3th GLOBAL MEETING
WG & Core Group meeting of the COST Action CA19114
Network for Optimized Astatine Labeled Radiopharmaceuticals

Date:	October 1th – Octorber 4th, 2024
Place:	*Nantes, France*  ***THE 3RD AND FINAL MEETING OF COST NOAR, THE EUROPEAN NETWORK DEDICATED TO ASTATINE-211 (astatine-net.eu)***
Complete list of participants:	**Core Group and Working Groups Leaders:** Jean-François Gestin Emma Aneheim Antero J. Abrunhosa Marek Pruszyński Penelope Bouziotis Andreas Tue Ingemann Jensen Dana Niculae Emilija Janevik Laurent Navarro Sture Lindegren François Guérard Stig Palm **Participants:** Allard Mathilde Aneheim Emma Angot Christophe Antero Abrunhosa Apostolova Paulina Back Tom Bajrami Ismet Balkin Ethan Bilodeau Denis Bitlis Arcan Blaseg Udo BODERE Françoise Bonnet Jean BOURGEOIS Mickaël

Bouziotis	Penelope
Calais	Jeremie
Carsten	Kramer
Cazzola	Emiliano
Cecile	Bourdeau
Chaize	Clara
Chérel	Michel
Chouin	Nicolas
Cui	Tongjiang
Custodio	Camille
Damas	Liliana
De France	Gilles
De Schepper	Stijn
Do Carmo	Sergio
Domingos	Carla
Donnard	Jerome
Duval	Samuel
Edwards	Richard
Ekinci	Deniz
Ellinor	Hansson
Elvas	Filipe
Eve	Dave
Eychenne	Romain
Fanier	Sylvain
Feng	Yutian
Fouinneteau	Romain
Fujioka	Sunao
Fysikopoulos	Lefteris
Gabriel	Bahuaud
Galland	Nicolas
Garcia-Arguello	Segundo Francisco
Gaschet	Joelle
Gauché	François
Gaugler	Marie-Helene
Gautier	Gaëlle
Gazzola	Sophie
Gestin	Jean-François
Gkikas	Antonis
Gonnot	Amandine
Gourni	Eleni
Guérard	Francois
Guillet	Sébastien
Gülaldi	Nedim C.M.
Gülaldı	Demet
Haddad	Ferid

Happel	Steffen
Harousseau	Jean-Luc
Harray	Jerome
Heinrich	Tobias
Herth	Matthias
Heuze Vourc'h	Nathalie
Hoehne	Aileen
Hrynchak	Ivanna
Hsiaoju	Lee
Huynh	Truc (Sally)
Ingemann-Jensen	Andreas
Issac	Delphine
Ivanovska	Emilija
Jalilian	Amirreza
Jan Jensen	Holger
JANIAK	Tomasz
Jankovic	Drina
Jashari	Armend
Jean-Luc	Lefaucheur
Johnson	Dave
Kabayama	Kazuya
Koers	Lucas
Kolenc	Petra
Kumlin	Joel
Le Gal	Julien
Le Saec	Patricia
Leidermark	Erik
Lethimonnier	Franck
Li	Yawen
Li	Feize
Ligeour	Mathilde
Lindegren	Syure
Liu	Yang
Lonnroth	Milton
Loussouarn	Anthony
Lugat	Alexandre
Mahboob	Gharibi
Maingueneau	Clémence
Marshall	Graham
Martin-Gauthier	Joelle
Metello	Luis F.
Mikolajczak	Renata
Mirković	Marija
Mo Kang	Choong
Moffitt	Gregory

Moreau	Aurélie
Navarro	Laurent
Neumaier	Bernd
Niculae	Dana
Ohnuki	Kazunobu
Paillard	Alexandra
Palm	Stig
Palmer	Max
Paulo	Antonio
PILATIS	EIRINAIOS
Prezeau	Tony
Prince	Deidre
PRUSZYNSKI	MAREK
Radović	Magdalena
Rajkovača	Zvezdana
Reymond	Adrien
Rivière	Karine
Rousseau	Caroline
Royer	Anne
Santos	Sofia
Sarah	Chaib
Scutnaire	Bruno
Seeman	Johanna
Senturk	Murat
Sergi-Lindell	Francesco
Sevenois	Matthijs
Sora	Fallaha
Sosabowski	Jane
Spahiu	Fakir
Stanković	Aljoša
Szucs	Zoltan
Tabacaru	Gabriel
Takamatsu	Masayuki
Taki	Kazuya
Tereshatov	Evgeny
Thonon	David
Ukon	Naoyuki
Valeix	Richard
Viana	Alice
Vranjes-Djuric	Sanja
Washiyama	Kohshin
Watabe	Tadashi
Wheldon	Carl
Wilbur	Scott

	Yokell	Daniel
	Young	Jennifer
	Zahi	Ilyes
	Zalutsky	Michael
	Zhuo	Weibin
	Zimmermann	Richard
	Zirn	Loïc
	Zyuzin	Alexander
Responsible minutes:	Emilija Janevik Laurent Navarro	

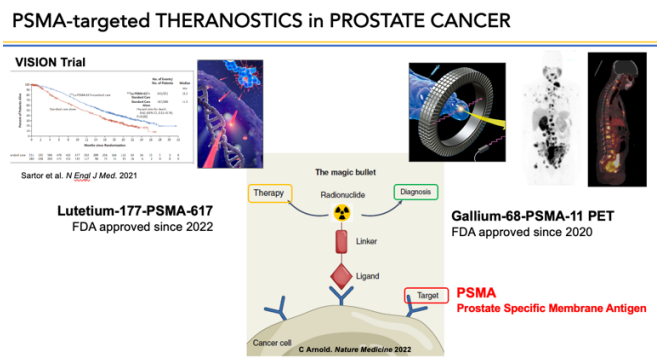
MEETING PROGRAM

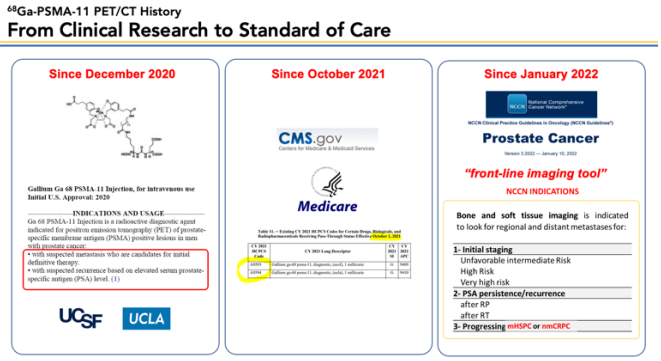
Tuesday, October 1st, 2024 / Nantes

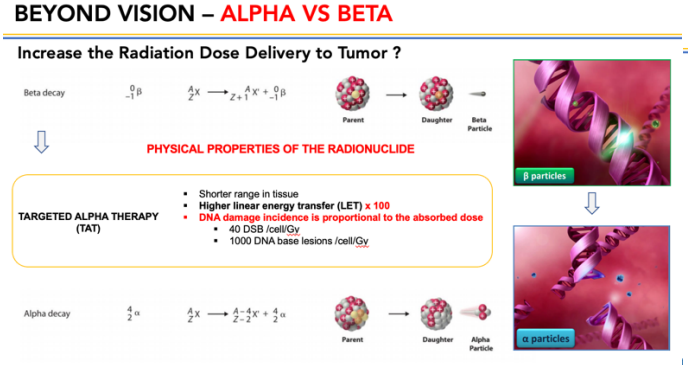
17.00 **Registration**

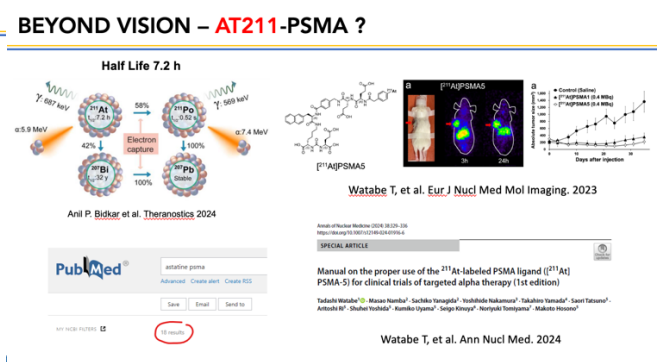
18.00 **Welcome address**
Speakers: Jean-François Gestin (Action Chair) and Emma Aneheim (Action Vice Chair)
Opening greeting from the Acting Chair and Action Vice Chair:
Welcome to all attendees, and thank you for your interest and support. Acting Chair and Action Vice Chair expressed there gratitude to the core team, working group leaders, MC members, and industry partners for their collaboration over the past four years, starting from the time of the pandemic, as well as to COST Office for their support and funding of the project.
The Acting Chair introduced **Dr Jérémie Calais** as the invited lecturer for the opening of the 3th Global meeting

18.15 Invited lecture: **"PSMA-targeted Lu177 Therapy :From research to standard-of-care"**
Dr Jérémie Calais - PluvictoTM from clinical research to Market Autho- rization
Associate Professor, Department of Molecular and Medical Pharmacology
Director, UCLA Theranostics Program
Director, Clinical Research Program
Ahmanson Translational Theranostics Division
University of California, Los Angeles









19.30 **Cocktail reception**

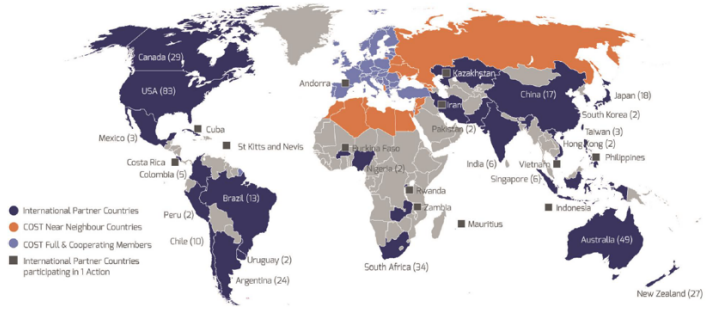
Wednesday October 2nd, 2024 / Nantes

08.00 Welcome : Opening address
Dr. Emma Aneheim & **Dr. Jean-François Gestin**

08.15 **Dr. Jean-François Gestin -** COST NOAR Project
Objective: Introduction of COST Action
Official start : March 2020
Kick off meeting (virtual), October 22, 2020
The Action will end on Monday, October 21, 2024

- Inter-governmental program dedicated to the financing of European and international research networks
- EU funding in addition to member countries
- Management by the COST association based in Brussels

Organization structure with members - 160 members, 37 MC members, 21 EU Countries

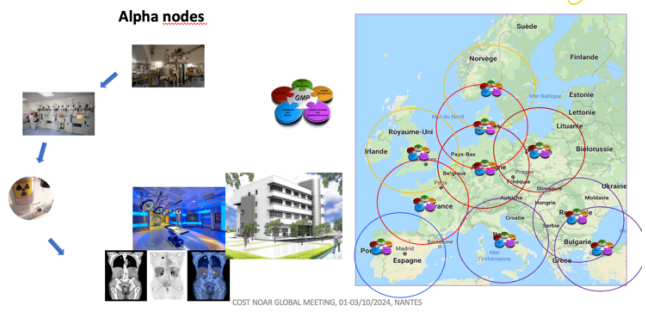


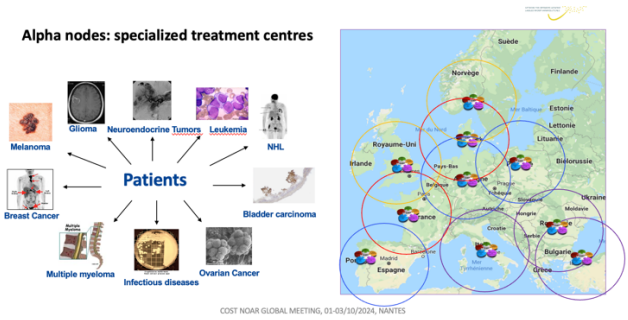
The Acting chair was presented for what is COST made
T**o finance:** All disciplines, all types of partners (academic, private, associations, institutional ...), and Network activities only (**no funding for equipment or research staff**):

Meetings, workshops, conferences,
Short stay missions,
Training schools,
Dissemination actions including publication (open access).

Provided budget quite low **-** Approximately 100.000€/year for a duration of the project of 4 years, according to the number of countries participating in the action.

The Acting chair presented the ambition to built an European Network:





08.25 Progress and prospects

WG 1: Production: what has been achieved - **- Astatine-211 targetry, production, extraction, back- up, logistics**

WG Leader: **Dr. Sture Lindegren**
Objective: To ensure reliable and sustainable astatine-211 production and development of a standardized purification method. This WG will focus on astatine-211 production in order to ensure reliable access to inject patients with therapeutic doses of qualified astatine-211 within the ATNodes in Europe.
Tasks:
T.1.1. Establishing producer catalogue and astatine-211 production procedure
T.1.2. Automating processes
T.1.3. Proposing alternative production solutions
T.1.4. Researching the relevant intermediate (radiochemical) form(s) and final; (radiopharmaceutical) form for astatine-211 delivery
T.1.5. Controlling stability, measuring radiolysis, defining present species
T.1.6. Organising intra and extra cluster logistics / EU territorial grid / back-up

Deliverables, milestones and estimated delivery month

D.1.1. Final forms for astatine-211 delivery (radiochemical or radiopharmaceutical) (m12)

D.1.2. Reference documents (including catalogue of producers) for the production of astatine-211 freely available, open source (m27)

D.1.3. Proposing alternative production solutions National and European Logistics guidelines on the production of astatine-211 and related radiopharmaceuticals (m48)

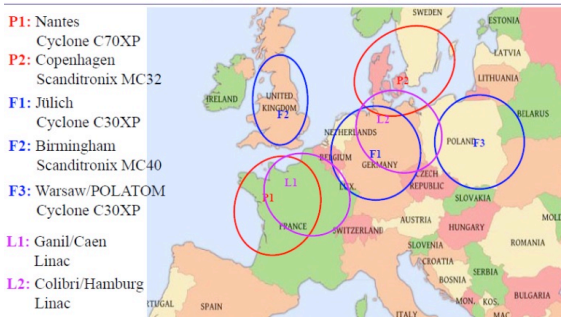
WG1 achievements

- Final forms of Astatine-211 Delivery
- Reference documents (including catalogue of producers) for the production of astatine-211 freely available, open source
- Proposing alternative production solutions National and European Logistics guidelines on the production of astatine-211 and related radiopharmaceuticals

Transport Challenges for ^{211}At

- α-emitter (stigma)
- Early state
- Half-life 7.2 h
- Require on demand production
- Regulation/cross-border transport
- Long distant transport / air cargo

^{211}At Production capacity overview Europe



Dr. Holger Jan Jensen - Copenhagen cyclotron
Chief Cyclotron Physicist,
Department of Clinical Physiology, Nuclear Medicine & PET,
Cyclotron and Radiochemistry unit, 3982
Copenhagen, Denmark.

Objective: **^{211}At production status, Copenhagen, Denmark** including:

- Status of the Cyclotrons in Copenhagen
- Production detals , yields,
- Upgrades: Ion Source, High power int. Target,
- Re-inventing the wheel for ^{211}At Production in Copenhagen

Scanditronix MC32

Transport range:
by flight or by car?

WG1:
Flight "impossible"/
VERY difficult due to long check-in and check-out times.

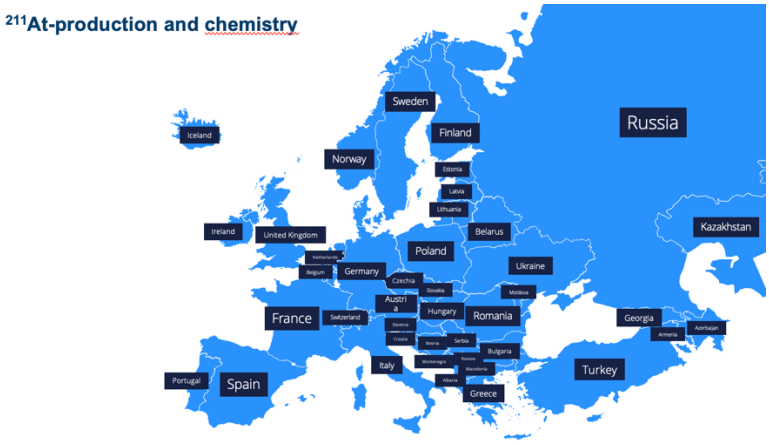
WG1:
Car is the best option.

HJ: Rule-of-thump distance ≤ $T_{½}$.

Dr. Bernd Neumaier - Julich cyclotron

Objective: Progress and prospects: INM-5 Forschungszentrum Jülich

- Presentation dedicated tot he way and stage od construction oft he new cyclotron facility for Radionuclide production at the cyclotron, Radionuclide production and Cleanroom with Radiopharmaceutical production.
- The presentation included detailed ^{211}At Production/Separation/Chemistry, Production yield with Comparison of different target-types
- Obtained results:
  - Molten Target
  - Irradiation: 50-55 µA, appr. 1 h, 50 µAh
  - Yield: 1250 -1780 MBq EOB (γ-line, integration and efficiency)
  - Mean value: 1575 MBq (31.5 MBq/µAh)
  - 0.012 % At-210
  - a-Beam energy: 28.7 MeV (isotope ratio ^{211}At/^{210}At)
  - → Extrapolation: 35 MBq/µAh x 50 µA x 4 h = 7 GBq
- Synthesis of **4-[^{211}At]At-l-phenylalanine**



^{211}At-European Landscape

Pr. Carl Wheldon - Birmingham cyclotron
School of Physics and Astronomy, University of Birmingham
Objective: Astatine-211 production at the Birmingham Cyclotron Facility
The presentation contained:

- Overview of the Birmingham Cyclotron Facility - Twelve beam lines — two exit the vault and Hot filament ion source / Also 46 MeV 14N4+ and 70 MeV 14N5+ for nuclear physics.
- Current radioisotope production - Rb-81, F-18 , Cu-64, Zn-62, Mn-52
- At-211 production development - Birmingham is part of a project funded by the UK Government with the Medical Radionuclide Innovation Programme (MRIP). The project is leded by **Queen Mary's University London** (PI: Jane Sosabowski) involving King's College London .This project aims to establish the first UK production of Astatine-211. **Production will take place at Birmingham.**
- At-211 production: **Atley Solutions Ltd** is supporting in design of target station and the Bi-209 target and are supplying the targets for irradiation
- At-211 purification and synthesis: Atley will provide a C100 module for purification of astatine and synthesis of at-211-labelled compounds in Lon
- Targets and irradiations - Target-holder for external beam is a modified design based on the one used by Copenhagen Hospital (Holger Jensen) with the first irradiations planned for mid-October 2024 with ~ 5 eµA.
- Advert of the new High Flux Accelerator-Drive Neutron Facility (HF-ADNeF)

Dr. Renata Mikolajczak - Polatom cyclotron
Objective: CERAD – a 30 MeV cyclotron in Poland (POLATOM cyclotron)
The presentation started by introducing **CERAD** - **Center of Design and Synthesis of Radiopharmaceuticals for Molecular Targeting, Action 4.2: Development of modern research infrastructure of the science sector with Coordinator: National Centre for Nuclear Research**

- **Cyclone® 30 XP ; proton- deuteron- alpha,**
  - Proton (H- accelerated) 15 - 30 MeV 350µA and 2 exits
  - Deuteron (D- accelerated) 9 - 15 MeV 50 µA with 2 exits
  - Alpha (He2+ accelerated) (29) - 30 MeV 50 µAe with 1 common exit with H+

The presentation included detailed CERAD – layout of the ground floor and stages of Installation and commissioning planned**,** technical specifications (Proton and deutron acceleration system, Alpha particle acceleration system).
The conclusion of this presentation was presenting the question and suggestion how to choose the right cyclotron for Therapy stressing the point what is the best for Alpha radio immuno therapy, is **^{211}At is one of the best using IBA Cyclone 30 XP (proton- alpha)**

Dr. Gilles de France- Ganil LINAC
Objective: **Activities on the production of ^{211}At at GANIL**

The presentation provided :

- GANIL overview
- Opportunities at GANIL using the LINAC
- Current limitations for ^{211}At
- The REPARE Project - Research and dEvelopements for the Production of innovAtive RadioElements, including their own objectives - To study ways to increase ^{211}At production through the ^{209}Bi(α,2n) reaction and to take advantage of the characteristics of SPIRAL 2 beam (up to 80MeV and mAe of α)

The speaker presented the main results:

- WP1: - measurements of production cross section using an alpha beam and evaluation of calculation codes (inventory calculations)
- WP2: - design and manufacturing of a high power solid Bi target and test production run
- WP3: - design study of high power liquid Bi target and No to go
- WP4: - Test bench and measurements of physico-chemical properties of Rn for a possible Rn/At generator

As a next steps are predicted following:

- Installation of the irradiation station in a dedicated area
- Plan more production runs (1-2/months of LINAC time)
- Shipments to ARRONAX, CYCERON
- Structure the activity at various levels (ongoing actions):
  - Local: radiolabelling of VLA4 antibody with At as a POC
  - Regional: reinforce the link with the Nantes area
  - National: create a network of labs/hospitals/industrial partners interested in alphatherapy

International: PRISMAP+, ITN MC network, COST

09.25 **<u>WG2A: Chemistry & Radiochemistry: what has been achieved</u>**

<u>WG2A</u> Leader: **Dr. François Guérard**

Objectives: Development of radiolabelling strategies adapted to different vectors.

This WG was focused on building different astatine-211 radiolabelled vectors in order to establish the preclinical proof of concept for some of them that will be pushed forward through the clinical development.

Tasks:

T.2.1. Setting up couples: vector / astatine-211:

- Innovating the design of more stable ligands.
- Developing modelling techniques confronted with physico-chemical measurements in order to optimize the astatine-211 ligand binding.

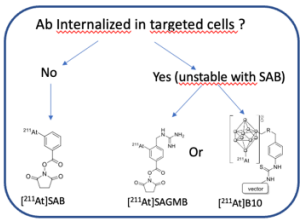
T.2.2. Setting up theranostic aspects: vector / imaging agents.

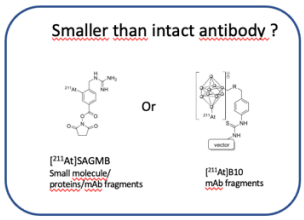
T.2.3. Sharing aspects of toxicology studies to prepare drug files.

T.2.4. Automating, optimizing, and standardizing of radiolabelling protocols for clinical trials.

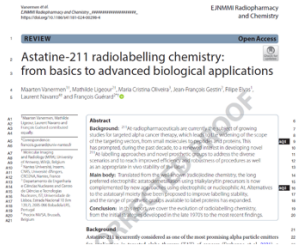
What has been achieved:

- Identification of the most advanced prosthetic groups for the Proof of concept





This work has been synthesized in a review article (in press)



Dr. Matthias Herth - University of Copenhagen

Objective: ASTATINATIONS and their in vivo applications

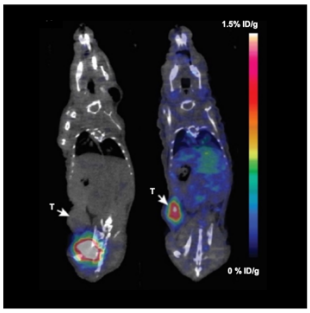
- Development of Labeling Methods
- Development of Small Molecule and Peptide ^{211}At-based Radiopharmaceuticals
- Minimize De-Astatination
- Increase Cell Internalization - as therapeutic efficacy is positively correlated
- Internalized alpha-emitters increase therapeutic efficacy due to recoil energy of the daughter (ca. 5% of the total release energy)
- DE ASTATINATION – rational drug design
- Hypothesis - De-Astationation is reduced when the ^{211}At is attached to an area that lies deep down in the pocket of the receptor and ^{211}At can be substituted for a phenyl ring of the naphtyl moiety of PSMA-617
- Receptor-Ligand-Binding

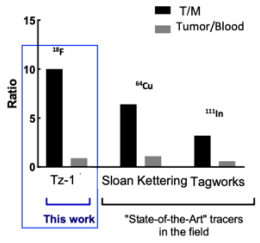
DRUG DEVELOPMENT

- Cmpd Library and In Vitro Characterisation, In vivo Selection - Selected to be translate as a compromise between affinity and internalization, in vivo tumo uptake and retention and excretion profile

HOW TO SYNTHESIZE THE PSMA REFERENCE CMPDS AND PRECURSORS - Solid Phase Peptide Synthesis and Precursor Synthesis

CHALLENGES AND SOLTION TO ASTATINATE PSMA DERIVATIVES and NEW CHEMISTRY - Precursor Synthesis and Labeling
DRUG DEVELOPMENT - Precursor Synthesis and ^{211}At-Labeling, In vivo Evaluation and Correlation between lipophilicity, diffusion & non-specific binding
IN VIVO SELECTION, CELL INTERNALIZATION AND TUMOR BINDING and TREATMENT STUDIES IN TUMOR-BEARING MICE – PILOT DATA
PRETARGETING STRATEGIES - Proof-of-Concept



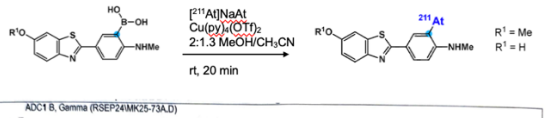


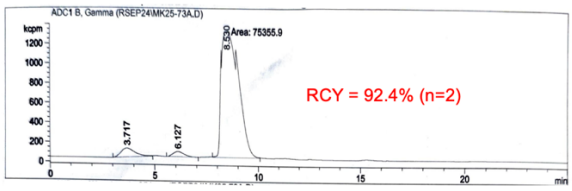
Dr. Yawen Li - University of Washington
Department of Radiation Oncology
University of Washington, Seattle, WA, United States

Objective: Validation of the Semi-Automated At-211 Isolation Process Using Te-packed Columns for Routine Production

- At-211 Isolation Using Tellurium-Packed Columns
- Previous Semi-Automated At-211 Isolation System
- Current Semi-Automated At-211 Isolation System
- Semi-Automated At-211 Isolation Process
- At-211 Production Runs
- Radiochemical Purity - Radio-iTLC
- Radiochemical Purity - Radio-HPLC
- ICP-MS analysis
- Secondary Te Column
- *Closo*-Decaborate(2-) Astatination
- Cu-Catalyzed Astatination

The semi-automated Te-column consistently achieved high isolation yield, along with superior radiochemical and chemical purity, demonstrating its potential for use in routine production
Modifications such as chemical-resistant equipment and the addition of a 0.2-micron filter to reduce tellurium impurities have ensured process robustness and consistent product quality
The isolated ^{211}At demonstrated high RCYs for astatination reactions using *closo*-decaborate(2-) and boronic acid labeling methods





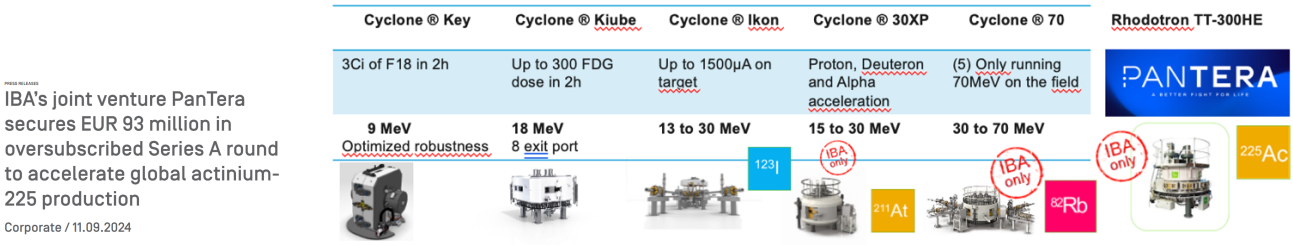
Sean W. Reilly et al., *Org. Lett.* 2018, 20, 7, 1752−1755
Emily K. Kirkeby, et al., *Appl. Radiat. Isot.*, 2023, Vol 191, 110555

10.00 Industrial Presentations

- **IBA - Leading particle accelerator technologies**
Bruno Scutnaire RadioPharma Soltuions

Objective : IBA – Global leader in particle beam technology
IBA Radiopharma Solutions – Installed Base Europe
IBA as a key partner – one stop shop for equipment, and more

- IBA Radiopharma Solution offers the widest range of cyclotron, from 9 MeV up to 70MeV, extensive targetry, chemistry modules and associated services
- IBA solutions will allow you to reach **highest production capacity** as demonstrated in more than 300 radiopharmacies around the world.



- IONETIX - Astatine-211 Commercial Supply
David M. Eve, Vice President, Ionetix Alpha

Objective: Ionetix Astatine-211 Commercial Supply Chain with Ionetix Commercial At-211 Cyclotron Platform, Ionetix Commercial At-211 Manufacturing Platform including Ionetix Commercial At-211 Program Status
U.S. Based Astatine-211 Services:

- At-211 supply
- CDMO/CMO services
- FDA Regulatory support
- Logistics

- NUSANO - supplying the fight against cancer
Greg Moffitt, Director of Target Development

Objective: Commercial operations begin 2025
Production Capabilities
^{211}At: Worldwide Production
Capability of production – 25+ different isotopes, up to 12 simultaneosly
^{211}At Production - ^{211}At yields: 0.44-1.1 mCi/µAhr[1]
^{211}At Production - ^{211}Rn generator for ^{211}At - expand our service region

10.15 Dr. Ferid Haddad - Arronax cyclotron for Lu-177 and Ac-225
on behalf of the GIP Arronax Team and Prisma@subatech, Nantes Université

Objective: Radionuclides and radiopharmaceuticals development at ARRONAX
ARONAX - Accelerator for Research in Radiochemistry and Oncology at Nantes AtlantiX

- Creation date 2008
- End of commissioning (dec 2010)
- 70 workers (including Phd students)
- Soon 2 cyclotrons (C70XP and Kiube 180)
- ISO 9001 certify since 2014

ARRONAX is at the heart of a pluridiciplinary cluster
Beam characteristics:

- Multi-particles: proton, deuteron and alpha particles
- High energy: up to 70 MeV (protons, alpha particles)
- High intensity: up to 750 µA in dual proton beam mode

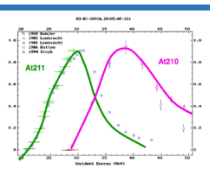
A versatile facility:

- 2000 m^2 of restricted area / 6 vaults / 3 lines of hot cells for radionuclides production / 3 lines of hot cells for sterile radiopharmaceuticals production

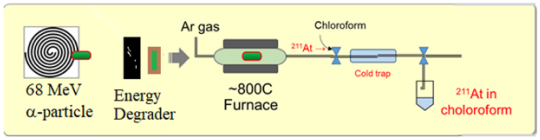
Aronax radiopharmacy (Nantes university hospital/ Arronax)
Arronax PIPELINE
Astatine – 211 - Astatine-211 production route used @Arronax:

$^{209}Bi + \alpha \rightarrow {}^{211}At + 2n$

coproduction of ^{210}At



Production scheme:



The beam energy degrader made of graphite
→ changing its thickness allows to change the At210/At211 ratio

Target preparation using evaporation under vacuum
Dry extraction of ^{211}At
Improving our ^{211}At production process

10.30 Break - Industrial exhibition

11.00 **<u>WG2B: Biology: what has been achieved</u>**

WG2B Leader: **Dr. Joelle Gaschet/ presented by Dr. François Guérard**

Objectives: Inventory of vectors properties proposed and selected for astatine labelling in order to establish the preclinical proof of concept for some of them that will be pushed forward through the clinical development

Deliverables & Milestones:

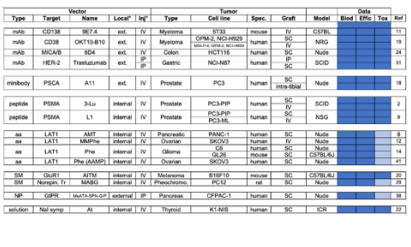
Catalogue of validated radiolabelling techniques dependent on vectors including advantages and disadvantages, and multi-centre diffusion

Preclinical proof of concept

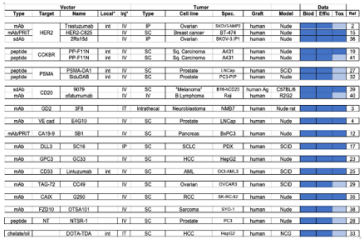
- Overview of the in vivo preclinical studies using ^{211}At, ^{213}Bi,^{149}Tb, ^{225}Ac and ^{227}Th
- Only studies presenting 3 sets of data: Efficacy, Toxicity, Biodistribution

What has been achieved:

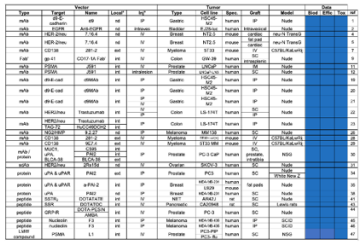
^{211}At Preclinical studies : Joëlle Gaschet & Mathilde Allard



^{225}Ac Preclinical studies : Joëlle Gaschet & Mathilde Allard

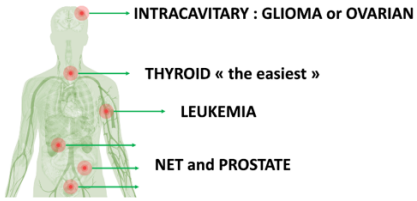


^{213}Bi Preclinical studies : Sanja Vranjes-Djuric & Drina Jankovic



What has been achieved

➢ **Fruitfull inter-WG discussion about the « best » clinical indications in Coimbra, May 2023 (to be continued by WG4...)**



What has been achieved

^{149}Tb Preclinical studies : Sanjav Vranjes-Djuric & Zorana Milanovic

Vector					Tumor					Data			
Type	Target	Name	Local*	Inj*	Type	Cell line	Spec.	Graft	Model	Biod	Effic	Tox	Ref
mAb	CD20	Rituximab	ext	IV	Lymphoma	Daudi cells	human	IV	SCID				2
peptide	PSMA	PSMA-617	int	IV	prostate	PC-3 PIP	human	SC	Nude				6

Dr. Emma Aneheim - University of Gothenburg
Tom Bäck, PhD, Researcher
Targeted Alpha Therapy group, University of Gothenburg, SWEDEN

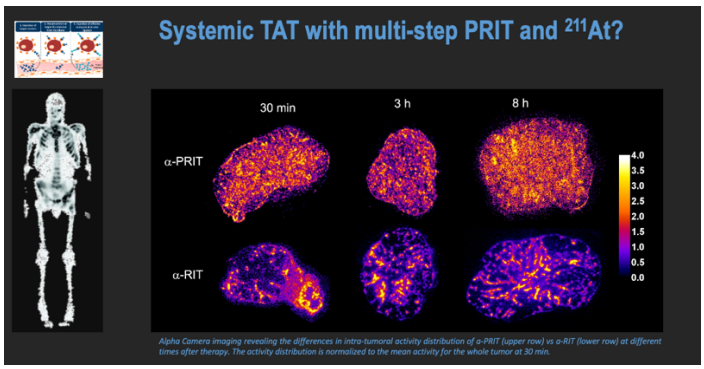
Objective:
Develop and evaluate TAT
Derive parameters for dosimetry
Verify and validate dosimetry

Intra-peritoneal **a**-RIT with ^{211}At for Ovarian Cancer

- Clinical Trial Phase I a/b, ^{211}At-MX35-F(ab')$_2$
- Preparing a Phase I c, ^{211}At-trastuzumab (IgG)
- Planning for a Phase II/III
- Effects on normal organs
- Derive parameters for dosimetry

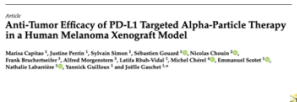
A Novel Method for Real-Time Quantification of Radioligand - Binding to Living Tumor Cells In Vitro

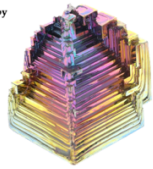
- Evulauation using micro tumours and spheroids
- Systemic TAT with multi-step PRIT and ^{211}At?



Dr. Michel Chérel - University of Nantes
CRCI²NA Nuclear Oncology

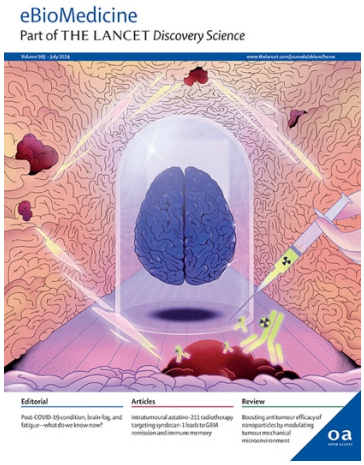
Objective : Alpha particles in Nantes - A little journey with our colleagues from IETU Karlsruhe


Anti-Tumor Efficacy of PD-L1 Targeted Alpha-Particle Therapy in a Human Melanoma Xenograft Model



Use PD-L1 for TAT to target the tumor and its stroma using anti-PDL1.

- alpha RIT in solid tumors - NET
- ^{211}At in Multiple Myeloma
- Alpha-RIT : ^{211}At-anti-mCD138 - Fractionated doses protocol, survival curves, Repeated doses protocol, Repeated doses - survival curves
- Preclinical study of Targeted Alpha Therapy using ^{211}At-labeled phenylalaline derivative in a syngeneic Multiple Myeloma model
- Alpha-RIT : ^{211}At-Phenylalanine - Amino acid transporter LAT-1 and Dose escalation and efficacy study of ^{211}At-APA



eBioMedicine
Part of THE LANCET Discovery Science

Brain intratumoural astatine-211 radiotherapy targeting syndecan-1 leads to durable glioblastoma remission and immune memory in female mice

Loris Roncali,[a,b] Séverine Marionneau-Lambot,[b,c,d] Charlotte Roy,[b,e] Romain Eychenne,[b,f] Sébastien Gouard,[b,d] Sylvie Avril,[g] Nicolas Chouin,[b,g] Jérémie Riou,[b] Mathilde Allard,[b] Audrey Rousseau,[a,b] François Guérard,[b] François Hindre,[a,e] Michel Chérel,[b,d,j,k,*] and Emmanuel Garcion[a,e,j,k,**]

Glioblastoma : an unmet clinical need

Locoregional targeted radiotherapy in GBM - Single injection of [^{211}At]-9E7.4

- [^{211}At]-9E7.4 radiotherapy reveals a major survival benefit and generates long-term survivors
- Long-term memory response - Survivors rechallenge with a new contralateral graft in the striatum
- Radiobiology - Alpha particles can destroy cells in G0 phase
- Radiobiology of astatine-211
- ^{211}At-anti-CD138 induces DNA double-strand breaks
- ^{211}At-anti-CD138 increases cytoplasmic dsDNA levels

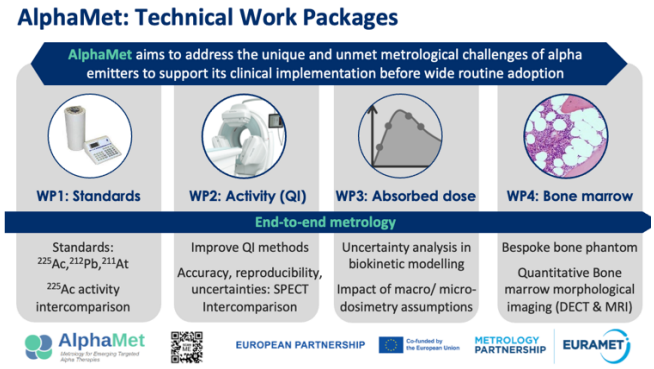
- ^{211}At-anti-CD138 can induce IFN-b secretion
- Intravesical [^{211}At]At-anti-CAIX mAb

11.30 **<u>WG3: Improving dosimetry: what has been achieved</u>**

WG Leader: **Dr. Stig Palm**

Objective: Construct and validate computer models for estimating absorbed dose to tumours and healthy tissues. This WG will focus on dosimetry to predict efficacy and risks associated to the use of the different astatine derivates. Absorbed (radiation) dose must be estimated to both tumours and healthy tissues. This is necessary to fulfil radiation safety regulations, but also to predict efficacy and risks within the context of personalized medicine. Dosimetry is thus a crucial component for selecting and optimizing the best vectors for astatine-211 delivery. However, consensus on best dosimetry techniques for alpha-emitters such as astatine-211 are lacking and need to be developed.

Tasks:
T.3.1. Collecting data on stability and biokinetics from all consortium members.
T.3.2. Constructing biokinetic models that provide the best fit to the collected data.
T.3.3. Proposing new experiments that will test/validate the new models.
T.3.4. Simulating decay of astatine-211 to the predicted distribution sites.
T.3.5. Generating (predicted) maps of absorbed dose to tumours and healthy tissues for a range of vector/astatine-211 combinations.
AlphaMet: Consortium



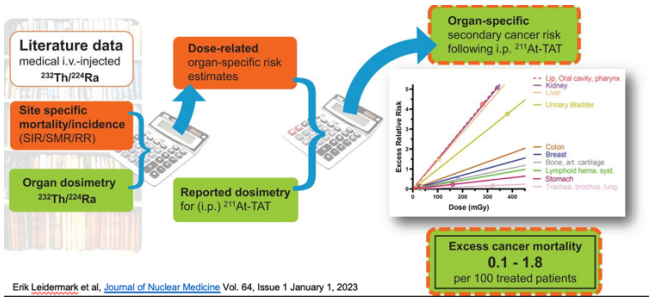
AlphaMet: Survey on the Use of Alpha Emitters

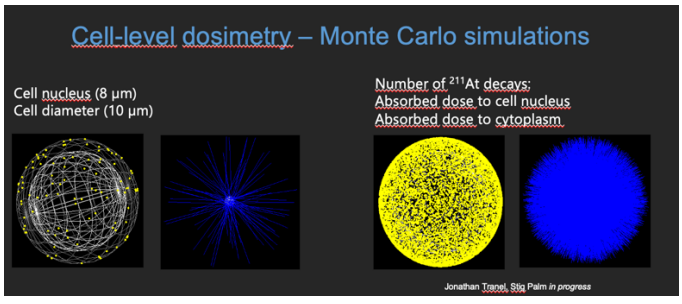
Dr. Tom Bäck- University of Gothenburg
Researcher
Targeted Alpha Therapy group, University of Gothenburg, SWEDEN

Objective: Summary from Gothenburg – Dosimetry/ Dosimetryiology
Can dosimetry predict biological outcome of TAT?

- TAT with ^{211}At → Same mean absorbed dose to whole kidney
- Different kidney toxicity due to different sub-organ dose distribution?

Non-uniform dose distribution in tumours - Both in macro tumours and micro tumours
Dynamic simulation and dosimetry model - Intra-peritoneal ^{211}At-RIT for ovarian cancer
Estimating the risk for secondary cancer following TAT with ^{211}At intraperitoneal radioimmunotherapy
Dynamic simulation and dosimetry model - Intra-thecal TAT with ^{211}At-RIT for children with neuroblastoma
Dynamic simulation and dosimetry model - Intra-thecal TAT with ^{211}At-RIT for children with neuroblastoma

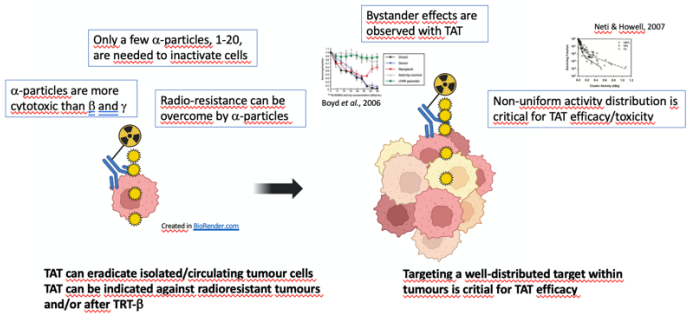




Dr. Nicolas Chouin - University of Nantes
CRCI²NA Inserm U1307, Nuclear Oncology research team

Objective : TAT a translational journey - What we learn as a group and as a community… with dosimetry

Summary from the history:



Comparison of alpha-emitters – At-211 and Bi-213 in Multiple myeloma
Breast cancer metastases model (Song *et al.,* Cancer Res, 2009)
2010: (non-uniform) activity distribution at micrometric scale… revealed
The [^{211}At]At-9E7.4 radiotherapy is efficient against glioblastoma
Mean asborbed dose delivered to GB tumours - Estimated mean absorbed dose to GB tumour > 300 Gy (for 100 kBq of ^{211}At-9E7.4)

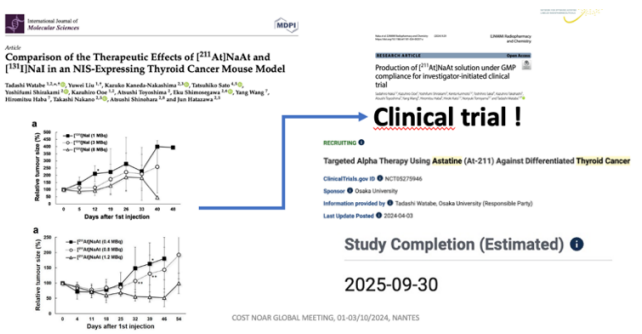
On-going work :

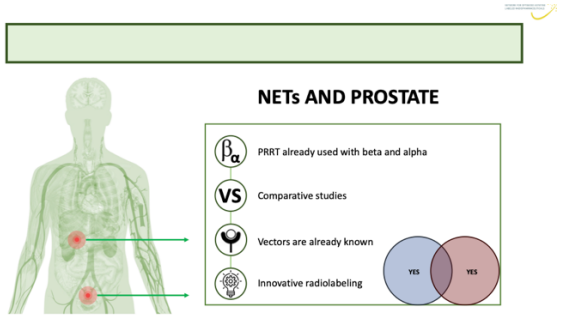
- Comparison of alpha-emitters ^{225}Ac vs ^{211}At - Impact on haematological toxicity
- Spectroscopic autoradiography (^{225}Ac
- Standardization of practice in autoradiograph

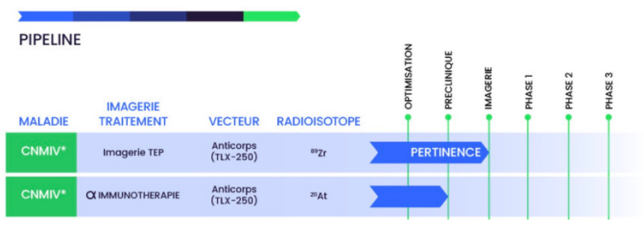
12.00 **<u>WG4: Clinical applications: what has been achieved</u>**

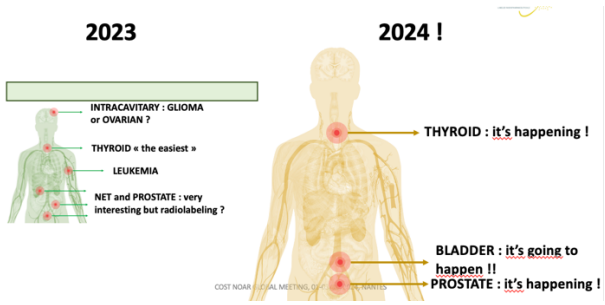
WG Leader: **Dr. Alexandre Lugat/ presented by Mickaël Bourgeois**
CRCI2NA, team 2 : nuclear oncology
Nuclear Medicine Department,
GIP ARRONAX
CHU Nantes

Objective: Feedback and standardization of clinical practices.
This WG will focus on establishing which pathologies are best adapted to benefit from treatment with astatine-211 targeted therapy and prove the clinical potential. It will also focus on the organizational, regulation and economic aspects in order to evaluate the European practices and to propose a standardization of practices.
Tasks:
T.4.1. Identifying relevant pathologies for the use of astatine-211.
T.4.2. Analysing the practices of each member country and regulatory aspects.
T.4.3. Evaluating the cost of therapy in each member country.
T.4.4. Logistics and patient networking.
T.4.5. Assessing the issue of radioactive waste.









Dr. Scott Wilbur - University of Washington
[1]Translation Science and Therapeutics Division and Clinical Research Division
Fred Hutch and Fred Hutch Cancer Center
[2]Department of Radiation Oncology and [3]Division Of Hematology and Oncology
School of Medicine, University of Washington
Seattle, WA USA

Objective: Update Of Fred Hutch/UW Clinical Trials Using ^{211}At-labeled mAb-B10 Conjugates

Status of Fred Hutch/UW ^{211}At Clinical Trials

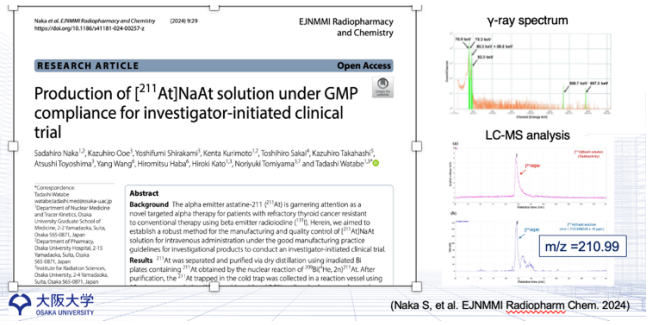
- Introduction to Allogeneic Hematopoietic Cell Transplantation
- Reduced-intensity HCT For AML
- Treatment Plan of FH 9595
- Peripheral Blast Clearance After ^{211}At-BC8-B10
- Treatment plan and Results

Clinical Hold of ^{211}At-BC8-B10 Protocols

- FDA requiring dosimetry based on imaging
- While not part of the Clinical Hold - FDA requiring size-exclusion HPLC (UV & radio) in validation runs

Dr. Tadashi Watabe - University of Osaka
Department of Radiology, Graduate School of Medicine,
Osaka University

Objective: Clinical Application of Targeted Alpha Therapy using Astatine (^{211}At)



From basic research to clinical trials – preclinical to clinical

Research collaboration in Osaka University

- Biodistribution in rats (3hrs) : ^{211}At vs ^{123}I
- [^{211}At]NaAt: cellular uptake (K1-NIS)
- DNA double strand break : ^{211}At vs ^{131}I
- [^{211}At]NaAt: treatment effect (K1-NIS)
- Extended single intravenous toxicity study
- In the blood test, males (50 MBq/kg) and females (50 MBq/kg) showed a decrease in white blood cell and platelet counts on day 5, and recovery on day 14.
- Toxicity tests of [^{211}At]NaAt (50MBq/kg) in mice
- Clinical trial drug manufacturing for [^{211}At] drugs - under GMP standard in Osaka University Hospital. from Bi-target irradiated alpha-beam containing At-211 is brought in from an external accelerator facility.
- Alpha-T1 study: [^{211}At]NaAt for thyroid cancer
- PSMA Theranostics using ^{211}At
- [^{211}At]PSMA-5 : new alpha therapy for prostate cancer
- Histology of normal mice ([^{211}At]PSMA-5): Day1
- Alpha-PS1 clinical trial (Phase-1: First in human)
- Manufacturing of clinical trial drug: [^{211}At]PSMA-5

12.45 Industrial Presentations

- **GLOBAL FIA**

Graham Marshall, Global FIA, Fox Island WA, USA

Objective: Modular Isotope Purification – the Production of ^{211}At

Presentation related to the flow-based fluid handling modules developed and demonstrated to automate the processing of an ^{211}At-bearing cyclotron target into A_b-labelled ^{211}At in <2 hours with minimal product handling from one processing module to the next.

What was included:

- three fluid handling modules to achieve the desired automated isotope-handling procedures
- flow-based sensors for measuring temperature, pressure, pH, conductivity, and radiation were incorporated into the flow manifold for closed-loop control of time-sensitive process steps as well as real-time feedback of critical process steps and monitoring of system performance
- A simplified dose measuring device based on a Geiger–Müller tube was built and tested

^{211}At Process Unit Operations - Product Processing Modules:

- Target dissolution and matrix exchange
- Solid phase extraction (SPE) and pH adjustment
- Radio-labeling and de-salting (SEC)
- (Optional) Product de-watering for transportation of solid

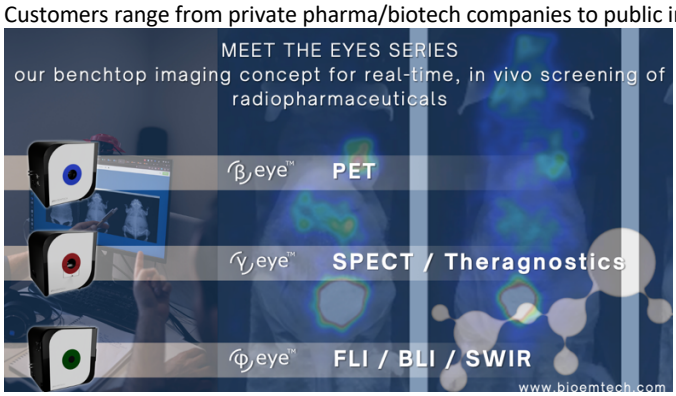
- BIOEMTECH

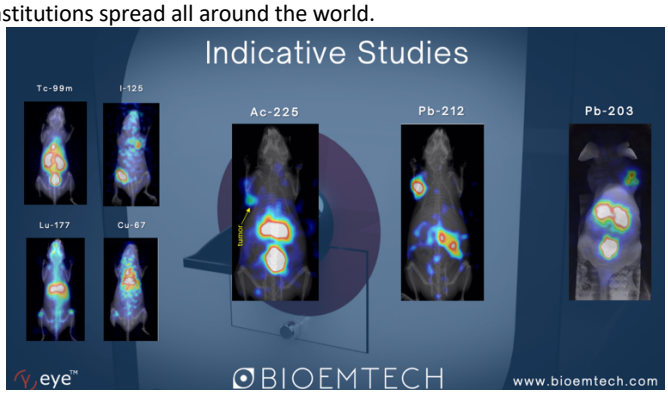
Objective: Embracing scientists translate ideas into results

BIOEMTECH's mission is to accelerate preclinical research of promising drugs, towards clinical translation, through high quality services and products.

Infrastructure: Headquarters and Preclinical Platform inside NCSR Demokritos (Athens, Greece).

Customers range from private pharma/biotech companies to public institutions spread all around the world.





Features

Field-Of-View of 50 mm x 100 mm, suitable for whole body mouse imaging

AI generated x-ray for anatomical mapping purposes

Small footprint of 44 cm (L) x 46 cm (W) x 40 cm (H) – Truly desktop

- INVISCAN

Objective: Applications on small Animals - Internal Vectorised Radiotherapy Lu-177 At-211 Ac-225

Imaging of [^{68}Ga/^{177}Lu]-AZ-93 for diagnosis and radiotherapy

- Mice bearing PSMA-positive tumours
- Tracer: [^{68}Ga]Ga-AZ-093 5.5 to 7.4 MBq (PET/CT imaging)
- [^{177}Lu]Lu-AZ-093 41 MBq (SPECT/CT imaging)
- PET : 8 min acquisition time at 10, 30, 60, 90, 120 min post injection
- SPECT : 20 min acquisition time at 1, 3, 24, 48 h post injection (SPECT/CT)

Imaging of [^{68}Ga/^{89}Zr/^{177}Lu] based teranostic pairs in tumors

- Balb/c nude mice, injected with tumor cells at right posterior flanks
- Tracer: [^{68}Ga]Ga-NOTA-ABDC2 4.3 MBq PET : 10 min at 1h, 4h, 8h post injection
- [^{89}Zr]Zr-DFO-ABDC2 4.1 MBq PET : 10 min at 6h, 72h, 144h post injection
- [^{177}Lu]Lu-DOTA-ABDC2 13.5 MBq SPECT imaging 1 week after treatment (SPECT/CT)

Comparison of the energy spectra : Alpha-SPECT-mini system

Siemens Symbia Clinical SPECT System (Johns Hopkins University School of Medicine

13.00 Lunch Break - Industrial exhibition

14.30 **WG5:**

WG Leader: **Dr. Dana Niculae** - Dissemination: what has been achieved

Objective: Made the technology visible and accessible to researchers, patients, EU practitioners, and industries. This working group focused on creating conditions to overcome barriers to the development of astatine therapy by identifying therapeutic candidates and facilitating their transfer and development.

Tasks:

T.5.1. Identifying the exploitable results (patent potential check) and constituting patent application files.

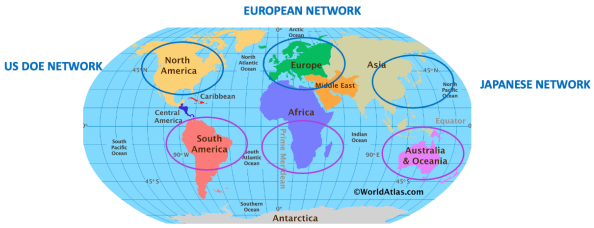
T.5.2. Industrial transfer.

T.5.3. Dissemination of project results to relevant stakeholders.

T.5.4. Participating in existing lobbying groups.

T.5.5. Communicating to patients and practitioners.
T.5.6. Creating referent contacts for research and industry.
This working group was successful in achieving all its desired outcomes. Some of these may be less visible due to the novelty of the treatment approaches for malignant diseases, highlighting the need for both clinicians and patients to be better informed and involved in the future.
What has been achieved so far:

- Meetings
- Dissemination
- Budget
- European initiatives NMEU, Japan Astatine Community



Project Communication Coordinator: **Dr. Emilija Janevik** - Communication: what has been achieved
Implementation of the Communication Plan with Key Messages - planned and realized

- Highlight the significance of Astatine-labeled radiopharmaceuticals in medical research.
- Showcase the goals and expected outcomes of the NOAR project.
- Emphasize the potential impact on advancements in cancer diagnosis and treatment.

The NOAR COST project effectively disseminated information, engaged stakeholders, and fostered collaboration within the radiopharmaceutical research community, ultimately contributing to the success and impact of the project.
Communication Objectives realized :

- Ensured effective communication between groups, provide timely notices for requirements and meetings, optimize results for all communications and project expectations, and measure the outcomes of the communication strategy to revise it as needed.

Engaging Partners in the Project:

- Created a bridge between the project and the networks they are involved in, provided input for the project's website, communication materials, and media channels.
- Disseminated the activities and results of the project through their social media channels.
- Shared the activities and results of the project at specific events and fairs.

Preparation of Science Communication plan
Communication Channels used for implementation of the Science Communication Plan
COST Academy / training - Education and Outreach by developing educational materials and resources for the professionals
Impact of Scientific Publications to increase the interest and investment in Astatine-211
Impact of Scientific Publications to increase the interest and investment in Astatine-211
Impact of Scientific Publications to increase the interest and investment in Astatine-211
Regular Core Groupmeetings of the Core Group, on Zoom every Monday at 3 p.m.

14.50 **Young researcher pathways**
Short Term Scientific Mission: what has been achieved - **Dr. Marek Pruszynski & Dr. Penelope Bouziotis**
STSM committee:
Dr. Marek Pruszyński (STSM Chair)
Dr. Petra Kolenc Peitl (STSM Co-Chair)
Dr. Penelope Bouziotis (Committee Member)
Dr. Andreas Tue Ingemann Jensen (Committee Member)

The STSM applicants were engaged in an official research programme as a PhD Students, postdoctoral fellow or employed by, or affiliated to, an institution, organisation or legal entity which has within its remit a clear association with performing research.
STSMs were intended and realised to promote young researchers: PhD students and Early Career Investigators (ECI).

STSM done since 2021

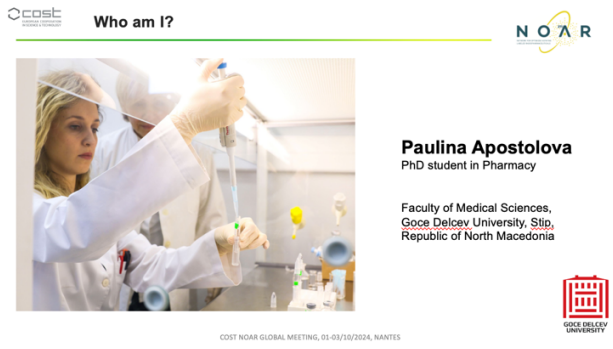
	Aplicant's name	Dates	Days	Title	Home Institution	Host Institution
2021	**Matthijs Bart Sevenois**	2021.08.30-2021.09.12	14	Investigation of production strategies to increase the At-211 yield	Research Cluster Imaging and Physical Sciences (BEFY), In vivo Cellular and Molecular Imaging Lab (ICMI), Laarbeeklaan 103 - 1090 Brussel, **Belgium** Prof. Dr. **Peter Covens**, Radiation Protection & Dosimetry Expert	Copenhagen University Hospital, PET and Cyclotron unit, KF3982, Blegdamsvej 9, DK2100 Copenhagen, **Denmark** Dr. **Holger Jan Jensen**, Chief Cyclotron Physicist
2022	**Chiara Timperanza**	2022.02.14-2022.03.18	33	Poly-L-Lysine radiolabeling with astatine-211 using arylboronic acid chemistry	University of Gothenburg, Department of Medical Radiation Sciences, Sahlgrenska Academy, Gula stråket, 2b, Gothenburg, **Sweden** Dr. **Emma Aneheim**	Nantes Université, CRCI2 NA, INSERM U1307-CNRS U6075, 8 quai Moncousu, BP 70721, 44007 Nantes cedex 1, **France** Dr. **François Guérard**
	Matthijs Bart Sevenois	2021.08.30-2021.09.12	14	Investigation of production strategies to increase the At-211 yield	Medical Imaging Research Group, In vivo Cellular and Molecular Imaging Lab (ICMI), Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, **Belgium** Dr. **Matthias D'Huyvetter**	GIP ARRONAX, 1 rue Aronnax, CS 10112, 44817 Saint-Herblain cedex, **France** Prof. **Férid Haddad**, Directeur GIP Arronax
	Paulina Apostolova	2022.09.15-2022.10.16	32	Antibody labeling and quality control using 211At - a new experiment and a new challenge for cancer treatment	Goce Delcev University, Faculty of Medical Sciences, Krste Misirkoiv 10A, 2000 Stip, **Republic North Macedonia** Prof. **Emilija Janevik-Ivanovska**	Nantes Université, CRCI2 NA, INSERM U1307-CNRS U6075, 8 quai Moncousu, BP 70721, 44007 Nantes cedex 1, **France** Dr. **Joëlle Gaschet**

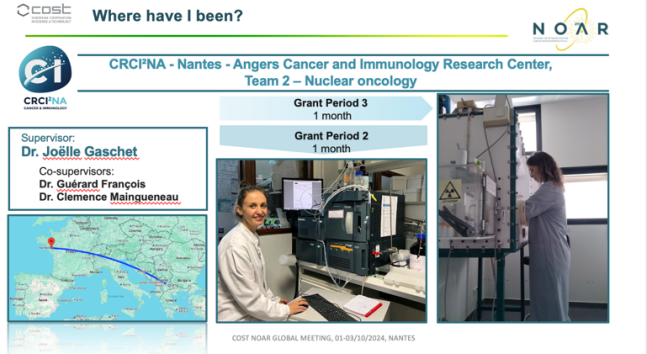
	Aplicant's name	Dates	Days	Title	Home Institution	Host Institution
2023	**Lucas Mues genannt Koers**	2023.08.27-2023.09.01	6	Target processing, separation and labelling of Astatine-211	Forschungszentrum Juelich, Juelich, **Germany**	University of Gothenburg, Department of Medical Radiation Sciences, Sahlgrenska Academy, Gula stråket, 2b, Gothenburg, **Sweden** Dr. **Emma Aneheim**
	Paulina Apostolova	2023.09.08-2023.10.06	29	Preparation and characterization of bioconjugates for astatine-211 radiolabeling	Goce Delcev University, Faculty of Medical Sciences, Krste Misirkoiv 10A, 2000 Stip, Republic North **Macedonia** Prof. **Emilija Janevik-Ivanovska**	Nantes Université, CRCI2 NA, INSERM U1307-CNRS U6075, 8 quai Moncousu, BP 70721, 44007 Nantes cedex 1, **France** Dr. **Joëlle Gaschet**

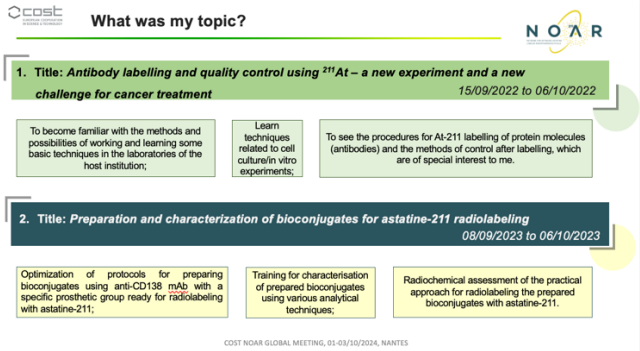
	Aplicant's name	Dates	Days	Title	Home Institution	Host Institution
2024	**Clemence Maingueneau**	2024.04.01-2024.04.18	12	Development of electrophilic astatine-211 labelling of antibodies modified by boronic derivatives	Nantes Université, CRCI2 NA, INSERM U1307-CNRS U6075, 8 quai Moncousu, BP 70721, 44007 Nantes cedex 1, **France** Prof. **Jean-Francois Gestin**	University of Gothenburg, Institute of Clinical Sciences, Department of Medical Radiation Sciences, Gothenburg, **Sweden** Dr. **Emma Aneheim**
	Tomasz Janiak	2024.07.15-2024.07.19	5	Gaining experience with the preparation of Bi targets for producing 211At in a cyclotron	National Centre for Nuclear Research, Radioisotope Centre POLATOM, **Poland** Prof. **Renata Mikołajaczak**	Forschungszentrum Jülich GmbH Institute of Neuroscience and Medicine INM-5: Nuclear Chemistry, **Germany** Prof. Dr. **Bernd Neumaier**
	Max Palmer	2024.09.22-2024.09.26	5	Queen Mary University of London: Sharing best practice for setup and operation of an astatine-211 facility with CRCI2NA	Queen Mary University Of London, London, **United Kingdom** Prof. **Jane Sosabowski**	Nantes Université, CRCI2 NA, INSERM U1307-CNRS U6075, 8 quai Moncousu, BP 70721, 44007 Nantes cedex 1, **France** Dr. **François Guérard**

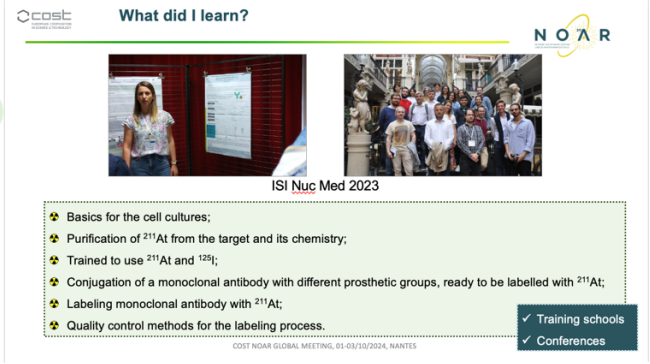
15.00 **STSM Testimonies (round table):**
Who am I? Where I have been? What was my topic? What did I learn?

Paulina Apostolova

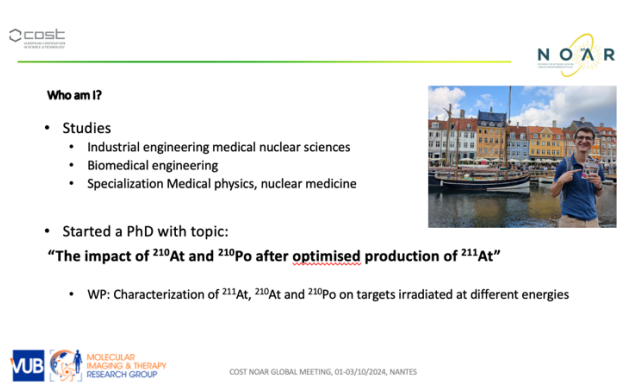


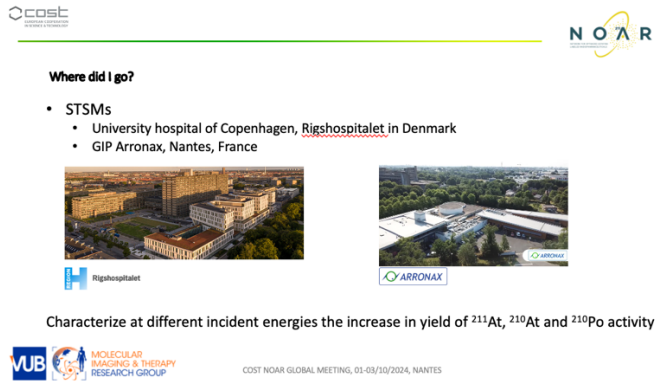


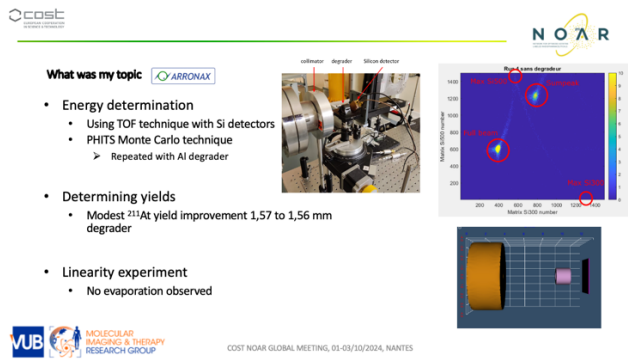


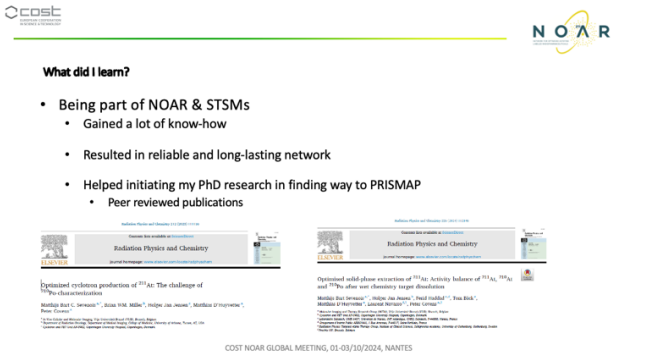


Matthijs Seve- nois









Clémence Maingueneau

Short Term Scientific Mission

- Who am I?
- Where I have been?
- What was my topic?
- What did I learn?

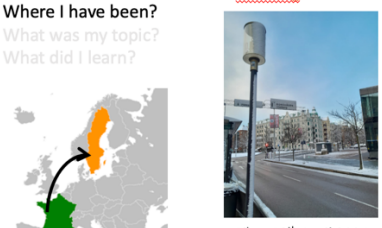
Post doctoral researcher in CRCI²NA lab in Nantes

Research Center in cancerology and immunology in Nantes

Short Term Scientific Mission

- Who am I?
- Where I have been?
- What was my topic?
- What did I learn?

Göteborg Sweden



1st to 18th April 2024

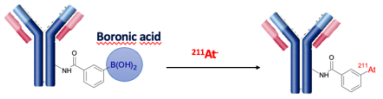
Department of Medical Radiation Sciences

Short Term Scientific Mission

- Who am I?
- Where I have been?
- What was my topic?
- What did I learn?

^{211}At labelling of modified Antibody with boronic acid functions

Berdal, Marion, *et al.* 2021 [1]



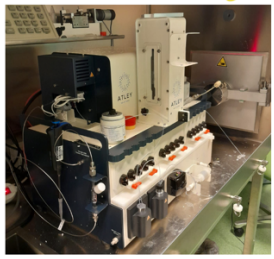
- What about electrophilic way ?

[1] Investigation on the Reactivity of Nucleophilic Radiohalogens with Arylboronic Acids in Water: Access to an Efficient Single-Step Method for the Radioiodination and Astatination of Antibodies ». *Chemical Science* 12:1458-68.

Short Term Scientific Mission

- Who am I?
- Where I have been?
- What was my topic?
- What did I learn?

A lot !



Lucas Koers

Tomasz Janiak

Who am I?

POLATOM Radioisotope Centre POLATOM
NCBJ

RESEARCH DEPARTAMENT R&D

- Laboratory of Active Substances
- Laboratory of Radiopharmaceuticals
- Laboratory of Radionuclides
- Laboratory of Preclinical Research

Tomasz Janiak

Education: 2000-2006
Warsaw University of Technology,
Faculty of Production Engineering - Msc.Eng
Field of Study: Automation and Robotics
Speciality: Flexible manufacturing systems

Research Scientist in Laboratory of Radionuclides

- Development of methods for the preparation of solid targets for irradiation in cyclotron;
- Development of methods for the manufacture of sealed sources for medical and industrial applications;
- GMP-compliant production of radiopharmaceuticals for clinical trials - somatostatin analogues with ^{90}Y and ^{177}Lu

GMP production in RC POLATOM

RESEARCH TEAM LEADER

Short-Term Scientific Mission

What was my topic?

Gaining experience with the preparation of Bi targets for producing ^{211}At in a cyclotron.

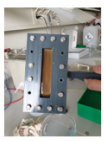
Where I have been?

The visit of the STSM was carried out at 15-19.07.2024 in Forschungszentrum Jülich GmbH, Institute of Neuroscience and Medicine, INM-5: Nuclear Chemistry, Jülich, Germany.

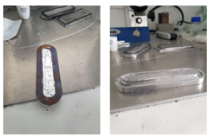
Supervisor during the visit - Mr. Lukas Koers

What did I learn?

Methods of preparing Bi targets:



Electrochemical



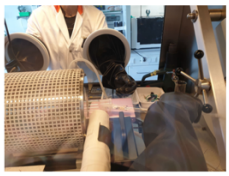
Melting

Sedimentation

Pressing Bi Powder

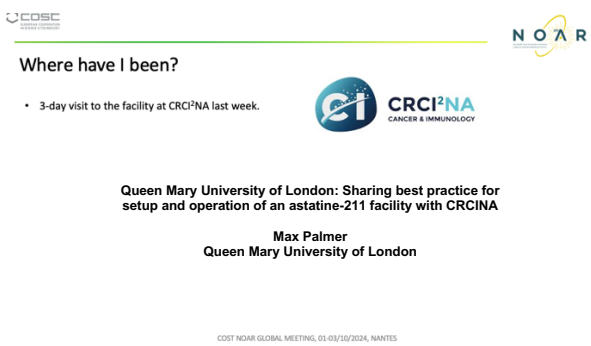
IBA CYCLONE 30XP in Julich

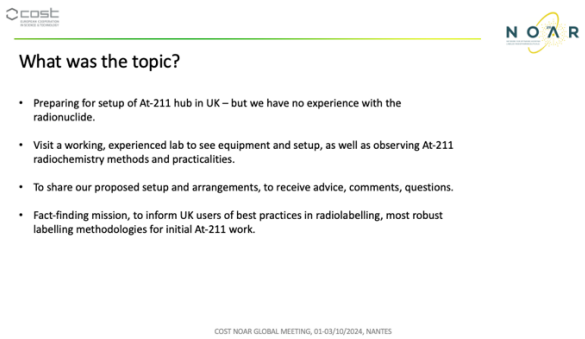
Target station for irradiation in cyclotron

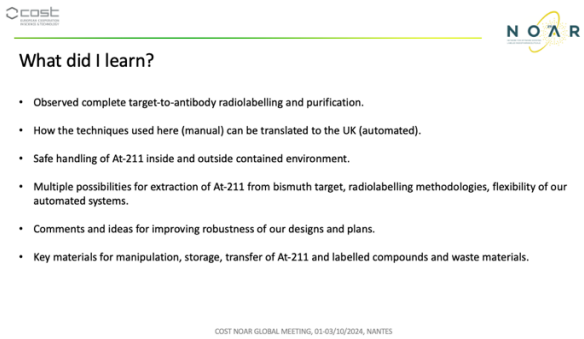


Dry distillation of At-211, produced on the IBA cyclotron, from a target prepared by the sedimentation method

Max Palmer







15.30 The «Scandinavia» Ecosystem- Moderators**: Milton Lönnroth & Dr. Andreas Ingemann Jensen**
Sweden - **Milton Lönnroth**
Gothenburg ecosystem and on-going projects Atley Solutions
Denmark - **Dr. Andreas Ingemann & Dr. Francesco Sergi-Lindell** Copenhagen ecosystem and on-going efforts: Infrastructure developments around Copenhagen, start-up projects, TetraKit Technologies, Theranostic Solutions & PreTT

16.00 Break - Industrial exhibition

16.30 The «Pays de la Loire» Ecosystem - Moderators**: Dr. Joelle Gaschet & Dr. Jean-François Gestin**
Joelle Martin-Gauthier - Nantes Metropole

Dr. Ferid Haddad - Arronax Nantes
The **ARRONAX** project is supported by:
- **Regional Council of Pays de la Loire**
- **Université de Nantes**
- **French government** (CNRS, INSERM)
- **European Union**

Objective: The development of a radiopharmaceuticals is a multidisciplinary adventure
- **A cluster of academic labs have been set to cover all expertise**
- **Academic cluster is part of a stronger network which includes industry**

^{211}At as a case study : from bench to bedside
- Astatine-211 production scheme used @Arronax:
- Production batches are use to fuel the whole research scheme
- Chemical properties and quantum chemistry of astatine-211
- Development of innovative radiolabelling methods
- Biological studies of Astatine in different models
- Astatine-211-labeled anti-mCD138 in mouse syngeneic multiple myeloma
- Translation to clinics

Pr. Jen-Luc Harousseau - West Institute of Cancerology (ICO)
Johanna Rolland, Nantes Mayor, Nantes Métropole President

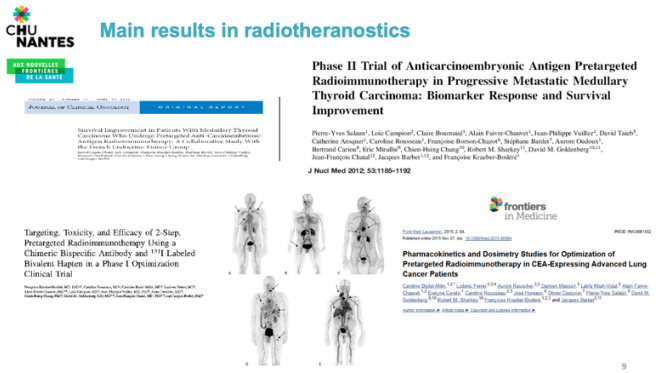
Pr. Françoise Kraeber Bodéré - University Hospital Center (CHU)

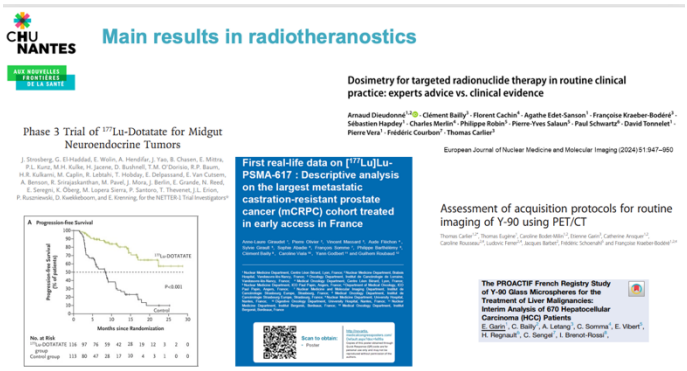
Pluridisciplinary research since more than 15 years in a favorable ecosystem in 3 Research Axis

Axis 1-Radiotheranostics and radionuclide therapy (Dr C. Bailly)
Axis 2-Innovative radiopharmaceuticals (Pr C. Bodet-Milin)
Axis 3-Quantitative imaging, data processing and AI (Dr T. Carlier)

Clinical Research unit - 106 clinical studies

- Non interventional research: 4
- Diagnostic studies : 8
- Studies phase III : 6
- Studies phase I/II : 6
- In faisability studies 18
- Imaging studies (prestation): 82





Dr. Franck Lethimonnier - ITMO Santé

Address major biomedical research challenges

In France

- 300 research units
- 34 clinical investigation centers
- 50 support service units

In Europe and worldwide

7,000 international cooperation agreements with 106 countries

National Thematic Institutes

Health Technologies Institute

- Exploration/diagnosis
- Intervene/treat
- Real life follow-up & prevention
- Modeling

Targeted Alpha Therapy: Inserm initiative

In 2021, Inserm and CNRS identified alphatherapy:

- As a strategic axis supporting innovation and reindustrialization in France, within the framework of the national Biotherapy-Bioproduction acceleration strategy
- As an opportunity to develop partnerships with key french industrials
- As a promising approach to address the challenges of the French Cancer Plan (2021-2030)

A national research program currently under development and seeking funding, including:

- Innovative radiopharmaceutical-biotherapies,
- Anti-cancer antibodies coupled with alpha-emitting radioisotopes, including Astatine-211.

17.20 Industrial Presentations

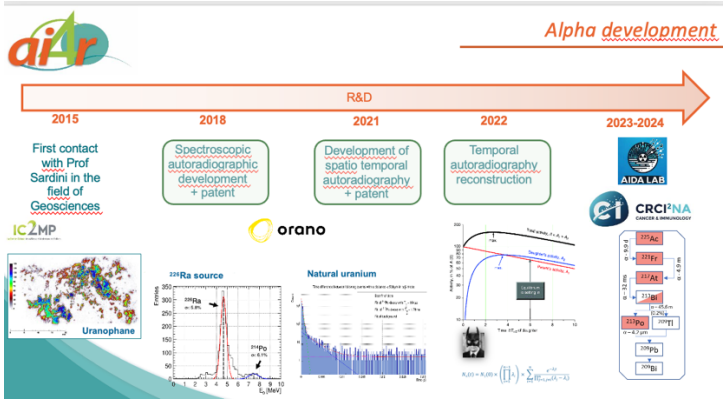
- AI4R – Atlantic Instrument for Reserch

Objective: The BeaQuant and BeaQuant-S / New instrument based on new technologies, developped from latest technologies in particle physics.

Main goal: Visualize and quantify precisely radiopharmaceuticals in biological tissue sections and in rock slices for geological studies

Sensitive to every charge particle:

- Insensitive to X and γ radiation
- Linearity on 5 magnitude
- Sensitivity: order of mBq



Real-time imaging
Direct quantification in counts
Large field of view: 20x20 cm² , 18 slides on the BeaQuant
Image with a high spatial resolution with every emitter β^-, β^+ and α
A very high performance tool to analyse alpha emitters
Sensitivity: 5.10^{-4} cpm/mm^2, order of mBq
Linearity: 5 orders of magnitude
Safety: No toxic gas

The perfect complementary tool for preclinical imaging

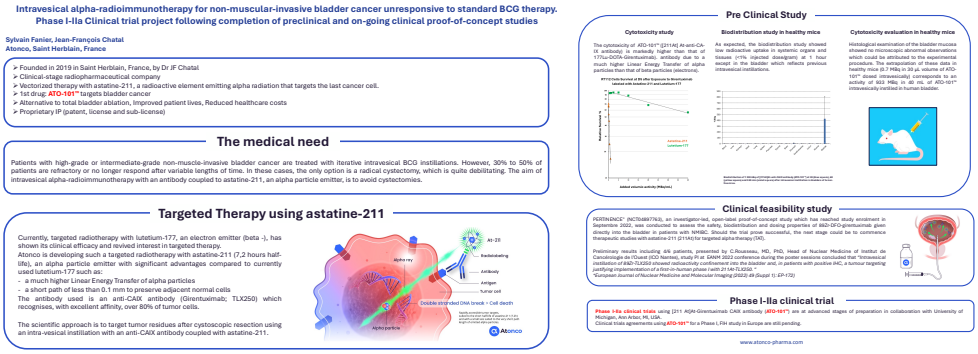
- CHELATEC

- ATONCO - Astatine against cancer

What is ATO-101 and How ATO-101 could revolutionize bladder cancer treatment

At-211 - Next generation of Radiotherapeutics (vs emerging Ac-225)

Stable targets and shorter half live (7.2h)
Easier and safer production
Preserve the rivers and the planet
Larger and easier patient care



Clinical strategy

- Optimize agenda of time to Marketing Authorization in EU and USA
- Accomodate to Astate-211 production capacity in EU and USA and patient recruitment rates
- Comparing Single dose versus Fractional dose instillation
  - Proposed phase I/IIa study - single doses in the US >> FDA
  - Proposed phase I study - fractional instillations in Europe >>EMEA

17.45 Photos + Interviews + Press

19.30 Gala Dinner

Thursday, October 3rd , 2024 / Nantes

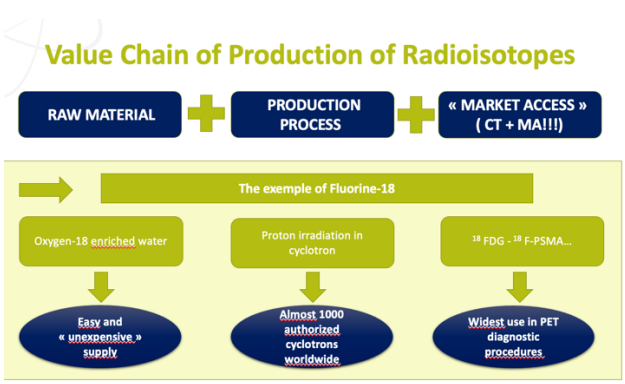
08.00 Welcome – What's next?
Dr. Emma Aneheim & Dr. Jean-François Gestin

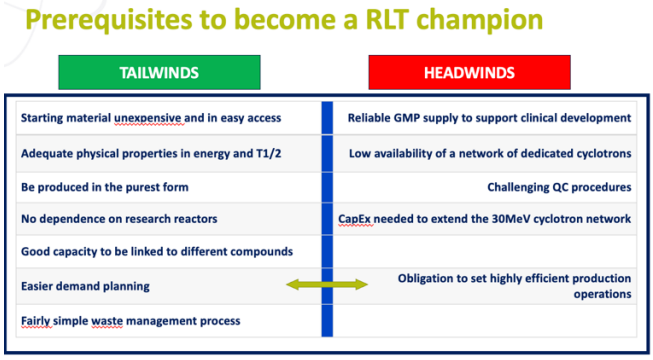
08.15 The European Ecosystem & The European initiatives - Moderators**: Dr. Emma Aneheim & Dr. Jean-François Gestin**

Dr. Jean Bonnet – NMEU
The Radioisotopes and Nuclear Medicine Industry - Facing the Challenge of Theragnostics

The industrial challenges linked to theragnostics:

- Never forget the basics of the Value Chain of Production of Radioisotopes
- Secure the supply of currently approved isotopes
- Be prepared for the next « champion isotope »





Dr. Renata Mikolajczak -PRISMAP - The European medical radionuclides programme / Isotopes for imaging and medical treatment

PRISMAP on track:

- 32 projects from 4 calls - https://www.prismap.eu/access/user-projects/
- >60 deliveries of 15 different radionuclides for 28 projects
- Technical manager hired
- Helpdesk in place - https://www.prismap.eu/access/helpdesk/
- 5 projects completed
- 2 projects published already
- One abstract highlighted as oral presentation at EANM'24 congress

PRISMAB:

1. Provide access to new radionuclides and new purity grades for medical research/ The development of the services
2. Create a common entry port and web interface for the starting research community
3. Enhance clarity and regulatory procedures to promote research with radiopharmaceuticals
4. Unlock the biomedical research through better data on radionuclides
5. Ensure the long-term sustainability of PRISMAP

Dr. Jérôme Harray - IHI: accelerate EU

Dr. Alice Viana - Oncidium foundation

Objective: Supporting Cancer Patients and Enhancing Access to Radiotheranostics Worldwide

Oncidium is a Belgian based, patient focused foundation. The mission is to support, promote & accelerate the development of radiotheranostics for cancer care worldwide, notably through a network of Ambassadors representing the work of the foundation on a local and global scale.

Important preliminary remarks :

- non-profit foundation
- public-interest organization
- fully independent from any other company, organization, hospitals etc.

Oncidium activities are based around 3 pillars: Access, Education and hope.

The foundation is committed to improve **ACCESS** to radiotherapeutics-based treatments for patients that could benefit from it.

The idea is to have Key Opinion Leaders, experts etc. , join this network and lead the mission of Oncidium as we are the ones that know about the challenges and opportunities in the country.

Education is also targeted on the website and initiatives for the healthcare community (oncologists, urologists, nuclear medicine and industry).

Each month is published "Theranostics Insights" focusing on a specific radiopharmaceutical.

Every year they share a review, called "Radiotheranostics TODAY" with exclusive content by Ambassadors and friends of the foundation about challenges and opportunities in the radiotheranostics field.

On the education page of the website, we maintain a regularly updated list of radiopharmaceuticals on the market and under development.

Oncidium collaborate with some organizations and companies to host webinars regarding radiotheranostics matters.

RLT-Connect: a collaborative platform to enable radioligand therapy for patients who could not otherwise afford it.

09.00 **The International Ecosystem**

Dr. Koshin Washiyama - Japan Astatine Community network - A Hub for Skills and Knowledge of ^{211}At and the Gateway to the World Astatine Community

Development of a biostable ^{211}At labeling method aimed at application to targeted alpha therapy of cancer

Prof. Hiroyuki SUZUKI (Chiba University)

To know how Japan Astatine Community have selected Astatine among many promising therapeutic radionuclides and under what strategy we've been working, please read our advertisement article on Astatine, which was published this year in Nature. You can take our reprints from the backside table with two Japanese sweets free!


Don't forget to take our reprints from the backside table with two Japanese sweets free!

Nature Focal Point on Radiology in Japan

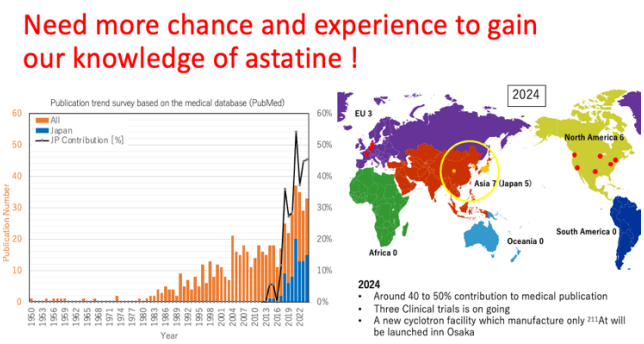
ADVERTISEMENT FEATURE

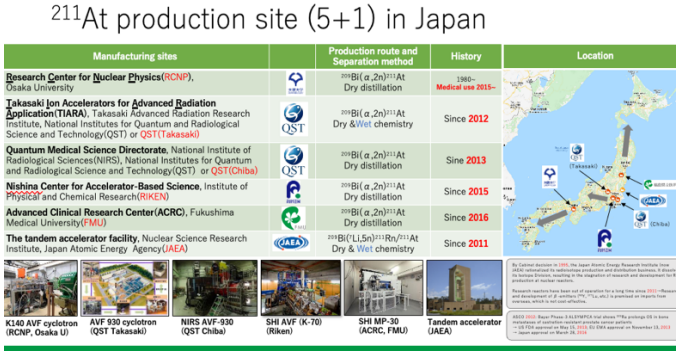
21March2024

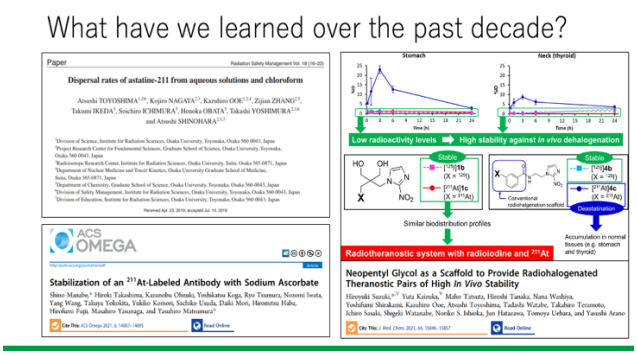
ASTATINE-211: JAPAN'S STRATEGIC WEAPON AGAINST CANCER

Japan is working to develop a new and interesting ACCELERATOR-BASED RADIONUCLIDE THERAPY.

大阪大学 OSAKA UNIVERSITY　福島県立医科大学 FUKUSHIMA MEDICAL UNIVERSITY







Dr. Sunao Fujioka - Alpha Fusion Inc.,
^{211}At based drug development biotech

What Alpha Fusion is doing

- ^{211}At pipeline R&D - Focus on ^{211}At clinical development to achieve earliest commercialization
- ^{211}At supply chain - Work closely with supply key stakeholders across Japan and WAC given the short half-life

JAC – industry perspective - Efficient transportation to cover 125M population across Japan – apprx. 2000Bn JPY (12Bn Euros) oncology drug market overall

Summary:

- Astatine is a promising alpha-emitting radionuclide for TAT
- Astatine is provided to many users through the short-lived RI supply platform and Fukushima Medical University's own network in Japan
- Astatine-related medical articles with Japanese involvement accounted for 40-50% of the world's astatine publications in the last five years.
- These continuous effort since 2011 resulted in the first milestone(Phase-1 studies).
- We are still running towards next milestone with the bottom-up activities of the Japan Astatine Community collaborating with the World Astatine Community.

Dr. Ethan Balkin - American network
Federal Program Manager for Radioisotope Production R&D
Office of Isotope R&D and Production
Office of Science
U.S. Department of Energy

Objective: DOE Isotope Program Update on the University Isotope Network vis-à-vis At-211 - Production of ^{211}At to develop a new market and meet US domestic demand

- Produce and/or distribute radioactive and stable isotopes that are in short supply; includes by-products, surplus materials and related isotope services
- Maintain the infrastructure required to produce and supply priority isotope products and related service
- Conduct R&D on new and improved isotope production and processing techniques which can make available priority isotopes for research and application. Develop workforce.
- Ensure robust domestic supply chains. Reduce U.S. dependency on foreign supply to ensure National Preparedness.

The DOE Isotope Program University Isotope Network (UIN):

- Invest in R&D and develop production capabilities
- Unique infrastructure capabilities & expertise
- Workforce Development

^{211}At Production Capabilities in the U.S.

- University of Washington
- University of California – Davis
- Texas A&M University
- Duke University
- University of Pennsylvania

DOE Isotope Program UIN Evolving Strategy:

- DOE IP recognizes that the production and isolation of ^{211}At can be challenging. However, we believe that success dramatically increases with cooperation.
- Generation of a notable new literature and general knowledge of the stability and robustness of the product supply chain to encourage clinical evaluation and eventual adoption.
- Maximize the UIN's capability to support U.S. domestic ^{211}At researchers.
  - Continue to develop production capability at the university sites via grant funding.
  - Gas trapping and generator development can extend shipping range, two approaches are being explored.
  - Explore opportunities for commercialization of ^{211}At with U.S. private industry.
  - Explore opportunities for development of bench-top accelerators optimized for ^{211}At production.

Promote international cooperation and technology exchange.

09.45 Industrial Presentations

- ACS - TR-ALPHA Cyclotron

Objective: TR-ALPHA Cyclotron

- purchased by Alpha Nuclide (Ningbo) Medical Tech. Ltd: Jan 2023
- Design & Manufacturing Completion: Apr 2024
- Factory Testing: Oct 2024
- Installation/Commissioning: Jan 2025
- Isochronous cyclotron accelerating He^{2+} to a max. energy of 30 MeV.
- External ECR ion source providing stable, low emittance He^{2+} beam up to 1.1 e-mA at 30 kV.
- Designed for production of large quantities of At-211.
- No beam extraction.
- Configured for irradiation of internal targets.

Highlights:

- Dedicated to alpha production.
- Easy to operate.
- fully automated.
- Vertical acceleration plane; allowing easy maintenance.
- Smaller Vault/Facility required.

- ALPHA NUCLIDE

- TELIX , Burnaby, BC, Canada

Telix company provide turnkey solutions for commercial radioisotope production:

- ISO 9001:2015 Registered
- registered Engineering Firm in BC, Canada
- have a Service License with Canadian Nuclear Safety Commission
- have a traceable supply chain and inventory of enriched stable isotopes
- operate R&D and manufacturing activities within our Quality and Safety programs

Intentionally Focused on Cu-64, Ga-68, Zr-89, Tc-99m and:

- Technology transfer with SOPs, draft MBRs and checklists
- Applications training hands-on training for on-site staff
- We spend a lot of effort on regulatory alignment, US being our first focus – it is very important to us that our products can be used commercially (goes back to our intentionally focused product line)
- Responsive and highly trained technical support

10.00 Coffee Break - Industrial exhibition

10.30 New Actors - Moderators**: Dr. Antero Abrunhosa**

Dr. Kazunobu Ohnuki - National Cancer Institute of Japan. New perspec- tive on handling the Astatinated compounds (virtual)

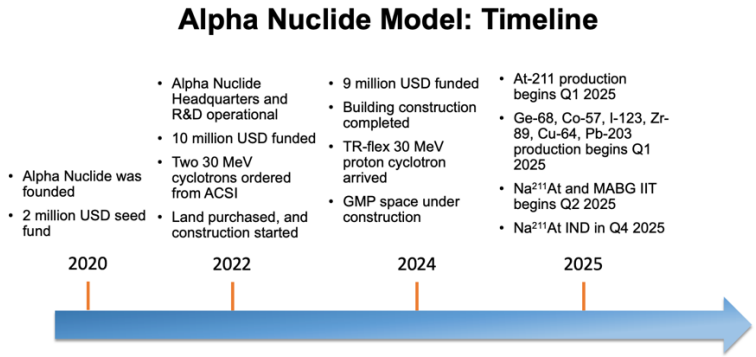
Dr. Choong Mo Kang - Korea Institute of Radiological and Medical: At-211 production and R&D at KIRAMS Science, Seoul

- Introduction of KIRAMS and Division of Applied RI
- Medical Cyclotrons in KIRAMS
- MC-50 Cyclotron Beam Lines
- Bi-209 target preparation
- Production of Astatine-211 in KIRAMS – production record (2023-2024)
- Radiolabeling test – labeling of small molecules and antibody conjucates
- Targeted alpha therapy – treatment of HER2 expressing gastric cancer, pheochromocytoma, neuroendocrine tumors
- Theranostic research using 211At/123I pair
- HPLC control of labeled antibodies with Astatine-211 – trastuzumab
- In vitro therapeutic efficacy

Dr. Yutian Feng - Chinese Network
CEO, Alpha Nuclide Inc.
Assistant Professor, Duke University Medical Center
Objective: Innovation Driven Solutions to the ^{211}At Supply Chain in China: The Alpha Nuclide Model

- Radiopharmaceuticals in China: Challenges and Opportunities - Radionuclide Production, Radiopharmacy/CDMO, Nuclear Medicine/Hospital
  Radiopharmaceuticals in China: Challenges and Opportunities -
- Alpha Nuclide: First and Only TRT focused - Radionuclide Supplier + CRO + CDMO in China
- Alpha Nuclide Radiochemistry R&D
  - Level B RAM licensed radiopharmaceutical lab was completed in 2022 – 16 radionuclides including ^{211}At, ^{225}Ac, ^{212}Pb and ^{68}Ge are licensed
  - 2 cGMP processing labs, fully equipped radiochemistry R&D lab
  - In-house cell culture lab and animal facility
  - Suitable for preclinical and R&D studies
- Alpha Nuclide Cyclotron facility
  Innovation 1 – the TR-Alpha cyclotron
  - Co-developed with ACSI, first in the world
  - First cyclotron that is designed specifically to produce At-211
  - Small footprint – cost effective and more regulation-oriented

  Innovation 2 – compact facility for At-211 production and radiopharmaceutical formulation
  - Maximize efficiency
  - Cost effective
  - Quick turn around – 24 h lead time for patient dose
- Alpha Nuclide Model: Localized Production and Supply



Dr. Feize Li - Sichuan Univertsity (virtual)
Dr. Fei Yu, Institute of Nuclear Medicine at Tongji University, China
Objective: Chinese reserchers working on At-211 radiopharmaceuticals

- Unique advantage – higher energy, shorter range, better hypoxia tolerance and easier shielding

China started in1990 while international research on astatine -211 and gradually progressing
Stable production of astatine-211 using the CS-30 cyclotron in 2003 with outstanding contribution to the syntesis, separation and application
First research using astatine-211 octreotide targeting somatostatin receptor2 (SSTR2) and continue with various small peptides, monoclonal antibodies, single domain antibodies and biomimetic nanomaterials as carriers.
Efforts in preclinical studies and less in clinical investigations
Book published in 2022 by Prof. Yutian Feng and co-invited “strategies and Application of Targeted Alpha-Particle Therapy”

Dr. Gabriel Tabacaru - Texas A&M University

Objective: Fundamental research (Astrophysics and Fundamental nuclear physics and nuclear chemistry), Aerospace industry chip testing (NASA, JPL, Boeing, Lockheed Martin, Amazon, SpaceX, Intel, Texas Instruments,…) and Radioactive Isotopes production for medical research
Production

- K150 Cyclotron (88")
- Use of newly acquired ion source (D-Pace Inc., versatile, produces negative ions and positive ions) or ECR Ion Source (home made)
- Energy 28.8 MeV, external irradiation

Target system

- Bismuth deposit on aluminum
  - Melted, pressed and machined
  - Fused using ultrasonic soldering device
- Slanted rectangular (10 deg) – obsolete
- Disk – current setup

Target extraction

- Manual extraction
- Air in the target chamber checked for airborne astatine

Target processing

- Target dissolved in HNO_3
- Automated system reduces hands-on time

Target processing ^{211}At separation
Shipments - Texas A&M is the newest member of the DOE Isotope Program's UIN! We joined in 2023.
Q&A

11.50 Future of the Network
Dr. Jean-François Gestin - NOAR Europe
Objective: NOAR EUROPE - Network for Optimized Astatine labelled Radiopharmaceuticals ^{211}At users community in EU

- Capitalize on COST NOAR activities
- Consolidate the network of academic and industrial users
- Provide access to a dedicated community with up-dated knowledge
- Facilitate the development of ^{211}At in EU
- Favor transfer to industry for patient benefits
- Communicate and disseminate
- Make it happen!

Several topics to address –
<u>Securing EU supply</u>

- Establish a network (Back-up) of producers & close delivery
- Favor repurposing of existing 30 MeV cyclotrons for astatine-211 production
- Favor Increasing astatine-211 output per irradiation time
- Giving supports to acquire new dedicated cyclotrons in European countries
- Contribute to the development of new technologies (LINAC, Generators, …)
- Contribute to the delivery to EU laboratories

<u>Radiochemistry</u>

- Improvement of extraction, radiolabeling yield and stability
- Establishment of best practices for labeling targeting vectors
- Establishment and up-scaling of drug manufacture under GMP
- Automatization of the full process
- Transfer of knowledge to EU academic labs

<u>Preclinical</u>

- Provide more evidence of efficacy and comparative studies with other radionuclides, in different pathologies
- Development of innovative vectors (scaffolds, targets, delivery strategies, …)
- Stay tuned to new approaches in biology

<u>Regulatory & Clinical</u>

- Regulatory and stability concerns during transportation by road or air
- Regulatory landscape and available clinics for astatine-211 drug trials
- Radiation safety / Handling of astatine-211 and decay products at laboratories and clinics

<u>Meetings & Dissemination</u>

- Organization of virtual WG meetings (4/Year)
- Organization of Scientific meetings only for members (1/Y)
- Co-organization within the WAC of International meetings (1/2Y)
- Organization of Pre-symposium bringing together academic and industrials
- Lectures: Scientific presentations or presentation to a panel of non-experts
- Common communication, paper review, …..

Improve communication to practicians & patients.

Europe

Identification and common answer to EU calls to finance:

- Improvement in production yield & sites
- Preclinical research
- Clinical POC
- Network consolidation

Participation to NMEU (therapy group & lobbying)

Participation to PRISMAP+ (thematic node)

European Network - European Network & Research platform

Dr. Koshin Washiyama

Objective: The Past and Current of the World Astatine Community

Roots of the World Astatine Community:

- Formation of the WAC was catalyzed by the 66th International Atomic Energy Agency General Conference At-211 Side Event hosted by the Atomic Energy Commission of the Cabinet Office of Japan on September 27, 2022.
- During the side event Dr. Jean-François Gestin of the University of Nantes, France, Dr. Mitsuru Uesaka, Chairperson of the Japan Atomic Energy Commission and Dr. Ethan Balkin of the United States Department of Energy Isotope Program (DOE IP) shared the views and status of At-211 production capabilities of their respective countries/unions, and agreed to continue an open exchange of information, technology transfer as permitted, and collaborative research among regional production networks established by individual countries and organizations.

Cape Town, the birthplace of WAC

- Subsequently, at the 12th International Symposium on Targeted Alpha Therapy (TAT'12) held in Cape Town, South Africa, astatine-related stakeholders from the European Union (EU), Japan and the United States of America (U.S.), along with an IAEA observer, gathered to formally announce the formation of the WAC and begin to codify a frame work for its form and function.


Dr. Ethan Balkin - WAC

Objective: Changes and New Additions

For the European community, while the COST action is ending, NOAR Europe is an exciting opportunity! And pleased to welcome China to the WAC

- Outreach to New & Potential Producers - South Africa and Latin America\
- Upcoming Events

  Prof. Jean-François Gestin will be jointly organizing a session on Alpha-emitters at the upcoming iSRS Conference in Australia (May 11-15, 2025).

  WAC will begin rotating workshops to provide a forum to discuss At-211 scientific and clinical developments and to encourage collaborations.

  1. First workshop will be held either just prior to or just after the 2025 Annual Meeting of the Society of Nuclear Medicine and Molecular Imaging in New Orleans, Louisiana USA (June 21-24)
  2. Second workshop will be held just prior to the 2026 Workshop on Targetry and Target Chemistry in Nara, Japan
  3. Additional Workshops will be announced annually

Dr. Jean-François Gestin - Survey presentation

Q&A

12.10 Industrial Presentations

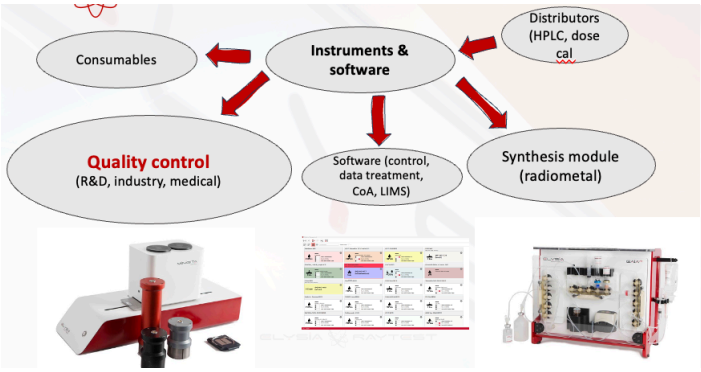
- ELYSIA

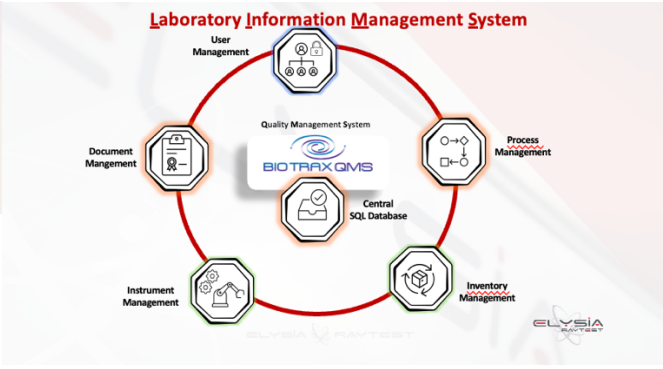
Elysia Spin-off Uliège (2014) and Raytest (radiodetection, 90's)

Elysia QC solutions

- Complete Radio-HPLC
- Radio Detector (GABI)
- TLC scanners (miniGita)
- Multi Channel Analyzer (Mucha NOVA)
- Filter Integrity Test > Safira
- Preparative HPLC detectors

- Ionization Chambers
- Automated Radio Active Sample Preparation Module
- QC Tests covered
- Alpha- Beta-LC-flow Monitors : radio-HPLC
- Flow cells
- At-211 measurements : RAMONA
- Alpha, beta, Gamma and MCA probes for MINIGITA





- TRISKEM

- Based in Rennes (France)
- Main product line: extraction chromatographic resins
- Staff : 20
- R&D and TechSupport group: 4 RadChem PhD, 2 Technicians + 1 PhD student
- R&D: Development of new resins, techniques and applications
- Products used in several domains

Working in the field of Extraction chromatography and intersts in Radiopharmacy:

- Radionuclide production/purification
    - Resin and method development 'cold'
        - Cooperation with cyclotrons & reactors (NL, RN producers,…)
        - Equipment provider (targetry, synthesizer,…)
    - Separation of radionuclides (mainly radiometals) from irr. targets
        - Diagnostics: Zr-89, Cu-64, Ga-68, Ge-68, Ti-44/5, Tc-99m, Sc-43/4…
        - Therapy: alpha emitters (Ac-225, Pb-212,…), Lu-177, Tb-161, Cu-67, Sc-47…
    - Requirements for resins:
        - No selectivity for target material, high selectivity for product
        - Elution under 'soft' conditions in small volume => labelling/injection
        - Fast kinetics
        - Combining several resins can facilitate the separation
            - Conversion (high acid to dilute acid, e.g. Ga-68)
            - Removal of impurities upfront (e.g. Cu-64)

Quality control

- Cartridge based methods (e.g. Sr-90 in Y-90,…)
    - Use of "TK-SrScint cartridges"?
- **"Sheets"**
    - p.ex. DGA sheets (functionalized TLC for Ra-223, Ga-68, Pb-212,…. => CVUT Prague),

CU Sheets (QC of Cu labelled compounds),…

- Decontamination of effluents/waste (Ge-68, lanthanides, radioiodine,…)
- 'Recycling'/valorization of long-lived RNs (Ge-68,…) and target materials
- Radiolysis stability (polymer, radical scavengers,…)
- Determination of radionuclides (mainly used in therapy, generally Lu-177 and Ac-225) in environmental and bioassay samples

Interest on Astatine-211

- Looking for collaboration
- At separation on a cartridge after target dissolution
    - Option: TK400 Resin (long-chained alcohol based), elution typically in NaOH
    - Interested to test other resins (TK401/2, TK200,…)
- Rn-211/At-211 generator
    - Inert support impregnated e.g. with with long-chained alkenes, alcohols,…
    - Mixture of several extractants on a resin bead
    - Possibility to retain Rn and Po, elution of At?

12.30 **Dr. Richard Zimmermann** - Will 211At really happen?

Objective: Switching from betas to alphas

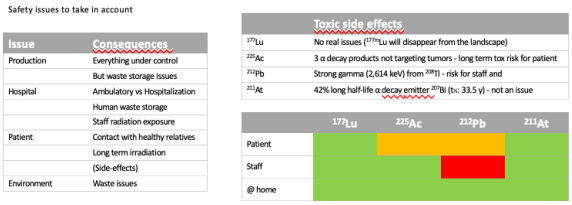
- ^{177}Lu exclusively based on *nca* ^{177}Lu
- ^{161}Tb: same profile, same production tools, … same issues
- ^{67}Cu: still one isolated company developing drugs labeled with ^{67}Cu
- ^{131}I non metallic atom of interest for BBB crossing - main use: thyroid
- ^{90}Y high energy, no gamma - main market in local therapy (liver - brachytherapy)
- Alphas in general are considered for relapsing patients
- ^{225}Ac tested as substitute for all ^{177}Lu drugs developed so far
- ^{225}Ac mainly used in patients non-responsive to ^{177}Lu
- … but, if ^{177}Lu is inefficient, ^{225}Ac-analogues will do the job, is not true

RVT further evolution

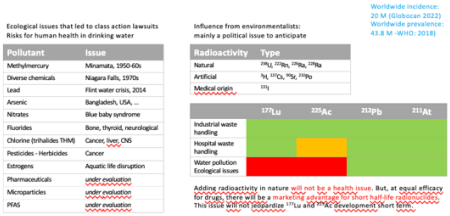
Thinking out of the box: beyond today's standard use of Radiotheranostics

- From third to second to first line treatments
- Combined or cocktail therapies
  - Evolution of RVT will follow evolution of chemotherapy
  - Need of approved drugs (alpha and betas) and 15-20 years
  - ^{225}Ac + ^{177}Lu already tested: better efficacy proven
  - Future: combined betas+ alphas, introducing AEs/CEs, mix with chemo, …
  - Important role to play for ^{161}Tb (beta+AE) or ^{212}Pb (beta+alpha)
  - ^{211}At: Probably major role for combined ^{131}I/^{211}At (beta/alpha) or ^{123}I/^{211}At (AE/alpha)
  - Other advantage: same production tool for ^{123}I and ^{211}At
- Evolution of NM in pediatry
- Evolution of veterinary nuclear medicine

Safety



2034: From 30,000 to 1,000,000 patients treated a year



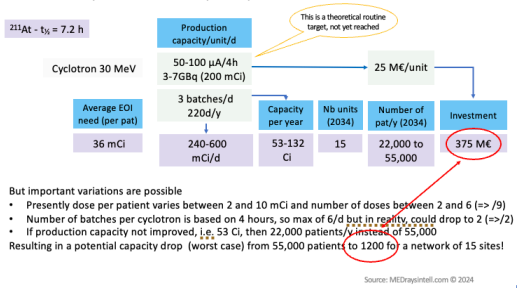
2034: Long term needs' assumptions

	Average dose per patient	Average dose (pre-labeling)	EOI dose per patient	Nb doses Per patient	Average amount per patient (EOI)
^{177}Lu - $t_{½}$ = 6.7 d	75 mCi	200 mCi	400 mCi	2 to 6 – average 3	1.2 Ci
^{225}Ac - $t_{½}$ = 10.0 d	200 µCi	300 µCi	330 µCi	2 to 6 – average 3	1.0 mCi
^{212}Pb - $t_{½}$ = 10.6 h	3 mCi	6 mCi	20 mCi	2 to 6 – average 3	60 mCi
^{211}At - $t_{½}$ = 7.2 h	3 mCi	6 mCi	12 mCi	2 to 6 – average 3	36 mCi

- 177Lu-Pluvicto is approved on the basis of 6 times 200mCi injected. On this basis, the average amount EOI per patient would be 6 Ci, not 1.2. Real life average reported number of doses per full cycle is 3.5 (due to drop out, no-show, death, …)

Source: MEDraysintell.com © 2024
Lancet Oncology 2024
Zimmerman 2023 - JNM 2024

2034: ^{211}At production capacity



2034: Future ^{211}At-labelled drug world manufacturing capacity

- If we trust these figures, a full network of 15 dedicated production centers will cover the main US+EU markets and will be sufficient to treat a maximum of 55,000 patients a year
- Each additional target of 55,000 patients/year will need an investment of €375M
- ^{211}At is adapted for orphan drug indications, not blockbuster indications (prostate, breast, lung …)
- Each drug/company will want to control its own network, so there will be as many networks of 15 cyclotrons as marketed drugs
- … as € 375M is a small amount compared to a potential yearly revenue of 55K pat x 100K€ = €5.5B
- … and a small investment compared to an additional reactor (> 1B€), sources for ^{225}Ac (presently 3x200M€), and even to the investment realized so far for giving access on this same territory to ^{18}F (800+ cyclotrons - €4B)

Producing ^{211}At will NOT lead to exceptional CoGs - there is no reason not to invest in ^{211}At

Why should I invest in Astatine-211 rather than in … ?

Two types of investors

- A: Companies investing in the manufacturing tools: €20 to 400M
- B: Companies investing in the drug development : €200M to €10B

If development of drug is successful, B will acquire A

The existing ^{211}At-producing network is mainly based on academic centers

Of the utmost importance for developing new technologies and new drugs in the field

… providing that the research activities are covered by IP

Also of high importance for industry as part of their learning curve

That can be used during the ramping up phase but not further than Clinical Phase II (GMP)
… but, as they cannot be acquired at a later stage for commercial production (except Ionetix, Nusano, …), of no interest for investors
The cost of development of a drug targeting 27,000 patients is almost the same as for a drug targeting 5M patients
Development of a 'me-too' drug can become really expensive
Summary and conclusions

- ^{211}At production yields need to be improved
- ^{211}At is best appropriate in development of drugs for orphan diseases (<50K patients)
- Each player will want to control its own production network (15 cyclotrons)
- To keep the control and to reach market target, he will have to invest about € 375M /drug/indication
- On the long term, ^{211}At may have a role to play in brain disease (together with ^{123}I/^{131}I)
- ^{212}Pb will put pressure on ^{225}Ac, but ^{211}At will not jeopardize ^{225}Ac or ^{212}Pb
- We are missing molecules with IP in original indications

Q&A

13.10 Lunch Break - Industrial exhibition

14.40 **Dr. Antero Abrunhosa** - Survey analysis

14.55 **Dr. Emma Aneheim & Dr. Jean-François Gestin**
Closing remarks &Farewell

15.10 **All MC representatives - MC meeting**
1) End of Action NOAR
2) Creation of NOAR EUROPE/WAC
3) Discussion on the survey result
4) Discussion on future NOAR EUROPE membership and budget

Presentation of the budget during the 4 years:
All Grant Periods have been approved by MC and Scientific Officer of the COST Action :
From 01/11/2020- 31/10/2021 = 73.841,50€
From 01/11/2021- 31/10/2022 = 95.699,55€
From 01/11/2022- 31/10/2023 = 132.653,08€
From 01/11/2023- 21/10/2024 = 152.490,00€
Total amount = 454.687€/4years

Presentation of the 01/11/2023- 21/10/2024 period

Actions / CA19114 / Periods / Period 4 / Grant

Financial period: **AGA-CA19114-4**
From **01/11/2023** to **21/10/2024**

Contact Us

Total	Grant budget (a)	Expenditure					Delta (g=f-a)
		Actuals (b)	Accruals (c)	Total (d=b+c)	Forecast (e)	Total (f=d+e)	
Meeting	74 235.00	11 006.75	1 632.43	12 639.18	54 640.00	67 279.18	-6 955.82
Training School	1 585.00	1 212.64	0.00	1 212.64	0.00	1 212.64	-372.36
Short-Term Scientific Mission Grant	40 780.00	5 100.00	0.00	5 100.00	35 680.00	40 780.00	0.00
Virtual Mobility Grant	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Inclusiveness Target Countries Conference Grant	4 000.00	0.00	0.00	0.00	4 000.00	4 000.00	0.00
Dissemination Conference Grant	6 500.00	4 000.00	0.00	4 000.00	2 500.00	6 500.00	0.00
Dissemination and Communication Products	4 500.00	0.00	0.00	0.00	4 500.00	4 500.00	0.00
Other Expenses Related to Scientific Activities (OERSA)	1 000.00	0.00	0.00	0.00	1 000.00	1 000.00	0.00
Virtual Networking Support Grant	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Networking expenditure	**132 600.00**	**21 319.39**	**1 632.43**	**22 951.82**	**102 320.00**	**125 271.82**	**-7 328.18**
Eligible Networking expenditure	132 600.00	21 319.39	1 632.43	22 951.82	102 320.00	125 271.82	-7 328.18
FSAC 15% of Eligible Networking expenditure	19 890.00	3 197.91	244.86	3 442.77	15 348.00	18 790.77	-1 099.23
Eligible Costs	**152 490.00**	**24 517.30**	**1 877.29**	**26 394.59**	**117 668.00**	**144 062.59**	**-8 427.41**

Grant budget - Budget as per Contractual Grant Agreement
Actuals - expenditure recorded for payment and sent to bank
Accruals - expenditure to be/or claimed pending to be reimbursed
Forecast - value/amount of future activities planned or committed

16.30 Coffee Break & End of meeting

Friday, October 4th , 2024 / Nantes

08.00 Core Group meeting

Revision of the final work and budget

The final work was presented to the Core Group members by the Action Chair. The discussion focused on how to continue in the coming months and create a platform for future work and collaboration. NOAR-EU was promoted, highlighting its goals, development path, and as a starting point for new projects and industrial collaboration.
A draft version of the budget was presented and discussed. The budget aligned with the planned and realized activities.

Discussion and preparation of the content for the Final Achievement Report, as well as the progress of the Final Action Dissemination, including deliverables

The Action Chair opened the discussion about the submission of the Final Achievement Report, which needs to be submitted after the end date of the COST Action.
The main objective of the Final Assessment of the COST Action was to identify how well the Action has:

- Implemented networking activities
- Developed S&T activities toward the Action's MoU objectives
- Achieved its MoU deliverables
- Achieved additional outputs and achievements, including projects resulting from Action activities and co-authored Action
- Engaged the TAT and WAC communities
- Promoted NOAR-EU
- Produced publications and achieved communication, dissemination, and exploitation of Action results

In addition, the Final Assessment of the Action will include:

- Information on potential success stories, emerging topics, and potentially important future developments
- Identification of impacts (the short- to long-term scientific, technological, and/or socioeconomic changes produced by the Action, whether directly or indirectly, intended or unintended)
- Collection of data necessary to demonstrate COST performance and impact

Preparation on the Newsletter No4

The final newsletter for the COST NOAR project will address topics from the 3rd Global Meeting, as well as the mission, responsibilities, and duties carried out during the project. T

his newsletter will provide important information about the project's outputs and key insights as we conclude the story.

16.30 – 18:00 **Conclusion – Minutes writing**