

# Vaccines

Dedicated to the Honor and Legacy of Dr. Ronald Herberman

SITC's Advances in Cancer Immunotherapy Regional Program  
in Pittsburgh



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# Disclosures

## Conflicts of Interests:

Hideho Okada, MD, PhD is an inventor of the IL-13R $\alpha$ 2 (345-353:1A9V) peptide, for which an exclusive licensing agreement has been executed with Stemline, Inc.

However, this presentation does not discuss anything related to this invention.



# Scope of Presentation

- Introduction for Cancer Vaccine
- Sipuleucel-T: an example of “passively personalized” vaccines
- Phase III study targeting MAGE A3: an example of “off the shelf” vaccines
- Glioma Actively Personalized Vaccine (GAPVAC)



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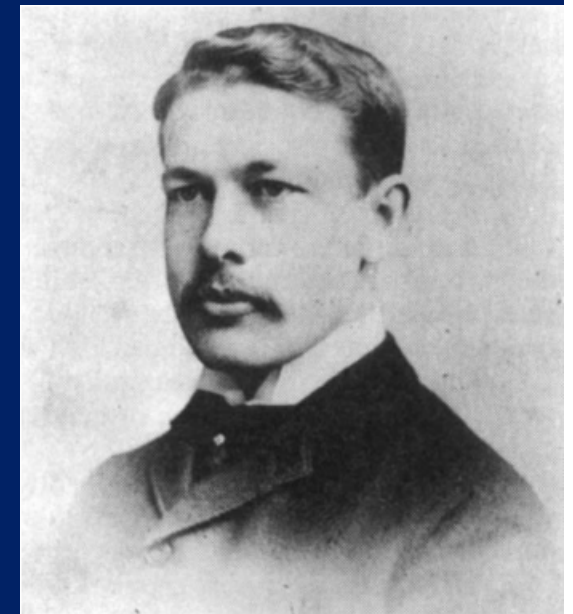
# What is Cancer Immunotherapy?

- The main premise is stimulating the patient's immune system to attack the malignant tumor cells. There are two fundamental concepts.
- 1) Immunization of the patient (**active immunotherapy: e.g. cancer vaccine**), in which case the patient's own immune system is trained to recognize tumor cells as targets to be destroyed.
- 2) Administration of **effector cells** or **therapeutic antibodies\*** as drugs, in which case the patient's immune system is recruited to destroy tumor cells by the therapeutic antibodies (**passive immunotherapy**).
  - \* Some argues that checkpoint blockades, such as anti-CTLA4 and anti-PD1/PD-L1 as “active” immunotherapeutics, which I agree.



# History of Cancer Vaccines

- Observations of a relationship between infection and cancer regression date back to at least the 18th century.
- **Coley's vaccine** or Mixed Bacterial Vaccine is a **mixture consisting of killed bacteria of species** *Streptococcus pyogenes* and *Serratia marcescens*, named after William Coley, a surgical oncologist who developed the mixture in the late 19th century as a treatment for cancer.



# Cancer Vaccines

- The term cancer vaccine refers to a vaccine that either prevents infections with **cancer-causing viruses** (e.g. HPV vaccine for cervical cancers), or treats **existing cancer or prevents the development/progression of cancer** (Therapeutic cancer vaccines)
- As of 2013 there are two approved prophylactic cancer prevention vaccines. These are for the cancer causing viruses HPV and HBV.
- A big question – **can immune system target cancers that are NOT induced by viral or bacterial infection?**





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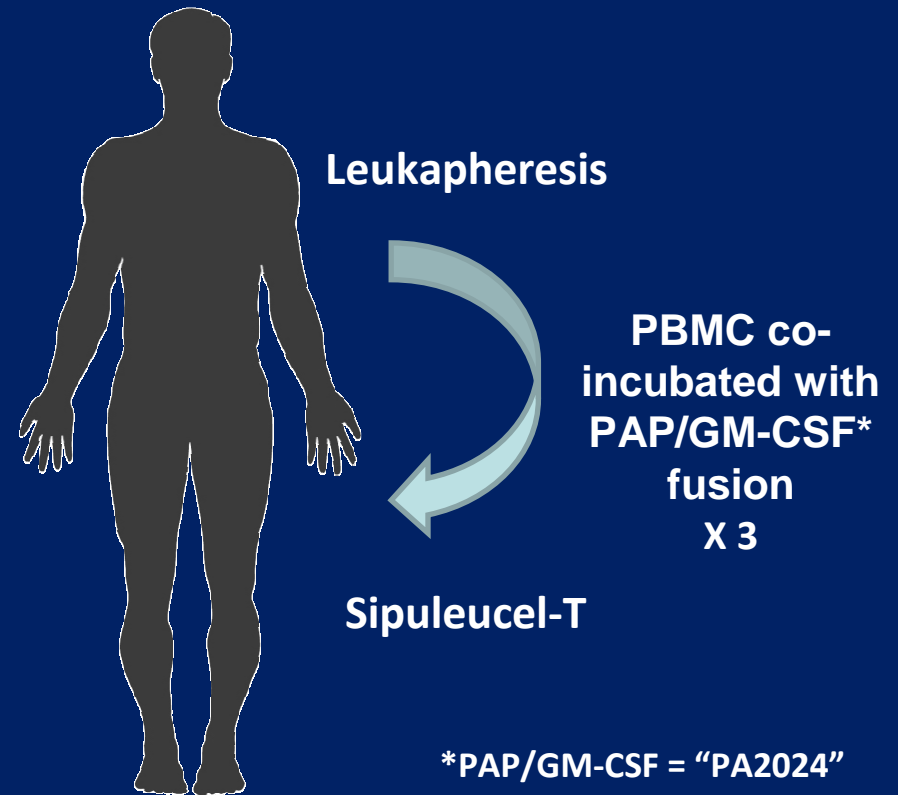
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# Sipuleucel-T

- Sipuleucel-T: an autologous cellular immunotherapy targeting prostate cancer
- Patient-derived peripheral blood mononuclear cells are co-cultured with **Prostate Acid Phosphatase (PAP)-GM-CSF fusion protein**.
- Cultured cells are reinfused.



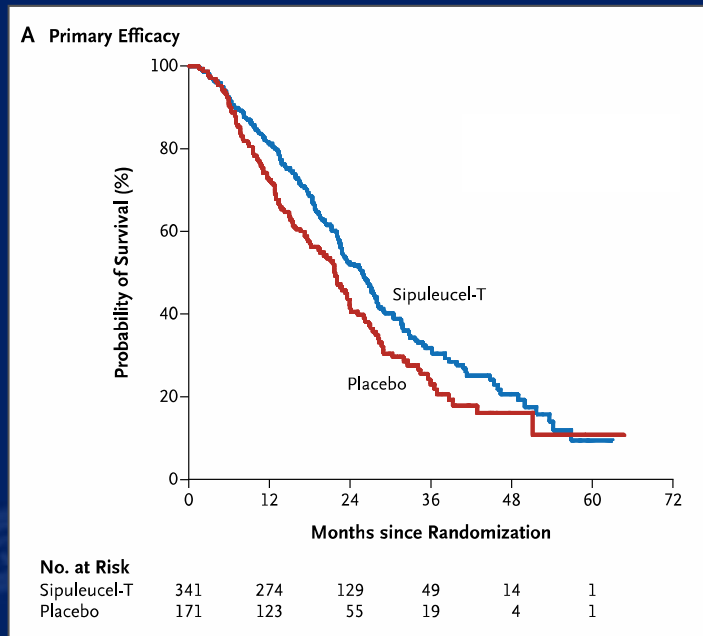
Courtesy of Dr. Laurence Fong (UCSF)

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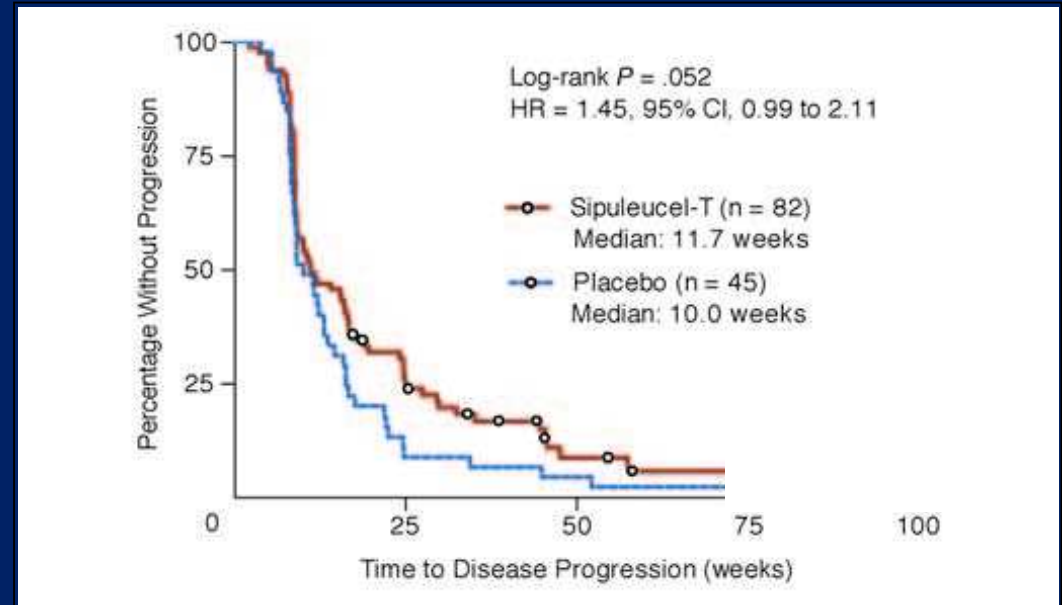


# Sipuleucel-T improves overall survival in patients with metastatic castration resistant prostate cancer (CRPC)

## Overall Survival



## PFS



In April 29, 2010, the FDA approved this as the first vaccine against non-viral cancer for asymptomatic or minimally symptomatic metastatic CRPC.



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# Challenges

- Costly therapy
- Progression while undergoing treatment
- Other therapies (abiraterone and enzalutamide can induce clinical responses)
- Future directions: Combination therapies...
  - Sip-T/Abiraterone
  - Sip-T/Ipilimumab
  - Sip-T/IL-7



Courtesy of Dr. Laurence Fong (UCSF)

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# GSK MAGE-A3 Vaccine

- MAGE-A3 antigen is present only on particular cancers:
  - NSCLC (1/3)
  - Melanoma (3/4)
  - Bladder cancers
  - Myeloma
  - Esophagogastric cancers
- Recombinant protein mixed with adjuvant (GSK uses the term antigen-specific cancer immunotherapy (ASCI) rather than cancer vaccine)



## A double-blind, randomized, placebo-controlled Phase III of recMAGE-A3+AS15 (“cancer immunotherapeutic”) in patients with MAGE-A3 positive resected stage III melanoma (DERMA)

- Expressed in about 65% of Stage III melanomas.
- MAGE-A3 cancer immunotherapeutic consists of recombinant MAGE-A3 protein and a novel immunostimulant AS15 (a combination of QS-21 Stimulon® adjuvant, monophosphoryl lipid A, and CpG7909, a TLR-9 agonist, in a liposomal formulation).
- Evaluated the efficacy and safety in Stage IIIB/C melanoma patients with macroscopic nodal disease, whose MAGE-A3+ tumors had been surgically resected.



## A double-blind, randomized, placebo-controlled Phase III of recMAGE-A3 + AS15 in patients with MAGE-A3 positive resected stage III melanoma (DERMA)

- The study did not meet its first co-primary endpoint as it did not significantly extend disease-free survival (DFS) when compared to placebo in the MAGE-A3 positive population.
- In line with the Independent Data Monitoring Committee's unanimous recommendation, GSK will continue the DERMA trial to assess the second co-primary endpoint, which is DFS in the gene signature positive sub-population. This is to identify a subset of MAGE-A3 positive patients that may benefit from the treatment (An 83 gene expression signature; Ulloa-Montoya F et al. J Clin Oncol. 2013 ). Results from this analysis are expected in 2015. Until then, GSK will remain blinded to all safety and efficacy data.
- GSK is continuing to evaluate the same drug in another independent Phase III study (MAGRIT) in Non Small Cell Lung Cancer (NSCLC) following surgical removal of the primary tumor with first data anticipated in the first half of 2014.



<http://www.gsk.com/media/press-releases/2013/the-investigational-mage-a3-antigen-specific-cancer-immunotherapy.html>

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# Glioma Actively Personalized Vaccine Consortium (GAPVAC)

- 14 organizations in Europe and the US join forces to develop a completely novel approach to fight cancer.
- The consortium will be led by Immatics biotechnologies GmbH (Coordinator) and BioNTech AG (Vice Coordinator).
- Multi-national clinical trial treating glioblastoma patients with **fully personalized therapeutic vaccines** planned to start in 2014
- European Union supports GAPVAC with 6 million EUR



# Issues in the Current Forms of Glioma Vaccines

- Current “Universal” vaccines, such as use of peptides for “shared antigens”.
  - Never know whether each patient’s tumor express any or all of the targeted antigens
- Current “Personalized” vaccines, such as the use of autologous whole glioma cells.
  - Risks for inducing autoimmune responses to the normal brain cells because glioma cells express both tumor specific and non-specific proteins.



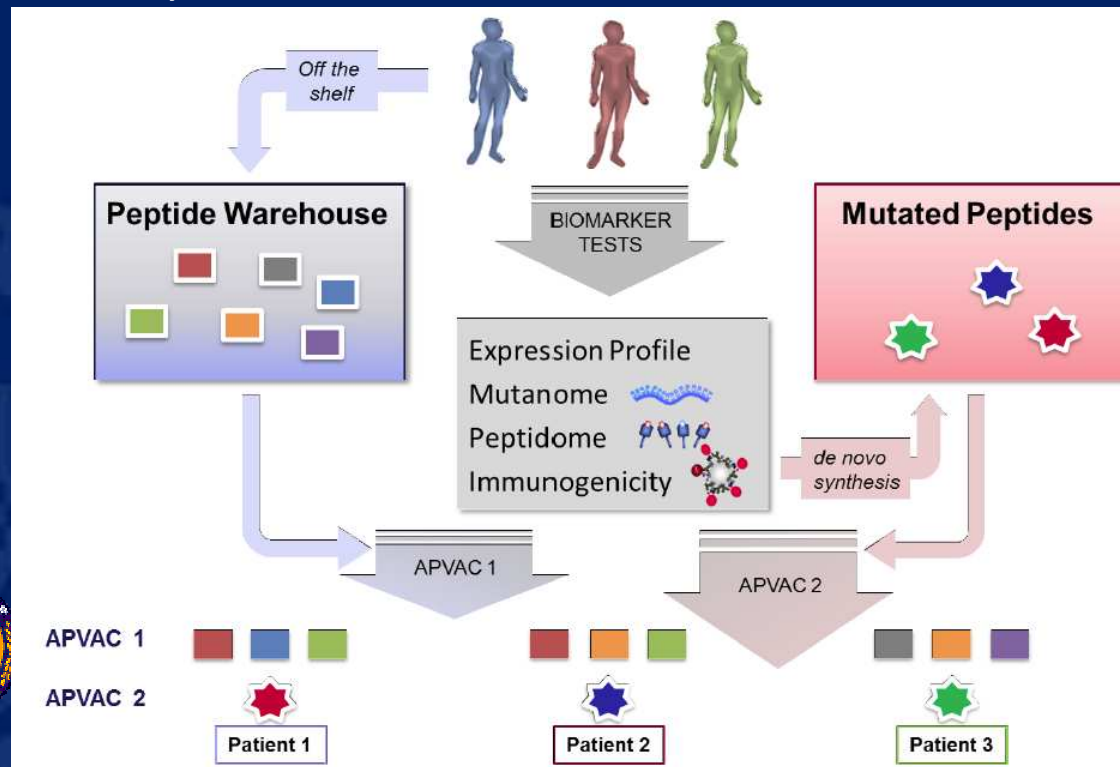
# Ideally “personalized” vaccines should

- Truly reflect each patient’s own gene-expression and mutation status.
- Not include antigens from normal brain cell components.
- Not neglect patients who are negative for the “biomarker” (such as HLA-A2)



# Two sorts of personalized antigen peptides

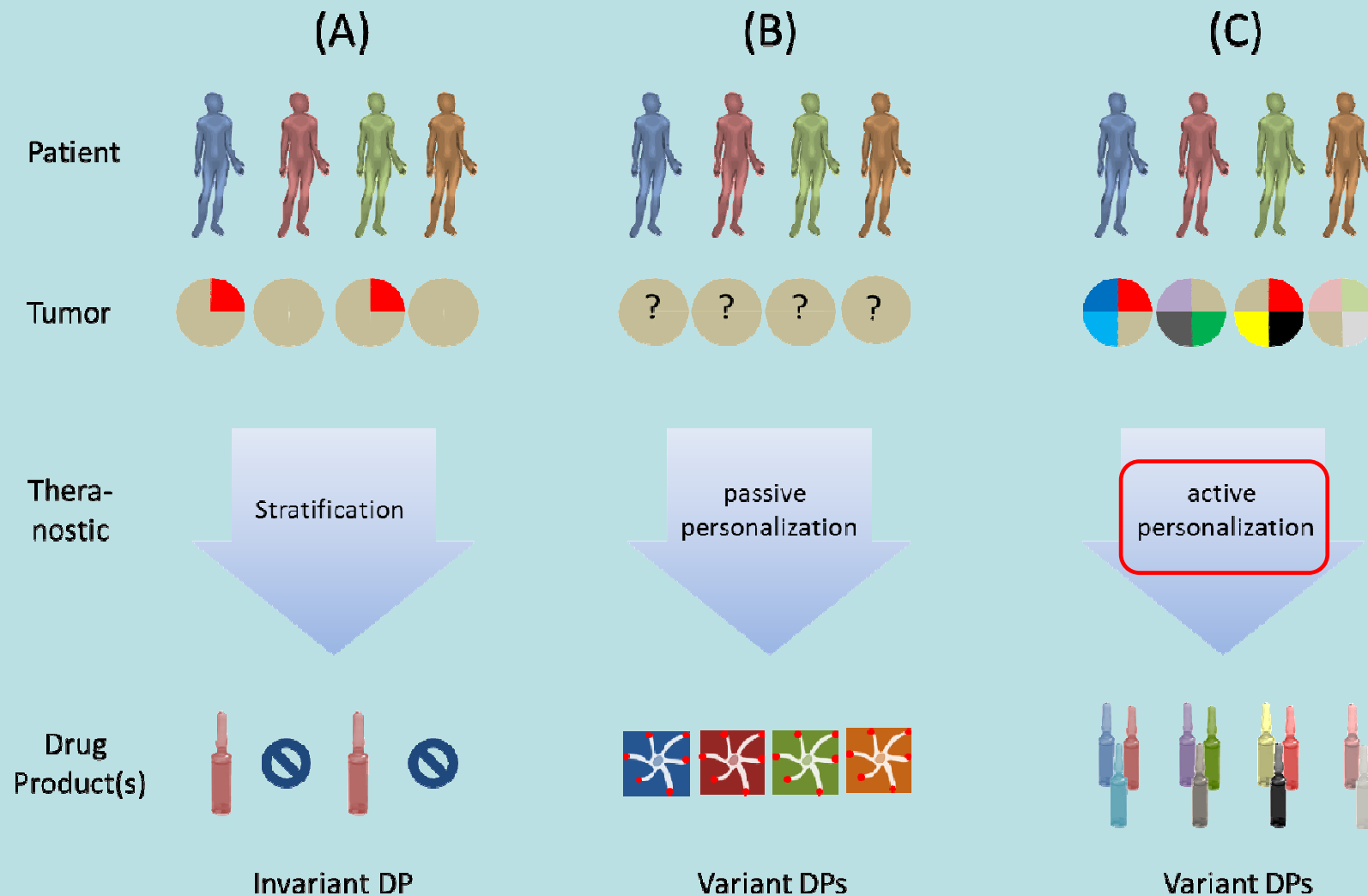
- **Tumor-associated peptides highly overexpressed in the tumor tissue of a particular patient.**
- **Tumor-specific mutated peptides.** Cancer genome instability and subsequent selective pressure leads to the accumulation of tumor mutations. Thus mutated peptides are also exclusively expressed on HLA molecules on tumor but not on healthy cells and therefore are not expected to induce immunological tolerance or auto-immunity.



Courtesy of Immutics  
Biotechnologies,  
GmbH



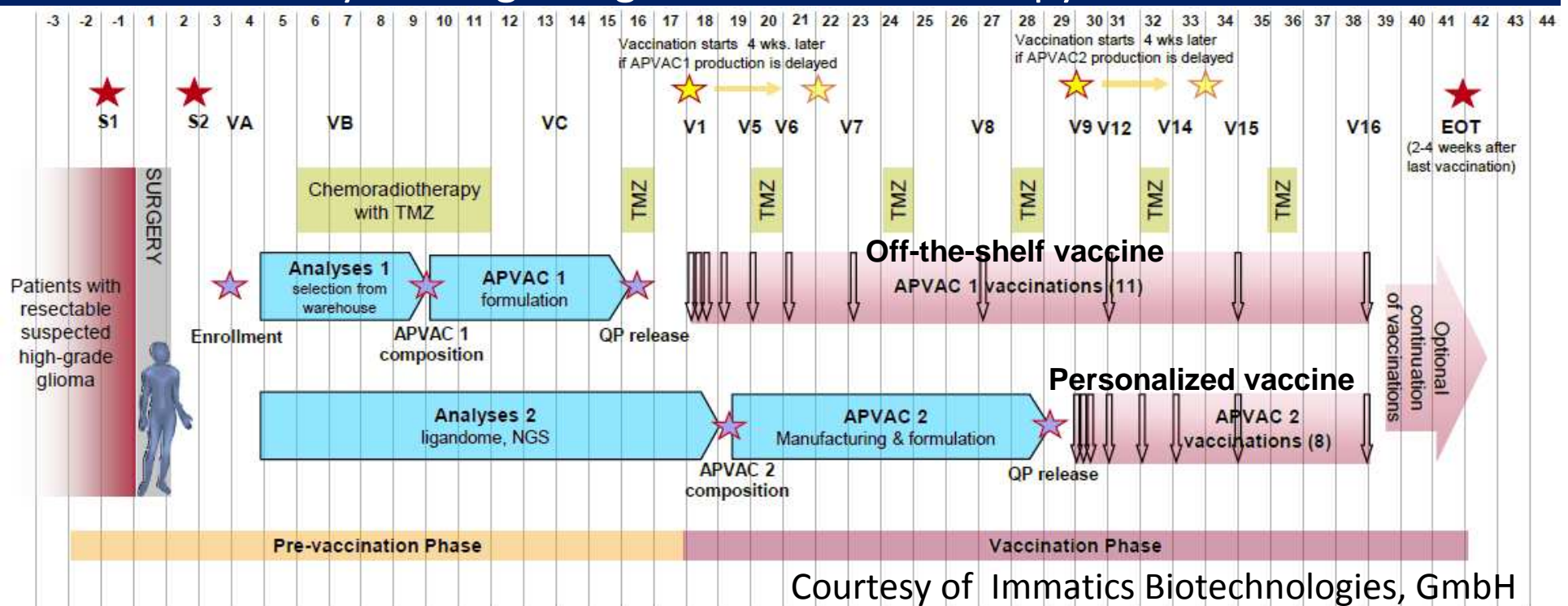
# Three levels of personalisation



Courtesy of Immatics  
Biotechnologies, GmbH

# Schema for the phase I study in glioblastoma

- The preparation of a personalized GBM vaccine is estimated to **take less than 5 months**, but this duration can be significantly shortened with the ongoing progress of technologies.
- During this waiting period HLA-A2-negative patients will receive standard therapy, HLA-A2-positive patient will receive standard therapy and off-the shelf vaccinations for shared antigens. About **70% of patients are expected to be stable** by the beginning of the vaccine therapy.





# Conclusions

- Sipuleucel-T represents the only FDA approved vaccine for treating cancer.
- The path to vaccine development is complicated by:
  - Complex biology
  - Challenging endpoint
- Multiple vaccines have progressed to phase 3 trials
- Combination therapies with vaccines are currently being explored.



Courtesy of Dr. Laurence Fong (UCSF)

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I am stopping my talk



- though our work will never stop at any time!  
THANK YOU!

