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Commentary

Is it enough just to demonstrate that the advanced therapy medicinal products do work or we would prefer to keep walking on the Moon?

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ABSTRACT

After several decades of continuous yet bumpy progress the advanced therapy medicinal products reached the stage when the first drugs with well documented efficacy started to be registered. However, in the disturbing chain of events, many of them were discontinued because of the lack of return on investment. By comparing this phenomenon to the fact that humans did not return to the Moon for already 50 years, primarily because of the lack of dedicated funds, this commentary proposes strategies how to avoid menace of the dead end threating to suffocate progress of the advanced medical therapies. While treatments for rare diseases can be defended by mixture of altruistic, inspiring and rational reasons, mostly covered by the fact that regardless of the price of the newly developed therapy, the total burden remains low, common diseases should be addressed in a different way. This needs to include precise modelling of the benefits which advanced therapy medicinal products bring for every condition, taking in account reduction of the costs of long, often life-long support of patients affected by such diseases. Without intention to steal romantic view on the scientific progress, powerful yet very expensive tools of advanced therapy medicinal products require urgent top-down decisions which include selection of priorities based on the financial modelling. Instead of spontaneous exploration in all directions, this commentary proposes an arranged marriage between scientific community and big investors sustained by combination of governmental requirements in the form of real time data sharing, reimbursement warranties according to demonstrated efficacy and clear recognition of the primary targets with accompanying pre-defined financial frameworks.

One thing above all is for sure: although hankering after constant climb and if you wish, after immortality has been proven problematic for Icarus and Faust, we cannot escape our nature. While there will be humans, there will be efforts to travel further, to build higher, to change more. There will be no peace in the minds till we find the cure for the last known disease and there will be no end in humans' wish to prolong our lives. So, the constant progress in all scientific fields, even despite possible moral dilemmas is imminent to us, earthy humans.

But in the same time, humans can behave strange. We tend to admire our progress regardless how unimportant it can be. So let's ask ourselves: indeed, do we keep the speed and much more importantly, the quality of moving forward constant? With a great sadness we have to admit that we don't. In series of recent analyses, it has been clearly shown that many scientific fields, including biomedicine are slowing down pace of their progress dramatically! Letting aside a ridiculous inflation in number of published papers bringing quantities which can be handled only by AI (with the hope that this process will not launch automatic shutdown caused by boredom), decline in several parameters of high quality - disruptiveness from 1950s till today is constant and rather sharp. So the major disruptiveness index (defined as a measure of how many articles will cite only that article without mentioning its predecessors), presented as well in the count of unique words used, dropped down for incredible 4 times! [1] (Btw, that parameter in physics and social sciences dropped down even more). Even more, majority of drugs which are launched on the market in the last two decades are “me too”, i.e. they are designed as slightly modified variants which act on already known molecular pathways and

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which in great majority of cases do not bring significant improvements [2].

So why is the pace of our progress slowing down? While placing the focus of this text on something else, let's just accept the fact that we are suffering from several problems. The paradigm of low hanging fruits is declaring that finding ways to cure what is caused by rather straightforward mechanisms was easier goal to achieve (e.g. antibiotics for infectious diseases, angioplasty for heart infarction, antihypertensive for hypertension, surgery for prolapse of the intervertebral disc, etc), all the rest what has been left is of a tougher sort. Our enemies which we still need to overcome are draining their dark energy by either very complex processes occurring in a very complex tissue (e.g. stroke) or they require the most sophisticated approaches overlapping with domain of God itself (e.g. genetic engineering for genetic disorders). So, do we really lack disruptive therapies for treating the toughest of the toughest?

While recently at the open public discussion aimed to promote awareness of brain diseases we were having a chat with a large group of lay people, someone mentioned a cure for cancer, as one of the most common examples of the medical progress in everyday language, and then someone else added: “If we have landed to the Moon already more than 50 years ago, we don't need to bother with doubts that all the diseases will become curable soon”. Alas! What a controversial statement! Indeed, we have landed on the Moon in 1969 and after that, a few times more till 1972. And then, that symbol, one of the most prominent we ever had, a proof of our supreme, almost God-like capability has been abruptly abandoned. Regardless of being in the core of the passion for discovering new spaces and despite its enormous scientific and symbolic importance, for more than 50 years we have not even tried to walk on the Moon again. Why?

While reading a series of articles written by experts in space research, which can all be summarized in: “Yes, we can, but it's too expensive, so, sorry, we won't do that again” [3], it is so tempting to draw a line connecting the space travel – stars, with the field of the regenerative medicine – stem cells. Advanced therapy medicinal products (ATMP) had and still have to pass many obstacles to become recognized as a fully relevant category of medical products, in their efficiency comparable to any others. However, while there is a growing list or reports coming from academia in which ATMP have been successfully used to cure otherwise fatal diseases; just for example read a wonderful case of successfully treated inherited junctional epidermolysis bullosa [4], it is important to stress that such expensive procedures require and at their start have attracted investments from industry, which recognized a possible chance for profit. Fighting on both battlefields, struggling to fulfil complex biomedical and regulatory requirements which often reminded on passing between Scylla and Charybdis (FDA and EMA), we have witnessed full registration of a rather long list of drugs which do exhibit therapeutic effects. The author of this text remembers very well one day in October 2009, when all major newspapers in Belgium were writing about a big success: EMA announced a full approval of ChondroCelect, ATMP based on autologous cartilage transplantation for knee patented by TiGenix from Leuven. Three years after, a huge study which involved 7 countries in addition confirmed its efficacy [5]. But alas! That was just an introduction in the very sad chain of events, never ever seen before in the history of drug development to such extent. Four years after registration and after providing a clear proof that ATMP works, Tigenix informed EMA about withdrawal of the product due to financial reasons. The product did not succeed to enter into reimbursement scheme in majority of countries and with the procedure which required expensive two-step surgical procedure, it could not sustain its existence. A very similar destiny, sometimes even linked to direct bankruptcy of the companies happened or they are just happening with several more products, including and not limited to Glybera, the first ever registered gene therapy for the treatment of lipoprotein lipase deficiency and Skysona, a therapy of fatal cerebral adrenoleukodystrophy. These and many others have been proven as therapeutically efficient, but most of them are not available anymore or they are in the process of withdrawal because “lack of the profit” [6–8].

So, what on earth is going on here? From the dawn of ATMP it became clear that we are playing with an expensive toy. Either cultivation and manipulation with stem cells, especially in the clinical-grade set up or manipulation with genes require a very large budget. Focused research with the goal to bring therapy for a particular disease is in the most of the cases not possible to finish without involvement of the industry. They (sometimes) have the budget ready for investment, but their absolute priority is return on investment. So are we now entering the phase which Moon travellers entered 50 years ago? Are we facing the dead end?

Without any doubt, we live in an interesting time. While spectrum of our research tools keeps becoming wider and a chance to do what has never been done before is increasing every day, we are proportionally faced with ethical and financial issues. With ATMP we have the tools, we know the methods, we see the path, but is it leading us anywhere? More than ever an army of scientists which spend their days and nights growing cells and injecting gene constructs should get much more precise instructions about budgetary categories within their final products should fit into. Although these words sound genuinely terrifying, for the first time in the history of biomedicine the question can you cure it is covered by the another one: how much it would cost?

With a wish to propose some general directions which we need to take, let's make a clear distinction between two very much different groups of diseases: rare and common. Although it is rather probable that registering a product/protocol which can significantly help to patients with rare diseases will not bring profit for the inventor by itself, simply because there are no enough patients for whom the product will be bought, we should take a position that in those cases national levels – governments, but as well in the case of Europe, European Commission should become involved as an interested party. When thinking about conditions under which national levels should intervene, experience from some European countries like Germany or UK suggests that everything should be done to open channels for fast and accurate exchange of data needed to estimate the efficacy, which is a prerequisite for reimbursement. For example, in the case of CAR-T therapy, Germany reimburses expenses based on individual patient outcomes, while UK defines the reimbursement rate based on long term follow up of all available data [9]. It cannot be stressed strong enough that without any exceptions, all data gathered during development and treatment by ATMP should be available in shared repositories, for example within Data Analysis and Real World Interrogation Network (DARWIN EU). Since number of treated patients with such products is very small, it is not surprising that attempts in the recent past, where every EU country negotiated their own terms, often failed. For example, separate negotiation of Bluebird for Zynteglo and Skysona in EU led to withdrawal from the European market [10]. One of the major reasons for this failure was lack of the minimum amount of critically needed data for precise estimation of benefits, which brings us back to one of the major messages about the need for more unified and harmonized approach of EU in this matter. In other words, EU Commission should get mandate to become strongly involved by setting up obligatory regulations in sharing the data needed for precise calculation of benefits, which will then help member states, but as well all other countries who would accept these regulations to intervene with their budgets.

Unfortunately, several attempts to solve this on bilateral and multilateral levels failed due to the fact that despite launching several initiatives in which a need for cross-border data sharing has been discussed as a policy issue, medical care together with sensitive medical data firmly remained in the hands of the member states. However, it seems that we are finally approaching the solution. European parliament accepted the cross-national data sharing strategy which in the next few years expect EU to become a space in which "data can flow within and across sectors, for the benefit of all" [11]. Keeping the momentum from the Sars-Cov2 pandemics, when a common strategy for ordering the vaccine unified EU, European Health Union and European Health Data Space are becoming the reality [12]. Coming back to the main topic of this article, one of the elements which will be very useful is not only a common European database which includes data from all clinical trials, but as well a set of instructions which defines harmonized format of medical files with procedure how to share them across borders without obstacles. Since in total we don't expect many users of the product for rare diseases, governments will not lose on that side, but their budget should be seen as investment in maintaining the pace of developing new therapies. From the past experiences, it is highly possible that some of the bricks in the process of building a new defence against certain pathologies, although not profitable by themselves, will be highly needed to perform other, even more disruptive steps. Such way of thinking is already supported by some regulatory levels. For example, in the Netherlands, cost-effectiveness analyses are dismissed when the total budget impact is smaller than 10 million euros [13]. In other words, reimbursement of ATMP for rare diseases has at least three possible benefits: altruistic, because we will save lives; inspiring, because we will demonstrate that less and less diagnoses are out of our reach and rational, because experience from those steps might lead to something even more disruptive.

Completely another strategy we should have with common diseases. As an example, let's think about one of the most common for which we desperately need a disruptive approach – stroke. It is obvious that a very expensive drug for stroke would bring enormous problems for total budgets, because of the high incidence of this pathological condition. However, here one should take in account that annual support of the patients who suffer from the consequences of the stroke are, at least in the Western countries, very high, reaching up to 60.000 usd per year [14]. When you combine these numbers with a high possibility that a patient after stroke incident lives another 10 or even more than 20 years, we are coming to the cumulative expense which might easily cross a psychological line of 1 M usd. In other words, if we would design ATMP which would reduce cost of post-stroke support for only 20%, we are roughly talking about treatment of 200.000 usd which might still be profitable. However, since we are talking about enormously large number of potential patients, without any doubts we need harmonized involvement of governments, which should be able to offer various types of benefits for investors. One of the possible might be prolongation of the patent rights, because in the current situation, inventors are focused on the grace period of 20 years after which they lose exclusive rights. If more time is needed to fully recover their starting investment, we should think of such possibility as well. It is important to recognize that very recently The European Federation of Pharmaceutical Industries and Associations (EFPIA) in their white paper points out towards two major elements in this matter: promoting patients access to ATMP and increasing sustainability of the health care systems. In a very concrete manner, new reimbursement schemes are proposed: those which distribute costs over time and implement adaptive budget analyses [15].

At the end, let's be realistic. Not everything that we face during development of new drugs can be improved, but nothing will be improved until we remove red herrings from the focus. Biomedical science was for centuries coloured in romantic shades comparable to art, but we simply cannot oust money from the equation any more. It would be enormous loss for humanity if ATMP would make the same turn like space research and if we would be forced to spend next 50 or more years just thinking of cells and gene constructs which saved lives to only several patients. Here is the simple fact: we still face enormous burden of life-long support of still untreatable diseases, so there is enormous budget sitting somewhere there. By using symbolic language, we could see this as borrowing from the funds which would be otherwise spent in the future for support of untreatable conditions and use them now to boost development of ATMP. But this should be done in a smart, well calculated way. Every scientist involved in development of new treatment is strongly emotionally tied to its work and they will always defend their newly discovered products by their hearts. But we don't have enough sources and time to let everyone walk in direction they choose freely. More than ever we need better defined top-down approach with clearly stated diseases for which we aim to develop ATMP and with the estimated end price of the final product which cannot be crossed to become acceptable. Examples of such calculations already exist [16]. If this would involve a clearly written list of medical conditions which will be fully reimbursed before some others, simply based on realistic calculations, let's make such priority lists. Everything seem to be much better than letting us to sink into despair because of the fear that investments will not pay off. So, once again, this is a call to use already available data and to make precise simulations in which domains we shall invest all our energy and funds, to achieve the goals without regretting afterwards. With the strong hope that emotions, love and humanity will not disappear from the equation, we need a well-planned arranged marriage between investors and scientists which will stay on the same side to prevent lose-lose outcomes. In other words, it would be such a shame to shut down the engines of enormously powerful ships in garages of our scientific institutions and not to continue to travel. Regardless how sweet or bitter lands are waiting for us somewhere there.

Declaration of competing interest

None.

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