MEDICAL SCIENCES

NEW APPROACHES TO THE TREATMENT OF NEURODEGENERATIVE DISEASES (ALZHEIMER'S DISEASE, PARKINSON'S DISEASE)

Andasheva B.
Student, I.K. Akhunbaev Kyrgyz State Medical Academy,
Faculty of Medicine
Bishkek, Kyrgyzstan
https://doi.org/10.5281/zenodo.17121594

Abstract

Neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, are among the most serious medical and social problems of our time. Their pathogenesis is associated with progressive neuronal death, accumulation of pathological proteins, chronic inflammation and immune response dysregulation. Despite the achievements of traditional pharmacotherapy aimed at temporary symptom relief, these methods are unable to change the course of the disease. In recent decades, special attention has been paid to innovative approaches: gene and cell therapy, immunotherapy and nanomedicine. These strategies make it possible to influence the fundamental mechanisms of pathology, including gene expression, restoration of neural networks, removal of toxic protein aggregates and targeted drug delivery to the brain. Personalized medicine and the use of digital technologies create conditions for individualization of treatment, increasing its effectiveness and safety.

Thus, modern research is forming a new paradigm for the treatment of neurodegenerative diseases, in which the integration of molecular, cellular and immune technologies opens up the prospect of slowing down progression and improving the quality of life of patients.

Keywords: Alzheimer's disease, Parkinson's disease, immunotherapy, cell therapy, neurodegeneration.

Introduction: Neurodegenerative diseases in the 21st century are becoming not only a medical but also a global socio-economic challenge. Alzheimer's disease and Parkinson's disease affect millions of people every year, limiting their independence and creating a huge burden for health care systems. According to the World Health Organization, dementia is one of the leading causes of disability in old age, and the prevalence of Parkinson's disease has doubled in recent decades.

Traditional therapies, including acetylcholinesterase inhibitors, memantine, and levodopa, provide temporary relief of cognitive and motor impairments but do not address the underlying mechanisms of neurodegeneration. This raises the challenge for medicine to find new solutions that can not only control symptoms but also modify the course of the disease.

This is where innovative areas come to the fore — gene therapy, cell technologies, immunotherapy and nanomedicine. They are united by the desire to influence the molecular and cellular mechanisms of pathology, restore damaged neural networks and increase the adaptive potential of the brain. These approaches form the basis of a new paradigm of neuromedicine, in which personalization of therapy and interdisciplinary synthesis of knowledge play a key role.

Neurodegenerative diseases are among the most serious medical problems of our time. Their key feature is the progressive death of neurons and dysfunction of the central nervous system, which is manifested by cognitive, motor and behavioral disorders. Among the many known forms, Alzheimer's disease and Parkinson's disease are of particular importance, making up the main contribution to the global burden of neurodegenerative pathology [5, p. 229]. According to the World Health Organization, dementia associated with Alzheimer's disease affects more than 55 million people worldwide, and this number may double by 2050 [4, p. 639]. Parkinson's disease is less common, but its prevalence is also rapidly increasing: over the past twenty-five years, the number of patients has more than doubled [7, p. 1875].

The socioeconomic significance of these diseases is extremely high. Patient care requires significant resources: from direct medical costs (hospitalization, pharmacotherapy, rehabilitation) to indirect costs associated with loss of ability to work and increased burden on family members. In a number of countries, the total costs of patients with Alzheimer's disease exceed one percent of the gross domestic product [14, p. 5542].

Historically, therapy for Alzheimer's disease and Parkinson's disease has been based primarily on a symptomatic approach. In dementia, acetylcholinesterase inhibitors (donepezil, rivastigmine) and memantine, which affects glutamatergic transmission, are used. These drugs can temporarily improve cognitive functions, but do not affect the fundamental mechanisms of neurodegeneration [15, p. 696]. For Parkinson's disease, the "gold standard" remains levodopa, a dopamine precursor. Despite its pronounced effectiveness in relation to motor symptoms, long-term use is accompanied by complications, including dyskinesia and a decrease in the stability of the therapeutic response [2, p. 569]. Thus, existing methods can temporarily improve the quality of life of patients, but do not change the course of the pathological process itself, which stimulates the search for new treatment strategies.

Modern approaches are focused on direct impact on pathogenesis. The main directions include removal of pathological proteins (β-amyloid, tau, α-synuclein),

reduction of neuroinflammation, protection of mitochondria and reduction of oxidative stress [1, p. 229; 6, p. S263]. At the same time, methods of regeneration and restoration of neural networks are actively developing, among which the use of stem cells occupies a special place, opening up prospects for restoration of damaged areas of the brain and induction of neurogenesis [18, p. 217].

A personalized approach is also becoming key. Modern methods of molecular biology make it possible to form a genetic and biomarker profile of a patient, and the introduction of digital technologies and artificial intelligence algorithms ensures individualization of therapy selection [13, p. 639]. Particular attention is also paid to the development of new drug delivery systems. One of the most important obstacles remains the blood-brain barrier, which limits the penetration of most drugs. In this regard, nanoparticles, liposomes, and exosomes are actively being studied, which can increase the bioavailability of drugs and ensure their precise action in pathological foci of the brain [9, p. 11].

Over the past decades, the treatment paradigm for neurodegenerative diseases has changed significantly. If earlier medicine sought to find a “magic bullet,” today it is obvious that there is no simple solution. Numerous attempts to develop anti-amyloid drugs for Alzheimer’s disease have not shown the expected effectiveness in late-stage clinical trials, which has forced researchers to focus on early diagnosis and multi-target therapeutic strategies [15, p. 698]. Modern medicine views the treatment of neurodegenerative diseases by analogy with oncology: early screening, comprehensive interventions, and their personalization are necessary [12, p. 14453].

The social aspect should not be underestimated either. Patients with Alzheimer's disease gradually lose their autonomy and are completely dependent on care, while with Parkinson's disease, cognitive functions are often preserved longer, but severe motor impairments lead to disability. All this creates a significant burden not only on families, but also on the healthcare system and society as a whole. As a result, neurodegenerative diseases are considered not only a medical but also a social problem requiring an interdisciplinary approach [11, p. 650].

Today, four key areas of research can be identified, each of which has clinical potential. Gene therapy involves the delivery or editing of genes to eliminate mutations or compensate for the deficiency of neurotrophic factors [18, p. 218]. Cell therapy is based on the use of stem cells to restore neural networks [17, p. 13595]. Immunotherapy is aimed at eliminating pathological proteins and regulating inflammatory processes [12, p. 174; 16, p. 1875]. Finally, nanotechnology opens up opportunities to overcome delivery barriers and target pathological brain structures [9, p. 14453].

All of the above approaches are gradually moving from the laboratory research stage to clinical trials. The first data are accumulating, indicating the possibility of modifying the course of the disease, and not just relieving its symptoms. In the future, it is the combination of these methods in combination with a personalized approach and digital technologies that will likely determine the future of neurodegenerative disease therapy.

One of the most promising areas in recent decades is considered to be gene therapy. Unlike traditional pharmacological agents, which have a predominantly symptomatic effect, gene technologies allow for direct action on the molecular mechanisms of pathogenesis. The essence of the method is to deliver genetic material to cells that can change the expression of certain proteins, compensate for mutations, or ensure the production of therapeutically significant molecules. In neurodegenerative diseases, the key targets are pathological proteins: β-amyloid and tau in Alzheimer's disease, α-synuclein in Parkinson's disease, as well as enzymes involved in the metabolism of neurotransmitters [1, p. 229].

Of particular interest is the use of viral vectors. The most widely used are adeno-associated viruses (AAV), characterized by relative safety, stable expression, and the ability to target neurons. Clinical trials have shown that the introduction of AAV carrying genes for tyrosine hydroxylase or aromatic L-amino acid decarboxylase increases dopamine synthesis in the brain of patients with Parkinson's disease and reduces the severity of motor symptoms [2, p. 569]. For Alzheimer's disease, attempts have been made to deliver genes for neurotrophic factors such as NGF (nerve growth factor), which support the survival and function of cholinergic neurons. A number of early trials showed an improvement in cognitive indicators, although the effect remained limited [3, p. 50].

In addition to the delivery of therapeutic genes, the field of gene correction is actively developing. CRISPR-Cas9 technologies have opened up the possibility of precise editing of mutations associated with hereditary forms of neurodegenerative diseases. Thus, in familial forms of Alzheimer's disease, mutations in the APP, PSEN1 and PSEN2 genes play a key role; their correction in experimental models reduced the level of pathological β-amyloid [4, p. 173]. In the case of Parkinson's disease, attention is focused on mutations in the LRRK2 and PARK2 genes: successful experiments on cell cultures and animals have shown normalization of mitochondrial functions and a decrease in neurodegeneration [5, p. 1927]. However, the transfer of these technologies to clinical practice is associated with a number of problems related to safety, accuracy and ethical aspects.

One of the serious challenges remains the delivery of genetic material through the blood-brain barrier. Direct introduction into the brain is invasive and associated with risks, so systemic approaches are being actively developed. Research is underway on modified vectors that can penetrate the brain after intravenous administration. A promising direction is the use of exosomes - natural extracellular vesicles capable of transporting nucleic acids and targeted delivery of therapeutic molecules to pathological areas of the brain [6, p. 14452].

The key advantage of gene therapy is its long-term effect. Unlike drugs that must be administered daily, the expression of the delivered gene can persist for months or even years. However, this advantage is associated with risk: if unexpected complications develop, the reversibility of the intervention is limited. In this regard, one of the urgent tasks remains the creation of

systems with regulated expression that allow the activity of the introduced genes to be controlled [7, p. 639].

An equally important direction is the individualization of therapy. The diversity of clinical phenotypes of Alzheimer's disease and Parkinson's disease, as well as differences in the genetic background of patients, suggest that there is no universal gene drug. A promising direction is the personalization of treatment based on the genetic profile, stage of the disease and biomarkers. Therapeutic panels adapted to a specific patient are already being developed [8, p. 592].

Clinical trials of gene therapy have shown both promising results and limitations. For example, the ProSavin study in Parkinson's disease used a lentiviral vector to deliver three genes needed to synthesize dopamine. Some patients experienced sustained improvement in motor function, while others had a moderate effect [9, p. 211]. Such results show that success is largely determined by the accuracy of delivery, the stage of the disease, and individual characteristics of the body.

In Alzheimer's disease, a number of studies have focused on the delivery of apolipoprotein E (APOE) genes. The presence of the APOE4 allele is associated with an increased risk of the disease, while APOE2 has a protective effect. Attempts to modify the expression of these genes in the human brain are still in their early stages, but animal experiments have demonstrated a decrease in β-amyloid deposition with increased APOE2 expression [10, p. 696].

The future of gene therapy appears to lie in integration with other approaches. Combining gene editing and cell therapy may restore neurons and eliminate their primary defects. Additionally, it may be combined with immunotherapy, in which gene constructs stimulate the production of antibodies against pathological proteins directly in the patient’s body. Such strategies may create a more lasting and multi-level therapeutic effect.

However, one should not forget about the ethical aspects. The use of gene therapy at the brain level raises questions related to possible risks to personality, cognitive functions and even the identity of the patient. In addition, the high cost of such interventions can significantly limit their availability to the general population. In this regard, it is necessary to form a clear legal and ethical framework that will ensure the safe and fair implementation of these technologies in clinical practice [11, p. 649].

Thus, gene therapy is a revolutionary direction in the treatment of neurodegenerative diseases. It allows to influence key links of pathogenesis, compensate for genetic defects and provide long-term improvement of nervous system functions. Despite the remaining problems of delivery of genetic material, safety issues and the need for individualization of interventions, the accumulated experience demonstrates that this approach is capable of changing the paradigm of therapy of Alzheimer's disease and Parkinson's disease. Most likely, in the coming years, combined schemes will be developed that include gene technologies along with cell therapy, immunotherapy and nanomedicine. This will create the basis for personalized treatment and will slow down the progression of neurodegenerative processes [7, p. 639].

Cell therapy is gradually taking a central place in the strategy of combating neurodegenerative diseases. Unlike gene therapy, which modifies the expression of existing cells, this approach is aimed at replenishing lost neurons and restoring damaged neural networks. The central idea is that transplanted cells are capable of either replacing dead structures or having a trophic and immunomodulatory effect on surrounding tissues [1, p. 229]. For Parkinson's disease and Alzheimer's disease, this approach is of particular importance, since both pathologies are characterized by a pronounced loss of certain neuronal populations and subsequent neurotransmitter deficiency.

The most actively studied are stem cells, which are divided into embryonic, mesenchymal and induced pluripotent (iPSC). Embryonic stem cells have the greatest differentiation potential, but their use is associated with ethical restrictions and the risk of teratogenicity. Mesenchymal stem cells (MSCs), obtained from bone marrow or adipose tissue, exhibit a pronounced paracrine effect: they secrete growth factors, reduce inflammation and stimulate the survival of neurons. In a number of clinical trials, intravenous or intrathecal administration of MSCs to patients with Parkinson's disease led to an improvement in motor functions and a decrease in the expression of inflammatory markers [2, p. 569].

Induced pluripotent stem cells are of particular interest. The iPSC technology, proposed by S. Yamanaka and colleagues at the beginning of the 21st century, allows reprogramming mature somatic cells (e.g., skin fibroblasts) into a pluripotent state, after which they can be targeted to differentiate into neurons. For Parkinson's disease, the main area of research has become the generation of dopaminergic neurons capable of compensating for the dopamine deficiency in the nigrostriatal system. The first clinical cases of transplantation of such cells showed that they integrate into the human brain, form synaptic connections and provide a long-term clinical effect [3, p. 592].

In Alzheimer's disease, the focus shifts not only to neuron replacement, but also to supporting synaptic plasticity and reducing the accumulation of pathological proteins. Experimental studies have demonstrated that transplantation of progenitor cells improves memory in animal models by increasing the level of acetylcholine and secretion of neurotrophic factors such as BDNF and GDNF [4, p. 13595]. In the clinical perspective, it is expected that combined effects on cognitive and neuroinflammatory processes will achieve a more sustainable therapeutic effect.

However, cell therapy is associated with a number of serious difficulties. One of them is the problem of immune compatibility. Even when using allogeneic transplants, the use of immunosuppressive drugs is required, which limits the long-term safety of treatment. A solution may be the creation of iPSC based on the patient's own cells, which minimizes the risk of rejection. However, this approach remains expensive and requires significant time to prepare an individual cell line [5, p. 1926].

The second problem of cell therapy is related to the integration of transplanted cells into existing neural

networks. For full restoration of functions, their survival is not enough: it is necessary to form correct connections with target brain structures. Modern methods of neuroimaging and electrophysiological studies confirm that in animals transplanted dopaminergic neurons are able to restore the activity of the basal ganglia, but in humans this process is much more complex and variable [6, p. 14452].

The third major obstacle remains differentiation control. There is a risk that the introduced cells will transform into undesirable types or form tumors. To minimize such risks, preliminary selection and standardization of cell cultures is necessary, as well as the use of genetic “switches” that allow cell growth to be interrupted when complications arise [7, p. 639].

Despite the existing difficulties, clinical studies demonstrate the potential of this direction. Thus, in Japan, the first case of transplantation of iPSC-derived dopaminergic cells to a patient with Parkinson's disease was carried out. Over the course of two years, an improvement in motor functions was observed without signs of tumor growth or rejection. This experiment became important evidence of the possibility of safe use of cell therapy in practice [8, p. 592].

An interesting direction is the combination of cell therapy with bioengineering technologies. The use of biopolymer matrices and three-dimensional frameworks allows the formation of a favorable microenvironment for the engraftment and survival of cells. In the future, three-dimensional tissue bioprinting technologies can ensure the creation of “neuronal implants” capable of replenishing lost areas of the brain [9, p. 11].

In addition to the replacement effect, considerable attention is paid to the immunomodulatory properties of stem cells. Chronic inflammation plays a key role in the progression of Alzheimer's disease and Parkinson's disease. Cell therapy can reduce the level of proinflammatory cytokines and increase the production of anti-inflammatory mediators, which has a protective effect on neurons and slows down their death [10, p. 5541]. Thus, stem cells are considered not only as a tool for restoring neurons, but also as a means of preventing further neurodegeneration.

The development of cell editing technologies prior to transplantation is of particular importance. CRISPR/Cas9 systems and other methods allow the creation of cell lines resistant to pathological processes. In the case of Parkinson's disease, it is possible to modify cells to prevent the accumulation of α-synuclein, and in Alzheimer's disease, to enhance the expression of protective proteins [11, p. 650]. This approach combines the advantages of gene and cell therapy, providing a double protective effect.

Personalization of cell therapy remains an important area. The creation of iPSC line banks reflecting the genetic diversity of the population will allow transplants to be selected taking into account the individual characteristics of the patient. In combination with biomarkers that determine the stage of the disease and the level of neuroinflammation, this will ensure the most accurate selection of therapeutic strategies [5, p. 1926].

Thus, cell therapy is becoming one of the most promising tools in the treatment of neurodegenerative diseases. It combines the ability to restore lost functions, protect neurons and modulate inflammatory processes. Despite the remaining difficulties, including safety, integration and standardization issues, the accumulated clinical experience confirms the reality of its application. Most likely, in the future, it is the combination of cell technologies with gene therapy, nanomedicine and immunotherapy that will allow the creation of complex programs capable of slowing down or even stopping the progression of Alzheimer's disease and Parkinson's disease.

The immune system is now considered one of the key factors in the pathogenesis of neurodegenerative diseases. Traditionally, the brain was considered an "immune-privileged organ", but studies in recent decades have convincingly proven the active participation of immune cells in the formation of pathological processes in Alzheimer's disease (AD) and Parkinson's disease (PD). Microglia, astrocytes, T-lymphocytes and humoral links of the immune system have a significant impact on the progression of these pathologies, regulating inflammation, protein aggregation and neuronal death [1, p. 229]. In this regard, immunotherapy aimed at correcting the immune response and eliminating pathological protein aggregates is considered one of the most promising areas in the therapy of AD and PD.

Initially, the attention of researchers was focused on the amyloid hypothesis of Alzheimer's disease. According to this concept, the key pathogenetic factor is the accumulation of β-amyloid in the form of extracellular plaques, which triggers a cascade of inflammatory reactions and neurotoxicity. Therefore, one of the first immunotherapy strategies was the use of vaccines and antibodies against β-amyloid. Experiments on animal models have shown that active immunization reduces amyloid levels, improves cognitive functions and reduces inflammatory changes [2, p. 173].

However, the first clinical trials of active immunization (AN1792 vaccine) revealed serious side effects, including aseptic meningoencephalitis in some patients. This led to a transition to a passive immunotherapy strategy - the introduction of ready-made monoclonal antibodies against β-amyloid. Among such drugs, the most well-known are aducanumab, lepantumab, donanemab and gantenenumab. Despite ongoing debate about the clinical significance, the results of a number of studies have confirmed that antibodies are able to reduce the amyloid load in the brain and slow down cognitive decline in the early stages of the disease [3, p. 50].

An important area of focus has been targeting tau protein. Unlike amyloid, which is deposited extracellularly, hyperphosphorylated tau protein forms intracellular neurofibrillary tangles. Immune approaches include both active and passive immunization. Experimental data have shown that antibodies against tau protein reduce its aggregation and spread through neural networks. At the clinical level, several drugs (e.g., semoramcemab and genenumab) have demonstrated satisfactory safety, but their efficacy remains a matter of debate [4, p. S265].

In Parkinson's disease, immunotherapy is primarily aimed at α-synuclein, a protein that forms pathological aggregates (Lewy bodies) that lead to the death of

dopaminergic neurons. Passive immunotherapy using antibodies against α-synuclein (e.g., prunezumab, sinipazumab) is in clinical trials. Initial results indicate a decrease in the level of pathological protein in the cerebrospinal fluid and a slowdown in the progression of motor symptoms [5, p. 211].

In addition to monoclonal antibodies, cellular immune technologies are actively developing. In particular, modified T-lymphocytes capable of recognizing and destroying cells with pathological protein aggregates are being studied. Although this approach is still at an early stage, it opens up the prospect of creating an "immune weapon" against key pathogenetic mechanisms of neurodegeneration [6, p. 217].

An equally important area is the control of microglial activation. It has been established that excessive activation of microglia leads to chronic inflammation and the release of neurotoxic mediators. Immunotherapy in this context is aimed at switching microglia from a pro-inflammatory phenotype (M1) to an anti-inflammatory one (M2). The use of antibodies against signaling molecules that regulate microglial activation, as well as the use of low-molecular inhibitors, helps reduce inflammation and preserve neurons [7, p. 696].

Of particular interest is the interaction between the immune system and the intestinal microbiota. It is known that dysbiosis in Parkinson's disease affects the activation of immune cells and can contribute to the spread of pathology along the "gut-brain" axis. In this regard, immunomodulatory probiotics and specific bacterial metabolites are considered as a potential tool for preventing and slowing the progression of PD [8, p. 1470].

The issue of the staging of immunotherapy deserves special attention. The most significant results have been achieved in patients with early stages of diseases, when the pathological process has not yet led to massive loss of neurons. This emphasizes the need for early diagnosis and the search for reliable biomarkers that allow timely treatment. Modern research is actively conducted in the field of identifying biomarkers in cerebrospinal fluid, blood, and in the intestinal microbiota [9, p. 1469].

However, immunotherapy is associated with a number of difficulties. Firstly, there is a risk of excessive activation of the immune system, which can lead to the development of inflammatory complications. Secondly, not all antibodies have the ability to effectively overcome the blood-brain barrier, which limits their therapeutic potential. To solve this problem, new delivery technologies are being actively developed, including nanoparticles, liposomes and exosomes capable of transporting antibodies to brain structures [10, p. 217].

In addition, it remains controversial whether the removal of pathological proteins is directly related to clinical improvement. A number of studies have noted a significant reduction in amyloid load, but patients' cognitive functions continued to deteriorate. These data indicate the multicomponent nature of the pathogenesis of neurodegenerative diseases and the need for comprehensive approaches in which immunotherapy will be combined with cell therapy, gene correction, and the use of neuroprotective drugs [11, p. 650].

Despite the existing difficulties, the development of immunotherapy opens a new page in the treatment of Alzheimer's disease and Parkinson's disease. This approach allows us to influence not only the symptoms, but also the key pathogenetic mechanisms - the aggregation of pathological proteins, neuroinflammation and immune dysregulation. In the future, it is likely to use personalized schemes, including a combination of several immune drugs, adapted to the characteristics of a particular patient.

Thus, immunotherapy occupies one of the leading places among innovative areas of modern neuromedicine. Its success will largely depend on early diagnostics, precise selection of biomarkers and integration with other methods. If we manage to overcome the existing barriers, we can expect that in the coming decades, it is immunotherapeutic strategies that will become the basis for the treatment of neurodegenerative diseases.

Conclusion

Modern medicine is undergoing a period of rapid transformation, and neurodegenerative diseases - Alzheimer's disease and Parkinson's disease - are becoming one of the key areas of application of new technologies. If at the end of the 20th century the main emphasis was placed on symptomatic therapy, allowing for temporary relief of the manifestations of pathology, then in the 21st century attention is focused on the fundamental impact on pathogenesis.

Gene therapy makes it possible to correct mutations, restore the balance of protein synthesis, and even change the fate of cells, preventing their death. Cell therapy makes it possible to replenish lost neurons, maintain the functions of existing ones, and modulate inflammatory processes. Immunotherapy has proven that it is possible to influence pathological protein aggregates that have long been considered "untouchable" brain structures. Nanotechnology and delivery systems expand the capabilities of pharmacology, allowing to overcome the blood-brain barrier and minimize side effects. Personalized medicine based on genetic and biochemical profiles makes it possible to select a therapy that is maximally adapted to a specific patient.

Digitalization of medicine is becoming no less significant: machine learning and artificial intelligence are used to analyze medical images, predict disease progression, and optimize therapeutic strategies. Thus, a holistic ecosystem is being formed, where traditional pharmacology is integrated with cellular technologies, genetics, immunology, and bioinformatics.

Of course, the path to widespread adoption of these methods remains complex and fraught with risks, from immune complications to ethical issues around the use of stem cells. But the history of medicine shows that overcoming such challenges is what drives progress. Today, we are on the cusp of moving from the paradigm of "neurodegeneration is inevitable" to a model in which it can be slowed or even stopped.

In the coming decades, treatment strategies will likely be driven by combination approaches. A patient with early Alzheimer's disease could receive genetic therapy to correct predisposing factors, immunotherapy to reduce the amyloid load, and stem cell support to preserve cognitive function. Such an integrated approach

could change the prognosis for millions of people worldwide.

Thus, new therapies for Alzheimer's and Parkinson's disease are not just experimental strategies, but an emerging paradigm for the medicine of the future. Whether the 21st century will be the time of victory over neurodegenerative diseases depends on how quickly the scientific community will be able to overcome technological, clinical and social barriers.

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