**MATERIAL TRANSFER AGREEMENT**

Within the framework of the missions of University of Orleans (hereinafter “**UNIVERSITY**”), a French public scientific and technological establishment, having its registered office at Château de la Source – B.P – 6749 – 45067 Orléans CEDEX. **UNIVERSITY** desires to promote the advancement of science by providing the material described below and by granting a non-exclusive and non commercial utilization right to the scientific community in a research purpose only.

Accordingly, **UNIVERSITY** has provided the European Mouse Mutant Archive (hereinafter “EMMA” which is a non-profit repository for the collection, archiving via cryopreservation and distribution of relevant mutant strains essential for basic biomedical research) with said material.

In particular, **UNIVERSITY** agrees to transfer the Biological Material developed by **UNIVERSITY** Laboratory described below (hereinafter “**UNIVERSITY Laboratory**”) and especially by the scientist responsible of such biological material (hereinafter the “**Scientist**”) to the benefit of the Institution and the Investigator (hereinafter jointly referred to as “**RECIPIENT**” and hereafter described), subject only to the RECIPIENT's strict respect of the conditions stated in the present agreement (hereinafter referred to as the “**Agreement**”).

| InstitutionInvestigator employer |  |
| --- | --- |
| ***Investigator****Asking for Original Material* |   |
| ***Site of investigation***Address where Research shall be conducted |  |
| ***Original Material*** *description and quantity* | Describe in appendix 1 |
| Scientist who will provide the Material | [Mr. Jean-François CLOIX – Neurobiology Laboratory Researcher -Jean-Francois.Cloix@univ-orleans.fr 02 38 49 49 79] |
| UNIVERSITY Laboratory | Neurobiology Laboratory directed by Mr. Tobias Hevor , based in University of Orleans, Physics and Chemistry building – B.P 6759 – 45067 Orleans CEDEX 2 |
| ***Research*** *Which shall be carried out by the Investigator through the use of Original Material (Research shall be completed with an Appendix, which shall be an integrative part of the Agreement)* |  |

**TERMS AND CONDITIONS OF THIS AGREEMENT**

**Preliminary Article - Definitions**

(i) Commercial Purposes: The sale, lease, license, or other transfer of the Material or Modifications to a for-profit organization. Commercial Purposes shall also include uses of the Material or Modifications by any organization, including RECIPIENT, to perform contract research, to screen compound libraries, to produce or manufacture product for general sales, or to conduct research activities that result in any sale, lease, license, or transfer of the Material or Modifications to a for-profit organization.

(ii) Material: Original Material, Progeny and Unmodified Derivatives. The Material shall not include: (a) Modifications or (b) other substances created by RECIPIENT through the use of the Material which are not Modifications, Progeny or Unmodified Derivatives.

(iii) Modifications: Substances created by RECIPIENT which contain/incorporate the Material.

(iv) Original Material: The research material being transferred by **UNIVERSITY**, including all relevant data.

(v) Progeny: Unmodified descendant from the Material, such as virus from virus, cell from cell, or organism from organism.

(vi) Unmodified Derivatives: Substances created by RECIPIENT which constitute an unmodified functional subunit or product expressed by the Original Material. Some examples include: subclones of unmodified cell lines, purified or fractionated subsets of the Original Material, proteins expressed by DNA/RNA supplied by **UNIVERSITY** Laboratory or monoclonal antibodies secreted by an hybridoma cell line.

**Article 1 - Object**

1.1 RECIPIENT acknowledges that this Agreement is entered into in order to encourage scientific collaboration aimed at further development and application of the Original Material and exchange of technical data.

1.2 **UNIVERSITY** agrees to supply, via EMMA, the Original Material to RECIPIENT under conditions set forth herein.

**Article 2 - Supply of Original Material**

2.1 EMMA shall send the Original Material to the Site of investigation to the attention of the Investigator.

2.2 EMMA could not be held responsible for the possible damages of transport.

**Article 3 - Use**

3.1 RECIPIENT agrees that the Material:

(a) is to be used solely for purpose of Research described here before;

(b) will not be distributed or released to any third parties for any purpose;

(c) will not be used in human subjects, in clinical trials, or for diagnostic purposes involving human subjects;

(d) is to be used only in compliance with all laws and regulations applicable to the Material; and

(e) is to be used only at RECIPIENT place and by scientists working in RECIPIENT’s laboratory or under the RECIPIENT direct responsibility.

3.2 RECIPIENT shall have the right, without restriction, to distribute substances it has created through the use of the Original Material only if those substances are not Progeny, Modified Progeny, Unmodified Derivatives, or Modifications.

3.3 Without prior written consent from **UNIVERSITY**, RECIPIENT may NOT provide Modifications for Commercial Purposes. If RECIPIENT wishes to use or obtain a license of the Material or Modifications for Commercial Purposes, RECIPIENT may first require a commercial license from **UNIVERSITY** and **UNIVERSITY** has no obligation to grant such a license to RECIPIENT. RECIPIENT acknowledges that **UNIVERSITY** can, in addition, grant a license, exclusive or non-exclusive, sell or assign all or part of said rights under the Material to third parties, subject to antecedent rights held by others.

3.4 RECIPIENT acknowledges that the Material is or may be the subject of a patent application.

Except as provided in this Agreement, no express or implied licenses or other rights are provided to RECIPIENT under any patents, patent applications, trade secrets or other proprietary rights of **UNIVERSITY**, including any altered forms of the Material made by **UNIVERSITY**.

3.5 RECIPIENT acknowledges that nothing herein shall create, or be construed to create any license to RECIPIENT or any obligation to enter into any other agreement.

**Article 4 - Property**

4.1 **UNIVERSITY** retains ownership of the Material, including any Material contained or incorporated in Modifications.

Furthermore, **UNIVERSITY** retains all rights it may have in accordance with intellectual property laws under inventions, in particular patentable, which could result from the use of the Original Material by RECIPIENT.

4.2 Modifications realized only by **UNIVERSITY** shall be the entire property of **UNIVERSITY**.

Modifications realized by both **UNIVERSITY** and RECIPIENT, or by the sole RECIPIENT, shall be the co-ownership of **UNIVERSITY** and RECIPIENT.

4.3 RECIPIENT retains ownership of those substances created through the use of the Material or Modifications, but which are not Progeny, Unmodified Derivatives or Modifications (i.e., do not contain the Original Material, Progeny, or Unmodified Derivatives). A co-ownership agreement shall be negotiated for said substances which result from collaborative joint efforts between **UNIVERSITY** and RECIPIENT.

4.4 With exception to articles 4.1, 4.2 and 4.3 disposals here-above, ownership of all Research results, patentable or not, shall be function of the inventive contribution of the participants to their achievement. In case that all or part of the Research results could be protected by a new patent application naming one or more **UNIVERSITY** and RECIPIENT inventors, the parties shall consult each other to define the modalities of such a patent application filing, and its exploitation conditions.

4.5 RECIPIENT will not file, or have filed in the name of third parties in any country, any patent application, or intellectual property rights (copyrights, trademarks,...) claiming Material, Modifications, or any other material that could not have been made without the Material, or manufacture or use method(s) of the Material or Modifications.

4.6 RECIPIENT undertakes to supply to **UNIVERSITY**, free of charge and within the best delay, the Modifications resulting from the use of Material.

**Article 5 - Publication - Confidentiality**

5.1 This Agreement shall not be interpreted to prevent or delay publication of Research findings resulting from the use of the Material or from its Modifications. RECIPIENT shall supply **UNIVERSITY** with a copy of all publication draft.

5.2 In accordance with scientific customs, the contributions of those who have made Material available or of collaborators, if any, from **UNIVERSITY** will be reflected expressly in all written or oral public disclosures concerning Research using the Material by acknowledgment or co-authorship, as appropriate. The origin of the Material and any applicable patent notices must be included in such disclosures.

5.3 Nothing however in this Agreement shall be construed as conferring rights to use in advertising, publicity, or otherwise the name of **UNIVERSITY**.

5.4 RECIPIENT undertakes to respect and maintain strictly confidential all information identified as confidential received from **UNIVERSITY** Laboratory.

RECIPIENT ensures that its personnel and any other persons in its service in any respect whatsoever respect and agree to respect the confidential nature of said confidential information.

RECIPIENT undertakes to use confidential information only in the framework of the present Agreement.

Article 5.4 disposals shall take effect on the enter into force of the present Agreement and shall stay in force for a five years period, notwithstanding expiration or earlier termination of the present Agreement.

**Article 6 - Warranties**

6.1 RECIPIENT accepts the Original Material "as is" and acknowledges that it is experimental in nature and that it should be used with prudence and appropriate caution, since not all of its characteristics are known and it may have hazardous properties. **UNIVERSITY** makes no representations and extend no warranties of any kind, either expressed or implied. No warranties, express or implied are offered by **UNIVERSITY**, or by the inventors as to the merchantability or fitness for a particular purpose of the Material or against infringement. **UNIVERSITY** and its president, officers, employees, or agents assume no liability and make no representations in connection with the Material use by RECIPIENT. RECIPIENT will defend, indemnify and hold harmless **UNIVERSITY**, its directors, officers, employees, and agents from any damages, claims, or other liabilities which may be alleged to result or arise from the use of the Material or information related thereto.

6.2 **UNIVERSITY** makes no representation that the use of the Material will not infringe any intellectual property right of any third party.

**Article 7 - Terms of contract**

7.1 This Agreement enters into force at the last date mentioned on signature page and shall be terminated on the earliest of the following dates: (a) 2 years from the date of signing this Agreement, or (b) on completion of RECIPIENT's current Research with the Material, or (c) 30 days after sending by either party to the other of a termination written notice, provided that:

- if termination should occur under (a) or (b), RECIPIENT shall discontinue its use of the Material and shall, according to **UNIVERSITY** instructions, return or destroy any remaining Material. RECIPIENT shall, at its own discretion, also either destroy the Modifications or remain bound by the terms of this Agreement related to Modifications, and

- in the event **UNIVERSITY** terminates the Agreement under (c) other than for breach of this Agreement or for cause such as an imminent health risk or patent infringement, **UNIVERSITY** will defer the effective date of termination for a period of up to one year, upon request from RECIPIENT, to permit completion of Research in progress.

7.2 At the expiration date of said period or at the effective expiration date, RECIPIENT shall discontinue its use of the Material and shall, according to **UNIVERSITY** instructions, return or destroy any remaining Material. RECIPIENT shall, at its own discretion, also either destroy Modifications or remain bound by the terms of the Agreement related to Modifications.

**Article 8 - Miscellaneous**

8.1 This Agreement shall be governed by the laws of France. The French court shall have sole jurisdiction for any litigation related to interpretation or execution of the Agreement, which parties shall not solve in an amicable way.

8.2 This Agreement constitutes the complete Agreement between **UNIVERSITY** and RECIPIENT with respect to the subject matter hereof, and supersedes all prior oral or written understandings, communications or agreements not specifically incorporated herein. If any provision of this Agreement is held to be unenforceable for any reason, such provision shall be reformed only to the extent necessary to make it enforceable, and such decision shall not affect the enforceability (i) of such provision under other circumstances, or (ii) of the remaining provisions hereof under all circumstances.

In witness whereof, RECIPIENT and **UNIVERSITY** have executed this agreement as of the date below written.

|  |  |
| --- | --- |
| **UNIVERSITY**Signature*\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*Name : Title : Date :       | **RECIPIENT**Signature\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_*(Authorized signatory of the Institution)*Name :      Title:      Date :       |
| READ, UNDERSTOOD AND AGREED TO BY THE UNIVERSITY SCIENTIST :Signature\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Name:      Title:      Date:       | READ, UNDERSTOOD AND AGREED TO BY THE INVESTIGATOR :Signature\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Name:      Title:      Date:       |

**APPENDIX 1: Material Description**/**Quantity.**

In various animals methionine sulfoximine (MSO) induces tonico-clonic seizures resembling the most striking form of human epilepsies. Brain glycogen could be considered as an energy store for neuronal activity, with high relevance in epilepsies. Selection of two lines of mice based upon differences in their latency to MSO-dependent seizures was undertaken.

Random crosses involving eight inbred mice strains performed such a selection. We generated the starting population in which the first MSO challenge (75 mg/kg, ip) was performed. Two groups of 16 breeding pairs were established by mating mice having the shortest (MSO-Fast) and the longest (MSO-Slow) convulsion latencies. Mating and selection by latency to MSO (75 mg/kg, ip) was carried out over six generations. MSO-Fast mice presented a significantly shorter MSO latency, and were more susceptible to MSO than MSO-Slow ones. EEG alterations were observed during the pre-convulsive period when MSO-Fast mice were submitted to 75mg/kg of MSO, and MSO-Slow ones to 200mg/kg. Using another convulsant, kainic acid, the latency to convulse of MSO-Fast mice was significantly shorter than that of the Slow ones, whereas no difference was observed in response to pentylenetetrazole. MSO-dependent convulsions were completely antagonized by MK-801, and partially by valproic acid, suggesting a preferential involvement of glutamatergic pathways. The increase in brain glycogen content induced by MSO is significantly lower in MSO-Fast than in MSO-Slow. At the onset of seizures the degradation of accumulated glycogen was higher in MSO-Slow mice than in MSO-Fast ones. Moreover, a positive correlation was observed between the magnitude of latency toward MSO-induced seizures and brain glycogen content in the eight parental strains used for selection. A striking proportionality between the content of glycogen and 5-hydroxytryptamine (5-HT) was observed in cerebral cortices of both selected lines. However, the cortical 5-HT level is higher in MSO-Fast than in MSO-Slow, and it is significantly decreased at the onset of seizures in both lines. Brain glycogen content is implicated in the developed model of mice with different latency to MSO-dependent seizures: The higher the brain glycogen content, the longer the latency; and 5-HT is involved in the control of latency to seizures-induced by MSO in these two lines.

The model that we have developed for MSO “sensitive” and “resistant” mice could allow for a better understanding of MSO mechanisms of epileptogenesis, and it may also constitute a useful approach for therapeutic actions of drugs. Moreover, such a model could lead to a better understanding of MSO mechanisms of epileptogenesis, and the relationship between epileptogenic and glycogenic MSO effects. It might serve as a model for studying the reason why epileptogenesis occurs.

Nowadays, we had performed 4 additional challenges of the two lines by increasing the pressure selection. Afterward, we had realized 9-10 inbreeding crosses for both lines. We can provide EMMA with such inbreed mice of MSO-Fast and MSO-Slow lines. In MSO-Slow mice we obtained only one line of inbreed mice. Conversely, in MSO-Fast mice we obtained two inbreed lines diverging after the 3rd inbreeding cross.