Nucleic Acid Based Vaccines:
Case Study: GRNVAC1 hTERT-LAMP mRNA Transfected Autologous DC

The iSBTC Oncology Biologics Development Primer
Gaithersburg, MD, February 29, 2008
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GRNVAC1 and GRNVAC2

- Rationale for telomerase as target for immunotherapy
- Rationale for hTERT-LAMP mRNA transfected DCs as immunotherapy
- Discussion of AML Phase II study:
  - Manufacturing and regulatory implementation
  - Design, objectives and clinical execution
- Practical lessons of implementing an mRNA transfected autologous cell POC study
  - Preview: Manufactured product → Patient!
- What comes next?
  - GRNVAC2: an allogeneic, bulk manufactured hESC-DC follow-on product for broader development
Structure and Function: Telomeres and Telomerase

**TELOMERES**
- TTAGGGG repeats at ends of all chromosomes
- Shorten with cell division
- Accelerated loss under stress

**TELOMERASE**
- hTERT = catalytic protein subunit
- hTR: Template RNA
- Synthesizes telomeric DNA
- May have other roles (eg, “capping,” stress resistance)
Hallmarks of Cancer
(Hannahan and Weinberg, Cell, 2002)

Cellular immortalization by telomerase is a requisite step for carcinogenesis.
### hTERT as a TAA: Tumor vs. Normal Cytotoxicity

<table>
<thead>
<tr>
<th>hTERT/ Cancer Cells</th>
<th>hTERT/ Normal Cells</th>
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<tbody>
<tr>
<td>• Overexpressed</td>
<td>• Low expression most normal cells</td>
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<td></td>
<td>• Transient expression activated or stem/progenitor cells</td>
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<tr>
<td>• Sensitive to CTLs with specificity for TERT</td>
<td>• Low or no sensitivity to hTERT CTLs:</td>
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<tr>
<td></td>
<td>• DCs, keratinocytes, CD34⁺; Vonderheide et al, 1999</td>
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<td>• CFUs/LTC, in vitro; Danet-Desnoyers et al, 2005</td>
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<td>• CFUs, LTC-ICs pre-/post vaccination; Brunsvig et al, 06</td>
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<td></td>
<td>• Clinical studies without normal stem cell effects</td>
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</tbody>
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- Vonderheide et al, 1999, 2001, etc.
- Su et al, 2002
- Minev et al, 2000
- Nair et al, 2000, 2005
hTERT-LAMP mRNA DCs: Discovery & Early Development

- TERT mRNA transfected DCs in murine models: induced CTLs and produced anti-tumor immunity in mice; Nair et al, Nature, 2000
- Transfection with hTERT-LAMP Chimeric RNA enhances CD4+ response; Nair et al, Cancer Res, 2002
- Prostate Ca Phase I Trials at Duke:
  - hTERT vs hTERT-LAMP
  - 3 vs. 6 injections: Su et al, JI, 2005
  - Prime boost regimens: Unpublished Study Reports
Duke Prostate Ca Phase 1 Trial


- 23 Subjects Vaccinated
- Generally Well Tolerated
- Marked Anti-Telomerase Immune Response After Six Weekly Vaccinations
- hTERT-LAMP Induces CD-4⁺ As Well As CD-8⁺ Anti-Telomerase T Cells
- Impact On Circulating Tumor Cells And PSA Doubling Times

Telomerase Specific Immune Response

Clearance of Circulating Tumor Cells (9/10 Patients)

Prolongation of PSA Doubling Time
GRNVAC1
Boost Optimization (Subsequent Studies)

Subjects Boosted 6 Times Biweekly Up to 45 Weeks After Prime

-10  -5   0   5   10  15  20  25  30  35  40  45  50  55  60  65  70  75  80  85  90  95  100  105

Serum PSA ng/ml

-10  -5   0   5   10  15  20  25  30  35  40  45  50  55  60  65  70  75  80  85  90  95  100  105

Study Weeks
GRNVAC Program: Geron Development

- Geron, in collaboration with T. Cech, clones hTERT: 1997
- Geron licenses Duke method of ex vivo DC production and RNA transfection from Argos Therapeutics, Inc: 2004
- Tech transfer: Duke to Geron Product Development: 2004-2005
- Tech transfer: Geron to Lonza cGMP manufacturing: 2005-2006
- RAC and IND filings/approvals for Geron studies: 2006
- Site qualification, training, approvals, contracting: 2007
- First patients accrued: AML remission Phase II POC: 2007
- Future transition to second generation product: hES-DC (GRNVAC2)
GRNVAC1 hTERT mRNA Transfected DC Production

1. Leukapheresis harvest
2. Ficoll centrifugation:
   - Monocyte enriched PBMCs
3. hTERT-LAMP mRNA Transfection (Electroporation)
4. Cryopreserved DC Vaccine

- Plasmid
- mRNA
- Mature DCs for harvest
- Immature DCs
- Incubation with cytokines
- DC maturation: Further incubation; additional cytokines

(Phenotyping, testing; disposition
1 x 10^7 viable cells/ dose post-thaw)
GRNVAC1 Manufacturing Product Flow

Clinical Trial Site:
- Leukapheresis

CMO (Lonza):
- GRNVAC1 Manufacturing
  - Leukapheresis Product
  - GRNVAC1 Product
- Cryo-Storage
  - Paperwork

Gerent:
- QA Review of Batch Production Records
  - Disposition
- GRNVAC1 Product
- Patient

**Path of Product**
Rationale for AML Trial

- High telomerase expression in high risk varieties with unmet medical need
- Remission as MRD setting with potential for monitoring
- Timing: CR → Consolidation → Off Chemo/Observe
- Intersperse leukapheresis with consolidation, vaccinate after consolidation completed
- Immune response important for AML (eg, graft vs leukemia effect)
Phase II Trial in AML Patients in CR

• To test ability to generate anti-hTERT immune response among intermediate-to-high risk AML patients
• Eligibility:
  – Intermediate/high risk cytogenetics or other high risk molecular
  – Within 6 months of CR1 or in CR2
  – Completed at least one cycle of consolidation
  – May complete 1 to 3 additional cycles of consolidation after leukapheresis and before start of vaccination
  – In CR or early relapse at time of start of vaccination
• Primary Objective:
  – Feasibility and Safety
• Secondary objectives:
  – hTERT ELISPOT response in majority of patients
  – PFS
  – Candidate biomarker for MRD response: WT1 PCR
  – Observe responses to “early relapse” (detected in between leukapheresis and vaccination)
Phase II AML in AML Patients in CR

- Enroll up to 30 patients; assure ≥ 20 evaluable (> 2 vaccinations)
- Vaccination Schedule:
  - 6 weekly intra-dermal injections
  - 1 month rest
  - 6 boost injections every other week
  - Monthly extended post-boost vaccination (dependent upon product yield and continued CR)
- Investigators/Sites:
  - Dr. John DiPersio, Washington University
  - Dr. William Blum, Ohio State
  - Dr. Robert Collins, UTSW
  - Dr. Hanna Khoury, Emory University
- Status:
  - Successful harvest, manufacturing, vaccination of initial patients
GRNVAC1 Case Study “Talking Points”

Challenges, Issues, Lessons Learned:
Strategic, Regulatory, Operational
Practical Implications of Manufacturing & Regulatory Aspects of mRNA Transfected Autologous Product

- RAC Review; RNA →
- cGMP manufacturing →
- Cryopreserved product, excipients →
- Process time; lot release testing including 28 day mycoplasma →
- Clinical populations differ (host factors and response) →
- POC Phase II design for GRNVAC1 (patient specific) →
- IBC Approval at sites
- Capacity limited; scheduling; identifiers
- Yields vary
- Dose preparation steps at sites required: training and maintaining trained status
- Time patients stable and remain on study from enrollment to vaccination
- Input material a source of variability
- Immunomonitoring, including test qualification, sample collection and prep
- Design, population, endpoints may differ for future product (GRNVAC2)
**Autologous product → complex site implementation**

- **Key Lesson**: Challenge goes beyond direct production steps: Think through all the steps from the site’s point of view!

- Multiple facilities and staff at each site must be “on board:”
  - Leukapheresis
  - PBMC preparation for immunologic testing
  - Cryo-storage
  - Thawing, washing cells for delivery
  - CFR compliant sterility testing

- “On board” includes:
  - Identification, qualification, documentation
  - Training in standardized protocol specific procedures
  - Staff changes during course of study; periodic renewal
  - Scheduling and coordination of multiple components at site and with sponsored centralized manufacturing facility

- No “magic bullet;” just great sites, good preparation, communication and team-work!
Recognitions

Lonza (Walkersville) Manufacturing, Quality and Project Management Teams

Investigators (and their coordinators):
- John DiPersio, Washington University
- William Blum, Ohio State
- Robert Collins, UTSW
- Hanna Khoury, Emory University

Geron Clinical
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- Neeru Batra

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