

A photograph of the Roswell Park Cancer Institute building, a large, modern, multi-story structure with a curved facade and prominent windows. The building is surrounded by greenery and a clear sky with a bright sun in the upper right corner. The text "ROSWELL PARK" is visible on the upper part of the building's facade.

Translational Immunology for Glioma: From Bench to Bedside



ROSWELL
PARK
CANCER INSTITUTE

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Neuro-Oncology

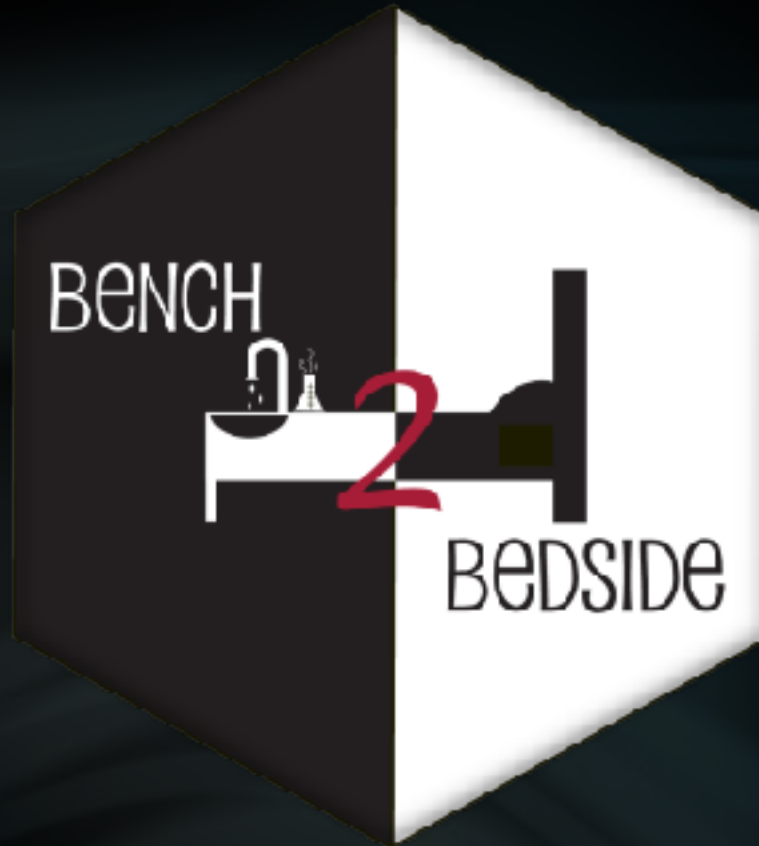
Disclosure:

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.

Objectives

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



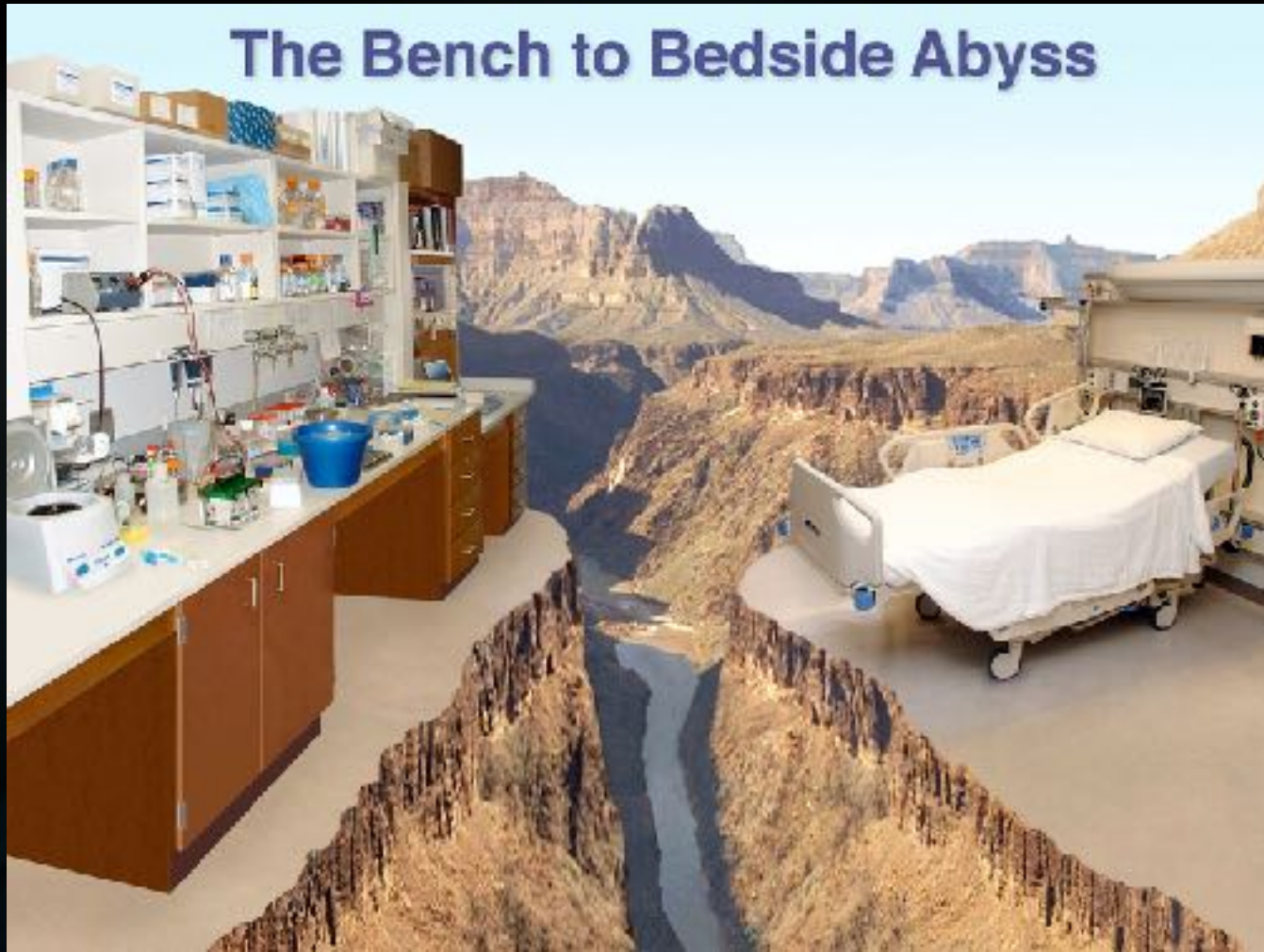
Translational... Sounds good... What does it mean?

Translational is a “Process”

- The process of bringing new medicines to clinical practice.
- 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.

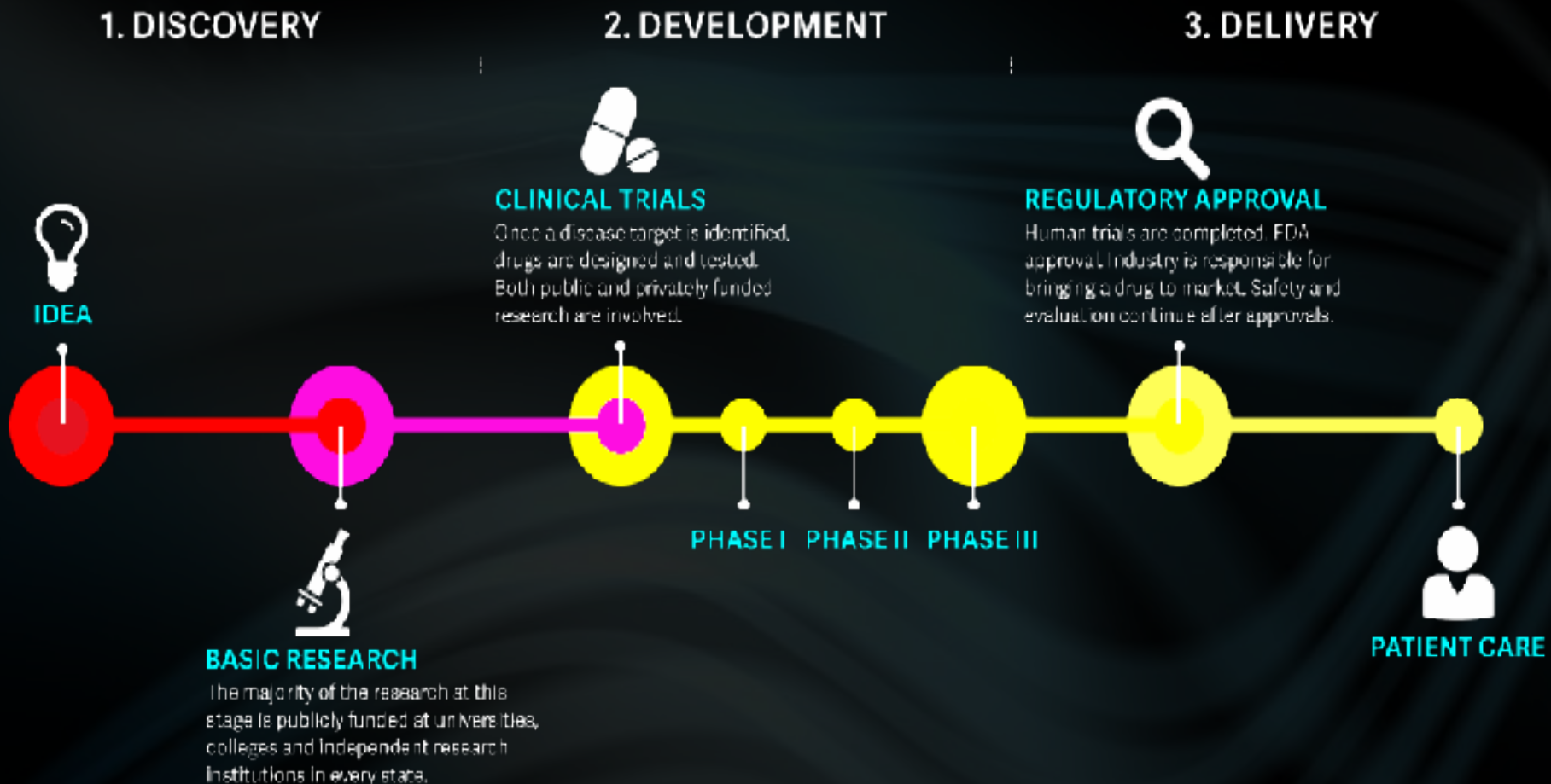


The Bench to Bedside Abyss



Reality of “Bench 2 Bedside”

Translational Process : Step by Step



Step 1: Bridging Basic Science into Clinical Science

- Basic science concept
- Does your prototype agent have activity?
- Basic science efficacy
 - Does it work in a reproducible model?
 - Does it work in a well-established model?
 - Gut check/Ready for prime time?
 - Can't keep tinkering, is this "the one?"
- Pre-clinical manufacturing
 - How hard is it going to be to scale up from a few µg in the lab to simple)
 - Who will do it and where? (bigger problem)
 - Are all your studies GLP/GMP? Wait...what...



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) detailed records 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”

Step 2: Pre-clinical to clinical science

"It worked in the lab, now what?"

- Pre-clinical animal toxicity testing...
- Must use GMP grade drug...
 - you did make your stock to GMP? Right? Are you sure?
 - Does agent still work when made by someone else?
- Performed under GLP
- No toxicity = great news
- Now you can write an IND
- What's an IND?



Step 3: 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 is the FDA interested in?
 - Drug stability
 - Purity
 - Freedom from infectious agents, pyrogens, contaminants
 - **Safety** (generally two species)

IND

- The IND is a living document
- Everything from this point forward is appended to the IND, all clinical data, all chemistry data & even all new preclinical data.
- Format is largely up to the investigator...some better than others. Basic framework, but very modifiable.
- FDA wants to be aware of anything and everything that can affect safety.
- It is on you to provide what they need. Standards must be met, FDA does not have to approve.



* 2017: FDA Recently changed to electronic CTD (Common Technical Document) format...
...yes hard copy was/is still used 1 year ago.

Pre-clinical to clinical IND

- Pre-IND meetings...discuss requirements, decide what is needed or not...you only get 3 meetings
- 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 dosing)

Design the Clinical Trial

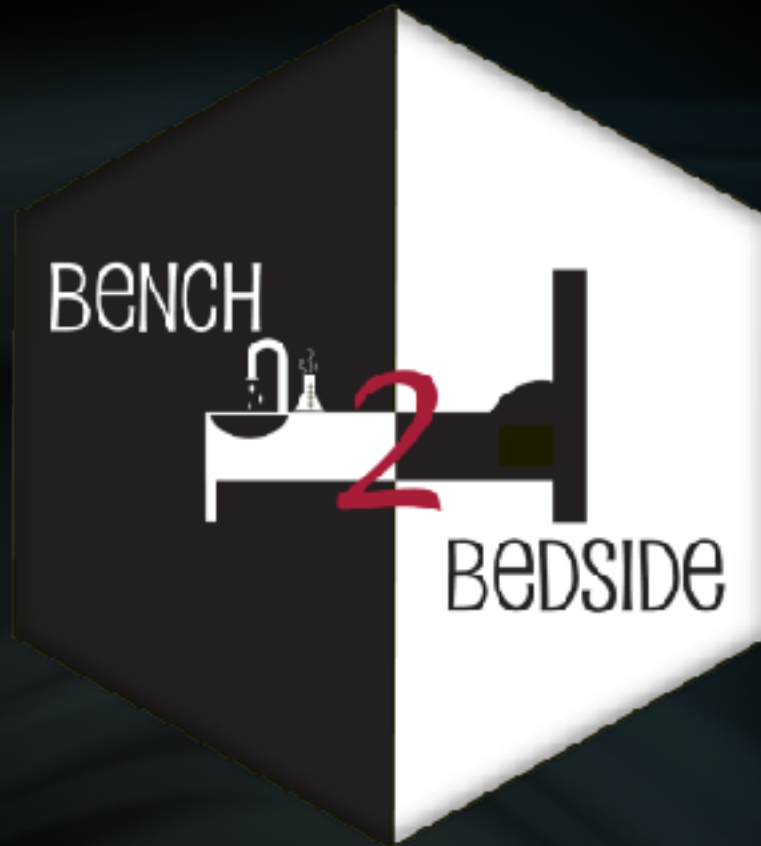
- Phase I – Safety, Safety, Safety
 - (do find a way to look for efficacy signals)
- Indication?
- One dose level? Escalating dose?
- One cohort? 2-3 cohorts?
- Repeat dosing?
- Readout?
- How many patients?

- Protocol (and a patient consent) need review by committees (SRC, IRB etc)
- Interestingly protocol approval can occur either before or after the IND-FDA submission

I submitted it now what?

- 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

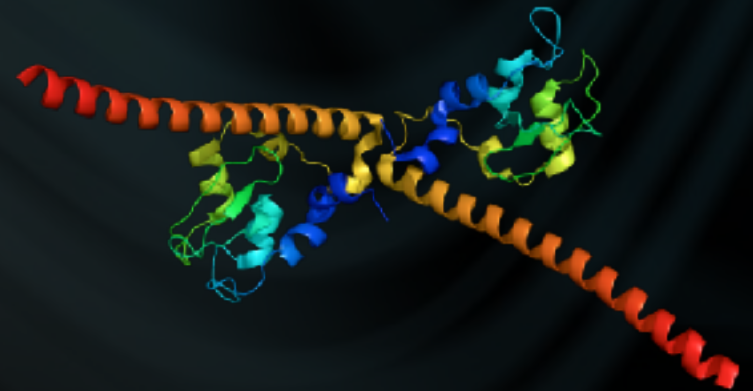
“No news is good news”



Neuro-Oncology Clinical Translatable Science

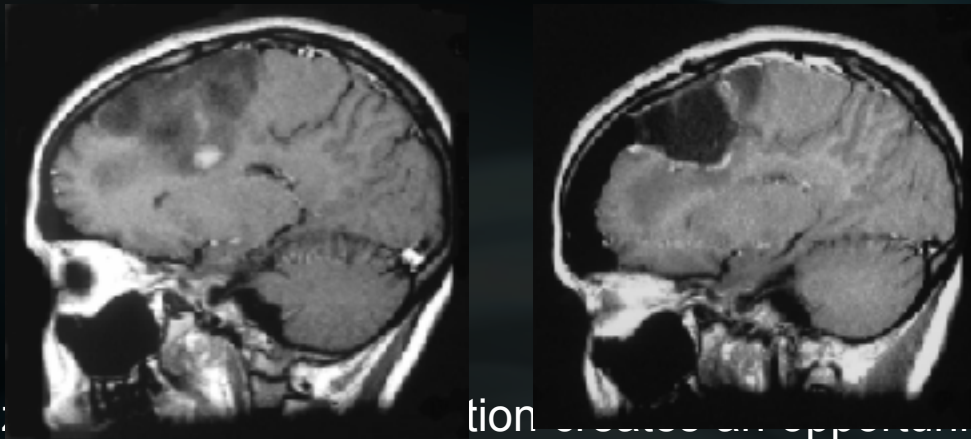
The Target: Survivin

- Inhibitor of apoptosis protein (IAP) with complex function
 - Nuclear, Cytoplasmic, Mitochondrial, other areas...
 - Multiple survivin isoforms
- Technically a Fetal-Oncogene, very limited expression in normal non-proliferating adult cells
- Present in 95% of glioblastomas
 - And many other cancers



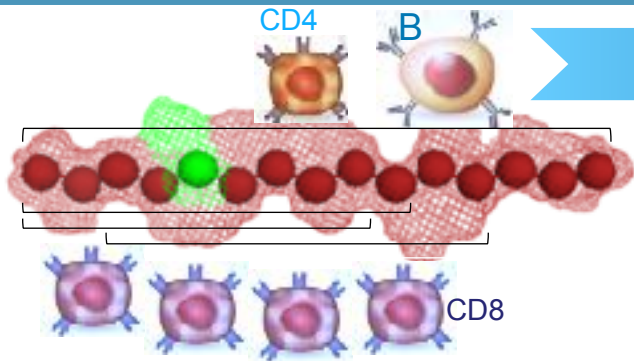
Approach: Immunotherapy

- Why I/O? Glioma doesn't metastasize. Control commonly fails from recurrence due to residual microscopic disease.
- Unique aspect to glioma. After resection, immune responsiveness temporarily returns to patients until the tumor recurs.



- Immunization creates an opportunity for an immune response to develop and prevent the progression of residual microscopic disease.

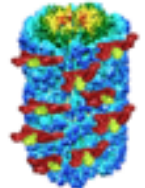
Immunogen: SurVaxM



SurVaxM

Robust Multi-Faceted Tumor Kill

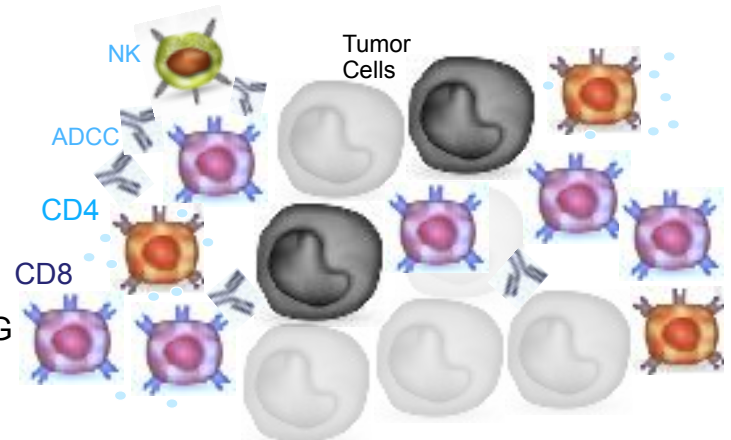
- CD8+ T cells are supported by tumor specific CD4+ T cells
- added antibody-specific mechanisms (ADCC, NK cells)



SurVaxM-KLH-construct

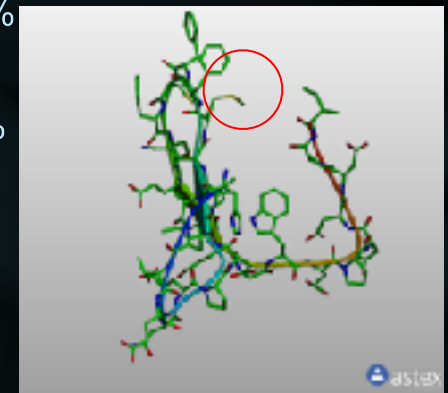
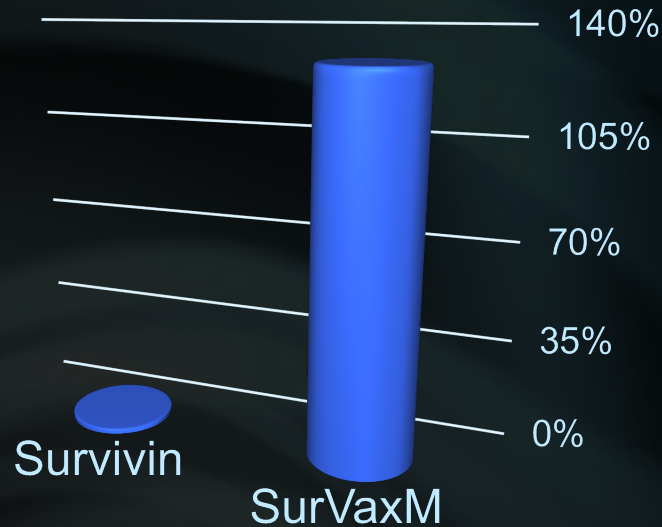
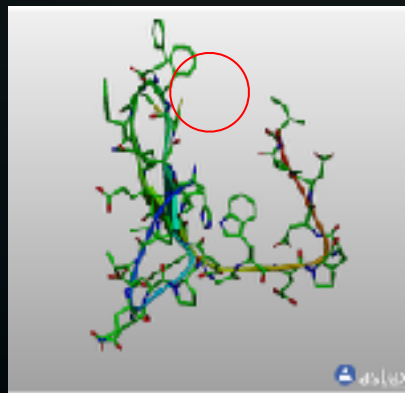
- SLP, reverse neo-Immunogen
- triggers **mid-affinity** TCR
- **confirmed multi** CD8+ T cell epitopes
- CD4+ T cell epitopes
- B cell recognition (Antibody)

- potent biological adjuvant
- high density immunogen
- Emulsified in Montanide ISA 51VG
- Adjuvant GM-CSF
- activates and matures DC



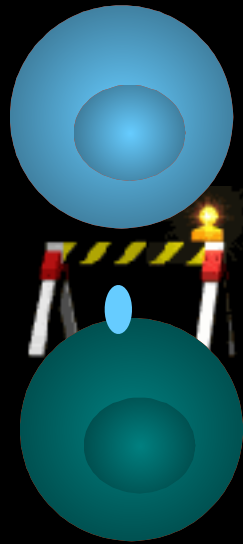
Discovered & Developed exclusively at RPCI

SURVAXM – ENHANCED MHC I BINDING



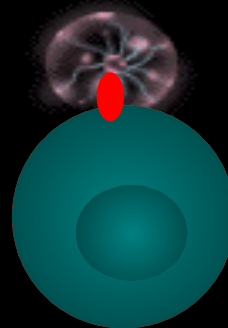
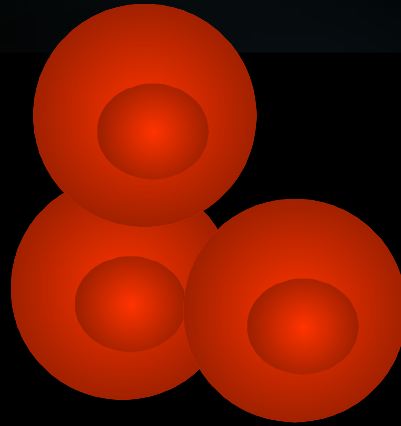
1. Mimic greatly enhances MHC-I binding (HLA-A*02)
2. SurVaxM stimulates a potent immune response
3. Immune response cross-reacts to wild type survivin in tumor cells

Stimulation of anti-tumor or auto-immunity



Normal Peptide
"Self"

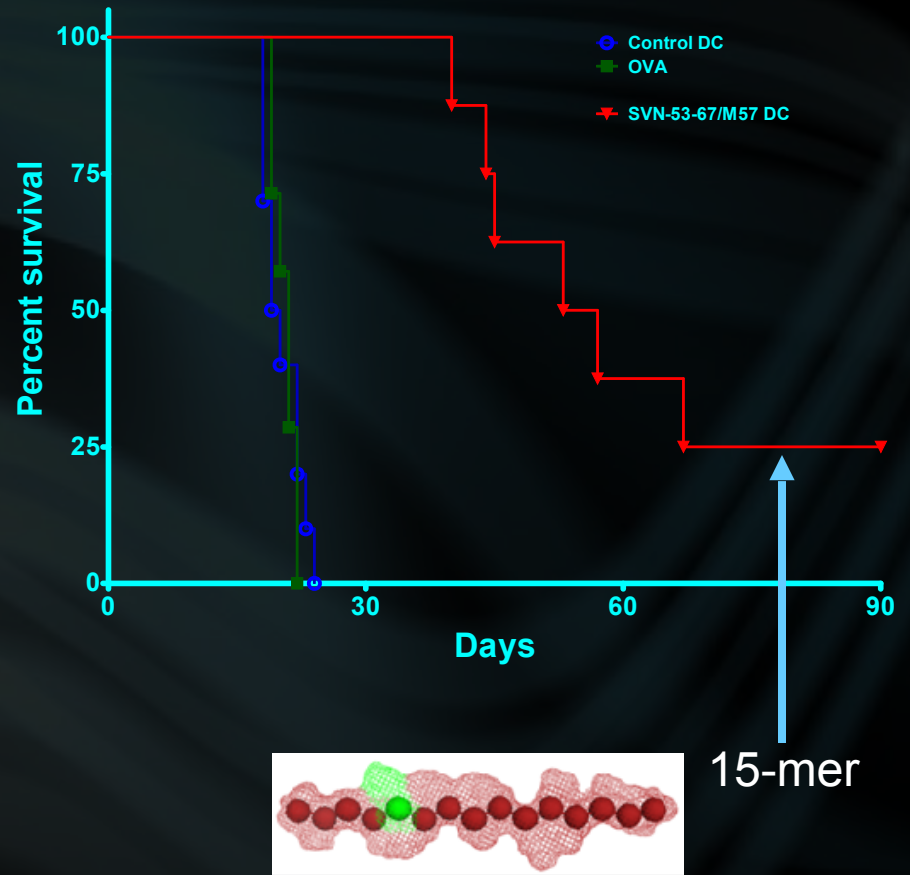
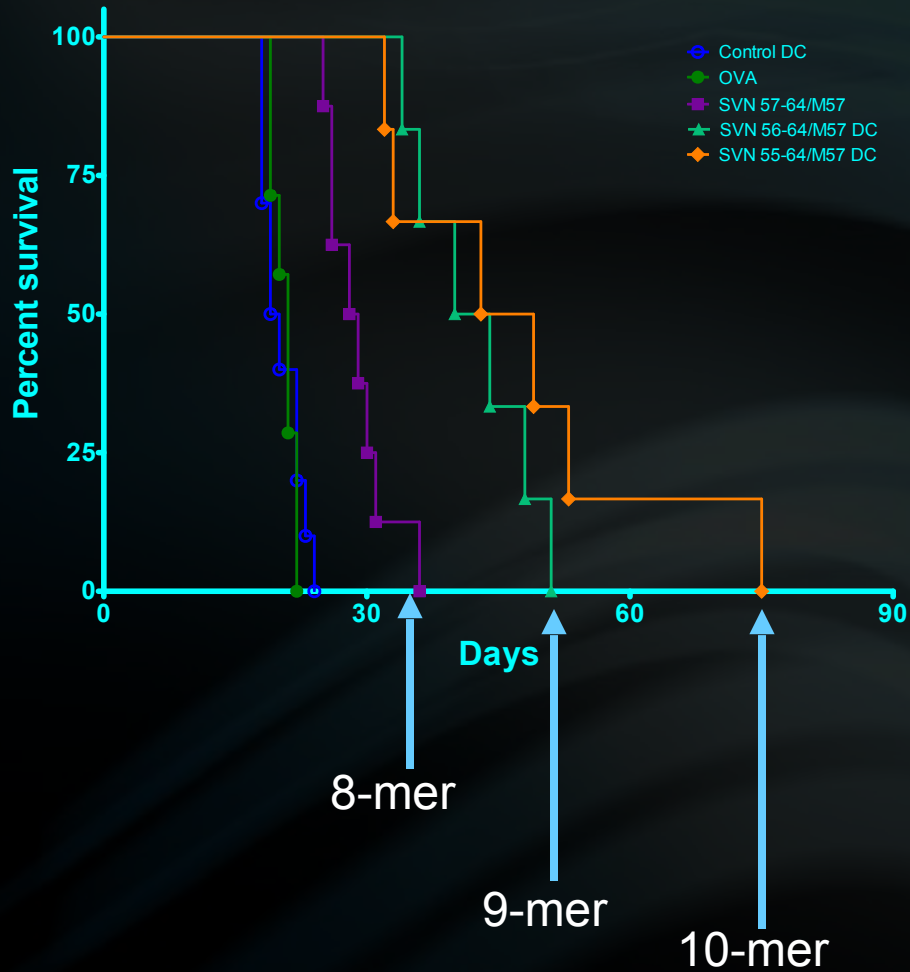
T cell receptors
(TCR) only detects
2-3 AA &
conformation



Slightly different peptide conformation.
Appears as
"Non-Self" & triggers inactive TCR, goal
is find one cross-reactive to "Self"

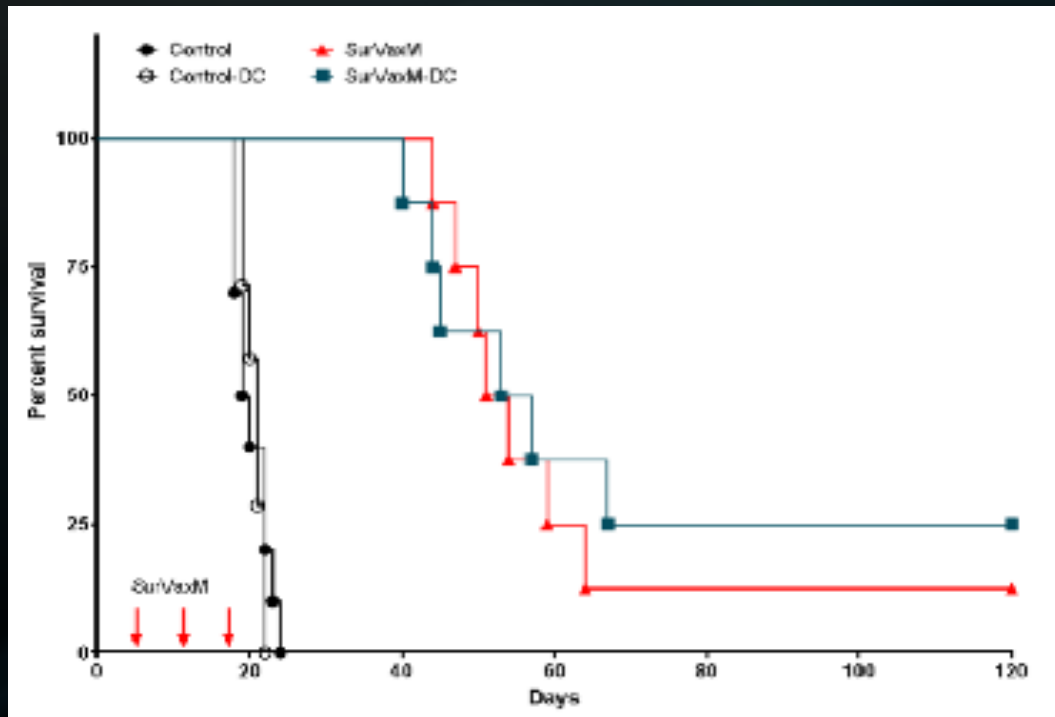
Normal Peptide
Now Recognized as
"Non-Self"

SLP Immunogen Design: Intracranial Glioma Survival Studies

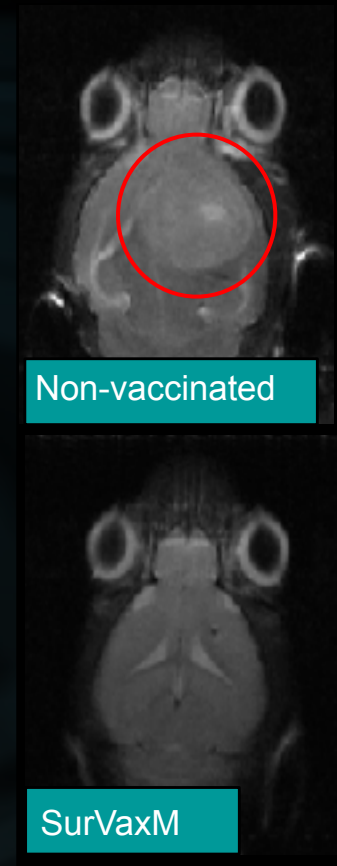


SurVaxM – Preclinical Efficacy Model in Glioblastoma

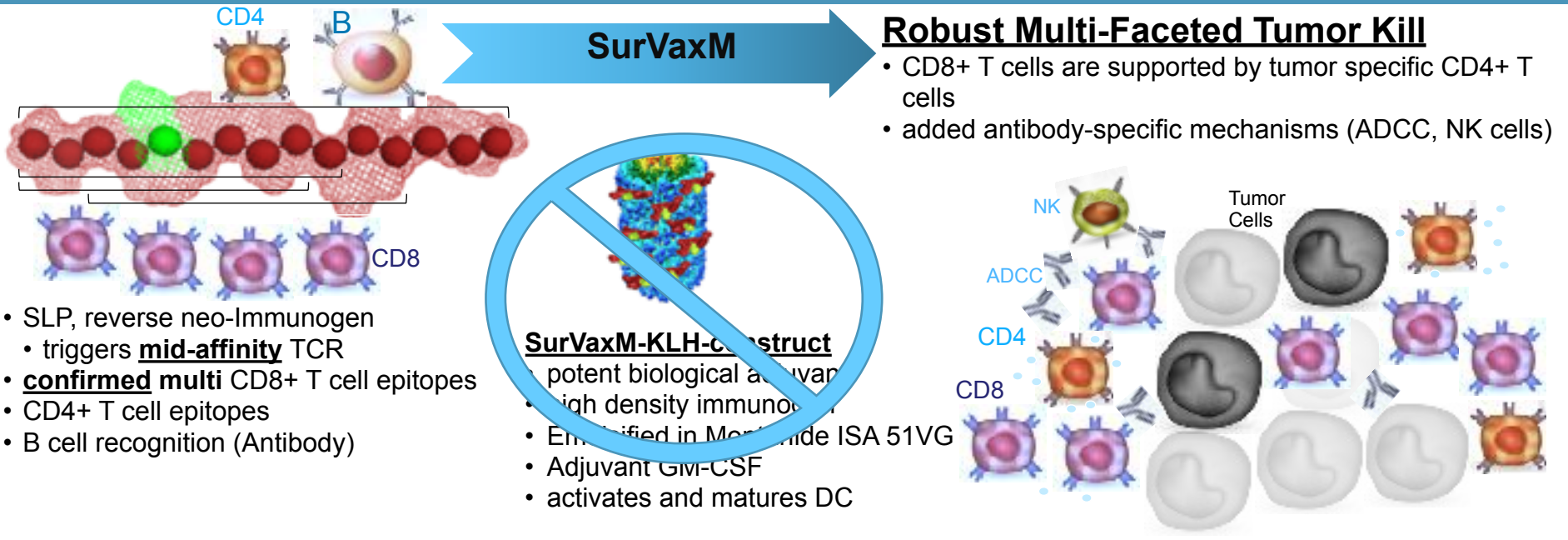
- Survival of C57BL6 mice intracerebral GL261 glioma



- Vaccination 4 days after tumor implant
- Injection once a week for 4 weeks
- $n=8$ each arm



Formulation Troubles: Remember the Process



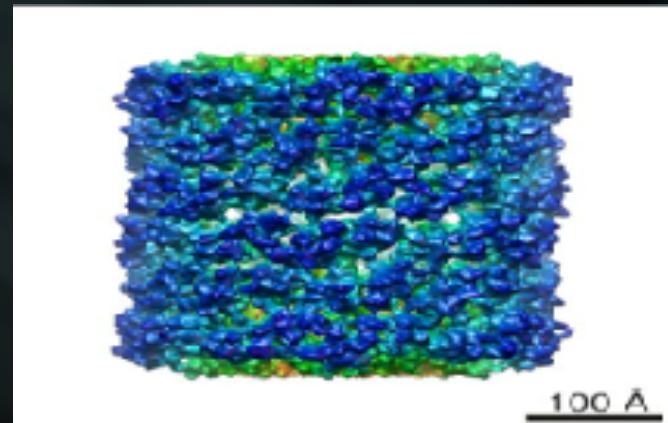
SurVaxM: Immunogen is a GMP cell-free lyophilized peptide, prepared emulsified in clinical grade Montanide ISA 51 VG, with clinically approved GM-CSF and injected subcutaneously.

Not enough to ensure final product is GMP, all components in production must be GMP as well

Clinical Hold?

- Non-GMP KLH
- Vaccine re-synthesis

Keyhole Limpet Hemocyanin



Everything must be GMP for clinical use



- Vaccine re-synthesis
 - Aquaculture KLH

Non-GMP KLH = \$60/gram



GMP KLH = \$18,000/gram

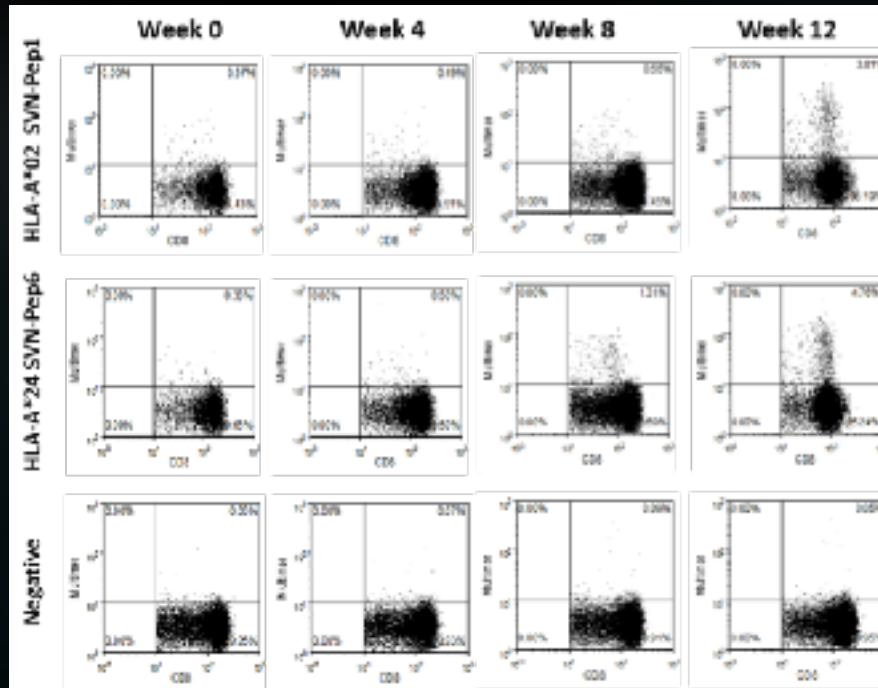
Step 4: SurVaxM Phase I Trial Design

(Phase I is to test SAFETY)

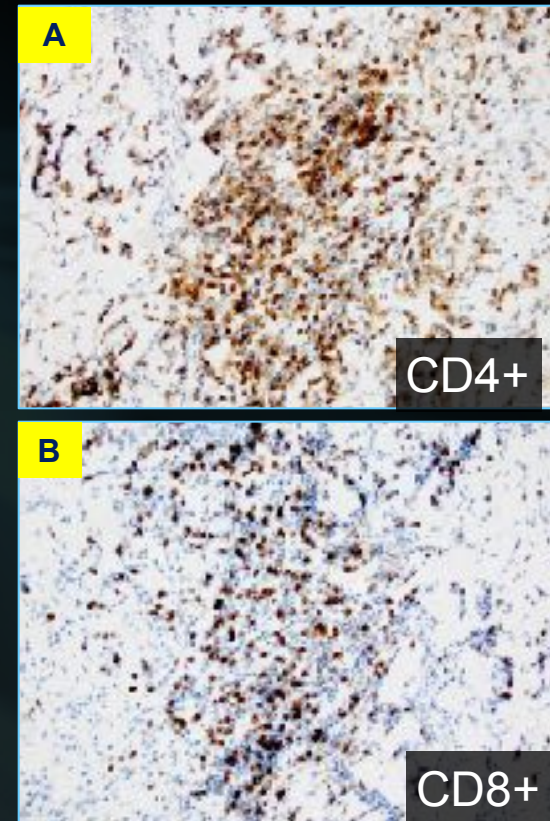
- Target confirmed: Survivin-positive recurrent malignant glioma
- Patient can react: HLA-A*02 and HLA-A*03
- Power: Single Arm of 9 patients (Safety is endpoint)
- Delivery & Dosage: 500µg, SubQ, Montanide & GM-CSF.
- Endpoints:
 - Primary: Toxicity, tolerability and immunologic effects
 - Secondary: PFS and OS
 - Tertiary: Radiologic response

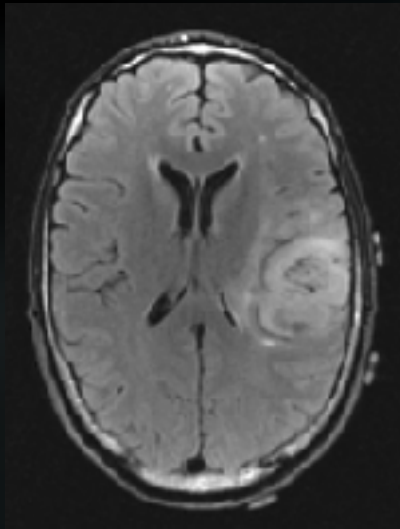


Phase I Results: Immunomonitoring



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

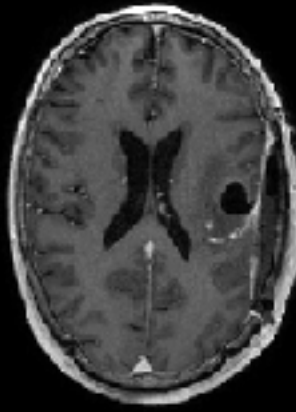




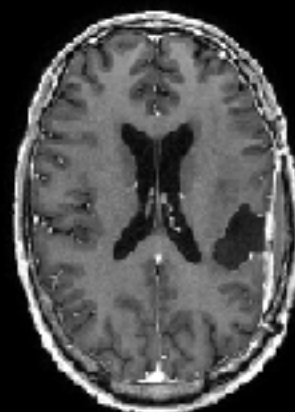
- 37 yo man with glioblastoma
- Surgery, XRT, temozolomide
- Recurrence after 5 months
- Re-resection and vaccine
 - Recurrence confirmed histologically



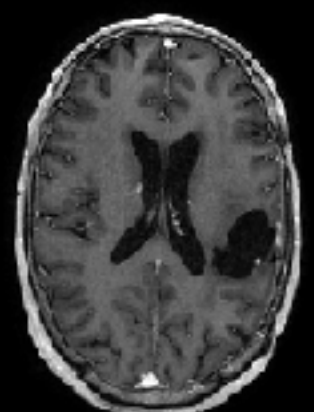
- R



L R



- R



6/12

Recurrence – 5 mo.
Post-op #1

8/12

Post-Op #2

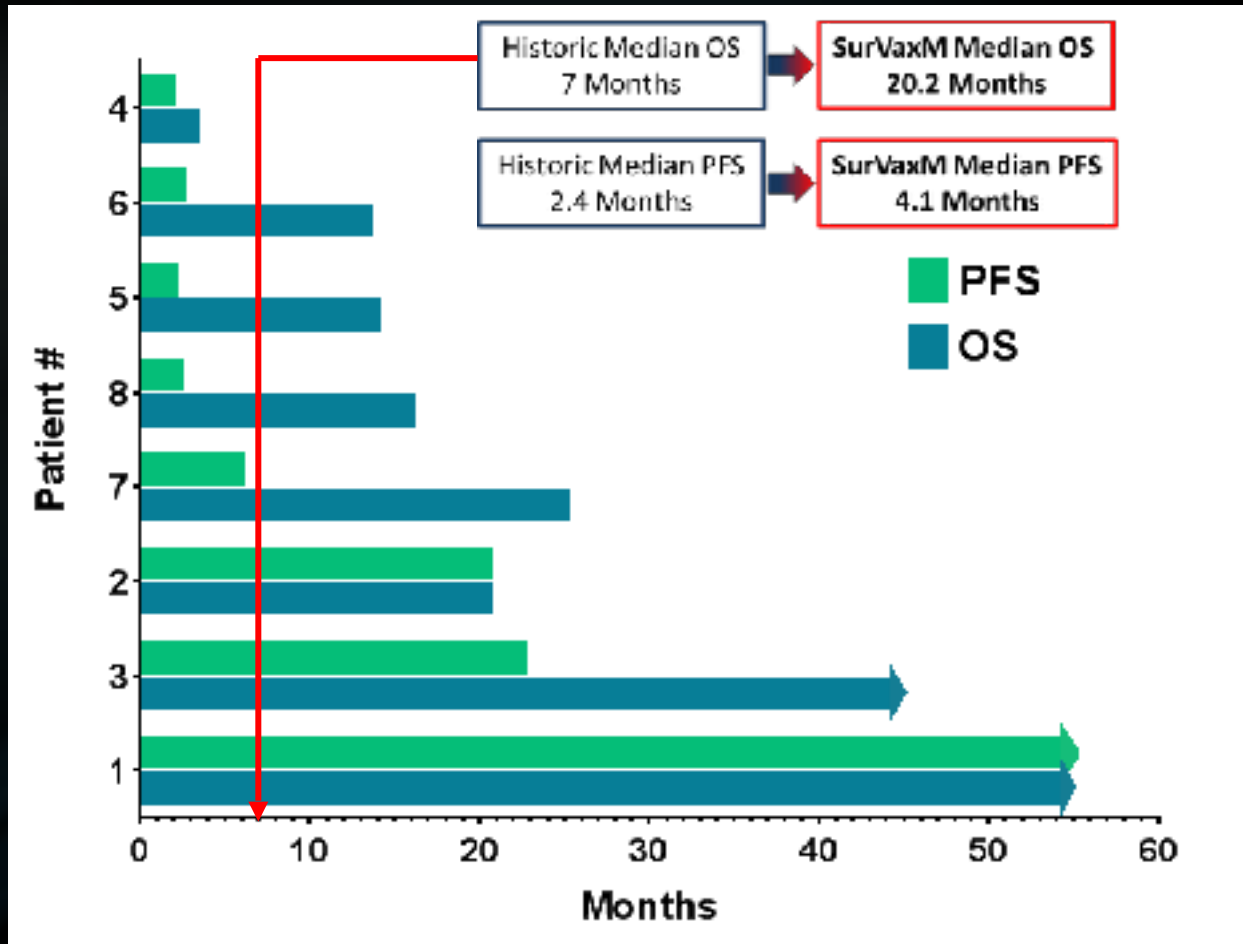
9/12

On-study

7/15

34-mo Post-vax

Phase I Results: PFS, OS of SurVaxM in Recurrent Glioma



7/8 Survived
> 12 months

2 alive
> 44 months

> 54 months

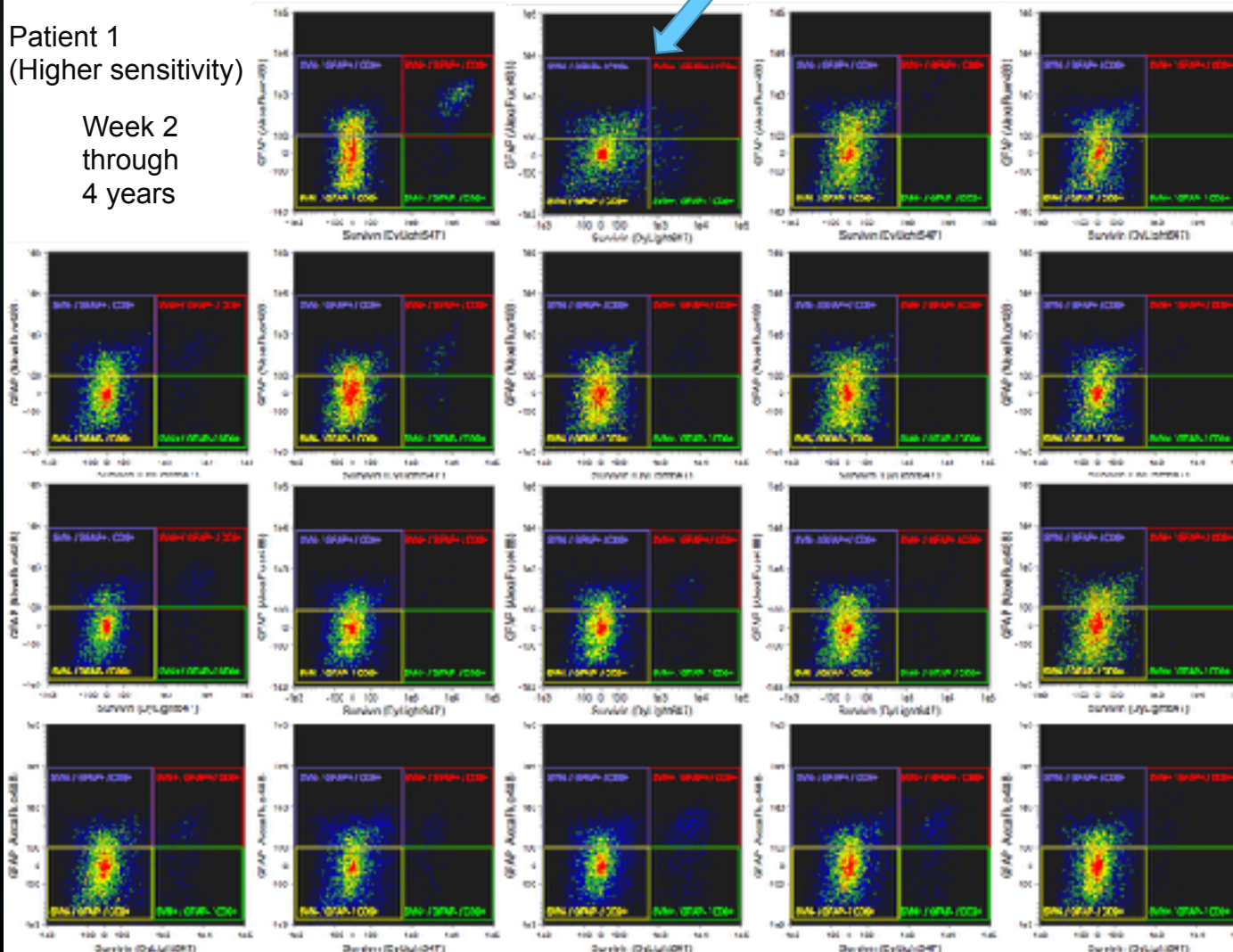
Phase I : Recurrent Glioma: Completed, Safe, non-toxic, signals of efficacy

Corollary Studies: What else can we learn from translational science? Biomarkers?: Exosomes GFAP:CD9:Survivin

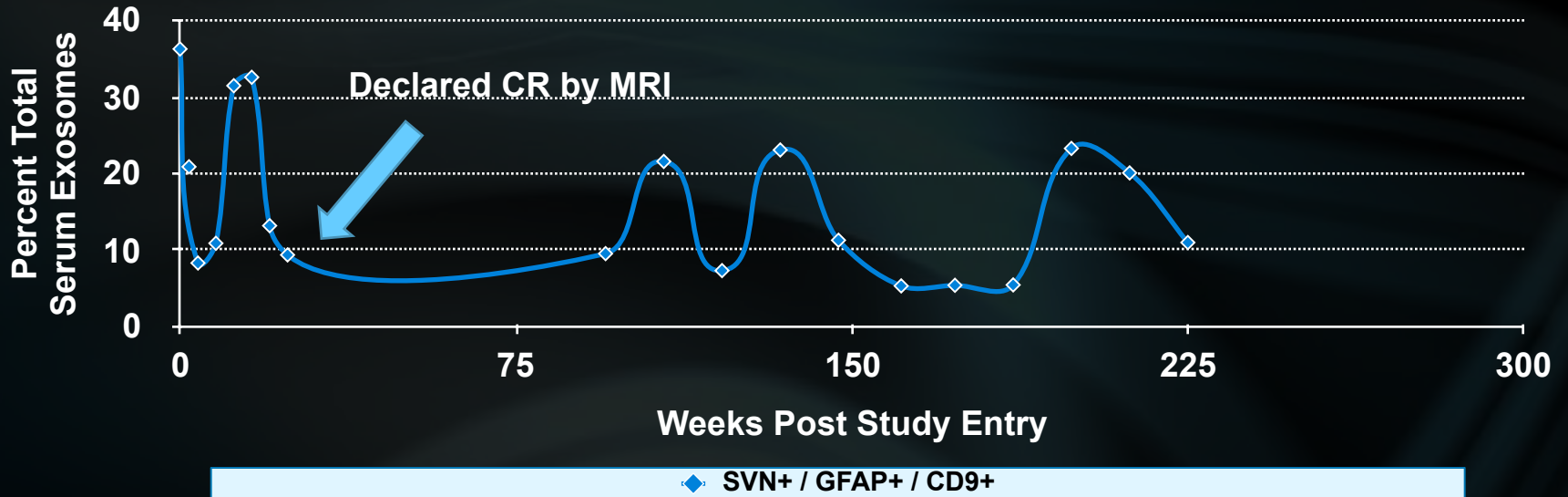
Immune Flare?

Patient 1
(Higher sensitivity)

Week 2
through
4 years

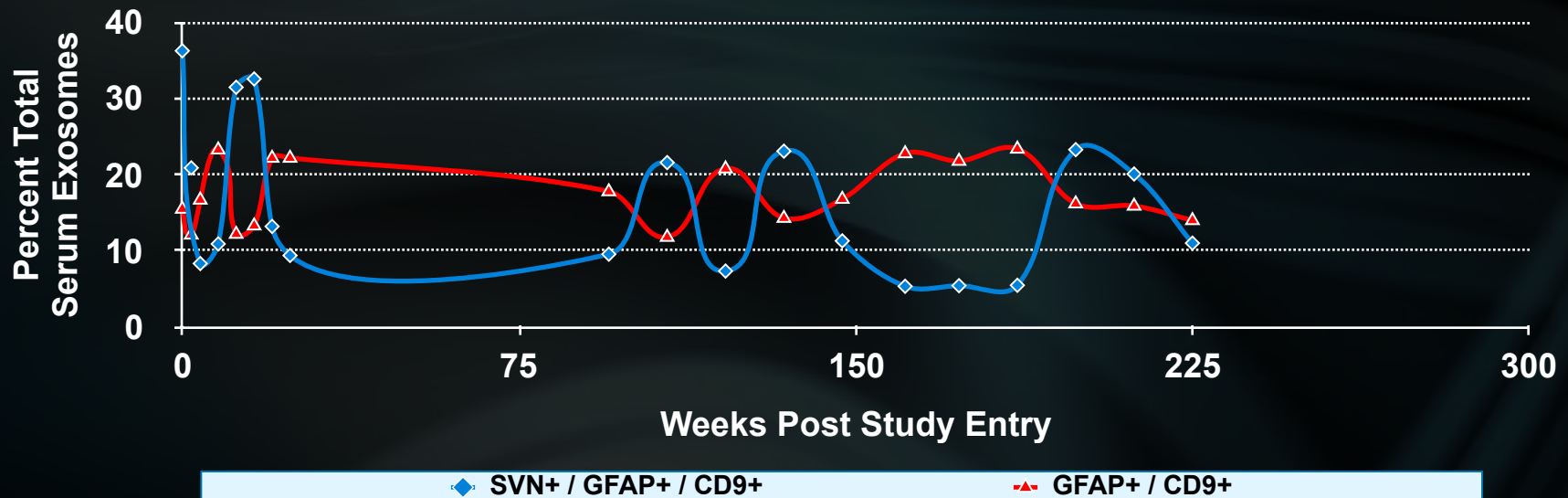


Phase I: GFAP:CD9: Survivin Exosomes



- In terms of immunity, an oscillating pattern of survivin exosomes appear over time

Phase I: GFAP:CD9: Survivin Exosomes



- Pattern of survivin positive exosomes is inverse of survivin negative exosomes
- GFAP expression on exosomes is present in both forms.
- Signaling possible pattern of micro-tumor growth/immune rejection?
- MRI negative throughout

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
- Might have found a new biomarker

Step 5: 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.

SurVaxM Phase II Design

- Power: 50 patients compared to historical arm
- Target: Newly diagnosed survivin-positive glioblastoma
- Dose/Delivery: Immunogen established in Phase I & SOC
- Reactivity: HLA-A*02, -A*03, -A*11 and -A*24
- Multi-Center: RPCI, Cleveland Clinic, Dana-Farber, Mass General, Beth Israel
- Endpoints:
 - Primary: 6 month PFS, OS & Safety
 - Historical comparison well defined (usually)
 - Secondary: OS, imaging, immune responses
- Submit protocol to FDA...wait 30 days and go...
- Currently recruiting, 39 of 50 patients have been enrolled

Step 6: 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.

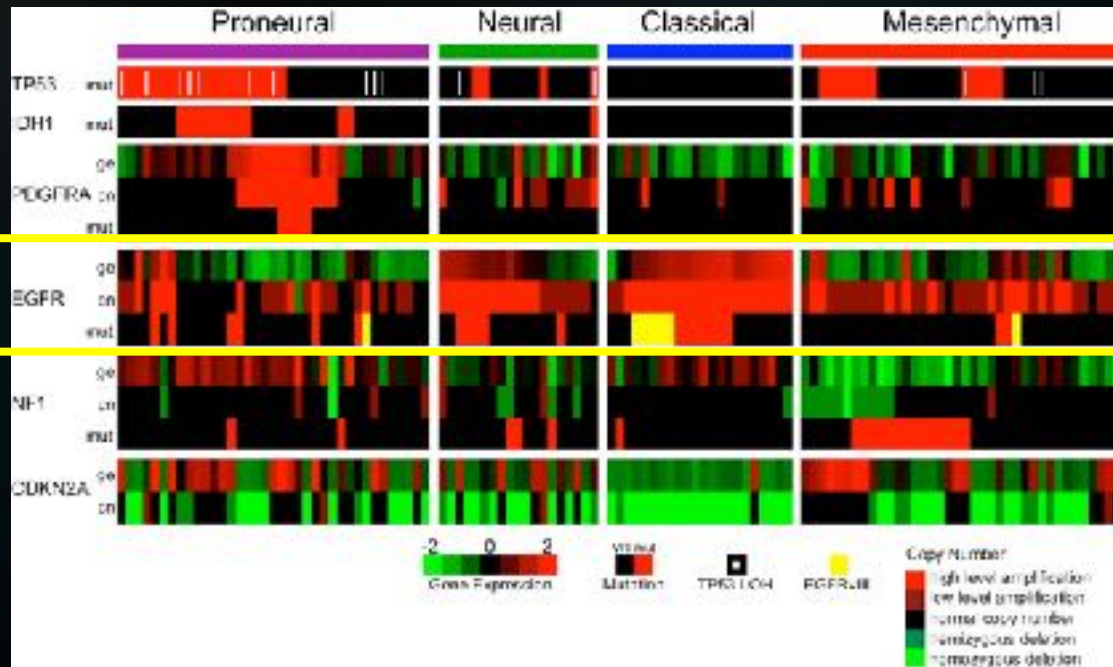


Celldex was informed of the failure of the Rintega phase III study known as ACT IV on Friday evening following an interim analysis conducted by independent data monitors. The study enrolled patients with a certain type of glioblastoma multiforme (GBM), an aggressive brain tumor.

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.

EGFRvIII...



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

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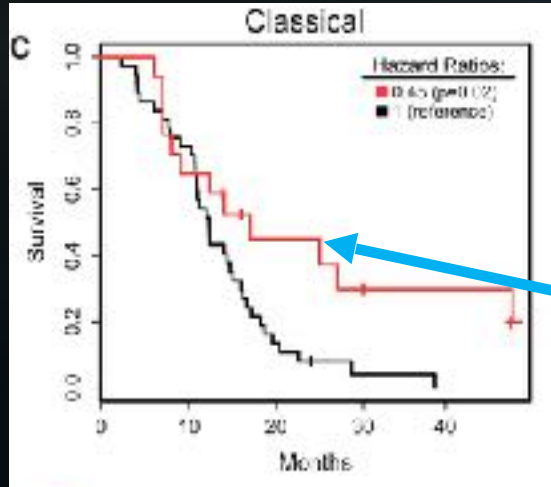
- “Glioblastoma” is a mix of 4 somewhat distinct molecular subtypes of tumors.

- wtEGFR amplification is a signature feature of GBM present in nearly 75% of cases, amplified in 40%.

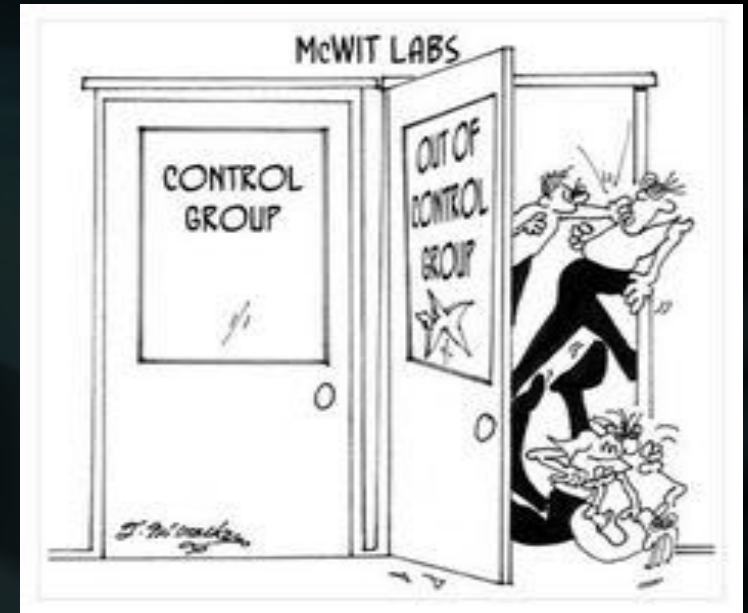
- Rintega failure: superselection for EGFRvIII (6% of GBM) compared to total population

...which selects for a much more favorable prognosis

Glioblastomas Receiving Treatment



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



The wrong trial design or bad patient population can kill a promising new agent

Recent Immunotherapy Success & Failures...

Biology or Design?

Dendreon: Provenge (Cellular Vaccine for Prostate Cancer)
4/29/2010 - APPROVED! - Cost too much, bankrupt...



Immunocellular: ICT-107 (Glioblastoma Peptide Immunogen)
1/27/2014 Fails Phase II...unforeseen HLA restriction...
6/2016 New trial design with HLA restriction started



Merck: Keytruda
2015-2017 – APPROVED! for NSCLC, Renal, Hodgkin's...



BMS: Opdivo
2015-2017- APPROVED! for Melanoma, Bladder, Renal...
8/5/2016 Fails Phase III for NSCLC?

Target: >5% PD-L1 expression
(Merck targeted >50% PD-L1)

4/4/2017 Fails Phase III for rec glioblastoma? vs only Avastin?



Steps 6 through 714: Not there yet...the Commercialization Process



Patents..... Foreign Patents...
Portfolio... Sub-license...

IP...



Take to market...

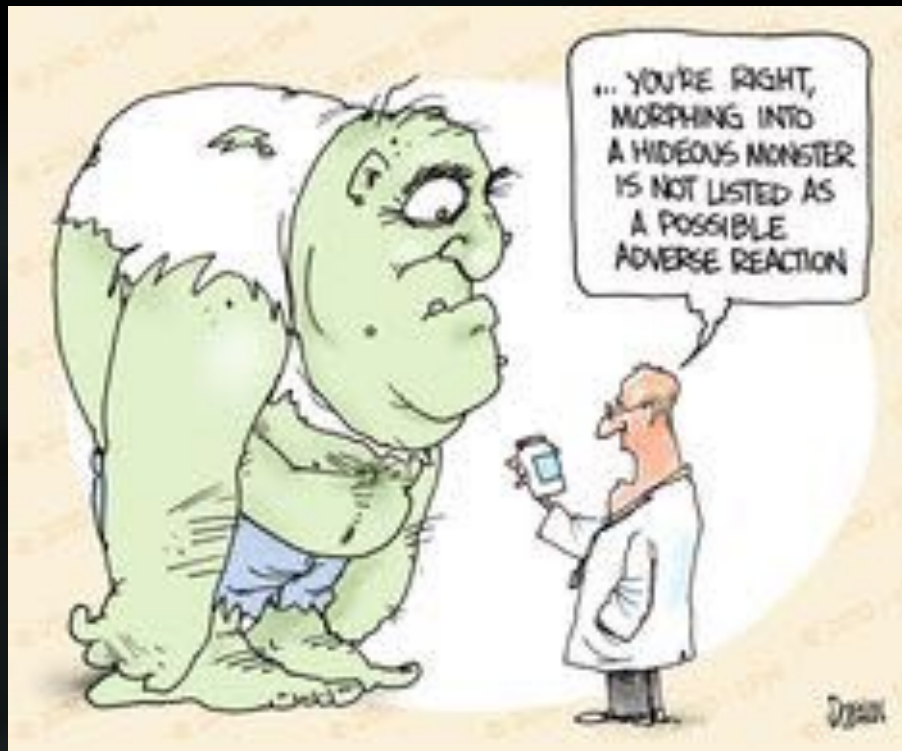
Sell...

Partner...

Go Public...

Invest...

Marketing...



Clinical translation is about efficacy & safety...

...but still needs to be properly designed!

