

# Research Unit Self-Assessment report

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**2025-2026 EVALUATION CAMPAIGN**  
GROUP A

October 2024



# 1- GENERAL INFORMATION FOR THE CURRENT CONTRACT

## 1-1 Unit Identification

**Unit name:** UMR1296 "Radiations: Defense, Health and Environment"

**Label and number:** UMR1296

**Main scientific field:** SVE: Life, Health and Environmental Sciences

**Panel 1:** SVE7: Prevention, Diagnosis and Treatment of Human Diseases

**Panel 2:** SVE6: Human Physiology and Physiopathology, Ageing

**Minor scientific field:** SHS Human and Social Sciences

**Panel 1:** SHS3: The Social World and its Diversity

**Panel2:** SHS4: The Human Mind and its Complexity

**Executive summary:** The U1296 Unit "Radiation: Defense, Health Environment" was initially created in January 2019 out of the current university period of creation of the research units under the number UA8. In January 2021, the UA8 became U1296 with the support of the National Health Institute (INSERM) and the Ministry of Army and the Army Health Service (SSA). It is noteworthy that the UA8/U1296 project has been reviewed in two years once by HCERES committee and twice with INSERM committees. At mid-term (2022) Lyon 2 University became the only University supervisory body of the Unit and U1296 became the UMR1296 Unit.

The UMR1296 Unit aims to better understand the biological consequences of exposure to radiation in particular and to DNA-breaking agents in general, in a clinical, military, environmental, spatial or professional contexts, by studying more particularly the impact of the individual factor in the repair and signalling of DNA damage. By extension, this Unit also deals with some aspects of the human and social sciences (risk perception, law and regulations, history of sciences), commercial valorization (partnerships with private companies) and is aiming to develop some teaching projects intended for the general public, health professionals, institutional decision-makers and scientific journalists. Since the two successive creations of the UMR1296 have been supported by INSERM, SSA and University Lyon 2 and since it was composed of 7 Unit poles (UP) including Radiobiology, Defense, Health, Environment and SSH, the executive team is logically composed of the representatives of each institution and UP. Hence, the governance of the UMR1296 Unit has been ensured by one Director, Nicolas Foray, radiobiologist, Senior Researcher at INSERM and by 3 Deputy-Directors, Diane Riccobono, Medical Doctor in Chief Officer (SSA), Pr. Béatrice Fervers, oncologist and epidemiologist (CLB) and Pr. Marie Préau, professor in social psychology of health (University Lyon 2). Each Director manages his/her own expertise item of research and animates the group essentially supported by one supervisory Institution. Hence, while the functioning of each group is generally independent, the Directors are in charge of the interaction and collaborative subject between the UPs. They also serve as a centralized decision committee for the dissemination of knowledge and communications of the data acquired in the Unit to the whole public, since a number of items remain case sensitive.

During the period of reference, thank to regular and constant success in funding, the 4 groups of UMR1296 have produced abundant and significant research efforts in their fields dispatched in 7 Ups. In addition, some original works were able to be produced between groups. Hence, during the first five years in common (UA8+reference period as UMR1296), each group has confirmed its high degree of expertise in its field. However, these five years may be still too short and the multidisciplinary meta-field too wide to produce the same quantitative amount of work in intergroups.

### List of the research unit's supervisory institutions and bodies:

- INSERM (major supervisory institution, with delegation to communicate with HCERES)
- SSA (NB: registered as supervisory institution by the National Registre of Research Structures while no convention has been signed with the other supervisory institutions)
- University Lyon 2 (becomes supervisory institution ad mid-term (2022))

### Doctoral school(s) of affiliation:

Considering the multidisciplinary features of the research items treated by the UMR1296 unit, each HDR searcher of the unit belongs to one of the 3 following Doctoral schools of the Universities of Lyon:

- ED205 : EDISS (Interdisciplinaire Sciences et Santé),
- ED512 : INFOMATHS (Informatique et mathématiques),
- ED485 : EPIC (Education Psychologie Information Communication)
- ED561 : HOB (Hematology, Oncology, Biotherapy)

## 1-2 Presentation of the unit

### 1.2.1 History

**Radiobiology** is defined as the study of the biological and clinical consequences of an exposure to ionizing radiation (IR). More specifically, radiobiology gathers all the physical chemical, molecular, cellular, tissular and clinical features of any radiation-induced event. Radiobiology may also concern the regulatory, law and ethical aspects of any exposure to radiation, whether medical, occupational or environmental.

**To revitalize research in radiobiology in France.** In 2017, the great majority of radiobiology research units in France, in Europe and in developed countries essentially focused their research on the medical applications of radiobiology, and more particularly the items related to radiotherapy and its technological advances. Hence, a more generalist vision developing a more integrative radiation biology with all the scenarios of exposure to IR (Defense, health, environment; accident, therapy, occupational), the industrial/commercial valorisation potentials, the clinical relevance of the mechanistic and cellular models, the law/regulatory frame of the predictive assays developed for radiosensitivity/radiosusceptibility/radiodegeneration<sup>1</sup> remained poorly documented. Since 2014, our Group of Radiobiology (GRad) of the U1052 INSERM Unit (Cancer Research Centre of Lyon) situated in the anti-cancer Centre Léon-Bérard (CLB) campus proposed a mechanistic model based on the radiation-induced nucleoshuttling of the ATM protein (RIANS), a major actor of the DNA damage and signalling, to explain the individual response to IR in different scenarios of exposure [1-3]. Such model was notably based on a collection of human fibroblast cell lines collected from cancer patients treated to radiotherapy, notably thanks to the radiation oncologists of the CLB. Such collection, named COPERNIC, is one of the largest collection gathering fibroblasts with a large spectrum of different radiosensitivity [1, 4]. Hence, together with the RIANS model and the COPERNIC collection, to develop a unified, multidisciplinary and translational approach to evaluate the risks linked to DNA double-strand breaks (DSB) became possible.

**To sustain translational approach with clinicians of CLB.** Such approach was early consolidated by the privileged links established between the GRad and the clinicians (radiation oncologists and radiologists) of CLB, making the access to their medical accelerators and CT scans a routine for radiobiologists. To our knowledge, this was the first example of a medical radiation facility in which radiobiological studies for high and low doses can be organized in routine. In parallel to the work in radiotherapy/radiology, the GRad also initiated collaborations with the "Cancer and Environment" CLB unit (Dir. Pr. B. Fervers) whose aim was the study of the role of the environmental factors in the occurrence of specific cancers, notably the occupational ones. It is also noteworthy that the « Cancer and Environment" CLB unit developed the website [www.cancer-environnement.fr](http://www.cancer-environnement.fr) aiming to facilitate the access of information and data to the patients and their relatives, health specialists, clinicians and scientists. Such dissemination of knowledge performed by the « Cancer and Environment" CLB unit has been fully integrated in the National Plan about Health and Environment (Mesure 24 du Plan National Santé Environnement). While there is increasing evidence that metals and pesticides may be toxic and/or carcinogenic, the RIANS model initiated by the GRad was also found relevant for the toxic/carcinogenic agents of environmental interest [5, 6]: the interaction between the GRad and the "Cancer and Environment" CLB Unit became therefore natural to produce a real synergy in eco-genotoxicology research through a transversal and original approach in the evaluation of the risks. Similarly to this CLB unit, the GRad has established close links with the CLB research group of Sandrine Wittmann that developed original works to modulate the radiosensitivity of tumours through viral and immunological approaches that should lead to novel anti-tumoral immunotherapy. Such research action appeared very complementary to that of the GRad that focuses rather on the radiation response of the human healthy tissues: the CLB research group of Sandrine Wittmann was therefore very naturally integrated in the new UA8 Unit since its creation, bringing a more basic approach in molecular biology and concerning both health tissues and tumors [7-9](Fig. 1).

**To link the academic labs to the National Defense Issues.** By considering the geopolitical context during the 2017-2019 with the increase of the nuclear and radiological terrorist risks and the worldwide instability, but also with the complexity of the radiobiological phenomena related to the military and industrial use of IR, the National Army Biomedical Research Institute (IRBA), dependent on the French Army Health Service (SSA) wished sustaining a close collaboration with academic labs to better complete its missions of National Defense. The Department of the biological effects of radiation (DEBR) of IRBA proposed to create a dedicated research Unit around the Nuclear Radiological (NR) risk together with our GRad with several items of military interest: notably, a better molecular understanding of and countermeasures against 1) acute irradiation syndrome; 2) electrosensitivity with notably the frequencies of military interest; 3) mixed stress including nanoparticles; 4) biological effects of stratosphere radiation (Fig. 1).

**A unit that was evaluated twice:** The U1296 Unit "Radiation: Defense, Health Environment" was initially created in January 2019 out of the current university period of creation of the research units under the number UA8. In January 2021, the UA8 became U1296 with the support of the National Health Institute (INSERM) and the Ministry of Army and the Army Health Service (SSA). It is noteworthy that the UA8/U1296 project has been reviewed in two years once by HCERES committee and twice with INSERM committees. At mid-term (2022) Lyon 2 University became the second supervisory body of the Unit.

<sup>1</sup> *Radiosensitivity* is the proneness to radiation-induced adverse tissue events after high doses of radiation, essentially after radiotherapy, attributable to cell death. *Radiosusceptibility* is defined as the proneness to radiation-induced cancer; attributable to cell transformation. *Radiodegeneration* is defined as non-cancer effects attributable to mechanisms other than cell death like aging, and include cataracts and circulatory diseases.

**The integration of experienced socio-psychologists in the Unit:** initiated by Pr. Marie Préau in the 2019-2021 through the PhD work of Manon Britel, a PhD student of the groups of Psychology of Lyon 2 (GRePS) to study the perception of the radiation-induced risks of individuals from whole public, patients, clinicians or stakeholders. In September 2021, some of the research professors from the GRePS laboratory joined the Unit. Seven research professors, 9 doctoral students, 5 research engineers (on contract) and 3 post-doctoral fellows as well as an administrative manager, all being staff of the University Lyon 2, left GRePS to form a new thematic group in the Unit within U1296, corresponding to a Unit Pole Human Social Sciences or PÔPS. At mid-term (2022) Lyon 2 University became the second supervisory body of the Unit. At this end of the reference period, this same subgroup has grown (9 EC, 13 doctoral students, 3 research engineers, 5 post-doctoral fellows, one ATER).

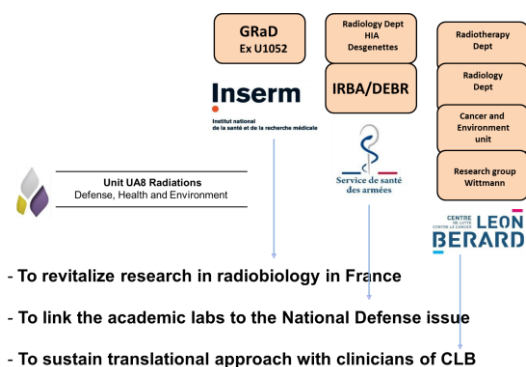


Figure1: The 3 axes on which the creation of the UA8 unit was based in 2017

### 1.2.2 Location of the unit

**The U1296 unit is a multi-site one-team unit** composed of 7 Unit poles (UP) (UP Radiobiology; UP Defense; UP Health; UP Environment and Space; UP Human Social Sciences or PôPS; UP Valorization; UP Communication and Dissemination). Only the UP Defense is based on Brétigny/Orge at the seal of IRBA/SSA. All the other UPs are based in Lyon (the social psychologists of the Pole HSS in the University Lyon 2, the radiobiologists, clinicians and epidemiologists in the campus of the CLB) (Fig.2). Why such a location in Lyon for the headquarters of the U1296 Unit?

**The civil assets of the site of Lyon.** The Auvergne Rhône-Alpes region is one of the most nuclearized region of France with two large nuclear power plants (Bugey and Tricastin). There is also a number of companies using radionuclides or diverse radioactive sources requiring a regulatory follow up in agreement with the radiological protection rules, notably like companies performing industrial gammagraphy. Privileged interactions were facilitated with the Lyon Division of the National Nuclear Safety Authority (ASN). A first meeting was already organized in January 2019. With regard to the International institutions whose seal is Lyon, the presence of the International Agency for Research on Cancer (IARC) at the very close vicinity of the CLB campus permitted the organization of numerous joint meetings and exchanges about the estimation of the risks linked to hazardous agents. A collaboration was also established for the regular publication of French translation of the IARC Monographs on the [www.cancer-environnement.fr](http://www.cancer-environnement.fr) web portal of the Environment Pole of the Unit. Furthermore, several U1296 Unit members regularly contributed to various IARC working groups. This was notably the case of Pr. B. Fervers and J.F. Doré. With regard to the medical institutions, the Lyon area is the second hospital and university place in France with several faculties of Medicine, 6 hospitals, and one of the highest concentrations of clinicians using radiation (radiation oncologists, radiologists, nuclear medicine clinicians and medical physicists). Particularly, the Hospices Civils de Lyon (HCL) manage all the University Hospitals in Lyon and the U1296 Unit interacted with the Service of Radiology of Lyon-Sud Hospital and with the Service of radiology of Women Mother Children Hospital since 2018. In parallel, Dr Jean-Thomas Bachelet (from Croix-Rousse Hospital) pursued a PhD thesis in the U1296 Unit about the radiosensitivity of genetic syndromes associated with facial dysmorphism [10-13]. Interestingly, this thesis provided a new vision of the radiation response of bones (see below). In addition to these interactions with HCL clinicians, a more cultural link with HCL was initiated since 2016. In fact, some former HCL physicians were the most important pioneers of radiation with the first service of radiology opened in France by Etienne Destot [14], the first radiobiology experiments by Claudius Regaud [15], the first anti-cancer radiotherapy in the world by Victor Despeignes [16] and the first study of quality-insurance in radiotherapy by Fabien Arcelin [17]. While N. Foray has published the first biographies of these radiation pioneers to better understand the radiobiological concepts evolution, a very rich cultural patrimony was preserved by HCL curators. A number of exhibitions were therefore co-organised.

**The military assets of the site of Lyon.** With regard to military facilities, Lyon is the seal of an Army Hospital (the Army Hospital Desgenettes) and to the unique French Army Health School (EMSLB). Hence, this site was a real opportunity to integrate in the U1296 Unit more medical teams concerned by radiations like radiologists and more military medicine students to insure a large dissemination of knowledge and a complete teaching about radiobiology. In addition to the Army Hospital and the EMSLB, two other military entities, the unique decontamination regiment of the French Army (UMDA) and the nuclear rapid action force (FARN) make the site of Lyon the most appropriate for the U1296 Unit headquarters. With regard to the Army Hospital Desgenettes, a close collaboration has been established between the GRaD and the Radiology Service of the hospital. The access to the CT scans and the interventional radiology facilities has been offered to the GRaD and now to the U1296 unit staff in the frame of research projects related to low-dose

effects and risks linked to exposure to CT scans (two papers have been published already in collaboration). With regard to the Army Health School of Lyon-Bron (EMSLB) is the unique Army Health School in France. Its mission is to insure the initial teaching for the future physicians and pharmacists of the Army. The recruited students follow the standard lectures and courses of the non-military Faculty of Medicine and Pharmacy but they also receive additional specific courses. Interestingly, it is noteworthy that the IRBA/DEBR staff currently participates to the EMLB courses. Furthermore, the U1296 Unit has welcomed an average of 4 EMSLB students per year as Master students. With regard to the Decontamination Regiment (Medical Unit of Decontamination, UMDA) is situated in the La Valbonne camp at 28 km from the site of the U1296 Unit. A link with the UMDA would permit the Unit to better mimic and work in exact contamination conditions exposure to radiation or genotoxic stress. An exchange and reciprocal visits with the U1296 Unit will be scheduled in 2025. Finally, with regard to the nuclear rapid action force (FARN), after the nuclear accident of Fukushima-Daiichi, Electricité de France (EDF) has proposed to the Nuclear Safety Authority (ASN) to form special commando forces that could intervene in less than 24 h on a damaged nuclear power plant to limit the risks and the consequences of the accident. Such FARN forces has been created in 2012. FARN staff can bring autonomous means of water, air and electricity supplies. EDF is the first electricity supplier in the world to equip such commando forces. Three commandos have been integrated in Paluel (Normandie), Dampierre (Centre) and Bugey (Sud-est) nuclear power plants. The Bugey nuclear power plant is situated at 30 km far from Lyon. Each commando is composed of 5 teams of 14 men. The U1296 Unit will favour a close collaboration with the Bugey FARN and an interaction is foreseen from September 2025.

### 1.2.3 Structure of the unit

As evoked above, **The U1296 unit is a multi-site one-team unit** composed of 7 Unit poles (UP) (UP Radiobiology; UP Defense; UP Health; UP Environment and Space; UP Human Social Sciences or PôPs; UP Valorization; UP Communication and Dissemination) (Fig. 2). The first 5 UPgather members whose expertise and research action is clearly distinct from the other UP members (INSERM radiobiologists; IRBA radiobiologists; civil clinicians; CLB epidemiologists-cartographers and Université LYON 2 social psychologists, respectively). Since the creation of the Unit, such structure has preserved both the cohesion between the different items and encouraged the dialog between the different research actors. Overall, it has also ensured a certain independence of action as a team substructure would permit it. In addition, such a structure has facilitated the applications of the UPs to separated sources of financial supports: as the figure 3 illustrates it. In practise, the sources of financial supports being very different for military staff, radiobiologists, environmentalists or social psychologists; there was neither conflicts nor internal arbitrage necessary since 2019 (Fig. 3). During all these years, we have never considered a Unit member as "belonging" to one specific UP. Indeed, each UP should be taken as a specific think tank rather than a formal substructure. Let's develop each UP in few words

- **UP1: Fundamental radiobiology:** such a pole has gathered all the research works related to the individual response to radiation notably the development of the mechanistic and mathematical models (these last ones were developed with the mathematicians of the Camille Jordan Institute of Lyon I University). The UP1 also gathers radiobiologists and experts in DNA damage and repair who are mostly INSERM staff.
- **UP2: Defense:** such a pole has gathered all the research actions related to the National Defense, and notably the research items linked to NR risks: radiation syndrome; 2) electrosensitivity with notably the frequencies of military interest; 3) mixed stress including nanoparticles; 4) biological effects of stratosphere radiation as already mentioned above. Logically, this pole gathers, at least, all the military staff of the Unit.
- **UP3: Health:** such a pole has gathered all the research works related to the radiotherapy and radiology. Particularly, the questions raised by radiation oncologists like the rationale of the choice of a specific radiotherapy modality (hypo/hyperfractionation; secondary effects, ...) and those raised by radiologists about the potential risks related to repeated radiodiagnosis sessions are representative examples of research actions performed in UP3. All the actions of UP3 are closely linked to those of UP1. The staff working in this UP is mostly clinicians.
- **UP4: Environment and Space:** such a pole has gathered all the research works related to questions raised by chemotherapy, environmental toxics and carcinogens like metals, pesticides and even electromagnetic waves, i.e. agents that may be considered as direct or indirect DNA breakers. This UP gathers the staff of the Cancer and environment unit of the CLB but actions are also linked to UP1 for mechanisms and UP3 for chemotherapy. For practical reasons, all the works related to space radiobiology have been considered in this UP.
- **UP5: Human social sciences or POPS:** such a pole has gathered all the research actions related to the questions raised by the risk perceptions of different publics, by law and regulatory features raised by the introduction of the individual factor in the evaluation of the radiation-induced risk for radiosensitivity and radiosusceptibility. This UP gathers the staff of socio-psychologists of University Lyon 2.
- **UP6: Valorization:** such a pole has gathered all the actions related to valorization of the data obtained by the Unit throughout. This is notably the case of the creation of the NEOLYS DIAGNOSTICS company, of licenced patents, Soleau envelope and deposited database related to human radiosensitivity the licensed patents related to the diagnosis of the Alzheimer's disease but also the creation of the ESIL company of the development of third-generation radioprotectors.
- **UP7: Teaching and dissemination:** such a pole has gathered all the actions related the teaching lectures and courses that the U1296 unit members provided and the communication and dissemination of our data acquired by the Unit. This is notably the case of numerous press releases, invited conferences and books for the general public.



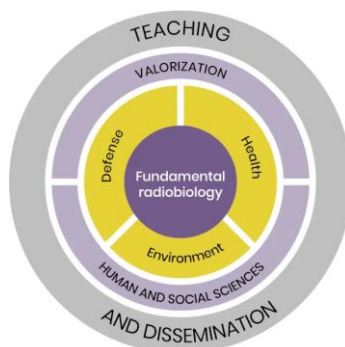


Figure 2: The 7 Unit Poles (UP) of the U1296 Unit

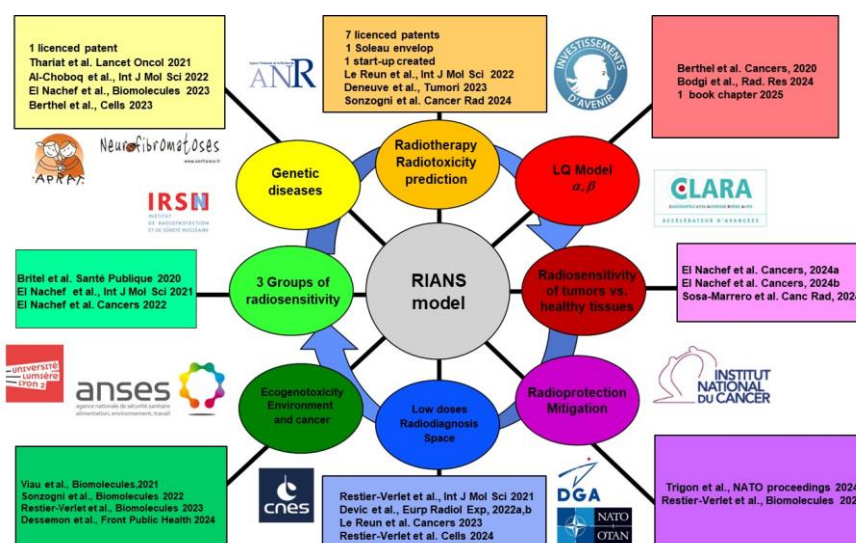


Figure 3: Schematic illustration of the structure of the Unit centralized around the development of the RIANs model. Each sub-item can be supported by independent financial support. Some examples of publications are given for each sub-item.

There are 3 types of financial supports for the Unit (see also self-assessment unit chapter below)

- **Research projects « Défense »:** these supports are current and constant and generally provide from the Army General Direction (Direction Générale de l'Armement (DGA)). They insure an operational research for all the objectives of National/European Defense as well as internal nonpublished expertise. However, for obvious reasons, their amount is not always made public.
- **Clinical trials:** Mainly provided by INCa, DGOS or the European consortiums, the Radiotherapy and Radiology Departments are involved in 25 and 5 clinical trials, respectively.
- **Academic research projects:** the sources of financial support have been various with the Future Investment Project INDIRA (APP Radioprotection et Sûreté Nucléaire - RSNR) whose GRad is coordinator (3 MEuros). The INDIRA project began in 2013 and will end in 2024. Another recurrent source of support is the CNES with about 50 kEuros per year since 2013. The other sources of support are EDF, plan Cancer, Cancéropôle CLARA, ARC and FRM and more recently ANSES.

#### 1.2.4 Teams, platforms, shared services

**CLB irradiation facilities:** Studies in radiobiology are mainly characterized by the use of research irradiators (sources or accelerators) and more rarely medical accelerators (radiotherapy), CT scans or mammographs. These facilities are frequently scattered throughout the national territory for historical, practical or regulatory reasons. Consequently, radiobiologists must frequently organize the transport of cells, their irradiation, preparation and transformation on the site itself. Although such practice is usual when the nature of the radiation is exceptional (ex: heavy ions, protons, synchrotron X-rays, space radiation facility), it is a major constraint for an everyday use of irradiation. Since 2009, it should be emphasized that all the routine irradiations performed by the GRad and now by the U1296 Unit have been carried out on the CLB site with medical radiation facilities (radiotherapy and radiodiagnosis), in the same conditions as patients. Thanks to privileged interactions with the clinicians of the CLB, the access to the radiation facilities for radiobiologists has become a routine. The U1296 unit staff manage the weekly schedules for all the other teams/units users (notably the U1052 INSERM Unit). Again, this deliberate choice to perform radiobiological experiments in medical

irradiation equipment avoids any problem of extrapolation with energy, dose, dose-rate, and any physics characteristics with research irradiators. Another advantage in using medical radiation facilities is that dosimetry for cells irradiation is certified by the medical physicists of the CLB, in agreement with the current regulations and good practice of laboratory. One of most remarkable aspects of the CLB irradiation platforms is that it concerns CT scans, mammographs or interventional radiology equipment, which is nearly unique in Europe and permits to investigate the low-dose radiation effects in realistic situations.

**The IRBA sites** also offered specific radiation facilities in open access for the U1296 unit staff. Particularly, the IRBA/DEBR has non-ionizing radiation facilities that permit to cover all the research about the biological effects of electromagnetic waves. See also the PLATON platform section below. All the radiation facilities whose access were offered to the Unit staff on the CLB, the IRBA sites (see also self-assessment Unit chapter) In addition to medical irradiators, molecular and cellular experiments require secured cell culture boxes (L2, PSM2), storage sites (liquid nitrogen, -80°C, -20°C, cold room), laboratory benches for biology molecular and biochemistry. The research facilities attributed in the CLB site and also present in the IRBA site were available for the Unit staff.

**The COPERNIC collection and its sub-collections:** Since 2004, the INSERM radiobiologists of the Unit have collected skin fibroblasts from patients treated with radiotherapy for their cancer and/or who have shown various radiosensitivity reactions. In 2004, the COPERNIC network of radiotherapists brought together approximately thirty radiotherapists. In 2014, the COPERNIC network doubled [1, 4]. In 2024, it tripled. Each week, the UP Health received at least 1-2 skin biopsies for a request for radiosensitivity expertise. In addition to this collection, which has become one of the largest collections of human cells with different radiosensitivity, UP Health has accumulated skin fibroblasts from patients suffering from well-characterized genetic syndromes associated with radiosensitivity (e.g. neurofibromatosis; RACKHAM sub-collection [18]), radiosusceptibility and/or radiodegeneration (e.g. Alzheimer disease, MATMAHA collection [19] but also from electrosensitivity (DEMETER sub collection): immunofluorescence data obtained from  $\gamma$ H2AX, pATM and MRE11 biomarkers have been gathered in a common data base that has been deposited.

**The POLLUX platform:** Created in 2023 at the initiative of the UP Environment, the Pollux facility aims to provide a technical and methodological support to the research teams in their studies of exposure to physical, chemical and biological DNA-breaking agents and the associated biological and clinical consequences. This facility will contain a large volume of data on environmental exposures (natural or anthropogenic) on a variety of spatial and temporal scales, making it possible to adapt to the needs of the unit poles (fundamental radiobiology, health, environment and space, human and social sciences, defense). In practise, the data mobilised may be derived directly from the Unit data (simulation from the development of models, metrology from data collection campaign) but also from institutional databases. The aim is to be able to provide the most reliable possible reconstruction of exposures, taking into account the spatio-temporal changes in individuals and their geographical environments, in order to reduce, as far as possible, the biases associated with the assessment of exposures. As well as providing access to exposure data tailored to the studies, the facility will also provide analysis methodologies to take into account environmental co/multi-exposures and the influence of the modes of transport of exposed individuals on their exposure. Lastly, the UP Health of the Unit will perform biological experiments by exposing in vitro some reference human cells to the studied agents. Some dose-effect curves will be obtained and the genetic statuses sensitive to the studied agents will be identified.

**The future PLATON platform:** in the last trimester 2024, the U1296 Unit acquired two aneuchoid chambers and the completed associated devices to generate in order to facilitate the exposure of cells to electromagnetic waves in the frame of our research project. Once installed and functional, the access of such facility will be proposed, as an open-access platform, called PLATON, to other Research units.

#### 1.2.5 Size and composition of the teams during the reference period

With regard to the time investment in research, another important specificity of the Unit is the drastic difference between the regulatory statuses of IRBA members, clinicians of CLB or LYON 2 University and INSERM scientists vis-à-vis their time devoted to research. Indeed, the military radiobiologists of IRBA are members of the Army Health Service and therefore may be commanded to go to special external military operations. Hence, their time devoted to research is never 100%. This specificity should be taken into account. Similarly, the time devoted to research for clinicians is also reduced and depends on their tasks, their service and their mission of teaching. Hence, aware of this situation, we have deliberately chosen to score very rigorously the exact contribution of the permanent members of Unit (it is however noteworthy that all the values provided below were calculated on the reference period and do not represent exact value for each year: these values may be overestimated:

- According to the list of the personnel who may be involved in Unit during the period of reference, we scored 102 members including 28, 5, 27 and 43 staff of the groups INSERM, IRBA, CLB and LYON2, respectively.
- The general sex-ratio H/F of the Unit is 32/68 on average. For the 4 groups, it is 40/60, 40/60, 34/66 and 28/72, respectively.
- With regard to the age, the age of the Unit is about 40 on average. For the 4 precited groups, the average age is 45, 50, 39 and 36, respectively. Such findings illustrate well that the radiobiology and overall, the radiopathology require a long experience in the field and suffer from a bad renewal of the generations of the searchers (the average age of the technicians and engineers is much lower (33 on average).
- The calculation of the ETP is particularly difficult for all the reasons evoked above. Hence, we have, as a first step, shared ETP is ETP Researchers or assimilates and ETP Engineers, Technicians Administratives (ITA) and (Table 1).

- The table 1 shows that the 4 groups are unequal vis-à-vis their importance in terms of staff. However, their composition is the reflect of their need and their constraints. It is noteworthy that it is a strategic choice of IRBA group to reduce the group to the permanent research staff and not ITA. Furthermore, the composition also reflects well the difficulties of recruitment for the different institutions like INSERM, IRBA, CLB and University LYON 2.

**Table 1:** Major staff features of the Unit and the 4 groups staff during the reference period

	Group INSERM	Group IRBA	Group CLB	Group LYON 2	Unit
Total workforce	28	5	27	42	102
ETP Research + Post-docs	6.4 + 2	5	12.9 + 4	13.5	48.8
PhD students	5	1	3	11	20
ETP ITA	5	0	6	16	27

With regard to the financial support, we report in the table 2 the total grants, projects and contracts obtained on the reference period. Again, such amount of money may have been obtained and partially spent before the reference period. Therefore, the calculated total amounts described in the table 2 may overestimate the financial support of each group. However, in order to refine the analysis and to avoid biases, we have indexed these figures to the ETPR values and on the basis of one average year (Table 2). The calculations of the table 2 show that the Unit staff got a huge amount of money to reach the requirements of their projects on the reference period. The source of financial support is regular and permits a great development for the Unit. Interestingly, divided by the ETPR, or both the ETPR and year show relatively equivalent figures: about 254 kEuros/ETPR and about 42 kEuros/ETPR/year, which represent impressive values.

**Table 2:** Major financial features of the Unit and the 4 groups staff expressed in kEuros during the reference period

	Group INSERM	Group IRBA	Group CLB	Group LYON 2	Unit
Total support (kEuros)	2302	900 + ? <sup>a</sup>	4559	4697	>12428
Average support/ETPR	~274	> 225	~270	~348	>254
Average support/year	~383	> 150	~760	~782	~2071
Average support/ETPR/year	~45	>37.5	~45	58	~42.3

With regard to the publications, about 219 publications have been provided by the Unit during the period of reference. Again, significant differences appeared in the number and the nature of the publications. However, unlike with the financial support, the publications/ETPR is twice higher for groups INSERM and IRBA than the groups CLB and LYON 2 may be reflecting a larger diversity of supports in the last two groups (table3)

**Table 3:** Major publications features of the Unit and the 4 groups staff during the reference period

	Group INSERM	Group IRBA	Group CLB	Group LYON 2	Unit
Articles	47	39	78	42	219
Reviews	13				
Publications/year	10	6.5	13	7	36.5
Publications/ETPR	7	7.8	4.6	3	4.48
Books chapters	6	2	1	8	
Books	3			2	
Patents	8 licensed				



## 1.2.6 Scientific orientations of the unit and its teams

### 1.2.6.1 A unit based on a mechanistic model of the molecular response to radiation

At the creation of the UA8 and thereafter the U1296 unit, the General Direction of INSERM asked us to fund the Unit on a biological model that would serve as a common trunk for all the Unit poles. Since the general aim of the Unit is to better understand the individual response to ionizing radiation, we focused on a biological model of the repair and signalling of DNA double-strand breaks (DSB) that, if unrepaired, can result in cell lethality, or if misrepaired, can cause potential cancer onset [20]. The ATM protein was shown to be a key-actor of radiation response and the DSB signalling and its homozygous mutations confer the most severe radiosensitivity in humans [21-25]. Because of the current general hypothesis that DNA damage are at the origin of any cellular radiosensitivity [26], the ATM protein has long been considered as mainly nuclear even if there was no clear evidence of the absence of cytoplasmic ATM forms. Furthermore, the fact that some genetic syndromes were found to be associated with radiosensitivity while they are caused by mutations of proteins that stay in cytoplasm suggested that the radiation-induced molecular events in nucleus do not explain all the human radiosensitivity [27-30]. To date, conversely, there is an increasing evidence that ATM kinase is also a cytoplasmic protein and that cytoplasm may play a significant role in the individual radiation response [26]. In 1998, Oka and Takashima and Lim. et al were the first group to evoke the cytoplasmic form of ATM [31, 32]. Thereafter, a number of reports provided solid evidence of the existence of cytoplasmic forms of ATM and also suggested a nucleoshuttling of ATM with different experimental approaches [33-38]. In parallel, from 40 untransformed human fibroblasts representing 8 different genetic diseases (CELLINE collection) and 100 derived from patients showing post-radiotherapy tissue reactions (COPERNIC collection), the radiation-induced ATM nucleo-shuttling (RIANS) was shown to be one of the most reliable predictor of radiosensitivity [1, 2, 20, 39]. A classification of radiosensitivity in three groups was proposed [20] (Fig. 3):

- group I: fast RIANS; complete DSB repair, radioresistance and low cancer risk;
- group II: delayed RIANS; incomplete DSB repair, moderate radiosensitivity and high cancer risk;
- group III: gross DSB repair defect, hyper-radiosensitivity and high cancer risk.

### 1.2.6.2 The numerous direct applications of the RIANS model developed in the Unit in the period of reference

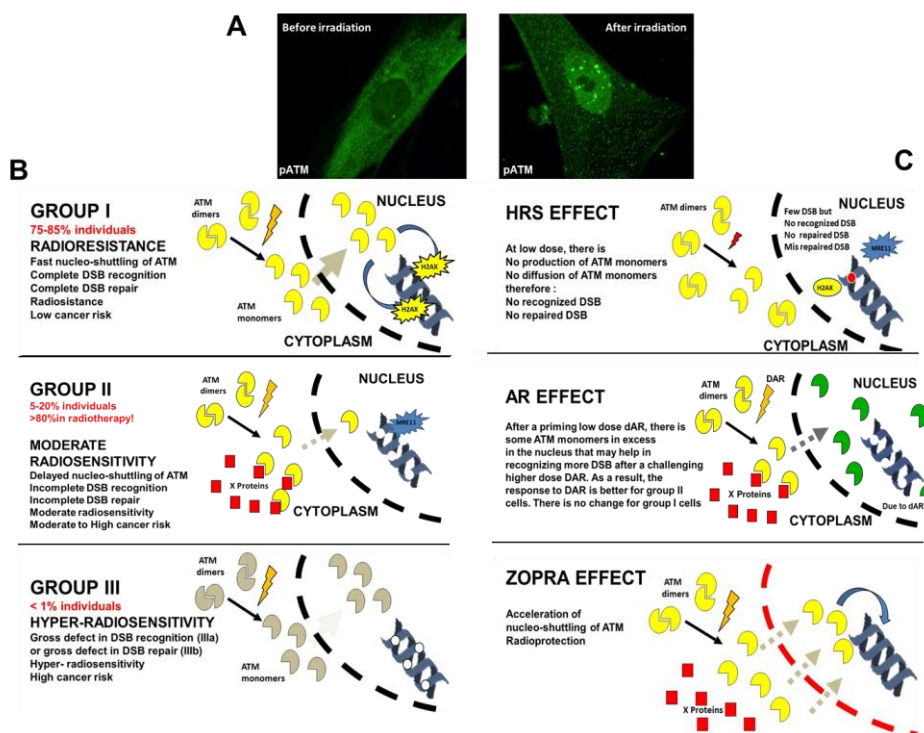
Mechanistically, the two major hypotheses of the RIANS model are that ATM is mainly situated in cytoplasm as dimers formed by two autophosphorylated (pATM) monomers at serine 1981 and that ionizing radiation trigger the monomerization of the cytoplasmic ATM dimers in a dose-dependent manner as suggested already in literature [40, 41]. Thereafter, the ATM monomers, that are the active forms of the protein, diffuse in nucleus, probably more easily than dimers for steric reasons [2]. Active ATM monomers phosphorylate H2AX ( $\gamma$ H2AX) which triggers the non-homologous end-joining (NHEJ) DSB repair and phosphorylate some nucleases, like MRE11, which inactivates the MRE11-dependent recombination-like DSB repair pathway responsible for cancer proneness or genomic instability [2]. Once DSB are repaired, the proximity of the two active ATM monomers helps in forming a dimer, which produces nuclear pATM foci. This last step is supported by a ratio of 2 observed routinely between the number of early  $\gamma$ H2AX foci and the early pATM foci as shown previously [42]. Any delay of the RIANS leads to radiosensitivity and/or genomic instability as validated by the COPERNIC fibroblasts collection [1]. The hyper-radiosensitivity of ATM-mutated cells is naturally explained by the absence of an ATM kinase activity in nucleus (no DSB are recognized by NHEJ) while that of *LIG4*-mutated ATM-mutated cells is explained by a gross repair defect by NHEJ (all the DSB are recognized but they are not repaired by NHEJ) [2]. At this stage, to our knowledge, there is no other relevant model that could explain qualitatively and quantitatively the individual radiation response

Since the creation of the UA8 and thereafter the U1296 Unit, we have considerably amplified the medical application and the theoretical features of the RIANS model. These novel developments can be considered as major advances of the Unit Poles Fundamental radiobiology, Health, Valorization. Since 2017, and more particularly during the reference period, a number of publications are related to the RIANS model (Fig. 4) [43].

- **the RIANS model as a basis for predictive assays:** in 2016 we published with the first 100 COPERNIC fibroblasts that the largest number of pATM foci after 2 Gy (pATMmax) is inversely proportional to the severity grade of post-RT tissue reactions. Six years later, the same relationships were another set of 1000 new fibroblast cell lines, whatever the molecular, cellular or tissue endpoints [1, 44-46].
- **the RIANS model as a mechanistic interpretation of the linear-quadratic (LQ) model:** the LQ model is at the basis of the radiobiology. In 2016, we demonstrated that the RIANS model can lead to the LQ formula, providing therefore the first biological interpretation of the LQ model since 1970. Thanks to the COPERNIC data cumulated during the reference period, we found that the  $\beta$  LQ parameter is a gaussian function of the  $\alpha$  LQ parameter, which permits to revisit the LQ model and to express it as a function pATMmax. For the first time to our knowledge the LQ model becomes a function of the molecular features of a single protein, namely ATM [2, 47, 48]
- **the RIANS model as a mechanistic interpretation of the radiosensitivity of syndromes caused by mutations of cytoplasmic proteins [27-30] :** thanks to the introduction of the X-proteins in the RIANS model (see above), we were able to provide a molecular explanation of the radiosensitivity of a number of radiosensitive syndromes, documenting the classification of radiosensitivity in 3 groups. To date, more than 25 genetic syndromes have been shown to obey the RIANS model.
- **the RIANS at the origin of the development of new radioprotector agents:** unlike the anti-oxidative approach that reduces the reactive oxygen species (ROS) of the water radiolysis and therefore reduce the number of DNA breaks, the RIANS model suggests that to stimulate and enhance the RIANS may result in increasing the number of

DSB recognized and therefore repaired. Such approach was called pro-episkevic and statins+bisphosphonates have shown a higher radioprotection power than antioxidative drugs [27-30]. Some new episkevic drugs are in development: a patent is in preparation.

- **the RIANs model as a basis of a new vision of the RBE/LET relationship:** the relationship between the relative biological efficiency (RBE) and the linear energy transfer (LET) is a basic feature of radiobiology of heavy ions. The ionization produced by the particles will conditions quantitatively the monomerization of the ATM. For example, if the impacts with matter are very localized, the number of ATM monomers induced by radiation will be limited, which may affect the DSB recognition. Conversely, if the ionization is very homogeneous, more ATM monomers may be mobilized. In a paper published in 2019, we have revisited with the RIANs model the question of the impact of the LET upon the biological response [42].
- **the RIANs model as a mechanistic interpretation of the radiobiological phenomena specific to low-dose** like the hyper-radiosensitivity of low-dose (HRS) [2], the adaptive response (AR) and the hormesis [49]. At low dose, the ratio between the ATM monomers induced and the number of DSB induced can be very different. Particularly, in group II proteins X can sequester all the ATM monomers in cytoplasm, which can enhance the biological effect even at low dose (0.2 Gy for the HRS phenomenon). Conversely, below 25 mGy the number of DSB can be nil while the number of ATM monomers diffusing in the nucleus is significant and can participate to the recognition of spontaneous DSB (ex: hormesis). Hence, for the first time to our knowledge, the RIANs model is the only mechanistic model that provides also biological interpretation to the HRS, AR and hormesis phenomena.
- **the RIANs model at the origin of biomarkers specific to accelerated aging or else to cancer proneness** In a systematic review published in the reference period, we pointed out that aging syndrome are characterized by perinuclear protein X while cancer syndromes are characterized by proteins X dispatched in the cytoplasm. Hence, in aging cells, ATM monomers interact with perinuclear proteins X form progressively a perinuclear pATM crown around the nucleus of the aging cells. In 2023, we pointed out that fibroblasts from Alzheimer's disease (AD) show perinuclear pATM crowns compose of ATM-pAPOE complexes. Interestingly, lens cells at high passages mimicking cataracts and bone cells irradiated at the low-dose-rated gamma-rays that reigns



**Figure 4. The RIANs model and its applications in the radiobiological phenomena. (A).** Representative image of pATM immunofluorescence before or after irradiation (2 Gy) in a human normosensitive control fibroblast cell line. **(B).** Schematic illustration of the three groups of radiosensitivity defined from the RIANs model. **(C).** Schematic illustration of the hyperradiosensitivity to low doses (HRS) and the adaptive response (AR) phenomena and of the effect of the combination of statins and bisphosphonates (ZOPRA) on the RIANs [43].

### 1.2.6.3 The numerous indirect applications of the RIANs model developed in the Unit in the period of reference

Some other applications of the RIANs model concern other genotoxic stress of environmental (metals, pesticides), military (inter-tissue differences, radioprotector, electromagnetic waves, mixed stress), HSS (different individual statuses) interest. Furthermore, the applications of the RIANs model have been at the basis of new patents and valorization products. Hence, although UP Defense, Environment, HSS have developed their own specific methods and projects (see portfolio), the RIANs model has permitted, all along the reference period, to consider all the UPs as a very large multidisciplinary and translational approach covering mathematics, biology, genetics, and even human and social sciences. While the UPs Fundamental radiobiology and Health have produced the great majority of papers related to the RIANs model, it is a fact that each of the other UP was at the origin of 2 publications related to the RIANs model, at least.

- **UP Defense :** In parallel with investigations about the acute irradiation syndrome in which we will see that the RIANs model is involved (see portfolio), the development of efficient countermeasures (**radioprotection and radiomitigation**) represents a specific feature of the mission of IRBA/DEBR [50]. Until to date, anti-oxidative drugs and the cytokines family have been investigated in order to provide efficient countermeasures. Besides, this last research axis has been particularly developed in USA by the Armed Forces Radiobiology Research Institute (AFRRI) associated with the academic labs and the private companies. In the frame of the RIANs model, a novel radioprotection approach appears with bisphosphonates and statins combinations [29]. In parallel, **mixed stress** situation (e.g. irradiation+other genotoxic stress) may involve RIANs (see next bullet).
- **UP Environment:** While the UP Environment has mainly focused on epidemiology and geographical studies related to carcinogenic agents [51, 52], UPs Fundamental Biology and Environment have published 2 papers in common about the biological effect of **metal species** [6] and of **pesticides** [5]. In these two papers, we have shown that metals and pesticides+metals may act like overexpressed X proteins on ATM monomers by preventing their nucleoshuttling. It was therefore the first time that the validity of the RIANs model was extended to genotoxic agents other than ionizing radiation. Interestingly, the group II individuals who suffer already from an incomplete DSB recognition due to overexpressed X-protein are more sensitive to metal species and pesticides contamination. It is noteworthy that pesticides act on cells through metal interaction rather than alone. It is noteworthy that pesticides and metals are of major research interest with regard to testicular cancer risk, a privileged field of the group Environment.
- **UP human social sciences (POPS):** the University Lyon 2 has created the psychosocial research group (GRePS) in 2007. The main mission of the GRePS is to federate and promote research in the field of **social psychology**. Its activity also concerns teaching for master students and doctorants. It is in this frame that Manon Britel, a social psychologist has worked on the CLEPSYDRE project (2013 - 2016) for her master and now her PhD (see below) in the UA8 Unit. The CLEPSYDRE project has aimed to study the social representations of the individual radiosensitivity for stakeholders, radiation oncologists and patients to propose some recommendations in terms of communication and vocabulary [53, 54]. This PhD thesis work devoted to the radiation-induced risks perceptions of women concerned by mammography, general public and clinicians has begun in october 2016 and was supported by UA8 Unit, GRePS and the National Institute of Radioprotection and Nuclear Safety (IRSN). This PhD thesis ended in December 2019. In the meantime, a second social psychologist, Sarah Chakra, from the GRePS, joined the UA8 Unit to initiate a work about radiation-induced risks perceptions of workers. Altogether, these works illustrate well the common interest of the Unit with the GRePS for social human sciences related to radiation. During the reference period, the effort of psychologists of the UP HSS focused on minority of sensitive individuals (group II): the RIANs model can be therefore considered as a common trunk for all the operational UPs.
- **UP commercial/economic valorization:** Between 2014 and 2019, the RIANs model was the subject of 7 licenced patents, 1 Soleau envelop, 1 deposited database and the creation of the NEOLYS DIAGNOSTICS company whose Nicolas FORAY was co-founder. Again, the links of interest between N. Foray, the Unit and NEOLYS DIAGNOSTICS have been verified by the INSERM Ethics/Deontology Committee. In 2019 the NEOLYS company changed from beholders and the link between the Unit and the new company became more distant. However, another licensed patent was also shared between the two entities, that concerned by the early diagnosis of the Alzheimer 's disease [19]. Lastly, a new company, named ESIL, that develops a new radioprotector agent, has been funded with Nicolas Foray as co-founder. A licensed patent has been deposited in 2024 about this drug. **Altogether, the RIANs model has been related to 8 licenced patents, 1 Soleau envelop, 2 deposited database and 2 start-up company.**
- **UP Teaching and dissemination:** The RIANs model has been taught continuously in various lectures and courses, whether French or not, notably ensured by N. Foray and M. Bourguignon all along the reference period. These courses concern radiation-oncologists, radiologists, experts in radioprotection and staff in radiology and radiodiagnosis. The RIANs model is a very useful approach to disseminate our knowledge with the "take-home message: we are not equal face to radiation". Vis-à-vis the general public, a number of conferences have been done all along the reference period (about 1 per month) and the cartoons explaining the different application of the RIANs model have been produced and shown in the website of the Unit in **open access** (see also portfolio).

### 1-3 Research environment

As already mentioned, the Unit can be shared in four groups with each, a dominant institution: INSERM radiobiologists, IRBA searchers, CLB Cancer epidemiologists and University Lyon 2 psychologists. Each of this group has a specific environment and partner structures:

- **INSERM radiobiologists:** all along the reference period, this group was the coordinator of a PIA project (INDIRA, see portfolio) that aims to develop knowledge about individual radiosensitivity. From this PIA Project, whose call was initiated after the Fukushima accident, the Unit has been regularly in contact with the National Nuclear Safety Authority (ASN) that published, in February 2019 from the data of the Unit, a Decree recommending radiologists to take into account individual radiosensitivity. In the scale of Europe, in the frame of the EURATOM calls the UP Fundamental Radiobiology has been proposed to be coordinator of the CHORUS project gathering, at least, one radiobiology lab from each country of the geographical Europe. Unfortunately, this project was not retained but the federation of the European radiobiology labs permits us to obtain 30kEuros from the MRSEI call to build a web of the European radiobiology lab called CIRCLE. A particular interaction and exchange agreement has been made with the Maria Skłodowska-Curie National Research Institute of Oncology (Gliwice Branch), Poland (internship of 2 PhD students), and the American University of Beirut, Lebanon, internship of 2 master students). Lastly, it is noteworthy that the UP Fundamental radiobiology was a leader group for the French Speaking Society of Radiobiology with a number of congresses or seminars organised and its activities of dissemination. In addition to these privileged interactions with some National Institutions, it must be stressed that our Unit currently interact with the National Space Agency (CNES) that supports every year our Unit in space radiobiology research in general and in stratospheric balloons expeditions (see portfolio).
- **IRBA staff:** the searchers of the IRBA, members of the Unit and expert of NR risks naturally and currently interact with the NATO staff and their US, German, Polish counterparts with who they have organized specific seminars. This is notably the case of the International IMRIS workshops organized by the SSA/IRBA every two years (see below). They are also members of the organizing committee for a NATO master class on software tools for the triage of irradiated victims (STARS). Moreover, the Laboratory of Biological Dosimetry of Irradiations (LDBI), is involved in biodosimetry network currently assessing inter comparison with the biodosimetry lab of ASNR in France but also in Europe. Indeed, this lab is a permanent member of the European biodosimetry network RENEb organizing European exercises every one to two years. Furthermore, the non-ionizing radiation team is in permanent collaboration with DGA TA (aeronautic technics) and CEA (Gramat) to evaluate the biological effects of weapons systems. The IRBA staffs has showed an active participation in key international conferences, including ConRad (Munich), the International Congress of Radiation Research, and the CBRNE Research and Innovation Conference. Nationally, URAD participates to the congresses of the French Society for Radiation Biology (Société Française de Biologie des Radiations - SFBR) and French Society of Extracellular Vesicles Meeting, emphasizing its influence within both European and global scientific communities. The UP Defense scientific contributions are marked by key innovations in biological dosimetry, particularly through AI-assisted models for detecting chromosomal aberrations and reconstructing exposure scenarios, improving radiation risk assessment accuracy. In collaboration with the Bundeswehr Institute of Radiobiology, the UP Defense strengthens its global influence in radiation research. These advancements reinforce the UP Defense role in advancing radiation protection and medical applications.
- **CLB cancer epidemiologists:** the UP Environment team maintains strategic partnerships that significantly enhance both national and international visibility. A cornerstone of these efforts is the privileged and ongoing collaboration with the World Health Organization's International Agency for Research on Cancer (WHO/IARC), based in Lyon. This partnership supports multiple joint research projects and facilitates visiting scholar exchanges, reinforcing the international scope and recognition of our work. In particular, the Environment and Radiation team at IARC is co-investigator of the TESTIS case control study, and part of the CANCEPT national cancer prevention research network led by Pr. Béatrice Fervers. Moreover, the team members actively contributed to the 5th European Code against cancer, coordinated by IARC, and Pr. Béatrice Fervers is member of the Scientific Advisory Panel of the IARC@60 international conference. Also, the CLB cancer epidemiologists have a strong involvement in the cancer prevention initiatives of several European scientific consortia in the field of cancer research and prevention, which are important opportunities for synergy. Such consortia include, the Joint action EUCanscreen and Join action Prevent NCD. Nationally, the team has established robust collaborations with leading research institutions. Notably, the partnership with Inserm U1018 enables access to and use of the extensive E3N-Generation cohort data, a key resource for advancing epidemiological research. Furthermore, interdisciplinary collaboration is strengthened through the co-supervision of doctoral theses: two in biostatistics, jointly conducted with the LBBE laboratory (Lyon) and the Bordeaux Population Health Center, and one in exposure assessment with the Ecole Centrale Lyon. These collaborations not only enhance research capacity but also foster long-term academic and scientific synergies across institutions. CLB cancer epidemiologists are member of several national expert groups and scientific committees, including the ANSES Expert Committee (CES) "Assessment of the risks related to air environments"; the Scientific Council on Epidemiological Surveillance around Major Industrial Areas, and the Expert Committee on the Monitoring the Incidence of Cancers Related to Occupational Activity" (Sicapro), Santé Publique France; the Scientific Committee on Public Health and Environment, Fondation de France; and the Commission for Children Victims of Prenatal Pesticide Exposure (CIEVEPP).



- **Université Lyon 2 psychologists :** the majority of UP HSS (PÔPS) researchers are attached to the Institute of Psychology at the University of Lyon 2, which is the only psychology training programme on the site. A Simeone and C Bauquier are attached to the Institut de Sciences de l'éducation et de la formation (ISPEF) at Université Lyon 2. The members of the PÔPS are involved at both local and national level in a number of PIA projects. Firstly, on a local level, in 2022, the SHAPE-Med@Lyon project (Structuring one Health Approach for Personalized Medicine in Lyon), was a winner of the Programme d'Investissement d'Avenir 4 (PIA4) 'Excellences' of France 2030. This project focuses on transdisciplinarity in healthcare and aims to bring the One Health approach into line with the 5 Ps of medicine (participative, predictive, evidence-based, preventive and precision). The University of Lyon 2 is co-sponsor of the project with the University of Lyon 1, the Hospices Civils de Lyon and Inserm. The project is run by a board of three scientists, Marie Préau represents the University of Lyon 2 and the wider social sciences and humanities. This is a major investment and has led the entire PÔPS to make a significant contribution to this initiative. The PÔPS has also received funding for 6 research projects as part of the ANR budget for this project. It is noteworthy that in the last call 2024 of SHAPE-Med@Lyon, 7 projects are held by UP Environment or UP Health. Also as part of the France 2030 projects, the EUR EID@Lyon was a winner of the AMI Métiers d'Avenir as part of the acceleration strategy for emerging infectious diseases (EID) and CBRN threats (CBRN), which aims to strengthen our preparedness against the risks of a major new health crisis (EID or CBRN). Marie Préau (PÔPS) is co-supervisor of this EUR and one of the doctoral students, who is now a doctoral student and the course's educational engineer (Costanza Puppo). The emergence and spread of infectious diseases is facilitated by human activities, which have a major impact on the functioning of socio-ecosystems and health. EID@Lyon is part of a global, systemic and complex analysis of health, integrating the interrelationships between human health, animal health and the health of ecosystems and, more broadly, the environment. EUR EID@Lyon therefore aims to train the next generation of innovators and scientific experts who will be able to understand, anticipate and manage the infectious risks of tomorrow. The strengthened links between research, training, hospitals and socio-economic partners are designed to provide a global and transdisciplinary vision of health issues. In addition, in 2024, the Lyon site was also the winner of the EVEREST University Hospital Institute project, which focuses on transdisciplinary approaches to liver disease. In this project, the entire social and participatory sciences dimension is led by Marie Préau of the PÔPS and involves at least 5 people from the team. The IHU started its scientific activity in mid-2024 and will expand through projects funded by internal tenders within the IHU. The team plans to recruit at least two post-doctoral students on this theme.



## 1-4 Consideration of the recommendations in the previous report

Here is a strict copy of the recommendations of the previous report. It must be stressed that these recommendations have been done in a special context: there is no setback of more than 6 months after the creation of the Unit.

**EXPERTS COMMITTEE MEMBERS** Chair: Ms Catharine WEST, University of Manchester, United Kingdom Experts: Mr Xavier COUMOUL, Université de Paris, Paris (representative of Inserm CSS) Mr Jurgen FUTTERER, Radboudumc, Netherlands Ms Karin HAUSTERMANS, University Hospitals Leuven, Belgium ; Mr Marek JANIAK, Military Institute of Hygiene and Epidemiology, Poland ; Ms Marjorie JUCHAUX, CNRS, Orsay (supporting personnel)

**HCÉRES REPRESENTATIVE** Mr Jean-Edouard GAIRIN

**REPRESENTATIVES OF SUPERVISING BODIES** Ms Marie-Josèphe LEROY-ZAMIA, Inserm ; Mr Jean-Christophe AMABILE, IRBA ; Ms Marina Rousseau-TSANGARIS, Centre Leon Berard (partner)

**INTRODUCTION HISTORY AND GEOGRAPHICAL LOCATION OF THE UNIT** The Radiation: Defense, Health & Environment UA8 unit was created in January 2019 as an expansion of the Group of Radiobiology (GRad) of the U1052 INSERM unit. It was created to bring together a multi-disciplinary team covering all aspects of radiobiology (research field for all poles). The headquarters and overall coordination of the unit is located on the Center Léon-Bérard (CLB) campus in Lyon. CLB is a comprehensive cancer center linked to the University Claude Bernard Lyon (UCBL). The other main research structure of the UA8 unit is located at the Institut de Recherche Biomédicale des Armées (IRBA) in Brétigny-sur-Orge. While CLB/UCBL are the headquarters, activities will take place on multiples sites. The local (in or close to Lyon) research ecosystem includes or will include: the University Lyon 2, the Hospices Civils de Lyon (HCL), the Army Hospital HIA (hôpital d'instruction des armées) Desgenettes, the Army Health School of Lyon-Bron EMSLB (Écoles Militaires de Santé Lyon-Bron), the Medical Unit of Decontamination UMDA (Unité Médicale de Décontamination des Armées), in La Valbonne and the Nuclear Rapid Action Force FARN (Force d'action rapide nucléaire) in Bugey. The National Space Agency (CNES) in Paris, and the University Paris-Saclay are and will also be associated in the project.

**MANAGEMENT TEAM** The heads of the unit are Mr Nicolas Foray (co-director, INSERM) and Mr Michel DROUET (co-director, IRBA). Ms Béatrice FERVERS is the deputy director.

**HCÉRES NOMENCLATURE** SVE 5 : Physiologie, physiopathologie, cardiologie, pharmacologie, endocrinologie, cancer, technologies médicales

**THEMATICS** The « Radiation: Defense, Health & Environment » Unit is dedicated to human radiobiology research. At initiation, the unit had the following research topics: high dose radiobiology; low dose radiobiology; environmental radiobiology; and socio-radiobiology. For the 2012-2025 period the research themes are re-defined as: fundamental radiobiology (pole 1), defense (pole 2), health (pole 3), environment and space (pole 4), and human social sciences (pole 5). Fundamental radiobiology covers mechanisms of radiosensitivity and susceptibility to radiation effects; it also includes targeting radioresistance and modulating immune responses. The defense research topic covers acute radiation effects (high dose); individual biodosimetry assays; radioprotection and radiomitigation; electromitigation and response to multiple genotoxic agents. Health research will compare radiotherapy modalities, introduce a radiosensitivity assay into routine clinical practice, and evaluate risks from low dose radiation. The environment and space pole will research aspects of space radiobiology (e.g., impact of individual radiosensitivity; role of statins and bisphosphonates as radioprotectors); electroradiosensitivity and environmental genotoxicology. The human social science pole will study psychosocial perceptions of radiation risks and how radiation protection regulations would incorporate individual measurements of radiosensitivity.

**GLOBAL ASSESSMENT OF THE UNIT** Establishing the unit is an achievement and an excellent initiative for France. The policy behind its establishment is to reinvigorate radiobiology in France, which is underpinned by the willingness of national institutions (Inserm, Army) to bring together cross-cutting and multidisciplinary expertise (clinical, military, scientific) from different organizations, research cultures and disciplines. The unit aims to stimulate radiobiology in France, link academic laboratories with national defense priorities in radiation research and expand radiation research relevant for patients undergoing radiotherapy for cancer. Key scientific objectives are to better understand the biological consequences of exposure to radiation (and DNA-breaking agents in general) and the impact of inter individual differences in the repair and signaling of DNA damage. An original feature of the unit is the co-study of fundamental (including space and defense-related), clinical (radiotherapy, radiology, nuclear medicine) and sociopsychology radiobiology. During the first year of its creation the unit has defined its strategy and brought together different groups to develop a sense of belonging. As it was only formed in January 2019, the unit as a whole has not yet achieved international recognition. The multi-disciplinary and multi-site research pose a threat to the timely delivery of objectives and training/teaching activities could overwhelm resources. The research strategy would benefit from reducing the coalescing emphasis on the RIANS (Radiation-Induced ATM Nucleo-Shuttling) model, which oversimplifies radiation effects. RIANS is of interest to increase understanding of the effects of radiation, but there is limited international interest in its use as a routine radiosensitivity test. There are absences from the strategy that can be

addressed as the unit builds in strength, e.g., consideration of other assays of radiation sensitivity / susceptibility / exposure; radiation hormesis including immunostimulatory, anti-inflammatory, anti-neoplastic, and other potential beneficial effects.

**Our commentaries :** First, we must stress again that the HCERES committee gave some commentaries but with a short setback compare to the creation of the Unit and a number of features may have been forgotten by the HCERES committee :

-« *The multi-disciplinary and multi-site research pose a threat to the timely delivery of objectives and training/teaching activities could overwhelm resources* ». To date, the facts demonstrate that the multidisciplinary and the transversality of the items treated in the Unit are a wealth and not a threat and, some months after the COVID pandemic, the technology as permitted to work in several and more complex structures than before. Surprisingly, earlier in the text, the Committee recognized the multidisciplinary and the integrated nature of the radiobiology treated as an original feature.

-« *The research strategy would benefit from reducing the coalescing emphasis on the RIANs (Radiation-Induced ATM Nucleo-Shuttling) model, which oversimplifies radiation effects* ». First, The HCERES Committee has forgotten that the RIANs model as a common trunk was imposed by Inserm to accept the creation of the Unit. Second, the abundance of the literature provided from the RIANs model and its applications during the reference period and further is a proof that our approach was very well justified. The RIANs model is not necessarily a simple model but, conversely, unlike the others, it has permitted to provide the biological interpretation of numerous radiobiological phenomena.

-« *RIANs is of interest to increase understanding of the effects of radiation, but there is limited international interest in its use as a routine radiosensitivity test.* » Such statement can be easily contradicted by publications published in common by European Consortium of radiobiologists, by international textbooks, invited conferences and successive proofs published by the Unit and other teams in the world. It must be stressed that, to date, the RIANs model is the only approach providing a biological interpretation of the LQ model and a quantitative relationship between pATMmax and CTCAE grade. Besides, the general conclusions of the INDIRA PIA project (manuscript in preparation) show quantitative comparisons between the different radiosensitivity predictive assays in the benefit of the RIANs model. A potential conflict of interest may have been revealed between the President of the HCERES committee and the Unit.

-« *There are absences from the strategy that can be addressed as the unit builds in strength, e.g., consideration of other assays of radiation sensitivity / susceptibility / exposure; radiation hormesis including immunostimulatory, anti-inflammatory, anti-neoplastic, and other potential beneficial effects* ». One year later these Commentaries, we published a biological interpretation of the RIANs model for the hormesis phenomenon and other low-dose specific effects. Three years later, the biological interpretation of radiation sensitivity / susceptibility/degeneration was provided from the RIANs model. To date, still in the frame of the RIANs model, immunostimulatory, anti-inflammatory, anti-neoplastic, and other potential beneficial effects are being investigated.

Finally, after these commentaries about our Unit, we would like to stress on two important facts:

- These commentaries, that mainly focused on the RIANs model did not concern the other UPs notably the projects related to Defense, Health, Environment, Space and HSS : there was no particular comment for these UPs
- The major focus on the RIANs can be explained a posteriori by the fact that the President of the Expert Committee developed a concurrent approach of the RIANs model to predict radiosensitivity by using radio-sequencing and polymorphisms. This reveals therefore a potential conflict of interest. We should be therefore more cautious when choosing the members of the expert committee for the next evaluations.

## 2- PORTFOLIO INTRODUCTION

### 2-1 Justification of the choices of the items for the portfolio

In order to describe the most representative works of the U1296 Unit during the reference period (2021-2024), it was natural to investigate the research actions according to the 7 UPs (Fundamental radiobiology, Defense, Health, Environment and Space, Human Social Sciences, Economic valorization and knowledge dissemination). While the Unit is a one-team unit but composed of 4 different groups of experts, such a presentation by UP permits a good balance between the specific themes of each group (INSERM radiobiologists, SSA/IRBA staff, CLB epidemiologists and Université Lyon 2 social psychologists) and also allows the description of the research works resulting from inter-group interactions. However, the research field is large. As detailed in the above section, the RIANS model must be at the basis of the majority of the research actions of the Unit. Hence, following the recommendations of the HCERES governance according to the size of the Unit, the Portfolio will contain specific items that represent the great majority of the publications and the most significant productions during the reference period: we have tried to offer the most significant results in the portfolio and to leave the most relevant ones on the most varied media supports (Fig. 5).

- **UP Fundamental radiobiology:** A focus will be done on the PIA INDIRA project that N. Foray has coordinated. For 11 years, the INDIRA Project (3 MEuros including 1.3 for the Unit), coordinated by N. Foray, belongs to the PIA 2 Call that was launched after Fukushima accident. The INDIRA project has permitted considerable advances in the understanding of the individual response to radiation. This project has generated more than 30 publications and 7 patents at least (see Excel file). An exhaustive summary has been included in the portfolio. The paper establishing inter-correlation between radiobiological parameters may be a summary of all our approach these last years [55].
  - **UP Defense :** one paper about the novel radioprotection drugs [56] and the organization of IMRIS Seminars, that gather the most important teams working on the military radiation research were chosen to illustrate the postfolio.
  - **UP Health :** one paper about the Radiobiological specificities for the stereotactic irradiation, another application of the RIANS model [57]
  - **UP Environment and Space:** With regard to cancer and environment part, 2 papers about the critical challenges in the relationship between environmental exposures and cancer risk have been included in the portfolio for the Environment [51, 52]. Paper about RIANS model and pesticides has been also added: [5]. With regard to space, a review presenting a new paradigm for space radiation research and a paper to be submitted for the stratospheric balloons with be detailed below [58, 59].
- UP HSS (PôPS):** Four very different research products have been chosen to illustrate the action of the PôPS during the period of reference [60]: the HSS study of the INDIRA PIA project; a paper about the COVID-19 pandemic, an invited conference about AIDS and the creation of Master of sociopsychology.
- **UP Valorization:** the article that has been at the origin of a licenced patent about the early diagnosis of the Alzheimer's disease [19].
  - **UP Teaching and dissemination:** Research works about 5 pioneers of radiation from Lyon notably through 5 short-movies available on our Website and Youtube in French and English language.

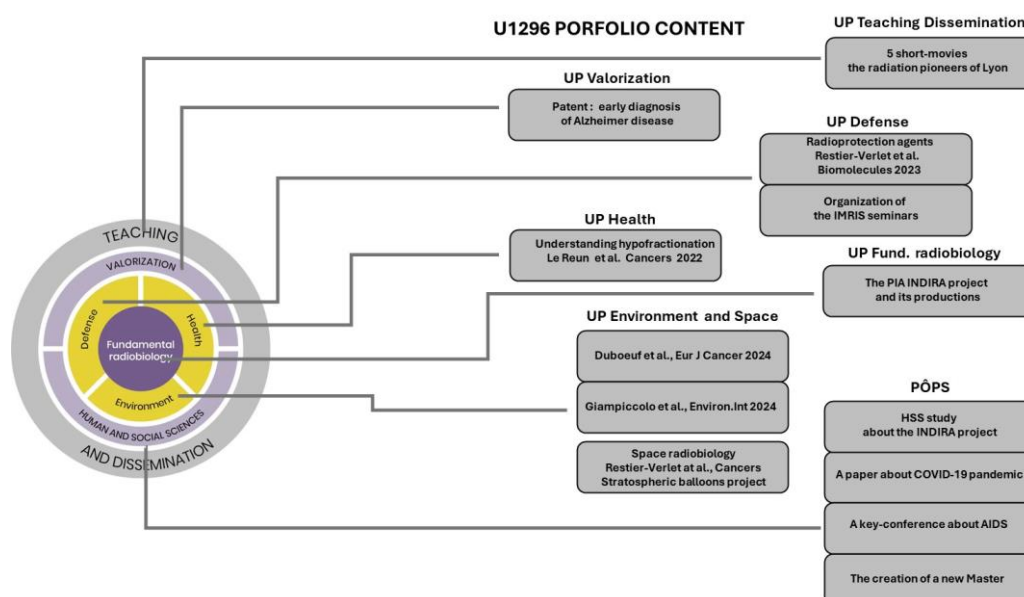


Figure 5 : Schematic content of the portfolio

### 2.1.1 UP Fundamental radiobiology

**Introduction:** As mentioned above, the Future Investment Project (PIA2) INDIRA was the largest project that has supported the Unit since its creation: from 2013 until 2014, INDIRA represents 1.3 MEuros of financial support to reach 2 aims: 1) the development of the most reliable predictive assay for quantifying radiosensitivity and 2) the quantitative estimation of the radiosensitive subpopulation in a population of apparently healthy individuals. It is noteworthy that the Unit was the coordinator team of the INDIRA project with 2 CEA teams, 1 Emergency Medical Service of Paris (SAMU 75) and the CLB as partners. For the team 1 (ie the Unit), the aim1 corresponds to the development of the RIAN model and biomarkers while the 2 CEA teams, team 2 and 3, have focused on another approach or methodology (genomic approach and hair follicles, respectively). With regard to the aim 2, The SAMU75 team organized a skin sampling in their apparently healthy staff : 30 individuals (all men) were samples and deriving fibroblast cell lines composed the collection INDIRA to estimate the radiosensitive subpopulation in a radioresistant donors. The INDIRA project was at the origin of about 35 publications

**Description of the related productions :** The production related to the INDIRA project gathers nearly all the publications performed in the frame of the UP Fundamental radiobiology. Particularly, the productions related to the RIAN model concern : 1) the radiobiological characterization of about 25 genetic diseases that confirm and document the RIAN model [43]; 2) the molecular interpretation of the three low-dose specific radiobiological phenomena (HRS, hormesis and adaptive response) by the RIAN model [49, 61, 62]; 3) the molecular interpretation of the three notions of radiosensitivity radiosusceptibility and radiodegeneration and their specific biomarkers [63-65]; 4) the introduction of the notion of pro-episkevia (see below) [56]; 5) the last category of paper are about the mathematical aspects of all the application of the RIAN model : this concerns notably the quantitative inter-correlation between radiobiological parameters and the estimation of the radiosensitive subpopulation [55]. Thanks to the publications related to the RIAN model, 3 books and have been published on the different features of the RIAN model. Furthermore, the Unit has participated to a number of chapters of the international textbook of radiobiological, representing a significant contribution to most of the chapters. It is also noteworthy that the notions and the definitions of radiosensitivity, radiosusceptibility and radiodegeneration have been progressively adopted by EURATOM, which proves the recognition of the Unit at the national, European and international levels (e.g. articles, books, artistic creations).

**Description of the related training activities:** All the items concerned by the INDIRA project have been currently presented in a number of conferences and courses all around the world. First, it must be stressed that Pr. Michel Bourguignon, dean of the Unit, former commissary of the National Nuclear Safety Authority (ASN) is also French representant of France at the International Commission for Radiological Protection (ICRP) and vice-president of the scientific committee of EURATOM. From these functions, he has disseminated the most recent data and notions developed by the Unit at the highest level, and introduced the RIAN model, the individual radiosensitivity in a number of papers or official texts. Furthermore, Pr. Michel Bourguignon and Nicolas Foray are involved in a number of University and professional courses linked to the NRBC diploma for the SSA, masters of cancerology of Grenoble and of Lyon, specific formations radiology manipulators, radiologists and radiation oncologists. More recently, in 3 years, Nicolas Foray has given invited conference in all the regional webs of radioprotection advisers in France and in the radioprotection formation of staff of the Geneva Hospital (HUG).

**Description of the "external collaborations" and the regional actions:** The Unit has been involved in a number of whole public events to reinforce the action of research and its most recent results. This is notably the case of a number of Days of Science, exhibition about the use of X-rays during the WW1 and a series of conferences in local association for the history of sciences. Lastly, note that the INDIRA project is a PIA2 project that involved the SAMU75, i.e. an institution that is directly involved in the mass accident crisis and a group of brain-storming with SAMU75 and CEA will be formed at the end of the year 2025 together with FARN and RMDA. In parallel, the same approach will be adopted with regional occupational physicians whom some are already member of the Unit.

With regard to the economic point of view, it must be stressed that the INDIRA project is at the origin of the creation 2 start-up companies (NEOLYS for the predictive assays and ESIL for the new agents of radioprotection), 1 Soleau envelope, 2 databases deposited and 9 licensed patents (7 for the predictive assays, 1 for the diagnostics of AD and 1 for the new agent of radioprotection).

**Dissemination of knowledge:** With regard to the dissemination of knowledge, as evoked above, a number of conferences for the general public, TV, radio and written press media have been implied in the diffusion of the results obtained and our web site show some short-movies about the mechanisms discovered.

### 2.1.2 UP Defense

**Introduction :** Significant advances in our understanding of the biological response to ionizing radiation and radiation protection strategies have marked this reference period. The UP defense has focused on developing models of radiation-induced lesions to evaluate the therapeutic efficacy of novel strategies. Among these, the study of the secretome of mesenchymal stem cells has shown promising results for musculoskeletal injuries and severe hematopoietic damage. In collaboration with CEA-DAM, the UP Defense has analyzed the combined effects of several existing treatments for internal contamination, aiming to optimize their efficacy. Additionally, UP Defense participated to a clinical project with the Hôpital d'Instruction des Armées Bégin, identifying urinary and serum biomarkers predictive of radiation-induced cystitis, an essential advancement for monitoring patients exposed to radiation [66, 67]. The thesis work completed during the reference period resulted in the development of a murine model for musculoskeletal lesions following high-dose localized irradiation and an exploration of the impact of the Shh signaling pathway in myogenesis [68] Meanwhile, the UP Defense has investigated the biological risks associated with emerging technologies and the war-



related exposome. Particular attention has been given to the effects of electromagnetic waves and exposure to environmental contaminants from military activities. Among these, propellants used in missiles and rockets are of particular concern due to their potential toxicity. Furthermore, research on high-dose alumina nanoparticle inhalation combined with hydrogen chloride gas has revealed a strong pulmonary pro-inflammatory response [69]. Ongoing studies are now expanding to extrapulmonary tissues to better characterize systemic effects and, ultimately, determine occupational exposure limits for personnel exposed acutely or repeatedly. The UP Defense commitment to training young researchers has led to the initiation of four theses, further strengthening the scientific dynamics of the department. Additionally, UP Defense plays a central role in two major European projects funded by the European Defense Fund, consolidating its international presence and impact.

Overall, the UP Defense has also focused its efforts on new radioprotective drugs for military management before exposition on the battlefield. Particularly, interaction with the UP Fundamental Radiobiology has led to a novel type of radioprotection agent. Indeed, the RIANS model suggests that if numerous ATM monomers can diffuse more rapidly in the nucleus of irradiated cells, more DNA damage will be recognized and therefore repaired. Such strategy is different from the anti-oxidative approach that consists in reducing the process of the radiation-induced water radiolysis and impacting on the production of reactive oxygen species (ROS) responsible for the formation of the DNA damage. We have named "pro-episkevic" (from the ancient greek episkeve, repair) such novel approach. A first princeps paper has been published in 2023 by both UP Defense and Fundamental Radiobiology staff. This paper belongs to the PortFolio [56]. Another focus will be done also on the IMRIS Seminars organized by the UP Defense and that became an actual success for the community (see below)

### **Description of the related productions:**

The radiation protection strategy with chemical agents has long been based on an antioxidative approach consisting in reducing the number of radical oxygen and nitrogen species responsible for the formation of the radiation-induced (RI) DNA damage, notably the DNA double-strand breaks (DSB), whose subset participates in the RI lethal effect as unreparable damage. Conversely, a DSB repair-stimulating strategy that may be called the "pro-episkevic" approach (from the ancient Greek *episkeve*, meaning repair) can be proposed. The pro-episkevic approach directly derives from a mechanistic model based on the RI nucleoshuttling of the ATM protein (RIANS) and contributes to increase the number of DSB managed by NHEJ, the most predominant DSB repair and signaling pathway in mammals. Here, three radioresistant and three radiosensitive human fibroblast cell lines were pretreated with antioxidative agents (N-acetylcysteine or amifostine) or to two pro-episkevic agents (zoledronate or pravastatin or both (ZOPRA)) before X-ray irradiation. The fate of the RI DSB was analyzed by using  $\gamma$ H2AX and pATM immunofluorescence. While amifostine pretreatment appeared to be the most efficient antioxidative process, ZOPRA shows the most powerful radiation protection, suggesting that the pro-episkevic strategy may be an alternative to the antioxidative one. Additional investigations are needed to develop some new drugs that may elicit both antioxidative and pro-episkevic properties and to quantify the radiation protection action of both types of drugs applied concomitantly [56].

In addition, the UP Defense organizes the International Military Radiation and Innovation Symposium (IMRIS). Initially a small gathering of thirty participants, this event has evolved into a major symposium, with seven editions held biannually. The symposium now attracts approximately one hundred participants and serves as a key platform for the dissemination of research and innovation in radiobiology. It brings together military and civilian scientists from around the world, underscoring the DEBR's commitment to fostering scientific collaboration in the fields of radiobiology, environmental toxicology, and the biological effects of electromagnetic radiation. Over the years, the symposium has become increasingly international, with past participants from institutions such as the Armed Forces Radiation Research Institute (USA), Bundeswehr Institute for Radiobiology (Germany), Roma 3 University (Italy), the Czech Military University, and the UK National Institute for Health and the Naval Medicine Institute. The event also provides a venue for discussing emerging risks, including recent advances in radiobiology, clinical studies, biomarkers, therapeutic strategies, and the exposure risks linked to new defense technologies, such as the exposome and electromagnetic radiation.

**Description of the related training activities:** The UP Defense is deeply involved in training and supervision, significantly enhancing the institution's educational offerings. The UP Defense has successfully supervised five doctoral theses, with two recently defended, and currently supports three ongoing PhD projects focusing on radiation-induced injuries and toxicology. Additionally, The UP Defense has mentored two Master students, including one in an apprenticeship program, concentrating on nanoparticle inhalation and extrapulmonary toxicity. IRBA staff play a pivotal role in higher education, offering specialized lectures at both national and international levels. Notably, they contribute to programs such as the University Diploma in Applied Radioprotection in Occupational Medicine (Université Paris Cité) and the Training of Trainers for Military Medical Decontamination Units (École du Val-de-Grâce). These initiatives, led by the Head of the UP Defense, ensure the development of high-level expertise in radioprotection. Two projects highlight their focus on innovation, particularly through collaborations with non-academic partners. These partnerships are central to advancing research in areas with significant societal implication.

**Description of the "external collaborations" and the regional actions:** The INCREASED project (2021-2024) (AID; ANR-ASTRID), led by UP Defense, exemplifies co-production with non-academic stakeholders, such as the French Nuclear Safety and Radiation Protection Authority (ASNR). This initiative uses artificial intelligence to improve the detection of chromosomal aberrations in radiation dosimetry. By bringing together radiation protection experts, AI developers, and healthcare professionals, it enhances radiation exposure monitoring in high-risk environments like nuclear sites and healthcare facilities. The societal impact is substantial, strengthening risk management and optimizing interventions in



case of mass exposure, thus contributing to national public health security. In the RABBIO clinical project (2021-2024), (DGA) the UP Defense integrated the Cureety TechCare platform, a telemedicine solution, into a patient-centered care model. This platform (owns by hospital BEGIN) allows prostate cancer patients to complete quality-of-life questionnaires remotely, facilitating continuous engagement and real-time treatment adjustments. Based on co-production between healthcare teams and patients, the project highlights the role of digital tools in advancing clinical research and improving patient care, while also contributing to scientific knowledge.

The UP Defense participation in national and international bodies, such as the CBRN Med Working Group, NATO sciences and technology organization working groups and the Ministry of Armed Forces, ensures its contribution to public policy discussions and the management of radiological risks. It also plays a significant role in guiding the scientific community on radiological safety through expert groups, including those focused on internal contamination and radiological accidents. In addition, the UP Defense has engaged in collaborations with national authorities such as the Ministry of Health, providing expertise on radiation management in emergency situations.

**Dissemination of knowledge:** The UP Defense is engaged in the dissemination of scientific knowledge through various outreach initiatives aimed at a broad range of stakeholders, including the general public, institutional actors, and the scientific community. A key initiative is the creation of a Massive Open Online Course (MOOC) on Nuclear Risk (NR), which serves as a vital educational resource. This platform provides accessible training for military health service personnel and broadens its impact internationally through translations and supplementary modules. These efforts play a crucial role in enhancing the expertise of professionals in radiological risk management, thereby contributing to improved health security at regional, national, and international levels.

### 2.1.3 UP Health

**Introduction:** Among the numerous productions of the UP Health, one can distinguish all the papers related to the better understanding of the molecular mechanisms involved in a given radiotherapy modality and the evaluation of the radiation-induced risks for the application of low doses like with the CT scan and mammography exams. It is noteworthy that our papers related to CT scan and individual radiosensitivity reveal that, even at doses of mGy order, significant differences between the yields of DNA double-strand breaks have been observed, documenting the potential risks of radiation-induced cancers after repeated diagnosis exams. Conversely, considering the huge technological advances for radiotherapy modalities, involving both improvements in tumor targeting and hypo-fractionation of the dose. During the reference period, hypo-fractionated stereotactic body radiation therapy (SBRT) was the subject of a number of discussions with regard its anti-tumor capacity. However, no mechanistic model was still proposed to explain the potential interest of such modality. Thanks to the RANS model and the interpretation of the hypersensitivity to low doses (HRS) phenomenon, we have demonstrated in one paper that each SBRT session can be viewed as hyperfractionated dose delivery by means of hundreds of low dose minibeam. Under current SBRT conditions (i.e., low dose per minibeam and not using ultra-high dose-rate), the response of HRS-positive tumors to SBRT may be enhanced significantly. Interestingly, similar conclusions were reached with HRS-positive and HRS-negative untransformed fibroblast cell lines, suggesting that the HRS phenomenon may also impact the risk of post-RT tissue overreactions. Hence, we deliberately focused on this paper in this section [57].

**Description of the related productions :** The paper published in 2023 demonstrated the possible occurrence of the hypersensitivity to low dose (HRS) phenomenon in SBRT modality in both tumor and healthy cells [57]. In HRS-positive cells, the response to SBRT was found exacerbated. Notably, a subset of highly damaged cells can appear and increase the efficiency of the treatment. Hence, each SBRT session can be viewed as hyperfractionated dose delivery by means of hundredso document these findings in other SBRT modalities and, even, to better evaluate the risk of exposing HRS-positive healthy tissues and the benefit of treating HRS-positive tumors. To our knowledge, it is the first time that SBRT, notably Cyberknife, is associated with a specific mechanistic model, depending on the mechanistic model and the occurrence of HRS phenomenon. Such paper was associated with some other papers and reviews that consolidate the mechanistic model proposed [57].

**Description of the related training activities:** The training activities associated with this work were obviously given in the frame of the professional formation of the radiation-oncologists. However, we can also cite a series of international invited conferences, notably in Poland during which the new model on interpretation of Cyberknife and SBRT was presented (see portfolio).

**Description of the “external collaborations” and the regional actions:** Such work was at the origin of a close collaboration between the unit and the THERYQ company, a start-up supported by FRANCE 2030 for building the FLASHtherapy machines. Such company has offered us the access of their prototypes so that we will be able to compare the different modern radiotherapy modalities and propose specific mechanistic models in the frame of the ERATOSTHENE project.

**Dissemination of knowledge:** As specified above, there were a series of international invited conferences, notably in Poland during which the new model on interpretation of Cyberknife and SBRT was presented.

### 2.1.4 UP Environment and Space : Cancer and Environment

**Introduction:** The UP Environment and Space of the Unit has been at the forefront of high-quality research investigating the links between air pollution and breast cancer. The main research focus of the UP Environment and Space of Unit U1296 has been the investigation of the links between air pollution and breast cancer. Although many links between air pollution and breast cancer risk have been identified in the literature, several uncertainties still remain. Two major limitations stand out: (1) the lack of precision in exposure assessment, and (2) the failure to account for multiple exposures. Most studies consider only exposures at the place of residence or at the location of diagnosis, often without access to complete residential histories due to missing information. Furthermore, associations between exposure and breast cancer risk are typically assessed pollutant by pollutant, despite the fact that in real life, individuals are continuously exposed to a wide range of chemical substances. This approach overlooks potential synergistic or antagonistic effects between pollutants. To explore these issues further, two doctoral theses were completed and defended in December 2024 (Marie Ramel Delobel and Camille Giampiccolo). In this context, two scientific articles have made notable contributions in addressing these challenges. The first, authored by Duboeuf (2024) [51], focuses on integrating workplace exposures into the assessment of breast cancer risk. The second, authored by Giampiccolo (2024) [52] introduces the use of advanced statistical methods to account for multiple simultaneous exposures in breast cancer risk analysis.

**Description of the related productions :** These two publications were based on a case-control study nested within the French E3N generation cohort (5222 incident BC cases/5222 matched controls). For each woman, the average of the mean annual exposure to eight pollutants (benzo(a)pyrene, cadmium, dioxins, polychlorinated biphenyls (PCB153), nitrogen dioxide (NO<sub>2</sub>), ozone, particulate matter and fine particles (PMs)) was estimated from cohort inclusion in 1990 to the index date. (XENAIR project), based on the significant positive associations observed between breast cancer and the risk of breast cancer and exposure to single pollutants (BaP (OR=1.09; 95% CI=(1.01-1.17)), NO<sub>2</sub> (OR=1.10; 95% CI=(1.02-1.18)), PCB153 (OR=1.14; 95% CI=(1.05-1.23)), PM<sub>10</sub> (OR=1.12; 95% CI=(1.04-1.20)), and PM<sub>2.5</sub> (OR=1.12; 95% CI=(1.04-1.22))), the team investigated innovative approaches to tackle the challenges raised when assessing the health impact of air pollutants. The methodological developments supporting this work involved the compilation of air pollution data from 1990 to the present, covering around thirty pollutants. Innovatively, the team examined long term exposure to NO<sub>2</sub> and PM not only at the residential address but also at the workplace, and developed an approach to further integrate exposure during commuting. The results further suggests that residential PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub> concentrations are strongly correlated with workplace exposures [51, 52]

To date, very few studies have assessed the combined effects of exposure to multiple air pollutants on breast cancer (BC) risk. The team examined the effect of multiple simultaneous exposures to correlated air pollutants using advanced statistical approaches (Bayesian profile regression (BPR), Bayesian kernel machine regression (BKMR), quantile G-computation (QGC)). The analyses using the BPR model indicated a positive joint effect of high-level exposures to several pollutants, including nitrogen dioxide (NO<sub>2</sub>), particulate matter (PM), and polychlorinated biphenyl 153 (PCB153), on breast cancer risk. A consistent increase in BC risk compared to the reference cluster was observed for 3 clusters: cluster 9 (OR=1.61; CrI=1.13,2.26), cluster 16 (OR=1.59; CrI=1.10,2.30) and cluster 15 (OR=1.38; CrI=1.00,1.88) characterised by high levels of NO<sub>2</sub>, PMs and PCB153 [51, 52]. The research performed has led to major advances in understanding in the association between chronic air pollution exposure and the risk of breast cancer.

**Description of the related training activities:** Our Unit Pole is fully engaged in teaching activities, particularly at Université Lyon 1, the Catholic University of Lyon, and École Centrale de Lyon, through academic modules on **cancer and the environment, epidemiology, environmental exposure sciences, geomatics, and climate change**. Béatrice Fervers coordinates the UE cancer and environment module with the Master Cancer (between 35 and 50 students annually). **Six PhD theses** have been carried out within the team: Manon Gouez (2023), Rémi Ratajac (2020), Margot Guth (2023), Olivia Pérol (2023), Marie Ramel Delobel (2024), Camille Gianpiccolo (2024), Houssein ElHajj (ongoing), Léopold Jouffroy (ongoing). Since 2019, we have also supervised around **ten interns per year**.

**Description of the “external collaborations” and the regional actions:** Since 2019, the Environment Unit has developed, sustained, and expanded a wide range of external collaborations. The Environment Unit entertains privileged links with the WHO/IARC whose seal is in Lyon collaborating on several projects and allowing visiting periods for our scientists. In the field of atmospheric exposure assessment, a strong partnership has been established with the École Centrale de Lyon, particularly with the Fluid Mechanics and Acoustics Laboratory, through the supervision of a doctoral project. The team also collaborates closely with ATMO Auvergne-Rhône-Alpes, the regional air quality monitoring agency.

On the epidemiological side, the team works in close collaboration with INSERM Unit U1018, particularly on health data from the E3N cohort. Additionally, partnerships with the LBBE (Biometry and Evolutionary Biology Laboratory) in Lyon and the Bordeaux Population Health Center have supported the development of doctoral research projects in biostatistics.

The sharing and use of knowledge involve methods and tools that transform research and experience into accessible and usable information for the public, policy actors and wider stakeholders. These activities enhance individuals', communities', and systems' abilities to adapt. and integrate health promotion and prevention into sustainable development. Ultimately, knowledge sharing is essential for fostering societal resilience to health and environmental challenges. These activities are part of The French Cancer Primary Prevention Transdisciplinary Research Network CANCEPT, led by the Environment Unit labelled and funded by INCa, aims to substantially increase our ability to transform actionable knowledge on nutritional and environmental cancer causes, and their interaction into innovative

cancer prevention grounded in transdisciplinary research, field expertise and stakeholder knowledge. To achieve its ambitious goal of overcoming current fragmentation in cancer prevention, the CANCEPT network gathers a key group of internationally renowned institutions and researchers with complementary high-level expertise in cancer prevention research.

At the regional level, we are strongly involved in the areas of pesticide and PFAS contamination.

Regarding pesticides, the SIGEXPOMETROINFO project aimed to enhance public awareness of pesticide exposure among citizens of the Lyon Metropolis through a collaborative knowledge transfer strategy. This initiative was co-developed with key stakeholders, including the Metropole, experts from CLB, CLARA, and the CANCEPT network, as well as citizen representatives. A key component of this effort is a responsible communication approach, designed and implemented in partnership with the Coam agency. This collaborative work culminated in the co-creation and rollout of the "PROTECT OURSELVES FROM PESTICIDES!" awareness campaign, launched at the end of 2024. The campaign specifically targets young people, parents, and the general public within the Lyon Metropolis, reinforcing the team's commitment to impactful knowledge dissemination and public engagement. The work performed by the team will be presented at a multinational conference "Prevention in Action: Sharing and Using Knowledge to Transform Practices", currently being organised by the team in collaboration with Département de médecine sociale et préventive de l'École de santé publique de l'Université de Montréal (ESPUM) / Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM)

To investigate the links between PFAS exposure and cancer risk, the ASTEROPA project encompasses several areas of work at the epidemiological, environmental, and societal levels. The project is structured around three main objectives aligned with these domains : 1/ To analyze the association between PFAS exposure and the risk of testicular germ cell tumors (TGCT) within the framework of the national multicenter case-control study TESTIS ([in link with LEBERCA Laboratory](#)); 2/ To examine, at a fine spatio-temporal scale, the determinants of PFAS contamination among the population of the Lyon metropolitan area, by modeling PFAS atmospheric emissions and their transfers through the environment, as well as by utilizing existing measurement databases across various environmental compartments ([in link with Ecole Centrale de Lyon](#)); 3/ To engage a group of citizens, along with public policy stakeholders, in the design, implementation, and dissemination of research projects, with the aim of steering the research toward socially relevant issues, benefiting from local knowledge, and facilitating knowledge transfer ([in link with ENTPE and Laboratoire Triangle Sciences Po Lyon](#)).

**Dissemination of knowledge:** Elements highlighting research Number of public conferences: 253 public events between 2018 and 2024 (inclusive), with 2020 and 2021 being COVID years. This includes conferences, stands, and public outreach activities both within and outside the institution :

- Media coverage: 171 articles published in mainstream media between 2018 and January 2025, covering events, research projects, and expert interviews.
- WEB PORTA : This reference website was developed to provide validated and accessible scientific information (evidence-based) to healthcare and prevention professionals, patients, caregivers, and the general public on the links between environmental, occupational, and behavioral exposures and cancer risk. The website underwent a redesign in 2022 to enhance its mobile and tablet usability, as over 80% of users access it via these devices. The navigation is now more user-friendly and engaging, and the user experience has been improved. New features include a search engine, a quiz module, and a contact form for connecting with the team. The portal recorded 1.6 million visits in 2024 and hundreds of external references. It ranks first on Google Handbooks.
- WEBINAR ON AIR POLLUTION : The Cancer Prevention Department of CLB presented the results of the XENAIR study, funded by the ARC Foundation, on Monday, October 3, 2022. This large-scale study aimed to investigate the association between breast cancer risk and chronic low-dose exposure to 8 atmospheric pollutants. 267 participants. A video replay of the conference is available on Youtube : <https://www.youtube.com/watch?v=Lvn2CmqtFMU>

### 2.1.5 UP Environment and Space : Space radiobiology

**Introduction:** The U1296 is the only radiobiology Inserm Unit that is currently and regularly supported by the National Space Agency (CNES). While the research action has been gathered under the acronym ICARE, two major actions are driven simultaneously: 1) all the space radiobiology related to ISS and deep space and 2) all the space radiobiology related to stratosphere (flights of stratospheric balloons containing human cells of interest). With regard to the first item, we have demonstrated that, unlike what literature suggest, the heaviest ions are also the rarest. Furthermore, there is a big controversy about radiation and particles frequencies of impact cells from spacecraft staff: indeed, we have demonstrated space radiation is a bath of gamma-rays of very low dose rate and a random rain of secondary particles of low energy. The low dose rated gamma-rays may reach deep tissues (like bones or heart) and increase the risk of accelerated aging while the secondary particles energy deposition is much more severe but limited in space and surface. They may concern specific tissues like lens or skins [58]. With regard to the stratospheric balloons, we have built special gondola containing different containers made of specific shielding (wood, lead, aluminium, ...). In each container, human cells (bones, skin, lens and heart) were maintained frozen during the flight. In another container, dosimetry devices were arranged and calibrated to assess dose and contribution of neutrons, ions and gamma to the dose. It must be stressed that the 3 flights performed in the stratosphere represent worldwide premieres [59].

**Description of the related productions :** Radiation impacting astronauts in their spacecraft come from a "bath" of high-energy rays (0.1-0.5 mGy per mission day) that reaches deep tissues like the heart and bones and a "stochastic rain" of low-energy particles from the shielding and impacting surface tissues like skin and lenses. However, these two components cannot be reproduced on Earth together. The MarsSimulator facility (Toulouse University, France) emits, thanks to a bag containing thorium salts, a continuous exposure of 120 mSv/y, corresponding to that prevailing in the

International Space Station (ISS). In the paper [70], by using immunofluorescence, we assessed DSB induced by 1-5 weeks exposure in ISS of human tissues evoked above, identified at risk for space exploration. All the tissues tested elicited DSBs that accumulated proportionally to the dose at a tissue-dependent rate (about 40 DSB/Gy for skin, 3 times more for lens). For the lens, bones, and radiosensitive skin cells tested, perinuclear localization of phosphorylated forms of ataxia telangiectasia mutated protein (pATM) was observed during the 1st to 3rd week of exposure. Since pATM crowns were shown to reflect accelerated aging, these findings suggest that a low dose rate of 120 mSv/y may accelerate the senescence process of the tested tissues. A mathematical model of pATM crown formation and disappearance has been proposed. Further investigations are needed to document these results in order to better evaluate the risks related to space exploration [70].

While some physico-chemical features of the stratosphere are similar to those existing at the equatorial surface of Mars, few balloon campaigns have dealt with the biological effect of stratospheric radiation on human cells. In the paper [59], we present data from a campaign of 3 stratospheric balloon flights in which human cutaneous fibroblasts, epithelial lens, osteoblasts and heart myocytes and fibroblasts were exposed frozen to stratosphere in multi-alveolar containers containing boxes made of different shielding materials. Active and passive dosimetry was ensured all along the flight. Once returned in the laboratory, cells were thawed and a 30 min-24 h repair time was applied to them. Recognition and repair of the DNA double-strand breaks (DSB) were investigated. Despite a relatively low dose, flights revealed that stratosphere radiation produce severe DSB: their severity increases with repair time according to the nature of the exposed tissues until the formation of unrepairable highly damaged cells (HDC) cell. Lens and bones cells appeared to be the most radiosensitive [59].

**Description of the related training activities:** The Unit is still not involved in courses specific to space exploration since no diploma related to this very specific item exists. However, in 2024, the Life Science Committee of CNES has organized a Master specific to the jobs related to aerospace and space: the radiobiologists of the Unit will be involved in this Master. A PhD trainee and a post-doctorant have been supported by CNES during the reference period.

**Description of the “external collaborations” and the regional actions:** The space radiobiology requires large investments and this is notably the case for organizing and designing balloons flights campaigns. However, two start-ups were essential in the space radiobiology research project: the ATTA02, prototype making company that has signed a collaboration agreement with the unit and ESIL, the company that developed new radioprotection agents.

**Dissemination of knowledge:** The communication about space exploration is a very popular subject for the whole public and the demand of the Communication service of CNES to respond to journalists is very high. Hence, in addition to the specific seminar or exhibition about space exploration, an average of 3 press releases per year and the participation of about 3 chapter books or books about space exploration and its hazardous aspects have been produced by the Unit.

## 2.1.6 UP Human social sciences (PôPS)

**Introduction:** Four very different research products have been chosen to illustrate the action of the PôPS during the period of reference : the HSS study of the INDIRA PIA project; a paper about the COVID-19 pandemic, an invited conference about AIDS and the creation of Master of sociopsychology.

### **Description of the related productions :**

Bauquier, C., Ginguéné, S., Leroy, T., Doumergue, M., Lebrun, N., Della Vecchia, C., Mabire-Yon, R., Leveaux, S., Sagaon-Teyssier, L., & Préau, M. (2024). Measuring reconceptualization and reprioritization during France's first COVID-19-related lockdown in women with and without a history of cancer: an adaptation of the SeiQol-DW and PGI. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*, 33(5), 1423-1431. <https://doi.org/10.1007/s11136-024-03626-y> [60]

This article is particularly emblematic of the work carried out by the PôPS, in terms of its theme, theoretical approach and methodologies, as well as the study itself. The RAR2C study was set up internally at the PôPS at the time of the first lockdown of the COVID-19 pandemic. The aim of the study was to take a cross-sub-disciplinary approach to the current situation and to bring together teaching researchers, doctoral students and post-doctoral fellows who had not necessarily had any joint projects up to that point. The aim was to gather urgent data on people's experiences of the pandemic by comparing groups of potentially vulnerable people (cancer patients and their carers) with the general population. The study was conducted using the Seintinelles participatory research platform. From a theoretical point of view, this study investigates quality of life and used a response shift theoretical approach. In other words, it sought to understand how individuals adapt to stressful situations in the face of the arrival of covid and lockdown. The methodological approach proposed in this article is particularly innovative. Many studies propose a cross-sectional approach to quality of life. A lot of studies propose to investigate quality of life by dimensions but without measuring the importance of each dimension for individuals. In this article, the aim was indeed to measure quality of life, but to understand how the most important dimensions had changed in the face of the pandemic, and particularly in the face of the initial lockdown. We sought to find out whether the fact of having had a history of cancer led to a greater reprioritisation of certain dimensions in the face of the pandemic or not. Finally, this article was published in a leading journal on quality of life.



*Ferraz D. Community-based research (CBR) for advancing PrEP access among key populations. 25th International AIDS Conference - AIDS 2024. July 22-26 2024, Munich, Germany*

The International AIDS Conference is the world's leading scientific meeting dedicated to the fight against HIV. Organised every two years by the IAS (International AIDS Society) - the largest independent association of HIV professionals, with over 13,000 members worldwide - it brings together thousands of participants from a wide range of backgrounds. In 2024, more than 11,000 people took part in Munich, Germany. Being invited as a featured speaker is a major mark of recognition for scientists, political leaders and activists committed to the global response to HIV/AIDS. In 2024, 26 personalities were invited to speak as featured speakers at the opening of each day of the conference, in plenary sessions with no concurrent programming. These guests included Françoise Barré-Sinoussi, winner of the Nobel Prize for Medicine in 2008, Helen Clark, Prime Minister of New Zealand from 1999 to 2008 and Administrator of the United Nations Development Programme (UNDP) from 2009 to 2017, and Winnie Byanyima, Executive Director of UNAIDS. Dr Ferraz's lecture focused on the analysis of community-based approaches in HIV prevention research. It reflects international recognition of the scientific importance of the work she is carrying out with other colleagues at UMR1296 and in collaboration with the European Commission.

**Description of the related training activities:** Creation of a new Master Psychologie Clinique, psychopathologie et psychologie de la santé, Université Lyon 2, septembre 2022 by the POPS. This new master's program, which did not exist at the Lyon site, opened in September 2022. It is the result of collaborative work with health professionals in the field and research professors in clinical psychology and social psychology, all involved in preventive issues and the management of somatic illnesses. This master's degree is co-led by the PÔPS and a research professor in clinical psychology, and the responsibilities of the first and second master's degrees are shared by another EC from the PÔPS. This new master's degree is part of a strong demand in the field in terms of training health psychologists capable of practicing in a wide variety of settings, whether institutional, associative, medical, social, but also in the field of public health research in particular. This master's degree concretizes the very strong links established by the PÔPS with the Hospices Civils de Lyon, a link currently being formalized through the establishment of an SHS department at the HCL largely driven by health psychology. This master's degree is very attractive (around 1,200 applications per year for 30 places) and has an excellent placement rate (90% within 6 months). The master's degree is linked to the EUR EID@Lyon as well as another master's program run by the UCBL: the global health program in the Public Health specialization. This involves, through shared teaching, training a pool of students on site who will be able to respond to future health crises in particular.

POPS is involved in the master's programme in social psychology as well as the master's in public health specializing in global health.

### 2.1.7 UP Valorization

**Introduction :** In the frame of the RIANS model, we have evoked above that all the aging syndromes are characterized by perinuclear over-expressed X-proteins. Interestingly, when pATM-immunofluorescence was applied to skin fibroblasts from Alzheimer's disease (AD) patients, a perinuclear ATM crown appeared. We identified the APOE protein as the X-protein specific to AD. Hence, a patent was deposited with the NEOLYS DIAGNOSTICS company to early diagnose AD in skin fibroblasts from patients [19].

**Description of the related productions :** instead of the patent document, we have deliberately chosen to describe the princeps paper pointing out the pATM crowns in AD cells. In the 1980s, cells from AD patients were reported to be sensitive to ionizing radiation. In order to examine the molecular basis of this radiosensitivity, the ATM-dependent DNA double-strand breaks (DSB) signaling and repair were investigated by applying an approach based on the radiation-induced ataxia telangiectasia-mutated (ATM) protein nucleoshuttling (RIANS) model. Early after irradiation, all ten AD fibroblast cell lines tested showed impaired DSB recognition and delayed RIANS. AD fibroblasts specifically showed spontaneous perinuclear localization of phosphorylated ATM (pATM) forms. To our knowledge, such observation has never been reported before, and by considering the role of the ATM kinase in the stress response, it may introduce a novel interpretation of accelerated aging. Our data and a mathematical approach through a brand-new model suggest that, in response to a progressive and cumulative stress, cytoplasmic ATM monomers phosphorylate the APOE protein (pAPOE) close to the nuclear membrane and aggregate around the nucleus, preventing their entry in the nucleus and thus the recognition and repair of spontaneous DSB, which contributes to the aging process. Our findings suggest that pATM and/or pAPOE may serve as biomarkers for an early reliable diagnosis of AD on any fibroblast sample [19].

**Description of the related training activities:** to the notable exception of academic courses like masters, it is too early to teach these data in neurology or gerontology courses.

**Description of the "external collaborations" and the regional actions:** in the frame of the regional LYONShapeMED call that promote multidisciplinary works, the project MAHATMA, coordinated by N. Foray (400 kEuros) with neurologists from Lyon Hospitals and mathematicians from University Lyon I was accepted in September 2024 to document, and confirm the pATM-APOE crowns as a specific biomarkers of AD. It is also noteworthy that the PROMETHEUS project, aiming to develop a model of the formation of the pATM crowns has reached the Phase 2 of the general call of ANR.

**Dissemination of the knowledge:** A short-movies describing the progressive formation of pATM crowns in AD cells is now available in open access in our web site [www.radiobiologie.fr](http://www.radiobiologie.fr). A campaign plan of dissemination of knowledge is in progress in the frame of the MAHATMA project.



### 2.1.8 UP Dissemination and Communication

**Introduction:** At the beginning of the 20<sup>th</sup> century, the Lumière Brothers have encouraged the medical doctors of Lyon to work on the medical application of the newly-discovered X-rays in December 1895. Such sponsorship consisted more particularly to provide X-rays tubes, Ruhmkorff's coil and source of energy (e.g. Radiguet's pile). We have therefore identified 5 radiation pioneers from Lyon: Etienne Destot, Victor Despeignes, Claudius Regaud, Léon Bouchacourt and Fabien Arcelin [14-17, 71]. The originality of our approach to write the biographies of each of them is that we have contacted their descendants and establish with them fruitful discussions about the perception of the member of these family with the pioneers. A number of familial document and objects have been exchanged.

**Description of the related productions :** 5 biographies about these pioneers have been published and 5 short-movies are available in our Unit website : Etienne Destot performed the first radiographies of bone fractures ; Victor Despeignes performed the first anti-cancer radiotherapy ; Claudius Regaud was the first radiobiologist to work on hypo/hyper-fractionation ; Léon Bouchacourt published the first paper about human radiosensitivity ; Fabien Arcelin was the first radiologist to describe the kidney stones by X-rays analysis. [14-17, 71]

**Description of the "external collaborations" and the regional actions:** Since these pioneers are originated from Lyon or its suburbs or its region, a number of associations promoting local and science history demanded whole public conferences that N. Foray gave in all the period of reference.

**Dissemination of the knowledge:** As said above, short-movies describing the life and the works of such pioneers are in open access in our web site [www.radiobiologie.fr](http://www.radiobiologie.fr). It is noteworthy that the book about Victor Despeignes written by Nicolas Foray was awarded by the National Academy of Sciences and the French Society for medical history [72].

### 3- ASSESSING ITS OWN RESULTS

As mentioned above, the UMR1296 Unit ("Radiations: Defense, Health and Environment") is composed of four groups that were already very structured before the creation of the Unit and whose goals of research were very well characterized by their institution of origin (Inserm, SSA, CLB and Lyon 2). Such specific composition of the Unit has therefore enriched both its production and its multidisciplinary nature. Indeed, it must be stressed that all along the reference period, the constant production of each UP was accompanied by significant efforts to produce inter-UP works, projects and articles: hence, each UP and group has brought a plus-value to the approaches adopted already.

#### 3-1 Unit's self-assessment

##### Evaluation part 1: the unit's scientific objectives, organisation and resources

**Standard 1. The unit has set relevant scientific objectives for itself and has structured itself accordingly.**

The structure of the Unit in UP has the great advantage to ensure independence for searchers with very specific backgrounds and opportunity to work and collaborate closely with staff of the other UPs. Even if the articles linking two different UPs, at least, are not more abundant than the papers produced by a single UP, they are significant and provide new items in the general field: new radioprotector agents, mechanistic model for a given radiotherapy modality; RIAN model linked to metals and pesticides; aging effect of space radiation; perceptions of radiation-induced risks for patients, medical doctor or general health staff, pATM crowns and AD disease diagnosis, ... Current inter-pole seminars (SIP) permit inter-pole exchange (organized every 2 or 3 weeks) and serve as an emulation for enhancing the multidisciplinary and transversality of the approaches of the Unit. The SIPs serve also to a first talk for young master or students in their very first presentation: the audience, composed of Unit members, may be useful for improving oral presentations and the criticism is always constructive in these conditions, particularly for the practise of English.

While the staff from all the other UPs shared experimental biology in common, the introduction of a UP devoted to Human Social Science (UP HSS or PÔPS) was an actual bet: how to complete our research in general radiobiology or genotoxicity by perception risks study? Since its creation, the PÔPS, the only research team affiliated with an Inserm unit within the University of Lyon 2, has adopted the scientific requirements and aimed to align the scientific cultures of its two supervisory bodies, in particular through the investment of its members in the academic and institutional life of the University but also of Inserm (e.g. Pr. Marie Préau, head of the POPS, is vice-president of the CSS6 Inserm). This involved building a positioning and acculturation of Inserm for all members, while taking into account the requirements linked in particular to the CNU of reference for all the POPS members. From a scientific animation perspective, the PÔPS operates through seminars bringing together the entire team one Tuesday morning per month from 9 a.m. to 12 p.m. During these seminars, a discussion on team news takes approximately one hour, and then two PÔPS members self-designate to welcome a guest speaker and organize scientific discussions or workshops related to this invitation. Young researchers, including doctoral students, postdoctoral fellows, and research engineers (including interns when they are currently enrolled), meet on the same Tuesday afternoons to exchange ideas and organize knowledge transfer workshops, both theoretical and methodological. This time of exchange between young researchers is a key moment for building a collective dynamic of support but also for preparing for larger group seminars. Indeed, each laboratory seminar is organized and led by one or more doctoral students, which increases their involvement. The deployment of international research projects, particularly in southern countries, represents a major challenge for the team, which has built strong, long-term collaborations with Africa and Brazil in particular. The hosting of a Brazilian intern from the Brazilian Ministry of Health and Fiocruz University in the fall of 2024, following the arrival of a Brazilian EC around the CPJ 2024, represents opportunities for project construction but also for preparing young PÔPS researchers for international mobility.

Finally, considering the size of the Unit and of the groups, it appears still too risky to us to propose a multi-team unit, the teams corresponding to the groups.

## Standard 2. The unit has resources adapted to its activity profile and research environment and mobilizes them.

**With regard to the financial resources:** Independently of the yearly dotation of INSERM and University Lyon 2, and as mentioned above in the Table 2 and figure 3, we demonstrated that one of the direct advantages of our structure is that each UP develops so different items of research that they are rarely concurrent on the same calls and on the same type of funding. It is also noteworthy that the Unit policy of funding was not to take any percentage from each of the funded projects to feed a common pot. Each UP budget has always been considered as independent of the others. When a common meeting was organised, it was financed either by the yearly fu of the institution of origin or with a contribution of each UP, result of a good agreement between UP leaders. It is noteworthy that the project involving an interaction between UP was financed in the same way. However, there may be some rare exception to these rules. Indeed, the PÔPS, even though it was attached to U1296, remained also financially attached to the University of Lyon 2 and therefore benefited from a specific allocation and continued to manage research contracts via the dedicated manager. Nevertheless, the PÔPS has always supported the requests of its members both in terms of contributions to scientific events and for the funding of APCs for scientific publications (to the extent of the institution's agreements, which themselves depend on more global agreements such as the Couperain agreements).

There are 3 types of financial supports during the reference period (see also self-assessment unit chapter below)

- **Research projects « Défense »:** these supports are current and constant and generally provide from the Army General Direction (Direction Générale de l'Armement (DGA)). They insure an operational research for all the objectives of National/European Defense as well as internal nonpublished expertise. However, for obvious reasons, their amount is not always made public.
- **Clinical trials:** Mainly provided by INCa, DGOS or the European consortiums, the Radiotherapy and Radiology Departments are involved in 25 and 5 clinical trials, respectively.
- **Academic research projects:** the sources of financial support have been various with the Future Investment Project INDIRA (APP Radioprotection et Sécurité Nucléaire - RSNR) whose GRad is coordinator (3 MEuros). The INDIRA project began in 2013 and will end in 2024. Another recurrent source of support is the CNES with about 50 kEuros per year since 2013. The other sources of support are EDF, plan Cancer, Cancéropôle CLARA, ARC and FRM and more recently ANSES. More recently, the PIA4 permits the structuration of the SHAPEMED@Lyon calls whom the Unit has taken already a great benefit by participating and/or coordinating 5 projects.

**With regard to the human resources and the recruitment policy:** First, it is noteworthy that, in addition to the financial constraints, some space constraints in the campus of CLB may limit the recruitment rate, whatever its level. This is particularly true for the CLB Epidemiologists group, but overall, for the INSERM radiobiologists one. At the searcher level, these two groups endeavor to present one searcher-candidate every year to the CSS INSERM commission. However, it must be noted that such candidates may have a long and complete experience in our lab whatever in radiobiology or in the environmental epidemiology. The last searcher having integrated the Unit is Audrey Bouchet (CRCN Inserm) since October 2020 i.e. just before the reference period but this was personal moving reason. With regard to the recruitment of Technician-Engineer-Administrative (ITA) staff, we have to convince INSERM general Direction first, for the creation of a new position. The last ITA position created for the Unit was that of Laurène Sonzogni (more than 8 years spent in the lab as non-permanent position) during the reference period. Again, during the same period of reference, the Engineer Assistant (AI) Adeline Granzotto was upgraded to the Study Engineer (IE) position. Hence, considering the current difficulties to recruit and upgrade ITA/Searcher staff positions and the size of our Unit, our Unit is in the good standard ratio. However, it is noteworthy that there is still no administrative staff in the INSERM radiobiologists group and it is the two ITA INSERM staff (IE Adeline Granzotto; AI Laurène Sonzogni) who have in charge most of the administrative tasks in addition to their experimental work. Finally, with regard to the recruitment of student, PhD doctorants and post-doctorants, we receive monthly very numerous applications for the different positions, which demonstrate the attractivity of our Unit. Considering again the financial and space constraints, we prefer to recruit master students to, thereafter, pursue in PhD. Hence, the selection rate of the students in Master is of high rate: we try to have already one paper submitted at the end of the master to facilitate the works in PhD.

In the UP Defense, the recruitment policy of ministry of defense, it is extremely limited for security reasons, especially for scientists out from European union. Nevertheless, Master 2 students can join the unit as well as PhD students who get a military status during their thesis.

From the perspective of welcoming new staff, the PÔPS, which has had dedicated premises since January 2022 on the PDA campus, has set up, via the study engineers, a welcome booklet containing administrative information. In addition, each year, a back-to-school meeting organized by the management aimed to provide all the information on the functioning of the PÔPS and U1296 from a scientific, institutional and operational point of view. All PÔPS theses are funded through thesis grants from national research organizations or CDUs via the ED EPIC (at least one grant/year, competitive) or by CIFRE theses (Michelin, Association Danaecere) and more recently via the EUR EID@Lyon. Two joint supervisions are underway with the University of Sousse in Tunisia and the Joao Institute in the Amazon.

All non-tenured researchers have always been considered young researchers without distinguishing them from doctoral students and post-doctoral fellows. The latter have therefore always been able to contribute to all scientific activities: training, scientific activities, conferences (communications). The PÔPS is very attentive to supporting young researchers (doctoral students and post-doctoral fellows) towards academic careers, whether it is MCF recruitment for example at the University of Lausanne or Lyon 2 University but also to preparation for the Inserm competition (a candidate is

currently being prepared for 2025). The recruitment policy has always been open both to the interdisciplinary scientific position in health but also to the international (CPJ) and an epistemology open to participatory approaches in particular. A large part of the PÔPS doctoral students come from the Master of Social Psychology at Lyon 2 University but also from external recruitment from different training courses. For some, it was after a period of work as a research engineer that the commitment to a thesis was built, which made it possible to co-construct thesis projects consistent with the scientific and methodological anchors of the PÔPS.

### **Standard 3. The unit has premises, equipment and technical skills suiting and appropriate for its scientific policy and to reach its research objectives.**

**-The INSERM radiobiologists group:** the group is situated on the CLB campus until December 2024 (see Trajectory chapter). The INSERM group represents 100 m2 with offices, L1, L2 and microscopy rooms to reach its missions, molecular and cellular experiments require secured cell culture boxes (L2, PSM2), storage sites (liquid nitrogen, -80°C, -20°C, cold room), laboratory benches for biology molecular and biochemistry. In addition to the devices that belong to the group, the CLB hospital part has a number of complex and last-generation medical accelerator devices for radiotherapy like Cyberknife®, designed for stereotaxic radiosurgery, stereotactic body radiotherapy but also 3D conformal radiotherapy and intensity modulated radiotherapy (IMRT). IMRT is also operational in the CLB via tomotherapy or arctherapy devices. The Department of Radiotherapy of CLB has also an Intrabeam device for intraoperative radiotherapy and a complete facility for brachytherapy. With regard to radiodiagnosis, CLB has the most modern equipment for imaging and interventional radiology with a privileged partnership with SIEMENS company. It must be stressed here that the GRad and now the Unit has established sustainable links between radiation oncologists and radiologists but also with the technical staff of the two departments. Practically, an easy access to the radiotherapy and radiology medical facilities has been given to the GRad researchers so that they can irradiate cells in routine 3 days a week at least, before or after the patients' treatment. Hence, the GRad has been able to develop radiobiology projects with a rigorous and certified dosimetry (insured by medical physicists) in exact conditions of radiotherapy or radiodiagnosis. Besides, to date, the GRad and now the UA8 Unit insured the cells irradiation planning for both platforms engineer is needed. In order to increase the surface and the number of devices for its new projects (e.g. the devices for exposing the cells to electromagnetic waves), the INSERM group has proposed the occupation of the former service of radiology of the former military Hospital Desgenettes in Lyon (see Trajectory chapter). Finally, it must also be stressed that a number of projects required some specific irradiators that are not in the CLB or IRBA campus; Such specific experiments are current and a special collaboration agreement is generally signed before any experiments.

**- The IRBA staff group:** The Army Hospital Desgenettes and the IRBA sites also offer specific radiation facilities in open access for the Unit staff. Particularly, the IRBA/DEBR has non-ionizing radiation facilities that permit to cover all the research about the biological effects of electromagnetic waves as well as ionizing radiation exposure devices (X generator and cobalt source).

**The CLB epidemiologists group :** like the psychologists (see below) the epidemiologists requires only computers and WiFi access. An entire step of the building is reserved for them on the CLB campus and new buildings are foreseen to extend their activities.

**The LYON 2 psychologists Group:** its research action requires only computers and WiFi access. The PÔPS has a full-time manager to oversee all research projects and team activities. All members meet in the dedicated PÔPS offices on the institution's PDA campus. It is also within this framework that collaborations with citizens involved in research projects are developed, with numerous group sessions allowing for acculturation, the sharing of values, and co-construction

### **Standard 4. The unit's practices comply with the rules and directives laid down by its supervisory bodies in terms of human resources management, safety, the environment and the protection of data and scientific assets.**

The Unit was one of the first Unit of Inserm that promotes the new managerial values defined by Inserm during the reference period. We wish to promote in the Unit the 6 core values cited by INSERM as well as 2 specific additional values, to better illustrate our sense of belonging to a research laboratory that develops projects of high societal interest and the state of mind in which we wish to work. These values and their definition constitute the preamble to the internal rules chart of the Unit that was accepted at our first general assembly at the beginning of 2019. It is noteworthy that Nicolas Foray was member of the special INSERM committee (2<sup>nd</sup> High-potential INSERM staff committee - promotion 2014-2015) for writing and defining these values.

**Ethics** establish the criteria for responsible behavior in the respect of oneself and others. It is a matrix value, the purpose of which is to make people aware of the societal implication of all their actions at the individual and collective level.

**Social responsibility** consists of conducting quality research respecting all collaborators, partners and research participants, while ensuring the primacy of the general interest over private and personal interests. It also involves reporting on its activities transparently vis-à-vis private companies.

**Collective commitment** promotes well-being at work, encouraging team spirit, cooperation, exchange of know-how and mutual support among staff that are essential to the development of excellence within the Unit.

**Creativity and Innovation**, concern all our activities. While it is possible to be creative alone, innovation is the result of teamwork. Creativity and innovation are key factors in the sustainability and dynamism of our Unit. They must be based on coherence between the projects and the overall strategy of the Unit.

**Equity:** Fairness means taking into account in a fair way individual needs and working environments, so that equal opportunities and treatment in employment, working conditions, evaluation and career development is assured for everyone. Equity is a necessary condition for the well-being and motivation of all.

**Integrity** implies that everyone in the Unit behaves in a fair and honest manner and makes sure not to expose oneself to links of interests that could unduly influence him in the performance of his duties. It is not limited to scientific integrity.

**Respect for differences:** Our Unit brings together many research actors whose status, training, experience, methods and functions can be very different. We are committed to respecting these differences in dialogue and emulation.

**Eco-responsibility:** Throughout our research, we are committed to respecting the environment by protecting it from pollution and waste.

**Parity in the Unit:** As part of its letter n°8, the Scientific Council of INSERM is "aware that the inequality of female and male careers is a vast social problem, which is also present in the INSERM. He notes that inequalities are as much in the career development of women as in the composition of all bodies (commissions, juries, etc.) that decide. It is indeed observed that the inequalities are not corrected spontaneously. Making the behavior and procedures move, raising awareness of the problem to decision-makers is essential and is a first step towards correcting these inequalities ". Parity is one of INSERM's values. A first estimate in the workforce of the Unit showed 25 women for 17 men among 42 permanent members (i.e. about 60% of women). Note that in the INSERM radiobiologists group, the number of female staff represents more than 60% of the workforce. Thus, the direction of the Unit commits:

- to ensure the gender balance in the recruitment of new staff members of the Unit
- to compose standing committees and Ad Hoc committees so that strict parity is guaranteed
- to appoint the technical and scientific managers of each division, respecting strict parity.

**Scientific integrity:** According to the "Corvol's report" presented to the Minister of Research in 2016: "Scientific integrity is the integrity and honest conduct that must govern all research. Consubstantial with all research activity, it is on it that knowledge is based. Scientific integrity is not a question of morality but it is based on universal moral principles according to which it is bad to "lie, steal ...". The quality and reliability of scientific production depend on it. It is on her that the society of knowledge is founded in order, in a word, to "believe in science". As much as ethical issues are debated, so much scientific integrity is not discussed. It is self-respecting, it is a code of professional conduct that should not be broken. It is essential in science, as are the professional codes of ethics for doctors and lawyers. " Due to the specificities of the Unit (safety rules set by both the defense and protection aspects of industrial property and the importance of scientific and public health issues), scientific integrity will be controlled directly and indirectly:

- For each pole, the person in charge of each project, as a supervisor, will be responsible for the control of the possible falsifications and plagiarism of his students and subordinates
- Fair and very clear rules of the authors will be fixed before any publication project
- No publication can be submitted within the framework of the Unit without its principles and results being presented at a scientific laboratory meeting.
- The Quality Control Committee may at any time verify the good performance of the experimental data
- Special arrangements will be made for confidential defense data.
- For any dispute, it is the Direction Board and finally the Director who will decide of any action.

**Safety and protection of staff and data :** As with scientific integrity, the structural specificities of the Unit impose several strict rules that are both relevant to good practice and regulatory. Through training for new entrants (in the form of interviews, presentations and forms to be read and approved) and by specific rules of procedure, the Hygiene, Safety and Defense Committee will raise awareness of the protection and safety of people, equipment, data, knowledge and know-how to meet the requirements of defense, industrial property (good IT practices and quality assurance) and manipulations of data related to medical confidentiality (patient's file, CNIL, ethics, etc ...). Due to the sensitivity of certain subjects (defense, nuclear, waves, environment, genetics), the governance will organize dedicated expert seminars for all members or at least project leaders and scientific and technical responsables. In particular, each year, the Unit will solicit qualified personalities (military, DGSI, INSERM defense official, business leaders) to ensure lectures with a high level of professionalism in terms of protection and security in the unit.



**Internal and Hygiene and Safety (H&S) rules:** Since the Unit is based on two major sites (IRBA site in Brétigny-sur-Orge, CLB campus in Lyon) and by considering the fact that INSERM researchers, CLB clinicians and IRBA military physicians should obey and respect both their institutional H&S rules and the H&S rules of the sites in which they work, the Internal rules document should collect all the H&S rules in question. In addition, in the CLB campus, since some experiments will be performed with the IRBA staff, we have proposed to create a protected area with restricted access. Since the space available for the Unit are still not defined, such project is in discussion yet. At the Brétigny-sur-Orge IRBA site, the internal rules are those of a military restricted area with guards and video surveillance. In the CLB campus, the Internal rules are those of a standard Hospital access to labs limited by a personal badge.

Inside CLB site labs, the H&S rules are those of L2 and L1 biosafety level labs with standard air conditioned and pressure requirements. There is no additional biological and chemical risk to the standards of L2 level. When cells are irradiated, exposure to radiation is performed in radiotherapy, radiology or nuclear medicine department before the beginning of the treatment of the first patient in the morning or after the last treatment in the afternoon. It means that such time schedule generally requires a worktime outside the standard 9-18h. All the experiments requiring actions early in the morning, late in the evening or during week-end is systematically performed by two members of the Unit, at least. There is no particular risk linked to the irradiation of cell since all the equipments are X-ray generators. Specific rules will be established for the Nuclear Medicine facility access in which the use of radionuclides will represent the major radiation-induced risks.

According to INSERM and CLB rules, each member of the Unit is followed by the INSERM GP with one consultation a year. Any change in the definition of the tasks are notified and there is a regular contact and discussion between the Director and the H&S Officer of the Unit and the Regional H&S Officer of INSERM.

## Evaluation part 2. The unit's scientific results, influence and attractiveness

### Standard 1. The unit is recognized for its scientific achievements, meeting quality criteria.

#### EXCELLENCE OF THE SCIENTIFIC ACHIEVEMENTS

The scientific achievements of the Unit have been developed in the Portfolio Introduction. However, we propose here a synthesis of the different achievements of the unit

**- INSERM radiobiologists group:** The INSERM radiobiologists group have developed numerous applications of the RIANs model that leads, in the reference period, to more than 35 publications. Several types of application have been done: 1) the radiobiological characterization of more than 20 genetic diseases with the determination of the X-protein specific to the diseases; 2) a particular focus on the Alzheimer's disease: the X-proteins specific to this disease and the possibility to predict Alzheimer's disease with the pATM perinuclear crown; 3) the radiobiological characterization of some human tissues (notably the lens cells) with the determination of the X-protein specific to the tissue; 4) the objective definition of the three notions radiosensitivity, radiosusceptibility, radiodegeneration, their specific biomarkers and the corresponding mechanistic models; 5) the biological interpretation of the 3 low-dose specific effects like the hypersensitivity of low doses (HRS) hormesis and adaptive response; 6) the definition of the pro-episkavia notion and the comparative study with different radioprotection agents; 7) a first paper about the calcium-dependence of the bystander effect; 8) a paper demonstrating that only the HRS-positive tumor cells may respond to the hyper-fractionated stereotactic radiotherapy; 9) a technical paper about the pattern of the  $\gamma$ H2AX foci to refine the measurement of the DSB and SSB.

Together with the previous papers about the biological interpretation of the linear-quadratic (LQ), the RIANs model is a basis of novel paradigm of the individual response to ionizing radiation based on the ATM nucleoshuttling. All these findings have been supported by the PIA INDIRA project but also by other projects more specific. For example, we have recently (sept 2024) obtained a project called MAHATMA (from the PIA4 SHAPEMED@Lyon call) to develop the pATM crowns observed in aging cells as a biomarker of Alzheimer's disease (400 Keuros with 150k Euros for the Unit).

The RIANs model has been also introduced in more specific questions, notably the use of new generation multi-spectra CT scan combined with photoactivable nanoparticles through the EU FETOpen SCANNnTREAT project (ended in July 2024). In this project, nanoparticles (NP) introduced in tumors may be photoactivable by CT Scan X-rays to trigger Auger electrons cascade and a very high local dose. Our Unit was responsible for assessing the number of DSB induced by the different types of NP, to optimize the SCANNnTREAT technology in tumor but overall while not impacting on healthy tissues. Some experiments were also done with the separated components of each NP type to ask whether a potential radio-decomposition of the components may produce toxicity. The pATMmax biomarker was also introduced in these experiments and has shown its interest to valorize and secure the clinical transfer of any radiotherapy and/or radiodiagnosis modality. To all these projects correspond a number of invited conferences at the international, national and local scale. Some Polish team has adopted our approach and confirmed the bases of our model. Finally, the world community of radiobiology has organized exchanges to edit, for the first time, a Radiobiology text book, with all the most recent knowledge in the field : our Unit was one of the most present in writing chapters of this textbook.

With regard to space radiobiology, two major achievements have been done: 1) unlike a great confusion in literature from which the heavy ions are of interest for impacting astronauts, we have shown that the impact of ions heavier than He is about 1 impact per km per century! Furthermore, a number of authors forget the effect of the shielding that change qualitatively and quantitatively the flux of particles impacting on the astronaut. Our eletter in Science Advances reveals such discrepancy. We have demonstrated that space radiation can be summarized as a “bath” of low-dose-rated gamma-rays and a random “rain” of secondary particles from the shielding. This paradigm confirms that the heavy ions component is negligible with regard to the two previous components, unlike a great majority of reports. The “bath” raises the problem of the dose-rate effect and the impact of deep tissues. The “rain” raises the problem of bystander and the impact of surface tissues. This new paradigm upsets the evaluation of risks induced by space radiation. 2) The works on the stratospheric balloons although linked, with the importance of shielding, are not directly related to this paradigm and can be pursued independently. It must be stressed here that the organization of the flights and all the associated data are considered as premiere in the field.

**- IRBA staff Group:** UP Defense, as IRBA/DEBR is internationally recognized for its excellence in radiobiology and biomedical sciences, addressing key national and global challenges such as radiation-induced pathologies, radioprotection, and the biological effects of ionizing radiation. Through collaborations with leading institutions like CEA, ASNR, and European partners, the unit enhances its impact on scientific advancements. During the reference period, it has contributed significantly to research, notably in radiation-induced muscle damage and regeneration, the identification of biomarkers for individual radiosensitivity, and the development of advanced radiotoxicology methodologies. Additionally, innovative countermeasures using the secretome of mesenchymal stromal stem cells have been developed to mitigate acute radiation syndrome. Actively competing for national and international funding, the unit has secured support from DGA and European programs such as RESILIENCE and COUNTERACT. Its excellence is further demonstrated through leadership roles in scientific societies like SFBR and ERRS and in NATO working groups, as well as editorial board memberships in Frontiers journals, and the recognition of its contributions with the ministry of defense medal for NRBC hardening, highlighting its impact on radiobiology and radioprotection in defense and security contexts.

**- CLB Epidemiologists group:** Between 2019 and 2024, the CLB Environment Unit has achieved several notable advancements in the areas mentioned above. In terms of exposure assessment, the team successfully developed simulation models capable of estimating atmospheric concentrations of various pollutants across the entire French territory over an extended time period (1990-2024). This progress was further enhanced by a methodological breakthrough enabling the reconstruction of exposure during daily mobility, moving closer to a more realistic and dynamic view of individual exposure profiles. The results highlighted two key findings: (1) exposure measured solely at the residential address often underestimates true exposure levels, and (2) depending on the pollutant, the mode of transportation contributing most to overall exposure varied significantly. Lastly, in-depth work on multiple and correlated exposures led to the publication of several scientific articles. This research demonstrated the impact of cumulative exposures on breast cancer risk and revealed clusters of elevated risk in pollution hotspots across France. Notably, the models developed consistently align with a life-course approach by enabling high-resolution spatio-temporal exposure assessment over extended periods (exceeding 20 years), thereby capturing the long-term dynamics of environmental risk. Direct access to patient records and cohorts further enabled deeper investigation into the impact of environmental exposures on patient outcomes—for example, recent analyses examining how environmental radon exposure influences lung cancer survival."

**-University LYON2 psychologists group :** PÔPS aimed to carry out research in social psychology in the field of health, drawing on the various areas of expertise in educational psychology, work psychology and the social psychology of health. During this period, 15 community based research (CBR) projects were carried out within the PÔPS team. This is a founding theme for our team. Initially developed in the field of HIV research, which very early on included people affected by HIV in the research, via the French National Agency for AIDS Research (ANRS MIE) and voluntary groups such as TRT-5, CBR has become an object and a tool. So, since the first CBR projects (2009 Partages), the challenge for PÔPS has been not only to deploy the participatory and co-construction approach, but above all to think about and grasp the diversity of the issues raised by CBR. The aim was to reflect on the issues involved in carrying out this research in a variety of contexts and populations. The epistemological challenges posed by the diversity of the populations involved and the possible contexts necessarily lead to adjustments and open-minded postures that are respectful of CBR. The aim is therefore to understand the processes at work when CBR is carried out with populations that are ‘naturally’ involved or committed, versus populations where community mobilisation is absent and/or complex, for example because of communication issues (Carpentier, 2024; Baillat, 2024; Bauquier, 2017). The team aims to produce knowledge to understand and describe how the involvement of researchers in identifying needs can have an impact on the development of CBR, or to question the multidimensional or even intersectional aspect of communities and the consequences of these multiple identities for the implementation of CBR. Based on empirical data from a variety of contexts (HIV, cancer, aphasia, rural environment), the aim is to exemplify the many questions raised by the deployment of CBR rooted in social psychology by identifying the epistemological, methodological and even theoretical issues involved. It is with this in mind that a number of doctoral students have been trained and are now involved in post-doctoral projects or have been appointed as ECs, particularly those based on RCs (ANR RURAL, IRESPETAPES, ANRS TAGG PICC, ANR DRACONIS). The skills acquired in this field are recognised at national and international level, as demonstrated by the many guest lectures (M. Préau and D Ferraz) (Ferraz IAS; Préau 2024).

## **INTERNATIONAL, NATIONAL and LOCAL-SCALED PROJECTS :**

Considering the huge number of projects allocated to the Unit during the reference period, and the impressive amount of money obtained, we propose the reader to go to the table 2 analysis or to the Excel file associated to this document.

## **PRICES - AWARDS - DISTINCTIONS :**

N. Foray - Price of the National Academy of Medicine and the French Society of the Medical History (2021)

M. Bourguignon - Silver Medal of the Health Service of French Army (2023)

A. Bouchet - Price Platet-Mathieu of the Académie des Sciences, Belles-Lettres et Arts de Lyon (2023)

M. Valente - Hardening NRBC medal, bronze level (2024)

## **Standard 2. The unit's research activities produce high-quality scientific output.**

The policy of production and dissemination may be different from the groups according to their composition, and their host institution. However, some subjects may be highly-sensitive and any press release or conferences must be prepared with caution, in consultation and dialogue. It is noteworthy that, during the reference period, the dissemination of the data provided from the Unit have been done in agreement with the principle of ethics and scientific integrity.

**-The INSERM radiobiologists group:** The group's principle is to support any student to present their work orally as long as it does not hinder its publication. We will also prefer peer-reviewed publication in open access first. We also ensure that this does not hinder any patent filing. Regarding publications, a real opportunity has emerged over these last 5 years: that of being able to publish work without a time limit in open access (eg MDPI, Frontiers). Even if this corresponds to publishers who are very aggressive in terms of marketing, we judged that their review, potentially also in open access, was of high quality. Thus, most of our work was published during the reference period in Cancers, Int J Mol Sci, Cells and Biomolecules, journals which have impact factors higher than 4 on average.

**-The IRBA staff group:** The UP Defense prioritizes quality over quantity in its research dissemination strategy, targeting high-impact, internationally recognized journals such as International Journal of Radiation Biology and International Journal of Molecular Sciences. The unit's research has made significant contributions to radiobiology and biomedical sciences, reflecting its leadership in these fields. Junior researchers are actively supported in knowledge dissemination through opportunities to present at major conferences, such as ERRS and SFBR, and the IMRIS conference. The unit encourages junior researchers to present their work annually, ensuring their visibility and development. Additionally, all junior researchers are members of SFBR, which enhances their professional engagement. The unit closely monitors dissemination activities across teams and provides tailored support to less active researchers, offering writing assistance, mentoring, and workload adjustments. Annual individual reports track progress, including training, publications, and SIGAPS scores, which reflect scientific productivity and impact. Researchers not meeting the target of 1.5 publications per year are identified and offered specific support, such as literature reviews or re-engagement with research topics to enhance

**-The Université Lyon 2 psychologists group:** The group has set up discussions in order to prioritize the supports and places of scientific valorization of its work in coherence with both disciplinary and sub-disciplinary priorities and constraints (in particular for careers, whether young researchers or ECs) but also the societal issues raised by the research questions worked on. Thus, sometimes it was a question of favoring conferences or disciplinary publication support allowing to respond to the constraints of CNU in particular and sometimes to promote work and its more thematic scope via thematic conferences (AFRAVIH, AIDS IMPACT). From the point of view of publication media, the group has been very attentive to monitoring developments relating to scientific valorization, via monitoring the value of indicators (impact factor, citation indices), consistency with institutional policies (if any) (Couperain Agreement). Numerous discussions, particularly related to the fact that 4 PÔPS doctoral students have been or still are members of the institution's Research Commission and an EC member sits on both the CR and the Scientific Integrity Committee of the institution and is vice-president of a specialized scientific committee of Inserm (CSS6) (therefore in charge of the evaluation and recruitment of Inserm researchers), led to discussions on developments in publication media, the lists, not always fixed, of predatory journals and the need for strategies to be implemented within the Unit. To this end, the individuals responsible for these topics within the institution were invited to provide more detailed presentations, such as the Couperain agreements. The entire group also follows the institution's recommendations regarding the maximum amount of ACPs (xxxx). In addition to systematically completing HAL, PÔPS members were invited to complete a team ZOTERO file to facilitate the collection of information on the topic.

### Standard 3. The unit participates in the animation and management of its community

#### EDITORIAL ACTIVITIES

<u>N. Foray</u>	Editor-in-Chief of International Journal of Low Radiation from 2011 to 2021 Editor of European Radiation Experimentals since 2017 Editor of Biomolecules since 2020
<u>M. Bourguignon</u>	Editor-in-Chief of Radioprotection since 2020 Guest Editor Annales des Mines - Special Issue January 2025 : "Ionizing radiation : their risks and their management"
<u>D. Riccobono</u>	Editor in Frontiers in Pharmacology since 2023 Guest Editor in Médecine et armées - Special Issue May 2024 : « the NR threat »
<u>D. Praud</u>	Editor of Frontiers in Environmental Science since 2020 Editor of Frontiers in Public Health journal since 2020
<u>E. Vayre</u>	Editor-in-Chief Psychologie du travail et des organisations
<u>M. Préau</u>	Editor in Bulletin de Psychologie
<u>D. Ferraz</u>	Editor in Global Public Health

#### EXPERTISE ACTIVITIES

**- UP Fundamental Radiobiology and UP Health:** N. Foray participates currently to a number of think tanks and committees to review various types of projects and grants : NaSA, ESA, InCa, Inserm, Ligue, CNES, ANR, AVIESAN, University of Normandie, University of Edmonton (Canada). Even if it is outside from the reference period, it is important to note that N. Foray was Member of the INSERM Special expertise committee about the consequences of the Nuclear Trials in French Polynesia between 2019 and 2020 and that he provides a 2<sup>nd</sup> report about the Thesis of Dr. Christian Sueur, psychiatre, about the same subject (this last report was published in 2021). Lastly, N. Foray and M. Bourguignon were the only French Academic Searchers participating to the NATO workshop about the Regional strategy for medical response as part of the disaster management case of radiation emergency caused by the war in Ukraine (Bucarest, Romania, 19-21 September 2023).

**-UP defense** The UP is involved both in ionizing radiation, biodosimetry and non-ionizing radiation expertise. D. Riccobono is the French leader for the NATO CBRN medical working group whom aim is to redact standardized texts for the management of CBRN victims in battle fields. With M. Valente, she is also involved in a NATO science and technology organization working group on radiological victim management and supports two of the discussion proposals, one on internal contamination treatment and the other on radiocombined injury management. M. Valente is also a key member of RENEb, a European biodosimetry network participating with its lab to annual inter comparison of irradiated samples. Moreover, he organized with ASNR a PIRATOME exercise in 2024 for the preparation to Olympic Games. Concerning non-ionizing radiation, F. Del Vecchio is the French leader in a NATO science and technology organization working group on biological effects of radars and a key member for a European expertise group RF-BIO on the same field of expertise.

**-UP Environment :** CLB cancer epidemiologists are member of several national expert groups and scientific committees, including the ANSES Expert Committee (CES) "Assessment of the risks related to air environments" (Delphine PRaud); the Scientific Council on Epidemiological Surveillance around Major Industrial Areas (Thomas Coudon), and the Expert Committee on the Monitoring the Incidence of Cancers Related to Occupational Activity" (Sicapro) (Béatrice Fervers), Santé Publique France; the Scientific Committee on Public Health and Environment, Fondation de France (Béatrice Fervers); and the Commission for Children Victims of Prenatal Pesticide Exposure (CIEVEPP) (Béatrice Fervers).

**UP HSS or POPS :** The POPS is involved in various research networks within which it promotes theoretical, conceptual, and methodological contributions (REFLIS Network, founding member; QOL and Cancer Platform; National Network for QOL/RPS Research in Health). POPS members contribute to expert bodies at various levels. From an international perspective, as a member of the scientific committees of the AIDS IMPACT (International Behavioral and Psychosocial Science Conference), members of the Scientific Council of the International AIDS Society, and co-chair of the SHS track within the Scientific Council of the European AIDS Society Paris 2025. Some POPS members are involved in expert bodies for research projects. A POPS member has chaired the ANRS Specialized Scientific Commission 14 - Epidemiology and Social Sciences since 2020. A member is one of the three scientists on the PIA4 Shape Med@Lyon project office. A member contributed to the drafting of the PEPR MIE (2023) and is also a member of the ANRS-MIE MVT group. From a



national perspective, a PÔPS EC has been a member of the SAB of ISSPAM (Institute of Public Health AMU, since 2022), the Scientific Council of Vetagrosup (since 2023), and the scientific council of the SHAPE MED @ Lyon project (since 2022). One of the members of the PÔPS was responsible for the scientific animation of the Health axis (2019-2023) of the MSH-LES as well as the SHS axis of the CLARA cancer center (2015-2020). Several members of the unit are members or chairpersons of call for projects juries (CSS14 ANRS Presidency since 2020; chairperson of the ANR Public Health Jury (2022) and then participatory research (2024). Members of the POPS are also members of international (FRSQ, xxxx), national (BPI, ANR, ANR RA COVID MP, ANR France Liban MP, ANR COVID RESILIENCE MP, IRESP, INCa, La Ligue, Agence de Biomédecine, Maladies Rares) and local (Cancéropole CLARA, Vinatier, Cancéropole Grand Ouest, AMIDEX (AMU), Université de Lorraine, xxxx) call for projects juries.

Call for proposals juries to be entered here: INCa, La Ligue, INCa thesis grant, FRM, Vaincre la Muco, canceropoles, Univ Nantes, Univ Lorraine, AMU, FRSQ, AMIDEX, APPI, BDS-UL2, MSH, IRESP (2023), INCa (2021); CDU EPIC Doctoral School - University of Lyon (2015, 2016, 2017, 2018, 2019, 2023); University of Montpellier (2021)

CSS6 Inserm (MP-VP)

Want to see if we include scientific advice? (PREVENT, COMPARE, Seintinelles, HIV-cure? ...

## **CONGRESS ORGANIZATION**

**UP Fundamental Radiobiology and Health:** For more than 10 years, the UP has been the driving force behind the SIRLaF society (the French Speaking Society of Radiobiology whose N.Foray was a co-founder and the former President for 8 years). N. Foray and the UP staff and has directly organized or contributed to organizing at least 4 successive congresses of around a hundred people. The change of the SIRLAF society into the French Society of Radiation Biology (SFBR) allowed the UP staff to take a break from this organization, which represented a significant amount of work every two years. Today, we wish to change the scale with the construction of a European network of radiobiologists to promote integrative radiobiology (ANR MRSEI, CIRCLE Project).

**UP Defense:** The Defense Cluster at IRBA, actively contributes to the scientific community through the organization of and participation in major national and international events. The unit plays a leading role in conferences such as ConRad (Munich), the International Congress of Radiation Research, and the CBRNE Research and Innovation Conference, while also engaging in specialized national meetings like the French Society of Extracellular Vesicles Meeting. The unit is also integrated into several international, European, and national research networks, including projects funded by the European Defense Fund, and collaborates with institutions like the Bundeswehr Institute of Radiobiology and the French Nuclear Safety and Radiation Protection Authority (ASN). In addition, URAD fosters scientific exchange by organizing prestigious events such as the StTARS Masterclass, dedicated to radiation triage, and the international IMRIS congress, reinforcing its role in structuring the field of radiobiology, radiation protection, and medical countermeasures. These initiatives strengthen collaborations with leading experts and contribute to the strategic development of the discipline. Finally, as said above, the UP Defense organizes the International Military Radiation and Innovation Symposium (IMRIS). With seven editions held biannually, the symposium now attracts approximately one hundred participants and serves as a key platform for the dissemination of research and innovation in radiobiology. It brings together military and civilian scientists from around the world, underscoring the DEBR's commitment to fostering scientific collaboration in the fields of radiobiology, environmental toxicology, and the biological effects of electromagnetic radiation. Over the years, the symposium has become increasingly international, with past participants from institutions such as the Armed Forces Radiation Research Institute (USA), Bundeswehr Institute for Radiobiology (Germany), Roma 3 University (Italy), the Czech Military University, and the UK National Institute for Health and the Naval Medicine Institute.

**UP Environment:** Pr. Béatrice Fervers is member of the Scientific Advisory Panel of the IARC@60 international conference. Conférences EJC France-Quebec, conference national pesticides, Conférence INCa RISP,

**UP HSS or POPS :** The PÔPS was responsible for organizing the Colloquium on patient partnership with the RESHAPE laboratory in Lyon in September 2024. Several members of the PÔPS were co-organizers of a workshop in Paris on the human subject as an object of management as well as the day of the Partnership Chair "La Défense en perspectives" and one of the members was co-president of the Organizing Committee of the Congress of the International Association of French-Speaking Work Psychology (AIPTLF) in July 6-9, 2021 in Paris.

## **INVITATION OF LEADING SCIENTISTS**

**UP Fundamental Biology :** Through 3 successive EIFFEL project exchanges, we have welcomed 3 times for one month Pr. L Bodgi, former member of the Unit and Assistant Professor of the American University of Beirut (Lebanon).

In the frame of a PhD exchange, two PhD students from the Maria Sklodowska-Curie National Research Institute of Oncology (Gliwice Branch), Poland has spent 3 months each in the lab to get savoir-faire about radiobiology techniques.

**UP HSS or PÔPS:** The UP welcomed Dr/Dulce Ferraz (CPJ), a Brazilian researcher with close links to the Universities of Sao Paulo, Fiocruz and the Salvador de Bahia School of Public Health. This international involvement is linked to the themes and methods she is working on, and has led to various projects in Mali (ANRS GUNDO SO), Senegal (SidactionTAGG PICC), Colombia (ANRS COCO) and Brazil (ANRS COBRA, ANRS PISTAS), as well as the completion of a thesis funded by an Article 51 project in French Guiana, always using a participatory approach.

### **Standard 4. The unit's scientific output respects the principles of scientific integrity, ethics and open science. It complies with applicable guidelines in this field.**

**Gender dimension:** Integrating gender and equity into a scientific project helps produce more inclusive, representative, and relevant results. This fosters innovation by taking into account diverse perspectives and needs. Equity strengthens the ethical legitimacy of research by ensuring equal access to scientific opportunities. Our Unit member will respect these principles in their composition.

**Open science :** Open Science practices will be adopted to ensure transparency and collaboration. All data, methodologies, and codes will be openly shared to allow replication and peer verification. Preprints and open-access publishing make our findings widely accessible. We engage with the scientific community through open peer review and collaborative platforms. All along our projects, we will publish in our website some summaries dedicated to the general public about the advances of the project.

**The FAIR principles:** The FAIR (Findable, Accessible, Interoperable, Reusable) principles are also essential for ensuring effective and sustainable research data management in our projects. To apply these principles, our data will be made easily discoverable thanks to unique identifiers and clear metadata: our data will be sent in response to simple request, notwithstanding the preparation of a patent.

**-Inserm radiobiologists group :** Inserm is actively committed to Open Science, aiming to make research accessible and transparent. Their policy encourages the free dissemination of scientific results, fostering collaboration and innovation. They support the provision of open access data and publications to maximize the impact of research. Inserm also promotes transparency in scientific methods and processes. Finally, they encourage the scientific community to adopt these practices to accelerate advances in the field of health.

Inserm places great importance on scientific integrity, considering it an essential pillar of research. Their policy aims to promote ethical, honest, and responsible practices in all stages of scientific work. They implement training and resources to raise researchers' awareness of integrity issues. Inserm also encourages transparency and rigor in data collection, analysis, and publication. Finally, they have mechanisms in place to prevent, detect, and address any form of dishonesty or scientific fraud.

**-University Lyon 2 psychologists Group:** All PÔPS productions are posted on HAL. The DORA charter on scientific publication has been promoted and discussed within the PÔPS.

The circulars proposed by the OHRIS network dedicated to scientific integrity are systematically distributed and discussed at the PÔPS seminar (which is facilitated by the fact that Marie Préau is a member of the institution's scientific integrity committee (2022-2024)).

Discussions on co-authorship are held at the laboratory seminars, particularly as most of the publications are the result of multi-disciplinary projects that involve a variety of scientific positions and cultures. The aim of these discussions is to encourage authors to take into account the career and promotion issues facing doctoral and post-doctoral students.

Insofar as a significant number of projects are carried out using a community/participatory approach, the PÔPS has considered how to promote the authorship of the people involved in this research and the promotion of citizens (co-signature with female patient researchers (CLARA PErce neige, IMPAQT projects) or associative players (ANRS Gundo SO, ANRS Prevenir projects)).

All ethical and legal issues have always been a strong theme of POPS seminars and support for young researchers, this has been facilitated by the fact that Marie Préau is a member of Inserm's Ethical Evaluation Committee (CEEI) (since 2016). In fact, the very purpose of research projects that very frequently include health data and sensitive data has led to projects being systematically submitted both to the CEEI and, since it has been in place, to the institution's DPO. A data management plan (DMP) is systematically requested and carried out in collaboration with the person in charge of

the subject in the institution's Research Department. The PÔPS has always tried to pool the rules and resources of its parent institutions (UL2, Inserm) in order to meet these challenges, which have changed considerably over the years of its mandate. Collaboration with the dedicated services of the supervisory bodies is promoted in order to maximise resources and approaches that are not always clear or accessible from an individual point of view.

The unit has always supported researchers and young researchers in submitting research projects for national and international public research funding. The team has adapted to changes in the institution's research department, which has provided increasingly detailed support over the years. The contribution of the PÔPS's ECs has been of great help in building responses to calls for projects. The chairmanship of the CSS14 (Marie Préau), dedicated to the evaluation and funding of projects in the field of HIV, as well as the chairmanships of ANR committees (Arnaud Siméone), enable fruitful exchanges for all members and contribute to the training of young researchers. In addition, particularly in the context of participatory research projects, the PÔPS has established strong links with various research organisations and associations in Africa and South America, and over the years has sought to build on these links with projects that are consistent both from a scientific point of view and in the way they respond to societal issues. For example, the ANRS GUNDO project in Mali is based on previous international research (ANRS PARTAGES) with 5 countries and research and association structures in each country, and lead to the GUNDO SO project. The GUNDO SO project, in which a doctoral student was involved, open the way to the TAGG PICC project in Senegal, with the aim of improving the quality of life of people living with HIV.

The same applies to participatory research in cancerology, notably with the Seintinelles platform and the IMPAQT group (CLARA Perce Neige project, CLARA Ancolie, INCa Edelweiss), as well as in the field of tick-borne diseases (ANR CONVERGENT). This work requires multi-disciplinary collaborations and collaboration with the general public, and requires time to set up these collaborations, which can then be enhanced by a series of projects that meet the expectations of the teams and general public involved (Inrae Tous Chercheurs Initiative and CITIQUE Platform, ANR Convergent project).

In the same way, the PÔPS has been involved in international projects, particularly in Africa and South America, since its creation, thanks to its interest in participatory approaches. Strong links have been forged with various organisations, and these have been further strengthened by the arrival of Dulce Ferraz (CPJ), a Brazilian researcher with close links to the Universities of Sao Paulo, Fiocruz and the Salvador de Bahia School of Public Health. This international involvement is linked to the themes and methods she is working on, and has led to various projects in Mali (ANRS GUNDO SO), Senegal (SidactionTAGG PICC), Colombia (ANRS COCO) and Brazil (ANRS COBRA, ANRS PISTAS), as well as the completion of a thesis funded by an Article 51 project in French Guiana, always using a participatory approach.

As a result of Marie Préau's strong involvement in the PIA4 EXCellence SHAPE MED project and the recruitment of Dulce Ferraz to work on the psychosocial issues of One Health approaches (DF), PÔPS has been heavily involved in projects funded in this area. The PÔPS is a co-sponsor of 2 ANR SHAPE MED projects and a partner in 4 others. This has been an essential opportunity for the PÔPS to set up cross-disciplinary projects with local researchers, which may have been a weak point until now.

One of the indicators of recognition of participatory approaches is the number of guest lectures given by POPS CEs on the subject, and in particular Dulce Ferraz's invitation to the IAS international conference in 2024 (Ferraz, 2024), as well as Marie Préau's fifteen or so invitations to scientific conferences to explain the issues involved. The team has gained recognition for its expertise in these approaches (University of Salvador de Bahia, Fiocruz Brasília, University of Liège, University of Quebec in Montreal, AFPSA Conference, INCa/ABM, Réseau Nacre). The same applies to the work carried out by Emilie Vayre and Christine Morin Messabel on gender stereotypes and workers' health (DARES).

As part of its local health contract, the city of Lyon has set up a Scientific Council appointed in 2024, of which Marie Préau is a member

## Evaluation part 3. Contribution of Research Activities to Society

The actual contribution of research activities to society strongly depends on the nature of the UPs.

### Standard 1. The unit stands out by the quality of its interactions with the cultural, economic and social world.

**-UP Fundamental radiobiology and UP Health :** the INSERM radiobiologists interact with the CNES and three private companies (ESIL, NEOLYS, ATT02) and such interactions permitted to obtain one post-doctorant and one PhD co-funded by CNES and NEOLYS. Furthermore, one PhD thesis CIFRE has been financed by NEOLYS and one will be financed by ESIL from September 2025. In addition, The pharma IBSA has funded the Unit to accelerate research about aging and infertility (CASSIOPEE project). Finally, with regard to history of radiation, there are strong interaction (convention) between the association Patrimoine Médecine Santé Lyon that promotes the valorisation of the medical heritage in Lyon.

**- UP Defense :** The SSA scientists interaction with cultural economic and social world is limited but the LDBI has participated to the Forum innovation défense, 2022 and the Journée Innovation en santé de défense, 2023. For both, the aim was to promote the importance of artificial intelligence for data analysis of biomarkers after mass casualties' irradiation.

**- UP Environment :** The CLB Epidemiologists interact the International Agency for Cancer Research (IARC) allowing visiting periods for scientists of the team. Moreover, the team is involved in scientific boards of private companies (Meersens) and, institutional or territorial agencies (AtmoAuRA, Anses, ARS, Santé Publique France, Métropole de Lyon, Ville de Lyon, ADEME and CLARA)

**- UP HSS PÔPS :** The PÔPS is characterized by a research activity fundamentally rooted in civil society and its diverse representatives, including non-profit organizations (Tous chercheurs Network, International AIDS Coalition, ARCAD AIDS, Seintinelles, Solidarité Paysans, Réseau Convergence Jeune (Afrique), Des arbres et des Hommes, Voisins Malins, France Aphasie). Marie Préau sits on the Scientific Councils of non-academic organizations such as La Ligue, Seintinelles, and the Jury for the INRAE Participatory Research Award. Finally, PÔPS members are active members of the participatory research network established by the Inserm Science and Society Unit (C Bauquier, M Pannard, M Préau, D Ferraz). The PÔPS is engaged in scientific research that is fundamentally anchored in a societal perspective, so whether it concerns the themes or the collaborations built, they are thought out with this in mind and shared within the PÔPS in order to pool, for example, the training deployed during research projects. Thus, within the framework of community research, it is essential to offer training in the research approach, data collection, and data analysis. The researchers (young and senior) involved in these frameworks pool and cross-reference the skills acquired and the materials used to better adapt them to the specificities of the questions and target audiences (research training for the IMPAQT group of patient researchers reused in the training of citizen researchers of Solidarité Paysans in the ANR RURAL project and again used for the training of smart neighbors in the INCa DEPISTMALIN project. The PÔPS aims to establish CIFRE funding that aligns with its research practices with non-academic partners, whether companies like Michelin or non-profit organizations (Danaecare), or through research collaborations with field actors such as the Conservatoire National de la Danse. Various members of the PÔPS sit on the boards of directors of various international organizations: AFRAVIH (Francophone Alliance of Health Professionals Against HIV and Chronic Viral Infections)(Marie Préau), AIPTLF (French-Speaking International Association of Work Psychology) (Emilie Vayre), and ENOP (European Network of Organizational Psychologists). They also serve on the boards of national organizations: AFPSA (Francophone Association of Health Psychology), R<sup>2</sup>QVT en santé (Quality of Life at Work Network), AFPTO (French Association of Work and Organizational Psychology), and local organizations: ONCO AURA (Auvergne Rhône-Alpes Regional Cancer Program). Furthermore, Emilie Vayre is a member of the French Committee for the Delivery of EuroPsy Certification (CoFraDec EuroPsy) and of the Commission responsible for evaluating the level of foreign diplomas in psychology (for access to the title of psychologist in France) at the Ministry of Research.

### Standard 2. The unit develops products and services for the cultural, economic and social world.

With regard to the economic valorization, the Unit is at the origin of the creation 2 start-up companies (NEOLYS for the predictive assays and ESIL for the new agents of radioprotection), 1 Soleau envelope, 2 databases deposited and 9 licensed patents (7 for the predictive assays, 1 for the diagnostics of AD and 1 for the new agent of radioprotection; It is more than probable that this list will be extended to the data about electrosensitivity in the next months.

It is noteworthy that the unit gathers different collections of human cells and notably the collection COPERNIC that ranges one of the largest spectra of radiosensitivity. All these collections are registered in the Ministry of Research, in agreement with National regulations. The COPERNIC collection is the result of service, only addressed to any radiation oncologist that would like to prevent any secondary effects of their patient after RT by providing us skin biopsy. A report of radiosensitivity diagnosis implying the RIANS markers is sent to the demanding practitioner.

In addition to the technological savoir and savoir-faire of the Unit, the Unit possesses two aneuchoid chambers to expose cells to electromagnetic waves to investigate electrosensitivity in the next months.



In terms of social and cultural actions, the unit develops currently some short-movies in open access on its websites about the mechanistic models but also on the works about history of radiation research.

Finally, we should not forget that the Unit is closely associated to SSA that represents a unique tool of National Defense and Sovereignty.

### **Standard 3. The team shares its knowledge with the rest of society and contributes to societal debates.**

All the subjects of research treated by each UP can be easily related to subjects of societal debates:

- Works with the rare genetic diseases (UP Fundamental radiobiology and UP Health)
- Works related to the prediction of aging diseases via pATM crowns (UP Fundamental radiobiology and UP Health)
- Works about the risks related to atomic bombs or nuclear power plant accident (UP Defense)
- Works related to the prediction of secondary effects of post-radiotherapy radiosensitivity reactions (UP Health)
- Works related to the potential risks of radiation-induced cancer after low-dose diagnosis exams (UP Health)
- Works related to the risks of cancer linked to air pollution, pesticides, UV,... (UP Environment and Space)
- Works related to the risks of cancer/aging after exposure to electromagnetic waves (UPs Environment and Defense)
- By definition, all the works of the UP HSS (POPS)

Obviously, some subjects may be more sensitive than the others and can be addressed to different categories of the whole population in respect of integrity and ethics. The leaders of each UP have a good experience in exchanging with media.

**UP Fundamental Radiobiology and UP Health :** For example, it is noteworthy that Nicolas FORAY was named corresponding searcher with media for the Fukushima accident by the General Director of Inserm and, the dean of the Unit, Pr. Michel Bourguignon was a former Commissioner of the ASN. Furthermore, the INSERM, Lyon 2, CLB and even CNES communication cells are very operational and good advisers for writing press releases with searches. During the period of reference, a number of press releases have been produced by the Unit and no negative comments was produced. Considering the expertise of the staff Unit, the Unit has been solicited by theconversation.com to write a series of two papers about the potential nuclear risk linked to the russia-ukraine conflict. These two papers were the most cited of the website for 3 months. A translation In Spanish has been done for these articles.

Always in respect of integrity or ethics, a number of public debates have been organized by or have concerned the Unit staff during the reference period. In the close future, in collaboration with the Université des Métiers du Nucléaire (Nuclear jobs University), a series of debates involving the Unit staff in some Lycees interested in Nuclear Jobs.

**UP HSS PÔPS:** As a result of their research themes and collaborative methodologies with stakeholders in the field, PÔPS members are called upon to give presentations or introductory talks to the general public or more specific groups. More than 30 conferences have been given on the areas of expertise of PÔPS members: gender issues in education and training (ANACT, Institut des hautes études de l'éducation et de la formation - IH2EF), etc. Christine Morin Messabel has a dense training activity for various audiences, including senior civil servants, on issues of gender stereotypes (Direction Interrégionale des Services Pénitentiaires, Ministère de l'Éducation, Rectorat Lyon, Marseille). Emilie Vayre was also interviewed by the Haut Conseil à l'Égalité entre les femmes et les hommes in September 2022 (report 'Pour une mise en œuvre du télétravail soucieuse de l'égalité entre les femmes et les hommes' published in February 2023) and by the Délégation aux entreprises du Sénat in February 2021 (report 'Évolution des modes de travail, défis managériaux : comment accompagner entreprises et travailleurs ?' published in July 2021) ; The skills acquired in community based research have also been the subject of more than 20 presentations in a variety of contexts (public conferences organised by the City of Lyon and Le Vinatier), as well as for audiences of healthcare professionals led by Marie Préau, Dulce Ferraz, Myriam Pannard and Charlotte Bauquier. Christine Morin Messabel took part in a study for the CSEN (Conseil Scientifique Éducation Nationale) for the CSEN (Conseil Scientifique Éducation Nationale). This study was presented in the report 'Making equality between girls and boys a new stage in the implementation of the lycée of the 21st century', published in 2021. Some members of the PÔPS are involved in popularisation activities, notably via the media outlet 'TheConversation.com' (Préau, 2019 and Préau, 2021) on a variety of topics (HIV care and tick-borne disease prevention).

### 3-2 Synthetic self-assessment

In the previous HCERES self-assessment report for the creation of the U1296 Unit, we mentioned 15 missions specifically regarding the achievement in terms of ionizing and non-ionizing radiation research. As a first step of synthetic self-assessment, we analysed the achievement rate of each of the 15 items:

1. To better understand the bases of the molecular, cellular and tissue responses to genotoxic stress in general and ionizing/non-ionizing radiation in particular, by developing mechanistic models of DNA damage repair and signalling that must be realistic and relevant for human cells and exposures to stress. This basic approach concerns both mechanisms of resistance and sensitivity to stress. Although this first item is very general, we can state that, the development of the RIANs model and this applications draws a new emerging paradigm of the individual response to ionizing radiation (for the non-ionizing radiation see item 10)) The success of the RIANs model, the elucidations of a number of enigma of radiobiology, its validity for a number of diseases and its definition of radiosensitivity, radiosusceptibility and radiodegeneration suggests a very large spectrum of validity. As proof of concept, considering the number of reports published already, but since the work of the acute irradiation syndrome is still not complete, one can reasonable attribute to this item an achievement rate of 75%.
2. To respond to specific National Defense needs in an efficient and secure approach, notably by a better understanding of the acute irradiation syndrome and investigating the new radiation protection approach. The investigations of the acute irradiation syndrome with the RIANs paradigm are still in progress: a number of key-results have been obtained but the interaction between ATM and cytokines are still to elucidated. With regard to the new protection approach, the major features of pro-episkevia have been already published. One can reasonably attribute to this item an achievement rate of 60%.
3. To better define and quantify radiosensitivity and/or radiosusceptibility and/or radiodegeneration through dedicated human cells collection and predictive assays with the highest possible statistical robustness for realistic exposures to radiation, whether at high or low doses. For these three essential notions, several reviews and articles have been published already to define them and to propose specific biomarkers. To date, these are the major theoretical concept generated from the RIANs model. We need now to extend the predictive assays to several types of cells and irradiation scenario. One can reasonably attribute to this item an achievement rate of 75%.
4. To meet the needs of radiotherapists and medical physicists to help them choose innovative radiotherapy modalities by quantifying the radiation-induced benefit/risk for tumour and healthy tissues. Through the paper of Le Reun et al., we have provided a first molecular interpretation of the hypofractionated stereotactic radiotherapy modality, suggesting that only the HRS-positive tumors may be of interest. Some experiments are in progress the same question but about the FLASHtherapy. Again, the RIANs model is the basis of concept to investigate the different interplays between the different molecular and clinical parameters. Since the proof of concept is here but because there is still a number of different modalities in radiotherapy that require a radiobiological characterization, notably via the elucidation of the impact of dose-rate and the bystander effect in each modality. One can reasonably attribute to this item an achievement rate of 75%.
5. To meet the needs of radiologists and nuclear medicine physicians concerned by low doses by quantifying radiation-induced risk reliably and in realistic conditions for patients and workers. Thanks to the RIANs model, the 3 major low-dose specific radiobiological phenomena like HRS, hormesis and adaptive response are resolved. As written above, the bystander effect, generally considered as a low-dose specific phenomenon remains to be resolved. Through a first paper that link Ca<sup>2+</sup>-ions-release to bystander effect, we have already the bases to pursue the research about the molecular features of the bystander effect. One can reasonably attribute to this item an achievement rate of 75%.
6. To propose an original and realistic model for space radiobiology by estimating risks reliably. From our works and through different reviews, we have demonstrated that space radiation can be summarized as a "bath" of low-dose-rated gamma-rays and a random "rain" of secondary particles from the shielding. This paradigm confirms that the heavy ions component is negligible with regard to the two previous components, unlike a great majority of reports. The "bath" raises the problem of the dose-rate effect and the impact of deep tissues. The "rain" raises the problem of bystander and the impact of surface tissues. This new paradigm upsets the evaluation of risks induced by space radiation. The works on the stratospheric balloons although linked, with the importance of shielding, are not directly related to this paradigm and can be pursued independently. Therefore, one can reasonably attribute to this item an achievement rate of 90%.
7. To better prevent the consequences of exposure to radiation, by chemical or pharmaceutical means of radiological protection and/or mitigation based on relevant biological bases. As said above, the concept of pro-episkevia was introduced by a first pape. From this paper, it appears that the mitigation, unlike the radioprotection, will be a notion difficult to reach because of the probable irreversibility of some molecular and cellular events. Hence, this item rejoins the half of the item 2 related to pro-episkevia: new radioprotection drugs have to be developed with the help of the ESIL company. Therefore, one can reasonably attribute to this item an achievement rate of 90%.

8. To better quantify the genotoxic/carcinogenic risk linked to the exposure of chemical or physical agents that break DNA directly or indirectly, notably like agents of environmental interest, especially in the case of multi-stress (eg metals, pesticides, endocrine disruptors, ...). On one hand, the item 3 was reached by the development of RIANs biomarkers specific to radiosensitivity and/or radiosusceptibility and/or radiodegeneration. On another hand, our papers on pesticides and metals have showed that the nucleoshuttling of the ATM protein can be disturbed by simple molecules that we can call "X-molecules". Such model gives rise to a more general one: SIANS for stress-induced ATM nucleoshuttling model that is therefore one of the most important applications of the RIANs one. For the next future, we should document the list of the X-molecules. One can reasonably attribute to this item an achievement rate of 90%.
9. To encourage transversal and multidisciplinary approach linking molecular biology, epidemiological studies and SHH approach to better consider the risk, notably in terms of environment. During the period of reference, we made the project to perform a transversal study (the BACCHUS project) about the use of pesticides by winegrowers combining molecular and cellular investigations, epidemiological and geographical research on high risk of cancer and an HSS study about the perception of the risks for the winegrowers. Such study would involve 3 different UP at least. Unfortunately, the COVID-19 pandemic delayed the preparation of such ambitious study. We will set up this study in the next two years. One can reasonably attribute to this item an achievement rate of 0%.
10. To propose an original model to explain the individual sensitivity to electromagnetic waves 50%. The DEMETER project, aiming to provide the first molecular definition of the human radiosensitivity has cumulated considerable, practical (COVID-19) and administrative (changes in regulation) delays since 2014 before that the collection of fibroblasts from self-assessed electrosensitive patients to be ready for experiments. In April 2024, we have submitted a paper showing that all (26/26) the electrosensitive fibroblasts belong to the group II of radiosensitivity. A first model based on spontaneous, X-rays-induced and H202-induced data has been proposed. One can reasonably attribute to this item an achievement rate of 75%.
11. To better understand the social representations of radiation risk through the study of the thoughts, beliefs, behaviours and attitudes of the public concerned and to propose recommendations both for the content and the form of the information delivered by the practitioners to the patients. Thank to the thesis of Manon Britel, some milestones have been already reached: HSS studies about patients treated in radiotherapy, and radiation oncologists have been published; the HSS study attached to the INDIRA project and corresponding to both apparently healthy individuals and medical staff will be summarized in a paper in preparation. However, we should go on associate the HSS and radiobiology. A detailed plan of work will be built to this aim in the next months. One can reasonably attribute to this item an achievement rate of 65%.
12. To participate in the development of a new radiation protection regulations that would take into account individual risk, dose repetition, radiation energy: This item is most ambitious of the 15 items proposed. It should be the result of one 5-year mandate work. The publications related to the individual radiosensitivity are originated from data subset and so large documentation that quantitative features can be already pointed out in novel recommendations. However, the dose repetition and the radiation energy do not represent data subset sufficiently documented to be solid bases of new definitions of weighting factors (for energy or for tissue) or correcting factor (for dose repetition). Works are still in progress. One can reasonably attribute to this item an achievement rate of 33%.
13. To valorise laboratory achievements with patents, registered databases or to fund start-up companies: With two start-ups, 9 licensed patent, 1 Soleau envelop and 1 database, we are convinced that our data have been valorized at a maximal rate. This was made possible thank to our privileged interactions with valorization institution like INSERM-transfert and our committee of valorization composed of very good experts in this field. One can reasonably attribute to this item an achievement rate of 100%.
14. To disseminate knowledge on radiobiology and the balance between benefits and risks notably through a "Radiation School". Because of the COVID-19 pandemic and the recent move of the INSERM radiobiologists from the CLB campus, this project has been delayed. A recent agreement with the University of the Jobs of Nuclear Industry (Université des Métiers du Nucléaire) will permit to schedule some courses and conferences to share, with the general public, the different features of radiobiology. One can reasonably attribute to this item an achievement rate of 33%.
15. To encourage interactions between the Unit and foreign laboratories at the European and international scale. The previous chapters have shown that the Unit interact with a number of European and International labs. Such efforts will be pursued. This is notably the case with our web of Radiobiology Labs to promote integrative radiobiology (ANR call, MRSEI, CIRCLE Project). It is noteworthy that a similar approach has been initiated by D. Riccobono for the Military Radiobiology labs (see xxx). One can reasonably attribute to this item an achievement rate of 100%.

The average achievement rate for these 15 items is 69% on the reference period (4 among 6 years) which fits to the 4/6 value (=66%).

The SWOFT analysis was summarized in Figure 6.

	POSITIVE FEATURES	NEGATIVE FEATURES
INTERNAL STRUCTURE	<b>STRENGTHS</b> <ul style="list-style-type: none"> <li>- The RIANS model has provided a lot of applications</li> <li>- Each group is high-level expert of its field</li> <li>- Each group has obtained important financial supports</li> <li>- The number of publications is high.</li> </ul>	<b>WEAKNESSES</b> <ul style="list-style-type: none"> <li>- Some European projects were obtained by the Unit but their number is still poor. Is it due to the field?</li> <li>- The recruitment of young researchers is poor. Is it due to the field?</li> </ul>
EXTERNAL ENVIRONMENT	<b>OPPORTUNITIES</b> <ul style="list-style-type: none"> <li>- Some radiobiological labs that develop unique savoir-faire may join the Unit</li> <li>- The Unit may be installed in the former Radiology Service of the Military Hospital of Lyon</li> </ul>	<b>THREATS</b> <ul style="list-style-type: none"> <li>- The positions for radiation research are not renewed</li> <li>- Left from the CLB, the INSERM group is still not fixed</li> </ul>

Figure 6 : SWOT analysis of the UMR 1296 Unit



## 4- UNIT TRAJECTORY

### A geopolitical context highly favorable to a re-funding of UMR1296

Since the creation of UMR1296, the geopolitical context has deteriorated further, particularly with the Russo-Ukrainian conflict, which has revealed more than ever the lack of operational resources to respond to a total war. Among the challenges, nuclear and radiological (NR) risk once again emerges among the national defense priorities. In fact, understanding individual responses to genotoxic and/or carcinogenic stress is essential for the development of countermeasures. In this sense, biomathematical modeling and the future use of artificial intelligence (AI) would accelerate these processes and constitute a real added value for the Unit and a major innovation for radiobiology. The very close collaborations established between the Unit and the Camille Jordan Institute (University LYON 1) during the reference period (2021-2024) and even earlier, also point in this direction (see below). A particular aspect of the current geopolitical context is the strengthening of space studies with the creation of the French Air and Space Force, which gives even greater meaning to the Unit's specific research activities.

### A Necessary Refocus on Ionizing Radiation Biology

Major changes will occur to the structure of UMR1296 for the next term :

- For reasons of site policy, the INSERM group (UP Fundamental Radiobiology and UP Health) is leaving the CLB campus, and the CLB group (UP Environment) is joining the U1052 Unit, which then becomes the only unit on the CLB campus.
- The LYON 2 group (POPS) is joining taskforces with epidemiologists and occupational physicians from the Hospices Civils de Lyon to form a new unit, which will be headed by Professor Marie Préau.
- The IRBA wishes to be represented in the Unit project with a larger staff to better represent the various research issues in radiopathology and NR risk (in progress).
- The CEA's Radiotoxicology Laboratory, a unique laboratory in France with expertise in radioactive contamination, would be integrated into the Unit to cover all research on non-medical internal radiation (currently underway).
- In the medium term, it is possible to envisage one or more laboratories from the new Nuclear Safety and Radiation Protection Authority (ASNR) being integrated into the Unit so that it could become a sort of wall-free Institute of Radiobiology, bringing together all the different sub-themes of general radiobiology, particularly those concerned with mass crises.
- In terms of dissemination, the Unit will be partnered with the Nuclear Professions University, which is very active in the AURA region and created by the nuclear industry to promote the training necessary to provide the country with comprehensive knowledge and expertise on the construction of nuclear reactors, including the associated risks.
- In terms of commercial development, a new startup, ESIL, specializing in the development of next-generation radiation protection drugs, will support research in space radiobiology, notably through the funding of CIFRE theses. In addition, the firm THERYQ, specializing in the construction of FLASH therapy irradiators, supported by France 2030, will also assist us in research on new modalities of modern radiotherapy.
- CNES will provide us with regular support (since 2014) for both experiments on stratospheric balloons (new base in Brazil) and on the International Space Station.
- Finally, Professor Laurent Pujo-Menjouet, a mathematician at the Camille Jordan Institute (Lyon I), who has been heavily involved in our group for several years (around ten publications, co-leadership of a cancer plan project "MICROMEGAS" (€280,000) in 2013, and a ShapeMED@Lyon project "MAHATMA" (€400,000) in 2024, is proposing to form a new group within the Unit, the biomathematics group. It is also worth noting the co-supervision of several Master's and PhD students, as well as the acceptance in phase 2 of the PROMOTHEUS project in the 2025 ANR general call for proposals. In this context, it therefore seemed natural to approach the University of Lyon I to become a Unit's supervisor

## Encouraging Preliminary Results

During the reporting period (2021-2024), the Unit's activities produced encouraging preliminary results that demonstrate the soundness of the Unit's scientific foundations:

- As part of the DEMETER (ANSES) project, a publication was submitted on the mechanistic understanding of the phenomenon of electrosensitivity (sensitivity to electromagnetic waves) using the RIAN model. This is a first in this particular research sector.
- As part of the Defense Cluster, a systematic study of the interactions between ATM and cytokines in response to very high doses of radiation should lead to a first molecular interpretation of acute radiation syndrome (ARS), which would constitute a significant scientific event in this field.

In addition to its action on ARS, a new-generation radiation protection agent developed by the startup ESIL could mitigate the molecular effects of aging on cells irradiated under space conditions and on diseases associated with neurodegeneration such as Alzheimer's disease. The formation of perinuclear ATM-APOE coronas, specifically observed as a basis for early diagnosis, is the subject of the MAHATMA project, obtained as part of the ShapeMED@Lyon structuring projects (co-leaders: N. Foray (INSERM) and L. Pujo-Menjouet (Camille Jordan Institute - Lyon I). The RIAN model also appears valid for genotoxic chemical agents such as metals or pesticides (20,21), which provides the basis for a generalized mechanistic model for all DNA-damaging stresses, both separately and in combination (exposome), making it possible to address the cumulative risk of associated low doses, which can undoubtedly no longer be considered negligible, since their effects are additive.

## What can the UMR bring to Lyon 1 University?

Hence, future and extended UMR 1296 would be composed of government institutions (INSERM, SSA, CEA, ASNR) whose role in the event of an international conflict is essential. The Unit will thus place Lyon 1 University at the heart of a preventive defense approach by bringing together the knowledge and expertise of institutions with which few universities in the region are partners. Thus, combining Lyon I and its expertise in biomathematics with the SSA, the CEA, Inserm, and perhaps in the short to medium term, a radiobiology component of the ASNR would constitute a unique hub in France and a significant added value for the University of Lyon I. In the most nuclear-armed region of France, where major defense structures exist, the region's leading university would thus demonstrate its role in knowledge, understanding, and anticipation of the greatest perils of our time.

In addition to its national scope and its active presence in times of crisis, the UMR will be able to bring to Lyon I a coherent and comprehensive body of knowledge in radiobiology, a scientific discipline truly born thanks to the Lumière Brothers. This body of knowledge will be able to be advantageously linked to Lyon's already rich medical platform in radiotherapy and radiodiagnostics (CLB, Hospices Civils de Lyon, CERMEP, etc.) and also be integrated into certain existing teaching programs in cancerology or preparing for careers in the nuclear industry, such as the Professional Bachelor's degree in "Radiation Protection, Dismantling and Nuclear Waste: Project Manager" (RD2) and the Master's degree in "Synthesis, Aging and Characterization of Materials for Nuclear Power and New Energies." This will provide an even better opportunity to integrate Lyon I into the promotion of nuclear careers, as advocated by the President of the Republic, particularly through the University of Nuclear Careers, a partner of the new UMR.

Applications of the RIAN model, particularly the early diagnosis of degenerative diseases using pATM crowns and premature ovarian insufficiency syndromes, involve collaboration, particularly through already funded projects (e.g., the MAHATMA project), between UMR staff and university hospital staff from Lyon I (neurologists, human fertility specialists, dermatologists, geneticists, etc.). Finally, with regular support from CNES, Lyon 1 University will be able to leverage the Unit's original work in space radiobiology through stratospheric flights, which represent genuine scientific firsts. The Lyon Institute of Nuclear Physics could advantageously complement the expeditions with the astrophysics expertise of Lyon I researchers.

## The new UMR 1296 with the LYON I label: a 5-year trajectory

The overall objective of the new UMR1296 remains to better understand the individual response to ionizing radiation and genotoxic stress in general, while still being guided by the RIAN model. The reorganization of the Unit would make it possible to address, for the first time, in a single French laboratory, the issue of accidental irradiation of both industrial and military origin, whether internal (radionuclides) or external (external sources). Indeed, this new structure would allow for a better understanding of the molecular aspects of acute radiation syndrome, i.e., the individual response to very high doses. Resolving this syndrome would constitute a new first in the field and would advance our knowledge of the mechanisms of inflammation by studying the interaction between cytokines and the ATM protein.

At the same time, the analysis of the molecular mechanisms involved in new radiotherapy modalities such as FLASH therapy or proton therapy is in line with the research and development that the UMR can conduct, particularly in collaboration with new and innovative startups such as THERIQ. Thanks to the RIANS model, we are moving towards "à la carte" radiotherapy, with radiotherapy modalities specifically designed for specific conditions of healthy tissue and tumors. Such an approach will most likely be leveraged by numerous patents.

As part of space radiobiology studies, the construction of a new balloon launch base in Brazil offers us a tremendous opportunity to probe, for the first time, the famous South Atlantic Anomaly (SAA), a magnetic receptacle for charged particles that travel through the magnetosphere. The intense proton flow rates (5,000 p/cm<sup>2</sup>/s) are responsible for the dose peaks recorded above the SAA. Through several flight campaigns, exposing cells at the heart of the SAA will allow us to better select the most appropriate shielding and discover previously unobserved biological effects. Here again, supported by the startup ESIL, the development of next-generation radioprotective drugs will guarantee us an original application that will also be of interest to the French Air and Space Force.

Finally, as part of the radiobiological characterization of rare genetic diseases, whether associated with a high risk of cancer or a high risk of degeneration (accelerated aging), a unique anatomical map of the human body will be created to identify tissues at risk of radiosensitivity, radiosusceptibility, or radiodegeneration to inform radiation protection risk calculations. Our Unit will thus participate in the work of the International Commission on Radiological Protection (ICRP), an independent international body that proposes future radiation protection recommendations, which are then translated into national laws. This highly ambitious systematic work will be carried out only by UMR1296, in its new configuration, thus linking multi-scale models for the first time. Throughout these developments, the biomathematics group will provide mathematical modeling, as well as the use of AI to optimize protocols and extend the validity of mechanistic models. The new UMR will remain a single-team unit and will have approximately forty members of all statuses.

## REFERENCES CITED IN THE TEXT

1. Granzotto, A.; Benadjaoud, M. A.; Vogin, G.; Devic, C.; Ferlazzo, M. L.; Bodgi, L.; Pereira, S.; Sonzogni, L.; Forcheron, F.; Viau, M.; Etaix, A.; Malek, K.; Mengue-Bindjeme, L.; Escoffier, C.; Rouvet, I.; Zabet, M. T.; Joubert, A.; Vincent, A.; Venezia, N. D.; Bourguignon, M.; Canat, E. P.; d'Hombres, A.; Thebaud, E.; Orbach, D.; Stoppa-Lyonnet, D.; Radji, A.; Dore, E.; Pointreau, Y.; Bourcier, C.; Leblond, P.; Defachelles, A. S.; Lervat, C.; Guey, S.; Feuvret, L.; Gilsoul, F.; Berger, C.; Moncharmont, C.; de Laroche, G.; Moreau-Claeys, M. V.; Chavaudra, N.; Combemale, P.; Biston, M. C.; Malet, C.; Martel-Lafay, I.; Laude, C.; Hau-Desbat, N. H.; Ziouche, A.; Tanguy, R.; Sunyach, M. P.; Racadot, S.; Pommier, P.; Claude, L.; Baleyrier, F.; Fleury, B.; de Crevoisier, R.; Simon, J. M.; Verrelle, P.; Peiffert, D.; Belkacemi, Y.; Bourhis, J.; Lartigau, E.; Carrie, C.; De Vathaire, F.; Eschwege, F.; Puisieux, A.; Lagrange, J. L.; Balosso, J.; Foray, N., Influence of Nucleoshuttling of the ATM Protein in the Healthy Tissues Response to Radiation Therapy: Toward a Molecular Classification of Human Radiosensitivity. *International journal of radiation oncology, biology, physics* **2016**, 94, (3), 450-60.
2. Bodgi, L.; Foray, N., The nucleo-shuttling of the ATM protein as a basis for a novel theory of radiation response: resolution of the linear-quadratic model. *International journal of radiation biology* **2016**, 92, 117-131.
3. Berthel, E.; Foray, N.; Ferlazzo, M. L., The nucleoshuttling of the ATM protein: a unified model to describe the individual response to high- and low-dose of radiation? *Cancers* **2019**, in press.
4. Sonzogni, L.; Granzotto, A.; Le Reun, E.; Al-Choboq, J.; Bourguignon, M.; Foray, N.; Bodgi, L., Prediction of radiotherapy toxicity: 20 years of CERNIC radiosensitivity diagnosis procedure. *Cancer radiotherapie : journal de la Société française de radiotherapie oncologique* **2024**.
5. Sonzogni, L.; Ferlazzo, M. L.; Granzotto, A.; Fervers, B.; Charlet, L.; Foray, N., DNA Double-Strand Breaks Induced in Human Cells by 6 Current Pesticides: Intercomparisons and Influence of the ATM Protein. *Biomolecules* **2022**, 12, (2).
6. Viau, M.; Sonzogni, L.; Ferlazzo, M. L.; Berthel, E.; Pereira, S.; Bodgi, L.; Granzotto, A.; Devic, C.; Fervers, B.; Charlet, L.; Foray, N., DNA Double-Strand Breaks Induced in Human Cells by Twelve Metallic Species: Quantitative Inter-Comparisons and Influence of the ATM Protein. *Biomolecules* **2021**, 11, (10).
7. Shekarian, T.; Sivado, E.; Jallas, A. C.; Depil, S.; Kielbassa, J.; Janoueix-Lerosey, I.; Hutter, G.; Goutagny, N.; Bergeron, C.; Viari, A.; Valsesia-Wittmann, S.; Caux, C.; Marabelle, A., Repurposing rotavirus vaccines for intratumoral immunotherapy can overcome resistance to immune checkpoint blockade. *Science translational medicine* **2019**, 11, (515).
8. Melero, I.; Gato, M.; Shekarian, T.; Aznar, A.; Valsesia-Wittmann, S.; Caux, C.; Etcheberry, I.; Teixeira, A.; Marabelle, A., Repurposing infectious disease vaccines for intratumoral immunotherapy. *J Immunother Cancer* **2020**, 8, (1).
9. El Alaoui, M.; Sivado, E.; Jallas, A. C.; Mebarki, L.; Dyson, M. R.; Perrez, F.; Valsesia-Wittmann, S.; El Alaoui, S., Antibody and antibody fragments site-specific conjugation using new Q-tag substrate of bacterial transglutaminase. *Cell Death Discov* **2024**, 10, (1), 79.
10. Bachelet, J. M.; Al-Choboq, J.; Granzotto, A.; Ferlazzo, M. L.; Sonzogni, L.; Berthel, E.; Devic, C.; Foray, N., Radiobiological characterization of skin fibroblasts from a young patient suffering from the Immunodeficiency Centromeric instability Facial anomalies type 1 (ICF1) syndrome. *Archives of Medical and Clinical Case Reports* **2022**, in press.

11. Bachelet, J. T.; A., G.; Ferlazzo, M.; Sonzogni, L.; Berthel, E.; C., D.; Foray, N., First Radiobiological Characterization of Skin and Bone Cells from A Patient Suffering from the PI3KCA-Related Overgrowth Spectrum (PROS) Syndrome. *Archives of Medical and Clinical Case Reports* **2020**, 4, 1052-1066.
12. Bachelet, J. T.; Combemale, P.; Devic, C.; Foray, N.; Jouanneau, E.; Breton, P., [Management of craniofacial type 1 neurofibromatosis]. *Revue de stomatologie, de chirurgie maxillo-faciale et de chirurgie orale* **2015**, 116, (4), 209-14.
13. Bachelet, J. T.; Granzotto, A.; Ferlazzo, M.; Sonzogni, L.; Berthel, E.; Devic, C.; Foray, N., First radiobiological characterization of the McCune-Albright syndrome: influence of the ATM protein and effect of statins + bisphosphonates treatment. *International journal of radiation biology* **2021**, 97, (3), 317-328.
14. Foray, N.; Amiel, M.; Mornex, R., Etienne Destot (1864-1918) ou l'autre père de la radiologie française. *Cancer Radiothérapie* **2017**, 21, 138-147.
15. Foray, N., [Claudius Regaud (1870-1940): A pioneer of radiobiology and radiotherapy]. *Cancer radiothérapie : journal de la Société française de radiothérapie oncologique* **2012**, 16, (4), 315-21.
16. Foray, N., [Victor Despeignes (1866-1937): How a hygienist became the first radiation oncologist]. *Cancer Radiothérapie* **2013**, 17, (3), 244-54.
17. Foray, N., Fabien Arcelin (1876-1942) ou comment on devient radiothérapeute quand on naît archéologue *Cancer Radiothérapie* **2017**, 21, 228-238.
18. Combemale, P.; Sonzogni, L.; Devic, C.; Bencokova, Z.; Ferlazzo, M. L.; Granzotto, A.; Burlet, S. F.; Pinson, S.; Amini-Adle, M.; Al-Choboq, J.; Bodgi, L.; Bourguignon, M.; Balosso, J.; Bachelet, J. T.; Foray, N., Individual Response to Radiation of Individuals with Neurofibromatosis Type I: Role of the ATM Protein and Influence of Statins and Bisphosphonates. *Molecular neurobiology* **2022**, 59, (1), 556-573.
19. Berthel, E.; Pujo-Menjouet, L.; Le Reun, E.; Sonzogni, L.; Al-Choboq, J.; Chekroun, A.; Granzotto, A.; Devic, C.; Ferlazzo, M. L.; Pereira, S.; Bourguignon, M.; Foray, N., Toward an early diagnosis for Alzheimer's disease based on the perinuclear localization of the ATM protein. *Cells* **2023**, 12, 1747.
20. Joubert, A.; Zimmerman, K. M.; Bencokova, Z.; Gastaldo, J.; Rénier, W.; Chavaudra, N.; Favaudon, V.; Arlett, C.; Foray, N., DNA double-strand break repair defects in syndromes associated with acute radiation response: at least two different assays to predict intrinsic radiosensitivity? *International journal of radiation biology* **2008**, 84, (2), 1-19.
21. Foray, N.; Priestley, A.; Alsbeih, G.; Badie, C.; Capulas, E. P.; Arlett, C. F.; Malaise, E. P., Hypersensitivity of ataxia telangiectasia fibroblasts to ionizing radiation is associated with a repair deficiency of DNA double-strand breaks. *International journal of radiation biology* **1997**, 72, (3), 271-83.
22. Taylor, A. M.; Byrd, P. J.; McConville, C. M.; Thacker, S., Genetic and cellular features of ataxia telangiectasia. *International journal of radiation biology* **1994**, 65, (1), 65-70.
23. Taylor, A. M.; Harnden, D. G.; Arlett, C. F.; Harcourt, S. A.; Lehmann, A. R.; Stevens, S.; Bridges, B. A., Ataxia telangiectasia: a human mutation with abnormal radiation sensitivity. *Nature* **1975**, 258, (5534), 427-9.
24. Savitsky, K.; Bar-Shira, A.; Gilad, S.; Rotman, G.; Ziv, Y.; Vanagaite, L.; Tagle, D. A.; Smith, S.; Uziel, T.; Sfez, S.; et al., A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* **1995**, 268, (5218), 1749-53.
25. Savitsky, K.; Sfez, S.; Tagle, D. A.; Ziv, Y.; Sartiell, A.; Collins, F. S.; Shiloh, Y.; Rotman, G., The complete sequence of the coding region of the ATM gene reveals similarity to cell cycle regulators in different species. *Human molecular genetics* **1995**, 4, (11), 2025-32.
26. Foray, N.; Bourguignon, M.; Hamada, N., Individual response to ionizing radiation. *Mutation Research Review* **2016**, 770, 369-386.
27. Ferlazzo, M. L.; Bach-Tobdji, M. K. E.; Djerad, A.; Sonzogni, L.; Burlet, S. F.; Devic, C.; Granzotto, A.; Bodgi, L.; Djefal-Kerrar, A.; Foray, N., Radiobiological characterization of tuberous sclerosis: A delay in the nucleo-shuttling of ATM may be responsible for radiosensitivity. *Molecular neurobiology* **2017**, 55, (4973-4983).
28. Ferlazzo, M. L.; Foray, N., Huntington Disease: A Disease of DNA Methylation or DNA Breaks? *The American journal of pathology* **2016**, 186, (7), 1750-3.
29. Ferlazzo, M. L.; Sonzogni, L.; Granzotto, A.; Bodgi, L.; Lartin, O.; Devic, C.; Vogin, G.; Pereira, S.; Foray, N., Mutations of the Huntington's Disease Protein Impact on the ATM-Dependent Signaling and Repair Pathways of the Radiation-Induced DNA Double-Strand Breaks: Corrective Effect of Statins and Bisphosphonates. *Molecular neurobiology* **2014**, 49, 1200-1211.
30. Bencokova, Z.; Devic, C.; Ferlazzo, M. L.; Granzotto, A.; Sonzogni, L.; Burlet, S. F.; Viau, M.; Bodgi, L.; Bachelet, J. T.; Combemale, P.; Balosso, J.; Foray, N., Radiobiological characterization of neurofibromatosis type I: the neurofibromin protein impacts on the ATM-dependent DNA damage repair and signaling pathway. *Molecular neurobiology* **2018**, in press.
31. Oka, A.; Takashima, S., Expression of the ataxia-telangiectasia gene (ATM) product in human cerebellar neurons during development. *Neuroscience letters* **1998**, 252, (3), 195-8.
32. Lim, D. S.; Kirsch, D. G.; Canman, C. E.; Ahn, J. H.; Ziv, Y.; Newman, L. S.; Darnell, R. B.; Shiloh, Y.; Kastan, M. B., ATM binds to beta-adaptin in cytoplasmic vesicles. *Proceedings of the National Academy of Sciences of the United States of America* **1998**, 95, (17), 10146-51.
33. Alexander, A.; Cai, S. L.; Kim, J.; Nanez, A.; Sahin, M.; MacLean, K. H.; Inoki, K.; Guan, K. L.; Shen, J.; Person, M. D.; Kusewitt, D.; Mills, G. B.; Kastan, M. B.; Walker, C. L., ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS. *Proceedings of the National Academy of Sciences of the United States of America* **2010**, 107, (9), 4153-8.
34. Barlow, C.; Ribaut-Barassin, C.; Zwingman, T. A.; Pope, A. J.; Brown, K. D.; Owens, J. W.; Larson, D.; Harrington, E. A.; Haeberle, A. M.; Mariani, J.; Eckhaus, M.; Herrup, K.; Bailly, Y.; Wynshaw-Boris, A., ATM is a cytoplasmic protein in mouse brain required to prevent lysosomal accumulation. *Proceedings of the National Academy of Sciences of the United States of America* **2000**, 97, (2), 871-6.
35. Boehrs, J. K.; He, J.; Halaby, M. J.; Yang, D. Q., Constitutive expression and cytoplasmic compartmentalization of ATM protein in differentiated human neuron-like SH-SY5Y cells. *Journal of neurochemistry* **2007**, 100, (2), 337-45.



36. Hinz, M.; Stilmann, M.; Arslan, S. C.; Khanna, K. K.; Dittmar, G.; Scheidereit, C., A cytoplasmic ATM-TRAF6-cIAP1 module links nuclear DNA damage signaling to ubiquitin-mediated NF-kappaB activation. *Mol Cell* **2010**, 40, (1), 63-74.
37. Li, J.; Han, Y. R.; Plummer, M. R.; Herrup, K., Cytoplasmic ATM in neurons modulates synaptic function. *Current Biology* **2009**, 19, (24), 2091-6.
38. Yang, D. Q.; Halaby, M. J.; Li, Y.; Hibma, J. C.; Burn, P., Cytoplasmic ATM protein kinase: an emerging therapeutic target for diabetes, cancer and neuronal degeneration. *Drug discovery today* **2011**, 16, (7-8), 332-8.
39. Bodgi, L.; Granzotto, A.; Devic, C.; Vogin, G.; Lesne, A.; Bottollier-Depois, J. F.; Victor, J. M.; Maalouf, M.; Fares, G.; Foray, N., A single formula to describe radiation-induced protein relocalization: towards a mathematical definition of individual radiosensitivity. *Journal of theoretical biology* **2013**, 333, 135-45.
40. Guo, Z.; Kozlov, S.; Lavin, M. F.; Person, M. D.; Paull, T. T., ATM activation by oxidative stress. *Science* **2010**, 330, (6003), 517-21.
41. Paull, T. T., Mechanisms of ATM Activation. *Annual review of biochemistry* **2015**.
42. Maalouf, M.; Granzotto, A.; Devic, C.; Bodgi, L.; Ferlazzo, M.; Peaucelle, C.; Bajard, M.; Giraud, J. Y.; Balosso, J.; Herault, J.; Biston, M. C.; Malet, C.; Foray, N., Influence of Linear Energy Transfer on the Nucleo-shuttling of the ATM Protein: A Novel Biological Interpretation Relevant for Particles and Radiation. *International journal of radiation oncology, biology, physics* **2019**, 103, (3), 709-718.
43. Berthel, E.; Foray, N.; Ferlazzo, M. L., The Nucleoshuttling of the ATM Protein: A Unified Model to Describe the Individual Response to High- and Low-Dose of Radiation? *Cancers* **2019**, 11, (7).
44. Belkacemi, Y.; Colson-Durand, L.; Granzotto, A.; Husheng, S.; To, N. H.; Majdoul, S.; Guet, S.; Herve, M. L.; Fonteneau, G.; Diana, C.; Le Bret, C.; Dominique, C.; Fayolle, M.; Foray, N., The Henri Mondor Procedure of Morbidity and Mortality Review Meetings: Prospective Registration of Clinical, Dosimetric, and Individual Radiosensitivity Data of Patients With Severe Radiation Toxicity. *International journal of radiation oncology, biology, physics* **2016**, 96, (3), 629-36.
45. Pereira, S.; Bodgi, L.; Duclos, M.; Canet, A.; Ferlazzo, M. L.; Devic, C.; Granzotto, A.; Deneuve, S.; Vogin, G.; Foray, N., Fast and binary assay for predicting radiosensitivity based on the nucleoshuttling of ATM protein: development, validation and performances. *International journal of radiation oncology, biology, physics* **2018**, 100, 353-360.
46. Vogin, G.; Bastogne, T.; Bodgi, L.; Gillet-Daubin, J.; Canet, A.; Pereira, S.; Foray, N., The Phosphorylated ATM Immunofluorescence Assay: A High-performance Radiosensitivity Assay to Predict Postradiation Therapy Overreactions. *International journal of radiation oncology, biology, physics* **2018**, 101, (3), 690-693.
47. Bodgi, L.; Canet, A.; Granzotto, A.; Britel, M.; Puisieux, A.; Bourguignon, M.; Foray, N., [The enigma of the biological interpretation of the linear-quadratic model finally resolved? A summary for non-mathematicians]. *Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique* **2016**, 20, (4), 314-21.
48. Bodgi, L.; Canet, A.; Pujo-Menjouet, L.; Lesne, A.; Victor, J. M.; Foray, N., Mathematical models of radiation action on living cells: From the target theory to the modern approaches. A historical and critical review. *Journal of theoretical biology* **2016**, 394, 93-101.
49. Devic, C.; Ferlazzo, M. L.; Foray, N., Influence of Individual Radiosensitivity on the Adaptive Response Phenomenon: Toward a Mechanistic Explanation Based on the Nucleo-Shuttling of ATM Protein. *Dose-response : a publication of International Hormesis Society* **2018**, 16, (3), 1-11.
50. Drouet, M.; Herodin, F., Mitigating radiation-induced toxicity: an overview of new approaches developed at the French Military Biomedical Research Institute. *Health physics* **2014**, 106, (6), 682-8.
51. Duboeuf, M.; Amadou, A.; Coudon, T.; Grassot, L.; Ramel-Delobel, M.; Faure, E.; Salizzoni, P.; Gulliver, J.; Severi, G.; Mancini, F. R.; Fervers, B.; Praud, D., Long-term exposure to air pollution at residential and workplace addresses and breast cancer risk: A case-control study nested in the French E3N-Generations cohort from 1990 to 2011. *European journal of cancer* **2024**, 210, 114293.
52. Giampiccolo, C.; Amadou, A.; Coudon, T.; Praud, D.; Grassot, L.; Faure, E.; Couvidat, F.; Severi, G.; Romana Mancini, F.; Fervers, B.; Roy, P., Multi-pollutant exposure profiles associated with breast cancer risk: A Bayesian profile regression analysis in the French E3N cohort. *Environment international* **2024**, 190, 108943.
53. Britel, M.; Bourguignon, M.; Foray, N., Radiosensitivity: a term with various meanings at the origin of numerous confusions. A semantic analysis. *International journal of radiation biology* **2018**, 94, (5), 503-512.
54. Britel, M.; Foray, N.; Preau, M., [Personalized medicine in radiotherapy: practitioners' perception]. *Sante publique* **2015**, 27, (5), 669-77.
55. Le Reun, E.; Bodgi, L.; Granzotto, A.; Sonzogni, L.; Ferlazzo, M. L.; Al-Choboq, J.; El-Nachef, L.; Restier-Verlet, J.; Berthel, E.; Devic, C.; Bouchet, A.; Bourguignon, M.; Foray, N., Quantitative correlations between radiosensitivity biomarkers show that the ATM protein kinase is strongly involved in the radiotoxicities observed after radiotherapy. *International journal of molecular sciences* **2022**, 23, (10434).
56. Restier-Verlet, J.; Drouet, M.; Pras, P.; Ferlazzo, M. L.; Granzotto, A.; Sonzogni, L.; Al-Choboq, J.; El Nachef, L.; Francois, S.; Bourguignon, M.; Foray, N., Molecular Influence of the ATM Protein in the Treatment of Human Cells with Different Radioprotective Drugs: Comparisons between Antioxidative and Pro-Episkevic Strategies. *Biomolecules* **2023**, 13, (3).
57. Le Reun, E.; Granzotto, A.; Petre, A.; Bodgi, L.; Beldjoudi, G.; Lacornerie, T.; Vallet, V.; Bouchet, A.; Al-Choboq, J.; Bourguignon, M.; Thariat, J.; Bourhis, J.; Lartigau, E.; Foray, N., Influence of the Hypersensitivity to Low Dose Phenomenon on the Tumor Response to Hypofractionated Stereotactic Body Radiation Therapy. *Cancers* **2023**, 15, (15).
58. Restier-Verlet, J.; El-Nachef, L.; Ferlazzo, M. L.; Al-Choboq, J.; Granzotto, A.; Bouchet, A.; Foray, N., Radiation on Earth or in Space: What Does It Change? *International journal of molecular sciences* **2021**, 22, 3739.
59. Restier-Verlet, J. e. a., Exposure of human tissues to stratosphere radiation behind different shieldings: data from a campaign of three balloon flights. *in prep* **2025**.
60. Bauquier, C.; Ginguene, S.; Leroy, T.; Doumergue, M.; Lebrun, N.; Della Vecchia, C.; Mabire-Yon, R.; Leveaux, S.; Sagaon-Teyssier, L.; Preau, M., Measuring reconceptualization and reprioritization during France's first COVID-19-related lockdown in women with and without a history of cancer: an adaptation of the SeiQol-DW and PGI. *Qual Life Res* **2024**, 33, (5), 1423-1431.

61. Devic, C.; Ferlazzo, M. L.; Berthel, E.; Foray, N., Influence of Individual Radiosensitivity on the Hormesis Phenomenon: Toward a Mechanistic Explanation Based on the Nucleoshuttling of ATM Protein. *Dose-response : a publication of International Hormesis Society* **2020**, 18, (2), 1559325820913784.
62. Devic, C.; Bodgi, L.; Granzotto, A.; Ferlazzo, M. L.; Sonzogni, L.; Bourguignon, M.; Foray, N., Le phénomène d'hypersensibilité aux faibles doses : une énigme de la radiobiologie enfin résolue ? *Revue de médecine nucléaire* **2016**, 40, 254-257.
63. El Nachef, L.; Berthel, E.; Ferlazzo, M. L.; Le Reun, E.; Al-Choboq, J.; Restier-Verlet, J.; Granzotto, A.; Sonzogni, L.; Bourguignon, M.; Foray, N., Cancer and Radiosensitivity Syndromes: Is Impaired Nuclear ATM Kinase Activity the Primum Movens? *Cancers* **2022**, 14, (24).
64. El Nachef, L.; Bodgi, L.; Estavoyer, M.; Bure, S.; Jallas, A. C.; Granzotto, A.; Restier-Verlet, J.; Sonzogni, L.; Al-Choboq, J.; Bourguignon, M.; Pujo-Menjouet, L.; Foray, N., Prediction of Cancer Proneness under Influence of X-rays with Four DNA Mutability and/or Three Cellular Proliferation Assays. *Cancers* **2024**, 16, (18).
65. El-Nachef, L.; Al-Choboq, J.; Restier-Verlet, J.; Granzotto, A.; Berthel, E.; Sonzogni, L.; Ferlazzo, M. L.; Bouchet, A.; Leblond, P.; Combemale, P.; Pinson, S.; Bourguignon, M.; Foray, N., Human Radiosensitivity and Radiosusceptibility: What Are the Differences? *International journal of molecular sciences* **2021**, 22, 7158.
66. Helissey, C.; Cavallero, S.; Guitard, N.; Thery, H.; Parnot, C.; Schernberg, A.; Aissa, I.; Raffin, F.; Le Coz, C.; Mondot, S.; Christopoulos, C.; Malek, K.; Malaurie, E.; Blanchard, P.; Chargari, C.; Francois, S., Correlation Between Electronic Patient-Reported Outcomes and Biological Markers of Key Parameters in Acute Radiation Cystitis Among Patients With Prostate Cancer (RABBIO): Prospective Observational Study. *JMIR Cancer* **2024**, 10, e48225.
67. Helissey, C.; Cavallero, S.; Mondot, S.; Parnot, C.; Yssaad, H.; Becherirat, S.; Guitard, N.; Thery, H.; Schernberg, A.; Breitwiller, H.; Chargari, C.; Francois, S., Correlation Between Serum and Urine Biomarkers and the Intensity of Acute Radiation Cystitis in Patients Treated With Radiation Therapy for Localized Prostate Cancer: Protocol for the Radiotoxicity Bladder Biomarkers (RABBIO) Study. *JMIR Res Protoc* **2023**, 12, e38362.
68. Rota Graziosi, E.; Francois, S.; Nasser, F.; Gauthier, M.; Oger, M.; Favier, A. L.; Drouet, M.; Jullien, N.; Riccobono, D., Comparison of Three Antagonists of Hedgehog Pathway to Promote Skeletal Muscle Regeneration after High Dose Irradiation. *Radiation research* **2024**, 201, (5), 429-439.
69. Bourgois, A.; Saurat, D.; De Araujo, S.; Boyard, A.; Guitard, N.; Renault, S.; Fargeau, F.; Frederic, C.; Peyret, E.; Flahaut, E.; Servonnet, A.; Favier, A. L.; Lacroix, G.; Francois, S.; Dekali, S., Nose-only inhalations of high-dose alumina nanoparticles/hydrogen chloride gas mixtures induce strong pulmonary pro-inflammatory response: a pilot study. *Inhal Toxicol* **2021**, 33, (9-14), 308-324.
70. Restier-Verlet, J.; Ferlazzo, M. L.; Granzotto, A.; Al-Choboq, J.; Bellemou, C.; Estavoyer, M.; Lecompte, B.; B., B.; Pujo-Menjouet, L.; Foray, N., Accelerated aging effects observed in vitro after an exposure to gamma-rays delivered at very low and continuous dose-rate equivalent to 1-5 weeks in International Space Station. *Cells* **2024**, in press.
71. Foray, N., [Leon Bouchacourt (1865-1949): How an obstetrician pointed out individual radiosensitivity]. *Cancer Radiotherapie* **2015**, 19, (8), 752-61.
72. Foray, N., *Victor Despeignes ou le premier traitement du cancer par rayons X*. Editions Glyphe: Paris, 2021.