Forty Years of ^{18}F-Labeled Compound Development in an Open Access Database

The success story of ^{18}F-FDG began in 1978 with the first publication of its synthesis by Ido et al. (*1*), followed in 1979 by the first images of ^{18}F-FDG in the human brain (*2*). The unexpected impact of ^{18}F-FDG contributed to the vigorous development of ^{18}F-labeled compounds and new products. Although data on more than 1,000 ^{18}F-labeled compounds have been published, many remain neglected or unexploited. The result is a lack of awareness of the potential applications of previously published ^{18}F radiopharmaceuticals. PET imaging combines the skills of various fields, including but not limited to nuclear physics, biology, chemistry, radiochemistry, and nuclear medicine. An open access database on ^{18}F compounds would contribute to the sharing of common knowledge that might enhance collaborative work and ensure a clearer overview of the potential of previous results.

Taking advantage of the growth of information technology, many open access databases or catalogs have been released (*3*). Two of these focused on imaging agents and/or positron-emitting compounds. From July 1998 to October 2004, Ren Iwata, PhD, from Tohoku University (Sendai, Japan) maintained a catalog of PET radionuclides and radiopharmaceuticals (*4*). The listing contains more than 1,600 references, the majority selected from 5 journals. Much of the content focuses on ^{11}C and ^{18}F isotopes and compounds, with their names or nicknames briefly classified by chemical classes or biologic targets. This work was not continued after 2004, and no relevant details on synthesis, biologic applications, or tests are included.

In 2004 the National Institutes of Health, through the Molecular Libraries and Imaging program, released the Molecular Imaging and Contrast Agent Database (MICAD), a free source of detailed information on molecular imaging probes and contrast agents, classified in chapters (*5*). In 2011, 1,000 chapters were available, with 42% (549 compounds) of database chapters describing PET imaging probes (~17% focusing on ^{18}F-labeled agents). MICAD (www.ncbi.nlm.nih.gov/books/NBK5330/) has the advantage of offering a search engine and direct links to PubMed, along with an extended description of probes and their applications. However, only 224 ^{18}F imaging agents (evaluated on humans and animals to yield in vivo data) have been entered into the database in the past 7 years, and the search engine is limited despite detailed descriptions for each compound. These drawbacks and the lack of a specific and exhaustive database focusing on ^{18}F-labeled compounds prompted us to build an open access database for researchers, students, authors, and reviewers in academic centers and radiopharmaceutical companies.

About DIRAC

The Database of Imaging Radiolabelled Compounds (DIRAC) was named in honor of Paul A.M. Dirac, 1933 Nobelist in physics, and his article published in 1931 introducing the theory of the antielectron (*6*). DIRAC is now available and open to the community at www.iphc.cnrs.fr/dirac.

To be useful, a database should include as many entries as possible along with a high level of data to enable the user to obtain both an overview and detailed information. The search engine should enable multifaceted searches to provide not only basic information on potentially interesting compounds but also a deeper view of specific topics. At the end of 2011 we began to build a database focusing on ^{18}F compounds published in the last 40 years. The database contains updated biologic and chemical data and associated selected references for each compound. As of September 1, 2012, the database included 1,036 ^{18}F-labeled compounds and 1,316 bibliographic references selected from more than 140 international peer-reviewed journals from 1971 to 2012. (Macromolecules were excluded and will be part of a planned extension of the database [*7*]). The content reflects the considerable work carried out by radiochemists and biomedical researchers as well as the expansion of ^{18}F-related publications over the past 4 decades. To ensure the validity and accuracy of selected references, the number of publications per year used in DIRAC was compared to the total number of ^{18}F-related published articles (extracted from PubMed). Almost 16% of the literature was selected for DIRAC, and a satisfactory correlation was seen between the numbers of selected papers and published articles each year.

Content

Initial data on more than 750 compounds were collected from ~140 scientific journals via publishers' Web sites or PubMed and Thompson Reuters Web of Knowledge. The list of compounds and references was cross-matched with Iwata's catalog and the MICAD database, resulting in identification of 200 and 25 additional compounds, respectively. ^{18}F-labeled products published in symposium abstracts were not added, excepted when they were mentioned in published articles or if they were closely related to already published structures.

For each compound a survey of the literature yielded biologic and chemical data that were used to build an accurate, updated, and integrated compound card. Each card contains a concise description of the ^{18}F imaging probe, its biologic data, a chemical drawing of the compound, and its names and most commonly used acronyms. Up to 4 names can be included for a single product, and we focused on the chemical name and the most commonly used acronym. Some compounds, however, are named differently by various authors, and some compounds share the same acronym.

The biologic data give an overview of tests performed, biologic targets of the probe, pertinent pathologies or biologic processes, and animal models used for metabolic, biodistribution, or PET imaging studies. Data included are the most representative of the biologic studies carried out with ^{18}F-labeled compounds and were chosen to give an integrated and, where possible, exhaustive view of results published for each PET probe. A brief classification of the development level of each PET imaging agent was originally planned, but the border between experimental and preclinical development was found to be too porous for an unambiguous classification. Only "not tested" and "clinical development" levels are included.

A chemical data field provides information on key chemical features or functional groups of the^{18}F-labeled molecules, and automated processes are mentioned when a fully described robotic synthesis has been published. More details about radiosynthesis (yield, specific radioactivity, precursor, and source of fluorine) might be desirable, but, in our opinion, selection and evaluation of such information could not be objective. In many cases, several syntheses have been

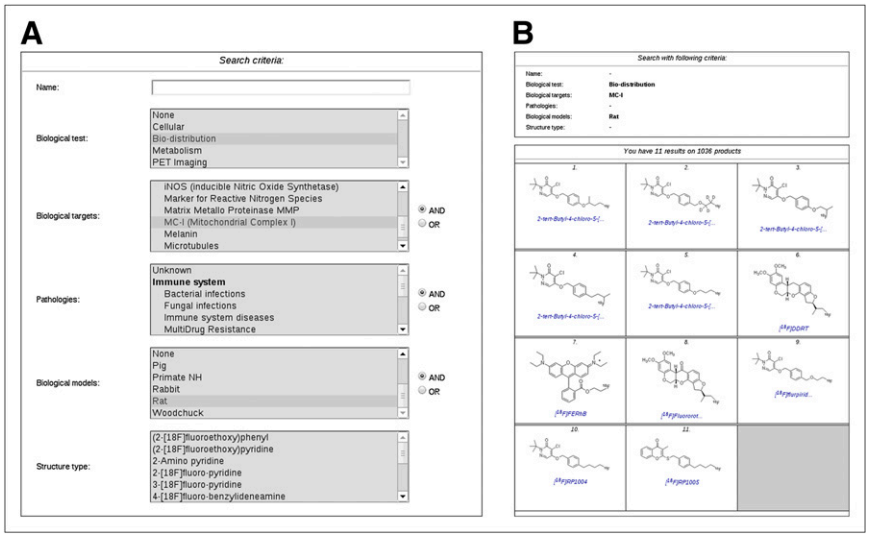

FIGURE 1. Screen capture of DIRAC (A) search window and (B) results window, in search performed using biodistribution for biologic test, rat as biologic model, and MC-I as biologic target.

reported, and pertinent chemical strategies are often related to the specific characteristics and plans of each laboratory. Moreover, rapidly evolving chemical methods will quickly "age" the validity of such data. One example is a recently published breakthrough in the use of nucleophilic ^{18}F-fluorine under palladium-mediated conditions for electrophilic aromatic substitution (*8*). The expansion of such a method will prompt a renewal in the radiosynthesis of many ^{18}F-labeled products.

The selected references box in DIRAC displays up to 10 reference titles related to the biologic application and synthesis of the title compound. Supplementary materials include the full list of available data for each field (targets, pathologies, animal models, chemical structures) with their respective occurrences in the database.

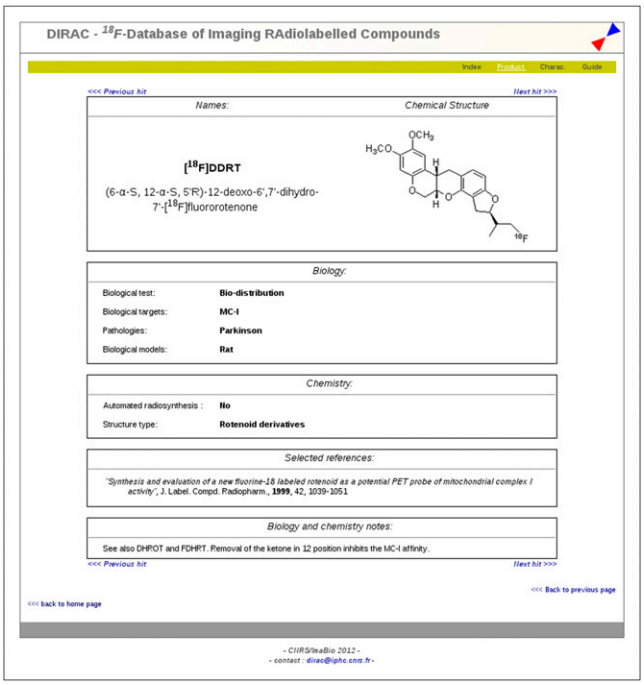

FIGURE 2. Screen capture of DIRAC product card.

The search engine uses a text box and 5 scrolling menus (and operator choices of AND and OR), enabling easy retrieval of results from the entire database (Fig. 1A). The results appear as a summary of the query along with a list of hits, their chemical structures, and first names. Each result is connected to the corresponding compound card. Figure 2 is the product card for ^{18}F-DDRT, a radiolabeled rotenoid-based probe targeting the mitochondrial complex (MC-I) under investigation for evaluation of Parkinson disease. The preliminary study was carried out on biodistribution in rats (*9*). The flexibility of the search engine allows easy retrieval of information that can be quite valuable for reviewers or authors. A search by chemical features gives the list of all compounds in the database belonging to the same category (eg, a search for tropane will give all tropane and nor-tropane derivatives). It can also display a general overview of the main chemical groups used with ^{18}F-fluorine for biologic applications.

Exploring the Database

Figure 1B shows the 11 compounds found when performing a search of ^{18}F-labeled molecules targeting MC-I and reported in biodistribution studies in rats. Figure 3 is an example of 10 selected chemical groups or key features and their occurrences in

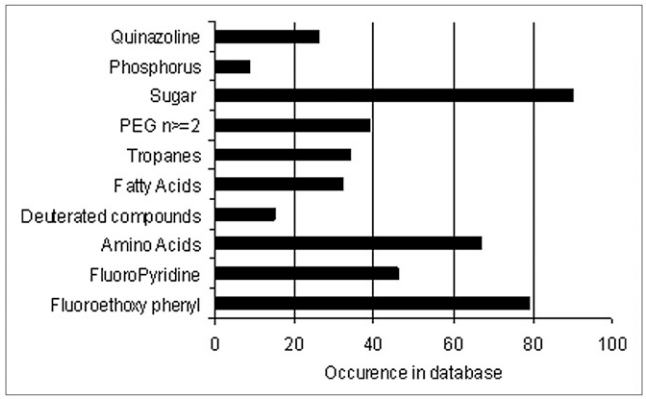

FIGURE 3. Selected chemical features or functional groups and occurrence in DIRAC.

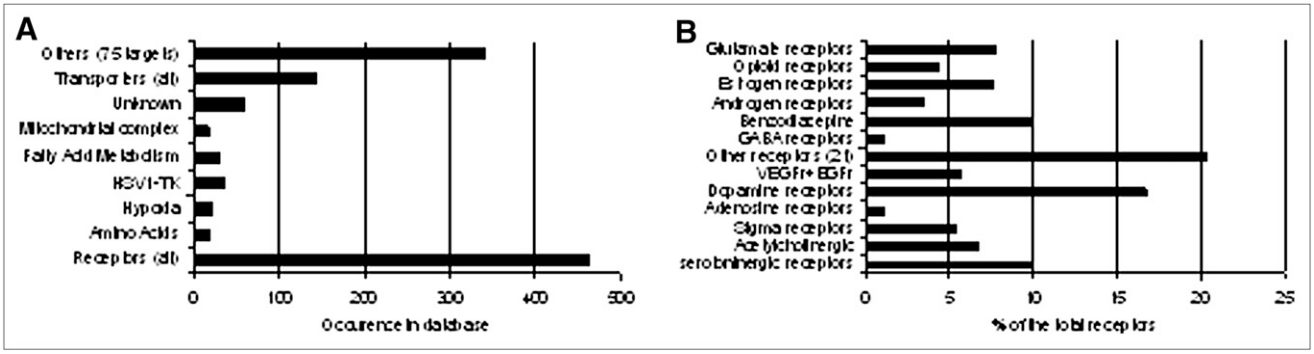

FIGURE 4. (A) Selection of biologic targets and occurrences in the DIRAC. (B) Percentage of occurrence of selected categories of receptors relative to total receptor occurrences in DIRAC. "Other receptors" entry regroups 21 subtypes of receptors, each accounting for <5%.

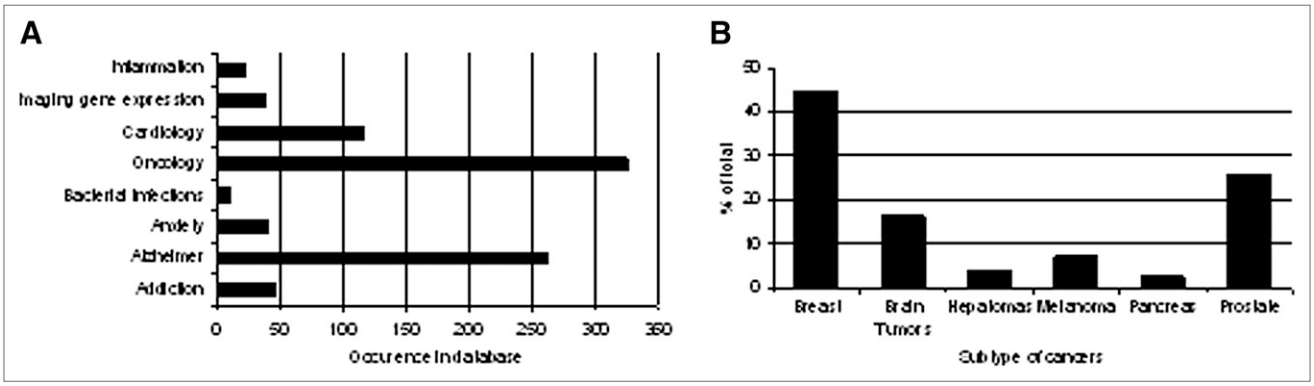

FIGURE 5. (A) Occurrence of selected pathologies in DIRAC. (B) Relative distribution (in percentages) of defined subtypes of cancer in DIRAC (undefined subtype excluded).

the database. Sugars, amino acids, and 2-^{18}F-fluoroethoxy-phenyl derivatives are among the most used. Tropanes and nor-tropanes represent only 34 compounds out of 1,036, but crossing the chemical search with the biologic targets shows that 76% target dopamine transporters.

The same approach conducted on biologic targets shows that receptors (all subtype fused) and transporters are the main targets of ^{18}F-labeled compounds (Fig. 4). A deeper look inside the receptors family can also be performed using the search engine. Figure 4B displays results obtained and highlights current interest in dopamine, serotoninergic, and benzodiazepine receptors.

The availability of a broad diversity of biologic models (especially knockout mice) offers the possibility to explore in vivo a growing number of pathologies in pertinent models. In 1998, Henry N. Wagner, Jr., MD, in "A brief history of positron emission tomography (PET)," declared "Today advances are being made chiefly in oncology, cardiology, and neurosciences." (*10*). Fourteen years later, oncology, cardiology, and neurosciences (especially neurodegenerative diseases) are among the most explored pathologies (Fig. 5). Other promising applications, such as gene expression imaging, are rapidly expanding as a result of progress in gene manipulation, modern molecular techniques, and therapeutic innovations (*11*).

An example of the potential of the database for retrieving relevant information is given in Figure 6. Starting from a chosen pathology and selecting various criteria, different levels of data can be obtained. Breast cancer is one of the major subtypes of cancer in the database. The main targets involved are receptors, and, among these, estrogen receptors are the most explored for breast cancer imaging. Forty-nine ^{18}F-fluorinated products designed for breast cancer imaging have been compiled in the database, 30 (61%) targeting (or intended to target) estrogen receptors, with 22 (73%) of these 30 including a steroid backbone in their chemical structures.

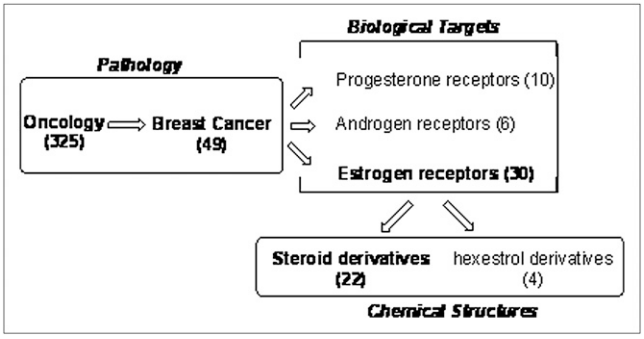

FIGURE 6. Scheme of information levels that can be displayed with DIRAC (numbers in brackets represent occurrence in each category).

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