Convocatorias 2016
Proyectos EXCELENCIA y Proyectos RETOS
Dirección General de Investigación Científica y Técnica
Subdirección General de Proyectos de Investigación

AVISO IMPORTANTE

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Es obligatorio rellenar los tres apartados (A, B y C). La parte C de la memoria no podrá exceder de 20 páginas.

Lea detenidamente las instrucciones para rellenar correctamente esta memoria, disponibles en la web de la convocatoria.

Parte A: RESUMEN DE LA PROPUESTA/SUMMARY OF THE PROPOSAL

INVESTIGADOR PRINCIPAL 1 (Nombre y apellidos)**:**

Gustavo García Gómez-Tejedor

INVESTIGADOR PRINCIPAL 2 (Nombre y apellidos)**:**

TÍTULO DEL PROYECTO: Interacción de partículas de baja energía y radicales en aplicaciones biomédicas de la radiación

ACRÓNIMO: PRIOR

RESUMEN Máximo 3500 caracteres (incluyendo espacios en blanco):

Este proyecto continúa el estudio de procesos atómicos y moleculares de interés en el uso biomédico de radiaciones. Estará principalmente enfocado en interacciones de protones de relativamente baja energía (<1 MeV), como partículas primarias, y en fragmentos aniónicos y radicales neutros de baja energía (< 100eV) como partículas secundarias. Electrones, positrones y positronio también serán considerados partículas secundarias generadas durante la irradiación y por lo tanto continuarán siendo objetos de interés. Los blancos seleccionados están formados por estructuras complejas que tienen relevancia en los modelos de tejido vivo. Las estructuras más simples están formadas por agua en diferentes configuraciones (moleculas, agregados y capas condensadas). También se considerarán sistemas biomoleculares de diferente complejidad (boques constituytentes de ADN y ARN) en combinación con nanopartículas metálicas (oro, platino, gadolinio) para modificar los patrones de daño por radiación.

Las interacciones básicas de las partículas primarias y secundarias con los blancos mencionados serán analizadas tanto experimental como teóricamente. Desde el punto de vista experimental se presentan nuevos diseños capaces de generar haces de protones así como radicales negativos y neutros para la medida espectroscopica de procesos de colisión. Experimentalmente se obtendrá información esencial sobre las probabilidades de interacción (secciones eficaces), el depósito de energía y los procesos de transferencia de carga.

Con respecto a la teoría, se deducirán nuevos potenciales multicentro para describir de forma realista la dispersión de partículas cargadas (elctrones, positrones y protones) por blancos complejos (moléculas poliatómicas, agregados moleculares y nanopartículas

metálicas). También se realizarán calculos de dinámica molecular con el fin de interpretar la fragmentación molecular observada

Los datos experimentales y teóricos obtenidos, complementados con la información sobre colisiones disponible en la bibliografía, serán integrados en un potente programa de simulación de amplio espectro. Este nuevo programa será una consecuencia de la integración de nuestro código para la Simulación de Trayectorias de Partículas de Baja Energía (LEPTS) con otros programas de simulación Monte Carlo de propósito general (GEANT4, GEANT4-DNA-http://geant4.cern.ch/) junto con modelos basados en ecuaciones de transporte.

Los modelos desarrollados serán validados en condiciones preclínicas mediante el diseño y realización de experimentos de complejidad creciente. Desde al irradiación de moléculas biológicas condensadas en interfases controladas hasta el análisis del daño inducido en entornos celulares vivos.

La motivación final de este amplio estudio es contribuir al conocimiento científico, tecnológico y a la destreza requerida para la futura implementación de una de las técnicas más prometedoras en el tratamiento del cáncer: hadron-terapia con la posibildad de utilizar nanoparticulas metálicas como radiosensibilizadores.

PALABRAS CLAVE: Colisiones ión-molécula, interacción de radicales, daño por radiación a nivel molecular, nanodosimetría

TITLE OF THE PROJECT: low energy Particle and Radical Interactions in biOmedical applications of Radiation

ACRONYM: PRIOR

SUMMARY Maximum 3500 characters (including spaces):

This project proposes to continue the study of atomic and molecular interactions with biologically relevant media, and their implications in biomedical uses of radiation. It will focus mainly on the relatively low energy (< 1MeV) collisions of protons as the primary particles, and low energy (< 100 eV) anionic fragments and neutral radicals as secondary particles. Electrons, positrons and positronium will also be considered as secondary particles generated during the irradiation, and therefore they will continue being subjects of interest. The selected targets are formed by complex systems which are relevant to model living tissue, with the simplest structures being formed by water in different configurations (i.e. isolated molecules, clusters and condensed layers). Different biomolecular systems will also be considered (DNA and RNA building blocks) with or without additional metallic (gold, platinum, gadolinium) nanoparticles, in order to modify the radiation damage patterns.

The basic interactions of primary and secondary particles, with the targets of interest are analysed both experimentally and theoretically. From the experimental point of view we present new designs to generate proton beams, as well as negative and neutral radicals for spectroscopic scattering measurements. Required information about interaction probabilities (cross sections), energy deposition and charge transfer processes will be experimentally determined.

As far as theory is concerned, new multicentre potentials will be derived for a realistic description of single charged-particle (electron, positron and proton) collisions with complex targets (polyatomic molecules, molecular clusters and metallic nanoparticles). Molecular dynamics calculations will also be performed to model the observed molecular fragmentation.

Experimental and theoretical interaction data, complemented with scattering information available in the literature, will subsequently be integrated into a powerful broad-scale simulation program. This new program will be a consequence of the integration of our Low Energy Particle Track Simulation code with other general purpose Monte Carlo programs

(GEANT4, GEANT4-DNA -http://geant4.cern.ch/), together with models based on transport equations.

The models will ultimatelly be validated in preclinical conditions by designing and performing experiments of growing complexity, from the irradiation of condensed biomolecular targets on controlled interphases up to detailed analysis of the induced damage in living cellular environments.

The final goal of this wide-ranging study is to contribute to the scientific and technological knowledge and expertise that is required to implement one of the most promising current techniques of radiotherapy for cancer treatment: hadron-therapy together with the opportunity of using metallic nanoparticles as radiation sensitizers.

KEY WORDS: Ion-molecule collisions, radical interactions, radiation damage at the molecular level, nanodosimetry

Parte B: INFORMACIÓN ESPECÍFICA DEL EQUIPO

B.1. RELACIÓN DE LAS PERSONAS NO DOCTORES QUE COMPONEN EL EQUIPO DE TRABAJO (se recuerda que los doctores del equipo de trabajo y los componentes del equipo de investigación no se solicitan aquí porque deberán incluirse en la aplicación informática de solicitud). Repita la siguiente secuencia tantas veces como precise.

1. . Nombre y apellidos: Lilian Ellis-Gibbings
   Titulación: Licenciado con máster en Física
   Tipo de contrato: Contrato de trabajo por obra o servicio
   Duración del contrato: temporal (hasta 15/08/2017)

2. Nombre y apellidos: Ali Traore
   Titulación: Licenciado con máster en Física de las radiaciones
   Tipo de contrato: Contrato de trabajo por obra o servicio
   Duración del contrato: temporal (hasta 15/09/2017)

3. Nombre y apellidos: Alexey Verkhovtsev
   Titulación: Licenciado con máster en Física
   Tipo de contrato: Contrato de trabajo por obra o servicio
   Duración del contrato: temporal (hasta 31/07/2017)

4. Nombre y apellidos: Kateryna Krupa
   Titulación: Licenciada en Química con máster en Física de las radiaciones
   Tipo de contrato: Contrato extranjero, Universidade Nova Lisboa
   Duración del contrato: temporal (hasta 31/07/2017).

5. Nombre y apellidos: Monica Mendes
   Titulación: Licenciada en Física con máster en Física de las radiaciones
   Tipo de contrato: Contrato extranjero, Universidade Nova Lisboa
   Duración del contrato: temporal (hasta 31/12/2018).

6. Nombre y apellidos: Patricia Sánchez Rubio
   Titulación: Licenciada en Física
   Tipo de contrato: Facultativo especialista de área (Hospital Puerta de Hierro)
   Duración del contrato: temporal

7. Nombre y apellidos: Jaime Martínez Ortega
   Titulación: Licenciado en Física
   Tipo de contrato: Radiofísico Hospitalario (Hospital Puerta de Hierro)
   Duración del contrato: indefinido

8. Nombre y apellidos: Rafael Plaza Aparicio
   Titulación: Licenciado en Física
   Tipo de contrato: Radiofísico Hospitalario (Hospital La Paz de Madrid)
   Duración del contrato: indefinido

9. Nombre y apellidos: María Dolores Marín Ferrer
   Titulación: Licenciada en Física
   Tipo de contrato: Radiofísico Hospitalario (Hospital La Paz de Madrid)
   Duración del contrato: indefinido

10. Nombre y apellidos: Oscar Vela Morales
    Titulación: Licenciado en Física
    Tipo de contrato: Técnico Superior (CIEMAT)
    Duración del contrato: Indefinido

B.2. FINANCIACIÓN PÚBLICA Y PRIVADA (PROYECTOS Y/O CONTRATOS DE I+D+I) DEL EQUIPO DE INVESTIGACIÓN (repita la secuencia tantas veces como se precise hasta un máximo de 10 proyectos y/o contratos).

1. Investigador del equipo de investigación que participa en el proyecto/contrato: Gustavo García Gómez-Tejedor
Referencia del proyecto: FIS2012-31230
Título: Interacción de la radiación a escala nanométrica y sus aplicaciones en radioterapia y radiodiagnóstico
Investigador principal : Gustavo García Gómez-Tejedor
Entidad financiadora: MINECO, Plan Nacional de Física
Duración: 01/01/2013-31/12/2015
Financiación recibida (en euros): 222.300,00
Relación con el proyecto que se presenta: muy relacionado
Estado del proyecto o contrato: concedido

2. Investigador del equipo de investigación que participa en el proyecto/contrato: Gustavo García Gómez-Tejedor
Referencia del proyecto: FIS2009-10245
Título: Estudio de procesos atómicos y moleculares con aplicaciones en el uso biomédico de radiaciones
Investigador principal : Gustavo García Gómez-Tejedor
Entidad financiadora: Ministerio de Ciencia e Innovación, Plan Nacional de Física
Duración :01/01/2013-31/12/2015
Financiación recibida (en euros): 272.250,00
Relación con el proyecto que se presenta: muy relacionado
Estado del proyecto o contrato: concedido

3. Investigador del equipo de investigación que participa en el proyecto/contrato: Gustavo García Gómez-Tejedor
Referencia del proyecto: FP7-PEOPLE-2013-ITN
Título: Advanced Radiotherapy, Generated by Exploiting Nanoprocesses and Technologies (ARGENT)
Investigador principal : Gustavo García Gómez-Tejedor
Entidad financiadora: EU- Marie Curie Actions-— Initial Training Networks
Duración: 01/06/2013-31/12/2017
Financiación recibida (en euros): 710.848,02
Relación con el proyecto que se presenta: muy relacionado
Estado del proyecto o contrato: concedido

4. Investigador del equipo de investigación que participa en el proyecto/contrato: Gustavo García Gómez-Tejedor (representante español)
Referencia del proyecto: DP140102854
Título: Modelling positron interactions for biomedical applications
Investigador principal : S. Buckman
Entidad financiadora: Australian Research Council
Duración: 01/12/2013-31/12/2017
Financiación recibida (en euros): 180.000,00
Relación con el proyecto que se presenta: muy relacionado
Estado del proyecto o contrato: concedido

5. Investigadores del equipo de investigación que participan en el proyecto/contrato: Gustavo García Gómez-Tejedor, P. Limão-Vieira
Referencia del proyecto: FCT/UNL
Título: Radiation Biology and Biophysics Doctoral Training Programme (RABBIT)
Investigador principal: P. Limão-Vieira

Entidad financiadora: Fundaçao para a Ciencia e a Tecnologia (FCT, Portugal)
Duración: 01/12/2013-31/12/2017
Financiación recibida (en euros): 240.000,00
Relación con el proyecto que se presenta: muy relacionado
Estado del proyecto o contrato: concedido

6. Investigador del equipo de investigación que participa en el proyecto/contrato: Gustavo García Gómez-Tejedor
Referencia del proyecto: COST Action CM1301
Título: CELINA (Chemistry for ELectron-Induced NAnofabrication)
Invest
Entidad financiadora: European Science Foundation
Duración: 01/06/2013-31/12/2017
Financiación recibida (en euros): 150.000,00
Relación con el proyecto que se presenta: algo relacionado
Estado del proyecto o contrato: concedido

7. Investigador del equipo de investigación que participa en el proyecto/contrato: Gustavo García Gómez-Tejedor
Referencia del proyecto: COST Action CM1301
Título: CELINA (Chemistry for ELectron-Induced NAnofabrication)
Investigador principal : P. Swiderek
Entidad financiadora: European Science Foundation
Duración: 01/06/2013-31/12/2017
Financiación recibida (en euros): 150.000,00
Relación con el proyecto que se presenta: algo relacionado
Estado del proyecto o contrato: concedido

8. Investigador del equipo de investigación que participa en el proyecto/contrato: Gustavo García Gómez-Tejedor
Referencia del proyecto: COST Action MP1002
Título: Nano-scale insights in ion beam cancer therapy (Nano-IBCT)
Investigador principal : A. Solov'yov
Entidad financiadora: European Science Foundation
Duración: 01/12/2010-31/12/2014
Financiación recibida (en euros): 150.000,00
Relación con el proyecto que se presenta: muy relacionado
Estado del proyecto o contrato: concedido

9. Investigador del equipo de investigación que participa en el proyecto/contrato: Gustavo García Gómez-Tejedor
Referencia del proyecto:
Título: Innovación docente en las fronteras de la química actual: de la nanotecnología a la atoquímica
Investigador principal : F. Martín
Entidad financiadora: Secretaría de Estado de Cooperación Internacional
Duración: 01/11/2011-01/11/2015
Financiación recibida (en euros): 140.000,00
Relación con el proyecto que se presenta: algo relacionado
Estado del proyecto o contrato: concedido

Parte C: DOCUMENTO CIENTÍFICO. Máximo 20 páginas.

C.1. SCIENTIFIC PLAN

1. Antecedents and state of the art

1.1 Antecedents

Since the discovery of X-rays, ionising radiation has been used in medicine both for diagnosis and therapy[1]. Co-60 gamma rays (1.17 and 1.33 MeV photon energies) have been customarily used for cancer radiotherapy since 1950, leading to the development of radiation dosimetry and the establishment of photon radiation treatment standards of absorbed dose to water (ICRU Reports, 50, 62, 64)[2]. Indeed, in the last 50 years, X-rays have dominated biomedical applications of radiation. Currently, linear accelerators (LINAC) provide most of the photon beams for radiotherapy treatments. It is worth noting that more than 50% of cancer treatment regimens use radiotherapy during one or more of their treatment steps. Current treatment planners are based on traditional dosimetry, i. e. total energy deposited per unit of mass in water monitored by ionisation chambers. In our present health system the LINAC is a versatile piece of equipment that plays an important role in medical physics practice, covering more than 90% of radiotherapy procedures. **Figure 1** shows the energy distribution of the photon beam generated by stopping 6 MeV electrons in a LINAC accelerator, as per the LINACs available to most public hospitals at present. As may be seen in this figure, they provide a broad energy distribution with an average energy around 1.5 MeV, close to the average energy of the gamma photons emitted by Co-60 (1.25 MeV), thus maintaining the absorbed dose standards developed for Co-60 treatments. In spite of its efficiency, photon therapy does present serious limitations which require additional research and development efforts. Although photon interaction probabilities are well known in this energy range, these interactions are relatively low in frequency and they are dominated by photoelectric processes. As such they generate high energy electrons, capable of traveling large lateral distances and even participate in electron-triggered local chemistry processes. As a consequence, irradiated areas are generally extensive and so require external conformation and time fractionated treatments to enhance the absorbed dose in the tumour volumes. State of the art photon radiotherapy notably improves this conformation by using intensity-modulated radiation therapy (IMRT), tomotherapy IMRT and stereotactic radiation therapy[3]. Nonetheless, traditional dosimetry does not account for low dose effects and the origins of side effects observed far from the irradiated areas are still unknown.

In year 2000 pioneering investigations from Leon Sanche's group (Sherbrooke University) demonstrated that low energy electrons (with kinetic energies below the ionisation threshold of the medium), are extremely efficient in inducing single and double strand breaks to DNA via electron attachment to its molecular constituents[4,5]. This was subsequently confirmed by relevant European groups through the study of single electron interactions with DNA and RNA bases[6,7]. Considering that a single 1 MeV primary particle generates on average 10^4 low energy secondary electrons, this finding raised a fundamental contradiction to the traditional concept that genotoxic damage is essentially due to ionising processes.

These considerations motivated a research programme that we launched in 2006, in order to study the atomic and molecular processes underpinning radiation-matter interactions and their implications in biomedical uses of radiation. The final objective of these studies (FIS2006-00702, FIS2009-10245 and FIS2012-31235) was to quantify secondary electron interactions, in terms of cross sections and energy loss patterns, with relevant components of living tissue (water, DNA, RNA and protein molecular building blocks) in order to integrate all the theoretical and experimental results into a powerful Monte Carlo simulation programme able to describe radiation damage at the molecular level, in terms of bond breaking and induced molecular dissociations.

Similar objectives motivated pioneering EU programs, in some of which Spanish research groups were represented (e.g. COST Actions P9, MP1002).

Figure 1

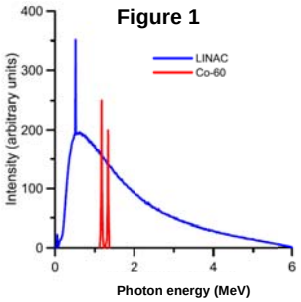
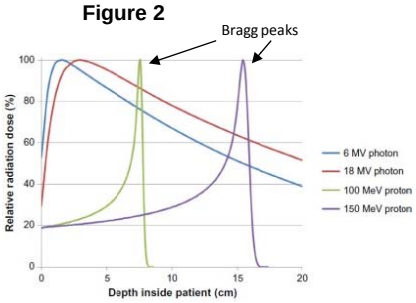


Figure 2



Technological advances and scientific research during the past few decades have attempted to concentrate the energy deposition in reduced volumes, inside the tumour, and using complementary tools, to personalize treatment plans[8]. This first aim has currently been partially achieved by using particle (proton and heavy ion) therapies, which concentrate most of the energy deposition around the Bragg peak (see **Figure 2**), and by high rate brachytherapy[3], which embraces image guidance[9] (computerized tomography, positron emission tomography-PET) and sophisticated models including specific molecular data and clinical parameters. Additionally, new radiosensitizers based on metallic nanostructures for both photon and charged particle irradiation are under investigation in preclinical conditions[10]. Metallic (gold, platinum and gadolinium) nanoparticles reinforce radiation effects not only because of their efficiency to generate Auger electrons, but also because of other aspects related to their specific location into the cell and their ability to induce perturbation to cellular membranes[11]. Primary and secondary particles also produce charged and neutral radicals which induce important damage; with the addition of nanoparticles this field is in need of critical and timely investigation to understand the role of nanoparticles as radiosensitizers.

These are the main features of biomedical use of ionising radiation in the current era of precision medicine. Furthermore those challenges have promoted numerous EU research projects within the past FP7 and the current Horizon 2020 – e.g. ENLIGHT (http://enlight.web.cern.ch/), ENVISION (http://envision.web.cern.ch/ENVISION/), ULICE (lice.web.cern.ch/ULICE/cms/index.php?file=home), PARTNER (http://partner.web.cern.ch/partner/cms/?file=home), BIOCARE (http://www.2020-horizon.com/BIOCARE-Molecular-Imaging-for-Biologically-Optimised-Cancer-Therapy(BIOCARE)-s30036.html), Nano-IBCT (http://www.cost.eu/COST_Actions/mpns/nano-ibct/), and ARGENT (http://itn-argent.eu/).

In the last 10 years our research group has been involved in some of these EU initiatives, by providing experimental and theoretical atomic and molecular interaction parameters and developing new modelling procedures capable of integrating the new findings into the biomedical uses of radiation. Important contributions from other Spanish groups covered a wide range of these new techniques. For example, pioneering Monte Carlo simulations with PENELOPE (Salvat et al.[12]) are now a reference for modelling electron and positron interactions in biomedical applications of radiation. Additionally, García-Molina et al.[13] proposed a detailed energy deposition model for hadrontherapy, while some years ago a GEANT4-based Architecture for Medicine-Oriented Simulation was developed at CIEMAT (http://fismed.ciemat.es/GAMOS/) which is currently in use for dose evaluations in radiotherapy. Particle transport simulations for medical accelerators have also been extensively carried out by Sanchez-Doblado et al.[14]. In the field of particle accelerators for radiotherapy, medical imaging and related detectors the IFIC-CSIC-UV and UPV-CIEMAT-CSIC groups (http://webific.ific.uv.es/web/en/medical, http://www.i3m.upv.es/view.php/Principal) are also actively contributing to the EU efforts on medical imaging[15, 16]and hadrontherapy[17]. Technical contributions to radiation detectors were published by Gomez et al.[18] and specific silicon devices for radiation detectors and medical imaging were developed by the IMB-CNM (http://rdg.imb-cnm.csic.es/).

Within this scientific and technical environment there is now the especially challenging situation of the imminent installation of the first hadron-therapy facility in our country. Using the experience acquired in previous EU facilities, and dose plans scaled from photon therapy, will ensure successful treatments from the opening in approximately two years' time. However there is no doubt that this also opens a new, powerful, opportunity for research and development into cancer treatment in this country, requiring great expertise and further investment. This is an excellent opportunity to allow bringing in relevant and close

contributions which different in nature but undoubtedly complementary to the advance and detailed knowledge of the underlying molecular mechanisms needed in cancer therapy.

1.2 Nanoscale radiation effects: state of the art

As mentioned above, the evidence of mutagenic effects induced by low energy electrons motivated the study of radiation damage at the molecular level. This explored a new dosimetry based not only on the total energy deposited but also on providing information about damage processes occurring on the nanoscale (nanodosimetry), i.e. in terms of bond breaking and induced molecular dissociations.

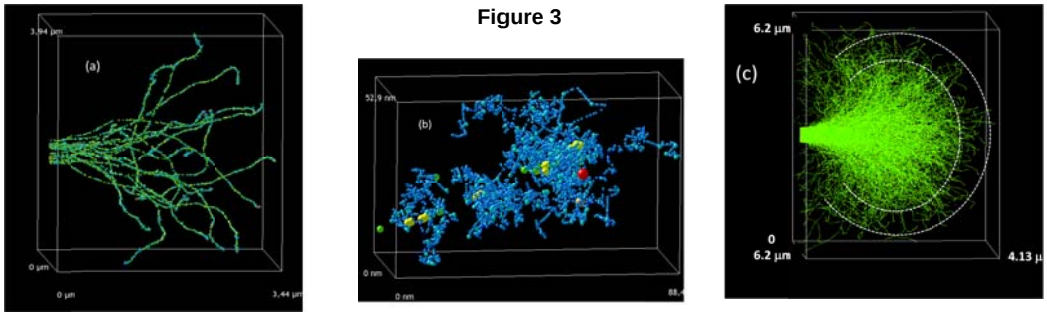
At this time most of the radiation models for photons, used for dose planning, were based on photon interaction data bases available in the literature[19] and they predicted energy deposition values and absorbed dose to water in agreement with standard ionisation chambers. Equivalent models for electron interactions used the same type of input data bases,[20] which in the case of electrons are based on scattering cross section calculations within the framework of the first Born approximation. Some years ago we demonstrated that this approximation does not apply for molecules, like those studied here for energies below 10 keV[21]. As such, the first goal of our research was to measure electron scattering cross sections and energy loss distribution functions for biologically relevant molecules (mainly formed by C, N and O atoms) in the energy range 0-10 keV. We therefore obtained accurate experimental data for elastic and the main inelastic (ionisation, electronic and vibrational excitation and total scattering) cross sections for relevant biomolecules (water, hydrocarbons, THF, pyrimidine)[22-36], aiming to benchmark representative data for comparison with calculations. Note that at these energies both integral cross sections and differential (both elastic and inelastic) cross sections, in order to sample the scattering angle after any single collision event, are needed. The huge amount of data required to model low energy electron tracks cannot be entirely provided by the experiments. In order to fulfil this gap and as part of our international scientific commitment, we thus developed a flexible optical potential method to calculate differential and integral elastic, as well as integral inelastic cross sections, by assuming an independent atom representation but including screening effects within the molecular structure[37]. This so called IAM-SCAR method provided cross section data for a large variety of molecules (from single water molecules[38] to biological macromolecules[39]) over a broad energy range (10-10000 eV). In addition, the same procedure was successfully applied to model clustering and condensation effects as well as to calculate an equivalent cross section for atoms and molecules in the condensed phase (liquids and solids)[40]. For energies below 10 eV we adapted some “ab initio” electron scattering calculations[41-43], and more recently we developed a multicentre scattering procedure based on the multiple scattering Schwinger equation[44].

Due to the relevance of positron interactions in understanding the collision processes underpinning Positron Emission Tomography, we also obtained experimental and theoretical positron scattering cross sections, including positronium formation, for most of the highlighted biologically relevant molecules[45-49] over a broad energy range (0-10000 eV).

In order to model radiation damage at the molecular level we have developed a Monte Carlo code to simulate low energy particle (electrons and positrons) tracks (LEPTS)[50]. This program is compatible with standard high energy (GEANT4-https://geant4.web.cern.ch/geant4/) and intermediate energy (GEANT4-DNA)[51] codes. By integrating these codes we have simulated single tracks for photons, electrons, positrons and high energy ions in different materials, though predominantly water, in different phases and stages of aggregation (gas, liquid and solid), until their final thermalisation thus providing information about the energy deposition, number and type of interactions as well as the number and type of molecular fragments induced in selected nano-volumes. As an example of the detail that is now generally obtained from these models, an output from the LEPTS code is given in **Figure 3**. In this example, 10 keV positrons are incident on a sample of liquid water in frame (a). The final 100 nm of one track is shown in frame (b) and it indicates the explicit detail that is now possible on a nanometre scale, such that the dose deposited in this nanovolume is readily calculated along with the number and type of interactions (indicated by the different coloured balls) this is nanodosimetry. An interesting outcome is that the region between the dashed lines in frame (c) is a volume where there is little energy deposition at the ends of the particle tracks, but where the energy of the secondary electrons

is such that processes like vibrational excitation and dissociative attachment dominate – the latter leading to bond breaks and potential damage.

Figure 3



This model has also been applied to specific brachytherapy treatments for prostate cancer (I-125 seeds)[52] and Ru-106 plaques for uveal melanoma[53].
Independent solutions of Boltzmann's equation provided information about relevant transport coefficients, which were used to check the consistency of the cross section data sets used in the simulations[54, 55]. Indeed both Monte Carlo simulations and transport equations have been proposed as complementary dosimetric tools in brachytherapy and PET scanning applications[56]. Additionally, to investigate the efficiency of inducing damage to biomolecules by attached electrons, we studied electron transfer processes in dissociating biomolecular targets which showed important bond-selective effects[57-59].

Figure 4

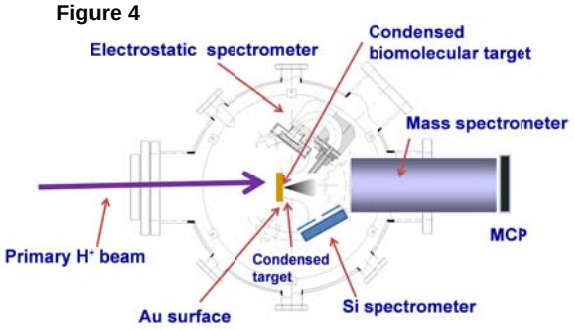


Figure 5

Finally, some validation experiments were designed to be performed in laboratories and hospitals in preclinical conditions. **Figure 4** shows a schematic of the experimental apparatus used to analyse induced damage on condensed molecules, both in vacuum and at atmospheric conditions[60, 61], and to compare those results with the predictions of the model. On the other hand, **Figure 5** shows the controlled irradiation of water phantoms using a medical LINAC device for a further comparison with the Monte Carlo simulation results.
These studies promoted important collaborations with international groups, which provided additional information to complete our modelling procedure (see section 4). Representative members of those groups are now taking part in the working group of this project, in order to execute some specific tasks according to their respective specialities.
The current status of modelling radiation interactions and their implications in biomedicine can be summarized as follows:

- **Photon irradiations** are well described in terms of interaction probabilities and energy loss by most of the dose planning systems. Available Monte Carlo (MC) codes (PENELOPE, GEANT4, PARTRAC, MCNPX) reproduce the standards for absorbed dose to water. Note that a correct application of these models requires conditions of electronic equilibrium and in general the cut-off energy for secondary electrons is relatively high (from 100 eV to 1 keV).
- **Electron and positron tracks** are simulated from high energies (MeV range) down to thermal energies (meV range) by different MC models using different input collisional data. The most specialised in the low energy domain (LEPTS, GEANT4-DNA) characterise radiation effects in terms of energy deposition (traditional dosimetry) and also in terms of the number and types of interactions occurring in selected nanovolumes (nanodosimetry). They are able to quantify the number and

type of generated positive, negative and neutral radicals, but the interactions of these with the molecular components of living tissue are not implemented yet (there is a lack of theoretical and experimental data on radical interactions with biomolecules). In the case of positrons, these models describe positronium formation at the end of the tracks but positronium physics is not yet implemented (instantaneous annihilation is currently assumed in all the cases).

- **Proton and heavy ion irradiation** are modelled in general for the high energies of the primary particles and relatively high cut-off energy for the secondary electrons (100 eV-100 keV). Most of the available models (GEANT4, GEANT4-DNA, TRACKS, LEPTS) use data based on high energy double differential cross section theory, supported by old experimental data[62,63], together with more recent single differential cross section calculations[64,65]. Considering that the Bragg peak occurs in the medium when the ion beam has acquired relatively low energies (80-150 keV), that the primary ions are fully stopped in the irradiated medium, that the average energy of the secondary electrons is much lower than 100 eV and that the number and type of damaging radicals created by both primary ions and secondary electrons is currently unknown, we can conclude that we are still far away from a realistic representation of ion interactions on the nanoscale. Macroscopic temperature effects and shock wave generation have been recently studied by means of the MBN-explorer program (http://www.mbnexplorer.com/), but this is not yet coupled with molecular level interaction models.
- **Further validation experiments** to compare experimental irradiation results in realistic condensed media with different model predictions are therefore still needed.

Taking into account all these considerations, the present research project extends significantly the boundaries of the aforementioned previous projects and will be focused on:

- Experimental and theoretical studies of negatively charged and neutral radical interactions with biologically relevant molecules, by using spectroscopic atomic collision devices and molecular dynamics techniques, respectively.
- Developing multicentre scattering potential methods for low energy electrons, positrons and protons colliding with biomolecular systems. Calculation of the corresponding “effective” cross sections for clusters, nanoparticles and condensed media.
- Undertaking an experimental study of positronium (an electron-positron pair) interactions in water and other biologically relevant media.
- Integrate the new experimental and theoretical results, as well as temperature and shock wave effects, into our modelling procedures (LEPTS, GEANT4-DNA, MBN-explorer).
- Further develop and improve our techniques for modelling proton, electron and positron transport in liquids.
- Design new validation experiments to compare with model predictions in the laboratory (condensed biomolecules on metallic surfaces) and preclinical situations (water phantom irradiation including living cells and nanoparticle targeting).

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2. Initial hypothesis, general objectives and adequacy of the Project to the Spanish Strategy for Science, Technology and Innovation

The **initial hypothesis** of our previous projects was that the fundamental atomic and molecular processes underpinning radiation interactions with biomolecular systems are the main cause of radiation damage, and that a better understanding of these elementary processes will help to solve problems not considered by traditional macroscopic radiation measurements. The main evidence for this hypothesis was the observation that initial molecular fragmentation is predominantly produced by very low energy secondary electrons and radicals. In the last few years, advanced radiotherapies have definitively verified this hypothesis. New trends in radiotherapy aim to concentrate radiation effects in small volumes inside the tumours, avoiding as much as possible radiation interactions with healthy tissue. This is the case for proton and heavy (C, O) ion beam therapies as well as complementary nanoparticle targeting procedures. Those previous projects have contributed notably to the pool of knowledge of these fundamental processes, as well as to the development of computational and instrumental tools for the description of radiation interactions on the nanoscale (nanodosimetry). However with the complexity of real living tissue, the wide variety of radicals formed and the necessity of extending the modelling procedures to more realistic representations, additional research work is urgently demanded. This requires the application of theoretical, experimental and modelling procedures to more complex targets, incorporating into the research programme new measurements (low energy proton scattering cross sections, ionic and neutral radical interactions with bio-structures), new calculations (multicentre scattering processes, quantum molecular dynamics in condensed media) and integrated modelling procedures (Monte Carlo and transport equations) which use these new data as well condensation and temperature effects. Additionally, some of the previous experimental systems devoted to the study of low energy electron and positron interactions (magnetically confined electron and positron beams) will be maintained in operation to provide required complementary data.

The general objectives of this proposal can be classified according to their related techniques as follows:

1. Instrumental designs: Setting up new experimental systems to provide intense positive, negative and neutral particle beams for radical interaction experiments.
2. Measurements: Cross section and energy loss distribution measurements for low energy (<10 keV) proton and low energy (< 100 eV) secondary species (positronium; negative and neutral radicals) interactions with biologicaly relevant molecules.
3. Theory: Multicentre scattering, temperature effects and quantum molecular dynamic calculations (molecules on surfaces and metallic nanostructures).
4. Simulation: Developing a broad-scale modelling procedure based on the integration of event by event Monte Carlo codes, molecular dynamics models, and transport equations.
5. Validation experiments: Checking the obtained theoretical and experimental data by comparison of model predictions with the radiation effects observed in laboratory and preclinical conditions.

The adequacy of the project to the Spanish and European scientific and technological strategy is a direct consequence of the above proposed objectives. The PRIOR project is based on the study of fundamental processes but with a clear application in the health area;

one of the preferential areas of the EU Horizon 2020 framework and considered as one of the challenges for society by the Spanish Research and Development 2016 plan. In particular, the imminent installation of the first Spanish hadrontherapy facility reinforces the adequacy and urgency of the project. In addition, the suitability of the topic of this project is also supported by the EU through funding related research initiatives (ITN-ARGENT, COST-Nano-IBCT) in which some members of the PRIOR team are also involved as well as others that are currently being evaluated. Furthermore, this project has an important role in training young researchers to prepare them as future radiophysicists. This is crucial given the new hi-tech profile demanded by the current radiation technology industry. Nowadays, providing job opportunities for young scientists is one of the main EU priorities. Finally, some of the mentioned goals of the project (free radical effects and multiscale modelling) are the subject of new EU proposals which are being considered for support within the ITN-Marie Curie programmes.

3. Specific objectives:

The above general objectives can be divided into specific tasks according to their field and the proposed methodologies. These specific objectives are listed as follows and details on the methodologies and people involved in each are given in the next section:

1.1. Designing and building high intensity ion sources to generate proton and negative ion beams for collision experiments (hollow cathode and radiofrequency discharges).

1.2. Adapting a crossed beam experimental set up for the study of negative ion and neutral radical interactions with biomolecular systems, including a laser system to generate neutral radicals by photodetachment of anions and all the elements required for controlling, synchronising and acquiring data. A bi-dimensional time of flight detector will also be incorporated to reconstruct the collision dynamics.

2.1. Total proton scattering cross sections with water and DNA building block molecules (THF, pyrimidine and pyridine), as well as energy loss spectrum measurements for low incident energies (0-10 keV).

2.2. Measurements of dissociation induced by negative (H^-, O^-, O_2^-, OH^-) ions to the above molecular targets (cross sections and reaction rates), for incident energies ranging from 0.1 to 100 eV.

2.3. Measurements of dissociation induced by neutral (H, O, O_2, OH) radicals to the above molecular targets (cross sections and reaction rates), for incident energies ranging from 0.1 to 100 eV.

2.4. Measurements of the total cross section for positronium scattering from water.

3.1. To develop new techniques to solve the problem of multicentre electron and positron scattering cross section calculations for low, intermediate and high energies (0-10000 eV).

3.2. Designing new scattering potentials for charged particle (electrons, positrons and ions) scattering in condensed media (liquid water, tissue equivalent materials).

3.3. Molecular dynamics calculations to model induced dissociation to water, pyrimidine and purine derivatives.

4.1. Incorporating the new theoretical and experimental (low energy proton and radical interaction cross sections) data into the low energy particle track simulation (LEPTS) procedure.

4.2. Including temperature and shock wave effects in the available proton irradiation simulation programmes (LEPTS, GEANT4-DNA,MBN-explorer).

4.3. Modelling particle transport in liquid water: combining Monte Carlo and Boltzmann's equation techniques.

5.1. Measuring induced dissociation to condensed molecules (H_2O, pyrimidine, pyridine, purine) on metallic surfaces (Au, Pt, Gd) by irradiating with 10 keV electrons/1 MeV protons and comparing with the model predictions.

5.2. Measuring induced cellular damage when irradiating aqueous cell solutions with high energy (1.5 MeV average energy) X-ray and low energy (30 keV) γ-rays (I-125 seeds). These experiments will be repeated adding Au, Pt and Gd nanoparticles to quantify their radiosensitization effects.

4. Methodology

Due to the multidisciplinary nature of this project, the research and working groups need to be formed by specialists in different areas. The particular topics are those demanded by the proposed objectives. The project participants belong to different institutions: Consejo Superior de Investigaciones Científicas (CSIC), Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Universidad Complutense de Madrid (UCM), Universidad Nacional de Educación a Distancia (UNED), Universidade Nova de Lisboa (UNL), Open University (OU), University of Vienna (UV), Australian National University (ANU), Flinders University (FU), James Cook University (JCU), the Institute of Physics Belgrade (IPB), University of Sherbrooke (SU) and the hospitals Puerta de Hierro (HPH), La Paz (HLP) and Ramón y Cajal (HRC) of Madrid.
Under the general coordination of the First Investigator, the participants and their respective institutions can be grouped according to their particular specialities:
-Fundamental experiments on atomic, molecular and nuclear interactions: G. García (CSIC), P. Limão-Vieira (UNL), F. Ferreira de Silva (UNL), A. Williart (UNED), J. C. Oller (CIEMAT), S. Buckman (ANU), M. Brunger (FU).
- Fundamental calculations on electron, positron and molecular interactions: F. Blanco (UCM), J. Gorfinkiel (OU), L. González (UV).
- Monte Carlo simulations and particle transport models: A. Muñoz (CIEMAT), Z. Petrovic (IPB), R. White (JCU).
- Instrumentation: O. Vela (CIEMAT), J. Martínez (HPH).
- Validation experiments in laboratory and preclinical conditions: M. E. Sanchez-Santos (HLP), L. Núñez (HPH), R. Colmenares (HRC), R. Aparicio (HLP), L. Marín (HLP), L, L. Sanche (SU).
- PhD young researchers: L. Ellis-Gibbings (CSIC), A. Traore (CSIC), A. Verkhovtsev (CSIC), K. Krupa (CSIC/UNL), M. Mendes (CSIC/UNL).

It is very important to emphasise that the proposed multidisciplinary objectives can only be reached with the contribution of all of these specialists. Scientists working on the fundamental studies and modelling are more visible on the higher impact publications of the group, but the contribution of specialists in biomedicine and related technologies, although they mainly appear in technical reports and lower impact journals, are essential for the correct evolution and success of the project.
The particular methodologies proposed for each general objective can be briefly described as follows:

4.1. Instrumental designs: We designed in the previous project a crossed beam experiment for studying electron transfer processes from anions to complex molecules (**Figure 6**). In order to calibrate the system we measured the electron transfer from O^- to nitromethane and the subsequent anionic fragmentation induced to the molecule. As shown in **Figure 7,** the anion beam is formed by a hollow cathode discharge triggered by a pulsed molecular beam generated by a supersonic expansion valve. The required anion species are then selected by time of flight or with the aid of an electromagnetic selector (Wien filter).

Figure 6

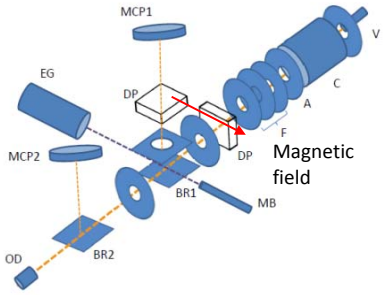
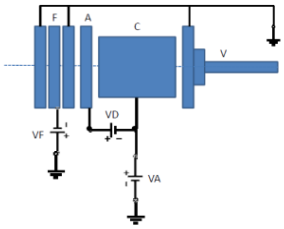


Figure 7



V, pulsed supersonic valve; **C,** hollow cathode discharge; **A**, anode; **F**, focusing lens; **DP**, deflecting plates; **BR**, beam reflector; **MB**, effusive molecular beam; **MCP**, multi-channel plate detector; **EG**, electron gun; **OD**, optical detector.

We propose here to incorporate an additional radiofrequency ion source (González-Gago et al., Spectrochim. Acta B, **76**, 159 (2012)), thus generating negative radicals to be introduced into the beamline. Neutral radical beams with well-defined kinetic energy will be produced by crossing a tunable laser beam with the anion radical beam, thus producing neutral beams by photodetachment. The MCP1 detector will also be upgraded with a bi-dimensional detector (80 mm microchannel plate+delay-line anode) to reproduce the collision dynamics.

The viability of the tasks related with the specific objectives of this group (1.1 and 1.2) are ensured by the experience of the working team with previous similar designs (DOI 10.1140/epjti/s40485-015-0023-9), together with the technical support from the designing department and mechanical workshops from CIEMAT (Laboratorio Nacional de Fusión) and CSIC (Centro de Física Miguel Antonio Catalán). Specific monitoring for the installation of the bi-dimensional detector will be provided by the Max-Plank Institute für Kernphysik (Heidelberg).

4.2. Measurements: Total cross sections of protons for scattering with the aforementioned molecules, in the energy range (0-10 keV), will be carried out by attaching the above ion sources to the transmission experimental system long in use by this research group for electron scattering measurements [Fuss et al., Phys. Rev. A **80**, 052709 (2009)]. Similarly, the new negative and neutral radical sources will be incorporated in the experimental setup shown in **Figure 6,** to measure the fragmentation induced to the projected molecular targets via electron transfer from the projectile. The efficiency of the hollow cathode discharge in producing anion radicals has been already checked. For positive and neutral fragments the new radio frequency source and the laser induced photo-detachment techniques will be respectively used. By adapting a bi-dimensional detector to the main TOF spectrometer (see **Figure 6**) information about the angular distribution of the induced fragments will also be available. Finally, positronium formation and its interaction with the proposed molecules will be investigated with the positron beamline at the Australian National University [Sullivan et al., Rev. Sci. Instrum. **79**, 113105 (2008)].

Specific tasks connected with this group of objectives (2.1, 2.2, 2.3 and 2.4) are supported by the long history of the involved specialists in crossed beam experiments with angular and energy resolution. No special contingencies can be expected for objective 2.1, as it is a natural extension of the total electron and positron scattering cross section measurements carried out in previous highly successful projects. Practical experience with reaction microscope systems developed at the ANU accounts for the incorporation of the bi-dimensinal detector linked to objectives 2.2 and 2.3. The most challenging aspect of these objectives is to generate neutral radicals from laser induced photodetachment of anion

fragments. This will require particular specifications for the laser and the initial anion density. If we are not able to reach these specifications, an alternative low-energy, high-intensity electron gun will be used instead of the laser. This will introduce additional noise due to the lack of energy selectivity, but will still allow achievement of the proposed objectives by us incorporating an additional particle filter. Objective 2.4 will be pursued at the ANU where the equipment and expertise required by the related task is available.

4.3. Theoretical calculations. The electron- and positron-molecule scattering technique we recently introduced (Blanco and García Chem. Phys. Lett. **645**, 71 (2016)), by solving a multicentre Schwinger equation for simple potentials, will be extended for more realistic optical potentials, including inelastic scattering processes. For lower energies (below 10 eV) we will continue applying the R-matrix procedure [Sieradzka et al., J. Phys. Chem. A 118, 6657 (2014)] to the new biomolecular targets, paying special attention to identifying resonances which can lead to molecular dissociation via electron attachment. Concerning low energy (< 1MeV) proton scattering from molecular targets, we will start with a similar procedure to that we successfully used for electrons and positrons, i.e. designing the potential scattering for proton-atom collisions. Another important piece of theoretical research proposed in this project is related to the molecular dynamics induced by energy or particle transfer to biomolecules. Previous investigations on the excited state dynamics in purine nucleobase derivatives [J. Am. Chem. Soc. **137**, 4368 (2015)], showed that surface-hopping dynamic simulations can provide a valuable tool for this purpose. The working group involved in the objectives related to the calculations (3.1, 3.2 and 3.3) is formed by a specialist in model potential scattering calculations (F. Blanco), an experienced low energy, from first principles, electron and positron interaction (UK R-matrix) methods researcher (J. Gorfinkiel) and a recognised specialist in “ab initio” molecular dynamics (L. González). Objectives 3.1 and 3.2 are further consequences of our 100% reached objectives in previous projects and we do not expect special difficulties. Objective 3.3 represents a new challenge, but the proven scientific capability of the group in solving the molecular aspects of the simulation and the technical support from related companies (Quantemol, MBN Research Centre) to provide the computing framework has made this objective quite realistic. Special attention will be paid to the combination of these available techniques to solve complex situations, such as high energy protons reaching metallic nanoparticles in water which are bound to DNA (see **figure 8**, http://itn-argent.eu/). For the situation shown in this figure, the theoretical contributions of this project are the proton interaction cross sections with water and the metallic component of the nanoparticle calculation. The latter will be achieved using the mentioned model potential, calculation of secondary electron interactions with the involved atoms and molecules, with the IAM-SCAR and R-Matrix procedures, and information on dissociative processes in water and biomolecular derivatives provided by the molecular dynamics calculations. These data are complemented with some experimental results and integrated into the modelling procedures described in the next section.

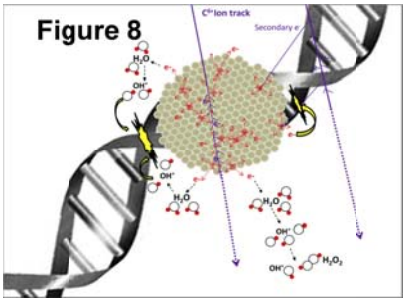


Figure 8

4.4. Simulation. The Monte Carlo (event by event) simulation procedure and transport models developed by the present team will be improved by incorporation of the above theoretical and experimental data. This implies that the physics of the further interaction of secondary particles (positive, negative and neutral radicals as well as positronium) will be incorporated in terms of cross sections and angular distributions. Concerning electron and positron transport, for relatively high energies (>30 eV) simply using realistic gas-phase cross section data appears sufficient to approximate the soft-condensed phase [A. F. Borghesani,

IEEE Transactions on Dielectrics and Electrical Insulation **13**, 492 (2006)]. However, below this energy there are a number of key physical processes that must be included in our electron/positron transport models. We will follow two different techniques, first simply modifying the single interaction cross sections by including the screening of surrounded molecules [Blanco et al., Int. J. Mass Spectrom. **365**-**366**, 287 (2014)] and then using our recently developed technique to account for the dynamic-structural properties of the medium through a quantity called the "dynamic structure function" [R. White and R. Robson, Phys. Rev. Lett. **102**, 230602 (2009)] which we have recently applied to positrons in liquid water [Robson et al., Nature Sci. Rep. doi:10.1038/srep12674 (2015)]. Results of these two approaches will be validated through measurements of some transport coefficients, such as the drift velocity. An important aspect of the integration of the MC and transport equation models, is the possibility of combining radical generation data provided by the MC track simulation with radical diffusion as modelled by the transport equations.
Another important feature to incorporate into our modelling procedures is to account for temperature effects. Energy deposition of primary and secondary particles will be distributed into translational, vibrational, and rotational energies of the molecular targets to define the local temperature. Temperature enters in the MC simulation as a reference parameter, which can modify probability distribution functions during the sampling procedure or the target density, if required. We will also investigate the connection between this new MC parameter with the macroscopic temperature and shock wave representation provided by the MBN-explorer.
Tasks connected with the specific objectives 4.1 and 4.2 imply incorporating obtained experimental and theoretical data into the modelling procedures. Thus we do not expect particular difficulties in doing so, apart from the above temperature control linked to the energy deposition processes. However, the connection between MC and collective transport modelling, objective 4.3, to model realistic environments (http://www.nature.com/articles/srep12674--) will require some extra work. We are progressing in that direction, but angular and energy distributions of the interacting particles in liquid media are not equivalent yet for both methods. We expect to obtain final adjustments to the input parameters from observed macroscopic properties [e.g. Garland et al. Phys. Rev. A **88**, 062704 (2013)].

4.5. Validation experiments. As we have already noted, an important aspect of this project is to validate the outcome of the modelling procedures, and their experimental and theoretical input parameters by comparing their predicted results with those observed in the laboratory. We plan to analyse the induced dissociation of condensed biomolecules on metallic surfaces (Au, Pt, Gd) by irradiating the target with high energy electrons and protons. Both the observed results and the output of the model are very sensitive to the role played by the secondary species - electrons and radicals. From the experimental point of view, low and high energy electron spectrometry (electrostatic and solid state spectrometers, respectively) as well as sensitive charged and neutral particle mass spectrometry (quadrupole and TOF spectrometers) will be used (see Figure 4). Additionally, target temperature will be accurately measured and controlled. Reproducing these conditions will be especially challenging for the models, so by comparing the results we will check the accuracy of the input parameters and the reliability of the different approaches used to represent the target conditions. Similarly, validation experiments in preclinical conditions will be carried out by irradiating water phantoms according to the arrangement shown in Figure 5. Special sample holders for b-lymphoblastoid cell lines in liquid media will be designed and constructed. These samples will be irradiated at different points in the water phantom, corresponding to very different energy deposition conditions (from almost 0 to the maximum absorbed dose). Biological alterations (necrosis, apoptosis and DNA damages) will be analysed through standard cell culture, flow cytometry and confocal microscopy techniques.

The specific objective 5.1 proposes to validate complete sets of input parameters by comparing the model predictions with the laboratory observations in the complex situations described above. These experiments will be simultaneously performed in two laboratories, L. Sanche's laboratory at Sherbrooke University and the Centre for Material Analysis (CMAM) of the Universidad Autonoma de Madrid, by using electrons and protons as primary particles, respectively. Primary and secondary particles interacting with solid substrates and condensed molecules is certainly a complicated environment. However, most of the required techniques have been in use by Sanche's group for several years and some time ago we started a collaboration to train another member of our group [Alizadeh et al. J. Chem. Phys. Lett **4**, 820 (2013)]. We not only consider these validation experiments feasible, but we believe that their results will constitute real achievement towards the objectives of the groups 1, 2, 3 and 4.

Finally, the objective 5.2 represents the first incursion of the present research group into living systems. Due to the lack of experience of some members of the research group, experts from the Hospital Puerto de Hierro de Madrid have been incorporated into this new project. In charge of these experiments will be the Head of the Service of Radiophysics (L. Núñez) of the hospital, supported by specialists from their research institute in biochemistry and biology (http://www.investigacionpuertadehierro.com/). Some verifications have already been carried out during this year by comparing models and radiation measurements, in order to prepare the equipment to introduce living cells into the analysis.

The feasibility of the proposed methodology has been demonstrated in our earlier research projects mentioned previously, where the percentage of achievement of the objectives was established by the review panels to be about 100%. Taking as an indicator of activity the total number of publications of the previous project (FIS2012-31230), up to now, we can summarise the following statistics:

- Total number of publications in peer-reviewed scientific journals: 66
- Publication composition: 1 Phys. Rev. Lett, 1 J. Phys. Chem. Lett., 1 Nature Sci. Rep., 1 Phys. Chem. Chem. Phys., 1 New J. Phys, 18 J. Chem. Phys., 1 J. Am. Mass Spectrom., 5 Phys. Rev. A, 4 J. Phys. Chem. A, 1 Rad. Research, 5 Chem. Phys. Lett., 1 J. Appl. Phys., 4 J. Phys. B, 2 Int. J. Mass Spectrom., 1 Int. J. Rad. Biol., 6 Appl. Rad. Isot., 4 Eur. Phys. J. D, 7 J. Phys. B Conf. Ser., 1 Eur. Phys. J. TI, 1 Am. Inst. Phys. Proc.
- Average impact factor: 2.66
- Percentage of achievement of the objectives: 100%

5. **Facilities, infrastructures and singular equipment**:

A majority of the equipment required to achieve the proposed objectives is already installed in the different participating institutions. Once the proposed adaptations are performed and the new designs incorporated, all of the equipment needed will be ready to carry out the project objectives.

Available infrastructures and equipment, indicating the required changes and new incorporations, can be summarized, per institution, as follows:

Instituto de Física Fundamental CSIC:

- Experimental apparatus for total electron scattering cross sections for biomolecular systems and energy loss measurements (transmission-beam technique). An additional RF ion source for proton scattering measurements will be incorporated.
- Magnetically confined electron beam apparatus for simultaneous differential and integral electron scattering cross sections from different molecular targets.
- Monochromatic transmission beam experiment for electrons incorporating a Time of Flight (TOF) mass spectrometer to analyse induced charged fragments and an optical (vacuum ultraviolet) spectrometer to analyse induced neutral fragmentation by electron impact.

- Crossed beam experiment for anions generated by a hollow cathode discharge and pulsed molecular beam (supersonic expansion valve) with a temperature controlled effusive molecular beam. Induced (positive/negative) fragmentation and energy release is analysed by up to three TOF spectrometers operating in coincidence. The MCP detector of the main TOF spectrometer will be replaced by a bi-dimensional 80 mm MCP with delay-line anode.
- Ultra-High-Vacuum chamber for the study of fragmentation induced in molecular targets condensed on metallic surfaces. Primary radiation is provided by alternative X-ray or electron gun sources (up to 60 keV), with the induced fragmentation being analysed by a TOF spectrometer for ionic fragments and a quadrupole mass spectrometer for neutrals. Electron spectrometry with angular resolution is carried out by a silicon spectrometer (high energy electrons) and an electrostatic hemispherical analyser (low energy electrons).
- CSIC mechanical workshop (for small pieces and experimental support)

Australian National University ANU:

- Magnetically confined positron beam apparatus for simultaneous differential and integral positron scattering cross sections from different molecular targets. It is currently being adapted to study positronium scattering processes.

Universidade Nova de Lisboa:

- Crossed beam experimental setup for the study of negative ion dissociation induced by charge transfer from neutral projectiles. Includes a high-resolution reflectron TOF mass spectrometer to analyse anionic fragments, and an electrostatic energy analyser to measure the kinetic energy release during the collision.
- Electron-molecule crossed beam experiment with angular analysis. Consists of an electrostatic monochromator and energy analyser in combination with a density calibration system by flow comparison.
- Photoelectron Spectrometer from a He(I) discharge for investigating molecular lowest-lying ionic states.

Universidad Nacional de Educación a Distancia:

- Complete alpha, beta and gamma conventional nuclear spectrometry systems: silicon, silicon (lithium), windowless silicon (lithium) to operate in vacuum chambers and several scintillator detectors.

CIEMAT

- Cluster CIEMAT computing facility.
- CIEMAT mechanical workshop (full equipment).
- CIEMAT electrical and electronics support workshop.

Hospital Puerta de Hierro:

- Linear (LINAC) accelerator, up to 10MeV, provided with water and tissue equivalent phantoms. Different size ionisation chamber and thermoluminescent dosimeters.
- Molecular counting techniques for DNA and RNA alteration analysis.
- Imaging flow cytometry analysis system.
- Confocal microscopy for cellular damage analysis.

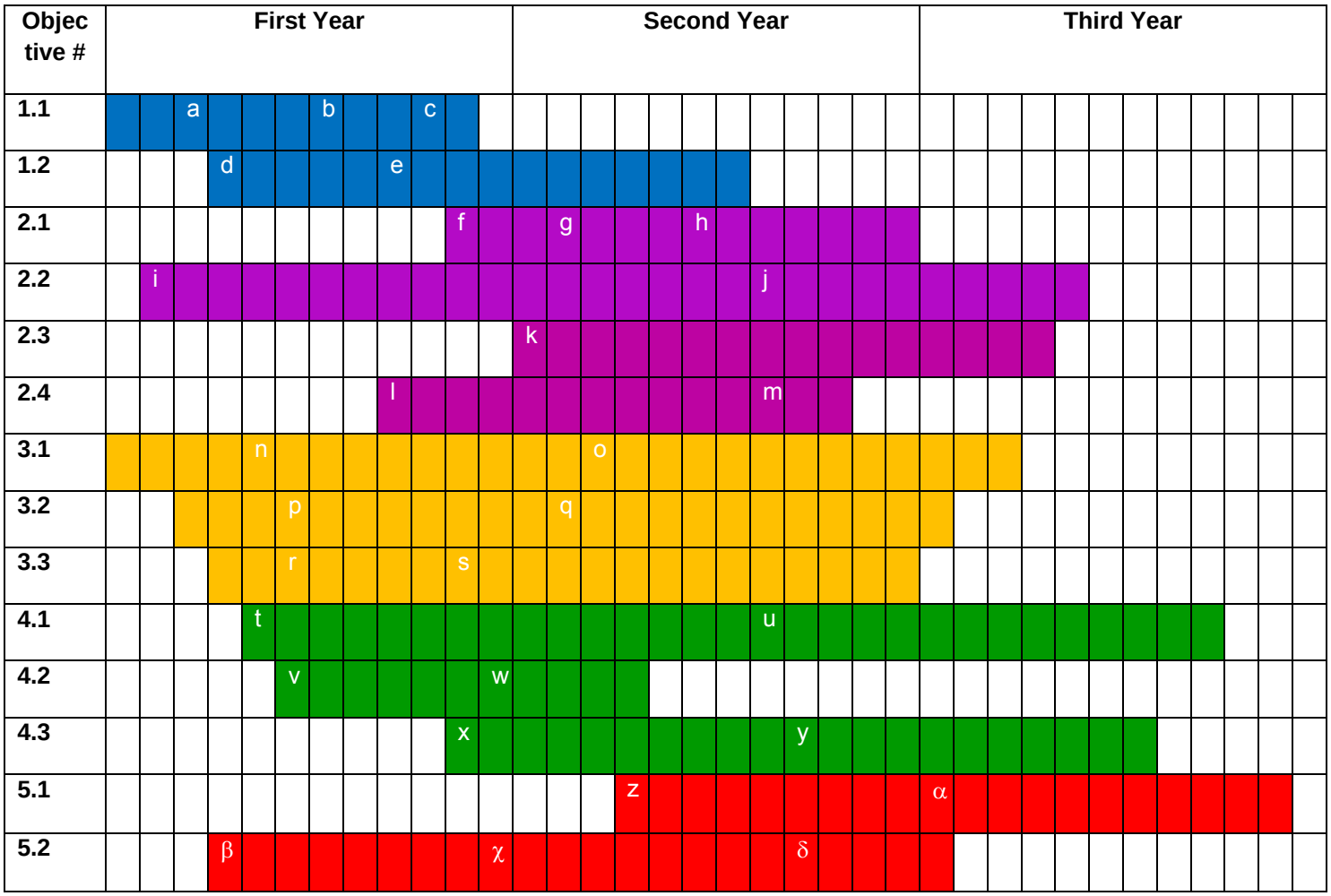
Hospital Ramón y Cajal:

- High rate brachytherapy sources: Iridium-192, cobalt-60.
- Related dosimetry equipment: water phantoms, ionisation chambers.

Hospital La Paz:

- Full Positron Emission Tomography (PET) equipment in combination with computerized tomography (CT) for diagnostics.
- Different PET sources for spectrometry and dosimetry.

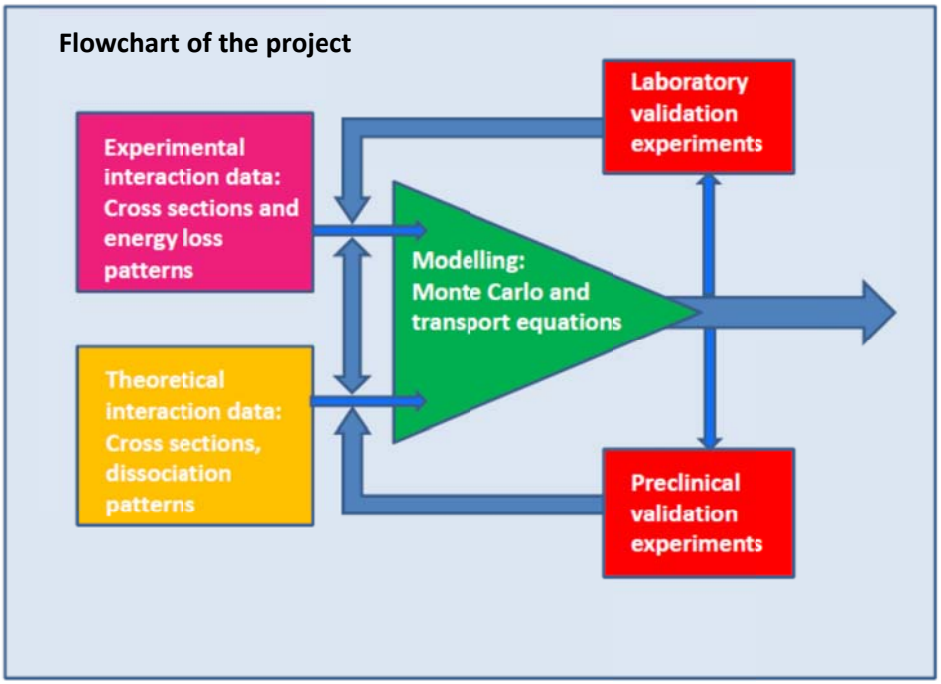
6. Objectives Timeline



Milestones:

[a]Construction of the hollow cathode discharge for anion beam production.
[b]Acquisition of electrical and control equipment for RF discharge generation.
[c]Construction of the RF discharge ion source.
[d]Acquisition of the laser system for photodetachment of negative ions.
[e]Installation of the bi-dimensional detector for the TOF spectrometer.
[f]Incorporation of the RF ion beam to the transmission-beam experimental system.
[g]Starting total proton scattering cross section measurements and energy loss in water and biomolecules.
[h]Comprehensive proton scattering from water data base for modelling.
[i]Starting induced dissociation to biomolecules by electron transfer from negative radical measurements.
[j]Installation of the bidimensional detector to the TOF spectrometer: angular resolution measurements.
[k]Starting induced dissociation to biomolecules by interaction with neutral radical measurements.
[l]Adaptation of the ANU positron beam for positronium interaction measurements.
[m]Positronium interaction database for modelling.
[n]Multicenter scattering calculations for electrons and positrons in water.
[o]Multicenter scattering calculation results for complex biomolecules (pyrimidine and purine derivatives).
[p]Polarisation potentials for O, C, N, H atoms in liquid water, to input into the IAM-SCAR procedure for modelling condensed molecules.
[q]Calculation of electron and positron scattering cross sections from condensed biomolecules.
[r]Molecular dynamics procedure to model dissociation of biomolecules.

[s]First calculations on dissociative processes in pyrimidine and purine derivatives.
[t]Updated data bases for modelling with the new theoretical and experimental cross section data.
[u]Incorporating radical interaction data to the MC simulation procedure.
[v]Defining the local temperature as a function of the energy deposition.
[w]Using the temperature as a reference parameter to control probability distribution functions and target densities.
[x]Developing transport equations for radical diffusion in gases and liquids.
[y]Combining radical generation models with radical transport equations.
[z]Starting experiments on electron interactions with condensed molecules (purine and pyrimidine derivatives) on Au surfaces.
[α]Starting experiments on proton interactions with condensed molecules (purine and pyrimidine derivatives) on Au surfaces.
[β]Construction of a tissue equivalent sample holder for living cell targets in aqueous media.
[χ]Analysis of radiation induced damage to living cells by LINAC x-ray beams, comparison with the model results.
[δ]Analysis of radiation induced damage to living cells by brachytherapy sources (I-125, Ir-192), comparison with the model results.



7. Contracting personnel requirements

In order to achieve the proposed objectives it will be essential to hire a full time technician (100%) devoted to the project. The professional profile would be an engineer with mechanical, electrical and electronics background to be involved in most of the tasks related to the general objectives 1 and 5. According to the proposed timeline of activities, a 32 month contract would be required.

C.2. EXPECTED IMPACT OF THE RESULTS

1. Scientific-technological, social and/or economic impact

The **fundamental processes** we propose to study in this project (ion scattering cross sections and energy loss, induced dissociation by charge transfer, multicentre scattering calculations, quantum molecular dynamics calculations for complex molecules) are crucial to understanding basic radiation-matter interactions and therefore we expect the results to be

published in the most relevant journals of the field (Physical Review Letters, Physical Review A, Journal of Physical Chemistry Letters, Physical Chemistry Chemical Physics, Journal of Chemical Physics, Journal of Physical Chemistry A, etc..).
Based on the fundamental studies, we propose technical developments (radiation measurement devices, simplified ion beam systems, modelling procedures) with possible technological applications that we expect to be published in applied radiation and instrumentation journals (Applied Physics Letters, Journal of Applied Physics, Radiation Research, International Journal of Radiation Biology, Physics in Medicine and Biology, etc..).
The estimated numbers of publications and PhD theses during the three years of the project are the following:
- 50 International publications in high profile journals (impact factor higher than 2.0).
- 40 Contributions to international conferences, meetings and workshops (at least 10 as an invited speaker).
- 4 Chapters in international books (by invitation).
- 4 PhD Theses submitted by members of the working group.

The multinational composition of the present working group ensures an international dissemination of the results. As already mentioned, research projects with similar objectives as those proposed here are currently running, or under evaluation, at the EU level and in other countries such as Australia, Korea, Japan and the USA.

The **radiation models** developed in this project, once validated by preclinical experiments, could constitute an excellent complement for treatment plans in radiotherapy. Additionally, they will provide reliable dosimetric tools for advanced radiotherapy techniques (hadron therapy in combination with nanoparticles as radiosensitizers). Although these latter techniques are not currently available in Spain, their implementation is imminent and therefore the scientific and clinical communities need to be technically prepared. These new techniques will represent an important improvement to the health system and social service. This is also an excellent opportunity to train young researchers for their future careers which are needed to pursue advanced scientific and technical activities in different societal environments (as professional at hospital/clinical units, companies) that deal/make use of radiation for treatment purposes or health carers. These students will also benefit from the installed capabilities and know-how of this consortium which has been in the fore-front of the most relevant achievements at the international level.
From the **economical** point of view, the multiscale modelling procedure proposed for development in this project could be distributed as a commercial product. This project works in close collaboration with appropriate companies to incorporate any output into their respective commercial activities: Spain (Anaxomics Biotech S. L.), Europe (Quantemol, Chematech and MBN-Research Center) and other countries (Gammasonics Ltd.), ensuring the installation and technical service as demanded by healthcare customers.
The **added value for these companies** is to test and characterize their products with the foremost technologies in Europe, and to exploit the knowledge and know-how of European scientific experts to further improve the quality and the application of their products (in particular nanoagents and software applications). They also expect new ideas to orient their innovation strategy and to develop new products regarding the medical needs of radiotherapy (with particular regard to the medical doctors and professionals of HPH, HLP and HRC involved in this project).

Expected results of the Project (2017-2019)

Result	Quantity (if applies)	Description

Scientific publications	50 articles	High profile publications with average impact parameter >2.5
Books	4 book chapters	Contribution to international editorial projects by invitation
Contributions to international conferences	40 contributions (more than 10 invited lectures)	International conferences on atomic and molecular interactions (ICPEAC, ECAMP, MOLEC) and biomedical applications of radiation (RADAM, ASRT, IRPA)
PhD Thesis	4 PhD thesis	Members of the working team submitting the PhD within the proposed activities
Technical documents	2 Complete manuals and guides of operation for the new experimental designs	Low energy proton scattering measurements operation system and crossed beam apparatus for anion and neutral radical interactions
Patents	1 Novel modelling software for nanodosimetry	Integrated Monte Carlo and transport equation programmes to evaluate radiation damage in terms of induced molecular dissociation (in collaboration with the associated company MBN-Research Center)
Databases for modelling purposes	1 Low energy secondary particle interactions (electrons, positrons, positronium and radicals) with water in different aggregation states	Contribution of this study to the big database project launched by the associated company Quantemol
List of characterised nanoagents	1 Compilation of properties nanoparticles and molecular reactive	Public document (available on the web)derived from the validation experiment with the collaboration of the associated companies Chematech and Anaxomics.
4 international project proposals	3 EU project submission to the Marie-Curie (2) and COST Action (1) programs. 1 Austrarial Reseach Council (ARC)-Discovery Project	1 Marie-Curie ITN on radical interactions and the other, in collaboration with the associated companies, on modelling radiation damage. The COST action will be also focused on modelling. The ARC project on positron and positronium interactions, transport, and dosimetry

2. **Dissemination plan:**

Dissemination of the scientific results of PRIOR will be achieved through publications and presentations at scientific meetings. Co-authorship of scientific papers by project members

will be one measure of the success of the project, and will be based on mutually agreed and internationally accepted standards for joint contributions in terms of intellectual development, documented effort and authorship of the work. Internal communication within PRIOR institutions will be conducted by regular e-mail contact, remote video conferencing and regular meetings. The internal documentation will be shared via Dropbox, for which every partner institution has access all the time.
Scientific and technological (including software) advances will be presented at related EU conferences open to scientific, industrial and clinical communities. PRIOR will have a strong world-wide web and social media presence to disseminate its results to a wider range of audiences. We will also produce an electronic newsletter both for project members and a wider audience, again using best practice from EU programmes in which the members of the project are involved. Moreover a webpage will be implemented in order to share and disseminate results and achievements with external audience. The website will be up-loaded and maintained on a regular basis, to keep the audience up to date with all the related developments and respective fall-out occurring even after the project end. Finally, we propose a series of seminars for the general public on radiation effects and their potential benefits in medicine, where we plan to have also a dedicated portal with updates and more relevant (general) information.

3. **Transfer of results**

As mentioned earlier, the integrated modelling procedure proposed here is expected to be distributed as a commercial product. Thanks to the previously noted close collaboration with experienced companies (Anaxomics, Quantemol, Chematech and the MBN Research Center), supplying medical instrumentation and software support, the link with possible customers is guaranteed.
This particular outcome could also be the subject of patenting and/or utility models.

C.3. TRAINING CAPABILITY OF THE APPLICANT TEAM

Due to the balance between fundamental and applied science, PRIOR represents a perfect framework for training young researchers with state-of-the art experimental and theoretical tools. The research group is formed by university professors, senior researchers, technical specialists, experienced radiophysicists, radiobiologists and medical oncologists together with early stage researchers. The daily activities and interaction with experts will give the young researchers a complete and wide-ranging view of the field, and help them develop knowledge and understanding of how to find the appropriate solutions. In addition young PRIOR researchers will attend specialised courses organised by the senior members of the group. Selected course topics include: Radiation-matter interaction processes - theory and practice, Monte Carlo simulation procedures, Medical dose planners for radiotherapy, Dissemination and Outreach activities.
In the last five years 4 members of the research teams of the previous projects obtained their PhD degree: A. Muñoz Roldán (2010), M. Fuss (2013), A. G. Sanz (2014) and J. C. Oller (2015). In addition 4 others are currently under the First Investigator's supervision and are performing their research advanced training reading for a PhD degree within the next 3 years.

C.4. ETHICS AND/OR BIOSECURYTY ISSUES

During the realization of the PRIOR activities and objectives, fundamental ethical principles will be respected and the participants will ensure compliance with ethical requirements. They will conform to current legislation and regulations in the countries where the research will be carried out. The PRIOR project does not include any experiments on animals.