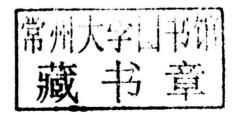


PERSONALIZED MEDICINE

Advances in Nanotechnology, Drug Delivery, and Therapy

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PERSONALIZED MEDICINE

This volume is dedicated to

my parents, Aimilia and Spiros, whose perspective on life, work, and behavior shows me the way to grow, improve, and progress as a human being by putting tasks and achieving targets, as well as keeping dreams alive, both as a person and in academia

my wife, Lila, and my kids, Emily and Spiros, whose continuous contact, devotion, and love show me the way to behave and better handle issues related to community and society, thus permitting me to follow dreams and run toward realistic targets

my students and colleagues for their trust, collaboration, and contribution that give me an opportunity to become a better teacher as well as to enrich knowledge, skills, and expertise, thus making research projects a reality and finally a success

Preface

The response of an organism to drugs has been challenging scientists through the years, and it must be considered as one aspect of the overall responses that living species exert to different environmental impacts and stressors within an ever-changing environment. To this regard, our knowledge of illness etiology and drug actions in the body goes in parallel with the scientific advances focusing to elucidate mechanisms and processes that contribute to the existence of life itself. In this way, understanding the pathophysiology of disease phenotypes as well as deciphering the underlying pharmacological mechanisms have long been set as the primary goals to be achieved, maximizing benefits in medical and pharmacy practice. Moreover, maximum efficacy and safety upon drug delivery, implying the improvement of pharmacotherapy profiles, is a long-desirable target for drug administration and coincides chronologically with the establishment of pharmacology as a basic and clinical discipline. Especially, over the past 80 years, medical and pharmaceutical specialties were given the capacity to suitably adopt scientific advancements coming from various research areas, thus providing health care practitioners with the suitable skills and expertise to improve disease prognosis and diagnosis as well as drug delivery clinical outcomes. As an example, if the scientific achievements will be considered over this period for the drug discovery and development era, one can easily came to the conclusion that it has been mainly influenced by fundamental advances in chemistry, physiology, and pharmacology, whereas specific contributions occurred at various decades from disciplines as these were being expanded through the years. Such examples refer to breakthroughs from microbiology in the 1930s and 1940s, from biochemistry and enzymology in the 1950s and 1960s, and from molecular biology and recombinant DNA (rDNA) technology from the middle of 1970s and onward.

Nowadays, advances in nanotechnology, genomic technologies, informatics, molecular biology and pharmacology have long held out the promise of transforming medical practice, drug development and delivery from a matter of serendipity to a rational pursuit grounded in a fundamental understanding of the mechanisms of life. As far as the drug-related research and clinical environment is concerned, pharmacogenomics revived pharmacogenetics and pharmacology research boundaries to keep pace with fastevolving life-imposed scientific advances. The application of pharmacogenomics focuses on the clinical translation of genomics data to predict and evaluate disease risk and progression, as well as the pharmacological response to drugs in individual patients or groups of patients. As a matter of fact, the clinically validated genomic knowledge of target receptors, ion channels, enzymes, or transporters could be an additional clinical factor in guiding personalized prescription of most, if not all, currently in practice, orally delivered drugs to achieve the best-possible efficacy and safety profiles. By definition, personalized medicine implies the management of a patient's disease in terms of prognosis, diagnosis, and drug delivery to achieve therapy with the best-possible medical outcome for that individual. To this end, the concept of personalized medicine has emerged as the way by which a suitable infrastructure setting in research, clinics, education and regulation could be built to hasten the translational efficiency of genomic, molecular and technological advancements into the practice of medicine and pharmacy. The latter means that both clinical and research efforts focusing on those concepts might formulate and broaden the era of personalized medicine and could facilitate as well as accelerate its practical utility in the clinical settings. This is considered a very important aspect toward achieving major benefits for personalized medicine worldwide. Such an approach was further supported by the notion that the possibility of focusing on the development of "personalized medicines" for specific individual patients could hardly be attained in practice, since it represents a very difficult task to be affordably achieved in terms of existing regulatory drug development issues, world-broad clinical utility, and therapy costs.

Personalized medicine, although in its infancy, represents already the next evolutionary step in medicine and pharmacy by gaining acceptance as an independent area of research to join the gap as well as connect experimentally the interfaces between the clinical settings with health-related basic disciplines. Through the application in everyday clinical practice of personalized medicine concepts, the improvement of prognosis, diagnosis, and therapy outcomes can be achieved in an affordable way as well in real time by permitting the stratification of patients suffering the same complex illness (e.g., cancer, cardiovascular disorders). It is expected to revolutionize the whole health and pharmaceutical care environment by focusing on the individualization approach both in research and in everyday clinical practice. This refers, among others, to disease risk assessment, diagnosis profiles, and new drug development approaches in order for the clinical translation of genomics information to be more efficiently achieved, thus maximizing drug delivery and prescription worldwide.

Having this in mind, the organization of a multidisciplinary approach toward serving better the clinical exploitation of the knowledge achieved thus far from cutting-edge genomics, innovative bioinformatics, and frontline nanotechnological advancements seems reasonable and attainable. Furthermore, this direction might more affordably permit the application of personalized medicine concepts in routine health care as well as cultivate the functional merger and unification of these core research directions into a common ground of "communication research language" to achieve the desirable personalized medicine targets. For example, by strengthening the clinical benefits of genomic knowledge as well as applying informatics methodologies and nanotechnological procedures and putting in perspective their advancements that contribute to personalized medicine, such an idea is gaining practical utility in clinical practice and drug delivery in a way that it connects the outcomes with specific markers and gene expression signatures of prognostic, diagnostic, and even therapeutic value. To this end, practical clinical utility worldwide could be faster and more efficiently achieved. And more importantly, by fulfilling the needs of broader clinical utility for personalized medicine, this also coincides with the active participation of health care educators in the advancements happening both in research and at the clinical level in order then to transfer their expertise and experience into future professionals through the creation of suitable education programs in medicine and pharmacy. Such direction is crucial, since the implementation of the curricula has to take into consideration the scientific approaches with practical clinical consequences in the profiles of individual patients for diagnosis and drug delivery outcomes.

Handbook of Personalized Medicine represents an effort to critically shape the era in which various advancements contributing to health care disciplines merge to formulate the structure needed for allowing personalized medicine concepts to emerge in everyday clinical practice. The latter implies that these advancements are clinically validated, getting practical utility and broad use, and meeting regulatory requirements, as well as receiving a final approval to enter health care. To achieve this goal, leading scientists in their areas of expertise with various scientific backgrounds have been invited to contribute. To this end, recent advancements in genomics and nanotechnology will be presented that create a fertile ground for pharmacogenomics and personalized medicine to advance prognosis and diagnosis profiles for specific groups or individual patients and move toward pharmacotyping in drug prescription, that is, the individualized specific drug and dosage scheme selection based on the patient's clinical and genetic data. Within this frame, this book is unique in its structure by including issues related to nanosystems and nanodevices, innovative drug formulations and nanotheranostics, molecular imaging and signatures, translational nanomedicine and informatics, predictability of drug effect behavior, genetic etiology of drug response heterogeneity, pharmacogeneticsguided drug prescription, pharmacovigilance and regulatory aspects, ethical and cost-effectiveness consequences, personal genome analysis, pharmacogenomics knowledgebase, education issues, and information-based medicine, as well as, last but not least, a framework and infrastructure to support personalized medicine utility for everyday clinical practice. This multidisciplinary Handbook of Personalized Medicine is also unique in its concept by including and presenting selective cutting-edge technological advancements from genomics, pharmacology, nanotechnology, informatics, and statistics

that focus on pharmacogenomics and personalized medicine and allow the practical utility of clinically relevant genomic knowledge to enter health and pharmacy care. The idea to present various topics addressing the practical utility of personalized medicine and pharmacogenomics in a feasible and cost-affordable manner for routine health care is also innovative for this book volume. The text, although organized in such a way that each chapter represents an independent area of research, simultaneously allows an easy manner for the reader to intercorrelate various subjects covered in separate chapters. I sincerely hope that the book will assist readers in understanding the multidisciplinary nature of the changes happening in health and pharmaceutical care sectors and also to enrich their knowledge and their own perspectives on how genomics, informatics, pharmacology, and nanotechnology affect health-related professions to better adjust themselves in the new setting.

From the beginning and upon completion of this volume, new scientific achievements have stressed toward the empowerment of personalized medicine decisions by working and building a more multidisciplinary infrastructure in research and clinics. It is, for example, very interesting to note the vast load of human and other complex genomes functional data published in September 2012 from the ENCODE Project Consortium (The Encyclopedia of DNA Elements; ENCODE) that provides new insights into genetic variability patterns seen in individuals and populations. As is pointed out, many previously clinically validated DNA variants are located within or very near to intergenic regions and other noncoding functional DNA elements, thus providing new ways to clinically translate genomic information by linking specific genetic polymorphisms and disease etiology and progression profiles. Such new genetic information impinges on the regulation of complex mechanisms involved in human genome function, which, in turn, may contribute to molecular pathophysiology mechanisms. The latter stressfully points toward a more multidisciplinary effort for a practical clinical utility infrastructure in the era of personalised medicine for the benefit of society and individual patients worldwide. And more importantly, as recently published, the application of an integrative personal "omics" profile analysis

that combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from a single individual has revealed the dynamics of this approach toward achieving personalized medicine decisions in clinical practice.

Last, but not least, the dynamic scientific environment that already exists in the era of nanotechnology and genomics with the potential to affect health care and drug delivery decisions needs more collaborative multidisciplinary efforts to make practical clinical utility of personalized medicine a maximum success. As a matter of fact, by crossing the borderlines of genomics with nanotechnology a fertile ground can be created to lead to the advent of "personalised nanomedicine" as a new discipline to enforce individualized therapeutic decisions with maximum safety and efficacy. To this end, a theme issue on "personalized nanomedicine" in the journal Advanced Drug Delivery Reviews has been recently coedited (October 2012) to define and exemplify that necessity in both research and clinical settings. The interested reader can follow such referred theme issues for further information and consideration.

I feel so deeply grateful, and I express my sincere thanks to all authors who contributed to this volume by taking time from their busy schedule, as well as presented their work and provided their personal perspectives on the concept of personalized medicine, thus making the initial multidisciplinary approach a reality and get its sense in the book.

Special thanks are also expressed to the Pan Stanford Publishing staff for their kind help as well as their work to see this volume being completed.

I cordially express my gratitude to my family members for their patience in all stages of this project, as well as for their continuous encouragement and the creation of such a supportive and creative environment that make this work finalized and complete.

> Ioannis S. Vizirianakis Thessaloniki, Autumn 2013

Contents

Pr	eface			xxxiii
1	Jaso	n H. Sa	nology toward Advancing Personalized Medicine Ikamoto, Biana Godin, Ye Hu, Elvin Blanco, In de Ven, Adaikkalam Vellaichamy,	1
	Mat	thew B	B. Murphy, Saverio La Francesca,	
	Terry	Schue	enemeyer, Bruce Given, Anne Meyn, and	
	Mauro Ferrari			
	1.1 Introduction			1
	1.2	Conve	entional Cancer Chemotherapeutics	3
		1.2.1	A Brief History	3
		1.2.2	A Summary of Conventional Anticancer	
			Drugs	5
	1.3	Conce	ept of Personalized Medicine	8
	1.4	Nano	technology in Medicine	8
	1.5	Inject	table Therapeutics	9
		1.5.1	Personalization by Design of Nanovectors with	
			Lesion-Specific Transport Properties	9
	1.6	Molec	cular Imaging	16
		1.6.1	Collection of Patient-Specific Data for Tailoring	
			Treatments	16
	1.7	Early	Detection	18
		1.7.1	The -Omic Technologies and Systems Biology:	
			Resolving the "Portrait of Health"	18
			1.7.1.1 Microarray technology	19
			1.7.1.2 Nanodiagnostics	20
			1.7.1.3 Nanofluidics	22
			1.7.1.4 Biomarker discovery	23
	1.8	Reger	nerative Medicine and Tissue Engineering	26

		1.8.1	Stem Ce	ells for Regenerative Medicine	27
		1.8.2		led Drug Release	28
		1.8.3	Nanote	chnology and Biomaterials	29
	1.9	The R	ole of Na	notechnology and Personalized	
		Medic		1	30
	1.10	Vanta	ge Points	s: Nanomedicine Advancing	
		Perso	nalized N	Medicine	31
		1.10.1	The Evo	olutionary Process of Personalized	
			Medicir	ne: The Real Drivers of Innovation	31
		1.10.2	A Physi	cian's Perspective	31
		1.10.3	A Regul	atory Consultant's Perspective	34
		1.10.4	A Biote	ch Startup CEO's Perspective	40
		1.10.5	A Patier	nt Advocate's Perspective	43
	1.11	Summ		-	45
2	DAIA	i Nanc	medicina	es toward Advancing Personalized	
_	RNAi Nanomedicines toward Advancing Personalized Medicine: Challenges and Opportunities for Targeted				
				une System	59
		Peer	tile illilli	une system	39
			luction		60
	2.1			Delivery Strategies of RNAi	61
		2.1.2		tion of siRNA into Clinical Practice	62
		2,1,2		In vivo delivery of siRNA	62
				Passive systemic siRNA delivery	64
			2.1.2.3	Active (cellular-targeted) systemic	01
			2.1.2.0	siRNA delivery	66
			2.1.2.4		00
				leukocytes	69
				reunocytes	0,7
3				ledical Imaging Technologies on	
	Individualized Patient-Specific Cancer Management:				
A Clinical Perspective			re -	81	
	Sand	Sandip Basu			
	3.1			Individualized Approach in an Era of	
		Evidence-Based Medicine in Oncology			82
	3.2			cular Imaging Is at the Forefront of	
		Perso	nalized (Cancer Medicine	83

	3.3	Medical Imaging Modalities with Significant Potential	
		toward Advancing Personalized Cancer Medicine	84
	3.4	Radionuclide Functional Imaging vs. Conventional	
		Morphological Imaging Methodologies: Advantages of	
		the Former with Regard to Materializing the Concept	
		of Personalized Cancer Medicine	85
		3.4.1 The Functional Radionuclide Modalities	85
		3.4.1.1 Targets in functional radionuclide	
		imaging that have a bearing on a	
		personalized approach in oncology	85
		3.4.1.2 Management of individualization in	
		various decision-making steps in	
		cancer with functional radionuclide	
		modalities	87
		3.4.1.3 Post-treatment disease surveillance	93
		3.4.1.4 Other advantages of whole-body	
		FDG-PET imaging	95
	3.5	Functional Molecular Imaging with US: The Potentials	
		toward Personalization	95
		3.5.1 Basic Principle	95
	3.6	Functional Molecular Imaging with MRI: The Potential	
		toward Personalization	98
		3.6.1 Molecular Optical Imaging	99
		3.6.1.1 Principle of bioluminescence imaging	100
		3.6.1.2 Principle of fluorescence imaging	100
		3.6.1.3 Translation into molecular imaging	101
	3.7	Conclusion	101
4	Boro	on Neutron Capture Therapy: Active Agents and Lipid	
	Carriers		
	Dim	itrios G. Fatouros, Gianpiero Calabrese, Eugen Barbu,	
	Mar	ta Roldo, Andriani G. Fatourou, and John Tsibouklis	
	4.1	Introduction	109
	4.2	Liposomal Carriers for Delivery to the Brain	111
	4.3	Boron Neutron Capture Therapy	112
	4.4	Liposomes and Boron	114
		4.4.1 Encapsulation of Boronated Agents into	
		Liposomes	114

		4.4.2	Boron-Based Liposomes	117
			4.4.2.1 Nido-carborane liposomes	117
			4.4.2.2 Closo-dodecaborate-based liposomes	118
			4.4.2.3 Closo-dodecaborate cholesterols	120
	4.5	Form	ulation Stability Studies	120
	4.6	Concl	usions	121
5	Cyto	toxicit	y Challenges in Development of Personalized	
	Nan	omedi	cines: Focus on Nucleic Acid Delivery Systems	129
	Lado	an Parh	amifar and S. Moein Moghimi	
	5.1	Intro	duction	129
	5.2	Nano	particle Toxicology	131
	5.3	Toxic	ity Considerations and Assessment of Polycation	
		Safety	in Gene Therapy	131
	5.4	Towa	rd Integrated Approaches	134
		5.4.1	Systems Biology	135
6	Drus	g Bioav	ailability and Gene Profiling: Challenges and	
			ties for Pharmaceutics and Personalized	
	(2.0	licine		141
	Afza	I R. Mo	hammed, Amr M. ElShaer, Rhys J. Jones,	
	FE. 1		n, and Craig A. Russell	
	6.1		duction	141
		6.1.1	Dosage Form Factors That Affect Drug	
			Bioavailability	142
		6.1.2	Physiological Factors of the Gastrointestinal	
			Tract That Affect Drug Bioavailability	145
		6.1.3	Mechanisms and Transport Routes of Drug	
			Absorption in the Gastrointestinal Tract	148
	6.2	Metho	ods of Assessing Drug Permeability	151
		6.2.1	In vitro Assessment of Permeability	152
			6.2.1.1 Excised tissue permeability assays	152
			6.2.1.2 Cell-based and membrane-based	
			permeability assays	152
			6.2.1.3 Physiochemical assessment of	
			permeability	155
		6.2.2		155
			6.2.2.1 In silico assessment of permeability	156