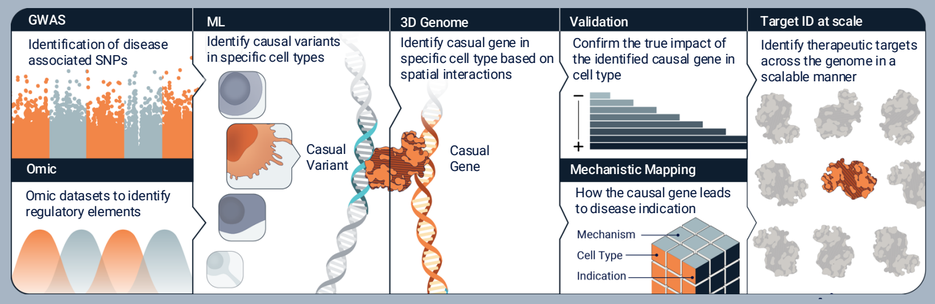
Illuminating the Dark Genome to enable drug discovery from human genetics

James Heward • James Smith • Lauren Owers • Brigid Davidson • Anna James-Bott • Emmanouela Repapi • Arnulf Hertweck • Basel Abu-Jamous • Stephen Harrison

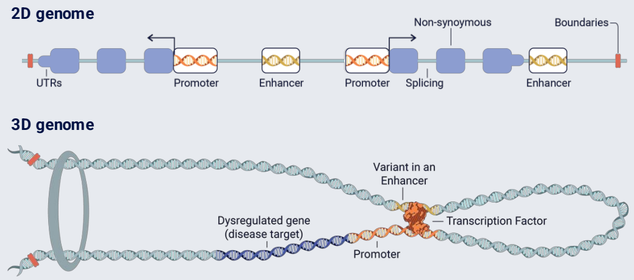
Nucleome THERAPEUTICS

Introduction — Nucleome platform unlocks human genetics for drug-discovery



- Genetic evidence increases **clinical success x2.6**[1-2]
- GWAS currently has the lowest increase in clinical success, likely due to **uncertainty** around causal gene identification
- Nucleome platform designed to solve human genetic variation with **precision & scale**, discover de-risked drug targets & provide unique insights into human disease via genetics

1 Nucleome uses principles of gene regulation to solve genetics

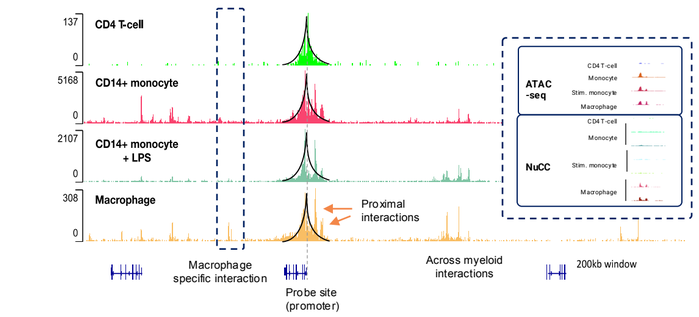


- Each GWAS signal must contain at least one variant altering gene **or** gene regulation
- NuML deep learning model **predicts variants** able to alter gene regulation
- Variants affecting enhancers require 3D genomics to be solved

2 Nucleome has developed best in class 3D genome technology

A **Only technique able to map at 1bp resolution and detect cell-specific 3D interactions**[3]

B



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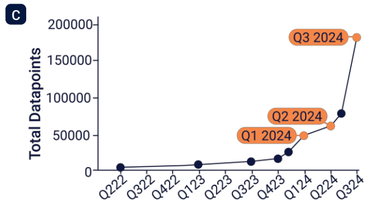
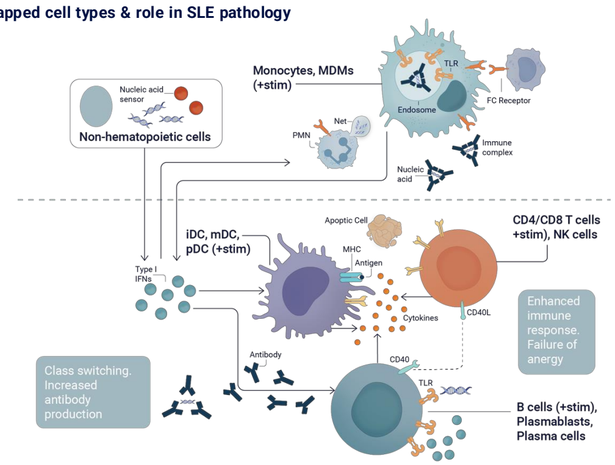


- **A** NuCC profiles showing 3D genome interactions with promoter of targeted gene. Each peak indicates a region which interacts with the promoter
- **B** Zoomed in plot showing NuCC and ATAC-seq
- **C** Improvements to NuCC has enabled dramatic increase in scale of analyses. Datapoint = Investigated gene or SNP x cell types x replicates

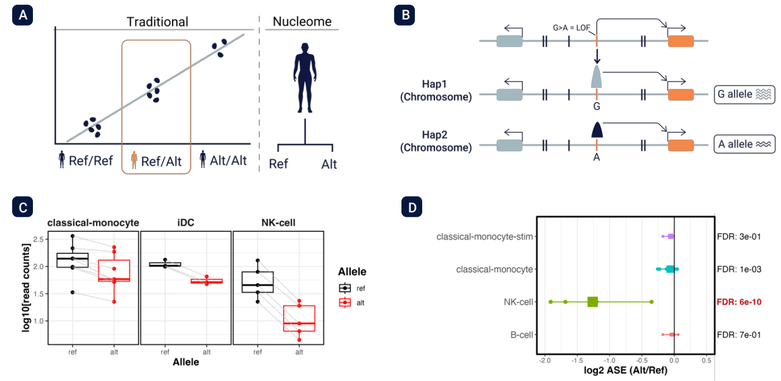
3 Technology applied to 1000s of autoimmune SNPs and multiple key cell types/conditions

3D mapped cell types & role in SLE pathology



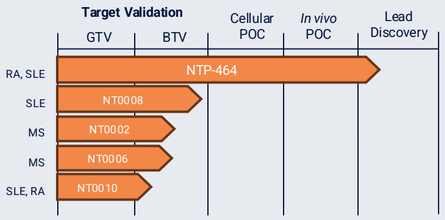
- Current focus on autoimmunity - ~3000 SNPs investigated to date
- 17 cell types examined so far, including *in vitro* derived models of rare cell types (e.g. plasma blasts & cells) and activation models

4 Nucleome has developed allele specific assays for validating SNP-gene interactions



- **A** Allele specific expression of heterozygotes ~10x more sensitive than traditional QTL approaches[4]
- **B** Nucleome has proprietary allele-specific assays for measuring activity of variants, 3D interactions and gene expression
- **C** Validation of variant: Example of disease-linked SNP that decreases enhancer activity in myeloid and NK cells
- **D** Validation of RNA: Effect of SNP C on expression of linked gene. Expression is lower on alternative allele in NK cells

Pipeline & outcomes



- First target (NTP-464) progressing through lead discovery
- Additional targets undergoing validation
- Use of additional Nucleome genetic analysis allows mapping of pathological mechanisms involving targets.

Conclusions

- Nucleome Therapeutics uses state-of-the art gene regulation approaches to solve population genetics with **precision and scale**
- We are validating several first-in-class genetically-validated drug-targets and are advancing NTP-464 through lead-discovery
- Gene regulation is the key to understanding human disease. Nucleome platform has applications beyond target ID e.g. patient selection biomarker identification, drug repurposing and pathological mechanistic mapping

References

1. Nelson et al. (2015). The support of human genetic evidence for approved drug indications. Nature
2. Genetics. Minikel et al. (2024). Refining the impact of genetic evidence on clinical success. Nature.
3. Hua et al. (2021). Defining genome architecture at base-pair resolution. Nature.
4. Zhabotynsky et al. (2022). eQTL mapping using allele-specific count data is computationally feasible, powerful, and provides individual- specific estimates of genetic effects. PLoS Genet.

Contact

Email : James.heward@nucleome.com

www.nucleome.com