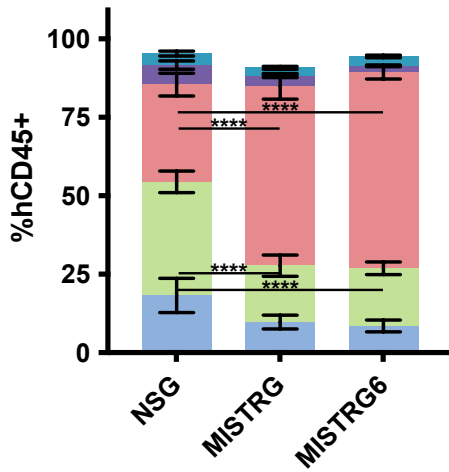


Supplementary Figure 1

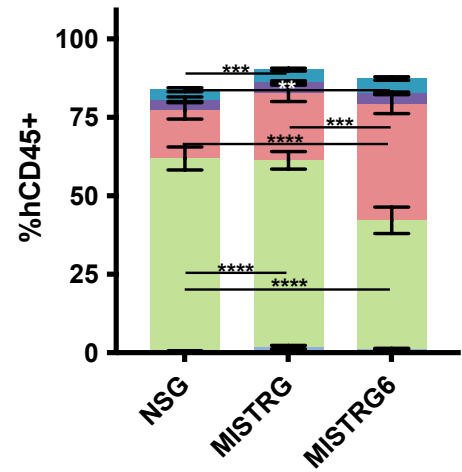
S1A.

FL



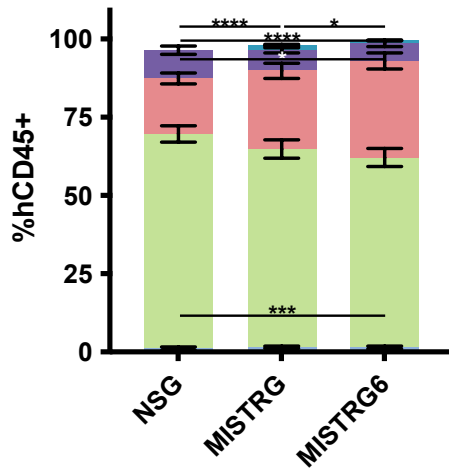
S1B.

MPB



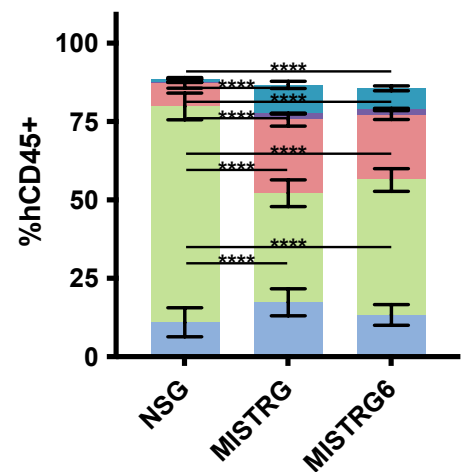
S1C.

BM



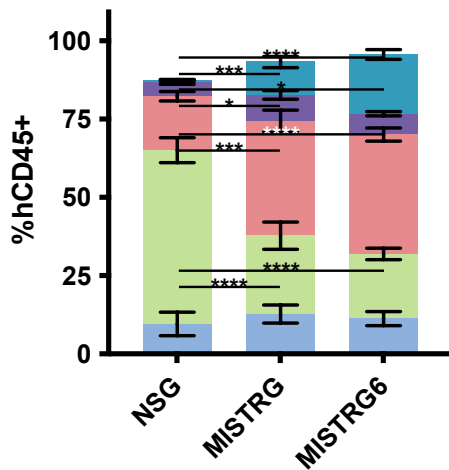
S1D.

Spleen



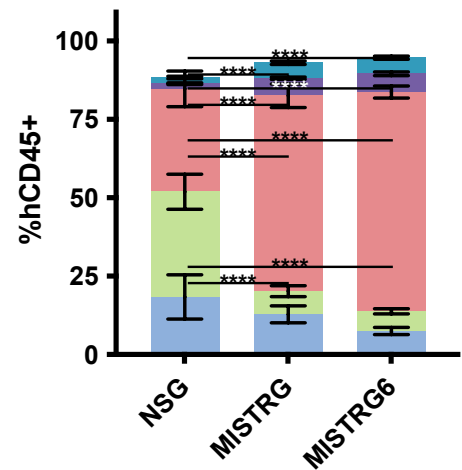
S1E.

Liver

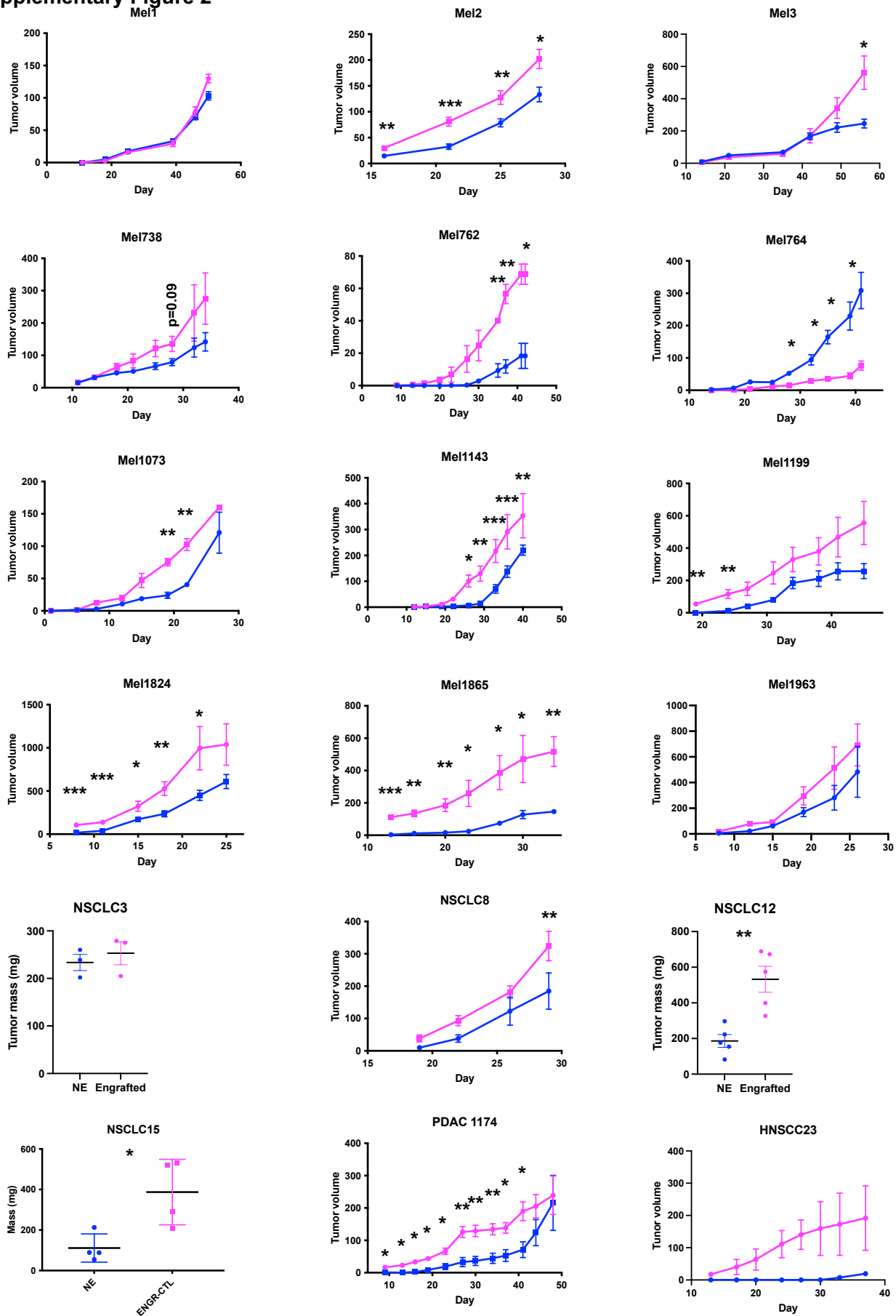


S1F.

Lung

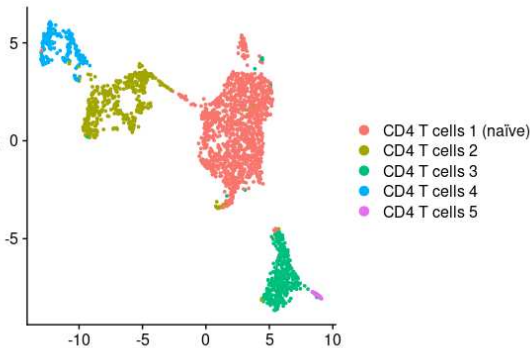


Supplementary Figure 2

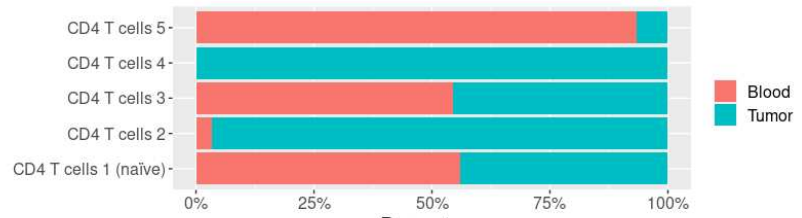


Supplementary Figure 3

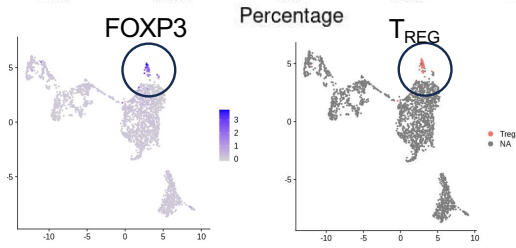
S3A.



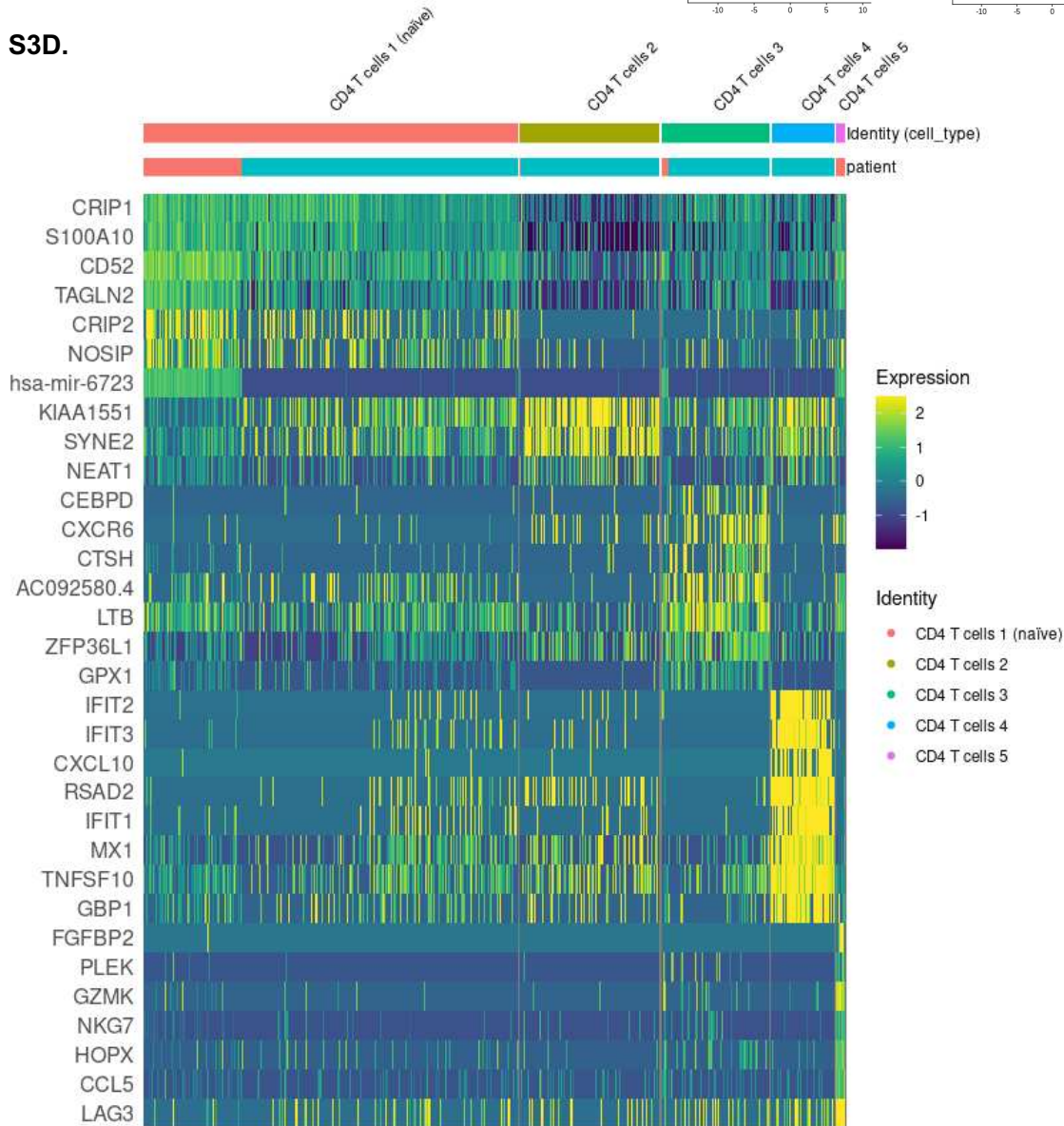
S3B.



S3C.



S3D.



Supplementary Table 1

| Patient | Age | Sex | Tumor Type | Diagnosis | CD34+ cell # | PDX? |
|---------|-----|-----|------------|-----------------------------------|--------------|------|
| 1 | 65 | F | NSCLC | Stage IA adenocarcinoma | <100k | |
| 2 | 73 | F | NSCLC | Stage IA adenocarcinoma | 150k | |
| 3 | 82 | F | NSCLC | Stage IA squamous cell carcinoma | 3.9 million | Yes |
| 4 | 56 | M | NSCLC | Stage IIB large cell carcinoma | 4 million | |
| 5 | 70 | F | NSCLC | Mucoepidermoid carcinoma | 5.1 million | |
| 6 | 57 | F | NSCLC | Adenosquamous carcinoma | 7 million | |
| 7 | 70 | M | NSCLC | Stage IB adenocarcinoma | 6.5 million | Yes |
| 8 | 62 | F | NSCLC | Stage IA adenocarcinoma | 6 million | Yes |
| 9 | 79 | M | NSCLC | Stage IIA squamous cell carcinoma | 3.7 million | Yes |
| 10 | 71 | M | NSCLC | Stage IA adenocarcinoma | 14 million | |
| 11 | 63 | F | NSCLC | Stage IA adenocarcinoma | 8.2 million | |
| 12 | 79 | F | NSCLC | Stage IV squamous cell carcinoma | 2.7 million | Yes |
| 13 | 54 | F | NSCLC | Stage II adenocarcinoma | 5.0 million | |
| 14 | 57 | M | NSCLC | Stage IV NSCLC | 2.5 million | |
| 15 | 72 | M | NSCLC | Stage IV adenocarcinoma | 3.6 million | Yes |
| 16 | 74 | M | NSCLC | Stage IV adenocarcinoma | 3.4 million | |
| 17 | 73 | M | NSCLC | Stage IV neuroendocrine tumor | 6.6 million | |
| 18 | 72 | F | NSCLC | Stage IV NSCLC | 4 million | |
| 19 | 79 | F | NSCLC | Stage IV NSCLC | 2.7 million | Yes |
| 20 | 78 | F | HNSCC | Stage II HNSCC of lateral tongue | 1 million | Yes |
| 21 | 63 | F | HNSCC | Stage IVa HNSCC of buccal mucosa | 2 million | Yes |
| 22 | 46 | F | Melanoma | Stage IV melanoma | 6 million | |
| 23 | 70 | F | Melanoma | Stage IIIc melanoma | 250k | |
| 24 | 62 | M | Melanoma | Stage IV melanoma | 2.2 million | |
| 25 | 67 | M | Melanoma | Melanoma | 1.8 million | |
| 26 | 61 | M | Melanoma | Stage IIIc melanoma | 100k | |
| 27 | 34 | M | Melanoma | Melanoma | 1.9 million | |
| 28 | 61 | F | Melanoma | Stage IV melanoma | 1 million | |
| 29 | 57 | M | Melanoma | Stage IV melanoma | 2.5 million | Yes |
| 30 | 55 | F | Melanoma | Melanoma | 2 million | |
| 31 | 42 | M | Melanoma | Stage IV melanoma | 4.8 million | Yes |
| 32 | 22 | M | Melanoma | Stage IIIc melanoma | 3 million | |
| 33 | 52 | F | Melanoma | Stage IIb melanoma | 4 million | Yes |
| 34 | 65 | M | Melanoma | Stage IV melanoma | n/a | |
| 35 | 71 | F | Melanoma | Melanoma | 500k | |
| 36 | 53 | M | Melanoma | Stage IIIc melanoma | 600k | |
| 37 | 71 | M | Melanoma | Melanoma | 80k | |
| 38 | 65 | M | Melanoma | Stage IIIc melanoma | 1.5 million | |
| 39 | 73 | M | Melanoma | Stage IIIb melanoma | 3.4 million | |
| 40 | 65 | M | Melanoma | Stage IIIb melanoma | 1.8 million | |
| 41 | 43 | F | Melanoma | Stage IIIc melanoma | 3.6 million | |
| 42 | 50 | F | Melanoma | Stage IIIc melanoma | 7 million | |
| 43 | 42 | M | Melanoma | Stage IIIc melanoma | 3.6 million | Yes |
| 44 | 54 | F | PDAC | Pancreatic adenocarcinoma | 1.2 million | |
| 45 | 48 | M | PDAC | Pancreatic adenocarcinoma | 2.5 million | Yes |
| 46 | 48 | M | Melanoma | Stage IV melanoma | 2.1 million | Yes |
| 47 | 67 | M | PDAC | Pancreatic adenocarcinoma | 1.6 million | Yes |
| 48 | 85 | F | PDAC | Pancreatic adenocarcinoma | 6.8 million | Yes |
| 49 | 80 | M | Melanoma | Stage IIIc melanoma | 1.95 million | Yes |
| 50 | 75 | F | Melanoma | Stage IIIb melanoma | 5.5 million | |
| 51 | 51 | M | Melanoma | Stage IIIc melanoma | 8.5 million | Yes |
| 52 | 74 | M | Melanoma | Stage IV melanoma | 5 million | Yes |
| 53 | 35 | M | Melanoma | Stage IIIc melanoma | 6.1 million | |
| 54 | 81 | M | Melanoma | Stage IIIb melanoma | 3 million | |
| 55 | 63 | M | Melanoma | Stage IIIc melanoma | 3.1 million | Yes |
| 56 | 35 | M | Melanoma | Stage IIIc melanoma | 3 million | |
| 57 | 60 | M | Melanoma | Stage IV melanoma | 1.4 million | |
| 58 | 64 | F | Melanoma | Stage IV melanoma | 2.5 million | |
| 59 | 57 | M | Melanoma | Stage IIIc melanoma | 4.5 million | |
| 60 | 51 | F | Melanoma | Stage IIIc melanoma | 2.6 million | |
| 61 | 58 | F | Melanoma | Stage IV melanoma | 2.4 million | |
| 62 | 48 | M | Melanoma | Stage IIIc melanoma | 1.76 million | Yes |
| 63 | 68 | M | Melanoma | Stage IV melanoma | 4 million | Yes |
| 64 | 30 | M | Melanoma | Stage IIIc melanoma | 12 million | |
| 65 | 79 | M | Melanoma | Stage III melanoma | 2.8 million | Yes |
| 66 | 47 | M | Melanoma | Stage IIIc melanoma | 2.4 million | |
| 67 | 42 | M | Melanoma | Stage IIIb melanoma | 4.6 million | Yes |
| 68 | 83 | M | Melanoma | Stage IIIc melanoma | 2.8 million | |
| 69 | 33 | M | Melanoma | Stage IIIc melanoma | 4.8 million | |
| 70 | 58 | M | Melanoma | Stage IIIc melanoma | 1.8 million | |
| 71 | 57 | F | Melanoma | Stage IIIc melanoma | 820k | |

Supplementary Figure Legends:**Supplementary Figure 1: MISTRG6 mice display robust peripheral blood and tissue engraftment of human cell types, including innate immune cells.**

A. Human hematopoietic cells in peripheral blood from mice of indicated strains engrafted with FL-derived CD34⁺ cells, including T cells (hCD3⁺, blue), B cells (hCD19⁺, green), myeloid cells (hCD33⁺, red), neutrophils (hCD66b, SSC^{hi}, purple), NK cells (hNKp46⁺, teal).

B. Human hematopoietic cell profiles in peripheral blood from mice of indicated strains engrafted with CD34⁺ cells isolated from mobilized peripheral blood (MPB) of adult donors.

C. Human hematopoietic cell profiles in BM from mice of indicated strains engrafted with FL-derived CD34⁺ cells.

D. Human hematopoietic cell profiles in spleen from mice of indicated strains engrafted with FL-derived CD34⁺ cells.

E. Human hematopoietic cell profiles in liver from mice of indicated strains engrafted with FL-derived CD34⁺ cells.

F. Human hematopoietic cell profiles in lung from mice of indicated strains engrafted with FL-derived CD34⁺ cells.

Supplementary Figure 2: Autologously-engrafted MISTRG6 mice support enhanced tumor growth in multiple patient models.

Tumor growth curves for non-engrafted (blue) and autologously engrafted (magenta) PDX mice representing indicated patients; * p<0.05, ** p<0.01, *** p<0.001, unpaired parametric t-test; bars indicate mean and S.E.M. Mel1 n=3 non-engrafted, n=8 engrafted; Mel2 n=13 non-engrafted, n=4 engrafted; Mel3 n=6 non-engrafted, n=5 engrafted; Mel738 n=3 non-engrafted, n=3 engrafted; Mel762 n=3 non-engrafted, n=3 engrafted; Mel764 n=3 non-engrafted, n=3 engrafted; Mel1073 n=4 non-engrafted, n=5 engrafted; Mel1143 n=5 non-engrafted, n=5 engrafted; Mel1199 n=8 non-engrafted, n=12 engrafted; Mel1824 n=6 non-engrafted, n=5 engrafted; Mel1865 n=4 non-engrafted, n=5 engrafted; Mel1963 n=5 non-engrafted, n=4 engrafted; NSCLC3 n=3 non-engrafted, 3 engrafted; NSCLC8 n=6 non-engrafted, n=6 engrafted; NSCLC12 n=5 non-engrafted, n=5 engrafted; NSCLC15 n=4 non-engrafted, n=4 engrafted; PDAC1174 n=4 non-engrafted, n=9 engrafted; HNSCC23 n=2 non-engrafted, n=3 engrafted.

Supplementary Figure 3: Blood and tumor-resident CD4 T cells display distinct transcriptional states including naïve and interferon-responsive subtypes.

A. Re-clustering of CD4 T cells reveals sub-structure of 5 clusters.

B. Cluster representation of CD4 T cell subclusters in tissues.

C. Expression of FOXP3 gene in a subset of CD4 T cells.

D. Heatmap indicating expression of top differentially expressed genes between each cluster, highlighting interferon activation signature of CD4 4 cluster.

Supplementary Table 1.

Clinical data of patients enrolled in prospective study collecting tumor and BM from solid tumor patients; indicated PDXs grew sufficiently for autologous humanized mouse modeling.