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Advanced drug delivery 2020 and beyond: Perspectives on the future

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Abstract

Drug delivery systems are developed to maximize drug efficacy and minimize side effects. As drug delivery technologies improve, the drug becomes safer and more comfortable for patients to use. During the last seven decades, extraordinary progress has been made in drug delivery technologies, such as systems for long-term delivery for months and years, localized delivery, and targeted delivery. The advances, however, will face a next phase considering the future technologies we need to overcome many physicochemical barriers for new formulation development and biological unknowns for treating various diseases.

For immediate and long-term progress into the future, the drug delivery field should use time and resources for more translatable research ideas. The drug delivery discipline has to continue working on basic, applied, translational, and clinical research in a concerted manner to produce drug delivery systems that work for patients. It is a time to focus our attention on things that matter. It is also a time to develop realistic research goals and outcomes, diversify drug delivery technologies, and take the collective responsibility for our actions.

Keywords

Drug delivery issues; preclinical-clinical correlation; nanomedicine; drug prices; optimal target diseases; diverse technologies

1. Drug delivery

Drug delivery (DD) can be defined as “the method and route by which an active pharmaceutical ingredient (API) is administered to promote its desired pharmacological effect and/or convenience, and/or to reduce adverse effects.” One can simplify it as “making drugs work better [1].” The drug delivery system (DDS) is a “formulation or device that delivers an API in site-directed applications or provides timely (*i.e.,* immediate, delayed, or

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sustained) release of the API. The system, on its own, is not pharmaceutically active, but improves the efficacy and/or safety of an API that it carries [2].”

Each API has a therapeutic window (TW) for a specific indication. The TW is defined by the range of safe and effective plasma concentrations of an API. The width of a TW is determined by a lower limit for efficacy and an upper limit for no noticeable adverse effects. The total concentration of an API in plasma is presented as a sum of free molecules, bound drugs to carrier proteins such as albumin and lipoproteins [3, 4], or confined in delivery carriers when injected as a nanomedicine [5, 6]. In this article, nanomedicine stands for nano-sized carriers of an API, such as a liposome, a micelle, or a polymer-drug conjugate. Drug efficacy and toxicity occur as consequences of pharmacological actions of a free API or, occasionally, its active metabolites [7].

For an API with a narrow TW, drug infusion has been an option to meet the window by adjusting infusion rates and most often practiced in hospitals. Portable infusion pumps are a viable means for ambulatory patients. The first generation of DD technology (DDT) was pictured to meet the TW of a given API by controlling or modifying drug release rates from a DDS for an extended period of time [8, 9]. DDT, based on this relatively simple concept, yielded many successes in oral medication and implantable DDS for convenience and reduced toxicity [10, 11].

DDT explores new delivery routes, as historically exemplified by the transdermal drug delivery system, for better control of a target medical problem or to improve patient convenience that leads to compliance [12, 13]. Aside from oral and enteral administration routes and transdermal DDS, it has expanded to pulmonary, ocular, vaginal, nasal, and rectal delivery routes for local and systemic effects [14–18]. All routes, other than oral, claim to avoid the first-pass hepatic metabolism. The ‘site-directed applications’ in the DDS definition may include that external and internal local DD that concentrates an API to demanding sites with fewer transport barriers, when systemic delivery is not a viable option for any reasons, would help patients. Ocular delivery is a representative case to treat medical problems in the eye locally [19].

1.1. Within the therapeutic window

Converting thrice-a-day to once-a-day oral dosage forms provides patients convenience and less exposure to high concentration peaks that go above the upper limit of the TW. This has been achieved by modifying the release rate from first-order like kinetics to more sustained or ideally a constant (zero-order) release rate for an extended period up to 24 hours. Examples include matrix dissolution-controlled, swelling-controlled, or osmotic pressure-controlled systems [20–22]. The window width of a given oral API determines a different degree of precision in the control of the release rate, despite the varying absorption rates of the released API in the gastrointestinal tract (GIT), thus selecting a controlled release technology. Also, various delayed release systems have been developed to target timing or site in the GIT, such as the colon [23, 24]. The DDT was once used to expand the life-span of the proprietary right of an API, but is employed from the discovery stage of new drug candidates in the pharmaceutical industry to make a best-in-kind formulation.

Long-term medication is often achieved by implantable devices that release an API at a constant rate for a planned period from months to years [25]. The implantable devices applied, for example, are contraceptive drugs and anti-HIV drugs [26, 27]. Maintaining constant drug concentration inside the implant and adopting a rate-limiting membrane without leakage is essential for such devices. The biocompatibility is mandatory. The device size also matters. The removal process of the implantable DDS should be in consideration. A tracing method of the device for elimination after the service time is often incorporated. Similar constant release devices are applied for vaginal and ocular delivery [28, 29]. Transdermal patches for local and systemic effects have enjoyed the drug market [30]. Transdermal DD (TDD) combines a constant rate of drug release and enhanced permeability through skin barriers, which was once not conventional in history.

The classical DDT of oral formulations, implantable devices, and transdermal patches become major pharmaceutical products by relatively simple mechanisms to achieve sustained or constant release rates to meet the therapeutic windows of an API with less frequency of toxic peak concentrations. TDD alters the biological properties of skin barriers by permeability enhancers and microneedle approaches, but externally and locally applied [31, 32]. Similar methods were used in the GIT for peptide/protein oral delivery, but delivery efficiency in humans remains to be proven.

For an API with a wider TW, a degradable depot system is preferred by a simple procedure for administration such as subcutaneous or muscular injections and devoid of surgical removal of the implant, but for a relatively shorter time than non-degradable diffusion devices.

1.2. Widening the therapeutic window

A recent nanomedicine concept has centered on altering the width of the TW. The lower limit of the TW for a given API and its specific indication can be further lowered by altering the API's biodistribution profiles, *i.e.*, by promoting the accumulation of the API at its desired action sites. In theory, the carrier extravasates through the leaky openings of blood vessels at the tumor and/or inflamed sites, penetrates into deep tissues, and stays for a long period by poor lymphatic drainage [33]. The nanomedicine releases the API over time for improved local bioavailability to target cells or is taken up by the cells. It creates two concepts of the enhanced permeability and retention (EPR) effect and drug affinity targeting approaches [34]. Thus, it was thought that for the same free drug concentration at the action site, the total plasma concentration can be maintained at a lower level. The EPR effect and targeting have served as the main disciplines of nanomedicine and polymer therapeutics [35, 36] and have been recently disputed and reviewed elsewhere [37].

Elevating the upper limit by reducing toxicity is another way of altering biodistribution profiles of an API through the size effect of the carriers, *i.e.*, significantly reducing the distribution volume of nanomedicine. Slow drug release also makes the free drug concentration low in plasma despite a high total concentration. Solubilization of poorly water-soluble drugs by new approaches [38, 39] is another DDT, if it also affects the release rate and drug bioavailability. Unfortunately, however, most nanomedicine is captured in the liver and spleen [40, 41].

Relatively less attention has been paid to controlling adverse effects of nanomedicine. Drug candidates are screened by efficacy at the beginning and most DDS are designed for efficacy, too. However, candidate drugs and delivery systems are often rejected, during clinical studies, due to unforeseen and unfavorable toxicity profiles. Numerous nanomedicine papers mention that by accumulating nanomedicine in the tumor sites reduces systemic concentration. This leads to reduced toxicity and elevates the upper bar of the therapeutic window, allowing a higher amount of dosing. The following real-world example shows that such anticipation is deviated. Doxil® has represented a nanomedicine with an EPR effect. It is stable, long circulating, and has a slow release rate with an optimum size range for enhanced permeability. Its claim is that it has passive targeting to solid tumors that have leaky vasculature for extravasation. Unexpectedly, the maximum tolerated dose (MTD) of Doxil® is lower than free doxorubicin due to acute palmar-plantar erythrodysesthesia (PPE) syndrome [42], while Doxil® had less toxicity to the heart [43]. Doxil® was favorable over free doxorubicin because it has an altered toxicity profile over efficacy. Meta-analyses concluded that there are no distinguishable differentials in efficacy between Doxil® and free Doxorubicin, despite Doxil® being justified by the EPR effect for better efficacy [44]. Nanomedicine with affinity to target cancer cells appears effective in limited liquid tumors, but the efficacy has not been apparent in solid tumors in clinical trials, while accompanying unforeseen adverse effects. Unlike DDT, aiming at the ‘within the TW,’ the efforts for ‘widening the TW’ are not so fruitful till today.

1.3. New delivery routes/pathways

Exploring new routes and pathways, which overcome critical biological and physiological barriers to help drug absorption and biodistribution to target disease sites and are reliable and practical in clinical settings, is an open area for future DDT.

1.3.1. Oral transepithelial delivery—Advised by industry (Pfizer), Lipinski’s rule of five [45] applies to reasonable oral bioavailability (BA) of drug candidates. The rule is related to molecular weight (MW≤500 Da); the number of H-bond donors (≤5); the number of H-bond acceptors (≤ 2×5 (=10); and lipophilicity (log P ≤ 5). Collectively, small molecules with an optimum balance between hydrophilicity and hydrophobicity are a good candidate for transepithelial delivery in the GIT. When any API violates more than 2 of Lipinski’s rule of five, the oral BA sharply drops. For large digestible biomolecules, oral delivery demands permeability enhancers and enzyme inhibitors. The outputs by such approaches have often been promising in rodent models but hardly translated in humans. This may serve as a typical example of a poor co-relationship of oral BA between species. Even small molecule oral BA among rodents, canines, non-human primates and humans do not coincide with each other [46]. Even without digestive enzymes, the size of the API, which can penetrate the epithelial layer by the aide of enhancers, is extremely limited, not larger than the size of insulin (MW 5,808) in most preclinical and clinical studies. With a successful enhancer system (*e.g.*, Eligen technology from Emisphere) in translation [47], the BA of oral Semaglutide (a lipidated GLP-1 receptor agonist: MW ~ 4,113), a recently launched product on the market, is estimated to be very low (~1%) in human patients (0.25, 0.5 or 1 mg inj. (Ozempic) per week versus a 3, 7 or 14 mg oral tablet (Rybelsus) per day) [48]. It is not certain that the approach will guarantee the specific absorption of an API,

demanding a complete fasting condition to avoid any co-transporting molecules for absorption in the GIT. The specific delivery method of large biologics or nanoparticles via an oral route will be one of the future promising technologies in DDT, as dreamed since the first oral insulin trial in 1923 [49].

1.3.2. Delivery to the lymphatic system—The lymphatic system has unique features for immunotherapy. Immune cells are rich in the lymphatic system. Lymphocyte populations in different human organs were estimated [50]: the majority of lymphocytes (~41%) in the lymph nodes (LN); ~15% in the spleen; ~22% of lymphocytes in the thymus and bone marrow (11% each); ~13% of the immune cells in the lamina propria of the gut and lung (6.5% each); 4.3% of the cells in the Peyer's patches in the GIT; 2.2% in the peripheral blood; and ~2.2% in the rest of the organs. In the body, there are approximately 500–700 LN and ~20% of them are mesenteric LN that host naïve T (~60%) and B (~25%) lymphocytes, memory T and B lymphocytes (~10%), and B-cell blasts (~2%) [51]. These data suggest that more than 18% of all lymphoids are associated with intestinal organs. Another interesting point is that ~45% of regulatory T (T_{reg}) cells are found in mesenteric LN and small intestine lamina propria [52, 53]. There are about twice as many $FoxP3^{+}/CD4^{+}$ T_{reg} cells in the lamina propria as in other peripheral lymphoid organs. The lymphatic system houses HIV transfected T cells and migrating cancer cells. Such features, taken together, suggest that the intestinal lymphatic system can be a target organ of various DDT. However, the DDS to the lymphatic compartment is not readily accessible. A small fraction of a dose, for instance, nanoparticles, is taken up by antigen presenting cells and moves to draining LN after intradermal injection. The M cells in the Peyer's patches samples nanoparticles from the GI tract, which uptake capacity is, however, not high enough in humans to absorb therapeutics for sufficient concentrations in the plasma. New delivery technology to the intestinal lymphatic system via the oral administration route will be new in the drug delivery community. If it becomes feasible to deliver vaccines and other biologics orally, this will be an entirely new route to modulate the gut immune system, as well as, a gateway for systemic immune control and the reprogramming of immune cells. The gut immune system is the most sophisticated one with both tolerance and immune development against biomolecules in foods. This would be the place to neutralize cytokine storms with less effect on a systemic level. This can also be the best place to find HIV transfected T cells. Lymph collected from most of the body (except from the upper right side) enters the thoracic duct including gut associated lymphatic tissues (GALT) and returns to the blood circulation via the left subclavian vein. When a drug is delivered to the intestinal lymphatic system via the oral administration route, it eventually enters through the thoracic duct, that collects lymph at a 1 mL/hour volumetric flow rate under physiological conditions [54], which would be a very confined and defined compartment to meet immune cells.

The immune system is thus a proper compartment for various therapeutic approaches such as immunotherapy and treating immune cells infected by a virus. This justifies finding a new route to deliver drugs to the lymphatic system. Digested fat molecules are absorbed into absorptive enterocytes, form chylomicron in the cells, and move to a lymphatic capillary (lacteals) in the intestinal villi after export from the enterocytes, instead of moving to portal veins. This fat uptake pathway is known to help uptake very water-insoluble vitamins.

Highly lipophilic drugs with log P>5, when taken with fat, are absorbed with fat molecules and transported to the intestinal lymphatic system riding the chylomicrons [55]. The uptake mechanism by the enterocytes before joining to chylomicrons is not fully elucidated. This approach is, however, not applicable for an API having a log P value lower than 5. Nanoparticle uptakes by microfold (M) cells in Peyer's patches in the intestine are known. Still, the uptake capacity is limited in humans because it has evolved to sample a tiny fraction of nanoparticles in the GIT for immune surveillance purposes. Intradermal injection of an API or nanoparticle has access to local dendritic cells that migrate to draining lymph nodes, but with a limited amount, as illustrated by intradermal vaccination.

When any novel delivery route to the lymphatic system is explored, it will open a new dimension in DD. The drug in the systemic lymphatic system may attack infected immune cells, reprogram immune cells, and neutralize excessive cytokines which can cause abnormal responses.

1.3.3. Delivery to the brain: Crossing the blood-brain barrier—Widely known, but still hypothetical, examples include discovering pathways to cross the blood-brain barrier (BBB). Glioblastoma and neurodegenerative diseases are often observed in the very young or aged population. Delivery of an API to the brain in a therapeutic quantity by a passive diffusional mechanism has been challenged due to poor permeability through the BBB. Receptor-mediated delivery has been one of the approaches [56], which has been hardly translated, due, most probably, to the limited capacity of such transports. A very recent approach of paclitaxel-angiopep-2 conjugate, which targets low density lipoprotein receptor-related protein-1 in the brain, has been translated and becomes positive in a Phase 2 study [57]. The olfactory route has been discussed for a while as an alternative delivery route to the brain [58]. Sensing smell demands only a small number of molecules in the air, and the smell sensitivity is species-dependent. It is not certain, however, if the olfactory route can deliver therapeutic amounts of an API to the brain. Physiological homeostasis is governed by the brain. For instance, energy homeostasis, linked to obesity, is controlled by the hypothalamus which communicates with peripheral networks in the body. This communication is primarily mediated by various cytokines which cross the BBB [59]. Liraglutide (a lipidated glucagon-like peptide-1 receptor agonist (GLP-1 RA)) is used as a type 2 diabetes mellitus (T2DM) medicine [60], as well as an anti-obesity drug [60, 61]. This indirectly suggests that Liraglutide crosses the BBB reaching the hypothalamus, where the GLP-1 receptor is located, even after being modified with a lipid molecule allowing it to bind to albumin. This observation can be exploited for delivery to the brain, crossing the BBB. Although this route would probably be regionally limited in the brain, it would still be a beneficial route if underlying mechanisms are properly understood and applied to new delivery systems.

2. Basic research vs. product development

2.1. Basic research, applied research, and clinical research

Basic research, also known as fundamental or pure research, represents the research performed to expand our knowledge and discover truths, without the thought of practical

ends [62, 63]. The main driving force for research is a scientist's curiosity about the unknowns. The knowledge generated by basic research over time becomes the source of answers for many important practical problems [62]. Basic research consists of sound scientific methodology, careful observation, and an unbiased description of an event, tools, and instruments for observation, measurement, use of models or analog systems, development of concepts, and testing of ideas [63]. The key to basic research is that each scientist should observe, experiment, and analyze the proper data in as objective a manner as possible. Wishful thinking has no place in the work of good scientists.

Applied research is the process of using the knowledge we have learned from basic science to solve practical problems facing us at the moment [64, 65]. Basic research is focused on exploring and understanding the interaction of variables in a system. On the other hand, applied research is designed to understand and quantify how effective a proposed system is at solving the problem. The key distinction is a preconceived "problem" that needs "solving". Applied research includes designing, implementing, and testing systems. Applied research often utilizes experimental rigor, but is mostly focused on evaluating the performance of a proposed system or application [66].

Clinical research, according to the National Cancer Institute, is defined as research in which people, or data or samples of tissue from people, are studied to understand health and disease [67]. Clinical research helps find new and better ways to detect, diagnose, treat, and prevent disease. Types of clinical research include clinical trials, which test new treatments for a disease, and natural history studies, which collect health information to understand how a disease develops and progresses over time.

The translation from fundamental discovery, *e.g.*, understanding of living systems and life processes, to surprising new insights followed by practical application often takes decades, if it happens at all. Naturally, basic research is often underappreciated. Both curiosity-driven and mission-oriented research need to be supported [68].

2.2. What is translational research?

Translational research is a scientific discipline that bridges the gap between basic and clinical research. Translational research is defined as the process of transforming research innovations into new health products and diagnostic and therapeutic methods [69]. Naturally, the translational researcher needs to have experience in both fields to understand the significance of the new discoveries of basic research and how they can be developed to benefit patients. The progress in translational research can only be realized in the clinical application. To make progress faster, basic research, applied research, and clinical research need to be understood as a continuum of research [69].

Cancer research has progressed from empirical trials to a mechanistic understanding. The mechanistic understanding of cancer, and any disease, for that matter, is the best way to achieve fast translational research for improved patient outcomes. The mechanistic understanding of cancer has contributed to targeted therapy through a more precise understanding of genetic, genomic, epigenetic, and immunobiological alterations of different cancer types [70]. Translational research encompasses an ever-expanding spectrum of

human physiology, genetics, pathophysiology, phenotyping, pharmacology, natural history, and/or proof of concept studies using interventional drugs or devices in appropriately selected disease models [71].

The following example shows the need for all scientists to know that being an expert in a basic discipline is not enough to achieve a successful translation of a finding from basic research. Professor Wim Hennink is one of the leaders in the drug delivery field. He was asked to review a manuscript for a highly ranked journal with an impressive double-digit impact factor [72]. The manuscript was about testing a new degradable polymer for delivery of doxorubicin and paclitaxel using a cell culture study. It is difficult to claim that the formulation could be used to treat cancer in humans. Thus, Professor Hennink provided a review indicating that PK studies would be necessary to show the *in vivo* efficacy. The author responded through the editor that the reviewer misspelled PK instead of pK_a, and there is no pK_a in their polymer because it is a neutral polymer without any charge. It is up to individuals how to respond to this. If a capable scientist makes a new polymer that can treat cancer in humans, isn't it required for the scientist to know the basic pharmacokinetics or how drugs work in humans? In this world of close collaboration between scientists of all disciplines, the collaborating scientists need to understand other research areas enough to understand what is required to make a successful translation. Knowledge in one specialty area may allow one to make something new, but it can make the same scientist blind to other things that are essential for successful translation.

2.3. From basic research to product development

There is a misunderstanding in product development. Although discoveries, innovations, and inventions in academia have significant scientific value, turning them into products requires much more than scientific merit and publication. It requires a robust, structured framework including project management, new product development, business development, and intellectual property management [73]. The academic researchers can further advance new technologies and innovations to the level that can attract investors. Either way, product development requires a lot more than a new idea or innovation. Basic research provides a significant picture understanding, and the technologies resulting from basic research are still in the earliest stage. Thus, a considerable investment of time and money is necessary to bring them to market. Successful commercialization depends on the size of the market opportunity, the risks of failure (*e.g.*, due to safety, development time, or product costs), competitive pressures, the strength of intellectual property, and the expertise of the commercialization team [74]. In general, the commercialization of technologies requires known market sizes for annual revenue opportunities, *e.g.*, $100 million for a medical device or diagnostic, and $500 million~$1 billion for a new drug. The average cost of drug development, depending on how it is calculated, ranges from $650 million [75] to >$2 billion [76]. Thus, it is not surprising that the minimum market size is a critical factor. One of the promises of drug delivery systems is to reduce the cost of drug development. Thus, new formulations can be developed even if the estimated revenue is less than a few hundred million dollars.

Trial and error is an effective tool for solving problems, because it produces ongoing, ‘works for now’ solutions to a complex and ever-changing set of problems [77]. The evolutionary process has no foresight. The repeated trial of variation and selection does not look for optimum solutions because they are not known and also, they keep changing. This evolutionary algorithm should also work in science when the answers are not easy to find. The result of the trial and error approach is easy to recognize as successful evolution leads to survival. The proven method of evolution has also been in effect in the drug delivery field. For the last few decades, a significant portion of the drug delivery scientists have focused on variations of existing methods, known as nanomedicine, to make it better. The successful evolution of a technique will result in a clinical product that helps patients live better. The time that such an evolution requires, however, is a luxury for us now. We need faster progress, and the field will advance faster if we all exercise positive foresight to seek out what we need to see, instead of just what we want to see.

There is a fundamental difference between research in academia and that in pharmaceutical and biotechnology companies. For publishing a scientific paper, a few successful experiments out of 10 or more can make a good research article, but for making a product, it has to work 100% of the time. The results of many published research articles are not reproducible, and this is mainly because the published research was done under a unique condition in the laboratory, instead of a general condition where patients reside. Even a Nobel Prize-winning scientist had to retract her latest paper due to the problem of irreproducibility [78, 79]. The reproducibility is especially crucial for translational research where the data have to be reproduced in human patients. For successful clinical translation of any technology, it has to be simple and robust. The formulation should work under most conditions of human patients or a subset of selected patients. The big question here is whether the mouse models, which almost all nanomedicine formulations have been tested, represent the human condition. Currently, efforts are directed to find other models that resemble the human condition better.

In his book “Antidote”, Barry Werth describes the underlying cause of the failure of one of the most respected pharmaceutical companies, Merck [80]. Its rapid uncontrolled growth exceeded its capacity to be managed effectively and that resulted in a series of unintended consequences. Growing big through mergers, buyouts, and the desire to dominate the worldwide markets caused managerial dysfunction and loss of philosophical grounding. The pressure of growing big resulted in technology overshooting, i.e., only marginally improved products, just to maintain the stock price. Imagine the pressure that nanomedicine startup companies face when all they have is unproven, but highly hyped nanomedicine that allowed rapid uncontrolled growth. More on this in the next section on nanomedicine.

The practice of producing anything that can make money, and thus, increasing the stock price is, obviously, not limited to the pharmaceutical industry. The drug delivery scientists need to possess extreme empathy. We need to produce formulations that treat and cure diseases in patents. Patients do not know what drug delivery systems are possible. We should provide formulations that really help patients, not merely those that can benefit only to extend research funding for another several years. Current drug delivery research on nanomedicine has been hiding behind the wall known as basic research. It is time to be

honest and accept that nanomedicine, after all, may not be a panacea of which the nano-scientists have been dreaming. Each scientist is different, but when most scientists think alike and do similar research on nanomedicine, the progress, especially in translational research, is bound to be slow. We all need to think differently, because each of us is a unique individual with distinctive ideas in what we do.

3. Current status of nanomedicine in cancer therapy

3.1. Social and strategic background

Liposome technology was first described in 1964 by Bangham [81] and initially named as 'Bangosome.' Gregoriadis was the first to propose the use of liposomes for drug delivery in 1971 [82, 83]. The polymeric micelle was reported in 1976 by Tuzar and Kratochvil [84]. Block and graft copolymers were used to construct polymeric micelles, and in 1985, Ringsdorf discussed the interactions between polymeric micelles and cells or model synthetic membranes [85]. Despite liposome and polymeric micelles falling within the size range of today's nanomedicine which was defined later, both were traditionally considered as colloidal particles.

The emphasis on nanomedicine was placed after a 40-year history of colloidal particles. The NCI Alliance for Nanotechnology in Cancer was launched in 2004 [86] and the program includes the Center for Cancer Nanotechnology Excellences (CCNEs), Innovative Research in Cancer Nanotechnology (IRCNs) and Cancer Nanotechnology Training Centers (CNTCs), which have lasted for 15 years. The program focused on development and translation of nanotechnology-based techniques and tools for 1) early disease diagnosis using *in vitro* assays and devices, and *in vivo* imaging techniques, 2) multifunctional therapeutic solutions, and 3) techniques for cancer prevention and control. Since then, colloidal particles were reborn with the prefix of 'nano' and nanotechnology in medicine.

In December 1969, activists, led by Mary Lasker, published a full-page advertisement in *The New York Times*, entitled "Mr. Nixon: You Can Cure Cancer" [87]. In the copy, Dr. Sidney Farber, Past President of the American Cancer Society, believes: "We are so close to a cure for cancer. We lack only the will and the kind of money and comprehensive planning that went into putting a man on the moon." The signing of the National Cancer Act in 1971 by Nixon [88] was considered a declaration of the War on Cancer. Since then, the federal government has spent well over $105 billion on the efforts till 2009 hoping that cancer would be cured [89]. However, the overall cancer death rate in 1970 was 198.6 per 100,000 Americans and 190.9 in 2003 [90]. There were no significant changes in cancer death rates for over 30 years since the National Cancer Act. In fact, the rate (216) was the highest in 1990. The consistency in the death rates around the year 2000 might make the NCI seek novel technology for cancer treatments. It seemed relevant to the rise in nanomedicine and the birth of the NCI Alliance that seriously impacted the global research community in drug delivery. Interestingly, the death rate continuously declined from 1991 with an almost constant rate drop and became 152.5 in 2017 [91]. The gains were made in melanoma and lung cancer survival. This decline has resulted from reductions in tobacco use, increased screening that allows for early detection of several cancers, and modest to large improvements in treatment for specific cancers [92]. The NCI Alliance program was

discontinued in 2020. In the meantime, Congress passed the 21st Century Cures Act in December 2016 authorizing $1.8 billion in funding for the Cancer Moonshot over 7 years [93]. The program aims to make more therapies available, while also improving our ability to prevent cancer and detect it at an early stage. Emphasis is placed on immuno-oncology.

3.2. Nanomedicine and tumors

Academic and industrial efforts have emphasized cancer nanomedicine among other disease categories for the last two decades. Cancer shows one of highest death rates, second to cardiovascular disease, and cancer frequency steadily increases with the aged population [94]. Fighting against or curing cancer has been demanded with historical and social background as briefly reviewed. Thus, cancer focus has been well nourished by research funding from federal agencies. Another reason would be based on hypothetical theories that therapeutic cancer nanomedicine can widen the therapeutic windows of conventional anticancer drugs, represented by the enhanced permeability and retention (EPR) effect and active targeting or tumor seeking hypotheses. A third reason would be based on antitumor effects of nanomedicine in rodent models where artificial tumors grow fast. The low hanging fruits from mouse models have made the younger generation believe nanomedicine would work in the real world, as theorized with mouse models. The EPR effect, coined by Dr. Hirosh Maeda in 1986 [95], was the most cited word in cancer nanomedicine. In fact, almost every scientific article starts with EPR and targeting in an introductory section for the last 20 years. This indirectly shows that most cancer nanomedicine has been justified by EPR and/or targeting. The accumulation of SMANC, a delivery system invented by Maeda, in solid tumors was claimed after IV injections of SMANC in an aqueous solution in mouse cancer models and hepatic arterial injection of SMANC/Lipiodol® in the clinical treatment of hepatocellular carcinoma [96]. The underlying picture has been that the unstable and leaky vasculature of solid tumors allows circulating nanomedicine to cross the vasculature (extravasation) in solid tumors.

The instability of the endothelial layer of tumor blood vessels has been explained by the tumor growth rates and associated cytokines for vascularization to supply oxygen and nutrients to actively proliferating cancer cells. A similar background was applied to inflamed areas where the vasculature mediators are excessively produced and they affect the vasculature to open the gaps for circulating immune cells [97]. The long circulating property of nanoparticles, while avoiding residential and peripheral macrophages and holding the most fraction of payload, is thought to be mandatory for improved accumulation in the solid tumors for a higher probability of hitting the openings of blood vessels in tumors. If such openings exist, their distribution, frequency, and dynamics in a clinical tumor are not fully known and more specifics are discussed in Maeda’s chapter in this volume. It may rely on tumor growth rates and location. When a patient is diagnosed with solid tumors, the history of tumor development is in a black box which cannot be discovered. Hypotheses in the theory include:

i) Nanomedicine stays for a long period of time at the tumor site because of poor lymphatic drainage while keeping blood vessels open.

The cells in normal tissues receive a supply of oxygen and nutrients by diffusion, as well as, the convectional flow of body fluid originating from the blood. The same holds for washing metabolic wastes away into the veins and lymphatic circulation [98]. The convectional mass transport in general is significantly faster than diffusional transport, which is controlled by hydraulic and osmotic pressure gradients. The nanoparticle retention effect in a tumor after extravasation is claimed by collapsed lymphatic drainage or by a slow diffusional process in a dense extracellular matrix. The lymphatic capillary has openings for nanoparticle entry, while the vacuole does not.

ii) Nanomedicine finds target cancer cells buried in the dense extracellular matrix under high interstitial pressure.

Scientists in nanomedicine depicted a variety of hypothetical cartoons to explain the EPR effect (leaky vasculature and collapsed drainage) for educational purposes. In addition, extravasated nanoparticles freely swim around to meet cancer cells by chance or by specific affinity interactions.

iii) Nanomedicine specifically interacts with target cancer cells for internalization.

It was Paul Ehrlich who proposed the possibility of targeting diseased cells by specific interactions based on the observation of specific staining of bacterial strains [99]. With the progress in antibody technology, conjugation chemistry, polymer chemistry, the first antibody-drug conjugate, and polymer architecture grafted with a targeting moiety and chemical drugs, the targeting concept triggered the creation of numerous versions of nanomedicines, naming them ‘a missile drug’ or target seeking drug (active targeting). This presumes no or minimal interactions with healthy cells, like staining of target bacteria. When a nanoparticle finishes a long odyssey with a variety of obstacles from the injection site to the vicinity of its target cells in 2–3 nanometer range for the secondary (affinity) interactions, the cells hold the nanoparticle on the surface then uptakes it. This can be proven by relative uptake rates in cell culture systems where at least a part of the cell surface is exposed to the culture medium which has freedom for movement without restriction and dynamics. In tumor tissues, the cancer cells are surrounded and packed with a dense extracellular matrix, neighboring cells and stromal cells. Even if there is cell membrane movement, the freedom or flexibility will be different from the free surface. Beside accessibility of nanoparticles to the target cells, the endocytic activity of the cells in a tumor (in particular, clinical tumors) is not known, most probably not at a similar degree as observed in culture systems.

3.3. The reality of the nano-dream

All relevant backgrounds of cancer fighting triggered a ground shaking earthquake at a specific time period, if not a time point, and the quake brought a nanomedicine dream that impacted scientists from various fields to develop a product that truly helps cancer patients. Since most cancer nanomedicines reformulate known drugs in oncology, a higher success rate than the approval rate of new oncology drug candidates (5.1% in oncology [1]) is anticipated [100, 101]. Due to a relatively short history, the number of clinical trials of nanomedicine is limited. However, except liposomal formulations, almost all clinical trials of long circulating and targeting nanomedicines, designed to meet the dominant hypothetical

theories, have not been successful for approval with the FDA so far. The lists of clinical trials of new delivery systems of nanomedicine, covering antibody-drug conjugates, polymer-drug conjugates, liposomal formulations, and micellar formulations with or without an affinity moiety to cancer cells, have appeared in almost every review article of cancer nanomedicine [102, 103]. Many of the reviews claim the triumph of cancer nanomedicine with clinical products of Doxil®, Abraxane, Genexol PM, and PEGylated proteins [104, 105]. “The clinical performance and toxicology profiles of such nanomedicines have been reviewed elsewhere [37, 106, 107] and their clinical outcomes are not as great as being anticipated by EPR effects.” Most designed cancer nanomedicines, if not all, for EPR effect and targeting have silently disappeared from the list of clinical trials. Examples include CALLA, Bind-4, NK-105, PK1 and PK2. This casts questions of why the success rate does not improve in clinical settings despite reformulating existing anticancer drugs, in most cases, to the nanomedicine. This should make us rethink the nanomedicine hypotheses and any additional factors.

3.4. Pharmacokinetics/pharmacodynamics (PK/PD) issues

As defined by the words ‘improving efficacy and/or safety of a given API’ for drug delivery, the 2nd generation of DDT was to widen the TW of an API, anticipating more API accumulation at target cells/tissues/organs while lowering systemic drug concentrations. However, this endows complexity that is associated with PK and estimating the free drug concentrations at the pharmacological action sites. The PD effects on cancer cells and other cells that are linked to tumor microenvironments may occur in different concentration ranges. Individual cancer cells will have heterogeneity in terms of drug sensitivity.

3.4.1. PK consideration—Most nanomedicine designs have centered on improving efficacy, without much consideration in PK and PK associated issues, which can be brought by the nature of nano-sized carriers. We have to remind ourselves that PK study is for modeling, because we cannot directly measure the time-dependent concentration profiles of a free API at its action sites and other locations besides blood in patients.

When an API is introduced into the body, the plasma free API concentration can be estimated from equilibrium constants between bound and free API. Various factors, including disease state that affects plasma protein concentrations, binding saturation, concentration-dependent binding constant, and competitive binding with other APIs, should be considered. The binding factors thus impact the free drug concentration at the action site and drug elimination. When a drug is injected in the form of a nanomedicine, the nanoparticles are distributed in the body and taken by phagocytic cells while releasing its payload and can be re-distributed over time. For instance, it may extravasate from the blood compartment to the peripheral region of a solid tumor by virtue of openings if they exist. However, according to Fick’s first law in mass transport, the blood concentration drops by clearance below the concentration in the tumor peripheral region, the particles diffuse back into the blood stream through the same openings with less resistance rather than penetrating into the dense extracellular matrix and cell clusters with high interstitial fluid pressure and transport resistance. Clinical evidence shows, a polymer drug was intravenously injected into tumor patients ~10 days before debulking tumor surgery. The distribution of the free

drug, drug with a spacer fragment and a polymer-drug conjugate in the dissected tumor mass were analyzed. Strikingly, the concentrations of the three species were higher in order of surrounding normal tissue > tumor peripheral region > tumors [108]. This order was observed in all tumors without exception although the sample number was low. It is understood that the central part of a tumor has a lower concentration with poor vascularization, high pressure and resistance to mass transport. Why was it low in the peripheral region where the EPR effect may exist? One possible reason could be 'easy-in/easy-out' through the same openings.

The next question is why the EPR effect is claimed in rodent models? A likely answer to it is that the openings are in a highly dynamic state of endothelium remodeling during tumor growth. The openings are short-lived by closing and new openings are formed in the fast-growing artificial tumors in the models. However, in slow-growing tumors, for example, in a clinical setting, the openings, if they exist, can be regarded as relatively long-lived when compared to the time scale of back diffusion for clearing. In healthy tissues, the conjugates get access slowly and maybe entrapped longer. The nanoparticle distribution can also be impacted by phagocytic cells in a tumor, peripheral circulation, liver and immune organs, that migrate around. The mixed nature of equilibrium binding, dynamic distribution and release rate make the free API PK analysis or prediction at its action sites extremely challenging, in particular for human patients. To understand the meta-analysis results of Doxil® vs. free doxorubicin for the therapeutic and adverse effects, the clinical outcomes should be fully simulated to yield no statistical differences in efficacy between the two [44]. Without understanding such parameters in a 3 to 4 -dimensional space (free drug, bound drug, nanoparticles, and phagocytic cells), as exemplified with 3-dimensional analysis of nanoparticle distribution in a solid tumor [109], it may iterate the failures of nanomedicine in clinical trials.

3.4.2. PD consideration—The TW of an API for target cancer cells and the concentration ranges that impact normal cells, that are linked to tumor microenvironments, are not identical. When the maximally tolerated dose (MTD) is applied for conventional chemotherapy, the concentrations overwhelm all cells, causing indistinguishable death of cancer calls, fast growing cells, sensitive immune cells and circulating endothelial cell precursors [110]. For instance, it is known that by the MTD approach, most T cells are damaged. However, T_{reg} and tumor associated macrophages (TAM) are more sensitive than T_{eff} cells to cytotoxic drugs [111]. This justifies that metronomic therapy, where an anticancer drug (or combination of drugs) is administered with a significantly higher frequency with a low dose, maintains low plasma concentrations, often below the TW, with short or no washout periods [112]. The metronomic approach often shows therapeutic effects, in particular, in treating cancers in companion animals in veterinary hospitals. The drug effects on target cells for efficacy and normal cells for toxicity would be altered by long circulating nanomedicine. Such toxicity is hardly emphasized in preclinical models and unseen or unforeseen toxicity in small animals should be carefully examined in larger animals before translation.

3.5. Hyped hypotheses

A missile drug was once a representative word of hype in drug delivery with nanomedicine, which specifically targeted diseased cells while saving healthy cells/tissues/organs. This brought a belief that a drug can be delivered to only target cells. This pictured a futuristic cancer nanotechnology, nano-robot (or nanobot) which can find target cells, located anywhere in the body, and kill them in the 1990s [113–115]. The nanobot needs a meter-range radar system to detect where the target cells exist without interference by others, energy to swim against the flow of viscous blood full of circulating cells or body fluid, and freely penetrate tumor tissues to access the target cancer cells. The moving parts should not interact with plasma proteins, thus, requiring perfect blood compatibility without any fouling. No artificial surface is known to be entirely free from protein absorption in the blood. The nanobot should carry a drug reservoir large enough to kill a high number of cancer cells, an engine for moving parts, a battery or power transmission system, injection mechanism, and so on. All these should be packed in a nano-sized body. In addition, all parts should be incorporated into biodegradable materials, of which the by-products are non-toxic. Nanobot construction might be far beyond current science and technology, although a rather simple experimental system is reported [116]. Similar fancy appears in nanomedicine drug delivery, which does not account for the realistic features of a physiological/biological system. In other words, drug delivery technology should be developed based on science, technology, and engineering and on reality in physiology, pathohistological, and biology in human patients, not on scientific fiction nor a mouse, but we need to learn how. For instance, macromolecules or nanoparticles carrying imaging agents would shine on clinical solid tumors, although most of the macromolecules/nanoparticles are accumulated in the peripheral region of the tumor where imaging would be heterogeneous. The scientists would then be able to explore how to co-relate imaging information from patients for patient specific tumor physiology, usefulness of therapeutic nanomedicine, or surgical help to identify tumor margins [117].

4. Preclinical-clinical relationship

It is mandatory to submit favorable preclinical results in efficacy and toxicology for any new drug candidate and experimental DDS for IND filing. IND approval permits Phase 1 clinical investigation. The low success rate of oncology drugs tells the majority of oncology drug candidates fail even when preclinical data looks promising, suggesting a poor connection of preclinical results to clinical outputs. Unforeseen toxicity from a preclinical toxicology study often becomes a primary cause of failure. An animal model is useful if researchers limit their interpretation of data within the boundary that the model serves. Any preclinical efficacy should be interpreted with caution and may not be extrapolated to human outcome without considering the species difference.

4.1. Modeling

Modeling in science and technology is categorized into two parts. Explanatory (descriptive) models make a particular feature of the world easier to understand, define, quantify, visualize, or simulate by referencing it to commonly accepted knowledge. On the other hand, predictive modeling is the process of creating, testing, and validating a model to best

predict the probability of an outcome. Most animal models in preclinical studies are for predictive purposes, while *in vitro* studies are often linked to explanatory modeling for a mechanistic understanding. With cancer nanomedicine, since the proof-of-concept data from animal models often fail in demonstrating reproducibility in humans, the term “model” for human diseases and disease treatment does not precisely fit the traditional “model” concept in science and technology. It is a simple screening process to judge go/no go for a given technology in humans. The availability in the literature as to the predictive power of mouse models for cancer nanomedicine is extremely limited.

There have been regular reports every five years for gene therapy clinical trials worldwide. The reports appeared in 2007, 2012, and 2018 in the Journal of Gene Medicine and summarized all gene delivery trials in humans, covering vectors, target diseases, and the status of clinical trials. The reported cases for analysis were 1309 by the year 2007 [118], 1843 by 2012 [119], and 2597 by 2017 [120]. There were only six marketed products that came out of 2597 trials up until 2017, even including in vitro transfection protocols. Even after counting recent FDA-approvals of Zolgensma® in 2019, Onpattro® in 2018, and Givlaari® in 2020 for inherited diseases, the success rate of gene therapy is ~ 0.16%, which is seriously lower than the average success rate (5–10%) of new drug candidates in all disease categories [121, 122]. Because no clinical trials are permitted without significant safety and efficacy data from preclinical studies, the gene therapy success rate supports that there is no noticeable relationship between preclinical and clinical outcomes, invalidating the role of rodent models in gene delivery technology.

There are various mouse models for cancer, and each model may have unique features to reflect clinical settings or purposes. For instance, a patient-derived orthotopic xenograft using cancer tissue may fit for screening drug candidates or finding combination protocols for personalized therapy [123]. On the other hand, one report claims that patient-derived 3-D organoids are more predictive than patient-derived xenograft models [124]. The following are a few sections describing the challenging issues in establishing the co-relationship of DDT and PK equivalence among animal species and associated physiological factors.

4.2. Bioequivalence in species

Species-specific physiological features can cause difficulties in the interspecies extrapolation of the performance of a drug and DDS [125]. The partitioning of therapeutic compounds into specific tissues is an additional factor. Cases which compare the bioequivalence of different formulations of the same drug in different species have been reported. Two different ampicillin formulations of aqueous trihydrate and oily suspension were intramuscularly injected into calves and swine to compare AUC in two domestic farm species. In calves, two showed similar AUC but were not equivalent in swine [126]. On the other hand, when two ivermectin formulations of an antiparasitic agent were SC injected into cattle and swine, swine had nearly identical T_{max}, but cattle had markedly different T_{max} [127]. PK parameters of the same drug among species were compared with benzylpenicillin in Camelus dromedarius and in sheep after administration of a single intravenous injection. It was concluded that benzylpenicillin elimination occurs more slowly in the dromedary than in sheep, and the use of the same dosage regimen for the two

ruminant species may lead to significant differences in plasma concentrations and therapeutic efficacy [128]. The experimental observations, although selected from many veterinary studies, collectively suggest that the subcutaneous and intramuscular environments, such as extracellular matrix density and body fluid turnover rates, for implants and injections, are not identical in two large animals.

An interesting study was conducted to find relative uptakes of four (4) different liposomes made of varying phospholipid compositions and filler lipids by mononuclear phagocytic system (MPS) in the liver and spleen in rats and mice at 4 hours post dose. There were large differentials between the two species and among the liposomes. It seems that in addition to the composition-dependent stability issue of liposomes, the macrophages in the liver and spleen interact with the liposomes and phagocytosis occurs at different rates despite that two rodent animals were compared. The liver and spleen are major organs for the uptake of circulating nanoparticles, while the remaining carriers are distributed in the body, including target sites. Extrapolating the biodistribution of liposomes in the human body from rodent data would be risky [129].

The weak predictive power in translation from rodent results of new drug candidates and DDS is not surprising at all. When toxicology comes into consideration, the preclinical and clinical relationship becomes further unforeseen because most toxicity results found in clinical tests (Phase 3) are hardly observed in laboratory animals. Regulatory authorities would pay more attention to toxicology than efficacy for approval.

4.3. Species dependent physiological and scaling parameters for drug delivery in cancer models

4.3.1. Plasma composition and osmotic pressure—The plasma compositions of proteins and lipoproteins vary with animal species [130–132]. The amounts of albumin, α1-glycoprotein, and total protein differ in mouse, rat, rabbit, monkey, dog, and human. In particular, the α1-glycoprotein content is significantly higher in rodents than in other animals [130]. Considering that lipoproteins are a major carrier of hydrophobic drugs in the blood, the difference in PK and PD of a drug is not surprising due to the different binding capacities of drugs. Most nano-sized carriers are more compatible with lipophilic drugs for drug loading and sustained release kinetics than hydrophilic ones. When the incorporated drug is released, there is a high chance it will bind with lipoproteins.

The plasma colloidal osmolarity also varies among the 21 animal species tested. Osmolarity (or osmolality at a constant temperature and pressure) is linked to the osmotic gradient, which may influence body fluid turnover rates, depending on the osmolarity in the extravascular space. Similarly, the hydrostatic pressure differentials among animals and/or by the living environment is anticipated. The pressure gradient is critical in determining the convectional flow of body fluid and determining the extent of extravasation of drug molecules and nanoparticles if there are large enough pores for the nanoparticles to enter [133].

4.3.2. Blood supply—A human has a standard bodyweight of 50–100 kg, a heartbeat rate of 70 stokes/min with ~5 L of blood, and an average cardiac output (CO) of 70 mL/

stroke. The average stroke volume is about 70 mL/stroke. A mouse has a 2 mL blood volume, 600 strokes/min, and a CO of 25 μL/stroke. The ratio of blood pumping volume per min to blood volume is 7.5 times higher in a mouse than a human. This roughly translates to the circulation in a mouse being 7.5 times faster than in a human.

The blood flow rates in individual human organs under basal conditions vary seriously. The normalized blood supply rate in mL/min/100 g tissue is the highest (360) in the kidney. The supply rate in the liver is 95. Bone and skin (in cold weather) receive as low as three and other organs except for the heart, brain, bronchi, muscles, thyroid gland, and adrenal glands receive as low as 1.3 [134]. The blood supply rate to tumors in humans is not known. It is simply assumed that there is a wide variation. The vasculature in a solid tumor, blood vessel density, and distribution are factors. The perfusion pattern also of blood in a tumor seems to be in a dynamic state. There is an example that explains the blood supply is critical for therapy. Hepatocellular carcinoma (HCC) receives blood from arteries; however, healthy tissue in the liver receives 75–80% of its blood supply from the portal vein, and the rest comes from arteries for oxygenated blood. This implies that drug delivery or supply to the HCC should be introduced to the hepatic arteries rather than by IV injection for effective therapy, as done with SMANC/Lipiodol® [96, 135]. For example, PK2 (polyHPMA conjugated with doxorubicin and galactose) for HCC cancer cell targeting was once labeled with an isotope for gamma camera imaging and IV injected into human patients. The image showed that the conjugate illuminated the liver, but not the tumor. Radioactivity was concentrated three-to-four times more in the healthy liver rather than in the tumor [136].

4.3.3. Tumor size—Assuming a spherical tumor with the density of ‘1’ of tumor tissue and 6 mm in diameter will occupy 0.45 weight% (wt-%), 10 mm 2.1 wt-%, and 15 mm 7 wt-% in a mouse with a 25 g body weight. According to the American Cancer Society, one of the breast cancer classifications is by size and the classes are **TX**: The doctor is unable to assess the primary tumor; **T0**: The doctor has not found evidence of a primary tumor [137]; **T1**: The tumor is 2 cm (0.79 inches (in)) or less in diameter; **T2**: The tumor is more than 2 cm (0.79 in) but less than 5 cm (1.97 in) across; **T3**: The tumor is larger than 5 cm (1.97 in) wide; **T4**: The tumor can be of any size, but it is growing into the chest wall or skin. This category includes inflammatory breast cancer. Thus, breast tumors of 5 cm in diameter is large in human patients. With the same density assumption, a tumor 50 mm in diameter is only 0.1 wt-% of a woman with a body weight of 65 kg, 30 mm in diameter is 0.02 w%, and 10 mm in diameter is 0.00075 w%. This simple calculation reflects the experimental tumors size in mice is not comparable to small scale clinical tumors.

4.3.4. Tumor growth rate—A solid tumor in an immune compromised or deficient mouse grows to sizes appropriate to measure in a few to several weeks after cancer cell inoculation. The growth depends on the proliferation rate of cancer cells and interactions with the tumor environment. The time period from epigenetic and genetic mutation, that transforms somatic cells to malignant cells, to diagnosis in human cancer patients is not known. It may take years. A paper reported that the tumor volume doubling time in breast cancer is approximately 150 days [138]. The growth rate of mammalian animals varies significantly from species to species. A lab mouse becomes an adult in ~3 months while a

human take ~20 years. The pathophysiology of the experimental tumors may not be identical to clinical tumors. This is particularly crucial in drug delivery (transport), in particular for nano-sized delivery systems. It is not known if there is any analogy in blood vessel distribution and density, instability of endothelial lining, blood vessel structure and leakiness, endothelial cell dynamics, blood flow rate, perfusion rate, the density and compositions of the extracellular matrix, cancer cell density, stromal cell populations, and the hypoxic area between experimental and clinical tumors, which would be all relevant to the growth rates and drug (or nanoparticles) transport from blood vessels to target cancer cells.

In summary, predictive power from lab animal cancer models to clinical translation is not known at all. There have been multiple occasions in almost every drug delivery conference that report tumor eradication by designed nanomedicines in mice. In scientific publications, numerous examples claiming curing cancer in mice exist. However, all theories may fit, at best, for artificial tumors in mice, not for clinical tumors in humans! The preclinical to clinical relationship of cancer nanomedicine is entirely missing.

4.4. Animal models for cancer immuno-oncology

Intact immune systems in model animals should be preserved for preclinical studies of immuno-oncology (IO) drugs. Representative models are syngeneic mouse models accommodating cancer cells derived from the mouse which have the same genetic background, genetically engineered mouse models which develop spontaneous tumors, and humanized mouse models that have human immune systems and human cancer. Each model has its own advantages and limitations.

The immune system is one of the most adopted defense mechanisms in living organisms to survive invading microorganisms and in parasites that survive the host immune attack. Accordingly, individual organisms or species have their unique immune systems depending on their living environment and routinely exposed pathogens. In humans, the living environment has kept improving by civilization, in particular, the supply of clean water by boiling or filtering which is entirely different from the environment of our ancestors and wild or domesticated animals. The immune system of an individual person responds differently when exposed to identical immune challenges. The same person shows different susceptibility to pathogens by body condition. If the same immune response by a given lab animal to experimental agents and/or conditions is anticipated in other species, including humans, it seems too naïve. The modeling of IO drugs with immunocompetent mouse models would thus become a more pressing concern in translation than cancer chemotherapy alone. It also becomes an independent research arena to improve translational probability or predictive power. The immune system in the tumor microenvironment interacts with cancer cells and evolves in its way in the models and individual patients. Predicting the translational power of experimental outputs from lab animals is premature at this infantile stage of IO. Still, the clinical success rate would presumably be even lower than oncology drugs and nanomedicine due to the complexity of diversified immune factors among species along with entirely different pathologies and physiologies of experimental tumors in rodents, as mentioned before.

5. The Future

5.1. Issues of yesterday and today facing the drug delivery field

Drug prices have been increasing much higher and faster than inflation, and it is hard to explain and difficult to accept for patients who need the drugs [139]. Probably the most disgusting price increase we have seen in years is when Turing Pharmaceuticals (now Vyera Pharmaceuticals) hiked the price of Daraprim, an old drug for parasitic infections, from $13.50 to $750 a pill in 2015. The list price of an EpiPen, which was about $50, reached $300 per auto-injector in 2016 by Mylan. Sovaldi introduced the first drug for curing hepatitis C without side effects in 2013. The only problem was that each pill costs $1,000, requiring more than $80,000 to get rid of the hepatitis C virus. Novartis introduced Zolgensma, a one-time gene-altering injection treatment for a severe form of spinal muscular atrophy in 2019, costing $2.1 million. These examples are painful, as it indicates that some pharmaceutical companies put the money above the caring of patients. We need to put these greedy incidences in the past. “Oh yes, the past can hurt, But the way I see it, you can either run from it or learn from it.” (Rafiki to Simba in *The Lion King*) [140].

We have to understand why what happened has happened and how we can solve it. The current status of drug delivery research is such that there have not been breakthrough drug delivery systems or technologies for the last few decades. The drug delivery scientists should be concerned by the current status, as the promise-first-with-little-outcome will eventually chip away the public’s confidence. As drug prices are soaring faster and higher than a rocket, the public will question the value of research. Is the treatment of cancer any better now with such promising nanomedicine? Do we understand how to prevent and/or treat Alzheimer’s disease? Can we prevent and treat opioid addiction? The beginning of the current stalemate on nanomedicine began with the nanotechnology initiatives that had good intentions but were executed with false promises and wrong approaches. We need to ask why the whole world was brought into the nanotechnology hype. The funding from the government has played an essential role. With no other particular ideas, the world followed America’s lead. In retrospect, it is amusing that the world paid great attention to nanotoxicology even before any credible nanoproducts were produced. Good scientists need a good collection of leaderships by experts in different research fields governed by funding agencies for a good investment of their time and ideas.

Time and resources, not well utilized, is a product of the lack of self-confidence of scientists. The mistake with nanomedicine is beyond the money spent. The field has been producing mostly me-too scientists who follow the same approach as others without any new ideas. Here, a question arises as to why the new generation of scientists repeat the same mistakes and focus their attention on incremental advances with a marginal return? This is basically technology overshooting, which makes a product more complicated with more functions that not many can use. Why are we still trapped inside the nanobox? We need good leadership by authentic scientists who are confident enough to try something radical, and who are ready to admit their mistakes, even if the radical idea remains another potential, but still learn from it.

The current system of research, publishing, and research funding is not working. It rewards those who participate in the faulty system. The self-promotion with exaggeration has been

fueled by the number game, such as the number of publications and the impact factors of the journals. This system also rewards the same old approach with only marginal improvements. The review system needs to change also. Change for change's sake may indeed become more disastrous than the current system but recognizing the need that the current system demands to be fixed or amended is the first step towards making a better system. Simply because a change is difficult or may be worse than no change should not be a reason to remain complacent. When we all understand that a real change is necessary, we collectively will find a better solution.

The question is how to break this cycle and free the young scientists who have an infinite future to explore new ideas. Solutions require breaking several inadequate systems apart. The way proposals are evaluated needs to change drastically to promote new ideas, instead of hype by famous and influential scientists which brings only marginal return. The job market needs to hire those with problem-solving skills, instead of the number of publications. Universities need to reevaluate their promotion systems by emphasizing creativity, instead of numbers of publications, external funding, and h-index, etc. All of us need to understand the source of the problem facing us. Under the current academic systems, many truly creative scientists have difficulty in their promotion/tenure evaluations. Those in power who can obtain a large sum of funding have no reason to change, just like politicians who get reelected by doing more or less the same thing. If they are indeed great scientists, they probably do not need all that money. We all need to encourage listening to our inner voice and expressing our opinion, even if it is very different from the norm.

5.2. Will the current drug delivery field continue without changes?

Public support for biomedical and pharmaceutical research has been dropping, and one of the reasons may be that the public has not seen any breakthrough advances in the treatment of major diseases, such as cancer, Alzheimer's disease, and diabetes. The public only feels that the drug prices are flying high without any justification. The problem in research funding has been most pronounced in the United States, and this may lead to yielding of the research superpower to other countries [141]. Researchers should take the bulk of this conundrum. Dr. Victor J. Dzau, the president of the National Academy of Medicine, and Dr. Harvey V. Fineberg, the presidential chair of the University of California, San Francisco, say researchers themselves need to be part of the solution, too. They write: "It is the responsibility of the research community to ensure that money for research will be used effectively and efficiently. A first step is to reduce redundancy and duplication of research through better grant selection and coordination." [141].

5.2.1. Responsibility of pharmaceutical scientists—All significant disasters in human history happened because those in charge failed to seek out more information. The disaster could have been mostly prevented if one actively sought out more relevant information. It is well known that politicians never admit their mistakes. If anything, they claim that they are more convinced with what they have done. What will happen, if scientists act the same way? Scientists are responsible not only for what they say, but also what they do not say on the information they have. When scientists are ready to admit their mistakes,

they are also open to constructive criticism which is essential for finding new, better, and smarter ways [142].

5.2.2. Changes in the research funding system—The current funding system has to change and evolve into a better one. Under the current system, a research proposal receives a more favorable score if an investigator has published many papers in high impact journals. These are all acceptable, if all scientists have enough funding to do their research. When drug delivery scientists want to do inspiring work, they have to start with why, e.g., why do we choose a particular delivery system? Trying to explain the vision behind the idea will guide us to develop a successful product. It always appears too risky to try radical ideas, but that is how science advances. The radical idea in time turns into another idea that could be revolutionary. Pioneers who try radical ideas are the ones who pave the way for others who jump into the field later [143]. The work done by the pioneers may result in something else totally unexpected. One of the most perplexing implications of Darwin's theory is that humans are the unplanned product of a blind and random process [144]. Doing pioneering work requires research funding and time. Generating a large number of papers itself does not advance the field. It is one rare research article that everybody appreciates. "The flower that blooms in adversity is the most rare and beautiful of all." (The Emperor of China in *Mulan*) [140].

Procrastination is critical for creativity. For a true scientist who wants to find out why cancer cells behave as they do and how to control them, a publication may not be the first choice. Instead, trying to understand the mechanism should be the first step. This will inevitably delay the publication of her findings. Only at the last minute when things need to be delivered, the ultimate creativity erupts. The funding agencies should allow enough time for researchers to seek out the results. Measuring the number of publications and calculating the overall citations may not be the right way of tracking progress. A breakthrough finding in science does not necessarily come from expensive research projects. More importantly, the breakthrough finding does not come from a large number of publications. If the system of research funding and promotion is based on basic science, yes, true basic science, and the number of publications is not an issue, a substantial portion of scientists will do more meaningful research. It will not be easy to change the current funding systems, but breakthrough changes will occur only if we start to change. A journey of thousand miles begins with the first step.

5.3. Defining optimal target diseases for defined drug delivery technology

The progress in research has been painfully slow. A good example is the nanomedicine research which began in 2000 as a part of the National Nanotechnology Initiative [145]. Since the beginning of nanomedicine research, the underlying principle remains the same. This is mainly because familiarity is what people like. When new research proposals are reviewed, a familiar research topic with a slightly different concept, just to inject a feel of newness, receives the most favorable recommendations. There is an "optimal newness" for ideas, advanced yet acceptable. Scientists are exquisitely sensitive to the advantage of ideas that already enjoy broad familiarity [146]. This explains why most research proposals and articles focus on nanomedicine with just enough newness. This penalizes those who work on

elucidating the underlying mechanisms that may not necessarily present something ‘new’. Max Planck, the theoretical physicist who helped lay the groundwork for quantum theory, said that “a new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.” [146]. We may have to wait for the next generation of scientists who will take over the current ones.

5.4. Developing realistic dreams

The world is not all that bad. In fact, a lot of significant progress has been made. We are prone to focus on the negativity bias [147], but when we look at the data objectively, things are a lot better than we think [148]. Our dream of developing new drug delivery systems for curing many diseases should be based on reality. Being optimistic is important, but blind optimism is nothing more than futility. Bill Gates said, “Optimism requires being candid about the hard problems that still need to be solved. --- I’m always amazed by the disconnect between what we see in the news and the reality of the world around us.” [149]. Here, Hans Rosling’s quote is highly relevant. “Most important of all, we should be teaching our children humility and curiosity. Being humble, here, means being aware of how difficult your instincts can make it to get the facts right. It means being realistic about the extent of your knowledge. It means being happy to say, “I don’t know.” It also means, when you do have an opinion, being prepared to change it when you discover new facts. It is quite relaxing being humble, because it means you can stop feeling pressured to have a view about everything and stop feeling you must be ready to defend your views all the time.”

5.5. Need to diversify drug delivery technologies

A diversified investment works because it lowers overall risk, and it is the best defense against a financial crisis. Nobody will invest their entire asset to just one stock. Nanomedicine is just one technology, and it is hard to understand why the entire drug delivery field spends all its resources on this. The future of drug delivery is anybody’s guess. We need to train the next generation of scientists to solve problems that are new with no easy answers. To prepare for an uncertain future is to diversify our technologies to minimize the potential damage of uncertainty and maximize the opportunities that certainly will come to us. When we face the future, it is certain that failure is more common than success [150].

5.6. Responsibility of drug delivery scientists

The current drug delivery scientists are the products of our time. History will judge how well, or not well, the current scientists have done. Regardless of how history will judge the current drug delivery scientists, we have to explore everything to where our imagination leads by getting out of functional fixedness and liberate ourselves from the confined research topics [151]. Basic research has no boundary. There is absolutely no need that we all think alike and do similar things. Each of us, in particular young scientists, need to find their own voice. Doing the same things as what others are doing and making it slightly better for the sole purpose of publication is probably not what a real scientist does, but the current environment has created it as a tool for survival. This needs to change. It would be wonderful if we know what that change should be. Nobody knows the answer. Instead of

asking what the alternatives are, we all should realize that the changes are necessary and experiment with different systems, and in time we will find a better one.

Current advances in health care have stemmed in large part from fundamental research funded by the National Institutes of Health (NIH), which traces its roots to 1887 [152]. Further progress is expected to be made from gene editing, cancer immunotherapy, precision medicine, to name a few. Such basic research is also vital for the prevention of various diseases. The beauty of basic research is that it will eventually reduce the cost of overall drug development by shortening the translational timeline. Whether one does basic, applied, clinical, or translational research, the ultimate goal is to make all people around the world live healthier. We should direct our efforts to something really important, i.e., making people have a better quality of life by eliminating and/or minimizing the undesirable effects of many unwanted diseases.

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