HAAH-Based Cancer Therapeutics, Diagnostics, Radio-immuno-imaging, and Vaccine Therapy

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HAAH – an α-ketoglutarate dependent dioxygenase that hydroxylates aspartate and asparagine residues in EGF-like domains of proteins

In malignant cells, HAAH is a transmembrane protein, found on the surface of > 20 different cancer cells

High HAAH gene expression associated with malignant transformation, invasiveness and motility

US patents: 7 issued, 7 pending

Panacea has exclusive worldwide license to all therapeutic and diagnostic applications
HAAH-Based Integrated Cancer Management

Diagnostics (Companion)

Joint Venture

In House

CLIA and FDA (USA) Cancer Testing Laboratory (International)

Serum Tests

New Subsidiary

Imaging

In House

FB50-NL
Normal

FB50-HCC
Liver Cancer

Gene Expression

HAAH-Based Cancer Management (Personalized)

In House

New Subsidiary

In House

Toxin-Antibody Drug (Cytotoxic Agents)

Vaccine (DNA/Protein)

Naked-Antibody Drug (Cytostatic Agents)

Therapeutics (Immunotherapy)

Tissue Test

Serum Tests

Gene Expression

In House

Joint Venture

FB50-NL
Normal

FB50-HCC
Liver Cancer

HAAH-Based Cancer Management (Personalized)

In House

New Subsidiary

In House

Toxin-Antibody Drug (Cytotoxic Agents)

Vaccine (DNA/Protein)

Naked-Antibody Drug (Cytostatic Agents)

Therapeutics (Immunotherapy)
~23% of liver cancer cases are attributable to chronic infection with hepatitis C virus.

~ 170 million individuals worldwide are chronic carriers of HCV

HAAH is strongly expressed in HCV-associated HCC
Prostate tissue isolated from men with no disease, benign prostatic hyperplasia (BPH) or prostate cancer were stained with antibodies (FB50) against HAAH and counterstained with hematoxylin. Antibody staining was detected using the Vectastain kit (Vector Labs).
HAAH Expression in Lung Cancer

Detection of HAAH in lung tumor section by immunohistochemical staining with monoclonal anti HAAH (FB50)
Immunohistological detection of HAAH using paraformaldehyde fixed tissue specimens treated with monoclonal anti-HAAH (FB50) followed by a biotinylated secondary antibody, peroxidase streptavidin / diamino benzidine (DAB). Note distinct staining of involved ducts (A). Adjacent uninvolved tissue does not stain (B).
Serum HAAH Concentration in Prostate Cancer

Specificity = 93%  Sensitivity = 95%

*Men > 50 years of age, cancer-free
Serum HAAH Concentration in Lung Cancer

Specificity = 91%, Sensitivity 99%

* Includes 50 smokers.
Serum HAAH Concentration in Lung Cancer by Stage

Specificity = 90%, Sensitivity 98%

<table>
<thead>
<tr>
<th>Stage</th>
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<tr>
<td>Smokers</td>
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<tr>
<td>Stage I</td>
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<td>18.4</td>
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<td>Stage II</td>
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<td>Stage III</td>
<td>15</td>
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<td>Stage IV</td>
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Serum HAAH Concentration in Breast Cancer

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<th>Condition</th>
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<tr>
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<td>Known to be in Remission</td>
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Breast Cancer

Specificity* = 91%  
Sensitivity = 94%
Over-expression of HAAH as found in liver cancer tissue results in cell surface localization of HAAH.

Surface localization is confirmed by dual staining with a membrane specific dye (Di-I).
Anti-HAAH antibodies inhibit tumor cell proliferation, demonstrating potential as cytostatic agents.
In vivo Efficacy of Anti-HAAH Monoclonal Antibody

Primary Liver Cancer Xenograft Model

- Three weekly IP injections of anti-HAAH antibody decrease tumor growth in a xenograft model of primary human liver cancer

Untreated

Treated
Collaboration with MIT has produced an engineered, high-affinity, fully-human, anti-HAAH antibody (PAN-622)

- Entirely human sequence
- 10-fold higher binding affinity compared to best murine antibody
- Inhibits tumor cell function \textit{in vitro} and internalizes after binding
In vivo Efficacy of PAN-622

- Tumors established Day -3 with $10^7$ FOCUS cells (hepatic cancer cell line)
- Antibody injected IV 3X/wk, Days 0-25 (last injection marked with arrow)
Twice-weekly IP injection of anti-HAAH antibody prevents growth and metastasis of established human colon cancer in a mouse xenograft model of human colon cancer metastasized to the liver.
PAN-622 – A Promising Cancer Therapeutic

- PAN-622 - “Naked” HAAH monoclonal antibody
- Indication: Hepatocellular Carcinoma (Liver cancer)
- Process development completed and manufacturing underway
- Formal preclinical toxicology and ADME initiated
- IND submission 2009
- Phase I clinical trial to begin 2009
PAN-622 – Toxin Conjugate

- Indication: Cholangiocarcinoma (Bile duct cancer)
- Binding, internalization, and cytotoxicity demonstrated \textit{in vitro}
- Preclinical efficacy study to begin 2009
- Formal preclinical toxicology and ADME to begin 2009
- IND submission 2010
- Phase I clinical trial to begin 2010
Cancer Immunotherapy

Active Immunotherapies (Antigen Presentation)
- DNA-Based Immunotherapy
  - Naked Plasmid Vaccine
- Antigen Presenting Cells (Autologous or Allogeneic)
  - Cancer Cells (Autologous or Allogeneic)
  - Cancer Associated Antigens
  - Dendritic cell Maturation

Passive Immunotherapies (Monoclonal Antibodies: chimeric, humanized, all-human)
- Naked Antibody
- Antibody Toxin Conjugate

Immune Augmentation (General Immune Enhancers)
- Nutriceuticals e.g., Native Lactoferrin
- Pharmaceuticals e.g., rh Lactoferrin
Cancer Vaccine Therapy

- Antigen presenting cells, such as dendritic cells (DCs) are isolated from the patient, treated outside the patient (ex-vivo) with a cancer antigen and re-administered to the patient.
- Treated DCs recruit other components of the immune system to attack cancer cells.
- More than 200 clinical trials have been reported over the past two decades.
- DCs are optimal targets for immunotherapy development.
- DCs are very prominent – they have unique potential to stimulate and subsequently control the immune response to foreign antigens.
- DCs can be manipulated ex-vivo to extend augment their response to not-so-foreign antigens.
Since 1995 more than 300 clinical trials using dendritic cell vaccine therapy against cancer have been conducted involving 3,000 patents.

This approach has been directed against more than two dozen cancer types, including melanoma, prostate cancer, colorectal cancer and multiple myeloma.

The reports have come from 20-25 countries (US and other Pacific rim as well as Europe).

Autologous DC vaccine therapy has shown a remarkable safety profile; **safe with no significant side effects.**
Panacea’s DC Vaccine Therapy Approach

- HAAH as Tumor Specific Antigen:
  - HAAH is specifically expressed on the surface of all malignant cells
  - HAAH is associated with proliferation, motility and invasiveness phenotypes of cancer cells
  - Neutralizing or inhibiting the cell-surface HAAH reverts cancer cells to normal phenotype
  - Anti-HAAH antibodies have proven efficacy in \textit{in vitro} and \textit{in vivo} models
  - Recombinant HAAH is an excellent immunogen

- A novel apheresis apparatus has proven to be much faster, efficient, and cost-effective compared to standard techniques

- \textit{Ex-vivo} approach uses both stimulation by adjuvants and inhibition of tolerance by gene silencing

- DCs target strong cellular and antibody immune responses intended to heighten therapeutic benefit of therapy

- Vaccine therapy approach is strengthened by use of HAAH-based diagnostic (theranostics)
HAAH Antibody-based Radio-immuno-imaging Agent

Targeting Cancer
- PAN 622 – all-human sequence anti-HAAH monoclonal antibody

Radioisotopes
- Technetium 99
- Indium 111
- Gallium 67

Modalities
- X-ray
- PET
- MRI

Approved Products
- Verluma (Nofetumomab)
- OncoScint (Satumomab)
- CEA-Scan (Arcitumomab)
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