ANKARA YILDIRIM BEYAZIT UNIVERSITY
AYBU

The clinical use and (near) future use of the CAR T-cells in Asia and Middle East

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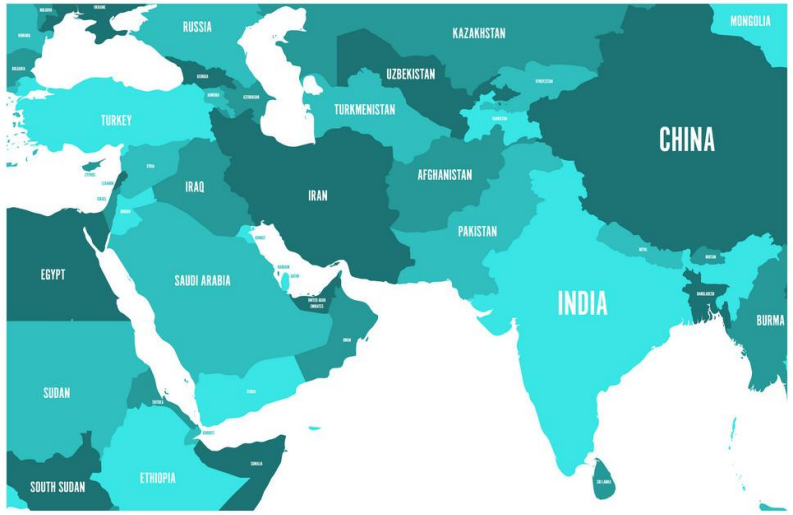
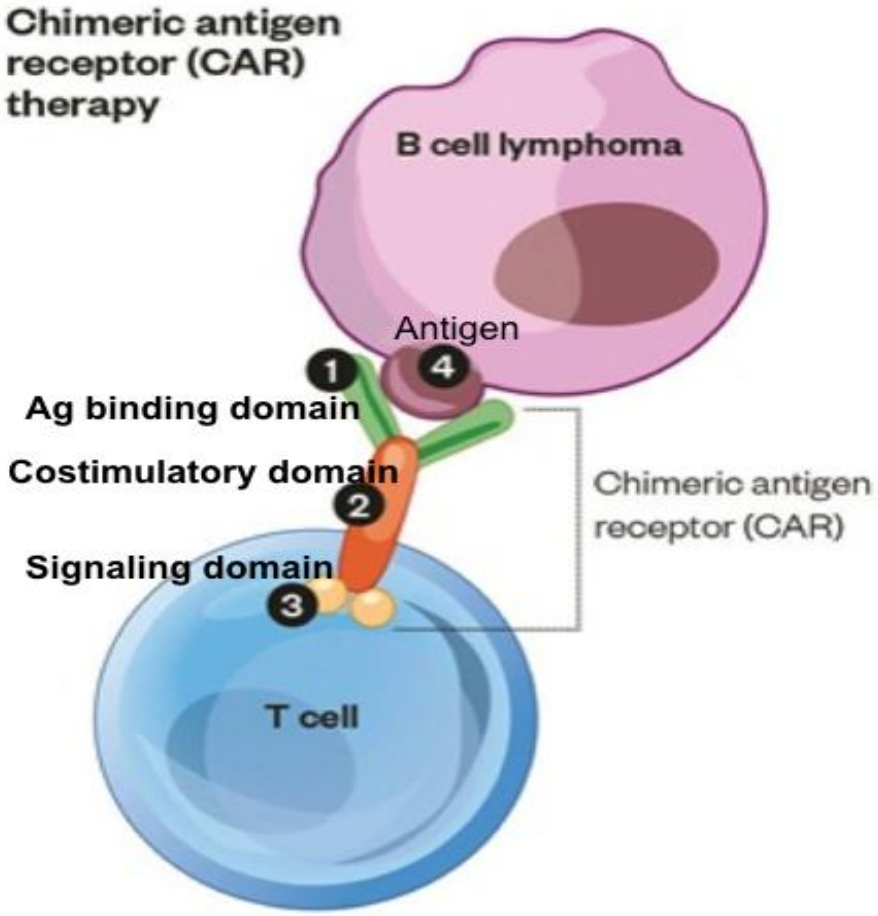


ASFA
American Society for Apheresis

14 May 2019, Portland/USA

Chimeric Antigen Receptor - CAR T-cells

- CARs are genetically engineered artificial T-cell receptors.
  - redirect T-cells and
  - enhance their recognition of tumor antigens.
- Theoretically these modified cells could be directed against any antigens and
  - have an increased capability to kill target tumor cells.
- This procedure is actually an individualized treatment method.

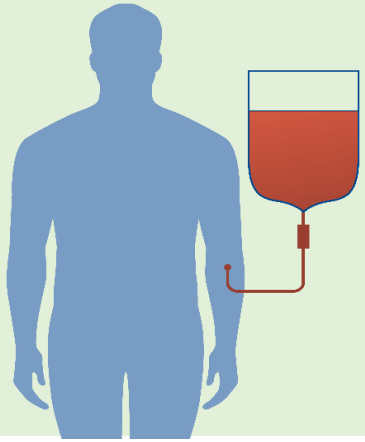


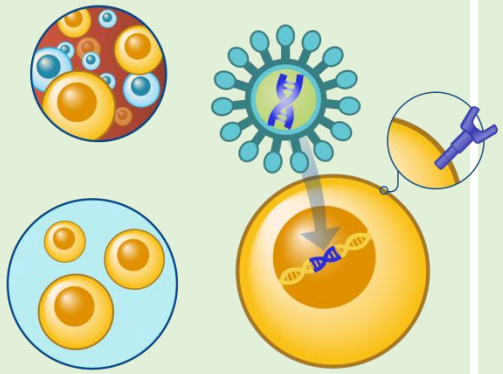
Maus MV, et al. *The Oncologist*. 2016;21:608–617

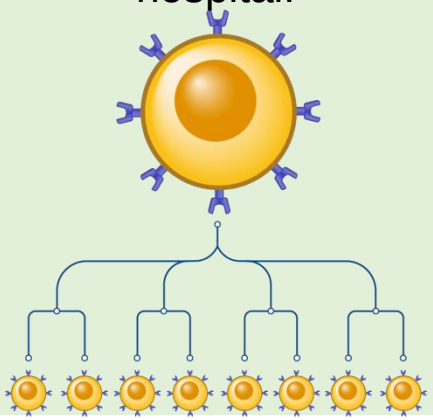
Pule, M; Finney H; Lawson A. "Artificial T-cell receptors". Cytotherapy 2003, 5 (3): 211-26. Barrett DM, Singh N, Porter DL, Grupp SA, June CH. Chimeric antigen receptor therapy for cancer. Annual review of medicine. 2014; 65:333-347. June CH, Maus MV, Plesa G, et al. Engineered T cells for cancer therapy. Cancer Immunol Immunother. Cancer Immunol Immunother. 2014 Sep; 63(9):969-75. Maus MV, Grupp SA, Porter DL, June CH. Antibody-modified T cells: CARs take the front seat for hematologic malignancies. Blood. Apr 24 2014; 123(17):2625-2635.

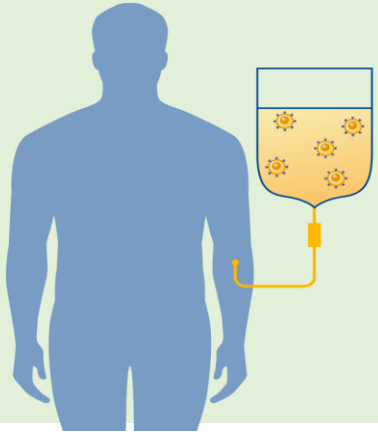
Manufacturing and Delivery of CAR T-cells
Overview

LEUKAPHERESIS	CAR T CREATION	CAR T EXPANSION	CAR T INFUSION	MONITORING
Peripheral Blood Mononuclear Cells are collected via standard leukapheresis and transported to a manufacturing facility.	T cells are activated. CAR-encoding genetic material is transferred via lentiviral vector into T-cell DNA.	CAR T cells are expanded to therapeutic dose, formulated and cryopreserved. QC/QA testing and release. Shipment of treatment back to hospital.	CAR T cells are infused into patient following lymphodepletion. CAR T cells target antigens on tumours and destroy the cells.	Patient is closely monitored after CAR T cells infusion with a long term follow-up plan.









PBMCs: peripheral blood mononuclear cells; QC: quality control; QA: quality assurance

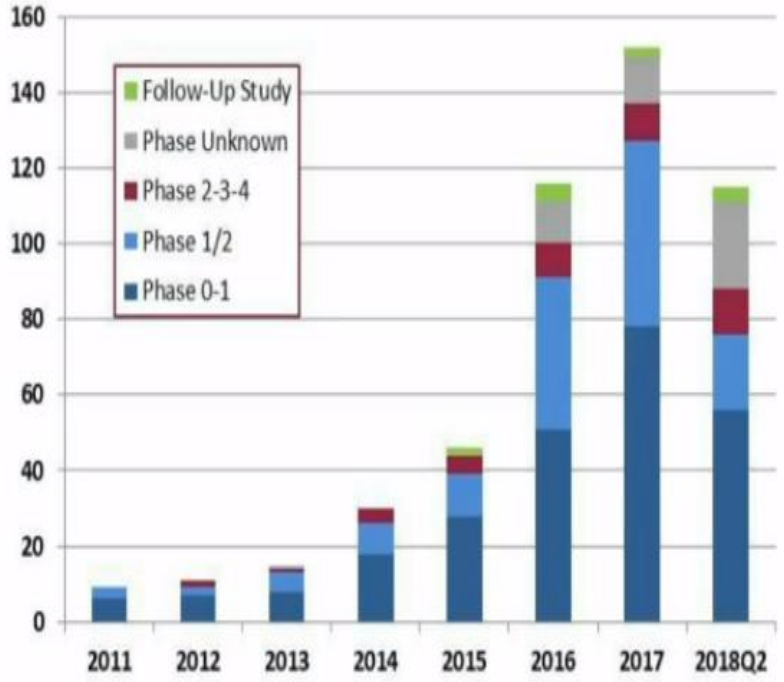
Adapted from Mato A, et al. *Blood*. 2015;126:478-485. Davila ML, et al. *Oncoimmunology*. 2012;1:1577-1583. Davila ML, et al. *Int J Hematol*. 2014;99:361-371. Tumaini B, et al. *Cytotherapy*. 2013;15:1406-1415.

CLINICAL USE

The Clinical Use of the CAR T-cells
Clinical Trials

- Clinical trial activity increased dramatically in 2016 and continues at a rate of nearly **100** new trial registrations each year.
- In the United States alone, over **1000** patients have now received CAR T-cells, and several open studies are looking at the long-term effects in responders.
- In the EU, **351** patients have received CAR T-cells (93% clinical trials) since 2018.

CAR T Cell Trials: world wide

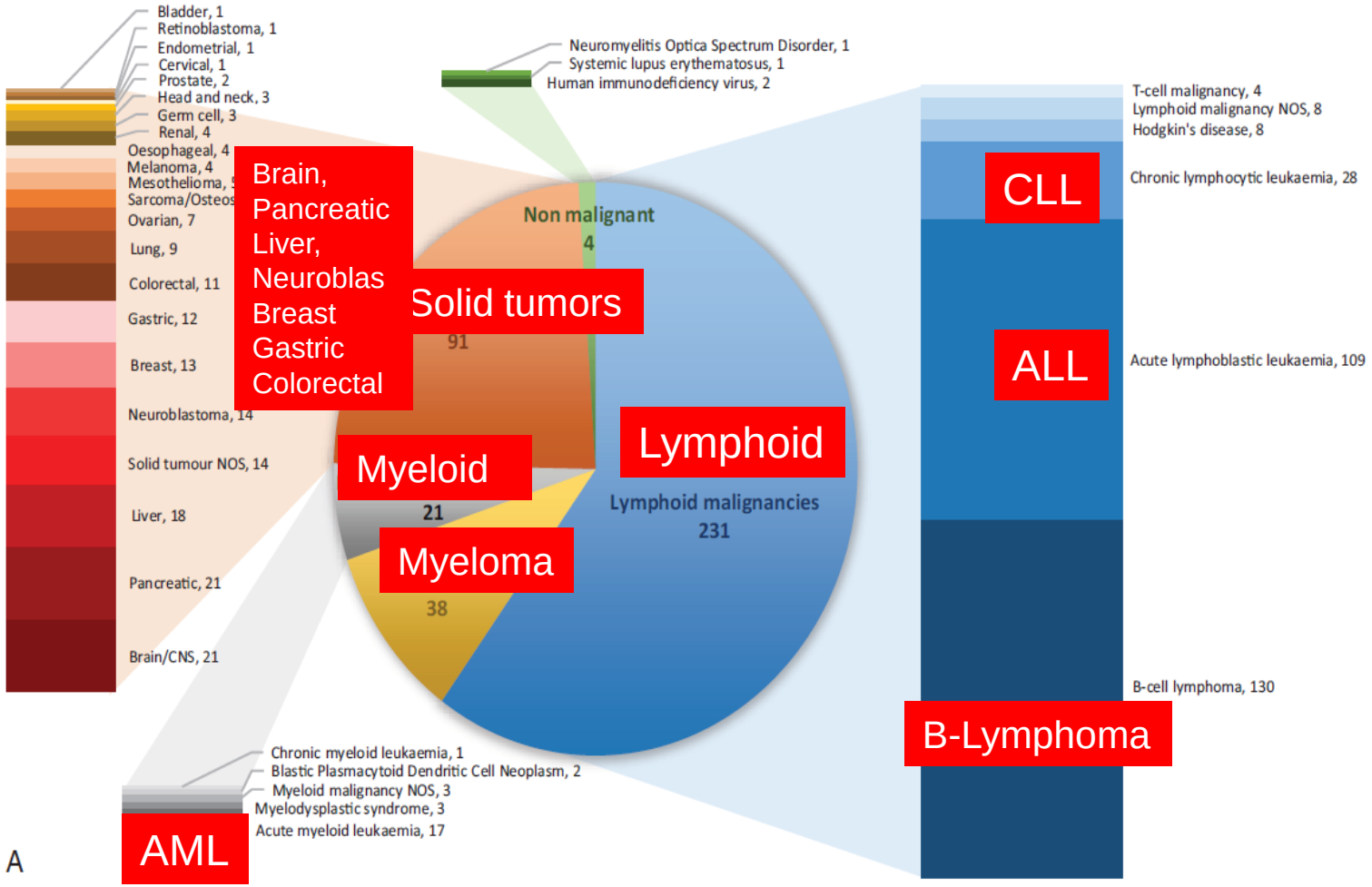


https://celltrials.org/

A graph of CAR-Immunotherapy trial numbers and phase versus time shows the explosion of CAR-Immunotherapy trials since 2014 and the appearance of follow-up studies since 2015. There were 115 new CAR-Immunotherapy trials registered worldwide during the first half of 2018, and 41% of them were not registered in ClinicalTrials.gov. Comparing them to the 152 trials in 2017, we see there is 51% increase in number of trials versus half of last year, and the number of late phase trials is on track to double.

The Clinical Use of the CAR T-cells
Indications in clinical trials

1. **Lymphoid malignancies**
   - Acute Lymphoblastic Leukemia
   - Lymphomas
     - DLBCL, FL, MCL
   - Chronic Lymphocytic Leukemia
2. Solid Tumors
   - Brain, Pancreatic, Liver, Breast, etc
3. Multiple Myeloma
4. Myeloid malignancies
   - AML/MDS



Charrot S, Hallam S. CAR-T Cells: Future Perspectives. HemaSphere, 2019;00:00–00. Boyiadzis et al. Journal for ImmunoTherapy of Cancer (2018) 6:137

CHALLENGES

Challenges for the Clinical Use of CAR T-cells

CAR T-cell Centers in EUROPE

SURVEY RESULTS

134 responses

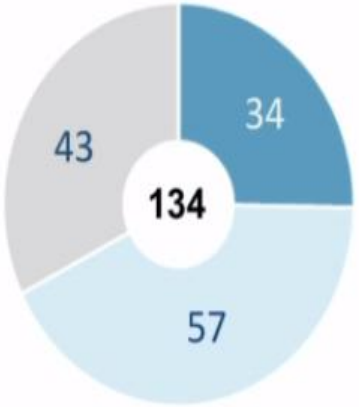
22 countries

351 patients

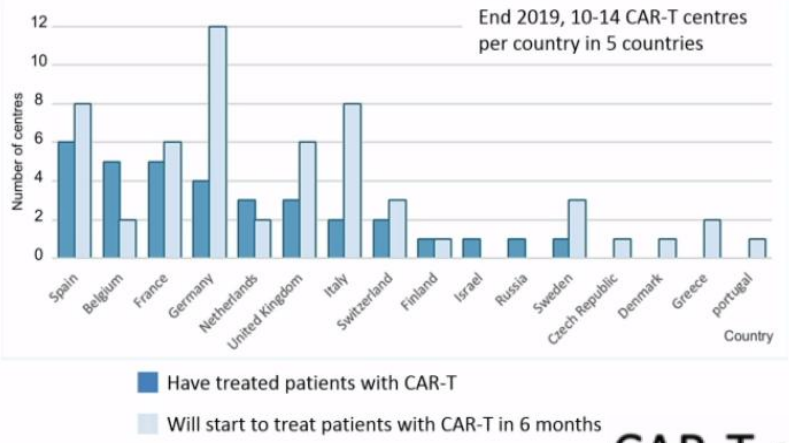
(93% Clinical Trials

Has your centre treated patients with CAR-T cells?

- Yes
- No, but we will start treating patients with CAR-Ts during the next 6 months
- No



European Centres CAR-T

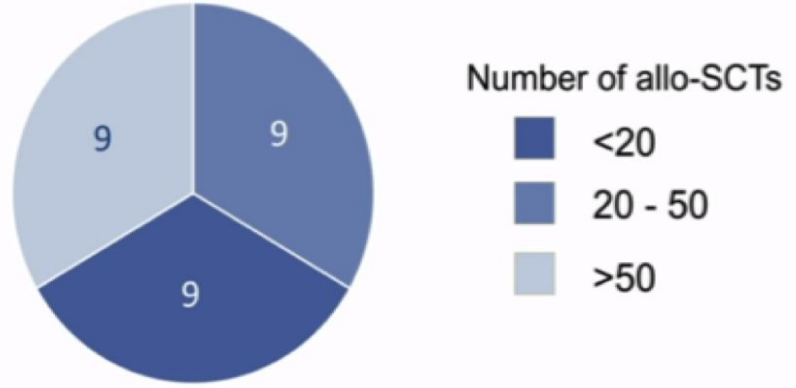


Patient characteristics N=351

	Frequency (%)
Age	
Pediatric (<18 years)	37%
Adult (≥18 years)	63%
Type of disease	
Acute lymphocytic leukemia	42%
Non-Hodgkin Lymphoma	34%
Multiple myeloma	5%
Chronic lymphocytic leukemia	1%
Other (e.g. solid tumor/AML)	6%

CAR-T centres performing Allo-SCT

27 of 34 centres performed allo-SCTs in 2018



Ispizua U. An EBMT survey on CAR-T cell activity in Europe, on behalf of the Cellular Therapy & Immunobiology Working Party

Challenges for the Clinical Use of CAR T-cells

Difficulties - World

- Although there are important advances in modified T-cell treatment in hematological malignancies, there are also some difficulties to overcome.

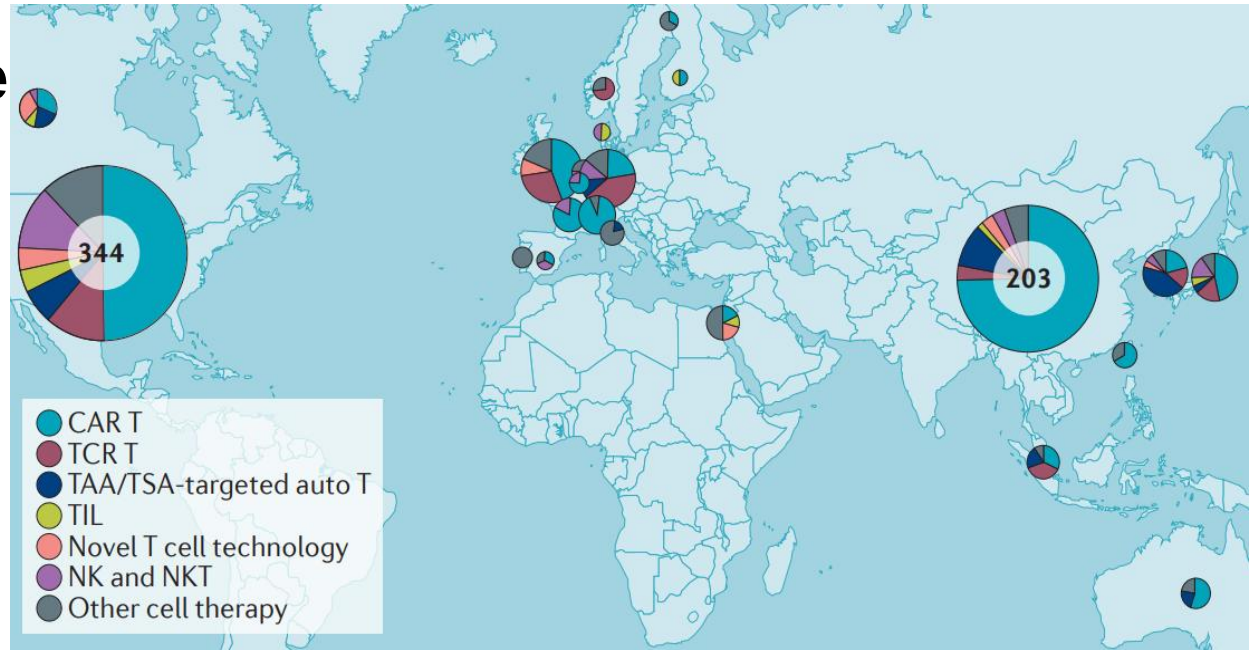
1. First, this treatment method **should be accessible widely** in order to allow more patients benefiting from this promising therapy (**Availability**).
2. Secondly, there is a **need for guidelines** about the value of this treatment modality (**Guidelines**).
3. Thirdly, since this treatment is relatively new, **the all medical team members** dealing with this treatment **should be adequately trained (Education)**.
4. Fourthly, more clinical **research should be performed** in order to decrease the toxicities of this treatment and increase its effectiveness in the future (**Clinical Trial**).

Maude SL. CD19-targeted CAR T-cell therapy for ALL. Blood 2015;125(26):4017-23. ASCO: Clinical Cancer Advances 2018. Available at www.asco.org/research-progress/reports-studies/clinical--cancer-advances-2018/advance-year. Accessed April 5, 2018.

Challenges for the Clinical Use of CAR T-cells
Difficulties - Asia and Middle East

From a feasibility perspective, in the Asia and Middle East, some challenges can be expected.

1. **Lack of cellular therapy experience**
2. **Lack of clinical trial experience**
3. **Lack of trained staff**
4. **Regulatory challenges**
5. **Logistic challenges**
6. **Financial challenges**

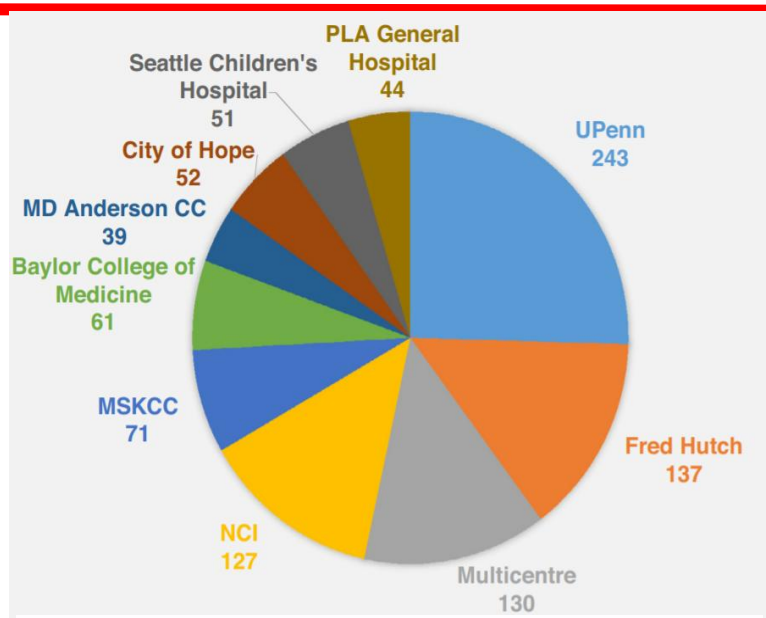


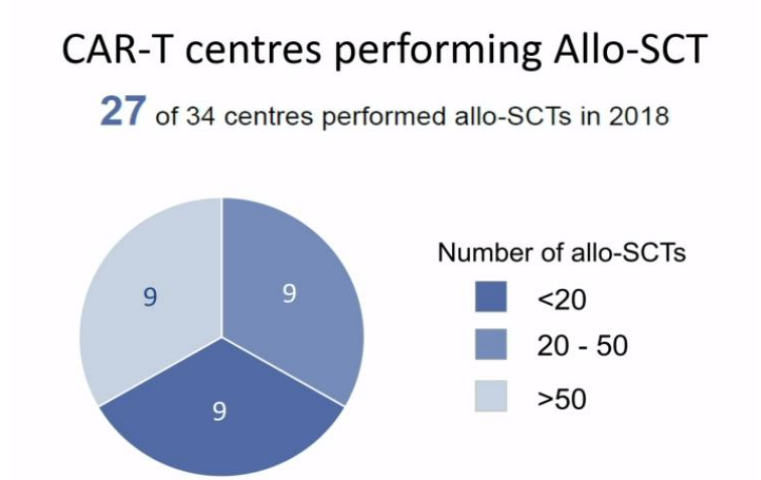
https://www.businesswire.com/news/home/20181120005377/en/Global-CAR-Cell-Therapy-Market-Opportunity-Clinical

Challenges for the Clinical Use of CAR T-cells

Feasibility in SCT Centers

- **SCT centers** are feasible options for clinical use as in the US and EU.
- From the feasibility perspective, I do not foresee any major challenges to CAR T-cell therapy especially in **Turkey, Israel, Iran** since:
  - Conceptually, CAR T-cell therapy is fairly similar to what we have been doing in SCT.
  - They have the accreditation, expertise, health professional teams, and infrastructure to perform the therapy safely and effectively.
  - They have all the quality processes, basic physical and organizational structures and facilities to make it happen.
    - Easily recognize complications and deal with them appropriately.





Philipp Vormittag , Rebecca Gunn , Sara Ghorashian and Farlan S Veraitch. A guide to manufacturing CAR T cell therapies. Current Opinion in Biotechnology 2018, 53:164–181. Ispizua U. An EBMT survey on CAR-T cell activity in Europe, on behalf of the Cellular Therapy & Immunobiology Working Party

Take Home Message - Centers

- CAR T-cell centers:
  - We have enough number of transplant centers in Turkey (90 SCT centers).
    - 45% out of them perform allo-SCT.
    - 3 of them have JACIE accreditation.
    - All have accreditation by The Ministry of Health Accreditation Institute.
  - In the EU & US, CAR T-cell treatment is likely to be restricted to a small number of clinical centers, thus most likely patients will need to travel.
  - In summary, I think we will see a spread of these products over the next ten years, and they will become more common.

Challenges for the Clinical Use of CAR T-cells

Accreditation of CAR T-cell Centers

- **Extra accreditation is required if cell therapies will be applied outside of the SCT centers.**
  - Local health authorities must be key for the safe and effective delivery of CAR T-cell therapy.
  - National and/or international institutions (i.e. FACT/JACIE) should define standards for cell therapy centers to become accredited to deliver CAR T-cells specifically.
  - Its initiative is critical to be able to broaden the applicability of these sorts of cell therapies outside of the major SCT centers.
    - SCT centers might be accredited by national and/or international authorities for the additional cell therapy portion of the standards.
- CAR T-cell centers have to have SOP, dealing with all kinds of things, including admitting patients to send to the emergency room, if required, recognizing CRS, and having ICU care.

Maus MV, Nikiforow S: The why, what, and how of the new FACT standards for immune effector cells. J Immunother Cancer 5:36, 2017

Challenges for the Clinical Use of CAR T-cells

Lack of cellular therapy experience

1

- Nations such as Uzbekistan, Saudi Arabia and Qatar have founded nascent SCT programs while **Turkey, Israel and Iran** are more established in the stem cell field.
- Central Asia & Middle East seem to **be highly lacking in number of stem cell transplant centers**.
  - First dedicated stem cell treatment centre was opened in Tashkent just in 2014 in Central Asia.
  - First dedicated stem cell treatment Centre was opened in Dubai just in 2018 in Middle East.

Table 1 Overview of stem cell research in the Greater Middle East (GME)

	Country	% Total Articles	Article Count	Model Organism (%)	Developmental Stage (%)
Primary Nations	Israel	57.8	440	•Human: 58.1 •Murine: 37.7 •Other: 4.2	•Adult: 57.0 •Embryonic/Fetal: 23.0 •Post-Natal/Cord Blood: 20.0
	Turkey	23.1	176	•Human: 90.1 •Murine: 9.9 •Other: 0.0	•Adult: 88.1 •Embryonic/Fetal: 7.4 •Post-Natal/Cord Blood: 4.5
	Iran	11.7	89	•Human: 47.2 •Murine: 47.2 •Other: 5.6	•Adult: 65.2 •Embryonic/Fetal: 28.1 •Post-Natal/Cord Blood: 6.7
Remainder of Published Nations	Saudi Arabia	2.5	19	•Human: 75.9 •Murine: 17.2 •Other: 6.9	•Adult: 89.5 •Embryonic/Fetal: 1.8 •Post-Natal/Cord Blood: 8.8
	Egypt	1.6	12		
	UAE	0.8	6		
	Pakistan	0.7	5		
	Lebanon	0.5	4		
	Tunisia	0.5	4		
	Kuwait	0.4	3		
	Morocco	0.3	2		
	Jordan	0.1	1		
TOTAL		100	761	•Human: 65.3 •Murine: 31.1 •Other: 3.6	•Adult: 67.2 •Embryonic/Fetal: 18.6 •Post-Natal/Cord Blood: 14.3

Surveyed nations without stem cell research publications were: Afghanistan, Algeria, Bahrain, Djibouti, Iraq, Libya, Mauritania, Oman, Palestine, Qatar, Somalia, Sudan, Syria, Yemen.

- >90% of stem cell research is performed in Israel, Turkey and Iran.

https://www.bakerinstitute.org/media/files/Research/2d211a80/ST-Pub-StemCell-ME-May2010.pdf

https://www.bakerinstitute.org/media/files/Research/2d211a80/ST-Pub-StemCell-ME-May2010.pdf https://www.middleeastmedicalportal.com/regenerative-medicine-in-the-middle-east/

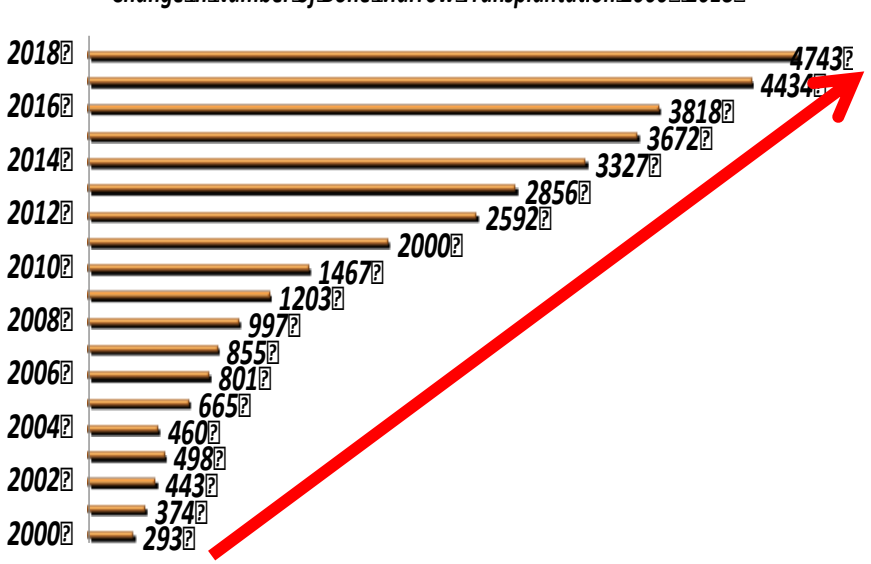
Altuntas, et al. First hematopoietic cell transplantation in Uzbekistan: Progress through education and cooperation. Trans & Apher Sci 2016; 54(1):60-2.

Challenges for the Clinical Use of CAR T-cells

Ongoing Increase in Transplant Rates in TURKEY

- Particularly, the **last decade** witnessed a remarkable increase in SCT activity in Turkey.
- As of 2018, **4743** SCTs (**997 pediatric** and **3746 adult)** were performed in Turkey.
  - **Transplant rates** per 10 million inhabitants were **592**.
  - **There were 90 SCT centers (57 adult & 33 pediatric centers)**.
- Total SCT procedures in Turkey increased **177%** in the last 5 years and **791%** in the last 10 years.

HSCT 2018	Auto	Allo	MSD	MUD	HAPLO	Cord	Total
Adult	2316	1430	853	429	148	1	3746
Pediatric	126	871	454	343	73	38	997
Total	2442	2301	1307	772	221	39	4743



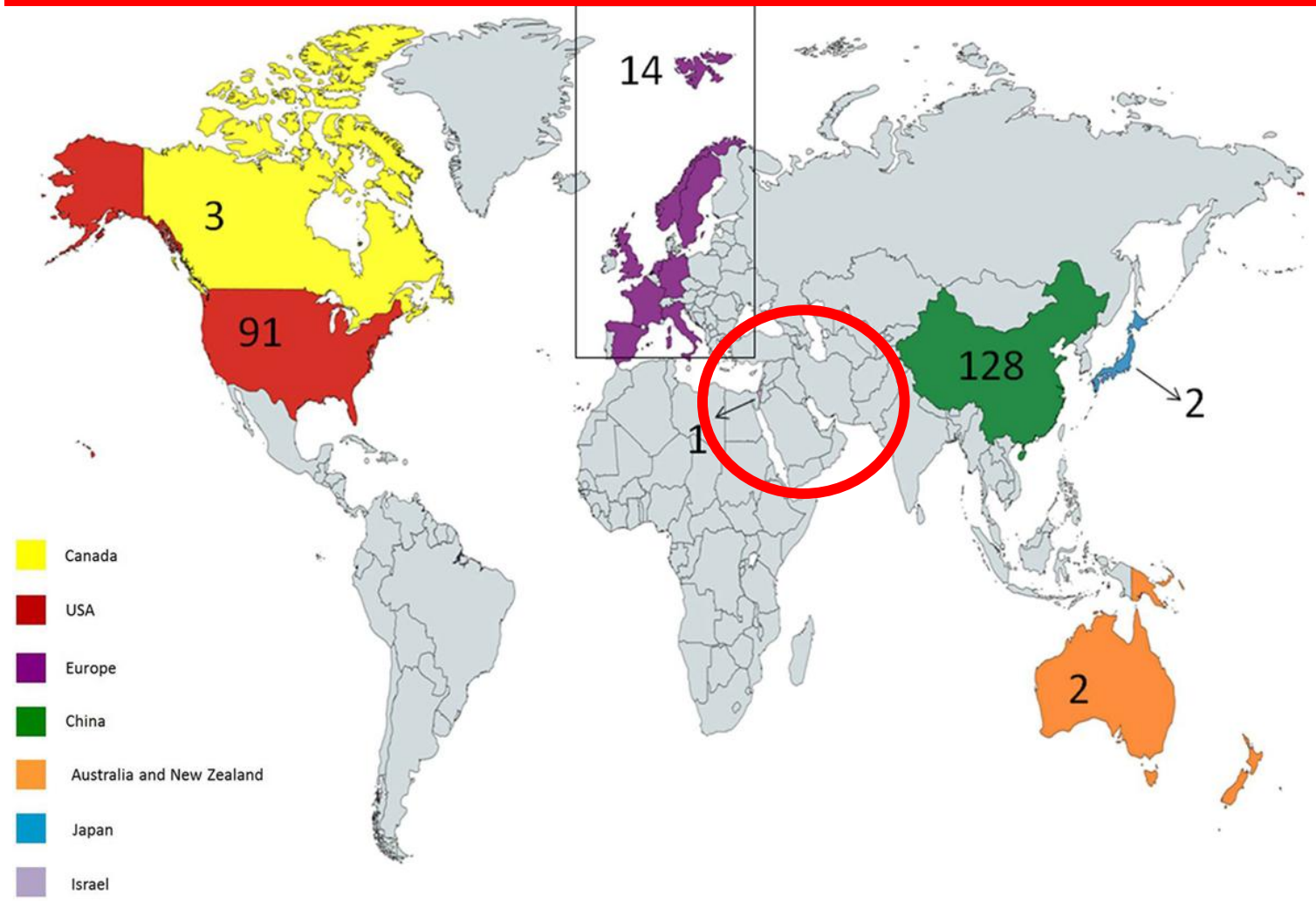
Altuntas F, et al. Hematopoietic cell transplantation activity of Turkey in 2014: ongoing increase in HCT rates. Trans & Apher Sci 2016;54(1):53-9

Take Home Message - Experience

- Experience:
  - We have an advanced experience on stem cell therapies. However, we have no CAR T-cell therapy experience.
  - We perform more than 4700 SCTs annually, which are more than 2300 allo-SCTs per year.
  - CAR T-cell therapy is fairly similar to that we have done in BMT.
  - Therefore, we are ready to have experience CAR T cell therapy at the clinical trials.

Lack of clinical trial experience

Geographical distribution of ongoing CAR T-cell therapy clinical trials for cancer



Most of the clinical trials are conducted in the US, China, Europe.

Middle East and Central Asia are unlucky in terms of clinical study which is a deficit for near future use of CAR T-cells.

Elahi R et al. Front Immunol. 2018;9:1717

Challenges for the Clinical Use of CAR T-cells

Lack of trained staff & guidelines

3

- Education and training have critical importance for clinical use of CAR-T cells.
- All team members dealing with this treatment **should be adequately trained**.
- Guidelines and algorithms should be created for this novel therapy.
  - Algorithms will be key to optimize the effectiveness and safety of CAR T-cell therapy.
  - Guidelines are required for monitoring, grading and managing of toxicities.
  - Medical teams need to know how to monitor these patients for recurrence or relapse.
  - We should work on how to educate medical teams and what the right algorithm is for treating these patients.
- Lack of trained staff is one of the main challenges for the implementation of CAR T -cell treatment in these regions.

Altuntas, et al. First hematopoietic cell transplantation in Uzbekistan: Progress through education and cooperation. Trans & Apher Sci 2016; 54(1):60-2.
ASCO: Clinical Cancer Advances 2018. Available at www.asco.org/research-progress/reports-studies/clinical--cancer-advances-2018/advance-year. Accessed April 5, 2018.

Take Home Message - Education

- Education:
  - We have enough trained staff to perform the cellular therapy safely and effectively.
  - It’s not just about giving the right cells to right patient, but having the right facilities and staff available to administer the therapy and deal with the side effects.
  - The most important aspect is to have the right treatment for the right patient at the right time in an affordable way due to limited financial resources.

Challenges for the Clinical Use of CAR T-cells
Regulatory challenges

- In the majority of the region, there is no legal framework regulating stem cell research.
- In the Medial East, only **Israel and Turkey** have recognized national stem cell policies.
- Regulations governing regenerative medicine and cellular therapies are primarily led by US FDA and European Agencies such as Human Tissue Authority, **European Union Directives** in the Middle East region.
- Human cells are currently regulated as biologics and every country should provide their own guidelines and regulations.

https://www.bakerinstitute.org/media/files/Research/2d211a80/ST-Pub-StemCell-ME-May2010.pdf

Take Home Message - Legislation

- Legislation:
  - We have rules and regulations regarding SCT but we also need to have them for cellular therapy.
  - We do not have any legal regulation for cellular therapy.
  - However, I am quite optimistic that our Ministry of Health will issue new regulations for this important therapy in the near future based on the EU directives.
    - There is no single regulatory pathway.
    - The patient's own cells are governed by the blood product and transplant legislation.
    - CAR T-cells are governed according to genetically modified organisms (GMO) legislation which need a facility with GMP certification as well as a license to handle genetically modified organisms.
  - In summary, CAR T-cells are governed by to advanced therapies regulations.

https://www.ema.europa.eu/en/documents/report/report-car-t-cell-therapy-registries-workshop_en.pdf
bit.ly/CW84_CARTCell-Revolution

Challenges for the Clinical Use of CAR T-cells

Availability - World

- Availability is another challenging issue for clinical use for CAR T-cell around the world.
- Two companies offer CD19 CAR T-cell therapy in all over the world:
  - They have a centralized manufacturing system.
    - requires the distribution of large numbers of patient-specific products around the world.
- The bigger question is whether
  - Such a centralized manufacturing strategy will continue to be the model (Pharmaceutical Model) or
  - These complex cell therapies will be manufactured using a GMP (SCT model):
    - Every treatment center may establish its own closed system; the patient's cells, vector, and cytokines are added, and 1 to 2 weeks later, ships the product.
- At the end of the day, there could be different models.

Take Home Message - Availability

- Availability:
  - Turkey would be reasonable country for the application of this therapy.
  - If CAR T-cell centers are established in Turkey:
    - bring advantageous & benefits for success rate of this therapy
    - save time and money
    - could be cost effective
- If availability is not solved, then every country will turn into closed systems.
  - Therefore, every center will produce it's own CAR T-cell product.

Debbie King (2017). FDA Approves First CAR T-Cell Therapy – The evolution of CAR T-Cell Therapy. (CAR T Cell Therapy Workflow) Retrieved from https://cellculturedish.com/fda-approves-first-car-t-cell-therapy-the-evolution-of-car-t-cell-therapy/
bit.ly/CW84_CARTCell-Revolution

Challenges for the Clinical Use of CAR T-cells
Logistic challenges

- From a feasibility perspective, any major challenges to CAR T-cell therapy may not be expected in the US or EU as they have practiced blood and marrow transplantation for several decades.
- However, in the Asia and Middle East, **feasibility and logistic challenges** can be expected.
  - Quality
  - Time
  - Experience
  - Patient management and follow-up

https://www.bakerinstitute.org/media/files/Research/2d211a80/ST-Pub-StemCell-ME-May2010.pdf

Financial challenges - World

- A major concern with CAR T-cell therapy is its financial toxicity.
  - Tisacel is priced at $475,000; Axicel at $373,000 per infusion.
  - The total cost of CAR T-cell therapy is likely to be higher:
    - Patients need examinations, an extensive workup, cell collection and processing, and hospitalization for several days.
- The bigger question is whether **insurance will pay for CAR T-cell therapy or not.**
- We need to work on the reimbursement policies around CAR T-cell therapy.
  - Manufacturers may need to think of a model of value or outcome-based pricing.
    - For example: Patients only pay if they respond by 1-3 months.
- Unfortunately, the majority of the region will not be lucky to have access to CAR T-cell therapy in the current conditions.

https://www.businesswire.com/news/home/20181120005377/en/Global-CAR-Cell-Therapy-Market-Opportunity-Clinical
https://www.ascopost.com/issues/may-25-2018/logistics-of-car-t-cell-therapy-in-real-world-practice/

Take Home Message - Finance

- Finance:
  - Unfortunately, we do not have enough financial sources for the use of CAR T-cell therapies without any guideline and algorithms.
  - In this context, what we need is to have the right treatment for the right patients at the right time.
  - In other words, we have limited financial sources, therefore, we need to find some reasonable solutions through collaboration.
  - The price will be crucial in determining whether CAR T-cell therapy will be used in more than a small group of patients.
  - The high costs will certainly **limit the patient access**.

bit.ly/ECL_CAR-T_cost

Take Home Message - Reimbursement

- There should be an affordable model for reimbursement agencies for payment regarding the therapy.
- We should adapt a new system of a model of value based-pricing for Turkey
  - A value or outcome-based pricing model suggests that a drug's price should correlate with the benefit it provides rather than the development costs.
- **Even if they are effective, the high price would be unsustainable in Turkey as well as Middle East and Asia.**
- I am pretty confident that there won't be any hospitals in Medial East & Asia which will be providing CAR T-cell therapy for patients.

FUTURE

Conclusion- Clinical use

- CAR T-cell treatment is effective and clearly feasible particularly in B-cell malignancies.
  - The main purpose is the cure of hematological malignancies.
  - There is still a need for improvement in terms of the durability and the efficacy of modified T-cells while decreasing the harm of treatment to normal healthy tissues.
- In the near future, CAR T-cell treatment may be an alternative to SCT, especially in patients who are not eligible for transplantation.
- More clinical researches are required in order to further understand the role of CAR T-cell treatment.
- Neurologic complications and solid tumor management require further research.

Conclusion- Feasibility

- SCT centers would likely to **provide the CAR T-cell therapies.**
  - Because, they are pretty successful in providing adequate access to patients who need a transplant for hematologic malignancies.
- **Reimbursement agency' stance** on CAR T-cell therapy will largely dictate its future.
  - If they pay, there will be a real push to commercialization for novel cell therapies.
  - If they don't pay, then some centers might develop products for their own patients.
- Results of allogeneic CD19-directed CAR T-cells in patients with r/r B-ALL are encouraging.
  - Allogeneic, off-the-shelf, CAR T-cells might reduce the production delay.
  - This area still remains unclear and more studies should be conducted.

Conclusion- Asia & Middle East

- In the Central Asia and Middle East, feasibility and logistic challenges can be expected.
- In the **majority** of the region, there is no legal framework regulating stem cell or cellular therapy research.
- In the Middle East, only Israel and Turkey have recognized national stem cell policies.
- Middle East seems to be highly lacking in number of stem cell transplant centers.
- In summary, financial problems, lack of trained staff and cellular treatment experiences are the main challenges for the implementation of CAR T-cell treatment in majority of the region.

17th

International Congress of World Apheresis Association

Looking forward to host you in Istanbul

April 16-19, 2020