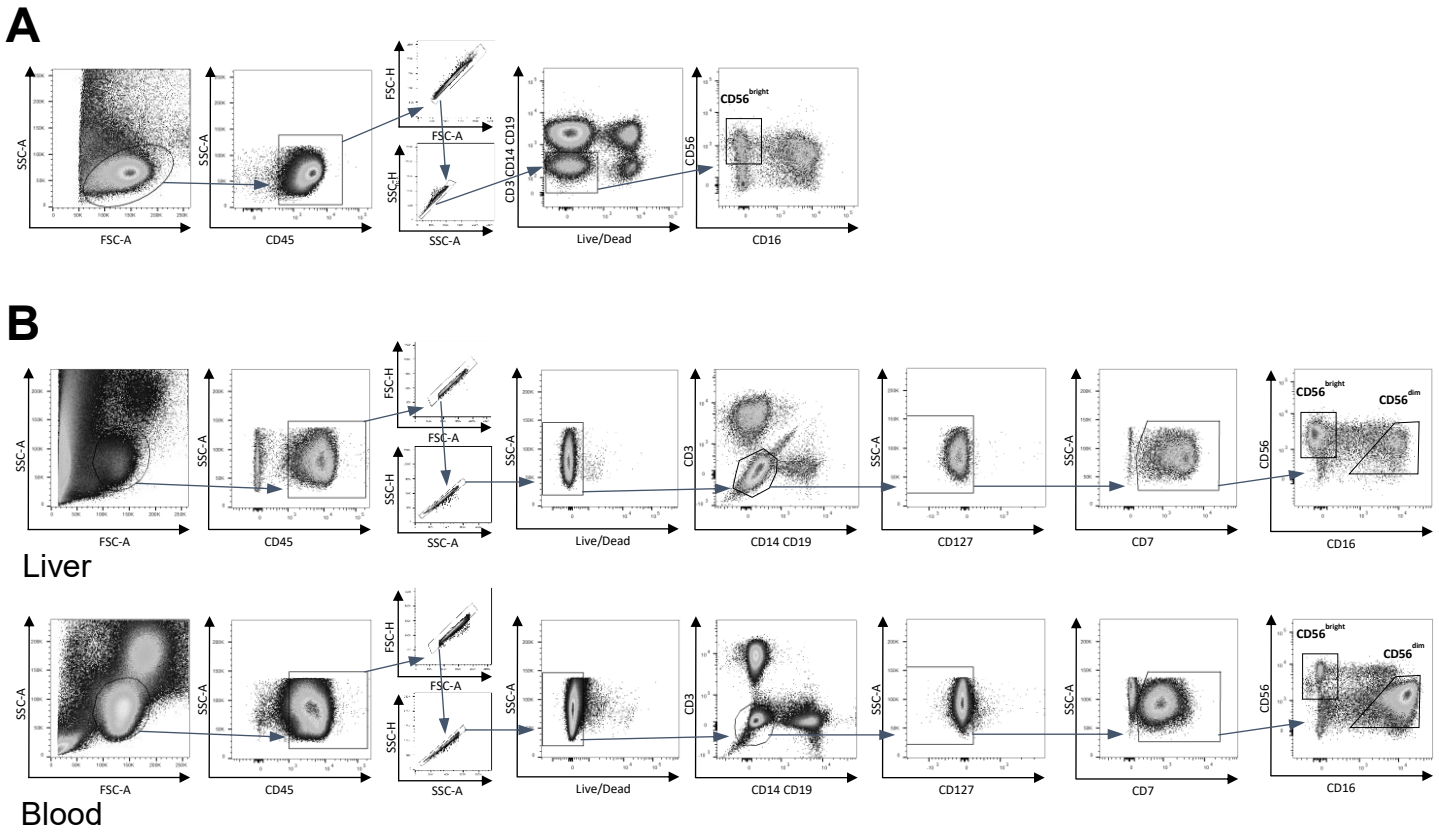
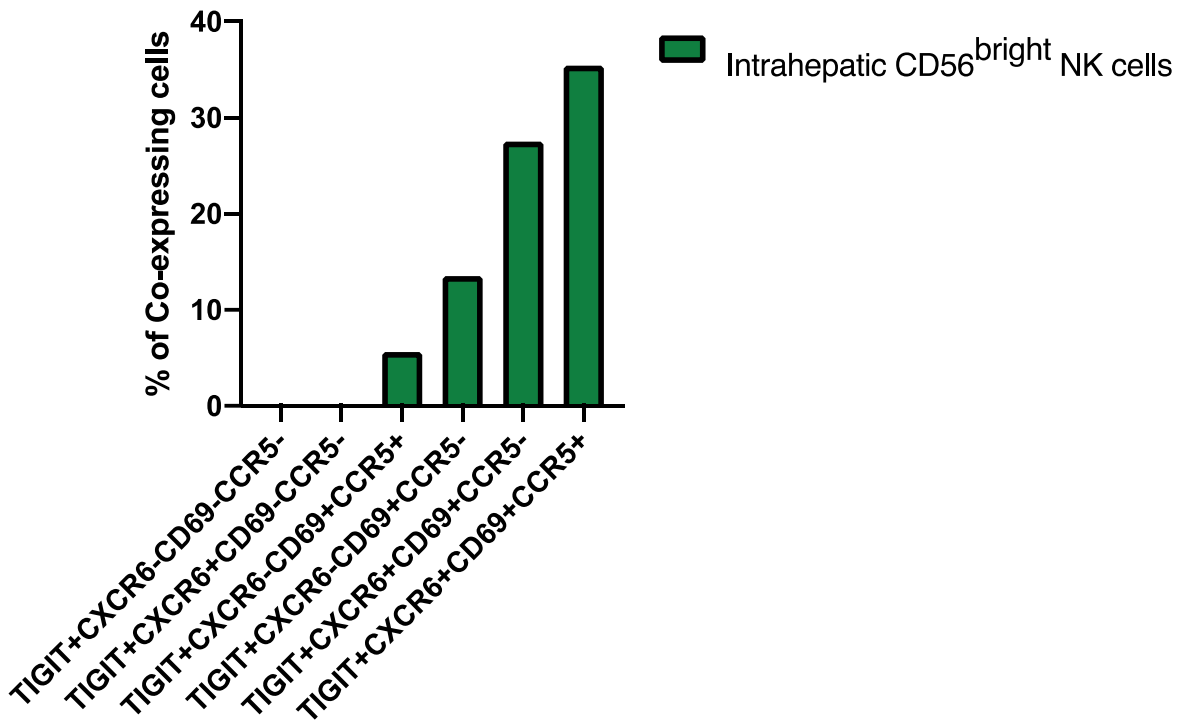
Supplementary Material



Supplementary Figure S1: Gating strategy for the identification of NK cells for single-cell mRNA analysis (A) and for phenotypical analysis (B).

Representative plots for the identification of $CD56^{bright}$ NK cells from liver samples (A+B) and PBMCs (B). (A) NK cells for single-cell mRNA analysis were defined as $CD45^{+}CD3^{-}CD14^{-}CD19^{-}CD16^{-}CD56^{bright}$ NK cells (B) NK cells for further phenotypical analysis were defined as $CD3^{-}CD14^{-}CD19^{-}CD127^{-}CD7^{+}CD16^{-}CD56^{bright}$ NK cells or $CD3^{-}CD14^{-}CD19^{-}CD127^{-}CD7^{+}CD16^{+}$ $CD56^{dim}$ NK cells.

Initial gating on FSC-Area and SSC-Area. Lymphocytes were identified using CD45. Exclusion of doublets (FSC Width and SSC Width). Zombie NIR was used as a Live/Dead marker.



Supplementary Figure S2: Co-expression analysis of *TIGIT* and markers for tissue-residency and/or tissue-homing in intrahepatic CD56^{bright} NK cells.
Graph displaying percentage of mRNA co-expression of *TIGIT* and markers for liver-residency and/or tissue-homing (*CXCR6*, *CD69*, *CCR5*) in intrahepatic CD56^{bright} NK cells.

Supplementary Table S1: Antibodies used for flow cytometry.

Antibody/Reagent (Dilution)	*Fluorochrome*	*Clone*	*Supplier*	*Cat#*
anti-CD3 (1:100)	BV510	UCHT1	BioLegend, San Diego, CA, USA	300448
anti-CD3 (1:100)	FITC	UCHT1	BioLegend, San Diego, CA, USA	300406
anti-CD3 (1:100)	BUV395	UCHT1	BD Bioscience, San Jose, CA, USA	563546
anti-CD7 (1:100)	BUV395	M-T701	BD Bioscience, San Jose, CA, USA	563845
anti-CD14 (1:100)	AF700	M5E2	BioLegend, San Diego, CA, USA	325614
anti-CD14 (1:100)	BV510	M5E2	BioLegend, San Diego, CA, USA	301842
anti-CD16 (1:100)	APC-Cy7	3G8	BioLegend, San Diego, CA, USA	302018
anti-CD16 (1:100)	BV785	3G8	BioLegend, San Diego, CA, USA	302046
anti-CD16 (1:100)	BUV737	3G8	BD Bioscience, San Jose, CA, USA	564434
anti-CD16 (1:100)	PE/Cy7	3G8	BioLegend, San Diego, CA, USA	302016
anti-CD19 (1:100)	AF700	HIB19	BioLegend, San Diego, CA, USA	302226
anti-CD19 (1:100)	BV510	HIB19	BioLegend, San Diego, CA, USA	302242
anti-CD45 (1:100)	BUV395	HI30	BD Bioscience, San Jose, CA, USA	563792
anti-CD45 (1:100)	AF700	2D1	BioLegend, San Diego, CA, USA	368514
anti-CD45 (1:100)	BV711	HI30	BD Bioscience, San Jose, CA, USA	564357
anti-CD56 (1:100)	BUV395	NCAM16.2	BD Bioscience, San Jose, CA, USA	563554
anti-CD56 (1:50)	BUV737	NCAM16.2	BD Bioscience, San Jose, CA, USA	564447
anti-CD56 (1:50)	BV786	NCAM16.2	BD Bioscience, San Jose, CA, USA	564058
anti-CD69 (1:100)	BV421	FN50	BioLegend, San Diego, CA, USA	310930
anti-CD69 (1:100)	BV605	FN50	BioLegend, San Diego, CA, USA	310938
anti-CD69 (1:100)	APC	FN50	BioLegend, San Diego, CA, USA	310910
anti-CD96 (1:50)	BV421	NK92.39	BioLegend, San Diego, CA, USA	338418
anti-CXCR6 (1:100)	PE-Cy7	K041E5	BioLegend, San Diego, CA, USA	356012
anti-CXCR6 (1:100)	PerCP/Cy5.5	K041E5	BioLegend, San Diego, CA, USA	356010
anti-TNFα (1:100)	PE/Cy7	MAb11	BioLegend, San Diego, CA, USA	502930
anti-CD107a (1:50)	BV711	H4A3	BioLegend, San Diego, CA, USA	328640
anti-CD127 (1:100)	AF700	A019D5	BioLegend, San Diego, CA, USA	351344
anti-CD226 (DNAM-1) (1:50)	BV605	11A8	BioLegend, San Diego, CA, USA	338302
Anti-CYP3A4 (1:50)	PE		Biorbyt Ltd, Cambridge, UK	Orb124579
Anti-PVR (1:50)	PE	SKII.4	BioLegend, San Diego, CA, USA	337610
Anti-PVR (1:50)	PE-Cy7	SKII.4	BioLegend, San Diego, CA, USA	337614
anti-TIGIT (1:50)	PE	A15153G	BioLegend, San Diego, CA, USA	372704
Mouse IgG1, κ isotype control (1:200)	PE	MOPC-21	BioLegend, San Diego, CA, USA	400112
Mouse IgG1, κ isotype control (1:200)	PE-Cy7	MOPC-21	BioLegend, San Diego, CA, USA	400125
Zombie Aqua Fixable Viability Kit			BioLegend, San Diego, CA, USA	423102
Zombie NIR Fixable Viability Kit			BioLegend, San Diego, CA, USA	423105

Supplementary Table S2: Primers used for single-cell mRNA analysis:

Target	*Forward primer (5‘ to 3‘)*	*Reverse primer (5‘ to 3‘)*
AHR	TAGGCTCAGCGTCAGTTACC	TGGCCTCCGTTTCTTTCAGTA
B2M	TTAGCTGTGCTCGCGCTAC	TTAGCTGTGCTCGCGCTAC
CCR5	TGAGACATCCGTTCCCCTACA	TGGCAGGGCTCCGATGTATA
CCR6	AGGCAGCGATGTCTGTGAA	AGCTCAAGCCCCAACATCA
CD38	ACCTCACATGGTGTGGTGAA	GTTGCTGCAGTCCTTTCTCC
CD69	TCACCCATGGAAGTGGTCAA	ACACACTTGTCAGACCCTGTA
CXCR3	AACTGTGGCCGAGAAAGCA	TTGAGGCAGCAGTGCATGTA
CXCR5	ATCTTCTTCCTCTGCTGGTCAC	GGTATTGTCCACGGCCTTCA
CXCR6	TCTCTGGAACAAACTGGCAAA	CTGGCTGCTGTCATTGAAAC
EOMES	CTGTGGCAAAGCCGACAATA	CTCATCCAGTGGGAACCAGTA
FCER1G	CAGCAGTGGTCTTGCTCTTAC	GGAGGGTGAGGACAATTCCATA
FCGR3A	CATTCTTTCCACCTGGGTACCA	AGTCCTGTGTCCACTGCAAA
GAPDH	GAACGGGAAGCTTGTCATCAA	ATCGCCCCACTTGATTTTGG
GZMK	ATCCACAGTGGGTGCTGAC	AGAGTGTGCGCCTAAAACCA
HLA-DRA	CGCTCAGGAATCATGGGCTA	CGCCTGATTGGTCAGGATTCA
IFNG	ACTGCCAGGACCCATATGTAA	GTTCCATTATCCGCTACATCTGAA
IL18	ACCAAGGAAATCGGCCTCTA	ACCTCTAGGCTGGCTATCTTTA
IL18R1	GGGAGGCACAGACACCAAAA	TGAAGACGTGGCCTGGGATA
IL22	TATCACCAACCGCACCTTCA	GTTTCTCCCCAATGAGACGAAC
IL2RB	CACCGCCCCATGTCTCA	CAGGGGCCGCCATTACA
IL7R	GGAGAAAGTGGCTATGCTCAA	CTGCGATCCATTCACTTCCA
IRF1	AACAAGGATGCCTGTTTGTTCC	TGGGATCTGGCTCCTTTTCC
IRF8	GGAGTCAGCTCCTTCCAGAC	CGCGTCGTAGGTGGTGTA
ITGA1	CGGTGGAAGACATGTTTGGATA	GCCAACTAACGGAGAACCAA
ITGAM	GCCGGTGAAATATGCTGTCTAC	GGTATTCTCTGAGGCCGTGAA
KLRB1	GGACATTCAACAGAGCAGGAA	CTCGGAGTTGCTGCCAATATA
KLRC3	CAGGCCTGTGCTTCAAAGAA	CACCAATCCATGAGGAAGGTAA
NCAM1	ATGCGACCATCCACCTCAAA	GTGACCTGCTCCTCTAATTCCA
NCR1	AACCATGCCTGGTCTTTCCC	TGCAAGGCTGGTGTTCTCAA
PDK1	ACCAAGACCTCGTGTTGAGAC	AAGACGTGATATGGGCAATCCA
PRF1	GTACAGCTTCAGCACTGACAC	CTGGGTGGAGGCGTTGAA
PTPRC	GTGGCTTAAACTCTTGGCATTT	GGGAAGGTGTTGGGCTTT
RORA	CAGCAGATAACGTGGCAGAC	GGCACACAATTGCCACATCA
RPL13A	GAGGCCCCTACCACTTCC	GCCGTCAAACACCTTGAGAC
RUNX3	AGCACCACAAGCCACTTCA	TCGGAGAATGGGTTCAGTTCC
S1PR1	TCATCGTCCGGCATTACAAC	ACACCACCGAGGTCAGTTTA
S1PR5	CGCCTTCATCGTGCTAGAGAA	GGAACATGGGAGCGTGGAA
SERPINB1	TGCCGGATGACATTGAGGAC	AGTCCACTCATGCAACTTTTCCA
SMAD4	CACCAAAACGGCCATCTTCA	GGAATGCAAGCTCATTGTGAAC
SMAD7	CTTCATCAAGTCCGCCACAC	TTGATGGAGAAACCGGGGAA
STAT1	ATGCTGGCACCAGAACGAA	GCTGGCACAATTGGGTTTCAA
STAT3	AGCATCGAGCAGCTGACTAC	CCATGTGATCTGACACCCTGAA
STAT4	GCAAGACGAATTTGACTACAGGTA	TCCTGATTCACCATGGCACTA
STAT5A	CCCAGGCTCCCTATAACATGTA	ATGGTCTCATCCAGGTCGAA
STAT6	TGTCCTGGTCGCAGTTCA	TCCAGGACACCATCAAACCA
TBX21	GGGCGTCCAACAATGTGAC	CCGTCGTTCACCTCAACGATA
TGFBR1	ACAGAAGTTAAGGCCAAATATCCC	GCTCCATTGGCATACCAACA

TGFBR2	TTCCCAGCTTCTGGCTCAAC	GGTCCCAGCACTCAGTCAAC
TIGIT	GTGGTGGTCGCGTTGACTA	TCCTGTCCAGCTGATTTTCTCC
TNFSF10	AGAAGGAAGGGCTTCAGTGAC	CCTGGACCTCCATCATAGCC
ZBTB16	AGCCACACGGCTCTCAAA	AGCTGCCACAGAACTCACA
ZEB2	AGGCCAATGGGCAAGAAGAA	AGGTCAGCAGTTGGGCAAA

Supplementary Table S3: Differentially expressed genes comparing patient derived ihCD56^{bright} NK cells *(liver)*, patient derived pbCD56^{bright} NK cells *(blood)* and healthy control pbCD56^{bright} NK cells *(blood control).*

Differentially expressed genes	Groups		
CCR5	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
CCR6	Ref group (liver)	.	
	Group 2 (blood)	0.996001	
	Group 3 (blood control)	p<0.05	*
CD38	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	0.000052642	***
CD69	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
CXCR3	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
CXCR6	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
EOMES	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
FCER1G	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
FCGR3A	Ref group (liver)	.	
	Group 2 (blood)	p<0.05	*
	Group 3 (blood control)	0.143934	
IFNG	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
IL18	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	0.657329	
IL18R1	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	0.148225	
IL22	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.001	**
IL2RB	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.05	*

IL7R	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	0.0560555	
IRF1	Ref group (liver)	.	
	Group 2 (blood)	p<0.05	*
	Group 3 (blood control)	0.474638	
IRF8	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
ITGA1	Ref group (liver)	.	
	Group 2 (blood)	p<0.05	*
	Group 3 (blood control)	0.20705	
ITGAM	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.05	*
KLRB1	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
KLRC3	Ref group (liver)	.	
	Group 2 (blood)	0	***
	Group 3 (blood control)	0.959982	
NCAM1	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	0.971472	
NCR1	Ref group (liver)	.	
	Group 2 (blood)	p<0.001	**
	Group 3 (blood control)	p<0.0001	***
PRF1	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	0.648428	
PTPRC	Ref group (liver)	.	
	Group 2 (blood)	p<0.001	**
	Group 3 (blood control)	p<0.05	*
RORA	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
RUNX3	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	0.640389	
S1PR1	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.001	**
S1PR5	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
SERPINB1	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.05	*

STAT1	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	0.878365	
STAT3	Ref group (liver)	.	
	Group 2 (blood)	0.227315	
	Group 3 (blood control)	p<0.05	*
STAT4	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
STAT6	Ref group (liver)	.	
	Group 2 (blood)	0.89722	
	Group 3 (blood control)	p<0.05	*
TBX21	Ref group (liver)	.	
	Group 2 (blood)	p<0.001	**
	Group 3 (blood control)	0.0931068	
TGFBR2	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
TIGIT	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***
TNFSF10	Ref group (liver)	.	
	Group 2 (blood)	p<0.05	*
	Group 3 (blood control)	p<0.001	**
ZBTB16	Ref group (liver)	.	
	Group 2 (blood)	p<0.0001	***
	Group 3 (blood control)	p<0.0001	***