Targeting PI3K in Women's Cancers

Dream Team Leader:
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BACKGROUND:

This project focuses on frequent mutations that occur in a set of genes that regulate the PI3K pathway, which is a complex signaling cascade that, in concert with other signaling networks, regulates cell survival and growth. The team will focus on the following three cancers that all have the P13K mutation: breast, ovarian and endometrial.

The scientists involved in this Dream Team are the pioneers who discovered the PI3K pathway and validated its role in human cancers. They and other investigators have developed a number of drugs to inhibit the PI3K pathway that are currently entering clinical trials.

To date, however, as with other "targeted" therapies, only a fraction of patients who enroll in these trials benefit, and it is not possible to predict which patients will respond positively. This means that many women will be given treatments that have no benefit to them or could cause unnecessary complications.

The goal of this Dream Team is to discover approaches that will predict which patients will respond positively to PI3K inhibitors. If successful, this will accelerate personalized cancer treatment that can be incorporated into standard practice.

The team has developed preliminary data that suggest ways in which to predict which patients will respond to PI3K inhibitors. Their challenge is to test their ideas in what scientists call "proof of concept" clinical trials.

One of their hypotheses is that since PI3K pathway mutations are frequent in breast, ovarian and endometrial cancers, it might be possible to develop a common set of techniques to predict which patients will benefit from PI3K pathway inhibitors.

In addition, while the PI3K pathway is sensitive to inhibitory agents, the growth/survival signaling networks involved in causing cancer are complex and often redundant. This means that the PI3K inhibitors alone are unlikely to be sufficient to eradicate tumors. Successful treatment will require combination therapies that overcome these biological complexities by hitting many different targets within the PI3K and other pathways.

THE GOALS:

This Dream Team has four specific goals for their project:

1. To develop molecular markers or imaging techniques that predict the subset of cancers likely to respond to PI3K pathway inhibitors.
2. To use these molecular markers to design and conduct clinical trials using single agents that inhibit the PI3K pathway. These trials will study patients with defined specific mutations to determine the impact of these mutations on the drug's efficacy.
3. To develop rational therapeutic combinations of PI3K pathway targeted drugs.
4. To design and conduct two multi-arm, molecular marker driven trials using a rational combination of a PI3K pathway inhibitor and another targeted therapy.

On the basis of these results, the team will develop clinical trials for breast, endometrial and ovarian cancer using the most successful drug combinations linked to appropriate biomarkers.

SIGNIFICANCE:

Despite its great potential to revolutionize cancer medicine by tailoring treatments to individuals, the implementation of personalized medicine has been relatively slow, and to date has not fulfilled its full promise.

The PI3K pathway is mutated in more cancer patients than any other signaling pathway, and these mutations are the most frequent events in women's cancers, making it an attractive molecular target for agents that inhibit these genetic aberrations.

If successful, this project will allow clinicians to use biomarkers and imaging techniques to predict which patients will benefit from PI3K pathway inhibitors and lead to the development of therapeutic combinations that will hit multiple targets in the complex pathways that contribute to cancer cell growth.

This work will help assure that patients receiving these therapies benefit from them and will also increase the overall pace of clinical trials targeting PI3K inhibitors.

RESEARCHER QUOTE (ATTRIBUTE TO CHARLES SAWYERS):

"The problem is that even though we know this pathway is commonly mutated in women's cancers, every cancer that develops doesn't necessarily have the same component missing or deleted or amplified. So even though there's a whole set of pieces of the puzzle that fit together, different patients have aberrations in different pieces of the puzzle. But the final conclusion is that they get cancer because of it.

"An analogy I like to make is that if you have a problem with one of the electrical circuits in your house and you want to turn off the circuit breaker so you can fix it, and you don't know the wiring diagram of your house, you would be going to the basement, flipping things off and then back to the third floor a dozen times or more before you get the right answer.

"If you have a wiring diagram, which is what we have been working on for the last 20 years or so, then you can make an educated guess--this is the circuit breaker, this should work for this event. Then when the patient comes in, we can test them and if see a particular event, we can say, this is the drug for you."