Ajeet Kaushik · Rahul Dev Jayant
Madhavan Nair *Editors*

Advances in Personalized Nanotherapeutics

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ISBN 978-3-319-63632-0 ISBN 978-3-319-63633-7 (eBook)
https://doi.org/10.1007/978-3-319-63633-7

Library of Congress Control Number: 2017958816

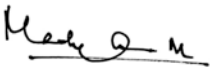
Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Endorsed by the Society of Personalized Nanomedicine

http://www.s-pnm.org/our-society.html

The Society for Personalized NanoMedicine (SPNM) aims to tailor medical intervention to patient- and disease-specific needs. The SPNM's mission is to promote research, serve as a source of information on current applications of nanotechnology, and foster the exchange of information and ideas on personalized nanomedicine. Our vision and goals are to merge interdisciplinary research in order to increase our understanding of current applications of nanotechnology. These applications include reconstructive surgery; targeted therapy; the latest research on nanodevices, drug development, and drug delivery; and the use of microelectronics and high-precision lithography for the production of nanocomposites for personalized medical use. The SPNM also promotes translational research that focuses on the interactions between the human immune system, substance abuse, HIV, and cancer, in order to create a solid ground for the development and application of groundbreaking medical devices and systems for superior diagnosis and treatment.



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Preface

Personalized health care management and optimization of the treatment of disease is crucial for improving the quality of health. Significant efforts have been made to design and develop novel nanotherapeutics strategies for the proficient monitoring and treatment of disease in a personalized manner. As per the state of the art, there are various strategies that involve the development of novel nanomaterials; novel drug delivery systems; the discovering of novel therapeutic agents; the integration of devices for better biosensing technology; and new therapeutic agents for the development of personalized nanomedicine to combat targeted diseases with no side effects. Besides nano-drug delivery, attention has also been focused on describing nano-enabled sensors, miniaturizing sensing systems, the interfacing of sensing components, and developing smart portable systems for point-of-care (POC) applications to detect biomarkers at very low levels in order to monitor the progression of targeted diseases. Such systems have also been used to assess the therapeutic efficacy of medicines that are specifically prescribed for the targeted diseases.

This book describes the fundamentals of nanomedicine; personalized therapeutics; novel nanomaterials for drug delivery; the role of nanotechnology in investigating therapeutic approaches; targeted CNS drug delivery; stimuli-responsive drug release; nano-enabled sensing systems for health care; and disease management. The future prospects of personalized nanotherapeutics and related challenges – with possible solutions – are also discussed. The book can be the source for new ideas to design and develop novel biomaterials, novel nano-formulations, targeted delivery, translational medicine, the scaling up of nanomedicine to a clinical phase, POC-sensing systems for rapid diagnostics, and the promotion of nano-pharmacology for next-generation personalized medicine.

This book will also be very useful for helping young scholars understand the exploration of state-of-the-art nanotechnology for personalized health care; it will also help researchers design their future investigations towards developing effective personalized nanomedicine and diagnostic healthcare systems. Numerous studies have reported on the design and development of nanomedicines with higher efficacy, but unfortunately such products are in the laboratory research phase only and need to be thoroughly tested, using pre-clinical or human models. Our book

can be a call for experts to explore multidisciplinary research for developing novel and effective approaches to exploring smart, efficient nanocarriers for site-specific, on-demand controlled drug delivery to combat targeted diseases, and smart sensing systems to detect targeted biomarkers at the fM level, for complete personalized healthcare.

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Chapter 1
Nanomedicine

Vinay Bhardwaj and Roozbeh Nikkhah-Moshaie

Abstract In this chapter, we start with the origin of nanotechnology and nanomedicine and the definition of nanomedicine in the USA and Europe. The size range of nanomedicine is discussed according to different definitions and regulations, and development of nanomedicine from lab to market is reviewed. Nanomaterials for nanomedicine is divided into two categories of polymer-based and metal-based. A brief explanation of most important nanomaterials including liposome, carbohydrates, gold, silver, and iron oxide in drug delivery and release, sensing and imaging are given. Nanomedicines already showed their potential and are promising to cure cancer, neurodegenerative disorders including NeuroHIV, Alzheimer's, and Parkinson's.

Keywords Nanotechnology • Nanomedicine • Nanomaterials • Nanocarriers • Drug Delivery

1 Genesis

The genesis of nanotechnology and nanomedicine can be dated back to a popular talk "There's plenty of room at the bottom" in December 29, 1959 at California Institute of Technology by late Dr. Richard P. Feynman, a Nobel laureate in physics [1]. Although he did not refer to the words "nano, nanotechnology or nanomedicine", he prophetically envisioned the unavoidable revolution in development of tiny machines and robots for biomedical applications. In an essay to his friend and graduate student he presented the first nanomedicine proposal, he wrote, it would be interesting if one could "swallow the surgeon". You put the surgeon, those tiny

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A. Kaushik et al. (eds.), *Advances in Personalized Nanotherapeutics*,
https://doi.org/10.1007/978-3-319-63633-7_1

robots inside blood vessel and the surgeon will move around inside your heart with little knife to slice defected heart valve. The concept of nanodevices, nanoknives, nanoscissors, which we still see on many cover pages of the books and magazines was in fact his original idea. Besides those two small inventions to win $1000 prize money for Dr. Feynman's challenge to the public, building of a tiny motor by a craftsman and writing by a Stanford graduate student on a 1/25,000 smaller surface, there were no noticeable breakthroughs to make Feynmans dream true until 1974. Late Dr. Norio Taniguchi, a professor at Tokyo University of Science coined the term "Nanotechnology" to describe control of semiconductor process on the order of nanometer [2]. Later, Dr. Kim Eric Drexler, an American Engineer at Massachusetts Institute of Technology proposed the idea of molecular nanotechnology in 1986 in his book "Engines of Creation: The coming era of nanotechnology". There is a controversy on the ontological status of the founding father of nanotechnology among Drs. Feynman, Taniguchi and Drexler. Authors of this chapter agree with a fairly recent sentimental statement by Dr. Richard A. L. Jones in 2006 in context to the creator of Nanotechnology. Though very unlikely and hard for many people to accept, US president Bill Clinton can be considered creator of nanotechnology as he is the first person to believe in potential of nanotechnology and nanomedicine. He launched $475 million National Nanotechnology Initiative (NNI) in 2000. The potential of nanotechnology in medicine "nanomedicine" was also realized at the beginning of this first initiative. US National Institutes of Health (NIH) launched 4-year program for nanoscience and nanotechnology in medicine in 2002 [3]. The nanotechnology funding has now grown to the proposed $1.4 billion budget for fiscal year 2017. Following US, other countries also invested heavily in nanotechnology initiatives, India's Department of Science and Technology's modest-size Nano Science and technology Initiative of a few crore rupees in 2001 has grown to 1000 crore nanomission in 2007, The European Commission's 1.3 billion euro in 2003 to current multi-billion budget, and other more than 60 countries are heavily investing in nano research and development.

2 Definition: What Can Be Considered a Nanomedicine

Although nanotechnology and nanomedicine has become widely adopted, it is surprising to know that none of the two has globally recognized definitions. And to enforce regulation, in particular safety assessment of nanomedicine, it is important to have a standard definition and classification of nanotechnoloigy and nanomedicine. Basically, every definition of nanotechnology and nanomedicine would include three elements. First, range of size, usually upper limit set to 100 nanometers (nm) diameter. Second, measurement and transformation at nanoscale, a significant progress has been achieved with the advancement of electron microscopy [4]. Third and most important motivating factor, nanoscale-specific properties and functions over micro and bulk scale. Both sides of the Atlantic Ocean have adopted different definitions. US NNI defines nanotechnology as the ability to understand, control, and

manipulate matter at the level of individual atoms and molecules, as well as "supramolecular" level involving clusters of molecules (in the range of about 0.1–100 nm) in order to create materials, devices, and systems with fundamentally new properties and functions because of their small structure [5]. However, many nanotechnologies/nanomedicines including US Food and Drug Administration (FDA)-approved, contradict this definition. Unique physiochemical properties from nanomaterials with cutoff >100 nm has been observed by scientific communities, for example, as compared to 70 nm size, 150–200 nm liposomes remain longer in the bloodstream allowing better therapeutics [6], plasmon resonance in 150 nm gold nanoshells is under clinical trials for thermal therapy of cancer [7], Myocet (180 nm) and Abraxane (130 nm) [8]. Due to this conflict in size of the nanotechnology or nanomaterilas, its definition undergoes continuous negotiation and revision. Fairly recent, European Commission's adopted new definition (2011) of nanomaterial "a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate, and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm [9]. Any revised definition like this has significant impact on nanotech industries as they have to abide by the new regulations, inclusion of number concentration over mass concentration that too more than equals 50 %, aggregates and upper size limited to 100 nm. An example of such an impact is that many European and American companies has started reformulating their products to a size >100 nm to bypass nanomedicine safety assessment. Contrarily, many Chief Scientific officers of the companies argued to this definition to increase nano cutoff to 300 nm [10] so that they already approved nanomedicines can retain the status. An illustration, a formulation with 40% particles of 90 nm and remaining 60% particles of 100 nm will not be considered nanomedicine according to this definition. US FDA approved nanomedicines Myocet, Abraxane, and many more, in particular liposomal nanomedicine are no longer nanomedicine according to the definition adopted by European Commission. Therefore, due to this conflict in size of the nanomedicine, it is important to inform readers that in this book we did not restrict to 100 nm as the cut off size to evaluate nanomedicine. Physio-chemical characterization of nanoparticles and nanomedicine for their shape, size, bioactive conjugation and release are also of great importance.

Broadly, nanotechnology is the engineering of functional systems at the molecular scale, and nanomedicine is a subset of nanotechnology with applications in medicine. It will not be incorrect to say that there is no nanomedicine but nanotechnology in medicine. According to European Science Foundation, nanomedicine is "the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body" [11]. According to United States' National Institutes of Health, nanomedicine is an offshoot of nanotechnology, which refers to highly specific medical interventions at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve.

3 Nanomedicine: Development from Bench-Side to Market

There are usually six developmental stages of a nanomedicine to reach market or patient (Fig. 1.1). (1) Synthesis and physiochemical characterization of the nanomaterial or nanoparticle, and (2) nanoformulation which is functionalization of nanoparticles for specific biomedical applications, followed by safety and performance testing (3) outside living body (in vitro usually at cellular level) or ex vivo, usually at tissue/organ levels (4) preclinical studies in mice, monkeys and other animal models (5) clinical trials in human, usually three phases, and finally (6) FDA approval for commercialization of the nanomedicine product. Majority of the nanomedicine proof-of-concept technologies/products die after in vitro testing either due to scarcity of capital to support preclinical and clinical testing or non-significant improvement when compared to already existing technologies/products. Most of the nanomedicine products fall under two categories, therapeutics and devices. Therapeutics has to go through a long process of FDA investigation before clearance, while 510 (k) premarket notification pathway for the medical devices makes the clearance fairly easy for the devices.

In this chapter we are giving you an overview of the nanomaterials and nanomedicine with a focus on FDA approved and clinically significant nanomedicines. Possible aspects of personalized nanomedicine including various nanomaterials

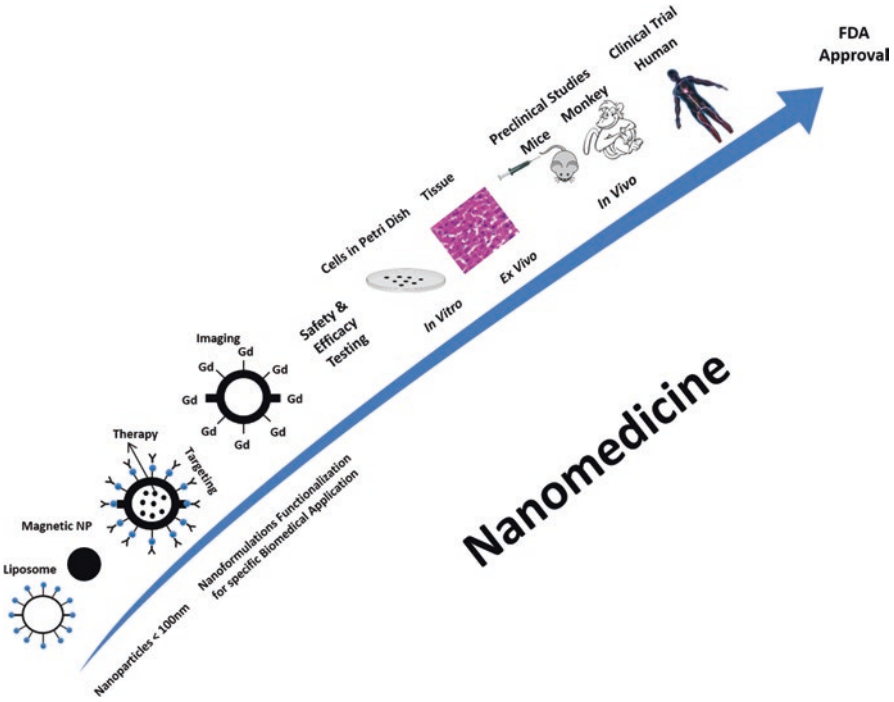

Fig. 1.1 Developmental stages of nanomedicine from lab bench to FDA approval for marketing and use in patients

with their important biomedical applications are discussed in subsequent chapters, image-guided therapy, targeted drug delivery, stimuli responsive drug delivery and controlled on-demand delivery with special emphasis on central nervous system drug delivery are described in this book.

In summary a nanoparticle can be modified for diverse medical applications. There are a few terms that are now being regularly used to further classify nanomedicine principle of design, for examples drug encapsulation (called nanoformulation) to treat cancer and neurodegenerative disorders, often called cancer nanomedicine and neuro-nanomedicine, respectively. Functionalizing nanoparticles with photosensitizer, heat generating dyes, or metal nanoparticles like gold and silver to achieve hyperethermia or photodynamic therapy, commonly called photo-nanomedicine. And regenerative nanomedicine, designing a polymer scaffold and impinging drug delivery nanocarrier, antimicrobial agents, etc., chitosan-based skin dressing with silver nanoparticles as anti-microbial agent is a typical example. Although photo-nanomedicine is discussed in this book to some extent, under section metal-based nanomedicine in this chapter, and subsequent chapters, readers interested in regenerative medicine are encouraged to read another book [12].

There are several hundreds of nanomaterials and their conjugates, for example, metallic nanomaterials, polymeric nanomaterials, metal-metal nanocomposites or hybrids, and metal-polymer nanocomposites, etc. To provide a clear understanding of the nanomaterials and the nanomedicine, we are dividing them in two broad categories as discussed below.

4 Polymer and Liposome-Based Nanomedicine

Most, if not all, polymer based nanomedicine uses either of two, (1) Liposomes and lipid based polymers, and (2) Carbohydrate and protein based polymers. Although there is a plethora of polymeric nanocarriers of medicine that are under clinical investigation, only the most successful are briefly introduced below and elaborated in subsequent chapters. For more details on polymer and liposome-based nanomedicine readers can refer to these review articles [6, 13, 14].

Since their discovery by Alec D. Bengham at University of Cambridge in 1964, liposomes have emerged to be the first and most successful nano drug delivery system or nanomedicine carrier. Liposome can simply be defined as a lipid bilayer structure or membrane around an aqueous compartment. The lipid component of the liposome can be man-made or synthetic depending on the desired properties. For example, a typical phospholipid-based liposome will have hydrophilic or aqueous core that allow encapsulation of hydrophilic drug, while the lipid membrane can encapsulate hydrophobic drug. Two biggest advantages of the liposomes are, first, a core-shell design allows better encapsulation strategy for the sustained drug release, and second, it allows encapsulation of both hydrophilic as well as hydrophobic drugs. However, these lipid based nanocarriers does not easily degrade, and toxicity is conceivable. Currently, there are approximately 12 clinically approved liposomal nanomedicine and around 80 under clinical investigation [15].

Carbohydrates, typically the polysaccharides have shown promising clinical success. Natural as well as synthetic polymers are used widely to deliver medicine. Some examples of commonly used carbohydrate polymers are chitosan, gelatin, cellulose, heparin, Polylactic acid, polyglycolic acid, and their copolymer poly(lactic-co-glycolic acid). Most widely used protein based polymer used in nano drug delivery is albumin. The inherent advantage of the carbohydrate and polymer based nanocarriers is their natural degradation by the enzymes present in the body that make these polymers and their degraded monomers highly biocompatible. However, their poor design, as compared to liposome's core-shell arrangement, is a limitation. Drug is usually conjugated to the polymer and susceptible to burst drug release. Synthesis of polymeric micelles by combining two or more polymers to form a core-shell arrangement is an alternate strategy used in the formulation of polymeric nanomedicine currently under clinical investigations.

5 Metal-Based Nanomedicine

Nanoparticles of metals, in particular noble metals, offer strong light scattering and absorption properties that holds the basis of their medicinal applications. The light scattering, for example Raman and Mie scattering is the basis of optical sensing and imaging, while light absorption to generate heat is the basis of photothermal applications. Most of the metal-based nanomedicine uses gold, silver and iron oxide. Bhardwaj et al investigated metal nanoparticles for cancer and neuro-nanomedicine, silver nanoparticles for their sensing and photo-thermal properties [16, 17], and magneto-electric nanoparticles for non-invasive drug delivery to the brain [18–20]. Gold and silver are excellent substrates for biosensor research, in particular surface-enhanced Raman spectroscopy (SERS) and surface-plasmon resonance (SPR) because of their unique localized surface plasmon resonance (LSPR) effect that arises due to the resonant oscillation of their free electrons in the presence of light [21]. While on the other hand, magnetization of iron oxide nanoparticles makes it a unique nanomaterial for magnetic-actuation for nano-electroporation, on-demand drug release, as well magnetic resonance imaging agent [19, 20], discussed in detail later in this book.

6 Nanomedicine: Progress, Prospects and Challenges

As per 2013 clinicaltrial data, there are roughly 250 nanomedicine products approved or under clinical investigation. Of 250, 54 are commercial and 46 are likely to be commercialized. Most of these nanomedicines products are either medical devices or therapeutics as categorized by U.S. Food and Drug Administration. There are 44 medical devices and 33 therapeutics so far. Among therapeutics, primarily drug delivery vehicle are liposome and polymer based nano therapeutics. A significant progress has been made towards developing nanomedicine for cancer therapeutics (Fig. 1.2). Most of the therapeutic nanomedicine have size below 350 nm (Fig. 1.3).

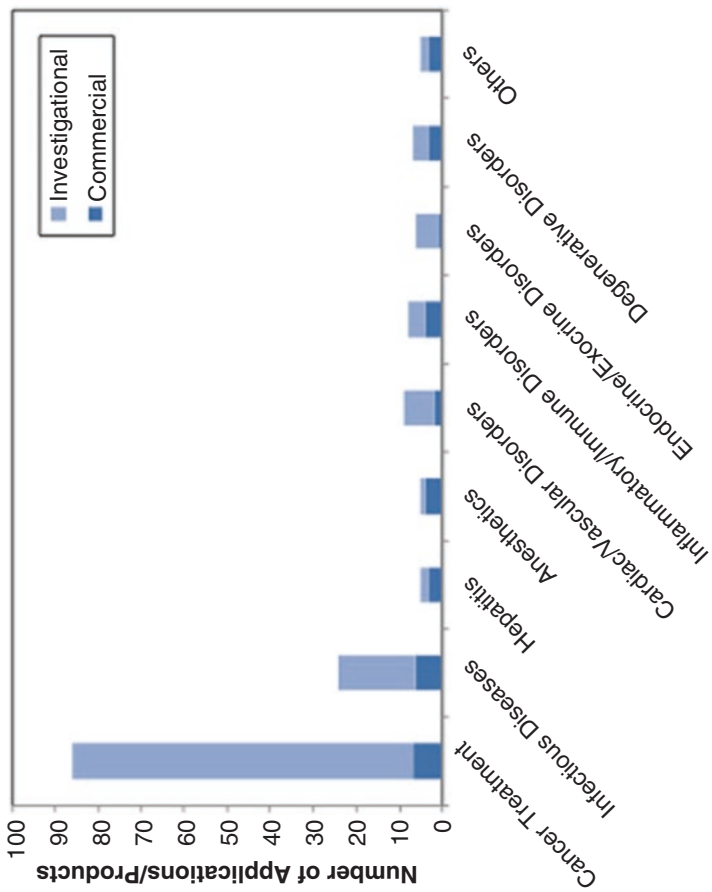

Fig. 1.2 Medical applications of commercialized and likely to be commercialized nanomedicines for therapy, as identified by year 2013. Adapted from Elsevier [22]

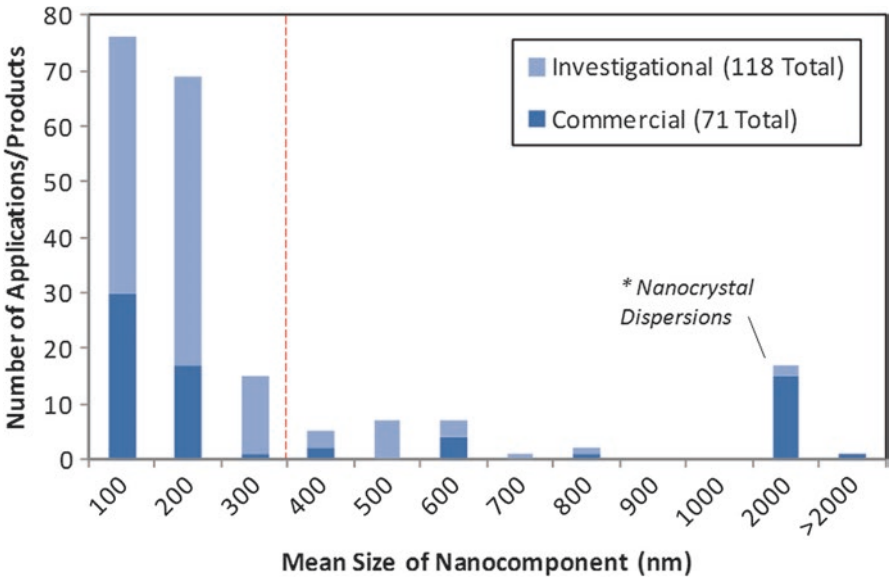

Fig. 1.3 Mean size of the nanomaterial reported in the nanomedicine approved for commercial use or likely to be commercialized. *Dotted line* indicates cutoff size used in this chapter to define nanomedicine or nanomaterials as most of them fall below this cutoff. Nanocrystal dispersion is highlighted as many products have roughly this size. Adapted from Elsevier [22]

Cancer is a major global health problem, a National Cancer Institute (NCI) initiative focused on the cancer nanomedicine. An improvement in the rate of cancer treatment has been observed with the advent of cancer nanomedicine. However, much efforts are required for other devastating diseases like neurodegenerative diseases that includes but not limited to brain cancer, neuroAIDS, Alzheimer's, Parkinson's etc. [18, 20, 23–25].

The biggest and debatable issue in the progress of nanomedicine is the size of the nanoparticles (Fig. 1.3). There is no defined cutoff any more, at least in practice, as evident by the nanomedicine products in market that are usually greater than 100 nm. The definition of nanomedicine and nanotechnology differ from country to country, and it's continuously evolving with the growing understanding of nanotechnology and nanomedicine.

7 Conclusion

Nanomaterials with size below 350 nm can be considered nanomedicine due to their effectiveness and working mechanism. Advancement in nanomedicine is occurring in both medical devices and therapeutics areas. Many nanomaterials with controlled and targeted delivery have been introduced to the market. However, much efforts are

being made in research on the design and development of new nanomaterials with on-demand release and minimum toxicity. More funding is required for research, preclinical, and clinical tests in order to develop and introduce safe and effective nanomedicine to the market.

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Chapter 2
Personalized Therapeutics: First Take Home Messages

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Abstract Personalized therapeutics is the emerging field in the medicine based on the individual's unique characteristics like genetic profile/alterations, epigenetic modifications, clinical symptoms, disease biomarkers and environmental factors which play a significant role in tailoring their therapies. Although there is a significant progress in personalized therapeutics towards the treatment of few genetic disorders and life threatening diseases, there is still plenty of work to be done to make the field progress in the treatment of various diseases and make these approaches useful to patients in rural areas as well. In this chapter we have briefed few updates in the field of personalized therapeutics application in the treatment of cancer, cystic fibrosis, stroke, psychiatry and asthma.

Keywords Personalized medicine • Chronic diseases • Next generation sequencing • Therapeutics

1 Introduction

Personalized medicine is the field of healthcare that consists of treating individuals according to their unique clinical, genetic, genomic, and environmental information. Personalized Medicine Coalition defines it as "the use of new methods of molecular analysis to better manage a patient's disease or predisposition to disease". In other words, personalized medicine is about making the treatment as

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A. Kaushik et al. (eds.), *Advances in Personalized Nanotherapeutics*,
https://doi.org/10.1007/978-3-319-63633-7_2

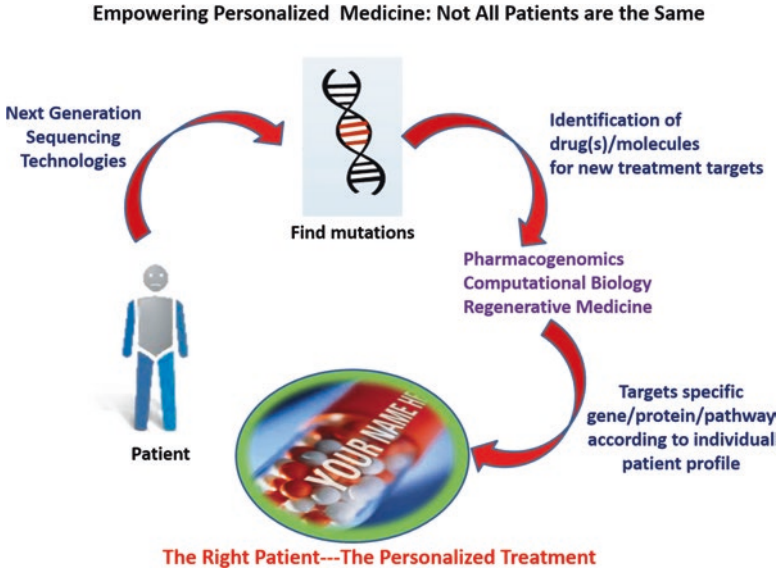

Fig. 2.1 Paving the way for personalized medicine. The promise of "personalized medicine," which is the tailoring of medical treatment to the individual characteristics, needs and preferences of each patient. The paradigmatic developments in science and technology offer new promise for developing targeted therapeutics and tools for predicting who will respond to a medical therapy or who will suffer ill effects by using next-generation technologies leads to identification of novel drug molecule(s) to target specific pathway(s)

individualized as the disease. The concept of personalized medicine dates back hundreds of years, but it was not until the turn of the twenty-first century when the Human Genome Project was successfully completed that personalized medicine became a more tangible concept. Currently, whole genome sequencing (WGS) is becoming one of the most widely used applications and is providing tremendous quantities of genome sequences relative to the past through public and private human genome sequencing projects throughout the world, which is a necessary component of personalized and precision medicine [1]. Now researchers are taking advantage of the Human Genome Project to learn how inherited differences in genes affect the body's response to medication and how these differences can be used to predict the effect of a medication on a particular individual and to prevent adverse drug reactions. Developments in the fields of genomics and other areas such as pharmacogenomics, computational biology, and regenerative medicine have played a significant role in developing tools to personalize diagnosis and treatment of diseases (Fig. 2.1).

Pharmacogenomics, which is "the study of how genes affect a person's response to drugs" is a significant area of personalized medicine where substantial progress has been made. It looks at variations in genes, such as liver enzymes, that code for

proteins responsible for converting medications into their active or inactive forms. For example, the liver enzyme known as CYP2D6 acts on a quarter of all prescription drugs; it converts the painkiller codeine into its active form morphine. People who have extra copies of the CYP2D6 gene produce an excess of CYP2D6 enzyme, which causes codeine to be converted to morphine very rapidly; resulting in a drug overdose. On the other hand, some people have a different version of the CYP2D6 gene, which can result in a nonfunctional enzyme that metabolizes codeine slowly, making it ineffective at relieving pain. The Food and Drug administration has included pharmacogenomics information, such as possible side effects and differences in effectiveness for people with certain genomic variation on the labels of more than 150 medications. These advances allow doctors to use pharmacogenomics information to select the best medication and the correct dose for individual patients. The field of pharmacogenomics is currently limited, but new approaches such as the development of tailored drugs to treat diseases such Alzheimer, cancer, and HIV/AIDS are under study in clinical trials.

Personalized medicine also includes anatomically-specific devices such as the tinnitus masker, which is a personalized electronic hearing aid device that generates a masking noise, sometimes referred as white noise, for an individual suffering from hearing loss and tinnitus. According to the American Tinnitus Association tinnitus is "the perception of sound when no actual external noise is present", and even though there is no scientifically-validated cure for this health issue, the tinnitus masker has proven to be very efficient at alleviating it. Another anatomically-specific device is the Artificial Pancreas Device System, which measures patient's glucose levels and delivers patients-tailored insulin doses in people with diabetes. A different, but also very significant personalized invention in medicine was the creation of a 3D printed tracheal split. Physicians at the University of Michigan and Akron Children's Hospital utilized a computed tomography image, computer-aided design, and 3D printing to make a bioresorbable airway splint to treat an infant diagnosed with tracheobronchomalacia, which is a life-threatening condition that happens when the airways walls are so weak that they collapse during coughing or breathing [1].

Personalized medicine has also made progress for chronic diseases such as cancer, asthma, and chronic obstructive pulmonary disease. All these new discoveries open the doors to more informed medical decisions, better targeted therapies, less medicine side effects and early disease intervention. It allows people to make preventive lifestyle choices that will help counteract any biological risk they might be facing. Even potentially lifesaving medications that could be taken off the market because they pose a risk for some people, could still be available for those who could benefit from them. Personalized medicine focuses on prevention, and making a transition from treating a disease to maintaining health. Finally, it reduces healthcare cost by allowing doctors to quickly select the effective therapy for an individual patient while avoiding the costs that ineffective treatments carry. Personalized therapeutics holds the future for medicine.