Keynote Speaker

Reflection on CAR T-cell Delivery in the NHS

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Reflection on **C**himeric **A**ntigen **R**eceptor CAR-T cell delivery in the NHS

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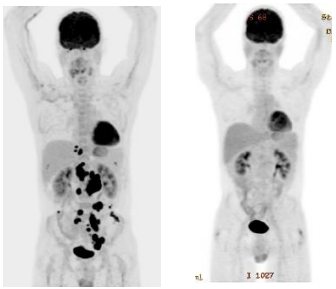

Pre Post
CAR-T cells

Disclosures

- Travel grants:
  - Amgen, Jazz, Pfizer, Bayer, Kyowa Kirin, Celgene, Kite/Gilead
- Honoraria for advisory board meetings:
  - Amgen, Novartis, Pfizer, Kite/Gilead, Celgene, Daiichi Sankyo
- Honoraria for lectures:
  - Takeda, Janssen, Kite/Gilead, Roche
- Research funding:
  - Janssen, Astra Zeneca, Novartis

Topics to cover

- What are CAR-T cells?
- CAR-T cell experience at the NCCC
- What are the challenges to deliver CAR-T cells?

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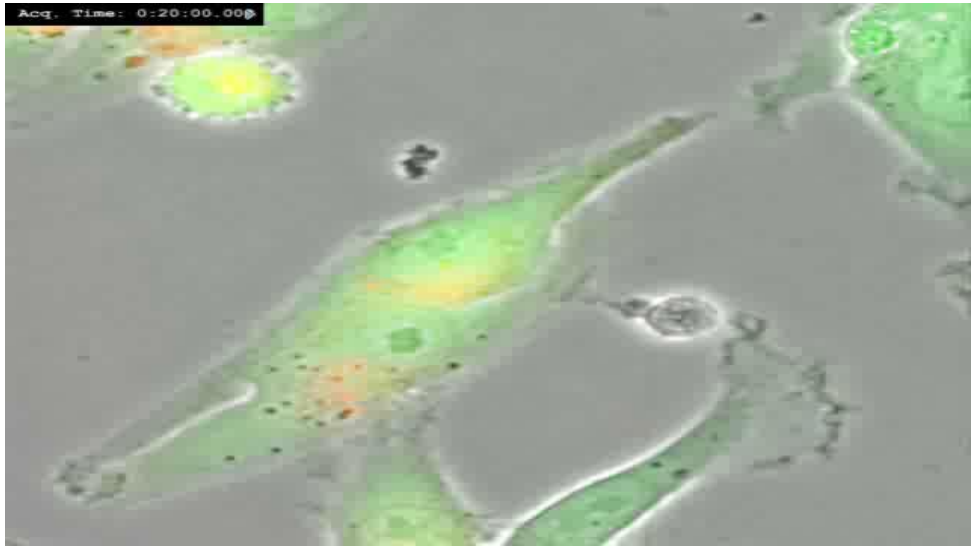
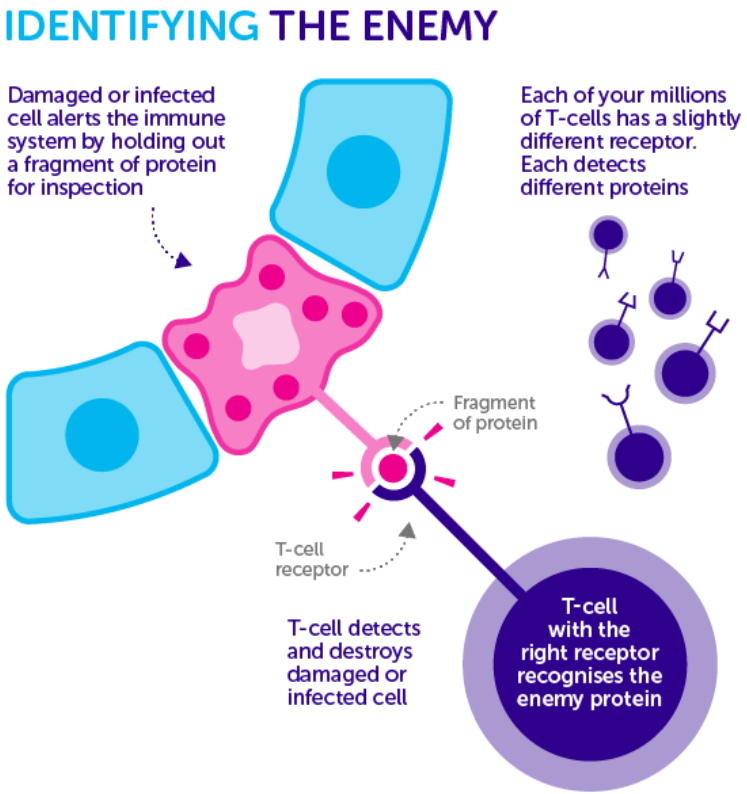
CAR T cells are serial killers!



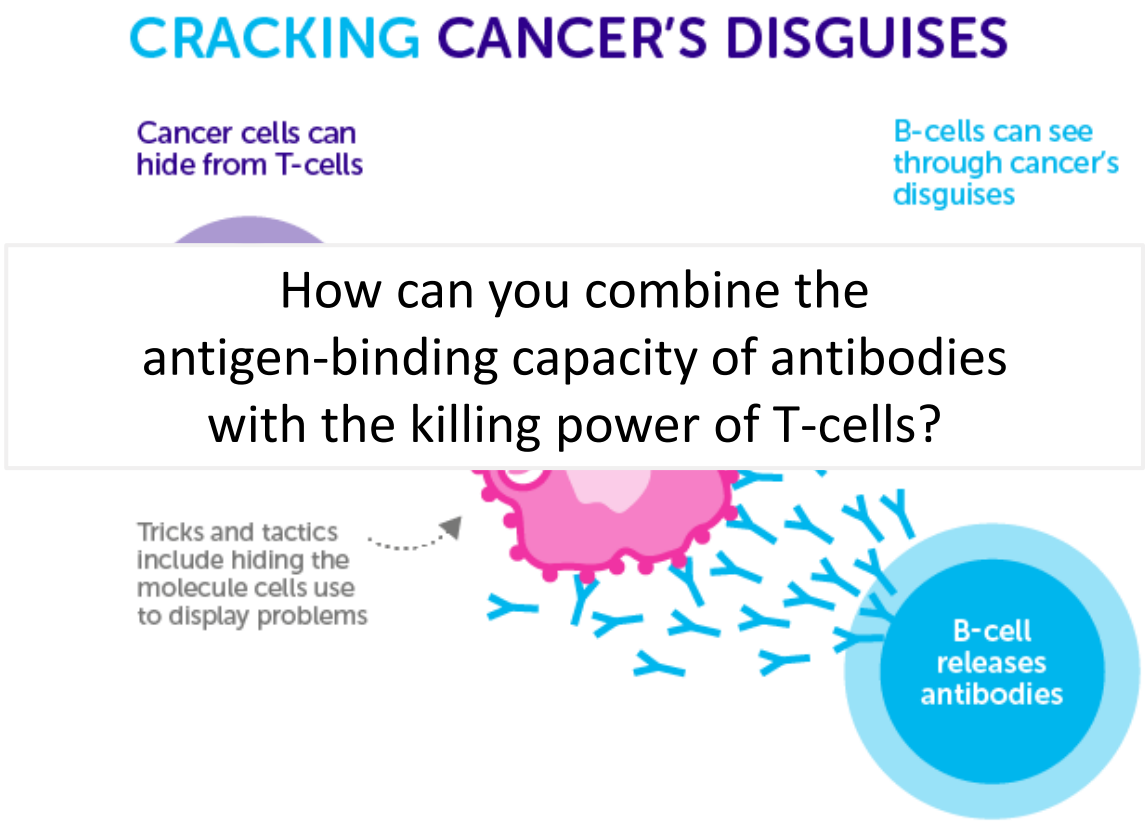
- Each infused CAR T cell can result in death of >100,000 tumor cells

Video: Provided by Dr. Laurence Cooper and Prof. Sattva Neelapu

Role of T-cells



Cancer cells escape T- cell recognition



Structure of B-cell and T-cell receptor

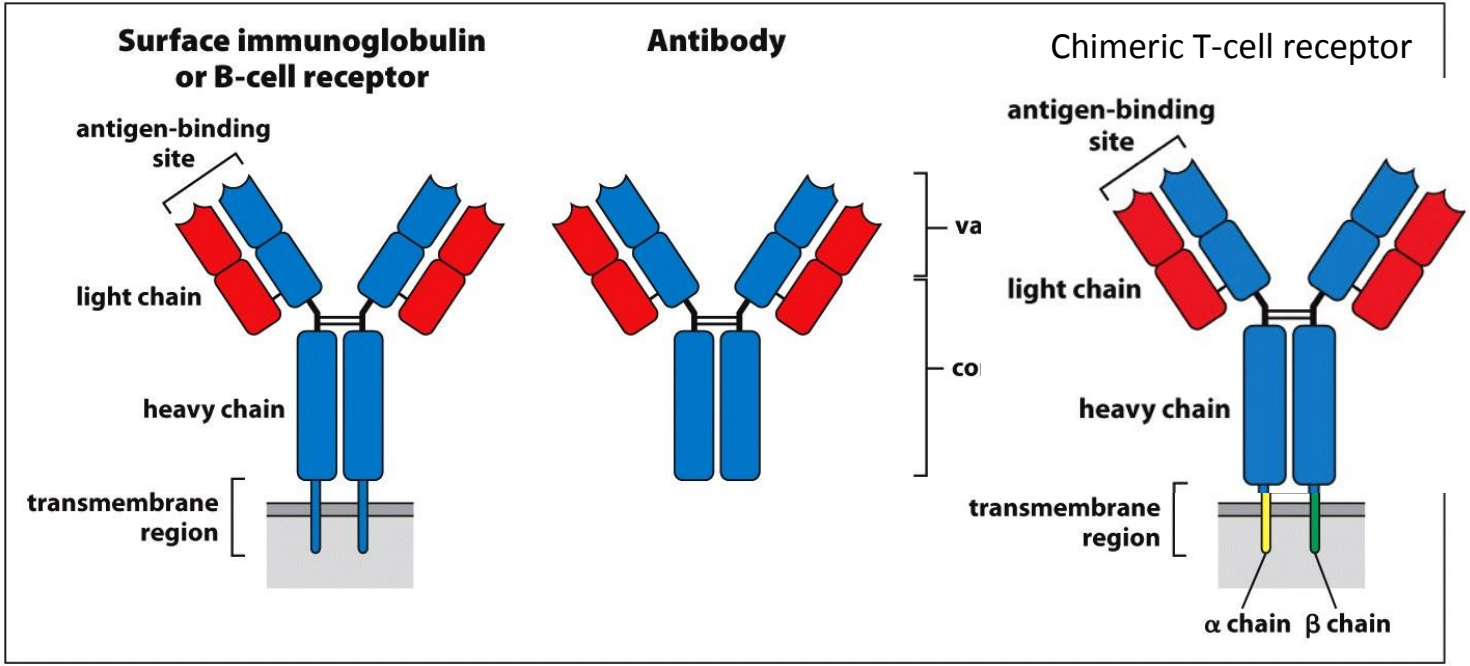
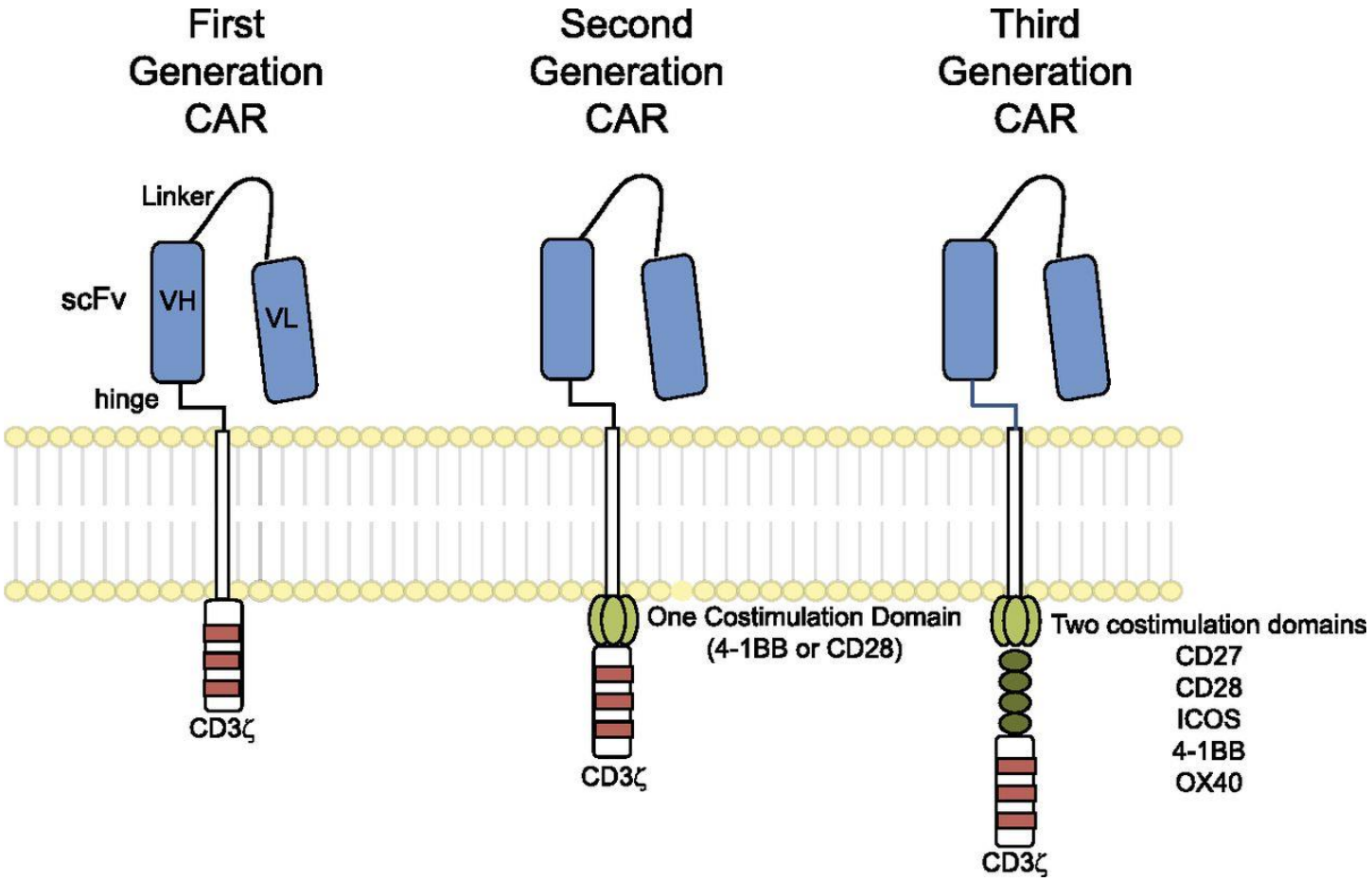


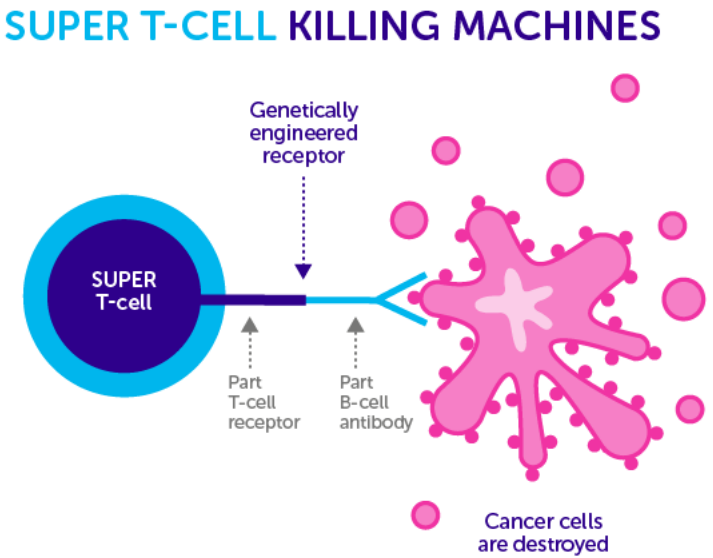
Figure 3.1 The Immune System, 3ed. (© Garland Science 2009)

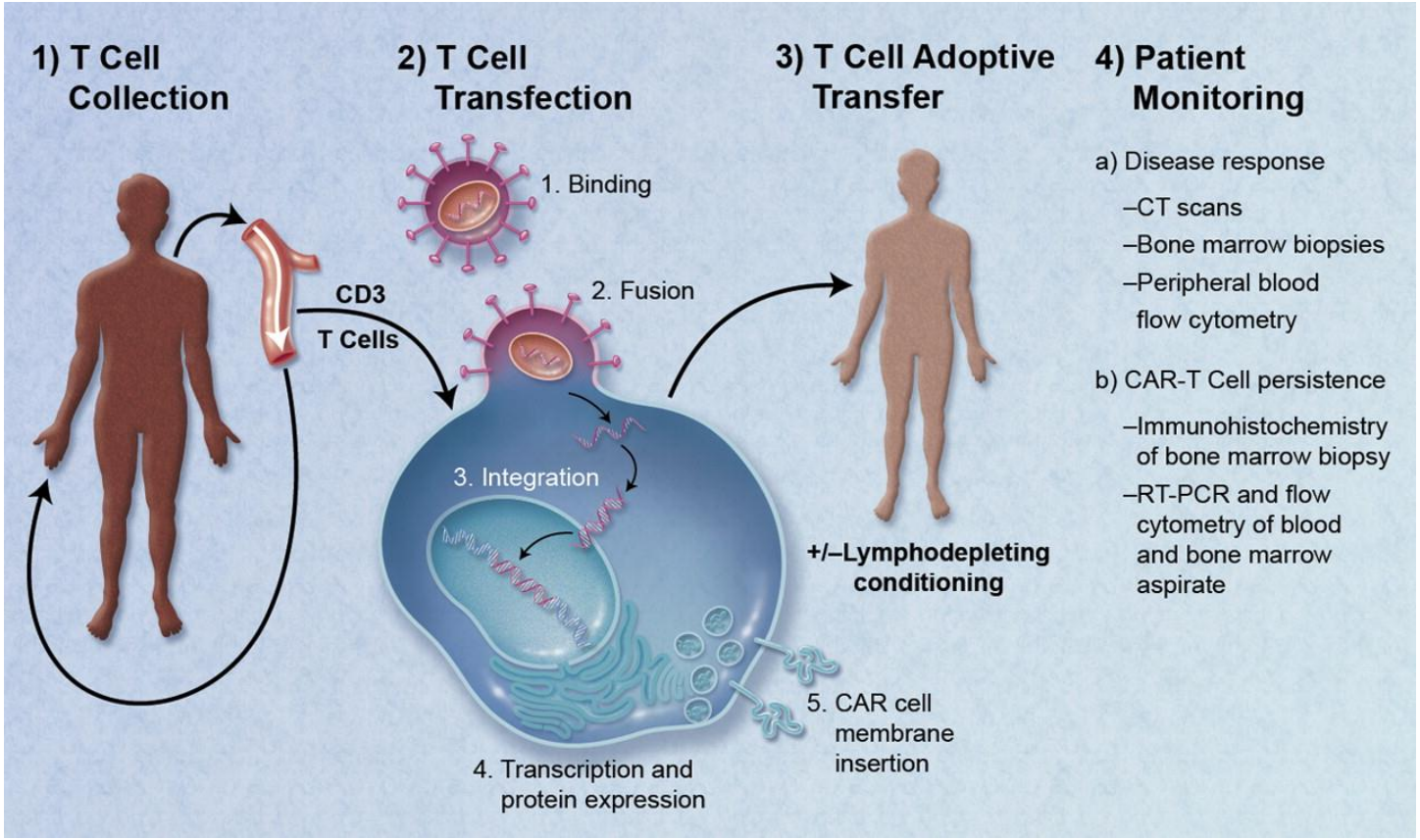


Maus et al. Blood 2013

Voilà!!!

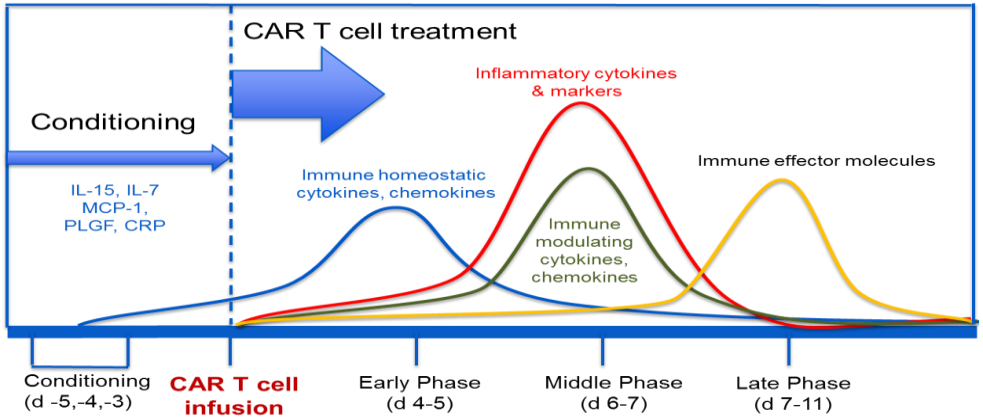
Chimeric Antigen receptor (CAR)-T cells

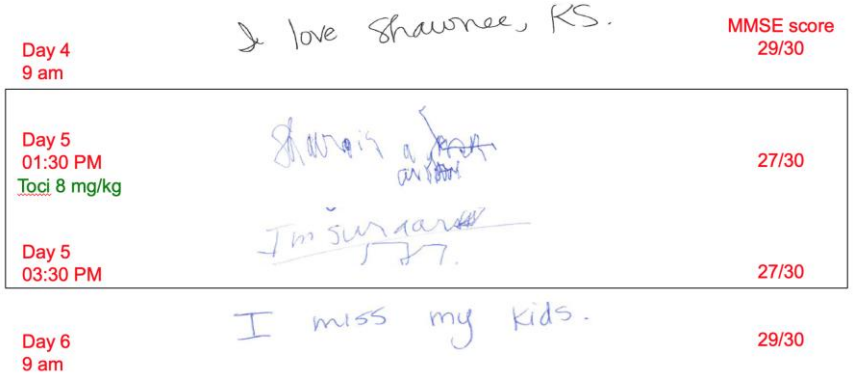



1) T Cell Collection
2) T Cell Transfection
3) T Cell Adoptive Transfer
4) Patient Monitoring
CD3
T Cells
1. Binding
2. Fusion
3. Integration
4. Transcription and protein expression
5. CAR cell membrane insertion
+/–Lymphodepleting conditioning
a) Disease response
–CT scans
–Bone marrow biopsies
–Peripheral blood flow cytometry
b) CAR-T Cell persistence
–Immunohistochemistry of bone marrow biopsy
–RT-PCR and flow cytometry of blood and bone marrow aspirate

Be ready for early toxicity

- High chance of cytokine release syndrome
- High chance of neurotoxicity
- Significant chance that patient might have to go to ITU for organ support
- Requires more senior clinicians input to manage toxicity

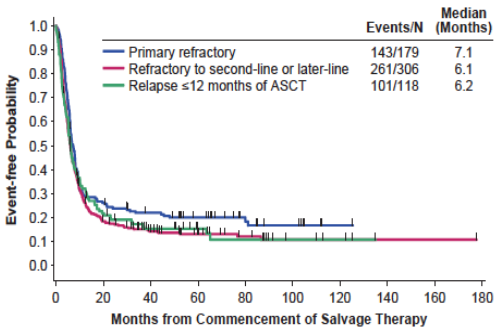




Outcomes

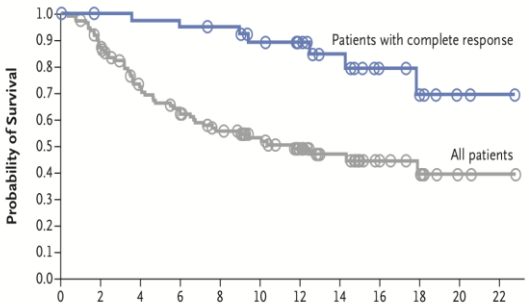
- Fast expansion of T-cells ⇢ 1.000 - 10.000 times
- Potential of killing trillions of cancer cells quickly
- High chance of achieving remissions
- Significantly better chance of achieving cures compared to standard therapies

Overall survival: SCHOLAR-1



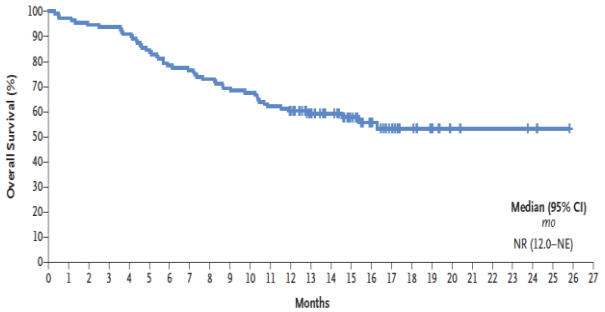
- N=636
- ORR=26%; CR rate=7%
- Median OS=6.3 months

Overall survival: JULIET



- N=111
- ORR=52%; CR rate=40%
- Median OS =11.1 months

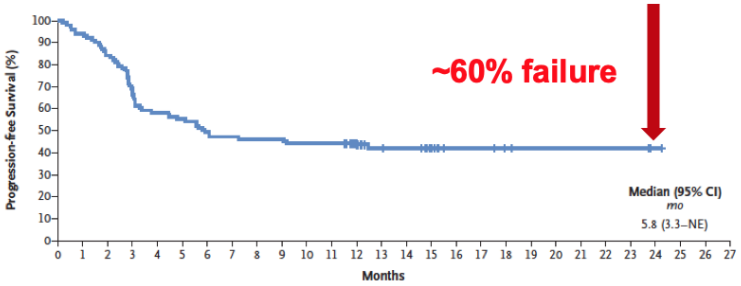
Overall survival: ZUMA-1



- N=108
- ORR=82%; CR rate=58%
- Median OS ≥18 months

Crump M et al. *Blood* 2017; 130: 1800-1808, Schuster SJ et al, NEJM, 2019; 380, 45-56 and Neelapu SS et al. *NEJM,* 2017;377:2531-2544

But current CAR-T strategies need to be improved



Neelapu, ASH 2018

Topics to cover

- What are CAR-T cells?
- CAR-T cell experience at the NCCC
- What are the challenges to deliver CAR-T cells?

CAR-T cell experience at the NCCC (I)

- Summer 2017 - Autolus CAR-T cell studies
  - Auto2 for R/R myeloma –first patient treated June 2018
  - Auto3 for R/R DLBCL
  - Auto 4,5 in set up for R/R PTCL
- March 2018 – establishment of NAATTC
- May 2018 – EOI call from NHSE to become CAR-T cell center
- June 2018 – Selected to be one of 8 CAR-T cell centers in the UK
  - August – November 2018 - JACIE, KITE and Novartis accreditations
- Second center in the country to deliver commercial CAR-T cells to adult patients with DLBCL
  - May 2019
    - reinfused 5 patients with commercial products
    - 3 further patients awaiting reinfusion
    - 2 further patients awaiting apheresis

CAR-T cell experience at the NCCC (II)

- Patients seen so far have come from our NE region, Scotland, Northern Ireland, Sheffield, Nottingham, Halifax and Hull
- May 2019 - First paediatric CAR-T patient being apheresed at GNCH to be treated for relapsed ALL

Initial responses and toxicities:

- 2 out 5 patients ended up on ITU
- 1 months PET: 2 partial remissions, 1 complete remissions
- 1 patient had progressive disease straight through therapy

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Local challenges at CAR-T cell centres (I)

- Capacity is biggest issue to deliver CAR-T cell therapies across all trusts
  - Apheresis slots
    - NUTH - new apheresis machine, new apheresis nurse, re-modelling of our apheresis unit
  - Stem cell lab freezing capabilities
    - new staff being employed
  - Requires more staffing as work load increases
    - NUTH - Business case for Apheresis nurses, Coordinator, CAR-T cell Clinical Nurse Specialist, doctors, pharmacist, ITU consultant, data managers
    - Might require different on-call cover structures as numbers go up
  - Ward capacity
    - NUTH - Need to develop other ways of giving treatment – ambulatory day unit
  - ITU capacity
    - Is an issue in other trusts less so at NUTH

Local challenges at CAR-T cell centres (II)

- Gaining accreditations from JACIE, Novartis and Kite/Gilead
  - Very labour intensive – thousand of hours of man power
  - Writing SOPs, developing pathways and guidelines

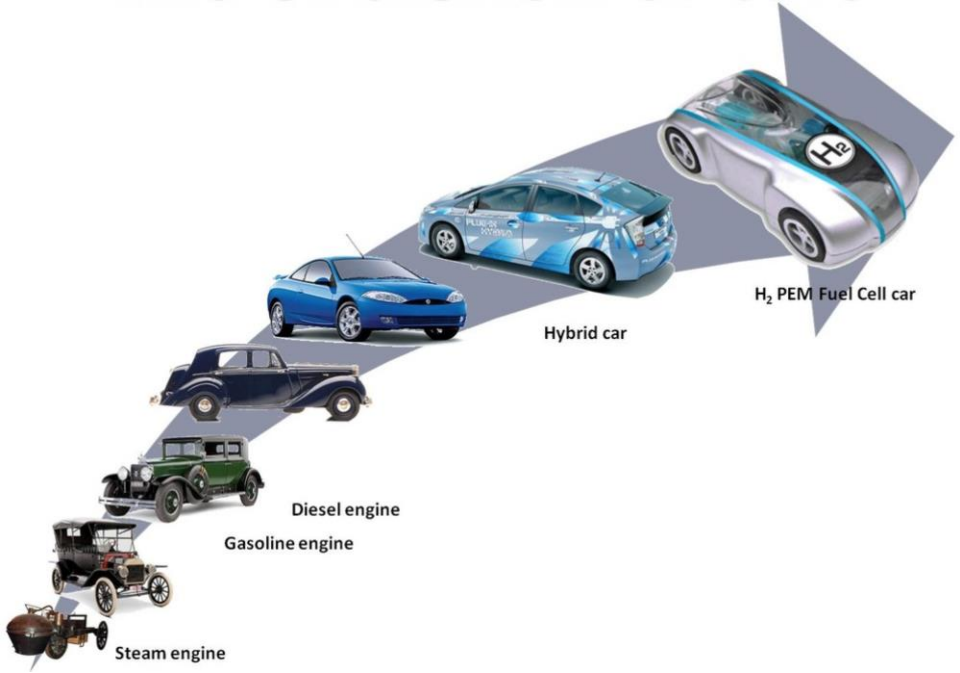
- Training of staff
  - NUTH - several hundred staff trained in dealing with CAR-T cell toxicity
  - Ongoing training (would be good to have an online module)

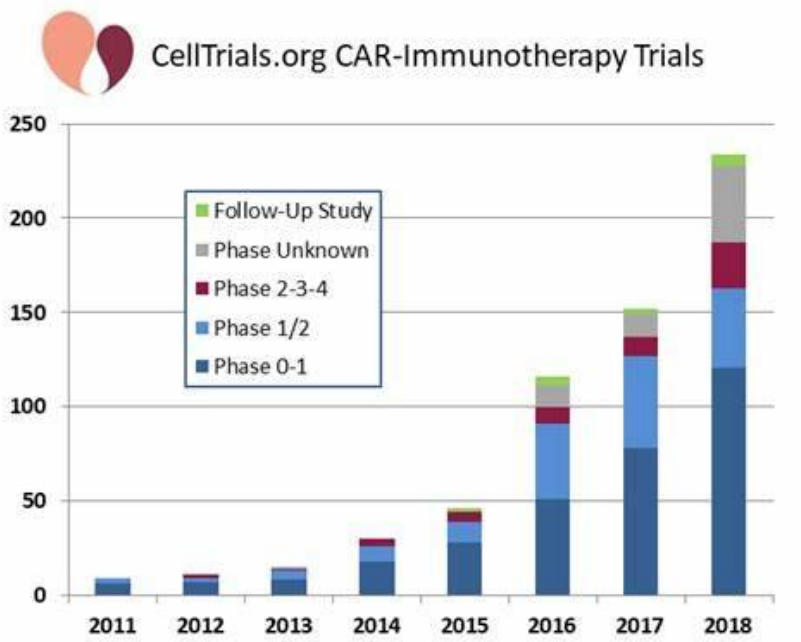
- Management of patients
  - Care requires good coordination between all teams
  - Weekly Car-T cell meeting to discuss outstanding patients (trials and non-trials)
  - Accommodation after discharge; accommodation for relatives, whilst patient in hospital

National challenges

- Costs significant for NICE approved CAR-T therapies (well above £300.000 including drug costs and NHSE tariff to trusts)
  - How will this be financeable if also other indications come on board?
- Only 7 adult centres – now estimated number of R/R DLBCL cases in UK probably around 300-500/year, R/R ALL below 25 years of age probably between 30-50
- Not certain if all appropriate cases are being referred from other centres
- Slot allocation with commercial companies not always straight forward
  - trusts need to become more flexible with apheresis slots
- Time consuming weekly national 2-hour panel meetings
  - at the moment required
- Sharing of protocols, experiences between CAR-T cell centres (current and future) needs to be streamlined

‘CARS’ research challenges (I)





‘CARS’ research challenges (II)

- Living at the beginning of a new era in cancer therapy
- Expect to see some significant inroads over the next decade in targeted immune effector cell therapy
- How do you get patient onto studies with potential better CAR-T cells if already commercial CAR-T cells available

- NUTH and NAATTC needs to be actively involved in this research

Conclusion

- Absolutely fascinating period
- Locally
  - Centres need to increase capacity
  - Share experience and SOP with other centres
- Nationally
  - Need to gather real world data
  - Communicate with all DGHs
- Companies
  - need to increase production capacities
  - develop immune effector therapy further to improve efficacy and reduce relapses