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Translating Science to Medicine: When Will the Rubber Meet the Road?

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Scientific advances over the past two decades have drastically expanded our understanding of cancer pathogenesis. While the central dogma set forth that RNA serves principally as an intermediate between DNA code and its protein end product, it is now known that transcription of noncoding DNA yields RNA molecules that contribute to biological processes through several mechanisms [1]. Prominent among these functional elements are long noncoding RNAs (lncRNAs), and a number of large, coordinated efforts in recent years have helped to drive knowledge of lncRNAs. Such efforts have yielded innovative resources such as the NCBI Reference Sequence (RefSeq) database [2], the UCSC genome browser database [3], and GENCODE, the reference human genome annotation for the ENCODE project [4]. More recently, our group built on these resources with MiTranscriptome (http://mitranscriptome.org), a pan-cancer study identifying tissue- and tumor-specific lncRNAs [5]. In total, MiTranscriptome yielded a consensus human transcriptome of 91 013 genes, of which nearly 70% were classified as lncRNAs. At the time of its development in 2015, the majority of lncRNAs in MiTranscriptome (79%) had not been annotated.

The wealth of genomic and transcriptomic data available today presents a striking juxtaposition, on one hand illustrating the exponential increase in knowledge attained in the last several years, and on the other hand serving as a humble reminder of how much remains unknown. For the practicing clinician, maintaining even a basic understanding of this information is an overwhelming—if not wholly unrealistic—pursuit. In this issue of *European Urology*, Ramnarine and colleagues [6] summarize the body of data characterizing lncRNAs implicated in prostate cancer (PCa). Specifically, the authors categorized previously identified lncRNAs according to one of four primary areas of carcinogenesis: (1) tumor risk/initiation; (2) tumor promotion; (3) tumor suppression; and (4) tumor treatment resistance. They furthermore sought to summarize potential clinical roles of lncRNAs as markers of risk, diagnosis, and prognosis/prediction, and as therapeutic targets.

As described by the authors, lncRNAs have great potential in cancer screening because they are frequently tissue-specific and can be detected in blood and urine. In addition to providing a less invasive means of testing, blood- and urine-based markers are advantageous in that they are thought to provide a more “global” assessment of the prostate disease state and risk. In other words, blood- and urine-based tests are less prone to misclassification due to sampling, an increasingly recognized pitfall of tissue-based testing in a multifocal, heterogeneous cancer such as PCa [7]. The application of lncRNAs to PCa began in 1999 with PCA3 [8]. Cancer-specific and readily detectable in urine, PCA3 has been studied in several settings with largely promising results [9]. Currently, PCA3 contributes to two clinically available diagnostic tests: (1) the Mi-Prostate Score (MiPS), in which it is combined with urinary TMPRSS2:ERG and serum prostate-specific antigen (PSA); and (2) the ExoDx Prostate IntelliScore, in which it is combined with TMPRSS2:ERG and the transcription factor SPDEF. Both tests have demonstrated an ability to reduce the number of unnecessary (negative) biopsies performed in the setting of elevated PSA [9].

While PCA3 is being incorporated into clinical practice to some extent, the current review highlights just how underdeveloped our understanding of additional lncRNAs

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remains. SChLAP1, MALAT-1, and PCAT-1 are only a few of the lncRNAs that have shown initial promise as potential clinical tools, but simply lack sufficient studies of clinical validity required to know if and how exactly they can be applied [10–12]. Indeed, while the identification of lncRNAs has been remarkable, the fundamental goal of applying this science to improving patient care remains largely unreached. So, it is important that we ask when these leaps in discovery will translate to clinical practice, and why, in large part, they have not.

The answers to these questions are certainly multifactorial, but the sheer volume of information reviewed by Ramnarine et al brings one possibility into focus. Considering the large and expanding body of genomic data and the increasing demands of contemporary clinical practice, it is more difficult than ever for clinicians to meaningfully contribute in both arenas. In other words, it is possible that the distance has grown too wide between scientists discovering our next breakthrough biomarker and clinicians implementing the studies necessary to prove its validity.

One approach to addressing this concern would be to encourage cross-talk between these arenas and increase the educational resources available to those clinicians. Our team has recently begun to develop an online curriculum to efficiently and effectively educate clinicians on the broad world of genomic data, how it can benefit our patients, and what busy clinicians can do to help in driving discovery. We would encourage our colleagues around the world to similarly explore such avenues aimed at advancing translational research through practical, multidisciplinary efforts. While the speed of science is unlikely to decline, practical efforts should be made to increase the speed and ease of education in parallel. Our hope is that such efforts will help to bring laboratory science and clinical medicine back to the same table, pushing discovery towards the ultimate goal of improving patient outcomes.

Conflicts of interest: Arul M. Chinnaiyan is listed as a co-inventor of a patent issued to the University of Michigan on the detection of ETS gene fusions and specific lncRNAs in prostate cancer. He is a co-founder of LynxDx, which is developing urine biomarkers of prostate cancer, some of which are referenced herein.

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