Biosimilar mAbs
Clinical issues
Regulatory perspective

EMEA Workshop

on Biosimilar Monoclonal Antibodies

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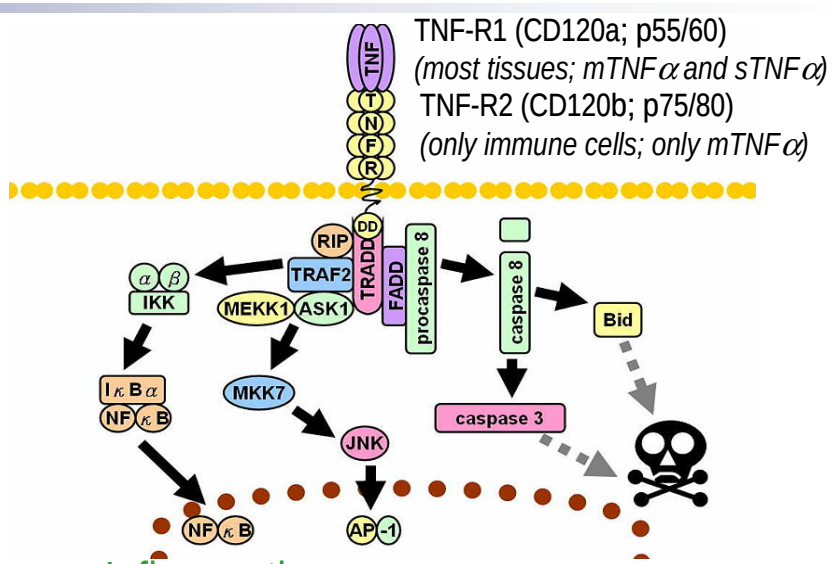
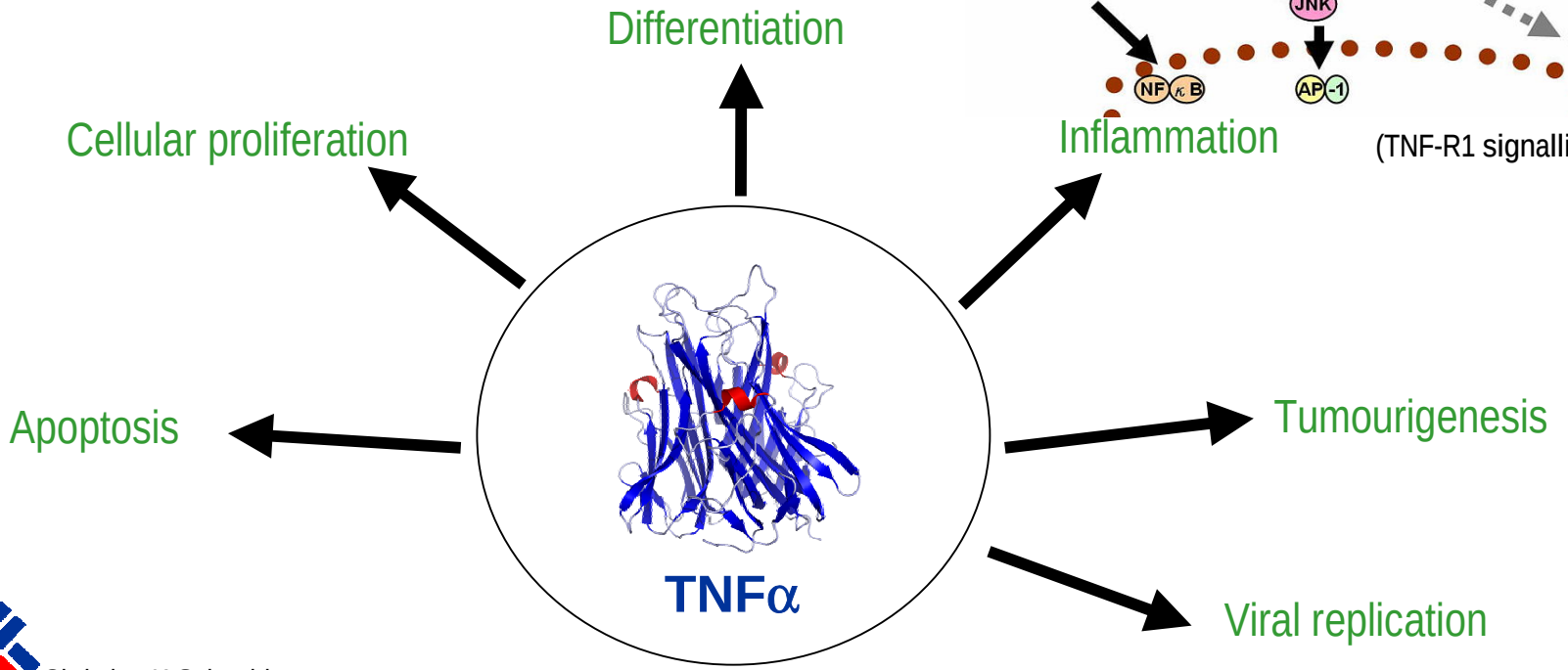
Mechanisms of action can be complex!

- **Example: TNFα antagonism**

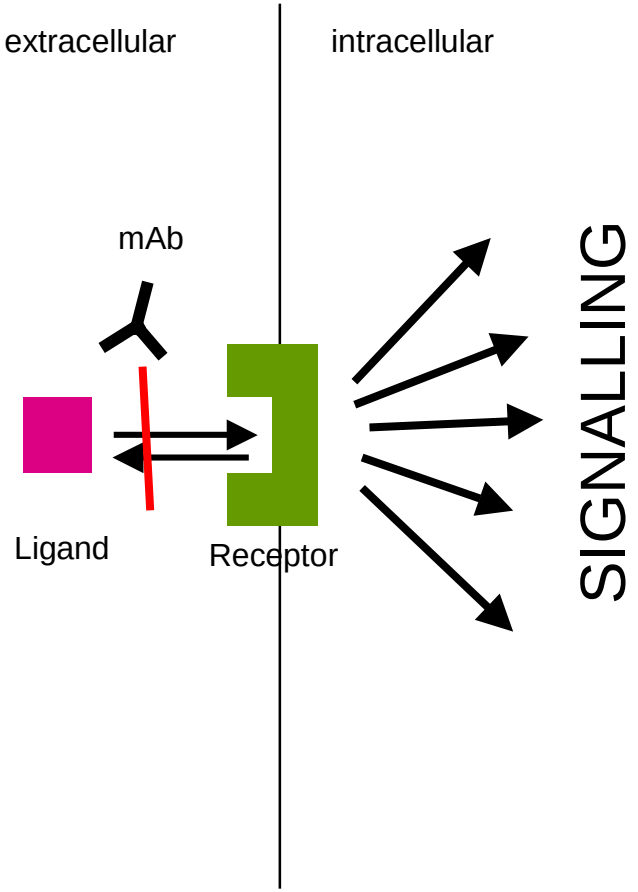


(TNF-R1 signalling)



Heretic‘s FAQ

(not necessarily my view…)



- **Can the mechanism of action be understood as a sole ligand-receptor interaction? (or its inhibition by a mAb?)**
- **Is it important what comes „after“?**
- **Does the mechanism of action have to be known?**

French illumination, 14th century (www.welt.de)

Licensed mAbs: Efficacy and safety

- **Example anti-TNFα antibodies*): How to design a biosimilar development programme?**

- **Licensed indications:**
  - **Rheumatoid arthritis**
  - **Adult Crohn‘s disease**
  - **Paediatric Crohn‘s disease**
  - **Ulcerative colitis**
  - **Ankylosing spondylitis**
  - **Psoriatic arthritis**
  - **Psoriasis**

Therapeutic equivalence?
Non-inferiority?

All indications?
Extrapolation of efficacy?
Extrapolation of safety??

What endpoints?
(Activity or Benefit?)
(Phase II or Phase III endpoints?)

*) example chosen since well suitable to explain regulatory issues

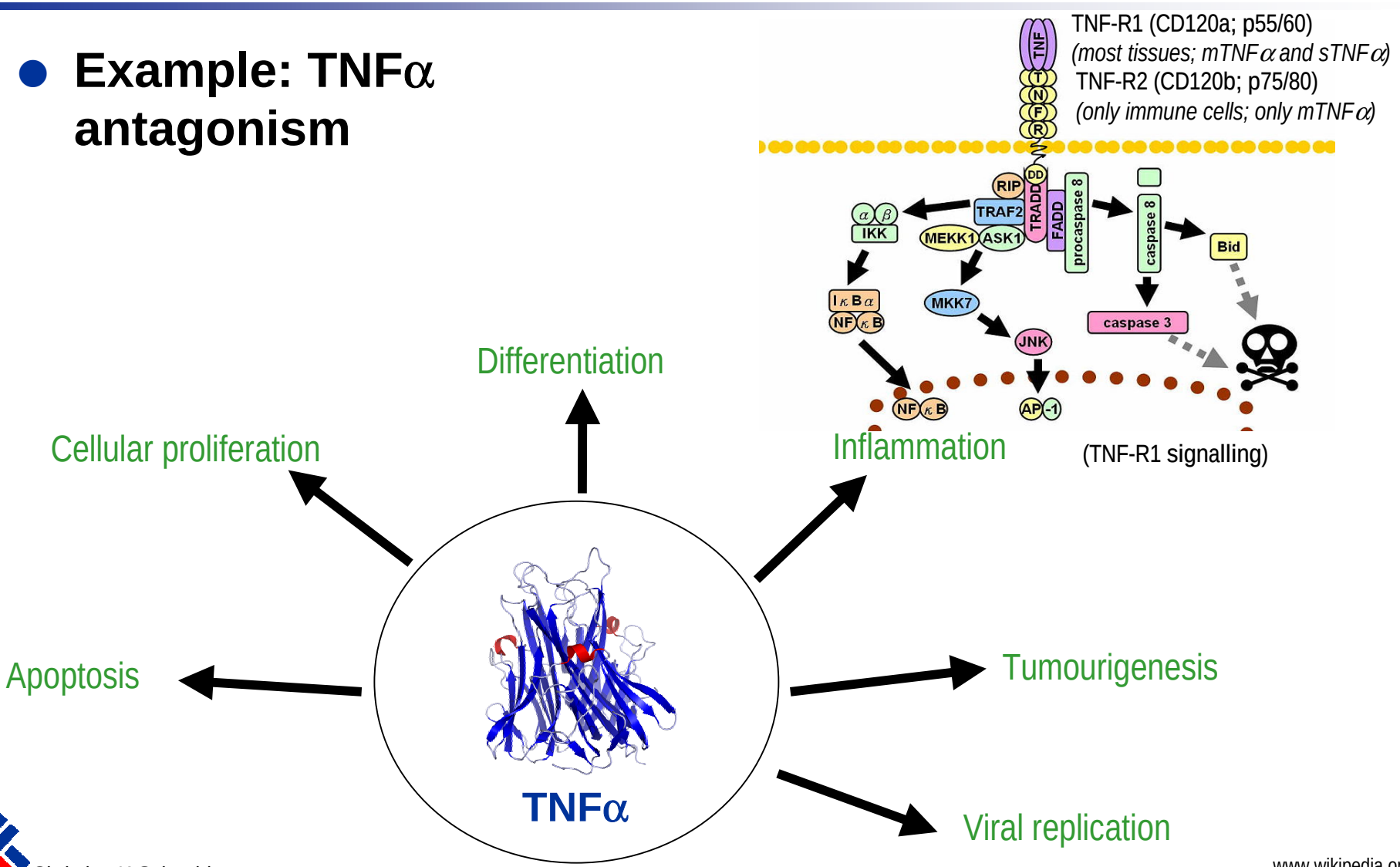
Extrapolation of indications

- ***Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues:***

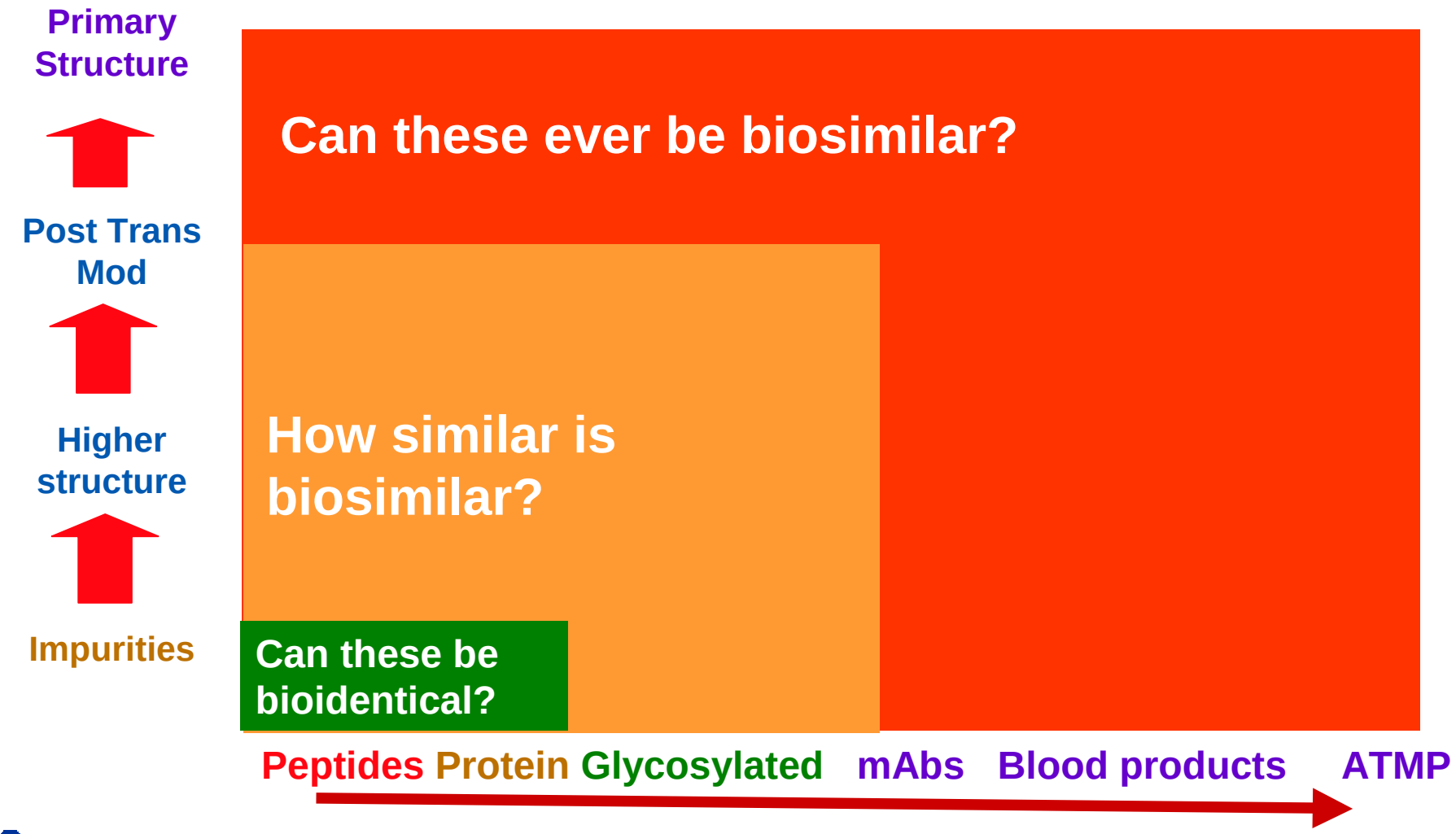
  - *„In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications."*
  - *„In certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product."*
  - *„Justification will depend on e.g., clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications."*
  - Distribution, density, avidity and other characteristics of these receptors per indication?
  - *„Possible safety issues in different subpopulations should also be addressed."*

Mechanisms of action can be complex!

- **Example: TNFα antagonism**

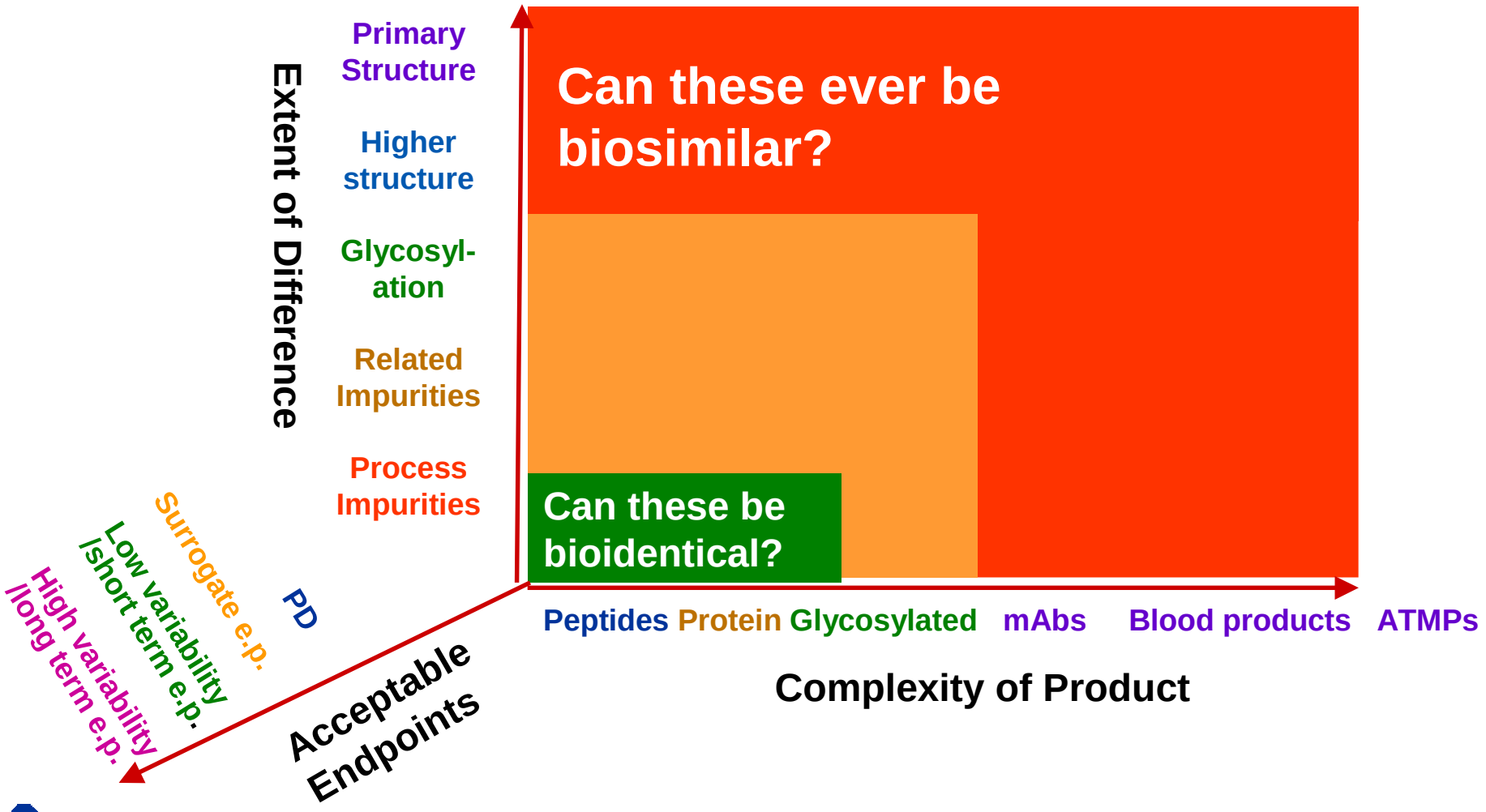


Spectrum of Uncertainty



Source: Cecil Nick, Parexel

Spectrum of Uncertainty



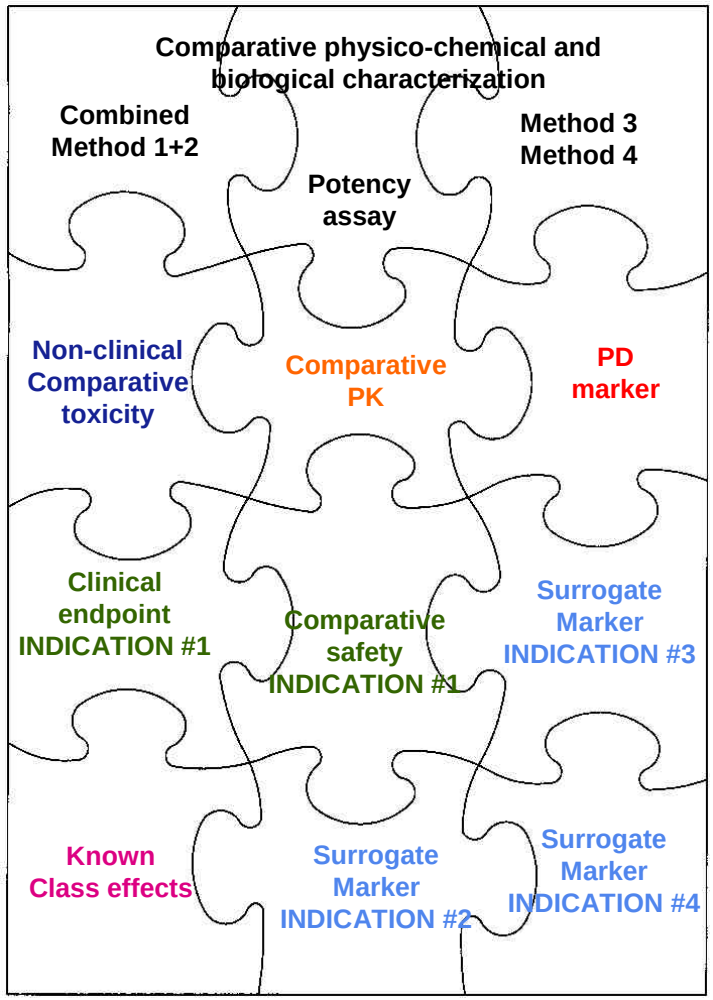
Source: Cecil Nick, Parexel

Extrapolation

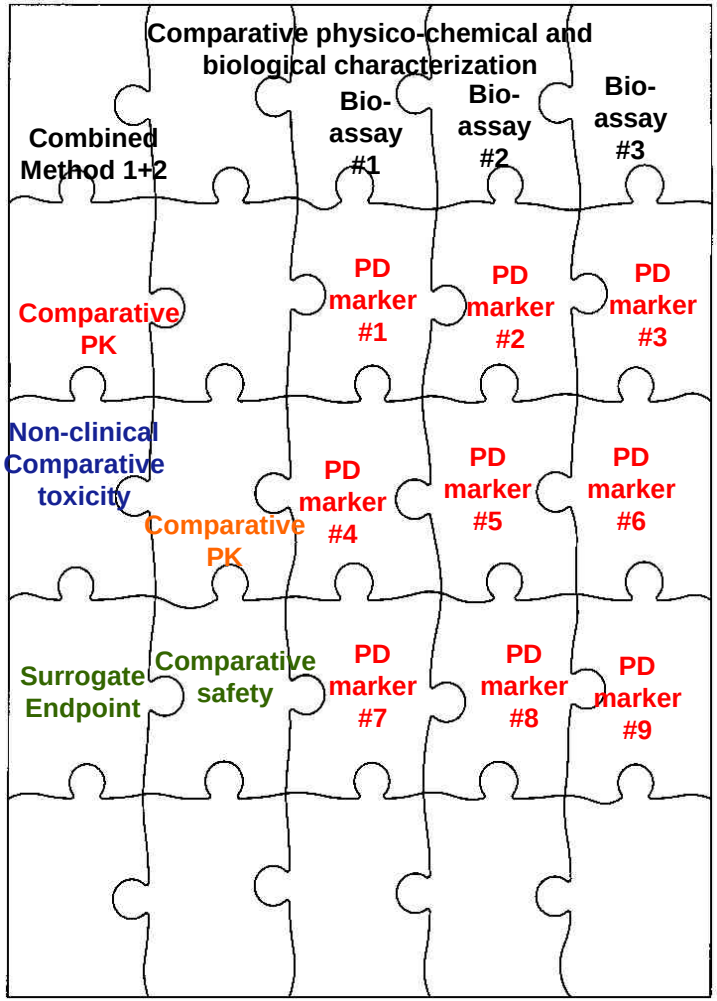
- **Extrapolation of indications:**
  - » What if mechanism of action is poorly understood? (e.g. interferons)
  - » What if clinical endpoints for other indication(s) are not sensitive enough?

- **Recent „milestones“:**
  - » Guideline on biosimilar LMWH (**extrapolation**)
  - » Reflection paper on biosimilar alpha-interferons (**„PD fingerprinting“**)

Case-by-case puzzle?



mAb 1



mAb 2

Immunogenicity

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PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BÉATRICE VIRON, M.D., AMIR KOLTA, M.D., JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D., VALÉRIE UGO, M.D., IRÈNE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

Immunogenicity

- **mAbs are not for substitution of endogeneous proteins like recent biosimilars (EPO, G-CSF,…)**
- **Is the perception of risk different?**
  - » Antibodies against mAbs are mostly anti-idiotype (not anti-isotype)
  - » Endogeneous IgG abundant!
- **Is Immunogenicity the „highest“ safety concern?**
- **…but immunogenicity nevertheless important!**

Practical issues

- **Acceptability of biosimilar mAbs, e.g. in the oncological setting?**
  (or: To what extent is the „biosimilar“ philosophy known to patients and physicians?)

- **How to practically deal with phase I PK/PD studies in patients:**
  - » Are usually single dose studies
  - » Cross-over?
  - » How to continue treatment? Switch to reference?

The floor is yours!