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Carbon-11. The Unique, yet Neglected Radionuclide for Drug Research

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Carbon-11

Compounds labelled with Carbon-11 are well suited for assay of metabolic functions. As radiopharmaceuticals (“*tracer*”) they allow to follow (“*trace*”) metabolic pathways without alterations. Measurement is performed outside the body by registration of the annihilation radiation (511 keV) in coincidence of the detector systems applied in Positron-Emission-Tomography (PET).

PET registration primarily results in a physical signal as the result of the emitted radiation of the radionuclide within the tracer. Therefore, specificity and selectivity of the PET measurement are determined by the radiopharmaceutical concept of the particular tracer.

In the late 1980ies, the upcoming PET Method drew great attention to carbon-11 and paved the way for the direct application of the “*Tracer Principle*” for which G.de Hevesy was awarded the Nobel prize in 1943.

Properties of Carbon-11

❑ ***Short half-life of 20 min***

The short half-life means a very low mass of 10^{-6} g and even less as a whole body dose. Metabolic processes to be examined by the PET Method remain unaltered by the administration of ^{11}C tracer.

❑ ***Emission of positrons***

Registration as gamma radiation after annihilation; radiation penetrates the body barrier. Thus, measurement outside the body is performed in registration by coincidence detector systems of a Positron-Emission-Tomograph (PET).

❑ ***Introduction of carbon-11 into a molecule***

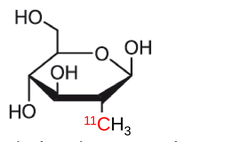
Labelling of a biomolecule applies a “*substitution*” of a carbon atom within the carbon skeleton by carbon-11. A large variety of synthetic routes allow the preparation of any ^{11}C tracer. Even more, the amount of radioactivity of the product is high enough for the subsequent experimental or medical measurements.

Examples of ^{11}C tracers

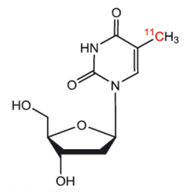
❑ ^{11}C-Methyl-2-deoxy-D-glucose
Assay of energy metabolism (tumors)

❑ ^{11}C-Vinblastine
Control of chemotherapy

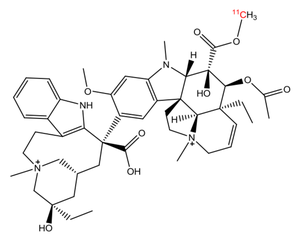
❑ ^{11}C-Thymidine
DNA synthesis (tumors)



^{11}C-Methyl-2-deoxy-D-glucose



^{11}C-Thymidine

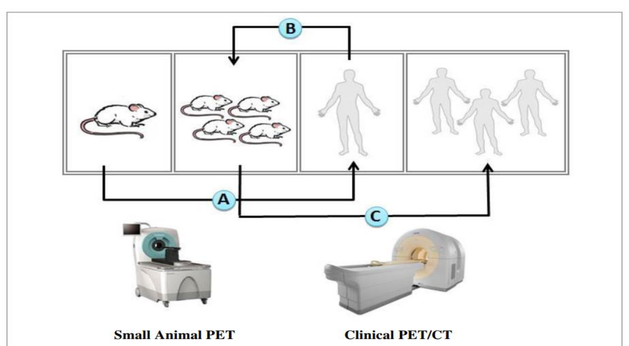


^{11}C-Vinblastine

Drug development

- Carbon-11 offers great and proven possibilities in the broad field of drug development. The compound of interest can be examined in just a few mice modelling the disease. Thus, the translation to humans is a direct step to only a few subjects (see Fig. below) and the results reflect the suitability according to the biochemical concept of application.
- Even more by specific activities, analytically determined, the pharmacological dose actually reaching the organ or tumor is directly measured.
- Efficiency of drug development is clearly enhanced and expenses are reduced by a factor hundred or even more, yet the PET Method practically is not in use.

- The PET Method facilitates and accelerates the development of new drugs when used in both small animal studies and the subsequent translation to (a few) patients as already suggested by M. Phelps, UCIA, in 2000.



Radioisotopes of carbon

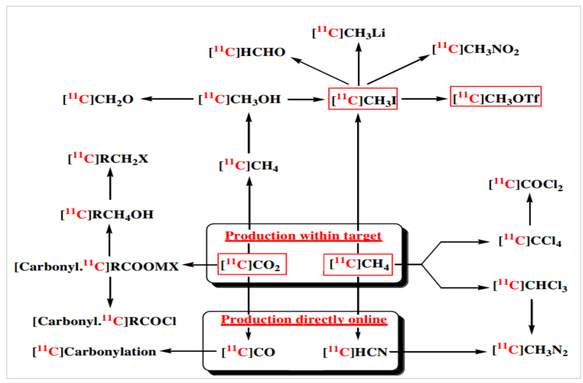
Among the various isotopes of carbon, carbon-11 and carbon-14 are the two important radionuclides, which are applied in biological and pharmaceutical studies.

In 1934 carbon-11 was first produced and identified by C.C. Lauritsen and H.R. Crane, and in 1940 carbon-14 was discovered by S. Ruben and M.D. Kamen in Berkeley, California. Compounds labeled with **carbon-14** are in broad use for *in-vitro* and in *ex-vivo* studies since a long time and will continue to play a key role in many areas of basic research in life-sciences. The ^{14}C labeled compounds follow the biochemical reactions and in a subsequent analysis the labeled products are determined. That allows the assessment of the metabolic reactions afterwards reflecting the on-going metabolism before the final analysis.

Labelling with **carbon-11**, however, opens the way to analyze metabolic pathways directly within the organism (in vivo) by means of external measurement.

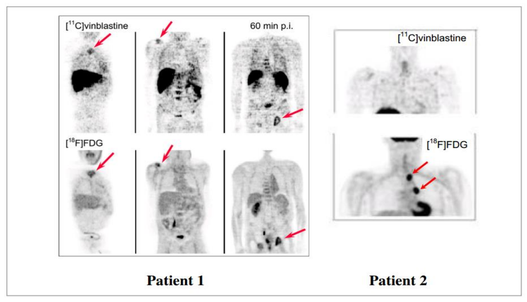
Production of carbon-11

As a neutron deficient radionuclide carbon-11 can only be produced by means of accelerators. The most important nuclear process is the $^{14}N(p,\alpha)^{11}C$ reaction by irradiation of nitrogen gas with protons (<16 MeV). Production is performed by a cyclotron on site and on demand. As self-shielded systems, no special building constructions are needed anymore. The cyclotron can be placed in any room just big enough to house it. Thus, a “*all around*” availability is assured. Via “*Hot Atom*” reactions the radionuclide is obtained as $^{11}CO_2$ or, if 5 % hydrogen are added to the target gas, as $^{11}CH_4$. In subsequent reactions various ^{11}C intermediates are prepared as synthons for the final synthetic introduction into the molecule of interest.



Example of a drug labelled with carbon-11 (11C-vinblastine)

- In Patient 1 whole body images 60 min after inj. of ^{11}C-vinblastine show increased uptake of ^{11}C vinblastine in multiple bone metastases of renal carcinoma. ^{18}FFDG-PET shows increased glucose metabolism.
- In Patient 2 no increase uptake of ^{11}C vinblastine were found in metastases as identified by increase glucose metabolism with $[^{18}F]$FDG.



Pharmaceutical drug development in industry

In pharmaceutical research (“*Big Pharma*”) the radiopharmaceutical approach with all the great possibilities is neglected since more than twenty years. Typically, clinical trials are reported to fail although the original preclinical data were very promising and, therefore, justifying a big investment for a clinical study. One of the most important explanations is *Multidrug Resistance* (MDR) which develops in cancer patients – sooner or later - during chemotherapy against any drug.

At the end of a clinical study, the immediate control is a PET measurement by tracers such as ^{11}C-verapamil, well known since the 1990ies. That is the way to identify those patients which principally had no chances to be treated and have to be excluded in the final statistical calculation of the particular clinical trial. Instead of the using the PET Method, the “tale” of extraordinarily high costs i.e. up to one billion US (10^9 US $) for a single new drug development remains to be spread around by pharmaceutical companies.

- The PET Method like CT and MRT, PET also is one of the *Molecular Imaging Modalities,* together with an appropriate radioactively labelled metabolite (*tracer*) it exhibits a method for direct assessment of biochemical processes as on-going within the organ or tumor.
- The Book describes radiochemistry and medical applications together with the perspectives in medical and clinical research.

Book (Print): ISBN 978-3-95663-081-1
eBook: ISBN 978-3-95663-118-4