

INRA, PFIE (PLATE-FORME D'INFECTIOLOGIE EXPÉRIMENTALE/PLATFORM FOR EXPERIMENTAL INFECTIOLOGY)

INRA, IMAGING/SURGERY PLATFORM CIRE (CHIRURGIE ET IMAGERIE POUR LE RECHERCHE ET L'ENSEIGNEMENT/SURGERY AND IMAGING FOR RESEARCH AND TEACHING)

INRA, BIOCONFINED FISH FACILITY IERP (INSTALLATION EXPERIMENTALE RONGEURS ET POISSONS / FISH AND RODENTS EXPERIMENTAL FACILITY)

(FR)

Research topics:	<p>PFIE (Plate-Forme d'Infectiologie expérimentale / Platform for Experimental Infectiology), together with the ISP research unit (Infectiology and Public Health), constitutes the "Pole for Animal Health", in Nouzilly, France. The "Pole" is part of the INRA research centre of Tours-Nouzilly (INRA Centre Val de Loire), which is entirely dedicated to research in animal biology and health. The PFIE main mission is to carry out <i>in vivo</i> experimental infections to study farm animal pathogens (viruses, bacteria, parasites, prions) including zoonotic agents. Most researches aim at studying the pathogenesis of infectious diseases and developing new tools to combat these diseases including novel vaccines or diagnostic methods. Animal experimental infections are carried out in BSL2 and BSL3 containments using laboratory animals (rodents, rabbits...), farm animals (poultry, pigs, small ruminants, cattle, and ponies) or certain wildlife species such as wild boars or badgers. Selected publications of studies performed in the INRA-PFIE facilities:</p> <ul style="list-style-type: none">• <i>Laloy E, Bréard E, Trapp S, Pozzi N, Riou M, Barc C, Breton S, Delaunay R, Cordonnier N, Chateau-Joubert S, Crochet D, Gouzil J, Hébert T, Raimbourg M, Viarouge C, Vitour D, Durand B, Ponsart C, Zientara S. Fetopathic effects of experimental Schmallerberg virus infection in pregnant goats. Vet Microbiol. Available online 14 October 2017</i>• <i>Herry V, Gitton C, Tabouret G, Répérant M, Forge L, Tasca C, Gilbert FB, Guitton E, Barc C, Staub C, Smith DGE, Germon P, Foucras G, Rainard P. Local immunization impacts the response of dairy cows to</i>
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- Martinelle, L., Dal Pozzo, F., **Sarradin, P.**, Van Campe, W., De Leeuw, I., De Clercq, K., Thys, C., Thiry, E., Saegerman, C. Experimental bluetongue virus superinfection in calves previously immunized with bluetongue virus serotype 8. *Veterinary research*, 2016, 47 (1): 73.
- **Riou M.**, Avrain L., Carbonnelle S., El Garch F., Pirnay J.P., De Vos D., Plesiat P., Tulkens P.M., Van Bambeke F. Increase of efflux-mediated resistance in *Pseudomonas aeruginosa* during antibiotic treatment in patients suffering from nosocomial pneumonia. *International Journal of Antimicrobial Agents*, 2016, 47: 77-83.
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- Guillon A, Chevaleyre C, **Barc C**, Berri M, Adriaensen H, Lecompte F, Villemagne T, **Pezant J**, **Delaunay R**, Moënné-Loccoz J, Berthon P, Bähr A, Wolf E, Klymiuk N, Attucci S, Ramphal R, **Sarradin P**, Buzoni-Gatel D, Si-Tahar M, Caballero I. Computed Tomography (CT) Scanning Facilitates Early Identification of Neonatal Cystic Fibrosis Piglets. *PLoS One.* 2015 Nov 23;10(11):e0143459
- Laloy E, **Riou M**, **Barc C**, Belbis G, Bréard E, Breton S, Cordonnier N, **Crochet D**, **Delaunay R**, **Moreau J**, Pozzi N, Raimbourg M, **Sarradin P**, Trapp S, Viarouge C, Zientara S, Ponsart C. Schmallenberg virus: experimental infection in goats and bucks. *BMC Vet Res.* 2015 Aug 22;11:221

- **Sarradin P, Viglietta C, Limouzin C, Andréoletti O, Daniel-Carliet N, Barc C, Leroux-Coyau M, Berthon P, Chapuis J, Rossignol C, Gatti JL, Belghazi M, Labas V, Vilotte JL, Béringue V, Lantier F, Laude H, Houdebine LM.** *Transgenic Rabbits Expressing Ovine PrP Are Susceptible to Scrapie. PLoS Pathog.* 2015 Aug 6;11(8):e1005077.

The CIRE platform aims at adapting high-end imaging and applied surgery methods to experimental models of large animals such as sheep, goat or pigs in order to study major functions from a holistic perspective. This internationally oriented platform provides a unique service for research, training purposes and industrial collaborations in two separate areas: health (human and animals) and breeding. A team of 13 staff members (including a veterinary surgeon, 3 imaging engineers, 5 technicians -FTE-) ensures anaesthesia, surgical procedures, *in vivo* imaging procedures, pre-and post-operative cares on behalf of the research teams. About 50 experimental protocols are performed each year. Given below are examples of studies performed at the INRA CIRE facility:

- *The benefits of magnetic resonance imaging methods to extend the knowledge of the anatomical organisation of the periaqueductal gray in mammals.* Menant O, Andersson F, Zelena D, Chaillou E. *J Chem Neuroanat.* 2016 Nov;77:110-120.
- *Computation of a high-resolution MRI 3D stereotaxic atlas of the sheep brain.* Ella A, Delgadillo JA, Chemineau P, Keller M. *J Comp Neurol.* 2017 Feb 15;525(3):676-692.

The IERP Biocontainment Fish facilities at INRA (Jouy-en-Josas research centre), a BSL2 building, allows experimental challenges of target species and model species. Only model species of fish are included in the VetBioNet TNA offer as installations dedicated to target species (rainbow trout) are already implicated in the EU project AquaExcel. As a complement to the Marine Scotland BSL3 experimental unit (see there), model species such as zebrafish and carp, juveniles and adult fishes, can be infected with a number of viral and

	<p>bacterial pathogens (in particular, SVCV for carp, and SVCV, IHNV, and possibly other BSL2 viruses and bacteria). The water is dechlorinated, and its parameters adjusted before injection into the system; water is also UV-irradiated in all recirculation systems. All experiments are realized at controlled temperature. Cited below is an exemplary study performed at the INRA IERP facility:</p> <ul style="list-style-type: none"> • <i>Imaging of viral neuroinvasion in the zebrafish reveals that Sindbis and chikungunya viruses favour different entry routes. Passoni G, Langevin C, Palha N, Mounce BC, Briolat V, Affaticati P, De Job E, Joly JS, Vignuzzi M, Saleh MC, Herbomel P, Boudinot P, Levraud JP. Dis Model Mech. 2017 Jul 1;10(7):847-857.</i>
<p>Activities and services currently offered by the infrastructure/installation :</p>	<p>Because PFIE, CIRE and IERP are routinely receiving requests to access their facilities from (international) external parties, potential users may directly contact the platforms through their dedicated webpages: https://www6.val-de-loire.inra.fr/pfie_eng/; http://www.val-de-loire.inra.fr/Dispositifs-et-plates-formes/CIRE; https://www6.jouy.inra.fr/ierp_eng/IERP-Unit</p> <p>The state-of-the-art equipment available in the various experimental facilities and the scientific support of the INRA research labs constitute a highly attractive and complementary environment for external users. The PFIE and CIRE installations are both ISO 9001 certified.</p> <p>PFIE: it provides about 15,000 m2 of experimental rooms, including 3 500 m2 in BSL2 and 4500 m2 in BSL3 (including two barns for 12 cows each) and isolators for small animals (mice and poultry). PFIE can supply SPF mice, SPF poultry, germfree chicks (chicken and quail), health controlled pigs and small ruminants as well as cattle and ponies.</p> <p>The following state-of-the-art equipment is available in BSL3 containment: devices for continuous telemetric monitoring of body temperatures in most species; complete set of endoscopy for broncho-, gastro- or laparoscopy for large and mid-sized animals; ultrasonography; <i>in vivo</i> or <i>ex vivo</i> imaging (fluorescence</p>

and/or bio-luminescence): IVIS Spectrum® (Perkin Elmer) for small animals or organs; Cell Vizio® Dual Band confocal laser endomicroscopy (Mauna Kea Tech.); Fluobeam® (Fluoptics); surgery rooms; automated haematology and biochemistry analysers.

At present (2017), the 45 staff include 10 engineers (including 2 veterinarians and 1 PhD), 22 animal technicians, 10 maintenance technicians and 3 administrative agents. PFIE welcomes access requests from all researchers, be it from the academic or private sector. The involvement of the PFIE in research projects ranges from routine work such as simple housing and caretaking, administration of reagents and pathogens by all routes, and sample collection to more sophisticated activities as, for example, participation in designing protocols or setting up dedicated animal models, including tailored solutions for unusual target species like badgers, wild boars or horses. More than 250 studies in all fields are carried out each year in the various buildings of the PFIE.

CIRE: a surface of 1000 m² including 3 surgical rooms (one for neurosurgery) is dedicated for surgery, pre- and post-operative cares and 300 m² are dedicated for *in vivo* imaging. The platform is endowed with a 3 tesla Siemens Magnetom Verio® MRI scanner, a Siemens Somatom® X-ray scanner, an Ultrasonix-Touch® ultrasonography, a Cellvizio® confocal laser endomicroscopy and a Siemens Arcadis Avantic® C-arm.

Users of the PFIE installation may take advantage of the CIRE equipment to image control animals as well as infected animals or organs, provided that the necessary biosafety measures can be implemented.

IERP: experiments are performed in flow-through or in recirculation systems, in racks of 12 aquariums (up to 18 for zebrafish only). Infections can be performed by bath, or through intra-muscular or intra-peritoneal routes, depending on the pathogen. The team of technicians and the scientific engineer have ample experience in the preparation and realisation of all relevant experiments after planning and discussion with scientists.

<p>Description of the access to be provided under VetBioNet TNA call:</p>	<p>Support offered under this proposal: in all three installations, the experienced staff is providing full technical and logistic support to users. Adjacent INRA laboratories can provide complementary expertise and additional technologies where necessary/requested. On demand, samples from infected animal models can be made available (remote access).</p> <p>PFIE: experiments can be carried out in open barns or in BSL2 or BSL3 suites for laboratory and large animals as well as in isolators, for small species. Users can be present and may actively participate in the experiment, according to their preferences and practical competencies. BSL3 and BSL2 laboratories are also available for the preparation of inocula or other minor tasks like sample processing for downstream analyses or haematological or biochemical analyses. All external users will be given a personal access to the animal rooms or lab dedicated to their own experiments, with total respect of confidentiality. Duration of work is directly linked to the objectives of the studies and can last 1, 2 or 3 months or more, the duration being only limited by the availability of the rooms and staff at the time of performance of the study.</p> <p>The unit of access is defined as one day. Duration of an access to the platform can typically range from 1 to 3 months, corresponding to 30 to 90 units.</p> <p>Access includes supplying animals, animal housing, preparation, feeding and daily care, consumables and participation of two technicians for inoculations, clinical examination, sampling, necropsies. The access also includes cleaning and disinfection of the experimental rooms as well as disposal of carcasses. Access does not include shipping of biological samples (inocula, blood, tissue samples etc.) at the end of the trial.</p> <p>CIRE: external users, including private enterprise researchers, can access the imaging and surgery facilities of the platform in cooperation with INRA researchers and/or the medico-surgery staff from the Tours university and hospital expertise. This eases the set-up of animal models that are close to human practices, to innovative surgical techniques and to the interpretation of imaging results. The CIRE installation</p>
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	<p>proposes a total of 20 days of imaging to its installation for the duration of the project.</p> <p>IERP: it can offer infection and imaging of model species of fish (whole body and confocal microscopy) to any external research group. The phenotyping platform VIM-TEFOR is available within the bio-contained facilities, allowing biphotonic/confocal real time microscopic imaging on site. The access unit is defined as one day of experiment (90 days are proposed, actual costs).</p>
<p>Animal species/pathogens that can be worked on in this infrastructure/installation:</p>	<p>PFIE: studies can be performed with laboratory animals (rodents, rabbit etc.), most livestock species including poultry (chicken, quail, ducks, and pigeons as well as germ free chickens and quail), cattle, sheep, goats, pigs and ponies, and some wildlife species such as badgers and wild boars.</p> <p>Almost all veterinary pathogens of risk categories 2 and 3 (except FMDV), including those causing zoonotic, vector-borne and emergent diseases.</p> <p>Examples of infection models using these species/pathogen and being well-established at the PFIE include:</p> <ul style="list-style-type: none"> - Tuberculosis, salmonellosis, mastitis, chlamydiosis, coccidiosis, prion diseases (mice) - Avian influenza, Marek's disease, salmonellosis, campylobacteriosis, <i>Escherichia coli</i> infections, coccidiosis, <i>Plasmodium</i> infections (poultry); - Bluetongue, Schmallenberg virus infection, Rift Valley Fever, brucellosis, tuberculosis, mastitis, Q Fever, toxoplasmosis, cryptosporidiosis, helminthiasis, prion diseases (ruminants); - Swine influenza, TGE, lung infections and biomedical models (pigs); - Flavivirus infections (including West Nile virus infections), Equine Infectious Anaemia, dourine (ponies). <p>CIRE: farm animals as well as certain wildlife species can be imaged, provided animals are efficiently anaesthetized. Infected animals or organs can also be brought into and imaged in the CIRE facility if they are safely placed in biosafety complying containers or sealed airtight bags.</p>

	<p>IERP: Possibility of experimental infection with any BSL2 pathogens and model species of fish, to obtain and analyse samples, including state-of-the-art imaging technologies such as biphotonic confocal microscopy.</p>
<p>Travel and subsistence costs:</p>	<p>According to INRA rules, travel and subsistence costs of applicants can be reimbursed on production of original receipts. Train or flight tickets can be also directly ordered by PFIE/INRA for the successful applicants. According to the amount of money available for this purpose in the project and the expected number of applicants, INRA may have to limit user reimbursements to 2 people for a stay of 3 days. This point will be examined on a case-by-case basis, according to the protocol duration and external user involvement.</p>
<p>Infrastructure/installation ethical rules:</p>	<p>Researchers submit their protocols for authorisation to the French Research and Education Ministry* via the Ethical Committees which, in France, are local and multi-institutional in their composition and range of activities. The INRA Centre of Tours-Nouzilly is linked to the Val de Loire Ethical Committee (CEEA-VdL, registered as CEEA # 19). The INRA Centre in Jouy-en-Josas where the IERP facility is located is counselled by the Comité d’Ethique en Expérimentation Animale du Centre INRA de Jouy-en-Josas et AgroParisTech (COMETHEA, registered as CEEA n°45, P. Laplagne).</p> <p>INRA complies with all the currently applicable French regulations** derived from the <i>Guidelines of the directive 2010/63/EU of the European Parliament and of the Council: Ethics in animal experimentation</i>.</p> <p>Internal procedures are defined and included into the ISO 9001 quality management system, Internal functioning rules, prevention and ethical guidance, and protocol related procedures.</p> <p>* http://www.enseignementsup-recherche.gouv.fr/cid70598/l-encadrement-reglementaire-de-l-utilisation-d-animaux-a-des-fins-scientifiques.html)</p> <p>** General: Décret n° 2013-118 du 1er février 2013 relatif à la protection des animaux utilisés à des fins scientifiques ;</p> <p>Biosafety : "Arrêté du 18 juillet 1994 consolidé en 1997 et 1998" ; guidelines from the "Haut Conseil des Biotechnologies", "Arrêté du 16 juillet 2007" ;</p>

Experimentation on animals using pathogens: code de la santé publique, articles L. 5311-1 (16o), L. 5139-1, L. 5139-2 et L.5139-3, R.5139-1 et R.5139-3; Décision du 20 Octobre 2010 portant sur la détention et l'emploi de microorganismes, et toxines, section VI du code du travail, articles R.361 60 à 65, R.232-5-3 à R.232-5-8 ; arrêté du 2 juin 1998 sur les installations classées pour la protection de l'environnement, la directive CE 2000/54/CE et les règlement liés au transport ou à l'élimination des agents infectieux.