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Gene- and Nano-Therapy for PAH: Could This Be the Future?

Announcer:
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Dr. Rajagopal:
So hello, my name is Sudarshan Rajagopal, and I'm Co-Director of the Pulmonary Vascular Disease Center at Duke University School of Medicine. And today I'll be talking to you about gene- and nano-therapy for PAH: could this be the future?

So what type of drugs do we use to treat disease? These can range from very small compounds called small molecules, which are the majority of drugs today, to peptides, which are small chains of amino acids, to larger structures, such as biologics. And these are - can be proteins, which are larger of course than peptides, or antibodies, which can then bind specific targets on cells. Then we also have other approaches such as gene therapies. So these could be antisense therapies, which are RNA-based therapies that prevent the synthesis of specific proteins. But we can also do gene therapy with adenovirus, which will increase expression of proteins, or we could alter the native proteins in the cell through CRISPR. And then we have cellular technologies, such as CAR-T cells and stem cells, which can have very complex effects.

Now, if you look at the drugs that are actually approved by the FDA, the vast majority of them still are small molecules. And these are just small chemicals that can bind to different targets. But as you can see, over time, we see an increasing number of biologics, and especially antibody-based therapies.

Now, there are other approaches to target these drugs to specific areas. And when it comes to pulmonary arterial hypertension, we frequently think about delivering drugs directly to the lungs. Now, historically, that hasn't been the approach as much; we've primarily use drugs that are either taken in an oral formulation, or given through an I.V., or other form, where it leads to systemic delivery. But if you target the lungs specifically, you might decrease side effects, and also better target the specific abnormal pulmonary vascular remodeling that characterizes the disease. So the idea would be that you have fewer side effects and more efficacy with this approach. And this could be through the inhalation of aerosols. And depending on the size of those particles, they can either be deposited in the upper airways, lung, or actually in the alveoli. But then there are other approaches where you can inject compounds that have nano-carriers that will specifically target the lung vasculature.

So I'm just going to highlight a few of these new therapeutic modalities in PAH. One is sotatercept. This is a biologic, so it's an antibody that targets activins, and it acts like an activin-ligand trap. So it prevents activins from binding to their receptors. And it allows BMPs, or bone morphogenetic proteins, to bind to BMPR2, and increase that signaling. This is a really novel approach.

We also have a number of new formulations of drugs for inhaled therapy. We have had inhaled treprostinil as a therapeutic approach and inhaled iloprost. But a lot of our other drugs in the PAH field have been systemically delivered. But now there are some clinical trials ongoing with drugs such as inhaled seralutinib or inhaled imatinib.

And then in earlier phases, we have gene therapy approaches to try to increase expression of proteins. An example of this would be

gene therapy approaches to increase the expression of BMP9, which is the natural ligand for BMPR2.

Then there are exosome-based therapies. So exosomes are secreted by cells, and they have really complex effects. They can have some RNAs, or ribonucleic acids, that lead to changes in expressions of proteins, or they may have other effects on cells by targeting proteins on the cells.

And lastly, there are also emerging stem cell therapies, which where usually the aim of these stem cell therapies is to replace abnormal cells with more normal cells. But these can also have complex effects through the secretion of what we call paracrine factors. That is that the stem cells secrete good factors that can have an effect to improve disease.

So to summarize, we now have a number of different ways of developing new drugs to treat diseases such as PAH. Now the current FDA approved therapies for PAH are small molecules, although we may see a biologic therapy approved shortly. Future therapies in PAH include biologics and novel delivery systems for different formulations of drugs to go directly into the lungs. And lastly, these new approaches have the promise to better target the molecular abnormalities in PAH, or target the lung directly, with fewer systemic side effects.

Thanks for joining me today.

Announcer:
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