

Therapeutic Antibody Designs for Efficacy and Manufacturability

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Mission: Design and apply innovative technologies to dramatically expand global access to biotherapeutics.



Antibodies undergo genomic recombination and somatic hypermutation in order to obtain their high levels of both antigen specificity and affinity. These very mechanisms by which the adaptive immune system is able to generate antibodies against any antigen also lead to molecular issues as therapeutic candidates. Large scale data capture in LabKey Biologics of sequence, cellular expression, purification, efficacy, biophysical characterization, and atomiclevel characterization will enable methods development to better predict and repair molecular attributes such as post translational modifications and stability. Pushing this level of molecular design earlier in the therapeutic pathway will help lower the cost of biologics-based therapeutics.



Biotherapeutics Cost

• Average development cost from discovery to market for a single drug in 2014?



Biotherapeutics Cost

- Average development cost from discovery to market for a single drug in 2014?
 - The estimated average pre-tax industry cost per new prescription drug approval (inclusive of failures and capital costs) is:

\$2.558 Billion

Yes, Billion. With a 'B'.



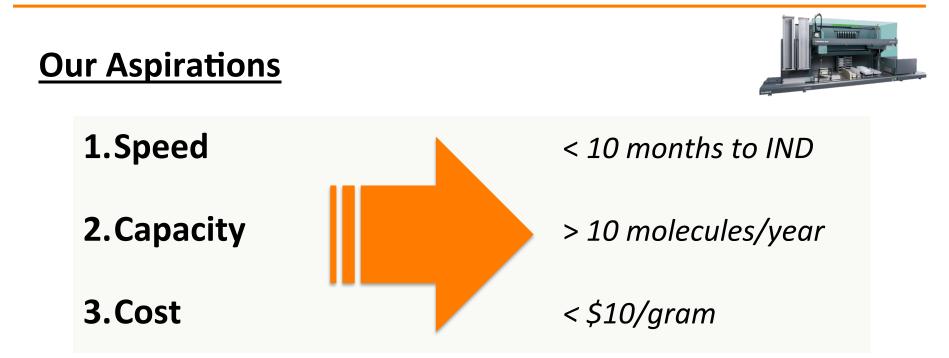
Just was formed to expand global access to important biotherapeutics

- Over 80% of the planet cannot afford most of the breakthrough therapeutics of modern biotechnology
- Just was formed to reduce the cost of biologics by at least 10x, making these therapeutics more accessible to a global population
- This will help expand markets for current therapies and lay a foundation for new therapeutic approaches



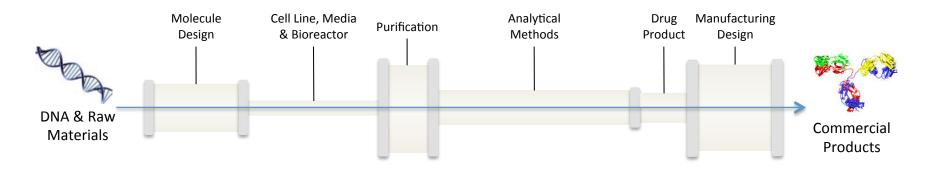


J. Design's integrated approach will dramatically improve the development and manufacture of biologics





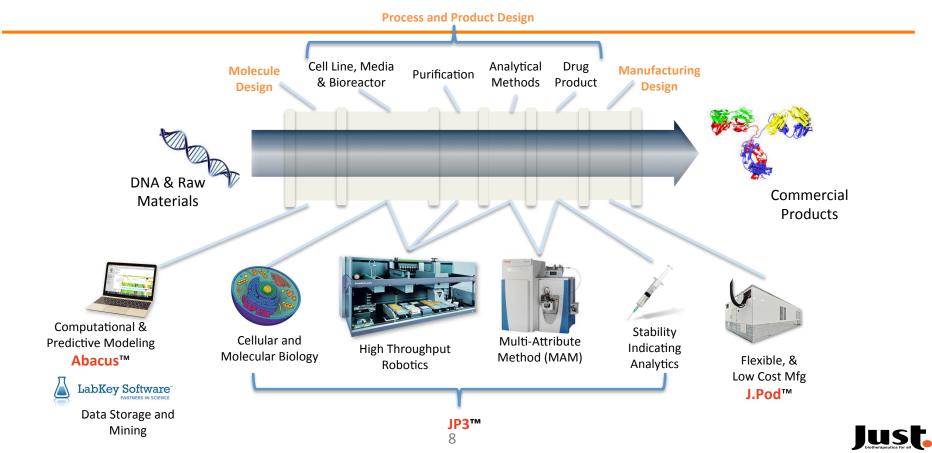
Functional bottlenecks limit our ability to improve product throughput and reduce costs



Technological solutions will focus on large data sets, high throughput capabilities, process intensification, and functional integration



J. Design will accelerate development, improve product throughput and reduce the over cost of biologics

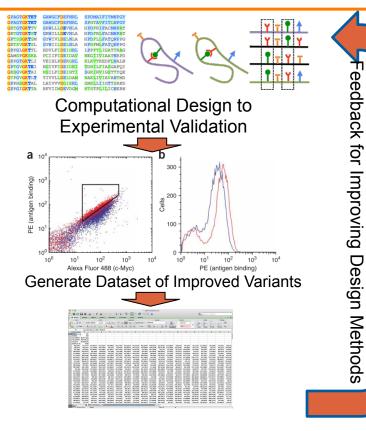


The Mutation of the Variable Domain Leads To Activity and Specificity, But Can Also Degrade Stability and Manufacturability

- Antibodies as therapeutics benefit from early design and engineering, e.g.
 - Deamidation/Isomerization
 - Alternate glycosylation
 - Non-standard cysteines
 - Folding/thermal stability
 - Much more
- Repair of these sites utilizing structure models and computational analysis is possible while retaining activity
- Therapeutic optimization is highly beneficial, but rarely done in the industry



BMGF Supported Postdoc: Computational Design and Experimental Validation for Improving Antibody Thermostability



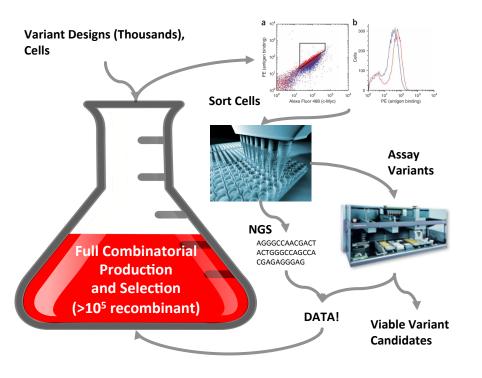
- Computational methods for designing libraries for improving thermostable antibodies
- Yeast display and cell sorting under stress conditions to generate a data set
 - High temperatures, guanidine, urea, ethanol, and low pH conditions.

Generates MUCH data 💦 LabKey

Data analysis / machine learning to improve design methods



Internal Technology Development for Ultra High Throughput Variant Production and Testing



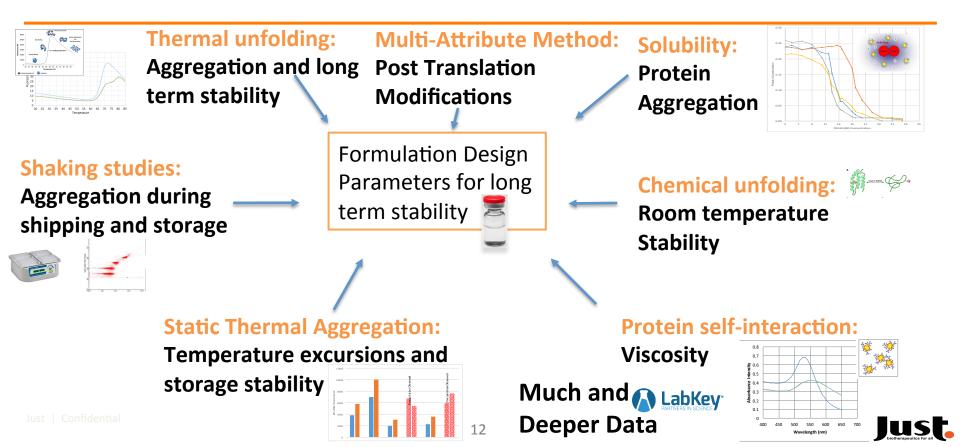
- Recombinant cellular transfection and expression (non-library approach)
- Bulk evaluation of binding and early characterization methods
- Deep sequencing to filter successful variants, data on everything
- Faster, cheaper, broader lead development



Generates MUCH data



Just is developing predictive screening tools correlate predictive tools with stability

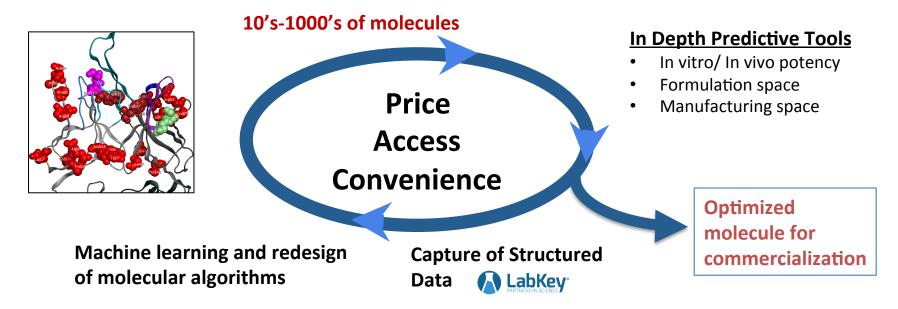


Ameliorating problems through design of the molecule

Computational analysis and repair sites using structural modeling

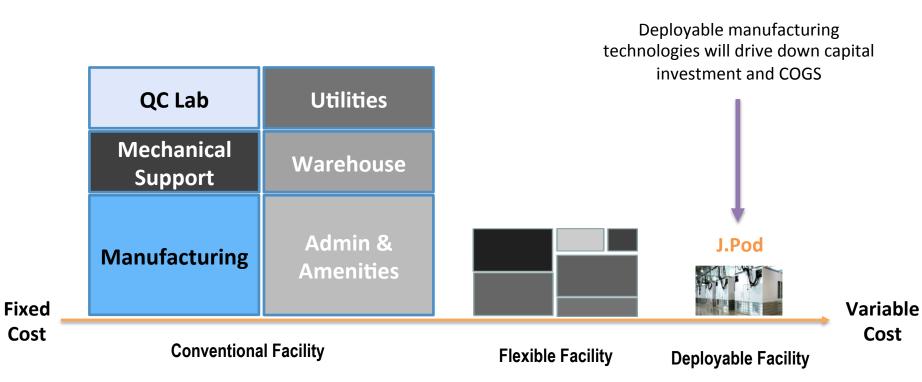
High Throughput Screening

- Potency/ neutralization
- Expanded biophysical analysis





Just's manufacturing platform will be capable of producing therapeutics at the lowest possible cost

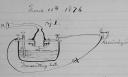




Data capture using traditional methods

- Capture data in lab notebooks, Word files, PowerPoint, email, brains, ...
- As an example, it can take three months of interviewing, reading, digging, to come up with a data set for a single measured attribute across a couple dozen molecules
- This should take three minutes
- Data is our lifeblood, and we throw it away





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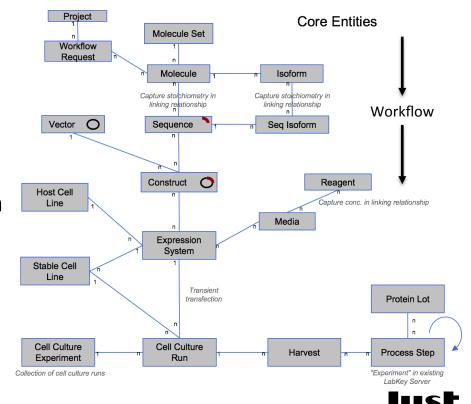
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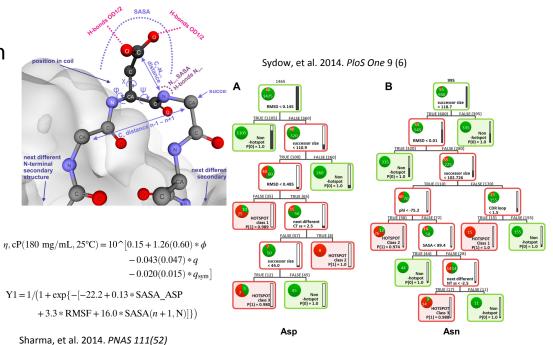
LabKey Biologics Enables Complete Entity Registration, Structured Data Capture, Workflow, Materials Mgt

- Structured data capture across all entities and resulting data enables deep data mining
- Very large variable space amenable to machine learning methods
- Applicable to novel molecular design methods, understanding core component interactions, process monitoring and improvements, automated control systems, ...



Current PTM Sites are Sequence-Motif Based or Data Poor

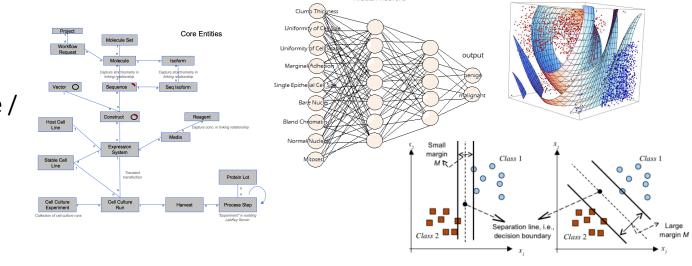
- Shared and public data sets that correlate sequence with data are small
- Rules-based methods are limited
- Molecular dynamics is too slow
- We need very large data sets connecting sequence, structure, conditions, and data – data mining / machine learning





What Do We Need?

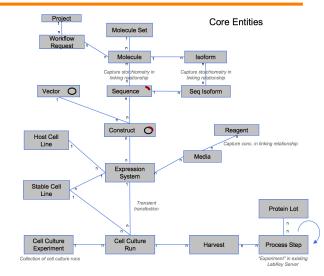
- Large numbers of antibodies and variants
- High throughput expression, analytics, efficacy, and biophysical characterization
- Database capture of sequence, structure, molecule level data, and residue level data
 data
- Data mining
- Machine learning
- Computer Science / Statistics / Bioinformatics Triple Majors





With all entities and data and timings and people and workflow and instruments and materials and dates and ...

- Show me all antibodies with HMW over X% and list purification pH, instrument used, and subtype
- Calendar time used for each step where do I need to automate or hire?
- What antibodies against this target have efficacy above X, aggregation below Y, with the least number of in silico hot spots?
- How do I optimize an antibody to fit a specific process?
- List protein aggregation levels for everything produced with media component X
- What attributes (media, oxygen, mixing, etc.) do I need to modify to optimize a bioreactor run in real time?





Why Do We Care?

- Treat the patient
- Broaden world-wide patient access to biologics
- Enable prophylactic use of biologics
- Open access to smaller disease populations







