VICI: a Shiny app for accurate estimation of Vaccine Induced Cellular Immunogenicity with bivariate modeling

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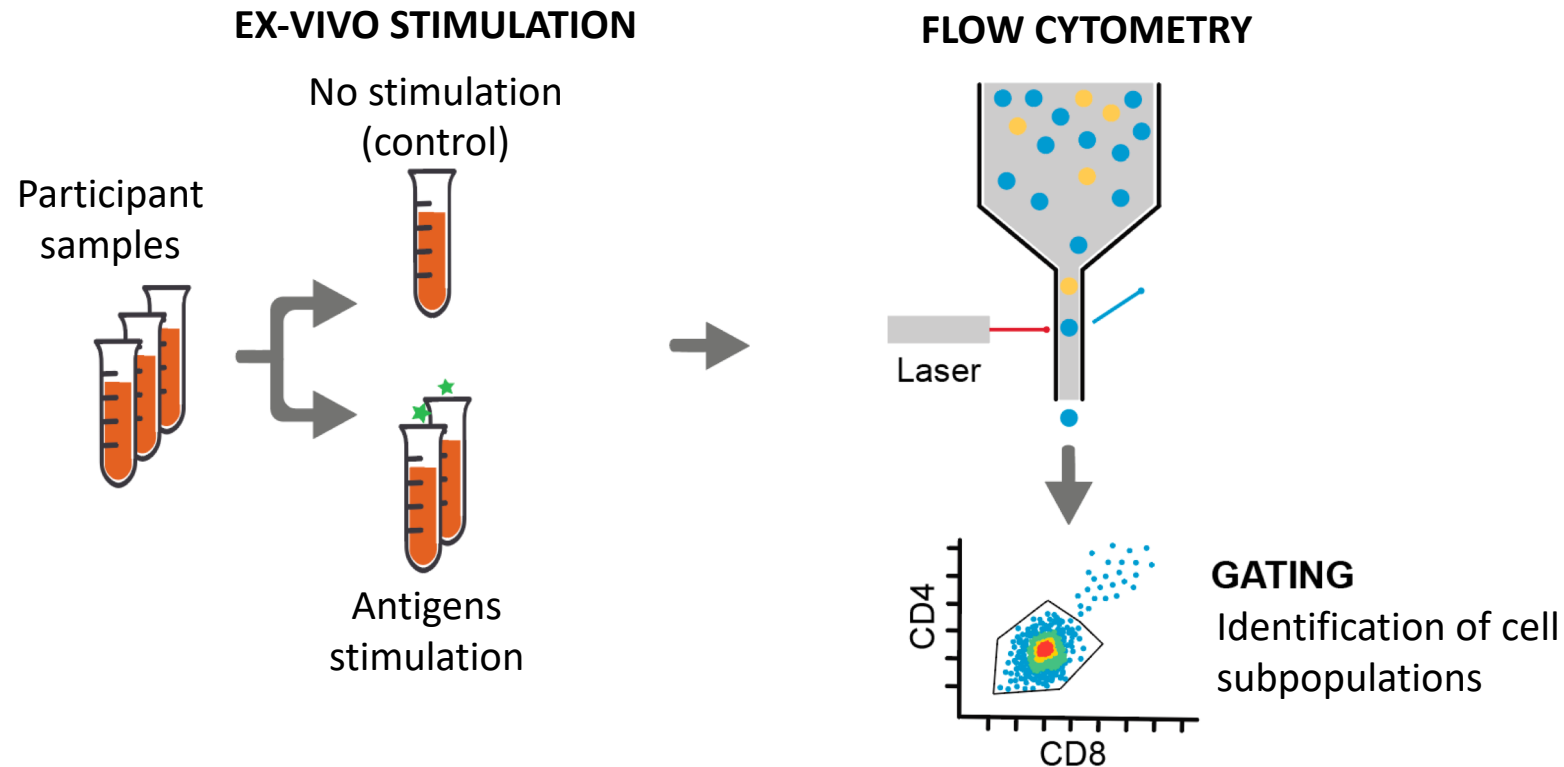3 Vaccine Research Institute (VRI), Créteil, F-94000 France.
4 Pôle de Santé Publique, CHU de Bordeaux, Bordeaux, F-33000 France
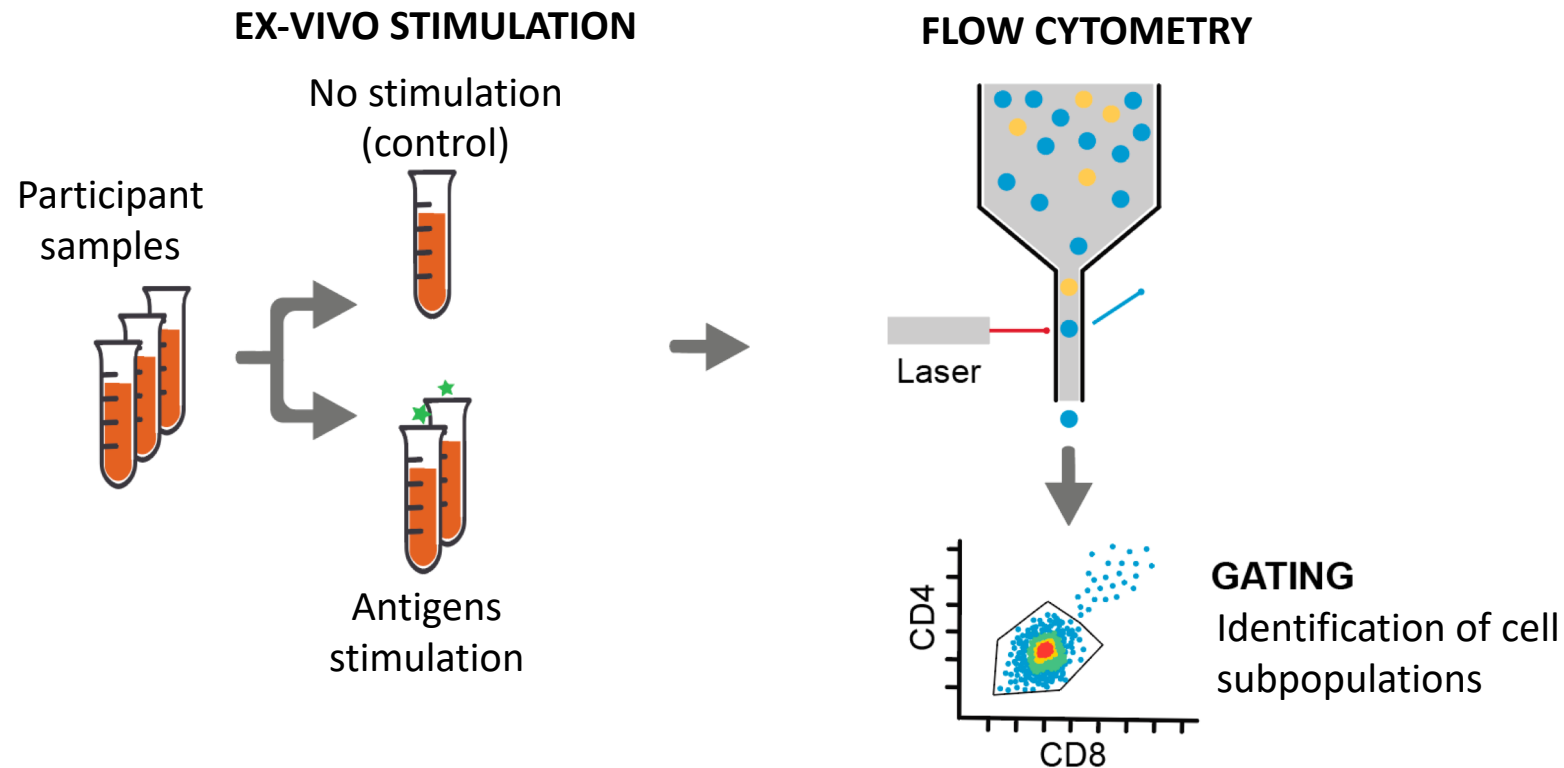
useR! 2019 - Toulouse

July 12th, 2019

Context: clinical vaccine development

- **Immunogenicity evaluation:** key step in phase 1 & 2 clinical trials
  - many immunological markers are measured at once,
    (in particular in the absence of protective correlates — such as in HIV vaccine trials)
  - Cellular response is evaluated with *intracellular cytokine staining* (ICS)

EX-VIVO STIMULATION

No stimulation (control)

Participant samples

Antigens stimulation

FLOW CYTOMETRY

Laser

CD4

CD8
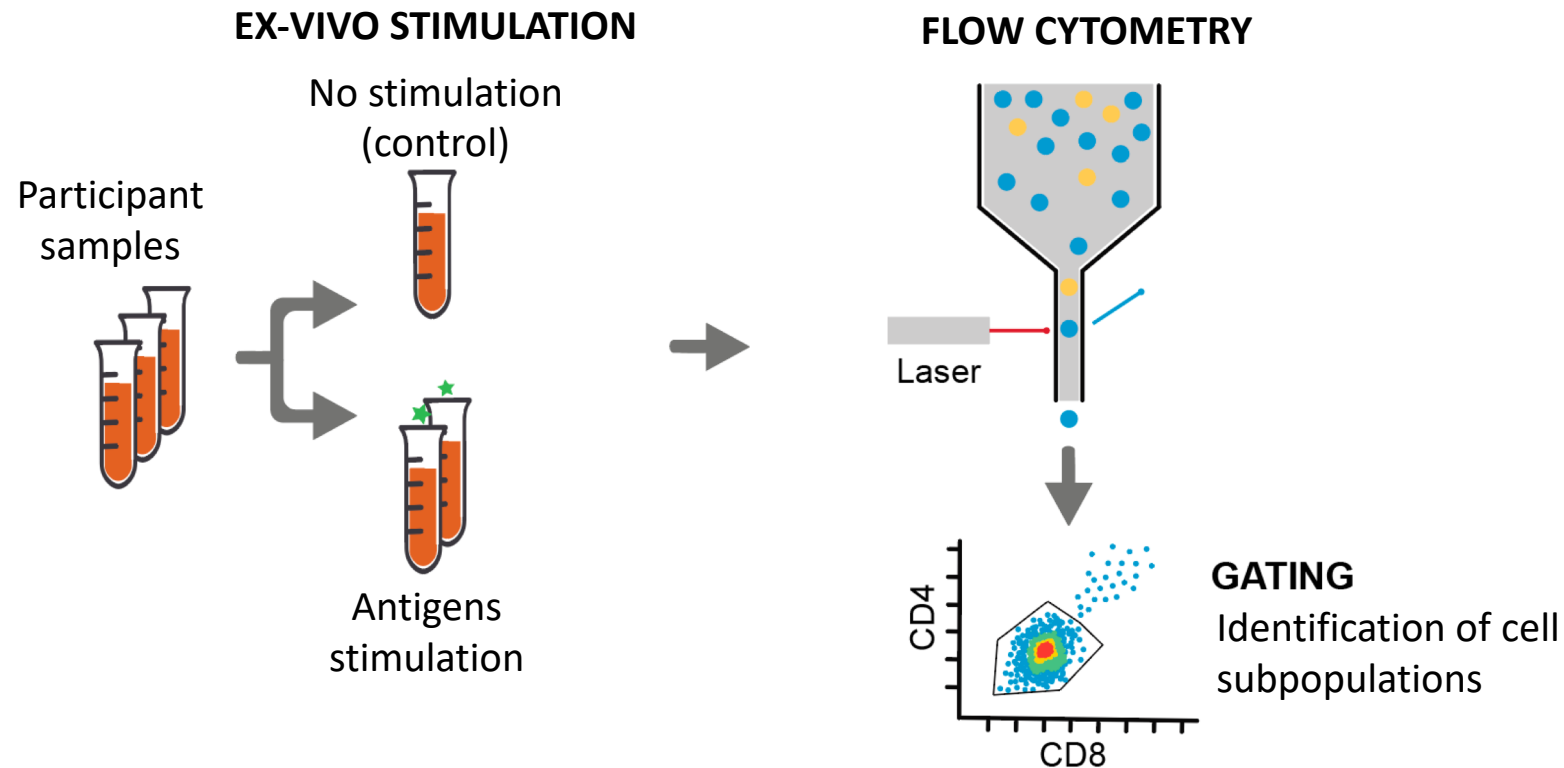
GATING
Identification of cell subpopulations

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Conventional statistical analysis of ICS data

- Comparing cytokine producing cell proportions between vaccine arms *after subtracting the non-stimulated response* (control) in each sample

- **Rational:** subtraction aims for the antigen specific response

- **Issues:** type-I error increase, bias, low statistical power

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NEED FOR A BETTER STATISTICAL APPROACH

Bivariate linear modeling

- **Dependent variables**: Y_i^{NS} the non-stimulated response & Y_i^S the specific stimulated response(s)

$$\begin{cases} Y_i^{NS} = \beta_0^{NS} + \boxed{\beta_1^{NS} V_i} + \varepsilon_i^{NS} \\ Y_i^S = \beta_0^S + \boxed{\beta_1^S V_i} + \boxed{\beta_2^S Y_i^{NS}} + \varepsilon_i^S \end{cases}$$

- <u>where</u>
  - V_i is the vaccine arm (eg vaccine vs placebo)
  - $Y_i^{NS} \sim N(\beta_0^{NS} + \beta_1^{NS} V_i, \sigma^{NS})$ and $\varepsilon_i^{NS} \sim N(0, \sigma^{NS})$
  - $Y_i^S \sim N(\beta_0^S + \beta_1^S V_i + \beta_2^S Y_i^{NS}, \sigma^S)$ and $\varepsilon_i^S \sim N(0, \sigma^S)$

- <u>Estimates</u>
  - $\boldsymbol{\beta_1^S}$: **vaccine effect on the stimulated response**
  - β_1^{NS}: vaccine effect on the non stimulated response
  - β_2^S: non stimulated response effect on the stimulated response

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SAS code

```
proc mixed data = DATATABLE;

class ID_PATIENT STIMULATION ;

model Y = STIMULATION STIMULATION*VACCINE STIMULATION* Y_NS / cl noint ;

repeated /type=VC grp=STIMULATION sub=ID_PATIENT ;

run ;
```

R code

```
mgls <- nlme::gls(myformul,
         data = transformed_data,
         weights = nlme::varIdent(value = c("1" = 1), form = ~ 1 | stim),
         method="REML"
)
```

Bivariate linear modeling

- **Dependent variables**: Y_i^{NS} the non-stimulated response & the specific stimulated response(s)

$$\begin{cases} Y_i^{NS} = \beta_0^{NS} + \beta_1^{NS}V_i + \varepsilon_i^{NS} \\ Y_i^{S} = \beta_0^{S} + \beta_1^{S}V_i + \varepsilon_i^{S} \end{cases}$$

SAS code

```
proc mixed data=...BLE;
cl...                    ...TION ;
...STIMULATION*VACCINE STIMULATION* Y_NS / cl noint ;
...VC grp=STIMULATION sub=ID_PATIENT ;
run ;
```

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✓ for statisticians

✗ for immunologists

VICI: shiny user interface   **https://shiny-vici.apps.math.cnrs.fr**

VICI: accurate estimation of Vaccine Induced Cellular Immunogenicity with bivariate modeling

Results   Data view   Additional Information

Data input

Choose a CSV/TXT file to import

Browse...	No file selected

☑ Header

Separator
- ○ Comma
- ○ Semicolon
- ● Tab

Input parameters

Model choice

inter-arm ▼

Variable specification

Select the column that identifies the subject ID

Please select a column name below ▼

Select the column that identifies the ICS response

Please select a column name below ▼

Select the column that identifies the stimulation

Please select a column name below ▼

Select the column that identifies the arm

Please select a column name below ▼

Run analysis

[Fit model]

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Arm effect on ICS response
taking into account background response levels
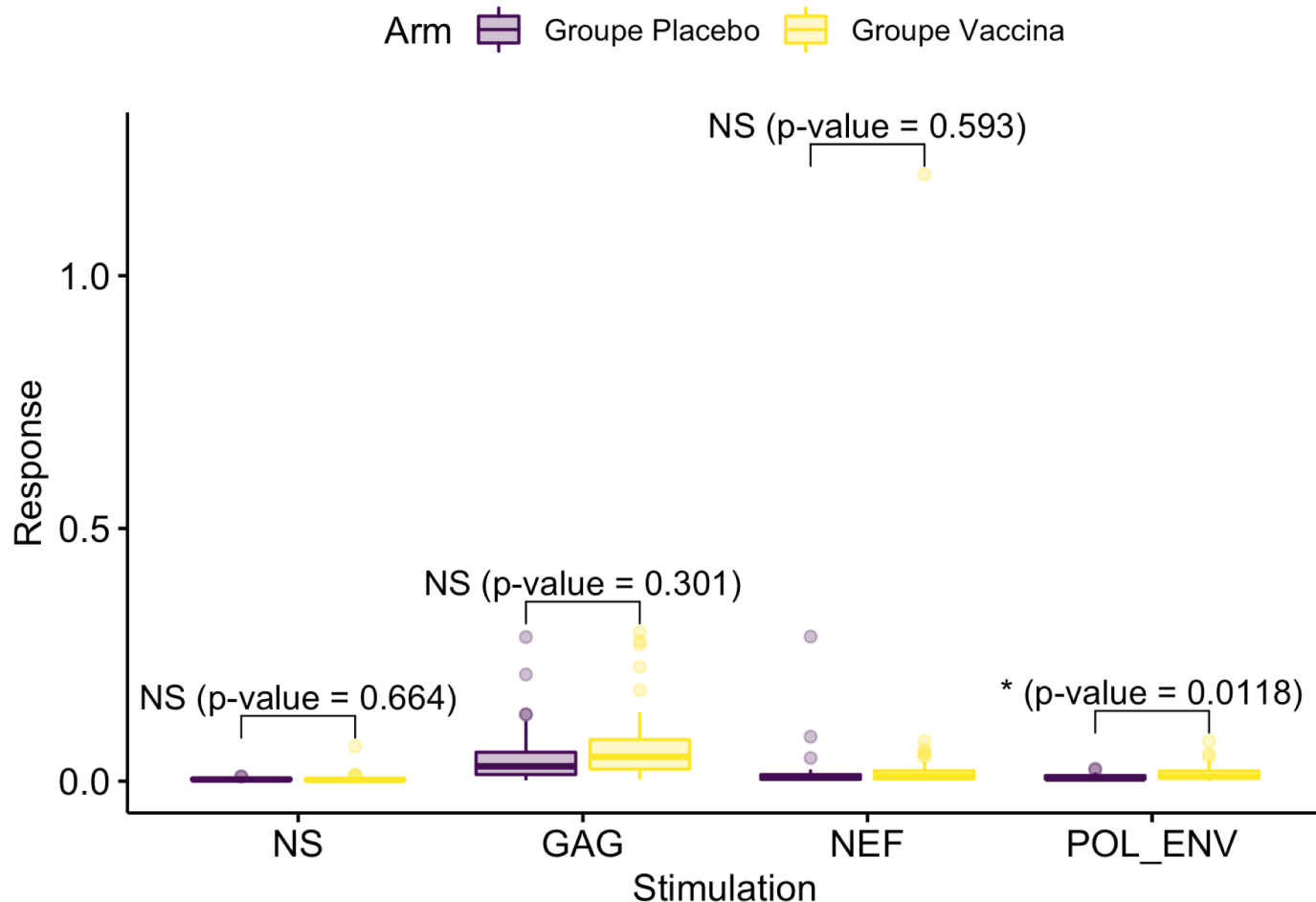
Dependencies:

- *DT*
- *ggplot2*
- *ggpubr*
- *magrittr*
- *nlme*
- *shiny*

VICI: shiny user interface

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VICI: accurate estimation of Vaccine Induced Cellular Immunogenicity with bivariate modeling

Results | Data view | **Additional Information**

Data input

Choose a CSV/TXT file to import

Browse... | Light_ICSdataW28.txt

Upload complete

☑ Header

Separator

○ Comma
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● Tab

Input parameters

Model choice

inter-arm

Variable specification

Select the column that identifies the subject ID

USUBJID

Select the column that identifies the ICS response

ptot_IFN_CD4

Select the column that identifies the stimulation

POOL

Select the value that identifies background samples

NS

Select the column that identifies the arm

ARM

Select the value that identifies the reference arm

Groupe Placebo

Run analysis

Fit model

Statistical model:

$$y_i^{NS} = \beta_0^{NS} + \beta_{GroupeVaccina}^{NS} GroupeVaccina_i + \varepsilon_i^{NS}$$

$$y_i^{GAG} = \beta_0^{GAG} + \beta_{GroupeVaccina}^{GAG} GroupeVaccina_i + \beta_{NS}^{GAG} y_i^{NS} + \varepsilon_i^{GAG}$$

$$y_i^{NEF} = \beta_0^{NEF} + \beta_{GroupeVaccina}^{NEF} GroupeVaccina_i + \beta_{NS}^{NEF} y_i^{NS} + \varepsilon_i^{NEF}$$

$$y_i^{POL_ENV} = \beta_0^{POL_ENV} + \beta_{GroupeVaccina}^{POL_ENV} GroupeVaccina_i + \beta_{NS}^{POL_ENV} y_i^{NS} + \varepsilon_i^{POL_ENV}$$

Number of estimated model parameters: 15

AIC	-2 Res. loglikelihood
-1402.4379	-1432.4379

	NS	GAG	NEF	POL_ENV
Variance	0.004369	0.017156	0.000056	0.000151

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Conclusion

- **Bivariate modeling**
  - Better statistical performances than conventional approach

- **Shiny app deployed**
  https://shiny-vici.apps.math.cnrs.fr

- **R package** *vici* **available**
  - GitHub *https://github.com/borishejblum/vici*
  - Soon on CRAN

- **User community:**
  - VRI Immunologists
  - Wider community