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Importance of Fluorine and Fluorocarbons in Medicinal Chemistry and Oncology

Farid Menaa[1]*, Bouzid Menaa[2] and Olga N Sharts[1,2]

[1]*Fluorotronics, Inc., Department of Oncology, Stem Cells and Nanomedicine, 2453 Cades Way, Bldg C, San Diego, CA 92081, USA*
[2]*Fluorotronics, Inc., Department of Chemistry and Nanobiotechnology, 2453 Cades Way, Bldg C, San Diego, CA 92081, USA*

Abstract

Carbon-Fluorine (C-F) can serve as a molecular tag for many applications in medicinal chemistry and oncology such as identification (i.e. screening), imaging (i.e. tracing) and analytical characterization. Thereby, fluorination, a chemical process to add a fluorine atom into a single molecule or a complex matrix materials (e.g. compounds) is largely used in the pharmaceutical field to confer some interesting properties to cancer drug compounds (e.g. enhancement of bioavailability). It is further more recently used for labelling some biological molecules of interest (i.e. peptides, nucleic acids) or nanomaterials (i.e. nanoparticles) which are of high importance for cancer chemo- and biotherapy (e.g. immunotherapy) as well as for tumor (*aka* tumour)/cancer imaging (i.e. staging/prognosis, biodistribution, cancer diagnosis and therapy). Indeed, In addition to be easy-to-handle, efficient, soluble, smaller and cheaper, C-F bond is more stable than fluorescent dye, less toxic than fluorine radioisotopes, and less harmful than radio-waves. We have developed a patented technology called carbon-fluorine spectroscopy (CFS *aka* Spectro-Fluor®) along with methods and applications to not only specifically and sensitively detect C-F bonds in raw pure compound, complex materials but also to screen (e.g. drug discovery and drug security) as well as to trace F-molecules *in vivo* for improved medical care, particularly but not limited to the oncology sector (e.g. tumor/cancer imaging, development of new F- reagents, F-biomolecules, and anti-cancer agents).

In this paper, we reviewed and discussed the major physical-chemical properties of C-F bond, the main applications of fluorocarbons as well as the state-of-art imaging technologies that use fluorine for clinical and research and development (R&D) oncology purposes (e.g. drug design, drug discovery, drug delivery and molecular imaging). An emphasis is put on the use of safer, unlabeled fluorinated molecules thanks to the emerging and promising CFS-derived platform green technology that allows to reliably detecting unlabeled C-F molecules. Overall, we conclude that fluorine is a magical atom for molecular diagnosis and therapy that does not always need to be labelled.

Keywords: Fluorination; Carbone-Fluorine; Oncology; Nanomedicine; Pharmacy; Medicinal chemistry; Green chemistry; Green technology; Technological innovation; Carbon-fluorine spectroscopy; Nuclear magnetic resonance; Magnetic resonance imaging; Positron emission tomography

Abbreviations: ADCs: Antibody-Drug Conjugates; C-F: Carbone-Fluorine; C-T: Computed Tomography; CFS: Carbone Fluorine Spectroscopy; iRNA: Interference RiboNucleic Acid; miRNA: Micro iRNA; MRI: Magnetic Resonance Imaging; PCR: Polymerase Chain Reaction; ODN: Oligo Deoxy Nucleotide; PET: Positron Emission Tomography; NMR: Nuclear Magnetic Resonance; SiRNA: Small iRNA

Epistemology of Fluorine: From the Atom to Fluorocarbons

Fluorine (name derived from Latin *fleure*, meaning to flow) is the lightest of the halogens, the most reactive of all the elements. In 1886, a French chemist, Ferdinand Frederic Henri Moissant (1852-1907), was the first to isolate fluorine [1]. He used platinum electrodes to produce fluorine from the electrolysis of potassium fluoride (KF), a hydrofluoric acid. In 1872, Sir James Crighton-Browne postulated that a deficiency of fluorine was responsible for higher incidency of dental carries [2]. In 1892, a Belgian chemist Frederic Jean Edmond Swarts discovered the Cl/F exchange chemistry of the inorganic antimony trifluoride (SbF_3), a hydrofluoric acid (HF) widely used in dyeing and pottery [3]. The reaction, commonly called "Swarts reaction", has since been improved to be an industrial process for the preparation of organofluorine compounds, such as for the synthesis of dimethyl and trimethyl chlorosilanes [4].

Although fluorine is the thirteenth most abundant element in the earth's crust, fluoride concentrations in surface water are low and fluorinated metabolites are extremely rare [5]. Indeed, up-to-date, only 13 naturally occurring fluorinated organic compounds are known. Among them, we can cite the bacterial fluorinating enzyme 5'-fluoro-5'-deoxyadenosine synthase used by *Streptomyces cattleya* to naturally catalyze a fluorination reaction [5]. This microorganism can form carbon-fluorine (C-F) bonds using aqueous fluoride through a nucleophilic substitution mechanism.

This particular rarity of natural fluorination is of high industrial importance, with applications in pharmaceutical, biomedical, agrochemical and materials products.

Carbon-Fluorine Properties and Effects

The C-F bond is the most polar bond in organic chemistry, and thus the bond has a relatively large dipole moment with a significant -ve charge density on the fluorine atom and correspondingly a +ve

***Corresponding author:** Farid Menaa, Department of Oncology, Stem Cells and Nanomedicine, 2453 Cades Way, Bldg C, San Diego, CA 92081, USA, E-mail: dr.fmenaa@gmail.com

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charge density on carbon [6]. Because the C-F bond has a much greater dipole moment than does the carbon-hydrogen (C-H) bond, a stronger binding with dipolar water might be expected [7]. The electrostatic nature of the C-F bond renders it the strongest one in organic chemistry [6]. Further, C-F displays isoelectronic effects to oxygen (-O) atom and hydroxyl (-OH) group, and the high electronegativity of fluorine (-F) frequently alerts chemical reactivity. However, the (-F) atom itself is almost non-polarizable, and thus, despite the charge localization on (-F), it is a poor hydrogen-bonding acceptor [6]. Although the polarizability of (-F) in the C-F bond is relatively low, considering its position in the periodic table, the dispersion interactions of C-F with water are reasonably expected to be more attractive than those of C-H with water [8]. Therefore, a fluorocarbon surface could be argued to be more hydrophilic than the corresponding hydrocarbon. A plausible resolution could be that the fluorocarbon with a molecular cross-section of 28.3 $Å^2$ [9] occupies sufficiently more volume and surface area in water than the corresponding hydrocarbon with molecular cross-section of 18.9 $Å^2$ [10]. It has recently be found that (poor) interaction of water with a hydrophobic solute/surface, such as fluorinated surfaces, is primarily a function of van der Waals interactions and is substantially independent of electrostatic interactions [7].

Overall, fluorination displays the following properties [11]: (i) enhancement of thermal stability (C-F: 10^7 Kcal/mol), (ii) increase of lipophilicity and hydrophobicity, (iii) improvement of the molecular bioavailability, and (iv) capability of mimicking enzyme substrate (comparable in size to H, 1.47Å *versus* 1.20Å).

Eventually, organofluorine affects nearly all physical, adsorption, distribution, metabolism, and excretion properties of a lead compound. Its inductive effects are relatively well understood (e.g. enhancement of bioavailability by reducing the basicity of neighboring amines). In contrast, exploration of the specific influence of C-F single bonds on docking interactions, whether through direct contact with the protein or through stereoelectronic effects on molecular conformation of the drug, remains poorly characterized and needs more attention.

Fundamental Applications of Fluorocarbons in Oncology

The specific features of the fluorine in the formation of fluorocarbons make it attractive in the design of non-viscous but polar organic compounds, with a polarity limited to influencing the intramolecular nature of the molecule and intermolecular interactions with the immediate environment [6]. C-F bonds are unique in nature, more stable than fluorescent dyes due to their covalent interactions, much less toxic than radioisotopes, certainly less harmful at long-term exposure than radio-waves while inexpensively incorporated into molecules [12,13]. Therefore, C-F bond can generally be used as [12,14-18]: (i) a molecular security label to enhance the safety of an anti-cancer agent (i.e. useful within a prevention and banning program of counterfeited or substandard drugs), (ii) tracing an anti-cancer compound during the synthesis or the production cycle, providing necessary improvement in productivity and efficiency across various stages of the pharmaceutical development (i.e. discovery, synthesis and production cycles, clinical and post-approval stages), subsequently bringing the product faster to the market, (iii) internal (e.g. *ex-vivo*, *in situ*, *in vivo*) and/or external labels (e.g., surface, *in vitro*) of pharmaceutics (e.g. drugs) and/or biologics (i.e. peptides, proteins including antibodies, nucleic acids, cells) and/or various nanomaterials (e.g. gold nanoparticles, fullerenes including nanocarbon tubes, diamondoids, nanogels, nanoemulsions, nanoporous silica glasses, lipid-based nanopolymers) to characterize them (e.g. identification, screening, detection, assessment of biodistribution, metabolism, structure and function), as well as to validate or design new bio-therapeutics (e.g. F-nanoencapsulated anti-cancer drugs) with enhanced bioavailability or new tracers (i.e. unlabeled C-F), improved stability and less toxicity for long-term imaging and/or pharmacological studies (e.g. progressive/controlled drug release to targeted tumor).

Thereby, fluorine substituents have become a wide spread and important drug component in pharmaceuticals, particularly for the pharmaceutical oncology segment. Thereby, thanks to the development of safe and selective fluorinating agents, more than 50% of the marketed drugs are fluorinated, including many anti-cancer agents such as fluorinated taxane anticancer agents and 5-Fluorouracil (5-FU) (Figure 1), this later being an anti-cancer compound employed for several decades since its discovery in 1957 by Charles Heidelberger et al. [12,13,19-22].

Also, fluorinated solvents and/or reagents for biological and clinical use in oncology are valuable. It is the case of perfluocarbons (e.g. perfluorodecalin, perfluorobron) which can serve as red cell substitutes (*aka* artificial blood substitutes) for untransfusable patients with severe cancer-induced anemia and hypoxia [12,13,23-25], and also as fluorine tumor imaging agent [26,27].

More recently, fluorinated analogues of the canonical α-L-amino acids have gained wide spread attention as building blocks that may endow peptides and proteins with advantageous biophysical, chemical and biological properties [28]. Recently, we developed a new molecular approach to label proteins and reliably detect them using non-labelled fluorinated aromatic amino-acids along with the use of the unique carbon-fluorine spectroscopy (CFS) [29]. Thereby, we were able to detect biomarkers of cancers as well as transcriptional targets of tumor suppressor genes (e.g. p21 Waf1/Cip1-downstream target of p53, the "guardian of the genome") after *ex vivo* protein fluorination using cancer cells and an original established protocol involving only one unlabelled non-fluorinated antibody [29].

Further, the use of fluorinated-amino acids to increase the stability of oligomeric structures such for anti-cancer peptides is valuable, but still at its premisses. Indeed, peptide therapeutics is a promising field for emerging anti-cancer agents [12,30]. Benefits include the ease and rapid synthesis of peptides and capacity for modifications. Current research focuses on developing peptides that can (i) serve as

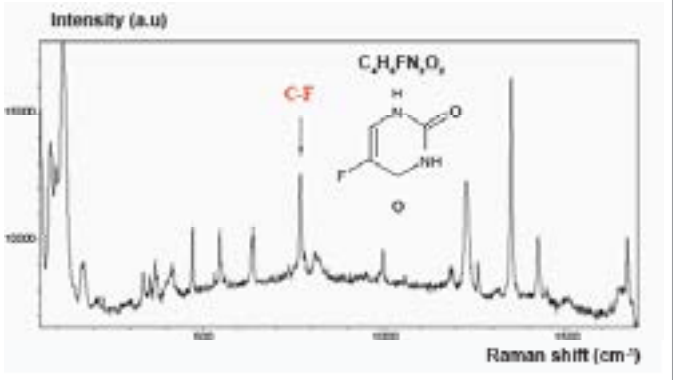

Figure 1: Carbon-Fluorine Spectrum of 5-Fluorouracil, the oldest synthetic anti-neoplastic agent. Excitation was performed at 510.6 nm by copper-vapour pulsed laser of 100 mW average power. 60 fg in 100 µm spot size was largely sufficient to detect this fluorinated drug.

tumor targeting moieties (i.e. tumor-homing peptides that can carry biologically active cargo to tumors or tumor vasculature), and (ii) permeabilize membranes with toxic consequences for tumor cells (i.e. apoptotic or necrotic cell death through disruption of cell or organelles membranes). For instance, amphiphilic peptides with clusters of hydrophobic and cationic residues showed considerable anti-cancer toxicity [30]. The main challenge still lies on improving delivery to tumors, minimizing non-specific toxic effects and discerning pharmacokinetic properties in order to produce a powerful therapeutic peptide for cancer treatment. Interestingly, a very recent study indicated that ^{18}F-labeled peptides can be reproducibly prepared as stable aluminium-fluorine (Al-F) complexes with good radiochemical yield and high specific activity using a simple, one-step, lyophilized kit followed by a rapid purification through solid-phase extraction (SPE) then provided the ^{18}F-peptide ready within 30 minutes for patient injection [31].

Besides, the development of F-antibodies (i.e. durable bi-functional antibody that can be used both as F-biodrugs and F-biotracers) is also highly desirable, in particular the monoclonal ones, which can be then both specific and sensitive and might overcome some important limitations such those associated with current antibody-drug conjugates (ADCs) for onco-therapy (e.g. aggregation, insolubility) and/or with cancer immunotherapy protocols (e.g. low sensitivity or specificity) [12].

Eventually, those applications using labelled fluorine are, for some of them, widely used following diverse protocols involving radioisotopes, fluorescent dyes. Nevertheless, there is still a paucity of reports regarding the alternative use of unlabeled C-F bond. Therefore, the use of C-F bond as an unlabeled tag remains undeniably challenging in oncology and cancer stem cells research since it has shown good promises for analytical characterization of F-molecules (e.g. F-drugs, F-biologics) and F-applications (e.g. compounds screening and tracking, metabolism-based assays, early imaging diagnosis, nanomaterials-based (bio)drug delivery for efficient therapy) [12,13,29].

Nowadays, only carbon-fluorine spectroscopy (CFS) - later named Spectro-Fluor® -, an innovative and powerful technology recently pioneering by our group and further developed for multiple uses (e.g. biomedical, pharmaceutical, food, material and environmental sciences), is really capable to qualitatively and quantitatively detecting unlabelled C-F bonds, and so enlarging applications in oncology (e.g. cancer drug discovery and delivery, cancer imaging) [12,13,29]. We practically expect from our previous *in-vitro* and *ex-vivo* studies many advantages over the conventional molecular imaging systems for *in-vivo* applications (e.g. in terms of safety, toxicity, comfort for the patients and small animals; reliability, cost-effectiveness, practical use for the practitioners and researchers).

Eventually, nucleic acid-based fluorinated derivatives such as nucleosides or oligonucleotides (*aka* bioprobes or primers) connected to highly fluorinated chains or labelled with one or more fluorine atoms have been developed [32,33]. They have been increasingly investigated due to their high potential for biomedical applications (e.g. radiofluorinated oligodeoxynucleotide (ODN) probe for use along with positron emission tomography (PET)) [33,34]. In oncology, this development has indeed its importance considering that some F-nucleic acids such as F-interference RNAs (e.g. siRNAs, miRNAs) can be used to more efficiently silent some genes and proteins of interest [35]. Also, F-oligonucleotides could be used to enhance the reliability of gene amplification by polymerase chain reaction (PCR). They have been recently used to image gene expression changes (i.e. uptake and distribution) in human tumor/cancer cells to monitor early tumor response to treatment using liposome-transfected ^{18}F-labeled oligonucleotide probe [36].

Eventually, fluorination of cancer cells, cancer progenitor cells and "cancer stem cells" (*aka* initiating and/or propagating cells), using green approaches, shall provide further insights on carcinogenesis, cancer prognosis and cancer diagnosis.

Fluorous-Technologies for Clinical and R&D Oncology

Nuclear Magnetic Resonance (NMR)

Fluorine NMR-based spectroscopy has recently emerged as a versatile, reliable and efficient tool for performing binding and biochemical assays. Different libraries of fluorinated compounds, designed by maximizing the chemical space around the fluorine atom, are screened for identifying binding fragments and for detecting putative fluorophilic hot spots on the desired macromolecular target. A statistical analysis of the fluorine NMR chemical shift, which is both a marker of the fluorine local environment and X-ray structures of fluorinated molecules, has resulted in the development of the 'rule of shielding', useful method for 'lead optimization' and designing novel chemical scaffolds that recognize distinct (onco-) protein structural motifs [37]. Interestingly, recent studies [38,39] reported the usefulness of ^{19}F-amino-acid (i.e. 5-fluoro-DL-tryptophan (5FW) or 3-fluoro-L-tyrosine (3FY)) as a dual NMR and fluorescent probe of α-synuclein, a molecule which plays a central role in Parkinson´s disease (PD). Indeed, analysis of such types of proteins (i.e. onco-proteins), highly proned to conformational changes (and aggregation), presented difficulties with conventional proton NMR, but according to the authors, it can be circumvented when non-native ^{19}F nuclei are incorporated at specific sites within the amino-acid sequence [38]. *In fine*, ^{19}F-NMR is then particularly suitable for characterization of unfolded structures because ^{19}F chemical shifts are highly sensitive to local environments and conformations [38]. Subsequently, it could be used to monitor the insertion and conformation changes of a ^{19}F-labeled cell penetrating peptide attached to the N-terminus of a protein (e.g. α-synuclein) upon interacting with the cellular plasma membrane, because of the ^{19}F resonance decrease [39]. Furthermore, the incorporation of fluorine analogs of fluorescent amino acids (e.g. 5FW) allows for complementary studies of protein microenvironment via fluorescence spectroscopy [38] and protein sub-localization within the cell via confocal fluorescence microscopy [39].

Magnetic Resonance Imaging (MRI)

^{19}F-MRI spectroscopy is a a promising tool for monitoring (cancer-) stem cell-based therapy, especially when those cells are labeled with perfluorocarbons (PFCs). Indeed, cells conventionally loaded with functionalized supramagnetic iron oxide nanoparticles (SPIONs) appear hypo-intense on MR images but the contrast generated by iron oxide labeled cells is neither specific due to ambiguous background nor quantitative. ^{19}F-MRI can also be used for applications to assess the metabolism and/or biodistribution of F-drugs.

A recent study using human neural stem cells (NSCs) efficiently labeled with ^{19}-perfluoropolyether (PFPE) with little effects on viability or proliferation and differentiation capacities, has shown for the first time that ^{19}F-MRI can be utilized for tracking human NSCs in brain implantation studies, which ultimately could aim for restoring loss of function after acute and neurodegenerative disorders [40]. This study suggests that stem cells (SCs) involved in the initiation and/or propagation of tumor cells can also be labeled and monitored by

^{19}F-MRI, which is tremendously useful for better understanding the general oncogenesis/carcinogenesis process (e.g. cancer staging, dynamism of tumor microenvironment). Moreover, the labeling of stem cells can be useful to control *in situ* tissue engineering and so, become very useful in regenerative medicine. For instance, a very recent study reports the good performance of ^{19}F-MRI to describe the association of the central zone with more aggressive prostate cancer [41]. Other studies used chemical-shift selective ^{19}F-MRI to directly detect a specific intra-tumoral F-drug (e.g. 5-FU) trapping/retention (i.e. in solid tumors such hepatoma, in case of 5-FU), biodistribution (i.e. specific tissue uptake such as liver and kidneys, in case of 5-FU) and catabolism (i.e. major catabolite such as α-fluoro-β-alanine was detected in case of 5-FU) in tumor-bearing rats [42,43].

Besides, MRI can be coupled with other imaging technologies such as computed tomography (CT). As an example, 3D images and 2D models based on MRI/CT image fusion provided a powerful tool for the visualization of jaw tumors by defining the relationship between tumors and adjacent structures, thereby assisting the subject-specific preoperative planning, surgical simulation, and intraoperative guidance for tumors [44]. MRI/CT also obtained a better estimation of the organ tumor size than CT alone, which tends to overestimate it, and is then a quite useful combination in 'radiotherapy planning' for localized cancers (e.g. rectal carcinoma, prostate carcinoma can be treated by more adapted radio-therapeutic doses consequently decreasing organ complications) [45,46].

Positron Emission Tomography (PET)

PET is a common and powerful analytical method for medical diagnosis, particularly in oncologic sector where it was extensively used for many years. Indeed, PET is a non-invasive imaging technique that provides functional or metabolic assessment of normal tissue or disease conditions and is playing an increasing role in cancer radiotherapy planning. The application of fluorinated radiotracers in PET studies for imaging in cancer patients, include 2-^{18}F-fluoro-2-2-deoxy-D-glucose later referred to as ^{19}FDG, fluorinated nucleosides, fluorinated amino-acids (e.g. ^{18}F-fluoroethyl-l-tyrosine (FET), ^{18}F-fluorothymidine (FLT), ^{18}F-fluoro-α-methyltyrosine (FMT)) as well as fluorinated peptides among others. FDG is the « working horse » in oncology, including neuro-oncology, *albeit* FET is highly useful for glioma detection. FDG is a glucose analog that is taken by cells in a similar fashion as glucose, phosphorylated by hexokinase to ^{18}F-FDG-6-phosphate but cannot undergo further glycolysis, and hence is trapped in the cell. In fact, more studies are required to really understand the full metabolism of ^{19}FDG. ^{18}F-FDG or ^{19}F-FDG are the most often applied radiolabels in such studies because of [47]: (i) increased glucose metabolism in most types of tumors, (ii) their low positron energy with high abundance (96%) and a path length in tissue of approximately 0.1-0.2 cm, (iii) their relatively long half-time (110 min.) of the isotope, allowing extensive and complex imaging protocols including dynamic studies and investigations of slow metabolic processes, and (iv) their relatively good efficacy and safety. The low emitting energy results in a marginal risk for the patient because of the short range as well as the limited dose of emission.

Thereby, it has most recently shown that, in the evaluation of a regional lymph node based in primary Merkel cell cacinoma (MCC), a rare but agressive skin cancer, ^{18}F-PET (*aka* PET-FDG) is significantly more sensitive and equally specific than traditional CT and, both techniques were more sensitive than clinical examination alone [48]. Interestingly, amino-acid analogs such ^{18}F-choline and ^{18}F-acetate can alternatively be used to FDG because of their higher specific to tumor cells, so they could play an important role both in differentiating cancers from benign conditions and in diagnosing cancers with either low FDG uptake or high background FDG uptake [49,50].

Further, the coupling PET/CT has been used in a most recent study to detect distant metastases (DMs) increase -especially in the lung (93%) and bone (43%) - with high sensitivity (86%), specificity (84%), accuracy (84%) in patients with recurrent head and neck squamous cell carcinoma (HNSCC) [51].

Interestingly, PET can also be coupled with MRI. Indeed, PET/MRI fusion seems to be highly accurate in T(tumor)-staging of tumor entities for which MRI has traditionally been favored, (e.g. HNSCC). By adding functional MRI to PET, PET/MRI may improve diagnostic accuracy, owing to its capability to differentiate scar tissue from recurrence of tumors (e.g. rectal cancer) and so, play an important role in cancer staging. With regard to N(node)-staging, PET/MRI did not seem to provide considerable benefits as compared to PET/CT and provided similar N-staging accuracy when applied as a whole-body staging approach [52]. Besides, a recent study showed that PET/MRI fusion is superior to PET/CT in characterizing pancreatic tumors, offering better mapping and fusion image quality [53]. Corroborating the importance of PET/MRI, another recent study that aimed to compared FDG PET/MRI, FDG PET/CT, MRI and CT imaging, showed that PET/MRI was the most reliable for focal invasion assessment and tumor size delineation in patients with advanced buccal squamous cell carcinoma (BSCC), while PET/CT had the lowest confidence level which may limit its use in the clinical setting [54]. Nevertheless, a very recent comparative study assessing the performance FDG PET/MRI with FDG PET/CT as the reference standard in the staging of lung cancer (i.e. bronchial carcinoma) showed that PET/MRI had as good potential as PET/CT to characterize tumor lesion (i.e. pulmonary masses) and tumor stage with quality [55].

Eventually, advanced studies evaluating the reliability of FDG-PET/CT compared to ^{19}F-MRI/CT in cancer patients are requested.

Carbon-Fluorine Spectroscopy (CFS)

As we could observe from conventional imaging techniques, quantitative and qualitative analyses of fluorinated molecules represent an important task. Nevertheless, the common molecular detection methods include molecular labelling using radioactive isotopes or fluorescent dyes. However, these types of detection require expensive safety and precautionary measures (e.g. especially with isotopes) or have limited sensitivity and stability (e.g. case of fluorophores *aka* fluorochromes). In this context, we have developed and validated CFS, a green technology derived from a non-competitive family of devices called PLIRFA™ ("Pulsed Laser Isochronic Raman and Fluorescence Apparatus") for multiple R&D applications across the biomedical, pharmaceutical and life sciences spectrum [12,13,29]. The key feature of the patented CFS is based on the discovery of a characteristic Raman signature of carbon-fluorine bond(s) in the fingerprint spectral area of 500 cm^{-1} and 800 cm^{-1} allowing detection, characterization, imaging, monitoring, screening and measurement of C-F utility, fluoro-nanomaterials, fluoroorganic compounds, fluoro-molecules, fluoroorganic impurities or fluoro-degradation products [12,13,29]. CFS not only represents an innovative, disruptive, green, affordable, cost-effective and flexible analytical tool of high resolution but also a reliable discovery tool notably in terms of reproducibility. Thereby, CFS represents a major advance over conventional Raman spectroscopy since it allows (i) highly specific and ultrasensitive detection (ppm-ppb level or <10 cells) of C-F bonds (-C-F, $=CF_2$, $-CF_3$); (ii) detection

and characterization of any other halo-organic bonds or unlabeled molecules regardless the physical state (solid, liquid or gas) which can be done via glass, polymer containers, or quartz vials; (iii) real-time analysis and ultrafast data acquisition (0.1 second per data point from 1000 average pulses); (iv) quantitative determination of any fluorinated substance since the emitted C-F bond(s) signal is directly proportional to the analyte concentration; (v) structural characterization of molecules (e.g. determination of molecules length with high resolution permitting to discriminate molecular analogs differing from only one carbon) ; (vi) preservation of the sample integrity (i.e. non destructive and non-invasive technology); (vii) analysis with little or no sample preparation (i.e. no solvents requirement); (viii) easy use and data interpretation (e.g. development of convenient and powerful softwares); (x) low maintenance (e.g., calibration); (xi) operation with one laser source functioning in 3 modes using adequate time-gating and time-delays: fluoro-Raman, general pulsed Raman, or two photons excitation/time resolved fluorescence; (xii) use of CFS anywhere thanks to a new generation of compact devices (e.g., portable convenient design); (xiii) the technology to be versatile, flexible and progressive (e.g. possibilities to be coupled to diverse technology platforms/ systems such as high throughput screening (HTS) systems (i.e. Arrays/ CFS hybrid device), chromatography (i.e. high-performance liquid chromatography (HPLC)/CFS), imaging (i.e. PET/CFS, laser confocal microscope (LCM)/CFS, atomic force microscopy (AFM/CFS), which are under development).

Although many studies have been performed *in-vitro* and *ex-vivo* to respectively characterize non-labelled C-F tagged molecules [12,13,29], ongoing promising studies are focused on molecular and tissue imaging *in-vivo*.

Conclusion

Despite recent advances in diagnostic and therapeutic modalities (*aka* theranostics modalities), cancer remains a major source of morbidity and mortality throughout the world. Moreover, the incidence of many cancers, including the skin, prostate, breast, and kidney cancers, continues to increase. The signature roles of fluorine in medicinal chemistry, diagnostic and therapy are now firmly established. The presence of fluorine in pharmaceuticals (i.e. radiopharmaceuticals, F-drugs) has had a major impact on a plethora of important medical applications, such as those cited above (e.g. treatment and imaging). The small attractive unlabelled C-F bond along with the innovative CFS technology, which aims to become the « gold standard technology » is offering huge green alternatives to the conventional technologies, and shall be undeniably an asset in the oncology and medicinal chemistry areas. Eventually, fluorine is a flourishing element that will very likely continue to contribute significantly in enhancing current and future medical advances (e.g. nanomedicine) by playing multifaceted roles.

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