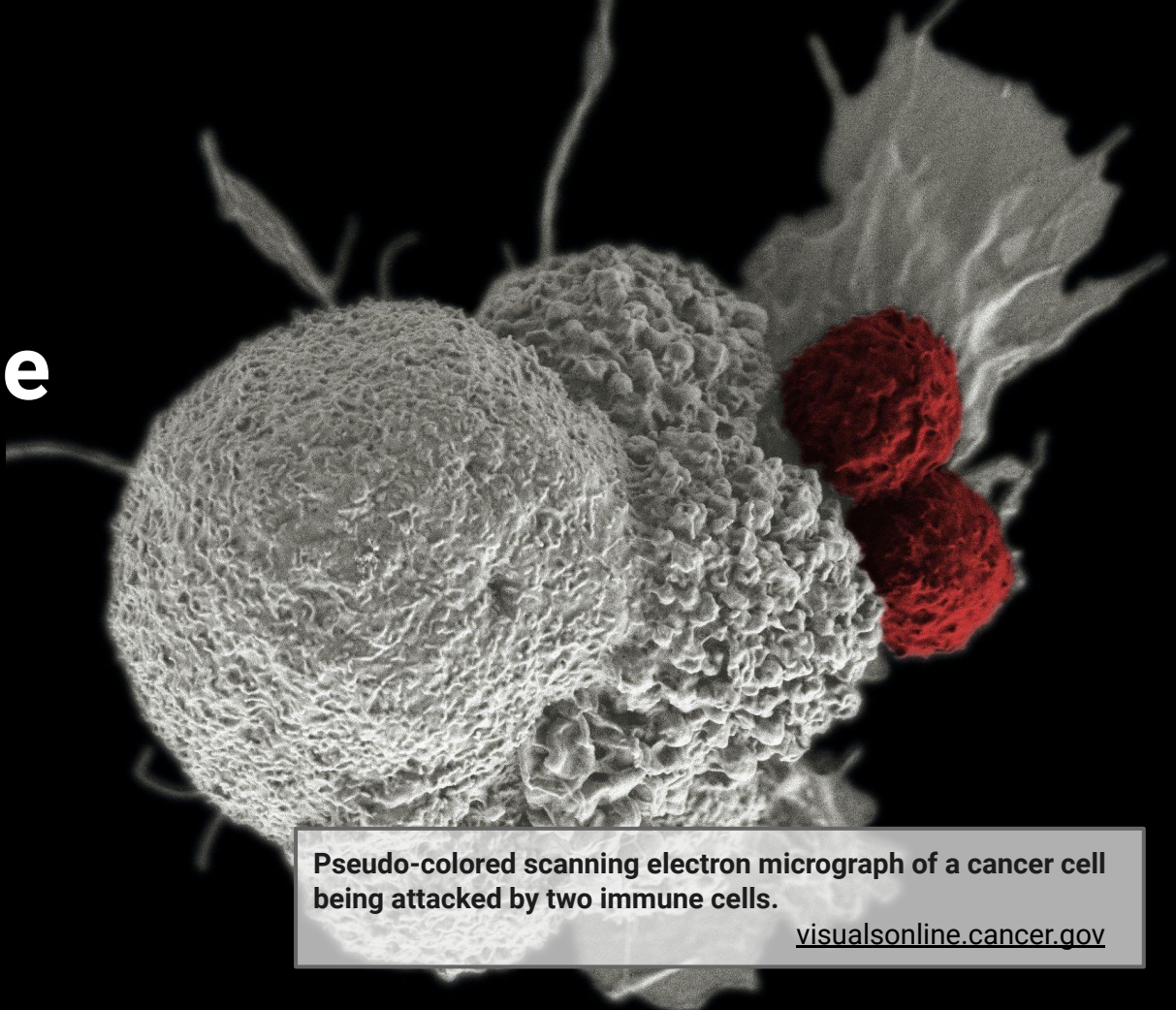
DEEP
PHARMA
INTELLIGENCE

Cancer Vaccine Industry

Landscape Overview

Q1 2022

www.deep-pharma.tech
info@deep-pharma.tech



Pseudo-colored scanning electron micrograph of a cancer cell being attacked by two immune cells.

visualsonline.cancer.gov

Table of Contents

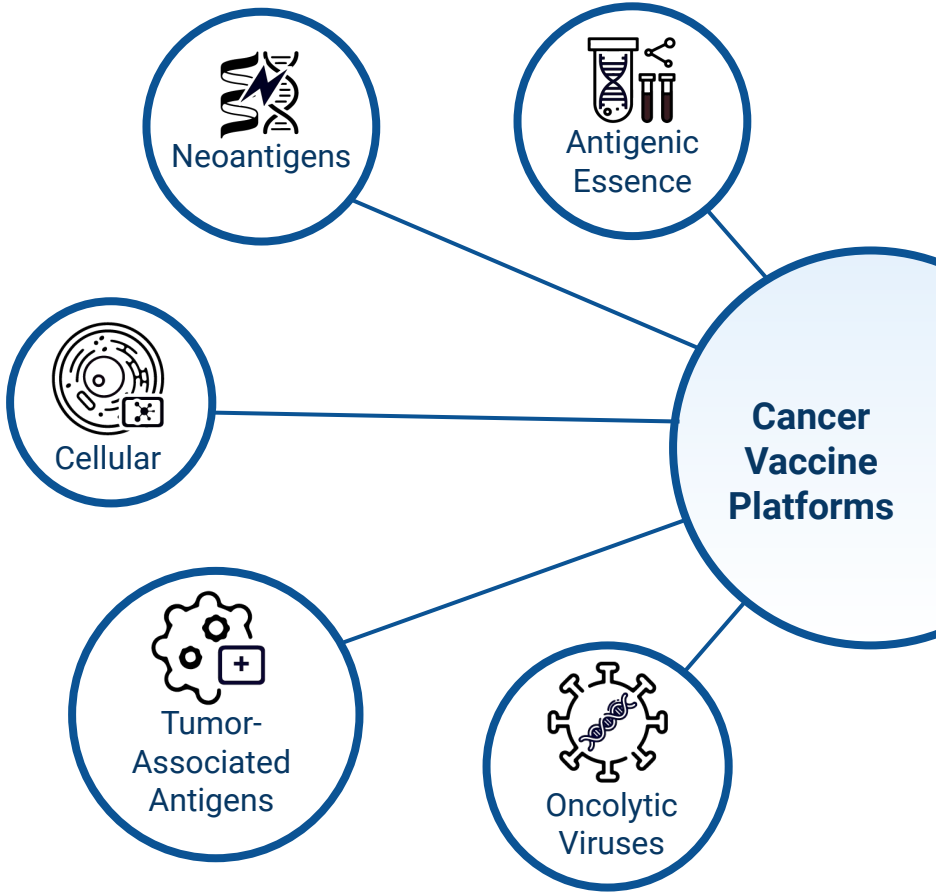
Intro: What is a Cancer Vaccine?

The most powerful weapon against malignancies can be hidden inside the host human body and it is called **immune system**. Cancer mechanisms usually trick our immune system but a proper therapy can turn our immunity back against the tumor.

That's the very aim of **cancer vaccination — to activate host immunity cells to destroy the tumour cells.**

There are multiple platforms developed to obtain cancer vaccines, in this report we are going to discuss 5 of such platforms, which serve as a basement for vaccines creation.

Some of these cancer vaccine platforms overlap and evolve out of each other while still have some unique distinguishable features which was a reason for suggested classification.



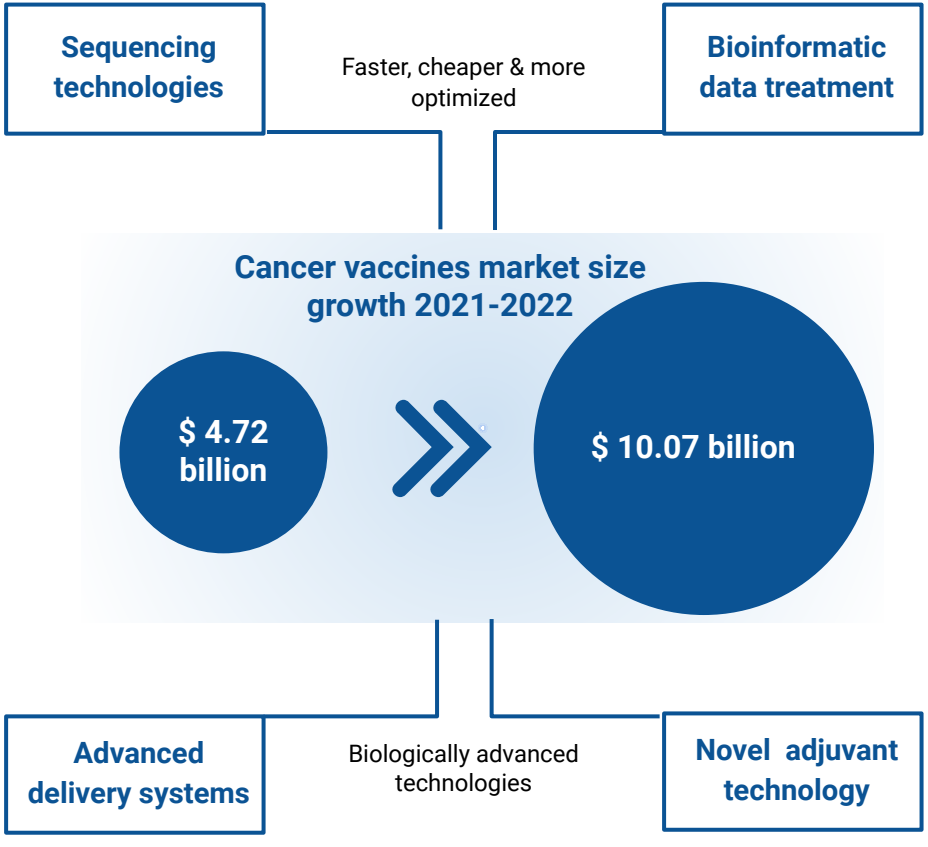
Cancer Vaccine Industry

At first, cancer vaccines didn't succeed: the enthusiasm and interest towards this technology dropped after seeing the high level of adverse effects versus low efficacy.

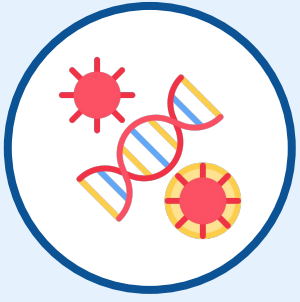
However, with the development of **sequencing technologies**, innovative **delivery systems, bioinformatic data treatment strategies** and vaccine **adjuvants** — cancer vaccines have more and more prominent chances to become deeply integrated into the market.

In 2021 the **market size** of cancer vaccines was estimated as 4.72 billion US$ and it is expected to reach **10.07 billion US$ in 2022.**

Considering this tendency, it is reasonable to say that cancer vaccines start forming a **separate branch of industry.**



Intro: Where is Cancer Vaccination Right Now?



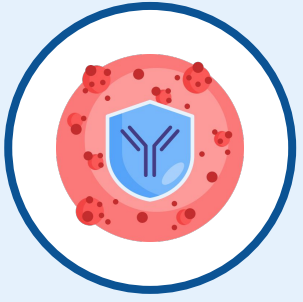
We learnt how to target tumors through their unique mutations - **neoantigens**

To prevent **tumour escape** we need to target multiple antigens on the tumour cell

cytotoxic CD8+ T-cells

We targeted **cytotoxic CD8+ T-cells** to kill the cancer cells

We need to engage **both CD8+ and memory CD4+ T-cells** to prolongate the effect

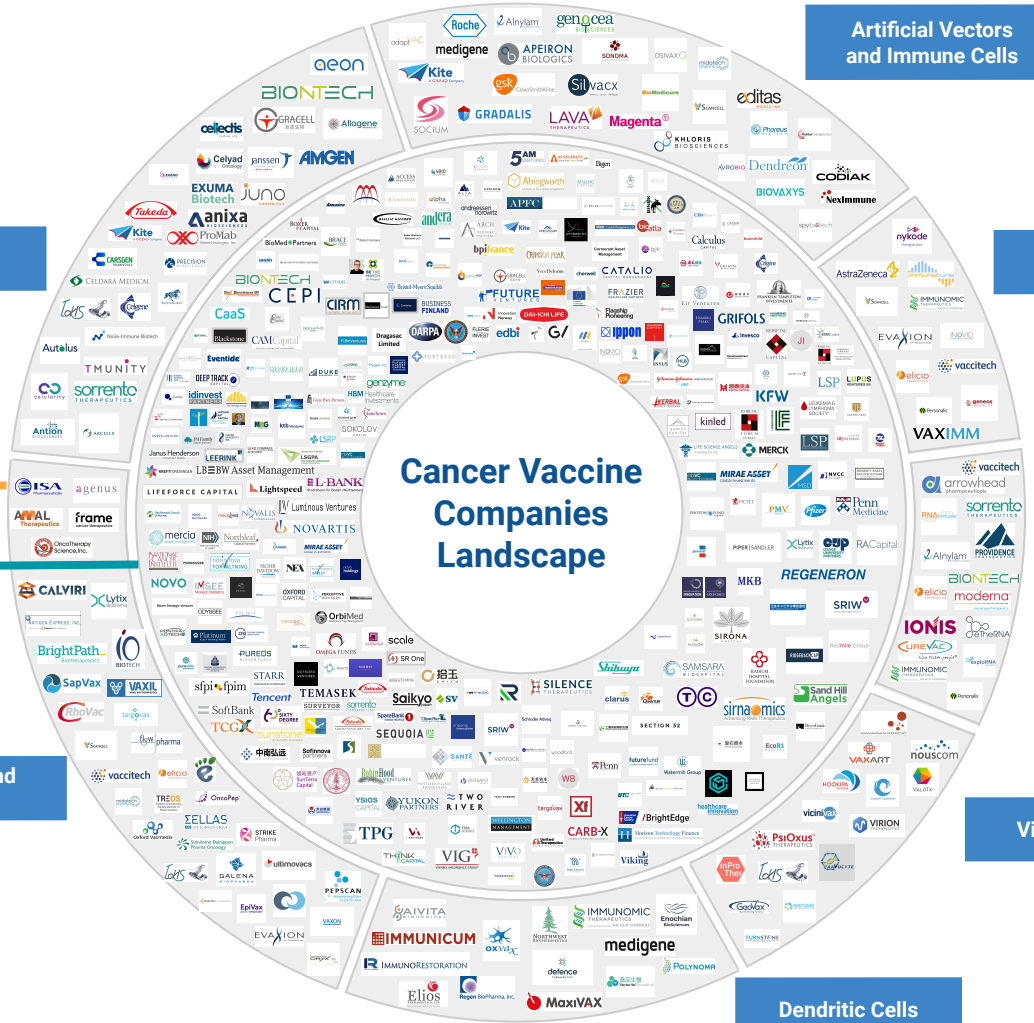


We found out that the **tumour lysates** can activate the immune response to cancer

Off-tumor effects became a severe reason for the damage so scientists are working to decrease them

Cancer Vaccines and Cell Immunotherapies by Delivery Form

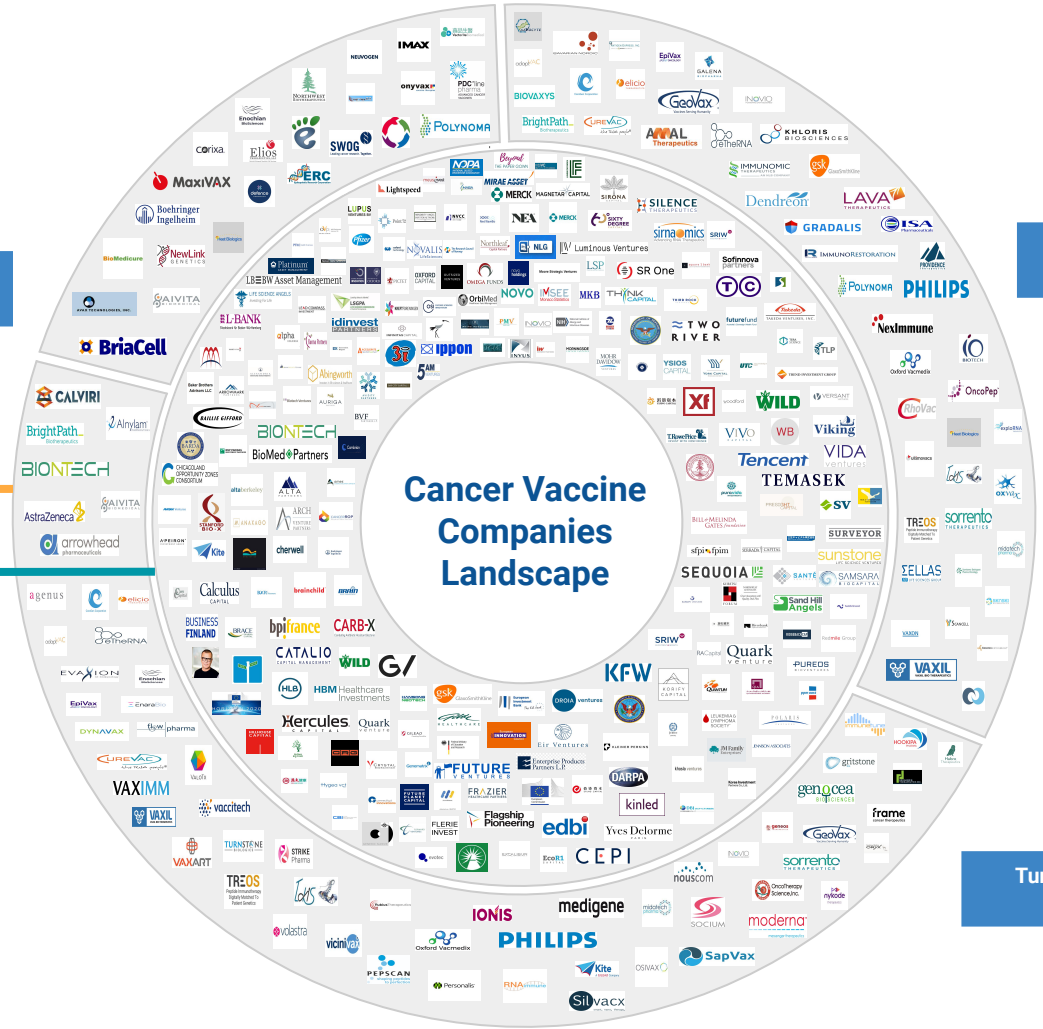
Companies - 130
Investors - 360



DEEP PHARMA INTELLIGENCE

Cancer Vaccines by Antigen Type

Companies - 115
Investors - 250



DEEP PHARMA INTELLIGENCE

Level of Cancer Vaccine Innovation of 30 Leading Companies in Drug Discovery Sector

Innovative Approach

1	Biobohemia
2	AiVita Biomedical
3	Gradalis
4	Editas Medicine
5	Genocea Biosciences (NASDAQ:GNCA)
6	Gritstone Oncology (NASDAQ:GRTS)
7	Heat Biologics (NASDAQ:HTBX)
8	NexImmune (NASDAQ:NEXI)
9	Oxford Vacmedix
10	IO Biotech
11	Scancell Holdings (LSE:SCLP)
12	Sorrento Therapeutics (NASDAQ:SRNE)
13	Ionis Pharma (NASDAQ:IONS)
14	Rubius Therapeutics (NASDAQ:RUBY)
15	Arrowhead Pharmaceuticals (NASDAQ:ARWR)

Classic Approach

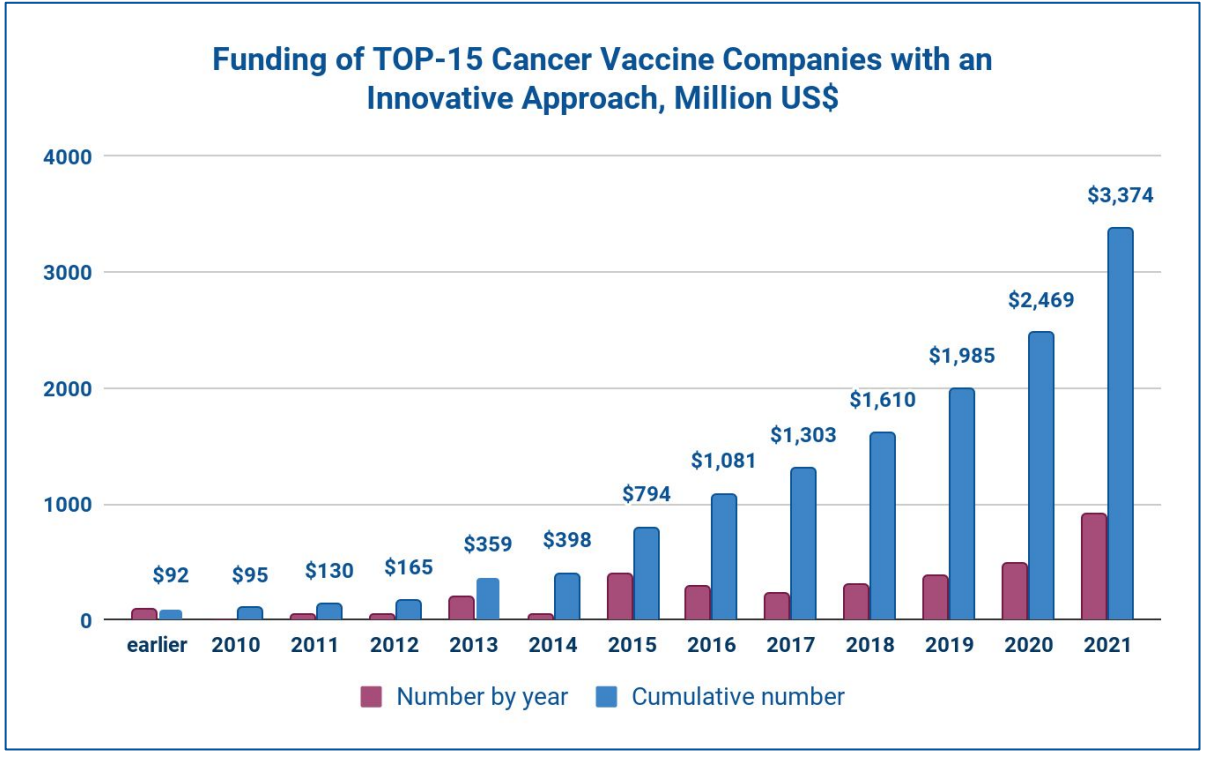
1	Agenus Inc. (NASDAQ:AGEN)
2	AstraZeneca (NSE:ASTRAZEN)
3	BioNTech (NASDAQ:BNTX)
4	CureVac (NASDAQ:CVAC)
5	Vaccitech
6	Enochian Biosciences (NASDAQ:ENOB)
7	Immunomic Therapeutics
8	Inovio Pharmaceuticals (NASDAQ:INO)
9	GlaxoSmithKline (NYSE:GSK)
10	Moderna Therapeutics (NASDAQ:MRNA)
11	Northwest Biotherapeutics (OTC:NWBO)
12	OncoPep
13	Gilead Sciences
14	PsiOxus Therapeutics
15	Nykode Therapeutics

Methodology: database creation followed by the detailed analysis of every individual use case by the quantitative and qualitative features such as: cancer vaccine category; complexity and development possibilities of the technology; number of similar products on the market/development pipelines; novelty of the product; addressment of the unmet needs etc.

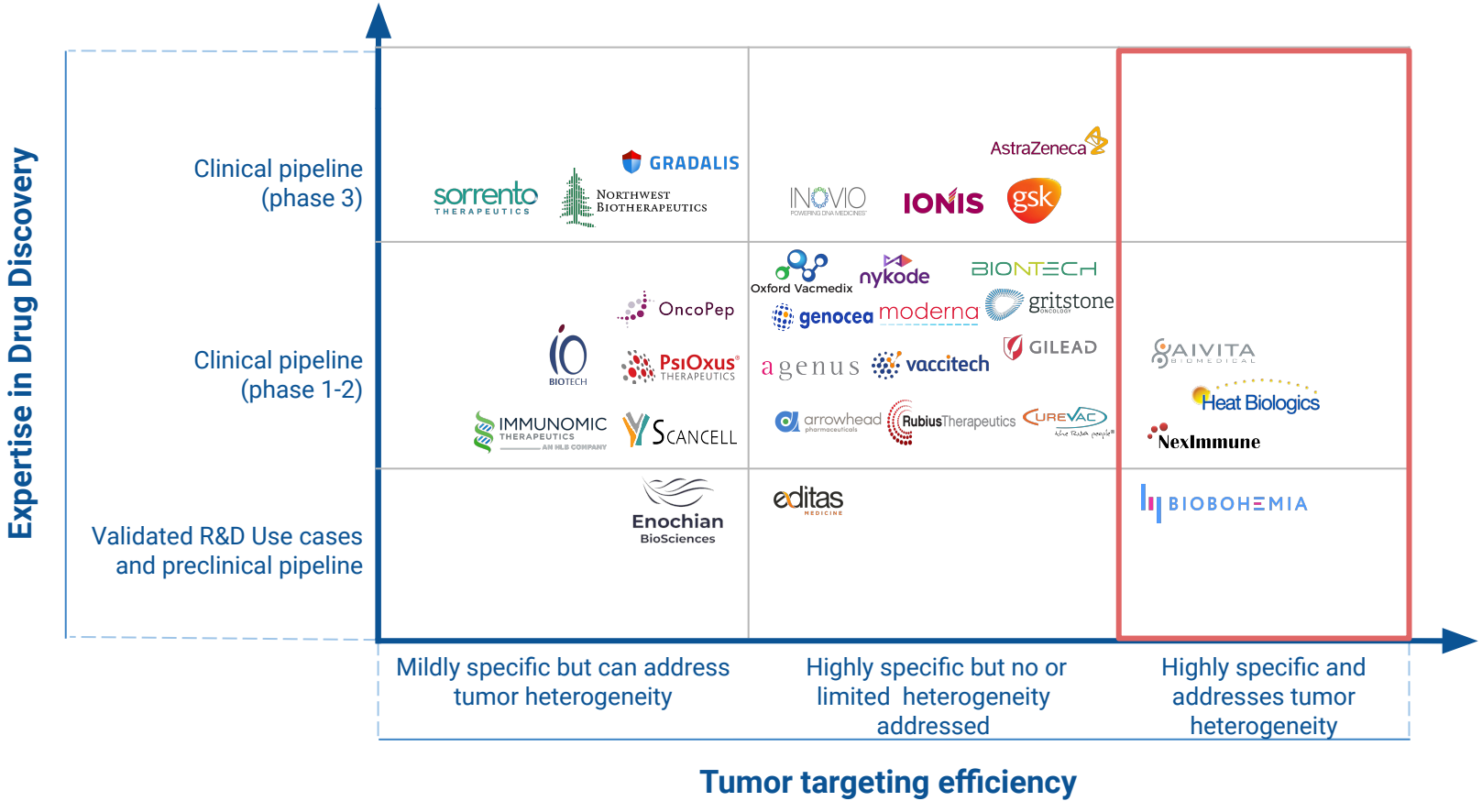
Comparison of Top-30 Leading Drug Discovery Companies Expertise in Cancer Vaccines R&D

Cancer vaccines development shifted into the direction of more **specific tumor targeting** due to **neoantigen platform**. Still, the tremendous majority of such neoantigen vaccines don't overcome the problem of tumor escape mutations and the heterogeneity of cancer cells.

Only restricted number of **innovative platforms** try to face and solve both issues of **highly specific tumor targeting and escape mutations prevention.** They apply **new approaches** on already developed platforms (such as whole-cell, neoantigen, TAA) or initialize **new platform (antigenic essence).**



Comparison of Top-30 Leading Drug Discovery Companies Expertise in Cancer Vaccines R&D

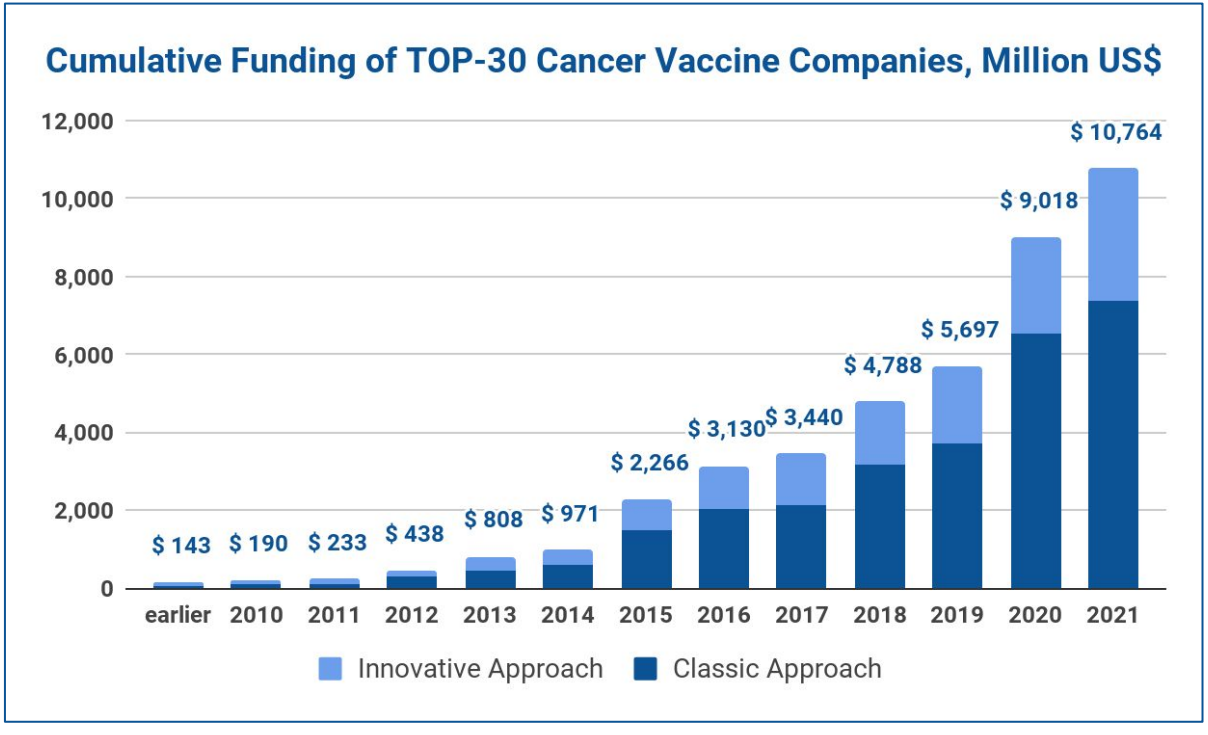


Comparison of Top-30 Leading Drug Discovery Companies Expertise in Cancer Vaccines R&D

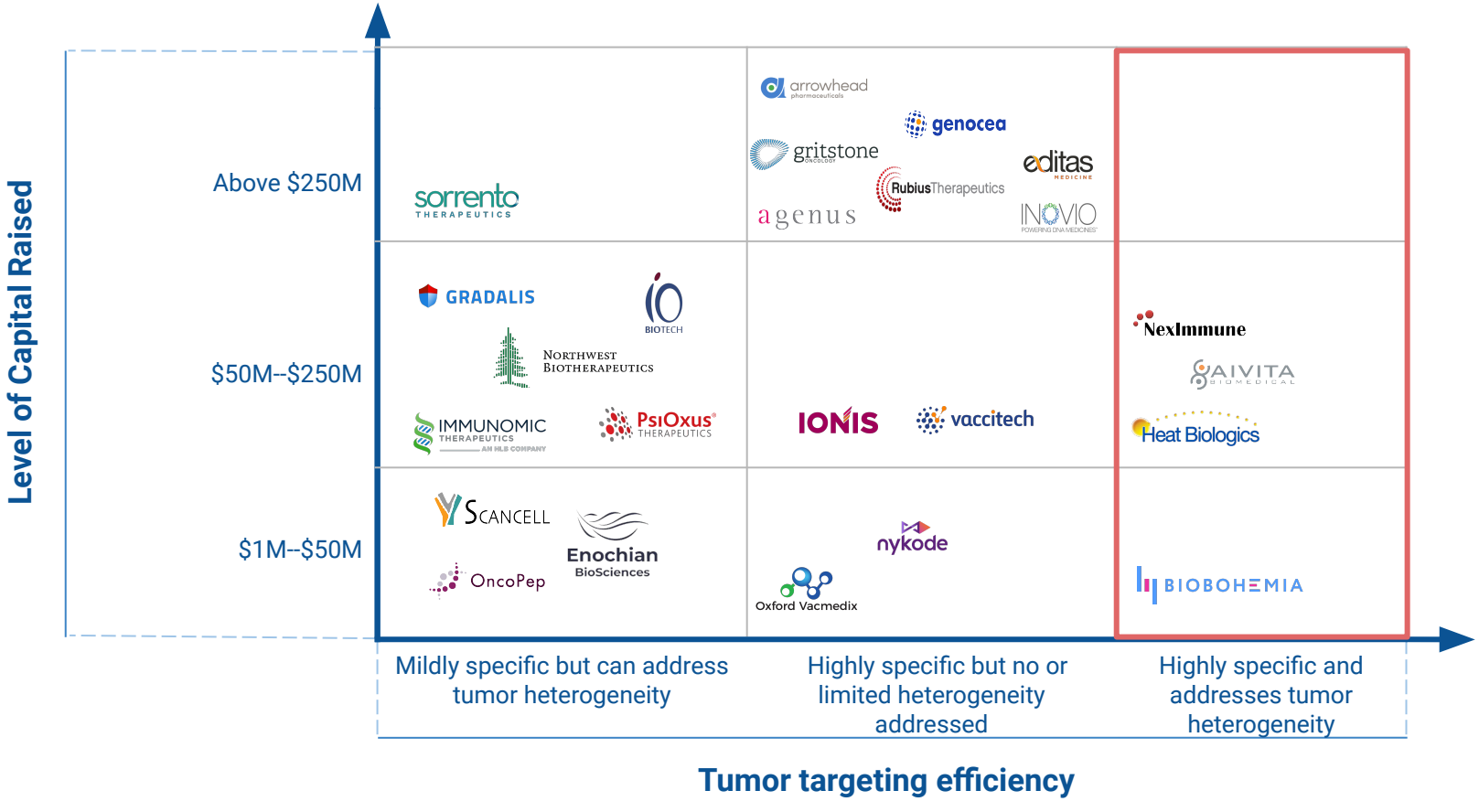
Cancer vaccine leaders belong both to big pharma companies with multiple directions and to fast-growing start-ups which are more oriented on cancer vaccine development only.

Such **big pharma** companies mostly keep up with **mainstream approaches** like neoantigens in the form of mRNA vaccines (Moderna Therapeutics and BioNTech) and raise funding from various sources.

At the same time there is a **drastic growth** experienced by companies who apply more **innovative approaches.** According to the study of TOP-15 cancer vaccine companies with innovative approach at the moment of Q2 2021 they already raised roughly twice as much as during the whole 2020 (**$850 million and $484 million** correspondingly).



Comparison of Top-25 Leading Drug Discovery Companies Expertise in Cancer Vaccines R&D



Neoantigen Platform

DEEP
PHARMA
INTELLIGENCE

DNA sequencing - first stage for neoantigens identification

Neoantigen Platform: Overview

Neoantigens represent a large platform in cancer vaccines fied and generally in tumor immunotherapy.

Neoantigens include antigens produced by **tumor viruses** integrated into the genome and antigens originated by **mutant proteins,** which are abundantly expressed specifically in cancer cells and have strong immunogenicity and tumor heterogeneity.

Currently a **considerable number of neoantigens** have been discovered, which are unique to tumor cells and are not affected by immune tolerance mechanism.

Neoantigens

Shared

Common across different cancer patients and not present in the normal genome

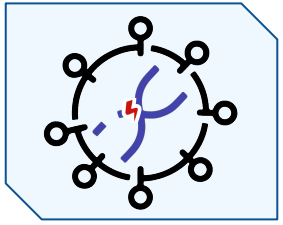
Shared neoantigens that are highly immunogenic have the potential to be screened for use as broad-spectrum therapeutic cancer vaccines for patients with the same mutated gene.

Private

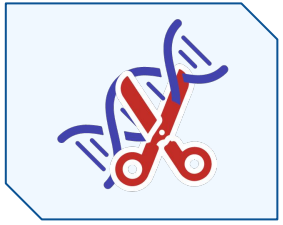
Unique to most neoantigens and completely different from patient to patient

Personalized neoantigen preparation drug can only be specifically targeted to each patient, that is, personalized therapy

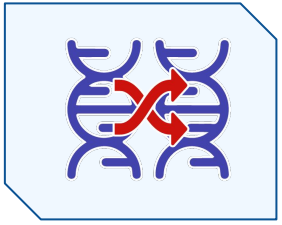
Viral infection



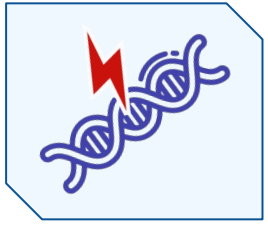
Alternative splicing



Gene rearrangement

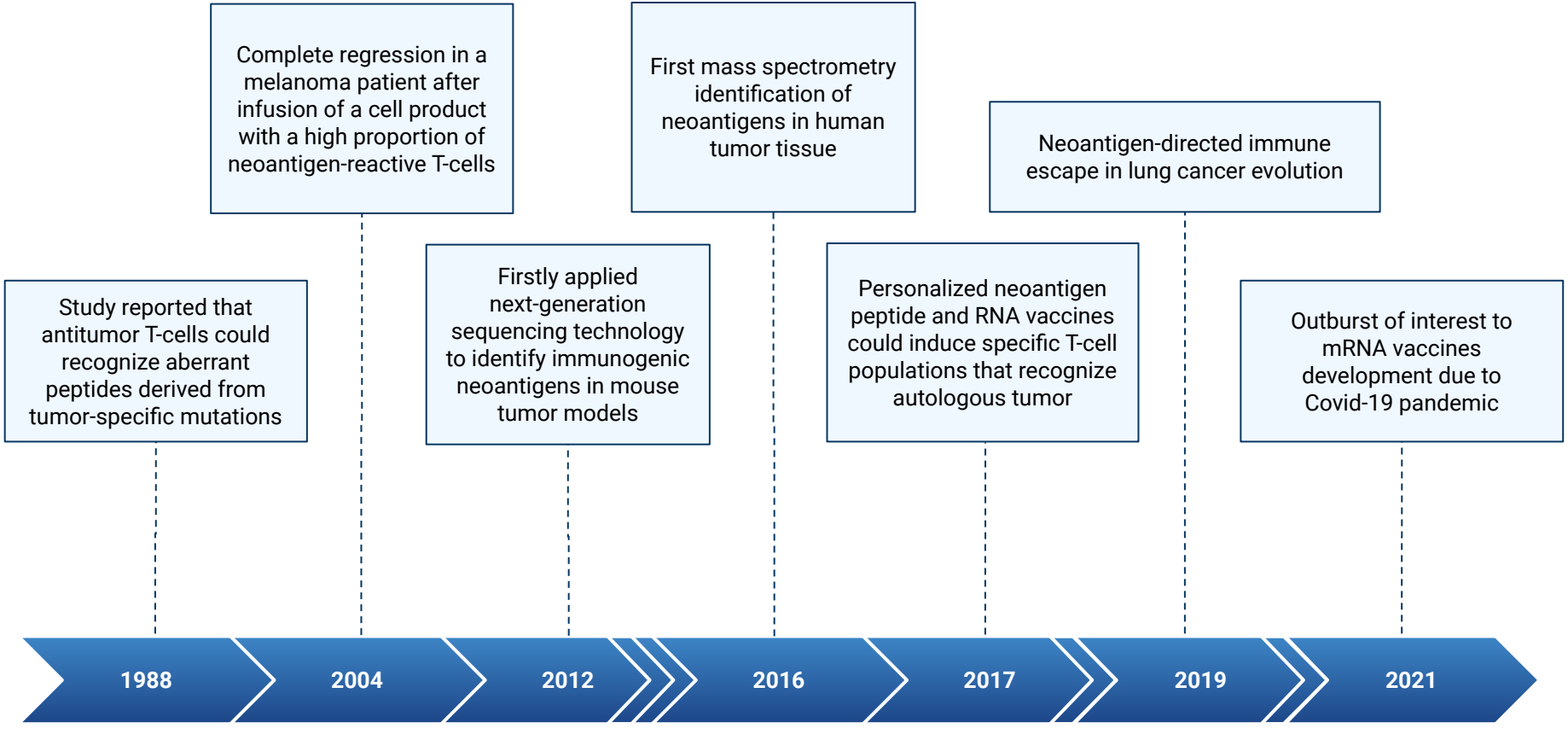


Protein coding sequence mutation



Zhang et al., Frontiers in Immunology (2021)

Neoantigen Platform: Development Milestones



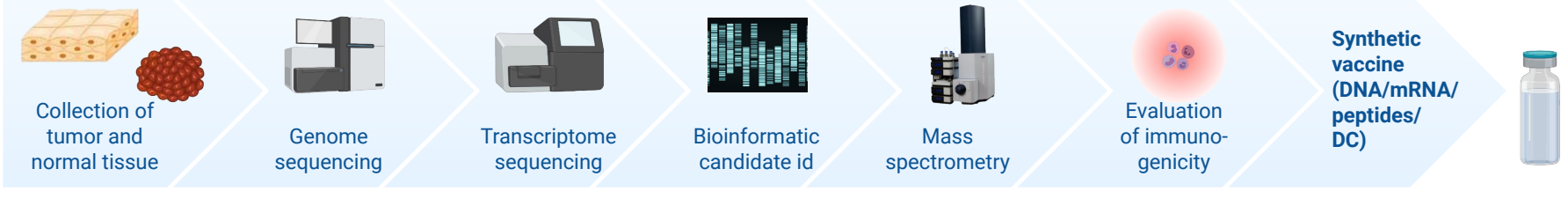
Jiang et al., Journal of Hematology & Oncology (2019)

Neoantigen Platform: Cancer Vaccines in Development

There are no yet approved neoantigen vaccines, but according to ClinicalTrials.gov search there are **190 cases** of neoantigen studies and none of them entered yet the third clinical phase (not considering HPV-vaccines). It is **30 more cases** compared to the search results in Q3 2021, which demonstrates a tremendous growth of interests in this cancer vaccines platform. Many of these studies have shown the good application value of neoantigen (Search term is “neoantigen”).

However, the study of neoantigen therapy starts relatively late and still in the laboratory stage. The **first stages** of neoantigen vaccines development are **complex and time consuming.** Even though genome and transcriptome sequencing technologies are actively developing, they remain a milestone together with **bioinformatic treatment of data.** As the result, the complications of neoantigen platform overlap with the well-known issues of sequencing cost, speed, data storage and analysis. However, with the rapid digitalisation and a broad introduction of artificial intelligence, smart robotics and data storage technologies these issues are expected to be at least reduced if not almost fully eliminated.

Step-by-step scheme of neoantigen cancer vaccine development

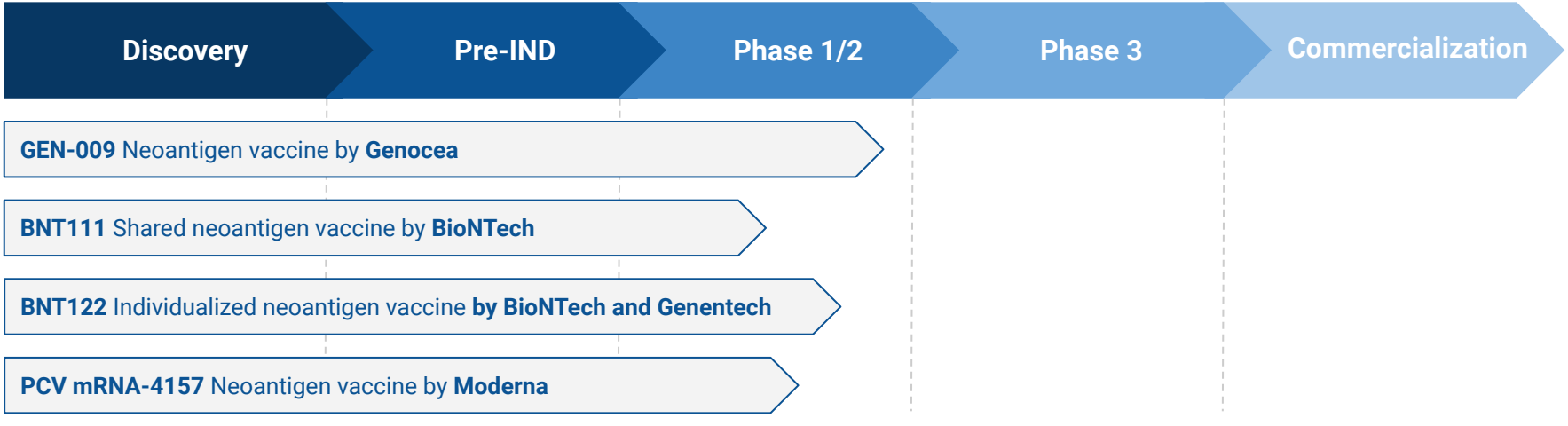


Neoantigen Platform: Cancer Vaccines in Development

Genocea Biosciences GEN-009 vaccine trial (NCT03633110) is now on the Phase 1/2a clinical trials and have shown the best efficacy among the current neoantigen personalization therapies with an estimated completion date of December 2022. The purpose of this study was to evaluate the safety, tolerability, immunogenicity, and antitumor activity of the personalized vaccine GEN-009 for the treatment of patients with **solid tumors,** which is targeted at a **broad range of cancers**. The results so far show that 40 doses of the vaccine have been administered and no dose limiting toxicity (DLT) occurred and so far, no patients who have received the vaccine have relapsed.

BioNTech and Moderna are big pharma leaders in development of cancer vaccines of various forms based of neoantigens. **BioNTech** has 6 cancer vaccines in development with **shared neoantigens** (FixVac platform) and 2 cancer vaccines owned together with **Genentech** based on **individualized approach** (iNeST platform).

Neoantigen cancer vaccines development pipeline



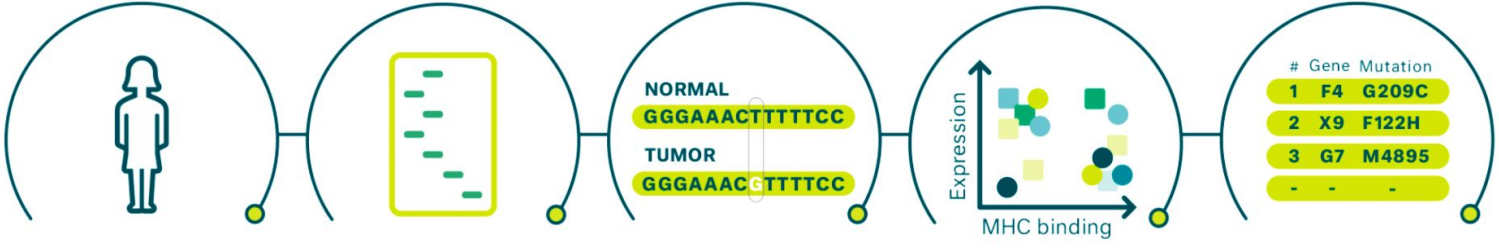
Neoantigen Platform: Key Players

BioNTech — big pharma company that mostly specializes on various cancer immunotherapies. They own technologies with

- developed mRNA platform
- cell therapies
- antibodies
- small molecule immunomodulators

BioNTech is oriented on individualized immunotherapy with patient-specific approach. It requires a complex bioinformatic data treatment, that is why the company gathered expertise in bioinformatics of mutation detection, cancer genomics and immunotherapy

BioNTech's validated patient-centric bioinformatic process

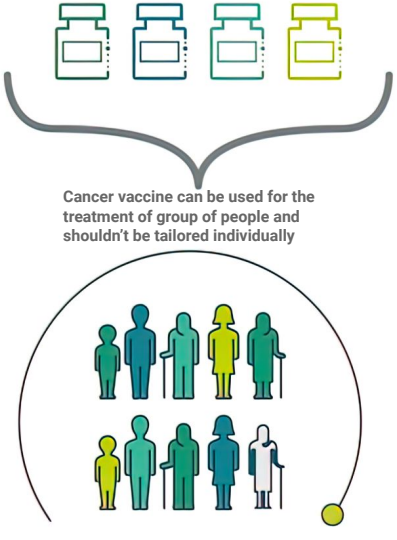


Source — BioNTech Approach

Neoantigen Platform: Key Players

FixVac — cancer vaccine with **shared neoantigens**

Contains selected combinations of unmodified, pharmacologically optimized mRNA, encoding known cancer-specific shared antigens; mRNA is delivered using lipoplex technology.



BNT 111 — Advanced Melanoma

BNT 112 — Prostate Cancer

BNT 113 — HPV16+ Head and Neck Cancer

BNT 114 — Triple Negative Breast Cancer

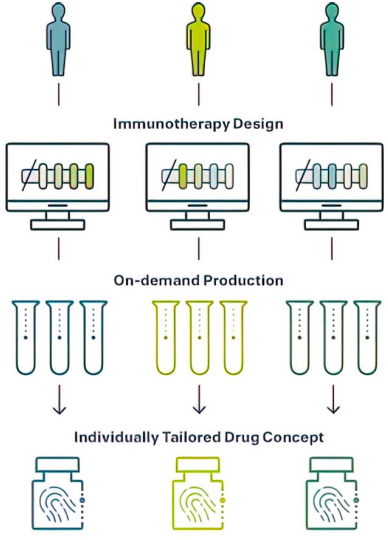
BNT 115 — Ovarian Cancer

BNT 116 — NSCLC

All of them currently are on phase 1 of clinical trials

iNeST — Individualized Neoantigen Specific Immunotherapy — cancer vaccine with **private neoantigens**

Contains unmodified, pharmacologically optimized mRNA encoding up to 20 patient-specific neoantigens, delivered by RNA-LPX formulation.



BNT 122 — Metastatic Melanoma

(currently on the phase 2 of clinical trials)

And for locally advanced or metastatic solid tumors

(currently on the phase 1 of clinical trials)

Rights are equally shared with Genentech

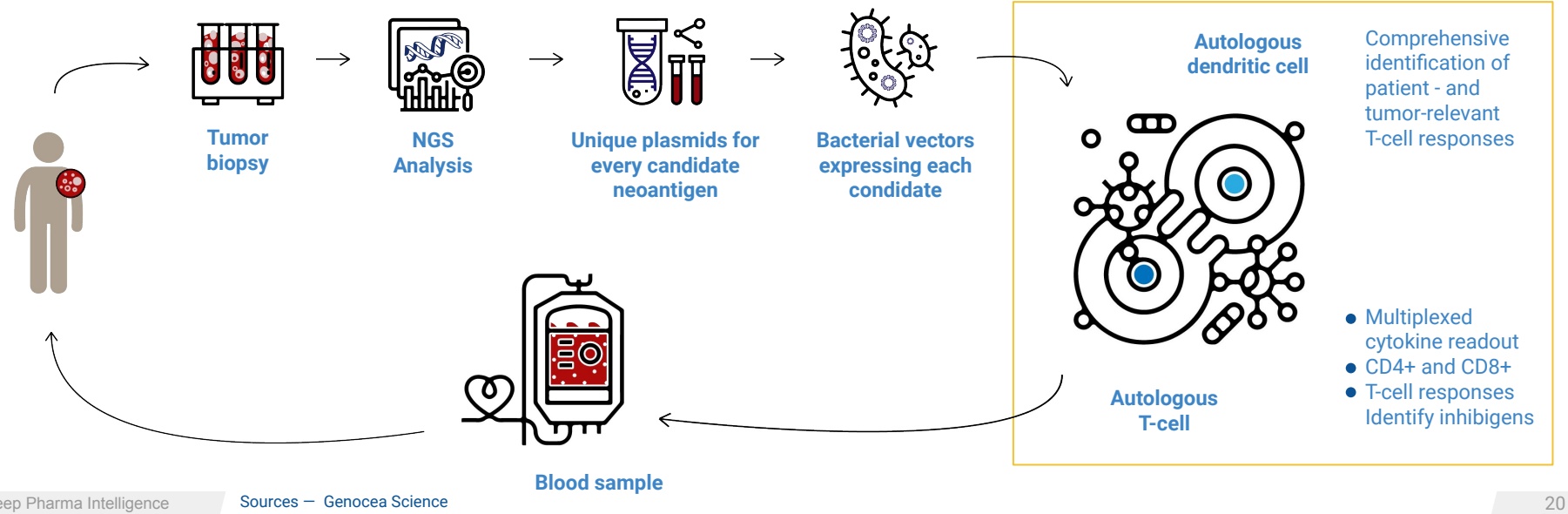
Sources — BioNTech Pipeline, BioNTech Platforms

Neoantigen Platform: Key Players

Genocea Biosciences owns an innovative approach for neoantigen vaccines development - ATLAS platform. It is a unique bioassay that enables a superior, patient biology-driven approach to identify targets of protective T cell responses. ATLAS zeroes in on only those **surface-presented antigens that trigger anti-tumor T cell responses.**

ATLAS is unique in the way that it can identify **pro-tumor inhibitory antigens** (Inhibigens), which subvert anti-tumor immune responses. Vaccination with such Inhibigens is proved to drive tumor hyperprogression in mice.

How does the Genocea's ATLAS approach work?



Sources — Genocea Science

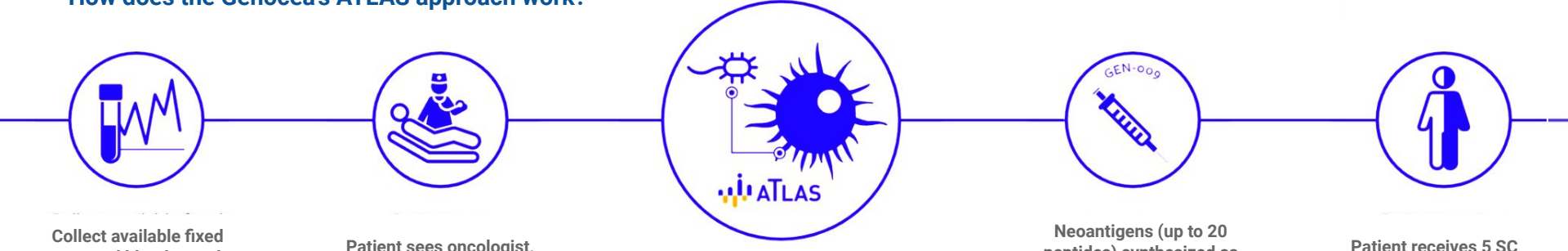
Neoantigen Platform: Key Players

Genocea Biosciences greatly focuses in the **antigen selection** for the best tumor targeting and destruction, which lies at the very basement of the ATLAS platform.

GEN-009 is a neoantigen vaccine candidate in a Phase 1/2a clinical trial to treat a variety of solid tumors. ATLAS identifies neoantigens optimized both to **patients' T cell responses and their tumors**, underscoring the advantages of the technology for neoantigen selection.

Other vaccine candidate **GEN-011** belong to the class of **adoptive T cell therapy**. GEN-011 Neoantigen-activated Peripheral T cells (NPTs) are peripheral blood T cells activated by the ATLAS-identified patient-specific neoantigens and expanded to create a **customized therapeutic.**

How does the Genocea's ATLAS approach work?



Collect available fixed tumor and blood sample, send for sequencing

Patient sees oncologist, begins SoC ICI

Inhibigens and neoantigens identified by ATLAS

Neoantigens (up to 20 peptides) synthesized as peptides and formulated with Poly-ICLC

Patient receives 5 SC doses over 6 months

Sources — Genocea Pipeline

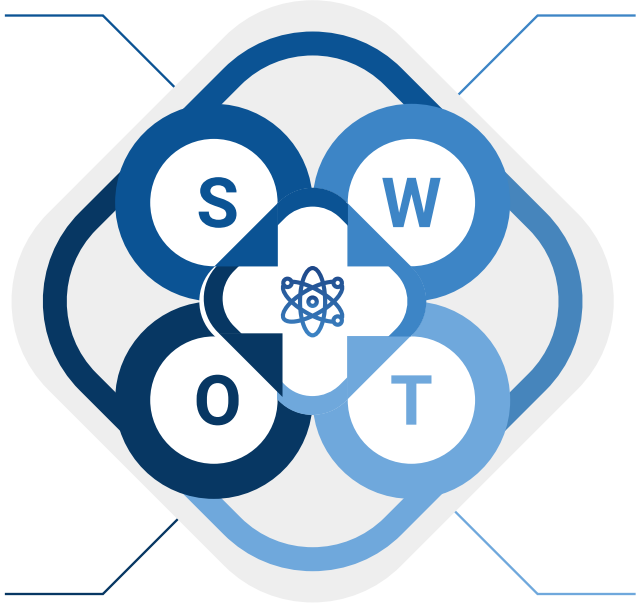
Neoantigen Platform: SWOT Analysis

Strengths

- Great financial support which moves the platforms faster to clinical research
- Absolute specificity to the tumor cells
- Already have products in clinical phase of development
- Cancer vaccine can be delivered in various forms

Opportunities

- Vaccines possibly can enter the clinical trials phase 3
- Neoantigen cancer vaccines might be the best personalized solution for cancer treatment



Weaknesses

- The development cycle of neoantigen vaccine is too long
- Preparation and delivery of vaccines remains a challenge
- The heterogeneity of the tumor is difficult to resolve with neoantigen platform
- Limited number of antigens meet the neoantigen criteria
- Expensive

Threats

- Platform has a limited number of directions to develop further in case of failure
- It might be substituted with novel platforms which are more cost-effective and highly specific for cancer cells at the same time

Tumor-Associated Antigens Platform

DEEP
PHARMA
INTELLIGENCE

Macrophages attacking cancer cells

Tumor-Associated Antigens Platform: Overview

Tumor-Associated Antigens (TAA) are self-proteins that are abnormally expressed by cancer cells.

It means they are **present both in healthy and cancer cells** and differ just by the level of exposure or presentation by cell.

This makes TAA slightly easier to discover compared to neoantigens, but at the same time TAA might cause **peripheral tolerability issues** in patients, lack of T-cell activation and collateral damage.

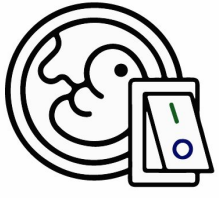
Even though TAA are used for the currently well-developed **CAR-T** technology, they still remain to be challengeable for cancer vaccines development.

Tumor-Associated Antigens

Overexpressed proteins

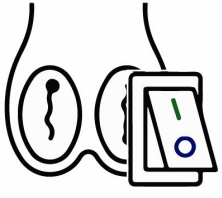
Detected both on healthy and cancer cells of human body but due to the **higher amount at malignant cells** their detection will be preferable

Differentiation antigens



Differentiation factors are meant to be present at cells only **during the early development** and are saved only in small subset of cells in developed body

Cancer testis antigens



Are not supposed to be present in healthy adult somatic tissues but are expressed in **testicles in male germ cells**

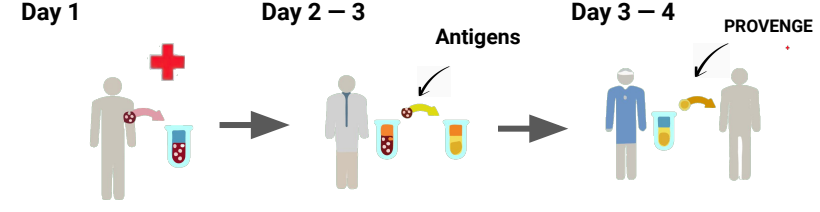
Tumor-Associated Antigens Platform: Development Milestones

Cancer immunotherapy field experienced at least two significant breakthroughs connected with **tumor-associated antigens platform:**

- Promising approval of **Provenge cancer vaccine** (sipuleucel-T) by FDA for the treatment of prostatic cancer, which used tumor-associated antigen as a target
- Development and approval of multiple **CAR-T therapies** which are based on targeting of TAA

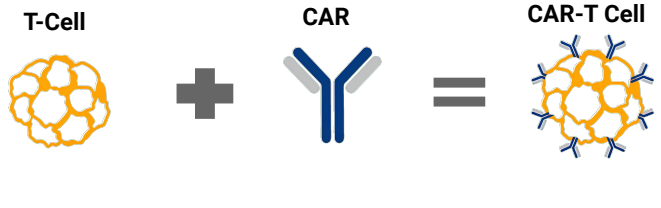
Dendreon

2010 - first FDA approved cancer vaccine



NOVARTIS Kite Pharma

2017 - first FDA approved CAR-T

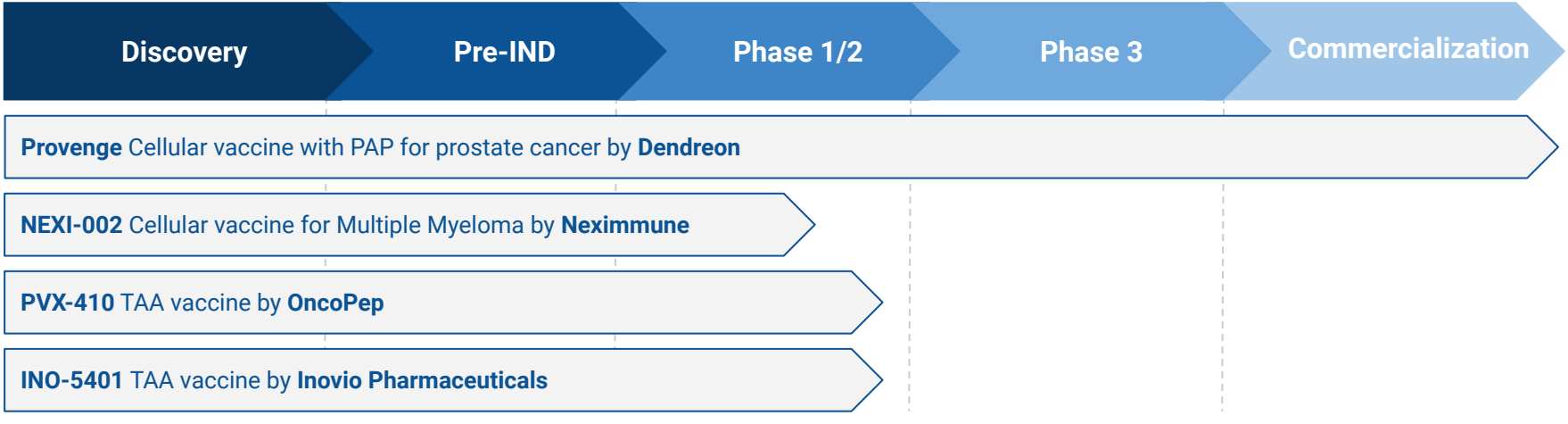


Tumor-Associated Antigens Platform: Cancer Vaccines in Development

Tumor-associated antigens is one of the most well-developed platforms, that's why there is plenty of clinical candidates even not considering CAR-T and counting only cancer vaccines. At the moment of our research there were roughly **200 cases** of tumor-associated antigens studies according to ClinicalTrials.gov search.

After approval of **Provenge in 2010** — no other cancer vaccine entered the global market. Provenge passed clinical trials stage with a low efficiency level, but just enough to pass it, so now it is not as frequently used as we could wish it were and toxic chemotherapy remains to be more effective way to treat prostate cancer.

Tumor-associated antigens cancer vaccines development pipeline



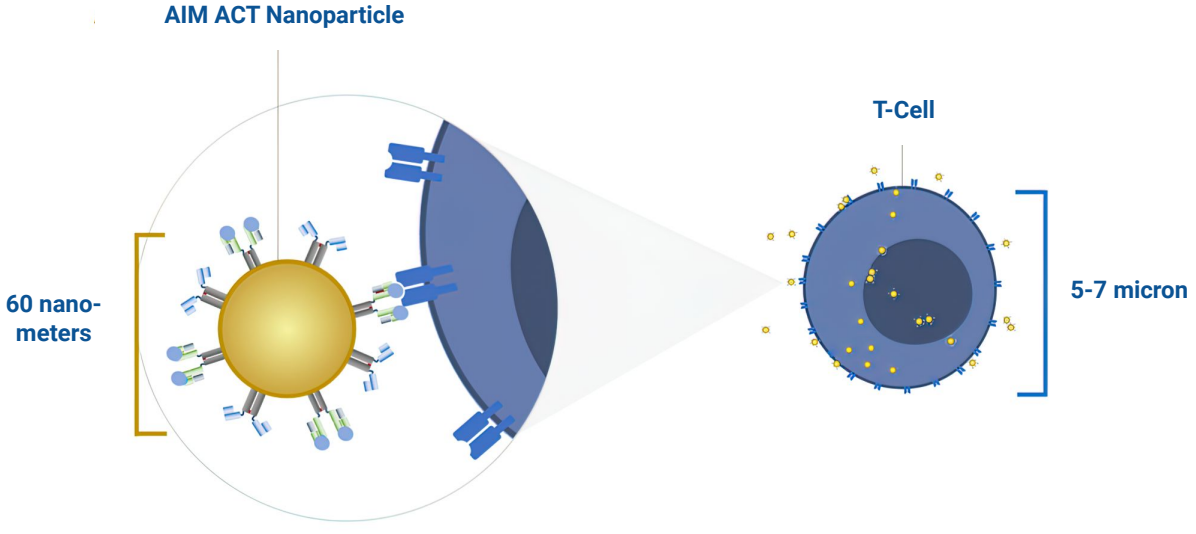
Tumor-Associated Antigens Platform: Key Players

NexImmune — biopharmaceutical company which implements an innovative approach to improve and develop tumor-associated antigens cancer vaccines. They own a nanotechnological Artificial Immune Modulation (AIM) platform.

NexImmune constructs **"synthetic dendritic cells"** in the form of **AIM nanoparticles,** which are capable of directing a specific T cell-mediated immune response.

During antigen presentation T cells can recognize **multiple antigens in the form of peptides.** This produces T-cells with multiple immune targets for a robust antitumor activity.

AIM™ Nanoparticles induce the production of both memory cells and cytotoxic effector cells. Effector cells will be the main direct mechanism to destroy tumor cells through the release of cytotoxic granules, while memory cells will store in the bloodstream.



Sources — NexImmune Technology

Tumor-Associated Antigens Platform: Key Players

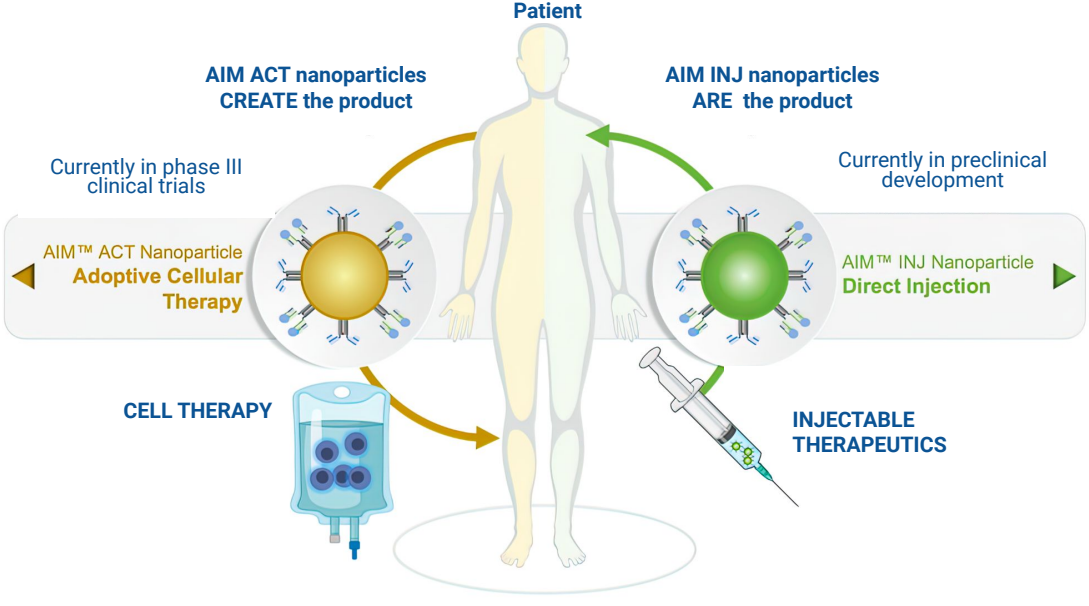
NexImmune is oriented on few principles in developing cancer vaccines with TAA:

- The ability to expand T cell populations that recognize and attack **multiple antigen-specific targets**
- **Consistency** in containing **T cell subtypes** that support anti-tumor potency, self-renewal, proliferation, and long-term T cell survival

AIM nanoparticles are designed to **mimic the immune functions of natural antigen presenting cells**, such as dendritic cells, by delivering two key immune-directing T cell signals

Adoptive cell therapy modality includes cancer vaccines in the form of **donor- or patient-derived T cells** for AML, multiple myeloma and solid tumors

Injectable modality is presented by **injectable AIM nanoparticles** for solid tumors



Sources — NexImmune Technology

Tumor-Associated Antigens Platform: Key Players

Inovio Pharmaceuticals is a biotech company which is oriented on **DNA medicines** development.

One of the main focuses of the company is HPV-vaccines with candidates on the third phase of clinical trials. At the same time there are promising cancer vaccine candidates with **tumor-associated antigens** in the **second phase of clinical trials.**

PRECISELY DESIGNED PLASMIDS (SynCon®)

SynCon uses a proprietary computer algorithm that has been designed to **identify and optimize the DNA sequence** of the target antigen.

PROPRIETARY SMART DEVICES (CELLECTRA®)

INOVIO's DNA medicines deliver **optimized plasmids** directly into cells intramuscularly or intradermally using one of INOVIO's proprietary hand-held **CELLECTRA® smart devices.**

INO-5401 cancer vaccine

WT1, PSMA, hTERT antigens for glioblastoma multiforme (with PD-1 inhibitor)

REGENERON

INO-5151 cancer vaccine

PSA, PSMA antigens for prostate cancer (with PD-1 inhibitor and immune modulator)

PARKER INSTITUTE FOR CANCER IMMUNOTHERAPY

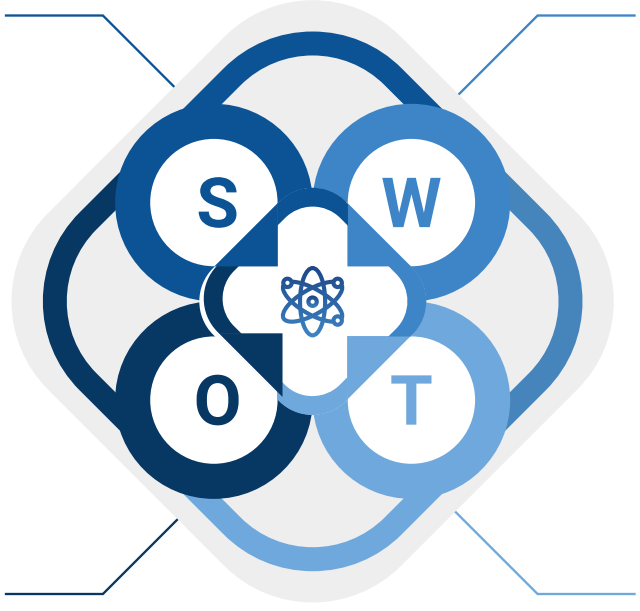
CANCER RESEARCH INSTITUTE

Sources — Inovio DNA Medicines Technology

Tumor-Associated Antigens Platform: SWOT Analysis

Strengths

- There are already examples of FDA approved immunotherapies using TAA
- Applicable to almost any tumor
- Lots of accumulated knowledge due to the long time of platform investigation



Weaknesses

- Cancer vaccines with TAA are not highly specific to tumor cells
- High number of adverse effects
- Peripheral tolerability risk

Opportunities

- Cancer vaccine candidates can enter phase 3 of clinical trials
- Using the experience of FDA approved immunotherapies cam improve the developing products faster

Threats

- his platform is likely to be pushed out of the cancer vaccines field by platforms with higher specificity
- Provenge cancer vaccine is seldomly used due to the low activity and high cost even though it was FDA approved

Cellular Platform

DEEP
PHARMA
INTELLIGENCE

Cellular Platform: Overview

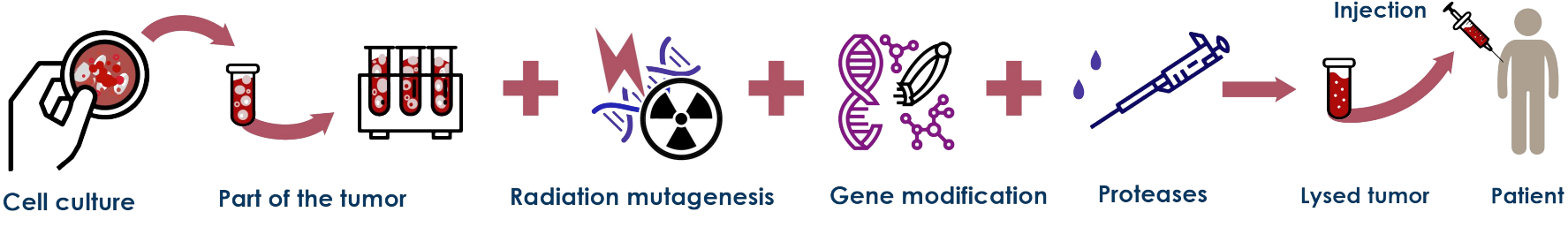
Whole-cell platform for cancer vaccines is **the earliest platform** developed with the principle “vaccinate with something you want to fight against”.

Whole-cell vaccines consist of the **all cellular antigens,** which means there are tumor-associated antigens and neoantigens included. Unlike TAA or neoantigen platform - whole-cell platform contains **both characterized and uncharacterized TAA and TSA.**

This approach is suitable, in theory, for any **solid tumor** regardless its mutation burden and the general process of its development takes less steps compared to TAA or neoantigen platforms.

Irradiated gene-modified tumor cells

Irradiated gene-modified autologous or allogeneic tumor cells, which were engineered to encode **immunostimulatory agents** including cytokines and **costimulatory molecules.**



Razi et al., Vaccines for Cancer Immunotherapy (2019)

Cellular Platform: Overview

Tumor cell lysates

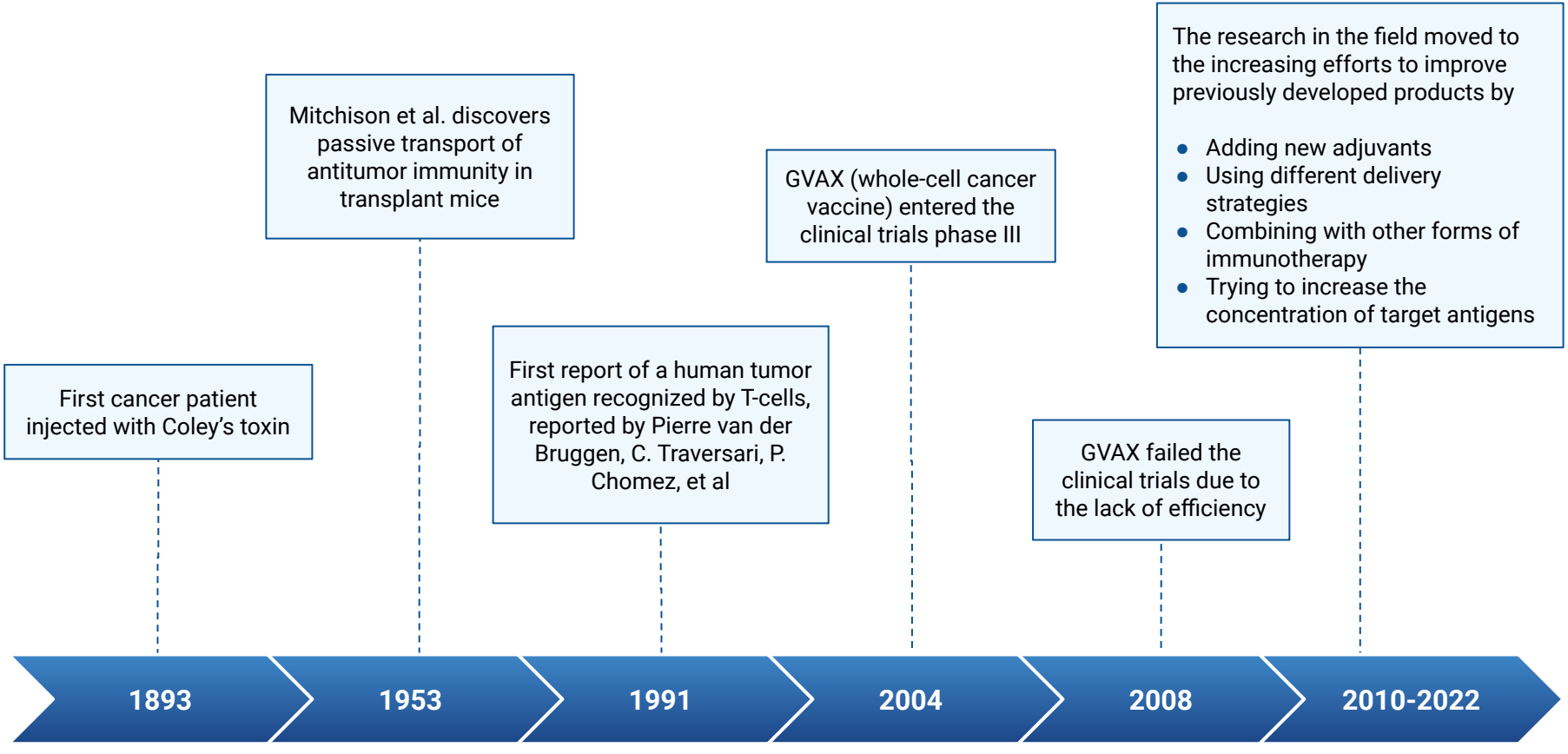
Whole tumor cell lysates contain all tumor cell antigens. **Autologous or allogeneic lysates** could be prepared in different ways leading to cell death: cells can be **frozen and thawed** repeatedly or irradiated with **ultraviolet B** (UVB)

Tumor-derived exosomes

Tumor cell derived exosomes could be obtained from ascites, pleural effusion, and plasma samples of patients; such exosomes comprise various tumor antigens, one of the leading antigens investigated is **heat shock protein**

Razi et al., Vaccines for Cancer Immunotherapy (2019)

Cellular Platform: Development Milestones



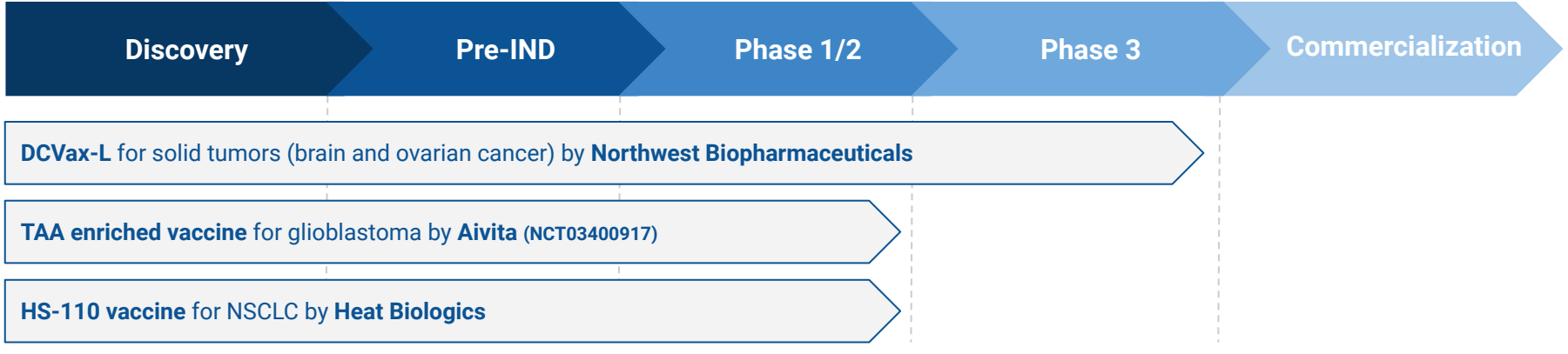
Cellular Platform: Cancer Vaccines in Development

Despite the large number of developed products — none of them has entered the cancer vaccine market yet.

Whole-cell platform for cancer vaccines is an attractive field for various ways of improvement to eliminate its considerable cons such as low efficiency and high toxicity. **Heat Biologics** is developing its two products: **HS-110 and HS-130** by implementing the pan-antigenic self-adjuvant technology. On the other hand **Northwest Biopharmaceuticals** has a classic approach for cancer vaccines development but focuses more on clinical application optimization for clinicians and patients.

Still, history of whole-cell cancer vaccines shows some failures such as one of the most advanced cancer vaccine candidates GVAX which resulted into higher mortality level in clinical trial phase 3 patients.

Cellular cancer vaccines development pipeline



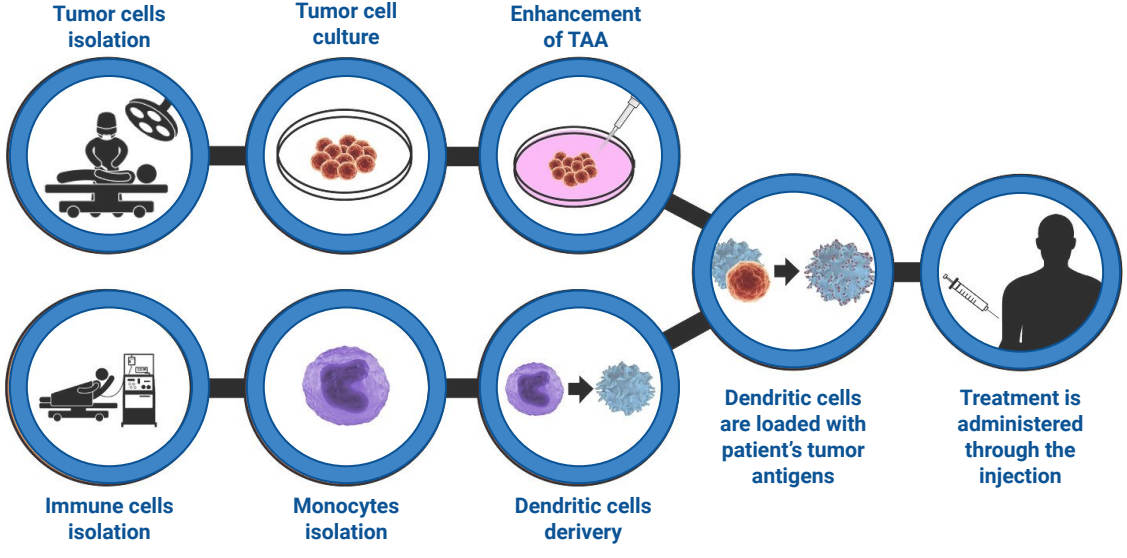
Cellular Platform: Key Players

AiVita Biomedical is a medicine company which develops personalized cancer vaccines with a set of TAA-enriched whole-cell antigens.

Their therapies are oriented to kill **tumor-initiating cells** (a small portion of the tumor mass which is the most prolific in the ability to generate additional cancer cells) while implementing **pan-antigenic approach.**

They developed **AV-GBM-1** - cancer vaccine in the form of autologous dendritic cells loaded with tumor antigens from a short-term cell culture of autologous tumor cells

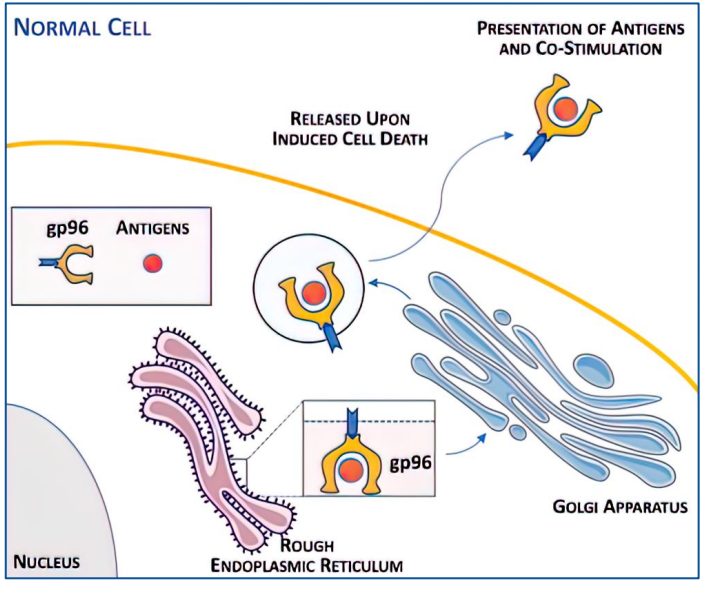
On the first steps the sample of the patient's tumor undergoes cell culture. The aim of this step is **enrichments with tumor-initiating cells** and their amplification. It is the most critical stage since it reduces the non-specific signals from cells. Selected in such way tumor cells are used to **load antigen-presenting (dendritic) cells,** which are delivered to the patient back in the form of subcutaneous injections.



Sources — AiVita Cancer Immunotherapy

Cellular Platform: Key Players

Heat Biologics — is a biotechnology clinical-stage company focused on developing its proprietary **"ImPACT" (Immune Pan-Antigen Cytotoxic Therapy)** adjuvant technology. It is first-in-class fully human adjuvant system that functions as an immune stimulator and an antigen-delivery system at the same time.



Leading product — HS-110 (viagenpumatucel-L)

Vaccine derived from irradiated human lung cancer cells genetically engineered to continually secrete **gp96-Ig**

Clinical phase II stage, in combination with checkpoint inhibitor

nivolumab (Opdivo®) or

pembrolizumab (Keytruda®)

Bristol Myers Squibb™ MERCK

HS-130

Vaccine derived from irradiated human lung cancer cells expressing the co-stimulatory fusion protein **OX40L-Ig**

Clinical phase I stage for a wide range of solid tumors

Sources — Heat Biologics Technology, clinicaltrials.gov

Cellular Platform: Key Players

Northwest Biopharmaceuticals — biotechnology company focused on discovering, developing and commercializing immunotherapy products that generate and enhance immune responses to treat cancer.

This company is fully focused of the development of whole-cell cancer vaccines based on **DCVax technology** (the technology which implements dendritic cells for a cancer treatment) or simply the direct usage of DC for cancer treatment.

Besides focusing on the development of cancer vaccine candidates, one of the Northwest Biotherapeutics priorities is a user-friendly approach for both patients and physicians.

Simplicity in the vaccine preparation, storage and delivery is one of the top values, which creates a multi-directional approach with a broad coverage of needs.

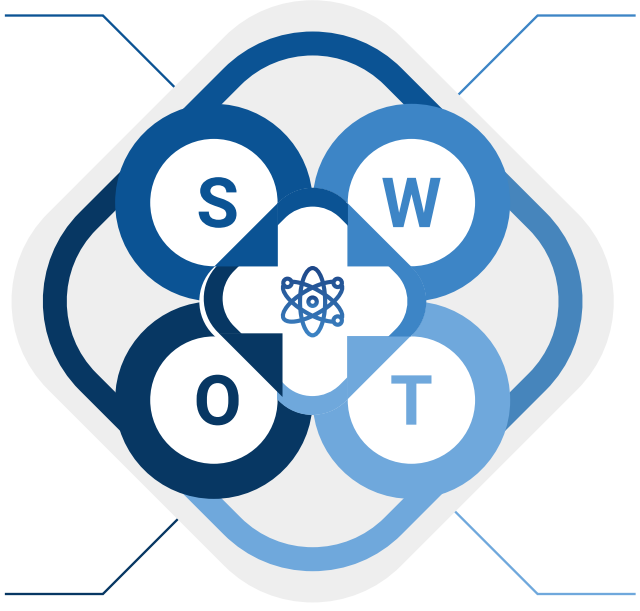
DCVax – L	DCVax-Direct
Dendritic cell cancer vaccine loaded with **cancer antigens from tumor lysate from the patient's own tumor tissue.** DCVax-L is expected to be used for any solid tumor cancers.	The partially matured dendritic cells are **injected directly into the patient's tumor(s)** — it is suitable for the situations in which the tumors are inoperable

Sources — Northwest Biopharmaceuticals Product Candidates

Cellular Platform: SWOT Analysis

Strengths

- Targeting of all cellular antigens
- Natural antigens composition
- Cost-effective



Weaknesses

- Cellular noise
- Low concentration of immunogenic antigens
- Higher toxicity due to non-specific targeting of healthy cells
- Low immunogenicity

Opportunities

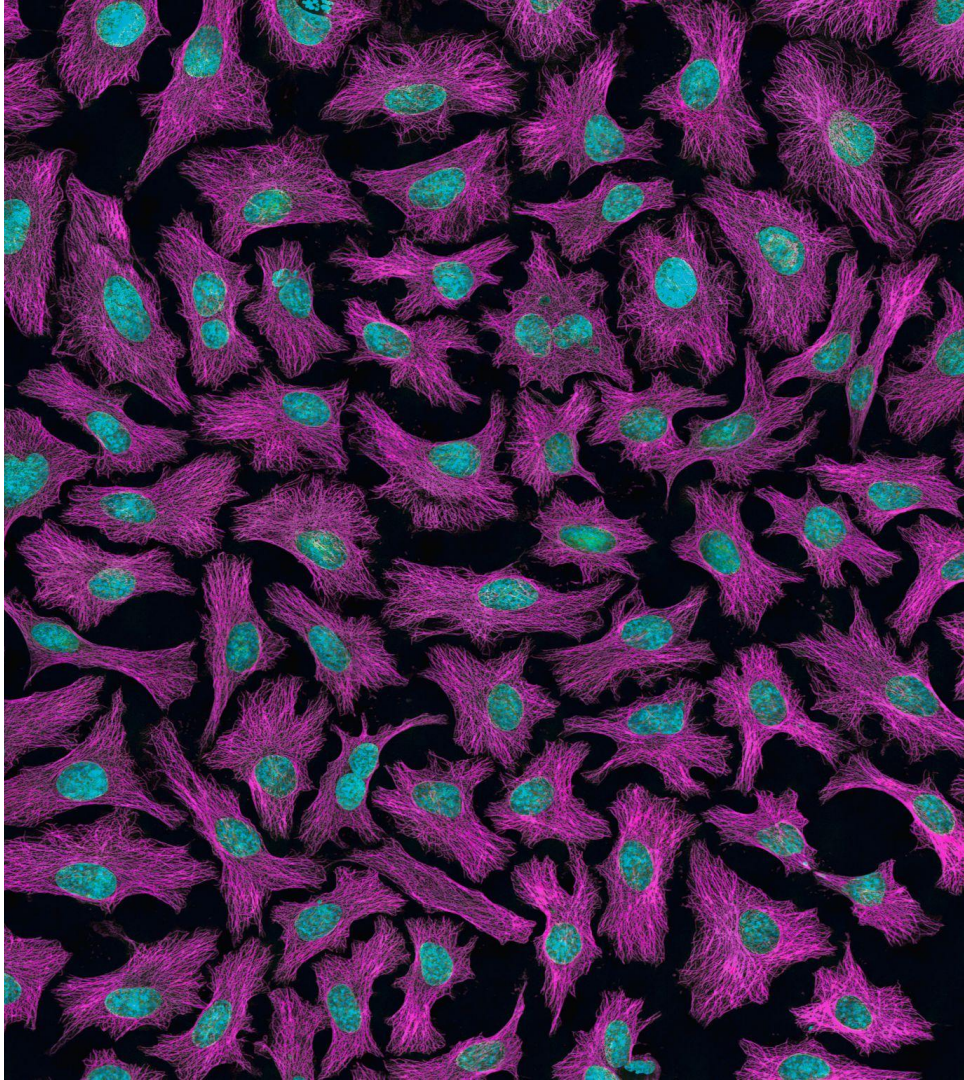
- The vaccines developed earlier in whole-cell platform which failed clinical trials might be upgraded with innovative platform

Threats

- It might not reach the needed level of efficiency on clinical trials even using adjuvants, checkpoint inhibitors and immune stimulators etc.
- It is likely to be substituted by more innovative platform
- GVAX (an advanced product in whole-cell cancer vaccine platform) failed clinical phase 3 with a high mortality rate

Antigenic Essence Platform

DEEP
PHARMA
INTELLIGENCE

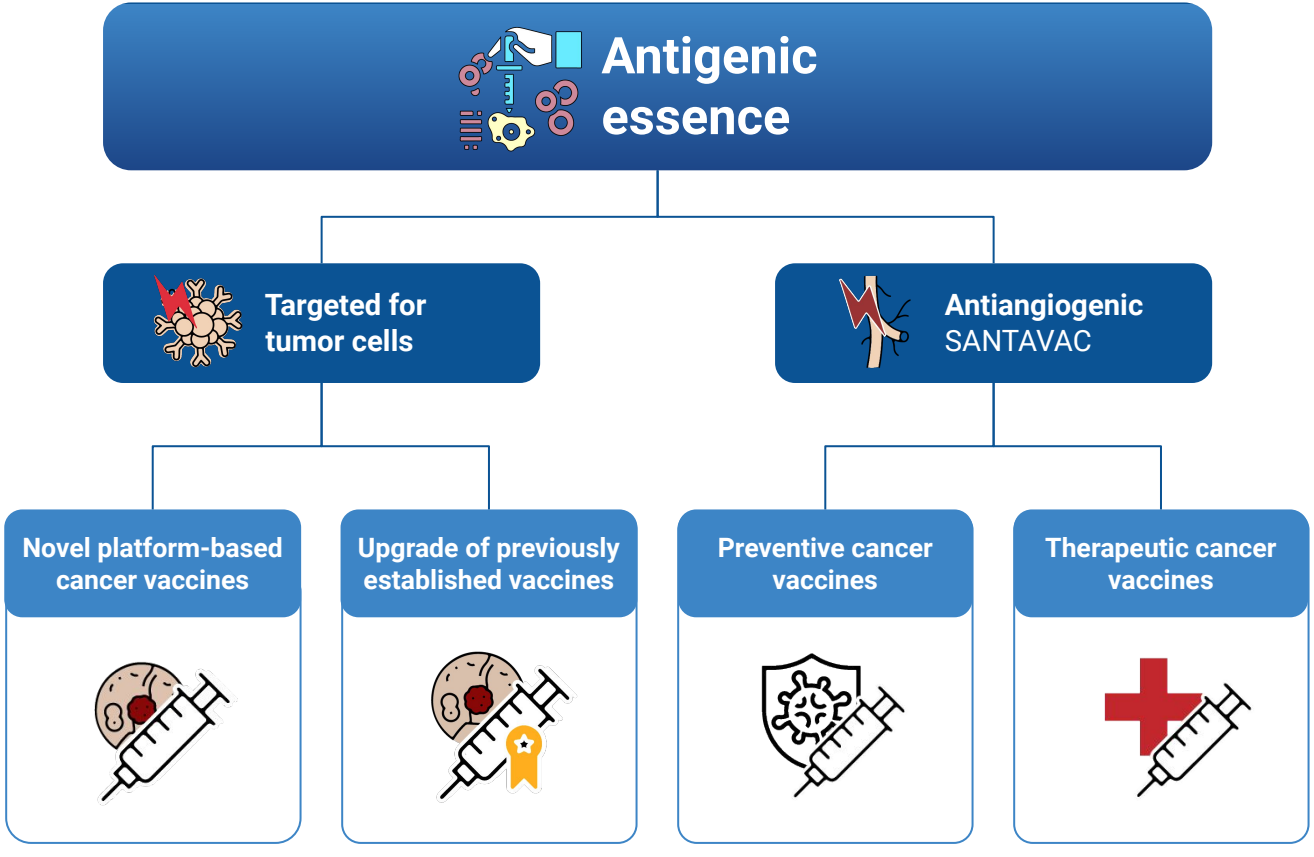


Antigenic Essence Platform: Overview

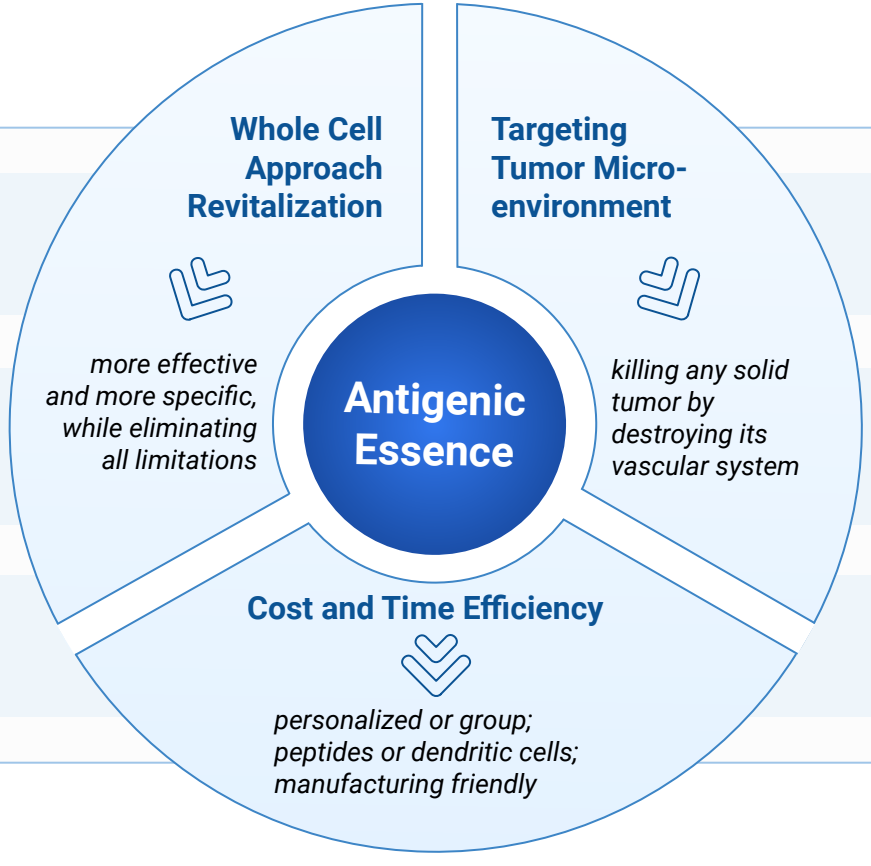
Antigenic essence platform is an **innovative platform** which can be considered as a **cellular vaccines revitalisation.** It implemented the lessons from other platforms and created a novel product.

Unlike whole-cell vaccines — antigenic essence includes only **surface- presented antigens,** recognised by immune system.

At the same time, unlike neoantigens or tumor-associated antigens — antigenic essence **targets a wide number of antigens** and doesn't require a complex data treatment and only limited application of one proteomics method.



Antigenic Essence Platform: Overview



Antigenic essence includes only visible for immune system antigens

The **size of antigens is optimal** to be presented by MHC to immune system

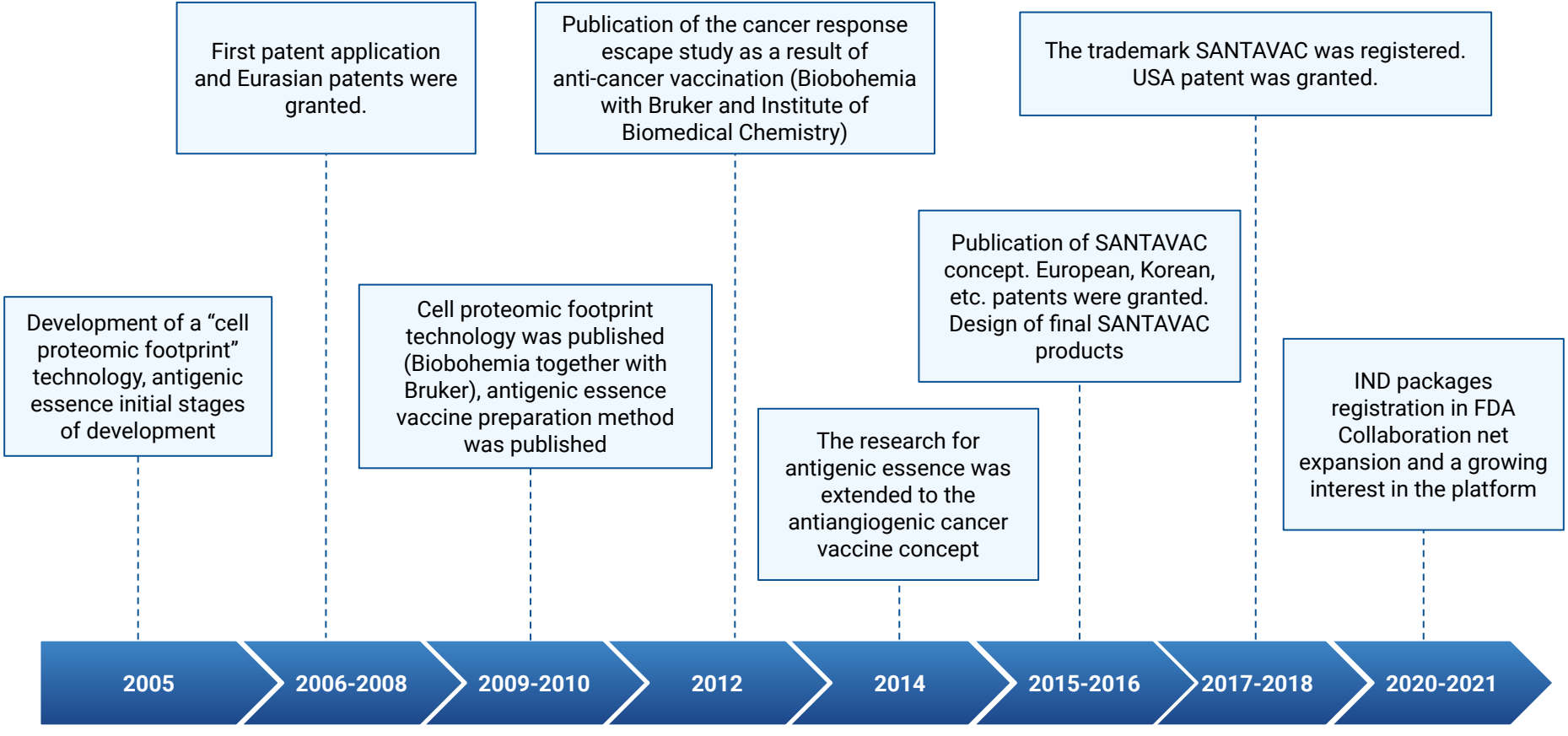
Antigenic essence is a **specific footprint** of cellular antigens

Antigenic essence can target not only cancer cells, but **endothelial cells too**

Antigenic essence can be a platform for the **universal medicine** for solid tumors

Targets the whole antigens spectrum - **revolutionary antiangiogenic** approach

Antigenic Essence Platform: Development Milestones



Hamid et al., Cancer Immunology and Immunotherapy (2017)

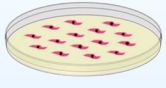
Antigenic Essence Platform: Cancer Vaccines in Development

Antigenic essence platform may be considered as a significant upgrade of whole-cell platform. It means that antigenic essence is

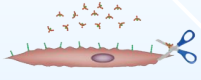
- Cost and time-effective
- Applicable for all solid tumors regardless their mutation burden status
- Applicable both for personalized or group medicine
- Can be used to direct tumor cells or vessels

This platform can be a a solution for previously failed whole-cell cancer vaccines or a good collaborator for developing ideas. Right now antigenic essence platform is **at preclinical stage** of development but according to analysed data it **should come to final phases of clinical trials** (for example **GVAX** and **CanVaxin**) and pass it due to significant revitalization of the technology.

Step-by-step scheme of antigenic essence cancer vaccine development



Cell line or primary cell culture



Antigenic essence preparation

Complex Omics approaches and bioinformatic data treatment are not needed

Only for quality control of antigenic essence products

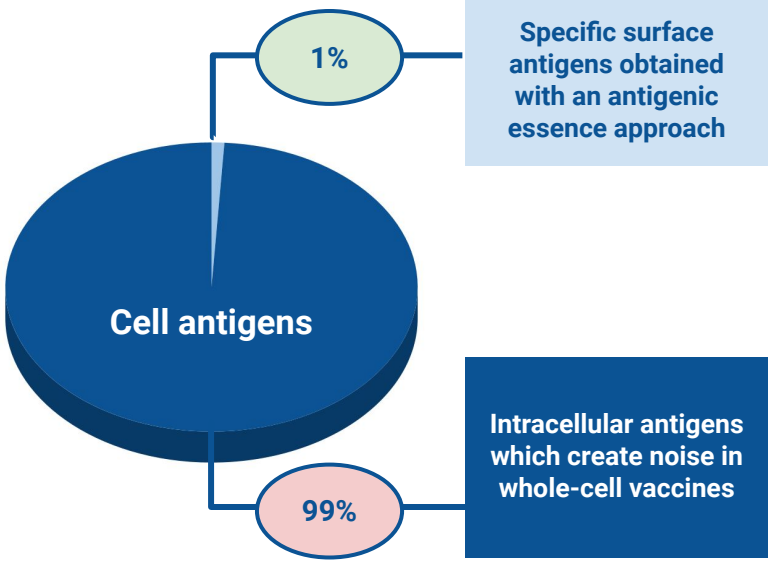
Mass spectrometry

Natural peptides or peptide-loaded DC vaccine

Antigenic Essence Platform: Key Players

Biobohemia, Inc. — biotechnology company focused on the development of cancer vaccines. They fully own an antigenic essence platform which is based on a deep knowledge in proteomics and provides the tool for a revitalization of cellular vaccines.

The antigenic essence technology allows to control the composition, as well as an efficient purification from ballast substances (cellular 'noise'), and evasion of MHC restrictions.



Naturally produced antigens by the tumor cells tend to induce the most accurate targeting of these cancer cells. Even though such native-cell antigens are obtained by the appliance of cellular vaccines platform, **whole-cell vaccines also have a tremendous majority of ballast intracellular proteins. This cellular noise**

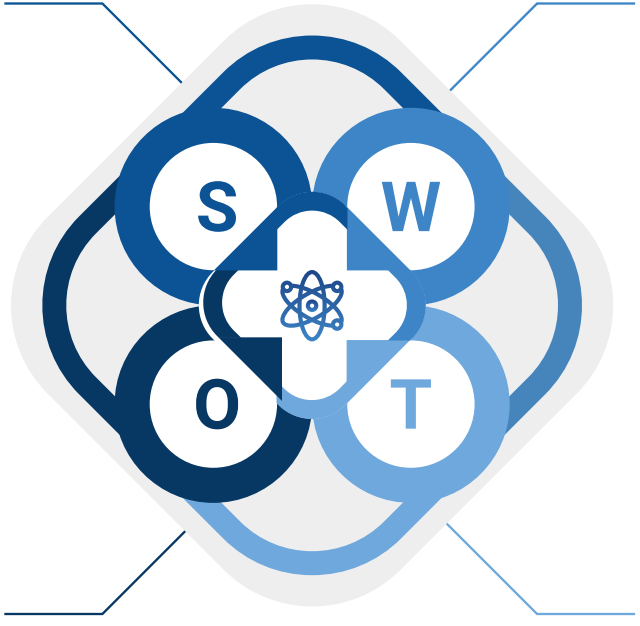
- **dillutes target antigens**
- **results into the undesired immune response**
- **reduces the cancer vaccine specificity**

That is why antigenic essence platform met the need to develop a novel cell-based cancer vaccine free from intracellular immunogenic molecules.

Antigenic Essence Platform: SWOT Analysis

Strengths

- Innovative platform which eliminates all the cons of previously developed platforms
- Targeting of only surface antigens visible for immune system
- High concentration of antigens
- Controllable set of antigens in doses



Weaknesses

- Not directed to target non-solid tumors (20% of cancer cases)
- Low public awareness about the new technology

Opportunities

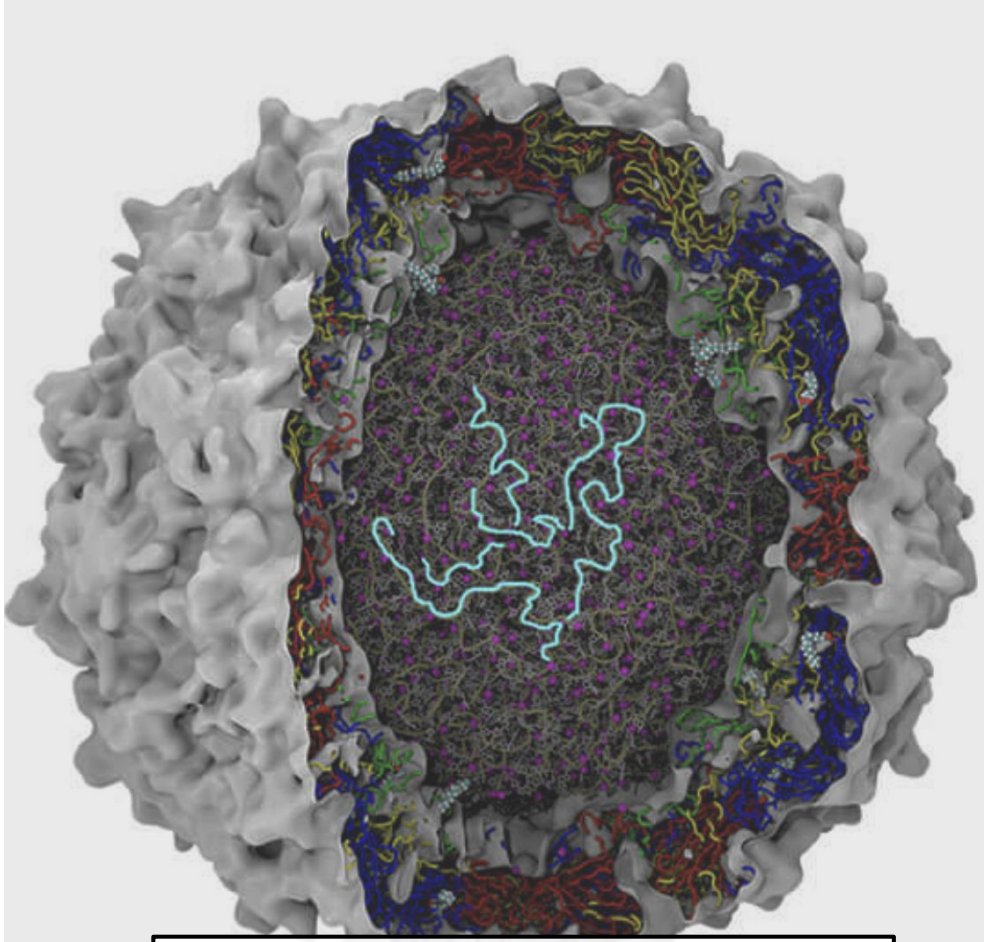
- Can be used to upgrade cellular vaccines developed earlier
- Can become a new emergent star of cancer vaccines market
- Potentially can cure any solid tumor
- Can become a leader in preventive cancer vaccines field

Threats

- The platform is not validated in preclinical study, although preliminary validation is strong
- Operational capacity, structuring business processes

Oncolytic Viruses Platform

DEEP
PHARMA
INTELLIGENCE



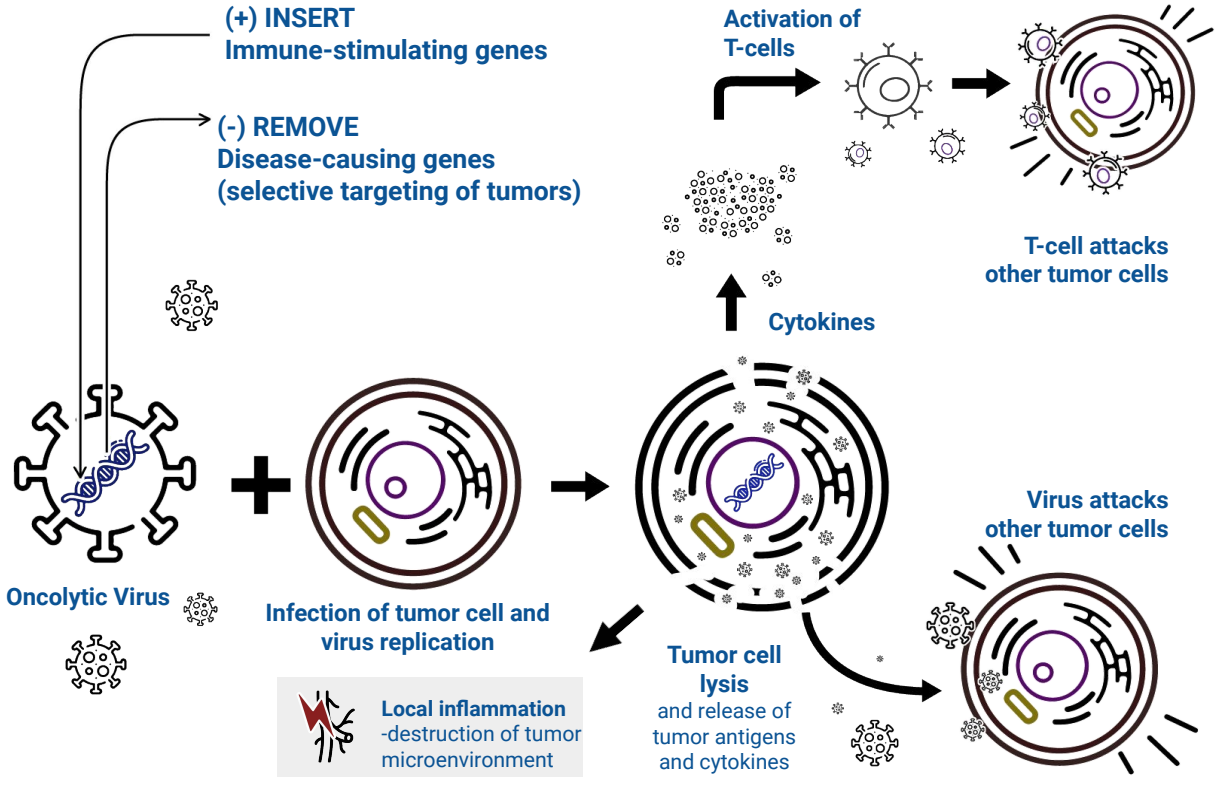
Engineered oncolytic poliovirus for cancer treatment
Credit: Duke Cancer Institute and cancer.gov

Oncolytic Viruses Platform: Overview

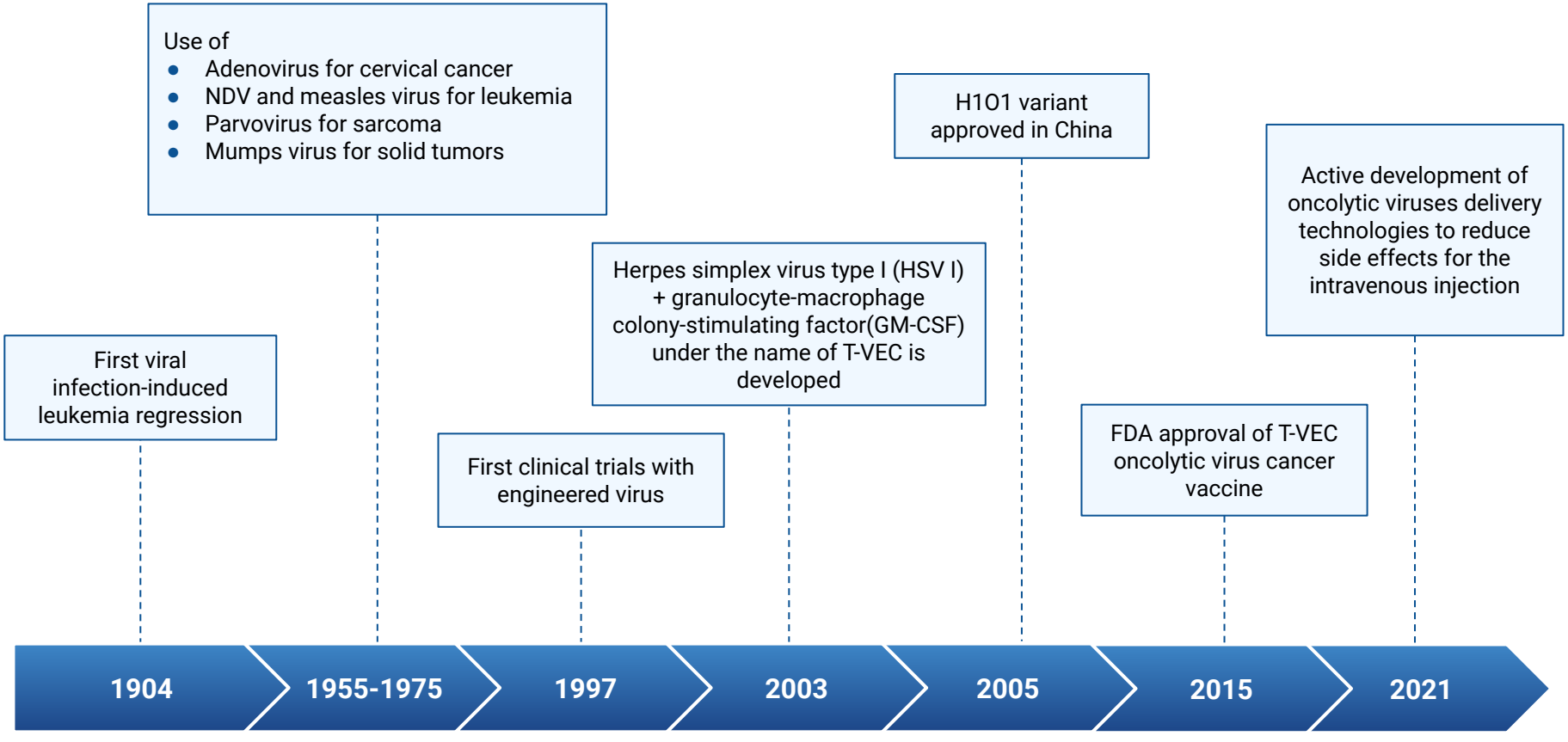
Oncolytic virotherapy is based on the property of some viruses to infect the cells and induce the cell lysis.

In case of cancer vaccination these viruses are **modified to target cancer cells** and enhance the immune response to completely destroy the tumor.

Oncolytic viruses cancer vaccines platform is greatly based on the neoantigens and tumor-associated antigens platforms, since the viruses and "taught" to target such antigens on the cancer cells. But due to the drastic uniqueness of the mechanism of action of such vaccines it is fair enough to separate them from other molecular and cellular cancer vaccines.



Oncolytic Viruses Platform: Development Milestones

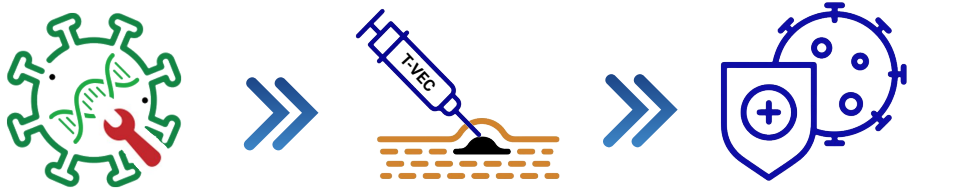


Hamid et al., Cancer Immunology and Immunotherapy (2017)

Oncolytic Viruses Platform: Cancer Vaccines in Development

For today there is one **FDA approved** oncolytic virus immunotherapy - **Talimogene laherpavepvec (T-VEC) owned by Amgen.**

Stil there is active development of oncolytic viruses which would target a wider spectrum of tumors and won't induce the formation of undesired antibodies by the immune system.



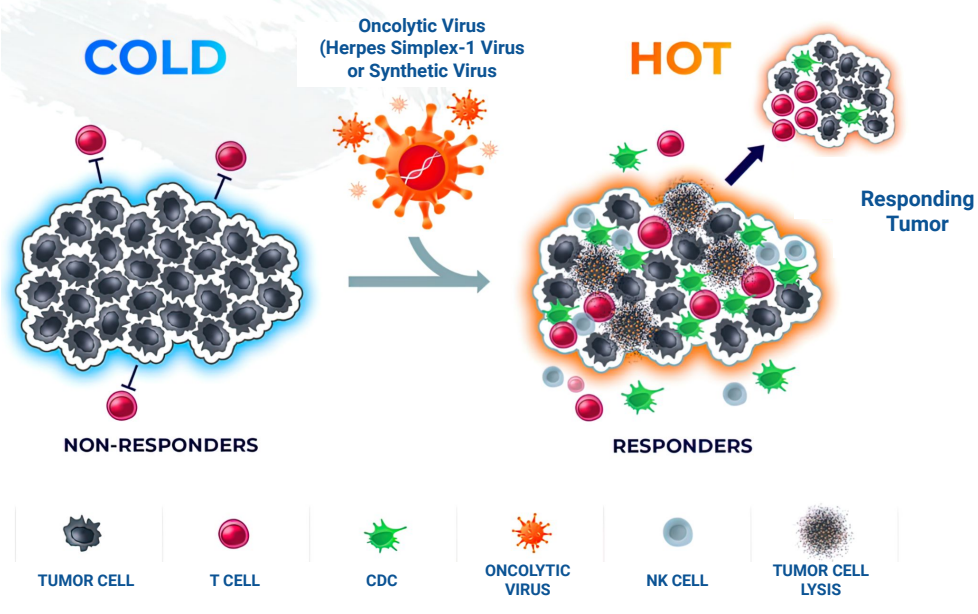
Oncolytic viruses cancer vaccines development pipeline

Discovery	Pre-IND	Phase 1/2	Phase 3	Commercialization

- **ONCR-177 HSV** for intratumoral injections by **Oncorus**
- **CAN-2409 Adenovirus** for prostate cancer by **Candel Therapeutics**
- **OLVI-VEC** for ovarian cancer by **Genelux**
- **ParxOryx** for GBM **by Oryx**

Oncolytic Viruses Platform: Key Players

Oncorus — biotechnology company which develops next-generation viral immunotherapies for oncology. Their technology enables immune system to target cold tumors converting them into hot tumors.



They state that their approach not only activates antitumoral immunity but also **stimulates the release** and presentation of a greater number and variety of **neoantigens.**

One more important mechanism is a synthesis of **transgenes** which influence **tumor microenvironment.**

Sources —Oncorus Technology

Oncolytic Viruses Platform: Key Players

Oncorus is moving into two directions in virotherapy field: Herpes Simplex Virus platform and viral RNA platform. The products of such platforms have different delivery approaches: directly intratumoral through the injection and intravenous respectively.

oHSV

ONCR-177 is a leading product of this platform which is an oncolytic virus which should be administered directly into the tumor site; consequently this induces **immunogenic cancer cell death** and drives llasting and systemic anti-tumor response

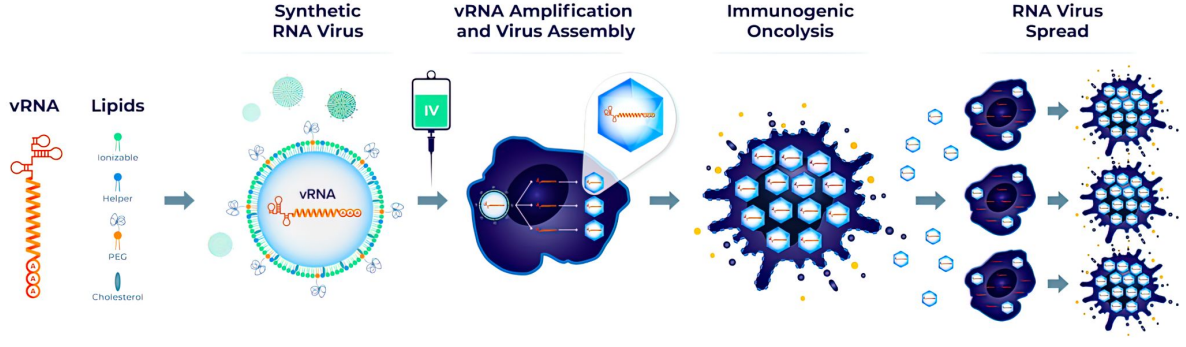
Oncolytic virus brings 5 immunostimulatory agents:

IL-12, CCL4, FLT3LG, anti-PD-1 and anti-CTLA-4

vRNA

This technology is supposed to be less immunogenic which should result into a lower non-specific immune response. Viral RNA is delivered in lipid nanoparticles.

Leading programs ONCR-021 and ONCR-788 are based on coxsackievirus A21 (CVA21) and Seneca Valley Virus (SVV) respectively



Sources —Oncorus Technology

Oncolytic Viruses Platform: Key Players

Candel Therapeutics focuses on preventing the recurrence and progression of cancer by applying viral immunotherapy. They are aimed to reach a low toxicity level which is well suited for the treatment of less aggressive or slower growing cancers.

Adenovirus Platform

CAN-2409 is an engineered gene construct encoding the thymidine kinase gene, which should be transported into infected tumour cells. Administered in the form of intratumoral injection.

multifactorial approach which enables virus-based vectors to activate cancer-killing mechanisms

HSV Platform

CAN-3110 is engineered to express the gene responsible for viral replication only when it is activated by a tumor-specific Nestin promoter. This provides a better regulation of immune response and precise targeting.

Oncolytic Viruses Platform: Key Players

Genelux is an innovative biopharmaceutical company which develops oncolytic virotherapy and combines it with other cancer vaccine approaches.

Their leading product is **Olvi-Vec** is currently on the stage 2 of clinical trials and it is stated that it can effectively fight multiple cancers (including both solid tumors and blood malignancies). Genelux owns a **Choice Discovery Platform to** develop an extensive library oncolytic viruses strains identified from multiple *in vitro* and *in vivo* selection criteria.

V2ACT (Virus and Vaccine (Neoantigen)-Enhanced Adoptive Cell Therapy) is a unique combinational approach for immunotherapy developed by Genelux.

This immunotherapy is aimed to produce a strong immune response and an outburst of primed cancer neoantigen-specific effector T cell precursors

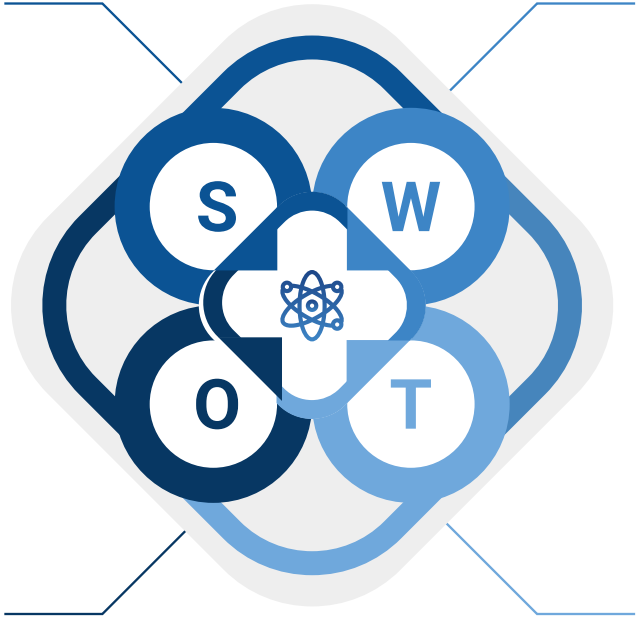
Olvi-Vec Immuno-Therapy Chemotherapy (platinum) refractory and/or resistant cancers			**Generation Oncolytic Virus**
	Regional (Advantages)	**Intravenous** (Advantages)	**Local** (Advantages)
Ability to target advanced and metastatic diseases	✓	✓	✗
Ability to target cancers without prolonged treatment burden	✓	✓	✗
Ability to target and treat tumors of varying sizes	✓	✓	✗
Robust immune activation profile	✓	✓	✗

Sources — Genelux Technology

Oncolytic Viruses Platform: SWOT Analysis

Strengths

- Can reach ‘cold’ tumors and turn them into ‘hot’ tumors
- Targets both tumor and its microenvironment
- Creates a strong immune response



Weaknesses

- Usually causes undesirable immune response with extensive antibodies production which neutralise the virus
- Limited number of the antigens which can be targeted
- Mostly needs to be administered through the injection

Opportunities

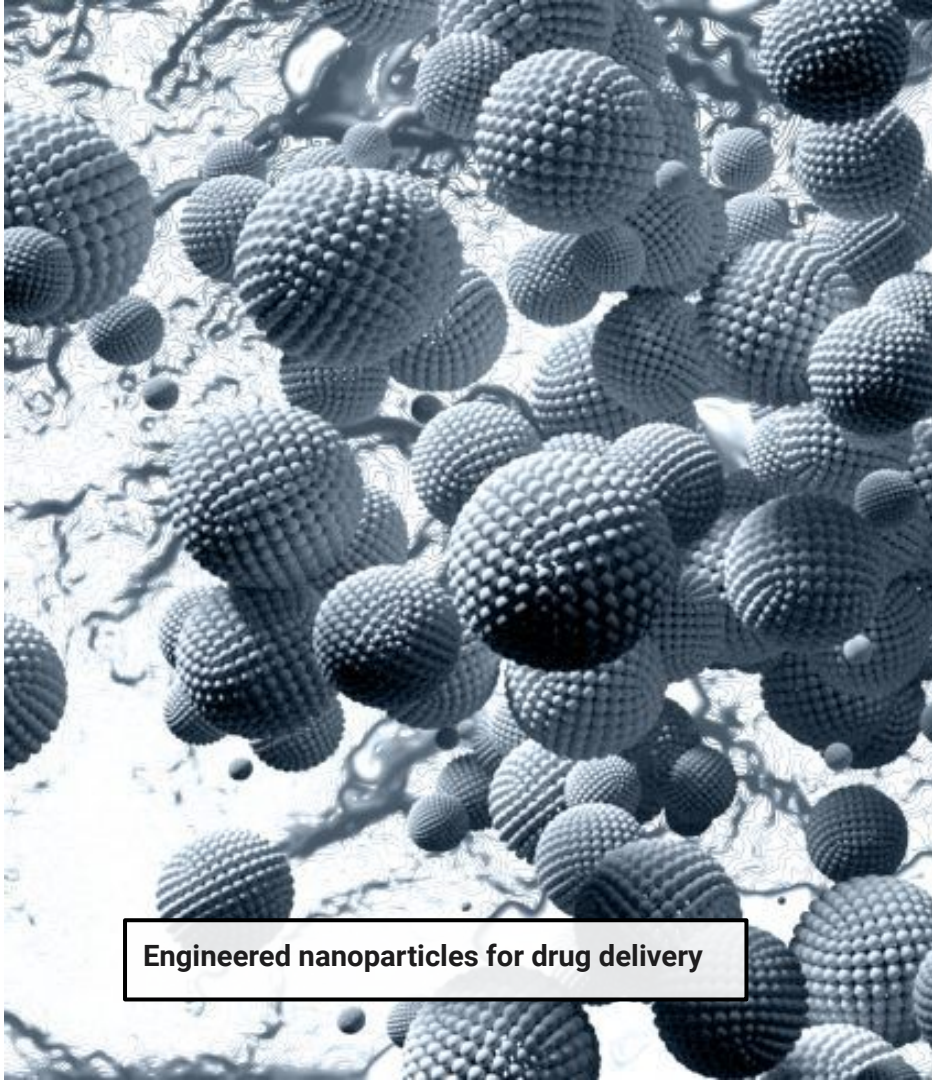
- Can be efficiently improved through combinational therapies
- Can become the main mechanism of the tumor immunization if it is not reachable for other therapies

Threats

- Severe side effects resulted by the viral activity regarding healthy cells
- Gene modified viruses injected into a human body might cause some ethical concerns

Cancer Vaccines Delivery Systems

DEEP
PHARMA
INTELLIGENCE



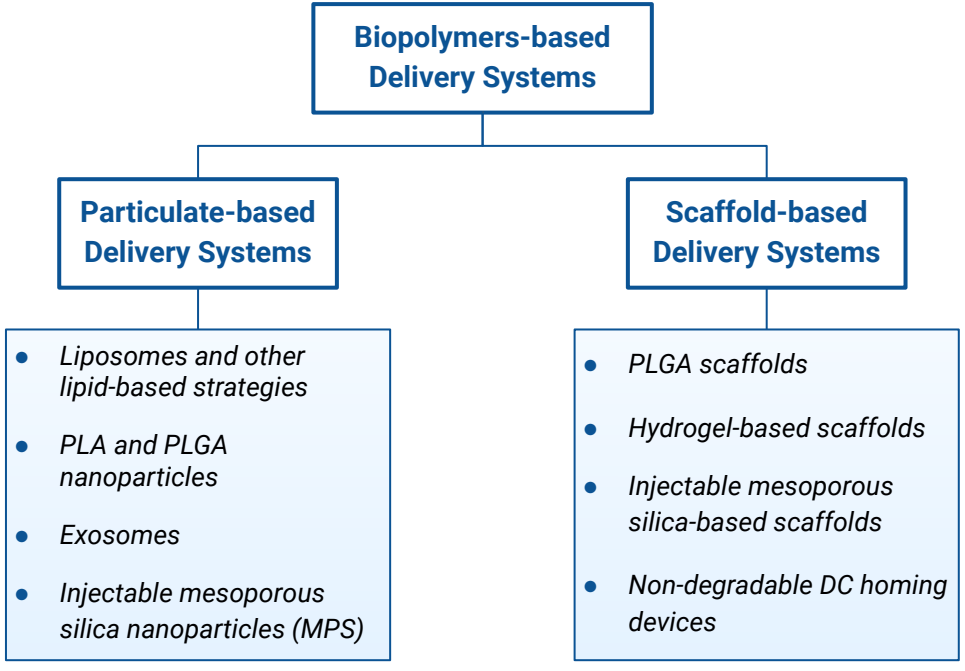
Engineered nanoparticles for drug delivery

The Need of Effective Delivery System

One of the main challenges in modern immunotherapy is **targeting cold tumors** (tumors surrounded by immunosuppressive cells) - the subclass of **solid tumors**. Implementing the appropriate delivery system is the primary way to overcome this challenge. Many clinical trials of cancer vaccines fail because of ineffective delivery methods. For example, vaccination using unmodified peptides generated an overall response rate of only 3% due to difficulty activating antigen-presenting cells.

Biopolymers-based delivery systems could enable spatiotemporal presentation to cells and the microenvironment, thus enhancing efficacy and reducing potential adverse effects. Nowadays, the science of biopolymers is rapidly developing, which allows the usage of different biopolymers to overcome various delivery challenges specific to each type of vaccine.

Combining advances in biomaterials with a deeper understanding of cancer immunology is critical for developing a clinically effective cancer vaccine platform.



Sources — Emerging biomaterial-based strategies for personalized therapeutic in situ cancer vaccines

Particulate-based Delivery Systems

Particulate-based approaches have long been utilized to improve therapeutic delivery to particular tissue areas while minimizing off-target and systemic side effects.

Liposomes

Liposomes have a hydrophobic outer layer and a hydrophilic inner core, making them ideal for encapsulating both hydrophobic and hydrophilic medicinal cargo.

✓ Stable
✓ Long depot action at the injection site
✗ Limited loading capacity
✗ Once released, vaccines become impossible to retrieve -> uncontrollable responses

Nanoparticles

Nanoparticles are used for oncotherapeutics delivery because they display target specificity to the tissue of interest, based on size, charge, surface properties and dissemination strategy.

✓ Limited off-target accumulation
✗ Limited delivery efficiency
✗ Limited loading capacity
✗ Limited to a cargo of peptides

Exosomes

Exosomes, microvesicles, and apoptotic bodies, which are membrane-bound extracellular vesicles released from the endosomal compartment of most eukaryotic cells, can be used as drug delivery vehicles.

✗ Many manufacturing challenges
✗ New technology which requires more research before trials in human

MPS Nanoparticles

Mesoporous silica-based (MPS) approaches aim to address the challenge in high variability in delivery efficacy dependent on cellular interactions by leveraging their well-established drug carrier properties and high versatility in conjunction with other materials.

✓ Silica is non-toxic material
✓ Large loading capacity
✗ New technology which requires more research before trials in human

Sources — Emerging biomaterial-based strategies for personalized therapeutic in situ cancer vaccines

Scaffold-based Delivery Systems

Scaffold-based vaccines are structures intended to initiate antitumor immunity locally at the implantation or injection site. For *in situ* cancer vaccines, most deliver stimulatory **adjuvants and antigens** to induce in situ DC homing and subsequent antigen-specific immune activation.

In general, in situ cancer vaccines utilizing scaffolds must be designed to address three key criteria. They should be **macroporous, clinically translatable**, and should **release immune potentiating adjuvants.**

Scaffold-based Systems

PLGA Scaffolds

PLGA scaffold is a biocompatible synthetic linear copolymer characterized by the modified surface for intracellular interactions.

Hydrogel-based Scaffolds

Hydrogel-based scaffold is crosslinked hydrophilic polymer insoluble in water that can be loaded with bioactive molecules forming an enriched microenvironment for cellular interaction.

Injectable Mesoporous Silica-based Scaffolds

Injectable mesoporous silica-based scaffold is system composed of nano-sized spheres or rods of silica in a predetermined non-specific geometric arrangement for loading with drug. It can be improved by addition of functional groups and capping treatment.

Non-degradable DC Homing Devices

Non-degradable DC homing device is an implantable stable medical device for sustained and constant release of therapeutic cargo for different medical applications.

Sources — Emerging biomaterial-based strategies for personalized therapeutic in situ cancer vaccines

Companies Applying Advanced Cancer Vaccines Delivery Systems

SilVacx — is a spin-off from Merck AG, which specializes on developing novel delivery systems for cancer immunotherapy, including cancer vaccines. SilVacx technology is based on **silicon dioxide nanoparticles**, which can help to make cancer vaccines material delivery in the human body efficient and cost-effective.

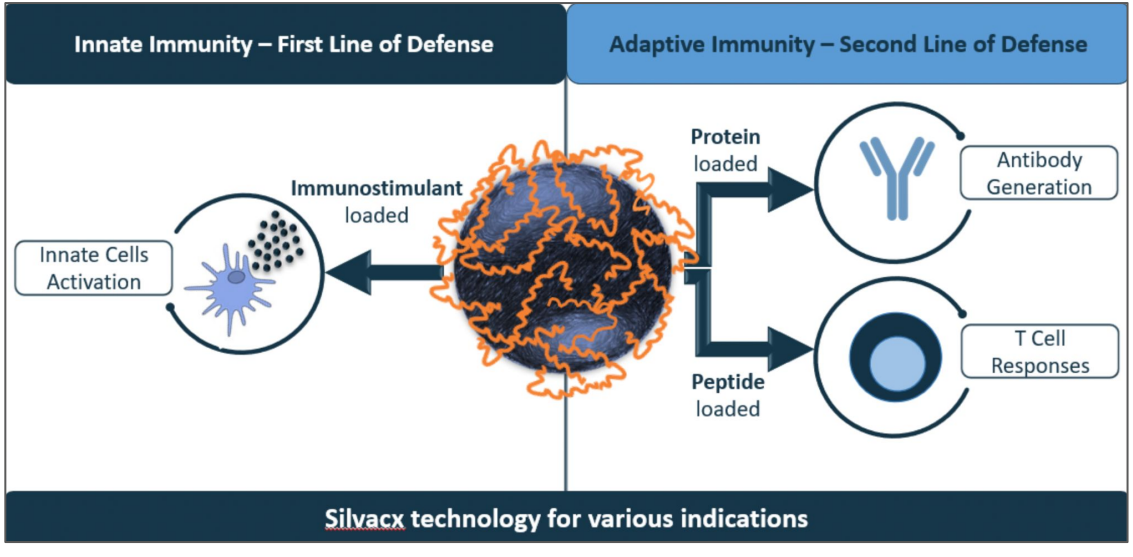
SilVacx project is supported by **Life Science Inkubator GmbH** (LSI), which is the first time LSI supported a research project originating from a pharma company. The platform is mainly oriented for therapeutic cancer vaccines, but can be used for preventive vaccines as well.

Currently the platform is designed for **neoepitope-based personalized** antitumor vaccines and extremely powerful for **HPV** (human papillomavirus) induced cancers.

SilVacx's technology provides

- stimulation of the **innate** immune system
- stimulation of the **adaptive** immune system

Virus-sized particles with a virus-like morphology provide an efficient uptake and processing of antigens by dendritic cells.



Sources — SilVacX

Companies Applying Advanced Cancer Vaccines Delivery Systems

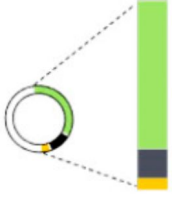
Osivax — is a clinical stage biotechnology company, which owns a novel proprietary **nanoparticle technology.** This technology - **oligoDOM -** can be applied for many types of vaccines, including cancer vaccines.

It is specifically designed to trigger superior T-cell responses, in addition to strong and sustained B-cell responses. In other words, it engages both cytotoxic and memory immune cells.

OligoDOM technology was tested with different antigens, as well as within different vaccine forms. It can be combined with recombinant proteins, or mRNA technology, leading to multiple value generation opportunities.

Currently Osivax is expanding their portfolio to include cancer targets, such as **HPV antigen.**

Single gene



Expressed

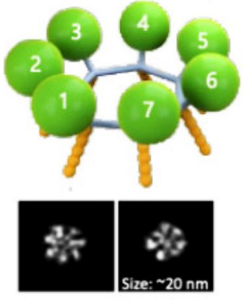
Protein monomer

Full length target antigen

Recombinant protein from a single gene with three synergistic domains

Auto-assemble

oligoDOM vaccine



A large, positively charged, highly immunogenic version of the antigen

Sources — Osivax Technology

Companies Applying Advanced Cancer Vaccines Delivery Systems

Midatech Pharma — is a pharmaceutical company focused on drug delivery technology and its application for various diseases, including cancer.

Midatech owns three drug delivery platforms which enable comprehensive improvement of biodelivery and biodistribution of 'on-market' and pre-approval drugs.

Q-Sphera

proprietary 3D printing technology that **encapsulates** medicines into **bioresorbable polymer microspheres** with precision characteristics

- Micro-encapsulation **PLGA polymer** depot system
- Advanced piezo printing technology
- Several million microspheres produced per second

MidaCore

ultra-small **gold nanoparticle** (GNP) drug conjugates

The small size and multi-functional arrangement of molecules around a gold core underpin MidaCore's ability to improve biodistribution and targeted drug delivery

MidaSolve

solubilises potent molecules that have minimal solubility at biological pH extending available routes of administration

Used for direct-to-tumor delivery

Sources — Midatech Pharma Technology

Companies Applying Advanced Cancer Vaccines Delivery Systems

Alnylam Pharmaceuticals is a biopharmaceutical company that develops therapy with an RNA interference (RNAi) approach. The company's therapeutic focus areas are genetic medicines, cardio-metabolic diseases, infectious diseases, central nervous system (CNS) and ocular diseases. For delivery of their therapy, Alnylam utilizes two delivery platforms - **lipid nanoparticles (LPNs)** and **conjugates**.

Lipid Nanoparticles

- Alnylam has an approved iRNA therapy that utilizes LNP-based delivery - **ONPATTRO® (patisiran)**.
- **LNPs** are chemically synthesized **multicomponent lipid formulations** (~100 nm in size) that encapsulate siRNAs and deliver the medicine to the target tissue.
- **LNPs** protect the drug from degradation by **ubiquitous nucleases**.
- **LNPs in ONPATTRO** have an affinity for **apolipoprotein E** which is expressed on the surface of hepatocytes, that allows the accurate delivery of siRNA to the liver.

Conjugates

- **Conjugates** are single chemical entities that have siRNA coupled to target ligands to aid them in finding their way to a particular cell or tissue in the body. The ligand attached to the siRNA has an affinity to the receptor on the target cell, which creates a **"lock and key" system**.
- Alnylam has developed two conjugate approaches to enable targeted delivery to the **liver** and the **central nervous system (CNS)**.
- The company utilises **GalNAc conjugates** that bind to the **asialoglycoprotein receptor** for targeting the liver, which is abundantly expressed on liver cells (hepatocytes).

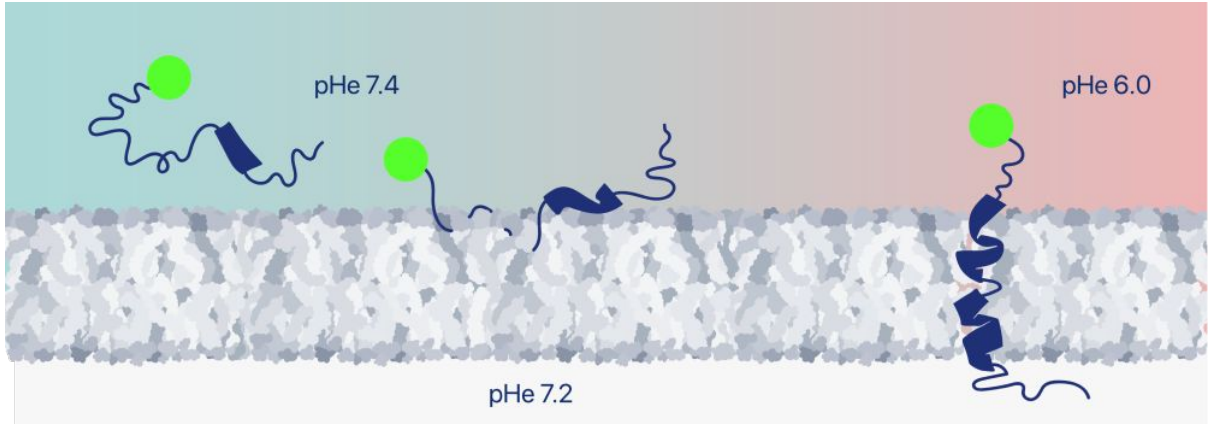
Sources — Alnylam Pharmaceuticals

Companies Applying Advanced Cancer Vaccines Delivery Systems

pHLIP is a company that develops peptide-based targeted delivery platforms to cure cancer, inflammation and other acidic tissue diseases. Their innovative platform **pHLIP®s** (**pH-Low Insertion Peptides**) is a platform technology of **pH-sensitive peptides** that exploit pH differences between healthy and diseased cells as a biomarker for targeting and delivering therapeutic and imaging agents to cells in acidic diseased tissues.

Molecular Mechanism:

- **pHLIP® peptides sense and target pH at cell surfaces**, where the pH is the lowest, thus providing high sensitivity.
- **pHLIP® peptides exploit folding and insertion across the cell membrane**, a cooperative process that gives high specificity.
- **pHLIP® peptides do not target or accumulate in cells with normal surface pH in healthy tissue.**



Sources — Philip Inc.

Companies Applying Advanced Cancer Vaccines Delivery Systems

Codiak Biosciences is a biopharmaceutical company focused on pioneering the development of exosome-based therapeutics. Codiak created the **engEx Platform**, which allows us to build and engineer exosomes with unique features, load them with a variety of therapeutic compounds, and guide their tropism to particular target cells. The platform uses exosome-associated proteins - PTGFRN and BASP1 – as scaffolds to direct proteins of interest (targeting ligands and therapeutic molecules) to the surface or the lumen of exosomes.

Exosomes have the potential to be a beneficial therapeutic method due to their capacity to selectively transport a wide range of therapeutic payloads to cells, opening the door to a wide range of possible applications in illnesses that have eluded other treatments.

Targeted Delivery

- Exosome tropism can be designed so they reach specific cell types in the body.
- The targeted delivery enhances drug efficacy and safety.

Immune Silent

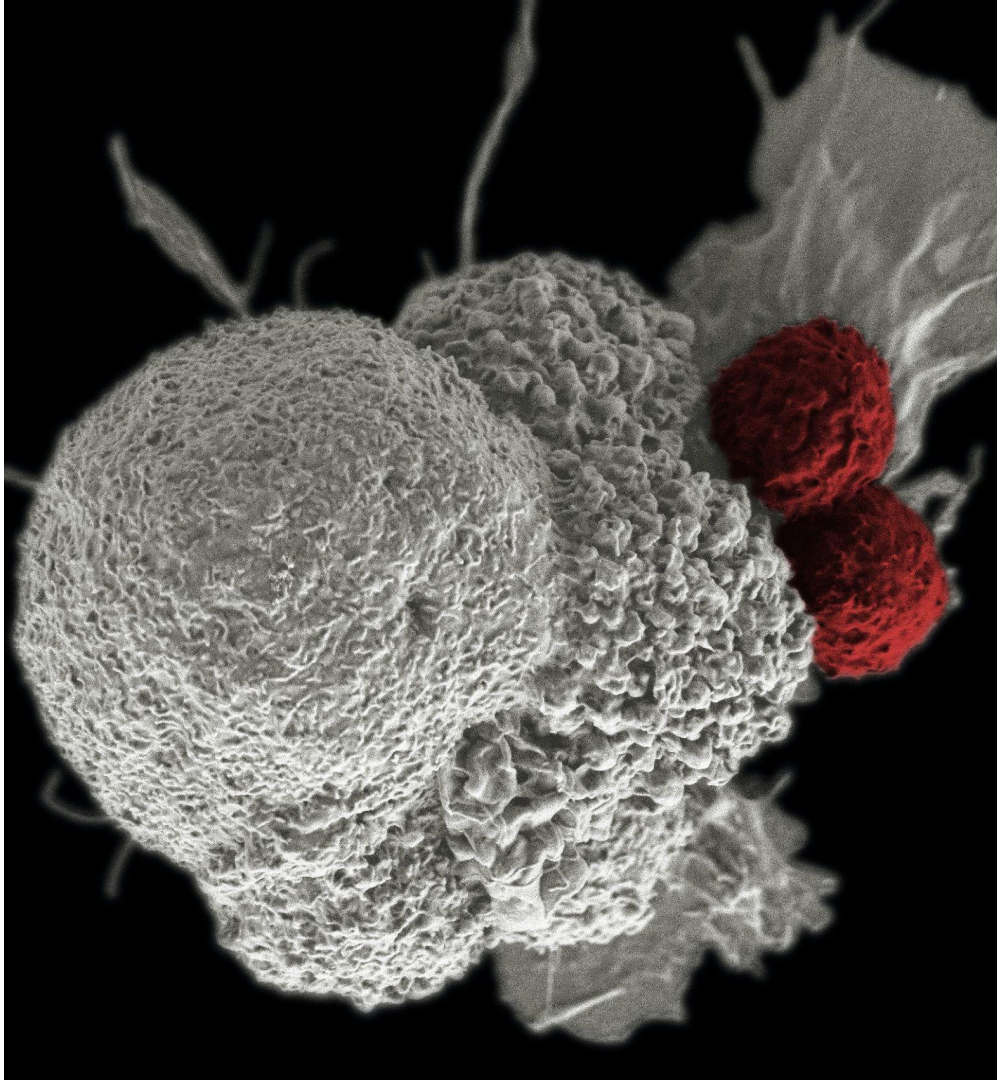
- Exosomes are composed of natural human proteins and lipids, making them inherently non-immunogenic.

Multi-Functional

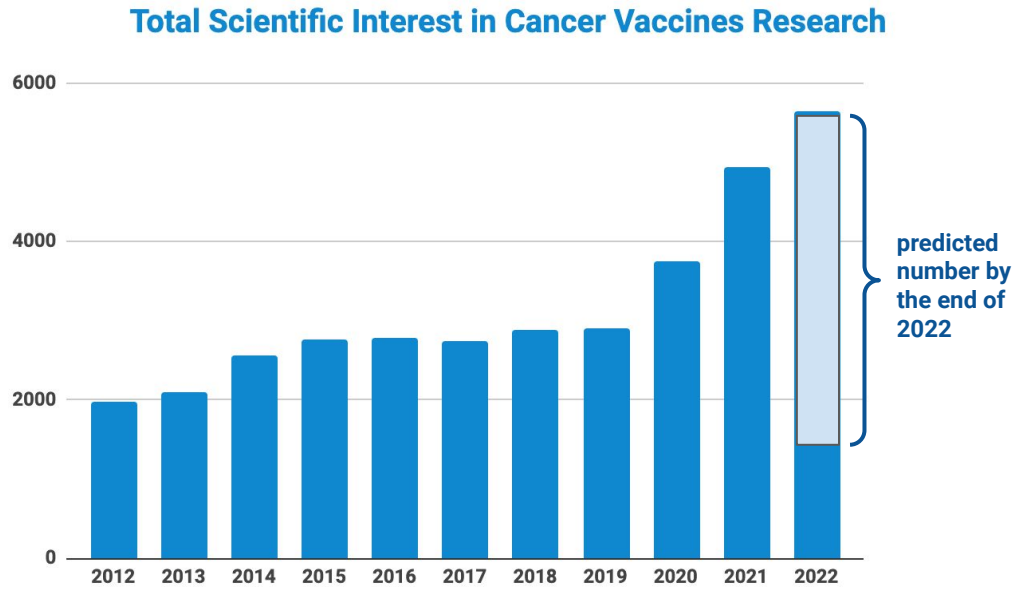
- Exosomes can be loaded with multiple different types of molecules and can influence their targets in multiple ways.

Key Takeaways and General Conclusions

DEEP
PHARMA
INTELLIGENCE



Key Takeaways

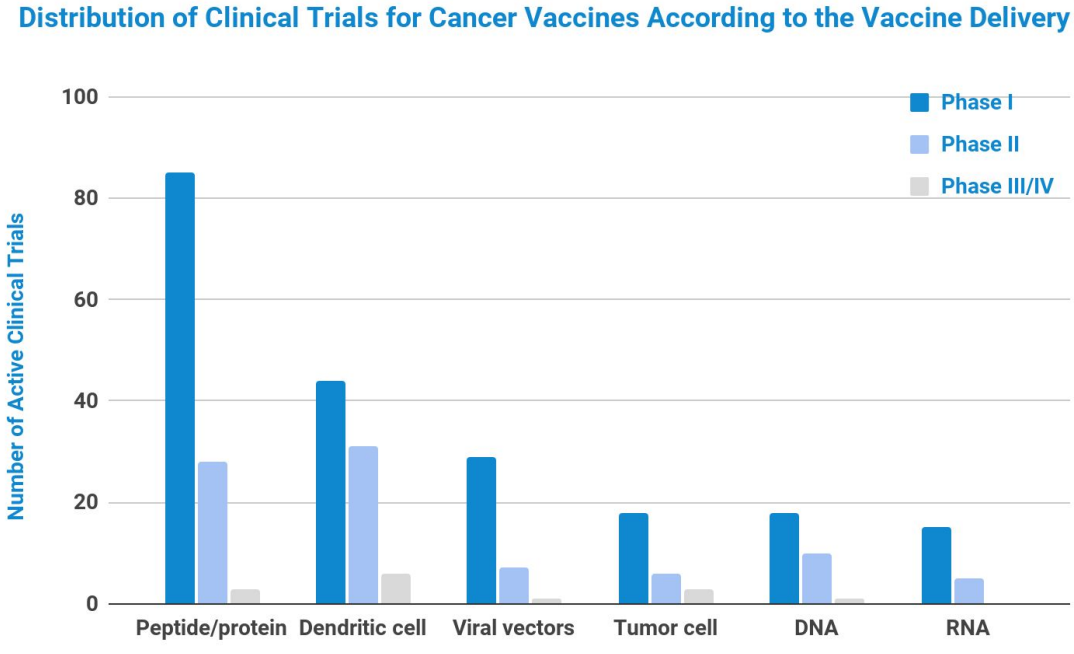


The graph demonstrates the growing number of publications mentioning cancer vaccines by year. Over a decade the annual publishing grew more than 2.5 fold and is expected to continue increasing.

- The interest in cancer vaccination is continually growing and is currently experiencing an outburst in 2021. This mature field of immunotherapy requires **novel approaches and revitalization solutions.**
- The most actively developing platform right now is **neoantigens platform,** which we observe from analysing the lead products of big pharmaceutical companies.
- The most **prominent research vectors** in the field of cancer vaccines are aimed at **enhancement of immunogenicity** while reducing a non-targeted damage of healthy cells, targeting **multiple antigens** and developing an **universal vaccine** for a broad spectrum of malignancies.

Sources — PubMed Database

Key Takeaways



The information is given according to the clinicaltrials.gov investigation by Cuzzubbo et al.

- Besides the common tendency of having the highest number of product candidates on the first phases of clinical trials, there is an even distribution of numbers depending on the delivery form of cancer vaccine.
- Peptide/protein form was represented by over 115 candidates on different stages of clinical trials being the leading platform for vaccine delivery to the target cells. Dendritic cells appear to be the second leader with already approved Sipuleucel-T.
- Fewer number of cancer vaccines are delivered in the form of DNA and RNA, which can be due to higher cost of development and younger age of the platform.

General Conclusions

- We have reviewed the 5 cancer vaccine platforms which are actively developing their products to enter the market of immunotherapy. As a result we conducted assessment of more than 150 companies and R&D centers, and detailed analysis of more than 30 of them.

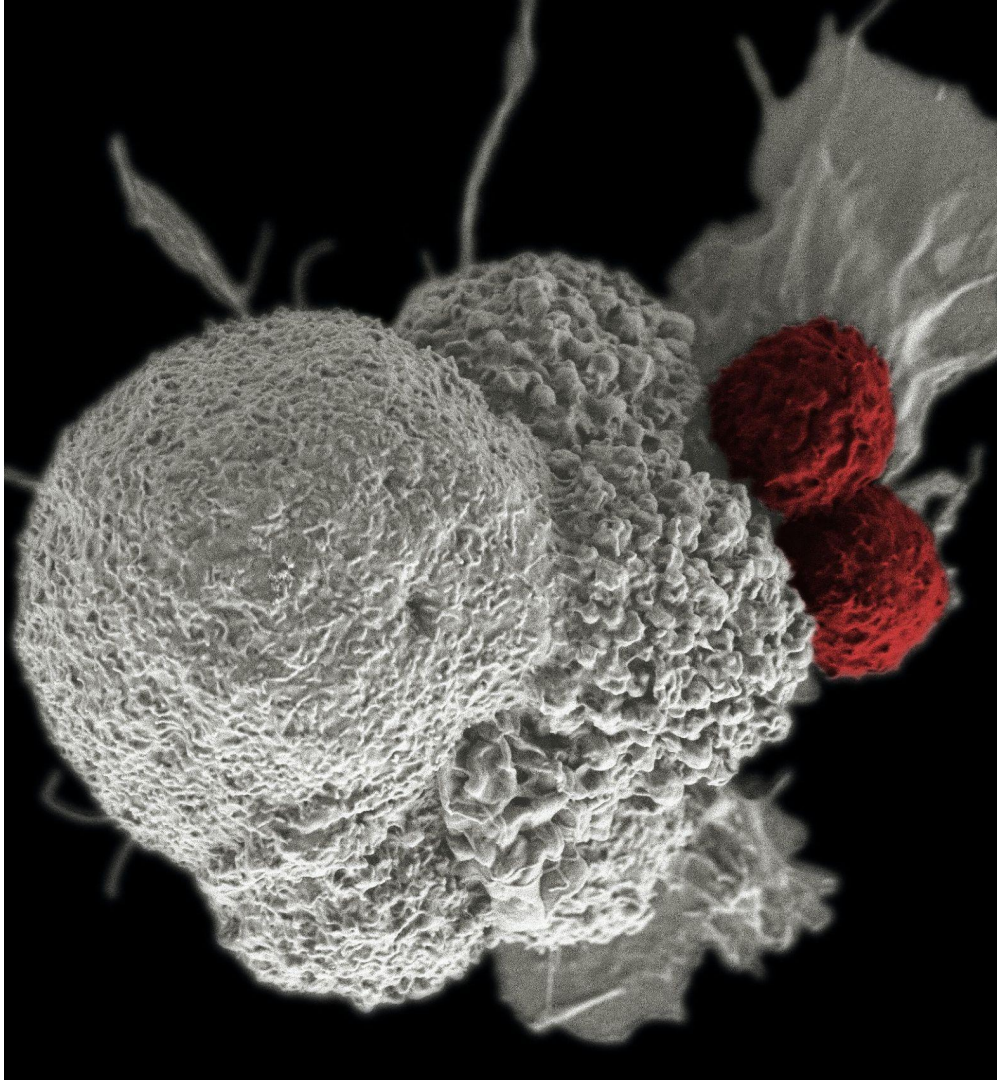
- Identified cancer vaccine platforms have distinguishable features and development timelines, as well as representative companies with the products pipelines. All the reviewed key player companies, in our opinion, possess strong R&D bases, have well-developed level of technology and intellectual property and large total addressable markets for their products.

- We believe that cancer vaccine development is moving into the direction of more specific tumour targeting while reducing side effects by the novel delivery methods, antigen identification applications or vaccine preparation process itself.

- Currently, the major attention is paid to neoantigen platform, but it will probably be pushed out with such growing cancer vaccine platform as antigenic essence, which is likely to combine a high specificity, efficiency and time- and cost-effectiveness.

Appendix:
List of Entities

DEEP
PHARMA
INTELLIGENCE



150 Cancer Vaccine Companies

1	AdaptVac	16	Autolus	31	Cellectis
2	Aeon Therapeutics	17	AVAX Technologies	32	Celularity
3	Agenus Inc.	18	Avrobio	33	Celyad
4	AiVita Biomedical	19	Bavarian Nordic	34	Codiak Biosciences
5	Allogene Therapeutics	20	BioMedicure	35	Corixa Corporation
6	Alnylam Pharmaceuticals	21	BioNTech	36	CureVac
7	Amal Therapeutics	22	BioVaxys	37	Defence Therapeutics
8	Amgen	23	Boehringer Ingelheim	38	Dendreon
9	Anixa Biosciences	24	BriaCell Therapeutics	39	Dynavax Technologies Corporation
10	Antigen Express	25	BrightPath Biotherapeutics	40	Editas Medicine
11	Antion Biosciences	26	Calviri	41	Elicio Therapeutics
12	Apeiron Biologics	27	CaroGen	42	Elios Therapeutics
13	Arcellx	28	CARsgen Therapeutics	43	Enara Bio
14	Arrowhead Pharmaceuticals	29	Celdara Medical	44	Enochian Biosciences
15	AstraZeneca	30	Celgene	45	EpiThany

150 Cancer Vaccine Companies

46	Epitopoietic Research Corporation
47	EpiVax Oncology
48	eTheRNA
49	Evaxion Biotech
50	ExploRNA Therapeutics
51	EXUMA Biotech
52	Flow Pharma
53	Frame Therapeutics
54	Galena Biopharma
55	GemVax & Kael
56	Geneos Therapeutics
57	Generex Biotechnology
58	Genocea Biosciences
59	Geovax
60	GlaxoSmithKline
61	Gracell Biotechnologies
62	Gradalis
63	Gritstone Oncology
64	Heat Biologics
65	Hookipa Pharma
66	Hubro Therapeutics
67	Immunetune
68	Immunicum
69	Immunomic Therapeutics
70	ImmunoRestoration
71	Imvax
72	Inovio Pharmaceuticals
73	InProTher ApS
74	IO Biotech
75	Ionis Pharmaceuticals
76	ISA Pharmaceuticals
77	Janssen Pharmaceuticals
78	Juno Therapeutics
79	Khloris Biosciences
80	Kite Pharma
81	Lava Therapeutics
82	Legend Biotech
83	Lytix Biopharma
84	Magenta
85	MaxiVAX
86	Medigene
87	Midatech Pharma
88	Moderna Therapeutics
89	Mustang Bio
90	Neuvogen

150 Cancer Vaccine Companies

91	NewLink Genetics Corporation
92	NexImmune
93	Noile-Immune Biotech
94	Northwest Biotherapeutics
95	Nouscom
96	NovaRx
97	Nykode Therapeutics
98	Onco Therapy Science
99	OncoPep
100	ONYvax
101	Oryx Translational Medicine
102	Osivax
103	Oxford Vacmedix
104	OxVax
105	PDC*line Pharma
106	Pepscan
107	Personalis
108	pHLIP
109	Phoreus Biotech
110	Polynoma
111	Precision BioSciences
112	ProMab Biotechnologies
113	Providence Therapeutics
114	PsiOxus Therapeutics
115	Regen BioPharma
116	Rhovac ApS
117	RNAimmune
118	Roche
119	Rubius Therapeutics
120	SapVax

150 Cancer Vaccine Companies

121	Scancell Holdings
122	SELLAS Life Sciences
123	Sensei Biotherapeutics
124	Silvacx
125	Socium Therapeutics
126	Sonoma
127	Sorrento Therapeutics
128	Southwest Oncology Group
129	SpyBiotech
130	Strike Pharma
131	Sumitomo Pharma Oncology
132	Takeda Pharmaceuticals
133	Takis Biotech
134	Targovax
135	Tmunity Therapeutics
136	NewLink Genetics Corporation
137	NexImmune
138	Noile-Immune Biotech
139	Northwest Biotherapeutics
140	Nouscom
141	NovaRx
142	Nykode Therapeutics
143	Onco Therapy Science
144	OncoPep
145	ONYvax
146	Oryx Translational Medicine
147	Osivax
148	Oxford Vacmedix
149	OxVax
150	PDC*line Pharma

390 Cancer Vaccine Investors

1	3B Future Health Fund	16	Amgen Ventures	31	Barer & Son Capital
2	4BIO Capital	17	Anaxago	32	BB Biotech Ventures
3	5AM Ventures	18	Andera Partners	33	Be The Match BioTherapies
4	Abingworth	19	Andreessen Horowitz	34	Bezos Expeditions
5	Accelerate New York Seed Fund	20	Apeiron Investment Group	35	Bill & Melinda Gates Foundation
6	Access BridgeGap Ventures	21	ARCH Venture Partners	36	Binex
7	Access Industries	22	Arix Bioscience	37	BioAtla
8	Adage Capital Management	23	ArrowMark Partners	38	BARDA
9	Aisling Capital	24	Asymmetry Ventures	39	BioMedPartners
10	Alaska Permanent Fund	25	Atlas Venture	40	BioNTech
11	Alexandria Venture Investments	26	Auriga Partners	41	Biox Biosciences
12	Algot Invest	27	BWVÄ	42	Birk Venture
13	Alliance of Angels	28	Baillie Gifford	43	Blackstone Group
14	Ally Bridge Group	29	Baker Brothers Advisors LLC	44	Blackstone Life Sciences
15	AFLA	30	BankInvest Biomedical Venture	45	BNP Paribas Private Equity

390 Cancer Vaccine Investors

46	BIVF
47	Boxer Capital
48	Bpifrance
49	Braavos Investment Advisers
50	Brace Pharma
51	Brain Asset Management
52	Brainchild Holdings
53	BrightEdge Fund
54	Bristol Myers Squibb
55	Business Finland
56	BXR Partners LLP
57	CaaS Capital Management
58	Calculus Capital
59	CIRM
60	California Technology Ventures
61	CAM Capital
62	Cambrian Biopharma
63	Cancer Rop
64	CARB-X
65	Care Capital
66	Casdin Capital
67	Catalio Capital Management
68	Celgene
69	Chartwave
70	CMMT
71	Cherwell Capital
72	CGPHH
73	Clal Biotechnology Industries
74	Clarus Ventures
75	CEPI
76	Connecticut Innovations
77	Cormorant Asset Management
78	Crimson Peak
79	Crystal Bioscience
80	Dai-ichi Life
81	DARPA
82	DBJ Capital
83	Deep Track Capital
84	Deerfield Capital Management
85	DTRA
86	DPCM LP
87	Dragasac Limited
88	EcoR1 Capital
89	EDBI
90	EFung Capital

390 Cancer Vaccine Investors

91	EIR Ventures
92	European Commission
93	European Innovation Council
94	European Investment Bank
95	Eventide
96	Evotec
97	F-Prime Capital
98	F1 BioVentures
99	FMRC
100	Flagship Pioneering
101	Flerie Invest
102	Fortress Investment Group
103	Franklin Templeton Investments
104	Frazier Healthcare Partners
105	Fund+
106	Future Planet Capital
107	Future Ventures
108	GeneMatrix
109	Genzyme
110	German Federal Ministry of ER
111	Gilde Healthcare
112	Gilead Sciences
113	GlaxoSmithKline
114	Global Bio Fund
115	Great Point Partners
116	Grifols
117	GV
118	Hambro Perks Ltd.
119	Hansongneotech
120	HBM Healthcare Investments AG
121	High-Tech Grunderfonds
122	Hillhouse Capital Group
123	Horatio Ventures NYC
124	Horizon 2020
125	Horizon Technology Finance
126	Hudson Bay Capital Management
127	Human Longevity
128	Hunza Ventures
129	Hygea VCT
130	Idinvest Partners
131	Imperial Innovations
132	infinitas capital group
133	Innovation Engine
134	Innovation Fund Denmark
135	Innovation Norway

390 Cancer Vaccine Investors

136	Inovio Pharmaceuticals
137	Invesco
138	Invus
139	Ippon Capital
140	Irving Investors
141	Janus Henderson Investors
142	Jebsen Capital
143	Jennison Associates
144	JIC
145	JM Family Enterprises
146	Johnson & Johnson Innovation
147	Jolly Innovation Ventures
148	Kaitai Capital
149	Keiretsu Capital
150	Keiretsu Forum
151	Keiretsu Forum Northwest
152	KfW
153	Khosla Ventures
154	King Star Capital
155	Kinled Holding
156	Kleiner Perkins
157	Korea Investment Partners
158	Korify Capital AG
159	Kreftforeningen
160	KSP
161	KTB Ventures
162	Kukje Pharma
163	Kurma Partners
164	Landeskreditbank BW
165	LBBW Asset Management
166	Lead Compass Investment
167	Leerink Partners
168	Leukemia & Lymphoma Society
169	Life Science Angels
170	Life Sciences Pennsylvania
171	Life Sciences Partners
172	Life Sciences Research Partners.
173	Lifeforce Capital
174	Lightspeed Venture Partners
175	Lilly Asia Ventures
176	Livzon Pharmaceutical Group
177	Loyal Valley Capital
178	LSP
179	LSP BioVentures
180	Luminous Ventures

390 Cancer Vaccine Investors

181	Lundbeckfonden Emerge
182	Lundbeckfonden Ventures
183	Lupus Ventures
184	M&G Investments
185	MBLVC
186	Mercia Asset Management PLC
187	Merck
188	Meusinvest (Noshaq)
189	Mid Atlantic Bio Angels
190	Minority Angel Investor Network
191	Mirae Asset Global Investments
192	MiraeAsset Financial Group
193	MKB & Technofonds Flevoland
194	Mohr Davidow Ventures
195	MCRF
196	Moore Strategic Ventures
197	Morningside Venture Partners
198	MRL Ventures Fund
199	MSD Partners
200	National Cancer Institute
201	National Institutes of Health
202	New Enterprise Associates
203	Nextech Invest
204	NextWaveBio
205	Nippon Venture Capital
206	Norinnova Forvaltning
207	Norinnova Invest
208	Northleaf Capital Partners
209	Norwegian Research Council
210	Novalis LifeSciences
211	Novartis
212	Novo Ventures
213	ODYSSEE VENTURE
214	Omega Funds
215	OrbiMed
216	Osage University Partners
217	Outsized Ventures
218	Oxford Capital Partners
219	Oxford Investment Consultants
220	Oxford Sciences Innovation
221	Oxford University Innovation
222	Penn Medicine Co-Investment
223	Perceptive Advisors
224	Pfizer Venture Investments
225	PFM Health Sciences

390 Cancer Vaccine Investors

226	Photon Fund
227	Picasso Kapital
228	Pictet Private Equity Investors .
229	Piedmont Capital Partners
230	Piper Sandler
231	Platinum Asset Management
232	PMV
233	Point72
234	Pontifax AgTech
235	PPM Oost NV
236	Presight Capital
237	Pura Vida Investments
238	Pureos Bioventures
239	Qatar Investment Authority
240	RA Capital Management
241	Radium Hospital Research Foundation
242	Redmile Group
243	Regeneron
244	Ridgeback Capital
245	Riverbank Capital Securities
2 46	Robin Hood Ventures
247	Rotating Boulder Fund
248	Runway Growth Capital
249	S.R.I.W.
250	SAIKYO
251	Såkorn Invest Nord
252	Sambrinvest
253	Samsara BioCapital
254	Sand Hill Angels
255	Sanofi Ventures
256	Sansei Capital Investment
257	Sante Ventures
258	Schroder Adveq
259	Section 32
260	Sequoia Capital
261	Serrado Capital
262	SFPI-FPIM
263	SSSB
264	Shibuya Kogyo
265	Shinhan-Cognitive Start-up Fund
266	Shiyu Capital
267	Silence Therapeutics
268	Sinobioway Group
269	Sirnaomics
270	Sirona Capital

390 Cancer Vaccine Investors

271	Sixty Degree Capital
272	Smooth River
273	Sofinnova Partners
274	SoftBank
275	Sorrento Therapeutics
276	Sosei CVC
277	South China Venture Capital
278	Sparebanken Nord-Norge
279	SR One
280	Stanford University
281	Summer Capital
282	Sunstone Life Science Ventures
283	SunTerra Capital
284	Surveyor Capital
285	SV Health Investors
286	Syncona Partners LLP
287	T. Rowe Price
288	Takeda
289	Takeda Ventures
290	TCG Crossover
291	Technofund Flevoland
292	Temasek Holdings
293	Tencent
294	Tera Science
295	Teralys Capital
296	The Future Fund
297	The Longevity Fund
298	The Watermill Group
299	Third Rock Ventures
300	TPG
301	Trend Investment Group
302	Trygve Schiorbeck
303	Two River
304	U.S. Department of Defense
305	UCLB
306	United Therapeutics
307	University of Pennsylvania
308	UTC Investment Co.
309	venBio Select Advisor
310	Venrock
311	Versant Ventures
312	Vienna Insurance Group
313	Viking Global Investors
314	Vivo Capital
315	Wageningen Business Generator

390 Cancer Vaccine Investors

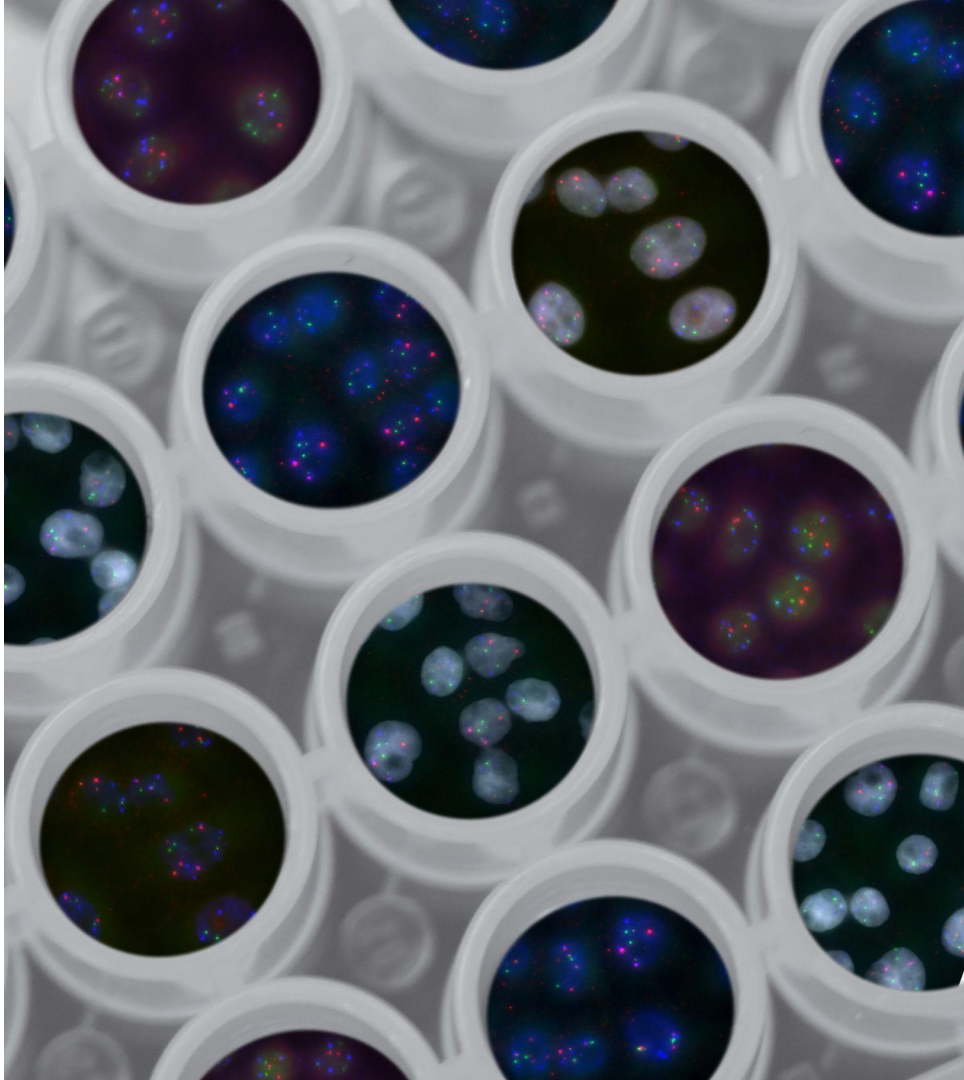
316	Wellington Management	331	Bill Maris	346	Mason Ng
317	Westlake Village BioPartners	332	Blackstone Credit	347	Matthew Katz
318	Woodford Investment	333	Boris Nikolic	348	Mitzi Krockover
319	Xfund	334	Cardinal Partners	349	Novo Holdings
320	YTLO	335	Cédric Delorme	350	Oxford Technology Management
321	Yijing Capital	336	Citadel	351	Oystein Rekdal
322	York Capital Management	337	David Castle	352	Polaris Partners
323	Ysios Capital	338	DCI Partners	353	Quantum Technology Partners
324	Yukon Partners	339	Duke Management Company	354	SCALE AI
325	4PPF Group	340	Healthcare Innovation	355	SFC Co
326	Alexandria Venture	341	Heritage Group	356	Starr Insurance Companies
327	Alpha Holdings	342	HLB Co	357	Thynk Capital, LLC.
328	Alta Partners	343	Ibis Capital Partners	358	Tony Robbins
329	Arie Belldegrun	344	Jacque J. Sokolov	359	VI Partners
330	BiGEN	345	John Sigurd Svendsen	360	Alice Ventures

390 Cancer Vaccine Investors

361	Alta Berkeley Venture Partners
362	Ames Seed Capital
363	Avidity Partners
364	Bay City Capital
365	Biotechnology Value Fund
366	Chicagoland Investors
367	CRG
368	Droia Ventures
369	Excalibur Fund Managers
370	Forward Ventures
371	GF Securities
372	Global health sciences venture fund
373	Hercules Capital
374	HP WILD HOLDING AG
375	InterWest Partners
376	Iowa Capital Management
377	Magnetar Capital
378	Midwest Oilseeds
379	National Institute of Allergy and Infectious Diseases
380	NLG Advisors
381	OVP Venture Partners
382	Quark Venture
383	Square 1 Bank
384	Terra Magnum Capital Partners
385	TLP Investment Partners
386	Vida Ventures
387	Ziff Capital Partners
388	3i Group
389	Enterprise Partners
390	WILD Group Management

Overview of Proprietary Analytics by Deep Pharma Intelligence

DEEP
PHARMA
INTELLIGENCE



About Deep Pharma Intelligence

DEEP PHARMA INTELLIGENCE

Deep Pharma Intelligence is producing regular analytical reports on major areas of high-potential in the pharmaceutical and healthcare industries, maintaining ratings of companies and governments based on their innovation potential and business activity in the BioTech space, and providing strategic consulting and investment intelligence services to top-tier clients, including major investment funds and banks, family offices, insurance companies, government organizations, and big pharma companies among others. The company is a joint venture between the two highly specialized UK-based market intelligence hubs in Pharma / BioTech space:

DEEP KNOWLEDGE ANALYTICS

Pharma Division of Deep Knowledge Analytics (PD-DKA), a specialized subsidiary of Deep Knowledge Analytics (DKA), the leading analytical entity specifically focused on deep intelligence of the high-potential areas in the pharma industry, including artificial intelligence (AI) for drug discovery sector.

Deep Knowledge Analytics Pharma Division serves as the main source of investment intelligence and analytics for AI-Pharma, a specialized index hedge fund for the AI in the drug discovery sector. PD-DKA's insights are frequently covered by top media such as Forbes and the Financial Times, and are acknowledged by top pharma executives.

Recently, MIT named this division a top technology think-tank, acknowledging the AI ranking framework it developed.

Bio Pharma Trend

BPT Analytics (BiopharmaTrend) - a rapidly growing analytical portal and media resource, dedicated to tracking emerging companies (startups/scaleups), innovations, investments, and trends in the pharma and biotech space.

BiopharmaTrend's reports and articles were referenced by Deloitte, Forbes, and other high profile media and consulting companies.

BiopharmaTrend is a media partner to a number of top-tier conferences and symposia in preclinical and clinical research, and healthcare research.

Overview of Proprietary Analytics by Deep Pharma Intelligence

Deep Pharma Intelligence (DPI) is a strategic partner to the leading Life Science organizations, investment institutions (VC funds, investment banks), and governments across the globe — in matters related to investments, strategic positioning, and policy development in the areas of pharmaceutical and biotech research, and healthcare tech.

While Deep Pharma Intelligence is regularly producing open industry reports covering high-growth sectors in the Life Sciences, including artificial intelligence (AI), digital health, and new therapies, some of the more in-depth research is only available to our clients and strategic partners under the "**Proprietary Analytics**" category.

Our range of proprietary services includes custom consulting projects, based on the specific customer needs, as well as a collection of pre-produced "ready-to-use" proprietary reports, produced by our research team, covering general trends and specific action ideas and strategy insights related to the most promising investment prospects (e.g. new technologies, biotech startups), M&A prospects (e.g. pipeline development targets), and strategic growth ideas (trends profiling, industry overviews etc).

Services:

- Investment landscape profiling, identifying investment ideas in the biotech/healthcare tech space
- Preliminary due-diligence (business, science and technology, intellectual property (IP) profiling, freedom of operation assessment, legal assessment etc)
- Comprehensive due-diligence (deep business, science and technology assessment, IP and legal assessment, growth potential assessment etc)
- Infringement analysis of technology (i.e. If you plan to partner or invest in a data-analytics biotechs, or AI-development vendors, it is essential to understand their technological assets, both in terms of innovation potential and in terms of legal protection and non-infringement risk management)
- SWOT analysis of companies and technological sectors, competitive profiling
- Industry profiling and growth strategy development for top-tier companies and governments.

Overview of Proprietary Analytics by Deep Pharma Intelligence

Proprietary Reports

There are a few 40+ page reports delivering practical answers to these specific questions in order to optimize the short and long-term strategies of biopharma corporations and other institutions related to the industry, with a newly updated edition being released each quarter, incrementally increasing the precision, practicality and actionability of its technological and financial analysis.

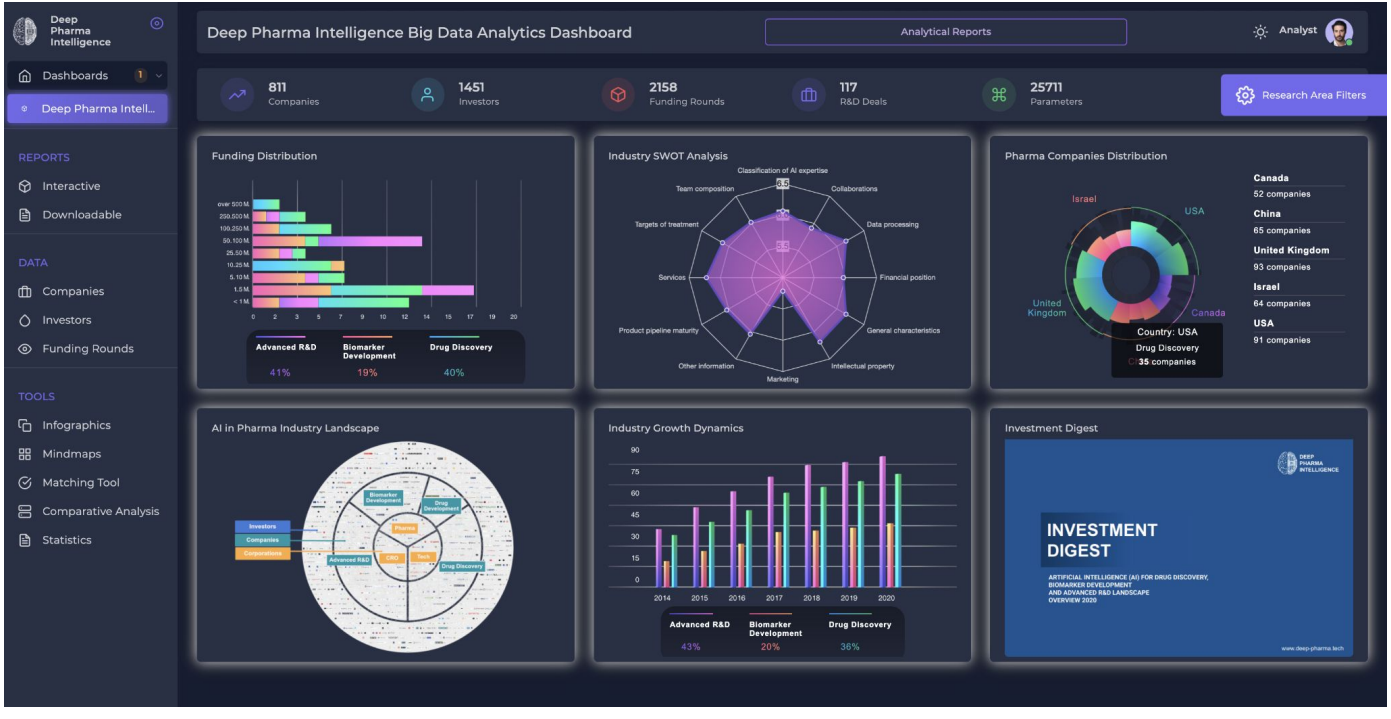
Our reports are supported by our rapidly developing data mining engine, data visualization platform and analytics dashboards.

The value our reports can deliver:

- Deep analysis of the deal-making prospects in the biotech and healthcare tech space, identification of top mini-trends and larger tendencies in innovations and technology adoption (e.g. AI, blockchain, eHealth tech, longevity biomarkers, new therapeutics and therapies etc.)
- Tangible forecasts on the 3-5 years horizon, providing an overview of future scenarios of the development of various technologies in the pharma industry
- Practical guides for adopting various technological solutions and best practises, vendor profiling and contract research strategy building
- Analysis of key market players in the emerging and high-growth areas of the pharmaceutical and biotech industries.

The parties who gain early access to these reports will have deep expertise on how their strategic agendas can be optimized in order to leverage novel research, new technologies, and emerging market opportunities, and stay competitive in a rapidly-changing technological environment, and taking into account shifting global priorities and trends.

Deep Pharma Intelligence: Analytical Dashboard



Our company is building a sophisticated cloud-based engine for advanced market and business intelligence in the pharmaceutical and healthcare industries. It includes data mining engine, infrastructure for expert data curation, and advanced visualization dashboards, including mindmaps, knowledge graphs, and 3-dimensional visualizations.

Visit our dashboard to learn more: **www.platform.dkv.global/dashboards/ai-for-drug-discovery**

Deep Pharma Intelligence: Analytical Reports

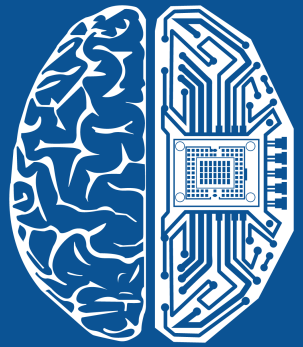
Artificial Intelligence for Drug Discovery Landscape Overview, Q1 2022 is an analytical report created by Deep Pharma Intelligence company that aims to provide a comprehensive overview of the industry landscape in what pertains adoption of AI in drug discovery, clinical research and other aspects of pharmaceutical R&D.

Learn more:
www.deep-pharma.tech/ai-in-drug-discovery-2022-q1

Landscape of Advanced Technology Companies in Pharmaceutical Industry Q4 2021 is an analytical report that provides insights about the expansion of technology developers and vendors into the pharmaceutical space, and their increasing role and influence on the overall success of drug discovery and pharmaceutical business.

Learn more:
www.deep-pharma.tech/technology-report-q4-2021

DEEP
PHARMA
INTELLIGENCE



Link to the Report: www.deep-pharma.tech/landscape-of-cancer-vaccines

E-mail: info@deep-pharma.tech | **Website: www.deep-pharma.tech**