EHA - Scientific meeting on recent advances in the pathogenesis and treatment of secondary acute myeloid leukemias

Uniklinikum Würzburg

Session 3: Special situations

Development of AML after CAR-T cell treatment

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eha

Medizinische Klinik und Poliklinik II
Direktor: Prof. Dr. H. Einsele

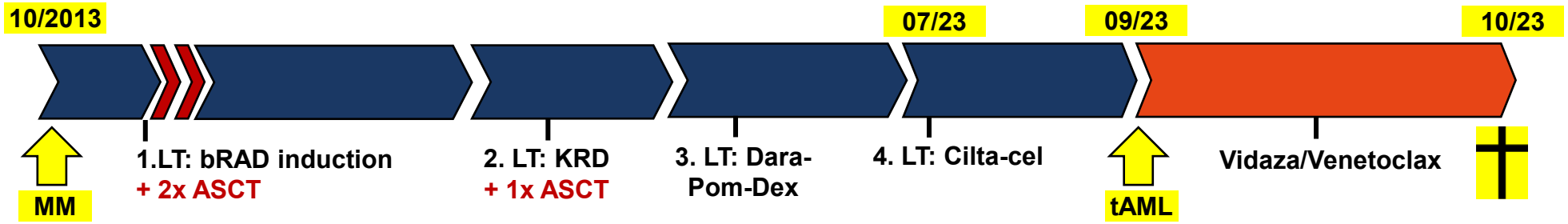
MEDIZINISCHE KLINIK UND POLIKLINIK II

Disclosures

- none

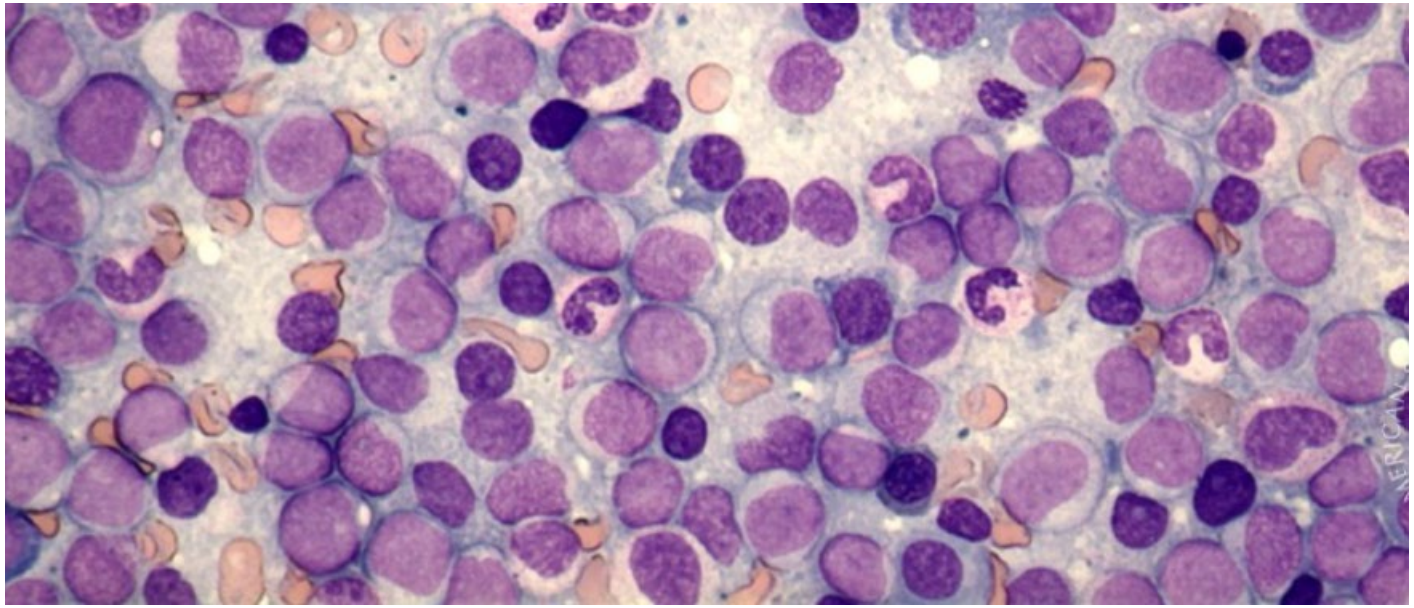
- Case report of a secondary primary malignancy after CAR-T cell treatment
- Incidences of SPM
- „Critical“ aspects in CAR-T cell manufacturing process
  - Clonal hematopoesis
- Prevention strategies
- Therapy of AML after CAR-T cell treatment
- T-cell malignancies

Case report



63 yr-old man, IgA kappa MM

Comorbidities:
- Struma multinodosa II°
- Axonal PNP
- Typ C gastritis
- BPS I°



https://imagebank.hematology.org/image/4172

Treatment consent form

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also trigger **non-infectious cystitis**. The urine may contain blood (**haemorrhagic cystitis**). However, this side-effect can be prevented with medication.

- Cyclophosphamide can also rarely cause allergic pneumonia (**pneumonitis**) or a build-up of water in the lung tissue (**pulmonary oedema**).

Possible delayed effects

- Years after chemotherapy, **another (new) cancer may develop**. The chances of reoccurrence depend, among other factors, on the type of disease present and the selected treatment method.

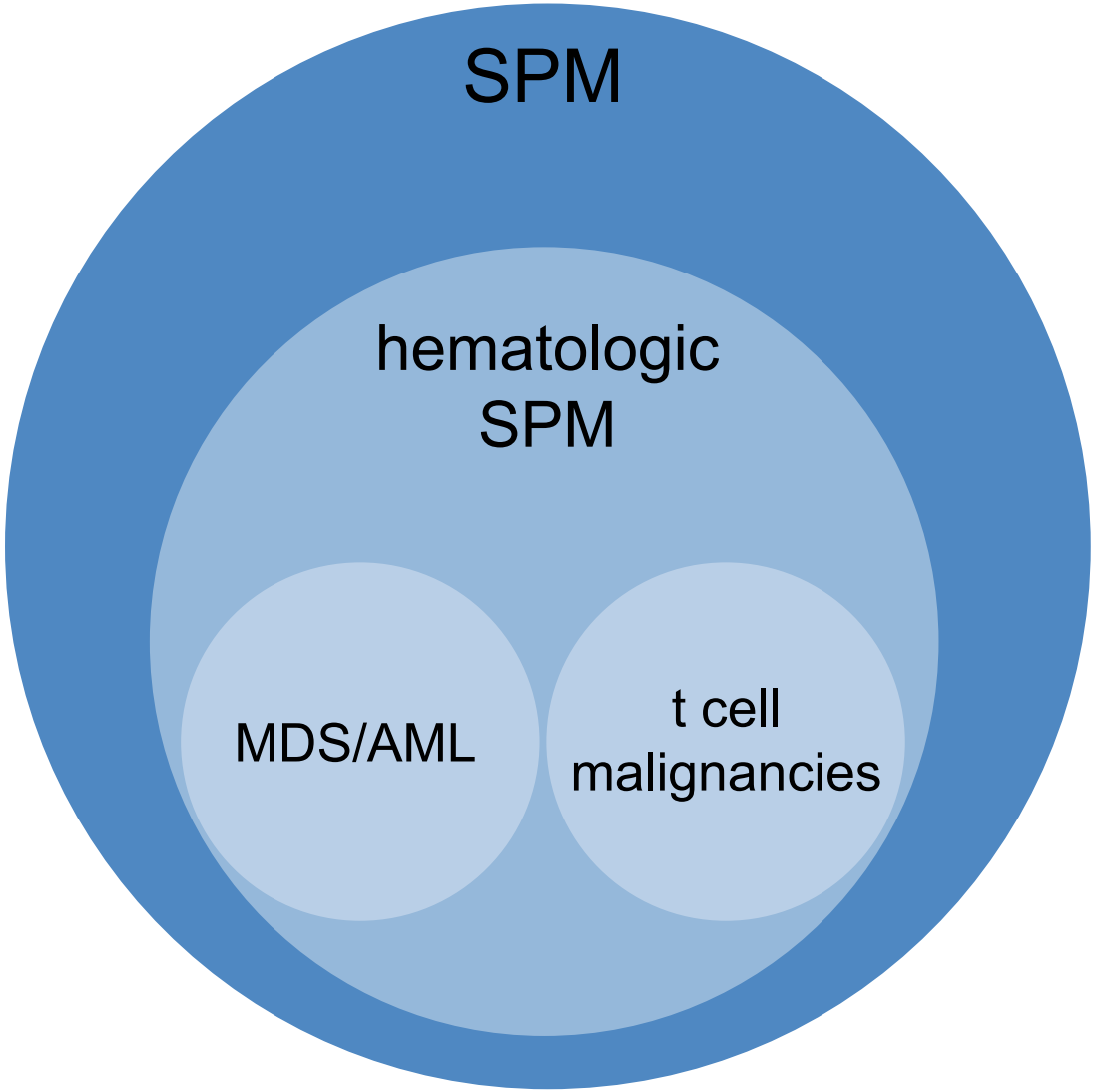
Side-effects of the CAR-T cell infusion

- The CAR-T cells are infused shortly after they are defrosted. Patients therefore generally feel the coolness of the infusion which often makes them shiver. This **slows their heart rate** which is not obvious to the patient in most cases and which resolves without

Definition

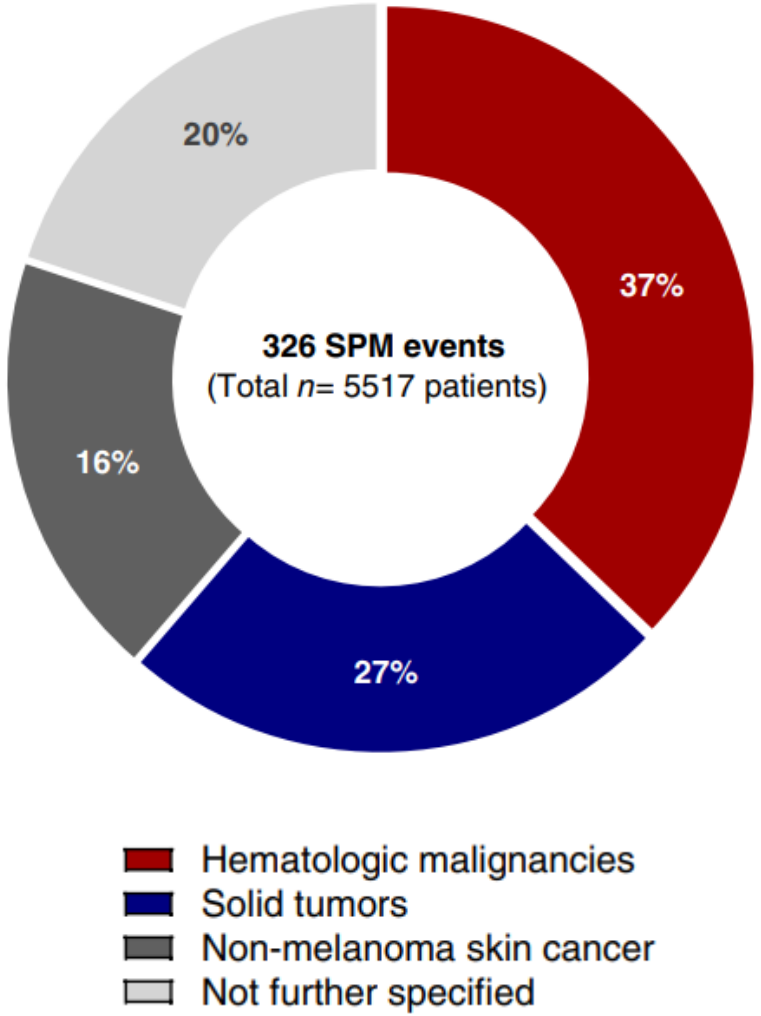
Secondary primary malignancies (SPM):

new, distinct cancer arising in addition to the first one



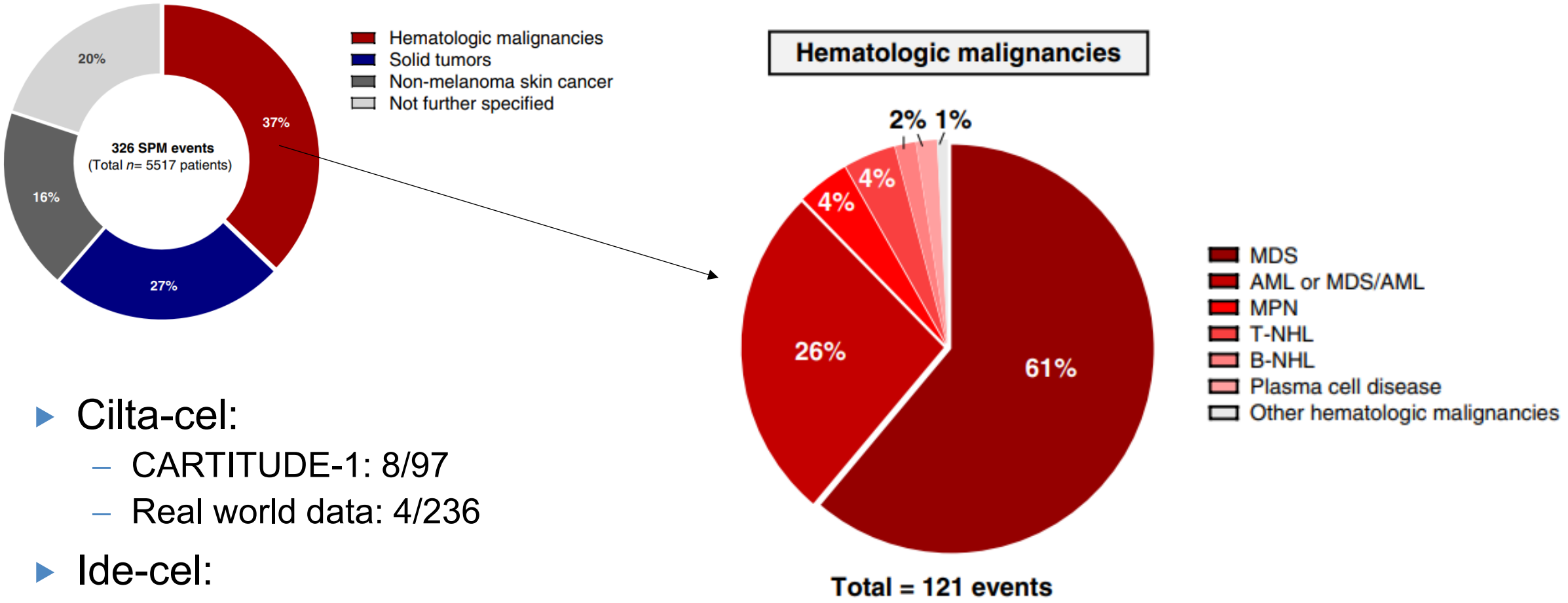
Secondary primary malignancies (SPM) after CARs

Clinical trials	4%-16%
RWE	2.2%-4.5%
Meta-analysis from 18 clinical trials and 7 real-world studies - median follow-up of 21.7 months	6.0%
Median time to **SPM**	9 months



Tix et al. Clin. Can Res. 2024
Bouziana S, Bouzianas D. Int J Mol Sci. 2024

Incidences of hematologic SPM after CAR-T



- Cilta-cel:
  - CARTITUDE-1: 8/97
  - Real world data: 4/236
- Ide-cel:
  - KarMMa-1: 2/62
  - Real world data: 6/350

Tix et al. Clin. Can Res. 2024
Martin et al. JCO. 2022

Hansen et al. JCO. 2025
Lin et al. Nat Med. 2023

CAR-T cell manufacturing

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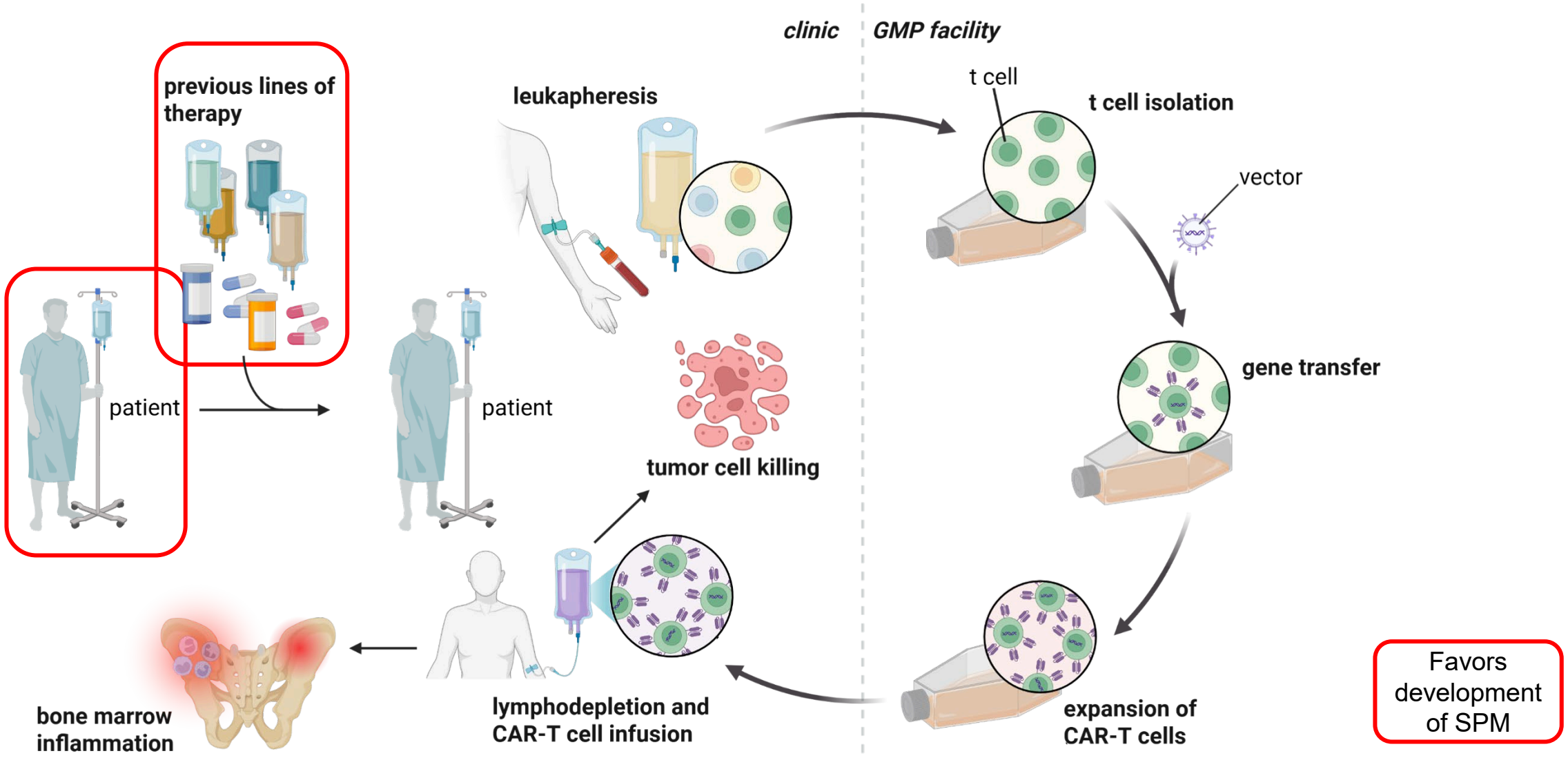
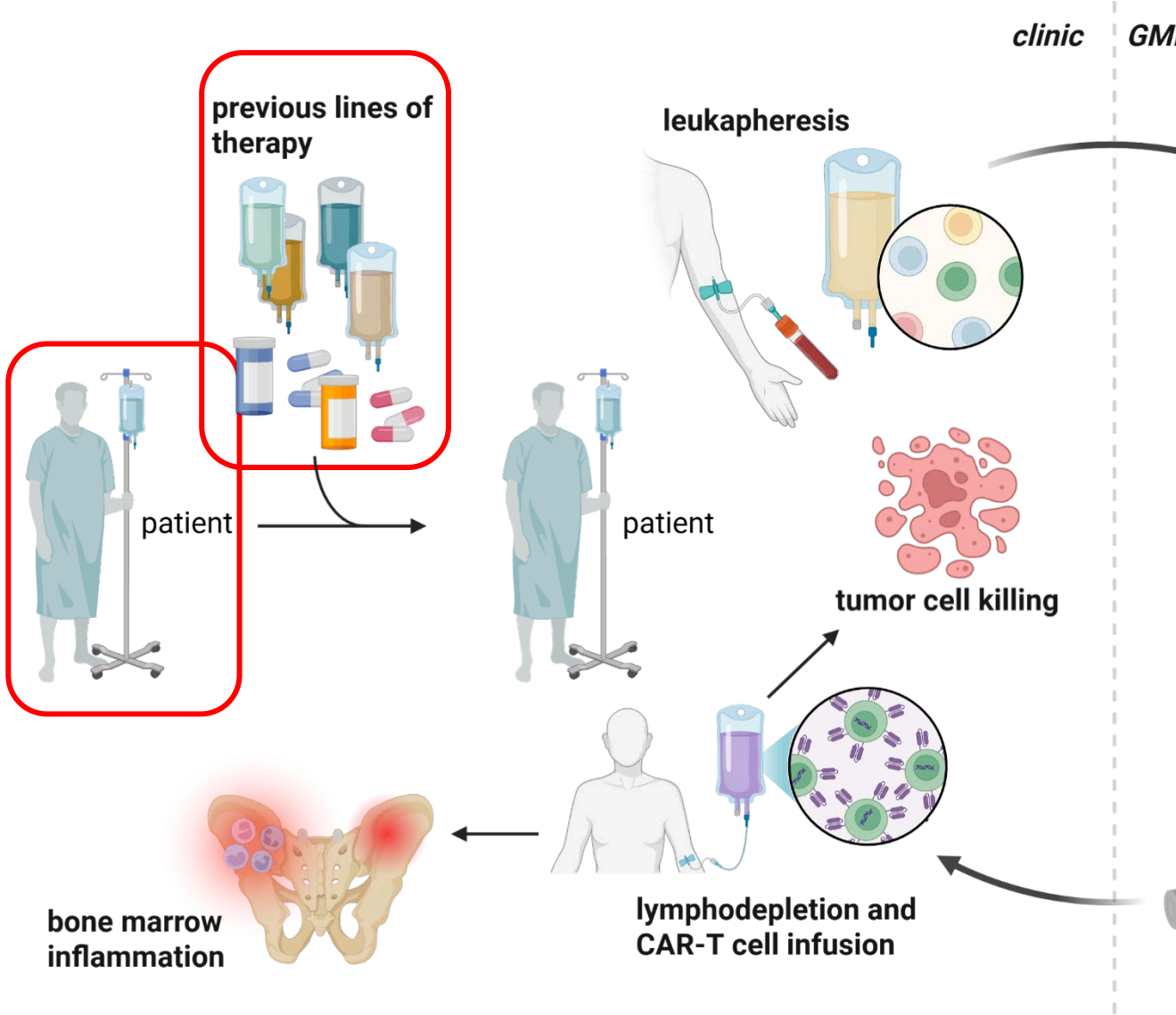


CAR-T cell manufacturing

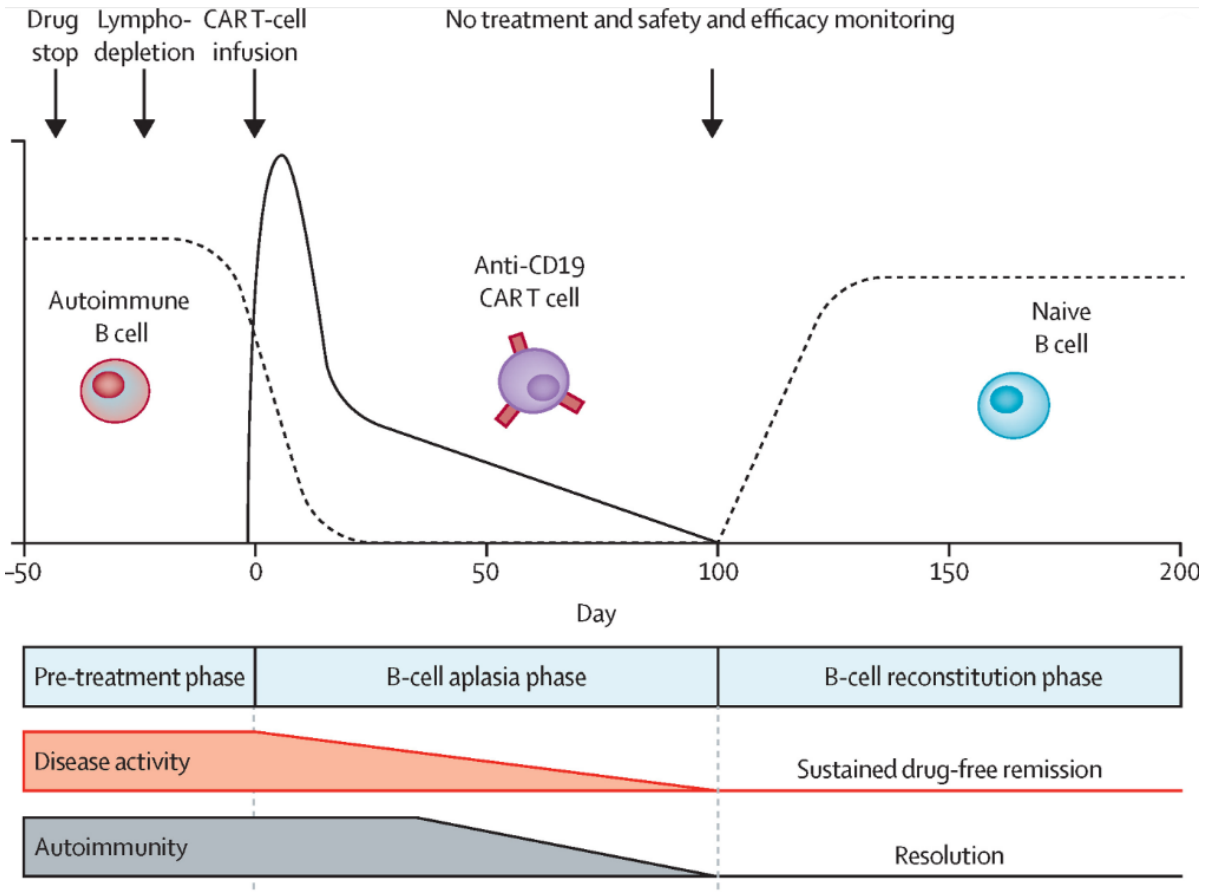
- Disease (subtype)
- Age
- Comorbidities
- Previous chemotherapy
- Previous radiotherapy



Are CAR-T cells the cause for SPM?

CAR-T cell therapy in autoimmune disease

- Aim: resetting immune system
- Advantages compared to malignancies:
  - No high amounts of chemotherapy in previous lines
  - Less T cell exhaustion
- No reports of SPMs in autoimmune disease so far
  - Short follow up
  - Only few cases



Schett et al. Lancet. 2023

CAR-T cell manufacturing

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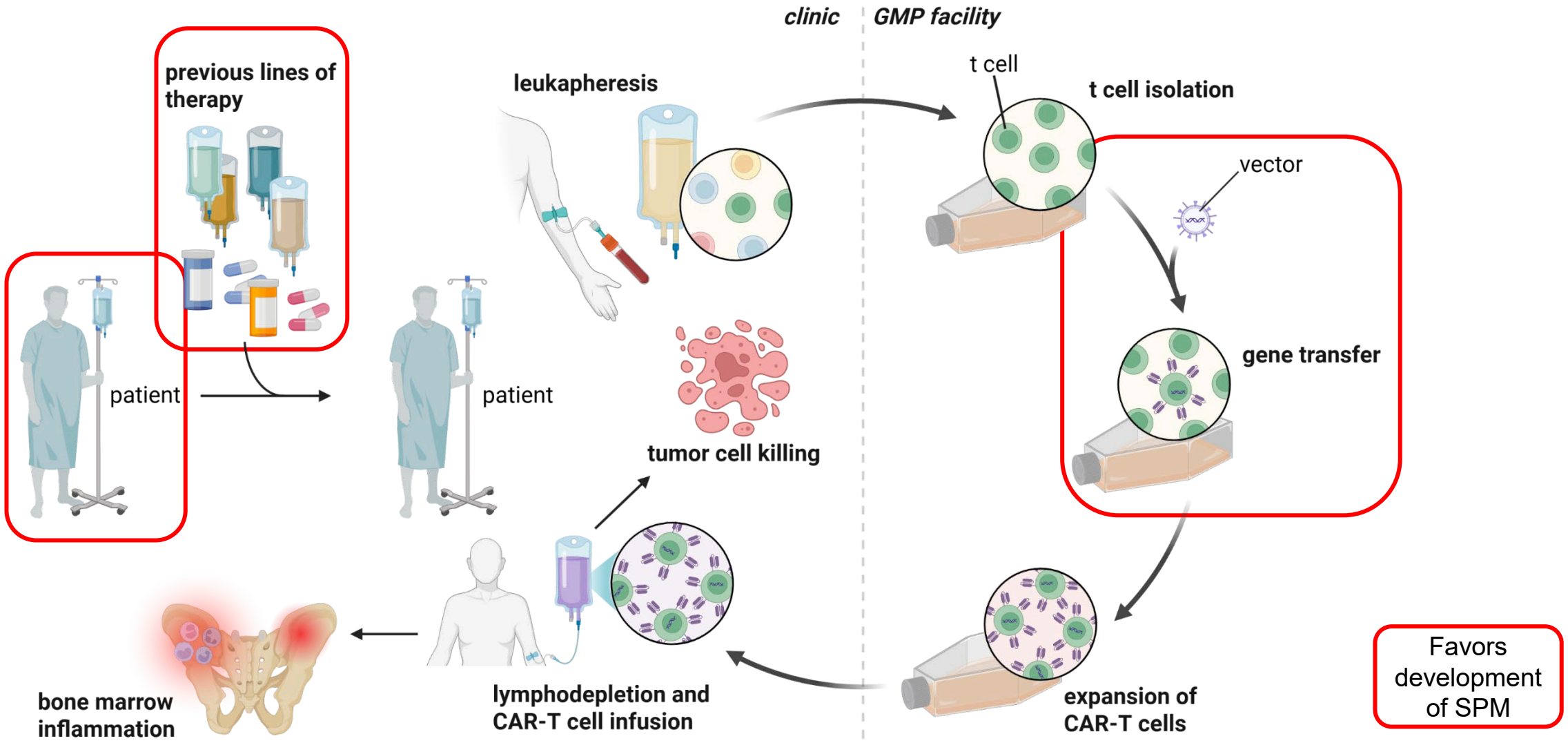

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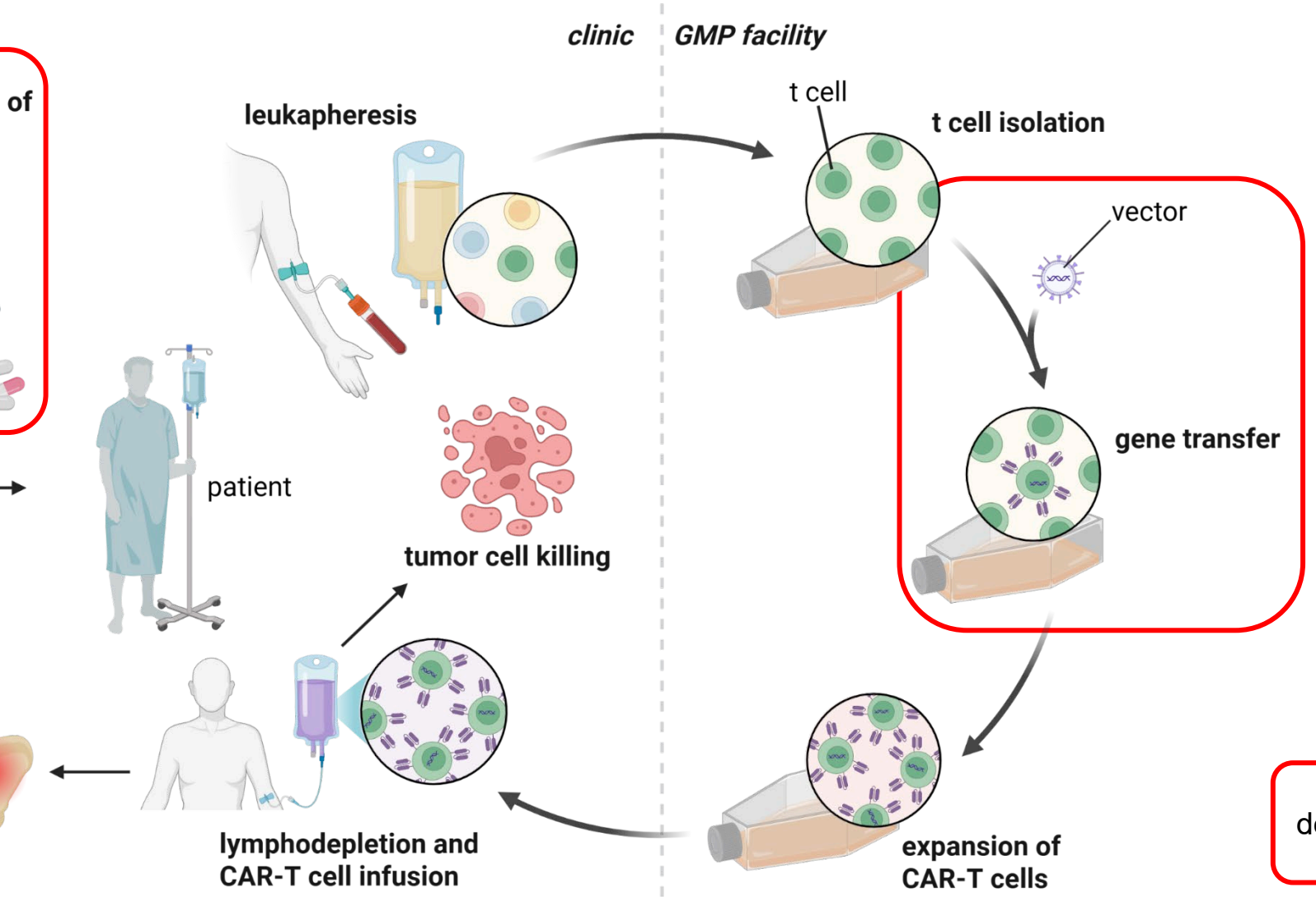
CAR-T cell manufacturing



- Retro-/lentiviral
- Vector copy number

Favors development of SPM

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CAR-T cell manufacturing

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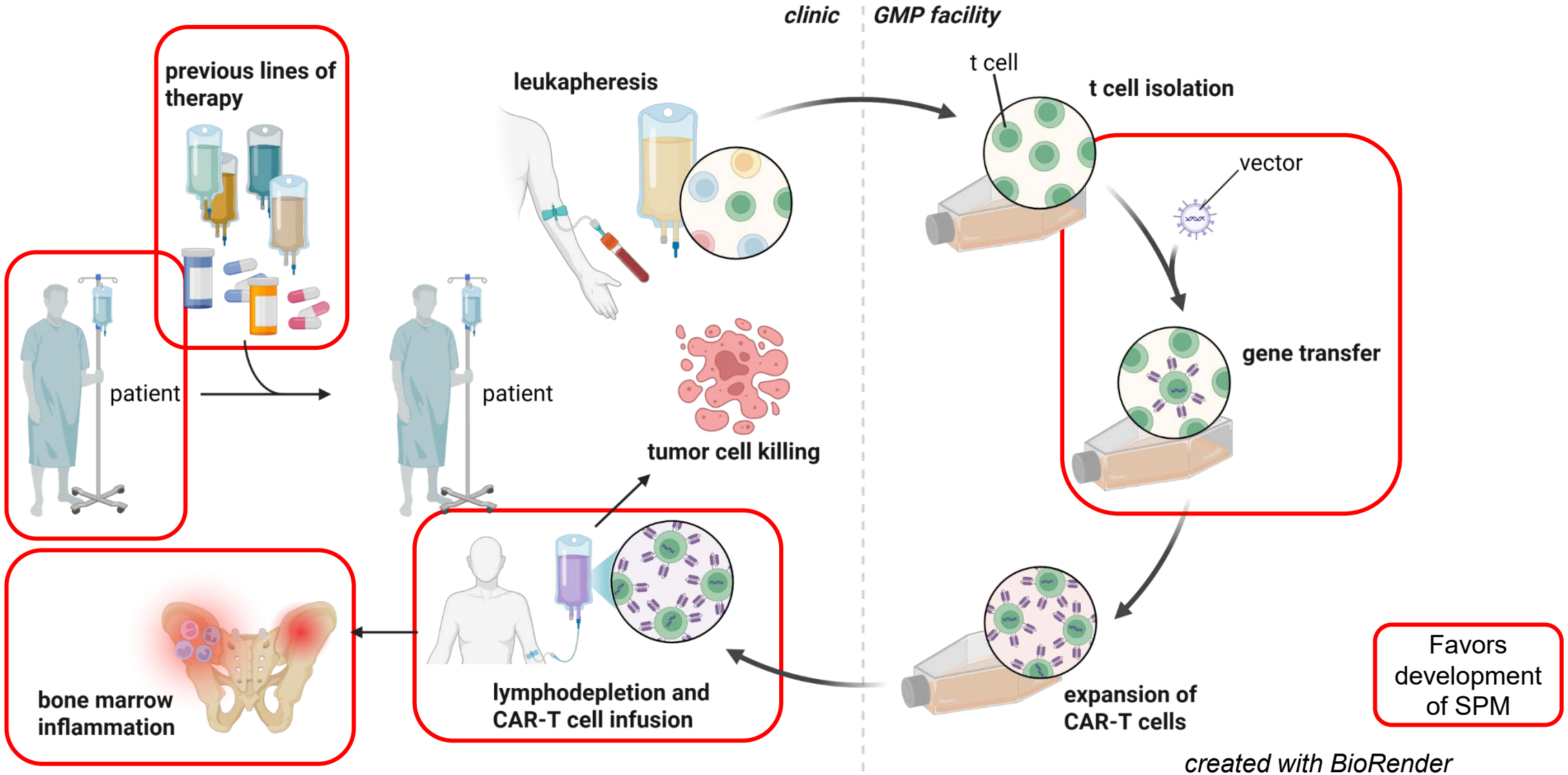

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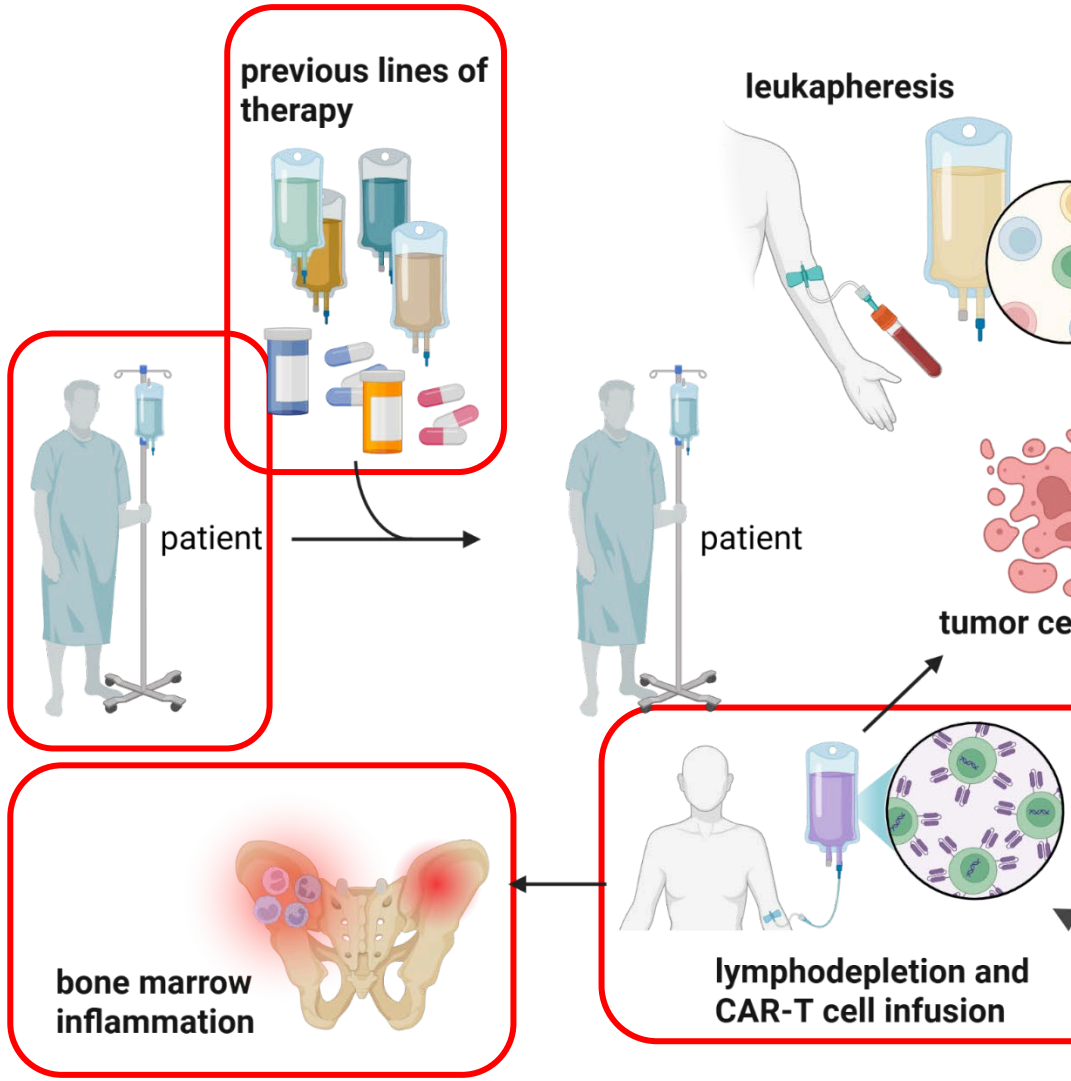
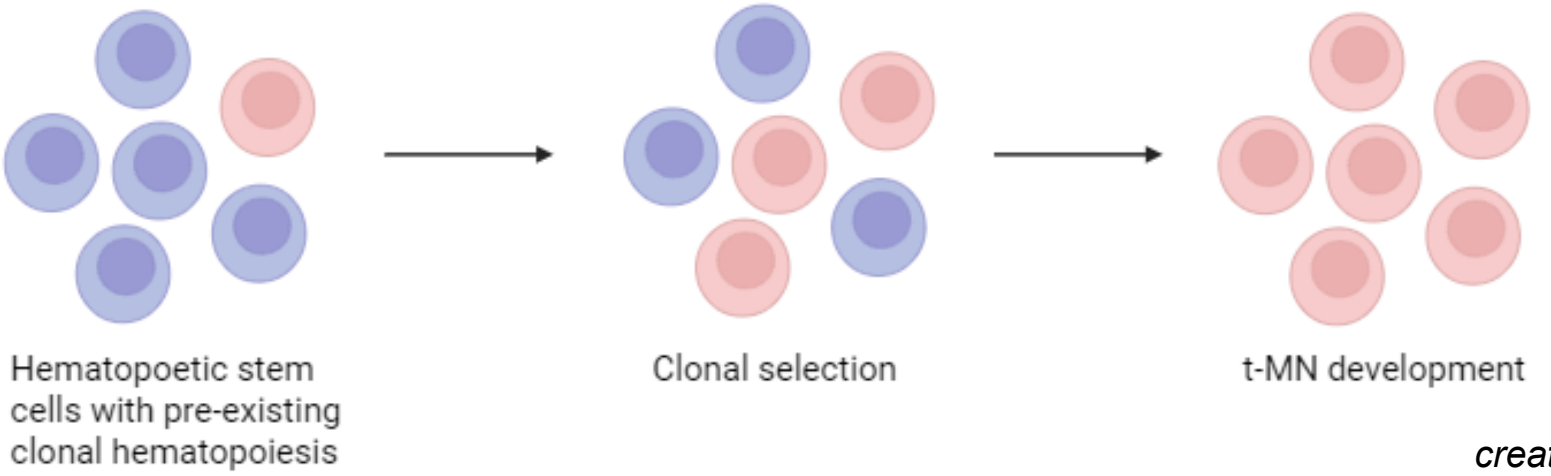
CAR-T cell manufacturing

- Lymphodepletion
  → DNA damage
- CRS: proinflammatory milieu
  → selection of preleukemic clones
- Prolonged aplasia
  → clonal selection of mutated cells



Clonal hematopoesis (CH)



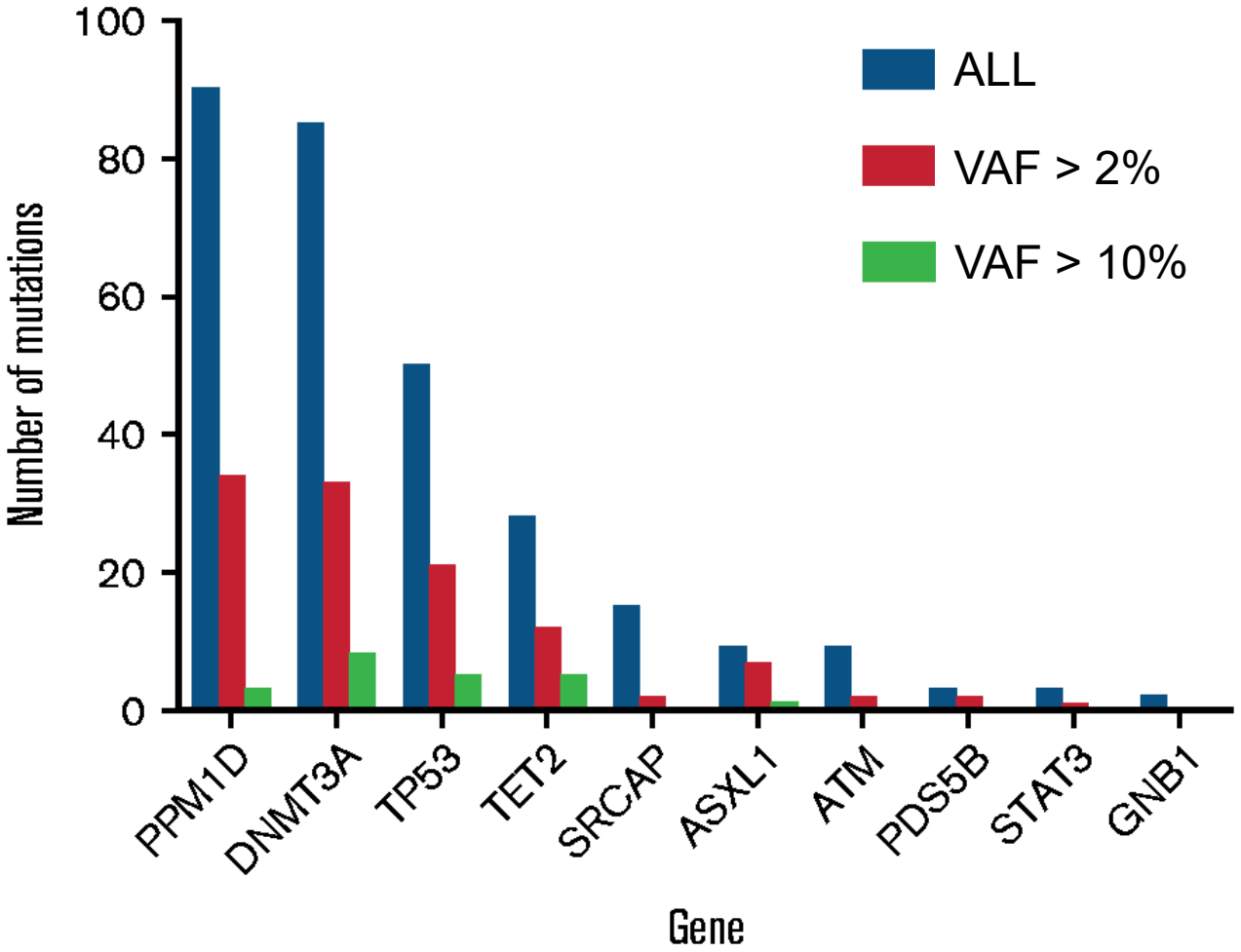
created with BioRender

- Mutations in hematopoetic cells without diagnosed hematologic malignancy
  → DNMT3A, TET2, TP53
- CHIP: VAF ≥ 2%
- How does CAR-T impact CH and t-MN risk?
  - Lymphodepleting chemotherapy vs. inflammation related to CRS?

Miller et al. Blood Adv. 2021

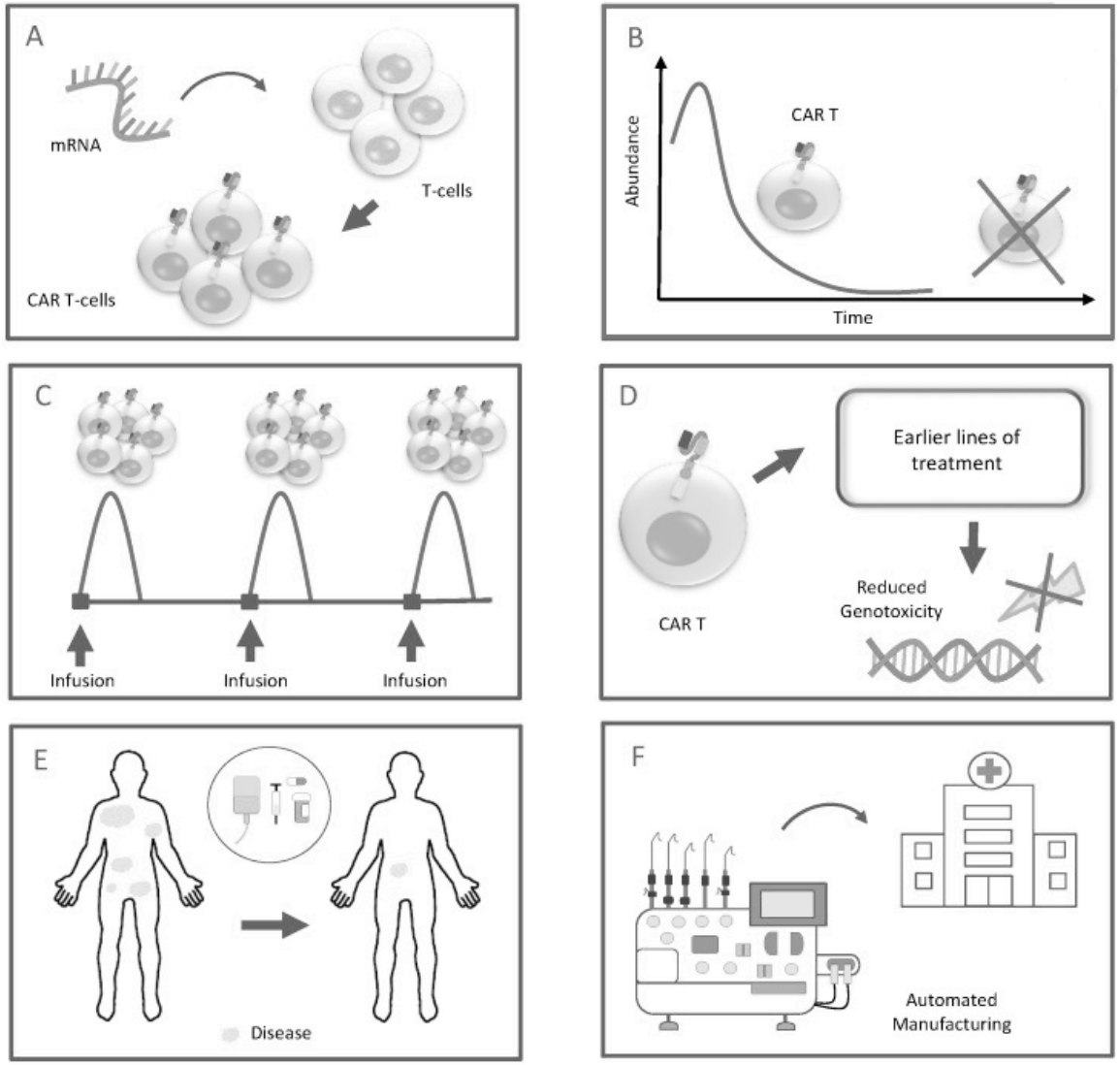
Clonal hematopoesis

- 154 patients receiving CAR-T
  - 144 NHL
  - 10 MM
- CH very common:
  - VAF > 0.4% in 76% of patients
  - VAF > 2% in 48% of patients
- 3 patients developed t-MN, 2/3 TP53 mutant AML
- Age < 60 years: Associated with higher likelihood of CR and CRS ≥ grade II
- No difference in OS or PFS



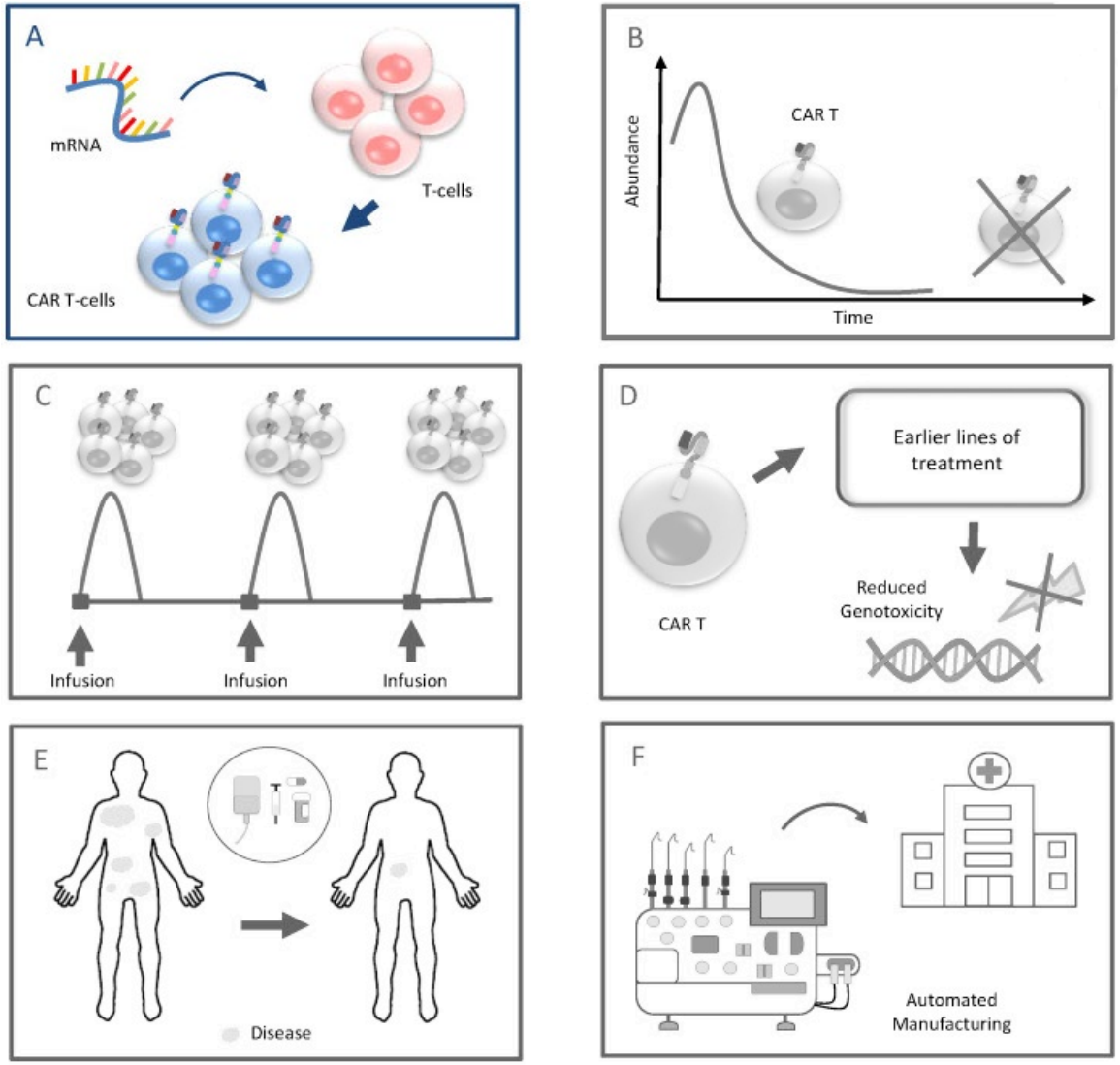
Miller et al. Blood Adv. 2021

Prevention strategies



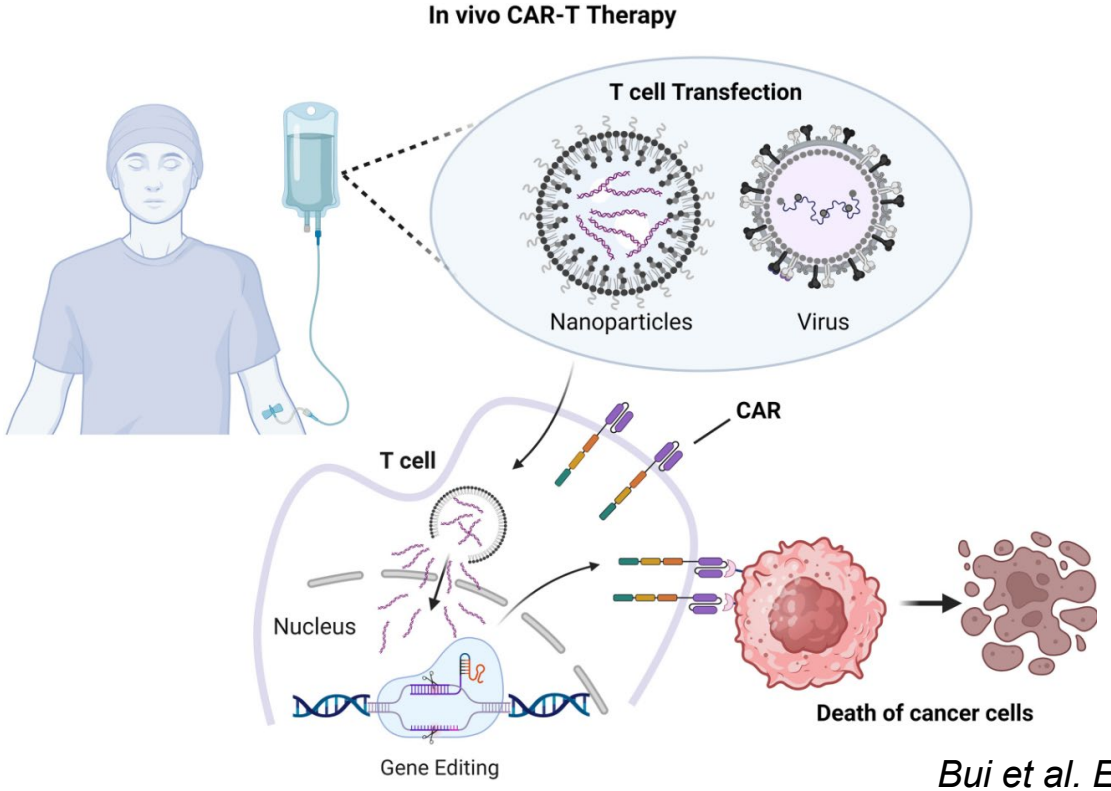
Bouziana et al. Int J Mol Sci. 2024

Prevention strategies

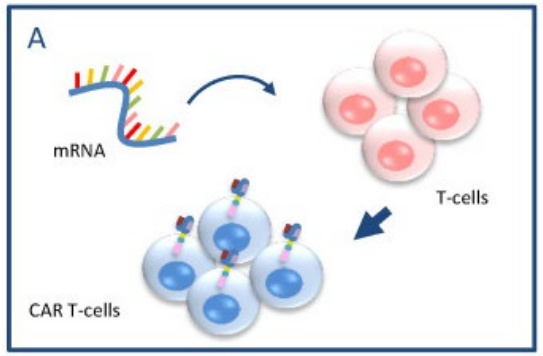


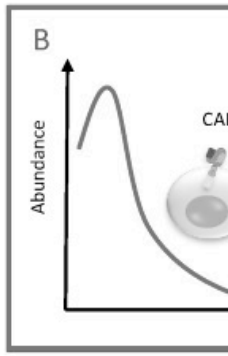
Bouziana et al. Int J Mol Sci. 2024

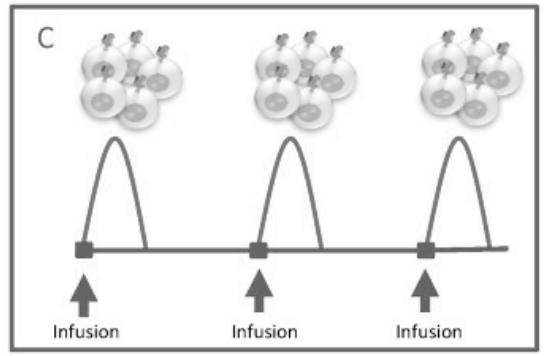
Prevention strategies

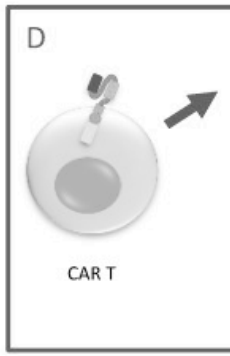


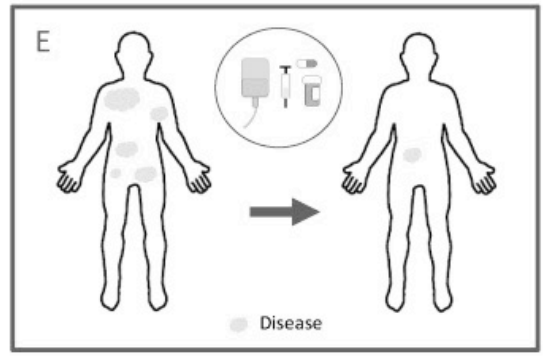
Bui et al. EBioMedicine. 2024

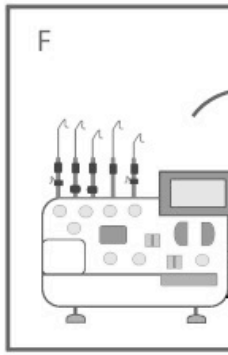






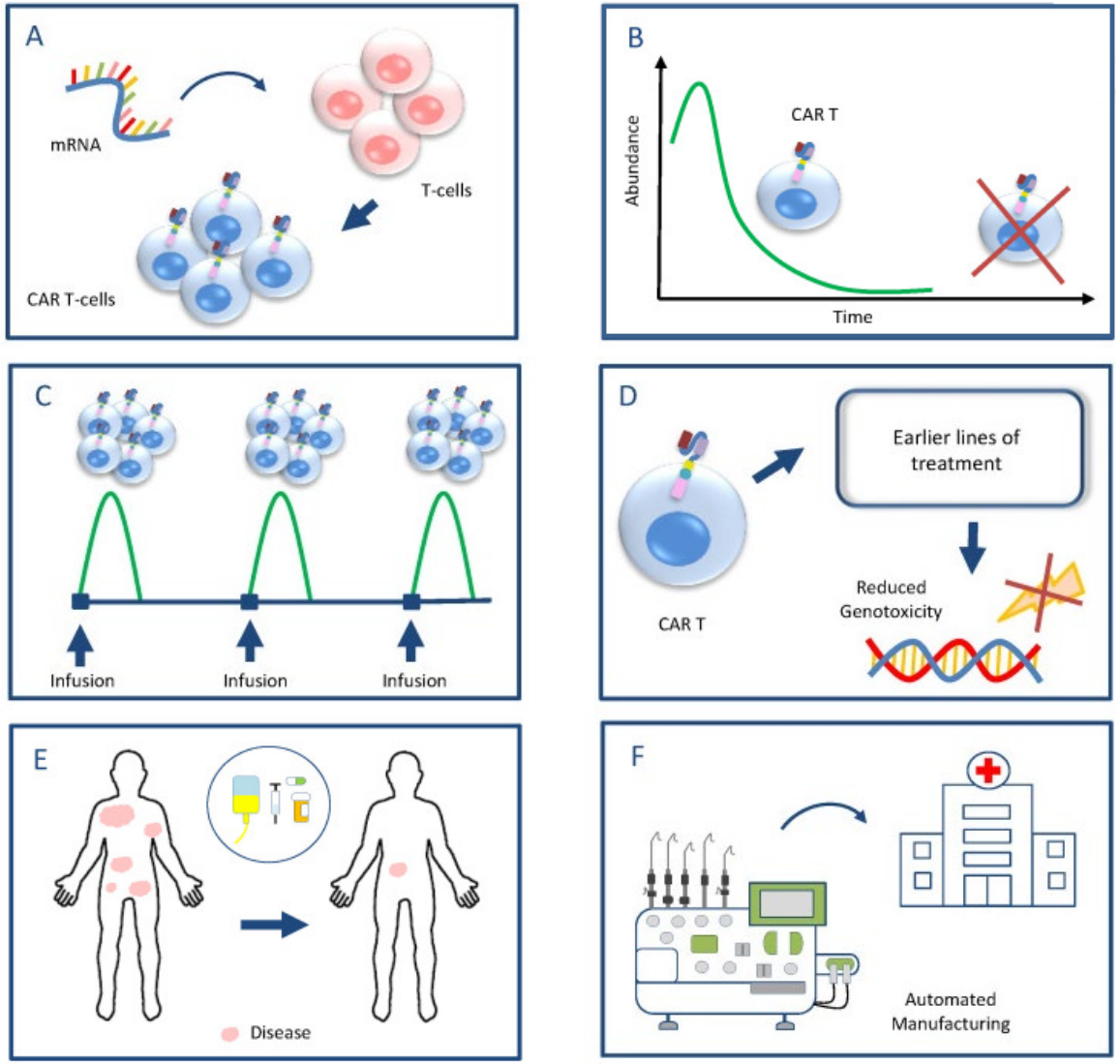






- *In vivo* gene transfer
  - Less inflammation
- Gene engineering: 4-1BB mutation
  - Less cytokine production

Prevention strategies



Bouziana et al. Int J Mol Sci. 2024

Therapy of AML after CAR-T cell treatment

- Not standardized
- Fit patients:
  - Induction therapy: CPX-351
  - Transplant in first CR
- Unfit patients:
  - Hypomethylating agents +/- venetoclax
- Relapse:
  - targeted therapy + venetoclax
  - HMA + venetoclax
- Clinical trials recommended

Marconi et. al. Front Oncol. 2024
Green et Wang. Blood. 2025

T cell malignancies

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FDA

November 28, 2023

WARNING: T CELL MALIGNANCIES

See full prescribing information for complete boxed warning

We have become aware of the risk of T cell malignancies with serious outcomes, including hospitalization and death, following treatment with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies”

BRIEF REPORT

CAR+ T-Cell Lymphoma after Cilta-cel Therapy for Relapsed or Refractory Myeloma

S.J. Harrison,[1,2,3,4] C. Touzeau,[5,6,7] N. Kint,[8] K. Li,[9] T. Nguyen,[4] C. Mayeur-Rousse,[10] M. Rahman,[1,2] Y. Le Bris,[6,7,10] J. Er,[1,2,11] J. Eugene-Lamer,[12] N.M. Haynes,[3,4] J. Li,[3] R.C. Abbott,[3,4] C. Bodet-Milin,[6,7,13] A. Moreau,[12] E. Letouzé,[6,7] N. Lendvai,[14] J.M. Schecter,[14] W. Deraedt,[15] A. Banerjee,[9] T. Lengil,[14] M. Vogel,[16] B. Foulk,[9] H. Zhao,[9] D. Smirnov,[9] A. Slaughter,[17] C. Lonardi,[18] E. Lee,[19] L. Marquez,[14] A. Sankari,[20] V. Plaks,[9] J.O.C. Filho,[21] N. Patel,[21] D. Geng,[21] T. Gastinne,[5] H. Kelly,[1,2] I.S. Tiong,[1,2,4] M. Eveillard,[6,7,10] P. Chevallier,[5,6] S. Lade,[1,2] P. Moreau,[5,6,7] S. Grimmond,[22] J. Oliaro,[3,4] B. Tessoulin,[5,6] and P. Blombery[1,2,4,22]

Science

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HOME > SCIENCE > VOL. 288, NO. 5466 > GENE THERAPY OF HUMAN SEVERE COMBINED IMMUNODEFICIENCY (SCID)-X1 DISEASE

REPORTS

Gene Therapy of Human Severe Combined Immunodeficiency (SCID)-X1 Disease

MARINA CAVAZZANA-CALVO, SALIMA HACEIN-BEY, GENEVIÈVE DE SAINT BASILE, FABIAN GROSS, ERIC YVON, PATRICK NUSBAUM, FRANÇOISE SELZ, CHRISTOPHE HUE, STÉPHANIE CERTAIN, [...], AND ALAIN FISCHER +3 authors Authors Info & Affiliations

SCIENCE · 28 Apr 2000 · Vol 288, Issue 5466 · pp. 669-672 · DOI: 10.1126/science.288.5466.669

JCI The Journal of Clinical Investigation

Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1

Salima Hacein-Bey-Abina, … , Alain Fischer, Marina Cavazzana-Calvo

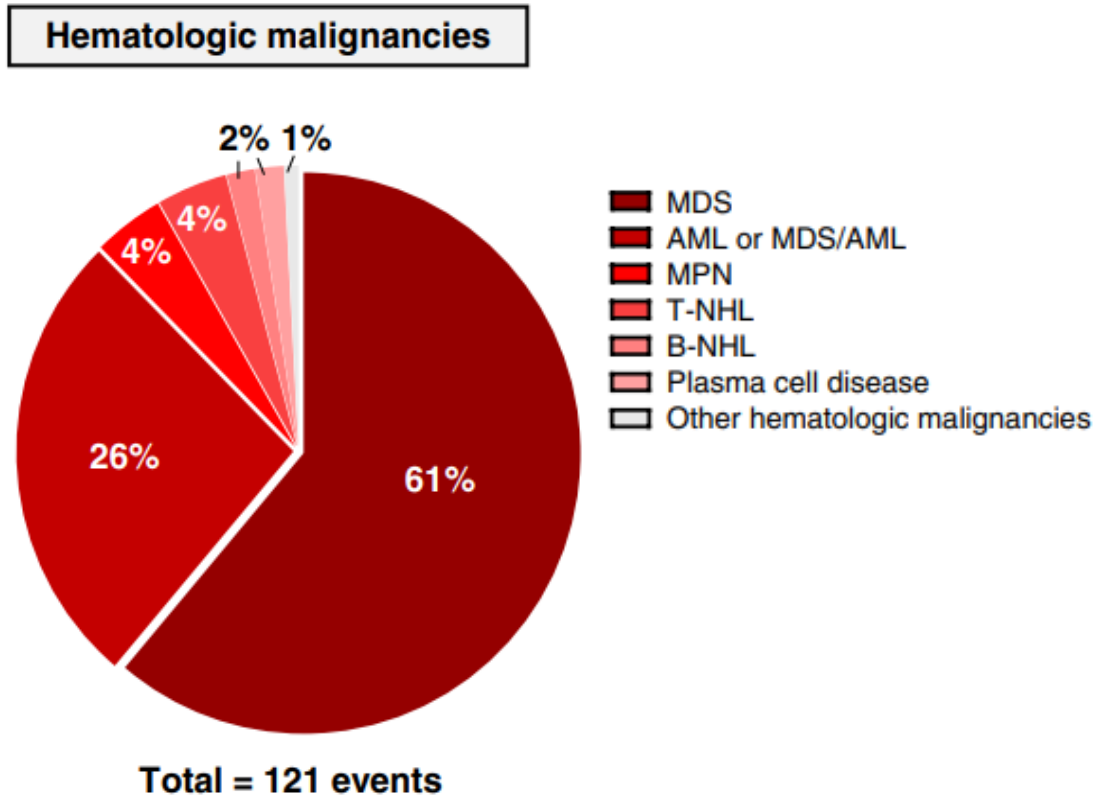
J Clin Invest. 2008;118(9):3132-3142. https://doi.org/10.1172/JCI35700.

Research Article

Incidence of T cell malignancies

	CAR-T patients	Cases	Percentage
Meta-analysis	5517	5 cases	0.09%
DESCAR-T registry	3066	1 case	0.03%
UPenn	449	1 case	0.2%
OSU	246	0 cases	0%
Stanford	724	1 case	0.1%

4% of hematologic SPM



FDA report: 22 cases of secondary t cell malignancies, 14/22 within 2 years

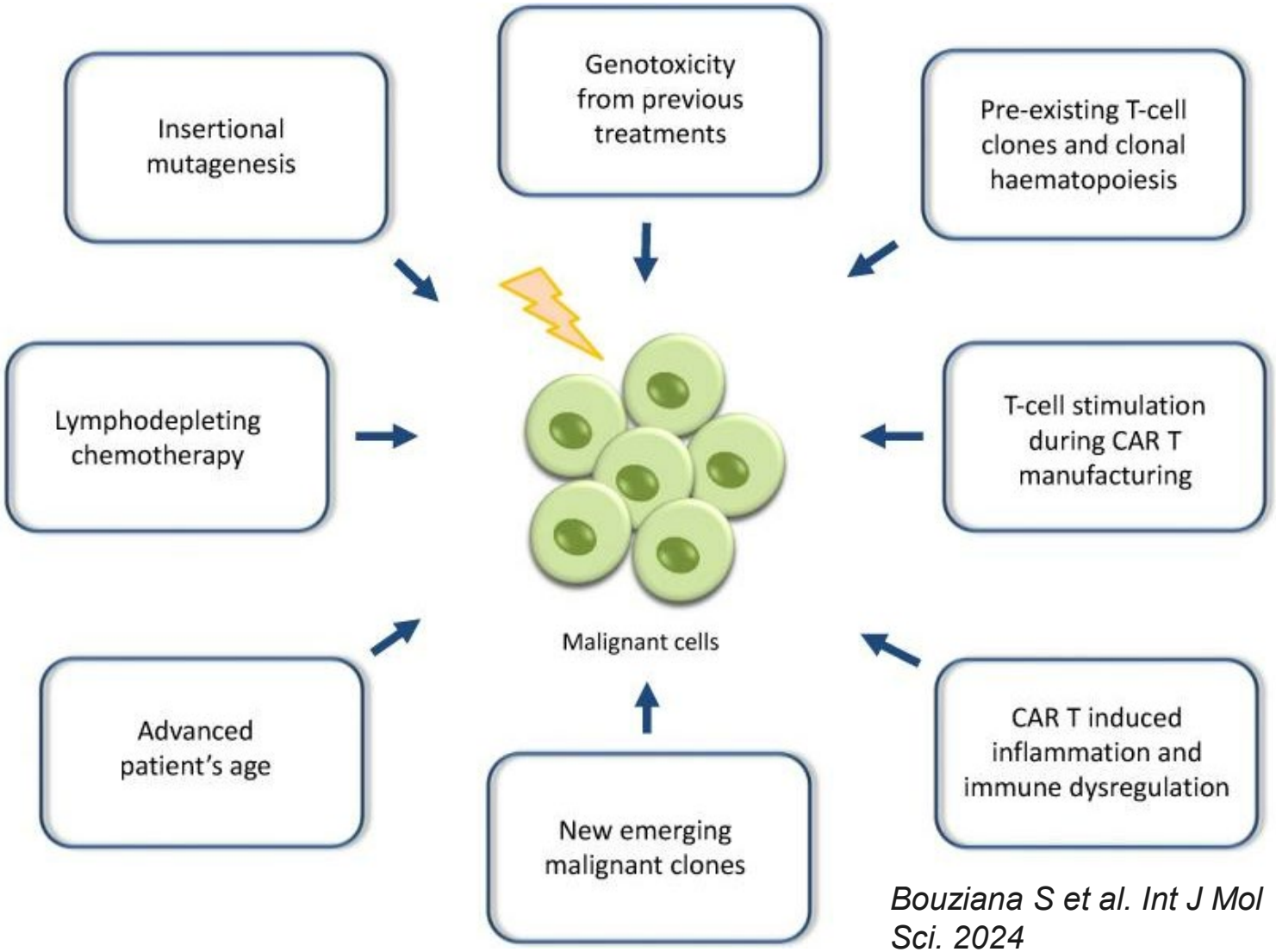
- CAR transgene identification only in 3 cases

Bouziana et al. Int J Mol Sci. 2024
Tix et al. Clin. Can Res. 2024
Dulery et al. Nat Med. 2025
Ghilardi et al. Nat Med. 2024
Umyarova et al. J Hem Onc. 2025
Hamilton et al. NEJM. 2024

T cell malignancies

- Multiple cases with concurrent TET2 mutations
  - Potential sign of pre-existent clonal expansion
- Association with insertional mutagenesis vs. independence of CAR transduction
- No validated screening or prevention strategy

Summary – SPM after CAR-T cell therapy



Bouziana S et al. Int J Mol Sci. 2024

- Important complication
- Multifactorial model
- Independent of disease entities and CAR-T products
- Unclear if SPM rates are higher with CAR-T than with standard-of-care therapy
- Importance of long-term follow-up

Alexandre Trubert
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Verena Konetzki
Zeno Riester

Hudecek Lab

Thank you for your attention!

Uniklinikum Würzburg

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Candidate for EHA Board Elections 2025 (Vacancy 2)

Prof. Dr. Michael Hudecek

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