CNRS patent portfolio related to Central Nervous System Disorders
Patents list for licensing opportunities

- **I/ Alzheimer & Parkinson’s Diseases**
  1 « Selective mGluR4 agonists for use in the treatment of neurodegenerative diseases »
  Ref: 00262-01
  2 « New heterocycle derivatives with neurotrophic properties »
  Ref: 02056-01
  3 **UPCOMING TECHNOLOGY** « Novel DYRK1A inhibitors for the treatment of Cognitive impairment in Alzheimer’s Disease »
  Ref: 05433-01
  4 « Pyrido[3,2-d]pyrimidine derivatives inhibitors of CDK1, CDK5, GSK3 et/ou DYRK1A and their use in the treatment of cognitive impairment »
  Ref: 02882-01
  5 « sPRR as dual biomarker of neurodegeneration and neuroregeneration »
  Ref: 04907-01
  6 « New cellular and animal model of Parkinson’s disease »
  Ref: 05155-01

- **II/ Psychiatric Disorders**
  1 « Use of Spadin for the diagnostic and therapeutic monitoring of depression »
  Ref: 01424-06
  2 « Selective mGluR4 agonists for use in the treatment of schizophrenia or anxiety »
  Ref: 00262-01
  3 « A human TREK-1/HEK cell line: a highly efficient screening tool for drug development in neurological diseases »
  Ref: 05287-01

- **III/ Prion Diseases**
  1 « Anti-prion drugs and screening methods »
  Ref: 63027
  2 « Highly sensitive prion blood detection test »
  Ref: 00425-01

- **IV/ Pain**
  1 « Selective mGluR4 agonists for use in the treatment of pain »
  Ref: 00262-01
2 « Novel antagonist toxins of T-type calcium channels and use in Analgesia »
Ref: 01839-01

3 « New target for Pain Treatment, and New tools for the Research on Endogenous Morphine »
Ref: 04170-01

- **V/ Addiction**
1 « Use of Simvastatin or derivatives in the Treatment of Cocaine Addiction »
Ref: 03377-01

2 « Opioids Addiction Prevention and Treatment, and tools to study endogenous morphine »
Ref: 04170-01

- **VI/ Orphan diseases**
1 « Use of a BKCa opener as a treatment of Fragile X-Syndrome and KCNMA-1 related autism»
Ref: 04388-01

2 « New therapeutic peptide for Huntington’s Disease »
Ref: 04195-01

3 « New Treatment of Cognitive Impairment in Down Syndrom »
Ref: 02833-01

4 « Use of Guanabenz Derivatives for the Treatment of Huntington’s disease »
Ref: 86877-07

5 « Novel DYRK1A inhibitors for the treatment of cognitive impairment in Down Syndrome »
Ref: 5433-01

6 « Use of Calcium Channel Blockers for the Treatment of Spinal Muscular Atrophy »
Ref: 04678-01

7 « Ion channels Macroarray for Autoantibodies Detection in LCR »
Ref: 04731-01

- **VII/ Medtech**
1 « Method for Real Time Monitoring of Patients to Predict Epileptic Seizures »
Ref: 84506-02

2 « Non-Invasive System for the Detection of Electrophysiological Neuronal Activity »
Ref: 00062-01

3 « Novel Device for Focal Extracellular Electrical Stimulation of the CNS »
Ref: 01131-01

4 « Protein macroarrays for detection of autoantibodies towards ion channels in CNS »
Ref: 04731-01
New tools to investigate Hemispheric Specialization » Ref: 04724-02
I/ Alzheimer & Parkinson’s Diseases

Selective orthosteric mGluR4 agonists for use in the treatment of neurodegenerative diseases

CONTEXT

The role of metabotropic Glutamate receptors (mGluRs) is mostly to modulate the glutamatergic synaptic transmission in comparison to ionotropic glutamate receptors (iGluRs) which play an essential role. As such they allow a fine tuning which is required in CNS disorder treatments.

Recently, several allosteric modulators (AM) have been discovered, mainly mGlu4R Positive AMs. They were shown to be neuroprotective and to provide beneficial effects in animal models of Parkinson’s disease, pain and anxiety.

TECHNICAL DESCRIPTION

The patents cover series of metabotropic glutamate receptor agonists. These compounds activate selectively subtype receptors of group III (mGlu4R, mGlu6R, mGlu7R, mGlu8R). Among them, 3 compounds have been selected so far:
- LSP1-2111 that preferentially activates mGlu4 receptor in comparison to mGlu7R and mGlu8R
- LSP4-2022 that is highly potent at mGlu4 and selective towards mGlu8
- LSP1-3081 that activates preferentially both mGlu4 R and mGlu8R than mGlu7R

DEVELOPMENT STAGE

The in vitro pharmacology, pharmacokinetics and CNS disposition of LSP1-2111, as well as in vitro brain electrophysiology studies are available. Our data show a fairly rapid clearance with little metabolization as expected with polar compounds. In vivo LSP1-2111 also exhibited systemic activity in animal models of Parkinson’s disease and anxiety. LSP4-2022 exhibited remarkable antihyperalgesic effect of in neuropathic or inflammatory pain models.

PUBLICATIONS

- Metabotropic glutamate receptor subtype 4 selectively modulates both glutamate and GABA transmission in the striatum: implications for Parkinson’s disease treatment.

Our Reference
00262-01 to 05

Keywords
Hypophosphorous acid; metabotropic glutamate receptors; brain disorders; agonist; antagonist

Patents
#1: WO 2007052169 published on May 10, 2007
#3: WO2012156931 published on November 22nd, 2012

Commercial Status
Exclusive or non-exclusive licenses

Laboratory
Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, a CNRS and University Paris Descartes laboratory (UMR 8601), in Paris, France.

http://www.biomedical.univ-paris5.fr/umr8601/

- Metabotropic glutamate receptor 4 novel agonist LSP1-2111 with anxiolytic, but not antidepressant-like activity, mediated by serotonergic and GABAergic systems.
  Wierońska et al. Neuropharmacology. 2010 Dec;59(7-8):627-34.
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  Goudet et al. FASEB J. 2012 Apr;26(4):1682-93
- Role of mGluR4 in acquisition of fear learning and memory.
- Group III and subtype 4 metabotropic glutamate receptor agonists: Discovery and pathophysiological applications in Parkinson's disease.
  Amalric et al. Neuropharmacology. 2012 Jun 1
**New Heterocycle Derivatives with Neurotrophic properties**

**CONTEXT**

Neurotrophic factors have been shown to possess strong neuroprotective and neuroregenerative properties in neurodegenerative diseases. However, their clinical use is limited because of their inability to cross the blood brain barrier, and their delivery into the lesioned areas of the brain by surgery is linked to undesirable side effects. Neurotrophin-like small molecules could provide an interesting therapeutic alternative avoiding neurotrophin administration and its side effects.

**TECHNICAL DESCRIPTION**

In an attempt to develop drugs mimicking endogenous neurotrophic factors formed by hybridation of natural compounds, the inventors have designed and synthesized three series of new heterocycle derivatives: quinoline, quinoxaline and tryptamine series. A cell-based screening of this low molecular weight and easy to synthesize compound collection led to the characterization of compounds exhibiting **neuroprotective and neuritogenic properties in the nanomolar range** on mesencephalic dopaminergic (DA) neuron primary cultures in spontaneous or MPP⁺⁺-induced neurodegeneration. A lead compound was identified in each series:

The most potent neurotrophic compounds are easy to synthesize, do not present any cytotoxicity at the CI5 of 10 nM and do not show toxicity in mice on a chronic treatment at 300 mg/kg/day (for 15 days) when administered per os or intra-peritoneal. They present physical-chemical properties compatible for penetration of the BBB, and this was demonstrated by ex vivo HPLC/MS analyses. They present a very promising profile for the first curative treatment of neurodegenerative diseases such as Parkinson disease, and significant results of in vivo studies performed on 6-OHDA lesioned rats and MPTP intoxicated mice will soon be released.

**DEVELOPMENT STAGE**

These new derivatives are currently studied to be used alone or in association with known drugs for the treatment of **Alzheimer disease, Parkinson disease, Multiple Sclerosis or Stroke**. In vivo studies are currently being performed on 6-OHDA lesioned rats and MPTP intoxicated mice, two of the most pertinent animal models of Parkinson disease. This work has received the financial support of the programme "Emergence of high potential products or services" of the Agence Nationale pour la Recherche.

**PUBLICATIONS**

Tryptamine-derived alkaloids from Annonaceae exerting neurotrophin-like properties on primary dopaminergic neurons.

**Our Reference**

N° 02056

**Keywords**

CNS ; neurodegenerative; quinoline; tryptamine; quinoxaline

**Status of Patent**
- Priority patent application FR0854921 filed on 07/07/2008 entitled "Dérivés hétérocycliques utiles dans le traitement des maladies neurodégénératives" WO2010007179 published in 01/21/2010, extension in USA, EP, JP, CA and CN
- Priority patent application n° FR0951303 filed on March 2, 2009 entitled "Dérivés indoliques pour le traitement de maladies neurodégénératives" WO20100100133 published in 09/10/2010, extension in USA, EP, JP, CA and CN
- Priority patent application n° FR1152645 filed on March 30, 2011 entitled "Dérivés amino-quinoxalines pour le traitement de maladies neurodégénératives"

**Inventors**

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**Commercial Status**

Collaborative agreement, Exclusive or non-exclusive licenses

**Laboratory**

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http://www.biocis.u-psud.fr/

Chemicals possessing a neurotrophin-like activity on dopaminergic neurons in primary culture.

Novel DYRK1A inhibitors for the treatment of Alzheimer’s Disease

UPCOMING TECHNOLOGY

CONTEXT

Down syndrome (DS) is the most common genetic disorder with a frequency of 1 in 700 live births worldwide, and it is associated with an increased risk of Alzheimer’s disease. DYRK1A is considered a pathogenic factor in Down syndrome and has been implicated in the abnormal hyperphosphorylation of tau in Alzheimer’s disease brain.

TECHNICAL DESCRIPTION

The inventors have designed new azaindole-based Dyrk1A inhibitors that demonstrate potent inhibitory activity against Dyrk1A and high affinity in ATP-binding site. In vitro evaluation and computer-guided molecular design were used to select the appropriate candidates. No cytotoxicity has been detected, and primary data obtained on wild-type and Down Syndrom model mice are very promising. This work is financially support of the programme “Emergence of high potential products or services” of the Agence Nationale pour la Recherche.
Pyrido[3,2-d]pyrimidine derivatives inhibitors of CDK1, CDK5, GSK3 and/or DYRK1A and their use in the treatment of cognitive impairment

CONTEXT
The cognitive impairment in neurodegenerative diseases has been related to hyperactivity of the kinases CDK1, CDK5, GSK3 and/or DYRK1A.

TECHNICAL DESCRIPTION
The inventors have designed new Pyrido[3,2-d]pyrimidine derivatives that demonstrate potent inhibitory activity against CDK1, CDK5, GSK3 and/or DYRK1A. In vivo experiments on animal models of various neurodegenerative diseases are ongoing in collaboration with the American Institute for Neurodegenerative Disorders.
sPRR as dual biomarker of neurodegeneration and neuroregeneration

CONTEXT

The cerebrospinal fluid (CSF) is a sample of choice for biomarker discovery. However, proteomic approaches have been met with limited success due to the difficulty in identifying in CSF samples proteins that truly originate from neurons and that actually reflect neuronal dysfunction or death. Although apoptosis is a major mechanism of neuronal death in many neurodegenerative disorders, apoptotic neurons are often sparse in the brain of patients, making even more uncertain the identification of biomarkers of neuronal apoptosis in CSF.

Neuroregeneration, contrary to neurodegeneration, refers to the neuronal multiplication or differentiation or the synaptogenesis. Such mechanisms may include generation of new neurons, glia, axons, myelin, or synapses. So far, only a few biomarkers of neurogenesis are known.

The increasing frequency of neurodegenerative diseases and the lack of early and specific diagnostic and prognostic biomarkers necessitate the discovery of such new biomarkers of these diseases as well as biomarker for neurogenesis.

TECHNICAL DESCRIPTION

Stable isotope labeling by/with amino acids in cell culture (SILAC) is a technique based on mass spectrometry that detects differences in protein abundance among samples using non-radioactive isotopic labeling. Adapting this technique to detect neuronal secretome, Marin et al. have found that the extra cellular soluble part of the (pro)renin receptor (sPRR) was one of the proteins most differentially expressed in supernatants of apoptotic and surviving neurons.

Indeed, sPRR level was found elevated in conditioned medium of living neurons in culture, while decreased in the conditioned medium of dying neurons. Preliminary results from the co-inventors groups show that sPRR can be measured in CSF.

![Graph showing sPRR levels in CSF of controls and AD patients](image)

* Neurobiotech CSF biobank. Controls: hydrocephalia, migraine, headache, memory complaints...

DEVELOPMENT STAGE

CSF from patients having various neurodegenerative diseases are currently being tested.
These biomarkers are to be used for the **diagnostic and/or prognosis of neurodegenerative diseases**, in particular Alzheimer’s disease, dementia with Lewy bodies, fronto-temporal dementia, Parkinson’s disease, amyotrophic lateral sclerosis, as well as for the **follow up of neurodegenerative diseases treatments**.

Conversely, they may be used for the diagnostic and/or prognosis of diseases implicating a **neuronal proliferation**, such as glioblastomas, as well as for the follow-up of their **antiproliferative treatments**.

Last, these biomarkers may be useful for the **screening of new compounds** liable to treat neurodegenerative diseases and **to assess the efficacy of neuropsychiatric drugs**.
New cellular and animal toxic model of Parkinson’s disease

CONTEXT

Parkinson’s disease (PD) is the second most common neurodegenerative disease, affecting 1% of the population over 55 years of age. The main features of PD are tremor, rigidity, bradykinesia, and postural instability; however, these motor manifestations can be accompanied by nonmotor symptoms such as olfactory deficits, sleep impairments, and neuropsychiatric disorders. This disease is characterized by a loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), a profound deprivation of dopamine (DA) in the striatum, and the presence of intracytoplasmic inclusions called Lewy bodies (LB), which are composed mainly of α-synuclein and ubiquitin.

Breakthroughs in the last two decades using cellular and animal models have helped to identify specific events of the pathology. Most popular models include those produced by 6-hydroxydopamine (6-OHDA), 1-methyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and paraquat, as well as several genetic animal models like those related to alpha-synuclein, PINK1, Parkin and LRRK2 alterations.

A common feature of all toxin-induced models is their ability to produce an oxidative stress and to cause cell death in DA neuronal populations that reflect what is seen in PD. There are some drawbacks to the use of these models such as the time factor in these models versus the time factor in the human condition, or no consistent LB-like inclusion formation.

TECHNICAL DESCRIPTION

This new model of Parkinson Disease is induced by a new and easy-to-synthesized chemical compound. Our data shows that the hallmarks of PD (α-synucleine aggregation, caspases activation, inhibition of mitochondrial complex I) appear in a much slower manner than with MTPT or MPP+: cell death in SH-SY5Y cells after an exposition to the compound during 96h is equivalent to that observed after a 6h-incubation with MPP+.

Preliminary data in rats and in mice show that the treatment of an animal with this compound also induces symptoms of early stages of Parkinson Disease: α-synuclein accumulation in the striatum, mitochondrial respiratory chain inhibition, REM sleep troubles, etc...

BENEFITS

The slower rate of appearance of the hallmarks of PD compared to the other models should enhance the research on the very first steps of the disease.

This tool may be used for the screening of new drugs or the research for new biomarkers.

INDUSTRIAL APPLICATIONS

In vitro and in vivo screening of PD therapeutic strategy

DEVELOPMENT STAGE

Cellular model is standardized and ready to use

Rat and mouse models further characterization is ongoing

Our Reference
N° DI 05155-01

Keywords
Parkinson’s disease, cellular model, animal model, toxic model

Status of Patent
Priority patent application n° FR1260979 filed on November 19, 2012 entitled "Modèle chimique d’une maladie neurodégénérative, procédé de préparation et utilisations"

Inventors
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Christophe Morin
Michaël Rivard
Céline Laurencé
Sonia Lehri-Boufala

Commercial Status
Exclusive or non-exclusive licenses, Collaborative agreement

Laboratory
Institut de Chimie et des Matériaux de Paris Est (ICMPE), a CNRS – Université Paris-Est Créteil laboratory (UMR7182) in Vitry, France.
http://www.icmpe.cnrs.fr
Use of Spadin as a Biomarker for Depression

CONTEXT
Depression can affect from 5 to 20% of the general population. Its diagnostic is generally based on behavioural symptoms and there is a lack of reliable blood-based diagnostic assays.

TECHNICAL DESCRIPTION
Spadin is a natural peptide derived from the neurotensin receptor-3 (NSTR3) that is released in the blood. Using amplified luminescent proximity homogeneous assay and an optimised monoclonal antibody, the inventors have analysed samples coming from a cohort of depressed and/or anxious patients versus healthy samples. Rouen mice, which are a model of depression, are also tested. The preliminary data indicate that the detection of Spadin may be used as a biomarker of the depressive pathology, and also for therapeutic monitoring.

BENEFITS
- Blood-based detection technique
- One biomarker, one monoclonal antibody
- cheap and easy technique

INDUSTRIAL APPLICATIONS
The biomarker may be used for the diagnostic or the therapeutic monitoring of depression.

This work is supported by a grant of the National Agency of Research (ANR) in the category “Emergence”.

Our Reference
01424-06

Keywords
Neurotensin, peptide, pain, depression, psychiatric, biomarker

Status of Patent

Inventors
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Commercial Status
Exclusive or non-exclusive licenses

Laboratory
Institut de Pharmacologie Moléculaire et Cellulaire, a CNRS and University de Nice Sophia Antipolis (UMR 6097), in Valbonne, France. http://www.ipmc.cnrs.fr

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Selective orthosteric mGluR4 agonists for use in the treatment of schizophrenia and anxiety

CONTEXT
The role of metabotropic Glutamate receptors (mGlurS) is mostly to modulate the glutamatergic synaptic transmission in comparison to ionotropic glutamate receptors (iGluRs) which play an essential role. As such they allow a fine tuning which is required in CNS disorder treatments.

Recently, several allosteric modulators (AM) have been discovered, mainly mGlu4R Positive AMs. They were shown to be neuroprotective and to provide beneficial effects in animal models of Parkinson’s disease, pain and anxiety.

TECHNICAL DESCRIPTION
The patents cover series of metabotropic glutamate receptor agonists. These compounds activate selectively subtype receptors of group III (mGlu4R, mGlu6R, mGlu7R, mGlu8R). Among them, 3 compounds have been selected so far:
- LSP1-2111 that preferentially activates mGlu4 receptor in comparison to mGlu7R and mGlu8R
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- LSP1-3081 that activates preferentially both mGlu4 R and mGlu8R than mGlu7R

DEVELOPMENT STAGE
The in vitro pharmacology, pharmacokinetics and CNS disposition of LSP1-2111, as well as in vitro brain electrophysiology studies are available. Our data show a fairly rapid clearance with little metabolism as expected with polar compounds. In vivo LSP1-2111 also exhibited systemic activity in animal models of Parkinson’s disease and anxiety. LSP4-2022 exhibited remarkable antihyperalgesic effect of in neuropathic or inflammatory pain models.

PUBLICATIONS
- Metabotropic glutamate receptor subtype 4 selectively modulates both glutamate and GABA transmission in the striatum: implications for Parkinson’s disease treatment.

Our Reference
00262-01 to 05

Keywords
Hypophosphorous acid; metabotropic glutamate receptors; brain disorders; agonist; antagonist

Patents
#1: WO 2007052169 published on May 10, 2007
#3: WO2012156931 published on November 22nd, 2012

Commercial Status
Exclusive or non-exclusive licenses

Laboratory
Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, a CNRS and University Paris Descartes laboratory (UMR 8601), in Paris, France.
http://www.biomedical.e.univ-paris5.fr/umr8601/
Metabotropic glutamate receptor 4 novel agonist LSP1-2111 with anxiolytic, but not antidepressant-like activity, mediated by serotonergic and GABAergic systems.

Wieronska et al. Neuropharmacology. 2010 Dec;59(7-8):627-34.

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A novel selective metabotropic glutamate receptor 4 agonist reveals new possibilities for developing subtype selective ligands with therapeutic potential.

Goudet et al. FASEB J. 2012 Apr;26(4):1682-93

Role of mGluR4 in acquisition of fear learning and memory.


Group III and subtype 4 metabotropic glutamate receptor agonists: Discovery and pathophysiological applications in Parkinson's disease.

Amalric et al. Neuropharmacology. 2012 Jun 1
A human TREK-1/HEK cell line: a highly efficient screening tool for drug development in neurological diseases

CONTEXT

TREK-1 potassium channels are involved in a number of physiopathological processes such as neuroprotection, pain and depression. Molecules able to open or to block these channels can be clinically important. Having a cell model for screening such molecules is of particular interest.

TECHNICAL DESCRIPTION

The inventors have developed the first available cell line that constitutively expresses the TREK-1 channel. This cell line has been fully characterized with regards to the modulation properties of the TREK-1 channel that is expressed. The results show that all its properties are retained: it is opened by stretch, pH, polyunsaturated fatty acids and by the neuroprotective molecule, riluzole and it is blocked by spadin or fluoxetine. In addition, the inventors have also demonstrated that the h-TREK-1/HEK cell line is protected against ischemia by using the oxygen-glucose deprivation model.

INDUSTRIAL APPLICATIONS

High Throughput Screening on the TREK-1 target for drug discovery.

PUBLICATIONS

A human TREK-1/HEK cell line: a highly efficient screening tool for drug development in neurological diseases.
III/ Prion Diseases

Anti-Prion Drugs and Screening Method

CONTEXT

Prions are infectious proteins responsible for certain neuro-degenerative diseases of spongiform encephalopathy type in mammals, such as Creutzfeldt-Jacob’s disease in humans or also the so-called ‘mad cow disease’ in bovines. These infectious agents do not contain nucleic acids, in difference with others traditional agents (bacteria, viruses for example). Several research teams disclose tests for detecting molecules with anti-prion activity. These tests, carried out on a mammal model or on rodents, do not allow performing high-throughput screening because of limited safety conditions (P3 laboratory) and cell culture conditions (significant handling). There stills a great need for an efficiency test of screening for the identification of drugs against prion-derived diseases.

TECHNICAL DESCRIPTION

This invention describes a new, rapid, yeast-based, two-step screening test for anti-prion drugs. Compounds isolated using this method can then be tested against mammalian prions. This new screening method allowed the identification of new compounds active against budding yeast prions which are also active against mammalian prions. Some known active molecules against mammalian prions were also evaluated in this yeast based assay. They are also active against yeast prions, which definitely validate the method. This patent application also describes novel anti-prion compounds that the Laboratory has already identified and which are currently being protected by the CNRS.

BENEFITS

Although based on yeast prions, the method and kit described in this invention allow the identification of active molecules against mammal prions. The main advantage of such screen resides in its complete harmlessness allowing it to be carried out in a standard level L2 molecular biology laboratory, not as required in previous techniques, in a level P3 laboratory. Moreover, the great ease to use and its very low cost make it possible to carry out high-throughput screening.

INDUSTRIAL APPLICATIONS

This innovation can be used for identifying and testing new drugs that are potentially active against prion-derived diseases, but also potentially active against other neurodegenerative disorders that involve an abnormal aggregation of proteins.
**Highly Sensitive Prion Blood Detection Test**

**CONTEXT**

Transmissible spongiform encephalopathies (TSE - Creutzfeldt-Jakob disease in humans, BSE, scrapie, CWD in animals) are characterized, post-mortem, by accumulation of the pathological prion protein PrPSc in brain tissue. This unconventional infectious agent is transmitted by blood transfusion, contaminated feed, food or health products.

So far, no commercially blood screening assay is available to detect prion agent in blood. Indeed, standard procedures used to detect PrPsc in tissues have failed in blood samples. Several studies have suggested that the infectious forms circulating in blood may have different physicochemical properties from those accumulating in tissues, especially concerning their high sensitivity to proteinase K digestion.

**TECHNICAL DESCRIPTION**

The present invention relates to the use of a family of thienyl pyrimidine compounds that induce a specific oligomerization of PrPSc dimers and trimers through aggregation/stabilization, allowing efficient amplification of blood PrPSc for its reliable detection in various samples and early diagnosis of TSE.

**BENEFITS**

Our technology provides:
- a very high sensitivity and specificity of PrPSc detection compared to standard procedures (x1000000), which may apply to various detection technology (western-blotting, Elisa, fluorescence technology)
- a potential ante-mortem diagnosis from biological fluids and poorly concentrated tissues with rapid amplification of PrPsc without the need of proteinase K digestion step

**INDUSTRIAL APPLICATIONS**

The mains applications of this technology are:
- blood tests for Creutzfeldt-Jakob diseases and possibly other human prionopathies (Parkinson’s, Alzheimer’s and Huntington’s diseases),
- blood tests for animal prion diseases, post-mortem and ante-mortem tests on tissues for veterinary purposes
- safety of blood products (93 millions blood donations annually)

**DEVELOPMENT STAGE**

This technology has already proved its efficiency on blood samples spiked with contaminated brain homogenates. Studies are ongoing on blood samples from a prion hamster model and from human patients.

A manufacturable kit is in preparation to allow easy, fast and cheap screening of blood products.

**PUBLICATION**

Selective orthosteric mGluR4 agonists for use in the treatment of pain

CONTEXT
The role of metabotropic Glutamate receptors (mGlRs) is mostly to modulate the glutamatergic synaptic transmission in comparison to ionotropic glutamate receptors (iGlRs) which play an essential role. As such they allow a fine tuning which is required in CNS disorder treatments. Recently, several allosteric modulators (AM) have been discovered, mainly mGlu4R Positive AMs. They were shown to be neuroprotective and to provide beneficial effects in animal models of Parkinson's disease, pain and anxiety.

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The in vitro pharmacology, pharmacokinetics and CNS disposition of LSP1-2111, as well as in vitro brain electrophysiology studies are available. Our data show a fairly rapid clearance with little metabolization as expected with polar compounds. In vivo LSP1-2111 also exhibited systemic activity in animal models of Parkinson's disease and anxiety. LSP4-2022 exhibited remarkable antihyperalgesic effect of in neuropathic or inflammatory pain models.

PUBLICATIONS
- Metabotropic glutamate receptor subtype 4 selectively modulates both glutamate and GABA transmission in the striatum: implications for Parkinson's disease treatment.

LICENSING OPPORTUNITIES
V – 03/2013
- Metabotropic glutamate receptor 4 novel agonist LSP1-2111 with anxiolytic, but not antidepressant-like activity, mediated by serotonergic and GABAergic systems.
Wierońska et al. Neuropharmacology. 2010 Dec;59(7-8):627-34.
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Goudet et al. FASEB J. 2012 Apr;26(4):1682-93
- Role of mGluR4 in acquisition of fear learning and memory.
- Group III and subtype 4 metabotropic glutamate receptor agonists: Discovery and pathophysiological applications in Parkinson's disease.
Amalric et al. Neuropharmacology. 2012 Jun 1
Toxin Peptide Antagonist of T-type Calcium Channels for use in Analgesia

CONTEXT

Transmission of the pain signal by the nervous system involves neuronal receptors which convert the painful stimulus into an electrical signal. The nociceptive neurons, which react specifically to pain stimuli, possess a unique repertory of ion channels that represent ideal targets for new analgesic drug development. Among them, T-type Calcium channels, and in particular CaV3.2, have been shown to be specifically implicated in nociception.

TECHNICAL DESCRIPTION

The inventors have identified PspTx3, a 28 aa-peptide derived from the venom of a spider Theraphosidae, that efficiently inhibits CaV3.2. Besides, PspTx3 revealed to also efficiently inhibit NaV1.7, a sodium channel implicated in pain conduction and a very interesting target for pain treatment.

Using a mouse model of chronic pain induced by sciatic nerve lesion, the peripheral injection of the toxin (subcutaneous injection in the leg) showed a much more potent effect on nociception compared to morphine.

No cardiac toxicity could be detected.

INDUSTRIAL APPLICATIONS


Our Reference
01839-01

Keywords
Peptide; T-type calcium channel; Analgesic

Status of Patent
Priority patent application FR 2940973 filed on January 15, 2009, entitled «Identification d'une nouvelle toxine antagoniste de canaux calciques de type-T à visée analgésique.» and granted on May 24, 2013


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Fabrice MARGER
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Commercial Status
Exclusive or non-exclusive licenses

Laboratory
Institut de Génomique Fonctionnelle UMR 5203, a CNRS – INSERM and University of Montpellier laboratory (UMR 5203), in Montpellier, France.

http://www.igf.cnrs.fr
New target for Pain Treatment, and New tools for the Research on Endogenous Morphine

UPCOMING TECHNOLOGY

CONTEXT

Morphine is the gold standard for pain relief in hospital settings. Endogenous morphine (EM), structurally identical to morphine from plants, has been characterized in mammals and its biosynthesis pathway has been shown to derive from dopamine. The functional role of endogenous alkaloids remains to be elucidated, a growing number of groups have highlighted the potential use of EM and its derivatives as physiopathological markers for infection, inflammation, bulimia and anorexia, Parkinson disease, alcoholism or various mental disorder. Yet, there are only very few tools to study this hard-to-detect molecule, which are expensive, or display low sensitivity or poor reproducibility.

TECHNICAL DESCRIPTION

The inventors have identified a complex made of creatine kinase (CK-B, brain and CK-M, muscular) and endogenous morphine-like alkaloids in tissues including mouse brain.

INDUSTRIAL APPLICATIONS

A powerful detection tool of endogenous morphine is currently being developed using this interaction.

The identified binding site may also be of interest in the development of new therapeutics aiming at treating morphine addiction, or alleviating pain.

Our Reference
04170-01

Keywords
Drug addiction; endogenous morphine

Status of Patent
Priority patent application FR2971160 filed on February 8, 2011, entitled « Utilisation de créatine kinase pour la prévention ou le traitement d’un addiction »

Extension : WO2012107673

Inventors
Yannick GOUMON, Alexis LAUX and Denise STUBER

Commercial Status
Exclusive or non exclusive licenses

Laboratory
Institut des Neurosciences Cellulaires et Intégratives, UPR 3212, a CNRS – Université de Strasbourg laboratory in Strasbourg, France

http://inci.u-strasbg.fr
Use of Simvastatine or Derivatives in the Treatment of Cocaine Addiction

CONTEXT

In 2000, it is estimated that 14 million persons in the world are consuming cocaine, and the use of this drug is in constant increase in young populations. At present, there is no standard pharmacological treatment for cocaine addiction, conversely to the persons suffering from problems with opiates who can benefit from substitute treatment. Indeed, prescriptions to cocaine consumers usually aim at attenuating secondary effects of cocaine abuse, such as anxiety or sleep problems. Psychotherapy also remains an option to accompany cocaine consumption reduction and withdrawal.

TECHNICAL DESCRIPTION

While studying cocaine addiction processes, in an effort to identify new molecules to treat this cerebral disease and avoid relapse, the inventors have discovered a new role for simvastatine that is well-known in the treatment of cardiovascular diseases.

Using animal models of drug addiction, many studies have been focused on the identification of molecules that would diminish cravings in one acute injection. Yet, the experimental approach developed by the inventors is much closer to a human use, because the therapeutic agent is administered during several weeks after the drug withdrawal and the risk of relapse is evaluated after interruption of the treatment.

BENEFITS

The experiments have shown that daily intraperitoneal injections of low doses of this molecule for 20 days during the withdrawal have a very strong effect on cravings reduction. This was assessed by an addiction-related behavioural test modelling relapse in humans.

This therapeutic agent may be a very interesting help in facilitating abstinence and preventing relapse to cocaine addiction. In addition, the results obtained allow the inventors to anticipate that this effect may also be observed for other drugs, such as nicotine.

INDUSTRIAL APPLICATIONS

Long-term and efficient therapies are yet to be developed for cocaine addiction treatment. Simvastatine has been used as a human therapeutic agent for years, it is well tolerated and bears very few adverse effects, even after a long chronic treatment period. Hence, preclinical and clinical studies should be facilitated. Analogs of simvastatine could also be developed.
Opioids Addiction Prevention and Treatment, and New tools for the Research on Endogenous Morphine

UPCOMING TECHNOLOGY

CONTEXT

Morphine is the gold standard for pain relief in hospital settings. Endogenous morphine (EM), structurally identical to morphine from plants, has been characterized in mammals and its biosynthesis pathway has been shown to derive from dopamine. The functional role of endogenous alkaloids remains to be elucidated, a growing number of groups have highlighted the potential use of EM and its derivatives as physiopathological markers for infection, inflammation, bulimia and anorexia, Parkinson disease, alcoholism or various mental disorder. Yet, there are only very few tools to study this hard-to-detect molecule, which are expensive, or display low sensitivity or poor reproducibility.

TECHNICAL DESCRIPTION

The inventors have identified a complex made of creatine kinase (CK-B, brain and CK-M, muscular) and endogenous morphine-like alkaloids in tissues including mouse brain.

INDUSTRIAL APPLICATIONS

A powerful detection tool of endogenous morphine is currently being developed using this interaction.

The identified binding site may also be of interest in the development of new therapeutics aiming at treating morphine addiction, or alleviating pain.

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Extensions : WO2012107673

Inventors
Yannick GOUMON, Alexis LAUX and Denise STUBER

Commercial Status
Exclusive or non exclusive licenses

Laboratory
Institut des Neurosciences Cellulaires et Intégratives, UPR 3212, a CNRS – Université de Strasbourg laboratory in Strasbourg, France

http://inci.u-strasbg.fr
VI/ Orphan diseases

Use of a BKCa opener as a treatment of Fragile X-Syndrome

CONTEXT

Fragile X-Syndrome (FXS) is the most common cause of inherited mental retardation and affects 1 in every 2000 men and 1 in every 4000 women, together representing nearly 500,000 persons in Europe and USA. This disease is caused by the expansion of a single trinucleotide gene sequence (CGG) on the X-chromosome, and results in a failure to express the protein coded by the FMR1 (Fragility Mental Retardation 1) gene.

In normal individuals, FMR1 is a RNA-binding protein that is believed to regulate the transcription and translation of a substantial population of mRNA, and it plays important roles in learning and memory. It also appears to be required for normal neural development since it is involved in development of axons, formation of synapses, and the wiring and development of neural circuits. Its mutation leads to its silencing, and results in a spectrum of characteristic physical and intellectual limitations, as well as emotional and behavioral features which range from severe to mild in manifestation.

To date, there is no cure for the Fragile X-Syndrome and current therapeutic strategies rely on behavioral therapy, special education, and when necessary, treatment of physical abnormalities.

TECHNICAL DESCRIPTION

It has recently been shown that the silencing of FMR1 is leading to a 50% reduction of the level of KCNMA1, the sub-unit of the large-conductance Ca2+ and voltage-activated K+ (BKCa) channel (Liao et al., PNAS 2008). BKCa channels have a tetrameric structure, each monomer of the channel-forming alpha subunit being the product of the Kcnma1 gene, and this reduced level of KCNMA1 protein results in a functional impairment of the channel activity. BKCa channels are expressed in almost every tissue in our body and participate in many critical functions such as neuronal excitability, determination of action potential duration and frequency, neurotransmitter release and vascular tone regulation.

Using the BKCa channel opener BMS204352, the inventors have been able to restore a normal BKCa channel activity in a FXS patient cell culture in a similar manner than what they observed in lymphoblastoid cultures of an autistic patient with a de novo 9q23/10q22 translocation (Laumonnier et al. Am J Psychiatry 2006).

Working with fmr1-KO mice, the FXS animal model, Dr Briault and Dr Perche have now shown that BMS204352 allows behavioral recovery in a surprisingly efficient manner.

DEVELOPMENT STAGE

The research team is now strengthening preclinical data and setting up a clinical trial. As a medical geneticist, Dr Briault has established close relationships with hospitals and with French and international patient associations that are active in the field of Fragile-X syndrome research and will support and/or collaborate to his action.

Interestingly, BMS204352 has been clinically developed by Bristol-Myers Squibb up to Phase III before it failed to improve stroke's issue, and therefore has a good ADMET profile. The molecule is now free to operate.
New therapeutic peptide for Huntington’s Disease

CONTEXT

Huntington’s disease (HD) is a neurodegenerative genetic disorder that usually becomes noticeable in middle age. It affects muscle coordination and provokes cognitive decline and dementia. HD is caused by an autosomal dominant mutation of a gene called Huntingtin (Htt) leading to an abnormal repeat number of the amino acid Glutamine (Q) in the protein (PolyQ-Htt). This mutant form of the protein has altered activities and is prone to form protein aggregates. It is toxic to certain types of cells, especially in the brain where neurons are particularly affected.

There is at the present time no cure for HD, and the available treatments aim at reducing the severity of some of its symptoms.

TECHNICAL DESCRIPTION

One therapeutic strategy that is explored is the prevention of aggregates caused by the polyQ domain in mutant Huntingtin. The invention is based on the discovery published in 2008 that the aggregation of PolyQ-Htt may be prevented by its wild-type counterpart.

Considering the size of the wild-type protein, around 600 amino acids, the inventors have looked for smaller but still active peptides isolated from Htt. One of them, pep42, turned out to be particularly interesting.

BENEFITS

The small size of the peptide is more appropriate for a use as a therapeutic compound than the Htt whole protein, while it retains its full anti-aggregates activity.

INDUSTRIAL APPLICATIONS

This peptide may be used as a treatment of HD, alone or in combination with other strategies, and administered as a peptide alone or integrated in a lentivirus allowing its expression.

DEVELOPMENT STAGE

In vitro and in vivo data have been obtained and are still in progress. Vectorisation strategies for the peptide are studied. In particular, its fusion with the TAT penetrating sequence has been very efficient to allow its transport through the blood-brain barrier. This work is financially supported by the programme “Emergence of high potential products or services” of the Agence Nationale pour la Recherche.
A huntingtin peptide inhibits polyQ-huntingtin associated defects.
Arribat Y, Bonneaud N, Talmat-Amar Y, Layalle S, Parmentier ML, Maschat F.
New Treatment for Cognitive Impairment in Down Syndrome

CONTEXT

Trisomy 21 (T21), or Down Syndrome (DS), is the most common form of intellectual disability in human. We consider that a population of about 1 million people in Europe and in the United States is concerned by this pathology. Currently in Europe the number of conceptions of children with DS increases with later age of motherhood, but less than 1/1000 child are born with DS, thanks to prenatal diagnosis.

DS is characterized by variable degrees of cognitive impairment - including deficits in memory, learning capacity or both. While advances in teaching methods and a trend toward educational mainstreaming has led to an improvement in cognitive development in those who have DS, there remain constitutive impairments that cannot be fully addressed through pedagogic methodology alone.

TECHNICAL DESCRIPTION

Initially developed by Merck Sharp & Dohme for the treatment of Alzheimer’s disease, GABA alpha5 inverse agonists are very promising for the treatment of Down Syndrom-related cognitive impairment.

DEVELOPMENT STAGE

The development is ongoing with MSD’ GABA alpha 5 inverse agonist.

PUBLICATIONS

Chronic Treatment with a Promnesiant GABA-A α5-Selective Inverse Agonist Increases Immediate Early Genes Expression during Memory Processing in Mice and Rectifies Their Expression Levels in a Down Syndrome Mouse Model.

Specific targeting of the GABA-A receptor α5 subtype by a selective inverse agonist restores cognitive deficits in Down syndrome mice.
Use of Guanabenz Derivatives for the Treatment of Huntington’s disease

CONTEXT
The prevalence of Huntington’s disease (HD) is estimated to 3-7 per 100,000 people in western Europe. HD is caused by a faulty gene on chromosome 4. This gene produces a protein called Huntingtin and leads to a damage of the striatal neurons. The progressive degeneration of these neurons causes gradual physical, mental and emotional changes. At this time, there is no way to stop or to reverse the course of HD. HD is characterized by expansion of CAG codons translated in polyglutamine (polyQ) and causes aggregation of the affected protein. The aim of the invention concerns non toxic compounds capable of treating polyglutamine expansion associated diseases.

TECHNICAL DESCRIPTION
The present invention relates to chlorine Guanabenz derivatives (inhibitors of aggregated proteins) for treating Huntington’s disease and other polyglutamine expansion associated diseases. More specifically, it relates to the use of the molecule of formula (I) wherein R=H or Cl and the phenyl group is at least substituted twice, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating polyglutamine expansion associated diseases. Guanabenz and Chloroguanabenz specifically reduce accumulation of a pathogenic fragment of Huntingtin in a transiently transfected cellular model of HD.

BENEFITS
Guanabenz is a drug already in clinic to treat hypertension. This invention makes it possible to develop a new application of the chlorine Guanabenz derivatives.
Guanabenz is a novel drug candidate for Huntington’s disease treatment.

INDUSTRIAL APPLICATIONS
The Guanabenz derivatives described in this invention promote clearance of mutant Huntingtin and this opens new applications in preventing or treating pathological of polyglutamine expansion associated diseases such as HD. Furthermore this invention will be more generally applicable to all protein misfolding diseases. The commercial applications and potential markets in such therapeutics are huge.

DEVELOPMENT STAGE
Information about the molecular mechanism by which Guanabenz enhances clearance of misfolded proteins is a prerequisite for clinical development. The inventors are exploring the pathway by which the Guanabenz increases the cellular capacity to degrade aggregation-prone proteins.
Novel DYRK1A inhibitors for the treatment of cognitive impairment in Down Syndrome

CONTEXT

Down syndrome (DS) is the most common genetic disorder with a frequency of 1 in 700 live births worldwide, and it is associated with an increased risk of Alzheimer’s disease. DYRK1A is considered a pathogenic factor in Down syndrome and has been implicated in the abnormal hyperphosphorylation of tau in Alzheimer’s disease brain.

TECHNICAL DESCRIPTION

The inventors have designed new azaindole-based Dirk1A inhibitors that demonstrate potent inhibitory activity against Dyrk1A and high affinity in ATP-binding site. In vitro evaluation and computer-guided molecular design were used to select the appropriate candidates. No cytotoxicity has been detected, and primary data obtained on wild-type and Down Syndrom model mice are very promising.

This work is financially support of the programme “Emergence of high potential products or services” of the Agence Nationale pour la Recherche.

Our Reference
05433-01

Keywords
Down’s syndrome, Alzheimers, Kinase inhibitors, CNS

Status of Patent
French priority patent application to be filed in November 2012

Inventors
Robert DODD
Jean DELABAR

Commercial Status
Exclusive or non-exclusive licenses

Laboratories
Institut de Chimie des Substances Naturelles, a CNRS laboratory in Gif-sur-Yvette, France.

www.icsn.cnrs-gif.fr

UMR4413, a Université Paris Diderot laboratory in Paris, France.
Use of Calcium Channel Blockers for the Treatment of Spinal Muscular Atrophy

UPCOMING TECHNOLOGY

CONTEXT
Spinal muscular atrophy (SMA) refers to inherited neuromuscular disorders that are characterized by degeneration of spinal motor neurons leading to muscular weakness and atrophy. SMA is incurable to date and existing treatment remain unsatisfactory, thus although it occurs with a frequency of 1:10,000, it remains the most common fatal autosomal disease in infants.

TECHNICAL DESCRIPTION
Using a screening test based on the monitoring of SMN accumulation in Cajal Bodies of SMA fibroblasts, the inventors have shown that calcium channel blockers of the type phenylalkylamines were very efficient. In particular, flunarizine exhibited very promising results. This molecule is also known as SIBELIUM® and is currently used for the treatment of pediatric migraine.

INDUSTRIAL APPLICATIONS
In vivo experiments are programmed.
**Ion-channels Macroarrays for Auto-Antibodies Detection in LCR**

### CONTEXT
Recently evidence for autoimmunity towards ion channels in central nervous system disorders has emerged. These disorders include Morvan’s syndrome, Rasmussen’s encephalitis, limbic encephalitis, multiple sclerosis, etc. Detection of such autoantibodies is useful for the diagnosis and classification of these diseases.

### TECHNICAL DESCRIPTION
This invention provides a unique method for detection of autoantibodies directed against membrane proteins. Anti-ion channel antibodies in the cerebrospinal fluid of patients are detected by using an ion channel macroarray. As a diagnostic tool, the method can be used to detect antibodies directed against specific targets. The method can also be used to identify new ion channel targets in patients that are not positive for antibodies directed against targets already known.

### BENEFITS
This method has important advantages over current methods that are based on immunocytochemistry of membrane proteins:
- Easier and cheaper
- Not restricted to targets already described

### INDUSTRIAL APPLICATIONS
This innovation could be used for multiple applications as:
- Diagnosis and prognosis of autoimmune diseases
- Screening / Identification of new antigenic targets

### DEVELOPMENT STAGE
Accomplished tests: **Prototype available**.
The method has been validated using CSF from patients suffering of encephalitis with anti-NMDA receptor antibodies. 43 patients, 17 of them with anti-NMDAR antibodies detected by immunocytochemistry, were tested. 88% of the positive patients (15/17) were detected using the new method. The specificity for negative patients is 100%.
Current developments: detection of new targets in autoimmune disorders associated with hyperexcitability.

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**Our Reference**
04731-01

**Keywords**
Protein macroarray, autoimmune disease, autoantibodies, ion channels, neuronal disorders, diagnosis, prognosis, screening

**Status of Patent**
Priority patent application n° FR12 50956 filed on February 1, 2012, entitled "PUCES A PROTEINES, PREPARATION ET UTILISATIONS"

**Inventors**
Franck CHATELAIN, Michel MAZZUCA, Véronique ROGEMOND, Marie Madeleine LARROQUE, Jérôme HONNORAT, Florian LESAGE

**Commercial Status**
Exclusive or nonexclusive licenses, Collaborative Agreement

**Laboratory**
UMR7275 « Institut de Pharmacologie Moléculaire et Cellulaire (IPMC) » Valbonne, France. www.ipmc.cnrs.fr
Method for Real-Time Monitoring of Patients to Predict Epileptic Seizures

CONTEXT
There is still a great need for efficient system for epileptic seizures prediction.

TECHNICAL DESCRIPTION
A method to detect changes in the dynamic properties of brain electrical activity has been used to characterize and differentiate physiological and pathological conditions, and to predict epileptic seizures. Changes in the dynamic properties of brain electrical activity are detected by constructing reference dynamics of a normal EEG comparing these reference dynamics with the dynamics of a test segment, and computing the similarities over the entire EEG recordings by sliding the test segment periodically.

INDUSTRIAL APPLICATIONS
The main application of this invention is to predict epileptic seizures. Two kinds of equipment can be designed based on this invention: equipment for clinical use in neurosurgical units or portable (or insertable); equipment used with a set of electrodes and worn permanently by the patient to predict a future seizure. This technology is being investigated by the European consortium EPILEPSIAE.

Our Reference
84506-02

Keywords
Epileptic seizures, monitoring, brain electrical activity

Status of Patent
US patent application: 09559334 filed on April 27, 2000 entitled "Method for the medical monitoring in real time of a patient from the analysis of electroencephalograms to characterize and differentiate between physiological or pathological conditions, and a method for anticipating epileptic seizures" and granted on August 27, 2002 under n° 6442421. US patent application: 10046696 filed on January 17, 2002

WO2006108966

National phases: EP, US

Inventors
F. VARELA, M. LE VAN QUYEN, J. MARTINERIE, M. BAULAC,

Commercial Status
Exclusive or non-exclusive licenses, collaborative agreement

Laboratory
Neurosciences cognitives et Imagerie cérébrale, a CNRS laboratory (UPR 640) in Paris, France. http://cogimage.dsi.cnrs.fr/
**Electrophysiological Neuronal Activity**

**TECHNICAL DESCRIPTION**

The invention concerns a method for representing a dynamic functional image of the brain. It consists in acquiring for a specific duration a plurality of electrophysiological signals of cerebral activity from a set of electrodes placed on the scalp of the subject; locating the set of neuroelectric generators in the cerebral volume from a three-dimensional image of a set of successive cross-sections of the brain and applying the inverse problem; discriminating in the active zones comprising neuroelectric generators the synchrony existing between the pairs of electrophysiological signals/neuroelectric generators in a plurality of frequency bands, to detect groups of discriminating neural networks.

![Diagram of a head with electrodes](image)

**INDUSTRIAL APPLICATIONS**

The invention is useful for non-invasive study of provoked or unprovoked functional anomalies, such as epileptic events. This technology is being investigated by the European consortium EPILEPSIAE.

**Our Reference**

00062-01

**Keywords**

NON-INFRINGEMENT;
NEURONAL ACTIVITY;
BRAIN IMAGING

**Status of Patent**

FR0507848: Priority patent of invention filed on: 7/22/2005 entitled: "Procédé et dispositif de représentation d'une image fonctionnelle dynamique du cerveau, par localisation et discrimination des générateurs neuroélectriques intracrâniens et leurs applications"

Extensions:
PCT: WO2007010114
EP1906822,
US2009054800

**Inventors**

MARTINERIE, Jacques (CNRS); BAILLET, Sylvain (CNRS); GARNERO, Line (CNRS); LACHAUX, Jean-Philippe (CNRS); LE VAN QUYEN, Michel (INSE) and RENAULT, Bernard (CNRS)

**Commercial Status**

Exclusive or non-exclusive licenses

**Laboratory**

Laboratoire de neurosciences cognitives et imagerie cérébrale, (UPR640), Paris, France. http://cogimage.dsi.cnrs.fr/

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**Novel Device for Focal Extracellular Electrical**

**LICENSING OPPORTUNITIES**

V - 01/2011
Stimulation of the CNS

CONTEXT

Electrical extracellular stimulation of the central nervous system has been used empirically for several decades, with peripheral nerve, deep brain, and spinal cord stimulation paradigms used routinely to treat motor function loss and neurological disorders such as neuropathic pain, movement disorders, Parkinson disease, or epilepsy. Nowadays, electrical microstimulation using microelectrode arrays undergoes a strong interest for the development of neural prosthesis, such as retinal, sub-cortical or cortical implants. An important issue for achieving the best efficacy of such device requires the precise control of the spatial extent of a stimulus.

TECHNICAL DESCRIPTION

Here, we propose a new electrode configuration that improves the focality of electrical stimulation without the need to consider multipolar electrodes. In this configuration, we introduce a ground surface surrounding all the electrodes of the array (Figure A). Stimulations are delivered between each electrode of the array and the ground surface. Using this configuration, a stimulation is all the more focal that the surface conductance of the ground surface with respect to the extracellular medium (shown here for values between 400 S/m\(^2\) and 40000 S/m\(^2\)) is high. This is shown in Figure B, where the activation threshold is plotted against distance to the electrode for a compartmental stellate neuron model moved along a line above the stimulation electrode.

For comparison, the focality of stimulation obtained by a monopolar (M, black) and a concentric bipolar (CB) configuration is shown.

BENEFITS

It should be noted that an important practical advantage of the proposed configuration is the trade-off it offers between stimulation focality and required current. Indeed, better focality can be achieved with currents less than two times higher than with the monopolar configuration, while much stronger currents (about 17–26 times stronger) are needed with the concentric bipolar configuration. This gain in current amplitude is important to reduce electrode deterioration and to design low-consumption implantable devices for which battery life is an important practical issue.

INDUSTRIAL APPLICATIONS

In vitro microelectrode arrays, in vivo neural prosthesis, cochlear or retinal prosthesis, cortical implants, brain-computer interfaces

DEVELOPMENT STAGE

As shown in Figure B, the improvement in stimulation focality is all the best that the conductance of the ground surface is high. Current developments focus on the achievement of low impedance materials for the ground surface to obtain best focality.
Protein Macroarrays for detection of Autoantibodies towards Ion Channels in central nervous system

CONTEXT
Recently evidence for autoimmunity disorders has emerged. These disorders include Morvan’s syndrome, Rasmussen’s encephalitis, limbic encephalitis, multiple sclerosis, etc. Detection of such autoantibodies is useful for the diagnosis and classification of these diseases.

TECHNICAL DESCRIPTION
This invention provides a unique method for detection of autoantibodies directed against membrane proteins. Anti-ion channel antibodies in the cerebrospinal fluid of patients are detected by using an ion channel macroarray. As a diagnostic tool, the method can be used to detect antibodies directed against specific targets. The method can also be used to identify new ion channel targets in patients that are not positive for antibodies directed against targets already known.

BENEFITS
This method has important advantages over current methods that are based on immunocytochemistry of membrane proteins:
- Easier and cheaper
- Not restricted to targets already described

INDUSTRIAL APPLICATIONS
This innovation could be used for multiple applications as:
- Diagnosis and prognosis of autoimmune diseases
- Screening / Identification of new antigenic targets

DEVELOPMENT STAGE
Accomplished tests. Prototype available. The method has been validated using CSF from patients suffering of encephalitis with anti-NMDA receptor antibodies. 43 patients, 17 of them with anti-NMDAR antibodies detected by immunocytochemistry, were tested. 88% of the positive patients (15/17) were detected using the new method. The specificity for negative patients is 100%.

Current developments: detection of new targets in autoimmune disorders associated with hyperexcitability.

Our Reference
04731-01

Keywords
Protein macroarray, autoimmune disease, autoantibodies, ion channels, neuronal disorders, diagnosis, prognosis, screening

Status of Patent
Priority patent application no FR12 50956 filed on February 1, 2012, entitled "PUCES A PROTEINES, PREPARATION ET UTILISATIONS"

Inventors
Franck CHATELAIN, Michel MAZZUCA, Véronique ROGEMOND, Marie Madeleine LARROQUE, Jérôme HONNORAT, Florian LESAGE

Commercial Status
Exclusive or non-exclusive licenses, Collaborative agreement

Laboratory
UMR7275 « Institut de Pharmacologie Moléculaire et Cellulaire (IPMC) » Valbonne, France. www.ipmc.cnrs.fr

Prototype available
New tools to investigate Hemispheric Specialization

CONTEXT

Hemispheric specialization (HS) is a remarkable trait of the human brain organization. In about 80% of humans, the left hemisphere is specialized (or dominant) for language regardless of their tongue, gender, or culture. Although much less documented, the right hemisphere is usually considered specialized for spatial functions. Surprisingly, little is known on the relationship between these two features, with several questions remaining unanswered or unexplored.

TECHNICAL DESCRIPTION

To investigate these issues, the inventors have elaborated a test comprising 15 exercises documenting verbal and spatial skills, structural features, and neural networks for motor, language and spatial functions. This functional battery is intended for use simultaneously with Magnetic Resonance Imaging to visualize the most active cerebral zones.

Data were collected for 453 individuals and combined with social, demographic and genetic data. This information has been organized as a relational database named BIL&GIN (Brain Imaging of Lateralization). The BIL&GIN raw data acquisition and pre-processing has been described at Organization for Human Brain Mapping 2012 meeting:

BIL&GIN: a database for the study of hemispheric specialization
Laurent Petit, Fabrice Crivello, Emmanuel Mellet, Gael Jobard, Laure Zago, Marc Joliot, Guy Perchey, Bernard Mazoyer, Nathalie Tzourio-Mazoyer

BENEFITS

Interestingly, the database contains a large proportion of left-handed individuals, whose hemispheric specialization remained to be understood.

This battery of functional exercises and database are intended for use by the academic research community as well as by neurosurgeons.
**FIST SA in figures**
FIST SA is the acronym of France Innovation Scientifique et Transfert (France Scientific Innovation and Transfer). It was created in Paris in 1992 as a private company in order to focus on the transfer of innovative patents from French government-funded research organization (CNRS) to industry. Today, it represents €4.2 millions of sales.

A professional and specialized team
With the benefit of a large range of technical competences, our team comes along from the protection of the invention to its licensing contract.

A range of services
The different services proposed by FIST SA are also available for private and start-up companies:
- Intellectual property and valorization strategies
- Partners research and negotiations
- Patent portfolio management
- Patent mapping/ Intellectual property landscape
Technology Transfer Success: examples

**Taxotere®:** Sanofi Aventis

**Navelbine®:** Pierre Fabre
Chemotherapy drug approved in treatment of non-small cell lung cancer and also of breast cancer, ovarian cancer, or Hodgkin's disease.

**Lupuzor®:** ImmuPharma / Cephalon Inc
Drug that specifically modulates the immune system of Lupus patients. Lupuzor™ has successfully completed phase I, Phase IIa and Phase IIb studies. Sublicense to Cephalon inc. by ImmuPharma in 2009.

**Selectiose®:** PFDC - AVENE
Sélectiose®, amphiphilic derivative of Rhamnose reduces skin hypersensitivity and irritation and controls skin inflammation response. Marketed in cosmetic product line (Trixera+) in 2008 by AVENE.

A collaboration success story: CENTRON C1S
Fifteen years ago, a collaboration between a laboratory affiliated to the CNRS, the « Groupe d'Etudes des Semi-conducteurs », and RMS, a division of the Schlumberger Company now integrated to the Itron/Actaris group, developed semi conductive straight structure III-V showing a magnetic field high sensibility and a low thermal drift.

The magnetic sensor then developed allowed the manufacture of a new generation of residential electricity meter, the CENTRON C1S. This technology was enlarged to all the meters product range by ITRON. At the moment, 30 millions of meters have been fixed up in the USA and other countries. 5 millions of meters are yearly produced.

**CNRS in figures**
**Budget for 2012**
Euros 3.3 billion of which Euros 677 million come from revenues generated by CNRS

**Personnel**
34,530 permanent employees
11,450 researchers
14,180 engineers and technical staff

**Organisation**
10 institutes (3 of which have the status of national institutes)
19 regional offices, ensuring decentralized direct management of laboratories
1,100 research units (95 % are joint research laboratories with universities and industry)
40 International Associated Laboratories (LEA+LIA)
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