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Cambridge Epigenetix: Improving Health through Measurement of the Epigenome

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Abstract: Cambridge Epigenetix is a biotech company founded in 2012 with an aim to develop and market innovative technologies for identifying epigenetic markers. These bio markers or chemical tags attached to the genome determine the activity of genes in different cells in a body in response to environmental changes and throughout the growth and aging processes. Many human diseases including cancers, diabetes and developmental disorders reflect aberrant epigenetic activity. Cambridge Epigenetix's technology allows scientists detect and quantify specific epigenetic markers in patient's cells. These epigenetic data allow clinicians to produce accurate diagnostics and drug companies to develop efficacious treatments. Application of epigenetic technology has a large potential for improving healthcare and Cambridge Epigenetix is ideally positioned to catalyse the epigenetics revolution.

Keywords: Epigenetics, genetics, epigenetics, biomarker, DNA methylation

1. The success story

Cambridge Epigenetix's vision is to improve human health through the accurate measurement of the epigenome. Cambridge Epigenetix has developed a novel technology called oxidative bisulfite sequencing (oxBS-Seq) which pioneers quantitative, single-base resolution sequencing of the modified bases methylcytosine (5mC) and hydroxymethylcytosine (5hmC). Based on the technology, the company created its flagship product called TrueMethyl® which enables analysis of the DNA methylome with unprecedented accuracy and opens new avenues for basic research, pharmaceutical discovery and diagnostics.

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1. Where did they start and the journey so far


Dr Jason Mellad

The oxBS-Seq technology was invented in the laboratory of Prof Shankar Balasubramanian at the Department of Chemistry, University of Cambridge. Prior to Cambridge Epigenetix, Prof Balasubramanian founded Solexa in 1998 as a university spinout to commercialise a new superfast way to sequence DNA. Solexa was acquired for $650m in 2007 by Illumina, which used its technology to become the world's market leader for reading genes. Cambridge Epigenetix, founded in 2012, is now aiming to reproduce the success of Solexa in the field of epigenetics. The CEO Dr Jason Mellad joined Cambridge Epigenetix in 2013 and served as a Business Development Manager before becoming the company's CEO. The company currently has a strong team of 30 industry leaders and epigenetics scientists, focusing on delivering improved epigenetics-based diagnostic assays. In 2014 Cambridge Epigenetix raised $5.5m financed by New Science Ventures, Syncona Partners and Cambridge Enterprise. More recently in 2016 the company secured the investment of $21m which is led by GV (formerly Google Ventures), with significant participation from Sequoia Capital.

2. The technology

To describe how the innovative TrueMethyl technology works, it may help to first review the basics of epigenetics science. Throughout a lifetime, our body is built and its function is regulated according to the genome, the DNA blueprint of an organism. Expression and activities of genes, components of the genome, are controlled by chemical tags attached to the genome. A record of such chemical modifications is called the epigenome. Whilst the underlying genome is largely unchangeable within an individual, the epigenome can be dynamically altered by environmental changes across different cell types and over time, essentially switching on or off genes in different circumstances. Whilst these chemical modifications of the genome are essential for normal development and adapting an organism to environmental changes, many human diseases including cancers, diabetes and developmental disorders reflect aberrant epigenetic activity. In fact, epigenetics can provide insights into diseases where genomics alone cannot.

The epigenetic markers include cytosine modifications such as 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC). In addition to the four basic nucleobases, cytosine (C), guanine (G), adenine (A) and thymine (T) that consist the basic building blocks of DNA, 5mC and 5hmC, modified variants of cytosine, are known as the 5^{th} and 6^{th} base respectively. Researchers have revealed that both 5mC and 5hmC play distinctive and important roles in development and disease pathogenesis. 5mC is generated when a methyl group is added to cytosine. When this methylation of cytosine occurs in the regulatory regions of genes, it recruits proteins that condense the surrounding chromatin and stably silence or suppress gene expression. 5hmC, on the other hand, is generated by oxidation of 5mC. Studies have indicated that 5hmC may be involved in up-regulation of gene expression. Loss of global hydroxymethylation has been shown to be associated with malignant human cancers such as melanoma and may serve as a strong diagnostic and prognostic indicator [1]. Dramatic changes in total 5hmC levels have also been implicated in the progression of major neurological disorders including Alzheimer's

disease, Friedrich's ataxia and Huntington's disease. Leading pharmaceutical companies have recognized the importance of 5hmC as a novel clinical biomarker in disease. For example, researchers at Novartis have identified an important role for hydroxymethylation in Fragile X syndrome, an inherited genetic condition that causes a wide range of developmental problems. Novartis discovered that quantifying 5mC and 5hmC at novel regions of the Fragile X syndrome genomic locus could be used to both diagnose the disease and determine patient responsiveness to mGlur5 antagonist therapy. This highlights the importance of accurately measuring both 5mC and 5hmC to truly understand epigenetic mechanisms in disease [2].

Recent studies have shown that at some sites in the genome the level of 5hmC can be comparable to the level of 5mC, emphasizing the importance of identifying these variants accurately [3]. However, traditional bisulfite sequencing cannot discriminate between 5mC and 5hmC, yielding a combined result of unknown proportions. To address this issue, at Cambridge Epigenetix Prof Shankar Balasubramanian and Michael Booth co-invented innovative TrueMethyl oxidative bisulfite sequencing (oxBS-Seq) technology, which utilizes a selective chemical oxidation that accurately distinguishes between 5mC and 5hmC [4]. Firstly, chemical oxidation converts 5hmC into 5-formylcytosine (5fC) (see Figure 1, right). Bisulfate treatment then converts 5fC and C to uracil which is read as T, leaving only 5mC to be detected by sequencing. This yields the **true levels of 5mC at single-base resolution**. Secondly, to separately detect 5hmC, a second bisulfite sequencing is run, omitting the oxidation step (Figure 1, left). This yields (5mC+5hmC), from which the specific **5hmC bases are identified by quantitative subtraction**.

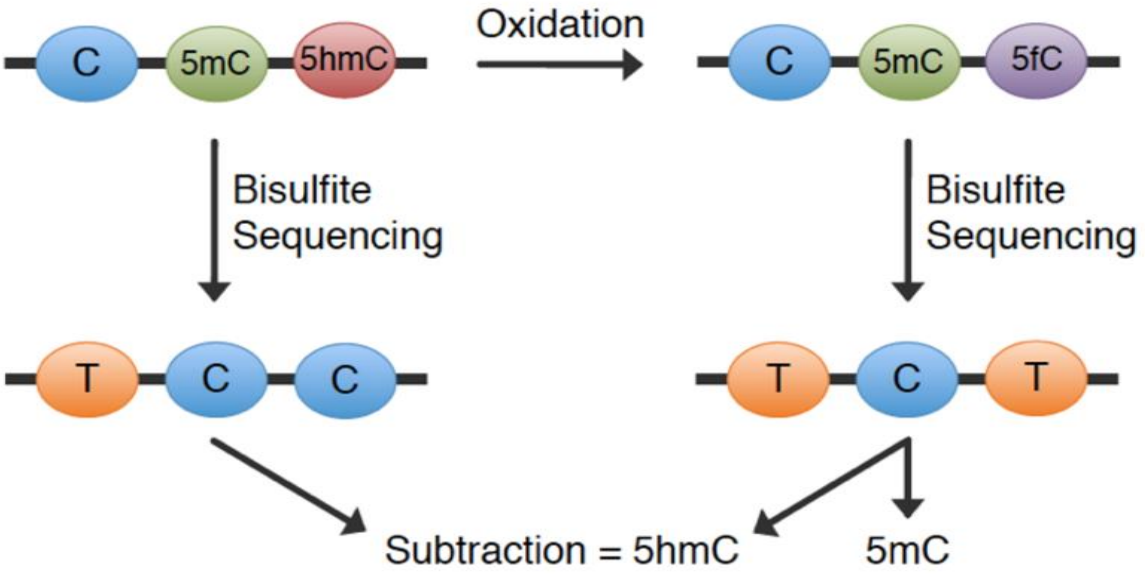

Figure 1. TrueMethyl oxidative bisulfite sequencing (oxBS-Seq) technology adapted from Cambridge Epigenetix website.

TrueMethyl is based on the oxBS sequencing methodology first published by Booth *et al* 2012 in Science but has undergone significant optimization enabling a more robust and rapid quantitative measurement of 5mC and 5hmC in parallel and at single-base resolution.
TrueMethyl is compatible with a variety of common platforms including next generation sequencing and Illumina Infinium® Methylation EPIC arrays, as well as reduced representation

bisulfite (RRBS) and targeted assays. This technology can be used to assess the complete methylome of any species and is fully compatible with a wide range of sample types.

Cambridge Epigenetix also developed a novel technology to detect 5fC that is produced by oxidation of 5mC. TrueFormyl™ reduced bisulfite sequencing (redBS-Seq) allows robust, accurate and reproducible quantification of 5fC at single-base resolution. It utilizes selective chemical reduction of 5fC to 5hmC followed by bisulfite treatment to quantitatively decode 5fC. In a bisulfite-only sequencing run, 5fC is read as T (Figure 2, left). During redBS-Seq, chemical reduction selectively converts 5fC into 5hmC, which is resistant to bisulfite and sequenced as C (Figure 2, right). Comparison of results from redBS-Seq and bisulfite-only sequencing gives a quantity of 5fC at single-base resolution.

Like oxBS-Seq, redBS-Seq is platform agnostic and can be used with a wide range of analytical techniques including Sanger sequencing, Pyrosequencing, Infinium EPIC array and Illumina NGS.

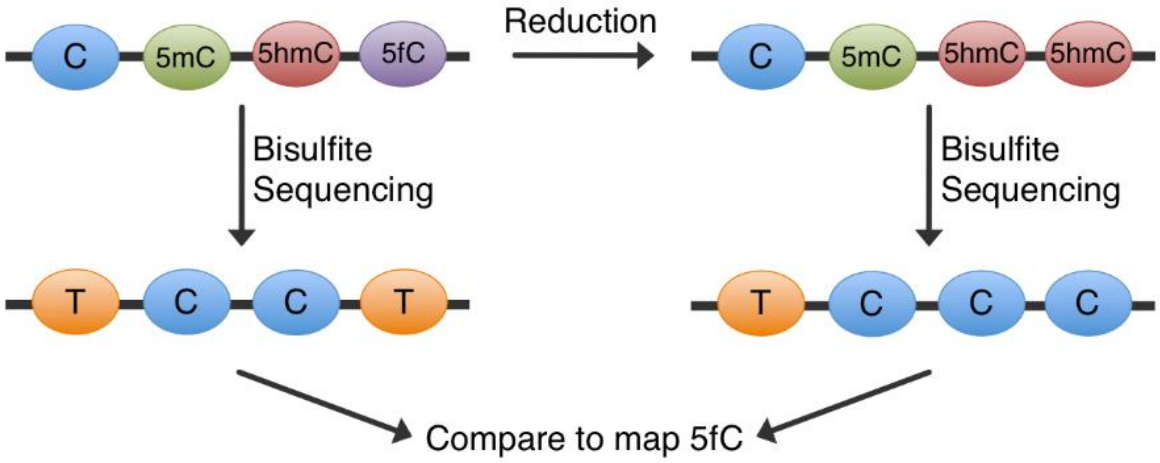

Figure 2. TrueFormyl reduced bisulfite sequencing (redBS-Seq) technology adapted from Cambridge Epigenetix website.

3. Looking to the future

Cambridge Epigenetix's mission is to realize the power of epigenetics by pioneering new biomarker discoveries and therapeutics and helping our partners do the same. Ultimately, Cambridge Epigenetix envisions the realization of routine sequencing of the epigenome for individuals, which leads to new discoveries that improve healthcare and wellbeing of every human being from the moment of conception to old age.

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Yoshiro Shiba is an advocate of Open Innovation. His work at Shionogi Europe involves identifying innovation and open science opportunities in UK and the continental Europe, and developing and managing research collaborations with academia, biotech and pharma partners. Yoshi obtained a PhD in Behavioural Neuroscience from the University of Cambridge, and subsequently worked as a research scientist at the university. Aside from working in his research laboratory, he served as a committee chair of a university-wide inter-disciplinary science seminar series. He was also involved in activities of the Innovation Forum, building professional networks of academic and industry experts and facilitating inter-sector conference organisations in Cambridge. Through these activities, Yoshi discovered his interest in working at a translational junction between research and application. This eventually led him to his current role in the Global Innovation Office, where he exercises his scientific knowledge to promote the transfer of discoveries from laboratories to clinical practice.