The remarkable efficiency of chaperone-based synthetic cancer vaccines

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Forward-looking statements

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Broad I-O portfolio ranges from early- to late-stage programs

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<th>Preclinical</th>
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Notes: AGEN1884 and AGEN2034 are being evaluated in 2L cervical cancer and undisclosed tumors. Recepta Biopharma S.A. has exclusive rights to AGEN1884 and AGEN2034 in Brazil and five other South American countries.
Agenus’ vaccines today

**Prophage™**
*Individualized*
Prepared from patient tumor
HSPs chaperone neo-antigens

**Phase 2**
NCT03018288… enrolling

**AutoSynVax™**
*Individualized*
Synthetic, on-demand, defined by tumor NGS, predicted neo-antigens
NGS & proprietary algorithms

**Phase 1**
NCT02992977… ongoing

**PhosphoSynVax™**
*Off-the-Shelf*
Synthetic, targeting tumor-specific phosphorylated neo-antigens
HLA ligandome MS & proprietary neo-epitopes

**Pre-clinical**
Proteins liberated from tumor cells and fractionated biochemically

Protein fractions tested in tumor rejection assays

Efficacy demonstrated with 1 – 20 µg HSP.
Heat shock proteins chaperone peptides

**Attributes of the antigenome**
- Includes non-self (mutated) antigens
- Products of random mutation
- Individually tumor-specific

**Cellular Peptides**
- Mutated/Normal

Inside cells peptides are chaperoned by heat shock proteins

- HSPs are present in all cells (normal, cancerous, infected) and act as protein chaperones within the cell
- HSPs carry the ‘antigenome’ of each cell, constituting the entire repertoire of antigenic peptides
- HSP receptors impart efficiency to antigen cross-presentation

IFNγ, IL-2
Heat shock proteins chaperone peptides

Cellular Peptides

Mutated/Normal

Inside cells peptides are chaperoned by heat shock proteins

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• Attributes of the antigenome
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  – Products of random mutation
  – Individually tumor-specific

Prophage Clinical status
A Randomized, Double Blind Phase II Trial of Radiation Therapy Plus Temozolomide and Pembrolizumab With and Without HSPPC-96 in Newly Diagnosed Glioblastoma (GBM). NCT03018288, enrolling; NCI sponsored
Versatility of Agenus’ chaperone-based vaccine platform

Recombinant heat shock protein 70 (Hsc70)

Hsc70-peptide complexes

Synthetic peptides containing T cell epitopes:
- Patient & tumor-specific
- Post-translational mods.
- Viral

Bioinformatics Ligandomics

Tumor/viral genome

QS-21 Stimulon® Adjuvant

Vaccine PRIME

Pre-manufactured, targeting shared phosphorylated, viral, and other common neo-antigens

Vaccine BOOST

On-demand, defined by tumor NGS, targeting patient-specific neo-antigens

Wald Vaccine 2011
Tanne 3rd CRI-CIMT-EATI-AACR 2017
QS-21 Stimulon® generates strong antibody, cell-mediated and innate immune responses

- Based on saponins extracted from Chilean soap bark tree
- Primes innate immune pathways and drives antigen cross-presentation
- Extensive experience: Safe & well tolerated in >50,000 patients
- Partnership with GSK
  - Shingrix shingles vaccine US/CA approval (>90% efficacy rate)
  - Mosquirix malaria vaccine expected to launch in 2018
  - Component in several clinical stage vaccine programs with GSK
Use of linker-ligand peptides to enhance Hsc70 binding

Ligand sequences of bacterial and mammalian HSP70s previously reported using phage display
- A variety of peptides tested
- Suggestions of structure-activity relationships (SAR)
- Dissociation constants in range of 1~100 micromolar

**Linker-ligand improves loading of Hsc70, activity**

- Use of linker-ligand sequences improves extent to which peptides load onto Hsc70
- Less peptide needed to achieve high loading onto protein

**Preclinical study**

**Day TC-1 challenge**  
Prime | Boost | Boost
---|---|---
0 | 5 | 9 | 15

**Without linker**  
Hsc70-peptide complex (38%)

**With linker**  
Hsc70-peptide complex (80%)

**Figure:**

- TC-1 challenge
- Prime
- Boost
- Boost
- Hsc70
- HPV E6/E7 peptides

**Graph:**

- PBS
- Hsc70-peptides (no linker) + QS21
- Hsc70-peptides (+ linker) + QS21

**Tumor Volume (mm³):**

- N=10/group

**Days post tumor injection:**

- 0
- 1
- 0
- 2
- 0
- 3
- 0
- 5
- 0
- 1
- 0
- 2
- 0
- 3
- 0

**Legend:**

- Hsc70
- HPV E6/E7 peptides
All three components of vaccine contribute to effect

*Induction of powerful memory response*

Preclinical study

![Diagram showing tumor volume changes over days after tumor implant]
Remarkable efficiency of Agenus’ vaccine platform

HPV E7 epitope

MC38 neo-epitopes

Implications for peptide manufacturing:
- Only ~1.4 - 2.8 µg each peptide required for a Hsc70/QS21-based neo-antigen vaccine dose in humans

Prime Boost

Day 0 7 14

Immune monitoring by ELISPOT
Comparison to benchmark vaccine format

CT26 tumor challenge

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Immunological monitoring

Restimulation conditions

I F N - γ + spots / 250k cells

Comparison to benchmark vaccine format

Hsc70-peptides + QS21
Peptides + poly (I:C)

35x – less antigen

Peptides in vaccine:

<table>
<thead>
<tr>
<th>CT26 neo-epitope*</th>
<th>Seq + high affinity Hsc70 binding motif (not shown)</th>
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<td>3</td>
<td>DKPLRRNNSYTSMAXIGMPLDSFRA</td>
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<td>4</td>
<td>EVIQTSKYYMRDVAIESAWLLELAPH</td>
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<tr>
<td>5</td>
<td>VILPQAPSGPSYATYLQPAQAQMLTTP</td>
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*As defined by Kreiter et al. Nature 2015
Vaccine combination with immune modulating antibodies

Vaccine + αCTLA-4 antagonist

N=4-5/group

Restimulation conditions

Vaccine combination with immune modulating antibodies

Vaccine + αOX40 agonist

N=3/group

Restimulation conditions

Pool C
T26 neo-epitopes
Neo-epitope 1
Neo-epitope 2
Neo-epitope 3
Neo-epitope 4
Neo-epitope 5

IFN+ spots/500k cells

IFN+ spots/500kcells

IFN+ spots/500k cells

N=3/group

Restimulation conditions

Pool C
T26 neo-epitopes
Neo-epitope 1
Neo-epitope 2
Neo-epitope 3
Neo-epitope 4
Neo-epitope 5

Vaccine + Isotype
Vaccine + αCTLA-4 Ab

Vaccine + Isotype
Vaccine + αOX40 Ab

N=4

-5/group

N=3/group

N=3/group
Vaccine Platforms
Agenus vaccine candidates educate the immune system

**Prophage™**
- Prepared from patient tumor
- HSPs chaperone neo-antigens
- Individualized
- *Phase 2*
  - NCT03018288… enrolling

**AutoSynVax™**
- Synthetic, on-demand, defined by tumor NGS, predicted neo-antigens
- NGS & proprietary algorithms
- Individualized
- *Phase 1*
  - NCT02992977… ongoing

**PhosphoSynVax™**
- Synthetic, targeting tumor-specific phosphorylated neo-antigens
- HLA ligandome MS & proprietary neo-epitopes
- Off-the-Shelf
- Pre-clinical
Phosphopeptide Tumor Targets (PTTs): novel class of cancer neoantigens

• Phosphorylation not represented by mutations

• Aberrant kinase activities in cancer leads to phosphorylation of self-proteins

• Neo-epitopes that trigger immunity

• Neo-epitopes shared across cancer types and individuals
PTTs are presented by MHC class I and can be recognized by TCRs

- Phosphate group exposed and accessible to TCR
- Phosphate group also participates in binding MHC molecules and can increase binding affinity

State-of-the-art analysis identifies PTTs from patient samples

Resected Human Tissue or Cell Line → Lysis → Immunoaffinity Purification → STAGE Tip Sample Cleanup

- **0.5 g tissue or 500 million cell equivalents**

**Biological Characterization of T cell Responses**
- Resected Human Tissue or Cell Line
- **Lysis**
  - Tumor
  - Normal
- **Imunoaffinity Purification**
- **Tissue Comparison**
  - Tumor
  - Normal
- HPLC-ESI-MS/MS Analysis and Manual Validation
  - **IMAC Phosphopeptide Enrichment on IDA-Iron(III) beads**

**Tissue Comparison**
- IFNγ
- TNFa
- IL-2
- CD107a

**HPLC-ESI-MS/MS Analysis and Manual Validation**
- 10-200 Phosphopeptides present <1-100 copies/cell

**IMAC Phosphopeptide Enrichment on IDA-Iron(III) beads**
Analysis of primary cancer tissue versus tissues from “normal” donors allows us to select phosphopeptides that are unique to or upregulated in cancer tissue.

Phosphopeptide enrichment techniques combined with cutting edge mass-spec technology.

Selection Criteria
- Disease Target + other cancer targets
- T-cell memory response in healthy donors
- Prevalence in tumor tissue vs. normal
- Mapped to cancer-relevant pathways

“Normal” Tissue
- Ovary
- Kidney
- Skin
- Aorta
- Liver
- Small Intestine
- Bone Marrow
- Lung
- Jejunum
- Brain
- Pancreas
- Spleen
- Breast
- Prostate
- T cells
- Colon
- Sciatic Nerve
- Thyroid
- Heart
- Skeletal Muscle
- Vena Cava

Primary Cancer Tissue
- Colorectal Cancer
- Esophageal Cancer
- Glioblastoma
- Hepatocellular Carcinoma
- Intrahepatic Cholangiocellular Carcinoma
- Leukemia (AML, CLL, CML, ALL)
- Lung Cancer
- Melanoma
- Renal Cell Carcinoma

>200 tissue samples analyzed

> 2,000 Phosphopeptides identified

~ 20 specific molecular targets for critical indications

>200 tissue samples analyzed

> 2,000 Phosphopeptides identified

~ 20 specific molecular targets for critical indications
**Target Selection Guidelines:**

- Frequency among multiple allele-matched patient samples of a specific indication
- Prevalence in other tumor types
- Prevalence in tumor tissue vs. normal tissues
- Recognized by central memory T cells from healthy individuals
- Reflect common HLA subtypes

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Agenus has identified PTTs that are shared across patients within and between indications.
PhosphoSynVax™: POC with prototype vaccine

Phosphopeptide immunogenicity in HLA-A*02:01 and HLA-B*07:02 Tg mice

Day

0 7 14

Rx

Splenocytes harvested for ELISPOT

Immunization with

- Hsc70-peptide + adjuvant
- Peptide (low dose) + adjuvant
- Peptide (high dose) + adjuvant

PhosphoSynVax™: POC with prototype vaccine

Phosphopeptide immunogenicity in HLA-A*02:01 and HLA-B*07:02 Tg mice

N=3 mice/group

Phosphorylated targets

Non-phosphorylated targets

ex vivo stimulation conditions

PTT1  PTT2  PTT3

PTT1  PTT2  PTT3
24 individual mouse tumors from three tumor models analyzed

59 unique phosphopeptides identified

13 prevalent ones that can be used for:
  - Targeting in normal tissue
  - Immune response experiments in mice
  - Tumor control experiments in mice

3 phosphopeptides have an analogous human sequence which are observed in human cancer tissue
Multi-platform I-O portfolio well positioned for effective combinations

agenus

>12 programs •
3 mAb display platforms •
Bi-specific discovery •
Cell line development •
GMP mAb manufacturing •

Checkpoint Antibodies
Shape Immune response

Cancer Vaccines Educate
Immune system

Adoptive Cell Therapy*
Augment Immune system

agenus

• 3 platforms including
  PTT antigens
• Adjuvants, QS-21 Stimulon®
• GMP vaccine manufacturing

• Unique targets and product format strategy
• Leverages other platforms-discovery to manufacturing

*Program advancing through a separate subsidiary, AgenTus Therapeutics
agensus