RADIOISOTOPI: UN PONTE FRA LA FISICA NUCLEARE E LA MEDICINA

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- **1** The molecular imaging paradigm
- **2** Radioisotopes for medicine
- **3** The role of nuclear physics
- **4** The LARAMED project
- **5** Perspectives for LNL

All science is either physics or stamp collecting

Ernest Rutherford

Physics is to solve fundamental problems, the rest is stamp collecting

Anonymous

AN EXAMPLE: THE DISCOVERY OF TECHNETIUM-99m



Historical Notes

- 1 Technetium was the first artificial element discovered by Emilio Segré and Carlo Perrier in Palermo (1936).
- 2 Margaret Green and Walter Tucker developed the first Mo-99/Tc-99m generator (1958).
- **3 However, it was Richard Powell to recognize the potential use of Tc-99m as diagnostic tracer (1960).**

Technetium-99m



The Mo-99/Tc-99m Generator



The Pertechnetate Anion



Tc-99m Thyroid Imaging





Tc-99m Cardiac Imaging













4D Cardiac Images







The challenge in Science is not to make research, but to fully understand how much important your research might become.

Anonymous

THE MOLECULAR IMAGING PARADIGM: LOOKING INSIDE A LIVING, INTACT ORGANISM AT THE MOLECULAR LEVEL



Molecular Targets



Molecular imaging

- Molecular imaging is broadly defined as in vivo imaging of biological processes 'at the molecular' level.
- In principle, this can be accomplished by imaging the in vivo distribution of 'single molecules' interacting with the process.
- Nuclear imaging is a methodology using 'radiolabeled single-molecule probes' for collecting in vivo, diagnostic information.

FROM PHENOTYPE TO CHEMOTYPE





10⁻⁹ m

Sensitivity of Imaging Methods in Biology



DIAGNOSIS, THERAPY AND THERANOSTIC



Radiazioni in Medicina



The Golden Rule

Progress in the development of novel molecular probes has been always fundamentally driven by the introduction of new radionuclides.

Cardiac Imaging Agents

Tracer	Half-life	β⁺ Range in Tissues (mm)	Mechanism
⁸² Rb	78 s	2.6	Na/K-ATPase (perfusion)
¹³ NH ₃	10 min	0.7	Diffusion/metabolic trapping (perfusion)
¹⁸ F-FDG	110 min	0.2	Glucose transport/ hexokinase (viability)

Production of Fluorine-18



Decay of F-18





s

From: 0 To: 165618

R

A

Т

\$-1: 0.0 L-R: 8.2 Roll: 0.0

L

2-[¹⁸F]Fluoro-deoxyglucose (¹⁸F-FDG)



2-[¹⁸F]Fluoro-deoxyglucose (¹⁸F-FDG)



Rubidium-82 (Rb⁺)

- Rubidium-82 (Rb-82) is produced by decay of Strontium-82 (Sr-82)
- **75** second T¹/₂
- Kinetics:
 - Potassium analog
 - High extraction fraction at high flow rates

Rubidium-82









THE SPES-LARAMED PROJECT







The 70 MeV cyclotron installed at Legnaro National Laboratories



LARAMED

Laboratory for the production of exotic RAdionuclides for MEDicine

The SPES and LARAMED Laboratories



RI-LAB & RI-FAC



Cyclotron Production of Medical Radionuclides



Cyclotron Production of Astatine-211 at LNS



 $T_{1/2} = 7.214 h$ $E_{\alpha} = 5.2 MeV$

LARAMED PROJECTS

- ① LARAMED: Design and installation of a facility at LNL for research and production of medical radionuclides.
- ② APOTEMA: Theoretical assessment of nuclear reactions potentially usable for the production of ⁹⁹Mo and ^{99m}Tc by highcurrent cyclotrons.
- ③ TECHN-OSP: Development of a reliable technology for the cyclotron production and purification of ^{99m}Tc through the nuclear reaction ¹⁰⁰Mo(p,2n)^{99m}Tc.
- **(4) COME**: Experimental study of the nuclear reaction ⁷⁰Zn(p,x)⁶⁷Cu as a potential new route to the production of the medical radionuclide ⁶⁷Cu.
- **(5) TERABIO: Development of high-power targets for the production of non-standard therapeutic radionuclides by high-energy and high-current proton beams.**

Technetium-99m



Nuclear Reactor



Cyclotron Production of Tc-99m

¹⁰⁰Mo(p,2n)^{99m}Tc



Automated Purification Modules



Reactor



⁶⁸Zn(*p*,2*p*)⁶⁷Cu



National Isotope Development Center (NIDC)

October 2016: Isotope Now Routinely Available, Test Batch Recipients Requested Notice #63 October 25, 2016

The U.S. Department of Energy's Isotope Program is pleased to announce the routine availability of the isotope **copper-67** (Cu-67: t1/2 = 2.58 days).

Brookhaven National Laboratory currently has the capability of producing Cu-67 in an on-demand schedule using proton bombardment of a Zn-68 target. Additional production capabilities will come online at the end of October, 2016, at Argonne National Laboratory. Argonne's Cu-67 production will employ a phototransmutation (γ ,n) reaction, and will commence with weekly production for basic science and pre-clinical research (http://science.energy.gov/~/media/np/nsac/pdf/docs/ 2015/2015_NSACI_Report_to_NSAC_Final.pdf).

⁷⁰Zn(*p*,2*p*2*n*)⁶⁷Cu



⁷⁰Zn(*p*,2*p*2*n*)⁶⁷Cu



⁶⁴CuCl₂ in prostate cancer





Imaging of Glioma with Cu-64 Dichloride



Therapy of Glioma with Cu-64 Dichloride





Therapy of Glioma with Cu-64 Dichloride





PET^Cerebrale_Cu_MC

Novel Radioisotopes for Medicine

lsotope	Half-life	Decay	Energy (MeV)
Zn-63	38.47 min	β+	0.992
Mn–52	5.591 days	β+	0.244
Mn-51	46.2 min	β ⁺	0.970
Cu-64	12.8 hours	β ⁺ , β ⁻	0.65
Cu-67	61.83 hours	β⁻	0.577
Fe-52	8.3 hours	β ⁺	0.804

The ISOLPHARM Project

ISOL technique for radiopharmaceuticals development



Working group:

Alberto Andrighetto Stefano Corradetti Francesca Borgna Michele Ballan Elisa Vettorato

ISOLPHARM Method overview





ISOLPHARM² - ¹¹¹Ag for therapy?



¹¹¹Ag

- τ_{1/2}: 7,45 days
- γ emission
- Auger emission
- β^{-} up to 1036 keV

^{111}Ag production: SPES UCx target - PPB 40 MeV , 200 μA

Time	Produced	activity
[days]	[Bq]	[Ci]
0,5	9,46E+09	0,26
1	1,92E+10	0,52
1,5	2,85E+10	0,77
2	3,74E+10	1,01
3	5,4E+10	1,46
4	6,92E+10	1,87
5	8,29E+10	2,24
10	1,35E+11	3,66
15	1,68E+11	4,55
20	1,89E+11	5,11
25	2,02E+11	5,46
30	2,1E+11	5,68



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Acknowledgement of receipt

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Online

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RF

The ISOLPHARM patent



The use of ISOL technique for the production of radiopharmaceuticals is a INFN PATENT

Patent title:

«Method for producing beta emitting radiopharmaceuticals and beta emitting radiopharmaceuticals thus obtained»

EU patent

US patent

Docket No. 1674-028

		IN THE UNITED STATES PATENT AND THE	RADEMARK OFFICE
designated or elected Office) as follows:		PATENT OPERATION	
		Applicant: ISTITUTO NAZIONALE DI FISICA NUC	CLEARE
		First Named Inventor: Alberto ANDRIGHETTO	Examiner:
		Serial Number: not yet known	Art Unit:
		Filed: July 29, 2016	
		Title: METHOD FOR PRODUCING BETA EMITTI BETA EMITTING RADIOPHARMACEUTICALS T	NG RADIOPHARMACEUTICALS, AND HUS OBTAINED
			New York, NY 10020 July 29, 2016
		Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	
	21	PRELIMINARY AME	ENDMENT
euro-pct.xml 1200.pdf (5 p.)		Sir:	
PLYWO-1.pdfP1251EP00_201607 Communication and uments.pdf (2 p.)		This Preliminary Amendment is being filed to Preliminary Amendment prior to calculating the filin application as follows:	p reduce the filing fee. Kindly enter this g fee. Kindly amend the above identified
:34:D9:B7:74:A8		1	
Page 1 of 2			

CANADA patent

PCT/CA

Form for Request into National Phase under Articles 22 or 39 of the Patent Co-operation Treaty IN THE MATTER OF PCT International Application: PCT/IB2014/067093 filed December 18, 2014 lication #) (international filing date

Istituto Nazionale Di Fisica Nucleare (full name of applicant)

The above-identified applicant, whose full post office address is

Via E. Fermi, 40, I-00044 Frascati (RM), ITALY

ons the entire right in Canada to an invention entitle METHOD FOR PRODUCING RETA EMITTING RADIOPHARMACEUTICALS, AND

BETA EMITTING RADIOPHARMACEUTICALS THUS OBTAINED

ade by NDRIGHETTO, Alberto

Country

whose full post office address is:

c/o Istituto Nazionale Di Fisica Nucleare - Laoratori di Legnaro, Via ell'Università, 2, I-35020 Legnaro (PD), ITALY

as described in the said international application and any amendments thereto

2. The applicant(s) claim(s) protection afforded by section 28(1) of the Patent Act in relation to the following prior filed applicatio

Date of filing Application No

January 31, 2014	MI2014A000145

(3) The applicant(s) hereby nominate(s) Marks & Clerk who resides or carries on busine (a) the applicant(a) interformatical matrix a constraint of outway, Ontario, Canada K1P 0B6 to Canada at the following address: 180 Kent St, Suite 1900, Ottawa, Ontario, Canada, K1P 0B6 to be his/their representative for the service of any proceedings taken under the Act.

(4) TIAN Toar Detitionerijk hereby sepointis) Marka & Chris whose fail post office address is P.O. Bogo and B. B. Dawa, Orania G. Barka, M. 1985 an a hist viterie sept. with full power to solve a section of the section of the section of a solve section 21 of the Pattern Rules and to revoke such appointment, to sign the petition and drawings, to amend the specification and drawings, to prosecute the application, and to receive the patternit granted on the said application; and ratify/les any act done by the said appointe in respect of the said application.

(5) The applicant(a) hereby request(a) commencement of national phase procedures consequent to the designation of Canada in such international application and prays that a patent be granted to him/them for said invention.

Signed at Ottawa, Canada, this 28th day of July, 201
- Unraks & Clark
Agent for Applicat

LARAMED meeting, 30th November 2016

From Anatomy to Molecules



First X-ray Image



PET/CT/MRI Molecular Image

Collaborations

University of Ferrara

St. Orsola Hospital-University of Bologna

University of Bologna

University of Mlan 'Bicocca'

University of Pavia

Istituto Oncologico Veneto (IOV)

LASA-University of Milan

National Research Council

ARRONAX GIP, Nantes, France

PET University Institute, Republic of Macedonia

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Science owes more to steam engine than steam engine owes to Science L.J. Henderson (1917)

THANK YOU

