DMAb ™ Technology: The Transformational Potential of Next Gen DNA Medicine in Rare Disease

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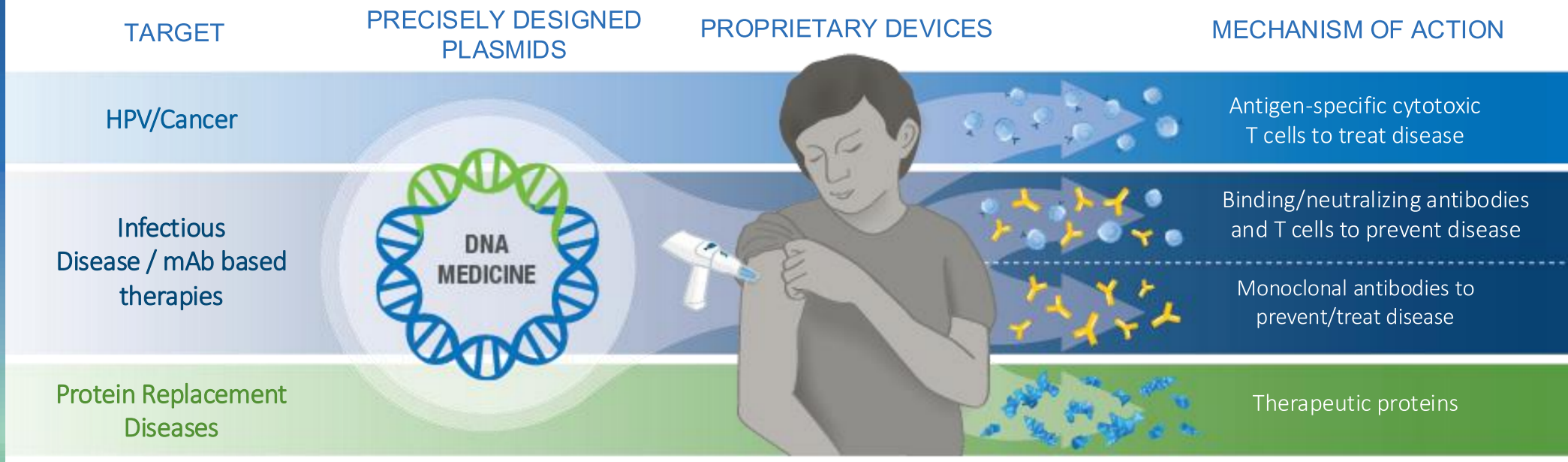
Company Highlights

- Clinical-stage biotech focused on developing and commercializing DNA medicines to treat and protect people from HPV-related diseases, cancer, and infectious diseases
- Lead program INO-3107 for treatment of Recurrent Respiratory Papillomatosis (RRP) - preparing to submit BLA, could be the first DNA medicine available in the US if approved
- Platform technology that enables the design and delivery of therapeutics and vaccines that enable the patient's body to produce their own disease fighting tools
- Deep clinical pipeline of therapeutic and vaccine candidates providing multiple near- and mid-term catalysts

INOVIO's DNA Medicines Platform



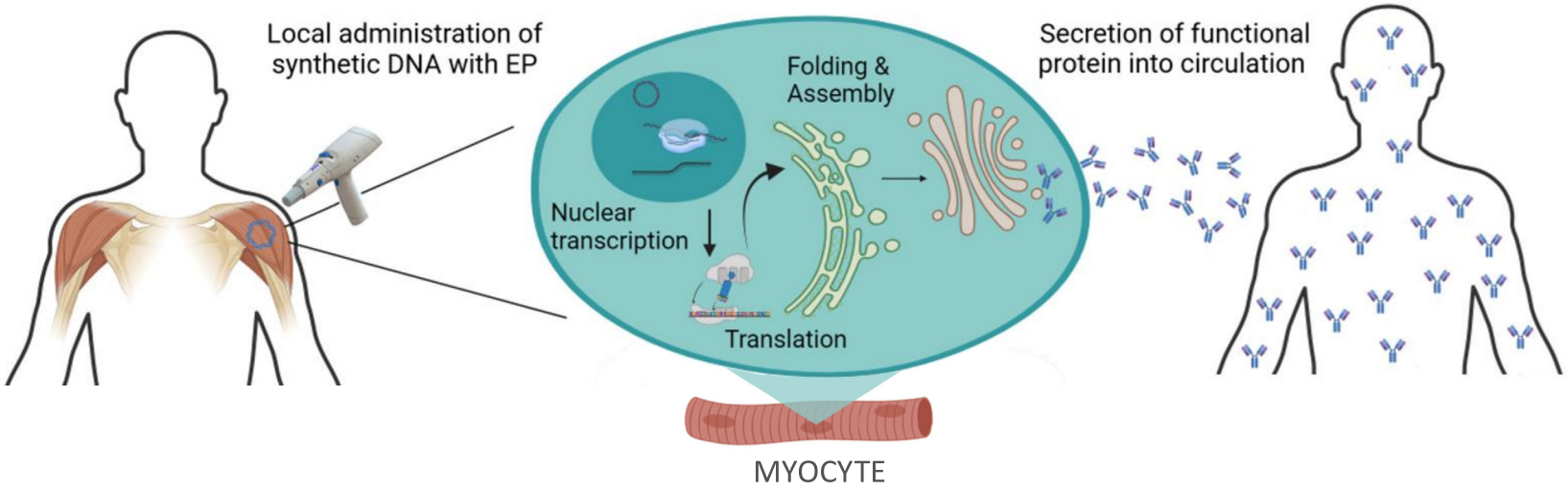
In Vivo Protein Production:

Teaching the body to make its own disease-fighting tools

DMAb™

DNA ENCODED MONOCLONAL ANTIBODIES

The Next Generation of DNA Medicine



DMAb technology enables in vivo production of monoclonal antibodies (mAbs)

- DNA is administered via CELLECTRA device to enable local expression of the genes coding for the antibodies in the deltoid muscle.
- DMAbs are expressed and assembled in myocytes and secreted into the blood where they can circulate in the body.

Utilization of Enhanced Delivery Technology to Develop a DMAb as a COVID-19 Medical Countermeasure

Human Clinical Data – Proof of Concept

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Ongoing Phase 1 Proof-of-Concept Trial Evaluating DMAbs for COVID-19 - Interim Results

- Dose escalation study to evaluate the safety, tolerability and pharmacokinetic profile of mAb AZD5396 and mAb AZD8076 following EP delivery of optimized DMAb AZD5396 and DMAb AZD8076
- Available in preprint on Research Square
- Healthy Volunteer Study, N=44

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SARS-CoV-2-DMAB01 Clinical Study Design

- Phase 1 open-label, single-center, dose escalation study focusing on safety and PK
  - Design allows for exploration of dose response; multiple doses & examines durability
  - Funded by DARPA, DoD
- MAbs COV2-2130 (2130) and COV2-2196 (2196), the precursors of AZ's EVUSHELD (AZD7442) were selected to be designed as DMAbs, AZD5396 and AZD8076
  - The MAbs neutralize non-overlapping epitopes on the viral spike receptor binding domain
- Recombinant human hyaluronidase (Hylenex®) is used when dose is prepared to increase plasmid transfection efficiency & plasmid administered with side-port needle & unique EP parameters

Cohort	n	Dose Each dMAb AZD5396 and AZD8076	Doses per dMAb	Dose Schedule (Day, D)	Total Dose per dMAb	Total Combined Dose dMAbs
A1	4	0.5 mg	1	D0	0.5 mg	**1 mg**
A2	3	1 mg	1	D0	1 mg	**2 mg**
B	6	0.5 mg	2	D0, D3	1 mg	**2 mg**
C	6	1 mg	2	D0, D3	2 mg	**4 mg**
D	5	0.25 mg	2	D0, D3	0.5 mg	**1 mg**
E	5	2 mg	2	D0, D3	4 mg	**8 mg**
F	5	0.5 mg	2	D0, D3	1 mg	**2 mg**
G	5	0.5 mg	4	D0, D3 D28, D31	2 mg	**4 mg**

Source: Protocol for dMAb-AZD5396 and dMAb-AZD8076. Version 6.7; IB for dMAb-AZD5396 and dMAb-AZD8076. Version 6.1

Treatment Administration is Well Tolerated

Number of Subjects with Elicited Local Reactions by Maximum Severity Grade Per Person in the First 7 Days After Last Dose

	None	Mild	Moderate	Severe	Total
Pain	2	27	15	0	**44**
Pruritis	40	4	0	0	**44**
Erythema	25	16	3	0	**44**
Swelling	40	3	1	0	**44**
Scab	4	40	0	0	**44**
Infection	44	0	0	0	**44**
Other events	32	7	5	0	**44**

Other Events: soreness with movement; muscle soreness; numbness at injection site (left deltoid); hematoma after the electroporation (the swelling was 3.0 cm after 30 min)

https://www.researchsquare.com/article/rs-6066550/v1

Minimal Systemic Adverse Events Reported

Elicited Adverse Events for the First 10 Days After Final Dose

	Subj[a]	Event	Mild	Moderate	Severe	Day 0	Day 3	Day 7	Day 10
Hypotension	1	1	1	0	0	0	0	1	0
Hyperhidrosis	0	0	0	0	0	0	0	0	0
Erythema (systemic)	0	0	0	0	0	0	0	0	0
Headache	3	4	4	0	0	1	2	1	0
Dizziness	0	0	0	0	0	0	0	0	0
Myalgia (pain in muscle)	4	4	2	2	0	2	1	0	1
Arthralgia (pain in joints)	1	1	1	0	0	0	0	0	1
Fever	0	0	0	0	0	0	0	0	0
Peripheral Edema	0	0	0	0	0	0	0	0	0
Other[b]	2	2	2	0	0	2	0	0	0
Total	**9**	**12**	**10**	**2**	**0**	**5**	**3**	**2**	**2**

[a]Table columns show the total number (n) of subjects, events, number of events by severity grade, and number of events by observed visit day of reaction.
[b]Nausea during injection; tiredness

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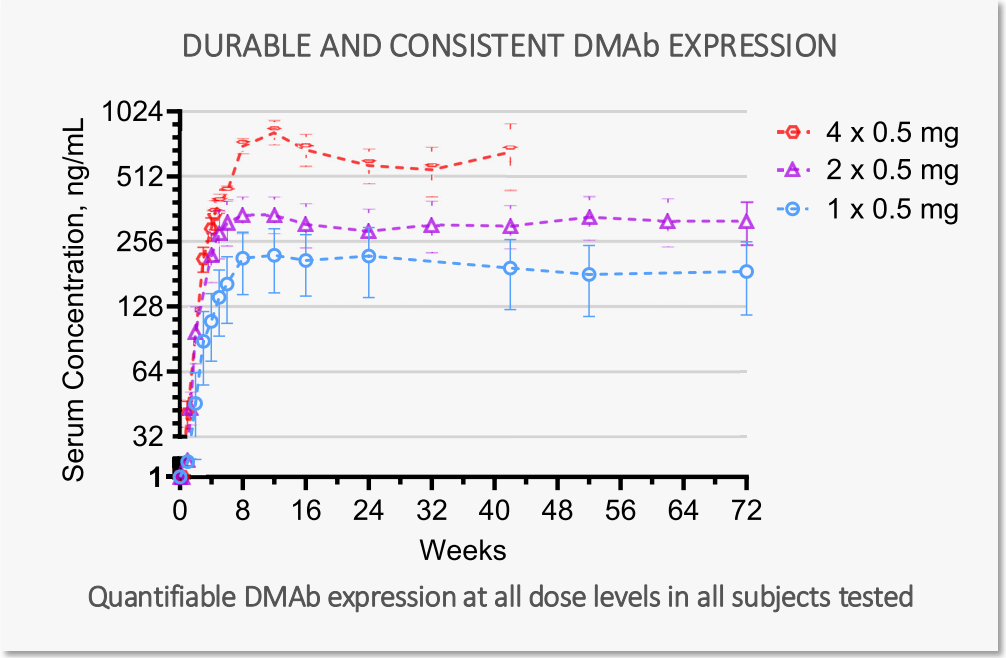
Ongoing Phase 1 Trial: Key Takeaways From Interim Data

- **Long-lasting in vivo antibody production**: DMAb levels remained stable for 72 weeks in all participants reaching that timepoint
- **No anti-drug antibodies (ADA):** no immune rejection of the DMAbs detected across ~1,000 blood samples
- **Effective target binding**: expressed DMAbs successfully bound to SARS-CoV-2 Spike protein receptor-binding domain, confirming functional activity through week 72
- **Re-dosing at days 28 & 31 achieved DMAb levels over 1 µg/ml:** Redosing appeared to be more effective at increasing DMAb concentrations compared with escalating single doses



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Applicability of Platform to Rare Disease

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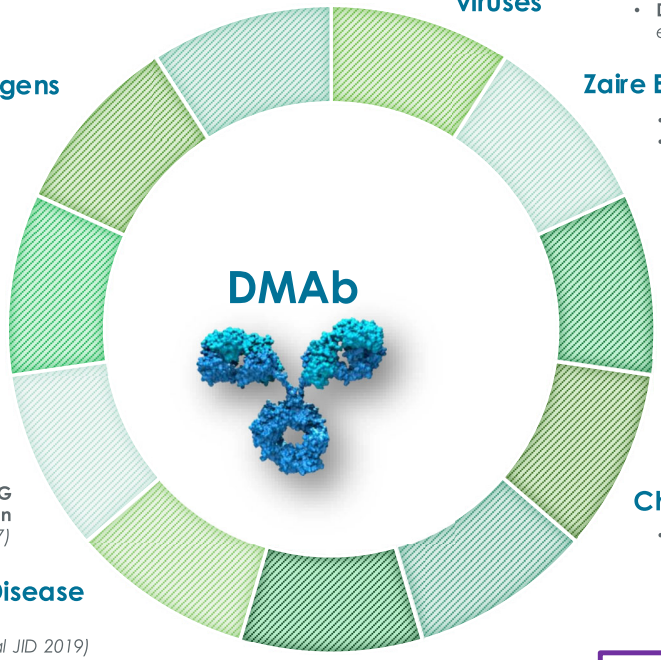
Feasibility Shown in Multiple Disease Models



PCSK-9

- **Delivery of anti PCSK-9 in mice lowers LDL cholesterol** (*Khoshnejad et al Mol Ther 2018*)

Influenza A & B viruses

- **Broadly neutralizing pan-influenza A & B approach**
- **Delivery of multiple antibodies** (*Elliott et al NJV 2017*)
- **Demonstrated disease protection in pig model** (*McNee et al. JI 2020*)

Cancer Antigens

- **Demonstrated HER2/CD3 dBTEs can reduce tumor burden in mice** (Perales-Puchalt et al. JCI Insight. 2019)
- **Delivery of anti PSMA in mice impacted tumor challenge** (*Muthumani et al Cancer Immuno 2017*)

Zaire Ebolavirus

- **DMAb modifications and mouse model development**
- **Pre-exposure protection against highly lethal challenge in mice** (*Patel et al Cell Reports 2018*)

Checkpoint Inhibitors

- **Delivery of CPI in mice impacted and protected against tumor challenge** (Perales-Puchalt et al. *Oncotarget. 2019, Duperret et al. Cancer Res 2018*)

Dengue virus (DENV)

- **Protection against ADE** (*Flingai et al. Sci Rep 2015*)

Zika virus

- **scFV approach**
- **Protection from disease in NHPs** (*Esquivel et al. Mol Ther. 2019*)

Multi-drug resistant Pseudomonas aeruginosa

- **Multiple forms of DMAbs: monospecific, bispecific IgG**
- **Lowering pathogen burden and complementation in antibiotic resistant model** (*Patel et al Nat Comm. 2017*)

Chikungunya virus (CHIKV)

- **Rapid protection & complementarity with a vaccine** (*Muthumani et al., JID 2016*)

Lyme Disease

- **DMAb modifications** (*Yang et al JID 2019*)

HIV

- **Delivery of multiple DMAbs to**
- **a single animal**
- **>10ug/ml in NHPs** (*Wise et al JCI 2020*)
- **DNA encoded post translational modifications** (*Xu, Wise et al EbioMed 2018*)

SARS-CoV-2 – In P1 clinical trial

- **Highly potent DMAbs expressed in vivo** (candidates under clinical evaluation)

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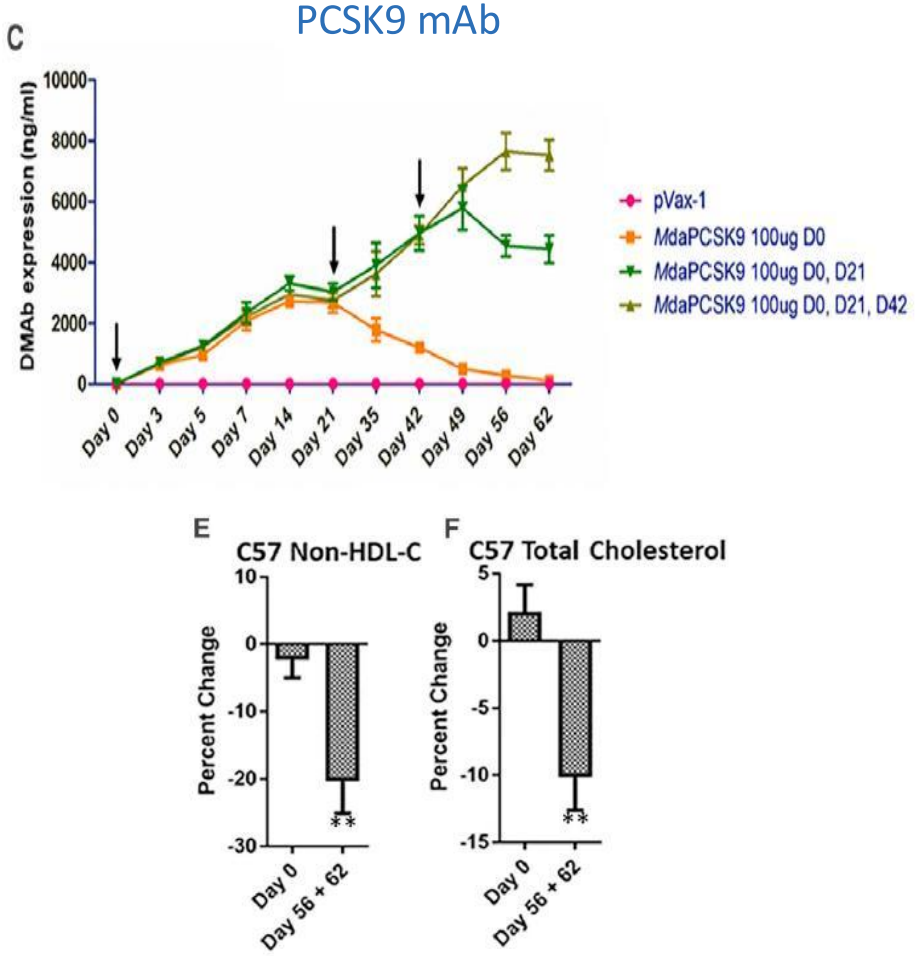
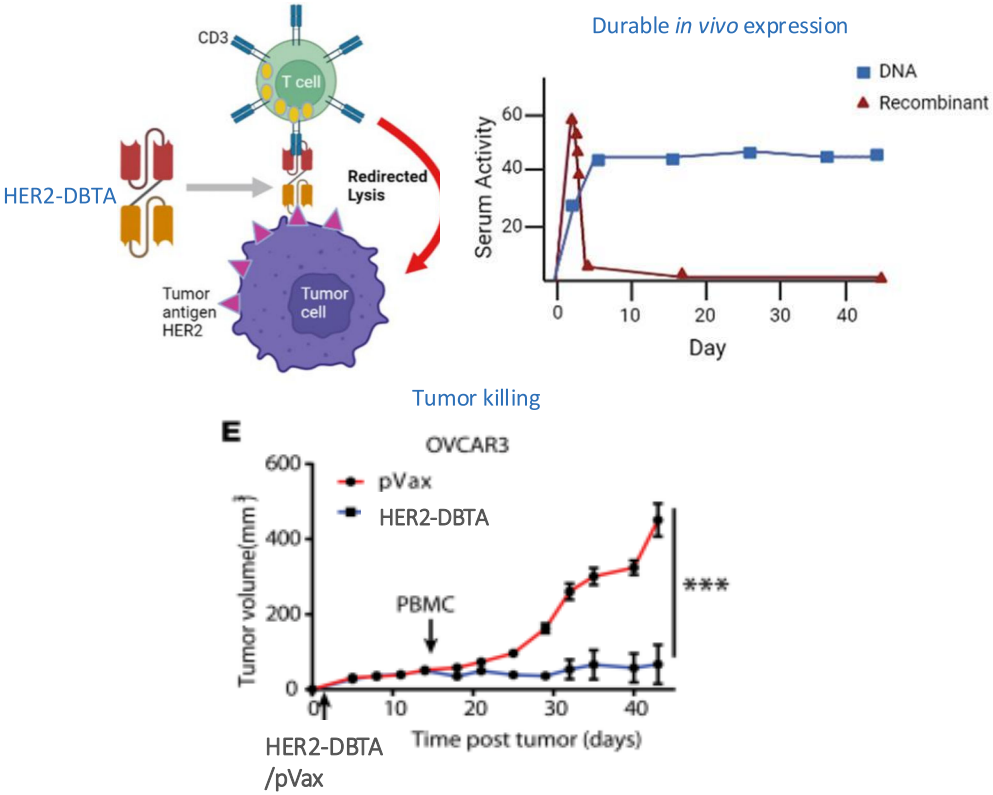
Activity Demonstrated in Multiple Different Animal Models

PCSK9 mAb



Khoshnejad M, et. al; Mol The.2018 Nov 15;27(1):188-199

DNA-encoded bispecific T cell activator (DBTA)



Perales-Puchalt A, et al; JCI Insight. 2019 Apr 18;4(8):e126086

Examples of Enzyme Replacement Therapy Targets for DNA Encoded Proteins (DPROT™) That Are Within Current Platform POC Parameters

Disease	Deficiency/ Dysfunction of	Existing Target	Proprietary Name	Protein Size Criterion	Therapeutic Expression Criterion	Benefit/Risk
Severe combined immune deficiency	Adenosine deaminase enzyme (ADA)	Elapegademase	REVCOVI	FAVORABLE	FAVORABLE	FAVORABLE
Perinatal/infantile and juvenile onset hypophosphatasia (HPP)	Tissue-nonspecific alkaline phosphatase (TNSALP) enzyme	Asfotase alfa	STRENSIQ	FAVORABLE	FAVORABLE	FAVORABLE
Wolman disease	Lysosomal acid lipase enzyme	Sebelipase alfa	KANUMA	FAVORABLE	FAVORABLE	FAVORABLE
Mucopolysaccharidosis (MPS)	Lysosomal enzyme/s Involved in glycosaminoglycans degradation	Vestronidase alfa (beta-glucuronidase)	MEPSEVII	FAVORABLE	FAVORABLE	FAVORABLE
Niemann-Pick disease types A and B	SMPD1 acid sphingomyelinase enzyme	Olipudase alfa	XENPOZYME	FAVORABLE	FAVORABLE	FAVORABLE
Alpha-mannosidosis	Alpha-D-mannosidase enzyme	Velmanase alfa	LAMZEDE	FAVORABLE	FAVORABLE	FAVORABLE
Fabry disease	α-GAL A enzyme	Pegunigalsidase alfa	ELFABRIO	FAVORABLE	FAVORABLE	FAVORABLE

Comparative Profiles of Investigational mAbs / Protein Replacement Platforms

Attribute	DNA	mRNA	Viral Vectored
Known integration into host cell genome	No	No	AAV: Potential LV: Yes
Tested in humans	Yes	Yes	AAV: Yes LV: No for mAbs LV: Yes gene therapy
Well tolerated	+	+/-	-
Time to peak plasma concentration	~8-12 weeks	As early as 24 hours (IV)	~1-4 weeks
Duration of expression	Over 72 weeks	~6 months	Long-term
Known anti-drug antibodies (ADA)	No	No	AAV: Yes
Risk of anti-vector antibodies developing	No	No	Yes

Abbreviations: AAV, Adeno Associated viruses; LV, lentivirus; n.a., not applicable.

Note: Characterization of attributes of each platform was based on single investigational product and indication: DNA-Mabs, SARS-CoV-2-dMAB, two doses; mRNA-MAbs, Chikungunya virus mRNA-1944, one dose; AAV-PG9 Abs (HIV) and Lentivirus Vectored-DNA-MAbs SARS-CoV-2-dMAB.

Deal, C.E.;Carfi, A.;Plante, O.J. Advancements in mRNA Encoded Antibodies for Passive Immunotherapy. Vaccines 2021, 9, 108

DMAb/DPROT™ Technology Has Potential as a New Treatment Paradigm in Rare Disease

- Platform has demonstrated ability for long-term protein secretion
- Safety data supports its future tolerability profile
- Highly differentiated from existing platforms
- Based on existing POC data, platform may be suitable for the treatment of many rare diseases
- Seeking development partnerships

Thank you.

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