national PKU alliance

While progress in developing new treatments for PKU has been made, there is still a significant unmet medical need for individuals with this condition. Many academic researchers and industry companies are actively working on applying the latest medical technologies to PKU to develop new therapies, management tools, and an eventual cure for PKU, which we have outlined below. The landscape is always changing, and it is our goal to provide ongoing updates on their progress, whether in development or available commercially.

Using Chaperone Therapies to Restore Enzyme Activity

Some PKU mutations can be corrected by using pharmacologic chaperones that help to guide the enzyme to restore its ability to break down phenylalanine (Phe). There are two known approaches to this for PKU depending on the mutations: BH4 chaperones or PAH chaperones.

BH4 Chaperone

The PAH enzyme needs a naturally occurring cofactor or chaperone to function properly and break down Phe. This cofactor is called BH4 (short for tetrahydrobiopterin). In approximately 25% of people with PKU, they may benefit from receiving BH4 which can help restore enzymatic function in the PAH enzyme. Because of this, companies have created a synthetic form of BH4 to help these individuals with PKU break down Phe. The generic name of these synthetic forms of BH4 are known as sapropterin and sepiapterin.

- Sapropterin is currently commercially available from: BioMarin Pharmaceuticals and marketed under the name of Kuvan®, Cycle Pharma and marketed under the name of Javygtor, Endo International (formerly Par Pharmaceuticals) and marketed as sapropterin dihydrochloride.
- Sepiapterin is currently in clinical trials and being developed by PTC Therapeutics.

PAH Chaperone

Other PKU mutations impact the active form of the PAH enzyme, which may reduce or inhibit its ability to break down Phe. For individuals affected by these mutations, a small-molecule chaperone could bind to PAH allowing it to achieve a more active form to make it a more functional enzyme to better break down Phe.

- PAH Chaperones are currenty being developed by Pluvia BioTech, Agios Therapeutics, and SOM Biotech.

Adding a functional enzyme

For PKU mutations that are not responsive or minimally responsive to chaperone therapies, other treatment approaches can be used by adding an enzyme that can break down Phe. Given the challenges with manufacturing the PAH enzyme, such as requiring a chaperone to function, researchers have been able to create other enzymes that can also break down Phe. This type of treatment is called “enzyme substitution therapy.” Two alternative enzymes that can break down Phe that are being studied as PKU therapies are phenylalanine ammonia lyase (PAL).

Administering the PAH Enzyme by Injection

One approach to administer the PAH enzyme is via injections into the skin to break down Phe in the body. The PAL enzyme has to be synthesized to reduce the body’s immune response so that it won’t be destroyed. This treatment is currently only available for adults with PKU and is marketed by BioMarin Pharmaceuticals under the name of Palynziq™.

Administering the PAL Enzyme by Mouth

Researchers are exploring ways to deliver the PAL enzyme via probiotic bacteria. In order to achieve this approach, the PAL enzyme is developed by genetically modifying gut bacteria to break down Phe. It is anticipated that similar to probiotics, these engineered probiotic bacteria would be delivered orally and will break down Phe in the upper intestines before the Phe can be absorbed by the body. These orally administered enzymes are then excreted and not expected to go into the blood. It is not yet known whether these enzymes will be exposed to Phe in the gut long enough to be effective.

- Administration of the PAL enzyme by mouth is currently being developed by Perseo Pharma.

Excretion of Phe in the Urine

One approach to help lower Phe in the body is by enhancing its excretion in the urine. The kidneys typically reabsorb Phe from the urine and back into the bloodstream via special transporters. There is an oral medication that can inhibit this transporter which will limit the Phe from being reabsorped so that it can be excreted in the urine. Jnana Therapeutics is currently studying an oral medication in clinical trials that helps the body eliminate Phe through the urine.

Using Genetic or Cellular Therapies

Instead of correcting the dysfunctional PAH enzyme or providing an enzyme substitution therapy, several innovative genetic techniques are being developed to use the body's genetic machinery to produce a functional PAH enzyme within its own cells. This can potentially be accomplished through both genetic and cellular therapies.

DNA provide the instructions that tell our body how to function. RNA receives these instructions from DNA to produce proteins, including enzymes, to carry out processes in the body. In individuals with PKU, there is either missing or incorrect information in the DNA that provide the instructions to make the PAH enzyme, resulting in a defective enzyme that cannot break down Phe. Therapies are being developed to target RNA and DNA to fix any errors to assist the body to make a functioning PAH enzyme which can break down Phe.

DNA that can instruct the body to make a PAH enzyme can be added to the body by various gene therapy techniques. In these approaches, genetically engineered cells that can express a functioning PAH enzyme can be administered to the body and will target the liver where they would be expected to grow and supply functional PAH. These cells are located in the liver but remain separate from the body's DNA. The challenge with this approach is that the cells in the liver are constantly regenerating, which can dilute out those that contain the new PAH DNA, and thus may be less effective over time. There are currently a few companies that have begun clinical trials using this approach, including Sanofi and NGGT.

CRISPR/Cas9 genomic editing technology allows permanent modification of the DNA necessary to make functional PAH within organisms with a one-time administration. The RNA can also be targeted to be corrected to allow for the synthesis of a functional PAH enzyme. However, there are many PAH gene mutations which makes it difficult to create a drug that can work for multiple people with PKU. This approach is still very experimental, and more work needs to be done before clinical trials can be conducted.

While there are not currently any gene therapies on the market, many academic and industry researchers are working hard to better understand these treatment approaches in hopes of one day being able to achieve such a treatment for PKU.

Management

Currently, individuals with PKU can get their blood Phe tested by either going to the laboratory to have a blood draw or by collecting their blood on a filter paper card via a finger prick which is then mailed to the lab. These approaches are inefficient, time consuming, and results are typically reported weeks after the sample was taken, leading to challenges with medical management. Many companies are working to develop a blood Phe monitor that can be used at home or in clinics that would provide results in minutes in an effort to more easily track blood Phe levels. While these monitors will not be able to eliminate the need to get a blood Phe test at the lab to guide clinical management, they are an exciting advancement that would allow individuals to have more frequent blood Phe levels.

There are many academic and industry groups working hard to develop home Phe monitors, with two companies already conducting clinical trial testing. These devices will need to be approved by the Food and Drug Administration before they can be made available commercially. Those companies conducting clinical trials include Aptatek Biosciences in the United States and Allworth Diagnostics in Europe. Those companies still working on finalizing their home blood Phe monitors include In Vitro Diagnostic Solutions (IVDS), Egoo, and Circa Biosciences.