



Mini Review

Personalized medicine in hematology – A landmark from bench to bed

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ABSTRACT

Personalized medicine is the cornerstone of medical practice. It tailors treatments for specific conditions of an affected individual. The borders of personalized medicine are defined by limitations in technology and our understanding of biology, physiology and pathology of various conditions. Current advances in technology have provided physicians with the tools to investigate the molecular makeup of the disease. Translating these molecular make-ups to actionable targets has led to the development of small molecular inhibitors. Also, detailed understanding of genetic makeup has allowed us to develop prognostic markers, better known as companion diagnostics. Current attempts in the development of drug delivery systems offer the opportunity of delivering specific inhibitors to affected cells in an attempt to reduce the unwanted side effects of drugs.

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1. Introduction

Personalized medicine attempts to identify individual tailored treatments based on the susceptibility profile of each individual. Precision medicine utilizes both conventional medicine and cutting edge technology to concur the disease proven to be resistant to conventional medical techniques. The borders of personalized medicine are defined by limitations in technology and our understanding of biology, and pathology of various conditions. Current advances in technology have enabled us

to uncover the molecular makeup of diseases and translating these findings to actionable targets has led to the development of small molecular inhibitors. Monitoring disease outcome utilizing companion diagnostics has also assisted physicians in routine patient care. To date serious efforts are directed in increasing the efficacy of drug delivery to reduce the undesired side effects of medications (Fig. 1). Despite the current advances there are fundamental limitations on implementing personalized medicine into daily practice. Here we lay out the steps from bench to bedside for personalized therapeutics in hematology and explore the complex problems at each steps. We will first discuss the discovery platforms, and compare the existing technologies. Major discoveries utilizing these platforms will be discussed followed by summarizing the targeted inhibitors developed which are currently in clinical practice. Next we will briefly discuss the advantages of small molecular inhibitors over existing chemotherapeutic regimens and explore conditions that affect the drug

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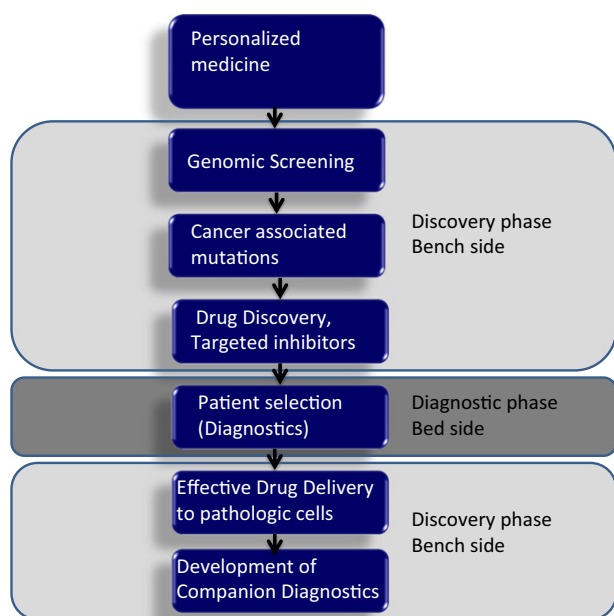


Fig. 1. Implementation of personalized medicine requires combining discovery platforms and clinical practice. Early stage of discovery requires interrogation of large numbers of samples to uncover the somatic genomic alterations of tumor cells. Further studies on genomic mutations are conducted to demonstrate that the aberrations are driver mutations and therefore actionable. Small molecular inhibitors are developed to target proteins intercepting these alterations. Patients are screened in clinics to ensure that they carry the desired mutation targeted by small molecular inhibitors. Intermediate end-point biomarkers are identified and studied in the audit trail as early predictors of anti-tumor activity.

response to these inhibitors (pharmacogenomics and pharmacovigilance). Finally we will discuss the drug delivery systems that could potentially enhance the outcome and limit the undesired effects of these medications.

Advances in human genetics have clearly demonstrated the contribution of specific genes to certain malignancies [1–3]. Such genomic alterations are functionally manifested as dysfunctional proteins leading

to aberrant signal transduction [4–7]. Consequently, discovering genomic alterations underlying various conditions is a fundamental step in implementing precision medicine. Selecting an appropriate screening technology is crucial for both discovery and diagnostics. In the era of genomic innovation, several platforms are available [8–11]. Mass spectrometric genotyping, allele-specific PCR-based technologies, hybrid-capture massively parallel sequencing technologies, and whole-genome sequencing are among the available platforms [12,13]. For discovery purposes, sequencing of the entire genome would be the preferred option, but, for diagnostic purposes, one must presently focus on cost-effective platforms that cover actionable cancer-associated mutations (MassArrays) [14] (Fig. 2).

Though personalized medicine appears to bring us ever closer to a step away from the cure for cancer, the reality is far more complicated. Despite current advances in genomics, there is still a long path to decoding all cancer-associated mutations, let alone the signaling pathway of new and novel mutations which would be an additional area to explore [15]. In both hematologic and solid tumors, a large fraction of affected proteins is represented by kinases, which are essential for physiological functions of cells, such as cellular growth and development [16–18]. Blocking these molecules usually drives the cells into developing compensatory mechanisms, and cancer cells eventually escape the inhibition, developing tumor resistance [19,20]. Another obvious challenge is excessive toxicity by nonselective inhibition of both mutant and wild-type proteins by some inhibitors [21–24]. Additional factors can affect efficacy of treatment. In particular, some genetic variations can alter the drug response of individuals, and this should be taken into consideration with drug dosing [25,26]. Therefore it is crucial to develop companion diagnostics by combining genomic information with proteomics as well as personal medical history and family history data to tailor the desired agent for targeting the neoplastic cells [26–29]. Consequently, it is essential to develop prognostic biomarkers to both screen the outcome of the treatment and screen for residual disease [30–33].

Another limited challenge in personalizing cancer therapy is the limited technologies in drug delivery [34]. It is essential to deliver the appropriate inhibitors to the affected cells; however, advancement in the development of nanoparticles that can achieve selective cellular

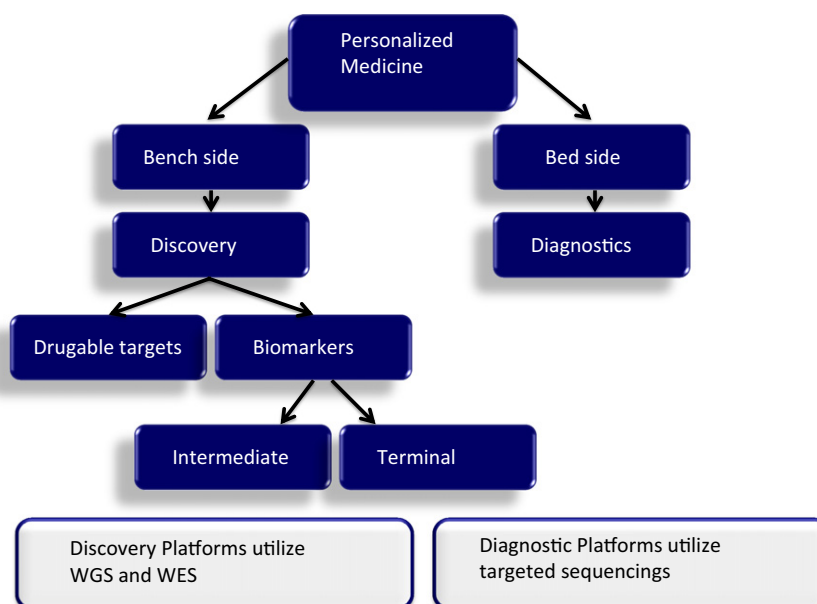


Fig. 2. Steps from bench to bedside for personalized medicine: Discovery of drugable targets lay out the path for development of targeted inhibitors. Usually more comprehensive platforms, such as whole genome sequencing (WGS) and whole exome sequencing (WES) are used at this step. It is well established today that the sole presence of a target in tumor cells does not guarantee the drug response. To determine the best group of patients who would benefit from targeted inhibitors, both intermediate and terminal genomic biomarkers are in need. Again, comprehensive platforms (WGS and WES) are used for discovery purpose. Patient selection for targeted inhibitors (diagnostics) could be run using less expensive techniques, i.e. targeted sequencing.

targeting remains limited [35]. The use of nanoparticles has thus been restricted primarily to a reduction of drug toxicity, as evidenced by the success of Doxil (liposomal doxorubicin), which decreases cardiotoxicity [36–38]. Fortunately, our understanding of the interactions between nanoparticles and living cells continues to improve. A conceptual understanding of biological responses to nanoparticles is essential for developing safer targeted drug delivery in the future.

2. Discovery platforms

Almost a decade after the completion of the first genome sequencing, genome research composes the main core of discovery in various cancers [39–41]. The classical discovery platform used for sequencing the human genome was a capillary based electrophoresis (CE) system [42–44]. Although this system was developed by Fredrick Sanger in the late 70s, it was the most widely used technique for over two decades. The high cost of sample processing along with the restriction on clinical scalability led to the emergence of new technologies based on hybrid capture and massively parallel sequencing (MPS) [45–47], better known as next generation sequencings (NGS) [48–50]. These profiling platforms enable the investigators to detect point mutations, copy number alterations, and chromosomal aberrations using a single run and a small amount of DNA input [51,53,54]. These platforms are highly sensitive (i.e. they detect genetic alterations in small allele fractions) and fairly scalable (i.e. they can be tuned for resolution and coverage) [52]. Last but not least, these platforms are rather affordable and they have brought down the cost of the sequencing of the entire genome to 5000 USD per samples. It is suggested that these new sequencing instruments could sequence several samples in less than a day [52]. Table 1 summarizes the advantages and disadvantages of Sanger and NGS.

Several discoveries in field of hematology were made utilizing the discovery platforms. For instance ALK, PDGFR and FGFR are all discovered using sequencing platforms (Sanger/NGS). BRAF-V600E discovery in LCH and ECD was based on targeted sequencing. The cutting edge medications developed targeting genomic alterations are discussed in the next section.

3. Diagnostic platforms: PCR based technologies and massively parallel sequencing

It is well known that most hematologic malignancies are caused by genomic alteration (point mutation, chromosomal aberrations, copy number variations), and therefore complete understanding of these diseases can only be achieved by comprehensive screening of a large number of clinical samples. Despite the fact that the cost of sequencing of the whole genome has dropped significantly in the past decade (from 3 billion USD to roughly 5000 USD), screening a large number of clinical samples could still impose economic challenges. Also, most of the

information provided by whole genome sequencing (WGS) cannot be fully interpreted [55,56]. Despite the fact that there are over 800 new small molecules on developmental pipeline [57–59], the number of drugable targets currently available in clinics is less than 30 [59,60]. The economic impact of a large scale application of WGS along with limited clinical applicability of information obtained from whole genome is suggestive for the utilization of alternative tools for diagnostic purposes.

One of the first platforms developed for high throughput screening of clinical samples in oncology was a mass spectrometric base genotyping platform developed by Garraway and colleagues for the detection of cancer-associated mutations [61]. They relied on the fact that a large subset of cancer-associated driver mutations affects hotspot amino acids. This led to the development of multiplex allele-specific PCR platforms [61–63]. This platform enabled us to detect a BRAF-V600E mutation in Langerhans cell histiocytosis (LCH), a disease which, until this observation, was known as a reactive-inflammatory one [64–66]. Despite the high sensitivity of this platform, it had a very limited coverage and was biased to a subset of genes. It was also unable to detect chromosomal aberrations and large indels [67]. To overcome these shortcomings, NGS platforms were adapted for enrichment of subsets of the human genome. By scaling these platforms and enriching a subset of genome, e.g. on exons or targeted genomic sequences for drugable targets and predictive biomarkers for drug response, several questions could be addressed for a fraction of the cost of WGS (Table 2) [68–71, 132].

Whole genome sequencing (WGS) enables identification of coding mutations and copy number alterations (amplifications and deletions), but its ability to detect chromosomal translocation in commercially available probes is rendered due to the lack of intronic sequences in capturing probes [72]. Stromal contaminations and genomic heterogeneity could also complicate the interpretation of data. On the other hand, targeted sequencing can achieve a larger depth of coverage and consequently higher sensitivity at a comparable cost [52]. This approach could be very useful for clinical samples with low preservation (samples derived from formalin fixed tissue) and high stromal contamination, or in the case of hematologic tumors, contamination by bystander cells [73–75].

On the other hand, to fully understand the genetic background of a disease we must know the extent of gene expression as well. Chromatin immunoprecipitations (ChIP-Seq) could unravel the mutation and methylation statuses of gene regulatory sites and determine the activation status of genes, and consequently gene expression [76,78]. Transcriptome sequencing (RNA-seq) [76] captures the expressed genome of cancer cells enabling robust detection of deregulated genes [77], and gene fusions [78–80]. Combining expression data with genomic findings could shed light on the pathomechanisms of the disease and facilitate the design of targeted inhibitors (Table 3). Clinical applicability of these techniques is quite important and FDA has recently approved several NGS instruments for clinical applications.

Table 1
Comparison of Sanger sequencing with next generation sequencing.

	Advantages	Disadvantages
Sanger	<ol style="list-style-type: none"> 1. Long reading sequences, easy assembly in read outs (especially for GC rich highly repetitive DNA areas) 2. Smaller depth of sequencing required for good coverage 3. Easy to analyze 4. Relatively small data storage required 	<ol style="list-style-type: none"> 1. Low sensitivity (high allele frequency of cancer needed) 2. Scalable to few genes only 3. Unable to detect chromosomal aberrations 4. Insensitive to copy number alterations 5. High cost per base 6. Large amount of startup material required (1–3 µg) 7. Slower turnaround time
NGS	<ol style="list-style-type: none"> 1. High sensitivity (tumor heterogeneity and stoma contamination will not be troubling) 2. High depth of sequencing is feasible 3. Scalable to entire genome 4. Detects chromosomal aberrations 5. Detects copy number variations 6. Low cost per base 7. Small amount of startup material required (50 ng) 8. Quick turnaround time 	<ol style="list-style-type: none"> 1. Short reading sequences, challenges in assembly of the reads 2. Complicated data analysis 3. Large data storage required

Table 2
Comparison of PCR based technologies with massively parallel sequencing technologies.

	Advantages	Disadvantages
Genotyping platforms (PCR based technologies)	<ol style="list-style-type: none"> 1. High sensitivity 2. High specificity 3. High reproducibility 	<ol style="list-style-type: none"> 1. High cost 2. Relatively low throughput 3. Unable to detect chromosomal aberrations 4. Dependent on probe design; could be used for detection of hotspots (e.g. cancer-associated mutations) 5. Labor intensive
Massively parallel sequencing (hybrid capture techniques)	<ol style="list-style-type: none"> 1. High sensitivity 2. High specificity 3. Relatively low cost 4. Ease of use (small labor) 5. Targets large sections of DNA and consequently covers large number of genes 6. Could be tuned for coverage and data output 	<ol style="list-style-type: none"> 1. Uniformity and sensitivity depends on design of probes 2. Commercially available capture sets could be rather inflexible for individual need

4. Targeted therapies and current drugs

Targeted therapies or small molecular inhibitors block the proliferation of cancer cells by intercepting their specific target [81–84]. Since their range of action is smaller than general chemotherapy agents, the adverse effect caused by these inhibitors is smaller as well and they are better tolerated by patients [85–88]. This seems to be a success story, but the final picture is complicated. These inhibitors are not curative, and disease relapse remains a fairly common complication in these malignancies. Several reasons could be attributed to disease relapse, among which is the escape of tumors cells which obtain new surviving mutations and the evolution of new neoplastic populations due to weakened immune response. On the other hand, there are obvious caveats in targeting cancer cells with very specific molecular inhibitors. First of all, most of the small molecular inhibitors currently available in clinics are targeting protein kinases [89–91]. These are an essential cellular component and blocking these molecules could result in cellular compensation. This could manifest either as overproduction of the inhibited protein (upregulation on the gene level), or escalating alternative compensatory pathways for survival. Second, the delivery of these molecules to the affected cells is limited by tissue vascularization and cellular uptake. This forces physicians to escalate the dose of inhibitor in compensation, leading to undesirable side effects. Currently there are several small molecular inhibitors in clinical practice. Table 4 summarizes the current small molecular inhibitors in clinical practice [92–96,130,131].

“In the future we should drive our focus on enhancing the patient’s response based on their unique genetic makeup using appropriate companion diagnostics (pharmacogenomics) along with targeting the driver event”. Also, to maximize the benefits of small molecular inhibitors, we must deliver the targeted agents to a susceptible population based on individuals’ susceptibility profiles determined by companion diagnostics. Eventually, a better outcome will be achieved by matching the right therapy to the right parties, taking us a step closer to a potential cure for these malignancies. Last, but not least combining well designed

collaborations between private sectors and academics will expedite the drug discovery process [130,131].

5. Pharmacogenomics and drug response

Pharmacogenomics is the science that studies the role of inherited and acquired genetic variations to drug response. It correlates gene expression and single nucleotide polymorphism (SNP) with both drug toxicity and efficacy to optimize therapeutic regimens for each individual [97,98]. One of the classical examples of pharmacogenomics is the effect of CYP450 variants on the dosing of warfarin [99–101,111].

There are several fundamental differences between cytotoxic chemotherapies and small molecular inhibitors. Dose-related toxicities have traditionally been considered key end points of Phase I trials and the maximum tolerated dose (MTD) was regarded as the optimal dose providing the best efficacy with manageable toxicity. Recently, development of targeted inhibitors has challenged the paradigms used in cytotoxic chemotherapy trial design. In precision medicine pharmacokinetic (PK) and pharmacodynamic (PD) end points tend to take a backseat to toxicity. Molecularly targeted agents do not always maintain the same dose–toxicity relationship as cytotoxic agents and tend to produce minimal organ toxicity. Furthermore, molecular therapeutic agents usually result in prolonged disease stabilization and provide clinical benefit without tumor shrinkage, a characteristic seen with cytotoxic agents, therefore necessitating alternative measures of anti-tumor efficacy. These end points include biologically relevant drug exposures, PD biomarker measures of target inhibition, and intermediate end-point biomarkers, such as molecular biomarkers (Fig. 3).

In the field of cancer, pharmacogenomics is complicated by the fact that two genomes are involved: the germline genome of the patient and the somatic genome of tumor, the latter of which is of primary interest [102]. This genome predicts whether specific targeting agents will have a desired effect in the individual. On the other hand, germline pharmacogenetics can identify patients likely to demonstrate severe toxicities when given cytotoxic treatments. For example, germline SNPs in the gene encoding the enzyme thiopurine S-methyltransferase

Table 3
Cancer genome profiling techniques.

	WGS	Target capture	RNA-Seq
Scale	Whole genome	Targeted areas of genome (whole exome, actionable genome)	Transcribed region of genome
Substrate	DNA	DNA or cDNA	cDNA
Application	Research	Diagnostic	Diagnostic, research
Limitations	Cost, ability to interpret the data	Unable to detect chromosomal aberrations Biased to gene within the targeted region	Sensitivity limited to transcribed genome
Advantages	A single platform give information on point mutations, chromosomal aberrations and CNV	High sequencing depth on a given cost, adaptable to individual needs	Detects novel transcripts with low level of expression Detects non-mutational events

CNV: copy number variations, cDNA: complementary DNA.

Table 4Targeted inhibitors used in treatment of hematologic malignancies. Data adapted from NCI: <http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted>.

Gene	Genetic alterations	Tumor type	Targeted agent
<i>Receptor tyrosine kinase</i>			
ALK	Mutation, CNV	Anaplastic large cell lymphoma	Crizotinib
FGFR1	Translocation	CML, myelodysplastic disorders	Imatinib methylase
FGFR3	Translocation, mutation	Multiple myeloma [113]	PKC412, BIBF-1120
FLT3	CNV	AML	Lestaurtinib, XL999
PDGFRB	Translocation, mutation	CML	Sunitinib, sorafenib, imatinib, nilotinib
<i>Non-receptor tyrosine kinase</i>			
ABL	Translocation (BCR-ABL)	CML, AML	Dasatinib, nilotinib, bosutinib
JAK2	Mutation (V617F) translocation	CML, myeloproliferative disorders	Lestaurtinib, INCB018424
ERK1/2	Mutation	Mantle cell lymphoma, CLL	Ibrutinib
<i>Serine–threonin kinase</i>			
Aurora A and B kinase	CNV	Leukemia	MK5108
BRAFV600E	Mutation	LCH, ECD [110], hairy cell leukemia [112]	Vemurafenib (PLX4032)
Polo like kinase	Mutation	Lymphoma	B12536
<i>Non-kinase targets</i>			
PARP	Mutation, CNV	Advanced hematologic malignancies, CLL, mantle cell lymphoma	BMN 673
<i>Antibodies</i>			
CD20		Hodgkin lymphoma	Rituximab
CD52		B-cell chronic lymphocytic leukemia	Alemtuzumab
CD20		Non-Hodgkin lymphoma	Ibritumomab tiuxetan
<i>Apoptotic agents</i>			
Proton pump inhibitors		Multiple myeloma, mantle cell lymphoma, peripheral T-cell lymphoma	Bortezomib, pralatrexate

CNV: copy number variations, AML: acute myeloid leukemia, CML: chronic myeloid leukemia, LCH: Langerhans cell histiocytosis, ECD: Erdheim Chester disease.

(TPMT) can result in increased sensitivity to mercaptopurine as a result of decreased drug metabolism, whereas the number of TA repeats in the promoter region of *UGT1A1* can increase the toxic effects of irinotecan again as a result of decreased drug metabolism. Therefore, understanding the variable response to drugs is quite pressing in oncology where

cytotoxic agents have narrow therapeutic indices and severe side effects [103,108,109]. Table 5 summarizes the companion diagnostics developed by the FDA for the treatment of hematologic malignancies.

Generalization and clinical application of pharmacogenetics are rather challenging in precision medicine. Most of the affected individuals have

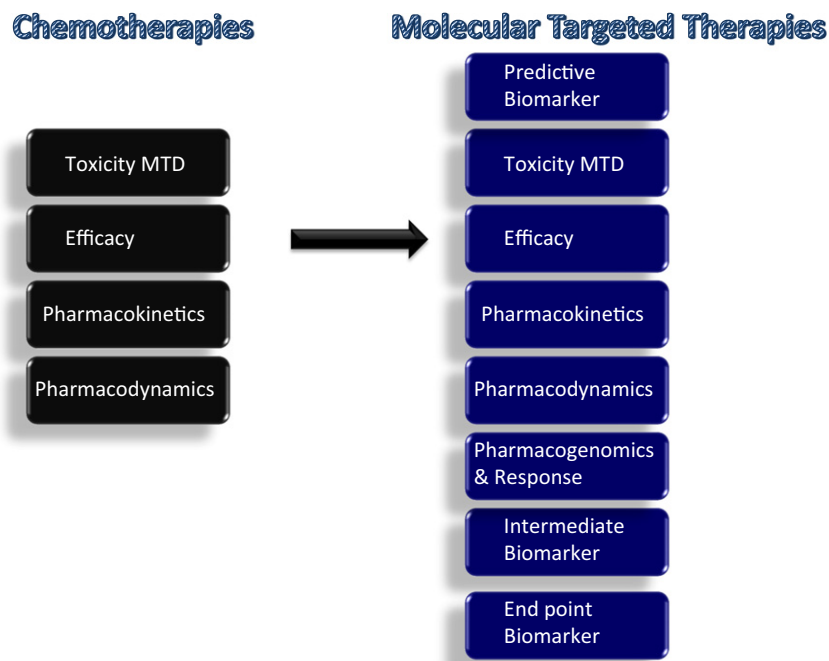


Fig. 3. Comparison of standard chemotherapy with novel molecular targeted therapies: Dose-related toxicities have traditionally been considered key end points of Phase I trials and the maximum tolerated dose (MTD) is regarded as the optimal dose that provides the best efficacy with manageable toxicity. Pharmacokinetic (PK) and pharmacodynamic (PD) end points tend to take a backseat to toxicity. Recently, development of targeted inhibitors has challenged the paradigms used in cytotoxic chemotherapy trial design. Molecularly targeted agents do not always maintain the same dose–toxicity relationship as cytotoxic agents and tend to produce minimal organ toxicity. Furthermore, molecular therapeutic agents usually result in prolonged disease stabilization and provide clinical benefit without tumor shrinkage, a characteristic seen with cytotoxic agents, therefore necessitating alternative measures of anti-tumor efficacy. These end points include biologically relevant drug exposures, PD biomarker measures of target inhibition, intermediate end-point biomarkers, such as circulating tumor cells and other molecular biomarkers, including functional imaging.

Table 5

Companion diagnostics and anticancer treatments in hematology. Data are obtained from FDA pharmacogenomics website (<http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>).

Anticancer treatments approved by FDA carrying companion diagnostics	
Biomarker with pharmacokinetic effect	TPMT (mercaptopurine, thioguanine)
Biomarkers with pharmacodynamic effect	UGR1A1 (irinotecan, nilotinib)
	EGFR (cetuximab, erlotinib, gefitinib, panitumumab, afatinib)
	KRAS (cetuximab, panitumumab)
	ABL (imatinib, dasatinib, nilotinib)
	BCR-ABL (bosutinib, busulfan)
	ALK (crizotinib)
	C-kit (imatinib)
	HER2/neu (lapatinib, trastuzumab)
	ER (tamoxifen, anastrozole)

Genes in bold are used for companion diagnostics of the drugs mentioned in the brackets.

unique profiles in their tumors in addition to the fact that every individual has a unique SNP profile at a germline level. If a certain type of cancer carries several driver mutations then the choice of targeted therapy becomes complicated. In disseminated tumors, the picture would be further complicated by inter-tumor and intra-tumor heterogeneity of cancer [104–107]. Therefore, a greater understanding of the complexities of multiple gene modifiers of outcome, and the statistical challenge of understanding such data, will be needed before individualized therapy can be applied on a routine basis.

Consequently, tumor heterogeneity makes the use of combination therapies attractive. If an individual carries several driver mutations which inhibitors should be prescribed? What would be the appropriate dosing of each? How will drug interactions affect the picture? How can we increase the therapeutic index? Addressing these questions seems particularly pressing in the era of abundance of targeting inhibitors and the enormous economic pressures on healthcare providers.

6. Drug delivery

Effective drug delivery could substantially increase the efficacy of small molecule inhibitors in cancer. Currently, several nanoparticulate platforms are under investigation [114]. A desirable carrier would be able to incorporate and release drugs with defined kinetics, should have stable formulation for extended shelf life, should be highly specific for its target, and should be bioinert [115]. Biological materials such as albumin, phospholipids, synthetic polymers, and even solid components can be used as substrates for nanoparticles [116,117] (Table 6).

Ideally, the particles could be readily conjugated with a targeting ligand to facilitate specific uptake by target cells [118]. This would result in increased efficacy by increasing drug concentration in the intended target cells as well as in decreased systemic toxicity by reducing non-specific uptake [119]. Unfortunately several drug delivery matrix (nanoparticles) used by the pharmaceutical industry imposed risk to

Table 6

Structure and applications of nanoparticles.

Particle class	Material	Application
Natural material	Chitosan	Gene delivery
	Dextran	Small molecule delivery
	Gelatin	
	Liposome	
Silica variants	Silica nanoparticles	Gene delivery
	Branched polymers	Drug delivery, gene delivery
Dendrimers	Poly(lactic acid)	Drug delivery, gene delivery
	Poly(cyano)acrylates	Small molecule delivery
	Polyethyleneimine	
	Block copolymers	
Polymer carriers	Polycaprolactone	

the patients [120,121]. These toxicities varied depending on the surface properties of nanoparticles [122,123], chemical composition [119,124], their half life [125] and distribution [126]. Among the in vivo side effects of nanoparticles, pulmonary inflammation (PSP), pulmonary neoplasia (PSP), immune response (polystyrene, CB, DEP), and platelet aggregations (PM, latex-aggregate surface) are well established [127,128].

In order to achieve enhanced delivery, reduced toxicity, and eventually enhanced therapeutic index, development of long-circulating and target-specific nanoparticles is needed. A conceptual understanding of biological responses to nanomaterials is necessary for development and safe application of nanomaterials in drug delivery in the future. Furthermore, a close collaboration between those working in drug delivery and particle toxicology is necessary for the exchange of concepts, methods, and know-how to move this issue ahead.

To date the most common vehicle used for targeted drug delivery is the liposomes. These molecules are non-toxic, non-hemolytic, and non-immunogenic even upon repeated injections. Liposomes are biodegradable and can be designed with various half-lives. Liposomes are currently used in cancer therapies (metastatic breast cancer, advanced melanoma, colorectal cancers) but their high cost creates severe limitations [129].

7. Future directions

Currently, there are huge amounts of screening data available at the genomic level. One of the shortcomings is our limited understanding of the functional importance of these findings. It is curtailed to distinguish driver genomic events from passenger ones. Today, there are over 800 new drugs (targeted inhibitors) in the development pipeline. At this point, our shortcoming is not the availability of targeted inhibitors but rather our limitations on the delivery of these molecules to the affected cells with a high degree of specificity. Next, we must improve our ability to get the targeted inhibitors designed for malfunctioning cellular components into the affected cells. By increasing the efficacy of targeted drug delivery, we will both reduce the unwanted side effects of antineoplastic agents on healthy cells and increase their cytotoxicity on affected cells. Lastly, we should be aware of the economic effects of precision medicine. An outstanding high cost will not be sustainable in the long term, so development of technologies for cost reduction should not be ignored.

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