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Hypes, hopes and translational challenges on the path to cures

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Unsustainable growth in health care expenditures has paralleled increased barriers and challenges on the path to cures, with very few effective novel treatments emerging from the translational Valley of Death despite billions of dollars invested in promising strategies like precision medicine, gene therapy, immunotherapy and stem cell therapy. Nevertheless, it seems that there is not a single month that goes by without an announcement of a possible cure, often generating an emotional rollercoaster in patients and their families, not to say the enormous time-consuming efforts imposed on physicians and health care providers in general, who get bombarded by inquiries of hopeful patients and their relatives.

How can anyone distinguish between hypes and hopes, between inflated or misleading press releases and the cautious optimism needed to identify an effective treatment or even a possible cure? The challenge is complex but thanks to modern digital technologies, databases and internet connectivity, more information is currently available that can help make that critical differentiation. Open access to on line search engines, expert opinions, the availability of increasingly more competent and prepared disease-specific foundations, as well as patient advocate networks, altogether provide a trustworthy resource and possible guidance in the direction of enabling patients and their families to make more informed decisions. Information on ongoing clinical trials is available on www.clinicaltrials.gov, which includes inclusion and exclusion criteria to inform patients and their families of who might be a potential candidate for any selected therapeutic strategy announced. The sites also identify those who could be of assistance to help screen possible trials for patients. Thus, many patients and their families now know how to screen for new proposed treatment and clinics, and can select trials listed on www.clinicaltrials.gov. These sites can help patients identify centers that follow a rigorous review process of the proposed interventions through proper ethic committees and appropriate informed consent procedures. Therefore, the clinical trials are reviewed and implemented under strict guidelines.

Much of the hype generated from research progress announcements have generally resulted from over-interpretation of the realistic translational potential of pre-clinical studies, such as small animal studies, which often represent a poor predictor of clinical translational relevance. Diabetes, for example, has been "cured" in over 400 rodent studies, however, none of these treatments has so far to be able to "cure" Type 1 Diabetes in humans. A similar story can be told for cancer. Furthermore, preclinical studies that require the use of large animals, the use of which raise even greater ethical concerns, often do not offer suitable model systems that reflect the targeted clinical condition in humans, such as the case of many autoimmune diseases for which there are no equivalent large animal models. In addition, drug combinations that may be needed in the clinical setting may not be available or effective for treatment in the selected pre-clinical model system.

Frequently, too much emphasis is placed on the requirement of mechanistic pre-clinical studies before being allowed to proceed to a pilot clinical trial, thus wasting years of time, effort and precious research funds. In many instances, the best hope for testing clinical relevance and safety of a therapeutic strategy is through a pilot clinical trial, followed by validation in a rigorously designed prospective randomized, controlled trial. If effective, the mechanistic details of the therapy can then be determined.

Regulatory agencies are becoming increasingly aware of the need to streamline the regulatory process without imposing unnecessary and excessive

animal trials, with the related unsustainable costs and delays in the path to clinical testing. Organization such as Faster Cures (www.fastercures.org), The Cure Alliance (www.thecurealliance.org), the Manhattan Institute Project FDA (www.manhattan-institute.ore/projectfda/) and 21st Century Cures (www.energycommerce.house.gov/cures) are joining the collaborative effort to address and resolve some of these challenges to expedite better treatments and cures for disease. Several countries are leading the way in innovation and streamlining of the regulatory process to make sure that the regulatory infrastructure and guidelines can be modernized and can keep the pace with scientific innovation and pipeline discovery.

One of the greatest challenges is the translation of precision medicine into routine clinical care, with the implementation of actionable genes, biomarkers and big data. Other challenges include the approval of trials that utilize multiple drugs and/or sequential-integrated therapeutic strategies involving combinations of cell therapies, devices, and biologics.

Despite the hypes of recent decades, there are indicators that can allow us to be cautiously optimistic and confident that novel therapeutic strategies are within reach, that the mission to find better treatments for diseases is indeed possible. In the area of Type 1 Diabetes, for example, the long-term results of clinical islet transplantation have substantially improved in the past 15 years and significant steps forward have been made in the area of generating unlimited sources of insulin-producing cells. Immunomodulation, immune barrier technologies and immune tolerance induction, both to allow for immunosuppression-free allograft survival and to reverse autoimmunity by restoration of self-tolerance, have made significant progress in preclinical model systems and in clinical pilot trials. Intervention trials in T1D have shown for the first time the potential to preserve beta cell function, rather than delaying beta cell destruction following T1D onset. The failure of testing mono-therapies and single-agent strategies have led the scientific community to question the often imposed "single new entity" testing dogma. This dogma was imposed by review study sections and regulatory agencies and was based on the previous century's paradigm that single agents had to be tested one agent at a time to fully understand their safety, efficacy and mechanism of action. Fortunately, this paradigm has been progressively replaced by the awareness that multiple synergistic and possibly sequentially integrated strategies may be needed to address complex challenges of chronic diseases. One example is the reversal of an autoimmune process and restoration of self-tolerance, or prevention of rejection and recurrence of autoimmunity following transplantation of insulin-producing cells in Type 1 Diabetes. Another example is the use of genomic sequencing and big data analyses to identify networks of actionable genes regulating an individual's cancer, then using high throughput sequencing of large drug libraries to match drugs with the networks. In this strategy lies the hope of applying precision medicine to effective targeted cancer therapies[1-5].

Too often efforts to streamline and facilitate clinical translation have been derailed and deliberately labeled as attempts to "deregulate" the system or favors to some obscure multinational economic interests. The failure to streamline and facilitate clinical translation has only helped promote inactivity, insurmountable barriers and road blocks to the development of cost-effective cures by imposing unsustainable developmental times and costs for clinical translation of a possible novel therapeutic option. Interestingly, a major paradox has emerged: unsustainable growth in health care expenditures paralleled by increased barriers and challenges of the pathway to better therapies and cures. The enormous health care market, which in the US alone represents over $2.5 trillion per year, or approximately 20% of the GDP, has favored the emergence of new models and strategies that consider and capitalize on the care of one-third of the population affected by chronic degenerative and incurable disease conditions, thus, an enormous conflict of interest exists. The result is that very little is invested in prevention, cure, or eradication of disease conditions, while trillions are spent, and profits made, on the daily care of these patients. To compound the conflict of interest, research and development industrial complex has arisen, whose purpose is to develop increasingly expensive new drugs that may extend life span in the presence of a terminal disease condition by only a few weeks. Their economic success depends on the demonstration that the few additional weeks of life-span are statistically significant in a phase 3 clinical trial endpoint and not on the overall benefit the drug has on quality of life and real benefit to the patients. These new drugs are often approved and introduced to the market at exorbitant prices. One has to ask whether these unsustainable (or sustainable by selected

portions of the population) costs of health care are the result of deregulation of cost-containment/control for approved therapies, or are the natural consequence of a system in which bringing to market of new successful molecular entities can take ten years and cost in excess of $7 billion?

If the cost and time for developing a new treatment option keep increasing, fewer and fewer physician-scientists will be willing to choose a career in clinical translational research, while established scientists will be forced to abandon to abandon the pursuit of clinical translational research. In parallel, fewer and fewer multinational blocks will decide which strategies to bring forward, not necessarily for their impact on quality of life and increasing lifespan, but for considerations related to expanding markets for incurable diseases, therefore determining when and who will be able to access a potential new cure based upon economic convenience. The costs for such treatments will become progressively more unsustainable by the health care systems, or unattainable by underinsured families who are unable to cover the costs of these treatments. The domino effect generated by the current system is resulting in a state of emergency that all interest parties and concerned individuals should address. Together we need to collaboratively discuss possible solutions in the interest of hundreds of millions who are affected by chronic degenerative and incurable diseases[6].

Here are possible solutions:

- Engage all key players (academic, regulatory, industry, patients, insurances, health care reimbursement agencies and insurances) to develop strategies to reduce the domino effect produced by sky-rocketing R&D costs and a lengthy regulatory approval process;
- Develop integrated solutions (i.e., doubling NIH funding alone will not address the translational "Valley of Death");
- All decisions and proposed strategies should be consistent with the final goal of developing cures in the fastest, most efficient and safest way possible (Figure 1);
- Develop and implement accelerated pathways for approval of pilot clinical trials, with subsequent temporary approval for promising therapies that do not impose safety concerns for the general population but that still require validation in rigorous prospective controlled trials (i.e., Arnold Caplan's progressive approval; Japan and other countries recent guidelines)[7];

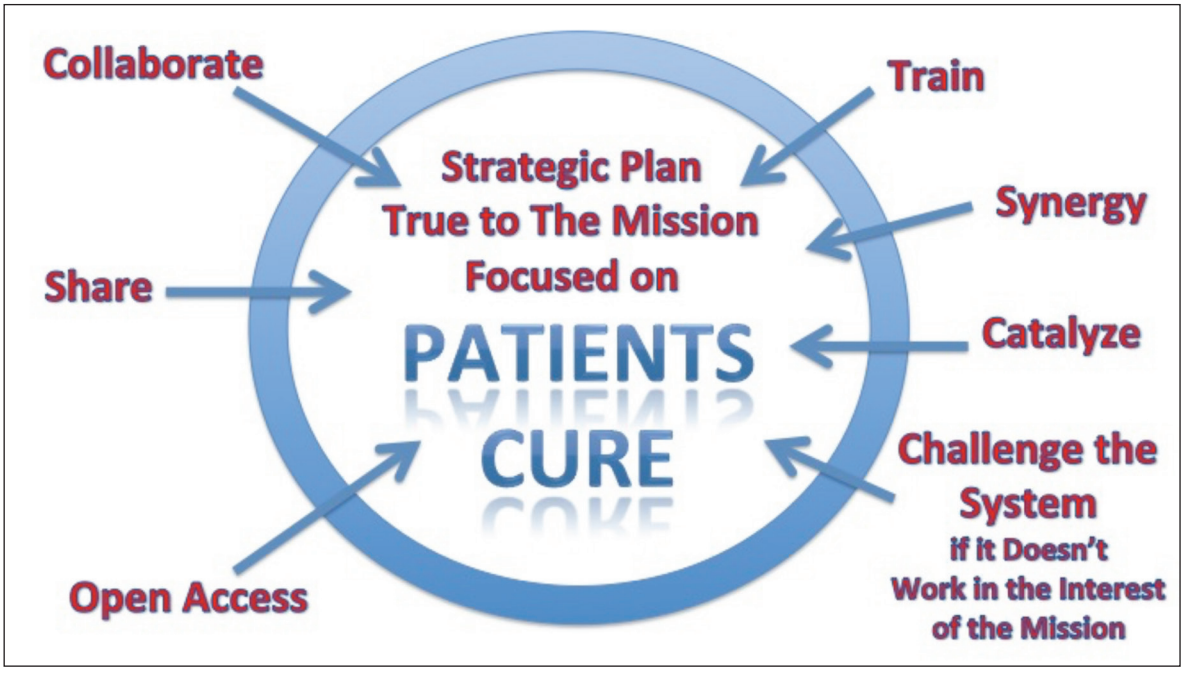

Figure 1. Proposed patient-centric model for guiding decision-making process towards the development of novel treatment strategies in the fastest, most efficient and safest way possible. Every yes/no decision should answer the central question: is this strategic decision helping us to move towards a potential new cure in the fastest most efficient and safest way possible?

- Mandate real-time, open access full disclosure of results and all side effects/serious adverse events, after initial conditional approval, with established stopping rules;
- Promote Public-Private-Partnership to reduce R&D costs and their collaborative interaction with regulatory and reimbursement agencies, for development of more efficient regulatory paths, but with definition of cost-control mechanisms for approved therapies that may result from more cost-effective R&D pathways.

Despite the challenges and the hypes of the past decades, greater progress needs to be made on the path to better treatments and even cures. Translational research efforts with early collaborative involvement of regulatory agencies and all key players could facilitate the development of novel therapeutic strategies in a clinically relevant timeframe. Doing so would offer realistic means to justify a renewed, yet cautious optimism for the potential development of new cures in more efficient and timely manner, while keeping patient safety central.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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