Translational Immunology for Glioma: From Bench to Bedside

ROSWELL PARK CANCER INSTITUTE

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Disclosure:

Michael Ciesielski, PhD – *Chief Scientific Officer. Co-Founder, & Equity Shareholder of MimiVax; Co-Patent holder of SurVaxM*

MimiVax, LLC is a spin-out company of Roswell Park Cancer Institute formed to commercialize the SurVaxM vaccine.

MimiVax

Objectives

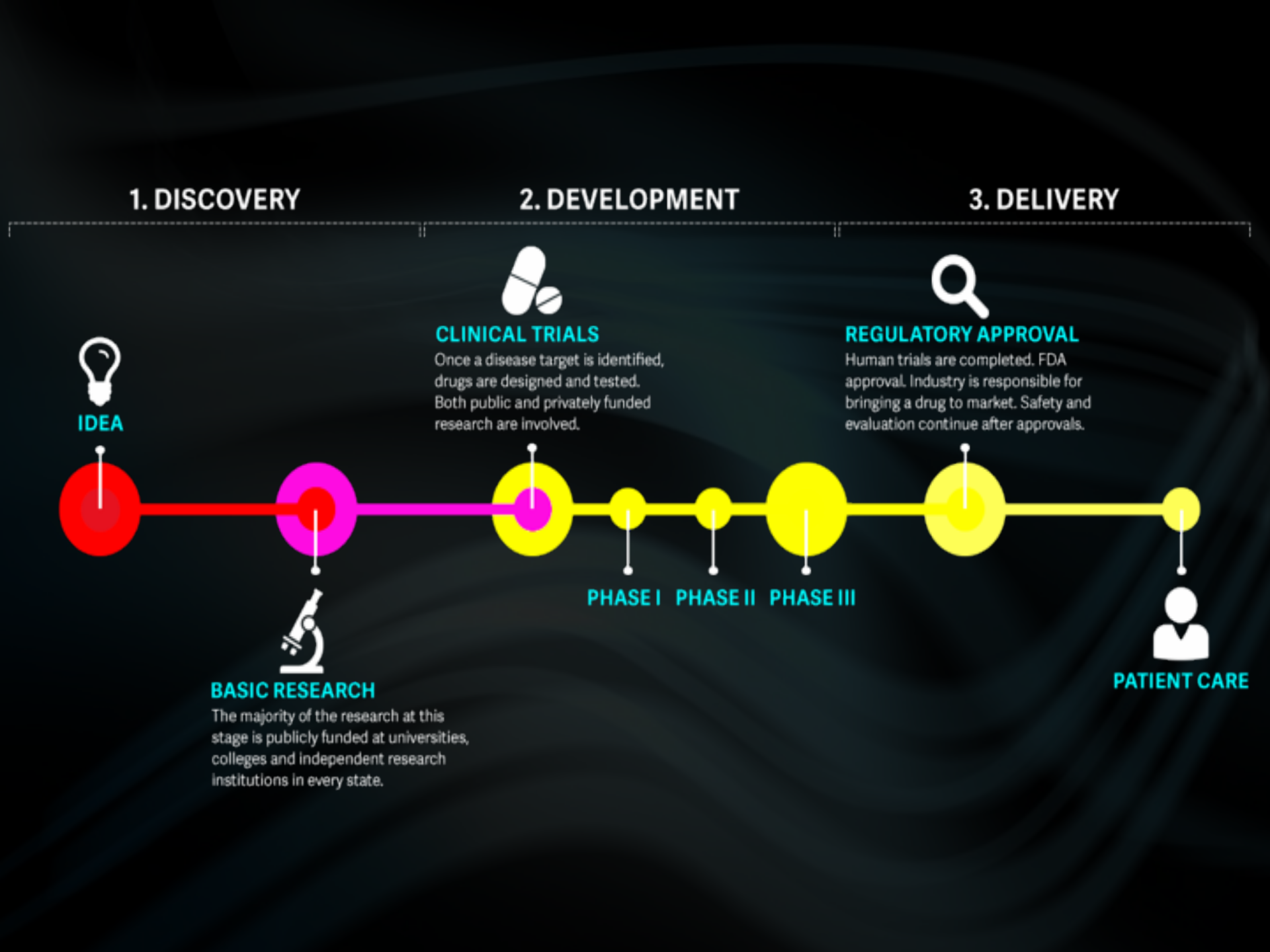
- Translational Research Overview (What is it?)
  - Clinical Studies (Glioma)
  - Scientific Example (Survivin Vaccine)


BENCH
2
BEDSIDE

Translational "Process"

- The process of creating new medicines is complex, time-consuming, and costly.
- Moving from concept to market can take between 10 and 15 years and cost developers as much as $1 billion.
- For every drug that ultimately receives approval from the FDA, some 5,000 to 10,000 compounds don't make it through the process.


The Bench to Bedside Abyss


1. DISCOVERY
2. DEVELOPMENT
3. DELIVERY
IDEA
BASIC RESEARCH
The majority of the research at this stage is publicly funded at universities, colleges and independent research institutions in every state.
CLINICAL TRIALS
Once a disease target is identified, drugs are designed and tested. Both public and privately funded research are involved.
PHASE I
PHASE II
PHASE III
REGULATORY APPROVAL
Human trials are completed. FDA approval. Industry is responsible for bringing a drug to market. Safety and evaluation continue after approvals.
PATIENT CARE

Bridging Basic Science into Clinical Science Step 1

- Basic science concept
- Basic science efficacy

- Pre-clinical manufacturing
  - How do we make lots of it?

- Pre-clinical toxicity…
  - Is it safe in animals?

GLP

- Good Laboratory Practice (GLP) embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. (Logs, Reports & SOP's)

- GLP is a "Process"

GMP

- Good Manufacturing Practice (GMP) ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. (Batch Record)

- GMP is a “System”

Pre-clinical to clinical
Step 2

- Pre-clinical animal toxicity…
- Must use GMP drug
- Performed under GLP

- No toxicity = great news
- Now you can write an IND
- What's an IND?

Investigational New Drug application

- An application to FDA seeking permission to test a drug or biologic in humans (license to a clinical trial)

- 3 Parts:
  - Chemistry Manufacturing and Controls (CMC)
  - Clinical trials documents and amendment (IRB approved!)
  - Pharmacology & Toxicity studies in animals

- What are they interested in?
  - Drug stability
  - Purity
  - Freedom from infectious agents, pyrogens, contaminants
  - Safety (generally two species)

IND

- The IND is a living document
- Everything is now appended to the IND, all clinical data, all chemistry data & all new preclinical data.
- Format is largely up to the investigator…some better than others.
- FDA wants to be aware of anything that can alter safety.
- They will not waste time if they can't find information.

Pre-clinical to clinical
Step 3

- Pre-IND meetings…you get 3
- IND Submission
- The Center for Biologics Evaluation and Research (CBER) regulates vaccine products
  - Chemistry, Manufacturing and Controls (CMC)
    - Stability testing program
    - Activity assays
  - Toxicity
    - Which species
    - Dose bracketing
  - Phase I clinical trial design and dose selection

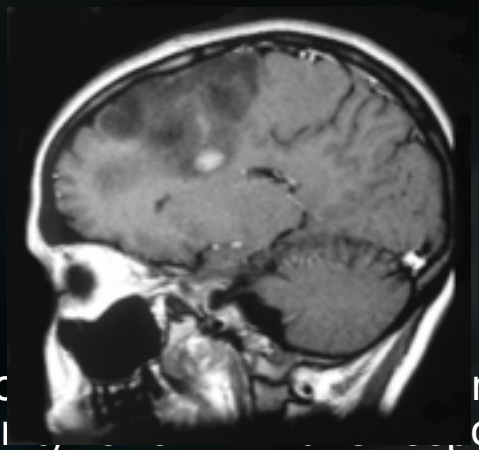
When is it ok to open the phase I clinical study?

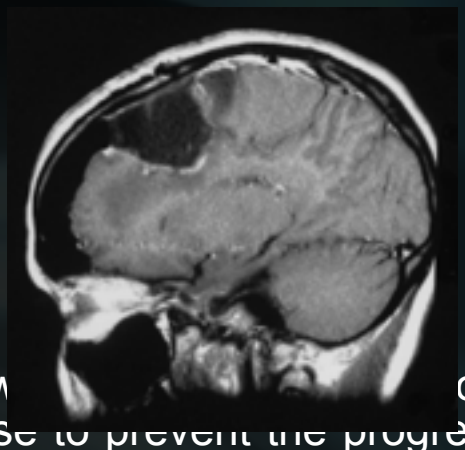
- IND submission starts the “countdown clock”
- 30 days from the day the IND packet is sent to the FDA
  - FDA can ask for clarifications or additional documentation
  - Clinical HOLD or request for modification
  - If no word is heard, the investigator may begin the study after 30 days

“No news is good news”

Glioma Immunotherapy

- Control of malignant gliomas commonly fails from recurrence due to residual microscopic disease.
- After resection, immune responsiveness temporarily returns to patients until the tumor recurs.

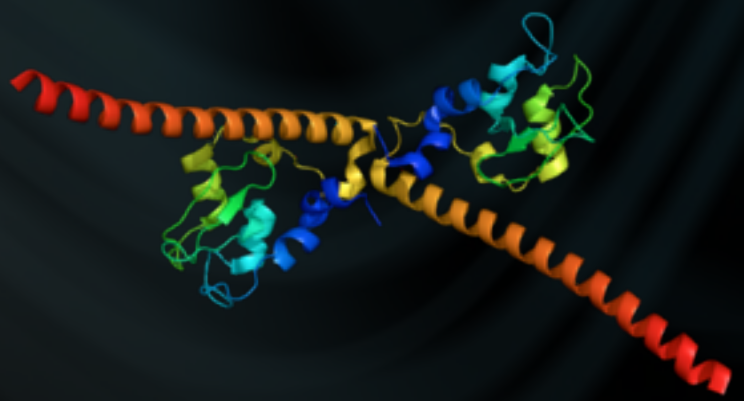




- This pro[illegible]n w[illegible]on after resection creates an opportu[illegible]onse to prevent the progression of residual microscopic disease.

The Survivin Molecule as a Target

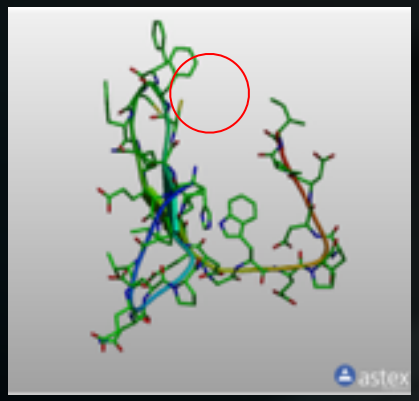
- Inhibitor of apoptosis protein (IAP) with complex function
- Very limited expression in normal cells
- Expression in tumors associated with poor prognosis
- Present in 95% of glioblastomas
  - And many other cancers

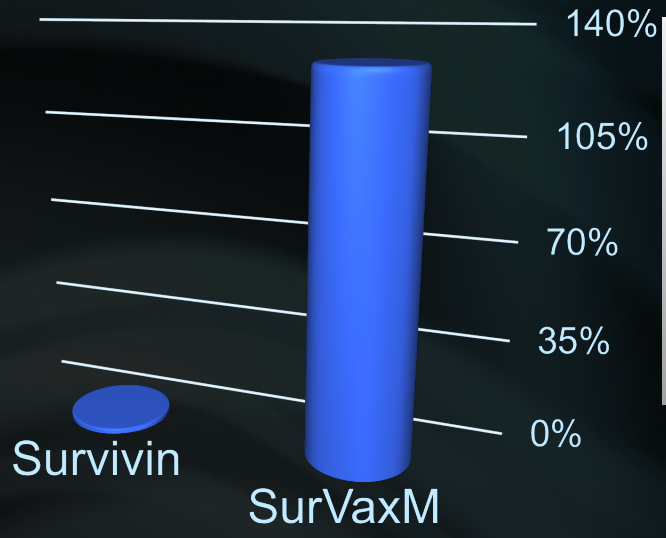


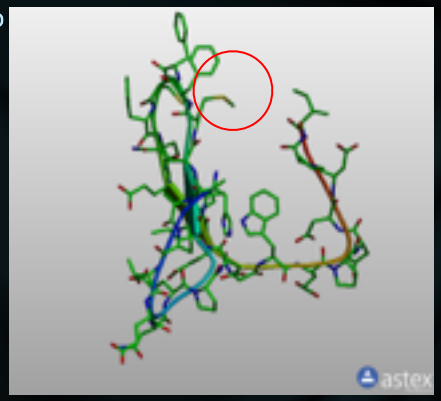
Survivin Vaccine Design (SurVaxM)

- Molecular mimic
  - Enhanced MHC class I binding
  - Cross-reactive to wild type survivin
- Long peptide
  - MHC class II binding – helper support
  - Limited HLA restriction
  - Multiple CD8+ T cell epitopes
  - Antibody responses

SURVAXM – ENHANCED MHC I BINDING

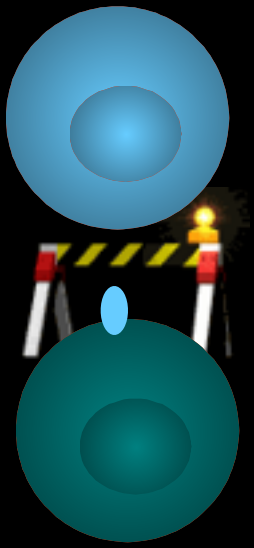




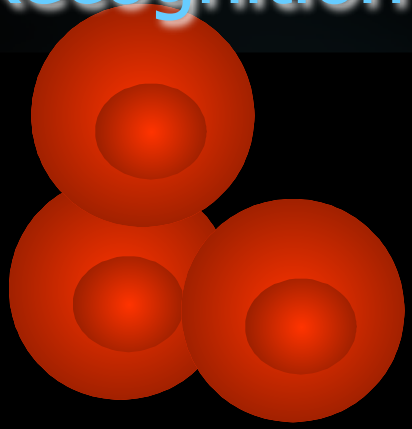


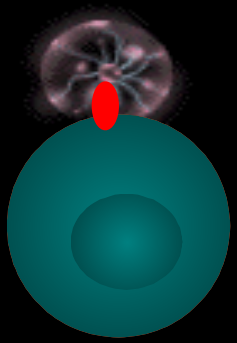
1. Mimic greatly enhances MHC-I binding (HLA-A*02)
2. SurVaxM stimulates a potent immune response
3. Immune response cross-reacts to wild type survivin in tumor cells

Altered Peptide Recognition and tumor cells



Normal Peptide
"Self"

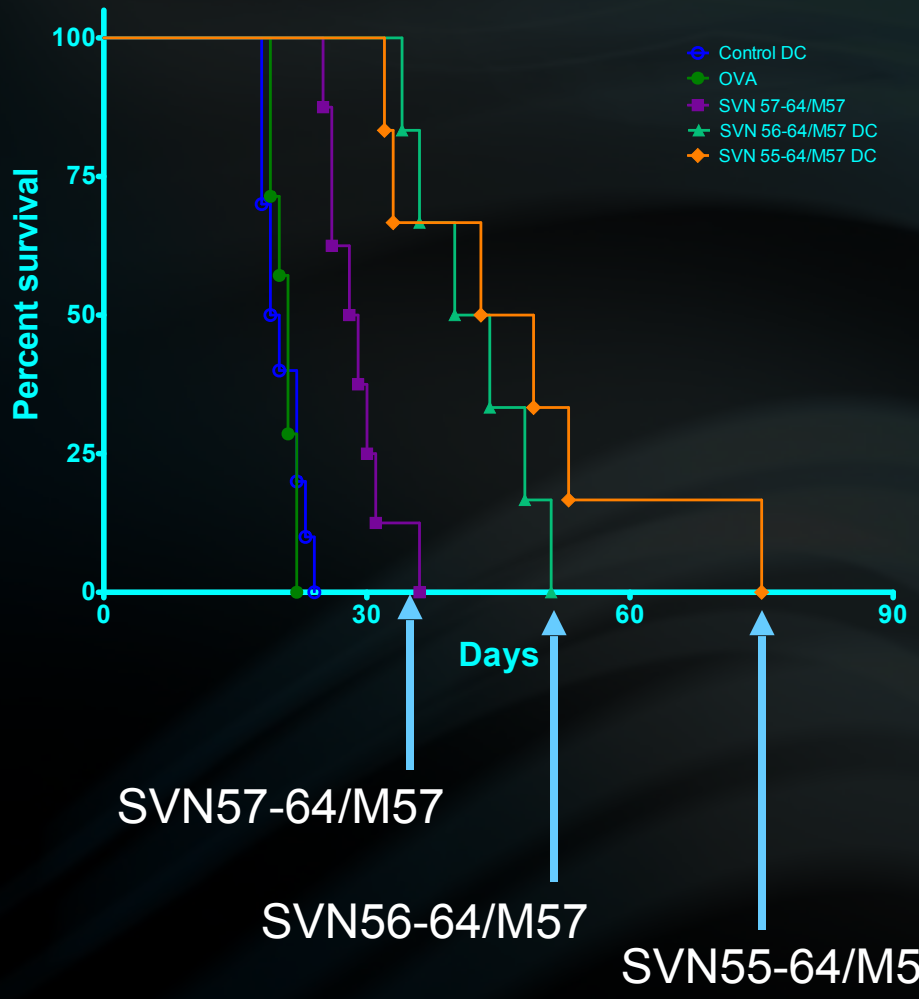


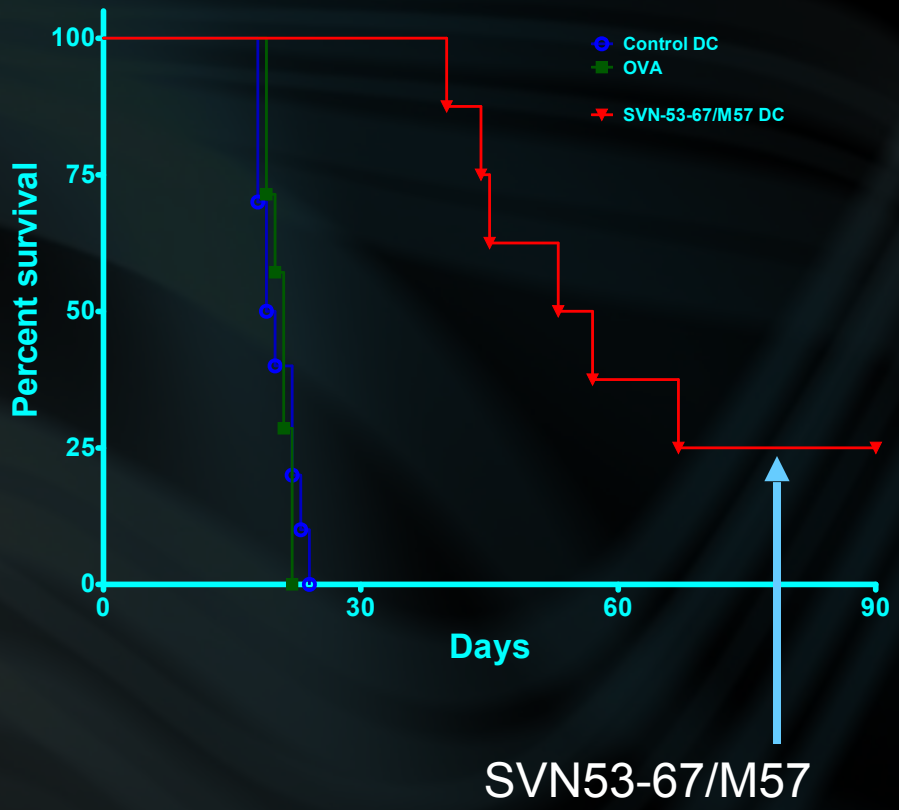


Altered Peptide
"Non-Self"

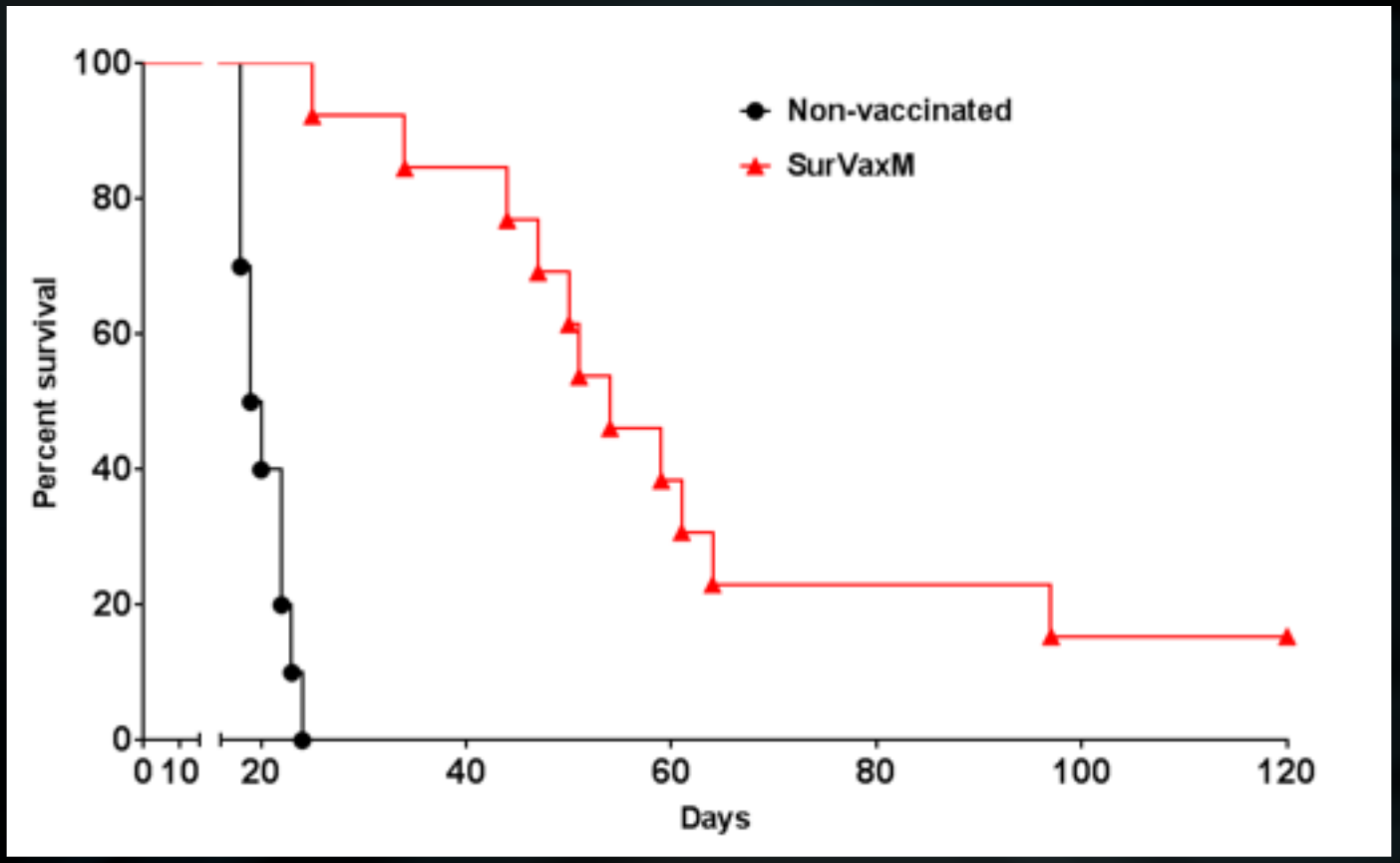
Normal Peptide
"Non-Self"

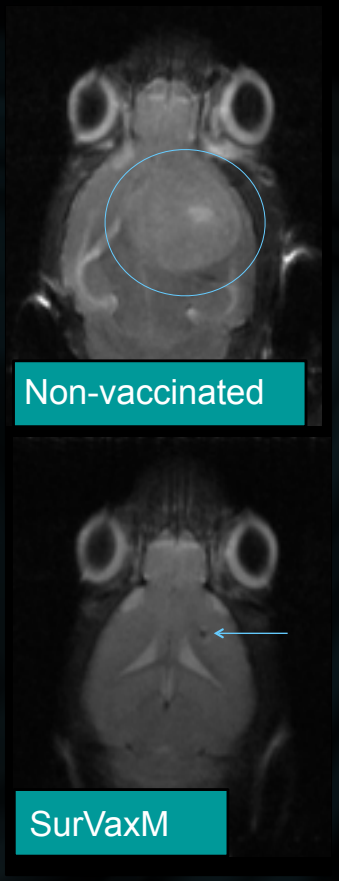
Vaccine Design: Intracranial Glioma Survival Studies





SurVaxM: Effectiveness in Mouse Glioma





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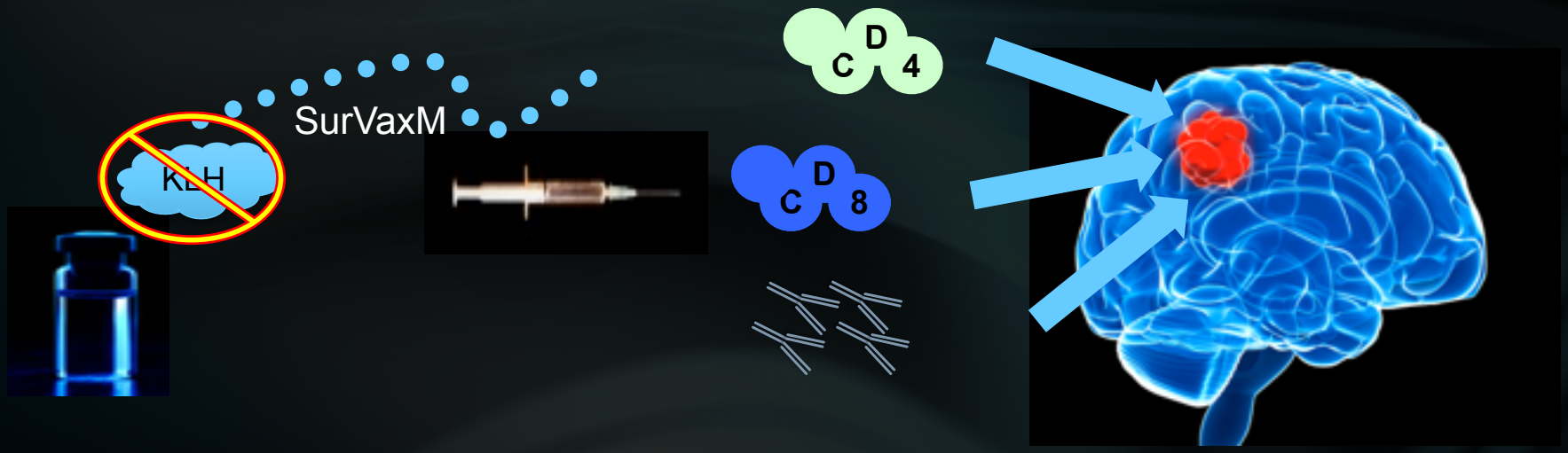
SurVaxm (The Vaccine)

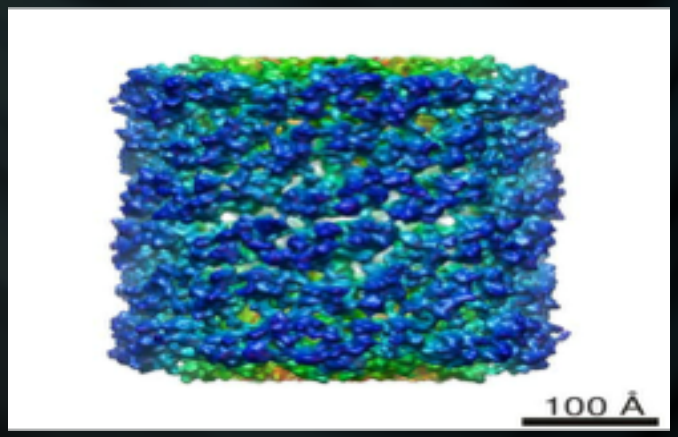


SurVaxM: A long peptide vaccine targeting survivin present in cancer cells. Vaccine is a cell-free lyophilized peptide, prepared emulsified in Montanide ISA 51 VG, served with a side of GM-CSF and injected subcutaneously. The resulting immune response generates tumor-specific $CD4^+$ & $CD8^+$ T cells as well as antibodies.

Clinical Hold

- Non-GMP KLH
- Vaccine re-synthesis

Keyhole Limpet Hemocyanin



Back to GMP!

- Vaccine re-synthesis
  - Aquaculture KLH

Non-GMP KLH = $60/gram

→

GMP KLH = $18,000/gram

Phase I Trial Design

- Survivin-positive recurrent malignant glioma
- HLA-A*02 and HLA-A*03
- Single Arm of 9 patients
- SubQ with Montanide and GM-CSF adjuvants

- Primary: Toxicity, tolerability and immunologic effects
  - Secondary: PFS and OS
    - Tertiary: Radiologic response

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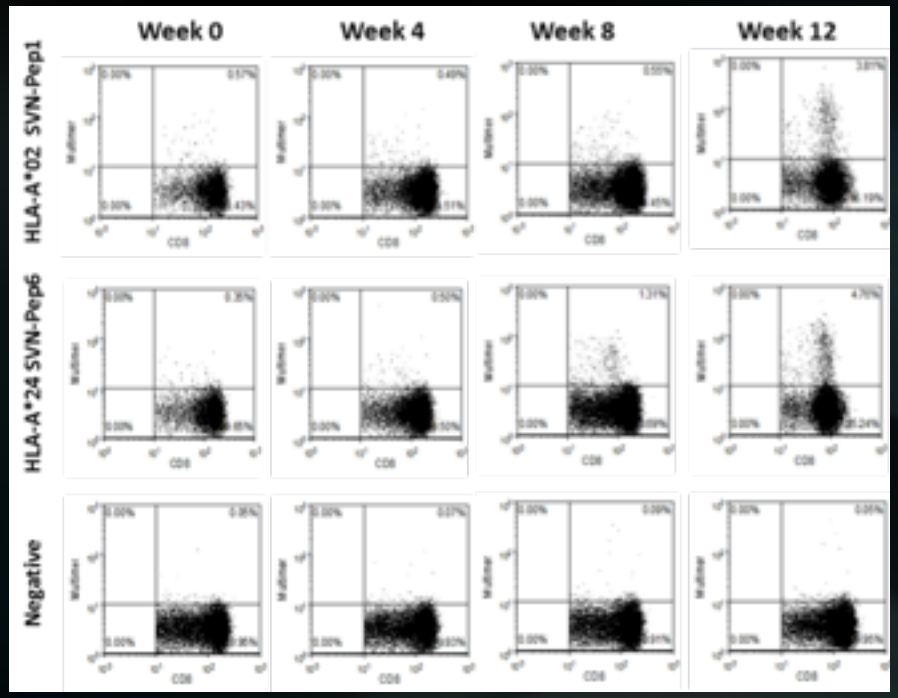
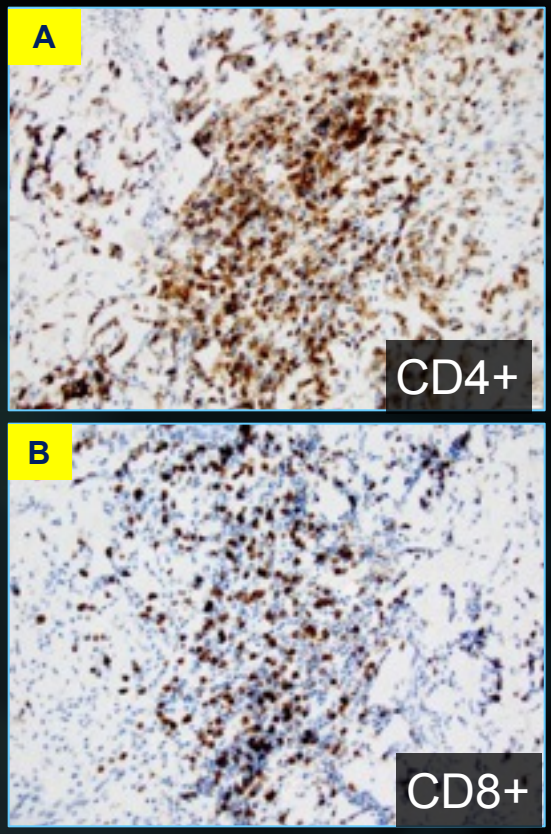
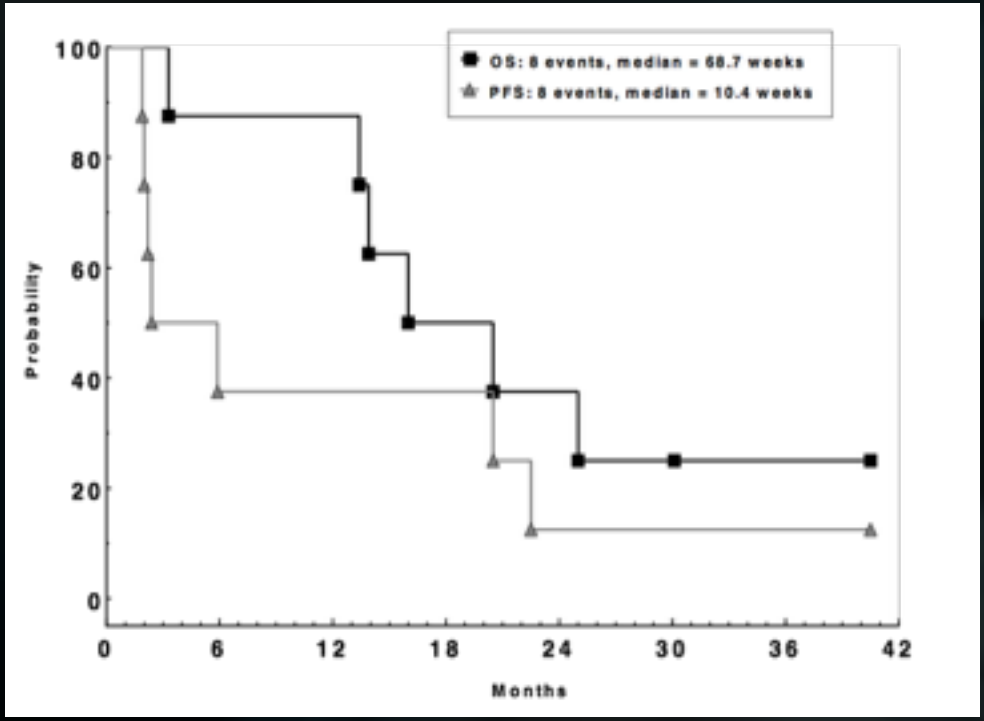
Phase I: CD8+ T cell Response



Binding of MHC-peptide complexes (multimers) to CD8+ T cell receptors in patients measured at weeks 8-105 following first vaccination are shown.



Phase I Study Results



OS					
3 mo.	6 mo.	12 mo.	24 mo.	36 mo.	Median
87.5%	87.5%	87.5%	37.5%	25%	16 mos.

PFS					
3 mo.	6 mo.	12 mo.	24 mo.	36 mo.	Median
50%	37.5%	37.5%	12.5	12.5%	2.4 mos.

Phase I Study: SurVaxM in recurrent glioma - Historical control median OS = **7 months**

SurVaxM median OS = **16 months**

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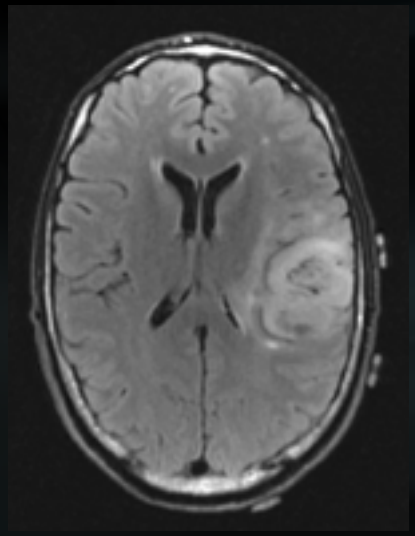
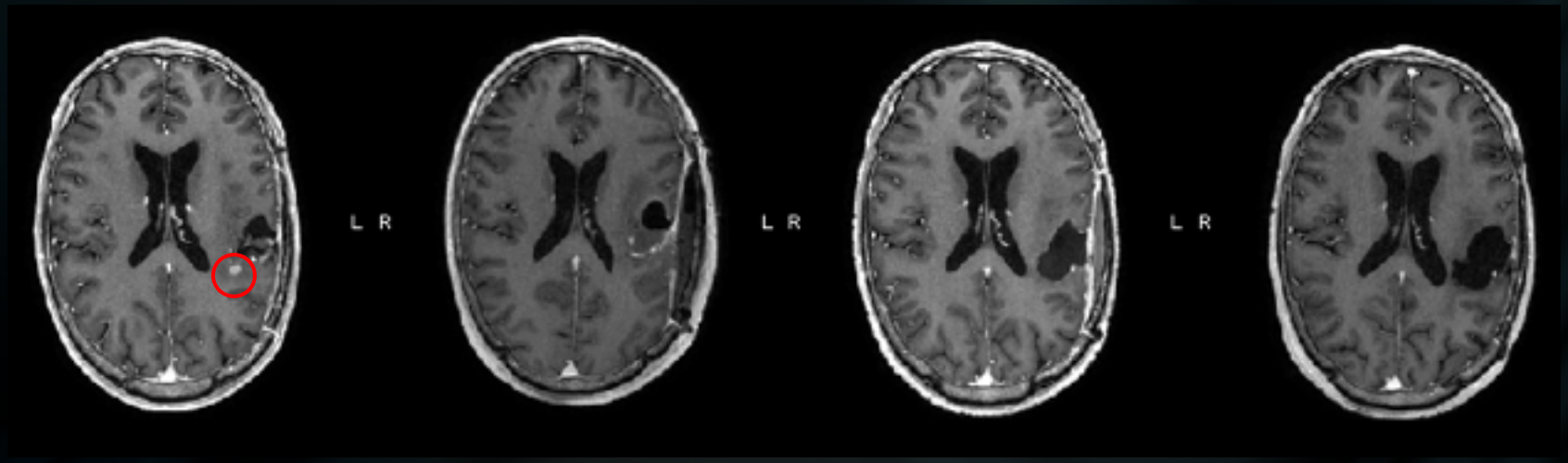


- 37 yo man with glioblastoma
- Surgery, XRT, temozolomide
- Recurrence after 5 months
- Re-resection and vaccine
  - Recurrence confirmed histologically



6/12
Recurrence – 5 mo.
Post-op #1

8/12
Post-Op #2

9/12
On-study

7/15
34-mo Post-vax

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SurVaxM Phase I "First in Human" Clinical Trial in Recurrent Malignant Glioma

- Appears to be safe and tolerable
  - Grade I injection site reactions mainly
  - Fatigue, myalgia
- Immunogenic: CD8+, CD4+ & antibodies
- No autoimmunity observed

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MniVax

Phase I to Phase II

- Phase 1: Initial testing is conducted in a small number of patients to determine if the drug is reasonably safe.

- Phase 2: Testing evaluates the drug candidate's effectiveness and safety in a group of patients (generally 30 to 300). Drug developers examine the side effects and potential risks of the drug and the initial indications of its effectiveness.

Phase II Design

- 50 patients with newly diagnosed survivin-positive glioblastoma
- Vaccine plus standard therapy
- HLA-A*02, -A*03, -A*11 and -A*24

- Primary: PFS primary end point
  - Historical comparison well defined,
  - 95% of all glioblastoma express survivin
- Secondary: OS, imaging, immune responses

- Submit protocol to FDA…wait 30 days and go...

- Currently recruiting, 11 of 50 patients have been dosed

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Phase III & Beyond

- Phase 3: The drug is tested in a large group (often 1,000 or more people) to gather evidence about the safety, effectiveness, benefits, and risks of the drug. Usually double blinded and randomized. Phase 3 studies provide key information used by FDA in deciding whether to approve a drug for use. (Average phase 3 = $20M)

- NDA: New Drug Application. Request for approval to market a drug to patients. This application contains the results of all animal and human studies of the drug, as well as information on its manufacturing. The agency reviews the application and decides whether the drug can be approved or needs additional testing.

Traversing the Valley of Death

Pitfalls…

- Some simple…
  - protocol amendments
  - deviations (reason for GLP/GMP)
  - paperwork
- Some not so simple...
  - fatal trial design
  - financing
  - efficacy

Celldex Brain Tumor Vaccine Fails Pivotal Clinical Trial

By **Adam Feuerstein** | 03/07/16 - 07:08 AM EST

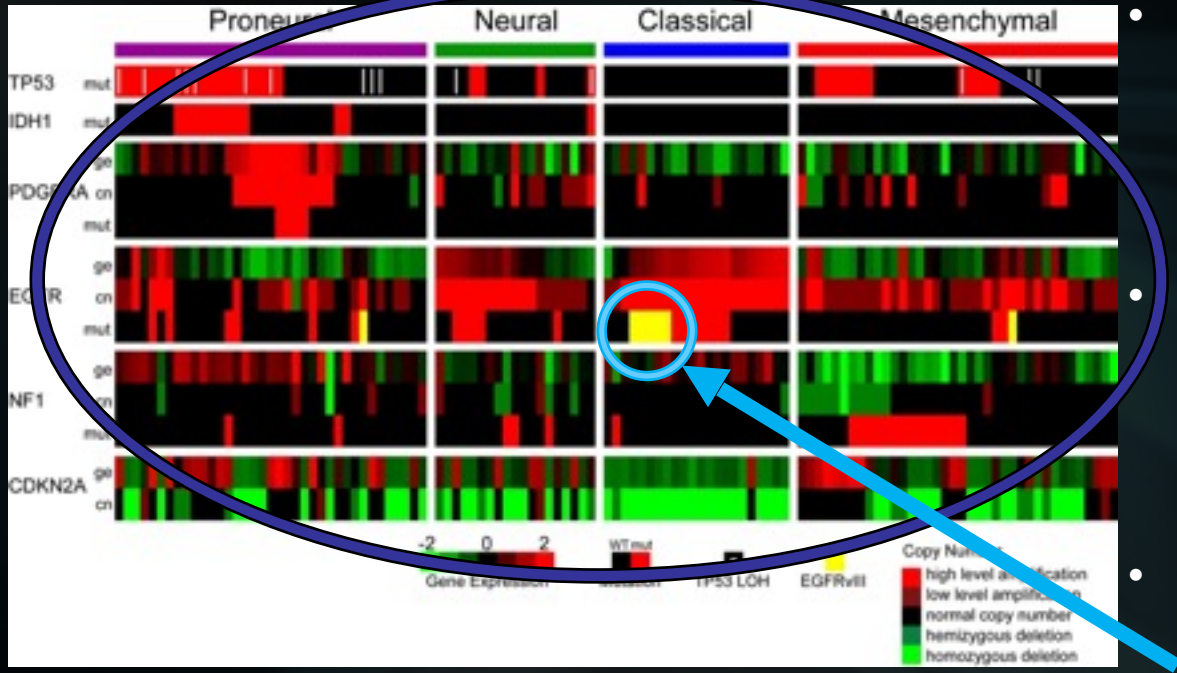
There's bad news out of **Celldex Therapeutics** (CLDX - Get Report) Monday morning. The pivotal brain tumor clinical trial involving the company's experimental cancer vaccine Rintega was stopped for futility.

Celldex was informed of the failure of the Rintega phase III study known as ACT IV on Friday evening following an interim analysis conducted by independent data monitors. The study enrolled patients with a certain type of glioblastoma multiforme (GBM), an aggressive brain tumor.

At the interim analysis, Rintega was found to reduce the risk of death by just 1% compared to the control arm. However, at the median, Rintega-treated patients fared worse, surviving 20.4 months compared to 21.1 months for the control arm, the company said.

As a result, Celldex is discontinuing clinical development of Rintega. Obviously, the company's plans to seek approval for the product in the U.S. or Europe are also being shelved.

Careful consideration to clinical trial populations

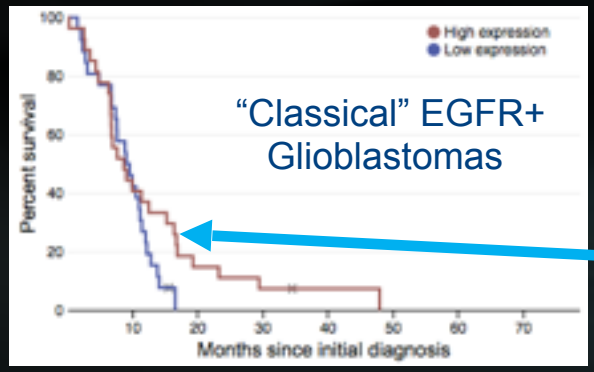


- "Glioblastoma" is a mix of 4 somewhat distinct molecular subtypes of tumors.
- As a whole Glioblastoma patients have a median overall survival of 14-16 months
- EGFRvIII is only in 20% of classical types…

Cancer Cell 2010 17, 98-110DOI: (10.1016/j.ccr.2009.12.020)

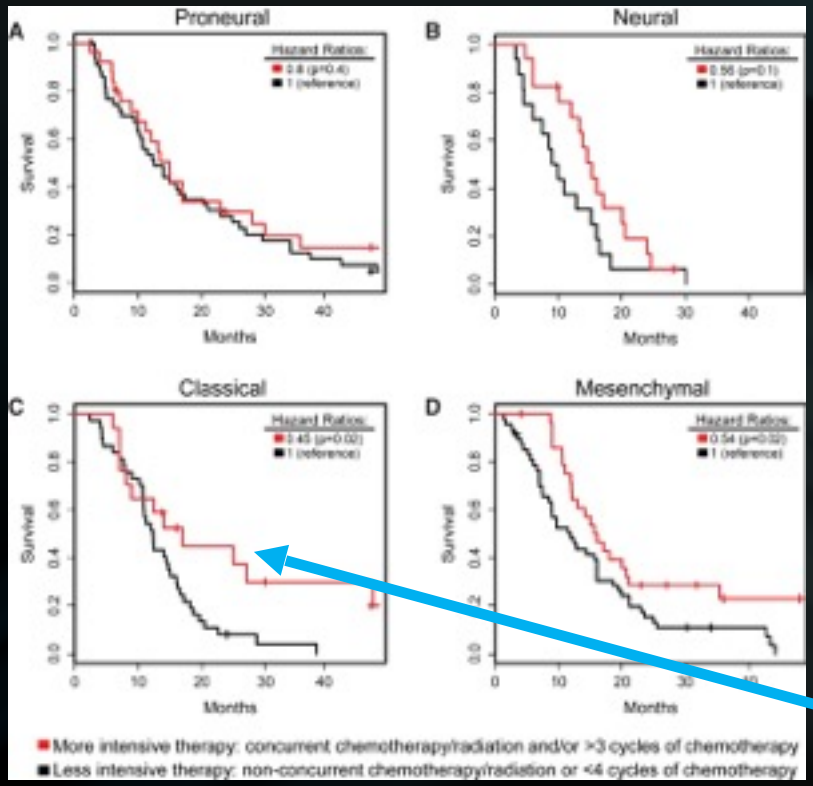
EGFRvIII+ glioblastoma is a super-selected subgroup…

…which selects for a much more favorable prognosis



"Classical" EGFR+ Glioblastomas

EGFRvIII Glioblastomas Receiving Treatment



EGFRvIII expressing "classical" glioblastoma have better prognosis all by themselves

Cancer Cell 2010 17, 98-110DOI: (10.1016/j.ccr.2009.12.020)

Not there yet…
The Commercialization Process

Patents……

Foreign Patents…

Portfolio…

Sub-license…

IP…

Take to market…

Sell…

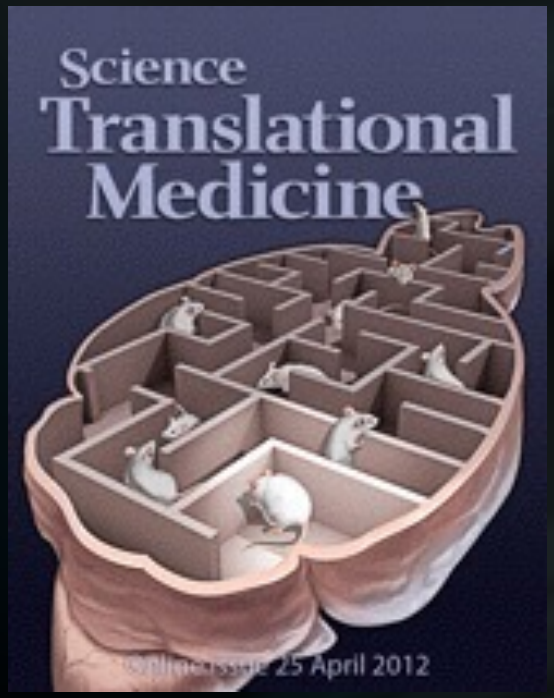
Go Public…

Partner…

Marketing…

Invest…

SurVaxM Development Timeline



Discovery

- 2006 • Invention of SurVaxM peptide
- 2007 • National Brain Tumor Foundation Award ($50,000)
- 2008 • Patent Filed

Pre-Clinical

- 2009
- 2010 • Completion of pre-clinical efficacy studies
- 2010 • Initial meetings with FDA
- 2011 • Completed FDA-mandated GMP API scale-up
- 2011 • Completed GLP toxicity studies
- 2012 • Patent Awarded (US)
- 2012 • First IRB approval granted
- 2012 • IND approved by FDA

Phase I

- 2012 • American Cancer Society Award ($720,000)
- 2013 • Phase I clinical trial in recurrent glioma patients open
- 2014
- 2015 • Phase I clinical trial in recurrent glioma completed

Phase II

- 2015 • Private investment offering ($1.5 Million)
- 2016 • Phase II trial in newly diag. glioblastoma patients open
- 2016 • Phase I trial in multiple myeloma open

Clinical translation is about efficacy & safety

Jason underwent surgery, radiation and chemotherapy, but, despite the aggressive treatments, his cancer recurred. He and his wife felt like they were out of options.

"It was a whole new take on the care I was getting, and I knew this amazing research could help me and other patients in the future," said Jason.

More than three years later, Jason is without evidence of the disease. He is stable medically, feels healthy and no longer has intense headaches.

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