Compte-rendu scientifique annuel

RECHERCHE HOSPITALO-UNIVERSITAIRE

RHU

Acronyme du projet

Projet ANR- 1x-RHUS-00XX

Rapport couvrant la période du 01/01/2020 au 31/12/2020

Titre complet du projet	
Mots clés	
Etablissement coordinateur	
Date de début du projet	
Date de fin du projet	
Site web du projet	

Champs pré-remplis par l'ANR et amendables par le RST

[1]

RST: Responsable scientifique et technique du projet	
Prénom, Nom	
Téléphone	
Courriel	
Date de rédaction	

Champs pré-remplis par l'ANR et amendables par le RST

Chef de projet (si différent du RST)	
Prénom, Nom	
Téléphone	
Courriel	

[1] **Recommandations :** l'objet de ce rapport limité en nombre de pages est de préciser les éléments importants de la vie du projet durant l'année écoulée. Il comporte trois volets :

Volet 1 - Compte-rendu scientifique (résumé, avancement, impact socio-économique…), rempli par le RST

Volet 2 - Indicateurs, rempli par le RST

Volet 3 - Eléments financiers (relevé de dépenses signé et autres éléments financiers), fournis le cas échéant par chaque partenaire

Nous vous invitons à la rédaction en langue anglaise du présent compte-rendu scientifique.

RESUME PUBLIC / PUBLIC SUMMARY

Résumé public et diffusable du projet intégrant son avancement et les faits marquants depuis le début de celui-ci. Cette partie sera actualisée chaque année. Maximum 20 lignes - 2500 caractères (1/2 page par résumé).

Les traitements de référence pour le cancer de la prostate (chirurgie ou radiothérapie) parviennent à obtenir un bon contrôle tumoral mais présentent un risque important d'effets secondaires qui peuvent affecter la qualité de vie des patients. Un tel risque est limité avec la thérapie focale par ultrasons focalisés de haute intensité (HIFU), qui permet de traiter juste le volume tumoral et laisser le reste de la prostate intacte.

Le projet PERFUSE vise, d´une part, à fournir une évaluation clinique actualisée du traitement HIFU focal appliqué aux cancers localisés, et d'autre part à une amélioration des performances d'imagerie et thérapie afin de perfectionner les résultats du traitement focal. PERFUSE met en synergie l'expertise académique de chercheurs compétents en applications des ultrasons à la thérapie, d'urologues, oncologues, radiologues et biologistes, avec les compétences reconnues internationalement des compagnies privées EDAP TMS et Vermon, spécialisées réciproquement dans les HIFU et dans les transducteurs ultrasonores pour les applications médicales.

À ce jour trois études cliniques prospectives et une étude ancillaire ont démarré. Une prolongation de la période d'inclusion, un assouplissement des critères de sélection et l'ajout de plusieurs centres investigateurs ont été nécessaires afin d´augmenter les taux d´inclusion pour deux essais.
Deux systèmes d´aide au diagnostic ont été développés en parallèle et ont achevé des résultats intermédiaires qui se comparent bien aux performances de l´état de l'art.
Des nouvelles approches pour la mesure de l´élasticité des tissus prostatiques ont été implémentées : l´élastographie IRM qui prévoit la présence d'un vibreur périnéal, et l´élastographie passive qui permet la détection à l´échographie des lésions HIFU.
Des simulations et une étude clinique rétrospective (en cours) ont mis en évidence la grande variabilité des performances du traitement en fonction du taux de perfusion des patients et du volume cible, ce qui a orienté les équipes vers le développement de nouvelles stratégies de tir moins dépendantes de ces paramètres (séquences C-shots).
Le projet se consacre également à des nouvelles technologies de transducteurs (CMUT) qui permettront d'augmenter la résolution du traitement et l'imagerie de guidage. Un prototype de sonde CMUT a été testé avec des résultats encourageants, bien que la production du prototype industrialisable ait été retardée.

RESUME PUBLIC / PUBLIC SUMMARY

Résumé public et diffusable du projet intégrant son avancement et les faits marquants depuis le début de celui-ci. Cette partie sera actualisée chaque année. Maximum 20 lignes - 2500 caractères (1/2 page par résumé).

Reference treatments for prostate cancer (surgery or radiation therapy) achieve good cancer control but present an important risk of side effects which may affect patients' life quality. Such a risk is limited with high intensity focused ultrasound (HIFU) focal therapy, which allows treating only the tumor volume and leave the rest of the prostate intact. This treatment is performed using an endorectal probe connected to the HIFU device, the FocalOne®, and is supported by multiparametric MRI and targeted biopsies to properly characterize the cancerous foci and control the absence of cancer in the rest of the prostate.

The PERFUSE project will provide, on the one hand, an updated clinical evaluation of the HIFU focal treatment applied to localized cancers, and on the other hand an improvement of the imaging and therapy performances allowing ultimately to refine the results of focal treatment. PERFUSE synergized the academic expertise of researchers in ultrasound therapeutic applications, urologists, oncologists, radiologists and biologists, with the internationally recognized skills of the private companies EDAP TMS and Vermon, respectively specialized in HIFU and in ultrasonic transducers for medical applications.

To date, three prospective clinical trials and an ancillary study are ongoing. An extension of the inclusion period, a relaxation of some selection criteria and the addition of further investigator centers were required to increase the inclusion rate for two trials.
Two computer aided diagnosis systems were developed in parallel and achieved intermediate results which compare well with the state-of-the-art performances.
New approaches for the measurement of prostatic tissue elasticity were implemented: MRI elastography which requires a perineal vibrator, and passive elastography which allows for the echographic detection of HIFU lesions.
An in-silico study and a clinical retrospective study (still ongoing) highlighted the great variability of treatment performance as a function of the patients‘ perfusion rate and of the target volume. This oriented the teams towards the development of new tir strategies less dependent on these parameters (C-shot sequences).
The project is as well dedicated to new transducer technologies (CMUT) which will allow increasing treatment resolution and improving guidance imaging. The characterization of a CMUT probe prototype achieved encouraging results even if the production of the industrial design prototype is delayed.

Volet 1 – Avancement scientifique

Toutes les données transmises ci-dessous sont confidentielles

A. UNITES DE RECHERCHE PARTENAIRES DU PROJET :

Fournir la liste des unités de recherche actuelles (code RNSR, nom du laboratoire, sigle, code postal).
Vous trouverez votre code RNSR à cette adresse :
https://appliweb.dgri.education.fr/rnsr/ChoixCriteres.jsp?PUBLIC=OK

Code RNSR	Nom du laboratoire	sigle	Code postal

B. ETAT D'AVANCEMENT DU PROJET

Il s'agit de la partie majeure du compte-rendu scientifique annuel. Décrire ici l'état d'avancement du projet par rapport au contenu de la convention et de ses annexes sur les différents volets : gouvernance/organisation, avancement des travaux. Préciser les difficultés rencontrées, les éventuelles réorientations réalisées ou envisagées, les perspectives pour l'année à venir. Maximum 3 pages – 12 200 caractères.

1 RESUME DES RESULTATS OBTENUS DANS L'ANNEE

Résumé scientifique de l'état d'avancement du projet détaillant les avancées majeures et difficultés rencontrées. Précisez l'ensemble des actions, tâches, jalons, livrables réalisés, abandonnés, et ceux non prévus à l'origine.

WP1

Task 1.1 & 1.2 : HIFUSA (multicenter F-HIFU phase III study for low risk patients) & FOCALE (multicenter F-HIFU phase II study for intermediate risk patients)

As the recruitment rate registered in 2020 for both clinical trials was lower than expected, a robust mitigation strategy was implemented. The inclusion period was extended to 36 months, an inclusion criterion was relaxed for the HIFUSA trial, the monitoring of the clinical investigator centers was intensified and several dissemination actions were undertaken. This strategy allowed to improve the enrollment rate (Fig.1) which is no longer raising concern for the FOCALE trial while is still lower than expected for the HIFUSA trial.

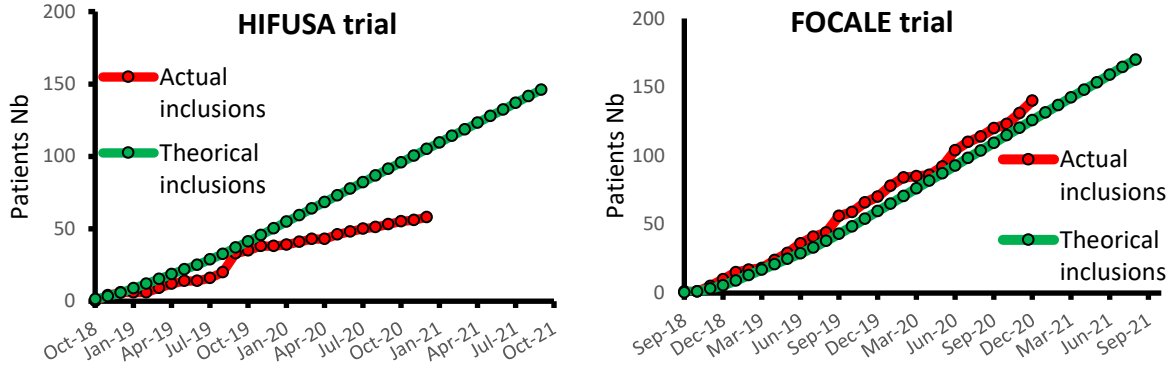

Fig 1. Theoretical and actual inclusion curves for the HIFUSA and FOCALE trials

Task 1.3: Salvage F-HIFU treatment with PSMA-PET-MRI guidance after EBRT failure

After the inclusion of the first patient in June 2020, the recruitment rate keeps low. Among the several caused identified, physical limitations due to patients' morphology hinder the PET-MRI exam, and radiotherapists propose alternative salvage protocols.

Task 1.4: "Ancillary" study, biological response evaluation

The ancillary study is based on the hypothesis that HIFU-focal treatment will actively modulate the systemic immune response in prostate carcinoma patients either with low risk (FOCALE) or with recurrence after radiotherapy (PSMA) by generating inflammation and the release of antigens that will favor an immune response against the tumor.

We monitored immune cell phenotypic and functional changes in blood of 26/46 patients enrolled in FOCALE study at Lyon site (*WP1.2*) at inclusion, D1, M1 and M3 and compared results with a cohort of healthy donors (HD) (n=15, men, [50-64] y). Using validated 14 colors flow cytometry panels (Fortessa x20, partly funded by the program) we investigated in depth modulations induced by HIFU treatment on the phenotype (activation markers, KIR/KAR, differentiation, proliferation) of immune cells.

At inclusion, FOCALE patients did not differ from HD in adequacy with the early tumor stages recruited in this study. At D1, HIFU induced a strong but transient increase in white blood cell number due to increased number of neutrophils and inflammatory monocyte recruited in the blood to counteract the high inflammatory HIFU procedure. B cell numbers declined at D1 until M1. In contrast at D1 other immune cell subsets (T cells, DC, NK cells) were not altered. Interestingly, whereas NK cell numbers were never modified all along the follow-up, in several patients, their expression of KIR was increased whereas KAR and GzB were reduced at D1 suggesting that HIFU reduced NK cell functionality. At M1, T cells and DC subset numbers declined. These quantitative alterations were restored at M3. However, at M1 and M3, $CD4^+$ T cells expressed activation markers (PD1, ICOS, CD39) and, for several patients $CD8^+$ T cells expressed more GzB at D1 or M1. All these results suggest that HIFU treatment affects the systemic immune response. All these results have to be related with efficacy of HIFU treatment, clinical data at inclusion as well as other parameters analyzed (CTC, PCA3 levels in urine) to explain the inter-patients' differences.

WP2

Task 2.1.1: Collaborative computer-based database

The XNAT platform is operational and all 290 patients in the CLARA-P/prostatectomy radio-anatomical correlation database (which collects pre-operative MRI images and surgical specimen images with histological cancer location of patients prostatectomized between 2008 and 2014) have been loaded, along with lesion contours. This task is therefore considered complete.

Task 2.1.2: Creation of a quantitative CAD system

The entire CLARA-P/prostatectomy database was used to select the best quantitative models. A database of 100 patients who had pre-biopsy MRI was then used to define a 90% sensitivity threshold for ISUP≥2 cancers and select only one model for the peripheral zone (PZ) and one model for the transition zone (TZ).
The CAD combining the PZ and TZ models was then tested on a third database of 160 patients who had pre-biopsy MRI. It gives, for the detection of ISUP≥2 cancers, results which are identical to the PI-RADSv2 score assigned by specialized uro-radiologists.
A patent application is being processed. The scientific paper (already written) will be submitted as soon as this invention declaration is filed.

TASK 2.1.3: Investigation of complementary Machine Learning Techniques

We designed of novel deep supervised architecture with an attention model on the prostate peripheral zone. Performance evaluated on a series of 98 patients of the CLARA-P database was shown to compare well to state of the art performance. This study was presented at the MIDL 2020 international conference in July 20. We are currently investigating an extended version of this model allowing the detection of lesions of the peripheral and transition zones, including more than 200 patients of CLARA-P whose exams were acquired on three different scanners. Preliminary results indicate that performance generalize well with data coming from different populations, as can be encountered with imaging data pooled over different clinical centers. An article will be submitted to an international journal within the next few weeks.

TASK 2.1.4: Multicenter clinical evaluation

In agreement with the Scientific Advisory Board, it was decided to begin constituting the prospective cohort planned by the CHANGE clinical trial without waiting for the finalization of the CADs. The CHANGE protocol has been submitted to the North West III Data Protection Committee (ID-RCB: 2020-A02785-34) and accepted on January 22, 2021. First inclusion is expected by the end of March 2021.

Task 2.2.1: MR Elastography for Prostate Cancer

A prototype device for MR elastography of the prostate was assembled and was tested in phantoms. The article is being prepared (deliverable D2.2.1). The next step will be clinical evaluation (deliverable D2.2.3). We are now preparing to apply for regulatory approval for use in human healthy subjects.

Task 2.2.2: Passive elastography for HIFU lesions

An in vivo study on 10 pigs was performed until the end of January 2021. A total of 35 lesions could be performed on the livers of these pigs through the cecum which mimicked the rectum to ensure the safety of the treatment. Tissue elasticity was assessed on B-mode images before and after treatment. Lesion size and position relative to the liver surface were measured by MRI and confirmed by dissection. The comparison of these results with those obtained by passive elastography is under analysis and will allow to determine the clinical potential of this technique for the follow-up of lesions in the prostate.

WP3

WP3.1 : Innovative HIFU strategies

Task 3.1.1 : Perfusion estimation of prostate tissue with pre-operative MRI – "Retro" Study

The results of the RETRO trial on the performance of 31 HIFU treatments allowed analyzing the relation between success rate (necrotic volume/tumor volume) and perfusion in the target zone (wash-in). In order to retrieve a more pronounced correlation between the two parameters, further recruitments are required; a protocol for a retrospective trial was submitted to the HCL Ethical Committee and will allow pursuing this analysis on 100 patients.

The in-silico study on the incidence of the perfusion on focal treatments of prostate cancer with the Focal One® was finalized (deliverable 3.1.1.b, 1FCH20-0002 23/06/2020 report). It allowed to highlight that, for the focal targets, the treatment protocol should be reformulated in order to cover the target zone with elementary necroses whose power and space-time spacing ensure the contiguity of the lesions whatever the position of the targeted area and independently of the thermal diffusion effects (conduction and perfusion).

Task 3.1.2 : C-Shot HIFU Sequence

A new ´´C-shot strategy´´ was used to develop a treatment protocol which met the criteria defined in the deliverable 3.1.1.b. The simulations allowed determining the shots´ power law and a set of parameters related to the spatio-temporal spacing between shots.

Task 3.1.3 : Perfusion-Guided HIFU Treatment – "C-Shot" dose escalation study

The ´´C-shots´´ protocol is currently being integrated in the Focal One®. The preclinical trial is foreseen for the second semester 2021, after which a clinical mono-centric trial is envisaged to validate this new treatment strategy.

Task 3.1.4 : US Per-operative Perfusion Measurement

We performed simulations that invalidated our hypothesis. We therefore resorted to our backup plan, i.e. to measure temperature instead of perfusion. A new experimental setup is being developed for that purpose.

WP3.2 : Innovative technological rupture for focal HIFU

Task 3.2.1: Design and industrial integration of miniature cMUTs on high density therapeutic HIFU transducers with embedded ultrasound imaging

This sub-task has been dedicated to the development of a prototype V2 (industrial design).

- Numerical modeling studies and transducer specifications have been completed.
- Vermon, leader of the task 3.2.1 has announced its repositioning within the project (Oct 2020), as a CMUT integrator (not any more as the CMUT manufacturer due to financial difficulties linked to COVID19 crisis)
- LabTAU becomes now the leader of 3.2.1 and is subcontracting the fabrication of the CMUT arrays. Specifications have been identified by the partners for a tender (ongoing with UCBL & LIP).
- Vermon will then integrate the subcontracted CMUT structures.
  The goal is to perform the scientific proof of concept with the prototype V1 (not the industrial design) and to conclude the project with the development of prototype V2 (viable design).

Task 3.2.2: Preclinical study of high resolution HIFU under US guidance

This sub-task has been dedicated to the characterization of a prototype V1 (not the industrial design).

- HIFU pressure fields measurements have been completed. Mid-term robustness and reliability tests are ongoing. Driving channel at high energy in a safe mode: a dedicated hardware has been developed (protection board, Edap/LabTAU), in agreement with Verasonics (manufacturer of the VANTAGE ultrasound driving system). An extension cable is under manufacturing (Vermon) to allow starting of tests at higher energy.
- In-vitro US imaging trials (ongoing): tissue phantom, real human prostate.
- Preclinical in-vivo studies will start in May 2021 (ICE) with prototype V1.

TASK 3.2.3: Industrial integration of the new USgHIFU medical device for high resolution prostate focal therapy

This sub-task will be dedicated to the characterization of the prototype V2 (industrial design).

- The development of a dedicated multi channels amplifier (Edap) is on stand-by, until the fabrication of prototype V2 is more advanced
- A clinical packaging has been developed for prototype V1, compatible with the clinical Focal-One(Lab) platform. This will be reusable for prototype V2.
- In-vitro trials have been performed (LabTAU & Edap) with prototype V1 to run a 3D treatment planning with the platform (gel phantom). This will be directly transferable for V2

1 LISTE DES PUBLICATIONS DE L'ANNEE DANS LE CADRE DU PROJET

Seules les publications effectives dans lesquelles la référence au projet est mentionnée (avec date de publication) doivent être listées.

Prostate cancer semantic segmentation by Gleason score group in bi-parametric MRI with self-attention model on the peripheral zone.
Audrey Duran, Pierre-Marc Jodoin, Carole Lartizien.
Proceedings of the Third Conference on Medical Imaging with Deep Learning, PMLR 121:193-204, 2020.

2 LISTE DES BREVETS DEPOSES/OBTENUS DANS L'ANNEE ET DANS LE CADRE DU PROJET

Seuls les brevets sur les travaux financés par le projet (avec date de dépôt ou d'extension) doivent être listés. Indiquez également les déclarations d'invention, enveloppes SOLEAU.

Two invention disclosures were submitted in 2020:
- a method for filtering out compression waves in MR elastography
- a method for detecting and/or characterizing prostate cancer using magnetic resonance imaging and a computer aided diagnostic system.

3 IMPACT SOCIO-ECONOMIQUE / SOCIO-ECONOMIC IMPACT

Décrire l'impact socio-économique du projet.

Renforcement des partenariat(s) avec l'(es) entreprise(s) du *consortium*, et relation(s) contractuelle(s) établie(s) : ***licences, cessions de licence d'exploitation, nouveaux produits et/ou services mis en place chez les partenaires entreprises découlant des recherches du projet RHU… Maximum une demi-page – 2100 caractères.***

Etablissement de relation(s) contractuelle(s) avec de nouvelle(s) entreprise(s) : ***licences, cessions de licence d'exploitation…***
Maximum une demi-page – 2100 caractères.

Discussions were initiated with the BK Medical System operator to pilot the future designated CMUT imaging probe with a clinical BK US system. A one-by-one non-disclosure agreement was signed for EDAP, Vermon and the LabTAU. The consequence of these preliminary discussions is the lowering of the number of elements from 256 to 192 for direct compatibility with the BK US scanner certified for the clinic.
Several French and international companies were as well contacted regarding the possibility of integrating in the FocalOne® a new US scanner which would provide access to the raw data required for standard passive elastography.

***Renforcement/ Emergence de sociétés (start-up(s), spin-off(s) etc.) partenaires du projet ou directement issues des travaux RHU** : levées de fonds réalisées, accords de licence, paiement d'upfront/milestones etc, start-ups créées…. Maximum une demi-page – 2100 caractères.*

***Actions entreprises pour la diffusion des connaissances, enseignements, site web** (hors publications dans des revues scientifiques). Maximum une demi-page – 2100 caractères.*

The Hospices Civils de Lyon promoted a communication campaign in order to foster recruitments for HIFUSA and FOCALE clinical trials. With the help of a communication trainee employed by the Direction of Clinical Research, we prepared a flyer and a poster, which, once approved by the Ethics Committee, were distributed and affixed in the urology and radiology consulting rooms of the investigator centers. We wrote a dissemination article explaining the principles and advantages of focal therapy and implemented a system of crossed references to improve the visibility of the clinical trials and of the scientific work performed within the PERFUSE RHU in the internet. As a result, the RHU website registered several contacts from patients wishing to be recruited in the trials.
A workshop addressed to the scientific community was foreseen but finally canceled because of the COVID-19 pandemic; it will take place in the first half of 2021.

***Autre(s) type(s) de valorisation des résultats** (savoir-faire, logiciels, dépôts à l'APP, prototypes, nouveaux produits ou services…). Maximum une demi-page – 2100 caractères.*

***Utilisateurs hors périmètre du projet** (décrire qui, utilisateurs publics ou privés, a eu accès aux plateformes, collections, bases de données... ; comment et sous quelles conditions financières). Maximum une demi-page – 2100 caractères.*

C. MOYENS MIS EN PLACE

1.MOYENS HUMAINS

Il est recommandé d'effectuer un suivi annuel des emplois (nombre d'enseignants chercheurs, chercheurs, post doctorants, doctorants, administratifs, ingénieurs et techniciens). Ce suivi sera demandé dans le cadre du rapport final afin de documenter l'adéquation entre l'atteinte des objectifs et les moyens.

***Moyens humains.** Il s'agit de présenter le nombre de personnes financées sur fonds IA RHU pour la période concernée (personnel technique, personnel médical, personnel non médical, post-doctorants, doctorants, en précisant les recrutements de l'année). Maximum 1 page – 4200 caractères.*

Hospices Civils de Lyon :
Camille BENETON - Clinical research associate (urology) - Non medical staff
Estelle RICCI - Clinical coordinator (urology) – Non medical staff
Marine DUBREUIL - Clinical research associate (radiology) – Non medical staff
Sabine DEEBER - Clinical research associate (radiology) – Non medical staff
Adeline MANSUY - Clinical coordinator (radiology) – Non medical staff
Estelle BRAVANT - Statistician – Non medical staff
Julien BERTHILLER – Data manager – Non medical staff
Marina NGUON - PH vigilant – Medical staff
Silvain GOUTTARD - Software engineer – Technical staff

Catherine CERESER - Clinical project manager - Non medical staff
Océane BRASSART - Clinical project manager - Non medical staff

Centre Léon Berard:
Lucrèce AIMADE - Technician – Technical staff
Pauline WAJDA – Engineer – Technical staff (recruited in 2020)
Stephan LANGONNET – Technician – Technical staff (recruited in 2020, CLB/LabTau)

UCBL - LabTau:
Sophie RAQUIN - Scientific project manager –Technical staff
Caterina MONINI - Scientific project manager –Technical staff (recruited in 2020)
Thomas PAYEN - Post-doctoral researcher (LabTau/EDAP)
Ivan SUAREZ - Post-doctoral researcher
Alice GANEAU – Engineer – Technical staff
Tristan DERUELLE – Ph.D. student
Tristan JAOUEN – Ph.D. student

UCBL – Creatis :
Audrey DURAN - Ph.D. student

EDAP TMS :
Emmanuel BLANC – CTO –Technical staff
Nicolas GUILLEN - Project manager –Technical staff
Nicolas LAISNEY - Software manager –Technical staff
Olivier NALLET - Mechanical design manager –Technical staff
Didier VELUT- Application specialist –Technical staff
Charline FAURE – Clinical Research Associate –Non medical staff
Clear JOSSAN- Head of clinical department - Non medical staff
Jean-Pierre GIRAUD - Bio-statistician –Technical staff
Bernard MAISON - Software engineer - Technical staff
Loic VAUGELADE - Technician - Technical staff
Laurie BRUNEL- Engineer - Technical staff

VERMON:
Pierre BOUCHEZ - R&D engineer – Technical staff (recruited in 2020)
Dominique GROSS - R&D engineer – Technical staff
Cyril MEYNIER – Senior R&D engineer – Technical staff
Nicolas SENEGOND – Senior R&D engineer – Technical staff

2. REUNIONS INTERNES DE CONCERTATION AU *CONSORTIUM*

Indiquer les dates, lieux, thèmes abordés, partenaires et correspondants de l'ANR éventuellement présents. Précisez la dénomination et la composition de ces structures de concertation en annexe.*

Date	Dénomination*	Lieu	Partenaires présents	Thème de la réunion
25/2/20	Steering committee 7	HEH	PERFUSE members	WP status reports, scientific discussion
03/3/20	Internal meeting	HEH	HCL, CERMEP, LIP, PM	Implementation of the PSMA trial
13/3/20	Internal meeting	HEH	HCL, LabTau, Creatis, LIP, PM	Strategies for CAD(s) valorization
21/4/20	Internal meeting	/	HCL, LabTau, LIP, PM	CHANGE trial protocol
18/5/20	Internal meeting	/	Creatis, LIP, PM	Machine Learning CAD database
26/5/20	Steering committee 8	/	PERFUSE members	WP status reports, scientific discussion
18/6/20	Internal meeting	HEH	RST, LIP, PM	ANR mid-term report
21/7/20	Internal meeting	/	Vermon, LIP, PM	Status report WP 3.2
23/7/20	Internal meeting	/	EDAP, LIP, PM	Status report WP 3.1
01/9/20	Internal meeting	/	LabTau, Creatis, LIP, PM	Exchanges upon the 2 CAD(s)

Date	Dénomination*	Lieu	Partenaires présents	Thème de la réunion
10/9/20	Internal meeting	HEH	RST, LIP, PM	PERFUSE status report
14/9/20	Internal meeting	HEH	HCL, LIP, PM	HIFUSA & FOCALE trials monitoring
01/10/20	Steering committee 9	/	PERFUSE members	WP status reports, scientific discussion
16/10/20	Internal meeting	/	Vermon, EDAP, Labtau, LIP, PM	Vermon financial issue
21/10/20	Internal meeting	HEH	SC, LIP, PM	CMUT production
04/11/20	SAB meeting	/	SAB, PERFUSE members	WP status reports, scientific discussion, possibilities for CMUT production
03/12/20	PERFUSE consortium	/	Consortium, LIP, PM	Financial strategy to support CMUT production
08/12/20	Internal meeting	/	Vermon, EDAP, Labtau, LIP, PM	Technical specifications of CMUT transducers

Periodical meetings :

Date	Dénomination*	Lieu	Partenaires présents	Thème de la réunion
Weekly	Internal meeting	HEH	LIP, PM	Management – Administration
Weekly	Internal meeting	HEH	SC, PM	Weekly status report
Monthly	Internal meeting	/	EDAP, LabTAU, Vermon, PM	Status report & actions WP 3
Bimonthly	Internal meeting	/	EDAP, Labtau	C-shot sequences technicalities
Bimonthly	Internal meeting	/	Vermon, Labtau, EDAP	CMUT probe technicalities

** comité de pilotage, assemblée générale, bureau, comité scientifique indépendant, consortium, etc.*
HEH : Hôpital Edouard Herriot, Lyon
SC : scientific coordinator
PM : project manager
/: video-conference

3. AUTRES MOYENS NECESSAIRES AU PROJET (LE CAS ECHEANT)

Indiquer le résultat des demandes d'autorisations administratives ou de moyens techniques ou expérimentaux éventuellement nécessaires au projet.

Two authorization requests were submitted for approval to an ethical committee for the HIFUSA clinical trial in 2020.
Amendment Nb. 5:

- 12-months extension of the inclusion period.
- Modification of an inclusion criterion.
- Inclusion of a foreign investigation center.
- Addition of descriptive documents addressed to patients to support enrollment.

➔ Favorable notification, 07/10/2020

Amendment Nb.6:

- Possibility to include patients remotely.
- Modification of the expected events due to HIFU treatments with the Focal One® according to the new version of the Focal One® user manual.
- Addition of the 48 months follow-up for the patients who will benefit from a secondary curative treatment.

➔ Favorable notification, 03/03/2021

Two authorization requests were submitted for approval to an ethical committee for the FOCALE clinical trial in 2020.
Amendment Nb. 5:

- 12-months extension of the inclusion period.
- Inclusion of a foreign investigation center.
- Complementary information addressed to patients recruited in the ancillary study

- Addition of descriptive documents addressed to patients to support enrollment.

➔ Favorable notification, 08/10/2020

Amendment Nb.6:

- Possibility to include patients remotely.
- Modification of the expected events due to HIFU treatments with the Focal One® according to the new version of the Focal One® user manual.
- Addition of the 48 months follow-up for the patients who will benefit from a secondary curative treatment.

➔ Notification still pending

Following the annual report and the meeting in date 01/12/2020, the Independent Oversight Board gave a favorable opinion on the continuation of the HIFUSA and FOCALE clinical trials without modifications of the protocols.

D. COMMENTAIRES LIBRES

Commentaire général à l'appréciation du RST, sur l'état d'avancement du projet, les interactions entre les différents partenaires, les difficultés rencontrées…

Several scientific milestones have been achieved owing to good and fruitful interactions between the different teams. Nonetheless, we met some difficulties:

- In 2020 the Covid 19 sanitary crisis had a major impact on research activities: the laboratories were closed for 2 months and resumed their activities only gradually. In terms of clinical research activity at the Hospices Civils de Lyon, patient recruitment was hindered for several months, even if it did not totally cease during the lock down owing to the online consultations.

- The inclusion rate for the HIFUSA trial is still insufficient in some investigator centers. Amendments to the protocol were introduced in 2020 to compensate for lower than expected patient recruitment. The relaxation of the MRI visibility criterion and the inclusion of a foreigner investigator center should allow the enrollment of 100-120 patients during the extended inclusion period. This should allow reaching a sufficient statistical power to make relevant conclusions. The primary endpoint of the trial (evaluated 48 months after the recruitment), however, will not be disclosed before the end of the PERFUSE project.

    - The inclusion rate for the PSMA trial is lower than expected. Several causes have been identified:
    - Too stringent inclusion criteria.
    - Physical limitations due to patients'morphology: the Gamma Camera and the antenna narrow in a significant way the PET-MRI tube, which becomes inaccessible for overweighed patients.
    - Alternative radiotherapy salvage protocols.

    - We performed a financial reorganization of the WP 3.2 in order to fund the production of the CMUT transducers, as mentioned in the document sent the 15th of December to M. Dussaule. A call for tender is in progress.

E. ANNEXES

1. ANNEXE 1 : REUNIONS INTERNES DE CONCERTATION AU *CONSORTIUM*

Précisez la dénomination et la composition de ces structures de concertation.*

Dénomination	Composition
Steering committee	**HCL** Olivier ROUVIERE – Albert GELET – Adeline MANSUY – Estelle RICCI - Catherine CERESER – Martine MICHON – Océane BRASSART – Julien BERTHILLER
	EDAP Nicolas GUILLEN – Emmanuel BLANC – Claire JOSSAN
	VERMON Nicolas SÉNÉGOND
	Centre Léon Bérard Christophe CAUX – Christine CAUX
	Université Claude Bernard Lyon 1 LabTAU : Sebastien CROUZET – Cyril LAFON – Rémi SOUCHON – Stefan CATHELINE- Françoise CHAVRIER – Apoutou N'DJIN – Thomas PAYEN – Ivan SUAREZ – Alice GANEAU – Tristan DERUELLE – Tristan JAOUEN – Caterina MONINI CREATIS : Carole LARTIZIEN, Audrey DURAN
	LIP Cédric TROLLIET – Catherine OUDIN
PERFUSE consortium	**HCL** Olivier ROUVIERE
	EDAP Nicolas GUILLEN - Emmanuel BLANC
	VERMON Nicolas SÉNÉGOND
	Centre Léon Bérard Christophe CAUX
	Université Claude Bernard Lyon 1 LabTAU : Sébastien CROUZET CREATIS : Carole LARTIZIEN
Scientific advisory board	Benoît GALLIX Fréderic SOTTILINI Martina MARTINS

** comité de pilotage, assemblée générale, bureau, comité scientifique indépendant, consortium, etc.*

2. ANNEXES EVENTUELLES

Compte-rendu(s), autorisations obtenues, modification du calendrier initial, GANTT.

Compte rendus CoPil, Gantt + milestones

Volet 2 – Indicateurs

Toutes les données sont à renseigner en année civile et ne doivent pas être reportées sauf en cas de rapport consolidé demandé dans le cadre de l'évaluation à mi-parcours.

A. INDICATEURS GENERAUX

PUBLICATIONS

Nombre d'articles mentionnant le projet, publiés dans une revue référencée dans le web of science, PubMed, au cours de l'année. Il s'agit d'articles dans lesquels le projet est nommément cité et qui n'auraient pas été publiés sans lui.

Année	Publications mentionnant le soutien financier du PIA pour le projet	Autres publications (monographies, ouvrages collectifs, actes...) *

2020	**1**	

** mentionnant le soutien financier du PIA pour le projet*

DOCTORANTS

Nombre de thèses financées entièrement ou au moins pour moitié par le projet, initiées sur l'année de suivi *	**Nombre de thèses CIFRE ou équivalent initiées l'année de suivi ***	**Nombre de thèses financées entièrement ou au moins pour moitié par le projet, soutenues sur l'année de suivi ****	**Nombre de thèses CIFRE ou équivalent soutenues l'année de suivi ****
0	**0**	**0**	**0**

** il s'agit du nombre de thèses initiées sur les thèmes du projet*

Nombre de doctorants financés avec un contrat CIFRE ou équivalent (c'est-à-dire cofinancés au moins à 50% par une entreprise) pour l'ensemble des partenaires, dont la thèse s'appuie sur le projet et qui ne pourrait aboutir sans celui-ci.

*** pour le « nombre de thèses soutenues », on recensera le nombre total, en fin d'année civile, de thèses soutenues sur les thèmes du projet,*

FORMATION

Nombre de doctorants financés avec un contrat CIFRE ou équivalent (c'est-à-dire cofinancés à plus de 50% par une entreprise) pour l'ensemble des partenaires, dont la thèse s'appuie sur le projet et n'aurait pu aboutir sans celui-ci.

Année	**Nombre de doctorants (hors CIFRE et équivalents) travaillant spécifiquement pour le projet**	**Nombre de doctorants CIFRE ou équivalent travaillant spécifiquement pour le projet**
2020	**3**	**0**

ELEMENTS DE VALORISATION

Nombre d'éléments de valorisation en lien direct ou indirect avec le projet. Il s'agit d'éléments qui n'auraient pas été créés sans lui.

Nombre de brevets actifs	Nombre de brevets déposés dans l'année	Licences d'exploitation (obtention / cession)	Créations d'entreprises ou essaimage	Enveloppes SOLEAU	Dépôts à l'APP
	2				

Nombre de nouveaux produits et nouveaux services en lien direct ou indirect avec le projet. Il s'agit de produits ou services qui n'auraient pas été créés sans lui.

Nouveaux produits	Nouveaux services

SOINS

Nombre d'essais cliniques observationnels et thérapeutiques en cours dans le cadre du projet *	Nombre d'essais cliniques observationnels et thérapeutiques menés à bien dans le cadre du projet *	Nombre de recommandations de prévention ou de prises en charge s'appuyant sur des travaux issus du projet**
5	1	

** Il s'agit du nombre d'essais cliniques observationnels et thérapeutiques, de promotion académique ou industrielle dont l'investigateur principal travaille au sein du projet. Les détails concernant la promotion des essais (académique ou industrielle) pourront être précisés.*

*** Il s'agit du nombre de recommandations publiées par des agences de santé (HAS, INVS, OMS etc.) qui citent des travaux publiés dans le cadre du projet.*

TABLEAU DES COFINANCEMENTS

Cf. définition dans notice jointe, à remplir pour l'année 2020

Etablissement Coordinateur / Partenaire ayant obtenu le financement	Type cofinanceur	Nom cofinanceur	Nature / Objet du financement	Montant sur lequel le cofinanceur s'est engagé sur la durée du projet (en €)	Montants perçus en 2016 (en €)

A joindre :

F. INDICATEURS SPECIFIQUES DU PROJET

1) LAUNCH OF THE PERFUSE RHU WEBSITE: http://www.rhu-perfuse.fr

Objective: To develop a website allowing a national and international external visibility. The website should integrate a collaborative sharing platform with secure access that allows for the exchange of documents between members (presentations, reports, etc.), and a contact form allowing people interested in the project to contact the team.
Planned delivery date: M7
Effective delivery date: M11

2) PATIENTS´ INCLUSION RATE IN THE PROSPECTIVE CLINICAL TRIALS

Objective: To reach the planned number of recruited patients in the HIFUSA/FOCALE/PSMA (WP1) and CHANGE (WP2) prospective clinical trials.
Planned delivery date : M60
Applied workaround: Since the enrollment rates for FOCALE and HIFUSA trials are lower than expected, a mitigation strategy was implemented. Several inclusion and exclusion criteria were relaxed and an extension of 2 years of the inclusion period was obtained for both clinical trials. The follow up of the clinical investigator centers was intensified, four French centers were additionally involved as clinical investigators and a Swiss clinic will be included soon. In parallel, several dissemination actions addressed to different audiences were performed to reach an increasing number of potential patients.

3) Ga^{68} PSMA PRODUCTION

Objective: To ensure the production of Gallium (Ga^{68} PSMA) required to carry out the PSMA trial as originally planned (number of patients, inclusion period, total study duration and examinations). The following logistic difficulties have to be overcome: the maximum duration of use of a Gallium generator is 12 months, thus the study requires the provision of two generators; a period of 3 to 6 months to obtain ANSN accreditations for the production of Ga^{68} PSMA by the CERMEP provider is expected.
Planned delivery date: M60
Effective implementation: The production of Ga^{68} PSMA is carried out in the nuclear medicine department of the HCL ´´groupement Hospitalier Sud´´(CHLS). The radiotracer is then transported to the CERMEP, where the injection is performed for the acquisition of the PET-MRI images. The budget foreseen for the purchase of the Gallium generator was used to cover the Gallium production by the CHLS service, and its transportation. The first patient was included in the PSMA trial at M31.

4) IMPLEMENTATION OF A MULTIPARAMETRIC-MRI COMPUTER AIDED DETECTION (CAD) SYSTEM FOR PROSTATE CANCER

Objective : To discriminate ISUP≥2 cancers in the peripheral and transition zones; to develop a CAD system robust to heterogeneous data (MRI images produced by different manufacturers); to provide, eventually, a suspicious lesions mapping.
Planned delivery date: M60
Planned workaround: Tolerance with regard to the achieved performances**.**

5) INTEGRATION OF A PASSIVE ELASTOGRAPHY TECHNIQUE IN THE FOCAL ONE™

Objective: To develop an ultrasound-based passive elastography methodology for the evaluation of the quality of the necrosis in HIFU lesions of the prostate.
Planned delivery date: M60
Planned workaround: Modification of the parameters and of the imaging spatial resolution; development of a stand-alone version of the passive elastography technique that may be used independently of the EDAP FocalOne® device.

6) CMUT PROBE CONCEPTION

Objective: To manufacture an ultrasound probe based on CMUT technology to achieve satisfactory performance for prostate therapy and imaging. The expected performances (power, operating time, etc.) are defined in the specifications established by WP 3.2 during the first year of the project.
Planned delivery date: M36
Status: delayed task. Due to the financial impact of the Covid19 pandemic, the company Vermon is no longer able to cover the CMUT probe manufacturing partially by its own funds.
Applied workaround: In order to overcome this issue, in agreement with the PERFUSE consortium and the ANR, we partially reallocated the budget of the work package 3.2 in order to have the CMUT chips manufactured by another service provider (via a call for tender). Vermon will be in charge of the electronic integration and of the packaging of the probe.

Compte-rendu du SAB