vaccibody

Manufacturing, Regulatory and Logistics Challenges in the Rapidly Evolving Area of Individualised Therapeutic Cancer Vaccines: The Road to FASTdna at a Low Cost One-Stop-Shop

Neo Antigen Summit, Boston

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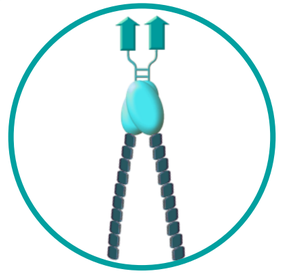
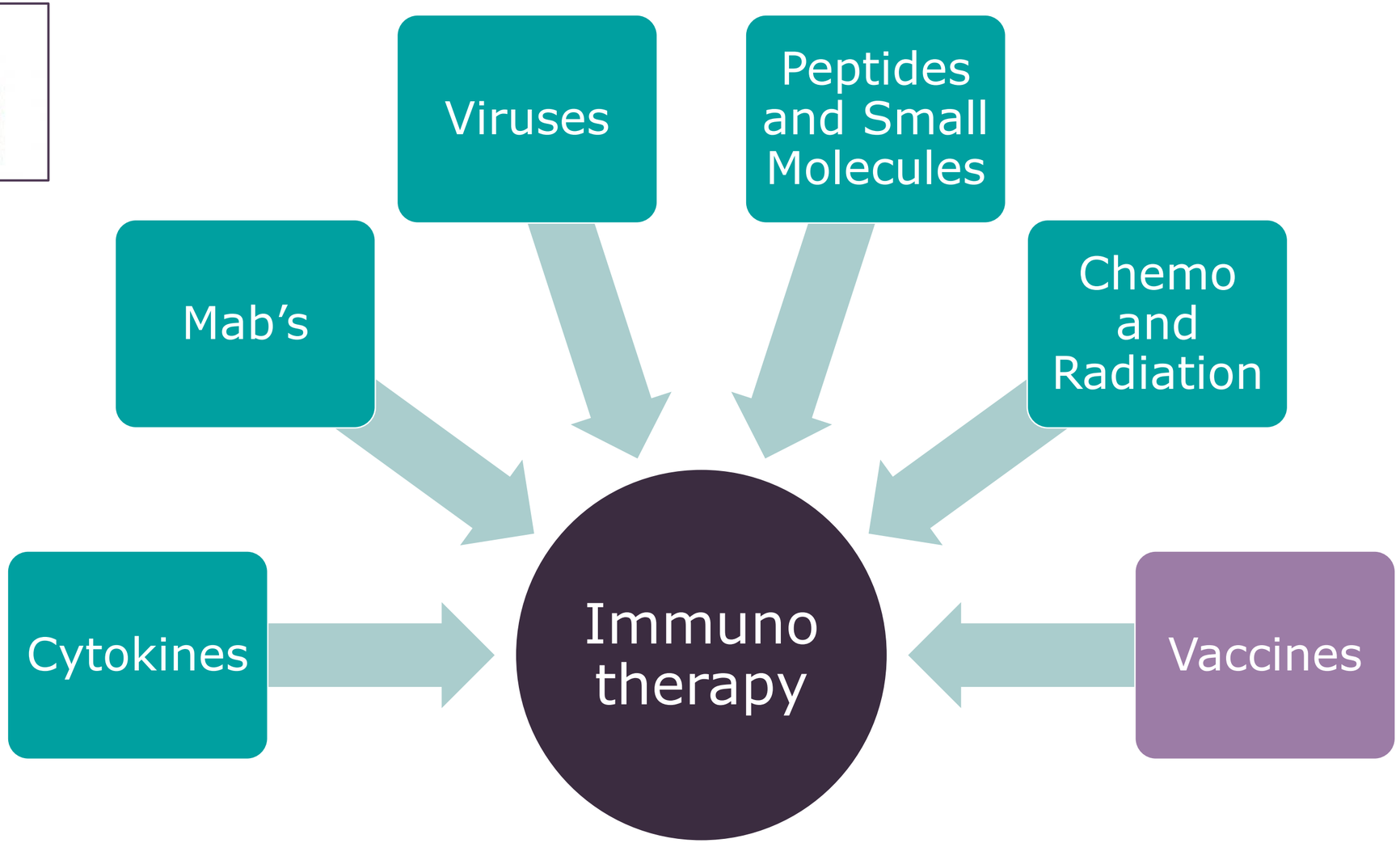
Vaccibody – General information

- Oslo, Norway based therapeutic cancer vaccine biotech, established in 2007
- Originates from University of Oslo
- Privately owned
- ~20 employees, whereof 15 hired over last 18 months
- Two main programmes: VB10.16 (common antigens) and VB10.NEO (individual neoantigens)

Content

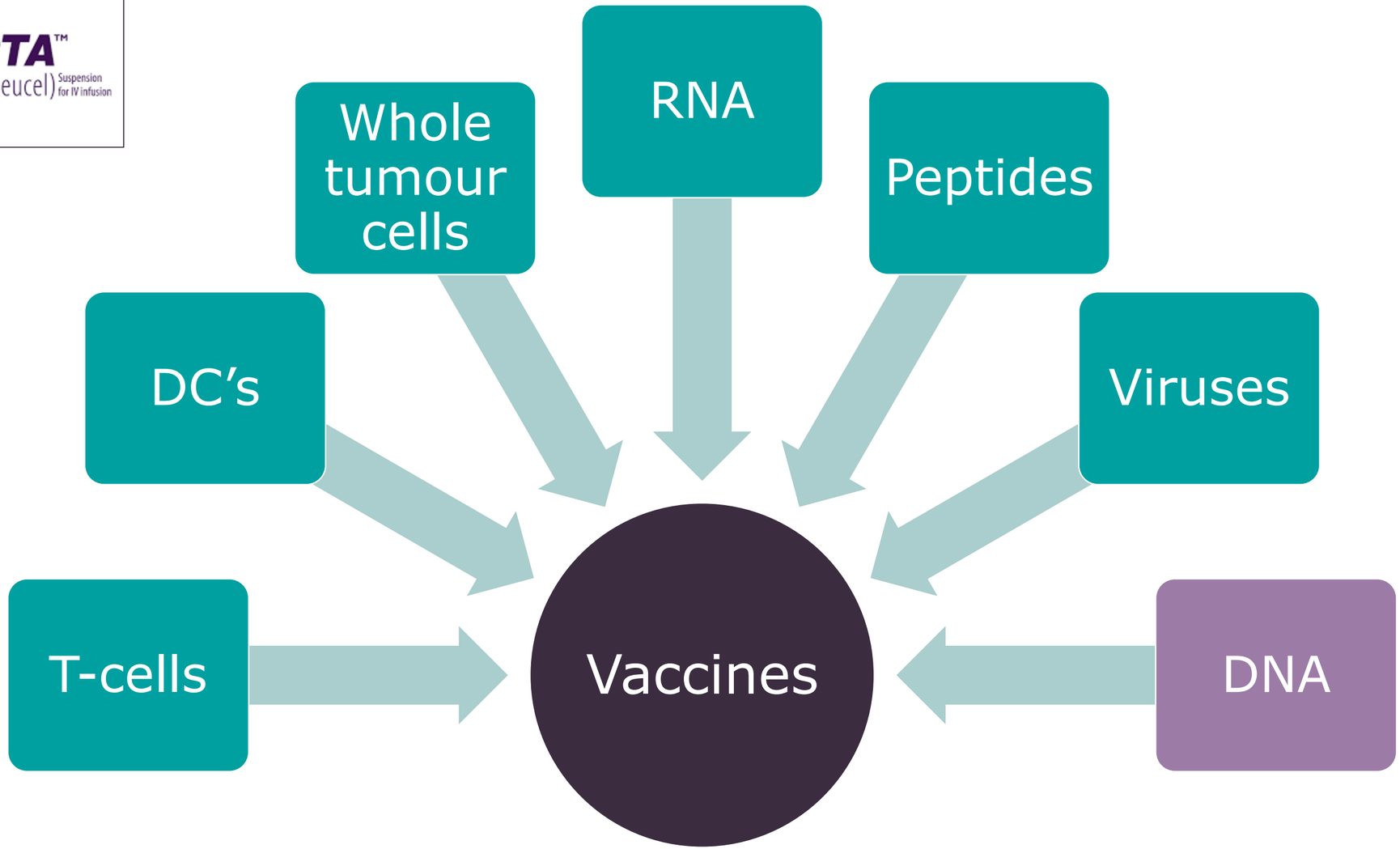


Cancer Immunotherapy

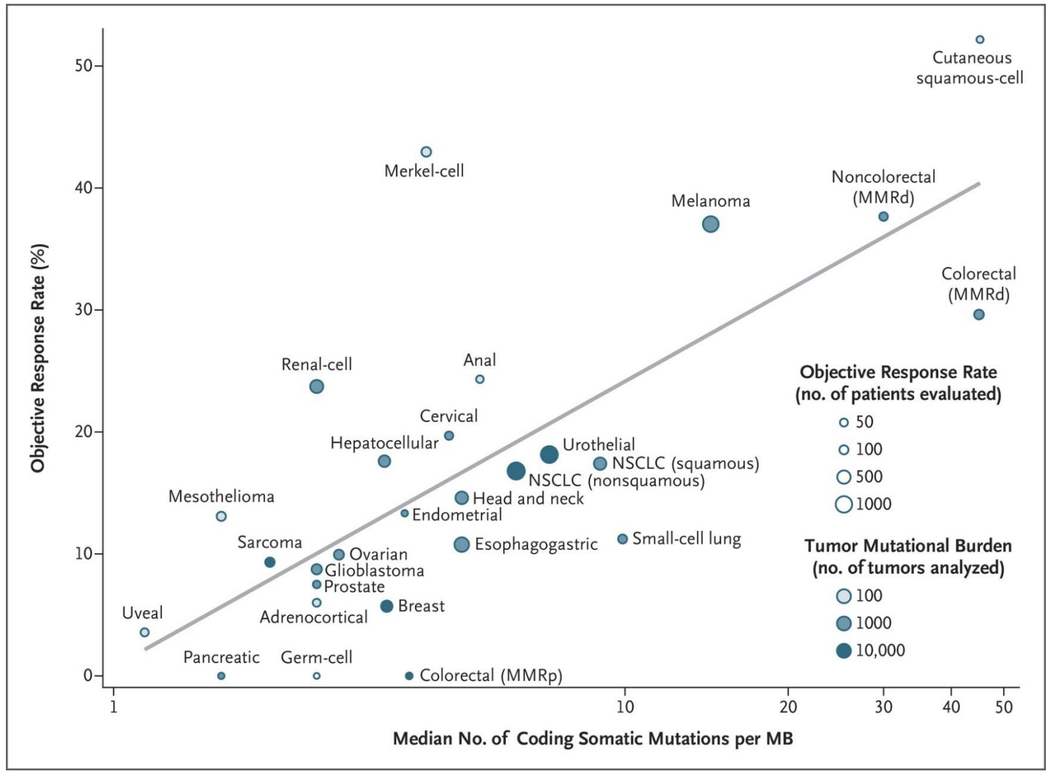


Therapeutic Cancer Vaccines

NOW APPROVED
YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusion



Check Point Inhibitors – Relationship with neoantigens



Strong relationship between mutational burden and response to CPI

CPI responses limited to already existing neoantigen-specific T cell repertoire

Opens up for an important role of immune responses to neoantigens in cancer immunotherapy

Cancer neoantigen vaccines are the **optimal tools** to activate truly specific, strong and broad neoantigen specific T cell responses

Yarchoan et al., 2017 NEJM

Proof of Concept published in Nature Letters July 2017

LETTER

doi:10.1038/nature22991

An immunogenic personal neoantigen vaccine for patients with melanoma

Patrick A. Ott[1,2,3*], Zhuting Hu[1*], Derin B. Keskin[1,3,4], Sachet A. Shukla[1,4], Jing Sun[1], David J. Bozym[1], Wandi Zhang[1], Adrienne Luoma[5], Anita Giobbie-Hurder[6], Lauren Peter[7,8], Christina Chen[1], Oriol Olive[1], Todd A. Carter[4], Shuqiang Li[4], David J. Lieb[4], Thomas Eisenhaure[4], Evisa Gjini[9], Jonathan Stevens[10], William J. Lane[10], Indu Javeri[11], Kaliappanadar Nellaiappan[11], Andres M. Salazar[12], Heather Daley[1], Michael Seaman[7], Elizabeth I. Buchbinder[1,2,3], Charles H. Yoon[3,13], Maegan Harden[4], Niall Lennon[4], Stacey Gabriel[4], Scott J. Rodig[9,10], Dan H. Barouch[3,7,8], Jon C. Aster[3,10], Gad Getz[3,4,14], Kai Wucherpfennig[3,5], Donna Neuberg[6], Jerome Ritz[1,2,3], Eric S. Lander[3,4], Edward F. Fritsch[1,4†], Nir Hacohen[3,4,15] & Catherine J. Wu[1,2,3,4]

- 6 patients with melanoma (stage III/IV)
- 97 neoepitopes delivered as long-peptides with polyICLC (SC)
- CD4 dominated responses

LETTER

doi:10.1038/nature23003

Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

Ugur Sahin[1,2,3], Evelyna Derhovanessian[1], Matthias Miller[1], Björn-Philipp Kloke[1], Petra Simon[1], Martin Löwer[2], Valesca Bukur[1,2], Arbel D. Tadmor[2], Ulrich Luxemburger[1], Barbara Schrörs[2], Tana Omokoko[1], Mathias Vormehr[1,3], Christian Albrecht[2], Anna Paruzynski[1], Andreas N. Kuhn[1], Janina Buck[1], Sandra Heesch[1], Katharina H. Schreeb[1], Felicitas Müller[1], Inga Ortseifer[1], Isabel Vogler[1], Eva Godehardt[1], Sebastian Attig[2,3], Richard Rae[2], Andrea Breitkreuz[1], Claudia Tolliver[1], Martin Suchan[2], Goran Martic[2], Alexander Hohberger[3], Patrick Sorn[2], Jan Diekmann[1], Janko Ciesla[4], Olga Waksmann[4], Alexandra-Kemmer Brück[1], Meike Witt[1], Martina Zillgen[1], Andree Rothermel[2], Barbara Kasemann[2], David Langer[1], Stefanie Bolte[1], Mustafa Diken[1,2], Sebastian Kreiter[1,2], Romina Nemecek[5], Christoffer Gebhardt[6,7], Stephan Grabbe[3], Christoph Höller[5], Jochen Utikal[6,7], Christoph Huber[1,2,3], Carmen Loquai[3*] & Özlem Türeci[8*]

- 13 patients with melanoma (stage III/IV)
- 125 neoepitopes delivered as ivt-RNA (intranodal)
- CD4 dominated responses

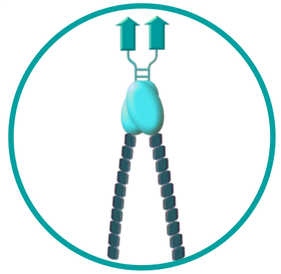
- Neoepitope vaccines elicit a broad and strong tumour-specific immune response
- Both peptide and RNA neoantigen based vaccines elicits predominantly CD4 T-cell responses

Ott et al., Nature Letters 2017
Sahin et al., Nature Letters 2017

Content

1. Introduction - Cancer Immunotherapy - Vaccines

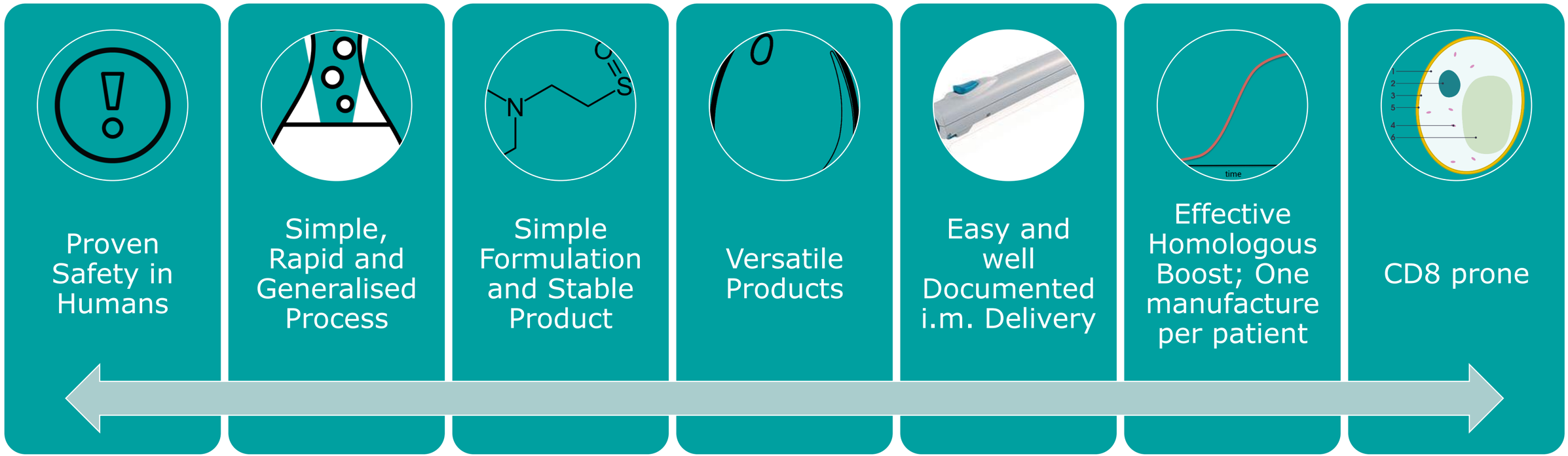
2. Vaccibody's Cancer Vaccine Strategy



3. Vaccibody Supply Chain - Experiences

4. Future Road to FASTdna

VB10.NEO Development of Naked DNA Plasmid as Personalised Therapy



DNA plasmid is considered an ideal platfrom for bringing individualised neoantigen vaccines to the market as viable products

Vaccibody – Proprietary Vaccine Technology Platform

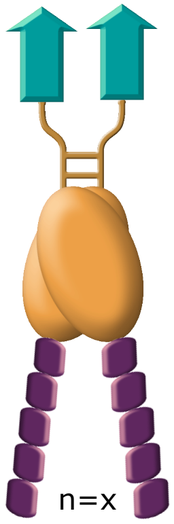
The Vaccibody Technology Platform was developed based on the concept of **targeting antigen to APC** in order to create more efficacious vaccines.

Exchangeable DNA Cassette

Vaccibody DNA Vaccine Plasmid

VB10.NEO

In vivo expression



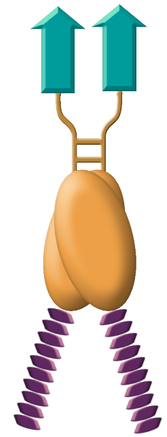
Vaccibody in Protein Format

Target to Antigen Presenting Cell

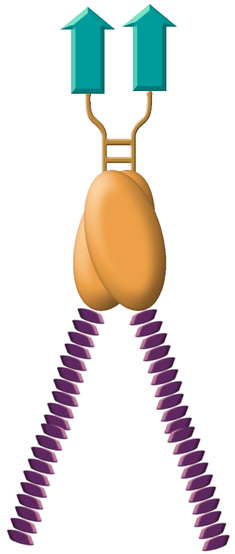
Dimerization for crosslinking target receptor

Antigen moiety

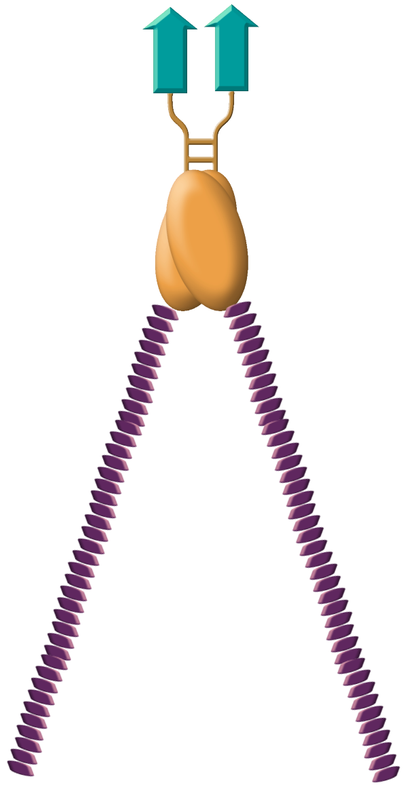
VB10.NEO – A Robust Vaccine Format



VB10.NEO-X



VB10.NEO-XX



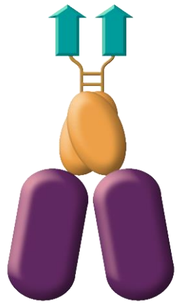
VB10.NEO-XD

>90 different VB10.NEO constructs with >450 neoepitopes prepared to date with up to 40 neoepitopes in one construct

Learnings from the Clinic – VB10.16 Frontrunner of Vaccibody Platform

VB10.16

- HPV16 specific therapeutic DNA vaccine (against viral neoantigens E6 and E7)
- First indication precancerous cervical lesions (CIN 2/3)
- Exploratory proof of concept clinical trial completed enrolment and treatment (Ph I/IIa)



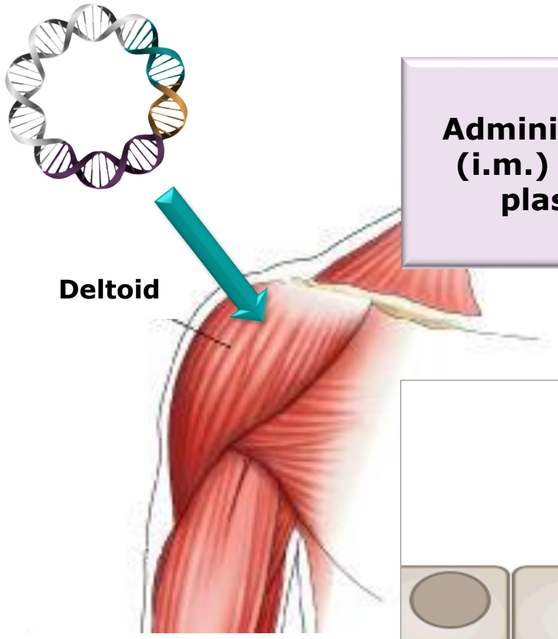
SAFETY: No drug-related SAEs observed

DOSING: 3 week vaccination intervals induces strongest responses

DELIVERY: Needle free and painless

EFFiCACY: Clinical efficacy correlates strongly with T-cell response. 32 subjects treated in total

Mechanism of Action – Intrinsic Adjuvant

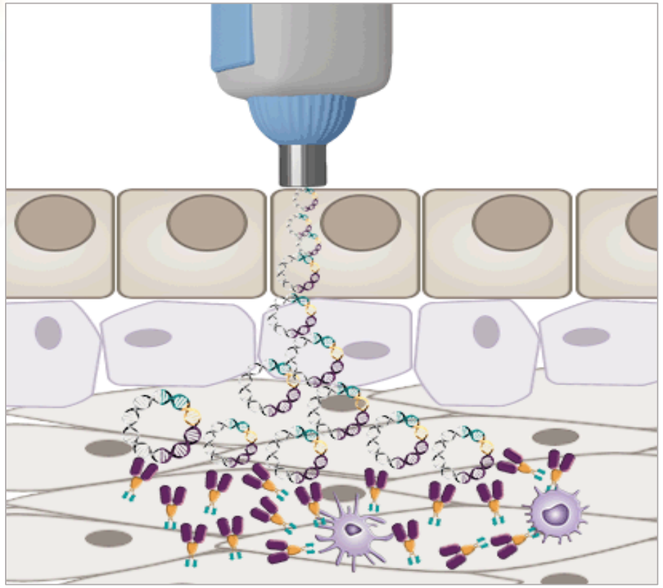


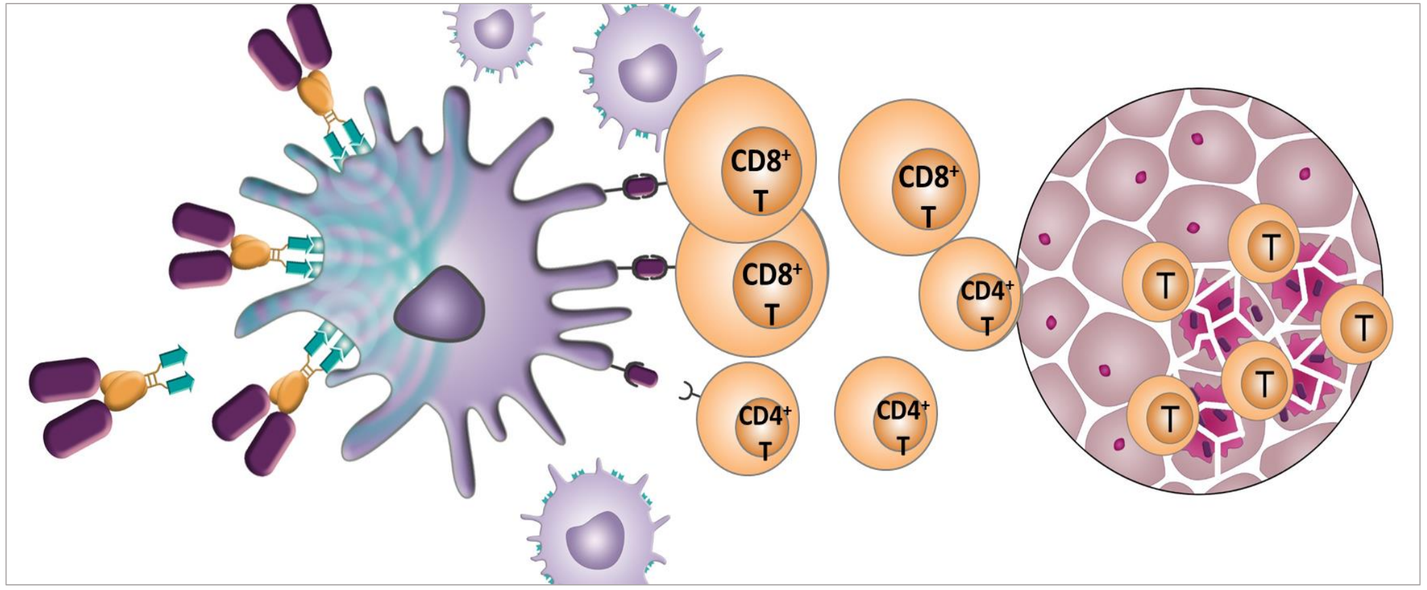
Administration (i.m.) of DNA plasmid

***In vivo* protein expression and secretion**

Chemokine MIP-1α

Target – Attract –Mature –Deliver-Cross-present

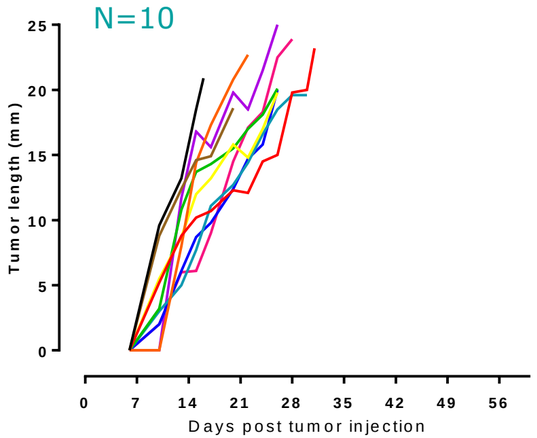




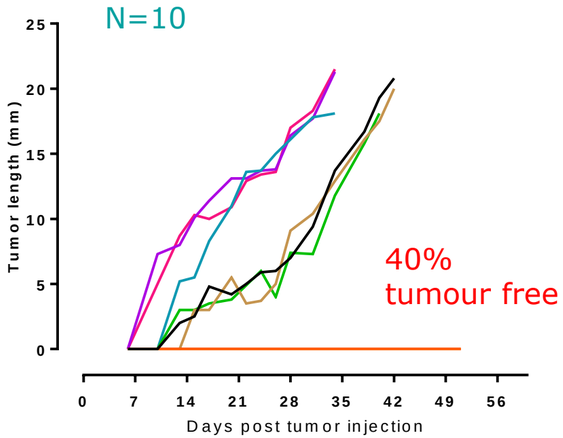
Vaccibody Induces Tumour Protection as Monotherapy

CT26 colon carcinoma model

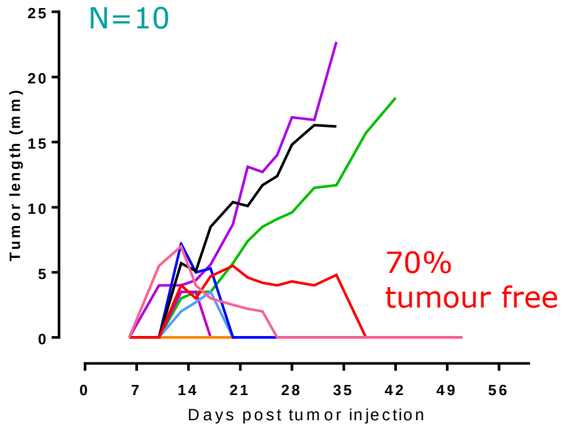
Control



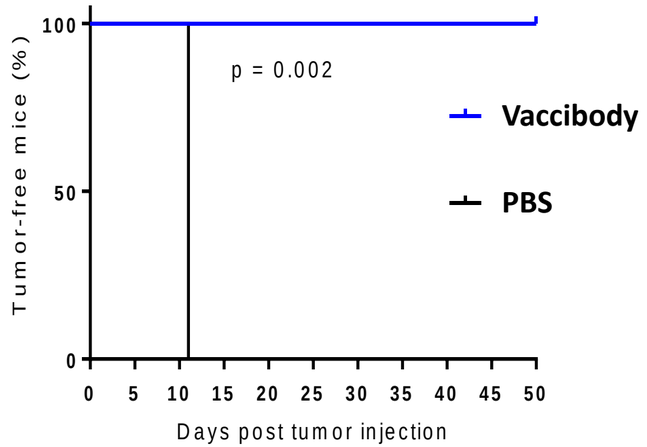
Vaccibody Monotherapy



Vaccibody Combination Therapy



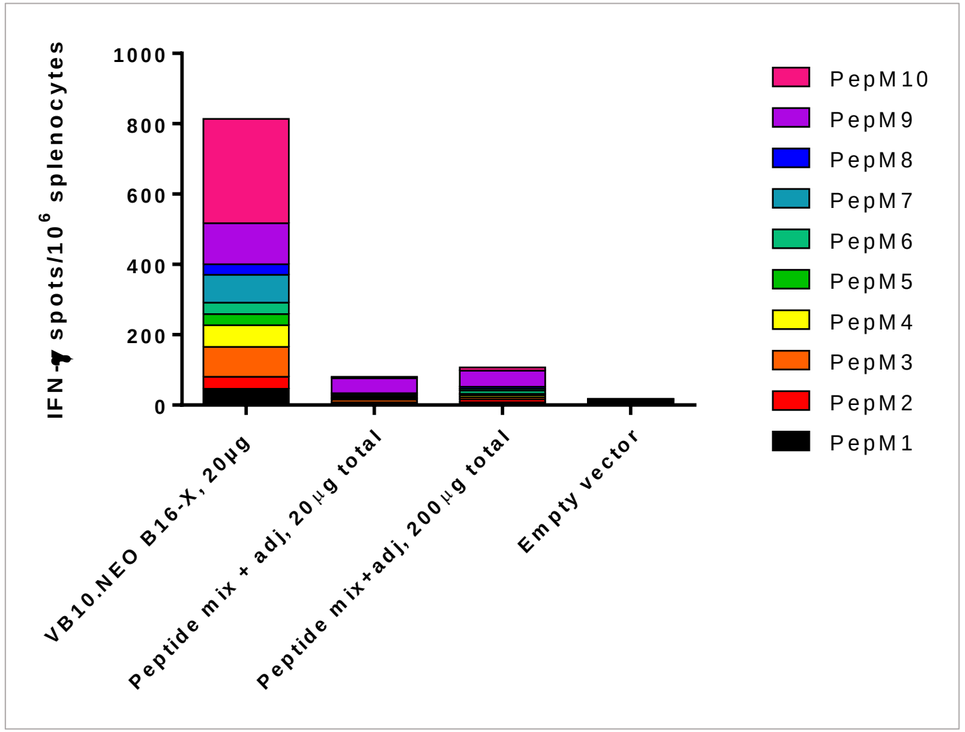
Re-challenged mice are protected



- The Vaccibody vaccine induces strong CD8+ T cell responses and **tumour protection as Monotherapy**
- Combination with anti-PD-1 immunotherapy induced enhanced anti-tumour responses in mice involving **complete tumour regression** of large, established tumours
- **Long-term memory responses** ensure effective anti-tumour responses after a 2nd tumour challenge in surviving mice with no sign of tumour growth

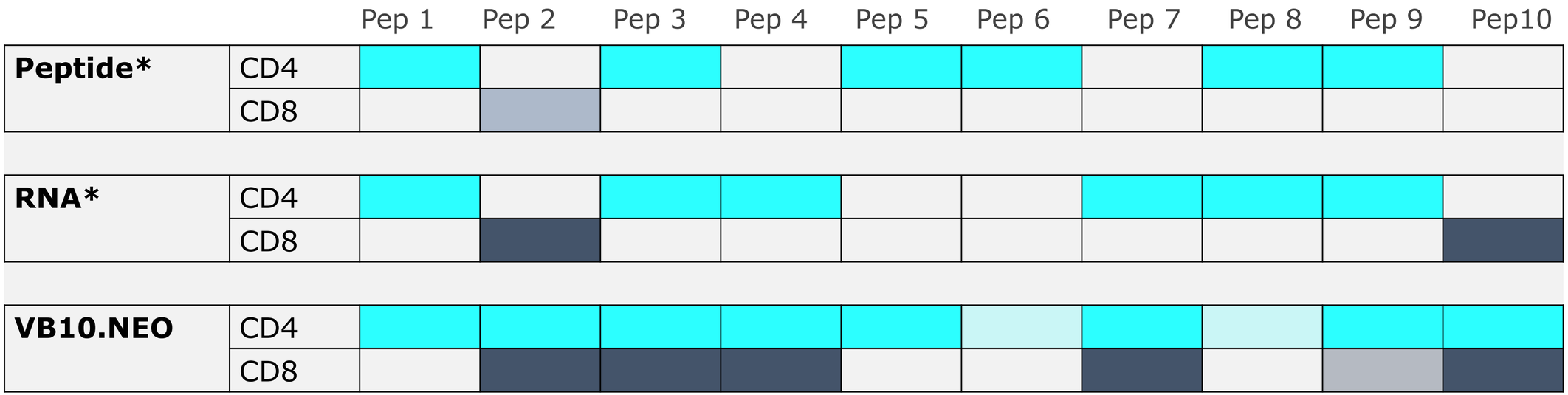
VB10.NEO induces Rapid, Broad and Strong responses to multiple Neoepitopes by single Vaccination

- VB10.NEO induces a broader and stronger response than Peptide + Poly (I:C) Adjuvant vaccines after a single immunization.
- VB10.NEO vaccinated animals respond to all 10 neoepitopes after a single immunization.
- Immunodominant neoepitopes differ between delivery vehicles



B16 melanoma

VB10.NEO generates a broader immune response profile dominated by CD8+ T cells than competing technologies



* Tested IFN-γ CD4 and CD8 T cell response against 10 identical neoepitopes from B16 melanoma

Peptide and RNA vaccines induces primarily CD4 T cell responses, while VB10.NEO induces strong, dominating CD8 responses to the identical neoepitope sequences

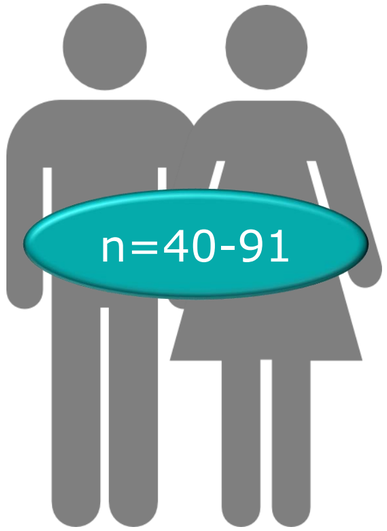
* Castle et al., 2012 and Kreiter et al., 2015

Clinical Trial VB N-01

VB N-01: An open labelled first human dose phase 1/2a study to evaluate safety, feasibility and efficacy of multiple dosing with individualised VB10.NEO immunotherapy in patients with locally advanced or metastatic melanoma, NSCLC, clear renal cell carcinoma, urothelial cancer or squamous cell carcinoma of head and neck, who did not reach complete responses with current standard of care immune checkpoint blockade

VB10.NEO

VB N-01



- **Melanoma**
- **NSCLC**
- **Clear Renal Cell Carcinoma**
- **Urothelial Cancer**
- **Squamous Cell Carcinoma of the Head and Neck**

- Approved CPI as SOC
- Moderate to high mutational load

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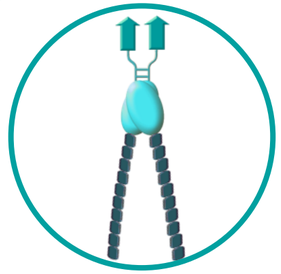

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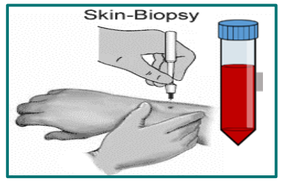
4. Future Road to FASTdna

VB10.NEO Supply Chain



Sequencing and NeoSELECT™

Gene synthesis

Cloning into VB10 MP

Manufacturing of BDS

Fill & Finish

Vaccibody Solution to Personalised Cancer Treatment

1. Tumour biopsy and sequencing

2. Neoepitope selection (TSNA)

NeoSELECT™

3. Vaccine manufacturing (n=1)

-DNA: Robust, rapid, cost-effective, stable, safe.

-up to 40 neoepitopes

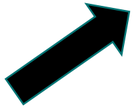
4. Vaccine administration and immunogenicity

-Needle-free

-Target, Attract, Mature, Deliver, Cross-present

-Rapid, strong, long-lasting

-CD8 dominated



Vaccibody provide a Rapid, Cost-effective and Efficacious solution

Supply Chain Flowchart - VB10.NEO personalised DNA vaccine - Orchestration

Clinical site

Tissue biopsy

- Pathology
- IHC

- Exome & RNA sequencing
- HLA typing

vaccibody

Peptide synthesis

Gene synthesis

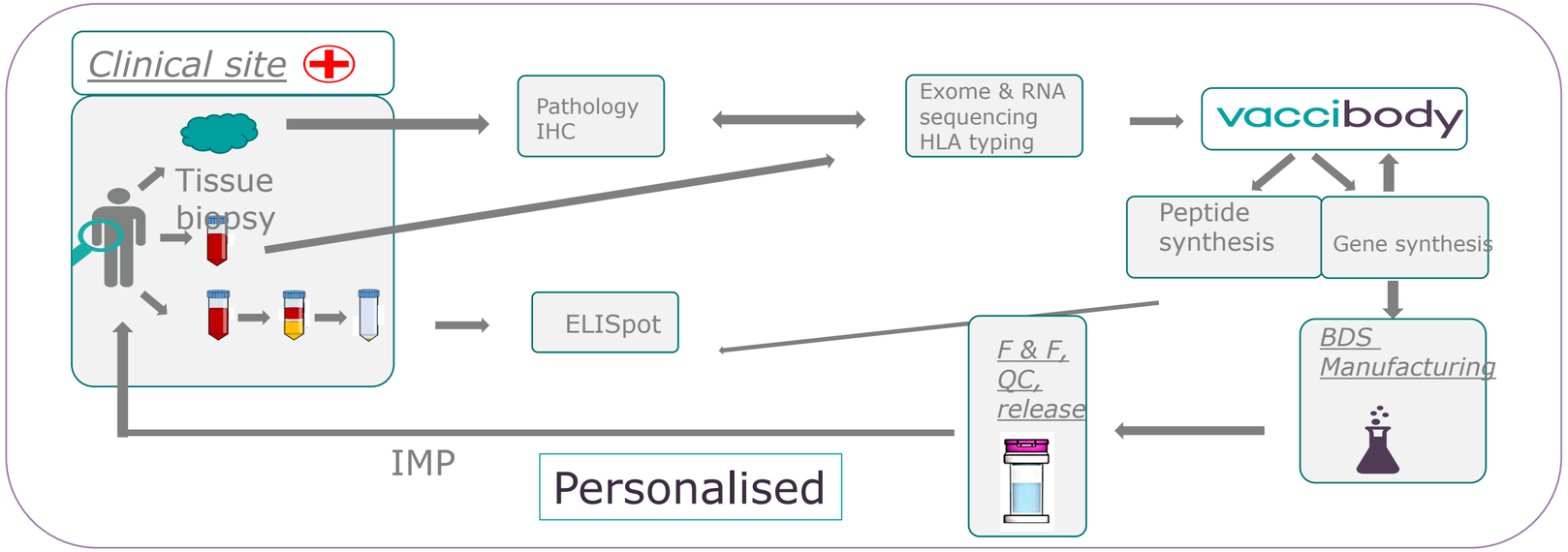
Plasmid Manufacturing

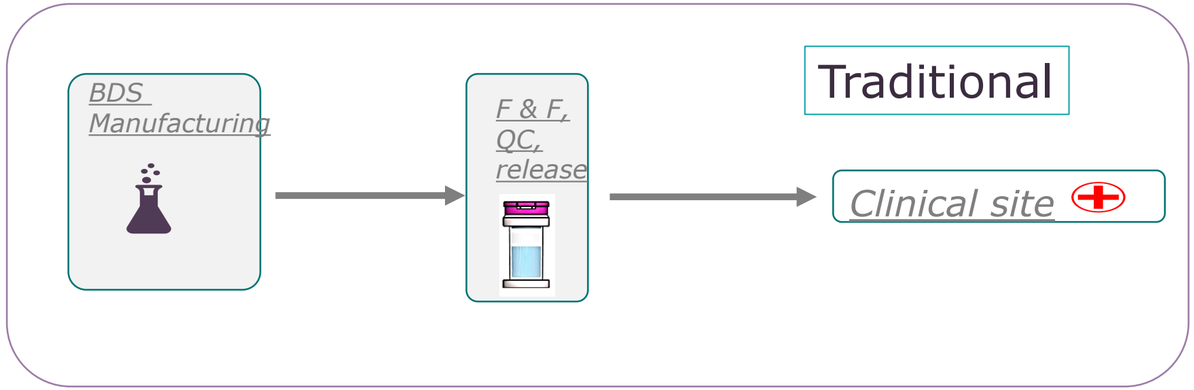
Fill & Finish

ELISpot

IMP

Differences between traditional drugs and personalised vaccines





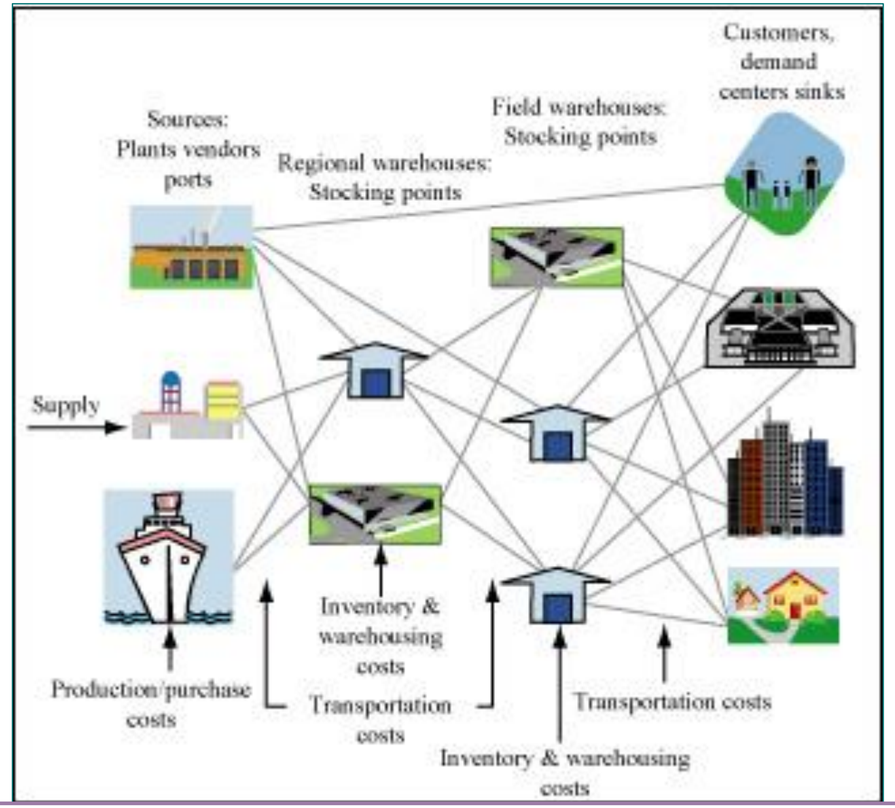
- Complexity of Supply chain
- Criticability of supply chain lead time
- Logistics
- Scaling out versus up
- Integration of clinic and CMC
- Cost
- Risk profile
- **Regulatory framework**
- **CMO/collaborator requirements**
- **Technologies and expertise**

Personalised Medicine Tracking Challenges

Tracking of **all** samples is instrumental in order to

- ✓Ensure chain of custody for all patients
- ✓Ensure transparent communication to and from the various service providers regarding time lines for receipt of material and potential delays
- ✓Ensure an optimal lead time for patient vaccine supply

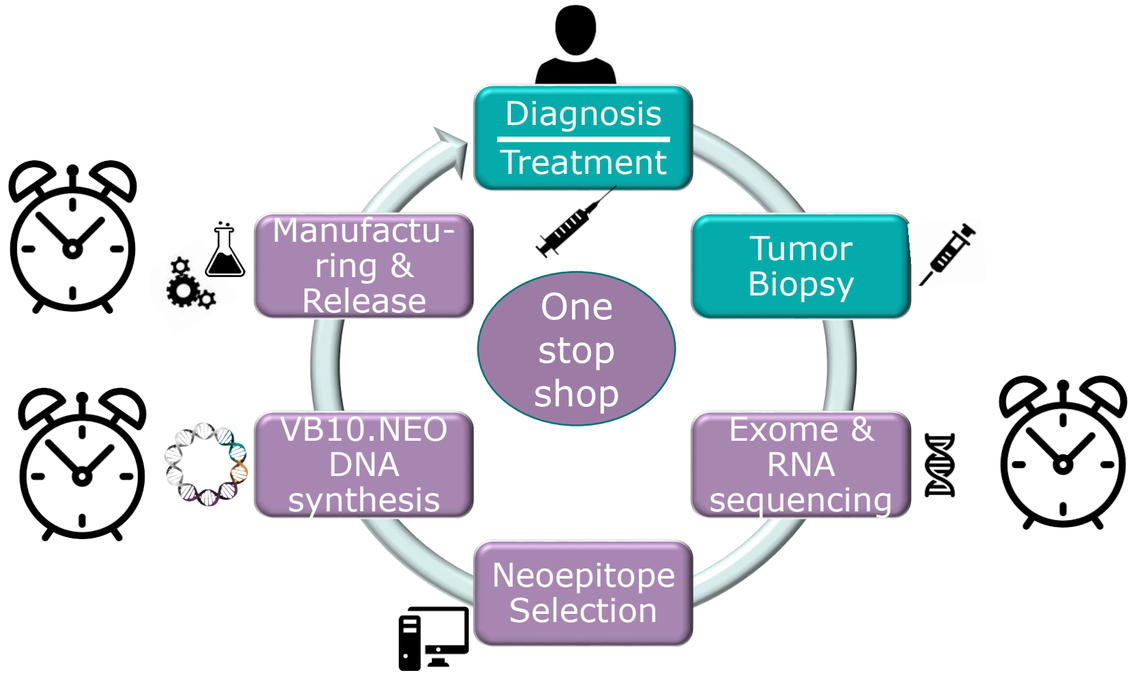
Logistics and Tracking Mitigation



- Establishment of a dedicated tracking team with preclinical, clinical and CMC responsibilities within the supply chain
- Same courier used for all shipments, spesialised within the area of pharmaceuticals
- Designed cloud based customised software solution, **TrakCel** to ease tracking and information sharing throughout supply chain.

Initial supply chain experience

One-stop-shop early in development



- Access to $
- Resource
- Maturity of process

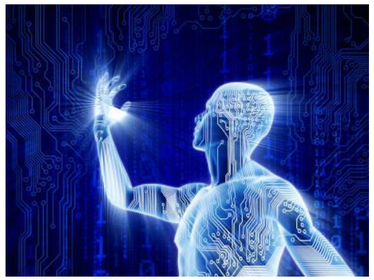
Main hurdles in the development of personalised vaccines

Regulatory

- ✓ Framework not sufficiently established and simplification outcomes not predictable
- ✓ Dependent on continuous interaction with authorities to build confidence that data generated are sustainable

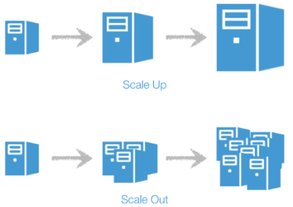
Technology

- ✓ State of the art technology not satisfactory to significantly reduce time or too expensive
- ✓ Complexity of product is such that state of the art technology cannot be used



CMOs – Collaborators

- ✓ Mindset of traditional drug developer
- ✓ Scale out capacity
- ✓ Document review process
- ✓ Cost profile
- ✓ Time lines
- ✓ Logistics
- ✓ Playing in tune



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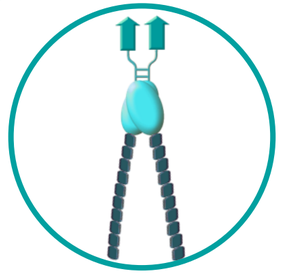

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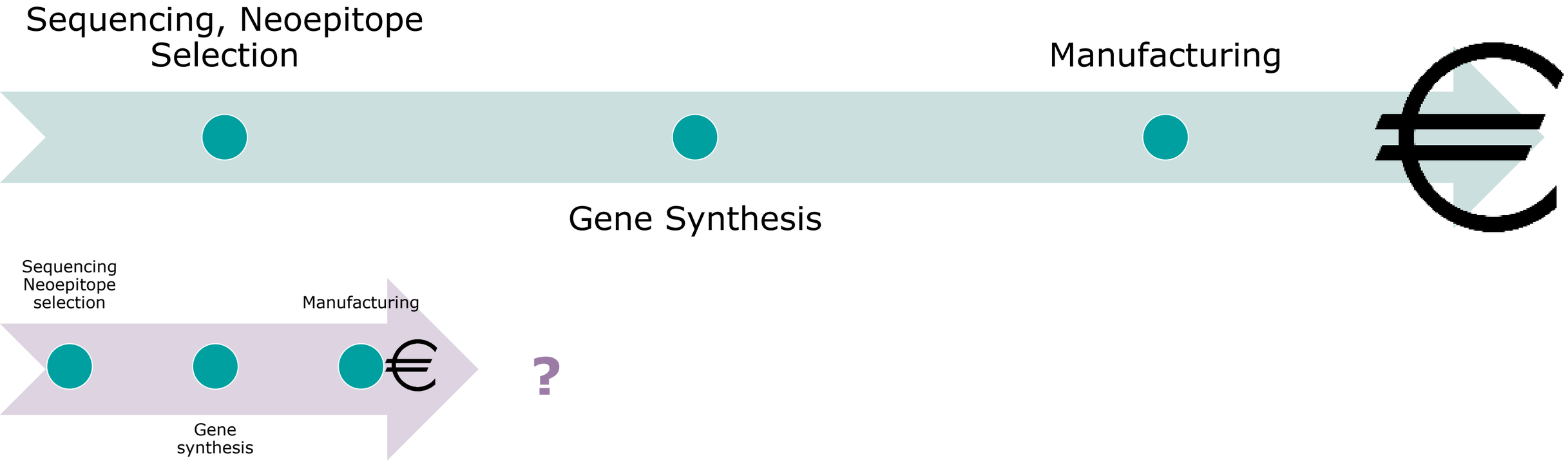
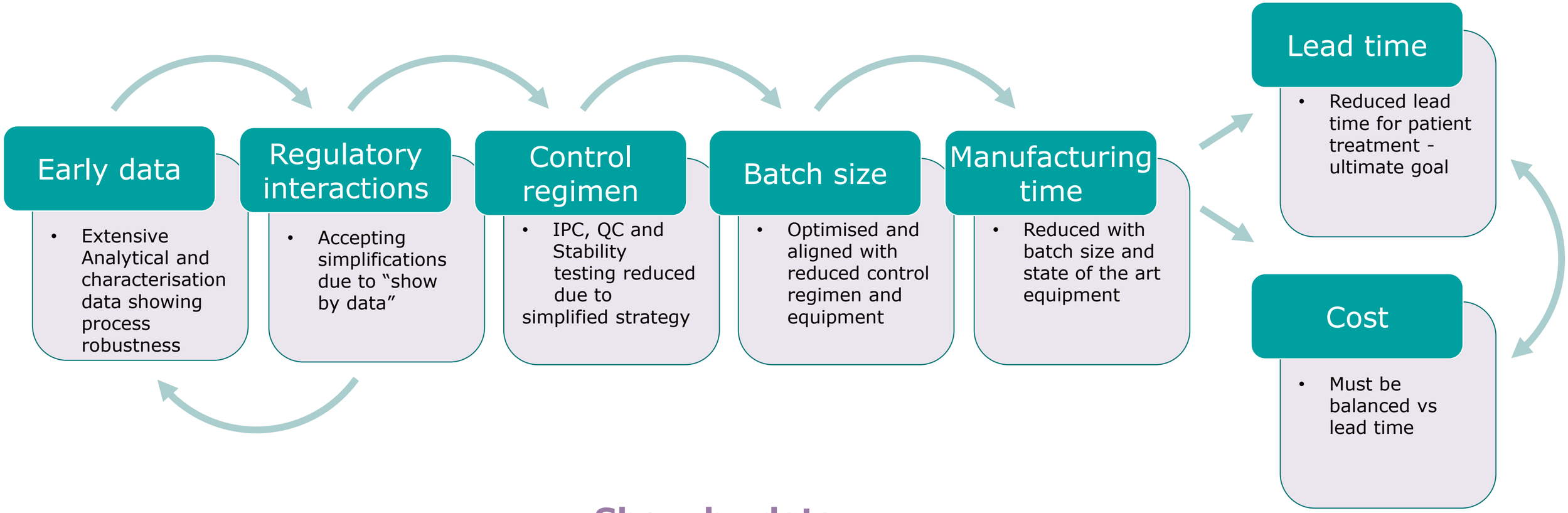
Ultimate Goal - Lead Time and Cost



Lead time - weeks

Sustainable Supply Chain for Late Clinical Phase and Commercial

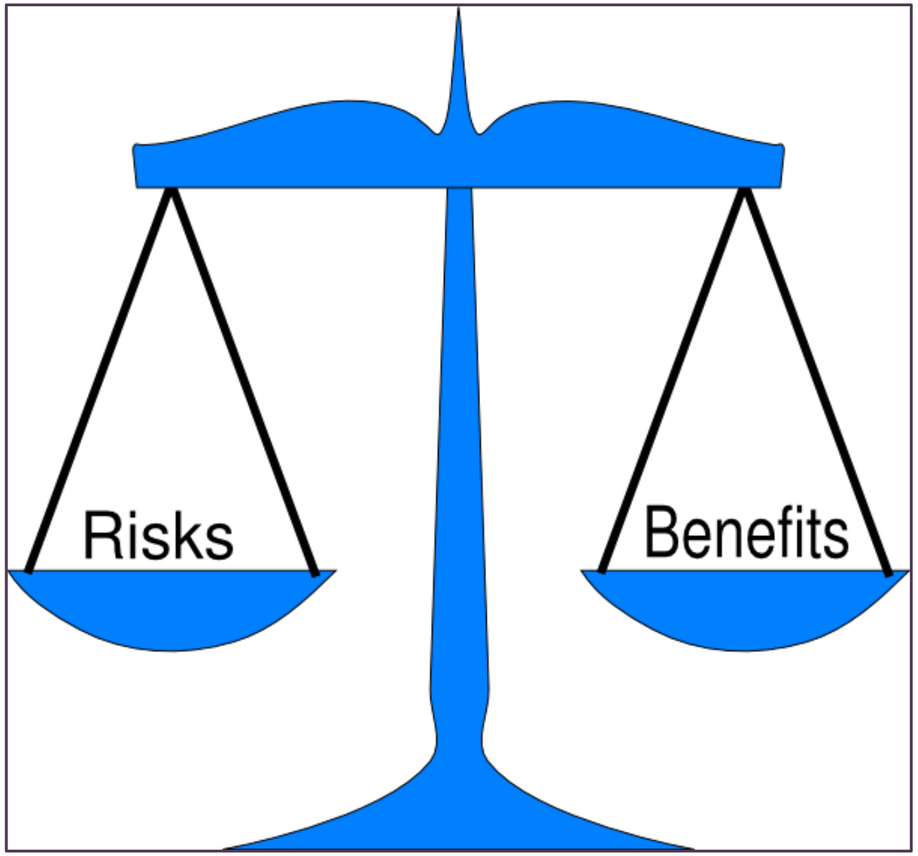


Show by data

Viable Products for Market and Patients

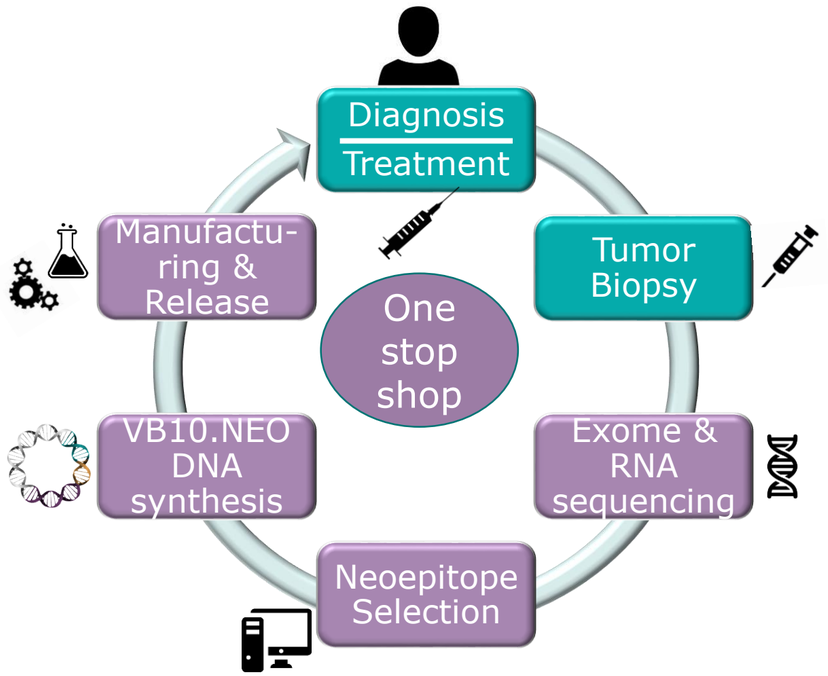
- Drug Substance not isolated
- Most QC at-line
- Sterility data available after administration
- Multiple drug product manufacturers
- Cost effective
- Very short lead time
- High quality products

FASTlab Concept in light of Risk–Benefit assessments for the Patients



Stringency

One-stop-shop is the Optimal Solution to FASTdna



- ✓ Technology driven
- ✓ Optimised design for scale-out capacity
- ✓ Equipment, balance of single use, lead time and cost
- ✓ Fill and finish - direct continuation of manufacture of active ingredient
- ✓ Expertise in bioinformatics, sequencing, gene synthesis, plasmid manufacture, aseptic manufacture, QA QC and logistics

Eventually: One-stop-shop where entire supply chain is integrated and sponsor is in control

Final Take Home Messages

- Appreciate the importance of regulatory expertise – hire or use consultans with previous experience within personlaised medicine. Close interactions with regulatory authorities from preclinical stage,
- Explore and monitor the development of state of the art technologies throughout the supply chain and how this can be utilitised to reduce time and cost during development and for the commercial product
- The more seamless, automated and closed the manufacturing and entire supply chain are the less pitfalls and opportunities for surprises
- Do not underestimate the logistics challenges and sure that tracking and mapping of entire supplychain is performed continuously

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