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## **Animal breeding in the age of biotechnology: the investigative pathway behind the cloning of Dolly the sheep**

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**Abstract:** This paper addresses the 1996 cloning of Dolly the sheep, locating it within a long-standing tradition of animal breeding research in Edinburgh. Far from being an end in itself, the cell-nuclear transfer experiment from which Dolly was born should be seen as a step in an investigative pathway that sought the production of medically relevant transgenic animals. By historicising Dolly, I illustrate how the birth of this sheep captures a dramatic redefinition of the life sciences, when in the 1970s and 1980s the rise of Neo-Liberal governments and the emergence of the biotechnology market pushed research institutions to show tangible applications of their work. Through this broader interpretative framework, the Dolly story emerges as a case study of the deep transformations of agricultural experimentation during the last third of the twentieth century. The reorganisation of laboratory practice, human resources and institutional settings required by the production of transgenic animals had unanticipated consequences. One of these unanticipated effects was that the boundaries between animal and human health became blurred. As a result of this, new professional spaces emerged and the identity of Dolly the sheep was reconfigured, from an instrument for livestock improvement in the farm to a more universal symbol of the new cloning age.

**Keywords:** Genetics, breeding, cloning, embryo, animal, sheep, agriculture, Dolly, Edinburgh, Scotland, biotechnology, recombinant DNA, Thatcherism.

## Introduction

Dolly the sheep is one of the most significant animals in modern biomedicine. The embryo from which she was born was obtained by introducing the nucleus of a mammary gland cell of another sheep into an egg, making this the first mammal to be cloned from adult genetic material. Dolly's public presentation in February 1997 – six months after her birth – sparked intense debates about the limits of cloning technology and its potential use in producing exact copies of human beings. Little is known, however, about the objectives of the scientists who created the sheep and the specific context of the cloning experiments.<sup>1</sup>

This paper will address this gap by placing the cloning of Dolly the sheep within an established tradition of agricultural and animal experimentation, a tradition that neither started, nor concluded with her birth. Dolly was born in Roslin, a small village of 2,000 inhabitants near Edinburgh, and the home of a research institute which is today one of the most important centres in animal biotechnology. She lived at the Roslin Institute until her untimely death in February 2003, after contracting an incurable pulmonary disease. The remains were donated to the National Museum of Scotland, where the stuffed body is exhibited in its Science and Technology galleries (see Figure 1). Shortly before the launch of the exhibit, the Museum's Director described Dolly as "a striking reminder of Scotland's record of scientific achievement".<sup>2</sup> Dolly remains one of the Museum's most popular exhibits, and has become a symbol of Scottish national pride.

## INSERT FIGURE 1 AROUND HERE

Dolly's permanent exhibition at the National Museum of Scotland points to a sense of place and belonging in her creation. This paper will attempt to disclose this local dimension and connect it to the global debates about cloning that proliferated after Dolly's initial public presentation. I will do this by considering the cloned sheep not as an end in itself, but as issuing from a strong tradition of experimentation in Scottish agricultural science. This tradition can be traced back at least to the nineteenth century, and developed in a complex network of laboratories working on breeding research. The animal breeding methods stemming from this tradition interacted with new biotechnologies in the cloning experiments at the Roslin Institute.

By reconstructing this experimental and institutional trajectory, I seek to show the *investigative pathway* behind the cloning of Dolly. The concept of an investigative pathway was proposed by F.L. Holmes to explore the careers of a number of twentieth-century biologists. Holmes drew heavily on laboratory notebooks and other sources that reflected the intricate histories of the scientists' laboratory results. These histories often differed from the accounts that scientists or journalists delivered after the fact, in the sense that the experiments did not result from an *a priori* logic, and in the sense that research instruments that were highlighted retrospectively may have played a more modest role at the time of the events (Holmes 2004). In the case of Dolly, the investigative pathway in which the cloning experiments arose derived from complex interactions between biotechnologies – namely the newly emerging recombinant DNA methods – and other pre-existing techniques from genetics, developmental and cell biology. Contrary to what might have been suggested by the tone of subsequent public debates, the ultimate objective of the cloning experiments was not producing

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<sup>1</sup> Apart from popular and autobiographic literature (Wilmut et al. 2000; Kolata 2011), the most comprehensive scholarly investigation of Dolly is a monograph written by sociologist Sarah Franklin. In it, she explores the long-standing commercial exchange of sheep across Britain and its former Empire, as the basis of scientific research around this animal which led ultimately to the cloning experiments (Franklin 2007b). Other academics have addressed the public and regulatory debates around Dolly (Suk et al. 2007), as well as the models of biomedical innovation in which the cloning experiments were conducted (Fransman 2001; Clay and Goldberg 1997).

<sup>2</sup> <http://news.bbc.co.uk/1/hi/scotland/2930537.stm> (last accessed June 2015).

exact copies of especially fit sheep. The aim rather was to obtain genetically modified animals that would express, in their milk, proteins with therapeutic properties for humans.

Mapping Dolly's investigative pathway traces also the historical transformation of agricultural experimentation, the overarching theme of this special issue. During the last decades of the twentieth century, the conduct of agricultural science was deeply reconfigured by the emergence of the biotechnology market and the rise of Neo-Liberal governments. These governments, and none more so than that of Margaret Thatcher in Britain, forced scientists to find tangible commercial outcomes of their work, and new recombinant DNA techniques were seen as a preferred instrument for medical application. In the case of Dolly, the introduction of the genetically modified animals programme within which she was born required major professional and institutional reorganisations. This blurred the boundaries between animal experimentation and scientific work on human health, and the cloning of the sheep was a by-product of this transition. Historians have shown how the crossing of such boundaries can lead to unanticipated consequences, such as new identities for animals, and redefined forms of scientific networking and public engagement (Bresalier and Worboys 2014; Degeling 2009; Schlich et al. 2009; Gradmann 2010). In what follows, I will show how the animal modification programme in Edinburgh resulted in new research spaces and a tide of media coverage in which Dolly was given an identity that did not correspond with the original goal of the experiments.

The main source for my research will be *Towards Dolly*, an archival collection which is gradually being made available at the University of Edinburgh, documenting the history of the Roslin Institute and its forerunners (mainly the Institute of Animal Physiology and Genetics Research, the Poultry Research Centre and the Animal Breeding Research Organisation).<sup>3</sup> This paper represents a first step in the historical exploitation of these sources and offers a detailed analysis of the first materials that have been catalogued: the institutional annual reports. I will start by reviewing the early breeding work in Edinburgh (Kim 2007, ch.3; Marie 2008; Wilmot 2007) and its redefinition in the early 1980s, following a number of political shifts in Britain that especially affected the agricultural sciences (Thirtle et al. 1991; Cooke 1981). I will then examine the research programme called biopharming within which the cloning experiments were conducted. The biopharming programme required a complex alliance between breeders, human and mouse geneticists, as well as embryologists, molecular and cell biologists. Through the analysis of this alliance and the way the cloning experiments were received by the public, I will draw some general conclusions about agricultural experimentation as a category and what the changing nature of this category across time hides and shows to the outsider.

### **Animal breeding and its institutionalisation in Edinburgh**

The practice of breeding is as old as agriculture and has always involved strategies to optimise the process of hereditary transmission from parents to offspring plants or animals (Harwood 2004; Müller-Wille and Rheinberger 2007, Part III). These attempts at controlling heredity preceded the 'rediscovery' of Mendel's laws, and were heavily connected to trade, and the national or imperial interests of countries.<sup>4</sup> James Cossar Ewart, Professor of Natural History at the University of Edinburgh, had been experimenting from the late nineteenth century onwards on both exotic

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<sup>3</sup> <http://www.archives.lib.ed.ac.uk/towardsdolly/> (last accessed June 2015).

<sup>4</sup> Agricultural historian E.J. Russell has documented a long tradition of trade, exchange and mating of different domestic and farm animals that can be traced back, at least to the Early Modern period. As Sarah Franklin has shown, from the late eighteenth century onwards, English sheep were introduced into Australia and played an important role in the wool trade, setting up international connections that later became visible in the work at the Roslin Institute (Franklin 2007b, chs.3-4; Russell 1966). For other studies of the political and economic use of agriculture in France, Germany, Italy, the US, Mexico, Portugal and Spain see Harwood 2005; Matchett 2006; Bonneuil and Thomas 2009; Saraiva 2010; Camprubí 2010; Santesmases 2013; von Schwerin 2013; Barahona et al. 2005.

animals brought from Commonwealth colonies, like the zebra, and indigenous Scottish species such as sheep, horses and fish. Given the lack of facilities at the University, he conducted the breeding experiments in a private farm at Penicuik, a small town 10 miles south of the city (see Figure 2).

During the early years of the twentieth century, Ewart realised that it was time to academically institutionalise breeding, as a field that would form a bridge between the emerging discipline of genetics and the necessities of farmers, a socially and financially significant community at that time. He persuaded the University to establish the first Lectureship in Genetics in the UK (1911), and then lobbied for the creation of a research department, capitalising on the increasing financial support that the British Government was providing for agricultural and rural modernisation.<sup>5</sup> The Development and Road Improvement Act, passed in 1909, led to the establishment of a commission that supported research into the modernisation of agriculture, making it less dependent on cereal breeding, and more focused on livestock, protein production and animal health (Jones 2004; Teich 1995; Olby 1991; Palladino 1990; Vernon 1997: 312ff). This political agenda and Edinburgh's strong record in the investigation of animal disease (Kim 2007, ch.2) enabled Ewart to obtain funds from the Board of Agriculture for Scotland. In 1919, he founded the Department of Research in Animal Breeding, which was later expanded into the Institute of Animal Genetics (Wilmot 2007: 421ff; Marie 2008: 924ff).

In 1931 – one year after the foundation of the Institute of Animal Genetics – the British Government established the Agricultural Research Council (ARC), a body that sought to transform the institutions that the 1909 Act had created into “an intellectual community” (DeJager 1993: 131). The activity of these institutions had mainly included basic research, given that the objective with which they were created was addressing gaps in agricultural knowledge. The ARC sought to connect this basic research with the requirements of farmers, turning the new agricultural knowledge into increased food productivity. The structure and policy of the ARC were modelled on those of the Medical Research Council: this had been created shortly before World War One with the remit of supporting basic research which would, in the long term, lead to practical applications (Vernon 1997: 324).

The role of the ARC became crucial with the outbreak of World War Two and the dramatic food shortage problems that followed (Thirtle et al. 1991: 128-9; Ord and Stocken 2005). With the spread of food rationing in the UK after the War, the ARC created a number of experimental breeding stations across the country. Two of these were located in Edinburgh: the Animal Breeding Research Organisation (ABRO, 1945) and the Poultry Research Centre (PRC, 1947) (Clarke 2007: 321ff; Henderson 1981: 49ff). C.H. Waddington, who was by then an emerging figure in the attempts to unite embryology and genetics (Armon 2012), moved north from Cambridge to become Chief Geneticist at ABRO and Professor of Animal Genetics in the University of Edinburgh (Falconer 1993; King 1981: 279ff).<sup>6</sup>

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<sup>5</sup> The lectureship was awarded to the then promising geneticist A.D. Darbishire, who was killed in World War One (Ankeny 2000: 339ff). The role of head of the Department – and later director of the Institute of Animal Genetics – fell therefore to F.A.E. Crew, a charismatic but inexperienced researcher at that time, who became a widely consulted expert in the field of animal genetics (Hogben 1974). See also <http://libraryblogs.is.ed.ac.uk/towardsdolly/2013/11/11/remembering-arthur-dukinfield-darbishire-1879-1916/> (last accessed June 2015).

<sup>6</sup> ABRO was earlier known as NABGBRO (National Animal Breeding and Genetics Research Organisation) and was located in London. It moved to Edinburgh when Waddington was appointed in 1947. Another emerging site of animal agricultural science after World War Two was Cambridge, where the ARC established research centres in animal reproduction and physiology which would be merged with the PRC and ABRO in the 1980s (Wilmot 2007: 425ff; Polge 2007; see below). See also G. Bulfield (1999) “Eighty years ago...”, *Roslin Institute Annual Report, 1998–1999*, pp. 24–25. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/5/1. On the development of breeding science after World War Two and rise of pig as a research object see Woods 2012; Brassley 2007.

## INSERT FIGURE 2 AROUND HERE

The initial plan involved a division of labour, as a consequence of which the more basic laboratory research would be conducted at the Institute of Animal Genetics, while ABRO and the PRC were focusing on the breeding experiments. However, as time went by, ABRO and the PRC became increasingly independent from the University and created a network of experimental farms across Britain that were coordinated by a field laboratory in Roslin. During the 1950s and 1960s, both institutions developed independent research programmes and they distanced themselves from fundamental work on genetics, with the exception of a limited amount of scientists focusing on the breeding of mice.<sup>7</sup> The two main goals of the programmes were improving livestock health and enhancing their reproductive rates. These lines of research chimed with the knowledge-bridging agenda of the ARC, despite limited contact with the rural farming world. The main link with local livestock owners at ABRO and the PRC was the Animal Diseases Research Association, which had been founded in the 1920s by a group of Scottish farmers and, after World War Two, had a strong institutional and academic presence in the Moredun Institute (Kim 2007: 24ff; Crew 1971).

The annual reports of ABRO and the PRC reveal that, by the end of 1969, they had consolidated as reference centres in animal breeding, developing a research portfolio that included work on pigs, cattle, chickens and sheep. The overall objective of their projects was improving the commercial yield of farm animals either by augmenting their birth rates or making their offspring more resistant to disease. For this, they designed a wide research approach that included insights from genetics (selective crossing of livestock), embryology (intervention in animal pregnancy) and biochemistry (control of metabolism). Despite the inherently applied nature of their research, both ABRO and the PRC were largely funded by public institutions – namely the ARC – and lacked any real urgency in seeking support outside academia.<sup>8</sup> This equilibrium between public funding and the perceived usefulness of their research began to be questioned with shifts in British politics in the 1970s.

### Funding crisis and the reorganisation of agricultural research

ABRO's annual report for 1973 opened with a rather unusual lead article. H.P. Donald, the former Director of that institution, stated that ongoing political and demographic changes had resulted in a renewed relationship between town and country, as well as changing perceptions of the value of agricultural research. The passage of time had configured a new urban majority that included a "diminishing number with farming backgrounds and a ready sympathy for the agriculturalist's point of view". This meant that the "prospect of a protein shortage or a general food shortage" seemed to occasion "little public concern". For this new urban majority, which included science administrators and policy-makers, the value of the research conducted in ABRO and the PRC was perceived as "potential rather than actual." This prompted both institutions to revisit the "old

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<sup>7</sup> This autonomy and distance from basic genetics mirrors the gap between scientific theory and practice that other historians have shown in early twentieth-century agriculture (Wieland 2006; Theunissen 2008).

<sup>8</sup> "Current research projects", *ABRO Report – January 1970*, pp. 45–48. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1. The academic literature on the early work of ABRO and the PRC is surprisingly thin. However, the *Towards Dolly* project is developing a blog, curated by the archivist Clare Button, with substantial information on these two institutions, as well as the Institute of Animal Genetics and Ewart's early work, see <http://libraryblogs.is.ed.ac.uk/towardsdolly/> (last accessed June 2015).

meaningless phrases” on which they had founded their scientific activity: “helping farmers and raising efficiency” in livestock management.<sup>9</sup>

Donald’s article was written two years after the publication of the very influential *Rothschild Report* (1971). Victor Rothschild, the author of the report, had chaired the ARC during the 1950s and had subsequently been Head of Research at the Shell oil-and-gas firm. The report had been commissioned by the then newly elected Conservative Prime Minister Edward Heath, who created a central policy review committee chaired by Rothschild with the aim of evaluating public expenditure in science. Rothschild’s main recommendation was that the funding mechanism of the ARC and other State research councils be transformed, such that a substantial part of the income they received would be awarded in the form of contracts rather than Government grants. Those contracts would be issued by a particular customer – public or private – and oriented towards a tangible short-term outcome (Wilkie 1991, ch.5; Gummett 1991: 21ff).

The implementation of Rothschild’s recommendations in British science policy began during the mid-1970s. The money that research councils could freely spend in funding basic science was substantially reduced, with institutions expected to secure contracts in order to complete their R&D budgets. These contracts were formalised between the councils, a scientific institution that would develop the work, and a company or public administration with a research necessity. Their fulfilment was closely monitored by the Government to ensure the timely delivery of the stated output. Many researchers, especially within the biomedical sciences, actively opposed the contract system as an intrusion into their freedom of inquiry, thus enabling the Medical Research Council to partially reverse the scheme in the early 1980s (Chadarevian 2002, ch.11). However, the situation was more difficult within the agricultural sciences, given that Rothschild’s previous experience in the ARC had led to the identification of this council as one of the alleged culprits of following purely academic interests and not addressing the needs of the country (Thirtle et al. 1991: 129-30; Henderson 1981: 99ff).<sup>10</sup>

The contract system was significantly expanded by Margaret Thatcher after she became Prime Minister in 1979. Thatcher had been Secretary of State of Science and Education when the Rothschild’s report was published, and strongly endorsed the principle of committing public research expenditure to concrete deliverables (Agar 2011). Thatcher was especially enthused about private entities engaging in contracts with State-supported research institutes, given that this would save the Government money in R&D funding. Another alleged advantage of commercial participation was that it would push public institutions to adopt the more efficient organisational and operational models of private industry. During the 1980s, privatisation of part of the R&D budget and optimisation of research resources – as part of a broader Neo-Liberal strategy of State withdrawal – became defining characteristics of Thatcherite scientific policies (Henderson 1981, chs.14-15; Gummett 1991: 24ff).

At that time, recombinant DNA techniques were seen as a model for industrial involvement in the application of basic science. Recombinant DNA had been developed in the mid-1970s by a team of molecular biologists in the United States, and patented as a set of techniques that allowed the alteration of the basic structure of the DNA molecule. Some of its inventors and a number of universities, mainly in the Bay Area of California, subsequently created biotechnology start-up companies to develop commercial products based on those techniques. The majority of the marketed products had an intended medical application, either as therapeutic substances obtained

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<sup>9</sup> H.P. Donald: “New tasks for livestock geneticists”, *ABRO Report – January 1974*, quotes from pp. 7–8. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1.

<sup>10</sup> A similar debate developed in the US during the mid-to-late 1970s, with some scientists, commentators and policy-makers suggesting that State-funded laboratories should only produce new animal or plant varieties at the request of industrial actors (Hightower 1978; Kloppenburg 2005; Clarke 2007: 320ff).

through artificially produced genes, or tools to diagnose hereditary diseases (Yi 2011). The strong British tradition in molecular biology, together with the perception that the UK was lagging behind the United States in the industrial application of research, led Thatcher to adopt biotechnology as a focus area in her early R&D programmes (Balmer and Sharp 1993).<sup>11</sup>

In this context, ABRO scientists started to look at the possibility of introducing recombinant DNA expertise into their breeding research. ABRO's 1983 report announced the establishment of a molecular biology programme and described the events that had preceded its implementation as a "traumatic time" which had "inevitably left its scars."<sup>12</sup> The picture of agricultural science that the Rothschild Report had presented to Whitehall had resulted in increasing Government cuts to the ARC budget, in the hope that this would push its research centres to find industrial partners and become more cost efficient. In 1985, ARC became the Agriculture and Food Research Council (AFRC), a change of name that reflected the major review undertaken of its scientific activity, and the subsequent drastic restructuring of the research institutions it supported.

One year later, the AFRC amalgamated ABRO and the PRC with the Institute of Animal Physiology in Babraham (Cambridgeshire), in order to form the Institute of Animal Physiology and Genetics Research (IAPGR). The new institute was divided into two research stations, one based in Edinburgh and the other in Babraham, with joint budget management and administrative services. The merger was designed to optimise financial and technological resources, paving the way for more budget cuts and redundancies. This resulted in tensions between the two stations, which continued to publish separate research reports until the late 1980s. The last ABRO report acknowledged that many researchers had seen the amalgamation as a "betrayal" of their hard work and assured readers that Edinburgh would continue "to be recognised as the centre for animal genetics research in the UK". In apparent anticipation of what would follow, the report concluded that, "ideas and principles" were "stronger and more important than institutions".<sup>13</sup>

### **The unanticipated biopharming project**

The establishment of the molecular biology programme required ABRO to return to a close cooperation with the University of Edinburgh. In 1984, one year into the programme, ABRO's lead scientists' report declared molecular biology a means to "learn a lot" about the control of "characteristics of commercial importance" in livestock.<sup>14</sup> However, these scientists lacked the expertise to transform this generic interest into a research agenda that would enable the use of recombinant DNA in farm animals. This led ABRO's Director, Roger Land, to seek advice on the fundamental work on genetics that the University had conducted independently from the breeding scientists. In the mid-twentieth century, following the increasing separation between ABRO and the

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<sup>11</sup> This perception of industrial underperformance in the UK was to a large extent fuelled by prior examples of alleged British failure to patent biological discoveries that were then commercially exploited in the United States, such as penicillin and monoclonal antibodies – the latter developed in 1975. Historians have critically addressed this notion of a failure (Chadarevian 2011; Liebenau 1987) and placed it within a long history of perceived decline of the British industrial potential when compared to the US (Edgerton 1996).

<sup>12</sup> "Comment", *ABRO Annual Report – January 1983*, p. 3. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1.

<sup>13</sup> "Preface", *ABRO Annual Report – January 1986*, p. 1. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1. The IAPGR's Cambridge Research Station was based in Babraham Hall, a nineteenth-century estate surrounded by vast amounts of land that had been bought by the ARC in 1948, as part of the post-World War Two establishment of breeding research centres (see above). Since then, it had housed the Institute of Animal Physiology, an institution with substantial expertise in biochemistry, animal health and reproductive biology. See "Origins", *IAPGR – Report for 1988–89*, p. 8. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/4/1.

<sup>14</sup> "Comment", *ABRO Annual Report – January 1984*, p. 3. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1.

Institute of Animal Genetics, researchers in the latter institution had moved away from livestock breeding and become integrated into the broader Department of Genetics in the University. Thirty years later, this Department became Roger Land's main source of expertise.

The first University geneticist Land approached was John Bishop, who was working on the role of RNA during the process of gene expression in chick and mammalian cells.<sup>15</sup> One of Bishop's associates was John Clark, a postdoctoral researcher who had conducted a PhD on satellite DNA at the neighbouring Clinical and Population Cytogenetics Unit, a Medical Research Council-funded human genetics institution associated with the University (Chadarevian 2015). Both researchers were studying the genes in hepatic cells in mice. Bishop proposed that Clark would join ABRO at the end of the project, given his strong background in animal gene expression. Bishop's second recommendation to Land was Richard Lathe, an assistant director of the French biotechnology company Transgene, which specialised in conducting genetic engineering research for external customers; among others, the company had developed a vaccine against rabies for the animal health firm Rhône Mérieux.<sup>16</sup> Lathe was appointed coordinator of ABRO's molecular biology programme and, after his unexpected departure in 1985, Clark took over as leader of the programme.

ABRO's new programme built on the development, during the early 1980s, of transgenic mice, that is, mice with an extra gene introduced into their DNA molecule via recombinant techniques. Those extra genes enabled the mouse cells to produce medically or commercially useful substances (Haraway 1997, ch.2; Myelnikov 2015). The Edinburgh breeding scientists had experimented with mice since the early years of ABRO and the PRC, but using them as models for animal disease rather than as objects of molecular analysis. Clark's expertise, derived from the University's long-standing tradition in basic genetic research, was essential for the introduction of recombinant DNA into ABRO's research on mice.

Given that the development of transgenic mice had largely occurred in the United States, the Edinburgh scientists felt that they were lagging behind "in an important area of genetic research". ABRO's 1985 annual report considered that the previous research focus on mice was inadequate, and presented the molecular biology programme as a means to provide "the seeds for redress."<sup>17</sup> This programme, thus, resonated with the official scientific policies of the UK, characterised by a feeling of national underperformance and the will to find commercial outcomes for the new techniques of molecular biology. However, due to the limited familiarity of the breeding scientists with these new techniques, they could only draw up a generic programme that built on existing knowledge in human and mice genetics. The interaction of Clark and Lathe – ABRO's new recruits – with the previous breeding expertise available at this institution gave the programme a life of its own and, unexpectedly, scaled up the experiments from mice to sheep, and from animal to human health.

#### *From mice to livestock, from agriculture to medicine*

The molecular biology programme sought to use the mice technology as a platform for two purposes: first, for the creation of a system to introduce and express foreign genes in "cultured mammalian cells"; and second, for the *in vivo* incorporation of that system "into the genomes of

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<sup>15</sup> Peter Harper's interview with Nick Hastie, Cardiff University's Genetics and Medicine Historical Network, 26th May 2004, transcript available at <http://www.genmedhist.info/interviews/Hastie> (last accessed June 2015).

<sup>16</sup> R. Lathe, M.P. Kieny, R. Drillien, J.P. Lecocq: "Vaccin contre la rage et procedee pour sa preparation", European patent number EP0162757B1, filed in 1985 and awarded in 1990, available at <http://www.freepatentonline.com/EP0162757.pdf>, last accessed June 2015.

<sup>17</sup> "Comment", *ABRO Annual Report – January 1985*, p. 4, both from Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1.

both laboratory and farm animals”<sup>18</sup>. In the mid-1980s there was uncertainty over the concrete benefits that would result from the addition of genes to the genomes of higher organisms, as well as the question of whether recombinant DNA methods would work in those complex genomes. Lathe and Clarke soon realised that solving those uncertainties demanded expertise beyond molecular genetics in mice.

The production of transgenic mammals required the injection of the foreign gene in the animal’s embryo, so it would be incorporated into the genome during development into adulthood. This led Lathe and Clark to seek the cooperation of Ian Wilmut, a developmental biologist who had joined ABRO during the early 1970s. Before this, he had worked as a doctoral and postdoctoral researcher at the Animal Research Station in Cambridge, an institution that had become an important centre in animal reproductive biology under the leadership of Christopher Polge (Wilmut et al. 2000: 14ff; Polge 2007). During his early years at ABRO, Wilmut continued his prior work on the transfer of embryos to surrogate mothers in cows and sheep, with the aim of improving birth rates in both species.<sup>19</sup>

With the establishment of the molecular biology programme in the mid-1980s, Wilmut started collaborating with Lathe and Clark, and their joint research proved mutually beneficial. It enabled Wilmut to control the genetic basis of animal development, while Lathe and Clark could follow the development of the genes after their injection into the embryos. This collaboration was gradually consolidated into a team in which Lathe and Clark were in charge of isolating the foreign genes, while Wilmut incorporated them into the genomes of the target animals. Wilmut was simultaneously involved in another programme that investigated “pathways underlying genetic variation in reproduction”<sup>20</sup>.

Historians have shown how the practice of animal experimentation leads to the formation of heterogeneous groupings, their activity often resulting in unanticipated consequences and crossovers between animal and human research (Bresalier and Worboys 2014; Kirk and Worboys 2011). ABRO responded to the stringent financial conditions of the 1980s with the amalgamation of Lathe, Clark and Wilmut’s expertise, as part of a programme that sought to introduce new molecular techniques into the breeding of farm animals. The outcomes of this amalgamation transcended the original goals of the programme, however, and the day-to-day application of these techniques led to research that used animals for the improvement of human health. This line of research was called biopharming and consisted in the production of transgenic sheep that secreted, in their milk, proteins that were of therapeutic use in humans.<sup>21</sup> Biopharming in Edinburgh was

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<sup>18</sup> Research programme number 10: “Investigations of genome engineering using the techniques of molecular biology and its potential in animal breeding”, *ABRO Annual Report – January 1984*, p. 42. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1. A scheme of the technique that Lathe, Clark and Wilmut developed to produce transgenic sheep, as described in ABRO’s 1986 report, can be found at <http://libraryblogs.is.ed.ac.uk/towardsdolly/files/2012/06/immunogeneticsabroreport1986v3.jpg> (last accessed June 2015),

<sup>19</sup> I. Wilmut, D.I. Sales, C. Manson, G. Newell: “Non-surgical transfer of cattle embryos: a field trial”, *ABRO Annual Report – January 1978*, p. 41 and I. Wilmut, D.I. Sales: “Does hormonal imbalance cause death of embryos in sheep?”, *ABRO Annual Report – January 1982*, pp. 25–30. Both from Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1. As Franklin has shown, another offshoot of these embryo transfer techniques was animal and human IVF, which was substantially developed in Australia during the early 1980s by researchers who had also worked at the Cambridge Animal Research Station (Franklin 2007a).

<sup>20</sup> “Research programme”, *ABRO Annual Report – January 1984*, pp. 40 and 42. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1.

<sup>21</sup> Biopharming referred to the use of plants and animals as living factories to produce substances of commercial utility. The field was viewed with interest at the time by the scientific and industrial communities (Milne 2012).

shaped by the conjunction of Clark and Lathe's expertise in recombinant DNA with the traditional breeding science agenda of ABRO, as embodied in Wilmut's research on animal reproduction.

The use of living organisms to produce substances of practical utility had been a common industrial practice, from the chemical and pharmaceutical industries of the early twentieth century to the more recent biotechnological firms (Bud 1993). This strategy had been adopted by Transgene in the development of the rabies vaccine, the main project for which Lathe had worked before moving to Edinburgh. However, ABRO's choice of sheep as a living factory – the animal on which Wilmut had focused his previous research – represented a scaling-up when compared to the microorganisms – yeast or bacteria – that had been selected previously to produce the target substances. In the case of ABRO's biopharming project, the substance that the sheep secreted was intended to improve human rather than animal health. This crossover of the animal-human boundary constituted an unprecedented shift in the objectives of the Edinburgh breeding organisations, though there was a precursor in the previous work of Clark and Bishop, which used mice as models for human genetics.

Clark, Lathe and Wilmut intended the initial transgenic proteins to be used in the treatment of haemophilia and lung diseases. Shortly after the beginning of their collaboration in 1986 they moved to Roslin. This was a result of the merger of ABRO and the PRC with Cambridge's Institute of Animal Physiology, and the establishment of the IAPGR.<sup>22</sup> Roslin had been a field laboratory that coordinated work at the experimental farms of ABRO and the PRC, and subsequently housed the latter institution. Following the merger, it became the base of the Edinburgh Research Station of the IAPGR, and the home of the molecular biology team, except for Lathe who returned to France. In 1987, the remaining team members created a biotechnology company to exploit the proteins produced by the transgenic sheep. This company was initially called Caledonian Transgenics, but soon went by the name of Pharmaceutical Proteins Limited (PPL). The firm started receiving income from larger pharmaceutical multinationals in exchange for future rights over the therapeutic proteins.<sup>23</sup> This enabled PPL to establish a systematic collaboration with the Edinburgh Station of the IAPGR, in which the company provided part of the funding for the biopharming project and benefited from access to the results (Fransman 2001; Clay and Goldberg 1997).

#### *Neo-Liberal policies and animal identity*

The creation of PPL represented the culmination of a strategy by which the Edinburgh breeding scientists adapted to the hostile administrative and funding environment of the 1980s. This strategy involved not only introducing molecular biological techniques, but also undergoing a professional

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<sup>22</sup> R. Lathe: "Molecular tailoring of the farm animal germlines", *ABRO Annual Report – January 1985*, pp. 7–10; J. O. Bishop, A. L. Archibald, A. J. Clark, R. F. Lathe, J. P. Simons, I. Wilmut: "Germline manipulation of livestock", *ABRO Annual Report – January 1986*, pp. 22–26. Both from Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1. The animosities that resulted from the merger (see above) meant that the Edinburgh researchers initiated little interaction with the Institute of Animal Physiology, despite the extensive expertise in recombinant DNA and reproductive biology available there. Wilmut's former institution, the Animal Research Station, had become part of the Institute of Animal Physiology shortly before his move to Edinburgh. Following the merger, both institutions were housed in Babraham – the base of IAPGR's Cambridge Research Station. See Polge 2007 and B.A. Cross: "Foreword", *IAPGR – Edinburgh Research Station Report for 1986–87*, p. I. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/4/1.

<sup>23</sup> M. McClenaghan, A. L. Archibald, J. P. Simons, C.B.A. Whitelaw, I. Wilmut, A.J. Clark: "The mammary gland as an organ for protein production", *IAPGR Report for 1988–89*, pp. 74–75; "Pharmaceutical Proteins", *Roslin Institute Annual Report 1993–94*, pp. 16–17. Both from Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference numbers Coll-1506/4/1 and Coll-1506/5/1.

shift that resembled that molecular biologists had experienced the decade before. In the 1970s, the status of molecular biologists as basic scientists became less important than their ability to present their results as applicable to medical problems, and to develop start-up biotechnology companies to exploit the commercial opportunities behind them. This new identity met the requirements of the Neo-Liberal governments that were elected in Britain and the US. As time went by, reducing public expenditure in science became a priority for those governments. If the potential applications of academic research could be foregrounded, it would attract private investment in the future potential of these applications. Thus part of the transgenic sheep project was funded by PPL, and indirectly by larger pharmaceutical companies interested in the economic potential of biopharming.

The Edinburgh biopharming project transformed the identity of sheep as an object of breeding science. Literature has shown how “the very same animal” can adopt different roles in research, “depending on its contingent and individual life story” (Schlich et al. 2009: 322). Medical researchers that work with animals can use them as patients, disease models or providers of valuable outputs for humans, such as organs in xenotransplantation. The adoption of one role or another depends on changing and uncontrollable socio-political pressures, as much as on scientific interests. For instance, the engagement of veterinary surgeons with work animals started decreasing in the early twentieth century as a consequence of the mechanisation of labour, and the emergence of companion pets (Degeling 2009). Similarly, the emergence of Neo-Liberal scientific policies in 1980s Britain led the Edinburgh scientists to use sheep as a means for the improvement of human health, rather than pursuing breeding as an end in itself.

These contingent research transitions often give rise to a considerable amount of rhetoric. When in the 1970s molecular biologists presented their knowledge as applicable to medical problems, they wanted to create a protected space in which they could freely pursue their research agendas. These agendas included not only the medical application of recombinant DNA, but also less fashionable topics, methodologies and target molecules (Suárez-Díaz 2010; García-Sancho 2011). An analysis of the public discourse of the Edinburgh breeders suggests that a similar strategy was at work with the biopharming project. The lead article of the 1984 research report of ABRO, written one year after the introduction of the molecular biology programme, highlighted the new opportunities it presented, but warned readers that they should not expect the new techniques to be “used on the farm in the short term.” Recombinant DNA was rather “a new exciting area of science” that added to the possible options ABRO “might try to discover for the future.” In that same report, the embryo transfer technologies that Wilmut had developed – without help from the molecular sciences – were presented as more immediately applicable, given their potential to be incorporated by companies in animal fertility treatments.<sup>24</sup>

By embracing recombinant DNA, the Edinburgh scientists were seeking an “integrated” approach to animal genetics, one in which “different areas of research” could be fruitfully combined “from the statistical to the molecular” levels.<sup>25</sup> This involved using the recombinant techniques as tools that could be added to more traditional breeding experiments. The role of Wilmut’s embryo manipulation technologies in the early development of the molecular biology programme is an example of this combination. However, the political framework in which recombinant DNA was introduced resulted in a shifting of the breeding scientists’ investigative pathway towards new goals. Wilmut’s collaboration with Clark and the other molecular biologists shifted the context in which his embryo transfer technologies were applied, from agricultural to medical objectives, and from animal to human improvement.

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<sup>24</sup> “Comment”, *ABRO Report – January 1984*, pp. 3–4. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1. See also Land 1985.

<sup>25</sup> “Preface”, *ABRO Report – January 1986*, p. 1. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/1/1.

### **Dolly, before and after**

The first outcome of Wilmut's collaboration with the molecular biologists was Tracy, a transgenic sheep born in 1990, and carrying in its mammary gland a foreign gene that coded for the protein AAT, used for the treatment of emphysema and cystic fibrosis.<sup>26</sup> The team realised that the animal couldn't express the protein in adult form, and started looking for a way of inserting the extra gene before, rather than after, the formation of the embryo. It was in this context that Wilmut started looking for a suitable cloning technology, one that would enable him to create an embryo by inserting a cell nucleus into an egg and then to transfer that embryo to the sheep.

The main difficulty for the cloning technology was the question of how to make the nucleus of an adult cell suitable for an embryo. To this end, the team benefited from the arrival of Keith Campbell, who joined the IAPGR in 1991 after having worked at the Marie Curie Institute and Sussex University on cell programming and reprogramming in cancer. Coming from the field of human biomedicine, Campbell added to the heterogeneous mix of expertise in the biopharming project. His knowledge of how cells mutate and alter their normal development during disease was crucial for eliminating the adult characteristics of the cell nucleus to be inserted into the egg. This enabled the team to clone three sheep, Megan and Morag – from the cell nuclei of embryos in 1995 – and Dolly – from the nucleus of an adult mammary gland cell in 1996 (Campbell et al. 1996; Wilmut et al. 1997; see Figure 3).<sup>27</sup>

### **INSERT FIGURE 3 AROUND HERE**

In 1993, the AFRC had split the Edinburgh and Cambridge Research Stations of the IAPGR, due to their having acted as independent institutions during the seven years of their merger.<sup>28</sup> The Edinburgh component was renamed the Roslin Institute and, in 1997, this institution organised a highly attended press conference in which Dolly was publicly presented. This was followed by unprecedented media attention. Campbell and Wilmut received innumerable interview requests, seeking explanations of the ethical implications of cloning and its potential application to humans. Wilmut's greater willingness to respond to these requests resulted in his becoming the visible face behind Dolly. As a consequence, he became the scientific spokesperson addressing the growing social interest in the experiments.<sup>29</sup>

Historians have shown how the heterogeneity of animal research networks – especially those with potential human health applications – often results in their scientific activity becoming

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<sup>26</sup> A.J. Clark, A.L. Archibald, M. McClenaghan, J.P. Simons, C.B.A. Whitelaw, I. Wilmut: "High level expression of biomedical proteins in the milk of transgenic animals", *IAPGR Report for 1990–91*, p. 53. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/4/1.

<sup>27</sup> K. Campbell: "Multiplying farm animal embryos by nuclear transfer", *Roslin Institute Annual Report 1994–95*, pp. 24–27; I. Wilmut: "New developments in embryo transfer", *Roslin Institute Annual Report 1995–96*, pp. 26–30. Both from Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/5/1. Megan celebrated her tenth birthday in 2005 and was the oldest cloned animal at the time. For a scheme of the cloning technique used in Dolly see <http://www.roslin.ed.ac.uk/public-interest/dolly-the-sheep/technical-aspects-of-cloning/> (last accessed June 2015).

<sup>28</sup> One year afterwards, in 1994, the AFRC acquired its current denomination as Biotechnology and Biological Sciences Research Council (BBSRC).

<sup>29</sup> Campbell always remained behind the scenes in the public dissemination despite, according to Wilmut, deserving 66 per cent of the credit of the cloning experiments. A lack of recognition may have had an emotional impact on Campbell, who left Edinburgh in 1999 and died in violent circumstances in 2012: <http://www.telegraph.co.uk/news/uknews/1512377/I-didnt-clone-Dolly-the-sheep-says-prof.html> and <http://www.telegraph.co.uk/news/uknews/10065584/Scientist-behind-Dolly-the-sheep-killed-himself-by-mistake-in-drunken-fury.html> (last accessed, June 2015).

interconnected with public engagement campaigns. The alignment of interests in those campaigns, harmonising the views of scientists, regulators, animal owners and other stakeholders, is a crucial factor for ensuring the successful application of research results (Bresalier and Worboys 2014). This alignment was far from perfect in the Dolly story, since the nature of the public debates that unfolded tended to obscure the original motivations behind the cloning experiments. The focus of media coverage and social debates was on the possible use of the Roslin techniques in perpetuating especially fit sheep and, potentially, other animals including humans. This created a vision of cloning as an end in itself. However, within the original biopharming project of Clark and the other molecular biologists, nuclear transfer was just a means to produce embryos of transgenic sheep secreting proteins for human medicine. The public reaction was, to some extent, fuelled by the intense public relations activity of the Roslin Institute after Dolly's presentation. In an attempt to draw maximum benefit from their new media profile, the Institute's internal publicity department actively engaged with the public debates and forecasted applications of cloning in fields such as xenotransplantation and animal production, which were beyond the scope of the original line of research.<sup>30</sup>

This gap between scientific objectives and media discourse resulted in the experiments following the presentation of Dolly receiving less media attention. In 1997, six other sheep were born in the Roslin Institute. Besides being cloned, the genome of these sheep had been modified with the addition of foreign genes coding for the protein factor IX, which helps blood clotting and is used in the treatment of haemophilia (Schnieke et al. 1997). The most viable of these sheep was named Polly, whose birth represented something of a culmination of the biopharming project that Clark had initiated in ABRO during the mid-1980s, Wilmut and Campbell having contributed with a technology that allowed transgenic sheep to be produced in practice. PPL followed the birth and growth of Polly in search of commercial drug development opportunities in sheep milk. However, the public impact of this achievement was significantly lower than had been the case with Dolly. The scale of the achievement was, by comparison, even understated in the Roslin Institute reports.<sup>31</sup>

Despite the degree of protein expression being higher in Polly than in Tracy, the first of Roslin's transgenic sheep, it was still tight for viable industrial developments. This led the Roslin Institute to broaden its strategy and, in 1998, it created another start-up company, Roslin BioMed, engaged in exploiting other commercial opportunities behind the transgenic technology. A substantial part of the patent protecting this technology was sold to the US pharmaceutical multinational Geron, which acquired Roslin BioMed only one year after its foundation.<sup>32</sup> Campbell,

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<sup>30</sup> "Potential benefits from cloning / nuclear transfer", "Uses of cloning in farm animal production" and "Moral and ethical concerns", *Roslin Institute Annual Report, 1996–97*, pp. 22–23, 24–25 and 26–27. Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/5/1.

<sup>31</sup> "Nuclear transfer: a brief history", *Roslin Institute Annual Report, 1996–97*, pp. 18–19; J. Clark: "Genetic modification of livestock", *Roslin Institute Annual Report, 1997–98*, pp. 32–41. Both from Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/5/1.

<sup>32</sup> By that time, the Roslin Institute had already expanded its influence to the US, given that in 1993 PPL merged with a company in Virginia that produced transgenic cows and pigs. Following Geron's operation, PPL retained the part of the patent of the transgenic technologies that related to biopharming. However, it faced persisting problems in developing commercially viable products and around 2004 PPL went to liquidation and dissolved. "Stock market values: PPL therapeutics at £110m", *Roslin Institute Report, 1995–96*, pp. 18–19; "Roslin BioMed", *Roslin Institute Annual Report, 1997–98*, pp. 20–21; "Roslin signs six year deal with Geron", *Roslin Institute Annual Report, 1998–99*, pp. 14–17. All from Wellcome Trust *Towards Dolly* archival project, Edinburgh University Library Special Collections, provisional reference number Coll-1506/5/1. On the commercial activity and liquidation of PPL see Reid and Smith 2006.

who had been attempting to produce commercially viable transgenic animals since the birth of Polly, decided to migrate to the University of Nottingham that same year (1999).

Wilmot continued to use the cloning technology, but gradually shifted the objective of his experiments to obtaining embryonic stem cells rather than transgenic animals. After 2008, he stopped using cloning after Shinya Yamanaka at the University of Kyoto developed a technique to produce pluripotent stem cells without the necessity of creating embryos (Wilmot et al. 2011). That same year, Wilmot became the founding director of another scientifically ambitious institution in Edinburgh, the Medical Research Council Centre for Regenerative Medicine. There he has developed his late career far away from cloning and agricultural research. Wilmot's move from agricultural science to human biomedicine illustrates the historical significance of the investigative pathway underlying the cloning of Dolly, and the Roslin Institute's other transgenic sheep.

## Conclusions

It is a well-known fact in the animal genetics community, but still largely unknown among other scientists and STS academics, that the ultimate objective behind the birth of Dolly was not cloning a sheep, but using it as a tool to improve human health. Building on this, I have reconstructed the historical investigative pathway in which Dolly was inserted, with the aim of uncovering the hidden rationale behind the experiments and, at the same time, showing how the notion of agricultural experimentation changed in the latter part of the twentieth century. The heated political and financial debates in which agricultural research was immersed in the decades preceding Dolly – with the Rothschild Report and its application by Thatcher – led to a situation in which agricultural experimentation became a largely rhetorical category, one that was used in the administrative and planning stages that precede bench science. As such, the category of agricultural experimentation illuminates as much as it conceals the history of late-twentieth century agricultural science, highlighting some research practices while hiding others.<sup>33</sup>

Both agricultural science and its experiments were frequently invoked in scientific and policy reports throughout Dolly's investigative pathway. The category of agricultural experimentation underwent a crucial transformation between the 1970s and 1980s. While it had been identified with breeding knowledge ever since the 1909 Development Act, and later by the Agricultural Research Council, agricultural experimentation now became equated with direct transformations in either animals or plants. This led to concomitant changes in the expectation of how these experimental practices would benefit users outside academia. Whereas prior to 1970 there was a widespread belief in the long-term application of knowledge, the policies following the Rothschild Report sought tangible and commercially viable outcomes by modelling the agricultural sciences in the emerging biotechnology industry.

This created a gap between policy expectations and laboratory practice, given that neither science administrators nor the breeding researchers in charge of institutions such as ABRO knew how to introduce recombinant DNA into farm animals. Consequently, the day-to-day implementation of this new notion of agricultural experimentation led to unanticipated outcomes. In Edinburgh, the development of ABRO's molecular biology programme during the 1980s required institutional and professional alliances that had a profound impact on both agricultural research spaces and experimental animals.

At the level of research spaces, the implementation of a policy that prioritised applications of agricultural science had the paradoxical effect of turning the attention of Edinburgh's experimental stations back to basic work on genetics. While after World War Two both the Poultry Research Centre and ABRO had become increasingly independent from the University of Edinburgh, in the 1980s they needed to collaborate with the Department of Genetics in search of the necessary

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<sup>33</sup> For a similar approach to rhetoric in the history of molecular biology see Abir-Am 1985.

expertise to produce transgenic animals. The input of the University-based geneticist John Bishop was crucial for the hiring of John Clark and Richard Lathe, the former bringing key knowledge from mouse and human genetics, and the latter shifting the research agenda of the breeding scientists towards the production of drugs, in line with the emerging biotechnology industry. These necessity-driven alliances seem to have played a more important role in the Dolly story than the top-down institutional mergers, such as the formation and later split of the Institute of Animal Physiology and Genetics Research.

The new genetics expertise incorporated in the breeding institutions crucially transformed the identity of the animals with which they worked. Lathe's previous experience in the biotechnology industry and Clark's prior work with mice models reconfigured the use of sheep in Edinburgh from objects of fertility treatments to living laboratories for the production of therapeutic substances for humans. As in other historical experiences of the crossover of the animal-human boundary (Bresalier and Worboys, 2014; Schlich et al, 2009; Degeling, 2009; Gradmann, 2010), the research led to particularly heterogeneous networks and an intense public engagement campaign. In Lathe and Clark's cooperation with Ian Wilmut and later Keith Campbell, the new recombinant DNA techniques entered two-way interactions with more traditional methods of breeding science such as embryo manipulation and cell biology. The projected users of breeding science also shifted from animal health institutions and the food industry to pharmaceutical multinationals that became the main customers of the Edinburgh-based biotechnology start-up PPL.

Despite all of these reconfigurations, a constant feature throughout the Dolly story was that the agricultural experiments the Edinburgh breeders conducted never reached, in full, the users for whom they were originally intended. ABRO's mid-1970s reports admitted that regardless of the official policies of the Agricultural Research Council, the impact of their work on farmers had been potential rather than actual.<sup>34</sup> Similarly, PPL struggled to produce a transgenic sheep that secreted therapeutic substances on a commercially viable level. The fact that the intended objectives of agricultural experimentation remained unfulfilled may go some way towards explaining why the main historical fact documented in this paper remains publicly unknown, despite being common knowledge among the insiders of the story: while Dolly was a successfully cloned animal, the longer-term outcomes of the cloning and transgenic experiments have not yet fully reached the human clinic.

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<sup>34</sup> On the absence of farmers in the history of agriculture see Palladino 1990; Olby 1991; Vernon 1997; DeJager 1993 and Woods 2012.

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