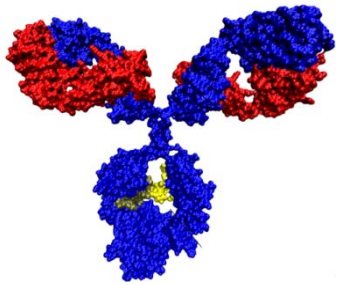
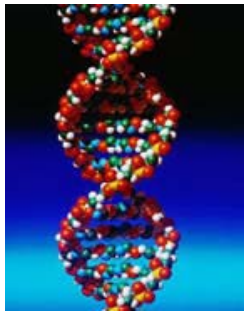
Biopharmaceutical Companies Discover, Develop & Manufacture Protein Drugs

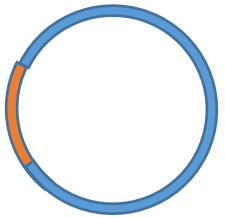
Mike Tarlov, Chief Biomolecular Measurement Division, MML



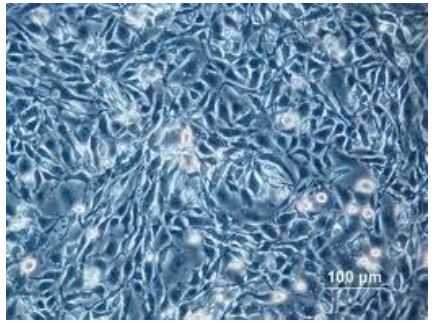
Protein therapeutic candidate



Gene of interest



Clone into expression vector



Transfer into host cell

Cell Culture

Purification

Fill & formulation

Success and Growth of Protein Therapeutics… But Concerns That Trend May Be Unsustainable

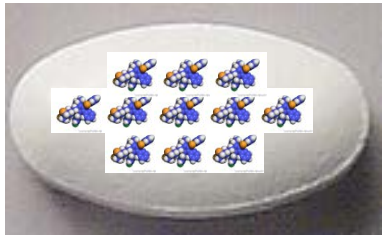
- 7 of top 10 selling pharmaceuticals worldwide are protein therapeutics[1]
- 2015 sales of ~$115B for protein therapeutics in US… but are the fastest growing US healthcare cost[2]
- Growing demand and cost threaten to limit patient access

"High-priced "specialty drugs" represent just 1 % of the prescriptions for Blue Cross' members, but 25 % of drug spending, a share that is rising rapidly. That's not sustainable." [2]

Tony Dodek, Assoc. Chief Medical Officer, Blue Cross Blue Shield of Massachusetts

[1] Source: Evaluate Pharma, Sandoz analysis
[2] Boston Globe, May 29, 2015

Measurement Challenges of Biologics Contribute to Cost of Manufacturing and Development



“API”

“Drug substance”

- Manufacturing processes remain frozen
  - Process change requires regulatory review
  - Hinders adoption of innovative approaches/technologies to improve efficiency & product quality
- Challenges in developing generic versions: biosimilars
  - Regulatory pathway for biosimilars established in 2010
  - Estimated cost savings of $250B through 2024 (Dr. Steve Miller, Express Scripts)
  - First biosimilar approved March 2015, but not on market

NIST Program in Biomanufacturing

- Measurement science, standards, and data to support development, manufacturing, & regulatory approval of protein therapeutics
  - Extensive stakeholder input & interactions (regulatory, biopharma, instrument vendors, academia)
  - Relevant, innovative and robust tools
  - Open data sharing, crowd-sourcing approach

<u>Partners and Stakeholders:</u>

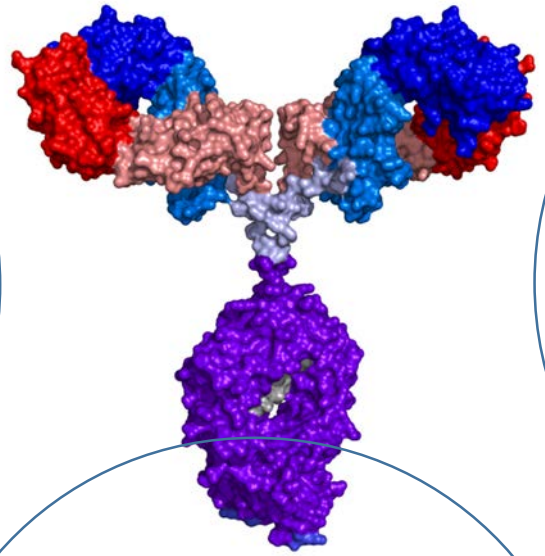
janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson
AMGEN
MedImmune
FDA
Genentech A Member of the Roche Group
Lilly
Bristol-Myers Squibb
Pfizer
SANDOZ Biopharmaceuticals
biogen idec
gsk
MERCK
NOVAVAX
MACROGENICS
NovaDigm THERAPEUTICS
United Therapeutics CORPORATION

"NIST Biopharmaceutical Measurment Roundtable" held annually since 2012

NIST Biomanufacturing Program Areas

Protein Stability/Biophysical

- *Particulates, Aggregation*
  - **(Surrogate Protein Particle SRM 1989)**
  - *Flow microscopy*
  - *AFFF, SEC*
- *Stability predicting tools*
  - *Neutron scattering*
  - *Raman and Red edge spectroscopy*
- *Rheology*
  - *Micro-viscosity*
  - *Shear effects*



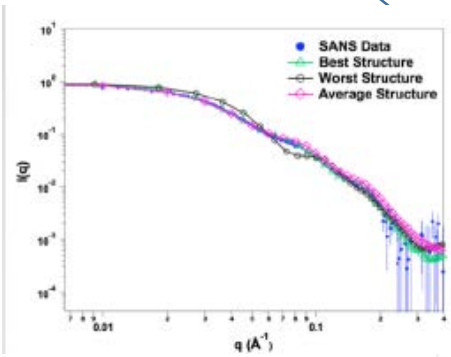
Protein Structure

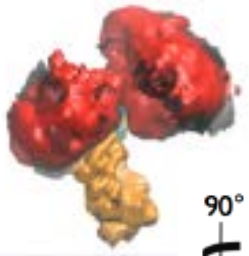
(NISTmAb RM 8671)*

- *Primary structure, modifications*
  - *Mass spectrometry*
  - *MS library*
    - *Peptides, glycans, glycopeptides, all modifications*
- *Protein folding*
  - *FT-IR, DSC/fluorimetry, Raman optical activity*
- *Higher-order structure*
  - *HDX-MS*
  - *NMR*
  - *Neutron scattering*

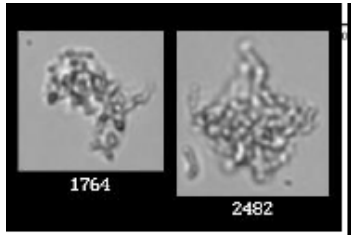
Production Cell Variability

- *Cell line ID*
  - Multiplex PCR
- *Production cell expression*
  - Fluorescence imaging
- *Host cell*
  - MS Library
    - HCP peptides, glycans metabolites

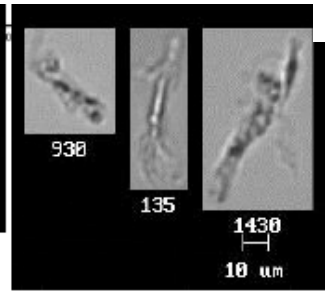




90°

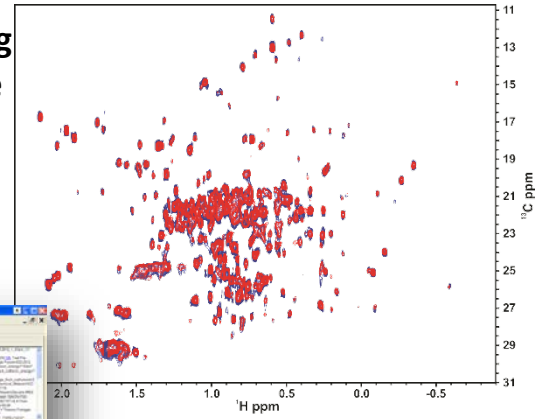


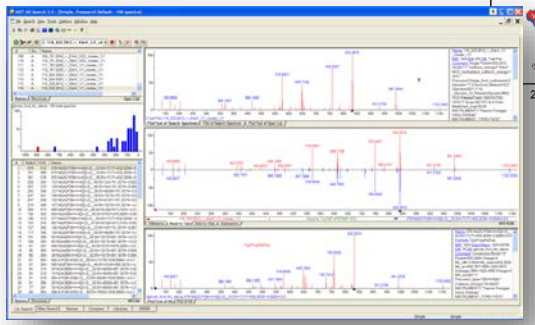
Agitated IgG



ETFE in water

2D NMR Mapping of mAb Structure

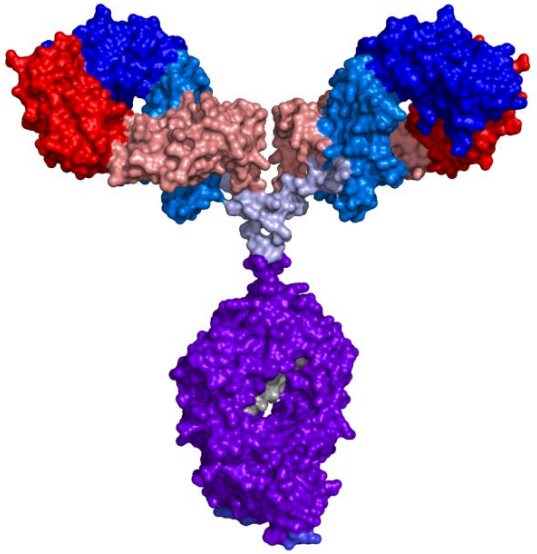




Building a Universal mAb Mass Spectral Library

NISTmAb Reference Material

PIs: John Schiel, Patricia Formolo



First of its kind mAb (IgG1) reference material used for:

- **Determining that measurement system is working properly**
- **Assessing performance of new analytical technologies**

NISTmAb attributes:

- **Humanized mAb (IgG1κ) donated by MedImmune LLC**
- **Frozen bulk "Drug-like substance"**

"Crowd-Sourcing" of NISTmAb characterization:

- **Extensive interlaboratory characterization: Biopharma (11 companies, 44 participants), FDA, instrument, academia**
- **Interlab study basis for 3 volume ACS book series. 1st volume published Dec. 2014: http://pubs.acs.org/isbn/9780841230262**
- **To certify for concentration and issue as SRM by end of 2015**
- **Reference Data: peptide, glycan, glycopeptide spectra (~4000 spectra) as part of NIST MS Library; NMR and chromatographic data also**