Patient-Specific Vaccines (Personalized Immunotherapy) for Non-Hodgkin’s Lymphoma:
Scientific Background & Clinical Trial Results

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Medical Science Liaison
Genitope Corporation

Objectives

• Describe the manufacturing methods for the NHL vaccines being studied in clinical trials
• Review Phase 2 clinical trial results
• Summarize the Phase 3 trials
  – Patients, treatment schema and endpoints

Idiotype Vaccine Production Methods


Clinical Trials

• Stanford/NCI
  – Proof of concept
• BioVest/Accentia BioPharmaceuticals
  – In partnership with NCI
  – BioVaxId™
• Genitope Corporation
  – MyVax® Personalized Immunotherapy
• Favrille
  – FavId®
• Others
  – CellGenix
  – Large Scale Biology
  – Dendritic cell vaccines

Passive Immunotherapy: Monoclonal Antibodies (mAbs)

• mAbs target a particular antigen
  – Proven efficacy
  – May be combined with chemotherapy
• Disadvantages
  – Not tumor-specific; targets are often found on normal cells as well as tumor cells
  – Relies on one arm of the immune system (humoral)
  – No immunological memory
  – Temporary anti-tumor effects

Next Generation: Personalized Active Immunotherapy

• Immunization with tumor-specific proteins to induce host anti-tumor immunity
• Potential advantages
  – Tumor-specific
  – Potentially durable responses
  – Polyclonal humoral and cellular immunity
  – Immunological memory
  – Can be integrated with standard treatment regimens
  – Use does not preclude subsequent therapies
• Potential challenges
  – Requires tumor sample from patient for production
  – Methods for generating anti-tumor immunity still not optimal
Clinical Trials
- Stanford/NCI – Proof of concept
- BioVest/Accentia Biopharmaceuticals – In partnership with NCI – BioVaxId™
- Genitope Corporation – MyVax® Personalized Immunotherapy
- Favrille – FavId®
- Others – CellGenix
- Large Scale Biology – Dendritic cell vaccines

Personalized Immunotherapy
- Clinical evidence that individualized, tumor-specific immunotherapies are feasible
- Levy and colleagues1 validated the idiotype (Id) as a target by using anti-Id mAbs to treat human B-cell lymphoma
- 45 patients were treated with anti-Id antibodies over 12 years
  - 66% overall response rate2
  - 18% complete response rate2
  - Some patients remain tumor free3


Idiotype Vaccine Production Methods

Native Id Proteins
Hybridoma
Mammalian Cells
Insect Cells
Bacteria
Plants

Whole Id
Id Fragments


First Generation: Hybridoma Production Method

Tumor Biopsy + Fusion
Myeloma cell
Tumor Id Protein
Hybridoma
KLH carrier protein
Adjuvant
Immunization
Vaccine Production

Initial Clinical Experience: Proof of Principal
- Used hybridoma or “rescue fusion” method for production of idiotype
- 1988 Stanford1
  - First human idiotype vaccine trial for lymphoma
  - 32 of 41 patients were in first remission
  - 49% of patients demonstrated immune response


Idiotype Vaccination: Impact on Overall Survival*


Graph showing probability of first remission for patients with and without idiotype vaccination.
Clinical Results From the Stanford Study

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>41</td>
<td>4.4</td>
</tr>
<tr>
<td>Id immune response +</td>
<td>20</td>
<td>7.9+</td>
</tr>
<tr>
<td>Id immune response –</td>
<td>21</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*FFP measured from end of chemotherapy

Initial Clinical Experience: Proof of Principal

- Used hybridoma or “rescue fusion” method for production of idiotype
  - 1988 Stanford
    - First human idiotype vaccine trial for lymphoma
    - 32 of 41 patients were in first remission
    - 49% of patients demonstrated immune response
  - 1994 NCI
    - Patients in first remission (CR) showed reduction in PCR-detectable (bcl-2 positive) tumor cells in peripheral blood

Early Experience With Active Idiotype Vaccination

<table>
<thead>
<tr>
<th>Response</th>
<th>Hsu et al (N=41)</th>
<th>Bendandi et al (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral response, n (%)</td>
<td>13 (32%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Cellular response, n (%)</td>
<td>3 (7%)</td>
<td>19 (95%)</td>
</tr>
</tbody>
</table>

Clinical outcome

- 4.4 years (all patients)
- 7.9 years (IR+)
- 1.3 years (IR-)

Complete response rate: 18 (90%)

Clinical Trials

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- Favrille
  - FavId®
- Others
  - CellGenix
  - Large Scale Biology
  - Dendritic cell vaccines

BioVest's 6-step Hybridoma Production Method

1. Requires 2 cm of fresh tissue placed into tissue culture medium
2. Single cell suspensions are made and fused with the heterohybridoma cell line
3. Cell lines secreting the Id are screened using PCR and gene sequencing techniques
4. Id-secreting cell lines are grown in bioreactors
   - Cultured in ACUSYS® hollow fiber bioreactor systems
   - Well-established technology, used routinely for mass production of diagnostic and therapeutic proteins
5. Idiotype protein is purified using affinity chromatography techniques and the protein is then conjugated to KLH
6. Dispensed to physician for immunization of patient; given with GM-CSF

Retrieved on October 31, 2005 from
http://www.accentia.net/?page=nhl_pi_manufacture&sub_menu=nhl&sub_sub_menu=physician_info

NCI Phase 3 Vaccine Trial

- Accrual: 5 years
- Follow-up: 3 years
- Id-KLH/GM-CSF
- KLH/GM-CSF
- n = 250
- Assign CR (60%)
- 2:1 Randomization
- n = 123

Study Duration
- Months 0 6 14 20
Biovest/Accentia Phase 3 Trial

- 22 clinical trial sites across the US
  - listed on the Accentia BioPharmaceuticals website at:
    http://www.accentia.net/?page=clinical_trials
- 2 additional sites planned
  - San Francisco
  - Texas

Clinical Trials

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Idiotype Vaccine Production Methods

- Native Id Proteins
  - Hybridoma
  - Mammalian Cells
  - Bacteria
  - Plants
  - Whole Id
  - Id Fragments


MyVax® Personalized Immunotherapy Production & Immunization Process

- Acquire tumor sample
- Generate mammalian cell line for production
- Produce and purify rId protein
- Formulate immunotherapy (rId-KLH)

Figure provided by Genitope Corporation

Molecular Biology

- Requires little tumor tissue
  - >0.1 gram, or ~0.3 cubic cm of tissue, but < 1.0 gram
- Does not require viable cells
- Allows use of either fresh or frozen tissue
- Different types of tissue are acceptable
  - Excisional lymph node (LN), FNA, core needle biopsy, peripheral blood, bone marrow or extranodal tissue
  - Tissue must pass "adequacy assay" confirming tumor cells express the idiotype properly (~90% are adequate*)
  - High success rate: >99% for those tumors deemed "adequate"
  - Scaleable and reproducible
  - Hundreds of personalized immunotherapies have been produced for use in clinical trials

* Data on file, Genitope Corporation
Genitope's Specimen Experience*

<table>
<thead>
<tr>
<th>Specimen Source</th>
<th>Additional biopsy required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excisional Lymph Node: Snap Frozen</td>
<td>5%</td>
</tr>
<tr>
<td>Excisional Lymph Node: in OCT</td>
<td>6%</td>
</tr>
<tr>
<td>Excisional Lymph Node: Fresh</td>
<td>7%</td>
</tr>
<tr>
<td>Fine Needle Aspirates (FNA): Frozen</td>
<td>9%</td>
</tr>
<tr>
<td>Lymph Node Core Needle: Frozen</td>
<td>13%</td>
</tr>
<tr>
<td>Lymph Node Core Needle: Fresh</td>
<td>29%</td>
</tr>
<tr>
<td>Bone Marrow Core or Aspirate</td>
<td>30%</td>
</tr>
<tr>
<td>Peripheral Blood</td>
<td>71%</td>
</tr>
<tr>
<td>Inflammatory Tissue</td>
<td>10%</td>
</tr>
</tbody>
</table>

* Data on file, Genitope Corporation

Cell Culture

Image Not Available

Production

Image Not Available

MyVax® Personalized Immunotherapy


t/og/sediment

Recombinant Id Protein

Keyhole Limpet Hemocyanin (KLH)

(adjuvant)

+  

GM-CSF (sargramostim) (adjuvant)

Images provided by Genitope Corporation

Trials in Follicular Lymphoma Using MyVax® Personalized Immunotherapy

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Disease</th>
<th>Induction Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitope 1991</td>
<td>Follicular Lymphoma</td>
<td>Chemotherapy (CVP or CHOP)</td>
</tr>
<tr>
<td>Genitope 2000-04</td>
<td>Follicular Lymphoma (&quot;watch and wait&quot;)</td>
<td>No chemotherapy</td>
</tr>
<tr>
<td>Genitope 2000-07</td>
<td>Follicular Lymphoma (pivotal Phase 2 trial)</td>
<td>Chemotherapy (CVP or CHOP)</td>
</tr>
<tr>
<td>Genitope 2002-09</td>
<td>Follicular Lymphoma (pivotal Phase 2 trial)</td>
<td>Failed CVP chemotherapy, rituximab salvage treatment</td>
</tr>
<tr>
<td>Genitope 2003-03</td>
<td>Follicular Lymphoma (pivotal Phase 3 trial)</td>
<td>Chemotherapy (CVP)</td>
</tr>
</tbody>
</table>
Genitope 9901: Indolent B-Cell Lymphoma

Evaluate the ability of MyVax® Personalized Immunotherapy to stimulate a specific anti-idiotype immune response in previously untreated indolent B-cell lymphoma.

Genitope 9901: Summary of Adverse Events

Reactions were mild to moderate in severity and transient in duration.

Injection-site reactions:
- Erythema 100%
- Pain 89%
- Induration 86%
- Pruritis 64%
- Bruising 64%
- Inflammation 32%

Genitope 9901: Immunizations

- Outpatient immunizations
- Treatment schedule
  - Day 1: Id-KLH and GM-CSF
  - Day 2: GM-CSF (self-injection)
- Subcutaneous injections
- Two separate injection sites
  - Bilateral anterior thighs
  - Recruits dendritic cells to two areas
  - Decreases local toxicity

Genitope 9901: Conclusions

- 21 evaluable patients received chemotherapy to best clinical response
- Favorable safety profile
  - All patients experienced mild-to-moderate injection-site reactions
  - Most AEs reported were mild-to-moderate and transient in duration
- Both CR and PR patients demonstrated anti-Id immune responses
- Immune response rates similar to those seen with “rescue fusion” hybridoma production method
- Molecular rescue is a reliable method for producing idiotype protein

Genitope 2000-04: “Watch and Wait”

Evaluate the ability of MyVax® Personalized Immunotherapy to stimulate a specific anti-idiotype immune response in patients with follicular lymphoma who have not received chemotherapy.
Genitope 2000-04: Conclusions

- Evaluable patients: 15
- Immune responses seen in 11 patients
  - Humoral responses: 9
  - Cellular responses: 2
- Demonstrated immune responses could be elicited in untreated patients
- Increasing the number of immunizations improved overall immune response
- No dose-limiting adverse effects
- Results suggest further trials are warranted in this population


Genitope 2000-07: Abbreviated Course of GM-CSF

Evaluate whether an abbreviated course of GM-CSF as an adjuvant to MyVax® Personalized Immunotherapy is sufficient to elicit a specific anti-idiotypic immune response.


Genitope 2000-03: Pivotal Phase 3 Trial

- Trial opened in December 2000
- Trial was closed to registration in May 2004
- Last patient was randomized for immunization in June 2005
- First interim analysis mid-2005
  - DSMB recommended the trial be continued
- Second interim analysis planned for mid-2006
- If necessary, final analysis will occur in mid-2007

Genitope 2002-09: Rituximab Rollover Trial

- Enrolment in 2003-03 Phase 3 Study + Biopsy Obtained for Manufacture of MyVax® Personalized Immunotherapy
- Patients failing 6 cycles of CVP chemotherapy who
- Rest Period 29 Weeks
- Arm A
- Day 1: 4 X 1400 mg
- Day 2: 2 X 1400 mg
- Day 3: 1000 mg
- Days 1-4: 280 mg
- Day 5: 1000 mg
- Day 6: 280 mg
- Day 7: 1000 mg
- Rituximab 2 Doses

- Arm B
- Rest Period 13 Weeks
- Rituximab 2 Doses
- Rest Period 29 Weeks
- Day 1: 4 X 1400 mg
- Day 2: 2 X 1400 mg
- Day 3: 1000 mg
- Days 1-4: 280 mg
- Day 5: 1000 mg
- Day 6: 280 mg
- Day 7: 1000 mg
- Schema provided by Genitope Corporation

Schema provided by Genitope Corporation
Genitope Phase 2 Trial Roll-over (Id-KLH after Rituximab)

• Allows patients to receive their MyVax® Personalized Immunotherapy if they fail to qualify for randomization in the Phase 3 pivotal trial

• Evaluate overall effect of rest period on the immune response rate
  – 26 weeks compared to 13 weeks

Results of Clinical Trials

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  – Proof of concept

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• FavId
  – FavId®

• Others
  – CellGenix
  – Large Scale Biology
  – Dendritic cell vaccines

Idiotype Vaccine Production Methods

Native Id Proteins

Hybridoma

Mammalian Cells

Insect Cells

Bacteria

Plants

Recombinant Id Proteins

Whole Id

Id Fragments


FavId® Production Process

KLH conjugation

Id Protein production

Insect cell culture

8 weeks

Cloning of Id gene

GM-CSF

Immune

Biopsy

Insect cell culture

KLH conjugation

8 weeks

Id Protein production


FavId® Production Process

KLH conjugation

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Cloning of Id gene

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Immune

Biopsy

Insect cell culture

KLH conjugation

8 weeks

Id Protein production


Phase 2 Trials with FavId®

• FavId® as Single Agent

• FavId® following Rituximab

Phase 2 FavId® as Single Agent: Treatment Schema

Biopsy

FavId® production

FavId® + GM-CSF

CT Scans

Months: 0 3 6 9 12 15 18 21 24

Induction

Boost

Provided by Favrille, Inc, San Diego, CA.
**Phase 2 FavId® as Single Agent**

- 29 patients with relapsed FL were immunized
- 6 monthly immunizations; if stable disease, allowed to continue vaccine every 2 months for 1 year, then every 3 months until disease progression
- Mean number of prior treatments = 2.5
  - Chemo, rituximab or combination (chemo + rituximab or RIT)
- Overall response rate = 15%
  - 27 patients evaluable for efficacy (1 CR, 3 PR)
  - 4 patients with minor responses (at least 25% tumor shrinkage)
- Median time to progression (TTP) = 12.3 months
- Can induce T-cell anti-Id immune responses


**Phase 2 FavId® Following Rituximab: Treatment Schema**

**Phase 2 FavId® Following Rituximab**

- 103 patients enrolled
  - 11 PD post Rituximab
  - 92 evaluable patients (received ≥ 1 dose of FavId®)
    - 50 Relapsed/Refractory
    - 38 Treatment naïve
- Received 4 weekly doses of rituximab to response
- Immunizations x 6 monthly followed by maintenance injections every 2 months for 1 year, then every 3 months until progression
- 32 of 45 (72%) relapsed/refractory patients were progression-free at a median follow-up of 12 months
  - Compared to 40% of historical control patients treated with rituximab alone (Witzig, 2002, JCO, 20: 2453)
- 35 of 43 (82%) previously untreated patients were progression-free at median follow-up of 9 months
- Anti-KLH antibody responses were generally not seen until B-cell recovery


**Favrille Phase 2 Conclusions**

- Rapid, efficient manufacturing technology
  - Uses recombinant baculovirus
  - Production time of 8-12 weeks
- FavId® is safe, immunogenic and clinically active in follicular lymphoma


**Favrille Phase 3 Trial: Design**

**Favrille Phase 3 Trial: Key Points**

- Double blind, randomized (1:1), placebo controlled
- N=342
- Rituximab followed by Blinded Injection
  - FavId® or Placebo along with GM-CSF
- Treatment naïve or relapsed/refractory follicular NHL
- Primary endpoint TTP
Favrille Phase 3 Trial: Inclusion

- Follicular NHL Grades 1-3 (WHO criteria)
- Performance Status (ECOG) of 0 or 1
- ≤2 prior therapies for NHL
- Candidate for treatment with rituximab:
  - Treatment naïve
  - Refractory to prior chemotherapy
  - Relapsed after prior 6 month response to rituximab
- Absolute granulocyte count ≥1,500/mm³
- Platelets ≥75,000/mm³
- Hgb ≥ 10 gm/dL

Favrille Phase 3 Trial: Exclusion

- ≤ 2 year response to chemo + rituximab combination
- Fludarabine within 9 months
- Prior Zevalin® or Bexxar®
- Prior idiotype vaccine or KLH
- Allergy to GM-CSF
- Concurrent immunosuppressive therapy

Favrille Phase 3 Trial: Dose/Schedule

<table>
<thead>
<tr>
<th>Drug</th>
<th>Supplied by</th>
<th>Dose</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Site</td>
<td>375 mg/m²</td>
<td>Q wk x 4</td>
</tr>
<tr>
<td>FavId® or Placebo</td>
<td>Favrille</td>
<td>1 mL of Blinded Injection Sub-Q</td>
<td>Q mo x 6, then Q2 mo x 6, then Q3 mo until PD</td>
</tr>
<tr>
<td>GM-CSF (Leukine®)</td>
<td>Favrille</td>
<td>250 mcg</td>
<td>D 1-4 (beginning day 1 of blinded injection)</td>
</tr>
</tbody>
</table>

Favrille Phase 2 Companion Trial

- Provide FavId® to patients who did not receive their vaccine during participation in the Phase 3 trial
- Patients will have experienced either:
  - PD after Rituximab (prior to randomization) or
  - PD after Placebo/GM-CSF
- Salvage therapy administered at discretion of physician
- Salvage therapy may not consist of:
  - Allogeneic transplantation
  - Purine analogues (i.e., fludarabine, cladribine)
  - Other investigational agents
- FavId® must start within 4 months of completing salvage therapy
Summarize: Ongoing Phase 3 Clinical Trials of Patient-Specific Vaccines in NHL

- Accentia BioPharmaceuticals (open to accrual)
  - BioVaxId™ or KLH if CR after PACE chemotherapy
- Favrille (open to accrual; anticipate closing trial to accrual at the end of 2005)
  - FavId® or placebo after rituximab
- Genitope Corporation (closed to accrual; awaiting results of trial)
  - MyVax® Personalized Immunotherapy or KLH after response to CVP chemotherapy

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Idiotype Vaccine Production Methods


CellGenix Technologie Transfer GmbH

- IdioVax®
  - Recombinant human Fab-fragments
  - “Therapy of patients suffering from B-cell NHL”
- Clinical Phase II Trials
  - Performed in cooperation with the University Hospital and the Center for Clinical Research in Freiburg, Germany
  - Uses cell-targeting molecules that allow a more selective, non-toxic tumor therapy
- November 2004 - orphan drug status in EU
  - Phase 3 trial being designed with EUMA


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- Others
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  - Dendritic cell vaccines

Idiotype Vaccine Production Methods

Large Scale Biology Corporation

- "LSBC has created a platform to make customized patient-specific therapeutic vaccines…"
  - Manufacturing process enables the generation of vaccines in 6-10 weeks, compared to the several months required to produce similar products.
- "LSBC’s vaccines offer potentially curative therapy, and have been shown to be safe and immunogenic in our successfully completed early-stage clinical trials."
- "LSBC is poised to enter further clinical development of its NHL vaccines as well as explore partnering opportunities for accelerated commercialization of this product."

Retrieved on October 21, 2005 from http://www.lsbc.com/thera.html#vaccines

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Antigen-Pulsed Dendritic Cell Vaccine Production Method

2001 Stanford: Dendritic Cell Vaccine

- 35 follicular NHL patients
- Antigen-pulsed dendritic cells (DCs) were given IV monthly x 3, followed by a 4th infusion 2-6 months later
- Each IV infusion was followed 2 weeks later by SQ injections of Id-KLH without DCs

2001 Stanford: Dendritic Cell Vaccine (cont.)

- 15 of 23 (65%) who completed the vaccination schedule mounted T-cell or humoral anti-Id responses
- 16 of 23 patients (70%) remain without tumor progression at a median of 43 months after chemotherapy
- 18 patients had residual tumor at the time of vaccination
  - 4 of 18 (22%) had tumor regression
- 6 patients with disease progression after primary DC vaccination received booster injections of Id-KLH protein
  - 3 of 6 patients had tumor regression (2 CRs and 1 PR)
- Conclusions:
  - Id-pulsed DC vaccination can induce T-cell and humoral anti-Id immune responses and durable tumor regression
  - Subsequent boosting with Id-KLH can lead to tumor regression despite apparent resistance to the primary DC vaccine


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Summarize: Patient-Specific Vaccines for Follicular NHL

- Idiotype (Id) is a tumor-specific target
- Tumor tissue is required to manufacture
  - Production method guides acquisition and handling
  - Tumor tissue must be sent to manufacturing facility
- Standard cytoreductive therapy is often administered
  - Chemotherapy
  - Monoclonal antibody therapy
  - Combination therapy (chemo + mAb)
- Easy to administer, generally well tolerated
- Favorable safety profile, MTD does not appear to apply
- Potential advantages of active immunotherapy
- Therapeutic personalized immunotherapies are currently under investigation
  - Elicit an active immune response
  - Have been associated with long-term remissions

Conclusions from Completed Phase 2 Id-KLH Vaccine Trials in NHL

- Promising evidence of anti-tumor activity
  - Multiple arms of the immune system recruited
  - Apparent long-lasting effects
- Recombinant Id proteins can routinely be produced using different production methods
- Immunizations are well tolerated
- Phase 3 trial results are needed to prove benefit

Summarize: Ongoing Phase 3 Clinical Trials of Patient-Specific Vaccines in NHL

- Accentia BioPharmaceuticals (open to accrual)
  - BioVaxId™ after PACE chemotherapy with CR
- Favrille (open to accrual; anticipate closing trial to accrual at the end of 2005)
  - FavId® after response to Rituximab
- Genitope Corporation (closed to accrual; awaiting results of trial)
  - MyVax® Personalized Immunotherapy after response to CVP chemotherapy

Questions

- Optimal immunization schedule
  - Frequency
  - Duration
  - Route
- Mechanism(s) of action
  - Optimize or maximize immune responses
    - Minimal disease
    - Effect of chemotherapy on regulatory T cells
    - Adjuvants

Thank you!