INSTITUTE OF FUNCTIONAL GENOMICS

Biomedical Campus Arnaud de Villeneuve - Montpellier - FRANCE



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Université Montpellier

An institute dedicated to the genomics of cellular and intercellular communication in Neuroscience, physiology and cancer biology, bridging molecular & cellular knowledge with integrated functions, and dysfunctions, of different organs, including the brain

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INSTITUT DE GÉNOMIQUE FONCTIONNELLE

☑ **3 RESEARCH THEMES**
- ✓Cancer Biology
- ✓Neurosciences
- ✓Physiology

☑ **23 TEAMS**

☑ **7 TECH FACILITIES**
- ✓Genomics
- ✓Proteomic
- ✓Small Animal Imaging
- ✓Pharmacological screening
- ✓Vectorology
- ✓Functional exploration
- ✓Biostatistic

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Looking forward to seeing you on site!

Philippe Marin, Director of the IGF

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Biomedical Campus Arnaud de Villeneuve - Montpellier - FRANCE

- One of the **major basic research centers in Montpellier** (330 members, 23 research teams).

- Located in **a dynamic campus that includes several renown research institutes** such as the Institute of Human Genetics and the Center for Structural Biochemistry, the **medical school** and several **hospitals**.

- A **multidisciplinary institute focused on cell signaling and communication mechanisms** involved in health and disease in the fields of neuroscience, cardiology, endocrinology and cancer biology.

- **An outstanding scientific environment benefiting from state-of-the-art technological facilities** including genomics (deep sequencing facility), proteomics (high-resolution mass spectrometry), medium throughput pharmacological screening, imaging, structural biology and animal facilities (mice, zebra fish and drosophila).

NEUROSCIENCE TEAMS AT IGF

17 research teams that cover major fields of Neuroscience
and use multidisciplinary approaches in a large number of preclinical models
as well as in clinical studies in Neurology and Psychiatry

ARTERO Sylvaine - COURTET Philippe
Environnement, biomarqueurs, neuropsychiatrie

BOURINET Emmanuel
Dynamique cellulaire des canaux calciques et nociception

FRANÇOIS Amaury
Réseaux neuronaux du toucher affectif et social

JEANNETEAU Freddy
Hormone, stree et plasticité

LEBON Guillaume - GOUDET Cyril
Mécanismes moléculaires et structuraux de la neuromodulation

LORY Philippe
Canaux ioniques - excitabilité neuronale et canalopathies

MARCHI Nicola - AUDINAT Étienne
Recherche cérébrovasculaire et gliale

MARIN Philippe
Neuroprotéomique et signalisation des pathologies cérébrales

PERISSE Emmanuel
Circuits neuronaux et codage de la valeur

PERROY Julie
Physiopathologie de la transmission synaptique

RASSENDREN François
Signalisation purinergique et inflammation du cerveau

RONDARD Philippe
Neurorécepteurs, dynamique et fonctions

TROUCHE Stéphanie
Circuits de la mémoire appétitive et aversive

VALJENT Emmanuel
Codage moléculaire et neuronal des comportements

DUFFAU Hugues - HUGNOT Jean-Philippe
Plasticité cérébrale, cellules souches et tumeurs gliales de bas grade

GRANIER Sébastien - MOUILLAC Bernard
Pharmacologie et biologie structurale des protéines membra- naires

MOLLARD Patrice
Réseaux et rythmes dans les glandes endocrines

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TEAM	**Environment, Biomarkers, Neuropsychiatry**
Team leader Email	Sylvaine Artero and Philippe Courtet sylvaine.artero@inserm.fr – philippe.courtet@umontpellier.fr
url address	https://www.igf.cnrs.fr/index.php/en/h-teams-en/ht-artero-courtet-en
Keywords	Suicidal behavior, Alzheimer Disease, inflammation, blood brain barrier, brain imaging, nutrition, microbiota, cohorts
RESEARCH TOPIC	Environmental conditions, whether exogenous (psychosocial stressors, lifestyle, pathogens…) or endogenous (diet, immunity, microbiota…), shape our brain, the cognition and the behavior by acting on individual genetic vulnerability. Our main objective is the identification and study of potentially modifiable environmental factors (vulnerability or protective) and biomarkers of neuropsychiatric pathologies. One axis is the development of biomarkers of suicidal behavior. Based on several and large cohort studies of depressed patients, we perform comprehensive analysis of clinical, biological and neuroanatomical (MRI) factors that could help to identify patients at risk for suicide. Specifically, the biological aspects involve parameters of peripheral inflammation, indices of permeability of the BBB, miRNA and other genomic markers that could regulate this pathway from peripheral inflammation to suicidal behaviour (or vice versa). The interplay with strong environmental determinants of suicide such as childhood maltreatment and loneliness and social isolation is also understudy Other main axis concern the role of sugars (ie refined carbohydrates) in the onset of cognitive decline. Based on large cohort in general & clinical populations, we perform multilevel analysis including clinical, MRI, metagenomics (gut and salivary microbiota) and metabolomics markers to better understand the harmful effect of sugars on brain ageing. We also examine the interactions between excessive sugar consumption and periodontal disease leading to inflammation dysbiosis and insulin resistance, keys mechanisms in Alzheimer Disease.
Recent publications	-Gentreau M, Maller JJ, Meslin C, Cyprien F, Lopez-Castroman J, Artero S. Is Hippocampal Volume a Relevant Early Marker of Dementia? Am J Geriatr Psychiatry. 2023; 15:S1064-7481. -Gentreau M, Chuy V, Féart C, Samieri C, Ritchie K, Raymond M, Berticat C, Artero S. Refined carbohydrate-rich diet is associated with long-term risk of dementia and Alzheimer's disease in apolipoprotein E ε4 allele carriers.Alzheimers Dement. 2020; 16:1043-1053. - Lengvenyte A, Belzeaux R, Olié E, Hamzeh-Cognasse H, Sénèque M, Strumila R, Cognasse F, Courtet P. Associations of potential plasma biomarkers with suicide attempt history, current suicidal ideation and subsequent suicidal events in patients with depression: A discovery study. Brain Behav Immun. 2023; 114:242-254. - Risch et al. Sensitivity to ostracism is blunted in suicide attempters only when they report suicidal ideation. J Affect Disord. 2023;15:337:169 - Lengvenyte et al. Associations of white blood cell and platelet counts with specific depressive symptom dimensions in patients with bipolar disorder: Analysis of data from the FACE-BD cohort. Brain Behav Immun. 2023 108:176-18

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TEAM	**Calcium channel dynamics and nociception**
Team leader Email	emmanuel.bourinet@igf.cnrs.fr
url address	https://www.igf.cnrs.fr/index.php/en
Keywords	Somatosensation, chronic pain, touch, mouse genetics, human DRG & spinal cord, calcium channels
RESEARCH TOPIC	Pathophysiology of primary afferent and dorsal spinal cord neurons focusing on chronic pain and alterations of touch
Recent publications	Yadav, A., et al., *A cellular taxonomy of the adult human spinal cord.* **Neuron**, 2023. **111**(3): p. 328-344 e7. Huzard, D., et al., *The impact of C-tactile low-threshold mechanoreceptors on affective touch and social interactions in mice.* **Sci Adv**, 2022. **8**(26): p. eabo7566. Fayad, S.L., et al., *Centrally expressed Cav3.2 T-type calcium channel is critical for the initiation and maintenance of neuropathic pain.* **ELife**, 2022: e79018. Defaye, M., et al., *The neuronal tyrosine kinase receptor ligand ALKAL2 mediates persistent pain.* **J Clin Invest**, 2022. **132**(12). Beaulieu-Laroche, L., et al., *TACAN Is an Ion Channel Involved in Sensing Mechanical Pain.* **Cell**, 2020. **180**(5): p. 956-967 e17. Candelas, M., et al., *Cav3.2 T-type calcium channels shape electrical firing in mouse Lamina II neurons.* **Sci Rep**, 2019. **9**(1): p. 3112. Francois, A., et al., *The Low-Threshold Calcium Channel Cav3.2 Determines Low-Threshold Mechanoreceptor Function.* **Cell** **Rep**, 2015. **10**(3): p. 370-382.

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TEAM	**Stress hormones & plasticity**
Team leader Email	Freddy Jeanneteau Freddy.jeanneteau@igf.cnrs.fr
url address	https://jeanneteau-lab.cnrs.fr/
Keywords	Engram trapping, behavior, imaging, disease models, electrophysiology, optogenetic, chemogenetic, photometry
RESEARCH TOPIC	Strategies to modify disease trajectories (autism, Alzheimer, PTSD, depression, Prader-Willi, obesity). This requires the longitudinal inspection of minimally invasive biological metrics (behavior, in vivo imaging) in the same individuals overtime. In the recent years we explored the roles of: Oxytocin for treating aggression outburst due to hypersomatostatinergic state in the lateral septum of Prader-Willi syndrome Vasopressin for treating social deficits in an autism model BDNF for promoting the mnemonic effects of stress in the brain with benefits on the progression of amyloidogenesis PDGF-BB acts as trophic factor to regenerate the neurogliavascular unit in epilepsy.
Recent publications	Dromard et al. Disengagement of somatostatin neurons from lateral septum circuitry by oxytocin and vasopressin restores social-fear extinction and suppresses aggression outbursts in Prader-Willi syndrome model. Biological psychiatry. 2023 Dromard et al. Loss of glucocorticoid receptor phosphorylation contributes to cognitive and neurocentric damages of the amyloid-β pathway. Acta Neuropathol Commun. 2022 Jun 22;10(1):91. Huzard et al. The impact of C-tactile low-threshold mechanoreceptors on affective touch and social interactions in mice. Sci Adv. 2022 Jul;8(26):eabo7566 Dromard et al. Dual imaging of dendritic spines and mitochondria *in vivo* reveals hotspots of plasticity and metabolic adaptation to stress. Neurobiol Stress. 2021 Sep 21;15:100402. Borie et al. Correction of vasopressin deficit in the lateral septum ameliorates social deficits of mouse autism model. J Clin Invest. 2021 Jan 19;131(2):e144450 Arango-Lievano et al. Regeneration of the neurogliovascular unit visualized in vivo by transcranial live-cell imaging. J Neurosci Methods. 2020 Sep 1;343:108808 Arango-Lievano et al. Persistence of learning-induced synapses depends on neurotrophic priming of glucocorticoid receptors. Proc Natl Acad Sci U S A. 2019 Jun 25;116(26):13097-13106.

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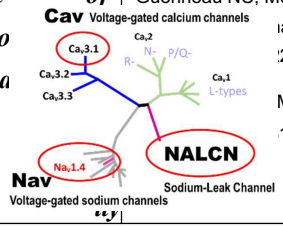
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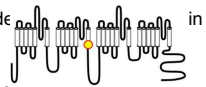
TEAM	**Structural and Molecular Mechanisms of Neuromodulation**
Team leader Email	cyril.goudet@igf.cnrs.fr ; guillaume.lebon@igf.cnrs.fr
url address	https://www.igf.cnrs.fr/index.php/en/h-teams-en/ht-lebon-goudet-en
Keywords	GPCRs; Adenosine; Glutamate; Pain; Structural biology; Molecular, Cellular and Preclinical Neuropharmacology; Photopharmacology; Pain
RESEARCH TOPIC	In a multiscale approach, we aim to understand neuromodulatory mechanisms of therapeutic interest, from the molecular to the organism level. Neuromodulation is a slow adaptation of neuronal activity resulting from the action of neuromediators on slow-acting metabotropic receptors, typically, G Protein Coupled Receptors (GPCRs). An imbalance between the excitatory and inhibitory systems is observed in most neurological diseases, due to a dysregulation of neurotransmission and neuromodulation mechanisms. From the therapeutic point of view, GPCRs thus appear as interesting targets to monitor neuronal activity, as shown by the fact that about half of the current marketed drugs are acting directly or indirectly on GPCRs. Among CNS disorders, we are especially interested in chronic pain and its neuromodulation by two neuromodulators, adenosine and glutamate. Adenosine plays notably an important role in inflammation while glutamate is the main neuromediator involved in pain transmission. Neuromodulatory actions of adenosine and glutamate occur through two families of GPCRs, composed of four and eight subtypes, respectively. The projects developed in the team are at the interface between the field of chemistry and biology. By combining structural biology (X-ray crystallography and cryo-EM), molecular, cellular and preclinical pharmacology and photopharmacology, our team explore the structure and function of adenosine and glutamate receptors, their signalling complexes and their functional interplay, at the animal, cellular in primary cells, and protein levels.
Recent publications	Pereira et al. Photopharmacological manipulation of amygdala metabotropic glutamate receptor mGlu4 alleviates neuropathic pain. ***Pharmacol Res*** (2023). 187, 106602; Lebon, G. Steering G protein activation by mGlu heterodimer. ***Cell Res*** (2023). 33, 735-736 ; Nasrallah et al. Agonists and allosteric modulators promote signaling from different metabotropic glutamate receptor 5 conformations. ***Cell Rep*** (2021). 36, 109648. Gregory & Goudet. International Union of Basic and Clinical Pharmacology. CXI. Pharmacology, Signaling, and Physiology of Metabotropic Glutamate Receptors. ***Pharmacol Rev*** (2021). 73, 521-569. Lebon, G. Fine-tuning receptor-G protein activation and signaling. ***Science*** (2020). 369, 507-508 ; Ricart-Ortega et al. Mechanistic Insights into Light-Driven Allosteric Control of GPCR Biological Activity. ***ACS Pharmacol Transl Sci*** (2020). 3, 883-895. Zussy et al. Dynamic modulation of inflammatory pain-related affective and sensory symptoms by optical control of amygdala metabotropic glutamate receptor 4. ***Mol Psychiatry*** (2018). 23, 509-520. Nasrallah et al. Direct coupling of detergent purified human mGlu(5) receptor to the heterotrimeric G proteins Gq and Gs. ***Sci Rep*** (2018). 8, 4407.

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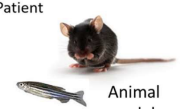
TEAM	**ION CHANNELS IN NEURONAL EXCITABILITY AND DISEASES**
Team leader - Email	**Philippe LORY** - philippe.lory@igf.cnrs.fr
url address	https://www.igf.cnrs.fr/index.php/en/h-research-en/hr-departments-en/hr-neuroscience-en/hr-lory-en
Keywords	T-type calcium channels, sodium leak channels, skeletal muscle sodium channels, channelopathies, neurodevelopmental diseases, muscle weakness, cerebellar disorders, mouse models, zebrafish models, chromaffin cells & hormone secretion, electrophysiology, behavioral studies, *in vitro* cellular models, cellular and molecular analyses, *in silico* modeling
RESEARCH TOPIC	***We use molecular to integrative approaches to decipher the roles of ion channels (e.g. Cav3, NALCN, Nav1.4) in neuronal excitability and their implication in physiology and diseases***
Recent publications ➔ *reviews representati ve of Lo tea*	Monteil A, Guérineau NC, Gil-Nagel A, Parra-Diaz P, Lory P, Senatore A. New Insights into the Physiology and Pathophysiology of the Atypical Sodium Leak Channel NALCN. **Physiol Rev. 2023**. PMID: 37615954. Nicole S, Lory P. New Challenges Resulting From the Loss of Function of Nav1.4 in Neuromuscular Diseases. **Front Pharmacol. 2021** 12:751095. PMID: 34671263. Guérineau NC, Monteil A, Lory P. Sodium background currents in endocrine/neuroendocrine cells: Towards

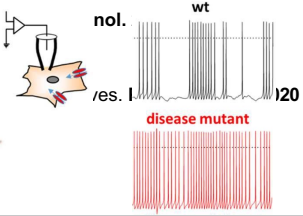






GoF – LoF mutations
SCA42 / SCA42ND
IHPRF / CLIFHADD
SCW …





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TEAM	**Cerebrovascular and Glia Research**
Team leader Email	Nicola Marchi (nicola.marchi@igf.cnrs.fr) & Etienne Audinat (etienne.audinat@igf.cnrs.fr)
url address	https://www.igf.cnrs.fr/index.php/en/h-research-en/hr-departments-en/hr-neuroscience-en/hr-marchi-audinat-en
Keywords	Neurovascular unit, pericyte, astrocyte, microglia, inflammation, synaptic transmission, epilepsy, neurodevelopment, stroke, environmental contaminants
RESEARCH TOPIC	We study neurovascular unit cells in central nervous system (CNS) disease settings. By using a translational research approach, we investigate how reactivity or plasticity of glia-pericyte structures and blood-brain barrier permeability contribute to neuro-inflammation, compounding to pathological neuronal modifications. We integrate in vivo, in vitro laboratory and clinical approaches to discover pharmacological entry-points and biomarkers of CNS diseases that are contingent to neurovascular unit dysfunction.
Recent publications	Garcia V*, Blaquiere M*, Janvier A, Cresto N, Lana C, Genin A, Hirbec H, Audinat E, Faucherre A, Barbier EL, Hamelin S, Kahane P, Jopling C, Marchi (2023) PIEZO1 expression at the glio-vascular unit adjusts to neuroinflammation in seizure conditions. Neurobiology of Disease (In press) Canet G, Zub E, Zussy C, Hernandez C, Blaquiere M, Garcia V, Vitalis M, DeBock F, Moreno-Montano M, Audinat E, Desrumaux C, Planel E, Givalois L, Marchi N (2022) Seizure activity triggers tau hyperphosphorylation and amyloidogenic pathways. Epilepsia DOI: 10.1111/epi.17186 Forner-Piquer I, Klement W, Gangarossa G, Zub E, de Bock F, Blaquière M, Maurice T, Audinat E, Faucherre A, Lasserre F,Ellero-Simatos S, Gamet-Payrastre L, Jopling C, Marchi N '2021) Varying modalities of perinatal exposure to a pesticide cocktail elicit neurological adaptations in mice and zebrafisch. Environmental Pollution 278, 116755. Doi: 10.1016/j.envpol.2021.116755 Forner-Piquer I, Faucherre A, Byram J, Blaquiere M, de Bock F, Gamet-Payrastre L, Ellero-Simatos S, Audinat E, Jopling C, Marchi N (2021) Differential impact of dose-range glyphosate on locomotor behavior, neuronal activity, glio- cerebrovascular structures, and transcript regulations in zebrafish larvae. Chemosphere. 267:128986. doi: 10.1016/j.chemosphere.2020.128986 Thion MS*, Mosser CA*, Ferezou I, Grisel P, Baptista S, Low D, Ginhoux F, Garel S*, Audinat E* (2019) Biphasic impact of prenatal inflammation and microglia depletion on the wiring of neocortical inhibitory circuits.Cell Reports 30;28(5):1119- 1126.e4. doi: 10.1016/j.celrep.2019.06.086

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TEAM	**NEUROPROTEOMICS AND SIGNALLING OF BRAIN DISORDERS**
Team leader Email	Philippe MARIN philippe.marin@igf.cnrs.fr
url address	https://www.igf.cnrs.fr/index.php/en/h-teams-en/ht-marin-en
Keywords	Serotonin, G protein-coupled receptor, neuronal signalling, neurodegenerative disorder, psychiatric disorder, synaptic transmission, synaptic plasticity, proteomics
RESEARCH TOPIC	The team is developing a neuroproteomic project that has two main objectives: i) to characterize the signaling networks associated with several serotonin receptors and their role in various neurological and psychiatric disorders (mood disorders, schizophrenia, Alzheimer's disease, neuropathic pain), ii) to identify biomarkers of neurological disorders and determine their impact on these diseases. It is based on a multidisciplinary strategy based on (phospho)proteomic approaches associated with biochemical, electrophysiological and behavioral studies.
Recent publications	• Dupuy V, Prieur M, Pizzoccaro A, Margarido C, Valjent E, Bockaert J, Bouschet T, Marin P*, Chaumont-Dubel S*. Spatiotemporal dynamics of 5-HT₆ receptor ciliary localization during mouse brain development. **Neurobiol Dis.** 2023 Jan;176:105949. doi: 10.1016/j.nbd.2022.105949. PMID: 36496200. • Sengupta S, Mondal M, Prasasvi KR, Mukherjee A, Magod P, Urbach S, Friedmann- Morvinski D*, Marin P*, Somasundaram K*. Differentiated glioma cell-derived fibromodulin activates integrin-dependent Notch signaling in endothelial cells to promote tumor angiogenesis and growth. **Elife**. 2022 Jun 1;11:e78972. doi:10.7554/eLife.78972. PMID: 35642785 • Conejero I, Collombier L, Lopez-Castroman J, Mura T, Alonso S, Olié E, Boudousq V, Boulet F, Arquizan C, Boulet C, Wacongne A, Heitz C, Castelli C, Mouchabac S, Courtet P, Abbar M, Thouvenot E. Association between brain metabolism and clinical course of motor functional neurological disorders. **Brain.** 2022 Sep 14;145(9):3264-3273. doi: 10.1093/brain/awac146. PMID: 35445242. • Fumagalli A, Heuninck J, Pizzoccaro A, Moutin E, Koenen J, Séveno M, Durroux T, Junier MP, Schlecht-Louf G, Bachelerie F, Schütz D, Stumm R, Smit MJ, Guérineau NC, Chaumont-Dubel S, Marin P. The atypical chemokine receptor 3 interacts with Connexin 43 inhibiting astrocytic gap junctional intercellular communication. **Nat Commun.** 2020 Sep 25;11(1):4855. doi: 10.1038/s41467-020-18634-y. PMID: 32978390. • Berthoux C, Hamieh AM, Rogliardo A, Doucet EL, Coudert C, Ango F, Grychowska K, Chaumont-Dubel S, Zajdel P, Maldonado R, Bockaert J, Marin P*, Bécamel C*. Early 5-HT6 receptor blockade prevents symptom onset in a model of adolescent cannabis abuse. **EMBO Mol Med.** 2020 May 8;12(5):e10605. doi: 10.15252/emmm.201910605. Epub 2020 Apr 24. • Pujol CN, Dupuy V, Séveno M, Runtz L, Bockaert J, Marin P, Chaumont-Dubel S. Dynamic interactions of the 5-HT6 receptor with protein partners control dendritic tree morphogenesis. **Sci Signal.** 2020 Feb 11;13(618):eaax9520. doi: 10.1126/scisignal.aax9520. PMID: 32047117. • Murat S, Bigot M, Chapron J, König GM, Kostenis E, Battaglia G, Nicoletti F, Bourinet E, Bockaert J, Marin P*, Vandermoere F*. 5-HT(2A) receptor-dependent phosphorylation of mGlu(2) receptor at Serine 843 promotes mGlu(2) receptor-operated G(i/o) signaling. **Mol Psychiatry**. 2019 Nov;24(11):1610-1626. doi: 10.1038/s41380-018-0069-6. PMID: 29858599

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TEAM	**Neural circuits and value coding**
Team leader Email	emmanuel.perisse@igf.cnrs.fr
url address	https://www.igf.cnrs.fr/index.php/en/h-teams-en/ht-perisse-en
Keywords	Value coding, dopamine, learning and memory, nociception, Drosophila, decision-making
RESEARCH TOPIC	**The main goal of the lab is to decipher how, in the fly brain, values (absolute and relative) are assigned to sensory stimuli during learning and later used to make appropriate value-based/economic decisions**. We are notably interested in understanding how prior experience can modify the perception of ensuing sensory experience which participates in the mechanisms of how flies perceive and compare value between experiences to signal relative value. To tackle such evolutionary-conserved brain processes, the lab is using the fruit fly *Drosophila melanogaster* as a model combining sophisticated genetics, *in vivo* two-photon calcium imaging, molecular biology and high-resolution behavioural analysis.
Recent publications	Villar ME*, Pavão-Delgado M*, Amigo M, Jacob PF, Merabet N, Pinot A, Perry SA, Waddell S and **Perisse E**. (2022) Different dopaminergic neurons signal absolute and relative aversive value in the *Drosophila* mushroom body. **Current Biology**, 32:1- 17. Felsenberg J, Jacob PF, Walker T, Barnstedt O, Edmondson-Stait AJ, Pleijzier MW, Otto N, Schlegel P, Sharifi N, **Perisse E**, Smith CS, Lauritzen S, Costa M, Jefferis GSXE, Bock DD and Waddell S. (2018) Integration of Parallel Opposing Memories Underlies Memory Extinction. **Cell** 175, 1–14. **Perisse E***, Owald D*, Barnstedt O, Talbot C, Huetteroth W and Waddell S. (2016) Aversive learning and appetitive motivation toggle feed-forward inhibition in the *Drosophila* mushroom body. **Neuron**, 90, 1-14. (*equal contribution) Huetteroth W, **Perisse E**, Klappenbach M, Burke CJ, Lin S and Waddell S. (2015) Separated representations of sweet taste and nutrient value in rewarding dopaminergic neurons in *Drosophila*. **Curr Biol**, 25, 1-18. Owald D, Felsenberg J, Das G, **Perisse E**, Talbot C, Huetteroth W, Waddell S. (2015) Activity of defined mushroom body output neurons underlies learned olfactory behavior in *Drosophila*. **Neuron**, 86, 1-11.

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TEAM	**Pathophysiology of synaptic transmission**
Team leader Email	Julie Perroy julie.perroy@igf.cnrs.fr
url address	https://www.igf.cnrs.fr/index.php/en/h-teams-en/ht-perroy-en
Keywords	Protein dynamics, cell signaling, synaptic transmission and plasticity, learning memory, behavioral flexibility, autism spectrum disorder
RESEARCH TOPIC	Understand how molecular dynamics at synapses controls cell signaling, neuronal networks and learning
Recent publications	**Sakkaki* S, Cresto* N**, Chancel R, Jaulmes M, Zub E, Blaquière M, Sicard P, Maurice T, Ellero-Simatos S, Gamet-Payrastre L, Marchi# N, **Perroy# J** *Dual-Hit: glyphosate exposure at NOAEL level negatively impacts birth and glia-behavioural measures in heterozygous shank3 mutants.* Environment International - in press **Areias* J, Sola* C, Chastagnier Y, Pico J, Bouquier N, Dadure C, Perroy J, Szabo V**. *Whole-brain characterization of apoptosis after sevoflurane anesthesia reveals neuronal cell death patterns in the mouse neonatal neocortex.* Sci Rep. 2023 Sep 7;13(1):14763. doi: 10.1038/s41598-023-41750-w. PMID: 37679476 Bousseyrol E, Didienne S, Takillah S, Solié C, Come M, Ahmed Yahia T, Mondoloni S, Vicq E, Tricoire L, Mourot A, **Naudé J**, Faure P. *Dopaminergic and prefrontal dynamics co-determine mouse decisions in a spatial gambling task.* Cell Rep. 2023 May 30;42(5):112523. doi: 10.1016/j.celrep.2023.112523. Epub 2023 May 17. PMID: 37200189 Mota É, Bompierre S, Betolngar D, Castro LRV, **Vincent P**. *Pivotal role of phosphodiesterase 10A in the integration of dopamine signals in mice striatal D1 and D2 medium-sized spiny neurones.* Br J Pharmacol. 2021 Dec;178(24):4873-4890. doi: 10.1111/bph.15664. Epub 2021 Oct 4. PMID: 34399440 **Moutin E, Sakkaki S**, Compan V, **Bouquier N**, Giona F, **Areias J, Goyet E, Hemonnot-Girard AL, Seube V, Glasson B**, Benac N, **Chastagnier Y, Raynaud F**, Audinat E, Groc L, Maurice T, Sala C, Verpelli C, **Perroy J**. *Restoring glutamate* *receptosome dynamics at synapses rescues autism-like deficits in Shank3-deficient mice.* Mol Psychiatry. 2021 Dec;26(12):7596-7609. doi: 10.1038/s41380-021-01230-x. Epub 2021 Jul 30. PMID: 34331007

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TEAM	**PURINERGIC SIGNALING AND BRAIN INFLAMMATION**
Team leader Email	Francois RASSENDREN francois.rassendren@igf.cnrs.fr
url address	https://www.igf.cnrs.fr/index.php/en/h-research-en/hr-departments-en/hr-neuroscience-en/hr-rassendren-en
Keywords	Purinergic signaling, P2X receptors, microglia, neuroinflammation, neurodegenerative disorder, chronic pain, biosensors, RNAseq
RESEARCH TOPIC	The team is developing a project that has two main objectives: i) To understand the roles of purinergic signaling in neuro- inflammatory conditions (Alzheimer's disease, neuropathic pain) and, ii) To develop purinergic and inflammatory biosensors. It is based on a multidisciplinary strategy based on transgenic mice, transcriptomic, proteomic, behavior and live microscopy imaging. Our team belongs to the French national network “Ion Channel Science and Therapeutics” http://www.labex-icst.fr/en
Recent publications	• Hua J, Garcia de Paco E, Linck N, Maurice T, Desrumaux C, Manoury B, Rassendren F, Ulmann L. Microglial P2X4 receptors promote ApoE degradation and contribute to cognitive deficits in Alzheimer disease. Cell Mol Life Sci. 2023; 80(5):138. • Hemonnot-Girard A L, Meersseman C, Pastore M, Linck N, Rey C, Chebbi A, Jeanneteau J, Ginsberg SD, Lachuer J, Reynes C, Rassendren F, Hirbec H. Comparative analysis of transcriptome remodeling in plaque associated and plaque distant microglia during amyloid-ß pathology progression in mice. J. Neuroinflammation 2022; 19(1):234. • Ollivier M, Beudez J, Linck N, Grutter T, Compan V, Rassendren F. P2X-GCaMPs as Versatile Tools for Imaging Extracellular ATP Signaling. eNeuro 2021; 8(1):ENEURO.0185-20.2020. • Audinat E, Rassendren F. Glial Mechanisms of Inflammation During Seizures. Inflammation and Epilepsy: New Vistas, 88, Springer International Publishing, pp.45-70, 2021, Progress in Inflammation Research, ⟨10.1007/978-3-030-67403-8_3⟩. • Hemonnot-Girard A-L, Valverde AJ, Hua J, Delaygue C, Linck N, Maurice T, Rassendren F, Hirbec H. Analysis of CX3CR1 haplodeficiency in male and female APPswe/PSEN1dE9 mice along Alzheimer disease progression. Brain Behav Immun 2021; 91:404–417. • Er-Lukowiak M, Duan Y, Rassendren F, Ulmann L, Nicke A, Ufer F, Friese MA, Koch-Nolte F, Magnus T, Rissiek B. A P2rx7 Passenger Mutation Affects the Vitality and Function of T cells in Congenic Mice. iScience 2020; 23(12):101870. • Moutin E, Hemonnot AL, Seube V, Linck N, Rassendren F, Perroy J, Compan V. Procedures for Culturing and Genetically Manipulating Murine Hippocampal Postnatal Neurons. Front Synaptic Neurosci. 2020; 12:19. • Zabala A, Vazquez-Villoldo N, Rissiek B, Gejo J, Martin A, Palomino A, Perez-Samartín A, Pulagam KR, Lukowiak M, Capetillo-Zarate E, Llop J, Magnus T, Koch-Nolte F, Rassendren F, Matute C, Domercq M. P2X4 receptor controls microglia activation and favors remyelination in autoimmune encephalitis. EMBO Mol Med. 2018; 10(8). pii: e8743. • Hirbec H, Marmai C, Duroux-Richard I, Roubert C, Esclangon A, Croze S, Lachuer J, Peyroutou R, Rassendren F. The microglial reaction signature revealed by RNAseq from individual mice. Glia. 2018; 66(5):971-986

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Montpellier - FRANCE

TEAM	**Neuroreceptors for glutamate – from structure to physiopathology**
Team leader Email	Philippe RONDARD (DR1 INSERM) philippe.rondard@igf.cnrs.fr
url address	https://www.igf.cnrs.fr/index.php/fr/h-teams-fr/ht-rondard-fr
Keywords	Metabotropic glutamate receptors, allostery modulator, single domain antibody, VHH, schizophrenia, Alzheimer
RESEARCH TOPIC	Our aim is to establish the proof of concept that **innovative camelid antibodies (nanobodies)** have strong potential **as therapeutic drugs to treat brain diseases**. Schizophrenia and Alzheimer's disease are used as examples of psychiatric and neurodegenerative diseases, respectively. Indeed, there is an urgent need for innovative therapies to treat brain disorders such as psychiatric and neurodegenerative diseases. Immunotherapies have proved to be efficient in many medical areas, but there is nearly no antibody-based therapeutics for a brain disease to date, mostly due to their little brain penetration. Our objectives are to **establish the proof-of-concept that nanobodies, by targeting neuroreceptors are new emerging drugs**. The metabotropic glutamate receptors (mGluRs), a family of eight G protein-coupled receptors (GPCRs), controlling synaptic transmission are used as models. mGluRs are important drug targets for many brain diseases, including schizophrenia and Alzheimer. We have recently developed nanobodies as allosteric modulators of the receptors mGlu2, 4 and 5. We found that nanobodies anti-mGlu2 cross the blood-brain barrier and reverse cognitive deficits in schizophrenia mouse models up to 7 days at least, after a single peripheral injection.
Recent publications	- Meng J, et al (2022) Nanobody-based sensors reveal a high proportion of mGlu heterodimers in the brain. Nat Chem Biol *18*, 894-903. - Haubrich J, et al (2021) A nanobody activating metabotropic glutamate receptor 4 discriminates between homo- and heterodimers. Proc Natl Acad Sci U S A *118* (33):e2105848118. - Scholler P, et al (2017) Allosteric nanobodies uncover a role of hippocampal mGlu2 receptor homodimers in contextual fear consolidation. Nat Commun 8 (1):1967.

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TEAM	**Brain plasticity, stem cells and glial tumors**
Team leader Email	Hugues Duffau and Jean-Philippe Hugnot h-duffau@chu-montpellier.fr; jean-philippe.hugnot@umontpellier.fr
url address	
Keywords	Neuroplasticity; Low-grade gliomas; Molecular biology; Human connectome; Brain mapping; Glioblastomas; Genomics; Spinal cord
RESEARCH TOPIC	Mapping the brain connectome and investigating mechanisms of brain plasticity Deciphering the meta-networking brain Exploring the molecular heterogeneity and malignant transformation of diffuse low grade glioma Glioma microenvironment and cellular heterogeneity Exploring human adult neural stem cells using the spinal cord as a model
Recent publications	Persistence of FoxJ1⁺ Pax6⁺ Sox2⁺ ependymal cells throughout life in the human spinal cord. Ripoll C, Poulen G, Chevreau R, Lonjon N, Vachiery-Lahaye F, Bauchet L, **Hugnot JP.** Cell Mol Life Sci. 2023 Jun 17;80(7):181. Intraoperative functional remapping unveils evolving patterns of cortical plasticity. Ng S, Valdes PA, Moritz-Gasser S, Lemaitre AL, **Duffau H**, Herbet G. Brain. 2023 Jul 3;146(7):3088-3100. Contribution of the medial eye field network to the voluntary deployment of visuospatial attention. Herbet G, **Duffau H** .Nat Commun. 2022 Jan 17;13(1):328. RNA Profiling of Mouse Ependymal Cells after Spinal Cord Injury Identifies the Oncostatin Pathway as a Potential Key Regulator of Spinal Cord Stem Cell Fate. Chevreau R, Ghazale H, Ripoll C, Chalfouh C, Delarue Q, Hemonnot-Girard AL, Mamaeva D, Hirbec H, Rothhut B, Wahane S, Perrin FE, Noristani HN, Guerout N, **Hugnot JP.** Cells. 2021 Nov 27;10(12):3332. Revisiting the Functional Anatomy of the Human Brain: Toward a Meta-Networking Theory of Cerebral Functions. **Herbet G**, **Duffau H.** Physiol Rev. 2020 Jul 1;100(3):1181-1228.

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TEAM	**Molecular and structural pharmacology of membrane proteins**
Team leader Email	sebastien.granier@igf.cnrs.fr & bernard.mouillac@igf.cnrs.fr
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Keywords	Opioids, biased ligands, safer painkiller
RESEARCH TOPIC	Pain, G protein-coupled receptors, molecular and structural pharmacology
Recent publication	Ref. 1: Molecular insights into the biased signaling mechanism of the μ-opioid receptor. Cong X, Maurel D, Déméné H, Vasiliauskaité-Brooks I, Hagelberger J, Peysson F, Saint-Paul J, Golebiowski J, Granier S#, Sounier R#. **Mol Cell.** 2021 Oct 21;81(20):4165-4175.e6.

Opioid receptors are G protein-coupled receptors (GPCRs), a family of transmembrane proteins expressed on the cell surface and regulating cellular responses to extracellular stimuli. Humans have 800 types of GPCRs, which contain the targets of ~40% of marketed drugs. Most of them have similar shapes and two main output "ports" toward the interior of cells (G protein or arrestin dependent signaling pathways). Driven by the stimuli (e.g. drug molecules), a GPCR can change to different conformations, which open/close the ports in specific ways to trigger different cellular responses and body reactions. Our team has determined how different opioid painkillers open/close the two ports of the mu opioid receptor separately (and trigger different cellular responses), by stabilizing specific conformations. This work, published in the **Molecular Cell** journal (Ref.1), combined computer simulations, NMR spectroscopy and live-cell pharmacology assays. It describes the mechanism of this nanodevice in atomistic detail. Based on this study we have discovered a novel family of molecules that bind and activate the opioid receptors *in vitro* in a biased manner. Moreover these original molecules named Biopioids (Biased opioids) are active *in vivo* in a mice model of thermal pain sensitivity. We are currently investigating the structure-activity relationships of this family of molecules and are comparing their effect *in vivo* with opioids known for their severe side effects (such as morphine) in order to demonstrate the usefulness of biopioids as safer painkiller.

