Advanced Accelerator Applications

A Novartis Company

RADIOLIGAND CANCER THERAPIES

WHO IS AAA?

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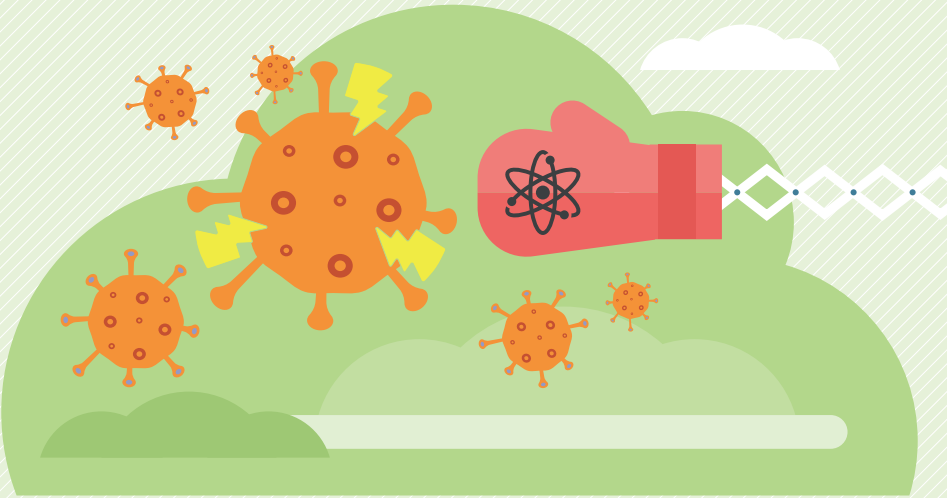

WHAT ARE TARGETED RADIOLIGAND THERAPIES?

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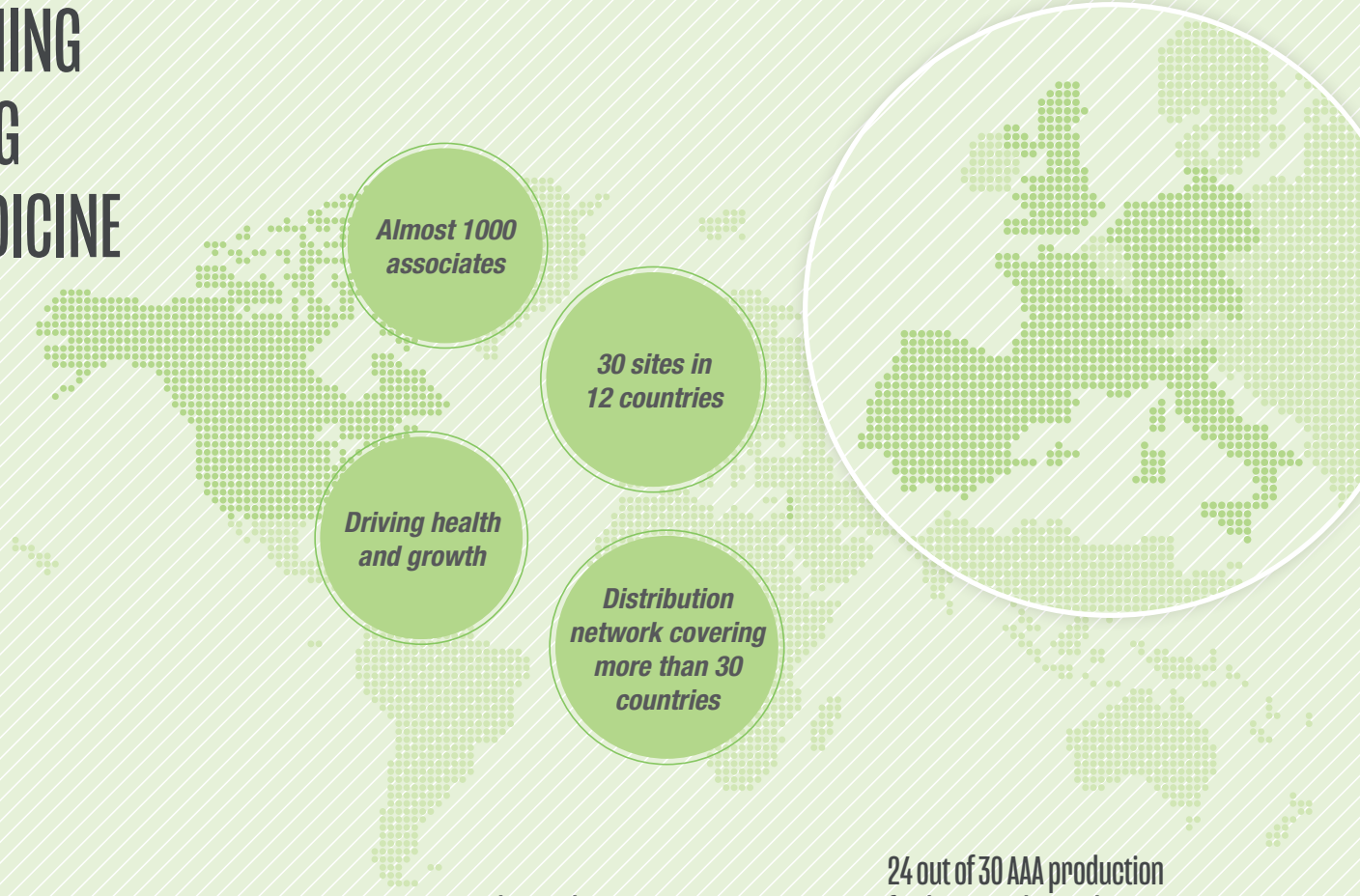
AAA IN EUROPE - TRANSFORMING LIVES OF PATIENTS BY LEADING INNOVATION IN NUCLEAR MEDICINE



What we bring to Europe

A highly skilled workforce

Sustained investment through our conduct of R&D

Sophisticated supply chain

Making medical innovation accessible on a global scale

24 out of 30 AAA production facilities are located in Europe

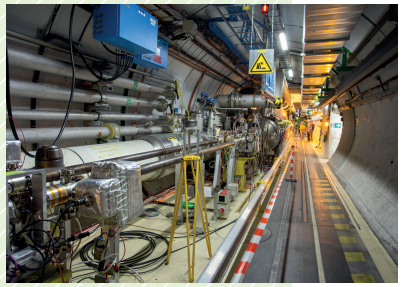
France: 7 sites
Spain: 5 sites
Italy: 4 sites
Portugal: 2 sites
Germany: 2 sites
Switzerland: 1 site
Netherlands: 1 site
Poland: 1 site
UK: 1 site

A Novartis company since 2018[1], Advanced Accelerator Applications (AAA) is an innovative medicines company developing precision targeted drugs with radioactive components – a pioneer and leader in radioligand therapy (RLT).

AAA was founded in 2002, as a **spin-off from the European Organization for Nuclear Research (CERN)** and has a legacy as market leader in the development and delivery of radiopharmaceutical products for diagnostic imaging. During the early years, AAA specialised in the reliable manufacturing and delivery of imaging agents with very short shelf-lives for ready-to-use administration. This included the development of in-house manufacturing processes for both radioisotope production and final drug formulation.

For the past several years, the company has increasingly focused its efforts on developing radioligand therapeutics, alongside diagnostics. AAA now offers an integrated approach to patient management based on the targeting of a single receptor expressed by cancer cells with both diagnostic and therapeutic agents, otherwise known as theragnostics.

Theragnostics combines the use of targeted diagnostics and therapeutics, so physicians can "treat what they see".



CERN research centre

Radioligand therapy *is a milestone development in cancer therapy. The approach combines tumour targeting and internal radiation. This allows to "treat what we see".*

RADIOLIGAND THERAPY: PARADIGM SHIFT IN CANCER CARE

RLT utilises a novel approach to tumour-targeting that introduces a paradigm in cancer care.

Radioligand therapies are composed of a targeting molecule attached to a therapeutic radioisotope. They are administered intravenously, and the cancer-targeting molecules are attracted to receptors expressed by the tumour cells, allowing the radiation to be targeted to the tumours.

As a result of this targeted approach, treatment may be delivered to multiple tumour sites around the body, while impact to healthy tissues is minimalised. Other cancer therapies, such as chemotherapy and immunotherapy, target all cells within the body.

Patients[2]

- Well tolerated treatment positively impacts quality of life
- More effective care through targeted approach

Physicians[3]

- Better ability to diagnose and stage disease
- Ability to select effective therapies for eligible patients

Healthcare systems[4]

- Reduce costs from unnecessary treatment
- Improved patient management & outcomes

Radioligand therapy production

1. Isotope supply

Radioisotope, for example Lutetium 177, is produced in a nuclear reactor following which it is delivered to a production facility and evolved to a liquid Active Pharmaceutical Ingredient (API).[5]

Did you know?
Small molecules (such as peptides) are used as delivery vehicles for the radionuclides to cancer cells.

2. GMP Production

Following the same example, Lutetium 177 is combined with the carrier ligand DOTATATE using a sterile chemical synthesis process called radiolabelling. The result: 177Lu-DOTA solution.[6]

3. Quality control

177Lu-DOTA solution is sterilised and purified.

4. Transport

The solution is transported in sterile, specific conditions to preserve stability.

Did you know?
To deliver the treatment on time, sometimes there is a need to produce a second dose and transport it via two different routes.

5. Patient delivery

The solution is intravenously administrated to the patient within a specific time frame of its production.

This time frame is determined by the specific half-life of the isotope used.

THE NEED FOR POLICY ACTION

Radioligand therapy has the potential to change the disease outlook for patients with rare cancers and those impacted by society's most prominent cancers.

Neuroendocrine tumours are a rare disease with limited treatment options, which is still all too common in rare diseases. Of the 6,000–8,000 rare diseases in the world only 6% have treatment options[7]. Radioligand therapy now provides a treatment option for advanced, progressive, SSTR positive gastroenteropancreatic neuroendocrine (GEP-NET) patients, thus marking continuing hope for rare disease patients and progress to the public health goal of extending treatment options in rare diseases[8]. RLT is becoming increasingly relevant also in the treatment of patients with metastatic and castration-resistant prostate cancer[9] (mCRPC), a leading health threat for men globally[10]. Prostate is the second most frequent diagnosis made in men and the fifth leading cause of death worldwide.

This renaissance in cancer care needs to be supported by policy action to turn potential into reality.

AAA is pioneering the field of nuclear medicine as well as bringing true innovation in manufacturing processes, supply chain and patient care in the field of oncology and beyond. We are in the midst of a paradigm shift, and it is AAA's vision that this renaissance in cancer care is matched by policies that guide increased R&D, support an expansion of public-private collaborations and fundamentally rethink the infrastructural requirements needed to deliver truly personalised modern healthcare. The prerequisite of RLT is that it requires a healthcare community that is trained and prepared for its proliferation and a healthcare infrastructure that recognises its potential. In this vein AAA is also committed to supporting the construction of these policies in a collaborative way with policymakers and the healthcare community.

1 Radioligand therapy relies on adequate infrastructure to fulfil its promise to patients.

Increasing European hospitals' readiness for the delivery of RLTs is crucial for the successful and sustainable uptake of this treatment option for patients. Hospitals have significant infrastructure needs in terms of the number of physicians, nurses

and other hospital staff specialised in RLTs, as well as in terms of hospital wards and diagnostic infrastructure to facilitate treatment (i.e., PET Scanners). This paradigm shift requires new hospital adaptations to take into account the future needs of the expanding field of RLT. National and supranational funding mechanisms, such as the Recovery and Resilience Facility, the Cohesion Policy Funds and InvestEU, can play a key role in supporting regional infrastructural developments to improve hospital capacities.

2 Radioligand therapy needs specialised education for its integration in cancer care.

To promote the uptake of RLT in mainstream cancer care, it is essential to bridge the knowledge gap that currently exists among health professionals, resulting from the innovative nature of this treatment and the multidisciplinary approach it entails. In fact, RLT requires a multi-disciplinary approach to education which brings together at once healthcare professionals across multiple specialties in order to facilitate discussion on cross-cutting topics of relevance for the adoption into cancer care.

The European Commission, in the Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) Action Plan[11], also recognises the importance of improving workforce education and training as one main deliverable of the Plan. There are several opportunities and tools that can contribute to this scope, such as the Inter-specialty Cancer Training Programme under Europe's Beating Cancer Plan[12] or funds from the Erasmus+ Programme and Horizon Europe.

3 Radioligand therapy needs an up-to-date and aligned legislative framework for radiotherapeutics and radioprotection.

In a time of continuous medical innovation, the legislative framework needs to be up-to-date and prepared to embrace progress. The current legislation for radiopharmaceuticals dates back at least two decades and does not distinguish between therapeutic and diagnostic, creating inconsistencies or obstacles that could be avoided with a revision of the legislation. One main incongruence lies in the exemptions to the standard requirement for marketing authorization, which still reflect the specificities of radiodiagnostic tracers, no longer in line with emerging clinical practice.

This necessity fits within the goals of current EU policies, such as the Pharmaceutical Strategy for Europe[13], which highlights the need to drive innovation through a stable and flexible regulatory environment. To ensure maximum use of innovative therapies, the revision must also take into account the harmonisation of regulations covering radioprotection and medicinal products, which at the moment is not harmonised and not fully compatible with the current trends[14].

4 Radioligand therapy has the potential to become an integrated practice in national cancer care.

Mainstreaming radioligand therapy into cancer care needs the support of national and regional systems for a sustainable uptake for patients. Nowadays, healthcare systems and legislative frameworks are rapidly evolving at national and supranational level to keep pace with innovation. As such, it is essential to ensure that RLT is embedded in the process and that Member States have a harmonised and consistent approach towards this goal. The establishment of National Comprehensive Cancer Centres as well as Knowledge Centres on Cancer to guide Member States on best practices in cancer care - as envisaged by the Europe's Beating Cancer Plan[15] - are just a few examples of the opportunities to promote awareness of RLT in a more widespread and coordinated way and ensure it becomes an integrated practice in national cancer care.

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