Working towards building a "Value Added Proposition" for Immunogenicity Prediction and Risk Management

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Causes of Immunogenicity

- Product related factors
  - Sequence differences between therapeutic protein and endogenous protein, glycosylation differences, PEGylation,
  - Post translational modifications
    - Oxidation
    - De-amidation and degradation
  - Tertiary structure & Conformational changes
    - Aggregation
  - Storage conditions
  - Production/purification processes
    - Host cell proteins, Excipients
  - Formulation
    - Solubility, stability, Liquid v/s Lyophilized
  - Route, dose and frequency of administration
- Host/Patient related Factors
  - Immune status of patient
    - Radiotherapy, Chemotherapy
    - Autoimmunity, inflammation, infection
    - HLA Haplotype

Current paradigms in Predictive Immunogenicity

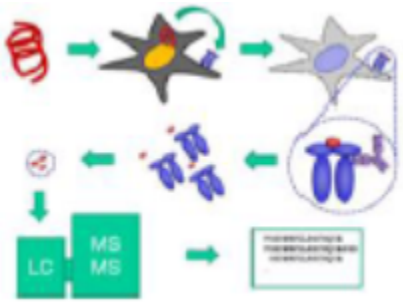
- In-silico, In-vitro methods are available but predictive power can be limited
- Animal models do provide the in-vivo perspective but do not necessarily reflect what happens in humans
- Key issue is: Multiple factors contribute to immunogenicity
- Current strategies and tools address one risk factor at a time
- Need to measure and assess the cumulative effect of multiple factors in predicting immunogenicity outcome –
  This is a paradigm shift in the making
- Can predictive immunogenicity be a population based science or would it be more effective with a personalized medicine “like” approach?

  Paradigm shift worth considering

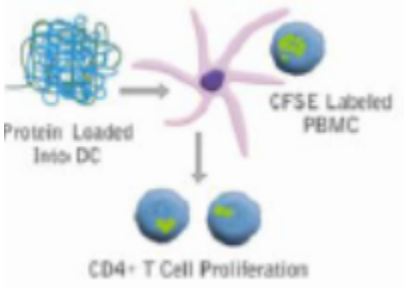
Current approaches in predicting immunogenicity

In-silico Predictions

In-vitro Confirmations



Ex-vivo Confirmations



Price tag: ~$500K

De-immunization

"One Loop"

Clinic → ? → **Validation of the Clinical results & Utility**

Questions that need clarity:

How many loops are necessary?
What is the time and costs required for each loop?
How can this be efficiently introduced in a tight development timeline?

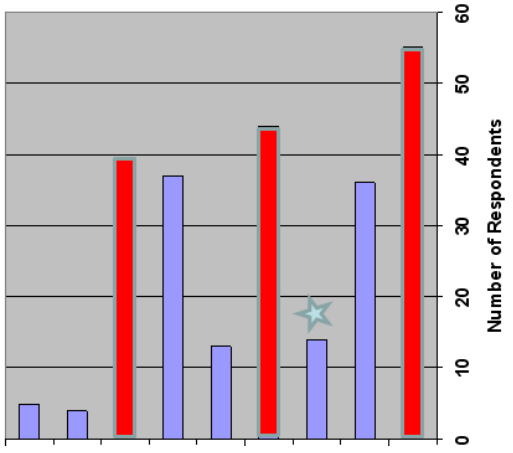
Other Key Factors

Dose
Route of Admin.
Frequency of Admin.

TPIFG Survey Message

Key Gaps

Proof of Concept/Validation
Benchmarking of Tools
Database prediction correlation
Cost



Reasons why these Gaps have developed

- **Lack of confidence in value**
  - Even if all the T epitopes are muted does it translate to "No Immunogenicity Product"?
  - At present "lack" of predictive Immunogenicity info or "unfavorable results" is not a block for licensing
  - Familiarity of tools is there but many are not using them? Why?
  - What are sponsors getting for results (Success/Failure?)
  - Legal component as an impediment. We seem to be stuck at this point.
- **Time and Cost Impressions**
  - Cost: $500K v/s $55 million for a single Phase IIb/III/OLE type trial. Is cost really the concern?
  - Time: "The loop" = ~ 4months.
    - Delays in decision making, months to order, minimalistic approach of Expt data and ad-hoc combining of CRO & internal data, don't know what to do with the data, two years go by and Dev. timelines have progressed, frustration of the internal stake holders
- **In summary**
  - Lack of clear understanding of Risk/Benefit ratio & the "**Value added Proposition**" for this effort leads to little investment in this area

Measures taken by international Community to address these Gaps

Key Objectives being addressed

–Need identification of few selected methods that are validated and reproducible

–Need to demonstrate the human/clinical relevance of these methods

Actions Undertaken

–Initiation of cross Industry/Academia consortium and/or shared database to cumulatively evaluate clinical correlation of predictive methods

Gaps that still need to be addressed

–Develop industry standards (White Papers/Recommendations) through sharing of experience to select clinically relevant tools

–More data should come in the public domain (Publications) both favorable and unfavorable results

–Risk factors have been identified but the understanding of the extent of influence of each of these factors in concert is still not well developed

–Key is to increase confidence in decision making…predicting relevance in context of a biotherapeutic and its specific indication

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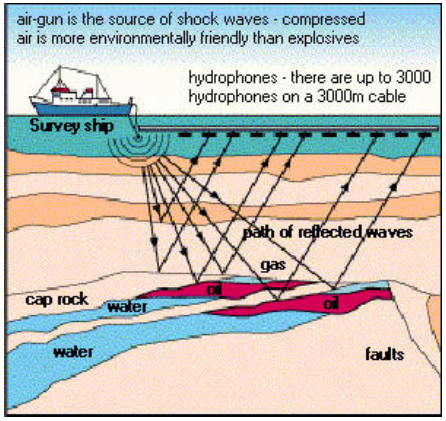
Predictive tools used in Oil drilling: Parallel Case Analogy

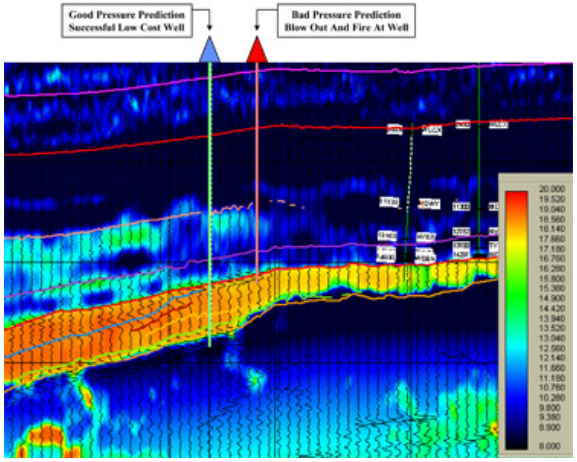


Current Methods: Used prior to well drilling

- Sensitive gravity/magnetometers measure tiny changes in the Earth's gravitation field indicating flowing oil.
- Electronic Sniffers: Detect the smell of hydrocarbons
- Seismology: Artificial shock waves pass through rock layers. Interpretation of the reflected waves predicts location of oil flows

Risks :Environmental
Cost : Huge in Penalties

Challenge: unexpected surges of high-pressure during drilling can lead to leaks (Danger Zones)



New Advanced Technologies: Pore & Fracture Pressure analysis

Blue well: Drilled using a robust pore pressure and fracture pressure prediction.
Result: Safely drilled well , no incidence, less budget and time

Red well: Drilled without a robust pore pressure and fracture pressure prediction.
Result: Completely opposite to the Blue. **Incurred costs 50 times more** than the projected costs of prediction

Courtesy of Fusion Petroleum Technology.

Learnings: Need to build case studies of systematically calculated Cost basis of performing Immunogenicity Prediction v/s not doing it

"Cost basis" comes from the "Costs" associated with risks

Mange. Decis. Econ. 28: 469-479 (2007)

FDA Critical Path Initiative 2004: Agency & Industry to lower Drug development costs

17 Biotherapeutics costs analysis: 522 Biotherapeutics rec. Prots & mAbs FIH between 1990 to 2003, Terminated as well as Approved

Parameters: Dev Time, Success rate, Phase Transition Probability, Out of Pocket costs, Cost of Dev. Failures

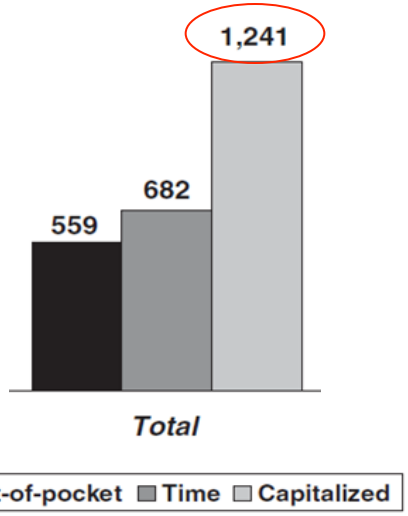
Databases: Tufts Center for Study of Drug Dev. (CSDD) data

Clinical Phase Costs/Inv. Biotherapeutic

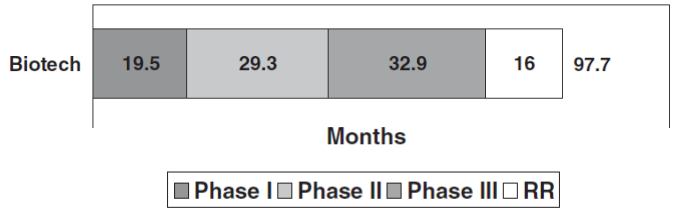
Table 1. Out-of-pocket Preclinical and Clinical Period Cost per Investigational Biopharmaceutical Compound (In Millions of 2005 dollars)[a]

Testing phase	Mean cost ($)	Probability of entering phase (%)	Expected cost ($)
Preclinical	59.88	100	59.88
Phase I	32.28	100	32.28
Phase II	37.69	83.7	31.55
Phase III	96.09	47.1	45.26
Total			168.97

[a] All costs were deflated using the GDP Implicit Price Deflator.

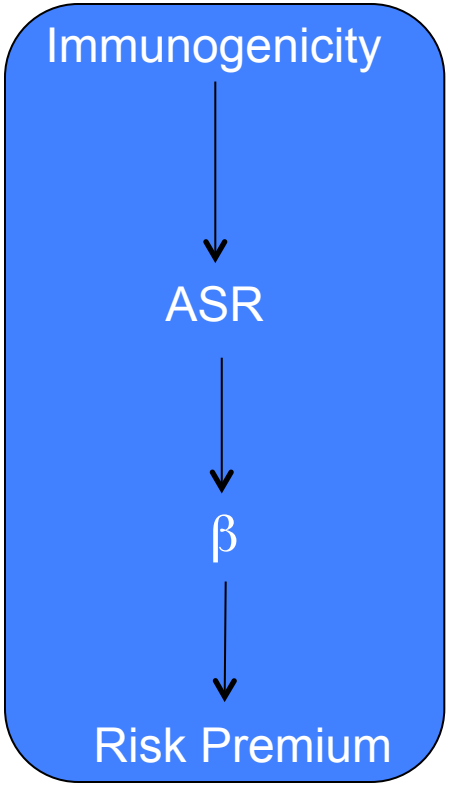


Phase Transition Probabilities

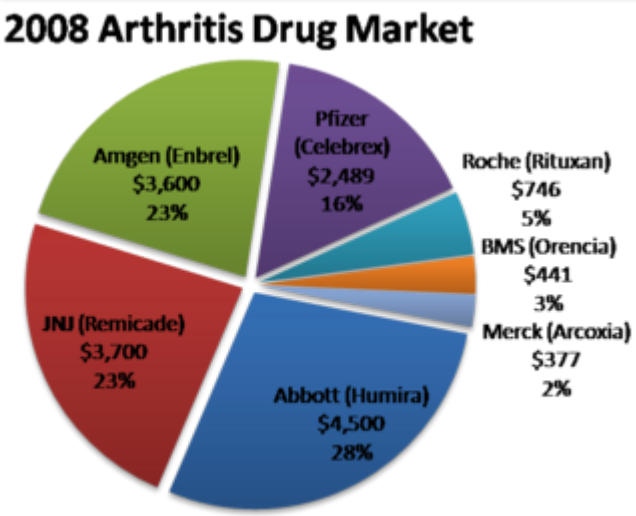


$$\text{Phase T.Prob} = \frac{\text{No. Progressed from Ph (A) to Phase (B)}}{\text{Total Progressed + Total Failed}}$$

Overall clinical approval success rate (ASR)= 30%



Value of predicting and minimizing immunogenicity



Arthitis Drug Market Analysis
wikinvest.com/wiki/Arthritis_Drug_Market

Humira sales touch $9 Billion in 2012 (2 Fold Growth) in Four years
Humira is 50% of all Abbot drug sales (Now AbbVie)

Pressures on pricing

- **Patent expiry in ~2 years**
- **Oral SM market erosion**
- **Biobetter competition**

Pharma Times, June 26, 2012

The Wall Street Journal, Business Wire)
February 25th, 2013

Role of Immunogenicity as a powerful differentiator

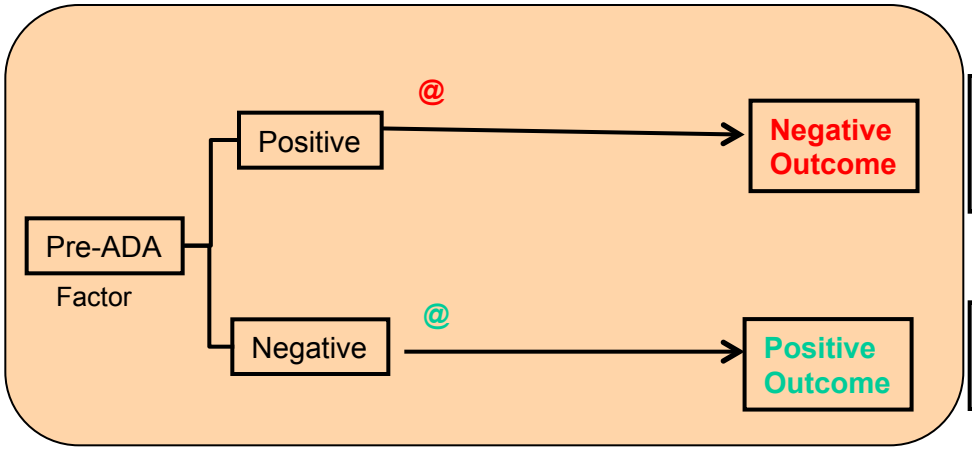
•Humira label: 1-12% NAb positive in 1 year (Projections 35%)
•Due to NAb +ves patients need to be switched

•Ablynx ATN-103 (ozoralizumab) in Phase IIb OLE: 0.75% NAbs @ EOS
•57% patients reached DAS28 remission, with 70% reduction in 3 months

•Affymax: Drug Omontys – 19 Anaphylactic reactions – 3 deaths
•Product recall in post-marketing (No issues in Clinical Trials)
•Repairing Negative safety perception
•Improved competition's ability to strengthen relations with customers

Use of Modeling to ascertain the costs and value of the effort

Simplistic Model Structure: The Concept



Theoretical Concept

Costs associated with the decision of recruiting pre-ADA +ve w/o predictive efforts

Costs associated with Predictive efforts that led to a +ve outcome

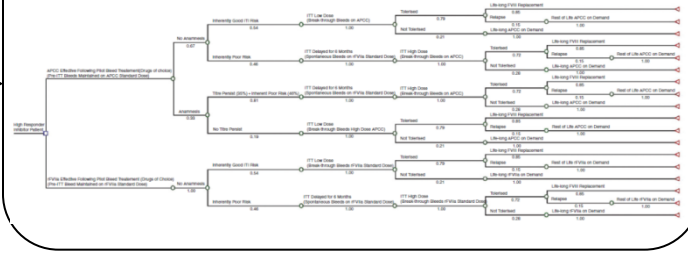
Determine incremental costs of predictive Immunogenicity in a given drug/indication Treatment, prospectively or retrospectively

"VP" @ = Fraction = Cost/Outcome probability

Factors

Product Factors	Patient Factors
Dose	Pre-ADA Status/Titer
Aggregation	Indication
T Epitope	Immune Status
T Regitope	Conc. Meds
B Epitope	MHC Haplotype
Allosteric/Structural	

Decision Analysis Software



Potential Output

- **Estimate the costs associated with Immunogenicity Risks & resulting Treatment Outcome**
- **Estimate the impact on the success and failure rate influenced by Predictive efforts**
- **May eventually evolve into a tool to study the cumulative effect of risk factors**

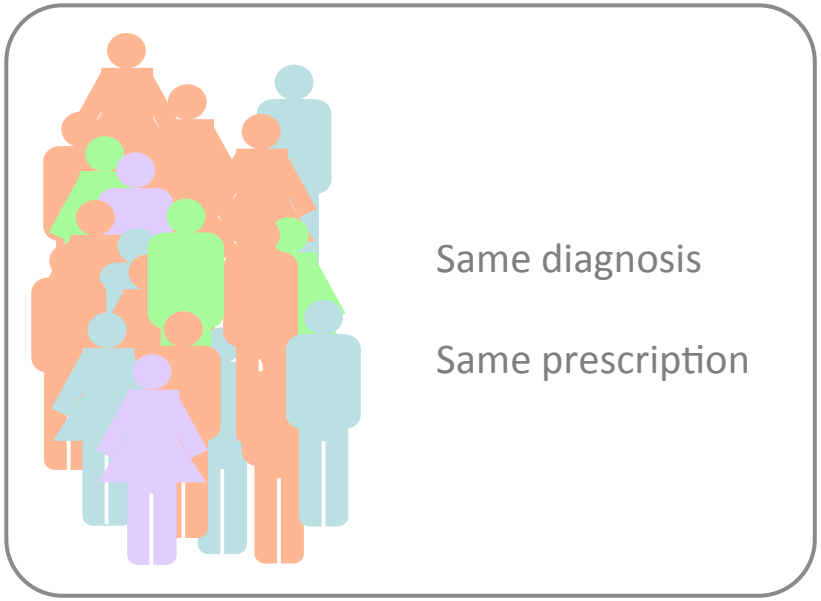
Possibilities with a Model

- May provide answers to questions like is there a correlation between a given factor with the outcome of the treatment (Success/Failure)?
- This may help assess the impact on Net Present Value (NPV) of the investment that goes in prediction and re-engineering a given drug, such that we are maximizing the Approval/Failure ratio?
- May help us to visualize if an optimized Biotx may significantly lower the cost of Immunogenicity Management?
- May help stratify factors by relevance for analysis in different phases of Drug Development

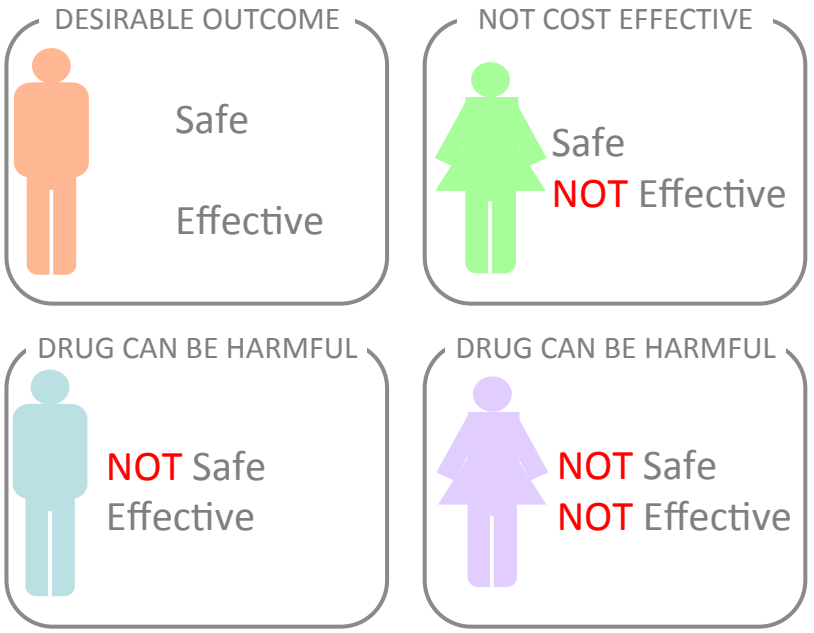
- **Such an effort can be done at the company level or at a Cross Industry level.**
- **Uncertainty due to variability in the model can be improved through use of trial data**
- **Threshold analysis for every variable will continue to improve and validate such a model**
- **We may be able to make informed decisions on use of "tools" where it makes sense**

What really happens when we start considering host factors?

Medical practice based on population responses



In an individual the prescription can elicit one of four responses



Some day we may have predictive immunogenicity tools & models can drive towards a desirable outcome of safe and effective medicine

….but with what level of specificity??

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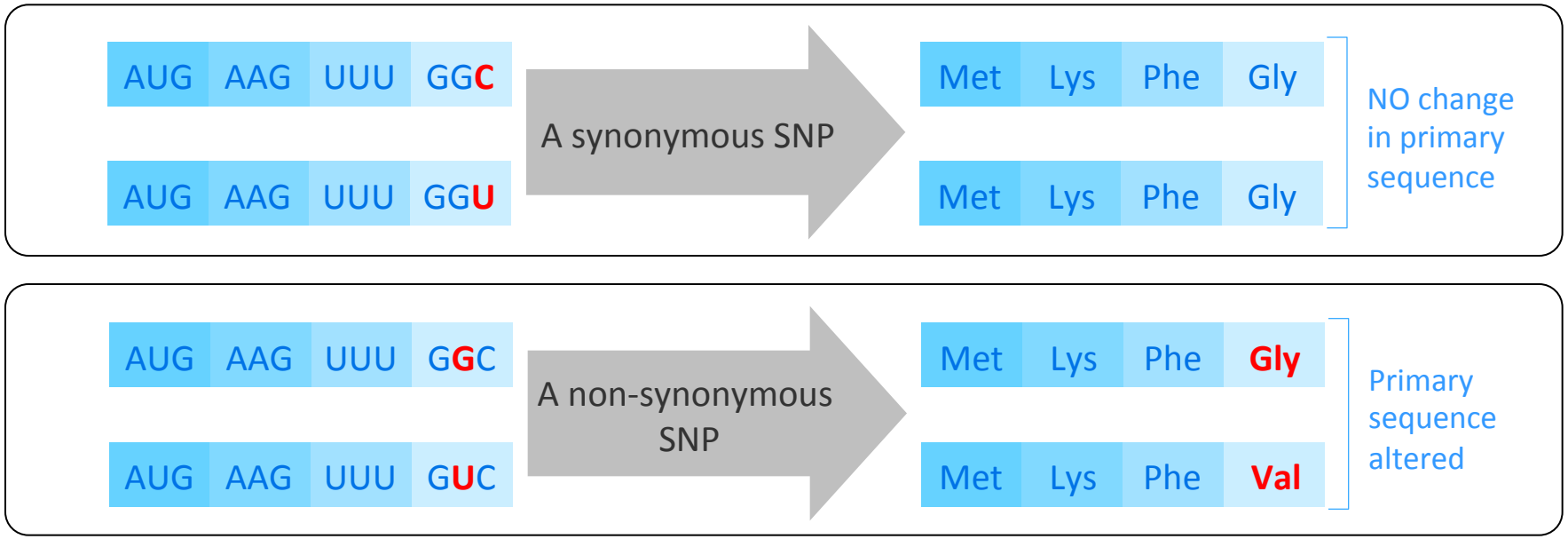
A Touch of reality….

A DNA variation in 1% of population: Polymorphism

SNPs: Difference of single nucleotide base



Critical mass of studies demonstrate synonymous changes in the genetic code affect protein levels & conformation with physiological consequences

Sauna & Kimchi-Sarfaty (2011) Nature Reviews Genetics 50: 683

Ack. Z Sauna, FDA

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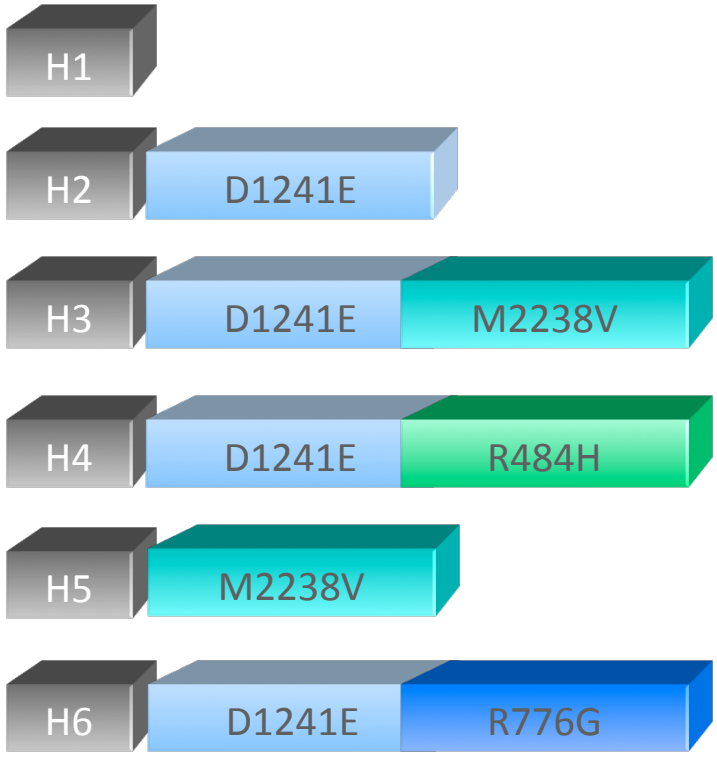
Polymorphisms in the *F8* gene and a case study for predictive immunogenicity

FVIII Haplotypes



Non-synonymous (ns)-single nucleotide polymorphisms (SNPs) in the *F8* gene vary in human populations
(e.g. the *F8* gene in African Americans is more polymorphic than in Caucasian individuals)

The prevalence of ADA was higher among patients who potentially received mismatched FVIII (as a consequence of their underlying polymorphisms) than among patients receiving the matched FVIII infusion

FVIII drug-products

Modified from: Viel KR et al. N Engl J Med 2009;360:1618-1627

Ack. Z Sauna, FDA

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Is it then possible to predict immunogenicity in every individual?

Polymorphism/mutation LFLLSTRQNVEGSYEGAYAPVLQDFRSLN {FVIII sequence of patient; "self"}

wild type LFLLSTRQNVEGSYDGAYAPVLQDFRSLN {sequence of infused FVIII; "foreign"}

Determining the distribution of MHC alleles that bind to the "foreign" peptides can:

- Identify epitopes likely to be immunogenic in the entire population
- Identify at-risk ethnicities, populations or individuals
- Address the possibility of developing personalized therapeutics

Modified from: Yanover C., Jain N., Pierce G., Howard T.E. and Sauna Z.E. Nat. Biotechnol. (2011) 29: 870-873.

Mismatches between the infused drug and the endogenous protein is a predictable risk factor for immunogenicity

Ack. Z Sauna, FDA

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Taking Predictive Immunogenicity towards Personalized Medicine

In such cases tools like in-silico, T cell epitope, MHC binding, APC assays, ex-vivo T-Cell assay all become relevant

Analysis:

- Which MHC class-II alleles bind to the "Foreign" epitopes?
- How common are these MHC Class-II alleles?
- What is the distribution of these alleles in the general population v/s specific ethnic groups?
- Are the "Foreign" sequences generated by processing?
- Do they even bind to MHC in vivo? Note: MHC themselves are very polymorphic.

How generalized should this approach be? Does it apply to human mAbs therapeutics? Should this be only considered for life threatening disorders?

Is personalized predictive immunogenicity an overkill or will it truly benefit the patient In a cost effective manner?

Acknowledgements

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