Institutional Profile

The USC Epigenome Center

The University of Southern California (USC, CA, USA) has a long tradition of excellence in epigenetics. With the recent explosive growth and technological maturation of the field of epigenetics, it became clear that a dedicated high-throughput epigenomic data production facility would be needed to remain at the forefront of epigenetic research. To address this need, USC launched the USC Epigenome Center as the first large-scale center in academics dedicated to epigenomic research. The Center is providing high-throughput data production for large-scale genomic and epigenomic studies, and developing novel analysis tools for epigenomic research. This unique facility promises to be a valuable resource for multidisciplinary research, education and training in genomics, epigenomics, bioinformatics, and translational medicine.

KEYWORDS: bioinformatics ■ bisulfite ■ epigenetics ■ epigenome ■ genome ■ histone methylation ■ modification ■ sequencing

Epigenetic mechanisms can exert a powerful effect on cellular phenotype, as evidenced by the large diversity of genetically identical, but epigenetically distinct cell types in higher eukaryotes. Nevertheless, epigenetics has long been a somewhat overlooked corner of molecular biology, with molecular genetics occupying center stage for the past few decades. Many scientists attribute this to the obvious central importance of genetic mechanisms to biology. I would like to offer an alternative explanation. Reductionist molecular biology took off once we acquired the ability to isolate and amplify discrete segments of the genome or transcriptome. Initially this was achieved by **biological amplification** in plasmids or phage vectors. This was followed by signal amplification using hybridization technologies with radioactive or fluorescently labeled probes. Enzymatic amplification by the PCR provided an even faster and more straightforward way to accomplish enrichment for segments of the genome. All three of these amplification principles erase epigenetic information. Thus, for decades the basic tools of molecular biology have rendered scientists oblivious to the incredibly rich tapestry of epigenetic information present in their biological samples. This technological hurdle has held back the development and appreciation of the field of epigenetics.

Significant advances have been made in the past decade to overcome this problem. The solution has been to use affinity enrichment for epigenetic marks, or to modify DNA in a DNA methylation-dependent fashion by enzyme digestion or sodium bisulfite conversion prior to further analysis. Most recently, these techniques have migrated from locus-specific amplification to array-based hybridization, and now to sequence-based analysis using next-generation sequencing platforms. As epigenetics has moved to genome-wide analyses, it has become clear that researchers in this field need access to high-throughput genomic technologies and accompanying computational biology and genomic bioinformatics. With this recognition, the University of Southern California (USC) Epigenome Center (CA, USA) was conceived in 2007 and launched in 2008.

Epigenetics research at USC

The University of Southern California has a rich history in epigenetics research, dating back to 1980 with the discovery by Dr Peter Jones of the effects of azanucleoside drugs on DNA methylation [1]. The program grew with the recruitment of Dr Michael Stallcup to the USC Keck School of Medicine in 1985, with his focus on transcriptional regulators, and resulted in the first demonstration of a causal link

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between histone modification and gene expression [2]. Dr Peter Laird was recruited to the USC/Norris Comprehensive Cancer Center in 1996 following his publication demonstrating a causal relationship between DNA methylation and mouse tumorigenesis [3]. Subsequently, Dr Laird established key technologies in the field of DNA methylation research, including the development of the combined bisulfite restriction assay (COBRA) and MethyLight assay [4,5]. Dr Chih-Lin Hsieh was recruited in 1997, bringing expertise in the role of DNA methylation in transcriptional control [6]. Recent recruitments have expanded the focus on histone modifications and chromatin structure, and their effects on transcription, with the recruitments of Dr Judd Rice (2003) and Dr Woojin An (2004). Dr Allen Yang rejoined USC to strengthen translational epigenetics, with a focus on clinical trials with epigenetic inhibitors. Other investigators at USC have shifted their research interests to epigenetics, as excitement in this field grew. Dr Darryl Shibata, Dr Kim Siegmund, and Dr Simon Tavaré use variations in DNA methylation patterns in human colonic crypts and tumors to model the kinetics of stem, progenitor and tumor cell lineages [7]. Dr Joe Hacia is applying his genomic expertise to developing epigenetic profiles of B-cell lymphomas [8], while Dr Ite Laird-Offringa is developing DNA methylation markers for the early detection of lung cancer and mesothelioma [9]. Epigenetic and epigenomic bioinformatics has flourished with pioneering work by Dr Siegmund, Dr Paul Marjoram and Dr Jonathan Buckley [10].

Birth of a center

The USC Epigenome Center launched administratively on July 1, 2007, with Dr Peter Laird appointed as the Founding Director. An internal Faculty Advisory Committee was assembled in the fall of 2007, and meets regularly to advise on development strategy. Data production started in the new facilities in December, 2007. An External Advisory Board was finalized in early 2008, and participated in an inaugural symposium and celebration on April 11, 2008. The USC Epigenome Center website was established in 2008, and can be viewed at [101].

The facility currently occupies the entire ground floor of the newly constructed Harlyne Norris Research Tower of the USC/Norris Comprehensive Cancer Center. The University, Keck School of Medicine and the Norris Comprehensive Cancer Center are highly supportive of the USC Epigenome Center, providing prime-quality space, and facilitating a US\$10 million philanthropic gift from the Norris Foundation to launch the center. The Epigenome Center currently has a fully equipped Illumina® (CA, USA) BeadLab for GoldenGate®, Infinium™, and BeadXpress® technologies, and multiple Genome Analyzer IIx instruments with paired-end modules. Dr David Van Den Berg is the Director of Data Production, while Christine Lavoie who oversees administrative, personnel and financial matters as the Managing Director. Dr Jonathan Buckley is the Director of Bioinformatics. The USC Epigenome Center can house approximately 20 laboratory personnel and 30 bioinformatics and administrative staff. The Center currently has approximately 25 faculty, staff, postdocs and students.

Bioinformatics

The rapid evolution of next-generation sequencing technologies has resulted in a dramatic drop in cost per sequenced base-pair. With ever decreasing costs of data production and with increasing amounts of data available in public databases, the bottleneck to biological analysis is shifting from data production to data processing, storage and analysis. In recognition of this trend, the USC Epigenome Center has assigned almost as much floor space to epigenomic bioinformatics and computational biology as to data production. Much of the current faculty and staff recruitment plans are in the areas of bioinformatics, computational biology and biostatistics. The vision is to create an interactive environment in which biologists, programmers, statisticians and computational biologists work side by side and exchange ideas to tackle epigenomic analyses.

Prospects

The USC Epigenome Center serves as both a data production center for customers within and outside USC, and is funded through many NIH grants. In addition, it is actively developing new epigenomic

analysis technologies, and participating in major collaborative initiatives. For example, the USC Epigenome Center is responsible for all high-throughput epigenomic data production within the National Cancer Institute- and National Human Genome Research Institute-funded Cancer Genome Atlas (TCGA), as part of a collaboration with Dr Stephen Baylin (Johns Hopkins University, MD, USA). The Center also participates in the 'Stand Up To Cancer' (SU2C) Epigenetics 'Dream Team', led by Dr Baylin and Dr Peter Jones. As participation in such genome-scale projects expands over the

next few years, the USC Epigenome Center will likely grow to be a recognized force in epigenomic analysis.

Financial & competing interests disclosure

Peter W Laird is a consultant for Epigenomics, AG, and for Celgene Corporation. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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Website

- 101 USC Epigenome Center website
<http://epigenome.usc.edu/>