



Orano Med Media Kit

Inauguration ceremony
for the ATLab Indianapolis

Brownsburg, June 6, 2024



Orano Group in brief

“Develop know-how in the transformation and control of nuclear materials for the climate, and for a healthy and resource-efficient world, now and tomorrow”

In 2023:

€4,8 Bn in revenue

€30,8 Bn of firm orders

In the TOP 3 worldwide in its core activities

17,500 employees

As a recognized international operator in the field of nuclear materials, Orano delivers solutions to address present and future global energy and health challenges. Its expertise and mastery of cutting-edge technologies enable Orano to offer its customers high value-added products and services throughout the entire fuel cycle.

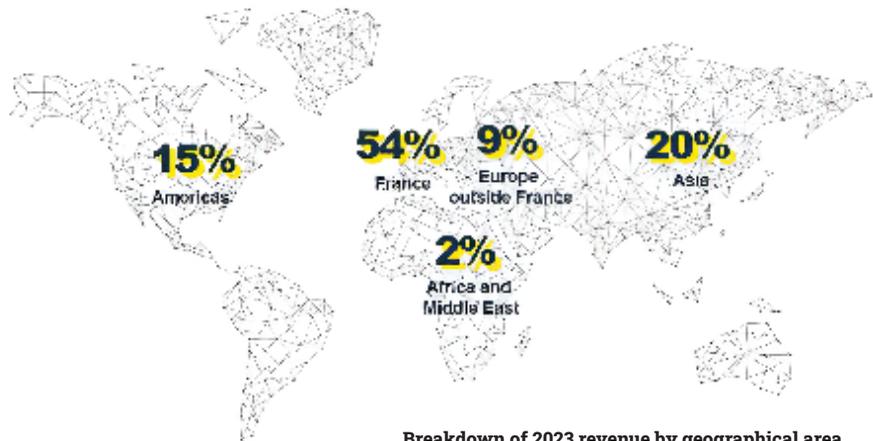
Every day, the Orano Group's 17,500 employees draw on their skills, unwavering dedication to safety and constant quest for innovation, with the commitment to develop know-how in the transformation and control of nuclear materials, for the climate and for a healthy and resource-efficient world, now and tomorrow.

Breakdown of 2023 revenue by activity:

28% mining

27% front end

45% back end



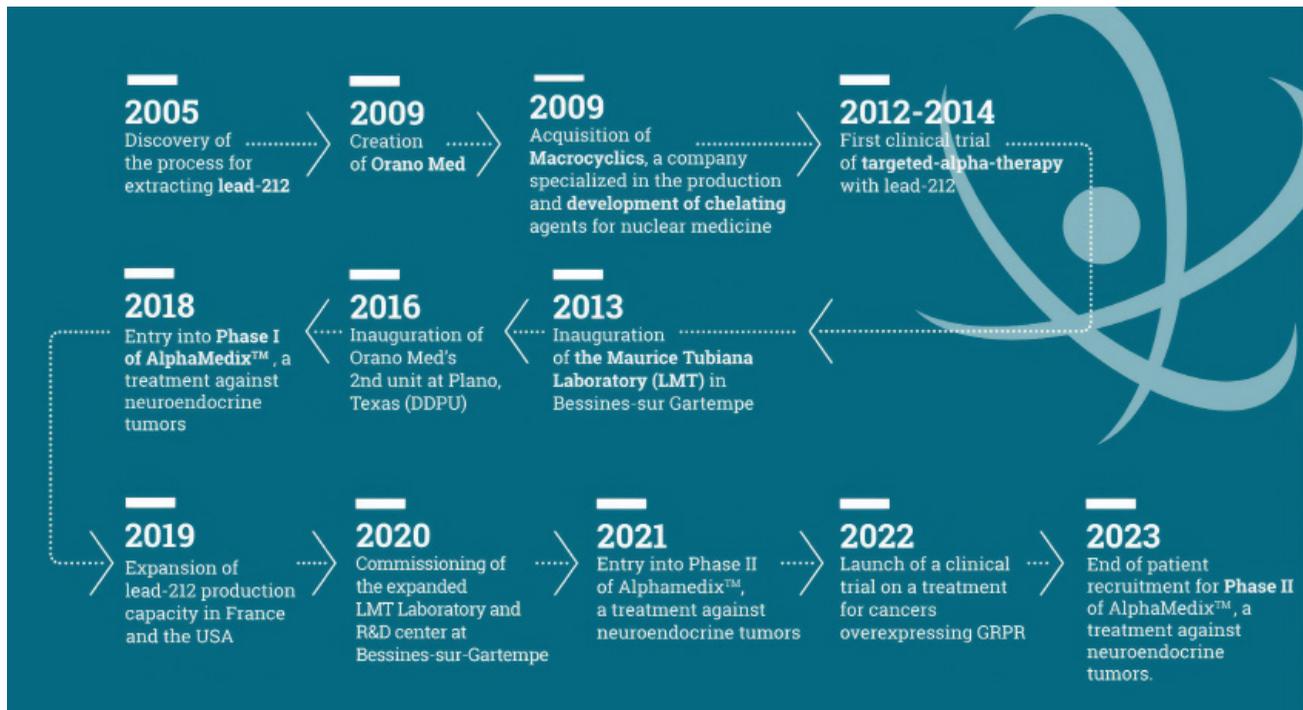
Breakdown of 2023 revenue by geographical area

Orano Med: Our history

In the early 2000s, Areva (now Orano) looked at opportunities to use material derived from its core nuclear energy activities. Nuclear medicine and Radioligand Therapy quickly appeared very promising. Lead-212 was identified as offering tangible scientific prospects, and Orano had the necessary know-how to meet the challenges involved in its procurement.

With sufficient resources to produce lead-212 in larger quantities, the project soon launched to demonstrate the feasibility of extracting and purifying this isotope. Successful results from conclusive preclinical studies with the National Cancer Institute in the U.S. led to the creation of Orano Med in 2009.

Orano Med, a subsidiary of the Orano Group, is a clinical-stage biotechnology company developing a new generation of targeted therapies against cancer using the unique properties of lead-212 (^{212}Pb), a rare alpha-emitting radioisotope and one of the most potent therapeutic payloads against cancer cells.



Our mission



Orano Med seeks to develop a new generation of targeted therapies against cancer using the unique properties of lead-212, a rare alpha-emitting radioisotope and one of the most potent therapeutic payloads against cancer cells.

Although oncology research has made tremendous progress in recent years, medical needs remain unmet for many types of cancer. Our approach, known as **Targeted Alpha Therapy (TAT)**, opens up promising prospects for patients not responding to existing treatments.

Our strategy

Making successful Targeted Alpha Therapy a reality.

Orano Med's strategy has two goals:

- developing a robust pipeline of lead-212-based therapies,
- providing a reliable supply chain for these innovative drugs.

Orano Med masters lead-212 chemistry and conjugation technology (including proprietary antibody site specific conjugation via its subsidiary Macrocyclics acquired in 2011) and is able to radiolabel lead-212 to various biological vectors (peptides, antibodies, etc.) targeting antigens or receptors expressed in a wide range of cancers.

Orano Med currently employs 120 people, including 50 in France and 70 in the U.S.

The Company has:

- A research laboratory dedicated to the development of lead-212 alpha therapies, located in the United States (Texas)
- Manufacturing facilities in France and the United States (see Industrial platform Section)

Our research activities

Develop a pipeline of lead-212-based anti-cancer treatments



We focus our developments on areas of high unmet needs where lead-212 labeled compounds could make a difference and, since 2016, our preclinical facility in the United States (Plano, Texas) has accelerated the transition of our molecules into clinical research.

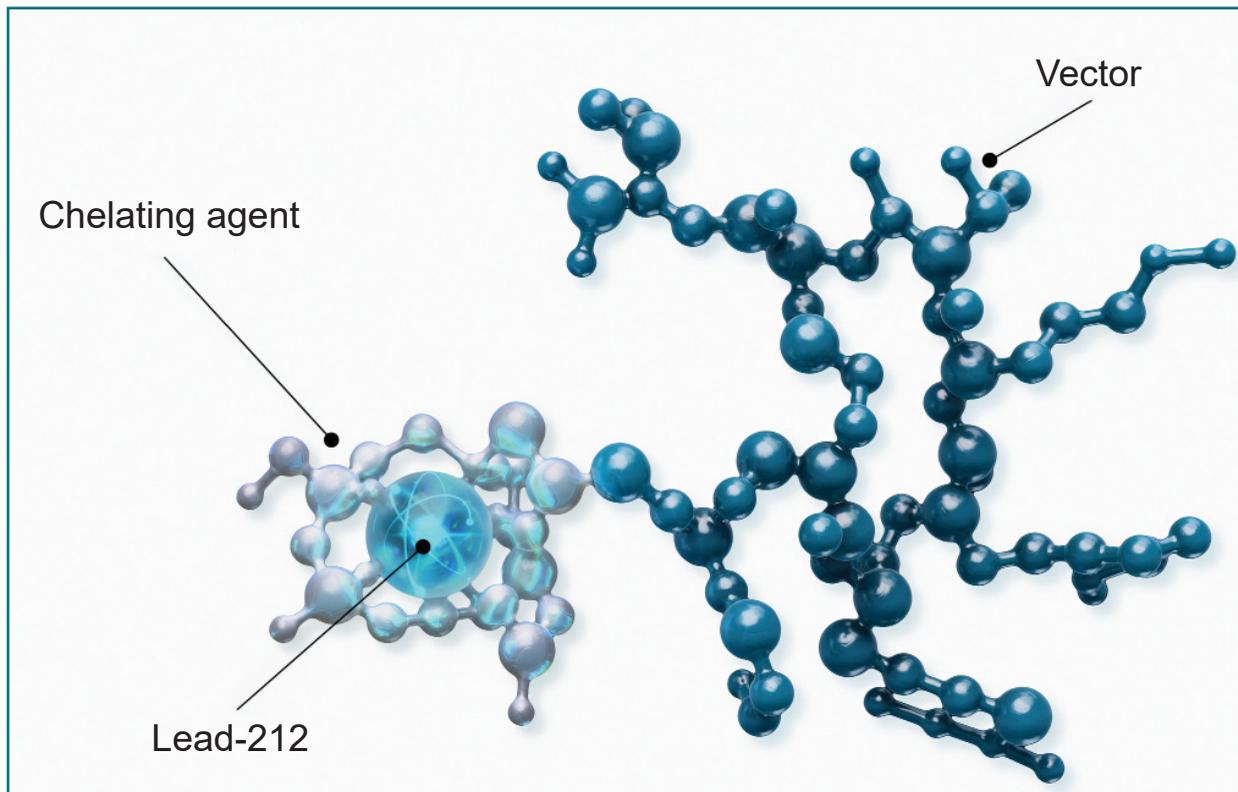
Produce and ensure the availability of drugs



Because reliability of supply of alpha emitters has long hindered the development of TAT, we are also investing in our production facilities in France and in the United States. Our facilities currently have the capacity to supply all the lead-212 necessary to conduct clinical trials and we are ramping up to industrial production capacity to meet commercial needs.

Lead-212 Alpha Therapy

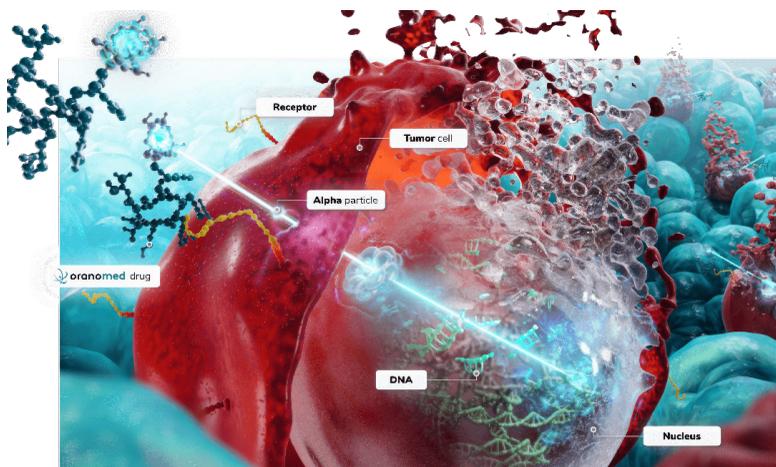
TARGETED ALPHA THERAPY : A powerful way to treat cancer



Targeted Alpha Therapy relies on a simple concept: combining the ability of biological molecules to target cancer cells with the short-range cell-killing capabilities of alpha-emitting radioisotopes.

The drugs developed by Orano Med consist of:

- an atom of lead-212 an in vivo generator of alpha emitters
- a biological vector (peptide, antibody, etc.) specifically targeting tumor cells,
- a chelating agent to bind the lead-212 to the vector.



lead-212 can be combined with a wide range of targeting vectors, thereby vastly increasing the potential range of applications in oncology.

AlphaMedix

AlphaMedix™ is the most advanced drug candidate developed by Orano Med with its American partner RadioMedix.

This is a targeted alpha therapy with lead-212 against neuroendocrine tumors, a heterogeneous group of rare neoplasms that originate from neuroendocrine cells. These neoplasms occur mostly in the gastrointestinal tract and pancreas, but can also occur in other tissues including thymus, lung, and other uncommon sites such as ovaries, heart, and prostate.

AlphaMedix™ obtained particularly promising results in clinical trials in humans conducted between 2018 and 2021. AlphaMedix™ entered Phase 2 clinical trials in 2021 to assess its efficacy in the treatment of neuroendocrine tumors. After completing enrolment of PRRT-naïve patients in 2023, we have finished enrolling the second cohort of patients who progressed on prior Peptide Receptor Radionuclide Therapy. The FDA Breakthrough Therapy Designation for AlphaMedix™ in gastroenteropancreatic neuroendocrine tumors (GEP-NETs), was an important milestone to expedite the development of this new Targeted Alpha Therapy with lead-212.

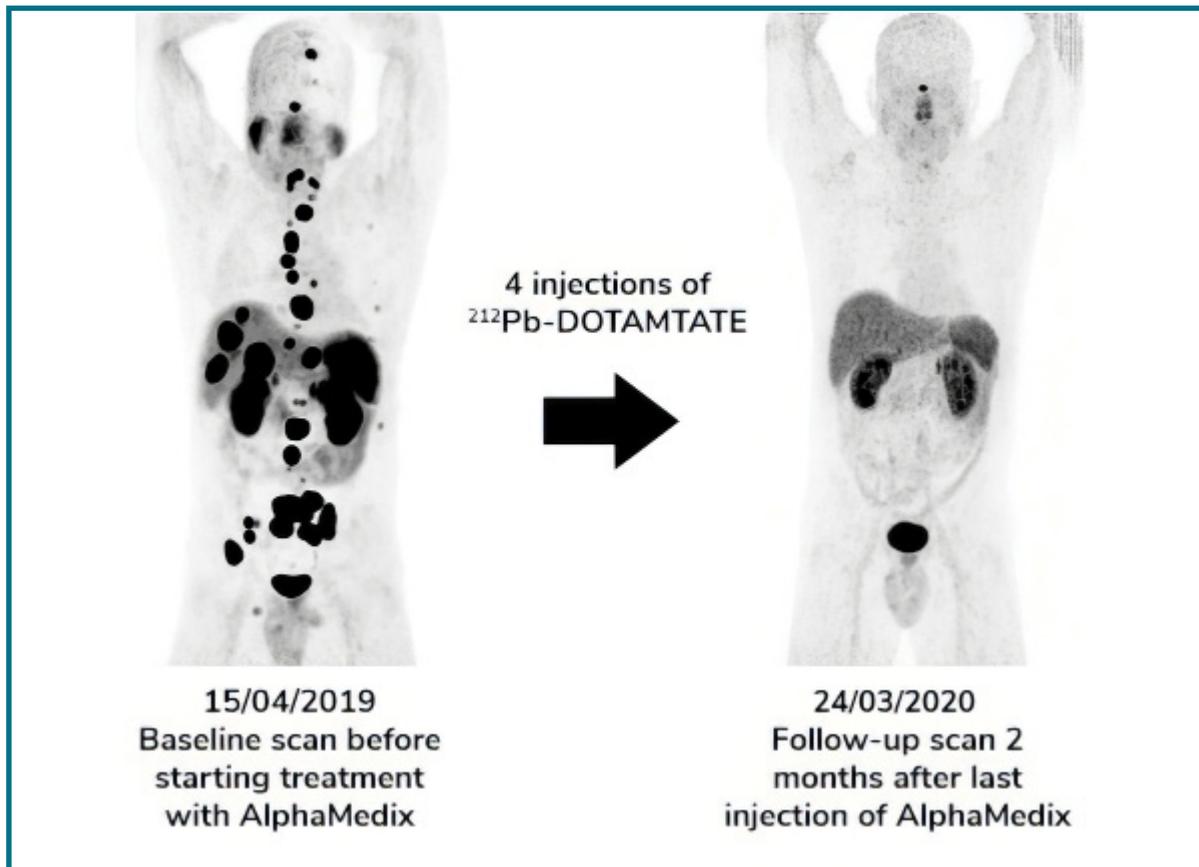
Superiority of targeted alpha therapy in the fight against cancer

Two types of isotopes can be used in radioligand therapies: emitters of alpha or beta radiation. Currently, only beta therapies are commercially available. However, alpha particles have **two key benefits** for applications in oncology:

1 - Improved biological efficacy

Alpha decay consists of the emission of a helium nucleus (alpha particle) together **with linear energy transfer which is 100 times higher than that of beta radiation**. The alpha radiation thus causes **irreparable double-strand breaks in the DNA** of cancer cells in immediate proximity to the emission while beta radiation has more of a tendency to cause single-strand breaks.

As a result, **alpha emitters** are considered as the most powerful payloads to be found for targeted therapies with fewer than five particles needed to kill a cancer cell versus hundreds of beta emitting isotopes or thousands of chemotherapy toxins.



Patient with metastatic neuroendocrine tumors included in the Phase 1 clinical trial of AlphaMedix (lead-212-DOTAMTATE), a drug currently being developed by Orano Med and RadioMedix.

2 - Toxicity limited due to short range of emission

The alpha particles only travel **a very short distance into the tissue: only 2 to 5 cell layers** (compared to more than 50 with beta radiation). They thus deposit a very large amount of energy over a very short distance. This results in an increased cytotoxic potential toward cancer cells while **limiting toxicity to nearby healthy cells**.

Why lead-212?

Lead-212 has all the qualities required for application in radioligand therapies:

- **Half-life of nearly 11 hours facilitates the management of radioactive waste and effluents** and allows treatments to be administered on an outpatient basis, placing less constraints on hospitals;
- **Only a single alpha emission in its decay chain**, limiting the circulation of free radioactive isotopes (not chelated to the vector) and **thus the toxicity to healthy organs**;
- It has particularly stable chelating agent, allowing **effective targeting** of cancer cells;
- Another isotope of lead, lead-203, is an imageable gamma emitter, allowing **the development of theranostic approaches with lead-203/lead-212**.

Moreover, Orano Med has developed an entirely chemical production process. This makes it more reliable and less costly than other processes usually used for the production of radioisotopes by cyclotron or in a nuclear reactor.

Preclinical and clinical development

Orano Med has equipped itself with all the tools necessary for the preclinical and clinical development of lead-212-conjugated molecules with:

A preclinical laboratory dedicated to the development of lead-212 Targeted Alpha Therapy treatments in the U.S. (Plano, Texas).

This lab is fully equipped to conduct the necessary preclinical studies to develop new molecules as well as to perform activities of peptide synthesis, bioconjugation, radiolabeling, and analytical testing.



A second preclinical laboratory in France in partnership with Roche (Razès, Haute-Vienne), to develop novel, advanced alpha radioimmunotherapy techniques.

Two clinical trials launched by Orano Med are currently in progress:

- Phase 2 clinical trial on neuroendocrine tumors with AlphaMedix™
- Phase 1 clinical trial on different types of solid tumors with an anti-GRPR peptide as a targeting molecule

It takes almost 15 years for a molecule of therapeutic interest to become a marketed treatment. The whole process is strictly regulated. The various trial phases are described below.

Types of trials		Study population	Primary goal
Clinical trials	Phase 1	Twenty healthy or sick volunteers, depending on the molecule studied	Observation of the molecule's evolution in the body over time (kinetics) and evaluation of its tolerance.
	Phase 2	A few dozen to a few hundred patients with the targeted disease	Evaluation of drug efficacy and evaluation of its tolerance.
	Phase 3	A few hundred to a few thousand	Evaluation of the drug's efficacy on a larger cohort of patients. Volunteers are often divided into two groups to compare the efficacy of the drug candidate with a reference treatment or placebo.
Placing on the market			
Post market safety monitoring	Phase 4	Large group	Long-term monitoring of drug use under real-life conditions, to detect rare adverse effects, late complications or prescribing bias

Pipeline

A Diverse pipeline of lead-212-labeled compounds

Based on the unique properties of lead-212, Orano Med is developing a multi-asset portfolio to combine lead-212 with diverse biological vectors targeting or binding to different specific cancer receptors or antigens. Our pipeline is composed of a mix of partnered compounds and internal developments.

In particular, we have partnered with the Roche group over 10 years ago to develop a new tumor cell targeting technology for applications in targeted alpha therapy. Orano Med also partners with other biotechs with particularly promising cancer cell targeting technologies, such as Molecular Partners.

Program	Indication	Discovery	PoC	Pre-IND	Phase 1	Phase 2/3	Partner
AlphaMedix™	Neuroendocrine tumors						▼
²¹² Pb-GRPR	Solid tumors (breast and prostate cancer)						▼
²¹² Pb-PSMA	Prostate cancer						▼
²¹² Pb PRIT	Solid tumors						▼
²¹² Pb - DARPIn-DLL3	Small-cell lung cancer						▼
²¹² Pb PRRT	Undisclosed target						▼
²¹² Pb PRRT	Undisclosed target						▼
²¹² Pb PRRT	Undisclosed target						▼
²¹² Pb PRRT	Several targets					Undisclosed	
²¹² Pb TAT	Several targets					Undisclosed	

Industrial platform

Orano Med has developed a patented chemical process allowing production of lead-212 on a large scale and at a reasonable cost.



Development of targeted alpha therapy has long been hindered by a lack of supply of alpha emitting radioisotopes meeting three important criteria: purity meeting radiopharmaceutical standards, reliable production capacity sufficient to meet global needs, and economic competitiveness.

With a unique and proprietary source of raw material (thorium-232), Orano Med has developed a process allowing **production of very high-purity lead-212 on a large scale and at a reasonable cost.**

Large-scale, reliable and independent lead-212 production capacity

lead-212 is a radioactive element from the decay chain of thorium-232, a radioisotope that occurs naturally on Earth. From the Orano group's former activities, Orano Med has **22,000 drums of purified thorium-232 at its disposal, a sufficiently plentiful stock of raw materials to cover global needs for Targeted Alpha Therapy.**



Moreover, after initial extraction of the daughter elements it contains, the thorium-232 is retained. Given this radioisotope's extremely long half-life (14 billion years), it will produce descendants again, allowing lead-212 to be extracted again a few years later. **Every drum can thus be re-used indefinitely to produce lead-212.**

The **patented, entirely chemical process**, developed by Orano Med consists of several successive steps of extraction and purification of descendants of thorium-232: radium-228, thorium-228, radium-224 and finally lead-212. Not needing either nuclear reactors or particle accelerators, **the chain for the production of lead-212 and the drugs is fully integrated within Orano Med** and is independent of external radionuclide suppliers.

Facilities that are unique in the world



In order to produce lead-212-conjugated drugs and distribute them, Orano Med has developed a global industrial platform.

In France at Bessines-sur-Gartempe in the Haute-Vienne, the Laboratoire Maurice Tubiana (LMT) is implementing the upstream phase of the process: the production of radium-228 and thorium-228 from which the doses of lead-212 will be extracted. It can also call upon the support of its associated research and development center (Centre de Recherche et Développement – CRD).

Orano Med is thus continuously optimizing its processes to be better and better at meeting the challenges of industrialization, quality, and protection of the environment, as well as the specific demands of its partners. A larger facility is being planned for the future to industrialize this process and cover global needs in the drug commercialization phase.

The Laboratoire Maurice Tubiana can also produce lead-212 for clinical trials in Europe.



In Plano, Texas, U.S., the **Domestic Distribution & Purification Unit (DDPU)** produces lead-212 for North America from precursors supplied by the LMT. It also manufactures drugs for clinical trials in accordance with GMP standards assembling lead-212 with the chelating agent and the targeting molecule.

In the U.S., Brownsburg, Indiana, the first **Alpha Therapy Laboratory (ATLab)** will commence the large-scale production of lead-212 radioligand therapies and their distribution in North America, from thorium-228 supplied by the LMT.





In France, an ATLab is also under construction in Onnaing, near Valenciennes. Likewise, it will commence the large-scale production of lead-212 radioligand therapies and their distribution in Europe as of 2025. Based on a modular design, further production lines may be added in the future to allow for the manufacturing and distribution of several drugs simultaneously.

Given the half-life of lead-212(10.6 hours), the drugs must be produced close to hospitals. The construction of other AT Labs are planned to cover global needs.

Inauguration of Orano Med's ATLab in Indianapolis



Orano Med's new facility in Brownsburg, near Indianapolis, is designed for the large-scale production of cancer treatments with lead-212, known as targeted alpha therapies.

This is the world's first industrial-scale pharmaceutical facility dedicated to the production of lead-212 targeted alpha therapies.

This location was chosen for its proximity to major national and international distribution networks, with the second largest FedEx hub ensuring reliable transport of radiopharmaceutical products, and its high concentration of pharmaceutical companies and skilled workforce.

A similar manufacturing site is currently under construction in France, in the metropolitan area of Valenciennes, to ensure the production and distribution of treatments in Europe.

ATLab Indianapolis key figures:

- 25 direct jobs
- An investment of \$20 million
- 30,000 ft² (2800m²) of floor space
- Manufacturing capacity of 5,000 doses a year, with the aim of producing ten times that number by the end of the decade
- 8 lines of shielded hot cells of 100 metric tons each for lead-212 production
- 2 drug production lines of 55 metric tons each

Glossary

Alpha Therapy: Targeted alpha therapy uses the properties of a vector to recognize cancer cells and alpha radiation to destroy them while limiting the impact on nearby healthy cells.

Theranostic approach: This approach combines imaging to first map cancer cells in the body and then radioligand therapy to target and destroy them.

Chelating agent: A molecule that binds a metal (in this case lead-212) to the tumor-targeting vector.

Cyclotron: A cyclotron is a particle accelerator that uses the combined action of an electric field and a magnetic field to accelerate and confine particles in a restricted space. These facilities enable the production of numerous isotopes used in nuclear medicine.

Half-life: The half-life is the time it takes for half the atoms of a certain isotope to decay naturally. It does not depend on the environment (temperature, pressure), but is a property linked to the radioactive element.

Isotope: isotopes are atoms with the same number of electrons - and therefore protons, to remain neutral - but a different number of neutrons.

Peptide: Peptides are short chains of amino acids that act as bricks for proteins. They are used in oncology to target tumor cells.

Radioimmunotherapy: Radioimmunotherapy uses an antibody labeled with a radionuclide to deliver cytotoxic radiation to a target cell. It is a form of radioligand therapy.

Radioligand therapy (RLT): New generation of targeted therapies. It involves combining tumor cell-targeting molecules with a radioactive atom whose radiation destroys cancerous lesions.

Radiolabeling: Technique for using radioactive tracers in various fields, notably chemistry and biology. Radiolabeled substances are molecules or atoms in which an element is replaced by a radioactive isotope.

Ionizing radiation: Radiation is an emission of energy and/or a beam of particles. Certain types of radiation (X-rays and gamma rays) are said to be ionizing because they emit «rays» of sufficient energy to transform the atoms they pass through into ions (an atom that has lost or gained one or more electrons).

Thorium: Thorium is a chemical element, a metal in the actinide family, with symbol Th and atomic number 90. It was discovered in 1829 by Swedish chemist Jöns Jacob Berzelius and named after Thor, the Norse god of thunder.

About Orano

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For more information, visit www.orano.group

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About Orano Med

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For more information, visit www.oranomed.com

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