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ADVISORY REPORT

Exploring the environment to promote distribution of knowledge and transfer of technology in the field of medical radionuclides in Germany and the methods to support countries with weaker economies

Author

Dr. Syed M. Qaim

Professor,

Forschungszentrum

Jülich, Jülich,

Germany

Chair,

Standing Committee

on Education

and Training, WCI

Editor-in-Chief,

Radiochimica Acta

Syed Muhammad Qaim was educated up to M.Sc. at the Government College and Punjab University, Lahore, Pakistan. He did Ph.D. at Liverpool University, D.Sc. at Birmingham University, England, and Habilitation at Cologne University, Germany. In 1970 he joined the Institute of Nuclear Chemistry of the Research Centre Jülich and worked there in various capacities (Scientific Coworker, Group Leader, Division Leader, Acting Director, Vice Director) till his formal retirement in 2006. Since then he has been associated with his old institute in an advisory capacity. He also worked for about 18 years at Cologne University as Professor in Nuclear Chemistry. Since 2003 he holds a teaching assignment at the Jülich Campus of the Aachen University of Applied Sciences (FH), as well as an Honorary Professorship at his old Alma Mater (Government College University Lahore) in Pakistan.

Prof. Qaim has contributed to fundamental nuclear chemistry, nuclear data for energy- as well as non-energy related applications, and accelerator radionuclides for medical applications. He has published 415 research papers and edited 4 books. His most recent book on Medical Radionuclide Production was published in 2020 by Walter de Gruyter (Berlin/Boston). He has given special lecture courses at the universities in Assiut (Egypt), Debrecen (Hungary) and Rajshahi (Bangladesh), as well as at international schools of the IAEA. He was Co-Director of three courses at ICTP, Trieste. Presently he is a Tutor of an international course on Radioisotopes held every year in Seoul, Republic of Korea. He represented Germany in OECD-NEA (Paris) and IAEA (Vienna) for more than 20 years, with Chairmanship of the IAEA-Nuclear Data Committee for 6 years. Currently he is the Chairman of the Standing Committee on Education and Training of the World Council on Isotopes (WCI). He has been working as the Editor-in-Chief of the international journal Radiochimica Acta for the last 26 years.

Prof. Qaim has received a large number of honours and awards of various kinds in about 10 countries of the world, among them the JARI Medal of Pergamon Press, the International Hevesy Medal of Nuclear Chemistry, the Becquerel Medal of the Royal Society of Chemistry, two Honorary Doctorates, the civil award “Sitara-i-Imtiaz” by the President of Pakistan, and Fellowships of the Pakistan Academy of Sciences (PAS), Islamic World Academy of Sciences (IAS) and the Third World Academy of Sciences (TWAS).

1. Introduction

The basic aim of development of science and technology is to benefit the whole mankind. Although this principle is generally accepted, possessive instincts and own economic interests during the industrial revolution in the 19th century created a big disparity in the standard of living of inhabitants in various geographical regions of the world. This is particularly evident while comparing the countries of the North to those in the South. On the other hand, a dormant moral realization has also been existing to improve the situation. Thus, from 1950s onwards, many of the technologically advanced countries started paying considerable attention to distribution of knowledge and technology not only within their own domains and neighbouring regions but also to some lesser developed countries. In this article I would like to describe some of my personal experience and views in this direction, while working in Germany for a period of more than 50 years. It is mostly related to teaching, research and development of technology within Germany, but also partly to transfer of knowledge and technology under various cooperative agreements to six other countries with weaker economies.

2. Working environment and available facilities related to radionuclide production at the Forschungszentrum Jülich (FZJ)

Originating from Pakistan and educated in UK as a nuclear chemist, I emigrated to Germany and was appointed as a research scientist in 1970 in the Institute of Nuclear Chemistry (INC) of the big national research centre, now called Forschungszentrum Jülich (FZJ), with the assignment to establish a “Nuclear Data and Radionuclide Production Group”. The major facilities available on site were two nuclear research reactors (MERLIN and DIDO), a powerful DT Neutron Generator, a fully equipped radiochemistry laboratory and a good technical workshop. Furthermore, access to an intermediate energy cyclotron (JULIC) was available. Later, a medium-sized cyclotron (CV28) and also two other smaller medical cyclotrons (JSW BC1710 and GE PETtrace) were procured. Some time ago the cyclotron CV28 was dismantled, and recently a 30 MeV IBA Cyclone 30 XP was installed. The available infrastructure has thus all along been ideal for performing research and development work. Furthermore, since the Head of the Institute has also invariably been a Professor at the nearby University of Cologne, many Ph.D. scholars have been actively working in the Institute. In the 1990s, I also become a Professor at the University of

Cologne, in addition to my responsibility at FZJ. Thus a blend of fundamental and applied research continued all my life.

The policy of future work was defined already in the mid 1970s. Research reactors were used for fundamental nuclear research as well as for neutron activation analysis. Since reactor-produced radionuclides were commercially available within Germany even at that time, it was decided not to enter that field but to devote our full attention to fundamental and applied aspects of accelerator-based production of radionuclides. Over the years, the emphasis got more and more shifted to radionuclides for Positron Emission Tomography (PET) because the cooperation between INC and the Institute of Medicine (IME) within FZJ grew closer and stronger.Today all the medically-oriented activities are merged in the Institute of Neuroscience and Medicine (INM) with Nuclear Chemistry (INM-5) as an important entity This report therefore deals mainly with accelerator-produced short-lived radionuclides for medical applications.

3. Overview of research and development work done at FZJ in relation to medical radionuclides

Research work carried out in nuclear chemistry at FZJ encompassed all aspects of radionuclide and radiopharmaceutical development using cyclotrons. Regarding radionuclides, investigations covered four areas, namely, nuclear data, high-current targetry, extensive chemical processing and quality assurance of the radioactive product. The original aim was to develop suitable methodologies for clinical scale production of radionuclides for Single Photon Emission Computed Tomography (SPECT), in particular the halogens ^{123}I and ^{77}Br, as well as short-lived standard PET-radionuclides (^{11}C, ^{13}N, ^{15}O and ^{18}F). After establishing routine production technologies of those radionuclides, the emphasis got shifted to longer lived novel positron emitters which are more useful for theranostic applications. In this context the basic production methodologies of a large number of novel radionuclides were developed using nuclear reactions on highly-enriched targets. They included, among others, ^{38}K, ^{51}Mn, ^{55}Co, ^{61}Cu, ^{64}Cu, ^{73}Se, ^{83}Sr, ^{86}Y, ^{94m}Tc, ^{120}I and ^{124}I. Furthermore, development work on the production of the therapeutic radionuclides ^{67}Cu, ^{76}Br, ^{103}Pd, ^{117m}Sn, ^{193m}Pt, etc. was also carried out. Based on research and development work carried out under my guidance, about 30 German and foreign scholars prepared their doctoral theses and submitted them to various universities within Germany or abroad (e.g. Egypt, Pakistan, Morocco, Malaysia, Turkey, Bangladesh, etc.). Those alumni now hold good positions in universities, research institutes or the industry.

As regards radiopharmaceutical development, carried out under the direction of other professors of nuclear chemistry at FZJ, a large number of known and new SPECT- and PET-tracers were established for clinical studies, and about 70 doctoral theses were submitted to the University of Cologne. The major emphasis has been on the synthesis of ^{123}I-labelled compounds for SPECT and ^{18}F-labelled compounds for PET investigations. The most prominent among them was the 2-]^{18}F]Fluorodeoxy-D-glucose which gained worldwide attention and thus revolutionised the whole field of PET imaging. Today about 50 full-fledged PET centres (consisting of a cyclotron, a radiochemistry laboratory and a PET scanner) exist in Germany, and more than half of those centres employ leading radiochemists trained at FZJ/University of Cologne. Some of the other alumni hold leading positions in the radiopharmaceutical industry or have become owners of small companies.

Through research and development activities in FZJ, scientific knowledge has been constantly flowing and extensively shared within Germany; it was also transferred to several other countries. On the other hand, a few other groups within Germany, e.g. those in Dresden, Leipzig, Mainz, Heidelberg, Karlsruhe and München, also contributed appreciably to the development of radionuclide technology and its transfer to others. However, the contribution of FZJ remains exceptional in terms of professional education and diversity of research areas pursued.

4. Overview of availability of medical radionuclides in Germany and contacts between academia and industry

Radionuclides and radiopharmaceuticals are extensively used in Germany for patient care (diagnosis and therapy). Besides university hospitals and big clinics, even some private practitioners have proper facilities for using them. Most of the radionuclides used are reactor produced. In the former East Germany, some radionuclides were produced at the Rossendorf reactor. During 1995 to 2003 some irradiations were also carried out at the DIDO reactor in FZJ to produce fission ^{99}Mo but its chemical processing was done in Belgium. Today, only tracer quantities of a few radionuclides are produced at the Mainz TRIGA reactor. Some efforts are also underway to utilize the München Research Reactor (FRM II) for irradiating samples for production of fission ^{99}Mo, and especially ^{177}Lu, by some associated companies. In general, however, almost all the reactor radionuclides used presently in Germany are imported from other European countries where research reactors for radionuclide production still exist. Several companies based in

Germany manage the import of those radionuclides in raw form. Further processing and dispensing are efficiently done by those companies. Because of the European Union (EU), the import procedures are well streamlined and the radioactive material is generally available at the planned time of application. Some examples are ^{99}Mo/^{99m}Tc and ^{90}Sr/^{90}Y generators, ^{125}I, ^{131}I, ^{177}Lu, etc.

Among the accelerator-based radionuclides, ^{123}I and ^{18}F are produced in large quantities in Germany in a few laboratories and dispatched by some intermediate companies to the users within Germany and other neighbouring countries. The fully equipped PET centres have their own production programmes of standard positron emitters for in-house use in patient care. Some of them also produce non-standard positron emitters, e.g. ^{44g}Sc, ^{45}Ti, ^{61}Cu, ^{64}Cu, ^{124}I, etc. for own research or for delivery to nearby satellite medical units. In those cases either commercial or cooperative agreements exist. Two other accelerator-produced short-lived positron emitters, namely ^{68}Ga and ^{82}Rb, used in a few PET centres without a cyclotron are, on the other hand, available from generator systems which are imported mostly from USA. Some attempts to produce ^{68}Ga at small medical cyclotrons for local use are also underway.

It should be pointed out that in this field of work the possibility of technology transfer from academia to industry is vigilantly under consideration. Occasionally a Ph.D. scholar may be financed by the industry for some collaborative effort, or preferential production rights may be purchased by a company from some research institution. Some young innovators interested in initiating their own start-ups, based on spin-off results, are generally encouraged to do so. The development of large scale production of an important novel radionuclide for general use is always pleasing to the originators, even if the production methodology was published in the open literature. This is, for example, the case with three novel positron emitters (^{64}Cu, ^{86}Y and ^{124}I) which were developed at FZJ about 30 years ago, but not patented. The industry is commercialising their production today.

5. Methods to support countries with weaker economies

5.1 Educational aid

In the framework of manpower and capacity building on a global scale, educational aid was provided by FZJ in the field of applied nuclear sciences to several countries under various programmes, namely

- Transfer of Knowledge through Expatriate Nationals (**TOKTEN**) Programme of UNO. This involved several short-term teaching/research visits of mine to Pakistani universities and research institutes over a period of 20 years.
- **TEMPUS** Programme of EU (after the breakdown of the iron curtain) for mobility of university teachers from Eastern Europe to Western Europe and vice versa. A cooperation was established between Debrecen (Hungary) and Cologne/Jülich (Germany) for development of teaching curricula (1995-2000). I travelled often to Debrecen to give short condensed special courses.
- Research Professorship of the Third World Academy of Sciences (**TWAS**) to me for short visits to Bangladesh for development of an M.Sc. course on "Radionuclide Technology" at the University of Rajshahi (2006-2011).
- Honorary Professorship of the Government College University Lahore (GCUL), Pakistan, to me with financial support of the National Talent Pool of Pakistan (**NTP**), the Higher Education Commission of Pakistan (**HEC**) and the International Centre for Theoretical Physics (**ICTP**), Trieste, Italy, for developing courses in Nuclear Data and Medical Radionuclides (2003 – to date).
- Short assignments to me for teaching at Assiut University, Egypt, under a **bilateral agreement** for improving M.Sc. curriculum (1987, 1995, 1999).
- Lectures by me at Advanced Training Schools on Nuclear Data and Radionuclide Technology for participants from developing countries held in various parts of the world under international sponsorships
- **IAEA** (Debrecen: 1978, 1982; Istanbul: 1980; Karlsruhe: 1984);
- **Bulg. Acad. Sci.** (Varna: 1981);
- **PAEC** (Nathiagali: 1984);
- **ICTP** (Trieste: 1980, 1999, 2007, 2013), the last three as Course Director;
- **COMSTECH** (Islamabad: 2013), as Focal Person;
- **KAERI/WCI/IAEA** (e-learning courses: Daejeon: 2020, 2021, 2022, 2023), the last three as Tutor.

Germany facilitated and supported my teaching activities at all the above-mentioned 15 Advanced Training Schools related to transfer of knowledge to countries with weaker economies.

5.2 Technical training and visits of foreign guests

As technical aid to developing and emerging countries, a large number of scientists, engineers and technicians from all parts of the world visited the INC of FZJ on individual basis. About 60 of them got research training in the area of nuclear data and radionuclide technology under my supervision. They came from more than 20 countries, among them China, Taiwan, Malaysia, Indonesia, Bangladesh, India, Pakistan, Israel, Turkey, Egypt, Morocco, Hungary and Brazil. In INC they all worked in harmony. The financial support was provided by the IAEA, Deutscher Akademischer Austauschdienst (DAAD) or some Indigenous Programme. A few scientists also came as experienced researchers from Ukraine and Russia (under Eastern Europe Programme of DFG) or from other countries under the auspices of the Alexander von Humboldt Foundation.

5.3 Joint research and development projects: bilateral agreements

A very special feature of the German support for science in countries with weaker economies consisted of establishment of long-term “bilateral cooperative agreements”, which at one time extended to about 35 countries of the world and covered diverse areas of science and technology. For a few favoured countries, several projects could run simultaneously. In this context, the projects and finances were globally approved by the responsible ministries of the collaborating countries. The movement of personnel in both directions and the procedures for donation of some research materials and small instruments by the German laboratory to the foreign counterpart were simplified. The transfer of bigger equipment, however, needed special approval of the trade export authorities. In Germany, the policy of collaboration was directed by the Federal Ministry of Science in consultation with the Ministry of Economic Cooperation but, for day to day activities, considerable autonomy was entrusted to the regional coordinating offices, termed as International Offices. One such office was located at FZJ.

During the period 1970 to 1990, cooperations with countries in transition, like Brazil, Egypt, India, Pakistan, Yugoslavia, etc. were favoured but in 1990s the emphasis got shifted to newly liberated countries in Eastern Europe and to South Africa. From 2017 onwards the DFG and the German Federal Ministry of Science have been allocating special funds to TWAS to support science in Africa.

The research group “Nuclear Data and Radionuclide Production” at FZJ collaborated inofficially with several research groups in Western Europe, North America and Japan on equal terms. But official bilateral research agreements were established with a few groups in Bangladesh, Egypt, Hungary,

Pakistan, South Africa and Ukraine (with some financing outside of the International Office). A list of those groups is given below.

1. Department of Applied Chemistry and Chemical Technology, Rajshahi University, Bangladesh (1996-2011).
2. Institute of Nuclear Science and Technology (INST), Atomic Energy Research Establishment, Dhaka, Bangladesh (1991-1996; 2008-to date).
3. Cyclotron Project, Egyptian Atomic Energy Authority (EAEA), Cairo, Egypt (1997-2007).
4. Radionuclide Production Division, Pakistan Institute of Nuclear Science and Technology (PINSTECH), Islamabad, Pakistan (1983-1991).
5. Physics Department, Government College University Lahore (GCUL), Lahore, Pakistan (2003-to date).
6. Radionuclide Group, iThemba LABS, Cape Town, South Africa (1998-2009).
7. Cyclotron Group, Institute of Nuclear Research of the Hungarian Academy of Sciences (ATOMKI), Debrecen, Hungary (1984-2002).
8. Institute of Experimental Physics, Debrecen University, Debrecen, Hungary (1982-2015).
9. Kharkov Institute of Physics and Technology (KIPT), Kharkov, Ukraine (1999-2002; 2010-2018).

The research results were shared by the participating laboratories in the form of joint publications or partly as doctoral theses. The nuclear data and production methodologies developed for a few novel radionuclides were jointly utilized. Some salient results are given below:

- **^{82}Sr/^{82}Rb generator** improvement, intermediate energy data (iThemba/ FZJ)

- **^{67}Cu, ^{103}Pd** production (FZJ/ KIPT)

- **^{81}Rb, ^{82m}Rb, ^{123}I, ^{124}I** production, data measurements using enriched gas targets (FZJ/ ATOMKI)

- **d(D_2) neutron source** optimisation at the cyclotron, neutron data measurements, nuclear modelling of isomeric cross sections (Univ. Debrecen/ FZJ)

- **^{76}Br, ^{124}I** production, nuclear modelling, radiochemical separations (FZJ/ Cairo).

Other joint achievements were:

Characterisation of Am(Be) and TRIGA reactor neutron spectra (Rajshahi/ Dhaka/ FZJ/ Univ.Debrecen); Integral tests of evaluated data (Dhaka/ Rajshahi/ FZJ); Production of cyclotron radionuclides ^{57}Co and ^{123}I at a reactor in tracer quantities (PINSTECH/ FZJ); Standardisation of production data of novel positron emitters (GCUL/ FZJ).

All projects and joint efforts thus involved a mixture of capacity building in economically weaker countries and science development in all participating laboratories. A total of about 200 research papers were published.

5.4 Donation of major equipment and transfer of technology to foreign countries

As mentioned above, transfer of knowledge and donation of small equipment have been occurring rather freely from Germany to other countries under cooperative scientific programmes; however, under strict control of intellectual property rights as well as national and international patent and trade regulations. For larger technology transfers, on the other hand, approvals of high-level authorities were required. Three special cases are described below.

i) Donation of a 111 GBq Am/Be source by FZJ to Rajshahi University, Bangladesh, with some radiation measurement equipment. The IAEA regulations were strictly followed, and the local supervision was done by the Bangladesh Atomic Energy Commission (BAEC).

ii) Donation of the old compact cyclotron (CV28) by FZJ to KIPT in Kharkov, Ukraine. A long process of approval was necessary.

iii) The transfer of technology related to the nucleophilic synthesis of the universal PET-agent 2-[^{18}F]FDG from FZJ to the whole world on a commercial basis had to undergo all procedures of approval because it was a big enterprise.

6. Concluding remarks

The above described activities should serve as an indicator of the working environment and typical available facilities for radionuclide production in Germany. The reactor-produced radionuclides for patient care are mostly imported from neighbouring countries, but the associated extensive chemical and pharmaceutical work is efficiently done by several companies within Germany. As regards accelerator-based radionuclides, short-lived positron emitters are produced and used in several clinics. The radionuclide ^{18}F is produced rather extensively and ^{123}I to a lesser extent. They are commercially distributed. Some novel radionuclides like ^{64}Cu, ^{86}Y and ^{124}I are produced at a few centres and used mostly within Germany. Fairly good information flow and cooperation exist between academia and industry.

There is strong support for transfer of knowledge and technology to countries with weaker economies in the area of peaceful applications of radionuclides, especially those related to human health. The scientific institutions also grant considerable freedom to individual scientists engaged in international activities. But it should also be emphasized that institutions can only create suitable conditions and atmosphere for cooperation and technology transfer. The real implementation and success of such endeavours depends on the enthusiasm and vigour of the collaborating partners on both sides. In this regard, feeling of joint venture, mutual trust and respect to one another are very important.

7. Suggestions and recommendations

- For technology transfer in a chosen field, bilateral agreements appear to be most effective; at the national level between two institutions and at the international level between two countries. The research and development work followed should have a character of joint venture.
- The two e-learning courses on radionuclides and radiopharmaceuticals, arranged every year by WCI in close cooperation with the KAERI and IAEA, offer excellent opportunities to young scientists and technologists in developing countries to gain more knowledge on Isotopes. This is particularly important because presently about 1000 new small medical cyclotrons are being installed in various parts of the world. The WCI should continue to support, further strengthen and modernise those e-learning courses.
- The WCI could start a series of webinars on special topics for the benefit of participants from all countries (both advanced and developing).
- The WCI could endeavour to get some funds from the industry to grant bursaries to young scientists from all countries to participate in its international conferences.

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