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

The iSBTC Oncology Biologics Development Primer
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Laurence Elias, M.D.
Executive Director, Oncology Clinical Development
Geron Corporation, Menlo Park, CA

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Outline

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

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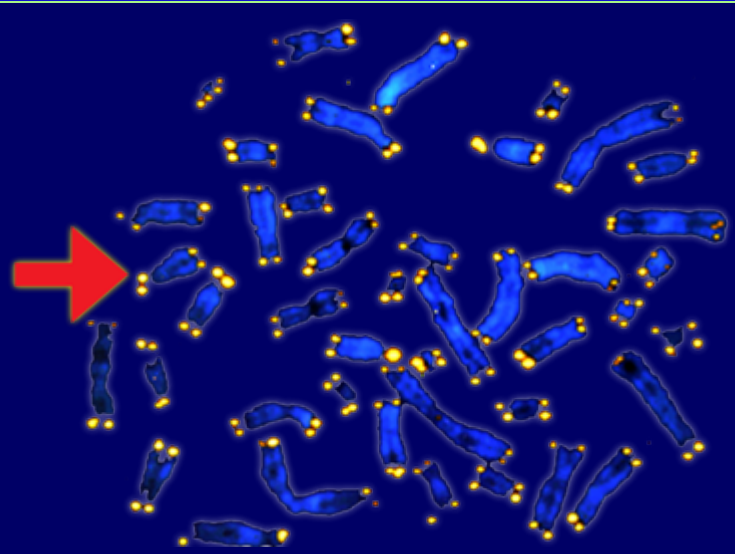
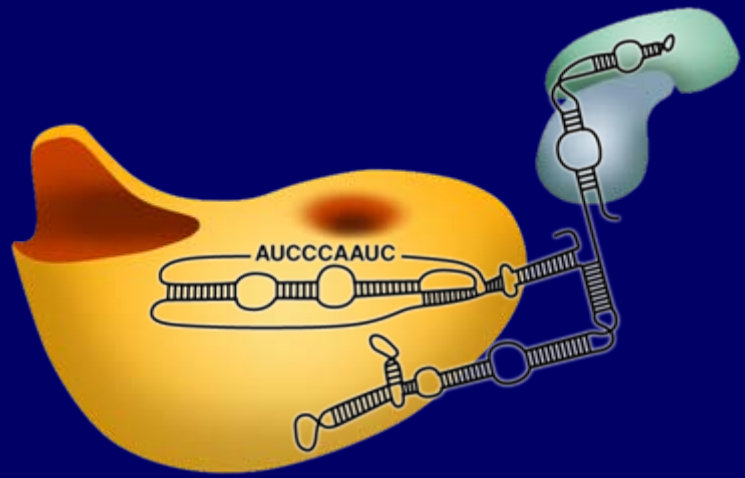
Structure and Function: Telomeres and Telomerase



TELOMERES

- TTAGGG 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)

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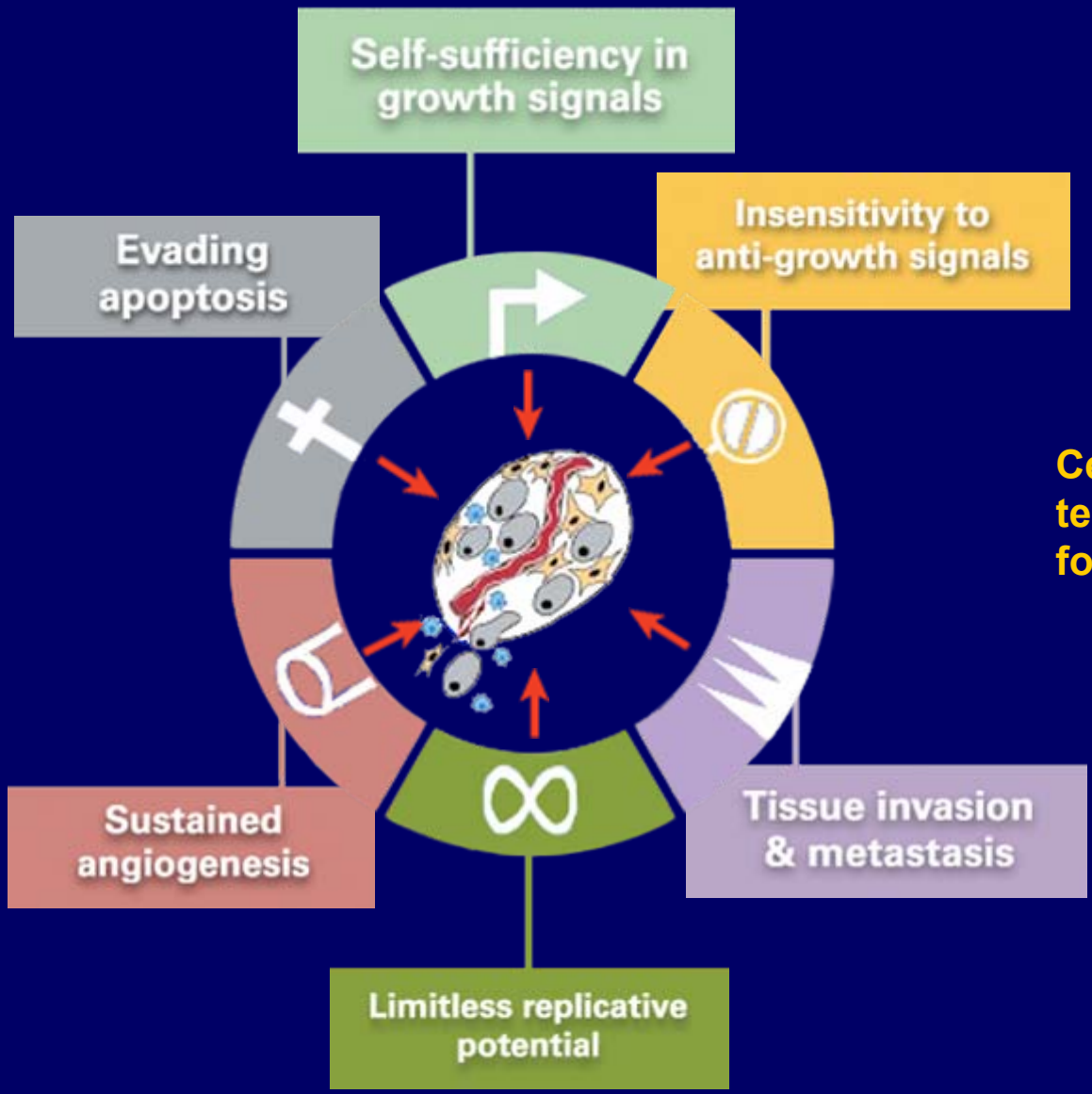
Hallmarks of Cancer

(Hannahan and Weinberg, Cell, 2002)



Cellular immortalization by telomerase is a requisite step for carcinogenesis

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hTERT as a TAA: Tumor vs. Normal Cytotoxicity

hTERT/ Cancer Cells

- Overexpressed
- Sensitive to CTLs with specificity for TERT
  - Vonderheide et al, 1999, 2001, etc.
  - Su et al, 2002
  - Minev et al, 2000
  - Nair et al, 2000, 2005

hTERT/ Normal Cells

- Low expression most normal cells
- Transient expression activated or stem/progenitor cells
- Low or no sensitivity to hTERT CTLs:
  - DCs, keratinocytes, $CD34^{+}$; Vonderheide et al, 1999
  - CFUs/LTC, in vitro; Danet-Desnoyers et al, 2005
  - CFUs, LTC-ICs pre-/post vaccination; Brunsvig et al,06
- Clinical studies without normal stem cell effects

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hTERT-LAMP mRNA DCs: Discovery & Early Development

- mRNA Pulsing of DCs yields superior antigen presentation and anti-tumor immunity; Nair, Gilboa et al, J. Exp. Med., Int. J Cancer, Nature Biotechnology, 1996 to 1999
- 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

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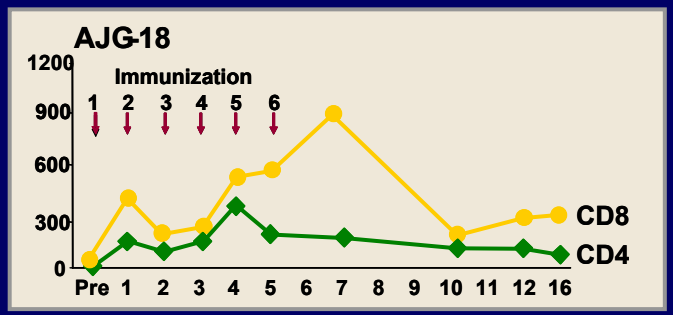
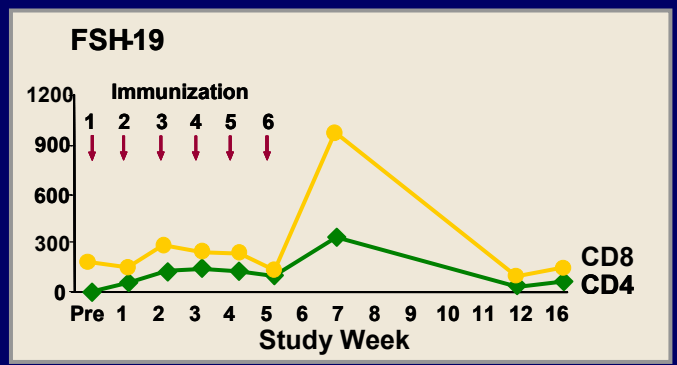
Duke Prostate Ca Phase 1 Trial

J. Immunol. 174: 3798 (2005)

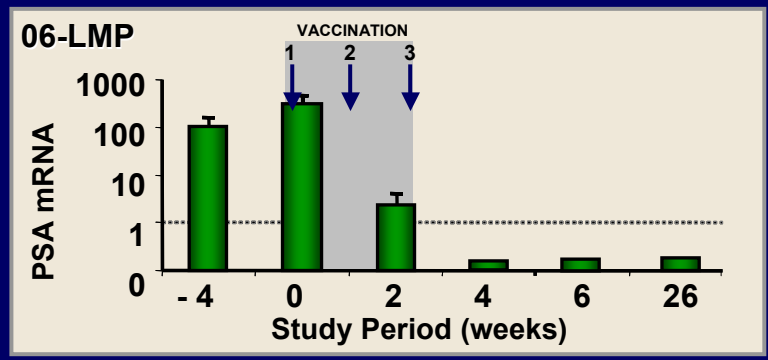
- 23 Subjects Vaccinated
- Generally Well Tolerated
- Marked Anti-Telomerase Immune Response After Six Weekly Vaccinations
- hTERT-LAMP Induces CD-4$^+$ As Well As CD-8$^+$ Anti-Telomerase T Cells
- Impact On Circulating Tumor Cells And PSA Doubling Times

Telomerase Specific Immune Response

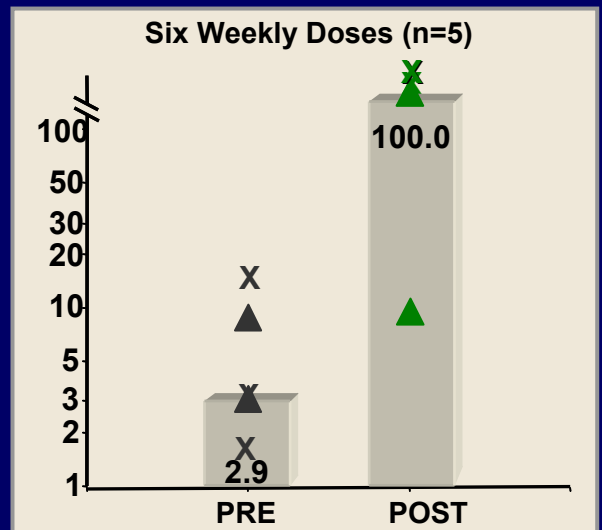




Clearance of Circulating Tumor Cells (9/10 Patients)

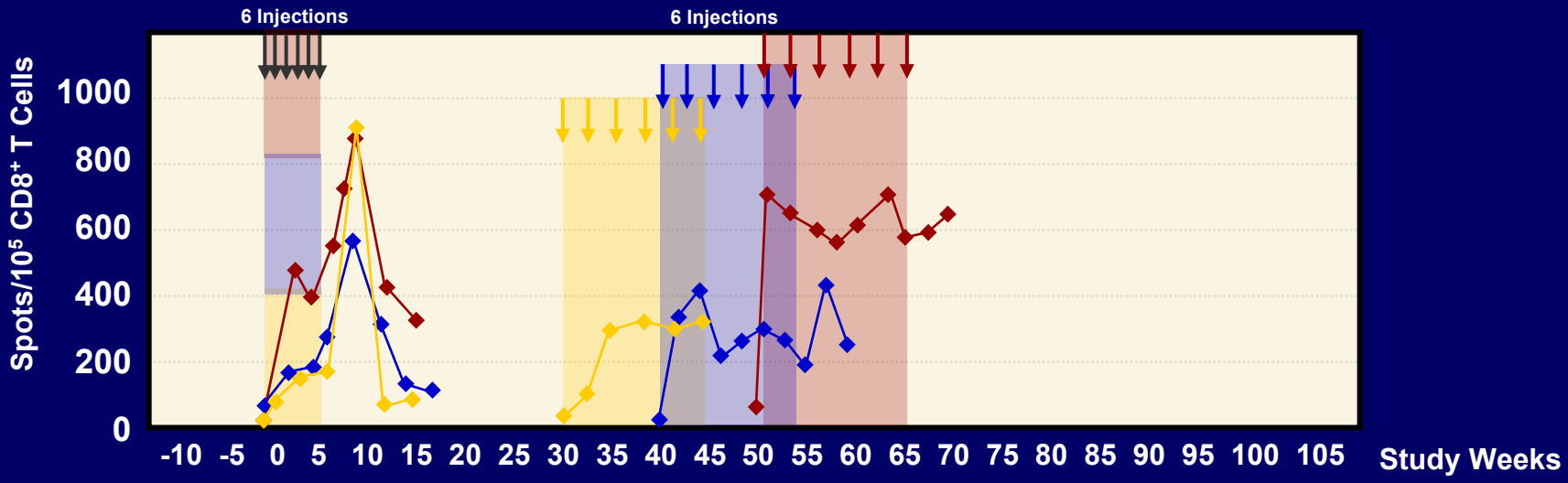


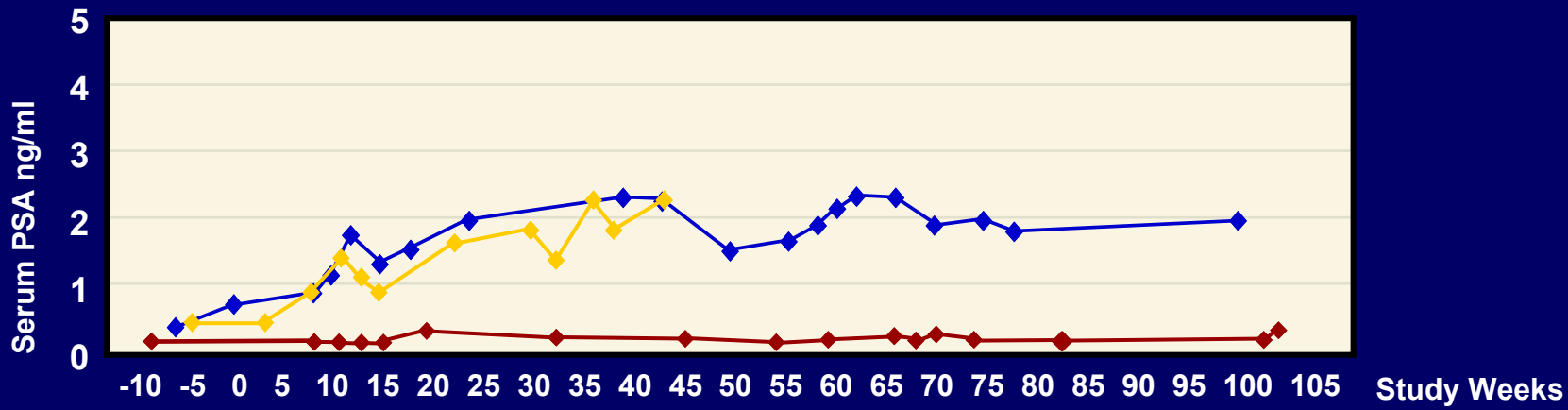
Prolongation of PSA Doubling Time



GRNVAC1
Boost Optimization (Subsequent Studies)

Subjects Boosted 6 Times Biweekly Up to 45 Weeks After Prime





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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

Leukapheresis harvest

Ficoll centrifugation

Monocyte enriched PBMCs

Incubation with cytokines

Immature DCs

hTERT-LAMP mRNA Transfection (Electroporation)

Plasmid

mRNA

DC maturation: Further incubation; additional cytokines

Mature DCs for harvest

Cryopreserved DC Vaccine

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

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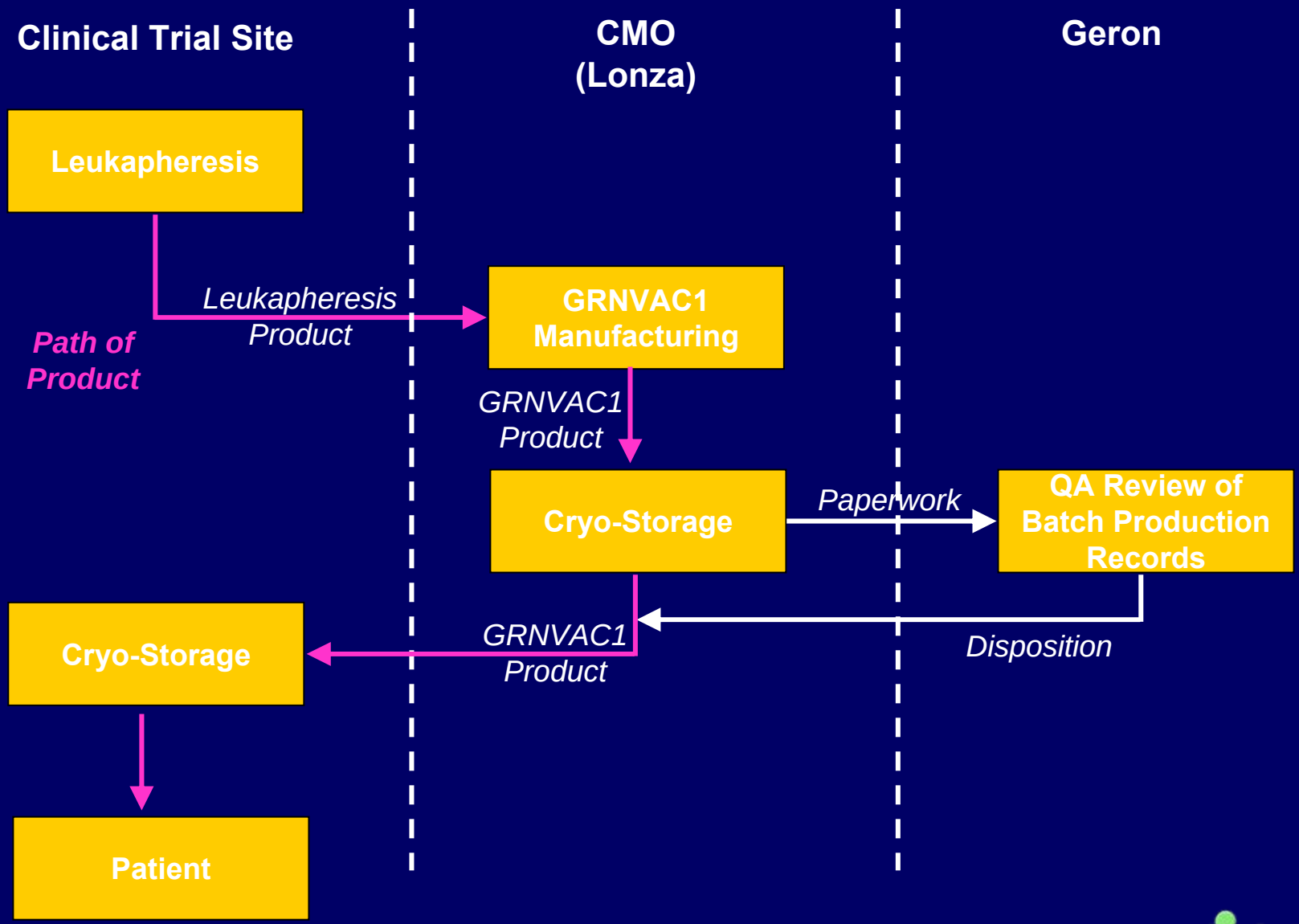
GRNVAC1 Manufacturing Product Flow



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

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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)

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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!

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