The Italian Pathways of Stem Cells

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Abstract In this contribution, we take a look at the future of stem cell research, with particular emphasis on human embryonic stem cells and induced Pluripotent Stem Cells (iPS). Their implications in terms of ethical and social issues are discussed through interviews with two top Italian scientists, Elena Cattaneo and Giuseppe Testa. In light of their answers, the introduction reflects on how stem cells research, interpreted from an STS perspective, allows us to observe the mutual adaptation between scientific practices which generate multiple biological artifacts, and the many ethical implications which characterize our biotechnological societies.

Keywords ethics; stem cells; standardization; bio-object; symmetry.

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1. Introduction[1]

In 2008, Geesink, Prainsack and Franklin affirmed that: "For stem cells, the future is now". This sentence, written 10 years after the publication of James Alexander Thomson's article (1998) about ES (Human Embryonic Stem Cells) in "Science", became even more explosive in 2009 thanks to the discovery of iPS (Induced Pluripotent Stem Cells) by Shinya Yamanaka. Stem cells represent what Giuseppe Testa and Elena Cattaneo build on and call the "Holy Grail" of scientific research. Stem cells research allows researchers to intervene in the development of cells in all directions, and this means being able to change the destiny of the cells – the dream of every scientist.

As in the best tradition of studies of scientific controversy, the worldwide picture of stem cells research sees science and society at loggerheads. Some scientists, together with those sectors of society who pro-

[1] Assunta Viteritti wrote the introduction and carried out both the interviews.

mote and sponsor adult stem cells research, believe that these cells produce results similar to those of embryonic stem cells. On the contrary, other scientists and sectors of society maintain that only human embryonic stem cells are capable of pluripotency, which allows them to differentiate into all types of cell. The juxtaposition between adult and embryonic stem cells seems to have been integrated, and in some ways overcome, with the emergence of iPS and the even more promising framework of cellular reprogramming. However, as the two scientists affirm in the interviews, many aspects of this important discovery still need to be perfected, and because of this, alternative pathways have not been set aside yet.

Today, many teams focus on the various pathways in stem cells research (adult, embryonic, amniotic, iPS, etc.), which do not exclude each other. In Italy, where embryonic stem cells cannot be produced, but can be used (by importing them from abroad), the debate has usually seen on the one hand the scientific community in favour of experimentation, and on the other religious authorities mostly against the use of embryonic stem cells. A similar situation can be found in Austria and Germany, while in the U.K. their use is legal (though limited to embryos no more than 14 days old). In 2011, the European Court of Justice defined the use of embryonic stem cells "immoral", and it appears likely that patenting the discoveries deriving from experimentation with this type of cells will eventually be forbidden (although up to now approximately 100 patents have been produced in Europe). There are no limitations, however, regarding experimentation with (and the use of) iPS. In the U.S., on the other hand, stem cells research is gathering *momentum* and producing results and patents, while in the rest of the world Universities and Asian research teams, encouraged also by the Nobel prize awarded to Yamanaka, are entering the field. All this recently prompted two English academics to speak of *experimental ethics* (Sleeboom-Faulkner and Simpson Durham 2013).

In the two interviews, we wish to offer a panorama of the research in this field from an Italian viewpoint, through the words of two top Italian scientists working in their home country. Their work testifies to the differing, potential pathways which stem cells research has taken throughout the world. Giuseppe Testa focuses on the iPS perspective, while Elena Cattaneo points out the use of embryonic stem cells in the neural field, also observing iPS and their prospects in the diagnostic and clinical field. The two scientists' narratives, far from being in contrast, are situated in an ideal *continuum*, where the cells' ethicality is not assumed as a starting point, rather as an ongoing outcome, an open issue able to pose further questions.

Drawing on the two interviews, several aspects concerning the relationship between stem cells and their social and ethical standing can be observed from a STS perspective. Firstly, the many types of stem cells, which have come to the fore in research and literature in the last few

years, pose a question crucial to STS, namely how to standardize what is not yet fully known. As Eriksson and Webster (2008) point out, standardizing stem cells is an exercise in standardizing different things, which are as yet unknown: here we are dealing with standardizing unstable knowledge to be used in biomedical research.

Another interesting issue posed by stem cells research – a core theme in laboratory studies and one examined by Karin Knorr-Cetina (1999) – is that of the *artificialization of the natural*, meaning a naturalization of research objects in the laboratory. Experimental conditions have an epistemic function, in which the nature of biotechnological objects is transformed into different states in order to be produced, observed, handled, codified, formalized and standardized.

Stem cells are not 'natural objects', but they reach such a status while being artefacts-in-the-making within biotechnological laboratory practice, where they assume their second *nature* as bio-objects. In their diverse versions, stem cells are, from time to time, *epistemic objects* (Knorr-Cetina 1999), *bio-objects* (Vermeule, Tamminen and Webster 2011) and *boundary object*s (Star and Griesemer, 1989; Bowker and Star 1999), in relation to the role they play and the ontology they assume in the scientific practices in which they are generated and involved.

A different aspect regards the impact post-genomic research and translational medicine have had on stem cells (particularly, but not only, iPS), strengthening genomic research at clinical, molecular and protein level. As Elena Cattaneo says, the innovation is that: "you take the patient's genome into the laboratory, and if you speak with the clinician you have all his clinical data": the link is no longer between the scientist and cells only, as there is much more. Testa tells us that for the first time in the history of medicine, iPs allows scientists to "tackle human genetic variability experimentally at molecular level". With the post-genomic phase, on the one hand the study of cells is placed in a wider context; on the other hand, the distance separating basic research (the workbench) and regenerative medicine (the cure) is reduced. In this process, the patient becomes a kind of *active experimenter of knowledge*. All this opens up unimaginable ethical scenarios, which go far beyond the issue of saying 'yes' or 'no' to the embryo. Such scenarios connect the 'do-it-yourself' of local practice in many laboratories all over the world, with ethical and political issues yet to be conjectured.

In conclusion, two issues seem to emerge: firstly, the quest for stabilization of stem cells knowledge; secondly, the type of *symmetry* between stem cells science and the social issues that arise.

Stem cells research contributes to produce a variety of experimental studies, various artefacts and many research questions. This plurality of scientific resources sustains and fosters diverse issues, being them scientific and technical, ethico-social or a mix of both. These are closely related to the specific fields to which stem cells are anchored, from the viewpoint of their use and development. Among these are the study of cellular

and genetic processes, the modelling of particular diseases, the experimentation of differentiating protocols and cellular reprogramming, cellular transplantation and others. Therefore, no single field of stem cells knowledge exists, rather there are multiple fields producing *rhizomatic* segments, all in search of experimentation, reliability, recognition and standardization. This happens because stem cells, in all their biotechnological inscriptions, activate multiple, non-converging research questions and diverse forms of stabilization (or non-stabilization).

Given their impact on *sensitive and ethical knowledge*, stem cells are especially linked to the issue raised by Giuseppe Testa regarding the *value-based commitment* to which science is subjected. Scientific knowledge, as directly and explicitly motivated by an external value-oriented customer base, attempts to manoeuvre, and to solve, the ethical and political issues which emerge on a technical level. However, according to the two interviewees, it does not seem that this element alone succeeds in contributing to the development *tout court* of stable, reliable, exportable and converging knowledge in the biotechnological field. Further issues arise when knowledge is commissioned from scientific practice by external ethical requests, as in the sensational case of the stem cells produced by Altered Nuclear Transfer. These issues are not easy to address, because it becomes necessary to demonstrate both the ethical nature and the achievable results of the knowledge, no simple task in a practical context. The combination of these and other stem cells research pathways, stimulated by scientific and ethical cases from within scientific practice (such as the case of embryonic stem cells, rather than iPS), contribute to producing fields of knowledge which, far from being alternatives or juxtaposed, imply a plurality of technoscientific options with multiple potential applications in the biomedical field.

These pathways open up scientific panoramas which are perhaps not immediately applicable, but which attempt to answer ethical issues, multiply research questions and to build future scenarios. One without the other is *unthinkable*, one calls out to the other, and generates it. The plurality of research into stem cells is activated in reply (or posed as a question) to the plurality of ethical issues the bench puts to the test: it is knowledge in search of stabilization which in the meantime opens up prospects, questions and visions of the future.

As Geesink, Prainsack and Franklin affirmed in 2008, "for stem cells, the future is now", but it can also be said that, at the same time, the future has not been written yet. We are taking part, or will take part, as our interviewees say, in a mutual adjustment of scientific practice capable of generating multiple biological artefacts and their multiple ethical implications. Perhaps this will contribute to building a more biotechnologically mature society.

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2. iPS, Bioscience and Value-oriented Customer Base

Giuseppe Testa received a PhD in Biology and Molecular Genetics from the European Laboratory of Molecular Biology (EMBL) in Heidelberg with a thesis on genetic engineering. He runs the epigenetic stem cell laboratory at the European Oncological Institute in Milan. His research focuses on the mechanisms which regulate stem cells differentiation in order to develop new regenerative therapies. He has done scientific work at the Max Planck Institute of Molecular Biology and Genetics at Dresden University and in other leading research centres in Europe, the US and Japan. In 2002, he founded the Science and Society Forum at the Max Planck Institute with a view to promoting awareness and debate on social implications of biotechnology. He went on to achieve a Master's degree in Bioethics and Biological Law at Manchester University. At the John Kennedy Faculty of Political Science at Harvard University, he was visiting fellow lecturing on the legal and political implications of biotechnologies. Author of numerous publications on genetic engineering and human disease models and studies of science and technology, he has received significant recognition including an honorary PhD in Biotechnology awarded by the European Association of Higher Education in Biotechnology (HEduBT) for his excellent research in the biotechnological field.

AV – *Can you tell me how you came to tap into stem cells in your scientific work?*

GT – It happened in 1997, after graduating, when I began my doctorate in Biological and Molecular Science at the University of Milan (the EMBL). At the time, stem cells were fundamentally a tool for producing mice with which we could study illnesses and reconstruct the functionality of genes. My PhD project involved leukaemia in mice, and I used a series of new techniques which adopted embryonic stem cells to produce mice. In that phase, the stem cells were a tool linked to man in a very indirect way. Up to '98-'99 embryonic stem cells fundamentally remained a working tool for research on mice. A lot of people thought that they would remain a kind of oddity, for a whole series of reasons including ideological ones, an idiosyncrasy in mice which wouldn't necessarily be found in other species. In '98-'99, though, human embryonic stem cells burst onto the scene, with all their new potential. An ethical/political controversy (which has also produced a wealth of STS literature) erupted and brought the bioethical conflict in western society to almost unheard-of levels of prominence. The day after the news about the Dolly cloning was announced, Clinton declared: "We must stop this from happening". There's a political investment in this we've never seen on other occasions. Naturally, those years were filled with great ferment, in the quest for that which I would have called in an article some years later the "Holy Grail": everybody hoped to get an embryonic stem cell without having to start from the embryo – some for ethical reasons, some for reasons of mere feasibility. Many said it would be impossible, that you would need to change

too many things to take a differentiated cell from our body, like skin or neurons, and make it into an embryonic stem cell. So in 1996, when I was at the first conference in which Yamanaka presented the data on iPS before it was published...I remember as if it were today the mix of excitement, sheer bewilderment and also great disbelief on the part of some. Then, too, the experiment had been carried out on mice. Ten years later, in 2007 (after Dolly), human iPS are generated. In ten years the prospects of regenerative medicine changed completely, and above all also changed the prospects regarding the role of medicine in making models for the disease. Today, fifteen years later, I find myself running a laboratory in which human iPS are used to model diseases.

AV – *So you switched your focus from embryonic stem cells to iPS…*

GT – Yes, we have never used human embryonic stem cells in the laboratory, but murine embryonic stem cells as scientific objects to be studied in themselves, their differentiation, above all in the neural line. After Yamanaka's work, we moved on to reprogramming through mouse iPS to study the epigenetic mechanisms which allow a cell to change its identity – surprising at that time, but not anymore. The other passage was moving on to human iPS. This time we don't use them to study the reprogramming mechanism, but as models for diseases. We reprogram patients' fibroblasts in iPS cells and we differentiate them into neural stem cells of the cortex, because cortex neurons are involved in autism and mental deficiency, the two illnesses we study.

AV – *In your opinion, do iPS solve the ethical problems arising from embryonic stem cells, or do they create new ones?*

GT – iPS don't solve the ethical problems, they pose several. They certainly allow us to do practically everything we want with our body, at least potentially. They open up a whole scenario of social, political and ethical options. For example, according to the Athens Group's last Consensus Conference, which I took part in some years ago, based on the results we have already obtained it's highly probable that in ten years time (bearing in mind the limits which always invest scientific prophecy and all necessary caution) we shall be able to produce functioning gametes from iPS cells. This means that we can take reproductive cells from the skin, for example. Given that the cost of sequencing DNA has fallen dramatically, we can hypothesize for the first time the mass production of embryos *in vitro* and the screening through sequencing. It's therefore difficult to say whether iPS either solve or create ethical problems. In the first place, I should say that there are technical issues. For example, they present a security problem linked to how they are generated. Our laboratory, for example, is one of the seven or eight in the world chosen as a reference point and where we use only the technique based on mRNA. This means

that we don't use viruses anymore…and this is an enormous step forward because we avoid integrating the virus into the cells, so we avoid a whole series of risks to the genome's integrity linked to the use of viruses (...) Furthermore, the more profound aspect is: how well do we know how to control iPS *in vitro*? If we want to use them to understand certain illnesses at specific stages of cells development, how do we know that these are the right ones? A lot remains to be done on this, because it's a job which involves the standardization of cellular models, to use the correct terms (...).

AV – *What's the story behind ethical stem cells? How was this term coined and how is it used in Italy?*

GT – It's talked about a lot in Italy. Every so often articles are published. There has even been talk of the Italian pathway to stem cells, but I've rarely heard the word "ethical" associated with stem cells in America. Of course, people speak of ethical solutions to the issue of stem cells. This story started in America, and was an attempt on the part of some bioethicists, politicians and investors to solve the bioethical controversy (...). A first example of what became known as ethical stem cells were the cells produced through Altered Nuclear Transfer (ANT), which became well-known also thanks to my work. In the American bioethics committee appointed by George Bush, there were people who opposed embryonic stem cells research and among them was a bioethicist doctor who called for the production of ethical pluripotent stem cells. He would never call them "embryonic" because they possess a certain type of genetic breaker which removes a gene from the future embryo. Without this gene the placenta does not develop. You start from the oocyte, the nucleus: at the time, there was talk of cloning. You remove this gene from the nucleus of a somatic cell, from the skin, for example, and then you insert an oocyte. Development commences, but it can never be successful because an essential component is missing. In my opinion, this example appears very interesting, this first triangulation is extraordinary: a bioethics committee (which in America is appointed by the President and is, therefore, a direct emission of executive authority) explicitly delegates to science the finding of a technical solution to a moral issue. In this, the U.S. have been very honest: a political solution cannot be reached, so let's seek a technical solution which can also solve our political problems. An artefact which is not an embryo, because it has never become an embryo and will never do so, is therefore produced. This idea from the bioethics committee is commissioned and translated into fact in the laboratory and subsequently published in *Nature* and this artefact is rendered morally legitimate by imitating nature, which is elected as the source of responses to dilemmas regarding values. We know that many episodes of natural insemination are unsuccessful because the embryo develops but does not take root: these precocious failures are a part of nature. In the ANT project we pro-

pose a kind of imitation of these natural failures in the laboratory. This brings us to an interesting point: who can say that also the end product of this strategy is never an embryo? What if I were to tell you that it starts off as an embryo, but then on the fifth day it dies because it needs that gene and it can't find it because it has been removed? As a matter of fact, this doubt induces the American bioethics committee to fly over from Germany one of the greatest scientists in the stem cells field and ask him: "How many genes need to be altered in order to be sure that this thing we've produced is no longer an embryo?". To me, our whole era lies in this question…

AV – *Has the knowledge gleaned from Altered Nuclear Transfer (ANT) become accepted? Does anyone work with them?*

GT – The work was published, and in 2005 ANT became a technological object. However, this was in 2005, and one year later, in June 2006, Yamanaka began to speak of iPS. I would say that the ANT story is well and truly over, even though it's an interesting one, rich in implications. Today nobody works with ANT anymore, but the idea of "value-oriented customer base", of scientists who are more and more engineers for commission, has become more of a reality, to a point where Yamanaka affirms in his first article that the driving force behind his accomplishing what everyone thought impossible, i.e. iPS, is also an answer to the ethical issues surrounding embryonic stem cells. That's what he says today.

AV – *So there's also a kind of value-oriented customer base research? A demand which doesn't arrive directly from the workbench, but arrives at the workbench...*

GT – I've cited the stem cells case as an example of how scientists become the executors of a value-oriented customer base, like an engineer or an architect who builds a bridge or a prison to order, in various articles. Of course, according to whether you build a prison or a bridge, the value-based commitment to helping people communicate or keeping them locked up is materially inscribed into that work. The political establishment says to the scientist: "Create a stem cell according to value-based criteria, using the latest biogenetic engineering techniques, so that your product doesn't give me any moral problems". The scientist goes into the laboratory, does this and publishes the outcome in the most prestigious journals in the world, also conferring an official stamp of recognition to his/her discovery. In my opinion, this is an example – not necessarily the only one, but surely absolutely unprecedented in this field – of explicit value-oriented customer base. The bio-scientist or biologist, however you want to call him/her, becomes the executor of a program of values. This is the most interesting aspect of iPS, over and above whether we've solved the ethical issues or not...

AV – *But today it's iPS that have this ethical label...*

GT – I don't think that embryonic stem cells present any ethical problem whatsoever. There are vast segments of our society that don't think so either. Undoubtedly, iPS don't need a human embryo produced by *in vitro* fertilization. There's a huge ongoing debate about this, and I've taken part in it with an article written together with two of my students in the "American Bioethics Journal". The classic argument of the bioethicists who oppose the use of embryos is that of the potential: "It's not the embryo itself that needs to be respected, but we must respect it because potentially it could become a person". However, Yamanaka's experiment definitively demolishes the argument of the potential, as I demonstrated in my article in "Stem Cell", and shows how it is open to attack in many ways. After the Dolly cloning and Yamanaka's work, some bioethicists raised doubts. If every cell has this potential and all that's needed is to make it manifest, this is the tombstone on the argument of the potential, unless you want to maintain the necessity of taking care of all our cells because they're all potential people. Therefore, I and others maintain that rather than closing the bioethics issue, as many would have wished, Yamanaka's experiment opens it up because it poses a problem linked to potentiality, transforming it into a property which is not associated with a certain type of cell, but with a cellular state which is somehow interchangeable. Of course, ethical problems have also been posed regarding embryonic stem cells. One of these was the De Coppi case, which Elena Cattaneo also mentioned in an article. This regards the theme of amniotic liquid stem cells, which were declared to be ethical by their discoverer. Before Yamanaka, embryonic stem cells bore the stigma of immorality, not only in Italy but worldwide. Therefore, any attempt to do the same things with other types of stem cell, including amniotic stem cells, was hailed as the 'Holy Grail'. These stem cells have been criticized too, though, by Elena Cattaneo herself and other scientists: although they are said to have the same properties as embryonic stem cells, it seems that with amniotic ones it is not possible to differentiate neurons.

AV – *This multiplicity of bio-objects would seem to allow and give voice to the articulation of a multiplicity of ethics as numerous as the multiplicity of ontologies produced with stem cells...*

GT – Exactly. One thing is certain: there is a plurality of ethics. At a time in which life sciences become more and more a kind of engineering do-it-yourself, assembling and disassembling, evidently an even greater plurality of customers becomes possible. If I think that the human embryo possesses a moral dignity right from the first day, I'll ask the scientist to imitate natural failure *in vitro*; or, for example, believing according to Muslim precepts that the soul arrives on the fortieth day, I'll ask for an em-

bryo that stops developing on day forty.

AV – *But do you believe that iPS are replacing embryonic stem cells in the laboratory?*

GT – Mainly, yes, but there's still a need for standardization and to have embryonic stem cells as a reference point, both for some demands of basic biology and for many prospective applications, to have the possibility of comparing iPS with Human Embryonic Stem cell. Having said this, there are many human stem cells, and many lines in the world. Some of them are well-known and standardized, so they are used as a reference point. Embryonic stem cells can be taken from embryos *in vitro*, generated in the majority of countries during assisted insemination attempts when the couple involved permits the donation of embryos. This limits the choice of the type of stem cell which can be obtained: the number of embryos is very limited, above all in the case of rare diseases such as Huntington's, for example. For this, iPS are extraordinary: if you want to study diabetes, you select fifty patients with diabetes so that they have the clinical characteristics which correspond to the requirements for the study, and produce the iPS from them. Therefore, in the study project you have a possibility of prospects which you can never have with embryonic stem cells. Today, iPS are both a point of arrival and departure. Human embryonic stem cells represent a *gold standard* reference point, but undoubtedly the further we go on, the more and more important iPS will become. In a context of STS sensitivity, embryonic stem cells represent a *gold standard* today in that they are a natural model but produced in the laboratory, given that the embryo is *in vitro*, transited in culture. Pluripotency, which is a property of the embryo *in vivo*, is captured *in vitro*. They seem more natural, while others (iPS, for example), seem more artificial, and for certain aspects they are: even though they are extracted, cultivated, etc., they undergo a process which is in itself unnatural. Therefore, embryonic stem cells are the *natural gold standard*, but as we go on, the more problems we pose regarding this notion, the sooner the day will come when we use only iPS. It's a natural process, and as Latour said, it's both a point of arrival and departure.

AV – *In your opinion, which of the stem cells pathways is the most promising today?*

GT – I should say that the first road is that of modelling diseases. In the history of medicine, our capacity for understanding human diseases has until now been limited by one important factor: that of accessing the patient's tissue, for obvious reasons, because it's in a person's body. Furthermore, the problem is accessing it in phases which make sense: for example, there are many brain banks, but of course of brains *post-mortem*. Obviously, for some illnesses this lack of material is less serious: blood

disorders, for example, which historically are those where the greatest progress has been made. But as far as disorders of the brain or other organs are concerned, we have been unable to gain access for a long time, and our only tool for modelling diseases has been the mouse. However, it's obvious that the mouse as an organism is intrinsically limited, above all because it doesn't give us the possibility of studying how human genetic variability contributes to diseases, unlike iPS (and this represents the great innovation of iPS). For the first time in the history of medicine, iPS allow us to tackle human genetic variability experimentally. For the first time, you can take an unlimited number of people with the same pathology, or differing degrees of the same pathology, and finally ask the question: "What contribution does their genomic variability make to this pathology?" (...). Of course, as this intellectual and practical challenge goes on, large-scale experiments for the pharmacological screening of these cells have already begun, and this is perhaps a sign of our times. In these cases, the area of application is certainly most promising. Then there's the other story, making Prometheus' dream come true: the idea that with iPS research we can make our skin a bank of replacement organs. One day we'll be able to take skin cells, or even hair cells, and produce *in vitro* first cells, then tissue, then one day organs, which at that point – being genetically identical to us – can repair, replace or maybe in the future even improve parts of our body without any problems of rejection. Obviously, there are a series of motives which can easily be understood and which are linked to the security of these approaches and an all-important level of regulation, as well as the feasible application of all this in a healthcare system. Let's say, however, that this future prospect, Prometheus' frontier, is what I can certainly see on our horizon, *albeit* one which is still far off.

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3. Scientific Reasoning and Plurality of Ethics

Elena Cattaneo, PhD in Biotechnology from Milan University, studied stem cells and brain progenitors at MIT in Cambridge, USA. On her return to Italy, she continued her stem cell research and started up new lines of research into Huntington's disease. In 1994 she founded her laboratory at the Faculty of Pharmacy in Milan, where she has been full professor since 2003. She founded the Unistem Stem Cell Research Center at the University of Milan. For many years her laboratory has been a member of the "Coalition for the Cure" promoted by the Huntington's disease Society of America (H.D.S.A., New York) and has taken part in research activities on behalf of the Hereditary Disease Foundation (H.D.F., Santa Monica, California). She has published many works on stem cell research and Huntington's disease, and among the numerous awards she has been given are the "Science award for Medicine" (2001) and the Italian Presidential Medal, which she received from Carlo Azeglio Ciampi. In 2002, she was nominated National Representative at the European Union for Genomic and Biotechnological Research (2003-2006) by the Ministry for

the University and Research. In 2007 she took part in the National Committee for Bioethics both as a member and Vice-President. From 2009 she has been coordinator of the European NeuroStemcell project funded by the 7th European Research Framework Program.

AV – *Was your laboratory the first in Italy to use human embryonic stem cells?*

EC – I believe so: in 2005, and later on with the EuroStemCell project, we were the first in Italy to receive ethical approval regarding the use of these cells at Milan University. Then, still in 2005, there was a referendum on medically assisted procreation, which set limits for embryonic research and posed some problems. At that time I was vice-president of the National Bioethical Committee, and I think the fact that I stated we used embryonic stem cells in my laboratory didn't go down well. In Italy, the limitations regarding the use of stem cells have always been those imposed by Law 40 on medically assisted procreation, which states that we cannot derive them ourselves, but we can obtain them from abroad and import them, as we did, in the context of the several international collaborations and EU-funded research consortia we belonged to. What really annoyed me for some time at the beginning was the code of silence, even among several of my colleagues: some of them came to my laboratory to try, understand and learn to use these cells, but when they should have spoken out and said that they used them in their laboratory work in Italy, most of them kept their mouths shut. I didn't want to be the one who got around the law and went abroad, but I wanted to eradicate the idea that a good scientist doesn't use stem cells and an unethical one does. In my opinion, this was and remains a trivialization of values. Therefore, with the referendum in 2005 I engaged with the Italian Radical party as I wanted to help them getting things the right way (...) initially in public they were declaring that it wasn't possible to work with stem cells in Italy and it wasn't true. Instead, I wanted people to know that we could legally work with these cells and I wanted people to know why I wanted to work with these cells.

AV – *Because it wasn't true that it was impossible to work with embryonic stem cells in Italy, and at that point you stated your position publicly.*

EC – Yes, of course they could be used in Italy and I didn't want to be branded with the mark of the unethical scientist. I wanted to express my opinions, explain the whys and wherefores. There was a vote and the referendum was lost and then immediately afterwards I was appointed to the National Committee for Bioethics in 2006. I believe I was chosen because I represented a certain stance, a scientist who both stated she used them and declared herself to be a Catholic. In the course of that year I organized a convention here in Milan and a public issue arose. I was vice-

president of the National Committee for Bioethics and Casavola, a Catholic jurist, was still president, and at a certain point he fired the three vice-presidents, including myself. I read in a newspaper that I was dismissed. I remembered talking with the president on the phone when I was nominated, as I wanted to make sure that he regarded as valuable for him and for the Committee to have a scientist as vice-president. Acting as vice-president was not a favour, for me. I remember approving the fact that the president of the Committee for Bioethics was a jurist, it gave me the feeling he was principled, someone who would seek the truth. I thought, however, that after being on the receiving end of a public attack at the convention in Milan, a plot hatched somewhere to make me bear the brunt: I was the one who used stem cells in my laboratory (...). I remember that one day, the Catholic jurist Francesco D'Agostino arrived at a meeting and said: "Scientists have published this article on amniotic stem cells. That's it! Embryonic stem cells get shelved!".

AV – *How many scientists sat on the Committee?*

EC – Myself, the pharmacologist Silvio Garattini and Emilio Piazza, a geneticist from Turin. In February 2007, there was an international workshop on embryonic stem cells in Milan and patently organized pandemonium ensued. I was harshly attacked by some Catholic students whom I later met and clearly understood to be incapable of having done everything by themselves. The message was directed straight at me, I knew I was their target because the convention had been organized by Fulvio Gandolfi[2] and myself. Had the convention itself been the target, the letter which was later made public would have been sent to the organizers, but I think I was their target because at the time I was the only declared Catholic who was both a member of the National Committee for Bioethics and worked with embryonic stem cells. The public letter, which also appeared in the press asked "How can you work with embryonic stem cells without asking yourself what an embryo is? Isn't it human life?". After becoming publicly involved I remained silent for weeks before replying in the national press. I consulted a lawyer and tried to understand whether there was anything I needed to protect myself from: he told me that at that moment there were no grounds for appeal, to stay alert. We spoke again, I paid his fee and stop. The story then appeared in the press and continued to circulate because something like this is fairly unusual in the university environment. And when you are in the middle of something like this you immediately realize that you are alone and that some people

[2] Expert in embryonic stem cells and the reproductive sphere. Full professor at the Faculty of Veterinary Science where he teaches Embryology and Genetic and Cellular Therapy, head of the Laboratory of Biomedical Embryology and one of the four founders of the Interdepartmental Center for Stem Cell Research – UniStem – at the University of Milan.

were enjoying this. I felt sick. I had colleagues accusing me of having brought politics into the university. I felt really left out in the cold but I received support from colleagues from different departments in Italy. This happened in February, then came March, April... I went back and forwards to the Committee in Rome every month and then in July Casavola fired the three vice-presidents and a month later I appeared before the Committee and asked to make a speech. I said that although I had decided to leave the Committee, before doing so I wanted to speak my mind. My speech can be found on the net[3]. I began by saying that I failed to understand how nothing should be said about us being dismissed: I had offered my services to the Committee without payment, taken on a lot of extra work as well as taking part in the meetings. Then I was thrown out of the vice-presidency on my ear and for no clear reasons, to my view, and nobody had anything to say. I started my speech and I went on to speak for 45 minutes. I said all I had to say, trying to reason things out, I mean, why what the President had done that wasn't right, then I resigned according to a text, which has since become public knowledge. This was in October 2007.

AV – *There was another story which saw you in the public eye, one also linked to the embryonic stem cell research theme …*

EC – This second story dates back to 2009, when a public tender notice regarding stem cells and their therapeutic prospects was issued by the ministry. My colleague Giuseppe Testa summarized all this in his contribution[4] in a curious way, as he linked our case (I carried it out along with two other scientists, Silvia Garagna e Elisabetta Cerbai) with that of two American researchers who opposed the Obama administration because it had come out in favor of embryonic stem cells. He put the two cases together and said that here in Italy there are researchers who aim to open up the research field to stem cells, while in the US those two researchers were tending to close it. A good piece. It was a tender notice from the Ministry of Health on stem cells and their potential application which included this phrase: "No embryonic stem cells". We contested this[5]. In any case, why should a government decide what scientific means can be used to achieve a goal? The government defines the aim, the means are up to the specialists, also because Law 40 permits the use of human embryonic stem cells. They are scientifically relevant, and blocking a scientist from

[3]http://159.149.74.38/webpage/Scandali/Cattaneo%20CNB%2026%20Ott%202007.pdf

[4] Testa, G. (2012) *Stem Cells and the Structuring of the Italian Biopolity*, in R.G. Mazzolini and H.-J. Rheinberger (eds.), *Differing Routes to Stem Cell Research: Germany and Italy*, Bologna and Berlin, il Mulino/ Duncker & Humblot, pp. 225-249.

[5] http://www.unipv-lawtech.eu/files/Appello_staminali_finale_CdS.pdf

doing research that is scientifically relevant and legal to me is an abuse of power. Anyway, we took legal action, we appealed to the court. Silvia Garagna is from Pavia, and she told me this issue cost her a lot. Together with colleagues at Besta Neurological Institute and Stefano di Donato[6] I had prepared a project and submitted it to that tender notice. In the meantime, we had requested a suspension, so you have to go to the Regional Administrative Tribunal to get the tender notice suspended and they decide whether it is valid or not. The Regional Administrative Tribunal refuses our request for a suspension, so we take it to the Council of State where it's refused again six months later. In the meantime the tender notice is published, and on expiry the money is assigned and we are left with our ideas in the drawer (…).

AV – *And was the project you presented ever evaluated? Did anybody ever tell you anything?*

EC – We never heard a thing. I had also written an accompanying letter in which I said that we were submitting, but were aware that, etc., etc. From a legal viewpoint, the two steps we took (Regional Administrative Tribunal and Council of State) requesting a suspension never got as far as the Tribunal, so the issue is still open. Six months ago our lawyer told me that they've got five years, and just continue to postpone it. I don't know whether this is because they've got better things to do, at this point the tender notice has already expired, the money has been assigned, the projects carried out and we haven't heard anything (...). I want my lab reimbursed by the State, as the State has prevented our ideas from being evaluated. The absurd thing is that in another national tender, a PRIN call for proposals, we stated that we use stem cells for our research... and we were funded. This aspect reminds me of the case of a German colleague, Oliver Brüstle, (this story too is narrated well in the book containing the article by Giuseppe Testa). In 1997, before the discovery of human embryonic stem cells, Oliver submits a patent for one of these differentiation methods. However, he had also foreseen the use of other cells, and the patent was extended to cover human embryonic stem cells, which in the meantime had been discovered. The patent process goes ahead, and when it reaches the European Patent Office it's blocked because in the meantime Greenpeace has sued Oliver because his patent is contrary to public order with reference to the EU directives on biotechnologies, which state that the human embryo cannot be patented. But these aren't human embryos, they aren't even cells, but only a differentiation method (...). Greenpeace sues and the case arrives in the German Federal Court, which decides not to make a ruling but to consult the European Court of

[6] Dr Stefano Di Donato, MD, was Chairman of the Department of Research, and Director of the Division Biochemistry & Genetics at the Istituto Nazionale Neurologico Besta, Milan.

Justice in order to find out what an embryo is. The European Court of Justice rules that the embryo and its derivatives cannot be patented. Therefore, following this logic, neither can anything connected with the product of conception, neither can you research and patent contraceptive methods (...). In any case, from a patent point of view, Germany still has to decide what to do, they're agonizing over this, there the case is proceeding, like in every other State (...). In Europe we may lose 300 patents, I believe all the European patents will expire: just think how happy they are about this in the US. They've killed off all the European patents linked to cultivating human embryonic stem cells, so obviously you can decide to patent them in the US or Japan. Oliver's story sure is crazy.

AV – *At a certain point, research fields which try to get around the embryo issue developed. There's talk of ethical stem cells. What can you tell me about this?*

EC – The story starts in the US in 2004, I believe, with some senators…I think the first was a senator or an expert from the ethics committee…and he says: "What if we create a blastocyst which has mutated?". It was a senator who clearly had an interest in the matter. So if we create a blastocyst which is mutated and can't take root in the uterus, this is ethical, it doesn't involve the embryo, we can isolate embryonic stem cells from such an entity. This issue was linked to therapeutic cloning, and the aim was to get the cells you want, so embryonic stem cells too, from a source believed not to be a person. Therefore, you modify this source so that it can never become a person. This was right in the middle of the Bush administration. Some scientists take cells from the skin of a mouse mutated for the gene which would make the blastocysts take root, they extract the nucleus, they put this nucleus in an oocyte with the nucleus removed, so now this is like therapeutic cloning. However, this oocyte with a new nucleus develops a blastocyst, which is mutated because the gene, which would make that blastocyst take root, has been cancelled from the original nucleus. They extract the embryonic stem cells with the idea that these are ethical because they're derived from a de-nucleated oocyte (...) there was a good commentary on this in the "New England Journal of Medicine" in 2004, which spoke of disaster in the distorted relationship between science and politics.

AV – *Does this ethical stem cells theme involve other research teams, perhaps also Yamanaka's?*

EC – Yes, of course, also Yamanaka. He has always said that an experiment published by others made him curious. At that moment people were looking for solutions, to my view not because they were ethical or non-ethical, but because they weren't able to go ahead with therapeutic cloning. If you take the stem cells, the fibroblasts and you unite them

with embryonic stem cells by using an adhesive, then you get bigger cells. However, the most interesting thing is this nucleus – that is, you pretend you have two nuclei – this nucleus is reprogrammed. So he says that when the two cells are placed in contact, inside there's stuff which reprograms the nucleus of an adult cell, and that's where he got the idea of reprogramming. He evaluated what can be in there, and started with 24 genes. Yamanaka says that reprogramming helps to avoid the ethical problem but he also says that we need human embryonic stem cells (...). When I travel around the world to conferences, this topic is not an issue, among scientists it isn't discussed like this, ethical stem cells and things like that are not spoken of. The so-called ethical stem cells are not an issue in the laboratory, but a public issue. Yes, maybe it's a topic for some scientists. For me, the ones that I have are ethical, and I don't know why I should have to find others. They are ethical and they produce the neurons we want to know more about Huntington's disease. No other stem cells can do it better nowadays. This idea of ethical stem cells assumes that some scientists are working with non-ethical stem cells, that some scientists are not ethical. That is, one can say that they don't work with embryonic stem cells because in his or her opinion they aren't ethical, but that doesn't mean they think that those who use them aren't ethical. Then again, in the application field no distinction is made between ethical and non-ethical. I can't remember a conference in which this was a topic for discussion, this is an ethical-philosophical debate, not a scientific one. I understand perfectly that society has the right to say ethical/non-ethical, or things like that, but in science we try to pursue things that work, that have reliable, rational prospects. And I see a lot of ethical values in this. That senator's famous experiment was binned despite the fact that it was published in "Nature", because it wasn't supported by scientific reasoning. It's obvious that if you mutate a gene from a blastocyst and you know from a whole load of experiments that it won't take root, where's the scientific strength in this? The value to be found in experiments is their scientific result: of course, if in future we have an amniotic stem cell, and they tell me it's ethical, and I can extract a wonderful neuron from it, I'll certainly work with it. Now, however, I certainly can't get the neurons I need for my studies on the disease from amniotic stem cells, and I want results, so I pursue them: if they're real, useful, credible results I pursue them (...).

AV – *However, some scientific objects have thus been labeled...*

EC – Whether they survive or not, it doesn't depend on their ethical label, but on their scientific value (...). In all sincerity, I find it difficult to imagine future scenarios, unlike many of my colleagues who are able to. I have to take one step at a time, and from what I see I should say that I think we still have to learn from methods of differentiating embryonic stem cells and they will continue. With regard to iPS, of course I'm very

curious to see how they behave. In my opinion, the key factor is that you take a mature cell and its genome and you can reprogram it into the laboratory and if you speak with the clinician, the clinician has all his clinical data. The innovation is in this combination of laboratory and clinician, more than in the cell itself. From a clinical point of view, they're really studying Huntington in a huge number of ways and they're coming up with extraordinary things with regard to symptoms (...) this means that in the genomes of different patients, there is something that distinguishes them, which is outside the gene: if you place their tissue, their cells, their genome *in vitro*, perhaps you find a method for studying things that you can't even imagine *in vivo*. You try to understand how they can be different as regards age at onset, because if you find this out you push the one with the first onset twenty years on, which is usually the timescale of the disease. If it's in the genome you take it to the laboratory and you study it with the iPS, differentiating the neuron, etc., and what distinguishes the two genomes and what functional aspects distinguish them: however, in order to work well with iPS, you must be familiar with embryonic stem cells (...). Then there's the big issue of cellular reprogramming as scientific knowledge, there's this DNA, which unravels and begins to talk. This is disturbing, aside from the therapies and the illness, this is scientific knowledge to be placed on a pedestal (…). With stem cells or iPS you can intervene in the process of cellular development in every direction. This means you can modify the cells' destiny. This word, destiny, is the one we'd all like to hold in the palm of our hand, and in the laboratory you can hold it in your hand and here they attack you saying you're a scientist who wants to modify cellular destiny so you become like Frankenstein.

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