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**

**De-immunization**

**Price tag: ~$500K**

**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.

**Key Gaps**
- Proof of Concept/Validation
- Benchmarking of Tools
- Database prediction correlation
- Cost

**TPIFG Survey Message**

![Diagram with various nodes and connections representing the workflow of predicting immunogenicity.](image)
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
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

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

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>
<thead>
<tr>
<th>Testing phase</th>
<th>Mean cost ($)</th>
<th>Probability of entering phase (%)</th>
<th>Expected cost ($)</th>
</tr>
</thead>
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<tr>
<td>Preclinical</td>
<td>59.88</td>
<td>100</td>
<td>59.88</td>
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<td>32.28</td>
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<tr>
<td>Phase II</td>
<td>37.69</td>
<td>83.7</td>
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<tr>
<td>Phase III</td>
<td>96.09</td>
<td>47.1</td>
<td>45.26</td>
</tr>
<tr>
<td>Total</td>
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</table>

Phase Transition Probabilities

Phase T.Prob = No. Progressed from Ph (A) to Phase (B) / Total Progressed + Total Failed

Overall clinical approval success rate (ASR) = 30%

Immunogenicity

ASR

β

Risk Premium

Value of predicting and minimizing immunogenicity

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

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

Arthritis Drug Market Analysis
wikinvest.com/wiki/Arthritis_Drug_Market

Pharma Times, June 26, 2012

The Wall Street Journal, Business Wire
February 25th, 2013
Use of Modeling to ascertain the costs and value of the effort

**Simplistic Model Structure: The Concept**

```
Pre-ADA
Factor

Positive
@
Negative

Positive Outcome

Negative Outcome
```

“VP” @ = Fraction = Cost/Outcome probability

**Factors**

- **Product Factors**
  - Dose
  - Aggregation
  - T Epitope
  - T Regitope
  - B Epitope
  - Allosteric/Structural

- **Patient Factors**
  - Pre-ADA Status/Titer
  - Indication
  - Immune Status
  - Conc. Meds
  - MHC Haplotype

**Decision Analysis Software**

**Theoretical Concept**

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

**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

DESIRABLE OUTCOME
Safe
Effective

NOT COST EFFECTIVE
Safe
NOT Effective

DRUG CAN BE HARMFUL
NOT Safe
Effective

DRUG CAN BE HARMFUL
NOT Safe
NOT Effective

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??

REGENERON
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


Ack. Z Sauna, FDA
Polymorphisms in the *F8* gene and a case study for predictive immunogenicity

**FVIII Haplotypes**

H1

H2

D1241E

H3

D1241E

M2238V

H4

D1241E

R484H

H5

M2238V

H6

D1241E

R776G

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**

Kogenate®

H1

Recombinate®

H2


Ack. Z Sauna, FDA
Is it then possible to predict immunogenicity in every individual?

Polymorphism/mutation \( \text{LFLLSTRQNVEGSYEGAYAPVLQDFRSLN} \) \{FVIII sequence of patient; “self”\}

Wild type \( \text{LFLLSTRQNVEGSYDGAYAPVLQDFRSLN} \) \{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


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