Deployment of the immunogenicity risk assessment assay-suite for protein design, risk assessment and de-immunization

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The immunogenicity assay-suite can be deployed for :

1. Protein design
2. Risk assessment
3. De-immunization
4. Retrospective analysis

Protein design – Aim and strategy

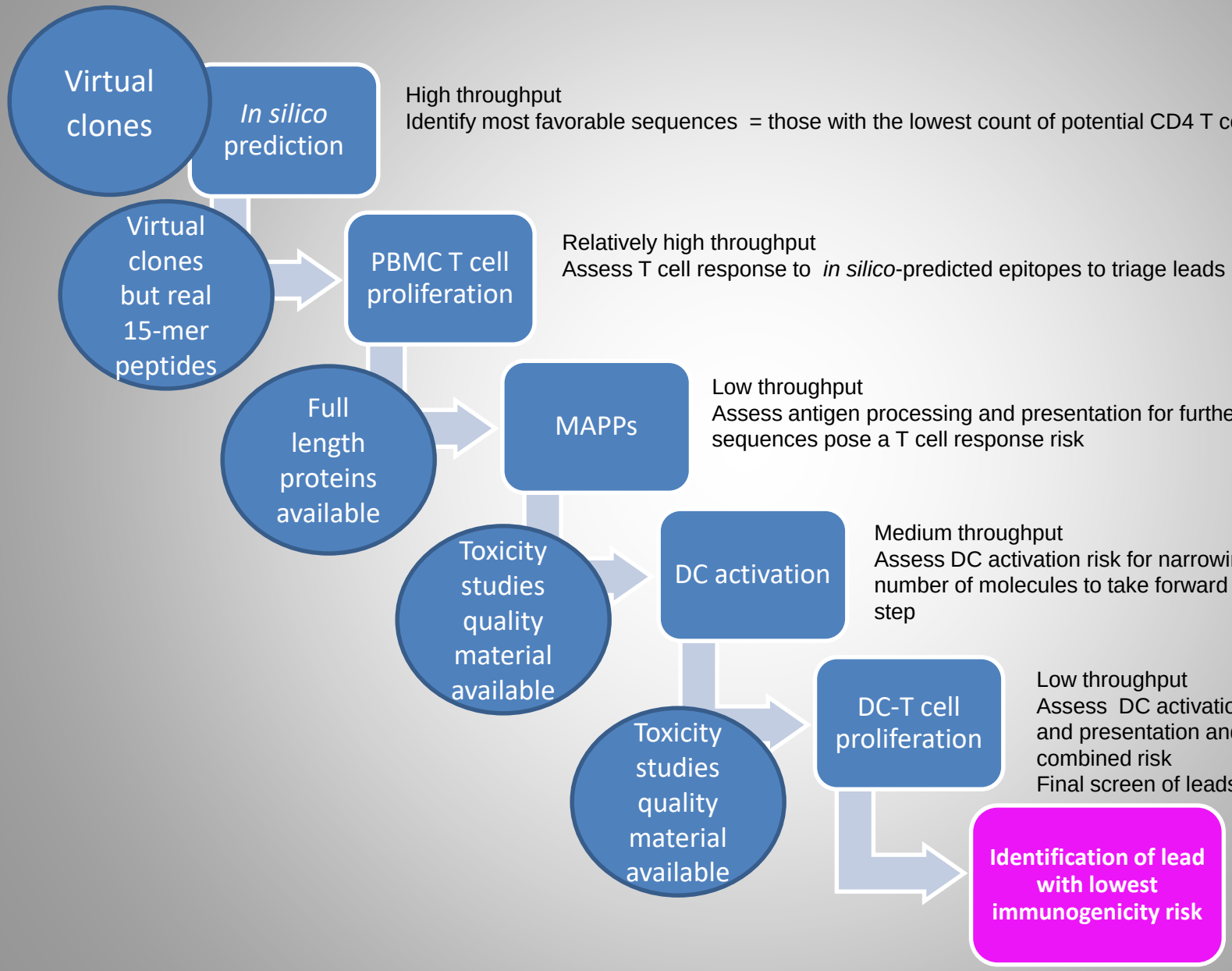
- The aim is to use the tools to guide design and screening of leads to **select the candidate which exhibits the lowest immunogenicity risk**

- Even though often called “predictive immunogenicity” assays, not a single assay outcome can be directly correlated with ADA clinical incidence

- Hence, we use a suite of assays that assess the risk at each step of the immune cascade that leads to ADA development

- This can include :
  - *In silico* analysis
  - PBMC T cell proliferation assay
  - MAPPs assay
  - DC activation assay
  - DC-T cell proliferation assay

Protein design – Conceivable immunogenicity strategy



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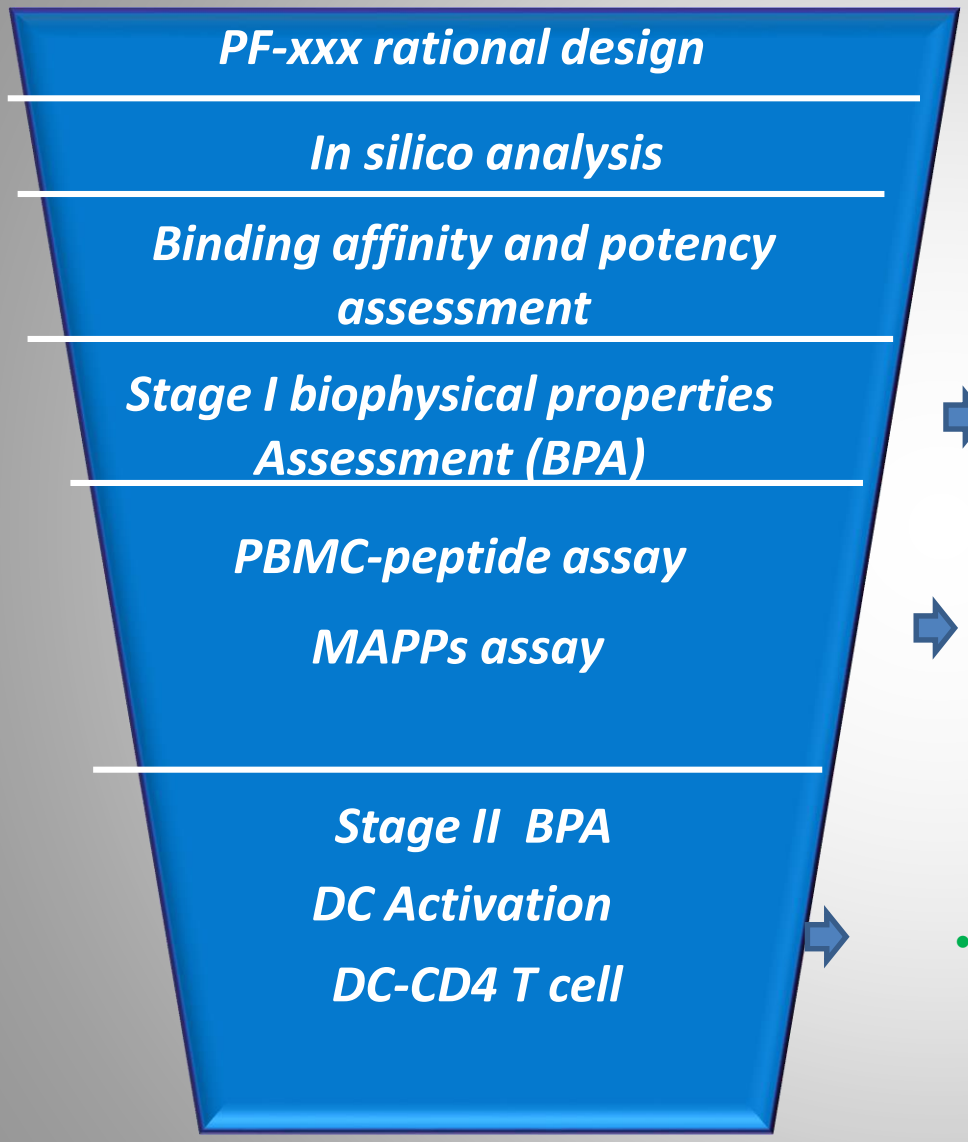
Protein design – Integrated candidate selection funnel

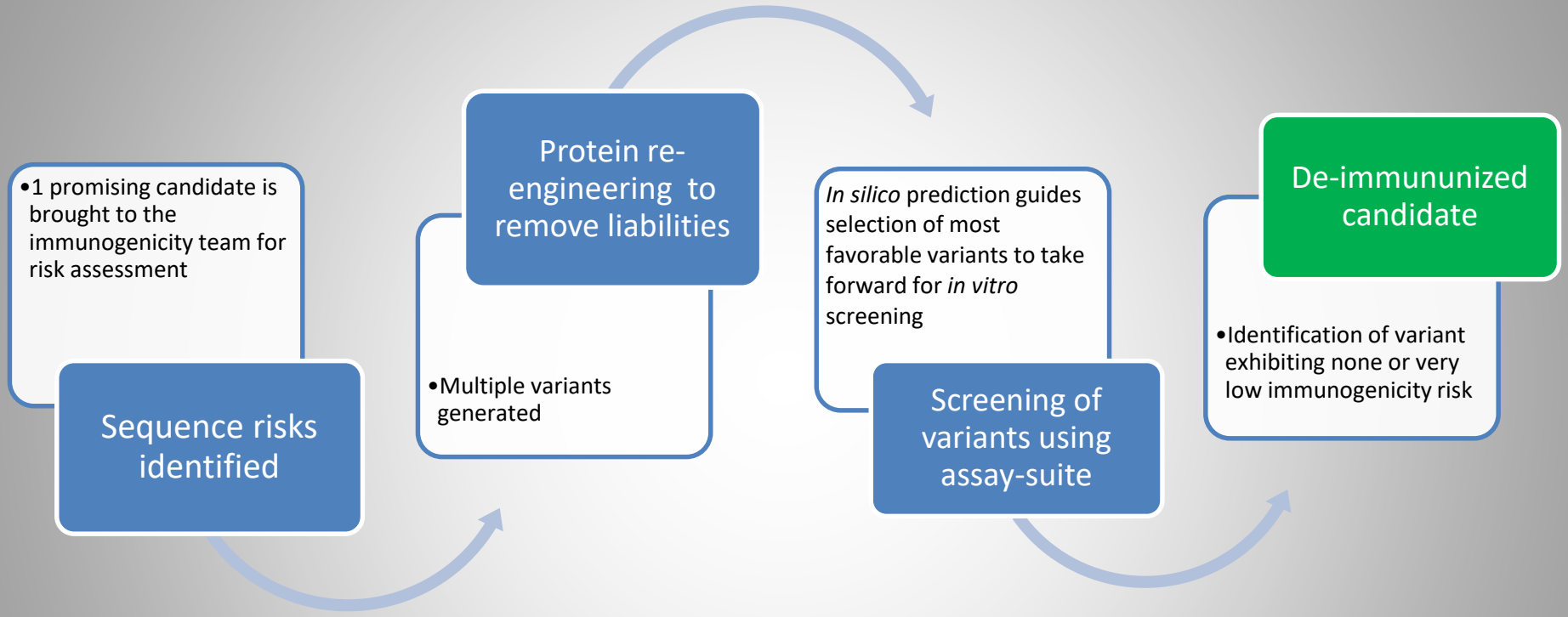


- > 100 clones
- 85 clones selected
- 19 clones selected
- 10 clones selected
- 2-4 preferred clones selected
- Lead Candidate selected

Application to Risk Assessment

- The tools can be used as part of the immunogenicity risk assessment of a designated clinical candidate prior to IND
- Results will be incorporated to the Immunogenicity Risk Assessment and Mitigation Plan (IRAMP)
- IRAMP will cover assessment of many other risk factors, such as mechanism of action, intended study/patient population, co-medication, route of administration etc., and estimate the overall immunogenicity risk of the clinical candidate
- What assay(s) to perform will depend on the desired level of information, budget, timelines, hence might vary for each program

Application to De-immunization : Timing is key !



- Time is needed to go back to the drawing board and screen de-immunized variants

Post-hoc analysis : another potential use of the immunogenicity assay-suite

- To increase our understanding of factors pertaining to ADA development
- To gauge the value of the risk assessment tools in the context of the overall risk assessment (IRAMP)
- To help weigh out each assay risk
- To generate data contributing to the development of mathematical models of immunogenicity prediction

Take home messages

- A suite of *in silico* and *in vitro* assays is available to assess the risk at each step of the immune cascade thought to lead to ADA development
- Timing is key to have an opportunity to 1) influence design; 2) de-immunize a candidate
- Not a single assay nor the overall risk will predict ADA clinical incidence, but will estimate the likelihood of ADA development
- The assays can be applied retrospectively to advance understanding of the mechanisms of ADA development and increase confidence in risk assessment

Some of the challenges we face

Come and join the discussion at EIP's NCIRA* working group monthly meetings !

- What assay to run and when during development to best deploy the suite?
- Do our assay cycle times fit protein engineering timelines ?
- How do we define our cut-offs and/or risk categories ?
- How do we manage MOA-associated interference in the assays ?
- How do we reconcile conflicting results ?
- How do we weigh each assay risk to calculate an overall risk ?
- How do we assess B cell risk ?
- …
- …

* Non-Clinical Immunogenicity Risk Assessment

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