Fast and cost-effective oral delivery technology of personalized T-cell vaccines based on a live attenuated bacteria platform

April 26, 2018

European
NEOANTIGEN
Summit
Supercharging Immunotherapies
& Cancer Vaccines

VAXIMM

How can we overcome manufacturing challenges in personalized neoantigen-targeting approaches ?

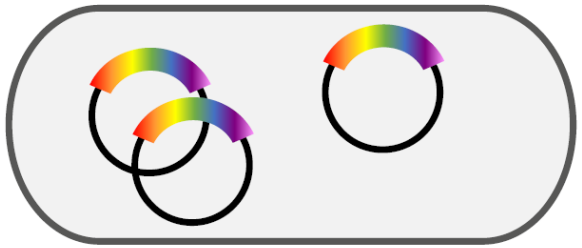
- Delivery platform
- Neoantigen targeting personalized approaches
- Manufacturing features
- Technical and immune proof of concept in animals
- Platform clinical proof of concept by lead product

Delivery Platform

Unique Ty21a Platform with Broad Potential
… for systemic antigen-directed T-cell activation

Bacterial carrier (Ty21a)…

- Live attenuated vaccine strain
- Approved travelers' vaccine (typhoid fever, Vivotif®)
- Oral vaccine naturally infects cells in the gut
- Applied >250 million times
- Excellent safety record and well tolerated

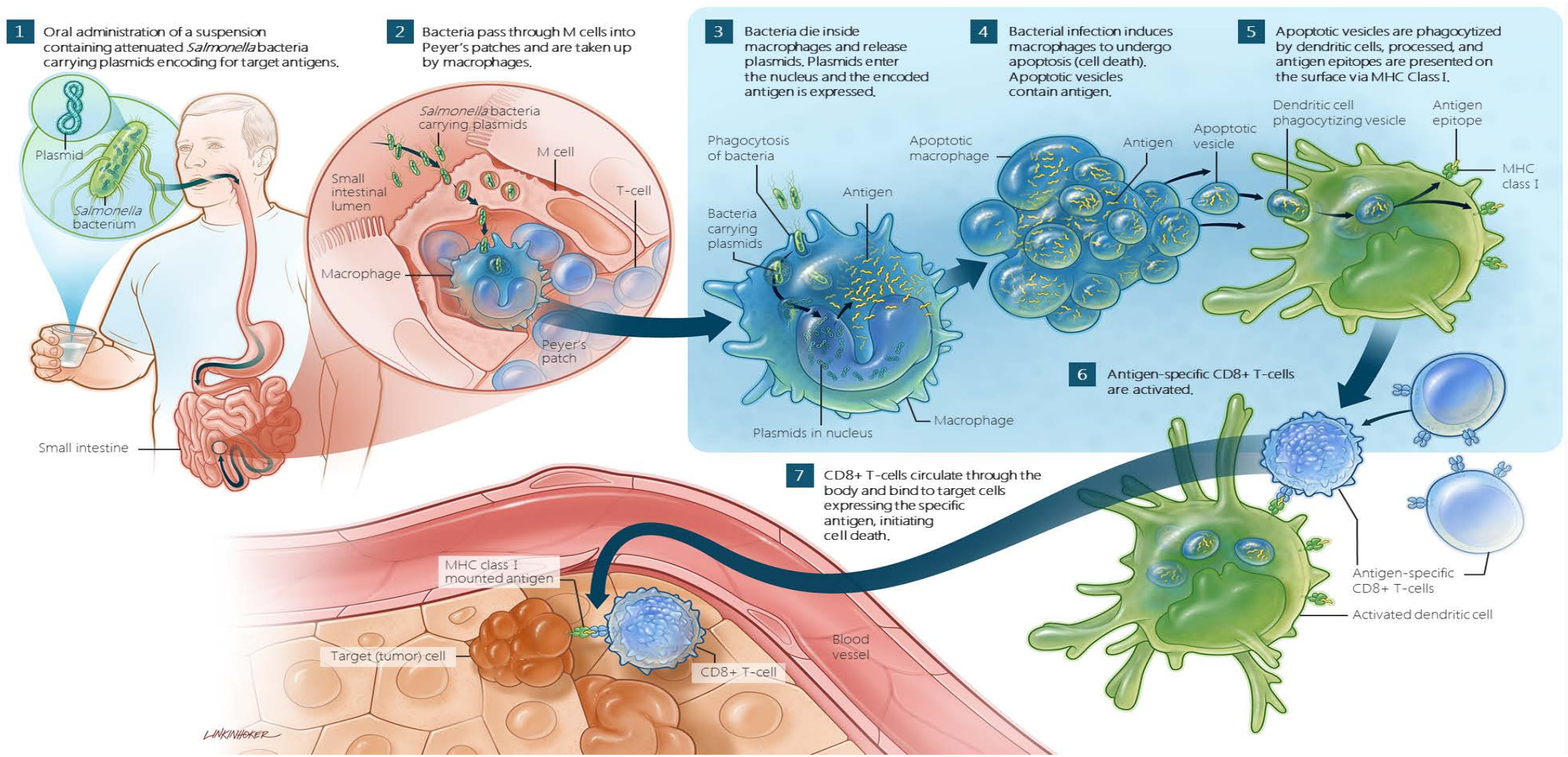


… containing eukaryotic expression plasmids

- Encoding the cDNA of the desired targets
- Plasmid is dormant within the bacterial carrier
- Drives strong expression of target antigen in infected cells within the patient's Peyer's patches
- Clinical safety/ immunogenicity/ efficacy demonstrated with a VEGFR-2 construct (VXM01) in pancreatic cancer and glioblastoma
  - VEGFR-2 consisting of 1356 amino acids corresponding to appr. 4000 base pairs

Intra-lymphatic Delivery via Oral Administration

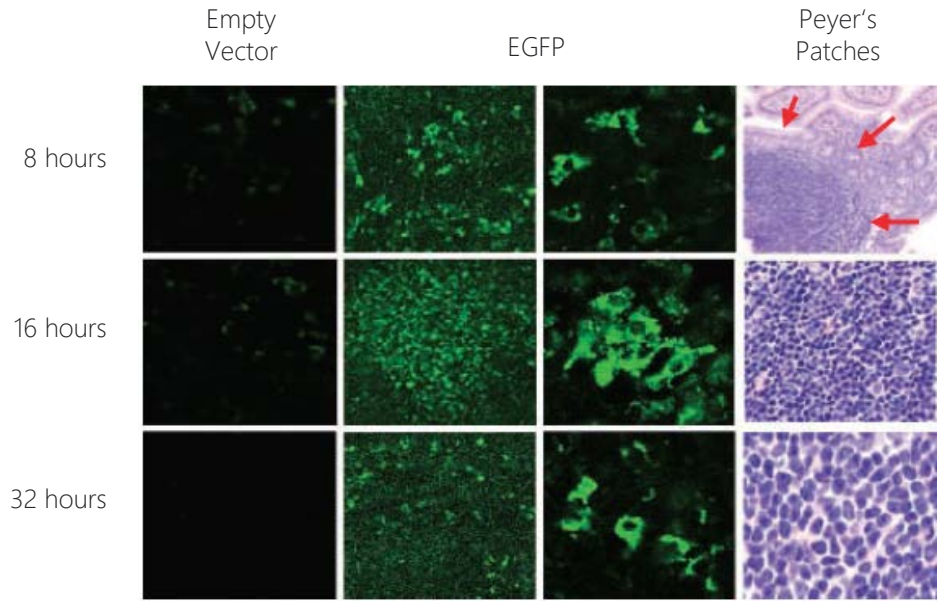
… leading to systemic target specific T-cell activation



Confirmation of Mechanism of Action

… transient antigen expression and T-cell homing

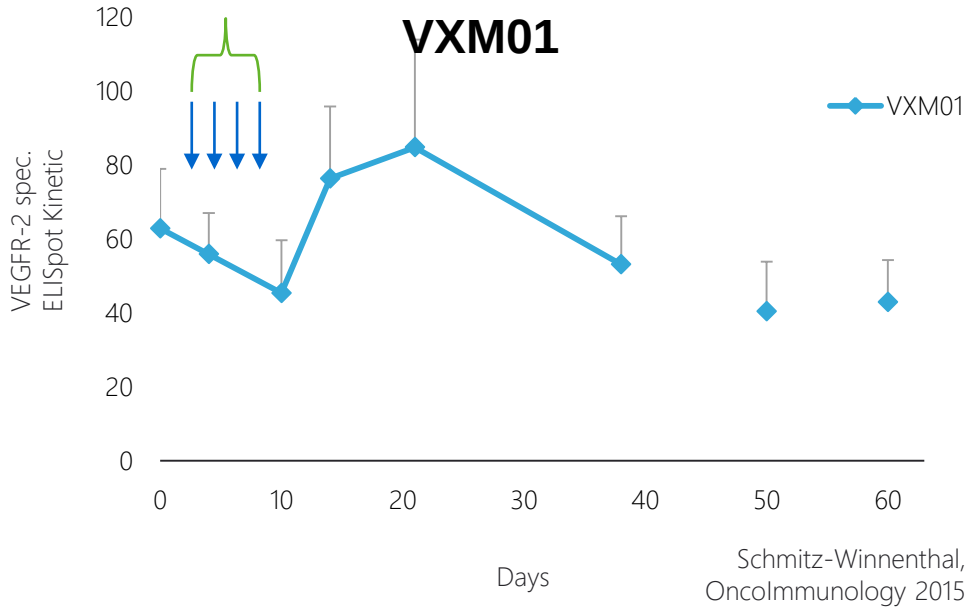
Transient EGFP antigen expression in mouse Peyer's patches



Xiang, Canc Res 2005

Transient homing of human antigen-specific T-cells to immunization site without boosting

Homing period up to 3 days after last vaccination

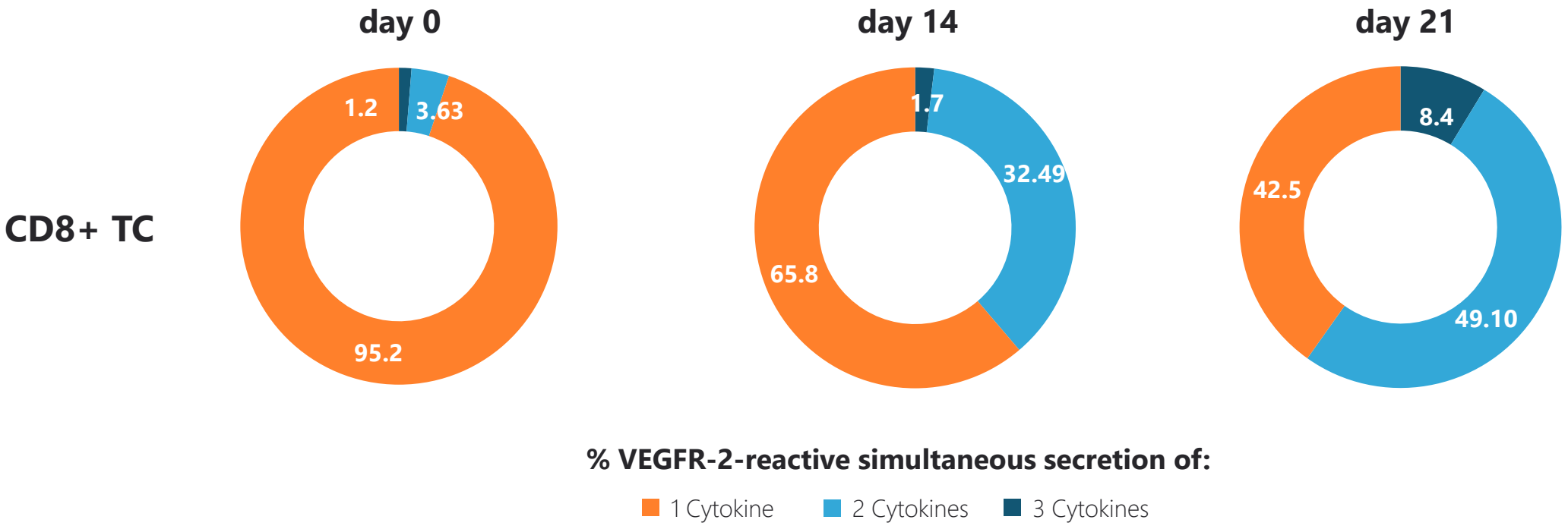


Schmitz-Winnenthal, OncoImmunology 2015

T-cell Activation in VXM01-treated Patients

… can produce multi-functional T-cells

CD8+ T-cells secreting multiple cytokines demonstrate stronger activation



Representative patient, Schmitz-Winnenthal et al., OncoImmunology2015

Proprietary Platform
… with key differentiating features

Natural, efficient & easy way to activate T-cells

Strong transient antigen expression allowing specific T-cells to target the tumor

- Oral delivery targeting the lymphatic tissue of the gut
- Repeated dosing possible
- Self-adjuvanted through concomitant bacterial Ty21a infection

High safety and good tolerability

Readily combinable with other immune therapies

- Approved carrier bacterium, with excellent longstanding safety record
- Low therapeutic doses of typically 10^6 to 10^7 CFU, factor 100-1000 below Vivotif® dose
- No anti-vector immunity and little to no vector-related side effects
- Suitable for multi target approaches

Fast and easy manufacturing

Attractive cost of goods

- Plug and play system
- Established methods (GMP manufacturing, QA/QC, etc.)
- Ideally suited for neoantigen / personalized vaccine approaches:

  Objective is 15 days manufacturing time after identification of the neo-epitopes

Neoantigen Targeting Personalized Approaches

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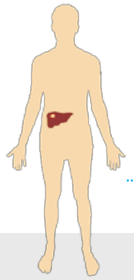
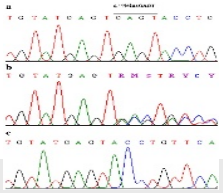
Personalized vaccine
… identifying neoantigens

Tumor biopsy & healthy tissue sample(s) from patient

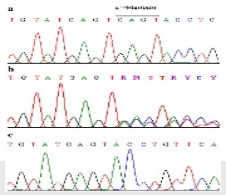


Genome sequence & mutation analysis/ identification of TAAs

Selection of mutational epitopes /neoantigen(s)

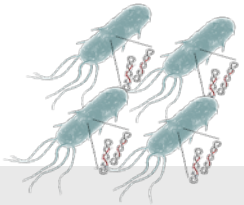


VXM

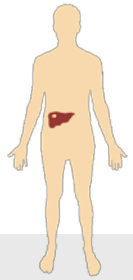


Synthesis of cDNA coding for multi-(neo)antigen polypeptide(s) Cloning of plasmid DNA, verification of sequence

Transformation of Ty21a recipient strain



Small batch Treatment of patient with personalized neoantigen vaccine (+off the shelf products)



Major Hurdles to Overcome
… delivery technologies

Challenges faced in personalized neo-antigen approaches

- Limitation in number of epitopes
- Time to needle
  - Time to oral administration after identification of neo-antigens
- Manufacturing costs for individualized therapies
- Scalability of the manufacturing process
- Individual QC analytics per product and product specification
  - Sterility testing for parenteral / intravenous drugs
- Incompatibilities in galenic formulation of drug product
- Long-term stability of drug product
- Doses to be administered
- Patient treatment during time from identification of neo-antigens to availability of personalized drug product

Competitive Landscape

… technologies for neoantigen vaccination

Overview of established approaches

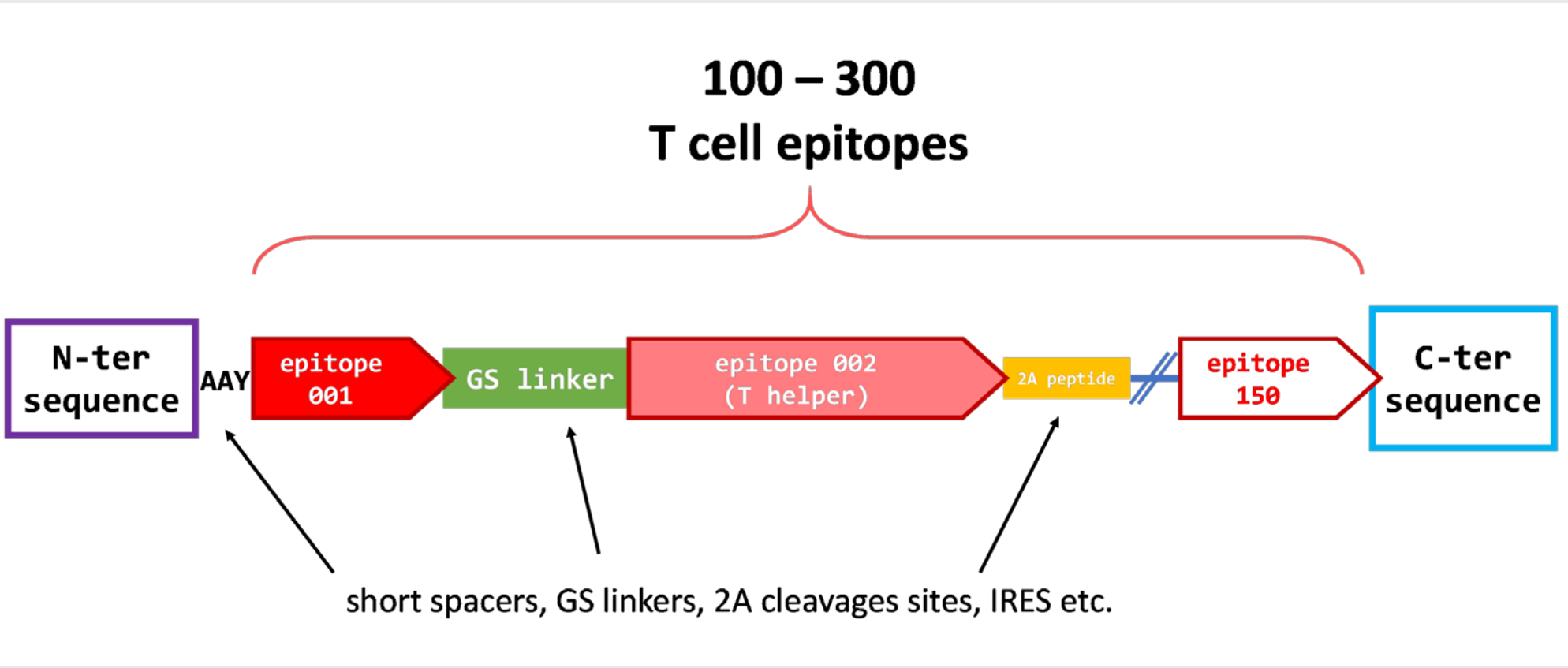
Delivery Technology	Ease of manufacturing	Route of Administration
Listeria based vaccines	+++	Intravenous
mRNA	+	Intranodal Intravenous Intradermal
Viral Vectors	+	Intradermal
Peptides	+	Intradermal
Dendritic Cells	+	Intravenous
DNA	+++	Intramuscular

Manufacturing Features

Less Limitation in the Number of Epitopes

… in "string-of-beads" encoding insert

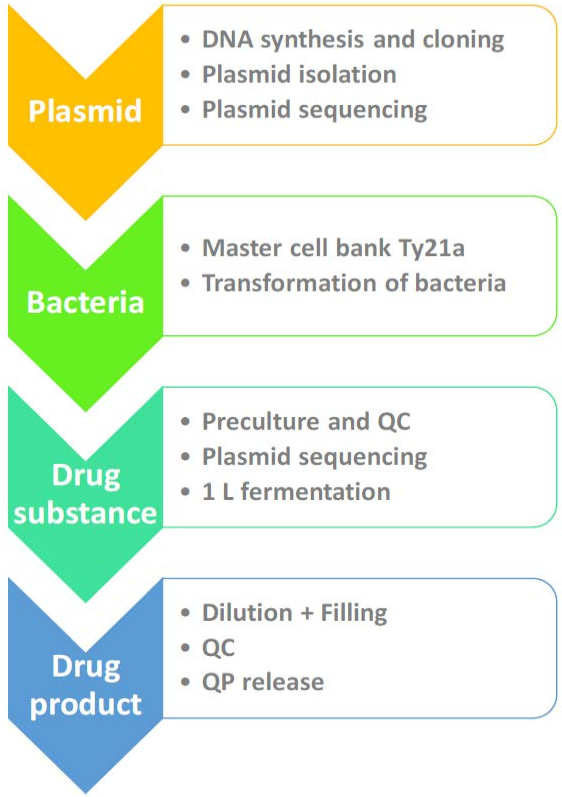
High number of epitopes can be encoded



Straight-Forward Bacterial Fermentation Manufacturing

… in small scale at low costs

Robust manufacturing in a 1 L bacterial fermentation with disposable fermenters



- Master cell bank of empty Ty21a bacteria
- Plasmid individually synthesized
- Overnight culture for drug substance fermentation in 1 L scale
- Dilution to target concentration based on CFU
- Quality control analytics including plasmid sequencing
- QP release

- Objective is to minimize the manufacturing time to 15 days after neoantigen identification in a dedicated facility

Straight-Forward Bacterial Fermentation Manufacturing

… in small scale at low costs

Short time to administration after identification of neo-antigens

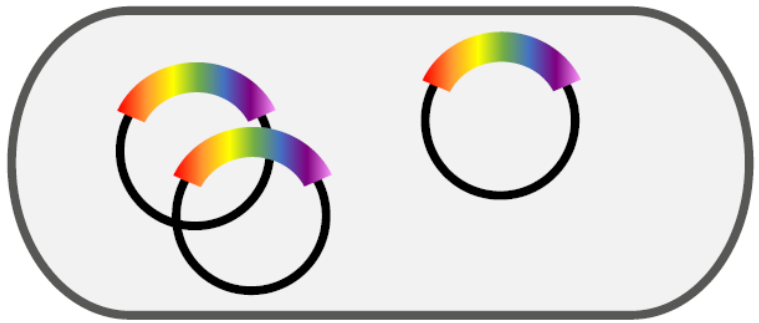
Delivery Technology	N2N time
VAXIMM	Neoantigen discovery **+ 15 days**
Company A*	115 days
Company B*	90 days
Company C*	75 days

**according to published data*

- Competitive in terms of
  - Time to administration after identification of neo-antigens
  - Manufacturing costs due to overnight bacterial fermentation in small scale
  - Upscaling not required due to high yield of bacteria
    - Net bacteria yield in the 10^{11} CFU range
    - Allowing filling of drug product sufficient for years of treatment

Quality Control Analytics for One Defined Product
… in drug substance and drug product

Generic specification per individual construct with difference in encoding insert only

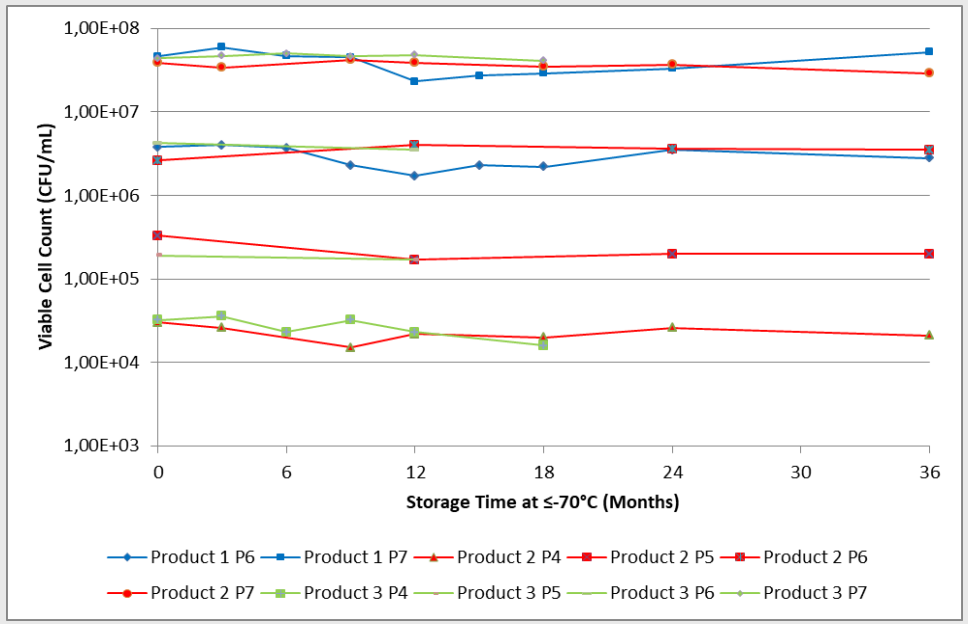


- Quality control assays established and validated through ongoing clinical development stage products
- Individual difference in encoding insert only
  - Sequencing to be performed
- No sterility testing required
  - Oral administration
  - Live bacteria-based constructs

Stable Pharmaceutical Formulation

… without risk of incompatibilities due to the nature of the product

One defined product with documented stability – no galenic incompatibilities

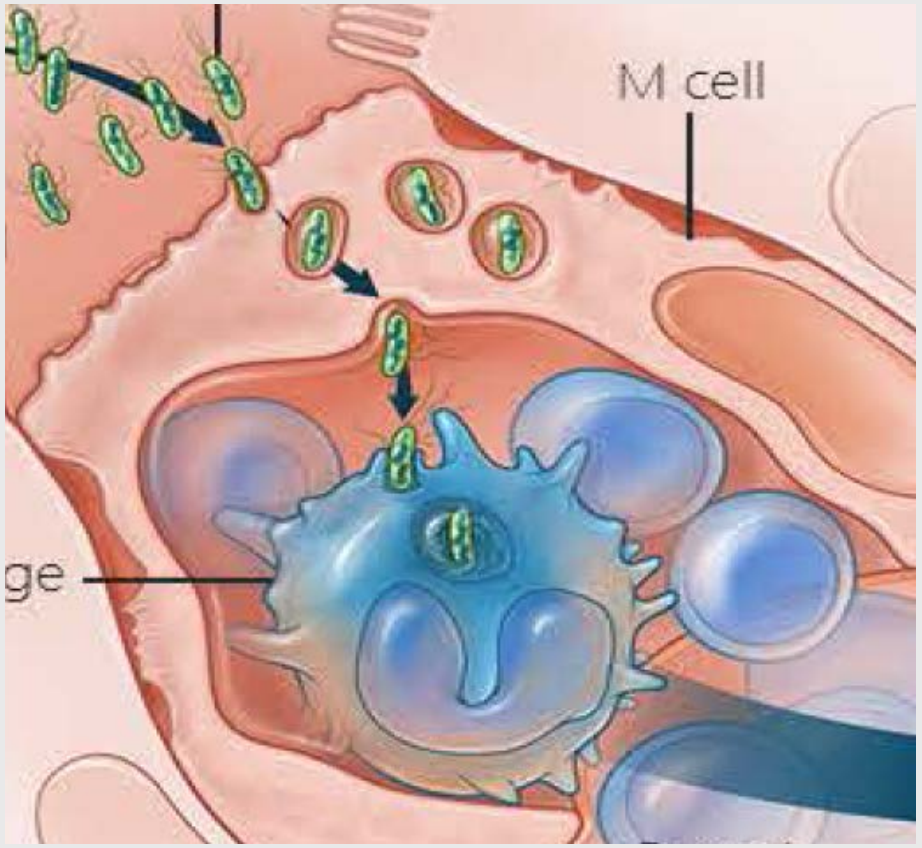


- Epitopes are encoded in the DNA plasmid
- Expression of neo-antigens in the Peyer's patches
  - No incompatibilities on the level of administration as the peptide manufacturer is the human body
- Drug substance and drug product formulations stable for 3 years as established for clinical-stage products

Very Low Doses of DNA Plasmid Administered

… far lower exposure than with other treatment modalities

Exposure to VXM DNA plasmid lower than with RNA or intradermal DNA



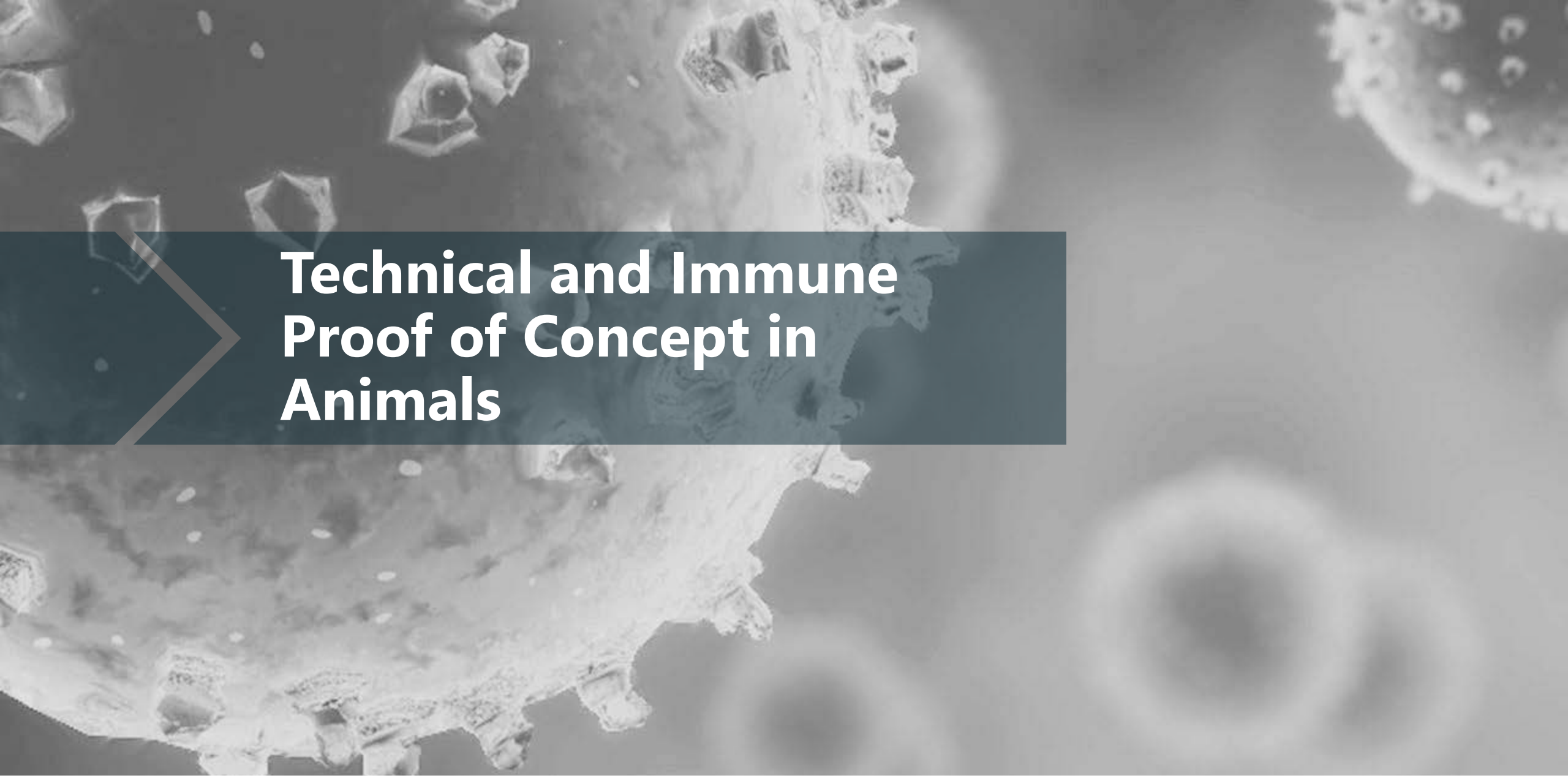
- Plasmids in 10^7 CFU live bacteria correspond to appr. 1 ng DNA
- For comparison
  - RNA intranodal: 500 – 1000 µg (*Sahin et al., 2017*)
  - Synthetic long peptides s.c.: 0.3 mg of each peptide (*Ott et al., 2017*)

VXM-NEO Phase I Checkpoint Inhibitor Combination Study

… personalized combined with shared antigen treatment

Clinical phase I study

- Identification of neoantigens in cancer indications with relevant mutational load
- Pre-treatment with off-the shelf shared antigen oral immunotherapies
- VXM-NEO treatment in combination with SoC checkpoint inhibitors



Technical and Immune Proof of Concept in Animals

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VXM-NEO

… Technical and pre-clinical immune PoC demonstrated

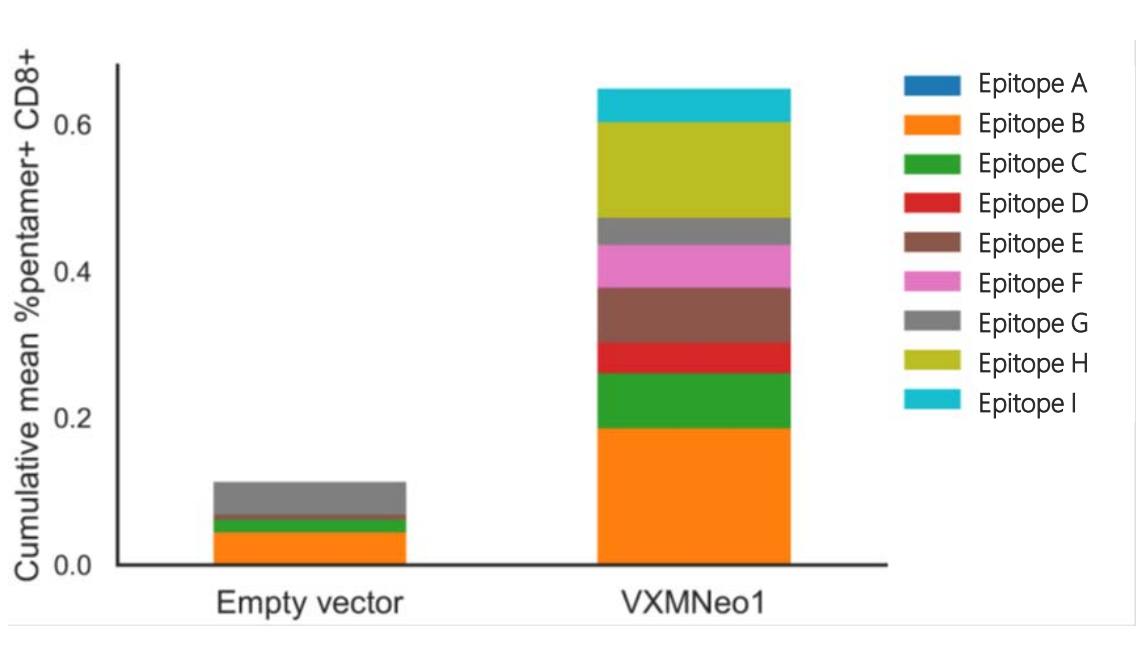
Construct with 9 dominant CD8 epitopes cloned

–VEGFR-2	2 epitopes	9 identical peptide pentamer flow cytometry reagents used
–MSLN	2 epitopes	
–WT-1	1 epitope	
–CEA	3 epitopes	Additional HPV reagent as negative control
–OVA	1 epitope	

VXM NEO Multi-Epitope Platform
Immunological PoC in animals

VXM-NEO – epitope-specific CD8+ T-cell responses

CD8+ epitope-specific T-cell responses



- Epitope-specific T-cell response against 7 out of 9 epitopes detected

Platform Clinical Proof of Concept by Lead Product

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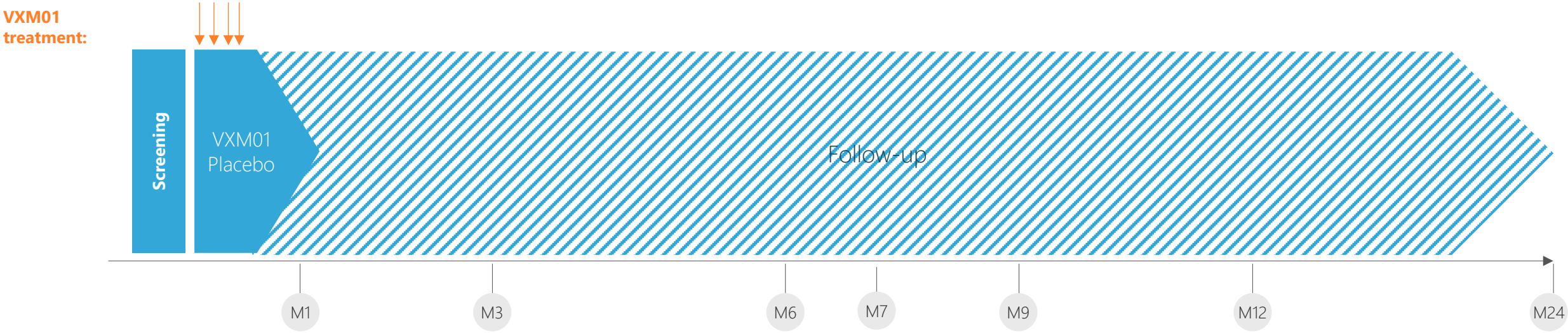
VXM01 Pancreatic Cancer Clinical Trial Completed

... first-in-human study part 1 with initial administration only

Locally Advanced or Inoperable Pancreatic Cancer



- 1st line, plus gemcitabine background chemotherapy or stand alone
- Testing five doses 10^6 CFU through 10^{10} CFU n=6 each vs. placebo n=15
- Read-out:
  - Safety
  - Biomarker
  - T-cell response
  - Survival

Prof. Beckhove
Immunomonitoring
NCT

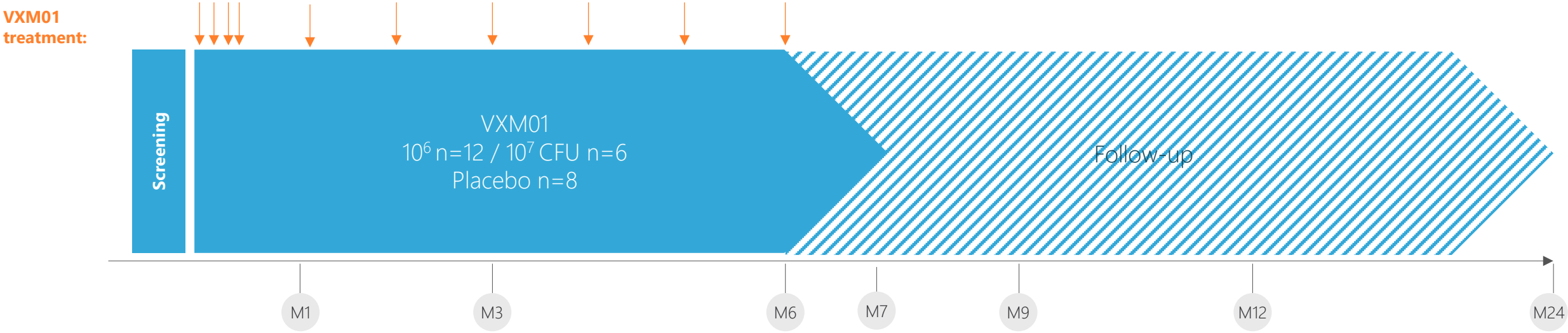
PD Dr. Schmitz-Winnenthal
PI

Prof. Haefeli
Head Clinical Pharmacology

VXM01 Pancreatic Cancer Clinical Trial Completed

… first-in-human extension including boosting

Locally Advanced or Inoperable Pancreatic Cancer



- 1st line, plus gemcitabine background chemotherapy or stand alone
- Testing two doses
- Read-out:
  - Safety
  - Biomarker
  - T-cell response
  - Survival

UniversityHospital Heidelberg
NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
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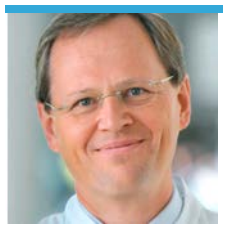


Prof. Haefeli
Head Clinical Pharmacology

VXM01 Pancreatic Cancer Clinical Study

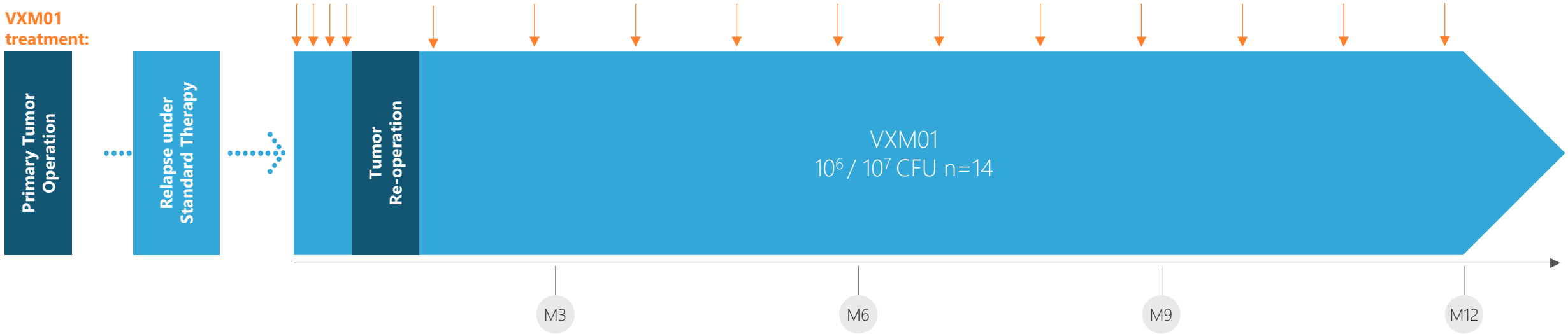
… a successfully completed randomized Phase I/II program

- VXM01 treatment causes activation of VEGFR-2-specific T-cell response in patients
- Perfusion rates were used as biomarker, supporting the notion of VEGFR-2 -specific T-cell activation
- VXM01 (incl. boosting) was very well tolerated
- Continued VXM01 treatment led to improved survival, correlating with immunological response to VXM01
- Metastatic load was markedly reduced in one patient following VXM01 treatment

- **VXM01 showed early signs of clinical efficacy in pancreatic cancer**
- **First clinical validation of the oral Ty21a T-cell therapy platform**
- ***Schmitz-Winnenthal et al., OncoImmunology 2015 and OncoImmunology 2017***

VXM01 Clinical Trial Currently Ongoing
… in glioblastoma

Glioblastoma



- Relapsed patients who are candidates for re-operation
- Initiation treatment prior to re-operation (continued post-op)
- Monocenter trial in Heidelberg
- Two VXM01 doses 10^6 or 10^7 CFU
- Patient number expanded beyond 8 patients
- Comprehensive read-out pending
  - T-cell response
  - High-res. brain tumor vasculature imaging
  - Immunohistochemistry on tumor samples
  - Clinical response
- Patient-specific prolongation of VXM01 treatment beyond one year initiated in 2 patients
- Seven out of 14 patients treated survived more than 1 year
- Interim data presented at ASCO 2017, abstract accepted for ASCO 2018

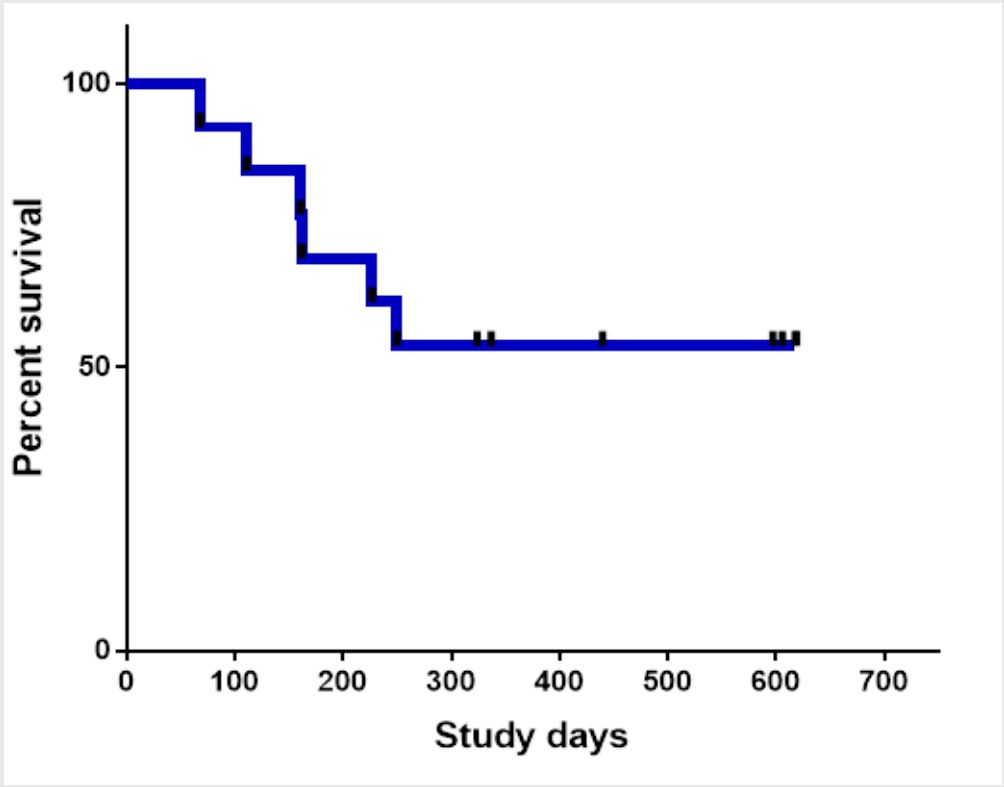
Prof. Wick, PI

NCT

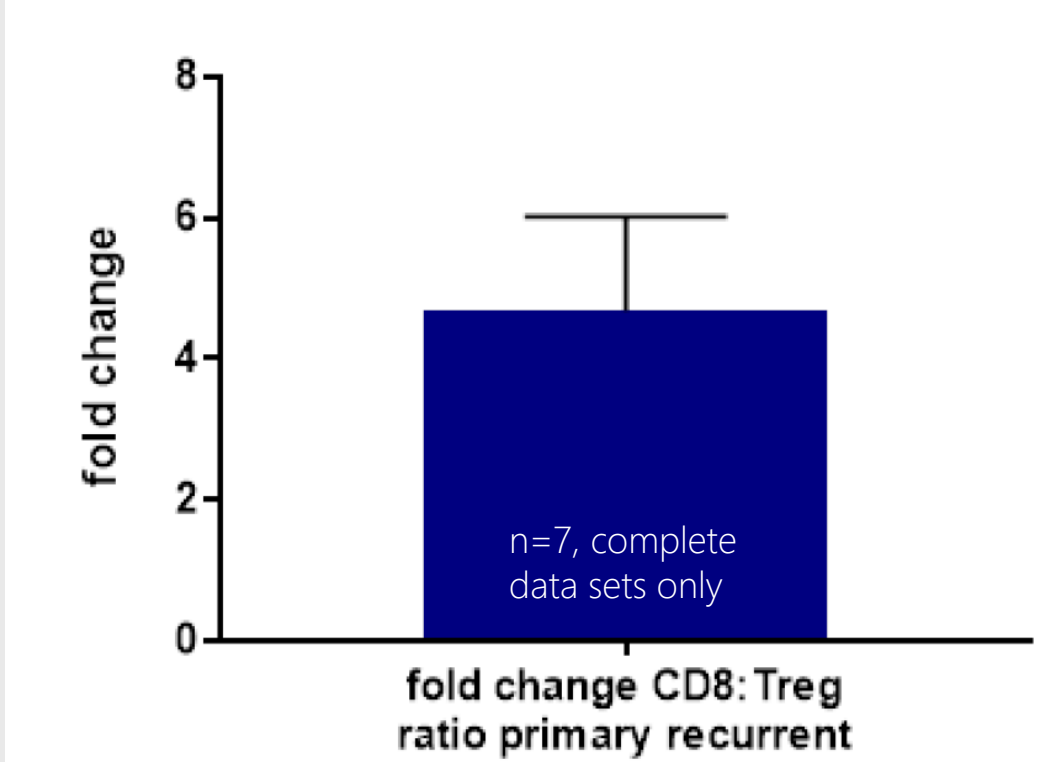
Promising Survival of Recurrent Glioblastoma Patients

… 7 out of 14 survived more than one year

Survival curve



CD8+/Treg ratio increased in recurrent tumor



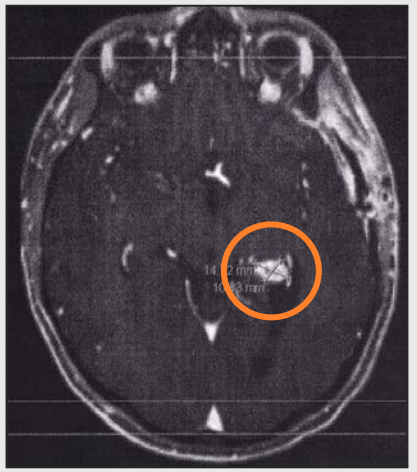
Patients with Favorable Course of Disease

… in recurrent glioblastoma

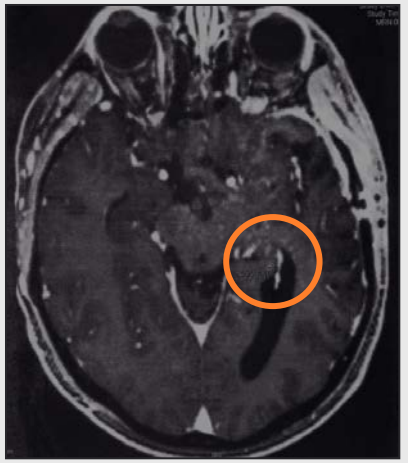
1st patient

- Patient 2603 (male, 47 y), candidate for re-operation,
- **Not operated** due to tumor shrinkage under VXM01 treatment
- VXM01 treatment without other anti-cancer therapy during study up to week 12
- **Partial response (PR)** after 12 weeks under VXM01 monotherapy
- **Complete response (CR)** after additional 15 weeks under VXM01 and 6 doses of anti-PD1 treatment
- Durable response with significant clinical benefit
- Progressive disease at week 36
- High VEGFR-2 expression on tumor neovasculature in primary tumor

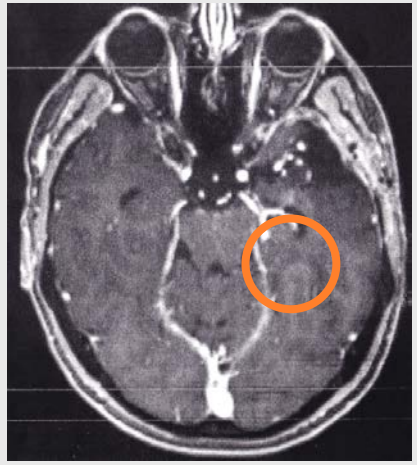
Baseline



Week 12 – PR



Week 27 – CR

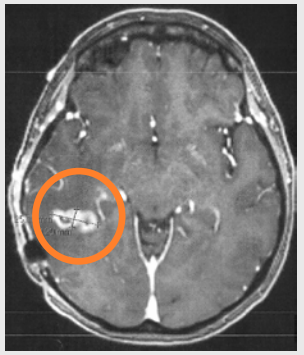


Patients with Favorable Course of Disease
… in recurrent glioblastoma

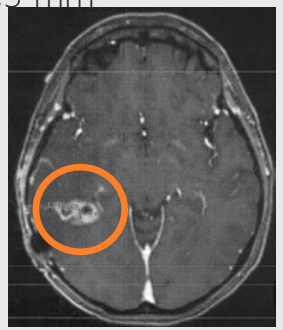
2nd patient

- Patient 2605 (female, 55 y), candidate for re-operation
- **Showed stabilization** of tumor growth after VXM01 treatment before re-operation
- VXM01 monotherapy treatment up to week 10
  - Initiation treatment plus boosting after reoperation
- Favorable post-operative course of disease – under VXM01 + chemotherapy from week 10 to week 36
- **Stable Disease (SD)** at week 76
- VEGFR-2 expression on tumor cells in primary tumor, but no expression on recurrent tumor cells after VXM01 treatment
  - Indicator of VEGFR-2 targeting effect

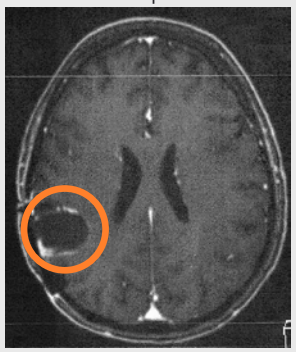
Baseline
25,1 x 10,2 mm



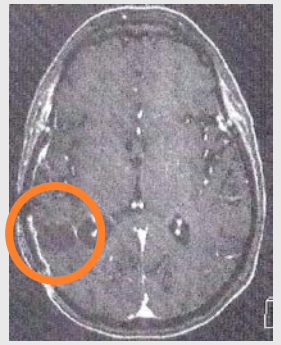
Day 35 –
Before Re-operation
24,6 x 12,3 mm



Week 12 –
7 Weeks after Re-operation



Week 76 –
71 Weeks after Re-operation



Patients with Favorable Course of Disease

… in recurrent glioblastoma

3rd patient

- Patient 2611 (female, 44 y), candidate for re-operation
- **Showed stabilization** of tumor growth after VXM01 treatment before re-operation
- Patient did not want to be re-operated
- VXM01 monotherapy treatment up to week 8
  - Initiation of additional nivolumab from week 8 onwards
- **Stable Disease (SD)** at week 36

Target Lesion	Tumor Diameter 1 [mm]	Tumor Diameter 2 {mm]
Baseline	14	11
Day 10	14	9
Day 21	14	10
Day 35	14	9
Week 12	14	10
Week 24	14	10
Week 36	11	10

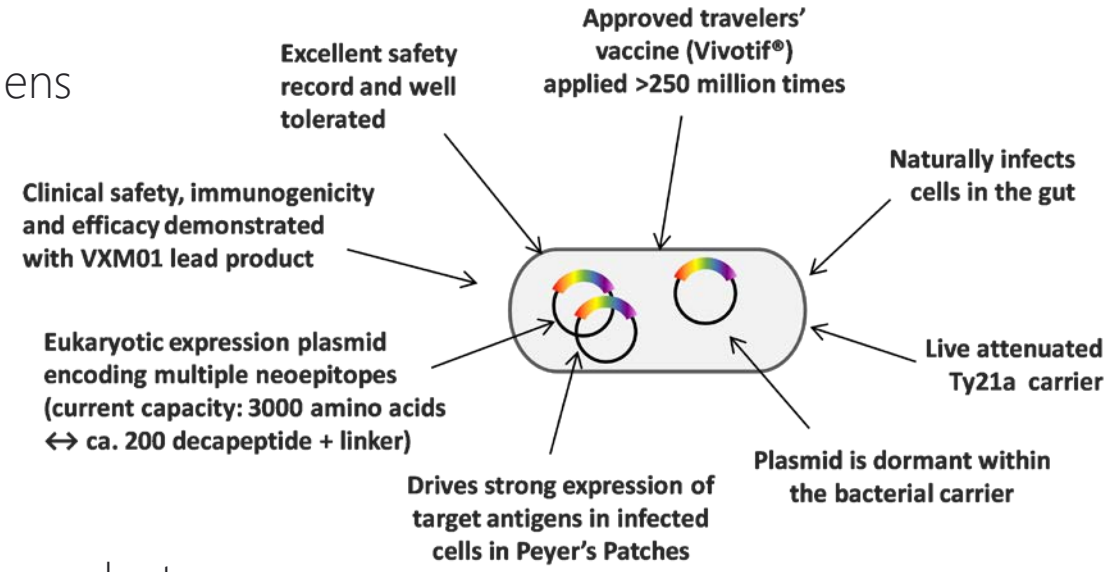
Summary

VAXIMM

Major Hurdles Can be Overcome
… by our VAXIMM delivery technology

Response to challenges faced in personalized neo-antigen approaches

- Less limited in number of epitopes
- Short time to oral administration after identification of neo-antigens
- Low manufacturing costs for established process
- QC analytics and generic product specification established
- No incompatibilities in galenic formulation
- Long-term stability of drug product
- Low exposure
- Patient treatment with off-the shelf constructs during time from identification of neo-antigens to availability of personalized drug product
- Immune and technical proof of concept shown in animals
- Platform clinically validated by lead product
  - ATMP certification by EMA and orphan drug designation for glioma in U.S. and E.U.



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