An interview with Professor Matthew Ellis at the NCRI 2017 Cancer Conference

Matthew Ellis*,¹

¹Lester & Sue Smith Breast Center, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

* Author for correspondence: mjellis@bcm.edu

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Matthew Ellis speaks to Roshaine Wijayatunga, Managing Commissioning Editor:

Matthew Ellis is Director of the Lester and Sue Smith Breast Center at Baylor College of Medicine. He is also Associate Director for Translational Research at the Dan L Duncan Center and a McNair Medical Institute Scholar.

What inspired you to study medicine & then move more specifically into medical oncology?

Well, the first question is more difficult than the second question! I knew I wanted to be a doctor from about the age of 8 and well, it was just based on an instinctive desire to go into medicine, I think this is quite common amongst physicians. Becoming a medical oncologist was a bit more thoughtful.

When I was doing internal medicine in London hospitals in the 1980s, two things struck me. HIV-AIDS, which was a new diagnosis and was a tragedy for young men, but also there was a slower burning, but no less striking problem with young women dying of breast cancer. One of my friends went into HIV research, but I decided to go into breast cancer research, really in response to seeing so many women in the hospital dying of metastatic disease.

Your lab focused on “generating new & optimizing current treatment strategies for patients across the breast cancer spectrum”. Can you tell us a little about one of the research projects your lab is working on currently?

We do work on a variety of different things, and something I have been working on for a long time is the cause of endocrine therapy resistance, which is, of course, you could argue easily, is the major cause of death from breast cancer. The patients who have hormone receptor-positive disease get an appropriate endocrine agent, but it is not curative and they develop resistance. Recently, we have been probing the cause of what many people call intrinsic endocrine therapy resistance, so in other words, right from the moment the tumor is diagnosed, the endocrine drugs are not working effectively. We diagnose this on the basis of measuring something very simple – the proliferation index with a Ki-67 stain. So, if you do Ki67 at baseline, and then perhaps after 2–4 weeks or 2–3 months of endocrine therapy, and remeasure the Ki-67, about 20% of tumors have significant ongoing proliferation despite the very potent estrogen suppression associated with the aromatase inhibitor. So, we have been probing the cause of that, and we recently came up with a surprising answer, which involves mismatch-repair complex formation, and this conclusion is published recently in *Cancer Discovery*.

The bottom line is that tumors that have a defect specifically in the MUTL complex, in other words, if *MLH1*, *PMS1* or *PMS2* are mutated or under-expressed this is associated with intrinsic endocrine therapy resistance and is related to the fact that those repair complexes signal to *ATM* – when they form, they activate *ATM*, which activates *CHK2*, which checks CDK4/6. Without this mechanism, the negative regulation of CDK4/6 is lost and ER+ cells can enter the cell cycle without estrogen receptor stimulation. This could explain why CDK4/6 inhibitors such as palbociclib, ribociclib and abemaciclib are effective, after endocrine therapy resistance has ensued. The accurate prediction of CDK4/6 effectiveness has implications because some patients develop breast cancer as a consequence of germline *ATM* mutation or germline *CHK2* mutation, and when patients develop breast cancers in those germline settings, they are almost always ER-positive. Having delineated these pathway components as

important to endocrinotherapy in breast cancer suggests that chemoprevention with endocrine agents might be less effective, but a CDK4/6 inhibitor might be. Thus, we are beginning to unravel the relationships between DNA repair, palbociclib sensitivity and endocrine therapy resistance in these studies.

What impact will the integration of big data science or 'omics' have on the future of breast cancer research?

Well, it is absolutely everything! Until you do big data science and do large-scale studies that allow you to see the patterns at the DNA, RNA, protein and phosphoprotein levels in the context of accurately defined clinical outcomes one is never going to make a proper diagnosis for a patient. Breast cancer, I would say, is one of the most complicated malignancies that we face as oncologists. We used to treat it as a monomorphic disease, it is a proliferation of cells, it occurs in the breast and for certain unfortunate individuals the disease spreads around the body and the patients succumb to it. But this is just a syndromic description of the problem. These descriptions do not say what is the actual cause of death from cancer in each patient at a molecular level. To get to that answer, we have to use big data to find the different subsets. We need to move beyond the transcription-based subtypes – luminal A, luminal B, HER2-enriched, basal, among others because they are not powerful enough to detect the cause of poor outcome and therefore direct treatment. The biggest problem in breast cancer is making the correct diagnosis – which is not, *"Does she have breast cancer?"* but *"What exact type of breast cancer does she have?"*, or occasionally, *"he"* have, because without that information, you will never get to a cure, because you do not understand what the molecular basis for the disease.

You presented a lecture at this year's NCRI Cancer Conference on 'Breast Cancer genomics & the Clinical Proteomic Tumor Analysis Consortium'. Can you tell us a little about your presentation & the Clinical Proteomic Tumor Analysis Consortium?

The history behind Clinical Proteomic Tumor Analysis Consortium is interesting. This is the third phase of funding. When it was first funded, it was in response to some controversial data about diagnosing ovarian cancer from the blood using mass spectrometry-based proteomics where investigators came up with some erroneous conclusions because they had not controlled pre-analytical variables, and the reproducibility was not there, and so, the National Cancer Institute invested in a benchmarking process trying to get MS-based analysis to be a reasonably quantitative science. The program is called the Clinical Proteomic Tumor Analysis Consortium (CPTAC). I was not involved in this first phase, but I was involved in the second phase, where having achieved more confidence in the analytical approaches we took tumors that had been already genomically characterized, at the DNA and RNA level by the The Cancer Genome Atlas (TCGA) were analyzed using new MS instruments and a technique called tandem mass tagging, which is more quantitative. We were able to generate some really nice proof of principle papers on the proteogenomics of colorectal cancer, breast cancer and ovarian cancer. These are proving great resources because there are so many proteins that do not have a decent antibody to detect them, but with peptide sequencing, one is conducting an unbiased survey of the proteome and one can observe the way protein perturbations track mutations or transcriptional subtypes in ways that are more unbiased than can be achieved with antibody-based technologies.

The third phase of CPTAC has expanded massively because of the success of second phase and we are doing a variety of different tumors that have not been profiled yet including, lung cancer in two different forms – squamous- and adeno- and brain-cancer – glioblastoma, as well as endometrial cancer and kidney cancer and leukemia as examples. All these tumors types will have full proteogenomic analysis where we analyze the DNA, RNA, protein and phosphoprotein on a standardized format. Then, finally, we are getting to the process of what we call 'microscaling' because to do analyses previously, we needed a piece of tumor about the size of a pound coin, about 100 mg of tumor. The drive toward microscaling, which is achieved by better informatics, sample preparation and instrumentation, we are cutting the amount of tissue we need by about 80%. This is necessary because we need to be able to get a proteogenomic profile, for example, whole genome sequencing, transcriptome and then the proteome and the phosphoproteomic analysis on about 20 mg wet weight, which is about the size of a core needle biopsy, which the standard sampling technique used for translational oncology. We are looking forward to generating some data in really important clinical contexts, like neoadjuvant therapy in breast cancer, and relate it to a more sophisticated look at the tumor with drug response and resistance.

Do you see tailored therapeutic approaches to be the future of breast cancer therapy? What improvements do we need to see in this area of research?

A much bigger emphasis on precision diagnostics and not just at the DNA and RNA level. Everyone is focusing on the DNA, but the computer screen of life is composed of proteins so if you do not measure the output of the genome and the transcriptome at the protein level and probably, more importantly, at the level of the post-translational modifications like phosphorylation, we are never going to understand how complicated cancer genomes execute the hallmarks of cancer. So, I think if it were me, I would invest more on developing precision diagnostics that achieve proteogenomic data integration and then drive toward biological precision and studies that demonstrate utility. I think people should realize that the instrumentation for proteomics has improved dramatically and will make this kind of research really quite feasible even for clinical diagnostics in my opinion.

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