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## AGREEMENT

Between

INSERM  
("INSERM")

and

THE WELLCOME TRUST ("THE TRUST")  
as Trustee

### 1 BACKGROUND

- 1.1 THE TRUST of 183 Euston Road, London NW1 2BE, United Kingdom has funded and will continue to fund, research at The Wellcome Trust Centre for Human Genetics in Oxford ("THE CENTRE").

The results of the said research and all intellectual property and other property deriving therefrom are vested in THE TRUST.

- 1.2 INSERM has funded and will continue to fund research at INSERM U36, Pathologie Vasculaire et Endocrinologie Rénale, Collège de France, 3 rue d'Ulm, 75005 Paris, France under the direction of Dr Pierre Corvol, and at INSERM Unit 358, Génétique des Maladies Humaines, Hôpital Saint Louis, Bâtiment INSERM, 75010 Paris.

The results of all such research and all intellectual property and other property deriving therefrom are vested in INSERM.

- 1.3 THE CENTRE under the direction of Dr Mark Lathrop ("Dr Lathrop") and INSERM through Dr Pierre Corvol, Dr Xavier Jeunemaitre (INSERM U36) and Dr Florent Soubrier (INSERM U358, Batiment INSERM, Hop St Louis, 75010 Paris) and their colleagues wish to collaborate in a programme of work concerned with the identification and characterisation of genetic markers and/or genes involved in, or causative of, cardiovascular disease ("the Programme").

- 1.4 The Parties have thus agreed to enter into this Agreement which sets out the obligations of each of them and terms and conditions relating to the ownership, protection and exploitation of property, intellectual property and the results arising from the Programme and other matters to be negotiated between the Parties from time to time.

## 2 THE PROGRAMME

- 2.1 An outline of the Programme and the contributions of each Party are given in the Schedule. The detail of the Programme will be agreed by the Parties from time to time. Each of THE CENTRE and INSERM agrees to carry out at its own cost and expense those parts of the Programme allocated to it unless agreed otherwise.
- 2.2 The Parties agree to comply with all local laws and government regulatory requirements applicable to their conduct of the Programme and particularly any regulations and guidelines relating to DNA collections. It is recognized that DNA samples and the computerized files containing the corresponding clinical and biological information will be transferred under conditions guaranteeing the anonymity of patients.
- 2.3 Each Party shall keep or cause to be kept detailed records of the Programme in sufficient detail and in good scientific manner appropriate for patent purposes which properly reflect all work done and results achieved under the Programme in scientific notebooks and upon request shall make copies of those records and notebooks available to the other.
- 2.4 Each Party shall report to the other at a minimum of quarterly intervals on its progress under the Programme and on all information and results arising from the Programme.
- 2.5 Each Party agrees for the duration of the Programme not to collaborate in any work for or with a commercial or non-commercial third party the same as or closely similar to the Programme or forming part of the Programme and not to transfer or release to any third party any materials used in or arising out of the Programme without first discussing and agreeing in writing with the other Party such collaboration or transfer of materials and the terms thereof. Further, any proposal for an extension of the Programme or use of data generated by the Programme in collaboration with or by any third party shall first be agreed to between the Parties hereto in writing.

### 3 LICENCES

- 3.1 Subject to the provisions of Clause 4.3(a) the ownership of property and/or intellectual property relevant to the Programme and in existence at the date of signature of this Agreement ("Existing Property and IP") shall remain with the originating Party. Details of INSERM's Existing Property and IP are given in part 1 of the Schedule and of THE TRUST's Existing Property and IP in part 2 of the Schedule.
- 3.2 INSERM shall disclose and make available to THE CENTRE the Existing Property and IP set out in part 1 of the Schedule insofar as this is necessary in order to carry out the Programme and shall grant THE CENTRE a non-exclusive licence to use the same for the purposes of the Programme. Where INSERM is supplying property to THE CENTRE, it shall supply such quantities as the Parties agree are necessary to enable THE CENTRE to perform the Programme.
- 3.3 THE CENTRE shall disclose and make available to INSERM the Existing Property and IP set out in part 2 of the Schedule insofar as this is necessary in order to carry out the Programme and shall grant INSERM a non-exclusive licence to use the same for the purposes of the Programme. Where THE TRUST is supplying property, it shall supply such quantities as the Parties agree are necessary to enable INSERM to perform the Programme.

### 4 OWNERSHIP

- 4.1 Subject to the provisions of Clause 4.3(a) the ownership of property and/or intellectual property arising from the Programme ("Programme IP") shall be determined as follows:
- (a) if developed solely by one Party, it shall belong to that Party provided that any Programme IP generated by THE CENTRE shall belong to THE TRUST;
  - (b) if developed jointly by INSERM and THE CENTRE it shall belong to THE TRUST and INSERM jointly.

In the event of any difficulty in deciding whether any particular property shall fall into Category (a) or Category (b) in this Clause 4.1 the matter shall be decided by agreement between Dr Lathrop and Dr Corvol.

- 4.2 For Category 4.1(a), the filing, prosecution and maintenance of patent applications and patents shall be the responsibility of THE TRUST or INSERM as appropriate at its own cost and expense.

For Category 4.1(b), the responsibilities of filing, prosecution and maintenance of patent applications and patents shall be agreed on a case-by-case basis. Costs and expenses shall be shared equally between THE TRUST and INSERM.

Each Party shall keep the other informed of all matters relating to patent filings and on request make available to the other copies of patent applications. If either Party shall wish to abandon any patent application or patent it shall first offer it to the other for adoption. The other Party shall use its best endeavours to notify the offering Party within thirty (30) days of being offered any patent or patent application, whether or not it wishes to accept such offer. On adoption, the ownership and other obligations and expenses shall transfer to the adopting Party.

- 4.3 (a) Whereas each Party has obtained the necessary consents from any third party to use materials, property or intellectual property for the purposes of the conduct of the Programme, the Parties hereby recognise that the commercial exploitation of the results of the Programme may necessitate further licence or transfer of rights from such third parties and each of INSERM and THE TRUST hereby agree to use all reasonable endeavours to obtain such rights for the purposes envisaged by this Agreement.
- (b) Subject to the provisions of Clause 4.3(a) and with regard to commercial interest in and commercial exploitation of the Programme IP, the following shall apply:
- (i) each Party will notify the other of any approaches or other expressions of interest from commercial organisations; and
  - (ii) the Parties shall discuss and agree the strategy to be adopted with regard to commercial exploitation including but not limited to issues such as:
    - the commercial organisations to be approached;
    - the method and timing of the approach;
    - the structure or nature of collaborative programmes with industry;
    - deal structures, licence terms and procedures for negotiation;
    - the responsibilities of each Party in pursuing these matters;

- the share of the costs of commercial exploitation and the share of any net revenue (not research funding) between them;
- the rights of any third parties subsisting in the Existing IP or Programme IP and the method by which these shall be addressed.

4.4 Subject to Clause 4.3 each of INSERM and THE TRUST shall be free to exploit the Programme IP vested in it pursuant to Clause 4.1(a) unless otherwise agreed between the Parties. Each of INSERM and THE TRUST shall inform the other of the nature of any rights to be granted to any third party over the Programme IP the subject of Clause 4.1(a) prior to grant of such rights.

## 5 CONFIDENTIALITY

Subject to the provisions of Clauses 4.3 and 4.4 or unless otherwise agreed in writing, each Party shall keep and the Programme IP secret and confidential and not disclose the same to any third party. The obligations of confidentiality shall be subject to the usual exceptions relating to information in the public domain. These obligations shall apply in each case for five (5) years post-termination of these Heads of Agreement.

## 6 PUBLICATION

6.1 Each Party agrees to submit or procure the submission of a copy of any proposed publication relating to the Programme, including abstracts for public oral presentations, to the other at least thirty (30) days prior to submission for publication or oral presentation. The Party to whom the submission is made shall have the right:

- (a) to propose modifications to the publication for patent reasons; or
- (b) to request delaying publication or presentation for sixty (60) days to enable patent applications to be filed.

If any patent application cannot be completed within the sixty (60) day period, then a thirty (30) day extension may be requested, such request not to be unreasonably withheld.

Permission to proceed with the publication or other dissemination of results obtained from the Programme shall be authorised by the signatures of Dr Mark Lathrop for and on behalf of THE CENTRE and/or by Dr Pierre Corvol for and on behalf of INSERM or their nominated representatives from time to time.

## **7 USE OF NAME**

Neither Party shall use the name of the other for advertising or publicity purposes without its consent.

## **8 TERM AND TERMINATION**

8.1 Subject to the provisions for earlier termination and for termination for breach/insolvency on usual terms, this Agreement will become effective as of the date of signature by both Parties and shall remain in effect until 31 December 1997 unless otherwise agreed between the Parties.

8.2 Termination of this Agreement shall not affect the accrued rights of the Parties arising in any way as at the date of termination and in particular, but without limitation, the right to recover damages against any other Party and all provisions which are expressed to survive this Agreement shall remain in full force and effect.

8.3 Upon expiry or termination of this Agreement each Party shall return to the other all Existing Property and IP supplied to it by the other Party and shall have no further right to use or exploit the same.

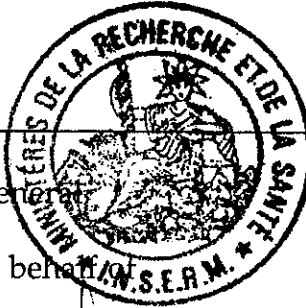
## **9 OTHER TERMS**

9.1 Neither Party may assign its rights and obligations under this Agreement without the prior written consent of the other, except that THE TRUST may assign its rights and obligations to an affiliate.

9.2 The validity, construction and performance of this Agreement shall be governed by the laws of England and all disputes relating thereto shall be subject to the non-exclusive jurisdiction of the English courts.

Signed by:

C. GRISCELLI  
Director General




For and on behalf of  
INSERM

Date:

  
2 8 NOV. 1996

Signed by:

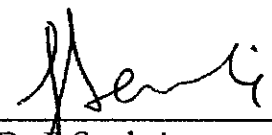
  
Dr P Corvol  
Director of Laboratory No 36

For and on behalf of  
INSERM

Date:

5/11/96

Signed by:

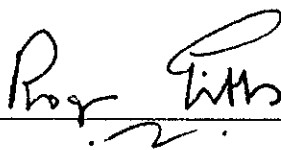
  
Dr J Soubrier  
Director of Laboratory No 358

For and on behalf of  
INSERM

Date:

12/11/96

Signed by:



SIR ROGER GIBBS  
Print Name

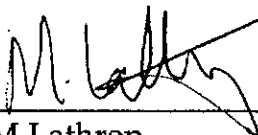
CHAIRMAN  
Title/Position

For and on behalf of  
**THE WELLCOME TRUST**

Date:

9 OCTOBER 1996

Acknowledged by:



Dr M Lathrop  
Director

**THE WELLCOME TRUST CENTRE  
FOR HUMAN GENETICS**

Date:

Oct 20 1996



## THE SCHEDULE

### THE RESEARCH PROGRAMME

The aim of this programme is to find new genetic loci responsible for human hypertension in hypertensive families recruited at Hospital Broussais, Paris. Genotyping of affected subjects from hypertensive families will be performed by positioned markers evenly distributed on the genome.

### PART 1

#### CONTRIBUTION OF INSERM UNIT 36

a) Since 1988, INSERM U36 has recruited in the Broussais Hospital a large collection of hypertensive families. The transfer of clinical, biological information and of DNA from INSERM to THE CENTRE contains information corresponding to:

- 237 hypertensive families with:
  - 555 hypertensive sibling corresponding to 438 hypertensive sibling pair.
  - 164 siblings either normotensive or with uncertain diagnosis of hypertension.
  - 247 parents (153 mothers, 94 fathers) of these hypertensive siblings.
  - 44 offspring of the hypertensive sibships.

Total of 1010 subjects identified.

- These families correspond to the complete recruitment of hypertensive families during these 5 years. It includes the following families members/BRO 001 to BRO 400, from NEV 001 to NEV 006, PES 001 to PES 003, STG 001, TOU 001 to 010, HYP 001 to HYP 102, CAN 001 to 002, VAN 001.

b) All clinical, biological and hormonal information has been collected and computerised by INSERM Unit 36. A data base "HYPEGENE" has been designed for this purpose.

- c) Genetic material (DNA samples, immortalised lymphocytes) has been collected and stored by INSERM Unit 36.
- d) INSERM Unit 36 will be in charge of maintenance of the data base and of the genetic material. In addition, recruitment of new families will be continued by INSERM Unit 36.

## **PART 2**

### **CONTRIBUTION OF THE CENTRE**

The Wellcome Trust Centre for Human Genetics has expertise in the characterisation of genetic markers for linkage studies of multifactorial diseases such as hypertension. The Centre will contribute through characterisation of approximately 300 markers spanning the human genome in the hypertension family panel. The data generated from these studies will be contributed to a joint clinical and genetic database for use by the two parties.

## **PART 3**

The coordinated effort between INSERM and THE CENTRE requires the transfer of tools and expertise from one centre to the other.

### **CONTRIBUTIONS BY INSERM TO THE CENTRE**

- Transfer of DNA of all recruited hypertensive families until April 1994. The amount of DNA will be sufficient to perform around 350 genotypes ie. around 50 µg (or less when this amount is not available for a given patient).
- Transfer of the computer file containing clinical and biological information required for the linkage analysis (as set out in Schedule 1).
- Transfer of information on the pedigrees.

### **CONTRIBUTIONS BY THE CENTRE TO INSERM U36 OR BROUSSAIS HOSPITAL**

Implementation of the programmes allowing a statistical analysis of the results obtained with markers on the database of hypertensive families.

## **PART 4**

### **EVALUATION AND DEVELOPMENT OF RESULTS**

Results obtained at THE CENTRE will be analysed in consultation with INSERM scientists.

### **DURATION OF PROGRAMME**

The Programme will last until 31 December 1997.

During the Programme, the hypertensive data base will not be given by THE CENTRE to another group for a concurrent project of positional cloning.

### **INFORMATION**

The secondary exploitation of the results from linkage will be done in priority by P Corvol, X Jeunemaitre, F Soubrier and M Lathrop.