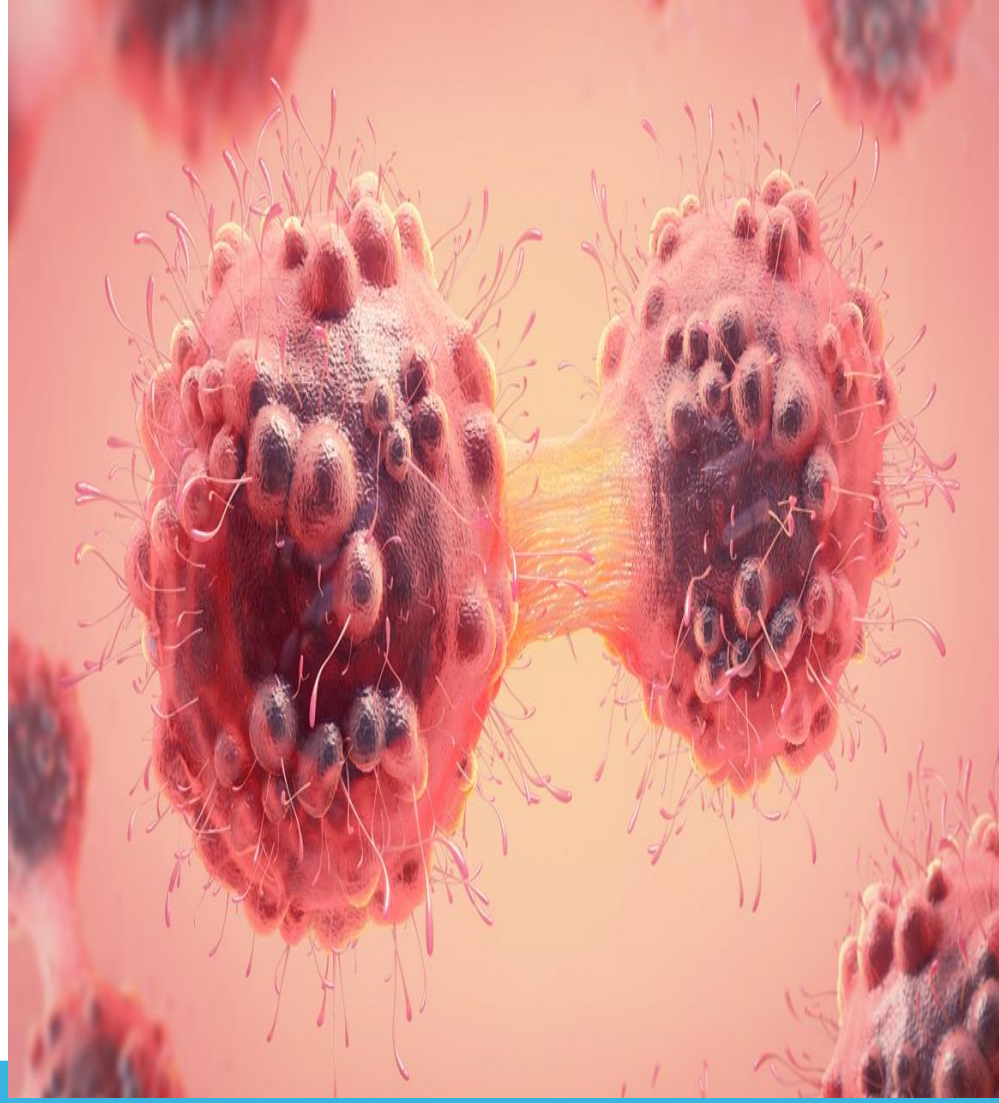
BIOLOGICAL TREATMENT OF CANCER

Cancer is a global health problem, . After heart disease, it is the second most common cause of death.

In the United States, the estimated number of new cancer cases in 2020 , more than 1million. in Iraq, more than 33 thousand new cases and 19 thousand death in 2020. The combination chemotherapy has been the primary choice of treatment.

But the dose limiting toxicity is significant with nonspecific toxicity to healthy cells. The emergence of Multidrug resistance (MDR) also presents s a significant challenge for the successful treatment of cancer where by cancer cells become cross resistant to many of the chemotherapeutic agents used.



Types of Biological therapy

Immunotherapy

It is a type of cancer treatment based on the body's natural defenses or by turn the body's immune system to fight the cancer by the material which made by the body such as WBC, organs and tissue of the lymph system, or in the laboratory to improve immune system.

How it works ?

Immunotherapy includes a wide variety of treatments that work in
different ways.

- By boosting the body's immune system in a very general way.
- Helps to train the immune system to attack cancer cells specifically.
- Giving immune system components, such as man-made immune system proteins.

TYPES OF IMMUNOTHERAPY

The main types of immunotherapy now being used to treat cancer are:

- Monoclonal Antibodies
- Cancer Vaccines
- Non – Specific Immunotherapies
- Engineered Antibodies

Monoclonal antibodies

- Many copies of a specific Antibody can be made in the lab. These are known as Monoclonal Antibodies (mAbs or moAbs).
- These Antibodies can be useful in fighting diseases because they can designed specifically to only target a certain antigen, such as one that is found on cancer cells.
- Over the past 15years, the US FDA has approved about a mAbs to treat certain cancers.

TYPES OF MONOCLONAL ANTIBODIES

Two types of monoclonal antibodies are used in cancer treatment:

- **Naked mAbs** are antibodies that work by themselves.
- **Conjugated mAbs** are those joined to a chemotherapy drug, radioactive particles, or a toxin.

a) Radiolabeled Antibodies

b) Chemolabeled Antibodies

c) Immunotoxins

Naked Monoclonal Antibodies

- Naked mAbs can work in different ways. Some may boost a person's immune response against cancer cells. Other work by blocking specific proteins that help cancer cells grow (some may do both).
- For example – Herceptin (trastuzumab) is an antibody against the HER 2/neu protein. It is used to treat breast and stomach cancers that ha
protein.

Conjugated monoclonal antibodies

Monoclonal antibodies attached to a radioactive substance, drug, or toxin, are called ***conjugated mAbs.***

The mAb is used as a homing device to take one of these substances directly to the cancer cells.

This lessens the damage to normal cells in other parts of the body.

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Non- Specific Immunotherapies and Adjuvants

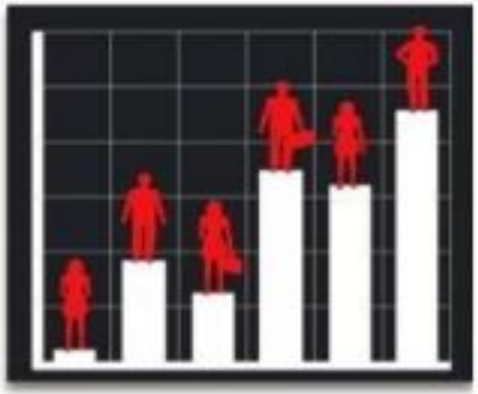
Non- specific immunotherapies don't target cancer cells specifically.

Cytokines:

- Cytokines are chemicals made by some immune system cells. They are crucial in controlling the growth and activity of other immune system cells and blood cells in the body.
- Cytokines are injected, either under the skin, into a muscle, or into a vein.

Interleukins

- Interleukins are a group of cytokines that act as chemical signals between white blood cells.
- Interleukin-2 (IL-2) helps immune system cells grow and divide more quickly.
- When a man-made version of IL-2 was approved by the US Food and Drug Administration in 1992 to treat advanced kidney cancer, it became the **first true immunotherapy** approved to be used alone in treating cancer.



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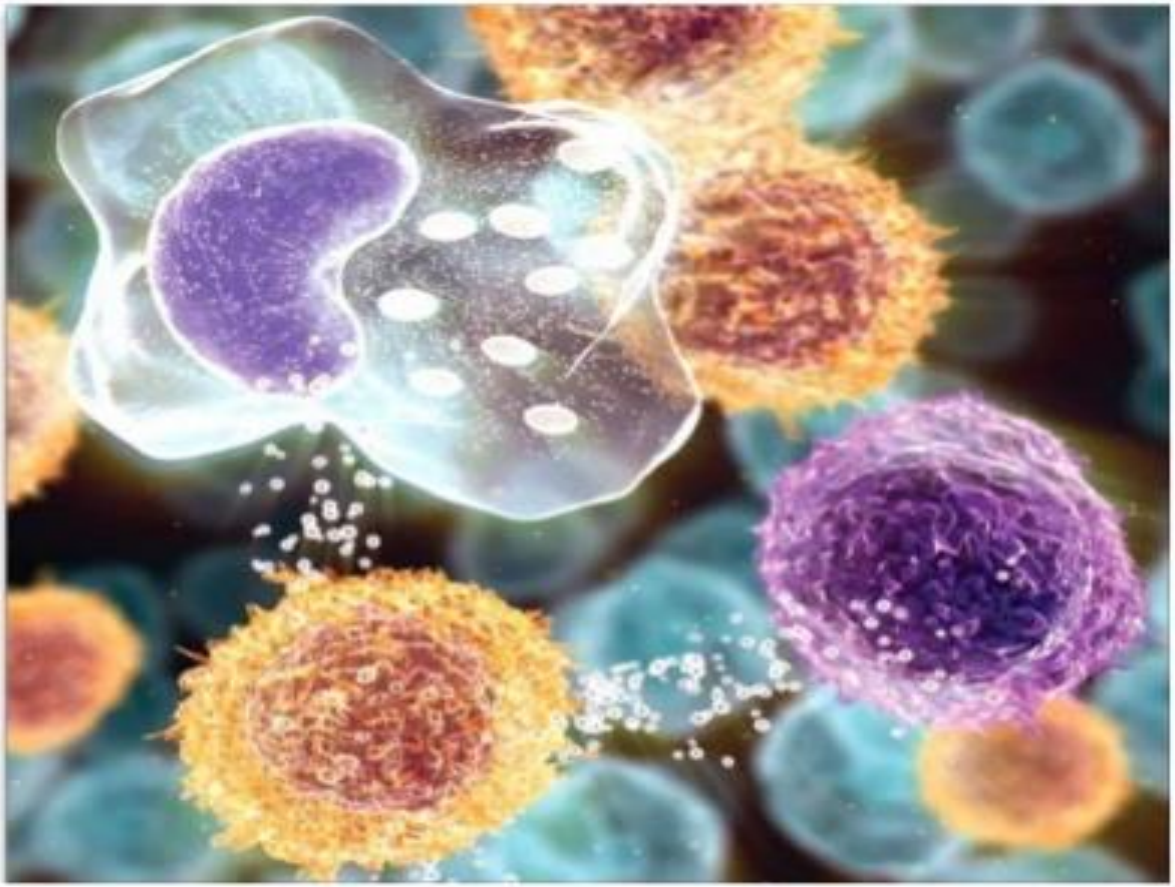
Interferons

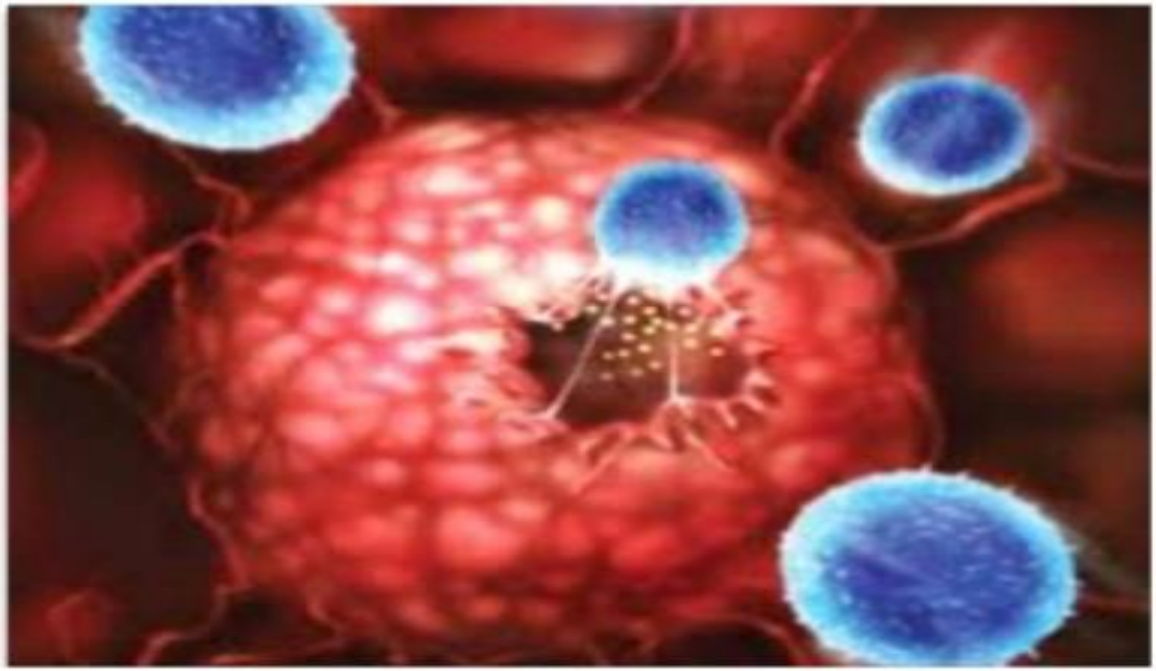
- These cytokines, first discovered in the late 1950s, help the body resist virus infections and cancers. The types of interferon (IFN) are named after the first 3 letters of the Greek alphabet:
- IFN-alfa
- IFN-beta
- IFN-gamma.



Cancer vaccines

Cancer vaccines

- The goal is to help treat cancer or to help prevent it from coming back after other treatments.



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Cancer vaccines

Most attempts so far have tried to generate antibodies against surface antigens expressed on many tumors

Generally unsuccessful because :

- **lack of specificity**
- **expression of antigen on normal cells**
- **and inability of antibodies to provide protection**

Viruses vaccines

There are vaccines that can prevent healthy people from getting certain cancers caused by viruses. Like vaccines for the chicken pox or the flu, these vaccines protect the body from these viruses. This type of vaccine will only work if a person gets the vaccine before they are.

There are 2 types of vaccines that prevent cancer approved by the U.S. Food and Drug Administration (FDA):

- **HPV vaccine:The vaccine protects against the human papillomavirus(HPV). If this virus stays in the body for a long time, it can cause some types of cancer. The FDA has approved HPV vaccines to prevent:**

Cervical, vaginal, and vulvar cancers, Anal cancer

Hepatitis type B Virus (HBV): **This virus can cause liver cancer infected with the virus. HBV vaccine can prevent this cancer**

- **They can:**
- **Keep the cancer from coming back**
- **Destroy any cancer cells still in the body after treatments end**
- **Stop a tumor from growing or spreading**

Immune checkpoint inhibitor

A type of drug that blocks proteins called immune checkpoints that are made by some types of immune system cells, such as T cells. These checkpoints help keep immune responses from respond more strongly and sometimes can keep T cells from killing cancer cells. When these checkpoints are blocked, T cells can kill cancer cells better.

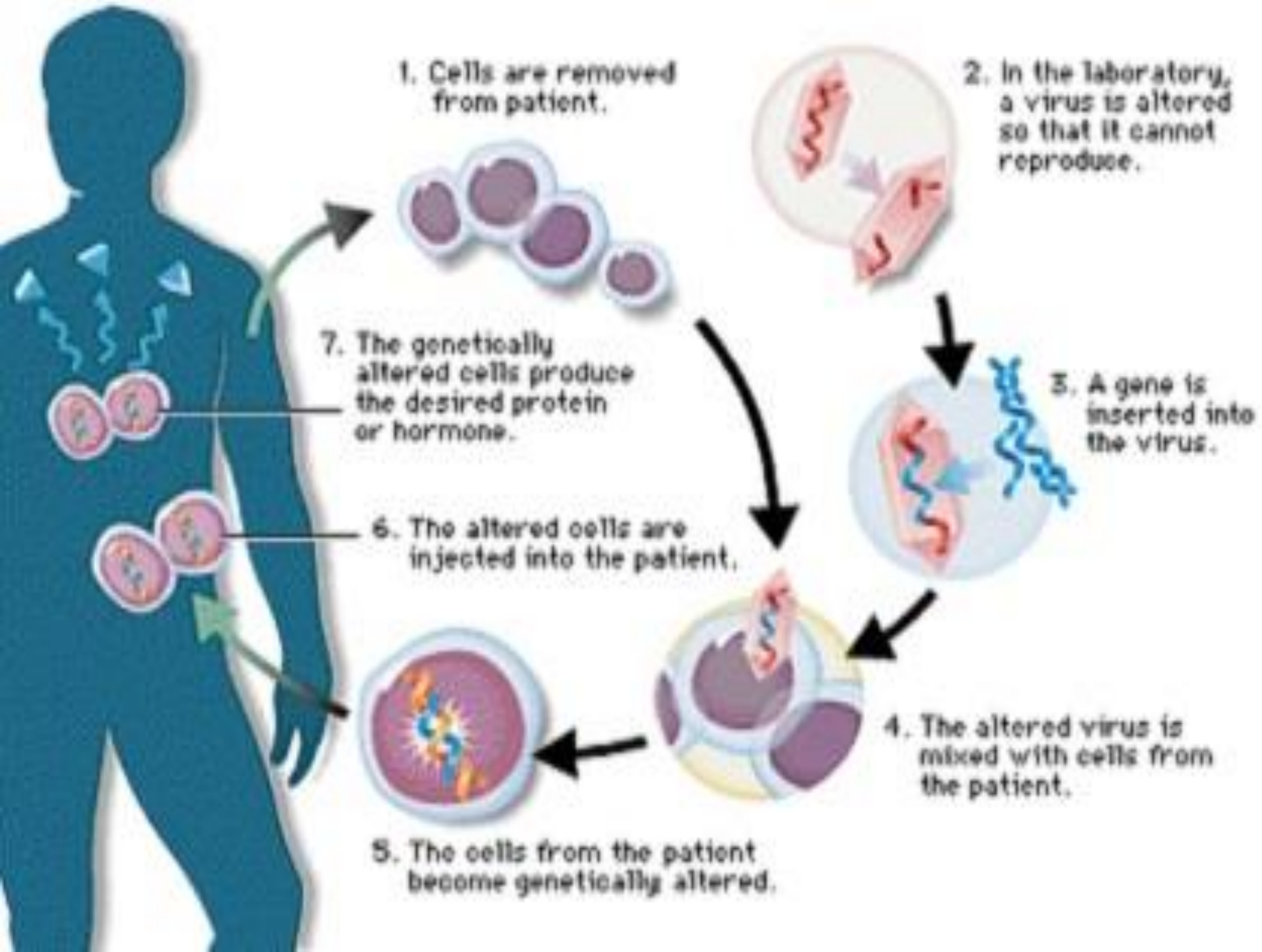
Gene therapy

Gene therapy refers to cancer treatment at the molecular and physiological level, it based on alter the defective (mutated) gene or missing (deleted)gene with healthy copy by vector. More than 60% of all on-going clinical gene therapy trials worldwide for cancer treatment.

- **delivery of nucleic acids into a patient's cells as a drug to treat disease.**
- **by hold the code for proteins that enable cells to grow, function, and divide. When a gene is defective, it can give rise to proteins that are unable to do their job.**

- **Some researcher used adenoviral vector-based gene therapy as oncolytic vector for treatment prostate cancer.**
- **The explained gene therapy strategies which can generate good results in early stage clinical trials and potential in both, Loco-regional setting and metastasis of cancer.**
- **Another gene therapy strategy has been used for cancer treatment, such as anti-angiogenic gene therapy, immune modulation and stimulation by gene therapy, genetic manipulation of apoptotic and tumor invasion pathways .**

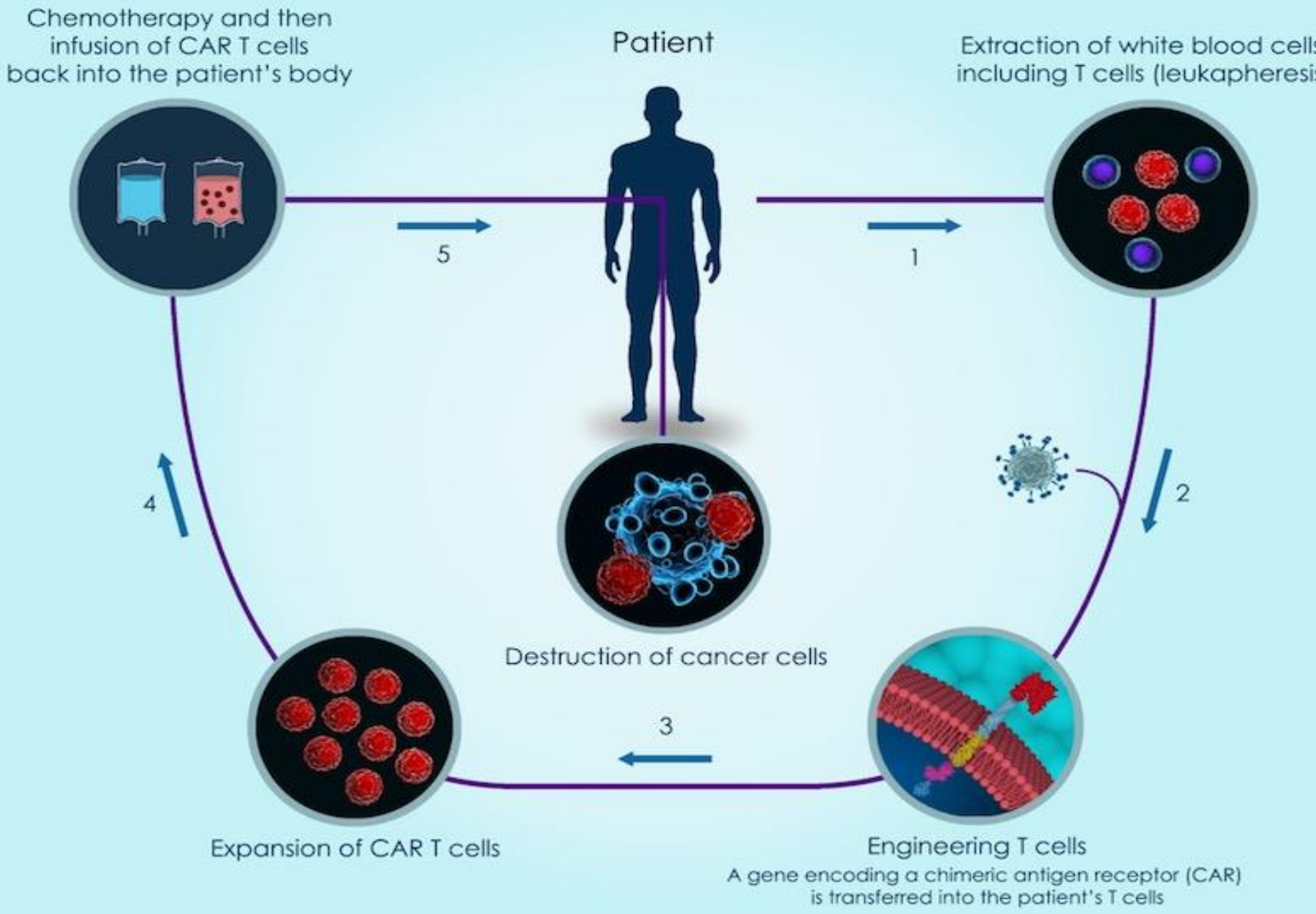
- Another form of gene therapy involving gene therapy is cancer vaccines.
- This approach involves collecting tumor cells from a patient and engineering them with genes that cause them to be more clear to the immune system.
- The altered cells are then re-infused into the patient along with an immune-stimulating compound.
- The patient's immune system release a vigorous attack not only on the newly-infused cancer cells but also on similar cells throughout the body.

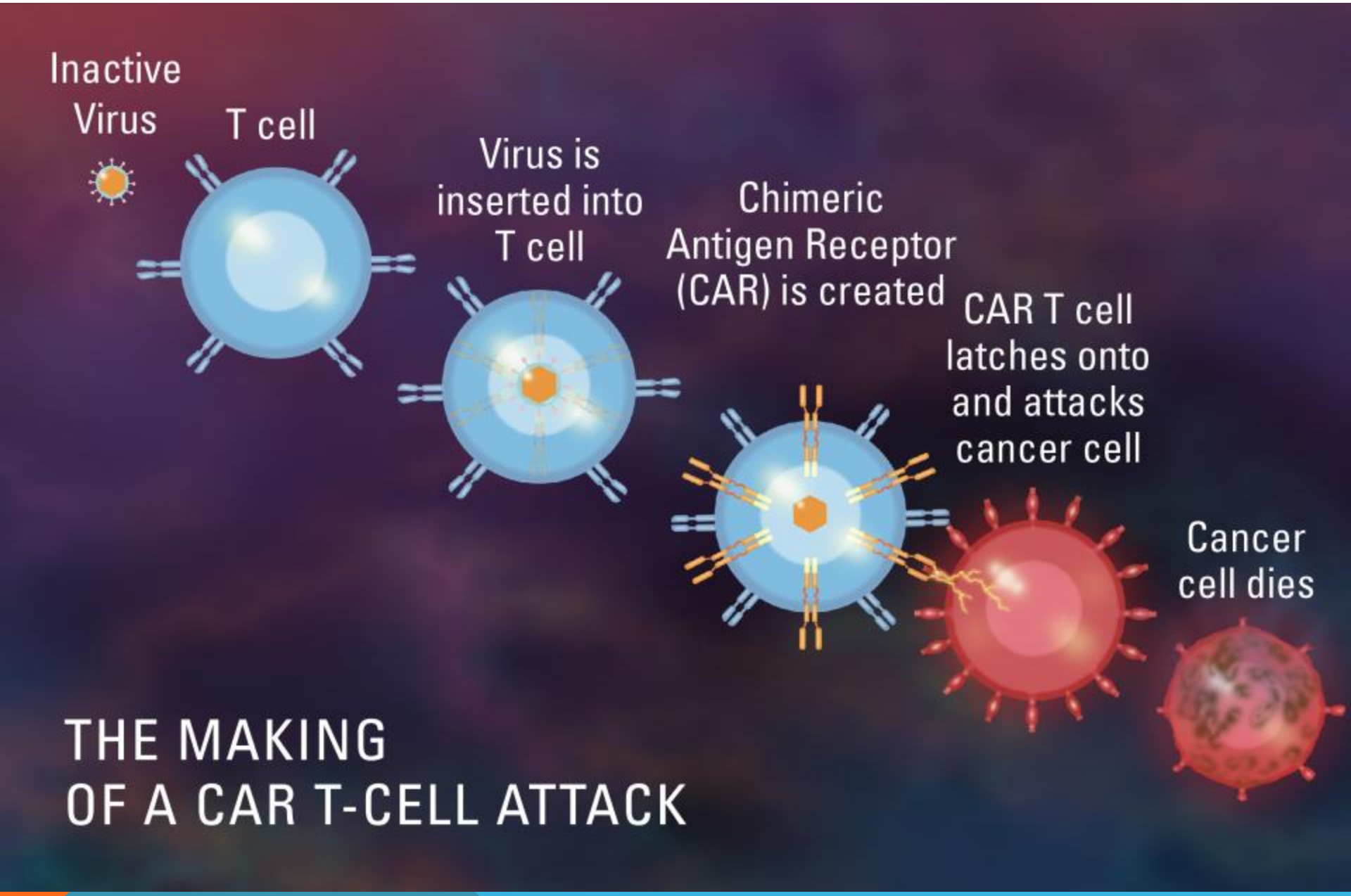

1. Cells are removed from patient.
2. In the laboratory, a virus is altered so that it cannot reproduce.
3. A gene is inserted into the virus.
4. The altered virus is mixed with cells from the patient.
5. The cells from the patient become genetically altered.
6. The altered cells are injected into the patient.
7. The genetically altered cells produce the desired protein or hormone.

- **T-cell transfer therapy,** which is a treatment that boosts the natural ability of T cells to fight cancer. In this treatment, immune cells are taken from person tumor, selected or changed in the lab to better attack the cancer cells, grown in large batches, and put back into person body through a needle in a vein..

In 2018, we saw the first approval of a cell therapy for cancer. The technology, called CAR-T cell therapy,(Chimeric antigen receptor)consists of taking immune T-cells from the patient and genetically engineering them to target a specific cancer antigen.

The technology is so far only available for treating certain rare forms of blood cancer. Several players are developing a new generation of CAR-T treatments that can target a wider range of cancers.


Chemotherapy and then infusion of CAR T cells back into the patient's body
Patient
Extraction of white blood cells, including T cells (leukapheresis)
5
1
4
2
Destruction of cancer cells
3
Expansion of CAR T cells
Engineering T cells
A gene encoding a chimeric antigen receptor (CAR) is transferred into the patient's T cells


Inactive Virus
T cell
Virus is inserted into T cell
Chimeric Antigen Receptor (CAR) is created
CAR T cell latches onto and attacks cancer cell
Cancer cell dies
THE MAKING OF A CAR T-CELL ATTACK

Hormone therapy

Hormonal therapy means blocking the hormone receptors, it only uses for cancer that are sensitive to hormone or hormone dependent like breast and prostate cancer. For example, tamoxifen and aromatase inhibitors which used for treatment breast cancer in post - menopausal in women.

The study by Shah and Wong reported that hormone replacement therapy (HRT) not been used for women with history of breast cancer because the estrogen is a growth factor for most breast cancer.

Viral therapy

Viral agent have been developed to be harmless to normal tissue and selective to kill malignant cells, Some viruses tend to infect and kill tumor cells. Known as oncolytic viruses, this group includes viruses found in nature as well as viruses modified in the laboratory to reproduce efficiently in cancer cells without harming healthy cells.

the field of oncolytic virotherapy began as a science more than a century ago when it was noted that cancer reduction sometimes occurred spontaneously in patients following certain viral infection.

The mechanisms by which the virus can kill tumor cells:-

- **Once viruses have entered the tumor cell, the rapid growth and division of tumor cells as well as decreased ability of tumor cells to fight off viruses make them advantageous for viral replication compared to non-tumorous cells, hence, the virus makes copies of itself until the cell bursts.**

- Some oncolytic viruses may work—at least in part—by triggering an immune response in the body against the cancer.
- overcoming **immunosuppression , this is done through the disruption of the microenvironment** of the tumor cells that prevents recognition by host immune cells. The dying cancer cell by viruses can releases materials, such as tumor antigens, that allow the cancer to be recognized, or "seen," by the immune system.

- Most oncolytic virus therapies have been tested in patients with melanoma or brain tumors, and most treatments have been given as injections into tumors.

- Two new studies highlight efforts to expand the number of cancer types treated with oncolytic virus therapies as well as the methods of delivery:
  - One of the studies found that **an oncolytic virus delivered intravenously could cross the blood–brain barrier and enter brain tumors**, killing tumor cells. The treatment uses a type of virus known as a reovirus, which causes mild symptoms of a cold or stomach bug in children.

- **In the second study, researchers tested the Maraba virus, which was originally isolated from a species of sand fly in Brazil, as a way to sensitize tumors to immunotherapy in a mouse model of breast cancer.**
- **In both studies, the researchers found that giving oncolytic virus therapy prior to surgery may alter the body's immune response and enhance the effects of subsequent treatment with a checkpoint inhibitor.**

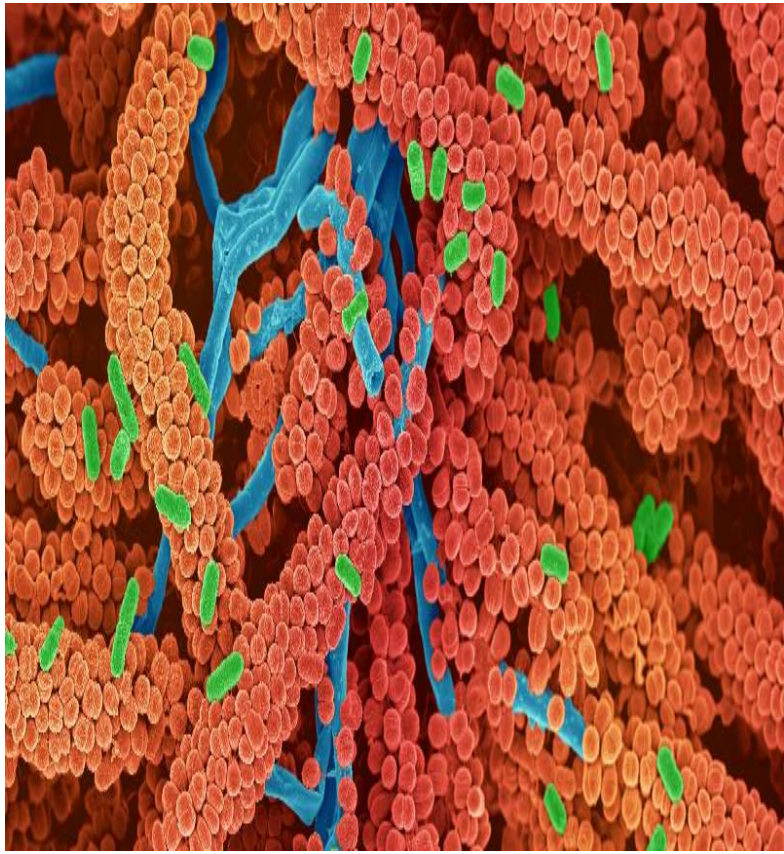
Newcastle disease virus (NDV) is a virus that causes a deadly infection in many kinds of birds. In humans, NDV causes mild flu-like symptoms or conjunctivitis (an infection of the eye that is also called pink eye) and/or laryngitis (an irritation and swelling of the voice box and the area around it).

- Newcastle disease virus (NDV) is a virus that is of interest because it replicates more quickly in human cancer cells than in most normal human cells and because it can kill these host cells NDV can be used to directly kill cancer cells, or it can be given as a cancer vaccine.
- oncolytic effects of NDV was potential use in the treatment of various tumours (colon cancer, lung cancer and melanoma). Furthermore, clinical trials have suggested that several NDV strains have the potential for cancer virotherapy with few side-effects compared with traditional treatment.

In Iraqi, first trail on Newcastle virus as viral therapy against cancer cells was performed by AL-Shammari (2003), then followed by other studies. One of these studies, al-shammari and his team suggested that NDV was synergistic with 5-Fluorouracil (5-FU) at low doses when used as a combination therapy on different cancer cells, and there were very mild effects on non-cancer cells, as well as, the combination of a virulent, non-pathogenic NDV–LaSota strain with a standard chemotherapeutic agent, 5-FU, has a synergistic effect on different tumor cells in vitro, suggesting this combination could be an important new therapy for treating cancer.

Bacteria in cancer therapy

- Bacteria are carcinogens and tumor promoters. Bacteria produce toxins that disrupt the cellular signal and regulation of cell growth. Also, they are potential tumor promoters through inducing inflammation.



- **Some bacteria strains notable for causing cancer like strains include *Helicobacter pylori*, which is associated with gastric cancer, *Salmonella typhi* which is associated with hepatobiliary carcinoma *Campylobacter Jejuni* which is associated with small intestinal lymphomas**

- **The enzymes produceed by bacteria are potential carcinogens, such as peptidyl arginine deaminase (PAD) enzymes that are found in oral bacteria and associated with pancreatic cancer.**

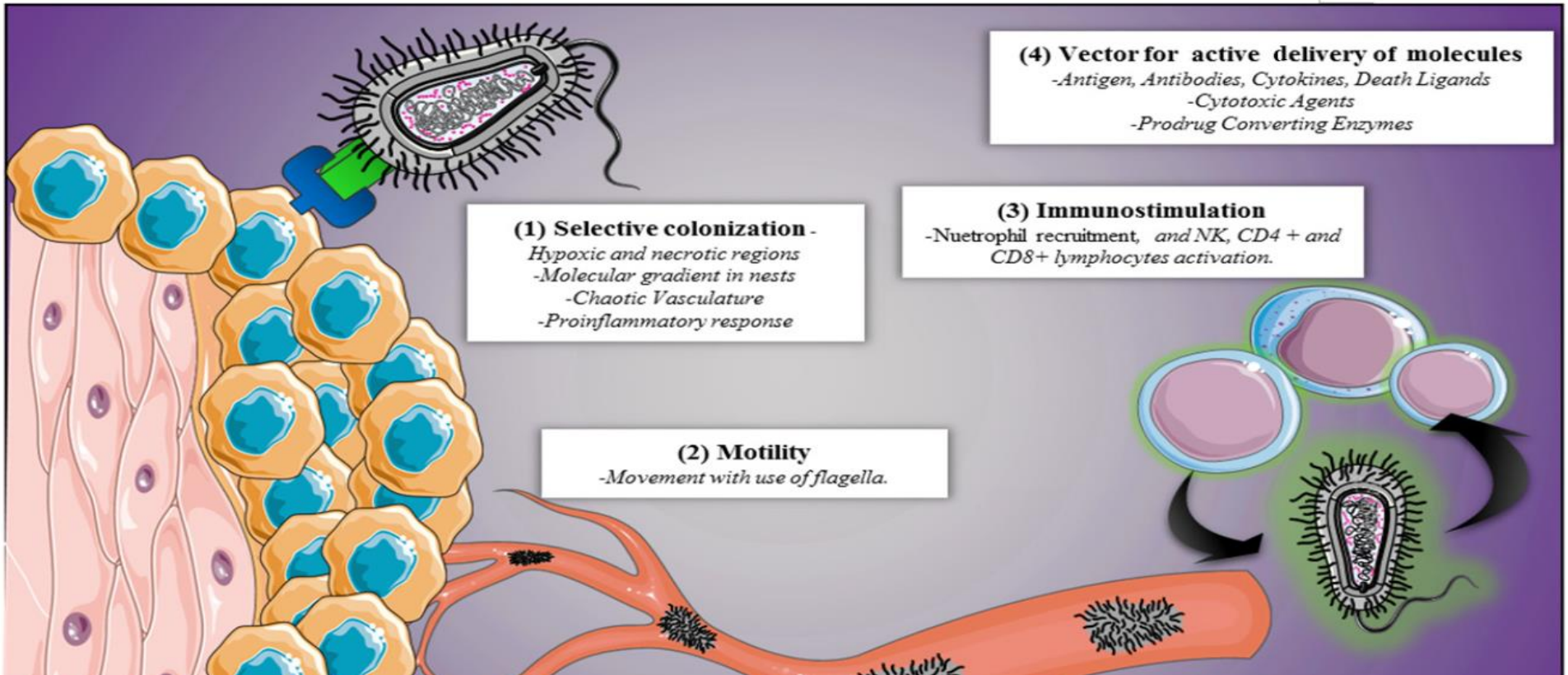
- **In contrast to other bacteria that have shown great potential for cancer therapy. Bacteria of many species demonstrate the surprising ability to invade and colonize solid tumors, which often results in neoplasm growth reduction, and in some instances, complete tumor clearance.**

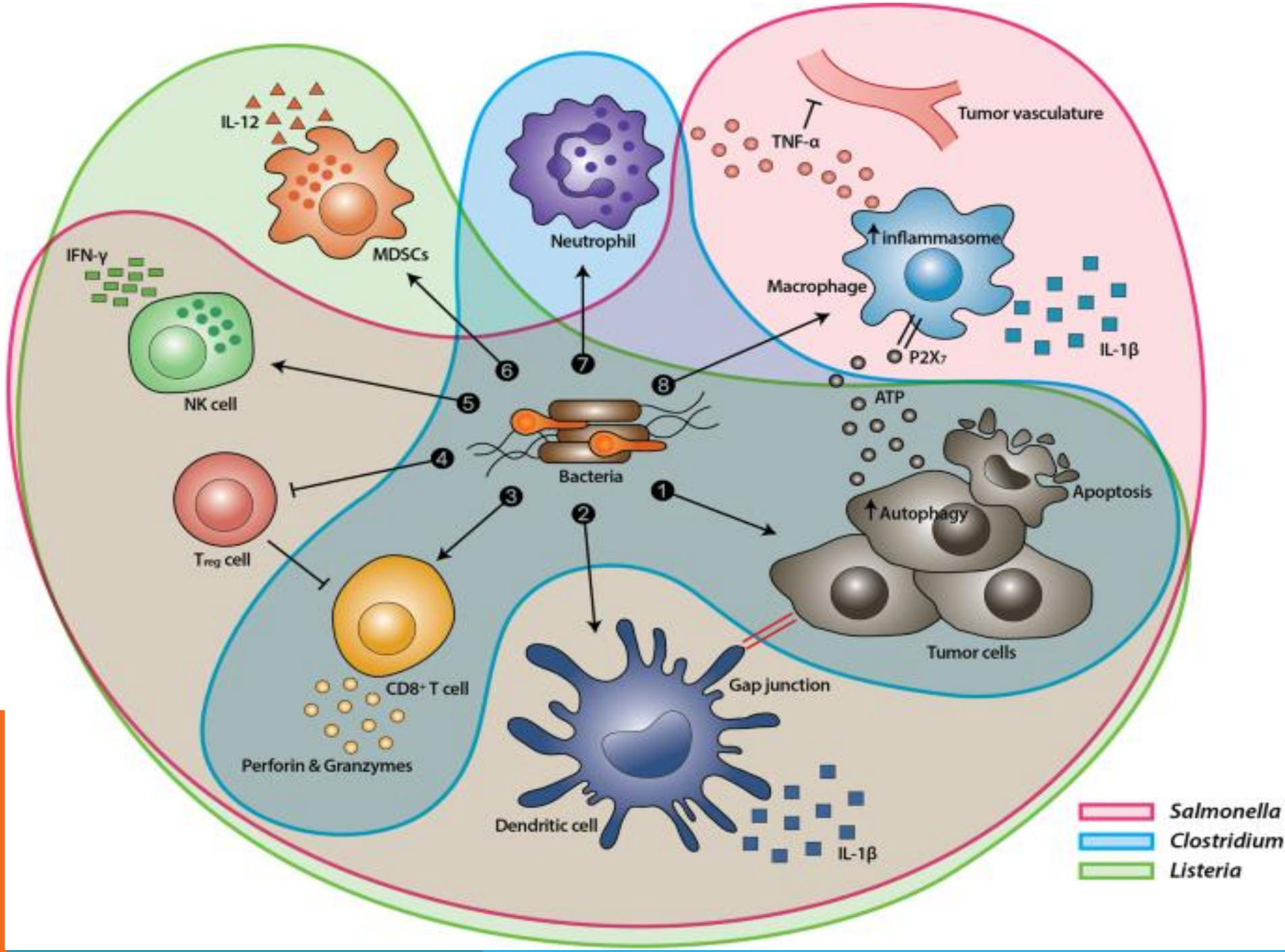
- **Different strains of *Clostridia*, *Bifidobacteria* and *Salmonella* are capable of colonizing the hypoxic area of the tumor and destroy the tumor cells. Therefore, they are potential strains for selective tumor targeting therapy, hence, the bacteria and their spores are used in the target specific therapies, also in delivering the prodrugs and various protein to the tumors.**

- **Bacteria create anti-tumor effects through the depletion of nutrients required for cancer cell metabolism ..**
- **The tumor tissues that are deoxygenated nurture the accumulation of obligate anaerobic bacteria – which only survive in the anoxic region .**

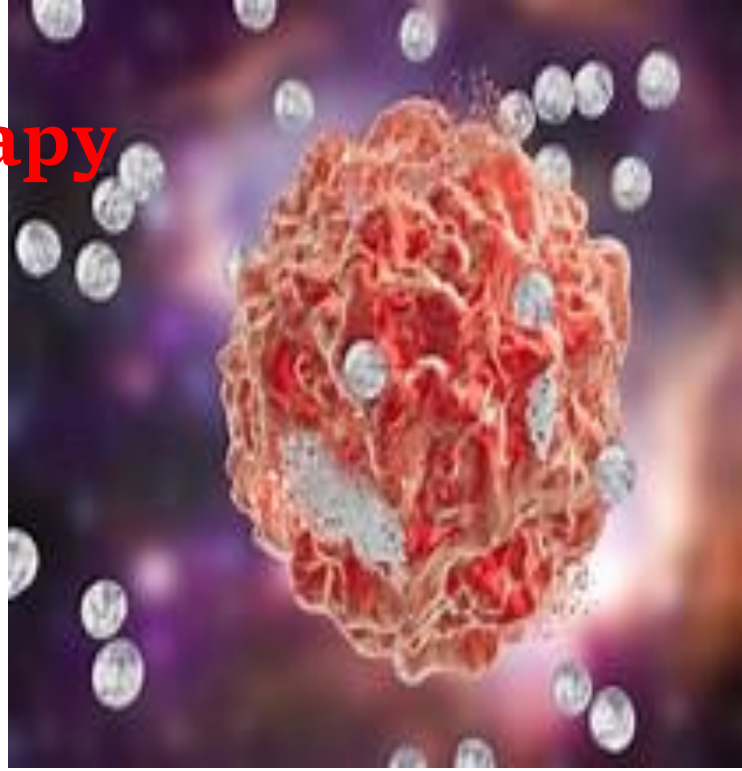
- **Observation has shown that the systemic administration of *Salmonella* bacteria flushed into the solid tumor through severe haemorrhaging area, the area which leads to necrotic regions in which bacteria proliferate, colonized the tumor and decreased the proliferation of the tumor.**
- **The necrotic regions are formed because of the reduction of oxygen and nutrient supply, which leads to the breaking down of blood vessels in the hemorrhagic area.**

This causes the tumor cells in the center of the tumor to die from starvation and suffocation. The tumor microenvironment may be lead to bacterial survival and growth, as it may provide protection from the host immune system and nutrients




IL-12
MDSCs
Neutrophil
Tumor vasculature
TNF-α
inflammasome
Macrophage
P2X7
IL-1β
IFN-γ
NK cell
ATP
Bacteria
Apoptosis
Autophagy
Treg cell
CD8+ T cell
Tumor cells
Gap junction
Perforin & Granzymes
Dendritic cell
IL-1β
Salmonella
Clostridium
Listeria

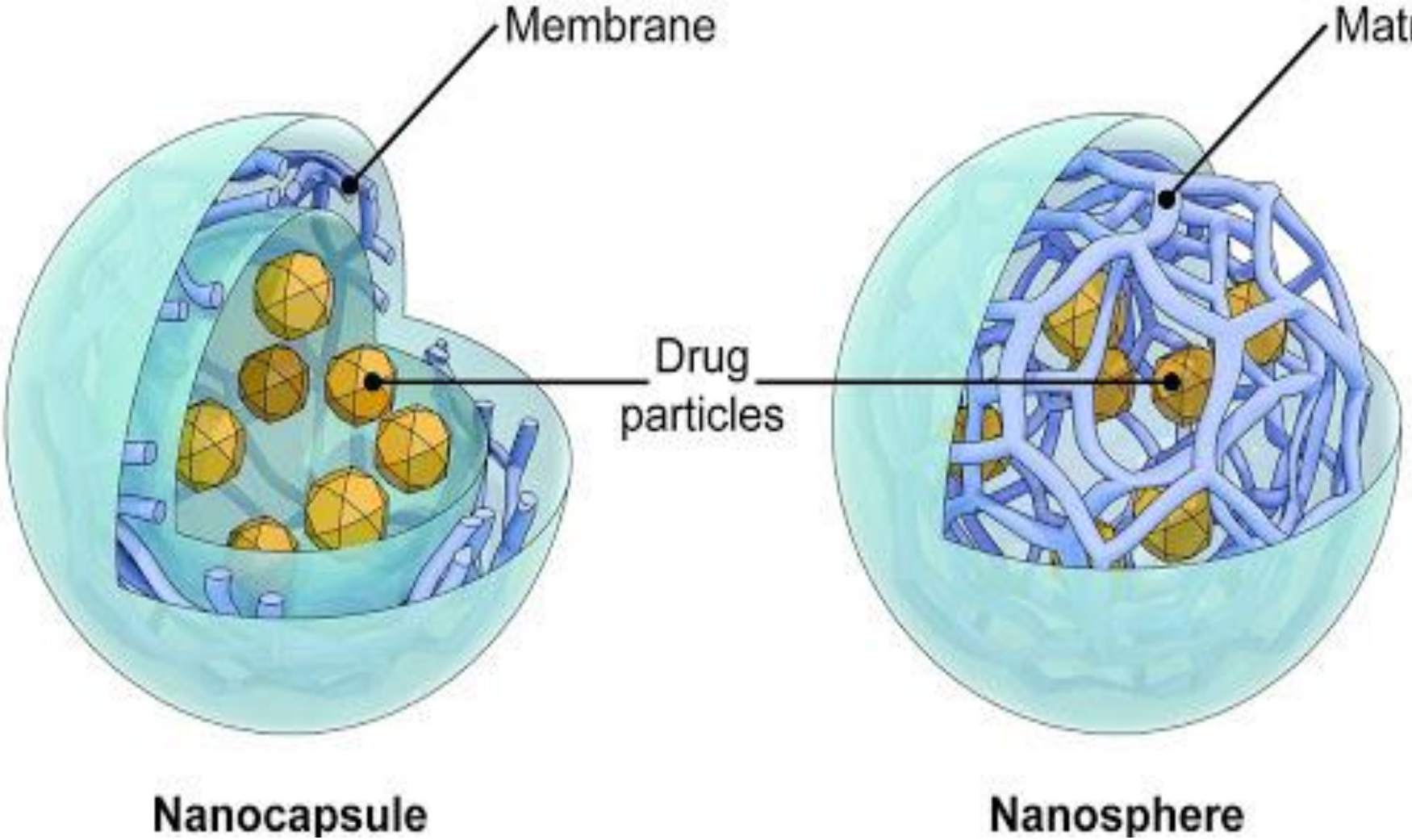
Nanoparticles in cancer therapy

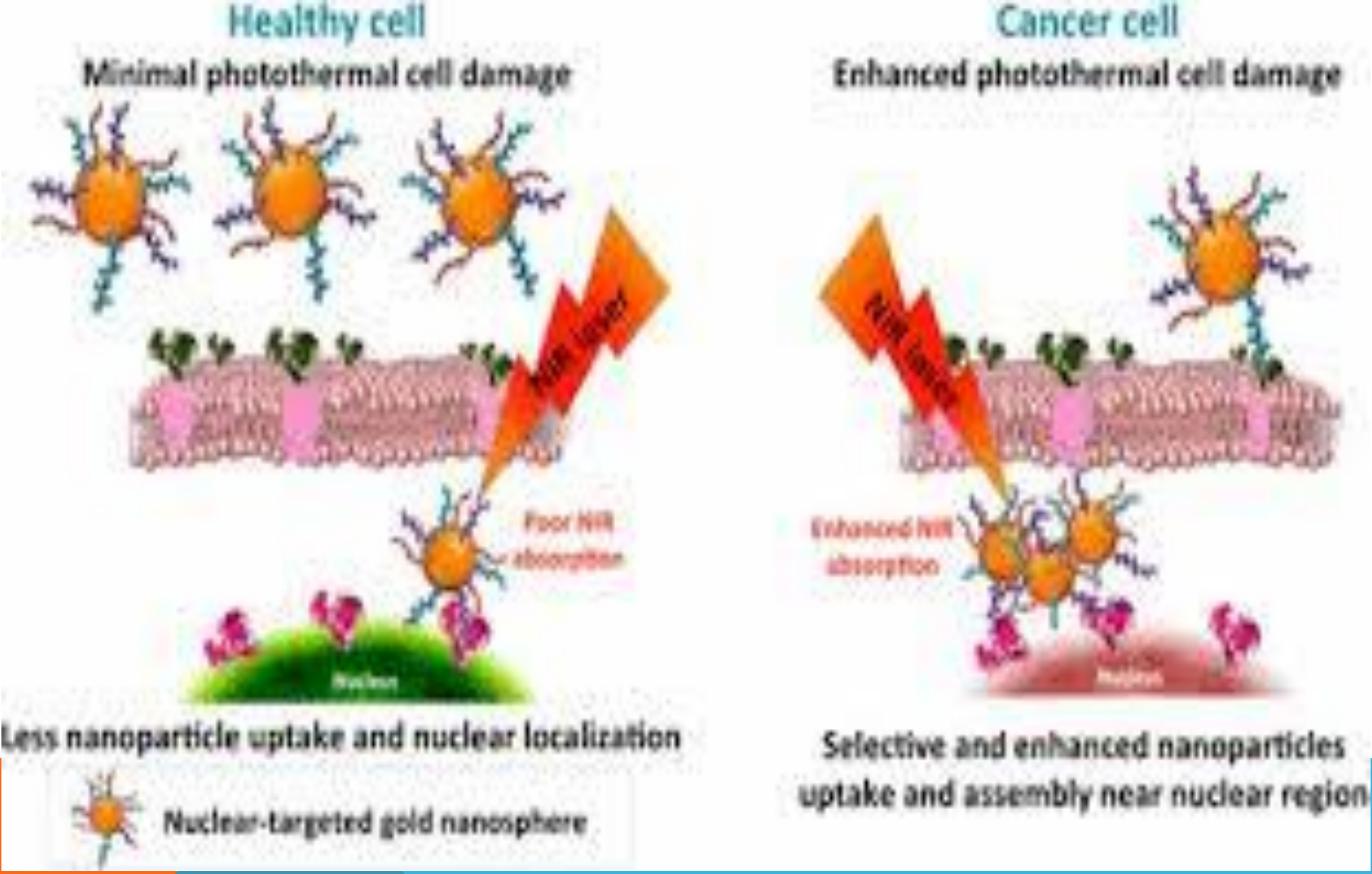


Due to the small size of nano particles, it can be of great use in oncology, such as

- **biomedical engineering for controlling invasive**
- **metastasis behavior of melanoma cells , and enhanced permeability and retention effect caused by leaky tumour vasculatures for better drug accumulation at the tumour sites, these benefits are promising candidate of NPs to replace current chemotherapy.**

- in addition. NPs can enhance the intracellular concentration of drug in cancer cell, while avoiding toxicity in normal cells.
- As a clinical trails, different type of NPs were used for cancer therapy such as Carbon nanotubules encapsulated anticancer drug molecules inside the nanotubes, then release it near cancer cell membrane and protect drug from being degraded in the body.
- also can reduce tumour growth through remarkable heating efficiency for iron oxide nanoparticles via heat-induced tumoral cell apoptosis and massive denaturation,cancer cell die at 42℃ while the normal cells die


Membrane
Matrix
Drug particles
Nanocapsule
Nanosphere


Healthy cell
Minimal photothermal cell damage
Poor NIR absorption
Less nanoparticle uptake and nuclear localization
Cancer cell
Enhanced photothermal cell damage
Enhanced NIR absorption
Selective and enhanced nanoparticles uptake and assembly near nuclear region
Nuclear-targeted gold nanosphere

Nanoparticle coating

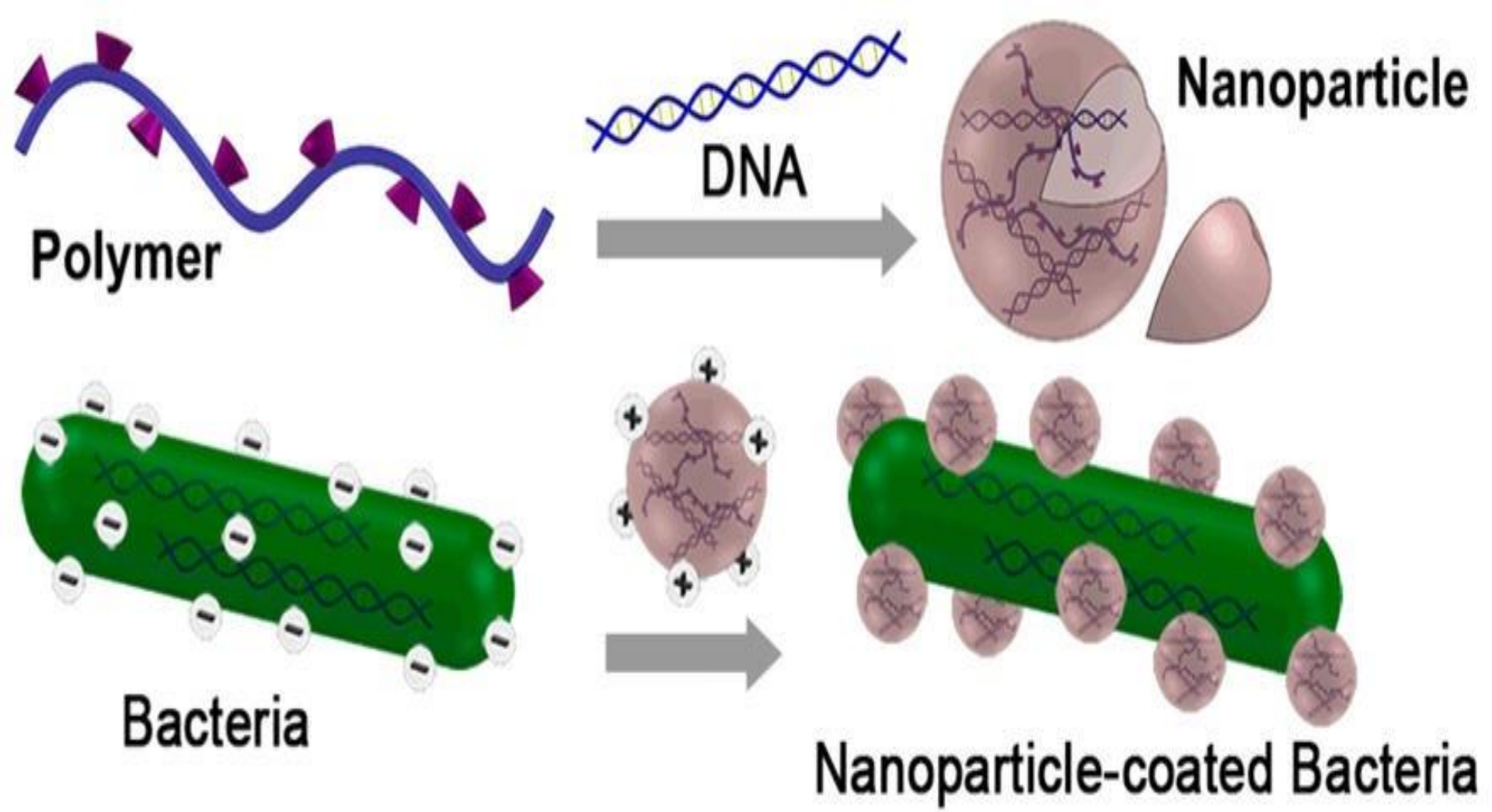
The researchers show for the first time that nanoparticle-coated bacteria have a much better chance than uncoated bacteria of overcoming these two hurdles and evoking stronger immune response. The nanoparticles contain positively charged polymers, which self-assemble onto the negatively charged cell walls of the *Salmonella*e due to electrostatic interactions. The coated bacteria can better tolerate the acidic stomach and intestines, Due to these advantages, the nanoparticle-coated bacteria are more likely to reach the lower gut to initiate the desired infection.

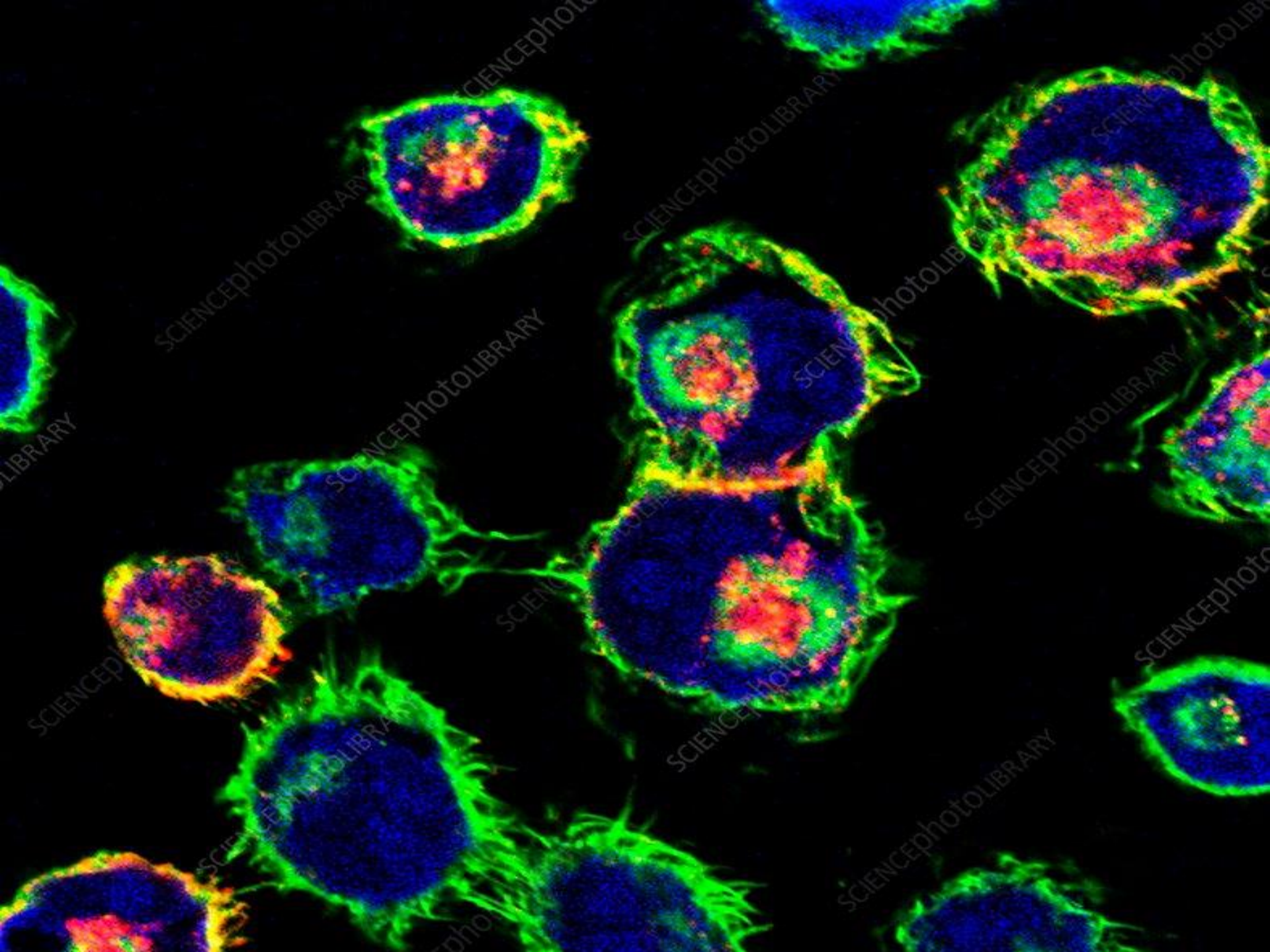
- **One oral DNA vaccine that researchers have been working on is called NP/SAL, which suppresses tumor angiogenesis (blood vessel formation). Many tumors secrete angiogenic factors such as vascular endothelial growth factor (VEGF) to promote blood vessel formation, which can eventually lead to tumor metastasis. The NP/SAL vaccine stimulates the immune system to produce T cells and cytokines (chemical messengers), which in turn interfere with the VEGF pathway, reducing blood vessel formation and ultimately inhibiting tumor growth.**

In this strategy, the challenge lies in getting the vaccine to the right place, which is the lower gut, from where it is spread into the blood. One way to do this is by inserting the vaccine into the DNA of live bacteria such as *Salmonellae* that reduced their toxicity to the safe levels. When the vaccine (carried by the bacteria) is reached to a patient, the bacteria invade the body as in a typical bacterial infection, colonizing, reproducing, and spreading their DNA and the vaccine with it.

The researchers found that 60% of mice vaccinated with NP/SAL carried by nanoparticle-coated bacteria survived the full 35-day study duration without tumor growth. The mice also lost almost no body weight, reflecting the low toxicity of the vaccine.

The researchers expect that this strategy of using nanoparticle-coated bacteria as DNA vaccine vectors can be applied to a wide variety of vaccines, and potentially used to treat a wide spectrum of cancers.


Polymer
DNA
Nanoparticle
Bacteria
Nanoparticle-coated Bacteria



Curing cancer is certainly one of the big challenges of the 21st century.. This has revealed the huge variability that can be found between not only different types of cancer, but also between patients with the same type of cancer.

Finally, there are four new technologies new approaches to tame the immune system in the fight against cancer are getting us closer to a future where cancer becomes a curable disease.

Personalized vaccines

cell therapy (cell-mediated therapy)

gene editing

microbiome treatments

are four technologies that will change the way cancer is treated.


THANK
YOU