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Designing a new class of Biotherapeutics to Improve Patient Experience and Access

Dr. Christopher Pirie
Chief Executive Officer & Co-Founder

Virvio
www.virvio.com

Interview conducted by:
Lynn Fosse, Senior Editor
CEOCFO Magazine

CEOCFO: ***Dr. Pirie, what is the idea behind Virvio?***
Dr. Pirie: Virvio is spun out of the University of Washington based on technology from the laboratory of Professor David Baker, which is built upon the Rosetta software package for computational protein design. In the past year or two we have developed the capability to design *de novo* synthetic mini-proteins capable of high affinity, high specificity interactions with drug targets.

CEOCFO: ***How does that differ from currently recognized drugs?***
Dr. Pirie: The products of our process are small, hyper-stable alternatives to traditional biotherapeutics or monoclonal antibodies, such as Herceptin® (trastuzumab) and Humira® (adalimumab). These are drugs that bind to targets in our bodies that elicit pharmacological affects. However, what we are making is cheaper to produce, more potent, and easier to administer and distribute.

CEOCFO: ***Would you explain how the drug works in the body?***
Dr. Pirie: The drug target interactions in many cases are identical to those of known neutralizing antibodies, as we call them. These are antibodies that bind to a particular drug target and block a protein, protein interaction or block a mechanical transformation and thereby elicit an effect. The primary difference is that the way that monoclonal antibodies are traditionally administered is by injection or infusion. The extreme thermals and protolytic stability or our proteins and their extremely small size allows them to be formulated and administered by, say, inhalation, as was recently demonstrated in our work on influenza that was published in *Nature* last year and other diseases, such as for the GI where we can formulate for oral administration or dermatological disease with topical administration.

CEOCFO: ***Has the medical community been looking for a better way or is it just the natural progression will lead people towards what you can do better?***
Dr. Pirie: The short answer is yes. The Holy Grail with administration is oral. Most patients prefer to have a pill they take in the morning or at night and that is the end of it. Certainly, in some parts of the country and parts of the world, access to clinicians and healthcare facilities is limited. A classic example is insulin. There has been a long effort to develop oral insulin and inhaled insulin as alternative means to the traditional needle injection.

CEOCFO: ***Where are you in development today?***
Dr. Pirie: I mentioned the proof of concept work in influenza. There is also, as described in that same work, a binder against the botulism neurotoxin. Since then we have gone on to develop candidates with similar affinities and specificities to more than a half a dozen different drug targets, as yet unpublished. At the same time the company is attempting to develop relationships in the pharmaceutical industry and partnerships around using this design technology to create further candidates across diverse disease areas. In the near term our focus is on respiratory diseases like influenza,

idiopathic pulmonary fibrosis, and asthma, for which there are early stage candidates in each area and then, as I mentioned, gastrointestinal and dermatological diseases down the road.

CEOCFO: ***How have you decided what to work on first or in what order?***
Dr. Pirie: Some of that is historical. Some of the first *de novo* interfaces designs that were done in the Baker Lab were based on known, bodily-neutralizing antibodies against influenza. This is a common theme in the development of the technology wherein we rely upon known structural information about an interaction between an antibody and its drug target. From there we design our synthetic mini-proteins. We have gone further to do, what we call, one-sided design, where we only know the drug structure of the target with no known neutralizing antibody interactions. The trajectory of our development efforts is driven, in part of course, by technological feasibility with the available structural information about a drug target or neutralizing interactions as well as the attractiveness and opportunities in the market thereof.

CEOCFO: ***What have you learned through your early testing that surprised you?***
Dr. Pirie: We had a great appreciation, and certainly the industry has had a great appreciation, for the powers of the Rosetta software to do *de novo* structure prediction for many, many years. This has really been the ultimate tool for taking a protein sequence and understanding its structure. Only in the past couple of years have we really come to capture its ability to flip that problem on its head and ask, "Given a desired structure or function what are the possible primary sequences that achieve that structure and function?" When I joined this team and this effort, this was merely an idea. Over the course of the past couple of years even I have been surprised by the robustness with which this is possible using Rosetta. I mentioned the publication in Nature; there was also a publication a month or two before in Science that described the power of the software to design, from scratch, sequences that have never before been seen in nature that fold with incredible fidelity to high thermal stability and proteolytic resistance. The thing that surprised me the most is the robustness of the design process that I think quite dramatically outperforms the traditional selection techniques of old-school protein engineers like myself.

"We can design hundreds and hundreds of different folding architectures, not to mention the almost innumerable sequences that achieve them, that we can then use to address different drug epitope shapes."- Dr. Christopher Pirie

CEOCFO: ***Is there much research in this area? What is the competitive landscape?***
Dr. Pirie: We look at it in two different ways. There are a number of companies developing pharmaceutical or biopharmaceutical assets in the non-antibody scaffold space, as we call it. Most, if not all of these, fall into the category of what we call first generation scaffolds. These are structures taken from nature and then diversified to create libraries of variants from which you screen naively to find a lead. That is a very traditional protein engineering approach, using proteins from nature that fundamentally were not evolved to behave like drugs. They evolved for some other function and we are simply co-opting them to try and develop them as drugs. In the other dimension there is computational design, increasing computing power and sophisticated modeling software continues to influence the healthcare space all the way from clinical trials down to drug discovery. In the drug discovery space you have the full spectrum of companies like Atomwise or Protagonist Therapeutics who are using compute and design to generate small molecule drugs or small peptide drugs all the way to companies like Visterra that use compute to redesign the CDR loops of full monoclonal antibodies. Virvio and our technology kind of fit somewhere in the middle. We are *de novo* designing fully synthetic mini-proteins that are in the forty to fifty amino acid range that are highly structured and highly stabilized. This is really kind of a unique offering in two ways. One is the size of those proteins and their fully synthetic design. There is really no one else capable of this level of synthetic architecture. The other is the diversity or structural space that we access. In this size range we can design hundreds and hundreds of different folding architectures, not to mention the almost innumerable sequences that achieve them, that we can then use to address different drug epitope shapes.

CEOCFO: ***Where does your business experience come into play? How has it been helpful? How will it be helpful as you get further along with Virvio?***
Dr. Pirie: My experience with my first company, Manus Biosynthesis, was really pointed towards early stage customer engagement. This goes all the way back to my time at MIT, the Sloan entrepreneurship mantra of early stage customer engagement; very lean methodologies. With Virvio, part of our vision is not to grow and become yet another grand biotechnology company running clinical trials, but rather to leverage the powers of this technology to maximize its impact across disease targets and indications. The best way for us to be able to do that is to engage with biopharmaceutical and larger pharmaceutical industry customers at earlier stages, to collaborate with them utilizing their expertise in a particular

disease area and around particular disease targets and to help generate new assets for them to develop in the clinic and eventually take to market.

CEOCFO: ***Lay out the next year or so. What will you be doing?***
Dr. Pirie: For us, the technology is at a very exciting stage where, as I mentioned, we have some candidates in development across a couple of different respiratory disease areas. We are at a very critical junction where are answering one of most important questions for any new protein therapeutic modality, which is immunogenicity. We are investigating this using different animal models and human primary cell immunogenicity. We are also testing different manufacturing methods. These molecules, given their unique folding characteristics, have the potential to be chemically synthesized, rather than produced recombinantly, like traditional biotherapeutics. Therefore, we are continuing to push on both of these fronts as well as the preclinical development and toxicology around a specific asset as we move all of them towards IND models.

CEOCFO: ***Address our readers in the investment and health communities. How does Virvio standout?***
Dr. Pirie: We are amongst a set of the latest manifestations of how computational technologies are influencing the healthcare space broadly. I mentioned already some of the other folks working in this area in the drug discovery space. Our technology represents a unique opportunity to make a meaningful difference in the drug discovery process by pushing a new design paradigm and in the lives of patients as we ease administration and access.

CEOCFO: ***Is there anything that people might miss or that is under the surface when looking at Virvio?***
Dr. Pirie: When we talk about drug discovery there are all manner of tools and modalities out there today because of the incredible work of many molecular biologists and chemists who have come before. However, what I think is really important from the way our company looks at new drug discovery and I think that the industry is pivoting towards looking at drug discovery is to really think about the patient experience. For so long, the challenges have resided largely in how we discover these new molecular entities. I believe we are now at a juncture where the process of discovery is beginning to be so robust that we can extend or challenge ourselves further to ask, not just how do I generate a protein that interacts with the drug target with high affinity and specificity, but how can I further tailor that protein to enable subsequent formulation for administration and distribution, such that I am directly impacting the patient experience in a positive way. We want to help empower patients to really change their mode of disease management by applying our technology to important diseases.