Arming the patient's immune system to fight cancer

CMC outsourcing in small virtual biotech company

28.02.2018

Subjects

- Introduction to Targovax and technology platforms
- Outsourcing to CDMOs
- Selection of CDMO

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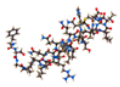
- **Introduction to Targovax and technology platforms**
- Outsourcing to CDMOs
- Selection of CDMO

Targovax

- Small biotech company in antigen specific cancer immunotherapy
- Located in Oslo and Helsinki
- History



2007-2012
115 pts treated in ATAP

1st ph I trial

3 Orphan Designations

2007 2009 2012 2013 2014

Oncos founded

ONCOS-102 IND

2 collaborations
Mesothelioma trial initated

Melanoma trial initated

2015 2016 2017 2018

Oncos and Targovax merger

IPO

TG01 data
OSE main board
TG02 trial initiated
TG02 data

Melanoma data
Mesothelioma data

1st TG01 trial

Orphan Designation

1989 1998 2002 2010 2011 2013

OUS and Norsk Hydro
TG program (~230 pts)

Hydro's pharma program discont.

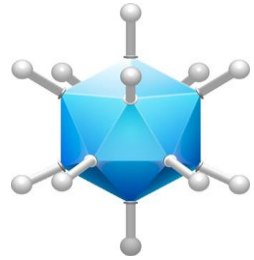
Long term survival data
Targovax founded

TG01-01 trial initated

Targovax has two immuno-oncology programs in clinical development

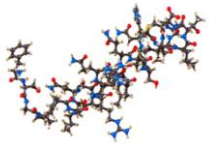
ONCOS
Oncolytic virus

- Genetically **designed adenovirus**
- Makes **cancer antigens** visible to immune system
- **Induces T-cells** specific to patients' tumor

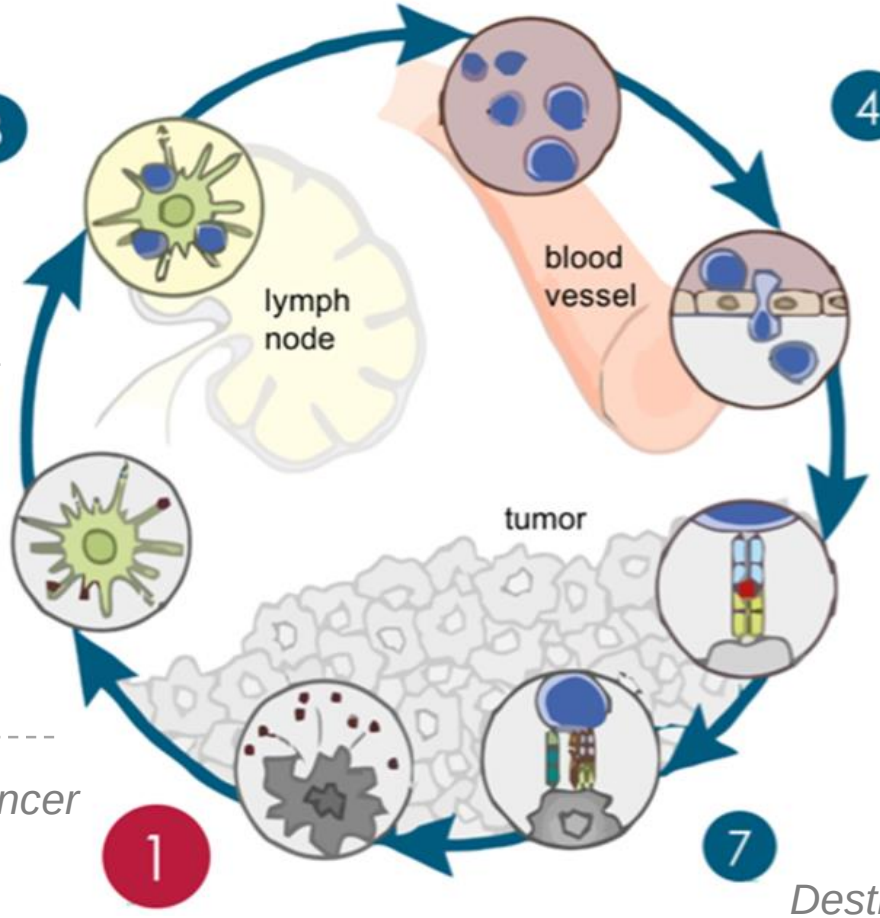


TG
RAS neoantigen vaccine

- Cocktail of **synthetic peptides**
- Mimics cancer causing **RAS neoantigens**
- **Induces T-cells** specific to **RAS mutations**



Targovax strategy is to boost the effect of immunotherapy by targeting multiple aspects of the cancer immunity cycle



1 *Release of cancer antigens*

2 *Cancer antigen presentation*

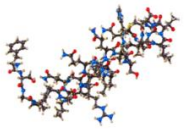
3 *T-cell activation*

4 *T-cell trafficking*

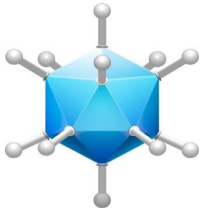
5 *T-cell tumor infiltration*

6 *Cancer cell identification*

7 *Destruction of cancer cells*



TG01
Peptide vaccine

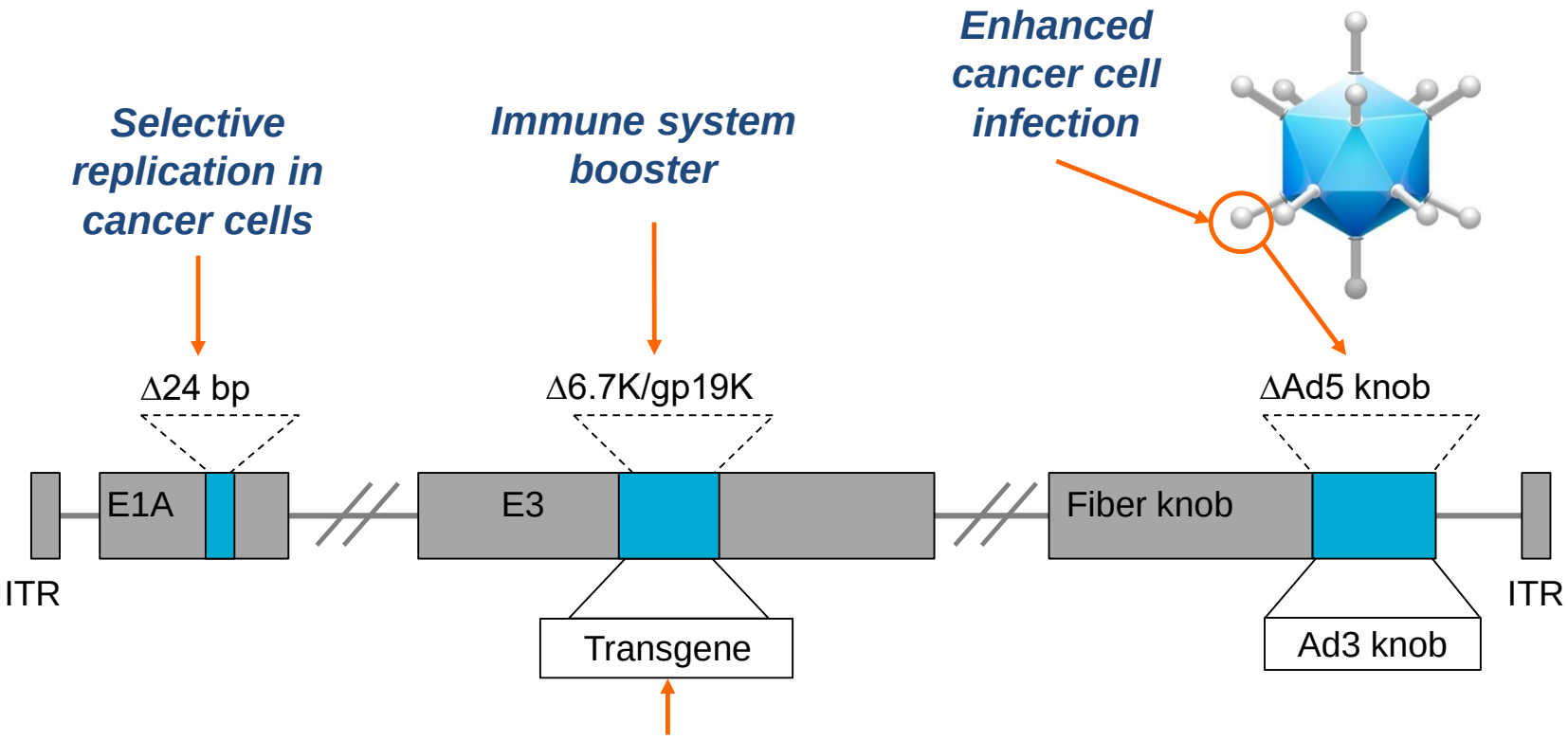


ONCOS-102
Oncolytic virus

Checkpoint inhibitors
Yervoy, Keytruda, etc…

Adapted from Chen et al. Immunity 2013; 39:1

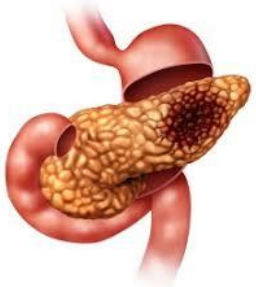
ONCOS-102 is a cancer targeting adenovirus armed with an immune stimulating transgene



- *GM-CSF transgene*
- *Triggers innate immune response and recruits APCs*

Resected pancreatic cancer is the lead indication, but all RAS mutated cancers are potential TG targets

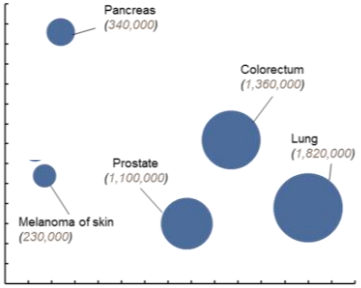
1. **Pancreatic cancer** (resected)
2. **Colorectal cancer**
3. **Lung cancer** (NSCLC)
4. **All mutRAS cancers**



- **TG01 lead indication**
- Completing phase I/II
- Planning phase II/III
- > 90% RAS mutated
- **40.000 patients**

- **TG02 lead indication**
- Phase I trial recruiting
- 50% RAS mutated
- **Up to 500.000 patients**

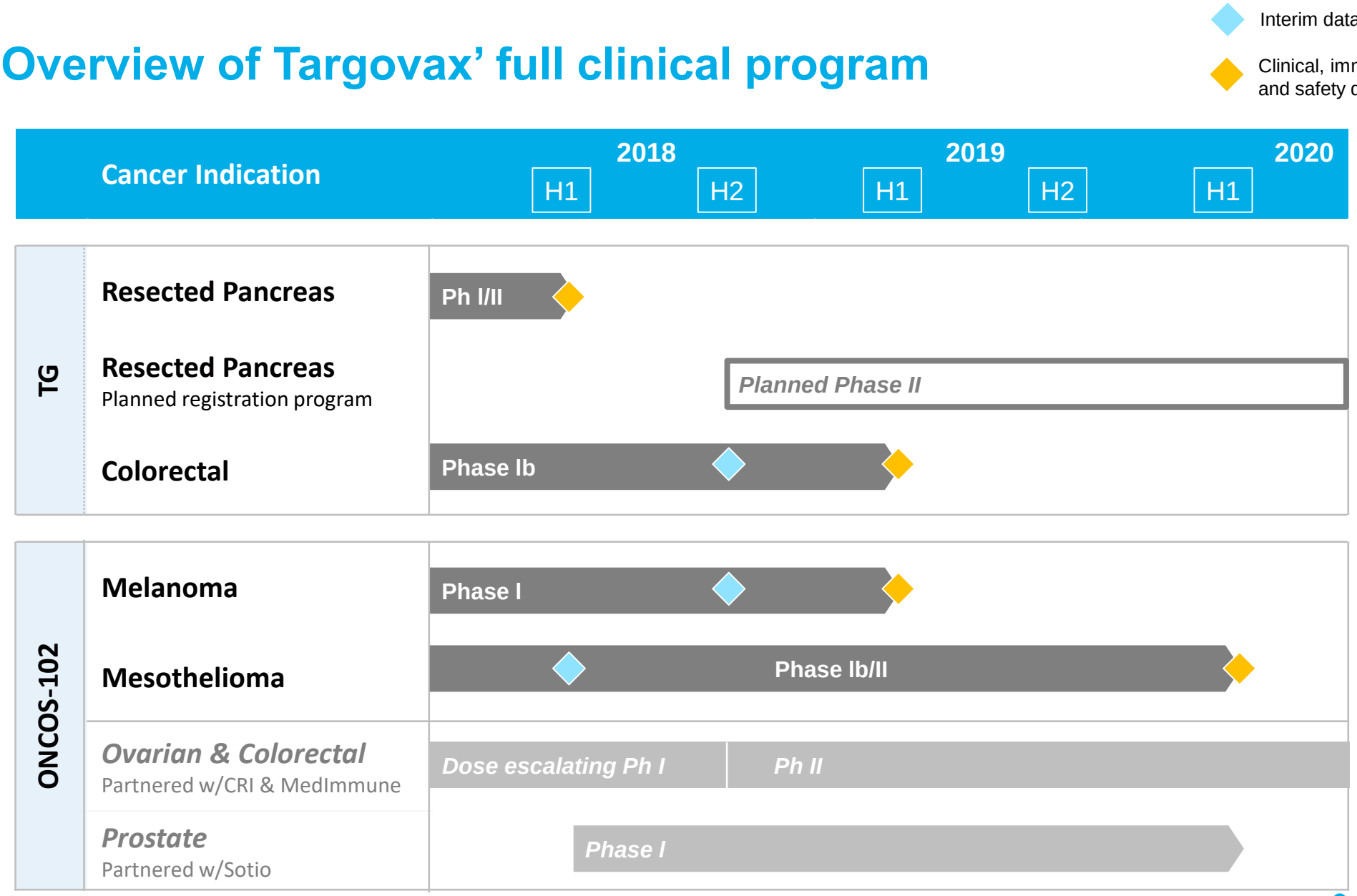
- **TG02 potential future indication**
- 30% RAS mutated
- **Up to 500.000 patients**



- **TG02 + TG03 ultimate long-term potential**
- 30% of all cancers
- **Up to 30% of all cancer patients**

Source: Global data, Riva et al. Plos One 2017 Estimated total addressable patient number with RAS mutations in US, EU and China

Overview of Targovax' full clinical program



Subjects

- Introduction to Targovax and technology platforms
- **Outsourcing to CDMOs**
- Selection of CDMO

Targovax strategy for CMC outsourcing

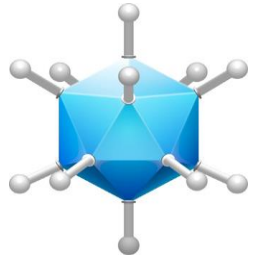
- Targovax is a virtual company and will outsource:
  - All development work and validation for manufacture processes and analytical methods for our IMPs.
  - GMP manufacture and quality control, and supply to clinical trials towards commercialization.

- Key CDMO and contract laboratory selection criteria:
  - Need to have in place quality standards to supply IMPs and commercial products to relevant markets, including EU, US and others as appropriate.
  - Need to have with high competency, skills and regulatory knowledge for the relevant outsourced scopes and products.

Targovax uses three IMPs in the clinical programs

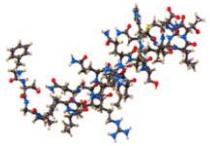
ONCOS
Oncolytic virus

- Genetically **designed adenovirus** 5
- Produced from human cancer cell line



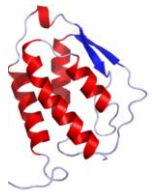
TG
RAS neoantigen vaccine

- Mixture of 7-8 **synthetic peptides** of 17 amino acids
- Lyophilized drug product

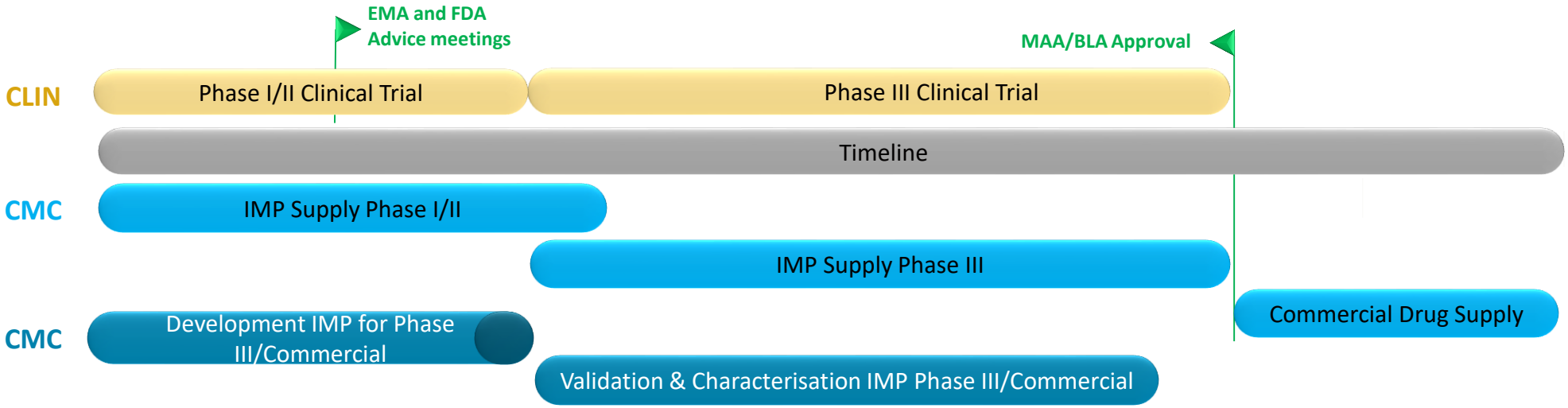


GM-CSF
Immunomodulating adjuvant

- **rHuGM-CSF** expressed from *E.coli*
- Lyophilized drug product



IMP supply and development for clinical trials



- Regulatory Affairs
- CLIN
- CMC IMP and Drug Supply
- CMC Product development

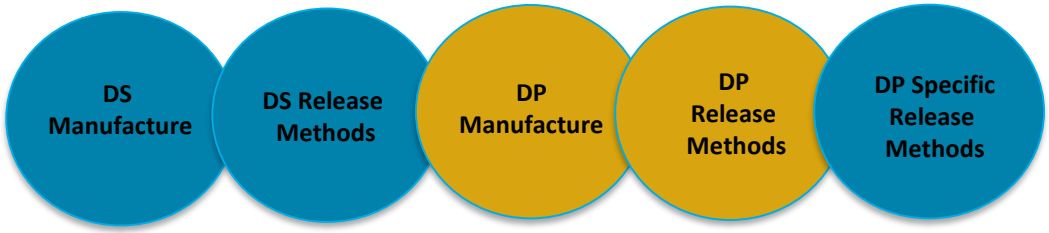
CLIN Clinical development
CMC Chemestry Manufacturing and Controls
EMA European Medicines Agency
FDA Food and Drug Administration

MAA Market Authorisation Application
BLA Biologics License Application

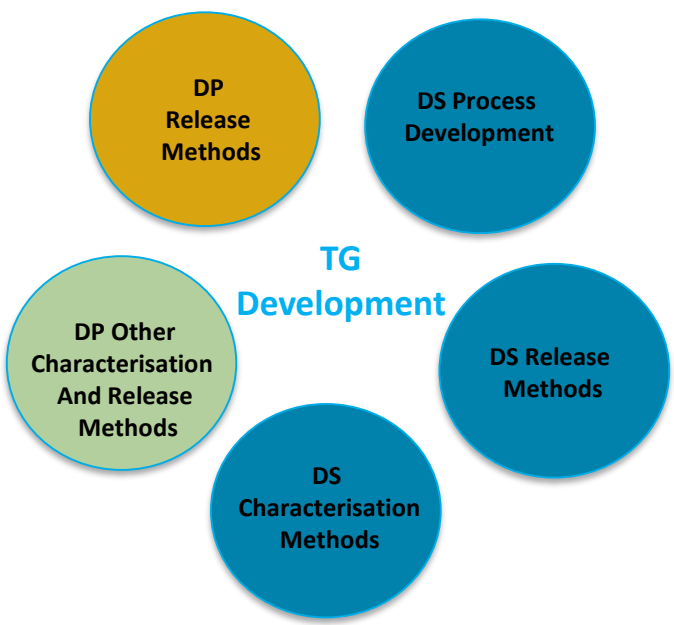
- Targovax is outsoucing all development, manufacture and analytical testing for 3 IMPs
- Currently
  - Supply of IMPs to clinical Phase I/II trials
  - Development of manufacture process and analytical methods for Phase III and commercial product

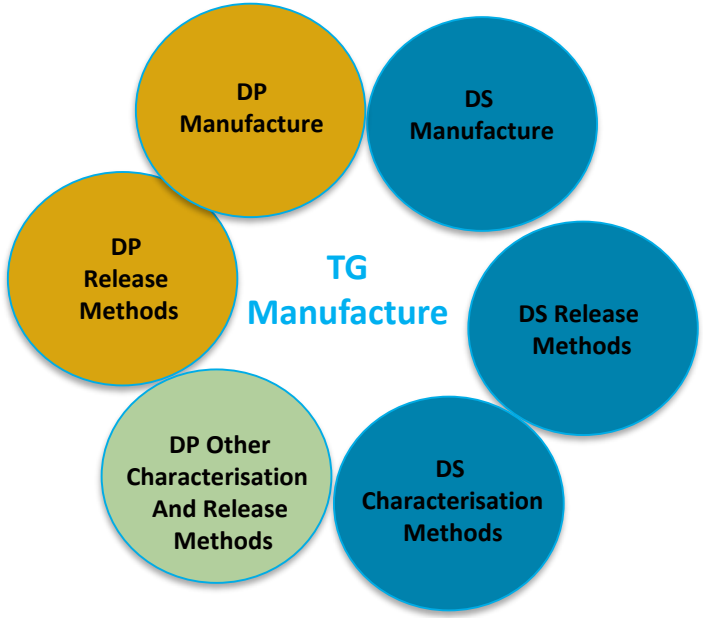
TG peptides

- Supply of TG to Phase I/II clinical trials:

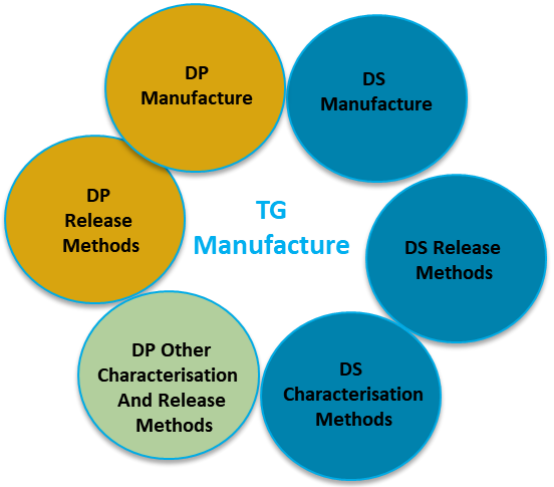


- Development & manufacture of TG for Phase III clinical trials





TG peptides



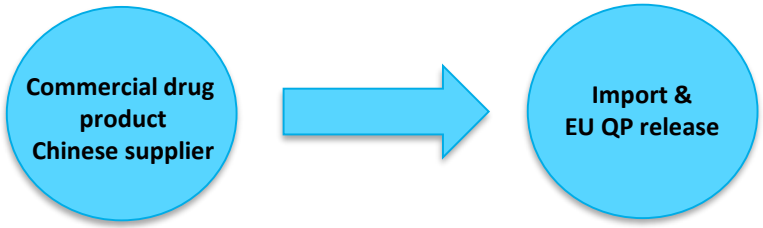
The CDMO picture for TG peptides

- Well known middle size CDMO for DS manufacture
  - Long history with Targovax
  - Financial strong
  - Located in central Europe, but global company
  - Strong expertise in development and manufacture of peptides
  - Regulatory compliant to EU and FDA GMP
  - Strong project management

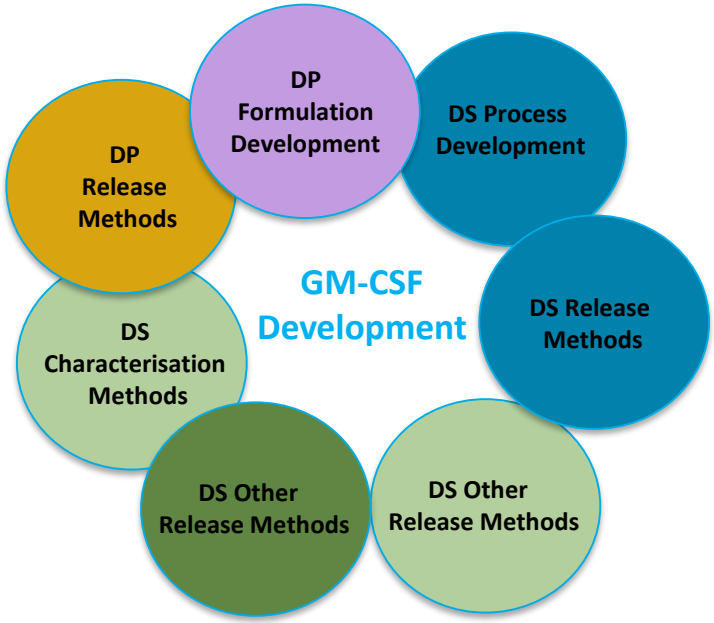
- Small CDMO for current DP manufacture
  - Strong and long time connection to DS CDMO
  - Communication mainly organized by DS CDMO
  - Limited capacity for large batch sizes
  - Limited methodologies for DP release testing

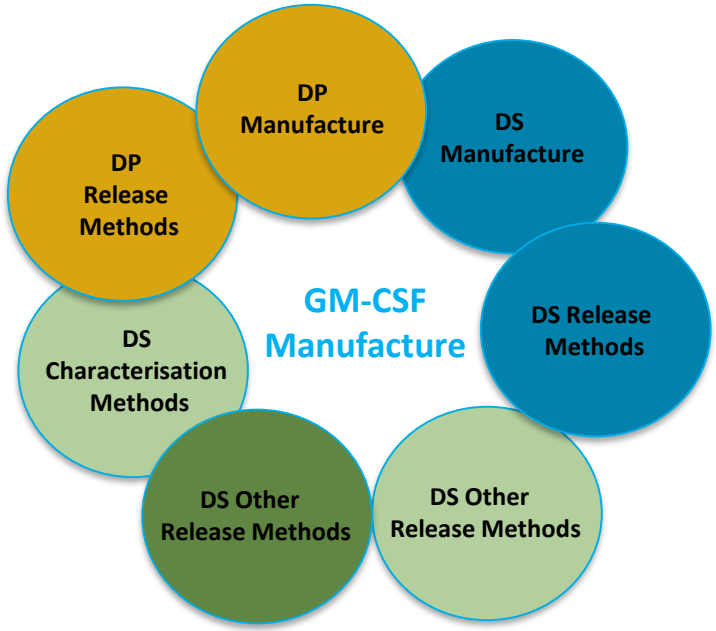
Recombinant GM-CSF

- Supply of GM-CSF to Phase I/II clinical trials:

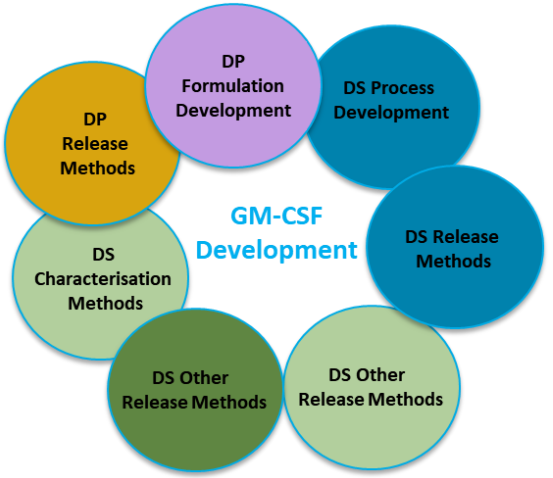


- Development & manufacture of GM-CSF for Phase III clinical trials:





Recombinant GM-CSF



The CDMO picture for GM-CSF

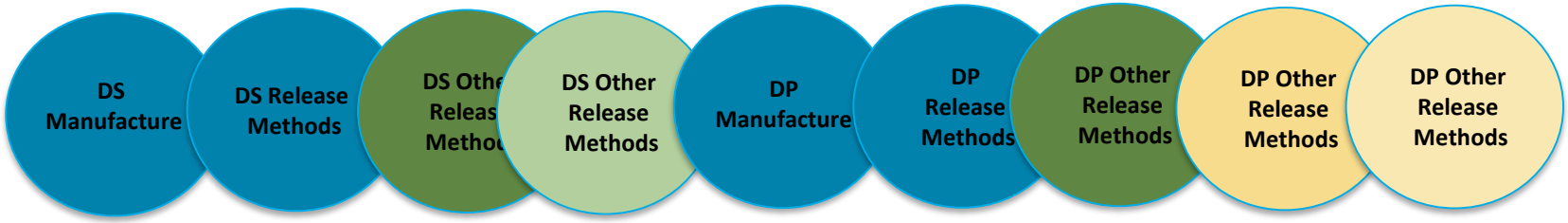
- Well known small/middle size CDMO selected for DS manufacture
  - Financial strong
  - Located in central Europe
  - Strong expertise in development and manufacture of recombinant proteins
  - Regulatory compliant to EU and FDA GMP
  - Contracts with other CDMOs for additional testing methodologies
  - Strong project management

- Small size CRO for formulation development
  - Large flexibility (order of work packages, experimental design)
  - Strong expertise in formulation development
  - Request high involvement from customer (experimental design & decision making)

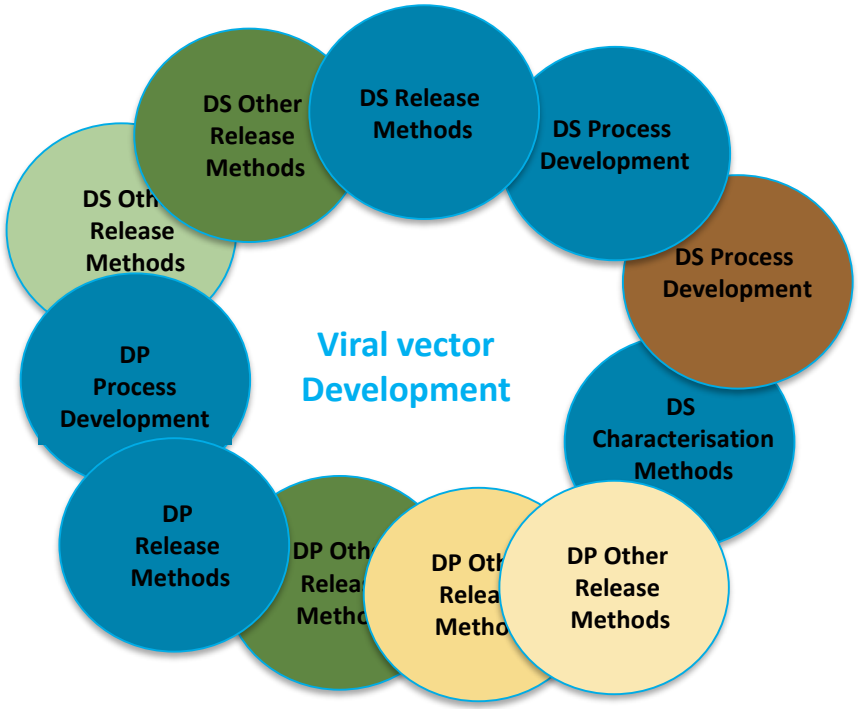
- CDMO for DP manufacture is not selected

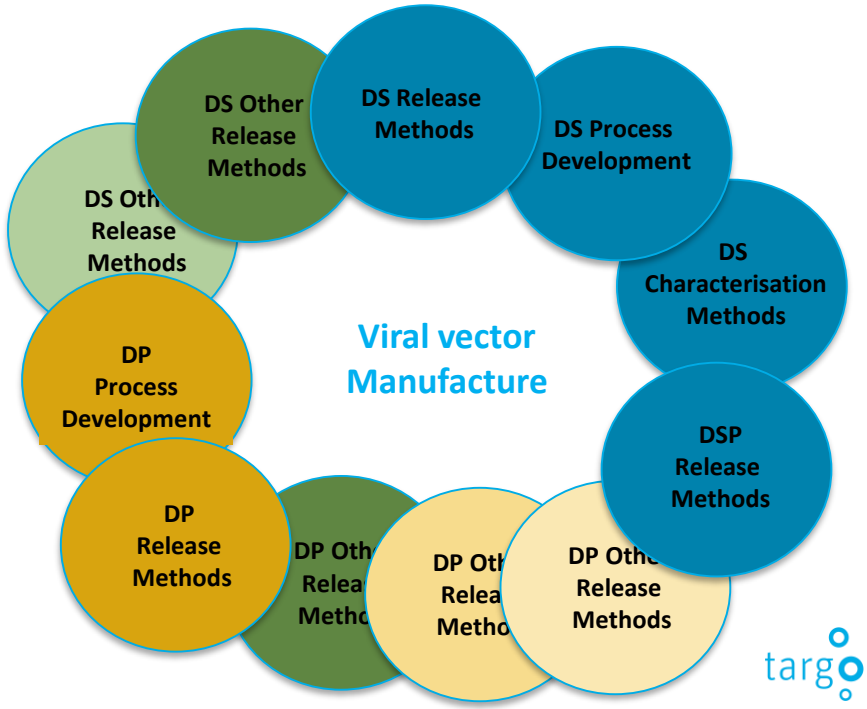
ONCOS-102 Viral vector

- Supply of ONCOS-102 viral vector to Phase I/II clinical trials:

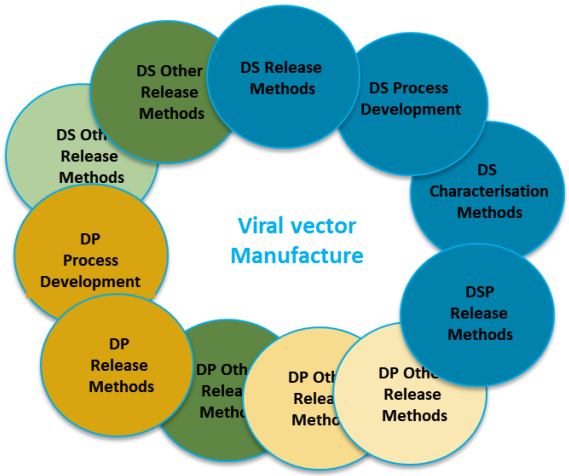


- Development & manufacture of ONCOS-102 viral vector for Phase III clinical trials:





ONCOS-102 viral vector



The CDMO picture for ONCOS-102

- Small CDMO for DS and DP manufacture
  - Long history with ONCOS
  - Located in Finland
  - Strong expertise on cell culture, viruses and quality control testing
  - Regulatory compliant to EU GMP
  - Strong project management
  - Strong involvement from Targovax
  - Limited capacity for large batch sizes of DP

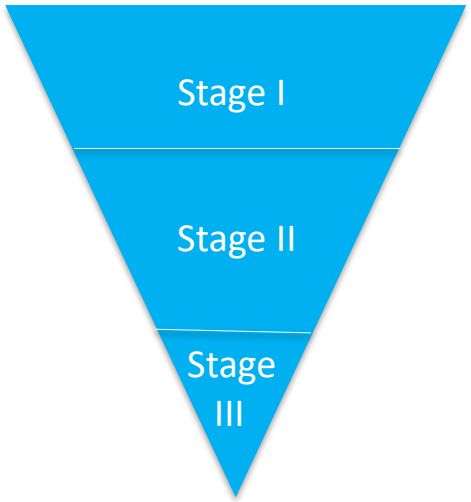
- Several CDMOs for additional quality control testing on DS and DP stage
  - Well known testing labs
  - Contracted mainly by Targovax
  - Coordination responsibility and contracts to be moved to CDMO selected for DS and DP manufacture

Subjects

- Introduction to Targovax and technology platforms
- Outsourcing to CDMOs
- **Selection of CDMO**

Selection of CDMO

- Assessment of DP CDMO for TG peptides, GM-CSF and ONCOS-102
- Define the strategy and goals
  - Strategic decision with long-term consequences
- Define your team: CMC, QA, Regulatory, BD
  - Identify stakeholders



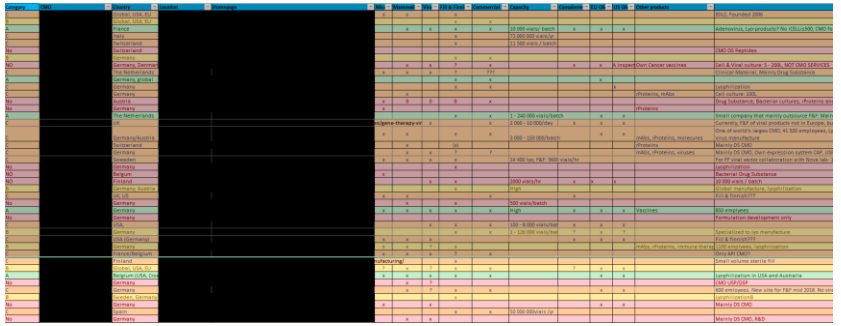
Search by Internet / Networks / Consultans / Other CMOs	50 CMOs
Emails / Company presentations / Calls / Meetings	5-10 CMOs
Request for proposals / Proposals /Audits	3-5 CMOs

Selection of CDMO – Stage I

- Definition of Targovax specific requirements: Operations, Technical, Quality, Business
  - Location
  - DS and/or DP
  - Technology and equipment
  - Safety, containment, e.g. biosafety levels
  - Capacities
  - Regulatory compliance (EU, US)

- Availability of CDMOs, e.g. ” Directory of Biopharmaceutical Contract Manufacturers” – 80 CDMOs

- Matrix: CDMO services vs. requirements



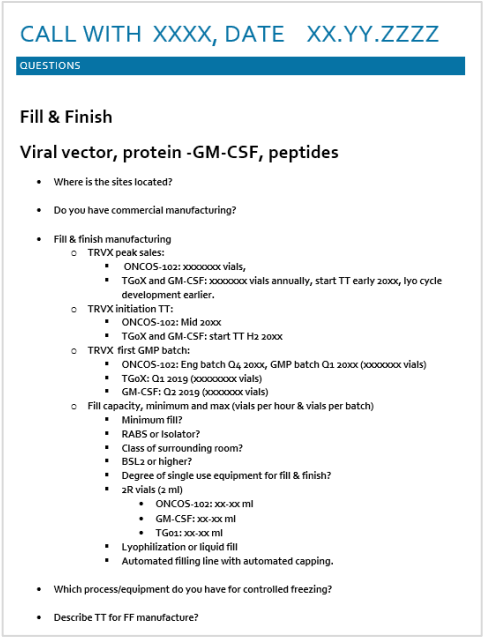
- CDMO, consultants & personal contacts
  - Recommendations

- Partnering conferences / Trade shows

- First screening

Selection of CDMO – Stage II

- Direct contact with CDMO
  - Emails / calls / presentations / meetings
  - Request for Information (RFI) based on criteria
    - Technical
      - Confirmation of data from Stage I
        - More detail info vs requirements
        - Premises, technology and equipment
        - Capacities (batch sizes, new customers)
        - Analytical capability
    - Quality
  - CDA – Confidential Disclosure Agreement
  - Ballpark figures
    - RFI & CDMO questionnaire
  - Site visits – Define the agenda
    - Facility tour
    - Financial strength
    - Project management, communication, transparency
    - Staff competency and trust
    - Track record
- Second screening



CALL WITH XXXX, DATE XX.YY.ZZZZ

QUESTIONS

Fill & Finish

Viral vector, protein -GM-CSF, peptides

- Where is the sites located?
- Do you have commercial manufacturing?
- Fill & finish manufacturing
  - TRVX peak sales:
    - ONCOS-102: xxxxxxx vials,
    - TGoX and GM-CSF: xxxxxxx vials annually, start TT early 20xx, lyo cycle development earlier.
  - TRVX initiation TT:
    - ONCOS-102: Mid 20xx
    - TGoX and GM-CSF: start TT H2 20xx
  - TRVX first GMP batch:
    - ONCOS-102: Eng batch Q4 20xx, GMP batch Q1 20xx (xxxxxxx vials)
    - TGoX: Q1 2019 (xxxxxxxx vials)
    - GM-CSF: Q2 2019 (xxxxxxx vials)
  - Fill capacity, minimum and max (vials per hour & vials per batch)
    - Minimum fill?
    - RABS or Isolator?
    - Class of surrounding room?
    - BSL2 or higher?
    - Degree of single use equipment for fill & finish?
    - 2R vials (2 ml)
      - ONCOS-102: xx-xx ml
      - GM-CSF: xx-xx ml
      - TG01: xx-xx ml
    - Lyophilization or liquid fill
    - Automated filling line with automated capping.
- Which process/equipment do you have for controlled freezing?
- Describe TT for FF manufacture?

Selection of CDMO – Stage III

- Request for proposals (RFP)
  - Scope of services, technical data and milestones
  - Proposal
    - Commercial proposal (breakdown in all project and manufacture costs)
      - Design for a competitive bidding process
    - Proprietary technology
    - Master program incl. Gantt chart
    - Sub-contractors
    - Contract conditions
    - GMP certificates & Site master file
    - Financial statements
    - References

- Proposal evaluation (and previous evaluation)

- Technical Due Diligence / Quality audits
    - 1-3 CDMO

- Selection of Targovax CDMO for DP manufacture
    - Term Sheet, Letter of Intent
    - Master Service Agreement, QA agreement

CDMO learnings

- Building trust and good working relationship
- Frequently communication & site visits – transparency
- Be present on CDMO site
- Stepwise approach to CDMO services - development
- CDMO full responsibility of sub-contractors
- Master Service Agreements & QA agreements
- Budget with additional costs