In search of innovative therapeutics for neuropsychiatric disorders: The case of neurodegenerative diseases

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Cette revue a été écrite à la suite d'une séance thématique de l'Académie national de Pharmacie, tenue le 19 mars 2014 et intitulée « A la recherche de thérapeutiques novatrices pour les maladies du cerveau : le cas des pathologies neurodégénératives ».

Résumé

La littérature médico-scientifique récente a souligné l'absence de médicaments innovants pour les pathologies neurodégénératives comme la maladie de Parkinson ou d'Alzheimer. Or la forte prévalence de ces pathologies, revers de l'allongement de l'espérance de vie, entraîne un coût économique et social considérable. Malgré cela, les grandes firmes pharmaceutiques réduisent leurs activités de recherche en neuropharmacologie. Pourquoi la progression indiscutable des connaissances en neurosciences et sur la physiopathologie de ces maladies ne s'est pas traduite en innovations ?

Cette revue propose quelques explications sur l'origine possible de cette impasse et expose quelques solutions envisageables pour accélérer l'identification de médicaments innovants.

- Poursuivre l'effort des recherches fondamentales et cliniques mais avec une approche translationelle et réellement collaborative.
- Améliorer considérablement les études précliniques en construisant de meilleurs modèles animaux de ces pathologies, en introduisant l'emploi de nouveaux marqueurs et méthodologies donnant l'assurance que la molécule testée atteint bien sa cible et avec efficacité.
- Instaurer une nouvelle organisation de recherche renforçant les interactions entre recherche préclinique et clinique avec une ouverture transdisciplinaire, la mise en place de structures de recherche précompétitives dépassant le niveau national et associant équipes de recherche académiques à celles des start-up et des laboratoires pharmaceutiques.
- Renforcer l'ouverture de relations avec les autorités réglementaires dès le stade préclinique et surtout au moment du passage vers des études cliniques.
- Reconnaitre la place des associations de patients dans cette nouvelle organisation.

Ces nouvelles dispositions devraient assurer la découverte de médicaments efficaces pour lutter contre ces pathologies.

Mots clés: maladies neuropsychiatriques, développement préclinique et clinique, modèles animaux, collaboration précompétitive, organisation de recherche pharmaceutique .

Abstract

The recent medical literature highlights the lack of new drugs able to prevent or treat neurodegenerative diseases such as Alzheimer disease or Parkinson disease. Yet, the prevalence of these diseases is growing, related to increasing life expectancy, and is leading to a rise in their economic and social cost. At the same time, pharmaceutical companies are reducing or halting their investment in neuropharmacological research. Why have advances in basic neuroscience and our understanding of these diseases not allowed innovative discoveries in drug research?

This review will try to explain this failure and suggest possible solutions:

- Develop basic and clinical research but with the emphasis on translational and truly collaborative research.
- Improve preclinical studies by developing more appropriate animal models, using new biomarkers and methodologies such as imaging suitable for clinical trials, providing worthwhile information on the ability of the drug to reach its intended target and induce significant pharmacological changes.
- Build a new system of research management, based on stronger interdisciplinary relations between preclinical and clinical research and including the introduction of international precompetitive research between academic teams, start-up companies and pharmaceutical laboratories.
- Hold early discussions with the regulatory authorities during preclinical studies and at the beginning of clinical trials in order to validate the methodological approaches.
- Involve patients' associations in this new organization of research.

These changes should help to ensure the discovery of effective treatments for these pathologies.

Keywords: drug discovery, neuropsychiatric disorders, animal models, clinical research, précompétitive collaboration, medication development, research management.

A few years ago, in January 2008, a special session was held at the French Academy of Pharmacy to review perspectives on Alzheimer disease. A lecture was given by Frédéric Checler and Luc Buée [1] concerning new therapeutic avenues at the late preclinical stage and during clinical development of the disease. They emphasized strategies such as the inhibition of α-secretase or β-secretase in order to reduce the production of β-amyloid. These targets, as well as the reduction of Tau protein, were also highlighted in a set of reports [2-4] that had been published two years before in a commemorative tribute to the first anatomopathological report on this disease by Alois Alzheimer. Unfortunately, none of these drugs successfully completed phase III clinical studies [5,6]. This was not the first failure in a long list of drugs developed to slow down the course of the disease. However, these failures must be seen in light of the fact that "*studies of solanezumab for Alzheimer's disease have shown that there is a 36% rate of false diagnosis of Alzheimer's disease in clinical trials that were made in expert centers but based only on clinical criteria*" [7] .

A quite similar situation arose in the case of another major neurodegenerative pathology, namely Parkinson disease. For this disease, a symptomatic strategy consists in correcting the behavioral disturbances caused by the degeneration of nigral dopaminergic neurons ending in the associative and motor striatal territories. This was first achieved using DOPAtherapy, which remains the gold standard treatment, and is only mildly challenged by the use of dopaminergic agonists. Indeed, dyskinesia, one of the main undesirable adverse effects of DOPA therapy, is only moderately reduced by using dopaminergic agonists. Moreover, some behavioral effects, such as excessive gambling [8], are also observed with the use of dopaminergic agonists. Another strategy, the use of neuroprotective agents in Parkinson's disease, also remains unsuccessful.

The development of new pharmacological treatments remains a major difficulty, whatever the brain pathology, acute or chronic. A recent report [9] for brain injuries such as stroke states that "*In the past 10–15 years, dozens of clinical trials for stroke neuroprotection – involving thousands of patients – have failed*". A similar issue has arisen in the case of translational studies in neuropsychiatric pathologies. For example, a large, comparative, multicenter clinical study, including 1432 patients treated either by perphenazine, olanzapine, quetiapine, risperidone, or ziprasidone, led to the conclusion that medication with perphenazine, a first generation antipsychotic, or olanzapine, a second generation medication or "atypical" antipsychotic, did not bring significant improvement, whereas the patients treated with the other drugs discontinued their treatment, a consequence of an insufficient efficacy/tolerance ratio [10]. As reviewed by Alison Abbott [11], such results provoked shock wave when the codes used to mask the

name of the drugs were broken: "*that was frustrating and humbling for the research community*".

In view of these failures, one might have expected pharmaceutical companies to start expanding their preclinical neuroscience research facilities. Yet, as emphasized in the literature [9,11,12], virtually all the major companies have recently withdrawn from neurosciences, a choice explained by the pressure to rein in costs coupled with the lack of any return on investment in these fields. However, the incidence of neurodegenerative pathologies is rising, largely related to the increasingly longer life expectancy. Consequently, the economic cost is increasingly heavy, with "*a greater socio-economic burden than cancer, cardio-vascular diseases and diabetes combined*" ([9, see 13-15 for more detailed reports]. Moreover, as a rough estimate, the majority of patients suffering from these diseases are in developed countries, offering a creditworthiness contrasting with the situation for some tropical diseases such as malaria. On the other hand, it is commonly assumed, in the case of blockbuster drugs, that prolonged treatment in large populations of patients offers the prospect not only of large profits, but also of an increased risk of adverse events, leading to judicial inquiries. In line with this, pharmaceutical companies are aware that drugs targeting the main neuropsychiatric disorders are exposed to scientific, clinical and commercial risk. They are now turning to orphan diseases such as amyotrophic lateral sclerosis instead of Alzheimer or Parkinson disease [16].

It is most certainly frustrating to compare present times with the situation that existed in the early 1960s and the advent of psychopharmacology. At that time a new era was beginning, with the introduction in therapeutics of the first antipsychotic agent, the first anxiolytic agent, the first antidepressants, such as IMAO and tricyclic agents, and dopatherapy. Then, it was presumed that advances in genetics, physiology and neurochemistry of the brain, neuropathology and the identification of neurotransmitters and their receptors would lead to more efficient, more selective and safer drugs. But, as reported by Abbott [11], "*fifteen years ago, we were naively optimistic".*

Some fifty years ago, no one was in doubt that neurosciences could attain a very high level of knowledge of how the brain functions and how it is altered in the disease state. Yet, this better knowledge of cerebral development, physiology and behavior also tells us that the brain is far more complex than we realized. The same paradox holds true for our understanding of neuropsychiatric disorders.

Why is innovation so difficult in the area of neuropsychiatric disorders?

At first glance, it would seem that innovation should focus on the prevention and

progression of diseases. Yet, the management of acquired symptoms also needs to be substantially improved, while avoiding adverse effects. A less ambitious goal is to treat only a part of the symptoms in order to give patients a better quality of life. For instance, it is well established that the occurrence of falls, related to gait disorders and postural instability, is frequent in the elderly population and is commonly observed in parkinsonism. This symptom is not related to the dopaminergic lesion but to the loss of cholinergic neurons within the pedunculopontine nucleus, a part of the mesencephalic locomotor region [17]. Thus, this provides a rationale for the prevention of falls.

In order to develop new therapeutic approaches for neuropsychiatric disorders, several features of the diseases should be taken into account, making innovation very complex.

- Neurodegenerative diseases often occur in the elderly population.
- Their etiology is related to a wide range of factors, including genetic, developmental and environmental factors, which vary in weight and are variable in each patient and according to his/her own history.
- Cerebral development during the prenatal period is a complex sequence of events, including neurogenesis and migration of neurons, alteration of which might influence the subsequent development of neurological disorders [18,19].
- Some neurodegenerative disorders are associated with a failure in the migration of inhibitory interneurons to the cerebral cortex [19] or to the striatum. This might be the case, for instance, in the development of Tourette syndrome [20]. Such a defect of the migration of GABAergic neurons to the cerebral cortex, inducing an impaired excitatory/inhibitory balance, might be involved in various other neuropsychiatric disorders [19]. Cerebral development also involves a variation of the ionic intra/extracellular balance, which could also be altered. In line with this, it is also important to stress that changes in the ionic homeostasis of chloride occur before and after birth [21]. Interestingly, cortical or subcortical failure [21] could remain asymptomatic, or could lead to the expression of pathological symptoms with an onset delayed by several years, from birth to the end of the cerebral development during adolescence or as a consequence of environmental or psychosocial triggers. Thus, another important issue is to identify these factors with the aim of prevent the occurrence of disease in at-risk individuals. In line with this, several reports strongly suggest that the use of cannabis might trigger schizophrenia in some individuals [22-24].
- There is general agreement that a delay occurs between the onset of the degenerative process and the first expression of the clinical symptoms. Several

hypotheses might explain this latency. First, individuals each have physical and cognitive abilities that allow them to maintain their performances close to the normal level through a sort of buffering effect. Second, many biological systems allow the deficit due to the first steps of the degenerative process to be compensated for. Interventions of dopaminergic, serotoninergic and glutamatergic mechanisms have been described in Parkinson disease, in which the symptoms appear a mean 5 to 6 years after the onset of the disease [25-27].

- Among the neurodegenerative diseases, Huntington disease is an exemplary textbook case that illustrates the difficulties in understanding the pathological mechanisms [28]. The relationship between the pathological process and a mutation in a single gene is obvious: the mutation corresponds to an expanded number of CAG repeats in the huntingtin gene, which codes for polyglutamine in the protein. Expression of the symptoms starts after a long delay depending on the number of CAG repeats. Consequently, detection of this genetic feature makes it possible to determine the mean delay to disease onset. However, in spite of these favorable characteristics, there is no treatment able to prevent or slow the expression of this disease.

This example with a monogenic disease due to a single mutation, demonstrates why it is so difficult to develop an effective therapy to prevent the onset or the first stages of a degenerative process characterized by complex interactions between genetic, epigenetic and environmental factors. Indeed, several issues remain unresolved. First, how will it be possible to detect the presence of such developmental alterations, in order to identify the population at a high risk of developing such disease? Second, how can the onset of the degenerative process be detected? Before these difficulties can be resolved, a few requirements will need to be taken into account [29]:

- The need for biological markers is a major priority, not only to obtain an early and accurate diagnosis but also to assess the therapeutic efficacy and side effects of neuroprotective drugs. Recent reports emphasize the progress made in the identification of biomarkers, for instance for Alzheimer disease [30 and especially 31, a detailed contribution by the International Working Group and the US National Institute on Aging–Alzheimer's Association], but the jury is still out on identification of the best biomarkers in the cerebrospinal fluid (amyloid level or, more convincingly, Tau and phosphorylated Tau levels). In addition, the analytical procedures need to be standardized and harmonized [32-34]. Importantly, such biomarkers should be first characterized in experimental models used in preclinical studies aimed at validating targets for neuroprotection. Some of these measurements are coupled with PET scan or MRI imaging, an option that is

interesting for research purposes but appears to be widely debatable as a diagnostic tool, due to the high cost of these tests and the great number of patients who would need to be analyzed. Furthermore, the benefit of early diagnosis is still debatable in the absence of neuroprotective treatments.

- Another way of achieving an early diagnosis is to detect the first clinical changes that are predictors of the main symptoms. Such a concept is especially relevant for Parkinson's disease. Indeed, non-motor symptoms, such as olfactory dysfunction, dysautonomia and mood and sleep disorders, occur years before the expression of akinesia, rigidity and tremor, the triad of parkinsonian motor symptoms [35,36].

- Ideally, the best animal models should allow such symptoms to develop. This is the case with primate models of Parkinson disease, in which difficulties in initiation and in choice of motor program can be detected very early in the course of the disease [37]. Similarly, sleep disorders develop in MPTP-intoxicated monkeys before the occurrence of any motor symptoms [38,39].

Symptom improvement remains difficult since it is now clear that the main ones, for example the motor symptoms in Parkinson disease, are accompanied by a wide range of non-motor disorders, such as depression, apathy, dysautonomia and sleep disorders, that also need to be alleviated. Many of these disorders result in major disability and affect quality of life [36]. Furthermore, some of them, such as hypomania, impulse control disorders and gambling, are even related to the dopaminergic therapy itself.

Thus, there are many difficulties that could account for the lack of effective treatments for neurological disorders. Nevertheless, there are strong ethical, social and medical arguments against pharmaceutical companies withdrawing from this field. Indeed, a clear analysis of these difficulties should lead to a search to identify new strategies and organizations willing to sustain innovative research.

What are the solutions to develop new drugs for neuropsychiatric disorders?

Several review articles, cited in the introduction, emphasize the need to develop better therapies but also contain proposals for solving this issue [9,11,12 see also 40-42]. First, all of them advocate a reinforcement of preclinical research. Second, they point to the limitations of the animal models currently used and suggest they should be improved. Third, they emphasize the need to develop new ideas and new organizations for research on drug development in a context marked by a withdrawal of many pharmaceutical firms from the field of neurosciences.

More and more basic research but with a translational trend

Research has to move from serendipity or accidental discovery to new, evidence-based models. But, as reported by Abbott [11], "*We'd been tuning the engine, when what we really needed was a new engine"*, introducing the idea of applying new strategies whilst withdrawing from the replication and implementation of known mechanisms [40]. This implies setting other targets than those previously chosen, such as moving from the too simple receptor-ligand interaction towards a more subtle action on the different allosteric sites present on receptors coupled to ion channels as well as metabotropic receptors coupled with G-protein, taking into account their various isoforms [43]. It is well known that the nervous system uses many neuropeptides, frequently colocalized with classical neurotransmitters within the synaptic vesicles. Nevertheless, the title given by Leslie Iversen to a short survey, "*Neuropeptides: promise unfulfilled?"* published in 1993 [44], remains valid at least regarding the therapeutic applications.

These needs also increased attempts to develop translational research between basic research and the clinical field. It is really important to fill the gap between medical reality and some current biomedical research that has "*few points of interaction with real medical problems*" [45]. This opinion should not be misconstrued as indicating opposition to experimental studies on animals, since the author voiced a vigorous plea for physiological studies in intact normal animals in order to understand the complexity of the whole body and to acquire knowledge on functional capacities. Nutt and Attridge [42] wrote that there is a need to look "*outside the box*". As a matter of fact, this is a current issue in basic as well as applied research. Innovation arises from a cross-cultural trade-off between researchers at the most basic research level and clinicians, a difficult challenge but one that must necessarily be met. Then "*molecular biology researchers have gone full circle from genotype to phenotype knock-out and knock-in animals of neurological disorders and evaluating in animal central nervous system models*" [41]. This open-minded attitude helps to track down new drugs resulting from advances in neurosciences as well as drugs otherwise used in other branches of medicine [42].

Such a strategy is nicely illustrated by an example arising from the psychiatric field. In autism, it was noticed that babies expressing the first signs of the disease maintained the prenatal type of chloride distribution, resulting in an intracellular excess of chloride. In the normal condition, at birth, the oxytocin surge prompts an inversion of this ratio, allowing GABA receptors linked to chloride ionic channels to play their usual inhibitory function. The administration of bumetamide, a diuretic antagonist of a chloride cotransporter, to babies with an early expression of autism restored the normal extra/intracellular ratio of chloride and alleviated the symptoms [46-49].

The successes of this collaborative study demonstrate how open collaboration between basic scientists and clinicians can be fruitful, leading to innovative therapies with an old drug.

Solutions to improve animals models of neuropsychiatric disorders

Preclinical studies are a prerequisite in translational research in order to allow the most reliable testing of new drugs before their use in clinical trials. They help to avoid two major pitfalls: a lack of clinical efficacy and the occurrence of unacceptable adverse effects, including toxicological issues [for examples, see 50]. Yet, the reliability of experimental models needs to be greatly improved as "*too many compounds that seem to treat a disease in animals end up having little impact in humans*" [12]. Based on the results of animal studies, too many drugs have been introduced too quickly, a really costly and unethical mistake leading to unsuccessful clinical trials. A greater likelihood of success could be achieved with a stricter observance of the fundamental principles of preclinical studies, named the three pillars: drug exposure at the target site, target occupancy and functional modulation of the target [51]. Nevertheless, in the case of drugs intended to act on the central nervous system, it can be difficult to identify the target (or targets), due to a limited understanding of the disease [52]. In addition, there are some basic explanations for the failures that have occurred:

- The specificity of the brain, and, more specifically, the blood–brain barrier, which strongly limits the access of the drugs to the nervous system. Hence, *in vitro* trials cannot be reliably predictive of efficacy in the clinical setting. An additional difficulty arises as drugs cross the blood–brain barrier more easily in rodents than in primates [53];
- The neurodegenerative diseases are associated with ageing, whereas the classical tests are conducted on quite young rodents;
- Pharmacological tests are performed on normal animals and do not account for possible changes in reactivity or in pharmacokinetics induced by the disease [50].
- There are some interactions between hormonal impregnation and brain activities, but the animals used are almost exclusively male.

Generally speaking, it is not easy to obtain animal models of neuropsychiatric disorders and more especially of neurodegenerative diseases [54]. For instance, the characterization of cognitive and emotional/motivational impairments, such as those observed in many neurodegenerative diseases, is very difficult to identify and measure in rodents. However, such symptoms can more easily be modeled in non-human primates [37,55-58]. As quoted by McLeod [59], the use of suitable animal models should be

improved whereas new models have to be developed. The general criteria for validating animal models, as stated by Willner [60], namely predictive, face and construct validity, remain valid. The limitations of animal models have been discussed within the American College of Neuropsychopharmacology. A review [50] reports the main conclusions of the discussions and the proposals that were made to improve these models. Even though they were made some years ago, these conclusions and proposals remain valid today. It was recognized that "*the use of whole animal models is an integral part of CNS drug discovery*". The authors emphasized the need for preclinical and clinical measures to be "*as closely as possible homologous*" in a translational effort. This is especially relevant in Alzheimer disease models. In a recent review on this topic [61], the authors list three categories of reasons that could account for the failure of these models in the translation of preclinical results to patients:

- The models are based on an incorrect hypothesis, and do not reflect the clinical disease in humans;
- The model investigates a relevant target, but which has a different reactivity in humans versus animals, or differences in drug pharmacokinetics impede it in reaching its target or in reaching its target at the appropriate concentration (see, for example, a comment and a report on the failure of a clinical trial of a neuroprotective drug in progressive supranuclear palsy [62,63];
- The clinical trial has an inappropriate design, particularly with regard to the dose or administration regimen, the duration of treatment before the endpoint evaluation and the criteria used to determine the endpoints.

One common criticism relates to the need to improve the predictive value of animal tests, for example by using similar motor and behavioral scales and similar biomarkers in both the preclinical and clinical trials [50]. Moreover, such tests should enable treatment efficacy to be monitored, especially in the case of a neuroprotective drug. The use of brain imaging methods offers interesting possibilities in preclinical studies and sound comparison with clinical tests [42,64,65]. The following are particularly suitable in research on brain diseases:

- Magnetic resonance imaging (MRI), which could be combined with magnetic resonance spectroscopy providing information on tissue bioenergetics. Both these techniques allow longitudinal studies on the effect of a treatment. MRI devices have been designed for rodents, allowing comparison with human MRI studies.

- Positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) provide accurate data on the distribution of the labeled drug to the different cerebral structures, and provide information on occupancy of receptor

sites [65]. Special devices are needed to perform such studies on rodents owing to the spatial resolution of around 1 to 2.5 mm, an irreducible physical parameter.

The acquisition of imaging data, especially those obtained with PET, is expensive, but provides data that are reliable enough to go on with a new molecule of interest on the basis of the accessibility and activity on the aimed target. Furthermore, the expense involved will be far less than the losses that would be incurred if a clinical trial were launched on an erroneous assumption. The situation in France is that pharmaceutical companies can have access to publicly funded research facilities and platforms dedicated to the use of imaging in animal models, mainly investigating neurodegenerative diseases.

It is reasonable to expect that the improvement of animal models, better identification of targets and use of biomarkers and new methodologies, such as imaging, will enable sound preclinical trials to be performed.

Towards a new organization of drug research

There are many reasons why pharmaceutical companies have left the field of the neurosciences [see16,42]. This withdrawal from research leaves the door open "*to rethink how academia and industry can work together for the public good"* [12]. In fact, the gap between academic researchers and pharmaceutical industries has appeared progressively over time for many reasons, including, first, the large growth of academic research institutions, and their ability to perform their research in-house. This has led to a change in their relationship with pharmaceutical companies [66].

Innovative research needs to build on new ways of collaboration between the different partners: academic basic scientists and clinicians involved in clinical research, start-up companies in biotechnology, frequently interfaced with academic structures, pharmaceutical industries and also patient lay organizations.

The distance between basic science and clinical research has long been a key issue in translational research for neuropsychiatric disorders. Leaders of academic research have consequently been trying to bridge the gap between basic and applied research, especially in the clinical field. Some years ago, a first step was taken with the creation of clinical units dedicated to clinical pharmacology or translational medicine, called centers of clinical investigation. These centers allow access to patients for therapeutic trials. In these centers it is possible to run "*small-scale carefully monitored studies*" in a "*learn and confirm approach*" in contrast to the larger and more expensive clinical trials [66]. In France, these "Centers for Clinical Investigation (CIC)" allow clinical trials to be performed using academic funding in collaboration with pharmaceutical companies. More specialized research institutes in the neurosciences are localized within

university hospitals, such as the ICM (Brain and Spinal Institute) located at the Pitié-Salpêtrière Hospital in Paris, which enables preclinical, clinical and industry research to be performed in one place, and gives companies the opportunity to work in a biotech incubator located in the Institute. The general scientific and clinical goal is to bridge the gap between basic scientists and clinical researchers and to mobilize all the various partners to work on the identified scientific projects.

Another illustration of the work undertaken to improve the effectiveness of drug research in France is the creation of AVIESAN (Alliance nationale pour les Sciences de la Vie et de la Santé). This umbrella structure was founded in 2009 with the aim of developing synergies between all the research organizations involved in the fields of biology, life sciences and health [67]. The AVIESAN alliance is composed of ten thematic institutes, including one that concentrates on neurosciences, cognitive sciences, neurology and psychiatry [68]. A few years ago it was hard to imagine that researchers in these fields would agree to cooperate and work together. Now, these institutes are promoting better coordination between programs, expanding transdisciplinary and translational research with a trend towards clinical applications and making it easier to develop industrial and European partnerships.

There is another way of inducing new relationships, namely precompetitive collaboration between academic research and industry research, where "*competitors share early stages of research that benefit all*" [69]. This new concept relies on a public-private partnership and can be defined as "*open collaborations between companies that usually are intellectual property competitors*" [70]. There is evidence that fundamental biological research leads to an exponential accumulation of data whereas "*the barriers to information sharing have never been lower* "[69]. In line with this, the general purpose of precompetitive collaboration is to reach the following goals: (1) facilitate data sharing, with development of mutual standards[71]; (2) enable high throughput of new data, using new biological technologies in genomics and proteomics; (3) improve the discovery of biomarkers and models of disease by the accumulation of shared knowledge; (4) promote product development [72,73]. It is assumed that breakthrough therapies will arise from the integration of knowledge and expertise from multiple sources [74]. A first precompetitive collaboration was reported with the announcement of collaboration between Astra Zeneca and the Naomi Berrie Diabetes Center at Columbia University Medical Center [75]. As with the other major pharmaceutical groups, the first motivation was to develop institutional relationships instead of the personal relationships between academics and industrialists that often encountered in the past. In Europe, such precompetitive collaboration is being initiated with the Innovative Medicine Initiative (IMI) Joint

Undertaking (IMI JU) launched in 2007, under the patronage of the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) in order to boost the discovery and development of new and safer drugs. Two projects are related to neuropsychiatric diseases, grouping together a large set of multidisciplinary expertise using coherent evaluation in their approaches: (1) *"Novel methods leading to new medications in depression and schizophrenia"* has provided a big database for therapeutic research in psychiatry; (2) the IMI PharmaCog project [76] is devoted to Alzheimer disease with a focus on *"Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development"*. This program includes new approaches to evaluate treatment efficacy, with identification of markers based on imaging, cognitive, electrophysiological and biochemical approaches, usable in animals as well as in patients, and able to predict the dose range and efficacy of new molecules in order to define the priorities, as comprehensively detailed in a recently published report [77].

Precompetitive collaboration also has to take into account difficulties related to cultural shortcomings in the personality of academic researchers and industrial researchers [74]. The question of intellectual property can be seen as a critical issue with divergent interests between confidentiality and fast publication [66,69,70,74]. This is reported as a limitation on precompetitive collaboration [70], but there have been some positive proposals on this subject [73]. Another issue is related to the multiple sources of financial support, often originating from both public and private sources, and the subsequent sharing of intellectual property. Yet, consortia agreements can easily resolve this issue. The management of communication and data exchange also requires constant attention due to the large number of organizations involved: for example, in PharmaCog, there are 12 academic partners, 12 large pharmaceutical groups, 5 small and medium-sized firms, and 1 patients' association (Alzheimer Europe), with, in addition, the active presence of the European Medicines Agency [73,77].

Another topic of importance is the relationship between the different partners involved in drug research and the regulatory authorities, such as the EMA in Europe [78], and the Food and Drug Administration (FDA) in the United States. Their guidelines and scientific advice result, at least in their initial versions, from bilateral discussions between representatives of pharmaceutical companies and public authorities. It is beyond the scope of this review to give a detailed description and to assess how regulatory authorities could boost research on innovative drugs. A discussion on some of the methodological features is more relevant. For example, a group of scientific advisors validate new endpoints to be used in clinical trial evaluation in Alzheimer disease: for example,

determination and follow-up of hippocampal size through anatomical MRI, PET imaging of amyloid deposit and determination of β amyloid and tau protein in cerebrospinal fluid. Standardization of these markers will then enable their use in preclinical and clinical trials [see 78 and follow > Human regulatory > Scientific advice and protocol assistance > Qualification of novel methodologies for medicine development], Similar observations could be made regarding the multidisciplinary guidelines due to the International Conference on Harmonisation (ICH) of scientific and technical requirements for registration of pharmaceuticals for Human use [79]. ICH bring together the regulatory authorities and pharmaceutical industry in Europe, Japan and USA. Among the ICH contributions, some guidelines, like M3, are related to preclinical safety studies. Finally, these dialogues increase the intelligibility of the problem, validate the proposals of researchers for new methodologies, and allow sounder choices to be made when moving from preclinical to clinical studies.

Another partner should not be neglected in the long road towards the development of innovative therapeutics, namely the patients' associations. There are numerous philanthropic foundations, such as The Michael J. Fox Foundation for Parkinson's Research [80], and patients' associations, such as Association France Parkinson and Association France Alzheimer. The latter two and other associations dedicated to brain diseases have together created an umbrella organization named "Federation pour la Recherche sur le Cerveau" [81]. Initially, their activity was directed at supporting and informing patients and their families, collecting information about undesirable side effects from a pharmacovigilance standpoint and raising public awareness of neuropsychiatric diseases. However, patients' organizations have gradually become partners in research activities: (1) funding of research projects and grants to young investigators, a system offering considerable flexibility; (2) more recently they have become active players within research organizations, such as PharmaCog, submitting patients' claims and also urging the public administration to promote research on these diseases. Moreover, their advocacy can be helpful in the process of recruiting selected cohorts of patients for clinical studies. This interface even extends to brain donation for research purposes through a special organization: Neuroceb [82], aimed at collecting brains for a brain bank and partly financed by Association France Parkinson, ARSEP and Association France Alzheimer. This unique organization can be used for anatomopathological research and to better understand the pathophysiology of neurodegenerative disorders.

Some of the topics discussed in this review such as redefining the target, translational research, utility of a brain bank and use of suitable animal models, are of utmost importance for the identification of new targets for neuroprotection, especially in

the field of Alzheimer disease. Until now, the “amyloid hypothesis” was seen as the main clue to explain the development of the disease. A toxic effect was attributed to the accumulation of β amyloid protein. At the same time, others have pointed to the accumulation of paired microtubule-associated protein tau, which might also be related to the neurodegenerative process. As this anatomopathological stigma was also observed in other neurodegenerative diseases, the concept of tauopathies was introduced. However, the β amyloid protein remained the target and much research, using various biological possibilities, was consequently directed at preventing the production and accumulation of this peptide in order to reduce the amyloid-related damage. Only recently, the “amyloid hypothesis” was strongly questioned in a report concluding that accumulation of β-amyloid is a consequence and not the cause of the neuronal lesion [83]. Thus, tau protein appears as another interesting target with some interesting features: (1) the expression of IP3 kinase is increased in the brain of patients suffering from Alzheimer disease, a change correlated with hyperphosphorylation of tau protein [84]; (2) the interaction of a protein FKBP52 belonging to the immunophilin family with abnormal tau induces the formation of oligomers evolving into a fibrillar structure [85]; (3) the topographical progression of lesions and of neurofibrillary deposit localized using an immunoreaction for hyperphosphorylated tau protein follows a predictable sequence, roughly from subcortical nuclei close to the brainstem towards neocortical areas [86,87]; (4) convergent results [88, 89], conclude in favor of a propagation, in a prion-like manner, of pathogenic tau protein in Alzheimer disease. Similar mechanisms might be involved in α-synuclein pathology in Parkinson’s disease [90].

These studies on neurodegenerative disorders illustrate how translational research can influence clinical trials and identification of targets for neuroprotection.

Now, a new era in drug research is beginning. First, preclinical studies need to improve in terms of the animal models used and their predictive values, with the use of markers that will be suitable in animals as well in patients. Second, a major shift in approach is now apparent with an undeniable trend towards translational research. Third, the development of new methods of coordinating research is leading to greater integration of all researchers, including both basic scientists and clinicians. All these developments are clear evidence that the distant and sometimes suspicious [66], relationships that used to exist between researchers, pharmaceutical companies and clinicians have largely called into question and are being replaced by a new model allowing stronger integration between all partners. All these factors give cause for optimism and bode well for the future of CNS drug discovery.

Disclosure of interest : The authors declare they have no conflict of interest concerning this article.

The research leading to these results has received funding from the program "Investissements d'avenir" ANR-10- IAIHU-06.

Acknowledgments :

The authors thank the following colleagues who gave stimulating and comprehensive lectures during the meeting held on 19 march 2014 at the French Académie nationale de Pharmacie, which nicely contributed to some ideas expressed in this Review.

- Pr J-C.Corvol , *Director of the Clinical Investigations at the Center of Brain and Spinal Chord, Pitié-Salpêtrière University Hospital, Paris*
- Dr E. Bézard, *Research Director, INSERM, Neurodegenerative Diseases Institute, CNRS UMR 5293, Bordeaux University, Bordeaux*
- Pr O. Blin, *Clinical Pharmacology Director, Clinical Investigations Center, La Timone University Hospital, Marseille*
- Dr Y. Ben Ari, *Founder and Emeritus Director of INMED, INSERM Emeritus DRCE, and CEO of Neurochlore*
- J-M Laurent, *President of the French Federation for Brain Research, Vice-President of France-Parkinson*

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