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Chapter 8: Theranostic Nanoparticles- Dual Function Platform for Diagnosis & Treatment in Alzheimer's disease

Susanta Kumar Sahu[1], Nihar Ranjan Das[2*], Zeenath Banu[3], Rakesh Kumar Nayak[4], Sushil Kumar Sahoo[5], Serakam Panduranga Vittal[6]

[1]*Department of Pharmacology, Maa Tara Tarini College of Pharmacy, Berhampur, Odisha, India*
[2]*Department of Pharmacology, GITAM Deemed to be University, Visakhapatnam, 530045, Andhra Pradesh, India*
[3]*Department of Pharmacology, RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad, Telangana-500027, India*
[4]*Department of Pharmacology, Roland Institute of Pharmaceutical Sciences, Berhampur, 760010, Odisha, India*
[5]*Department of Pharmacology, Dadhichi College of Pharmacy, Cuttack, Odisha,754002, India*
[6]*Department of Medicine, GIMSR Medical College, Visakhapatnam, 530045, Andhra Pradesh, India*

**Corresponding author*
Dr Nihar Ranjan Das: ndas@gitam.edu
ORCID iD: https://orcid.org/0000-0001-6883-6523

Abstract

Alzheimer's disease (AD) remains one of the most challenging neurodegenerative disorders, marked by progressive memory loss, cognitive decline, and irreversible neuronal damage. Traditional approaches to AD diagnosis and treatment face major limitations—late detection, poor blood–brain barrier (BBB) penetration, and a lack of real-time treatment monitoring. Theranostic nanoparticles, integrating both therapeutic and diagnostic functions into a single nanoscale platform, offer a groundbreaking solution. These smart carriers can cross the BBB, selectively bind to Alzheimer's biomarkers such as amyloid-beta plaques and tau tangles, deliver targeted drugs, and simultaneously enable advanced imaging modalities like MRI, PET, and fluorescence for real-time monitoring. By merging early detection with precision drug delivery, theranostic nanoplatforms have the potential to slow or even halt disease progression while minimizing systemic side effects. This chapter explores the design, mechanisms, applications,

and clinical potential of theranostic nanoparticles in Alzheimer's, highlighting their transformative role in the future of personalized neuromedicine.

Keywords: *Alzheimer's disease, Amyloid-beta, Blood–brain barrier, Nanomedicine, Targeted drug delivery, Theranostic nanoparticles*

1. Introduction to Theranostics and Alzheimer's Disease

1.1 What is Theranostics

In the traditional approach to medicine, diagnosis and therapy occur in separate stages. First, physicians diagnose a disease using various imaging or laboratory tests. Then, treatment is initiated often broadly targeted, sometimes with limited success especially in chronic or complex conditions.

Theranostics is an emerging concept in advanced medicine that merges diagnosis and therapy into a single, integrated system(Kumar & Antal, 2025). These nanoparticles are ultra-small, multifunctional carriers typically less than 100 nanometres in size(Yang et al., 2025). It allows healthcare professionals to not only detect disease but also treat it simultaneously with a single platform. This dual-functionality creates an advanced level of precision medicine. This "see-and-treat" platform enables early disease detection, targeted drug delivery and real-time monitoring, all within a single system(Wang et al., 2023) (Figure 8.1).

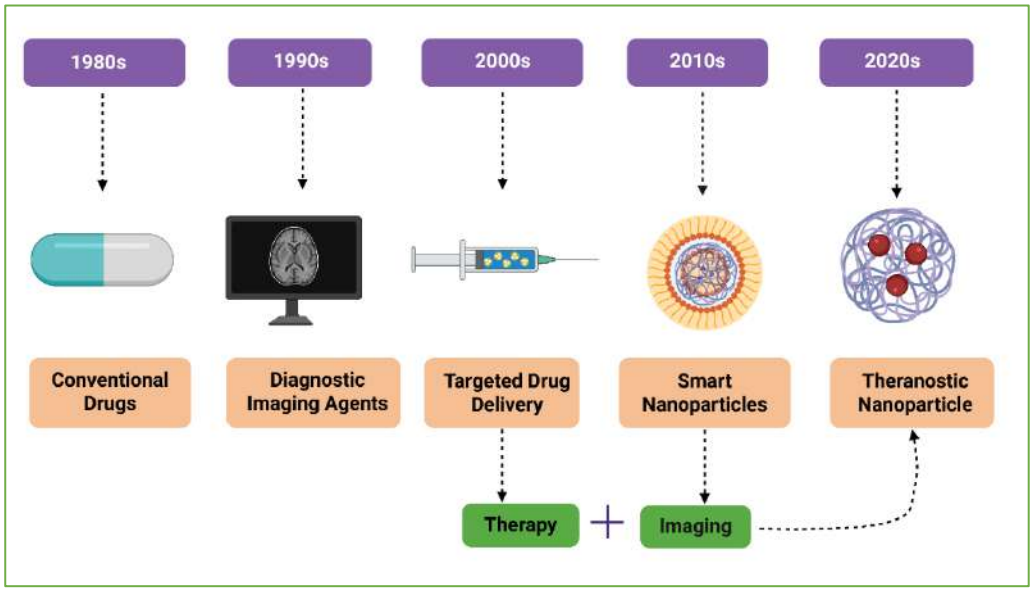

Figure 8.1. Timeline — Evolution from Nanomedicine to Theranostics: This figure illustrates the chronological progression from conventional drugs in the 1980s to theranostics nanoparticles in the 2020s. In the 1990s, advances in diagnostic imaging expanded disease detection capabilities. The 2000s introduced targeted drug delivery systems, representing the therapy component, while the 2010s saw the development of smart nanoparticles with advanced imaging functions. These two streams therapy from the 2000s and imaging from the 2010s merged to create theranostics nanoparticles, integrating diagnosis and treatment within a single platform (Kiran et al., 2021).

1.2 Why Theranostics Matters in Neurodegenerative Diseases

Neurodegenerative diseases particularly Alzheimer's Disease (AD) is one of the greatest neurological challenges of our time, affecting millions of people globally(Wang et al., 2024). It is marked by progressive memory loss, cognitive decline and eventually a loss of independence, identity and quality of life(Xia et al., 2025). What makes Alzheimer's especially daunting is its silent progression, it begins quietly in the brain, often years before any symptoms are noticeable. By the time forgetfulness or confusion emerges, much of the neuronal damage is already irreversible.

In Alzheimer's disease early detection and precise treatment are critical yet conventional methods often fall short(Parul et al., 2025). Conventional imaging methods like MRI or PET scans can only detect the disease at a later stage and available medications mainly provide temporary symptomatic relief(Paduvilan et al., 2025). The disease involves complex pathological factors like amyloid plaques, tau tangles, oxidative stress and neuroinflammation, while symptoms only emerge after significant brain damage(Soni et al., 2025). Moreover, delivering drugs to the brain is challenging because the blood–brain barrier (BBB) not only blocks most therapeutic agents but also limits the effectiveness of early diagnostic tools in Alzheimer's disease(Kirit et al., 2025).

In this disease where early intervention is crucial and most drugs struggle to reach the brain due to the protective blood–brain barrier, theranostic nanoparticles offer a transformative solution(Polshettiwar et al., 2025). It enables early detection, targeted drug delivery and real-time monitoring into a single platform, which address the key limitations of current diagnostic and therapeutic approaches(Hemdan et al., 2024). These nanoparticles provide a more precise, responsive and effective strategy for managing Alzheimer's disease (Figure 8.2).

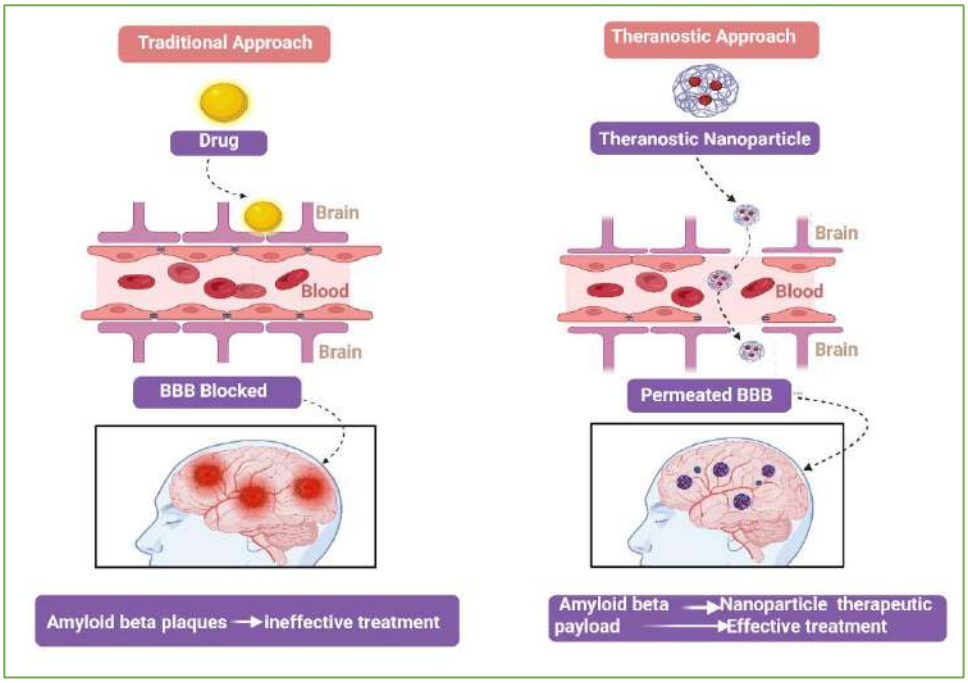

Figure 8.2. Traditional vs Theranostics Approach in Alzheimer's Disease: The figure compares conventional drug delivery with the theranostic nanoparticle approach for Alzheimer's disease. Traditional Alzheimer's treatments often struggle because most drugs cannot cross the blood–brain barrier (BBB). As a result, they rarely reach amyloid-beta plaques in sufficient amounts to make a real difference. Theranostic nanoparticles overcome this limitation by crossing the BBB, delivering their therapeutic load right where it is needed and at the same time providing imaging signals to monitor the treatment in real time(Francisco et al., 2024).

1.3 Current Challenges in Alzheimer's Disease Management

Treating Alzheimer's disease is difficult not just because of the disorder's biological complexity but also due to practical barriers that have persisted for decades(Safiri et al., 2024). Late diagnosis, weak drug performance, the challenge of crossing the blood–brain barrier and the inability to track therapy in real time are some of the main reasons why conventional care remains inadequate(Toader et al., 2024). Exploring these barriers in detail gives us a clearer view of where innovation is most needed.

Late Diagnosis Limits Recovery

Alzheimer's often develops silently over many years. By the time signs such as memory lapses or confusion appear, much of the brain has already suffered damage that cannot be reversed.(Reddi Sree et al., 2025). Conventional diagnostic tools such as MRI, PET scans or cognitive assessments detect Alzheimer's only in these later stages, missing the

crucial early window where intervention could make a real difference(Bhatia et al., 2025).

Limited Success of Existing Treatments

Current medications such as donepezil, rivastigmine and memantine focus only on symptom management(Cani et al., 2025). They neither stop the disease from advancing nor address its root causes. Additionally, many potential drugs that perform well in laboratory settings often fail in clinical trials due to low effectiveness in reaching the brain or due to unwanted systemic side effects(Senanayake et al., 2025).

The Blood Brain Barrier (BBB) Blocks Drug Entry

One of the biggest challenges in treating Alzheimer's is the blood–brain barrier-a protective shield that prevents most substances, including drugs, from entering the brain(J. Liu et al., 2025). While this barrier is essential for maintaining brain health, it also blocks more than 98% of therapeutic compounds, making it difficult for even the most promising drugs to reach their targets(H. Wu et al., 2025).

Lack of Real Time Monitoring

Current therapeutic approaches lack any real-time feedback. Once a drug is administered, doctors have no clear way of knowing whether it has reached the right location in the brain or if it's having the desired therapeutic effect(Tran et al., 2025). This lack of monitoring makes it hard to adjust or personalize treatment strategies effectively.

The obstacles in managing Alzheimer's make it clear that a single, integrated solution is needed. Theranostic nanoplatforms address this gap by offering early detection, efficient drug delivery across the brain's barriers and real-time monitoring(Dey et al., 2024) (Figure 8.3).

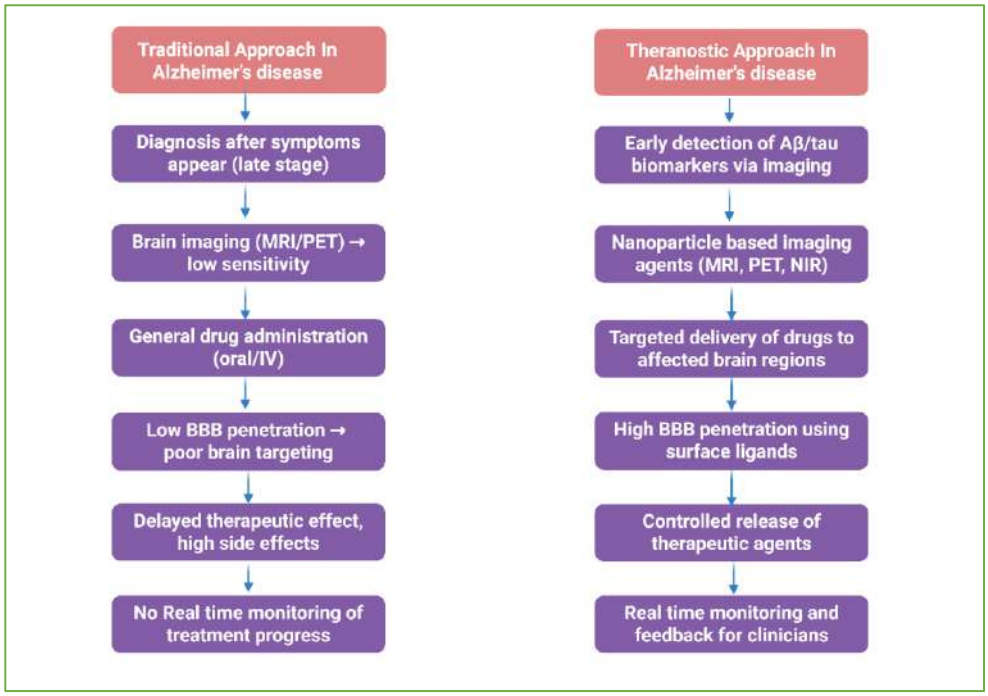

Figure 8.3. Traditional vs Theranostics Approaches in AD: In conventional route, diagnosis and treatment of AD are carried out separately causing delays and less effective outcomes. In contrary, theranostic pathway brings together both diagnosis and treatment allowing earlier detection, targeted delivery of drugs, real-time monitoring and a more personalized treatment (Tripathi et al., 2022).

1.4 Role of Nanoparticles as Theranostics Tools in Alzheimer's Disease

Nanoparticles (NPs) can be engineered to carry out very specific tasks in both treatment and diagnosis, thanks to their small size coming under 100 nanometers (Joseph et al., 2023). The tiny size provides high surface area. The ability of NPs to be modified with different coatings or ligands, make these valuable for theranostic applications in complex brain disorders such as Alzheimer's disease (Moorthy & Govindaraju, 2021). NPs have great ability to move past the blood–brain barrier (BBB), which normally blocks most medicines from reaching the brain (Qiao et al., 2024). By attaching molecules such as transferrin or ApoE peptides or by adding protective coatings like PEG, the NPs can be made more accessible to the brain tissues (Beygi et al., 2024).

In AD, it is essential to focus treatment on abnormal proteins like amyloid-beta plaques and tau tangles. Nanoparticles can be linked with antibodies, peptides or aptamers that recognize and attach only to these proteins (Toader et al., 2024). This selective targeting allows drugs to act directly where they are needed, improving treatment while reducing unwanted effects on healthy cells.

Another unique strength of theranostic NPs is that they can combine imaging and therapy within the same system (Suhag et al., 2024). MRI contrast dyes, PET tracers or fluorescent markers can be packed together with therapeutic compounds like anti-amyloid drugs, antioxidants or anti-inflammatory agents to simultaneously track while treating the disease (Chaparro et al., 2023). This "see-and-treat" approach supports early diagnosis and allows interventions to be carried out at the right time.

Some nanoparticle systems are specially designed for stimuli-responsive drug release (Fatima et al., 2024). They stay stable while circulating in the body and get activated once they encounter disease-specific conditions such as changes in pH, abnormal enzyme activity or oxidative stress. This ensures that the drug is released only where it is required ensuring precise and localized treatment (Ashok et al., 2022).

Having versatile abilities, NPs emerge as promising tools in AD theranostics. AD progression starts with mild preclinical alterations and advances toward profound cognitive impairment and loss of independence (Mark & Brehmer, 2022) demanding different clinical approach for each step. Theranostics nanoparticles with their dual capability for diagnosis and therapy present an opportunity to address these needs more effectively (Toader et al., 2024). The table below (Table 8.1) outlines the major stages of AD, their typical symptoms and the corresponding potential applications of theranostics nanoparticles.

Table 8.1: Alzheimer's Progression and Theranostics Interventions

Stage	Symptoms	Role of Theranostic Nanoparticles (Dey et al., 2024)
Preclinical	No visible symptoms	Early biomarker detection via imaging NPs
Mild Cognitive Impairment (MCI)	Slight memory issues, confusion	Targeted drug delivery to delay progression
Moderate AD	Cognitive decline, behavior changes	Combined neuroprotection and diagnostic imaging
Severe AD	Loss of speech, daily function	Anti-inflammatory and supportive treatment

2. Types of Nanoparticles Used in Theranostics

Liposomes

Liposomes are lipid based spherical vesicles that mimic cell membranes and can encapsulate both hydrophilic and hydrophobic drugs(Trucillo et al., 2024). Their biocompatibility and low toxicity make them ideal for brain applications. In Theranostics, liposomes can be co-loaded with therapeutic agents such as curcumin, which has anti-amyloid effects and contrast agents like iron oxide for MRI visibility(Hasan et al., 2024).

Dendrimers

These are highly branched, tree-like polymer structures with multiple surface functional groups that allow attachment of drugs, targeting ligands and imaging agents simultaneously(Moorthy & Govindaraju, 2021). For example, PAMAM dendrimers have shown promise in delivering siRNA to silence tau expression while being traced using fluorescence(Li et al., 2022).

Polymeric Nanoparticles

Biodegradable polymers like PLGA (poly lactic-co-glycolic acid) are widely used in sustained drug delivery(Lu et al., 2023). PLGA nanoparticles loaded with drugs such as memantine or donepezil can be functionalized with BBB-targeting ligands and fluorophores to enable both controlled therapy and optical imaging(Bagherpour et al., 2025).

Metallic Nanoparticles

Gold nanoparticles (AuNPs) and iron oxide nanoparticles (IONPs) are especially useful due to their dual functionality(Singh et al., 2025). AuNPs are excellent for CT imaging and photothermal therapy, while IONPs provide strong contrast in MRI and can be guided magnetically(H. Liu et al., 2025). These metal-based platforms are often coated with Aβ-targeting peptides or antibodies for site-specific action.

Quantum Dots

Quantum dots (QDs) are fluorescent semiconductor nanocrystals that emit bright, stable light upon excitation(Loskutova et al., 2025). They are primarily used for diagnostic imaging. Although their therapeutic potential is still being explored, QDs tagged with tau or Aβ-specific antibodies can provide high resolution images of disease pathology at the cellular level (Dey et al., 2024) (Table 8.2).

Table 8.2: Comparison of Theranostics Nanoparticles

Type of NP	Diagnostic Use	Therapy Delivered	BBB Penetration	Key Feature(Chaparro et al., 2023)
Liposomes	MRI, Optical Imaging	Curcumin, Donepezil	Moderate	High safety, dual cargo loading
Dendrimers	Fluorescence, Optical	siRNA, Anti-Tau therapy	High	High targeting precision
Polymeric NPs	MRI contrast, Sustained	Memantine, Rivastigmine	Moderate	Slow release, biodegradable
Gold NPs	CT, Photoacoustic	Aβ-targeted payloads	Moderate–High	Multi-modal use
Quantum Dots	Fluorescence Imaging	None (imaging only)	High	Sharp imaging, cell labelling

3. The Theranostics Platform: Dual-Action Design

Theranostics nanoparticles represent a sophisticated integration of therapeutic and diagnostic functionalities into a single nanostructure. This dual action design marks a shift from traditional "trial-and-error" treatment models to a personalized, responsive and targeted approach particularly essential in neurodegenerative diseases like Alzheimer's Disease (AD).

These advanced platforms can not only deliver drugs precisely to diseased regions of the brain but also visualize pathological hallmarks, monitor therapeutic efficacy in real-time, and adjust treatment protocols accordingly(A. Sharma et al., 2024). In diseases where early intervention is vital, theranostic systems open the door to timely and patient-specific care.

3.1 What Makes a Nanoparticle Theranostics?

The core idea behind theranostics is functional integration where a single nanoparticle acts both as a treatment vehicle and a diagnostic sensor. This is a major improvement over traditional drug delivery systems, which operate independently of any feedback mechanism.

While conventional nanoparticles serve either a therapeutic (e.g. drug carrier) or diagnostic (e.g. MRI contrast agent) function, theranostic nanoparticles are designed for:

- Seek out disease specific targets such as amyloid-beta (Aβ) plaques or hyperphosphorylated tau.
- Deliver therapy selectively to these targets.
- Provide real-time visualization through imaging modalities like MRI, PET or optical fluorescence.
- Minimize systemic side effects by avoiding healthy tissue.

In Alzheimer's, this approach is particularly relevant due to the invisible progression of pathology in early stages and the urgency of early intervention (Table 8.3).

Table 8.3: Comparison – Single Function vs. Theranostics Nanoparticles

Feature	Single-Function Nanoparticles	Theranostic Nanoparticles(Tripathi et al., 2022)
Purpose	Diagnostic or Therapeutic	Combined Diagnostic and Therapeutic
Monitoring Capability	Absent	Real-time imaging of drug distribution
Targeting Strategy	Passive accumulation	Active targeting with ligands/antibodies
Disease-Specific Delivery	Limited	Precisely directed to pathological sites

Application in AD	Symptom relief or detection	Early diagnosis + neuroprotection
Personalization	One-size-fits-all	Customizable for patient-specific biomarkers

3.2 Components of Theranostic Nanoparticles

A successful theranostic platform is built on four modular components, each optimized for its specific function: structural core, diagnostic element, therapeutic cargo and targeting ligand.

3.2.1 Core Material

The core serves as the backbone of the nanoparticle, dictating its physical stability, biocompatibility and payload capacity. It also affects the mode of imaging, circulation time and biodegradation.

Common Core Materials:

- Gold nanoparticles (AuNPs): Favourable for CT imaging, surface plasmon resonance and photothermal therapy(Aili et al., 2023).
- PLGA (poly-lactic-co-glycolic acid): A biodegradable polymer ideal for controlled drug release and high drug loading.
- Quantum Dots (QDs): Provide sharp, stable fluorescence for cellular imaging and pathology tracking.
- Iron oxide nanoparticles (IONPs): Serve as powerful MRI contrast agents.

The choice of core determines not only the route of administration and imaging modality but also the half-life and bioavailability of the entire system(Thangaleela et al., 2025).

3.2.2 Diagnostic Moiety

The diagnostic component enables real-time tracking and visualization of the nanoparticle's journey inside the body. This provides immediate feedback on:

- Whether the NP has reached the intended target
- The extent of drug release
- The change in pathology (e.g. shrinkage of Aβ plaques)

Examples of Diagnostic Moieties:

- Gadolinium (Gd^{3+}) or Iron Oxide (Fe_3O_4): Used for MRI imaging
- NIR (Near-Infrared) Fluorescent Dyes: For deep tissue imaging

- Radioisotopes (e.g., 64Cu, 18F): Enable PET/SPECT imaging
- Upconversion Nanoparticles (UCNPs): For dual-mode imaging with high penetration and low background interference(Butt & Bach, 2025).

These features transform a drug carrier into a diagnostic companion, enabling image guided therapy (IGT).

3.2.3 Therapeutic Payload

The therapeutic core is the functional agent responsible for treating the disease. These agents are carefully encapsulated or attached to maintain their stability and activity during circulation and are released upon reaching the target site.

Types of Therapeutic Payloads for AD:

- Aβ plaque inhibitors (e.g. monoclonal antibodies, β-secretase inhibitors)
- Tau aggregation blockers (e.g. methylene blue analogues)
- siRNA/mRNA for gene silencing
- Neuroprotective antioxidants (e.g. curcumin, EGCG)
- Anti-inflammatory compounds targeting glial activation(Reddi Sree et al., 2025)

Advanced release mechanisms are used to ensure drugs are discharged only at the disease site using triggers like:

- pH sensitivity (e.g. acidic microenvironments of Aβ plaques)
- Enzyme activation (e.g. overexpressed enzymes like MMPs)
- Redox gradients (e.g. high oxidative stress in AD)

3.2.4 Targeting Ligands

The most innovative aspect of theranostic nanoparticles is their active targeting ability. Surface ligands function as molecular guides, enabling nanoparticles to circulate through the bloodstream, cross the blood–brain barrier (BBB) and selectively target neurons affected by Alzheimer's pathology.

Common Targeting Ligands:

- ApoE-mimetic peptides**:** Target LDL receptors on the BBB
- Transferrin or lactoferrin**:** Exploit receptor-mediated transcytosis
- Amyloid-beta antibodies or aptamers**:** Target Aβ plaques

- RGD peptides**:** Direct NPs to integrin overexpressing cells (in neuroinflammation)

Ligand based targeting specifically toward diseased neurons bring a lot of precision in the treatment, thereby protecting healthy tissues and reducing toxicity (Nankar et al., 2022) (Figure 8.4).

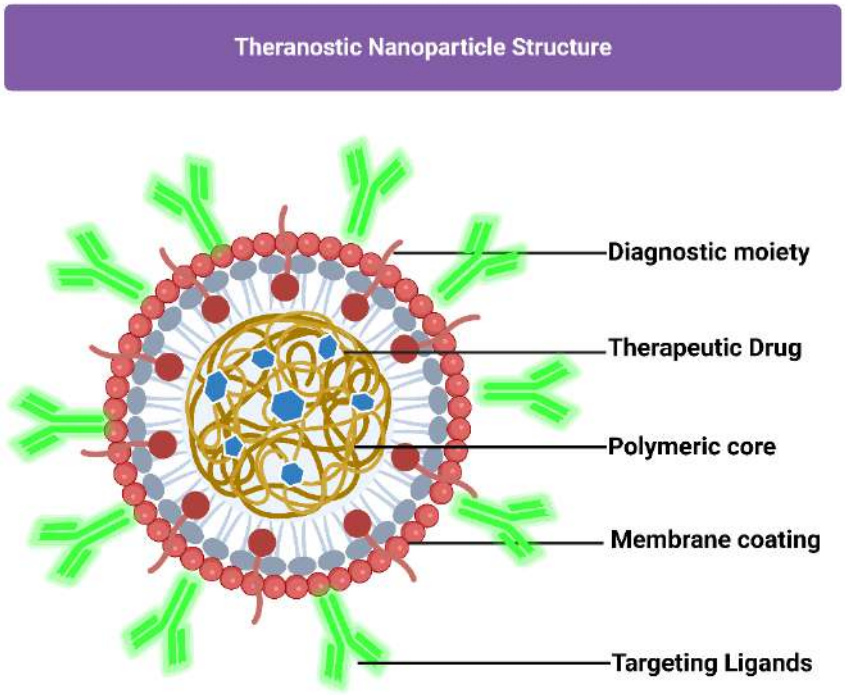

Figure 8.4. Architecture of Theranostics Nanoparticle: There is a central core made up of materials such as gold or biocompatible polymers, acts as the base and can be loaded with therapeutic drugs. Diagnostic elements like fluorescent dyes or MRI contrast agents can be incorporated for imaging alongside. Surface ligands are attached to direct the nanoparticle toward diseased cells allowing simultaneous diagnosis and treatment within a single system (Kiani et al., 2025).

This theranostic approach brings more advanced and adaptive healthcare strategies by introducing precision, personalization and efficiency into AD treatment.

4. Mechanism of Theranostic Nanoparticles in the Brain

Theranostic nanoparticles act as intelligent, multifunctional platforms that integrate therapy with diagnosis. Unlike conventional approaches, they not only deliver drugs efficiently to the brain but also allow real-time monitoring of disease processes. In the

context of AD, this dual role is especially valuable, given the complexity of the brain environment and the urgent need for targeted and well-controlled interventions.

4.1 Crossing the Blood–Brain Barrier (BBB)

The BBB acts as a highly selective shield, restricting the entry of most substances including the majority of conventional drugs into brain tissue (J. Liu et al., 2025). To overcome this challenge, theranostic NPs are designed with specialized mechanisms that enhance their transport across the BBB.

One such approach is **receptor-mediated transcytosis**, where nanoparticles are functionalized with ligands such as transferrin, ApoE peptides, or lactoferrin (Ding et al., 2025). These ligands mimic naturally transported biomolecules enabling the nanoparticles to be recognized and actively shuttled across the endothelial cells of the brain vasculature (Kirit et al., 2025). This mechanism effectively facilitates the delivery of therapeutic agents across the blood-brain barrier (BBB).

Another pathway adsorptive-mediated transcytosis relies on positively charged nanoparticles that interact electrostatically with the negatively charged cell membrane surfaces. This electrostatic interaction promotes the internalization process and allows nanoparticles to traverse biological barriers, such as the blood-brain barrier (BBB), through vesicular transport.

Furthermore, surface modifications including PEGylation (the process of attaching polyethylene glycol chains) or surfactant coatings such as polysorbate 80 enhance circulation stability and decrease immune clearance. These approaches also improve interactions with endothelial cells, which in turn reduces opsonization and facilitates a more effective transit of nanoparticles through the blood-brain barrier (Dong et al., 2025).

4.2 Target Recognition and Binding

Once theranostic nanoparticles penetrate the blood-brain barrier, they are engineered to identify and adhere to the key pathological characteristics of Alzheimer's disease (AD), including Amyloid-beta (Aβ). Aβ plaques serve as a fundamental marker for AD. Consequently, they have emerged as a vital area of interest for both diagnosis and treatment. Nanoparticles that are tailored with particular molecules, such as antibodies or peptides like KLVFF, are intended to directly attach to these plaque structures (Kotha et al., 2024). This targeting technique offers a dual advantage. It facilitates the early detection of the disease by enabling visualization of amyloid plaques, and it aids in the development of new therapies by allowing for the disruption of these plaques. This highly targeted method ensures that treatments are administered exactly where they are required, thereby enhancing their effectiveness.

Nanoparticles engineered with particular ligands can specifically target tau proteins, which represent a crucial pathological characteristic of neurodegenerative disorders

(Yang et al., 2024). By attaching to these tangles, the nanoparticles can assist in visualizing the progression of the pathology and may also disrupt or prevent the creation of these detrimental aggregates. This dual capability facilitates both imaging and therapeutic intervention (Kaur et al., 2023). This accurate targeting minimizes off-site toxicity and guarantees that both the imaging and therapeutic agents function precisely where required.

4.3 Triggered Drug Release

Theranostic systems are designed to administer drugs in a precise and targeted way. By concentrating the release of therapeutic agents at the site of the disease, these systems help to limit unnecessary exposure to healthy tissues and decrease the side effects often associated with traditional treatments (Lim et al., 2021). A frequent trigger for release is sensitivity to pH. In regions such as amyloid plaques or within cellular compartments like endosomes and lysosomes, where the environment turns more acidic, these pH-responsive nanoparticles decompose and discharge their drug payload (Shinn et al., 2022).

Another smart mechanism involves **enzyme-responsive release**. In Alzheimer's disease, certain enzymes like matrix metalloproteinases (MMPs) or cathepsins become elevated due to ongoing neuroinflammation(Radosinska & Radosinska, 2025). Theranostic nanoparticles can be coated with materials that these enzymes can recognize and cleave, triggering the release of the therapeutic agent precisely where it's needed.

Redox-sensitive systems also play a vital role. Diseased neurons often exhibit high levels of oxidative stress. Nanoparticles designed with redox-responsive linkers can sense this altered redox balance and release their drug cargo when they enter these stressed environments.

Together, these smart release strategies ensure that the therapeutic payload is delivered only at the site of disease—capturing the true essence of precision medicine.

4.4 Real Time Imaging and Monitoring

Theranostic nanoparticles carry both therapeutic and imaging agents giving doctors the ability to track treatment in real-time. These imaging agents include MRI contrast agents like superparamagnetic iron oxide, PET or SPECT tracers and fluorescent dyes or near-infrared (NIR) probes can be detected non-invasively(Shaghaghi et al., 2025). By including these agents, clinicians can see how nanoparticles spread in the brain, check if they are reaching their targets and even monitor drug release in real time(Rai et al., 2023). This real-time tracking gives important insights into how well the treatment is working.

Such feedback allows doctors to personalize therapy, adjusting it based on each patient's response. This level of precision is a big improvement over traditional Alzheimer's treatments, which usually lack such flexibility (Table 8.4; Figure 8.5).

Table 8.4: How Do They Help in Alzheimer's Disease?

Function	How Nanoparticles Contribute
Crossing the Blood–Brain Barrier	Engineered with surface ligands (e.g., **transferrin**, **ApoE**), or coatings like **PEG**, they sneak past the brain's natural defenses.
Targeting Aβ and Tau	Functionalized with **antibodies**, **peptides**, or **aptamers**, they bind precisely to **amyloid plaques** and **tau tangles**.
Dual Imaging + Therapy	Carry **MRI contrast agents**, **fluorescent dyes**, and **drugs** simultaneously—enabling real-time tracking and treatment.
Smart Drug Release	Respond to **pH**, **enzymes**, or **oxidative stress**, ensuring drugs are released only where and when needed.

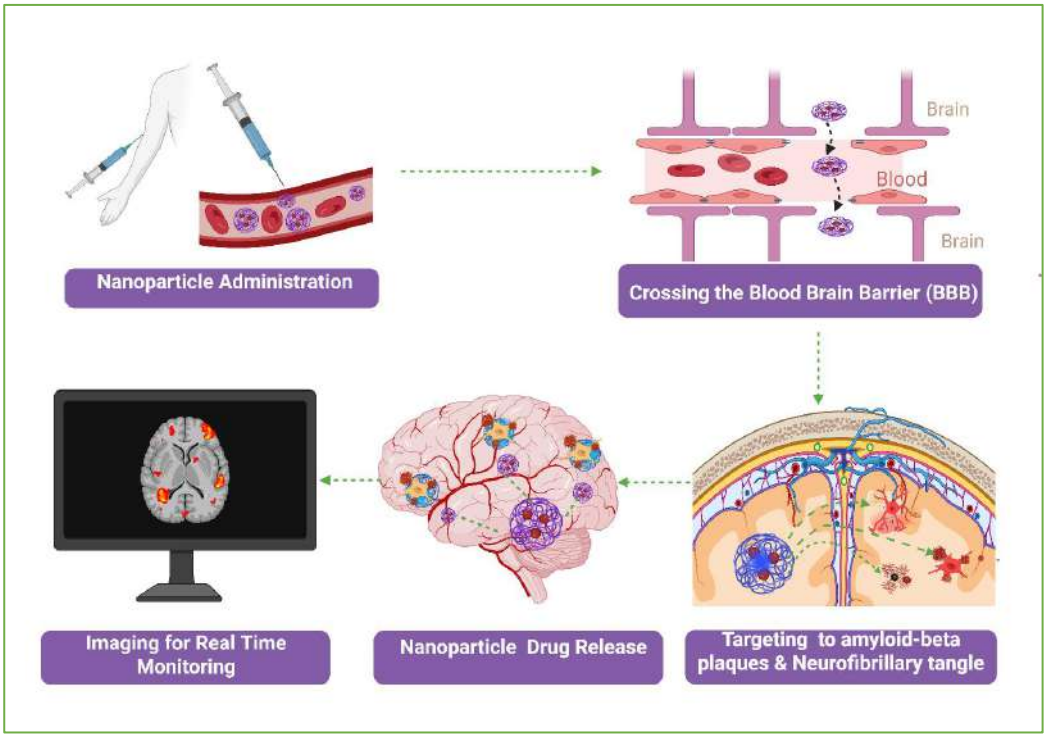

Figure 8.5. Mechanistic Insights into Nanoparticle Based Alzheimer's Therapy: A step-by-step flowchart showing how the nanoparticle system works. It begins with nanoparticle administration, followed by its passage across the blood–brain barrier through receptor-mediated transcytosis. The nanoparticle then binds specifically to amyloid-beta plaques or tau tangles, triggers the release of its therapeutic payload, and enables imaging for real-time disease monitoring (Poudel & Park, 2022).

5. Diagnostic Modalities Used in Theranostic Nanoparticles for Alzheimer's Disease

Theranostic nanoparticles revolutionize Alzheimer's diagnostics by merging imaging capabilities with targeted drug delivery. Unlike conventional diagnostic techniques that detect disease only at advanced stages, theranostic nanoplatforms offer real-time, sensitive and localized imaging even before clinical symptoms appear.

By integrating diagnostic agents such as MRI contrast materials, PET tracers or fluorescent dyes, these nanoparticles allow precise visualization of disease progression, treatment distribution and therapeutic response in the brain(Smeraldo et al., 2022). Below we explore the major diagnostic modalities enhanced by theranostic nanoparticles.

5.1 Magnetic Resonance Imaging (MRI)

MRI is one of the most commonly used non-invasive imaging tools in neurology. However, its resolution and contrast are limited when it comes to early Alzheimer's detection. Nanoparticles solve this by serving as contrast-enhancing agents.

- Iron oxide nanoparticles (SPIONs) are often used to increase image clarity by enhancing magnetic contrast.
- When conjugated with ligands targeting amyloid-beta, these NPs allow detection of early plaque accumulation, even before cognitive symptoms start(Savvidou et al., 2025).

Benefit: Excellent spatial resolution and deep tissue imaging.

5.2 Positron Emission Tomography (PET)

PET is highly sensitive and capable of detecting molecular changes. Theranostic nanoparticles labelled with radioisotopes like [^{18}F] or [^{64}Cu] help visualize early pathological features such as amyloid plaques or tau tangles.

- For example, Aβ-targeted PET-NPs can identify disease onset well before structural brain damage becomes visible.
- Dual modal nanoparticles combining PET and MRI allow simultaneous structural and molecular imaging(Tripathi et al., 2022).

Benefit: Early detection at molecular level; ideal for biomarker tracking.

5.3 Fluorescent and Optical Imaging

Fluorescent imaging is widely used in preclinical models for real time visualization of nanoparticle behaviour within brain tissues.

- Quantum dots, NIR dyes and carbon dots are common fluorescent agents integrated into theranostic nanoparticles.

- These can be tracked using near-infrared light, which penetrates deeper into tissue than visible light and offers sharper contrast (Sharon, 2025).

Benefit*:* High-resolution and real-time imaging in small animal models.

5.4 Biosensors and Sensing Platforms

Emerging theranostic designs include biosensing capabilities to detect Alzheimer's biomarkers (like Aβ, Tau or oxidative stress markers) in biological fluids like cerebrospinal fluid (CSF) or blood.

- Gold nanoparticles and graphene-based sensors can be incorporated into wearable or implantable devices for continuous monitoring.

- These smart systems detect biomarkers before visible changes occur in the brain(Chen et al., 2024).

Benefit*:* Potential for non-invasive, early-stage diagnosis.

Theranostic nanoparticles can be engineered for various diagnostic imaging platforms. Each offering unique advantages in sensitivity, brain penetration and detection specificity. The table below (Table 4) summarizes key imaging modalities, nanoparticle types employed, their signal mechanisms and primary applications in Alzheimer's disease diagnosis (Table 8.5; Figure 8.6).

Table 8.5: Diagnostic Imaging Modalities Enhanced by Theranostics Nanoparticles

Modality	Type of NP Used	Imaging Signal	Sensitivity	Brain Penetration	Main Use (Chowdhury et al., 2024)
MRI	Iron oxide NPs (SPIONs)	Magnetic contrast	Moderate	High	Structural brain imaging, Aβ plaque detection
PET	Radiolabelled NPs	Gamma radiation	High	High	Early detection of Aβ/Tau
Fluorescent Imaging	QDs, NIR dyes	Light emission	Very High	Moderate–High	Preclinical tracking of NP localization
Biosensors	AuNPs, Graphene NPs	Electrochemical/ Optical	High	Dependent on platform	Fluid-based biomarker detection

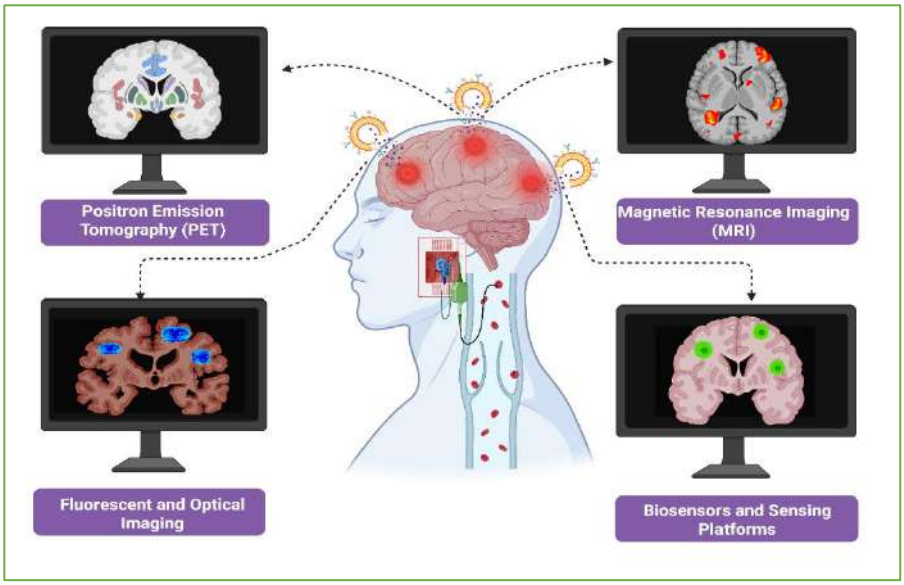

Figure 8.6. Multimodal Theranostics Nanoparticles for Brain Imaging and Biomarker Detection: The figure illustrates different theranostic nanoparticles targeting the brain. One nanoparticle is optimized for MRI imaging, another is labeled for PET scans, a fluorescent nanoparticle enables real-time visualization and a biosensor integrated with a wearable patch detects amyloid-beta in the blood(Pawar & Prabhu, 2025).

6. Therapeutic Agents and Pharmacological Aspects

Theranostic nanoparticles are more than just diagnostic probes, they are multifunctional delivery vehicles that carry potent pharmacological agents directly to the diseased brain(Christodoulou et al., 2025). By integrating drugs, genetic tools, antioxidants, anti-inflammatory compounds and neuroprotective peptides into a single nanosystem, they address the multifactorial pathology of Alzheimer's disease with greater precision(Abbas et al., 2025).

Encapsulation within nanoparticles enhances drug stability, improves blood–brain barrier penetration and enables controlled, site-specific release, minimizing systemic side effects.

1. Cholinesterase Inhibitors

Widely prescribed to manage cognitive symptoms, these agents work by increasing acetylcholine (ACh) levels in the brain. Drugs such as donepezil, rivastigmine, and galantamine suffer from poor BBB permeability when administered traditionally. Encapsulating them in PLGA nanoparticles or liposomes ensures higher brain uptake and sustained drug release, prolonging their therapeutic action(Mumtaz et al., 2025).

2. NMDA Receptor Antagonists

Memantine, a clinically approved NMDA receptor antagonist, protects neurons from glutamate-induced excitotoxicity. When loaded into PLGA nanoparticles or gold nanoparticles, its bioavailability improves significantly, reducing dosing frequency and enhancing neuroprotection(Narang et al., 2025).

3. Antioxidants

Oxidative stress accelerates neuronal degeneration in Alzheimer's. Curcumin, resveratrol, and N-acetylcysteine have strong antioxidant properties, but poor solubility and bioavailability limit their use. In theranostic systems such as liposomes, dendrimers, or quantum dots these compounds can not only neutralize reactive oxygen species (ROS) but also bind to amyloid plaques, enabling both therapeutic and imaging benefits(Yadav et al., 2025).

4. Anti-Tau and Anti-Amyloid Agents

Immunotherapeutic approaches using antibodies or aptamers against tau protein and amyloid-beta can reduce plaque and tangle burden. When incorporated into dendrimers or liposomes, these agents enable early visualization via imaging and targeted clearance of pathological aggregates(Dey et al., 2024).

5. Gene Silencing Molecules

Genetic modulation offers a way to tackle Alzheimer's at its root. siRNA, miRNA and antisense oligonucleotides targeting genes like BACE1 or APP can block amyloid-beta generation(Rabbani et al., 2025). Using PEGylated nanoparticles or PAMAM dendrimers to deliver these molecules protects them from breakdown and helps target the brain for effective gene (Khan, 2024).

6. Neurotrophic Factors and Peptides

Neuroprotective molecules like brain-derived neurotrophic factor (BDNF) and peptides such as NAP (NAPVSIPQ) help neurons survive and maintain synaptic plasticity(Lin et al., 2024). Encapsulating them in chitosan or PLGA nanoparticles protects them from instability and allows targeted, sustained release (Table 8.6).

Table 8.6: Advancing Pharmacological Therapy with Theranostic Nanoparticles

Agent Type	Drug/Compound	Mechanism	Nanocarrier Used	Outcome in AD Models (Mumtaz et al., 2025)
Cholinesterase Inhibitor	Donepezil	Increases ACh in synapses	PLGA, liposome	Improved cognition
NMDA Antagonist	Memantine	Reduces glutamate excitotoxicity	PLGA, gold NP	Neuroprotection

Antioxidant	Curcumin, Resveratrol	Reduces oxidative stress	Liposome, QDs	Decreased Aβ levels
Immunotherapy	Anti-Aβ, Anti-Tau antibodies	Plaque/tangle clearance	Dendrimer, liposome	Reduced neurodegeneration
Gene Silencing	siRNA (BACE1)	Blocks Aβ production	Dendrimer, PEGylated NP	Lowered amyloid burden
Peptides/Proteins	BDNF, NAP	Neuroregeneration	Chitosan, PLGA	Enhanced synaptic plasticity

7. Recent Advances and Case Studies in Theranostic Nanoparticles for Alzheimer's Disease

In recent years, theranostic nanomedicine for Alzheimer's disease has progressed from theory to promising preclinical and early clinical studies. Research increasingly shows that nanoparticles can simultaneously diagnose, target and treat Alzheimer's pathology with high precision. This section presents real-world examples, case studies and emerging technologies that demonstrate the practical potential of theranostic strategies in managing Alzheimer's disease.

7.1 Integrated Diagnosis and Treatment in Preclinical Models

In multiple animal studies, researchers have used nanoparticles that can both detect and treat Alzheimer's disease.

Example 1: Aβ-Targeted Liposomal Nanoparticles

A research project utilized liposomes infused with curcumin and marked with antibodies that specifically identify amyloid-beta plaques. These nanoparticles:

- Crossed the BBB effectively
- Illuminated Aβ plaques using fluorescent imaging
- Delivered curcumin at the target site, reducing plaque burden in transgenic mouse models (Agrawal et al., 2024).

Impact: By combining imaging and therapy, this system enabled real time tracking of disease progression and led to a noticeable reduction in behavioral deficits in mouse models.

7.2 Case Study: Magnetic Nanoparticles for Early Detection + Drug Delivery

Researchers from Korea designed iron oxide nanoparticles (IONPs) coated with PEG and an anti-Aβ antibody. These NPs:

- Provided high-resolution imaging via MRI

- Delivered rivastigmine, a cholinesterase inhibitor, at the site of plaque accumulation(McLoughlin et al., 2024).

Result*:* Imaging showed clear localization in AD-affected areas, while post-treatment analysis revealed improved cognitive performance in test animals.

7.3 Dual-Function Gold Nanoparticles

Gold nanoparticles (AuNPs) due to their unique optical properties have been explored for both photothermal therapy and biomarker detection. In one study:

- AuNPs were linked to a peptide that binds Aβ
- Used for photoacoustic imaging
- Also carried a beta-secretase inhibitor to reduce Aβ production(Gao et al., 2025).

Significance*:* This platform enabled early visualization and therapeutic modulation in a single dose demonstrating the real potential of theranostics.

7.4 Quantum Dots in Amyloid Imaging

Quantum dots (QDs) are tiny fluorescent nanoparticles. Though not commonly used for therapy due to toxicity concerns, some QDs have been developed for non-invasive brain imaging:

- Bound to tau or amyloid antibodies
- Tracked disease progression with cell-level resolution(Karthik et al., 2024).

Use Case: Real time monitoring of disease spread in mouse models, laying the foundation for non-invasive tracking in humans.

Recent research has demonstrated the versatility and effectiveness of theranostic nanoparticles in Alzheimer's disease models. These studies highlight how different nanoparticle types can simultaneously achieve diagnostic imaging and therapeutic benefits often resulting in improved disease monitoring and functional outcomes. The table below (Table 8.7) presents selected examples from 2020–2025 detailing nanoparticle design, diagnostic role, therapeutic payload and key findings.

Table 8.7: Notable Recent Studies on Theranostic Nanoparticles in Alzheimer's (2020–2025)

Study	Nanoparticle Type	Diagnostic Function	Therapeutic Payload	Outcome
(Dogra et al., 2020)	Iron oxide (PEG + Antibody)	MRI	Rivastigmine	Enhanced imaging + improved cognition in mice
(Khan et al., 2021)	Liposomal NPs	Fluorescence	Curcumin	Plaque reduction + visual imaging
(Rodriguez-Rios et al., 2022)	Gold NPs	Photoacoustic imaging	BACE1 inhibitor	Dual targeting of Aβ and inhibition of production
(Ye et al., 2023)	Quantum dots	Fluorescent imaging	None	Visualized tau tangles in real-time
(Kaur et al., 2024)	PLGA NPs	PET + MRI	siRNA (anti-tau)	Reduced tau expression + tracked therapy
(Y. Wu et al., 2025)	Polymeric theranostic NPs	Multi-modal imaging	siRNA (APP/BACE1)	Combined imaging and gene silencing, promising long term

7.5 Looking Ahead: What's Next in Theranostic Research?

Though most of these studies are still in the preclinical stage, their success is a powerful indicator of what's possible:

- Clinical trials on human-compatible theranostic systems are beginning to emerge.
- Multifunctional NPs combining gene editing tools (e.g., CRISPR/Cas9) with imaging are under development.
- Future platforms may include biosensors to deliver drugs only when specific biomarkers are detected in the brain.

With ongoing innovations, the dream of a single shot nanoparticle system that diagnoses and cures Alzheimer's in its earliest stage no longer feels out of reach.

8. Challenges and Future Prospects in Theranostic Nanomedicine for Alzheimer's Disease

While theranostic nanoparticles offer an exciting frontier in Alzheimer's care, several real-world obstacles must still be addressed before these technologies can become routine in clinical practice. From safety concerns to regulatory barriers, the path forward is filled with both opportunities and challenges.

8.1 Toxicity and Long-Term Safety

Although many nanoparticles show excellent results in lab experiments, their long-term safety in humans remains a concern. Certain materials like quantum dots or metal-based nanoparticles can accumulate in tissues or generate reactive oxygen species (ROS) leading to unintended side effects(N. Sharma et al., 2024). Moreover, the immune system may recognize and attack foreign nanocarriers which reducing their effectiveness or causing inflammation.

What needs to be done?
Extensive toxicological evaluations, including chronic exposure studies are essential to ensure that these materials are safe especially when used in the brain over extended periods.

8.2 Manufacturing and Scalability

Most theranostic systems are currently developed at a small scale in research labs using complex synthesis processes that are difficult to reproduce on an industrial level. The integration of both therapeutic and diagnostic agents into one nanoparticle adds layers of complexity to production.

Future need:
Simplifying nanoparticle design, optimizing large scale manufacturing protocols and ensuring batch to batch reproducibility will be crucial for commercial translation.

8.3 Blood Brain Barrier (BBB) Limitations Still Exist

While many nanocarriers can cross the BBB under controlled conditions, it remains a formidable barrier in human subjects. The efficiency of delivery seen in animal models does not always translate to humans due to differences in BBB structure and dynamics(Zeynalzadeh et al., 2024).

Next steps:
Innovative strategies such as biomimetic coatings focused ultrasound or transient BBB modulation may be explored further to enhance delivery without causing damage.

8.4 Regulatory and Ethical Hurdles

Theranostic platforms combine drugs with imaging agents making them hybrid products. This poses a unique challenge for regulatory agencies, as they don't always fit into

existing drug or device categories. Moreover, ethical considerations around neuro targeting technologies especially in vulnerable populations like the elderly must be addressed.

Solution forward:
Creating clear regulatory pathways and ensuring informed consent protocols will be essential as we move toward clinical applications.

8.5 Need for Personalized Theranostics

Alzheimer's disease doesn't affect every patient in the same way. Differences in genetic risk, disease progression and biomarker profiles mean that a one size fits all approach is unlikely to work. The future lies in customizing theranostic nanoparticles to target individual disease mechanisms.

Emerging approaches
Integration of AI driven diagnostics, genomic profiling and modular nanoparticle platforms may allow truly personalized nanomedicine solutions for AD(Dipankar et al., 2025).

Step 1: Nanoparticle Design (targeting + imaging + therapy)
⬇
Step 2: Preclinical Testing (in vitro + animal models)
⬇
Step 3: Toxicity & Pharmacokinetics Evaluation
⬇
Step 4: Regulatory Approval Pathway Definition
⬇
Step 5: Clinical Trials (safety → efficacy → large-scale validation)
⬇
Step 6: Industrial Production & Commercial Launch

8.6 Future Research Directions

As research advances newer possibilities are being explored:

- Stimuli responsive nanoparticles that activate only in the presence of specific enzymes or pH conditions.
- Multifunctional platforms that combine therapy, imaging and biosensing in real time.
- Remote controlled nanomedicine using magnetic fields, light or ultrasound for externally guided action.

- Neuroregenerative therapies, where nanoparticles carry factors that support neuronal repair not just disease suppression.

Theranostics nanoparticles are still at the frontier of innovation but the pace of progress is encouraging. With collaborative efforts between scientists, clinicians, engineers and regulatory authorities, we are getting closer to making them a clinical reality for Alzheimer's patients(Bhattacharya & Bhirud, 2025).

Conclusion

Alzheimer's disease continues to challenge modern medicine with its complex pathology, late diagnosis and limited treatment success. Traditional therapeutic approaches often fall short due to their inability to detect the disease early, penetrate the blood brain barrier or deliver drugs specifically to affected areas of the brain. Theranostics nanoparticles offer a promising shift from conventional methods by combining diagnostics and therapy into a single, intelligent platform. These ultra small, multifunctional carriers can cross biological barriers, recognize disease specific targets like amyloid beta plaques and tau tangles release drugs in a controlled manner and simultaneously provide real time imaging feedback. By enabling early intervention, targeted drug delivery and real time monitoring, theranostic platforms address many of the key limitations in current Alzheimer's care. Their customizable design also opens the door for future personalized therapies tailored to each patient's disease profile. However, for this technology to truly transform clinical practice, several challenges must still be overcome including safety validation, scalable production and regulatory clarity. Continued research, interdisciplinary collaboration and ethical oversight will be vital in bridging the gap between lab innovation and patient benefit. In essence, theranostic nanoparticles represent more than just a technical advancement, they embody a more precise, proactive and personalized vision of how we can fight Alzheimer's disease in the years to come.

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