

AGREEMENT BETWEEN INSTITUT PASTEUR
AND RECIPIENT OF THE TRANSGENIC ANIMALS

DB/EB-06/1024

1 - The transgenic mice NAS, as described in Appendix A mice developed by Dr Michel Cohen-Tannoudji, allows to visualize Notch activity *in vivo*. The transgenic mice NAS and all progenies and derivatives, (unmodified and modified mice after cross-mating or by *in vitro* or *in vivo* genetic modification of the original genome) herein after called "the animals" will be provided to the Recipient (Research Investigator), subject to the following terms:

2 – The animals will be used by the Recipient's Laboratory only for application in basic research program as mentioned of the Recipient mail dated 13 november 2006. Here attached in Appendix B.

The animals will not be used for any commercial purposes whatsoever by the Recipient's Laboratory or his Institution.

No other right or license is granted or implied hereby.

The animals will not be distributed to any other party, scientist, and laboratory either within the Recipient's Institution or external to his Institution and in particular to companies without the prior written authorization of the Director of Institut Pasteur.

3 – Institut Pasteur would like that the Research Investigator communicates to Dr Michel Cohen-Tannoudji (Institut Pasteur) the results obtained with the animals or their use at least thirty days (30) prior all public divulgation (orally or by paper).

4 – In all publications relative to the use of the animals by Recipient, the references of the animals will be employed will be employed and citation of Dr. Michel Cohen-Tannoudji et al's work will be made by the Recipient.

5 – The animals" are provided as a service. The Recipient and his Institution agree to waive all claims against Institut Pasteur from all damages arising from his use, storage and handling of the animals by the Recipient. All formalities relative to the importation of the animals will be taken by the Recipient and his Research Institution.

6 – The Recipient and the Research Institution agree not to claim or not to describe the animals or the applications of said biological material or a fragment of said "animals" in any patent application or equivalent rights.

The parties agree that know-how, inventions, data and other intellectual property generated by the Recipient and Research Institution within the scope of the animals during the research program as defined in paragraph 2 of the present agreement, will be the co-owned 50/50 by Institut Pasteur and the Research Institution.

The expenses relative to the patenting will be shared also 50/50 between the parties.

If the animals are bred with Recipient's animals of a different genetic strain, Institut Pasteur and Recipient will jointly own such cross-bred mice.

The Recipient agrees to take all actions reasonably required to ensure any Institut Pasteur rights in such property that may be developed or discovered by using the animals or a fragment of said animals above defined or by using the animals during the research program as defined here above.

7 –The animals, object of the present agreement, is a Genetically Modified Micro-organism (GMO), consequently, the receiver commits himself to comply with the related Law in force in his country.”

8 – Institut Pasteur will provide to the Recipient 2 males of the animals object of the present agreement. The Recipient of the animals is duly authorized by Dr Michel Cohen-Tannoudji to generate progenies during the duration of the Program estimated to 5 years and defined as in the above paragraph 2.

At the end of the Program as defined in the paragraph 2 of the present agreement, the Recipient agrees to cease breeding and prevent further breeding of the animals and certify that all remaining animals have been sacrificed.

9 – The Recipient and Research Institution agree that the animals will not be used in human subjects, in clinical trials, or for diagnostic purposes involving human subjects.

10 – This Agreement is governed by the laws of France.

If the foregoing terms are acceptable, please sign in the space below, have a representative of the Recipient’s Institution sign in the space indicated for the signature, and return two (2) originals of the present agreement for the attention of Dr Michel Cohen-Tannoudji (Unité de Génétique Fonctionnelle de la Souris, Institut Pasteur, 25 rue du Docteur-Roux – 75015 PARIS), and one (1) original for the attention of Danielle Berneman, Service des Brevets et Inventions » (Institut Pasteur).

After receipt, Institut Pasteur will arrange for prompt shipment.

The undersigned research Investigator (“Recipient”) and Research Institution agree and accept the foregoing.

<u>Name of Research Investigator</u>	<u>Research Institution</u>	<u>Institut Pasteur’s Scientist</u>	<u>Agreed by</u>
Recipient of the animals			
		Michel Cohen-Tannoudji	
			Institut Pasteur
	Represented by :		
Date :	Date :	Date :	Date :
Signature :	Signature :	Signature :	Signature :

APPENDIX A

The Notch signalling pathway plays a central role in the control of cell-fate decisions in a wide variety of cell lineages in invertebrate and vertebrate development. It is involved in the development of many cell types and modification of its activity can dramatically affect proliferation, differentiation and apoptotic events. Accordingly, genetic alterations of Notch pathway components have been implicated in various pathologies in humans, including cancer.

RBP-J, a DNA binding protein, is the effector of Notch activity in the nucleus and is used as such by the four mammalian Notch receptors. We have produced the *TP1-nlacZ* construct consisting of a *nls-lacZ* reporter gene under the control of a minimal Notch promoter and multiple RBP-J binding sites. Activity of this transgene is therefore expected to monitor the activity transduced by Notch receptors. The NAS transgenic mouse line has been derived by microinjection of the *Tp1-nlacZ* construct. Our studies indicate that *lacZ* expression can be detected in several tissues where Notch signalling is known to control cell-fate decisions. The NAS transgenic mouse is a valuable tool to report on Notch activity and therefore to study its function.

Description of the NAS line has been published in *Genesis*:

Souilhols, C., S. Cormier, M. Monet, S. Vandormael-Pournin, A. Joutel, C. Babinet, and M. Cohen-Tannoudji. 2006. NAS transgenic mouse line allows visualization of Notch pathway activity *in vivo*. *Genesis*. 44 :277-86.

Use of the NAS line to study a mouse model of CADASIL disease has been published in *Human Molecular Genetics*:
M Monet, M., Domenga, V., Lemaire, B., Souilhols, C., Langa, F., Babinet, C., Gridley, T., Tournier-Lasserre, E., Cohen-Tannoudji, M., and Joutel, A. The archetypal R90C CADASIL-Notch3 mutation does not compromise normal Notch3 function *in vivo*. *Human Molecular Genetics*, 2007, Apr 15;16(8):982-92. Epub 2007 Mar 1.

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APPENDIX B

Research program proposed by the recipient: