Metabolism of New Drug Modalities Research Advances

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Abstract:
The medicinal chemistry sector is rapidly evolving as innovative therapeutic strategies reshape how diseases are treated. Traditional small-molecule drugs, while effective, often face Challenges like low specificity toward targets and the emergence of resistance limited ability to modulate complex biological pathway. To resolve these challenges, newer forms of drug modalities have been introduced, providing superior modes of action. and expanded therapeutic reach. These modalities include peptides, peptidomimetics, monoclonal antibodies, antibody–drug conjugates, nucleic acid–based therapeutics, PROTACs (proteolysis-targeting chimeras), gene-editing tools, and RNA-based drugs such as siRNA and mRNA technologies. Their unique structures and mechanisms allow precise targeting of disease-related proteins, genetic material, or cellular pathways that were once believed to be non-targetable by therapeutic agents.

Recent advances in chemical biology, structural biology, and computational design have accelerated the development of these modalities, enabling improved stability, enhanced delivery systems, and better pharmacokinetic profiles. For example, lipid nanoparticles have revolutionized the delivery of RNA therapies, while bifunctional degraders like PROTACs offer an entirely new approach. They work by eliminating damaging proteins rather than simply blocking their activity. These innovations hold significant promise for treating cancers, genetic disorders, autoimmune diseases, and infectious diseases.

Overall, new drug modalities are transforming medicinal chemistry by expanding treatment options and supporting more individualized." and targeted interventions. As investigations proceed to improve their structure, stability, and delivery, these modern platforms are expected to serve as a key component in future drug development, discovery and precision medicine.

Key words:covering gene therapy, RNA-based therapeutics, protein degradation therapies, cell-based therapies, gene editing, and engineered proteins/peptides.

I. Introduction

Medicinal chemistry is undergoing a major transformation as innovative therapeutic platforms reshape how complex diseases are treated. Traditional small-molecule drugs, although effective in many conditions, often struggle to address intricate biological processes or "undruggable" targets. To bridge these gaps, a new generation of drug modalities has emerged, offering more precise, adaptable, and powerful treatment strategies.

Gene therapy: provides the ability to correct or replace faulty genes, enabling long-term solutions for genetic disorders.

RNA-based therapeutics:including mRNA, siRNA, and antisense oligonucleotides— allow direct modulation of gene expression and have gained global attention through advances in mRNA vaccine technology.

protein degradation therapies: such as PROTACs and Molecular glues, which remove proteins responsible for disease instead of inhibiting them.

cell-based therapies: including CAR-T cells and stem-cell-derived Therapies that administer living, engineerable cells capable of attacking cancer cells or repairing injured tissues.

Gene editing technologies: particularly CRISPR-based systems, offer Accurate alteration of DNA sequences, creating new possibilities for potentially curative therapies. Alongside these innovations, **engineered proteins and peptides:** provide highly specific Engaging with therapeutic targets while merging the benefits of biologic agents with enhanced stability and adjustable properties."

What are emerging modalities:

Emerging modalities represent a new wave of therapies that go beyond traditional chemical drugs and biologics. While conventional small molecules typically work by binding to proteins and biologics like antibodies act through immune pathways or outside the cell, these innovative therapies operate at a deeper level—directly influencing genes, RNA, or proteins in entirely new ways.

key features:

New ways of working: Instead of just blocking a protein, some therapies can remove or degrade it entirely.

Precision targeting: They can adjust gene activity or even edit the genome itself.

High specificity: Using specially engineered nucleic acids or cellular components, they can act with remarkable accuracy.

Personalization: Many treatments are tailored to an individual's unique genetic or molecular profile.

Examples of these cutting-edge approaches include gene and cell therapies, RNAbased treatments like mRNA or siRNA, gene-editing tools such as CRISPR, proteintargeting strategies like PROTACs or molecular glues, and designer proteins or peptides. Together, they open doors to therapies that were once considered impossible, offering hope for conditions that traditional drugs struggle to treat.

1.Gene therapy :(1to 5)

Definition:Gene therapy is a treatment method that aims to improve health by modifying a person's genes.

Types of Gene Therapy

1.Somatic Gene Therapy:
Targets non-reproductive cells (somatic cells).
Changes affect only the treated individual, not offspring.
Commonly used for treating genetic disorders, cancers, and viral infections.

2.Germline Gene Therapy:
Targets reproductive cells (sperm, eggs, embryos).
Changes are heritable, passed to future generations.
Highly controversial and currently not widely practiced in humans.

3.Ex Vivo Gene Therapy
The patient's cells are first collected from the body, then genetically modified in the lab under controlled conditions. After the desired changes are made, these improved cells are returned to the patient.
This method is widely used in treatments like hematopoietic stem cell therapy and CART cell therapy.

4.In Vivo Gene Therapy:
In this approach, the therapeutic genes are delivered directly into the patient's body using carriers such as specially engineered viruses.
It is particularly helpful when removing cells from the body for modification is difficult or not possible.

Mechanism of Gene Therapy

1. Gene Addition
This approach works by giving the body a fresh, healthy copy of a gene when the original one isn't working properly. It's like replacing a faulty instruction manual with a correct one so the cells can function normally again.

2. Gene Editing
By using powerful gene-editing tools like CRISPR-Cas9, researchers are able to go directly to the faulty DNA sequence and fix the mistake. Think of it as correcting a typo in the body's genetic code.

3. Gene Silencing (Knockdown)
Sometimes a gene produces too much of a harmful protein. Techniques like RNA interference help "turn down" or block this harmful gene, reducing its negative effects— similar to lowering the volume on a disruptive signal.

4. Gene Regulation
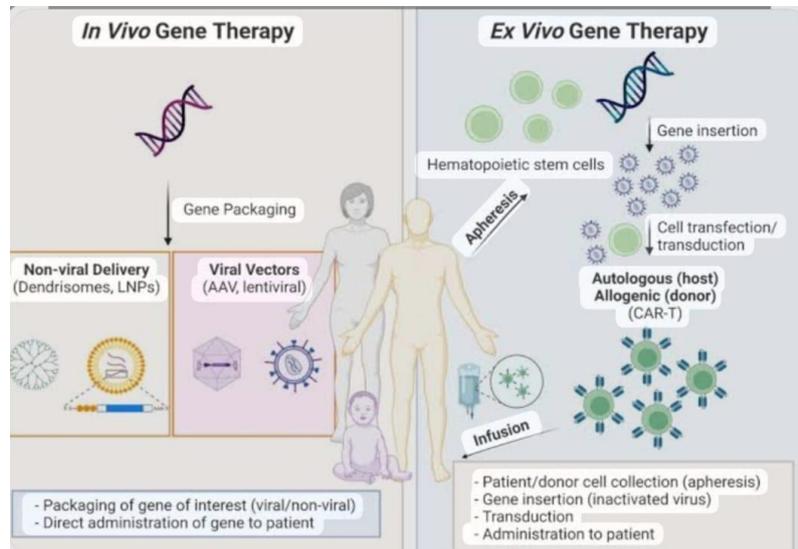
Instead of adding or cutting genes, this method adjusts how active a gene is. It can boost or reduce gene activity to bring the cell back to its normal balance, much like tuning a system to the right.

Delivery Methods:
Viral vectors (adenovirus, lentivirus, adeno-associated virus)
Non-viral vectors (liposomes, nanoparticles, electroporation)

Challenges of Gene Therapy

1. The Immune Response:
Sometimes the body's own defence system can mistake the delivery tools or the edited cells for harmful invaders. When that happens, it may attack them. which may make the therapy work less efficiently or cause unwanted reactions.

Delivery Efficiency:
Reaching the exact tissue or organ that needs treatment isn't always easy. Getting the therapy to the right place, in the right amount, is still a major challenge.

Duration of Effect:
Some gene therapies don't last very long. Their effects may fade over time, meaning patients might need additional rounds of treatment.

Off-Target Effects:
There's a risk that the genetic changes might accidentally happen in the wrong place, which could lead to unexpected problems.

Ethical Concerns:
When it comes to editing genes that can be passed on to future generations, many ethical questions arise. People worry about safety, fairness, and long-term consequences.

High Cost:

Gene therapies can be extremely expensive to create and use, making them difficult for many patients to access **Applications of Gene Therapy Genetic Disorders:**
Example: Severe Combined Immunodeficiency (SCID), Duchenne Muscular Dystrophy.

Cancer Therapy:
CAR-T cell therapy, oncolytic viruses.

Viral Infections:
Research into HIV and hepatitis B therapies.

Cardiovascular Diseases:
Gene therapy for promoting angiogenesis in ischemic heart disease.

Neurological Disorders:
Treating Parkinson's disease, spinal muscular atrophy (SMA).

Impact of Gene Therapy
Offers potential cures for previously untreatable genetic diseases.
Can reduce lifelong treatment burden for chronic conditions.
Advances personalized medicine, tailoring therapies to individual genetic profiles.
Stimulates innovation in biotechnology and pharmaceuticals.

Key Advances in Gene Therapy:
1.Precision genome editing (CRISPR-Cas9 and similar tools)
New gene-editing systems let scientists accurately correct genetic mistakes, almost like repairing an error in a digital file.
2. CAR-T cell therapy
Doctors can now modify a patient's own immune cells so they can specifically recognize and eliminate cancer cells, making treatment highly personalized.

3.   Improved AAV delivery systems
Small, non-harmful viruses called AAVs are being redesigned to carry therapeutic genes into the body more safely and effectively.
4.   Stem cell gene correction outside the body
Cells taken from a patient can be genetically fixed in the lab and then infused back, providing long-lasting benefits for conditions affecting the blood and immune system.
5.   Approved gene therapy medicines
Treatments like Luxturna and Zolgensma have proven that gene therapy can be successfully used in real medical practice, offering hope for people with rare hereditary diseases.
6.   Advances in RNA-based treatments
Therapies using mRNA or siRNA provide new ways to adjust how genes behave, allowing doctors to boost or silence specific genetic signals.

Example: Luxturna
Luxturna (voretigene neparvovec) is a ground-breaking therapy for people who have severe vision problems due to mutations in the RPE65 gene.

Purpose:
It is designed to help individuals with an inherited eye condition that gradually reduces their ability to see, especially in dim light.

How it works:
The treatment places a healthy version of the RPE65 gene directly into the retinal cells using a harmless AAV vector.
This gives the eye the correct instructions it needs to produce a vital protein for vision.

Impact on patients:

Many treated individuals show noticeable improvements in their ability to see in darker environments, helping them move around more independently and improving overall quality of life.

**2.RNA-Based Therapeutics: (5to10) Definition :**
RNA-based therapies are treatments that use RNA molecules to influence how genes are expressed or to help cells produce proteins that can treat diseases. Unlike traditional drugs that mainly target proteins, RNA therapies work at the genetic level, offering a precise way to address the root causes of illness.

• Types:

Types	How it works
small interfering RNA	Breaks down specific mRNA to stop harmful protein production
miRNA (microRNA therapeutics)	Fine-tunes networks of genes for broader regulation
ASO (antisense oligonucleotides)	Blocks mRNA translation or fixes RNA splicing errors
mRNA vaccines / therapies	Provides instructions for cells to make therapeutic proteins
Circular RNA (circRNA)	Stable RNA that allows longerlasting protein production
Ribozymes	Catalytic RNA molecules that cut target RNAs

Mechanism:

Mechanism	Purpose
Gene silencing	Switch off harmful genes that produce disease-causing proteins
Boosting gene expression	Increase production of helpful proteins
RNA editing	Correct genetic errors at the RNA stage
Protein replacement	Teach cells to produce proteins the body is missing
Immune activation	Stimulate the body's immune response (as in vaccines)
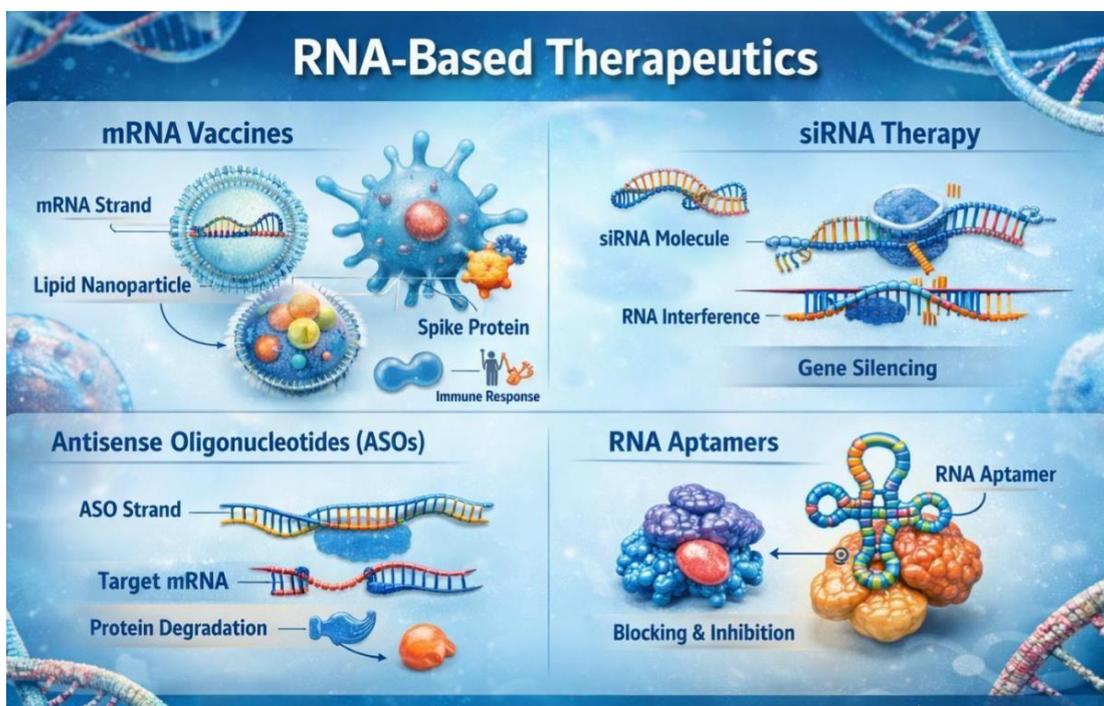
Delivery methods:
Non-Viral Methods:
Lipid nanoparticles (used in COVID-19 vaccines)
Biodegradable polymer carriers
Natural vesicles like exosomes Liver-targeted GalNAc conjugates **Cell-penetrating peptides:** Electroporation for ex vivo therapies **Viral Methods:**

• Adeno-associated virus (AAV)

• Lentivirus (mainly for gene-editing applications **Application:**
Genetic & Rare Diseases: Examples include Duchenne muscular dystrophy, spinal muscular atrophy, and transthyretin amyloidosis.
Cancer: Silencing oncogenes or boosting the immune system to fight tumors.

Infectious Diseases: COVID-19 mRNA vaccines, influenza, RSV, and HIV vaccines under research.
Cardiovascular & Metabolic Disorders: High cholesterol, diabetes, atherosclerosis. Neurological Disorders: Huntington's disease, ALS, and epilepsy in development stages **Major Advances in the Field:**
Pre-2015: First siRNA therapies approved by the FDA.
2020: mRNA COVID-19 vaccines proved the technology on a global scale.
Recent: Self-amplifying mRNA (saRNA) allows effective low-dose vaccines.
Emerging: Circular RNA for long-lasting protein production and personalized mRNA cancer vaccines tailored to patient-specific **tumors.**

Key Challenges
Despite impressive progress, RNA therapeutics face some hurdles
Stability RNA can be quickly broken down by enzymes in the body
Immune response   Some RNA or carriers can trigger unwanted inflammation
Targeted delivery   Hard to reach tissues beyond the liver
Manufacturing   Requires precise, high-quality production at scale
Side effects   Lipid nanoparticles or carriers can sometimes be toxic
Off-target effects   Risk of unintended gene silencing or editing

Examples of RNA Therapeutics:

Type	Drug
siRNA	Patisiran Amyloidosis

	Inclisiran High cholesterol	
ASO	Nusinersen (Spinraza) Spinal muscular atrophy	
mRNA Vaccines	Moderna mRNA-1273 COVID-19. PfizerBioNTechBNT162b2 COVID-19	
mRNA Therapy	mRNA-3705 Mitochondrial disorders (clinical trials)	
RNA Aptamer	Pegaptanib Macular degeneration	
CRISPR-RNA Editing	Cas9-gRNA therapies Sickle cell di & β-thalassemia	

3.Protein Degradation Therapies :(**13 to 18**)
Definition:
These are treatments designed to remove harmful proteins from the body instead of just blocking them.

Think of them as the body's "cleanup helpers" — they guide unwanted proteins to the cell's natural garbage-disposal systems so they can be broken down and removed.

This gives a deeper and more lasting effect than regular drugs that only turn off a protein.

Types of Protein Degradation Therapies
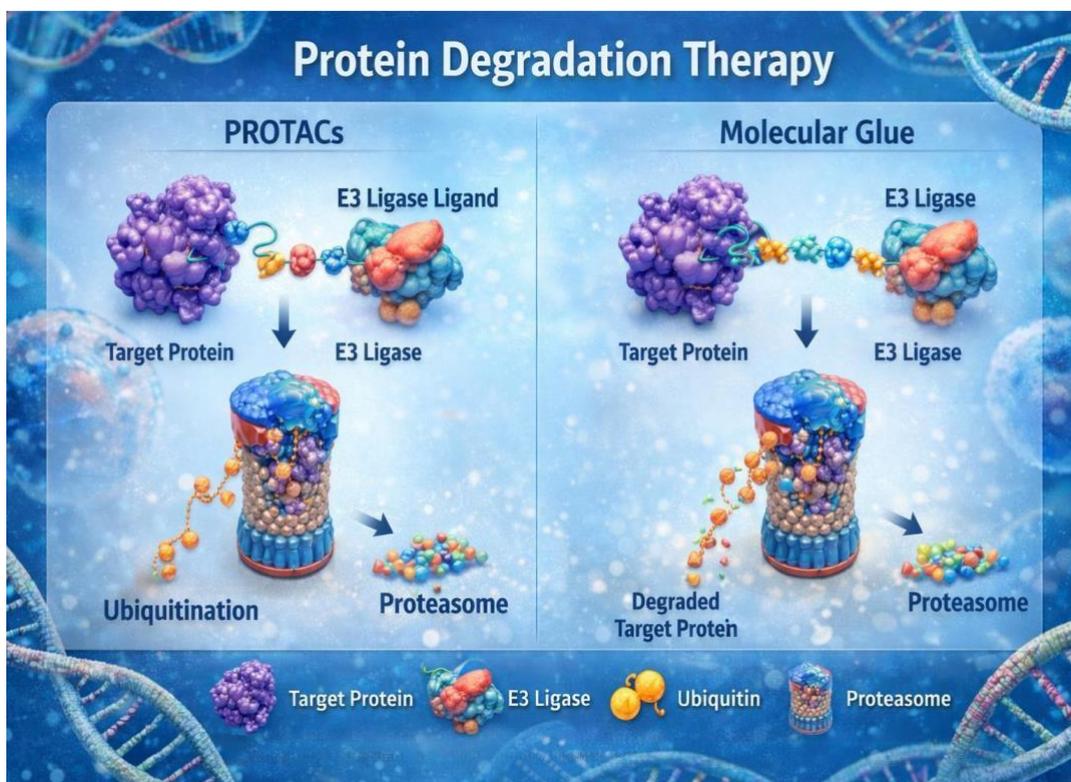**PROTACs**
Small molecules with two ends:
One end grabs the disease-causing protein,
The other end pulls in the cell's degradation machinery.
Together, they mark the protein for destruction.

Molecular Glues
Single small molecules that help a protein "stick" to a degradation enzyme so it gets removed.

LYTACs

Used for proteins on the cell surface or outside the cell.

They direct these proteins to the lysosome, a kind of recycling center.

AUTACs & ATTECs

These use the autophagy pathway — another cleanup system in cells — to break down harmful proteins, often used for large or aggregated proteins.

DUBTACs

These do the opposite: instead of degrading, they protect useful proteins from being broken down.

Mechanism

Depending on the type, these therapies use one of the body's natural waste-removal systems:

Ubiquitin–Proteasome System (used by PROTACs & molecular glues) The therapy attaches a "destroy me" tag (ubiquitin) to the faulty protein.

The tagged protein is sent to the proteasome, the cell's shredder.

The proteasome breaks it down into small pieces.

Lysosomal Pathway (LYTACs)

They pull membrane or extracellular proteins into the cell and send them to the lysosome for breakdown.

Autophagy Pathway (AUTACs, ATTECs)

These therapies bring large or aggregated proteins into autophagosomes, which later fuse with lysosomes and digest the contents.

Delivery methods

Oral tablets — for small molecules like PROTACs or molecular glues.

Injections/IV — for larger or more complex degraders like LYTACs.

Targeted carriers — nanoparticles or antibodies to deliver the drug to specific tissues Localized delivery — directly to tumors or tissues to reduce side effects.

Challenges

Even though they are promising, there are hurdles:

Big molecular size (especially PROTACs)

This can make them harder to absorb and deliver into cells.

Risk of affecting the wrong proteins

Unwanted protein degradation may cause side effects.

Limited E3 ligases available

Only a few enzymes can be used to tag proteins for destruction.

Drug resistance

Cells may mutate and become less responsive.

Complexity in manufacturing

Some degrader molecules are difficult to design and produce.

Applications:

Protein degradation therapies hold promise in many diseases:

Cancer – removing proteins that drive tumor growth.

Neurodegenerative diseases – clearing toxic protein clumps (e.g., in Alzheimer's or Huntington's).

Autoimmune disorders – eliminating overactive immune proteins.

Viral infections – targeting viral proteins.

Genetic diseases – removing misfolded or harmful proteins.

Key Advances :

First PROTACs have entered human clinical trials.

Discovery of powerful molecular glues that work with high precision.

New types of degraders (LYTACs, AUTACs, ATTECs) that can reach proteins once considered "untreatable."

Better structural biology and AI tools helping scientists design more efficient degraders.

Success in degrading difficult targets like transcription factors.

Examples

PROTAC Therapies

ARV-110 – removes androgen receptors in prostate cancer.

ARV-471 – targets estrogen receptors in breast cancer.

Molecular Glues

Thalidomide, lenalidomide, pomalidomide – used in blood cancers by degrading IKZF1/3.

CR8 – promotes degradation of cyclin-dependent kinase complexes.

LYTACs

LYTACs for EGFR and other membrane proteins (preclinical research).

AUTACs

Designed to remove protein aggregates in diseases like Parkinson's.

ATTECs

Used in lab models to degrade mutant huntingtin in Huntington's disease.

DUBTACs

Developed to stabilize CFTR protein in cystic fibrosis.

II. Conclusion:

The landscape of medicinal chemistry is undergoing a remarkable evolution as emerging drug modalities push beyond the limits of traditional small-molecule and biologic therapies. By acting

directly on genes, RNA, proteins, or even entire cells, these advanced platforms offer new ways to treat diseases that were once considered untreatable or difficult to manage. Gene therapy and gene-editing technologies provide long-lasting or even curative solutions for inherited disorders. RNA-based therapeutics introduce a flexible, programmable way to regulate gene expression or produce therapeutic proteins. Protein degradation therapies bring a transformational shift by eliminating harmful proteins instead of merely inhibiting them. Meanwhile, cell-based therapies and engineered peptides open powerful paths for personalized and highly targeted interventions.

Together, these modalities reflect a shift toward deeper biological precision, improved selectivity, and tailored treatment strategies. Continued advancements in delivery systems, computational design, structural biology, and manufacturing are helping overcome earlier challenges related to stability, immune reactions, and targeting. As research accelerates and more therapies reach clinical use, these innovative platforms are expected to redefine drug discovery and healthcare. Ultimately, emerging drug modalities represent a major step toward precision medicine—where treatments are not only more effective, but also more individualized, durable, and aligned with the underlying biology of disease.

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