



## ChromStretch: A New Horizon in Replication Fork Protein Discovery and Biomarkers in DNA Damage Repair

Transformative Insights into Protein Dynamics at Replication Fork for Next-Generation Drug Development

### Key advantages of ChromStretch

- **Single Molecule Precision:** Unveils intricate chromatin dynamics at individual replication forks, crucial for targeted therapy development. Dynamics of DNA damage response factors at single molecule level i.e  $\gamma$ H2AX, RPA, RAD51) and Chromatin landscape associated with replication stress response i.e PCNA, RPA, RAD51, RNP11,  $\gamma$ H2AX, H2AK15, H3K9me3 H3K9me2, H3K9me1, total H3
- **Rapid Analysis:** Accelerates the journey from sample to insight, catering to the fast-paced needs of therapeutic R&D.
- **High Throughput:** Analyzes large sample volumes simultaneously, enhancing efficiency in biomarker discovery.
- **Biomarker Discovery:** Identifies crucial biomarkers through detailed chromatin modification insights, opening new pathways for diagnostics and therapeutics.
- **Quantitative Insights:** Offers precise, quantitative data on chromatin modifications, supporting advanced therapeutic strategies. Compatible with wide-range of confocal to advanced, super-resolution, SIM to STED, microscopes for imaging.
- **Versatile R&D Tool:** Adaptable for a broad spectrum of research, from basic science to advanced therapeutic development.





### Potential impact

## **The Impact of ChromStretch Technology**

ChromStretch technology stands at the forefront of innovation in DNA Damage Repair therapeutic research offering unparalleled advantages. With its single molecule precision, ChromStretch unveils the intricate protein dynamics of chromatin at individual replication forks, a breakthrough crucial for the development of targeted therapies. This precision, combined with the technology's capacity for rapid analysis, significantly accelerates the journey from complex biological samples to actionable insights, meeting the urgent demands of therapeutic R&D. Furthermore, its high throughput capabilities allow for the simultaneous analysis of vast sample volumes, vastly enhancing the efficiency of biomarker discovery processes. This is complemented by ChromStretch's ability to identify critical biomarkers through detailed observations of chromatin modifications, paving new pathways for diagnostics and therapeutics.

In the recent publication [Gaggioli et al, Nature Cell Biology 2023](#) utilizing ChromStretch technology, researchers have made significant strides in understanding the role of G9A, a histone methyltransferase, under replication stress conditions—a crucial aspect for targeted therapy development in cancer and other diseases characterized by aberrant chromatin dynamics. By applying ChromStretch to visualize the transient accumulation of the H3K9me3 mark at replication forks, associated with G9A activity, at single-molecule resolution in human lung fibroblast cells, the study revealed a remarkable correlation between G9A-mediated chromatin modifications and replication fork stability under stress induced by hydroxyurea (HU).

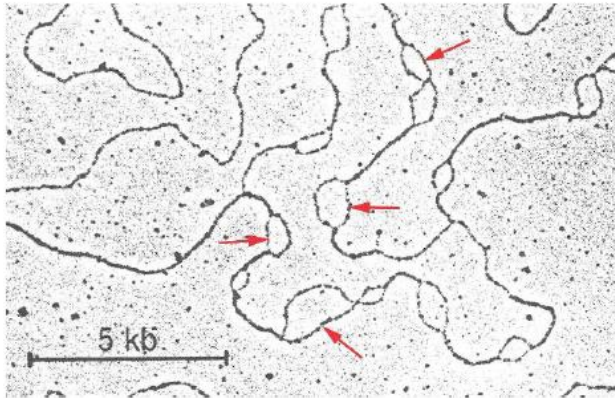
This nuanced insight was made possible by ChromStretch's unparalleled precision in mapping chromatin dynamics at individual replication sites, demonstrating a previously unappreciated layer of replication stress response.

Through ChromStretch, quantitative insights can be obtained into chromatin modifications, ChromStretch supports the development of advanced therapeutic strategies with a level of detail previously unattainable. As a versatile R&D tool, it adapts across a broad spectrum of research areas, from basic science to the cutting edge of therapeutic development, embodying the next step in the evolution of precision medicine.

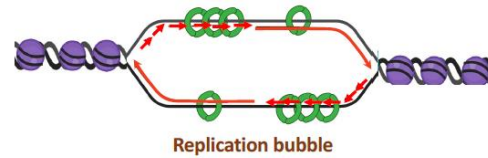




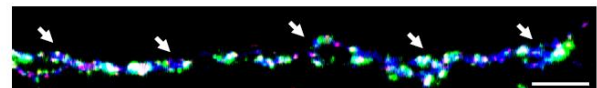
**Fig. 1 ChromStretch: Visualization of proteins associated with the replication fork at the single molecule level**



Replication bubbles imaged by  
Electron microscope



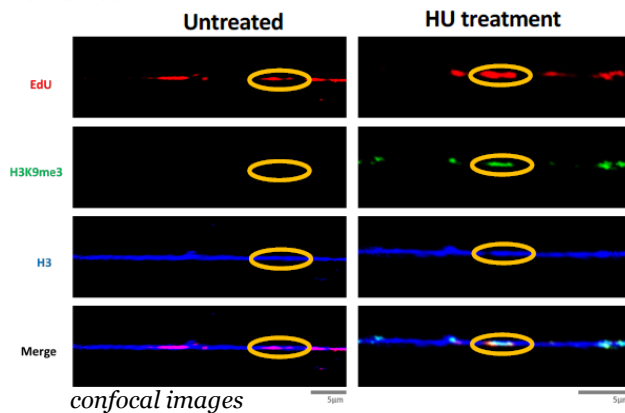
ChromStretch



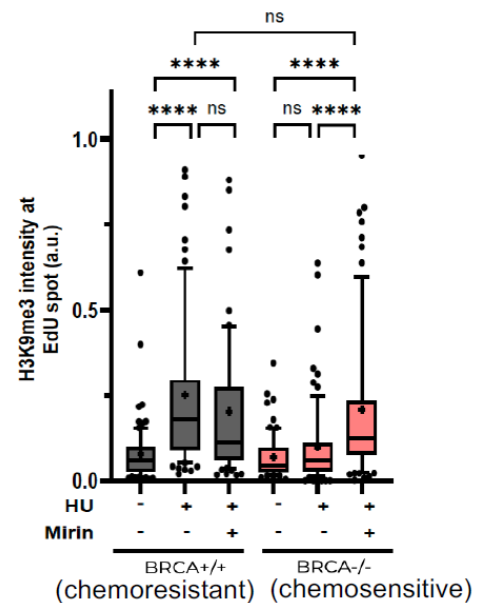
Replication bubbles imaged by  
super-resolution (SIM) fluorescent microscope

**Fig. 2 Casestudy: Identification of H3K9me3 as a biomarker for predicting response to drug therapy in ChromStretch**

ChromStretch



- H3K9me3 accumulates at replication forks upon replication stress
- Inhibition of G9a abolishes H3K9me3 at replication forks
- H3K9me3 levels reduces at degraded forks in BRCA<sup>-/-</sup> cells



(n > 150 replication bubbles quantified per sample)





## Fig. 3 Superiority of ChromStretch over existing chromatin dynamics analysis tools

Table of comparison synthetic lethality research vs vastly used iPOND vs ChromStretch

	SL Pipeline	iPOND-SILAC	ChromStretch
Duration	Days-week	Days-week	Hours-day
Genetic Screens	At cellular level	At molecular level	At molecular level
Validity	Require repetition	Accurate but laborious; involves many critical steps (e.g., risk factors such as sonication length, label differences, etc.)	Accurate in single experiment; less laborious
Number of markers that can be studied	2 marker at a time	Multiple marker	Multiple marker combinations possible (For forks: H3K9me3 & Rad51 with EdU) (For DNA damage: γH2AX & RPA)
Material Requirement	1 - 2 x 10 <sup>3</sup>	> 2 x 10 <sup>7</sup>	50-100 cells
Tissue applicability	?	NA	Promising
Cost efficiency	?	Expensive	affordable

Oncode Reference No. 2024-007

**Oncode investigator(s)** Nitika Taneja, Associate Professor

**References** [Gaggioli et al, Nature Cell Biology 2023](#)  
[Lo et al, Science Advance 2021](#)

**Patent status** PCT filing WO2023/172142

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