



Recognizing That The Best Is Yet To Come

Is The Reasons Behind The Recent Biotech Stocks Outperformance

The biotech sector recent performances might be forecasting the magnitude of its next flight into space. The implicit message it sent suggests that the biological revolution has accumulated enough knowledge for the industry to deliver on its extremely ambitious promises. The message is a wake up call for those who are still living in and sleeping with obsolete old realities.

While the biotech firms are growing their revenues, incomes and pipeline products, those who have eyes, but do not see and ears but do not hear are constantly missing the miracles being made in the laboratory and the clinic at a rising speed. They witnessed, but underestimated the evolution in the management of deadly viral infection, including HIV and HCV; the successful attempts to reverse fibrosis; from bone marrow myelofibrosis, to idiopathic pulmonary fibrosis, cystic fibrosis and liver cirrhosis. Textbooks, old and new, still affirm that only miracles could reverse fibrotic diseases and halt their debilitating and life threatening conditions created by the affected organs. The sleepers missed the fact that **human minds are capable of making miracles when they are fed with confirmed and validated knowledge. In biotechnology, the miracles are being made through the unparalleled knowledge about the molecules that contribute to the making of the vehicles of life and those that provide the maintenance of the living organs and their protection against all kind of malfunctions.**

The sector's recent market outperformance insinuated that investors who kept believing in the outdated information so that they missed benefiting from the biotech sector's surge have finally opened their eyes. The booming science per se could not wake them up on its own; the unprecedented rally in **Intercept Pharmaceuticals' (ICPT)** stock made the wake up call and succeeded. The stock surged over 400% in no time after the firm announced outstanding results of their **obeticholic acid (OCA)** drug in reversing non-alcoholic liver inflammation. The thunder and lightening caused by ICPT announcement and stock surge had the effect of chock waves that planted enough wisdom in the minds of the unwise that made them look back and realize how wrong they were to follow pessimistic views. They realized how misled they were when they got rid of their biotech stocks, or declined to invest in **AMGN, GILD, ILMN, VRTX, PCYC, REGN, INCY, SGEN, IMGN, CELG, BIIB, JAZZ, ALNY, ISIS** and the rest of the big winners.

The baby industry, they finally recognized, has grown up into a super adult industry hungry for knowledge and achievements in spite of the fact that they are fed tons of evidence-based information. The time has come for the biotech industry to deliver on its extremely ambitious promises. That's what they might have finally realized.

Sequencing the genome has reached the clinic. Treatments now exist for cystic fibrosis, HCV, HIV and many cancers. **Personalized medicine** is now applied in the clinic whenever the targeted protein on the disease pathway is identified and confirmed through the sequencing of cancers and patients' genomes. Aberrant genes are being identified and oral and injectable treatments are doing the genetic repair business. Most of the firms we picked for investment are major contributors to this revolution. VRTX is in, GILD is in, AMGN is in, SGMO is in, ALNY, ISIS, INCY, IMGN, SGEN, EXEL, ENTA and many that are expected to contribute are all in. Thanks to these firms, we have already opened the door of a new world of healing.

Finding New Small Stars

It is important to note that many academic researchers have established biotech firms based on great breakthrough discoveries. Many others have licensed their discoveries to small firms that they believed have the right people to design the best clinical trial plans and strategies and to successfully manage the firms' businesses and finances. We are in the process of looking for such firms. **In fact, we have already picked a couple of firms from among a dozen that can fulfill the promises of the biotechnology industry.**

What's in our portfolios now will soon host others that came to add to what has been achieved. In the past three months we listened to great Ideas, innovative approaches to treatments helped with great technological capabilities and state-of-the-art tools. Some of the designs have already been transformed into far-reaching therapeutics that would benefit millions of people who are living their day to day at the mercy of life-threatening diseases. Many of these dream treatments have reached mid- and late-Phase trials before they turn from privately held into publicly traded companies. We discussed these firms and we are ready to publish the outcome of these discussions in the part 2 of this letter.

BREAKTHROUGH CANCER IMMUNOTHERAPY *Inhibiting Immune Checkpoint Receptors*

For years, scientists tried to find out **why the immune system whose task is protecting the body from diseases fails to attack and eliminate cancer cells**. Not long ago, scientists recognized that a major limitation is **'T-cell exhaustion'** caused by upregulation of receptors whose original task is to tame the immune system when it loses its memory and its own body.

In healthy people, the receptors that inhibit the immune system cells serve as **immune checkpoints** that are meant to **prevent uncontrolled immune reactions, which hurt the body organs and systems instead of protecting them**.

Scientists hypothesized that developing monoclonal antibodies against one or more of these receptors that inhibit the immune system could rescue the exhausted cytotoxic T lymphocytes, enabling them to find their way to cancer cells and eliminate them. As a matter of fact, **Merck (MRK), Pfizer (PFE); Bristol-Myers Squibb (BMS)** and a few others developed antibodies that inhibit one or more inhibitory receptors. The good news is that in clinical trials the antibodies targeting the immune system's inhibitory receptors have demonstrated objective clinical responses in advanced cancer patients.

One of those monoclonal antibodies, **ipilimumab (Yervoy)**, has already been FDA approved in 2011 in the U.S. and in many other countries around the world for **metastatic melanoma** either as initial therapy or following a relapse. A small development-stage biotech company called Medarex has created ipilimumab (Yervoy) before it was acquired by Bristol-Myers Squibb (BMS), which now owns the drug. (Medarex was part of Prohost picks at the time of acquisition). Yervoy kills the cancer cells by inhibiting the **anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4)**, which belongs to the immunoglobulin superfamily of receptors.

Cancer cells produce antigens, which the immune system can use to identify the cancers and destroy them. The dendritic cells present the cancer antigens to cytotoxic T cells (CTLs) in the lymph nodes. The CTLs can then recognize the cancer cells by those antigens and destroy them. The problem is that with the antigen presented to CTLs, dendritic cells bring an inhibitory signal, which binds to a receptor CTLA-4, on the cytotoxic T lymphocytes, which turns off the cytotoxic reaction hence allowing the cancer cells to survive. By blocking CTLA-4 inhibitory signal, Ipilimumab allows the CTLs to destroy the cancer cells.

To make the story short: Enabling the immune system to use its weapons to attack and destroy cancer has been made possible with antibodies that inhibit the immune system disabling receptors known as the **immune Checkpoints**. This approach **differs** totally from that of **therapeutic vaccines**. The outcome of both approaches is the same, which is enabling the immune system to kill the cancers.

Immune System Inhibitors: In addition to **CTLA-4 cytotoxic cells' inhibitors**, other inhibitory receptors exist and include: **programmed cell death protein 1 (PD-1)**; **B and T lymphocyte attenuator**; **T-cell immune globulin**; **mucin domain-containing protein 3 (TIM-3)**; **V-domain immunoglobulin suppressor of T cell activation** and others

Warning: Results from targeting some of these immune Checkpoints have proven to bring better safety and efficacy than targeting others. That's why **not all the firms that developed monoclonal antibody immunotherapy products against one or another of these targets will have the same successful outcome**.

Getting The Best Out Of Cancer Immunotherapy

It is obvious that targeting **CTLA-4** with the approved monoclonal antibody **ipilimumab (Yervoy)** has advanced the treatment of metastatic melanoma. The problem, however, is that the treatment has many **adverse effects that are severe, life-threatening, and, in many cases, intolerable**. Nevertheless, as a first attempt of inhibiting an immune Checkpoint the drug has validated the concept that inhibiting the Checkpoints will relieve the cytotoxic T lymphocyte exhaustion and enable this army to locate and attack cancer cells. There is no doubt that Yervoy offered hope to the condemned. The good news though is that the bad safety profile does not seem to occur with drugs aimed at inhibiting PD-1 protein, and some other checkpoint proteins.

Merck's drug MK-3475: This drug could file soon for approval. It is an immunotherapy designed to restore the natural ability of the immune system cells to recognize and target cancer cells by selectively **blocking (PD-L1 and PD-L2) of the PD-1 protein**. By blocking PD-1, MK-3475 enables activation of the immune system's T-cells that target cancer by essentially releasing a brake on the immune system.

In spite the promising results that came from clinical trials on various cancers, Merck decided to test its anti-PD-1 antibody drug MK-3475 in combination with Pfizer's Inlyta for kidney cancer and **PF-05082566** in multiple cancer types. From **Incyte** it selected **test INCB24360** in combination with MK-3475 for non-small-cell lung cancer and with Amgen it selected **talimogene laherparepvec** for advanced melanoma.

Breakthrough Combinations Of cancer Immunotherapy

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products: **Inlyta** for kidney cancer and **PF-05082566** for multiple cancer types. From **Incyte** Merck selected **INCB24360 for non-small-cell lung cancer** and from **Amgen** it selected **talimogene laherparepvec (T-VEC)** for advanced melanoma.

INCYTE (INCY): Merck selected Incyte's oral drug **indoleamine dioxygenase-1 (IDO1) inhibitor, INCB24360**, for combination with its anti-PD-1 immunotherapy MK-3475. The trial for the combination will be a Phase I/II study in previously treated **metastatic and recurrent non-small cell lung cancer (NSCLC), and other advanced or metastatic cancers**.

Both Incyte's INCB24360 drug and Merck's MK-3475 drug are immunotherapies targeting distinct regulatory components of the immune system. Preclinical evidence suggests that the combination of these two agents may lead to an enhanced anti-tumor immune response than either agent alone. Phase I/II study will be evaluating the safety and efficacy of the combination in the previously treated metastatic and recurrent NSCLC. The Phase I portion is to establish a dose regimen of INCB24360 and MK-3475 and Phase II portion patients receiving MK-3475 will be randomized to receive either INCB24360 or a placebo. The study is expected

in the first half of 2014 and will be co-funded by Incyte and Merck and conducted by Incyte. Results from this first study with Merck will be used to determine whether further clinical development of this combination is warranted.

AMGEN (AMGN): Merck's decision to assess Amgen's Immunotherapy drug **Talimogene laherparepvec (T-VEC) in combination with MK-3475 for advanced melanoma could yield a breakthrough treatment for the condemning skin cancer**. Amgen drug is not a Checkpoint inhibitor like MK-3475, but acts **like a therapeutic vaccine** that boosts the immune system capability to destroy cancer cells. **T-VEC is an oncolytic immunotherapy** with the virus designed to replicate in cancer, **causing lytic cell death and releasing tumor-derived antigens**. The drug is also engineered to **express granulocyte-macrophage colony-stimulating factor (GM-CSF)**, which can help to further activate the immune system.

So, MK-3475 frees the T cells to find their way and kill the cancer and AMGN T-VEC boosts the reaction, accentuating the systemic anti-tumor immune response that targets the cancer cells.

Prohost Comments: Amgen and Incyte are precious firms. Their pipelines are rich with breakthrough products that promise escalating growth year after year. We have no intention to dispose of any of them at this time. They remain in Prohost portfolio #1 until further notice, which we doubt would be issued anytime soon.



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NEWS FROM THE STARS

GILEAD (GILD): Important news about insurers decision to favorably cover the new hepatitis C drug, which sells for \$84,000 for a 12-week course of treatment. **The insurers realized that the high price is cost effective compared to the costs of handling the complications of hepatitis C infection – cirrhosis, liver cancer, or liver transplant – the operation cost and the life-long cost of preventing transplantation rejections and other complications and side effects of medications etc.**

Gilead said it has been approached by big plans and some big HMOs about making sure that they can get access early and they are already engaged in negotiations with these insurers. **The conversations are confirmed to be very productive.**

In less than a month after FDA approval Gilead's HCV drug Sovaldi generated **\$139.4 million in sales**. The successful negotiations with the third party payers and the huge sales in the first 24 days following the FDA approval **must put an end to the critics' negative campaigns against GILD – especially those who are trying to mislead investors into believing that the high price of the drug is a problem that would erode the drug's sales.**

Attempts to nail GILD will not work. The market is vast, the prognosis of HCV is bad and the all-oral combination treatment provided by Gilead is life protector, halting the progression of this deadly infection.

A smart investor will not listen to fabricated frightening stories and sell GILD before the billions of dollars in revenues fill its coffers.

AMGEN (AMGN): See Above.

CELGENE (CELG): This stock is not in our portfolio but deserves to be: It has what's required to maintain and escalate its growth potential. We will post a separate article on this firm before its stock splits, which the firm announced it intends to soon do. Celgene's long-term outlook looks good with the firm raising its product sales as well as earnings outlook for 2015 and 2017. The reason the firm is not currently in our portfolio was a matter of preference. We preferred to invest in companies like **PCYC, VRTX,**

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REGN and what was a small oncology group, i.e., **INCY, IMGN, SGEN** and the elite firms **AMGN, GILD** and **ILMN**. We did great.

JAZZ (JAZZ): Stock hits 52-Week High after a strong projection at the J.P. Morgan conference. Analysts and investors liked its decision to acquire the global development, manufacturing and commercial rights to **ADX-N05 from Aerial BioPharma**. The drug is for excessive daytime sleepiness in patients suffering from narcolepsy. Jazz projected crossing \$1 billion in revenues in 2014.

Prohost Comments: Jazz' success is in selecting drugs that sell and grow and in managing the business with professionalism and sense of knowledge that are rare to see around. **The stock soared, but the real growth of this firm might be starting now.** The reason we selected Jazz is that we saw Celgene in it. At the time we picked JAZZ, the stock was much cheaper than CELG. We were right.

ALNYLAM (ALNY): When Big Pharma demonstrate interest in Alnylam, it is a validation that this firm has, indeed, overcome the problem of its very difficult technology. In this respect, in January 2014, **Sanofi expanded its agreement with Alnylam** for the development of approaches to treat rare genetic diseases. Sanofi's Genzyme subsidiary will acquire a stake in Alnylam worth around \$700 million. This deal validates Alnylam's technology and provides ALNY with cash. More important, which will elaborate on separately in Prohost biotech website is the firm's products results. The company is on its way to realize a big dream.

ISIS (ISIS): We can say the same as ALNY.

We have a lot to say, but we have a storm after a storm, which made us miss scheduled meetings around our table and biotech firms' tables – all were required to put the correct assessment that is the outcome of these meetings.

**PART 2, OR a continuation of this Issue
will be posted TOMORROW after market hours**

WE WILL PRESENT

PORTOLA PHARMACEUTICALS

We will elaborate on this firm, which was founded in 2003 and headquartered in South San Francisco, California. [Portola Pharmaceuticals \(PTLA\)](#) spent ten years researching and producing novel therapeutics related mainly to blood coagulation, other blood diseases and inflammatory diseases. Two of its molecules had already reached late phase trials before Portola entered the public arena in May 2013. The two products target blood coagulation problems.

The first product, Betrixaban (FXa Inhibitor), is a long-acting oral anticoagulant specifically designed for once-a-day dosing. The drug has a **low peak-to-trough drug concentration ratio**, which minimizes anticoagulant fluctuations, hence increases the efficacy and tolerability of the drug.

The second lead product, Andexanet alfa (PRT4445*) is an antidote of Betrixaban. This is the first ever antidote to the anticoagulant drugs that induce their action by inhibiting Factor Xa. Andexanet alfa is designed to reverse bleeding in people treated with Factor Xa inhibitors and prevent bleeding in patients who are subjected to emergency surgical procedures while on Factor Xa inhibitor drugs. Currently, these people suffer uncontrolled bleeding episode or undergo emergency surgery. The FDA granted this savior drug breakthrough status with the potential of early approval.

We will analyze each and every aspect of this firm, which is attracting collaborators.

We will explain why the collaborators are coming and who they really are.

The Table with the Stocks' 1st Price Targets will be posted tomorrow

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