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Review

The Future of Precision Medicine: Targeted Therapies, Personalized Medicine and Formulation Strategies

Gopinath Rongala [1,†], Druva Sarika Rongala [2,*,†] and Appalaswamy Naidu Rongala [3,†]

[1] Department of Pharmaceutics, Philadelphia College of Pharmacy, St Joseph's University, Philadelphia, PA 19104, USA; gr10854477@sju.edu
[2] College of Pharmacy and Health Sciences, St. John's University, New York, NY 11439, USA
[3] Independent Researcher, Hyderabad 500072, Telangana, India; drrasnaidu60@gmail.com
* Correspondence: druvasarika.barji19@my.stjohns.edu
† These authors contributed equally to this work.

Abstract

Medicine is accelerating rapidly, offering the advantages of site-specific delivery, minimized side effects, and improved treatment outcomes. A diverse array of chronic diseases, such as cancer, diabetes, asthma, myocardial infarction, and Alzheimer's disease, are often accompanied by severe adverse effects and limited specificity, necessitating concentrated attention on targeted therapies. Recent advancements in molecular profiling and understanding of target pathways have enabled the identification of specific biomarkers and gene targets. These advancements have led to the development of targeted therapies that focus on the specific molecular alterations responsible for disease progression. Such therapies offer a more personalized and effective approach to treatment. This review focuses on the benefits of targeted therapies compared to traditional therapeutics and provides an overview of currently available targeted therapies for chronic diseases. By highlighting these advancements, the review aims to illustrate the progress in disease treatment towards more personalized approaches. The goal is to underscore how targeted therapies have evolved and how they represent a significant shift towards personalized therapy.

Keywords: targeted therapies; personalized; molecular profiling; biomarkers; precision medicine

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1. Introduction

Global Health burden reports that non-communicable diseases like cancer, diabetes, asthma, myocardial infarction, COPD, Alzheimer's, and others have been attributed to 64.49% of global deaths in 2021 [1]. Conventional therapeutic approaches for these major disease conditions have employed a one-size-fits-all strategy; however, these fell short in addressing the heterogeneous nature of disease conditions [2]. Current in-depth understanding of disease mechanisms has highlighted the need for tailored therapies for the treatment of these complex diseases. Personalized medicine (PM), also referred to as individualized or precision medicine, integrates knowledge of genetic profile, disease status, and other individual factors of each patient to tailor therapies that are most effective and safe [3,4]. This approach identifies the use of therapies to alter the molecular mechanisms of disease conditions [5]. For example, in the treatment of NSCLC, the presence of a specific biomarker indicates whether a patient is likely to benefit from specific drug treatment [6,7]. PM helps to avoid treatments that may increase the risk of adverse effects, making it more cost-effective and precise. According to the Personalized Medicine Coalition (PMC), in 2023, over a third of new drug approvals by the U.S. Food and Drug Administration (FDA)

were categorized as personalized medicine, representing a significant advancement in the field of personalized healthcare [5].

Targeted therapies (TTs) are characterized by their ability to specifically disrupt crucial molecules involved in disease progression, such as kinases, cytokines, enzymes, receptors, ion channels, and proteasomes [8–13]. By targeting these precise molecular components, these therapies often achieve enhanced efficacy and reduced side effects [14,15]. The global landscape of drug development is increasingly dominated by targeted therapies. In 2023, the FDA approved approximately 86% of novel drugs as targeted therapies, underscoring their growing prominence [16]. Furthermore, there has been a noticeable increase in targeted therapies for rare diseases, such as Pompe disease and paroxysmal nocturnal hemoglobinuria [17]. This expanding repertoire of novel drug approvals across diverse medical conditions offers promising prospects for the future, suggesting that ongoing advancements will yield even more effective and personalized treatment options.

In this review, we explore targeted and personalized therapies for several prevalent chronic diseases: cancer, diabetes, asthma, myocardial infarction, and Alzheimer's disease. These conditions significantly contribute to global health concerns and mortality rates, underscoring the critical need for more effective and individualized treatment strategies. By examining advancements in targeted therapies across these diverse diseases, we aim to highlight innovative approaches that address the unique molecular and pathophysiological features of each condition and discuss the potential for these therapies to improve patient outcomes and advance precision medicine.

Benefits of Targeted Therapies and Personalized Medicine

Targeted therapies present multiple benefits by directing drug delivery specifically to diseased cells, thereby sparing healthy cells from unnecessary exposure. This approach reduces dose-dependent toxicity and minimizes adverse reactions. Additionally, it helps mitigate the development of drug-resistant cancer cells [18]. Targeted therapies enhance drug specificity and cellular uptake, facilitating the delivery of potent therapeutic agents to the intended site at adequate concentrations while reducing off-target accumulation in other organs. However, it has become increasingly clear that developing a drug molecule for a specific disease is not sufficient to ensure therapeutic efficacy. Proper formulation design and optimization are crucial to achieving the desired therapeutic outcome. Table 1 describes the targeted therapies approved by the FDA.

Personalized medicine offers numerous advantages by tailoring treatments to an individual's genetic and physiological profile, leading to more effective therapies with fewer side effects. It enhances diagnostic precision, enabling doctors to identify the exact disease early and choose the best treatment and dosage based on a patient's unique characteristics. This approach also reduces the cost and time of drug development by integrating pharmacogenomics into clinical trials, improving safety and efficacy. By aligning diagnosis and therapy, personalized medicine improves patient outcomes and is expected to become a key part of modern medical practice. Table 2 describes the FDA-approved personalized therapies.

Table 1. FDA approved targeted therapies: Comprehensive overview by disease conditions [19–32].

Drug	Dosage Form	Molecule Type	Indication	Target	Year
Trastuzumab	IV	Large Molecule (mAbs)	Breast cancer	HER2	1998
Pertuzumab	IV	Large Molecule (mAbs)	Breast cancer	HER2	2012
Margetuximab	IV	Large Molecule (mAbs)	Breast cancer	HER2	2020
Tucatinib	Tablet	Small Molecule (kinase inhibitor)	Breast cancer	HER2	2020
Lapatinib	Tablet	Small Molecule (kinase inhibitor)	Breast cancer	HER2	2007
Everolimus	Tablet	Small Molecule	Breast cancer	mTOR	2014
Palbociclib	Tablet	Small Molecule	Breast cancer	CDK4/6	2015
Neratinib	Tablet	Small Molecule (kinase inhibitor)	Breast cancer	HER2	2017
Alpelisib	Tablet	Small Molecule	Breast cancer	PI3K	2022
Capivasertib	Tablet	Small Molecule	Breast cancer	AKT	2023
Elacestrant	Tablet	Small Molecule	Breast cancer	ESR1	2023
Rucaparib	Tablet	Small Molecule	Prostate cancer	PARP	2020
Olaparib	Tablet	Small Molecule	Prostate cancer	PARP	2020
Bevacizumab	IV	Large Molecule (mAbs)	NSCLC	VEGFR	2018
Sotorasib	Tablet	Small Molecule	NSCLC	KRAS	2021
Gefitinib	Tablet	Small Molecule (tyrosine Kinase Inhibitor)	NSCLC	EGFR	2015
Erlotinib	Tablet	Small Molecule (tyrosine Kinase Inhibitor)	NSCLC	EGFR	2013
Afatinib	Tablet	Small Molecule (tyrosine Kinase Inhibitor)	NSCLC	EGFR	2013
Dacomitinib	Tablet	Small Molecule (tyrosine Kinase Inhibitor)	NSCLC	EGFR	2018
Osimertinib	Tablet	Small Molecule (tyrosine Kinase Inhibitor)	NSCLC	EGFR	2015
Mobocertinib	Capsule	Small Molecule (tyrosine Kinase Inhibitor)	NSCLC	EGFR	2021
Lazertinib	Tablet	Small Molecule (Kinase Inhibitor)	NSCLC	EGFR	2024
Amivantamab	IV	Large Molecule (mAbs)	NSCLC	EGFR	2024
Tepotinib	Tablet	Small Molecule	NSCLC	MET	2024

Table 1. *Cont.*

Drug	Dosage Form	Molecule Type	Indication	Target	Year
Crizotinib	Tablet	Small Molecule	NSCLC	ALK	2011
Ceritinib	Tablet	Small Molecule	NSCLC	ALK	2014
Lorlatinib	Tablet	Small Molecule	NSCLC	ROS	2018
Sotorasib	Tablet	Small Molecule (tyrosine Kinase Inhibitor)	NSCLC	KRAS	2021
Adagrasib	Tablet	Small Molecule (tyrosine Kinase Inhibitor)	NSCLC	KRAS	2022
Alectinib	Tablet	Small Molecule	NSCLC	ALK	2024
Esartinib	Tablet	Small Molecule	NSCLC	ALK	2024
Tepotinib	Tablet	Small Molecule	NSCLC	c-Met	2021
Capmatinib	Tablet	Small Molecule	NSCLC	c-Met	2022
Larotrectinib	Tablet	Small Molecule	NSCLC	TRKA/B/C	2018
Repotrectinib	Capsule	Small Molecule	NSCLC	TRKA/B/C	2023
Cetuximab	IV	Large Molecule (mAbs)	CRC	EGFR	2004
Panitumumab	IV	Large Molecule (mAbs)	CRC	EGFR	2006
Regorafenib	Tablet	Small Molecule (Multi-Kinase Inhibitor)	CRC	VEGFR-1/2/3	2012
Tislelizumab-JSGR	IV	Large Molecule	Esophageal squamous cell carcinoma	PD-L1	2024
Tovorafenib	Tablet	Small Molecule	Pediatric low-grade glioma	BRAF fusion/rearrangement/V600	2024
Zanidatamab	IV	Large Molecule (mAbs)	Biliary tract cancers	HER2	High priority review
Fruquintinib	Capsule	Small Molecule	CRC	VEGFR1/2/3	2023
Olutasidenib	Capsule	Small molecule	Acute myeloid leukemia	isocitrate dehydrogenase-1 (IDH1)	2022
Pirtobrutinib	Tablet	Small Molecule	Chronic lymphocytic leukemia	BTK	2023
Quizartinib	Tablet	Small Molecule	Acute myeloid leukemia	FLT3	2023
Epcoritamab-BYSP	SC	Large Molecule Bispecific antibody	Diffuse large B-cell lymphoma	CD20, CD3	2023
Ritlecitinib	Tablet	Large Molecule Bispecific antibody	Diffuse large B-cell lymphoma	CD20, CD3	2023
Asciminib	Tablet	Small Molecule (tyrosine Kinase Inhibitor)	Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML)	BCR-ABL1	2021

Table 1. *Cont.*

Drug	Dosage Form	Molecule Type	Indication	Target	Year
Talquetamab-TGVS	SC	Large Molecule Bispecific antibody	Myeloma	CD3 receptor and G proteincoupled receptor class C group 5 member D (GPRC5D)	2023
Elranatamab-BCMM	IV	Large Molecule Bispecific antibody	Myeloma	B-cell maturation antigen (BCMA) and CD3	2023
Mosunetuzumab-AXGB	IV	Large Molecule Bispecific antibody	Refractory follicular lymphoma	Bispecific CD20 and CD3	2022
Dapagliflozin	Tablet	Small Molecule	Diabetes	SGLT2	2012
Canagliflozin	Tablet	Small Molecule	Diabetes	SGLT2	2013
Bexagliflozin	Tablet	Small Molecule	Diabetes	SGLT2	2023
Sotagliflozin	Tablet	Small Molecule	Diabetes	SGLT2	2023
Lixisenatide	IV	Large Molecule (Poly peptide)	Diabetes	GLP-1	2016
Exenatide	SC	Large Molecule (Poly peptide)	Diabetes	GLP-1	2005
Semaglutide	IM	Large Molecule (Poly peptide)	Diabetes	GLP-1	2017
Albiglutide	IM	Large Molecule (Poly peptide)	Diabetes	GLP-1	2014
Dulaglutide	IM	Large Molecule (Poly peptide)	Diabetes	GLP-1	2014
Tirzepatide	SC	Large Molecule (Poly peptide)	Diabetes	GLP-1	2022
Sitagliptin	Tablet	Small Molecule	Diabetes	DPP-4	2006
Saxagliptin	Tablet	Small Molecule	Diabetes	DPP-4	2009
Linagliptin	Tablet	Small Molecule	Diabetes	DPP-4	2012
Alogliptin	Tablet	Small Molecule	Diabetes	DPP-4	2013
Teplizumab-MZWV	IV	Large molecule (mAbs)	To delay the onset of stage 3 type 1 diabetes	CD3	2022
Omalizumab	SC	Large Molecule (mAbs)	Asthma	IgE	2003
Mepolizumab	SC	Large Molecule (mAbs)	Asthma	IL-5	2015
Reslizumab	IV	Large Molecule (mAbs)	Asthma	IL-5	2016
Benralizumab	SC	Large Molecule (mAbs)	Asthma	IL-5Rα	2017
Dupilumab	SC	Large Molecule (mAbs)	Asthma	IL-4Rα	2017
Tezepelumab	SC	Large Molecule (mAbs)	Asthma	Thymic stromal lymphopoietin (TSLP)	2022
Montelukast	Oral (Tablet)	Small Molecule	Asthma	LTRAs	1998
Aducanumab-AVWA	IV	Large Molecule (mAbs)	Alzheimer's disease	Amyloid β	2021

Table 1. *Cont.*

Drug	Dosage Form	Molecule Type	Indication	Target	Year
Lecanemab-IRMB	IV	Large Molecule (mAbs)	Alzheimer's disease	Amyloid β (Aβ)	2023
Donanemab-AZBT	IV	Large Molecule (mAbs)	Alzheimer's disease	Amyloid β	2024

IV: intravenous; SC:Subcutaneous; IM: Intramuscular; HER2: Human Epidermal Growth Factor Receptor 2; mTOR: Mammalian Target of Rapamycin; CDK4/6: The cyclin-dependent kinase 4 and 6; PI3K: Phosphatidylinositol 3-kinase; AKT (PKB): Protein kinase B; PARP: Poly (ADP-ribose) polymerase; VEGFR: The vascular endothelial growth factor receptor; KRAS: Kirsten rat sarcoma 2 viral oncogene homolog; ALK: Anaplastic lymphoma kinase; ROS: Reactive oxygen species; c-Met: c-Mesenchymal-epithelial transition factor; TRKA: Tropomyosin receptor kinase A; IDH1: Isocitrate dehydrogenase 1; BTK: Bruton's tyrosine kinase; FLT3: FMS-like tyrosine kinase 3; CD20 × CD3 bispecific antibodies (bsAbs); BCR-ABL1: Breakpoint cluster region gene-ABL1 (Abelson) gene; CML: chronic myeloid leukemia; GLP-1: The glucagon-like peptide-1; DPP-4: Dipeptidyl peptidase 4; IgE: Targeting immunoglobulin E; IL-5: Interleukin 5; IL-4Rα: Interleukin-4 receptor alpha; LTRAs: Leukotriene Receptor Antagonists.

Table 2. FDA approved personalized therapies: Comprehensive overview by disease conditions [5,33–36].

Drug	Dosage Form	Molecule Type	Indication	Receptor/Target	Year
Datopotamab Deruxtecan-DLNK	IV	Large Molecule (ADC)	Unresectable/metastatic HR+, HER2- breast cancer	TROP2	2025
Treosulfan	IV	Small Molecule	Conditioning for stem cell transplant (AML, MDS)	Alkylating agent	2025
Mirdametinib	Oral tablet	Small Molecule	Neurofibromatosis type 1 (plexiform neurofibromas)	MEK1/2 inhibitor	2025
Vimseltinib	Oral tablet	Small Molecule	Tenosynovial giant cell tumor	CSF1R	2025
Durvalumab	IV	Large Molecule (mAbs)	Muscle-invasive bladder cancer	PD-L1	2025
Denosumab-BMWO, Biosimilar	SC	Large Molecule (mAbs)	Osteoporosis, cancer-related skeletal events	RANKL	2025
Denosumab Biosimilar	SC	Large Molecule (mAbs)	Osteoporosis, cancer-related skeletal events	RANKL	2025
Inebilizumab	IV	Large Molecule (mAbs)	Immunoglobulin G4-related disease	CD19	2025
Nitisinone	Oral capsule	Small Molecule	Alkaptonuria	HGA dioxygenase inhibitor	2025
Atrasentan	Oral tablet	Small Molecule	IgA nephropathy	Endothelin A receptor	2025
Beremagene Geperpavec	Topical gel	Large Molecule (gene therapy)	Recessive dystrophic epidermolysis bullosa	COL7A1 gene	2025
Mepolizumab	SC	Large Molecule (mAbs)	Eosinophilic COPD phenotype	IL-5	2025
Roflumilast Foam	Topical foam	Small Molecule	Scalp/body psoriasis	PDE4 inhibitor	2025
Clesrovimab	IM	Large Molecule (mAbs)	RSV prevention in infants	RSV F protein	2025
Lenacapavir	SC	Small	HIV prevention (PrEP)	HIV capsid protein	2025

Table 2. *Cont.*

Drug	Dosage Form	Molecule Type	Indication	Receptor/Target	Year
Donanemab-AZBT	IV	Large Molecule (mAbs)	Alzheimer's disease	Amyloid beta (Aβ); ApoE ε4 status	2024
Deuruxolitinib	Tablet	Small Molecule	Alopecia areata	JAK1/2; CYP2C9 status	2024
Lisocabtagene Maraleucel	IV	Large Molecule	Mantle cell lymphoma	CD19	2024
Gene Therapy For Metachromatic Leukodystrophy	IV	Large Molecule	Metachromatic leukodystrophy	ARSA gene	2024
Gene Therapy For Aadc Deficiency	IV	Large Molecule	Aromatic L-amino acid decarboxylase deficiency	DDC gene	2024
Gene Therapy For Hemophilia B	IV	Large Molecule	Hemophilia B (congenital factor IX deficiency)	Factor IX gene	2024
Repotrectinib	Capsule	Small Molecule	NSCLC	ROS1	2023
Pegunigalsidase Alfa-IWX	Injection	Large Molecule (Enzyme)	Fabry disease.	Alpha-galactosidase A, globotriaosylceramide (Gb3)	2023
Iptacopan	Capsule	Small Molecule	Paroxysmal nocturnal hemoglobinuria.	Factor B, alternative complement pathway	2023
Sparsentan	Tablet	Small Molecule	Proteinuria associated with primary immunoglobulin A nephropathy.	UPCR	2023
Leniolisib	Tablets	Small Molecule	Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome.	PI3Kδ	2023
Velmanase Alfa-TYCV	Injection	Large Molecule (Enzyme)	Non-central nervous system of alpha-mannosidosis.	Alpha-mannosidase, mannosidase alpha class 2B member 1	2023
Lecanemab-IRMB	Injection	Large Molecule (mAbs)	Alzheimer's disease.	ApoE ϵ4	2023
Toripalimab-TPZI	Injection	Large Molecule (PD-1PD-L1 Inhibitors)	Nasopharyngeal carcinoma.	Programmed death receptor-1 (PD-1)	2023
Elacestrant	Tablets	Small Molecule	Breast cancer.	ESR1, HER2, ER	2023
Cipaglucosidase Alfa-ATGA	Lyophilized powder for injection	Large Molecule (Enzyme)	Pompe disease	Lysosomal acid alpha-glucosidase (GAA)	2023
Tofersen	Injection	Large Molecule (Neurologics, Antisense Oligonucleotides)	Amyotrophic lateral sclerosis (ALS).	SOD1	2023
Nedosiran	Injection	Large Molecule (RNAi Agents)	hyperoxaluria type 1.	Hepatic lactate dehydrogenase	2023

Table 2. *Cont.*

Drug	Dosage Form	Molecule Type	Indication	Receptor/Target	Year
Rozanolixizumab-NOLI	Injection	Large Molecule (Fc Receptor Antagonists)	Generalized myasthenia gravis.	AChR or MuSK Ab	2023
Palovarotene	Capsules	Small Molecule	Reduction in volume of new heterotopic ossification in fibrodysplasia ossificans progressiva.	BMP/ALK2	2023
Capivasertib	Tablets	Small Molecule	Breast cancer, in combination with fulvestrant.	HR, HER2 biomarkers, PIK3CA/AKT1/PTEN	2023
Quizartinib	Tablets	Small Molecule	acute myeloid leukemia,	FLT3 internal tandem duplication	2023
Pozelimab-BBFG	Injection	Large Molecule (Complement Inhibitors)	CHAPLE disease.	Terminal complement protein C5	2023
Eplontersen	Injection	Large Molecule (Neurologics, Antisense Oligonucleotides)	Polyneuropathy of hereditary transthyretin-mediated amyloidosis.	Transthyretin	2023
Zilucoplan	Injection	Large Molecule	Myasthenia gravis.	AChR Ab	2023
Retifanlimab-DLWR	Injection	Large Molecule (PD-1PD-L1 Inhibitors)	Metastatic Merkel cell carcinoma.	Programmed death receptor-1 (PD-1)	2023
Omidubicel	Suspension IV	Large Molecule (Hematopoietic Progenitor Cells, Cord Blood)	Hematologic malignancies		2023
Beremagene Geperpavec-SVDT	Topical gel	Large Molecule (Dermatologics)	Dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain gene.	collagen type VII alpha 1 chain gene.	2023
Delandistrogene Moxeparvovec-ROKL	Suspension IV	Large Molecule	Duchenne muscular dystrophy (DMD)	DMD gene	2023
Valoctocogene Roxaparvovec-RVOX	Suspension IV	Large Molecule (Clotting Factors, Gene Therapy)	Hemophilia A		2023
Exgamglogene Autotemcel	Suspension IV	Large Molecule (autologous cellular immunotherapy)	Sickle cell disease.	Sickle cell disease, BCL11A gene	2023
Lovotibeglogene Autotemcel	Suspension IV	Large Molecule (Hematologics, Kinase Inhibitor)	sickle cell disease	Sickle cell disease, β-globin gene	2023
Abrocitinib	Tablets	Small Molecule	Atopic dermatitis.	Janus kinase 1 (JAK1)	2022
Tebentafusp-TEBN	IV	Large Molecule (Monoclonal Antibodies)	Uveal melanoma.	Human leukocyte antigen (HLA)-A02:01	2022

Table 2. *Cont.*

Drug	Dosage Form	Molecule Type	Indication	Receptor/Target	Year
Mitapivat	Tablets	Large Molecule (Pyruvate Kinase Activators)	Pyruvate kinase deficiency.	Pyruvate kinase (PK)	2022
Nivolumab And Relatlimab-RMBW	Injection	Large Molecule (PD-1PD-L1 Inhibitors, Monoclonal Antibodies)	Metastatic melanoma.	PD-1, LAG-3	2022
Lutetium (177lu) Vipivotide Tetraxetan	Injection	Large Molecule (Radiopharmaceuticals)	Prostate cancer.	Prostate-specific membrane antigen (PSMA)	2022
Vutrisiran	Injection	Large Molecule (RNAi Agents)	Hereditary transthyretin-mediated amyloidosis.	Transthyretin (TTR)	2022
Olipudase Alfa	Injection	Large Molecule (Enzymes, Metabolic)	Acid sphingomyelinase deficiency (ASMD).	Acid sphingomyelinase	2022
Futibatinib	Tablets	Small Molecule	Cholangiocarcinoma.	FGFR2	2022
Mirvetuximab Soravtansine-GYNX	IV	Large Molecule (mAbs)	Ovarian cancer	Folate receptor alpha (FRα)	2022
Olutasidenib	Capsules	Small Molecule	Acute myeloid leukemia.	Isocitrate dehydrogenase 1 (IDH1)	2022
Adagrasib	Tablets	Small Molecule	NSCLC	KRAS G12C	2022
Lenacapavir	Tablets and Injection	Large Molecule	Human immunodeficiency virus (HIV) infection.	HIV-1	2022
Ciltacabtagene Autoleucel	Injection	Large Molecule (CAR-T Cell Therapies)	Refractory multiple myeloma	B-cell maturation antigen (BCMA)	2022
Betibeglogene Autotemcel	Suspension IV	Large Molecule (Clotting Factors, Gene Therapy)	beta thalassemia	Beta-globin	2022
Elivaldogene Autotemcel	Suspension IV	Large Molecule (Regenerative Therapy)	active cerebral adrenoleukodystrophy.	Adrenoleukodystrophy protein (ALDP)	2022
Etranacogene Dezaparvovec-DRLB	Suspension IV	Large Molecule (Clotting Factors, Gene Therapy)	Hemophilia B	Functional variant (R338L) of human factor IX	2022
Nadofaragene Firadenovec-VNCG	Suspension	Large Molecule (Biological Response Modifiers)	Bacillus Calmette-Guérin-unresponsive bladder cancer	Human interferon alfa-2b (IFNα2b)	2022
Cabotegravir And Rilpivirine	Injection	Large Molecule (HIV, NNRTIs, HIV, Integrase Inhibitors)	HIV infection	HIV-1 integration (cabotegravir); HIV-1 replication (rilpivirine)	2021
Tepotinib	Tablets	Small Molecule	NSCLC	MET exon 14 biomarker	2021

Table 2. *Cont.*

Drug	Dosage Form	Molecule Type	Indication	Receptor/Target	Year
Evinacumab-DGNB	Injection	Large Molecule (Lipid-Lowering Agents)	hypercholesterolemia	Homozygous FH (hoFH) status	2021
Casimersen	Injection	Large Molecule (Neurologics, Antisense Oligonucleotides)	Duchenne muscular dystrophy	DMD gene exon 45	2021
Fosdenopterin	Injection	Small Molecule	Molybdenum cofactor deficiency (MoCD)	MoCD Type A status	2021
Dostarlimab-GXLY	Injection	Large Molecule (PD-1PD-L1 Inhibitors, Antineoplastics Monoclonal Antibody, Monoclonal Antibodies)	Endometrial cancer	dMMR; PD-L1	2021
Amivantamab-VMJW	Injection	Large Molecule (Antineoplastics EGFR Inhibitors, MET Tyrosine Kinase Inhibitors)	NSCLC	EGFR exon 20	2021
Sotorasib	Tablet	Small Molecule	NSCLC	KRAS G12C	2021
Infigratinib	Capsules	Small Molecule	Cholangiocarcinoma	FGFR2	2021
Odevixibat	Capsules	Small Molecule	pruritus in PFIC	ABCB11 biomarker in PFIC Type 2 patients	2021
Avalglucosidase alfa-NGPT	Injection	Large Molecule (Enzymes, Metabolic)	Pompe disease	Lysosomal acid alpha-glucosidase (GAA) deficiency biomarker	2021
Belzutifan	Tablets	Small Molecule	Von Hippel-Lindau (VHL) disease	UGT2B17 and CYP2C19	2021
Mobocertinib	Capsules	Small Molecule	NSCLC	EGFR exon 20	2021
Avacopan	Capsules	Small Molecule	Adjunct therapy for active severe vasculitis (GPA and MPA)	ANCA	2021
Asciminib	Tablets	Small Molecule	Chronic myeloid leukemia (CML)	Philadelphia chromosome (Ph+) and T315I mutation biomarkers	2021
Efgartigimod alfa-FCAB	Injection	Large Molecule (Fc Receptor Antagonists)	Generalized myasthenia gravis (gmg)	Anti-acetylcholine receptor (AChR) antibody	2021
Inclisiran	Injection	Large Molecule (PCSK9 Inhibitors)	Heterozygous familial hypercholesterolemia (hefh) or clinical ASCVD	PCSK9 mRNA	2021

Table 2. *Cont.*

Drug	Dosage Form	Molecule Type	Indication	Receptor/Target	Year
Lisocabtagene Mar Aleucel	Cell suspension for infusion.	Large Molecule (CAR-T Cell Therapies)	Refractory large B-cell lymphoma (DLBCL, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B)	CD19	2021
Idecabtagene Vicleucel	Cell suspension for intravenous infusion.	Large Molecule (CAR-T Cell Therapies)	Refractory multiple myeloma	BCMA	2021
Avapritinib	Tablets	Small Molecule	Metastatic gastrointestinal stromal tumor (GIST)	PDGFRA exon 18	2020
Bempedoic Acid	Tablets	Small Molecule	Familial hypercholesterolemia who require additional lowering of LDL-C	FH biomarker (LOLR, APOB, PCSK9)	2020
Tucatinib	Tablets	Small Molecule	Metastatic breast cancer	HER2	2020
Pemigatinib	Tablets	Small Molecule	Cholangiocarcinoma	FGFR2	2020
Sacituzumab Govitecan-HZIY	Injection	Large Molecule (Antineoplastic Topoisomerase Inhibitors)	Metastatic triple-negative breast cancer	ER, PR, HER2	2020
Capmatinib	Tablets	Small Molecule	Non-small cell lung cancer (NSCLC)	MET exon 14	2020
Selpercatinib	Capsules	Small Molecule	Lung and thyroid cancers	RET fusion	2020
Inebilizumab-CDON	Injection	Large Molecule (Monoclonal Antibodies)	Neuromyelitis optica spectrum disorder	AQP4	2020
Fostemsavir	Tablets	Small Molecule	HIV infection	HIV-1 expression levels	2020
Risdiplam	Oral solution	Small Molecule	Spinal muscular atrophy	SMN2	2020
Oliceridine	Injection	Small Molecule	Acute pain	CYP2D6	2020
Viltolarsen	Injection	Large Molecule (Neurologics, Antisense Oligonucleotides)	Duchenne muscular dystrophy	DMD gene exon 53	2020
Satralizumab-MWGE	Injection	Large Molecule (Monoclonal Antibodies)	Neuromyelitis optica spectrum disorder	AQP4 biomarker	2020
Pralsetinib	Capsules	Small Molecule	Treatment of non-small cell lung cancer (NSCLC)	RET fusion biomarker	2020
Lonafarnib	Capsules	Small Molecule	Treatment of progeroid laminopathies	LMNA and/or ZMPSTE24 biomarkers	2020
Lumasiran	Injection	Large Molecule (RNAi Agents)	Treatment of hyperoxaluria type 1	HAO1 biomarker	2020

Table 2. *Cont.*

Drug	Dosage Form	Molecule Type	Indication	Receptor/Target	Year
Setmelanotide	Injection	Large Molecule (Melanocortin Agonists)	Treatment of obesity due to pro-opiomelanocortin (POMC) deficiency	POMC, PCSK1, or LEPR biomarkers	2020
Berotralstat	Capsules	Small Molecule	Treatment of hereditary angioedema types I and II	C1-INH biomarker	2020
Margetuximab-CMKB	Injection	Large Molecule (Antineoplastics, Anti-HER2)	Treatment of breast cancer	HER2 biomarker	2020

IV: intravenous; SC:Subcutaneous; IM: Intramuscular; UPCR-: Urine protein-to-creatinine ratio; PI3Ks: Phosphoinositide 3-kinases; APOE ε4: Apolipoprotein E epsilon 4; AD: Alzheimer's disease; ESR1:Estrogen receptor 1; SOD1: Superoxide dismutase 1; ALS: Amyotrophic lateral sclerosis; AChR-MG: Acetylcholine receptor Abs positive myasthenia gravis; MuSK-MG: Muscle-specific tyrosine kinase Abs positive myasthenia gravis; ALK2: Activin receptor-like kinase 2; BMPs: Bone morphogenetic proteins; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; PIK3CA/AKT1/PTEN: PIK3CA: Phosphatidylinositol 3-kinase catalytic subunit alpha; AKT1: Protein kinase B; PTEN: Phosphatase and tensin; DMD: Duchenne muscular dystrophy; BCL11A: B-cell lymphoma/leukemia 11A; JAK1: Janus kinase 1; PD-1:Programmed death protein 1; LAG-3: Lymphocyte activation gene 3; KRAS G12C: Kirsten rat sarcoma viral oncogene homolog glycine-to-cysteine mutation at codon 12; MET: Mesenchymal-epithelial transition; NSCLC: Non-small cell lung cancer; HoFH: Homozygous familial hypercholesterolemia; LDL: low-density lipoprotein cholesterol; PD-L1: Programmed death-ligand 1; CRC: Colorectal cancer; dMMR: deficiency in mismatch repair; UGT 2B17: UDP-glucuronosyltransferase; ANCA: Antineutrophil cytoplasmic antibodies; PCSK9 mRNA: Protein (Proprotein convertase subtilisin/kexin type 9 A messenger RNA; CD19: Cluster of Differentiation 19; BCMA: B-cell maturation antigen; PDGFRA exon 18: Platelet-derived growth factor receptor alpha exon 18; GISTs: Gastrointestinal stromal tumors; LOLR: Loss of Liver Reserve; apoB: Apolipoprotein B; CVD: Cardiovascular disease risk; RET: Rearranged during Transfection fusion; AQP4 antibody: Aquaporin-4 antibody; SMA: Spinal Muscular Atrophy; CYP2D6: Cytochrome P450 family 2 subfamily D member 6; LMNA: Lamin A/C; ZMPSTE24: Zinc Metallopeptidase STE24; HAO1: Hydroxyacid Oxidase; POMC: Pro-opiomelanocortin; PCSK1: Proprotein convertase subtilisin/kexin type 1; LEPR: Leptin receptor; C1-INH: C1 esterase inhibitor.

2. Cancer

2.1. Targeted Therapy and Precision Medicine in Cancer

Cancer remains one of the leading causes of death globally, with a significant impact on public health [14,37]. In 2022, approximately 20 million new cancer cases and 10 million cancer-related deaths were reported worldwide [38]. Projections for 2024 estimate that 2,001,140 new cancer cases will be diagnosed in the United States, with 611,720 fatalities expected [39]. By 2040, the global incidence of cancer is anticipated to reach 28.4 million cases, underscoring the urgent need for the development of effective therapies to treat cancer patients [40].

Traditional cancer treatments are often tailored based on factors such as tumor location, size, biology, the extent of spread, and the patient's overall condition [41]. These treatments typically include localized options like surgery and radiation therapy, as well as systemic treatments such as chemotherapy, which can be used individually or in combination [42–45]. These therapies can be further classified based on their pharmacological actions into categories such as conventional chemotherapy, radiopharmaceuticals, immunotherapies, and targeted therapies, which include hormone therapies and inhibitors of oncogenic mechanisms, angiogenesis, or immunomodulation. Conventional chemotherapeutic agents act by inhibiting actively proliferating cells by disrupting their DNA synthesis, blocking mitosis (anti-mitotic agents) and covalent binding with proteins [46]. Chemotherapy is associated with non-selective action against actively proliferating normal cells, resulting in severe systemic side effects and toxicity [47,48]. Radiation therapy involves the use of high-dose radiation to targeted disease sites, delivered externally using a machine (external beam radiation therapy) or internally via radioactive substances placed directly into or near the tumor [49]. However, a major challenge includes the deposition of radiation doses into healthy tissues [31]. Hence, these traditional cancer treatments (chemotherapy and radiation) often have broad and non-specific effects, leading to significant side effects [50].

Tumor cells are characterized by specific genetic biomarkers that distinguish them from healthy cells, facilitating rapid proliferation and differentiation [51]. Targeted anticancer therapies aim to inhibit the growth and spread of tumor cells by selectively targeting these biomarkers [10] (Figure 1). This approach, known as "precision medicine," focuses on the mechanisms of oncogenesis with higher specificity towards cancer cells or their microenvironment [52]. The use of targeted treatments is guided by the molecular characteristics of each patient's tumor, such as tumor differentiation, genetic alterations such as mutations/overexpression of oncogenes, loss of function of tumor suppressor genes, and proteomes [7,53]. Currently, most targeted therapies are used as monotherapy. Advances in molecular profiling have enabled the identification of specific gene expression patterns in different tumor types, aiding in the selection of targeted therapies [54]. Recent developments in genomic profiling and next-generation sequencing (NGS) have greatly improved targeted cancer therapies, leading to better outcomes for patients. Emerging technologies such as CRISPR and artificial intelligence (AI) are advancing personalized medicine by enabling the detection of actionable mutations and improving the design of treatment strategies [55].

The first targeted therapy approved by the U.S. Food and Drug Administration (FDA) was trastuzumab, marketed under the brand name Herceptin. It received FDA approval on 25 September 1998 [56]. Trastuzumab is a monoclonal antibody that targets the HER2/neu receptor and is used in the treatment of HER2-overexpressing breast cancer and metastatic gastric or gastroesophageal junction adenocarcinoma [57]. Numerous FDA-approved targeted agents have been developed, targeting pathways such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), rearranged during transfection (RET), mesenchymal-epithelial transition (MET), V-RAF murine sarcoma viral oncogene homolog

B1 (BRAF), C-Ros oncogene 1 (ROS1), as well as molecules targeting programmed death receptor 1 (PD1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA4), which are now standard care for selected patients [58–62].

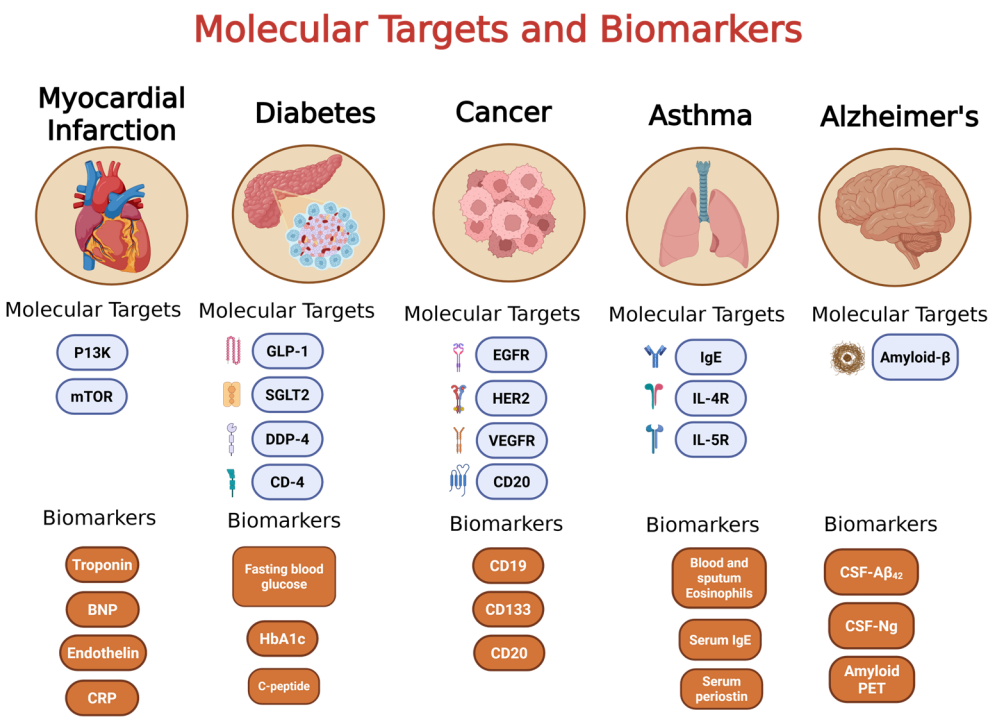


Figure 1. Overview of Key Molecular Targets and their Biomarker for various disease conditions.

Between 2020 and 2025, the FDA approved several personalized cancer therapies, showcasing major progress in biomarker-guided precision oncology. Targeted small molecule inhibitors were approved for tumors driven by specific mutations, including sotorasib and adagrasib for KRAS G12C, pemigatinib and futibatinib for FGFR2-altered cholangiocarcinoma, selpercatinib and pralsetinib for RET fusions, capmatinib and tepotinib for MET exon 14 skipping NSCLC, quizartinib for FLT3-ITD AML, and repotrectinib for ROS1-positive NSCLC. Antibody-based agents also expanded, including durvalumab (PD-L1), toripalimab (PD-1), retifanlimab (PD-1), and ADCs such as datopotamab deruxtecan-DLNK (TROP2) and mirvetuximab soravtansine (FRα). Immunotherapies broadened across tumor types, and CAR-T cell therapies such as lisocabtagene maraleucel and idecabtagene vicleucel gained approval for refractory lymphomas and multiple myeloma. Collectively, these therapies underscore the rapid shift toward molecularly defined personalized cancer treatment approaches designed to improve precision and patient outcomes.

2.2. Types of Targeted Therapies in Cancer

There are several targeted therapeutic agents used clinically as cancer therapeutics. The two major classes of cancer molecular targeted therapy include small molecule kinase inhibitors (SMKIs) and monoclonal antibodies (mAbs).

2.2.1. Small Molecule Kinase Inhibitors (SMKIs)

Protein kinases have a crucial role in cell growth, proliferation and differentiation [63]. Protein kinases undergo dysregulation, which commonly includes autonomous activation of the receptor, chromosomal amplification, activation by gain-of-function genetic mutation, and gene amplification leading to cancer progression [64]. These are categorized into receptor tyrosine kinases, non-receptor (cytoplasmic) tyrosine kinases, serine/threonine

kinases, and lipid kinases based on their subcellular localization, substrate type, and hallmark roles in cancer [65].

Protein kinases are therefore extensively explored as tumor therapeutic targets. These are classified based on their mechanism of action into six categories. Type 1 Inhibitors act by binding to the ATP-binding pocket of the active conformation of the kinase [48]. The best example of this inhibitor is Gefitinib, which is an EGFR tyrosine kinase inhibitor that binds to the intracellular tyrosine kinase domain to inhibit tumor progression [66]. Type II inhibitors commonly include drugs like imatinib, dasatinib, and sorafenib that bind to inactive kinase conformation [67–69]. Type III and type IV inhibitors, being allosteric in nature, bind either to a site next to the ATP-binding pocket or one remote from the ATP-binding pocket located in the kinase substrate-binding site, thereby causing suppression of kinase activity [70]. Type V inhibitors like Lenvatinib act as bivalent inhibitors bound to two different portions of the kinase [71]. Lastly, Type VI inhibitors, also called irreversible inhibitors that covalently bind to an enzyme to inhibit kinase activity [8]. Dacomitinib and afatinib are clinically approved EGFR-TKIs for the treatment of NSCLC [72].

Typically, small-molecule inhibitors are taken orally, unlike monoclonal antibodies, which are administered through the parenteral route. The production of small-molecule inhibitors involves chemical synthesis, which is generally more cost-effective compared to the complex bioengineering required for monoclonal antibodies [73]. Additionally, small molecule inhibitors often have short half-lives, necessitating daily dosing [74]. Imatinib, one of the pioneering and most successful small-molecule inhibitors, was approved in 2002 for treating chronic myeloid leukemia [75]. It works by inhibiting an always-active tyrosine kinase caused by the translocation of chromosomes 9 and 22 [76]. This genetic anomaly is present in nearly all chronic myeloid leukemia patients, leading to a complete hematologic response in 98% of cases [76]. More recently, small molecule inhibitors targeting the EGFR pathway have been employed to treat solid tumors, such as non-small cell lung cancer [58]. Small-molecule drugs predominantly target proteins, particularly enzymes and receptors, which may result in limited activity against membrane-associated and secretory proteins. Additionally, the variability in metabolic processes complicates the precise adjustment of the dose of SMKI, making it difficult to attain optimal therapeutic efficacy [77].

2.2.2. Monoclonal Antibodies (mAbs)

Monoclonal antibodies are immunotherapy-based therapeutics that directly target the tumor cells while simultaneously promoting long-lasting anti-tumor immune responses [78]. Monoclonal antibodies (mAbs) are proteins produced by B cells that specifically recognize and bind to target antigens. There are five major isotypes of mAbs: IgG, IgA, IgM, IgD, and IgE. Among these, IgG, particularly the IgG1 and IgG4 subclasses, is commonly utilized in the development of therapeutic monoclonal antibodies due to its extended half-life and high affinity for target antigens. These antibodies are designed to exert a range of effects, including the targeted elimination of cancer cells [77]. The monoclonal antibodies possess an antigen-binding (Fab) region that recognizes and binds to the antigen, resulting in highly specific targeting of cancer. These have half-lives ranging from days to weeks (thereby reducing the dosing frequency) [73].

Monoclonal antibodies exert their anticancer effects through multiple mechanisms: They could act by recruiting host immune functions (including natural killer cells and the complement cascade) to attack the cancer cell; these are referred to as cytotoxic mAbs. For example, the first mAb approved in 1997 for B-cell lymphoma was rituximab. It induces B cells to become cytotoxic and initiates blocking of the CD20 antigen on B lymphocytes [79]. They can also bind to receptors, thereby inhibiting the auto-activation of essential cancer progression pathways [78]. For example, Cetuximab is an mAb that acts by blocking

ligand binding and receptor dimerization of EGFR [80,81]. They can also act by carrying a lethal payload, such as a drug, radioisotope, or toxin, to the target cell (i.e., conjugated monoclonal antibodies).

One of the primary challenges associated with monoclonal antibodies (mAbs) is their high production cost [82]. As multimeric proteins, mAbs require complex eukaryotic expression systems for large-scale production with high purity, which contributes to their expense [83]. Another significant limitation is the potential for antibody-related side effects, including long-term immune system activation, suppression of other cellular functions, and inherent immunogenicity [77]. These adverse effects can complicate the therapeutic use of mAbs. Additionally, the low penetration efficiency of mAbs into target tissues and their long serum half-life present ongoing challenges [59]. Prolonged serum half-life, while beneficial for sustained exposure, can also increase the risk of immune-related adverse events. Monoclonal antibodies are composed of protein structure, which undergoes degradation in the gastrointestinal tract; hence, monoclonal antibodies are commonly administered intravenously. They do not undergo hepatic metabolism, so they are not subject to significant drug interactions. mAbs are metabolized to peptides and amino acids in several tissues, by circulating phagocytic cells or by their target antigen-containing cells or by their target antigen-containing cells. The metabolism and pharmacokinetics of mAbs can differ significantly depending on the type of cancer being treated, influenced by various factors such as tumor characteristics, patient-specific variables, and the tumor microenvironment. One key factor is target expression, where tumors with high levels of the targeted antigen may experience faster clearance of the drug due to increased binding and more rapid uptake. The tumor microenvironment, often characterized by a lower pH and elevated enzyme activity, can also affect mAb stability and degradation, impacting their half-life and therapeutic effectiveness. Additionally, cancer type-specific factors such as the expression of certain receptors may lead to accelerated receptor-mediated endocytosis and degradation of mAbs, altering their bioavailability and response. Patient variability, including genetic polymorphisms affecting Fc receptor function or other immune-related pathways, can further influence the distribution and metabolism of mAbs. Finally, when used in combination therapies, mAbs may undergo altered pharmacokinetics, as cytotoxic agents can modify immune system function, potentially affecting the antibody's clearance or therapeutic activity [84]. A comprehensive understanding of these factors is essential for optimizing mAb-based therapies, allowing for more personalized treatment strategies that enhance efficacy and minimize side effects.

In recent times emergence of a novel concept called antibody–drug conjugate (ADC) has been developed to bridge the gap between mAbs and cytotoxic drugs with the aim of improving the therapeutic window [85]. Antibody–drug conjugates (ADCs) are a class of targeted therapeutics that consist of monoclonal antibodies (mAbs) specifically engineered to bind to tumor-associated antigens, covalently linked to cytotoxic payloads through a carefully designed chemical linker [86]. These ADCs consist of a three-component structure: an antibody that selectively binds to a target antigen, a highly potent drug (payload) that induces targeted cell death, and a linker that connects the antibody to the drug [87]. This configuration facilitates the selective delivery of potent cytotoxic agents to malignant cells while minimizing off-target toxicity to healthy tissues. ADCs are often referred to as "biological missiles" due to their precise targeting mechanism, where the antibody acts as the "guidance system" and the cytotoxic payload serves as the "warhead." Upon administration, the ADC circulates in the bloodstream, where the antibody specifically binds to its corresponding antigen on the surface of target cells. Following binding, the ADC-antigen complex is internalized by the target cell via endocytosis. Once inside the cell, the payload is released through lysosomal degradation, leading to the activation of

cytotoxic effects and ultimately triggering apoptosis in the target cell [59]. Thus, enhancing the therapeutic index and widening the therapeutic window with reduced systemic toxicity. The approval of Mylotarg™ (gemtuzumab ozogamicin) for treatment of adults with acute myeloid leukemia (AML) marked a significant milestone in targeted therapies of cancer [20].

2.3. Nanotechnology in Cancer Treatment

Nanotechnology is emerging as a critical tool in targeted therapy and personalized medicine, particularly for treating rare and chronic diseases. Nanomedicines enable the implementation of the concept of "vectorization," also referred to as drug targeting [18]. Doxil® (Doxorubicin HCl Liposome Injection) allows the drug to accumulate in tumor tissues due to enhanced permeability and retention (EPR). This EPR effect is not classified as a targeted therapy in the strict sense because it is passive targeting. It is passive because it does not involve any specific interaction between the drug delivery system and tumor cells. Even though many nanotechnology-based drug delivery systems primarily rely on the EPR effect for passive targeting (like Abraxane® and Doxil), products like MM-302 provide both passive (EPR) and active targeting (targeted therapy). The strategy to achieve this combined effect is due to the attachment of ligands (like antibodies, peptides, or small molecules) that target specific receptors on cancer cells. The modification of Doxil with anti-HER2 monoclonal antibody fragments resulted in a targeted formulation that demonstrated anticancer efficiency against tumor lines overexpressing HER2, far superior to that of control non-targeted liposomes both in cell culture and in in vivo models [88]. HER2-targeted PEGylated antibody–liposomal doxorubicin conjugate (MM-302) targets HER2-overexpressing tumor cells, delivers doxorubicin to tumor cells, and limits exposure to healthy cells such as cardiomyocytes. MM-302 demonstrated superior antitumor activity compared to both doxorubicin and PEGylated liposomal doxorubicin [89]. Similarly, the US-FDA recently approved Margetuximab in the year 2020 as a combination chemotherapeutic for use in adult patients suffering from metastatic HER-2 positive breast cancer. The Margetuximab is a chimeric antibody that binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2), inhibits tumor cell proliferation, reduces shedding of the HER2 extracellular domain, and mediates antibody–dependent cellular cytotoxicity (ADCC) [21].

3. Diabetes

3.1. Targeted Therapy and Personalized Medicine in Diabetes

Diabetes is a chronic metabolic disorder characterized by high levels of glucose in the blood. It affects approximately 422 million individuals globally, with a disproportionate burden falling on low- and middle-income countries. The disease has a significant impact on mortality rates, directly causing about 2 million deaths annually [90]. Diabetes is classified into three main types. Firstly, Type 1 diabetes is characterized by little or no insulin production due to autoimmune destruction of beta cells, leading to insulin deficiency. Type 1 diabetes is commonly seen in children and young adults [23]. Secondly, Type 2 Diabetes (T2DM) is the most common diabetes, characterized by insulin resistance, usually occurring in adults. Thirdly, gestational diabetes develops due to the combination of insulin resistance, which is naturally heightened by the hormonal changes of pregnancy, and the inability of the pancreas to produce enough insulin to overcome this resistance [91]. T2DM is due to mutations in either a single gene (monogenic diabetes) or multiple genes (polygenic mutations). As mono-target therapy fails in managing blood glucose levels and the other comorbidities, personalized medicine could exploit new clinically available multi-target drugs [22]. The concentration of cases in less economically developed nations

highlights the need for targeted interventions and improved healthcare access in these regions to address diabetes.

3.1.1. Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RAs)

GLP-1, a peptide hormone, is naturally produced by specialized cells in the intestine (enteroendocrine L-cells), certain neurons in the brainstem's solitary tract, and some pancreatic α-cells. Released in response to eating, GLP-1 activates a specific receptor known as GLP-1R, a class B, G protein-coupled receptor. This activation plays a key role in stimulating insulin release, reducing glucagon secretion, slowing gastric emptying, and promoting feelings of fullness, helping to curb food intake. GLP-1 effectively reduces appetite and increases satiety in both healthy individuals and those managing obesity or diabetes.

A major hurdle in developing GLP-1 receptor agonists was GLP-1's extremely short half-life in the bloodstream, only about 2 min, due to rapid breakdown by the enzyme dipeptidyl peptidase-4 (DPP-4), which inactivates GLP-1 by removing two amino acids from its N-terminus, essential for receptor binding. To overcome this, scientists developed DPP-4-resistant formulations that could activate the GLP-1 receptor more effectively.

Clinical trials comparing various GLP-1 receptor agonists have demonstrated semaglutide's effectiveness over other options. The SELECT cardiovascular outcomes study showed that semaglutide, at a dose of 2.4 mg weekly, reduced the relative risk of major cardiovascular events by 20% compared to a placebo. Overall, GLP-1 agonists are considered safe, with most users experiencing only mild to moderate side effects such as nausea, vomiting, diarrhea, and constipation.

These agents have demonstrated particular efficacy in Type 2 Diabetes Mellitus (T2DM), not only for glycemic management but also for promoting weight loss. GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are both susceptible to inactivation by dipeptidyl peptidase-4 (DPP-4), stimulate insulin secretion post-prandially via the incretin effect [78]. The "incretin effect" describes the body's heightened insulin response after consuming glucose orally compared to an equivalent amount administered directly into the bloodstream. This effect is driven by incretin hormones, mainly GLP-1 and GIP, which are released by the intestines in response to food. These hormones boost insulin secretion and suppress glucagon release, helping to regulate blood sugar levels after eating. In type 2 diabetes, however, this response is often reduced, making incretin hormones a focus of diabetes treatment. In 2005, exenatide was first approved GLP-1 RAs for the treatment of T2DM.

Tirzepatide (Mounjaro®) is a dual-acting GIP and GLP-1 receptor agonist, used alongside diet and exercise to improve blood sugar control in adults with type 2 diabetes. By activating both GIP and GLP-1 receptors, which are linked to appetite regulation, tirzepatide helps reduce food intake and enhance fat metabolism. A study showed that tirzepatide led to significantly greater weight loss compared to semaglutide, with an average reduction of 15.3% in body weight at 12 months, versus 8.3% with semaglutide. These findings highlight tirzepatide's potential advantage for weight management in people with overweight or obesity [92].

3.1.2. Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

SGLT2 inhibitors, also known as gliflozins, target the sodium-glucose cotransporter 2 in the renal proximal tubules, effectively reducing blood glucose levels by promoting urinary glucose excretion. These agents inhibit renal glucose reabsorption, inducing glucosuria and consequently reducing glycemia. Studies have shown that SGLT2 inhibitors can lower HbA1c by approximately 1.0%. Moreover, the concomitant sodium excretion modulates tubuloglomerular feedback, reducing intraglomerular pressure, a mechanism

central to the nephroprotective effects observed with SGLT2 inhibitors [24]. Additionally, SGLT2 has been shown to reduce blood pressure and promote average weight loss of 2–3 kg over a period of 6 months [25]. Side effects associated with SGLT-2i are very minor, making gliflozins extremely well-tolerated drugs. The most frequently reported adverse effects are urogenital infections, particularly fungal infections, which tend to occur more frequently in women and older adults. These side effects are usually manageable and do not significantly impact the overall safety profile of the drug.

3.1.3. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

DPP-4 inhibitors, commonly referred to as gliptins, function by inhibiting the enzyme dipeptidyl peptidase-4, which is responsible for the degradation of incretin hormones such as GLP-1. This inhibition leads to increased insulin secretion in response to meal ingestion, facilitating improved glycemic control. The physiological role of DPP-4 in regulating incretin hormones, particularly GLP-1 and GIP, is well-established in the literature [93]. FDA-approved DPP-4 inhibitors include sitagliptin, saxagliptin, linagliptin, and alogliptin, while vildagliptin is approved by the European Medicines Agency (EMA). These medications exert their effects through incretin hormones, which are key regulators of glucose homeostasis after oral food consumption.

DPP-4 inhibitors are typically well-tolerated and do not usually cause hypoglycemia, unless used in combination with other medications that lower blood sugar. Common side effects observed with drugs like sitagliptin and saxagliptin include upper respiratory tract infections, nasopharyngitis, headache, urinary tract infections, and arthralgia. One of the significant advantages of DPP-4 inhibitors is their lack of associated weight gain and minimal risk of hypoglycemia, making them suitable for combination therapy with insulin. These drugs prevent blood sugar spikes, do not cause weight gain, and are associated with a low risk of hypoglycemia. Other benefits include their convenient oral administration, compatibility with other drugs, cardiovascular safety, and the absence of a requirement for blood sugar monitoring. Additionally, DPP-4 inhibitors may offer protective effects on pancreatic beta cells and have fewer gastrointestinal side effects, making them a favorable option, particularly for older patients.

3.2. Personalized Therapies for Diabetes

Although many antidiabetic medicines such as GLP-1 receptor agonists and SGLT-2 inhibitors have been successfully developed in recent years, single-target drugs are gradually failing to meet the therapeutic requirements owing to the individual variability, diversity of pathogenesis, and organismal resistance [94]. Figure 2 shows the schematic representation of personalized medicine in diabetes. Personalized medicine treatment for T2DM considers medical, social, personal, as well as phenotypic, biochemical and genetic factors. Key medical factors include the diabetes phenotype, available biomarkers (e.g., autoantibodies, urinary C-peptide and genetic tests) and the presence of medical comorbidities such as cardiovascular or renal disease. Treatment decisions should also account for the presence of other complications such as peripheral vascular disease, retinopathy and neuropathy [95]. In personalized medicine, treatment interventions must be based on individual patient genetic makeup, lifestyle factors, environmental influences, and specific health data. This field also incorporates cutting-edge technologies, such as continuous glucose monitoring and wearable devices, which enable patients to actively engage in the management of their diabetes [96]. Personalized medicine involves defining disease subtypes and defining biomarkers that can identify which patients are most likely to benefit from a specific treatment and which patients are most unlikely to respond or likely to experience side effects [97].

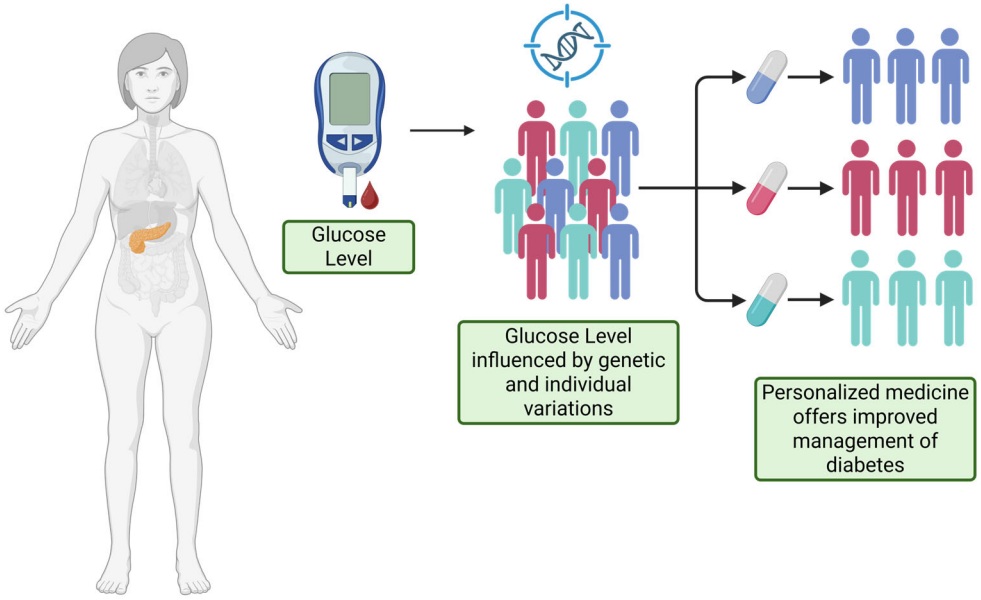


Figure 2. Schematic representation of personalized medicine in diabetes.

4. Asthma

4.1. Targeted Therapy and Personalized Medicine in Asthma

Asthma is a chronic respiratory disorder characterized by persistent airway inflammation, excessive airway sensitivity, and variable airflow obstruction [98]. The underlying inflammation causes the airways to become swollen and overly reactive to environmental triggers, leading to bronchoconstriction and difficulty in breathing [99]. This hyperresponsiveness, coupled with the ongoing inflammatory process, underpins the variability in airflow obstruction and the episodic nature of asthma symptoms, making it a highly individualized disease [99]. In recent years, targeted therapies have become essential in the treatment of severe asthma by focusing on distinct biological subtypes, or endotypes, and clinical characteristics, or phenotypes, of the disease. These treatments are specifically designed to interfere with the immune pathways and inflammatory mediators responsible for asthma, allowing for a more tailored approach to managing the condition. By identifying specific molecular targets such as cytokines and immune cells, these therapies offer more personalized and effective options for patients who do not respond well to traditional treatments. A personalized medicine approach in asthma recognizes the significant heterogeneity in disease presentation and treatment response, driven by genetic, environmental, and immunological factors [100]. Precision medicine in asthma now utilizes clinical biomarkers such as blood and sputum eosinophils, serum IgE, and FeNO to identify disease endotypes and guide targeted therapies [30]. Recent developments also include the use of artificial intelligence (AI) and machine learning to analyze patient data, predict exacerbations, and recommend personalized interventions, further enhancing individualized asthma management.

4.1.1. Asthma Endotypes and Phenotypes

Asthma is a heterogeneous disease that presents in various forms depending on the underlying biological mechanisms. Based on specific pathophysiological processes, asthma is divided into different subtypes, known as endotypes. Two major endotypes have been identified: Type 2 (T2)-high asthma and T2-low asthma, each driven by different immune responses [101,102].

T2-high asthma is the more prevalent subtype, driven by T2 inflammation, which involves cytokines like interleukin (IL)-4, IL-5, and IL-13 [103]. These cytokines are produced

not only by T-helper 2 (Th2) cells but also by type 2 innate lymphoid cells (ILC2s). Patients with T2-high asthma often present with elevated eosinophil counts and higher levels of immunoglobulin E (IgE) [104]. This subtype typically responds well to corticosteroid treatments due to the role of eosinophils in its inflammatory process.

T2-low asthma, less common, is characterized by non-eosinophilic inflammation, which mainly involves neutrophils. Unlike T2-high asthma, it is less responsive to corticosteroids and does not show elevated levels of IgE or eosinophils. Managing T2-low asthma often requires different therapeutic approaches, such as macrolide antibiotics or new biologic treatments that target alternative inflammatory pathways.

4.1.2. Targeted Therapies for T2-High Asthma

Several biologic therapies have been developed to target specific pathways involved in T2-high asthma. These therapies aim to reduce the inflammatory response driven by Th2 cells and other associated immune mechanisms.

Anti-IgE Therapy (Omalizumab): Omalizumab was the first biologic approved for asthma treatment and is specifically designed for allergic asthma [26]. It works by binding to IgE, a key antibody involved in allergic reactions, thereby preventing it from interacting with its receptors on immune cells [105]. This reduces the release of inflammatory mediators and has been shown to significantly decrease asthma exacerbations and improve lung function in patients with moderate to severe allergic asthma.

Anti-IL-5 Therapies (Mepolizumab, Reslizumab, Benralizumab): IL-5 is a crucial cytokine responsible for the growth, activation, and survival of eosinophils, a type of white blood cell involved in T2 inflammation. Targeting IL-5 has proven effective in reducing eosinophil counts and improving asthma control in patients with severe eosinophilic asthma. Mepolizumab and reslizumab directly inhibit IL-5, while benralizumab depletes eosinophils by targeting the IL-5 receptor on these cells [27–29,106].

Anti-IL-4 and Anti-IL-13 Therapy (Dupilumab): IL-4 and IL-13 are key cytokines that contribute to the development of airway hyperresponsiveness and mucus production. Dupilumab, an anti-IL-4 receptor alpha monoclonal antibody, blocks the signaling of both IL-4 and IL-13. This dual inhibition has shown greater efficacy compared to therapies that target IL-13 alone, making dupilumab a promising treatment for patients with severe T2-high asthma.

4.1.3. Targeted Therapies for T2-Low Asthma

T2-low asthma, characterized by neutrophilic inflammation, represents a more challenging subtype due to its poor response to corticosteroids and the lack of eosinophilic biomarkers. However, several targeted therapies are being explored.

IL-33 and TSLP Blockers: IL-33 and thymic stromal lymphopoietin (TSLP) are cytokines involved in the activation of innate immune responses in the airways. Both are currently being investigated as therapeutic targets in T2-low asthma. TSLP, for instance, plays a key role in activating dendritic cells and promoting Th2 responses, and its inhibition could be beneficial for patients with non-eosinophilic asthma [106].

5. Myocardial Infarction

5.1. Targeted Therapies and Personalized Medicine in Myocardial Infarction

Ischemic heart disease, particularly myocardial infarction (MI), is the leading cause of death globally, surpassing all cancer-related fatalities. A total of 146 deaths per 100,000 population are recorded in 2021, surpassing the deaths due to COVID in 2021 [107]. MI poses a significant challenge to healthcare systems worldwide due to its high mortality rates among both older adults and those under 65. It is primarily caused by atherosclerosis,

where plaques accumulate in the coronary arteries, restricting or blocking blood flow to the heart muscle [108]. This blockage results in irreversible damage to the myocardium within hours. While timely reperfusion through methods like percutaneous coronary intervention, coronary artery bypass grafting, or thrombolysis is crucial to restoring blood flow and rescuing heart cells, it can also lead to ischemia–reperfusion injury due to oxidative stress, exacerbating cell death in the short term [108,109]. The limited regenerative capacity of heart cells complicates recovery, as damaged cells are replaced by scar tissue, maintaining structural integrity but impairing heart function. This process can ultimately lead to heart failure. Following MI, the inflammatory response initiated by injured cells triggers the release of cytokines and the infiltration of immune cells like macrophages, which aid in clearing debris and promoting angiogenesis [110]. However, this inflammation can also expand the infarct until macrophages transition to a reparative role, characterized by fibroblast activation and collagen deposition, leading to scar formation. Despite compensatory mechanisms like ventricular dilation, chronic remodeling can result in impaired heart function and heart failure. Current treatments focus on rapidly restoring blood flow and managing inflammation, but no therapies directly enhance cardiac regeneration.

Ischemic heart disease is a major threat to human health, making new treatment strategies for myocardial infarction (MI) crucial. Recent therapeutic approaches have focused on cellular and molecular processes in MI. Current therapies like pharmacotherapy, gene therapy, protein therapy, cell therapy, and exosome therapy show promising clinical potential. Targeting molecular signaling pathways, such as PI3K/Akt, Notch, TGF-β/SMADs, and others, has shown positive results in both preclinical and clinical studies. These pathways, involved in inflammation, oxidative stress, fibrosis, and regeneration, form a complex regulatory network. Therapies targeting multiple pathways may offer more effective cardiac repair and MI prevention [109]. No nanodrugs are currently approved for treating myocardial infarction (MI), and about 20% of US FDA-approved nanodrugs are designed for cancer therapy [111,112]. Additionally, a clinical trial investigating liposomal methotrexate for MI (NCT03516903) was halted due to the COVID-19 pandemic [113,114]. Table 3 provides an overview of therapeutic strategies for myocardial infarction, including drugs, gene therapies, and cell therapies, highlighting their associated molecular markers and signaling pathways. These strategies aim to target key pathways such as PI3K/Akt, mTOR, MAPK, NLRP3/IL-1β, and TGF-β/SMADs to enhance cardiac function and promote tissue repair.

Table 3. Overview of therapeutic strategies for myocardial infarction [109].

Intervention	Therapeutic Strategy	Clinical Trial ID	Molecular Markers/Signal Pathways
Ivabradine	Drug (I(f) Current Inhibitors)	NCT05279651 (Phase III)	PI3K/Akt/mTOR
Rapamycin/Sirolimus	Drug (Immunosuppressants)	NCT00288210 (Phase IV)	mTOR
Losmapimod	Drug (p38 MAPK)	NCT02145468 (Phase III)	MAPK
Canakinumab	Drug (Monoclonal Antibodies-Anti-inflammatory)	NCT01327846 (Phase III)	NLRP3/IL-1β
Colchicine	Drug (Anti-inflammatory)	NCT04420624 (Phase II, III)	NLRP3/IL-1β
Erythropoietin	Drug (Cardioprotective)	NCT00367991	MAPK, TGF-β, Wnt, Sonic Hedgehog
Estradiol	Drug (vasodilation, improved Endothelial function and Anti-atherosclerotic)	NCT00377988 (observational)	RhoA/ROCK
Estrogen	Drug (vasodilation, improved Endothelial function and Anti-atherosclerotic)	NCT00005185 (Observational)	RhoA/ROCK
Nicorandil	Drug (anti-free radical and neutrophil modulating, vasodilatation)	NCT02449070 (Phase III)	RhoA/ROCK
Dexmedetomidine	Drug (anti-inflammatory)	NCT04912518 (NA)	RhoA/ROCK
Valsartan	Drug (Angiotensin II receptor blockers-ARBs)	NCT01340326 (Phase IV)	TGF-β/SMADs
Sildenafil	Drug (Vasodialtor)	NCT01046838 (Phase IV)	JAK2/STAT3, RhoA/ROCK
G-Csf	Drug (Cardioprotective)	NCT00756756 (NA)	JAK2/STAT3, NF-κB
Methotrexate	Drug (beneficial effects on vascular homeostasis and blood pressure control)	NCT01741558 (Phase II)	NF-κB
Metformin	Drug (Reduces LDL C)	NCT05182970 (Phase III)	TLR4
Melatonin	Drug (reduces mitochondrial dysfunction)	NCT03230630 (observational)	Notch, Hippo/YAP
Fasudil	Drug (reduced myocardial infarct size-preclinical)	NCT03753269 (Phase IV)	TGFβ1/TAK1, TGF-β2, TGF-β3, RhoA/ROCK
Statin	Drug (anti-inflammatory and antithrombotic, and antioxidant effects)	NCT01205347 (Phase IV)	PI3K/Akt/FOXO3a, TGF-β/SMADs, Sonic Hedgehog, RhoA/ROCK/ERK, PI3K/Akt/Nrf2/HO-1

Table 3. *Cont.*

Intervention	Therapeutic Strategy	Clinical Trial ID	Molecular Markers/Signal Pathways
Hirudin	Drug (antithrombotic)	NCT05847205 (Phase IV)	KEAP1/Nrf2/HO-1
Vegf-A165 Plasmid	Gene Therapy	NCT00620217 (Phase II)	VEGF/PI3K/Akt
Adgvvegf121 Cdna	Gene Therapy	NCT01174095 (observational)	VEGF/PI3K/Akt
Endocardial Adenovirus Vegf-D Gene Transfer	Gene Therapy	NCT01002430 (Phase I)	VEGF/PI3K/Akt
Bicistronic Vegf-A165/Bfgf Plasmid	Gene Therapy	NCT00620217 (Phase II)	VEGF(bFGF)/PI3K/Akt
Cd34+ Cell	Cell Therapy	NCT00313339 (Phase I)	PI3K/Akt, Sonic Hedgehog
Cd133+ Cell	Cell Therapy	NCT00529932	PI3K/Akt, Wnt
Epcs	Cell Therapy	NCT00936819 (Phase II)	VEGF/PI3K/Akt/eNOS, Dll4/Notch/Hey2, Sonic Hedgehog, Akt/HO-1
Mscs	Cell Therapy	NCT05043610 (Phase III)	PI3K/Akt/mTOR, Wnt/β-catenin, TGF-β/SMADs, Notch, Sonic Hedgehog

MAPKs: Mitogen-activated protein kinases (MAPKs); TGF-β: Targeting transforming growth factor-β; RhoA: Ras homolog gene family member A; ROCK: Rho-associated coiled-coil containing kinase; TGF-β: Transforming growth factor-β, Suppressor of mother against; JAK2/STAT3: Janus Kinase 2/signal transducer and activator of transcription 3; NF-κB: Nuclear Factor Kappa B; TLR4: Toll-like receptor 4; YAP: Yes-associated protein; PI3K/Akt/FOXO3a:PI3K: Phosphat dylinositol 3-kinase/Akt: Protein kinase/Forkhead box protein O3; ERK: Extracellular signal-regulated kinase; PI3K/Akt/Nrf2/HO-1: Phosphatidylinositol 3-kinase/Protein kinase B/Nuclear factor erythroid-2 related factor 2/Heme oxygenase; KEAP1/Nrf2/HO-1: Kelch-like ECH-associated protein 1/Nuclear factor erythroid 2-related factor 2/Heme oxygenase-1; VEGF, PI3K, and Akt: Vascular endothelial growth factor/Phosphatidylinositol 3-kinase/Protein kinase B PI3K/Akt/mTOR: Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR); Wnt/β-catenin is Wingless–Int (Wnt) signaling pathway.

5.2. Nanoparticles in Myocardial Infarction

5.2.1. Supramolecular Self-Assembled Nanoparticles

Yang Jiao et al. developed a biodegradable nanoparticle-based delivery system with strong macrophage evasion and cardiac targeting capabilities for treating myocardial infarction. They synthesized a p(DMA–MPC–CD) copolymer that combines self-adhesion, hydration lubrication, and a targeting peptide binding site through free radical copolymerization. This copolymer was then assembled onto melatonin-loaded dendritic mesoporous silica nanoparticles (bMSNs), with adamantane-modified cardiac homing peptide (CHP) incorporated via supramolecular host-guest interactions. The zwitterionic phosphorylcholine groups on the nanoparticles formed a hydration layer, enhancing lubrication and reducing friction, which prevented macrophage phagocytosis. In vivo bioluminescence imaging confirmed efficient cardiac targeting, while studies in mice showed that intravenously administered drug-loaded nanoparticles (bMSNs–Mel@PDMC–CHP) reduced cardiomyocyte apoptosis, mitigated myocardial fibrosis, and improved heart function [115].

5.2.2. Magnetic Nanoparticles

Various metal compounds have been used to treat myocardial infarction (MI), with recent studies focusing on iron oxide-based magnetic nanoparticles (MNPs) due to their high responsiveness to manipulation by external magnetic fields. Cheng et al. modified superparamagnetic iron oxide nanoparticles (SPIONs), labeled therapeutic cells, and injected them into specific areas of the pre-infarcted region to deliver the cells to the damaged myocardium without the need for open-chest surgery. They conjugated an FDA-approved SPION (ferumoxytol, used for treating anemia) with two antibodies: one targeting myosin light chain from injured cardiomyocytes and the other, anti-CD45, specific to bone marrow-derived stem cells. This dual-antibody conjugation enabled high-affinity binding of therapeutic cells to damaged cardiomyocytes both in vitro and in vivo.

To assess the distribution and effectiveness of stem cells in cardiac therapy, tracking the fate of injected cells using various imaging techniques is crucial. Cell labeling is achieved by introducing probes into the cells or incorporating reporter genes into the genome. This labeling approach utilizes a range of modern imaging modalities, such as magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), fluorescence imaging, bioluminescence imaging (BLI), and positron emission tomography (PET), to detect the signal [116,117]. To visualize stem cells using MRI, it is crucial to label them with an appropriate contrast agent. These agents enhance the signal from specific cells in vivo. Iron-containing particles are commonly used for this purpose. For instance, Hill et al. labeled mesenchymal stem cells (MSCs) from pigs with an iron fluorophore particle (IFP) to enable MRI detection after transplantation [118]. Superparamagnetic iron oxide nanoparticles (SPIONs), a smaller variant of IFP, are among the most widely used contrast agents for stem cell labeling. A major limitation of SPIONs is their inability to differentiate between viable and nonviable cells. Recent research by Huang et al. demonstrated that the persistent MRI signals were primarily due to extracellular, rather than intracellular, iron particles.

5.2.3. Nanotheranostics

The advent of nanotechnology in biomedicine and healthcare has led to a major advancement in disease prognosis and the development of effective treatments for chronic conditions. Nano-based platforms have become versatile tools for early and precise disease diagnosis. Additionally, they enable targeted drug delivery and allow for monitoring therapeutic responses at the cellular level. These platforms incorporate various therapeutic approaches, such as gene therapy, chemotherapy, photodynamic therapy (PDT), and

photothermal therapy, each providing distinct benefits in enhancing treatment effectiveness [113,119,120].

Nanotechnology offers a promising solution by enabling nanotheranostics, which combines diagnostics and therapy for more effective and safer treatments [121,122]. This approach also lowers costs and improves the efficiency of existing medications, diagnostic tools, and healthcare devices. Nanotheranostics allows for personalized treatments, especially for complex diseases like cancer and cardiovascular conditions, where conventional therapies often work only for select patient groups. By linking diagnosis and treatment, nanotheranostics offers more tailored therapies, improving patient outcomes [122]. The rapid advancement of nanotheranostics has greatly expanded the possibilities for molecular imaging and targeted therapy, introducing a diverse range of innovative agents. These include polymer conjugates, dendrimers, micelles, liposomes, nanoemulsions, self-nanoemulsifying drug delivery systems (DDSs), metal and inorganic nanoparticles (NPs), and carbon nanotubes, among others [123].

Preclinical studies have demonstrated that particulate systems like nanoparticles (NPs) and microparticles (MPs) are effective in delivering both cells and bioactive compounds for cardiovascular diseases (CVDs). Notably, NPs and MPs can transport therapeutic agents directly to the target site, minimizing side effects and toxicity in non-target organs. Their controlled release capability maintains the bioactive concentration of therapeutic molecules, reducing the need for repeated treatments. Additionally, these particles can be administered non-invasively, either systemically or directly into the myocardium via catheter technology, enhancing patient compliance. As delivery systems, they offer a promising approach to repairing damaged heart tissue following myocardial infarction (MI) [124].

5.2.4. PLGA-Based Polymeric Nanoparticles

Palma-Chavez et al. (2021) developed a multistage delivery system by coating poly lactic-co-glycolic acid (PLGA) nanoparticles with larger PLGA outer shells [125]. This system enhances the retention of insulin-like growth factor 1 (IGF-1), which is vital for regulating heart function, promoting cardiomyocyte growth, and supporting cell survival. Administering IGF-1 in PLGA-complexed nanoparticles boosts cardioprotection, reduces cardiomyocyte apoptosis, decreases infarct size, and improves left ventricular ejection fraction (LVEF) [126].

5.2.5. Dendrimers

Dendrimers are seen as a promising non-viral system for siRNA delivery due to their tunable structures and properties. Their cationic surfaces allow strong charge interactions with anionic siRNA, forming stable particles resistant to nuclease degradation. Additionally, dendrimers contain buffering amines that trigger a “proton sponge” effect, promoting endosomal escape and the release of siRNA into the cytoplasm. When siRNA targeting the angiotensin II type 1 receptor (AT1R) was delivered using an oligo-arginine-conjugated dendrimer, AT1R expression was significantly reduced in cardiomyocytes, leading to notable improvements in cardiac function compared to saline or empty dendrimer treatments [127].

Margulis et al. (2015) used a supercritical fluid system to load Celecoxib, a lipophilic nonsteroidal anti-inflammatory drug, into nanoparticles [128]. These Celecoxib-loaded nanoparticles helped reduce ventricular dilation and impairment of ejection function, while significantly enhancing neovascularization [128].

5.2.6. Apolipoprotein AI (Apo AI) Nanoparticles

A prior study showed that transgenic overexpression of apo AI or the injection of n-apo AI (CSL111) reduced myelopoiesis in animal models of atherosclerosis. These results

support the well-known anti-inflammatory effects of n-apo AI, which influence leukocyte activity and are expected to reduce leukocyte migration into cardiac tissue [129].

5.2.7. Lipid-Based Nanoparticles

Liposomes are considered promising for targeted drug delivery in myocardial infarction (MI) due to their similar morphology to cellular membranes and their ability to carry both lipophilic and hydrophilic drugs. These biodegradable, non-immunogenic, and non-toxic amphipathic nanocarriers can be engineered to enhance circulation time, reduce uptake by reticuloendothelial cells, and achieve precise targeting [130]. Liposome-based nanotheranostics provide attractive benefits for therapeutic applications, including extended blood circulation by avoiding renal clearance and minimizing high systemic levels of free drug in the extravascular, extracellular space. This helps to reduce the undesirable side effects commonly associated with many traditional drug formulations [131].

Effective treatment of coronary artery diseases (CADs), including myocardial infarction (MI), is hindered by the adult mammalian heart's poor regenerative ability, the complex pathology of these diseases, and challenges in drug delivery and retention. New therapies for MI are urgently needed due to the heart's limited regeneration post-injury. While various agents like cytokines, growth factors, and small molecules have shown promise in reducing cardiomyocyte death and supporting cardiac remodeling, their effectiveness is limited by inadequate delivery, absorption, and retention at the target site, and the myocardial EPR (enhanced permeability and retention) effect is only modest and short-lived. Nanoparticles (NPs) offer a promising solution, particularly if they can target the injured area using active targeting and EPR-independent methods. NPs could help prevent adventitial blood vessel activation in patients with low-grade plaques and enhance drug delivery to target sites, potentially preventing the development of neointimal vascular plaques. Research is ongoing into using exosomes as naturally targeted delivery systems and employing ligand-based targeting techniques [113].

Chase Board et al., in their review article, highlight the potential for personalized therapy for myocardial infarction (MI) through the use of PCSK9 inhibitors [132]. Excess cholesterol in the body is primarily cleared by receptors on liver cells, but a protein called PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibits this process, leading to increased cholesterol levels. PCSK9 inhibitors, either monoclonal antibodies or RNA-based therapies, bind to this protein and block its action, thereby lowering low-density lipoprotein (LDL) cholesterol in the blood. In 2015, the U.S. Food and Drug Administration (FDA) approved two fully human therapeutic monoclonal antibodies, alirocumab and evolocumab, for use in combination with statin therapy to lower LDL-C levels. These drugs inhibit PCSK9, a protein primarily expressed in hepatocytes but also found in endothelial and smooth muscle cells, kidney mesenchymal cells, the intestinal ileum, embryonic brain telencephalon neurons, and colon epithelia. Regarding SGLT2 inhibitors, on 5 May 2020, the FDA approved AstraZeneca's FARXIGA (dapagliflozin), an SGLT2 inhibitor, to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with reduced ejection fraction. The EMPA-REG OUTCOME trial demonstrated that empagliflozin (Jardiance) significantly reduced cardiovascular events, including myocardial infarction and heart failure-related hospitalizations [133].

6. Alzheimer's Disease

6.1. Targeted Therapies and Personalized Medicine in Alzheimer's Disease

In 2022, the World Health Organization released a framework for dementia research, estimating that around 55.2 million people worldwide are currently affected by dementia. By 2030, this number is expected to rise dramatically to 78 million. The financial toll is

also staggering, with the combined costs of medical care, social services, and informal caregiving anticipated to surpass $2.8 trillion globally. This growing challenge has profound implications for individuals, families, and entire societies [134,135]. Alzheimer's disease (AD), the most common form of dementia, mirrors these alarming trends and is a rapidly escalating global concern. In the United States alone, approximately one in nine people aged 65 or older, about 10.8% of this age group, are living with AD, with 1275 new cases diagnosed per 100,000 people each year [136,137]. AD is marked by the buildup of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) in the brain, leading to a cascade of damaging processes, including neuroinflammation, synaptic disruption, energy deficits in brain cells, and vascular issues. Together, these disruptions can ultimately lead to the death of neurons [135,138,139]. Personalized medicine (PM) will necessitate the seamless integration of neurology, neuroscience, and psychiatry into a unified health-care model, moving beyond isolated approaches. It represents biomarker-guided treatment at a systems level, incorporating in-depth understanding of the pathophysiology of neurodegenerative diseases alongside ongoing methodological advancements [140].

Our current understanding of AD's causes draws on several theories, such as the roles of amyloid and tau proteins, inflammation, oxidative stress, metal ions, excitotoxicity, the gut-brain axis, and disrupted autophagy. Despite decades of research, most drug trials have been halted due to limited efficacy or adverse side effects. However, the FDA's recent approval of aducanumab [31,141] and lecanemab [32,142] offers hope, as these drugs may modify disease progression. Treating AD in its early stages is crucial to slowing or potentially reversing neurodegeneration, though early diagnosis remains challenging [135,143]. Genetics plays a key role in brain disorders, with around 80% of these conditions having a genetic basis. The development of neurodegenerative diseases often involves complex genetic mutations, epigenetic changes (such as DNA methylation, histone/chromatin remodeling, and miRNA irregularities), and environmental influences. New sequencing technologies and tools for studying the epigenome are helping identify biomarkers that could enable earlier diagnosis, paving the way for preventive treatments. Advances in pharmacogenetics and pharmacoepigenomics are now making it possible to tailor treatments to each individual's genetic and epigenetic profile, offering a more personalized approach to managing AD [144].

In recent years, Alzheimer's disease (AD) treatment has shifted toward personalized therapeutic strategies, particularly those targeting amyloid pathology and genetic risk factors. FDA approvals such as aducanumab and lecanemab monoclonal antibodies directed against aggregated amyloid-β, represent a major transition toward disease-modifying therapy in patients with confirmed amyloid positivity by PET or CSF biomarkers.

6.1.1. Antisense Oligonucleotides

Antisense therapy leverages antisense oligonucleotides (ASOs) to adjust mRNA and help control abnormal protein production, effectively modulating gene expression [145]. Recent advancements in ASO design now allow these molecules to specifically target brain mRNA, marking a promising new therapeutic approach for Alzheimer's disease. By using short ASOs that pair precisely with mRNA through Watson–Crick base pairing, scientists can achieve the level of specificity needed to deliver these therapies directly to intended areas in the brain. Grabowska-Pyrzewicz and colleagues have outlined several approaches for regulating mRNA with ASOs [146]. In a recent phase 1 clinical trial involving 102 patients with mild Alzheimer's, a particular ASO compound, B11B080, was tested. The trial showed that this experimental drug reduced tau biomarkers, such as CSF t-tau, CSF p-tau181, and tau PET. Additionally, patients treated with this compound either maintained

or saw improvements in cognitive function, suggesting promising potential for ASOs in Alzheimer's treatment [147].

6.1.2. Small Molecules

Small molecules show promise in crossing the blood–brain barrier to reach and influence harmful enzymes in the brain. BACE1, a critical enzyme in the production of neurotoxic proteins associated with Alzheimer's disease, has been identified as a target for precision treatments [148]. Researchers like Ghosh and Oswal have synthesized various small molecules aimed at this enzyme [149,150]. Although Yao and colleagues reviewed several potential BACE1 inhibitors, preclinical studies indicated that, despite reductions in Aβ levels in the brain, cerebrospinal fluid (CSF), and plasma, none have successfully reached phase III trials due to serious side effects or limited therapeutic benefits [151]. The decline in cognitive function in Alzheimer's patients has been closely linked to the degradation of a key molecule by acetylcholinesterase (AChE), breaking it down into choline and acetate and thereby contributing to the loss of cholinergic neurons. Current medications, such as donepezil, rivastigmine, and tacrine, inhibit AChE to increase its availability in the synaptic cleft, which aids in symptom relief but does not stop the progression of Alzheimer's disease. New research into tacrine derivatives, however, is showing promise, with early studies suggesting that these compounds may simultaneously influence both AChE and tau-related enzymes like glycogen synthase kinase-3β. These effects may help inhibit enzyme-related breakdown and reduce the formation of toxic protein aggregates. Additionally, favorable predictions regarding these drugs' absorption and blood–brain barrier permeability open up exciting new therapeutic possibilities [152,153]. Valiltramiprosate, currently in phase 3 clinical trials till the end of 2024, and Blarcamesine are in clinical phase 2b or 3 (clinical trial number: NCT03790709) [154,155].

6.1.3. Antibodies

Recent clinical trials have explored monoclonal antibodies to target amyloid-beta (Aβ) in Alzheimer's disease (AD) [156]. While early studies showed some cognitive improvement with bapineuzumab in mild to moderate AD, later, phase 3 trials found no significant effect over placebo, despite evidence of Aβ clearance from the brain [157]. Meanwhile, two other antibodies, lecanemab (Leqembi®) and aducanumab (Aduhelm®), received FDA approval, though with modest statistical support [158]. The FDA's recent 2024 approval of lecanemab-irmb highlights ongoing interest, as patients showed improvements over placebo in cognition and function [159]. Interestingly, aducanumab's efficacy may be enhanced with low-dose ultrasound to better deliver the drug across the blood–brain barrier. While promising, side effects remain a challenge for broader use [160].

6.1.4. CRISPR/CAS9 Genome Editing

The CRISPR/Cas9 system has revolutionized biomedical science by enabling precise gene editing at targeted DNA sites, offering new avenues for personalized medicine. Using a guide DNA and the Cas9 protein, this tool can create double-strand breaks in DNA. If a sister chromatid is present, precise changes can be introduced via homology-directed repair, while non-homologous repair leads to gene knock-down. Recent advancements, highlighted by Nojadeh et al., showcase the potential applications of CRISPR/Cas9 in both lab and clinical settings [161]. For effective delivery into mammalian cells, adeno-associated viruses are commonly used, as they can infect various tissue types and remain active for extended periods [162].

This breakthrough has paved the way for additional gene-editing techniques, including methods allowing targeted delivery via guide RNA. In Alzheimer's research, CRISPR/Cas9 has shown promise for early-onset cases. Studies by Konstantinidis et al.

and Thompson reveal that disrupting the PSEN1M146L allele can reverse harmful amyloid-beta ratios, potentially offering a therapeutic path [163]. Similarly, research by Guyon et al. suggests that introducing the APP A673T mutation, which reduces amyloid plaque formation, could offer neuroprotective effects [164]. These advancements underscore the need for ongoing bioethical reflection to consider the broader impacts of such transformative technologies.

7. Conclusions

In conclusion, targeted therapies and personalized medicine represent a significant advancement in the treatment of chronic diseases, offering more precise and effective therapeutic options compared to traditional approaches. These innovative treatments focus on specific molecular targets, enabling personalized interventions tailored to the unique genetic and phenotypic profiles of patients. By improving treatment outcomes, minimizing side effects, and addressing the complexities of diseases like cancer, diabetes, asthma, and myocardial infarction, targeted therapies are reshaping the landscape of modern medicine. Continued research and development in this field holds the promise of further refining treatment strategies, advancing the goals of precision medicine, and improving patient care on a global scale.

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