Chapter-1
Introduction

1 Introduction

1.1 Neurodegenerative disorders

Neurodegenerative disorders impact nearly 30 million individuals, causing disability, cognitive impairment, and even death. These conditions are characterized by specific pathological changes in the brain and the degeneration of particular groups of neurons [1]. Among the most prevalent are Alzheimer's disease (AD) and Parkinson's disease (PD), which gradually lead to the dysfunction of brain neurons or the peripheral nervous system, resulting in cognitive disturbances. Additional neurodegenerative disorders include amyotrophic lateral sclerosis (ALS), Huntington's disease, frontotemporal dementia, and spinocerebellar ataxia. These disorders disrupt communication between nerve cells, affecting various functions such as locomotor abilities, speech, muscle coordination, cognitive functions, intelligence, behavior, and many more [2].

These conditions pose a significant threat to human health, and the risk of developing a neurodegenerative disease increases considerably with age. Given the current scenario, there is an urgent need to deepen our understanding of the exact causes of neurodegenerative disorders and explore novel methodologies for their treatment and prevention [3].

1.2 Alzheimer’s disease

AD is a devastating neurodegenerative disorder that is characterized by progressive cognitive decline and is the leading cause of dementia and mortality. The prevalence of AD is increasing, with the rising average life-span resulting in a dramatic increase in age-related disorders such as dementia [4]. In addition to its impact on patients, AD also has profound effects on their families and society as a whole [5]. With increasing life expectancy and an ageing population, AD has become a growing socioeconomic and medical problem in modern society [6]. This debilitating condition leads to a gradual loss

of memory, thinking skills, and the ability to carry out daily activities. It is estimated that around 50 million people worldwide currently suffer from AD, and this number is projected to triple by 2050 if effective preventive and therapeutic strategies are not developed [7]. In today's rapidly changing world of healthcare and medical advancements, AD stands out as a significant challenge that requires urgent attention and research efforts. In recent years, there has been a growing understanding of the pathophysiology of AD and the underlying mechanisms that contribute to its progression. As researchers continue to uncover the complexities of this disease, there is a pressing need for accurate diagnosis, effective treatment options, and support for those affected by this condition.

1.3 Symptoms of Alzheimer's disease

The symptoms of AD typically begin with mild memory loss and progress to more severe cognitive impairments over time. These cognitive impairments include difficulties with language, problem-solving, and decision-making. The neurodegenerative nature of AD also leads to behavioral and psychological changes, such as mood swings, agitation, and irritability. Furthermore, as the disease advances, individuals with Alzheimer's may experience disorientation, confusion about events, dates, and places, as well as suspicions about family, friends, and caregivers. As the disease progresses, individuals may also have difficulty speaking, writing, and walking.

1.4 Stages of Alzheimer's Disease

The gradual changes in the brain and behavior of AD patients have been summarized in a figure (**Figure 1.1**).

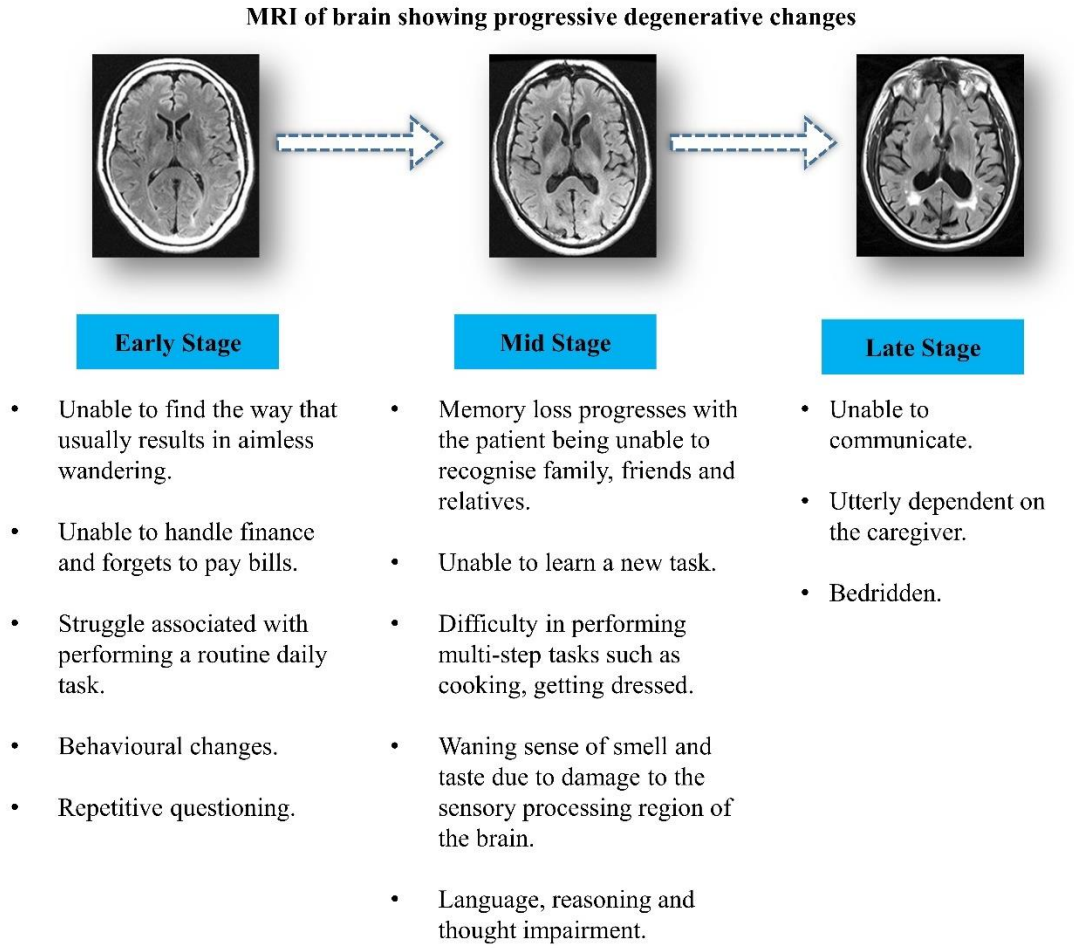

Figure 1.1 Stages of Alzheimer's disease

1.5 Diagnosis of Alzheimer's disease

Diagnosis of AD is a complex and challenging task due to various factors. These factors include the intricate pathogenesis of the disease, the high misdiagnosis rate, and the difficulty in identifying early-stage disease. AD features complex pathogenesis involving multiple pathophysiological processes, making diagnosing difficult [8]. In addition, clinical presentations of AD often overlap with other types of dementia, making it challenging to differentiate between them [9]. Moreover, the co-occurrence of multiple pathologies further complicates the diagnosis process. Furthermore, the availability of increasing biomarkers has opened up the possibility of diagnosing the early stages of AD before the onset of dementia [9].

The Alzheimer's Association provides a set of guidelines for the diagnosis of AD. The diagnostic process includes a physical examination and a neurological assessment to evaluate body reflexes, muscle coordination, strength, sensation, and eyeball movement. Additionally, mental examinations like the Mini-Cog test and the mini-mental state exam (MMSE) are conducted. The Mini-Cog test involves two tasks: firstly, the patient is asked to remember the names of three objects, which they are later prompted to repeat after a certain time. Secondly, the patient is asked to draw a clock with all 12 numbers and indicate a specified time [10].

The examination results may indicate the need for further investigation. The MMSE, a questionnaire-based assessment administered by a healthcare practitioner, evaluates various mental skills and has a maximum score of 30 points. Scores between 20 to 24 indicate mild dementia, 13 to 20 indicate moderate dementia and fewer than 12 indicate severe dementia. People with AD tend to experience an average decrease in their MMSE score by two to four points every year [11].

To diagnose other symptoms present in AD, depression and mood assessment tests are also conducted. Brain imaging using magnetic resonance imaging (MRI) or computed tomography (CT) is recommended to investigate the underlying cause of dementia. In some cases, dementia may be caused by factors other than AD, such as tumors, strokes, or trauma. For AD pathology diagnosis, specific PET ligands like Florbetapir, Florbetaben, and Flutemetamol are utilized [12-14]. Other tests involve estimating $A\beta_{1-42}$, hyperphosphorylated tau (p-tau), and total tau protein levels in cerebrospinal fluid [15].

1.6 Pathophysiology of Alzheimer's disease

In 1907, Dr. Alois Alzheimer published the results of an autopsy conducted on Auguste Deter, a 55-year-old woman who succumbed to a degenerative behavioral and cognitive disorder. The examination of Deter's brain revealed two distinct features: plaque composed of amyloid-β and neurofibrillary tangles (NFT) containing hyperphosphorylated tau protein. Alongside these classical hallmarks, AD involves intricate pathophysiological factors that are not fully understood. AD is associated with a multitude of pathways and targets, adding to the complexity of the condition [16].

Numerous hypotheses have been proposed to elucidate the multifactorial nature of this disorder, including the cholinergic hypothesis, Aβ hypothesis, tau hypothesis, and inflammation hypothesis. However, recent research has demonstrated that the widely accepted Aβ hypothesis, prevailing for the past two decades, fails to fully explain the intricate pathophysiology of this debilitating disease. Recent studies have shed light on the significance of Aβ oligomers in causing synaptic impairment, suggesting that they play a central role in disrupting brain function, among various other signals. Additionally, the formation of amyloid plaques, which typically occur later in life, appears to be a relatively delayed event in the progression of the disease [17].

According to the amyloid cascade hypothesis, the normal cleavage of APP involves α-secretase, while β- and γ-secretases lead to abnormal processing, resulting in an imbalance between the production and clearance of Aβ peptide [18]. This leads to the spontaneous aggregation of Aβ peptides into soluble oligomers, which then coalesce to form insoluble beta-sheet fibrils, eventually depositing as diffuse senile plaques [8]. Recent studies have highlighted the cooperative involvement of both neurons and associated astrocytes in producing $A\beta_{42}$ oligomers (**Figure 1.2**) [9]. These oligomers have been shown to induce oxidative damage, promote tau hyperphosphorylation, and

adversely affect synapses and mitochondria [6,7]. Additionally, $A\beta_{1-42}$ senile plaques are observed during later stages, attracting microglia and leading to the production and release of proinflammatory cytokines like IL-1β, TNF-α, and IFN-γ. This, in turn, stimulates nearby astrocytes and neurons to produce more $A\beta_{1-42}$ oligomers, further activating $A\beta_{1-42}$ production and dispersion [9]. Aβ oligomers are also responsible for the destruction of oligodendroglia (OLGs), resulting in oxidative stress due to their low reduced glutathione (GSH) content and high iron concentration, affecting their ability to scavenge oxygen radicals. $A\beta_{1-42}$ oligomers have an increased capability to damage cholesterol-rich membranes found in OLGs and myelin [19].

Previous studies have explored the pharmacology of Aβ receptors, with $A\beta_{1-42}$ monomers activating the neuroprotective signaling of insulin-like growth factor-1 receptor (IGF-1R). In contrast, $A\beta_{1-42}$ oligomers interact with a range of neurons' and astrocytes' membrane receptors, including RAGE, Frizzled receptor, insulin receptor, NMDA glutamate receptor, p75 neurotrophin receptor (p75NTR), a7 nicotinic ACh receptor (a7nAChR), ApoE receptors, formyl peptide receptor-like 1 (FPRL1/2), cellular prion protein (PrPc), and the calcium-sensing receptor (CaSR) [20].

The removal of Aβ oligomers from the brain involves various pathways, including proteolytic degradation by neprilysin and insulin-degrading enzyme (IDE), uptake by astrocytes and microglia, passive flow into the cerebrospinal fluid, and sequestration into the vascular compartment through the soluble form of the low-density lipoprotein receptor-related protein 1 (LRP1) [21]. Increased levels of NO observed in AD can decrease IDE enzymatic function, potentially leading to an increase in Aβ oligomer deposition in the brain and the development of AD [22]. Recent findings suggest a "contagion" like diffusion of $A\beta_{1-42}$ oligomers and hyperphosphorylated tau oligomers

via exocytosis or exosomes to closely associated target cells such as astrocytes and oligodendrocytes, turning them into producer cells of Aβ and tau oligomers [23].

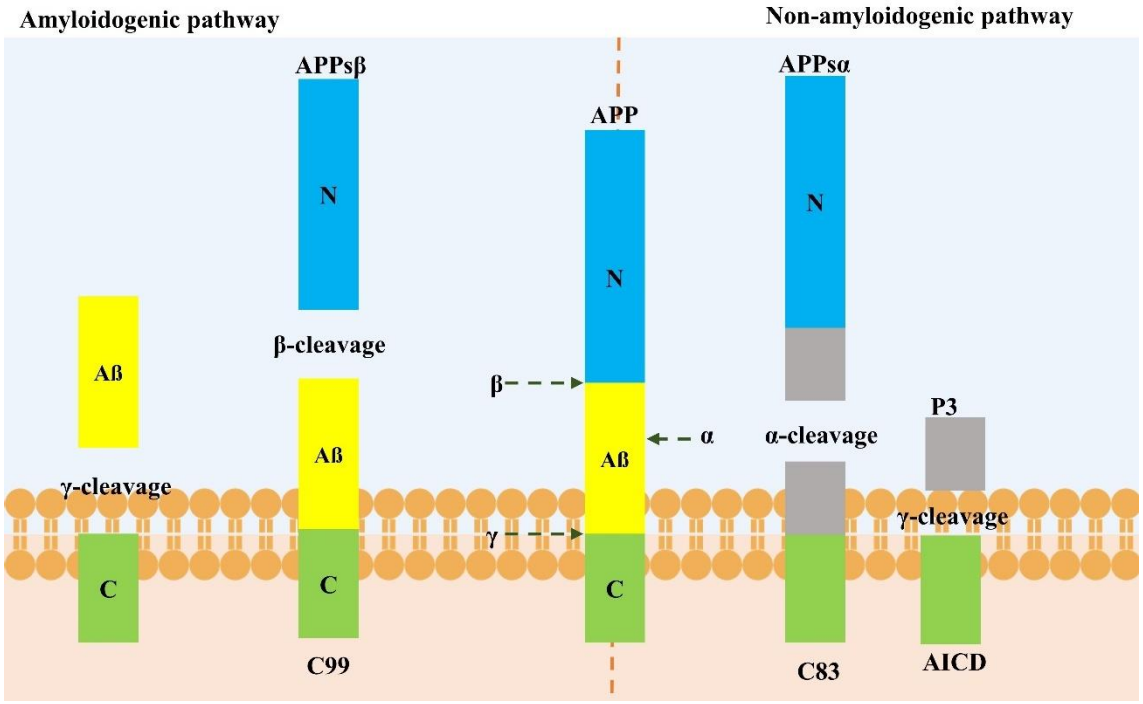

Figure 1.2 Metabolism of APP by secretases

Astrocytes have the ability to promote or reduce neurotransmitter release into enveloped synapses through the Ca^{2+} waves they respectively emit or absorb [12]. When neurons produce $A\beta_{1-42}$ beyond safe limits, toxic $A\beta_{1-42}$ oligomers overflow from neurons onto surrounding astrocytes, both cell types being equipped with $A\beta_{1-42}$ oligomer-binding receptors, accumulating or dispersing in the extracellular environment [9]. Due to the close physical and functional interconnections within the neurons' client group, the $A\beta_{1-42}$ oligomers released by neurons can directly bind to the a7nAChRs of partner astrocytes [23]. Signals from these receptors prompt the astrocytes to release the glutamate they have taken up from neuronal synapses. The discharged glutamate activates extrasynaptic NMDARs of the astrocytes' partner neurons, leading to Ca^{2+} surges, causing a cascade of events, including dysfunctional mitochondria emitting ROS, oxidative damage, caspase-3 activation, tau hyperphosphorylation, increased production of NO, ROS, and VEG-F,

resulting in the destruction of dendritic spines, neuronal synapses, and disruptions in astrocyte-neuron communication [24]. Studies have shown that a CaSR selective allosteric antagonist (calcilytic) NPS 2143 can specifically prevent the excess release of endogenous $A\beta_{42}$ from $A\beta_{25-35}$-exposed human astrocytes and neurons [25].

1.7 Management of Alzheimer's Disease

The only currently available treatments are symptomatic and aim to balance the disease's neurotransmitter imbalance. The use of three cholinesterase inhibitors (CIs) for the treatment of mild to moderate AD has been approved, i.e., Donepezil, Rivastigmine and Galantamine. Memantine, an NMDAR antagonist, is another treatment option for moderate-to-severe AD (**Figure 1.3**) [26, 27]. Additionally, amyloid-directed antibodies (eg, Aducanumab, Lecanemab) have been approved [28, 29]. More information about the FDA-approved drugs is summarized in **Table 1.1**. The behavioral signs of the illness are treated with antipsychotics and antidepressants at the same time.

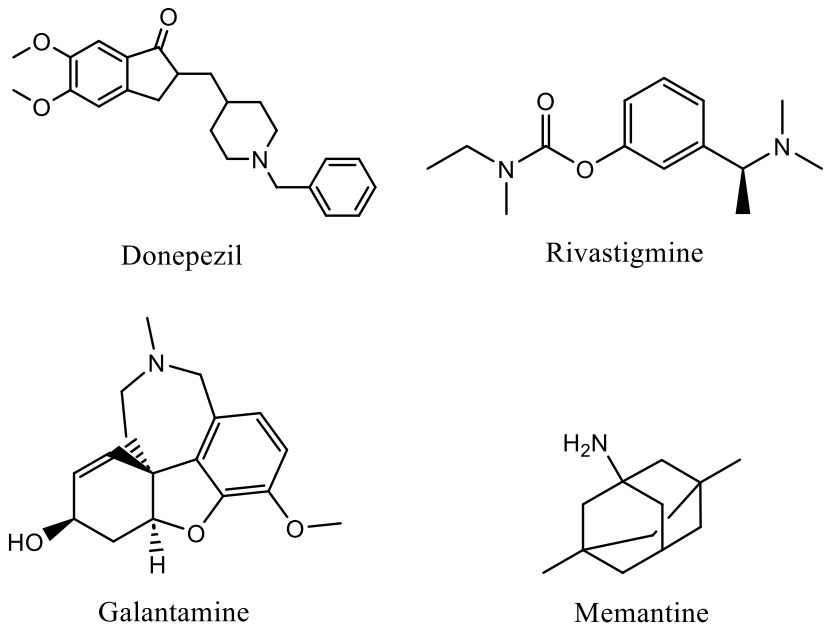

Figure 1.3 Chemical structures of FDA approved drug for the treatment of AD

Table 1.1 FDA-approved medications to treat AD

Drug	Mechanism of Action	Side effects	Administration
Donepezil	Cholinesterase inhibitor	Nausea, vomiting, diarrhea, insomnia, muscle cramps, fatigue, and weight loss.	Delivered orally once a day through a tablet that is either swallowed or dissolved in the mouth.
Rivastigmine	Cholinesterase inhibitor	Nausea, vomiting, diarrhea, weight loss, indigestion, decreased appetite, anorexia, and muscle weakness.	Delivered orally through a capsule twice a day or through a skin patch that is replaced once a day.
Galantamine	Cholinesterase inhibitor	Nausea, vomiting, diarrhea, decreased appetite, weight loss, dizziness, and headache.	Delivered orally through an extended-release capsule, tablet, or liquid. Extended-release capsule is taken once a day. Tablet and oral solution are each taken twice a day.
Memantine	NMDA antagonist	Dizziness, headache, diarrhea, constipation, and confusion.	Delivered orally through an extended-release capsule, tablet, or liquid. Extended-release capsule is taken once a day. Tablet and oral solutions are each taken once a day.
Memantine and Donepezil (manufactured combination)	Cholinesterase inhibitor and NMDA antagonist	Headache, nausea, vomiting, diarrhea, dizziness, anorexia, and ecchymosis (small bruising from leaking blood vessels).	Delivered orally through an extended-release capsule once a day.
Aducanumab	Immunotherapy-Removes abnormal beta-amyloid to help reduce the number of plaques in the brain.	Possible side effects include ARIA, headache, dizziness, falls, diarrhea and confusion.	Possible side effects include ARIA, headache, dizziness, falls, diarrhea, and confusion. Delivered through IV over one hour every four weeks.
Lecanemab	Immunotherapy-Removes abnormal beta-amyloid to help reduce the number of plaques in the brain.	Possible side effects include ARIA, headache, dizziness, falls, diarrhea, and confusion.	Delivered through IV over one hour every two weeks.

1.8 Artificial intelligence and Machine Learning in drug discovery

Machine learning (ML), a subfield of artificial intelligence (AI), studies the methods and mechanics of enabling machines to expertly carry out intelligent activities without being explicitly programmed for those tasks. In some recent jobs, including playing video games and picture identification, AI systems have come close to or surpassed human performance; nevertheless, these tasks have traditionally been extremely specific and focused. However, AI in its different forms is now successfully used in a wide range of fields and for difficult tasks, including robotics, voice translation, image analysis, and logistics, in addition to its continuous usage in molecular design [30].

Since the 1960s, medicinal chemistry has used AI to create molecules in a variety of ways and to variable degrees of success. Labeled training datasets are frequently used in supervised learning, which trains models. A common method for predicting characteristics, such as logP, solubility, and bioactivity for specific chemical compounds, is the quantitative structure-activity relationship (QSAR) approach. Contrarily, unsupervised learning, which does not rely on labels, is also well-liked in medicinal chemistry, where examples like principal components analysis, hierarchical clustering, and algorithms are frequently used to analyze and separate large molecular libraries into smaller collections of related compounds [31].

Since the development of atomistic theory, chemists have worked to predict the properties of compounds without synthesizing them. Although it is still difficult to define, Alexander Crum Brown argued in 1869 that a compound's physiological response is simply a result of its chemical makeup. After Hansch and Fujita's initial proposal of QSARs and their relationships in 1962, this field of study has continued to be active [31].

Figure 1.4 depicts a roadmap for discovering new drugs using AI. It starts with gathering data from various sources like databases, publications, and lab experiments. This data is

then processed and organized to feed into machine learning models. These models predict the properties of potential drugs, leading to the identification of promising candidates. The journey continues with optimizing these candidates, predicting their behavior in the body, and conducting virtual and laboratory tests. If successful, animal studies and, eventually, human clinical trials follow. Finally, after thorough evaluation, approved drugs reach patients. While still in its early stages, AI holds immense potential to revolutionize drug discovery by making it faster, more efficient, and ultimately, more successful in delivering life-saving solutions.

In particular, ClogP, which calculates the octanol/water partition coefficient, is a notable example of how the work on QSAR has advanced the practice of specific physicochemical property predictions [11]. Since the initial introduction of QSAR more than 50 years ago, there have been considerable increases in the number of modeling methodologies, molecular representations, and the volume of data and computing resources available. These datasets can now be used with techniques like deep learning that were previously inappropriate or unavailable due to the advancements in all of these domains. Predictive models can be created using the vast amounts of chemical structure data that are currently available, along with relevant, measurable endpoints. However, the availability of this data is still restricted, and even when it is, the quality is inconsistent. In this situation, it is anticipated that more advanced ML techniques will be able to handle this noisy data.

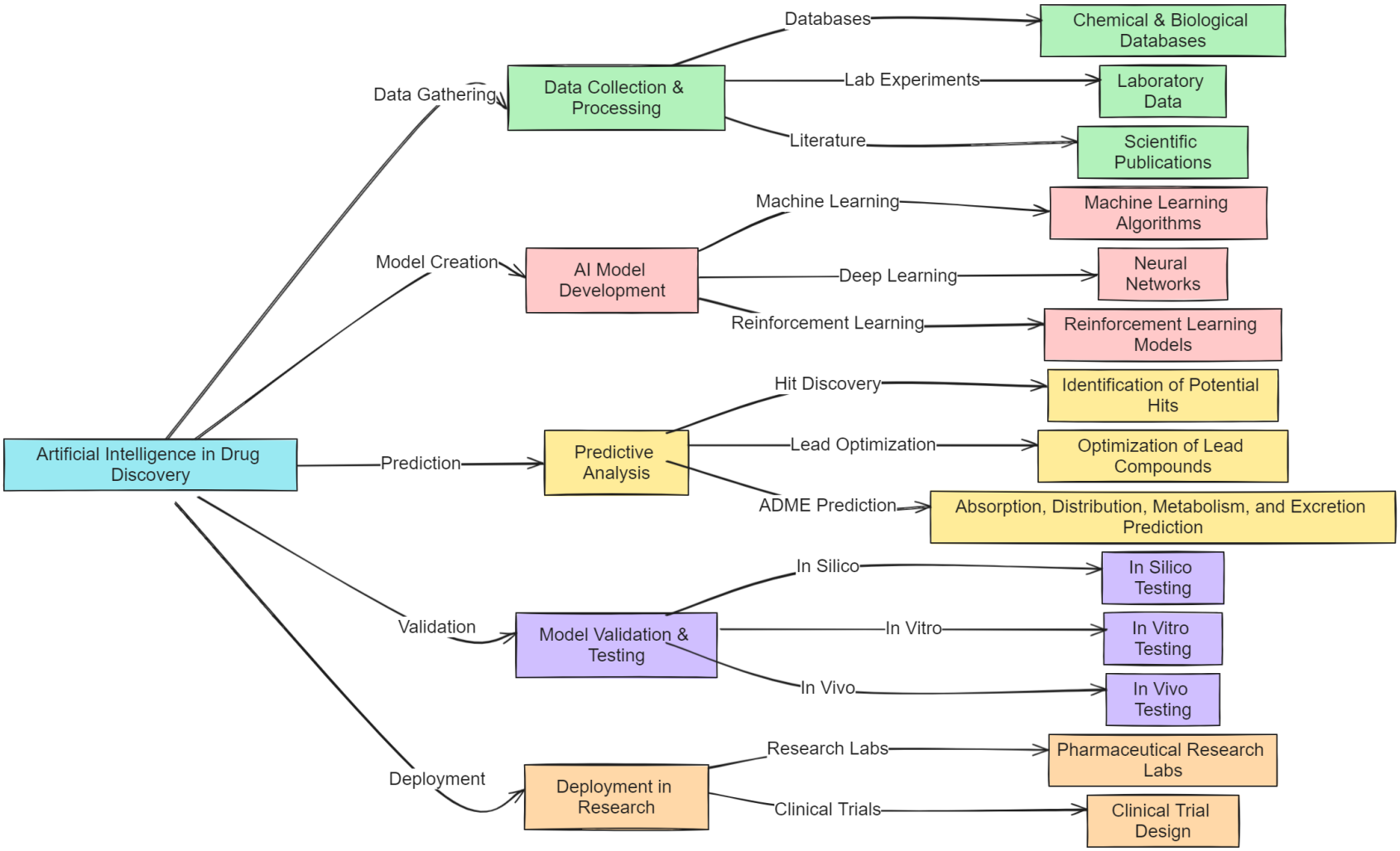

Figure 1.4 Flowchart summarizing the applications of AI in drug discovery

The Merck molecular activity challenge led to one of the earliest uses of deep learning for chemical property prediction, using multitask neural networks to predict many end points at once in addition to just one [32]. A very important field of research right now is deep learning in chemical property prediction [33].