Lossless Altered Histone Modification Analysis System (LAHMAS)

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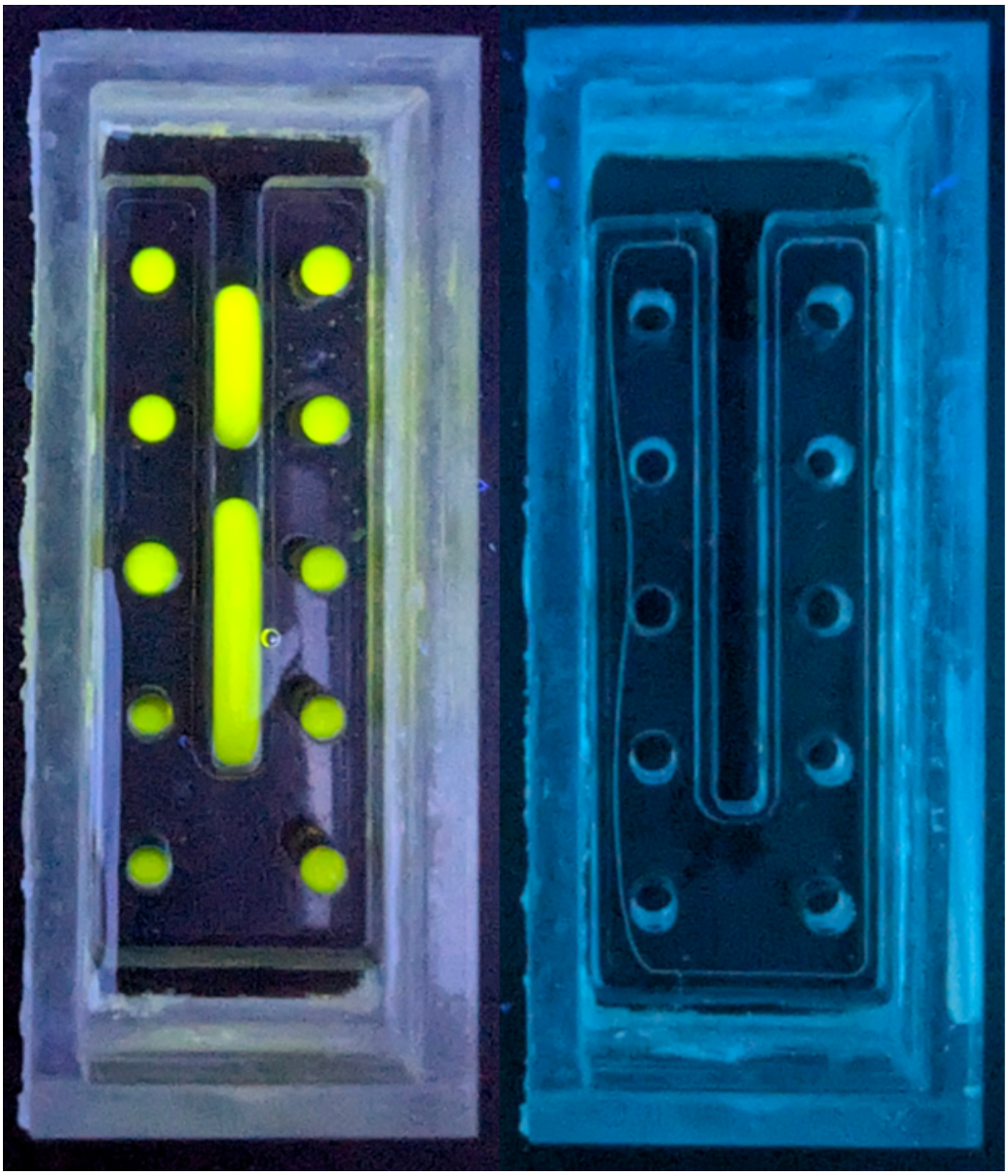
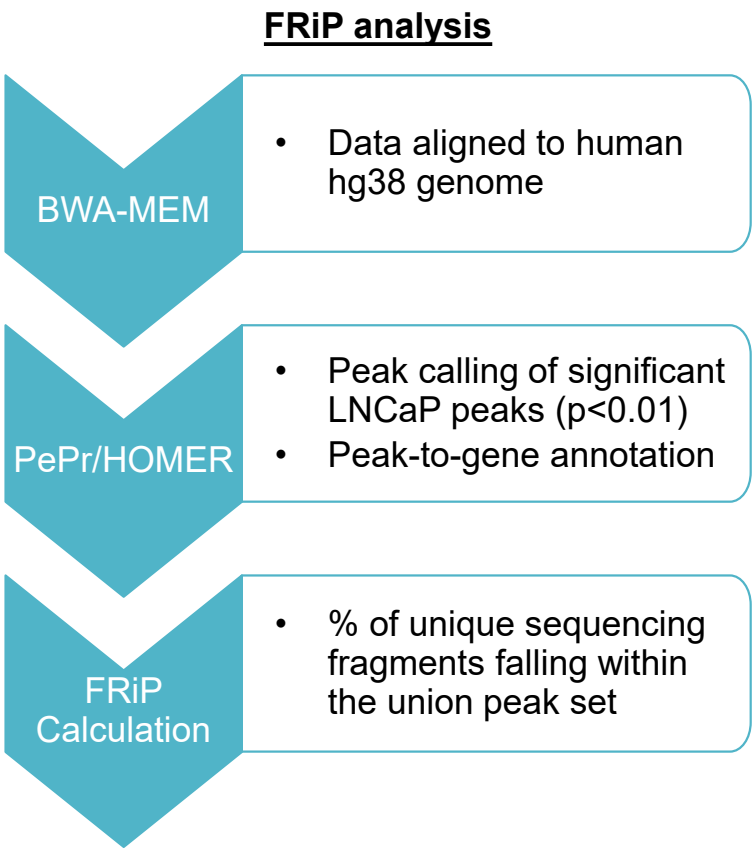
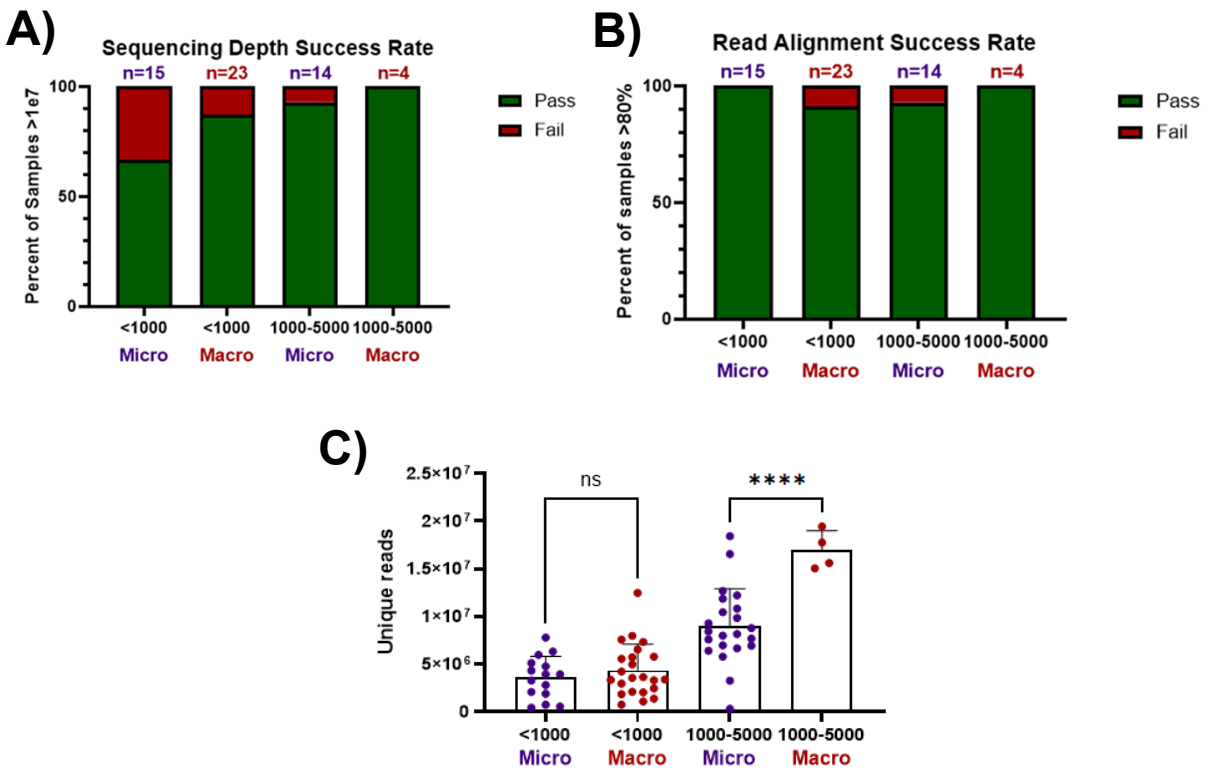


Supplementary Figure 1: Image of LAHMAS insert within device during and after adsorption-based fouling was utilized to test the ELR treatment in the devices after fabrication. Silicone oil and cell culture media containing 10% FBS and 1 µM fluorescein was added to devices and incubated overnight. Culture media was forcefully pipetted through the channels and allowed to settle into the wells. After overnight incubation, the devices were imaged under ultraviolet light (left). The devices were then inverted to drain the liquid and imaged under ultraviolet light to determine the extent of adsorption-based fouling (right). Any presence of fluorescein after devices were drained of liquid constituted a failure, since ELR must be ubiquitous across every surface to completely repel aqueous reagents. Unfouled devices (right) were rinsed thoroughly with isopropyl alcohol before use.



Supplementary Figure 2: Bioinformatic workflow for macroscale/microscale CUT&Tag. Sequencing data (bed files: 10.6084/m9.figshare.29345030) aligned to human hg38 genome with BWA-mem. Significant peaks called with PePr ($p<0.01$) and annotated to specific genes with the HOMER annotatePeaks. Union peak set to define a broad range of H3K27Me3 occupancy regions developed from all called H3K27Me3 peaks among a previously unpublished large-scale LNCaP CUT&Tag dataset. Fraction of reads that fell in peaks (FRiP) of union peak set calculated from all unique fragments from sequencing reads of a sample falling within the union peak set. FRiP scores generated after peak calling on a sample-by-sample basis.

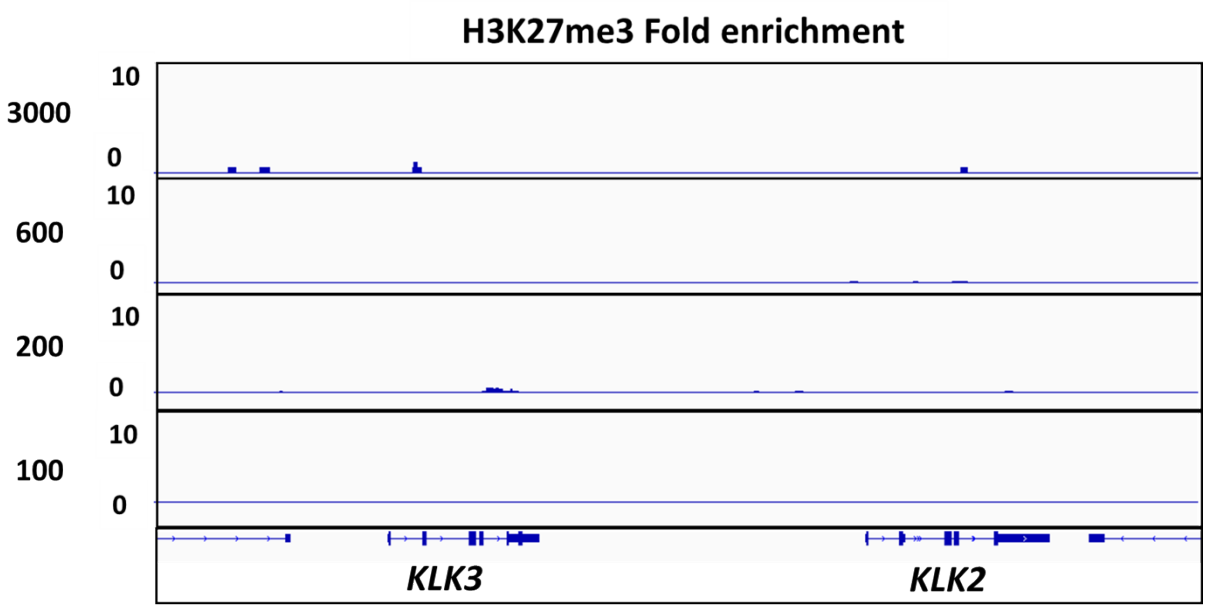
Supplementary Video 1: Beads are magnetically moved between the wells of the LAHMAS device. Hydrophilic nuclei and beads, when magnetically pulled between aqueous droplets through the oil phase, maintain a thin layer of aqueous fluid separating the analyte from the oil.



Supplementary Figure 3: Success rates for quality control metrics of CUT&Tag assays with inputs between 1000-5000 nuclei and lower than 1000 nuclei. The **A)** sequencing depth, **B)** alignment rate, and **C)** unique reads, between macroscale and microscale.

	LNCaP Range (Median)	**Patient-derived organoid**
Yield (ng/uL)	**0.147-5.15 (1.13)**	**5.36**
MACS FRiP	**1.79-29.91 (4.91)**	**10.21**
Unique Reads	**3260613-10454899 (6143742)**	**13098958**
MACS Peak Count	**428-18697 (737)**	**92629**
Alignment Rate	**98.36-99.73 (99.57)**	**88.7**
Sequencing depth	**7999318-24402610 (15555474)**	**26373122**

Supplementary Table 1: Average quality control metrics for LAHMAS CUT&Tag assays with LNCaP inputs between 600 and 2000 nuclei compared to primary PDOT sample.



Supplementary Figure 4: Sequencing tracks of H3K27Me3-tagged DNA fold enrichment over IgG negative control visualized on IGV viewer at the *KLK3* and *KLK2* genes. CUT&Tag assays were performed with a nuclear titration of 3000-600-200-100 in microscale.