

EDITORIAL

Why research in medicine needs a step back?

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*Discovery needs luck, invention, intellect -
none can do without the other*

Johann Wolfgang Goethe, a discoverer himself

Financial Times in 2008 published an apparently provocative article with the title “Drug research needs serendipity” [1]. In this visionary article the authors state that in the last two decades the Pharma industry did not introduce in the market new drugs that showed some effectiveness against major diseases, despite the huge investment; and they tried to propose some explanation for this. In their own words “What went wrong? The answer, we suggest, is the mis-measure of uncertainty, as academic researchers underestimated the fragility of their scientific knowledge, while pharmaceutical executives overestimated their ability to domesticate scientific research”; and again “Medical research is particularly hampered by the scarcity of good animal models for most human disease, as well as by the tendency of academic science to focus on the ‘bits and pieces’ of life – DNA, proteins, cultured cells – rather than on the integrative analysis of entire organisms, which can be more difficult to study”. I guess all the readers of these few sentences should realize that pharmaceutical industries have failed in their investment and the authors of the article provide an explanation: the academic researchers have overestimated their findings and the headquarters of the Pharmas were wrongly pretty sure to manage for a perfect control of what came from the scientific research. One paradox of this low effectiveness of the new drugs is that a new field in pharmacology is to discover the off targetting of the known drugs through their side effects [2] and this is leading to think about the use of drugs designed to be specific for a disease for the treatment of other diseases. But this is not surprising being the vast majority of the drugs that pioneered the pharmacology of neurologic diseases thought for other uses [3]. From the whole of this dreadful awareness some doubts may originate on the future of the current research, that is going without breaks in the same direction. However, the authors provide a possible attempt to adjust the sight, to course cor-

rect the way, all in all to change the strategy of research in medicine in order to get to results that really may change the health and therefore the fate of the whole humanity. They wrote that in the past the majority of the discoveries were done mostly through serendipity. In fact, serendipity was a fairly common occurrence in science. However, some information is needed on the origin of the word “serendipity”. The term was coined by Horace Walpole on January 28th of 1754 in one of the letters written to his friend Horace Mann. Walpole coined the term influenced by the reading of *The three princes of serendip* by the Persian poet Kushrau. In the story three princes are expelled from Serendip (then Ceylon and in modern day Sri Lanka), and along their travels they make discoveries due to sheer luck. The story of how Walpole had access to this literary piece is in itself full of serendipitous anecdotes and difficulties, however what is important to know for our purposes is that “serendipity” originally referred to discoveries by good luck or happy accidents [3].

We had clear examples in the past of discoveries that really changed the natural history of devastating diseases, such as infectious diseases, through incidental findings, that we can well re-call amazing moments of serendipity. The most known example of this is the discovery of penicillin. Fleming was studying *Staphylococcus* when one of his culture plates had become contaminated and developed a mold that created a bacteria-free circle. Then he found within the mold a substance very active against the vast majority of the bacteria infecting the human beings [4]. However, the Fleming’s example is the most known but for sure not the only one we can provide. One other example, while much less known, is that of the 1931 Nobel Prize Otto H. Warburg. He left overnight some plates containing tumor cells seeded in culture medium in the laboratory’s incubator with the usual 37 °C and O₂/CO₂ atmosphere. The morning after he realized that the O₂ dropped down within the incubator, expecting to find all the cells dead due to the hypoxic conditions; while the cells were pretty well and after an initial astonishment he thought that probably cancer cells did not need oxygen to live. After a series of experiments his conclusion was that differ-

ently to normal cells cancer cells do not need oxygen for their metabolism, while they fermentate sugar producing lactate, thus contributing to extracellular acidification. Warburg has become a mentor for scientists thinking that tumor acidity is a common phenotype of cancers, and that an antiacidic therapy is at list to be implemented with the current anti-cancer approach. The Warburg's discovery on tumor metabolism convinced me that it is crucial in science to have a look to what is occurring with an open mind; not thinking that what apparently looks a failure of your experiment is actually a failure, but hopefully something that may represent a discovery [5, 6]. Therefore, we should identify serendipity as part of the scientific process. With this approach my group of research got to nonmainstream discoveries, including the evidence that proton pump inhibitors (PPI) have a clear anti-tumor effect and improve the effectiveness of other drugs as well, in turn leading to clinical studies supporting the use of PPI in treatment of patients with different cancers [7-19]; that tumor cells face off the low nutrient supply of tumors by feeding on other cells, thus becoming cannibal [20-24], and sharing this activity with unicellular microorganisms [23], together with sharing specific cannibalism-related genes [24]; that cancer cells

under the pressure of a very hostile microenvironment release a huge amount of nanovesicles that are spilled over the body, representing the major determinants of tumor metastasis [25-38].

Max Planck said "Science progresses not because scientists change their minds, but rather because scientists attached to erroneous views die, and are replaced" and Otto Warburg used the same words when he realized the lack of acceptance of his ideas. Probably, we should re-think to research in medicine with a mind sufficiently unbiased from mainstream infrastructures, probably paying more attention to potential "unexpected discoveries". Probably, serendipity should be considered an essential part of the scientific method and, particularly, a tool for progress, and it should be taken as a rational approach to scientific practice, an attitude, and a happy accident. We should not think to serendipity as merely a luck, or chance, or happenstance; rather to a process in which a fortunate event leads to a discovery of a new solution for a problem unexpectedly.

It is hard to talk about a nonmainstream approach in *Research in medicine* [39], but this article was written with the hope to give only a contribute aimed at triggering a new deal in science in which to think and watch will represent a successful strategy.

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