OPPORTUNITIES

Hotspots of Innovation – Focussed Content for your Investment Decisions – by BioTalk GmbH

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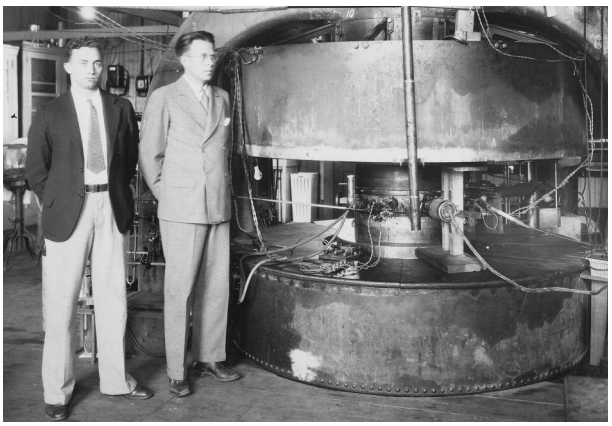
The Ultimate Future in Oncology?

Medical Isotope Therapy, the new Shining Star

Serge Perriard



M. Stanley Livingston (l), pioneer in accelerator physics and nuclear physicist and Nobel Prize winner Ernest O. Lawrence in front of a 27-inch cyclotron at the Radiation Laboratory, University of California, Berkeley, 1934.

In the industrialized world, one in every three people will be diagnosed with a cancerous tumor during their life time. About 22% of those patients are cured by surgical removal of the tumor. Radiation therapy is effective in about 12% of the patients with solid tumors, and another 6% benefit from both surgical intervention and radiation therapy. Only about 5% will be cured by chemotherapy alone.

The first goal of any cancer therapy is to stop the growth of the primary tumor. Despite enormous progress, every sixth cancer patient still dies because the growth of the primary tumor cannot be halted, with lethal consequence due to subsequent metastasis. In the last decades, the effectiveness of radiation therapy in particular has advanced with great strides. This has been achieved primarily by concentrating the radiation dose over a smaller volume. The improvements to target ionizing radiation for the treatment of localized tumors was largely dependent on the development of a safe high energy photon source, namely the evolution of the particle accelerator, which is known today as photon radiation therapy. The progress of cancer therapy is the result of modern external beam radiation treatment and the combined development of better chemotherapeutic drugs.

For more than 60 years, the treatment with proton radiation has also been constantly evolving. The **Paul Scherrer Institut (PSI) in Villingen Switzerland** has been pioneering this type of charged particle radiation treatment ever since. This somewhat more expensive form of external beam radiation therapy allows for a more precise targeting of radiation with the aid of magnetic fields. Until recently, this type of radiation therapy has only been applied to tumors of the eye, but since November 2013, the

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In this Issue

With this newsletter we will be introducing you to selected market segments, where we pinpoint a high innovation potential and interestinng investment opportunities.

Fighting Cancer with Yttrium-90

A new brachytherapeutic medical device is approaching FDA-approval

The developing technologies and the subsequent profits from medical devices based on medical isotopes are undergoing a constant change. At the same time, the era is approaching in which novel cancer therapeutics are becoming clinical realities. Advanced Medical Isotope Company (AMIC) is riding this new wave of brachytherapy for the treatment of solid tumors, and has submitted its first radio-therapeutic product, Yttrium-90 RadioGel™, aimed primarily to cure the most common malignancies in males, prostate cancer.

Michael Lindenmaier

AMIC is located in the traditional industrial area for US nuclear technologies, along the Columbia River in the Pacific Northwest. This firm however is establishing itself as a driving force for the curative powers of medical isotopes for the good of mankind through diagnostic tools in the emerging market for novel radiopharmaceuticals and medical devices. According to a new market analysis by Transparency Market Research, the volume for radiopharmaceuticals reached 3.8 billion USD in 2011, and is projected to expand to 12.2 billion USD by 2018.

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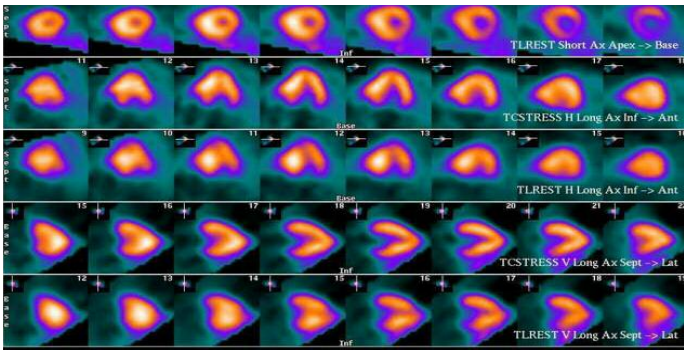
Gantry 2 at PSI has also been used for movable tumors, such as breast, prostate and lung cancers. The continued development of this technology relies on international cooperation with a number of well known companies in the areas of medical devices and diagnostics such as the market leader **Varian Medical Systems** as well as the Belgian **IBA group** and the Swedish company **Elekta** (**Nucletron**) for equipment, software and supplies for radio-oncology and brachytherapy applications

Internal Radiation Therapy

With the aim to target ionizing radiation only on the tumor itself and therefore minimizing the damaging effects on surrounding tissues, a newer type of radiation therapy known as brachytherapy (brachy- from the Greek, meaning close or near) has increasingly attracted attention. In contrast to external radiation therapy in which high energy radiation is focused from the outside onto the tumor, brachytherapy is working (with usually encapsulated) radiation sources that have been surgically placed at the location of the cancerous tumor. An even more progressive approach to internal radiation therapy has now been at the forefront for the treatment of solid tumors. In these unsealed internal radiation treatments, pharmaceutical

Implantation of seeds is less invasive then surgical removal. *Source: EZBG*

formulations containing medical isotopes that emit gamma-, beta- or gamma-radiation with different half-lives and depth of penetration are therapeutically employed. US companies **Nordion Inc.** and **Lantheus Medical Imaging** as well as the European firm **Eckert & Ziegler Group** (**Berlin**) are market leaders for medical isotopes and their medical applications. Another advantage of implanted brachytherapeutic devices are diminished side-effects through the constant positioning of the radiation source in relation to the tumor even when the patient moves or if, during treatment, the tumor is undergoing delocalization. Furthermore, this type of radiotherapy can be more cost effective and can be applied in a shorter time frame than conventional radiation from external sources. Depending on the type of tumor and its localization, brachytherapy is already equally or more effective than surgical intervention or conventional radiation therapy.



Tc-99m used in combined PET and CT / SPECT and CT for myocardial prefusion analysis in one single scan. *Source: TRIUMF*

Medical Isotopes for Diagnostics

Presently most medical isotopes are used for diagnostic procedures, and their use in cancer therapy still plays a significantly smaller role. Diagnostic imaging techniques such as Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) are able to visualize metabolic and functional properties for example in brain imaging and have also revolutionized the diagnosis and 3-D visualization of cardiac pathologies. The most frequently used isotope for these modern diagnostic imaging tools is technetium-99m, which is a product of Mo-99 decay. At this time, most of the Mo-99 is produced by neutron bombardment in nuclear fission reactor from enriched Uranium-235.

Global shortage

Nuclear reactors that use highly enriched uranium are of obvious geopolitical and environmental concern. Just two years ago, 90% of the global demand for Mo-99 was produced by four reactors of that type. The most important manufacturer for the North-American supply, about one third of the total global output, are the nuclear aging facilities at Chalk River Laboratories in Ontario Canada, which in 2006 were partially closed to install improved safety measures for earthquakes. And it is to be expected that Chalk River Laboratories will shut down altogether in 2016, which could very likely cause a global shortage of Mo-99, and as a result an inadequate supply of the most crucial medical isotope technetium-99m.

The race is on to find efficient processes to produce Mo-99, the raw material for Te-99m from other sources than enriched Uranium. Many such methods have been proposed and it will largely depend on the development of linear accelerators or cyclotrons that use Mo-98 from natural sources or alternatively to engineer reactors which utilize uranium salts that can be converted to Mo-99 through neutron bombardment. Some companies are looking for new ways to miniaturize these processes and device decentralized technologies. Leading manufacturers of cyclotrons are **Advanced Cyclotron Systems Inc.** (Richmond, Canada).

Linear accelerators might hold the key for easing the coming shortages. A leader in that field is **AccSys Technology**, (Pleasanton, CA,) a daughter company of Hitachi Inc., which is optimizing the process to obtain Mo-99 from naturally occurring Mo-98 through neutron bombardment. To brake the dependence of the medical isotope industry from the nuclear industry would mean to eliminate the political hurdles and to free the medical device industry from the constraints of security and environmental concerns that have plagued that industry for decades. Along these now value-adding supply chains, a new global, highly dynamic industry sector will emerge that particularly gives credence and a competitive edge to SMEs, which lead the way with new medical devices, or radiopharmaceuticals, not only offering finished products for the pharmaceutical end user but also derive their raw materials from novel processes through vertical integration. This newsletter is introducing just a few of them, namely **Advanced Medical Isotope Corporation**. Or the SHINE Medical Technologies in Madison Wisconsin, and equally innovative, ROTOP Pharmaka in Dresden, Germany, among others. ◊

This corresponds to a solid Compound Annual Growth Rage (CAGR) of 18.3%. This publicly traded company through the OTC Bulletin Board equity security exchange for smaller emerging technology corporations

RadioGel™ combines three main advantages over conventional tumor therapies: higher efficiency, improved safety, and reduced costs.

has been licensing in a number of exclusive patents for the RadioGel™ technology from the renowned US Battelle technology institute, an independent international research organization. AMIC now hold the rights to market this promising cancer therapeutic based on a biodegradable hydrogel polymer, which delivers Yttrium-90 microspheres directly into tumor tissues and thus forming a polymerized lattice at body temperature, holding the radioactive microspheres in place, and thereby releasing beta-radiation within the targeted volume, while avoiding damaging effects on other viable tissue in the vicinity of the tumor. This localized internal beta radiation source emits more intense ionizing radiation than gamma rays and therefore effectively damaging the DNA fast growing cancer cells, in addition to limited penetration depth compared to gamma radiation. As a result, this advanced medical isotope application leaves healthy tissue intact and also poses no risk to medical personnel involved in the administration of the therapeutic agent.

Yttrium-90 is a proven medical isotope that has been used successfully in other clinical applications. In form of this new polymer gel, it is particularly promising against a variety of tumors that are surgically difficult to remove such as certain cancerous tumors of the prostate, liver, breast as well as throat cancer. In some cases, RadioGel™ is also a promising therapeutic modality for patients with pancreatic cancers. In comparison to conventional treatments such as external radiation and surgery, this new therapy can reduce costs up to 75%.

Therapeutics first, then the diagnostic tools

AMIC is already generating moderate cash flow through the sales of their own medical isotopes that are produced by their in-house linear particle accelerators through proton bombardment of the oxygen isotope O-13. The aforementioned equipment has diverse application and is able to produce a variety of different isotopes. AMIC aims in the medium term to supply the expanding market with medical isotopes for diagnostic use. The chance for the company lies in developing new technologies to manufacture medical isotopes, such as technetium-99m, and take advantage of the projected global shortage of this crucial isotope for diagnostics after the year 2016 or 2018, when the closure of the most important Mo-99 producers will take place and thus create a critical shortage of the Te-99m supply. AMIC is following the strategy through the establishment of several GMP-conform production sites, and adapting its logistics and supply chain to the needs of an expanding market. In March 2013, AMIC created a strategic alliance with GSG International GmbH in Pfäffikon, Switzerland. This new global partner offers in addition to its expert position for medical isotope technologies and distribution channels in Switzerland, Germany and Russia, equipment and technologies for the allocation and production of Te-99m. While the combination of market shares and engineering technologies for the alternative production of Te-99m are advantageous to both firms, these partnership are also challenging endeavors and take time, also with regard to future risks. Furthermore, it is not clear to what extend the established nuclear industry can overcome the expected shortage in 2016, of Uranium-derived Mo-99 to obtain Te-99m, by the removal of political hurdles and by significant improvements with regard to safety issues by changing process and manufacturing protocols.

The compact LINAC PET Isotope Production systems (PULSAR®) are proton accelerators replace large and demanding cyclotron systems for the production of positron emitting isotopes.

Approval on the horizon

For AMIC, the medium range goal would be to establish itself as a manufacturer of these relevant diagnostic medical isotopes. Primarily, AMIC will focus on the development and approval of medical devices and pharmaceutical formulations with Yttrium-90 to reach the required size to become a global player in the market for medical isotopes. And through the clinical application of proprietary products in the area of brachytherapy, this company could significantly profit from these emerging radio-therapeutic agents.

Because RadioGel™ has been submitted for approval by the FDA as a Class III medical device and not as drug, one can expect an expedient decision by the FDA on its approval in the coming months. The other two products – in particular an Y-90 containing a paste for application after the tumor has been surgically removed – should be approved in 2015. Therefore, it can be reasonably expected that a significant increase of AMIC share-values will be taking place during 2014. ◊

Other Opportunities in the Radio-Oncology Market

Focus on Brachytherapy

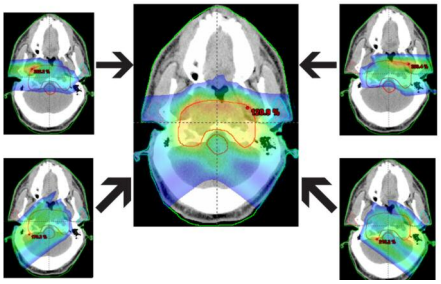
Eckert & Ziegler Gruppe, listed at the Prime Standard of the German stock exchange in Frankfurt is a global leader in the manufacturing and design of radioactive components for medical and scientific applications as well as for analytical instrumentation. The oldest subsidiary of this holding corporation, Eckert & Ziegler BEBIG GmbH (EZBG), which is traded by NYSE Euronext, originated in 1992 from the formerly state-owned East-German Zentralinstitut für Isotopentechnik, a then renowned research organization run by the former GDR's Academy of Sciences.
EZBG is the market leader for brachytherapy products in Europe. This Belgian firm has manufacturing facilities in Germany and smaller business units in different European countries and India.
With the take-over of Biocompatibles Inc., in September 2013, the 4th largest supplier of brachytherapy products for urological applications, EZBG has further enhanced its leader position for products against prostate cancer. Furthermore, this expanding corporation is a leading developer of Ruthenium-106-based radiopharmaceuticals for the treatment of eye tumors. While securely positioned in its holding company, which by itself generated revenues of about EUR 120 Mio. (2012), Eckert & Ziegler BEBIG GmbH with its timely emphasis on brachytherapy is in a perfect position to take advantage of this ever expanding market for radio-therapeutic products. *sp*

Eckert & Ziegler

Market Leader

Varian Medical Systems Inc. located in Palo Alto, California is the market leader for medical instruments and software for radio-oncology products, proton therapy systems and brachytherapy. Varian (NYSE: VAR) occupies globally about 6'400 employees with manufacturing facilities in North America, Europe and China, along with a number of smaller distributors worldwide.
Varian has its origins in the 1940's think-tanks that became the driving academic and technological forces of what is now Stanford University. There the ground work for the high frequency modulators, generating microwave-based particle accelerators had been lain down, and through this crucial engineering feat, the first medical linear particle accelerator was put to use there in the 1960, as it was now possible to focus high energy photons onto the tumor to be treated. Modern radiation therapy was born.
At present time Varian Inc. is strategically directing its research, production and regulatory groups to focus on the currently to be approved ProBeam™ proton therapy device (see lead article). With a cash flow of about USD 3 billions and excellent financial stability with considerable revenues, Varian's prospects are continued single digit growth and projected buyback programs. *sp*

VARIAN
medical systems



Selected Companies in the Nuclear Medicine Market

Company	Market / Produkts	Revenues	Kommentar	Titel	Plattform	P/E	Trend
Varian Medical Systems Inc.	Radiotherapy, Radiosurgery, Proton Therapy, Brachytherapy (see text above)	2.15 Mia. EUR	Expansion in software and proton accelerator expected	VAR	NYSE	19.1	↗
Eckert & Ziegler BEBIG GmbH	Oncology, Brachytherapy (see text above)	31.8 Mio. EUR (2012)	Significant expansion in ophthalmology possible	EZBG	OMX Nordic	9.8	→
Nordion Inc.	Sterilization technologies and medical isotopes	232 Mio. USD (2013)	Strong market position	NDZ	NYSE	2.59	→
Elekta AB	Oncology, Brachytherapy, Radiosurgery	1.4 Mia. EUR (2012/13)	No. 2 in Radiotherapy; No.1 in emerging Markets	EKTAB	OMX Nordic	24.2	→
Advanced Medical Isotope Corp.	Onkologie, Diagnostik / Radio-Gel™, medizinische Isotope	0.25 Mio. EUR (2012)	Approval for RadioGel™ expected in 2014/15	ADMD	NYSE:BB	na	↗

Imprint

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