PHYLOGICA

BREAKTHROUGH PEPTIDE THERAPEUTICS

Hot Copper – Submitted Questions

Science focused

1. Username: HESKUMDAI

Excellent. Thank you.
Can I kick it off with a request that you comment / expand on the excellent post by Hottod https://hotcopper.com.au/posts/31537816/single that outlined the opportunity with CRISPr and challenges that PYC could help resolve?

Answer from Rob Hayes, CSO

The CRISPr/Cas9 field is evolving one. Until March this year, much of the genome was still inaccessible to CRISPr/Cas9 because of DNA sequence requirements. However, David Liu and his team at the Broad Institute have now modified the Cas9 enzyme to remove much of that limitation. The same rapid progress is seen in the delivery of CRISPr/Cas9 into cells. Originally, the process was very inefficient, but the development of viral vectors, nanoparticles, and microinjection techniques are changing that.

So, what does Phylogica's FPP technology bring to the table, and why are CRISPr/Cas9 companies talking to us? It's because, despite progress in this field, the transformation of cells is still complicated, especially if you want to make a lot of changes in the genome. In contrast, attaching an FPP onto Cas9 is an easy process that requires no changes in manufacturing or processing. It's easy. There's no complex chemistry, and unlike nanoparticles or viruses, it's not expensive or difficult, and there are no threats of immunogenicity or toxicity. Indeed, every one of Phylogica's Cas9-FPP molecules comes with its very own built-in delivery system.

But the real advantage of our technology is cell-specificity. We showed in earlier work that we can find FPPs that are specific for certain cells types (e.g., brain endothelial cells). The delivery of CRIPSPr/Cas9 to specific cell types and tissues is a clear and valuable advantage that Phylogica's FPPs can provide.

2. Username: TONYINDO

Hi Phylogica, Quick question.... On the Operational Update Investor Call dated February 13, 2018, Dr. Robert Hayes mentioned that the challenge with regards to CRISPR / CAS9 has always been getting these large enzymes into cells and how inefficient the current delivery system is with regards to CRISPR / CAS9, with delivery and efficiency only at around 1% in many cells.

This recent in vitro CRE experiment has shown that not only successful delivery of CRE inside cells, but also being able do it in a cell specific manner. This presents a significant potential opportunity. What significance does this experiments' percentage hold for upcoming work that needs to be conducted in live animal testing and why is this experiments' data important for companies working in CRISPR / CAS9 space? Is one of the main reasons because the company's FPPs (in this in vitro CRE experiment) outperformed current delivery standard TAT, with over 50% more uptake into cells?

Answer from Rob Hayes, CSO

Yes, current delivery systems are inefficient, but they are getting better with nanoparticles and viral vectors. However, these improvements in efficiency are often offset by increase in cost, low throughput,

complexity and concerns about safety. For example, if you wanted to do a large-scale genomic screen, making hundreds of different nanoparticle formulations would soon become a daunting task. Wouldn't it be easier to use just one CRISPr/Cas9 complexed with a single FPP?

But, as I mentioned elsewhere, the real advantage of our technology is cell specificity. We've shown in earlier work that we can find FPPs that are specific for certain cells types (the first we announced were brain endothelial cells, there are more to come). The delivery of CRISPR/Cas9 to specific cell types and tissues is an obvious advantage that Phylogica's FPPs can provide.

Let's talk about CRE for a second. When this protein gets into the nucleus of appropriate cells, it causes a genetic rearrangement, causing those cells to turn from green to red. You can see this in cells and isolated tissues, and whole animals. If you attach an FPP to the CRE, you can then see where the FPP takes the CRE. We've done this in cells and tissues, and soon we'll be doing this in whole mice.

I'm sure you see the reason for doing this – it allows us to study the tissue specificity in our FPPs, and to determine whether our FPPs more effective than the competition. As we begin to look for FPPs that could play a role in disease (e.g., FPPs that are specific for heart muscle), the CRE mice will become a phenomenally powerful tool.

3. Username: TONYINDO

In the company announcement dated 05/09/17 below, the company highlighted that one of the key activities was to expand the number FPPs that have the ability to deliver drug cargo into cells. Other than the 1746 FPP, are there any other FPP from the list highlighted in the announcement (five new FPPs 38, 49, 51, 52 and 55) that are more potent at delivering cargo inside the nucleus of a specific tissue cell than the present lead candidate 1746 FPP? Also, when do you expect to go live with the CRE experiments on the live animal (in vivo) model and estimated time for completion?

Answer from Rob Hayes, CSO

We are constantly expanding the number of FPPs, both through screening and rational design. We are now focussing more on cell-specific FPPs, and so we have transformed several cell types (such as cardiac muscle cells) to facilitate that process. Many of these FPPs are many-fold more potent than 1746. However, I cannot give you a definitive answer to your question because we're in the middle of re-configuring our assays to make them faster, more accurate, simpler and compatible to automation. The best I can say is yes, most likely.

The Cre live animal experiments are scheduled to start in April, thanks to the help of Stanford University and Takada. The experiments will start small in number with our best characterized FPPs, and we'll extend the scope of these experiments when we have a large enough breeding colony.

4. Username: TONYINDO

The latest company announcement dated 02/03/18, highlighted that the CRE system will:
*** reduce testing time significantly (by half of the current testing regime).**
Will this now improve operations to achieve scale since the company has now reduced testing time by

half? Is this now at the stage of where automation comes into play? Has the company already engaged with contract research organisations (CROs) to drive scale?

Answer from Rob Hayes, CSO

We have been working with a few companies. With two, we mapped out a feasibility study. It became clear to everyone that automating our screening wasn't feasible because one of the steps in our regular manual process (forgive me if I don't elaborate further) wasn't compatible with automation – it slowed down the automation so much that the effectiveness and value were lost. We have, over the last month, rebuilt the screening process to replace that step. We'll now put the process back onto the automation rig and try again. The CRE system is a central part of the new process.

5. Username: TONYINDO

Hi Phylogica,
In the March 2012 video briefing, Dr. Paul Watt highlighted that many antibody companies and scaffold companies are displaying diversity *within one structural theme*. Is this one of the things that distinguishes Phylogica from other companies operating in and targeting the 'undruggable' space? If so, are you able to elaborate on this point please?

Answer from Rob Hayes, CSO

With scaffolds and antibodies, there is a single structure with very defined binding surfaces. (If you type monoclonal antibody into Google, you'll see lots of images, but they're mainly all the same). Often, scientists can find scaffolds or antibodies against a therapeutic target ("binders"), which explains the rise of antibodies as therapeutics over the last two decades. However, occasionally, suitable binders cannot be readily found, which leads to more complex screening approaches. For example, membrane-embedded proteins are difficult to generate high-quality antibodies against using conventional means.

In contrast, Phylomers libraries are highly complex, having many different shapes and structures. They come from a range of biodiverse organisms and contain over 70 billion individual members with a variety of different shapes and structures. Therefore, the chances of finding a binder in a Phylomer library against some targets is higher than finding one in an antibody or scaffold library.

6. Username: ANDREW65

Hi Phylogica
Can you please clarify.
With our fpp peptides, is each range of peptide, such as 1746 c27 BLA or SAR40 BLA as mentioned in pivot to platform presentation very specific in the type of cell they will penetrate.

To clarify the reason for the question, if our lead fpp's are injected into bloodstream will they penetrate the first cells they come into contact with or will they circulate in the blood until they find a specific cell type. Can our fpp differentiate between cancer cells, blood cells, heart, liver, kidney etc. Theere was conjecture that this was why blood bourne cancer became the target with imyc, ie blood cells would be the first thing contacted by iv transfusion of fpp.

Answer from Rob Hayes, CSO

Great question, but as we've only just started some of these experiments (with Cre mice), I'm not able to give you a satisfactory answer, but I would like to make a couple of points around your question while I have the chance.

Some of our FPPs are cell-specific, and others are promiscuous. 1746 enters all the cells we've tried very well, better than other CPPs such as TAT, etc. As we've announced, other FPPs are very specific, for example, brain endothelial cells. We now have others now coming out of our screens which are specific for different therapeutically essential cell lines, including cardiac cell lines, cancer, etc.

(By the way, when I say cell-specific, I usually think about a molecule getting INTO a cell, such as a brain cell. But the converse might be useful - an FPP, linked to a small molecule that gets into all tissues EXCEPT brain cells. You can imagine a role for such a system in preventing drug addiction).

Now that we're screening our peptide libraries for cell-specific FPPs, we find our hit rate is surprisingly high. To get the FPPs we want for the complete range of cells and tissues that we're interested in, we will need to turn to automation – see my reply to TONYINDO on progress on the automation front. I believe that our recent progress in the arena of bioinformatics is playing a prominent role in the recent upswing in finding new FPPs, together with our newly-built expanded libraries.