

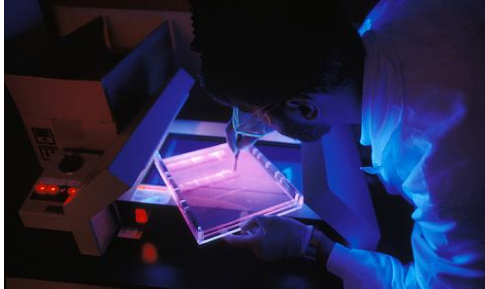


Glycoengineering better tolerated proteins

Focus on next generation antibodies



New key limitations



➤ **No extractive human material:**
International Standards :IU/L vs ng/L



➤ **outsourcing:** high diversity of procedures



➤ **New regulations:**

-Immunogenicity: protein folding & sugars

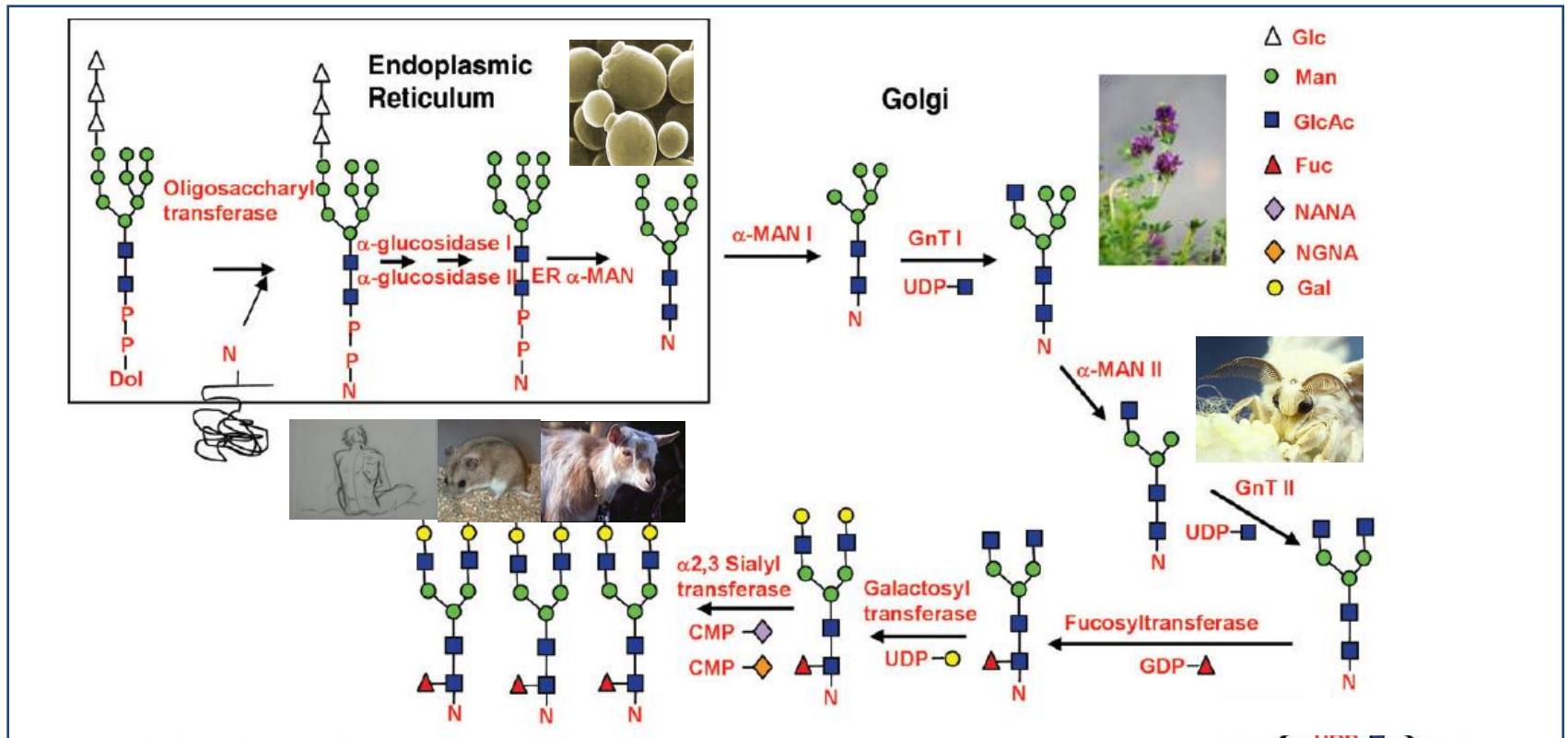
-Quality Attribute: glycosylation

- Performances of the product: efficacy (B/I)

What will be the appropriate reference????



N-glycosylation reflects the host cell machinery



Which glycome is best suited for activity?



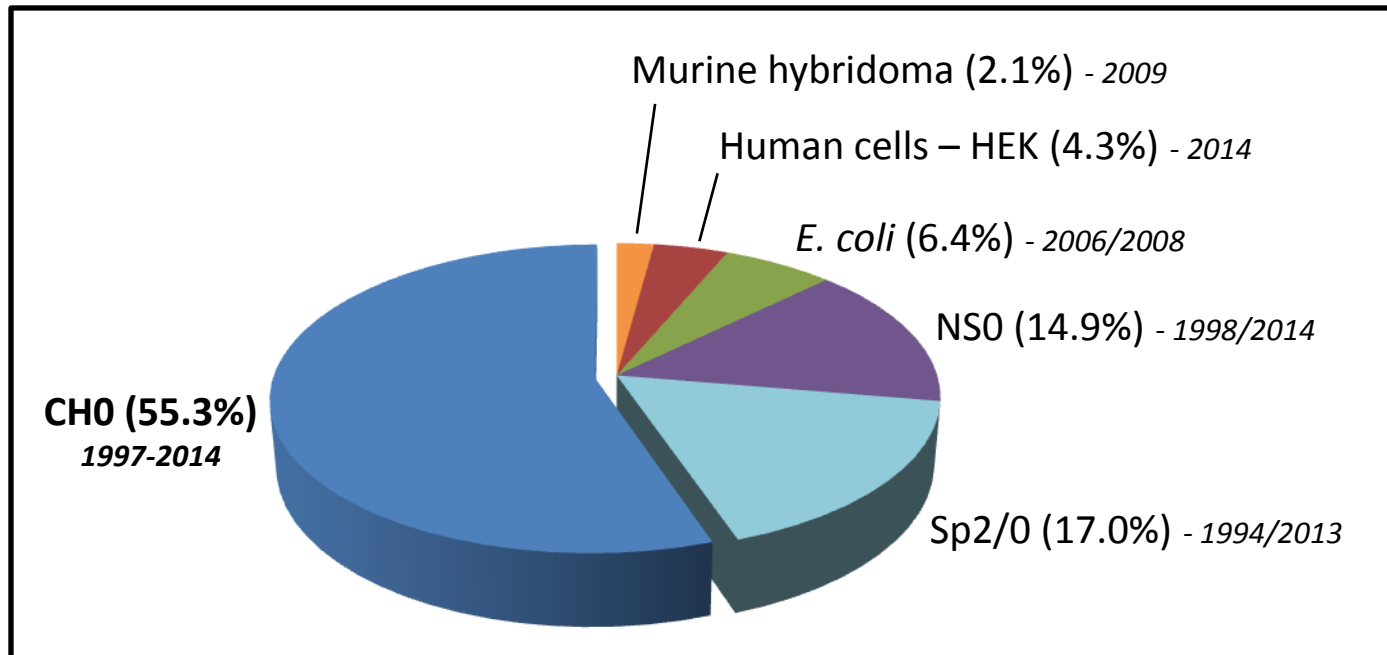
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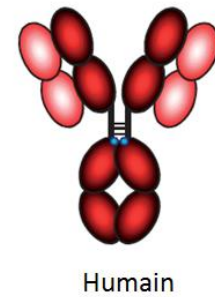
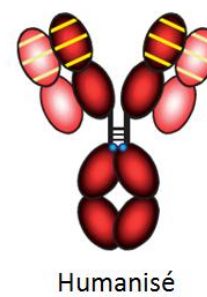
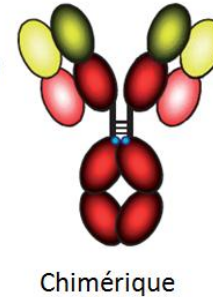
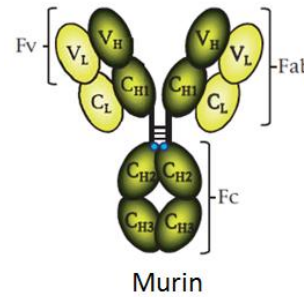
Bioproduction of therapeutic mAbs

- 58 mAb products approved since 1986
 - 47 approved products currently on the market
 - Over 300 candidates are currently in development
 - 70 mAbs estimated on the market by 2020

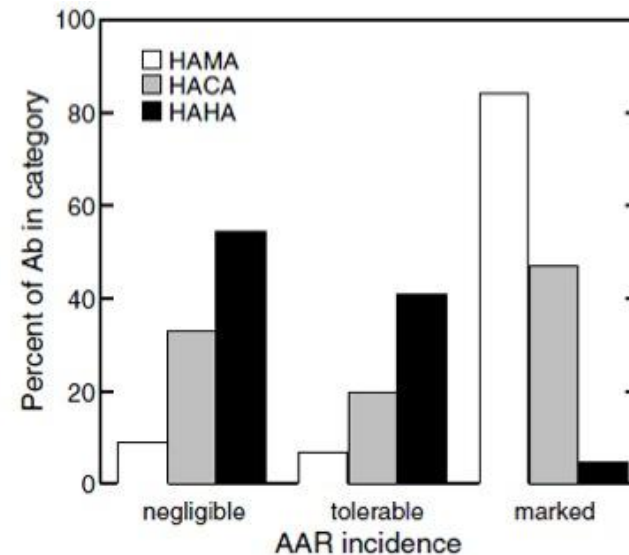
Production in various cell lines



Specific limitations of antibodies



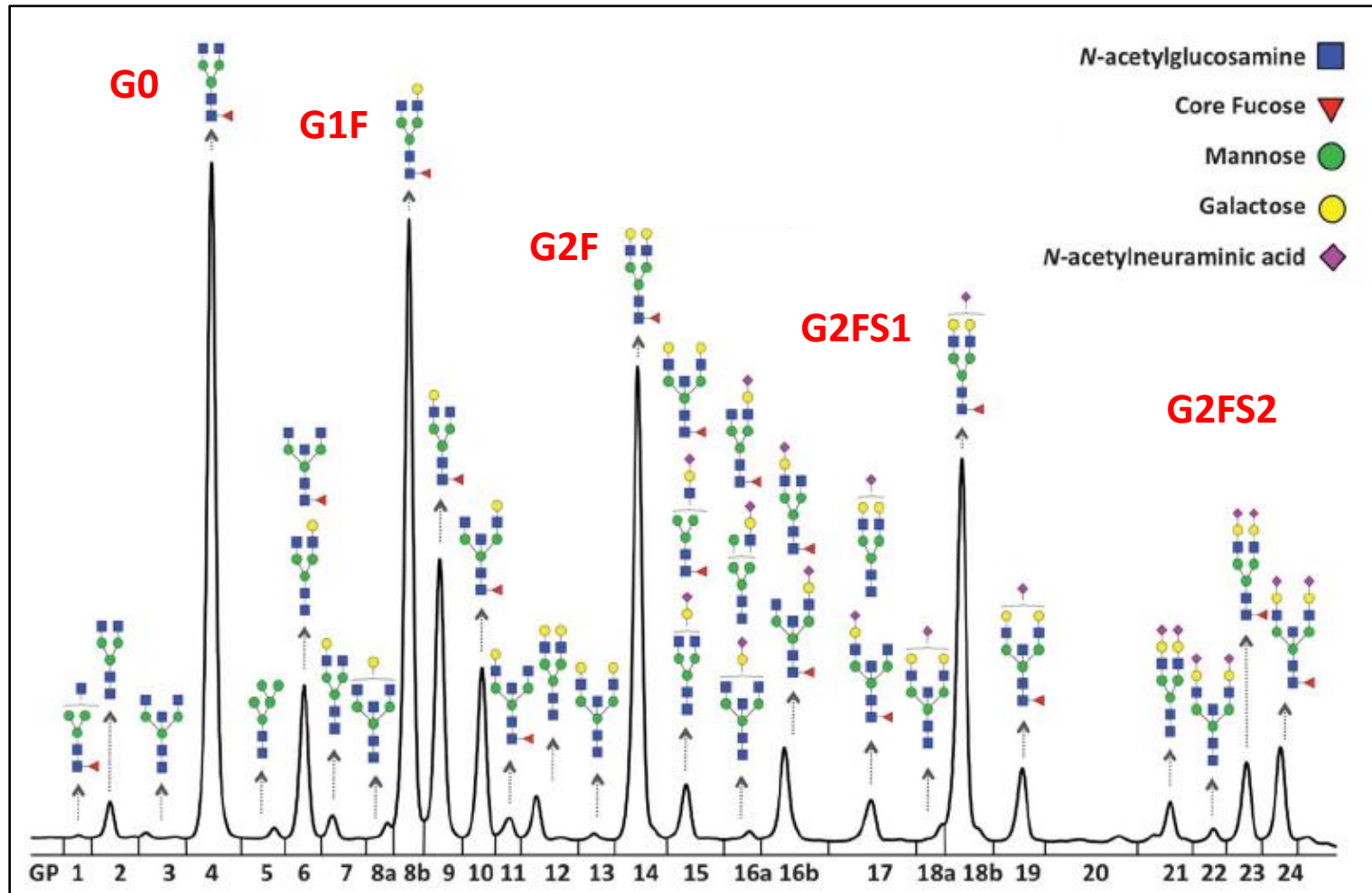
- **Immunogenicity :**
from 82% to 25% patients
in latest generations
- **Side effects**
(recurrence, infections, toxicity...)
- **Costs:** elevated for Health systems



www.genmab.com



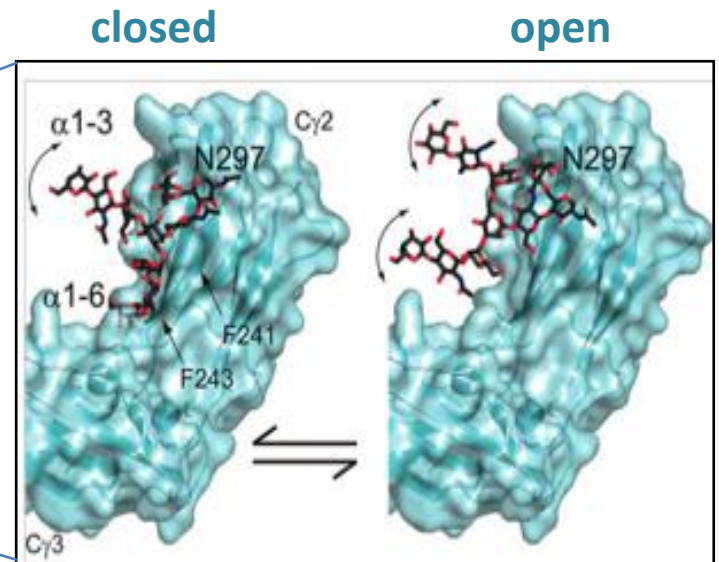
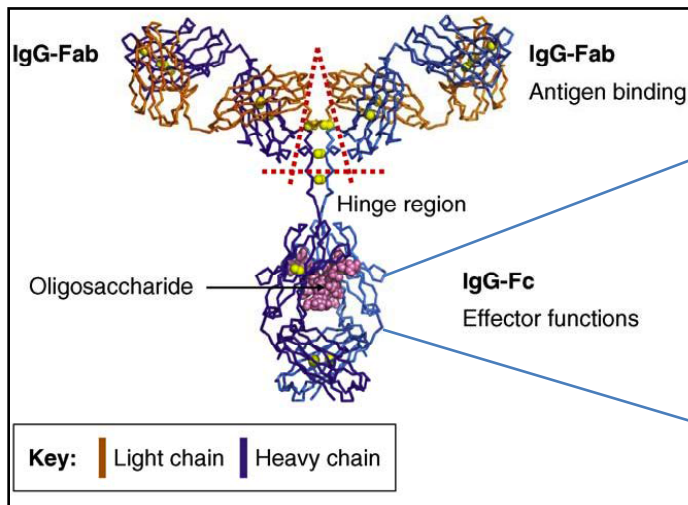
The serum IgG glycome: an inherited and physiologically regulated repertoire



Trbojevic Akmacic et al., 2015



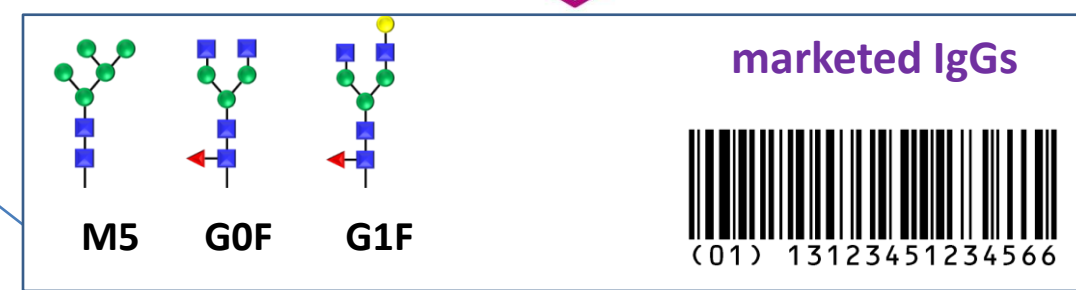
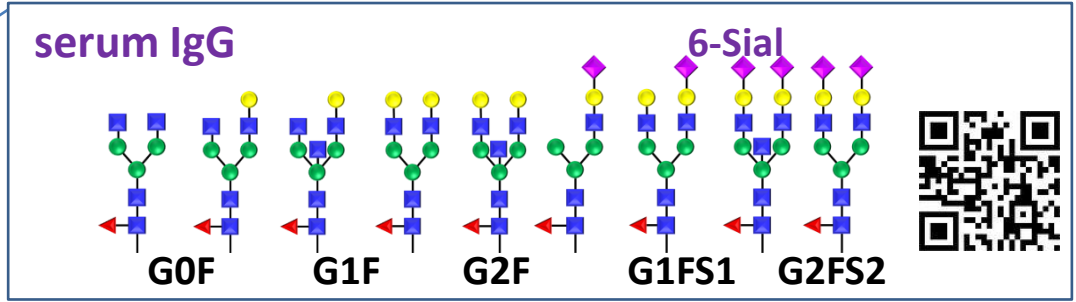
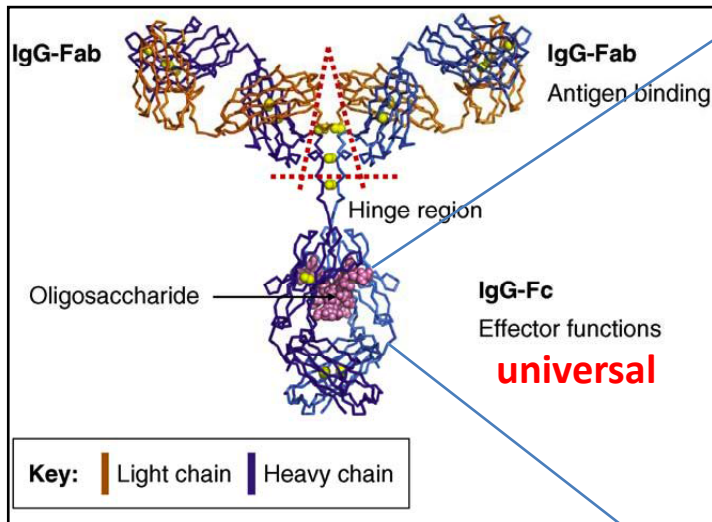
IgG glycans govern 2 conformations to modulate effector functions



Barb et al, Nature Chem Biol.2011



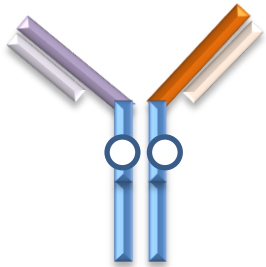
27 glycans encode effector functions



Optimization pathways: combining options

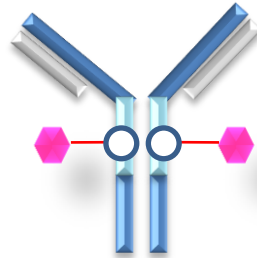
ongoing

new



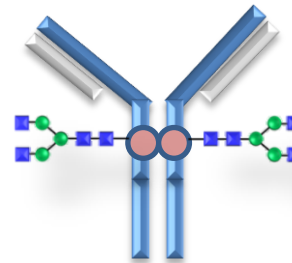
Fab engineering

ximab
zumab
mumab...
bispécifiques

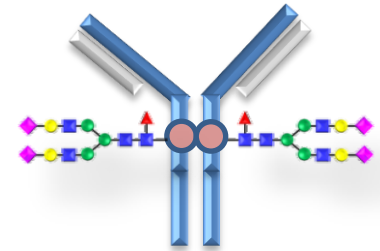


Fc engineering

ADC



Glycoengineering



- **No adverse immunogenicity**
- **High binding to the target**
- **order the target receptor**
- **Adapted PK**

Adverse Immunogenicity

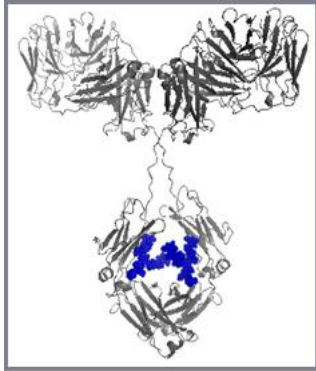


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Des Produits plus efficaces et mieux tolérés

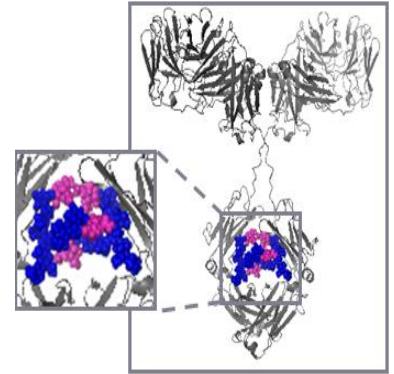
« en 2025, 1 biologique sur 2 sera un anticorps »
(LEEM, Santé 2011)



47 produits
>350 developement



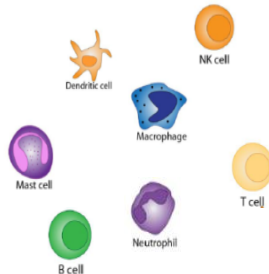
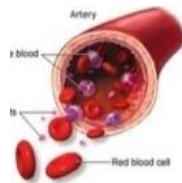
Glyco-Optimisation Fc
prévient la capture



Durée de vie:
5-8hr



Active
Immunogène



1. par le foie

ET

2. par le système
immunitaire (FcRs)

Durée de vie:
1 semaine



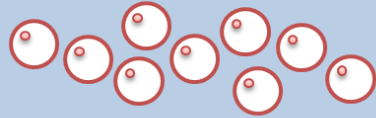
N'active pas
Non immunogène



DRUG APPROVED CELLS

GLYCOENGINEERED CELLS

PRODUCTION
RATE

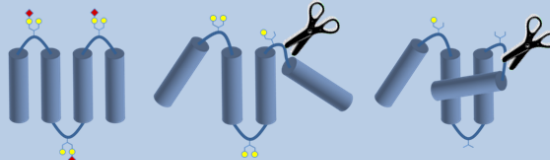


High Density/Low Secretion

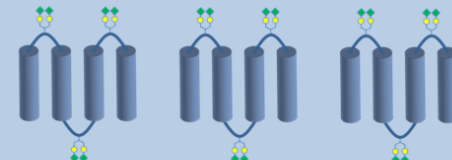


Low Density/High Secretion

IMMUNOGENICITY
& STABILITY



Misfolding → Proteolytic Cleavage



Mature Protein → Stable Protein

DOSING

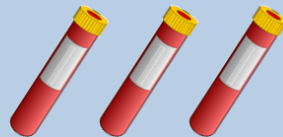


High Dose



Low Dose

BLOOD TESTING



Discordant



Accurate





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