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Biotherapeutic Immunogenicity Risk Factors – the science, reliability, and concepts for implementing predictive tools to improve their reliability

Mastering Immunogenicity, Cambridge, MA 12 Sep 2011

Bonita Rup, Pfizer

Pfizer

Concepts:

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- All biotherapeutics potentially immunogenic **under some circumstances**

- Risk varies considerably among products, patient populations and treatment regimens.

- Immunogenicity risk & mitigation planning well established, intended to focus resources where needed, continuing to evolve as does biotherapeutics field.

- Although based on immunological science, predictive value of risk factors needs improvement **in order to improve and refine management and mitigation strategies**.

4 Decades in Biotechnology: Evolution of Protein Therapies

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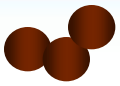
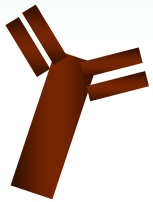
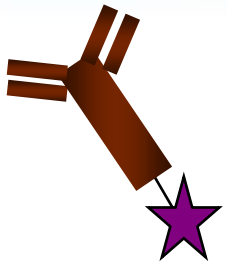


rDNA expression of human proteins

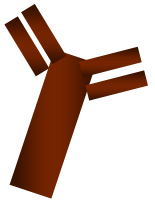


Humanized Antibodies

FC fusion proteins

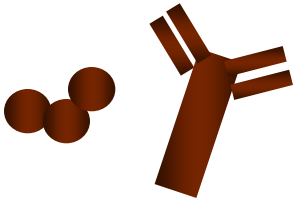


Antibody-conjugates

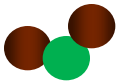


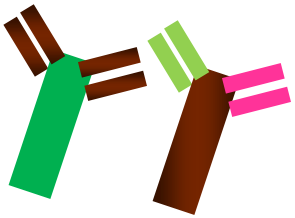
Human Antibodies

Novel scaffolds



Biosimilars





"Biobetter" proteins

IV injection/ infusions

Subcutaneous administration

Alternative delivery routes/ forms

Pfizer

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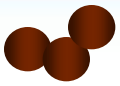

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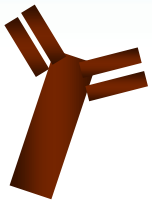

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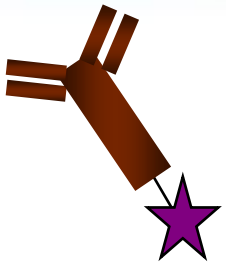

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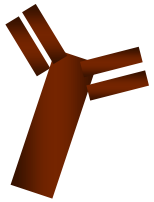

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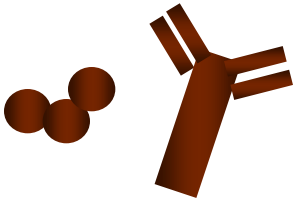

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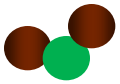

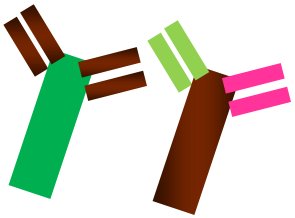

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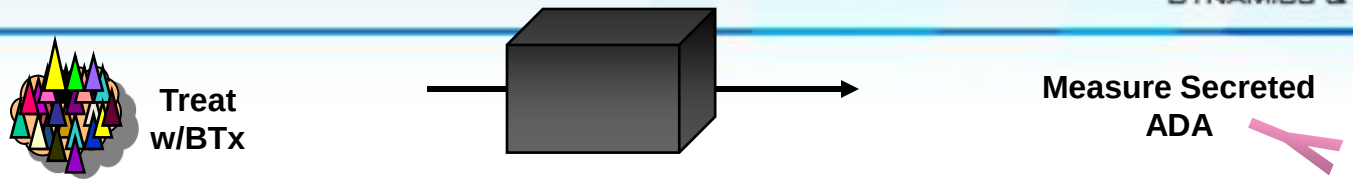
BTx Immunogenicity Assessment



Tiered Anti-Drug Antibody Testing

Pre- and Post-dose Samples

Screening Assay → **negative:** report result

positive

Confirmatory Assay → **negative:** report result

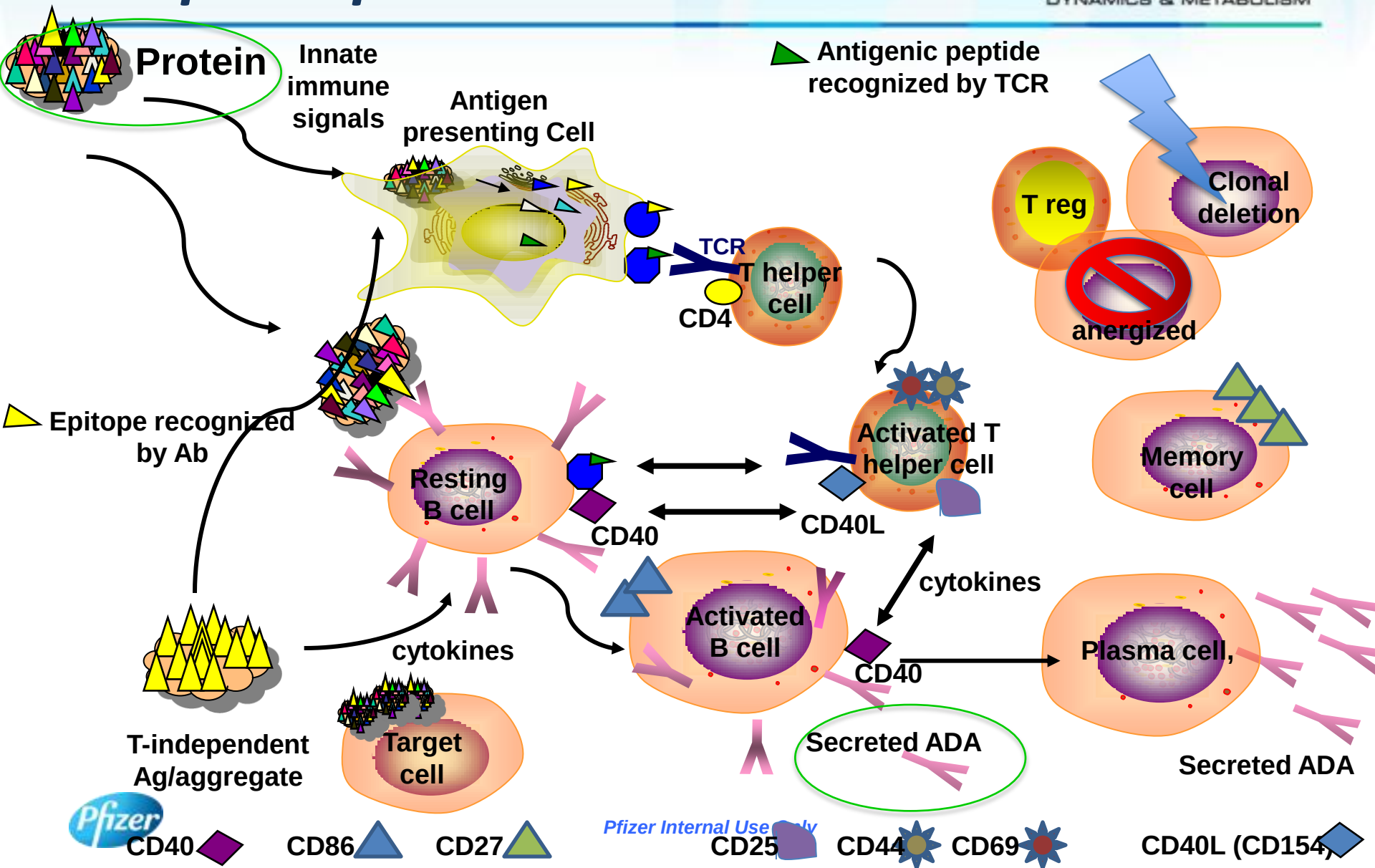
positive

Titer Assay → **positive:** report titer result

Neutralizing Ab Assay

Other Characterization

Immune response to a therapeutic protein



Risk-Based Approach

A Risk-Based Approach to
Immunogenicity Concerns of Therapeutic Protein Products
Part 2: Considering Host-Specific and Product-Specific Factors Impacting Immunogenicity

Amy S. Rosenberg, M.D. and Alexandra S. Worobec, M.D.

Because all protein therapeutics are potentially immunogenic, FDA has developed a risk assessment strat-

This may be due to the severe depletion of CD4+ T cells which are replenished slowly and are required for development

BioPharm International www.biopharminternational.com December 2004

~ 1999-2002 adverse event reports (rErythropoetin, rThrombopoetin)

- Pure Red Cell Aplasia & Thrombocytopenia reports related to Erythropoeitin and Thrombopoeitin NAb development
- Epo traced to changes in administration route, removal of HSA, Tween 80 in manufacturers' process

•~ 1993 adverse events (plasma-derived Factor VIII)

- Reports of increased pdFVIII inhibitor (NAb) in low risk population traced to manufacturing change (viral inactivation step)

What factors may influence development of an immune response?

Risk Category	Risk Factor
Product-related	Presence of foreign amino acids, structures
	Unusual post-translational modification
	Level of aggregates/impurities/degradants
	Presence of promiscuous MHC epitopes
	Self-protein in non-tolerizing environment
	Product Biology/Pharmacology
Patient/Subject Population-related	Immune status of patients
	Genetic profile (incl. HLA)
	Underlying disease
	Target biology
	Pre-existing antibodies
Treatment-related	Route of administration
	Dosing frequency
	Concomitant medications

What factors may influence consequences of an immune response?

Risk Category	Risk Factor
Product-related	Presence of endogenous counterpart
	Unique activity of counterpart
Patient/Subject Population-related	Compounding effect of existing deficiency
	Life-threatening disease
	Non-reversible/treatable AEs
	Replacement therapy
Treatment-related	Availability of alternative treatment
	Multiple/chronic treatment needed
	Concomitant medications

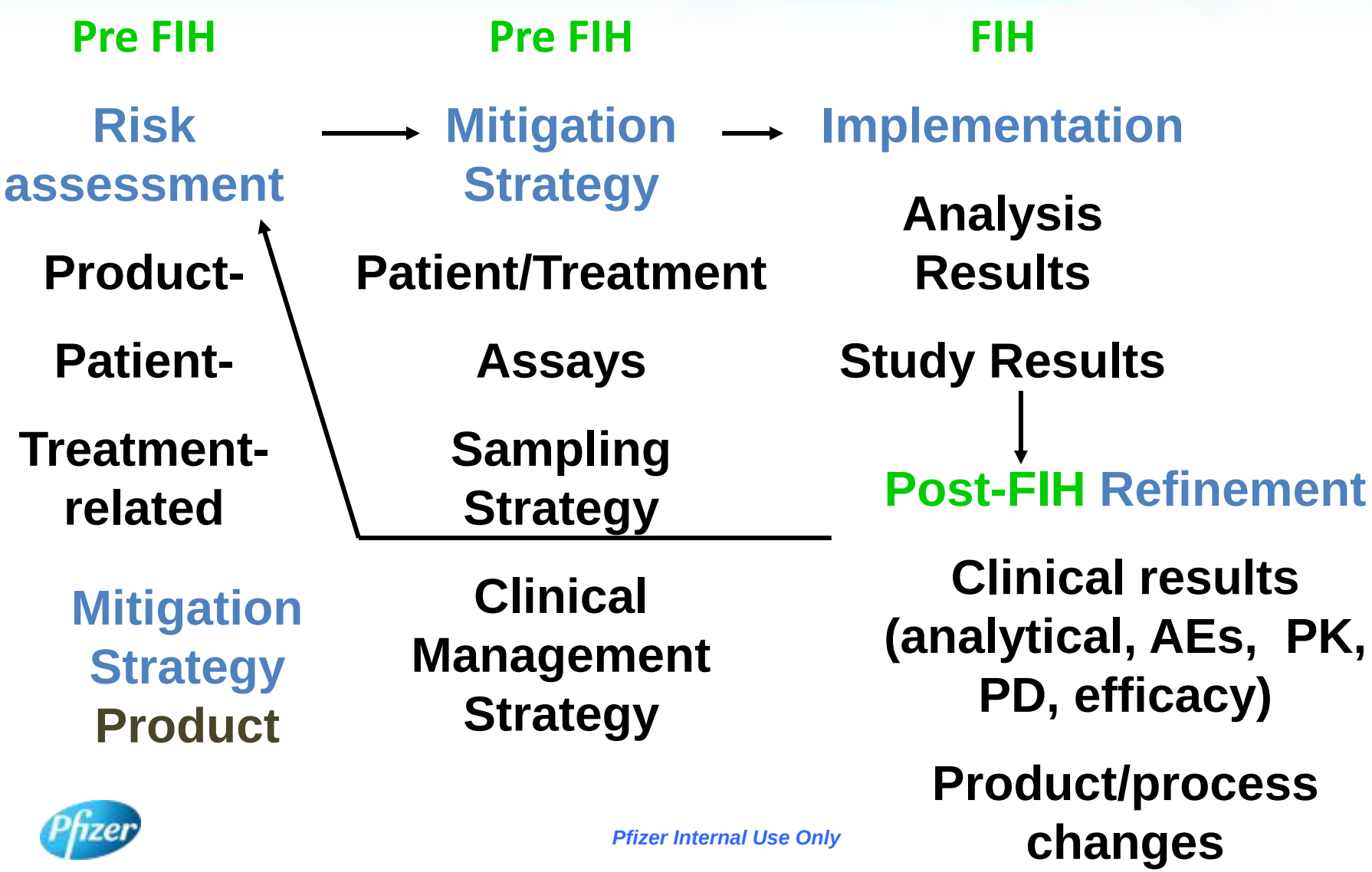
Neutralization of non-redundant endogenous counterpart?

Anaphylaxis? Other hypersensitivity? Immune complex disease?

Loss of effect**?**

Mild infusion rxn?

Immunogenicity Risk and Mitigation Planning



Implementation of Risk Based Approach

Use risk assessment to support design clinical analysis strategy. Examples:

Selection of study population

- **Patients with lower risk in earlier studies**
- **Different populations depending on risk category (development vs consequences)**

Type of testing to be conducted

- **Sensitivity of assays, orthogonal/characterization methods**

Timing of sample collection & analysis

- **More samples early vs frequency**
- **Drug levels cleared**
- **Monitor for transience/persistence**
- **Rapid turn-around of results**

Stage-Related Risk Questions

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- Candidate selection:
  - Is any candidate likely to induce immunogenicity; which has highest risk?
  - Will presence of foreign sequences (or other risk factor) result in increased immunogenicity; what mitigation strategy is most likely to decrease risk?
- Nonclinical Development:
  - Will ADA development limit the interpretability of my study; is the immunogenicity seen in nonclinical studies based on a translatable risk factor; findings relevant to humans?
  - Will aggregates/post-translational mods/impurities result in increased immunogenicity?
  - What mitigation strategies are most likely to decrease risk?
- Early Clinical Development:
  - If pre-existing x-reactive antibodies are present, are they likely to increase after dosing?
  - Is ADA observed after a single dose likely to increase or decrease after repeat dosing?
  - What consequences are likely to occur? What mitigation strategies are most likely to decrease/maintain risk profile?
- Later Clinical Development
  - Will a change in (manufacturing, dosing regimen, indication, patient population, assays), result in a change in immunogenicity profile?

Pfizer

Example

Protein x is an Fc fusion protein
Fc contains mutations x, y, x
Linker has unique sequence
Non-Fc portion has endogenous counterpart
Subcutaneous route of administration
Intended for chronic treatment of inflammatory disease

ADA development multiple dose toxicity studies
Hypersensitivity reactions

Low titer ADA development single dose FIH study
No clinical sequelae observed

Goal: Mitigation Strategies *Focus on Factors Predicted to Generate* Highest Risk

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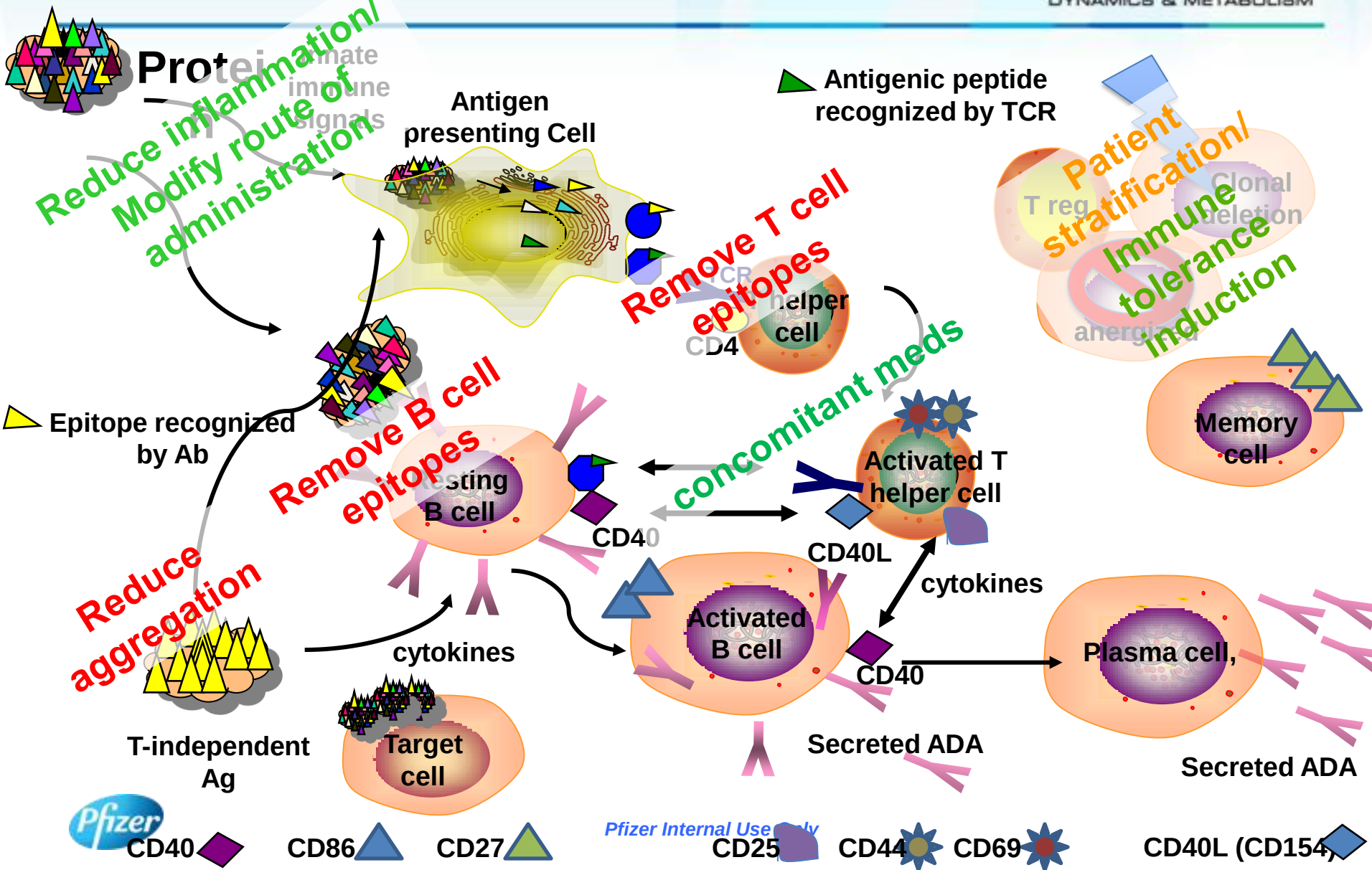
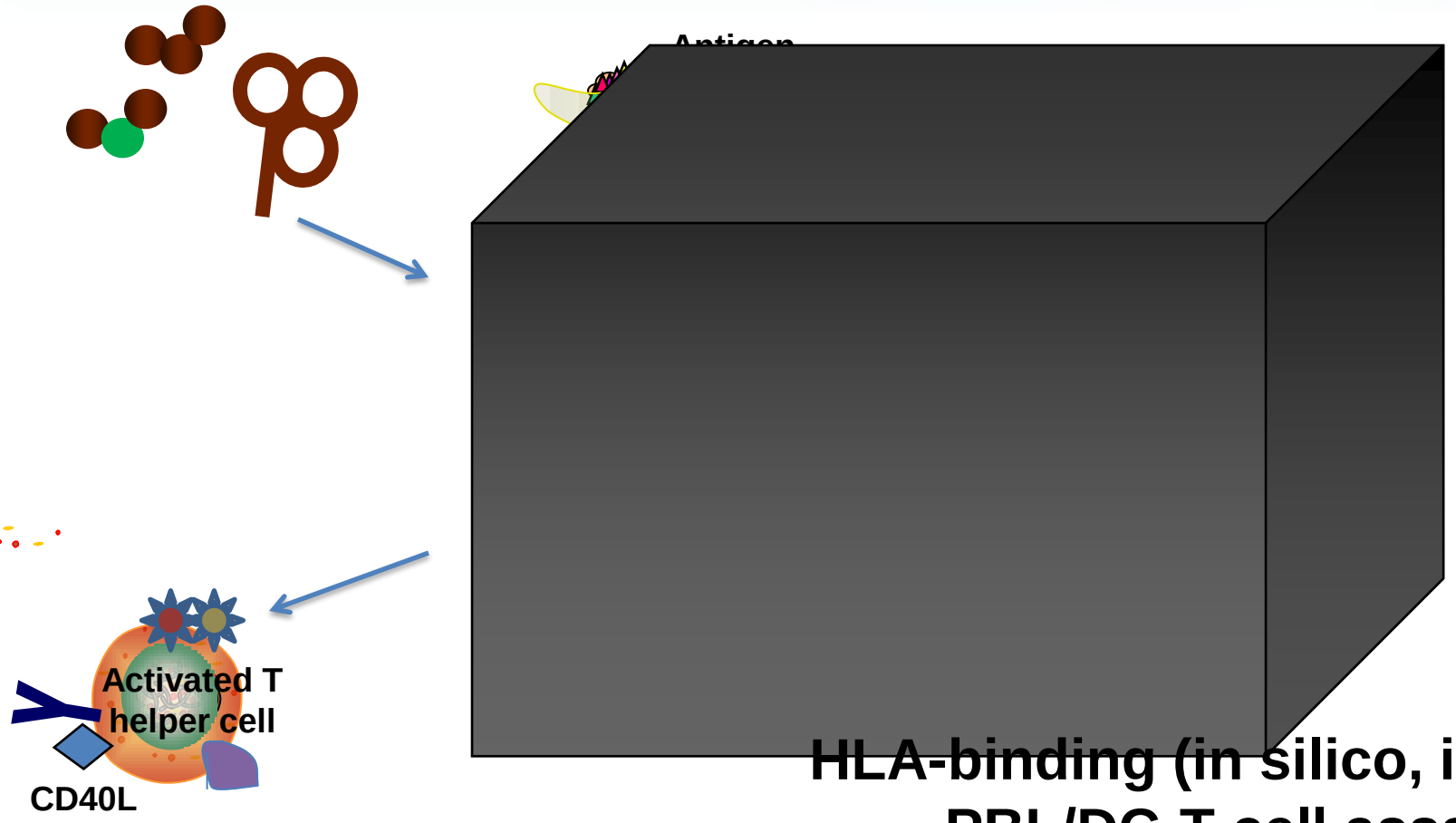


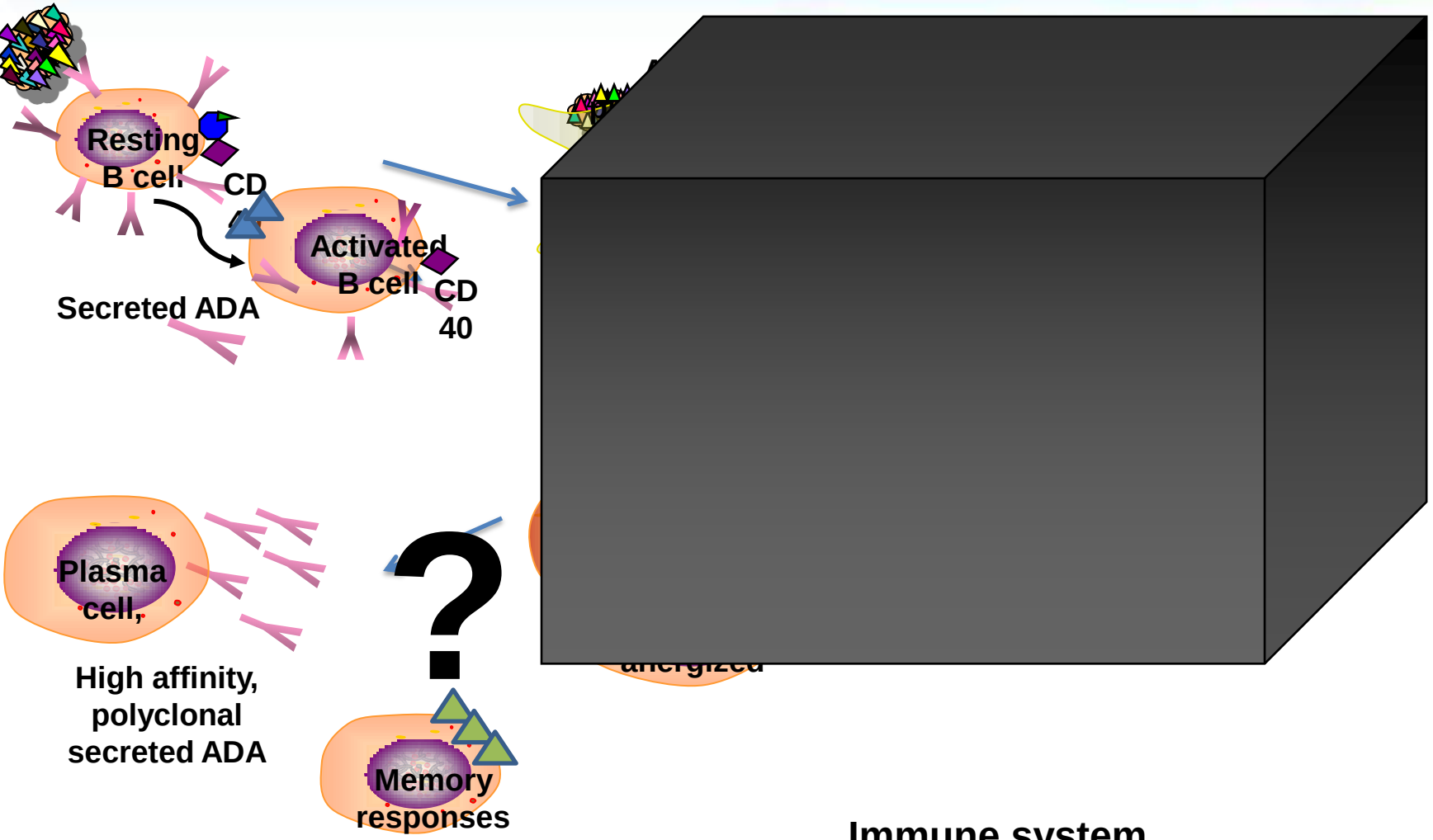
Risk Factor: Foreign Sequence



HLA-binding (in silico, in-vitro), PBL/DC-T cell assays

Immune system

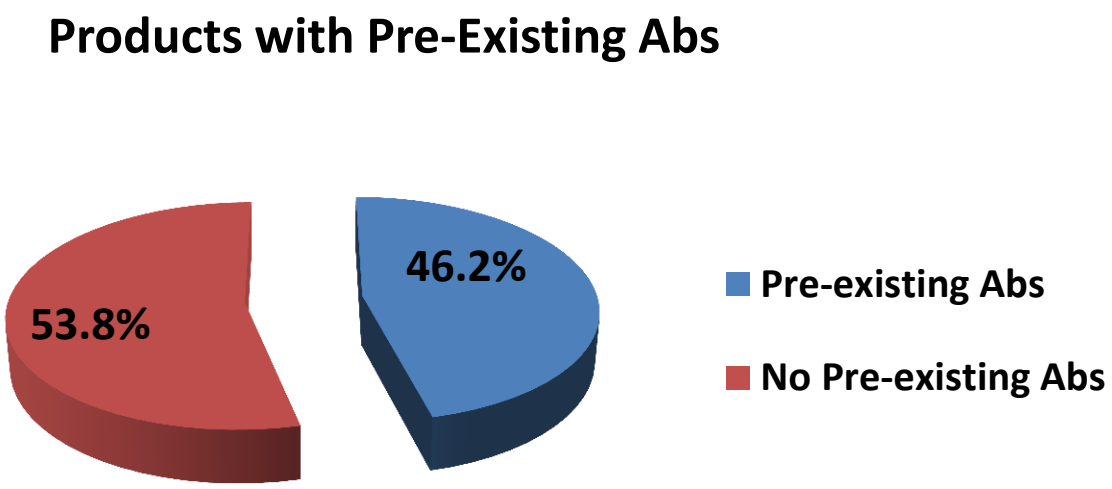
Risk Factor:Pre-existing ADA



Pre-Existing Abs to Biotherapeutics are relatively common

Survey of historical clinical immunogenicity data analysis:

13 biotherapeutics evaluated in ~ 40 clinical studies.



Unclear Association of Pre-Existing Abs to Immunogenicity Risk

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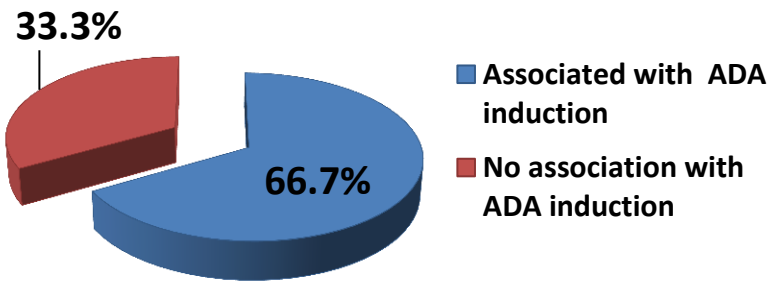
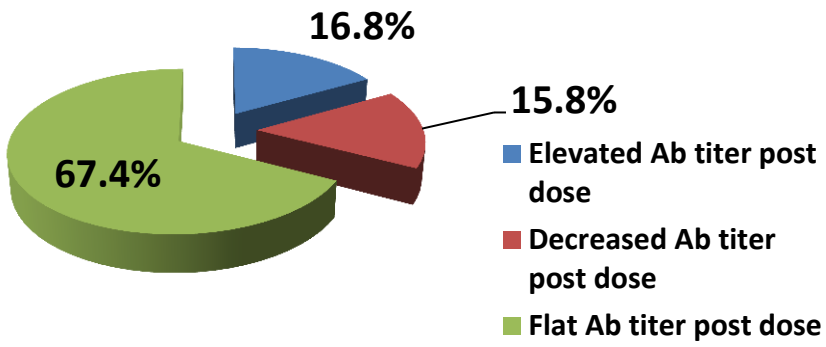
Comparison of pre-existing antibodies with post treatment ADA induction

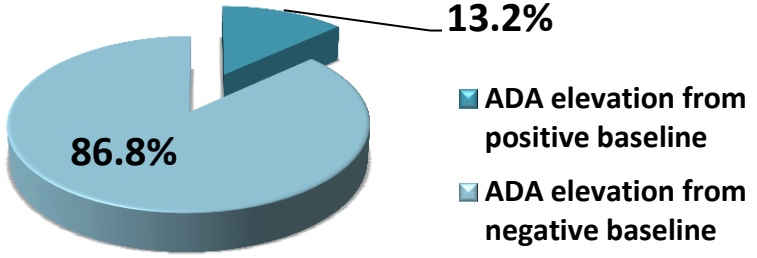
Products with Pre-Existing Abs



Subjects Positive for Pre-Existing Abs



Subjects from Studies Showing Pre-Existing Abs



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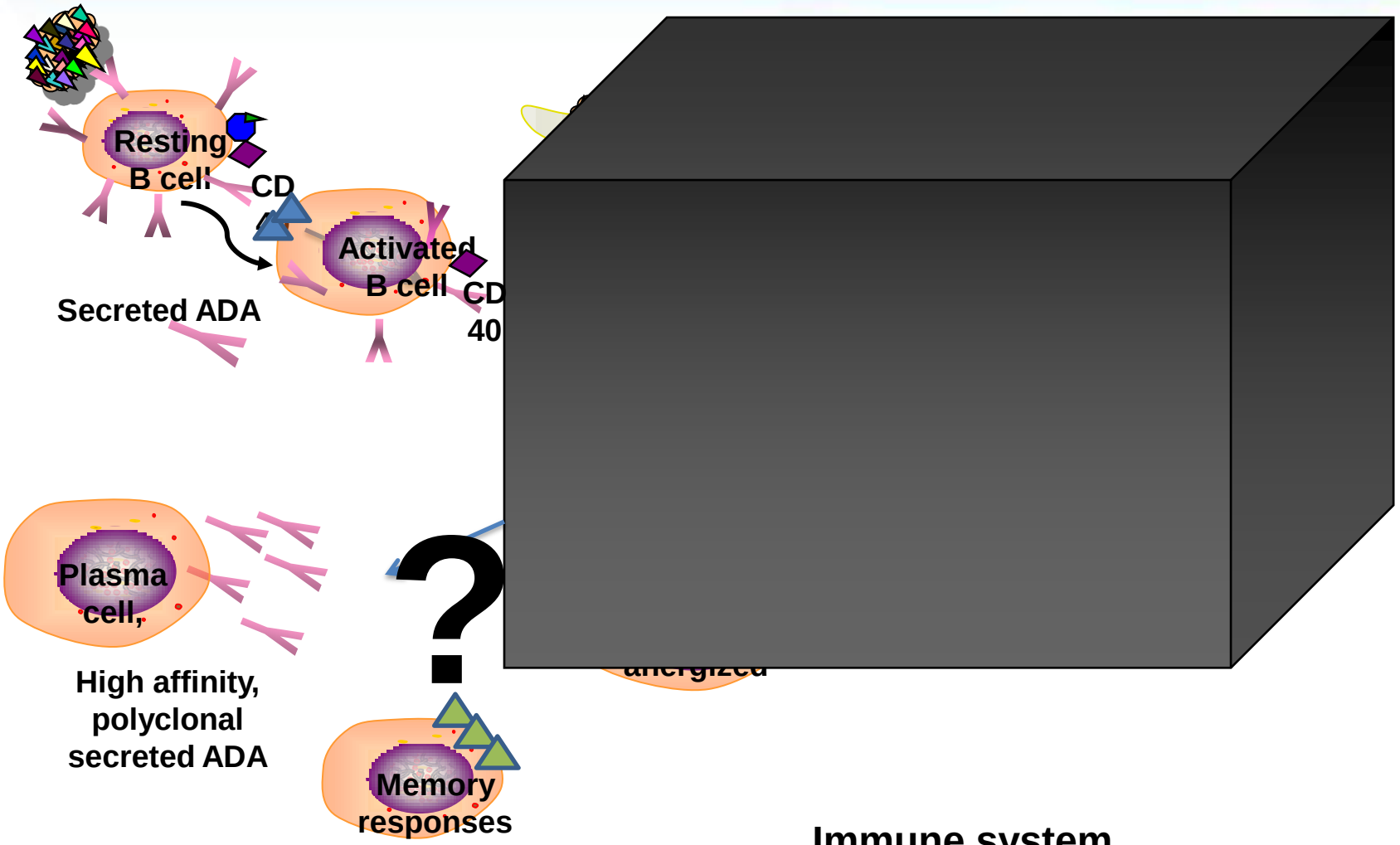
Risk Factor:Pre-existing ADA



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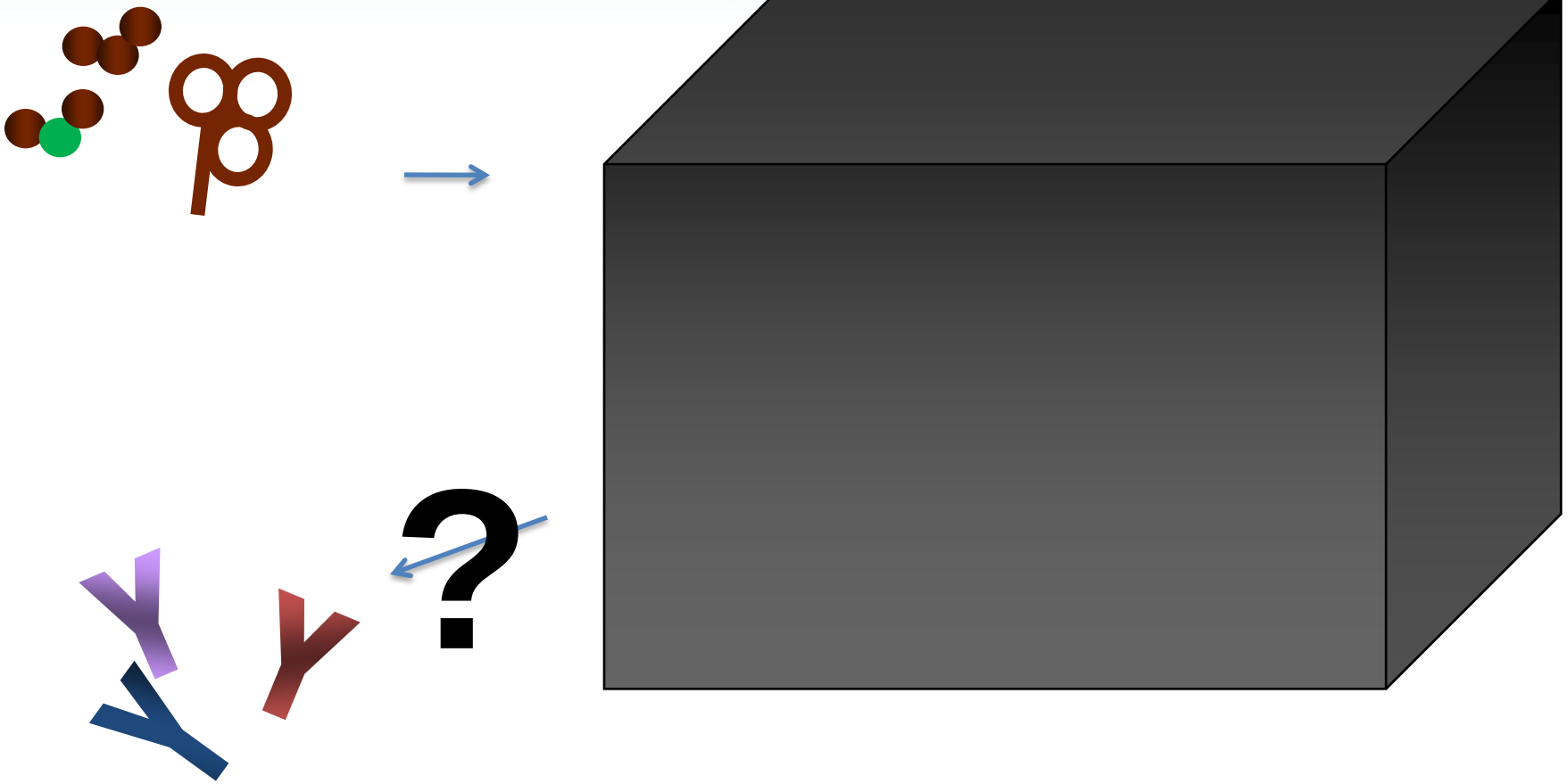


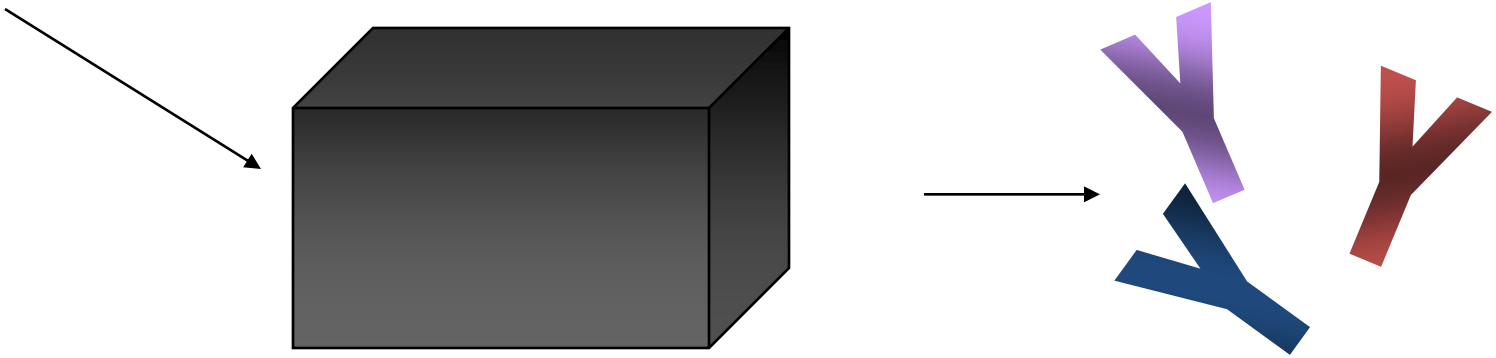
Will immunogenicity profile change if x changes? X =

Study patient population

Route of administration

Product formulation

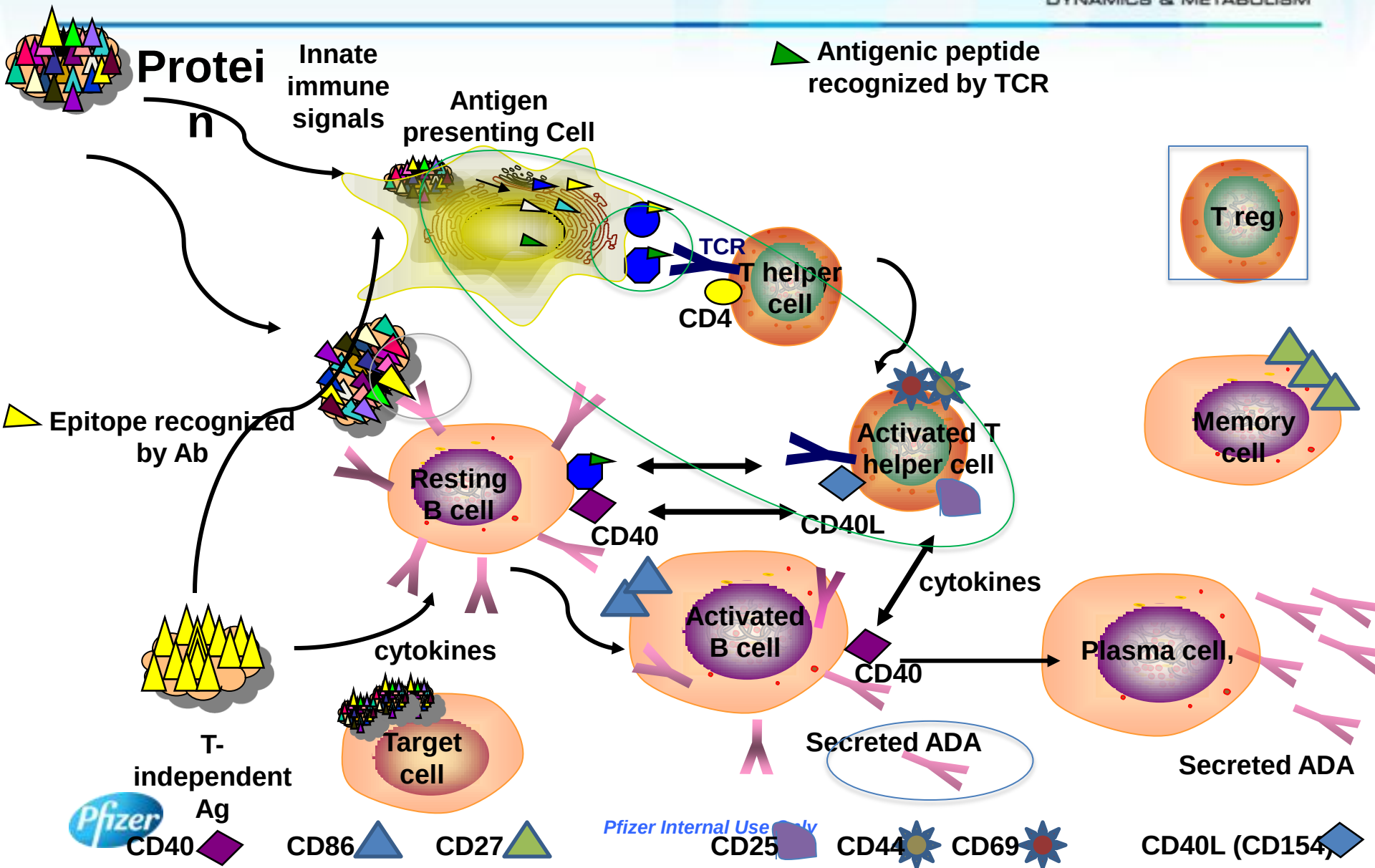
Manufacturing process



Immune system

ADA response?

"Predictive tools" = Markers for Risk Factors?



Summary

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Immunogenicity risk assessment is an expected aspect of biopharmaceutical development planning

Risk factors have been identified, but degree to which any risk factor increases probability of immune response & how different risk factors "interact" are poorly understood

Use risk assessment to guide nonclinical/clinical testing strategies

Need for tools to better understand key risk factors, increase confidence in decision making

Acknowledgements

- Pfizer PDM Colleagues, including
- Li Xue
- Tim Hickling
- Boris Gorovits