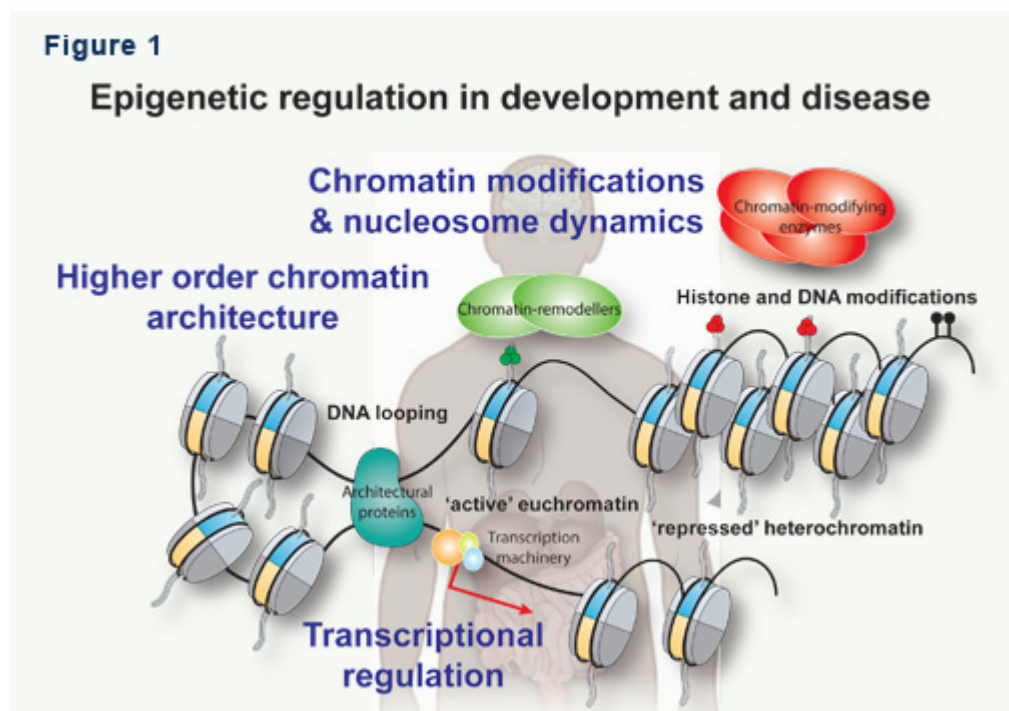


# Research

## Chromatin Dynamics & Disease Epigenetics

Epigenetic regulators help to establish cell-type specific gene expression patterns and maintain long-term cellular memory and identity. Together with transcription factors, they form the frontline mechanisms underlying developmental stability and cellular homeostasis. Accordingly, aberrant regulation of epigenetic mechanisms can result in cellular pathologies. Notably, recent genome-sequencing studies have uncovered recurring mutations in a large cohort of chromatin regulators that are causally implicated in cancer as well as in various human developmental disorders. Environmental influences can also contribute to disease pathophysiology via epigenetic mechanisms. These findings underscore an urgent need to evaluate the role of epigenetic processes in development and disease (**Figure 1**).



**Figure 1: Epigenetic regulation in development and disease.**

Chromatin is the basic regulatory unit of the eukaryotic genetic material. It comprises repeating arrays of nucleosomes, each consisting of 147 bp of DNA wrapped around a histone octamer. They are subjected to various post-translational modifications (depicted as colored circles) and demarcate different transcriptional domains (euchromatin vs heterochromatin) in the genome. This wealth of epigenetic information on the chromatin is further organized spatially, in a three-dimensional manner in relation to the nuclear structure. Distinct epigenetic and transcription factor complexes cooperate to instruct gene expression patterns, supervising cell fate decisions. Deregulation of epigenetic profiles (e.g., directly caused by genetic mutations in genes that encode for chromatin regulators or indirectly through environmental influences)

is frequently observed in human pathologies, including complex multifactorial diseases such as cancer, metabolic and neurological disorders.

Our goal is to work towards formulating a comprehensive understanding of the epigenetic basis of human diseases, and we seek to achieve this by interfacing basic mechanistic studies with translational research. Notably, the reversibility of epigenetic processes presents a therapeutic opportunity to restore proper gene expression patterns and revert diseased phenotypes towards normality. We are particularly interested in chromatin deficiencies that underlie age-related neurodegenerative disorders such as Alzheimer's disease, to understand how the affected epigenetic pathways interact with genetic risk factors, and ultimately identify epigenetic agents that may exert neuroprotective effects. We are also interested to study how transcriptional and chromatin aberrancies promote tumorigenesis and to identify new epigenetic targets in cancer. To address these questions, we employ mouse models and use human pluripotent cells to determine the functional causality of disease-associated variants, and utilize an assortment of molecular tools to interrogate epigenetic changes (eg., at the level of DNA and histone modifications, chromatin remodelling, as well as higher-order nuclear organization) during disease initiation and progression. In doing so, we aim to elucidate disease mechanisms that will guide the development of new epigenetic-based therapeutic modalities.

In the other major strand of research in the group, we are interested to explore the relationship between chromatin plasticity and cellular potency. We utilize different experimental models of tissue regeneration and epigenetic reprogramming. The latter includes natural reprogramming events that occur in early embryogenesis and germline, as well as during induced pluripotency *in vitro*. Our objective is to uncover unifying principles of cellular reprogramming, and to leverage this knowledge to re-engineer cellular phenotypes at will through manipulation of chromatin structure and function, for regenerative medicine applications.

We employ a varied experimental approach that includes the use of Next-Generation Sequencing technologies, genome-editing tools, biochemical and molecular assays, embryology, as well as stem cells and animal models to address our questions of interest (Figure 2).

**Figure 2**

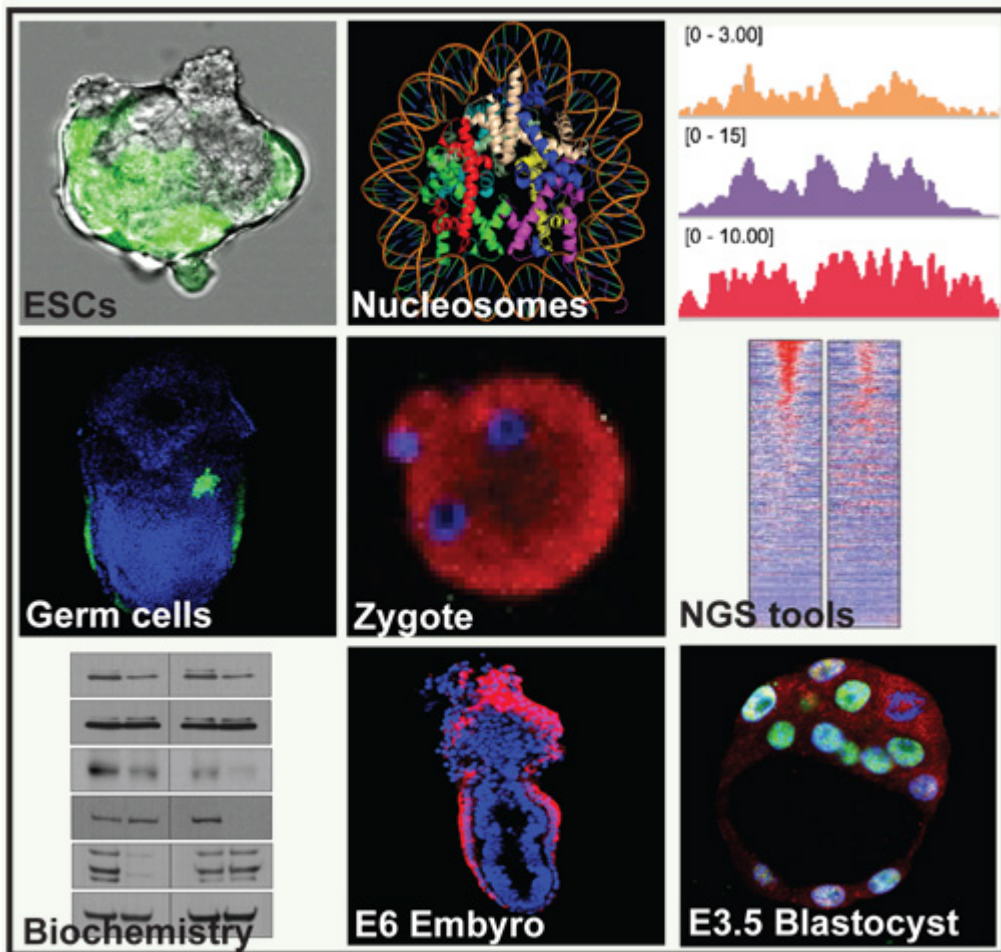


Figure 2: Collection of images depicting some of the different experimental systems and approaches used.

Key interests:

Chromatin biology | Neurobiology | Epigenetic reprogramming | Pluripotency | Germ cells | Disease modelling and regenerative medicine

We are constantly on the lookout for highly motivated students, postdocs, A\*STAR scholars and computational biologists to join our team! A number of different Ph.D. scholarships and postdoctoral fellowships are available for both local and overseas candidates. Interested applicants can contact Wee-Wei Tee ([wwtee@imcb.a-star.edu.sg](mailto:wwtee@imcb.a-star.edu.sg)) directly for more information.