Development of a Novel IL-12 DNA-based Immunotherapy in Combination with Chemotherapy for Treatment of Advanced Ovarian Cancer

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Celsion is a Fully Integrated Oncology Company with a Deep Pipeline and Multiple Product Platforms

LTSL

Lysolipid Thermally Sensitive Liposomes

ThermoDox:
Liposomal Doxorubicin

Phase 3 Study in HCC
Phase 2 Study in RCW

TheraPlas

DNA-based Non-viral Immunotherapy

GEN-1:
IL-12 Immunotherapy

Phase 1b in Ovarian Cancer
Pre-Clinical in Glioblastoma

TheraSilence

RNA-based Non-viral Carriers, Lung Specific

GEN-2:
Delivery siRNA, miRNA, mRNA

Pre-Clinical Delivery Cancer
Pre-Clinical Delivery PAH, ++

TheraPlas Platform

GEN-1: Ovarian Cancer

Ovarian Cancer

Large and Deadly Global Cancer

- **8th most diagnosed among women**
  - 225,000 annual incidence worldwide
  - 22K in US and 100K in developed countries
  - 17th most common cancer overall
- **5th highest mortality among women**
  - 5-year survival rate for all stages is 45%; survival rate reduces dramatically if not localized cancer
  - Less than 15% diagnosed with localized cancer, eligible for potentially curative surgery
  - 5th highest mortality among women, comprising 5% of total deaths among women
- **Local therapies**
  - Limitations of 1st line therapies: Ovarian cancer is not diagnosed early, has spread to regional/mets requiring combo regimens
  - Most common site of recurrence in abdomen– suggesting importance of intra-peritoneal (IP) administered therapy over traditional IV regimen
  - GEN-1 administered IP; ideal adjuvant to any IV, IP or oral therapy

Sources: Cancer Statistics, American Cancer Society; Globocan; SEER database

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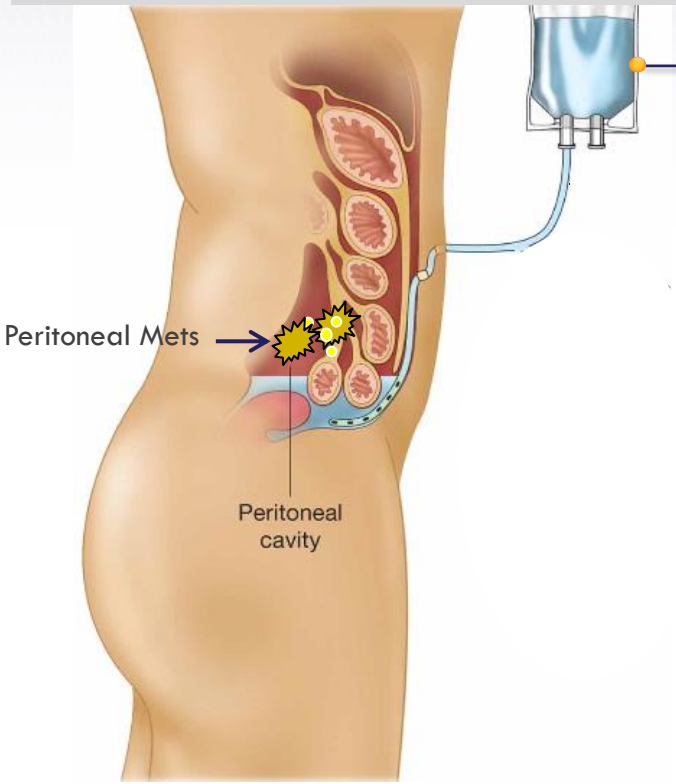
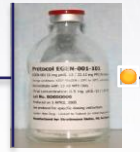
GEN-1 Concept & Rationale

Modulation of Immune Response by Local Production of a Powerful Immune Modulating Agent, IL-12

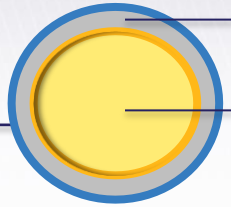
Persistent Delivery of IL-12 with a Single Administration of Formulated IL-12 Plasmid

(Distinct from IV Chemotherapy)





GEN-1



Stable Nanoparticles for Local Delivery

GEN-1causes the production of IL-12 at cancer site for several days

IL-12 addresses cancer by recruiting the immune system, inducing powerful anti-cancer mechanisms

Clinical experience in peritoneally metastasized ovarian cancer strongly supports Phase II trial in combination with first line treatment

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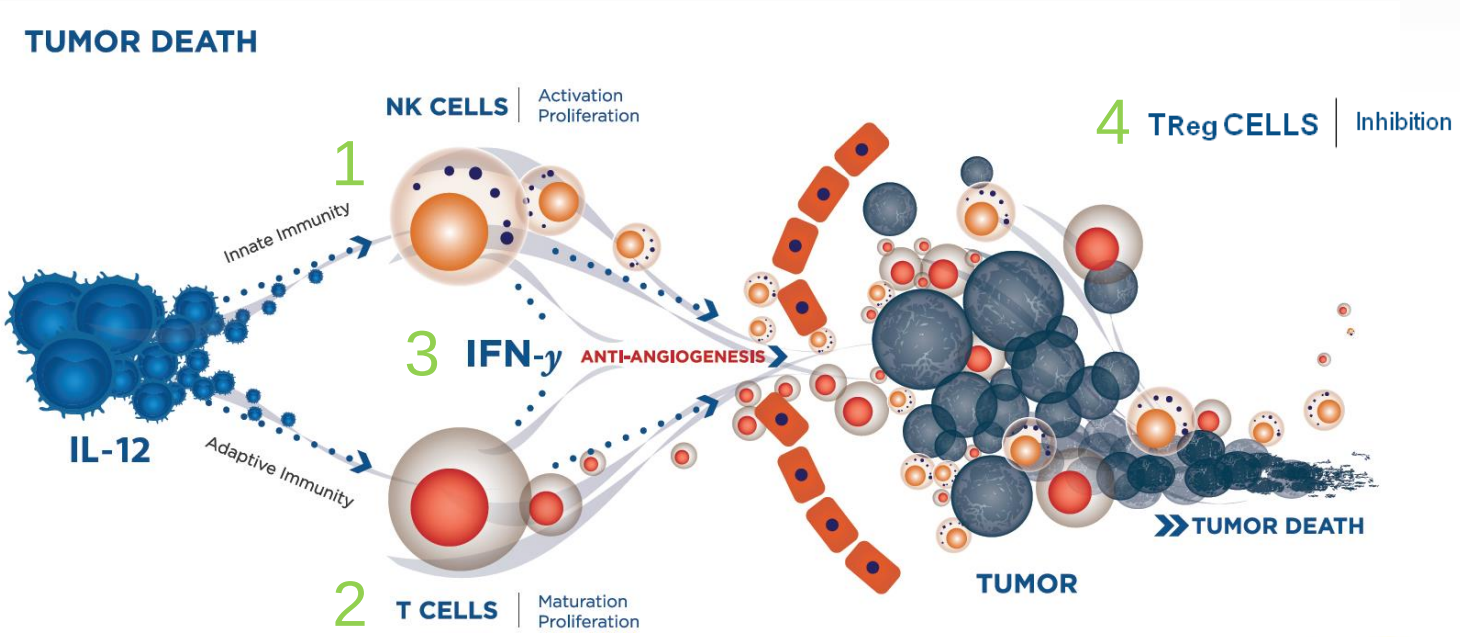
IL-12: A Powerful Immune Modulating Agent with Multiple Mechanisms of Action

Mechanisms of Action

1. NK cell Activation
2. T cells Activation
3. Anti-angiogenesis
4. Treg suppression



Evidence of IL-12 Immunostimulatory and Anticancer Activity

Epidemiologic Studies

- IL-12 mRNA Levels & Survival Rate
- IL-12 Levels & Disease Stage
- Prognostic Factor

Clinical Responses

- Melanoma
- Renal Carcinoma
- Cutaneous T-Cell Lymphoma
- AIDS-Associated Kaposi Sarcoma

Pre-Clinical Data

- Melanoma
- Renal Carcinoma
- Lymphoma
- Gastrointestinal
- Ovarian carcinoma
- Hepatocellular Carcinoma

Biological Responses

- Systemic IFN-γ Response
- NK Cell Response
- T Cell Response

Poor PK of rIL-12 has hampered its clinical development and warrants for alternative approaches to IL-12 therapy

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Alternate Approaches to rIL-12 Therapy

Preclinical

- PEG-Conjugated IL-12
- T Cell-based IL-12 Targeting
- Membrane-bound IL-12

Clinical

- Inducible Vectors
- **Formulated Plasmid (Celsion-EGEN approach)**

Reduce Serious Systemic Toxicity Associated with rIL-12 Treatment

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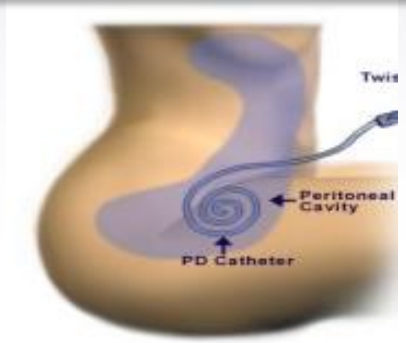
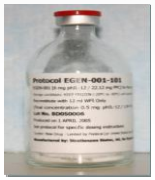
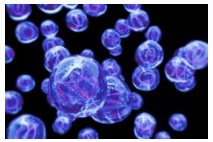
Local Delivery of IL-12 by Gene Transfer

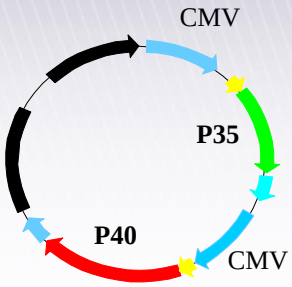
IL-12 Plasmid + Synthetic Vector

Local Intraperitoneal Delivery

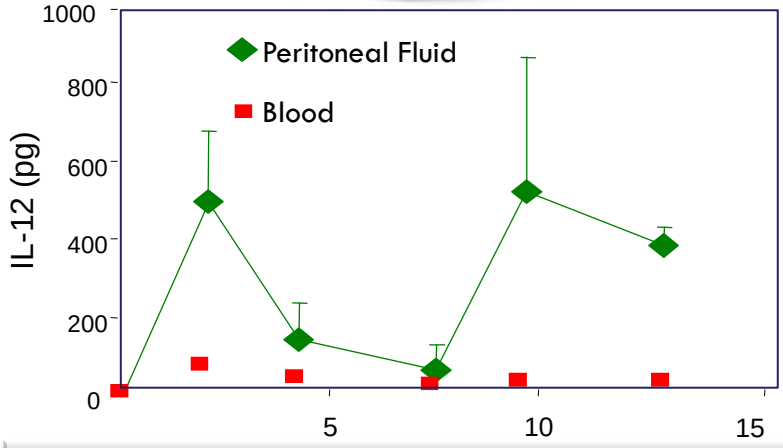




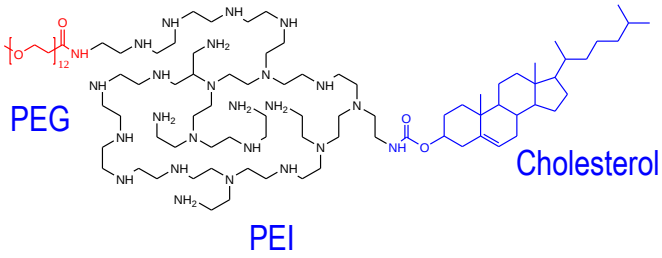




IL-12 Plasmid



No Systemic Levels of IL-12



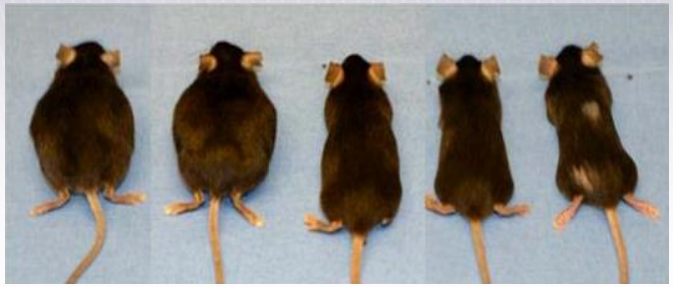
Delivery Lipopolymer

Preclinical Models of Activity

Anticancer Activity in a Peritoneally Disseminated Mouse ID-8 Ovarian Cancer Model

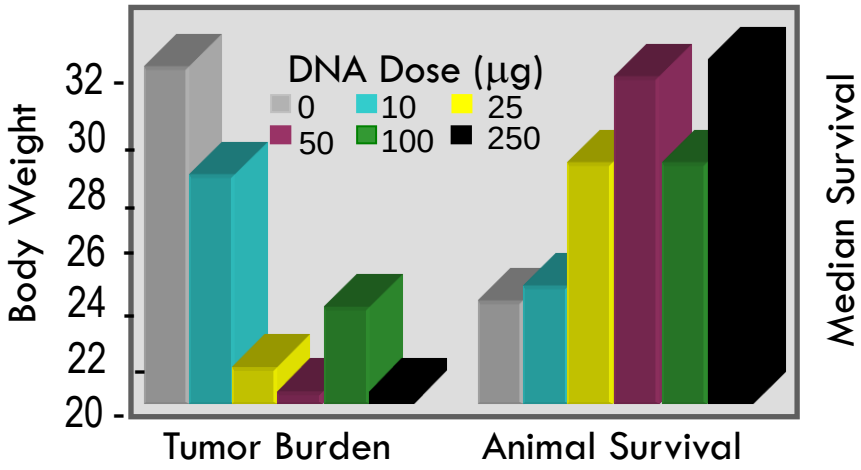
Attenuation of Tumor Ascites

(a)

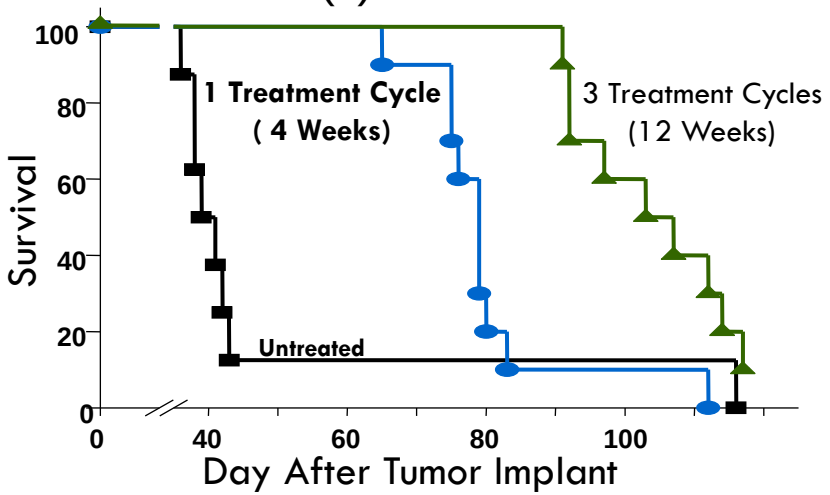


Untreated Control | 10 µg | 50 µg | 250 µg | Naive

(b)



(c)



(a, b)- 5 x 10^5 ID8 cancer cells implanted IP. Weekly GEN-1 initiated 20-25 days after tumor implantation; (c): comparison of treatment cycles

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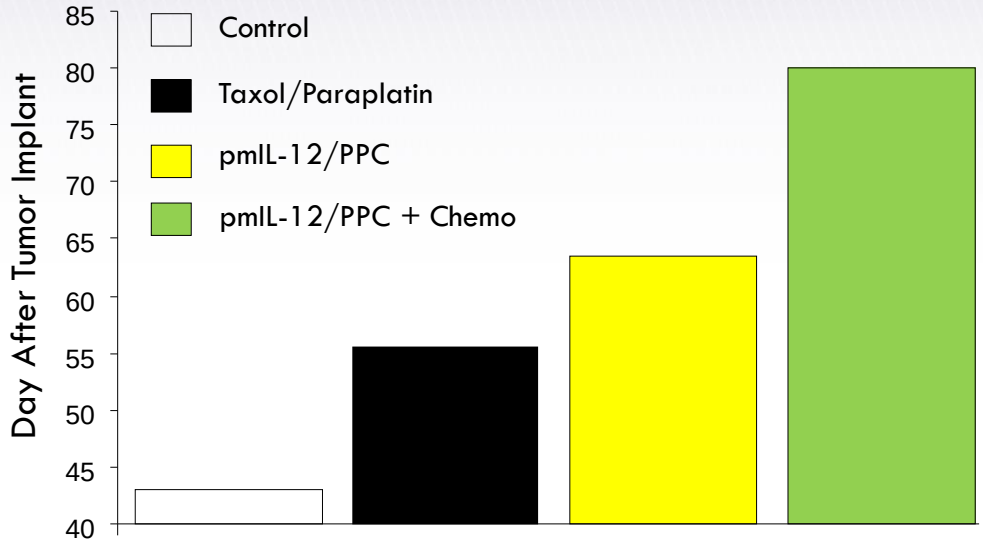
Enhancement of Chemotherapy Activity

Improvement in Median Survival by Combination Therapy



5×10^5 ID8 ovarian cancer cells were implanted IP. Taxol (3 mg/kg) and carboplatin (15 mg/kg) treatment (iv x 2 or 4) were started 14 days after tumor implantation; pmIL-12/PPC was given weekly for 4 weeks 18 days after tumor implantation.

Anti-cancer activity demonstrated in several cancer models as a single agent or with different chemotherapy agents

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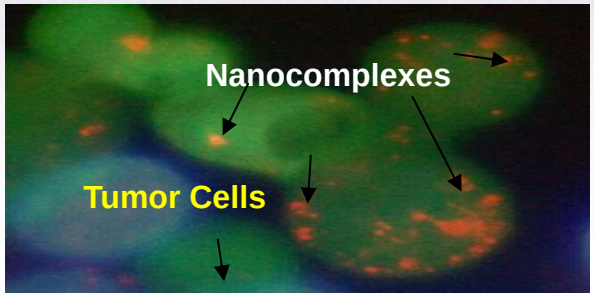
Mechanism of Action

Cellular Uptake of Nanoparticles, Production of IL-12 & Related Immune Cytokines in Peritoneal Fluid - Not in Blood

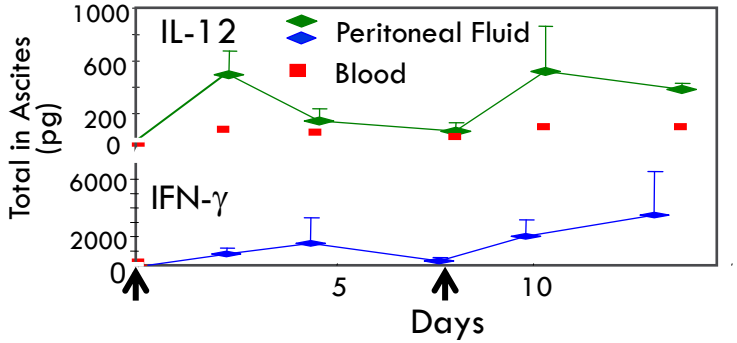
(a)

Tumor (green) Uptake of Nanoparticle (red)



(b)

Local Increases in Cytokines

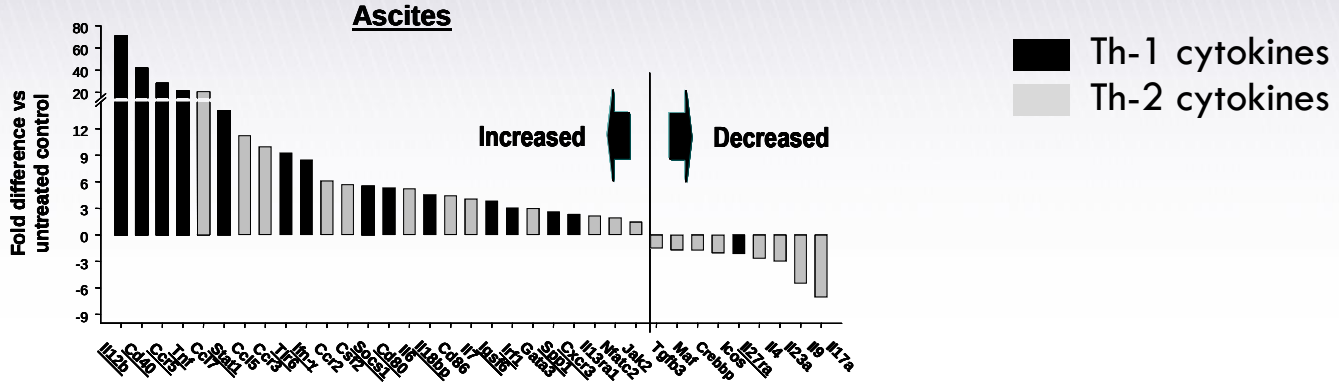


(a)- GFP expressing ID8 ovarian cancer cells were implanted IP in mice. Fluorescent-labeled plasmid was complexed with PPC and administered IP. Ascites were collected 4 h thereafter for fluorescence microscopy. (b)- 2.5 x 10^6 ID8 cells were implanted IP and pmIL-12/PPC (100 ug plasmid) was administered IP 39 days thereafter for a single injection or 2 injections (arrow). The ascites and serum were harvested for cytokine analysis.

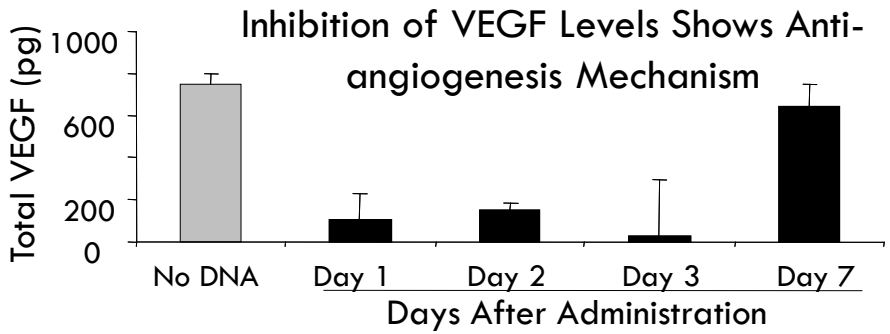
GEN-1 IP Activates the Adaptive Immune System & Inhibits VEGF Levels in Tumor Ascites in Mice

Increases in Tumor Suppressive Th-1 Cytokine Transcripts Show Activation of the Adaptive Immune System

(a)



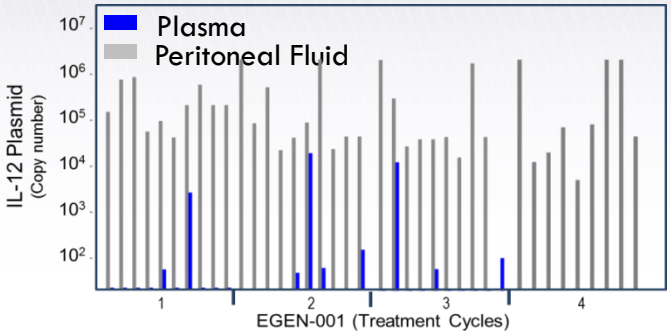
(b)



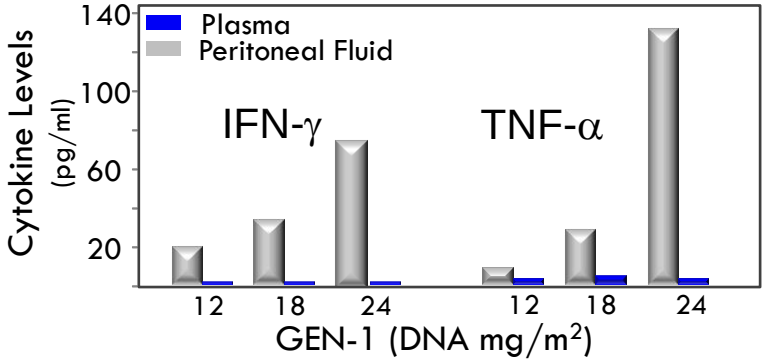
(a). 2.5 x 10^6 ID8 ovarian cancer implanted IP. pmIL-12/PPC administered weekly for 2 weeks. Animals were sacrificed next day and ascites and tumors collected for transcript analysis. (b). 2.5 x 10^6 ID8 cells were implanted IP and pmIL-12/PPC (100 ug plasmid) was administered IP 39 days thereafter for a single injection. The ascites and serum were harvested for VEGF analysis

Little Systemic Distribution of IL-12 Plasmid and Immune Cytokines Supports a Better Safety Profile over rIL-12

IL-12 Plasmid is Localized in Peritoneal Cavity with Little Distribution to Systemic Circulation in Ovarian Cancer Patients



IL-12-Mediated Immune Cytokine Levels are also Higher in Peritoneal Cavity than in Systemic Circulation of Ovarian Cancer Patients



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Clinical Studies

Clinical Experience to Date

Chemotherapy Pre-Treated Recurrent Ovarian Cancer

Single Agent Studies

Platinum-resistant recurrent ovarian cancer

- Phase 1 dose escalation – 0.6 to 24 mg/m^2 (n=12)
- Phase 2 – 24 mg/m^2 (n=20)

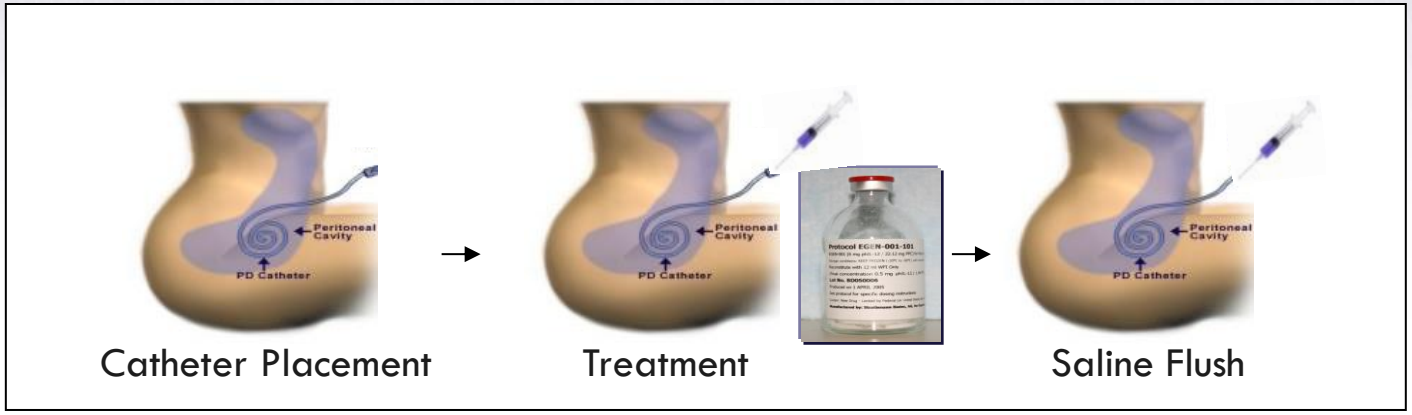
Combination with SOC

Platinum-resistant – 24 & 36 mg/m^2 of GEN-1 + Doxil (ongoing)

- Phase 1 dose escalation- 24, 36 mg/m^2 (n=16)

GEN-1: IP Clinical Trial Design

General Treatment Design



Screen/Cath (-3 Wks)

GEN-1 (Weekly Rx)

Ph I single agent dose escalation-
Ph I combo dose escalation-
Ph II single agent or Ph I Doxil combo-

4 weekly Rx
4, 6 or 8 weekly Rx
weekly until intolerable tox/PD

Final Analysis

Standard of Care

Safety Profile of GEN-1

Most Common AEs

(at least possibly attributable to GEN-1, mostly grade 1/2)

Single Agent

Phase-I Dose Escalation Study
(0.6 – 24 mg/m^2)

- Abdominal discomfort
- Fever & Chills
- Peritonitis (3/13)
- Catheter site discomfort
- ***No DLTs***

Phase-II Single Dose Trial (24 mg/m^2)

(sicker population than the above study)

- Abdominal discomfort
- Fever & chills
- Catheter site discomfort
- Nausea & Vomiting
- Anemia, leukopenia

Combination Agent

Phase-I Multi-dose with Doxil
(24, 36 mg/m^2)

- Treatment phase completed
- No apparent safety concerns

MTD has not been achieved

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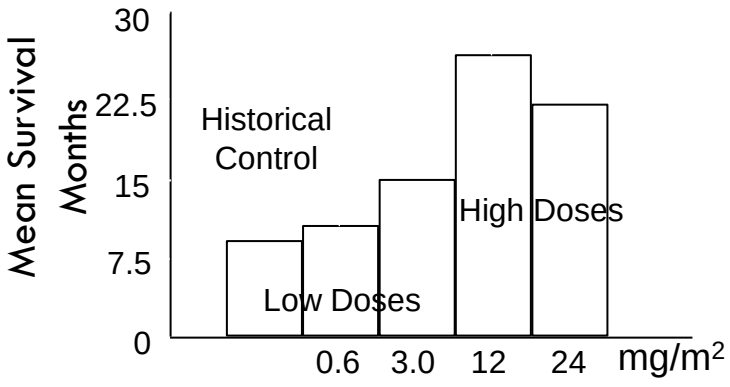
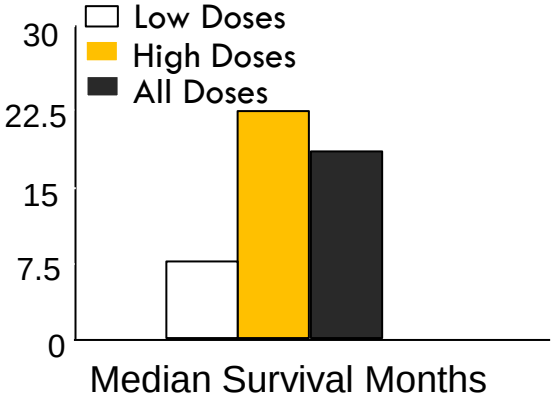
Phase I Dose Escalation Study of GEN-1

Platinum Resistant Ovarian Cancer Patients

Phase I Trial, n=12

Disease Control Rate (CR+PR+SD):	31%
Median Overall Survival:	18 months
Prior Chemotherapies:	4-6





Phase II Study of GEN-1

Platinum Resistant Ovarian Cancer Patients

Phase II Trial, n=20

Good Disease Control & Survival Rate in Platinum-Resistant Patients

Efficacy Results (24 mg/m^2)			
Progression Free Survival		Disease Control Rate	Overall Survival
Median	$\geq$ 6 months	(CR+PR+SD)	Median
3 months	30%	45%	10 months

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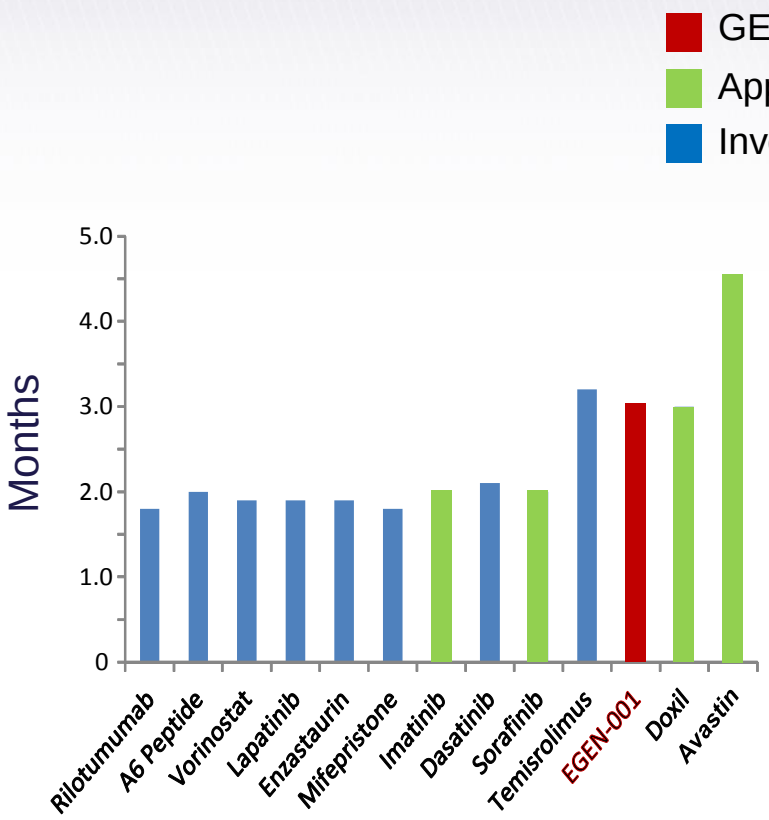
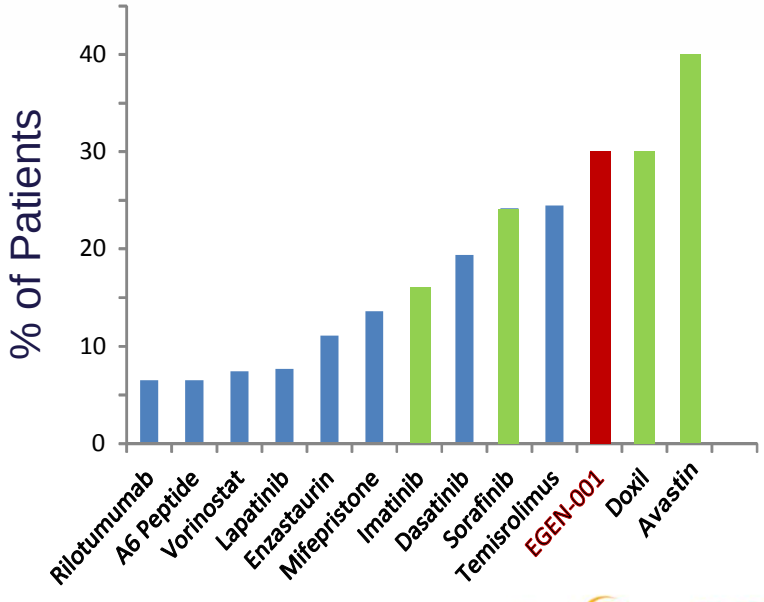
GEN-1 Single Agent Phase II Data Compares Favorably To Many Approved/Investigational Drugs

Progression Free Survival and 6-month PFS





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Phase Ib Trial: GEN-1 + Doxil

Platinum Resistant Ovarian Cancer

Safety, Biological Activity & Efficacy of Combination Therapy

Traditional 3+3 Escalation Design (n=16)

Dose Level	GEN-1 (mg/m^2)	Doxil (mg/m^2)	Status
1	24	40	Completed
2	36	40	Completed
3	36	50	Completed

- Treatment phase completed
- Scientific abstract submitted to ASCO, 2015

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Summary Clinical Experience to Date

Chemotherapy Pre-Treated Recurrent Ovarian Cancer

Single Agent Studies

Platinum-resistant recurrent ovarian cancer

- Phase 1 dose escalation – 0.6 to 24 mg/m^2 (n=12)
  - DCR (SD)– 31%, local delivery, biological activity, well-tolerated, no MTD
  - Better OS in a historically unresponsive population
- Phase 2 – 24 mg/m^2 (n=20)
  - DCR (SD)– 45%
  - Well-tolerated, no MTD

Combination with SOC

Platinum-resistant – 24 & 36 mg/m^2 of GEN-1 + Doxil

- Scientific abstract submitted to ASCO 2015

Current Development Strategy for GEN-1

1st Line Ovarian Cancer + Standard of Care in Neo-adjuvant Setting

Hypothesis

Addition of GEN-1 immunotherapy to front line chemotherapy in newly diagnosed patients (healthier immune system) will yield robust immune responses and durable clinical responses than with chemotherapy alone

Neo-adjuvant Approach

Neo-adjuvant approach (SOC before surgery) in ovarian cancer is gaining credence due to less traumatic follow up surgery and potential for clinical benefits

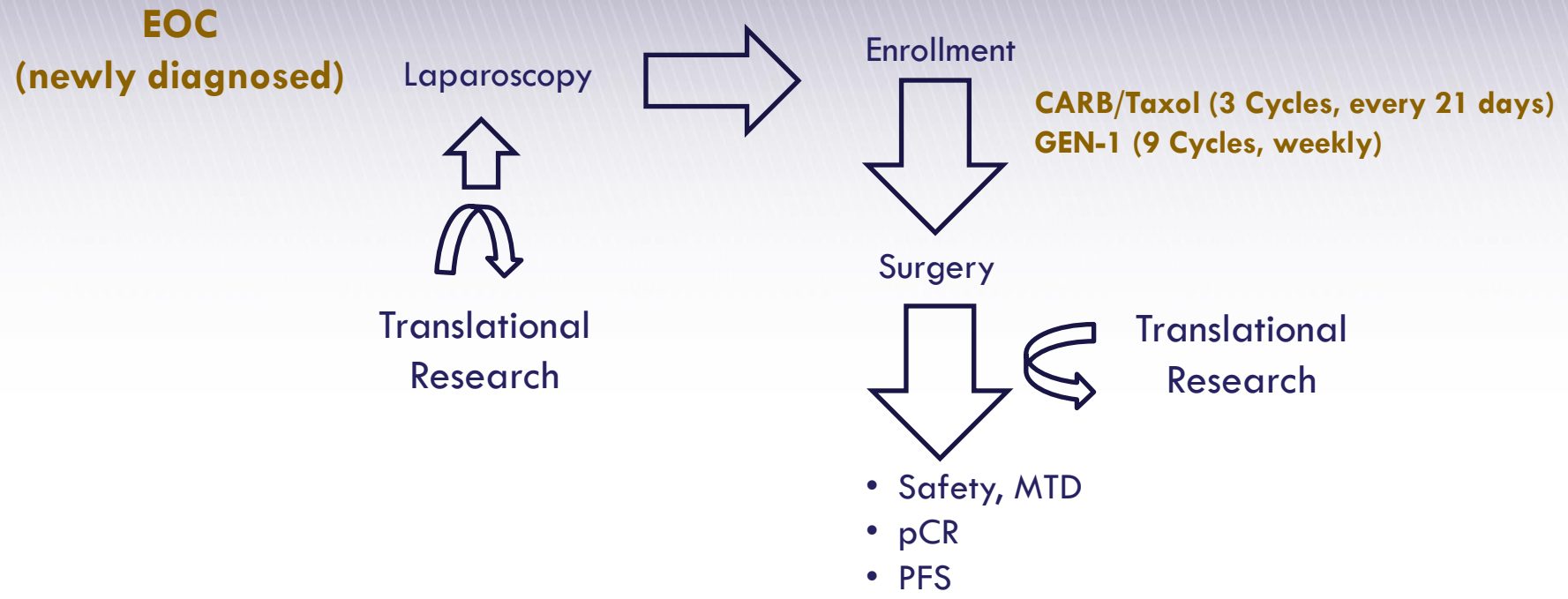
Current Development Strategy for GEN-1

1st Line Ovarian Cancer + Standard of Care in Neo-Adjuvant Setting

Rationale for GEN-1 immunotherapy in neo-adjuvant population

- Healthier immune system; no prior treatment with immunosuppressive drugs
- Potential for a robust immune response and durable effect lacking with chemotherapy alone
- Neo-adjuvant allows access to primary tissue and opportunity for detailed translational research potentially useful for better future study designs and stratification
- Local IP treatment for local disease is a recognized delivery mode
- Supportive results observed in clinical studies in difficult-to-treat disease

Phase I Dose Escalation of GEN-1 in Combination with Front Line Therapy (Study Submitted to US FDA)



Dose Escalation Scheme

Test Doses (mg/m^2): 36, 47, 61, 79, 103; highest previously tested (mg/m^2): 36
Rationale: No MTD in previous trials; ascending biological response at test doses

This study is designed to identify a safe dose of GEN-1and strong biological data to design a randomized phase II study in front line setting

Description of the Translational Research

Objectives:

- Determine pre-treatment Immune environment and changes elicited by GEN-1 Treatment in the Test Population

Rationale:

- Ovarian cancers are immunogenic where local immune environment plays a crucial role in disease onset, progression and control
- GEN-1 produces IL-12, a potent immune modulation agent
- Understanding the relationship between pre-treatment immune status and immunological and clinical responses will expand GEN-1 target identification and better design of a pivotal study in future

Summary

- Ovarian tumors are immunogenic; involvement of the immune system is well documented
- GEN-1 is a novel DNA-based immunotherapy
  - Produces IL-12, a potent immunomodulary agent, at tumor site w/o systemic toxicity
- Comprehensive preclinical data formed the basis of ongoing clinical development
- Clinical studies to-date have demonstrated:
  - Safety, biological activity, and encouraging clinical benefits in highly advanced chemo resistant ovarian cancer patients
- Compelling reasons to advancing GEN-1 immunotherapy in front line setting