BST281
Lab Session 10

Announcement:

- The last homework will be posted within this week, and you will have two weeks work on it.

- This is the last lab section that has material, the next three labs will be reserved for groups discussing final projects.

- Todays lab will be a background talk on ImmunoGenomics.

Our immune system

- The **immune system** is a host defense system comprising many biological structures and [processes](#) within an [organism](#) that protects against [disease](#).[1]
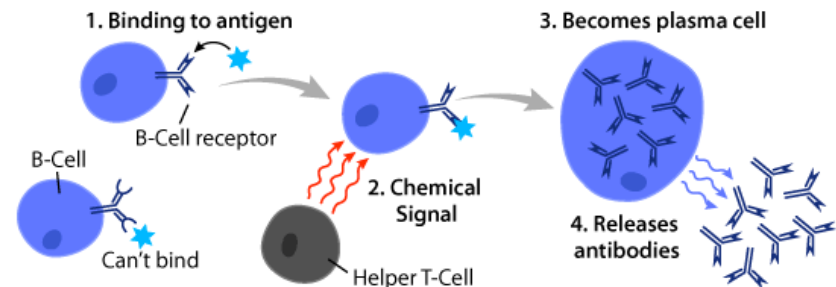
(1) Innate immune system
  - Surface barriers, inflammation, natural killer cells

(2) Adaptive immune system
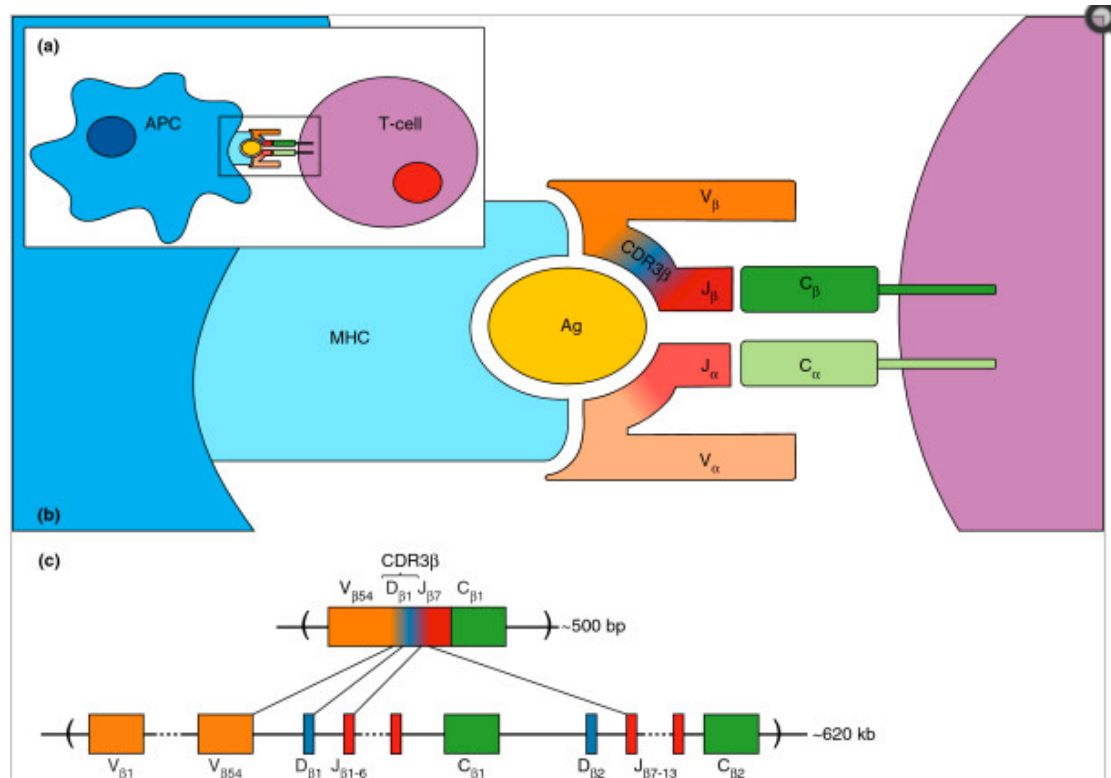 - Lymphocytes (T cells, B cells)
  - Immunological memory

- What is "repertoire of immune cells"?

https://www.youtube.com/watch?v=nWdyK3SRzO8

1. https://en.wikipedia.org/wiki/Immune_system
2. Image come from https://askabiologist.asu.edu/b-cell
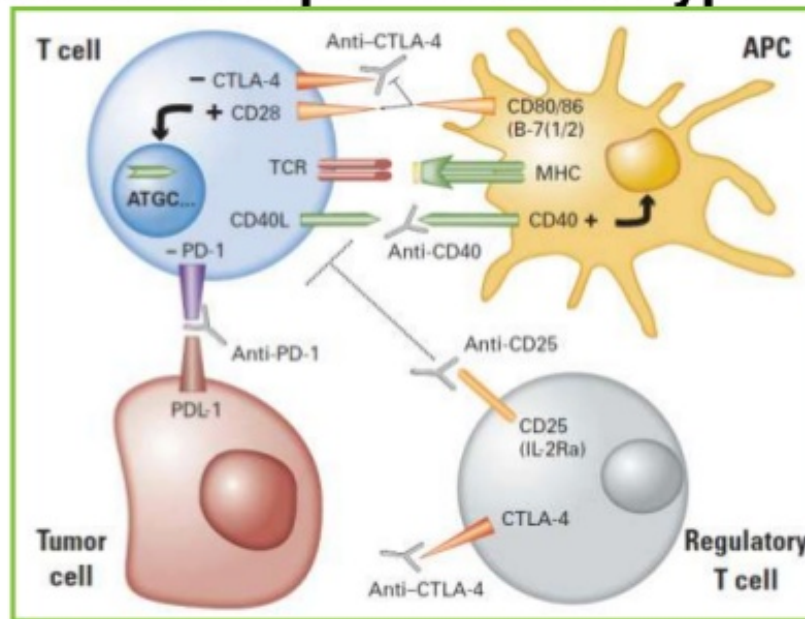
T cell repertoire analysis

Woodsworth, Daniel J, Mauro Castellarin, and Robert A Holt. "Sequence Analysis of T-Cell Repertoires in Health and Disease." *Genome Medicine* 5.10 (2013): 98. *PMC*. Web. 1 Oct. 2016.

Immunotherapy
e.g. PD-1 blockade
https://www.youtube.com/watch?v=AbmEt_E8kfo

CTLA-4 and PD-1 Blockade May Prolong T-cell Activation in Multiple Tumour Types

- Ipilimumab, an anti-CTLA-4 monoclonal antibody, was recently approved by the US Food and Drug Administration for use in patients with metastatic melanoma[2]

1. Kandalaft LE, et al. *J Clin Oncol* 29:925-933.
2. "Ipilimumab", http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm248478.htm.

Terminology

- Diversity (entropy)

$$H(X) = \sum_{i=1}^{n} P(x_i)I(x_i) = -\sum_{i=1}^{n} P(x_i)log_2 P(x_i) \text{ , } here \ X \in (CDR3, clonatype)$$

- Richness: total unique # CDR3s

Some Public TCR-Seq datasets

❖ Robins

❖ Hsu

❖ Robert

Disease/state	Treatment	Blood sample	Tumor sample
Healthy donor	/	587	/
Giloblastoma	DC vaccination	5	5
Melanoma	anti-PD-1	21	/

*TCRβ sequencing using AdaptiveBiotech ImmunoSeq deep resolution

TCR diversity correlates with age better than richness and is a potential indicator for immune function.
– Robins' dataset (587 HD)

F: entropy vs age — Correlation: -0.33
M: entropy vs age — Correlation: -0.36
F: entropy vs TCR count — Correlation:0.75
M: entropy vs TCR count — Correlation:0.65

Figure 2a: Scatterplot of **Entropy** and **Age** (by gender) **Figure 2b**: Scatterplot of **Entropy** and **Total count** (by gender)

Significant entropy difference between genders
– Robins' dataset (587 HD)
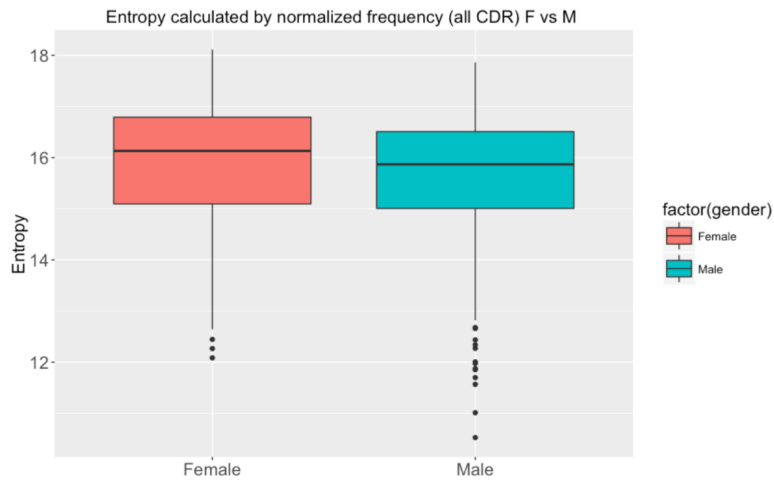
Figure 4: Boxplot of **Entropy** by gender

- female tend to have higher immune function than male in the same age group

TCR diversity correlates with age better than richness and is a potential indicator for immune function.
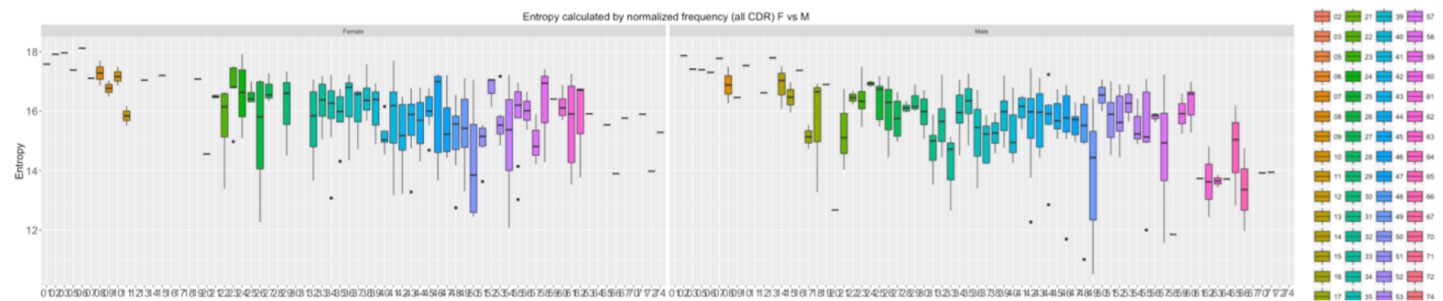## – Robins' dataset (587 HD)

Figure 3: Boxplot of **Entropy** calculated by normalised frequency using all CDR3s by **Age** in 2 genders
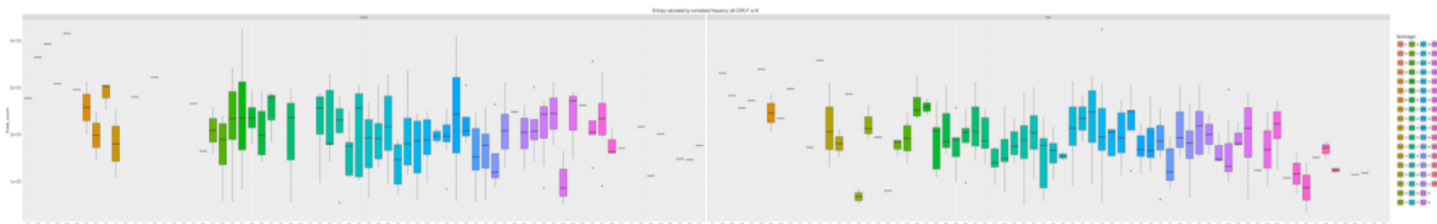

Figure 4: Boxplot of **Total unique CDR3 count** by **Age** in 2 genders

Cancer Immunology Research

TCR Sequencing Can Identify and Track Glioma-Infiltrating T Cells after DC Vaccination

Melody S. Hsu[1,2,*], Shaina Sedighim[1,*], Tina Wang[1,3], Joseph P. Antonios[1,4], Richard G. Everson[1], Alexander M. Tucker[1], Lin Du[5], Ryan Emerson[6], Erik Yusko[6], Catherine Sanders[6], Harlan S. Robins[6,7], William H. Yong[8,9], Tom B. Davidson[1,2,8], Gang Li[5,8], Linda M. Liau[1,8], and Robert M. Prins[1,8,10]
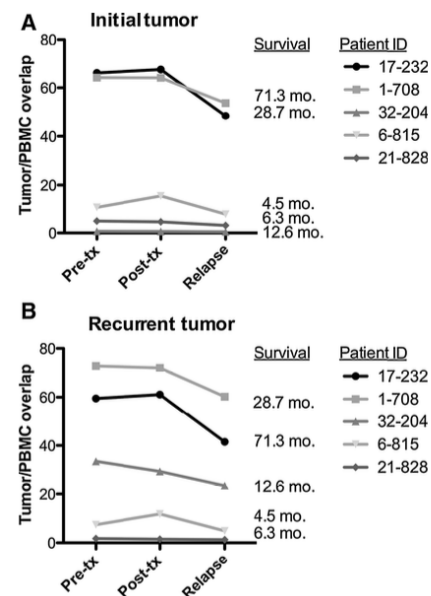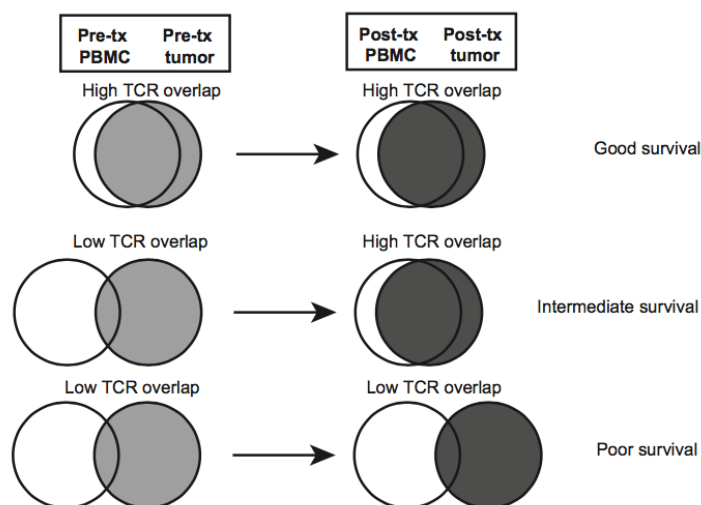
Increase of diversity and TCR count after treatment
– Hsu' dataset (5 tumor, 5 blood samples)

Figure1: DNA log Entropy for 20 samples of Hsu's

Figure3: Total AA count for blood samples of Hsu's

Figure4: Unique AA count for blood samples of Hsu's

Figure7: Total AA count for tumor samples of Hsu's
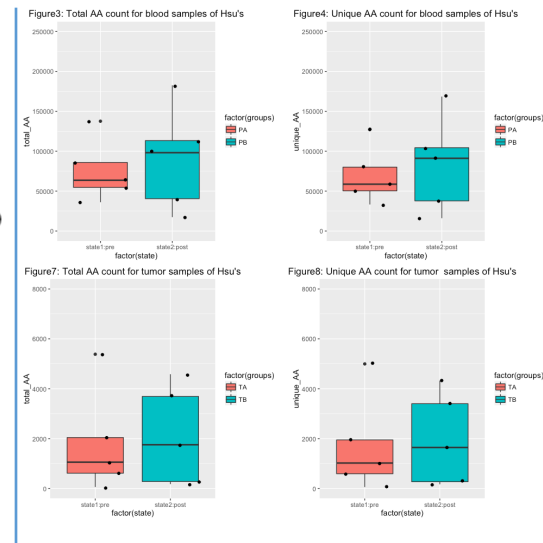
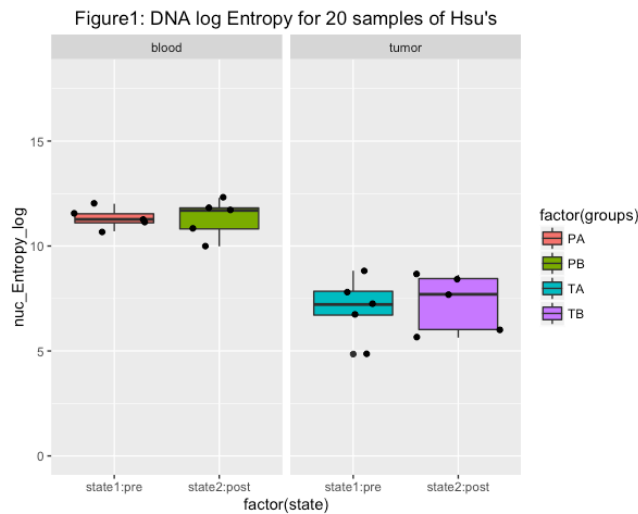Figure8: Unique AA count for tumor samples of Hsu's

Figure :TCR count in pre/post states

(top): Blood samples

(bottom): Tumor samples

- Shannon entropy (diversity) distribution does not distinguish between tumor and blood samples.
- Increasing pattern of TCR count (richness) from pre-treatment to post-treatment can be seen in both blood and tumor samples, while blood samples have 50-fold richness than tumor samples in general

Hsu, M. S., Sedighim, S., Wang, T., Antonios, J. P., Everson, R. G., Tucker, A. M., . . . Prins, R. M. (2016). TCR Sequencing Can Identify and Track Glioma-Infiltrating T Cells after DC Vaccination. *Cancer Immunology Research, 4*(5), 412-418. doi:10.1158/2326-6066.cir-15-0240

CTLA4 Blockade Broadens the Peripheral T-Cell Receptor Repertoire

Lidia Robert[1], Jennifer Tsoi[2], Xiaoyan Wang[1,3], Ryan Emerson[7,8], Blanca Homet[1,9], Thinle Chodon[1], Stephen Mok[1,2], Rong Rong Huang[4], Alistair J. Cochran[4], Begoña Comin-Anduix[5,6], Richard C. Koya[5,6], Thomas G. Graeber[2,6], Harlan Robins[7,8], and Antoni Ribas[1,2,5,6]

CyTOF

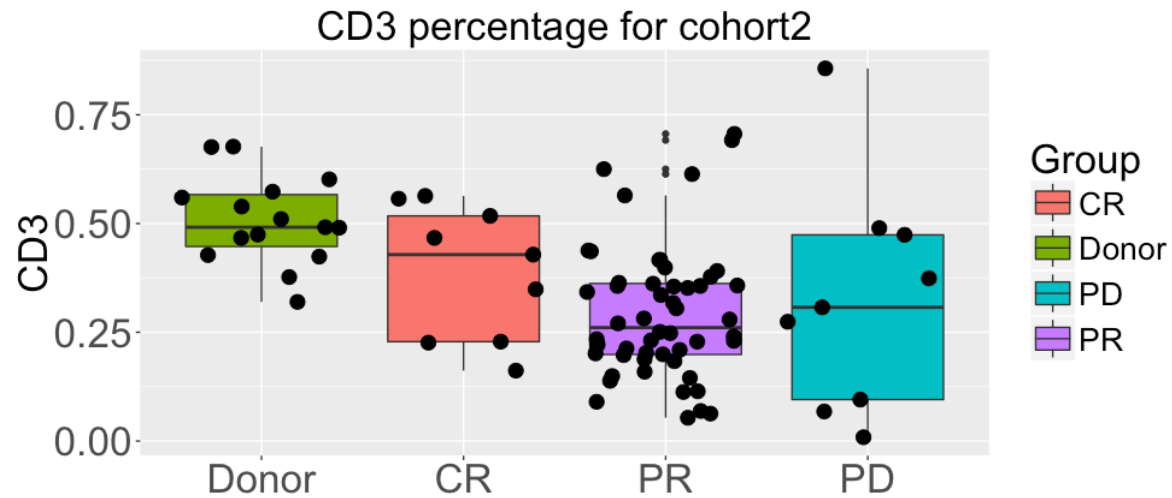http://cytof.scilifelab.se/

CyTOF data

CD3 percentage for cohort2
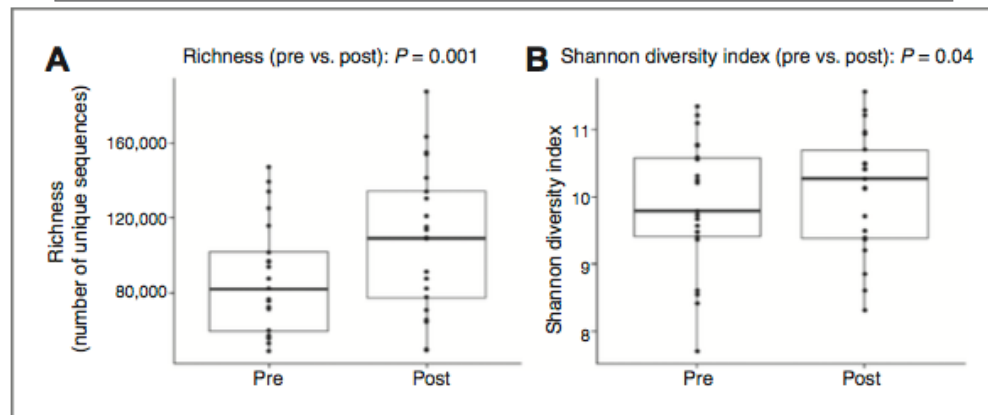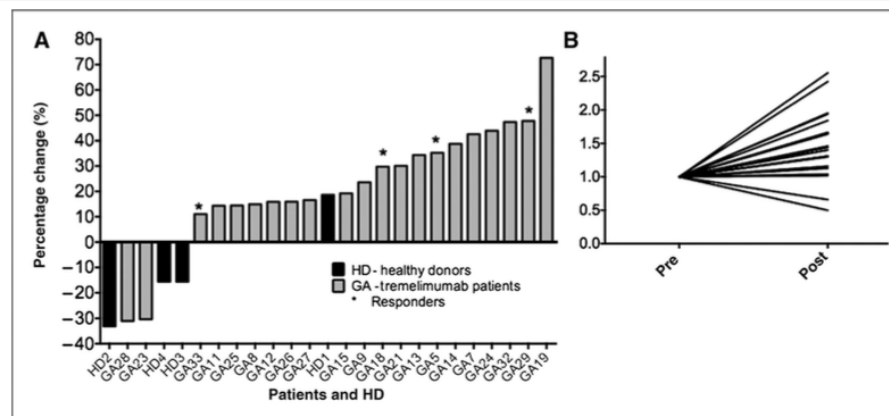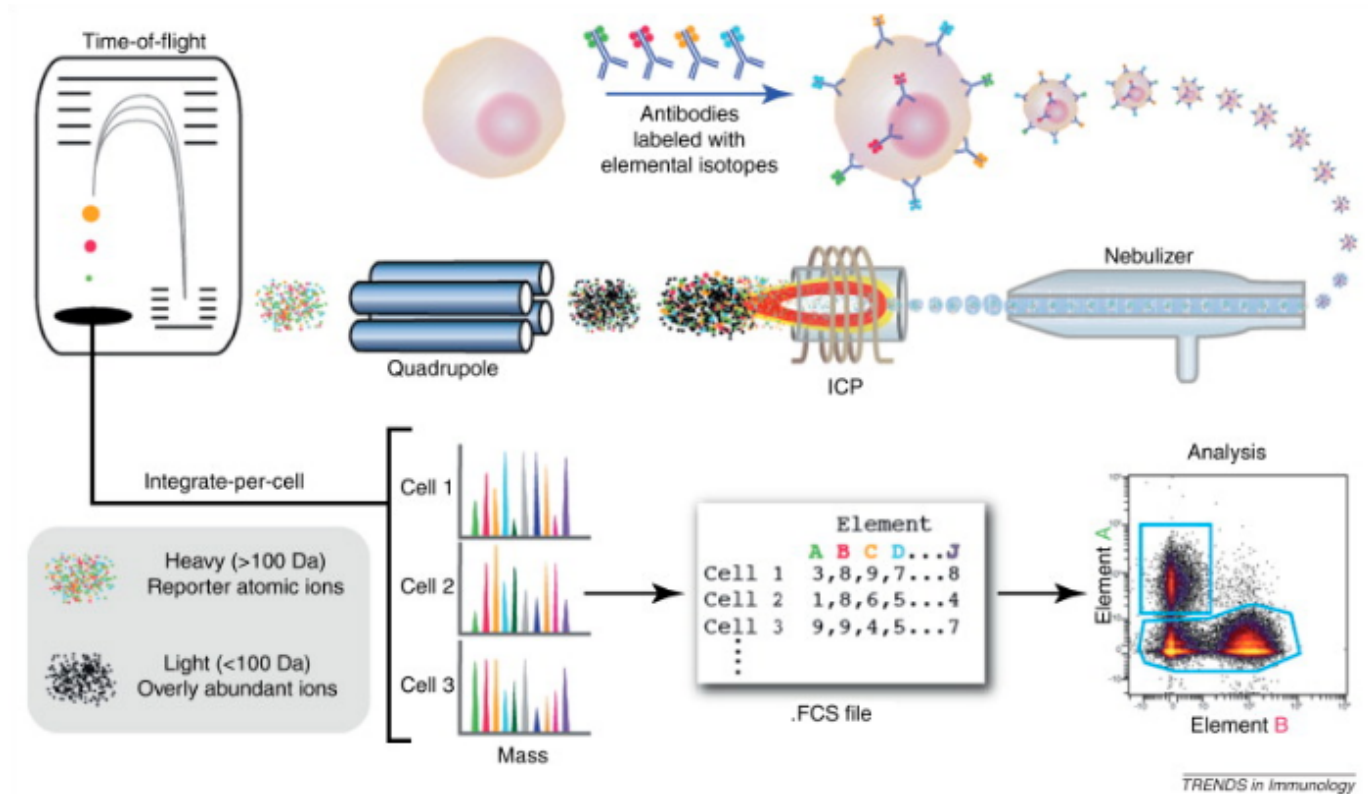
- Healthy donor has highest CD3 percentage (higher amount of T cells)