Role of Biomarkers in Personalized Medicine

10

Salman Ul Islam, Muhammad Bilal Ahmed, Haseeb Ahsan, and Young Sup Lee

Abstract

Biomarkers are a key tool in medicine, especially in the domain of personalized medicine. They are valuable for the early detection, prognosis, and diagnosis of disease as well as for the prediction of treatment response. They enable us to select appropriate individuals for treatment with personalized medicine and provide the right medication to the right patient. At present, the development of individually targeted patient therapy remains the key objective of the medical world. The achievement of this goal needs advances in biomarker discovery and the development of therapeutic strategies that can be optimized for individual drug and dose selection. This chapter discusses strategies for the use of biomarkers and their impact on drug development. Further, it highlights the establishment of enabling technologies involved in pursuing the goal of personalized medicine. It is important that regulatory agencies, clinicians, and scientists establish collaborations to address the challenges surrounding this field.

S. U. Islam
School of Life Sciences, BK21 FOUR KNU Creative BioResearch Group, Kyungpook National University, Daegu, Korea

Department of Pharmacy, Cecos University, Hayatabad, Peshawar, Pakistan

M. B. Ahmed · Y. S. Lee (✉)
School of Life Sciences, BK21 FOUR KNU Creative BioResearch Group, Kyungpook National University, Daegu, Korea
e-mail: yselee@knu.ac.kr

H. Ahsan
School of Life Sciences, BK21 FOUR KNU Creative BioResearch Group, Kyungpook National University, Daegu, Korea

Department of Pharmacy, Faculty of Life and Environmental Sciences, University of Peshawar, Peshawar, Khyber Pakhtunkhwa, Pakistan

A. Shehzad (ed.), *Cancer Biomarkers in Diagnosis and Therapeutics*,
https://doi.org/10.1007/978-981-16-5759-7_10

These challenges include enhancing approaches for the development of biomarkers, minimizing the cost of drug development, and delving into the contribution of next-generation sequencing tests in drug development.

Keywords

Biomarkers · Personalized medicine · Cancer · Screening · Diagnosis · Prognostication

10.1 Introduction

The Food and Drug Administration (FDA) has defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological and pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Food 2014). A biomarker is simply an indicator of an alteration in normal physiology. A biomarker can be any distinct alteration of DNA, RNA, or protein. Among other applications, biomarkers are used as tools for the early detection of cancer and the development of individualized treatment (Patel 2014; Ogunwobi et al. 2020; Pellino et al. 2018).

Biomarkers can be divided into various groups based on their biology, measurement, and purpose (Grecchi et al. 2012). Several categories of biomarkers defined by the FDA (Group 2016) and the European Medicines Agency (Barcikowska 2018) have been reviewed in an article by Karen D Davis and coworkers (Davis et al. 2020). With respect to biology, molecular, physiological, or morphological characteristics can be used as biomarkers. Currently, scientists working with translational and personalized medicine prefer molecular markers. However, physiological and morphological markers still play important roles in clinical assessment (Banin Hirata et al. 2014). The generation of objective measurements is a crucial characteristic of a biomarker, so that assay results are obtained with little or no dependence on the subjective decisions of the observer. Biomarker tests can produce quantitative, semiquantitative, or qualitative results. Biomarkers can be further subgrouped into drug response or diagnostic markers. Several other types can be defined based upon their specific applications, such as disease monitoring and surveillance, prognosis, diagnosis, safety/toxicology assessment, pharmacodynamic analyses, and stratification (Landeck et al. 2016).

10.2 Discovery and Validation of Biomarkers

The process of biomarker development is a systemized and directed task, starting from recognition of the need for a biomarker followed by candidate biomarker discovery, initial identification, and preliminary proof-of-concept investigations. During this process, the degree of validation evidence supporting the use of the biomarker exhibits the prime importance, which reaches to the highest level whenever intended purpose of the biomarker enters clinical practice (Food and Drug

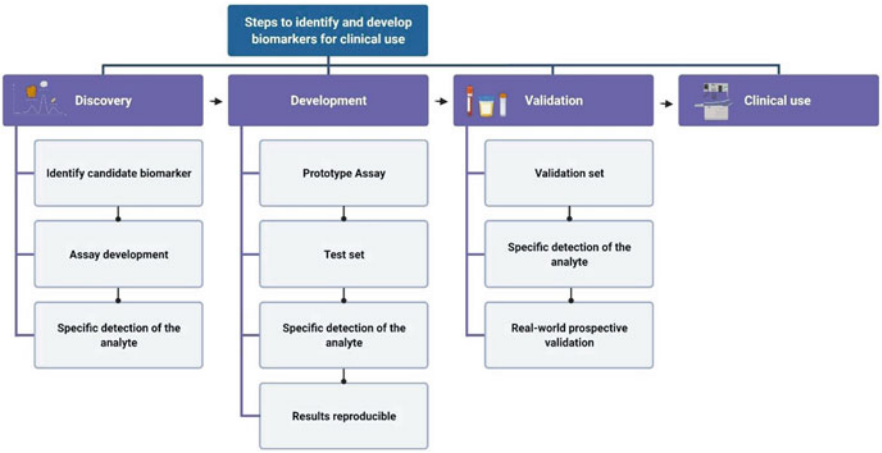

Fig. 10.1 Key steps for identifying and developing biomarkers for clinical use

Administration 2018) (Fig. 10.1). The biomarker development process may also include investigations concerned with the verification of reliability and accuracy of the detection method. Moreover, this process also encompasses the analysis of the connection between the biomarkers and the clinical outcomes.

Various levels of validation are required after the biomarker identification. Regarding analytical validation, it involves testing of the performance of the assay or detection technology in a way that is feasible for the purpose of the biomarker. Precision, dynamic range, and sensitivity of the detection method remain the noteworthy variables assessed during the analytical validation process. The clinical validation step is based on the assessment of the specificity and sensitivity of the biomarkers for identifying, measuring, or predicting the clinical outcome. Of note, specificity is linked with the rate of true negative findings, whereas sensitivity means the rate of true positive findings. In the biomarker validation process, the degree of evidence, required to provide the necessary confidence, is dependent upon context of use. The required degree of validation evidence is going to be increased, requiring further multisite validation data, as the context of use moves from research use to accepted utility in clinical trials/practice.

10.3 Biomarker's Role in Early Detection and Diagnosis

Identification of disease-based biomarkers is a crucial step of research supporting diagnosis and predicting prognosis in almost all types of human disorders. Biomarkers help establish guidelines for screening, response to treatment, and monitoring of disease progression. In the following sections, we use examples of certain critical biomarkers identified through various molecular biological

techniques for diffuse large B-cell lymphoma (DLBCL), which provide insights into disease mechanisms and pathogenesis.

10.3.1 B-Cell Lymphoma 2

B-cell lymphoma 2 (BCL-2), an oncogenic biomarker, is located on the mitochondrial outer membrane (Tilly et al. 2015). BCL-2 induces cell survival and inhibits apoptosis. BAX and BAK, pro-apoptotic proteins belonging to BCL-2 family, stimulate the release of cytochrome *c* from mitochondria, trigger the apoptotic signaling cascade, and are blocked by BCL-2 itself (Siddiqui et al. 2015). Considerable research has shown that BCL-2 chromosomal translocation t(14;18) occurs in DLBCL, resulting in elevation of BCL-2 levels as well as BCL-2-mediated resistance to the apoptotic cascade (Tilly et al. 2015; Akyurek et al. 2012) (Fig. 10.2). The presence of the BCL-2 chromosomal translocation t(14;18) has been observed in 20–30% of DLBCL cases, and is often associated with GCB-DLBCL-like variants (Akkaya et al. 2016). When this translocation is present, the cells become immortalized because of an elevated expression of BCL-2. High BCL-2 expression in DLBCL results in poor prognosis and shortened life span (Adams et al. 2019; Kawamoto et al. 2016). The inclusion of rituximab to standard chemotherapy helps to overcome the impact of BCL-2 on adverse prognosis (Chiappella et al. 2017; Frei et al. 2013). The prognosis remains consistently poor in "double hit lymphoma" (DHL), in which a BCL-2 translocation goes along with a translocation of MYC [t(8;14) for MYC, and t(14;18) for BCL-2] (Kawamoto et al. 2016). Patients representing lymphoma cells coexpressing BCL-2 and MYC showed a good response to ABT-737 (specific inhibitor of BCL-2), suggesting a key role for BCL-2 in DHL (Mason et al. 2008; Li et al. 2019).

10.3.2 B-Cell Lymphoma 6

Chromosomal translocations and mutations result in B-cell lymphoma 6 (BCL-6) being deregulated. Mice, which were engineered to constitutively express BCL-6, developed DLBCL in germinal center (GC) B cells (Baron et al. 2004; Cattoretti et al. 2005). Due to mutations in the BCL-6 locus, BCL-6 appears to be constitutively active in individuals with active B-cell lymphomas (Ye 2000; Cerchietti et al. 2010). Aberrant blockage of the BCL-6 repressive function causes genetic instability, which ultimately leads to neoplastic transformation (Aquino et al. 2014; Shustik et al. 2010). BCL-6 has also been shown to autoregulate its own transcription, and indirectly increases the expression of several genes, which then induce GC reactions (Basso et al. 2012). B lymphocyte-induced maturation protein 1 (BLIMP1) displaying a zinc finger domain (PRDM1)/B participates in the terminal differentiation of GC B cells to plasma cells, and is one of the protein directly regulated by BCL-6 (Alkodsi et al. 2019; Pasqualucci et al. 2006). PRDM1 appears to specifically inactivate ABC-DLBCL. The deregulation of BCL-6 and inactivation of PRDM1/

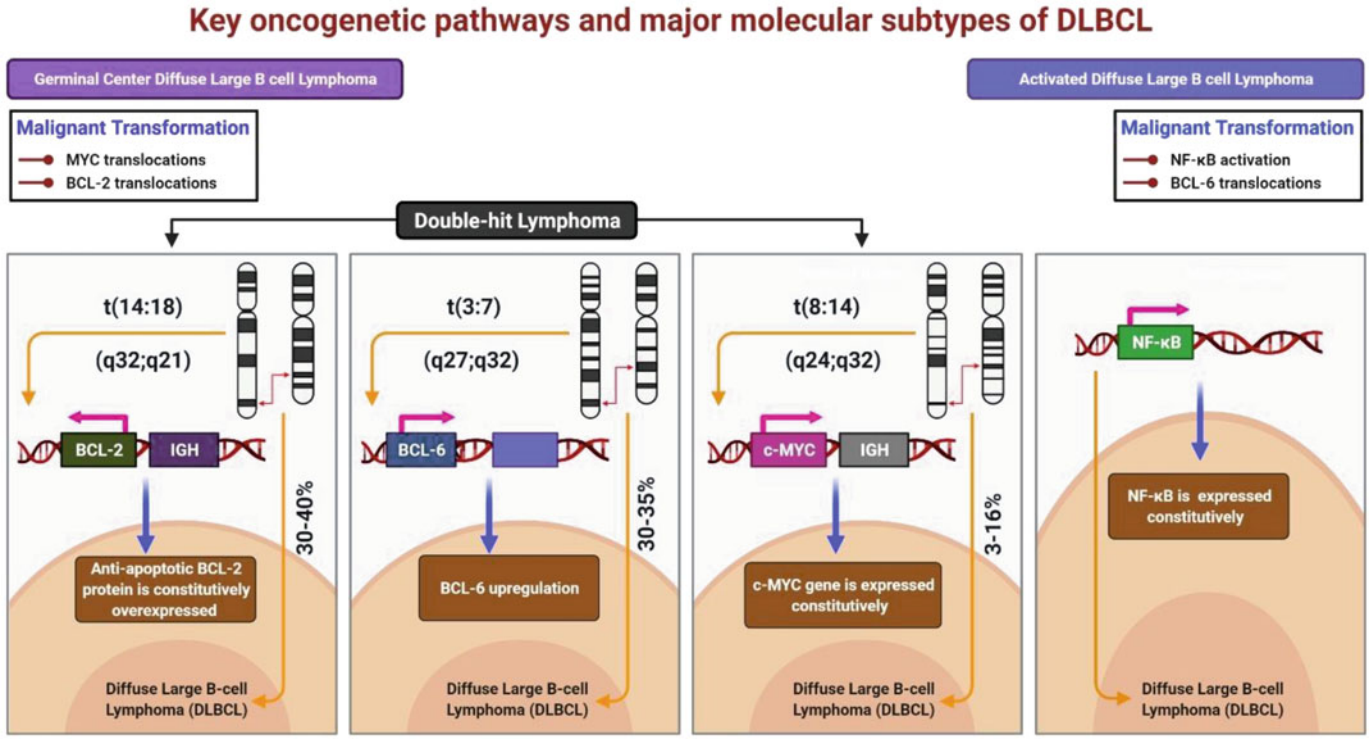

Fig. 10.2 DLBCL can develop from diverse oncogenetic alterations in B cells. Somatic hypermutations, gene amplification, and translocation of genetic material are the main oncogenic pathways involved in the development of DLBCL. The two important subtypes of DLBCL, the germinal center, and the activated type, have been described

BLIMP1 indicates the existence of alternative pathogenetic pathways causing inhibition of postGC differentiation; subsequently promoting lymphomagenesis (Pasqualucci et al. 2006; Vrzalikova et al. 2011; Wagner et al. 2011). The BCL-6 translocation and hypermutation at chromosome 3q27 with t(3;7) (q27;p12) was shown in 30–35% cases of DLBCL (Shustik et al. 2010), and frequent somatic mutations also occur in this chromosomal region. BCL-6 rearrangement is linked with poor outcomes in patients receiving rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP) (Shustik et al. 2010). Barrans and colleagues' study found that individuals with poor prognosis had BCL-6 rearrangements as well as MYC translocation and BCL-2 deregulation. This study demonstrates that the rearrangement of BCL-6 rarely appears as a sole genetic disorder in DLBCL (Barrans et al. 2010).

10.3.3 Nuclear Factor Kappa-B

Nuclear factor kappa-B (NF-κB) is one of the family of inducible transcription factors that is responsible for regulating multiple genes involved in a range of immune and inflammatory responses. NF-κB can modulate biological processes, such as stress responses, inflammation, B cell development, and lymphoid organogenesis (Hayden and Ghosh 2011). The activation of NF-κB is essential for growth and survival of various types of cancer cells. Lymphoid malignancies evade apoptosis by the constitutive activation of NF-κB signaling (Park and Hong 2016; Hoesel and Schmid 2013). Both the canonical and alternative NF-κB pathways get activated in DLBCL (Compagno et al. 2009; Davis et al. 2010; Nagel et al. 2014; Zhang et al. 2015). Activated B-cell (ABC) DLBCLs show classical NF-κB activation, as they have the potential for rapid phosphorylation and show frequent nuclear translocation of p50/p65 heterodimers, while showing minor nuclear translocation of p50/c-rel heterodimers (Davis et al. 2001). RelA/p65 and p50 are the major subunits of NF-κB participating in the classical NF-κB pathway, and nuclear translocation of RelA/p65 is significantly linked with poor survival in individuals with early stage DLBCL (Zhang et al. 2016). Multiple receptors, including CD40, BCR, and B-cell-activating factor, stimulate the NF-kB pathway in B cells (Hoesel and Schmid 2013; Ying et al. 2013; Young et al. 2015). The NF-κB activation is believed to be a hallmark of ABC–DLBCL (Camicia et al. 2015). Compared to GCB–DLBCL, a greater number of NF-κB-regulated genes appear in ABC–DLBCL. Hence, ABC-DLBCL lines are highly sensitive to the blockage of NF-κB. Mutations in CARD11 (a part of the CBM), stimulate the activity of NF-κB in ABC–DLBCL (Jiang and Lin 2012; Zachos et al. 2005).

10.3.4 MYC

MYC is a key regulator of cell proliferation and metabolism. Many oncogenic pathways stimulate MYC leading to malignant transformation (Miller et al. 2012).

The recombination of MYC with other genes has been observed in 3–16% of DLBCL cases (Akyurek et al. 2012; Montero et al. 2018). The frequently occurring t(8;14) (q24;q32) translocation involves MYC rearrangement in GCB–DLBCL, resulting in its upregulation (Akyurek et al. 2012; Kawamoto et al. 2016; Akkaya et al. 2016). In DLBCL, the fusion of MYC and Ig is known to result in the upregulation of MYC expression. A meta-analysis revealed that rituximab treatment did not overcome the consequences of MYC translocations (Zhou et al. 2014). In DLBCL patients who received R-CHOP therapy, MYC served as a prognostic factor, although these findings need further investigation (Akyurek et al. 2012). The presence of an n-MYC rearrangement in DLBCL patients is often linked with poor outcome (Chastain and Duncavage 2015; Logothetis 2014).

10.4 Role of Biomarkers in the Early Detection of Colorectal Cancer (CRC)

In order to enhance survival outcomes in individuals with asymptomatic CRC, early diagnosis is crucial. The sensitivity of CRC detection utilizing current FIT testing (100 ng/mL) was 73.8% compared with 92.3% for a stool-based DNA test (Stiell et al. 2003). The sensitivity of FIT testing for analyzing advanced precancerous lesions remained at 23.8% compared with 42.4% with stool DNA assays (Stiell et al. 2003). These parameters indicate the shortcomings of current diagnostic testing and indicate the difficulty of establishing reliable markers for the early detection of CRC. Ongoing noninvasive screening of stools is not sufficiently efficient and sensitive for detecting precancerous lesions with any confidence and may miss notable numbers of early CRC cases. It is, therefore, necessary to maintain a low threshold at which patients undergo the more invasive colonoscopy, and to use novel, advanced tools for identifying early CRC.

Prognostic biomarkers, including early recurrence and mortality rates, can be used to predict the progression of CRC (Patel et al. 2019; Pellino et al. 2018). A good example of the use of prognostic biomarkers is the use of KRAS, a member of the RAS proto-oncogene family of GTPases. Mutations in KRAS lead to an increased risk of recurrent metastatic CRC (Tsuchida et al. 2016; Margonis et al. 2015; Tie et al. 2011). Mutations in the BRAF are linked with decreased survival, encompassing progression-free survival, and up to 50% worse overall survival compared to wildtype BRAF (Guo et al. 2015; Venderbosch et al. 2014; Yokota et al. 2011) (Fig. 10.3). In the novel field of radiogenomics, prognostic sensitivity can be increased by the use of a combination of radiological and genetic features, which attain a higher sensitivity than can be achieved by either of these modalities in isolation (Badic et al. 2019; Horvat et al. 2019). A high-molecular-weight glycoprotein, carcinoembryonic antigen (CEA), has been successfully used as a biomarker in the detection of early recurrence in postoperative patients, although it exhibited despite low specificity and sensitivity (Chao and Gibbs 2009; Koulis et al. 2020). Investigators are hopeful that prognostic markers will change the thresholds at which

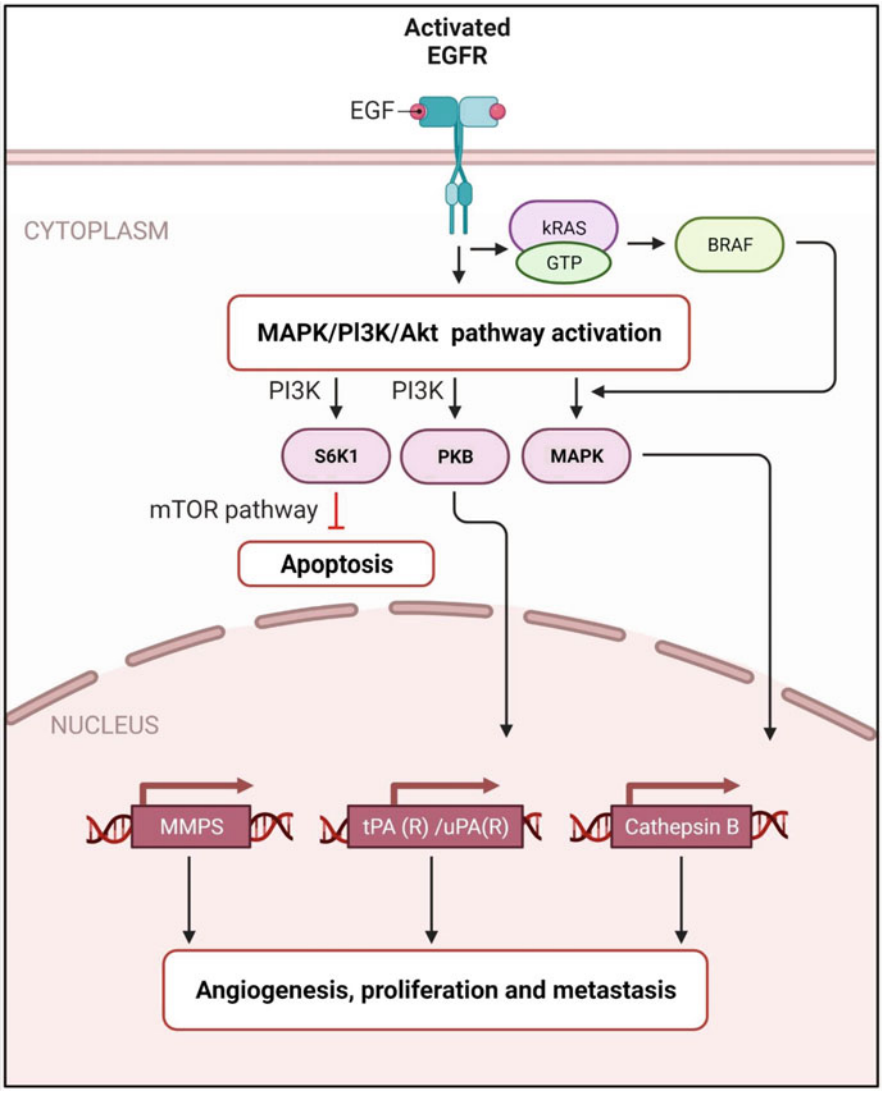

Fig. 10.3 Intracellular signals for CRC manifestation via EGFR. Activation of EGFR results in a change from GDP- to-GTP form of the KRAS, leading to increased concentrations of BRAF to the plasma membrane. BRAF activation leads to the stimulation of MAPK signaling pathway, which subsequently regulates proteins involved in angiogenesis, proliferation, and metastasis

individuals are given more potent therapy, provide further insights into recurrent disease, and improve the chances of early detection and intervention.

Predictive biomarkers can be used to tailor individual therapies according to molecular subtype. Mutations in KRAS are linked with poor responses to therapy with anti-EGFR receptor agents, including panitumumab and cetuximab (Karapetis

et al. 2008; Amado et al. 2008). Compared to the 4% decrease in KRAS mutants, a 16% increase in overall response rate was observed in patients with KRAS wildtype who received cetuximab and FOLFIRI. A topoisomerase inhibitor, irinotecan, utilized as part of a FOLFIRI strategy, is metabolized by diphosphate-glucuronosyltransferase 1A (UGT1A). Homozygosity for the UGT1A1*28 allele is linked with dose-dependent toxicity compared to the UGT1A1*1 genotype (Palomaki et al. 2009). Dihydropyrimidine dehydrogenase (DPD) metabolizes more than 80% of 5-FU (Koulis et al. 2020). DPYD*13 and DYPD*2A variants, however, contribute to increased toxicity of the treatment, and there is evidence that a reduction in 5-FU dose by 25–50% reduces its toxicity (Amstutz et al. 2018). These strategies may improve response to treatment, and decrease the toxicity resulting from ineffective interventions. They can also assist in making the adjustment of drug doses, to produce maximum benefit from a specific regimen. Although several biomarkers are currently under investigation, there is a clear need for more, and more effective, biomarkers. To date, only NRAS, KRAS, MSI, and BRAF status are recommended by national guidelines, for use in following CRC therapy response and predicting outcomes (Shinagawa et al. 2018).

10.5 Potential Biomarkers in Skin Cancer

Biomarkers have been extensively studied, and their use is well established, in skin cancer. Prognostic biomarkers are the most important type of biomarker in skin cancer. Tumor thickness is believed to be one of the most important and oldest prognostic biomarkers in skin cancer. The expression nuclear cell proliferation factor Ki-67 is another important example of a biomarker being used clinically (Gimotty et al. 2005). In ulcerated melanomas, there is close correlation between survival and CD2 count and number of tumor-infiltrating lymphocytes (de Moll et al. 2015). The presence of tumor marker protein S100 beta in blood is utilized to assess disease progression in skin cancer (Forschner et al. 2010). By the use of highly sensitive assays, KIT D816V can be detected in peripheral blood leucocytes from most patients with systemic mastocytosis, and is considered as a major step in early diagnosis of the disease (Arock et al. 2015). Active nuclear I kappa-B kinase is correlated with the risk of metastasis of cutaneous squamous cell carcinoma (Toll et al. 2015).

10.6 Biomarkers for Asthma

Asthma is a highly heterogeneous disease with several underlying mechanisms; different subsets or clinical phenotypes respond differently to standard therapy (Seys et al. 2019; Kuruvilla et al. 2019). Biomarkers have been validated for Type 2 asthma (Diamant et al. 2019). Sputum eosinophils or blood eosinophil counts, FeNO, and serum specific IgE have all been identified as important clinically applicable biomarkers (Alving et al. 2020; Diamant et al. 2019). The biomarkers

reflect different features of Type 2 inflammatory signaling, although some overlapping of Type 2 biomarkers can occur within individuals (Diamant et al. 2019). These biomarkers, along with specific clinical characteristics, have led to current guidelines using algorithms adapted to their use, which are hoped to be of value in predicting responses to therapies, and can be utilized to monitor subsequent therapeutic responses (Holguin et al. 2020; Agache et al. 2021). There are some confounders of the existing biomarkers. Fractional exhaled nitrous oxide (FeNO) has been shown to be correlated with dietary nitrate intake, smoking, virus infections, and bronchoconstriction, whereas systemic corticosteroids and parasites have been reported to be the most common culprits for circadian variation in blood eosinophils (Diamant et al. 2010). Oxidative stress is caused by an excess of reactive oxygen and nitrogen species. Investigators have reported multiple direct or indirect markers of oxidative stress, including glutathione disulfide, malondialdehyde, bromotyrosine, thiobarbituric acid, and isoprostane in plasma, urine, BAL fluids, and sputum of individuals with asthma. The levels of these markers were linked with the severity and clinical output of the disease (Comhair et al. 2000; Comhair and Erzurum 2002). The collection of exhaled breath condensate is another noninvasive analytical approach, which allows direct measurements of H_2O_2, pH changes, and numerous indirect by-products of oxidation, such as ethane and 8-isoprostane (Aldakheel et al. 2016; Thomas et al. 2013). The detection of high levels of urinary bromotyrosine represents another important noninvasive biomarker of oxidative stress for clinical use in patients with asthma (McDowell and Heaney 2020; Sze et al. 2020).

10.7 Significance of Biomarker Strategies in Drug Development

The significance of personalized strategies has been tested in phase I, II, and III clinical trials. A meta-analysis of phase I trials published over a 3-year period included 13,203 patients. It was found that, compared to approaches that did not utilize a biomarker, the biomarker-based cancer therapeutic strategies produced a longer median progression-free survival (PFS) time, and an improved response rate (Schwaederle et al. 2016). Phase II clinical trials were also reviewed in a meta-analysis of single-agent studies published over a 3-year period. Here also, the biomarker-based approach gave a higher median response rate, longer PFS, and better overall survival. Nonpersonalized targeted approaches had poorer outcomes than personalized, targeted strategies. The personalized strategies proved to be safer, and resulted in a lower treatment-induced death rate (Schwaederle et al. 2015) (Fig. 10.4). These investigations suggest that personalized therapy produces better outcomes, and may improve the effectiveness of cancer therapies during all phases of drug development (Schwaederle et al. 2015, 2016). The clinical utility of personalized medicine has, therefore, been established, at least for some biomarkers, but the cost/benefit ratio of targeted therapy is still a subject of debate (Aitken et al. 2018). Higher treatment costs may be ascribable to a longer treatment time due to enhanced survival instead of higher monthly drug costs (Chawla et al. 2018). The financial return from newly launched personalized drugs comes at a higher initial

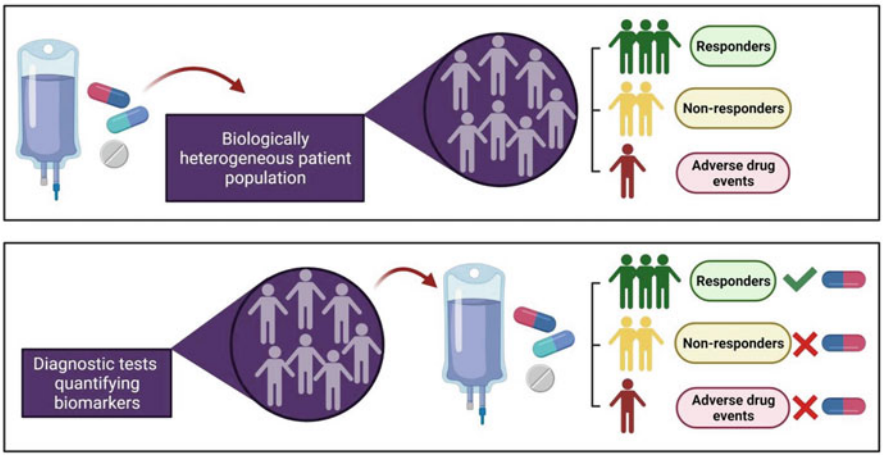

Fig. 10.4 General idea of personalized medicine. Biological variability can result in different outcomes (beneficial or harmful) for a population of patients (upper panel). Prediction of biomarker-based treatment response helps select appropriate patients for treatment and avoids the high risk of adverse drug incidents (lower panel)

investment, and use is prolonged due to better efficacies. It is expected that advanced technologies like artificial intelligence will influence cancer treatment and costs in the future (Mak and Pichika 2019).

10.8 Personalized Medicine in Conventional Therapeutic Approaches

New advances in the understanding of the underlying mechanisms of cancer have opened a new horizon of personalized medicine. One example is that of Bacillus Calmette–Guérin (BCG) vaccine therapy in non-muscle-invasive bladder cancer (NMIBC). During the year 1976, Morales and colleagues introduced the idea of utilizing BCG as a therapeutic and preventive approach in NMIBC (Moss and Kadmon 1991). BCG antigens provoke an immune response which attacks tumor cells, resulting in an anti-neoplastic effect when instilled during therapy (Saad et al. 2017). However, BCG treatment failed in many bladder cancer patients, and nearly 40% of them experienced recurrence (Alhunaidi and Zlotta 2019; Zlotta et al. 2009; Ślusarczyk et al. 2019; Lima et al. 2013). The ability to identify patients unlikely to respond to treatment would save time and hence, avoid progression of disease. Many investigations have been carried out to identify biomarkers which could be used to predict patient response to BCG. Good biomarkers would help physicians to effectively select candidates, and put poor responders on an alternative therapeutic strategy (Kamat et al. 2016). Patients with mutations in the AT-rich interaction domain 1A (ARID1A) were highly prone to recurrence of NMIBC after BCG therapy. This study suggested that the screening of BCG candidates could give

useful insights into patient prognoses (Pietzak et al. 2017). However, further investigations are needed to demonstrate the functionality of ARID1A as a reliable biomarker for BCG therapy. Researchers have also struggled to establish the predictive value of the tumor suppressor protein p53, for response of BCG in bladder cancer (PAGES et al. 1998; Berggren et al. 2001). p53 mutation was not found for predicting clinical response, but was utilized to predict cancer prognosis (Du et al. 2016; Malats et al. 2005). Cell adhesion molecules like sialyl-Tn (STn) and sialyl-6-T (s6T), which play roles in cell–cell adhesion and immune responses, were also included in trials for BCG response (Pinho et al. 2007). STn, alone or in combination with s6T, appeared to be linked with lower recurrence rates after BCG instillation, although the underlying mechanism remains poorly understood (Lima et al. 2013; Severino et al. 2017). Researchers also studied ezrin, a cell adhesion molecule, during BCG response, and found that the loss of ezrin was correlated with reduced survival (Palou et al. 2009; Andersson et al. 2014). During an investigation into BCG nonresponders versus responders, Kates et al. found that programmed death ligand-1 (PD-L1) appeared in nearly 25% and 4% of BCG nonresponders and responders, respectively. This study suggested that PD-L1 can be involved in the NIMBC-induced resistance to BCG therapy (Kates et al. 2020). As recent investigations lack standardization regarding response measurement criteria, study validation techniques, and cutoff points, further intensive and qualitative investigations are required to find a single biomarker which could be used to predict patients response to BCG therapy (Kamat et al. 2018).

10.9 Personalized Medicine in Novel Therapeutic Strategies

The existence of fibroblast growth factor receptor (FGFR3) mutations, fusions, and amplifications have been found in numerous tumors, including bladder cancer (Nogova et al. 2017). It has been shown that FGFR3 appears in bladder cancer preferentially in low-grade NMIBC, which indicates that FGFR3 may serve as a crucial marker for disease severity and management (Akanksha and Sandhya 2019). Researchers have utilized different techniques, such as the development of monoclonal antibodies and selective tyrosine kinase inhibitors, to interfere with FGFR3 signaling (Paul and Mukhopadhyay 2004; Qing et al. 2009). B701, a fully humanized immunoglobulin, resulted in significantly improved survival when included to novel PD-1 inhibitors or traditional chemotherapeutic agents (Holash et al. 2016). MFGR1877S, an antibody targeting the FGFR3 receptor, and LY3076226, a FGFR3 antibody conjugated to a cytotoxic drug (DM4), have shown promising results, and are currently in Phase I clinical trials (Qing et al. 2009; Surguladze et al. 2019). Investigators have also attempted to influence FGFR3 signaling at a more distal point utilizing tyrosine kinase inhibitors (TKIs). Pazopanib, a potent TKI, has shown partial responses in 7 out of 21 patients in a Phase II clinical testing (Necchi et al. 2012). During Phase II clinical trials, pazopanib monotherapy in individuals with advanced urothelial cancer (UC), showed partial response in seven patients and stable disease in 14 out of 41 patients

(Necchi et al. 2012). Although pazopanib showed encouraging results, two other TKIs, brivanib, and dovitinib, failed to show a strong response (Milowsky et al. 2014; Hahn et al. 2017; Ratain et al. 2011). It has been noted that drug molecules showing a more specific effect on the tyrosine kinase domain of FGFR produce more optimistic results. For example, erdafitinib, a small molecule inhibitor of FGFR approved for treating advanced or metastatic UC and marketed under the name Balversa, which harbors FGFR2/3 alterations, gave a response rate of up to 40%, although 37% of the responses were partial. However, the response rate was almost 60% among patients who previously received immunotherapy (Loriot et al. 2019). A few other TKIs, like infigratinib, AZD4547, and pemigatinib, are currently under trial (Marandino et al. 2019; Jones et al. 2016; Merz et al. 2021).

Boosting host immunity by blocking inhibitory receptors is another strategy extensively used in bladder cancer (Khalil et al. 2016). The primary signal for the stimulation of T cell is the recognition of antigens by the T-cell receptors (TCRs) presented by APCs via MHC. A second signal for T cell activation involves the binding of T cell CD28 with CD80/86 on APCs. The two most common immunomodulatory molecules, CTLA-4 and PD-L1, inhibit this interaction. CTLA-4 plays its inhibitory role in blocking the secondary signal by competing for CD80 and CD86 binding (Collins et al. 2002; Parry et al. 2005). PD-L1 blocks downstream TCR signaling and results in the inhibition of T cell responses (Sage et al. 2018). Strategies which block the inhibitory effects of these molecules would allow the immune system to attack the tumor more aggressively.

10.10 Bioengineering and Personalized Medicine

The concept of medicine is diverging from the "one size fits all" mentality. It usually occurs that patients having same disease respond differently to drugs. Therefore, now is the time to deeply understand this response and provide patients with individual treatment. Biomaterial engineers, specifically, can play a crucial role in making personalized medication a reality. Biomaterials can present different effects on cell growth and survival, and it is highly recommended that they should be screened via high-throughput approaches for a given application. For example, a dextran–dendrimer composite was shown to work as an adhesive differently in colon cancer than in colitis, which involves the same organ with a different environment (Artzi et al. 2009; Oliva et al. 2015). These studies suggest that the use of biomaterials cannot be generalized, and they must be designed according to the organ environment. The appropriateness of biomaterials for certain organs, tissues, or cells can be determined using a combination of small and large animal models (Vegas et al. 2016a, b; Lind et al. 2017). To avoid the use of living models, different extracellular matrix formulations can also be utilized to observe the effects of biomaterials on cell differentiation, proliferation, and apoptosis (Beachley et al. 2015). Optimal biomaterial formulations produced via novel engineering platforms can enhance personalized biocompatibility and therapeutic outcomes.

There is an emerging idea of "organ-on-a-chip platforms" for individualized drug-screening investigations. Scientists have developed a microfluidics-based model of human intestine, in which they recreated the complex gut microenvironment. This model paved the way for monitoring the interactions between the immune cells, gut microbiome, and bacteria. It also opened the way for the observation of the pharmacokinetics, absorption, and metabolism of drugs (Bein et al. 2018; Prantil-Baun et al. 2018). Drug pharmacokinetics, absorption, and metabolism potentials may also be used for designing personalized therapeutic strategies. Accurate and timely detection of treatment response is needed for accurate personalized treatment; the latter includes parameters, such as appropriate drug selection and dosing regimens. The commonly used techniques for acquiring these parameters, include urine and serum analyses, or imaging modalities, such as X-rays, MRI, CT, and ultrasound, which could be narrow in terms of testing frequency. It has been demonstrated that wearables and other novel technologies can help in overcoming the problem of infrequent measurements, which would thereby improve the design of personalized therapeutic strategies (Blicharz et al. 2018). Over time, new breakthroughs in personalized medicine have been introduced, encompassing the application of nondrug-based strategies like digital therapies, to cope with conditions such as cognitive impairment, mental health, and substance abuse (Kee et al. 2019; Davis et al. 2018; Cho and Lee 2019) (Fig. 10.5).

A common feature of these strategies is their ability to utilize only a subject's own data to direct only their own care. This approach has been exemplified regarding artificial intelligence-driven drug dosing and engineered cell therapy. Another advantage in the connection of personalized medicine and engineering is the parallel adjustment of intervention and diagnosis for ongoing therapy optimization.

10.11 Personalized Cell Therapy and Drug Delivery

A major advancement in personalized cancer treatment is the approval of chimeric antigen receptor T-cell (CAR-T) immunotherapy. Tisagenlecleucel (Kymriah, Novartis) was the first approved CAR-T therapy, which is being used for treating patients with acute lymphoblastic leukemia. During this treatment, T cells are removed from patient, reprogrammed, and expanded in a processing facility and are finally introduced to the patient (Prasad 2018). Axicabtagene ciloleucel (Yescarta, KITE Pharma/Gilead Sciences) has recently been approved for the treatment of aggressive non-Hodgkin's lymphomas (Roberts et al. 2018; Mullard 2017). Scientists worldwide are working to broaden the indications that are managed utilizing CAR-T. The approval of CAR-T remains an ideal shift for the FDA towards efficacious and safe living cell therapies. It has been demonstrated recently that nonviral approaches, like sleeping beauty transposition, can improve the scalability of CAR-T for broader deployment (Monjezi et al. 2017). This technique is based on the use of simple DNA minicircles for inserting CAR genes, which effectively reduces the risk of genotoxicity and mutagenesis associated with viral modalities (Fig. 10.6). It also reduces the cost of CAR-T engineering and minimizes the

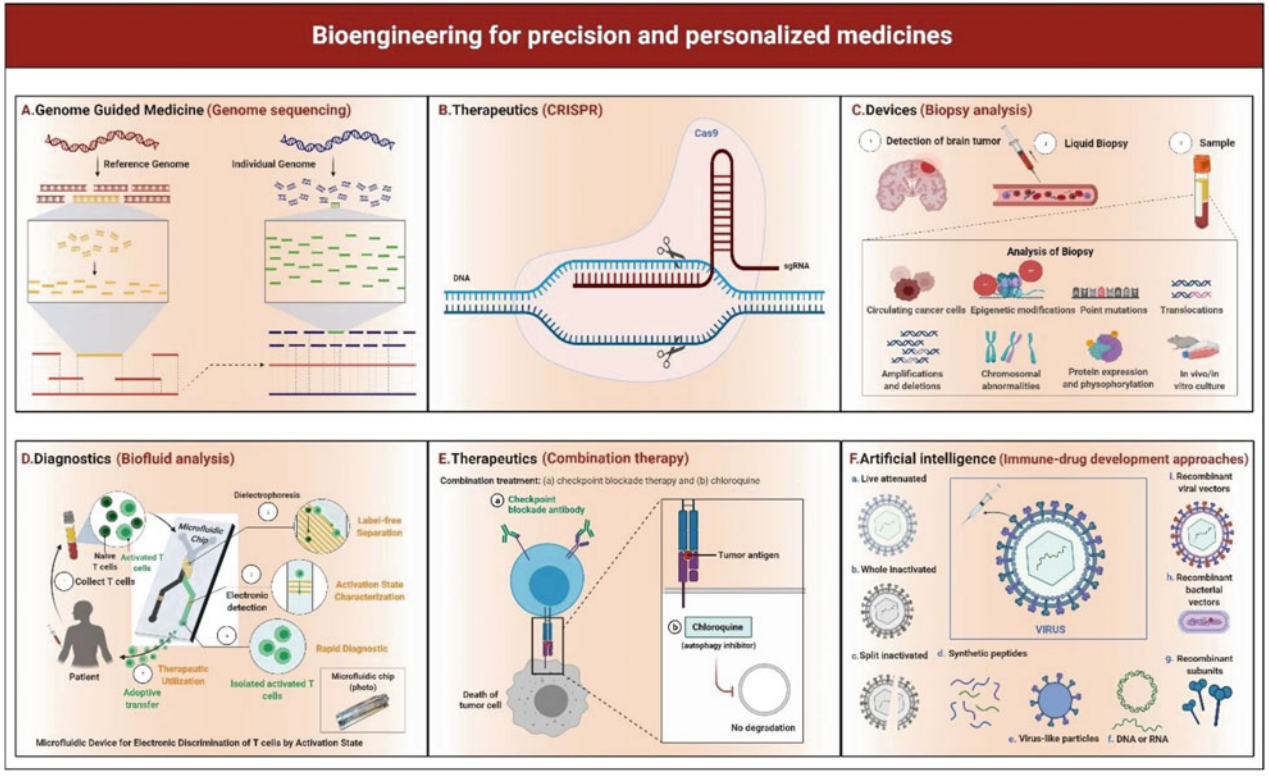

Fig. 10.5 From genome-guided medicine to CRISPR, multiple advanced and highly accurate technological platforms bridge engineering and personalized medicine together, improving clinical outcomes. Moreover, striking improvement in personalized medicine approaches may be realized by linking wearable technologies, artificial intelligence, and other engineering platforms

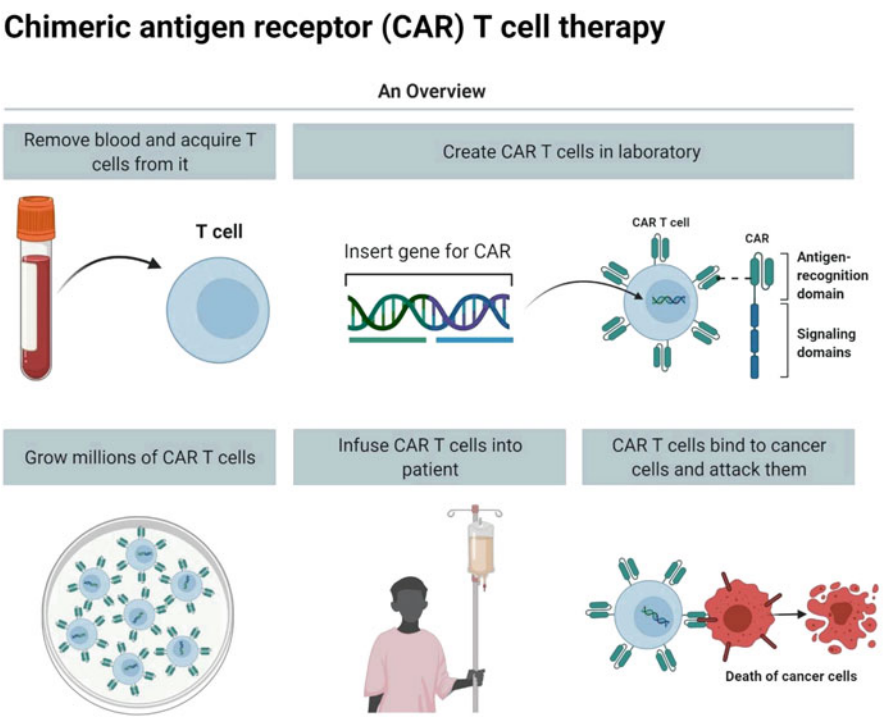

Fig. 10.6 How does engineered T cell therapy work? Enough blood is obtained from patients to collect T cells from it. T cells are purified and modified by viral vector transfection to express specific CARs/TCRs on their surface. Following amplification and quality control, engineered CAR-containing T cells are infused into the patient body to improve antitumor ability

regulatory hurdles faced. "Off-the-shelf" cell therapy, which does not need autologous T cells, is used by advanced engineering approaches for improving CAR-T manufacturing (Sadelain et al. 2017; Cooper et al. 2018; Ruella and Kenderian 2017). Zinc-finger nuclease technology, a novel tool composed of engineered DNA-binding proteins, facilitating targeted editing of the genome by creating double-strand breaks in DNA at user-specified locations, is being utilized for modifying both allogeneic and autologous cell therapies. This technology is expected to broaden the chances of off-the-shelf CAR-T manufacturing, and significantly decrease the treatment duration (Dolgin 2018).

It is now possible to reprogram induced pluripotent stem cells, obtained from a patient, to a desired cell like a brain cell, a specialized kidney cell, or a beta cell, which can be introduced into the body and will carry out their specific functions (Vegas et al. 2016b; Peruzzotti-Jametti et al. 2018; Ma et al. 2018). Mitochondrial replacement therapy (MRT) is an additional example of cell therapy implemented in the United Kingdom. Mutations in mitochondrial DNA (mtDNA), referred to as mitochondrial disease, can also be maternally transferred to the offspring, and leads to severe disorders, such as deafness, epilepsy, optic neuropathy, and diabetes

mellitus. In MRT, the healthy nucleus from a maternal egg with malfunctioning mitochondria is transferred to a healthy egg, including the donor mitochondria, without a nucleus, which can result in a fertilized egg containing nuclear DNA from two parents and mtDNA from a donor, thus eliminating the genetic disorder in children (Saxena et al. 2018).

Another particularly relevant area is the cellular engineering. Scientists have designed synthetic cells for the early detection of malignancy and diabetes (Danino et al. 2015; Courbet et al. 2015). With the application of synthetic cells and biosensors, scientists become able to detect early disease markers and deliver therapeutic entities to improve symptoms. This is a major goal of personalized medicine, wherein the cell is an autonomous therapy and sensor, delivering therapeutic entities without physician or patient intervention. During an investigation, chronic and acute psoriasis was observed by a population of synthetic cells implanted in mice, an approach which provided a new opportunity for personalized medicine (Schukur et al. 2015).

Delivering therapy in a personalized fashion is also a promising approach. Personalized biomaterial-mediated controlled release or 3D printing technologies are being introduced to serve as cornerstones for improving drug delivery. A study reported the tailored release profiles from 3D-printed tablets, enabling the customization of the temporal administration of the drug (Sun and Soh 2015). A technique termed stamped assembly of polymer layers (SEAL) has been successfully utilized to produce drug-loaded 3D microstructures with temporal drug release control (McHugh et al. 2017). Specific responses of individuals to combination therapy are often monitored by unique dosing profiles. Hence, these microstructures and tablets can be a feasible drug delivery platform for personalized medication.

10.12 Concluding Remarks and Future Directions

Many drugs show efficacy only in a subgroup of patients (Laserna-Mendieta et al. 2020; Wang et al. 2021). Therefore, the "hit-or-miss" utilization of these drugs is costly, ineffective, and puts patients at risk. Drug development is expensive and the number of FDA-approved drugs per billion US dollars of spending decreases by half every 9 years. The cost of launching a new drug exceeds one billion euro, and this exorbitant price raises concerns (Scannell et al. 2012). The era of personalized and precision medicine is expected to solve this problem. In this era, patients will no longer be restricted to dose escalation-defined administration protocols and target-based drug selection.

High failure rates are a major cause of the high research as well as development costs involved in discovery of drugs. Less than 1% of drug development projects launched result in the approval of a new drug. It has frequently been observed that, after several years of significant investments, drugs fail late in the clinical trials. It is alarming that the traditionally low success rates for new drug development projects in Phase II clinical trials decreased even further from 28% to 18%. In the past few years, insufficient efficacy has remained the most frequent reason for failure

(Arrowsmith 2011). Personalized medicine can help to address this challenge. Smaller sized clinical investigations conducted using biomarker-based stratification can show better results. It is recommended, even in clinical trials lacking a stratification strategy, to include biomarker candidates. It would also be supportive to acquire patients' informed consent, to enable retrospective assays conducted later. If retrospective assays produce favorable outcomes in biomarker candidates, these findings need to be verified in another prospective clinical study. Although such a protocol may increase the cost of the initial study, it could rescue a project. To support findings related to dosage, pharmacodynamic biomarkers are also recommended to be added more rigorously in clinical studies. This approach will have the benefit of increasing tolerance and establishing recommended dosage. Moreover, this approach could provide important experience in case of study failure. In this case, the pharmacodynamic biomarker represents a full-target engagement, showing that the target is not relevant to the disorder. When a biomarker engages the target insufficiently, it can indicate that the compound, rather than the efficacy of the molecular target, is the cause of the problem.

Scientists are of the opinion that future medical products can be introduced as a "double pack": the drug molecule and the diagnostic assay to identify the feasibility of the patient for this approach. This approach requires the creation of consortia, for closer collaboration between the pharmaceutical and the diagnostic industry (Salter and Holland 2014). Various models are in use for various categories of biomarkers, and many more are needed for different stages of the drug discovery and development process (Asadullah et al. 2015; Lessl et al. 2011; Dorsch et al. 2015). Studies have shown major inconsistencies between the number of biomarkers identified and the number reported ($\leq$150,000) and the few ($\leq$100) entered in clinic trials (Poste 2011). The reproducibility of publications is also an important issue (Prinz et al. 2011). High transparency and more coordinated efforts are needed for biomarker discovery, development, and validation, involving collaborations between academia and the diagnostics and pharmaceutical industry, since this process requires significant resources and complementary skills (Landis et al. 2012; Asadullah et al. 2015).

The Biomarkers Consortium (URL), the predictive safety testing consortium (URL), and the Coalition Against Major Diseases (URL) are noteworthy examples of successful consortia in the biomarker area, and it is expected that the number of collaborations would increase in future (Wholley 2014; Stephenson and Sauer 2014).

Scientists are expecting changes in the number of biomarkers tested. Currently, only one biomarker is used to guide a treatment protocol, whereas future molecular diagnostics may result in the simultaneous comprehensive profiling of several markers. This approach reflects a movement from the use of a single marker to a signature, which would allow us to choose the most suitable and potent therapeutic combination for each patient. Although in the discovery of biomarkers, panels of markers are frequently already measured, much remains to be done in validating candidates' biomarkers. Further improvements in precision and personalized medicine in the present population are required for a successful transfer of validated biomarkers and personalized medicine platforms into the clinical setting. Several

technology-linked validation challenges associated with ethics, healthcare economics, and data privacy need to be addressed (Reddy et al. 2020; Cohen 2019; Dinh-Le et al. 2019; Lee et al. 2019). Biomedical engineering, which is currently playing a key role in breakthroughs, is expected to eventually improve the human condition in an individualized fashion.

Author Contributions Y.S.L.: conceptualization, supervision; S.U.I., and H.A.: writing—original draft; M.B.A.: designed all the figures. All authors have read and agreed to the published version of the chapter.

Funding This research was funded by a National Research Foundation of Korea (NRF) grant from the Korean government (MSIT) (NRF-2019R1A2C1003003).

Conflicts of Interest The authors declare no conflict of interest.

References

Adams CM, Clark-Garvey S, Porcu P, Eischen CM (2019) Targeting the Bcl-2 family in B cell lymphoma. Front Oncol 8:636

Agache I, Akdis C, Akdis M, Canonica GW, Casale T, Chivato T et al (2021) EAACI biologicals guidelines—recommendations for severe asthma. Allergy 76(1):14–44

Aitken M, Kleinrock M, Simorellis A, Nass D (2018) Global oncology trends 2018: innovation, expansion and disruption, pp 2019-12

Akanksha M, Sandhya S (2019) Role of FGFR3 in urothelial carcinoma. Iran J Pathol 14(2):148

Akkaya B, Salim O, Akkaya H, Ozcan M, Yucel OK, Erdem R et al (2016) C-MYC and BCL2 translocation frequency in diffuse large B-cell lymphomas: a study of 97 patients. Indian J Pathol Microbiol 59(1):41

Akyurek N, Uner A, Benekli M, Barista IJC (2012) Prognostic significance of MYC, BCL2, and BCL6 rearrangements in patients with diffuse large B-cell lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab. Cancer 118(17):4173–4183

Aldakheel F, Thomas P, Bourke J, Matheson M, Dharmage S, Lowe AJ (2016) Relationships between adult asthma and oxidative stress markers and pH in exhaled breath condensate: a systematic review. Allerrgy 71(6):741–757

Alhunaidi O, Zlotta AR (2019) The use of intravesical BCG in urothelial carcinoma of the bladder. Ecancermedicalscience 13:905

Alkodsi A, Cervera A, Zhang K, Louhimo R, Meriranta L, Pasanen A et al (2019) Distinct subtypes of diffuse large B-cell lymphoma defined by hypermutated genes. Leukemia 33(11):2662–2672

Alving K, Diamant Z, Lucas S, Magnussen H, Pavord ID, Piancentini G et al (2020) Point-of-care biomarkers in asthma management: time to move forward. Allergy 75(4):995–997

Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ et al (2008) Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 26(10):1626–1634

Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JH, Swen JJ et al (2018) Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol Ther 103(2):210–216

Andersson G, Wennersten C, Gaber A, Boman K, Nodin B, Uhlén M et al (2014) Reduced expression of ezrin in urothelial bladder cancer signifies more advanced tumours and an impaired survival: validatory study of two independent patient cohorts. BMC Urol 14(1):1–8

Aquino G, Marra L, Curcio M, De Chiara A, Liguori G, Franco RJ (2014) Detection of myc rearranged by fluorescence in situ hybridization FISH: a diagnostic tool. WCRJ 1:e362

Arock M, Sotlar K, Akin C, Broesby-Olsen S, Hoermann G, Escribano L et al (2015) KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia 29(6):1223–1232

Arrowsmith J (2011) Trial watch: phase II failures: 2008-2010. Nat Rev Drug Discov 10(5):328–329. https://doi.org/10.1038/nrd3439

Artzi N, Shazly T, Baker AB, Bon A, Edelman ER (2009) Aldehyde-amine chemistry enables modulated biosealants with tissue-specific adhesion. Adv Mater 21(32–33):3399–3403

Asadullah K, Busch A, Gottwald M, Reinke P, Landeck L (2015) Industry–academia collaborations for biomarkers. Nat Rev Drug Discov 14(12):805–806

Badic B, Hatt M, Durand S, Le Jossic-Corcos C, Simon B, Visvikis D et al (2019) Radiogenomics-based cancer prognosis in colorectal cancer. Sci Rep 9(1):1–7

Banin Hirata BK, Oda JMM, Losi Guembarovski R, Ariza CB, Oliveira CEC, Watanabe MAE (2014) Molecular markers for breast cancer: prediction on tumor behavior. Dis Markers 2014: 513158

Barcikowska M (2018) Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease. Lekarz POZ 4(5):370–374

Baron BW, Anastasi J, Montag A, Huo D, Baron RM, Karrison T et al (2004) The human BCL6 transgene promotes the development of lymphomas in the mouse. Proc Natl Acad Sci U S A 101(39):14198–14203

Barrans S, Crouch S, Smith A, Turner K, Owen R, Patmore R et al (2010) Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol 28(20):3360–3365

Basso K, Schneider C, Shen Q, Holmes AB, Setty M, Leslie C et al (2012) BCL6 positively regulates AID and germinal center gene expression via repression of miR-155. J Exp Med 209(13):2455–2465

Beachley VZ, Wolf MT, Sadtler K, Manda SS, Jacobs H, Blatchley MR et al (2015) Tissue matrix arrays for high-throughput screening and systems analysis of cell function. Nat Methods 12(12):1197–1204

Bein A, Shin W, Jalili-Firoozinezhad S, Park MH, Sontheimer-Phelps A, Tovaglieri A et al (2018) Microfluidic organ-on-a-chip models of human intestine. Cell Mol Gastroenterol Hepatol 5(4):659–668

Berggren P, Steineck G, Adolfsson J, Hansson J, Jansson O, Larsson P et al (2001) p53 mutations in urinary bladder cancer. Br J Cancer 84(11):1505–1511

Blicharz TM, Gong P, Bunner BM, Chu LL, Leonard KM, Wakefield JA et al (2018) Microneedle-based device for the one-step painless collection of capillary blood samples. Nat Biomed Eng 2(3):151–157

Camicia R, Winkler HC, Hassa PO (2015) Novel drug targets for personalized precision medicine in relapsed/refractory diffuse large B-cell lymphoma: a comprehensive review. Mol Cancer 14(1):1–62

Cattoretti G, Pasqualucci L, Ballon G, Tam W, Nandula SV, Shen Q et al (2005) Deregulated BCL6 expression recapitulates the pathogenesis of human diffuse large B cell lymphomas in mice. Cancer Cell 7(5):445–455

Cerchietti LC, Ghetu AF, Zhu X, Da Silva GF, Zhong S, Matthews M et al (2010) A small-molecule inhibitor of BCL6 kills DLBCL cells in vitro and in vivo. Cancer Cell 17(4):400–411

Chao M, Gibbs P (2009) Caution is required before recommending routine carcinoembryonic antigen and imaging follow-up for patients with early-stage colon cancer. J Clin Oncol 27(36):e279–e280; author reply e81

Chastain EC, Duncavage EJ (2015) Clinical prognostic biomarkers in chronic lymphocytic leukemia and diffuse large B-cell lymphoma. Arch Pathol Lab Med 139(5):602–607

Chawla A, Janku F, Wheler JJ, Miller VA, Ryan J, Anhorn R et al (2018) Estimated cost of anticancer therapy directed by comprehensive genomic profiling in a single-center study. JCO Precis Oncol 2:1–11
Chiappella A, Castellino A, Nicolosi M, Santambrogio E, Vitolo U (2017) Diffuse large B-cell lymphoma in the elderly: standard treatment and new perspectives. Expert Rev Hematol 10(4):289–297
Cho C-H, Lee H-J (2019) Could digital therapeutics be a game changer in psychiatry? Psychiatry Investig 16(2):97
Cohen JJS (2019) Did CRISPR help—or harm—the first-ever gene-edited babies. 21
Collins AV, Brodie DW, Gilbert RJ, Iaboni A, Manso-Sancho R, Walse B et al (2002) The interaction properties of costimulatory molecules revisited. Immunity 17(2):201–210
Comhair SA, Erzurum SC (2002) Antioxidant responses to oxidant-mediated lung diseases. Am J Physiol Lung Cell Mol Physiol 283(2):L246–L255
Comhair SA, Bhathena PR, Dweik RA, Kavuru M, Erzurum SC (2000) Rapid loss of superoxide dismutase activity during antigen-induced asthmatic response. Lancet 355(9204):624
Compagno M, Lim WK, Grunn A, Nandula SV, Brahmachary M, Shen Q et al (2009) Mutations of multiple genes cause deregulation of NF-κB in diffuse large B-cell lymphoma. Nature 459(7247):717–721
Cooper ML, Choi J, Staser K, Ritchey JK, Devenport JM, Eckardt K et al (2018) An "off-the-shelf" fratricide-resistant CAR-T for the treatment of T cell hematologic malignancies. Leukemia 32(9):1970–1983
Courbet A, Endy D, Renard E, Molina F, Bonnet J (2015) Detection of pathological biomarkers in human clinical samples via amplifying genetic switches and logic gates. Sci Transl Med 7(289):289ra83
Danino T, Prindle A, Kwong GA, Skalak M, Li H, Allen K et al (2015) Programmable probiotics for detection of cancer in urine. Sci Transl Med 7(289):289ra84
Davis RE, Brown KD, Siebenlist U, Staudt LM (2001) Constitutive nuclear factor κB activity is required for survival of activated B cell–like diffuse large B cell lymphoma cells. J Exp Med 194(12):1861–1874
Davis RE, Ngo VN, Lenz G, Tolar P, Young RM, Romesser PB et al (2010) Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature 463(7277):88–92
Davis NO, Bower J, Kollins SH (2018) Proof-of-concept study of an at-home, engaging, digital intervention for pediatric ADHD. PLoS One 13(1):e0189749
Davis KD, Aghaeepour N, Ahn AH, Angst MS, Borsook D, Brenton A et al (2020) Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. Nat Rev Neurol 16(7):381–400
Diamant Z, Boot J, Mantzouranis E, Flohr R, Sterk P, van Wijk RG et al (2010) Biomarkers in asthma and allergic rhinitis. Pulm Pharmacol Ther 23(6):468–481
Diamant Z, Vijverberg S, Alving K, Bakirtas A, Bjermer L, Custovic A et al (2019) Toward clinically applicable biomarkers for asthma: an EAACI position paper. Allergy 74(10):1835–1851
Dinh-Le C, Chuang R, Chokshi S, Mann D (2019) Wearable health technology and electronic health record integration: scoping review and future directions. JMIR Mhealth Uhealth 7(9): e12861
Dolgin E (2018) Kite, Sangamo partner on gene-edited cell therapies. Cancer Discov 8(4):379–380
Dorsch H, Jurock AE, Schoepe S, Lessl M, Asadullah K (2015) Grants4Targets: an open innovation initiative to foster drug discovery collaborations. Nat Rev Drug Discov 14(1):74–76
Du J, Wang S-h, Yang Q, Chen Q-q, Xo Y (2016) p53 status correlates with the risk of progression in stage T1 bladder cancer: a meta-analysis. World J Surg Oncol 14(1):1–8
Food & DrugAdministration (2018) Biomarker qualification: evidentiary framework. Guidance for Industry and FDA Staff (Draft). https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM62. 8118

Food U (2014) https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram. Drug development tools (DDT) qualification programs. 2014

Forschner A, Eigentler TK, Pflugfelder A, Leiter U, Weide B, Held L et al (2010) Melanoma staging: facts and controversies. Clin Dermatol 28(3):275–280

Frei E, Visco C, Xu-Monette Z, Dirnhofer S, Dybkær K, Orazi A et al (2013) Addition of rituximab to chemotherapy overcomes the negative prognostic impact of cyclin E expression in diffuse large B-cell lymphoma. J Clin Pathol 66(11):956–961

Gimotty PA, Van Belle P, Elder DE, Murry T, Montone KT, Xu X et al (2005) Biologic and prognostic significance of dermal Ki67 expression, mitoses, and tumorigenicity in thin invasive cutaneous melanoma. J Clin Oncol 23(31):8048–8056

Grecchi S, Mazzini G, Lisa A, Armentero M-T, Bergamaschi R, Romani A et al (2012) Search for cellular stress biomarkers in lymphocytes from patients with multiple sclerosis: a pilot study. PLoS One 7(9):e44935

Group F-NBW (2016) BEST (biomarkers, endpoints, and other tools) resource [Internet]

Guo X, Xu Y, Zhao Z (2015) In-depth genomic data analyses revealed complex transcriptional and epigenetic dysregulations of BRAF V600E in melanoma. Mol Cancer 14(1):60

Hahn NM, Bivalacqua TJ, Ross AE, Netto GJ, Baras A, Park JC et al (2017) A phase II trial of dovitinib in BCG-unresponsive urothelial carcinoma with FGFR3 mutations or overexpression: hoosier cancer research network trial HCRN 12-157. Clin Cancer Res 23(12):3003–3011

Hayden MS, Ghosh S (2011) NF-κB in immunobiology. Cell Res 21(2):223–244

Hoesel B, Schmid JA (2013) The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer 12(1):1–15

Holash J, Schwartz K, Lau S (2016) B-701, a selective and potent inhibitor of fibroblast growth factor receptor 3 (FGFR3), may enhance the activity of bladder cancer therapies. Eur J Cancer 69(Suppl 1):S20

Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A et al (2020) Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 55(1):1900588

Horvat N, Veeraraghavan H, Pelossof RA, Fernandes MC, Arora A, Khan M et al (2019) Radiogenomics of rectal adenocarcinoma in the era of precision medicine: a pilot study of associations between qualitative and quantitative MRI imaging features and genetic mutations. Eur J Radiol 113:174–181

Jiang C, Lin X (2012) Regulation of NF-κB by the CARD proteins. Immunol Rev 246(1):141–153

Jones RH, Anthoney DA, Jones RJ, Crabb SJ, Hussain SA, Birtle AJ et al (2016) FIESTA: a phase Ib and pharmacokinetic trial of AZD4547 in combination with gemcitabine and cisplatin. J Clin Oncol 34(15 Suppl)

Kamat AM, Briggman J, Urbauer DL, Svatek R, González GMN, Anderson R et al (2016) Cytokine panel for response to intravesical therapy (CyPRIT): nomogram of changes in urinary cytokine levels predicts patient response to Bacillus Calmette-Guérin. Eur Urol 69(2):197–200

Kamat AM, Li R, O'Donnell MA, Black PC, Roupret M, Catto JW et al (2018) Predicting response to intravesical Bacillus Calmette-Guérin immunotherapy: are we there yet? A systematic review. Eur Urol 73(5):738–748

Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC et al (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 359(17):1757–1765

Kates M, Matoso A, Choi W, Baras AS, Daniels MJ, Lombardo K et al (2020) Adaptive immune resistance to intravesical BCG in non–muscle invasive bladder cancer: implications for prospective BCG-unresponsive trials. Clin Caner Res 26(4):882–891

Kawamoto K, Miyoshi H, Yoshida N, Nakamura N, Ohshima K, Sone H et al (2016) MYC translocation and/or BCL 2 protein expression are associated with poor prognosis in diffuse large B-cell lymphoma. Cancer Sci 107(6):853–861

Kee T, Weiyan C, Blasiak A, Wang P, Chong JK, Chen J et al (2019) Harnessing CURATE.AI as a digital therapeutics platform by identifying N-of-1 learning trajectory profiles. Adv Therap 2(9):1900023

Khalil DN, Smith EL, Brentjens RJ, Wolchok JD (2016) The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol 13(5):273–290

Koulis C, Yap R, Engel R, Jardé T, Wilkins S, Solon G et al (2020) Personalized medicine—current and emerging predictive and prognostic biomarkers in colorectal cancer. Cancers (Basel) 12(4):812

Kuruvilla ME, Lee FE-H, Lee GB (2019) Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol 56(2):219–233

Landeck L, Kneip C, Reischl J, Asadullah K (2016) Biomarkers and personalized medicine: current status and further perspectives with special focus on dermatology. Exp Dermatol 25(5):333–339

Landis SC, Amara SG, Asadullah K, Austin CP, Blumenstein R, Bradley EW et al (2012) A call for transparent reporting to optimize the predictive value of preclinical research. Nature 490(7419):187–191

Laserna-Mendieta EJ, Casabona S, Guagnozzi D, Savarino E, Perelló A, Guardiola-Arévalo A et al (2020) Efficacy of proton pump inhibitor therapy for eosinophilic oesophagitis in 630 patients: results from the EoE connect registry. Aliment Pharmacol Ther 52(5):798–807

Lee SS-J, Fullerton SM, Saperstein A, Shim JK (2019) Ethics of inclusion: cultivate trust in precision medicine. Science 364(6444):941–942

Lessl M, Bryans JS, Richards D, Asadullah K (2011) Crowd sourcing in drug discovery. Nat Rev Drug Discov 10(4):241–242

Li W, Gupta SK, Han W, Kundson RA, Nelson S, Knutson D et al (2019) Targeting MYC activity in double-hit lymphoma with MYC and BCL2 and/or BCL6 rearrangements with epigenetic bromodomain inhibitors. J Hematol Oncol 12(1):1–13

Lima L, Severino P, Silva M, Miranda A, Tavares A, Pereira S et al (2013) Response of high-risk of recurrence/progression bladder tumours expressing sialyl-Tn and sialyl-6-T to BCG immunotherapy. Br J Cancer 109(8):2106–2114

Lind JU, Busbee TA, Valentine AD, Pasqualini FS, Yuan H, Yadid M et al (2017) Instrumented cardiac microphysiological devices via multimaterial three-dimensional printing. Nat Mater 16(3):303–308

Logothetis CJ (2014) Prostate cancer bone metastases: not so systemic after all. Lancet Oncol 15(7):675–676

Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E et al (2019) Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med 381(4):338–348

Ma H, Wert KJ, Shvartsman D, Melton DA, Jaenisch R (2018) Establishment of human pluripotent stem cell-derived pancreatic β-like cells in the mouse pancreas. Proc Natl Acad Sci U S A 115(15):3924–3929

Mak K-K, Pichika MR (2019) Artificial intelligence in drug development: present status and future prospects. Drug Discov Today 24(3):773–780

Malats N, Bustos A, Nascimento CM, Fernandez F, Rivas M, Puente D et al (2005) P53 as a prognostic marker for bladder cancer: a meta-analysis and review. Lancet Oncol 6(9):678–686

Marandino L, Raggi D, Giannatempo P, Farè E, Necchi A (2019) Erdafitinib for the treatment of urothelial cancer. Expert Rev Anticancer Ther 19(10):835–846

Margonis GA, Spolverato G, Kim Y, Karagkounis G, Choti MA, Pawlik TM (2015) Effect of KRAS mutation on long-term outcomes of patients undergoing hepatic resection for colorectal liver metastases. Ann Surg Oncol 22(13):4158–4165

Mason KD, Vandenberg CJ, Scott CL, Wei AH, Cory S, Huang DC et al (2008) In vivo efficacy of the Bcl-2 antagonist ABT-737 against aggressive Myc-driven lymphomas. Proc Natl Acad Sci U S A 105(46):17961–17966

McDowell PJ, Heaney LG (2020) Different endotypes and phenotypes drive the heterogeneity in severe asthma. Allergy 75(2):302–310

McHugh KJ, Nguyen TD, Linehan AR, Yang D, Behrens AM, Rose S et al (2017) Fabrication of fillable microparticles and other complex 3D microstructures. Science 357(6356):1138–1142
Merz V, Zecchetto C, Melisi D (2021) Pemigatinib, a potent inhibitor of FGFRs for the treatment of cholangiocarcinoma. Future Oncol 17(4):389–402
Miller DM, Thomas SD, Islam A, Muench D, Sedoris K (2012) c-Myc and cancer metabolism. Clin Cancer Res 18(20):5546–5553
Milowsky MI, Dittrich C, Durán I, Jagdev S, Millard FE, Sweeney CJ et al (2014) Phase 2 trial of dovitinib in patients with progressive FGFR3-mutated or FGFR3 wild-type advanced urothelial carcinoma. Eur J Cancer 50(18):3145–3152
de Moll EH, Fu Y, Qian Y, Perkins SH, Wieder S, Gnjatic S et al (2015) Immune biomarkers are more accurate in prediction of survival in ulcerated than in non-ulcerated primary melanomas. Cancer Immunol Immunother 64(9):1193–1203
Monjezi R, Miskey C, Gogishvili T, Schleef M, Schmeer M, Einsele H et al (2017) Enhanced CAR T-cell engineering using non-viral Sleeping Beauty transposition from minicircle vectors. Leukemia 31(1):186–194
Montero J, Letai A, Differentiation. (2018) Why do BCL-2 inhibitors work and where should we use them in the clinic? Cell Death Differ 25(1):56–64
Moss JT, Kadmon D (1991) BCG and the treatment of superficial bladder cancer. DICP 25(12):1355–1367
Mullard A (2017) FDA approves first CAR T therapy. Nat Rev Drug Discov 16(10):669
Nagel D, Vincendeau M, Eitelhuber A, Krappmann D (2014) Mechanisms and consequences of constitutive NF-κB activation in B-cell lymphoid malignancies. Oncogene 33(50):5655–5665
Necchi A, Mariani L, Zaffaroni N, Schwartz LH, Giannatempo P, Crippa F et al (2012) Pazopanib in advanced and platinum-resistant urothelial cancer: an open-label, single group, phase 2 trial. Lancet Oncol 13(8):810–816
Nogova L, Sequist LV, Garcia JMP, Andre F, Delord J-P, Hidalgo M et al (2017) Evaluation of BGJ398, a fibroblast growth factor receptor 1–3 kinase inhibitor, in patients with advanced solid tumors harboring genetic alterations in fibroblast growth factor receptors: results of a global phase I, dose-escalation and dose-expansion study. J Clin Oncol 35(2):157
Ogunwobi OO, Mahmood F, Akingboye A (2020) Biomarkers in colorectal cancer: current research and future prospects. Int J Mol Sci 21(15):5311
Oliva N, Carcole M, Beckerman M, Seliktar S, Hayward A, Stanley J et al (2015) Regulation of dendrimer/dextran material performance by altered tissue microenvironment in inflammation and neoplasia. Sci Transl Med 7(272):272ra11
Pages F, Flam TA, Vieillefond A, Molinie V, Abeille X, Lazar V et al (1998) p53 status does not predict initial clinical response to bacillus Calmette-Guerin intravesical therapy in T1 bladder tumors. J Urol 159(3):1079–1084
Palomaki GE, Bradley LA, Douglas MP, Kolor K, Dotson WD (2009) Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review. Genet Med 11(1):21–34
Palou J, Algaba F, Vera I, Rodriguez O, Villavicencio H, Sanchez-Carbayo M (2009) Protein expression patterns of ezrin are predictors of progression in T1G3 bladder tumours treated with nonmaintenance bacillus Calmette-Guerin. Eur Urol 56(5):829–836
Park MH, Hong JT (2016) Roles of NF-κB in cancer and inflammatory diseases and their therapeutic approaches. Cells 5(2):15
Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV et al (2005) CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 25(21):9543–9553
Pasqualucci L, Compagno M, Houldsworth J, Monti S, Grunn A, Nandula SV et al (2006) Inactivation of the PRDM1/BLIMP1 gene in diffuse large B cell lymphoma. J Exp Med 203(2):311–317
Patel JN (2014) Application of genotype-guided cancer therapy in solid tumors. Pharmacogenomics 15(1):79–93

Patel JN, Fong MK, Jagosky M (2019) Colorectal cancer biomarkers in the era of personalized medicine. J Pers Med 9(1):3

Paul MK, Mukhopadhyay AK (2004) Tyrosine kinase–role and significance in cancer. Int J Med Sci 1(2):101

Pellino G, Gallo G, Pallante P, Capasso R, De Stefano A, Maretto I et al (2018) Noninvasive biomarkers of colorectal cancer: role in diagnosis and personalised treatment perspectives. Gastroenterol Res Pract 2018:2397863

Peruzzotti-Jametti L, Bernstock JD, Vicario N, Costa AS, Kwok CK, Leonardi T et al (2018) Macrophage-derived extracellular succinate licenses neural stem cells to suppress chronic neuroinflammation. Cell Stem Cell 22(3):355–68.e13

Pietzak EJ, Bagrodia A, Cha EK, Drill EN, Iyer G, Isharwal S et al (2017) Next-generation sequencing of nonmuscle invasive bladder cancer reveals potential biomarkers and rational therapeutic targets. Eur Urol 72(6):952–959

Pinho S, Marcos NT, Ferreira B, Carvalho AS, Oliveira MJ, Santos-Silva F et al (2007) Biological significance of cancer-associated sialyl-Tn antigen: modulation of malignant phenotype in gastric carcinoma cells. Cancer Lett 249(2):157–170

Poste G (2011) Bring on the biomarkers. Nature 469(7329):156–157

Prantil-Baun R, Novak R, Das D, Somayaji MR, Przekwas A, Ingber DE (2018) Physiologically based pharmacokinetic and pharmacodynamic analysis enabled by microfluidically linked organs-on-chips. Annu Rev Pharmacol Toxicol 58:37–64

Prasad V (2018) Immunotherapy: Tisagenlecleucel—the first approved CAR-T-cell therapy: implications for payers and policy makers. Nat Rev Clin Oncol 15(1):11–12

Prinz F, Schlange T, Asadullah K (2011) Believe it or not: how much can we rely on published data on potential drug targets? Nat Rev Drug Discov 10(9):712

Qing J, Du X, Chen Y, Chan P, Li H, Wu P et al (2009) Antibody-based targeting of FGFR3 in bladder carcinoma and t (4; 14)-positive multiple myeloma in mice. J Clin Invest 119(5):1216–1229

Ratain M, Schwartz G, Oza A, Rudin C, Kaye S, De Jonge M et al (2011) Brivanib (BMS-582664) in advanced solid tumors (AST): results of a phase II randomized discontinuation trial (RDT). J Clin Oncol 29(15 Suppl):3079

Reddy S, Allan S, Coghlan S, Cooper P (2020) A governance model for the application of AI in health care. J Am Med Inform Assoc 27(3):491–497

Roberts ZJ, Better M, Bot A, Roberts MR, Ribas A (2018) Axicabtagene ciloleucel, a first-in-class CAR T cell therapy for aggressive NHL. Leuk Lymphoma 59(8):1785–1796

Ruella M, Kenderian SS (2017) Next-generation chimeric antigen receptor T-cell therapy: going off the shelf. BioDrugs 31(6):473–481

Saad FT, Hincal E, Kaymakamzade B (2017) Dynamics of immune checkpoints, immune system, and BCG in the treatment of superficial bladder cancer. Comput Math Methods Med 2017: 3573082

Sadelain M, Rivière I, Riddell S (2017) Therapeutic T cell engineering. Nature 545(7655):423–431

Sage PT, Schildberg FA, Sobel RA, Kuchroo VK, Freeman GJ, Sharpe AH (2018) Dendritic cell PD-L1 limits autoimmunity and follicular T cell differentiation and function. J Immunol 200(8):2592–2602

Salter H, Holland R (2014) Biomarkers: refining diagnosis and expediting drug development–reality, aspiration and the role of open innovation. J Intern Med 276(3):215–228

Saxena N, Taneja N, Shome P, Mani S (2018) Mitochondrial donation: a boon or curse for the treatment of incurable mitochondrial diseases. J Hum Reprod Sci 11(1):3–9

Scannell JW, Blanckley A, Boldon H, Warrington B (2012) Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov 11(3):191–200

Schukur L, Geering B, Charpin-El Hamri G, Fussenegger M (2015) Implantable synthetic cytokine converter cells with AND-gate logic treat experimental psoriasis. Sci Transl Med 7(318):318ra201

Schwaederle M, Zhao M, Lee JJ, Eggermont AM, Schilsky RL, Mendelsohn J et al (2015) Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. J Clin Oncol 33(32):3817

Schwaederle M, Zhao M, Lee JJ, Lazar V, Leyland-Jones B, Schilsky RL et al (2016) Association of biomarker-based treatment strategies with response rates and progression-free survival in refractory malignant neoplasms: a meta-analysis. JAMA Oncol 2(11):1452–1459

Severino PF, Silva M, Carrascal M, Malagolini N, Chiricolo M, Venturi G et al (2017) Expression of sialyl-Tn sugar antigen in bladder cancer cells affects response to Bacillus Calmette Guérin (BCG) and to oxidative damage. Oncotarget 8(33):54506

Seys SF, Quirce S, Agache I, Akdis CA, Alvaro-Lozano M, Antolín-Amérigo D et al (2019) Severe asthma: Entering an era of new concepts and emerging therapies: highlights of the 4th international severe asthma forum, Madrid, 2018. Allergy 74(11):2244–2248

Shinagawa T, Tanaka T, Nozawa H, Emoto S, Murono K, Kaneko M et al (2018) Comparison of the guidelines for colorectal cancer in Japan, the USA and Europe. Ann Gastroenterol Surg 2(1):6–12

Shustik J, Han G, Farinha P, Johnson NA, Neriah SB, Connors JM et al (2010) Correlations between BCL6 rearrangement and outcome in patients with diffuse large B-cell lymphoma treated with CHOP or R-CHOP. Haematologica 95(1):96

Siddiqui WA, Ahad A, Ahsan H (2015) The mystery of BCL2 family: Bcl-2 proteins and apoptosis: an update. Arch Toxicol 89(3):289–317

Ślusarczyk A, Zapała P, Zapała Ł, Piecha T, Radziszewski P (2019) Prediction of BCG responses in non-muscle-invasive bladder cancer in the era of novel immunotherapeutics. Int Urol Nephrol 51(7):1089–1099

Stephenson D, Sauer J-M (2014) The predictive safety testing consortium and the coalition against major diseases. Nat Rev Drug Discov 13(11):793–794

Stiell IG, Clement CM, McKnight RD, Brison R, Schull MJ, Rowe BH et al (2003) The Canadian C-spine rule versus the NEXUS low-risk criteria in patients with trauma. N Engl J Med 349(26):2510–2518

Sun Y, Soh S (2015) Printing tablets with fully customizable release profiles for personalized medicine. Adv Mater 27(47):7847–7853

Surguladze D, Pennello A, Ren X, Mack T, Rigby A, Balderes P et al (2019) LY3076226, a novel anti-FGFR3 antibody drug conjugate exhibits potent and durable anti-tumor activity in tumor models harboring FGFR3 mutations or fusions. AACR

Sze E, Bhalla A, Nair P (2020) Mechanisms and therapeutic strategies for non-T2 asthma. Allergy 75(2):311–325

Thomas PS, Lowe A, Samarasinghe P, Lodge CJ, Huang Y, Abramson MJ et al (2013) Exhaled breath condensate in pediatric asthma: promising new advance or pouring cold water on a lot of hot air? A systematic review. Pediatr Pulmonol 48(5):419–442

Tie J, Lipton L, Desai J, Gibbs P, Jorissen RN, Christie M et al (2011) KRAS mutation is associated with lung metastasis in patients with curatively resected colorectal cancer. Clin Cancer Res 17(5):1122–1130

Tilly H, Da Silva MG, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A et al (2015) Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 26:v116–vv25

Toll A, Margalef P, Masferrer E, Ferrándiz-Pulido C, Gimeno J, Pujol RM et al (2015) Active nuclear IKK correlates with metastatic risk in cutaneous squamous cell carcinoma. Arch Dermatol Res 307(8):721–729

Tsuchida N, Murugan AK, Grieco M (2016) Kirsten Ras oncogene: significance of its discovery in human cancer research. Oncotarget 7(29):46717

Vegas AJ, Veiseh O, Doloff JC, Ma M, Tam HH, Bratlie K et al (2016a) Combinatorial hydrogel library enables identification of materials that mitigate the foreign body response in primates. Nat Biotechnol 34(3):345–352

Vegas AJ, Veiseh O, Gürtler M, Millman JR, Pagliuca FW, Bader AR et al (2016b) Long-term glycemic control using polymer-encapsulated human stem cell–derived beta cells in immune-competent mice. Nat Med 22(3):306

Venderbosch S, Nagtegaal ID, Maughan TS, Smith CG, Cheadle JP, Fisher D et al (2014) Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res 20(20):5322–5330

Vrzalikova K, Vockerodt M, Leonard S, Bell A, Wei W, Schrader A et al (2011) Down-regulation of BLIMP1α by the EBV oncogene, LMP-1, disrupts the plasma cell differentiation program and prevents viral replication in B cells: implications for the pathogenesis of EBV-associated B-cell lymphomas. Blood 117(22):5907–5917

Wagner SD, Ahearne M, Ferrigno PK (2011) The role of BCL6 in lymphomas and routes to therapy. Br J Haematol 152(1):3–12

Wang Z, Wang F, Wang C, Zhang J, Wang H, Shi L et al (2021) A Bayesian decision-theoretic design for simultaneous biomarker-based subgroup selection and efficacy evaluation. Stat Biopharm Res:1–24

Wholley D (2014) The biomarkers consortium. Nat Rev Drug Discov 13(11):791–792. https://doi.org/10.1038/nrd4439

Ye BH (2000) BCL-6 in the pathogenesis of non-Hodgkin's lymphoma. Cancer Invest 18(4):356–365

Ying CY, Dominguez-Sola D, Fabi M, Lorenz IC, Hussein S, Bansal M et al (2013) MEF2B mutations lead to deregulated expression of the oncogene BCL6 in diffuse large B cell lymphoma. Nat Immunol 14(10):1084–1092

Yokota T, Ura T, Shibata N, Takahari D, Shitara K, Nomura M et al (2011) BRAF mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. Br J Cancer 104(5):856–862

Young RM, Shaffer AL III, Phelan JD, Staudt LM (2015) B-cell receptor signaling in diffuse large B-cell lymphoma. Semin Hematol 52(2):77–85

Zachos JC, Röhl U, Schellenberg SA, Sluijs A, Hodell DA, Kelly DC et al (2005) Rapid acidification of the ocean during the Paleocene-Eocene thermal maximum. Science 308(5728):1611–1615

Zhang B, Calado DP, Wang Z, Fröhler S, Köchert K, Qian Y et al (2015) An oncogenic role for alternative NF-κB signaling in DLBCL revealed upon deregulated BCL6 expression. Cell Rep 11(5):715–726

Zhang M, Xu-Monette ZY, Li L, Manyam GC, Visco C, Tzankov A et al (2016) RelA NF-κB subunit activation as a therapeutic target in diffuse large B-cell lymphoma. Aging (Albany NY) 8(12):3321

Zhou K, Xu D, Cao Y, Wang J, Yang Y, Huang M (2014) C-MYC aberrations as prognostic factors in diffuse large B-cell lymphoma: a meta-analysis of epidemiological studies. PLoS One 9(4): e95020

Zlotta AR, Fleshner NE, Jewett MA (2009) The management of BCG failure in non-muscle-invasive bladder cancer: an update. Can Urol Assoc J 3(6 Suppl 4):S199