Zacks Small-Cap Research

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# Pieris Pharmaceuticals, Inc. (PIRS - OTC)

## *PIRS: Pieris Announces First Immuno-oncology Candidate…*

| | |
|---|---|
| **Current Recommendation** | **Buy** |
| Prior Recommendation | N/A |
| Date of Last Change | 04/08/2015 |
| Current Price (05/20/15) | $3.10 |
| **Target Price** | **$6.00** |

### UPDATE

On May 19, 2015, Pieris Pharmaceuticals, Inc. presented data on a novel anti-CD137 and HER2 bispecific immuno-oncology program at the UBS Global Healthcare Conference. This is the first of a series of immuno-oncology compounds that the company is currently working on, with plans to select a CD137/HER2 bispecific compound for advancement into the clinical by the end of 2015.

Last month we initiated coverage of Pieris Pharmaceuticals, Inc. with a 'Buy' rating and a $6.00 price target. The presentation of the first compound from the immuno-oncology franchise further strengthens the notion that Pieris' technology could be transformative.

## SUMMARY DATA

| | |
|---|---|
| **52-Week High** | **$3.75** |
| **52-Week Low** | **$2.65** |
| **One-Year Return (%)** | **N/A** |
| **Beta** | **N/A** |
| **Average Daily Volume (sh)** | **4,678** |
| **Shares Outstanding (mil)** | **29** |
| **Market Capitalization ($mil)** | **$91** |
| **Short Interest Ratio (days)** | **N/A** |
| **Institutional Ownership (%)** | **60** |
| **Insider Ownership (%)** | **2** |
| **Annual Cash Dividend** | **$0.00** |
| **Dividend Yield (%)** | **0.00** |
| **5-Yr. Historical Growth Rates** | |
| **Sales (%)** | **N/A** |
| **Earnings Per Share (%)** | **N/A** |
| **Dividend (%)** | **N/A** |
| **P/E using TTM EPS** | **N/A** |
| **P/E using 2013 Estimate** | **N/A** |
| **P/E using 2014 Estimate** | **N/A** |

| | |
|---|---|
| **Risk Level** | **Above Average** |
| **Type of Stock** | **Small-Growth** |
| **Industry** | **Med-Biomed/Gene** |

## ZACKS ESTIMATES

### Revenue
(In millions of $)

| | Q1 (Mar) | Q2 (Jun) | Q3 (Sep) | Q4 (Dec) | Year (Dec) |
|---|---|---|---|---|---|
| 2014 | 0 A | 0 A | 2.1 A | 0 A | 5.4 A |
| 2015 | 0.2 A | 0.3 E | 0.3 E | 0.3 E | 1.1 E |
| 2016 | | | | | 7.0 E |
| 2017 | | | | | 12.0 E |

### Earnings per Share
(EPS is operating earnings before non-recurring items)

| | Q1 (Mar) | Q2 (Jun) | Q3 (Sep) | Q4 (Dec) | Year (Dec) |
|---|---|---|---|---|---|
| 2014 | -$0.23 A | -$0.20 A | -$0.18 A | -$0.19 A | -$0.71 A |
| 2015 | -$0.13 A | -$0.15 E | -$0.16 E | -$0.17 E | -$0.61 E |
| 2016 | | | | | -$0.65 E |
| 2017 | | | | | -$0.59 E |

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## WHAT'S NEW

**Financial Update**

On May 13, 2015, Pieris Pharmaceuticals, Inc. (OTC: PIRS) announced financial results for the first quarter of 2015. The company reported revenues of $0.2 million, which was related to reimbursement fro the European Commission for the development of PRS-080. Net loss for the quarter was $3.7 million, which was comprised of $1.5 million in R&D expenses and $2.4 million in G&A expenses. Cash burn for the first quarter 2015 was $3.8 million and the company exited the quarter with $13.2 million in cash and cash equivalents, thus the company should have sufficient capital to fund operations into 2016. As of May 12, 2015, the company had 29.4 million shares outstanding along with 2.5 million stock options (0.6 million vested) and approximately 0.5 million warrants, thus giving a fully diluted share count of approximately 30.6 million shares.

**Pieris Hires Industry Experts**

On May 12, 2015, Pieris announced that Jean-Pierre Bizzari, M.D. has joined the company's Board of Directors. Dr. Bizzari was the Executive Vice President, Group Head, Clinical Oncology Development at Celgene Corporation where he directed the development and approval of a number of leading oncology products including REVLIMID®, VIDAZA®, ISTODAX®, and ABRAXANE®. Prior to working at Celgene, Dr. Bizzari was Vice President of Clinical Oncology Development at Sanofi-Aventis from 2002-2008 and Vice President, Clinical Development Oncology at Aventis from 1993-2002. He is a member of the Scientific Advisory Board of France's National Cancer Institute and Netrix Pharma and serves on the board of Halozyme Therapeutics, Inc., Celator Pharmaceuticals, Inc., and Transgene SA.

On May 14, 2015, Pieris announced it has engaged the services of Dr. Holbrook Kohrt, M.D., Ph.D. as Senior Advisor Translational Medicine Immuno-oncology. In addition, the company entered into a collaboration with Dr. Kohrt's research laboratory, where the company will gain access to the laboratories capabilities in immuno-oncology drug development, which includes access to tumor tissue samples and translational mouse models. Dr. Kohrt is an Assistant Professor of Medicine, Division of Oncology, at the Stanford University School of Medicine. His research is focused on developing novel therapeutic strategies to enhance anti-tumor immunity and on preclinical models of novel immunomodulatory antibodies.

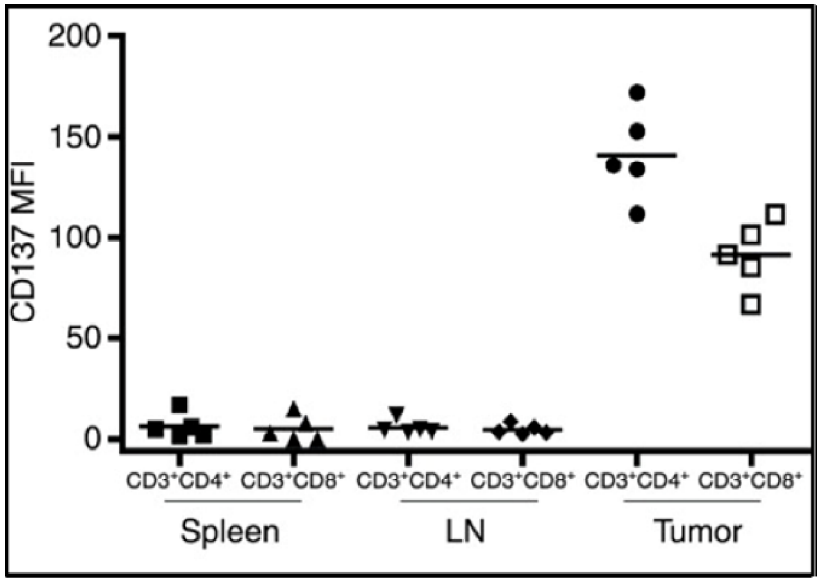
**PRS-343**

On May 19, 2015, Pieris CEO Stephen Yoder presented preclinical data on the company's new immuno-oncology (IO) program at the UBS Global Healthcare Conference. As part of the presentation, the company announced CD137 as a key target in the IO program and that PRS-343, a bispecific compound that contains a CD137-specific anticalin genetically linked to a HER2-specific monoclonal antibody, is the lead compound from that program.

***…CD137…***

CD137 (4-1BB, TNFSFR9) is a tumor necrosis factor receptor (TNFR) family member with costimulatory function that regulates T-cell proliferation and survival and is expressed on activated CD8+ and CD4+ T-cells (Watts, 2005). Since CD8+ T-cells play a pivotal role in tumor immunity, enhancing CD137 costimulation could promote the generation of protective antitumor immune responses. This idea has been validated through enhanced immunogenicity in tumor cells engineered to express CD137 ligand (Mogi *et al*., 2000) or anti-CD137 antibodies (Ye *et al*., 2002). Unfortunately, the use of systemic anti-CD137 antibodies can result in severe side effects such as liver toxicity (Grade 4 hepatitis), which which resulted in the cancellation of a Phase 1 clinical trial (Yao *et al*., 2013). Thus, the ability to stimulate CD137 in the tumor microenvironment could mitigate these systemic toxic effects.

Another important aspect of CD137 is that it is preferentially expressed in high levels on intratumoral T-cells (Palazón *et al*., 2012). This is shown in the following graph, where CD4+ and CD8+ T-cells were extracted from the spleen, lymph nodes, and tumor of mice bearing CT26 tumors. Only T-cells purified from tumors showed expression of CD137, whereas T-cells from other locations from the same mice did not show increased expression of CD137.




***Source*: Palazón *et al*., 2012**

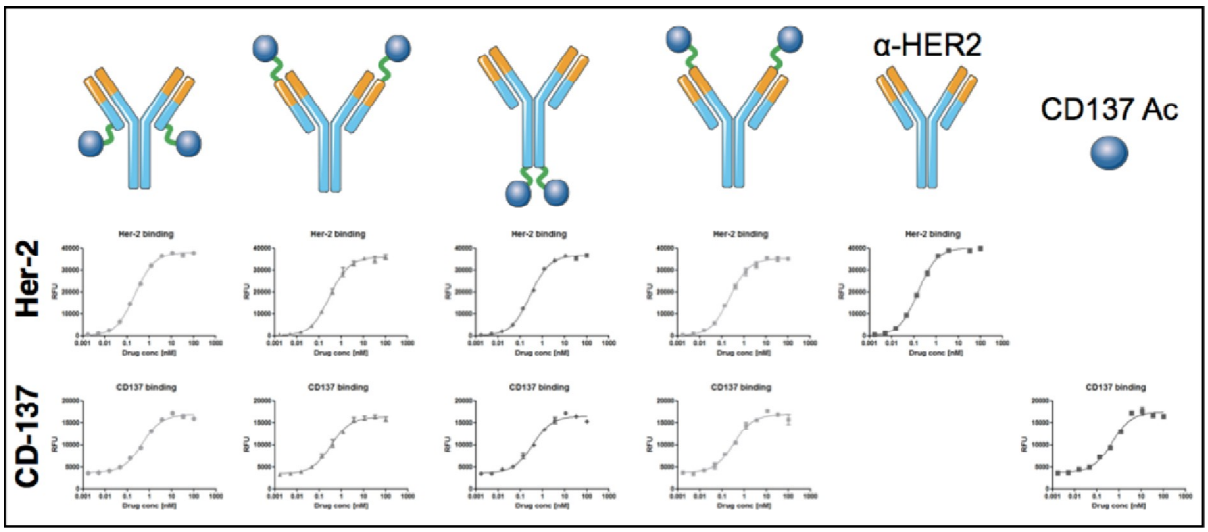
Importantly, the presence of T-cells with increased expression of CD137 was not only found in CT26 tumors, but also in tumors derived from B16-OVA melanoma cells and MC38 colon cancer cells, thus this phenomenon appears to be common to multiple tumor types. This same study showed that intratumoral injection of a CD137-specific antibody resulted in complete regression in 5 of 12 mice bearing CT26 tumors, and in a separate experiment intratumoral injection of the same antibody resulted in complete regression in 4 of 7 primary tumors and 5 of 7 secondary tumors that were not injected with antibody. Those results indicate that the ability to stimulate CD137 in the tumor microenvironment can lead to potent anti-tumor activity.

***…PRS-343…***

Pieris is developing PRS-343, a bispecific compound that consists of a CD137-specific anticalin covalently linked to a HER2 antibody (a derivative of trastuzumab). HER2 is a cell surface receptor that has been shown to play a role in the development and progression of a number of different cancer types, most notably in breast cancer, where it is overexpressed in 20-30% of breast tumors (Mitri *et al*., 2012). Trastuzumab (Herceptin™) is a monoclonal antibody that targets HER2 that has been shown to improve overall survival and disease-free survival in patients with HER2-positive breast cancer (Moja *et al*., 2012).

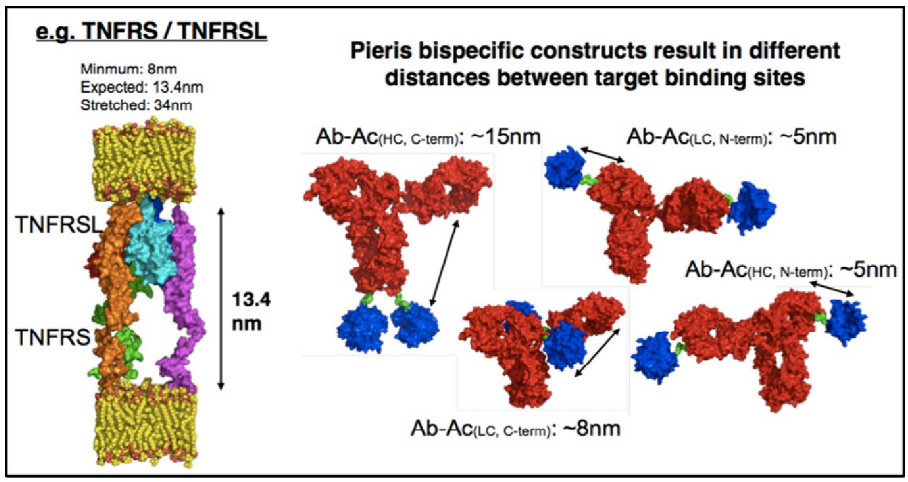
In addition to breast cancer, HER2 is overexpressed in a number of other cancers, including bladder cancer, gastric cancer, and ovarian cancer. In bladder cancer, five-year survival rates are approximately 48% for patients with HER2 negative tumors compared with 9.7% for patients with HER2 positive tumors (Sato *et al*., 1992; Scholl *et al*., 2001). In the aforementioned tumor types, HER2 is overexpressed in 20-30% of tumors. Importantly, HER2 has a low level of expression in normal adult epithelial cells (Press *et al*., 1990).

Pieris has done a number of studies on different CD137-specific anticalin's to identify the lead molecule to advance into clinical testing. The company revealed that this lead compound has a very high affinity for CD137 (~2 nM), activates T-cells in an *ex vivo* model, and binds to CD137 in a "non-competitive fashion". What this means is that binding of the anticalin to CD137 does not interfere with the binding of CD137 and its natural ligand. The flexibility of the anticalin platform is exemplified in the following graphic, which shows that no matter how the anticalin is attached to the monoclonal antibody, both entities retain the ability to bind to their respective ligands with essentially the same affinity.




***Source*: Pieris Pharmaceuticals, Inc.**

Another advantage of the flexibility of the anticalin platform is that the bispecific geometry of the molecule can be manipulated to create different pharmacodynamic effects. This is shown in the following graphic, where multiple distances between HER2 and CD137 binding can be tested to determine the optimal target synapse. Preclinical work such as this is ongoing, with selection of the drug candidate to advance into clinical testing most likely being completed by the end of 2015.




***Source*: Pieris Pharmaceuticals, Inc.**

## Conclusion and Recommendation

The IO space is one of the hottest fields in biotechnology right now, with large companies such as Amgen, Novartis, Bristol-Myers, Merck, and Astra-Zeneca all with multiple IO compounds in development. The first generation of targets that have lead to FDA approvals (Yervoy® for melanoma, Opdivo® for lung cancer) have targeted so called "checkpoint inhibitors", or proteins that keep the immune system from mounting a response, typically due to signals from the tumors themselves. While these products have shown impressive results, they are usually limited to a subset of patients in specific cancer types.

With PRS-343, Pieris is focused not on "releasing the brakes" of the immune system but rather "stepping on the gas" and inducing a heightened immune response in the tumor microenvironment. As discussed above, CD137 activation leads to proliferation and activation of tumor killing T-cells, and by attaching a CD137-specific anticalin to a monoclonal antibody targeting HER2, which is overexpressed in ~25% of a number of different tumor types, CD137-activation is likely to be limited to the tumor microenvironment. We are looking forward to seeing preclinical data on PRS-343 when it is available later in 2015.

In addition to the IO platform, Pieris is continuing work on PRS-080, which is currently in Phase 1 testing in healthy volunteers and is being developed for the treatment of anemia in chronic kidney disease, and PRS-060, an inhaled anticalin being developed for the treatment of asthma. The wide range of diseases being targeted by Pieris is indicative of the flexibility and adaptability of the anticalin platform, and could make Pieris highly sought after by larger biopharmaceutical companies over the next few years, both as a partner or an acquisition candidate. A number of companies with novel protein-binding platforms (most of which have been various monoclonal antibody technologies) have either been acquired or signed lucrative partnership deals over the past few years, as shown in the following table.

| Target | Acquirer/Licensor | Date | Total Deal Size |
|---|---|---|---|
| Abgenix | Amgen | December 2005 | $2,200 Million |
| Cambridge Antibody | AstraZeneca | May 2006 | $1,070 Million |
| Genmab | GlaxoSmithKline | December 2006 | $2,059 Million |
| Regeneron | Sanofi-Aventis | November 2007 | $1,122 Million |
| MorphoSys | Novartis | December 2007 | $1,000 Million |
| OncoMed | GlaxoSmithKline | December 2007 | $1,400 Million |
| PDL BioPharma | Bristol-Myers | August 2008 | $1,155 Million |
| Medarex | Bristol-Myers | July 2009 | $2,400 Million |
| Facet Biotech | Abbott Labs | March 2010 | $450 Million |
| Micromet | Amgen | January 2012 | $1,160 Million |
| Genmab | Johnson & Johnson | July 2012 | $1,135 Million |
| MacroGenics | Gilead | January 2013 | $1,115 Million |
| Seattle Genetics | Bayer | June 2013 | $520 Million |
| Amplimmune | AstraZeneca | October 2013 | $500 Million |
| Molecular Partners | Roche | December 2013 | $1,061 Million |
| CytomX | Bristol-Myers | May 2014 | $1,242 Million |
| Dutalys | Roche | December 2014 | $489 Million |

***Source*: Zacks SCR Napodano/Bautz**

One example from the chart above that really stands out is that of Micromet, which Amgen acquired in January 2012 for $1.1 billion. Micromet was a German company that reverse merged with CancerVax Corporation in 2006. The company developed a novel antibody technology known as Bispecific T-cell engagers (BiTE) that work by binding both a tumor associated antigen and a T-cell receptor. The FDA just recently approved Blinatumomab (BLINCYTO®), a BiTE compound that treats acute lymphoblastic leukemia, in December 2014.

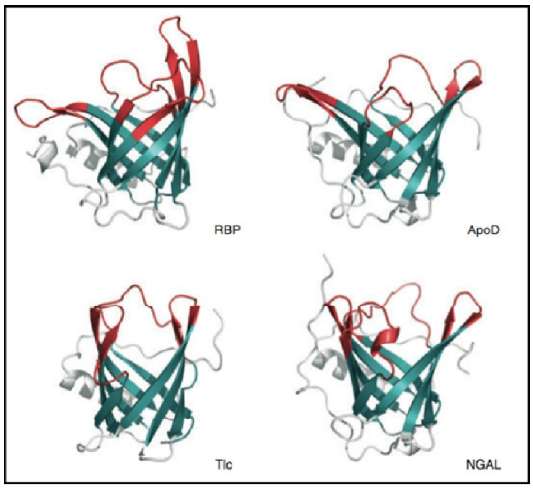
In the first half of 2008, Micromet had a market cap of approximately $80 million. Approximately 4 years later, it was acquired for $1.1 billion, a greater than 13-fold return for investors who got in early. Pieris is a German company that just recently went through a reverse merger and has a novel protein-binding technology that includes a bispecific compound that targets a tumor associated antigen and a T-cell receptor. Pieirs' current market cap is approximately $90 million. Whether the Pieris story will have the same ending as Micromet's remains to be seen, but we believe that the similarities are too great to not consider.

We are very optimistic about the future of Pieris and believe that the anticalin platform is a transformative technology that could lead to a number of novel treatments in a variety of diseases. Last month, we initiated coverage with a 'Buy' rating and a $6.00 price target and feel that investors with a longer-term horizon will be handsomely rewarded by an investment in Pieris.

## INVESTMENT THESIS

**Anticalins®**

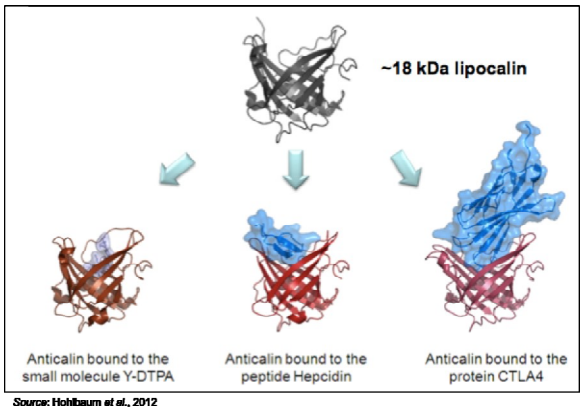
Lipocalins are a family of proteins found in many different organisms, including insects, bacteria, and humans, and are responsible for the storage and transport of hydrophobic and/or chemically sensitive compounds such as vitamins, lipids, and steroids (Skerra, 2008). The lipocalins share a conserved structural motif composed of eight anti-parallel β-strands that enclose a central axis. The open end of the molecules is supported by four loop regions that differ in both length and sequence. These regions confer unique binding capabilities to each lipocalin.




**Four representative lipocalins showing the conserved core structure (green) and the variable loop regions (red).**
***Source*: Skerra, 2008**

Lipocalins are quite similar to antibodies in that both compounds have variable loop regions supported by a rigid framework. However, lipocalins cannot naturally undergo the somatic hypermutations that confer antibodies with virtually unlimited binding capabilities, a property that has been utilized by biopharmaceutical companies to create some of the top selling medications in the world. In an effort to exploit the natural similarities between lipocalins and antibodies, Pieris scientists have developed a new class of novel, engineered lipocalins with unique binding specificities through the use of combinatorial biochemistry. These new compounds have been dubbed 'anticalins' (antibody + lipocalin).

The process of producing Anticalins® is quite similar to the methods currently employed to develop new monoclonal antibodies. A "scaffold" lipocalin molecule is first selected, and a library of modified lipocalins is produced through random mutagenesis at pre-determined amino acid residues in the loop regions. These libraries typically contain up to $10^{11}$ unique protein sequences, with unique binders to a molecule of interest able to be selected through a simple binding assay (Beste *et al*., 1999). Thus far, Pieris reports that all attempts to produce new Anticalins® to a novel antigen (ranging from small molecules to peptides to large proteins) have been successful.




*Source*: Hohlbaum *et al*., 2012

While sharing a number of properties with antibodies, Anticalins® also have a number of unique advantages over antibodies. These include:

***Size***: A monoclonal antibody is approximately 180 kilodaltans (kDa) and is composed of four polypeptide chains (two heavy chains of ~450 amino acids and two light chains of ~215 amino acids). This is in comparison to lipocalins, which are less than 20 kDa and are composed of a single polypeptide chain of ~180 amino acids.

***Ease of manipulation***: Antibody binding is controlled through six non-sequential variable regions spread across the four polypeptide chains. This means that in order to alter binding characteristics it is necessary to simultaneously manipulate each of these regions in concert. With only four variable loops spread across a single polypeptide chain, the binding site for lipocalins is much easier to manipulate.

***Ease of production***: The four polypeptide chains and large size of antibody molecules result in technical difficulties that must be overcome for proper production. This includes a complex cloning procedure and expression in a mammalian cell line in order to achieve proper glycosylation of the molecule, which increases the cost of production significantly. Conversely, lipocalins are a single polypeptide chain and are not glycosylated, thus they can be produced much cheaper and in greater quantities in a bacterial expression system.

***Tunable kinetics***: Pharmacokinetic parameters of monoclonal antibodies are indigenous to the specific class those antibodies belong to (e.g., IgG1, IgG2, IgG3, IgG4). Due to their small size, lipocalins have a short half-life in the bloodstream and thus modifications must be made in order to increase retention time in a patient. These modifications include covalent coupling to serum proteins (e.g., albumin) or the addition of various amounts of polyethylene glycol ('pegylation') that can fine-tune the Anticalin® half-life anywhere from hours to weeks.

***Mode of Delivery***: Due to their large size and inability to pass through the gastrointestinal tract, monoclonal antibodies can only be delivered via intravenous infusion or through subcutaneous injection. The much smaller size of Anticalins® means that they may be delivered through alternative means, particularly through an aerosol targeted delivery to the lungs, something that is not possible with monoclonal antibodies.

The anticalin platform has been validated through the production of a number of Anticalins® to a wide variety of targets starting with different lipocalin framework sequences. We discuss a few of these in detail below.

- Billin-binding protein: The billin-binding protein (BBP) from *Pieris brassicae* is a lipocalin of 174 amino acids that normally binds biliverdin $IX_\gamma$ (Schmidt *et al*., 1994). A library was composed by randomly mutating 16 amino acids of the BBP across the four loop regions and binders to various small molecules were recovered. This includes the Anticalin® FluA, which binds to fluorescein with a Kd value of 35 nM (Beste *et al*., 1999), and the Anticalin® DigA16, which binds to the cardiac steroid digoxigenin with a Kd value of 30 nM (Schlehuber *et al*., 2000). The BBP template was used for early validation work and, as a non-human polypeptide template, is not being pursued for therapeutic applications today.

- Human lipocalin 2: Human lipocalin 2 (Lcn2) is a 178 amino acid protein that binds bacterial ferric siderophores, a chelator, which bacteria use to scavenge up iron from the bloodstream. A library was constructed by randomly mutating 12 amino acid residues in the four loop regions, and from this library an Lcn2 variant was identified that bound to rare-earth and related metal ions as chelate complexes with the synthetic chelating agent diethylenetriamene pentaacetic acid (DTPA). Synthetic chelating agents are typically employed to develop antibody-drug conjugates (ADCs) that can target radioactive isotopes directly to tumors thereby decreasing systemic side effects (Trail, 2013). PRS-080 is an Anticalin® derived from Lcn2.

- Tear lipocalin: Tear lipocalin (Lcn1) is a major protein found in tears with a wide array of functions, including viral DNA inactivation, binding and releasing lipids, and binding microbial siderophores (Dartt, 2011). A naïve combinatorial library was constructed using Lcn1 as the scaffold and a variant that binds to vascular endotherlial growth factor (VEGF) was selected. This Anticalin® was then tested in a Phase 1 dose-escalation study (discussed in greater detail below) and found to be well tolerated with no antibodies produced by the subjects against the Anticalin® compound (Mross *et al*., 2013). For strategic reasons, Pieris has decided not to continue work with this Anticalin®. PRS-060 is an Anticalin® derived from Lcn1.

***…Proof of Concept Clinical Data…***

The ability to transform the Anticalin® platform from a novel academic pursuit into a drug producing modality was tested with the company's first clinical candidate, PRS-050. This compound was designed to bind to the vascular endothelial growth factor (VEGF) and inhibit blood vessel growth in large tumors. PRS-050 was selected from a tear lipocalin library and was shown to have very high affinity to VEGF, with low picomolar affinity. Overexpression of VEGF and/or its receptors has been documented in a wide range of solid tumors (Ferrara, 2004) and a number of clinical candidates targeting VEGF have been or are currently under development. Bevacizumab (Avastin®) is a monoclonal antibody that targets VEGF and is a highly successful drug, with sales of $7.1 billion in 2014.

PRS-050 was tested in a Phase 1 dose escalation clinical trial in patients with solid tumors to investigate its safety, pharmacokinetics, and pharmacodynamics (Mross *et al*., 2013). A total of 25 patients were evaluated after treatment with doses ranging from 0.1 mg/kg up to 10 mg/kg. Results showed that PRS-050 was well tolerated at doses up to 10 mg/kg. A maximum tolerated dose (MTD) was not reached. Importantly, no anti-drug antibodies were detected in any of the patients and there was no sign of cumulative toxicity.

The drug showed dose-proportional pharmacokinetics with a half-life of approximately 6 days. The activity of PRS-050 was exhibited by data showing no detectable VEGF in patients receiving a ≥ 0.5 mg/kg dose, indicating that PRS-050 was able to bind and saturate VEGF after dosing. Lastly, hypertension is a known side effect in some patients receiving anti-VEGF therapy, and in this study approximately 12% of patients had grade 3 hypertension, another indication of clinical activity.

Taken together, the data from this Phase 1 study support the continued development of Anticalin® compounds as potential therapeutics, as the pharmacokinetic/pharmacodynamics parameters of PRS-050 exhibited "drug-like" properties and administration of Anticalins® does not provoke the development of anti-drug antibodies. The company has not advanced PRS-050 further in clinical development for business and strategic reasons; however, the data generated from the Phase 1 trial certainly support the continued clinical development of products originating from the Anticalin® platform.

The aforementioned data showing the ability to modify various lipocalins to be able to bind a wide variety of substrates, from small molecules up to large proteins, along with positive proof-of-concept clinical data demonstrating good drug-like properties, shows the potential for this groundbreaking platform. In essence, it appears that lipocalins could be modified to bind to any conceivable target, thus **WE BELIEVE** that Anticalins® represent the next step in targeted biologic binding molecules and the Anticalin® platform represents a valuable technology platform for Pieris to be able to exploit.

**PRS-080**

Pieris is developing PRS-080 as a treatment for functional iron deficiency in anemic patients with chronic kidney disease. PRS-080 targets hepcidin, a naturally occurring peptide that regulates iron levels in the bloodstream.

***…Anemia in Chronic Kidney Disease…***

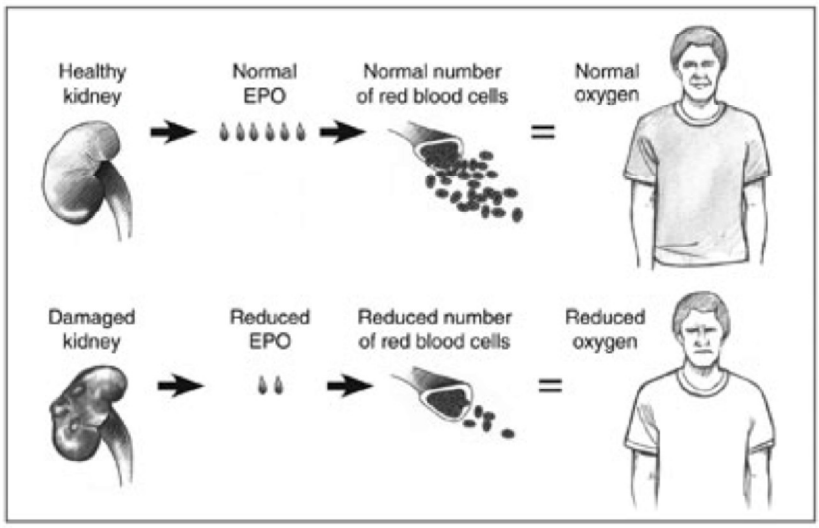
Chronic Kidney Disease (CKD) is a progressive loss of kidney function over a period of months or years. The National Kidney Foundation has divided CKD into five stages based upon the glomerular filtration rate (GFR). GFR is calculated based upon the amount of creatinine that the kidneys are able to filter compared to the amount of urine that is produced in a given amount of time and is expressed in terms of mL/min.

- **Stage 1** with normal or high GFR (GFR > 90 mL/min)
- **Stage 2** Mild CKD (GFR = 60-89 mL/min)
- **Stage 3A** Moderate CKD (GFR = 45-59 mL/min)
- **Stage 3B** Moderate CKD (GFR = 30-44 mL/min)
- **Stage 4** Severe CKD (GFR = 15-29 mL/min)
- **Stage 5** End Stage CKD (GFR <15 mL/min)

Dialysis is typically required once a patient's kidney function falls to 15% or less (Stage 5); however, it may be required before that if a patient experiences severe symptoms of CKD including fatigue, muscle cramps, nausea, or vomiting. Dialysis performs the functions of a normal, healthy kidney such as removing waste, salt, and extra water from the bloodstream as well as helping to regulate blood pressure.

A common side effect for those suffering from CKD is the development of anemia, which is a lack of red blood cells that results in a decreased capacity to carry oxygen in the bloodstream. There are a number of causes of anemia including a loss of blood (through trauma or internal bleeding), decreased red cell production (due to iron or vitamin B12 insufficiency), and increased red cell breakdown (due to genetic conditions or infections).

Anemia is a common condition of CKD, having first been linked to the disease more than 170 years ago (Bright, 1836). There are multiple factors that contribute to the development of anemia in CKD. One such factor is decreased erythropoiesis, which is the process by which new red blood cells are produced. It is controlled in part by the circulating cytokine erythropoietin (EPO), which is produced mainly in the kidneys. Most CKD patients have normal or slightly above normal levels of EPO, however their EPO levels are still considered inappropriately low relative to the degree of anemia because other anemic patients without CKD typically have 10-100 fold higher levels of EPO (McGonigle *et al*., 1984).




***Source:*** **NIDDK**

***…Treatment of Anemia in CKD…***

The current standard of care for anemic CKD patients is administration of iron and erythropoiesis-stimulating agents (ESAs), such as EPO, epoetin alfa, epoetin beta, and darbepoetin alfa. The introduction of recombinant EPO (and other ESAs), such as Amgen's Epogen® and Aranesp®, dramatically changed the treatment of CDK patients with anemia, as previous treatments consisted of blood transfusions that were associated with a number of adverse side effects such as secondary iron overload and infections (KDOQI, 2006).

A number of clinical studies have shown that administration of ESAs results in an improvement in symptoms of CKD patients along with an increase in erythropoiesis (Eschbach *et al*., 1987). However, a number of adverse side effects have been noted with ESA administration including hypertension, seizures, and clotting after dialysis. In addition, administration of ESAs does not reduce any anemia-related adverse events such as mortality, cardiac complications, or progression of kidney disease. In fact, administration of ESAs to reach a target hemoglobin level of >11 g/dl can increase the risk of death, cardiovascular complications, and stroke (Besarab *et al*., 1998).

The reason for the adverse events in anemic CKD patients after administration of ESAs appears to be due to the supraphysiologic doses of ESAs that result in off-target effects. In addition, 10-20% of anemic CKD patients are resistant to ESA treatment, thus alternative therapeutic options are necessary for this cohort of patients.

***…The Role of Iron in CKD Anemia…***

In addition to a deficiency in EPO, another factor that contributes to anemia in CKD is the altered homeostasis of iron levels. Iron is a vital element for many important biological reactions, including oxygen transport, cellular metabolism, and DNA synthesis. Excess iron is toxic, thus the level of iron available systemically and in cells must be tightly regulated (Britton *et al*., 1994). The human body has no effective means for excreting iron, thus the absorption of iron from dietary sources must be tightly regulated. Iron in the body is distributed between red blood cells, the liver, muscle cells, and macrophages of the reticuloendothelial system.

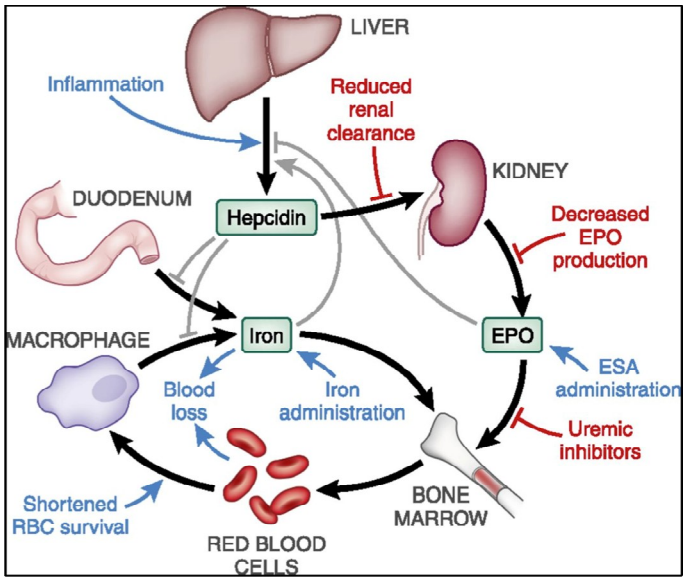
Most of the body's iron requirements are met through recycling of senescent red blood cells, which are phagocytosed by macrophages where it is stored until needed. Smaller amounts of iron are provided from dietary sources and liver stores. Loss of iron is unregulated, with most iron loss coming from skin and intestinal cell shedding and menstruation in reproductive-age women.

Hemodialysis patients typically have lower iron levels than healthy patients, as they lose more iron each year due to blood trapping in the dialysis apparatus and repeated phlebotomy (Malyszko *et al*., 2007). In addition, many CKD patients are on medications that increase erythropoiesis, which depletes iron reserves in the body. Lastly, CKD patients have a decreased ability to absorb dietary iron as clinical trials have shown that oral iron supplementation is no better than placebo in treating patients on hemodialysis (Macdougall *et al*., 1996). The end result is that many CKD patients have a true iron deficiency, which is manifested by low serum transferrin and low ferritin.

Some CKD patients have a functional iron deficiency (FID), which is characterized by low circulating iron levels that limits erythropoiesis even when these patients have sufficient iron stores in their body. These patients have low serum transferrin (a measure of circulating iron) and normal or high serum ferritin (a marker of body iron stores). FID is characteristic of a chronic inflammatory state, which in CKD patients may be due to an increased incidence of infections and/or the induction of inflammatory cytokines by the hemodialysis procedure.

Perhaps the most important finding regarding iron homeostasis in CKD patients was the discovery of the key iron regulatory hormone hepcidin (Krause *et al*., 2000; Park *et al*., 2001). Hepcidin is a 25 amino acid peptide produced in the liver and excreted into the bloodstream where it binds to ferroportin, an iron transporter found on duodenal enterocytes, reticuloendothelial macrophages, and hepatocytes (Donovan *et al*., 2006). Binding of hepcidin to ferroportin induces its internalization and degradation, resulting in iron accumulation in enterocytes, macrophages, and the liver. Hepcidin expression is induced by inflammatory cytokines, which is hypothesized to result in the sequestration of iron from invading pathogens (Babitt *et al*., 2010). This increased hepcidin expression results in many of the hallmarks of chronic diseases, such as CKD, including iron sequestration, hypoferremia, and anemia.

A number of studies have shown that hepcidin is elevated in CKD patients (Zaritsky *et al*., 2009). The hypotheses for this increase in hepcidin typically involve the increased inflammatory state of CKD patients as well as reduced renal clearance, since the kidneys remove hepcidin from the bloodstream. Taken together, **WE BELIEVE** that the data strongly suggest hepcidin is a novel pharmaceutical target for treating anemia in certain CKD patients, and that inhibiting hepcidin could result in increased utilization of iron stores in the body that would decrease anemia in this group of patients.

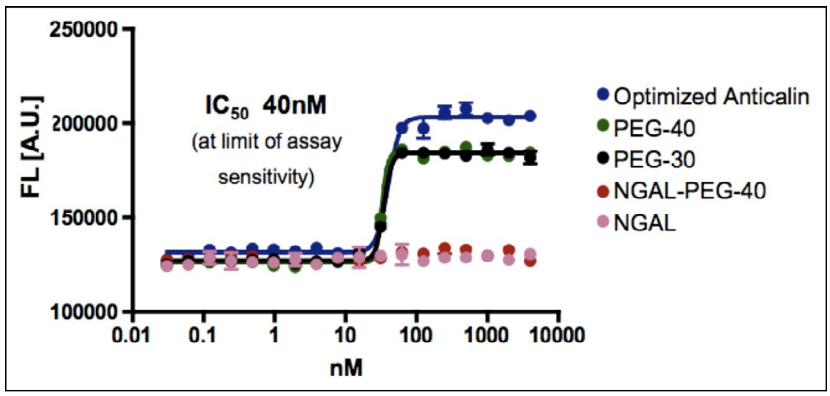



***Source*: Babitt *et al*., 2012**

***…PRS-080 Preclinical Data…***

PRS-080 was selected from a recombinant Anticalin® Lcn2 library based on its biophysical properties and ability to bind selectively and with high affinity to hepcidin. The protein binds to hepcidin with a Kd value of 50 pM while retaining no binding affinity for other proteins including hepcidin-20, enterobactin, human serum albumin, and VEGF.

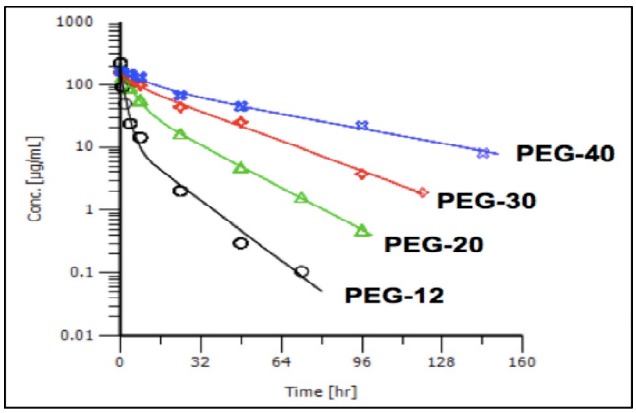
*In vitro* assays showed that PRS-080 inhibited ferroportin internalization and degradation. The assay utilized ferroportin that was covalently attached to green fluorescent protein (GFP), thus when ferroportin is on the cell surface the cells glow green and when ferroportin is internalized and degraded the cells no longer glow. This flurorescene can be quantified, and as shown in the following graphic the addition of PRS-080 (Optimized Anticalin®) to hepcidin prior to addition to the cells results in inhibition of hepcidin-induced internalization and degradation (represented by a higher fluorescence intensity toward the right of the graph).




*Source:* Babitt *et al.*, 2012

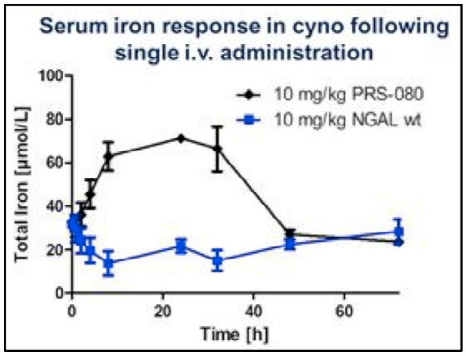
In the above graph, PEG-30 and PEG-40 refer to PRS-080 that has been covalently coupled with polyethylene glycol (PEG) of different molecular weights. This is necessary in order to increase the circulation half-life of Anticalins®, as due to their small size they are rapidly cleared via renal filtration. Importantly, pegylation of PRS-080 does not affect the binding characteristics, as the $IC_{50}$ value of pegylated PRS-080 is nearly identical to native PRS-080.

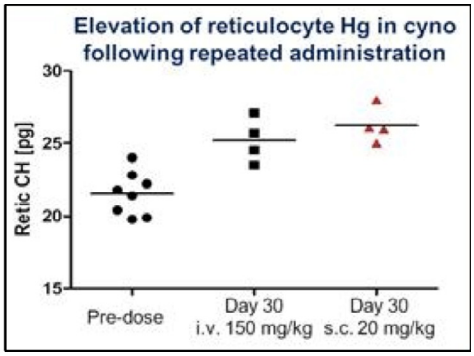
As mentioned previously, one of the advantages of Anticalins® compared to antibodies is the ability to optimize the pharmacokinetic parameters, which is done through the use of PEG of varying molecular weights. This property can be adjusted and matched with the target biology and intended clinical use. The clearance of different PEGylated versions of PRS-080 in rats is shown below. Pieris used this information to design PRS-080 to have an approximate 2-3 day half-life in humans by conjugating a linear PEG-30 to the drug candidate.




*Source:* Babitt *et al.*, 2012

The efficacy of PRS-080 was tested *in vivo* in cynomolgus monkeys since PRS-080 binds to cynomolgus hepcidin with the safe affinity as the human version. The data shows that total plasma iron increased after a single 10 mg/kg dose. In addition, after repeated doses there is an increase in reticulocyte hemoglobin, which is a precursor to erythropoiesis.




*Source:* Pieris Pharmaceuticals, Inc.

***…Clinical Development Plan for PRS-080…***

Based upon pharmacokinetic data generated in multiple species, Pieris has designed PRS-080 to have an approximate 2-3 day half-life in humans by conjugating a linear PEG-30 to the drug candidate. This again points to one of the clear advantages that Anticalins® have over monoclonal antibodies. A monoclonal antibody targeting hepcidin would likely have a half-life of at least two weeks. Pieris believes that a shorter half-life is appropriate for this condition as physiological levels of hepcidin are quite high in the target patient population, thus the high concentration would quickly saturate a hepcidin-binding drug. This means that more frequent dosing of drug is likely to be necessary to counteract the effect of the high concentration of hepcidin. The long half-life of a monoclonal antibody would likely lead to an accumulation of drug/antibody complex, something that can be avoided by an Anticalin® with a short half-life where the Anticalin®/hepcidin complex would be cleared more quickly from the body.

Pieris initiated a Phase 1 study of PRS-080 in healthy volunteers in December 2014 (NCT02340572). The trial is a placebo controlled, single ascending dose (0.2 to 40 mg/kg) evaluation of the safety and tolerability of PRS-080 in healthy male volunteers. The trial is being conducted in Germany and thus far four cohorts of patients have been dosed. The study is expected to enroll approximately 48 subjects, with 36 receiving PRS-080 and 12 receiving placebo. The primary outcome of the trial is the safety of PRS-080, with various secondary outcomes being investigated including the development of anti-drug antibodies and the changes in hepcidin concentration in the blood, total iron, transferrin saturation, and ferritin concentration.

The study is being funded in part through a $6 million grant from the European Commission. Patient enrollment should be completed by the middle of 2015, with topline data expected to be reported in the third quarter of 2015. Pieris has indicated that it has enough drug product available to move PRS-080 straight into a Phase 1b/2a clinical trial that should initiate in the fourth quarter of 2015. That study is likely to enroll anemic CKD patients and study the pharmacokinetics of a single dose. Data from that study should be available in the second half of 2016.

***…Other Treatments Under Development…***

A number of companies are developing treatments that target various aspects of hepcidin and iron metabolism.

**Lexaptepid**: Noxxon Pharma AG is developing lexaptepid pegol (NOX-H94), an anti-hepcidin spiegelmer, for the treatment of anemia of chronic disease. Spiegelmer's are RNA-like oligonucleotide therapeutics that bind to a target of interest to inhibit its activity. Lexaptepid was tested in a randomized, double blind, placebo controlled Phase 1 trial in 24 healthy males in which mild inflammation was induced before treatment with lexaptepid or placebo (van Eijk *et al*., 2014). Results showed that all subjects had a similar inflammatory response, however serum iron increased in lexaptepid treated patients while it decreased in placebo treated patients. The compound is currently in a Phase 1/2 clinical trial in dialysis patients with anemia that are functionally iron deficient.

**LY2787106**: This is a humanized monoclonal antibody being developed by Eli Lilly that binds to hepcidin and neutralizes its activity. A Phase 1 clinical trial of the drug in cancer patients with anemia was recently completed; however, results of the study have yet to be released.

**LY2928057**: This is a humanized monoclonal antibody being developed by Eli Lilly that binds to ferroportin and blocks the hepcidin/ferroportin interaction without inducing internalization of ferroportin. *In vitro* studies showed that the antibody does not inhibit iron efflux from ferroportin, and results in a dose dependent increase in serum iron levels (Witcher *et al*., 2013). The compound is currently in a Phase 1 clinical trial in hemodialysis patients.

**Hypoxia-inducible-factor prolyl hydroxylase (HIF-PH) inhibitors**: This class of compounds works by raising hemoglobin levels in a similar fashion to the natural effects of high altitude. By stabilizing HIF, through inhibition of HIF-PH, iron stores in the body are utilized to increase hemoglobin production.

- Roxadustat is being developed by Astellas Pharma and Fibrogen, Inc., with the compound currently in three Phase 3 trials in anemic dialysis patients. Phase 2 studies showed that the compound corrected and maintained hemoglobin levels in anemic CKD patients with no increase in blood pressure or requirement for additional iron infusions.

- AKB-6548 is being developed by Akebia Therapeutics, Inc. A Phase 2b trial showed that the compound significantly increased hemoglobin levels in a dose dependent manner compared to baseline. A Phase 3 clinical trial is expected to begin in 2015.

- GSK-1278863A is being developed by GlaxoSmithKline. The drug is currently in a Phase 2 trial in hemodialysis patients with anemia who are nonresponsive to EPO.

**Sotatercept**: This is a recombinant, chimeric protein consisting of the extracellular domain of human activin receptor type IIa and the Fc domain of human IgG1 being developed by Acceleron Pharma and Celgene Corp. It binds activin A and other members of the transforming growth factor-β superfamily of cytokines, thereby inhibiting their functional activity. The compound is currently in two clinical trials for the treatment of anemia in CKD patients.

***…Market Opportunity…***

Pieris is targeting anemic CKD patients who are on hemodialysis and are resistant to ESA and iron treatment (functionally iron deficient). There are an estimated 1.9 million patients worldwide who are on hemodialysis, with over 80% of them suffering from anemia (~1.6 million). Of these 1.6 million individuals, close to 25% are functionally iron deficient. These patients are easy to identify from a simple blood test, as they have low serum transferrin (a measure of circulating iron) and normal or high serum ferritin (a marker of body iron stores). There are close to 400,000 of these patients worldwide, with approximately 80,000 of them in the U.S. If we assume a yearly cost for PRS-080 between $5,000 and $10,000, this represents a sizeable market opportunity.

The company is also interested in examining potential applicability of PRS-080 in oncology related anemia, where the anemia is mediated by the inflammatory component of the cancer. The data garnered from the Phase 1 trial currently ongoing will help determine how much drug is necessary to see a response, which in turn will determine whether the drug can be delivered via subcutaneous administration. This mode of administration would greatly expand the potential patient population in the oncology setting.

**PRS-060**

PRS-060 is an Anticalin® drug candidate being developed for the treatment of asthma. It targets the interleukin 4 receptor (IL4Ra), a cell surface receptor that is expressed on immune cells in the lung epithelium and mucosal layer.

***…Background on Asthma…***

Asthma is a common, chronic lung disease that affects approximately 24 million individuals in the U.S. and approximately 195 million worldwide (World Health Organization). It is the most common chronic condition in children, with over 7 million suffering from the disease. In children, the disease most often begins presenting symptoms during the first five years of life, however an absolute diagnosis is typically not done until the child is six years of age or older due to a number of other conditions that children experience that mimic the symptoms of asthma. Asthma that develops in adults is known as adult onset asthma and is typically a more chronic condition, compared to the intermittent symptoms that children usually experience.

The inflammatory process plays a key role in the pathogenesis of asthma. The main feature that results in the typical symptoms of asthma (shortness of breath, wheezing, chest tightness, coughing) is smooth muscle contraction and inflammation that results in narrowing of the airway and obstruction (Barnes, 2008). Inflammation may be acute, sub-acute, or chronic with the presence of excess mucus and edema contributing to airway obstruction and bronchial reactivity. There are a number of recognized triggers that can exacerbate symptoms, such as allergic responses, exercise, and respiratory infections. The continued inflammatory response can potentially lead to structural changes in the lungs that include mucus hypersecretion and infiltration of inflammatory cells.

Clinically, asthma is described as being either intermittent or persistent, with symptoms then further classified according to severity (mild, moderate, or severe). While important for formulating a proper treatment modality, clinical classification does not address the underlying processes behind the disease.

***…Immunological Mediators of Asthma…***

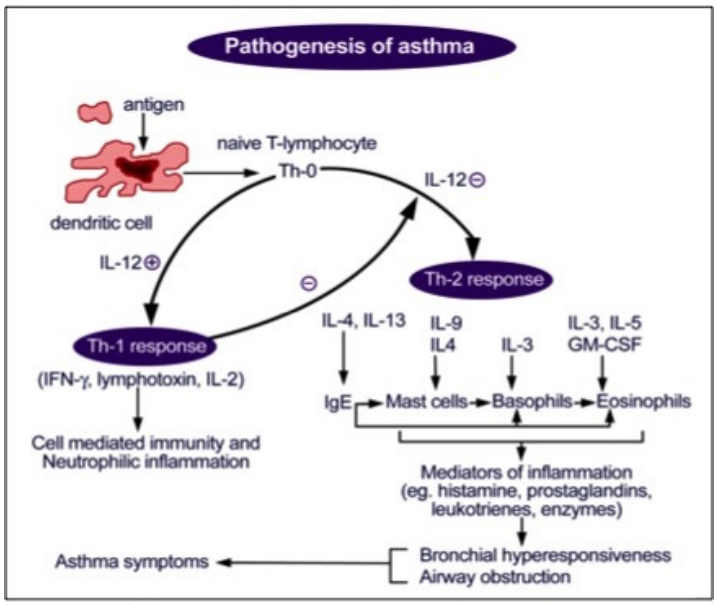
A host of different immunological mediators play a role in the development of asthma. These mediators work together to produce a pathological inflammatory response to allergens and other environmental triggers in genetically susceptible individuals (Vercelli, 2010). Pathologically, asthma is characterized by epithelial injury and infiltration by inflammatory cells, including eosinophils, lymphocytes, mast cells, and phagocytes (Holgate, 2011). The immunopathologic features are brought about by a variety of cytokines and other immunological effectors that promote a chronic inflammatory state.

- **Lymphokines**: These are immunomodulatory cytokines secreted by T cells and act as signaling molecules between cells. Included in this group are IL-4, IL-9, IL-13, and IL-17. IL-4 is responsible for increasing the production of immunoglobulin E (IgE) and increasing the production of Th2 cells. IL-5 production results in recruitment of eosinophils while IL-9 recruits mast cells. IL-13 increases the production of IgE (IL-4 and IL-13 both bind to the same cell surface receptor, IL4R). IL-17 recruits neutrophils and also increases production of cytokines by airway epithelial cells.

- **Proinflammatory cytokines**: The following cytokines are all produced by epithelial cells or macrophages and result in the promotion of a chronic inflammatory state: IL-6, IL-1β, TNF-α, and TSLP.

- **Chemokines**: These molecules are a family of small cytokines that act as attractants for leukocytes and include CCL2 and CCL5 (both attract T cells and dendritic cells), CCL11 (attracts eosinophils), and CXCL8 (attracts neutrophils).

- **Growth Factors**: These substances all promote cell survival once the cells have entered an area of inflammation and are mainly produced by surrounding epithelial cells. Included in this group are GC-CSF (increases growth of neutrophils and eosinophils), SCF (increases growth of mast cells), TGF-β (increases fibrosis), and VEGF (induces angiogenesis).



*Source*: Medscape

***…Treatment of Asthma…***

Currently there is no cure for asthma, thus the main goals of treatment are to prevent chronic and troublesome symptoms, reduce the use of rescue medications, maintain near normal breathing function, maintain normal activity level, and keep a patient's quality of life as high as possible.

There are two types of medicines that are employed to treat asthma: long-term control medicines (controllers) and quick relief medicines (rescue medicines). The long-term medicines work by preventing symptoms and treat the overall disease process and inflammation. The rescue medications work rapidly to open up narrowed airways when an acute asthma attack occurs or can be used as a prophylactic to prevent exercise induced asthma.

Quick Relief Medications

- ✓ Beta2-adrenergic agonists: These agents relieve bronchospasms by relaxing smooth muscles in the airways while also serving as bronchodilators. The most commonly used beta2-agonist is Albuterol sulfate (Proventil® HFA, Ventolin® HFA, ProAir® HFA) and is available in multiple forms (nebulizer, inhaler, oral solution). It is recommended for use as needed, however prolonged use may decrease its effectiveness over time. Other beta2-agonists include pirbuterol (Maxair® Autohaler) and levalbuterol (Xopenex®).

- ✓ Anticholinergic agent: Ipatropium (Atrovent®) may be added to beta2-agonist therapy for acute asthma exacerbations. This chemical is related to atropine and has anti-secretory properties, thus inhibiting secretions from glands lining the nasal mucosa.

- ✓ Oral corticosteroids: Oral steroids (prednisone, prednisolone, methylprednisolone) are used for short course therapy (3-10 days) to gain control of acute asthma episodes that do not respond to other medications. They can also be used for long-term control of severe persistent asthma, and can reverse the loss of sensitivity to beta2-agonist therapy.

Control Medications

- ✓ Inhaled corticosteroids: Inhaled steroids are the most potent anti-inflammatory agents as they are topically active and poorly absorbed, thus the least likely to cause adverse effects. These agents are not indicated to control acute asthma attacks. Examples of these medications include beclomethasone, fluticasone, budesonide, mometasone, and triamcinolone. Each of these medications decrease inflammation by inhibiting multiple inflammatory cell types and prevents the release of multiple inflammatory cytokines.

- ✓ Long-acting beta2-agonist/corticosteroid combinations: These inhaled combination products are utilized to decrease acute asthma exacerbations. Budesonide/formoterol (Symbicort®) works by relaxing the smooth muscles of the airways (formoterol) and decreasing the level of inflammation by inhibiting multiple types of inflammatory cells (budesonide). Additional medications in this class include mometasone/formoterol (Dulera®) and salmeterol/fluticasone (Advair®).

- ✓ Monoclonal antibody: Omalizumab (Xolair®) is a monoclonal antibody that binds selectively to IgE on the surface of mast cells and basophils. It reduces mediator release, thus preventing allergic response and is indicated for patients with moderate to severe asthma who have seasonal allergies and who do not respond to inhaled corticosteroids. Xolair® was tested in three Phase 3 clinical trials, however only two of those trials showed a reduction in the number of asthma exacerbations in Xolair® treated patients compared to placebo. In 2014, sales of Xolair® generated $1.5 billion in worldwide revenues.

***…The Role of T-Helper 2 Lymphocytes in Asthma…***

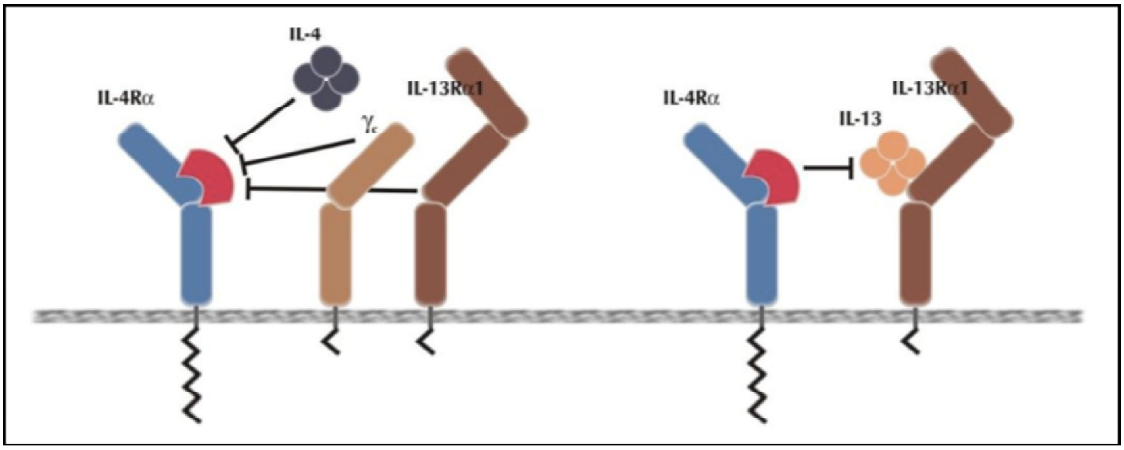
The development of certain types of T-cells plays a central role in asthma. These cells are produced after inhaled allergens are taken up by antigen presenting cells (dendritic cells) and travel to lymph nodes to interact with various immune cells, including naïve T-cells. Dendritic cells are capable of producing an assortment of immunological mediators and can also control tolerance or promote an immune response (Lambrecht *et al*., 2010). In addition, dendritic cells can control the type of immune response by promoting the differentiation of T-cells into various types of helper T-cells with varying functions. The differentiation of T-cells into T-helper 2 (Th2)-specific helper cells results in the formation of an allergic reaction and the production of pro-inflammatory cytokines including IL-4, IL-5, and IL-13 (Levine *et al*., 2010).

Another important asthma mediator is IgE (target of Xolair®), which is produced by B cells after stimulation with IL-4 and IL-13. IgE is secreted into the circulation, where it binds with mast cells and basophils. Upon the next encounter with allergen, the antigen is bound by IgE attached to the surface of mast cells and basophils, which in turn results in the production of histamine, leukotrines, and cytokines. This reaction happens very quickly (within minutes), and forms the basis for hypersensitivity reactions.

IL-13 has recently emerged as a potential therapeutic target for treating asthma as it is involved in airway hyper-responsiveness and airway structure, including the formation of fibrosis, airway smooth muscle proliferation, and goblet cell hyperplasia (Rael *et al*., 2011). IL-13 signaling occurs through a shared receptor with IL-4, the IL4Ra receptor.

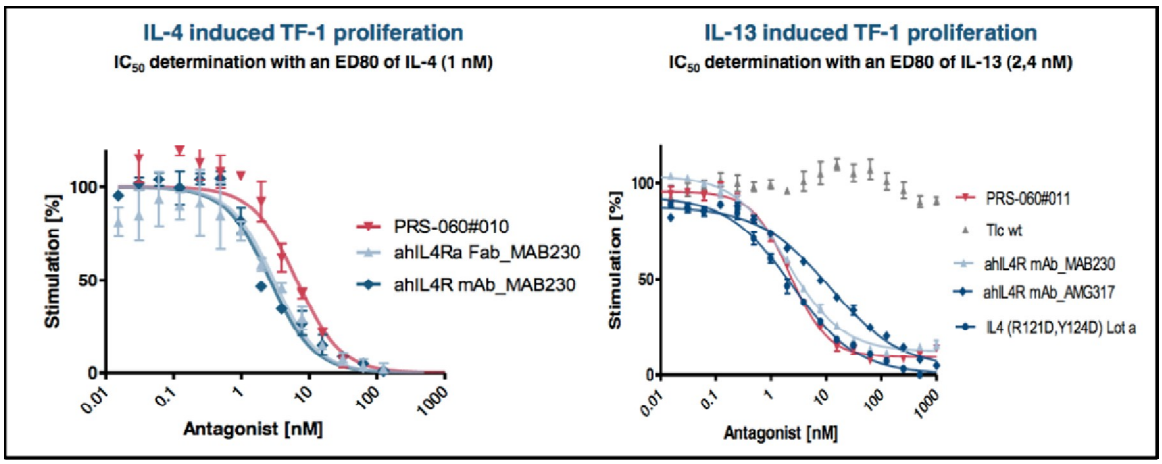
***…PRS-060 for the Treatment of Asthma…***

PRS-060 is derived from human tear lipocalin (Lcn1) and has very high affinity for IL4Ra (Kd ~ 20 pM) and does not bind to the related cytokine receptors IL6R, IL18R, and IL23R. By targeting IL4Ra, PRS-060 inhibits binding of both IL-4 and IL-13, as depicted in the following graphic.




***Source*: Hohlbaum *et al.*, 2011**

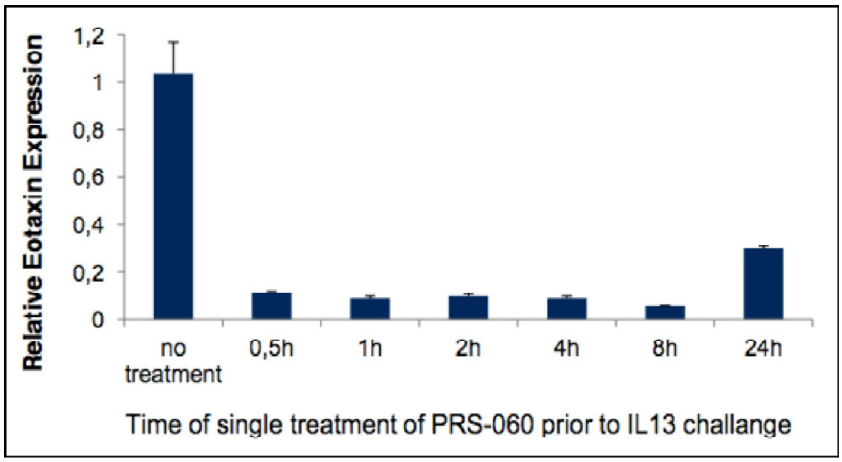
The inhibition of IL-4 and IL-13 binding by PRS-060 was shown in a series of preclinical experiments involving erythroleukemic (TF-1) cells that proliferate upon stimulation with a wide range of cytokines. The cells were preincubated for 30 min with PRS-060 or other IL4Ra antagonists prior to stimulation with IL-4 (left) or IL-13 (right). Cell proliferation was measured five days after treatment and graphed as a function of increasing amounts of IL4Ra antagonist. The results show that PRS-060 is able to inhibit both IL-4 and IL-13 dependent proliferation.




***Source*: Hohlbaum *et al.*, 2011**

One of the advantages that Anticalins® have over monoclonal antibodies is their mode of delivery can be modified depending upon the therapeutic target. In the case of PRS-060, which is targeting IL4Ra expression in the lung, inhalation delivery would be optimal as it is likely to decrease the systemic side effects that could arise from a chronic, systemic Th2-targeting medication. Pieris has conducted inhalation studies with PRS-060 in mice and determined that systemic concentration of PRS-060 is minimal when dosed by inhalation. Since most other asthma medications are dosed by inhalation, the ability to dose PRS-060 by inhalation represents a more convenient dosing regimen than monoclonal antibody treatments, which must be administered by injection at a doctor's office or other medical clinic.

Efficacy of inhaled PRS-060 is shown in the following graphic, in which eotaxin expression (a marker of airway inflammation) was induced by administration of IL-13 to the lungs of mice after pre-treatment with inhaled PRS-060. The data shows that eotaxin expression is inhibited for up to 24 hours following a single inhaled dose of PRS-060.




*Source*: Pieris Pharmaceuticals, Inc.

***…Clinical Development Plan for PRS-060…***

Currently, PRS-060 is still in preclinical development with the final IND enabling studies being conducted in 2015 in preparation for an IND filing in 2016. In support of these studies, Pieris recently announced the receipt of a research grant in collaboration with the University of Melbourne to advance PRS-060 through preclinical studies for inhaled delivery to treat asthmatics.

The current clinical plan calls for Pieris to test PRS-060 in healthy volunteers and then in patients with severe asthma. The goal of these pilot studies is two-fold: 1) the company could establish proof-of-concept for inhaled Anticalins®, which would provide evidence for an additional mode of administration for the company's products outside of subcutaneous and intravenous injections, the way that almost all biological therapies are administered now, and 2) establish that dosing of inhaled Anticalins® is practical and that the compound has the requisite pharmacokinetic/pharmacodynamic profile to be utilized as a therapeutic capable of positively impacting patients symptoms. We estimate that Phase 1 data for PRS-060 could be available in 2017.

***…Other Asthma Treatments Under Development…***

A number of biological agents have been developed against cytokines thought to play a role in the pathogenesis of asthma, including monoclonal antibodies directed against IL-5, IL-4, and IL-13.

- **Mepolizumab**: This is a humanized IgG1 monoclonal antibody that binds to IL-5 and prevents it from binding to its receptor on the surface of eosinophils. Prevention of binding is a way to reduce blood, tissue, and sputum eosinophil levels. In November 2014, GlaxoSmithKline announced the submission of regulatory filings in both the U.S. and E.U. for mepolizumab as a maintenance treatment for patients with severe eosinophilic asthma. The submission was supported by two Phase 3 studies (MENSA and SiRIUS), which both reported a reduction in the rate of asthma exacerbations in mepolizumab treated patients compared to those treated with placebo (Ortega *et al*., 2014; Bel *et al*., 2014). In addition, both studies reported that the safety profile of mepolizumab was similar to that of placebo.

- **Dupilumab**: This is a fully human monoclonal antibody that targets IL4Ra and prevents the binding of both IL-4 and IL-13 to the receptor. Two separate studies have shown that dupilumab treatment results in improved lung function and reduced exacerbations when administered together with the standard of care. Importantly, in the second trial, patients with both high and low eosinophil levels were evaluated, and the compound was equally effective in both cohorts suggesting that pre-selecting patients with high eosinophils may not be necessary for therapies that target IL4Ra. Regeneron Pharmaceuticals and Sanofi are developing the compound and the companies have indicated that Phase 3 trials of the drug will begin in patients with moderate to severe asthma in 2015. While targeting the same receptor as PRS-060, dupilumab is administered via subcutaneous injection.

- **Lebrikizumab**: This is a humanized monoclonal antibody that binds to IL-13 and prevents it from binding to the IL-13 receptor, which in turn binds to IL4Ra. The compound has been studied in two Phase 2b studies (LUTE and VERSE), which both showed that lebrikizumab is most effective in asthma patients who have a high blood level of the biomarker periostin, a protein shown to play a role in IL-13 mediated asthma. The drug is being developed by Roche and is currently being evaluated in two Phase 3 clinical trials (LAVOLTA I and LAVOLTA II) in patients with severe uncontrolled asthma.

***…Market Opportunity in Asthma...***

Of the 195 million individuals suffering from asthma in major developed markets worldwide, 25 million are in the U.S. Approximately 10% of asthma patients can be described as having severe or uncontrolled asthma. Of the patients with severe or uncontrolled asthma, approximately 50% of those have Th2-mediated disease. This is the patient population that Pieris will be targeting, as PRS-060 targets IL-4 and IL-13 initiated mechanisms, both of which arise from Th2 cells. This puts the worldwide target patient population at approximately 9.8 million, with approximately 1.3 million of those in the U.S.

While Pieris will initially be targeting the patient population mentioned above, the data that has been generated using dupilumab suggests that all patients with severe or uncontrolled asthma could respond to a therapy that targets IL4Ra; however, whether this will be the case with PRS-060 remains to be seen based upon clinical results. Of course, not limiting the patient pool to those with increased Th2 levels would greatly expand the potential market size.

**PRS-300 Series/PRS-110**

Pieris is developing a series of oncology therapeutics both independently and through various collaborations. The PRS-300 series of Anticalins® are designed to target “checkpoint proteins” and enhance the immune systems innate antitumor response, while PRS-110 is being developed in collaboration with Zydus Pharmaceuticals and is targeting MET, a cell surface receptor implicated in a number of different cancers.

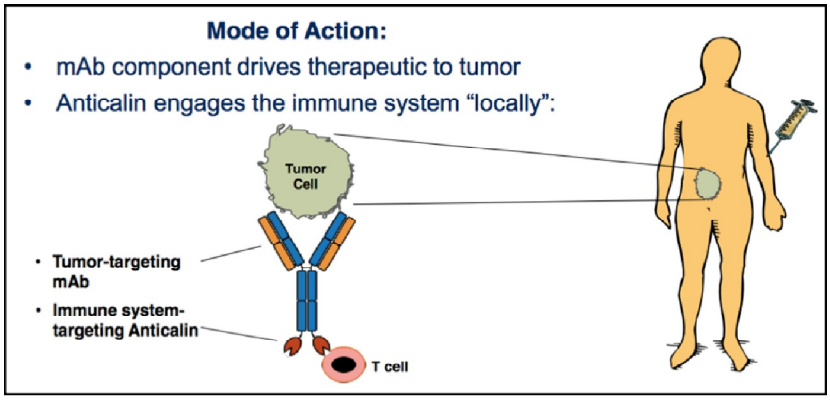
***…Immune Checkpoint Proteins…***

Immune checkpoints are a series of regulatory signaling pathways that are integral to the immune system and provide a means of maintaining self-tolerance and modulating the size and scope of an immune response. Recent research has shown that tumors many times develop means of exploiting these pathways to evade detection by the immune system. Many of these checkpoint pathways are initiated through ligand/receptor interactions, thus making them amenable to blockade with monoclonal antibodies or other binding moiety’s such as Anticalins®. Programmed cell death protein 1 (PD1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) are two checkpoint receptors that have been the most extensively studied in the context of clinical immunotherapy. Pieris has multiple checkpoint inhibitor programs and the company has disclosed an anti-CTLA4 Anticalin® under development. Other, undisclosed programs relate to multispecific proteins targeting a differentially expressed tumor target with one moiety and a costimulatory checkpoint molecule with another moiety.

CTLA4 Specific Anticalin®

CTLA4 is a cell surface receptor expressed on T-cells where it primarily regulates the amplitude of the early stages of T cell activation. After antigen-dependent activation, CTLA4 competes with the co-stimulatory molecule CD28 to bind to CD80 and CD82, thus attenuating the T-cell (Linsley *et al*., 1994). The critical role for CTLA4 in keeping the immune response in check is exhibited by the lethal systemic immune hyperactivation of *Ctla4* knockout mice (Tivol *et al*., 1995).

Pieris has reported the development of a CTLA4 targeting Anticalin® protein that was derived from a human lipocalin 2 library (Schönfeld *et al*., 2009). The company is planning to develop Anticalins® that bind checkpoint inhibitors as additions to monoclonal antibodies, such that the monoclonal antibody will bind a tumor-specific target and the Anticalin® will then engage the immune system cells in the tumor microenvironment. This approach has the potential to limit “off tumor” side effects as the engagement of the immune system should only occur in close proximity to the tumor.



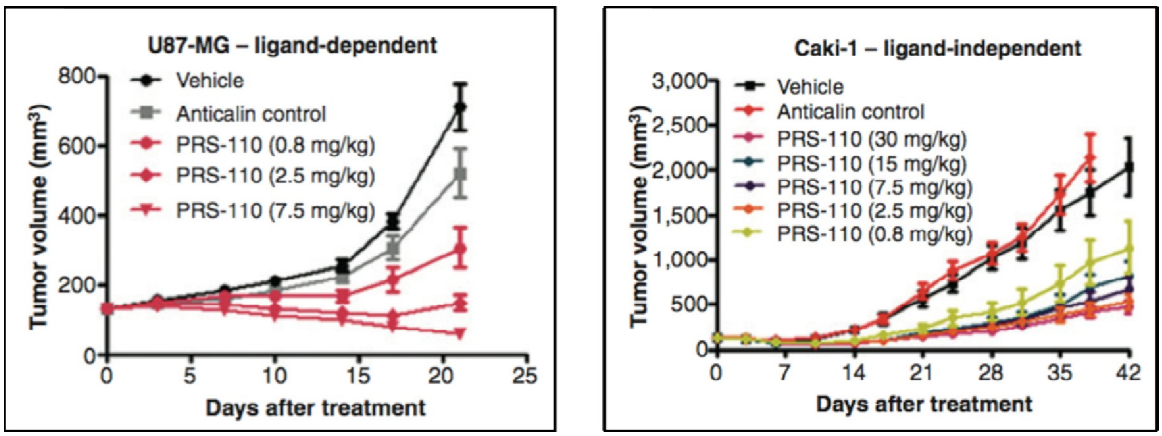

***Source*: Peiris Pharmaceuticals, Inc.**

***...MET…***

MET is a receptor tyrosine kinase with one known ligand, the hepatocyte growth factor (HGF). Binding of HGF to MET initiates a signaling cascade that controls different proliferative, migratory, and survival pathways implicated in tumor development (Comoglio *et al*., 2008). There are numerous reports showing a link between MET pathway stimulation and poor patient prognosis in a variety of tumor types (Garcia *et al*., 2007). In addition to stimulation by HGF, MET can also activate signaling pathways in a ligand-independent manner through gene amplification or mutation (Dulak *et al*., 2011). Thus, an effective treatment targeting MET must be able to inhibit both ligand-dependent and ligand-independent signaling.

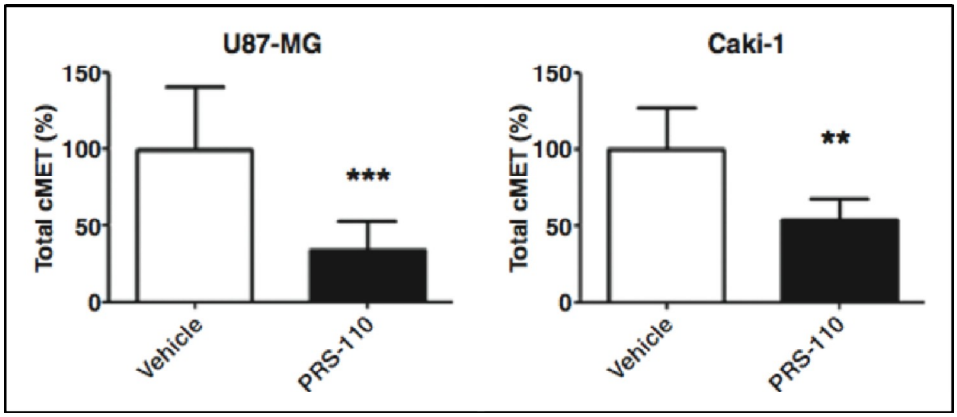
PRS-110 Preclinical Data

The ability of PRS-110 to limit ligand-dependent tumor growth was tested using the U87-MG xenograft mouse model. This model was chosen due to the expression of both MET and HGF in these cells as well as the known dependence upon HGF induced signaling for tumor growth. Tumor bearing mice were treated with varying doses of PRS-110 or placebo, and the results (bottom left) show a dose-dependent decrease in mean tumor volume, with treatment of 7.5 mg/kg resulting in tumor regression. The ability of PRS-110 to limit ligand-independent tumor growth was tested using the Caki-1 renal cell carcinoma xenograft mouse model. These cells do not express HGF but have activated MET signaling. Treatment of mice with PRS-110 after the tumors had reached a volume of 100 to 150 $mm^3$ resulted in a statistically significant reduction in tumor volume compared to mice treated with placebo (bottom right).




***Source*: Olwell *et al*., 2013**

Interestingly, when the levels of MET protein were analyzed following treatment it was shown that in both models the amount of MET protein was significantly decreased in PRS-110 treated samples compared to placebo treated samples, meaning that binding of PRS-110 had induced receptor internalization and degradation, a potentially novel mechanism of action compared to other MET-targeting therapeutics.




*Source*: Olwell *et al.*, 2013

**Partnerships**

Pieris has entered into a number of licensing, research, and development collaborations, including with Allergan, Inc. (AGN), Sanofi (SNY), and Daiichi Sankyo. In addition, the company has also established partnerships with Zydus Pharmaceuticals and Stelis Biopharma, two companies with expertise in clinical development, regulatory affairs, and biologics manufacturing.

- ✓ **Allergan**: In August 2009, Pieris entered into an agreement with Allergan, Inc. for use of the Anticalin® platform for the development of drug candidates against an undisclosed target. The agreement called for Pieris to supply drug candidates for the treatment of ocular diseases, with Allergan being responsible for the further development and commercialization of the candidates. Upon entering the agreement, Pieris received an upfront payment of $10 million with an additional $13 million due upon the achievement of various milestones. The company is not entitled to royalties from the sale of products originating under this agreement.

- ✓ **Sanofi**: In September 2010, Pieris entered into a collaboration and license agreement with Sanofi, which was subsequently amended in 2013, whereby Pieris is responsible for identifying drug candidates for undisclosed targets, with further development and commercialization activities conducted by Sanofi. Pieris handed over a drug candidate to Sanofi for further development in the fourth quarter of 2014. Upon signing the agreement, Pieris received an upfront payment of $4.2 million along with research funding with up to $31.5 million available upon the achievement of development milestones and up to $21.8 million available upon the achievement of commercialization milestones for the product. In addition, royalties of mid- to mid-high single digits are payable based upon the sale of products originating from this collaboration.

- ✓ **Daiichi Sankyo**: In May 2011, Pieris entered into a research and technology licensing agreement with Daiichi Sankyo whereby Pieris utilized the Anticalin® platform to discover novel drug candidates against two undisclosed targets chosen by Daiichi Sankyo. The two drug candidates have since been turned over to Daiichi Sankyo based upon the achievement of preclinical development milestones. Upon signing the collaboration agreement Pieris received $8.7 million and research funding with a total of approximately $242 million in potential milestone payments. In addition, Pieris will receive mid- to mid-high single digit royalties on the sale of products originating from this agreement.

- ✓ **Zydus**: In October 2013, Pieris entered into a development and license agreement with Zydus whereby Zydus will take the lead in advancing certain products through preclinical and clinical proof of concept development, including expenses related to drug manufacturing. Zydus retains the right to commercialize the products in India and other developing countries with Pieris retaining the rights to commercialize the products in developed markets. Each company will pay the other low-single digit royalties on the sale of products in the other companies respective regions.

- ✓ **Stelis**: In November 2013, Pieris entered into a joint development and license agreement with Stelis for the development of certain Anticalin® products initially focusing on the treatment and prevention of ophthalmology-related diseases. The agreement calls for Pieris to supply certain assets to the project while Stelis is responsible for establishing a production process for preclinical and clinical supplies of product and to perform preclinical and early clinical studies.

## PROJECTED FINANCIALS

**Pieris Pharmaceuticals, Inc.**
Income Statement

| Pieris Pharma | 2014 A | Q1 A | Q2 E | Q3 E | Q4 E | 2015 E | 2016 E | 2017 E |
|---|---|---|---|---|---|---|---|---|
| **PRS-080** | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| **PRS-060** | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| **PRS-343** | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| **PRS-050** | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| **PRS-110** | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| **PRS-NN** | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| **PRS-SNY** | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| **Licensing & Collaborative** | **$5.4** | **$0.2** | **$0.3** | **$0.3** | **$0.3** | **$1.1** | **$7.0** | **$12.0** |
| *YOY Growth* | - | - | - | - | - | - | - | - |
| **Total Revenues** | **$5.4** | **$0.2** | **$0.3** | **$0.3** | **$0.3** | **$1.1** | **$7.0** | **$12.0** |
| CoGS | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *Product Gross Margin* | - | - | - | - | - | - | - | - |
| R&D Expense | $5.6 | $1.5 | $1.8 | $2.0 | $2.4 | $7.7 | $16.0 | $19.0 |
| SG&A Expense | $7.0 | $2.4 | $2.8 | $3.0 | $3.3 | $11.5 | $15.0 | $20.0 |
| Other Expenses | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| Operating Income | ($7.2) | ($3.7) | ($4.3) | ($4.7) | ($5.4) | ($18.1) | ($24.0) | ($27.0) |
| *Operating Margin* | *-134.2%* | *-1700.8%* | *-1433.3%* | *-1566.7%* | *-1800.0%* | *-1619.6%* | *-342.9%* | *-225.0%* |
| Total Other Income | ($2.7) | ($0.0) | ($0.4) | ($0.4) | ($0.5) | ($1.3) | ($2.0) | ($2.5) |
| Pre-Tax Income | ($9.8) | ($3.7) | ($4.7) | ($5.1) | ($5.9) | ($19.4) | ($26.0) | ($29.5) |
| Taxes & Other | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *100%* |
| Net Income | ($9.9) | ($3.7) | ($4.7) | ($5.1) | ($5.9) | ($19.4) | ($26.0) | ($29.5) |
| | | | | | | | | |
| **Reported EPS** | **($0.71)** | **($0.13)** | **($0.15)** | **($0.16)** | **($0.17)** | **($0.61)** | **($0.65)** | **($0.59)** |
| *YOY Growth* | - | | | | | | - | - |
| Shares Outstanding | 13.9 | 29.3 | 31.0 | 32.0 | 34.0 | 31.6 | 40.0 | 50.0 |

*Source: Zacks Investment Research, Inc.* *Jason Napodano, CFA*

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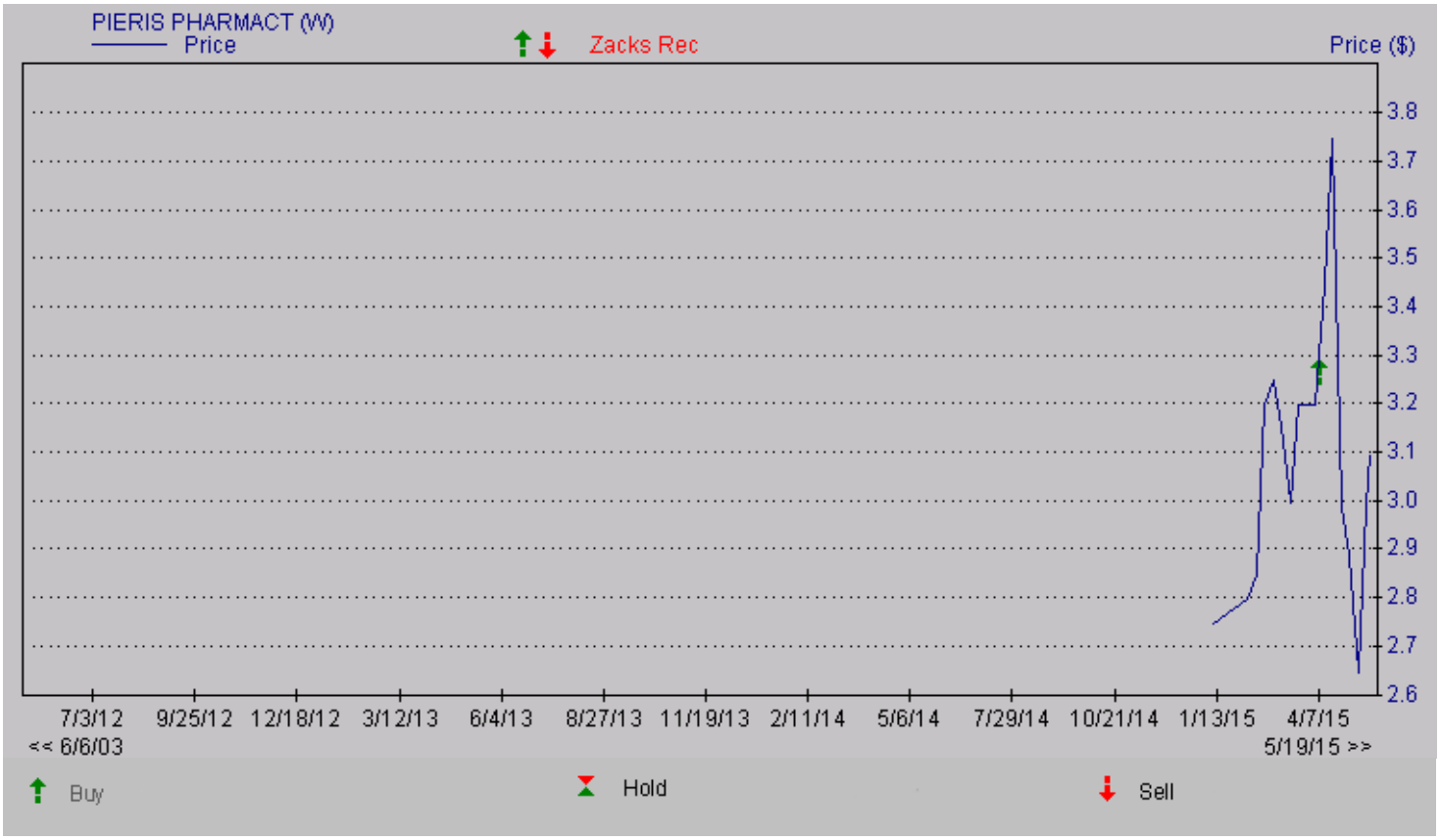


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