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## Génétique du développement humain

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agence d'évaluation de la recherche  
et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit

Genetics of Human Development

Department of Developmental Biology

From the

Pasteur Institute

CNRS

Mai 2010



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AERES report on the research unit  
Genetics of Human Development  
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From the  
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Le Président  
de l'AERES

Jean-François Dhainaut

Section des unités  
de recherche

Le Directeur

Pierre Glorieux

Mai 2010



# Research Unit

Name of the research unit: Genetics of Human Development

Requested label: Pasteur Unit

N° in the case of renewal

Name of the director: M. Kenneth McELREAVEY

## Members of the review committee

### Chairperson

M. Richard BEHRINGER, UTMD Anderson Cancer Center, Houston, USA

### Other committee members

M. Peter BECKER, Ludwig-Maximilians Universität München, Germany

M. Jonathan EPSTEIN, University of Pennsylvania, Philadelphia, USA

M. Patrick HARDY, EMEA, Saint-Vulbas, France

M. Roger PATIENT, University of Oxford, United-Kingdom

M. Philippe SORIANO, Mount Sinai Medical Center, New-York, USA

M. Thierry GRANGE, Institut Jacques Monod, Paris, France

M. Richard MOXON, Weatherall Institute of Molecular Medicine, Oxford, United-Kingdom

M. Gabriel WAKSMAN, University of London, United-Kingdom

### Committee members nominated by staff evaluation committees

M. Pascal DOLLE, CoNRS member

## Observers

### AERES scientific advisor

M. Jean-Antoine LEPESANT

### Pasteur Institute representatives

M. Tony PUGSLEY

M. Alain ISRAEL

### CNRS representative

M. André LE BIVIC



# Report

## 1 • Introduction

- **Date and execution of the visit:**

The review of the Département de Biologie du Développement/URA 2578 was held on March 1-3, 2010.

- **History and geographical localization of the research unit, and brief presentation of its field and scientific activities:**

The Département de Biologie du Développement/URA 2578 has a strong emphasis on mouse developmental genetics, initiated by its founders in the 1970's. However, over the last 10 years new model systems have been added, including *Drosophila*, zebrafish, and amphioxus as well as human genetics. The research focuses on the developmental processes that occur from fertilization to the generation and homeostasis of multicellular organisms. Areas of research emphasis include cell differentiation and lineage, organogenesis, gene regulation, RNA metabolism, epigenetics, Notch signaling, and disease resistance.

- **Management team:**

The URA is headed by Mrs Margaret Buckingham, whereas the Department is headed by Mr. Philip Avner. They work closely together to manage a highly cohesive, interactive, and productive enterprise.

- **Staff members (on the basis of the application file submitted to the AERES):**

Past Future  
1-09-2007/1-01-2011

	Past	Future
	1-09-2007	1-01-2011
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1,50	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file) = Permanent researchers EPST + I.PASTEUR	32,5	36,5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file) = researchers on short term contract-Postdocs	19	18
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) = ITA EPST + I. PASTEUR including research engineers	30,75 6	33,65 5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file) = ITA on short term contract	0	0
N6: Number of Ph.D. students (Form 2.8 of the report and 2.7 of the project file)	23	20
N7: Number of staff members with a HDR or a similar grade	18	19



## 2 • Overall appreciation on the research unit

- **Overall opinion:**

This research unit is considered one of the top developmental biology departments in the world, with multiple internationally recognized stars. The research themes of the teams comprehensively cover the central questions of developmental biology. There is a great tradition and strength in mouse genetics and embryology but also outstanding groups utilizing *Drosophila*, zebrafish, and other vertebrate systems. There is a good critical mass of research teams, with numerous tenured scientists, postdoctoral fellows, graduate students and technical staff. The department has a strong record of training, leading to tenured scientists being promoted within the department to Group or Unit leader status or leaving the department to initiate their own research groups at other institutions. The publication record overall is outstanding with papers in top peer reviewed journals. There is outstanding European and international visibility. Indeed, the head of the unit has just received the Lifetime Achievement Award from the Society of Developmental Biology based in the USA. The Department also appears very cohesive and well run with a focused research seminar program, technology seminars, symposia on special topics (Bio-Imaging), journal club, student-initiated Developmental Biology Club, monthly lab head meetings, and scientific retreats.

Although the Department excels in these areas, there are minor but potentially significant concerns by the tenured scientists, postdoctoral fellows, graduate students and technical staff that should be addressed to enhance training, mentoring, and communication. For graduate students, there was a desire to have regular research mentoring committees for feedback on their thesis research. For postdoctoral fellows, there was a desire for more infrastructure to facilitate research, particularly for information services (computing) such as wireless internet, site licenses for commonly used software and restrictions on computer hardware acquisition. For tenured scientists, there was a desire for enhanced core facilities and concerns about opportunities to supervise graduate students, applying for independent funding and publishing as last authors. For the technical staff, there was a desire for more communication between Institut Pasteur, Team Leaders and the above groups about the research enterprise.

The two Core facilities based in the Department are outstanding, however, deficiencies in certain IP Cores have significantly held back research progress by the departmental teams that must be addressed.

- **Strengths and opportunities:**

Many of the research teams are examining cutting edge topics. The group as a whole has scientific bravery addressing ambitious questions in genetics, developmental biology, and infectious disease. The Department has an outstanding international reputation. There appear to be a reasonable number of departmental collaborations that provide both intellectual and social cohesion. There are two outstanding Cores within Department, including the Mouse Genetics Engineering Center and Central Mouse Facilities. The creation of a Scientific Advisory Board would likely be beneficial to the Department, especially at this time when several senior faculty are nearing retirement age.

- **Weaknesses and threats:**

The teams require standard and cutting edge technologies to move their research forward and remain internationally competitive. These technologies include sophisticated microscopy, transgenic and knockout mouse production, flow cytometry, mass spectrometry, RNA-seq and ChIP-seq. Whereas the Mouse Genetics Engineering Center, the Central Mouse Facilities, and Imaging Core Facility within the Department were deemed outstanding, there were very serious deficiencies in IP Core Facilities that provide DNA sequencing, flow cytometry, and mass spectrometry. In addition, there is a serious deficiency in bioinformatics support to the teams. These deficiencies are significantly hindering research and forcing the teams to seek these technologies off campus. This is a serious threat to research for the department and IP.



- **Recommendations to the head of the research unit:**

The committee appreciates that this is a time of risk and opportunity for the Department because of the pending retirements of very prominent team leaders. The loss of these two prominent teams studying mouse genetics and development will leave a large scientific and leadership vacuum in the Department.

There are times when for whatever reasons there are gaps in funding for a unit. Apparently, there is currently no formal mechanism at the IP to provide bridge funding to maintain unit research integrity during these transient times. This poses a threat to research unit continuity.

- **Data on the work produced :**

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	35
A2: Number of other researchers (recorded in N3, <del>N4 and N5</del> ) who are active in research	16
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	5
A5: Number of PhD granted during the past 4 years	22

### 3 • Appreciation team by team

**Team:** Genetics of Human Development

**Team leader:** M. Kenneth McELREAVEY

- **Staff members:**

Past Future  
1-09-2007/1-01-2011

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file) ) = ITA EPST + I. PASTEUR including research engineers	1 0	1,30 0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	2
N7: Number of staff members with a HDR or a similar grade	1	1



- **Appreciation on the results:**

The team has made important contributions to the genetics of human disorders of sexual development (DSD) in the last 4 years, publishing 47 peer-reviewed manuscripts. There were 29 papers in which a member of the team was senior author and/or first author. They have exploited a very large collection of human samples of DSD, infertility, and controls to screen for mutations in candidate genes. The team has made new and important discoveries using this human genetics approach to identify alleles that correlate with reproductive pathologies. The team discovered that about 10% of 46 XY DSD are caused by dominant mutations in MAP3KI. In addition, in 2009, the team published a very high profile manuscript describing mutations in the orphan nuclear hormone receptor NR5A1 that are associated with ovarian insufficiency. Furthermore, two other manuscripts are under review at the very prestigious New England Journal of Medicine. These studies bring molecular clarity to a significant proportion of genetically based DSDs. These types of human genetic approaches can open up new molecular studies for the entire field of vertebrate sex determination pathways.

- **Appreciation on the impact, the attractiveness of the research team and of the quality of its links with international, national and local partners:**

The team is internationally recognized as one of the experts in the field of the genetics of human DSDs. The team successfully recruited a permanent investigator who has had a very significant and positive impact on the team. The nature of the team's research depends greatly on collaborations to acquire human samples that are essential for the team's studies.

- **Appreciation on the strategy, governance and life of the research team:**

The team is organized into gene mutation discovery and functional experimental studies. This is a good strategy for the research program.

- **Appreciation on the project:**

The medium and long-term scientific plans are good. In the next few years, gene mutation discovery is likely to identify the bulk of mutations linked to DSDs. Thus, it is prudent to expand the team's research into functional studies using embryonic stem cell systems. There is also a project proposed on epigenetic profiling of human sperm for imprinted loci. The functional studies are ambitious and creative. If these studies are successful, then much will be learned about the molecular mechanisms of germ cell specification and the supporting niche relative to mammalian fertility.

- **Conclusion:**

The team is one of a handful of internationally recognized experts and contributors to the human genetics of DSDs and fertility. The team is a strong balance of human genetics and mutation discovery and functional studies using embryonic stem cell technologies for germ cell specification and niche biology. Although the team can have up to 9 members there is only space available for a maximum of 6-7 individuals that is hindering research progress.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A+	A	A



INSTITUT PASTEUR

*Human Developmental Genetics*

Paris 28/04/2010

We have read the AERES report and we have no comments to make in reply to the evaluation report concerning the unit of Human Developmental Genetics that was produced by the AERES review committee.

Sincerely

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Human Developmental Genetics Unit  
Department of Developmental Biology

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**DIRECTEUR DE L'ÉVALUATION SCIENTIFIQUE**  
**INSTITUT PASTEUR**