Production d’isotopes innovants

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Nuclear data for applications in nuclear medicine

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Outline

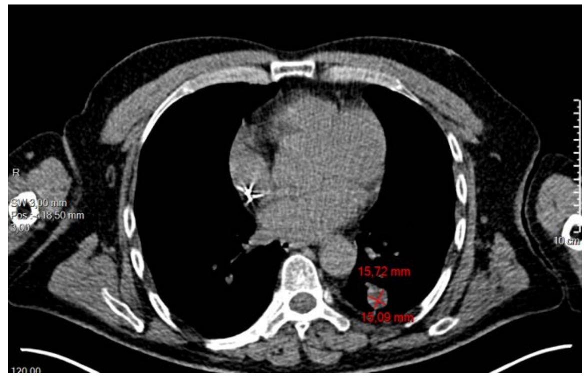
- Conventional imaging, therapy and nuclear medicine
- Challenges address to nuclear physicists
- Examples of what can be done
- Conclusions

Conventional imaging in oncology

Visualize and localize tumors, measure them and evaluate the response to treatments

Centre François Baclesse

Radiography



Centre René Gauducheau

Computerized Tomography Scanner

Institut Roi Albert II

Magnetic Resonance Imaging

These techniques allow to get accurate information on the morphology but give limited information on the metabolism

A gain can be obtain by coupling them with nuclear medicine technique (SPECT or PET) which gives these information

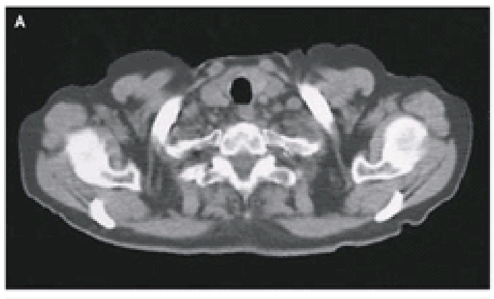
Great progress in the last ten years

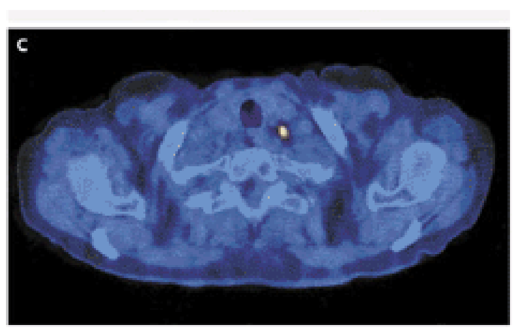
18FDG PET: whole body 3D mapping of a biomarker, non invasive

Multimodality: SPECT/CT, PET/CT then PET/MR

Morphology

Metabolism

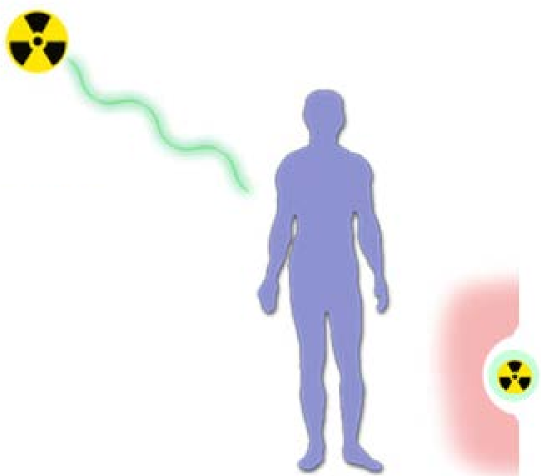




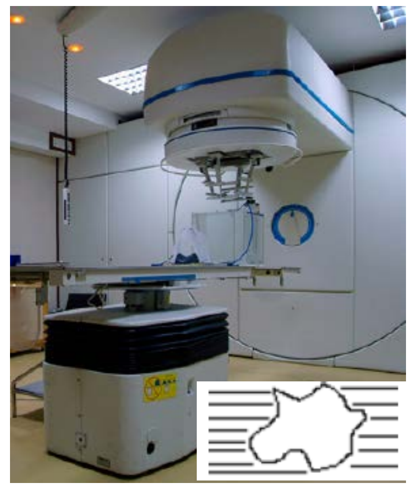
New targets, tracers and radionuclides (béta+, béta-, Auger and alpha)

Conventional radiotherapy

External beam radiotherapy:
- X rays, gamma, electrons
- Hadrontherapy



Brachytherapy
Curietherapy



Institut de cancérologie de l'Ouest

ProteusOne, IBA

Institut de cancérologie de l'Ouest

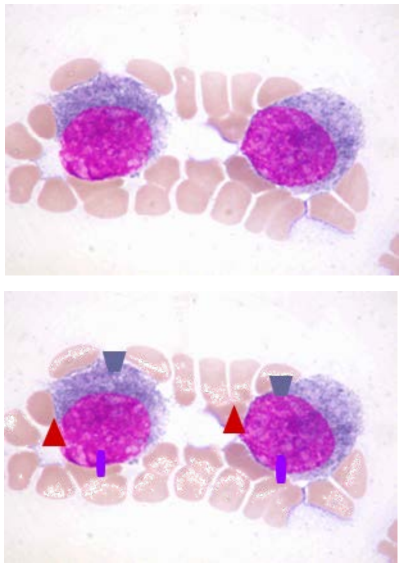
These techniques are very efficient to treat a localized disease

Limit: does not target disseminated disease or residual disease

This can be address by nuclear medicine techniques

Nuclear medicine

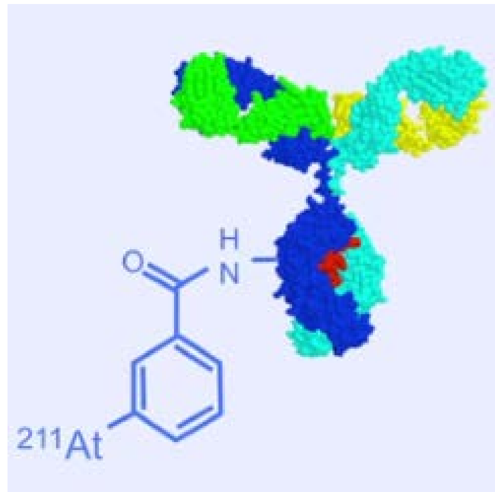
Molecular targeting



From Pr Kraeber-Bodéré

- Receiver: SMS
- Antigen: CEA
- Carrier: GLUT1
- …

Radiopharmaceutical



GIP ARRONAX

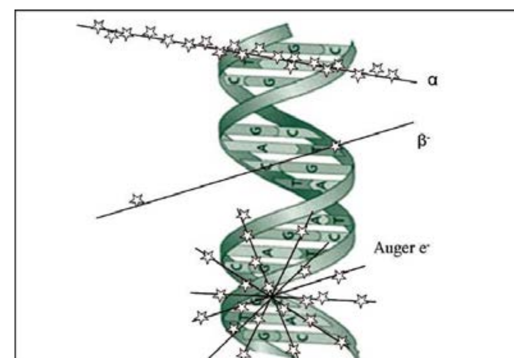
- Peptide
- Antibody
- NorA analog
- Glucose
- …

Siemens

Gamma: scint, SPECT/CT

General Electrics

Béta +: PET, PET/CT

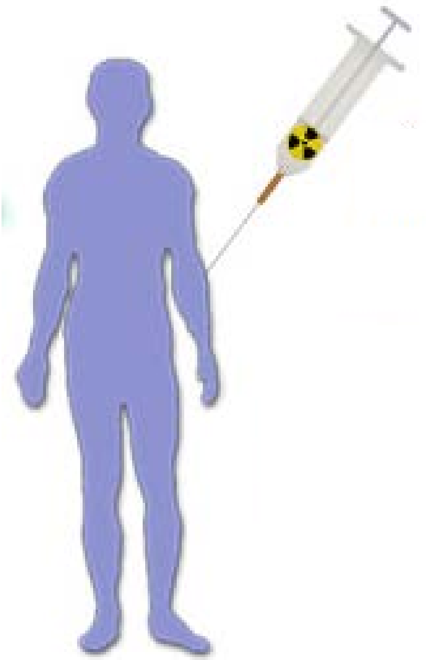


JCRT 6, 3, p. 239

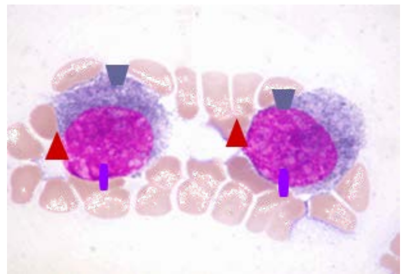
Alpha, béta-, Auger e-: therapy

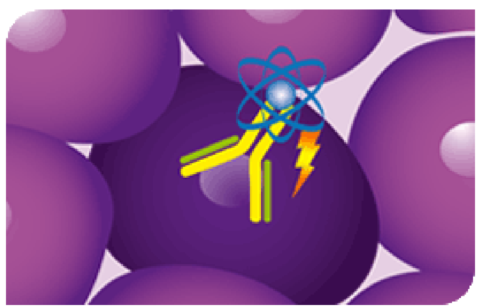
Imaging and molecular radiotherapies

Inject a tracer



Target a tumor marker

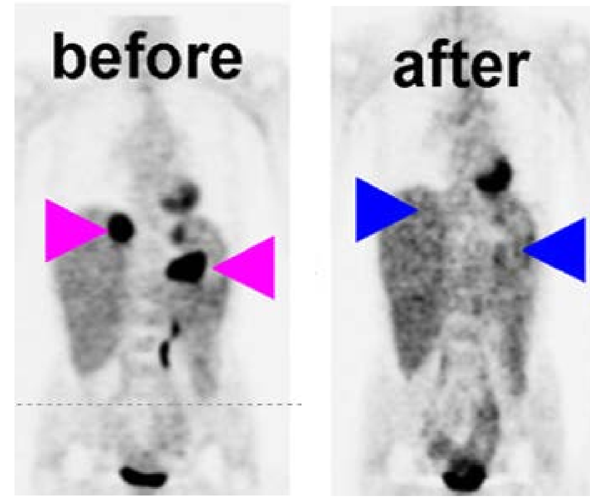




AREVA Med

γ, β+ →

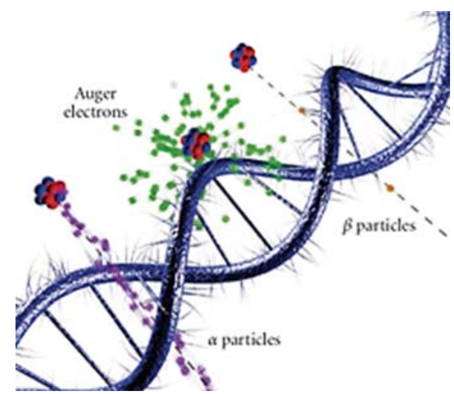
Detect the disease



NIRS, Shiba, MIC

β-, α, e_{Auger} →

Treat the disease



B.Q. LEE et al.

Theranostic radiopharmaceuticals

Predictive imaging,
companion diagnostic

Targeted therapy

THERANOSTICS

MOLECULE

WANTED

An adequate therapeutic nuclide

A corresponding positron emitter

= (Available matched) pair
of therapeutic and PET nuclides

WANTED

Molecules = targeting vectors

Identical or similar
radiolabelling chemistry

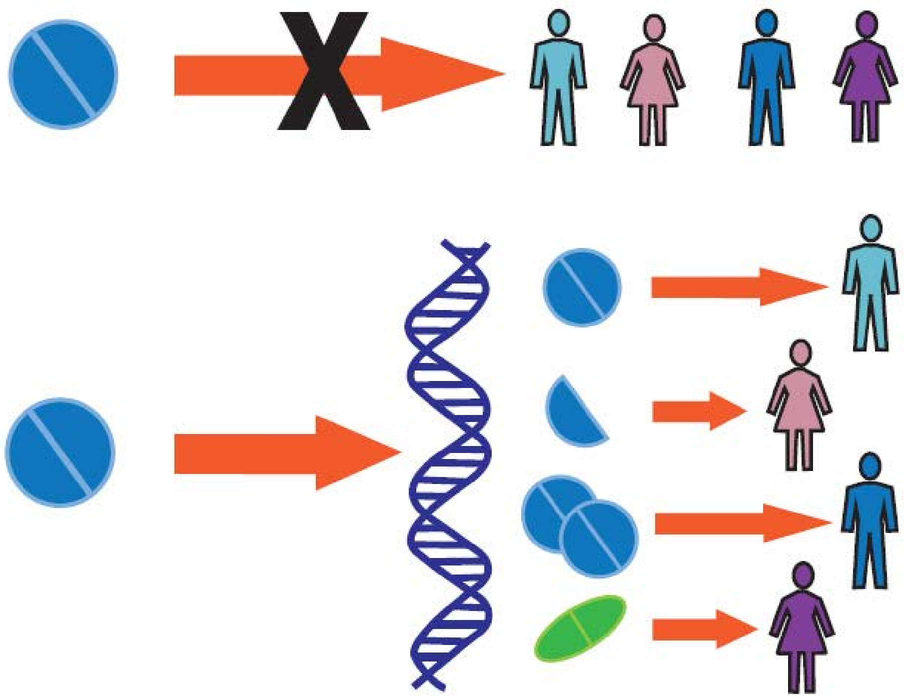
Pharmaceuticals 2017, 10(2), 56

Personalized nuclear medicine

Imaging and diagnosis

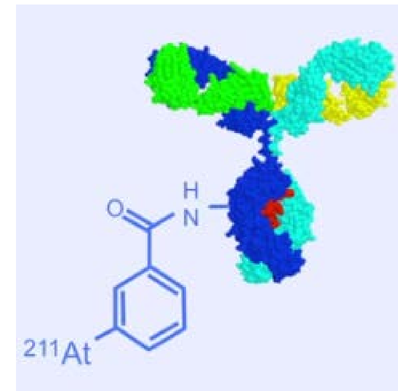
Choose the best treatment

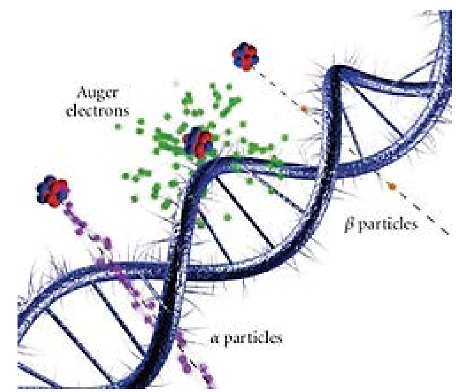
Evaluate its efficacy



Therapy

Destroy tumor cells





The Right Drug To The Right Patient For The Right Disease

At The Right Time With The Right Dosage

Challenges address to nuclear physicists

^{18}**FDG PET**: whole body 3D mapping of a biomarker, non invasive

Multimodality: SPECT/CT, PET/CT then PET/MR

In biology, **new vectors**: peptides, humanized antibodies, nanobodies …

New radionuclides are needed to match with these new vectors

A large set of radioisotopes with very different characteristics is suitable:

- **Radiation type** for the different applications
- Half-life – to match the **bio-distribution** time
- Chemical properties – to attach to the **vector molecule**
- Production yields – to get the **purest product**
- Production capacities – to envisaged **large scale use**

Role of the physicist

The nuclear physicist could have crucial contribution:

- Identify production route and define production process even large scale production (reactors, accelerators by spallation, fission or activation)
- Identify and quantify contaminants
- Define waste management process
- Help scientists working in a pluridisciplinary team (nuclear physicists are use to do that)
- Discuss with physicians to promote its use

Over the last years, several radionuclides have emerged:

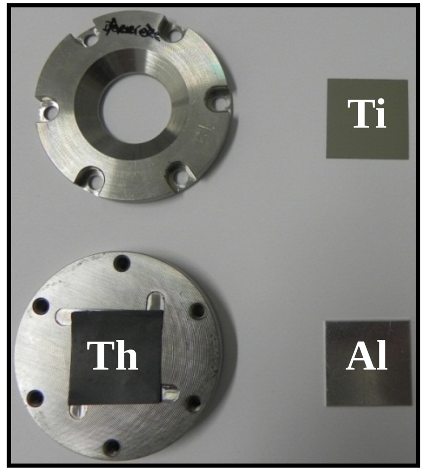
- Béta+: Cu-64, Ga-68, Zr-89 …
- Gamma: Sn-117m …
- Béta- : Ho-166, Lu-177 …
- Alpha: At-211, Bi-212, Bi-213, Ra-223, Ac-225 ...
- Theranostic: Sc-44/Sc-47, Cu-64/Cu-67, Ga-68/Lu-177 …
  Terbium quadruplet Tb-149, 152, 155, 161
- Auger: Sn-117m, Tb-155 (at the research level for the moment)

To do so, we possess facility (will possess) available for irradiations equipped with experimental techniques such as the stacked-foil technique

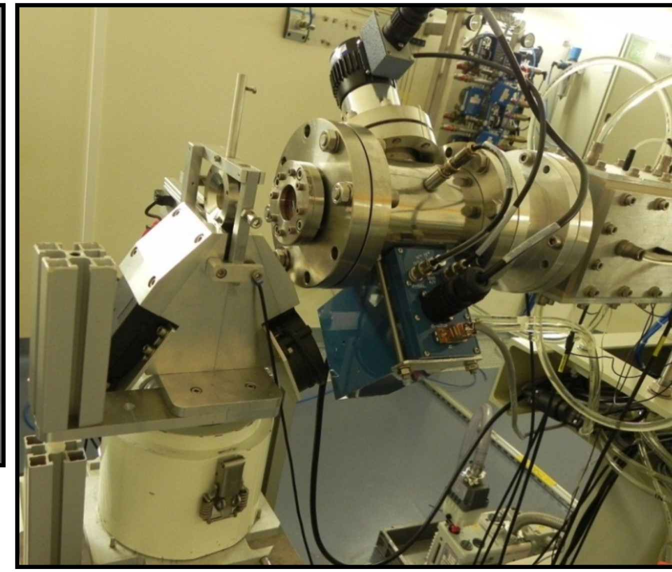
Stacked-foil technique

Stacked-foil technique:

- Target/monitor/degrader **pattern**
- **Thin** foils:
  E loss small and constant
- One cross section value per foil



Capsule and foils



Irradiation station and beam line

Activity and cross section:

$$\sigma = \frac{Act\,.\,A}{\chi.\,\Phi\,.\,\mathcal{N}_A\,.\,\rho\,.\,e\,.\,(1 - e^{-\lambda.t})}$$

Use of a Faraday cup:

- Beam dump placed at the end of the stack to control the intensity during the irradiation

Use of a monitor foil:

$$\sigma = \sigma'.\,\frac{\chi'.\,Act\,.\,A\,.\,\rho'\,.\,e'\,.\,(1 - e^{-\lambda'.t})}{\chi.\,Act'\,.\,A'\,.\,\rho\,.\,e\,.\,(1 - e^{-\lambda.t})}$$

- error on e, e': ≤ 1%
- error on t: negligible

IAEA recommended cross sections:

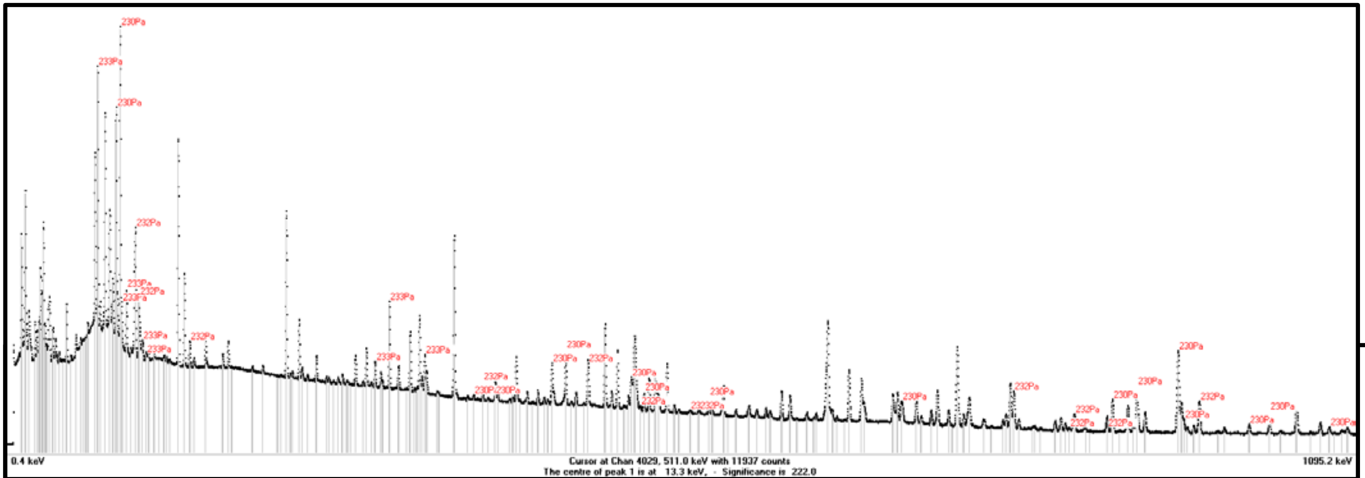
- 8 reactions available for protons
  ^{27}Al (2), ^{nat}Ni, ^{nat}Ti and ^{nat}Cu (4)
- 5 reactions available for deuterons
  ^{27}Al (2), ^{nat}Fe, ^{nat}Ni and ^{nat}Ti
- 6 reactions available for alpha-particles
  ^{27}Al (2), ^{nat}Ti and ^{nat}Cu (3)

Stacked-foil technique

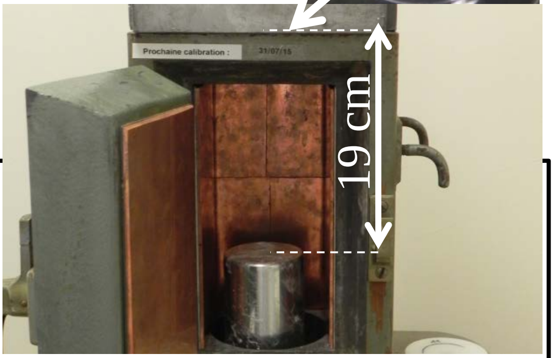
Gamma spectroscopy

- **HPGe** coaxial detector
- Dead time: < 10% (sum peak)
- Activity values: FitzPeaks
- $T_{1/2}$, E_γ, I_γ: Lund/LBNL, NNDC

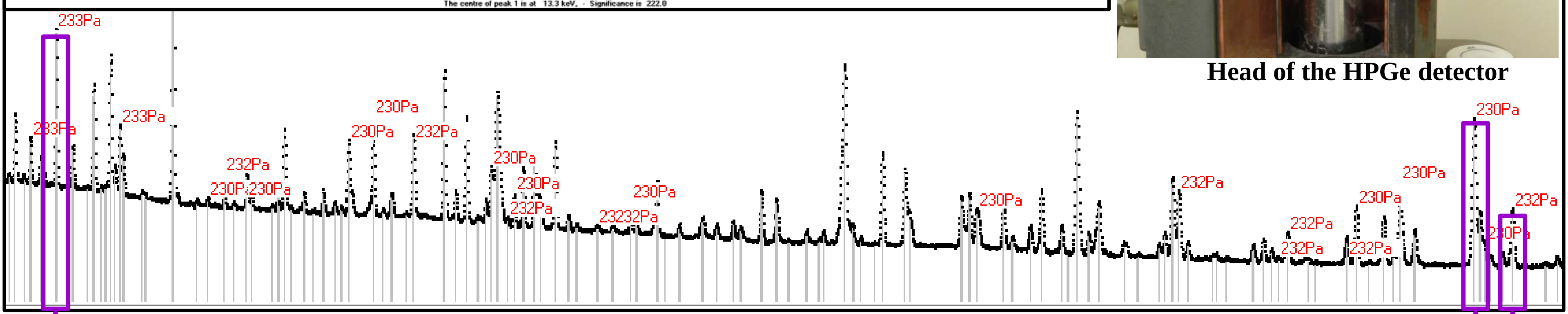
- γ spectra recorded on **8192 channels**
- FWHM:1.04 keV at 122 keV (^{57}Co)
1.97 keV at 1332 keV (^{60}Co)
- Energy and efficiency calibrations: Co and Eu



Target and monitor:
- ✓ counted twice
- ✓ during > 24 hrs
- ✓ 2 week delay

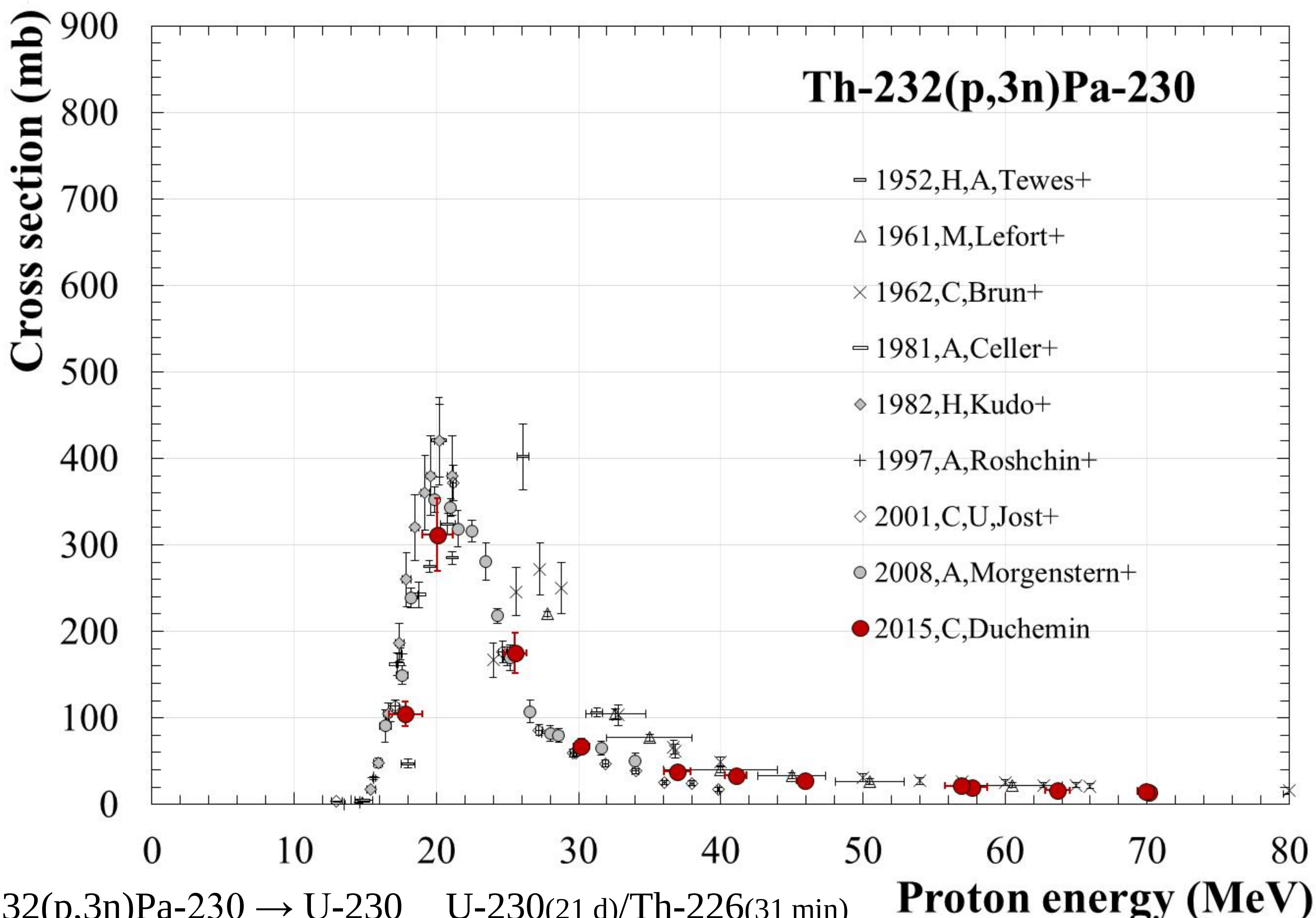


Head of the HPGe detector



γ rays used to extract production cross section of ^{230,232,233}Pa

Novel therapeutic nuclide



Th-232(p,3n)Pa-230 → U-230 U-230(21 d)/Th-226(31 min)

α RIT for leukaemia treatment 4 α cascade of 27.7 MeV *C. Duchemin et al., Phys. Med. Biol. 60 (2015) 931-946*

TALYS

Code for the simulation of nuclear reactions

Projectiles : n, p, d, t, He-3, α particles

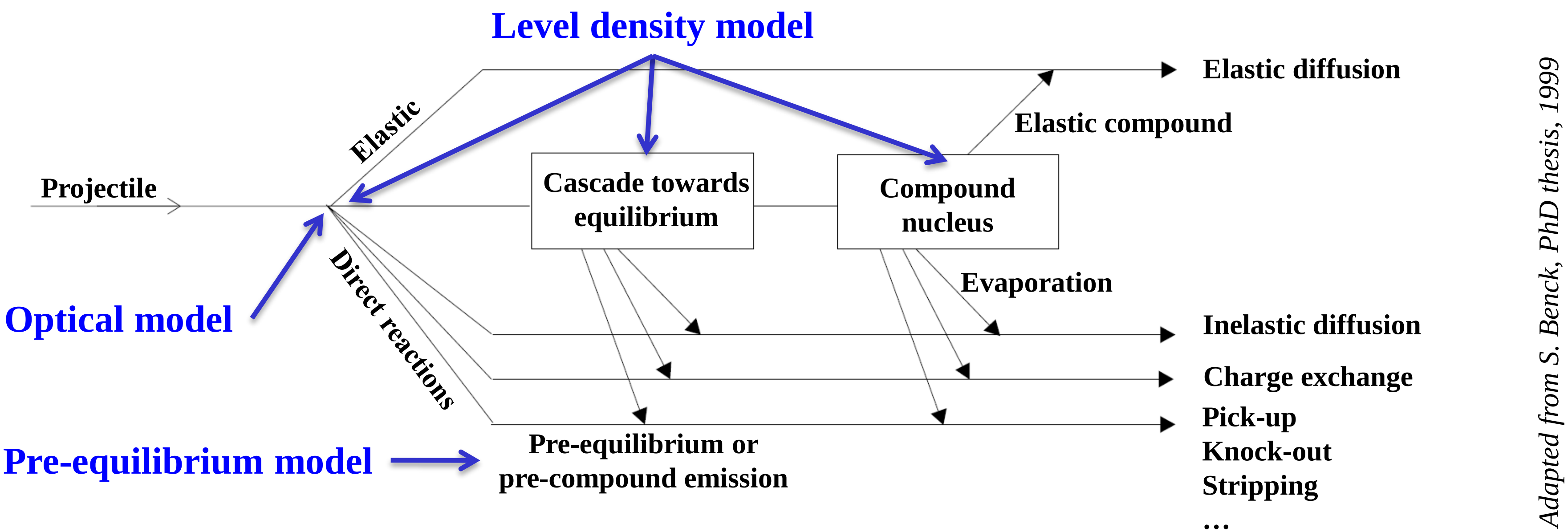
Many state-of-the-art nuclear models

Energy : 1 keV to 1 GeV

Provide a complete description of all reactions channels and observables

Targets : Z = 3 to 110

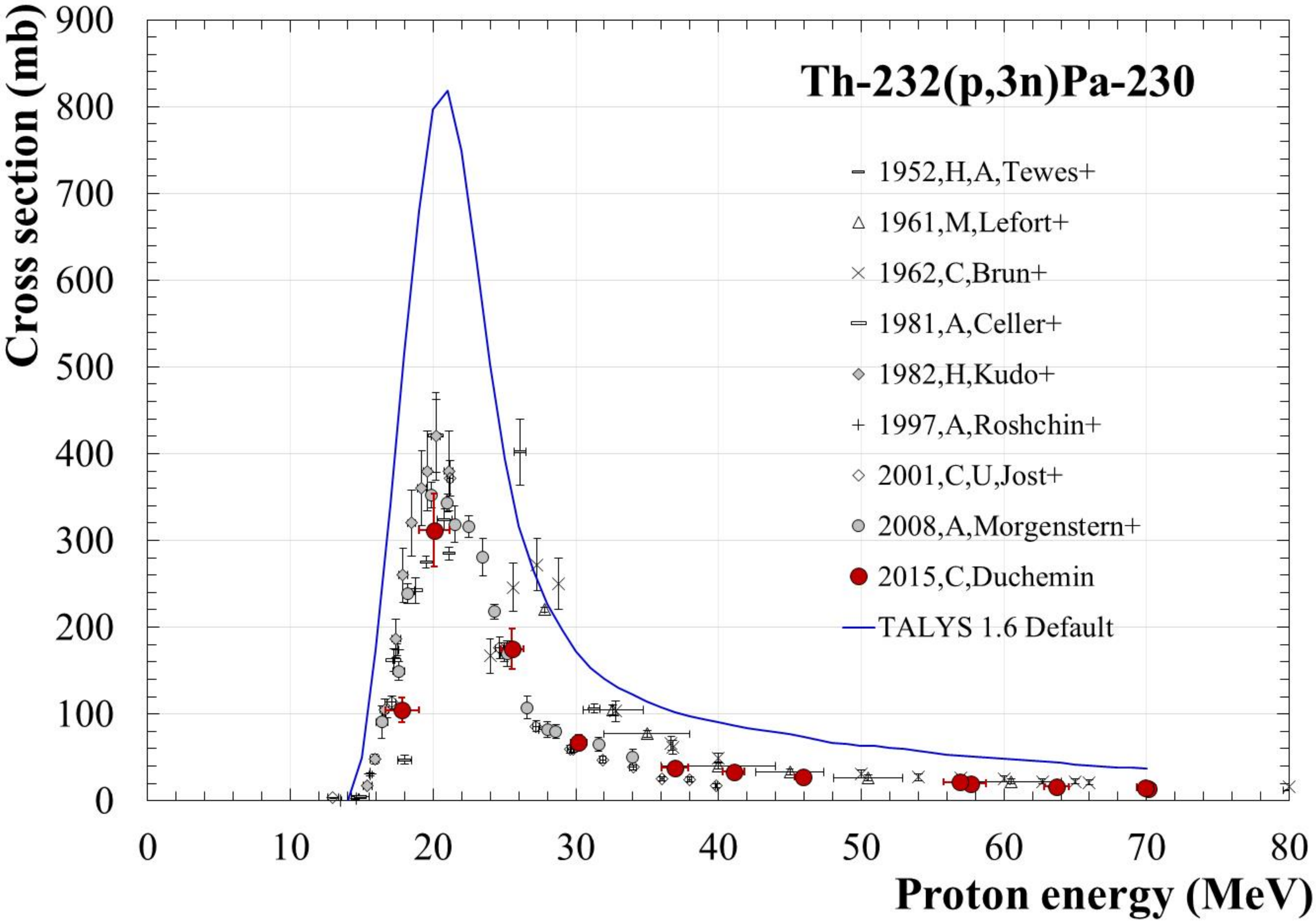
Nuclear reactions



⇨ Influence on the calculated production cross section values

Koning A.J. and Rochman D., Nucl. Data Sheets, 113, 2012

Novel therapeutic nuclide



C. Duchemin et al., Phys. Med. Biol. 60 (2015) 931-946

TENDL2015

Nuclear data library based on both default and adjusted TALYS calculations and data from other sources

By A.J. Koning[1], D. Rochman[2], J. Kopecky[3], J.Ch. Sublet[4], M. Fleming[4], E. Bauge[7], S. Hilaire[7], P. Romain[7], B. Morillon[7], H. Duarte[7], S.C van der Marck[6], S. Pomp[5], H. Sjostrand[5], R. Forrest[1], H. Henriksson[8], O. Cabellos[9], S. Goriely[10], J. Leppanen[11], H. Leeb[12], A. Plompen[13], and R. Mills[14]

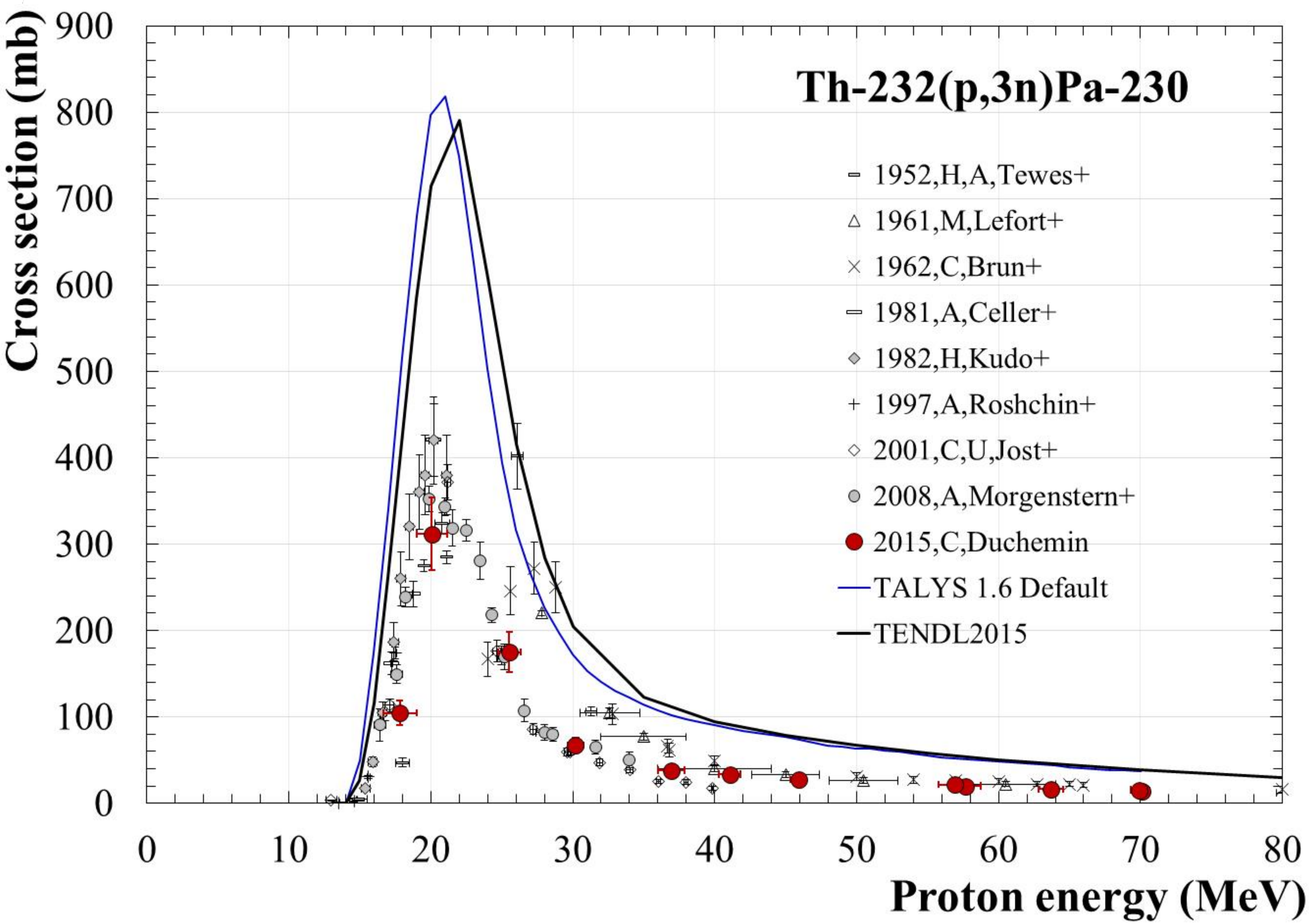
[1] IAEA, [2] PSI, [3] JUKO Research, [4]CCFE, [5]Uppsala Univ., [6]NRG, [7]CEA, [8]Vattenfall, [9]NEA, [10]ULB, [11]VTT, [12]ATI, [13]IRMM, [14]NNL.

TENDL2015 contains evaluations for :

- seven types of incidents particles (n, p, d, t, He-3, alpha-particle, gamma ray)
- all isotopes living more than 1 second (~ 2800 isotopes)
- all files are original except 15 (natural carbon from JENDL-4.0, ^{1,2,3}H, ^{2,3}He, ^{6,7}Li, ^{10,11}B, ^{9}Be, ^{14,15}N, ^{16}O and ^{19}F from ENDF/B-VII.1)

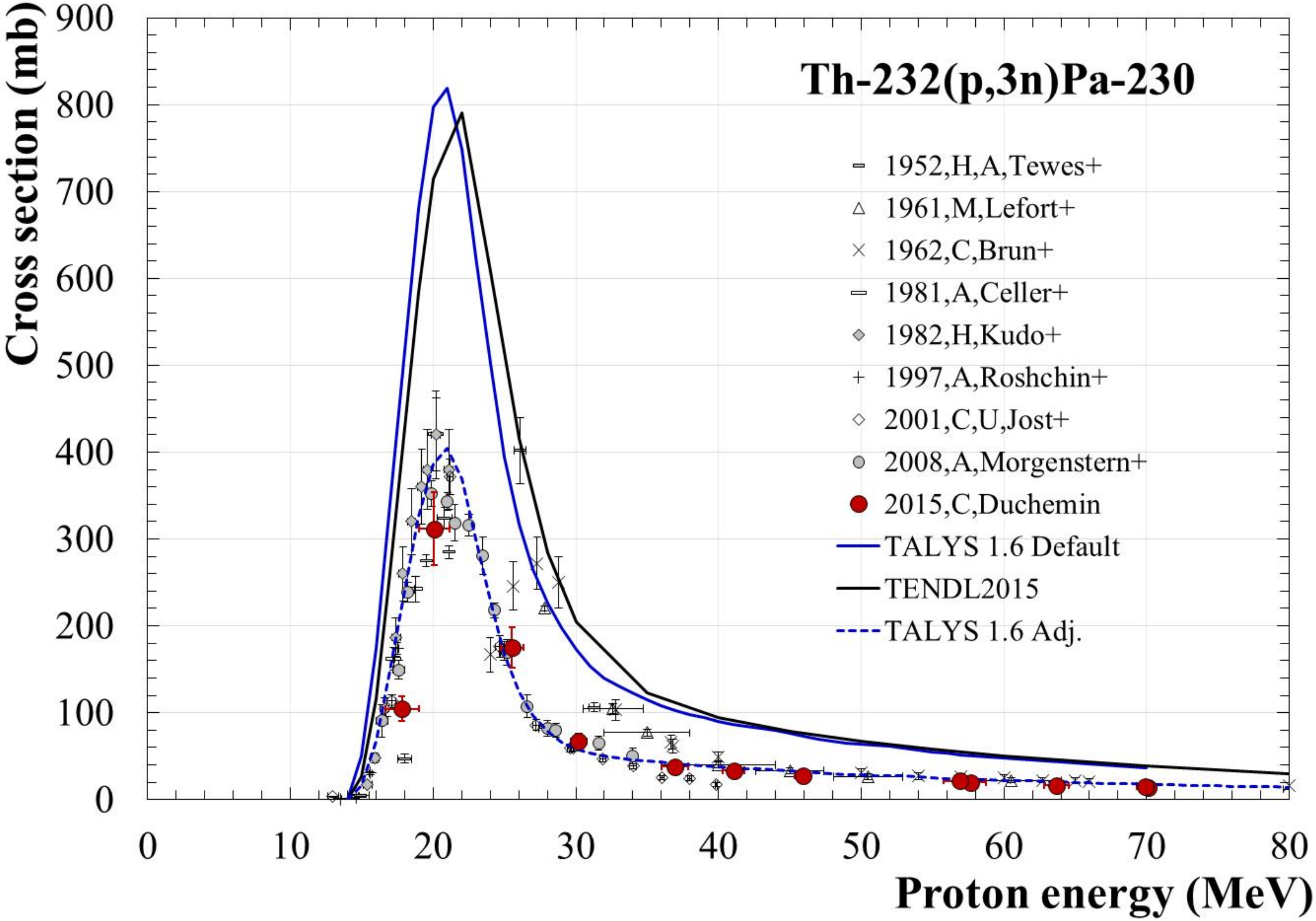
Koning A.J. et al., https://tendl.web.psi.ch/tendl_2015/tendl2015.html
Koning A.J. and Rochman D., Nucl. Data Sheets, 113, 2012

Novel therapeutic nuclide



C. Duchemin et al., Phys. Med. Biol. 60 (2015) 931-946

Novel therapeutic nuclide



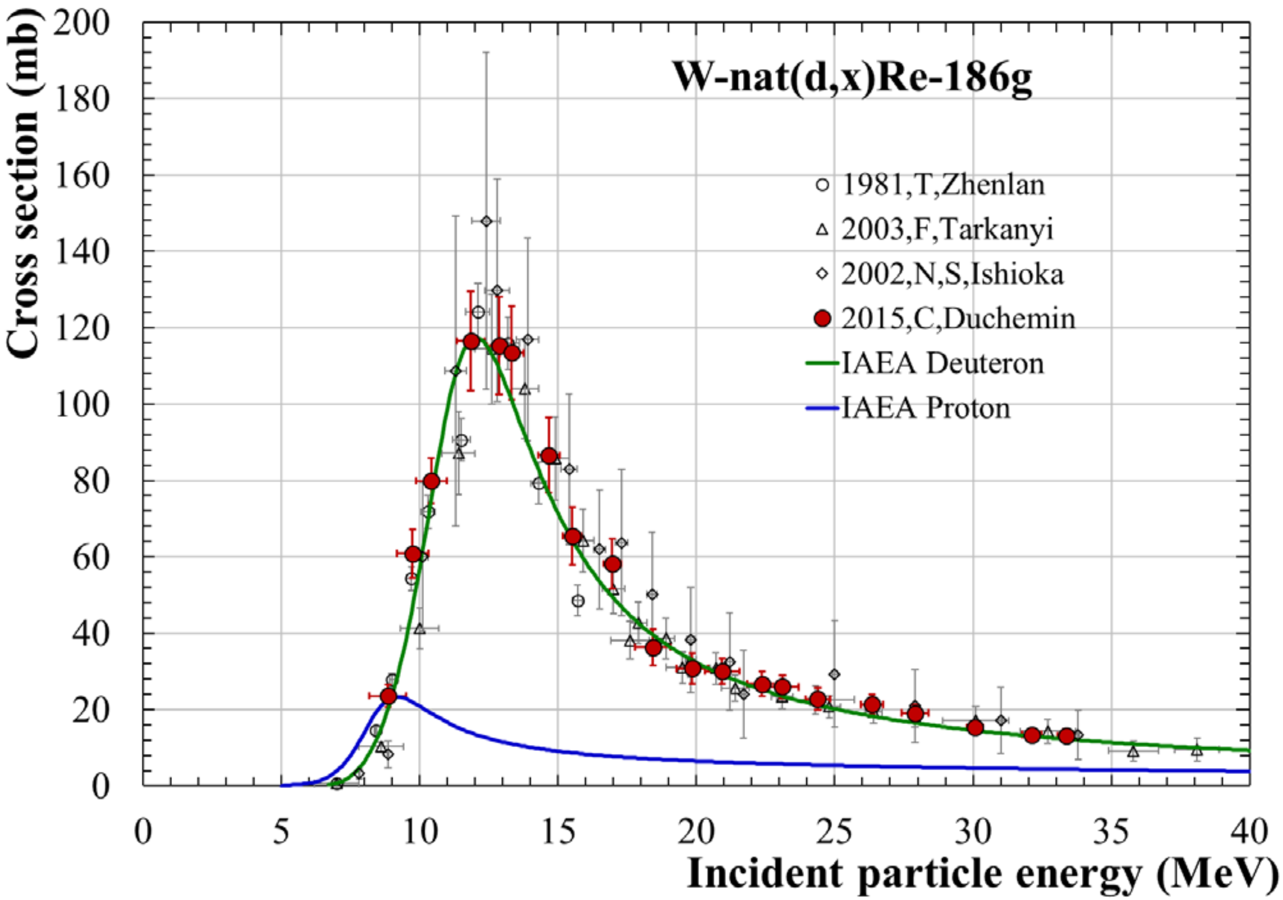
C. Duchemin et al., Phys. Med. Biol. 60 (2015) 931-946

Re-186g: proton/deuteron production route

Re-186g ($T_{1/2}$ = 3.7 d)

β- emitter
used in clinical trials
for the palliation of painful
bone metastases resulting from
prostate and breast cancer

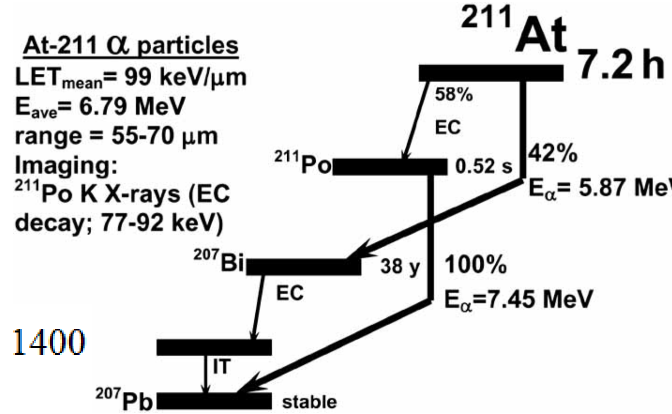
Deuteron induced reaction
has clearly a highest Re-186g
production cross section



C. Duchemin et al., Appl. Radiat. Isot. 97 (2015) 52-58

At-211: direct / indirect production

Targeted alpha-particle radiotherapy

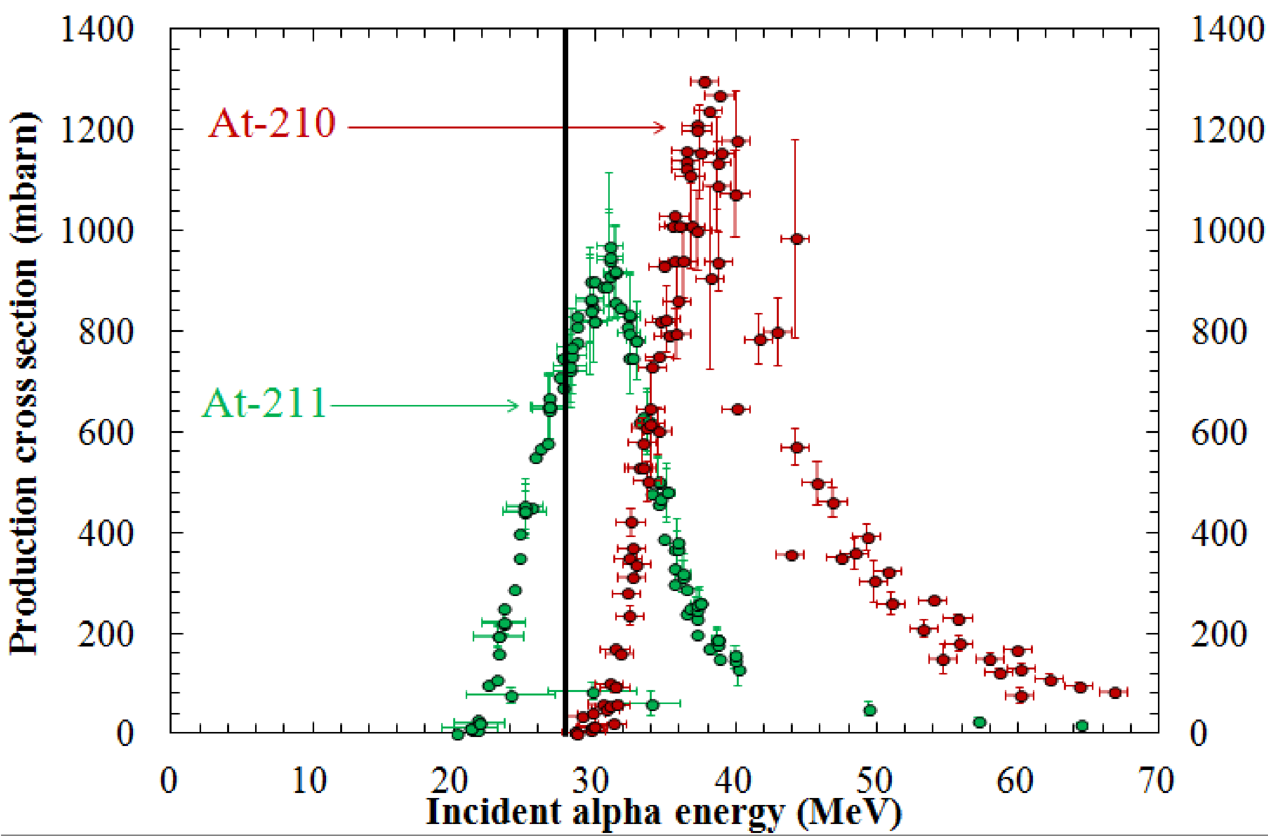


Current Radiopharmaceuticals (2008) 1. 177-196.

Direct production with alpha particles

Bi-209(α,2n)At-211, 20.7 MeV

Bi-209(α,3n)At-210, 28.6 MeV ⚠

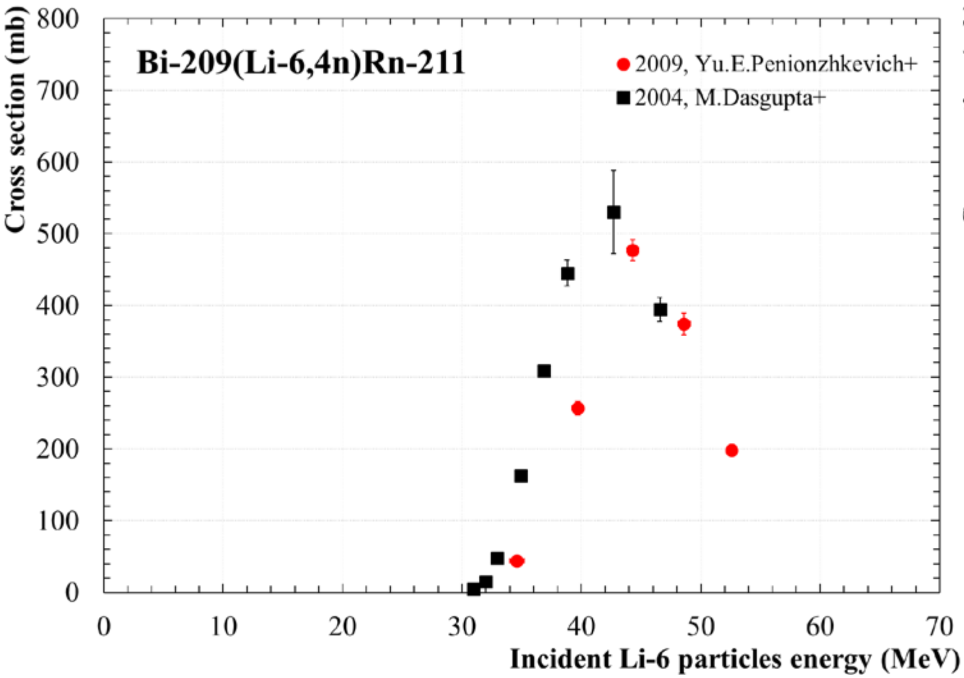


At-210, $T_{1/2}$ 8.1 h decays at 99.8% by EC to **Po-210** (138.4 days) and at 0.2% by α emission to Bi-206 (6.2 days)

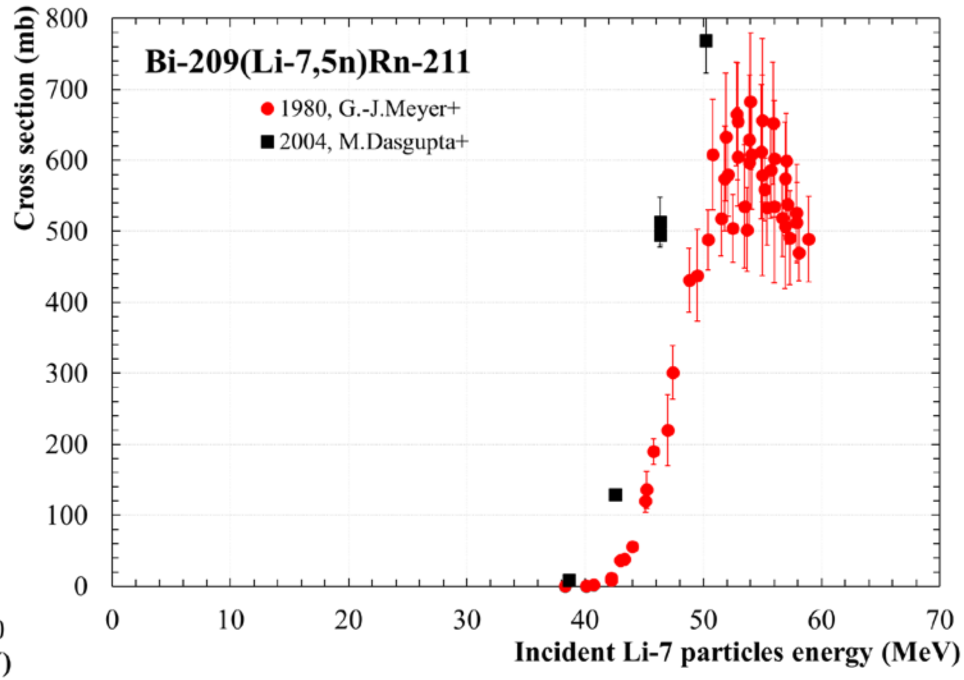
At-211: direct / indirect production

Indirect production with lithium beams

Bi-209(Li-6,4n)Rn-211, 28.5 MeV



Bi-209(Li-7,5n)Rn-211, 36.1 MeV

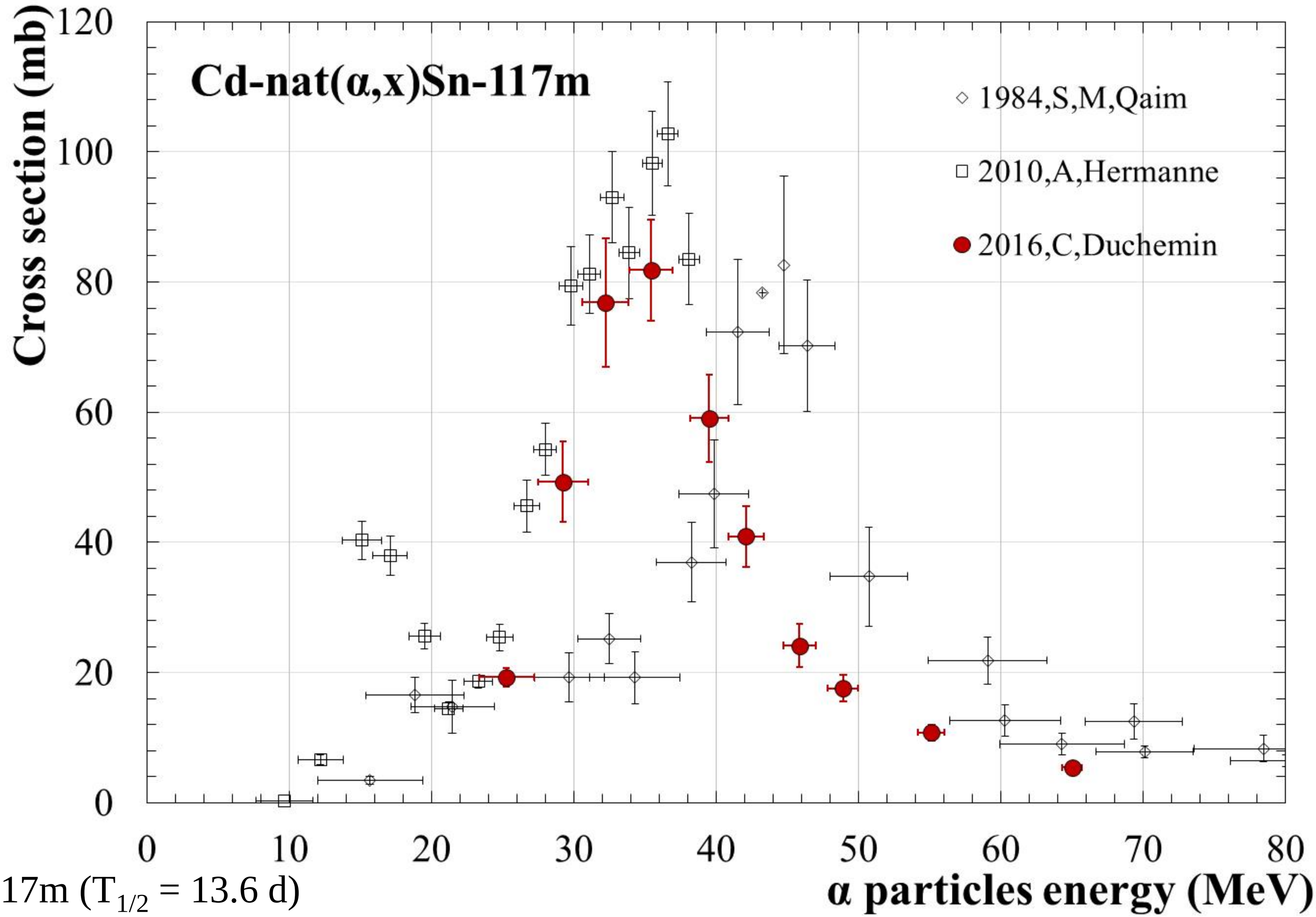


Rn-211 decays at 72.6% by EC to At-211 and by α decay to Po-207 with a 14.6 h half-life

Rn-210 decays at 3% by EC to **At-210** and at 96% by α decay to Po-206, $T_{1/2}$ 8.8 d ⚠

Astatine can be also available through the Rn211/At211 generator

Novel therapeutic and imaging nuclide



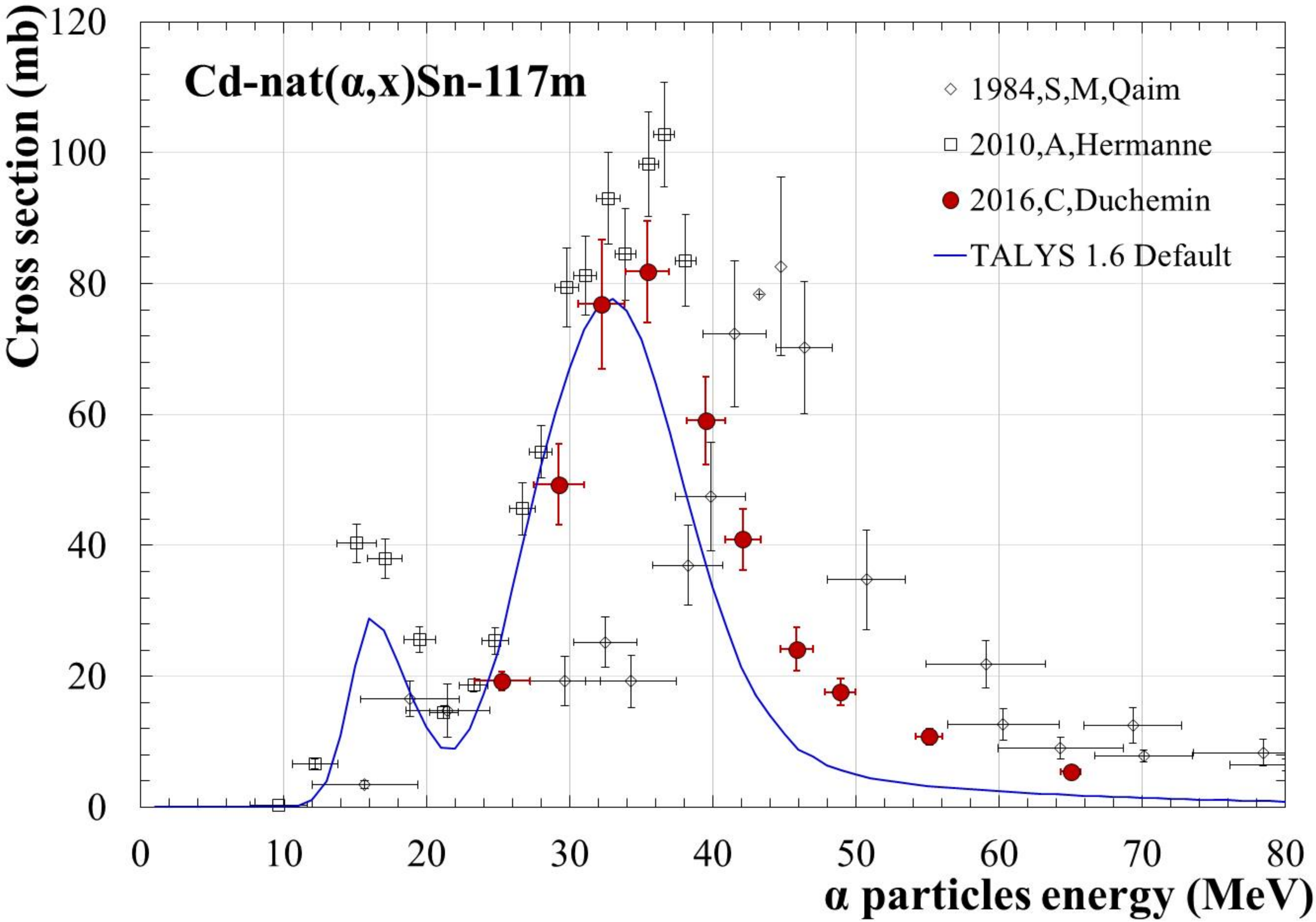
Sn-117m ($T_{1/2}$ = 13.6 d)

Conversion e- emitter used for the palliation of painful bone metastases

158 keV gamma ray suitable for SPECT imaging

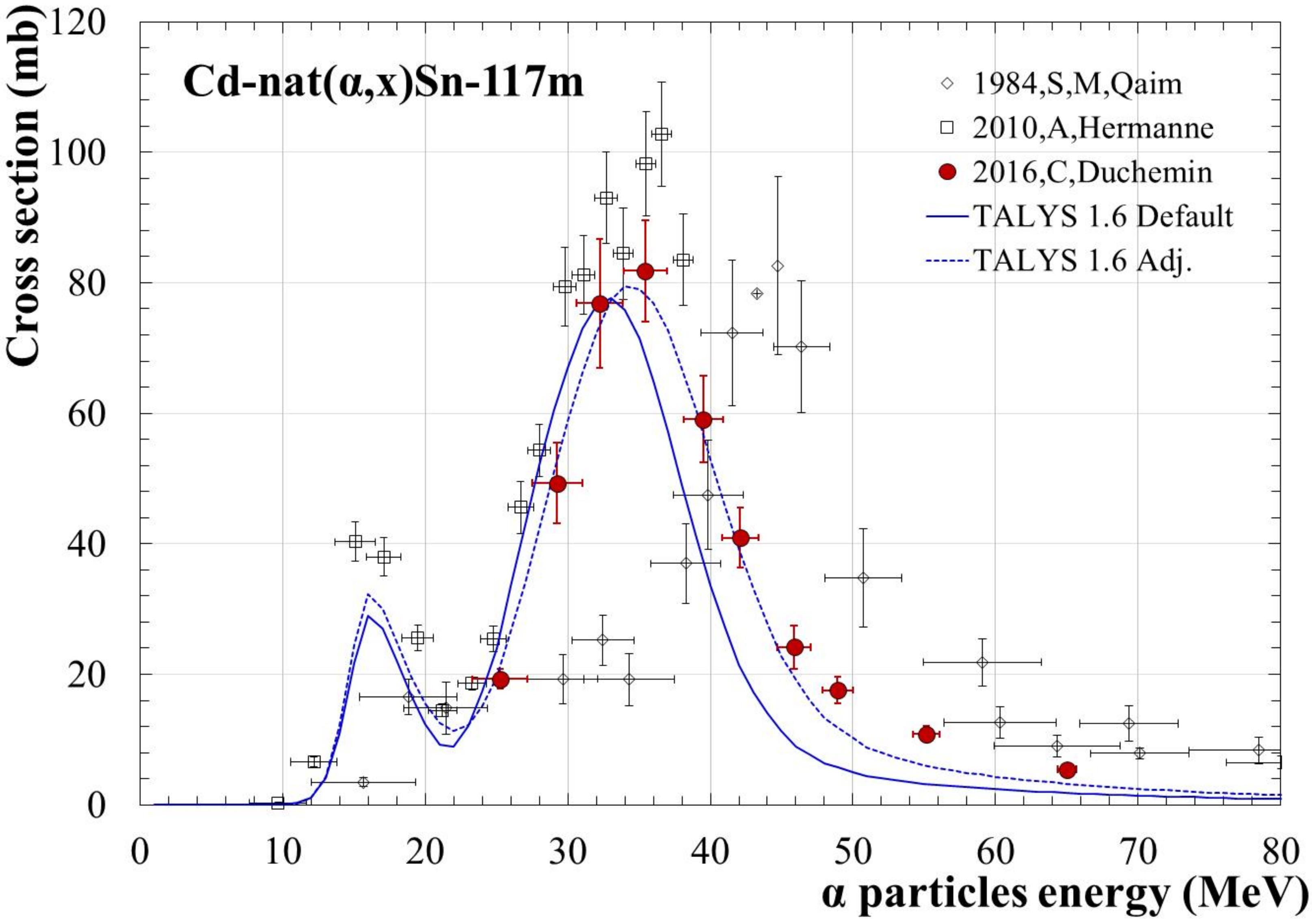
C. Duchemin et al., Appl. Radiat. Isot. 115 (2016) 113-124

Novel therapeutic and imaging nuclide



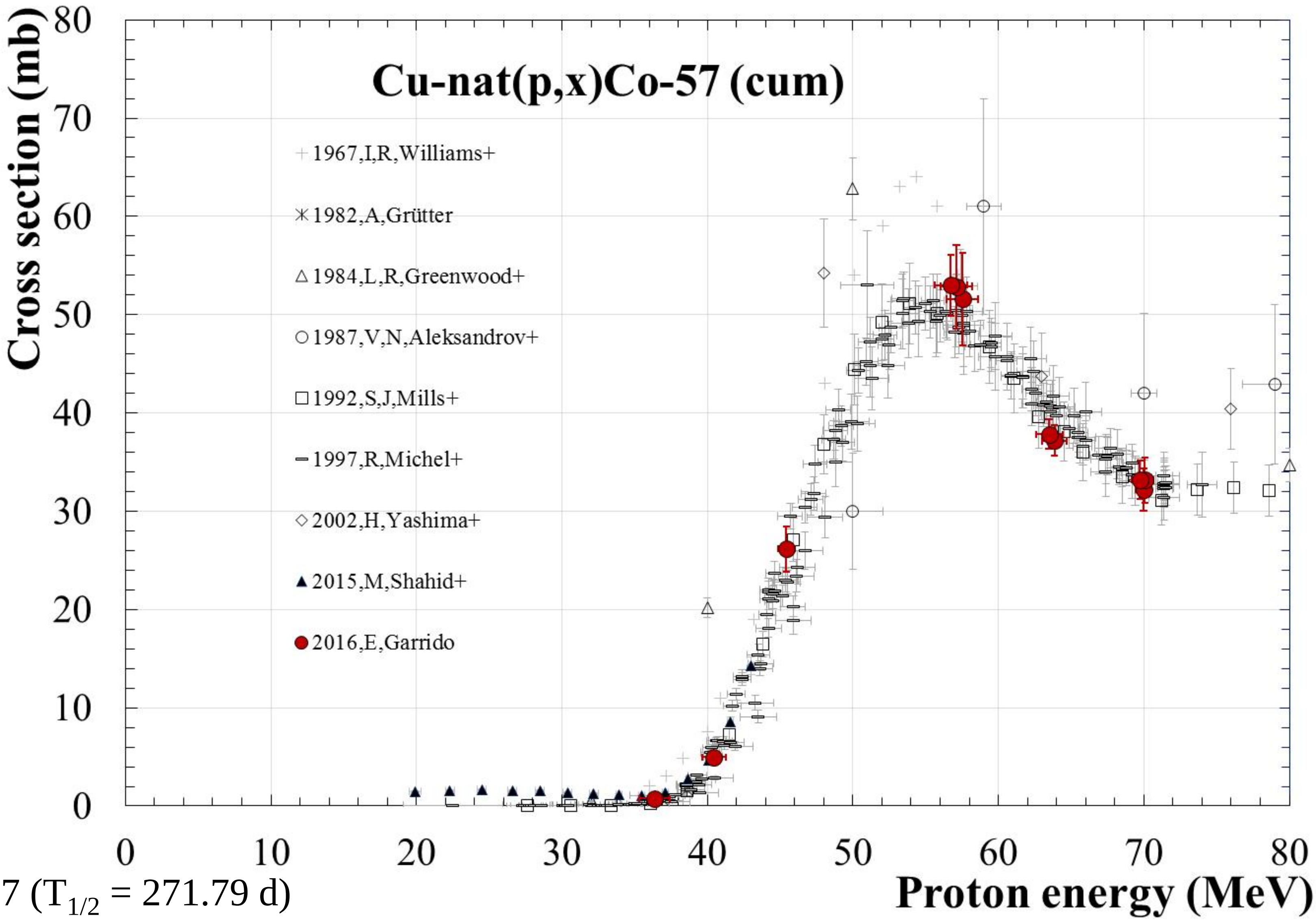
C. Duchemin et al., Appl. Radiat. Isot. 115 (2016) 113-124

Novel therapeutic and imaging nuclide



C. Duchemin et al., Appl. Radiat. Isot. 115 (2016) 113-124

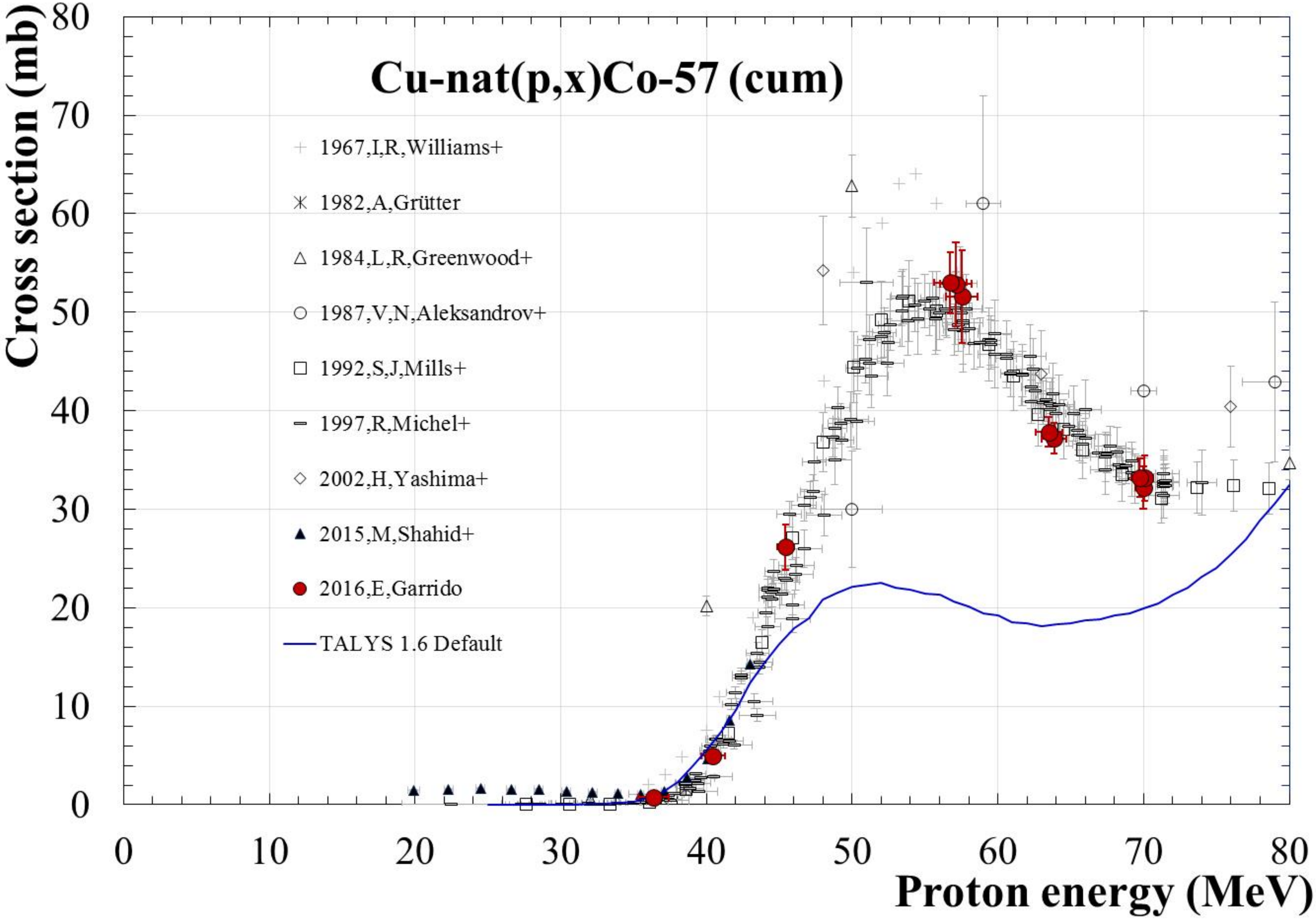
Monitor reaction



Co-57 ($T_{1/2}$ = 271.79 d)
EC process (100%) to stable Fe-57
Suitable for proton monitor reaction

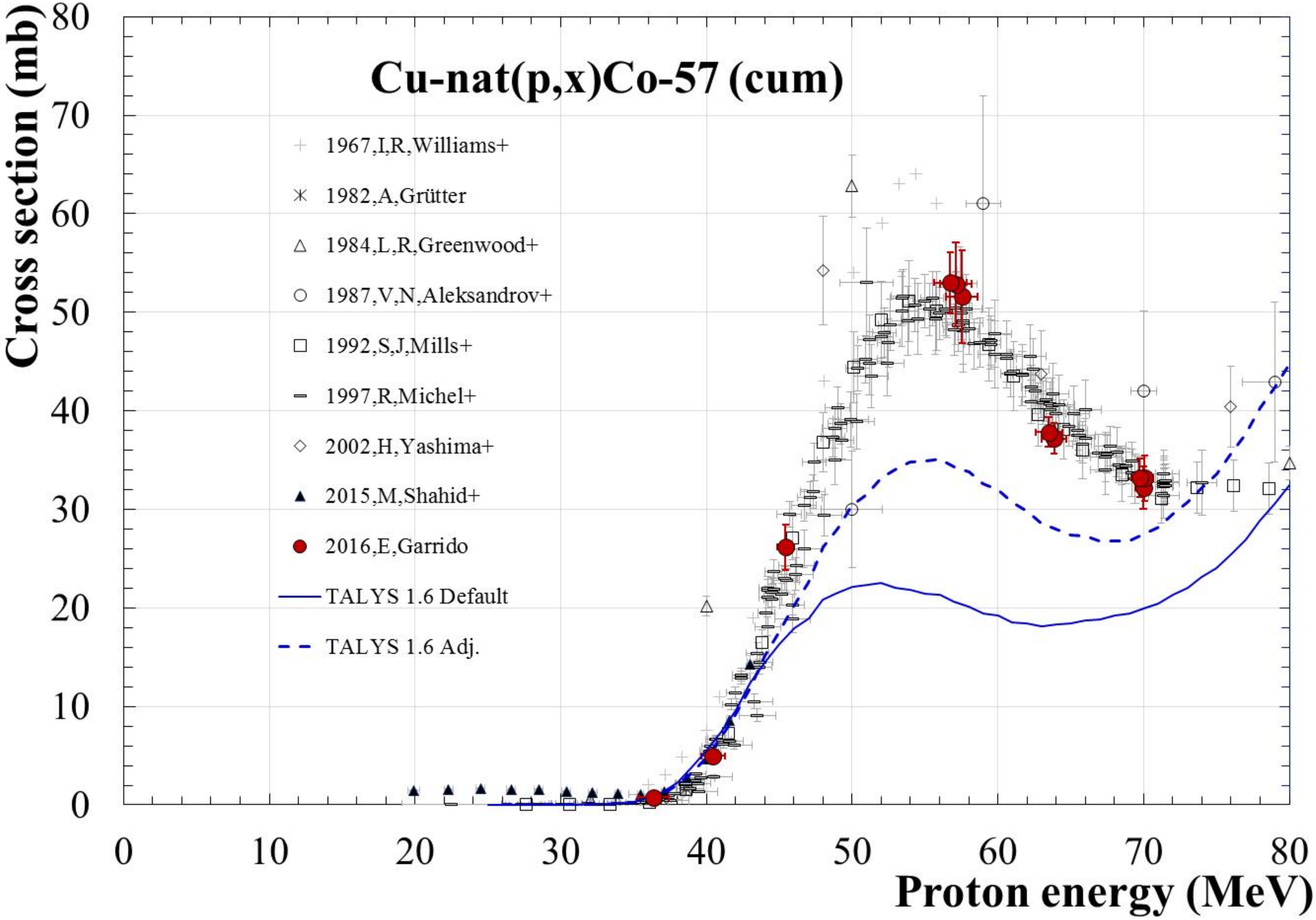
E. Garrido et al., Nucl. Instr. Meth. Phys. Res. B 383 (2016) 191-212

Monitor reaction



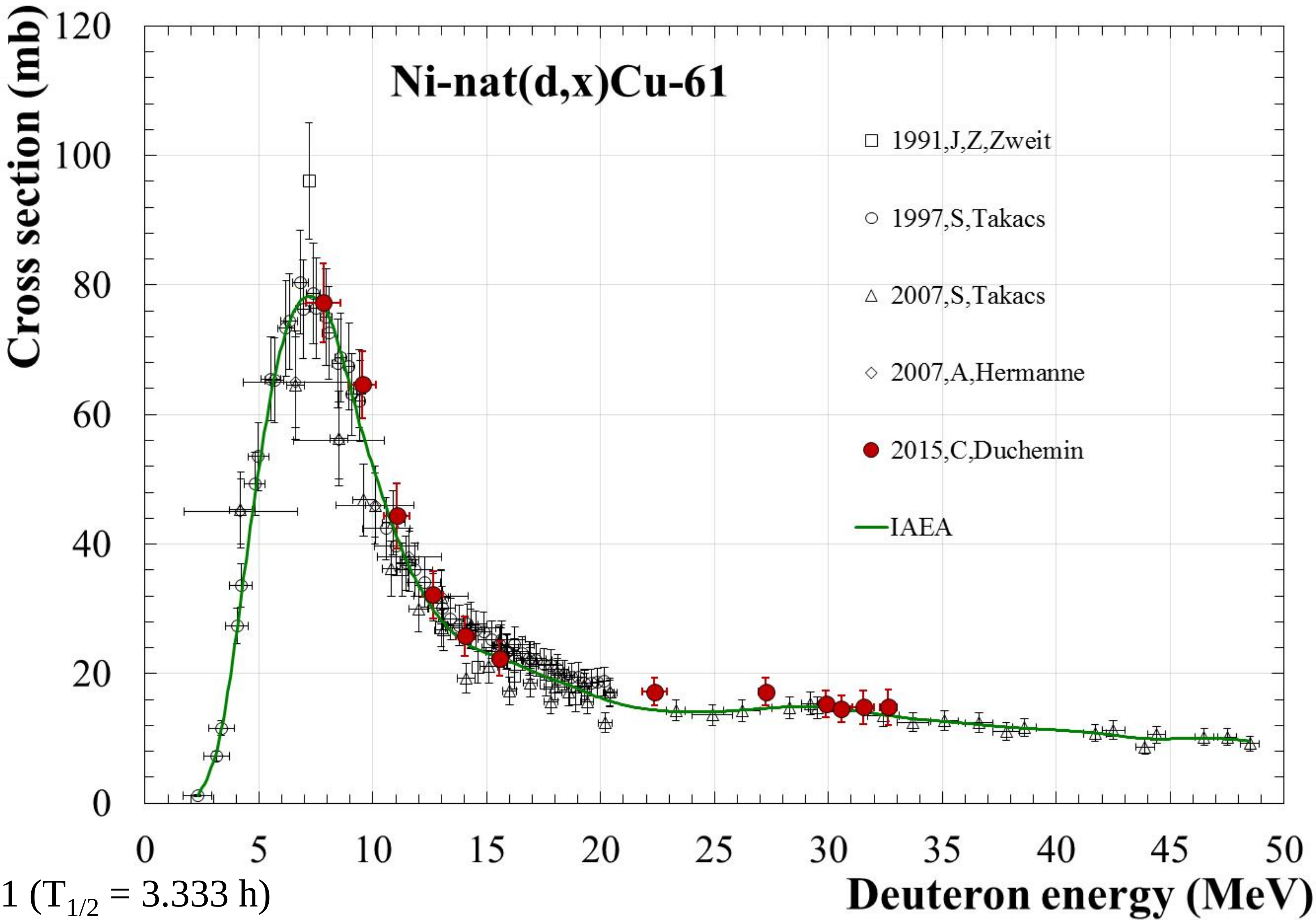
E. Garrido et al., Nucl. Instr. Meth. Phys. Res. B 383 (2016) 191-212

Monitor reaction



E. Garrido et al., Nucl. Instr. Meth. Phys. Res. B 383 (2016) 191-212

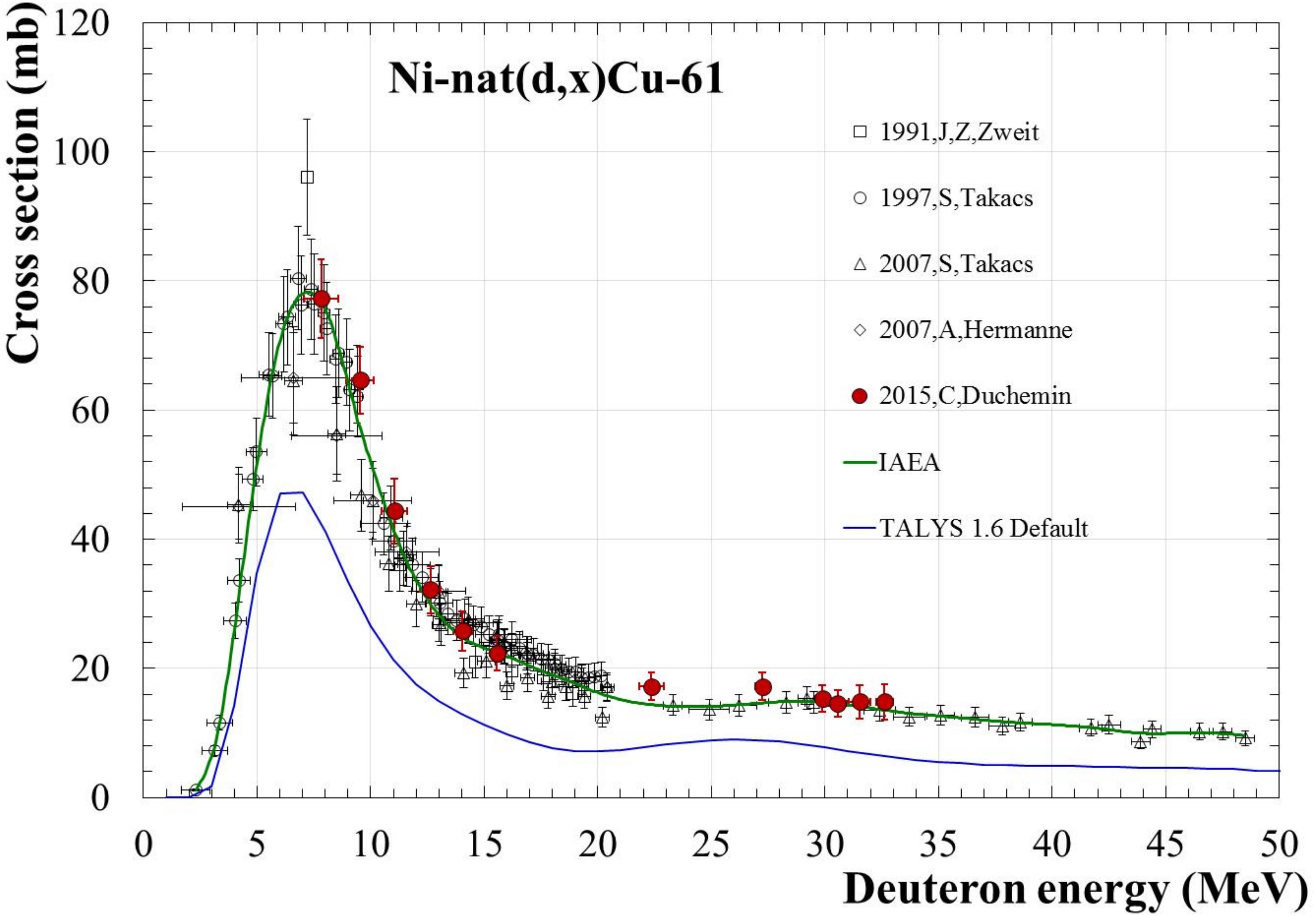
Monitor reaction



Cu-61 ($T_{1/2}$ = 3.333 h)
EC β^+ processes to stable Ni-61
Suitable for PET imaging

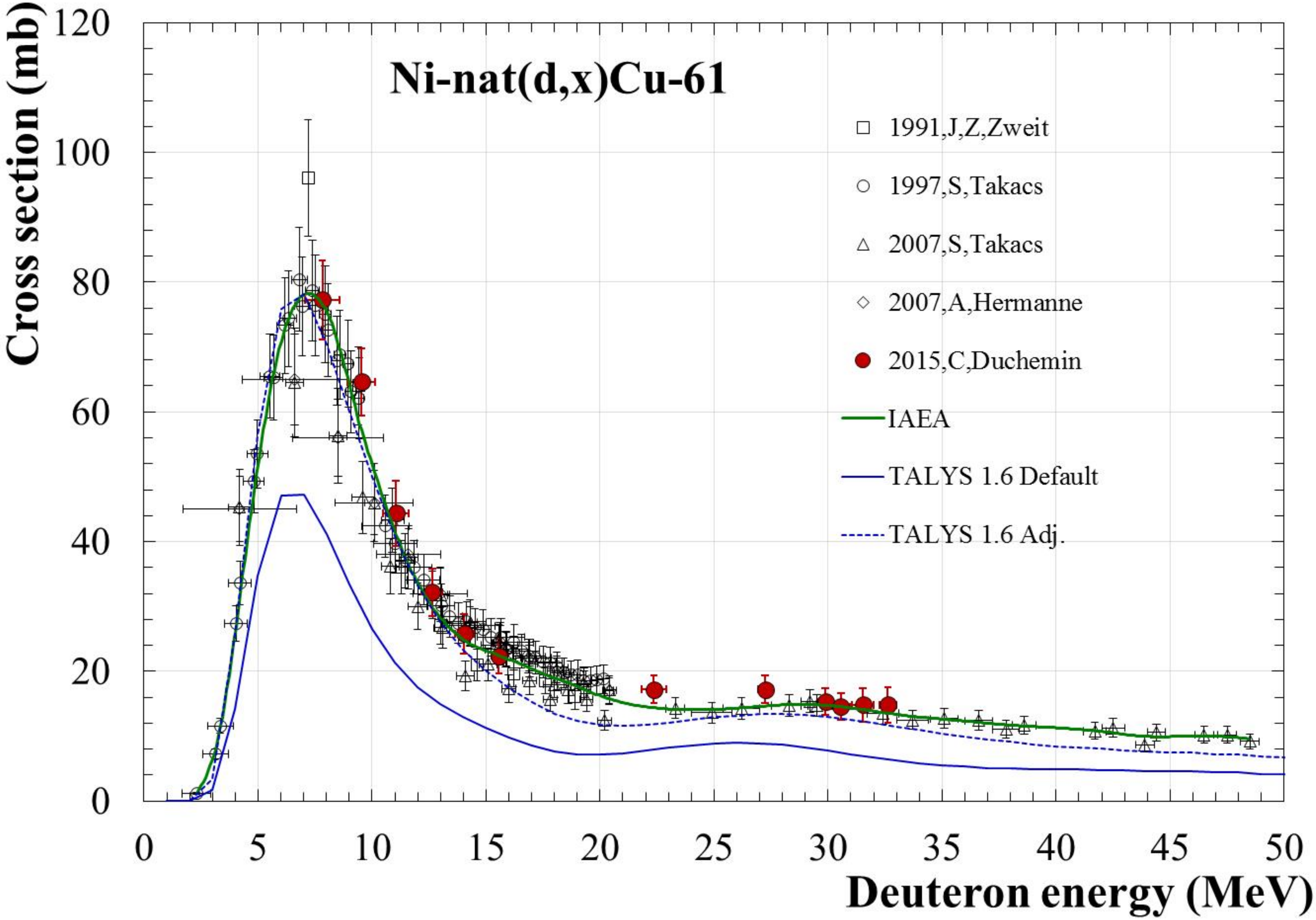
C. Duchemin et al., PhD thesis (2016)

Monitor reaction



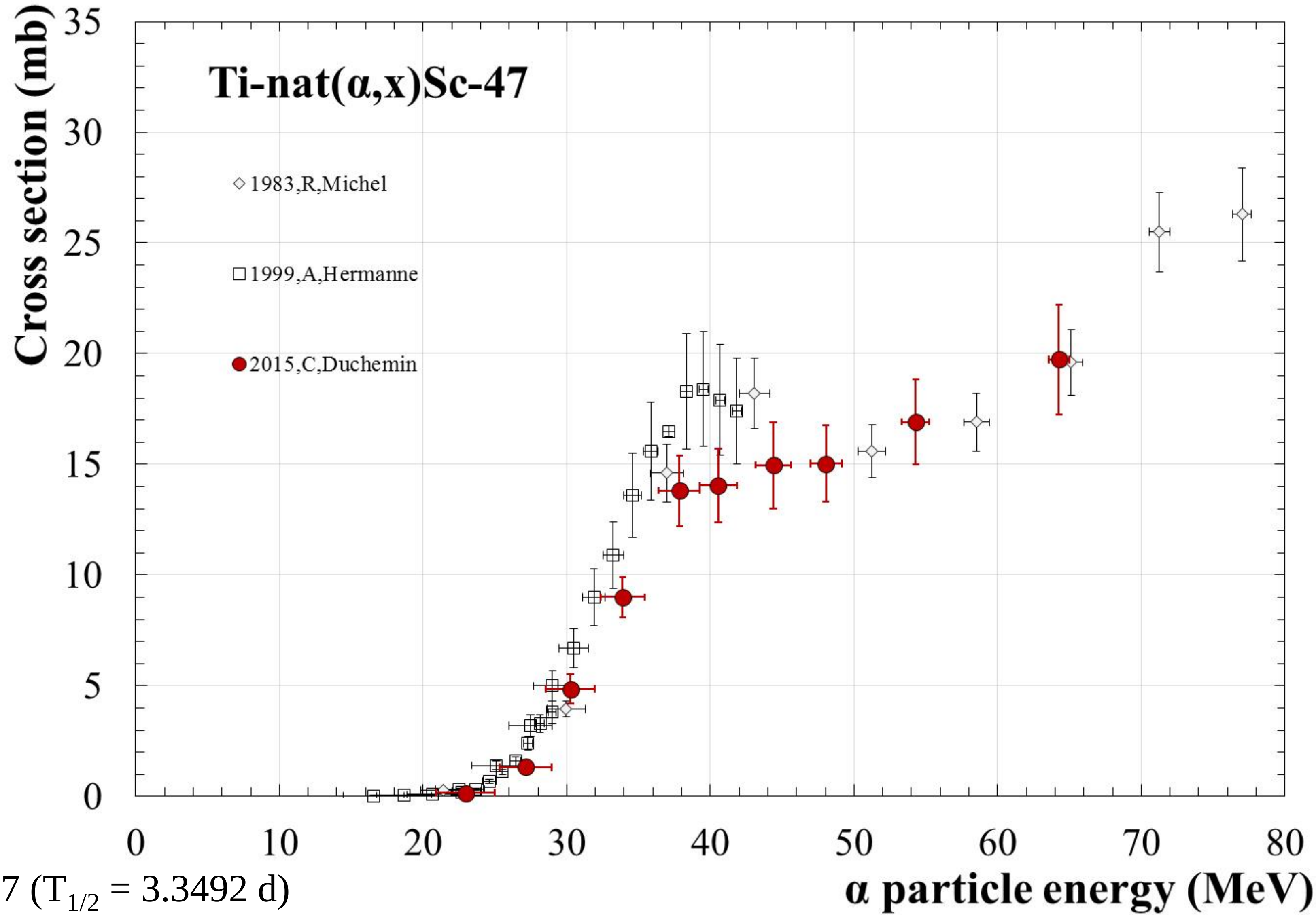
C. Duchemin et al., PhD thesis (2016)

Monitor reaction



C. Duchemin et al., PhD thesis (2016)

Monitor reaction



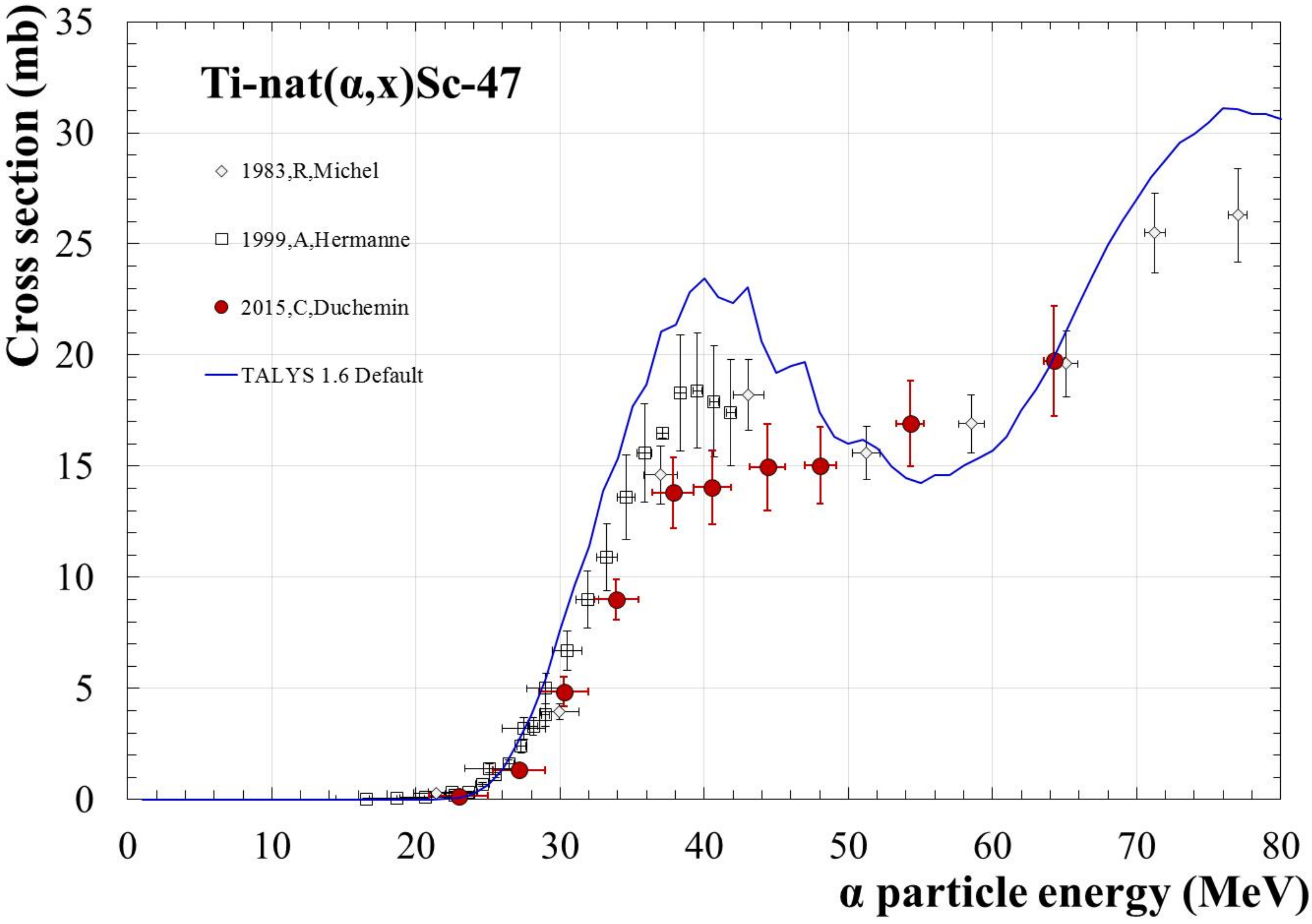
Sc-47 ($T_{1/2}$ = 3.3492 d)

β^- (100%) to stable Ti-47

Suitable for theranostic approach with the Sc-44

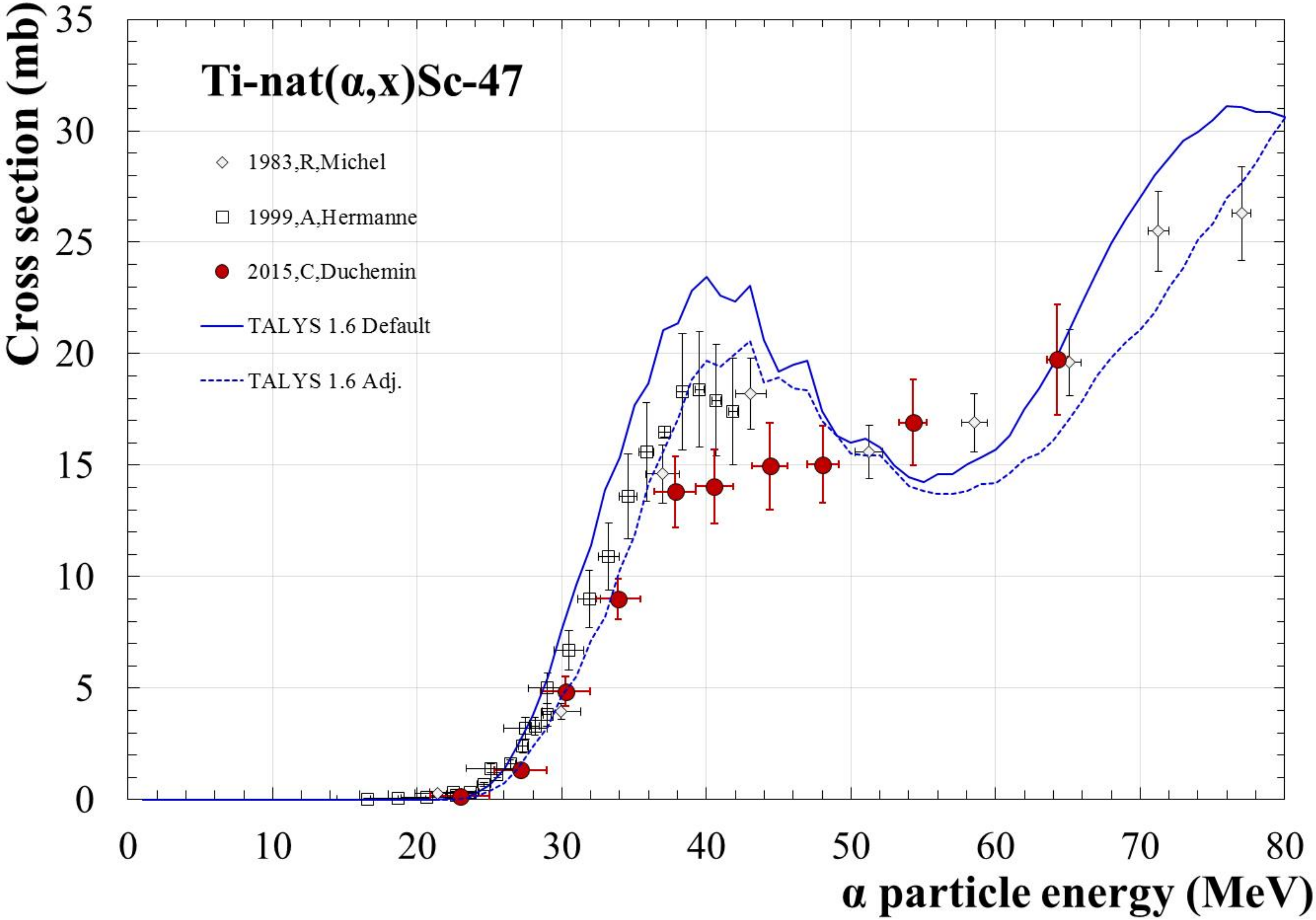
C. Duchemin et al., PhD thesis (2016)

Monitor reaction



C. Duchemin et al., PhD thesis (2016)

Monitor reaction

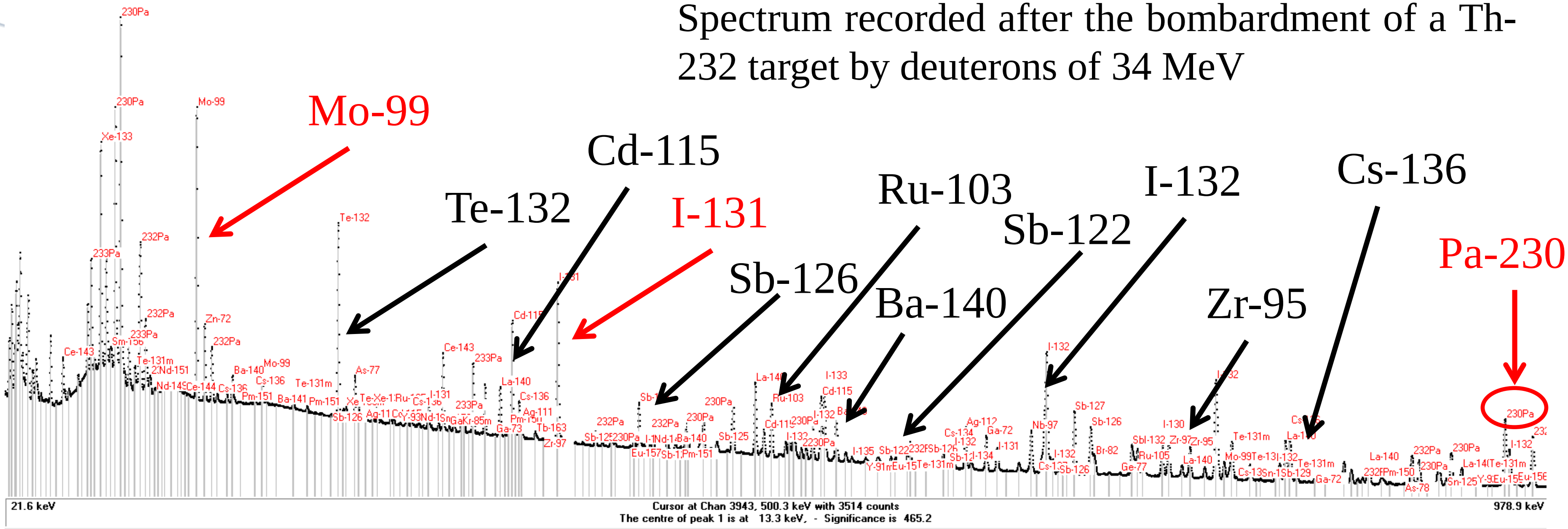


C. Duchemin et al., PhD thesis (2016)

Th-232 induced fission

Fission products

Spectrum recorded after the bombardment of a Th-232 target by deuterons of 34 MeV



Alpha emitters

U-230/Th-226

Ac-225/Bi-213

Th-227/Ra-223

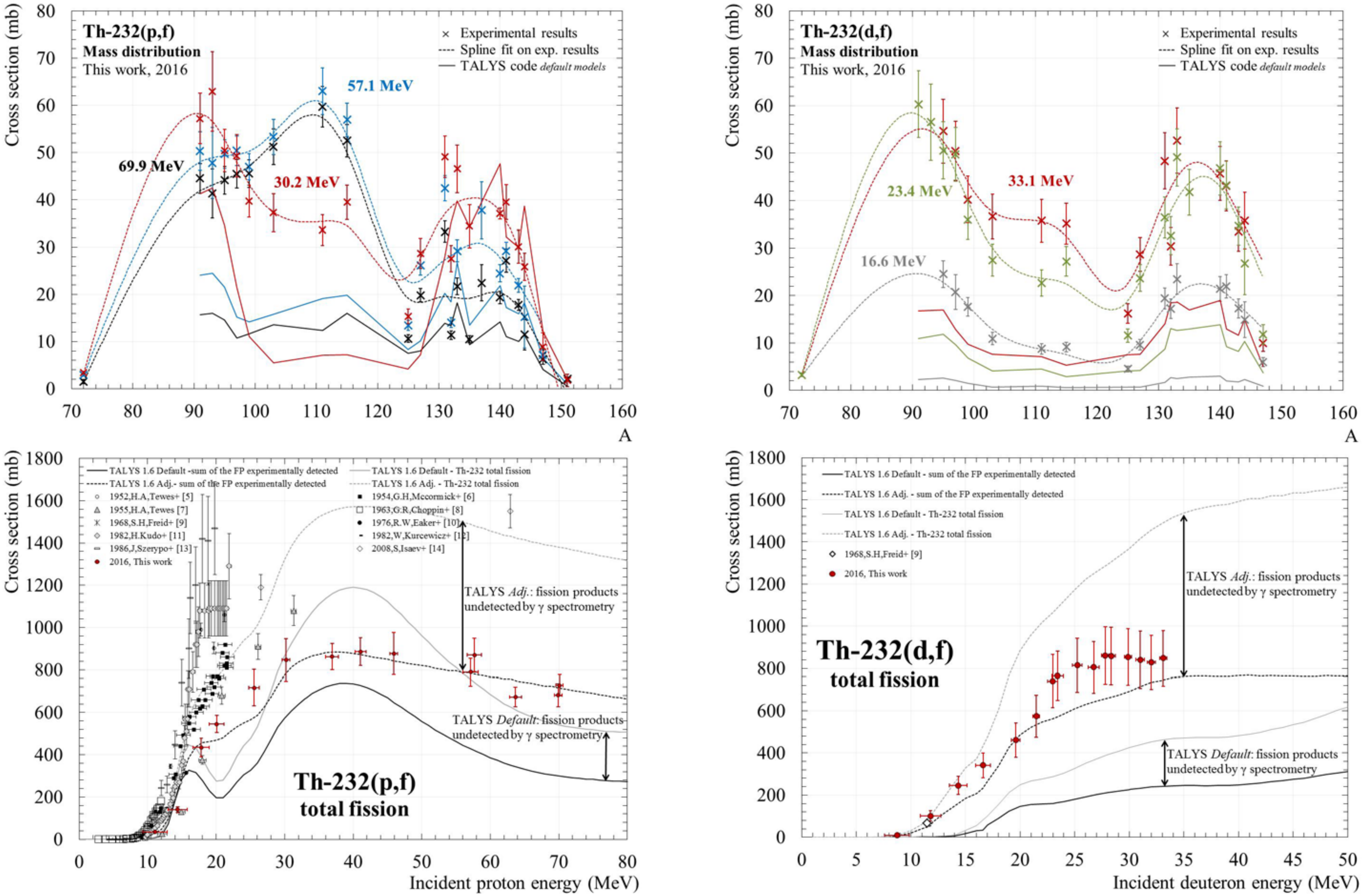
Proton beam

E_{proton} > 70 MeV

Radionuclide	$T_{1/2}$	α particle emitted during the disintegration cascade
Bi-213	46 mn	1
Ra-223	11 d	3
Ac-225	10 d	4
Th-226	30 mn	4
Th-227	19 d	4

From C. Duchemin

Th-232 induced fission

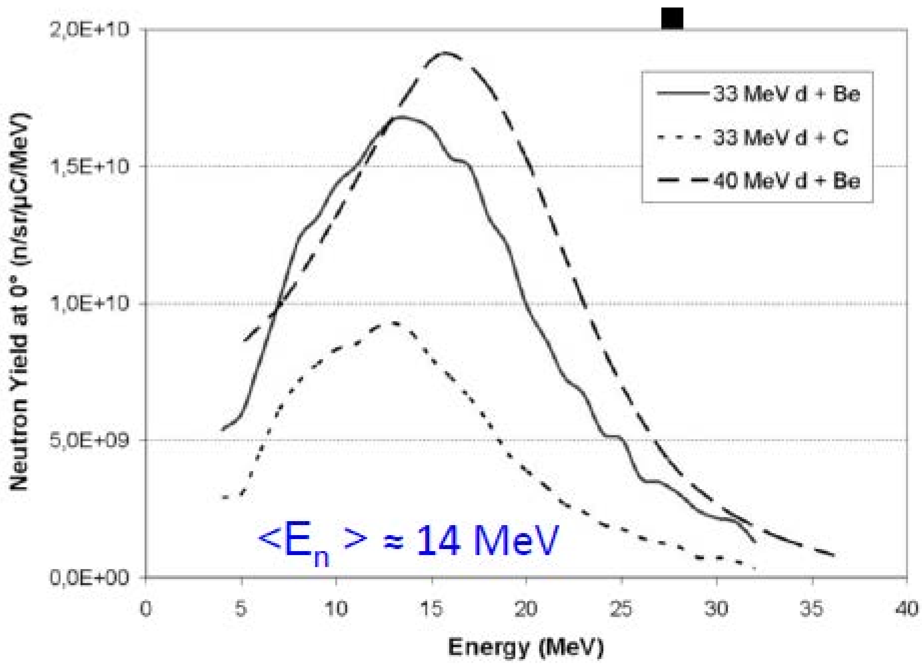


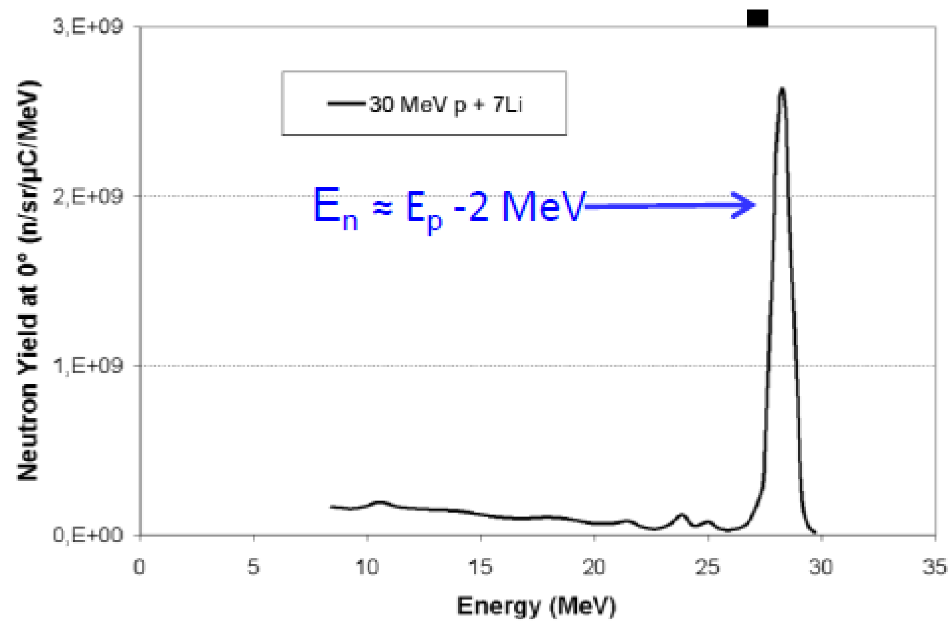
V. Métivier et al., EPJ Web of Conferences 146, 04058 (2017)

NFS beams

beam	P+	D+	ions	ions
A/Q	1	2	<3	<6 or 7
Max. I (mA)	5	5	1	1
Min. output E (MeV/A)	2	2	2	2
Max output E (MeV/A)	33	20	14.5	8
Max. beam power (kW)	165	200	44	48

P. Bertrand , Proceedings of HB2014





X. Ledoux , SPIRAL2 Training 2015

Conclusions

Nuclear medicine

Cyclotrons and **accelerators** being used **in an increasing number** of countries along with reactors

- Diagnosis (γ, β^+)
- Therapy (β^-, α, e_{Auger})

Many useful / potentially useful isotopes identified for applications in **nuclear medicine**

- Personalized medicine

The Right Drug To The Right Patient For The Right Disease
At The Right Time With The Right Dosage

Nuclear data

- **Accurate and reliable** sets of data
  Statistical + systematic errors < 10%
- Well defined **production routes and decay properties**
  neutron, light charged particules and ions
- **Optimum production** of **specific radionuclides**, minimization / elimination of **impurities**, **realistic dose calculations**, **monitor reactions**

Nuclear codes

Provide **a large set of nuclear data** in terms of targets, projectiles and energy range **to constrain and develop** predictive simulation tools of nuclear reactions

Thank you for your attention

Acknowledgments to the NFS Workshop organization committee

“Nuclear data for applications in nuclear medicine”

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