

"I have a dream"

Perspective Article

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"I have a dream that one day every valley shall be exalted, every hill and mountain shall be made low, the rough places will be made plains, and the crooked places will be made straight, and the glory of the Lord shall be revealed, and all the flesh shall see it together. This is our hope..."

(Martin Luther King, Washington D.C., August 28, 1963)

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Unfortunately, we are all witness to a dramatic failure in new, effective and possibly non-toxic therapies against major diseases. In fact, the diseases that were incurable seven decades ago remain incurable today, excluding of course infectious diseases. Cancer, as well as neurodegenerative diseases (e.g. multiple sclerosis, Alzheimer's) and autoimmune diseases (including Systemic lupus erythematosus, rheumatoid arthritis and scleroderma), all suffer from poorly effective and often extremely toxic therapies. However, while many of these diseases can be controlled as chronic diseases, cancer is becoming a sort of nightmare rather than a disease. This is for two main reasons: first, because the standard therapy did not show to be effective, largely under the expectancy, while extremely toxic and often destroying the patient's body rather than helping it in defeating the disease.

These two concepts are clearly expressed in two articles published in the last four years. The first one, by David Shaywitz and Nassim Taleb, was published in *The Financial Times* in 2008 (1), and discusses the reasons for this dramatic failure in drug discovery. In the authors' own words: *"The molecular revolution was supposed to enable drug discovery to evolve from chance observation into rational design, yet dwindling pipelines threaten the survival of the pharmaceutical industry. What went wrong? The answer, we suggest, is the mismeasure of uncertainty, as academic researchers underestimated the fragility of their scientific knowledge while pharmaceuticals executives overestimated their ability to domesticate scientific research."* Of course, there is no reason not to agree with these statements. There is a looseness between academic science and the pharma in biomedical research. There appears to be something like an "unrealistic ambition": we take the discoveries of scientists and we apply to the concept of research and development the potentially applicable findings coming from basic research. This approach has not achieved innovative or effective therapies for major diseases. Shaywitz and Taleb write further: *"For all the breathless headlines proclaiming breakthrough discoveries, the truth is that we still do not understand what causes most disease. Even when we can identify a responsible gene or implicate an important mutation, we have made only limited progress in turning these results into treatments."* Unfortunately, this is the truth, and moreover it

represents a dramatic truth. However, I fear we have to seriously regard for this truth, in order to find a way to overcome this “big, big problem.” Another important point from the same article is: “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.” Again, this is dramatically true. In fact, following the age of the big discoveries in medicine, where medical scientists often tested their ideas on their own bodies, today, biomedical research is mostly deprived of MDs or physicians, with positions instead filled by basic scientists, with no medical culture and – even worse – with no interest in discovery of “the causes of diseases.” The last point upon which I want to comment is: “Nevertheless, real scientific progress has occurred, inviting the question: why do pharmaceutical companies, which spend billions of dollars each year trying to turn advances into treatments, have so little to show for their efforts? Answer: spreadsheets are easy; science is hard.” I fear that the problem is that, during recent decades, “science” has become a sort of spreadsheet in its application. This is because the research projects in biomedicine were set up in a NASA-like way. Something like: “we want to get to the moon.” Yes; but discovery of the cause of diseases (in order to try to cure them) does not correspond with the will to get to the moon. The unforgotten genius and 1931 Nobel Prize for Medicine, Prof. Otto H. Warburg, suggested to all medical scientists at the beginning of the last century: “We can only cure what we can understand first.” I think that, really, we should reset our research in understanding diseases.

The example of cancer is emblematic, inasmuch as we continue to ignore the prime aetiology of tumours. The result is that, after more than 60 years from the introduction of chemotherapy in human beings, the gold standard anti-tumour strategies offered to cancer patients are still based on chemotherapy, surgery and radiotherapy, which physically try to destroy cancer with brute force rather than by selectively interacting with cancer cells’ unique biological characteristics. Actually, cancer represents an area with significant unmet medical need, with more than 20 million people worldwide being diagnosed annually and, despite the current available therapies, more than a million patients dying from this disease every year. There is an urgent need for safe and effective new treatments resulting in durable disease remissions and increased overall survival. At this point, I would like to introduce an article by Robert Gatenby (2), which proposes a change of strategy in the war against cancer. He begins by listing some facts: “The German Nobel laureate Paul Ehrlich introduced the concept of ‘magic bullets’ more than 100 years ago: compounds that could be engineered

to selectively target and kill tumour cells or disease-causing organisms without affecting the normal cells in the body. The success of antibiotics 50 years later seemed to be a strong validation of Ehrlich’s idea. Indeed, so influential and enduring was medicine’s triumph over bacteria that the ‘war on cancer’ continues to be driven by the implicit assumption that magic bullets will one day be found for the disease.” After so many years, we are still waiting for this magic bullet against malignant tumours and, of course, this is generating the idea that something went wrong along the way (or from the very beginning). Gatenby concludes: “However, in battles against cancer, magic bullets may not exist and evolution dictates the rules of engagement.” Actually, Gatenby proposes that a reasonable approach may be to set up therapeutic strategies aimed at controlling cancer rather than trying to cure it, through highly toxic drug combinations that are seemingly more destructive to the patient’s body than to cancer.

Altogether, these considerations suggest that we should proceed along two different - but parallel - paths in trying to find a way to cure diseases while at the same time avoiding treatments that are needlessly aggressive for the patient’s body (being extremely toxic and poorly effective). For this purpose, I would like to come back to a concept which in the past had a pivotal role in the identification of drugs proven effective in different diseases, namely ‘serendipity’.

Today, the word ‘serendipity’ is used in everyday language, though with different definitions, such as “the faculty of making happy and unexpected discoveries by accident,” and “the faculty of finding valuable or agreeable things not sought for” and “an accidental discovery” (i.e., “finding one thing while looking for something else”). However, the word itself has a very ancient origin. In fact, *serendip* was the old Arabic name for Ceylon, now known as Sri Lanka. The real origin of the word ‘serendipity’ comes from a Persian fairy tale telling of the Three Princes of Serendip who, during their travels, accidentally discovered numerous things they were not in fact on a quest for. In the 16th century, the tale was translated from Persian to Italian, and from Italian to French. Horace Walpole (1717-1797), an English man of letters, encountered it in a collection of oriental tales in French, and coined the English term ‘serendipity’ in a letter to his friend, Horace Mann, dated June 28, 1754. We should not forget that serendipity is one of the pivotal factors contributing to drug discovery. Whether we want to keep the definition whereby serendipity implies the finding of one thing while looking for something else, we should recall the discovery of penicillin first. Fleming was studying “staphylococcus influenza” when one of his culture plates had become contaminated, developing a mould that created a bacteria-free circle. Later, he found within the mould a substance that has highly resistant

against the vast majority of bacteria infecting human beings. Equally, serendipity played a key role in the discovery of a wide range of psychotropic drugs, including aniline purple, lysergic acid diethylamide, meprobamate, chlorpromazine and imipramine (3). It appears quite clear that, at least in the past, serendipity played a pivotal role drug discoveries – or, more precisely, in the discovery of drugs that were effective against different diseases. Thus, while we are confronted with an unbelievable failure in the discovery of effective drugs based on cross-communication between basic science and drug companies, we have to realize that this approach should be abandoned if we want to get to better results. Probably, we should have another look at the thousands of drugs on the market with different eyes. Probably, we would be better to think of the ‘off-targeting’ of drugs. In fact, there is an interesting approach using side-effects’ similarities for drug target identification, meaning that there is a trend in drug discovery based on the identification of common off-targets of different drugs through the evidence of common side effects (4). An example of the off-targeting approach comprises proton pump inhibitors, which in addition to having some off-targets in the central nervous system (4) have also been shown to have a potent anti-tumour effect, through the inhibition of proton pumps on tumour cells (which are similar, but not identical, to gastric proton pumps (5-10)).

However, in addition to thinking about the careful identification of effective off-targeting drugs, we should also think about different systems of drug delivery. In the strategic platforms for nanomedicine, it is clearly stated that nanomedicine seeks to exploit the improved (and often novel) physical, chemical and biological properties of materials at the nanometric scale. However, these documents specify that there is an urgent need for biomimeticism, namely the process of simulating what occurs in nature. Exosomes are nanovesicles, naturally released from almost every cell in our body and which, whether in a normal or a diseased state, deliver a mess of molecules including proteins, lipids and nucleic acids. They are able to interact with the target cells within an organ or at distance using different mechanisms, including ligand-to-receptor interaction (11-12) and fusion with the cell plasma membrane via the transfer of their contents within the cell cytoplasm (13). Thus, exosomes appear as a vectorized signalling system operating inside a donor cell by either binding to the membrane receptors or directly interacting with internal compartments of the target cell. These notions place the exosome at the centre of the real novelties in translational science, and mark it as a potential candidate autologous nanoshuttles for drugs potentially useful for the future strategies in nanomedicine. The future use of exosomes for new therapeutic and diagnostic approaches has to be

discussed and given serious consideration. Exosomes are becoming the real novelty in the identification of novel biomarkers. In fact, new tests offering the possibility of the contemporary characterization and quantification of exosomes in human body fluid have been set up recently (14). This dual potentiality of the exosome recommends the use of these nanovesicles as the ideal tool in ‘theranostics’. This new area of nanomedicine focuses on multi-disciplinary research to build new systems for various nanobiomedical applications, ranging from the medical use of nanopatform-based diagnostic agents, to therapeutic agents and even possible future applications of diagnosis and therapy - theranostics. Theranostics is the medical application of nanobiotechnology and refers to highly specific medical intervention at the nanoscale in diagnosing, curing and preventing diseases. It includes the early detection of diseases, the monitoring of therapeutic responses and the targeted delivery of therapeutic agents. Theranostics at the nanometric-scale encompasses, nanoprobes, nanocarriers and nanodiagnostics. However, the most important task of a theranostic strategy concerns theranostic nanoformulations, which deal with the development of new agents based on a ‘whole in one approach’ that should have its maximal application in the field of personalized medicine.. The exosome appears as the ideal nanovector for theranostics, with maximal potentiality for targeting the disease site with only minimal side effects. If successful, the proof-of-concept in the use of exosomes as the autologous nanovector for both the diagnosis and therapy of major diseases will allow for widespread preclinical and clinical applications.

I have a dream, as well: “that serendipity, ideas and an open mind, will drive new research in biomedicine, acquiring the best results with the aim of freeing human beings from the nightmare of incurable diseases”

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