Probe Biotech's Diverse Subsectors for Strong, Undervalued Companies: Van Leeuwenhoeck's Marcel Wijma

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COMPANIES MENTIONED

- Galapagos NV
- MDxHealth SA
- Prima BioMed Ltd.
- **Regeneus Ltd.**
- **Resverlogix Corp.**

The life sciences industry is evolving rapidly. Many say it's at the beginning of an explosive growth stage that will see the development and commercialization of novel therapeutics and diagnostics still being imagined in scientific laboratories today. This explosion of innovation also means an explosion of investment opportunity. In this interview with *The Life Sciences Report*, Marcel Wijma, chief research analyst at Van Leeuwenhoeck Institute, explores some smaller companies working on the industry's forefront.

Source: Gail Dutton of *The Life Sciences Report*

The Life Sciences Report: Marcel, you cover a wide range of life sciences companies that are developing tools, diagnostics, pharmaceuticals and regenerative therapies. What does being involved in each of these subsectors lend to an investor's portfolio?

Marcel Wijma: The healthcare sector in general covers most of the aging population, and thus is the investment sector that profits the most from the aging of the baby boom generation. When you look individually at the subsectors in healthcare, they have different dynamics and also hold different types of interest for the investor.

The cash cow, of course, has always been big pharma—the traditional pharmaceutical companies. These provide investors with a stable source of income in terms of dividends and a good growth rate. But when you look at last decade, that growth rate has diminished quite considerably. In the past few years, big pharma has experienced growth of only a few percent annually. The big chunk of the healthcare sector's overall growth is coming from other subsectors, like biotechnology.

*"We believe **Regeneus Ltd.** has the potential to become Australia's next success story in regenerative medicine."*

Biotechnology has been very successful in developing new products, whereas big pharma has failed to do so. That probably has to do with the different structures of the organizations. Big pharmaceutical companies now are more like sales and marketing organizations, and lack the capability to develop innovative new medicines in the quantities they need. They have turned to biotech to provide this kind of innovation. In that sense, big pharma is important for biotechnology in terms of mergers and acquisitions.

TLSR: Are the relative risks of biotech subsectors any different? For instance, is one safer or more volatile than another?

MW: Yes. When you look at the risk profile in general, it tends to be higher for biotech companies focused on developing new medicines, because it takes more money to develop a successful product and put it on the market. You also see

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certain very successful therapeutic areas, with quite lot of new drugs coming to market, while other therapeutic indications definitely have low success rates.

In oncology, for example, many new types of therapies have succeeded in the past few years. Therapeutics for central nervous system (CNS) disorders, in contrast, have had a very high failure rate. It's very difficult to develop good therapeutics for conditions like Alzheimer's or Parkinson's diseases, as the brain still is a black box for scientists. The biotech and pharmaceutical companies haven't succeeded in coming up with new therapies to cure these diseases or relieve their symptoms, because scientists don't fully understand their underlying causes.

Diagnostics, another of the subsectors, is profiting from ongoing developments in oncology because there is an important focus on detecting and treating cancer at much earlier stages. New diagnostic tests are very important in this endeavor.

*"**Resverlogix Corp.** may have the answer to developing a new generation of cardio drugs."*

Diagnostic companies also will profit from the fact that more tests are reimbursed by insurers. A few years ago reimbursement was an issue, but payers now see that detecting disease earlier helps reduce overall treatment costs.

TLSR: With so many companies pushing the frontiers of innovation in areas that are innovative, what should investors look for to determine the best candidates in any particular area?

MW: To select the right candidates it is important to look at their pipelines. Immunotherapies targeting cancer, rare diseases and auto-immune diseases that are in Phase 2 or 3 with expected news flow in the next 3–6 months are the best candidates. These companies have the best chances to get partnerships with big pharma, or to be part of merger and acquisition (M&A) deals. Experienced management with a good track record in deal-making would be the cherry on the cake.

TLSR: You follow a number of innovative companies with novel technologies that, in reports, you've mentioned are grossly undervalued. Can you tell us about some of them?

MW: Prima BioMed Ltd. (PBMD:NASDAQ; PRR:ASX) is an Australian immunotherapy company by origin, and listed on NASDAQ. It is active in immunotherapy with a broad pipeline aimed at developing therapies for several types of cancer and autoimmune disease. Next to its proprietary LAG-3 platform, its lead product is CVac, an autologous, dendritic cell-based cancer vaccine that's in clinical trials for ovarian cancer. The company recently released positive Phase 2 results that showed a clear overall survival benefit in second-remission patients with ovarian cancer. I feel these results will trigger a potential partnership with big pharma to start with a Phase 3 trial.

TLSR: What should make CVac interesting to investors, in addition to its fast-track and orphan drug status with the FDA?

MW: Prima BioMed's CVac is a good example of a successful immunotherapy, a therapy that has come a long way in recent years and is now on the brink of becoming a key player in oncology. We expect a partnership with a large pharmaceutical company in the near future. So far, the company has financed the development of CVac all by itself.

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Next to that, LAG-3 is an increasingly important immuno-oncology target, which is dominated by Prima BioMed. LAG-3 possibly has the ability to activate the immune system to kill cancer cells. When you look at the immunotherapy field, there are quite a lot of products already on the market and in development. I think that immunotherapy is the most important field of cancer drug development today.

Most advanced immune therapy under LAG-3 is IMP321, a soluble LAG-3 therapy. In cancer patients, IMP321 showed it could, in combination with chemotherapy in Phase 2a, double the clinical response rate compared to chemo alone.

TLSR: Regenerative medicine, also innovative, is beginning to see products in the marketplace. About 20,000 stem cell transplants are performed annually in the United States, and there are hundreds of companies with a regenerative medicine focus. Are there any companies you find particularly interesting?

MW: Regeneus Ltd. (RGS:ASX) is in the regenerative medicine/stem cell technology sector. The company has proprietary technology that derives stem cells from the body's own fat (adipose tissue) to treat a wide range of inflammatory diseases like arthritis and osteoporosis.

Regeneus also is developing a cancer vaccine. It takes tumor cells from the patient, regenerates them and returns them to the body, stimulating the patient's own immune system to fight the cancer. This can be done fairly easily, so the cost of developing this type of therapy is considerably lower. It is also probably more effective than current therapies. The company recently got approval in Australia to begin a first-in-human (Phase 1) trial to test its cancer vaccine. We believe Regeneus has the potential to become Australia's next success story in regenerative medicine, following the footsteps of Mesoblast Ltd. (MSB:ASE; MBLTY:OTCPK).

TLSR: Japan's new regenerative medicine laws, which took effect last autumn, make it significantly easier and less expensive to commercialize regenerative products in that country by granting conditional marketing approval while clinical trials are still being conducted. What do these new Japanese regenerative medicine laws mean for Regeneus' prospects?

MW: Japan is very progressive in the area of stem cells and regenerative therapy, and constitutes a large market for this therapeutic area. At the end of last year, laws took effect that make it easier for companies to develop therapies, get regulatory approval and put the therapies on the market. Regeneus wants to start a number of trials in Japan and is looking for a partner to do so.

> "Diagnostics is profiting from ongoing developments in oncology because there is a focus on detecting and treating cancer at earlier stages."

There will be other news coming out in the next 12 months, as well. Important news flow in the next few months will include the start of clinical trials with its product Progenza (off-the-shelf allogeneic stem cell treatment) in osteoarthritis, and with its cancer vaccine, for which it will enroll 21 patients.

TLSR: Is there another innovative yet undervalued company you have your eyes on?

MW: Yes. Galapagos NV (GLPG:NASDAQ; GLPG:BSE) has a partnership in place with AbbVie Inc. (ABBV:NYSE) to develop the JAK1 inhibitor filgotinib for severe rheumatoid arthritis patients who show an inadequate response to the drug

methotrexate. The share price went up dramatically after Phase 2 interim results were released. At the end of July, the company is expected to publish all the results of the 24-week trial in this indication.

If the results are positive, as they were in the interim analysis, AbbVie probably will exercise its option to in-license the drug, triggering a milestone payment of $200 million ($200M) to Galapagos.

For AbbVie, it's important to have a new product against rheumatoid arthritis in its pipeline because, currently, it has the largest-selling rheumatoid arthritis product on the market. It's called Humira (adalimumab), and has annual sales of $13 billion ($13B). Humira will go off-patent in a few years, so AbbVie needs a follow-up drug. AbbVie has development programs underway with other companies to develop an innovative follow-up to Humira, but the most important of those programs is the one with Galapagos.

TLSR: Is an acquisition likely?

MW: There are rumors AbbVie may consider acquiring Galapagos for this product. In the recent initial public offering (IPO) on NASDAQ, the company participated in the placement of new shares.

Another thing that is interesting—and feeds the rumors—is that AbbVie has other partnerships in place with Galapagos to develop cystic fibrosis therapeutics. The cystic fibrosis market is garnering a lot of interest from large pharmaceutical companies. Wall Street analysts estimate the cystic fibrosis market may exceed $6B within the next few years. AbbVie and other pharmaceutical companies are actively looking for a new generation of drugs to target that market.

TLSR: The field of epigenetics is also generating a lot of discussion in scientific circles, as the human genome project has made it possible to relate specific lifestyle and environmental exposures to genomic changes. Do you follow a company in that field?

MW: MDxHealth SA (MDXH:EBR) a Belgian molecular diagnostics company, is adding to its platform of diagnostics by developing an advanced epigenetic test for personalized treatment of cancer. Its technology, MSP (methylation-specific PCR), is extremely powerful and accurate. It can detect a single cancer cell from among 10,000 healthy cells—including stem cells—in any type of bodily fluid or tissue.

> "Immunotherapies targeting cancer, rare diseases and auto-immune diseases that are in Phase 2 or 3 with expected news flow in the next 3 –6 months are the best candidates."

MDxHealth is partnering with Exact Sciences Corp. (EXAS:NASDAQ), which in-licensed all the technology for a specific test against colon cancer called Cologuard. This is the first FDA-approved, noninvasive test for colon cancer. On the market since late 2014, it showed very good revenues during the first quarter of 2015.

MDxHealth is getting about a 5% royalty on these sales. Analysts estimate Cologuard can generate up to $1.5B in revenue within the next few years. That would give MDxHealth a very good income stream.

Its current market value of about $200M is very much below the projected royalty income from this test alone. Some people suggest MDxHealth may be a takeover target for Exact Sciences.

TLSR: Why is MDxHealth so undervalued?

MW: MDxHealth is still seen as European company, even though the market for its diagnostic test is predominantly in the U.S. What the company should do, to increase its visibility to U.S. investors, is have a dual listing on a U.S. stock exchange, like NASDAQ, as several European companies have done.

Recently, the company successfully raised $31M, which it will use to increase its sales and clinical affairs efforts in the U.S. and to accelerate product development (new tests for prostate cancer and bladder cancer). This could be the step up for a NASDAQ listing in the near future.

TLSR: Is there another company in epigenetics that you'd like to mention?

MW: Resverlogix Corp. (RVX:TSX) is a Canadian cardiovascular drug company that is active in targeting cardiovascular disease. It has a proprietary drug development platform that's based on targeting bromodomain and extra-terminal (BET) domain proteins. BET proteins have potential in many diseases, including cardiovascular disease, neurodegenerative disease and diabetes. BET bromodomain inhibition is an epigenetic mechanism that can turn disease-causing genes off, returning them to a healthier state.

TLSR: Resverlogix just received authorization to launch a Phase 3 clinical trial in Europe this fall for coronary disease. What are the challenges, and where are the opportunities, in an epigenetic approach?

MW: When you look at the current drugs for cardiovascular disease, they're usually statins. Their goal is to target bad cholesterol and promote good cholesterol. That, until now, was the standard of care for cardiovascular disease. Recently, there have been failures in the cardiovascular therapeutics area among new-generation drugs that target the promotion of good cholesterol—high-density lipoprotein (HDL). Regulating HDL has proven very difficult. Companies like Pfizer Inc. (PFE:NYSE) and Roche Holding AG (RHHBY:OTCQX) have experienced great disappointments in this area.

> "I think immunotherapy is the most important field of cancer drug development today."

The current, more innovative thinking is to reduce the risk of actually experiencing a heart attack. This new tactic, using epigenetics, is getting more emphasis from scientists and cardio specialists. The approach being developed by Resverlogix is a small molecule that can uncover the involved environmental and individual aspects of lifestyle that directly interact with the genome to influence epigenetic change in the DNA of a person. The company is targeting patients who have diabetes mellitus or chronic kidney failure who are at high risk for cardiovascular disease.

Resverlogix seems to have an interesting new way to deal with cardiovascular disease. With RVX-208, a first-in-class, small molecule, selective BET inhibitor, Resverlogix may have the answer to developing a new generation of cardio drugs.

TLSR: Do you think RVX-208 could become a potential blockbuster?

MW: Absolutely. RVX-208 could be very effective as a combination therapy with, for example, AstraZeneca Plc's (AZN:NYSE) Crestor (rosuvastatin calcium), with almost 24M new prescriptions or refills in the past year and annual sales in the U.S. exceeding $5B. Crestor is currently among the most prescribed drugs in the U.S.

TLSR: I noticed Resverlogix has a $68.8M loan from Citibank, payable in August 2017. This is fairly unusual in biotech financing, isn't it?

MW: That is correct. I haven't seen a biotechnology company without any revenue or cash flow that has been able to secure some type of loan. It's probably something that the company arranged when it was in a different position and had a different pipeline. However, last year, Resverlogix was able to renew this loan.

Resverlogix also gained a new investor in the form of China-based pharma company Shenzhen Hepalink Pharmaceutical Co. Ltd. Shenzhen Hepalink is a global pharmaceutical leader in the manufacturing and development of Heparin Sodium API. Heparin is widely used as an important anticoagulant therapeutic agent in high-risk cardiovascular disease patients around the world.

Hepalink gets 13% equity for a CA$35M investment, which strengthens Resverlogix's balance sheet. Resverlogix is using the funds to develop a cardio product for the Territories (China, Hong Kong, Taiwan and Macau). Resverlogix is eligible to receive sales-based milestone payments from Hepalink. Total sales based milestones and royalty payments are estimated in excess of $400M.

We strongly feel that Resverlogix is due for a significant rerating of the stock.

TLSR: Thank you for your insights, Marcel.

Marcel Wijma is founder and managing director of Van Leeuwenhoeck Inc. (VLI). VLI is actively engaged in the financial research of life sciences companies in Europe, North America and Australia. VLI provides institutional investors and other professional investors with independent, unbiased research on the real value of innovative life sciences companies.

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