The drug delivery field at the inflection point: Time to fight its way out of the egg

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Abstract

The world is becoming a better place, in part, by breakthrough findings by scientists. In the drug delivery field, many breakthrough formulations have been achieved helping patients deal with various diseases effectively. The recent progress, however, has been slowing down, and many important drug delivery problems have not been resolved. They can be overcome by understanding the causes and finding the remedies. For the last three decades, the field has been overwhelmed by nanotechnology, nanomedicine, and many nano-sized drug delivery systems. Disappointing outcomes of nano-sized formulations (nanoformulations) in clinical studies indicate that our overall approach of nanomedicine needs serious reevaluation. The limited advantages of nanoformulations were drastically exaggerated, and the assumptions used in nanomedicine and nanoformulations turned out to be inapplicable to clinical applications. The drug delivery field is at the strategic inflection point, and we all have to face the reality by absorbing the inconvenient truth and fight our way out of the egg to break the ill-conceived illusion of nanomedicine. Scientists are proud of their independent thinking and their work that can change the world, but the current climate does not allow them to be true scientists. The future of the drug delivery field depends on how effectively we can find talented young scientists with motivation, cultivate them with resources, provide them with an environment for the free exchange of ideas, and nurture them with purpose, passion, and the conviction of doing meaningful science.

Keywords: nano-sized drug delivery systems, nanoformulations, clinical trials, inflection point, inconvenient truth, advantage of nanoformulations, limitations of nanoformulations, future of drug delivery

1. A very brief history of science and drug delivery

When we look back at the history of scientific advances, we are always marveled by those who came up with ideas against the majority or with ideas that did not before exist. Nicolaus Copernicus, Johannes Kepler, and Galileo Galilei suggested that the Earth revolves around the Sun, based on the data, against the common belief by the majority at the time. Charles Darwin framed the theory of evolution from the data he collected at Galapagos. Sir Isaac Newton and Albert Einstein came up with theories of gravity and the fabric of time, respectively, that were not known to humans before their times. One question to ask is what unique characteristics allow them to come up with such earth-shattering ideas? There are no easy answers, as there are too many traits to be analyzed and simplified into a few parameters [1]. All those great scientists, however, were able to see problems where nobody else realized that they even existed [2, 3], and had "passionately curious minds" [4] to learn what they did not know based on scientific data and reasoning. The data-based deduction is what great scientists do. Fast forward to the Year 2017. Do we have such passionately curious minds around us now in the drug delivery field? The passionately curious minds lead to different ideas from existing dogmas, eventually leading to new findings that make real differences. The advances in science will occur fast, if different opinions are cherished. Having opposing views and discussing them leads to progress. The current political system where two opposing views fight constantly against each other appears to paralyze the government, but it is exactly the reason why the democratic society progresses, albeit slowly, without major catastrophe. The democratic society makes progress by trial-and-error, trying one idea at a time, and it works even though it seems painfully slow.

The history of the drug delivery field is less than 70 years old. The term "controlled drug delivery system" means a formulation that delivers a drug at a rate controlled by the formulation itself. Thus, a formulation that does not have a built-in mechanism of controlling the drug release rate is called an "immediate release" system. The controlled drug delivery includes "sustained release", "timed release", "extended release", "modified release", "programmed release", and others. The drug delivery technology began in 1952 with the introduction of the Spansule technology that delivers a drug for 12 hours [5, 6]. Compared with taking a drug every 6 hours or every 8 hours, twice-a-day formulation was a game changer in enhancing the patients' convenience and compliance. The introduction of the first revolutionary idea was followed by many controlled release formulations, especially for oral and transdermal administrations, over the next 30 years [7]. The mechanisms of controlled drug delivery were largely established during that period. Since the 1980s, however, development of clinically used products became sluggish. This was partly due to the difficulties in the mission of drug delivery systems. The mission requires much more than simply releasing a drug at a certain rate. The drug has to be delivered to targets overcoming biological barriers, and in some cases, the temporal drug delivery is required. The drug delivery field needs new revolutionizing concepts to improve drug delivery for treating heart disease, cancer, diabetes, Parkinson's disease, Alzheimer's disease, and various other diseases.

2. Drug delivery research: Where are we now?

Many drug delivery scientists contribute to the advances of drug delivery technologies in different ways ranging from basic study to product development. Developing a successful

clinical formulation requires synthesis of a new chemical entity, preformulation characterization, formulation design, biopharmaceutical characterization, process optimization, and scale-up manufacturing [8]. For each drug delivery system approved by the U.S. Food and Drug Administration (FDA), there are hundreds of formulations tested by many scientists and engineers. In the drug delivery field, whatever research area a scientist is engaged in, the ultimate goal is to contribute to or develop formulations making clinical impacts. Reviews on the history of drug delivery systems are available [9-11]. Here, the focus is on the drug delivery field for the last 30 years.

Many new oral and transdermal controlled release formulations have been introduced for clinical use. While each formulation may be unique, the underlying principles of controlling drug release remain the same as when they were developed several decades ago. Most of the oral formulations use either dissolution- or diffusion-controlled mechanisms, or a combination of both. Unlike oral and transdermal drug delivery systems, development of injectable long-acting depot formulations and targeted delivery intravenous formulations has been sluggish. The potential of new drug delivery technologies, especially based on nanotechnology, has not been translated into clinical formulations that benefit patients. It is necessary to understand where we are and what happened, so that we can escape from the current stalemate to expand our research horizons and to accelerate advances in drug delivery technologies for the future [12]. The following sections deal with the nature of nanomedicine and nanoformulations with critical assessments. The main intention of the analysis is to understand the situation correctly so that the correct answers can be found.

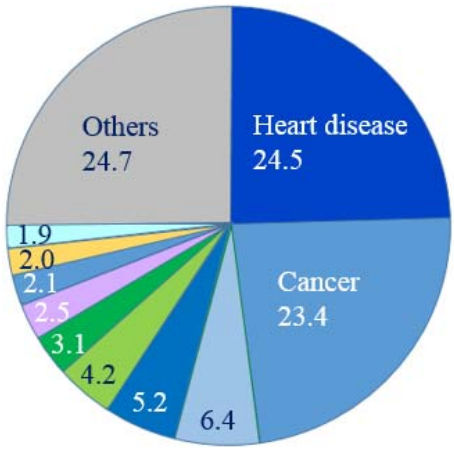
2.1. The 10 leading causes of death in U.S.A.

The Centers for Disease Control and Prevention (CDC) published leading causes of death for 2014 in the United States by age, sex, race, and Hispanic origin based on information from all death certificates filed in the 50 states and the District of Columbia in 2014 [13]. The 10 leading causes of death for males and females are shown in Figure 1. There are slight differences in rank order between males and females, but diseases of the heart, malignant neoplasms, and chronic lower respiratory diseases occupy half of all death. Stroke, Alzheimer's disease, diabetes, and influenza and pneumonia account for 11~16% of all death. When it comes to malignant neoplasms, there are dozens of different tumors occurring in the oral cavity and pharynx, esophagus, stomach, colon, rectum and anus, liver and intrahepatic bile ducts, pancreas, larynx, trachea, bronchus and lung, skin, breast, uterus, and other parts of the CNS [13]. Each of them requires different treatment. Each tumor is unique and does not represent others, and no single anticancer drug is able to treat all tumors.

As shown in Figure 1, there are many important diseases to treat, and even in cancer, there are many different types of tumors to conquer. Despite such diversity in diseases and tumor types, however, the majority of current research on drug delivery has been focused only on tumor-targeted drug delivery. Even in this highly focused research topic, little progress has been made after almost three decades of research. It is time to take a step back and absorb the fact and examine the current status of the drug delivery field. First, why does most of the current drug delivery research deal with only tumor-targeted drug delivery? Second, why has the progress in tumor-targeted drug delivery been so slow? Third, what are the reasons for the current stalemate

in drug delivery in general? Fourth, what can we do to overcome this conundrum? Without proper analysis and understanding of the current situation, further advances in the future will be hindered.

Males



Causes	Males	Females
Heart diseases	24.5%	22.3%
Cancer	23.4%	21.6%
Chronic lower respiratory diseases	5.2%	6.0%
Stroke	4.2%	6.0%
Alzheimer's disease	2.1%	5.0%
Unintentional injuries	6.4%	3.9%
Diabetes	3.1%	2.7%
Suicide	2.5%	
Influenza and pneumonia	2.0%	2.2%
Chronic liver disease and cirrhosis	1.9%	
Kidney disease		1.8%
Septicemia		1.6%
Others	24.7%	26.9%

Fig. 1. Percent distribution of the 10 leading causes of death, by sex: United States, 2014. (From [13]).

2.2. What are the definitions of nanotechnology, nanomedicine, and nanoformulation anyway?

For the last three decades, the drug delivery field has been overwhelmed by nanomedicine, which is an offshoot of nanotechnology. The term "nanotechnology" was defined as "science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers" [14]. The term "nanomedicine" refers to "highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve" [15]. It is further explained that "It is at this size scale - about 100 nanometers or less - that biological molecules and structures operate in living cells" [15]. These definitions sound magnificent and futuristic, but closer examination of the definitions to acquire better understanding makes it confusing. First, if the matter we are dealing with is larger than 100 nm, is it not qualified to be called nanotechnology? What are the scientific criteria that set the boundary at 100 nm? Would it make a sense, if the size is limited to 200 nm, 300 nm, or larger? Second, the description of nanomedicine is so generic that the term "nanomedicine" can be easily named by others, e.g., "molecular medicine". After all, if medical interventions are made at the molecular scale, isn't it better to call it "molecular medicine"? If engineering occurs at the molecular level, isn't it what we call chemistry, biochemistry, and molecular biology? The prefix "nano" has dominated the science throughout the world with no particular rationale; just like the prefix "i" dominated the market since the successful introduction of iPod. It is these arbitrary, generic definitions of nanotechnology and nanomedicine that set the stage of a decades-long stray from the otherwise more productive, useful, and practical path. Even nowadays, many scientists, engineers, and

clinicians who are not familiar with the drug delivery field think that nanotechnology or nanomedicine, will solve their research problems regardless of the nature of the problems.

In drug delivery systems, there are not many systems that are truly less than 100 nm in size. The drug delivery systems exist to deliver a drug, and the system less than 100 nm does not have enough reservoir space for effective drug delivery. Most polymer micelles, which are one of the main representatives of nanomedicine, are much larger than 100 nm, especially after a drug is loaded. The drug delivery systems are usually larger than 100 nm by necessity, but they are not really nanosystems according to the definition provided by the National Nanotechnology Initiative [14]. What nonsense! More correctly, what nano-nonsense!

For the drug delivery field the definition of nanomedicine described by the FDA may be more relevant. According to the FDA Guidance for Industry regarding nanotechnology products, nanomaterials are defined as materials that have at least one dimension in the size range of approximately 1 nm to 100 nm [16]. This follows the definition by the National Nanotechnology Initiative [14]. The FDA, however, chose to include a much broader meaning of nanomaterials by asking "Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)" [16]. This definition is very forgiving in the size limitation, and indeed many products can fall into the definition of the nanotechnology product. This is why when drug products containing nanomaterials in the U.S. were analyzed, more than 350 products were shown to contain nanomaterials [17]. This number, however, is misleading, because the number is based on mostly traditional formulations, such as liposome, emulsion, and drug crystals which were introduced several decades ago.

For practical reasons in the absence of a scientifically sound definition, any system less than about 1,000 nm will be regarded as a nano-scale system in this article. Drug delivery systems less than 1,000 nm have been called by various names, including nanoparticles, nanocrystals, polymer micelles, nanoliposomes, nanoemulsions, nanovehicles, nanostructures, nanopharmaceuticals, nanocarriers, and nanoformulations. In this article, specific names will be used if they were used in the references cited. Otherwise, the term "nanoparticle" or "nanoformulation" will be used to describe all nano-scale delivery systems.

Nanoparticles were used in drug delivery as early as in 1976 [18], and were distinguished from other delivery systems, such as liposomes [19]. In the heat of nanotechnology, however, liposomes and all other drug delivery systems morphed into nanoformulations. Such a name change does not alter the fundamental properties of delivery systems. It, however, makes people feel better, as it sounds more stylish and looks so modern. Drug targeting to tumors using nanoparticle and monoclonal antibodies was suggested before 1983 [20]. It was already understood that nanoparticles less than 100 nm in the systemic circulation could reach the extravascular sites through fenestrations in the endothelial cells of the blood vessels in the liver, spleen and bone marrow [20]. Capillaries in tumor regions were thought to be leaky, i.e., have greater permeability than normal, because of tissue inflammation [19, 21].

2.3. Why independent examination of nanoformulations is necessary

To understand why and how we ended up where we are now, we need an "independent" examination. The term "independent" here means an impartial approach between "confirmation bias" and "negativity bias". A mind with a confirmation bias seeks out data that support the preconceived idea, while a mind with a negativity bias does the same with the opposite goal. One can easily understand this impasse, if one spends 10 minutes watching a debate between Democratic and Republican politicians. Their views on the same event cannot be so opposite. We need to step back from a predetermined mind to find a breakthrough [22]. The former President Barak Obama mentioned that the new media ecosystem "means everything is true and nothing is true" [23]. Let's put one's ideology, ego and/or financial conflict [24] aside, and objectively investigate what happened in the nanomedicine field based on the data.

Talking about the truth and criticizing something that most believe is difficult. Quite often, those who criticize the mainstream idea are labeled as pessimistic or politically motivated, as if science has to rely on the majority opinion or blind optimism. Accurate data interpretation has nothing to do with one's feeling. If the data point to a different direction from the expected, a new direction should be explored. This is of course assuming that the data are not fake. In his book "Only the Paranoid Survive", Andy Grove pointed out that an industry going through a strategic inflection point follows a sequence of denial, anger, bargaining, depression, and ultimately, acceptance [25]. Not only businessmen but some parents who raised teenagers would also understand. Going through an unknown future requires an accurate grasp of the reality, identification of the source of the problems, and preparation for the future. Only those with an independent mindset can go through such due diligent work, because they are not biased and not influenced by internal and external factors.

2.4. Limitations of nanoformulations

Nanoformulations have been a darling of drug delivery scientists throughout the world. Because of so much affection, it has been slow to recognize the limitations and pitfalls of nanoformulations. The same is true with nanomedicine and nanotechnology. The limitations of nanoformulations can be easily appreciated by asking a few questions.

2.4.1. Are nanoformulations good only for tumor-targeted drug delivery?

Over the last 20 years, the number of publications on nanomedicine in drug delivery has been large totaling 24,665 by the end of 2016 as shown in Figure 2. The search terms "nano" and "drug delivery" were used in ScienceDirect to include nanomedicine and all other nano-based drug delivery systems. In 2016 alone 4,564 papers were published. If the search is changed to "nano" and "tumor", the total number of articles until 2016 becomes 20,251. It is assumed that anything nano used in papers dealing with tumors is for studying drug delivery to a tumor. More than 82% of the papers dealing with nanomedicine are about tumors. This is a large number of articles, and can be considered to be an indicator of high productivity. High productivity, however, is not the same as high quality or clinical relevance. Despite the large number of publications, the translation of the published studies to clinical applications has been disappointing [26, 27].

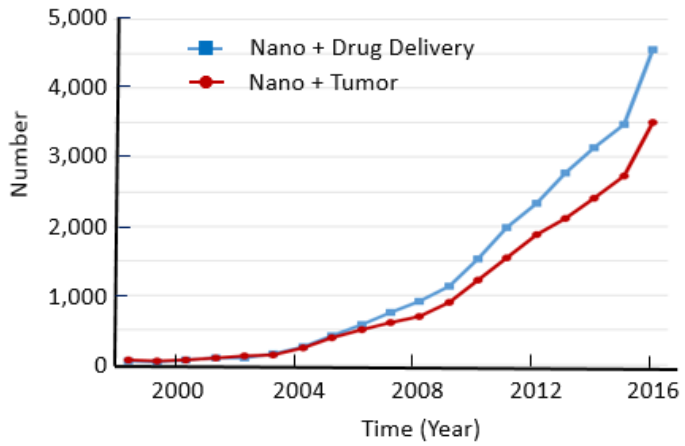


Fig. 2. The number of published articles on "nano + drug delivery" (blue) and "nano + tumor" (red) as a function of year. The search was done using ScienceDirect by Elsevier.

There are two important questions to ask regarding nanomedicine and tumors. First, why do the majority of papers on nanomedicine deal with only tumors? Is nanomedicine not useful or good enough to solve other medical problems? Unfortunately, the answer is that nanomedicine has not been able to solve any medical problems, including tumors. Second, why have so many research articles on drug delivery not been correlated with the number of new drug delivery systems that are approved by the FDA to benefit patients? It is important to find answers to these questions to determine what can be done to make the drug delivery research more clinically useful in the future.

2.4.2. What are the results of clinical studies of nanoformulations?

For any drug formulation to move forward, it needs to be tested for their safety and efficacy using various models, including *in vitro* cell cultures and small animal studies. In retrospect, a critical mistake many drug delivery scientists made was exercising their confirmation bias on "tumor-targeted nanoparticle systems" in its extreme. When a drug delivery system covered with a ligand or an antibody that binds to cancer cells is introduced to cells cultured in a petri dish, the system is expected to attach to the cells, just because the target cells are widely exposed to the system. The tragic mistake began here when many scientists called it "tumor-targeted" drug delivery. Such systems were subsequently tested in xenograft mouse models. Usually, human cancer cells are introduced into mice and the cells are allowed to grow for a few weeks. After introduction of "tumor-targeted" nanoparticles identified from *in vitro* cell culture studies, the tumor size decreases; usually smaller than the tumors treated with a control solution formulation. This was considered a confirmation of the cell culture study, and thus, the tumor targeting, at least in mice. This approach would have caused no concern, if the results observed in the mouse models were reproduced in clinical studies. Unfortunately, none of the nanoformulations that showed some efficacy in mouse models met the expectations in clinical studies.

Table 1 lists nanoparticle drug delivery systems that received media coverage when they were tested in clinical trials. In particular, 5 nanocarriers received attention in 2012. All 5 nanocarriers in clinical trials in 2012 were terminated by 2016 due to the lack of efficacy, as shown in the updated status column in Table 1. The safety study of CALAA-01 to treat solid tumor cancers by Calando Pharmaceuticals was terminated in October 2013 [28]. BIND

Therapeutics decided to halt the clinical trial of BIND-014 due to poor objective response rate on April 6, 2016 [29]. For NC-6004 (Nanoplatin), a clinical study to treat pancreatic cancer in Asia was last updated on January 8, 2014 [30], and its Phase I trial in head and neck cancers in Japan was discontinued on December 21, 2016 [31]. Nippon Kayaku Co., Ltd. announced on July 05, 2016 that the polymeric micelle anti-cancer drug NK105 by NanoCarrier did not meet the primary endpoint of statistical non-inferiority of progression free survival in a phase III clinical study [32]. Cerulean Pharma announced on August 19, 2016 that the Phase II combo study with its lead candidate CRLX101 failed when the cocktail treatment was tested against a standard-of-care option in patients with non-small cell lung cancer [33, 34].

Table 1: Nanoscale drug carriers in clinical trials in 2012. (From Reference [35]).

Company	Drug	Formulation	Status in 2012	Updated Status
Calando Pharmaceuticals	CALAA-01	A polymer nanocarrier containing gene-silencing RNA	Phase I	Terminated in 2013
BIND Biosciences	BIND-014	A polymer nanocarrier targeted to cancer cells carries docetaxel	Phase I	Terminated in 2016
Nippon Kayaku	NK105	A polymer nanocarrier containing paclitaxel	Phase III	Terminated in 2016
NanoCarrier	Nanoplatin (NC-6004)	A polymer nanocarrier containing cisplatin	Phase I/II	Terminated in 2014
Cerulean Pharma	CRLX101	A pH-sensitive polymer nanocarrier releases camptothecin in the acidic environment of cancer cells	Phase II	Terminated in 2016

Delivery efficiencies for cancer nanomedicines are low and not improving [36]. AuroLase® Therapy exploits optical properties of AuroShell® particles with a near infrared laser source to thermally destroy cancer tissue without significant damage to surrounding healthy tissue, but it did not show any efficacy [37]. in September 2016, Novavax stated that its respiratory syncytial virus (RSV) F-protein recombinant nanoparticle vaccine candidate failed a Phase III trial [38].

There are other nanoformulations in clinical trials as of 2016, but they are all based on liposomes and polymer micelles [39-42]. It is reminded that liposome was developed first in 1965 by Alec Bangham [43, 44], polymer micelles have been used since 1976 [45], nanoparticles were first prepared in 1976 [18], and nanocrystal formulations have been on the market since 1998 [46]. Does it make any sense that calling liposomes and polymer micelles nanoformulations and expect them to be more effective in treating diseases? The clinical trial results to date have brought somber reality of failed formulations to many nanomedicine researchers who started with both glitz and glamour in addition to hype. The bottom line is that the tumor targeting that might have been observed in some mouse models cannot be proven in the clinic [27]. The big idea driving this field is to transport cancer drugs directly to tumors, reducing side effects by avoiding contact with healthy tissue. But the clinical results in Table 1 have simply not delivered on the early promise of nanomedicine, leaving an open question about the future of nanoparticle research in cancer [34].

Almost all critical trials of nanoformulations have produced disappointing results, often because the mouse data are irrelevant to clinical applications. The *in vitro* studies on which they are based were themselves flawed [47]. An easy example of this is called "tumor targeting" based on *in vitro* cell culture studies. In addition, the results of inappropriate animal models were often exaggerated and used to reaffirm the existing dogma. Too many scientists conduct poorly conceived experiments with too few animals, fail to analyze them properly, and do not take all the steps necessary to reduce the risk of bias [47].

Translation of nanomedicines from preclinical proof of concept to clinical efficacy has been challenging at best [48]. An industry perspective on challenges and strategies in anti-cancer nanomedicine provides practical approaches. Since clinical cancers are so heterogeneous and inter-individual variations are very large, it is not practical to even assume that nanoformulations will improve treatment to all patients [48]. In the absence of animal models and testing protocols more relevant to human cancers, relying on the current xenograft mouse models is not expected to provide any clinically relevant information. More importantly, formulation-driven research needs to be converted to disease-driven development [12, 48]. Simply put, making more complicated nanoformulations will not improve the outcome, unless there is a better understanding of the disease itself. With all due respect to highly reputable engineers and polymer chemists who design complicated nanostructures, their nanoformulation-first approach is not working [12].

2.4.3. Are mouse data relevant to clinical application at all?

There may be many reasons for the lack of translation from mouse to humans. First, there are drastic differences in the body size between a mouse and a human. The tumors grown in mice have the size of 1~2 mm, which is equivalent to about 2~4 cm in humans, if proportional scale-up can be made. The blood volume of a mouse is about 2 mL, while that of a human is about 5 L. Such large differences make it very difficult to expect any extension of a result in a mouse study to a clinical study. Second, the results obtained in mouse studies were often exaggerated. Even in xenograft mouse models, none of the studies have shown complete reduction of tumors and full survival of the treated mice. All they have shown is a relatively larger decrease in tumor size as compared with the control treatment. The control treatment was simply using a solution formulation, and not the formulations used in clinical standard care [12]. Because of the inadequate selection of the control formulation in mouse studies, the results cannot be expected in humans where the control is the existing formulation proven to work in human patients. Thus, most nanoformulations do not show any better efficacy in clinical studies simply because the animal data are irrelevant and do not provide any insights into development of clinically effective formulations.

Even humans are not a good model for all humans. Many drugs work only for a fraction of people. A new chemical entity is approved by the FDA if it shows efficacy and safety. The efficacy is determined by comparing with that of the control. In clinical studies, the control is the best treatment mode currently available clinically. Many realize the limitations of mouse models representing human cancers [49], but continue using the same model. The question we should

ask now is whether this is what we want to continue. Do we continue doing the work that we know is not relevant in treating tumors in humans?

In retrospect, the lack of translation from mouse data to clinical applications is mainly due to our inability to see the fact and try to find excuses, because we are comfortable with the hypothesis we have, whether it is wrong or not. The fact is, we all have a tendency to dramatically underestimate the difficulty of what we are trying to solve, while dramatically overestimating our problem-solving ability [50]. Challenging to traditional ideas, Copernicus demonstrated that the known details about the motions and orbits of the planets could be explained *more simply* and *more coherently* by means of his basic assumption that the sun rather than the earth is at the center and the earth is taken to be the third planet circling the sun [51]. His simple explanation did not require any artificial and ad hoc assumptions. On the other hand, the previous geostatic system required a whole series of unrelated assumptions to explain the movements of planets observed at the time. Galileo believed that the geokinetic theory was simpler and more coherent than the geostatic theory, and it was also empirically superior in astronomy. Claiming that nanoformulations work and are better with no evidence is like appealing that the geostatic system is the fact. Explaining the clinical failures of the current nanoformulations requires a whole series of unrelated assumptions and excuses. All these difficulties in nanomedicine can be explained by one simple assumption that the enhanced permeability and retention (EPR) effect may exist in some mice (depending on how we define "enhanced"), but it is just not applicable to humans [52, 53]. It is time to escape from the excuses and denials to find real answers. As fittingly pointed out previously, several important pitfalls and conceptual drawbacks in tumor targeted drug delivery have to be acknowledged and corrected [54].

2.4.4. What about those formulations approved by the FDA?

A review article in 2014 describes the US FDA-approved nanopharmaceutical products which are categorized into liposomes, lipid-based (non-liposomal) formulations, PEGylated proteins/peptides/aptamers, nanocrystals, protein-drug conjugates, and surfactant-based formulations [55]. A recent article analyzing the drug products containing nanomaterials also showed similar but more extensive classifications [17]. Doxil® was the first liposome formulation approved by the FDA in 1995. Doxil is frequently hailed as a product of nanotechnology, but it does not make any sense. The efficacy of doxorubicin delivered by Doxil is the same as other formulations, but the side effect of cardiotoxicity was reduced [56]. If Doxil is truly a nanotechnology product, it is supposed to be more efficient than the previous doxorubicin formulations. The lipid-based formulations are for amphotericin B in colloidal dispersion. PEGylated proteins/peptides/aptamers have been approved since 1990, and they are simply chemically modified (to graft PEG) molecules. All nanocrystal formulations have been approved since 2002 for oral administration [46]. Polymer micelle-based formulations are yet to be approved by the US FDA. Abraxane is a paclitaxel-albumin complex that can be made by simply spray drying the mixture [57, 58]. Furthermore, it has shown only an incremental improvement over previous drugs [24, 59]. Surfactant-based formulations have been approved since 1966, and these are mainly for improving the solubility. One needs to understand that all the nanopharmaceutical examples frequently cited in the literature have, in fact, little to do with the potential that nanotechnology is supposed to bring. All the above examples show that the

field has seen no real progress in the development of nanoformulations. The absence of any clinical translation of nanoformulations has made many in the nanotechnology field anxious, and this has led to including anything that looks nano into the list of successful nanoformulations. This simply shows how difficult it is to develop new, effective formulations based on nanoparticles.

3. Simple and obvious reasons why nanoformulations do not work in tumor-targeted drug delivery

Some want to use isolated examples to claim the success of the nanomedicine [60], but the overall outcome of the nanomedicine field is a fatal failure [61]. Currently, the majority of research articles published in the Journal of Controlled Release (JCR) and many other journals deal with nanomedicine, mostly tumor-targeted drug delivery. While we have been making advances in developing targeted drug delivery nanoparticle systems, it is time for all of us to consider the future beyond nanomedicine. For the last few decades, the potential of nanomedicine has remained as just that, potential. When will we see the translation of the potential to tangible drug delivery systems that can benefit patients? The stories on nanotechnology in drug delivery are only isolated pieces that do not provide any hint as to what the complete puzzle of the future drug delivery technology is supposed to look like. To fully assemble puzzle pieces, let's examine obvious shortcomings of the nanoformulation approach, and thus, what else we should seek out.

3.1. The fundamental concepts of nanotechnology and nanomedicine are not clear

Nanotechnology has been considered as an enabling technology. If nanotechnology is such an enabling technology, however, why have nanoformulations been used only for targeted delivery to tumors? Why has none of the nanotechnology been used to treat other important diseases? Even for tumor targeting, no nanoformulations have been effective. The main problem is that nanoparticles have been simply assumed to have a targeting property. It was just an assumption based on *in vitro* cell culture studies. NIH Nanomedicine website [15] does not provide any scientific reasons or evidence why nanomedicine will be better in treating various diseases. The National Nanotechnology Initiative does not provide any scientific evidence either [14].

Under the section of "Fundamental concepts in nanoscience and nanotechnology", the National Nanotechnology Initiative says, "Although modern nanoscience and nanotechnology are quite new, nanoscale materials were used for centuries. Alternate-sized gold and silver particles created colors in the stained glass windows of medieval churches hundreds of years ago. The artists back then just didn't know that the process they used to create these beautiful works of art actually led to changes in the composition of the materials they were working with". It is well known that Michael Faraday was fascinated by the ruby color of colloidal gold [62, 63]. The size of colloidal gold particles ranges from a few nanometers to micrometers. Does this mean that the current nanotechnology is simply a rehash of the hundreds-year old technology? Then, what does nanotechnology really mean? The National Nanotechnology Initiative further describes, "Nanotechnology is not simply working at ever smaller dimensions; rather, working at the nanoscale enables scientists to utilize the unique physical, chemical, mechanical, and optical

properties of materials that naturally occur at that scale" [64]. It continues, "Nanoscale materials have far larger surface areas than similar masses of larger-scale materials. As surface area per mass of a material increases, a greater amount of the material can come into contact with surrounding materials, thus affecting reactivity". The larger surface area of nanoscale materials has a few advantages in drug delivery (see Section 3.3 below), but it still does not explain how nanotechnology, or nanomedicine, brings new properties that traditional drug delivery systems do not have, and thus improved treatment.

3.2. Many assumptions used in nanomedicine are not validated

As mentioned above, almost all nanomedicine papers deal with tumor-targeted drug delivery. This is simply due to the convenience that the concept of the EPR effect nicely complements what people want to believe. The simplicity of the EPR effect in a world of complexity makes incomplete data in the eyes of the inexperienced majority easier to understand and adapt it. As long as the hypotheses and assumptions in the literature help their papers get published, no questions on the validity of those hypotheses/assumptions need to be raised. But simply blaming such populace is beyond offensive and intellectual laziness [65]. What happened in the drug delivery field is decades in the making. For many drug delivery scientists, constructing a simple set of assumptions providing a concise answer to the targeted drug delivery problem was better than nothing, and there was nothing to lose, especially when the funding agencies were promoting nanotechnology based on similarly simple, unproven assumptions with excess funding.

If all we have is a hammer, every problem looks like a nail [66]. When all we have a targeted drug delivery project, every data look like an EPR effect. The EPR effect has become a dogma and has been often claimed as a universal property of all solid tumor types even though it is unlikely to be present and equal in all tumors [48]. It was easy to grasp a small portion of a big picture that supports weak theories while explaining away a slew of inconvenient facts [66]. The EPR effect is nothing more than trying to see a pattern when it is simply a random phenomenon [67]. This is called the Toynbee Phenomenon. The scheme is set first and then select the fact that fits into the scheme [67]. With the vast information of the history, selecting certain convenient facts that supports the prefabricated, desired scheme is easy. Fitting the data, regardless of the nature of the data, to the EPR scheme will not resolve the targeted drug delivery problem. Unfortunately, however, that is what most articles in nanomedicine have been dealing with.

The efficacy of drug delivery systems, nanoformulations or not, is influenced by a number of factors, including survival in the blood, preventing premature drug release, delivery to target tumors, surviving the tumor microenvironment, endocytosis, intra-tumoral distribution, and the drug release kinetics within the tumor, and the concentration of the released drug [48]. If any step in this process is not functioning properly, the overall efficacy will not be observed. Unless all factors critical to the efficacy of drug delivery systems are optimized, simply expecting enhanced efficacy solely based on the EPR effect is a flawed concept [48]. After all these years focusing on nanomedicine, there still remain three main problems with nanoformulations: delivery, delivery, and delivery [68].

3.3. The advantages of nanoformulations are limited

One important advantage of nanoformulations is in improving water solubility of poorly soluble drugs. Nanocrystals and polymer micelles, in particular, are highly useful in increasing the water-solubility of poorly soluble drugs [69, 70]. Taxol® is the first paclitaxel formulation approved by the FDA. The Taxol formulation consists of ethanol:Cremophor EL 1:1 mixture. Cremophor EL is polyoxyethylated caster oil [71]. The water solubility of paclitaxel is around 0.3 μg/ml, and it is too low to deliver the therapeutic dose of paclitaxel in an aqueous solution, Cremophor EL forms polymer micelles to maintain paclitaxel dissolved in the hydrophobic core [72-74]. Taxol is diluted first in aqueous solution (e.g., 0.9% sodium chloride injection, or 5% dextrose in Ringer's injection) to a final concentration of 0.3~1.2 mg/mL [75]. The prepared solution is a polymer micelle formulation that maintains the paclitaxel concentration 1,000~4,000 times higher than its water solubility. Taxane drugs are usually dissolved in polymer micelles, such as Cremophor EL or Tween 80 (= Polysorbate 80) [76]. The critical micelle concentrations of these surfactants are known to be lower than 0.01% (w/v) [77]. Despite the fact that the Taxol® formulation (ethanol:Cremophor EL) is a polymer micelle formulation, nobody in the drug delivery field has called it a nanoformulation. This is simply because calling Taxol®, which began its Phase I clinical trials in 1984, a nanoformulation destroys the very illusion of nanomedicine.

The role of other delivery systems, such as liposomes, emulsions, and nanocrystals, are all useful for improving the water-solubility of poorly soluble drugs. As the drug is loaded inside the delivery system, each nanoformulation may have different interactions with blood components to alter its biodistribution. Thus, in some cases, the delivery system may have different side effects as compared with a solution formulation. The clinical pharmacokinetic implications of such formulations are mainly due to increasing the drug solubility. It really has little to do with targeted drug delivery to specific organs or tissues. It is well known that the majority of intravenously administered nanoparticles end up in the liver, lungs and spleen. Despite this fact, treating cancer with nanoformulations in those areas has not been easy. If the efficacies of Abraxane (paclitaxel-albumin complex), Taxotere (docetaxel in Polysorbate), and Genexol (paclitaxel in polymer micelle), are examined from the water-solubility point of view, it makes sense why they are not any better than Taxol in efficacy. All those formulations simply work by increasing the water solubility of paclitaxel and docetaxel. Improving water solubility of many drugs through nanosizing results in improved bioavailability [70].

The presence of the large surface area on nanoparticles also allows grafting of larger number of molecules that interact with target cells, such as ligands and antibodies (i.e., cell-binding molecules). The larger number of cell-binding molecules may result in multiple binding, and thus cooperative binding to the target cells, leading to higher affinity. The surface of nanoformulations can also be conjugated with various functional molecules to improve cellular uptake and improved efficacy [78, 79]. These potentially improved functions of nanoformulations are indeed important. A more important point to consider, however, is that such interaction can occur only after nanoformulations are delivered to the target cells. Effective delivery of nanoformulations to the target cells, which may exist in various different parts of the body, is yet to be improved.

3.4. Nanomedicine confirmation bias has not been questioned

When assumptions are made, they are good for only a particular situation where assumptions were valid, or at least reasonable, but the assumptions that may work in one situation cannot be transferred to other situations without validation. Currently, assumptions of the EPR effect, which may be valid in certain xenograft mouse models, are used without questioning as if it is a validated theory [48]. One must ask the validity of any assumption derived from a controlled set of experiments.

Figure 3 shows two pictures of Professor Allan Hoffman, one of the pioneers in the drug delivery field. As we all know, Professor Hoffman is smiling whenever we see him. Thus, it is safe to assume that Professor Hoffman is always smiling. Under this assumption, most people who see Figure 3-B will accept the conclusion that Figure 3-B is simply an upside-down version of Figure 3-A. It is scientists' job to make sure that the assumption is valid, especially when the experimental condition is changed. Here, one can ask a simple question, "Is Professor Hoffman in Figure 3-B really smiling?" The answer can be easily found out by simply placing Figure 3-B upside-down again. Professor Hoffman in Figure 3-B is not smiling. (Well, some may still claim that he is smiling, but this is a discussion for another time).

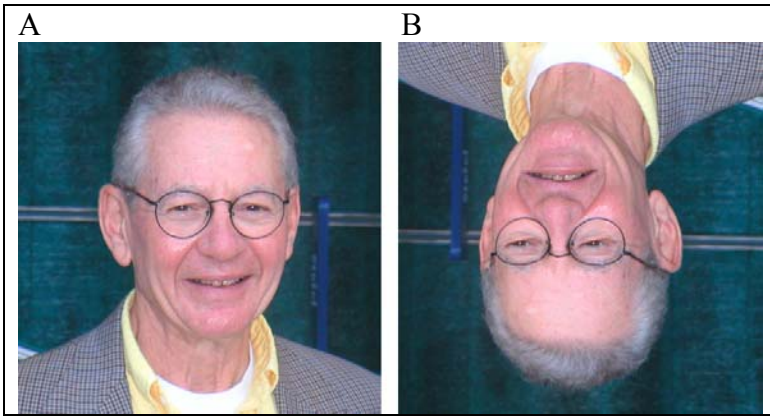


Fig. 3. A portrait (A) and an upside-down picture (B) of Professor Allan Hoffman (Modified from Reference [80]).

Once we have a certain preconceived idea on a certain topic, all data seem to explain what they know. It is hard to persuade them to challenge what they see and confirm independently. This confirmation bias is rampant in data interpretation. Quite frequently, we purchase goods, e.g., shirts or shoes, we do not need. The most common reason for wasting money on something that we don't use is that the shopper has faulty thinking, such as something really amazing is on sale, known as *choice-support cognitive bias* [81]. Another common reason is misperception of ourselves, or self-deception, causing purchase for fantasy, not reality [81]. This is what is happening in the nanomedicine field. There have been false assumptions that nanotechnology is better, the EPR effect allows passive targeting, PEGylation extends the circulation time in the blood, etc. All these assumptions may be valid under the condition they were derived, e.g., a certain formulation in a certain mouse model. Those assumptions are simply not valid when the experimental condition is changed. Extending such assumptions to humans is not warranted. The real downside of believing the EPR effect as a universal fact is that the data analysis begins with a wrong assumption, leading to an inaccurate conclusion. Jean François Champollion deciphered hieroglyphics, the ancient script of Egypt, written on the Rosetta Stone for the first time. He was

able to accomplish the feat by questioning his own most cherished beliefs [82]. His mindset was that it is our duty as scientists to question everything.

3.5. Nano on Reflection

The article entitled "Nano on reflection" describes how the different areas of nanotechnology have evolved during the last decade [83]. In the beginning, nanotechnology was hailed as a panacea for all problems. After decades of research and publication of tens of thousands of articles, the sentiment has soften a bit [83, 84]. While our understanding on the ability and toxicity of nanomaterials has improved, the initial potential of nanomedicine still remains as potential. It requires more time and long-term investment to overcome the hurdles and change the way we do science and engineering. The current status of nanotechnology can be best described by the comment by Joachim Schummer in the same article [85], and a few paragraphs from his comment are copied below.

"During the first decade, nanotechnology looked more like a global social movement rather than a developing research field. Because of vague definitions and unprecedented funding opportunities, nanotechnologies multiplied and grew at tremendous speed, largely by relabeling established research. If the hype had continued, the number of nano groups, centres and departments worldwide would nowadays outnumber those of physics and chemistry together [86]. That did not happen though. Nanotechnology did not turn into a new discipline of its own comparable to materials science and engineering, nor was it a temporary appearance. Instead it has developed into a large set of specialized research fields, as diverse as nanopore DNA sequencing and functional nanomaterials, each of which has established a remarkably stable interdisciplinary setting of outstanding productivity. At the end of the hype cycle, when public excitement vanishes, fields usually become more productive, albeit less visible. Although nanotechnology's current productivity, with potentially large impact on society, would require more social sciences and humanities (SSH) research, funding and interest therein have dropped. Perhaps one should rethink the role of the SSH within the hype cycle" [85].

One lesson to be learned from the nanoexperience is that any new technology requires long-term commitment to see its fruits, and simply creating hype with an exciting new name does not make it a breakthrough technology.

4. Drug delivery field at the strategic inflection point

A strategic inflection point is when the balance of forces shifts from the old ways of doing business to the new, and the change may be subtle but cause profound impact [25]. The drug delivery field is at a strategic inflection point. The old ways of doing business do not work anymore.

4.1. Why knowing the inconvenient truth should matter to all of us

Biomedical research in general has a "reproducibility crisis", and many studies' results cannot be duplicated and are untrustworthy, if not invalid [47, 87-90]. The issue is much deeper than just squandered time and money, as it is slowing the progress we need and diverting the

search for new treatments and cures [47]. This problem is exacerbated by professional pressure to publish splashy results to survive in a hyper-competitive environment. In this publish-or-perish culture, there are a lot of incentives to emphasize a portion of the results while leaving out inconvenient findings [47]. The nanomedicine hype to cure cancer has been drastically exaggerated by the possibility of massive financial reward. It is time to hold those disseminating the hype accountable.

There is a wrong perception that so-called "negative data" are not publishable. This is one of the reasons why all papers try to spin the minimal improvement, if any, as if a surprising conclusion exists. In truth, "negative data" are a positive discovery of what we thought was true is not really true [91]. Future research will face even more diminishing returns, unless we emphasize the importance of the inconvenient truth and are ready for a radical shift toward a new and more productive research paradigm [92]. Accepting inconvenient truth is painful, but that pain causes us to pay more attention, change, strive, innovate and survive [93]. We need to confront problems rather than avoiding them with sugar-coated false solutions.

4.2. Will the circle be unbroken?

The best ideas come in response to an important problem and thrive under constraints [3]. The key to creating a truly innovative culture is to elevate the importance of the problems. Clearly defining the problem at hand and constantly seeking out new problems brings innovations [3]. Solving a particular research problem starts with identifying and clearly defining the "right" problem. Finding answers to the "wrong" problem will simply waste our time. Once a problem is defined, experimental design is made based on the existing knowledge, or based on a hypothesis. If the obtained data are not able to explain the phenomena associated with the defined problem, then new experiments need to be done. Only after the data can explain various aspects of the problem, the drug delivery system can move to clinical studies. If the system fails in clinical studies, the problem needs to be defined again.

Many clinical trials of nanocarrier-based tumor targeted drug delivery have failed (Table 1). It is common that many clinical trials fail in Phase III. What is unusual here, however, is that clinical studies were done even in the absence of solid data supporting the efficacy of nanoformulations. All the data were collected from the xenograft mouse model and even those data do not show conclusively that the nanoformulations work. All they have demonstrated is that the tumor size is reduced more in comparison with the results of the control formulation, which in itself was a poor control. Currently, the step from data analysis and conclusion of preclinical studies to clinical outcome is

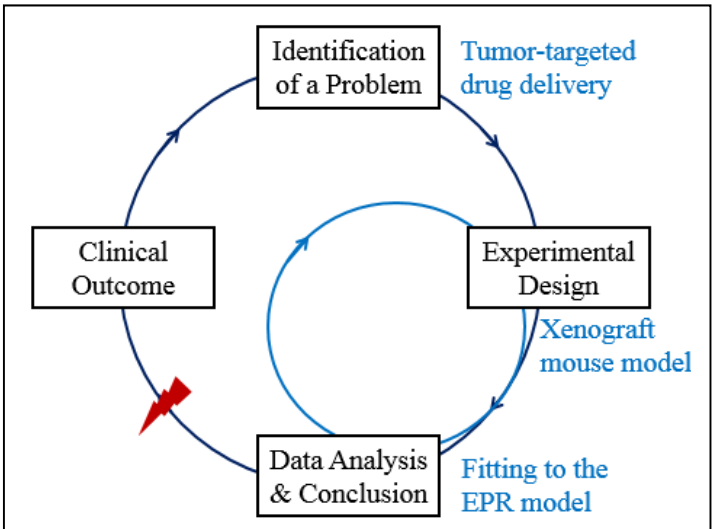


Fig. 4. The circle of problem solving to achieve a formulation for desired clinical outcomes.

broken (red symbol in Figure 4). To unbreak the circle in Figure 3, more careful preclinical studies need to be done. While expensive clinical studies are done to reap the financial awards, investing in clinical studies based on premature formulation designed on unsubstantiated data will only delay further progress. Without understanding the causes of the failures in clinical studies, future clinical studies will face the same outcome. All the failed clinical studies in Table 1 have not followed up why they failed. Instead, more excuses were made to justify continuing clinical studies. This odd behavior of repeating the same study while expecting a different result cannot be explained by a scientific mind.

4.3. How can the drug delivery field stand on solid ground again?

4.3.1. Accept failures as learning experiences

Preparing for an uncertain future is a daunting task. It is even frightening for many. One way of handling the uncertainty of the future is to diversify and be ready for failure, as it will be more common than success [94]. We need to prepare for an uncertain future by diversifying our technology portfolio. Whatever current technology is at the forefront, it will become obsolete soon. One common mistake we make is that new technology is expected to be better, but this is not necessarily the case. The only thing that matters is whether it provides an answer to the problem at hand. This is why clearly defining the right problem is critical. Once the adapted new technology does not work, we should be ready to try a different one. Clinging to the convenient assumptions that may allow publication will not provide any real answers. The wisdom of scientists comes from brewing two conflicting ideas at the same time [94]. The future uncertainty and ambiguity help us keep an open mind and empathize with different viewpoints [94]. Our inclination is to deny the future uncertainty and to avoid being left behind [67], and this is why so many scientists follow the popular, state of the art research topics which are quite often rewording of old ideas. Scientists who have the right questions with independent thinking and are able to adapt to ever changing situations will not be afraid of failure, as they know success always starts with failure [95]. Failures are in fact trials providing us with valuable experiences [22]. Elizabeth Turk, a stone sculptor, summarized the beauty of failures most elegantly: “Without an extreme number of failures, something truly original won’t ever be developed.”[96].

Our competitive culture gives much attention to mistakes and criticism, literally disturbing the soul. This is why we want to generate data that look very positive to a preconceived concept. Faced with a mistake, a loss, or a seemingly failed experiment, the right response is to acknowledge the set-back and change direction. Yet our instinctive reaction is denial [95]. Making changes is a good adaptation process. Being a scientist doing research leads to a joyous adventure only when we stretch beyond our known capacities while gladly affirming we may fail [97]. If and when we make a mistake, we can mentally raise our arms and say "how fascinating", and reroute our attention to higher purposes at the end [97]. The sense of higher purpose brings breakthrough power and innovation [22]. Such a spirit will allow us to boldly go beyond our previous boundaries. Genius is the ability to make the most mistakes in the shortest period of time [98]. If we collect all our mistakes and communicate them with open minds, then we all become genius.

4.3.2. Face the reality and deal with it

"How many times can a man turn his head, and pretend that he just doesn't see?" (Blowin' in the Wind by Bob Dylan).

The current situation of funding research in academia is not promising. More researchers apply for the limited pot of funding. Dr. Bernadine Healy, who was the first woman director of the National Institutes of Health in 1991, emphasized the need to discover the new medical Mozarts among many scientists in biomedicine [99]. Creativity or discovery depends not only on eureka moments, but also on persistent tedious lengthy work [100]. This is why scientists need long-term supporting systems to pursue their dream projects. Unfortunately, the current funding environment is not suited for Mozarts of science.

The current problem is partly ascribed to scientists themselves. Scientists should not be swindled by a clever trick or hype. Scientists are the ones who should evaluate the situation based on the data at hand. Unfortunately, many scientists become victims of the confidence game, simply because they do not examine the data available to them and follow the majority. Many scientists simply cite others to believe what they want to believe. We have a tendency to rely on others too much without question, just because it is from someone with a worldwide reputation. The confirmation bias has been dominating the field. The hype around new findings has been around as long as a salesman has been around. Nowadays, most hype in science stems from the perennial desire for simple solutions to complex problems. We have to appreciate how complex the nature is and how little we actually know [101]. In an ideal world, or indeed in a better world, rational action would not require bombastic rhetoric. If more federal money is appropriate for cancer research, then it should be provided, after a proper assessment of resources and priorities [102]. The scientists should have their own conviction to withstand the sweet talks by so-called visionaries who pretend to know the future. The simple fact is that nobody knows the future. But most scientists want to hear about a cozy bright future for self-comforting, in part due to the uncertain future they are facing. Unfortunately, the mainstream institution fails to deliver what the public deserves, and the populist approach has taken over the mainstream science.

The natural question, then, is how we can prepare for the future? If we consider the incremental advances we have made for the last 30 years, it would be a good idea to spend the next few decades reshaping the field with a new generation of scientists with new ideas and new research tools. We need to make sure they think differently rather than doing the same things that are shown to be ineffective. This requires a new generation of scientists who are courageous enough to doubt the current science.

5. Tomorrow is the beginning of a new Renaissance

5.1. Advances in science is an evolutionary process

The current situation of the drug delivery field can be described as swooning in quicksand. The field is slowly sinking into the positive illusion filled with confirmation bias instead of thinking with a passionately curious mind. It is time for us to face the reality and assess the situation accurately for the future. The situation we have today is a part of the evolutionary

process, and over time [103], things will sort out for the true innovative ideas to survive. In the evolutionary process, we are not as good as nature, as nature has infinite time to correct the error and we do not. It would be beneficial for all of us, if such evolution occurs faster. To achieve faster evolution, diverse ideas need to be tested. All evolution occurs as a result of random trials and errors, accepting the error and moving on with new trials. The beauty of the trial and error approach is that many different ideas are tested simultaneously for the best approach to emerge that can solve a problem at hand. It may not be the perfect one but good enough to overcome the difficulties. A series of problem solvers collectively make a big difference. The current problem is that we are unwilling to accept that there are errors in what we are doing. It is time to change from "positive illusions" to "divergent foresights". A good research plan requires a good research topic, new ideas, resources, manpower, and passion. The current climate on being a good researcher has compromised all these elements.

5.2. Why scientists should be proud of their work

Zhuang Zhou, one of the most influential philosophers in ancient China, said, "Those who give undue value on appearance are usually inexpert". This has a similar meaning to a proverb, "Empty vessels make the most noise". These stories and proverb have been interpreted with different significances, but they all provide a valuable lesson. The important thing is not what we see, but is what we do not see. Amateur golfers know all too well that a brand new, expensive golf club does not improve the game. Scientists should not be judged by the appearance, e.g., the number of publications, citations, prizes, funding, or recognition, as they are simply superficial self-rewarding artifacts of the system [104].

Measuring the quality of the work is difficult. This, however, should not be the reason not to use the quality as the main parameter of evaluating one's accomplishments. The current criteria of evaluating a scientist's achievements make the modern day Newtons and Einsteins difficult to achieve their breakthrough findings that require new ways of thinking. One approach to address this problem can start from academia. Universities can set up a new policy of evaluating professors up for promotion at any rank based on only the quality of a few key findings they have made, instead of long lists of publications and research funding. Such a policy will encourage all professors to strive for quality over quantity [47]. Such a policy can be used from the hiring step by a search committee, and extended to the review panels of the funding agencies. The downside of this approach is that it requires many hours or days of study to understand the topic by the committee or a review panel, but we should be ready to do it for the future.

Scientists and engineers have developed new technologies that have literally changed the world. It is the new knowledge that will improve our lives in the future. There are brilliantly successful scientists and engineers who were handsomely rewarded financially for their new findings, and we are all happy to see that happening. Most of them, however, dedicated their career to science and engineering for their love of the work, and a sense of pride being scientists and engineers. Scientists in academia and in industry spend countless hours to understand the facts. The fruits of their hard work are new ideas and new technologies that collectively improve our lives step by step. As more scientists try diverse ideas, the probability of making breakthrough findings becomes higher. The secret of Napoleon Bonaparte's success was known to be his stroke of the eye (or glance). He studied the details of the winning campaigns of the

great generals starting from Alexander the Great. Napoleon imitated the tactics of great generals in a new combination that fit his strategic situation in ever-changing circumstances. Napoleon always proceeded with two options [105]. Scientists should have at least two options in their work and always try to diversify their technology portfolio. Alexander the Great kept fighting, even after he conquered much of the world, for man's honor and the pursuit of immortal individual glory [106]. Scientists should continue fighting, and more importantly, doing their research for both honor and glory of us all.

5.3. Why leading scientists need to step aside

The mystery of science endures. As soon as we find an answer for a question, more questions spring forward. Scientists are not much different from economists in doing research, and a quote made for economists by Businessweek [107] apply equally well to scientists. The description on the economist is highly relevant to the scientist, and it is useful copying the text with minimal changes highlighted in the italic font. "*Scientists* cannot be expected to predict the future, but they should be able to identify threatening trends and to better understand the conditions that can turn *a hype into a scientific tsunami*. What's amazing is that the largest and most prestigious universities aren't placing more emphasis on such paradigm-shifting work. For young researchers trying to get published and land good jobs in academia, challenging the conventional wisdom - and questioning the workings of a *scientific* industry that provides lucrative backing to schools - can be perilous. The commanding heights are often occupied by tenured professors heavily invested in the status quo. --- Yet if better understanding of how *science* works is possible, it will come only through trial and error, the positing and refuting of theories" [107].

Max Planck, the inventor of quantum theory, is known to have said that science advances one funeral at a time, meaning that the death of a dominant person in a field frees others with different points of view to make their cases more freely, without offending established authority [108]. The power of established scientific hierarchies cannot be ignored. The dominance of a handful of powerful scientists often siphon the intellectual oxygen from a field, and it can be back in after their demise [108]. Only if the ideas of the star scientists are as ground breaking as those by Galilei, Darwin, Newton, or Einstein, the field will move to the right direction. The issue is when the direction is not into the right one. It will be just lost opportunities that could have otherwise been used for more important topics.

One way of preventing domination of star scientists in a field is for the field as a whole to establish a watchdog program that can guard against hype or unwarranted claims. In the stem cell field, the International Society for Stem Cell Research has issued "anti-hype" guidelines that "highlight the responsibility of all groups communicating stem cell science and medicine to present accurate, balanced reports of progress and setbacks."[104]. Still, segregating scientific fact from hype, fallacy, or fiction has become increasingly difficult even to the well-informed scientists [100]. Three patients who received intravitreal injection of autologous adipose tissue-derived "stem cells" to treat age-related macular degeneration experienced severe vision loss caused by deterioration of the most sensitive part of the retina [109].

As observed in the nanomedicine area, when high profile, "big ideas" result in only mediocre, if any, benefits, the funding agencies tend to continue with more funding to encourage

over-engineered formulations, more complex measurements, and more sophisticated instrumentation. Those in charge of the funding may think that, if the changes are made, it would mean that they made a mistake, and may believe that continuing the same policy can bring a chance of some sort of redemption [95]. They should adapt, i.e., reevaluate the program/progress and reset the existing topic to something more important and productive. The question on what type of research topics to fund is, in itself, a topic that deserves extensive discussion. It is usually encouraged to support basic, "blue sky" science for which it is impossible to set, predict, and promise specific deliverables [104]. This sounds good and easy, but it is difficult to distinguish the true "blue sky" science from extremely over-engineered, unnecessarily complicated approaches, or hype. The deliverable criteria should include tangible results that can advance the technology to develop clinical formulations or measurable reductions in mortality and morbidity. Young scientists who just begin their new scientific endeavor can be evaluated by their ideas, but more seasoned scientists need to show more concrete advances, not just the potential.

5.4. Why we need to focus on finding tomorrow's leaders and nurturing them

We cannot plan for innovation, but can organize for it through an integrated decision making process [110]. We need to create a place/community with shared commitments and beliefs to prepare for the fast changing world. The future depends on our ability to find future leaders. It is unlikely to find a mosquito preserved in amber carrying Albert Einstein's blood for us to clone him to build a better future. Then, a big question is where will we find tomorrow's leaders? How can we identify those who really have the right stuff? We need to utilize the concept of collective genius [110]. Each of us does not need or cannot be a genius, but all of us can contribute a slice of a genius to form a collective genius. Each collective genius can take the risk by pushing its boundary necessary to break the ground with constant nurturing and adaptation. We all need to adapt to new information that is constantly updated.

Once upon a time in China, there was a man who loved monkeys so much that he cultivated too many of them than he could handle. To save the cost of food, he one day informed the monkeys, "From now on, each of you will have only three acorns in the morning and four in the evening". Monkeys protested claiming that three acorns in the morning would make them hungry the whole day. As the plan changed to four in the morning and three in the evening all monkeys were pleased. This ancient Chinese story describes the current research funding situation. The annual increase in the research funding at the national funding agencies continues to lag behind the increase in the number of researchers, resulting in relative decrease in the funding available to each investigator. At the same time, the statistics indicates that the top 10% of the scientists spend 40% of the total research funding [111] with only marginal returns. Scientists should not be contented with programs favoring such uneven funding distribution and repackaged programs with reduced funding, but need to demand stable funding for all scientists to continue their research projects over a period of time enough to find answers. Quite frequently, some national funding agencies waste valuable resources to ill-conceived ideas. It is time that scientists decide the future of science, i.e., individual scientists should propose new ideas instead of the funding agencies.

Investing in research and development has been one of the primary forces driving the US economy since World War II, but that advantage has been shrinking lately [112]. There is no

easy solution for the disparity between available research funds and the number of scientific mouths to feed. The scientific ecosystem is fundamentally out of balance. There is no formula for predicting which research program will yield the next wonder drug or biomedical device. High standards and rules, more rigorously applied, can at least eliminate many unnecessary errors, and transparency can help bring the inevitable errors to light more quickly [47]. If we do not act now, the next generation of scientists will be at risk [113]. In May 2, 2017, the NIH Director announced that NIH would start a new point system in an effort to distribute grant money evenly, especially for early- and mid-career scientists, by limiting well-established investigators to the equivalent of 3 single-PI R01 awards [111]. This is a good initiative that should have been implemented decades ago.

Franklin D. Roosevelt, in his second inaugural address, said, “The test of our progress is not whether we add more to the abundance of those who have much; it is whether we provide enough for those who have too little” [114]. This statement also applies to the current funding situation. Some have way too much funding (considering the value of their outcomes), while others suffer from the lack of opportunities. Lack of support can stunt prospects for future leading scientists and potential geniuses, as they will never get a chance to be productive [1]. Some consider the amount of funding, along with the number of publications or awards, as superior scientific minds. This may be the case to a certain extent. But how many Nobel prizes were determined by the number of publications or awards? The superiority in a scientific mind should be determined by the magnitude of scientific contribution. By allowing more scientists to explore their ideas, more scientific contributions can be made.

The role of university or research institute is to encourage scientists to engage in new ideas. The tenure system was designed to protect faculty members, but recently, it became a misguided tool for redirecting the research efforts to something less desirable. The main criteria of tenure are the number of publications and the amount of research funding. Not many are able to spend time on a specific topic, as researchers have to follow the money. There is no time to do research for mechanistic understanding which takes a long time. There should be incentives for scientists to acknowledge that their research focus should be abandoned and help them switch to another potentially more fruitful research area [104]. There is a need for a more balanced approach for assessing scientific achievements and providing alternative measures of esteem to prevent academic researchers from being ‘lost in translation’ and ‘lost in the citation valley’ [115].

The current difficulties in obtaining research funding alienate highly qualified young scientists away from dedicating their career in scientific endeavors in academia and in research institutes. In the movie “Mr. Holland’s Opus”, Mr. Glenn Holland said, “Playing music is supposed to be fun. It's about heart, it's about feelings, moving people, and something beautiful, and it's not about notes on a page. I can teach you notes on a page, I can't teach you that other stuff.” [116]. Doing scientific research is very similar to playing music. We can teach young scientists the basic research tools through many lectures, but we cannot teach that other stuff; why doing research is supposed to be fun and something beautiful. We need to give time for young scientists to appreciate the research with their heart. The scientists in the drug delivery field are a part of one great community, and are all responsible for one another. We become angels when we begin to turn outwards [117]. We should feel blessed and lucky to be in a position to nurture young scientists.

5.5. Why creating a new environment for free idea exchange is critical

The massive success of Israel as an innovation giant is highlighted by a disproportional amount of successful startups located in the country, 4,800 startups with just over 7.7 million people [118]. One of the factors for such a success is that Israel is an immigrant and multicultural nation, allowing for diversity and different viewpoints which, in turn, allows for creativity and innovation, by encouraging the free flow of ideas and collaboration among individuals with very different perspectives [118]. Innovative ideas flourish when we are not limited to the conformity of the cozy environment and constantly struggle to sort out conflicting information and think a little harder.

Trying different, crazy ideas is important. The founder of FedEx was a MBA student at Harvard. His report on overnight shipping got a grade of C, because the professor thought that it was impossible [119]. Microsoft began with bold idea of setting a goal of a computer on every desk and in every home [120]. Amazon started with the goal of selling all the books in the world [119]. These great outcomes cannot be explained by a set of features [50]. Success comes with "cans" and continuous search of improvements [119]. Some projects will succeed greatly, and most projects may not. The best way to find a good idea is to try a lot of ideas [110]. Many different ideas will converse to one idea with breakthrough results. More often than not, people struggle to obtain the right answers to what prove to be the wrong questions [119]. "There is surely nothing quite so useless as doing with great efficiency what should not be done at all" [121]. The question of all questions is what question we should ask [122]. The drug delivery field needs to find the right questions. Sometimes, by sheer good fortune, promise and opportunity collide [1]. Luck plays an important role even in the lives of geniuses, not to mention ordinary successful people whether they are actors, artists, or scientists [123]. The key is that all of us should be ready to grab the luck when it knocks on our doors.

6. Epilogue

We are all successful, regardless of the outcome, as long as we do our best. Actor Robert De Niro, in his commencement speech at New York University's Tisch School of the Arts, said, "Always do your best. You're not responsible for the entire job, but your part in it. ... You will put your everything into everything you do. … There will be times when your best isn't good enough. There can be many reasons for this, but as long as you give your best, it's okay." [124]. In real life, there will never be straight A's or winning all the time. As long as we do our best each time, we can always shout "Next!" and will never quit.

To be even more successful, we need to detach ourselves from our own achievements and/or the technology we have developed. When we are emotionally tied to our own technology, because we have spent so much time or for other reasons, we lose our ability to see our own objectively. In this situation, we do not see what we should see. The danger of the invisible gorilla syndrome is that we will miss something really important [125, 126]. We cannot do whatever we want without facing any unintended negative consequences, and trying to reap only the benefits [127]. It is a singularly selfish act, and unfortunately, it exists in science. It is not enough for scientists to have an intention to do good research or open a new research field,

because it may result in only hype. It is imperative to actually achieve the goal. There needs to be accountability for those who promise big returns but are actively failing, as it is insidious to sell fancy ideas without backing them up with the promised outcome [127].

Sergio Garcia, after winning the 2017 Masters Championship in a playoff, said, “I was much better at committing to what I wanted to do, calming myself down, and accepting what was happening, good and bad. So not getting ahead of myself when I was making a birdie or an eagle or whatever.” [128]. Scientists should also commit to what they want to do, calm themselves, and feel confident accepting whatever is happening in their career, good and bad. Scientists, however, should never rely on hype or false confidence, but only on data. If the data change, our thinking needs to change, too. Such a plasticity, or flexibility, brings new ideas [22]. A journey of a scientist is like that of Santiago in Hemingway’s “The Old Man and the Sea”. On his way home after catching an 18-foot marlin, he lost the marlin’s entire carcass to sharks and brought home only its backbone, tail, and head. Santiago is a winner as he achieved his goal of catching a large marlin.

All scientists are highly successful when they achieve their personal goals, whether it makes them famous or not. Scientists are the ones who find purpose and meaning in their seemingly mundane day-to-day tasks of research [129]. It is the mindset that makes a difference in our lives. A janitor working at NASA told President Kennedy in 1962, “I am helping put a man on the moon.” Another janitor working in a hospital said, “I help patients heal faster.” [129]. As individual scientists pursue their own research problem and become a master of the issue, they are helping all human kind live a healthier life. What we do will lead to something even better and bigger, because today is the beginning of the next Renaissance [122]. Whatever happened in the past and whatever will happen in the future, we should learn from it and maximize the new opportunity that follows. This requires a new growth mindset freeing us from social comparisons, egos, and herd mentality. The next generation of scientists with such a mindset will make the drug delivery field a true winner.

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