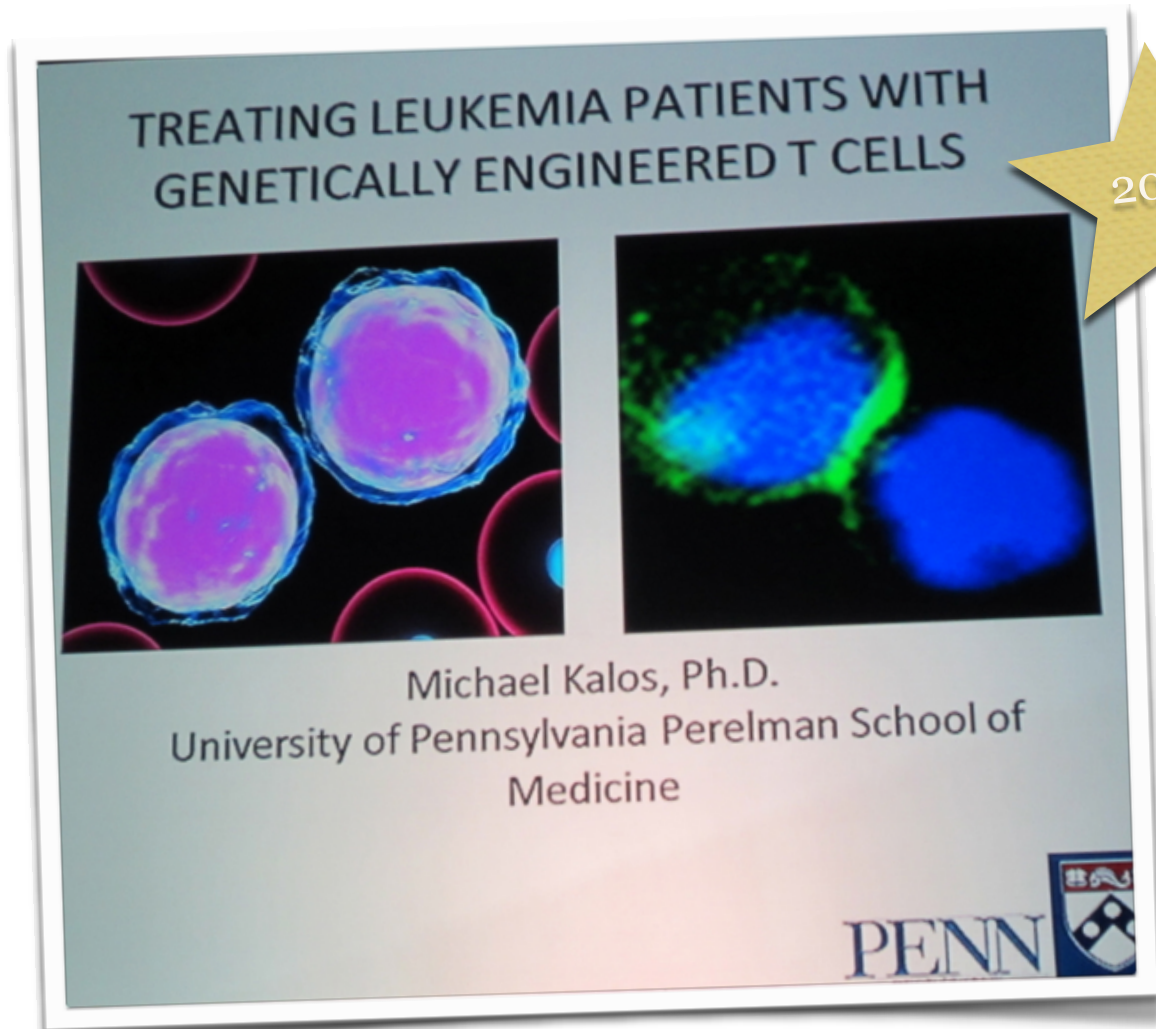


CHIMERIC ANTIGEN RECEPTOR TECHNOLOGY (CART)



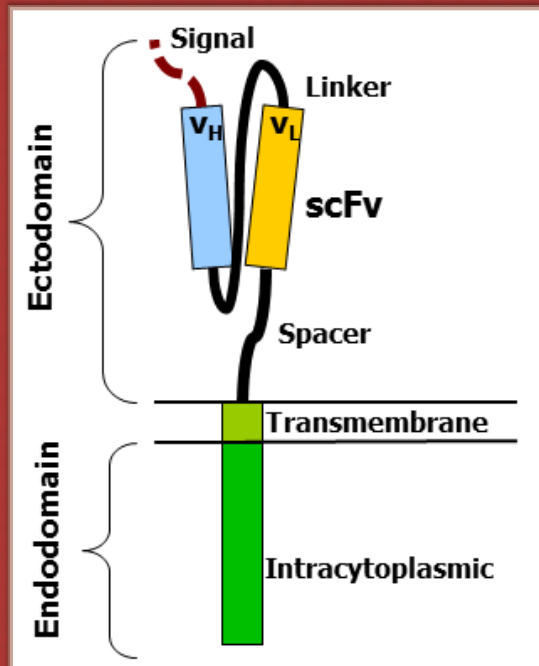
Review of recent data in *Science*
Translational Medicine & *New*
England Journal of Medicine

AN EXECUTIVE SUMMARY
SALLY CHURCH, PHD

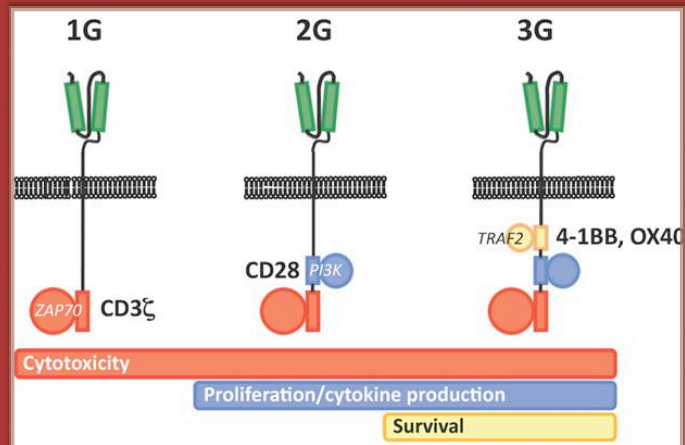
PHARMA STRATEGY REPORTS

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CHIMERIC ANTIGEN RECEPTORS



Graphics source: Wikipedia



Chimeric antigen receptors (CAR) involve fusions of single-chain variable fragments (scFv) derived from monoclonal antibodies, which are connected to transmembrane and endodomain elements via a spacer.

T cells that are genetically modified to express CARs can specifically recognise tumour antigens, and CAR-expressing T cells have been shown to have potent *in vivo* activity against some types of lymphoma and leukemia.

TUMOUR TYPES:

1. B-CELL ALL
2. B-CELL CLL
3. MYELOMA
4. MANTLE CELL LYMPHOMA
5. B-CELL NHL

AND POSSIBLY SOLID
TUMOURS IN THE FUTURE

NOTE: EACH TUMOUR TYPE
MAY HAVE A DIFFERENT
SPECIFIC TARGET SUCH AS
CD19, CD20, CD138 ETC2

The challenges with immunotherapy and stimulating the immune system...

Two of the main limitations with prior attempts at either retro-viral vectors or autologous immunotherapies have included the development of leukemia and immunogenicity, respectively. The latter involves the provoking of a *sustained* immune response.

The human immune system is highly sophisticated and able to recognise invaders such as pathogens and bacteria as foreign particles and mount an effective and appropriate immune response to deal with it.

In cancer, one problem is that the cells aren't foreign - the body's normal homeostatic system has gone awry, leading to proliferation and growth of many more human cells than usual.

Often, the immune system only recognises the presence of cancer when it is too late and overwhelmed with a large tumour burden.

In recent years, researchers have tried new approaches to develop a more potent and effective agent that can prime the immune system better.

How are the next generation immunotherapies making waves in cancer research?

In simple terms, making a cancer immunotherapy more effective involves the introduction of a foreign element so that the immune system can be triggered to attack the body's cancer cells.

CAR-MODIFIED T CELLS ARE PAVING THE WAY TO A NEW TYPE OF TREATMENT IN LYMPHOCYTIC LEUKEMIAS

What are chimeric antibodies?

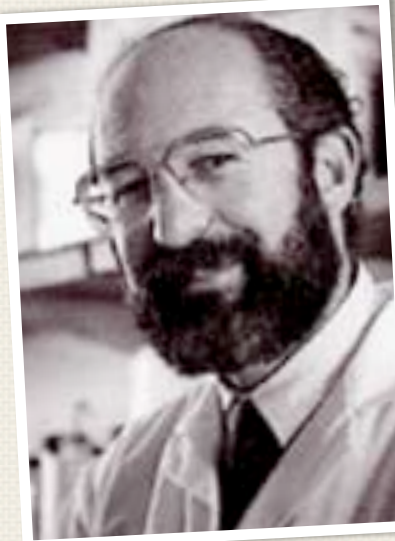
A chimeric antibody is an antibody that is made by combining genetic material from a nonhuman source, such as a mouse, with genetic material from a human being.

What are chimeric antigen receptors?

Chimeric antigen receptors (CARs) are fusion proteins containing antigen-recognition moieties and T-cell activation domains. T cells that are genetically modified to express CARs can specifically recognise tumour antigens, and CAR-expressing T cells have been shown to have potent in vivo activity against some types of lymphoma and leukemia.

Who is working in this field?

Several research groups have been working on CAR technology. Scientists at U Penn, led by Carl June, have evaluated their anti CD19 CART in CLL and ALL, while another group led by Renier Brentjens at Memorial Sloan-Kettering in New York have seen some promising results with their CART immunotherapies in B cell adult and pediatric ALL.



STANFORD

ONE OF THE PIONEERS OF RESEARCH WITH THE IMMUNE SYSTEM WAS THE WORK OF RON LEVY, WHO WAS LOOKING AT WAYS TO USE THE BODY'S IMMUNE SYSTEM TO FIGHT CANCER. HIS WORK IN THE 1980'S LED TO THE CREATION OF IDEC IN 1985 AND DEVELOPMENT OF THE FIRST MONOCLONAL ANTIBODY TO CD20, RITUXIMAB.



U. PENN

NOVARTIS AND U. PENN SIGNED A GLOBAL LICENSING DEAL IN AUGUST 2012 FOR THE CART TECHNOLOGY AIMED AT CD19, DEVELOPED BY CARL JUNE AND COLLEAGUES. THE AGENT, FORMERLY CALLED CART-19, IS NOW KNOWN AS CTL-019.

IT IS BEING TESTED IN B-CELL PEDIATRIC ALL AND CLL.



MSKCC

MSKCC HAVE ALSO BEEN FOCUSED ON DEVELOPING NOVEL TREATMENT APPROACHES FOR LEUKEMIAS & LYMPHOMAS.

THE WORK OF RENIER BRENTJENS LAB INVOLVES HARNESSING PATIENTS' OWN IMMUNE CELLS, SPECIFICALLY AUTOLOGOUS T CELLS, TO RECOGNIZE AND KILL THEIR OWN CANCER CELLS.

Recent papers in NEJM and Science & Translational Medicine have described a novel approach...

Why explore acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) with CART?

Results with a stem cell transplant in the first line setting are usually very good, but not all patients achieve a complete remission (CR). Children with relapsed or chemotherapy-refractory ALL have a poor prognosis, despite the use of intensive therapies.

Adults with ALL also generally have a much poorer prognosis due to more aggressive disease and additional translocations such as the Philadelphia chromosome.

Patients with refractory CLL who are heavily pre-treated with multiple prior therapies may have run out of available options.

Both ALL and CLL are thought to have CD19 surface antigens, which may be a viable target for autologous T cell immunotherapy using a specific CD19 chimeric antibody.

What does the process involve?

T cells from the leukemia patients were removed by apheresis and then transfected with the chimeric antibody before the adapted T cells are re-infused into the patient in a sequential process shown in the graphic on the next page. Patients are then monitored over time for disease response and T cell persistence.

What efficacy results have been seen with CART?

11 patients who had refractory ALL or CLL were treated at U Penn with CART-19/CTL-019 with very promising initial responses.

The engineered cells persisted at high levels for 6 months in the blood and bone marrow and continued to express the chimeric antigen receptor.

A specific immune response was detected in the bone marrow, accompanied by loss of normal B cells and leukemia cells that express CD19. Remission was still ongoing 10 months after treatment. In the CLL patients, they observed that:

“A CD19-specific immune response was demonstrated in the blood and bone marrow, accompanied by complete remission, in two of three patients.”

What sort of side effects have been reported with CART?

Apart from tumor lysis syndrome (TLS) in a couple of patients, the only other grade 3/4 toxic effect related to chimeric antigen receptor T cells was lymphopenia.

TLS occurs when there is a very rapid response, which may have an early or delayed effect. It is caused a massive cytokine cascade from the T cell stimulation. Patients may need to be hospitalised and treated appropriately to remove the excess potassium and other elements that may be involved in the spike. Brentjens et al., noted:

“Therapy was well tolerated, although significant cytokine elevations, specifically observed in those patients with morphologic evidence of disease at the time of treatment, required lymphotoxic steroid therapy to ameliorate cytokine-mediated toxicities.”

TLS is generally rare in CLL, but may be a reflection of the efficacy of the CART

procedure, particularly in patients with bulky disease or a high tumour burden.

At the recent American Society of Hematology (ASH meeting, Carl June noted that the researchers at Penn saw a delayed TLS in some patients, typically occurring around 50 days post infusion. None of their patients died from TLS.

Hypogammaglobulinemia was an expected chronic toxic effect.

What is the impact of treatment with CAR modified T cells?

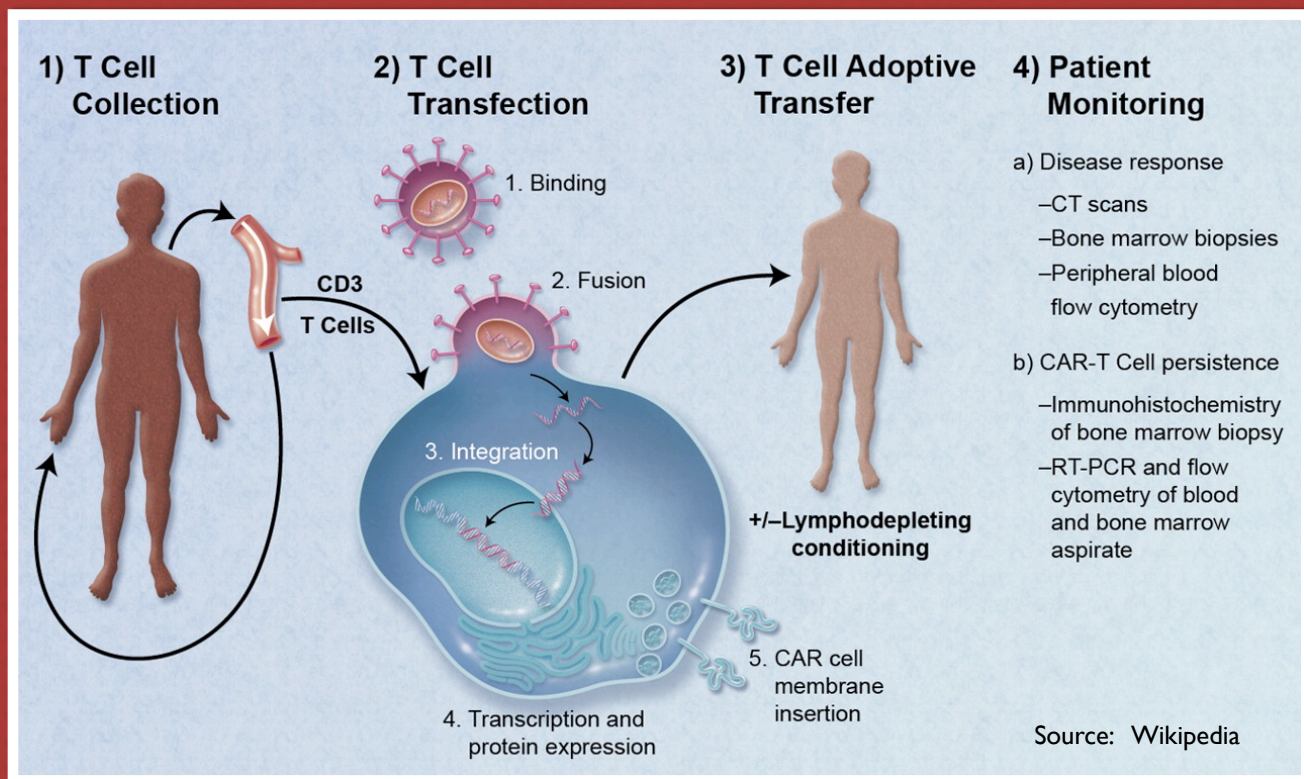
To date, I think this new approach is very exciting and may well lead to a new breakthrough in the treatment of refractory ALL after failure of SCT and in advanced CLL that has been heavily pre-treated.

Clearly the numbers of patients treated to date has been small, but the experimental techniques pioneered by Penn and MSKCC show considerable promise. CD19 is a particularly good target for CARs in these leukemias since expression is restricted to normal and malignant B cells.

We now need to see larger randomised phase III studies involving more centres and larger numbers of patients to validate the initial research. Longer follow-up time is also important to determine how effective and durable the responses are likely to be over the longer term.

References:

- Kalos et al., Sci Trans Med (2011).
- Grupp et al., N Engl J Med (2013).
- Brentjens et al., Sci Transl Med (2013).



USING ADOPTIVE TRANSFER OF T CELLS AS A CANCER THERAPEUTIC IS SEEN AS A PROMISING NEW TECHNOLOGY TO HARNESS THE BODIES IMMUNE SYSTEM TO FIGHT SOME TYPES OF CANCERS

Overall, the new generation chimeric antigen receptor–modified T cells with specificity for CD19 looks much more promising than earlier approaches, with more sustained efficacy responses in B cell pediatric and adult ALL and CLL. The initial trials, while small in terms of the sample size, are sufficiently encouraging to warrant further investigation.

One particular challenge with this approach is that the responses have been exceptionally rapid in some patients, resulting in tumour lysis syndrome (TLS). In some patients, delayed TLS has also occurred around day 50. This means that patients may need to be carefully monitored in tertiary rather than community centres where there is expertise and rapid response teams who can deal with the sudden crisis.

Novartis have clearly been planning ahead for CTL-019's development and additional CARTs by purchasing the Dendreon NJ manufacturing facility, which will already have undergone FDA inspection and evaluation of the SOP procedures to ensure that the apheresis samples collected from patients can be tracked individually.

Further trial expansion is expected to take place in randomised phase III studies to validate the initial findings on a broader scale beyond the initial centre that participated (U Penn). This will be key to future registrability of CTL-019 with Health Authorities.

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