

# **The Complex Genome: From Structure to Function**

Diwen (Steven) Gan

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## **Overview**

In eukaryotes, the genome is extensively compacted inside the nucleus, hierarchically organized at a multiscale of structural units. One of the most critical roles of these delicately regulated structures is the control of transcriptional dynamics. Transcriptional regulations have been recognized as the primary regulatory mechanisms coordinating cellular activities, responses, cell type and fate determinations. No doubt, regulations on transcription are hugely achieved by changes in regulatory factors and structural configuration. Yet, with more than two hundred years of study on the genome, we are just starting to realize the complexity lies within ...

The course is designed for students to learn:

- 1) Basic knowledge of the genomic structure and its role in transcriptional regulation.
- 2) Cutting-edge techniques and bioinformatics used in the field.
- 3) Practical experience in bioinformatic analysis.
- 4) Frontier research principles and methodology.
- 5) Mysteries and dilemmas remained unsolved.

## **Syllabus**

### **Week 1 – 1**

#### **DNA, Chromatin, and Transcription**

Introduction to the structure basis of DNA, nucleosomes, chromatins, and nucleus; Histone modifications and DNA methylations; Elements of genes and the transcription program; *Cis*- and *trans*-regulation.

### **Week 1 – 2**

#### **Methods to Discovery**

Quantification of gene expression (from RNA to proteins); Functional analysis of genes: fluorescent reporter assay, *in situ* hybridization, genetic perturbations (RNAi, CRISPR/Cas system, and protein degrons); Introduction to omics.

### **Week 2 – 1**

#### **Sequence, Omics, and Bioinformatics I**

Three generations of sequencing; Sequence alignment; Genomics and genome element (GWAS); Transcriptomics (RNA-seq & nascent RNA-seq).

## **Week 2 – 2**

### **Sequence, Omics, and Bioinformatics II**

Functional annotation (GO & KEGG); Epigenomics (ATAC-seq, ChIP-seq, BS-seq); Hi-C; Screening and lineage tracing.

## **Week 3 – 1**

### **Transcriptional Regulation I: Enhancers and Transcription factors**

Role of enhancers and TFs in transcription initiation, pause-and-release, etc.; Study higher-dimensional architecture of genomes; Model of enhancer-promoter interactions; Enhancer RNA.

## **Week 3 – 2**

### **Transcriptional Regulation II: Epigenetics**

Epigenetic landscape of the genome; Epigenetic marks of gene activation and silencing; Regulation and dynamics of epigenetics and chromatin remodeling; Epigenetics in development.

## **Week 4 – 1**

### **Transcriptional Regulation III: Condensates and Bursting?**

Lipid-lipid phase separation in cells; Novel (yet skeptical) theory of condensates/ clusters/hubs; Dynamics of condensate; Transcriptional bursting.

## **Week 4 – 2**

### **A Case of Study – Estrogen Receptor**

Estrogen response pathway; Binding of estrogen receptor; Mechanism of estrogen-induced transcription; MegaTrans enhancers.

## **Week 5 – 1**

### **A Case of Study – Enhancer-Promoter Contact and 3D Organization**

Global analysis of chromatin folding; Advanced technologies (Micro-C & MERFISH); Shaping of enhancer-promoter contact; Discoveries against canonical theory; Problems of heterogeneity.

## **Week 5 – 2\***

### **The 4D Genome and New Paradigm**

Summary of the hierarchical 3D structure of chromatin; Reconstruction of the 3D genome; Reorganization of the genome during development; Structure-determined phenotype and diseases.

## **Week 6**

### **Final**

Presentation and Q&A.