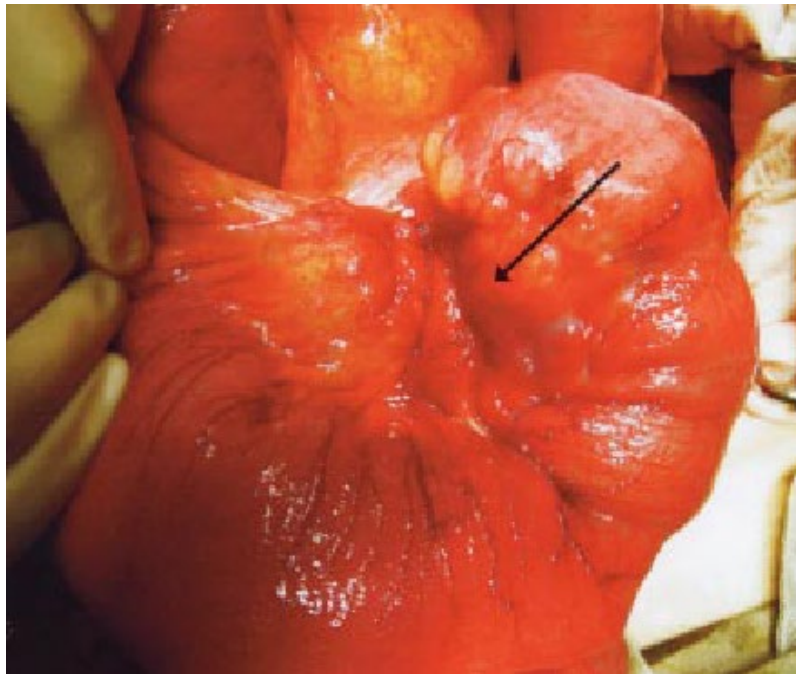
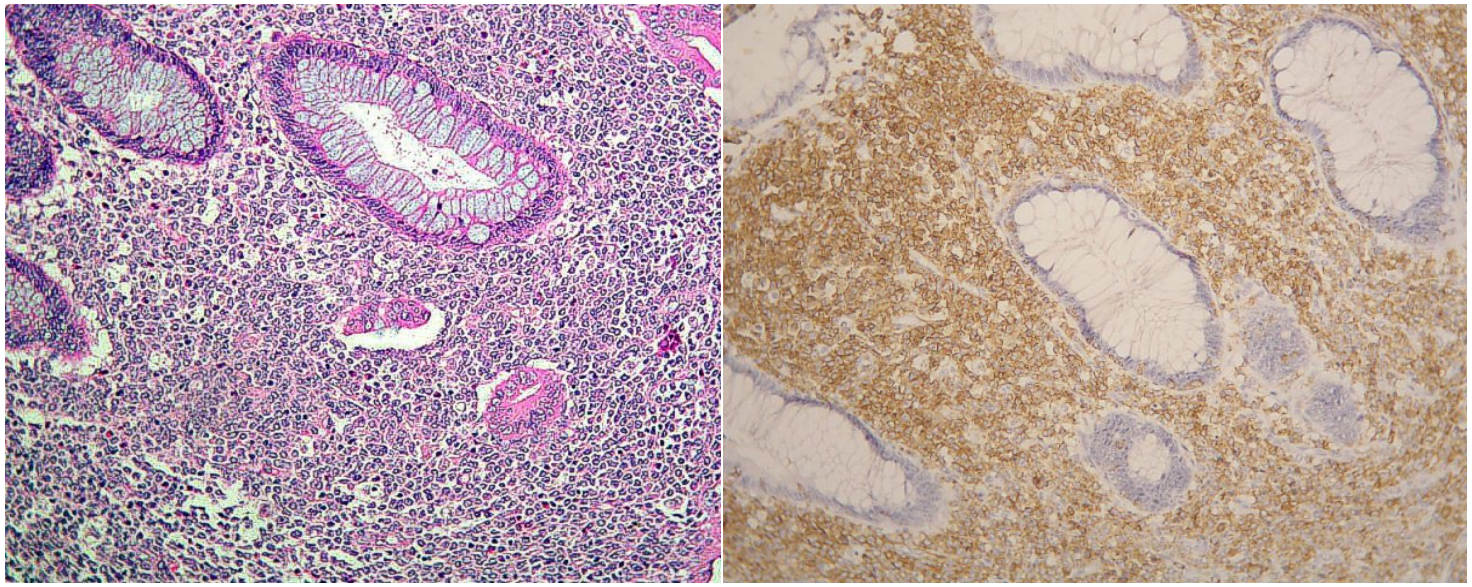
Donor Cell Leukemia (DCL): Mechanisms, Models & Clinical Challenges

Dan Wiseman
The Christie / University of Manchester

CASE STUDY: JW

- 34yF – pregnant (16wks)
- Small bowel obstruction
- Laparotomy performed:





Δ GRANULOCYTIC SARCOMA

- *Normal bone marrow*
- *Normal cytogenetics*
- *No variants on MGP*

→ **Watch & wait**

CASE STUDY: JW

- Spontaneous miscarriage (@22wks)
- Local recurrence (inc peritoneal thickening / ascites)

➢ DA (3+10) + GO → PR

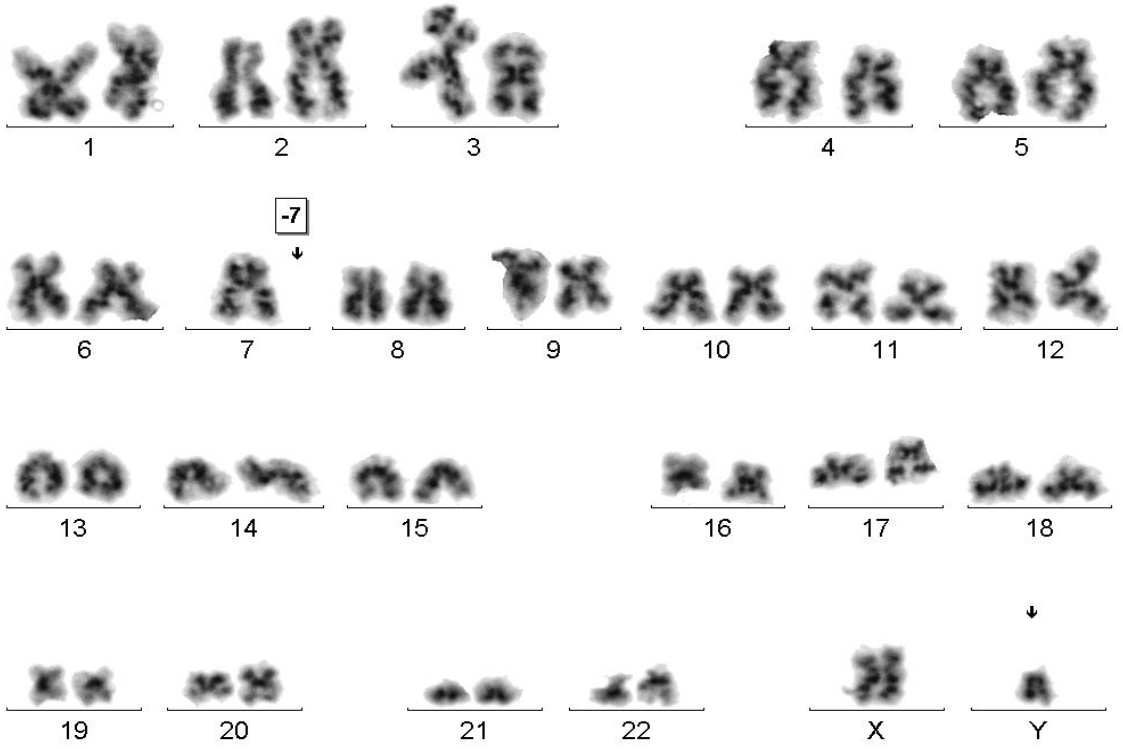
➢ FLAG Ida → CR

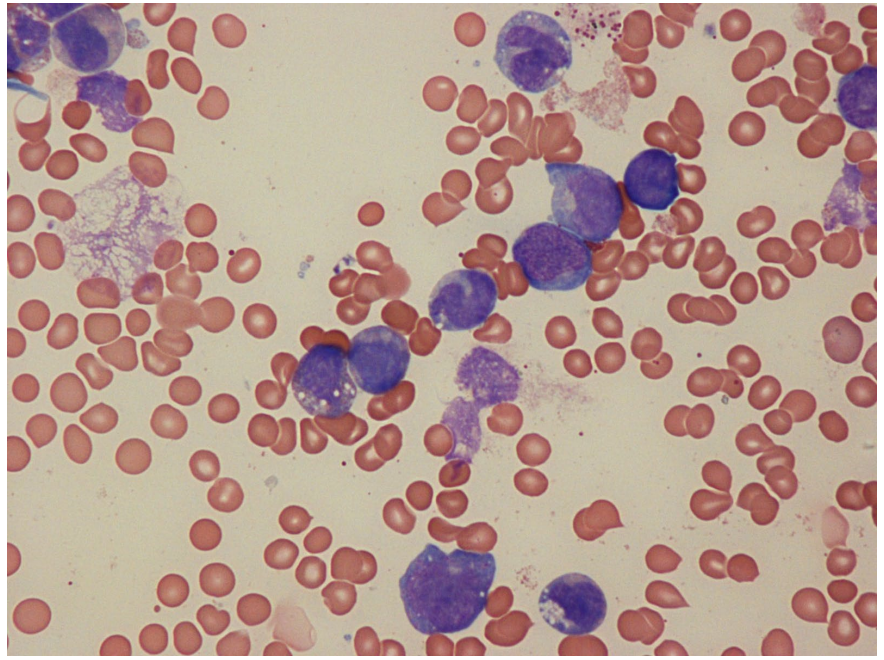
➢ Allo HSCT
    - MUD (37yM)
    - Myeloablative (CyTBI)
    - CsA + MTX GVHD prophylaxis

- Grade 1 aGVHD
- Later extensive cGVHD (skin/eyes/mouth/gut) → long-term steroids + ECP
- Continued in CR

CASE STUDY: JW

- Day + ~880:
- WCC 85.7 with circulating myeloblasts
- BM dysplastic with 40% blasts





- Cytogenetics: monosomy 7
- NGS → TET2 / DNMT3A / NRAS mutations
- Chimerism 100% donor
  (12 occasions; D+35 onwards)

Δ DONOR-DERIVED AML

64 cases from literature summarised

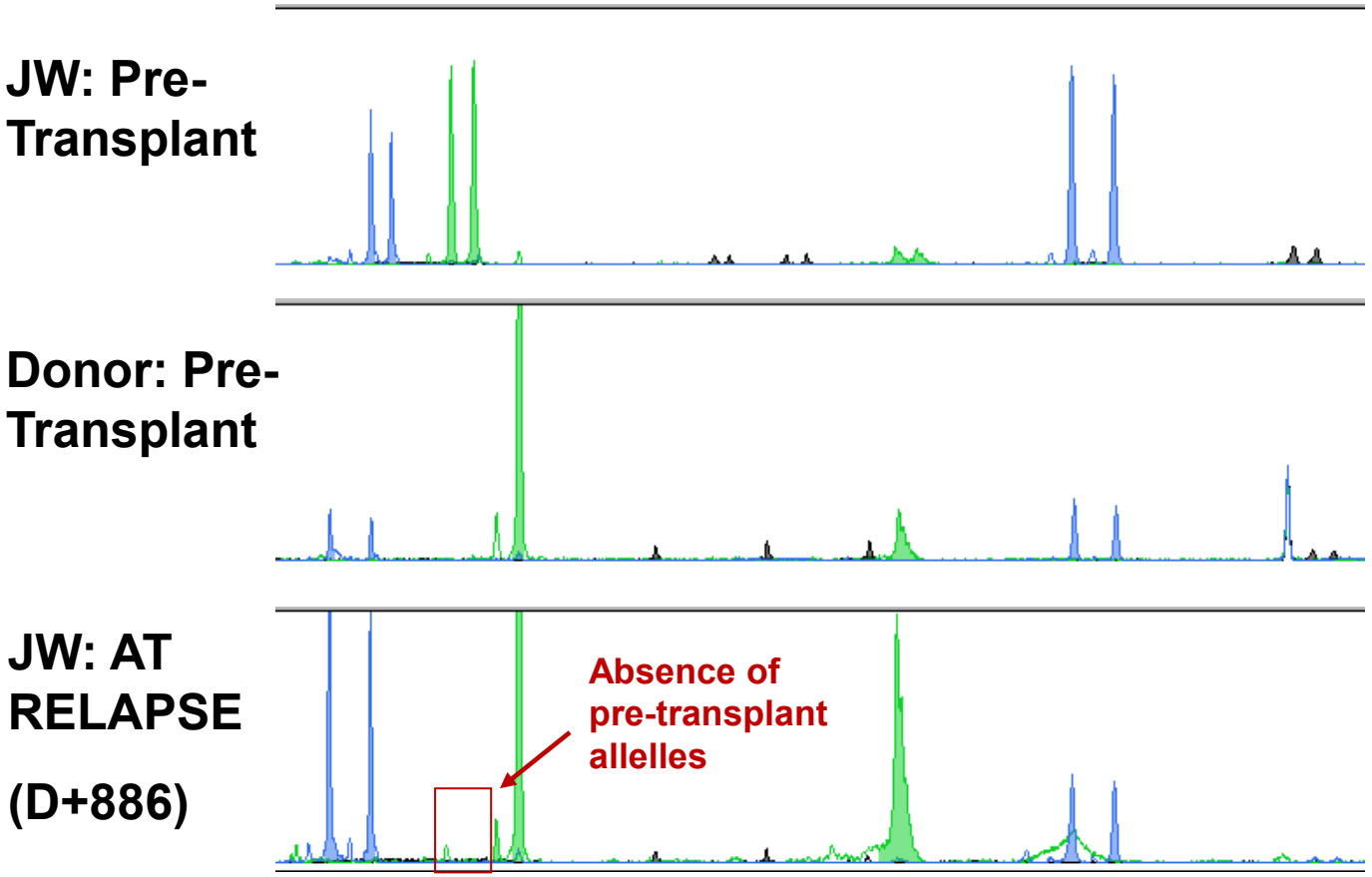
1. *Antigenic stimulation of susceptible donor clone?*
2. *Aberration in homeostatic mechanism governing lymphocyte maturation & proliferation?*
3. *Fusion of normal donor XY cell with recipient XX, followed by diploidization?*
4. *Oncogenic virus transferred from host to donor cells?*

DONOR CELL

RECIPIENT D+76

DCL Diagnosis

- Relies on ability to accurately establish donor origin of leukaemia relapse
- Early cases → XY karyotyping
  - *Insufficiently sensitive*
  - *Only ~50% = sex-discordant*
- Sensitivity improved:
  - FISH → VNTR → **STR**



DCL Incidence

- ???
- Leukaemia relapse risk post BMT ≈ 20-60%
  - *Phenotype may differ from original, but most = recipient origin*
- Boyd (1982): ***"5% of all relapses might be DCL"***

- *EBMT Survey (2005)*
  - 10,489 alloHSCT [1982-2003] (91 centres) → 14 (known) DCL

  → Est. incidence **124 per 100,000 transplants (= 0.124%)**
- *Ruiz-Arguelles (2006):*
  - Prospective, single institution study

  → *2 of 40 (**5%**) relapses = DCL*
- *Salter (2024 ASH Abstract):*
  - Single center (Ontario), n=205 sex-mismatched (2005-17)

  → 4 of 205 (**1.95%**) = DCL

DCL Incidence

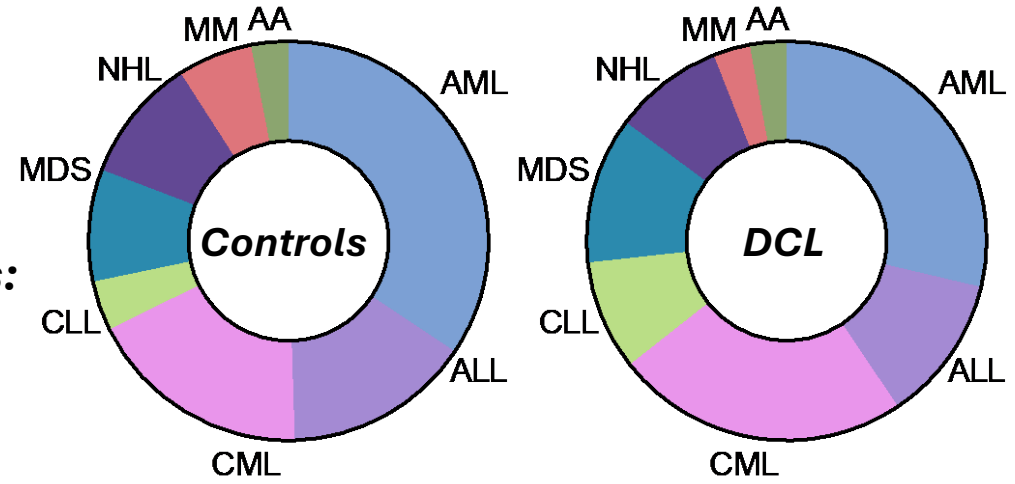
- Follow up EBMT survey:
- 305 centers → 80 responded
- **46,051 Allo → 38 DCL**
- Case controls (nested; 2:1)
- Median latency: **44mo (2-279)**

→Est. prevalence 80.5 /100,000

→Cumulative incidence:

@5y: 0.067%
@10y: 0.132%
@25y: 0.363%

Original diagnoses:



Engel et al (Leukemia 2019)

DCL Incidence

- Japanese registry survey (1974-2012):
- 36,870 Allo → **40 proven DCL**
- 25/40 in recipients ≥40y
- Median latency **22mo** (3-190)

→**Cumulative incidence:**

@5y: 0.12%
@10y: 0.13%
@15y: 0.16%

Kato et al (Leukemia 2016)

DCL Risk Factors?

40 DCL (36,870 Allo)

2019 EBMT Survey: Pathogenetic risk factor analysis:

		Control *n* = 67	Case *n* = 34	*p*-value
Donor age	>35	43 (64%)	18 (64%)	0.97
Previous auto HCT	Yes	5 (7%)	4 (12%)	0.48
Previous allo HCT	Yes	0	4 (12%)	0.01
Reduced-intensity HCT	Yes	26 (39%)	12 (35%)	0.73
TBI	Yes	41 (61%)	16 (47%)	0.18
Growth factor < 100 days	Yes	17 (25%)	16 (50%)	0.015
in vivo T-cell depletion	Yes	20 (30%)	14 (41%)	0.26
Acute GvHD grade II+	Yes	16 (24%)	10 (30%)	0.49
Chronic GvHD	Yes	36 (59%)	17 (50%)	0.40
Alemtuzumab	Yes	5 (7%)	5 (15%)	0.25
Anti-thymocyte globulins	Yes	15 (22%)	9 (26%)	0.65

Multivariable analysis:

	HR	95% CI	P value
Growth factors (first 100d)	**2.43**	1.15-5.13	0.02
In vivo T depletion	**2.59**	1.21-5.56	0.014
Prior Allograft	**4.08**	1.37-12.19	0.012

Engel et al (Leukemia 2019)

DCL Risk Factors?

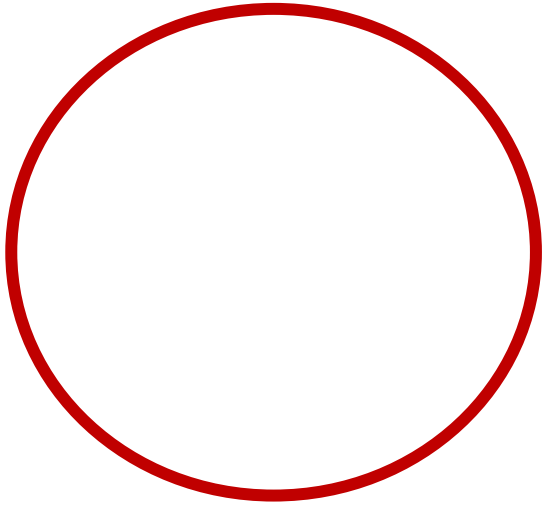
40 DCL (36,870 Allo)

2016 Japanese Survey:

- ***Higher risk with CB***
- ***Higher risk for older donors***
- ***<u>Not</u> more common with related donors***

Kato et al (Leukemia 2016)

DCL Pathogenesis (2011)



Wiseman (Biol Blood Marrow Transplant 2011)

DCL Pathogenesis

1. Accidental transfer of frank malignant clones

- Reported – but <u>v rare</u>
  - *Not responsible for vast majority of DCL*
- *Decreasing risk with improved donor screening protocols*

leukemic bone marrow resulted in normal engraftment, with complete chimerism two months after transplantation. The specific cytogenetic abnormalities of both the donor and the host leukemias disappeared one month after transplantation and remained undetectable for four more months. Six months after bone marrow transplantation, however, leukemia with the morphologic, immunohistologic, and cytogenetic abnormalities of the donor's leukemia developed in the recipient.

Methods

Cytogenetics

Chromosomes were prepared from 24-hour unstimulated bone

observed in more than 4000 marrow transplantations before this experience.[18,19]

References

1. Yunis JJ. New chromosome techniques in the study of human neoplasia. Hum Pathol 1981; 12:540-9.
2. Geissler D, Niederwieser D, Aulitzky WE, et al. Serum colony stimulating factors in patients undergoing bone marrow transplantation: enhancing effect of recombinant human GM-CSF. Behring Inst Mitt 1988; 83:289-300.
3. Thaler J, Denz H, Gattringer C, et al. Diagnostic and prognostic value of immunohistological bone marrow examination: results in 212 patients with lymphoproliferative disorders. Blut 1987; 54:213-22.
4. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. N Engl J Med 1986; 314:729-35.
5. Dexter TM. Stromal cell associated haemopoiesis. J Cell Physiol Suppl 1982; 1:87-94.

Niederwieser at l (NEJM 1990)

DCL Pathogenesis

~~1. Accidental transfer of frank malignant clones~~

2. Transfer of pre-leukaemic clones

- **Inherited/germline predisposition mutations**

	Inheritance	Onset	Malignancy	Other features
ANKRD26	AD	Variable	MDS, AML	Thrombocytopenia
CEBPA	AD	Variable	AML	
DDX41	AD	Adult	MDS, AML, NHL	
RUNX1	AD	Variable	MDS, AML, ALL	Thrombocytopenia, platelet defects
ETV6	AD	Variable	B-ALL, MDS, AML	Thrombocytopenia
GATA2	AD	Adolescent	MDS, AML	Immunodeficiency, lymphedema, hearing loss, warts

DCL Pathogenesis

~~1. Accidental transfer of frank malignant clones~~

2. Transfer of pre-leukaemic clones

❖ Inherited/germline predisposition mutations

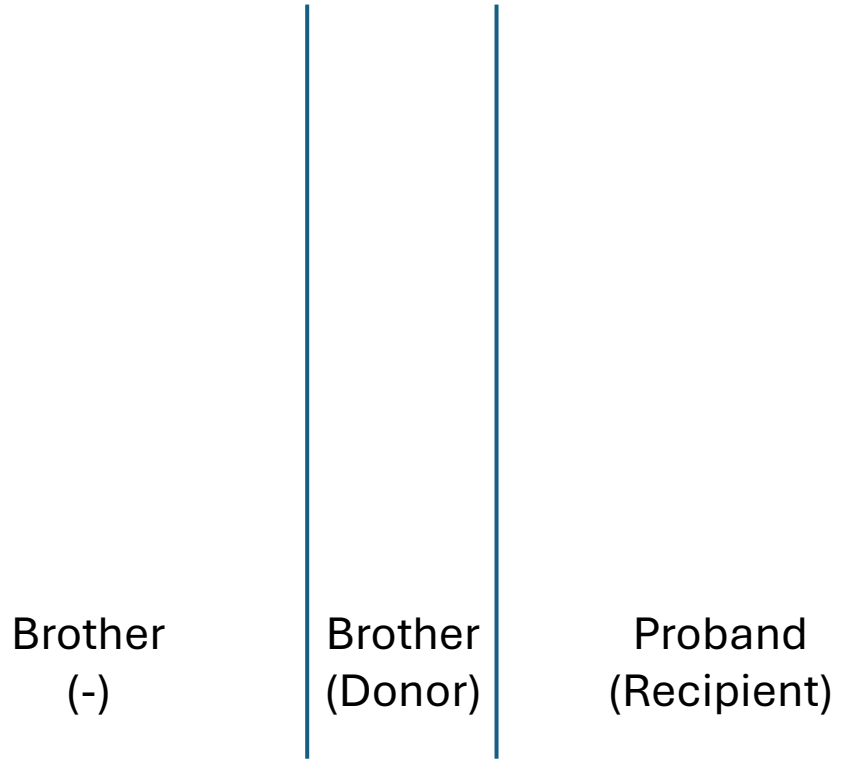
- **13.6% adult AMLs had germline variants** *(Yang et al, Blood 2022)*
- Some = common in population (e.g. DDX41 → 1 in 129 individuals)
- 404 MDS pt/related donor pairs: 7% shared likely pathogenic variants; +4% presumed germline variants (Feurstein et al, Blood 2022)

- **Many recent case reports of proven transfer → DCL**
- Transfer also:
  - → poor HSC mobilization
  - → delayed engraftment
  - → inferior outcomes
  - → higher relapse rates

❖ ***Should screen potential family donors if identified***

- *Somatic reconversion an issue*
- *Potential risk of promoting leukaemogenesis in HSC mobilization of donor*

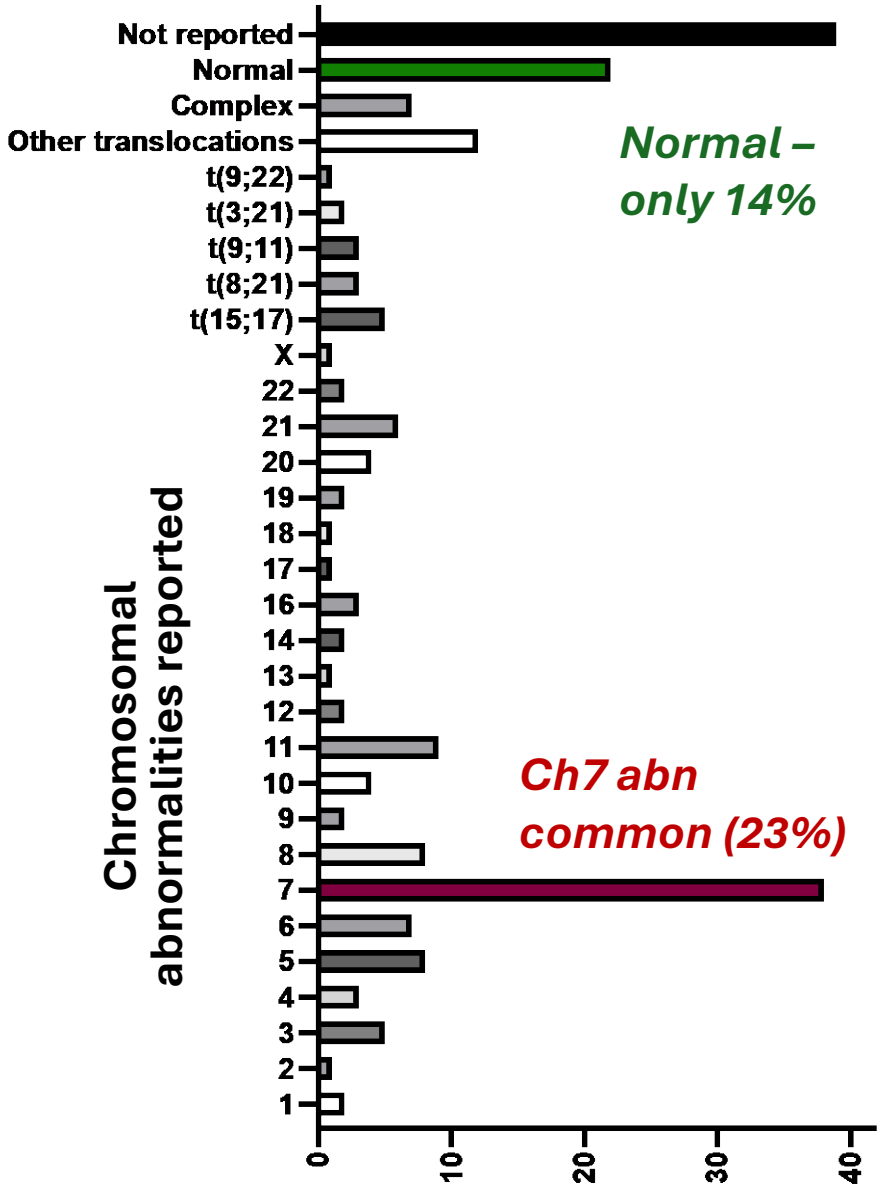
- **58yM AML:**



Berger et al (Leukemia 2017)

DCL Genetics

- 2021: Updated collation of reported DCL cases



Williams et al (Bone Marrow Transplant 2021)

DCL Genetics

- Most cases in literature from before NGS era
- **Williams et al (2021)**: linked 13 genes as recurrently mutated in DCL (sporadic cases only):

CEBPA ★	EZH2
GATA2 ★	IDH1
JAK2	IDH2
RUNX1 ★	CHEK1
DDX41 ★	XPD
ASXL1	XRCC3
DNMT3A	

★ *Germline from donor*

CHIP

DNA repair genes

- *NPM1/FLT3 barely reported*

Table 5 Proposed genes for donor screening prior to transplanation.

Germline

- Transcription factors: CEBPA, ETV6, GATA2, RUNX1
- RNA splicing: DDX41
- Cell signaling and growth: SRP72, TERC, TERT, TP53

Somatic

- Epigenetic modification: DNMT3A, TET2, IDH1/2, WT1, EZH2, SUZ12, EED, JARID2, ASXL1, KMT2, KMD6A, ARID2, PHF6, ATRX
- RNA splicing: SF3B1, SRSF2, USAF1/2, ZRSR2, SF1, PRPF8, LUC7L2
- DNA replication: STAG2, RAD21, SMC3, SMC1A, ATM, BRCC3, FANCL, NPM1, SETBP1, DDX41
- Transcription factors: ETV6, GATA2, IRF1, CEPBA, BCOR, BCORL1, NCOR2, CUX1
- Cell signaling and growth: FLT3, KIT, JAK2, MPL, CAL4, CXF3R, PTPN11, NF1, NRAS, KRAS,CBL, GNAS, GNB1, FBWX7, PTEN, TP53, CDKN2A

Williams et al (Bone Marrow Transplant 2021)

DCL Pathogenesis

~~1. Accidental transfer of frank malignant clones~~

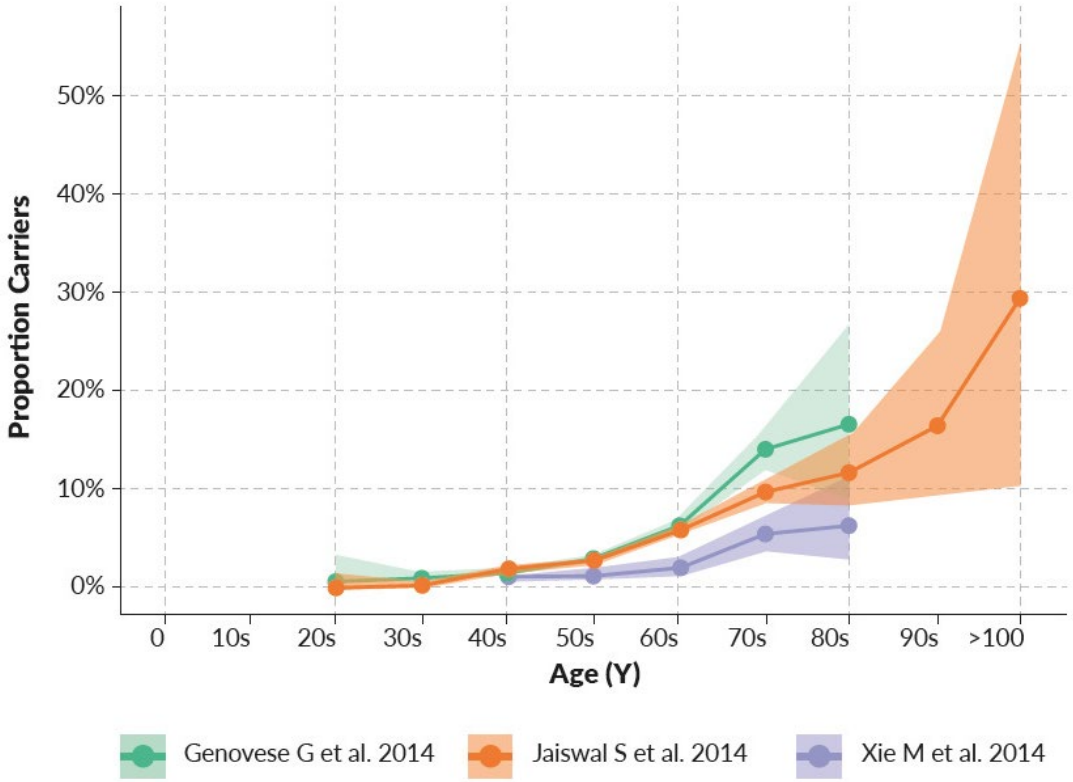
2. Transfer of pre-leukaemic clones

❖ Clonal haematopoiesis ("CHIP")

- Age-associated *myeloid* mutations
- Prevalence depends on limit of detection
  - >65y: ~20% (cutoff 2%)
    ~100% (cutoff 0.5%)
- **Implications of transfer ???**
- RAPID expansion in recipient → RISK
- When present CH clone *usually* engrafts

➢ ***Many case reports of DCL with proven CHIP transfer from donor***

Absolute risk LOW (0.5-1% /yr)
Relative risk HIGH (4-15x >background)



Wong et al (Sci Transl Med 2020)
Frick et al (JCO 2019)
Gibson et al (JCO 2022)

500 related donors (age ≥55y):

- 92 mutations (80 genes)
- Median VAF 5.9%
- [16% of all donors]

❖ **High incidence cGVHD**

Frick et al (JCO 2019)

500 related donors (age ≥55y):

- 92 mutations (80 genes)
- Median VAF 5.9%
- [16% of all donors]

❖ **<u>Low</u> incidence relapse/progression**

Frick et al (JCO 2019)

500 related donors (age ≥55y):

- 92 mutations (80 genes)
- Median VAF 5.9%
- [16% of all donors]

❖ **No impact on OS**

Frick et al (JCO 2019)

- **Serial engraftment of 24/25 CHIP clones**
  (exception: single SF3B1 K700E)
- **Disproportionate expansion in ≥50%**
- ***In all relapses: clonal dynamics paralleled decrease in donor chimerism***

2 cases of DCL
1) CBLC (VAF 8%)
2) ASXL1 + DNMT3A (VAFs 2-3%)

Extensive clonal evolution (new mutations) at DCL

DCL:
- ***2 of 80 CHIP+***
- ***0 of 426 CHIP-***

Frick et al (JCO 2019)

❖ **7yr longitudinal study of single case:**

DNMT3A CHIP mutation in both myeloid + lymphoid (ie early HSC)
ONLY myeloid cells accrued additional mutations

Herold et al (Leukemia 2017)

DCL Pathogenesis

1. ~~Accidental transfer of frank malignant clones~~
2. Transfer of pre-leukaemic clones

3. **OTHER FACTORS REQUIRED FOR DCL INITIATION / EXPANSION *IN VIVO***
    - ***Many donors never develop MDS/AML***
    - ***Usually longer latency in donor vs recipient***

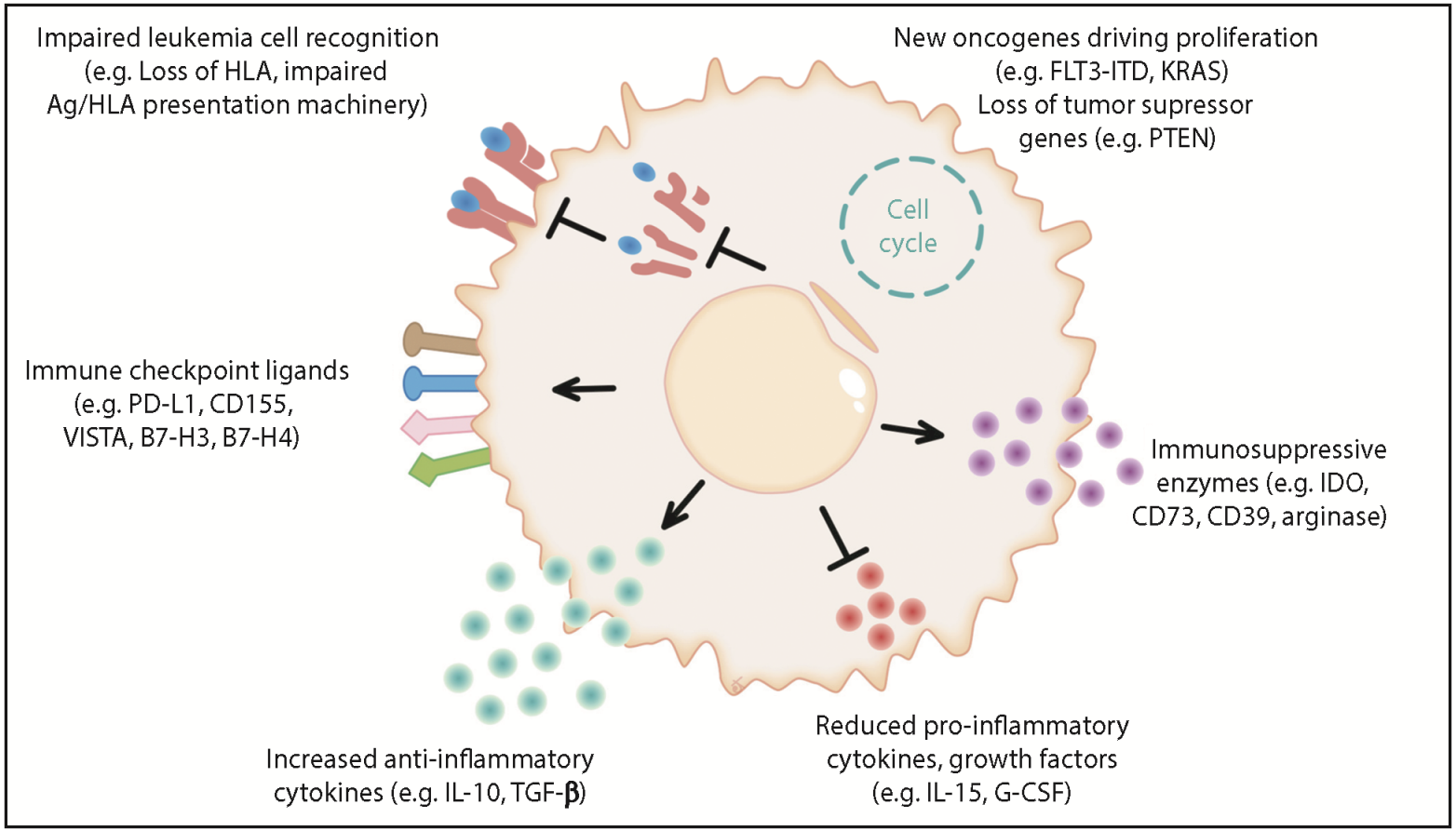
    - ***Impaired immune surveillance***
    - ***Telomere attrition***
    - ***Damaged BM microenvironment/stroma***
    - ***Bystander chemo-radiotherapy effect***
    - ***Chronic GVHD → inflammation (??)***

Defective immune surveillance ?

EBMT (n=38)

- *in vivo* T depletion

→**HR 2.59**



Mechanisms of immune evasion post Allo HSCT

Japanese (n=40)

- ***NO impact*** of GVHD prophylaxis (inc T depletion)

Engel et al (Leukemia 2019)

Zeiser & Vago (Blood 2019)

Kato et al (Leukemia 2016)

Defective immune surveillance ?

- Late-onset case of DCL: 20yM; 67mo post Allograft
  - *Original disease: Biallelic CEBPA; FLT3-ITD*
  - *DCL: Trisomy 11; IDH1 R119W (VAF 6.9%)*
  - Donor BM/fibroblasts: no “CHIP” mutations
  - WGS → Donor: *USP17L1, GLUD2, KIF4B, FLNA*
    DCL: Same + 31 additional mutations

Chen et al (Leuk Lymphoma 2023)

Defective immune surveillance ?

❖ ↓ Canonical NK cells

NK1 = Adaptive	NK2= Canonical

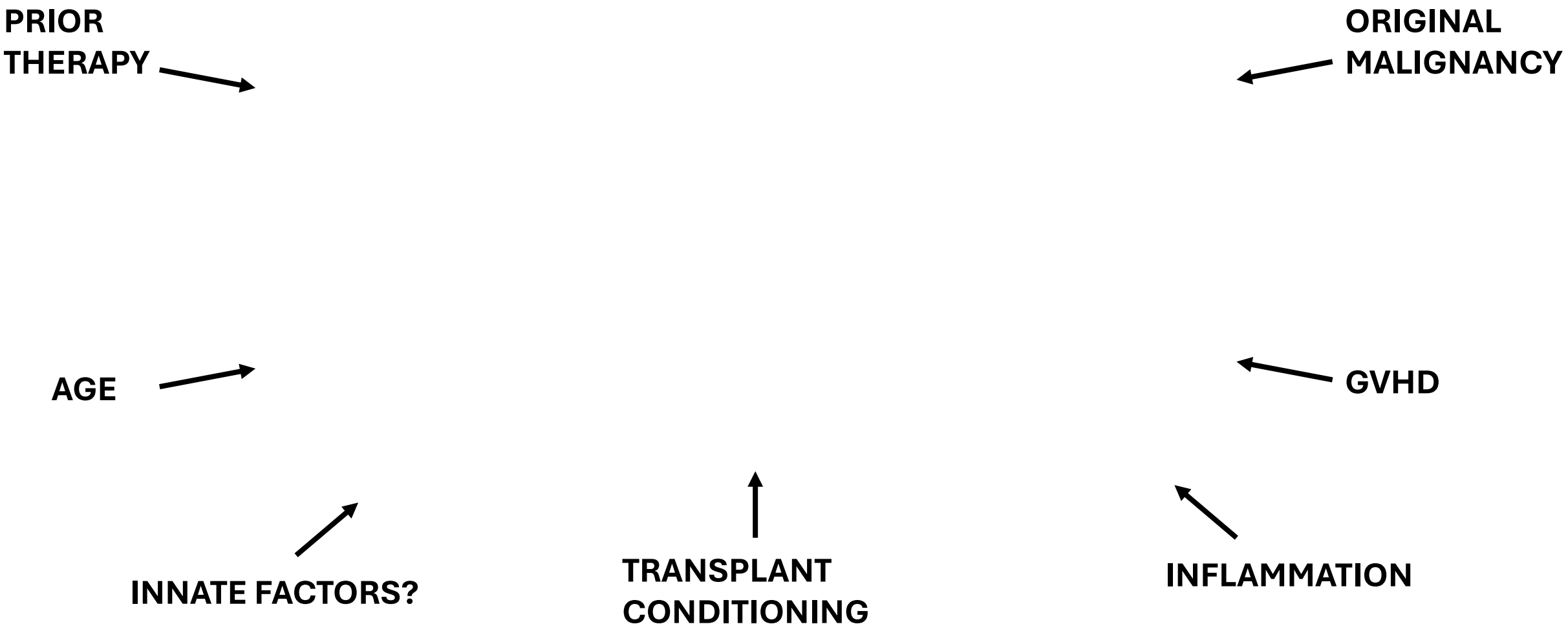
❖ ↑ CD8+ CTLs: BUT ↓ cytotoxicity scores

Module scores

❖ ?ROLE FOR DONOR CANONICAL NK CELL (FcεRIγ+NKG2C-) INFUSION IN DCL??

Chen et al (Leuk Lymphoma 2023)

Damage to microenvironment/stroma ?



Rafieemehr et al (Cancer Invest 2021)

Damage to microenvironment/stroma ?

- ***RT → defective fibroblastic CFUs***
- ***Conditioning → impairs MSC/fibroblasts for ≥12mo***

Abbuehl et al (Cell Stem Cell 2017)

Shipouniva et al (Leuk Lymphoma 2017)

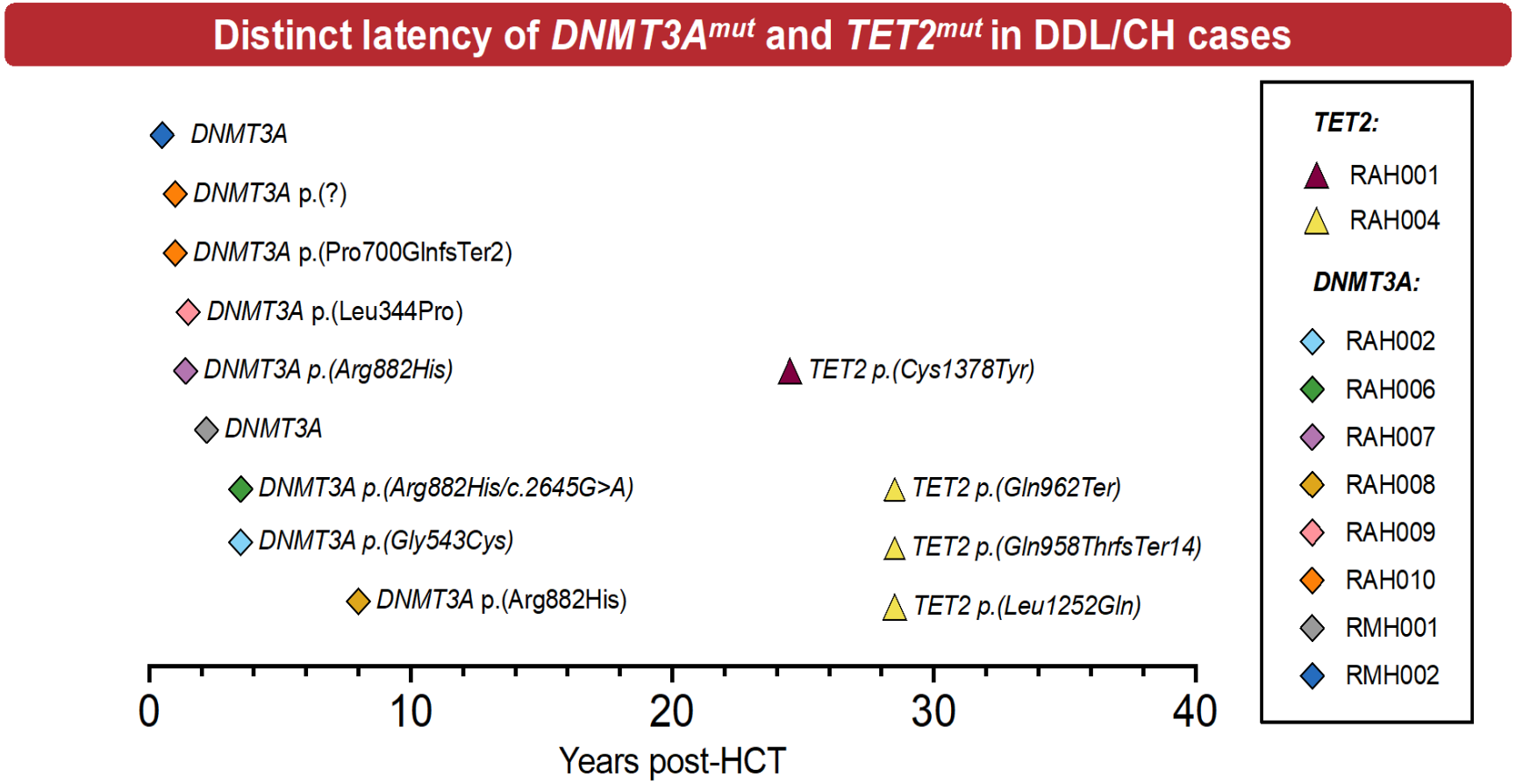
Damage to microenvironment/stroma ?

- ***Chemo (alkylator) of recipient BM promotes engraftment/expansion of preleukaemic clones***

Stoddart et al (Blood Cancer Discov 2020)

* DCL BM microenvironment promotes clonal expansion

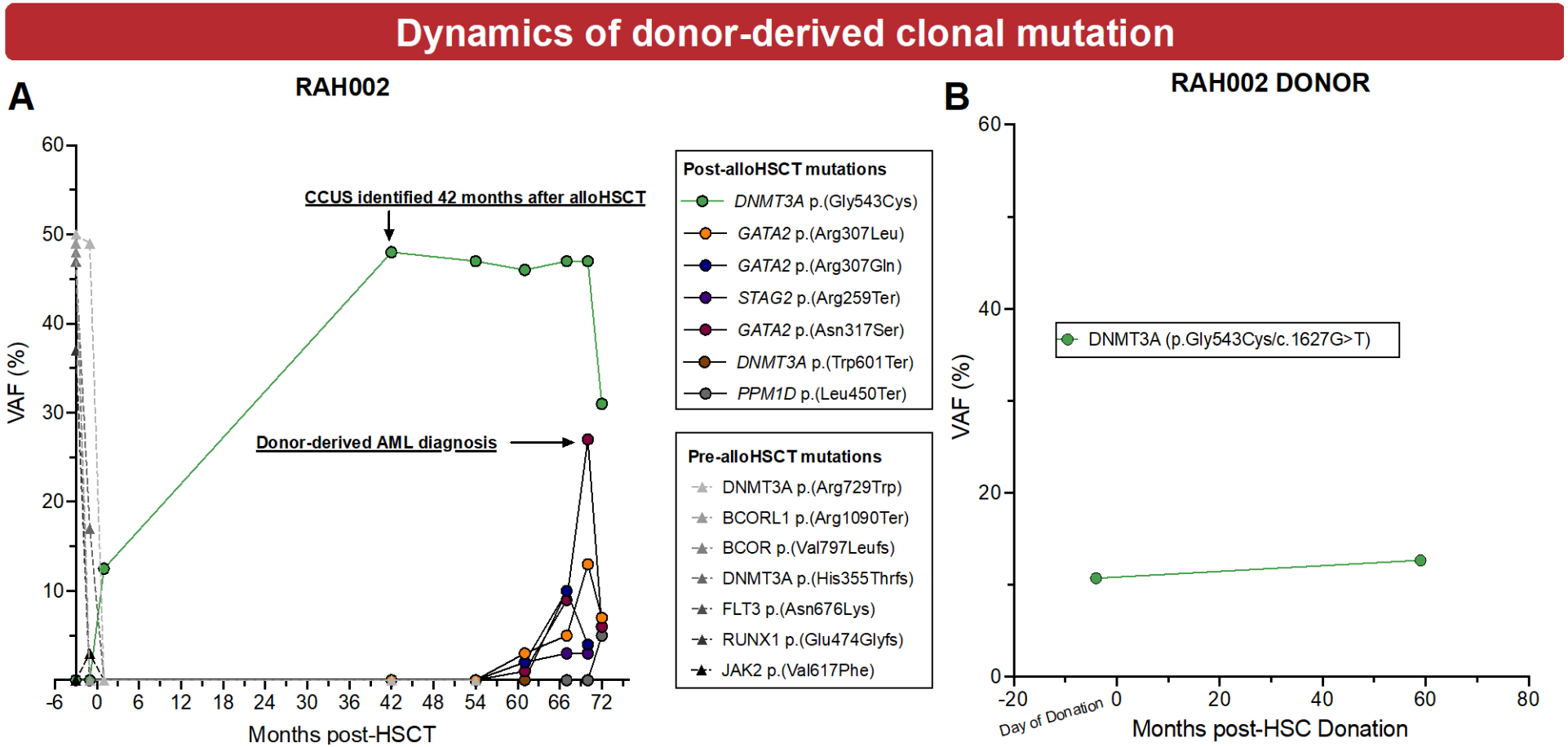
- Australian study – 15 DCL cases:



Wechalekar et al (ASH 2024)

* *DCL BM microenvironment promotes clonal expansion*

- Australian study – 15 DCL cases:



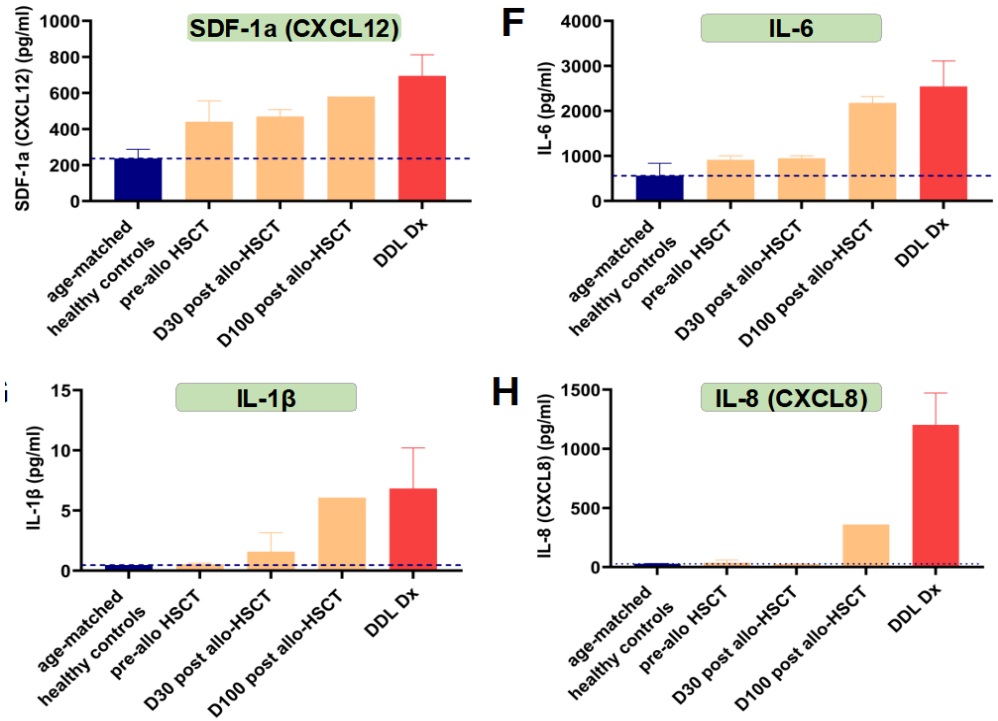
Wechalekar et al (ASH 2024)

* DCL BM microenvironment promotes clonal expansion

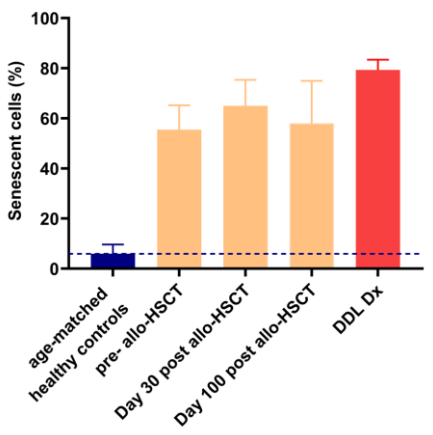
- Australian study – 15 DCL cases:

Bone marrow mesenchymal stromal are highly senescent and exhibit distinct defective proliferation and differentiation capacity

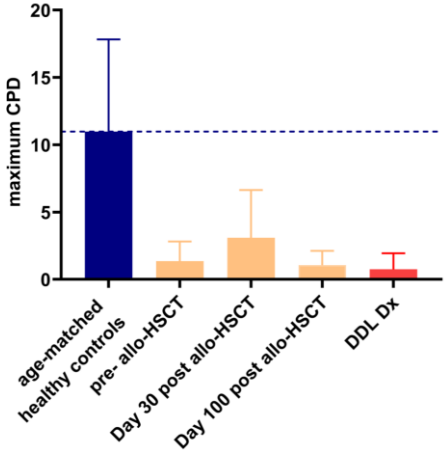
High levels of senescence associated secretory cytokines



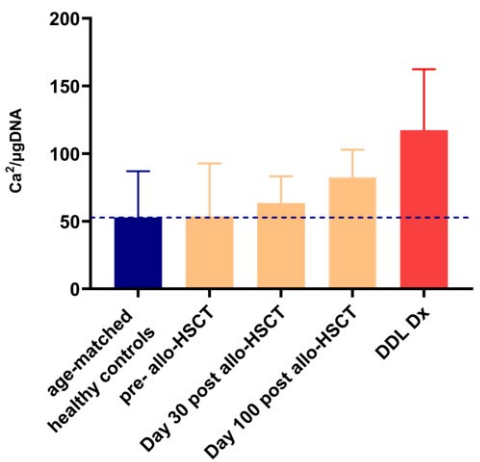
Profoundly senescent

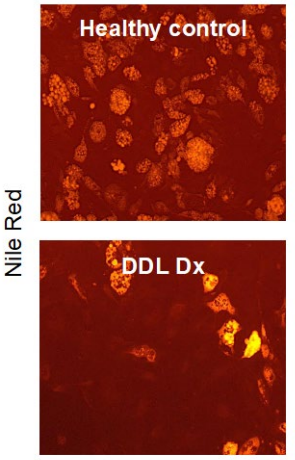


Poor proliferative capacity



Defective osteo- and adipogenic differentiation potential





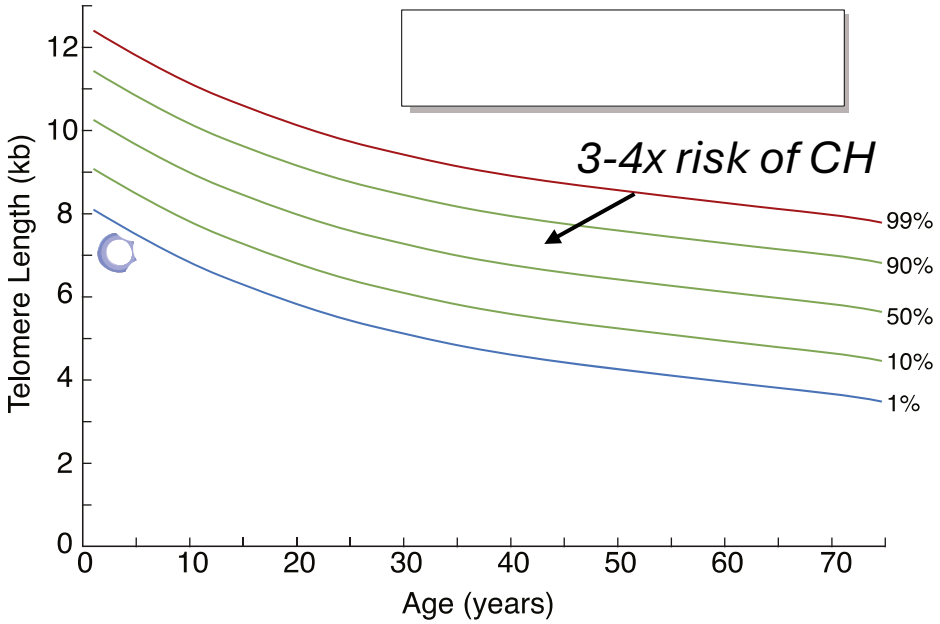
Wechalekar et al (ASH 2024)

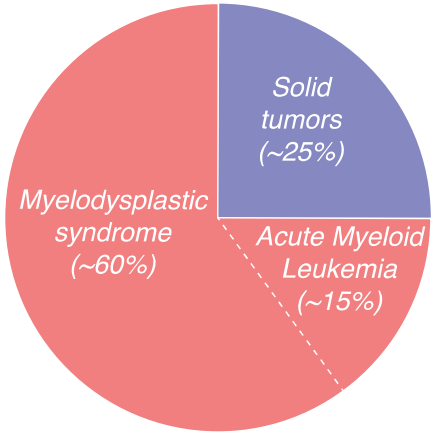
Telomere attrition ?

- Telomere shortening post HSCT
  - *Equivalent to ~15y (-40y) ageing*
  - *Mostly 1st year post-transplant*
  - *Early proliferative stress (→ senescence)*

❖ **Mouse models: Short telomeres → genomic instability → leukaemogenesis**

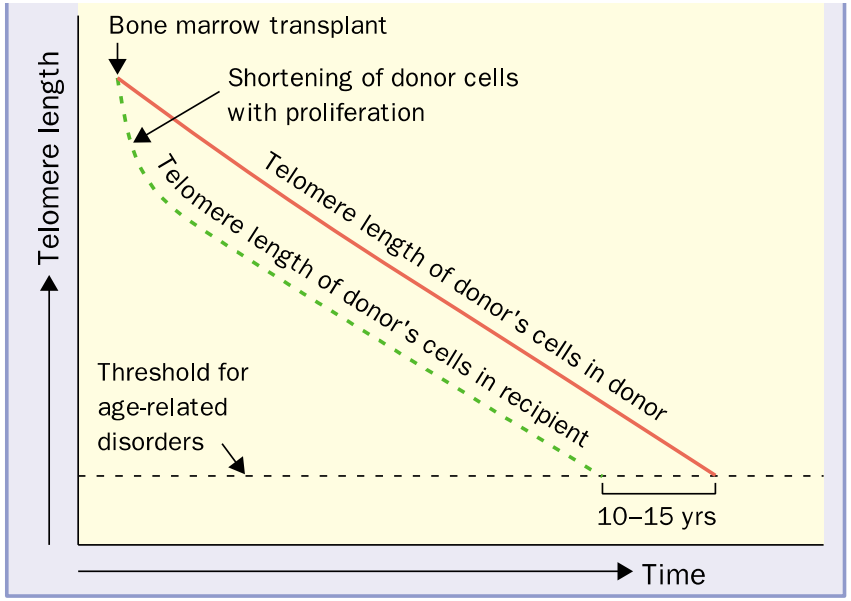
❖ ***Short Telomere Syndromes:***





Myeloid cancers

Solid tumors (common)
*Head and Neck SCC***
Anorectal SCC
Esophageal SCC

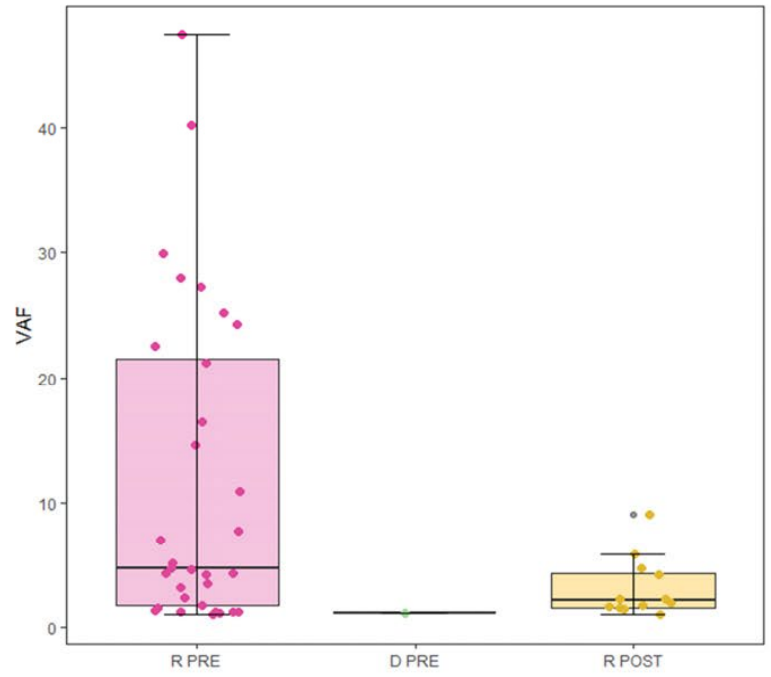


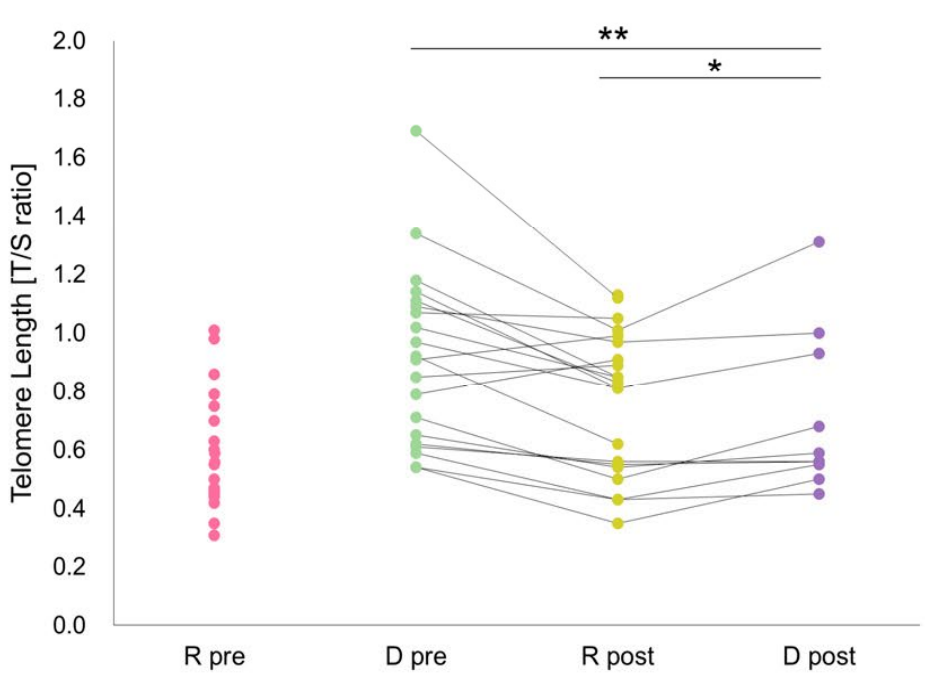
Gadalla (Blood 2020)

Baerlocher et al (Blood 2009)

Telomere attrition ?

- Longitudinal study of 21 MDS pts post Allo
- **38% → new somatic mutations (VAF≥1%)**
  - *<u>Much</u> higher rate vs 5183 age-matched controls*
- **Accelerated telomere shortening in ~all cases**





Kim et al (Int J Mol Sci 2024)

DCL – Treatment

- Poorly studied – rare / heterogeneous / anecdotal
- *?Best considered "new" AML (vs post-transplant 'relapse')*
  → standard re-induction chemo reasonable
- 2nd Allo attempted in some cases (limited success)

- **Overall prognosis is POOR**
  - EBMT survey: 29/38 dead (median 11mo)
  - Japanese survey: 4yOS 36.4%
  - Largest case report collection (n=162): mOS 9mo

- **Sustained remissions are achievable** in rare cases
  - *generally with Allo from new donor*

Engel et al (Leukemia 2019)
Kato et al (Leukemia 2016)
Williams et al (Bone Marrow Transplant 2021)

Donor Outcomes

- Outcome data on donors are limited (sporadic)
- Appears rare for donors to develop malignancy: but data sparse / likely underestimated
  - EBMT survey (1982-2003):
    - **0** reported malignancies in donors (/14 DCL)
  - EBMT updated survey (2021):
    - 25 donors with FU data (/38 DCL) → **2 AML, 5 chronic leukemia**
  - Japanese survey (2016):
    - **1 MDS** among 40 DCL donors
  - Largest case report series (2024):
    - 163 DCL → at least **5 AML, 2 MDS, 3 other malignancies**

Hertenstein et al (Haematologica 2005)
Engel et al (Leukemia 2019)
Williams et al (Transplant Cell Ther 2024)

Ethical Considerations

POINT Stem cell donors should be screened for CHIP

Amy E. DeZern and Lukasz P. Gondek

The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD

- CHIP is common – esp in older donors
- HIGH relative risk of MN (+ other pathology eg cardiovascular)
- *Precautionary principle*

COUNTERPOINT Stem cell donors should not be screened for clonal hematopoiesis

Christopher J. Gibson and R. Coleman Lindsley

- Insufficient evidence to support – no actionability of a +ve screening result
- Potential unintended negative consequences
- Need for clear consensus guidelines / standard methodological approaches / clinical infrastructure of donor notification & counselling

Gibson & LIndsley (Blood Adv 2020)
DeZern & Gondek (Blood Adv 2020)

A different type of "Donor Cell Leukaemia" (!)

- 51yF → ALL
- +8y after donor for brother (AA)
- Recipient still healthy
- **"Reverse" Allo from original recipient (!)**

Zhou et al (BMC Cancer 2020)

DCL: Summary

- **AML (or MDS/MPN) arising within cells of donor origin**
- Rare: Incidence 0.12-5%
- Heterogeneous latency – median 28mo *[longer than receipient-derived relapse]*
- Variable phenotype / genetics
  - *>20% carry ch7 abnormalities*
  - *CHIP/predisposition gene transfer in most (?all) cases*
- Poor prognosis – treat as *de novo* / on merits
- **Unique crucible to study:**
  1. **Dynamics/mechanisms of leukaemia initiation/expansion**
     - ***Multiple sequential BM biopsies typically performed – before / during / after***
  2. **Cell-extrinsic impacts (microenvironment; immune surveillance)**
     - ***Potential to track same clone in two BM contexts simultaneously***
- Ethical implications