DIVA: THE DUTCH ISOTOPE VALLEY

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ABSTRACT

DIVA (Dutch Isotopes Valley), the partnership between the Reactor Institute Delft (RID) of the Delft University of Technology, including the Department of Radiation Science and Technology (RST-TUDelft), URENCO, and NRG/PALLAS [1-5], aims to be able to continue providing patients with medical isotopes, but also to improve the quality of current and develop new medical isotopes for more accurate diagnoses and therapies for the treatment of more types of cancer. The three partners in DIVA cover both the development and the (industrial) reactor production of medical isotopes, comprising both the development of precursors and (enriched) stable isotopes (URENCO), the research for radiation conditions and required irradiation facilities (RID-TUDelft) and the final (industrial) routine production and marketing (NRG/PALLAS): DIVA makes this a coherent partnership, that works together with both the radiopharmaceutical industry and clinical end-users. With the DIVA partners The Netherlands has a worldwide unique combination of facilities and expertise needed for future development and production of medical isotopes.

1. Introduction

In Dutch hospitals, annually, some 500,000 nuclear medicine diagnostics are performed, and ca. 5,000 treatments of severe illnesses with medical (radio) isotopes.

Isotopes are forms of elements, and if these emit radiation, they are called radioactive and indicated as radioisotopes. Thus, ^{59}Fe is a radioisotope of the element iron (Fe), ^{99}Mo is a radioisotope of molybdenum (Mo) and ^{177}Lu is a radioisotope of the element lutetium (Lu). The emitted radiation can be used medically, for either diagnostics or for therapy, this in accordance with the characteristics of the emitted radiation.

For various reasons, among which the ageing of the population, the demand for medical radioisotopes for diagnostics and therapy increases every year. New developments in medical technology ask for more and new medical radioisotopes, to be offered and provided in nuclear medical diagnoses and treatments. DIVA (Dutch Isotopes Valley), the partnership between URENCO Nederland, the Reactor Institute Delft (RID) of the Delft University of technology and NRG/PALLAS (see Fig. 1 for their sites within The Netherlands), aims to facilitate the continuation of providing high quality radioisotopes to patients, and especially better medical isotopes for even more accurate diagnoses and therapies for the treatment of more types of cancer. The three partners in DIVA cover the domain of the development and production of medical isotopes (reactor), which means that both development work to precursors and (enriched) stable isotopes (URENCO), as the search for radiation conditions and required irradiation facilities (TUDelft), and the routine industrialized production (NRG/PALLAS) up to the eventual delivery to radiopharmaceutical industry or hospital end-users is covered.

2. The Partners

RID-TUDELFT

The Reactor Institute Delft [1] (RID) is a knowledge centre on nuclear topics, operating the Hoger Onderwijs Reactor (HOR), irradiation facilities, and neutron- and positron instruments. In conjunction with the scientific Department of Radiation Science and Technology [2] (RST) of the Faculty of Applied Sciences, RID accommodates resident and visiting scientists from a variety of scientific disciplines, educates students, professionals and scientists, and serves as an independent source of information for society on radiation- and nuclear-related issues. Over the years, the scientists around the reactor have gained a strong reputation in developing and using new and often unique instruments, irradiation facilities and methods.

In 2005, the decision was taken to upgrade the 2MW open pool research reactor. 12 years later we can clearly see that the 19 infrastructure issues defined by the IAEA for new built research reactors [3] hold also for a major upgrade. For the RID project OYSTER, Optimized Yield - for Science, Technology and Education – of Radiation [4], all 19 have been touched.

The program OYSTER will lead to an expected significant increase of the utilization of the research reactor by Dutch and International scientists from 2020 onward. RID will be fully prepared for innovative scientific developments with a safe and reliable reactor. In the DIVA context, RID develops concepts for new and flexible irradiation facilities, as well as new separation methods to produce radioisotopes having high specific activity.

URENCO Nederland

URENCO’s uranium enrichment site in the Netherlands is located in Almelo and employs around 260 people. Two separation plants, SP4 and SP5, are in operation. Former plants SP1, SP2 and SP3 were fully decommissioned and brought back to green field sites. The newest plant SP5 began operation in 2000 and houses over 80% of total site capacity. The Almelo site is unique because beside uranium enrichment they also produce Stable Isotopes. With these Stable Isotopes hospitals around the world treat hundreds of thousands of patients each year.

Since 1990 Stable Isotopes, a wholly owned business unit of URENCO, has employed URENCO's centrifuge technology to separate isotopes of other elements for a number of commercial purposes, supporting the medical industry and other key industrial applications. Although this is not a major part of URENCO’s business in purely financial terms, it is of considerable value from commercial, social and environmental perspectives.
Based at Almelo in the Netherlands, the existence and success of stable isotopes is testament to Urenco’s commitment to continuous development. While the separation of elements other than uranium has presented many new challenges, the development URENCO has committed to stable isotopes is now delivering value in two specific segments of the medical market: diagnostics and brachytherapy.

NRG

NRG is an internationally-operating nuclear service provider. The company produces isotopes, conducts nuclear technological research, is a consultant on the safety and reliability

of nuclear installations and provides services related to radiation protection. Research is performed for governments aimed at developing knowledge about nuclear technology.
NRG is a world market leader in the production of medical isotopes. In the Netherlands, NRG is the leading authority with regard to integral radiation protection. NRG operates the High Flux Reactor owned by the European Union.
The company has around 500 innovative employees with high quality know-how, and works for and with partners in healthcare, the energy market, industry, government and science.

PALLAS

PALLAS aims to realise a state of the art multifunctional nuclear reactor, which is suitable for mainly producing medical isotopes and for conducting nuclear technology research. This reactor will replace the current High Flux Reactor (HFR) in Petten (NL), which has been in operation for over fifty years and is approaching the end of its economic life.

As of December 16th 2013 the PALLAS organization is formally incorporated in an independent foundation: the Foundation Preparation Pallas reactor (PALLAS). This organization has the objective to acquire a licensed design, ready for construction, and for attracting funding for the second phase: the construction and commissioning.

Fig. 1. Nuclear sites within The Netherlands. North: NRG/PALLAS isotope production, URENCO enrich plant, Middle: RID/TUDELFT research reactor, NRG Nuclear consultancy, South-West: EPZ Nuclear Power Plant, COVRA disposal site for radioactive waste

3. DIVA

3.1 Unique DIVA

DIVA (Fig. 2) is unique because the collaboration between industry and university covers the production chain from precursors up to the marketing by the radiopharmaceutical industry.
Also on world-wide scale DIVA is unique: 1) Apart from Russia no country worldwide has a comparable production chain, and 2) In no country worldwide this chain is covered by a comparable coherent collaboration. This DIVA collaboration increases opportunities,

shortens the time lines between development and eventual application of new diagnostics and therapy, and makes that The Netherlands, in international perspective, has a unique and strong position in the delivery of materials for medical isotopes. For this the DIVA partners have

- a good infrastructure
- knowledge of business and operation
- technical and scientific know how
- a good international network

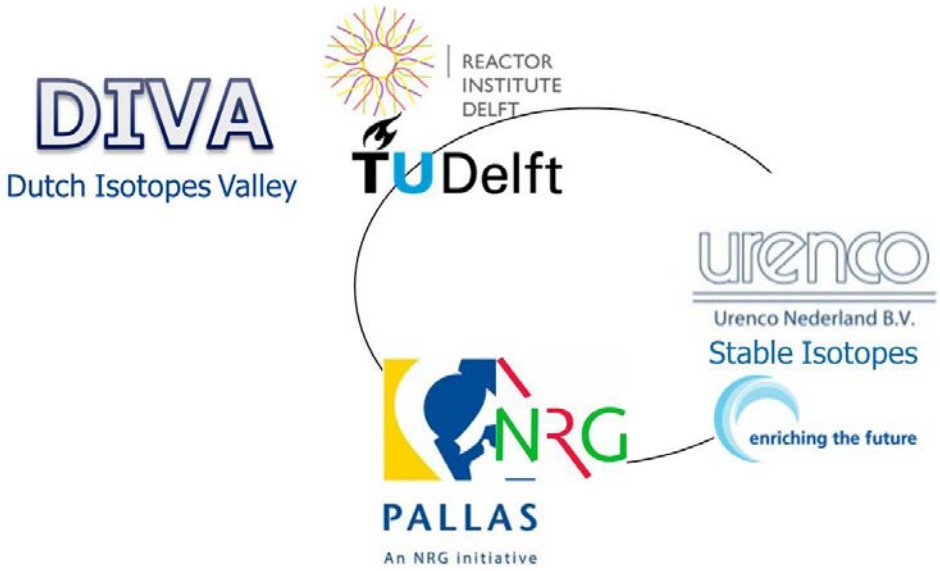

Fig. 2 DIVA Dutch Isotope Valley: RID-TUDelft, URENCO Stable Isotopes, and NRG/PALLAS.

3.2. Innovative DIVA

DIVA is innovative, renewing and pushing boundaries, because attention is paid to new isotopes (including e.g. isotopes for use in alpha radiation in therapy). The ageing of the population, de increasing demand for more early diagnostics, and the connected emerging developments in clinical physiology and the changing demands from radio-diagnostics and –therapy (nuclear medicine) all make that continuous development is necessary in isotope production. This goes both for the production *modes* as for the types of isotopes that are to be brought into production. Ever higher quality demands are put for these isotopes. The asked for ever-earlier recognition of disorders (e.g. cancer) within the human body (which maskes a succesfull treatment more feasable) demands for ever better and new radioisotopes; this follows from the way cancer is clinically distinguished from healthy tissues. DIVA is the worldwide unique answer to these challenges. DIVA is anticipated to lead to the more rapid development of new production modes, to faster solutions and easier availability of diagnostics and treatment, that are better financed.
The DIVA partners closely collaborate within various domains. Lines of R&D are negotiated and mutually tuned, and DIVA takes care of a structured working-together. As such, R&D issues of RID-TUDelft on molybdenum/technetium generators, and the use of stable enriched isotopes in clinical research have already resulted in new R&D lines within the URENCO stable isotopes division towards the production of the precursor ^{98}Mo. DIVA allows to approach clinical issues in a holistic manner, and research questions (in dialogue with clinical nuclear and general medicine) imply options that string together the future use and emerging clinical development of the use of isotopes.

3.3. DIVA and industry

DIVA contributes to the growing potential of Dutch industries in the worldwide marketing of (enriched) stable isotopes, has wide contacts with the clinical nuclear medicine groups, and provides a platform for a world-wide supply of medical radioisotopes. Applications are extensive and worldwide. Today, NRG covers 30 % of the world demand in molybdeen-99, and has all the necessary contacts with global radio-pharmaceutical industries. Worldwide, some 24,000 patient treatments with medical radioisotopes are performed on a daily basis, of with the isotopes are produced in NRG Petten. Spin-offs are already developing (Mo989: TUDelft spin-off on molybdeen-99, Quirem Medical: UMC Utrecht spin-off on holmium-166 poly-lactic acid spheres).

3.4. INSPIRING DIVA

DIVA is inspiring for employers and entrepreneurs because it shows how intensive collaboration can lead to the rapid development of new products. It is inspiring for the general population because DIVA makes that patients can get more rapid access to new methods for treatment and diagnostics. DIVA is inspiring for clinical sites because these can use more effective and costs-efficient treatment opportunities.

3.5. Next 5-10 years of DIVA

1. Guaranteed delivery of lutetium(Lu-177)
Worldwide, the lutetium-177 isotope is used more and more, especially in the treatment of tumors in internal organs. Demand is anticipated to strongly grow on a gloval scale. To be able to continue and guarantee delivery to hospitals, DIVA sets out to develop and bring new types of Lu-177 generators to the market: these generators may be an answer to the growing demand for more cost-effective Lu.
2. Guaranteed delivery of molybdenum (Mo)99)
Technetium-99, the (daughter) decay product of the radioactive molybdenum-99, is one of the most-used isotopes in medical (radio)diagnostics. New techniques are developed for the production of the mother Mo-99, out of Mo-98 (or Mo-100), without the need to use fissile (enriched) uranium. These new techniques may, within 5-10 years, help ensuring Tc-99 delivery and be an answer to the growing demand.
3. Routine production of Holmium (Ho-166)-polylactid acid microspheres
The innovative treatment of liver cancer with polylactic acid microspheres that carry radioactive Ho (Ho-166) asks for very specific irradiation conditions and irradiation facilities. Today, the irradiation of the Ho-polylactic acid microspheres is carried out in the HOR research reactor of RID-TUDelft, and in collaboration with the Utrecht Medical Center. At the moment new production modes are developed to be able to increase the Ho-166 activity within the microspheres without destroying the clinically necessary dimensional and integrity aspects of the organic spheres, this to ensure optimal production and wide-spread use.
4. R&D on the effects of (micro)elements in ageing diseases
Within health R&D issues, attention is growing for the role of chemical (micro)elements in age-related disease, such as e.g. Alzheimer or diabetis. DIVA, in collaboration with Meander Medical Center (one of the large Dutch general hospitals), develops clinical-analytical approaches and methods, on basis of the use of stable enriched isotopes, that may be used within 5-10 years in following the elements in relevant physiological processes to permit the doctor to justly interpret data in diagnostics, and decide towards a best possible treatment.

3.6. What is needed?

DIVA should be able to set up and form her R&D lines, both on basis of the contributing partners (RID-TUDelft, URENCO, NRG/PALLAS) and on basis of the attracted R&D funding (e.g.EU, Dutch funding agencies NWO, STW, and e.g. the Dutch Ministries of Education (OCW) and Public Health (VWS)).

4. References

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[5] PALLAS
www.pallasreactor.com/?lang=en