**Name of PI:** Evi Soutoglou
**Project Title:** DNA Damage Regulation at Lamina-Associated Domains: Implication in Premature Aging Syndromes
**Project Description:**
The nuclear lamina provides structural support to the nucleus and regulates key processes such as chromatin organization, transcription, and genome stability. Lamina-associated domains (LADs), comprising 40% of the human genome, play a crucial role in maintaining genome integrity. This project aims to unravel the mechanisms governing DNA repair at LADs, using innovative protein-targeting strategies to induce LAD-specific DNA breaks and isolate repair-associated factors. By identifying the proteins and pathways involved, this study will clarify how LADs suppress recombination and ensure their integrity. Hutchinson-Gilford progeria syndrome, linked to Lamin A mutations and progerin accumulation, will be used as a disease model to explore how nuclear lamina dysfunction compromises genome stability. The findings will advance our understanding of genome protection and may identify potential therapeutic targets for laminopathies and related disorders.

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**Name of PI:** Jon Baxter
**Project Title:** The Role of TOP2A in the DDR
**Project Description:**
Topoisomerase II (Top2) is essential for resolving topological challenges in cells and its activity is targeted by several cancer therapies. The unstructured C-terminal region of human Top2A interacts with the BRCT2 domain of MDC1, a key protein in DNA damage sensing and signalling. This project will investigate the role of Top2A in DNA damage checkpoint activation by exploring potential phospho-dependent interactions between Top2A and DNA damage signalling proteins. By defining the cellular role of these interactions, the project aims to uncover how Top2A functions as a platform for DNA damage signalling and its potential as a therapeutic target for cancer treatment.

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**Name of PI:** Dr. Chris Kok-Lung Chan
**Project Title:** Investigation of Chromosome Protection Mechanisms in Human Mitotic Cells
**Project Description:**
Effective DNA damage and repair responses (DDRs) are crucial to suppress cancer initiation and evolution. While DDRs are well studied in mammalian interphase cells, their role during mitosis remains poorly understood. This project will investigate how

human mitotic cells sense DNA damage and coordinate mitotic progression. Techniques such as CRISPR-genome editing, RNA interference, high-resolution microscopy, and live-cell imaging will be used to study the impact of DNA lesions on chromosome segregation in normal and cancerous cells. The goal is to gain a fundamental understanding of DNA replication, cell cycle regulation, and mitosis, advancing knowledge of DDRs and chromosome stability.

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**Name of PI:** Helfrid Hochegger
**Project Title:** Exploring New Cancer Targets Using Induced Degradation Approaches to Validate PROTAC Approaches
**Project Description:**
Cancer is a disease of deregulated cell division, and cell cycle control genes are prime targets in cancer therapy. PROTACs (Proteolysis Targeting Chimeras) offer a promising approach to target oncogenes for degradation. This project aims to develop new induced degradation approaches for setting up pre-clinical target validation pipelines focused on cell cycle control genes that drive tumorigenesis. The goal is to discover novel cancer targets and validate them using the PROTAC technology, paving the way for new therapeutic strategies.

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**Name of PI:** Jon Baxter
**Project Title:** Investigating the Role of Topoisomerase II in the DNA Damage Checkpoint
**Project Description:**
Topoisomerase II (Top2) plays a crucial role in resolving topological challenges within the cell and is targeted by various cancer therapies. This project aims to explore the phospho-dependent interactions between the C-terminal region of Top2A and several DNA damage signalling proteins, uncovering its role in the activation of the DNA damage checkpoint machinery. The research will investigate how Top2A functions as a platform for DNA damage signalling and whether this pathway can be targeted for therapeutic intervention in cancer.

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**Name of PI:** Evi Soutoglou
**Project Title:** The Role of Recombination in Centromeric DNA Stability
**Project Description:**
Centromeric DNA, due to its repetitive nature, is prone to recombination, a process once thought to be harmful. Recent research suggests that homologous recombination (HR) plays a protective role at centromeres, preventing illegitimate recombination and mutagenic events. This project will investigate the molecular factors involved in centromeric recombination and its role in centromere specification. By understanding

how recombination at centromeres contributes to genome stability, the project aims to shed light on its implications for cell identity and tumorigenesis.

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**Name of PI:** Aidan Doherty
**Project Title:** How Is Stalled DNA Replication Restarted in Human Cells?
**Project Description:**
DNA damage tolerance pathways enable cells to bypass lesions that block replication, ensuring genomic integrity. This project will investigate the role of PrimPol in restarting stalled DNA replication forks in human cells. By studying PrimPol's function in DNA replication, the project aims to understand how it maintains genome duplication efficiency and its overlap with other damage tolerance pathways. Insights from this research will help relate PrimPol's role in genome instability and diseases such as cancer.

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**Name of PI:** Aidan Doherty
**Project Title:** Understanding How DNA Replicases Function in CRISPR-Cas Adaptation
**Project Description:**
CRISPR-Cas systems provide prokaryotes with immunity against foreign genetic elements. This project will explore how CRISPR-associated Primase-Polymerases (CAPPs), along with Cas1 and Cas2, function in CRISPR-Cas adaptation. The project will investigate CAPPs' DNA synthesis activities, including primase, polymerase, and strand-displacement activities, and how they contribute to CRISPR adaptation processes. The research aims to provide new insights into the molecular mechanisms behind CRISPR-Cas immunity and related processes.

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**Name of PI:** Alessandro Bianchi
**Project Title:** Activation of Human Telomerase
**Project Description:**
Cancer cells activate telomerase to maintain telomere length, enabling immortality. This project will investigate the processes required for telomerase activation in human cells, focusing on the protein factors involved. The research will explore how telomerase activity is regulated and its implications for human ageing and health. Given that telomerase dysfunction is linked to genetic disorders, the project aims to provide insights into telomerase's role in ageing and potential therapeutic targets for related conditions.

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**Name of PI:** Matthew Neale
**Project Title:** Spatiotemporal Dynamics of Meiotic Proteins in Saccharomyces. cerevisiae
**Project Description:**
Genetic recombination during meiosis is essential for fertility and genetic diversity. This project will explore the spatial-temporal dynamics of chromosome binding and the redistribution of protein factors involved in genetic recombination in Saccharomyces. cerevisiae. The project will involve high-resolution microscopy, genome-wide methods such as ChIP-seq and Hi-C, and bioinformatic data analysis. It is ideal for a candidate with a background in genetics, molecular biology, and computational techniques.

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**Name of PI:** Matthew Neale
**Project Title:** Data Scientist: In Silico Exploration of Spatiotemporal Dynamics of Genetic Recombination in Saccharomyces.cerevisiae
**Project Description:**
This project will use bioinformatic analysis to explore the initiation and morphogenesis of meiotic recombination in Saccharomyces.cerevisiae. The project will involve developing analytical scripts to process and analyse genome-wide datasets, such as ChIP-seq and Hi-C. It is ideal for a candidate with a computer-science background, experience in bioinformatic analysis, and an interest in biological systems.

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**Name of PI:** Matthew Neale
**Project Title:** How Does Chromosome Organisation Impact DNA Repair and Genome Stability?
**Project Description:**
This project will explore the role of topoisomerases in DNA repair and genome stability. Using high-resolution methods such as Hi-C, the project will investigate topological changes during DNA double-strand break repair and their influence on genome architecture. By understanding how topoisomerases influence DNA repair pathways, the project aims to provide insights into genome stability and the effects of topoisomerase failure, particularly in the context of DNA damage and repair.