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Scientifically driven "proof of principle" trials: Current and future value to drug development

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Disclosure Information

Elizabeth M. Jaffee, M.D.

I have the following financial relationships to disclose

I will be discussing the investigational use of:

- GVAX
- Listeria Monocytogenes vaccines

Both licensed to Aduro Biotech with potential to receive royalties

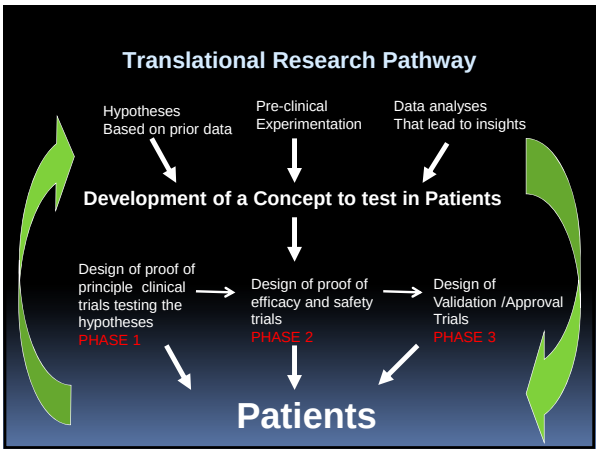
What is involved in translating a new lab concept into "first in man" clinical trials?

It took about 150 years to go from this first immunization to eradication of small pox worldwide!

THE SCIENCE AND TECHNOLOGY NEEDED TO CATCH UP TO THE OBSERVATION!

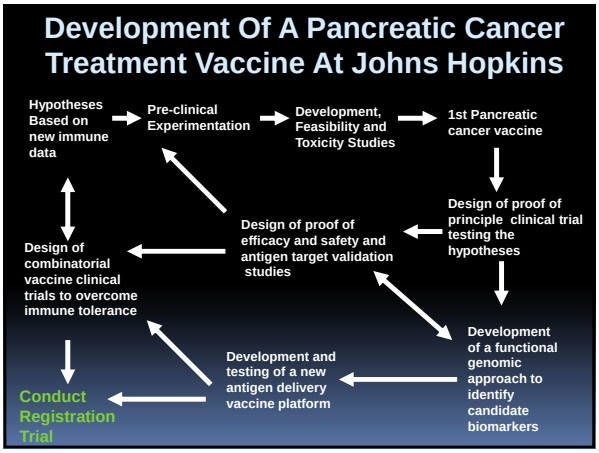
Since then translational research got even more complicated!

What is involved in translating a new lab concept into "first in man" clinical trials?

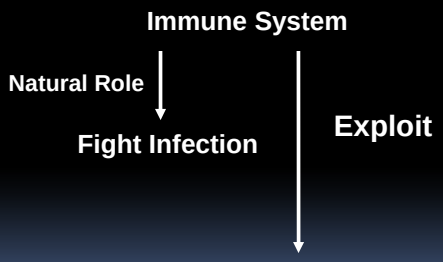


Key Points

- Many new drugs are targeted therapies (alter a specific biologic target)
- Testing new agents is facilitated by knowledge of a biomarker or surrogate marker of response associated with the targeted biologic pathway
  - Biomarkers are needed to demonstrate target modulation
  - Biomarkers are needed to optimize dosing and schedule
  - Biomarkers are needed to identify subsets of patients who may benefit from the new agent
- Early studies should be powered to address scientific markers of response rather than clinical response



Why Cancer Vaccines?



Question:

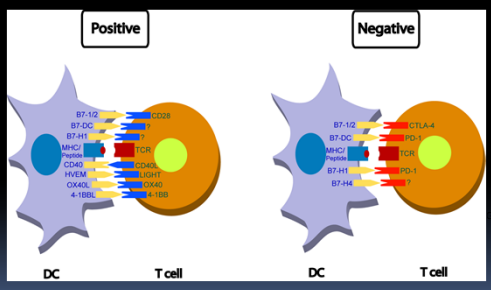
Why doesn't the body naturally fight developing cancers?

Hypothesis:

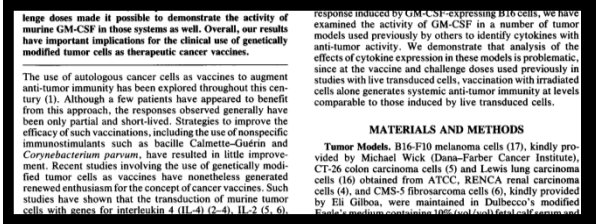
Unlike infection, cancer cells grow slowly and undergo insidious changes, and are therefore not recognized as dangerous. Rather, they are ignored by the immune system!

Can we trick the body into recognizing tumors as dangerous?

- The type of T cell response depends on whether the positive or negative signals dominate!
- Antigen presenting cells typically engaged in the proper context to activate immunity against any antigen – infectious or cancer



Mouse model used to test hypothesis



lenge doses made it possible to demonstrate the activity of murine GM-CSF in those systems as well. Overall, our results have important implications for the clinical use of genetically modified tumor cells as therapeutic cancer vaccines.

The use of autologous cancer cells as vaccines to augment anti-tumor immunity has been explored throughout this century (1). Although a few patients have appeared to benefit from this approach, the responses observed generally have been only partial and short-lived. Strategies to improve the efficacy of such vaccinations, including the use of nonspecific immunostimulants such as bacille Calmette-Guérin and *Corynebacterium parvum*, have resulted in little improvement. Recent studies involving the use of genetically modified tumor cells as vaccines have nonetheless generated renewed enthusiasm for the concept of cancer vaccines. Such studies have shown that the transduction of murine tumor cells with genes for interleukin 4 (IL-4) (2–4), IL-2 (5, 6),

response induced by GM-CSF-expressing B16 cells, we have examined the activity of GM-CSF in a number of tumor models used previously by others to identify cytokines with anti-tumor activity. We demonstrate that analysis of the effects of cytokine expression in these models is problematic, since at the vaccine and challenge doses used previously in studies with live transduced cells, vaccination with irradiated cells alone generates systemic anti-tumor immunity at levels comparable to those induced by live transduced cells.

MATERIALS AND METHODS

Tumor Models. B16-F10 melanoma cells (17), kindly provided by Michael Wick (Dana–Farber Cancer Institute), CT-26 colon carcinoma cells (5) and Lewis lung carcinoma cells (16) obtained from ATCC, RENCA renal carcinoma cells (4), and CMS-5 fibrosarcoma cells (6), kindly provided by Eli Gilboa, were maintained in Dulbecco's modified Eagle's medium containing 10% (vol/vol) fetal calf serum and

- Established the rationale for a clinical trial
- Suggested a safe starting dose, dose escalation range, and parameters for monitoring bioactivity in the clinic
- Toxicology studies performed using standard operating procedures to comply with regulatory (FDA) expectations

Translating new immunotherapies into patients requires developing the right series of human trials

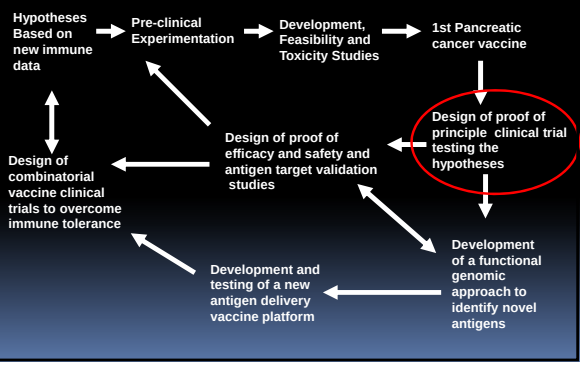
- As a clinical researcher/biologist, the first question I have is what are the trial options?
- As a translational scientist my major goal is to understand whether this new agent will work in patients and by what mechanisms
- Besides scientific rationale, I have preclinical feasibility, scheduling, and toxicology data to help drive the design

Best Option: Translational Clinical Trial

- A study that evaluates **BOTH** safety and bioactivity since this is a cancer targeted therapy that is likely to not reach a DLT
- Provide opportunity to obtain patient reagents for additional laboratory discovery studies and identifying more specific biomarkers of response

Used a 3x3 Phase I dose seeking design with additional patients enrolled on the most bioactive dose for correlative biomarker analyses

Development Of A Pancreatic Cancer Vaccine Program At Johns Hopkins



FDA plays an "interactive" role in translating laboratory concepts into the clinic and into "standard of care"!

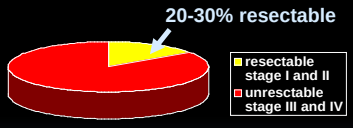
- Regulatory, Regulatory, Regulatory
  - Begins with an IND application
  - Continuous updates to IND application
  - Post-marketing surveillance
- Collaborator, Facilitator, Advisor
  - Pre-IND meetings
  - Advice from beginning to approval
  - Development of new regulatory "pathways" for new drugs, combinations, etc.

Clinical regulatory burden for a single "proof of principle" trial

Regulatory burden for cGMP production of one vaccine for single phase 1 study

Pancreas Cancer: Epidemiology & Stage at Presentation

Estimated US incidence (2007) ~ 37,170
Estimated US mortality (2007) ~ 33,370



Chemotherapy improves survival by a median of 10 months in metastatic patients

1-year survival all stages = 25-30%

5-year survival all stages = 4%

Few treatment options even for surgically resected patients. Can perform early clinical trials in best patient population – minimal residual disease with best immune system.

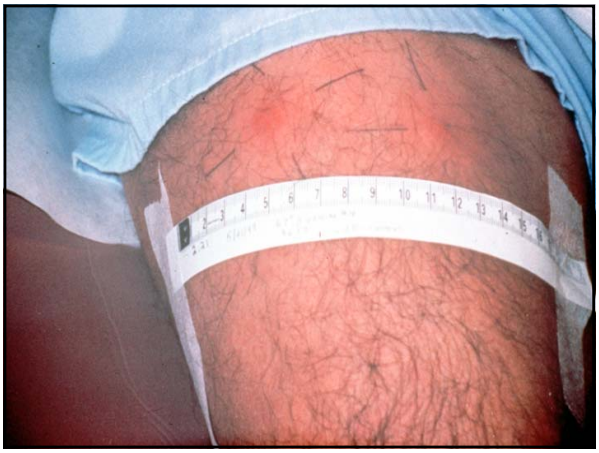
Phase 1 Study Demonstrates Safety and Immune Activity

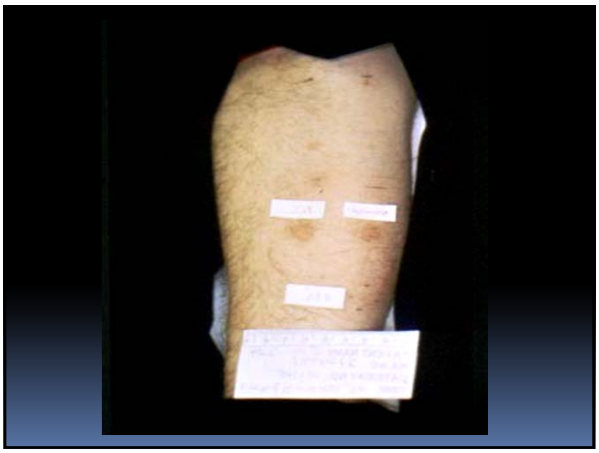
Novel Allogeneic Granulocyte-Macrophage Colony-Stimulating Factor–Secreting Tumor Vaccine for Pancreatic Cancer: A Phase I Trial of Safety and Immune Activation

By Elizabeth M. Jaffee, Ralph H. Hruban, Barbara Biedrzycki, Daniel Laheru, Karen Schepers, Patricia R. Sauter, Marti Goemann, Joanne Coleman, Louise Grochow, Ross C. Donehower, Keith D. Lillemoe, Seamus O'Reilly, Ross A. Abrams, Drew M. Pardoll, John L. Cameron, and Charles J. Yeo

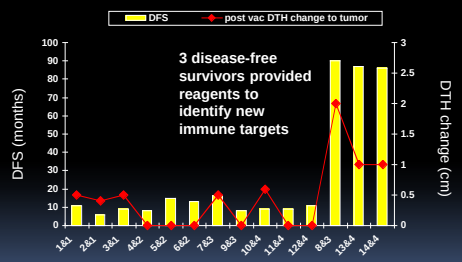
J Clin Oncol 19:145-156; 2001.

- **Demonstrated safety and identified optimal dose**
- **DTH responses to autologous tumor (crude biomarker of response) associated with DFS**
- **Immunized lymphocytes used to screen SAGE library to identify pancreatic cancer specific antigens – more specific biomarkers**



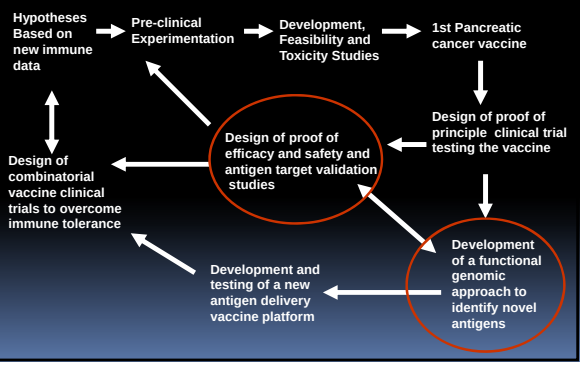


Post Vaccination DTH Correlates with Disease-Free Survival



Jaffee et al, J. Clin. Onc., 2001

Development Of A Pancreatic Cancer Vaccine Program At Johns Hopkins



Follow up single arm open label phase 2

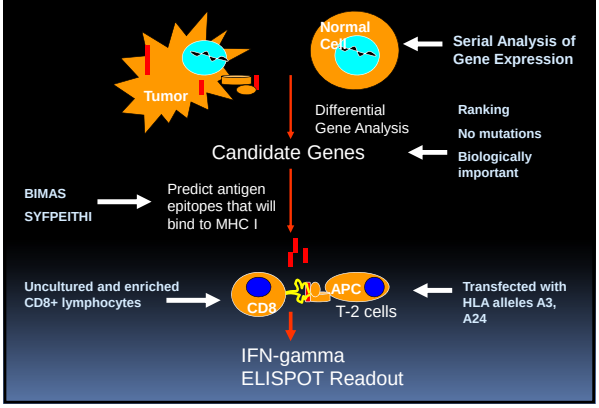
A Lethally Irradiated Allogeneic Granulocyte-Macrophage Colony Stimulating Factor-Secreting Tumor Vaccine for Pancreatic Adenocarcinoma: A Phase II Trial of Safety, Efficacy, and Immune Activation

Eric Lutz, PhD[*] §§, Charles J. Yeo, MD[**], Keith D. Lillemoe, MD††, Barbara Biedrzycki, NP[*], Barry Kobrin, PhD[*], Joseph Herman, MD, MSc†, Elizabeth Sugar, PhD¶, Steven Piantadosi, MD, PhD[***], John L. Cameron, MD‡, Sara Solt, BS[*], Beth Onners, RN[*], Irena Tartakovsky, MS[*], Miri Choi, BS[*], Rajni Sharma, PhD§, Peter B. Illei, MD§, Ralph H. Hruban, MD[*]§, Ross A. Abrams, MD ‡ ‖, Dung Le, MD[*], Elizabeth Jaffee, MD[***] §§ ¶¶, and Dan Laheru, MD[*]

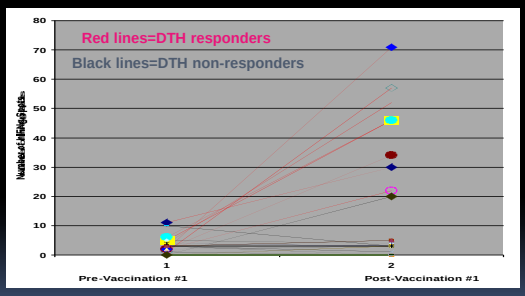
Ann Surg 11:1-8;2011

- **Estimate response rate and further assess toxicity**
- **Controversy over single vs control arm in phase 2**
- **Low rate (10%) of successful phase 3 following significant phase 2 study**
- **Identified new biomarker of response – Enhanced potency and T cell repertoire of mesothelin-specific CD8⁺ T cells**

Functional Genomic Approach for Antigen Identification



Mesothelin-specific T cell responses predict long-term disease free survival



Thomas et al. Journal of Experimental Medicine, 2004, 200(3):297-306.

Mesothelin is an immune target in patients

Mesothelin-specific CD8$^+$ T Cell Responses Provide Evidence of In Vivo Cross-Priming by Antigen-Presenting Cells in Vaccinated Pancreatic Cancer Patients

Amy Morck Thomas,[1] Lynn M. Santarsiero,[1] Eric R. Lutz,[1,2] Todd D. Armstrong,[1] Yi-Cheng Chen,[1] Lan-Qing Huang,[1] Daniel A. Laheru,[1] Michael Goggins,[3] Ralph H. Hruban,[3] and Elizabeth M. Jaffee[1,2,3]

J Exp Med 200(3):297-306; 2004.

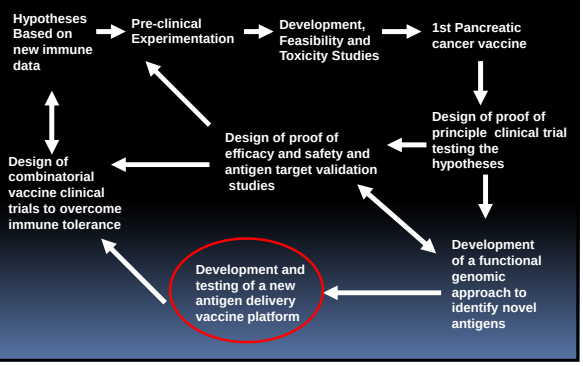
A Listeria Monocytogenes vaccine expressing mesothelin is safe and induces immunity

A Live-Attenuated Listeria Vaccine (ANZ-100) and a Live-Attenuated Listeria Vaccine Expressing Mesothelin (CRS-207) for Advanced Cancers: Phase I Studies of Safety and Immune Induction

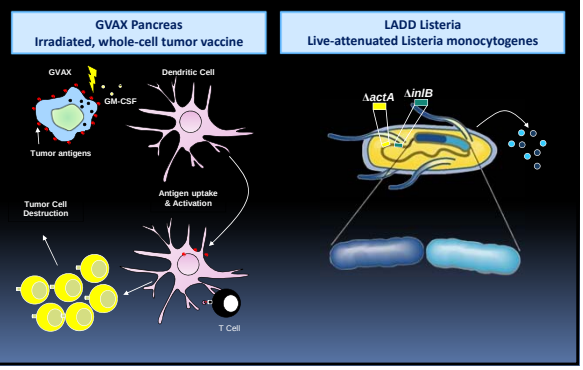
Dung T. Le[1], Dirk G. Brockstedt[4], Ran Nir-Paz[5], Johannes Hampl[6], Shruti Mathur[6], John Nemunaitis[7], Daniel H. Sterman[8], Raffit Hassan[9], Eric Lutz[1], Bentley Moyer[6], Martin Giedlin[6], Jana-Lynn Louis[1], Elizabeth A. Sugar[1,2], Alice Pons[1], Andrea L. Cox[1,3], Jordana Levine[3], Aimee Luck Murphy[4], Peter Illei[1], Thomas W. Dubensky Jr[6], Joseph E. Eiden[6], Elizabeth M. Jaffee[1], and Daniel A. Laheru[1]

Clin Ca Res 18(3):858-868; 2011.

Development Of A Pancreatic Cancer Vaccine Program At Johns Hopkins

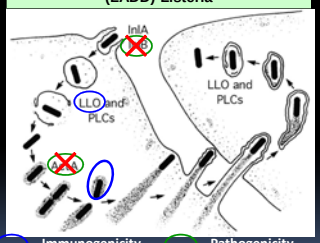


Two Vaccines May Be Better Than One! PRIME/BOOST Study – 2 Synergistic Mechanisms



What makes Listeria different?

Live-Attenuated Double Deleted (LADD) Listeria

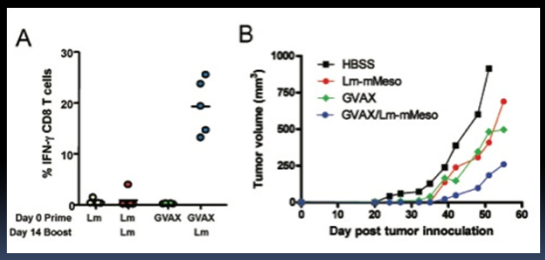


Tilney and Portnoy, 1989

Safety
- Targeted infection to Antigen presenting cells
- No cell-to-cell propagation
- Shown to be safe in phase I/II studies – no shedding
- Exquisitely sensitive to penicillin

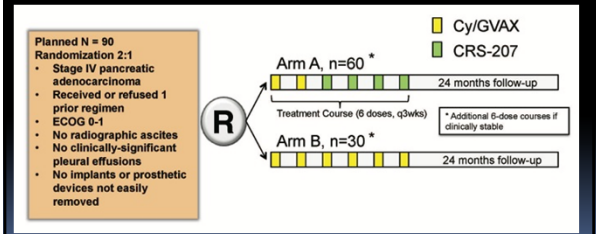
Immune Activation
- Dendritic cells targeted
- Extra- and intracellular host receptors engaged
- TLR 2,5,9 activation
- Antigens expressed intracellularly
- Induces IL-12 secretion

Preclinical Data Supporting GVAX as Prime and Listeria as Boost Vaccine



Study Design: Randomized Multicenter Phase II of GVAX Prime and Listeria Boost versus GVAX alone

Dung Le, et al. ASCO Abstract, 2013

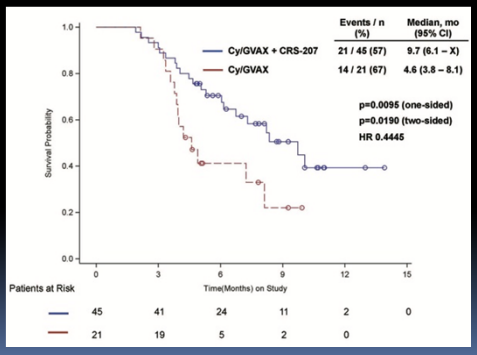


Low dose cyclophosphamide (Cy) given before each GVAX to deplete regulatory T cells

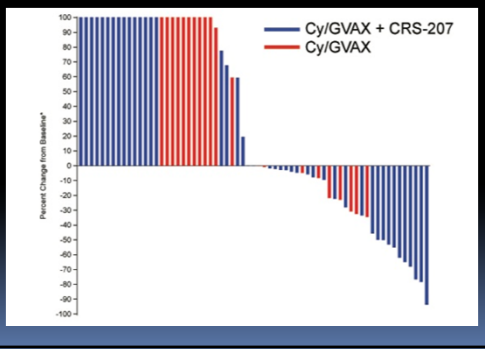
The Controversy over Phase 2 Studies

- The majority of drugs with a positive phase 2 result fail in phase 3
- Blamed on single arm rather than use of randomized controlled study
- Randomization in phase 2 usually not powered to compare the two arms
- Randomization does provide balance of patient demographics which is a benefit
- Drugs failure likely multifactorial – includes lack of an adequate biomarker for optimizing administration, schedule, dose, etc.

Overall Survival Benefit of Prime/Boost Vaccine



Percent Change From Baseline in the CA19.9 Biomarker



Where are we now?

- Aduro Biotech licensed IP from JHU
- Conducting multicenter randomized phase 2b while adapting vaccine for phase 3
- Phase 2 data was significant enough for FDA to grant accelerated approval status – phase 2b can therefore lead to provisional approval for therapy
- Preclinical studies suggest combining vaccine with T cell modulating agents that block T cell inhibitory signals will improve vaccine therapy
- Phase 2 studies underway testing combinations

Development Of A Pancreatic Cancer Treatment Vaccine At Johns Hopkins