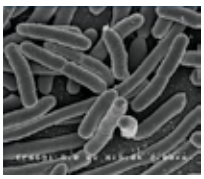
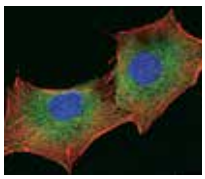
Project Leader **Hisao Masai** Genome Dynamics Project

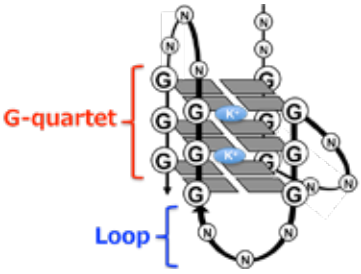
Genome Replication and Maintenance:
In search of unexplored messages in the genome

Precise duplication of genetic materials is central to the stable maintenance of genomes through generations. Defects in the genome copying processes would generate genomic instability which could ultimately result in various diseases including cancer. The goal of our studies is to understand the molecular basis of how the huge genomes are accurately replicated and the precise copies of the genetic materials are inherited to the next generation. Three billion base pairs of the human genome (2 meter long) are replicated with almost no errors during the 6-8 hr time span of the cell cycle. This requires an extreme level of coordination of temporal and spatial arrangements of chromatin organization and signaling events for initiation of DNA replication.

"We are trying to decipher 'unexplored messages' of the genome that are crucial for shaping the chromosomes, copying and reading out genetic information, and even for causing detrimental diseases."

We recently discovered novel and crucial roles of non-standard DNA structures in regulation of DNA replication and transcription. Notably, we found that G-quadruplex structures, which are widely present on genomes (estimated to be present at more than 370,000 locations on the human genome), regulate organization of chromatin architecture and initiation of DNA replication. Our major goal is to establish a novel principle of the genome by elucidating the fundamental and universal functions of G-quadruplex and other non-B type DNA structures in regulation of various genome functions. Through these efforts, we will also explore the possibility that mutations found in various diseases including cancer and neurodegenerative diseases are related to alteration and mal-formation of these non-B DNA structures, which are likely to be essential components of genomes but somehow have been disregarded in the past.



Masai H. et al. (2018) "Molecular architecture of G-quadruplex structures generated on duplex Rif1 binding sequences." ***J. Biol. Chem.*** in press

Moriyama K, Yoshizawa-Sugata, N, and Masai H. (2018) "Oligomer formation and G-quadruplex binding by purified murine Rif1 protein, a key organizer of higher-order chromatin architecture." ***J. Biol. Chem.*** 293:3607-3624.

You Z, and Masai H. (2017) "Potent DNA strand annealing activity associated with mouse Mcm2~7 heterohexamer complex." ***Nucleic Acids Res.*** 45: 6495-6506.

Yang C-C, Suzuki M, Yamakawa S, Uno S, Ishii A, Yamazaki S, Fukatsu R, Fujisawa R, Sakimura K, Tsurimoto T, and Masai H. (2016) "Claspin recruits Cdc7 kinase for initia-tion of DNA replication in human cells." ***Nature Commun.*** 7: 12135.

Kanoh Y, Matsumoto S, Fukatsu R, Kakusho N, Kono N, Renard-Guillet C, Masuda K, Iida K, Nagasawa K, Shirahige K, and Masai H. (2015) "Rif1 binds to G-quadruplexes and suppresses replication over long distances." ***Nature Struct. Mol. Biol.*** 22: 889-897.

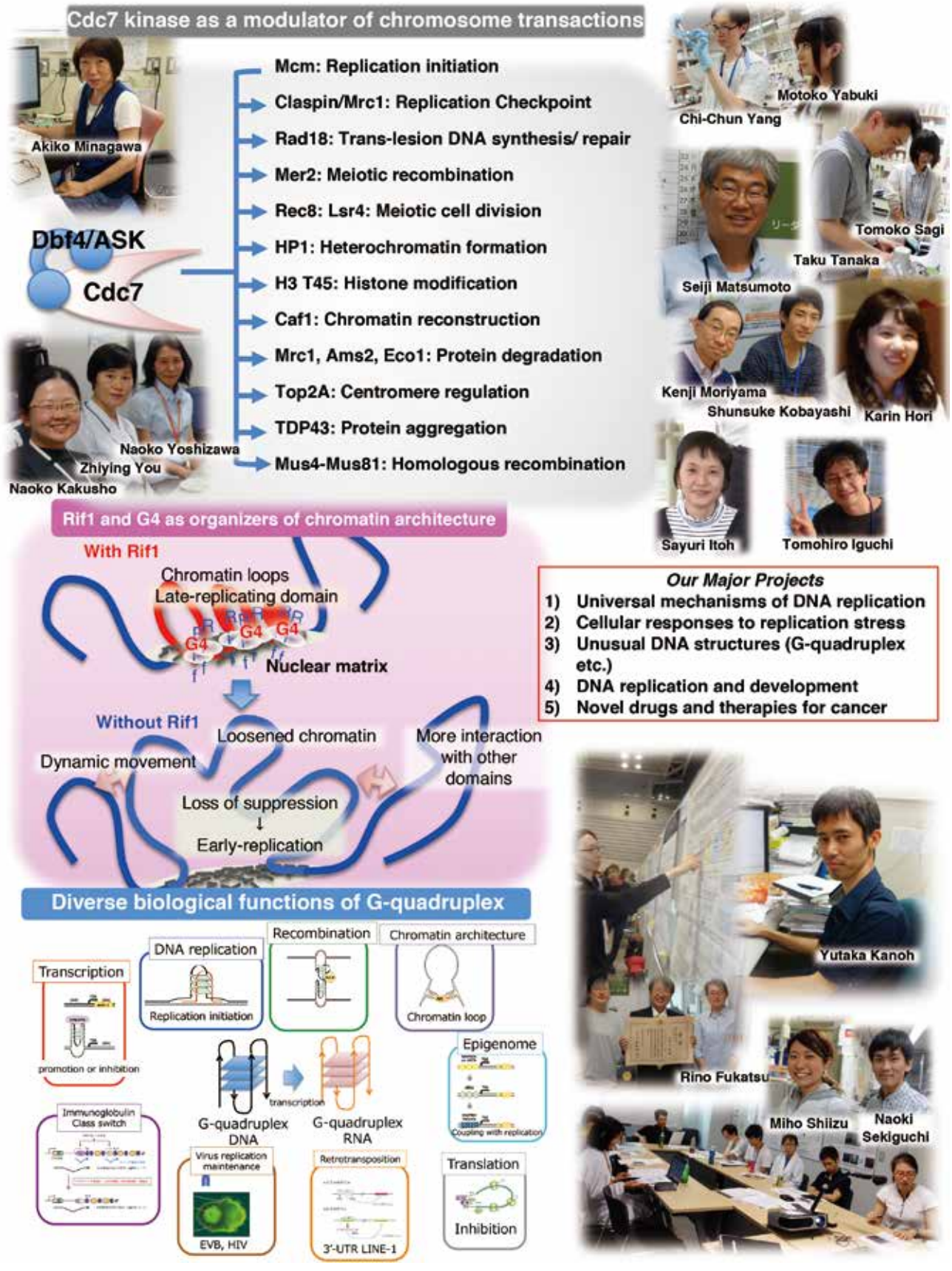
Yamazaki S, Ishii A, Kanoh Y, Oda M, Nishito Y, and Masai H. (2012) "Rif1 protein is a key regulator of the genome-wide DNA replication timing in human cells." ***EMBO J.*** 31: 3167-3177.

Hayano M, Kanoh Y, Matsumoto S, Shrahige K, and Masai H. (2012) "Rif1 is a global regulator of timing of replication origin firing in fission yeast." ***Genes and Development*** 26: 137-150.

Matsumoto S, Hayano M, Kanoh Y, and Masai H. (2011) "Multiple path-ways can bypass the essential role of fission yeast Hsk1 kinase in DNA replication initiation." ***J. Cell Biol.*** 195: 387-401.

Masai H, Matsumoto S, You Z, Yoshizawa-Sugata N, and Oda M. (2010) "Eukaryotic DNA replication; where, when and how?" ***Annual Rev. Biochem.*** 79: 89-130.

Genome Dynamics



Genome Dynamics