Novel TCRs for Cancer Therapy
This presentation contains forward-looking statements. These forward-looking statements are subject to risks and uncertainties, including the factors described under the Risk Factors section of Agenus’ most recent Annual Report on Form 10-K or Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission and made available on Agenus’ website at www.agenusbio.com. When evaluating Agenus’ and AgenTus’ business and prospects, careful consideration should be given to these risks and uncertainties. These statements speak only as of the date of this presentation, and the company undertakes no obligation to update or revise these statements. This presentation and the information contained herein do not constitute an offer or solicitation of an offer for sale of any securities.
AgenTus was developed from Agenus technology and expertise

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

**Checkpoint Antibodies**
- Shape Immune response

**Personalized Cancer Vaccines**
- Educate Immune system
- 3 platforms including PTT antigens
- Adjuvants, QS-21 Stimulon®
- GMP vaccine manufacturing

**Adoptive Cell Therapy**
- Augment Immune system
- Unique targets and product format strategy
- Leverages other platforms-discovery to manufacturing
AgenTus Therapeutics: differentiated cell therapy

**Precision Receptors**
- **T-Rx™ Mammalian Display** - Direct selection for function
- Targets optimal balance between activity and specificity

**Novel Targets**
- Proprietary target discovery and validation platforms
- Proprietary Phosphopeptide Tumor Targets

**Allogeneic Format**
- Allogeneic approach; “Off-the-shelf”
- Scalable, shorter diagnosis to treatment interval
TCR-based therapy can target the entire tumor cell proteome

**MoA**
- direct killing
  - T cell → tumor cell

**Targets**
- Extra-/Intra-cellular proteome
- Surface-expressed proteins

*Current Opinion in Pharmacology 2015, 24:113–118*
TCR:pMHC affinity is critical for TCR specificity and responsiveness

- **very low affinity TCR**
  - Physiological range: 100 µM
  - Low affinity naïve repertoire of T Cell receptors
- **physiological range**
  - ~10 µM
- **high affinity**
  - High affinity non-tolerant repertoire
  - Cross-reactivity energy
  - Very high affinity TCR

**Responsiveness**

Front Immunol, June 2013
Superior receptor discovery through T-Rx™ platform
A powerful engine for delivering efficient and specific TCRs

Applications
• Generate de novo TCRs
• Isolate natural TCRs
• Optimize natural or de novo TCRs
Phosphopeptide Tumor Targets (PTTs) are unique immunogenic cancer neo-antigens.

**Nature of change**

**Consequence for Proteins**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Over-expression</th>
<th>Ectopic Expression</th>
<th>Post-Translational Modifications (phosphorylation, glycosylation, etc.)</th>
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<tbody>
<tr>
<td>EML4-ALK</td>
<td>WT-1</td>
<td>Cancer-Testis Antigens</td>
<td>✓ Neo-epitopes that trigger immunity</td>
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<tr>
<td>Bcr-Abl</td>
<td>Telomerase</td>
<td>Embryonic Antigens</td>
<td>✓ Shared epitopes</td>
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<tr>
<td>KRAS</td>
<td>Survivin</td>
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<td>✓ Not represented by mutations</td>
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</tbody>
</table>

✓ Not captured by live vector or mRNA vaccines
State-of-the-art ligandome technology identifies PTTs from patient samples

Resected Human Tissue (tumor/“normal”)

Lysis

Normal

Tumor

Imunoaffinity Purification

STAGE Tip Sample Cleanup

Sample Cleanup

HPLC-ESI-MS/MS Analysis and Manual Validation

IMAC Phosphopeptide Enrichment

Biological Characterization of T cell Responses

Tissue Comparison

Normal

Tumor

IFN-γ  TNFα  IL-2  CD107a

0.5 g tissue or 500 million cell equivalents

10-200 Phosphopeptides present <1-100 copies/cell

PEGS, 2018
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

PTT Identification – Prioritization of unique molecular targets
MLL: an initial PoC target for PTT-specific TCRs

- Mixed lineage leukemia (MLL1): lysine methyl transferase 2A
- Encoded by KMT2A, member of SET protein family
- Transcriptional co-activator
- Translocations associated with driver mutations in leukemia
- PTTs initially detected in primary AML sample
  - 2 epitopes found associated with HLA B*0701
  - PTTs are germline: not associated with translocation

Anglin and Song. 2013: J Med Chem
Agenus identified the first fully-human phosphopeptide-specific TCR

Primary T-cell expansion platform

Central Memory T-cells

Autologous dendritic cells pulsed with phosphopeptides

No peptide

EPR(pS)PSHSM

10 days

CD8

EPR(pS)PSHSM pentamer

EPR(pS)PSHSM pentamer

TCR recovery by NGS

T-Rx™ display platform

Retroviral transduction with TCRs recovered after NGS

Natural folding, pairing, and anchoring

Multiple enrichment steps

aAPC co-culture

AGENt 04002
T-Rx™ enables identification of specific and functional TCRs

Hit panel screening in AKD-10R display cell line
Primary Human T Cells expressing the AGENt 04002 TCR kill AML cells presenting the cognate PTT

AGENt 04002 is activated by KG1a cells expressing B7 but not A2

AGENt 04002 specifically kills KG1a cells even at low E:T ratios
AGENt 04002 is extremely sensitive and phosphopeptide-specific

![Graphs showing the sensitivity and specificity of AGENt 04002 to phosphopeptide-specific PEGS, 2018](image_url)
AGENt 04002 Exhibits a high degree of target specificity

AGENt 04002: Alanine replacement scan

AGENt 04002: full AA replacement scan

- = tolerated AA alternative
- = loss of activity substitution
- = no substitution

Data Censored: sample assay shown

PEGS, 2018
On-going studies to characterize AGENt 04002

- Tumor control assessment *in vivo*
- *in silico* fingerprint analysis
  - off-target peptide prediction
- Target identification and validation

✓ More PTT targets added to AgenTus pipeline
NY-ESO-1: a prototypic C-T antigen with broad expression range

- **New York Eso**phageal squamous cell carcinoma-1
- Unknown function of protein
- Healthy tissue: testis
- Tumor: broad expression
  - Multiple myeloma, melanoma, sarcoma, ovarian carcinoma....
- SLLMWITQC: HLA A*0201
- Encoded by *CTAG1b* (gene duplication)
  - Same epitope in *CTAG2*

**CTAG1b mRNA expression**

TCGA (PMID 24084870)

1 RPKM --- 1 copy / cell

Percentages are tumors w/expression over 1 RPKM
de novo TCR discovery campaign: NY-ESO-1\textsubscript{157-165}

TCR α/β gene library source: Umbilical cord blood

AKD-10R Display Line

Natural folding, pairing, and anchoring

Multiple screening methods

Iterations to select hits with desired safety and efficacy

1\textsuperscript{st} round multiple targets

2\textsuperscript{nd} round NY-ESO PE

3\textsuperscript{rd} round NY-ESO APC

4\textsuperscript{th} round NY-ESO PE
**T-Rx™ delivers novel leads for HLA A*02-NY-ESO-1\textsubscript{157-165}**

**de novo TCR display Library:**
Umbilical cord blood-derived
\(~1\times10^9\) diversity

- >300 initial hits: NY-ESO – binding clones
  - 81 activating and signaling clones
- 7 NY-ESO-specific primary lead TCRs selected (activity and specificity)
- 1 TCR selected for lead improvement
- 2 lead improvement tracks
  - Guided selection (“\(\alpha/\beta\) chain shuffling”)
  - CDR3 mutagenesis (\(~1\times10^7\) for alpha and beta chains, each)
  - 20 improved leads selected for in-depth characterization
T-Rx™ delivers potent TCRs for HLA A*02:NY-ESO-1_{157-165}

Peptide sensitivity: T2 Cells

Target killing: tumor cells

AGENt NY-ESO-A

Reference TCR
AgenTus NY-ESO-1 TCRs display exceptional specificity

**Diagram:**

- **LEGEND:**
  - Green = wt AA
  - Red = tolerated alt. AA
  - White = loss of activity
  - Gray = no subst.

**Co-cultivation**

- Pulsed T2 cells
- AKD10R3 NY-ESO TCR

**Amino acid Comparison:**

- **AGENt NY-ESO-X**
- **AGENt NY-ESO-Y**
- **Reference TCR**

**Position:**

- S, L, M, W, I, T, Q, V
AgenTus NY-ESO TCR program

- Tumor control assessment *in vivo*
  - On-going

- Safety screens
  - Off-target peptide prediction/testing
  - Tissue cross-reactivity
  - Allo-reactivity

- Development candidate selection
AgenTus Therapeutics: differentiated cell therapy

**Precision Receptors**
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**Novel Targets**
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**Allogeneic Format**
- Allogeneic approach; “Off-the-shelf”
- Scalable, shorter diagnosis to treatment interval
Adoptive Cell Therapy

launch rapid immune attack against cancer

AgenTus: differentiated cell therapy advancing to unlock value

**Agenus**
- improve body’s existing immune attack on cancer
- **Immunomodulatory Antibodies**
- **Cancer Vaccines**
  - educate the immune system to see cancer

**Synergistic expertise**

**Combination Opportunities:**
- CPMs
- TME modulators
- Vaccines

**AgenTus Therapeutics**
## The Agenus portfolio

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<th>Product</th>
<th>Disease/Target</th>
<th>Partner</th>
<th>Preclinical</th>
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### Notes:
- AGEN1884 and AGEN2034 are being evaluated in 2L cervical cancer and NSCLC.
- AGEN1884 and AGEN2034 are partnered with Recepta for certain South American rights.
Acknowledgements

AgenTus
Bruno Lucidi, CEO

Mark Exley
Cherylene Plewa
Reed Masakayan
Xavier Michelet
Rashmi Choudhary
Mike Lofgren
Nick Kushner
Ben Wolf
Emily Walsh
Bob Stein

Marc van Dijk
Volker Seibert
Jan Bergmann
Eleni Chantzoura
Paul Ibbett
Assunta Diodato
Alvaro Sebastian
Matt Hancock
Alain Pralong

Agenus
Garo Armen, CEO

Cori Gorman
Dennis Underwood
John Castle
Mark Findeis
Paisley Myers
Erin Jeffery
Jennifer Buell
Michael Plater
Julie DeSander
Divya Vasudevan

Collaborators

Vic Engelhard (UVA)
Don Hunt (UVA)
Mark Cobbold (MGH)
Michelle Krogsgaard (NYU)
Chuck Drake (Columbia)