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 notizie di POLITEIA, XXIV, 91, 2008. ISSN 1128-2401 pp. 110-113

Report

Financing for Research on Embryonic Stem Cells: The Situation in Italy and its Origins. 3rd Italian National Congress of the Group of Italian Researchers on Embryonic Stem Cells

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> "Opened up to this vast and most excellent science, of which my work is mere the beginning, ways and means by which other minds more acute than mine will explore in remotest corners"

These are the words of Italian astronomer and physicist Galileo Galilei, who was sentenced to indefinite prison in San Macuto Palace, on which site the Group of Italian Researchers on Embryonic Stem Cells (IES Group) organized its 3rd National Congress on Research on Embryonic Stem Cells (Rome, 1 July 2008). These scientists strongly believe in the potential of human embryonic stem cells (hESCs), which are already the main focus of their research. A parallel thus emerges, as innovative and revolutionary scientific issues are discussed once again in this place. In the magnificent structure of the Refectory Room of the Chamber of Deputies at San Macuto Palace, IES scientists presented their research and discussed ethical aspects of its implications. In this site Galileo Galilei (1564-1642) was tried by the Inquisition for his advocacy of Copernican theory, which held that the Earth revolves around the sun. Since 1974 the Palace is an official site of the Italian Chamber of Deputies. The meeting was sponsored by the Consulta di Bioetica, Politeia, Unistem, Estools, and Emmeplus.

The main aim of the Congress was to highlight the need for an immediate and tangible opening to research on hESC in Italy. In fact, even while it is legally allowed to work on established hESC lines, it is prohibited to derive new lines from embryos; and even more limiting is the lack of funding from the Government. Consequently, a first and most crucial step is to improve the dialogue between science and both society and politics, in order to make known the potential, in terms of therapeutic outcomes, of hESC research.

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Opening speakers of the congress were Elena Cattaneo, pioneer of hESC research in Italy, and Andrew Smith, project manager from ESTOOLS. Cattaneo's speech highlighted the main aims of the meeting, to identify the role of the IES group and to inform the audience on the research carried by its members. Since 2002, the interest of the international scientific community in hESCs has strongly increased, shown by the augmented financial investment and by the number of participants at specific conferences. In this scenario, IES scientists must create a solid network in order to facilitate financial and practical aspects of their research (training of personnel, development of protocols, reporting of results, etc) and to sensitize the public towards the relevant ethical aspects of their research. In underlining the tremendous potential of hESCs as tools for studying human physiology, disease and new therapies development, she stated that IES researchers do not exclusively work on embryonic but also believe in the potential of adult stem cells. Cattaneo focused the attention on the nr.1 scientific discovery of 2007 (according to *The Times*): induced pluripotent stem cells (iPS, Takahashi et al., *Cell*, 2007), now receiving much interest by some Italian laboratories. This discovery, overcoming the ethical issues involving the use of embryos, would have never been possible without preceding research on hESCs. Last but not least she expounded the chronic problem of fund-raising in Italy and Europe, and of the long and laborious iter leading to a project approval by the EU. Taking a look outside academia, Andrew Smith described how the ESTOOLS consortium endorses lab research but at the same time tries to make it accessible to the public. Rescaled on an European level, with their 21 labs in 10 countries, the main targets of ESTOOLS resemble those listed by Cattaneo with regard to IES. In particular, ESTOOLS focuses on four different areas of activity: research and technology development (integration of funding and projects), dissemination of results (website, international public symposia), training (fellowships, lab staff exchanges, videos of lab techniques, and media training) and outreach (newsletters, trans-Europe telescope, ethic workshops). Most importantly, ESTOOLS promotes the development of integrated projects involving both academics and industrial partners: successful scientists should thus possess the skills of a good researcher and a good manager, be able to communicate with the public, be open minded and flexible.

After the welcome note of Carlo Flamigni, chairman of the session, Marisa Jaconi and Tiziano Barberi, top Italian scientists working on hESC outside Italy presented the results of their research on cardiac and skeletal muscle, respectively. Jaconi (University of Geneve), in particular, is working to develop animal free protocols and GMP-grade cell lines and to understand and control hES differentiation process for possible clinical applications. She also pointed out the pros and cons of iPS: no embryos are involved and no immune response is elicited but, on the contrary, a strong teratogenic effect would be possible due to their derivation through viral infection. Barberi (Beckman Research Institute of the City of Hope, Duarte, California) works on mesodermal progenitors isolation from pluripotent stem cells; he reported his latest achievements that follow his previous results on skeletal muscle (Barberi et al., *Nature Medicine*, 2007). The major efforts of his lab are directed on the development of more solid and

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reproducible protocols in order to take a step further towards clinical applications in general. Research activities inside the IES Research on hESC is applied in three different directions: studying embryonic development, controlling the differentiation in specific lineages, and clinical applications (e.g. drug screening and therapy development). All these research themes are equally important and tightly related, each of them needing the knowledge derived from the others to proceed; the IES group has competencies to cover them all.

IES new members

During the last year, four more research labs (Elvassore, Bianco, Gambari, Mantovani) joined the IES ranks and thus had the chance to present their projects to the audience and to the other members. Nicola Elvassore, Chemical Engineer from Padova University, supported the idea of coupling engineering and biotechnology skills to develop technologies serving biology. His laboratory already established hESC culture, and is currently developing devices (e.g. substrates, micro and macro-scaled bioreactors, ..) for the control of the culture microenvironment and thus of the cellular differentiation process. Bianco and Gambari's labs are studying two specific genetic diseases: McCune-Albright syndrome and -Thalassemia respectively. In particular, Riminucci (Bianco's lab) explained that such syndrome is caused by a mutation occurring in embryonic cells and Gambari underlined the importance of studying the activation of fetal -globin in thalassemic patients. For these reasons, they now both aim at using hESC for developing therapeutic strategies as they represent the closest *in vitro* human model. Mantovani, studying the transcription factors regulating stemness, recognizes how this research would greatly benefit from the use of hESC.

IES senior members

Cardiac differentiation is the leading theme for research by Condorelli and Cerbai. The first aims at reproducing the protocols for cardiomyocytes derivation from hESCs developed by Keller (Yang et al., *Nature*, 2008) and showed interest in adopting iPS cells cultures. The second is studying cardiac functionality and physiology in diseased heart *in vitro, in vivo* and *in silico*, using hESC as a cellular model. The teams led by Brevini and Oliviero focus on deriving new cell lines not originating from human embryos and thus overcoming the possible ethical issues. Brevini's group works on human parthenogenetic stem cell, which possess all of the main features of hESC but their potential for clinical application has yet to be tested. Riding the clamor of iPS cells, Oliviero succeeded in inducing iPS and obtaining a 100-fold increased yield by adding myc transcription factor to the original Yamanaka recipe (Takahashi et al., *Cell*, 2007). Another important application of hESC is gene therapy; the Sangiuolo group works on this application with regards to spinal muscular atrophy and cystic fibrosis. Elena Cattaneo and her prominent team working on neural differentiation have derived

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a population of neural crest precursors from hESC and are currently testing its differentiation potential, *in vitro* and *in vivo*, with a view to possible clinical application. Italian scientists here gathered, unequivocally demonstrated how their research hold an enormous social relevance and all expressed hope in the future possibilities deriving from their integration within the IES and in the common efforts in remodeling the Italian scenario.

Round table discussion: financing research on hESC

Why use embryos and why finance hESC-based research? These two major issues emerged during the meeting and the final discussion. In the near future there may no longer be the need for to discuss the rightness of using embryos for progressing science and research, said Demetrio Neri, followed by Gilberto Corbellini who underlined that it would be desirable that prejudices should not hinder successful research. In addition, besides the lack of funding for research in general and on hESCs in particular, it is clear that Italy needs deeply to reform its financing mechanisms. Even Senator Ignazio Marino, Deputy at the Italian Parliament and invited participant to the meeting, expressed his opinion firmly in these terms. It is unfortunately clear that government does not recognize science as crucial for the future of the country's economy. Mindful of his past experience as a scientist in the US, Senator Marino affirmed how Italy should not pose any ideological barrier to scientific research and, most important, should adopt absolutely new project-evaluation criteria. To date, only 10% of the research investments are allocated through peer review; the remaining 90% through unclear top-down methods. A reform of the entire system must thus be done, basing the entire distribution of funding on the mechanism of peer review in order to enhance meritocracy and transparency in the selection of projects. Barberi, active participant in the discussion, finally stated that there's no need for further speculation on the validity of peer review as it must be the sole and only method for a meritocratic evaluation of research projects. With a favorable legislative and financial environment supporting all areas of human embryonic stem cell research, the future promises to be very exciting for scientists interested in this field, and crucial for progress in clinical applications.

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