ALL THINGS NUCLEAR-PORTLAND LIFE UNIFYING SCIENCES NEWSLETTER

FALL EDITION

We are pleased to be sharing recent insights into recent developments in the radiopharmaceutical industry amidst the challenges faced by the broader biotechnology and life sciences sectors this year.

In an otherwise subdued fundraising landscape, targeted radionuclide therapies (TRT) companies stand out, securing close to US$1 billion in funds by mid-September. This surge, especially evident in the latter part of 2023, is headlined by RayzeBio, Inc.'s (RayzeBio) US$311 million initial public offering (IPO), trailed by ITM Isotope Technologies Munich SE's (ITM)* placements raising around US$280 million and Mariana Oncology's (Mariana) Series B funding at US$175 million.

2020-2021 witnessed about 90 cancer biotech companies' IPOs, powered by favourable capital costs, renewed faith in healthcare innovation during the early COVID-19 pandemic and the SPAC (special purpose acquisition companies) frenzy. However, the SPDR S&P Biotech ETF soared over 80% from March 2020 to February 2021, only to plummet over 60% by May 2022, owing in part to regulatory shifts in SPAC disclosures and tax implications. Consequently, IPO momentum slowed, with barely a dozen cancer biotech firms listing through 2022 and into 2023. The frenzy gave way to a period of recalibration and, we hope, a return to balance in both funding dynamics and overall biotech stock performance. Yet, as of September 30, 2023, the SPDR S&P Biotech ETF remains 58% and 10% below its February 2021 peak and this year's start, respectively. Radiopharmaceutical companies, however, have mostly outperformed these broader trends.

We see the recent outperformance of the radiopharmaceutical sector as a function of increased awareness of the benefits of TRT by the investment public, including specialty and generalist investors, driving investment flows into the limited number of publicly traded radiopharmaceutical stocks. As the investment rounds conducted by ITM and Mariana illustrate, we believe private companies with revenue generation and/or promising clinical development assets are also able to attract significant amounts of capital in an otherwise challenged funding environment.

Continuing our exploration of the radiopharmaceutical sector's resilience, we turn our attention to some other examples showcasing the industry's growth amidst broader challenges. Major pharmaceutical player Novartis AG (Novartis) currently holds what we believe to be some of the most prominent radiopharmaceutical commercial assets. Lutathera, which was approved in 2018 for neuroendocrine tumours, has consistently approached half-a-billion U.S. dollar revenue annually. Meanwhile, Pluvicto, approved in 2022 for metastatic castrate-resistant prostate cancer, is projected to hit around US$1-billion revenue this year after initial manufacturing challenges. Novartis is also expanding Pluvicto's applications in prostate cancer treatments, through its PSMAfore trial (for earlier lines of treatment), which is expected to yield data imminently, as well as PSMAddition, in hormone sensitive prostate cancer patients. In addition to therapeutics, newly approved imaging products using radioisotopes have also made waves. Lantheus Holdings, Inc.'s 18F-based Pylarify achieved half-a-billion dollars in sales in its first full year, while Telix Pharmaceuticals Ltd (Telix)'s 68Ga-based Illuccix recorded approximately US$100 million in sales in 2022 (a partial year for Illuccix).

The radiopharmaceutical industry's early successes have drawn the attention of investors as well as pharmaceutical companies, with many other oncology drug developers benchmarking their approaches against Pluvicto, for instance, due to its proven efficacy and safety profile.

As we write these lines, the acquisition of Point Biopharma Global Inc. (PointBio) by Eli Lilly & Co. (Lilly), announced on October 3, marks a recent development in a string of investments which large pharmaceutical companies have made in the radiotheranostics area, starting with Bayer AG and Novartis. The acquisition, in our opinion, underlines the increased prominence of this approach to treating cancer. In addition, at the end of July 2023, PointBio expanded its long-term supply agreement with ITM for n.c.a. (non-carrier-added) 177 Lutetium, which means that now Lilly is also acquiring a valuable supplier relationship, in an industry in which supply chain is of great importance.

While radiopharmaceutical is faced with some unique challenges – from the short shelf-life of many radioisotopes to intricate supply chains, as well as internal manufacturing issues, such as those with Novartis' Pluvicto – it underscores the industry's need for diversified cancer treatment strategies. We are heartened by the evolving methods of employing TRT for cancer treatment. Tools like the theranostic pairs of 203Pb and 212Pb, as well as 64Cu and 67Cu, augment the resources available to oncology experts. We remain confident that, fortified by innovation and increasing financial backing, the sector should consistently improve outcomes for cancer patients.

Thank you for your continued support as we navigate these exciting developments in the radiopharmaceutical landscape.

Warm regards,

*The PLUS** Team*

Recent Industry Developments

ITM's Lutetium-177 Production Facility: ITM has opened one of the world's largest production facility for lutetium-177, a vital medical isotope used in targeted cancer therapies. This facility is expected to increase the global supply of lutetium-177, meeting the growing demand for radiopharmaceuticals used in cancer treatment worldwide. Located near Munich, Germany, the facility is highly automated, and features a direct connection to Munich Airport for more efficient global distribution.

https://www.itm-radiopharma.com/news/press-releases/press-releases-detail/itm-opens-worlds-largest-lutetium-177-production-facility-for-targeted-radionuclide-therapies-against-cancer-644/

Telix Opens European Radiopharmaceutical Production Facility: Telix, an Australian biotechnology company, has inaugurated a nuclear medicine facility in Belgium. This facility provides Telix with a platform to enter the European market, potentially doubling its revenue-earning capacity. Telix's prostate cancer diagnostic agent, Illuccix, has seen sizeable growth in the U.S., and the new facility will enable the company to expand its production and distribution capabilities.

https://www.prnewswire.com/apac/news-releases/telix-opens-european-radiopharmaceutical-production-facility-301843531.html

Canada's First Center of Excellence for Molecular Imaging and Theranostics: A partnership between GE HealthCare, St. Joseph's Health Care London, and the Lawson Health Research Institute has led to the creation of Canada's first Center of Excellence for Molecular Imaging and Theranostics. This center aims to advance the field of theranostics, combining medical imaging with radiotracers for diagnosing and treating diseases like cancer more effectively. It will also apply PET/CT technology and expand access to radioisotopes.

https://hospitalnews.com/canadas-first-centre-of-excellence-in-molecular-imaging-and-theranostics/

Increased Production of Actinium-225: Canadian Nuclear Laboratories has signed an agreement with the Sylvia Fedoruk Canadian Centre for Nuclear Innovation to increase the global supply of Actinium-225, a promising new medical isotope for cancer treatment. This collaboration involves the use of targets made from Radium-226, which is extracted from legacy medical waste and should contribute to the commercialization of this product.

https://www.cnl.ca/cnl-announces-project-to-significantly-increase-production-of-rare-medical-isotope-actinium-225-a-promising-new-weapon-in-the-fight-against-cancer/

U.S. Food and Drug Administration (FDA) Approval for New PSMA-Targeted Imaging Agent: BlueEarth Dx has received FDA approval for its optimized radiohybrid Prostate-Specific Membrane Antigen (PSMA)-targeted positron emission tomography (PET) imaging agent, POSLUMA®. This agent is indicated for detecting PSMA-positive lesions in prostate cancer patients, aiding in diagnosis and treatment decisions. It is the first and only FDA-approved PSMA-targeted imaging agent using proprietary radiohybrid technology as of May 2023.

https://4078578.fs1.hubspotusercontent-na1.net/hubfs/4078578/POSLUMA%20approval%20press%20release%20FINAL%20for%20May%2030%202023.pdf

European Commission Grants Marketing Authorization: Curium Pharma has received marketing authorization from the European Commission for PYLCLARI™ (Piflufolastat), a radiopharmaceutical used in the detection of PSMA-positive lesions in adults with prostate cancer. This authorization allows its use in various clinical settings, including initial staging and localization of recurrence in prostate cancer patients.

https://www.curiumpharma.com/2023/07/28/pylclari-receives-ec-ma/

Radiopharmaceuticals for Neuroendocrine Tumors: Molecular Targeting Technologies, Inc. announced favourable findings from a 3-year follow-up study of EBTATE, a radiotherapeutic drug targeting gastroenteropancreatic neuroendocrine tumors (GEP-NETs). EBTATE selectively targets somatostatin receptor 2 (SSTR2) on GEP-NETs, offering an effective and lower radioactivity alternative to standard care.

https://www.biospace.com/article/releases/mtti-announces-favorable-three-year-follow-up-for-ebtate-in-neuroendocrine-tumors/

Positive Results for Copper Cu 64 PSMA I&T: Curium Pharma reported positive results from the Phase II SOLAR study of Copper Cu 64 PSMA I&T, which is used to detect metastatic prostate cancer using PET/CT imaging.

https://www.curiumpharma.com/2023/08/15/phase-2-solar-study-of-copper-cu-64-psma-it/

Pivotal Phase III Results for TLX250-CDx: Telix shared positive results from its pivotal Phase III ZIRCON study of TLX250-CDx in clear cell renal cell carcinoma (ccRCC). The study demonstrated TLX250-CDx's ability to detect extrarenal lesions, potentially impacting the staging and treatment of ccRCC.

https://telixpharma.com/news-views/new-zircon-phase-iii-data-presented-at-snmmi-potential-utility-of-tlx250-cdx-in-staging-and-monitoring-ccrcc/

Clarity Pharmaceuticals' Diagnostic Trial: Clarity Pharmaceuticals Ltd presented favorable imaging data from its Phase II diagnostic investigator-initiated trial of 64Cu SAR-Bombesin in prostate cancer. This radiopharmaceutical showed promise in detecting lesions, especially in patients who were negative on other standard of care imaging methods.

https://www.claritypharmaceuticals.com/news/bopeanm2023/

RayzeBio's IPO: RayzeBio, a radiopharmaceutical company, successfully undertook a US$311 million upsized IPO to advance its products through Phase 3 clinical trials. The company specializes in isotope actinium-225, known for its specificity and potency, with the aim of addressing unmet needs in cancer treatment.

https://www.businesswire.com/news/home/20230914457593/en/RayzeBio-Inc.-Announces-Pricing-of-Upsized-311-Million-Initial-Public-Offering

Artbio AS (Artbio)'s Entry into Radiopharmaceutical Development: Backed by F-Prime Capital and Omega Funds, Artbio focuses on alpha radioligand therapies. The company is developing therapies for prostate cancer and plans to initiate Phase I trials.

https://www.prnewswire.com/news-releases/artbio-launches-to-develop-new-class-of-alpha-radioligand-therapies-designed-to-maximize-therapeutic-potential-301856569.html

Mariana Series B Financing: Mariana, formerly known as Curie Therapeutics, raised US$175 million in series B financing. The company aims to transition into human trials, with a focus on MC-339, a radiopharmaceutical designed for small cell lung cancer.

https://www.businesswire.com/news/home/20230907143203/en/Mariana-Oncology-Announces-175-Million-Series-B-Financing

**About PLUS:

Portland Life and Unifying Sciences (PLUS) is a team within the Portland Holdings group of companies that focuses on healthcare that collaboratively helps the Portland Holdings group of companies to assess investment opportunities. The PLUS team is not a medical team and does not have deep long-standing expertise in TRT or areas relating to precision oncology.

Glossary:

203Pb means a radionuclide with a half-life of 51.9 hours.

212Pb means a radionuclide with a half-life of 10.6 hours.

68Ga means a radionuclide with a Half-Life of 68 minutes.

64Cu means a beta emitter radionuclide with a Half-Life of 12.7 hours.

67Cu means a beta emitter radionuclide with a Half-Life of 2.58 days.

Castrate-resistant means prostate cancer that no longer responds to testosterone-lowering treatment .

Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) means slow-growing neoplasms that arise from the neuroendocrine system of the gastrointestinal tract and pancreas. Gastrointestinal tract is mostly the stomach and intestines.

Isotope means each of two or more forms of the same element that contain equal numbers of protons but different numbers of neutrons in their nuclei, and hence differ in relative atomic mass but not in chemical properties; in particular, a radioactive form of an element.

Metastasis means the spread of cancer cells from the place where they first formed to another part of the body. In metastasis, cancer cells break away from the original (primary) tumour, travel through the blood or lymph system, and form a new tumour in other organs or tissues of the body. The new, metastatic tumour is the same type of cancer as the primary tumour. The plural form of metastasis is metastases.

No carrier added (n.c.a.) radionuclide is characterized as no carrier added in which no carrier atoms have been added and for which precautions have been taken to minimize contamination with staple isotopes of the element in question. It does not necessarily mean, however, 100% isotopic abundance.

Neuroendocrine tumour (NET) means a tumour that forms from cells that release hormones into the blood in response to a signal from the nervous system.

Precision oncology means molecular profiling of tumors to identify targetable alterations, is rapidly developing and has entered the mainstream of clinical practice.

Prostate specific membrane antigen (PSMA) means a membrane protein which contributes to prostate cancer's development and is seen in a higher amounts in prostate cancer cells.

Radioligand therapy means a targeted form of cancer treatment that delivers radiation directly to cancer cells. Radiopharmaceutical means a radioactive drug composed of a radionuclide and a pharmaceutical that is used for diagnosis or therapy.

Somatostatin means a peptide hormone that prevents the release of growth hormone from the pituitary gland.

Somatostatin receptors (SSTRs) means receptors that are expressed in high levels in gastroenteropancreatic neuroendocrine tumors.

Targeted radionuclide therapy (TRT) means a form of treatment that delivers therapeutic doses of radiation to malignant tumours, for example, by administration of a radiolabeled molecule designed to seek out certain cells.

Theranostics means a new field of medicine which combines specific targeted therapy based on specific targeted diagnostic tests.

****PLUS Team Members:**

Michael Lee-Chin, B.Eng.

Executive Chairman, Chief Executive Officer and Portfolio Manager, Portland Investment Counsel Inc.

Dragos Berbecel, MBA, CFA

Portfolio Manager, Portland Investment Counsel Inc.

Adrian Lee-Chin, CFA

Associate Portfolio Manager, Portland Investment Counsel Inc.

Hubert Walinski, Ph.D.

Chief Scientific Officer, Life Sciences, AIC Global Holdings Inc.

Ramon Arscott, M.D. , M.Sc. , D.Phil.

Chief Medical Officer, AIC Global Holdings Inc.

Rogerio Tippe, MBA

Director, International Business Development, AIC Global Holdings Inc.

Randy Peterson, Ph.D., MBA

Manager, International Business Development, AIC Global Holdings Inc.

*Michael Lee-Chin is a member of the Supervisory Board of ITM.

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Portland Investment Counsel Inc., 1375 Kerns Road, Suite 100, Burlington, Ontario L7P 4V7 Tel:1-888-710-4242 • www.portlandic.com • info@portlandic.com

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