UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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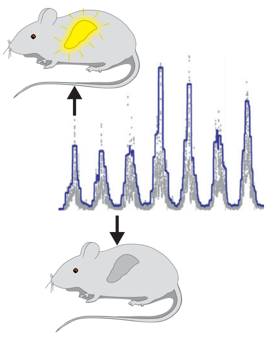
Observing live gene expression in the body

A team from UNIGE has developed a biotechnology that can be used in many biomedical sectors.

Most of our physiological functions fluctuate throughout the day. They are coordinated by a central clock in the brain and by local oscillators, present in virtually every cell. Many molecular gearwheels of this internal clock have been described by Ueli Schibler, professor at the Faculty of Science of the University of Geneva (UNIGE), Switzerland. To study how the central clock synchronizes subordinate oscillators, the researcher's group used a variety of genetic and technological tools developed in collaboration with a team of UNIGE physicists. In this way, the scientists were able to directly observe the bioluminescence emitted by 'clock genes' in mice for several months. This biotechnology is applicable to numerous sectors of biomedical research, which attracted the attention of the editors from the journal *Genes & Development*.



Measuring bioluminescence in real time enables a monitoring of the daily expression of clock genes in livers © Ueli Schibler

In mammals, there are many behaviors and biological functions that are regulated by internal clocks. Most of our cells have one, made from a family of 'clock genes', whose cyclic activity reaches a specific peak in 24 hours. These local oscillators are synchronized by a central 'pacemaker' in the brain which adjusts to light.

The firefly lights the way

The use of genetic engineering techniques enabled the study of molecular mechanisms that activate clock genes directly in cultured mammalian cells: 'We have coupled several of these genes to that of luciferase, the enzyme used by the female firefly for producing green light to attract males,' explained Ueli Schibler, member of the National Research Center *Frontiers in Genetics*. When a specific clock gene is activated in a cell that was transformed in this way, the light signal emitted can be measured using a highly sensitive bioluminescence detector. However, this device, which is capable of detecting signals on the order of a few photons, cannot be used for studying whole organisms. The contribution of André Liani's mechanical workshop, along with Jean-Pierre Wolf's and Luigi Bonacina's teams from UNIGE's Group of Applied Physics, was thus essential. These scientists developed a customized device that can accommodate mice for several months: 'We equipped it with reflective walls to deflect photons toward a highly sensitive photomultiplier tube to capture bioluminescence,' says André Liani.

The time these rodents spent in the bioluminescent device allowed to demonstrate that **the central clock generates signals**, some of which act directly on the liver oscillators

Follow the daily expression of clock genes live...

In collaboration with the University of Ulm and the Center for Integrative Genomics (CIG) of Lausanne, the biologists studied how the central clock synchronizes subordinate oscillators in mice. Various clock genes, coupled with the luciferase gene for light emission, were inserted into liver cells using a molecular vector. The time these rodents spent in the bioluminescent device allowed to demonstrate that the central clock generates signals, some of which act directly on the liver oscillators, and others which synchronize them indirectly by controlling the cycles of food intake.

...or the effect of a medication in mice

'This technology enables a drastic reduction in the number of mice needed for this type of experiment, and furthermore, it is applicable to many areas of biomedical research,' says Camille Saini, researcher in the Department of Molecular Biology at UNIGE and first author of this article. These complementary genetic and engineering technology tools could be used to directly follow certain biochemical effects of metabolites like cholesterol or glucose, as well as the response to potential treatments of diseases such as hypercholesterolemia or diabetes. Monitoring the response to various hormones, neurotransmitters and other biochemical messengers is also part of this application range.

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