neubase

The Future of Gene Editing is Stealth Editing™

Corporate Overview | June 2023

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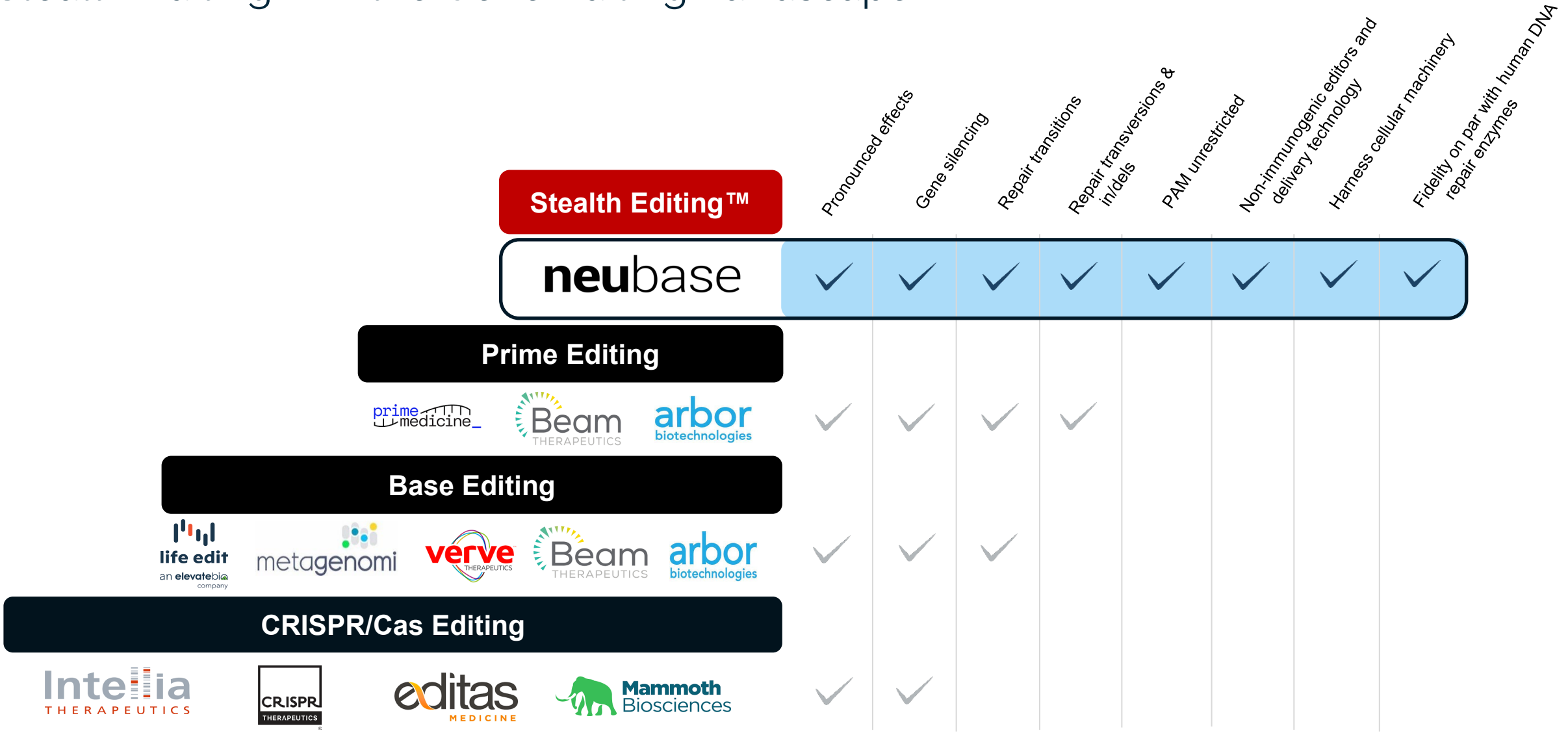
Stealth Editing™ in the Gene Editing Landscape



Immunogenicity from viral delivery systems and bacterial proteins presents a potential safety issue for patients receiving gene editing therapies

Stealth Editors™ - designed to fly under the radar of the immune system to effect high fidelity gene editing

Why Stealth Editors™

Non-viral Delivery

With a non-immunogenic system that can reach diverse tissues and cell types via systemic administration

Harnesses Cellular Mechanisms

Through the utilization of DNA repair machinery that has been refined over millennia to deliver precise on-target edits with minimal off-target edits

Pronounced *In Vivo* Effects

Through the resolution of pathogenesis in a titratable and re-dosable fashion

Broadly Applicable

Can achieve gene disruption/repair across multiple species and industries

In Vivo Editing Pipeline for Rare and Common Diseases

- Stealth Editors™ are likely safer and have more durable solutions for *in vivo* applications
- *In vivo* solutions are likely more cost-effective and safer than *ex vivo* solutions

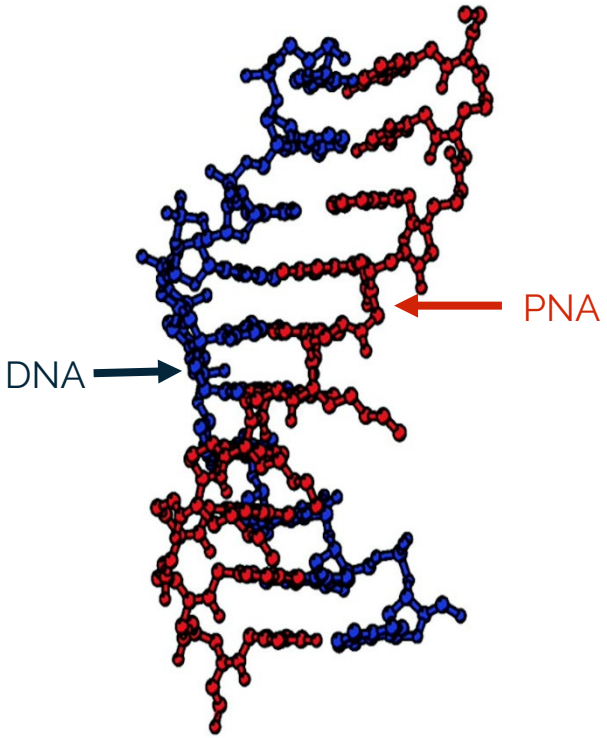
	Program	Target	Approach	Discovery / Preclinical / Clinical
Liver	Alpha-1 anti-trypsin disease	*SERPINA1*	Repair the PiZ mutation (E342K) of *SERPINA1* to increase serum levels of alpha-1-antitrypsin to address emphysema and liver disease	Prevalence ~33:100,000[1]
Liver	Undisclosed liver diseases	*Multiple*	Target selection in process	
Blood	β-thalassemia	*BCL11A*	Multi-base editing to disrupt the erythroid enhancer of *BCL11A* to induce hemoglobin switching only in red blood cells to correct the disease	Prevalence ~1:100,000[2]
Blood	Undisclosed blood diseases	*Multiple*	Target selection in process	
	Emerging	*Multiple*	Various human diseases and agricultural applications are being evaluated to identify uniquely addressable pipeline programs	

Ongoing target selection process: low competitive landscape, human genetic data, degree of unique ability to address causal mutation, availability of biomarker, short-term clinical endpoints, prevalence, unmet need, and *ex vivo* editing hits

[1]Brode SK, Ling SC, Chapman KR. CMAJ. 2012 Sep 4;184(12):1365-71; [2]https://rarediseases.org/rare-diseases/thalassemia-major/

Stealth Editors™ are Fully Synthetic and Non-Immunogenic

Peptide nucleic acids (PNAs) are modified to strand invade dsDNA in a highly selective way to form stable PNA-DNA complexes



Oligo donors (ODNs) are single-strands of DNA modified to eliminate immune responses and contain the correction

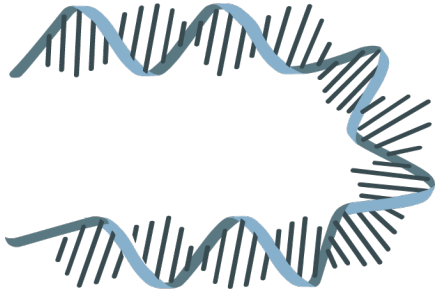
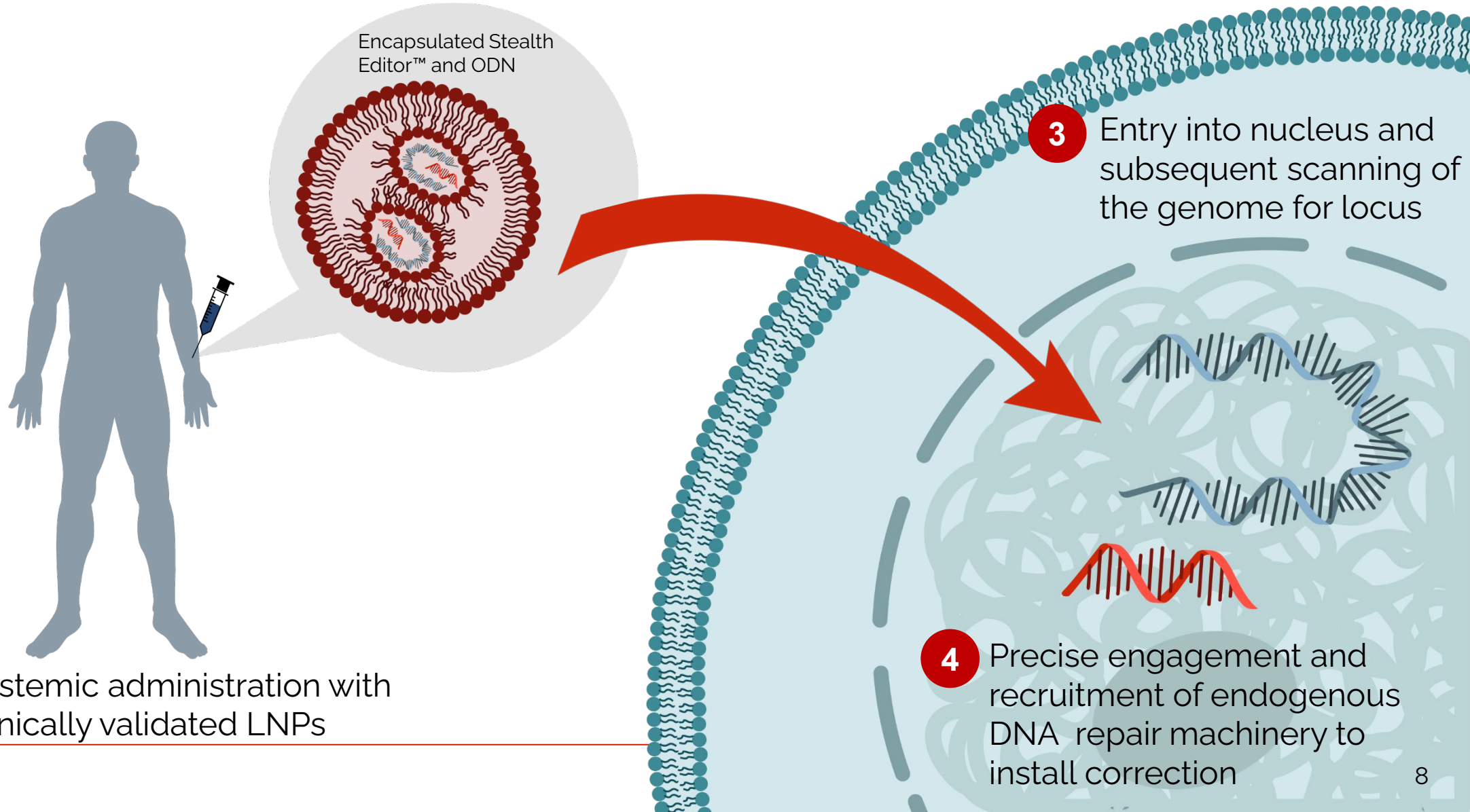


Image credit PNAS 2003, 100 (21), 12021

How Stealth Editors™ Work



1 Systemic administration with clinically validated LNPs

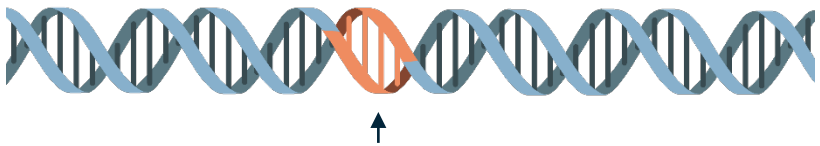
2 Stealth Editor™ enters the cytoplasm

3 Entry into nucleus and subsequent scanning of the genome for locus

4 Precise engagement and recruitment of endogenous DNA repair machinery to install correction

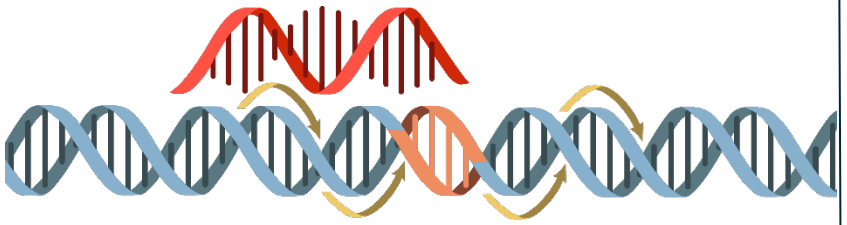
How Stealth Editors™ Work

1 A pathogenic variant in a gene sequence is selected for correction



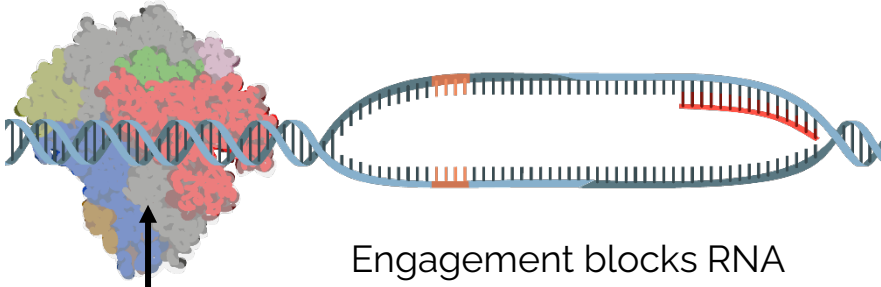
Target mutation or functional variant

2 A Stealth Editor™ scans the genome to identify the locus of interest



Modified peptide-nucleic acid queries sequences with high selectivity

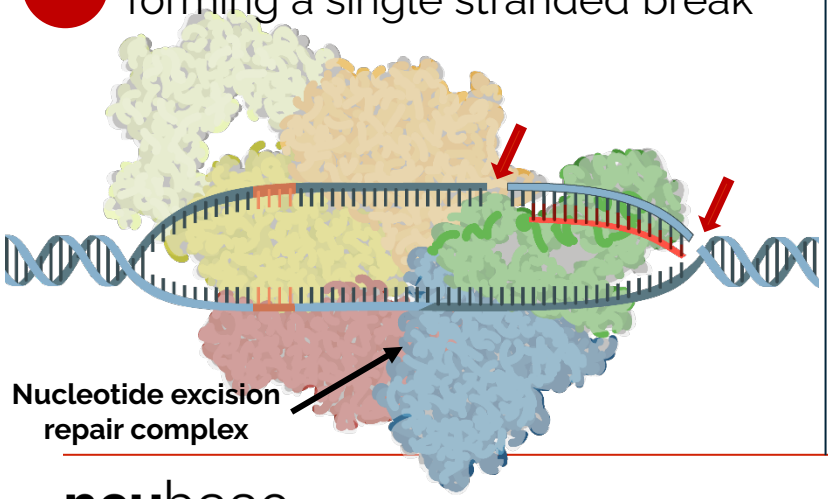
3 The editor engages proximal to the mutation and recruits repair machinery



RNA polymerase complex

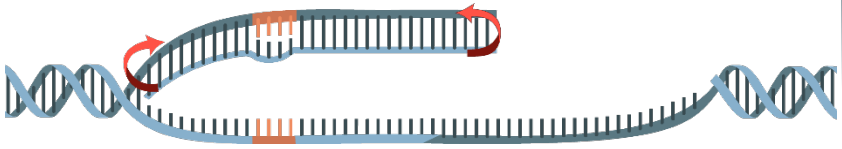
Engagement blocks RNA polymerase and/or causes helical distortion of genome which is sensed by cell

4 Target sequence is excised forming a single stranded break



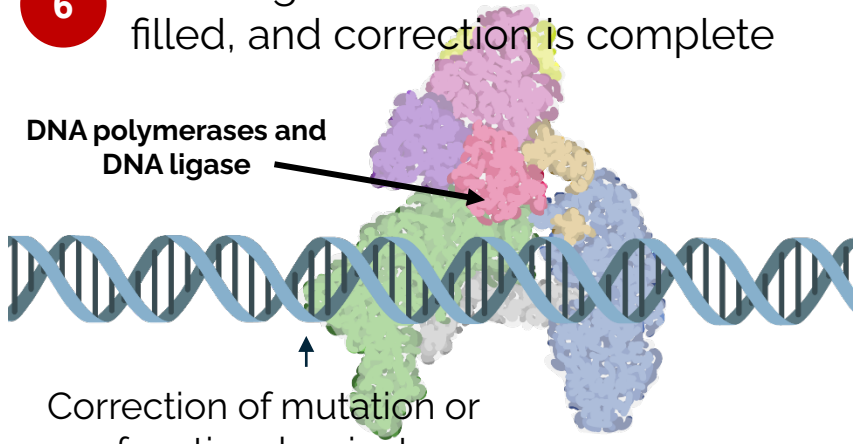
Nucleotide excision repair complex

5 A donor sequence engages in the flap and installs the donated sequence



Homology directed repair mechanisms install the ODN

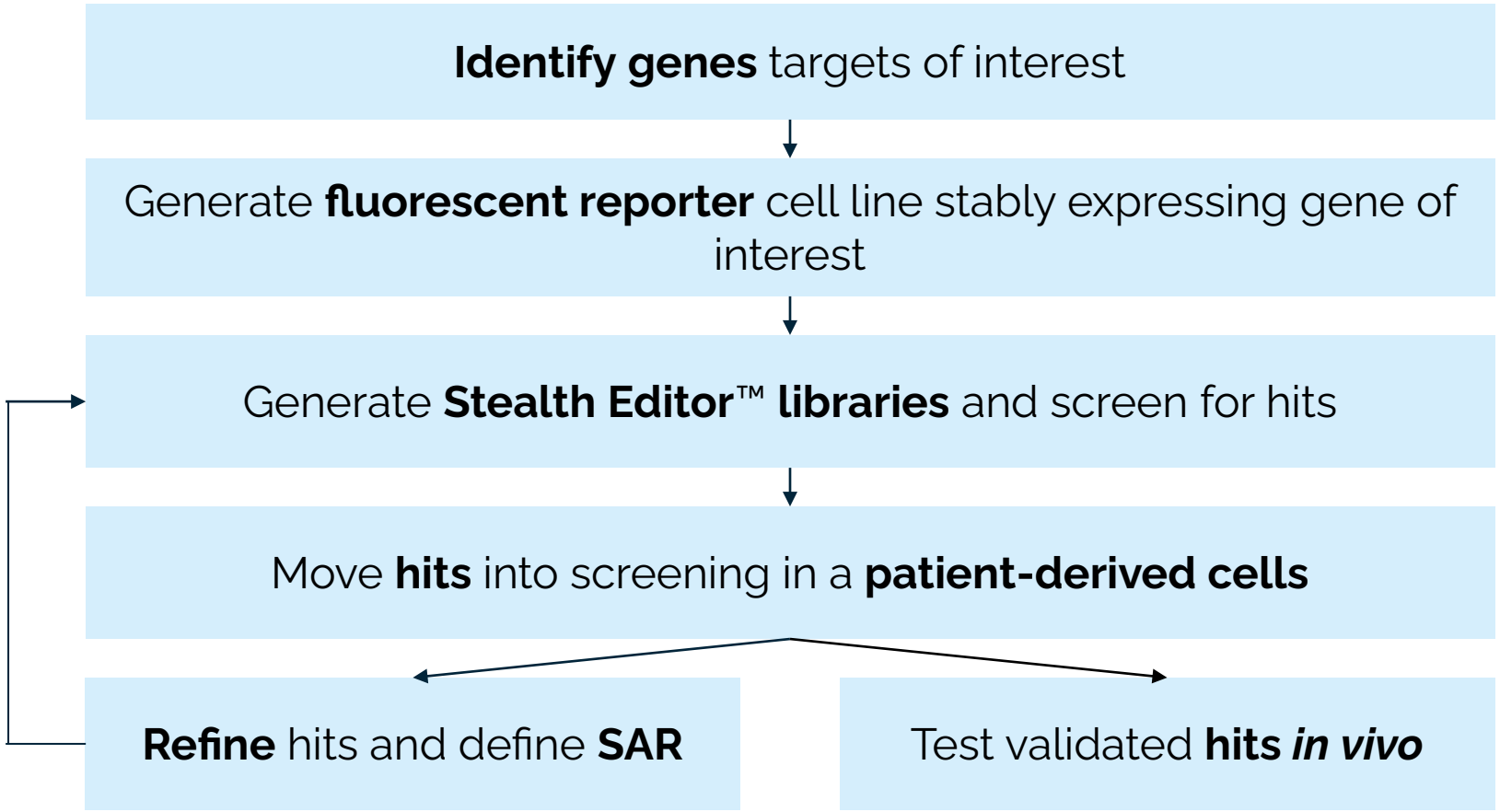
6 The single-stranded break is filled, and correction is complete



DNA polymerases and DNA ligase

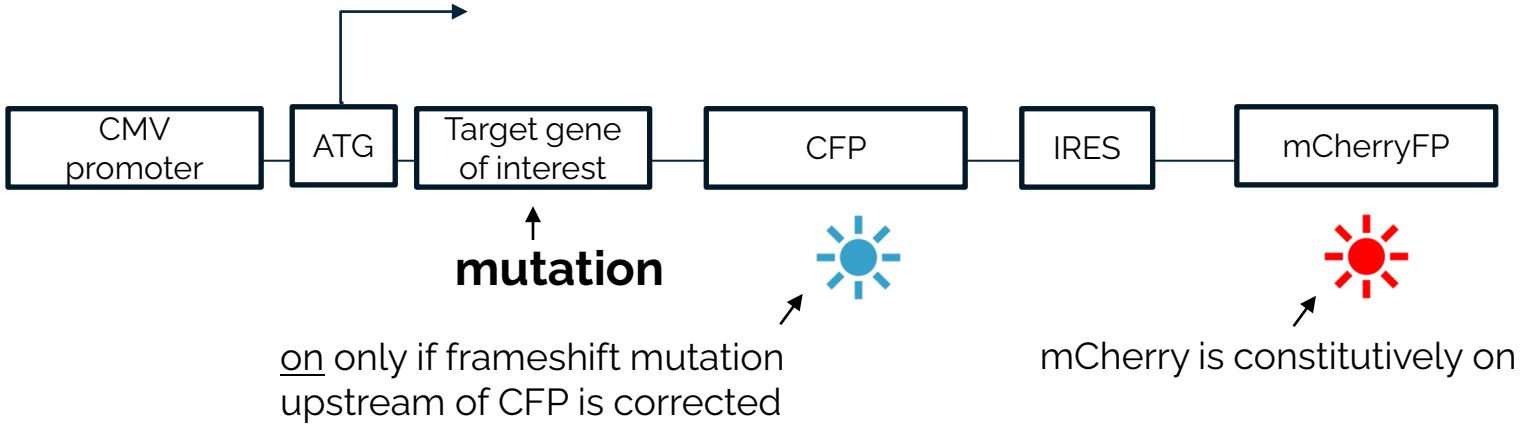
Correction of mutation or functional variant

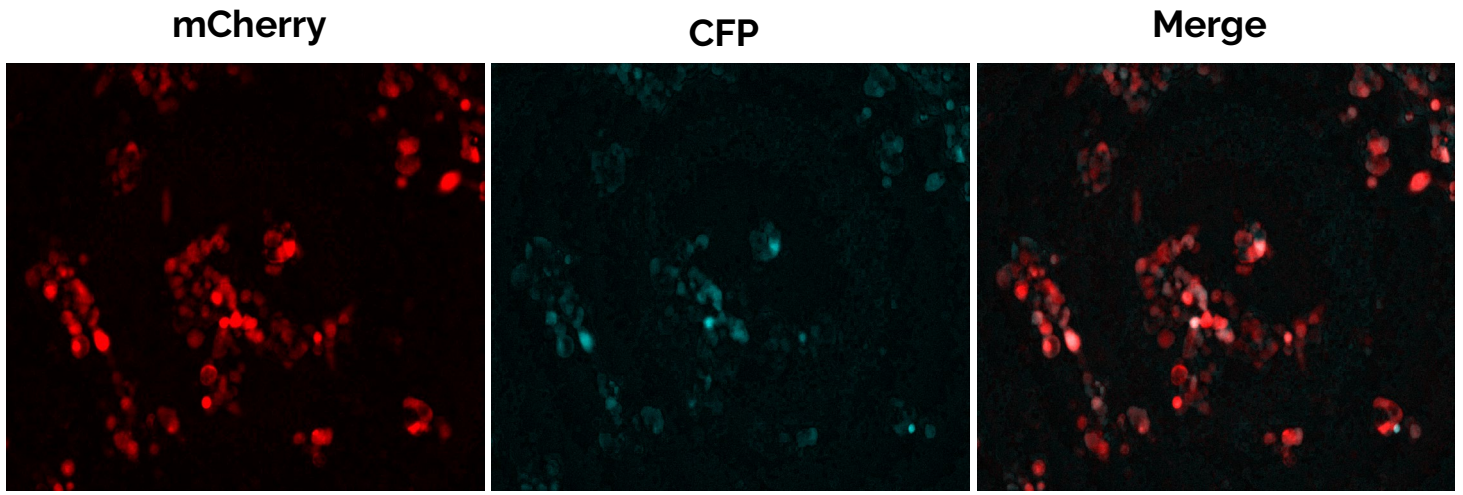
Realizing the Potential of Stealth Editing™

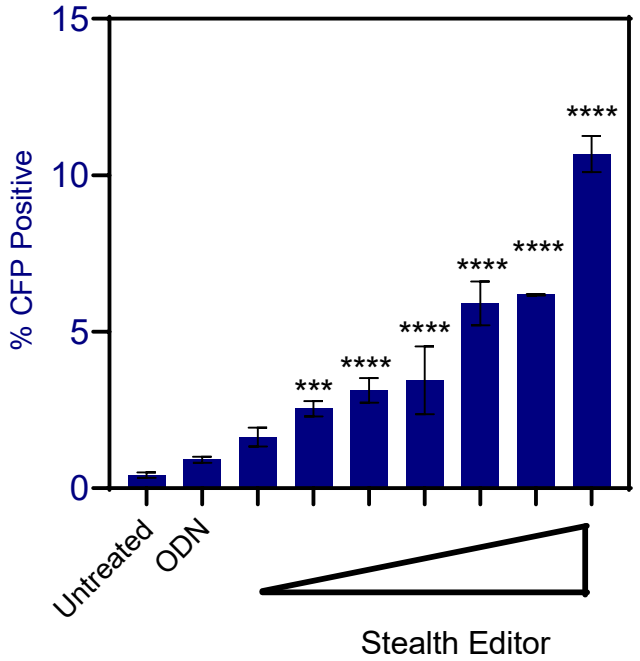


Rapid Target to Hit in Human Cells *Ex Vivo* in a Fluorescent Reporter System

Domain structure of fluorescent reporter[1]





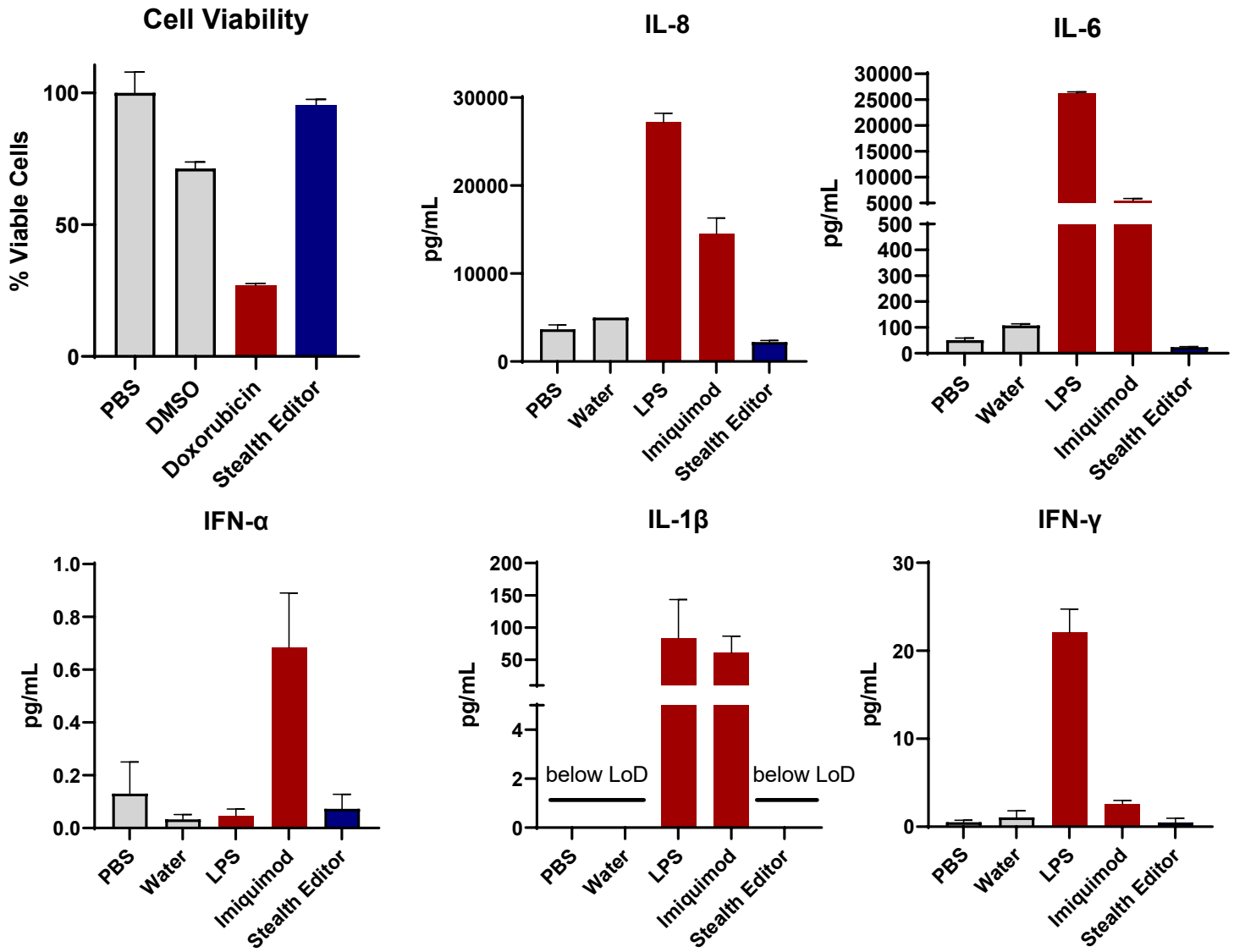


Stealth Editors™ are titratable, and editing efficiency is in-range for clinical benefit in various conditions and continues to increase with optimization

Graph represents the mean ±SD. Statistics were calculated using a one-way ANOVA with a multiple comparison post-hoc test to the untreated control. ***, $p < 0.001$; ****, $p < 0.0001$; [1]Kumar A, *et al*. BMC Genomics. 2019 Jul 24;20(1):609.

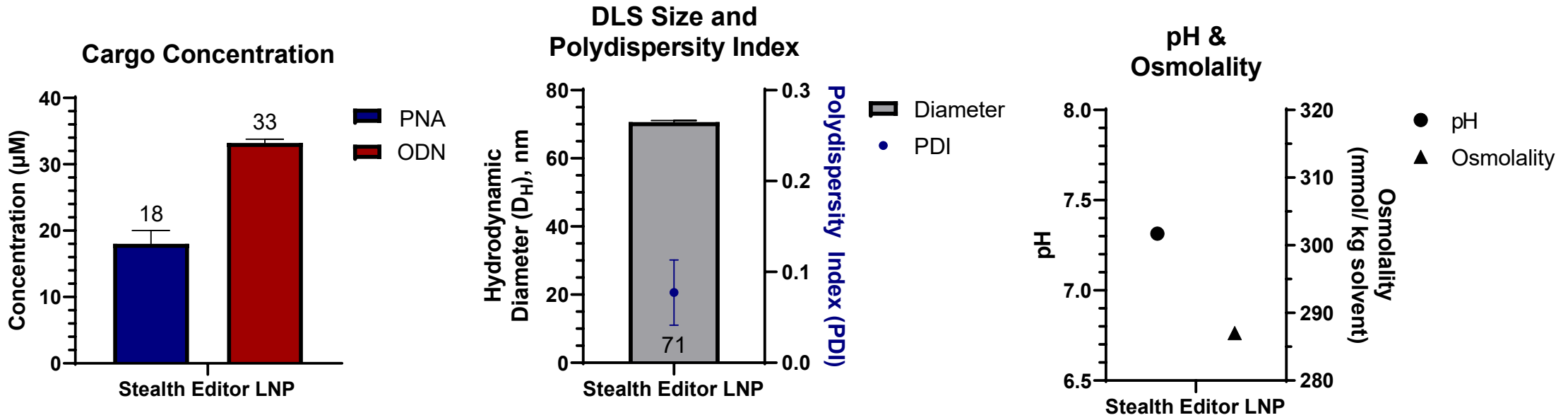
Stealth Editors™ are Non-Immunogenic in Human PBMCs

Stealth Editors™ don't affect cell viability and are non-immunogenic as measured by a cytokine panel



Data is representative of a panel of donors
Immune activator positive control LPS = 5 ng/mL
Immune activator positive control Imiquimod = 4uM
Stealth Editor = 5 uM

Stealth Editors™ are Delivered via Non-Immunogenic LNP Delivery Technology



Proprietary PNA chemistry enables co-encapsulation with ODN inside LNPs

- D_H = 71 nm
- PDI < 0.1
- pH = 7.3
- Osmolality = 287 mmol/kg solvent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