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Better prediction of immunogenicity of biopharmaceuticals in humans

Is it possible?

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EIP Copenhagen, February 7, 2012

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TNO

Better world through applied research

- Help solve major societal and economic problems

- Research and Technology Organisation
- Independent
- Not for profit
- > 4000 employees
- Founded in 1932

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Biomedical innovations

Refinement
Reduction and
Replacement of animal testing

Leading to better alternatives

- carcinogenicity/mutagenicity

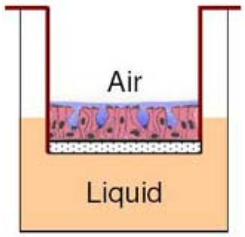
- reproductive toxicity

- immunogenicity

- microdosing

- zebrafish

- 3D human skin model with keratinocytes (genotoxicity)



- Human skin model (genotoxicity and photosafety)

- 3D airway model (genotoxicity, respiratory sensitization and absorption)


Safety testing biologicals

Facts:
o more and more biologicals on market
o 17% of global pharmaceutical sales in 2009,120 bn$ (IMS Health)
o expected to reach $239 billion by 2015 (http://www.salisonline.org/market-research/biologic-therapeutic-drugs-technologies-and-global-markets/)

Biologicals (derived from living sources):
Blood factors, thrombolytic agents, hormones (insulin), growth factors, interferons, interleukin based products, vaccines, monoclonals.

Biologicals may present a safety issue (immunogenicity)

No drug is 100% safe
-Benefit must outweigh foreseeable risk
-Drug is less safe if actual risk are greater then perceived risks (FDA)


Immunogenicity

Immunogenicity: therapeutic proteins can potentially induce an immune response when administered to humans
- Antibody dependent (anti-drug antibody) and antibody independent (complement, cytokine release syndrome)

Mechanism of anti-drug antibody formation not fully understood:

Several hypotheses:
- Classical response (recognition of non-human parts: t cell epitopes)
- Breaking B cell tolerance (T cell independent: direct binding to B cell: B cell epitope)

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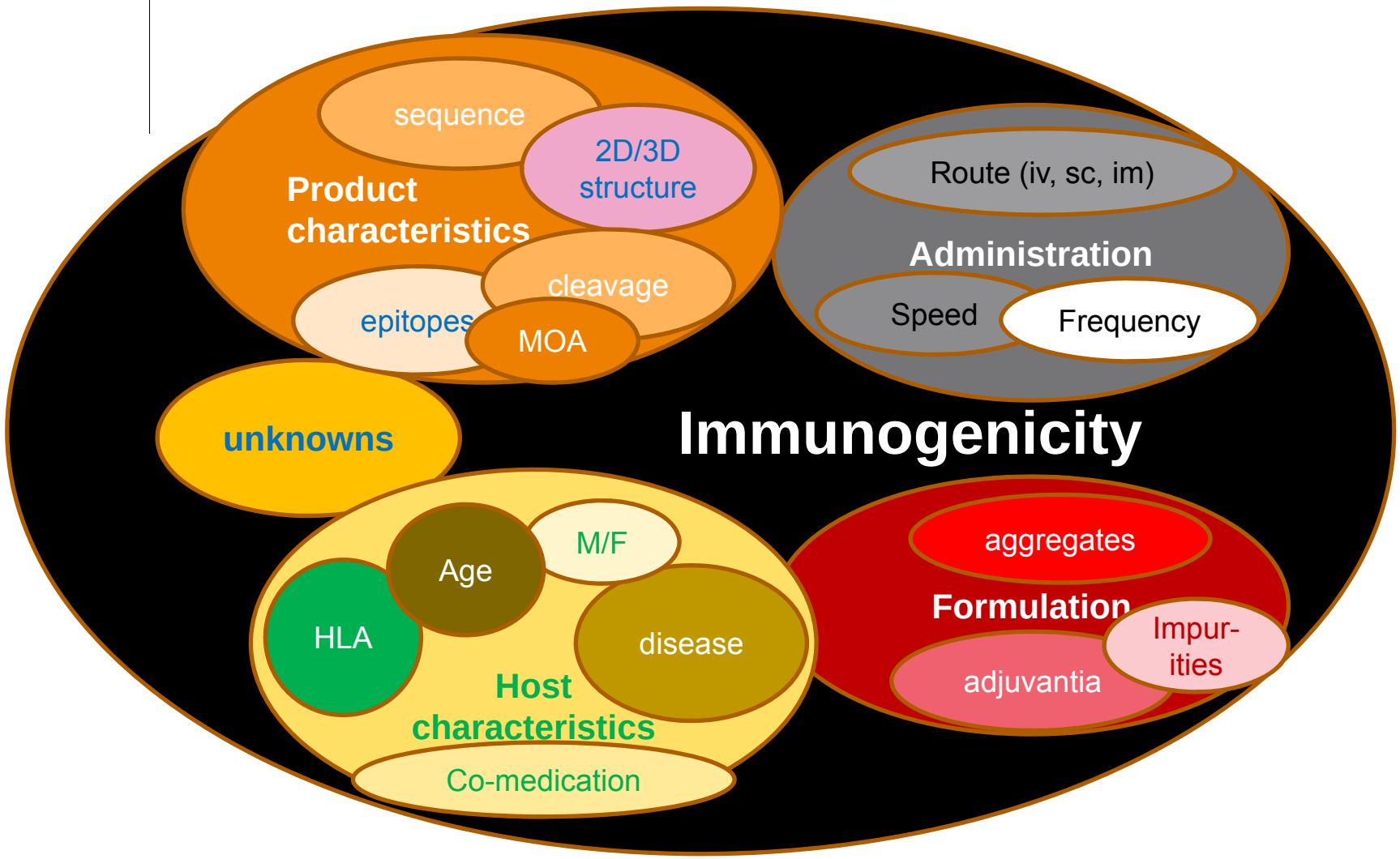
Multi-factorial



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Risk-assessment:

Examples of factors influencing the risk of immunogenicity

eTopic 24.1 Factors That Influence Immunogenicity of Antigens

Parameter	High immunogenicity	Low immunogenicity
Size	Large	Small
Dose	Intermediate	High or low
Inoculation route	Subcutaneous > intraperitoneal > intravenous > intragastric[a]	

http://www.wwnorton.com/college/biology/microbiology2/ch/24/etopics.aspx


Anti-drug antibodies

Anti-drug antibodies
- Neutralizing (Nab)
- Binding (Bab)

Consequences anti-drug antibodies:
- No effect
- Neutralization of drug activity
- Effect on pharmacokinetics (drug clearance ↑ or ↓) > toxicity
- Anaphylactic shock,
- Immune complex disease
- Cross reactivity with endogenous compounds (systemic auto-immune reactions)
- Effects on immune suppression (co-infections, virus induced neoplasia)
- Increased number of auto-immune diseases


State of the art

Difficulties concerning safety testing for biologicals:

- Biologicals must be tested in a species where the drug is biologically active
- Is the ADA detection sensitive enough?

- Impact of changes in manufacturing, processing
- Immunogenicity testing in a late stage of product development

- Poor preclinical predictivity of current models

→Improvement needed!

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State of the art: preclinical testing

- Numerous tests..
- Tests differ in endpoint, cut point, design, length, sensitivity, specificity,…..
- No harmonization (validated) of data and models
- Regulatory guidance lacking

Need for alternatives

part 1 Immunogenicity research in minipigs

Use of non-human primates (NHP) for testing biologicals is increasing, but at the same time due to societal pressure primate use is discouraged (EU). Is there alternative model to replace NHP?

Validation of the minipig as an alternative species for safety research* in non-human primates (focus immunogenicity).

Validation of immunogenicity testing in the minipig:
-Kineret (fusion protein), a human IL-1R antagonist
-Adalimumab (Mab, human IgG1) and Infliximab (Mab, chimeric IgG1κ), both TNF-α blockers

* Regulatory acceptability of the minipig in the development of pharmaceuticals, chemicals and other products. Van der Laan J.W. et al., J. Pharm. and Tox. Methods (2010) 184–195


Immunogenicity research in minipigs

Results:

- Kineret: ADA's in all Minipigs (> day 14)
  - ✓ Similar to NHP : 100% ADA's
  - ✓ In humans: 3.8-57.2% ADA
- Adalimumab: ADA's (neutralizing) in 11/12 Minipigs (> day 14)
  - ✓ Similar to NHP : ADA's (neutralizing)
  - ✓ In humans: 70-80 % of patients are ADA+
- Infliximab: No ADA's detected against Infliximab
  - ➢ Chimpanzee; infliximab biological active: minipig ADA+
  - ➢ *cynomolgus* monkey; infliximab biological inactive: no ADA's detected
  - ➢ Is absence in ADA's related to absence of biological activity of Infliximab?

Conclusion:

Comparable results are obtained in respect to the immunogenicity testing of Kineret, Adalimumab and Infliximab in Göttingen Minipigs to NHPs and humans


Need for alternatives
part 2 Immunogenicity toolbox

Current models incl. NHP models, do not always predict the human situation

1) Due to lack of homology between the human protein and the animal protein

2) Differences in immune system function between humans and other animal species

Probably not one single model will be sufficient to predict immunogenicity

Integrated approach

- Based on human immunogenicity data (anti-drug antibodies and clinical effects)
- Combination of pre-clinical tests: *In silico* models (B and T cell epitope mapping), *in vitro* tests, animal experiments
- Algorithm design

Developing a predictive toolbox

- Risk based model: predict relative immunogenicity (compared to known compounds)
- Retrieving historical data (databases, regulators, pharma/biotech, strategic collaborators)
- Basis of the toolbox are human clinical data
- Model is using Bayesian statistics (integrate over missing values) > algorithm
- Self learning with new data input

Plan:

- First version of the algorithm based on a narrowed field
- Selection of 4 candidate areas, biologicals for toolbox:

  TNF inhibitors: focus RA (2011), Interferons: focus MS (2011),

  Recombinant blood products (2012), Monoclonals: focus oncology (2012)
- Source: public domain (pubmed), FDA, EMA, partners.
- Approximately 70 fields in database.


Advantages of the toolbox

Advantages

- Making efficient use of all available (animal) data
- Data gathered from input in the toolbox will strengthen the model
- Provide new insight in immunogenicity mechanism behind selected groups of biologicals (non biased)
- Guide developers in assay choice/combination depending on type of biological
- Determine data gaps, develop new methods to fill the data gaps (e.g. new *in silico* or *in vitro* assays)


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Conclusions

- Immunogenicity is multi-factorial and difficult to predict
- Various models available, not harmonized, predictive value of individual assay?
- Data of different methods should be integrated in toolbox to predict relative immunogenicity
- The more data in the toolbox, the more reliable predictions
- Relevant human data from public databases and pharmaceutical industry will be collected as input for the algorithm of toolbox
- Collaboration with industry is needed to fill toolbox with relevant data
- Involve regulators to accelerate acceptance
- If proven to be predictive it reduce cost and the use of animal testing

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