

# Sixth Framework Programme

Life Sciences, Genomics and Biotechnology for Health  
Specific Targeted Research Programme

Prader-Willi Syndrome: a model linking gene  
expression, obesity and mental health

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The European Prader-Willi Syndrome Project

[www.pwseu.eu](http://www.pwseu.eu)

# PWS: phenotype and genotype

## Early phenotype:

- Neonatal hypotonia (severe floppiness at birth)
- Failure to thrive
- Hypogonadism

## Later phenotype:

- Characteristic physical appearance
- Short stature
- Intellectual impairment and learning disabilities
- Failure of normal secondary sexual development
- Severe over-eating and other behaviours
- High risk of affective disorder and psychotic illness

- **Genotype:**

- Two main genetic variants – absence of expression of maternally imprinted gene(s) at 15q11-13

# Aims of project

An integrated multidisciplinary investigation of Prader-Willi syndrome (PWS)

- Molecular biological studies of human tissue and knockout mouse models of PWS
  - Establishment of genetic mouse models
  - Investigation of neurobiological mechanisms and signalling pathways
  - Study of human hypothalamic tissue
- Establish the basis for future EU wide clinical studies by developing a clinical research database
  - Internet-based PWS research database
  - Testing of database and development of user manual

# Basic Science Project

## Basic science partners

- Francoise Muscatelli, CNRS, Marseille, France
- Bernhard Horsthemke, Universitat Duisburg, Essen, Germany
- Dick Swaab, Netherlands Institute for Brain Research, the Netherlands
- Alexander Huttenhofer, University of Innsbruck, Austria
- Mike Fainzilber, Weizmann Institute, Israel
- Johan Auwerx CERBM-GIE, France

## Other participants (basic science project)

- Jerome Cavaille CNRS, France

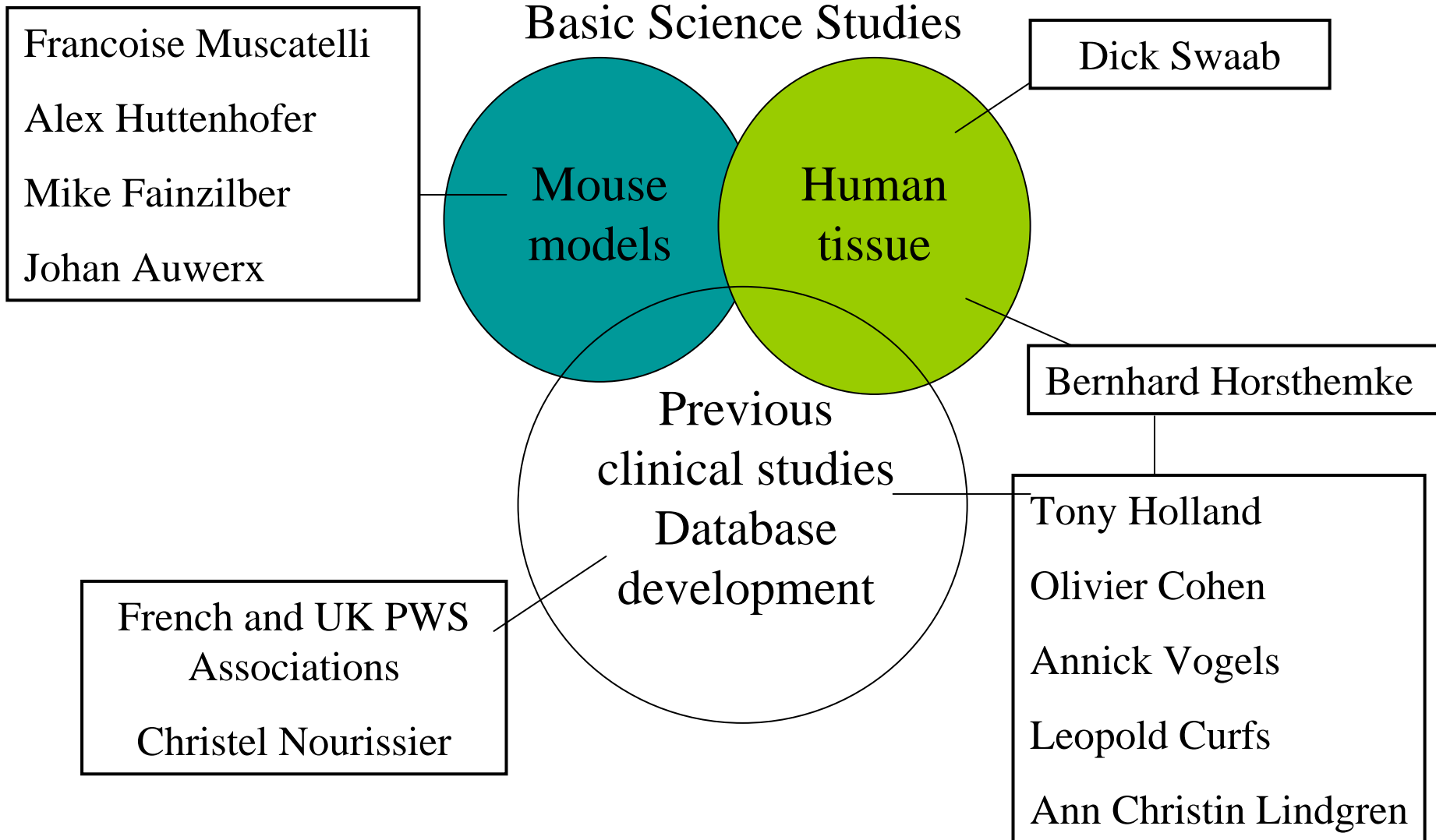
# Clinical Project

## The PWS European Database

### Clinical partners:

- Olivier Cohen, HC Forum, France
  - Leopold Curfs, psychologist, the Netherlands
  - Tony Holland, psychiatrist, UK
  - Bernhard Horsthemke, geneticist, Germany
  - Ann-Christin Lindgren, paediatric endocrinologist, Sweden
  - Annick Vogels, child psychiatrist, Belgium
- Other participants (clinical project)
    - Christel Nourissier, PWSA, France
    - Michael Boasis, HC-Forum, France
    - Oenone Dudley, France
    - Joyce Whittington, UK

# SCHEMATIC REPRESENTATION OF STUDY



# Research questions

- What is the nature of the genetic defect that results in PWS – single gene or contiguous gene syndrome?
- What is the consequence of the genetic defect on gene expression and subsequent genetic and regulatory pathways?
- How can such abnormalities account for the different aspects of the phenotype of PWS?
- What factors protect against or increase the risk or severity of specific aspects of the phenotype?

# Why multi-centred, international studies?

- Influences on the physical, cognitive, and emotional development trajectories of people with PWS across their lifespan
- Population prevalence 1: 54,000
- Sub-divisions
  - Genetic sub-type
  - Other genetic factors
  - Gender
  - Weight control
  - Early intervention
  - Growth and/or sex hormone replacement etc

# Why develop an EU database?

- To enable the reliable and lawful collection, management and analysis of data across many countries thereby having sufficient numbers of people with PWS to answer specific questions;
- Comparisons between countries allows the influence of different educational, health and social care policies on the lives of people with PWS to be investigated;
- Establishes a critical mass of inter-disciplinary clinical expertise to focus on a rare disorder and the development of best practice across the EU.

# Structure & content of the database

Index    Panels    Sub-panels    Fields

## Index

- Demographic, Diagnostic, Developmental
- Context
- Physical health
- Mental health and behaviour
- Cognitive and functional abilities
- Investigations and treatments

# Content of the database

- **INDEX**
  - Physical Health
- **PANELS**
  - Physical measurements (fields include Ht, Wt, BMI)
  - Physical illnesses (see sub-panels below)
  - Regulatory problems (fields include sleep apnoea etc)
- **SUB-PANELS**
  - Cardio-vascular
  - Central Nervous System
  - Endocrine/exocrine
  - Gastrointestinal
  - Genito-urinary
  - Musculo-skeletal/dermatological
  - Respiratory
  - Sensory/speech
  - General health screening
- **FIELDS**

# National PWS Associations

- Partnership in recruiting to the database and in managing database;
- Formulating research questions and facilitating research;
- Funding

# Progress and future

## Clinical project

- Completion of database May 2007
- Trial of database May 2007 until Nov 2008
- Development of Database manual (May 2007 until Nov 2008)
- Establishment of database administrative structures mid 2007
- Establishment of national partnerships for collaborative clinical studies across countries using the database 2007/2008 (Marie Curie)

# Benefits of project so far

- Brought together different research groups that may not have worked together;
- Brought together clinical and basic science perspectives;
- Focus for national PWS Associations across the EU;
- Basis for future EU wide collaborations