Identification of novel therapeutic targets in therapy-resistant breast cancer research

Yesim Polar, PhD, is an associate research professor of pathology and laboratory medicine at the Indiana University School of Medicine. Dr. Polar's research focuses on the identification of novel therapeutic targets in breast and thymic cancers that are resistant to standard-of-care therapy. She has published approximately 50 scientific journal articles in the field of cancer biology.

Yesim Polar, PhD

Associate Research Professor of Pathology & Laboratory Medicine

Indiana University School of Medicine

Thermo Fisher Scientific: What are your research goals?

Yesim Polar: As a translational scientist, the main goal of my research is to identify ways to prevent the development of cancer drug resistance and recurrence, particularly in breast cancer, and to improve the quality of life for patients. My research focuses on targets that alter the prognosis in breast cancers that are positive for a mutation in the gene that codes for estrogen receptor (ER). A recent work of mine describes a novel molecular function of a splicing factor—epithelial splicing regulatory protein 1, or ESRP1—in the poor prognosis of ER-positive breast cancer [1]. Basically, we show that overexpression of this gene alters the metabolic pathway genes and plays a role in ER-positive breast cancer resistance to endocrine therapies. This study also supports the epidemiological findings with obesity, which is a poor prognostic factor in ER-positive breast cancer.

"Overexpression of this gene [*ESRP1*] … plays a role in ER-positive breast cancer resistance to endocrine therapies."

Another research area is ductal carcinoma in situ (DCIS). These are breast lesions that are preinvasive or precancerous; however, some of them may recur or become invasive breast cancer. We study the parameters that are associated with the occurrence of these lesions. We use preclinical and clinical methods to understand transcription regulation and the mechanisms behind recurrence, and we develop or test therapeutic agents to target these markers. As for tools, we use next-generation sequencing (NGS) tools such as RNA-Seq, and more recently, microarrays such as the Applied Biosystems™ Clariom™ D Assays.

Thermo Fisher: What are some of your challenges and accomplishments?

Yesim Polar: The use of tools such as RNA-Seq has highlighted the importance of transcriptome profiling in cancer biology. This includes not only the coding and noncoding RNAs, but also splice variants. There are challenges: RNA-Seq is based on read counts, and the higher depth of sequencing provides better detection of the rare variants. Most of the cancer biology applications have used RNA sequencing, which generates reads of 30–40 million—these only target the high expressers. So, you need to go to a higher depth for the rare variants and low expressers, which is more expensive in the long run.

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Another challenge is the sheer amount of data you end up with. You have to have an expert bioinformatician to analyze the data, and it takes time to translate the analysis to the wet lab applications. Of course, you need a huge data storage system for this analysis. The introduction of the Clariom D Assays, on the other hand, has been a major blessing for researchers like me. This technique has huge advantages for transcriptome profiling. Mainly, it is probe-based. You have multiple probes for each exon and multiple probes for each exon–exon junction.

> "The introduction of the Clariom D Assays has been a major blessing for researchers like me."

This increases the accuracy and sensitivity of the assay. Secondly, we are using very challenging samples like formalin-fixed, paraffin-embedded (FFPE) tissues. These tissues are very precious, and usually we get very low amounts of RNA from them. And it's challenging because the RNA is fragmented. We have been successfully using the Applied Biosystems™ Clariom™ D Pico kits for these applications. Another aspect and unique advantage of the Clariom D Assay is that it provides a free software: Transcriptome Analysis Console (TAC). It is very user-friendly, and I can analyze the same data 10 times to get different perspectives. I can go to the wet lab, test the data, and come back and analyze further. So, it's time-efficient, which is accelerating the study.

Thermo Fisher: How does Thermo Fisher Scientific fit into your workflow?

Yesim Polar: We use the Clariom D Assays for discovery and verification because they are probe-based. The TAC software, as I mentioned earlier, is a big advantage—it provides you with a link from one application to another. You might have gene expression and alternative splicing data, and the software provides you with the link to other genome browsers like the UCSC browser, Ensembl genome browser, or if you want, to some protein databases to see where the exons are correlating to the protein domain links. In addition, there is a newer feature: When you click on the transcript ID, you can find the exact Applied Biosystems™ TaqMan® Assay that is relevant, and continue for further verification with TaqMan chemistry–based RT-qPCR approaches. It provides you with a very comprehensive, continuous tool to study every aspect of your story.

> "[Transcriptome Analysis Console] provides you with a very comprehensive, continuous tool to study every aspect of your story."

Thermo Fisher: What do you look for in a gene expression solutions provider?

Yesim Polar: The accuracy and sensitivity of the assay, timeline, and a user-friendly data analysis software package. And of course, in addition, a very knowledgeable and helpful technical support team.

Thermo Fisher: What are your future directions?

Yesim Polar: I will continue with the targets that we identified in ER-positive breast cancer and determine the therapeutic agents to alter these targets to prevent resistance and further chance of recurrence. Of course, it will be nice to see those studies translated into the clinical setting. I will also continue with the other story, ductal carcinoma in situ, and will further validate the markers that are important for recurrence of this disease and translation to the clinical setting.

Reference

1. Polar Y, Neelamraju Y, Goswami CP et al. (2019) Splicing factor *ESRP1* controls ER-positive breast cancer by altering metabolic pathways. *EMBO Rep* 20(2):e46078.

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