

"Commercial stem cells" damage medicine: medicine is aware

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Summary. A recent Editorial in the *NEJM* on the flourishing of stem cell clinics providing unproven treatments on a commercial basis and the widespread use of fake cell therapies in the US resonates with worldwide concerns on unproven therapies and in Italy, with the recent and luckily finished "Stamina case". The article brings into focus a resurgence of concern, awareness and willingness to stand up of the broad medical community, in a scenario in which fundamental values of science and medicine are at stake.

Le "cellule staminali commerciali" danneggiano la medicina: la medicina è consapevole.

Riassunto. Un recente Editoriale del *NEJM* mette a fuoco la diffusione del commercio di terapie cellulari fasulle negli USA e riporta alla memoria il recente caso Stamina, che ha contribuito a portare il fenomeno all'attenzione del mondo scientifico e medico su scala globale. L'articolo mette a fuoco la crescente consapevolezza del problema e del suo impatto non solo nel mondo scientifico come è stato finora, ma nel mondo medico in generale, poiché sono in gioco valori fondamentali propri della medicina.

The use of unproven cell therapies has plagued the fields of stem cell research and regenerative medicine with a growing negative impact¹. It is estimated that for each of the about 50,000 patients worldwide who in fact receive life-saving treatments based on the biology of stem cells (hematopoietic stem cell transplantation, aka bone marrow transplantation) each year, at least 3 patients in the US only travel abroad to receive an unproven, web-advertised "stem cell treatment", which is neither a treatment nor stem cell based. This situation has been repeatedly denounced in the scientific literature by stem cell scientists keen to maintain a high standard of scientific and medical rigor². The recent editorial by Taylor-Weiner & Graff Zivin in *The New England Journal of Medicine*³ (*NEJM*) is more than just another claim of the need for rigor, for several reason. First, the prestige of the publication venue indicates that the problem, formerly better known to basic scientists than to physicians, has attained the broadest medical horizon. Second, the article brings into focus the high prevalence of this phenomenon in the US, while most (but not all) of the previous concerns had focused on the prevalence and dimensions of the problem in Asia, the Caribbean area, or Europe. Third, the article brings into focus one specific type of cells, identified

by multiple commercial entities as a suitable tool for their business. Fourth, a specific case is made for enforcing FDA regulation in order to make them more effective in preventing patients' deceit, abuse and exploitation.

Medical awareness of the problem is essential. The commerce of unproven therapies does not belong to medicine, but its flourishing in areas for which an aura of "science & innovation" is commonly evoked (as is the case for stem cells and regenerative medicine) threatens medicine in a serious way. It is a practice that excludes a role for medical knowledge in the treatment of patients. A market logic underpins the purchase of treatments and hopes by patients who often have little hope, and less treatment options⁴. It replaces the doctor by a provider, typically a company in disguise as a "clinic". Nonetheless, doctors themselves participate in the practice, making it more difficult to fight. Many respectable doctors have (in good faith) been singing the song of regulatory bodies (such as the FDA, or the EMA in Europe) interjecting unnecessary obstacles to "medical innovation", i.e. to the use of an unproven type of intervention based solely on the individual doctor's judgement and courage, in the absence of scientifically proven safety and efficacy of the treatment⁵. This has often been claimed to be a fundamental engine of the discovery of new treatments, the virtues of which would resonate many times in the history of medicine. As applied to the use of cells (and of putative stem cells), this claim leads straight to the administration of unproven cell-based therapies for basically all ailments under the sun – autism or urinary incontinence, strokes or renal failure, arthritis or heart attacks⁶, all can be treated by cells, by stem cells, by the same cells, and by cells that have no chance to treat the disease, or relevance to the disease being treated, or to the physiology of the organs and systems being the site of disease. Medical innovation, it is said, is a genuine medical act, not intended to pursue knowledge, but to benefit the individual patient. Particularly if employing the patients' own cells, regulatory bodies should have no rights to interfere with a doctor's and a patient's choice^{4,7}. And after all, the treatment administered qualifies as an autologous graft, not as the use of a drug.

Multiple Courts have ruled against this stance in the US, validating the firm ban placed by the FDA. The winning argument in these cases was the circumstance that even if a patient's own cells are used in that patient only, inasmuch as grown in culture those cells are technically a drug, and as such their use should be validated through proper trials and approved for commerce by the FDA. There are many specific scientific and medical arguments that validate this approach. For the sake of brevity, suffice it to say that as far as cells are

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Invited and received october 26, 2015.

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grown *ex vivo*, what goes into the patient is different from what is harvested beforehand. Hence, a transplant it is not. In most cases, the cells do not engraft, and there is no graft without grafting. As a result, the administration of cultured cells outside of clinical trials and FDA regulation is banned in the US. This is one of the reasons why “stem cell tourism” flourishes outside of the US borders. What is less commonly appreciated, however, is the circumstance that many stem cell clinics operating abroad (for instance, in the Caribbean or in Mexico) are connected with commercial entities based in the US, and are used as mere offshore stations to which patients (and cells) are redirected. The worldwide thrust against regulation of cell therapies is solidly rooted in the US, where a constellation of think tanks and organizations campaign vigorously against the FDA and its unduly paternalistic role, which would prevent patients from accessing “therapies” and doctors from freely and creatively innovating⁷. These views emanate from a well characterized view of the economy and of free markets as the sole efficient regulators of human activities - in this case, medicine included. In these views, herbal medicine and medicine share identical rights of citizenship, there is no need for medical licensure, and no need for regulating the drug market. Patients should be “free to choose” (curiously, specifically when they have no choice), which means that commercial providers should be free to market unproven therapies. Unfortunately, extensive lobbying brings this view into the political arena, and loosening of government-enforced regulation may ensue, and is perhaps ensuing⁸.

While so-called “mesenchymal stem cells” have been a highly used tool for unproven therapies^{9,10}, the so-called “stromal vascular fraction” (SVF), which the *NEJM* Editorial focuses on, is one of the strategies evolved by commercial entities to circumvent the FDA ban to the use of cultured cells. SVF cells can be isolated and returned to the patient, with no intervening *ex vivo* culturing. Similar strategies have been used for bone marrow cells (subjected to *ex vivo* concentration by centrifugation, for example), and in Italy, this strategy is intensively pursued. All of these are useless, pointless, and meaningless from a biological and medical point of view. For example, even the editorial in the *NEJM* refers to SVF cells as “multipotent” (i.e., resembling a stem cell in some way), but in reality, multipotency has never been proven for such cells. So there is no connection between these cells and their use and any plausible stem cell property. What is being given to patients is simply a suspension of fat-derived cells, with no properties of stem cells, and no known therapeutic effect.

A stern defense of the role of regulation and regulatory agencies is the sole stance that medicine should take in this scenario, if the goal is to preserve medicine as an intellectual and moral act intended to help those who suffer^{11,12}. This may come across as not attuned with a populist rhetoric on patients’ free choices, markets as intelligent substitutes for medical knowledge, and innovation made in a doctor’s office. For these reasons, the attention the *NEJM* gave to the issue is important, and hopefully will be followed by more awareness and pronouncements of the medical community in defending the fundamental human values of medicine.

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