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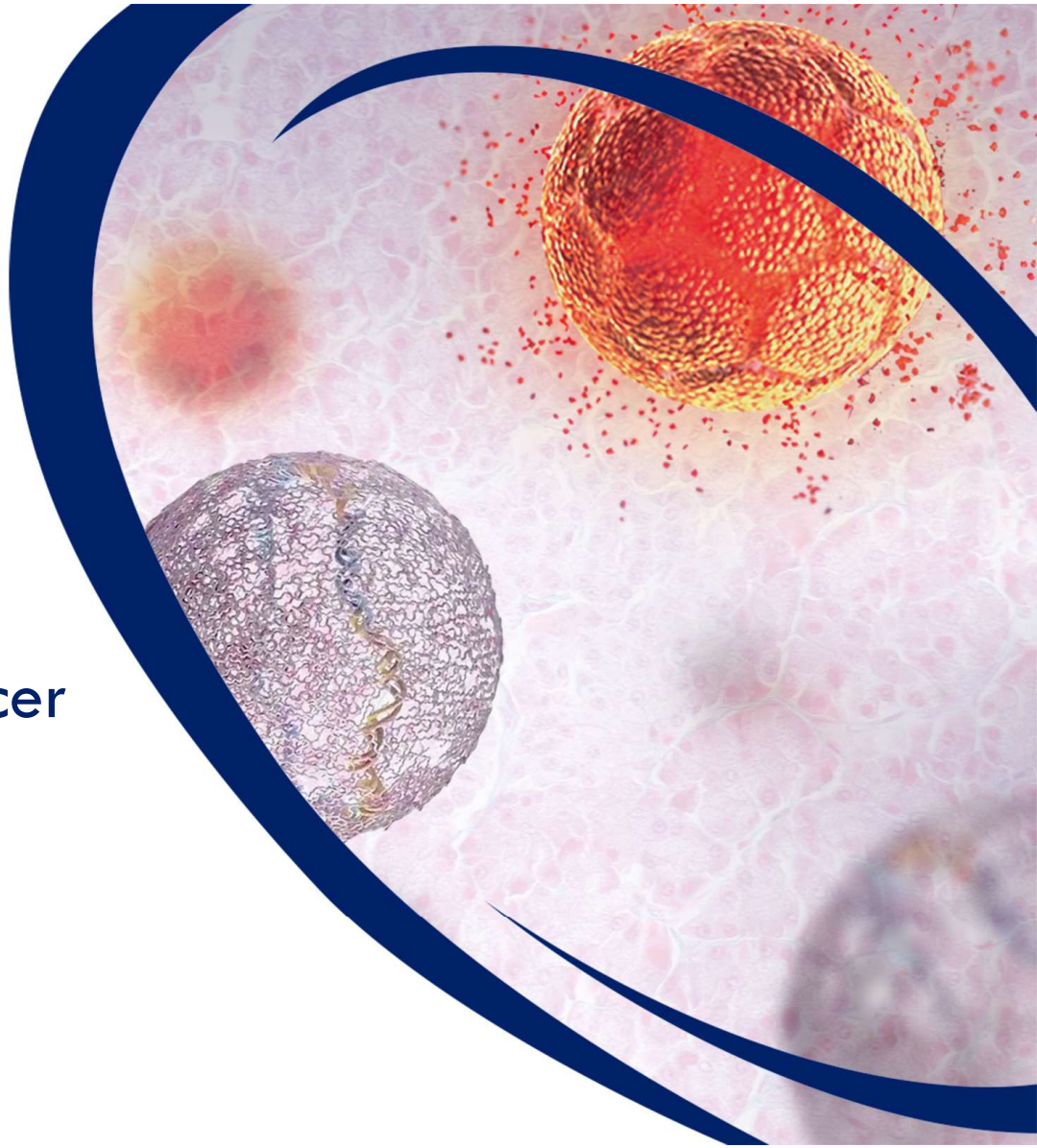
Novel DNA Approaches for Cancer Immunotherapies and Multivalent Infectious Disease Vaccines



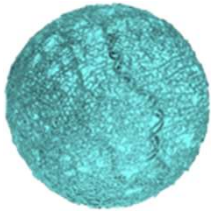
Celsion's Proprietary Plasmid DNA Technology Platforms

TheraPlas

- Polymeric Nanoparticle Delivers Plasmid DNA Coding for Therapeutic Proteins
- Safely Administered to Over 100 Patients To-Date

GEN-1 Immunotherapy

Localized Interleukin -12 Immunotherapy



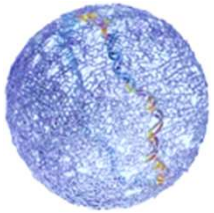
Phase II Evaluation in Advanced Ovarian Cancer
Orphan Drug Designation: U.S. and EU
Fast Track Designation

PLACCINE

- Plasmid DNA Vaccine Formulations (no virus or device)
- Designed for multiple antigens
- Option for the co-expression of immunomodulators

SARS-CoV-2

Multivalent Vaccine for COVID-19



Proof-of-Concept to Demonstrate PLACCINE
as Best-in-Class Vaccine Platform Using SARS-CoV-2 as a Benchmark

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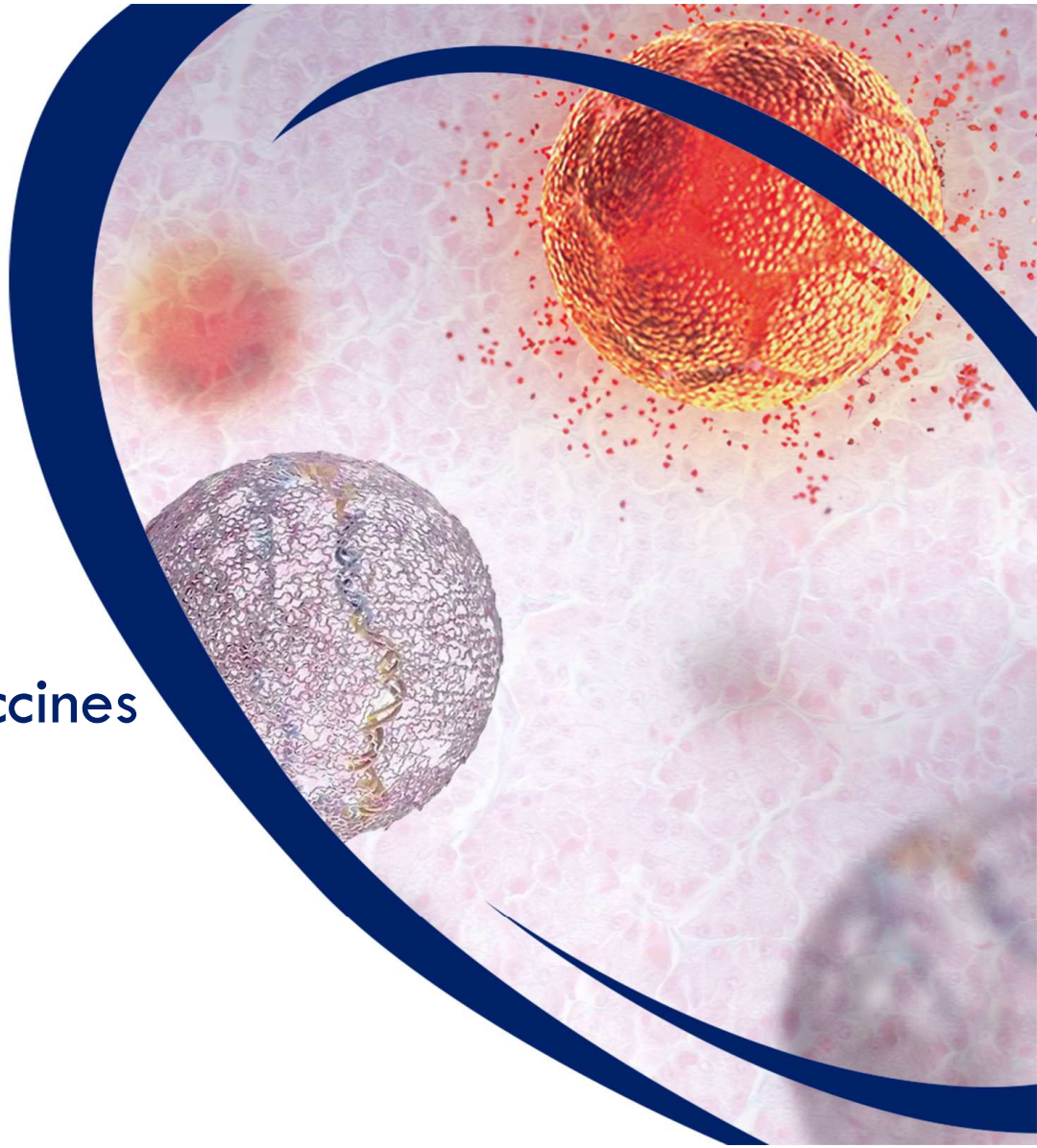
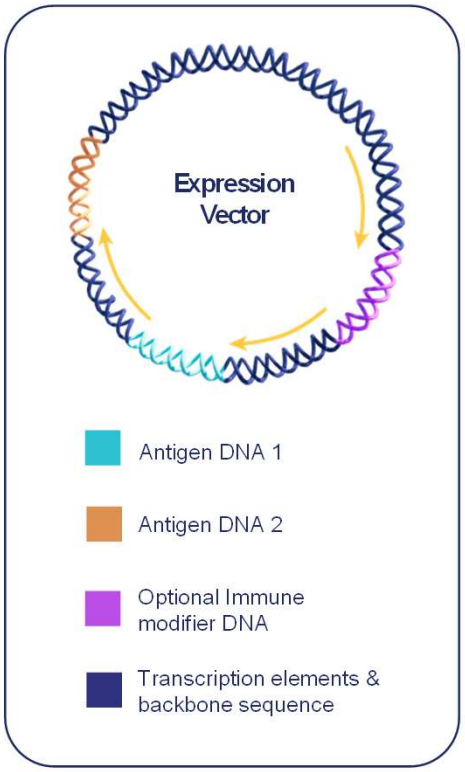
Multivalent Infectious Disease Vaccines



Multi-cistronic Formulated pDNA Vaccine Platform

Proprietary PLACCINE Platform Technologies



Up to 4 antigens have been successfully incorporated and expressed

PLACCINE pDNA System

PLACCINE Delivery Systems

-Synthetic Delivery Systems

- **Non-viral**
- **Non-device**

Nanoparticles/ Complexes

PLACCINE Vaccines

Intramuscular (IM) Administration

Humoral & Cell Mediated Immune Response

Potential Administration Routes

- Subcutaneous (SC)
- Intradermal (ID)

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Hypothesis: PLACCINE Provides a Best-in-class Nucleic Acid Vaccine Platform

Demonstrating Proof of Concept by Developing a multivalent SARS-CoV-2 Vaccine

Multivalent pDNA

- Broad-based protection and improved resistance to mutations.

Durable antigen exposure

- Compared to mRNA/protein vaccines yielding a more robust overall immune response.

Synthetic delivery system

- Independent of a virus or device.

Manufacturing

- Flexible design & generic process enabling a rapid response to pandemics/changing pathogen

Storage & distribution advantages

- DNA product stability compatible with standard vaccine storage and distribution models.

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PLACCINE Development Strategy

- **Vector Optimization-** Single Antigen Vectors
  - Antigen structure
  - Transcription elements
- **Multiple Antigen Vectors**
  - Optimized parameters from single antigen vectors
- **Formulation Development**
  - Synthetic delivery systems
  - Gene expression and immune response
  - Adjuvants
- **Immunogenicity in Mice and NHP**
  - IgG and T-cell responses
  - Neutralizing antibodies
  - Challenge studies
- **Evaluation with a Comparator Vaccines**

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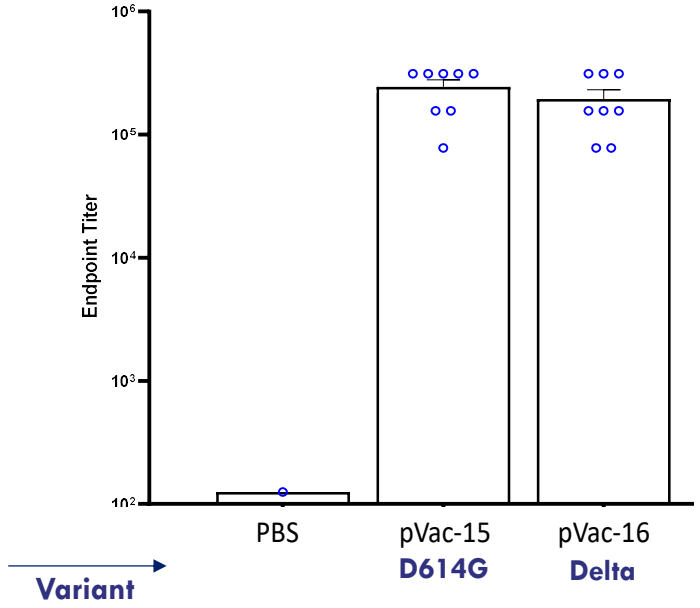
Single Antigen Vaccines based on Optimized Vectors & Formulation

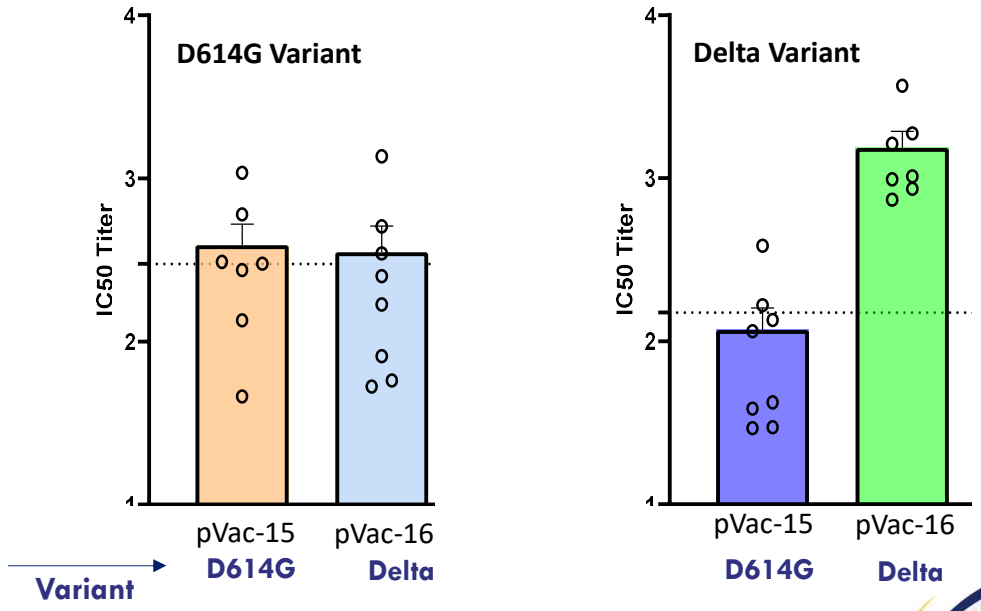
IgG and nAb Levels

- Single antigen vectors **pVac-15** (D614G), **pVac-16** (Delta)
- Formulation F3
- 125 µg DNA
- IgG titer and nAb (day 35)

PLACCINE IgG Titer Comparable to mRNA Vaccine (slide 10)



Neutralizing Antibody Titers Against Different Viral Strains Following PLACCINE Vaccination



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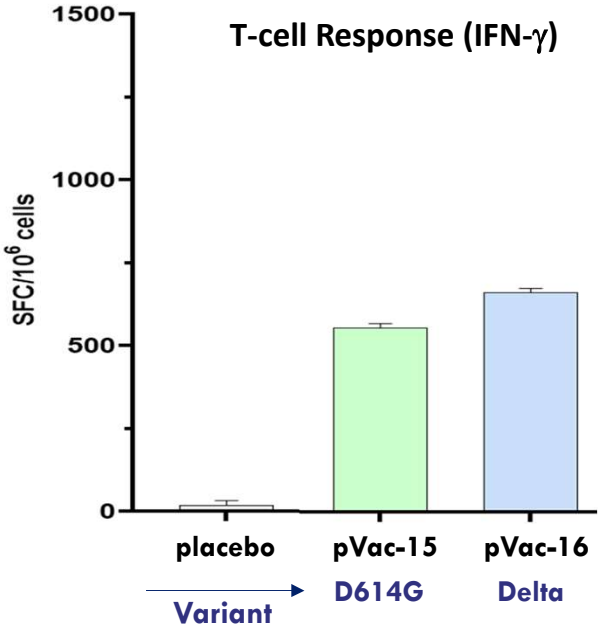
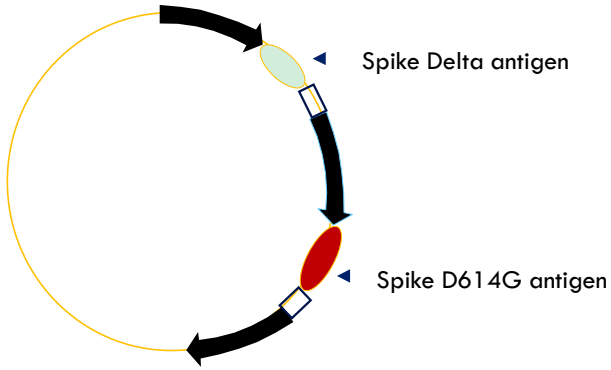
Single Antigen Vaccines based on Optimized Vectors & Formulation

T-cell Response

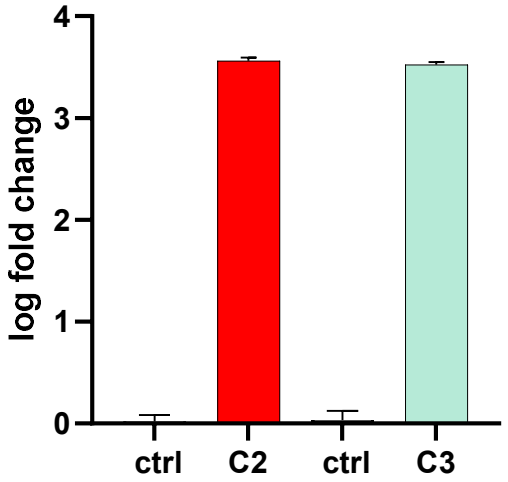
- Vector **pVac-15** (D614G), **pVac-16** (Delta)
- Formulation: F3
- 125 µg DNA
- IgG titer (day 35)



Multicistronic Vector Expressing Two SARS-CoV-2 Antigen Variants



Two-Variant Multi-cistronic Vector



Distinguishing between D614G and Delta by sequence-specific qPCR primers

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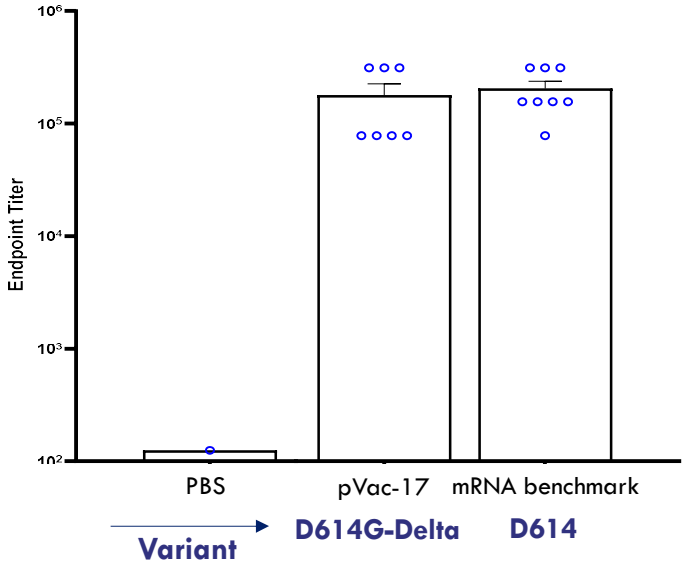
A Multicistronic PLACCINE Vaccine Protects Against Multiple Variants

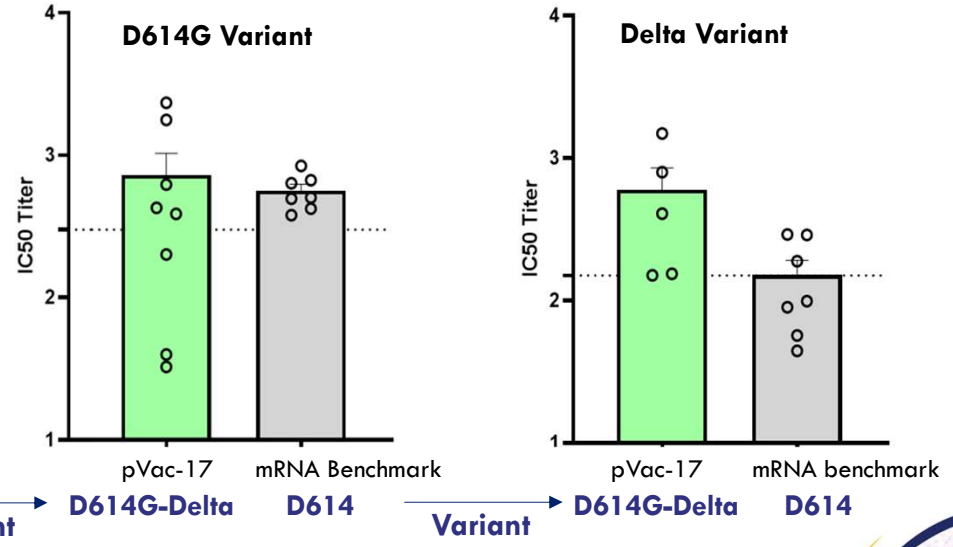
IgG and nAb Titers Comparable to a Commercial mRNA Vaccine

- Multicistronic vector **pVac-17**
- Spike antigen D614G, Delta
- Formulation: F3
- 125 µg DNA
- IgG titer (day 35)

IgG Titer



Neutralizing Antibody Titer



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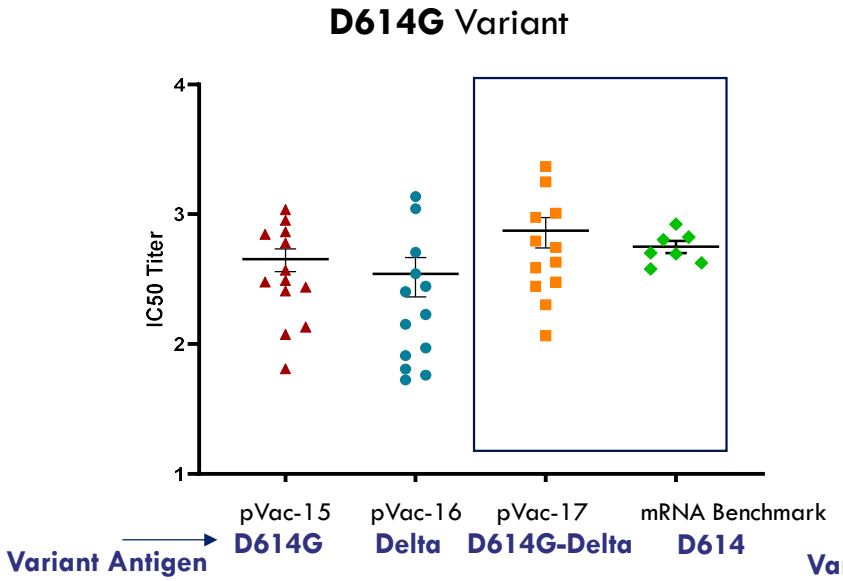
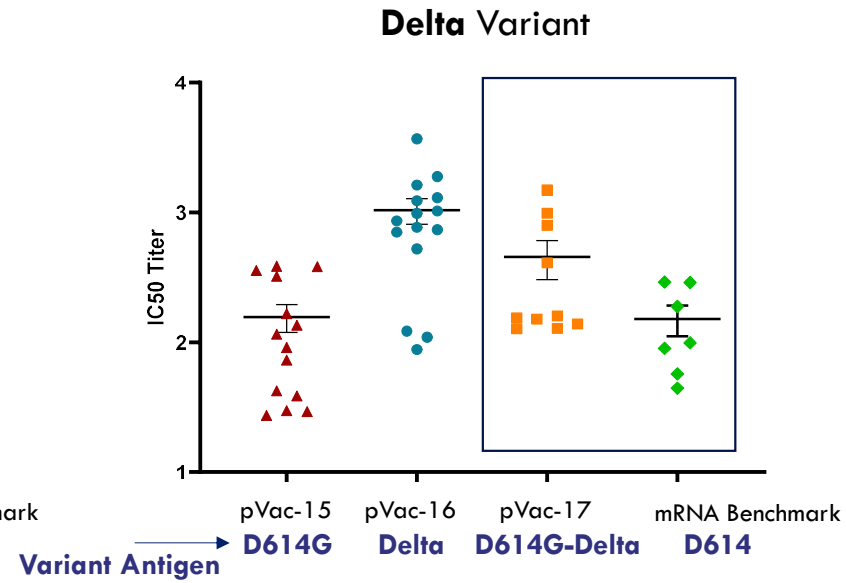
Combined data from Two Separate PLACCINE Studies

Neutralizing Antibody Response

- Vectors **pVac-15** (D614G)
  pVac-16 (Delta)
  pVac-17 (D614G+Delta)
- Formulation: F3
- 125 µg DNA
- IgG titer (day 35)





A Broad Vaccine Pipeline Opportunity Following Proof of Concept

Initial POC/Validation Target

Potential Pathogen Targets

HSV	RSV	Chikungunya	Mycobacterium tuberculosis
HIV	Dengue	Measles	Plasmodium falciparum
Hep C	Ebola	MERS-CoV	Toxoplasma gondii
	Zika	Yersinia pestis	

Future Pipeline Criteria

- Unmet need
- Conventional approaches ineffective
- Suitable for DNA approach

Potential Next Candidates

- CMV
- RSV
- Influenza

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Ongoing Development

- Immune response durability studies
- Dose response, safety toxicity, and biodistribution
- Challenge studies – rodent and NHP
- Stability studies at optimal commercial conditions

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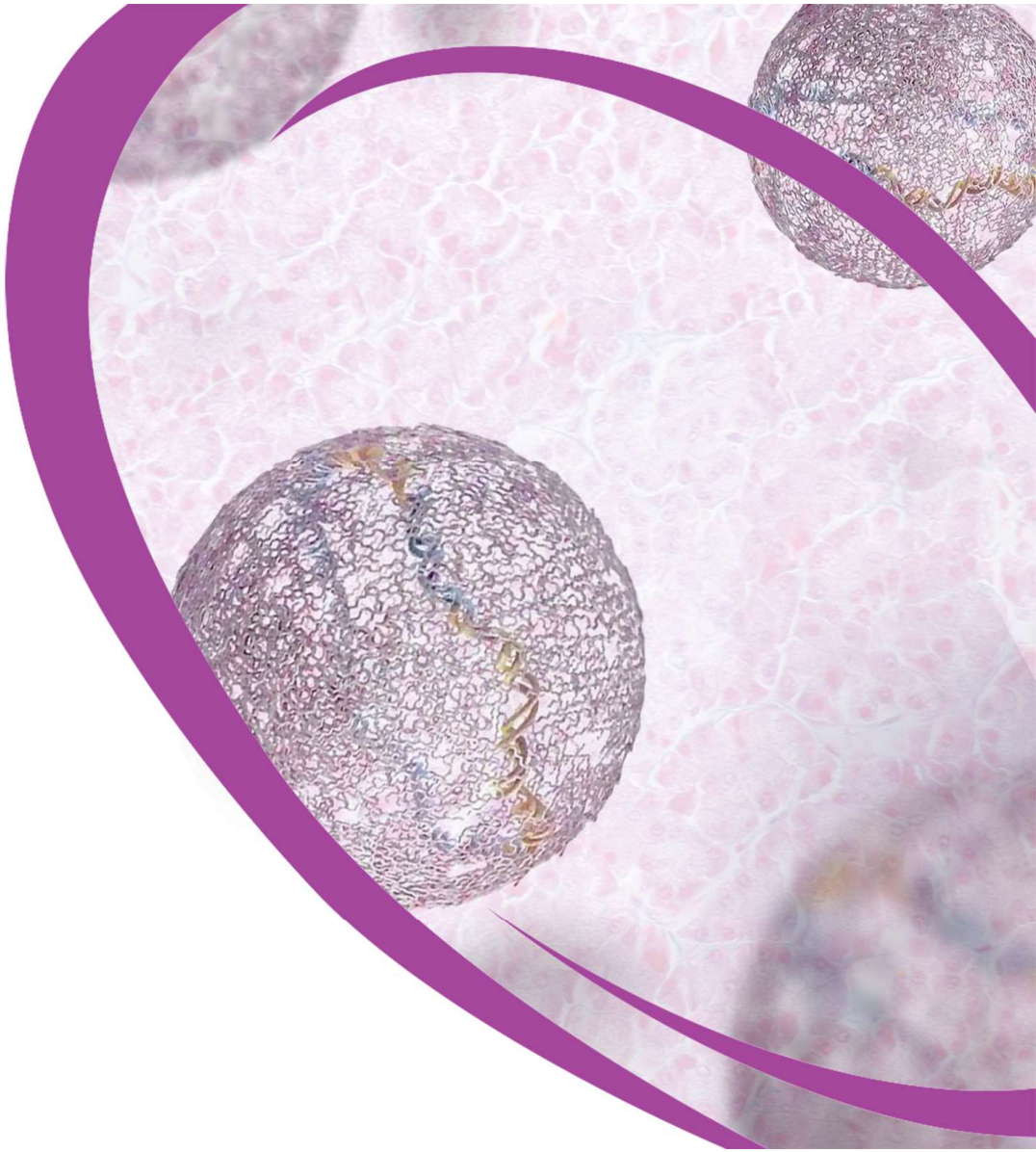
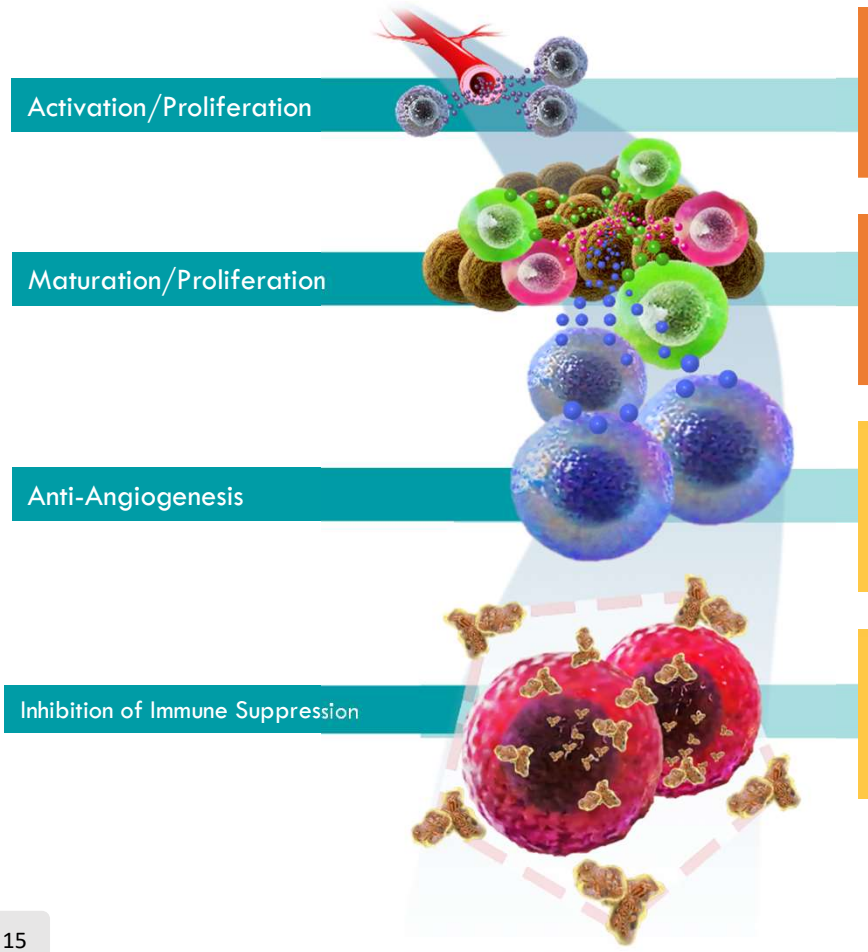
GEN-1 IL-12

IMMUNO-ONCOLOGY PROGRAM



IL-12: A Powerful Immune-Modulating Agent

Interleukin-12 Can Induce Anti-cancer Immunity Through Multiple Mechanisms



1. Stimulates the proliferation of CD-8 positive T-cells and natural killer (NK) cells and their cytotoxic activity against the tumor
2. Shifts the differentiation of naive CD-4 positive T-cells toward a TH-1 phenotype, further enhancing the immune response – Turns "cold" tumors into "hot" tumors
3. Promotes cellular production of the potent immune mediator IFN-γ and TNF-α. IFN-γ promotes the expression of anti-angiogenic molecules, halting the growth of new blood vessels that supply oxygen to the tumor
4. IL-12 inhibits regulatory T-cells that suppress immune responses by "hiding" the tumor from the body's immune system

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Anti-cancer Activity of rIL-12 Observed in Multiple Cancers

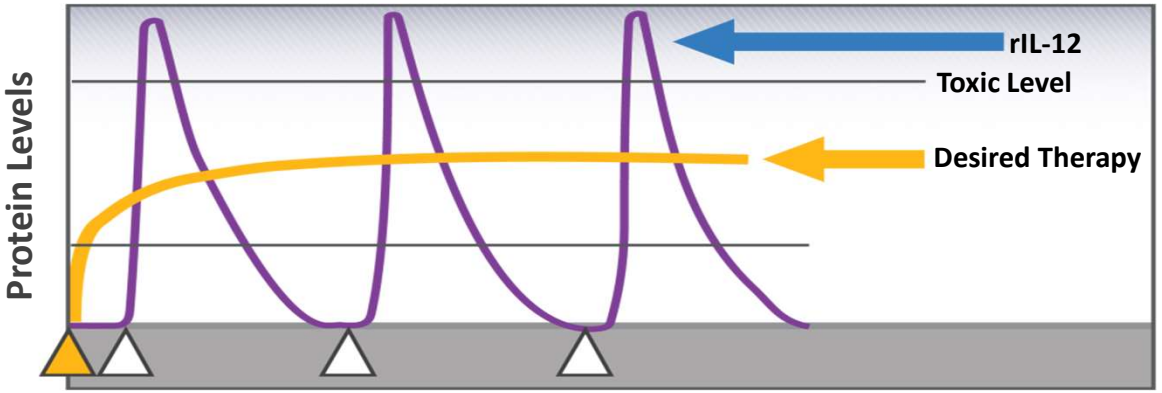
Serious Systemic Toxicity Warrants Alternate Delivery Strategies

CANCER INDICATIONS

- Melanoma
- Renal carcinoma
- Lymphoma
- GI cancer

SERIOUS SYSTEMIC TOXICITY

- Hematological
- Hepatic
- Neurological



- Therapeutic potential of rIL-12 is limited by poor pharmacokinetics when administered by multiple routes (IV, SC, IP).
- Clinically viable alternate strategies for IL-12 delivery are warranted

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GEN-1: DNA-based IL-12 Delivery by Intraperitoneal Administration

A safe alternative to rIL-12 therapy for peritoneal carcinomatosis of Gyn/GI Origin

- **GEN-1 Concept**
  - Local increases in IL-12 at tumor site for several months w/o systemic toxicity will be safer and more effective than rIL-12
- **Cancer Impact**
  - Persistent long-term increases in IL-12 will shift TME from immuno-suppressive to immunostimulatory
  - A pro-immune TME will inhibit tumor growth and predisposes it to rationale combination therapies

Local Expression of IL-12 Favors Immune Modulation in Tumor Microenvironment

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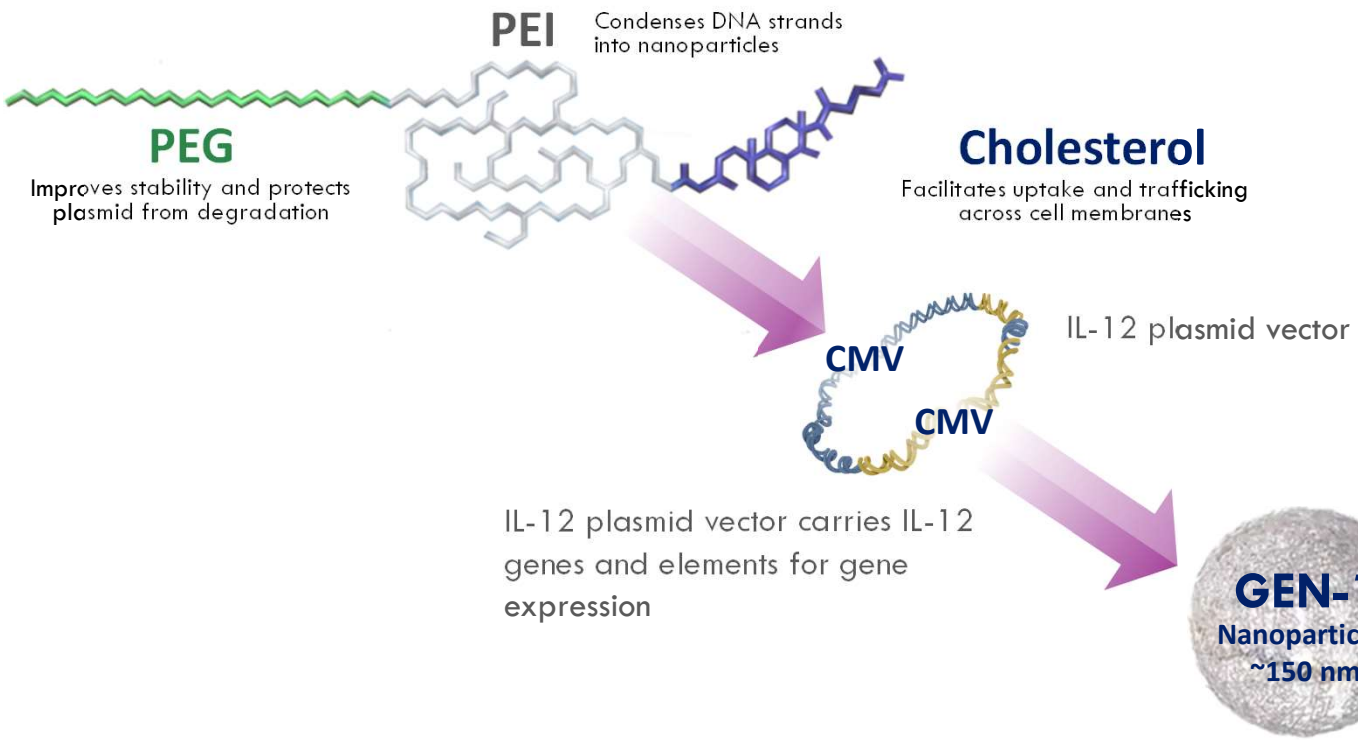
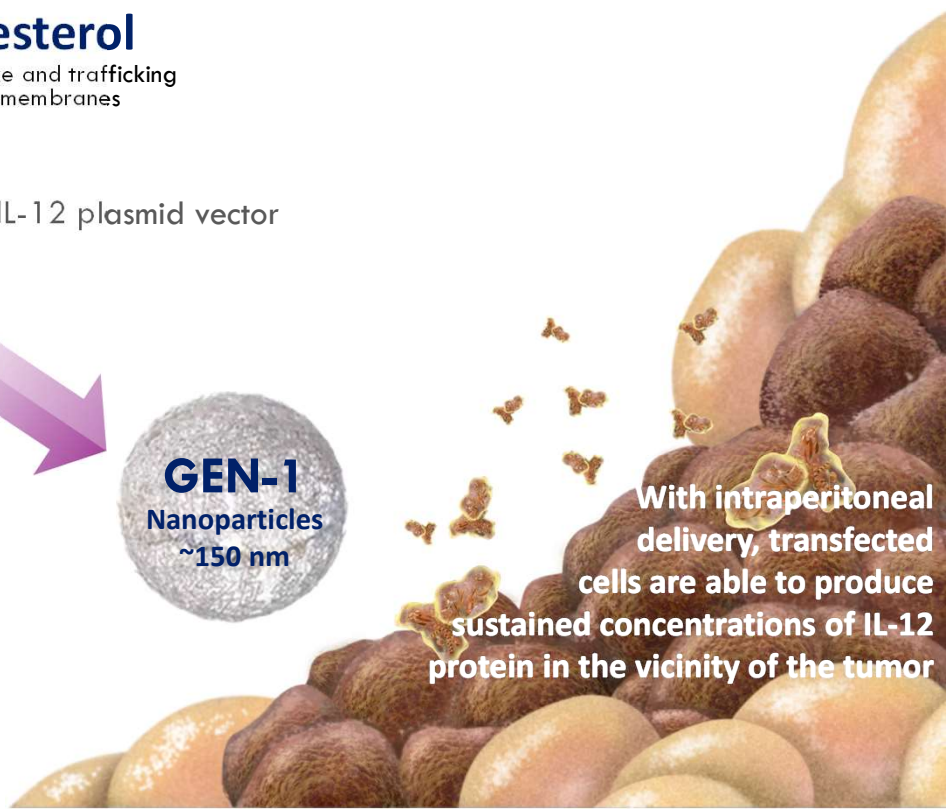
GEN-1 Composition

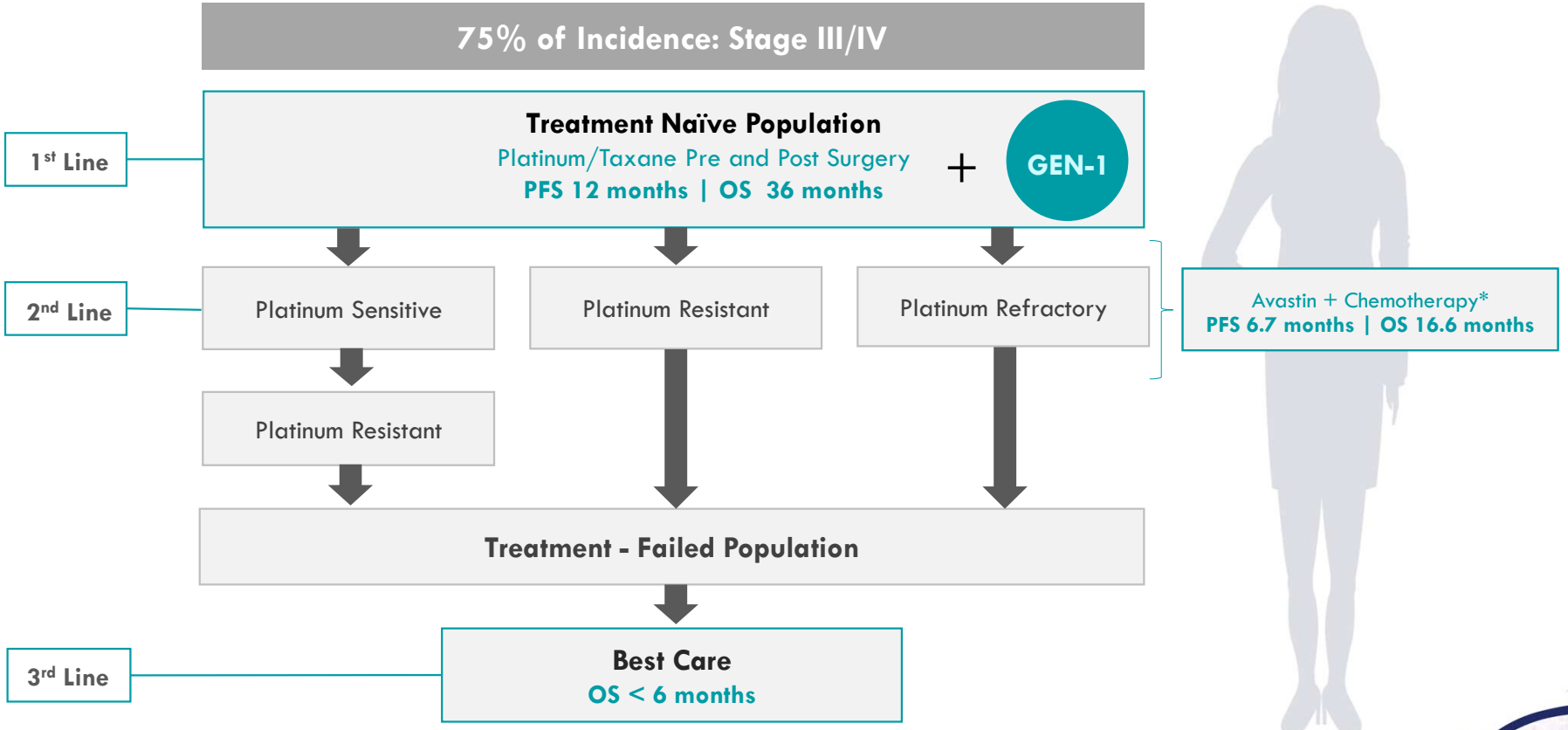
PPC - 3 Components: Polyethylene Glycol (PEG), Polyethyleneimine (PEI), Cholesterol + IL-12 Plasmid





Treatment Options in Advanced Ovarian Cancer Are Limited

Recurrence Rates are High and Survival Rates Low



*Aurelia Trial.

OVATION I: Phase I Trial of GEN-1 in Newly Diagnosed Ovarian Cancer Patients

- Neoadjuvant patient population
- Standard 3+3 design with ~30% dose increments + standard carboplatin (C) and paclitaxel (T)
- Eight weekly doses of GEN-1 before debulking surgery

Safety

Common AEs Attributed to GEN-1	Total (n, %)	Grade 1 & Grade 2 (n,%)	Grade 3 (n,%)	Grade 4 (n, %)	Grade 5 (n, %)
Nausea	9, 60%	9, 60%	0, 0%	0, 0%	0, 0%
Abdominal Pain/ Cramping	6, 40%	5, 33%	1, 6%	0, 0%	0, 0%
Fatigue	6, 40%	6, 40%	0, 0%	0, 0%	0, 0%
Vomiting	6, 40%	5, 33%	1, 6%	0, 0%	0, 0%
Diarrhea	5, 33%	3, 20%	2, 13%	0, 0%	0, 0%
Neutropenia	5, 33%	3, 20%	1, 6%	1, 6%	0, 0%

- Dosing: GEN-1 dosing ranged 36 mg/m^2 – 79 mg/m^2 **weekly during chemotherapy up to 8 doses**
- Safety Monitoring Board recommended starting dose of next trial: 100 mg/m^2
- One patient discontinued due to toxicity (altered taste)

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OVATION I Study: Dose-Dependent Clinical Responses Observed

- Standard 3+3 design with ~30% dose increments + standard carboplatin (C) and paclitaxel (T)
- Eight weekly doses of GEN-1 before debulking surgery

Clinical Responses*

	GEN-1	
	Low-Dose Cohorts 36 mg/mg² & 47 mg/mg²	High-Dose Cohorts 61 mg/mg² & 79 mg/mg²
Objective Tumor Response (CR/PR) RECIST 1.1	66%	100%
Interval Debulking Status R0 Resection Rate	33%	88%
Chemotherapy Response Score CRS 3 Rate	17%	50%

* Chemotherapy dose consistent across all GEN-1 dosing cohorts

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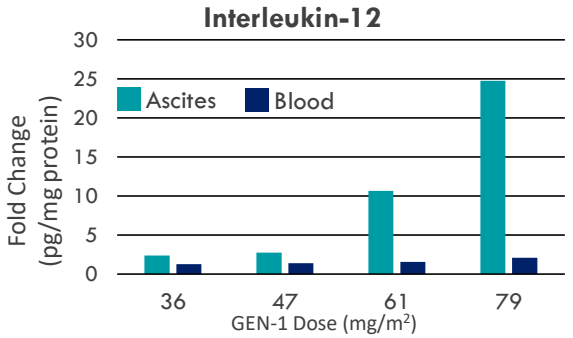
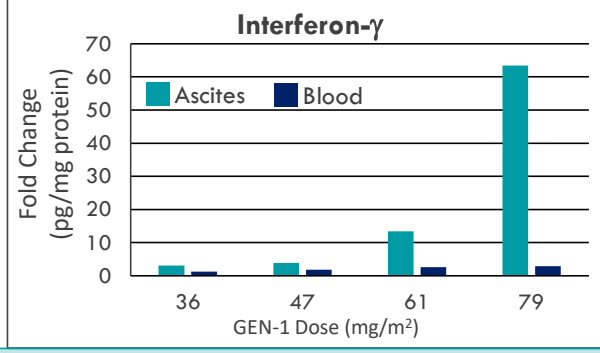
OVATION I Study Translational Data Sampling

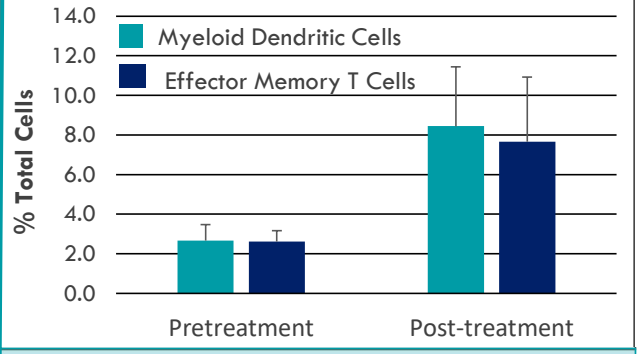
Ascites

Marked Dose-Dependent Increase in Anti-Cancer Cytokine Levels





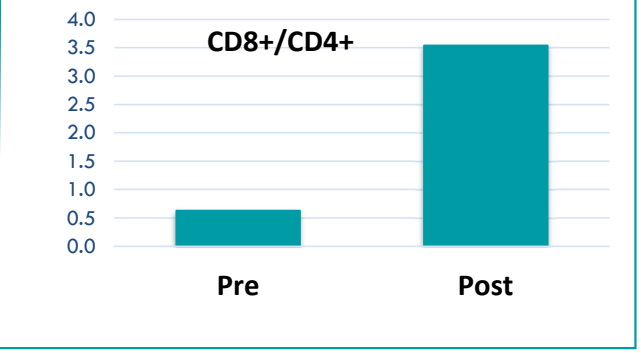
Increase in Dendritic and T_{EM} Cells



Tumor

Decrease in Immunosuppressive Biomarkers

Increase in CD8+/CD4+ in Tumor



- Increases in cytokine levels shows GEN-1's activity; Low cytokine blood levels underpin the safety profile of GEN-1
- Increase in anti-cancer dendritic cells & effector memory T-cells demonstrate activation of the cellular immune system
- Overall shift in tumor microenvironment to immunostimulatory

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GEN-1 OVATION 2 Ovarian Cancer Study

To Determine Efficacy and Biological Activity With NAC in Stage III/IV Patients

Newly Diagnosed Ovarian Cancer Tissue Collection

1 : 1 Randomization Added Control Arm to OVATION 2

Neoadjuvant Chemotherapy (NAC) + 8 weekly cycles of GEN-1

Interval Debulking Surgery Tissue Collection

Adjuvant Chemotherapy + 9 weekly cycles of GEN-1

Additional Treatment Regimen vs. OVATION I Trial Design

Continue GEN-1 treatment following surgery (Maintenance Therapy)

Ovarian Cancer Patients (FIGO IIIC & IV)

Up to 110 patients

14 patients in Phase I Run-in (100 mg/m²);

Up to 96 patients in Phase II

Randomized 1:1 NAC +/- GEN-1

Primary Endpoint

Progression Free Survival (PFS)

After 80 PFS events or at least 16 months, whichever is longer

Secondary Endpoints

- Clinical Response (ORR)
- Pathological Response
- Surgical Resection Scores (R0, R1, R2)
- Biological Response
- Safety

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GEN-1 OVATION 2 Ovarian Cancer Study

Phase I/II Open Label Controlled Trial

- Phase I Portion (N=14) Completed
- 100 mg/m² GEN-1 Dose Confirmed
- 22 Clinical Sites in U.S. and Canada
- Enrollment Expected to be Completed in Q3 - 2022

Interim Data (After 35 IDS)	NACT ONLY	NACT + GEN-1
Interval Debulking Surgery (IDS) R0 Resection Rate	56%	80%

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Summary

DNA Vaccines

- PLACCINE vaccine technology, independent of virus/device, potentially durable immunity and shelf-life
- Flexible design & generic manufacturing process better equipped for a rapid response to pandemic
- A multi-cistronic vaccine provides protection against multiple variants of pathogens addressing resistance issues

GEN-1

- An unprecedented pharmacology (local/durable/maintenance) of a powerful IL-12 immunocytokine
- GEN-1 IP treatment is associated with biologic and clinical activity with excellent safety
- OVATION 2 offers new hope to newly diagnosed advanced ovarian cancer patients
- Full enrollment in OVATION 2 is expected to be completed by 3rd Quarter of 2022

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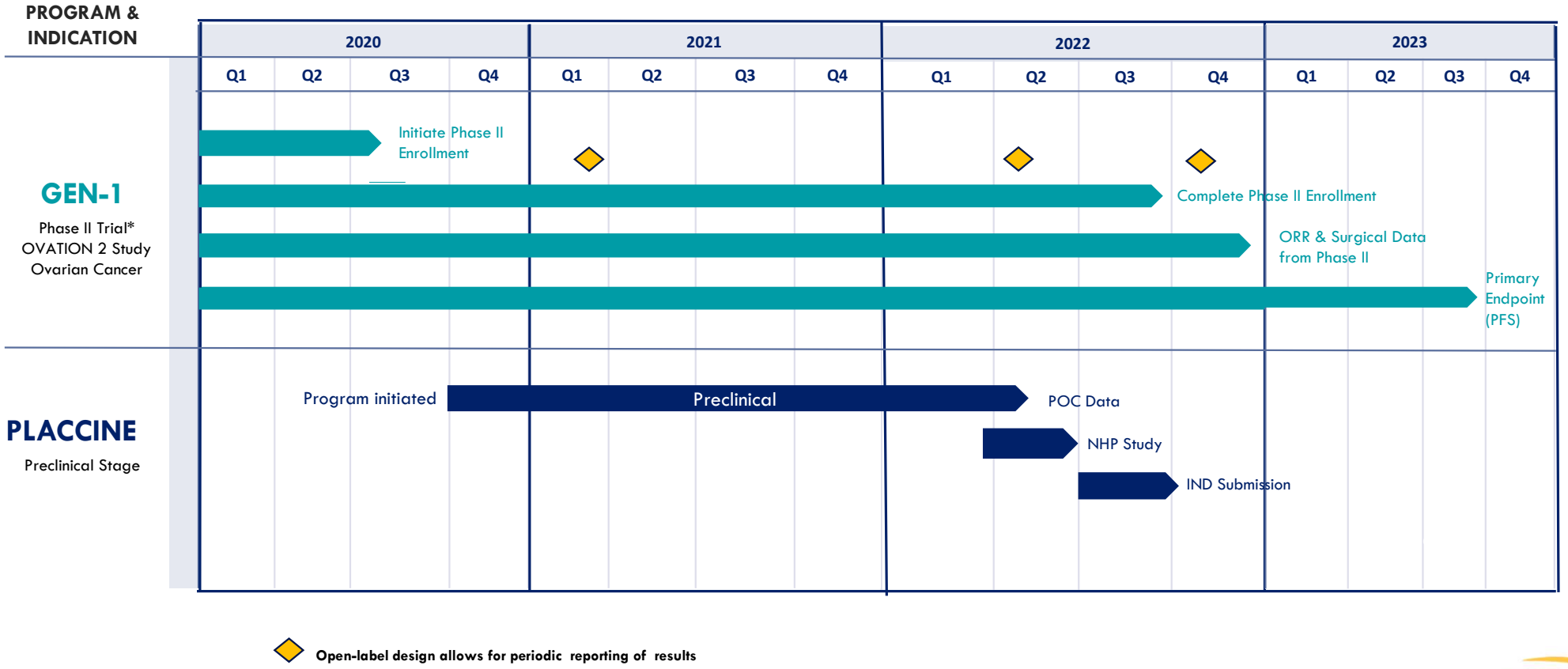
Pipeline Milestone Events

2022 - 2023



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