GENETICALLY ENHANCED CANCER THERAPIES

Hello!

I am Tapani Ronni

Science talks to translators and interpreters since 2012.

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About the speaker

- PhD in Genetics, University of Helsinki, Finland
- Postdoctoral fellow, University of California, Los Angeles
- Scientific interests: gene therapy, microbiology, immunology
- A full time medical translator since 2007 (English-Finnish)

Contents of this talk

- What is Cancer?
- Three Old Approaches to Cancer Therapy
  - Surgery
  - Chemotherapy
  - Radiation
- New Approach: biological drugs
  - Monoclonal antibodies
  - Tumor-infiltrating lymphocytes (TIL)
  - Checkpoint inhibitors
  - Genetically enhanced T cells (CAR-T)
- How do T cells work?
- How are CAR-T Cells made?
- CAR-T cells in lab and clinic
- Future prospects

What is Cancer?

- Not one disease but many
- A genetic disease – inherited or acquired
- Normal cells behave themselves and don't divide unless it is necessary
- Cancer cells ignore the signals from within and outside

What is Cancer? (cont'd)

- Cells regulate their lifespan and proliferation (division) for the benefit of the whole organism
  - Proto-oncogenes regulate cell growth; e.g. RAS
- A faulty proto-oncogene is called an oncogene
  - Mutation
  - Multiplication
  - Recombination
- Anti-oncogenes (tumor suppressor genes) inhibit cell growth; e.g. p53
- Cancer cell is like a speeding car that has a stuck gas pedal (faulty oncogenes) and worn out brakes (faulty anti-oncogenes)

Three Old Approaches to Cancer Therapy

- **Surgery** for solid tumors
  - Tumor excised along with some healthy tissue
  - But tumor may have already spread (metastasis)
  - Early detection and removal is important

Three Old Approaches to Cancer Therapy (cont'd)

- **Radiation therapy**
  - Internal therapy (brachytherapy)
  - External therapy (beam therapy)
  - Fatal DNA damage -> cell death
  - Important to pinpoint the dose to avoid side effects

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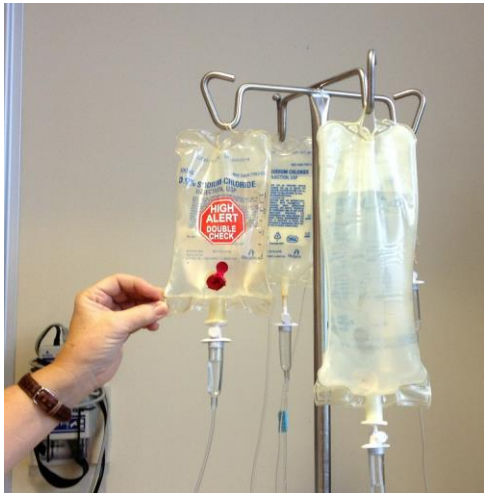
Three Old Approaches to Cancer Therapy (cont'd)

- **Chemotherapy**
  - Chemotherapy drugs inhibit cancer cell division
  - Cure or remission may be possible
  - Serious side effects also possible, due to systemic administration
  - Multiple drugs can be given as a combination



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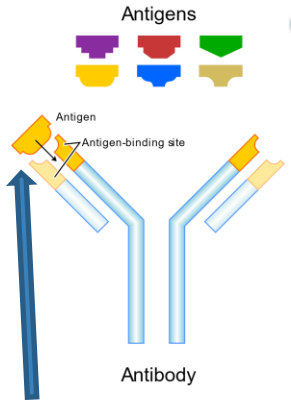
New therapeutic approaches are urgently needed

The three E theory

- **How does cancer escape the immune system surveillance?**
- **Elimination: it fails to escape, is destroyed**
- **Equilibrium: it mutates, reduced immunogenicity, staying dormant for years**
- **Escape: some new variant emerges that is able to avoid immune surveillance and grow exponentially -> cancer clinically detectable**

New Approach: biological drugs

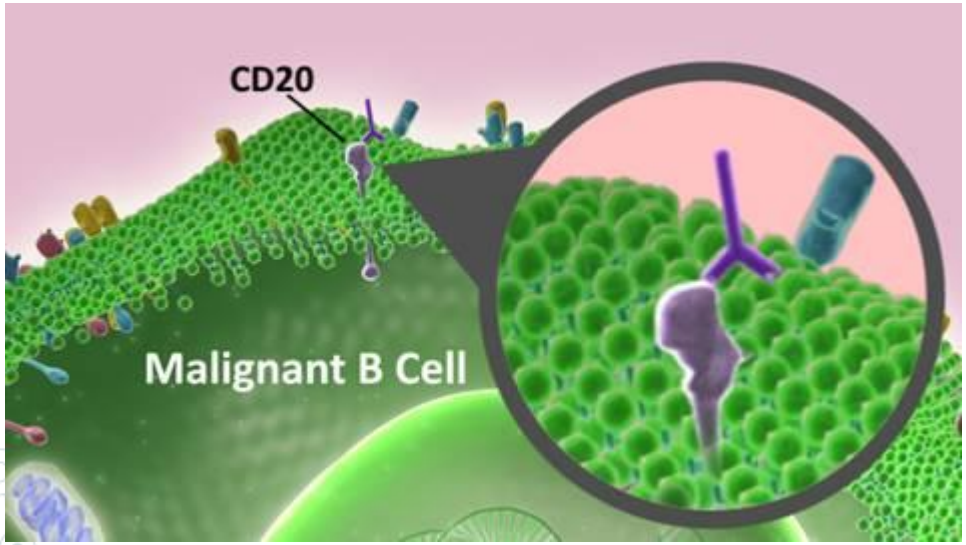
- **Monoclonal antibodies (mAbs)**



- **Derived from B cell hybridomas**
- **Each mAb recognizes a specific antigen on a cancer cell**
- **Can be made to carry a poison (targeted chemotherapy) or a radioactive molecule (radioimmunotherapy)**

New Approach: biological drugs (cont'd)

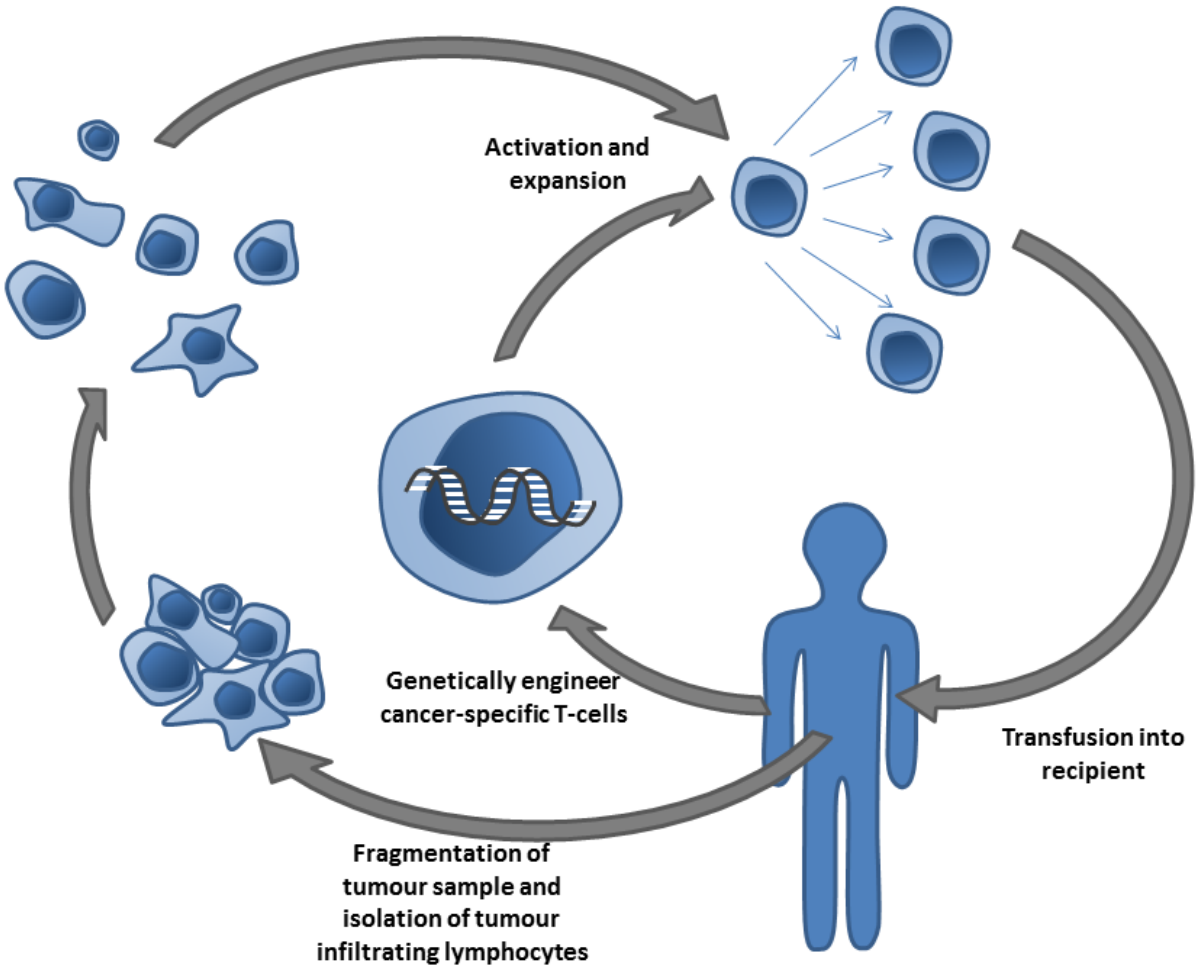
- Monoclonal antibodies are widely used in clinic
- Example: Rituximab targets CD20 on cancerous and healthy B cells
- Both are destroyed; healthy B cells are regenerated later from stem cells



New Approach: Tumor Infiltrating Lymphocytes

- A preparation of patient's own (autologous) lymphocytes that are manipulated and grown in vitro and returned to the patient
- Also cancer-specific T cells can be genetically engineered
- Lysis of tumor cells and tumor regression
- In clinical use against melanoma

New Approach: Tumor Infiltrating Lymphocytes (cont'd)

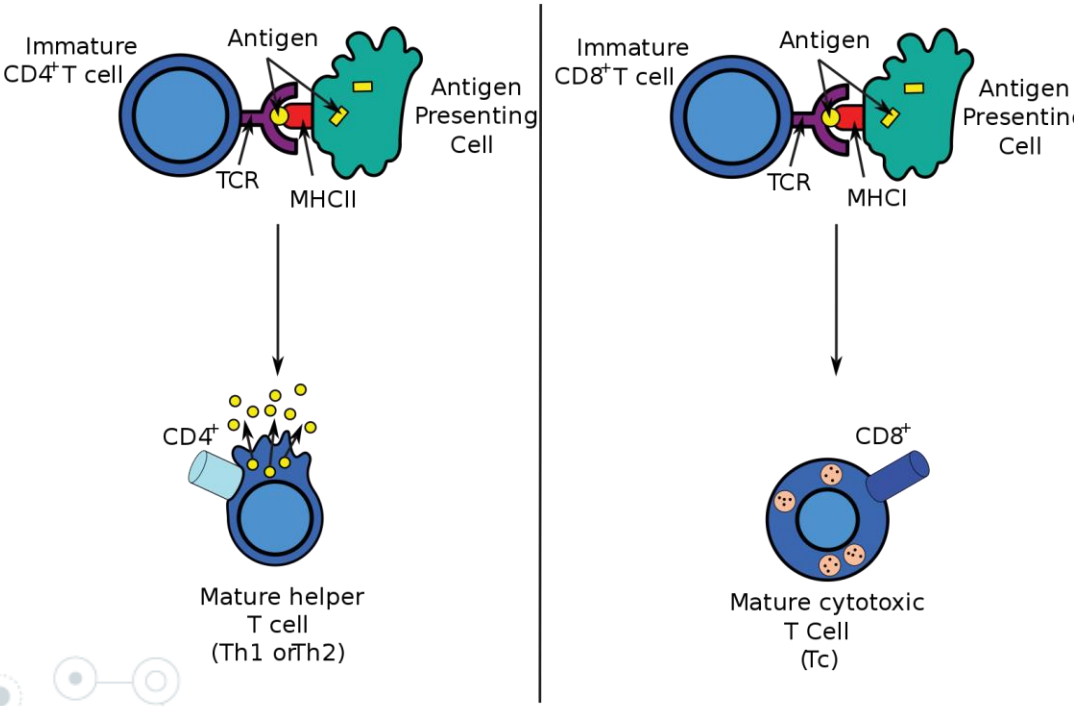


New Approach: CAR-T cells

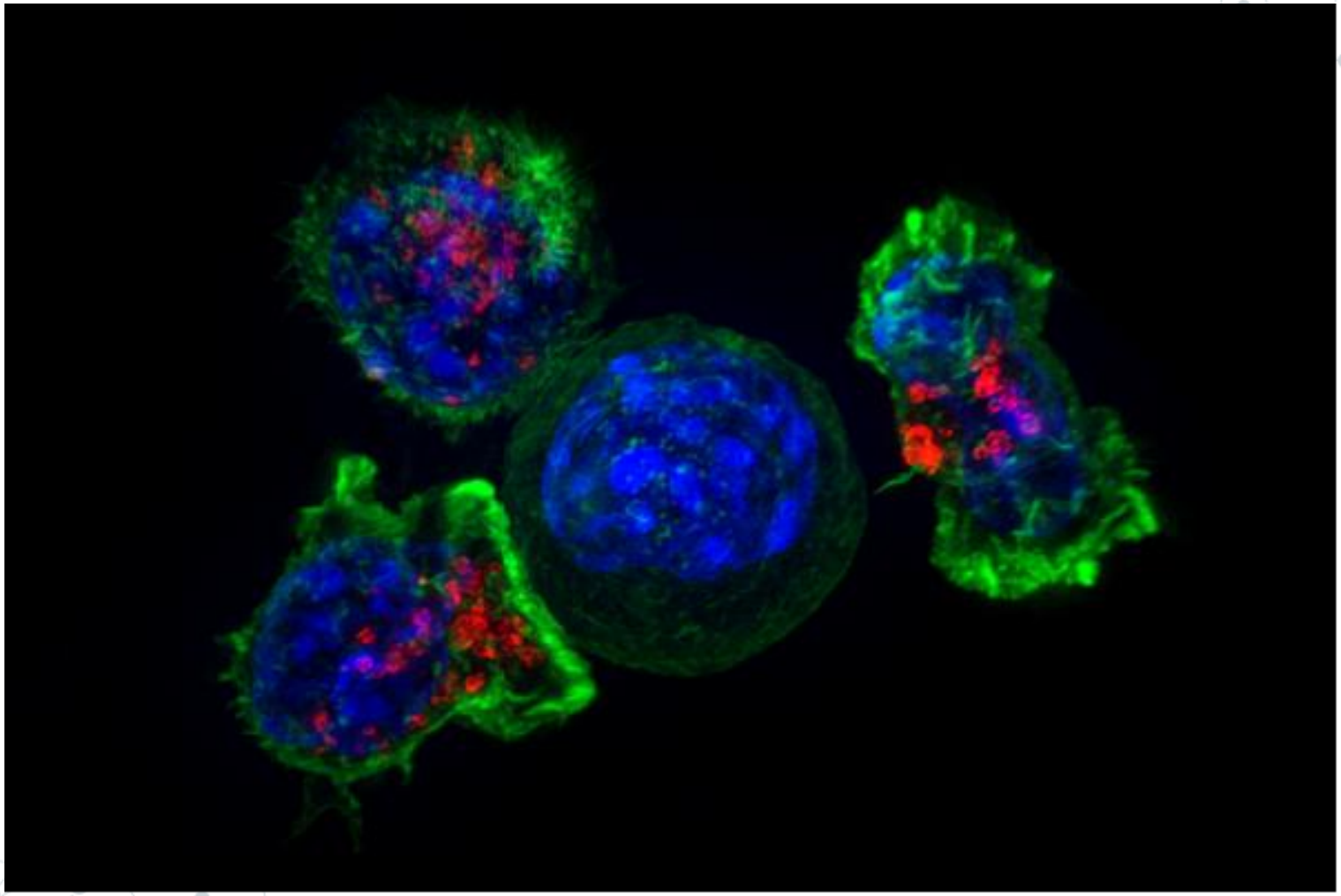
- **Chimeric antigen receptor T cells**
- **Genetically altered T cells that recognize and kill tumor cells in a designed manner**
- **To understand what these are we have understand how normal T cells work**

How do T cells work?

- T cells recognize antigen-MHC complex on target cell using their T cell receptor



Normal T cell vs. cancer



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Normal T cell vs. cancer (cont'd)

- Cancer cell antigen is recognized by the T cell receptor (TCR) specific for that antigen
- The antigen is displayed with a surface protein called major histocompatibility complex (MHC)
- MHC-antigen recognition is not enough, needs a costimulatory signal

Normal T cell vs. cancer (cont'd)

- **Costimulatory signal: CD28 on T cell binds CD80 on the cancer cell (activation)**
- **Excessive activation of T cells would be bad (autoimmunity) so there is a balance between activation and inhibition**
- **Inhibitory signal 1: CTLA-4 binds to CD80**
- **Inhibitory signal 2: PD1 binds to PD-L1 and PD-L2**

Normal T cell vs. cancer (cont'd)

- Cancer cells can inhibit the T cell response through the CTLA-4 and PD1 pathways
- Then the cell is not destroyed, T cell stays "off"
- What if you block this with anti-CTLA-4 or anti-PD1 antibodies?
- These antibodies are called **checkpoint inhibitors**

Checkpoint inhibitors enhance anti-cancer immune response

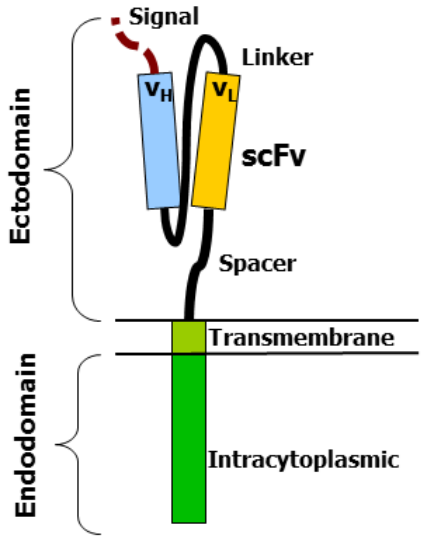
- **Checkpoint inhibitors can greatly enhance cancer therapy by enhancing the T cell response**
- **Nobel prize in Physiology or Medicine 2018**
- **James P. Allison and Tasuku Honjo**
- **https://www.nobelprize.org/prizes/medicine/2018/press-release/**

Checkpoint inhibitors on the market

- Pembrolizumab (Keytruda) is a mAb that binds to PD-1, is used against certain solid tumors
- Ipilimumab (Yervoy) is a mAb that binds to CTLA-4, is used against melanoma
- Atezolizumab (Tecentriq) is a mAb that binds to PD-L1, is used against non-small cell lung cancer and advanced urothelial carcinoma
- Lots of hype and excitement on the field
- Various combinations are currently under investigation

How are CAR-T cells different?

- **CAR-T cells have an genetically engineered T cell receptor that does not need MHC complex for antigen recognition**



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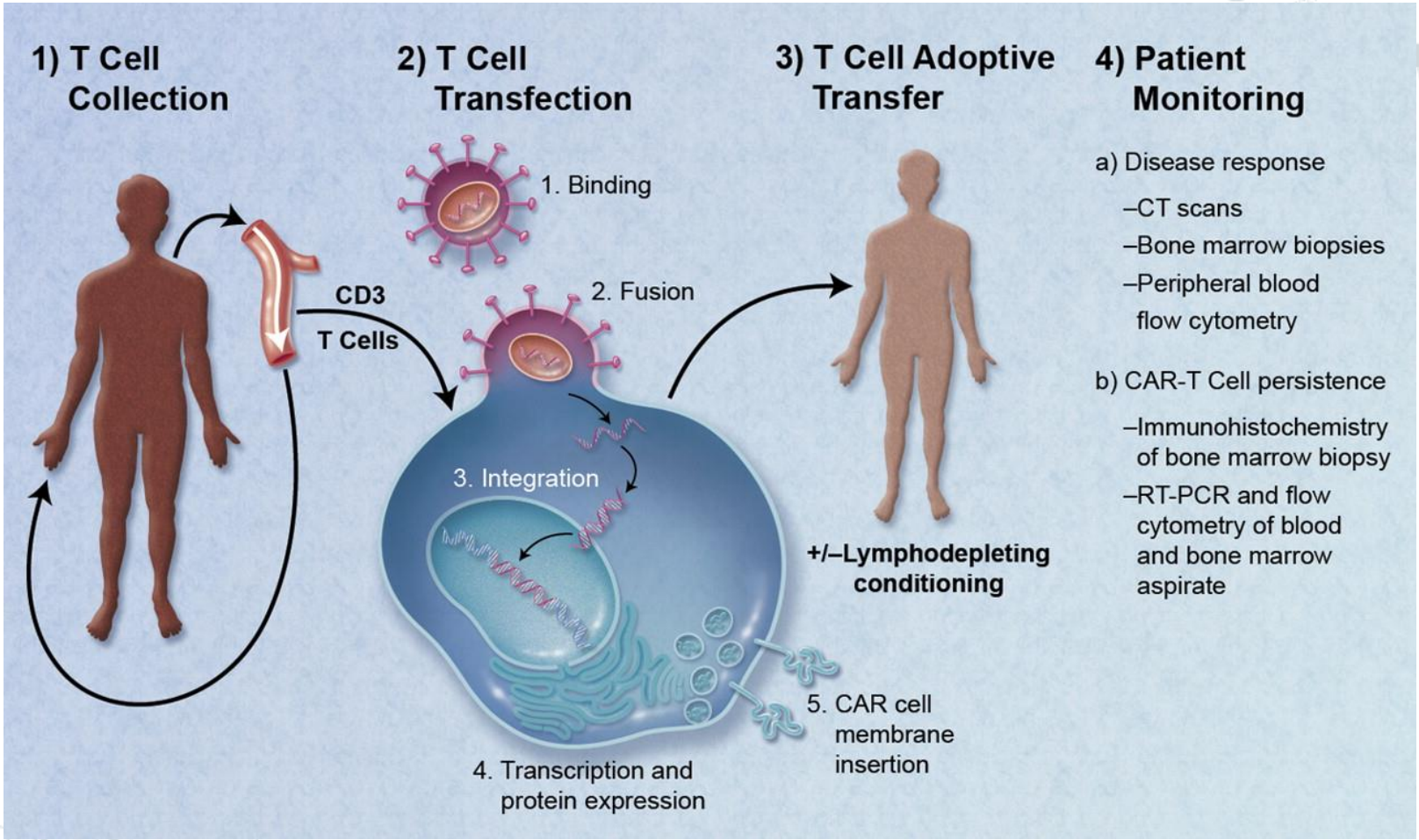
How are CAR-T cells used?

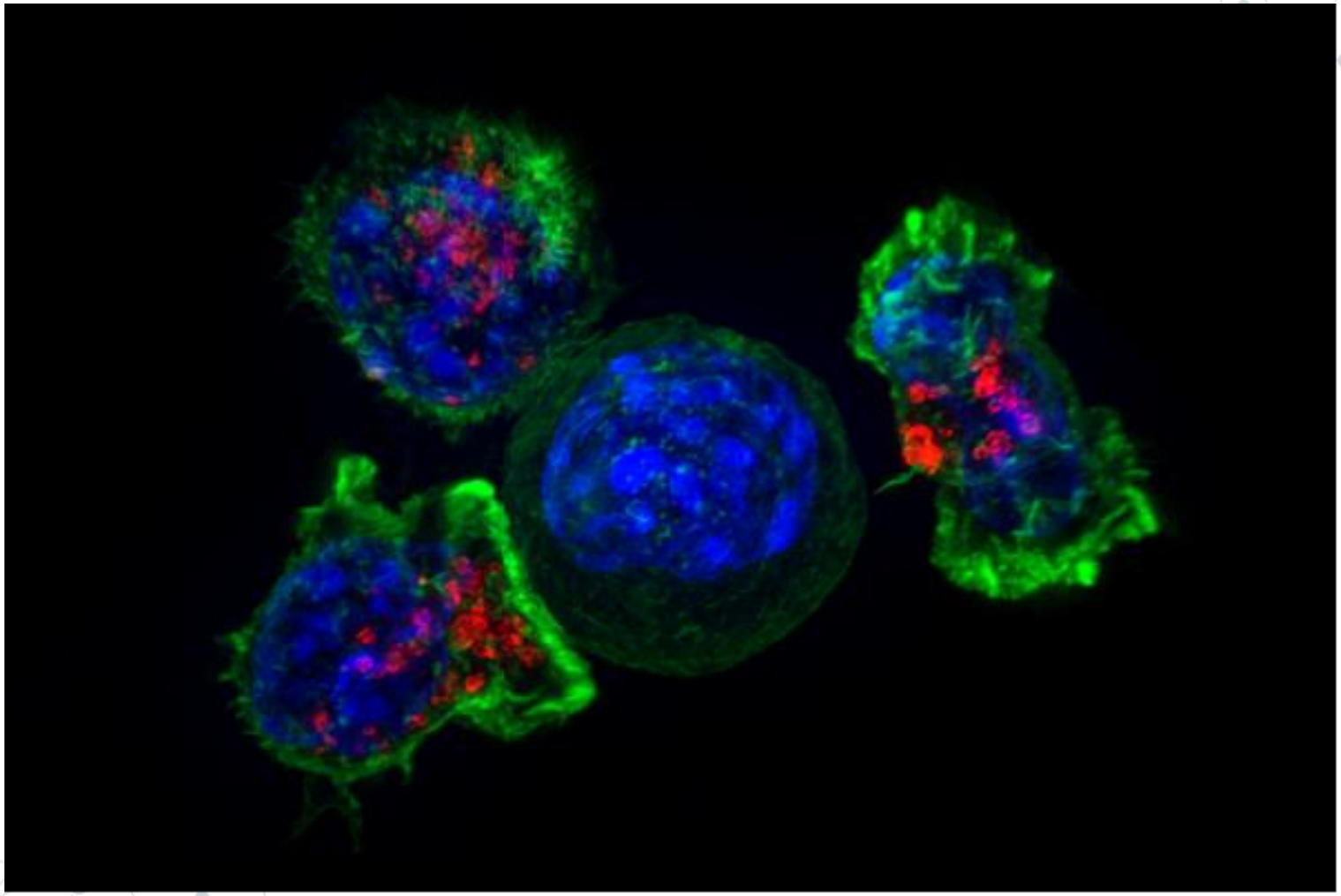


Public domain. Caron A. Jacobson and Jerome Ritz - http://bloodjournal.hematologylibrary.org/content/118/18/4761.full

How does CAR T cell kill cancer cells?

- Once CAR-T receptor binds to cancer antigen, T cell is activated
- Target cell is killed by cytolysis and also in some cases by apoptosis (programmed cell death)
- Once the target cell is dead the T cell can move on to the next target cell (a living drug)

CAR T-cells in action



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Safety issues

- **CAR-T therapy is very aggressive and can lead to two serious side effects:**
  - **Cytokine storm**
  - **Neurotoxicity**
  - **These can be alleviated by blocking the production of proinflammatory cytokines in the body**

Safety issues (cont'd)

- **CAR T-cells are only used for advanced cancer in clinical trials due to potentially serious adverse effects**
- **Multifunctional CAR T-cells that would recognize multiple tumor antigens would be very useful against tumor cell escape**
- **"Suicide" mechanisms and on/off switches are being developed**

CAR-T cells in the clinic

- October 21, 2018: 654 CAR-T clinical trials in Clinicaltrials.gov database

- Majority of these have indications of blood cancers (multiple myeloma, lymphoma, leukemia)

- Solid tumors much harder to treat

CAR-T cells in the market

- So far, two CAR-T based biological drugs have got FDA approval

- On August 2017 FDA approved tisagenlecleucel (Kymriah™) for certain children and young adults with a form of B-cell acute lymphoblastic leukemia (ALL)

- In a clinical trial with 63 ALL patients, the overall remission rate was 83%

CAR-T cells in the market (cont'd)

- On October 2017 FDA approved axicabtagene ciloleucel (Yescarta™) for patients with large-B-cell lymphomas as a third-line therapy
- In a clinical trial with 100 patients, half of the patients had a complete response – cancer disappeared completely
- 30% had a partial response

CAR-T cells in the market (cont'd)

- **Price:**
- **Kymriah $475,000 but only if there is a response within 1 month**
- **Yescarta $373,000**
- **Tailored therapies for each patient, cost is a serious concern**
- **Prices should drop with better technology**

CAR-T cells in the future

- Better, non-viral genetic engineering of T cells to allay safety concerns (secondary leukemia)
- Non-viral gene delivery would not need biosafety level III facilities
- Robust, industrial production of CAR-T cells should drive costs down and bring this therapy to wider use

CAR-T cells in the future (cont'd)

- **CAR-T cells combined with checkpoint inhibitors could be a very potent weapon even against solid tumors**

- **However, would they get out of control -> autoimmunity disease?**

Future Visions

- Genetically enhanced cancer therapies could be a paradigm shift in cancer therapy
- Patient-specific, tailored living drugs could suppress many cancers or cure them completely
- Expect a lot of work as a medical translator – clinical protocols, patent applications, entire dossiers for regulatory agencies

Further reading

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Thank you!

Any questions?

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