded by the Karolinska Institute, hence the likely acute embarrassment at the tarnished reputation of one of the world's most respected scientific centres) (Horton 2016).

Multiple investigations on topics ranging from research fraud to criminal misconduct were started following the airing of the documentary (Karolinska Institute 2016b). Four members of the Nobel Prize committee in Physiology or Medicine resigned. The Vice-Chancellor of the KI, Professor Hamsten, resigned after originally defending Macchiarini. *The Lancet*, who published Macchiarini's paper in 2011 where the results from the first synthetic trachea implant were reported, initially printed a statement that Macchiarini should be considered innocent until proven guilty—and referred to the Vice-Chancellor Prof. Hamsten's decision (Horton 2016). During 2015 and 2016, however, several co-authors asked to be removed from the 2011 paper. In April 2016, the *Lancet* printed an expression of concern, noting the 'ongoing uncertainty about the integrity of the work reported in this paper... while reserving a final decision for when current investigations are completed' (*The Lancet* 2016).

Public policy makers need to balance their desire for 'world-leading research' with governance mechanisms that can oversee risky science, and especially when both public and private actors are involved. In telling this story, the main timeline and actors in the great success—and subsequent crisis—of world-leading research in regenerative medicine can be summarized as follows. One key actor is the Swedish government, which through public policy, had the aim to spur innovation and economic development based on research excellence in selected fields, one of them being regenerative medicine. Others are the KI, which hired Macchiarini, as well as the KUH, where operations were performed, and HART who supplied technologies for growing the stem cells.

In the next section, we selectively review previous research on innovation policy and the governance of research and innovation in order to provide an analytical framework which is useful for structuring the case study and thereby developing a more nuanced discussion of how government and public policy can affect governance of

public–private partnerships involving the development and sharing of new knowledge.

3. Innovation policy understood through the governance of research and innovation

In this section, we propose a theoretical framework, which was inspired from previous work on a related issue by the authors (Reference removed during review). The framework will be used to structure the case study and analysis, using the three key constructs of governance, collective action, and a common resource pool.

The rationale for science and innovation policy is often based—even if loosely coupled—on social scientific understanding of science and innovation, which changes over time. A recent shift in the understanding the nature of the innovation process has led to a fundamental change in public policy for supporting innovation, according to *Borrás and Edquist (2013)*. Recent articles also question the usefulness of public policy recommendations based on academic research, when researchers are too far away from the political context of policy makers (*Flanagan and Uyarra 2016*) as well as when the policy design and instruments proposed is far from the reality of policy makers (*Martin 2016*). Previously, public policy for research and innovation was predominantly concerned with supporting science and addressing market failures hindering the application of new scientific knowledge, which is in line with the linear model of innovation. More recently, a range of policy instruments are being used that are based on a more critical view of economists' notion of market failures. For example, *Gerritsen et al. (2013)* examine the concept of knowledge governance and distinguish different foci in the literature such as network governance, self-governance, and reflexive governance, respectively. Put more simply, public policy has moved away from the economists tradition of 'market failure' arguments, and instead the foci become more problem-oriented and systemic, and thereby addressing a larger list of possible failures in a particular context (*Arnold et al. 2003*).

Our interpretation is that this change in foci for science and innovation policy is visible in two empirical trends, which also motivate the use of the concept of governance for capturing how innovation processes are being coordinated and regulated. First, there is an increasing number of soft policy instruments, e.g. public–private partnership, that focus on mutual, and voluntary, exchange of information and resources, where cooperation between the public and private is less steered by the government (*Borrás and Edquist 2013*). Second, there is the increasing use of project-based competitive funding of research having a thematic, multidisciplinary, focus (*Lepori et al. 2007*). These projects focus upon emerging technologies, such as nanotechnology and biotechnology, or societal challenges, such as 'Secure, clean and efficient energy' and 'Health, demographic change and wellbeing' (*European Union 2009; European Commission 2011*). In short, these two trends indicate that governments work with the ideas of governance, when many different actors are involved, and promote the interaction of heterogeneous actors in order to reach goals that go beyond excellence in science.

We would like to point out that one implication of this shift in understanding and in policy practice is that governance should not be confused with public policy instruments, and nor is policy only top-down. The actors are expected to cooperate on a voluntary basis toward a common thematic goal—possibly with some financial incentive from the government—but without top-down government

steering or purely driven by market coordination. We are also assuming that, in addition to promoting science and economic growth, policy makers want to ensure that issues of societal concern are addressed, such as distribution of benefits and financial gain, public hazards, and ethical conduct.

In political science, the concept of 'governance' refers to mechanisms, such as rules and norms, which regulate activities that are not entirely regulated through the market or the government (*Jessop 1997; Loorbach 2010*). As many actors interact, these actions constitute collective action. *Ostrom (1990)* has made a major contribution to the field, by focusing upon self-governance, where social entities voluntarily engage in regulating their own actions, and in ways that can solve social dilemmas. However, within science and technology studies, the concept of governance has been used for all forms of regulation, including collective self-regulation as well as regulation involving the market and government (*Borrás and Edler 2014*).

When both the institutions of science and the market are involved in the production of knowledge, our position is that the development and diffusion of new knowledge needs to be analyzed as a complex, and often self-organizing, process involving interactions and collaborations between both private and public actors (*Archibugi and Filippetti 2015; McKelvey 2014*). When defining the governance of such interactions we follow the broad approach proposed by *Borrás and Edler (2014)*, but in line with our focus on public policy we limit ourselves to the regulation of intended interaction, i.e. the conscious design of mechanisms guiding collective action toward meeting policy goals. Thus, in the context of this article, governance refers to mechanisms for coordinating and regulating intended interaction related to the development and diffusion of new knowledge. These mechanisms can include interactions that are a part of a collective action (self-governance), market mechanisms, scientific community practices as well as government regulations.

The intended interaction is in this article conceptualized as composed of two parts: collective action and common resource pool. For collective action, we focus upon the variety of actors involved, which may act individually and for different goals and incentives, but in some way create action and processes, which enable progress of a specific field of science and technology. We acknowledge that each actor may react to different imperatives and goals, and yet participate in collective action to promote science and innovation. Hence, the concept of collective action helps us highlight that public policy initiatives must address the increasingly complex interactions among heterogeneous actors with different interests and norms, including both private and public actors that are trying to achieve shared goals set by policy makers. For common resource pool, we focus upon the diverse resources that both enable the collective action and are also the outcome of the action. These resources include people, knowledge, equipment money, and other resources needed to both carry out the research and also translate those results into innovations.

Hence, the key concepts in the framework are collective action, common resource pool, and governance and they are linked as shown in *Fig. 1*. At the top, actors engage in the intended interaction to meet policy goals for research and innovation, i.e. the collective action made possible by the common resource pool. The arrows between the collective action and the common resource pool go both ways, because the common resource pool can be considered an outcome of the interaction, as well as an input to later collective action.

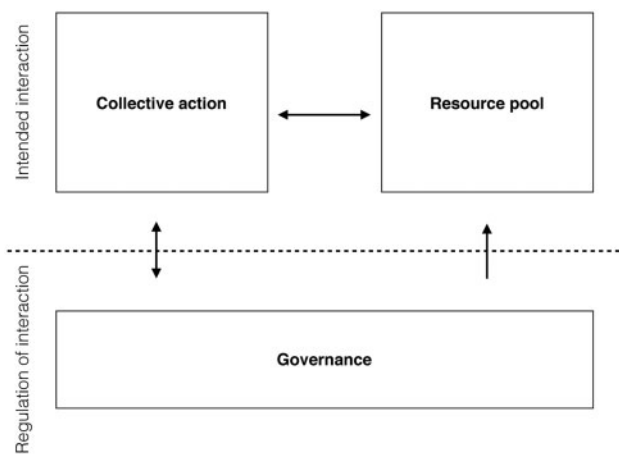


Figure 1. Governance of intended interaction initiated to meet policy goals.

At the bottom, governance is referred to as the regulation of the interaction among actors, as they engage in collective action and creating a common resource pool. Note that the dotted line thus distinguishes the intended interaction from the regulation of the interaction, i.e. its governance.

More specifically to explain Fig. 1, let us first use these concepts to introduce the broader field of regenerative medicine, before using it in relation to our case study described in the next section.

The research and clinical activities related to the trachea implants pioneered by Macchiarini and his collaborators belong to the field of regenerative medicine. Regenerative medicine is ‘a field of medicine devoted to treatments in which stem cells are induced to differentiate into the specific cell type required to repair damaged or destroyed cell populations or tissues’ (NIH, 2015: 23). Researchers and policy makers justify the high public investment in regenerative medicine with the argument that research is ‘game-changing’. For example, the Mayo Clinic website states ‘Regenerative medicine is a game-changing area of medicine with the potential to fully heal damaged tissues and organs, offering solutions and hope for people who have conditions that today are beyond repair’ (Mayo Clinic 2016).

Research in regenerative medicine is believed to create substantial economic value and offer opportunities for industrial innovation and national competitive advantage, which has made it a fast-moving international field of research and innovation fueled by large-scale public and private funding around the globe (Salter and Faulkner 2011; Salter and Salter 2010). However, concerns have been raised that the translation of basic research into workable therapies will be slow due to challenges related to regulation, reimbursement, and clinical adoption (Gardner and Webster 2016). This has led to policy responses stressing translational research, i.e. the leading role of the clinical-scientist, the promotion of ‘patient related research’, and the integration of the lab and the clinic (Vignola-Gagné et al. 2014), and the generation of innovation niches, i.e. collectively constructed socio-technical spaces for testing and developing novel technologies (Gardner and Webster 2016). In this way, policy makers support collective action for building a common resource pool (the intended interaction) amongst key actors in a medical innovation system (Metcalf et al. 2005) to stimulate research, innovation, and its wider adoption.

Despite beliefs of the game-changing nature of regenerative medicine, and the subsequent economic benefits, there also exist a

number of controversies around the ethical, legal, and social implications and how risks are controlled and regulated (Allyse 2010; Hogle 2014; Horst 2008). Thus, regenerative is not only a fast-moving field but also highly contested. Furthermore, examples of misconduct have been exposed in what was previously considered ground-breaking research, leading to retraction of articles in *Nature* (Cyranoski 2014). Hence, studying the issues related to governance of intended interactions is especially pertinent for regenerative medicine, given the fast pace, ethical considerations, risk regulation and the close connection between research and health-care practice.

4. The rise and fall of a research center in regenerative medicine at the KI

In order to understand the process of governance of intended interaction in regenerative medicine, we will follow the interaction among the main actors around a specific research center established to promote the translation of research in regenerative medicine into clinical practice. The case study is organized through our theoretical framework, using the concepts of collective action, resource pool, and governance. The case study is of the rise and fall of the Advanced Center of Translational Regenerative Medicine (ACTREM), a research center led by Paulo Macchiarini at the KI. The time frame of 2010–16 is set by the events leading to the recruitment of Macchiarini by KI and the KUH in December 2010, his joint tenure up until October 2013, when his contract with KUH was not renewed, and up until his dismissal by KI in March 2016.

The case study is based upon archival and electronic documentation related to the crisis described in Section 2. Due to the nature of the crisis, all parties have an interest in putting forward their own particular interpretation of the sequence of events. We have had three main methods to deal with it. One is to apply the basic idea of critical reflection of sources—who said it, why and what interest did they have in this interpretation. A second has been to use the popular press to build a structure of events, which can then be confirmed or discarded when we look the original sources. A third has been to try to find repeated accounts of similar events, known as triangulation by using multiple sources to check statements, as detailed below.

A variety of sources have been used and compared to each other. The majority of documents and websites are in Swedish and the authors have translated the content into English where appropriate. Due to open access laws in Sweden for public authorities like universities and research councils, the majority of documents can be assessed. However, a starting point is often needed, such as an organization, an event or decision or a name of a person involved. Hence, the extensive public press, such as blogs and newspaper articles, has been useful to track down such information, and in turn find the original documents. Thus, we have collected and analyzed a wide range of sources including documents from foundations and financiers, reports from KI, reports from investigations, official statements and press releases, unofficial viewpoints (blogs) from persons mentioned by name in the processes, scientific journal articles, websites, and reports in trade (medical) press. Moreover, KI has been active in social media, providing their perspective of the sequence of events, as documented on their website (Karolinska Institute 2016b). Recent reports from the various investigations have also been used, e.g. Asplund (2016), Gerdin (2015), and Heckscher et al (2016).

The case description is organized in three sections. Section 4.1 describes the building of ACTREM center, in the context of regenerative medicine in Sweden. Section 4.2 describes the activities within the research center, including cooperation with KUH and industry when performing the world's first human transplant of a synthetic trachea. Finally, section 4.3 describes the crisis that led to the closing of the center.

4.1 Building regenerative medicine through public policy funding and university ambitions

Below, we explain how the ACTREM center is a direct result of policy initiative by Swedish government, aiming to focus public and private funding to SRAs. Therefore, this subsection focuses upon the goals, imperatives and funding of the government and KI, and how this led to the creation of the ACTREM center.

4.1.1 Funding of SRAs in Sweden 2010–14

A large investment in regenerative medicine at KI was possible due to government's investment into the SRAs. We interpret this science and innovation policy as an answer to solve the popular perception of 'too much money, too little outcomes from universities'. This policy is part of the policy answer to a long-running debate about the Swedish paradox around R&D (see reviews in Swedish in [Ejermo and Andersson 2013](#); [McKelvey and Zaring 2016](#)). Instead of increasing the total funding to universities, the government identified a few research field, and only researchers in those fields could compete for SRAs.

The Swedish government initiated their SRA initiative following a proposal in the Swedish Research Bill of 2008. According to the Swedish Government Bill, a SRA should fulfill the following criteria: (1) Research that has the potential to be of highest international quality in the long term; (2) Research that can help address large societal needs and solve important problems in society; and (3) Research that is within an area that is important for Swedish businesses. Hence, these SRAs should help make Sweden internationally competitive as well as produce the highest international excellence in science ([Swedish Executive Government 2008](#)).

For the total SRA policy initiative, the government made an investment between 2010 and 2014 of a total of 590 million EUR, and twenty centers were financed, through five funding agencies,¹ and the Swedish Research Council took the lead in medicine. At the end of the SRA policy initiative, an evaluation was carried out, with the recommendation to make this additional money for 'scientific excellence' a permanent addition to the universities who had obtained the original SRAs ([Swedish Research Council 2015c](#)).

4.1.2 The StratRegen research program at the KI

In 2010–14 the KI received money from SRA for StratRegen² ([Karolinska Institute 2016c](#)), a 'strategic research program in Stem Cell Research and Regenerative Medicine' that 'supports research that advances our understanding of stem cell biology and approaches to bring regenerative medicine to the clinic, for future treatment of diseases for which there currently are no therapies' ([StratRegen 2016](#)). We estimate that this program received around 3 million EUR per year from 2010 to 2014 from SRAs, for a total of around 15.5 million EUR.³ Up through March 2016, the StratRegen website stated that they had helped recruit five world-leading medical doctors and researchers, including Paolo Macchiarini.

So why did KI want to develop research in regenerative medicine and recruit star scientists? The vision stated in a strategic document

from 2004 is 'KI will by 2010 be Europe's leading university within medicine and health care as well as the leading innovation center within life sciences in the Nordic countries and thereby be an important motor for development in the country and in the Stockholm region' ([Karolinska Institute 2004](#)). They specified the aim to be world-leading in stem cells and regenerative medicine, although at the time, they did not have so much on the translational research, especially the clinical side. KI was also active in commercializing medical research into innovation from the 1990s and on, involving, for example, KI Innovations AB and participation in the Stockholm entrepreneurship initiative STING.

The StratRegen program was used as a platform to obtain a number of large grants in regenerative medicine from various sources—including starting seven different research centers.⁴ The authors have made a rough estimation that KI obtained and spent a total between 33–50 million EUR on regenerative medicine between 2010 and 2014. Some centers are funded by private foundations such as the Knut and Alice Wallenberg foundation, some by public money such as the regional health authority and some by traditional research financiers.⁵ One of the centers was the ACTREM center led by Paolo Macchiarini.

4.1.3 The ACTREM center

Hence, one person recruited as a part of KI's ambitions to be world leading was Paolo Macchiarini. According to [Vogel \(2013\)](#), Paolo Macchiarini, Martin Birchall, and their colleagues carried out a trachea transplant operation in Barcelona using stem cells back in June 2008, which 'made medical celebrities of the surgeons who developed and implanted the artificial trachea. They were hailed as pioneers leading the world toward an amazing future of regenerative medicine in which doctors will make replacement parts to order'. Macchiarini and Birchall were called stars and super-stars of regenerative medicine. This likely helped motivate the fourteen professors at KI, who wrote a letter of support of Macchiarini's recruitment as visiting professor, and the unusually active involvement of KI's vice chancellor in the recruitment process, both of which contributed to a sequence of events where internal routines were not strictly followed and early warning signals about Macchiarini's past were ignored ([Heckscher et al 2016](#)).

When KI recruited Macchiarini as a visiting professor in December 2010, he was also employed part time as consultant and surgeon at the KUH. In March 2011, he became the director of ACTREM and Executive Director of the center was Philipp Jungebluth, who was earlier supervised by Macchiarini during his PhD studies at Medizinische Hochschule Hannover, Germany.

In February 2016, when the crisis was underway in Sweden, the ACTREM websites listed fourteen researchers and guests as active in ACTREM, as well as twenty-seven international collaborators, including companies and professors.⁶ The collaborators listed included University College of London (UCL) and Harvard Apparatus Regenerative Technology (HART). During 2010–14 Macchiarini was awarded grants for research and clinical development, for a total of 1.5 million EUR from the Swedish Research Council and the Swedish Heart and Lung Foundation.⁷ These grants were designed to extend his work with artificial scaffolds and stem cells for regenerative medicine to other organs, especially the human heart.

Each year, the StratRegen report to the government stressed KI's accomplishments in regenerative medicine, and specifically made mention of Macchiarini's work, not only on trachea but on 'new

synthetic organs to replace tissue and organs in the body in cases where there is no other therapy available' (Swedish Research Council 2012). KI reports many activities related to regenerative medicine which we interpret as building up a common resource pool: recruiting leading international scientists; developing the most modern equipment for research; support leading younger scientists; expanding a set of laboratories that specialize in techniques that are very complicated, and therefore cannot be mastered by individual research groups.

Moreover, KI stresses in these reports that it is the Institute which has published and done the synthetic trachea, and not only Macchiarini. This is strongly stated in their 2012 report:

When looking back to 2011, we are happy to report several scientific landmark discoveries at the Karolinska Institute that have been published in leading scientific journals and also highlighted in media around the world. One such example is the first transplantation of an upper airway (trachea) to a patient that suffered from a tumor in the airways that could not be surgically removed without replacing the upper airways. The new airway was made of synthetic material coated with the patient's own cells, so it would not be rejected after transplantation. This breakthrough was spearheaded by Professor Paolo Macchiarini, but was also based on a true collaboration by a number of research groups at the Karolinska Institute, ranging from molecular biologists to surgeons and transplantation immunologists. (Swedish Research Council 2012)

However, this scientific landmark made by Macchiarini and his collaborators at KI and KUH soon becomes heavily criticized, both among his collaborators, in the wider research community, and in public.

4.2 The first trachea implant operations using a synthetic scaffold

This section addresses the hiring and initial expectations and successes of the new KI visiting professor. When Macchiarini arrived at KI he was a star surgeon known as the pioneer who performed the 'first-in-man clinical transplantation of a stem cell based tissue engineered organ' in 2008 and had repeated such a surgery in 2010. He was expected to improve his method for airway transplants and 'adapt the procedure to other intrathoracic organs of increasingly complex architecture' (Karolinska Institute 2016d). Hence, we interpret that his primary role would be translational research connecting bioscience and clinical medicine as reflected by his dual appointment by KI and KUH.

The trachea (windpipe) implants operations carried out between KI and KUH were the first of their kind, world-wide. They were a continuation from previous operations that Macchiarini had performed in 2008 and 2010, where stem cells were used and said to be growing on a human scaffold (e.g. from cadavers). However, the operations at KI involved a synthetic scaffold (e.g. from polymers) instead of a human one. A synthetic scaffold should be used, because the research activities and goals of ACTREM were to integrate tissue engineering, using biological or synthetic scaffolds, with cell therapy, pharmaceutical therapy, and cells biology (Karolinska Institute 2016). Integrating these fields required interaction with private actors, to obtain the synthetic scaffolds. Moreover, the clinical side was quite important, as indicative by the distribution of scientific publications at the time, with many involving clinical procedures.⁸

Three patients underwent operations in Sweden, and all came from abroad. In June 2011, Macchiarini implanted a synthetic trachea into a cancer patient referred to KUH from the Landspítali University Hospital in Iceland. In November 2011, a second cancer patient received a synthetic trachea after having himself approached Macchiarini. This time the patient came from Maryland, USA. The third patient, a woman from Turkey was referred to KUH by her Turkish doctor, and she received a synthetic trachea in August 2012 and was re-operated in July 2013 following severe complications.

The first patient died in January 2014, 30 months after the operation. The second patient died in March 2012, less than 4 months after the operation. The third patient was still alive as of May 2015, 22 months after the re-operation, but was receiving intensive care at KUH in late 2015 (Gerdin 2015). Other reports, including the Swedish documentary, mention additional transplant operations outside Sweden⁹.

The details of the setting of these operations have much impact on interpreting later events. The decision to operate the patients at KUH using a novel method was taken based on the patient's critical condition and the lack of alternatives.¹⁰ Thus, these patients were not considered research subjects, and the decision to operate them did not follow the procedures needed for ethical approval of research studies (Asplund 2016). Despite that, the operation of these patients later became a subject of research publications describing the implantation and its outcome.¹¹ In addition, the operations involved what is called pharmaceuticals for advanced therapy. Stem cells were extracted from each patient's bone marrow and seeded and grown, in the hospital, on a custom made synthetic scaffold using specialized equipment. The equipment and the scaffold are considered relatively simple medical devices, but once a scaffold becomes seeded with stem cells it is classified, for regulatory purposes, as a pharmaceutical for advanced therapy. The use of such pharmaceuticals on human subjects requires approval of the Swedish Medical Products Agency, and such an approval was not obtained before the operations (Asplund 2016).¹²

Moreover, the scaffolds and specialized equipment needed for seeding and growing the stem cells were obtained outside KUH and KI. The scaffold for the first operation in June 2011 was supplied by Professor Seifalian at the UCL (Gerdin 2015, Jungebluth et al. 2011). The bioreactor used for seeding and growing the stem cells on the synthetic scaffold was provided by a German subsidiary of Harvard Bioscience (Hugo Sachs 2016; Jungebluth 2011). It was a further development of the bioreactor used by Macchiarini in 2008.¹³ Harvard Bioscience also supplied the scaffold and bioreactor for the second operation at KUH in November 2011 and the third one in August 2012. The scaffold provided by Harvard Bioscience was of different construction compared to the one provided by UCL. Instead of a porous solid construction it was a fiber construction (HART 2012).

Through this cooperation with Macchiarini, Harvard Bioscience intended to develop and market the *InBreath Airway Transplant System* including a synthetic scaffold and a bioreactor. The company had acquired the property rights to the bioreactor design before the first KUH operation. This was considered important at the time and reported in October 2013 that the company has 'completed the acquisition of all patent rights to synthetic scaffold-based trachea regeneration owned by Professor Macchiarini' (Harvard Bioscience 2013). HART is incorporated as a fully owned subsidiary in May 2012 and spun-off in November 2013 and traded on NASDAQ.

The initial responses to the operations with synthetic trachea transplant at KUH were extremely positive, both in the scientific

press and in mass media. The first operation was described and published as an article in *The Lancet*, which was initially published with twenty-four authors (Jungebluth et al. 2011). In a press release, Karolinska Institutet states: 'For the first time in history, a patient has been given a new trachea made from a synthetic scaffold seeded with his own stem cells' (Karolinska Institute 2011). Similar reports are made in scientific, trade and popular press, where Macchiarini is repeatedly called the 'Star Surgeon' and wide-ranging claims are made. However, soon after the publication of the *Lancet* article critical voices emerged.

4.3 The crisis and the closing of the center

The initial criticism started much earlier. Following the publication of the *Lancet* article in 2008 that reported the first stem cell human implant by Macchiarini and colleagues using biological donor scaffold (Macchiarini et al. 2008), concerns were raised about the validity of the assumption that the stem cells which were seeded onto the scaffold would reconstruct a fully functioning tissue once being implanted into the patient (Delaere and Hermans 2009; Wu et al. 2009). Similar concerns were also raised following the publication of the *Lancet* article reporting the first implant using a synthetic scaffold (Jungebluth et al. 2011). Once again, the major critique was that the case reports from the operation failed to provide convincing evidence of the assumed reconstruction of the trachea using the patient's stem cells (Delaere 2013; Vogel 2013).

Even though the first trachea implant made in 2011 was hailed as successful and published as clinically successful, it became apparent to physicians at KUH that the implants were not working as well as reported the 2011 paper. The stem cells had not grown to reconstruct the trachea. Furthermore, physicians at KUH invested much effort to attend to the critical condition of the third patient, following the operation. Their disbelief in the efficacy of the operations, combined with the fact that Macchiarini was not much involved in dealing with the complications during care after the operations, were important factors in the decision not to renew Macchiarini's contract with KUH in 2013, despite pressures from KI to do so (Asplund 2016; Krey 2016; Vilhjalmsen 2016).

In June 2014, 5 months after the death of the first patient implanted with the synthetic trachea, four physicians jointly employed by KI and KUH filed a formal complaint at KI.¹⁴ They claim that seven scientific articles authored by Macchiarini incorrectly—specifically too positively—describe the patients' condition and the functioning of the implant. Furthermore, they point out a failure to obtain proper consent from patients, as well as failure to obtain ethical permission from the Regional Ethical Board (Gerdin 2015; Karolinska Institute 2016b). Three of the physicians were co-authors of papers that were being criticized and one of the physicians had previously 'basically moved into the hospital to take care of the Turkish women [the third patient]' (Karolinska Institute 2016b; Vilhjalmsen 2016).

Also in June 2014, Prof Delaere at KU Leuven filed a formal complaint to KI in line with his previous criticism published in *The Lancet* (Delaere and Hermans 2009; Delaere 2013) and Vogel (2013).¹⁵

In Sweden, universities monitor the conduct of their researchers, and not a national board. Hence, the university internal Ethics Council investigates and makes decisions about matters of plagiarism, fraud, misrepresentation of data, misrepresentation of research processes, and other types of scientific misconduct. Furthermore, if a

formal complaint is filed, an investigation is required and should result in a formal response by the university.

Therefore, KI responded to the formal complaints, as required, with an internal investigation. In 2015 the Ethics Council and the Vice-Chancellor freed Macchiarini of suspicions of research misconduct. An external examiner, appointed in 2014, had come to different conclusions, but his conclusions were seen as input to the KI internal process rather than binding recommendations (Gerdin 2015; Hamsten and Samuelsson 2015a,b). Moreover, both the Swedish Research Council and Swedish Heart and Lung Fund withdrew Macchiarini's research grants shortly after the publication of the external examiner's report (Swedish Heart and Lung Fund 2016; Swedish Research Council 2015a,b).

The magnitude of the crisis for the governance systems of medical research and innovation can be understood through the subsequent investigations after the TV documentary and public outcry. By February 2016, 1 month after the airing of the documentary, fourteen separate investigations were started in Sweden (Karolinska Institute 2016e). Seven of the investigations were initiated by KI or KUH, six by government, and one by the Royal Swedish Academy of Sciences in association with the Swedish Society of Medicine.

Six of these investigations focused on procedures for handling investigations about scientific misconduct, and of these, five investigated the internal processes at KI. They covered issues ranging from their internal handling of the allegations of scientific misconduct (fraud), the details of the recruitment process, the reporting of extramural occupations, and also the delegation of responsibility between different actors in Sweden and within KI and KUH. Moreover, four of the investigations focused on Macchiarini's trachea implants as health care procedures, i.e. whether laws and regulations were broken, and in two cases the case was quickly passed on to the police and public prosecutor for investigations related to the death of the patients. Three of the investigations focused on the interface between research and clinical work in order to develop guidelines for research and health care organizations. Finally, KI also decided to reopen the original case of Macchiarini's scientific misconduct, where KI's internal ethics committee and an external investigator had come to different conclusions. Our interpretation is that the organizations involved were using these investigations, in order to try to determine whether existing norms and regulations were properly in place and followed, and whether new divisions of responsibility and procedures needed to be implemented.

After the long period during which KI leadership defended Macchiarini, despite a long-series indications from external organizations, KI finally decided to fire the clinical-scientist. The Staff Disciplinary Board at KI decided on 23 March 2016 to 'relieve Paolo Macchiarini of his duties as a researcher at KI. He is to be informed immediately that his contract has been rescinded'. Under Swedish labour laws, they had already given notice to him that his employment would end at the end of the year and his research center, ACTREM, would be closed (Karolinska Institute 2016f).

5. Analysis of the intended interaction and its governance

In this section, we analyze the case study of the rise and fall of the ACTREM in terms of governance, collective action, and a common resource pool. The analysis proceeds in two parts. First, we summarize the interactions between the actors participating in the collective action, through three different phases of engaging in collective

action for building the resource pool, using the resource pool, and dismantling the resource pool. Second, we use this understanding in order to interpret the case study using our framework.

5.1 Interactions during the rise and fall of the ACTREM center

This subsection focuses upon the actors and interactions during the building, using and dismantling of the common resource pool, defined as resources needed to engage in collective action and resulting from such engagement (Fig. 2).

The first time period (2008–10) can be seen as the initiation of the collective action, which is promoted by policy, and leads to the building of the common resource pool at KI. The dynamics of the case is driven by the interaction between government, represented primarily by the Swedish Research Council, and KI. At roughly the same time, both actors express clear goals for building world-class capabilities in regenerative medicine, and when the Swedish government proposes and funds a policy instrument—one type of collective action—KI is the obvious partner. StratRegen is funded and organized to allow KI to improve their capabilities in regenerative medicine, more broadly. However, despite sharing the goal of research excellence, the two actors are driven by different imperatives. The government is primarily driven by an economic imperative, i.e. the expectation that scientific excellence in regenerative medicine will in turn lead to innovation and economic development. KI, on the other hand, is driven by a scientific imperative, i.e. the expectation that excellence in stem cell research and regenerative medicine will help them become a leading medical university. Translational medicine, which in this case means efforts to translate scientific results from stem cell research into clinical practice, is one action aiming to accommodate these two different imperatives. Hence, part of the funding for StratRegen is assigned to translational medicine, thereby enabling the building up of a resource pool for such activities. More specifically, this intersection of resources and imperatives sets the stage for the hiring of a clinical-scientist, Paolo Macchiarini, who had become well-known for his translation of stem cell research to clinical practice involving the first stem cell based trachea transplant.

The second time period (2011–13) is characterized by the actors using this newly created resource pool. The dynamics are driven by the interactions between KI, KUH, scientific community, and industry, with our story focused around the ACTREM center. The collective action leads to the funding of ACTREM, not only by the SRA funding, but also additional individual project grants and in-kind funding by KUH and industry. Another part of the resource pool consists of Macchiarini's expertise and experience from previous biological implants. Moreover, the operations and research also rely on resources accessed through his networks, where he sources the technology and knowledge which is adapted to the use of synthetic scaffolds. His synthetic implants enjoy initial success and fame, but soon criticism is raised, both in the research community and inside his group. The main criticism is that his methods are flawed and that evidence for their success, as reported in scientific articles, is fabricated. There were also concerns about whether the operations had received appropriate regulatory approval, following the standards and procedure for research and clinical practice. At the end of this period, Macchiarini's employment at KUH is not renewed but he continues being employed at KI.

The third period (2014–16) is characterized by the dismantling of the resource pool, not of everything related to regenerative

medicine at KI but of the part associated with Macchiarini. The dynamics are again driven by the interactions between KI and the government. After formal complaints are filed against Macchiarini, KI is forced to investigate accusations of scientific misconduct, because universities have this responsibility in Sweden, and not a national authority. An external investigator was appointed, who delivered a critical report. Subsequently, a number of Swedish research funds, including the Swedish Research Council, withdrew Macchiarini's ongoing research grants even though the top management at KI continued to defend their star scientist. Moreover, even though the Swedish Research Council retracted Macchiarini's grant, they did apparently approve KI's reporting of the same research within the SRA initiative, where KI was positively evaluated and KI received continued funding (Swedish Research Council 2015c). Our interpretation is that the resource pool around Macchiarini was weakened, which also reduced the possibilities for collective action which could bridge stem cell research and clinical practice. The larger StratRegen resource pool at KI seemed not to be too much affected. However, the airing of the TV documentary where the allegations against Macchiarini, and how they were handled by KI, led to a crisis playing out in the public sphere. Finally, Macchiarini was fired and his center closed down. Moreover, the legitimacy of KI as a prestigious medical research university and guardian of the Nobel Prize in medicine was threatened and action was required at the government level to rebuild confidence.

5.2 Interpretation of the case using the theoretical framework

Using the above description of the main actors, their interactions and processes, this section presents our interpretations in relation to the theoretical framework. The results are also visualized in Fig. 3 below.

The actors involved in the *collective action* have the goal of developing and diffusing scientific research and innovations within regenerative medicine at the KI. The details in the case study show the complex interactions among heterogeneous actors, both private and public, within regenerative medicine. The goals and imperatives of the Swedish government were to stimulate world-leading and competitively useful research and innovation in this fast-moving and prestigious field of medicine. Even though the KI was already active in the field, the government made a very large investment through a particular public policy initiative (called SRAs) as well as investments through the 'normal' research councils and foundations funding medicine in general and regenerative medicine specifically. The scale of the SRA funding stimulates the specific case of collective action described in this article, which includes the hiring—by the KI and the KUH—of the clinical-scientist who was later pointed out as causing the subsequent crisis. Business interests are also involved, as visible through attempts to commercialize (patenting) and through the involvement of companies in supplying crucial elements for the surgeries. Thus, as visualized in Fig. 3, the collective action consists of actors and their interactions, defined in terms of goals and imperatives, public-private interactions and funding.

The *common resource pool* consists of research centers linked to the StratRegen project, but given our focus on the crisis, our attention is on one of the centers, the ACTREM. This research center is the organizational basis for Paolo Macchiarini's activities at KI and KUH. A resource pool can be accessed by the actors singularly and collectively, and used to develop new scientific knowledge and also innovations. More broadly, ACTREM works in an international

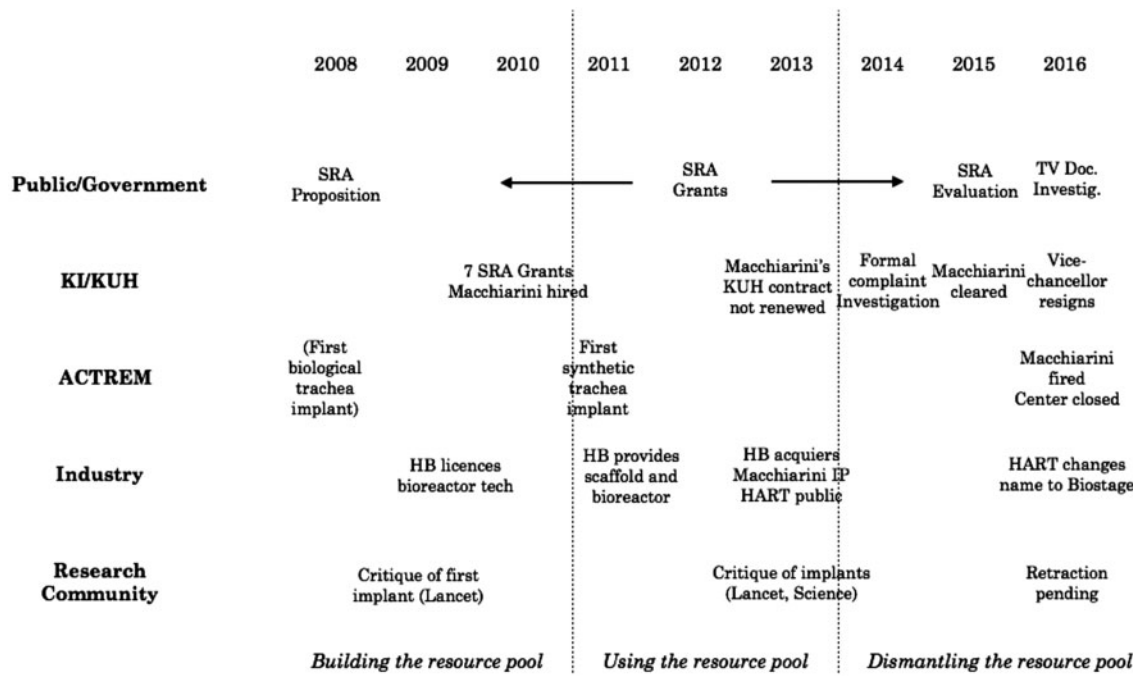


Figure 2. Sequence of major events 2008–16 in the rise and fall of the ACTREM center.

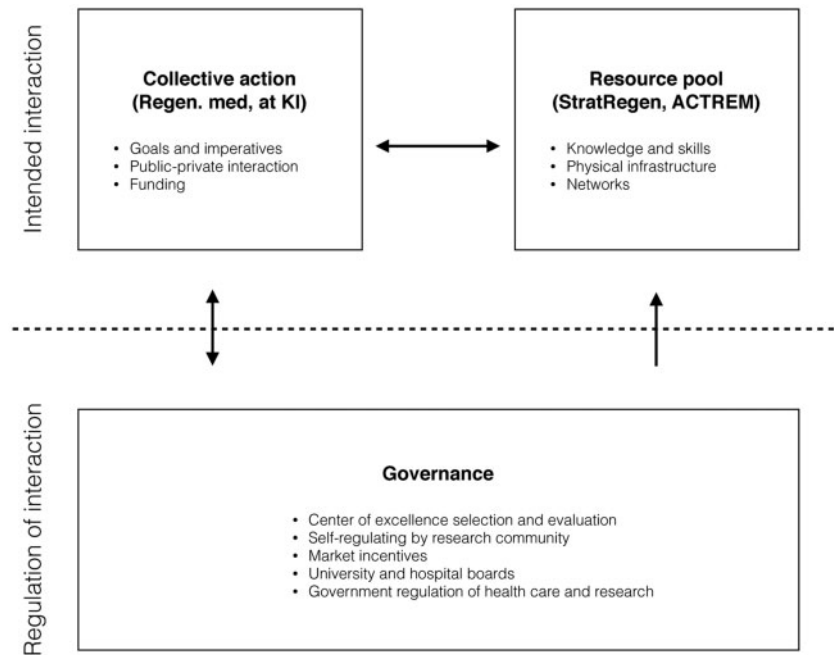


Figure 3. Interpretation of the case study in terms of the theoretical concepts of collective action, resource pool, and governance.

and local context, where KI also developed a wider set of capabilities in regenerative medicine, as illustrated in their reports to the government about how many different persons were involved. Engaging in the contested surgeries required access to a physical infrastructure of labs for stem cells, scaffolds, etc., as well as of hospital operating theaters. There were also networks locally, nationally, and internationally to not only obtain access to specialists but also to access patients. Thus, as visualized in Fig. 3, the common resource pool consists of knowledge and skills, physical

infrastructure, and networks needed to perform the operations using the synthetic scaffolds, and creating the possibility for their further development and wider adoption.

Governance is at the bottom half of Fig. 3, where we focus upon the regulation of the interactions rather than the interactions themselves. Governance is obviously a difficult challenge for policy makers, in this case. A striking observation from this case study is the sheer number and diversity of investigations that were initiated because of the crisis. Given that they arise during a crisis, they

highlight the multitude and complexity of the governance mechanisms related to the intended interaction.

In medicine, governance is needed for this type of collective action, in order to achieve cooperation as well as to regulate issues of social concerns, such as distribution of benefits and gains, public hazards, and ethical conduct. Some of the mechanisms, such as the process of selecting and evaluating centers of excellence and government regulation of health care and medical research, are top-down mechanisms where the government directly regulates the behavior of the participants. Other mechanisms, such as self-regulation by the research community and university and hospital boards, are self-regulatory, at least seen from the perspective of the policy maker. Commercial actors are involved, as well as patenting by a scientist and hence market mechanisms are also involved. Thus, as visualized in Fig. 3, the governance consists of a variety of elements to regulate intended interactions between the actors. We identify these as key: processes for selecting and evaluating centers of excellence receiving funding, self-regulating within research community, market incentives, university and hospital boards, as well as government regulation of health care and research.

6. Conclusions

The field of regenerative medicine in general—and our case study specifically—demonstrates a series of issues policy makers need to address, related to the governance of intended interaction of public and private actors for developing and sharing new knowledge. In concluding, we will identify and discuss four policy issues in relation to the results of our case analysis and selected literature related to the governance of research and innovation policy.

The first issue is about the complexity of governance. For research and innovation in regenerative medicine there is a myriad of governance mechanisms managed by different actors and addressing different aspect of the process. Few of them, however, are specific to the particular type of intended interaction. Each actor tries to enforce slightly different forms of governance on the others, which will promote their goals and imperatives. Thereby, one could say that each actor would like to recommend different sets of policy recommendations. The key point here is that the actors are linked through the intended interaction of creating world-leading research in regenerative medicine, which also has a societal impact through clinical practice and industrial innovation—a set of activities and interactions that require substantial self-regulation and alignment with a number of existing governance mechanisms, few of which that are specially designed for the task.

The second issue, from a public policy perspective, is that the government has a strong interest in promoting regenerative medicine for its expected economic benefits and contribution to employment, industrial innovation and competitiveness (Salter and Salter 2010). However, the government—and its agencies—play multiple roles. On the one hand, the Swedish government has singled out this high-prestige field, and thereby is attempting to push research and the university system in particular directions through selective large-scale funding. They are also expecting the knowledge generated to be shared and translated into industrial innovation and clinical use. On the other hand, the government is responsible for governance mechanisms that regulate the operation of university research, medical research (e.g. ethics committees), delivery of health care, and the introduction of new clinical procedures, including new drugs and medical devices.

Moreover, one problem for public policy makers is that existing governance mechanisms for research and clinical practice may not be well suited to address novelties related to regenerative medicine. We agree with Gardner and Webster (2016) who identify that one of the main translational challenge is the existing regulatory regime, which has been developed to govern drugs and medical devices, and is not well suited to regenerative medicine. As a consequence, there will be ambiguities in how the current regulatory framework should be applied, or extended, to address novel technologies, e.g. stem cell-based therapies, leading to iterative negotiation between clinicians and regulators when formulating quality and safety standards. Once the crisis is public it is difficult to acknowledge the existence of such negotiations, explaining the need and effort to find out what went wrong.

The third issue, from the perspective of the policy maker, is to understand the governance of the particular role of the university as an intermediary between the government and the individual research group. The university develops its own strategies, competes internationally, hires proficient researchers, etc., and is supposed to be actively promoting the values and norms of the international scientific community (autonomy, peer review, excellence). At the same time universities are reacting to funding and political pressure from the government and participating in intended interactions through collective action and the building of shared resource pools. In our case the pressure to perform is very high because, if successful, the university can expect a substantial increase in the base funding it receives from the government.

In the case study here, the strong financial incentives for excellence could be seen to have created tensions for the university. Scientific results might be controversial, especially if they belong to a fast moving and contested field, such as regenerative medicine. However, any uncertainties about the excellence of its research are unfortunate when the university is being evaluated. Thus, one interpretation of KIs continued support of Macchiarini, for months and years after outside organizations had retracted his access to patients (the hospital) and to research grants (public and private funding organizations), is that the university leadership had a strong incentive to promote and defend its activities within regenerative medicine, because of an national evaluation, which could provide an important source of funding and prestige in the national institutional context.

The fourth issue from the perspective of medical research and innovation is that experimentation of the kind performed by Macchiarini and his collaborators has a long history in medicine. Throughout history, new procedures have been tried out in the clinic before their implications have been fully understood. This experimentation has been based on cooperation between different organizations—specifically university, hospitals, and companies—and has, in retrospect, been considered very successful (Blume 1992; Rosenberg 2009; Schlich 2004). Different codes of conduct and ethical procedures have been developed for each of the actors involved in order to try to avoid negative outcomes, such as fraud, patient hazards, inhuman experimentation, etc. However, due to regulatory ambiguity and strong economic incentives, some studies suggest that these conditions may normalize action within organizations, either intentionally or unintentionally, that appears to outsiders as deviant (Hedgecoe 2014). KI's attempts to contain critique and to support their star scientist despite a mounting evidence of inappropriate behavior that had already resulted in the withdrawal of funding can be interpreted as attempts to normalize behavior that they, at least partially, considered important for successful medical research and

innovation, even if the behavior does not strictly follow the norms of science (Mulkay 1976).

In summary of the interactions between the above-mentioned issues, it is clear that investing large sums of money into strategic initiatives in highly competitive, fast moving, and prestigious field, and the hiring of start scientists can achieve policy goals of high scientific performance, and economic activities. However, such a policy also puts very high stakes and pressure for results, creates intense global competition for star scientists, and may open up for behavior by risk-taking individuals, that take advantage of regulatory ambiguities, to be normalized within prestigious organizations, despite being considered deviant by outsiders. Hence, we argue from the case study that if societal concerns and crisis are not—or cannot be—addressed, they may lead to a crisis of legitimacy for key actors and eventually the whole field supported by policy makers. Even later, after the crisis, when the problems and concerns that are identified have been addressed, there may remain a suspicion of whether or not the governance of for medical research and innovation is working slowing down the challenging task of translating new research findings into valuable clinical procedures.

Finally, for future research, we suggest a focus upon how policy affects risk-taking behavior and decision-making. One of the key insights from the case studied in this article is the awareness of how large-scale collective action, as in the case of the Swedish SRAs, creates strong incentives for risk-taking by multiple actors. From a governance perspective, the issue is how this risk taking can be regulated for each actor and for the medical research and innovation system as a whole, as well as how to deal with failures. More research is also needed about how governance mechanisms can be designed so that they encourage enough risk taking to develop radically new knowledge and innovation, while at the same time protecting the population against misconduct and fraud.

Notes

1. Swedish Energy Agency, Formas, Forte, Swedish Research Council and VINNOVA. All amounts are converted from SEK into EUR using the average currency conversion rate for 2010–14 as published by the Swedish Central Bank (www.riksbank.se).
2. In the documents and websites, the center has different names over the years, including StemKI, Center for Regenerative Medicine, and StratRegen.
3. The money was provided through the National Ministry SRA policy, which was in turn channeled through the Swedish Research Council.
4. Of the seven centers, the first six listed were visible on KI's website, as of March 2016. The seventh center, ACTREM, which had Macchiarini as director, was removed from the KI website and closed in February 2016.
5. A KI professor in this field also obtained an ERC grant in Spring 2016, but those sums is not included in the current calculations estimating the investment into regenerative medicine.
6. The ACTREM website was viewed and downloaded on 9 February 2016. The website might not have been current, as some publications were listed as in press in 2013. However it was updated with links to the KI investigation in 2015 finding him not guilty of research misconduct.
7. From the Swedish Research Council his group received 0.2 million EUR in 2011 for a 3-year project on an the bioengineering of the heart and 1.1 million EUR in 2012 for a 5-year project on the development of natural and bio-artificial

esophagus. From the Swedish Heart and Lung Foundation he received 0.17 million EUR in 2011 for a 3-year project on artificial heart.

8. In February 2016, fifteen articles in scientific journals were listed on the ACTREM website. Two articles were in *The Lancet*, listed as (2011 and 2013 in press) as well as articles in journals like *Biomaterials* and *The Annals of Thoracic Surgery*. Most of these articles focused on clinical research, i.e. reported outcomes from clinical procedures, rather than results from scientific laboratory experiments.
9. In late 2011 Macchiarini became the leading scientist of the International Scientific-Research Clinical and Educational Centre of Regenerative Medicine at the Kuban State Medical University in Krasnodar, Russia, where he, according to the documentary, also performed trachea implants at the university hospital.
10. In an written statement from 2014 Richard Kuylenstierna, who was responsible for ethical issues related to the first operation, stated that he had contacted the Medical Director at KUH, the Swedish Medical Product Agency, and the local ethics committee who advised that the decision was a matter of medical care ethics rather than research ethics (Gerdin 2015).
11. Most notable is the paper describing the outcome of the first implant (Jungebluth et al. 2011).
12. Asplund (2016: 129) comes to the conclusion 'the Macchiarini case demonstrates how one has selected informal rather than formal means for contacting the [regulatory] authorities. Some of those we have interviewed have seen this as an "infection effect" from KI, where there is a culture of cutting corners'. Furthermore, 'A number of academic leaders we have interviewed have reminded us that a lot of today's advanced surgery is based on bold actions by pioneers, even if it came at a cost of high initial death rates'. Hence, that cutting corners may be necessary for obtaining breakthrough knowledge.
13. HART was established as a separate unit in Harvard Bioscience in early 2009 and incorporated in May 2012. In a prospectus filed to the SEC in December 2012 it is reported that the company has acquired the intellectual property related to the bioreactor design used to create the landmark 2008 and 2011 tissue engineered implants (HART 2012). Early 2016, in the wake of the KI crisis, HART changed their name to Biostage (Biostage 2016).
14. The physicians claim that they informed Prof. Hamsten in February 2014 about their concerns and had series of meetings on the subject leading up to their Appeal for Investigation. Furthermore, they claim that they received a threat of immediate termination from KI in December 2014, apparently for having filed the allegations (Corbascio et al. 2015). They file another formal complaint shortly after. Both of these complaints were included in the investigation made by an external examiner on behalf of KI (Gerdin 2015).
15. According to his statement in social media, he says that he raised concerns as early as 2011 (via email to the then Vice Chancellor of KI).

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