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Targeted drug delivery strategies for precision medicines

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Abstract

Progress in the field of precision medicine has changed the landscape of cancer therapy. Precision medicine is propelled by technologies that enable molecular profiling, genomic analysis, and optimized drug design to tailor treatments for individual patients. Although precision medicines have resulted in some clinical successes, the use of many potential therapeutics has been hindered by pharmacological issues, including toxicities and drug resistance. Drug delivery materials and approaches have now advanced to a point where they can enable the modulation of a drug's pharmacological parameters without compromising the desired effect on molecular targets. Specifically, they can modulate a drug's pharmacokinetics, stability, absorption, and exposure to tumours and healthy tissues, and facilitate the administration of synergistic drug combinations. This Review highlights recent progress in precision therapeutics and drug delivery, and identifies

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Competing interests statement

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opportunities for strategies to improve the therapeutic index of cancer drugs, and consequently, clinical outcomes.

Introduction

Recent advances in the genetic understanding of cancers, gene sequencing and bioinformatics, and their application to pharmacology and drug development have led to the emergence of precision medicine. The central principle of precision medicine is that genetic, environmental, and lifestyle characteristics can be used to identify the optimal treatment strategy for each individual patient. Despite the powerful promise of this approach in clinical oncology, translation has been hindered by several issues, including drug toxicities and resistance. These issues can be mitigated by strategically designed materials for improved drug delivery.

This Review highlights recent progress in the emerging field of precision medicine, elucidates limitations of current strategies, and presents potential solutions using materials and drug delivery applications. We propose that the integration of the fields of materials science and cancer biology can translate to improved patient outcomes. Incorporating drug delivery strategies into drug development processes may facilitate the development of improved therapies. Specifically, an anti-cancer drug could then successfully reach the tumour at therapeutic doses, engage its target to actively inhibit a pro-oncogenic cellular mechanism, and avoid effects in healthy tissues that may result in dose-limiting toxicities.

To orient the reader to the contents of this Review, we first define its scope. The largest class of precision medicines inhibits enzymes — usually kinases — that are positioned in critical nodes of signalling pathways. This Review is primarily focused on this class of precision medicines, as a model for integrating targeted drugs with targeted drug delivery systems. We provide an in-depth discussion of the limitations of these agents. Although we primarily focus on kinase inhibitors, we will also briefly introduce other classes of drugs, such as monoclonal antibodies, nucleic acid-based therapies, and immunotherapies. The molecular properties of these other therapies can benefit from unique and important delivery approaches, which we discuss. This is not intended as a comprehensive review of kinase inhibitor therapies, other precision medicines, or drug delivery systems; excellent reviews have been published on each of these topics[1–3]. Our aims are to elucidate the major areas of improvement for precision medicines and how these can be addressed by drug delivery systems. We will highlight the translational value of integrative research that connects drug delivery to precision medicine.

Kinase inhibitors

Covalent phosphorylation and dephosphorylation of serine, threonine, or tyrosine residues in proteins are key enzymatic processes that modulate protein function in cells. Protein kinases — a class of enzymes that phosphorylate proteins — are integral components of cell-signalling networks, and regulate cell growth, differentiation, proliferation, survival, and apoptosis[4]. Many oncogenes encode mutant tyrosine kinases that are dysregulated or hyperactivated, and cause unregulated cell proliferation and invasion. With more than

500 kinases encoded in the human genome, there is potential to leverage kinase-targeted precision drugs for new or improved therapy[5]. Over the past 20 years, this class of proteins has been the focus of significant research effort, which has led to the U.S Food and Drug Administration (FDA) approval of more than 50 small-molecule protein kinase inhibitors to date[6]. Although a small subset of these approved inhibitors is used to treat non-malignancies, such as rheumatoid arthritis, the majority has been developed as targeted cancer therapeutics.

Kinase inhibitors in oncology—Kinase inhibitors are the largest class of precision medicines, because the transfer of phosphates is involved in all signal-transduction processes. Aberrant kinase signalling can thus cause oncogenesis in numerous contexts. Here, we provide a brief description of the main subclasses of kinase inhibitors to provide an overview of the landscape of these drugs; a much more comprehensive review of kinase inhibitors has been recently published elsewhere[5].

Proto-oncogenes drive uncontrolled cell proliferation and promote tumourigenesis. Thus, targeting the kinase protein products of these genes with kinase inhibitors can be a potent therapeutic strategy. Imatinib was the first kinase inhibitor that was approved by the FDA. This binds to BCR-Abl — a protein encoded by the proto-oncogene breakpoint cluster region protein fusion to Abelson murine leukemia (ABL) tyrosine kinase ABL1 (BCR-ABL) — resulting from a mutation formed by the combination of the BCR and ABL genes. Since its approval in 2001, imatinib's success in treatment of chronic myeloid leukaemia prompted the development of new kinase inhibitors[5]. For example, a targeted inhibitor of lipid kinase phosphoinositide 3-kinase catalytic subunit-α (PIK3α), alpelisib has been approved for breast cancer. Proto-oncogene mitogen-activated protein kinase (MAPK) is another key target for inhibitor development, because the MAPK pathway is crucial for regulating cell growth, and increased activity of proteins in this pathway is a hallmark of many tumours[7]. Pharmacological interest in the pathway has focused on developing inhibitors of receptor tyrosine kinases (RTKs), B-rapidly accelerated fibrosarcoma (BRAF), and mitogen-activated protein kinase kinase (MEK), among other related proteins[8].

The most predominant subclass of the kinase inhibitors is those that target RTKs. Imatinib, which is specific for a tyrosine kinase domain in Bcr-Abl, can also inhibit RTKs c-KIT and platelet-derived growth factor receptor (PDGFR)[4]. Other examples of kinase inhibitors that target RTKs include gefitinib (an epidermal growth factor receptor (EGFR) inhibitor approved in 2003 for non-small cell lung cancer), and regorafenib (an inhibitor of vascular endothelial growth factor receptor (VEGFR) approved for colorectal cancer in 2012)[5]. The TAM (that is, TYRO3, AXL, and MER) class of RTKs is involved in immune system regulation, especially inflammation, identification of apoptosis, and phagocytosis. TAM blockade can reverse tyrosine kinase inhibitor (TKI)-induced acquired clinical resistance, making this a powerful strategy for combination therapy.

Transcription-associated kinases, such as cyclin-dependent kinases (CDKs), are a powerful class of targets for treatment of malignancies, because CDK hyperactivity is a common mechanism of tumourigenesis. This is especially true for breast cancer cells, which can be arrested in the G1 cell cycle phase upon treatment with CDK4 and CDK6 inhibitors.

Abemaciclib — a CDK4/6 inhibitor — has been approved for combination therapy in advanced hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer[6]. However, the profiles of these drugs must be improved to minimize toxicity and therapeutic resistance. In the next subsection, we provide an overview of the limitations of kinase inhibitors and potential solutions using drug delivery and materials-based strategies.

Opportunities for drug delivery—Targeted drugs exhibit diverse toxicities. Although such side effects can sometimes be mitigated by supplementary medicines, this often results in a narrow therapeutic window, lowering the potential efficacy. Kinase inhibitors can affect one or more major organ or organ system through on-target toxicity, off-target toxicity, and other pharmacological limitations. The organ(s) in which side effects occur can be the same or different from the organ from which the primary tumour originates.

Drug delivery strategies may improve the pharmacological properties (including the pharmacokinetics and biodistribution) of kinase inhibitors by modulating several factors. The key in the design of a targeted drug carrier is knowledge of the specific drug's main problems, which may include its pharmacokinetics, biodistribution, on-target toxicities, off-target toxicities (especially dose-limiting toxicities), and drug resistance.

To address pharmacological issues, over the past several decades, nanoscale systems have been developed to modulate the pharmacological properties of cancer drugs. In 1995, the FDA approved the first nanoparticle drug formulation, Doxil, which is composed of liposomes containing the chemotherapeutic drug doxorubicin[9]. This demonstrated the importance of improving pharmacokinetic and biodistribution properties of chemotherapeutics to reduce toxicity: the cardiotoxicity of free doxorubicin results in cardiomyopathy, whereas administration of a passively targeted liposomal formulation mitigates toxicity, preventing negative effects on the heart. In addition to liposomes, other types of drug carriers have been developed, including polymeric nanoparticles, polymer conjugates (that is, dendrimers), silica carriers, gold nanoparticles or nanoshells, and carbon-based nanostructures (Table 1). These and other materials can be used to physically encapsulate, adsorb, or chemically conjugate small-molecule drugs or macromolecules. The drug loading efficiency of nanocarriers, which is defined as the fraction of drug in the total particle mass, is highly dependent on the nature of the specific nanocarrier and drug. Most nanoparticles currently exhibit relatively low drug-loading efficiencies[10], although new and improved approaches are underway (Figure 3)[11–13].

Nanomedicine for small-molecule therapeutics has focused on the encapsulation and delivery of chemotherapeutic drugs, such as paclitaxel and doxorubicin, to tumours. In particular, there has been an emphasis on engineering nanocarriers for improved localization. However, there is an urgent need to expand the set of targeted drugs, which is where precision medicine can have a crucial role. In the following subsections, we provide a discussion of specific key limitations of precision drugs and match each limitation to a potential delivery solution. Also importantly, even with the most effective drug delivery system, monotherapies rarely have lasting efficacy for cancer treatment. The need for potent

drug combinations results from a nearly inevitable tendency of cancer to return or develop resistance over time.

Dose-limiting toxicities: The severity of some side effects can prevent treatment of patients at efficacious doses. Such dose-limiting toxicities can hinder the utility of potent anti-cancer therapies, including kinase inhibitors. Examples of dose-limiting toxicities of kinase inhibitors include skin rash (MEK inhibitors), hyperglycaemia (phosphoinositide 3-kinase catalytic subunit alpha (PI3Kα) inhibitors), and haematologic toxicities (Abelson murine leukaemia viral oncogene (ABL) kinase inhibitors) (Figure 1, Table 1). In many contexts, dose-limiting toxicities are experienced in a subset of patients, resulting in broad adjustment of the drug dose for all patients. For example, high doses of LY2606368 — an inhibitor of checkpoint kinase 1 (CHK1) — result in neutropenia, which can cause dangerous susceptibility to infections[14]. In a phase I clinical study of LY2606368, seven of 45 patients experienced dose-limiting toxicity when treated at doses of 120 mg m^{-2} or higher. Thus, the recommended dose for the phase II trial was lowered to 105 mg m^{-2}. However, a lower dose may result in a limited degree of efficacy in different patients. Therefore, in the interest of developing the most efficacious treatment plans, it will be highly beneficial to formulate the drug to improve safety prior to determining the maximum tolerated dose[14]. This concept is also important for development of combination therapies, as most monotherapies are rarely effective long-term, and the use of materials and drug-delivery methods can improve the potential for avoiding additive dose-limiting toxicities of more than one drug. For example, in a recent phase 1B clinical study, a combination of FAK and MEK inhibitors (GSK2256098 and trametinib, respectively) required dose de-escalation[15]. Although the maximum tolerated dose of each drug alone had been established, the combination therapy required significant dose adjustment owing to side effects, such as neutropenia (which is immunocompromising) and thrombocytopenia (which can increase the risk of bleeding).

In addition to target specificity, consistent target engagement is important in cancer treatment. Induction of apoptosis and subsequent cancer cell death often require continuous target engagement. Thus, precision medicines are administered chronically until disease progression is observed, rather than by a predetermined schedule of cycles, as with conventional chemotherapies. Because of this relatively constant dosing, persistent low-grade toxicities must be considered in addition to the acute and severe toxicities that are measured for more traditional chemotherapeutic agents[16]. The new challenges have led to a wide range of dose-limiting toxicities identified in phase I trials of the targeted therapies, as they are based on the extrapolated safety profile of the study agents[17]. The need for alternative or complementary strategies to define dose-limiting toxicities is evident, as the FDA has requested dose-optimization as post-marketing requirements or commitments for many recent oncology drug applications.

Current efforts to ameliorate side effects of kinase inhibitors focus primarily on creative dosing schedules and optimized patient selection[18, 19]. Although these efforts are useful, they cannot overcome the inevitable limitations of poor drug delivery to the site of disease. In this Review, we urge pharmacologists and cancer biologists to leverage the vast options available in the field of drug delivery to remove the barriers to clinical success.

On-target and off-target toxicity: Both on-target and off-target toxicities can be dose-limiting. On-target toxicity is defined as toxic side effects that occur as a result of the drug successfully engaging its intended protein target, but in healthy tissue. By contrast, off-target toxicity results from poor target specificity, in which the drug interacts with unintended protein targets in diseased and/or healthy tissue. Cancer nanomedicine may improve the therapeutic index of drugs that demonstrate either of these toxicity profiles. Specifically, nanoparticle formulations enable active targeting of the encapsulated drug to the tumour site and malignant cells, avoiding detrimental drug activity in normal tissue and other organs. These concepts are discussed below.

On-target toxicities of kinase inhibitors occur when the drug affects the correct molecular target, but in the wrong context (that is, in non-cancerous cells). An example is mucositis — a painful inflammation and ulceration of the mucous membranes of the digestive tract, which results from treatment with analogues of mTOR (mammalian target of rapamycin) inhibitor rapamycin[25]. MEK inhibitors, which often exhibit specificity to the MAPK signalling pathway, can cause skin rash owing to inhibition of the pathway in normal skin cells[26]. This side effect and those involving ocular issues such as retinopathy can often be dose-limiting for this class of drugs[27]. Another example involves PI3K or AKT (protein kinase B) inhibitors, which cause hyperglycaemia in many patients owing to on-target toxicity that affects the insulin-signalling pathway[28]. TKIs that prevent angiogenesis in tumours by inhibiting VEGF receptors (VEGFR) have on-target toxic effects[29]. For example, inhibition of VEGFR leads to the decreased secretion of vasodilators from the vascular endothelium, which in turn leads to hypertension[30]. VEGFR inhibitors sorafenib and sunitinib carry a threefold increased risk of thrombotic events compared with control patients, and the on-target effect on VEGF inhibits its ability to maintain endothelial integrity[31]. Other classes of kinase inhibitors with demonstrable on-target toxicity are CDK and TRK inhibitors[31, 32].

Off-target toxicities of kinase inhibitors occur upon drug binding to different members of the same family of kinases or different classes of kinases[33]. For example, sorafenib targets at least nine different tyrosine kinases, including VEGFR, PDGFR, and Raf family kinases. Sorafenib, which is used in the treatment of metastatic renal cell carcinoma and hepatocellular cancer, shows wide-ranging toxicities that affect several organ systems. Sunitinib — another pan-kinase inhibitor — prolongs survival in patients with renal cell carcinoma, gastrointestinal stromal tumours, and other solid tumours. However, its off-target inhibition of 5′ adenosine monophosphate-activated protein kinase (AMPK) causes myocyte loss and ATP depletion, resulting in cardiotoxicity[34]. JNK (c-Jun N-terminal kinases) inhibitor SP600125 also binds to proteins involved in the PI3K/S6 pathway, which can potentially affect its efficacy and toxicity profile[35]. Aurora B kinase inhibitors are another example of drugs characterized by a poor safety profile at effective doses and potential off-target toxicity[36].

An interesting example of off-target toxicity is that of a non-kinase inhibitor, navitoclax, which inhibits the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2). Navitoclax was originally designed for B-cell lymphoma, but its clinical development was halted owing to inhibition of B-cell lymphoma-extra large (Bcl-xl) and induced myeloid leukaemia cell

differentiation protein (MCL-1) which resulted in thrombocytopenia (that is, abnormally low platelet levels)[37]. Subsequently, venetoclax — a derivative of navitoclax — was designed for improved Bcl-2 specificity. Venetoclax has proved much safer, and is now approved for treatment of several cancer types, including chronic lymphocytic leukaemia[38]. This example supports the idea that improved specificity is crucial for mitigating off-target toxicity. By contrast, on-target toxicity, which is especially prevalent with combination therapies, may be addressed with drug delivery strategies, such as nanoparticle or biomaterials systems.

Drug delivery solutions for mitigating toxicity: By developing drug delivery vehicles, researchers have improved the toxicity profiles of many drugs. Nanoparticle formulations enable packaging of low molecular-weight therapeutic cargo into carriers ranging from 10 to >100 nm in diameter (Table 2). The large size of the nanoparticles (relative to the free drug) reduces diffusion and extravasation across intact vasculature, thereby decreasing general systemic exposure and toxicity[39]. As mentioned in previous sections, liposomal and other drug formulations have been used to reduce systemic exposure. The following examples provide insights into more recent efforts to improve drug delivery and overcome on- and off-target toxicity of kinase inhibitors.

The aurora B kinase inhibitor AZD2811 can cause myelosuppression, which lowers the maximum tolerated dose, and thus limits efficacy. It has not been well-tolerated at effective doses in clinical trials[22]. An approach to improve delivery of AZD2811 encapsulated the drug in polymeric nanoparticles, termed Accurins, composed of poly-D,L-lactide (PLA) and poly(ethylene glycol) (PEG) block copolymers[23]. A diverse library of Accurins were developed through an ion pairing approach in which organic acid counterions were used to increase encapsulation efficiency and decrease rate of release of AZD2811 from the nanoparticles. The nanoformulation was optimized to control the release of AZD2811 over more than 1 week, resulting in prolonged target inhibition in tumour tissue and improved preclinical efficacy. This approach takes advantage of the effects of short- and long-term exposure of tumour cells to Aurora B kinase inhibitors. Whereas short-term exposure leads to cell cytostasis, prolonged inhibition forces cells into mitotic catastrophe, leading to cell death[40]. A phase I trial found that these nanoparticles had a favourable safety profile in patients with solid tumours. Specifically, the active targeting element improved tumour specificity of the drug localization, improving the toxicity profile of the drug and minimizing bone marrow toxicity[24].

Drug carriers can confer ‘stealthy’ properties to the drug, protecting it from interacting with proteins, and prolonging its bioactivity and circulation time. Stealthy, slow-release formulations, such as the aforementioned Aurora B kinase nanoparticles, are useful in preventing on-target toxicity. However, active targeting of the nanoparticle can further mitigate drug accumulation and on-target toxicity in healthy tissues. In one such example, a drug delivery system was developed to direct kinase inhibitors to tumours using P-selectin as a target on the tumour endothelium[41]. P-selectin is expressed on stress-activated vasculature (for example, tumour vasculature), stroma, and some cancer cells, and its expression can be upregulated by radiotherapy. P-selectin-targeted nanoparticles were synthesized using the polysaccharide fucoidan, which exhibits nanomolar affinity to P-selectin[42]. The nanoparticles were used to deliver the MEK inhibitor MEK163 to colorectal tumours in

murine xenograft models. This strategy facilitated target inhibition in the tumour while preventing drug accumulation in the skin, which is a common site of drug toxicity for this class of drugs, thus improving the therapeutic index.

The P-selectin targeting nanoparticle strategy was also used to deliver the PI3Kα inhibitor alpelisib in head and neck squamous cell carcinoma (HNSCC) models[43]. In this case, radiotherapy increased P-selectin expression and nanoparticle localization in the tumour. The combination treatment improved efficacy and abrogated the hyperglycaemia that is typically seen upon treatment with the free drug. The nanoparticle also enhanced the known radio-sensitization effects of the drug[44, 45]. Moreover, the combined treatment achieved durable responses in HNSCC patient-derived xenograft models.

Other than the aforementioned examples, few published preclinical studies have focused on the nanomedicine-based delivery of small-molecule precision drugs.

Other pharmacological limitations of kinase inhibitors: The pharmacological parameters of orally available small-molecule kinase inhibitors for targeted therapy range widely[46]. For example, the dosages can range from as little as 2 mg day^{-1} (trametinib) to almost 2,000 mg day^{-1} (vemurafenib) with a median of 250 mg day^{-1}. This reflects the large differences in their absorption, protein binding, pharmacodynamics and/or pharmacokinetics (Figure 2). Orally available targeted therapeutics with high rates of target protein binding (low dissociation constant, K_d), are efficiently distributed within most tissues. These parameters often lead to a large volume of distribution (that is, the theoretical fluid volume that would be required to contain the amount of drug present in the body at the same concentration as in the plasma) and a relatively long terminal half-life (that is, the time required to reach half the plasma concentration after reaching pseudo-equilibrium)[47]. The half-lives of about 25% of 41 listed drugs are 10 hours or less, and about 50% have half-lives of 24 hours or more. The data for some of these drugs are provided in Supplementary Table 1. In particular, vismodegib, vandetanib and sonidegib have remarkably long half-lives of 12, 19 and 28 days, respectively[78-]. Most inhibitors reach peak plasma concentration within 3–4 hours, with absolute bioavailability between 30–70%. Drugs that have very low absorption or short half-lives usually require higher and/or more frequent dosing. For example, lapatinib has only 20% absorption and a recommended dose of 1,200 mg per day, and vemurafinib has a 4-hour half-life and is often administered at 1,920 mg per day[48,49]. At the other extreme, the relatively long half-lives of some of these drugs can lead to difficulties in managing toxicities.

Kinase inhibitors can still be present at active concentrations in cells after they have been cleared from plasma, leading to adverse effects. For example, BCR-ABL- and JAK2 (Janus kinase 2 gene)-transformed cells can undergo apoptosis through prolonged intracellular drug accumulation and retention upon high-dose, pulsatile exposure[50–52]. Intracellular accumulation of kinase inhibitor may be quantified by direct drug detection and functional readouts. The potential for such accumulation should be considered when testing different dosing strategies (such as high-dose pulse, low-dose continuous or medium-dose intermittent) in clinical trials to find the most effective regimen[51]. Although this temporal dosing modulation has been studied mainly with small-molecule inhibitors in

haematological cancers (with BCR-ABL, JAK2, STAT3 and FLT3 mutations), recent studies suggest this type of strategy can enhance efficacy in other tumour types.

Nanoparticle targeting and formulations: Drug pharmacokinetics and biodistribution can be modulated by chemically modifying the chemical structure of the drug itself or by changing its formulation (Figure 3). Formulations are conventionally developed to solubilize drugs or improve bioavailability[53]. Nanoparticle formulations can be additionally used to substantially modulate many aspects of a drug including absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox)[54], which include but go beyond drug pharmacokinetic.

Three main strategies to localize nanoparticles to tumours involve[55]: passive accumulation into tumours via leaky vasculature; incorporation of targeting moieties for binding to cancer cells; and targeting nanoparticles to endothelial cells, stromal cells, macrophages or other immune cell types in the tumour microenvironment (Figure 4)[56].

Passive targeting: The size, charge, geometry, and composition of nanoparticles affect their localization, cell penetration, and rate of payload release. Optimization of these parameters helps to maximize efficacy and mitigate the toxicity of the payload[57]. Nanoparticle accumulation in the tumour microenvironment is attributed to passive extravasation by the enhanced permeation and retention (EPR) effect. This phenomenon is a consequence of angiogenesis of disordered, discontinuous, and highly fenestrated vessels in the tumour microenvironment[58]. Irregularities in the tumour vasculature, especially in fast-growing tumours, increase the permeability for macromolecules and nanomaterials relative to healthy tissue. In nearly all mouse tumour models, which are typically fast-growing tumours, nanoparticles preferentially localize to tumours as a result of leaky vasculature[59]. Although the EPR effect has been reported in humans, it has not been fully characterized across tumour types[3]. It may be possible, however, to determine vascular permeability prior to treatment to assess a patient's suitability for a nanoparticle therapy[60]. Leaky vasculature was cited as the mechanism by which a lipid nanoparticle formulation of cisplatin was attained 10- to 200-fold increased drug concentration in tumours during a phase I clinical trial[61]. These findings suggest that the EPR effect may be strategically used in clinical nanomedicine efforts going forward.

Targeting to specific organs: The physical and chemical properties of nanoparticles can be modulated to target them to specific organs and tissues(Figure 5)[62]. Delivery strategies involve localization of a therapeutic molecule to a specific organ[1,63,64,65,66,67,68–72,73]. Modulating the size and/or charge of nanoparticles can change the biodistribution to liver, spleen, lungs, or heart[74, 75]. Coating nanoparticles with ligands can also modulate biodistribution towards a specific organ. For example, galactose is used as a targeting ligand to bind to the asialoglycoprotein receptor, which is exclusively expressed in hepatocytes[76]. Other examples are vascular protein CD31/PECAM-1[77] to target the lungs[78] and brain[79], and bisphosphonates to target bone tissue[66]. Strategies can also involve different routes of administration or a complementary device. Examples of such strategies include nasal delivery using a nebulizer or atomizer to target the lungs[80], focused ultrasound with

microbubbles for intracranial delivery[81], and microneedle patches for delivery to or via the skin[82].

Active targeting of tumours: The development of nanoparticles modified to localize and be retained in disease microenvironments is often referred to as active targeting. Active targeting of nanoparticle drug carriers to cancer cells involves the functionalization or decoration of particles with targeting moieties to promote internalization into tumour cells and the surrounding microenvironment. Some of the most studied targets for nanomedicines include the transferrin receptor, folate receptor, cell surface glycoproteins, and epidermal growth factor receptor (EGFR)[39]. This cellular targeting strategy likely relies on the EPR effect for nanoparticle extravasation into the tumour microenvironment. For a comprehensive review of nanoscale drug delivery systems, see Ref. [83]. A summary and classification of these systems is provided in Table 2.

Active targeting to vasculature and integrins: The active targeting of nanoparticles to molecular targets on the tumour vasculature has been used as a strategy to improve drug localization in the tumour microenvironment. For example, molecular targets on tumours have included integrins, PSMA[84], platelet endothelial cell adhesion molecule (PECAM-1)[79], VEGFR[85, 86], caveolae[87], P-selectin[41] and E-selectin[88].

Neovasculature, which develops in response to tumour growth, often expresses new targets, such as PSMA, on its luminal surface. Several nanoparticle therapeutics target small-molecule drugs to PSMA-expressing tumour endothelium. To achieve this, drug carriers can be conjugated to antibodies[84] or small-molecule agents that bind to PSMA. Examples include polymer nanoparticles encapsulating docetaxel, as well as aurora B kinase inhibitor, as mentioned earlier[23, 84].

In addition to PSMA, selectins can be expressed on vasculature that becomes activated by immunostimulatory events and inflammation (such as in the cancer microenvironment or in response to ionizing radiation). Selectins appearing on the endothelial cells include E-selectin and P-selectin, which have been used to target both cytotoxic drugs and kinase inhibitors in pre-clinical studies[41, 88, 89].

Integrins are commonly used targets for tumour specificity of nanoparticles. Integrins are transmembrane glycoproteins involved in interactions of cells with other cells or with the extracellular matrix[90]. They are actively expressed on surfaces of vascular endothelial cells and have an important role in angiogenesis, leucocyte migration and tumour metastasis. Integrins are therefore attractive targets for delivering drugs for treatment of inflammatory diseases and cancer. For example, peptide sequences with the arginine-glycine-aspartic acid (RGD) motif have a strong affinity for integrins, particularly $\alpha v\beta 3$. RGD has been studied extensively at the pre-clinical stage and incorporated in polymer–peptide–drug conjugates, nanoparticles, liposomes and drug–peptide conjugates[91–93].

Targeted delivery of kinase inhibitors to integrins has also been reported. For example, an RGD-bound albumin carrier was used to deliver a p38 MAPK inhibitor, SB202190 [92]. This carrier demonstrated high affinity and specificity to $\alpha v\beta 3$-integrin and was internalized upon

binding. The drug cargo was then released into the cell for interference in inflammatory signalling cascades. In another example, MEK1/2 inhibitor PD0325901 was conjugated to cyclic RGD via a cleavable ester bond for integrin-targeted anticancer therapy[93]. These constructs displayed more potent dose-dependent anti-proliferation activity in cell-based assays than PD0325901, demonstrating that RGD–MEK inhibitor conjugates with an ester bond linkage can improve the anti-tumour efficacy of MEK inhibitors.

Mechanisms of resistance to kinase inhibitors: Like all drugs, the activities of kinase inhibitors can be limited by acquired resistance in the treated cells. Negative molecular feedback is essential for regulation of the intricate signalling network of a cell, and the regulation of signalling cascades is essential for homeostasis. Tumour cells can hyperactivate oncogenic signalling cascades despite the presence of these regulatory mechanisms. The release of negative feedback, which can result from pharmacological stresses, may result in adaptive responses and the activation of compensatory pathways that counteract the therapeutic intervention, leading to drug resistance and disease relapse[94]. Many drugs and targets can result in the activation of compensatory pathways and feedback mechanisms (Table 3).

Durable responses to inhibitors of the MAPK–ERK and PI3K–AKT–mTOR signalling pathways have been challenging to achieve. This is, in part, because of the extensive cross-talk and compensatory feedback between these pathways. Inhibition of mTOR, for example, was shown to activate both pathways leading to activation of ERK[95] and increased phosphorylation of AKT[96]. Upregulation of MAPK signalling results in adaptive resistance to PI3K, AKT and mTOR inhibitors. By contrast, enhanced PI3K signalling increases resistance toward EGFR[97], BRAF[98], and MEK[99] inhibitors. PI3K signalling is another important factor in the maintenance of RAS-dependent lung tumours[100]; further interaction between these two pathways is required for RAS-dependent angiogenesis[101]. Combining drugs to induce co-suppression of the mTOR and MAPK/ERK pathways results in superior anti-tumour activity in tumour models.

Increased expression and/or phosphorylation of membrane-bound receptor tyrosine kinases (RTKs) in response to the inhibition of the downstream pathways are also common. In KRAS (Kirsten rat sarcoma viral oncogene homolog)-mutant lung cancer, treatment with the MEK inhibitor trametinib leads to a compensatory response involving the membrane-bound RTK fibroblast growth factor receptor 1 (FGFR1)[102]. This compensatory signalling rebound can induce drug resistance and must be suppressed for an optimal activity of trametinib. An example in breast cancers is the induction of HER3 expression upon inhibition of the PI3K–AKT pathway in HER2-positive tumours. Several laboratories have demonstrated that suppressing this signalling cascade (by either specific PI3K or AKT inhibitors [103–105] or by treatment with anti-HER2 agents such as lapatinib[106]) increases the levels of HER3 (and in some cases also other RTKs). This results in augmented dimerization with other members of the HER receptor family, which can boost the activation of downstream pathways. The activation of different RTKs in response to therapy likely depends both on the tumour type and the therapeutic agent. In triple-negative breast cancer, the inhibition of the PI3K–AKT pathway results in both HER3 and EGFR activation, and the simultaneous blockade of both receptors seems to be important for enhancing activity of PI3K or AKT inhibitors[107].

Negative feedback can also occur between two pathways with no intuitive interplay. Reciprocal regulation occurs between the PI3K–AKT–mTOR pathway and androgen or oestrogen receptor signalling. In prostate cancer models deficient for PTEN, RTK upregulation or activation in response to the inhibition of the PI3K–AKT–mTOR pathway can also induce androgen receptor-dependent transcription, which in turn may limit the efficacy of endocrine therapy[108]. By contrast, ablation of the androgen receptor reduces the levels of the AKT phosphatase PHLPP, leading to hyperactivation of the AKT–mTOR axis. Combined pharmacological blockade of PI3K and the androgen receptor is therefore necessary to elicit profound antitumour activity in these models. In breast cancer, inhibition of the PI3K–AKT–mTOR pathway rapidly induces oestrogen receptor-dependent transcription[109]. In this case, however, the mechanism of the reciprocal cross-talk is epigenetic and depends on the direct interaction and phosphorylation of the methyltransferase KMT2D by AKT[110]. In the presence of AKT inhibition, KMT2D is unphosphorylated (that is, active) and can open the chromatin, allowing the transcription machinery of the oestrogen receptor to bind to specific DNA regions. In addition, in this case, co-inhibition of PI3K and the oestrogen receptor leads to superior activity to single-agent therapy. Early clinical studies assessing the co-suppression of PI3K and the oestrogen receptor in oestrogen receptor-positive breast cancer showed promising activity in breast cancer patients bearing tumours with mutations in *PIK3CA* — the gene that codes the α-catalytic subunit of PI3K (p110α)[111, 112].

The combination of two drugs may target pathways that — if simultaneously suppressed — result in a synthetic lethal effect. This is the case, for example, for the co-inhibition of the PI3K[113] or MEK[114] pathways and poly(ADP-ribose) polymerase (PARP). Depending on the tumour type, either PI3K or MEK inhibition creates a defect in DNA repair, rendering tumour cells more sensitive to PARP inhibitors. In both cases (and in different tumour types), these combinations are strongly synergistic, and many patients have benefitted from these therapies.

Although drug combinations have the potential to improve patient outcomes by mitigating resistance, additive or synergistic toxicities can emerge. Drug delivery approaches, as outlined in the next subsection, can avoid such toxicities.

Combating resistance to kinase inhibitors: Resistance to kinase inhibitors can potentially be mitigated by concurrent inhibition of compensatory pathways or by combining pathway inhibitors with conventional chemotherapy[115, 116]. Combinatorial strategies involving two or more drugs can be designed to block specific proteins and pathways to further sensitize the inhibition of the original target. The main limitation for this approach is the emergence of adverse side effects, which is often due to on-target toxicities. Inhibiting two or more pathway effectors simultaneously may improve the antitumor activity of the treatment but, at the same time, increases the probability of perturbing the physiological steady state of non-tumour cells. In fact, the vast majority of the combination strategies mentioned above are subject to dose-limiting toxicities. Therefore, despite the strong rationale for their clinical testing, many patients have to discontinue the treatment even if benefiting from it.

In addition, synergistic compounds often have differing physiochemical properties (for example, size, charge, lipophilicity and stability), which hinders co-localization within tumour tissues. These limitations, in addition to those described above, preclude the use of many therapeutic combinations lt. Thus far, few targeted drug delivery approaches have been attempted to specifically improve the therapeutic index of drug combinations. We have provided a summary of all drugs that have been used in personalized nanomedicines to inhibit these particular pathways in Table 4, highlighting EGFR, VEGFRs, PDGFRs and mTOR specifically.

In one study, a tumour-targeting nanoscale drug formulation was used to block both MAPK and PI3K signalling to selectively inhibit disease progression in vitro and in breast tumour xenograft-bearing mice[117]. Layer-by-layer self-assembly of oppositely charged polymers was used to develop vehicles to co-deliver small-molecule inhibitors of MEK and PI3K. This led to a 3.9- and 9.4-fold reduction in tumour-specific MAPK and PI3K pathway signalling, respectively, with associated tumour apoptosis and disease stabilization. The strategy also reduced dose-limiting hepatotoxic effects when compared to the free drug combination. Mice receiving untargeted, but dual drug-loaded nanoscale formulations, exhibited slowed (albeit still progressive) disease compared to controls. In another study, polymeric nanoparticles were used to conduct time-staggered targeted inhibition of EGFR combined with doxorubicin[118]. Specifically, the nanoparticles first released erlotinib and later doxorubicin, exhibiting much stronger anti-tumour effects in a subset of triple-negative breast cancer cells in vivo than simultaneous co-administration[118].

Summary: kinase inhibitors—Kinase inhibitors and other small molecule inhibitors (such as androgen receptor inhibitors) have unique and outstanding challenges that have been unmet by conventional approaches such as medicinal chemistry. Other than the aforementioned examples, few published preclinical studies have focused on the nanomedicine-based delivery of small-molecule precision drugs. Problems include conventional pharmacokinetic issues as well as both on-target and off-target toxicities, and multiple drug resistance mechanisms. The abilities to improve therapeutic index and combine multiple small molecule precision drugs with minimal toxicities may substantially improve the utility of these drugs in patients.

Other classes of precision medicines

Nucleic acids and gene editing—Nucleic acids and gene editing technologies have therapeutic potential for the personalized treatment of cancer and other diseases. Despite promising in vitro studies, it remains challenging to deliver these macromolecules to their intended targets without significant off-target effects. A main limitation is inadequate or inefficient transport of large, fragile, and negatively charged molecules like many proteins, DNA, short interfering RNAs (siRNA), and microRNA (miRNA) to their respective targets[119]. Unmodified nucleic acids, when administered intravenously, are often cleaved by serum endonucleases and can activate innate immunity. In addition, nucleic acids must reach the cytoplasm or nucleus of diseased cells to find their targets. Transport of such agents to both the target cells and the target compartments of these cells is a significant challenge[120]. Protein absorption and phagocytosis by the mononuclear phagocyte sysstem and entrapment

in the reticuloendothelial system results in clearance through the hepatobiliary system, which most likely prevents localization at the therapeutic target.

In the 1990s, RNA interference (RNAi) by double-stranded RNA (dsRNA) was discovered in animals to cause greater suppression of gene expression than single-stranded RNA (ssRNA)[121], which led to studies into dsRNA-induced gene silencing in human cancer cells[122]. In recent years, RNAi has become an important tool for gene silencing and drug development. The design of siRNAs — the most commonly used RNAi tool — has resulted in effective inhibition of endogenous and heterologous gene expression; this has the potential to be applied to modulate gene expression related to many genetic diseases. Because siRNA acts on the post-translational level, it avoids the mutation and teratogenicity risks of gene therapy. In addition, siRNA efficiently suppresses gene expression with just several copies in a single cancer cell, and the choice of targets is unrestricted[123]. However, there are several known off-target effects of siRNA delivery: siRNAs and/or their delivery vehicles can cause an inflammatory response; siRNA can induce sequence-dependent regulation of unintended transcripts (microRNA-like off-target effects); and exogenous siRNAs can saturate the endogenous RNAi machinery, leading to widespread effects on microRNA processing and function[124]. In addition, siRNA is efficiently degraded and removed by glomerular filtration, resulting in a short plasma half-life of less than 10 minutes[125]. Drug delivery systems for RNAi must be carefully designed to address these problems.

New genome-editing technologies include zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and the CRISPR–Cas9 RNA-guided endonuclease technologies[126]. ZFN is an artificial endonuclease, which is engineered by fusing DNA-binding zinc-finger proteins to the FokI DNA-cleavage domain[127]. ZFNs can be potential therapeutic agents for human gene therapy, including cancer therapy[128]. The greatest limitation for ZFNs is their low targeting density and small number of sites that they can effectively and selectively target[129]. Some studies show the application of ZFNs using cationic liposomes in vitro[130], but there is limited research into in vivo delivery of ZFNs.

Like ZFNs, TALENs consist of a DNA-binding domain and a C-terminal FokI endonuclease cleavage domain. TALENs, however, have lower cytotoxicity[131], greater design flexibility leading to a [132], and are easier to construct. However, a disadvantage of TALENs is their large size, which makes it difficult to deliver them in vivo. This is especially the case when using traditional viral vectors, which can also result in unwanted recombination results. To improve delivery, TALEN plasmids have been complexed with a proprietary blend of cationic polymers to target human papillomavirus (HPV) infection and cervical cancer in mice, with reduction in viral load and tumour size[133]. Moreover, TALEN proteins, which are incapable of penetrating cellular membranes by themselves, have been fused with cationic and hydrophilic proteins to facilitate membrane penetration[134]. Another conjugated TALEN protein with poly-Arg9 peptides (R9CPP) was able to transfect and have efficacy at levels comparable to vector-based delivery[135], demonstrating that alternative drug delivery methods may reduce unwanted side effects.

CRISPR–Cas9 (clustered regularly interspaced short palindromic repeats–CRISPR-associated nuclease 9) is another RNA-guided genome editing tool that provides several advantages over ZFN and TALEN. CRISPR–Cas9 systems have been used for antivirus and antiproliferation effects in a HPV-positive cervical carcinoma cell line and an Epstein–Barr virus-positive lymphoma cell line[136]. As with other gene therapy applications, delivery and editing efficiency has been a limitation for CRISPR–Cas9 systems. Several methods have been used for delivering the CRISPR–Cas system in vivo. For example, adeno-associated viral vectors have been used, but their small cargo capacity has prompted the investigation of other viral vector technologies[137]. In general, to further improve the in vivo delivery and targeting of gene-editing technologies to desired tissues and disease sites, innovative solutions are needed.

Several systems have been developed to efficiently deliver nucleic acids to cells in vitro, but few have been successfully developed for clinical use. Thus far, approximately 70% of gene therapy clinical trials have used modified viruses to deliver nucleic acids. However, viral vectors have several disadvantages, which include carcinogenesis, immunogenicity, variable target specificity, high cost, and limitations on cargo size.

Nanoparticles have been investigated to improve some of the problems with viral delivery of nucleic acids. Synthetic carriers tend to exhibit less immunogenicity than viral vectors, and patients do not have pre-existing immunity to non-viral vehicles[138]. A limitation of non-viral vectors for RNA delivery has been the lower efficiency than viral vectors[139]. However, recent developments in new polymers and lipids as delivery vectors[140–142], and a better understanding of nanotechnology for nucleic acid delivery[143], have led to improvements in efficiency. Materials composed of ionizable cationic lipids[144], self-assembled polyelectrolyte complexes of dextran-siRNA conjugates linked by disulfide bonds[145], and pH-triggered amphiphilic poly-L-lysine nanocarriers of siRNA[146] have been developed. A lipid-based nanoparticle coated with anti-CD38 monoclonal antibody to target mantel cell lymphoma has also been described[147]. Moreover, lipid nanoparticle-formulated siRNA targeting VEGF and kinesin spindle protein (KSP) has shown efficacy and demonstrated safety in humans[148]. Nanoparticle delivery systems using cationic liposomes or polymers can also be used as non-viral alternative for ZFN delivery into cells, as the cationic charge of the particle is attracted to the anionic charge of cell membranes.

As mentioned above, alternative technologies are needed to translate CRISPR technology for clinical use. Initial results showing delivery of the Cas9 protein along with a guide RNA (sgRNA) in vivo have been reported. Examples of materials developed for this purpose that have shown in vivo efficacy lipid-based nanoparticles[149, 150151152153]; cell-penetrating peptides[154]; and 7C1 nanoparticles, which are nanoparticles synthesized via blending C15 epoxide-terminated lipids with low-molecular weight PEI[155]. A recent study successfully demonstrated CRISPR editing via delivery of Cas9/sgRNA in the liver and lungs of mice to generate tumor models[156].

Immuno-oncology drugs—Cancer immunotherapy harnesses the power of a patient's own immune response against cancer[157]. This approach has improved overall survival of patients, including those with advanced-stage cancers[3, 158]. Stimulation of the immune

system can promote a rapid response to target tumour antigens, lead to adaptive immunity against tumour cells and provide effective protection against disease relapse. Checkpoint inhibitors, such as anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and anti-PD-1 (programmed cell death protein 1) monoclonal antibodies, along with chimeric antigen receptor (CAR) T-cell therapy, have shown preclinical[159] and clinical efficacy in many cancer types[160]. Currently, cancer immunotherapy is effective in only a fraction of tumour diagnoses within most patient cohorts[161], and has produced side effects, known as immune-related adverse events (irAEs).

Several synergistic strategies have been developed in an effort to improve cancer immunotherapy. The introduction of immunostimulatory tumour-derived antigens or nucleic acids to antigen-presenting cells can synergize with checkpoint strategies in animal models[162]. However, this strategy may produce off-target immunostimulation. Further, it is only effective when these agents reach the correct subset of T-cells and enter the tumour microenvironment. In addition, concomitant administration of antineoplastic drugs, such as cytotoxic chemotherapies or kinase inhibitors may promote synergistic anti-tumour effects. However, these drugs can cause immunosuppression or other immunomodulatory effects that may affect the potency of immunotherapy.

Patients treated with ipilimumab — an anti-CTLA-4 mAb — have experienced significant adverse effects of immune modulation that required corticosteroid treatment and/or discontinuation of the therapy itself. Although most clinically moderate to severe irAEs are reversible with appropriate medical care, endocrinopathies, such as hypophysitis and thyroiditis, are frequently irreversible side effects of checkpoint blockade therapy that require chronic hormone replacement. Although PD-1 pathway blockade results in less common high-grade toxicities than anti-CTLA-4 treatment, pneumonitis and pulmonary toxicity remain as concerns for anti-PD-1 therapy. In particular, life-threatening pneumonitis requires cessation of therapy and corticosteroid treatment.

CAR T-cell therapy, which generates a strong immune-mediated antitumour response through the ex vivo engineering of T-cells, has been recently approved by the FDA to treat paediatric B-cell acute lymphoblastic leukaemia. Cytokine-release syndrome, an on-target side effect of CAR T-cell therapy, involves a rapid and massive release of cytokines, resulting in precipitous hypotension and dangerously high fevers. An off-target effect of B-cell aplasia has also been noted, which results in affected patients needing chronic immunoglobulin treatment. Finally, potentially fatal cerebral oedema, along with other reversible neurotoxicities, such as confusion and seizure, has been reported with CAR T-cell therapy.

To address these limitations of immunotherapies, nanoparticle systems have been used to deliver therapies to the target tissues, protect the drugs from degradation, and increase bioavailability. Such systems have been reviewed elsewhere[163–165]. We discuss a few examples below. For induction of tumour immunity, nanoparticle delivery systems have been used to deliver tumour-specific antigens to lymph nodes and the antigen-presenting cells[166–168]. In these cases, the nanoparticle delivery systems can protect tumour antigens from degradation within the body and enhance targeted delivery of the antigens to the

lymph nodes. Some ongoing investigations harness active targeting strategies by attaching biological or chemical ligands to the nanoparticle surface. Similarly, adjuvants, which promote anti-cancer immune responses, can be targeted to antigen-presenting cells, thus enhancing immunotherapeutic effects[169].

Materials-based approaches have also enabled the design of novel implantable immunotherapies. For example, injectable scaffolds have been developed to recruit immune cells and increase vaccine efficacy[170] and deliver neoantigens for personalized anti-cancer vaccines[171]. The latter vaccine is a modular mesoporous silica microrod combined with polyethyleneimine that assembles in less than 3 hours, can be stored before or after antigen addition, and is injected using standard needles. The vaccine has been shown to significantly enhance the anti-tumour response to checkpoint blockade[171].

Delivery technologies have been developed for targeting immunotherapies to the tumour microenvironment. For example, a nanoscale metal–organic framework was used in combination with radiotherapy–radiodynamic therapy and immunotherapy. The combination treatment reduced immunosuppression in the tumour microenvironment to improve immunotherapeutic effects[172]. Nanoparticle-based delivery of drugs that modulate the immunosuppressive properties of the tumour microenvironment has also been shown to regenerate immune regulation of tumour cells[173]. Recent work suggests that delivery of haematopoietic stem cells conjugated to anti-PD-1 antibody-decorated platelets can improve the efficacy of leukaemia therapy [157]. These examples highlight the effective use of delivery systems to improve and overcome the limitations of current immunotherapies.

Clinical trials

The use of drug delivery strategies to improve targeted therapies has reached the clinic in a small number of cases (Table 5). For example, clinical trials have been initiated for the delivery of RNAi therapeutics and gene therapies. However, few trials have been conducted to test the efficacy of small molecule therapies, such as kinase inhibitors or anti-androgen therapy.

The first gene therapieshave now reached the clinic. In 2017, Spark Therapeutics obtained FDA approval for Luxturna — a therapy for a rare, genetic form of blindness. Subsequently, a gene therapy using nanoparticles was investigated in phase I and II trials (NCT01455389), using DOTAP and cholesterol to deliver the FUS1 gene. These trials were based on research identification of genes with tumour suppressor following homozygous deletions in the 3p21.3 region in lung cancer cell lines and primary lung tumours. Of the genes identified, the FUS1 gene demonstrated the highest level of tumour suppressor activity[174, 175].

Multiple clinical trials have been initiated using RNA therapeutics. A phase I/II study of TKM-080301 (NCT01262235) — a lipid nanoparticle formulation of PLK1-targeted RNAi — in patients with adrenocortical cancer showed anti-tumour efficac[176]. A phase I study of a liposomal formulation of siRNAs directed against ephrin type-A receptor 2 (EphA2) has been initiated at MD Anderson (NCT01591356)[177]. Similarly, a phase I trial of MTL-CEBPA, which is double-stranded RNA formulated into liposomal nanoparticle (SMARTICLES®), has been initiated for the treatment of advanced liver cancer

(NCT02716012)[178]. Although not an oncologic disease, it is worth noting that a patisiran — an siRNA to treat amyloidosis that is formulated in lipid nanoparticles — was the first siRNA therapy approved by the FDA in 2018 s.

Clinical trials for small-molecule therapeutics are also underway. A phase I trial to determine the safety of nanoparticle albumin-bound rapamycin when given together with temozolomide and irinotecan hydrochloride in refractory and relapsed paediatric solid tumours is currently recruiting patients (NCT02975882). In addition, a phase II trial (NCT02646319) using the same nanoparticle albumin-bound rapamycin in treating patients with advanced cancer with mTOR mutations is ongoing[179].

Clinical trials to deliver small molecule cancer therapeutics involve several types of delivery platforms. An epirubicin nanoparticle that targets the tumour microenvironment using micellar technology has been studied in patients (NCT03168061). The micellar nanoparticle is stable in the bloodstream, but the pH-sensitive nature of the micelles targets drug release within the more acidic tumour microenvironment. Another phase II trial is using CPC634 (CriPec® docetaxel) to treat advanced epithelial ovarian cancer, which has been resistant to platinum-based chemotherapy (NCT03742713). The nanomedicine is designed for enhanced tumour accumulation and localized drug release within the tumour. A phase I/II study of IMX-110, which is a nanoparticle that encapsulates curcumin (a stat3/NF-κB/poly-TKI) and doxorubicin, has been initiated in the treatment of advanced solid tumours. Nanoplatin, which is a formulation of cisplatin, is under phase III clinical evaluation in Asia for pancreatic cancer, and is currently in basket trials in the United States[180]. Overall, however, the scarcity of clinical trials involving targeted therapies using drug delivery systems highlights the under-exploration of targeted delivery strategies with these drugs.

Outlook

One of the main observations of this review is that personalized therapies are extremely diverse and that improvements, via drug delivery approaches, may look very different for different drugs. Major opportunities for the improvement of existing drugs include the drug's toxicities, pharmacokinetics, and biodistribution, among other properties. This means, for example, that a highly specific carrier may be more useful for a less specific drug, which is the case for antibody–drug conjugates that use very specific targeting systems to deliver non-specific but highly toxic cargo. In most cases, materials-based strategies, such as nanoparticles derivatized with targeting ligands, are much less specific than antibody–drug conjugates and thus could best be used to deliver a cargo with more specificity to molecular/cellular targets.

Approaches for addressing toxicities may differ markedly among drugs. The avoidance of a specific tissue or organs may attenuate a dose-limiting toxicity of one drug but not another. Materials strategies to avoid certain tissues, such as the kidneys or the brain, may be relatively simple. For example, hydrophilic nanoparticles, such as those coated by PEG, can avoid the brain as long as the blood–brain barrier is intact. By choosing material–drug combinations carefully, the therapeutic index of many drugs might be improved.

Drug delivery approaches have already shown the potential to improve pharmacological properties of therapies and enable the use of new drug classes. Several technologies for the delivery of multiple chemotherapies are already in the clinic. The first RNAi delivery systems have been FDA approved and several gene therapies are on the market. Approaches for the delivery of gene editing technologies are in their infancy, along with many of the editing technologies themselves. Precision small-molecule therapeutics are advancing in the clinic, with over 50 approved drugs. However, little clinical progress has been made in the targeted delivery of kinase inhibitors, anti-androgen therapies, and other new classes of small-molecule inhibitors.

The limited use of nanomedicine approaches to deliver small-molecule targeted therapeutics may be due in part to the low efficiency of drug loading and delivery of many vehicles. Further, the diversity of drug chemistries that must be integrated with drug delivery approaches can complicate synthesis. New strategies and vehicles to enhance drug encapsulation are under investigation, including drug nanocrystals[181182], solid lipid–drug particles[183] and polymeric nanoparticles[184, 185]. Recent works to improve nanoparticle development in silico portend the emergence of ‘nanoinformatics’ — a new subfield of nanotechnology[186]. For the design of drug carriers, quantitative structure–property relationship calculations have been used to predict colloidal aggregation[187181188, 189], drug loading in lipid formulations[167], and in vivo performance[190, 191]. Moreover, molecular dynamics simulations have been used to investigate supramolecular drug interactions[192–195] and vehicle selection for a particular drug[196]. With the aid of such computational efforts to facilitate nanoparticle development, the above issues may be addressed in the near future.

Nanotechnologies have also been used as tools to improve precision medicine strategies such as drug selection. For example, using a nanoparticle-based system, one study predicted the therapeutic potency of personalized anticancer medicines to a given tumor [197]. In this example, the investigators carried out the diagnostic stage through a multidrug screen performed inside the tumour, extracting drug activity information with single cell sensitivity. Such methods may be used in other contexts to choose delivery strategies.

The ability to better match nanoparticle technologies to patients who can benefit from them is critical for clinical trial design (Figure 6)[198–202]. Imaging methods to discern the likelihood that a nanoparticle therapy may penetrate a tumour is also at the clinical stages of testing[215,216]. Radiolabelled nanoparticles that measure EPR effect and vascular leakiness of tumours in a patient or cohort of patients may greatly facilitate the selection of patients for nanoparticle drug delivery-related treatments[215,203204, 205].

Other opportunities for personalized nanomedicine are the combination of drug-loaded nanoparticles with other modalities, such as radiation[43, 86], focused ultrasound, immunotherapy[206], and photodynamic therapy[207], which have been found to enhance anti-tumour efficacy of several nanomedicine treatments at the preclinical stage.

The regulatory environment must be considered carefully for drug delivery strategies. There is confusion in the fields of nanomedicine and drug discovery about how the encapsulation of existing drugs into nanoparticles may be considered by regulators[208].

Nanoparticle versions of existing drugs are usually considered as new drugs deserving of their own IsND (investigational new drug) application. In addition, the consideration of vehicle components, as separate entities or part of the final drug product, is also important. Resources are available, however, including the National Cancer Institute's Nanotechnology Characterization Laboratory (USA) and the European Nanotechnology Characterization Laboratory, to aid investigators in navigating these issues[209, 210].

Nanomedicines have resulted in few, but significant, approved therapies. Clinical trials for nanomedicine drugs are often initiated only after approval of the drug cargo, and after significant problems with that drug have been encountered. Thus, there are relatively few attempts to integrate drug delivery with precision medicines in preclinical research. We speculate that enthusiasm for nanomedicine drug delivery approaches is somewhat diminished by their complexity, especially with respect to scale-up and chemistry, manufacturing, and controls (CMC). We note, however, the clinical development of many types of antibody–drug conjugates — a similarly complex therapeutic platform — suggests that this complexity can be managed succesfully. Because of the outstanding issues with precision drugs, including narrower-than-expected therapeutic indices, drug resistance and toxicity associated with many therapeutic combinations, many opportunities exist to improve upon their pharmacologic properties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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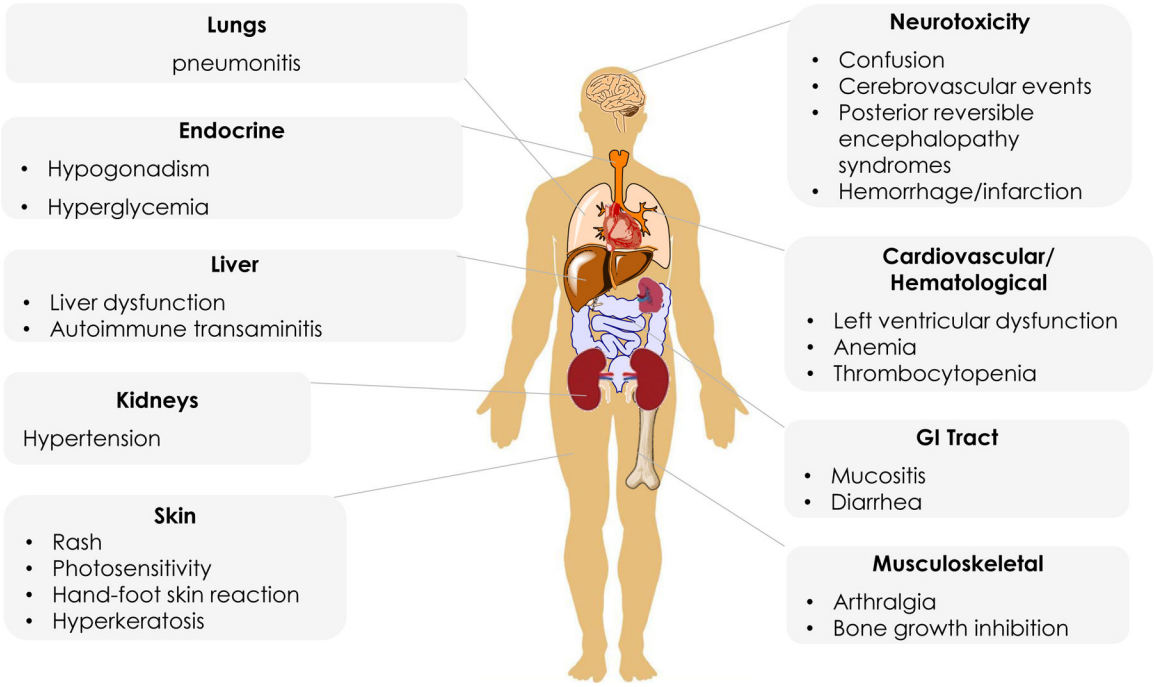

Figure 1. Major side effects of kinase inhibitors.

Kinase inhibitors, like all systemically administered therapies, can cause a wide variety of side effects. Nanomedicine may be used to prevent side effects such as neurotoxicities, hematological issues, skin rashes, hypertension, liver dysfunction, musculoskeletal problems, GI syndromes, and cardiovascular issues.

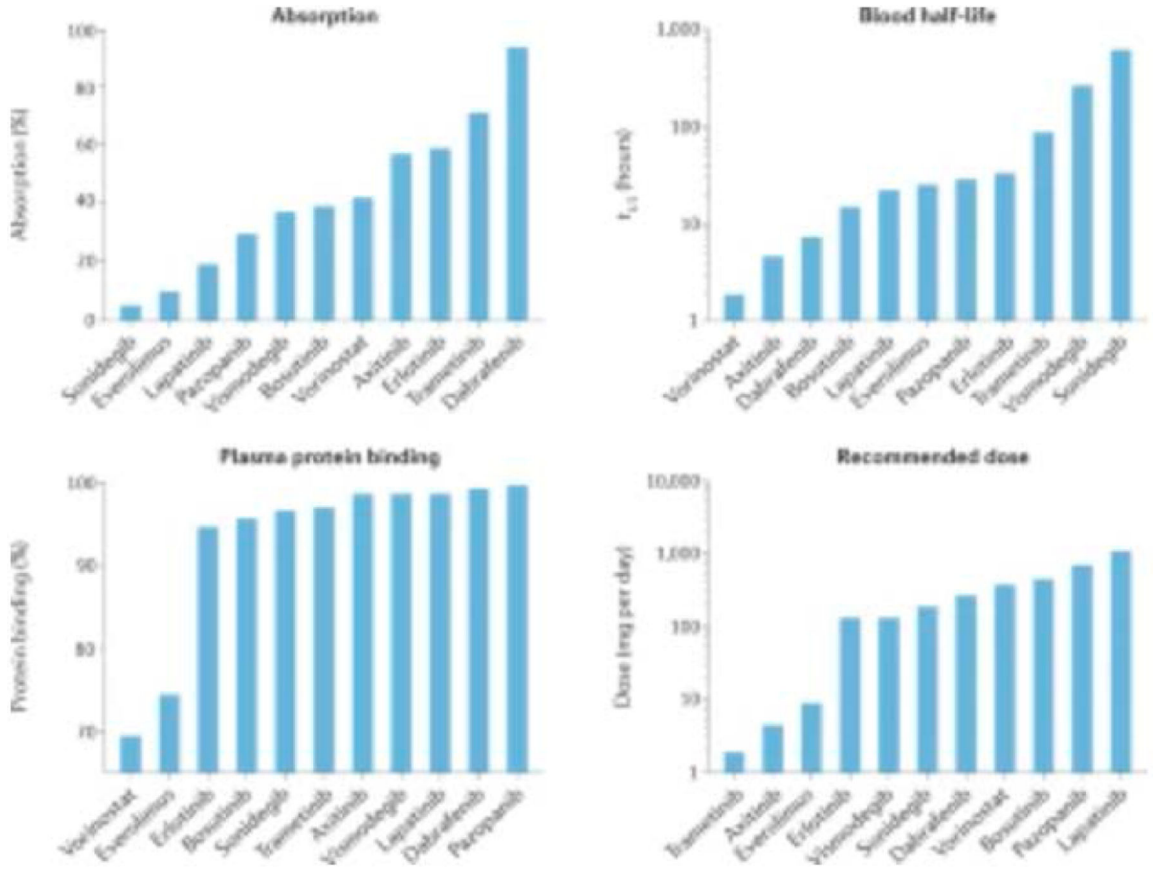

Figure 2. Pharmacologic properties of kinase inhibitors.

Absorption (**a**) half-life in the blood (**b**), plasma protein binding (**c**), and recommended daily dosage (**d**). The data were collected from online sources including DrugBank.ca, U.S. Food and Drug Administration pharmacology and toxicology reports, and European Medicines Agency reports.

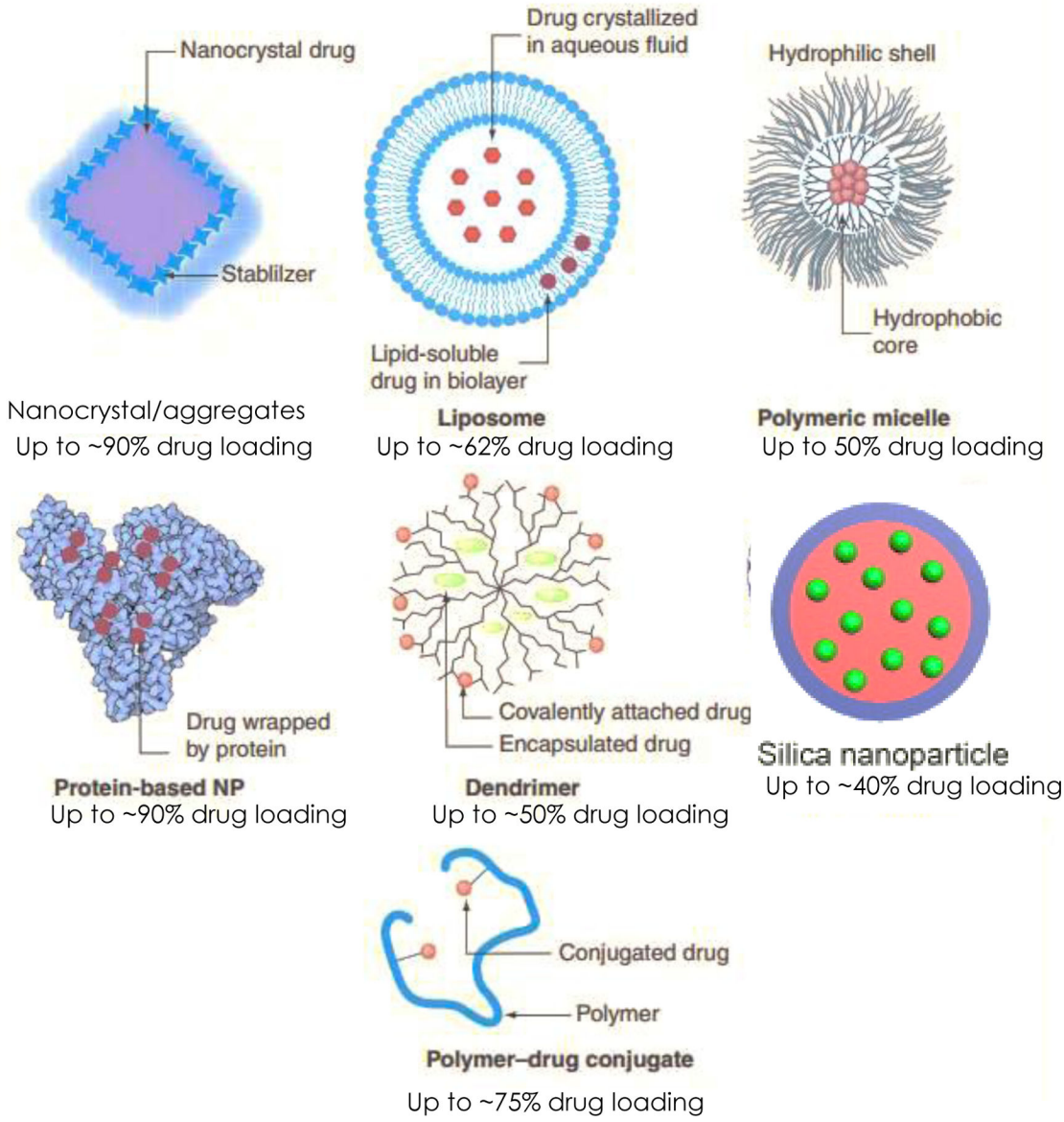

Figure 3. Nanoscale delivery approaches for high-loading small molecule cargoes.

Drug nanocrystals or nanoaggregates can be formed with the aid of stabilizers/excipients. Liposomal drug vehicles can encapsulate drugs in the bilayer of the micelle and/or as drug crystals in the interior[326]. Polymeric micelles are composed of amphiphilic polymers that typically enclose the drug in the core[327]. Protein-based nanodelivery systems can incorporate drug in hydrophobic regions of proteins and/or between multiple protein components[328]. Dendrimers can be designed to covalently attach the drug or encapsulate it between substructures[329]. Silica or other solid nanoparticles can incorporate/attach drugs within/onto a porous/solid matrix[330]. Drug loading is reported in mass (drug)/mass (total).

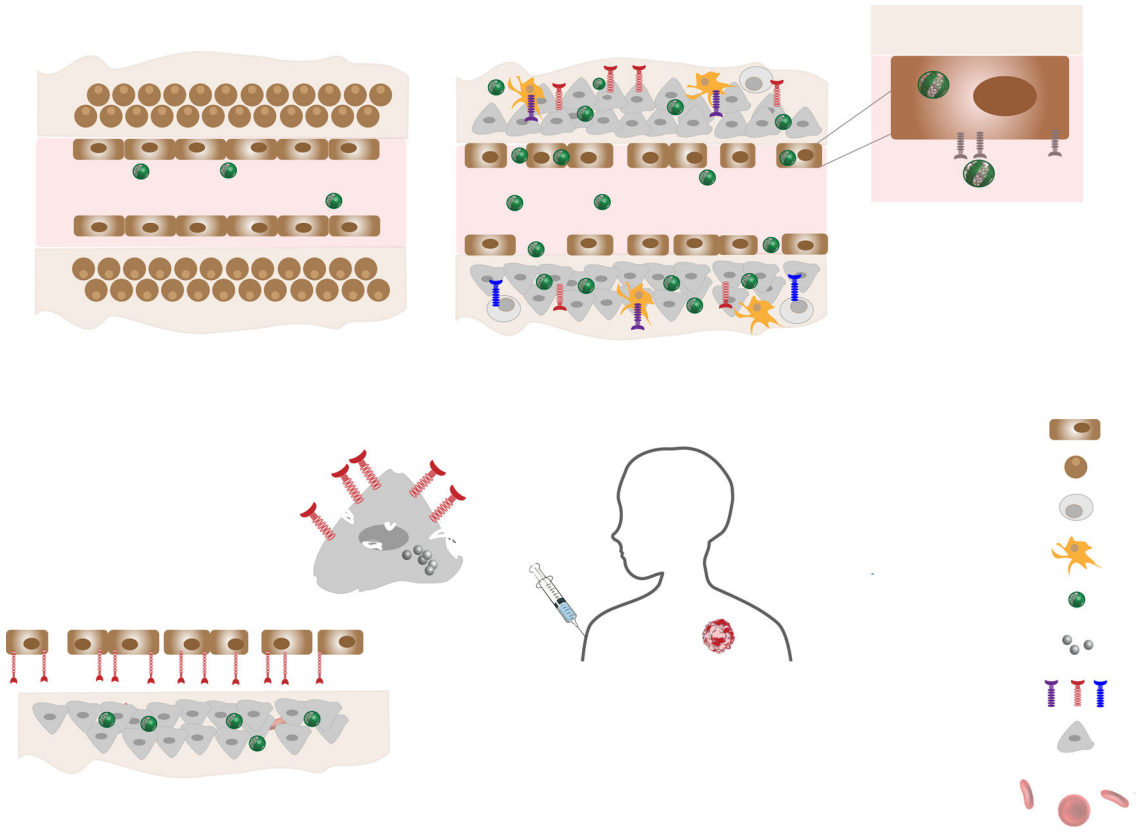

Figure 4. Routes and Targets in the Tumor Microenvironment.

Nanomedicine can be used to deliver drugs to the tumor site [right] and avoid penetration of normal tissue [left]. Passive targeting allows for appropriately sized nanoparticles to take advantage of the enhanced permeability and retention (EPR) effect that increases entry and retention due to leaky vasculature of some tumor types. Active targeting, made possible by receptor-binding moieties on the surface of the nanocarriers, can be used to improve specificity and penetration of tumors via transcytosis across endothelial cells or direct binding to receptors upregulated on cancer cells or other cell types in the tumor microenvironment (i.e. fibroblasts, tumor-associated macrophages).

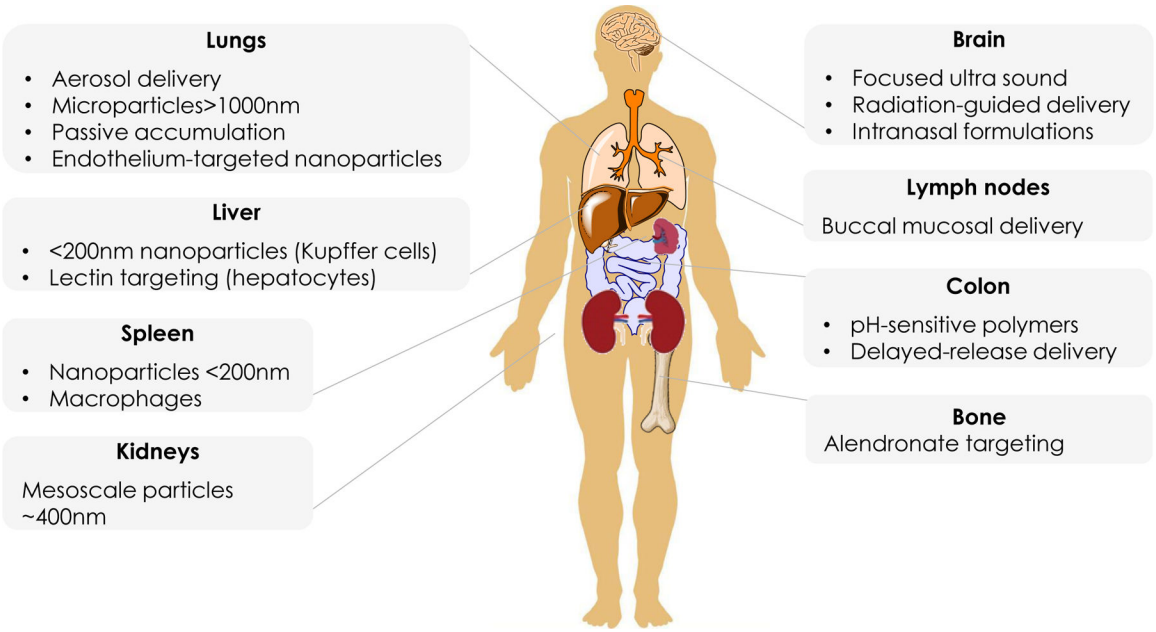

Figure 5. Organ targeting with drug delivery systems.

Nanotechnologies designed for targeted delivery to specific tissues.

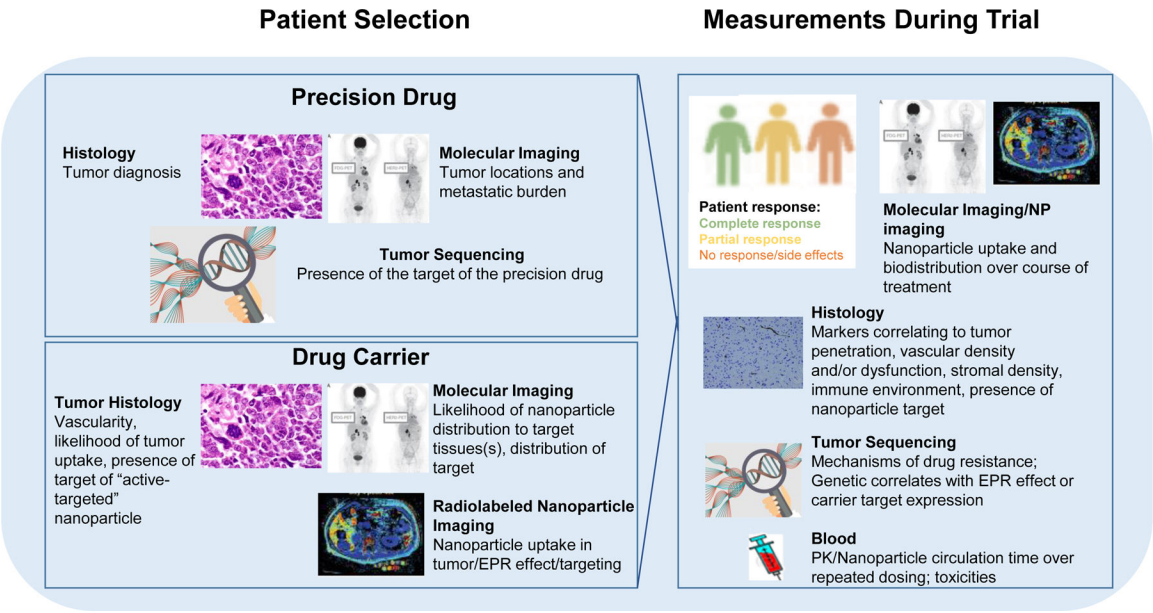

Figure 6. Proposed patient selection and clinical correlate measurements for a precision drug nanomedicine trial.

Left side: patient selection via (top) histology, molecular imaging, and sequencing of tumor for tumor diagnosis and to determine eligibility of the patient for the precision drug cargo. (Bottom) measurements to determine likelihood of uptake of the nanoparticle into the patient's tumors via histology, molecular imaging, and (when possible) imaging of a radiolabeled version of the nanoparticle. Left side: During the trial (right), patients will be monitored for toxicity/efficacy as in conventional clinical trials. Correlative measurements of tumor histology, imaging, and blood enable maximum information to be gained to determine indicators of which patients may best respond to the nanomedicine.

Table 1.

Side effects of common kinase inhibitors.

ABL, Abelson murine leukaemia viral oncogene; ALK, anaplastic lymphoma kinase; BRAF, B-rapidly accelerated fibrosarcoma; EGFR, epidermal growth factor receptor; GI, gastrointestinal; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase; VEGF(R), vascular endothelial growth factor (receptor).

Class	Drug	Organ or organ system	Adverse effect(s)	Ref.
ABL inhibitor	Bosutinib	Haematologic	Thrombocytopenia	211
		Haematologic	Anaemia	211
ALK inhibitor	Ceritinib	Lungs	Pneumonitis	212
	Crizotinib	Endocrine	Hypogonadism	213
BRAF inhibitor	Vemurafenib	Skin	Rash and/or photosensitivity	214
		Musculoskeletal	Arthralgia	214
	Dabrafenib	Liver	Liver dysfunction	215
		Skin	Hyperkeratosis	216
		Skin	Hand-foot syndrome	216
		Musculoskeletal	Arthralgia	216
		Endocrine	Hyperglycaemia	217
EGFR Inhibitor	Afatinib	Skin	Rash	218
		GI	Mucositis	218
	Vandetanib	GI	Diarrhoea	219
MEK Inhibitor	Trametinib	Skin	Rash	220
		Cardiovascular	Left ventricular dysfunction	220
		GI	Diarrhoea	217
mTOR inhibitor	Sirolimus	Cerebrovascular	Posterior reversible encephalopathy syndrome	221
PI3K inhibitor	Copanlisib	Renal	Hypertension	222
		Endocrine	Hyperglycaemia	222
	Buparlisib	Endocrine	Hyperglycaemia	223
		Neurological	Confusion	224
	Idelalisib	GI	Diarrhoea	225
		Liver	Autoimmune transaminitis	225
		Lungs	Pneumonitis	226
		Skin	Rash	225
Smoothened inhibitor	Vismodegib	Musculoskeletal	Bone growth defects	227
VEGF inhibitor	Bevacizumab	Cerebrovascular	Haemorrhage and/or infarction	228
		Cerebrovascular	Posterior reversible encephalopathy syndrome	229
VEGFR inhibitor	Regorafenib	Skin	Hand-foot skin reaction	230
	Cabozantinib	Skin	Hand-foot skin reaction	231

Class	Drug	Organ or organ system	Adverse effect(s)	Ref.
	Lenvatinib	Renal	Hypertension	232
	Axitinib	Cardiovascular	Left ventricular dysfunction	233
	Sunitinib	Cardiovascular	Left ventricular dysfunction	233

Table 2.

Common systems and material classes used for nanoparticle drug delivery.

Type of cargo and drug loading (mass of drug divided by total mass of nanoparticle) are specified for each delivery system.

Delivery system	Cargo	Drug loading (%)	Ref.
Polymeric nanoparticles	Small and macromolecules	0.5–20	234
Cationic polymers	Oligonucleotides	1–50	235, 236
Liposomal nanoparticles	Small and macromolecules	0.5–20	237–239
Nanocrystals	Small molecules	75–90	182, 240–242
Polymer–drug conjugate	Small molecules	1–10	243–245
Protein nanoparticles	Small and macromolecules	5–10	246–248
Inorganic nanoparticles	Small and macromolecules	1–25	249–253
Slow-release matrix or wafers	Small and macromolecules	5–40	254–256
Microneedle patches	Small and macromolecules	N/A	82, 257–259
Stimuli-responsive hydrogels	Small and macromolecules	10–70	260–262
Microparticles or nanoparticles for aerosol	Small and macromolecules	10–80	263–265
Carbon nanotubes	Small and macromolecules	1–10	68, 266
Dendrimers	Small and macro molecules	1–5	267–269

Table 3.

Compensatory pathways of common cancer targets.

This table shows several pathways targeted by existing precision drugs, and the associated cancer type. For each targeted pathway, compensatory pathways (examples listed) may be upregulated to result in therapeutic resistance. Gene and pathway abbreviations can be found at https://ghr.nlm.nih.gov/gene. EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; ALK, anaplastic lymphoma kinase; HER2, human epidermal growth factor receptor 2; TGFb, transforming growth factor beta; ERα, estrogen receptor alpha; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; BRAF, B-rapidly accelerated fibrosarcoma; JAK2, Janus kinase 2 gene; STAT, signal transducer and activator of transcription; AML, acute myeloid leukaemia; FLT-3, fetal liver tyrosine kinase-3; CML, chronic myeloid leukaemia; BCR-ABL, breakpoint cluster region protein fusion to Abelson murine leukemia (ABL) tyrosine kinase ABL1.

Cancer type	Target pathway	Compensatory pathways	Ref.
Lung and colon	EGFR	Ras-MAPK	270 271
		PI3K	
Lung	ALK	Ras-MAPK	272
		PI3K	
Breast	HER2	PI3K	273 274
		Ras-MAPK	
		TGFb	
		ERα	
		NF-κB	
Melanoma	BRAF	Ras-MAPK	275
		PI3K	
		Notch1	
Myeloproliferative neoplasms	JAK2	JAK-STAT	276 277
		PI3K	
		Ras-MAPK	
AML	FLT-3	Ras-MAPK	278
		PI3K	
		STAT	
CML	Bcr-Abl	Downstream Pathways of BCR-ABL	279
		Ras-MAPK	
		PI3K	
		STAT	

Table 4.

Drugs and targets that were studied in the context of personalized nanomedicine. ALK, anaplastic lymphoma kinase; Bcr-Abl, breakpoint cluster region protein fusion to Abelson murine leukemia (ABL) tyrosine kinase ABL1; BRAF, B-rapidly accelerated fibrosarcoma; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FLT3, fetal liver tyrosine kinase-3; mTOR, mammalian target of rapamycin; PARP, poly(ADP-ribose) polymerase; PI3k, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor.

Drug cargo	Target	Initial U.S. Approval Date	Ref.
Crizotinib	ALK	FDA approved in 2011	280, 281
Imatinib	Bcr-Abl	FDA approved in 2001	282, 283
Vemurafenib	BRAF	FDA approved in 2011	284285
Afatinib	EGFR	FDA approved in 2013	286
Erlotinib	EGFR	FDA approved in 2004	287, 288
Gefitinib	EGFR	FDA approved in 2003	289–292
Vandetanib	EGFR	FDA approved in 2011	293
Nintedanib	FGFR	FDA approved in 2014	294
Ponatinib	FGFR	FDA approved in 2012	294
Midostaurin	FLT3	FDA approved in 2017	295, 296
Rapamycin	mTOR	FDA approved in 1999	297, 298299, 300301, 302303
Olaparib	PARP	FDA approved in 2014	304, 305306
Alpelisib	PI3k	FDA approved in 2019	43
Sorafenib	RAF, VEGFRs, PDGFRs	FDA approved in 2005	307308, 309
Pazopanib	VEGFR	FDA approved in 2009	310
Sunitinib	VEGFR,PDGFR	FDA approved in 2006	311, 312313, 314315, 316

Table 5.

Clinical trials involving targeted delivery systems over the past 10 years.

TUSC2, Tumour suppressor candidate 2; EphA2, ephrin type-A receptor 2; siRNA, small interfering RNA; mTOR, mammalian target of rapamycin.

Clinical trial number	Year Commenced	Description
NCT01455389	2014 (currently active)	TUSC2- nanoparticles and erlotinib in stage IV lung cancer
NCT01262235	2010 (completed in 2015)	A dose finding study of tkm-080301 infusion in neuroendocrine tumours and adrenocortical carcinoma patients
NCT01591356	2015 (currently recruiting)	EphA2 siRNA for treatment of patients with advanced or recurrent solid tumours
NCT02716012	2016 (currently recruiting)	First-in-human safety and tolerability study of small activating RNA drug for hepatocellular carcinoma (MTL-CEBPA) in patients with advanced liver cancer
NCT01960348	2013 (completed 2017)	Study of an investigational drug (patisiran or ALN-TTR02), for the treatment of transthyretin-mediated amyloidosis
NCT02975882	2017 (recruiting)	Nanoparticle albumin-bound rapamycin, temozolomide, and irinotecan hydrochloride for the treatment of patients with recurrent or refractory solid tumours
NCT02646319	2016 (completed 2018)	Nanoparticle albumin-bound rapamycin in treating patients with advanced cancer with mTOR mutations
NCT03168061	2017 (currently recruiting)	Dose-escalation and expansion trial of epirubicin-conjugated polymer micelles (nc-6300) in patients with advanced solid tumours or soft tissue sarcoma
NCT03742713	2018 (currently recruiting)	Efficacy study of a drug delivery system (CPC634) that encapsulates the drugs CriPec® Docetaxel in platinum-resistant ovarian cancer
NCT03382340	2018 (currently recruiting)	Study of a nanoparticle formulation (IMX-110) combining curcumin and doxorubicin in patients with advanced solid tumours