Use of Chimeric Antigen Receptors as a Novel Cancer Immunotherapy Approach

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Abstract

- Immunotherapy consists of the use of immunologic principles against tumours. Unlike chemotherapy or radiotherapy, immunotherapy has the potential to induce such a dynamic immune response that can kill tumour cells for an extended period of time.
- The use of chimeric antigen receptors (CARs) in lymphocytes is an emerging immunotherapy approach. These receptors bind to tumour-specific antigens, promoting the activation of the host's immune cells, which results in a specific immune response against tumour cells.

Materials and Methods

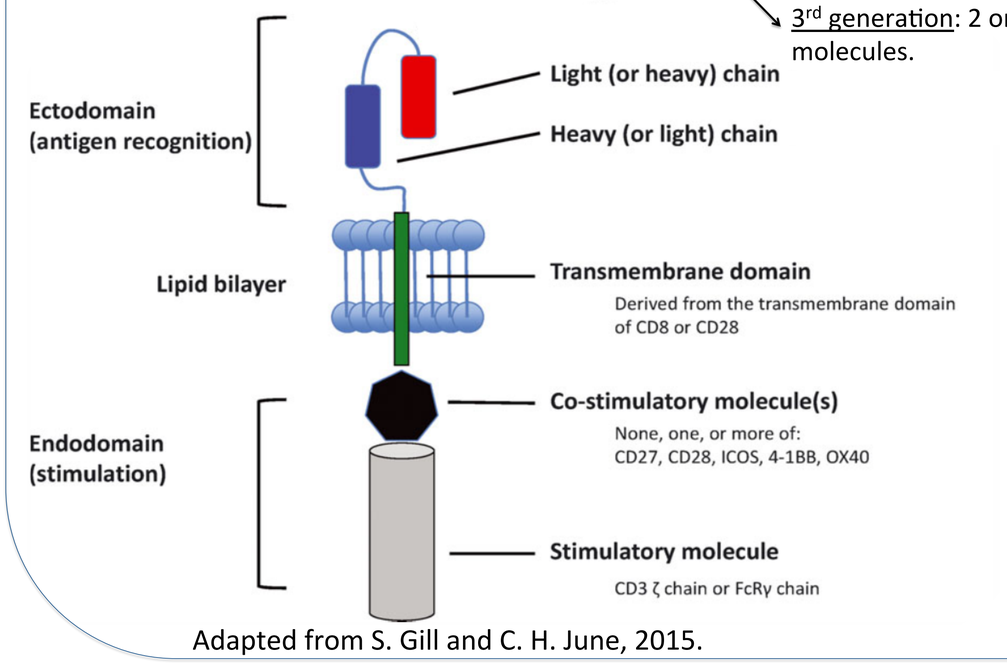
- **Search of scientific literature in PubMed**: reviews and recent papers about CARs and their use in pre-clinical and clinical trials were selected.
- **Use of Immunology books:** reading of the chapters concerning T-cell activation, antigen receptors, immune responses and autoimmunity.

Introduction to CARs

Structure:

- **Antigen-binding extracellular domain**: binding site of the antibody that targets the cognate antigen.
- **Trans-membrane domain**
- **Signal-activating intracellular domain:**
  - Stimulatory molecule: CD3 ζ chain
  - Co-stimulatory molecule: CD28, 4-1BB…

→ 1st generation: no co-stimulatory molecules.
→ 2nd generation: 1 co-stimulatory molecule.
→ 3rd generation: 2 or more co-stimulatory molecules.

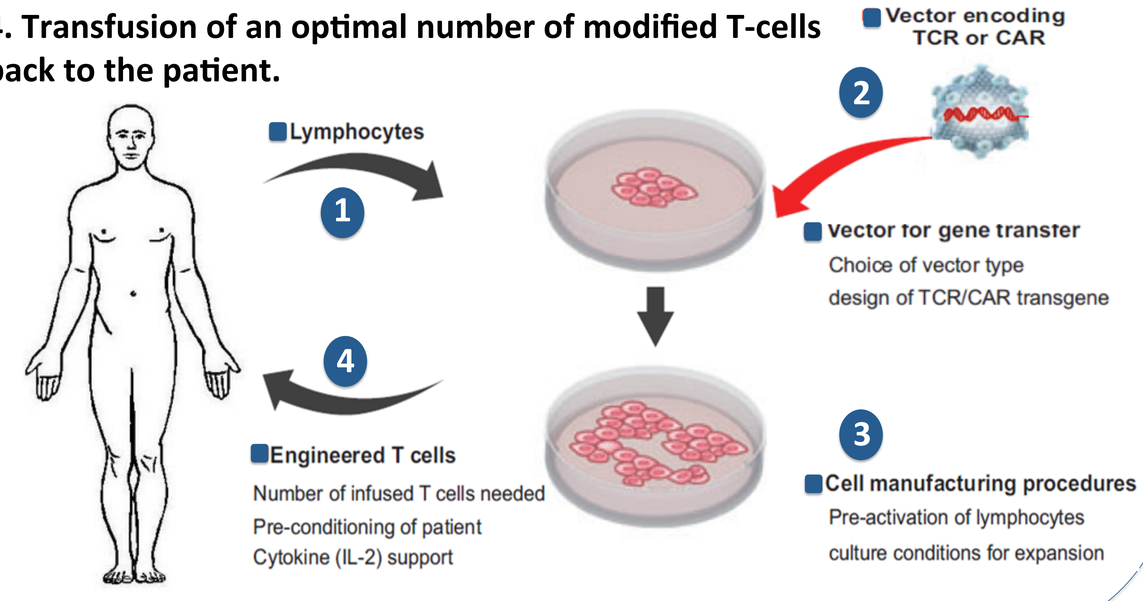


Adapted from S. Gill and C. H. June, 2015.

Ex vivo methods and genetic engineering

Steps for lymphocyte modification:

1. **Apheresis:** separation of T-cells from the rest of blood cell types.
2. **Internalization of CAR constructs into T-cells**. Strategies:
   a. Electroporation
   b. Viral vectors: most used strategy → Low immunogenicity; Permanent transgene expression; Low insertional mutation rate
   c. Transposon-based systems
3. **Expansion of T-cells** → Activating signals: Anti-CD3 activating monoclonal antibody; Supporting medium: IL-2 containing medium
4. **Transfusion of an optimal number of modified T-cells back to the patient.**



Adapted from M. Essand and A.S.I. Loskog, 2012.

Use of CARs in different tumours

Targeted antigen	Disease/hallmark of cancer	CAR generation	Used co-stimulatory molecule(s)	Stage of trial
CD19	ALL and CLL	2	CD28 or 4-1BB	Clinical
CD20	NHL	2	4-1BB	Clinical
CD22	ALL	3	CD28 and 4-1BB	Clinical
CD23	CLL	2	CD28	Clinical
CD33	AML	2	4-1BB	Phase I
Her2	Breast cancer	2	CD28	Pre-clinical
	Ovarian cancer	1	-	Pre-clinical
	Brain cancers	2	CD28	Clinical
Her3	Breast cancer	1	-	Pre-clinical
Her4	Breast cancer	1	-	Pre-clinical
CD133	GBM	3	CD28 and 4-1BB	Pre-clinical
α-follate	Ovarian cancer	1	-	Clinical
NKG2D ligands	Ovarian cancer	1	-	Pre-clinical
MUC16	Ovarian cancer	1	-	Phase I
Lewis-Y carbohydrate	Ovarian cancer	2	CD28	Pre-clinical
VEGF2	Tumour angiogenesis	3	CD28 and 4-1BB	Phase I

Table provided by the author.

Future approaches and main conclusions

Future approaches:

Considerations for the improvement of CARs in terms of efficacy increase and toxicity decrease:

- It is extremely important to use tumour-restricted antigens in order to decrease toxicity and off-target effects.
- Suggested measurements to decrease the likelihood of generating autoimmune reactions:
  - Splitting the modified T-cell doses.
  - Introducing suicidal genes into the CARs construct. These genes get activated in highly toxic environments, promoting the apoptosis of the modified T-cells.
- Economic and logistic costs: the modification of T-cells is performed for each individual's T-cells. The use of allogeneic lymphocytes is an alternative to this strategy.

Main conclusions:

- B-cell malignancies are the cancer types in which the use of CARs has provided the best outcomes and CD19 is the most successful target.
- The success of this approach relies on the development of modified T-cells able to overcome the hostile tumour microenvironment and to promote efficient and accurate cognate immune responses.

References

Only relevant references are cited below.

- S. Gill and C.H. June **Going viral: chimeric antigen receptor T-cell therapy for haematological malignancies.** *Immunological Reviews,* 2015.
- M. Essand and A.S.I. Loskog. **Genetically engineered T cells for the treatment of cancer.** *Journal of Internal Medicine,* 2012.