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Linking Statins to the Suppression of Aggressive Phenotypes of Triple-Negative Breast Cancer Cells

Announcer:
You're listening to a special focus on breast cancer from *Advances in Women's Health*, sponsored by Lilly

Dr. Birnholz:
Coming to you from the 42nd annual San Antonio Breast Cancer Symposium, this is ReachMD. I'm Dr. Matt Birnholz. I'm joined by Dr. Stephen Hiscox. He's leader of the Breast Cancer Molecular Pharmacology Group at Cardiff University in Cardiff, UK, and he is the senior author of a preliminary study on statins suppressing the aggressive phenotype of triple negative breast cancer cells which may occur through modulation of EGFR signaling. Dr. Hiscox, welcome to you.

Dr. Hiscox:
Thank you very much. It's a pleasure to talk to you.

Dr. Birnholz:
So this is a fascinating encounter when we're looking through a number of the different studies at the San Antonio Breast Cancer Symposium; in part because it's rare that one comes across two key words: statins and triple-negative breast cancer in the same poster. Can you talk to us about how this came about?

Dr. Hiscox:
Sure. So we had a longstanding interest in drug repurposing. And there was some evidence in the literature for the use of statins as anti-cancer agents against very solid tumors. We were interested to look initially at how effective these agents were across all forms of breast cancer. So we essentially did some screening work where we took cell lines representative of the major clinical subtypes and saw something that was really interesting that the most sensitive breast cancer subtype were the triple negative compared to the luminal A and luminal B subtypes, which weren't really sensitive at all to the effects of statins.

Dr. Birnholz:
And it's fascinating to hear. I mean, the prognosis for triple-negative breast cancer is obviously pretty poor. It is a sobering subtype to even speak about. No great molecular targets directly going after this particular subtype, and yet here we are getting to the heart of the matter, figuratively and metaphorically, looking at statins as a potential target. What were the design parameters of your study to help go about that possible hypothesis.

Dr. Hiscox:
So, once we'd done some preliminary screening and identified the triple-negative subtype as a potentially sensitive subtype to statins, we then wanted to delve in further, and so we broadened up the study to look at multiple cell lines representative of triple-negative versus multiple cell lines representative of the other subtypes. So we're not just comparing one cell line to one cell line because the danger to that is that you just pick up something that is specific to one particular cell line. So whilst the data that we present is from the typical MCF-7, luminal A versus triple-negative MJ-231's, we've screened these across a number of different triple-negative type modals, and luminal A and luminal B type models, and we still see this differential sensitivity. The triple-negative cell lines are much more sensitive to statin treatment in terms of suppression of growth. But not only growth, but this aggressive phenotype, migration, invasion, the things that you really don't want to see in their tumor cell behavior versus the luminal A. So we have a lot of preclinical data that would be supportive of our hypothesis that for as unidentified mechanism, the triple-negative are more sensitive. We-We think it's to do with EGFR, but we're still kind of investigating the actual mechanism of action for that.

Dr. Birnholz:
And that's exactly what the next follow-up question is going to be. You've postulated that the EGFR signaling pathway might be involved here. What are the steps that need to be taken to be able to either validate or refute that?

Dr. Hiscox:
So once we'd seen this differential effect, the next question for us was how? How is it that statins can achieve such a difference in tumor suppression between triple-negative and ER-positive luminal subtype? We had two working hypotheses; one is a generic suppression of cholesterol synthesis. Cholesterol being important for membrane composition, for lipid rafts, generic receptor tyrosine kinase signaling. And the other hypothesis was to do with EGFR. Again, utilizing some of these sort of early literature that suggested that the EGFR may be a pathway that's targeted by statins. And so based on those two hypotheses, we started to investigate membrane composition, EGFR signaling pathway, and the data that we're presenting at this year's San Antonio meeting suggests that in a few models of triple-negative breast cancer, is the EGFR pathway that's attenuated by statin? Now, the exact mechanism of that, we are still unsure about. How is it that statins get into the cell and suppress EGFR signaling? That could be through depletion of membrane cholesterol, and thereby interruption of membrane rafts. It may be a direct effect on the EGFR pathway components itself, but that's something we're currently investigating.

Dr. Birnholz:
What about the question of statins in general? Are all statins created equal in the eyes of EGFR signaling inhibition? Or is there a difference from one type to another?

Dr. Hiscox:
Yeah, so a really good question. We tried a number of different types of statins. Broadly speaking, they're either hydrophobic or lipophilic, and we find the greatest effects of the lipophilic ones and I wonder whether that is just simply due to the fact because the lipophilic didn't get into the cell better. Quite what they do in terms of mechanism of action, we're not sure about. But certainly the lipophilic ones are the sort of second generation statins as tend to be more effective in the triple-negative context. Although I would say, that whatever statins you're using, you still see this differential between luminal A and luminal B. It's just more pronounced with the more current statin agents than the lipophilic ones.

Dr. Birnholz:
Well, you're in a particularly great position of leading a whole team of researchers that can take various branching approaches to this. What do you think is next?

Dr. Hiscox:
For us, we need to really delve into this mechanism. We have some studies planned that will address cholesterol composition in the membrane more fully just to understand whether it is a generic effect. So not all triple-negative breast cancer will express the EGFR. If we can perturb generically receptor tyrosine kinase signaling, then that's really great because it means that these agents will have a more broader application to triple-negative disease. Of course, flip side to that is that they may well just be specific to the EGFR pathway. In which case, we've reduced the potential application clinically to a subset of patients who are triple-negative, but EGFR-positive. So we want to really flush that out and determine is it just the EGFR or is it other receptor tyrosine kinase pathways in these cells.

Dr. Birnholz:
Well, I'm very much looking forward to hearing more about the ongoing studies that are going to help elucidate this information better. This is a fascinating connection of statins and triple-negative breast cancer. I'm very grateful to you and your research team for diving into that.

Dr. Hiscox:
Thank you very much for your time. It was a pleasure to talk to you about our research in Cardiff.

Dr. Birnholz:
For more access to this and other episodes on breast cancer research and treatment, visit reachmd.com where you can be part of the knowledge. I'm Dr. Matt Birnholz. Thanks again for listening.

Announcer:
You've been listening to this special focus on breast cancer from *Advances in Women's Health*. To revisit any part of this discussion and to access other episodes in this series, visit reachmd.com/advancesinwomen'shealth. Thank you for joining us.