Concepts and Misconceptions of Drug Targeting

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GLOSSARY & ABBREVIATIONS
USED IN THE TEXT

3-WJ RNA	an assembly of thermodynamically stable three-way junction (3WJ) of the motor pRNA
5-LOX	arachidonate 5-lipoxygenase, a non-heme iron-containing enzyme (EC 1.13. 11.34) that in humans is encoded by the ALOX5 gene
A431	epidermoid carcinoma cell line expressing very high levels of the epidermal growth factor (EGF) receptor, and displaying a high basal activation of the MAPK pathway
A549	adenocarcinomic human alveolar basal epithelial cells developed from cancerous lung tissue
α_1AChR	α_1 subunit from the muscle AChR
AAV	recombinant adeno-associated viruses (AAV)
ABL 1	Abelson murine leukemia viral oncogene homolog 1 is a protein that, in humans, is encoded by the ABL1 gene (previous symbol ABL) located on chromosome 9
ACC1	acetyl-CoA carboxylase 1 gene
ACP6 gene	encodes lysophosphatidic acid phosphatase type 6, an acid phosphatase enzyme
AD	Alzheimer's Disease
ADCs	antibody-drug conjugates
ADHD	attention deficit hyperactivity disorder
ADP	adenosine diphosphate
AI	artificial intelligence
AKAPs	A-kinase anchoring proteins binding directly to PKA

ALK	anaplastic lymphoma kinase
ALT	alanine transaminase, a transaminase enzyme (EC 2.6.1.2)
AML	acute myeloid leukemia
anti-EGFR	anti-epidermal growth factor receptor
APC	antigen-presenting cells
APC	amino acid-polyamine-organo cation
APP	amyloid precursor protein
ArnT	transferase
ARSs	aminoacyl-tRNA synthetases
ASD	asparagine synthetase deficiency
ASGP-R	asialoglycoprotein receptors
ASNS	asparagine synthetase
AST	aspartate aminotransferase, an enzyme present in hepatocytes and myocytes that catalyzes the reversible transfer of an amine group from l-glutamic acid to oxaloacetic acid
ATAT1	α-tubulin acetyltransferase 1
ATM	a serine/threonine protein kinase that is recruited and activated by DNA double-strand breaks
ATP	adenosine triphosphate
ATR	serine/threonine kinase
ATR-CHK1	a pathway in DNA damage signaling and cancer that recognizes single strand DNA (ssDNA)
AUC	area under the curve
Aβ42	amyloid beta 42
Bax	apoptosis regulator, also known as bcl-2-like protein 4, is a protein that in humans is encoded by the *BAX* gene. *BAX* is a member of the Bcl-2 gene family
BBB	blood-brain barrier

BCEC	brain capillary endothelial cells
BCL-2	B-cell lymphoma 2
BCR-ABL	BCR-ABL fusion protein from BCR-ABL fusion gene. This gene is the *ABL1* gene of chromosome 9 juxtaposed onto the breakpoint cluster region *BCR* gene of chromosome 22
Bmi-1	a gene that encodes a ring-finger protein, a major component of the polycomb group complex 1 (PRC1)
BSA	bovine serum albumin
BT474	a human breast tumor cell line that supports mouse mammary tumor virus replication
C98	apoptosis regulator Bcl-2-like protein
C225	Erbitux (cetuximab, C225) a drug approved to treat metastatic colorectal cancer
cAMP	second messenger cyclic adenosine monophosphate
cAMP/PKA system	second messenger cyclic adenosine monophosphate (cAMP) activating protein kinase A (PKA)
CTAs	cancer/testis antigens
Cas9	CRISPR associated protein 9
CBIQD	2-(6-chlorobenzo(d) thiazol-2-yl)-1H-benzo[de]isoquinoline-1,3(2 H)-dione
CD20	B-lymphocyte antigen protein
CD38	(cluster of differentiation 38), also known as cyclic ADP ribose hydrolase, is a glycoprotein found on the surface of many immune cells (white blood cells), including $CD4^+$, $CD8^+$, B lymphocytes and natural killer cells
CD44	a cell surface adhesion receptor expressed in many cancers; and regulates metastasis via recruitment of CD44 protein to the cell surface
CD8+ T	a cytotoxic T cell (also known as T_C, cytotoxic T lymphocyte, CTL, T-killer cell, cytolytic T cell, CD8+ T-cell or killer T cell) is a T lymphocyte (a type of white blood cell) that kills cancer cells, cells that are infected (particularly with viruses), or cells that are damaged in other ways

CDK	cyclin-dependent kinase
CDK9	cyclin-dependent kinase 9
CHK1	checkpoint kinase 1
CHO-FR-beta	FR-beta-transfected Chinese hamster ovary cells
CLL	chronic lymphocytic leukemia
CLSM	confocal laser scanning microscope
C_{max}	the maximum drug concentration
CML	chronic myeloid leukemia
CNS	central nervous system
CpG	CpG oligodeoxynucleotides (or CpG ODN) are short single-stranded synthetic DNA molecules that contain a cytosine triphosphate deoxynucleotide ("C") followed by a guanine triphosphate deoxynucleotide ("G")
CR2	complement receptor type 2 (also known as complement C3d receptor, Epstein-Barr virus receptor, and CD21 (cluster of differentiation 21)), is a protein that in humans is encoded by the CR2 gene
C-reactive protein	a protein made by the liver; its levels in the blood increase when there is a condition causing inflammation somewhere in the body
CRISPR	clusters of regularly interspaced short palindromic repeats
CSF3R	colony stimulating factor 3 receptor
CSK	tyrosine-protein kinase CSK. Tyrosine-protein kinase CSK also known as C-terminal Src kinase is an enzyme that, in humans, is encoded by the CSK gene. This enzyme phosphorylates tyrosine residues located in the C-terminal end of Src-family kinases (SFKs) including SRC, HCK, FYN, LCK, LYN and YES1
CTCF	transcriptional repressor CTCF also known as 11-zinc finger protein or CCCTC-binding factor is a transcription factor that in humans is encoded by the CTCF gene
CVDs	cardiovascular diseases

CDK	cyclin-dependent kinases
daSTRs	disease-associated STRs
DCs	dendritic cells
DDS	drug-delivery system
DDSs	smart drug delivery systems
DDT	direct drug targeting
DHFR	dihydrofolate reductase
DMT	dimethyltryptamine
DNA	deoxyribonucleic acid
DO-FUdR	3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine
DO-FUdR-SLN	SLN incorporating DO-FUdR
DOX	doxorubicin
DSB	thiol-disulfide oxidoreductase pathway enzymes
DTI	drug-targeting index
DUBs	de-ubiquitylase enzymes
ECD	extracellular domain (ECD) α7/AChBP
ECM	extracellular matrix
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ENCODE 2012	encyclopedia of DNA Elements
eNP	expansile nanoparticle
EptA	transferase
eQTL	expression-quantitative-trait locus
ER	estrogen receptor
ER	endoplasmic reticulum

ER-chaperone	human chaperone proteins found in the endoplasmic reticulum (ER)
ERK	extracellular signal-related kinase
ESCRT	endosomal sorting complex required for transport
ET-1	endothelin-1 (ET-1), a peptide hormone with diverse biological actions
FA	fusidic acid
FA-LP	FA liposomes
FCM	flow cytometry
FDA	The Food and Drug Administration is a federal agency of the United States Department of Health and Human Services
Fgd	faciogenital dysplasia
fH	mouse factor H
FIM	fatal infectious mononucleosis
f-L-DNR	FR-targeted liposomal daunorubicin
FMR1	FMR1 gene encodes for FMRP protein that is present in many tissues, including the brain, testes, and ovaries
FR	folate receptor
FUdR	SP905-fluoro-2'-deoxyuridine
Fv/scFv	single-chain antibody Fv fragment
FYVE	domains that are highly conserved protein modules that typically bind phosphatidylinositol 3-phosphate (PI3P) on the surface of early endosomes
G4	G-quadruplex; RNA G4 secondary structures
G9a	enzymes that catalyzes methylation of histone 3 lysine 9
GAIM	general amyloid interaction motif
GAIM-Ig fusion	IgG1 Fc-GAIM fusion protein
GBM	glioblastoma multiforme

GCK	glucokinase
GDP	guanosine diphosphate
Geuvadis	genetic European variation in disease
GFP	green fluorescent protein
GPCR	G-protein-coupled receptors (GPCRs), a family of proteins that transduce extracellular stimuli into intracellular signals
Grp170	glucose-regulated protein 170
GTEx	genotype-tissue expression
GTP	nucleotide guanosine triphosphate
GTPases	a large family of hydrolase enzymes that bind to GTP and hydrolyze it to GDP
GWAS	the genome-wide association study
H3K9	histone 3 lysine 9
HAase	hyaluronidase
HCPs	heat shock proteins
HDAC6	histone deacetylase 6
HepG2	a human liver cancer cell line. The cells express 3-hydroxy-3-methylglutaryl-CoA reductase and hepatic triglyceride lipase activities
HER2	receptor tyrosine kinase
HER3	human epidermal growth factor receptor of the HER family that also includes HER1/EGFR/erbB1, HER2/erbB2, and HER4/erbB4. HER3 lacks or has little intrinsic tyrosine kinase activity
Hh	hedgehog signaling pathway
HIV	human immunodeficiency virus
HMT	histone methyltransferase
HO-1	heme oxygenase-1 is a Nrf2-regulated gene that is critical in the prevention of vascular inflammation

HOX	a subset of homeobox genes that specify regions of the body plan of an embryo along the head-tail axis of animals. Hox proteins encode and specify the characteristics of 'position', ensuring that the correct structures form in the correct places of the body
Hsp110	heat shock protein, a member of Hsp70 superfamily
HuPrP	human prion protein
IAPP	amylin, or islet amyloid polypeptide, an amino acid hormone produced by the pancreas
IBD	inflammatory bowel disease
IDP	conformational dynamics
ig-1R	sigma-1 receptor
IGF-1	insulin-like growth factor 1
IgG2a	anti-transferrin receptor antibody
IKK	inhibitor of nuclear factor-κB (IκB) kinase (IKK) that regulates the NF-κB signaling pathway
IL-10	interleukin-10
IL-6R	interleukin-6 receptor
IA	intra-arterial
IPF	idiopathic pulmonary fibrosis
J774	murine macrophage
JAK	family of nonreceptor tyrosine kinases (JAK1, JAK2, JAK3, TYK2)
JH	Janus homology
KB cells	KB cells are a subline of the KERATIN-forming tumor cell line HeLa, established via contamination by HELA CELLS. The cells are positive for keratin by immunoperoxidase staining. KB cells have been reported to contain human papillomavirus18 (HPV-18) sequences
K_{DC}	the 1st order rate constant of free-drug elimination

KG-1	human acute myelogenous leukemia cells
KMT2	lysine N-methyltransferase 2 family
LbL	layer-by-layer
LD	Lafora disease
L-DNR	non-targeted liposomal DNR
LEAPT	lectin-directed enzyme-activated prodrug therapy
LIF	leukemia inhibitory factor
LRH-1	liver receptor homolog-1 (also known as NR5A2 (nuclear receptor subfamily 5, group A, member 2)) is a protein that in humans is encoded by the NR5A2 gene. LRH-1 is a member of the nuclear receptor family of intracellular transcription factors
LncRNAs	long non-coding RNAs
Mab	monoclonal antibody; at the end of a generic drug name, -mab indicates that the drug is a monoclonal antibody
MAM	mitochondria-associated ER membranes
MAPK	mitogen-activated protein kinase
MCL-1	differentiation protein Mcl-1
MDA-MB-231	an epithelial, human breast cancer cell line
MED1	mediator subunit 1
MEK	extracellular signal-regulated kinase
Mips	peptidyl-prolyl cis-trans isomerases
miRNAs	microRNAs, small, non-coding RNAs
MLL (KMT2)	lysine methyltransferase 2 family (KMT2) proteins methylate lysine 4 on the histone H3 tail at important regulatory regions in the genome and thus impart critical functions through modulating chromatin structures and DNA accessibility
MLL	mixed-lineage leukemia
MLL5	assigned as KMT2E, is distinct from the other MLL (KMT2) family members

MM	multiple myeloma (MM) is a cancer of plasma cells resulting from the abnormal proliferation of malignant plasma cells within the bone marrow (BM) microenvironment
MMPC	multiple model predictive control
MO15	gene that encodes the catalytic subunit of a protein kinase that activates cdc2 and other cyclin-dependent kinases (CDKs) through phosphorylation of Thr161 and its homologues
MO25α	mouse protein 25α (MO25α) is a 40-kDa protein that, together with the STE20-related adaptor-α (STRADα) pseudo kinase, forms a regulatory complex capable of stimulating the activity of the LKB1 tumor suppressor protein kinase
MPA	microscopic polyangiitis
MR	(as in MR imaging guidance), magnetic resonance (MR) imaging system for guidance in surgical procedures
MR1	MR1 Gene (Protein Coding) MAIT (mucosal-associated invariant T-cells) lymphocytes represent a small population of T-cells primarily found in the gut. The protein encoded by this gene is an antigen-presenting molecule that presents metabolites of microbial vitamin B to MAITs
MRI	magnetic resonance imaging
mRNA	messenger RNA (mRNA) is a single- stranded RNA molecule that corresponds to the genetic sequence of a gene and is read by the ribosome in the process of producing a protein
MS	multiple sclerosis (MS) is a potentially disabling disease of the brain and spinal cord (central nervous system)
MSNs	mesoporous silica nanoparticles
MT	microtubules are polymers of tubulin that form part of the cytoskeleton and provide structure and shape to eukaryotic cells
MTD	maximum tolerance dose
mtDNA	mitochondrial DNA
mTOR	mTOR pathway controls the anabolic and catabolic signaling of skeletal muscle mass, resulting in the modulation of muscle hypertrophy and muscle wastage

mTORC1	mTORC1 (mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1) is a protein complex that functions as a nutrient/energy/redox sensor and controls protein synthesis. It is composed of mTOR, Raptor, GβL, and DEPTOR and is inhibited by rapamycin
MTX	methotrexate
MUC5B	mucin 5B, oligomeric mucus/gel-forming gene encodes respiratory tract mucin glycoproteins
Mur	a series of Mur enzymes that catalyze the biosynthesis of peptidoglycan precursor
nAChR	α7 nicotinic acetylcholine receptor
nAChR	nicotinic acetylcholine receptor
NADPH	co-factor nicotinamide adenine dinucleotide phosphate hydrogen
NAMs	negative allosteric modulators
NAPE	N-acyl-phosphatidylethanolamine
NCL	nanostructured lipid carriers
ncRNAs	a non-coding RNA (ncRNA) is a functional RNA molecule that is transcribed from DNA but not translated into proteins
NEMO	NF-kappa-B essential modulator (NEMO) also known as inhibitor of nuclear factor kappa-B kinase subunit gamma (IKK-γ) is a protein that in humans is encoded by the *IKBKG* gene. NEMO is a subunit of the IκB kinase complex that activates NF-κB
NF-kappaB	NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA, cytokine production and cell survival
NFP	peptide-based nanofiber
NIH	The National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services, is the nation's medical research agency making important discoveries that improve health and save lives
Ni-IgG2a	non-immune IgG2a

NIR fluorescence	near-infrared (NIR) fluorescence is a light wavelength of 650–950 nm, and is generally preferred for *in vivo* fluorescence imaging because of its good tissue penetration
NLC	nano lipid carrier
NMDA receptor	one of three types of ionotropic glutamate receptors, with the other two being the AMPA and kainate receptors. It is activated when glutamate and glycine (or D-serine) bind to it, and when activated it allows positively charged ions to flow through the cell membrane
NOX2	NADPH oxidase 2
NPT008	a fusion protein combining GAIM with the backbone of a human immunoglobulin
OX26	anti-transferrin receptor antibody
P14	p14 adaptor molecule is part of the late endosomal/LAMTOR (lysosomal adaptor and mitogen-activated protein kinase and mammalian target of rapamycin [mTOR] activator/regulator) complex, thereby contributing to the signal transduction of the extracellular signaling-regulated kinase (ERK) and the mTOR cascade
P21	p21 is a potent cyclin-dependent kinase inhibitor (CKI). The p21 (CIP1/WAF1) protein binds to and inhibits the activity of cyclin-CDK2, -CDK1, and -CDK4/6 complexes, and thus functions as a regulator of cell cycle progression at G_1 and S phase
p14ARF	p14ARF (Alternative Reading Frame) tumor suppressor is a protein product of the alternative reading frame (ARF) of the human INK4a locus which regulates a series of cell cycle regulatory proteins to promote cell cycle arrest in response to abnormal hyper-proliferative growth stimuli. p14ARF alterations are common in human cancers and, when inherited, confer susceptibility to cutaneous melanoma
P16INK4a	cyclin dependent kinase (CDK) inhibitor
PAGE4	prostate-associated gene 4
PAM	a protospacer adjacent motif, a 2 to 6-base pair DNA sequence immediately following the DNA sequence targeted by the Cas9 nuclease in the CRISPR

PAMs	positive allosteric modulators
PARP	poly (ADP-ribose) polymerase
PD-1	programmed cell death protein 1
PDT	photodynamic therapy
PEG	polyethylene glycol
PET	positron emission tomography
Pfmrk	an MO15-related protein kinase from *Plasmodium falciparum*
PGE2	prostaglandin E2 also known as dinoprostone is a naturally occurring prostaglandin which is used as a medication. It is a potent inflammatory mediator that is generated by cyclooxygenase 2 (COX2) conversion of arachidonic acid
PGs	proteoglycans
PhID	integrated pharmacology database
PI/PII/PIII	promoters of ACC1 gene
PI3K/AKT	a signal transduction pathway that promotes survival and growth in response to extracellular signals. Key proteins involved are PI3K (phosphatidylinositol 3-kinase) and Akt (Protein Kinase B)
PI3K/AKT/mTOR p	an intracellular signaling pathway important in regulating the cell cycle
PK	pharmacokinetics
PKA	protein kinase A; a family of enzymes whose activity is dependent on cellular levels of cyclic AMP (cAMP). Also known as cAMP-dependent protein kinase (EC 2.7. 11.11)
pLGICs	pentameric ligand-gated ion channels
PRC1	polycomb group complex 1
PreDPI-ki	a web-based server called PreDPI-Ki predicts drug-target interactions for drug discovery. It provides a high-confidence list of drug-target associations for subsequent experimental-investigation guidance

pre-mRNA	an RNA transcript first made in a eukaryotic cell; it is considered a pre-mRNA and must be processed into a messenger RNA (mRNA). A 5' cap is added to the beginning of the RNA transcript, and a 3' poly-A tail is added to the end
PRNP	prion protein gene
PCa	prostate cancer
PrPC	physiological cellular prion protein
PTEN	phosphatase and tension homolog; act as tumor suppressor
PTMs	post-translational modifications
PTX	Taxol (Paclitaxel) is a chemotherapy medication used to treat a number of types of cancer including ovarian, breast, lung, Kaposi sarcoma, cervical, and pancreatic cancer malignancies
PV	*Pemphigus Vulgaris* is a rare, severe autoimmune disease in which blisters of varying sizes break out on the skin and on the lining of the mouth and other mucous membranes. It occurs when the immune system mistakenly attacks proteins in the upper layers of the skin
RA	rheumatoid arthritis is a chronic inflammatory disorder that can affect more than just your joints. The condition can damage a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels
RACs	radionuclide-antibody conjugates
RBPs	risk-based process safety (RBPS) Management approach described in the CCPS (Center for Chemical Process Safety) book *Guidelines for Risk Based Process Safety, 2007.* It is based on *co*mmitting to process safety, understanding hazards and risk, manage risk, and learning from experience
RET	"rearranged during transfection", refers to proto-oncogene that encodes a receptor tyrosine kinase for members of the glial cell line-derived neurotrophic factor (GDNF) family of extracellular signaling molecules. *RET* loss of function mutations are associated with the development of Hirschsprung's disease while gain of function mutations are associated with the development of various types of human cancer, including medullary thyroid carcinoma, multiple endocrine neoplasias type 2A and 2B, pheochromocytoma and parathyroid hyperplasia

RNA	ribonucleic acid
Roadmap Epigenomics	The NIH Roadmap Epigenomics Mapping Consortium
RPMI8226	a cell line from a male with multiple myeloma. The cells produce and secrete Ig lambda light chain
RPT	repeat domain; defined as several (at least two) adjacent copies having the same or similar sequence motifs. These periodic sequences are generated by internal duplications in both coding and non-coding genomic sequences
R_R	the 1st order rate constant of drug release
rRNA	ribosomal RNA, a molecular component of a ribosome, is a part of the cell's essential protein-making process. rRNA makes polypeptides assemblies of amino acids that go to make up proteins
RT-qPCR	a real-time polymerase chain reaction, also known as quantitative polymerase chain reaction. RNA is used as the starting material that first transcribed into complementary DNA (cDNA) by reverse transcriptase from total RNA or messenger RNA (mRNA). The cDNA is then used as the template for the qPCR reaction
RT-PCR	quantification of steady-state m RNA levels by reverse transcription-polymerase chain reaction. The technique can be used to detect tumor cells in peripheral blood. Initially used for the diagnosis of hematological malignancies, it is now applied for detecting early metastases from solid tumors. At the current level of sensitivity, RT-PCR is able to detect a total of 1000 cancer cells in the circulating blood
sAMP	adenylyl cyclase
SAMs	silent allosteric modulators
SEER	surveillance, epidemiology, and end results
SET	multitasking protein, involved in apoptosis, transcription, nucleosome assembly and histone chaperoning
shBmi-1	recombinant plasmid inserted with Bmi-1 gene short hairpin RNA (shRNA) expression vector PGPU6/GFP/Neo-shBmi-1
Shp1 and Shp2	cytoplasmic tyrosine phosphatases implicated in the control of cellular proliferation and survival

shRNA	short hairpin RNA
SINE	short interspersed nuclear elements
siRNA	short interfering RNA
SLAMF7	SLAM family member 7 is a protein that in humans is encoded by the SLAMF7 gene
SLM	solid lipid microparticles
SLN	solid lipid nanoparticles
SMN2	survival of motor neuron 2 is a gene that encodes the SMN protein (full and truncated) in humans. The SMN protein is found throughout the body, with highest levels in the spinal cord
SMO	selective smoothened inhibitor
SNAgel	spherical nucleic acid-templated hydrogel
SNPs	single-nucleotide polymorphism
SPECT	single photon emission computed tomography
SRC	proto-oncogene tyrosine-protein kinase Src (also known as proto-oncogene c-Src, or c-Src (cellular Src; pronounced "sarc", as it is short for sarcoma)), is a non-receptor tyrosine kinase protein that in humans is encoded by the *SRC* gene. It phosphorylates specific tyrosine residues in other tyrosine kinases, and plays a role in the regulation of embryonic development and cell growth. An elevated level of activity of c-Src may be linked to cancer progression by promoting other signals
STAT3	signal transducer and activator of transcription 3
STRs	short tandem repeats DNA sequences
SUMO	small ubiquitin-like modifier (or SUMO) proteins are a family of small proteins that are covalently attached to and detached from other proteins in cells to modify their function. SUMOylation is a post-translational modification involved in various cellular processes, such as nuclear-cytosolic transport, transcriptional regulation, apoptosis, protein stability, response to stress, and progression through the cell cycle. SUMO proteins are similar to ubiquitin and are considered members of the ubiquitin-like protein family

supraPSs	supramolecular photosensitizers
SVA	hominids-specific class of retrotransposons (SINE-VNTR-Alu)
TA	therapeutic availability
TAT	targeted alpha therapy
TDDS	targeted drug delivery systems
TDS	transdermal delivery system
TE	transposable elements
TEC	tyrosine-protein kinase. Non-receptor tyrosine kinase that contributes to signaling from many receptors and participates as a signal transducer in multiple downstream pathways, including regulation of the actin cytoskeleton. Regulates the development, function and differentiation of conventional T-cells and nonconventional NKT-cells
TfR	human transferrin receptor
Th1	antigen-specific T-helper 1
TI	targeting index
TKI	tyrosine kinase inhibitor
TME	tumor microenvironment
TMED1	mutant tumor cells
TPZ	tirapazamine
TPZ@MCMSN-Gd3+	mesoporous silica-based theranostic nanoplatform -constructed by layer-by-layer assembly for excellent photodynamic/chemo therapy
Tregs	T cells (known as suppressor T cells), a subpopulation of T cells that modulate the immune system, maintain tolerance to self-antigens, and prevent autoimmune disease
TRIB	a protein kinase that in humans is encoded by the TRIB1 gene
U12	a type of introns; U12-dependent (minor) spliceosome
U266	human multiple myeloma cell line

UM-SCC-1	a unique human head and neck squamous cell carcinoma
UM-SCC-6	a unique human head and neck squamous carcinoma cell line
UPR	unfolded protein response
VEGF	vascular endothelial growth factor
VHHs	the variable domain of a heavy-chain antibody

PROLOGUE

A law of physics states that "…only light of energy that can cause transitions from one existing energy level to another will be absorbed". A similar rule applies to the action of drugs – for a drug to act on a given disease, it needs to interact/bind with the molecular structures associated with a disease, and elicit a therapeutic effect.

An additional complication arises since the same structures to which the drug can bind are present not only on the disease but also on the normal cells.

The purpose of "drug delivery" is to enable the administration of a therapeutic agent to the body so that it elicits the desired therapeutic effect. Various routes of administration may be employed such as the enteral (oral, sublingual, rectal), parenteral (via injections), inhalation, transdermal, and topical. The task of a simple drug formulation or a more complex drug-delivery system is to present to the target the required quantity of the drug for the required/optimal duration of time; in other words, to generate an optimal biodistribution and pharmacokinetics of the drug. Drug-delivery systems may determine the profile of drug administration, its absorption, its distribution throughout the body, and also its ultimate elimination. The overall aim is for drug delivery to generate optimal drug efficacy and safety, together with patient convenience and compliance.

The ultimate task of drug delivery is to target the drug action only to the cells of the disease (for example, cancer cells). Such a system must avoid the natural body-defense mechanisms and deposit the drug at its intended site of action. From that point, the fate of the drug is determined by the physicochemical and biological properties of the drug itself. Not all drugs, but only the drugs having the appropriate pharmacokinetic properties will benefit from the application of an appropriate delivery system.

This monograph focuses on the issues associated with developing site/cell/disease-targeted drug delivery systems and discusses its principles, requirements, progress to date, and issues. It concludes that efforts today have largely been based on false assumptions, and offers a new paradigm

for developing effective drug-targeting systems aiming at molecular structures that are uniquely associated with diseases.

So why is the disease targeting important? Let us take cancer as an example.

Cancer is the number two most lethal disease in the U.S.; some 1.7 million Americans were diagnosed with cancer in 2018; some 600,000 died. Over 15 million Americans cancer survivors are alive today.

John Horgan [1] published an illuminating article entitled "The Cancer Industry: Hype vs. Reality. Cancer medicine generates enormous revenues but marginal benefits for patients." It argues that "new treatments yield small benefits (at) big costs". Here are a few salient points.

- Spending on cancer care has increased from $125 billion in 2010 to $175 billion in 2020 [2];
- Progress in treating cancer is frequently described in terms that are not realistic, such as "promising", "breakthrough," "game-changer," "revolutionary," "groundbreaking", "making ~~cancer~~ history", etc. [3-6]
- According to Azra Raza M.D., "No one is winning the war on cancer" [7].

She believes that reports claiming advances are "mostly hype, the same rhetoric from the same self-important voices for the past half-century."

- Successful therapies have indeed been developed for specific blood, bone marrow, and lymph cancers. Treating solid tumors remains largely unsuccessful.
- There was a rapid increase in cancer mortality during the second half of the 20th century that peaked at around 1990; it has since been decreasing mainly due to the much-decreased use of tobacco use. However, the age-adjusted mortality rate for all cancers in the U.S. is in 2020 about the same as it was in 1930 [8, 9].
- Thun et al. [10] concluded that "without reductions in smoking, there would have been virtually no reduction in overall cancer mortality in either men or women since the early 1990s."
- Begley and Ellis [11] argued for raising the quality of preclinical cancer research. Cancer initiation and development have been linked to many factors such as oncogenes, hormones, viruses, carcinogens, and others; however, this general knowledge has not been sufficient to translate the accumulated scientific knowledge into effective

preventive or therapeutic entities. They reported that cancer clinical trials “have the highest failure rate compared with other therapeutic areas”.

- 72 new anticancer drugs approved by the FDA between 2004 and 2014 prolonged survival for an average of 2.1 months [12]. It would appear that “most cancer drug approvals have not been shown to, or do not, improve clinically relevant endpoints” including survival and quality of life [13]. The authors worried that “the FDA may be approving many costly, toxic drugs that do not improve overall survival.”
- Immune therapies that claimed to be “a revolutionary discovery in our understanding of cancer and how to beat it” have been estimated by Gay and Prasad to benefit “at best” fewer than 10 percent of cancer patients, and that is the “best-case scenario” [14].
- Data analysis showed [15] no reduction in all-cause mortality resulting from tests for many cancer types (breast, prostate, colon, lung, cervix, mouth, or ovaries) in asymptomatic patients. Some even argued that early screening for cancer should be abandoned [16].
- Interestingly, while far more money is spent in the U.S. per person on health care than in any other country, Europe, as well as Mexico and Brazil, have lower cancer mortality rates [17, 18].
- The reproducibility of cancer studies is considered by many to be very low [11, 19].

All the above problems should be considered when attempts are undertaken to develop new, disease-targeted drugs. The authors of “The Case for Being a Medical Conservative" [20] urge that medicine needs to “recognize the human body’s inherent healing properties and to acknowledge how little effect the clinician has on outcomes.”

Further, it should “recognize the limits of medicine and honor the Hippocratic oath: First, do no harm”.

In this volume, a paradigm is suggested that is based on 1) a comprehensive understanding of human disease at the molecular levels, and b) use this knowledge to identify and target new drugs to unique molecular structures associated with the disease.

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INTRODUCTION

Background & rationale

The concept of a "magic bullet" (*magische Kugel*, an ideal therapeutic agent), a drug that would seek out the locus of disease and "cure" it, introduced by Paul Ehrlich [21] in 1906, remains to this day a fantasy, a science fiction. An "ideal drug" envisaged by Ehrlich would be 100% effective all the time and would have no undesirable side effects. There are some "almost ideal" drugs such as vaccines, but they are still the exception rather than the rule. Additionally, ideal drugs should be easy to use and available at a low cost. Here we are concerned with high efficacy and no side effects only.

Traditionally drugs are discovered and developed largely through random testing of possible candidates, and partially by rational design. However, it is generally accepted that serendipity plays a big role in developing a successful drug. Nearly all administered drugs distribute generally throughout the body and bind to their target of action in any location the drug reaches, regardless of whether the target is associated with a disease or healthy cells. The need for controlling the distribution of drugs in the body and its pharmacokinetics gave rise to the field of drug delivery, i.e., approaches that control the manner and rate at which drugs enter the body (transdermal, oral, buccal, etc.), distribute within the body (e.g., by being attached to an inert macromolecule or a particle, etc.), and release the drug (e.g., by enzymatic cleavage of a covalent bond, change of pH, etc.), and sometimes coupled with external stimuli such as heat, magnetic field, light, etc. So-called controlled drug-delivery systems started to be developed in the 1950s [22, 23] and have been relatively useful and successful.

The concept of "drug targeting" followed later [24, 25], attempting to put into practice Ehrlich's idea that a drug molecule should accumulate in the target organ or tissue selectively to reach the pharmacodynamic concentration of the drug at the disease site while its concentration in nontarget organs and tissues is low, preferably below the toxicity level. However, effective disease-site-specific delivery systems have not yet been developed, not even when antibodies were used as drug carriers.

After more than 100 years, much research, and many claims for promising new targeting drug-delivery platforms under development, drug-delivery systems have not yet reached effective clinical application. Advances in biological and medical knowledge of diseases make it imperative that effective ways of delivering therapeutic agents to specific cells *in vivo* are found to turn such information into tools for preventing and curing diseases.

The aim of this monograph is critically to evaluate what has been done so far, elucidate the reasons why efforts so far have not been successful, and lead the way for finding new paradigms for generating new drugs and delivery approaches to bring about much better, more effective and safer precision therapeutics.

Among the most important areas when considering drug targeting is the mechanisms that underlie disease. The term "mechanism of disease" refers to defects in molecular and cellular processes that become starting points of specific pathologies. Knowledge of these defects at the molecular level is vital for designing appropriate and effective drugs and drug-targeting delivery systems.

Understanding the molecular and cellular basis of health and disease and how environmental factors influence the manifestation of disease phenotypes is essential for developing improved strategies for disease prevention and treatment. The mechanisms underlying human diseases most often relate to biological processes that are strongly conserved through evolution, such as cell communication, signal transduction, metabolism, inflammation, and immunity. These processes rely on interactions between multiple cell types, tissues, and organs of the whole organism. Animal models of disease are invaluable tools to study the complexity of disease phenotypes but it must be kept in mind that none of the available models represents exactly human diseases.

Key features in the process of dealing with a disease are:

- Symptoms – signs experienced by the patient that may be used to diagnose the disease;
- Diagnosis – a set of symptoms may suggest a diagnosis, confirmed by further physical examination and analyses (blood samples, X-rays, tomography, etc.);
- Mechanisms – i.e., molecular and cellular processes that initiate and progress the given disease; these are (almost) fully known only for very few diseases.