

R/Shiny tools for Immune Fitness Exploration

R/Pharma 2021

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T cell lymphocyte with receptors to kill cancer
cell in cancer immunotherapy 3D render

Disclaimer

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Outline

1 Background: Cancer and Immune Fitness

2 Radviz:: R package

3 FACS dose-response Shiny App

4 Incucyte TcellK2 Shiny App

5 Q & A

Acknowledgements

Special thanks to:

Biology/Oncology

- Cass Lowenstein
- Halley Oyer

Computational Biology

- Yann Abraham

TMEDS

- Bie Verbist
- Nick Hein

Cancer and Immune Fitness

Skin cells at 20x magnification

Cancer

Cancer is a leading cause of death worldwide, accounting for about 10 million deaths in 2020 [WHO]



Cancer

Cancer cells



Cancer cells

Cancer, T cells

T cells



T cells



Cancer cells

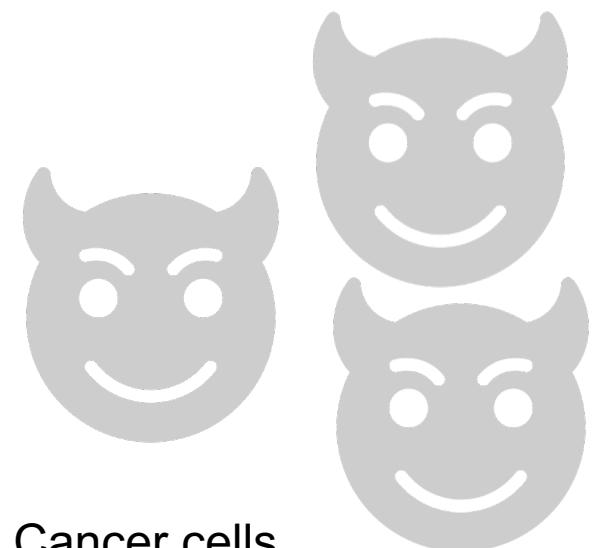
Cancer, T cells, and bi-specific antibodies

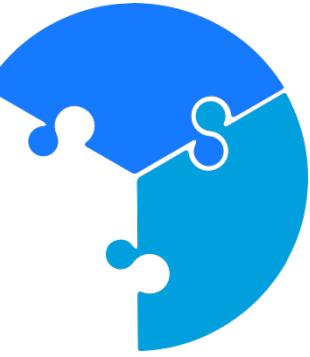
Bi-specific antibodies



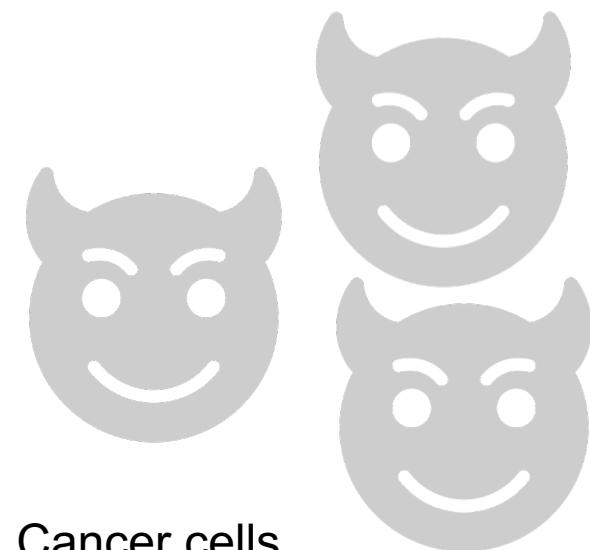


1. T cell composition

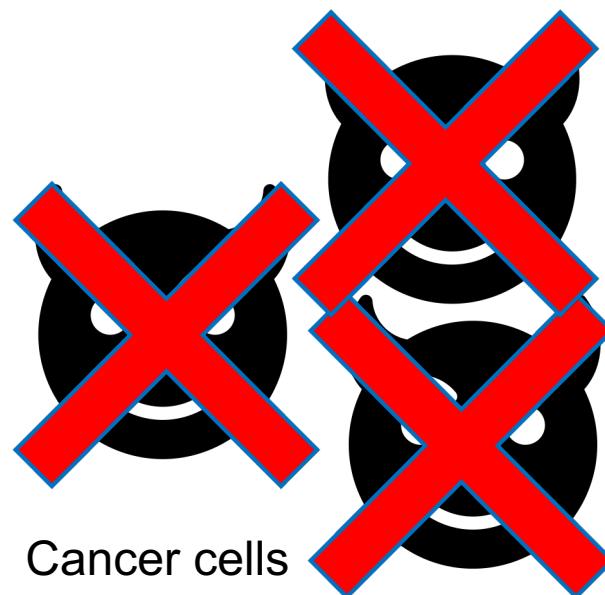
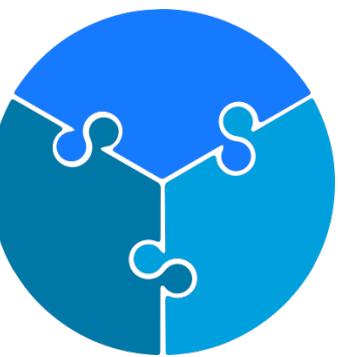




2. T cells activation and composition under different conditions



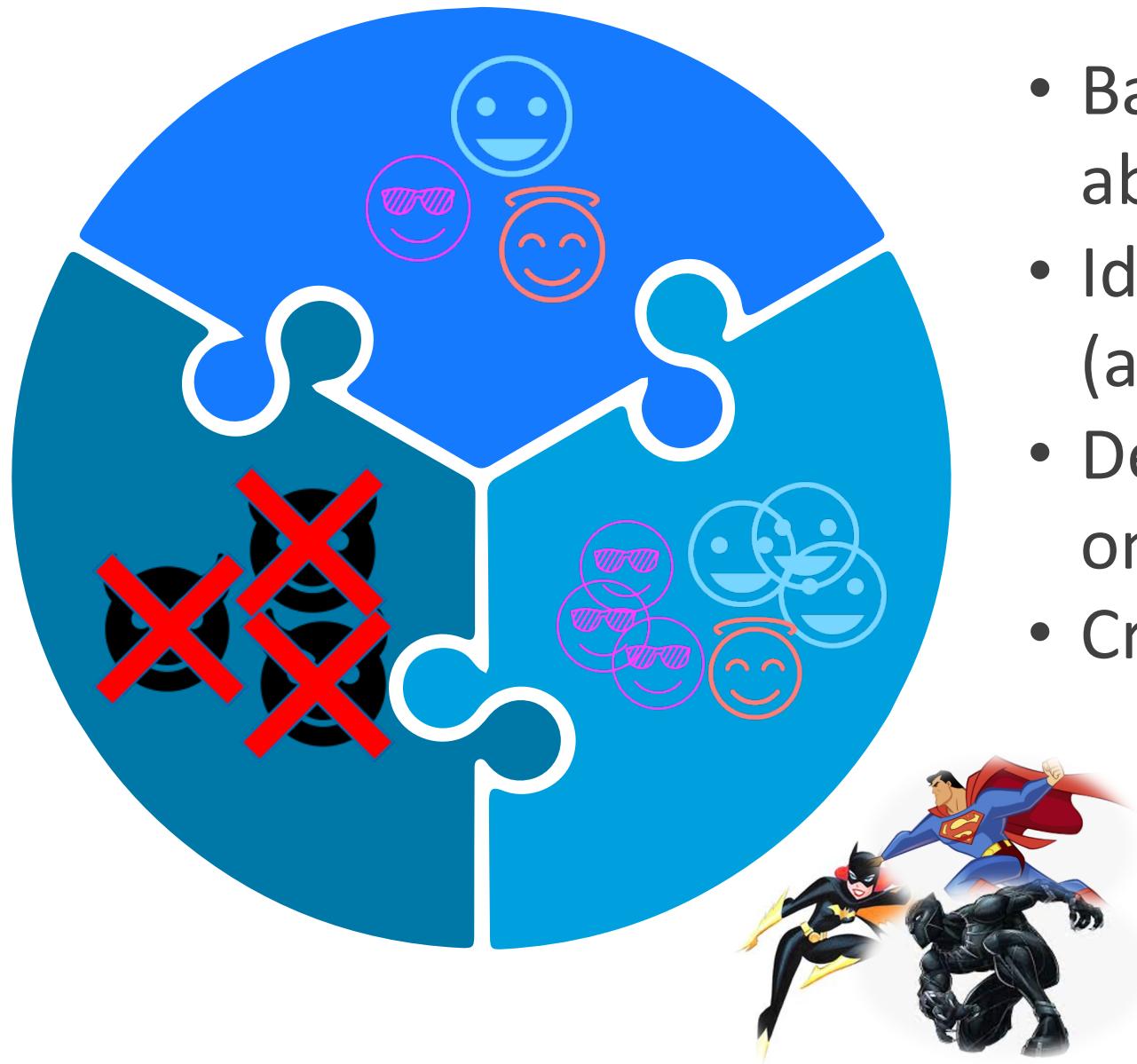
3. Killing of cancer cells under different conditions



Bi-specific antibodies

Immune Fitness Exploration

Why?

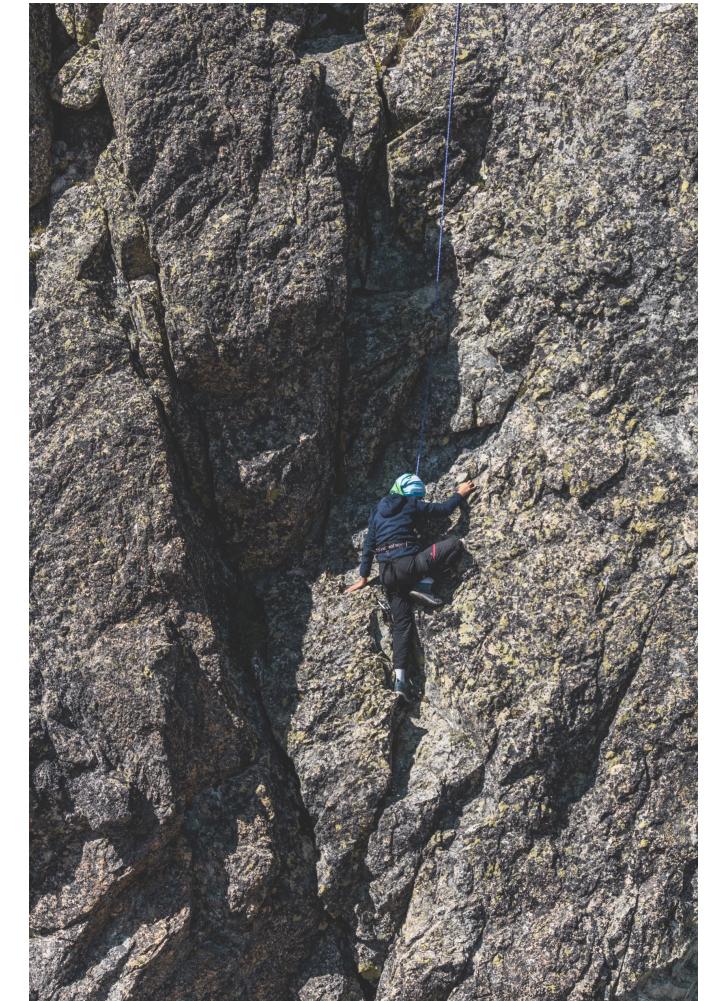


- Based on baseline immune composition learn about *responders*
- Identify *biomarkers* of immune system state (active or exhausted)
- Determine the impact of *current/prior therapies* on immune fitness and response to drugs
- Create *better drug candidates* for clinical trials

Immune Fitness Exploration Tools

Before R/Shiny Era

- *Labor-intense and repetitive*: many conditions of interest, many variables, many data files, mapping between files, *manual* analysis and report generation -> error prone
- *Heterogeneous*: different ways to transform and normalize data
- In need of specific *statistical methods, data visualization, and compound ranking*



(1) T cell composition

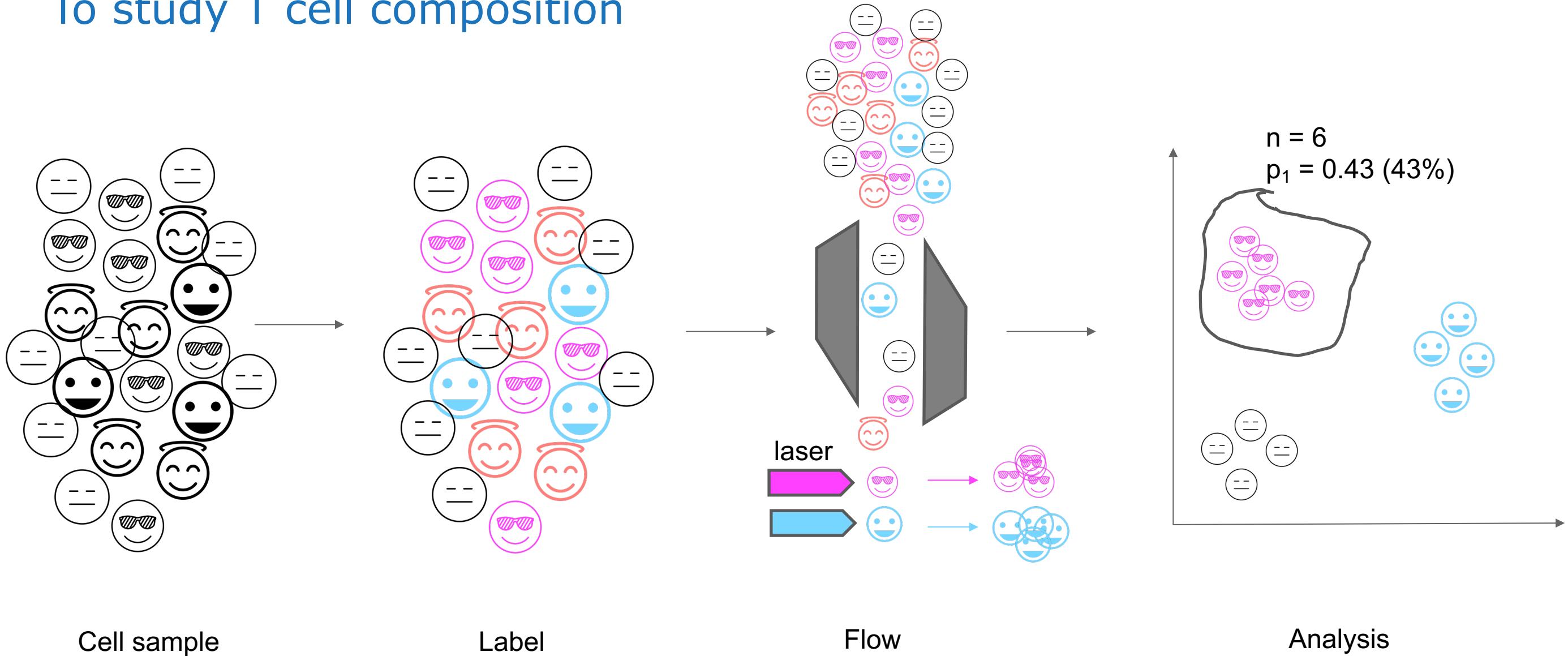
Radviz R package

Skin cells at 20x magnification



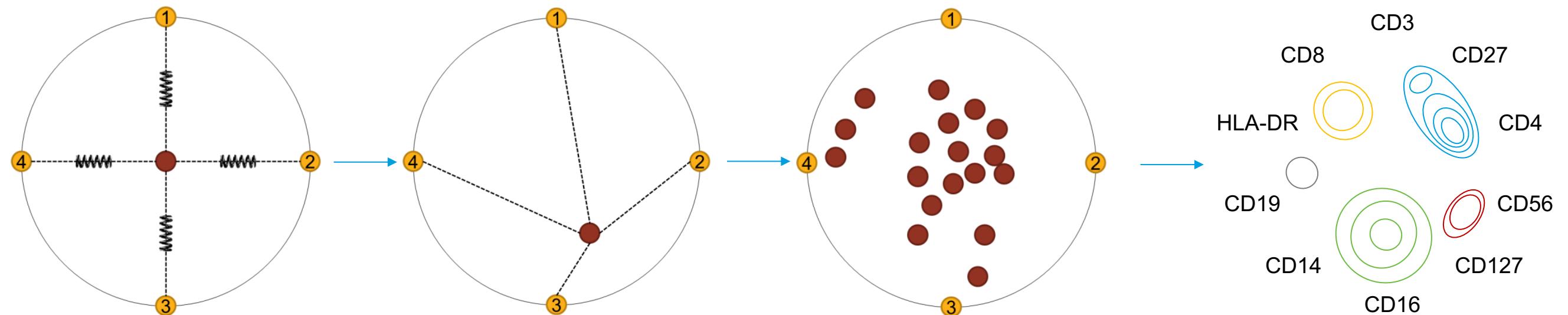
Fluorescence-activated cell sorting (FACS)

To study T cell composition



Radviz::

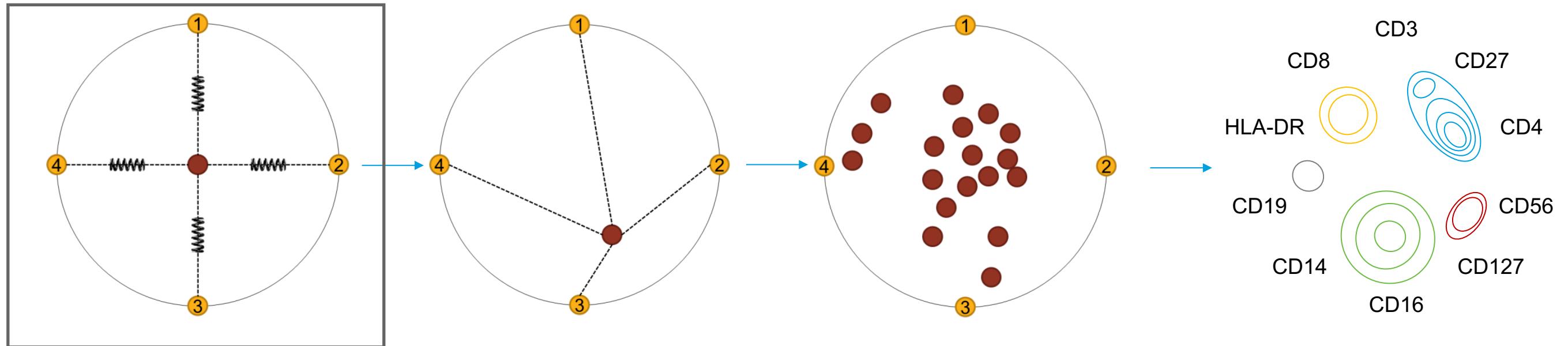
Visualize multidimensional T cell data in 2D



Courtesy of Yann Abraham

Radviz::

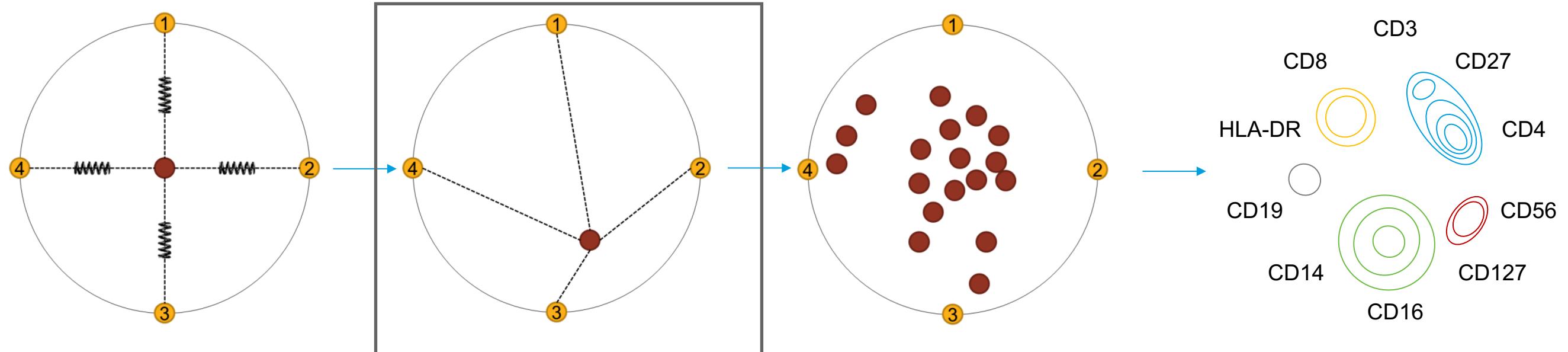
Visualize multidimensional T cell data in 2D



Courtesy of Yann Abraham

Radviz::

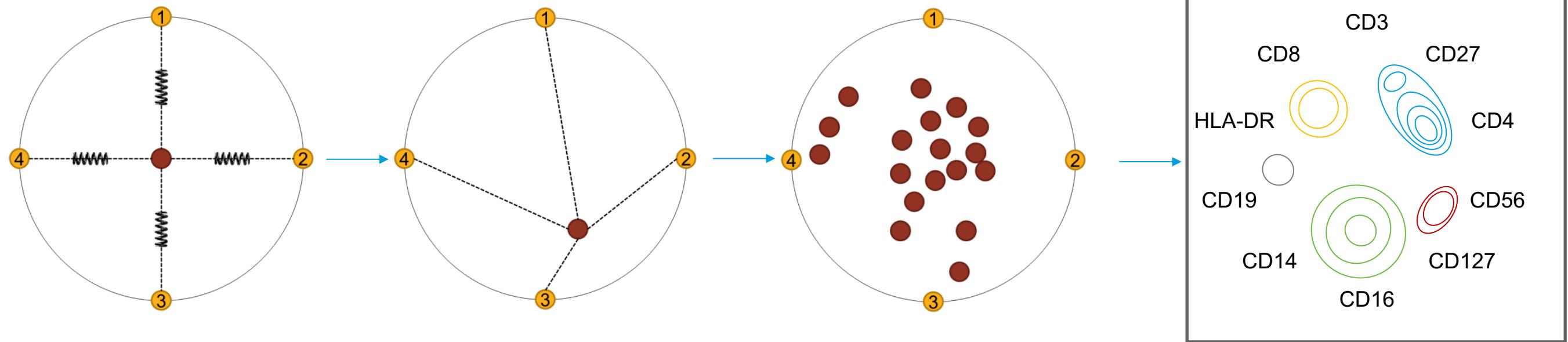
Visualize multidimensional T cell data in 2D



Courtesy of Yann Abraham

Radviz::

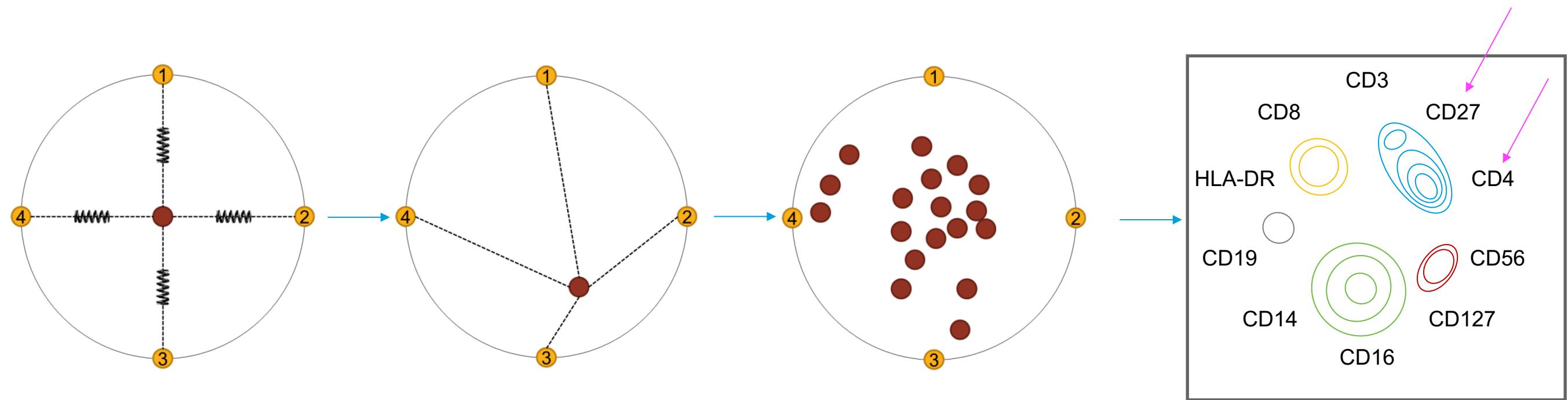
Visualize multidimensional T cell data in 2D



Courtesy of Yann Abraham

Radviz::

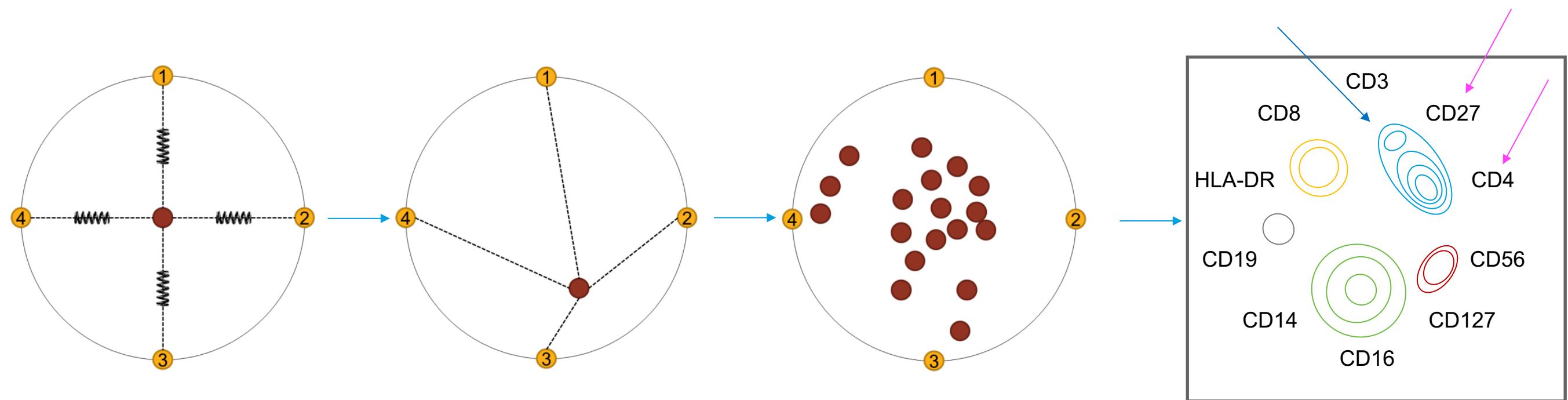
Visualize multidimensional T cell data in 2D



Courtesy of Yann Abraham

Radviz::

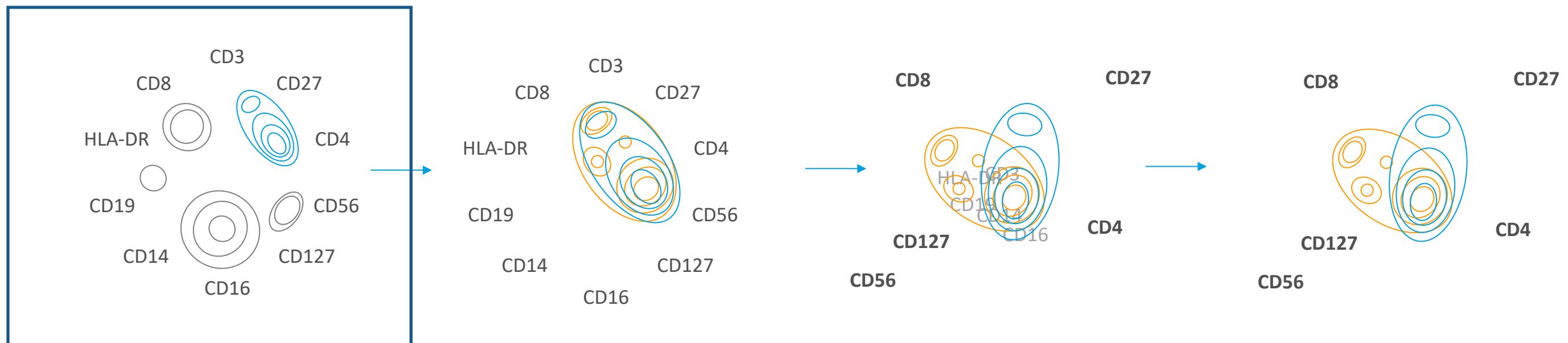
Visualize multidimensional T cell data in 2D



Courtesy of Yann Abraham

Freeviz

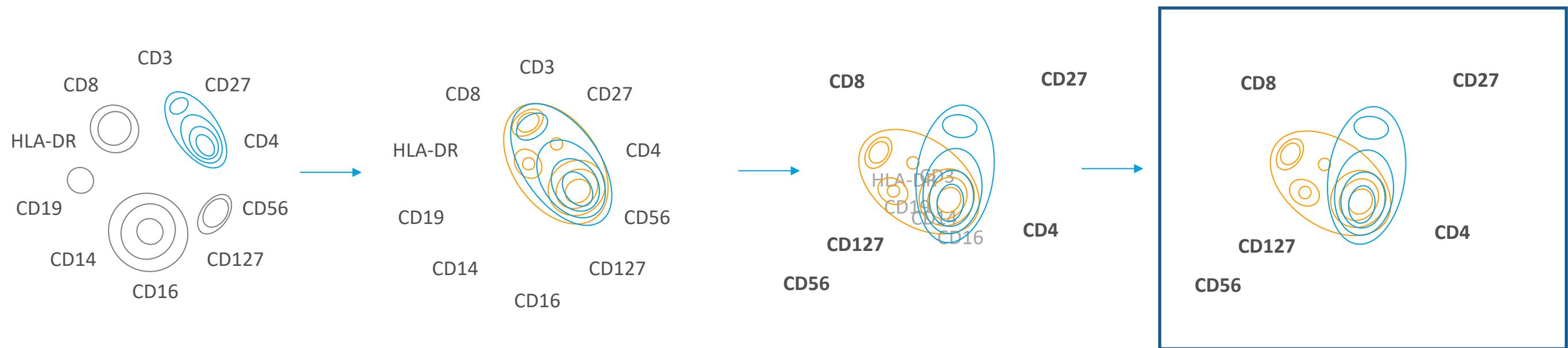
Compare T cell composition between Healthy and Cancer donors



Courtesy of Yann Abraham

Freeviz

Compare T cell composition between Healthy and Cancer donors



Courtesy of Yann Abraham

(2) T cell composition under different conditions

FACS dose-response Shiny App



Bi-specific antibodies

Skin cells at 20x magnification

FACS shiny app

Objectives and endpoints

- Compare treatment/conditions effect on different cell populations.
 - Provide overview on gating structure/cell populations identified
 - Perform normalization (optional)
- Allow dose response fitting for cell populations of interest (e.g activated T-cells) or ranking on curve characteristic for incomplete curves.
- Create overview tables allowing comparison of parameter estimates (EC50, max effect) across treatments/conditions



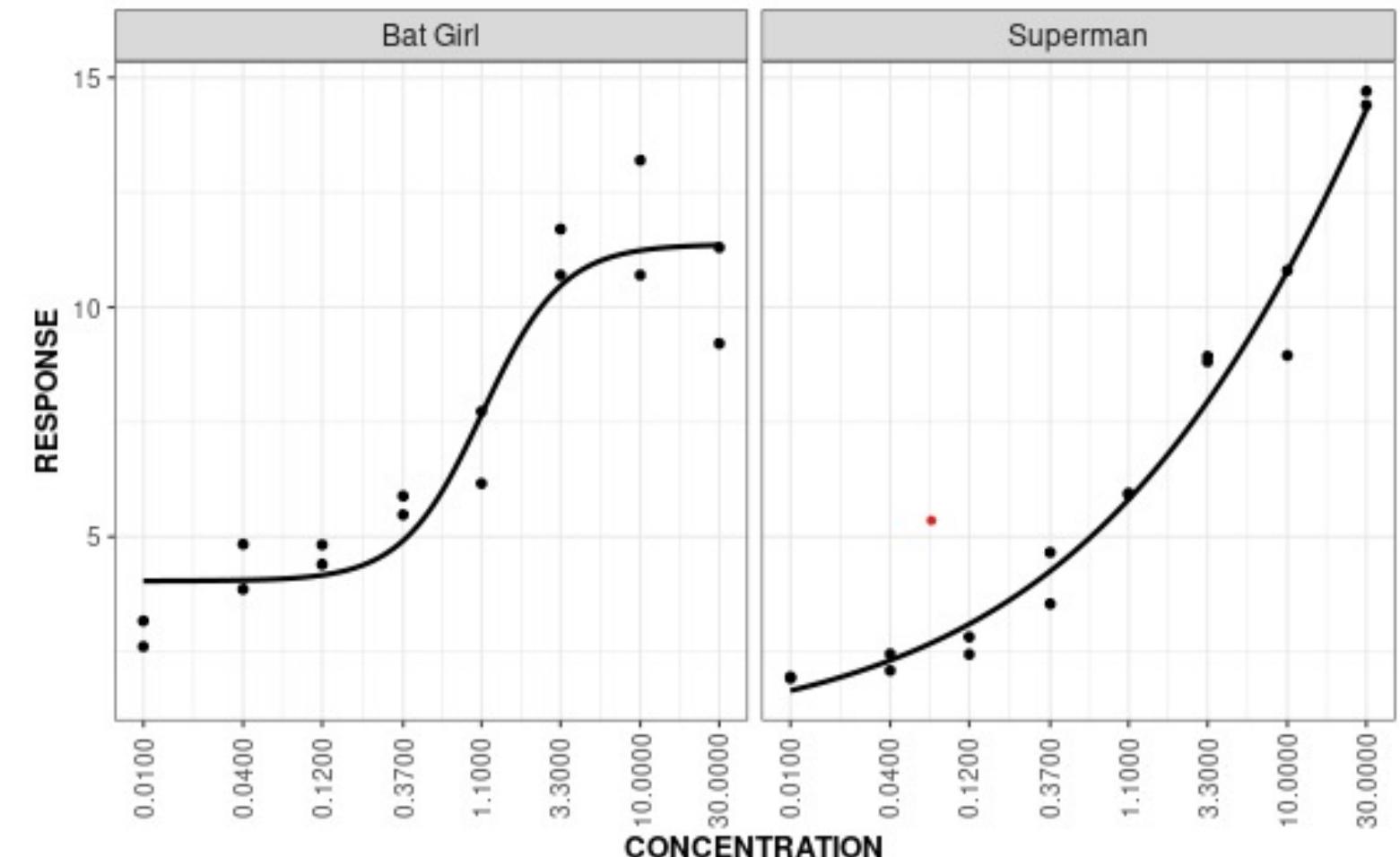
FACS shiny app

The screenshot shows the FACS shiny app interface. On the left, a dark sidebar titled "FlowJo Data" displays "Upload complete" for "flowjo_data1.txt" and includes "Next" and "Download Prism" buttons. The main area is titled "Plate Map Editor". It features a "Plate" dropdown set to "1", a "Load Plate Map" section with a "Browse..." button and a "No file selected" message, a "Wells" dropdown set to "96", a "Variable Choice" dropdown set to "Compound/Molecule", and a "Compound/Molecule" input field. Below these are two tables: one for "Compound/Molecule" mapping and another for the plate layout. The plate layout table has columns labeled A1 through A12 and rows labeled B1 through H12. Cells are colored according to a legend: Bat Girl (red), Black Panther (green), Superman (cyan), and Unknown (purple). The bottom of the editor includes a "Download Plate Map" button and a "Reset" button.

- Raw FACS assay data files (directly from machine)
 - Reduce errors made during preprocessing by automation
- Plate map files mapping plate information to raw data
 - Can be created/edited within app and saved for later

Dose response modelling

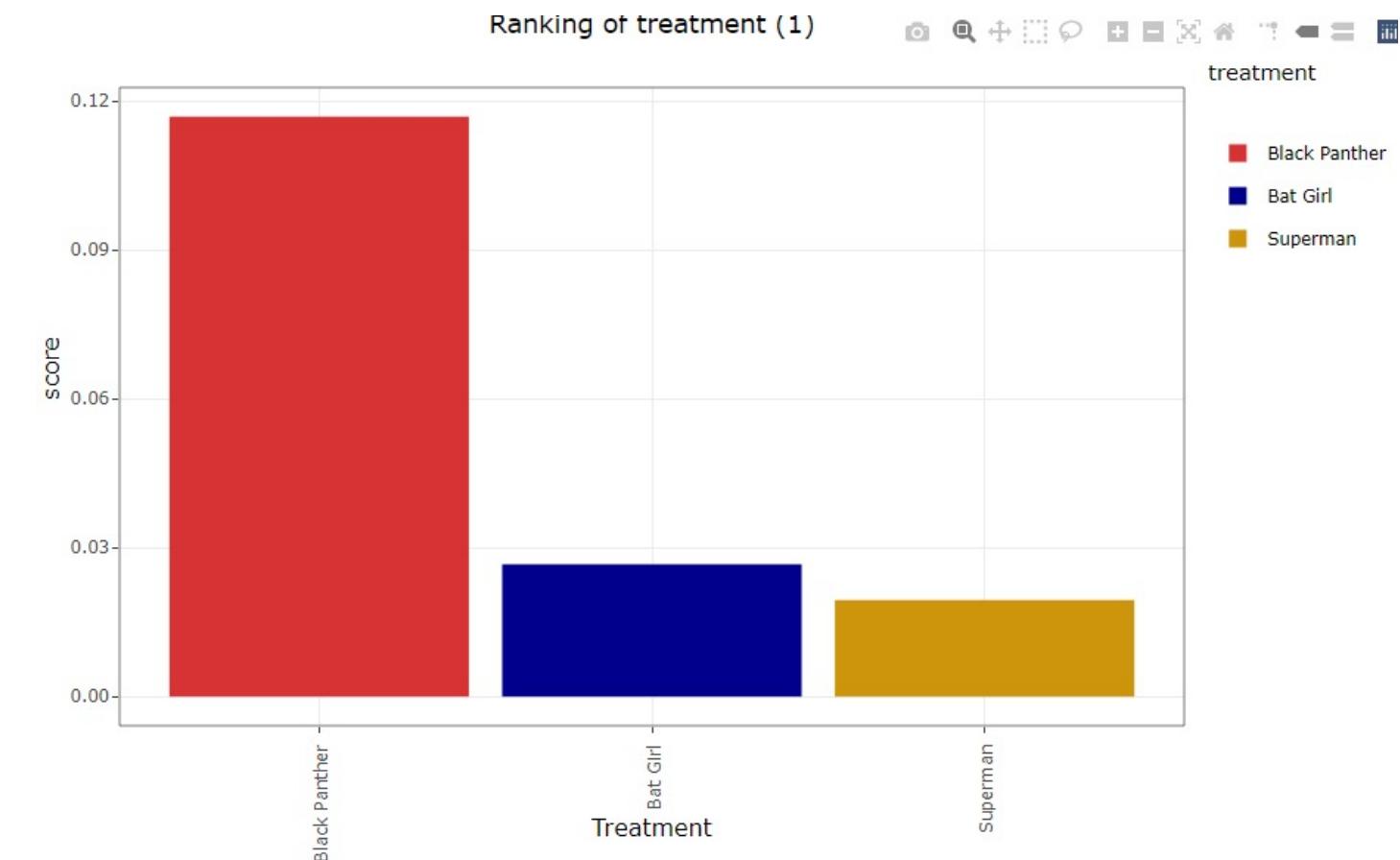
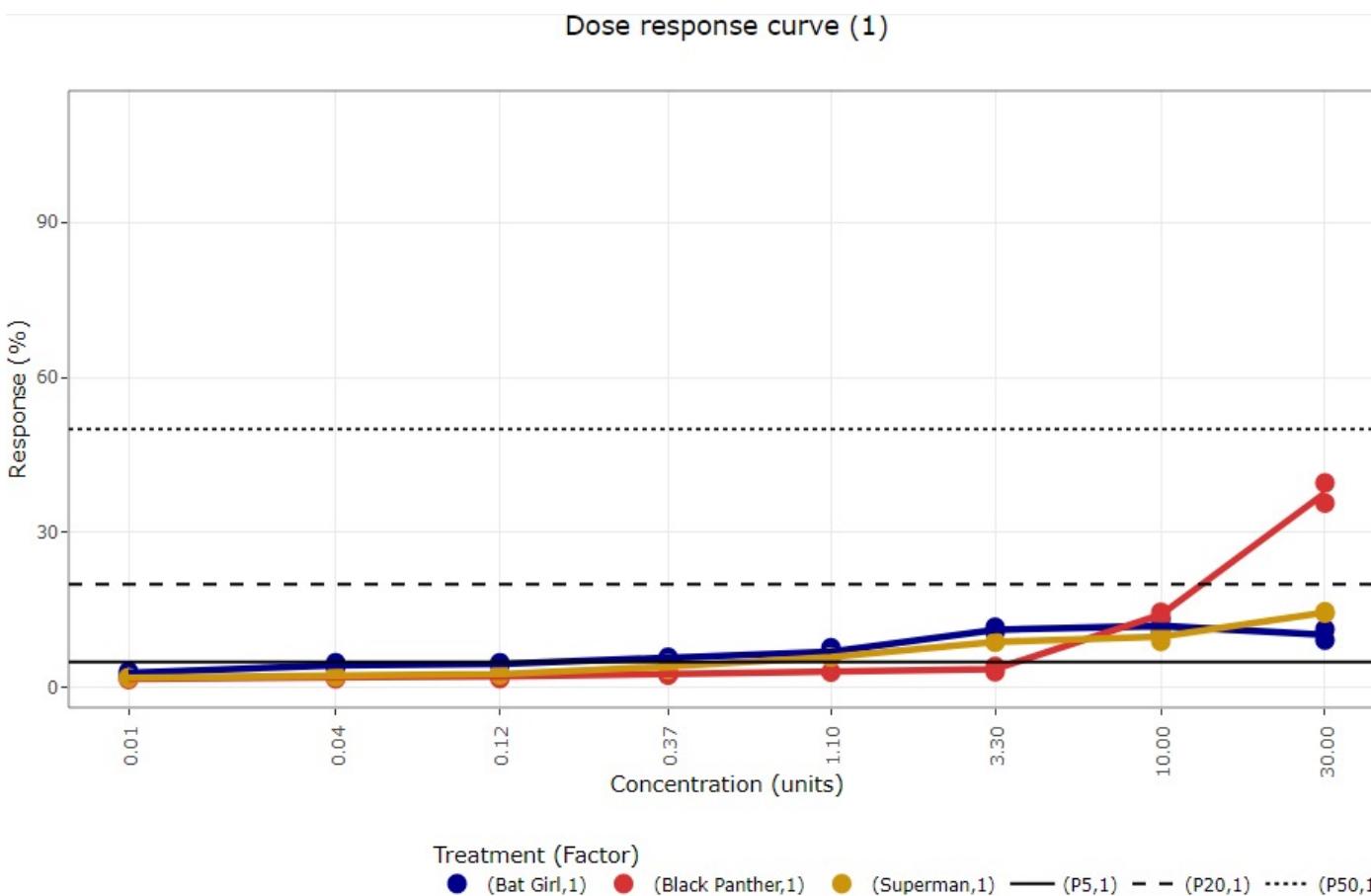
- Separate models for different conditions and populations
 - Single and multiple donor
 - Automatic selection based on data
- Pre checks eg
 - Number of unique dose concentrations



Note: Model(s) for the following compound(s) did not converge:
Black Panther

Exploratory compound ranking

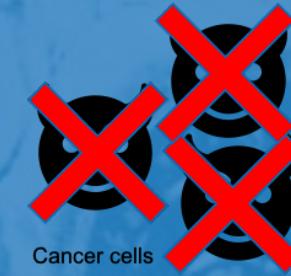
- Rank compounds by activity
- Useful when full dose response profile not available



Wilson Tendong (Janssen R&D)

(3) Killing of cancer cells

Incucyte Shiny App



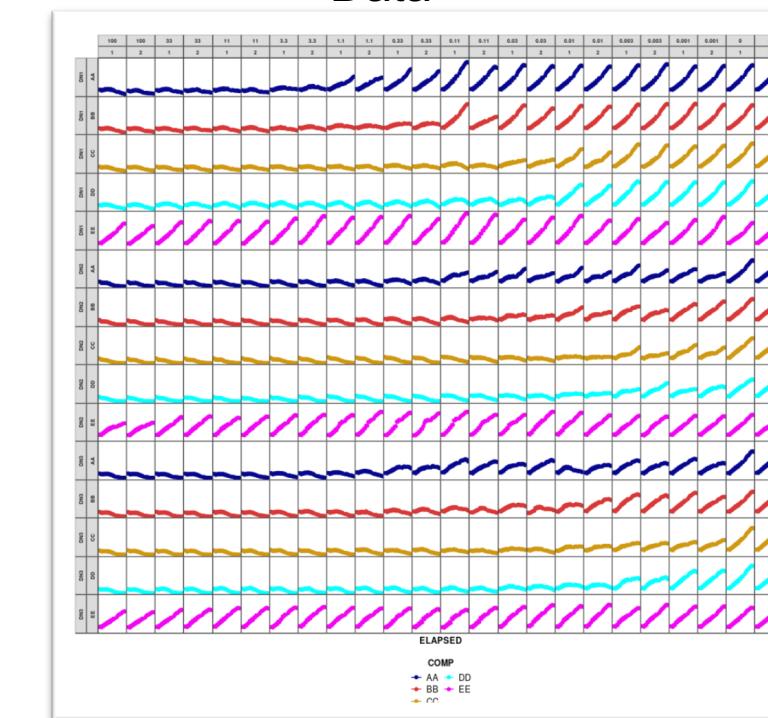
Skin cells at 20x magnification

Treatment comparison

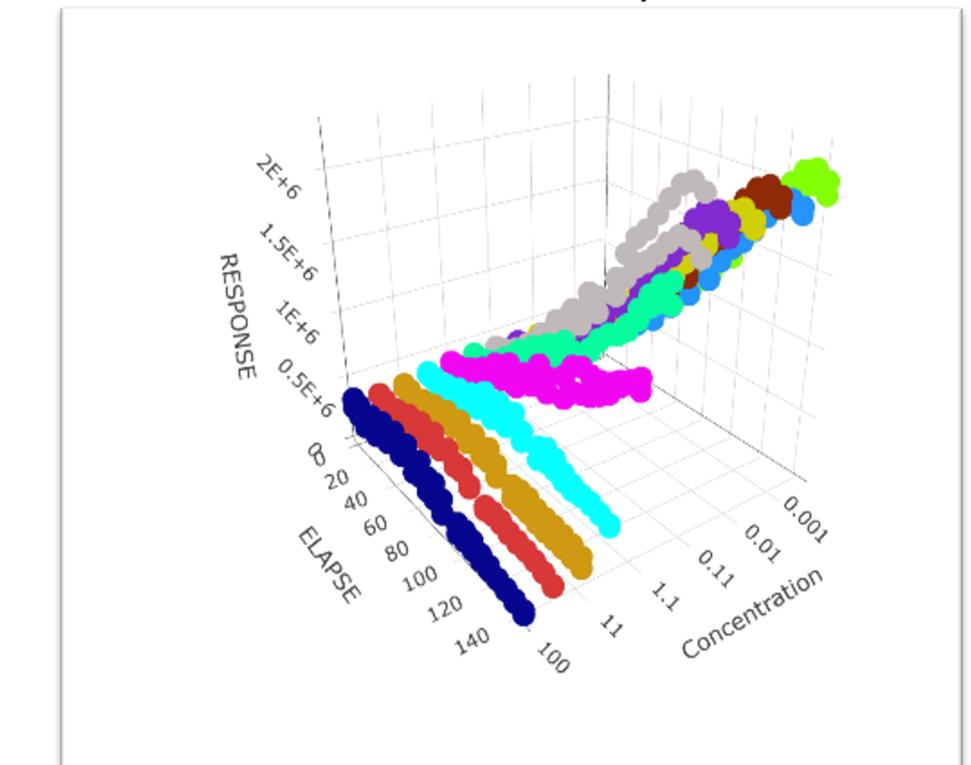
Multidimensional treatment assessment

- Compare treatment/condition effect across 3 dimensions
 - Amount of kill
 - Treatment Concentration
 - Exposure time of cancer cells to treatment
- Optimal treatment kills cancer cells
 - At low concentrations
 - Minimum exposure time to cancer cells
 - Maximum (100%) kill

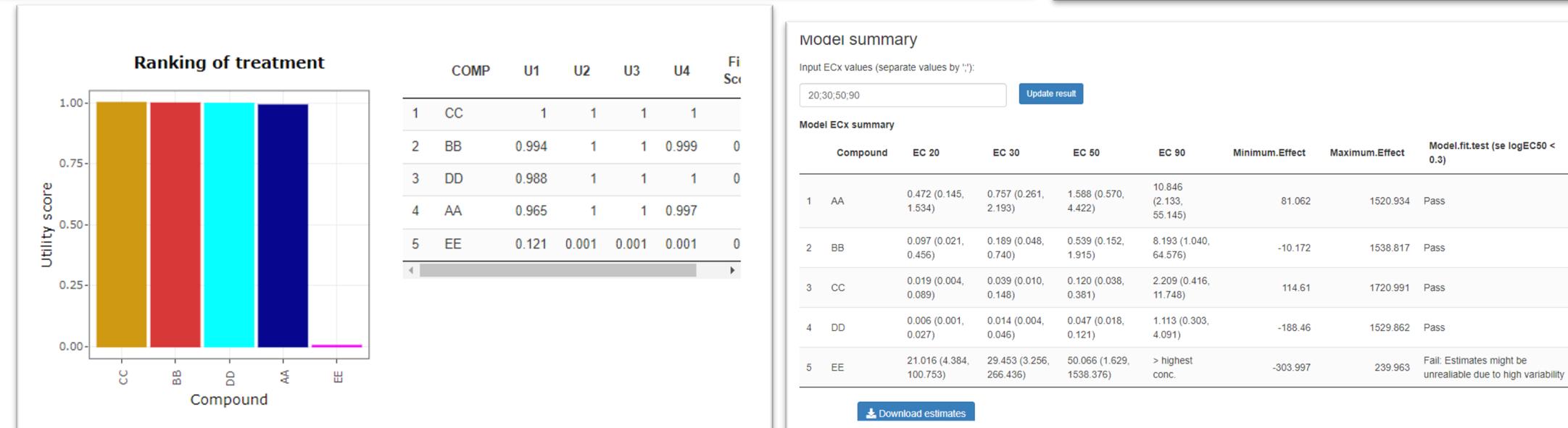
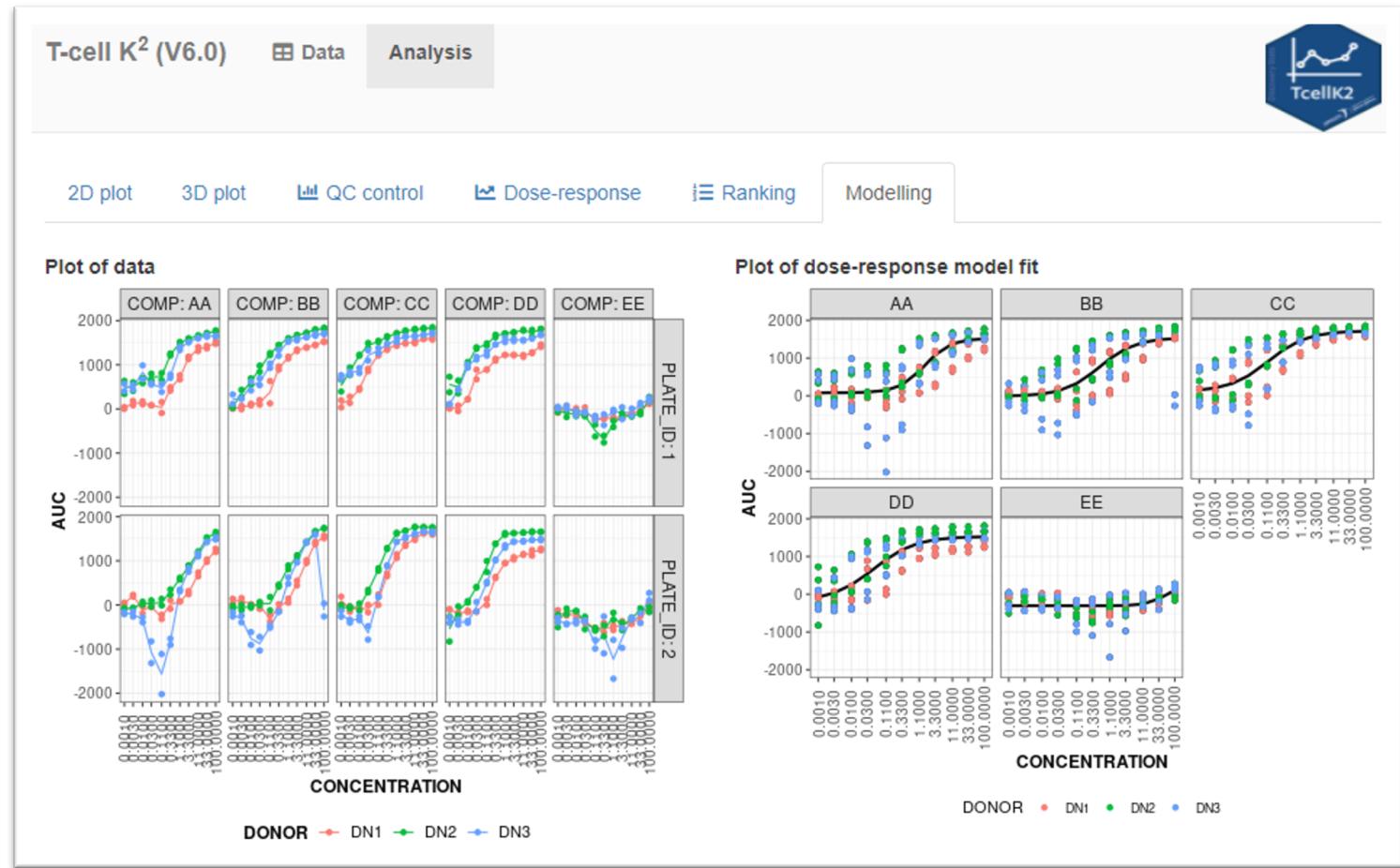
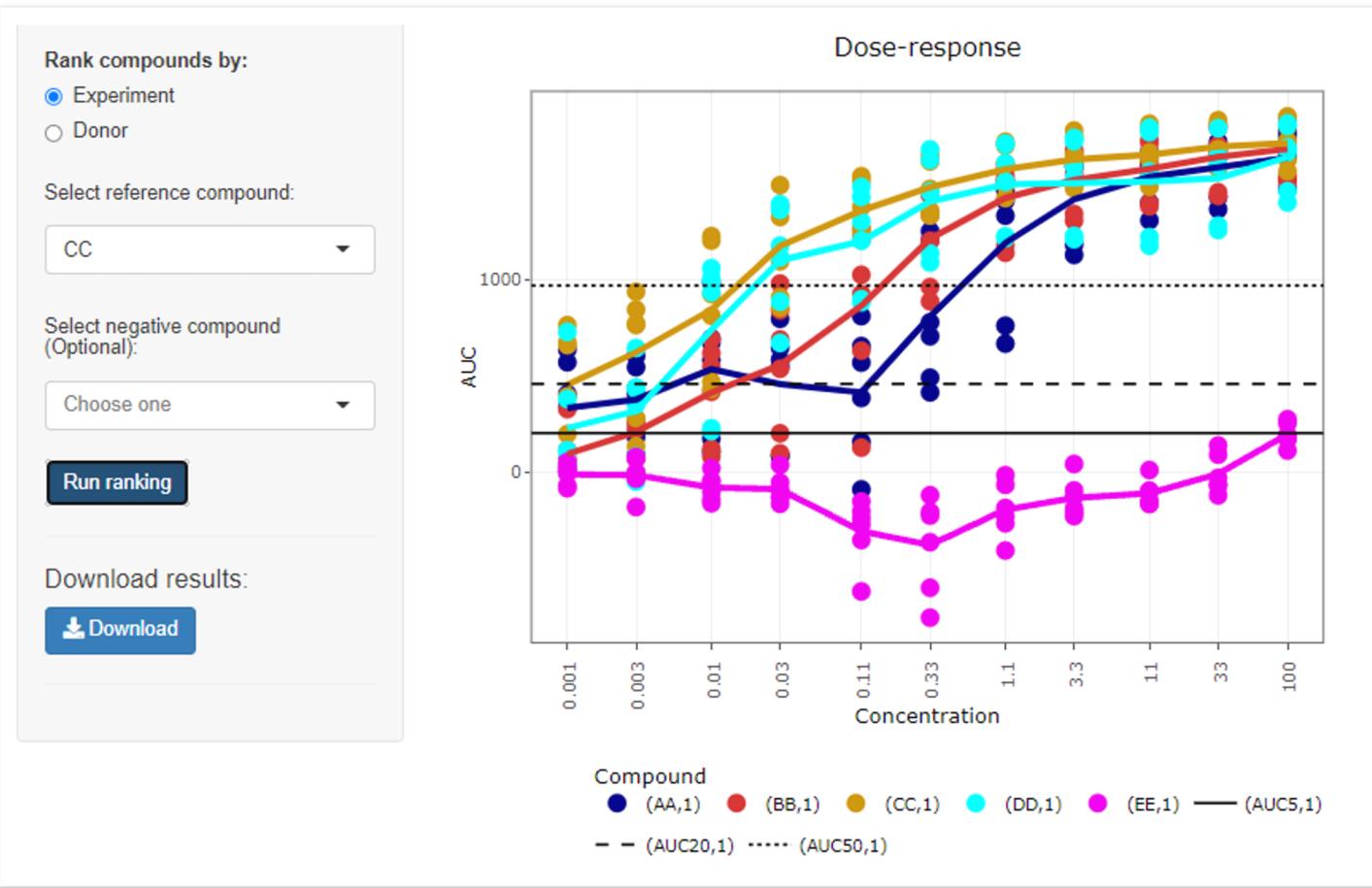
Data



3D visualization of a compound effect



Exploratory treatment ranking and DR modelling in app

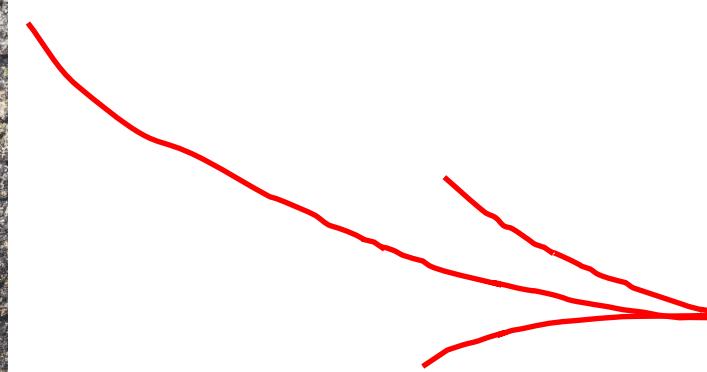
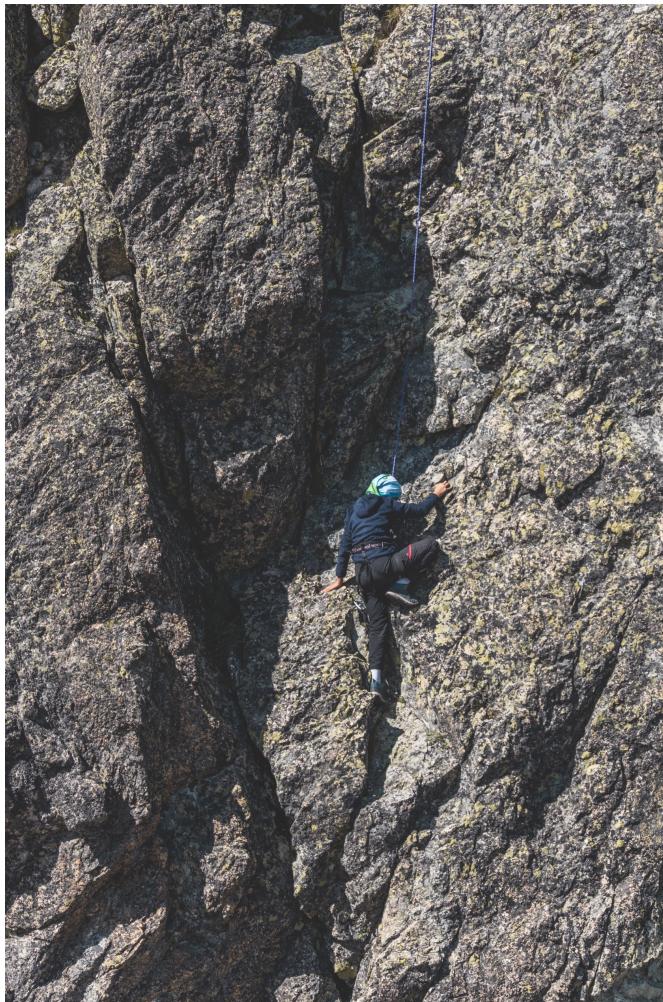


Summary

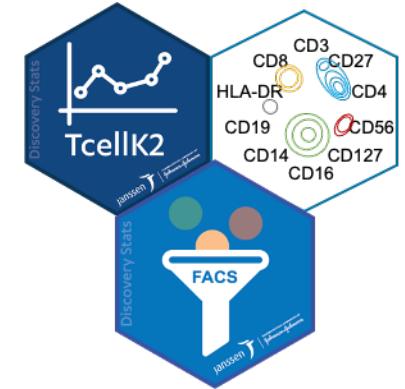
Skin cells at 20x magnification

Immune Fitness Exploration Tools

Before R/Shiny Era



After R/Shiny Era



A microscopic image showing a layer of skin cells. The cells are rounded with distinct nuclei and some cytoplasmic extensions. They are arranged in a somewhat organized pattern, though not perfectly aligned. The background is a light blue.

Thank you!

Skin cells at 20x magnification