The Invisible History of the Visible Sheep

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How a look at the past may broaden our view of the legacy of Dolly

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Executive summary

This report offers a new perspective on the legacy of Dolly the sheep by tracing the chain of experiments within which she was produced as the first cloned mammal in 1996. We argue that the media storm that followed her birth, with intense debates about the ethics of escalating the technology and obtaining exact copies of humans, obscured the underlying motivations of the experiments and the important role that the cloning technology has later played in stem cell research and regenerative medicine. By adopting a historical perspective, we show that Dolly should be placed within an established research project that started in the early-to-mid 1980s and sought to genetically modify – rather than copy – farm animals. She was not the start, neither the conclusion of the project, this suggesting that we need a broader framework to fully capture her impact. When, instead of Dolly, we focus on the genetic modification research within which she was produced, the ramifications of that project go as far as recent efforts to sequence the genome of the pig and use that information as a model of human biology and disease. We conclude that historical studies may help to chart the long-term impact of scientific projects, especially when they have been funded by different administrative agencies, due to their outputs spanning disciplines and species.

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Front cover image courtesy of the Roslin Institute.

1. Introduction

Dolly the sheep is regarded as one of the most iconic experimental animals of recent biomedicine. In July 1996, she became the first mammal to be born after the introduction of the cell nucleus of an adult sheep into an egg devoid of its nucleus (in normal reproduction, the egg nucleus contains half of genetic material of the newborn – coming from the mother – while the other half is provided by the father's sperm cell nucleus). Due to the lack of nucleus in her egg, Dolly was not a pool of her two parents: she rather shared 100% of genetic material with another sheep – the donor of the adult cell nucleus that had been transferred to the egg. She was thus a clone or a genetic copy of an existing adult sheep.[1]

Dolly was born at the Roslin Institute, a scientific centre six miles south of Edinburgh with a long tradition of animal breeding research that was largely supported by the UK Biotechnology and Biological Sciences Research Council (BBSRC) and its predecessor public funding bodies. In February 1997, days before the landmark publication in Nature (Wilmut *et al*, 1997), the scientists involved were surprised by an unexpected report in The Observer – they had intended to keep Dolly secret until the scientific article was out. The Roslin Institute then decided to organise a public presentation that attracted an unprecented level of media attention and stimulated far-reaching debates about the use of the technology – named 'nuclear transfer' within the scientific community and 'cloning' by the media. Given that Dolly was a genetic copy of another sheep, much of the public debate focused on the possibility of replicating the experiment in other species (Suk *et al*, 2007). The media and their audiences regarded with reservation this potential spread of the technology, especially to higher animals. In the months following Dolly's presentation, a consensus grew among scientists, society and policy-makers on the necessity of setting ethical boundaries and regulating the technology in order to avoid the potential cloning of humans.[2]

These debates were mainly speculative and addressed the imagined future uses of nuclear transfer (Holliman, 2004). Media and public imagination concealed both the limitations of the technology at the time of Dolly's birth and, more crucially, the reasons why the Roslin researchers wanted to clone a sheep. While Dolly is an almost universally known scientific figure, the logic and motivations behind her creation are rarely brought up, even within the scientific community. This asymmetry of knowledge becomes more pressing when we look at the experiments that both preceded and succeeded Dolly: cloning was not the final objective of the Roslin scientists and in the months following the public presentation, they produced additional sheep that went largely unnoticed. Instead of being copies of adult cells, these sheep had been genetically modified to incorporate features that were absent in their ancestors and valuable from a commercial viewpoint. In other words, the cloning of Dolly was not an end in itself, but a means for producing sheep that possessed unique genetic modifications rather than being identical to other animals.

Dolly's history has been particularly difficult to trace due to this lack of knowledge. Given the secrecy of her birth and subsequent simplification of media accounts, only a small group of insiders know the complex chain of experiments that sorrunded her creation. Dolly and nuclear transfer were neither the beginning nor the end of these experiments. With this in mind, in 2015 the BBSRC and the University of Edinburgh funded *Historicising Dolly*, a project to place the cloned sheep within a broader context of animal genetics research. Throughout 18 months, we organised a Collective Memory Event in which we gathered the scientists and stakeholders involved in the cloning experiments, recorded their recollections and made them publicly available in written and electronic form (Myelnikov & Garcia-Sancho, 2017)[3]. We also published two academic papers that reconstructed the line of research through which Dolly was produced and showed that the first experiments can be dated back to the early-to-mid 1980s (García-Sancho, 2015; Myelnikov, forthcoming). Our work portrays Dolly as the product of a long-term scientific project that was funded over more than a decade by the BBSRC and its institutional predecessors, the Agricultural Research Council (ARC) and the Agricultural and Food Research Council (AFRC) see table overleaf. The aim of that project was to genetically modify farm animals and use them to produce drugs for the treatment of human conditions. Cloning and nuclear transfer were just tools to achieve genetic modification rather than the ultimate objective of the experiments.

1 This adult sheep was not alive at the time of Dolly's birth, since scientists decided to use the nucleus of an adult cell that had been frozen and preserved years after the donor's death. Sharing 100% of genetic material meant that Dolly looked much alike the donor of this frozen cell, although behaviour and other characteristics are not determined by genes only: they rather derive from complex interactions between genes and the environment.

2 See, for example, "The cloning of animals from adult cells," fourth report of the UK Parliamentary Committee on Science and Technology, Session 1996-1997. See http://www.publications.parliament.uk/pa/cm199798/cmselect/cmsctech/1039/103903.htm (last accessed May 2017).

3 Electronic version available at http://www.research.ed.ac.uk/portal/en/publications/dolly-at-roslin(59056ace-04a4-4019-b033-936cd7297f71).html. The third author of this report, James Lowe, is currently investigating the history of the pig genome project, an international initiative that was conducted between 1990 and 2012. The Roslin Institute was a major contributor to this initiative and developed some of the technologies that made it possible out of the same project within which Dolly was produced. Lowe's work is supported by an ERC Starting Grant led by Miguel García-Sancho, the Principal Investigator of the Historicising Dolly project. For more information about the ERC grant see www.stis.ed.ac.uk/transgene (both links last accessed May 2017).

Due to the lack of nucleus in her egg, Dolly was not a pool of her two parents: she rather shared 100 % of genetic material with another adult sheep.

Building on our historical research, this report reflects on Dolly's legacy. Our work has enabled us to look in detail at the events that preceded Dolly and place the significance of her birth beyond the confines of cloning and the public debate it fostered. In order to capture this broader significance, it is essential to move the level of analysis out of Dolly and the nuclear transfer technology. In our research, we did not directly address the Dolly furore of 1997. Instead, we shifted our object of inquiry a decade back and investigated the previous genetic modification project. This enabled us to see a set of technologies, animals and goals within which Dolly and cloning were essential but rather time-specific parts. When Dolly is assessed against this wider horizon, the ramifications of the research that preceded her birth become far-reaching.

In what follows, we will use this interpretative framework to analyse what happened after Dolly. We will show that the impact of this piece of science – on both medicine and agriculture – can be seen more clearly when taking into account the project that led to Dolly's creation. To this end, the next section will review the long-term line of research that shaped the cloning of Dolly, the so-called pharming project. This project culminated at the Roslin Institute, but started and consolidated at two of its institutional predecessors, the Animal Breeding Research Organisation (ABRO, 1947-86) and the Institute of Animal Physiology and Genetics Research (IAPGR, 1987-93, see table below). We will then look at the main ramifications of the pharming project and how it informed research fields that are still highly influential in Roslin and beyond: stem cell science and animal genome analysis. The report will close with some considerations about the utility of history in scientific planning and policy. We will argue that historical research may show scientific continuities across time periods and institutional spaces that are administered by different funding agencies.

Summary of the different institutional antecedents of the Roslin Institute and BBSRC

Institution	Funding agency	Research project examples	Celebrity animals
Animal Breeding Research Organisation (ABRO), 1947-86	Agricultural Research Council (ARC), 1931-83	*Hereford* breed (long-term programme involving crossing of various generations of cows) Causes of scrapie (sheep disease)	None
Institute of Animal Physiology and Genetics Research (IAPGR), 1987-1992	Agricultural and Food Research Council (AFRC), 1984-1993	*Pharming* (production of transgenic sheep) *PiGMaP* (mapping of porcine genome)	*Tracy* (1990, genetically modified sheep)
Roslin Institute, 1993 onwards	Biotechnology and Biological Sciences Research Council (BBSRC), 1994 onwards	*Pharming* (production of transgenic sheep) *PiGMaP* (mapping of porcine genome)	*Megan and Morag* (1995, sheep cloned from embryo cells) *Dolly* (1996, sheep cloned from an adult cell) *Polly* (1997, both transgenic and cloned sheep)

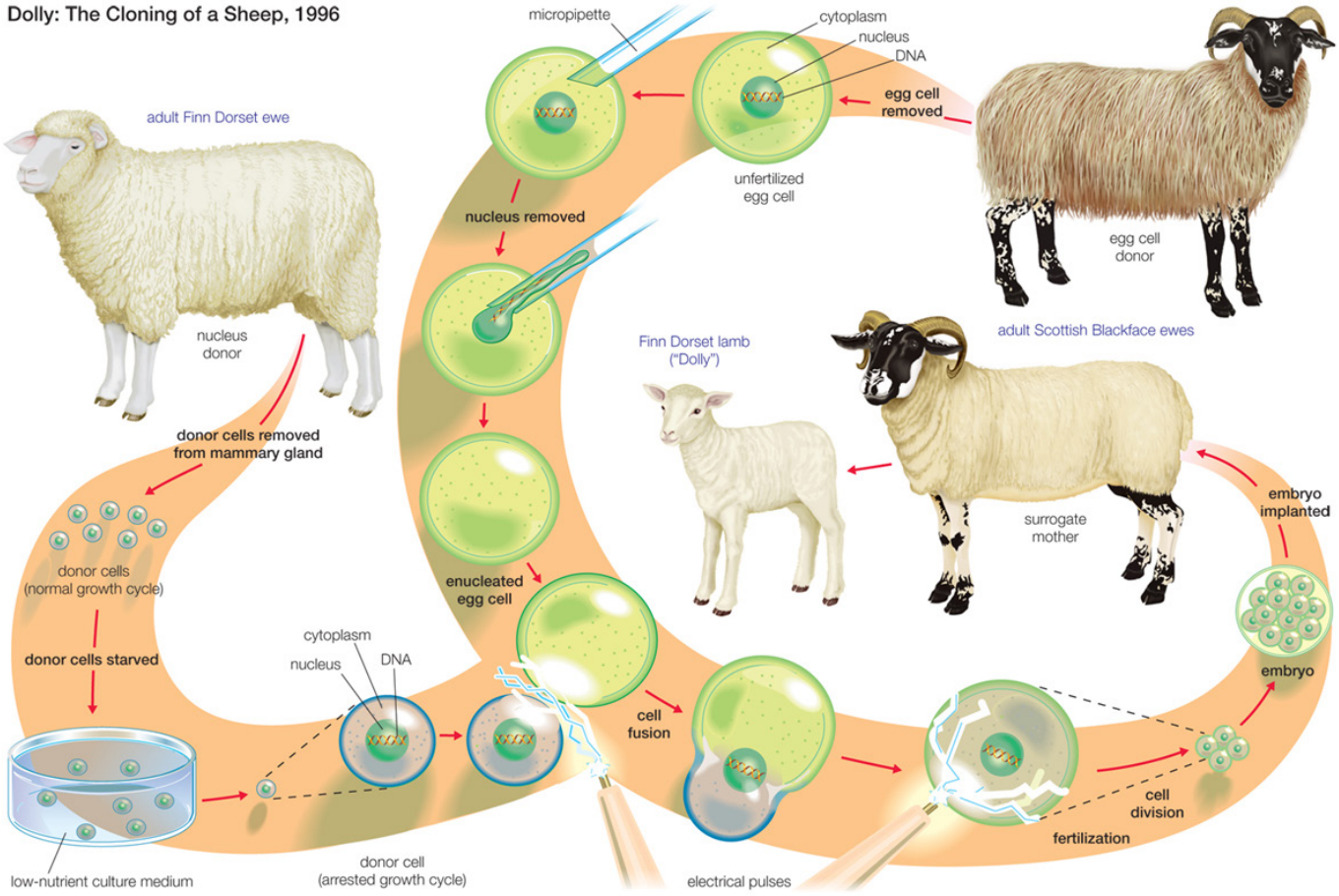

Figure 1: A scheme of the nuclear transfer technology.

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2. Dolly in history: genetic engineering and the Rothschild reform

The birth of Dolly was a step in a long-term research project that started in 1984 and culminated in 1997 with the birth of another sheep called Polly.[4] The first institutional home of this project was the Animal Breeding Research Organisation (ABRO), an institution that had been set in Edinburgh in 1947 with the aim of creating scientific knowledge to improve the commercial yield of livestock. ABRO had benefitted from sustained funding by the Agricultural Research Council (ARC), a body of the British Government that had been established in the 1930s and, following the persistence of rationing policies after World War II, had developed a UK-wide network of experimental stations to improve the productivity of agriculture (DeJager, 1993; Thirtle *et al*, 1991; Vernon, 1997). During its early years, ABRO enjoyed growing popularity among farming associations and designed extended, multi-generational breeding programmes that improved the health and food production of pigs, cattle and sheep (see table above). However, a number of socio-political transformations in Britain led to growing government scepticism about the utility of these contributions.

The changes started in 1971 with the publication of the Rothschild Report, commissioned by Edward Heath's Conservative government with the aim of improving the efficiency of public administration. The report was authored by Victor, 3rd Baron Rothschild, a former chairman of the ARC who had subsequently served as head of research of Shell, the oil-and-gas company. Controversially, Rothschild argued that publicly-funded research in the UK had served abstract, academic interests rather than the real needs of the country. He proposed a customer-contractor principle, in which government departments would decide how to spend a large proportion of the Treasury's budget for scientific research (Calver & Parker, 2016). This Government budget – called the science vote – had traditionally been split among the research councils and further distributed to universities and institutes in the form of grants. The councils' research institutes had been asked to plan their research activities over long periods of time and received block grants that were reviewed against scientific progress. It had been the ultimate responsibility of the scientists in charge of the institutes to decide how to spend the grants on a day-to-day basis.

After the implementation of the Rothschild model, the research councils' budgets were split between the science vote – that could still be directly spent in grants – and funds that needed to be requested to ministries and government departments. These public bodies would act as informed customers and support applied projects in which the research institutes would play the role of contractors. The funded projects were necessarily shorter-term and assessed against the timely delivery of concrete outputs, not just scientific progress. Rothschild was one of the first persons to apply the corporate term 'R&D' to publicly funded science. His model was founded on a sharp distinction between 'fundamental' and 'applied' research (Rothschild, 1972), with the former being left untouched by his reforms but given a substantially lower proportion of the research councils' funds: after the Rothschild Report, only about half of those funds could be spent on long-term projects with purely scientific objectives. The expenditure of the other half was conditioned to the formalisation of applied research contracts between the government, the councils and their institutes.

The agricultural sciences were one of the priority areas of Rothschild's reforms. His experience as head of the ARC had persuaded him that this institution was one of the main culprits of the perceived lack of impact of British science (Parker, 2016). Due to this, a significant part of the ARC budget was transferred to the Ministry of Agriculture, Fisheries and Food (MAFF), while other public bodies enjoyed greater flexibility to apply the customer-contractor principle – the Medical Research Council (MRC) managed to reverse it and recover direct control of most of its budget in the early 1980s (de Chadarevian, 2002, ch11; Wilkie, 1991, ch5). By that time, British society had substantially changed and the nutrition problems derived from World War II had long been forgotten. This made the ARC's scientific agenda, which was still significantly framed in augmenting the amount of food via animal and plant breeding, unappealing to an increasingly affluent and urban population.

Margaret Thatcher's election as Prime Minister in 1979 deepened Rothschild's reforms. Thatcher had been Secretary of State for Education and Science under Heath's Government and, despite being ambivalent about the 1971 Report, she saw in Rothschild's dual funding system an opportunity to keep supporting fundamental research – even with decreasing budgets – while reducing the cost and increasing the impact of applied science (Agar, 2011). Within agricultural research, this meant downsizing the

4 In this report, we will offer a very brief outline of the scientific project that led to the birth of Dolly, Polly and other experimental sheep. For a broader discussion of this project, its establishment and development up to the mid-1990s see García-Sancho, 2015.

5 One of our published papers offers a detailed analysis of both the ARC and ABRO's response to the political turmoil of 1970s and 80s Britain (Myelnikov, forthcoming). It suggests that the ARC's decision of focusing on a few strategic lines of research preceded any dramatic impact of Rothschild and Thatcher's reforms on its budget.

multi-generational breeding programmes requiring large and expensive amounts of farmland, and replacing them with more selective variation of a few animal species. In 1982, the ARC produced a strategic briefing that reflected this new philosophy and argued against a blanket cut of their breeding programmes in the face of financial hardship. Instead, the shrinking resources would be devoted to a few 'priority areas' with the potential of transforming the practice of breeding (ARC, 1982).[5] Shortly after this decision, in response to pressure from multiple advisory committees, the ARC changed its name into Agricultural and Food Research Council (AFRC), emphasising its move away from production and into areas such as food processing or storage.

In the turmoil of 1980s Britain, genetic engineering was regarded as an innovative field with potential of transforming traditional breeding research and making it less resource-intensive.

The ARC's plans originally involved reducing ABRO's activity by 80%. However, intervention from the farming sector, media, MPs and MAFF – now a key customer – meant the cuts were in fact 50%. ABRO's experimental farms outside Scotland were sold, early retirements implemented, some staff were made redundant and the funding of its research teams and programmes was dramatically reduced. This made clear that ABRO's research strategy needed to be redesigned in line with its smaller stock of land, animals and staff. ABRO's internal reports describe this transition period as a 'dramatic time' that 'inevitably left its scars.' They also acknowledge that some researchers interpreted the reforms as a "betrayal" of their hard work.[6]

In 1982, Roger Land was appointed as the new director of ABRO. He was in charge of navigating the ARC cuts and decided to focus on genetic engineering, which was then regarded as an innovative field with potential of transforming traditional breeding research. The techniques to cleave and reassemble genetic material had been invented in the mid-1970s under the name of recombinant DNA and tested in microorganisms (Rasmussen, 2014; Yi, 2015). Shortly before Land's appointment, they had been exported to mice and their application to agriculture had triggered growing expectations (Smith *et al*, 1986). In its strategic briefing, the ARC had set genetic engineering of plants as one of its priority areas. Land saw the expansion of this technique to animals as a niche and established a molecular biology programme at ABRO that was headed by two new recruits: Richard Lathe, a former worker of the French biotechnology company Transgéne, and John Clark, a geneticist with experience in the MRC Clinical and Population Cytogenetics Unit of the neighbouring University of Edinburgh.

The new programme materialised in a number of specific lines of research during the mid-1980s. One of the pioneering lines was called the pharming project and involved the use of recombinant DNA to produce genetically modified sheep. These sheep would carry in their DNA an extra, foreign gene that was absent in their parents. The additional gene would enable the modified sheep to express in their milk proteins to treat human illnesses.[7] Up to then, most of the genetic modification of farm animals had focused on increasing their size and therefore the amount of food they produced via inserting extra copies of the growth hormone gene – with little progress. With the pharming project, Lathe and Clark saw a new area of application that would enable them to commercialise the proteins in the form of drugs for human consumption. To this end, ABRO created a start-up biotechnology company called Caledonian Transgenics and soon renamed Pharmaceutical Proteins Limited, or PPL (Clay & Goldberg, 1997; Fransman, 2001).[8]

The pharming project became one of the few lines of research that survived increasing financial stringency. In 1987, the same year Caledonian Transgenics was founded, ABRO was forced to merge with another AFRC-supported institution, the Institute of Animal Physiology in Babraham, Cambridgeshire. This resulted in a large organisation called the Institute of Animal Physiology and Genetics Research (IAPGR), with two autonomous stations, one located in Edinburgh and the other in Babraham. The merger involved further redundancies of technical and administrative staff, as well as the eventual relocation of the Edinburgh Research Station from Edinburgh University's natural science campus – the King's Buildings – to Roslin. However, the pharming team benefitted from the Transgenic Animal Programme, a new funding stream the AFRC created to support work on genetic modification and stem cell research. By that time, Lathe

6 Quotes from ''Comment'', ABRO Annual Report—January 1983, p. 3 and ''Preface'', ABRO Annual Report—January 1986, p. 1. Wellcome Trust Towards Dolly archival project, Edinburgh University Library Special Collections, reference EUA IN23/1/1/2.

7 For a detailed description of the pharming project, its development and the events leading to its implementation see García-Sancho, 2015: 291ff. See also R. Lathe: "Molecular tailoring of the farm animal germline," ABRO Annual Report – January 1985, pp. 7-10. Wellcome Trust Towards Dolly archival project, Edinburgh University Library Special Collections, reference EUA IN23/1/1/2.

8 The establishment of Caledonian Transgenics was supported by venture capital raised by the Scottish Development Agency, a public body now called Scottish Enterprise and devoted to promote new business initiatives in Scotland (Myelnikov, forthcoming). The pharming approach – also known as biopharming – was also applied to plants and mobilised both scientific and commercial expectations (Milne, 2012).

had left Edinburgh and Clark become head of the molecular biology programme.

With this support, Tracy, the first genetically modified sheep to make significant quantities of a human protein, was born in Roslin, in 1990. Her DNA contained an extra gene that produced alpha-1-antitripsin (AAT), a protein used in the treatment of emphysema and cystic fibrosis. The production of the sheep was rather cumbersome and involved the injection of the foreign gene into Tracy's embryo. This process required additional expertise in the pharming team, in the form of tissue culture and veterinary professionals who surgically extracted the embryo, performed the gene's microinjection and re-implanted it into a surrogate mother.[9] Due to this, although the levels of protein expression in Tracy's milk were beyond the expectations, its production process was not suitable for an industrial development that would enable PPL to mass-produce drugs. The pharming project started diversifying in search of solutions and this led the team to move into new research areas.

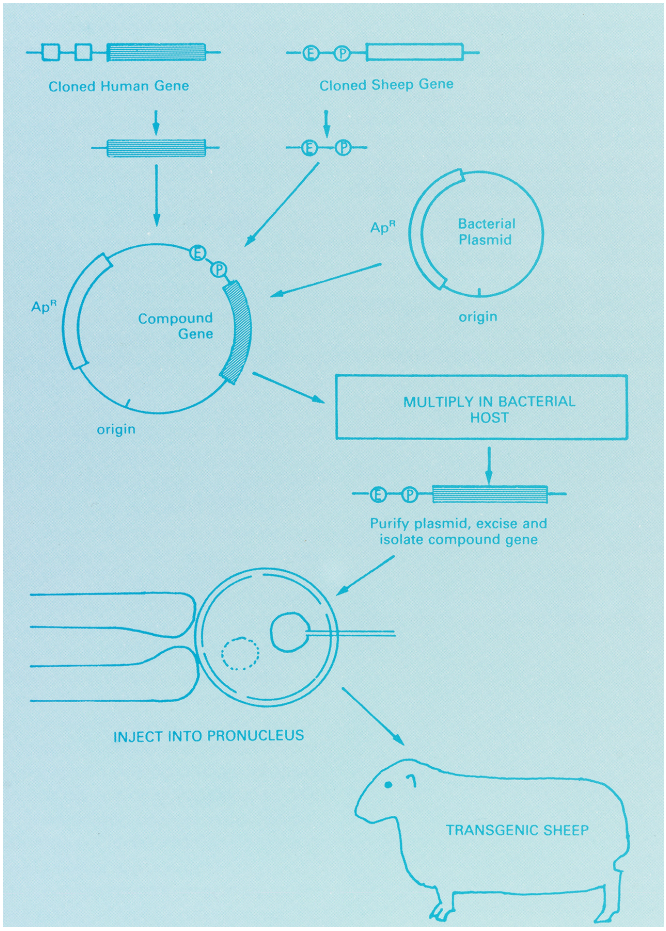

Figure 2: A schematic representation of the pharming project.
ABRO Annual Report – January 1986, p.22, reprinted with permission from Edinburgh University Main Library.

Tracy, the first transgenic sheep produced in Roslin.
Courtesy of the Roslin Institute.

9 For an account of Tracy's creation, see the printed volume of our Collective Memory Event, which names the full range of scientists and professionals involved in her creation (Myelnikov and Garcia-Sancho, 2017: 5ff). Also available at http://www.research.ed.ac.uk/portal/en/publications/dolly-at-roslin-a-collective-memory-event(59056ace-04a4-4019-b033-936cd7297f71).html

3. The ramifications of the pharming project

The Roslin scientists reacted in different ways to the difficulties in creating Tracy. Whereas some developed alternative techniques to produce genetically modified sheep and achieve the objectives of the pharming project, others applied the expertise that the project had already produced to new research areas. In what follows, we will focus on cloning as an example of the former strategy (develop alternative techniques) and animal genomics as representative of the latter (exportation of existing expertise to new fields). The most visible outcome of the pharming project was the cloning of Dolly in 1996, given that the drugs for human consumption it originally envisaged were never delivered on a commercial scale. However, towards the late 1990s, the same nuclear transfer technology that enabled the birth of Dolly started playing a crucial role in stem cell research and human regenerative medicine. This and the sequencing of the genome of farm animals such as cows and pigs can be seen as the main legacy of the pharming project; one that has been eclipsed by the publicity around the cloning of Dolly.

3.1 Cloning and stem cell research

Following the birth of Tracy, the pharming team started looking for a method that would increase the level of both successful birth and assimilation of genetic modifications by newborn transgenic animals. The team concluded that a promising avenue was introducing the genetic modification before rather than after the fertilisation of the sheep egg, thus avoiding embryo microinjection. A favoured procedure within this approach was using stem cells that had not differentiated during the development of the animals from embryo to adult form. If those cells were genetically modified and inserted into an egg, they would have the sufficient plasticity to express the extra, foreign genes during the development of the newborn animal. The production of genetically modified mice had been considerably eased and improved with the use of stem cells in the early-to-mid 1980s (Myelnikov, 2015, chs4-5). This type of cells were yet difficult to isolate in sheep.

The first role of nuclear transfer in Roslin was to complement the stem cell approach. The technique would enable the insertion of the genetically modified stem cell nucleus into an oocyte – unfertilised egg – thus producing the transgenic sheep. Ian Wilmut, a developmental biologist who had previously worked on embryo transfer to improve the birth rate of cows, sheep and pigs, was the person in charge of the development of this technology. He teamed up with Keith Campbell, a cell biologist who joined Roslin in 1991 to investigate how normal development could be reprogrammed. The objective of both scientists was to transform the stem cell nucleus into an embryo cell that could be assimilated by the oocyte and trigger the development of a newborn sheep (Myelnikov & Garcia-Sancho, 2017: 9ff).

> The first role of nuclear transfer in Roslin was to ease genetic modification rather than producing exact copies of sheep.

Due to the intricacies of this developmental process, Wilmut and Campbell decided to first test the technology without introducing any genetic modification. Out of these experiments, two sheep called Megan and Morag were born in 1995. Unlike Tracy, Megan and Morag were cloned animals, in the sense that their genetic material was an exact, unaltered copy of another sheep. However, the cell nuclei from which these two clones had been created belonged to a sheep embryo rather than an adult animal. This choice of nuclei was motivated by the difficulties of isolating stem cells after full sheep development: Wilmut and Campbell settled on embryo cells as the most equivalent available material (Campbell *et al*, 1996). By the time of these births, the IAPGR had been disbanded, and the Babraham and Edinburgh Research Stations become independent institutions again. The Edinburgh Station acquired its current denomination of Roslin Institute in 1993 and one year afterwards, the AFRC absorbed the biological component of the Science and Engineering Research Council to form the BBSRC.

The birth of Dolly was a more challenging interrogation of the nuclear transfer technology. Wilmut and Campbell managed to completely reverse and reprogram the development of an adult cell once inserted into the oocyte. This showed that the technology could work with any cell and overcame the difficulties of both working with embryos and obtaining sheep stem cells. The cell from which Dolly was cloned belonged to the mammary gland of an already deceased sheep. It had been isolated and frozen by the company PPL, which since its foundation had formed a team of experts in cell culture and preservation with the aim of accelerating the delivery of the pharming project. Dolly was kept secret for six months after its birth in July 1996, in order

Figure 3: The team in charge of the development of the nuclear transfer technology (in the top row, Wilmut is second from the left and Campbell first from the right). *Courtesy of the Roslin Institute.*

Megan and Morag. *Courtesy of the Roslin Institute.*

to protect the novelty of the Nature publication (Wilmut *et al*, 1997). After her presentation, the media furore arose and Wilmut gradually became the spokesperson for the experiments and, in the eyes of the public, the father of Dolly the sheep.

Dolly, as the first genetic copy of a fully developed sheep, superseded the popular fascination of Megan and Morag. The media storm, along with the increasing attention to Wilmut, focused the public debate on cloning and de-emphasised the other objectives of the pharming team. This was helped by the semi-autonomous status of the nuclear transfer experiments from a financial viewpoint. While the BBSRC funded the core of the pharming project – the genetic modification of sheep, as well as some early work on cell culture – research on nuclear transfer required additional support from PPL and the Ministry of Agriculture, Fisheries and Food (MAFF). This led the media and their audiences to regard cloning as a self-contained project rather than as a means for genetic modification. The group in charge of the nuclear transfer technology became increasingly independent from the pharming team and acquired its own interests, such as embryo development and stem cells. Furthermore, MAFF was not keen on being identified with genetic modification at a time in which the debate around GM crops was reaching its climax (Wynne, 2001).

A few months after the presentation of Dolly, six other sheep were born in Roslin. They were both cloned and genetically modified, in the sense that their embryos had been produced through the transfer into an oocyte of a cell nucleus to which a foreign gene had previously been added. The most promising of them was called Polly, a sheep that secreted in its milk the protein Factor IX, used in the treatment of haemophilia. This protein was derived from the insertion of an extra, human gene in Polly's DNA (Schníeke *et al*, 1997). Despite Polly representing the culmination of the pharming project, its birth went largely unnoticed: the media discussion remained focused on Dolly and cloning, without any significant mention of other sheep or the phenomenon of genetic modification. It is rather laborious to find descriptions or pictures of Polly, even in the research reports and internal publicity of the Roslin Institute.

Polly's birth was closely monitored by PPL, in the hope that Factor IX could be recovered from the milk and transformed into a commercial drug for human consumption. However, as in the case of Tracy, this development was hindered by practical problems: the levels of protein expression were tight for industrial drug production and the company found innumerable difficulties in clinical trials (Myelnikov & Garcia-Sancho, 2017: 19ff). In the face of this, the Roslin Institute created another start-up company to expand the commercial horizons of the pharming project. The new company, named Roslin BioMed and founded in 1997, would explore alternative applications of both the genetic modification and nuclear transfer technologies. PPL retained the specific patent that allowed the development of drugs from milk proteins.[10]

Shortly after the creation of Roslin BioMed, a team at the University of Wisconsin isolated the first human embryonic stem cells. These cells were derived from human embryos

10 After numerous attempts with sheep and pig, no commercial applications were found out of the pharming project and PPL ceased to exist in the mid-2000s (Reid and Smith, 2006). Other companies, namely Pharming in the Netherlands, commercialised human milk products out of this procedure. In 1990, Pharming produced Herman the bull, the first genetically modified bovine (Myelnikov and Garcia-Sancho, 2017: 7).

and had the same properties as in mice and sheep: due to their plasticity, they could become any tissue in adult form. The cells' plasticity meant that they could potentially be used in human medicine to regenerate any damaged tissue. Following a cardiac arrest or knee injury, patients could be inoculated with stem cells around the affected area, and they would develop into heart muscle or cartilage (Thomson *et al*, 1998). The efficiency of the new therapy was even greater if an adult cell nucleus from the patient was obtained and inserted into an oocyte to form an embryo. Sourcing stem cells from that embryo helped avoid immune rejection after patient's inoculation.

The Wisconsin team was funded by the US pharmaceutical company Geron. This company saw in the nuclear transfer procedure developed by Wilmut and Campbell an opportunity of complementing regenerative therapies with embryo cloning of patients' cells. In 1998, the year the Wisconsin group isolated the first stem cells form human embryos, Geron decided to acquire Roslin BioMed – only a few months after the foundation of the latter company. In exchange, Geron provided a five-year grant to the Roslin Institute that would fund any aspect in the investigation of cell development. This led Roslin to become a reference centre in developmental biology and stem cell research, and gradually shifted Wilmut's career from agricultural science to regenerative medicine.[11]

The US pharmaceutical company Geron saw in the nuclear transfer procedure an opportunity of complementing regenerative therapies with embryo cloning of patients' cell nuclei.

By the end of the 20th century, nuclear transfer was thus recast from a procedure to make genetically modified animals to a means for obtaining human embryonic stem cells. The scaling-up of cloning from sheep to humans was finally achieved, but not in the way the media and their audiences imagined. Far from being used as a reproductive technique – to create babies identical to adults – cloning was a source for obtaining embryos that would provide compatible stem cells for patients. In 2008, Shinya Yamanaka at the University of Kyoto developed a technique to produce pluripotent stem cells without the necessity of creating embryos. That same year, Wilmut announced that he would stop using cloning and became a founding Director of the Edinburgh Centre for Regenerative Medicine (Wilmut *et al*, 2011). Unlike the Roslin Institute, this new centre was focused on human medicine and fell into the remit of the MRC rather than the BBSRC. The association of stem cells with human patients led regenerative medicine to be identified with the MRC and partially eclipsed the role of the BBSRC in the emergence of this new field.

3.2 Farm animal genomics

The advent of genomic techniques in Edinburgh has roots in both the older animal breeding tradition of ABRO and the newer molecular orientation introduced following the reconfiguration of the programme of research at that institution in the early 1980s. As discussed above, financial stringency threatened ABRO, to the extent of this institution fearing closure. Within this uncertain context, informal debates between the Edinburgh scientists centred on the nature and direction of the envisaged research reconfiguration (Myelnikov & Garcia-Sancho, 2017: 8ff). Some, such as Clark's postdoctoral researcher, Alan Archibald, proposed giving an autonomous role to genome analysis of farm animals. However, until the late 1980s this line of research was rather subordinate to the pharming project: DNA mapping techniques were seen as tools for identifying genes that would produce transgenic animals.

In the aftermath of ABRO's reconfiguration, Archibald was successful in obtaining a research commission from MAFF to investigate the genetics of halothane sensitivity in pigs, having previously worked on cattle. Halothane is a veterinary anaesthetic that had been found to be connected to Porcine Stress Syndrome (PSS). During the early and mid-1980s, PSS had become a major problem in the food industry, leading pigs to suddenly die, and their meat to become pale, soft and exudative, and therefore unattractive to consumers. This problem had partially been caused by breeding techniques to reduce back fat, driven by consumer demand for leaner pork meat in Europe and North America from the second half of the 20th century.

In theory, using halothane as a test could enable breeding companies and farmers to exclude susceptible – halothane sensitive – pigs from breeding. However, given the impracticalities of this test and the fact that this was a recessive trait – it could be transmitted to offspring by

11 Campbell, on the contrary, continued producing genetically modified animals. He became a PPL scientist and led further attempts to commercialise the pharming procedure in the US. In 1999, he moved to the University of Nottingham and died prematurely thirteen years afterwards.

Figure 4 left: First meeting of the PiGMap project, held in Edinburgh in 1991 – Alan Archibald is wearing a Scottish kilt on the left. Right: The project's logo. *Courtesy of A. Archibald.*

apparently non-sensitive pigs – alternative means of removing this characteristic were sought. As with the human medical geneticists who in the mid-1980s attempted to identify and map disease genes (Lindee, 2005), it became a pressing matter for the livestock and breeding industries to identify the genetic basis of halothane sensitivity and PSS.

Halothane sensitivity was identified as a single-locus trait – i.e. connected to one gene and occupying a defined region of the chromosome. Of particular interest to the geneticists was the relationship of this gene with nearby genes, or linked genes that tend to be inherited together. If the relationships between the halothane sensitivity locus and other loci in the same chromosome could be established, then inferring susceptibility to PSS would be easier. The detection of linked genes or other biochemical markers – observable characteristics connected to these genes – could lead to the development of a more practical test than the application of halothane, and therefore allow farmers and breeding companies to eliminate the trait from herds.

With a number of researchers working on this problem across Europe and North America, linkage relationships were established, the condition was attributed to a particular mutation in a specific gene and biochemical tests for blood markers were developed. This offered breeders the opportunity to manage the responsible gene, and eradicate it if they so wished (O›Brien & MacLennan, 1991; O'Brien & Ball, 2013; Otsu *et al*, 1991). Thus the mapping of the linkage relationships between genes had enabled the livestock industry to put into practice a more precise and effective means of selection for animal breeding. Combined with the inspiration of the nascent work in human genetic mapping (Harper, 2008, ch7), this provided impetus for the Edinburgh-based researchers and their colleagues to press for a more general mapping approach to the pig genome.

A substantial part of this approach crystallised in the first European farm animal genetics conference, held in Edinburgh in 1989. In this conference, many of the participants in the work on halothane sensitivity helped to develop a plan to research two types of pig genome map: 1) a genetic map showing the position of linked genes on the chromosomes and 2) a physical map dividing the chromosomes into an ordered set of overlapping DNA fragments. Archibald and Chris Haley, of the Edinburgh Research Station (ERS) of the IAPGR, subsequently applied for and obtained grants from the AFRC and MAFF, in collaboration with their colleagues at the Cambridge Research Station, Elizabeth Tucker and Ross Miller.

In addition to this, a proposal was developed for a project named PiGMaP, with the cooperation and support of Hervé Bazin, a scientific staff member in the Directorate-General for Science, Research and Development of what was then the Commission of the European Communities (CEC). PiGMaP co-ordinated 11 European laboratories and obtained 1.2 million ECUs funding from the BRIDGE programme, part of the Second Framework Programme of the European Commission. The proposal started in 1991 and was based on flexible collaboration between the participants, following the model of European Laboratories Without Walls (ELWW).[12]

In Edinburgh, the work involved genetic linkage mapping

12 A.L. Archibald and E.M. Tucker: "Genome analysis," IAPGR – Annual Report 1990-91, pp.126-27 Wellcome Trust Towards Dolly archival project, Edinburgh University Library Special Collections, reference EUA IN23/3/1/1.

based on crosses between reference families of Large White and Chinese Meishan breeds. The aim of crossing two separate breeds was to enhance the heterozygosity (having different variants of the same gene) of the hybrid offspring, thus avoiding repetition and easing the mapping of different, interconnected loci. It was thus an effort that largely built on the old breeding work at ABRO. In addition, the Edinburgh researchers acquired a computer system and adapted an existing database for mouse genome data to use for the PiGMaP project. Software (CRI-MAP) was developed with new statistical tools specifically for the purpose of analysing the linkage data sent electronically from the PiGMaP participants (the ELWW grew to 21 laboratories – including some outside Europe – by the end of the first round of CEC funding in 1994). The project was coordinated from the IAPGR-ERS, principally by Archibald and Haley.

Part of the project was to develop techniques for future mapping of quantitative trait loci (QTL), genes thought to be relevant in economically important characteristics of livestock. This effort formed the main part of the second PiGMaP project (1994 to 1996), funded by the European Commission under the Third Framework Programme, and incorporating collaborators from 23 European laboratories. The Roslin scientists also collaborated with the French National Institute for Agronomic Research (INRA) on an informatics project (GEMINI: Genome Mapping Informatics Infrastructure, 1993 to 1995). This project was funded by the European Commission to develop databases and interfaces for the pig mapping initiative and the parallel, ongoing bovine genome work.[13] Bazin was instrumental in encouraging this application to the BIOTECH-1 programme, just as he was in helping secure funding for the PiGMaP initiative.

As well as PiGMaP, projects to map the pig genome were also underway in the US, at the Department of Agriculture Meat Animal Research Center in Nebraska, and there were also small Nordic and Sino-Danish collaborations. These networks cooperated with each other, to the point of establishing joint access and editorial responsibility for the PiGBASE data repository hosted in Roslin. They also compiled some consensus maps (Archibald *et al*, 1995; Rohrer *et al*, 1997), though no overall map integrating all of the linkage data of the various projects was produced.

A key figure in encouraging genomic work in Edinburgh was Grahame Bulfield. A mouse geneticist by background, he was based in another AFRC-owned institution in Edinburgh, the Poultry Research Centre, and became director of the ERS-IAPGR and then the Roslin Institute since 1988. Bulfield was also a member of the ad hoc Strategy Group of the Human Genome Mapping Project (HGMP), the first co-ordinated effort to produce a physical map of the human genome in the UK. In 1991, he wrote a lead article in the IAPGR annual report, stating that genomics should be the new frontier of animal genetics for the 21st century. Bulfield initially believed that Roslin should follow a 'twin-track' strategy in which the genomic techniques would identify suitable genes to produce transgenic animals. However, as time went by the PiGMap and parallel poultry and bovine genome efforts developed as autonomous ramifications of the pharming project, following a similar pattern to that of nuclear transfer and its application to regenerative medicine.[14]

Bulfield's role boosted collaboration between pig and human genome scientists. Researchers from the HGMP were invited to pig genome mapping meetings, and the techniques and standards employed in human genome mapping were adopted and adapted by the pig genome mapping community, for instance by using the same nomenclature and adhering to the Bermuda Principles, Fort Lauderdale agreement and the Toronto statement (Archibald *et al*, 2010). The increasingly comprehensive maps of human genes and human DNA sequences were used as an important basis of comparison for the pig mappers, and probes containing human DNA were used to identify markers in the pig genome. Comparisons took advantage of the evolutionary relatedness of humans and pigs, and therefore the relative similarity of their DNA.

In the late 1990s, the scientists involved in the genetic and physical mapping of the pig genome turned their attention to the prospect of sequencing, i.e. producing a full catalogue of the linear structure – the sequence – of chemical units integrating the pig DNA. At first, this was under the auspices of an 'agricultural genome,' a growing scientific and policy objective of that time in the US. Within a few years, however, the community had shifted its arguments towards sequencing the pig genome as a biomedical resource, as can be seen in the White Paper published by key figures in the pig genome research community in the US in 2002.[15] They cited the similarity between pigs and humans in their case. Although they were unsuccessful in securing funding from the National Institutes of Health for the project, the positioning of the pig as a biomedical model by members of

13 The Third European Framework programme funded genomic initiatives on cow and chicken to run in parallel with the pig work. The bovine genome project was coordinated in France, while the poultry effort was led by David Burt and Paul Hocking in Roslin (Grahame Bulfield, personal communication).

14 On the HGMP, see García-Sancho (2016) and "Human Genome Mapping Project (HGMP) – Ad hoc Strategy Group." Sydney Brenner's Collection, Cold Spring Harbor Laboratory Archives, reference SB/4/1/267. On the development of farm animal genomics and its connection with the HGMP, G. Bulfield: "From the trait to the gene – animal breeding in the year 2000?" IAPGR – Annual Report 1990-91, pp. 118-19. Wellcome Trust Towards Dolly archival project, Edinburgh University Library Special Collections, reference EUA IN23/3/1/1.

15 Rohrer G, Beever JE, Rothschild MF, Schook L, Gibbs R and Weinstock G (2002) 'Porcine Sequencing White Paper: Porcine Genomic Sequencing Initiative' https://www.genome.gov/pages/research/sequencing/seqproposals/porcineseq021203.pdf (last accessed May 2017).

the genome community has continued (Groenen *et al*, 2012; Kuzmuk & Schook, 2011; Schook *et al*, 2005).

Eventually, funding for the Swine Genome Sequencing Consortium was acquired from several sources: the BBSRC and DEFRA in the UK; the European Union; the US Department of Agriculture; Iowa and North Carolina State Universities, and different industrial associations, such as the National Pork Board in the US. A physical map of the pig genome was produced, and four Bacterial Artificial Chromosomes – large pieces of DNA – from the Children›s Hospital Oakland Research Institute, INRA-Toulouse and the Roslin Institute were sent to the Wellcome Trust Sanger Institute in Hinxton, Cambridgeshire, for whole genome sequencing. Sequencing took place primarily at the Sanger from 2006 to 2009, and the compilation of the genome was conducted in part by comparison with the human genome through a variety of techniques and aided by WuBLASTn, a tool that allows researchers to identify genomic regions with similar sequences.

With the passage of time, both genomic and cloning techniques moved away from animal genetic modification and into the realm of human medicine.

The genome of the pig was published in *Nature* in 2012, in a paper analysing the evolutionary implications of the data, and attempting to demonstrate the usefulness of the pig for biomedical research (Groenen *et al*, 2012). Certain specialist breeds of pig, such as the Göttingen minipig, are becoming common in biomedical laboratories, and the use of pigs as animal models of disease as well as in regulatory procedures is increasing (Kuzmuk & Schook, 2011). The spread of the domestic pig (*Sus scrofa*) as a biomedical model is limited in the UK however, and much smaller than sheep (*Ovis aries*) and mouse (*Mus musculus*), the most commonly used animal.[16] This is partly because of the existence of strict regulations governing the use of animals in research, which makes the pig an expensive animal to house and care for.

This biomedical connection continues to be an objective of the pig genome community today. However, the production of sequenced genomes and their annotation has occurred much later for the pig than for other key species used as models in human medicine, such as the mouse. The 'toolbox' is therefore less well-equipped. Furthermore, the pig genome community has predominantly been integrated by animal geneticists, with links to livestock and breeding industries. They have fewer links to and awareness of the needs of the biomedical research community and the pharmaceutical industry. Ironically, in the UK at least, the pig scientists have been far more integrated into the networks and methods of human genome mapping and sequencing than other animal genomic researchers.

The development of farm animal genomics in Edinburgh presents similarities with nuclear transfer, in the sense that both technologies originated as tools to achieve the objectives of the pharming project. However, with the passage of time both genomic and cloning techniques moved away from animal genetic modification and into the realm of human medicine. This distancing from agriculture may be in part linked to the long-term consequences of the Rothschild reforms and the promotion of a neoliberally-inspired science that prioritises urban, individual anthropocentrism. Societies after the 1970s became less attached – both emotionally and economically – to farms and perceived food production through breeding as unimportant. [17]

At a practical level, this anthropocentric shift makes Dolly's legacy difficult to capture from a BBSRC perspective. The very name BBSRC, adopted in 1994, left agriculture outside the acronym. This seems at odds with the council's institutional predecessors, the ARC and AFRC, which over more than fifty years showed a strong tradition of funding agricultural research. Moreover, regenerative and genomic medicine, the two areas where the pharming project leads in this report, are mainly under the auspices of the MRC today. The serendipitous pathway of Dolly and its transition from animal to human sciences highlights the limitations of capturing the past from a single-institutional lens, regardless of it being the MRC or the BBSRC in its current non-agricultural denomination. Historical research may help to overcome these barriers and document the legacy of long-term funding programmes that span across various administrations.

16 Home Office (2016) Annual Statistics of Scientific Procedures on Living Animals, Great Britain 2015 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/537708/scientific-procedures-living-animals-2015.pdf (last accessed May 2017).

17 This decline in the public image of agriculture is largely a consequence of the surpluses of food production that Western societies faced following post-World War II policies (Thirtle, et al., 1991). As a result, the European Common Agricultural Policy and other initiatives in the last third of the twentieth century have gradually shifted from production to productivity, this leading to biodiversity problems, difficulties in farming communities and new animal diseases such as PSS.

4. Conclusion: history in research planning and policy

The findings of our research project, summarised in this report, suggest that a historical approach to science may help the planning activity of administrative and funding agencies. There is currently a convergence of interests that may stimulate collaboration between historians and science policy institutions. Academic historians are realising the importance of 'following the money' to capture long-term developments and patterns in science (Edgerton, 2012). This involves expanding the range of people to be historically investigated and focus not only on scientists, but also on administrators in charge of the day-to-day running of funding programmes (García-Sancho, 2016: 77ff). Science policy institutions, on their side, are facing a growing volume of interdisciplinary areas that need to be funded through collaborative work across the humanities, natural and social sciences. In the UK, research councils are increasingly issuing calls for proposals across their domains and their officers have adopted the practice of looking at the past and constructing narratives that document the impact of the programmes they fund.[18]

The case study we have presented shows the utility of history for documenting the impact of pharming, a research project that spanned across councils and lasted for more than a decade. Addressing pharming historically means investigating different incarnations of funding agencies and their support to scientific institutions that also changed significantly over time. Most of the transformations we have evidenced are embedded in the change of name of the institutions involved, for instance the 1994 shift from the Agricultural and Food Research Council (AFRC) to the current Biotechnology and Biological Sciences Research Council (BBSRC). More importantly, the legacy of the pharming project can be captured in Ian Wilmut's career move from the BBSRC-funded Roslin Institute to the Medical Research Council Centre for Regenerative Medicine. History explains why these transitions occurred and, in so doing, assist research council officers to assess the impact of their fields beyond their institutional confort zones. A BBSRC officer may discover through our investigation that Dolly's cloning technique was crucial for the development of human stem cell research. Conversely, the MRC may find in agricultural rather than medical research the origins of cell therapy, one of its most promising funding areas today.[19]

Historical research may, thus, provide an inter-institutional lens that helps documenting and analysing long-term impact. Overall, our case study shows the importance of sustained funding beyond the usual three-year grant limits. The continued support of the AFRC and later the BBSRC to the Roslin scientists was essential for the key medical contributions that their research delivered and continues to deliver today. Ironically, these contributions did not develop according to plan and the research project within which Dolly was created – pharming – never fulfilled its stated objectives. This could be interpreted as a failure if the project is addressed from a narrow single-institutional perspective. However, if the MRC – as well as the BBSRC – is taken into the equation, a rich genealogy can be established between animal breeding and regenerative medicine, one that has the potential to inspire future cross-council initiatives.

Historical research may provide an inter-institutional lens that helps documenting scientific impact beyond the administrative boundaries of funding agencies.

The availability of archives that document those often serendipitous trajectories is crucial for historical research.[20] Apart from archival sources, a crucial piece of evidence for our work was the Collective Memory Event we organised half-way through the project. Inspired in an established tradition of witness seminars in the history of medicine (Tansey, 2006; Tansey, 2008), this event gathered the joint recollections of ten key players involved in the creation of Dolly. The participants included not only academic scientists, but also institutional managers, technicians and actors from the corporate world (Myelnikov & Garcia-Sancho, 2017). Their juxtaposed memories provided a unique picture of the intricacy of the experiments that preceeded the birth of the sheep, her overwhelming publicity and unexpected legacy. This technique could be fruitfully commissioned by the BBSRC or other research councils to document the history

18 Cross-council areas of research (http://www.rcuk.ac.uk/research/xrcprogrammes/) and an example of the BBSRC impact case studies: http://www.bbsrc.ac.uk/news/impact/ (last accessed May 2017).

19 This capacity of looking beyond institutional boundaries will become crucial in UK Research and Innovation, the new institution that will integrate the seven British research councils (see https://www.gov.uk/government/news/sir-mark-walport-will-lead-uk-research-and-innovation and https://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/inquiries/parliament-2015/inquiry1/, last accessed May 2017).

20 In 2012, the Wellcome Trust funded the project Towards Dolly to catalogue the records of the Roslin Institute and its predecessor organisations: http://archives.collections.ed.ac.uk/repositories/2/resources/85710 and http://libraryblogs.is.ed.ac.uk/towardsdolly/ (last accessed May 2017). This and the records of the BBSRC at the National Archives – along with some uncatalogued files held at its headquarters in Swindon – have been the main sources of our research.

and long-term impact of strategic areas. In our project, it has also fostered interdisciplinary collaborations with the researchers at Roslin, exemplified by a show we jointly organised at the Edinburgh Fringe Festival in August 2016 with occasion of the twentieth anniversary of the birth of Dolly.[21]

Rather surprisingly, the participants in the Collective Memory Event expressed doubts about the feasibility today of a project like the one that delivered Dolly (Myelnikov & Garcia-Sancho, 2017: 38ff). The short-termism of research grants and postdoctoral contracts make impossible a multi-decade research project that, like pharming, started with animal breeding in the 1980s and finished with human stem cells in the 21st century. Such a programme could also be deemed unsuccessful, since it did not deliver the outcomes that were stated in the original application. A look into the past through this type of events may, thus, inform the future and prevent linear and short-sighted science policy-making.

21 See trailer of the Fringe show (https://www.youtube.com/watch?v=LClmL5C9YJE&t=1s) and electronic version of the Collective Memory Event: http://www.research.ed.ac.uk/portal/en/publications/dolly-at-roslin-a-collective-memory-event(59056ace-04a4-4019-b033-936cd7297f71).html (last accessed May 2017).

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