Treatment of Advanced Neuroblastoma with EBV-Specific T-Lymphocytes Expressing a Chimeric Anti-GD2 Single Chain Antibody

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Neuroblastoma

- Cancer of childhood
- Approximately 550 new cases in the US each year
- Tumor cells are primitive neural crest

Neuroblastoma

- Approximately ½ of children with neuroblastoma will have widespread disease
- Treatment with multi-agent chemotherapy, surgery, radiation, and autologous transplant only results in 30% EFS at 3 years
- Long term sequelae in survivors including

Neuroblastoma

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- 21 open or developing NIH sponsored clinical trials including investigational

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IFN-γ Release of 14.G2a-ζ Transduced PBMC Upon Coincubation With C+ and C- Target Cells

Limitations of Chimeric T cells

- Poor activation through chimeric receptor pathway and signals through TCR-zeta chain alone are insufficient to prime resting T-cells *(Brocker T, Karjalainen K. J, Exp Med 1995; Brocker R, Blood 2001)*
- Lack of cognate help/co-stimulator molecules on tumor cells
- Consequence is poor functional activity

Experience with gene-marked

- Prevention and treatment of EBV-LPD post transplant

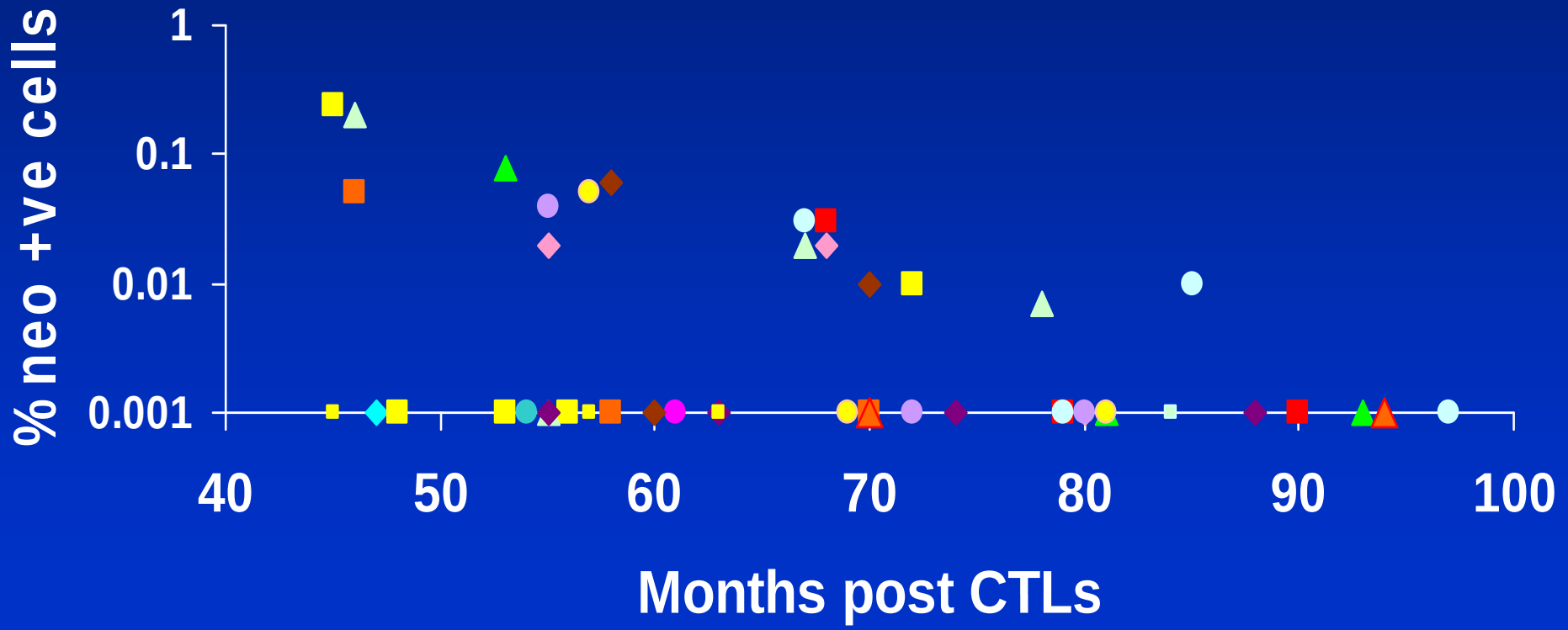
- Relapsed EBV+ve Hodgkin's

Neo DNA

CTL

Time post BMT (weeks)

Long Term Detection of Neo by Real Time PCR in PBM EBV CTL Study



Multiple Clones Persist

1) Multiple Vß subclasses on immunophenotyping

2) Multiple marked clones on inverse PCR

Markers

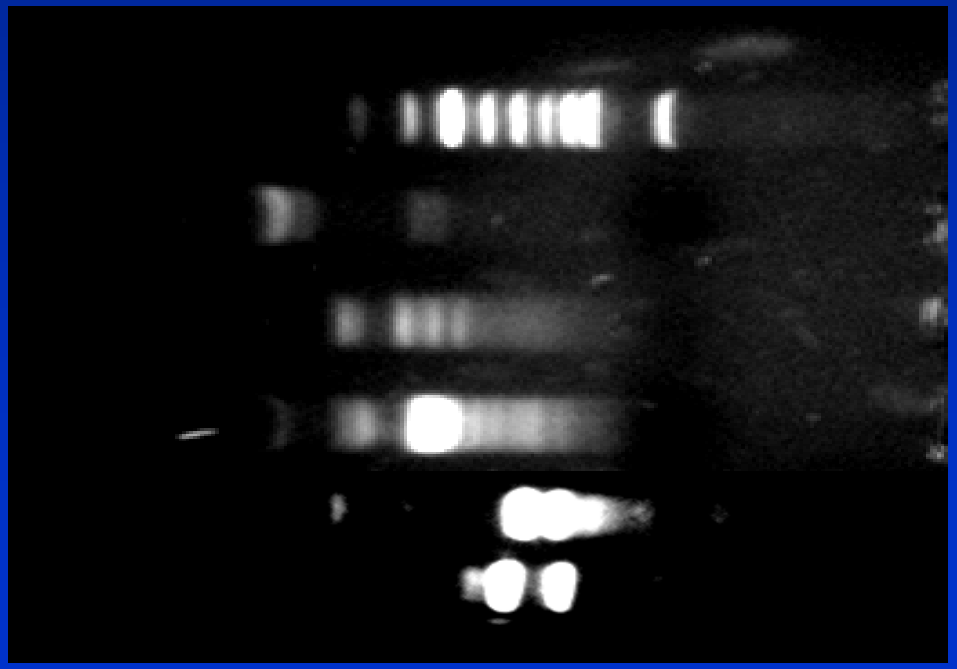
-ve control

+ve control

Patient 1

Patient 2

Patient 3



Human DNA involved in the virus integration site

Sequence analyses show non-coding or unknown sequences

Inv 3 chromosome 4 RP11-342E3 161701-161780

AACTTGAATTCTCTGCAGCATATCTAAGCTGTACATATACTTTTAGTT
CGACAAATTCTATTAATAGCTTAAATGGGATT

Inv 5 chromosome 15 RP11-573G7 109830-109906

CGATGTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTTACTT
TCACCAGCGTTTCTGGGTGAGCAAAAACATTA

Inv 7 chromosome 16 RP11-410N2 114096-114178

GACCTCCCAAAGCGCTGGGATTACAGGCGTGAGCCTCCGCGCCTGGC
CCTGGGCTATTACAGCACATCCTCAGCATCTAGTAC

Unknown sequence from 1 band

5' CGGATCCGTCGAGGGCCACGATGCGTCCGGCGTAGAGGATCTCTAGGCAAAGACGCCCTGA...../
3'GTTCTCCCCCTACACAGGTCTCACTAACATTCCTGATGTGCCGCAGGGACTCCGTCAGCCCGGTTTTTGTTTATAATA
AAATGCAAGAACAGTGTTCCCTTCAAGCCAGACTACATCCTGACTCTCGGCTTTATAAAAGAATGTTGAAGGGCTCTGT
GGACTATCTGCCACACGACTTTTAAGATTTTTATGCCTCCTGGATGAGGGATTTAGTCAATCTATCCTCGTCTATTTTGC
TGGCTTCTCCGTATTTTTAAATTTCTAGTTTGCACTCCCTTCCTGA

EBV Specific Cells With Chimeric Receptors

Hypothesis: EBV specific CTL with chimeric receptors will retain the known advantages of these cells (in vivo expansion, persistence and anti-EBV tumor activity) whilst developing new specificity against an additional tumor targeted by the chimeric receptor

Is a Clinical Study Justified?

- Longstanding safety and efficacy data with EBV CTL in humans
- Clinical experience with 14G2a MAb
- Preclinical safety data with GD2 chimeric EBV CTLs
- Preclinical safety data with murine antigen specific/chimeric T cells