1

CNS Drug Discovery in "The Century of Biology"

Dario Doller

Modulate Bio, Inc. Pagliuca Harvard Life Lab, 127 Western Avenue, Allston, MA 02134, USA

Acronyms

AD	Alzheimer's disease
AI	Artificial intelligence
CDD	CDKL5-deficiency disorder
CDKL5	Cyclin-dependent kinase-like 5
CGRP	Calcitonin gene-related peptide
Cryo-EM	Cryo-electron microscopy
CNS	Central nervous system
CSF	Cerebrospinal fluid
DALY	Disability-adjusted life-years
FDA	Food and Drug Administration
MCI	Mild cognitive impairment
MDMA	3,4-Methylenedioxymethamphetamine
MoA	Mechanism of action
PD	Parkinson's disease
POS	Probability of success
PPD	Postpartum depression
PTSD	Post-traumatic stress disorder
VC	Venture capital

1.1 Welcome to "The Century of Biology"!

The twenty-first century has been aptly dubbed "The Century of Biology" [1], an era where the boundaries of life sciences are continuously pushed, bringing unprecedented advancements to the forefront of drug discovery. The rapid growth in our understanding of the molecular and cellular foundations of life and groundbreaking discoveries in genomics, proteomics, and bioinformatics have collectively expanded our knowledge of biological systems. These advancements have laid the groundwork

Trends in CNS Drug Discovery, First Edition. Edited by Dario Doller and Kevin J. Hodgetts.

for novel approaches in drug discovery, particularly for brain diseases, where traditional methods have often fallen short.

Brain diseases, including Alzheimer's, Parkinson's, and various neuropsychiatric disorders, present a unique set of challenges due to the intricacy and experimentally challenging accessibility of the human brain, including the protective role of the blood–brain barrier. Newly developed insights have led to the identification of novel molecular targets and pathways involved in these diseases. This has opened up opportunities for designing innovative chemical modalities that can effectively modulate these targets and potentially alter the course of brain diseases [2–4]. While small molecules are the preferred type of modality when brain penetration is part of the target drug profile, increased mastery in drug design is provided by allosteric mechanisms, especially when target activation is required [5, 6].

In this chapter, we critically evaluate the progress made in the first quarter of this century toward delivering novel therapeutics for brain diseases by examining both the notable successes and the persistent challenges. Through this lens, we seek to understand how far we have come and what remains to be done in the ongoing quest to develop effective treatments for debilitating brain diseases. The impact of increasingly more powerful computational technologies (*e.g.* artificial intelligence (AI) or machine learning) in the context of brain diseases is discussed in the Epilog chapter of this work.

1.2 Understanding Brain Health Around the World

The importance and prevalence of mental health cannot be understated. Our brain is at the core of every action we take and every experience we have. It governs our thoughts, emotions, speech, movements, and even essential functions such as breathing, heart activity, and immune responses. When the brain suffers from disease or injury, it can profoundly impact our own lives as well as the lives of those around us. Brain health covers a wide spectrum of issues, including mental health conditions, neurological disorders, and cerebrovascular diseases. Conditions such as dementia, stroke, and depression are particularly significant, as they rank among the leading causes of death and disability worldwide.

According to a report from the Brain Health Initiative, derived from the Global Burden of Disease (GBD) study, the largest and most comprehensive effort to measure health loss from hundreds of conditions around the world over time, the numbers are staggering [7]:

- Over 18% of global health loss is linked to brain conditions.
- In 2021, brain conditions were responsible for more disability-adjusted life-years (522 million DALYs) than cancer (260 million DALYs) and cardiovascular disease (402 million DALYs).
- These numbers are expected to rise as populations grow and age, posing challenges for families, employers, and healthcare systems.

Dedicated scientists across all stages of drug discovery and development have been working very hard to develop new therapeutics to treat these diseases. Assessing the probability of success (POS) of a clinical trial is vital for clinical researchers and biopharma investors when making informed scientific and economic decisions. Effective resource allocation depends on accurate and timely risk assessment. A major hurdle in estimating the success rate of clinical trials is the lack of reliable information on trial characteristics and outcomes. Collecting such data is often costly, time consuming, and prone to errors. A number of such studies of success rates in clinical studies have been published [8–11]. A new estimate of drug development success rates and durations was developed using a very large sample of 406,038 entries of clinical trial data for over 21,143 compounds from 1 January 2000 to 31 October 2015. According to this study, the overall success rate for central nervous system (CNS) clinical trials is 15.0%, with Phase 1 to Phase 2, Phase 2 to Phase 3, and Phase 3 to approval rates of 73.2%, 51.9%, and 51.1%, respectively. Generally speaking, these rates are clearly low, and they do not include the preclinical research efforts. However, the overall POS for CNS trials is superior to oncology (3.4%) and comparable to autoimmune/inflammation (15.1%) and metabolic disease/endocrinology (19.6%) [12].

Even with significant progress in biomedical science and efforts to streamline the clinical and regulatory stages of drug development, the efficiency of clinical development has not improved and may even be declining. Concurrently, the cost of drug development continues to escalate, with recent estimates placing the average out-of-pocket expense for each new compound at $1.4 billion, and fully capitalized costs reaching $2.6 billion [13]. Translational insights play a major role in the clinical POS of drugs working through novel mechanisms of action. The timelines for 138 novel drugs and biologics approved by the Food and Drug Administration (FDA) from 2010 to 2014 were analyzed using an analytical model of technology maturation. The median initiation year was 1974, with a median of 25 years to reach the established point, 28 years to begin the first clinical trials, and 36 years to achieve FDA approval [14]. Another paper found similar conclusions [15], suggesting that investment in fundamental research in life sciences is a key step to improving mental health treatment options.

1.3 Where Are New CNS Drugs Coming from?

The chemistry and pharmacology of many recently approved drugs were reviewed in good detail, and they would not be discussed here [16]. Broadly speaking, a novel drug may come from projects of two types:

a) Targeting unprecedented biological targets.
b) New strategies for known targets that have not realized their therapeutic potential despite showing clinical efficacy.

When embarking on a new CNS drug discovery effort, both such strategies are feasible when the right conditions are present: a persistent unmet medical need,

clinical testing feasibility, appropriate financial support, and the potential financial reward for the scientific innovators and investors. Naturally, the risk profiles of these two types of projects are highly different. Disease mechanisms are significantly de-risked using the concepts of "validity" [17]. In drug discovery, several types of validity concepts are crucial for ensuring the accuracy and reliability of research findings, and their translation to the clinical setting. ***Construct*** validity assesses whether a test accurately measures the concept it is intended to measure. ***Content*** validity evaluates if the test comprehensively represents the domain it aims to cover. ***Face*** validity determines if the test appears to measure what it claims to measure. ***Criterion*** validity examines whether the test results correspond to a concrete outcome. Additionally, ***predictive*** validity is vital in drug discovery as it measures how well a test or model predicts future outcomes, such as the clinical efficacy of a new drug. These validity types help researchers develop robust and reliable methods for identifying and validating new drug targets and therapeutic compounds. It may reasonably be argued that for many brain diseases and at the current stage of predictive neuroscience knowledge, this strategy provides a safer risk management profile than starting anew with an unproven new target [18].

Despite the intellectual appeal of pursuing novel scientific discoveries (strategy "a") in CNS drug discovery strategy "b" is the one yielding the most current new drugs, and several billion-dollar biotechnology companies are pursuing strategy it. ***Alkermes*** has recently received FDA approval for Lybalvi®, a combination of a known antipsychotic drug (olanzapine) and samidorphan, a new drug that removes the gain weight side effect [19]. ***Karuna Therapeutics*** received FDA approval for KarXT, a combination of xanomeline (an effective antipsychotic tested in the 1990s but unacceptable due to peripheral cholinergic adverse effects) and trospium chloride (a generic muscarinic antagonist used for overactive bladder since the 1960s, which ameliorates peripheral cholinergic side effects of xanomeline while maintaining its efficacy) [20]. ***Axsome Therapeutics*** is developing AXS-05, a drug that combines two approved drugs, dextromethorphan (a cough suppressant with anti-inflammatory and neuroprotective effects) and bupropion (an antidepressant that acts on norepinephrine and dopamine receptors, and increases the bioavailability of dextromethorphan by slowing down its metabolism). AXS-05 has received breakthrough therapy designation and fast-track status from the FDA for Alzheimer's disease (AD) agitation and major depressive disorder. It is currently in Phase 3 trials for AD agitation and smoking cessation, and it has completed Phase 3 trials for major depressive disorder, showing that AXS-05 is effective and well tolerated in reducing symptoms of these conditions [21].

Over recent years, the neurosteroids allopregnanolone and ganaxolone have garnered significant attention for their potential in treating CNS disorders. Allopregnanolone, a naturally occurring neurosteroid, was approved by the FDA in 2019 as Zulresso for the treatment of postpartum depression (PPD). Similarly, ganaxolone, a very close synthetic analog of allopregnanolone, received FDA approval in 2022 as Ztalmy, used for the treatment of cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD), a rare form of epilepsy. This approval is particularly noteworthy, as CDD is a severe developmental epileptic encephalopathy caused by mutations in

the CDKL5 gene, leading to infantile-onset epilepsy that is often resistant to existing treatments. These approvals marked a significant milestone, as both compounds have been known for their physiological activity in humans for years, yet challenges in their formulation due to very poor aqueous solubility had kept these drugs from progressing into clinical use [22]. Building on the success of allopregnanolone (Zulresso), zuranolone (Zurzuvae) has emerged as an oral version of the drug, approved by the FDA in 2023 for the treatment of PPD. Unlike its intravenous predecessor, zuranolone offers the convenience of oral administration, making it more accessible and easier to use. Taken once daily for 14 days, zuranolone has been shown to alleviate PPD symptoms within 3 days, providing a much-needed alternative for new mothers.

The US FDA recently approved Vyalev™ (foscarbidopa and foslevodopa) for adults with advanced Parkinson's disease (PD), marking a significant advancement in the treatment of motor fluctuations associated with PD. Vyalev™ is the first and only subcutaneous 24-hour continuous infusion of levodopa-based therapy, allowing for personalized dosing throughout the day based on individual needs. Levodopa, first approved in 1970, has been a cornerstone in the management of PD, but its effectiveness diminishes over time, leading to motor fluctuations and dyskinesia. Vyalev™ addresses these challenges by providing continuous delivery, improving "on" time without troublesome dyskinesia, and reducing "off" time compared to oral immediate-release carbidopa/levodopa. The approval demonstrated significant increases in "on" time and reductions in "off" time, with most adverse reactions being mild or moderate. Vyalev™ offers a nonsurgical alternative for patients who no longer respond adequately to oral medications, representing a major step forward in the treatment of advanced PD [23].

Other drugs for CNS indications recently approved include ozanimod (Zeposia), an S1P receptor antagonist for treating multiple sclerosis, and daridorexant (Quviviq), an antagonist of orexin receptors for treating insomnia. These recent examples show that in CNS drug discovery, leveraging known mechanisms can still yield significant benefits for patients and that existing knowledge and mechanisms can be pivotal in developing improved effective treatments. The journey to create high-quality CNS drugs often extends over multiple iterations, with each version addressing previous shortcomings. This iterative process ensures continuous improvement, ultimately leading to more refined and effective therapies for patients.

1.4 Psychedelics as Potential Therapeutic Drugs

Over the past few years, psychedelics have captured the attention of researchers and clinicians as potential treatments for mood disorders, leading to a significant surge in the number of startups focusing on their regulatory clinical development and registration. This growing interest is driven by the potential therapeutic benefits of these substances and the increasing acceptance within the medical community. According to recent reports, there are now over 50 companies involved

in psychedelic drug development, with many of them trading on public stock exchanges. These chemicals, once synonymous with counterculture movements, are now being rigorously and aggressively investigated for their therapeutic properties. The journey of psychedelics from the fringes of society to the forefront of medical research is a reflection of their profound impact on the human mind and spirit.

Psychedelics such as psilocybin, lysergic acid diethylamide (LSD), and MDMA interact with the brain in unique ways, primarily by binding to serotonin receptors. This interaction results in altered states of consciousness and, more importantly, promotes neuroplasticity – the brain's remarkable ability to reorganize and form new neural connections. This neuroplasticity is believed to be the cornerstone of the therapeutic benefits observed in recent clinical trials.

MDMA is being investigated for its potential to alleviate the symptoms of post-traumatic stress disorder (PTSD). The results have been promising, with many patients reporting substantial reductions in their symptoms. However, a potential formal approval by the FDA has yet to be accomplished, and not without challenges. Recent controversy centers on the FDA's decision to reject MDMA as a treatment for PTSD [24]. This decision was influenced by several key factors. First, the FDA found the data submitted by Lykos Therapeutics, the company behind the application, to be lacking in demonstrating the drug's safety and efficacy. Additionally, the clinical trials faced criticism for functional unblinding, meaning participants could easily tell whether they were receiving MDMA or a placebo, which could bias the results. Moreover, an independent panel of experts voted overwhelmingly against approving MDMA for PTSD, citing concerns about the trial design and potential risks such as heart problems and abuse. Despite promising results from earlier studies suggesting that MDMA-assisted therapy could significantly ease PTSD symptoms, the FDA has requested additional late-stage studies. This decision has been a major setback for advocates of psychedelic therapy, although a path forward toward registration was identified [25]. MindMed is moving forward with MM402 ((R) – MDMA), a homochiral version of MDMA, seeking to differentiate it from the racemic drug [26].

Similarly, psilocybin, the active compound found in magic mushrooms, has shown significant promise as an antidepressant. Recent studies have demonstrated that psilocybin-assisted therapy can lead to substantial and lasting improvements in depression symptoms. Other organizations such as Johns Hopkins Medicine, Compass, and Cybin are at the forefront of this research, exploring various approaches to harness psilocybin's mood disorders effects by applying different strategies. For instance, Cybin is working on CyB003, a deuterated version of psilocin (the active molecule in prodrug psilocybin) designed to achieve oral antidepressant effects with a lower dose than classical psilocybin. Additionally, the use of prodrugs of psilocybin is being explored. Prodrugs are pharmacologically inactive compounds that are metabolized in the body to produce an active drug. Psilocybin itself is a prodrug of psilocin, the compound responsible for its psychoactive effects. By developing novel prodrugs, researchers aim to improve the pharmacokinetic properties of psilocybin, potentially reducing the duration of the psychedelic

experience while maintaining its antidepressant effects. ELE-101 is a synthetic, intravenous formulation of psilocin benzoate under study by Beckley Psytech. It is currently under investigation in Phase II studies as a potential medication for depression [27].

The potential of psilocybin as an antidepressant is immense, and ongoing research continues to explore its full capabilities. One of the key unanswered questions in this field is concerning the separation of the hallucinogenic effects from the antidepressant properties. Researchers are investigating whether it is possible to engineer out the hallucinations while retaining the therapeutic benefits [28].

On 3 February 2023, Australia announced that starting 1 July, authorized psychiatrists can prescribe drugs containing psilocybin, an active substance in "magic mushrooms," and MDMA for treatment-resistant depression and PTSD, respectively. Those are the only two conditions for which Therapeutic Goods Administration (TGA) has said there is "currently sufficient evidence for potential benefits" [29]. These two drugs, psilocybin and MDMA, are being reclassified as Schedule 8, or controlled drugs, for those uses. They will remain classified as Schedule 9 prohibited substances in all other circumstances.

Developing a drug that has been used illegally for decades or even centuries, such as psychedelics, versus developing a novel molecule thought to mimic the effects of these older drugs presents unique challenges and opportunities. Illegally used drugs come with a wealth of anecdotal and historical data on their effects, both positive and negative. This existing body of knowledge can provide valuable insights into their safety profile, effective dosages, and potential therapeutic uses. However, these substances also carry a stigma and legal barriers that can complicate their development and acceptance in the medical community. In contrast, developing a novel molecule designed to mimic the effects of an older drug requires extensive research and experimentation. These new compounds must undergo rigorous testing to establish their safety, efficacy, and pharmacokinetics. While they may lack the historical baggage of older drugs, they also do not benefit from the wealth of existing knowledge. The development process for novel molecules is often longer and more expensive, but it allows for more precise control over the drug's properties and potential modifications to enhance its therapeutic effects and reduce side effects [28].

The road to mainstream acceptance of psychedelics as therapeutic agents is not without challenges. Regulatory bodies such as the US FDA require extensive evidence of safety and efficacy before approving these substances for medical use. Ethical considerations also come into play, as the use of psychedelics must be carefully controlled to prevent misuse and ensure patient safety. Despite these hurdles, the future of psychedelics in the treatment of CNS disorders looks bright. Ongoing research and growing acceptance within the medical community suggest that these substances could become integral to psychiatric practice. As more data becomes available, psychedelics may offer new hope for patients struggling with conditions that have been resistant to traditional treatments.

1.5 CNS Drugs Acting at Novel Biological Targets

As we continue our journey through the landscape of CNS drug discovery, it is essential to explore the frontier of developing drugs targeting novel biological mechanisms. While leveraging known pathways has yielded significant advances, the complexity and diversity of the brain's biology necessitate the discovery and validation of new targets. These novel mechanisms offer the promise of addressing unmet medical needs, potentially providing more effective and precise treatments for a wide range of neurological disorders.

Since 2018, the journal *Nature Review Drug Discovery* has been publishing an annual series of manuscripts by Oprea et al., under the common title "Novel drug targets." In this series, the authors aim to investigate the mechanistic novelty of new therapeutics drugs introduced annually based on FDA approvals in the United States, as well as in Europe and Japan [30–35]. In their analysis, the authors annotate each drug according to the mode or mechanism of action (MoA) presented by the innovator in the primary literature or package insert information [36]. They define a drug with a novel mode of action as one that had not been previously modulated by an approved drug. Most interestingly, they also assign a therapeutic area of use to each novel MoA (*e.g.* oncology, hematological disorders (beyond cancer), infectious diseases, and CNS diseases). Between 2018 and 2023, only four therapies have been considered as aiming at CNS disorders: calcitonin gene-related peptide (CGRP) receptor antagonists, CGRP antibodies, a PET ligand for AD diagnosis, and an antisense oligonucleotide out of a total of 75 such entries. During that time, a total of 324 drugs were approved. In other words, *the number of drugs approved for CNS indications is relatively small, and among these,* ***the vast majority work through known mechanisms of action***.

The reason for this is likely related to the fact that, as a rule of thumb, CNS diseases are polygenic, and insufficient knowledge exists about their etiology (why the diseases happen) and pathophysiology mechanism(s) (how the disease affects the body) to confidently predict clinical efficacy of a therapeutic agent, which leads

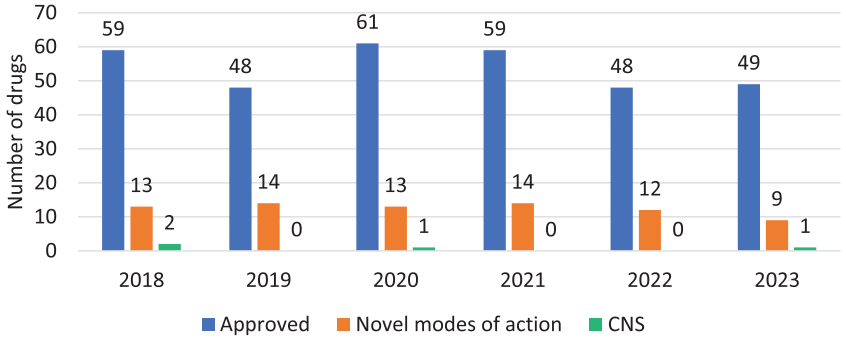

Figure 1.1 A comparison of the total number of drugs that received regulatory approval (blue), among these, those that work with unprecedented MoAs (orange), and among these, those for CNS indications (green), between 2018 and 2023.

to prolonged and costly late clinical studies. It follows that having positive clinical evidence of efficacy (provided by an early drug candidate that failed for other reasons) removes the major risk factor in brain drug discovery (Figure 1.1).

1.6 Starting with the End in Mind: Defining a CNS Disease

Defining a CNS disease is a complex and often challenging task due to the intricate nature of the brain and nervous system, as well as the overlapping symptoms and diverse manifestations of various CNS disorders. Despite these challenges, precise and accurate definitions are crucial for guiding research and development efforts aimed at discovering novel treatments. A clear understanding of the disease's underlying mechanisms, clinical presentation, and progression is essential for identifying therapeutic targets, developing effective interventions, and ultimately improving patient outcomes. By establishing well-defined criteria, researchers and clinicians can better coordinate their efforts, ensuring that new treatments are grounded in a comprehensive and nuanced understanding of the disease. However, this is not so easy. As an example, let's consider the case of AD.

AD is a progressive neurodegenerative disorder that affects millions of individuals worldwide. Despite its prevalence and impact, there is no single definition that encompasses all aspects of the disease. Over time, various frameworks have been developed to describe and understand AD, reflecting advances in scientific knowledge and shifts in clinical practice.

A recent historical perspective presented unanswered questions concerning AD pathogenesis, characteristic lesions, and the disease's clinical phenotype, especially for sporadic cases [37]. Another perspective from an expert group proposed "defining diseases biologically, rather than based on syndromic presentation, has long been standard in many areas of medicine (e.g., oncology), and is becoming a unifying concept common to all neurodegenerative diseases, not just AD" [38]. As a consequence, "AD could be defined clinically as encompassing cognitively normal people having a core 1 AD biomarker" [39]. Shortly thereafter, this view was challenged considering that "recent literature shows that the majority of biomarker-positive cognitively normal individuals will not become symptomatic along a proximate timeline." In the clinical setting, disclosing a diagnosis of AD to cognitively normal people with only core 1 AD biomarkers represents the most problematic implication of a purely biological definition of the disease as proposed in [39].

It seems there are different ways in which AD is being defined:

a) **Clinical definition**: Traditionally, AD has been defined clinically based on its characteristic symptoms and progression. The hallmark symptoms include memory loss, language difficulties, impaired judgment, and changes in behavior and personality. Diagnosis is often made through clinical evaluations, cognitive testing, and neuroimaging to rule out other causes of dementia. This clinical definition emphasizes the observable effects of the disease on the patient's cognitive and functional abilities.

b) **Pathological definition**: With advancements in neuropathology, AD has also been defined based on its underlying brain pathology. The two main pathological features are amyloid-beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. These abnormal protein accumulations disrupt neuronal function and ultimately lead to cell death. Postmortem examination of brain tissue is the gold standard for confirming an Alzheimer's diagnosis, highlighting the disease's distinct pathological characteristics.
c) **Biomarker-based definition**: Recent developments in biomarker research have led to new ways of defining AD. Biomarkers are measurable indicators of biological processes, and in the context of Alzheimer's, they include amyloid-beta levels in cerebrospinal fluid (CSF), tau protein levels, and neuroimaging markers such as amyloid PET scans. The National Institute on Aging and Alzheimer's Association (NIA-AA) has proposed a research framework that incorporates these biomarkers into the diagnostic criteria, allowing for earlier and more accurate detection of the disease, even before clinical symptoms manifest.
d) **Genetic definition**: Genetics also play a crucial role in defining AD. While the majority of cases are sporadic, several genes have been identified that increase the risk of developing the disease. The most well-known genetic risk factor is the APOE ε4 allele, which significantly raises the likelihood of developing Alzheimer's. Additionally, rare familial forms of the disease are linked to mutations in the APP, PSEN1, and PSEN2 genes. Understanding the genetic underpinnings of Alzheimer's helps in identifying individuals at risk and developing targeted therapies.
e) **Research and experimental definitions**: As our understanding of AD continues to evolve, so do the definitions used in research and experimental settings. For instance, the concept of "mild cognitive impairment" (MCI) has been introduced to describe a transitional stage between normal aging and AD. Research studies often use specific criteria to define MCI and early-stage Alzheimer's to investigate potential interventions and disease-modifying treatments. These experimental definitions are crucial for advancing scientific knowledge and developing new therapeutic approaches.
f) **Holistic and person-centered definition**: In recent years, there has been a growing recognition of the importance of a holistic and person-centered approach to defining AD. This perspective considers not only the biological and clinical aspects but also the social, emotional, and environmental factors that impact individuals living with Alzheimer's. Person-centered care emphasizes the dignity, preferences, and quality of life of patients, advocating for a more compassionate and comprehensive understanding of the disease.

Like most brain disorders, AD is a multifaceted condition that can be defined in various ways, each reflecting different aspects of the disease. These evolving definitions of AD highlight the complexity of this devastating condition. As research continues to advance, these definitions will likely be refined and expanded, ultimately improving our ability to diagnose, treat, and support individuals suffering from brain disease. It is part of the ambiguity of conducting scientific research, and we should embrace it rather than deny it.

As if these controversies were not enough, the use of amyloid antibodies as a treatment for AD has sparked a significant debate within the medical community. Passive immunotherapy for AD has been tried for decades without success. The FDA then opted for a biomarker-based approach as an important factor in their regulatory approval of therapeutic treatments for a number of brain disorders. However, since 2021, three amyloid antibodies have been approved for the treatment of AD: aducanumab (Aduhelm, approved in 2021 under the accelerated approval pathway); lecanemab (Leqembi, granted accelerated approval in January 2023, and later converted to traditional approval in July 2023 after a confirmatory trial verified its clinical benefit) [40]; and donanemab (Kisunla, approved in July 2024 after demonstrating a statistically significant slowing of cognitive decline in clinical trials). Proponents of this approach argue that these antibodies, which target amyloid-beta plaques in the brain, have shown promise in slowing the progression of the disease. Clinical trials have demonstrated that amyloid antibodies can reduce amyloid buildup and, in some cases, lead to modest improvements in cognitive and functional outcomes. However, critics point to the serious side effects associated with these treatments, particularly the risks of brain bleeding (hemorrhage) and swelling (edema) [41]. These side effects, collectively known as amyloid-related imaging abnormalities (ARIA), can be severe and potentially life-threatening. The occurrence of ARIA has led some experts to question whether the benefits of amyloid antibodies outweigh the risks, especially given the small magnitude of clinical improvements observed in trials.

The disagreement highlights the need for careful consideration of both the potential benefits and risks of amyloid antibody therapies. While these treatments offer a new approach to targeting the underlying pathology of AD, their safety profile must be thoroughly evaluated to ensure that they provide a net benefit to patients. Ongoing research and post-marketing surveillance will be crucial in determining the long-term viability of amyloid antibodies as a therapeutic option for AD.

1.7 Where to Go from Here

From the last section, we can imagine that if just *defining* a disease is so controversial, what can we expect for the task of *finding a treatment*, let alone a cure for it? Fortunately, a lot of energy and resources are also directed toward this goal.

A number of scientific leaders with deep expertise are the area of CNS drug discovery have recently presented their views on the current developments and defining breakthroughs needed to realize a major positive transformation in CNS drug discovery [42–47]. As a representative example, it is stated that "*In contrast to most fields of medicine, progress to discover and develop new and improved psychiatric drugs has been slow and disappointing. The vast majority of currently prescribed drugs to treat schizophrenia, mood and anxiety disorders are arguably no more effective than the first generation of psychiatric drugs introduced well over 50 years ago. With only a few exceptions current psychiatric drugs work via the same fundamental mechanisms of action as first-generation agents*." Followed by "*Together with existing drugs these*

newer agents and novel mechanisms could offer markedly improved functional outcomes for the millions of people still disabled by psychiatric disorders." [46] For the time being, it seems quite clear that uncovering more fundamental knowledge is required and that much work is needed before clinically meaningful therapies become available to patients of CNS diseases. However, this is a lot easier said than done.

Fundamental research is driven by curiosity and the quest for knowledge about the underlying mechanisms of nature, without any immediate application in mind. This type of research seeks to uncover the basic principles and building blocks of biological and chemical processes, which can then be used as a foundation for applied research. On the other hand, applied research is goal-oriented and focuses on finding practical solutions to specific problems. In the context of drug discovery, applied research aims to develop new therapeutic agents, optimize existing drugs, and translate scientific findings into real-world applications.

The differences between fundamental and applied research in drug discovery are becoming increasingly pronounced. Fundamental research often operates in the realm of "unknown unknowns," where scientists explore uncharted territories to discover new knowledge and concepts. In contrast, applied research tends to focus on "known unknowns," where researchers use existing knowledge to address specific challenges and develop targeted solutions. While technologies such as AI and cryo-electron microscopy (cryo-EM), and novel chemical modalities such as PROteolysis TArgeting Chimeras (PROTACs) [48] or bifunctional antibodies [49] have revolutionized applied research by enabling more efficient drug discovery and development processes, they do not necessarily help in uncovering the unknown unknowns. AI excels in analyzing large datasets, identifying patterns, and predicting outcomes based on existing information. Cryo-EM allows for high-resolution imaging of biomolecules, providing valuable structural insights for drug design. New chemical modalities create new opportunities for biological target functional modulation. However, these technologies rely on known frameworks to function effectively.

To uncover unknown unknowns, fundamental research remains essential. It involves open-ended exploration and hypothesis generation, driven by the curiosity and creativity of scientists. Discoveries made through fundamental research can challenge existing paradigms and open new avenues for applied research. While AI, cryo-EM, and novel modalities are powerful tools that enhance our ability to develop targeted therapies and understand complex biological systems, they complement rather than replace the need for fundamental research. The interplay between these types of research is crucial for advancing drug discovery and addressing the most pressing health challenges of our time.

Additionally, increasing amounts of research are being funded by private sources (venture capitalists or VCs), who naturally seek to recover their investments in the short term and focus more on applied research. VCs typically prioritize projects with clear commercial potential and shorter development timelines, which can lead to a greater emphasis on applied research at the expense of fundamental research. This trend further widens the gap between the two types of research,

as funding for fundamental research becomes increasingly limited. Despite these challenges, it is essential to maintain a balance between fundamental and applied research to ensure long-term scientific progress and the development of innovative therapies.

The Century of Biology holds immense promise for transforming human health through groundbreaking discoveries and innovative therapies. However, realizing this potential is fraught with challenges that must be addressed. The growing divide between fundamental and applied research, driven by the increasing influence of venture capital funding, risks limiting the exploration of unknown unknowns that are crucial for true scientific breakthroughs. Additionally, while technologies such as AI and cryo-EM have revolutionized applied research, they do not replace the need for fundamental research that uncovers new knowledge and paradigms. Balancing the pursuit of immediate commercial gains with long-term scientific progress is essential. By fostering collaboration, investing in fundamental research, and embracing a holistic approach to health and disease, The Century of Biology can indeed fulfill its promise of significantly improving human health and well-being.

References

1 Venter, C. and Cohen, D. (2004). The century of biology. *New Perspect. Q.* 21 (4): 73–77. https://doi.org/10.1111/j.1540-5842.2004.00701.x.

2 Blanco, M.-J., Gardinier, K.M., and Namchuk, M.N. (2022). Advancing new chemical modalities into clinical studies. *ACS Med. Chem. Lett.* https://doi.org/10.1021/acsmedchemlett.2c00375.

3 Choi, Y., Vinks, A.A., and van der Graaf, P.H. (2023). Novel therapeutic modalities: the future is now. *Clin. Pharmacol. Ther.* 114 (3): 493–496. https://doi.org/10.1002/cpt.2996.

4 Sven Fraterman, Wen Xie, Chun Wu, Maximilian Thielmann, and Brian Yudhistiara (2023). New drug modalities offer promise and peril. BCG Global. https://www.bcg.com/publications/2023/benefits-and-risks-of-new-drug-modalities (accessed 19 August 2023).

5 Doller, D. (2017). The "century of biology" and the evolving role of medicinal chemists in neuroscience. *ACS Chem. Neurosci.* 8 (1): 8–11. https://doi.org/10.1021/acschemneuro.6b00394.

6 Kenakin, T. (2024). Allostery: The Good, the Bad, and the Ugly. *J. Pharmacol. Exp. Ther.* 388 (1): 110–120. https://doi.org/10.1124/jpet.123.001838.

7 Brain health atlas. https://brainhealthatlas.org/ (accessed 12 May 2023).

8 Rosa M. Abrantes-Metz, Christopher P. Adams and Albert Metz (2004). Pharmaceutical development phases: a duration analysis. Federal Trade Commission. https://www.ftc.gov/reports/pharmaceutical-development-phases-duration-analysis (accessed 15 May 2023).

9 DiMasi, J.A., Feldman, L., Seckler, A., and Wilson, A. (2010). Trends in risks associated with new drug development: success rates for investigational drugs. *Clin. Pharmacol. Ther.* 87 (3): 272–277. https://doi.org/10.1038/clpt.2009.295.

10 Hay, M., Thomas, D.W., Craighead, J.L. et al. (2014). Clinical development success rates for investigational drugs. *Nat. Biotechnol.* 32 (1): 40–51. https://doi.org/10.1038/nbt.2786.

11 Smietana, K., Siatkowski, M., and Møller, M. (2016). Trends in clinical success rates. *Nat. Rev. Drug Discov.* 15 (6): 379–380. https://doi.org/10.1038/nrd.2016.85.

12 Wong, C.H., Siah, K.W., and Lo, A.W. (2019). Estimation of clinical trial success rates and related parameters. *Biostat. Oxf. Engl.* 20 (2): 273–286. https://doi.org/10.1093/biostatistics/kxx069.

13 DiMasi, J.A., Grabowski, H.G., and Hansen, R.W. (2016). Innovation in the pharmaceutical industry: new estimates of R&D costs. *J. Health Econ.* 47: 20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012.

14 McNamee, L.M., Walsh, M.J., and Ledley, F.D. (2017). Timelines of translational science: from technology initiation to FDA approval. *PLoS One* 12 (5): e0177371. https://doi.org/10.1371/journal.pone.0177371.

15 Spector, J.M., Harrison, R.S., and Fishman, M.C. (2018). Fundamental science behind today's important medicines. *Sci. Transl. Med.* 10 (438): eaaq1787. https://doi.org/10.1126/scitranslmed.aaq1787.

16 Jie Jack Li (2024). Chemistry and pharmacology of drug discovery|Wiley. Wiley.com. https://www.wiley.com/en-us/Chemistry+and+Pharmacology+of+Drug+Discovery-p-9781394225125 (accessed 14 August 2024).

17 Scannell, J.W., Bosley, J., Hickman, J.A. et al. (2022). Predictive validity in drug discovery: what it is, why it matters and how to improve it. *Nat. Rev. Drug Discov.* 21 (12): 915–931. https://doi.org/10.1038/s41573-022-00552-x.

18 Scannell, J.W. and Bosley, J. (2016). When quality beats quantity: decision theory, drug discovery, and the reproducibility crisis. *PLoS One* 11 (2): e0147215. https://doi.org/10.1371/journal.pone.0147215.

19 Drug approval package: lybalvi. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213378Orig1Orig2s000TOC.cfm (accessed 7 August 2023).

20 Brannan, S.K., Sawchak, S., Miller, A.C. et al. (2021). Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. *N. Engl. J. Med.* 384 (8): 717–726. https://doi.org/10.1056/NEJMoa2017015.

21 AXS-05 – axsome therapeutics. https://www.axsome.com/axs-portfolio/pipeline/about-axs-05 (accessed 7 August 2023).

22 Maguire, J.L. and Mennerick, S. (2024). Neurosteroids: mechanistic considerations and clinical prospects. *Neuropsychopharmacology* 49 (1): 73–82. https://doi.org/10.1038/s41386-023-01626-z.

23 Soileau, M.J., Aldred, J., Budur, K. et al. (2022). Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial. *Lancet Neurol.* 21 (12): 1099–1109. https://doi.org/10.1016/S1474-4422(22)00400-8.

24 Lykos therapeutics announces complete response letter for midomafetamine capsules for PTSD. Lykos Therapeutics – News Release Archive. https://news.lykospbc.com/2024-08-09-Lykos-Therapeutics-Announces-Complete-Response-Letter-for-Midomafetamine-Capsules-for-PTSD (accessed 9 November 2024).

25 Lykos therapeutics statement on recent FDA meeting. Lykos Therapeutics – News Release Archive. https://news.lykospbc.com/2024-10-18-Lykos-Therapeutics-Statement-on-Recent-FDA-Meeting (accessed 9 November 2024).

26 Pitts, E.G., Curry, D.W., Hampshire, K.N. et al. (2018). (±)-MDMA and Its enantiomers: potential therapeutic advantages of R(-)-MDMA. *Psychopharmacology* 235 (2): 377–392. https://doi.org/10.1007/s00213-017-4812-5.

27 Our pipeline. https://www.beckleypsytech.com/our-work/our-pipeline (accessed 9 November 2024).

28 Bethany Halford (2022). Drug companies are investing big in psychedelics, but can they engineer out the trip? Chemical & Engineering News. https://cen.acs.org/pharmaceuticals/drug-development/Drug-companies-investing-big-psychedelics/100/i9 (accessed 9 November 2024).

29 Administration (TGA), T. G (2023). Change to classification of psilocybin and MDMA to enable prescribing by authorised psychiatrists. Therapeutic Goods Administration (TGA). https://www.tga.gov.au/news/media-releases/change-classification-psilocybin-and-mdma-enable-prescribing-authorised-psychiatrists (accessed 6 July 2023).

30 Ursu, O., Glick, M., and Oprea, T. (2019). Novel drug targets in 2018. *Nat. Rev. Drug Discov.* 18 (5): 328–328. https://doi.org/10.1038/d41573-019-00052-5.

31 Avram, S., Halip, L., Curpan, R., and Oprea, T.I. (2020). Novel drug targets in 2019. *Nat. Rev. Drug Discov.* 19 (5): 300–300. https://doi.org/10.1038/d41573-020-00052-w.

32 Avram, S., Halip, L., Curpan, R., and Oprea, T.I. (2021). Novel drug targets in 2020. *Nat. Rev. Drug Discov.* 20 (5): 333. https://doi.org/10.1038/d41573-021-00057-z.

33 Avram, S., Halip, L., Curpan, R., and Oprea, T.I. (2022). Novel drug targets in 2021. *Nat. Rev. Drug Discov.* 21 (5): 328–328. https://doi.org/10.1038/d41573-022-00057-7.

34 Avram, S., Halip, L., Curpan, R., and Oprea, T.I. (2023). Novel drug targets in 2022. *Nat. Rev. Drug Discov.* 22 (6): 437–437. https://doi.org/10.1038/d41573-023-00068-y.

35 Avram, S., Halip, L., Curpan, R., and Oprea, T. I, (2024). Novel drug targets in 2023. *Nat. Rev. Drug Discov.* https://doi.org/10.1038/d41573-024-00057-9.

36 Santos, R., Ursu, O., Gaulton, A. et al. (2017). A comprehensive map of molecular drug targets. *Nat. Rev. Drug Discov.* 16 (1): 19–34. https://doi.org/10.1038/nrd.2016.230.

37 Villain, N. and Michalon, R. (2024). What Is Alzheimer's disease? An analysis of nosological perspectives from the 20th and 21st centuries. *Eur. J. Neurol.* 31 (11): e16302. https://doi.org/10.1111/ene.16302.

38 Jack, C.R. Jr., Andrews, J.S., Beach, T.G. et al. (2024). Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's association workgroup. *Alzheimers Dement.* 20 (8): 5143–5169. https://doi.org/10.1002/alz.13859.

39 Dubois, B., Villain, N., Schneider, L. et al. (2024). Alzheimer disease as a clinical-biological construct – an international working group recommendation. *JAMA Neurol.* https://doi.org/10.1001/jamaneurol.2024.3770.

40 van Dyck, C.H., Swanson, C.J., Aisen, P. et al. (2023). Lecanemab in early Alzheimer's disease. *N. Engl. J. Med.* 388 (1): 9–21. https://doi.org/10.1056/NEJMoa2212948.

41 Reish, N.J., Jamshidi, P., Stamm, B. et al. (2023). Multiple cerebral hemorrhages in a patient receiving lecanemab and treated with T-PA for stroke. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMc2215148.

42 Brady, L.S., Potter, W.Z., and Gordon, J.A. (2019). Redirecting the revolution: new developments in drug development for psychiatry. *Expert Opin. Drug Discov.* 14 (12): 1213–1219. https://doi.org/10.1080/17460441.2019.1666102.

43 Tricklebank, M.D., Robbins, T.W., Simmons, C., and Wong, E.H.F. (2021). Time to re-engage psychiatric drug discovery by strengthening confidence in preclinical psychopharmacology. *Psychopharmacology* 238 (6): 1417–1436. https://doi.org/10.1007/s00213-021-05787-x.

44 Scangos, K.W., State, M.W., Miller, A.H. et al. (2023). New and emerging approaches to treat psychiatric disorders. *Nat. Med.* 29 (2): 317–333. https://doi.org/10.1038/s41591-022-02197-0.

45 Andreassen, O.A., Hindley, G.F.L., Frei, O., and Smeland, O.B. (2023). New insights from the last decade of research in psychiatric genetics: discoveries, challenges and clinical implications. *World Psychiatry Off. J. World Psychiatr. Assoc. WPA* 22 (1): 4–24. https://doi.org/10.1002/wps.21034.

46 Paul, S.M. and Potter, W.Z. (2023). Finding new and better treatments for psychiatric disorders. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* https://doi.org/10.1038/s41386-023-01690-5.

47 Keezer, M.R., Bauer, P.R., and Sander, J.W. (2023). The future: moving from phenotypically defined diseases toward pathophysiological systems. *Can. J. Neurol. Sci. J. Can. Sci. Neurol.* 1–3. https://doi.org/10.1017/cjn.2023.30.

48 Farrell, K. and Jarome, T.J. (2021). Is PROTAC technology really a game changer for central nervous system drug discovery? *Expert Opin. Drug Discov.* 16 (8): 833–840. https://doi.org/10.1080/17460441.2021.1915979.

49 Kouhi, A., Pachipulusu, V., Kapenstein, T. et al. (2021). Brain disposition of antibody-based therapeutics: dogma, approaches and perspectives. *Int. J. Mol. Sci.* 22 (12): 6442. https://doi.org/10.3390/ijms22126442.