# SBRI
## Stem-cell & Brain Research Institute Lyon

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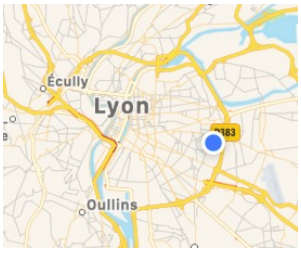
Université Claude Bernard Lyon 1

The Stem cell and Brain Research Institute (SBRI) research is a multidisciplinary with interests ranging from stem cells biology, developmental neurobiology, integrative and cognitive neuroscience and chronobiology disorders. SBRI research is organized in 6 teams and 2 international research platforms. SBRI is affiliated to INSERM and University de Lyon with strong links to INRAe and CNRS.

One common asset is the investigation of human and non-human primate specific features addressed at multiple levels of exploration ranging from the earliest embryonic developmental stages to the structure and function observed in the adult cortex.






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# Building the cerebral cortex


## Cell and molecular mechanisms:

Colette Dehay – Florence Wianny

Serge Nataf – Laurent Pays

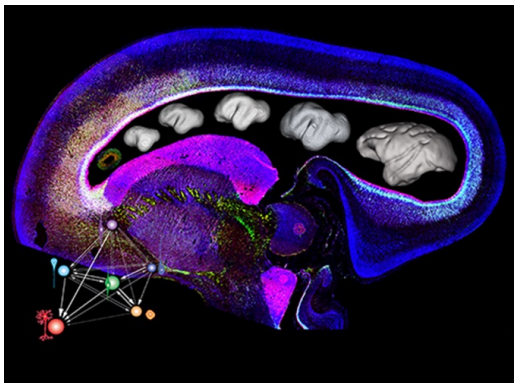
## Connectomics:

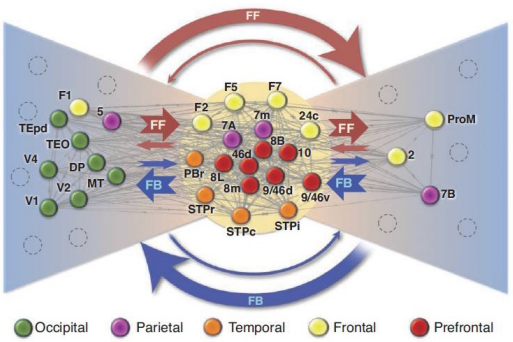
Julien Vezoli - Kenneth Knoblauch – Henry Kennedy


Our work has shown that the non human primate corticogenesis differs markedly from that in rodent and shares key features with the human primate. Our objective is to further characterise primate-specific features of corticogenesis and mechanisms at the origin of neurodevelopmental diseases. We mostly focus on cell-cycle control and neuronal migration in the non-human primate and in human cerebral organoïds.

Using modelling as well as large-scale and multimodal investigation of the connectome, our objective is to understand how the organization of interareal connections constrains the flow of information in the primate cortex. We are collaborating with the Allen Institute for Brain Science to characterize the molecular identity of interareal projection neurons in the cortex and develop the tools for their in vivo modulation.

One major joint question is how the key properties of primate-specific germinal zones contribute to unique structural features of cortical structure, connectome and function.






**CONNECTOMICS**




## Collaborations:

Washington University in St. Louis 1853 · RIKEN · University of Oxford · Institute of Neuroscience, Chinese Academy of Sciences – 1999 – · Donders Institute · University of Notre Dame · ESI · Allen Institute

## Sponsors:

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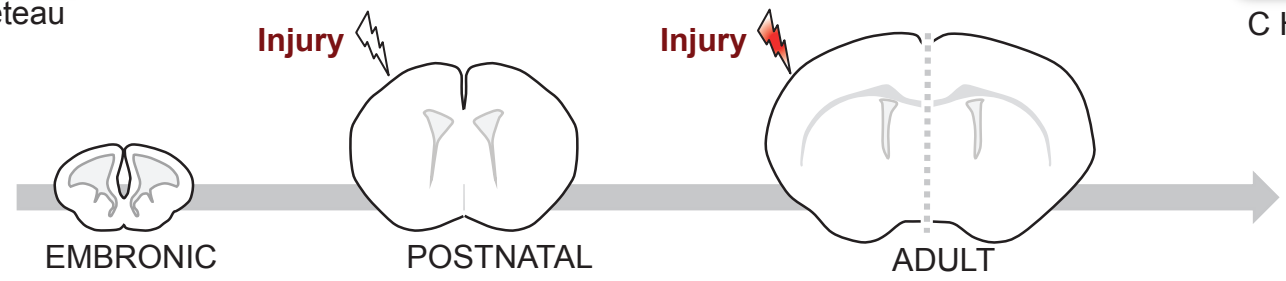


O Raineteau

# Cell Programming and Reprogramming in the Brain



C Heinrich

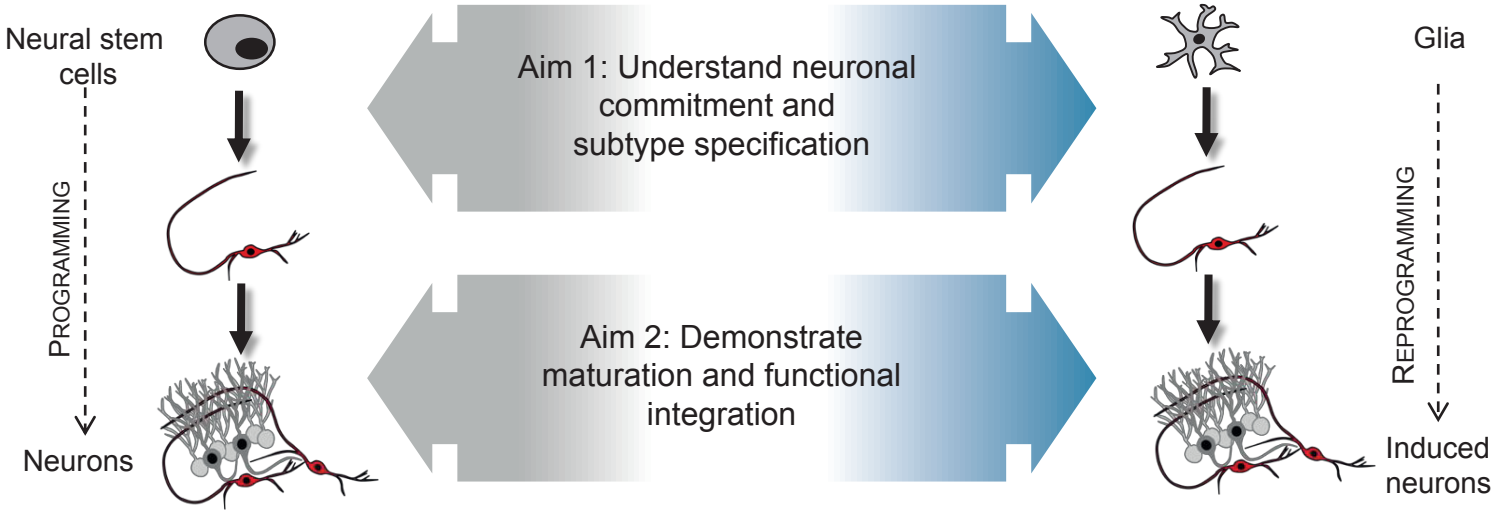



- Sustained germinal activity
- Capacity for circuit re-wiring

- Lost neurons are not replaced
- No capacity for effective regeneration

## PROGRAMMING REPROGRAMMING

Both recruitment of endogenous NSCs and direct lineage reprogramming appear as promising strategies to repair the injured brain Our team will pursue these two parallel and complementary axes of research. Regardless of the strategy chosen to promote cell repair in the CNS, both axes aim at answering the same fundamental questions:




**Methods**: single cell/nuclei transcriptomic; trans-synaptic tracing; viral and non-viral genetic manipulations…

FRM Fondation Recherche Médicale

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# Neurobiology of Executive Functions

– decisions, learning, motivation, exploration, feedback –

https://www.sbri.fr/team/5-neurobiology-executive-functions

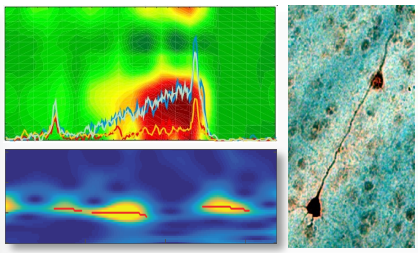
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Inserm La science pour la santé From science to health

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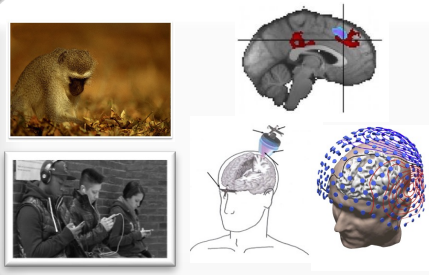
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A multi-PI team studying the neural basis of decisions, learning, and motivation in **humans and non-human primates** using neurophysiology, behaviour, computational modelling, anatomy, and intervention methods



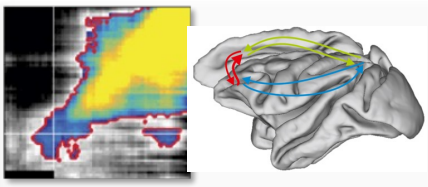
## Neurophysiology of decision-making and learning in the frontal cortex

Approaches: Acute and chronic neurophysiological recordings in monkeys: Spikes, LFP, ECoG. Imaging in humans and monkeys: MEG, fMRI, MRS. Behavioural testing in humans and monkeys. Cognitive models.
Interventions: TUS, Pharmacological manipulations, DREADDs



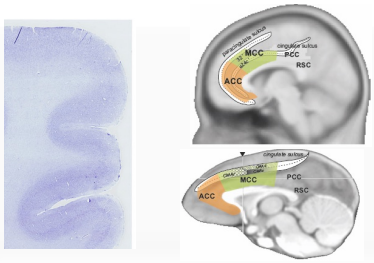
## Real-world and self-organized behaviour, motivation and social cognition

Approaches: Unconstrained & sequential decision-making in humans & monkeys, with cognitive modelling. fMRI imaging in humans. Social interaction tasks in monkeys, including field studies of social connections in free-ranging macaques, and fMRI.
Interventions: TUS, DREADDs



## Neural dynamics, neural communication, information coding & neural mass modelling

Approaches: Statistical and computational models of neural interactions, cortical circuitry. Analysis of continuous and discrete neural signals. Neural mass models and their validation in neurophysiological data.
Interventions: DREADDs with concurrent neurophysiological recordings




## Comparative functional anatomy of executive functions & social behaviour

Approaches: Comparative functional & anatomical fMRI imaging across the primate order: marmoset, macaque, chimpanzee, human. Comparative analysis of sulcal pattern and development. Comparative histological analysis of primate brains

## Collaborations

University of Puerto Rico · Université de Strasbourg · McGill University · Ghent University · University of Oxford · NIH National Institute of Mental Health · Donders Institute · Paris Brain Institute · Penn

GDR Groupement de recherche BioSimia Recherche biomédicale et primates non-humains

www.gdr-biosimia.com



**Emmanuel Procyk**



**Céline Amiez**



**Charlie Wilson**



**Jérôme Sallet**



**Matteo di Volo**

# Ecological Cognition and Computation

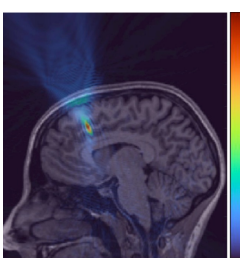
## PI: Nils Kolling

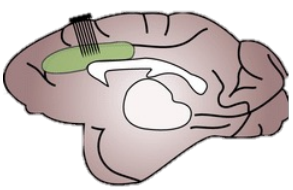
The primary aim of our team is understanding of how the human brain implements reward-guided decision making, learning and plans into the future. For this, we focus particularly on the role of the frontal lobes in generating choices and making predictions based on rewards and other features of the environment. However, we are also interested in more network-based perspectives and want to understand how cortical and subcortical interactions and dynamics implement task performance and behavioural or neural state shifts. Thus, we use a variety of methods, across species as well as across spatial and temporal scales. We also test our ideas using causal manipulations such as pharmacological interventions, brain lesions and more recently transcranial ultrasound stimulation.

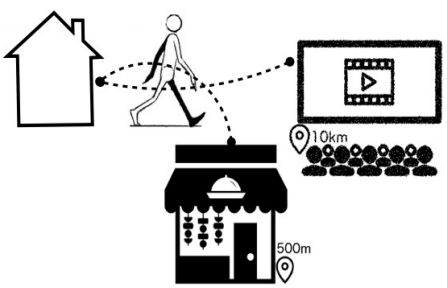
Some of our current interests include finding out how we predict future reward trends in changing environments to make better choices. We are also interested in how people manage to continuously pursue their goals and motivate their behaviour over extended time periods, sometimes to the point of failing to abandon them when necessary. In addition, our lab is working on other types of ecological cognitions such as credit assignment, emotion-decision interactions and social cognition.

Our team is heavily interdisciplinary drawing inspiration from economics, psychology, biology, computer science, engineering and beyond. We also use a diverse set of neuroscience methods to understand the underlying processes more deeply. In other words, we measure not only what regions are active (using fMRI) and the large-scale neural dynamics (using MEG and EEG), but also how populations of single neurons are involved (using electrophysical recordings) as well as the causal contributions of specific brain regions within larger networks (e.g. using Transcranial ultrasound stimulation). This is combined with generative cognitive models, purpose built to solve ecologically relevant challenges humans have evolved to overcome. Using large scale behavioural data we further link individual differences in the cognitive processes underlying our tasks to clinical dimensions and other real life individual differences.

If you are interested in any of those topics, in particular, if you want to work with us, please get in touch. We are currently hiring on many different levels (from Phd Student to Postdocs and Lab Manager). https://sites.google.com/view/ecc-team/home








## Collaborations

## Funding

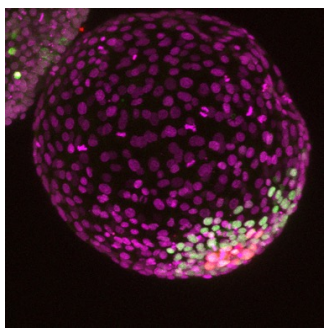
European Research Council
Established by the European Commission

# Pluripotent Stem Cells in Mammals:

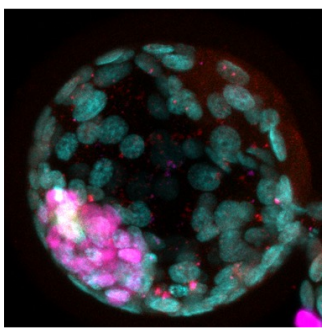
## Pierre Savatier

We are studying the molecular and cellular mechanisms responsible for embryo pluripotency in lagomorphs and primates, focusing on the signalling pathways, chromatin modifiers and cell cycle regulators that support pluripotency in the naïve state [1-5]. We are investigating how these factors can be manipulated in vitro so as to improve self-renewal and enhance the fitness of embryo-derived (ES cells) and induced pluripotent stem cells (iPS cells) [6, 7]. We also seek to generate ES and iPS cell lines capable of colonizing morulae to produce transgenic chimeras in rabbits and non-human primates [8], and we seek to apply these strategies to generate human iPS cells capable of colonizing non-human primate embryos and forming interspecies chimeras. This experimental paradigm is essential to study human early development [9].

Our team is a member of the Infrastructure Nationale en Biologie et Santé Ingestem, LabEx CORTEX, LabEx DEVweCAN, and LabEx REVIVE.



A rabbit blastocyst colonized by chimpanzee iPS cells (expressing the GFP)



A cynomolgus monkey blastocyst colonized by human iPS cells


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**Pierre Savatier**



**Marielle Afanassieff**



**Irène Aksoy**



**Nathalie Beaujean**



**Pierre-Yves Bourillot**

# Physiology and biotechnology of Embryonic stem cells

Bertrand Pain

The brain is a complex organ and any model for studying it in its normal and pathological aspects becomes a tool of choice for neuroscientists. Our team uses the model of brain organoids derived from human and animal induced pluripotent stem cells (iPSCs) to study neurotropic viruses and assess the neural toxicity of known drugs or in development.

First, by applying differentiation protocol to human iPSCs, we generate human cerebral organoids (hCOs) expressing early and late markers according to differentiation time. (Figure 1). Those hCOs are presently successfully infected by neurotropic viruses such as Henipavirus (NiV and HeV) and Flavivirus (TBEV and WNV) in collaboration with C. Matthieu (CIRI, U1111, Lyon) and M. Coulpier (VIRO, UMR1161, Maison-Alfort) respectively. These studies make it possible to better identify the infectious mechanisms of these particularly aggressive neurotropic viruses and to study the immune cell responses. This hCOs model opens also the way to screening and identifying antiviral molecules against these emerging zoonotic viruses.

Second, this model of hCOs makes it possible to assess the toxicity of drugs known or in development on the neural system. As part of the Previtox project, led by B. Clément (NUMECAN, U1241, Rennes), we evaluated the impact of various molecules such as valproic acid on the development of cerebral organoids (Figure 2). Their impact is also assessed at transcriptomic, proteomic and metabolomic levels. All of these analyzes confirm and thus highlight the relevance of this model for evaluating the potential toxicity of molecules on early neural development.

Even if the model of hCOs still remains imperfect to mimic the complexity of brain tissue with all the constitutive cell types and their complex interactions present in vivo, this in vitro model nevertheless has the advantage of allowing the first large-scale tests and screenings of many molecules and therefore of contributing to the 3R policy - replace, reduce and refine - of animal experimentation. The complexification of this model of hCOs thus remains a permanent objective to try to better mimic the living cerebral tissue.

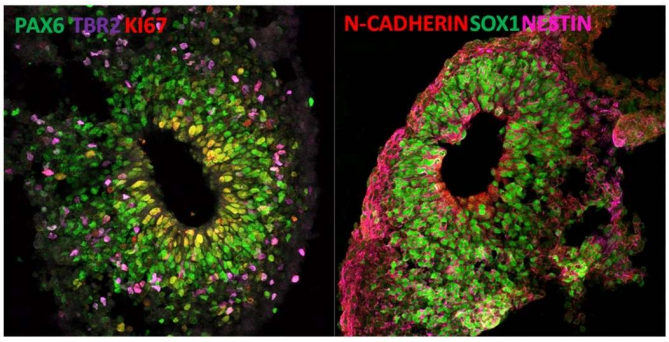



Figure 1 : Expression of markers on cerebral organoids obtained after 58 days

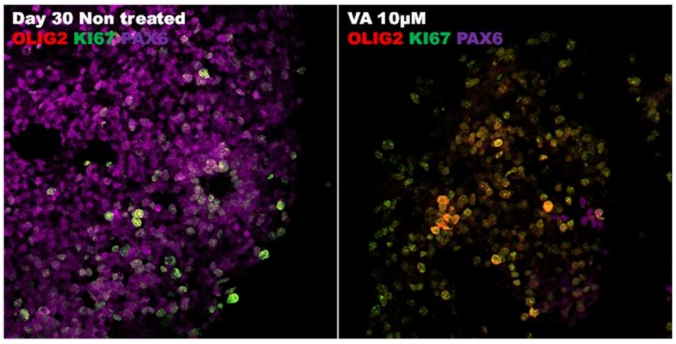



Figure 2 : Impact of Valproic acid (VA) on cerebral organoid.

# Clinical Research StemGamE

## Bruno Salle - Hervé Lejeune
## Ingrid Plotton – Elsa Labrune

Focus on human reproduction, epigenetic and stem cell biology.

Clinical axis → preserving fertility and improving assisted reproductive technologies.

- gamete quality
- ovarian and oocyte preservation
- Spermatogenesis in vitro.



**B. SALLE**



**H. LEJEUNE**

# Platform Connectomics

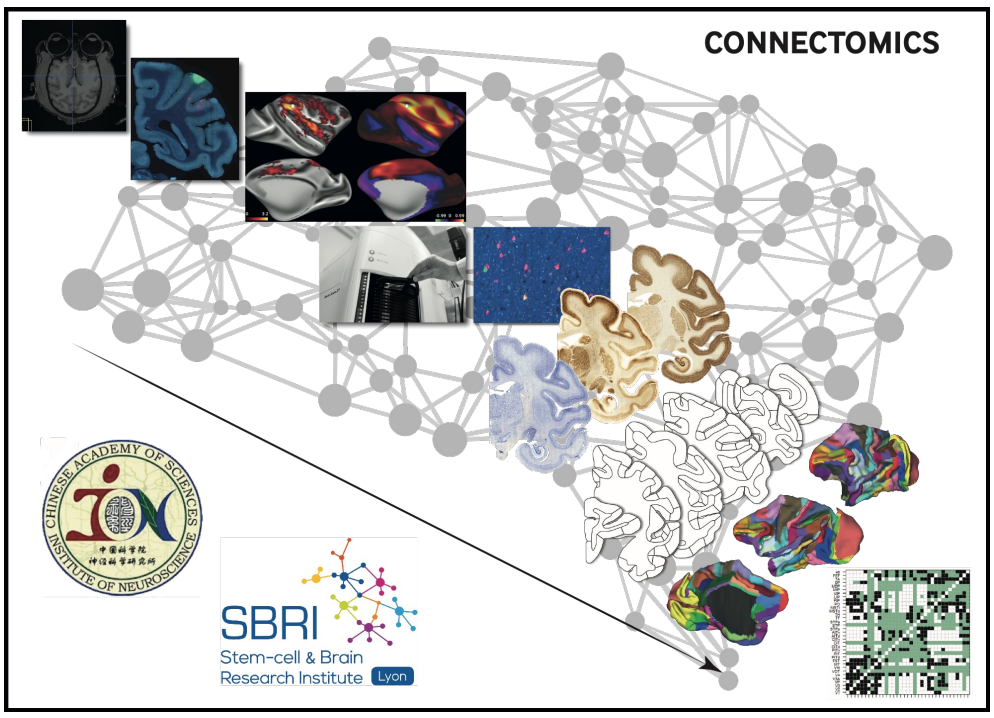
Henry Kennedy - Colette Dehay

A connectome is a comprehensive map of the connections of the nervous system. The Connectomics Platform is more specifically concerned with the investigation of the cortical connectome at the meso-scale. That is to say the comprehensive set of connections linking cortical areas in two model organisms, the macaque and the mouse. The fact that the connectome deals with comprehensive maps, means that there is a need to develop high-throughput analysis of connectivity. The platform is geared to analyzing the inputs to defined cortical areas that are determined using high-fidelity, high-sensitivity retrograde tracers .

The cortical connectome can be viewed as a graph and the analysis of the cortical graph exploits definitions and algorithms used in graph theory. The density of the cortical graph is very high (macaque 67%, mouse 97%). However, the range of weights of connections span 5 to 6 orders of magnitude, meaning that binary, connected/not-connected measurements are of little value. The determination of the weighted cortical graph requires accurate counts of labeled neurons in order to generate reliable and consistent connectivity profiles of individual areas.

The Connectomics Platform consists of three interrelated facilities: (i) a customized surgical suite for injection of tracers; (ii) a histology lab for preparing material for microscopic examination; (iii) microscope facilities.

Mouse and macaque databases that have been constructed by this platform can be obtain here : [http://www.core-nets.org](http://www.core-nets.org)





# Plateform PrimaStem

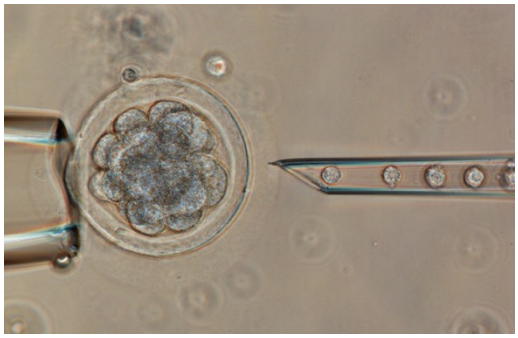
## Cloé Rognard – Pierre Savatier



PrimaStem is a cell biology platform dedicated to the derivation, reprogramming and genome editing of embryonic stem (ES) and induced pluripotent stem (iPS) cell lines in primates. In addition to human lines, we have a collection of pluripotent stem cell lines from Chimpanzee, Bonobo, Orangutan, Gorilla, rhesus and cynomolgus macaque and marmoset. PrimaStem also has a unique expertise in Europe in the production of cynomolgus rhesus macaque embryos for transgenic applications.



Injection of a spermatozoid into a cynomolgus macaque oocyte



Microinjection of pluripotent stem cells into a rabbit morula