Achieving Confidence in Measurements For Regenerative Medicine Products

Anne Plant

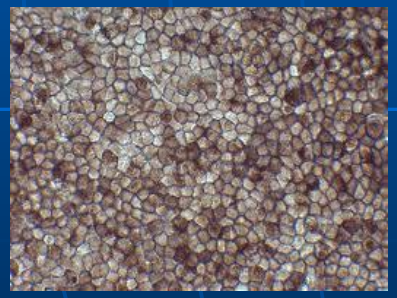
National Institute of Standards and Technology
Gaithersburg MD

anne.plant@nist.gov

Measurements: Fundamental Challenge

For Regenerative Medicine Products

What are the critical characteristics for clinical effectiveness and safety?



Quality Attributes

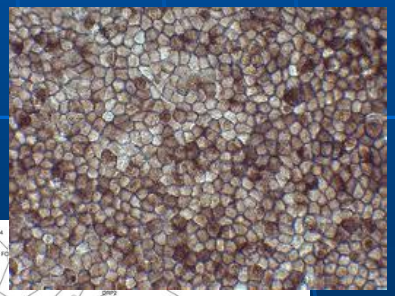
- Identity
- Quantity
- Purity/impurity
- Sterility
- Viability
- Biological activity

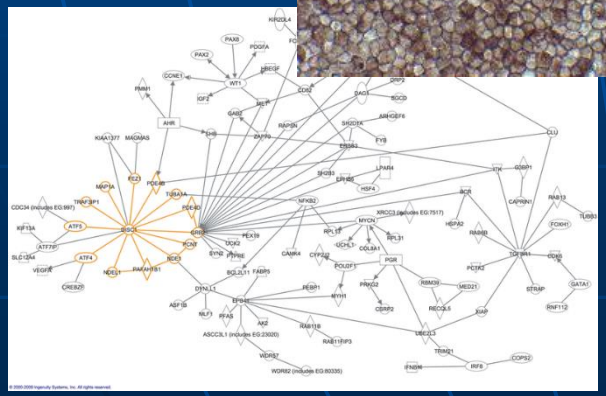
Ideal if MOA is established….

Measurements: Fundamental Challenge

For Regenerative Medicine Products

…. But MOA is often incompletely understood.





The Biology is Complex

- What *in vitro* metrics are predictive of *in vivo* response?
- Gaps in fundamental understanding.
- Lots of variables (clinical and analytical)
- Variation in starting materials (patients)
- Dynamic nature
- No ground truth

Challenges in Characterization of Product

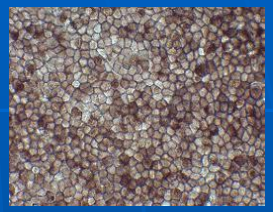
What to measure?

How to measure?

Is the measurement correct?

Is it meaningful to clinical outcome?

Can it be compared to and combined with other data?



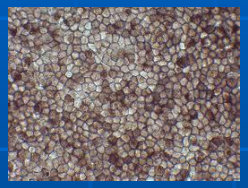
Comparability

Challenges in Characterization of Product during Manufacturing

"If you can not measure it, you can not improve it."
Lord Kelvin

I. Characterization of product

Assays to measure quality attributes



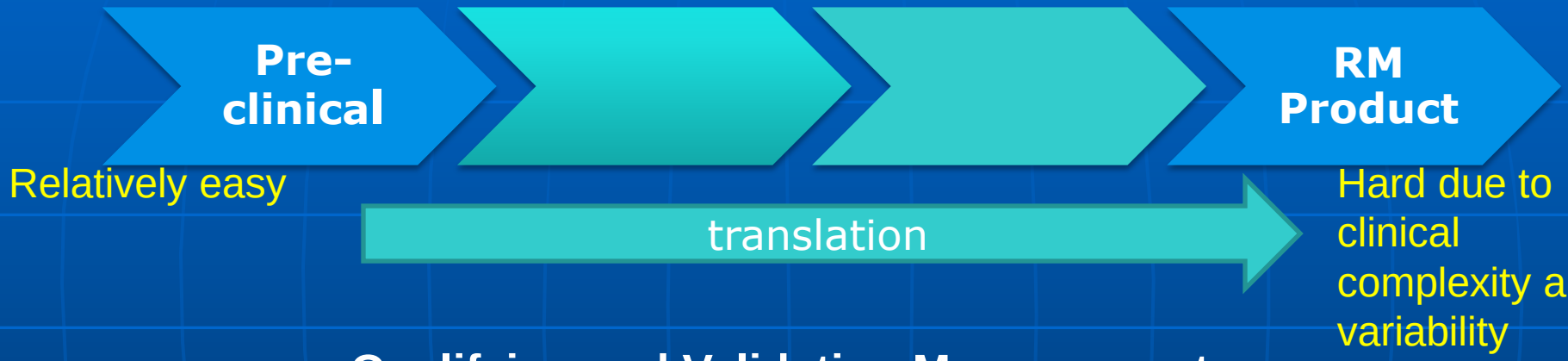
II. Control of the manufacturing process

Assays that assure consistency of product during

- Scale up
- Change in personnel, process, location
- Storage
- New analytical and culture equipment
- Improved assays
- Changes in raw materials

Comparability

Assuring Comparability
through Measurement Assurance



Qualifying and Validating Measurements

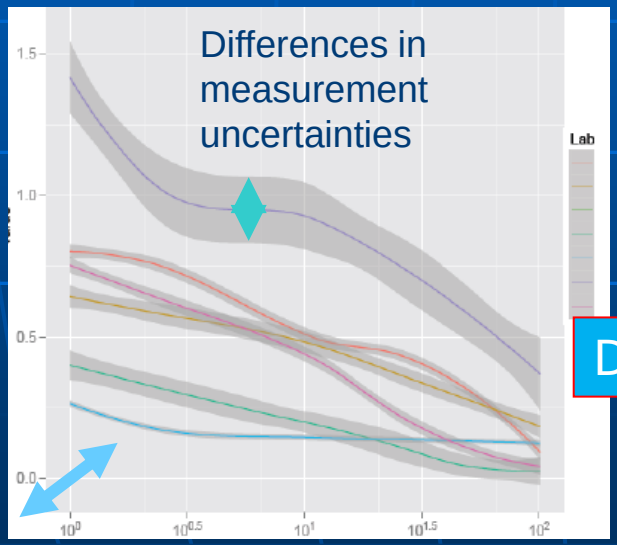
- *Precision: Reproducibility / Repeatability*
- *Accuracy*
- *Robustness / sensitivity / specificity*
- *Dynamic range / response function / LOD*

Measurement Assurance = Confidence in Measurements for Decision Making

Assuring comparability: Interlaboratory studies, Design of Experiment

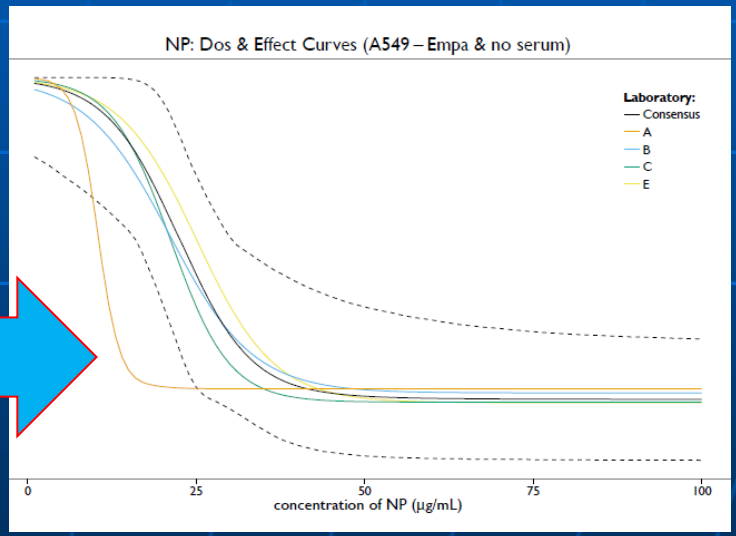
- We don't have problems in our lab.
- We know what we're doing. We get reproducible results.
- It 'works' for us.

Differences in absolute absorbance



Differences in response functions

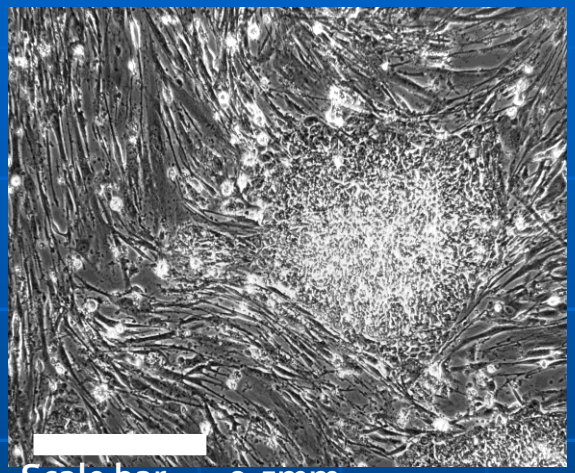
DoE



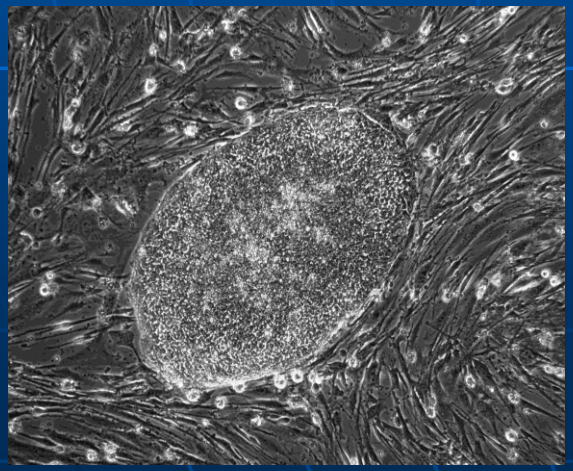
Result: robust protocol and comparable results

John Elliott

Assuring comparability: Testing assumptions



Scale bar = ~ 0.5mm



479 colonies scored by two experts

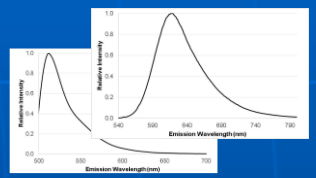
	Expert 2 Scores				
Expert 1 Scores	**1**	**2**	**3**	**4**	**5**
1	**7**	5	0	0	0
2	2	**31**	19	11	4
3	1	21	**52**	49	11
4	0	4	35	**105**	43
5	0	0	2	25	**22**

Experts are not perfect at classifying.

Assuring comparability in instrumentation: traceability to a reference material

NIST SRM 1934/ Calibrated fluorimeter

Fluorescein
Nile Red
Allophycocyanin (APC)
Coumarin 30



Different Manufacturers' calibration beads

Not comparable to one another

Equivalent Reference Fluorophore (ERF) Number

Comparable to one another

Light obscuration flow instrument

For accurate bead concentration

Flow Cytometry Quantitation Consortium

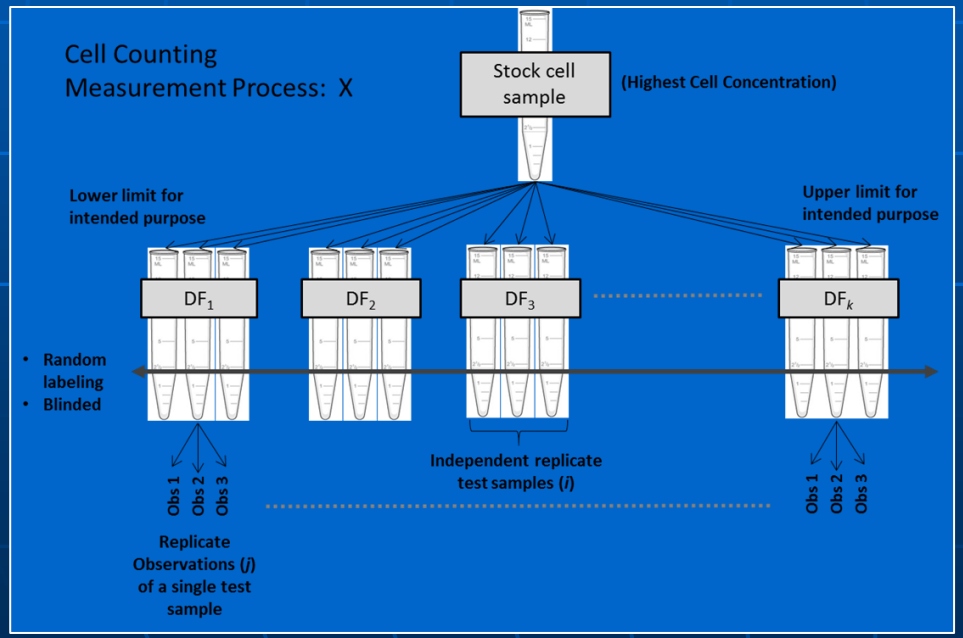
81 Federal Register 136 (15 July 2016), pp. 46054-46055

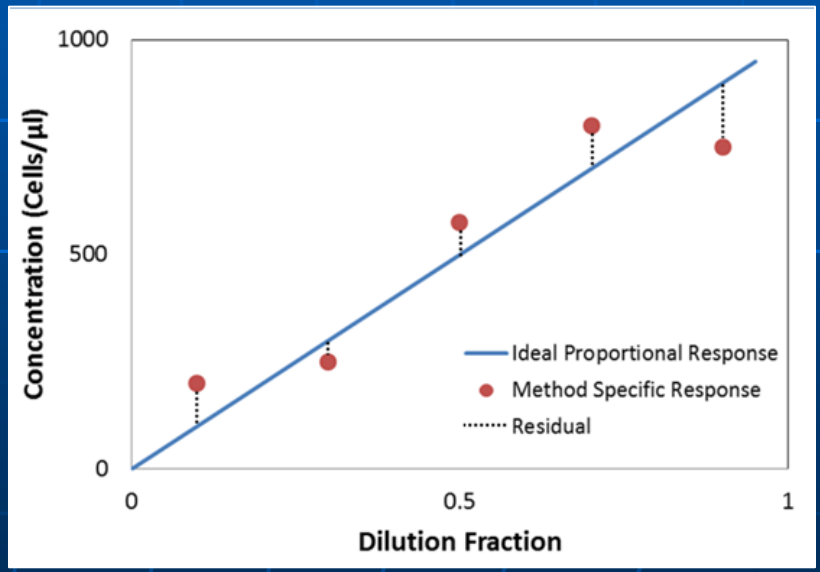
ERF Value Assignment to Cytometer Calibration Microbeads Submitted by Consortium Members

Lili Wang

Assuring comparability through statistical models

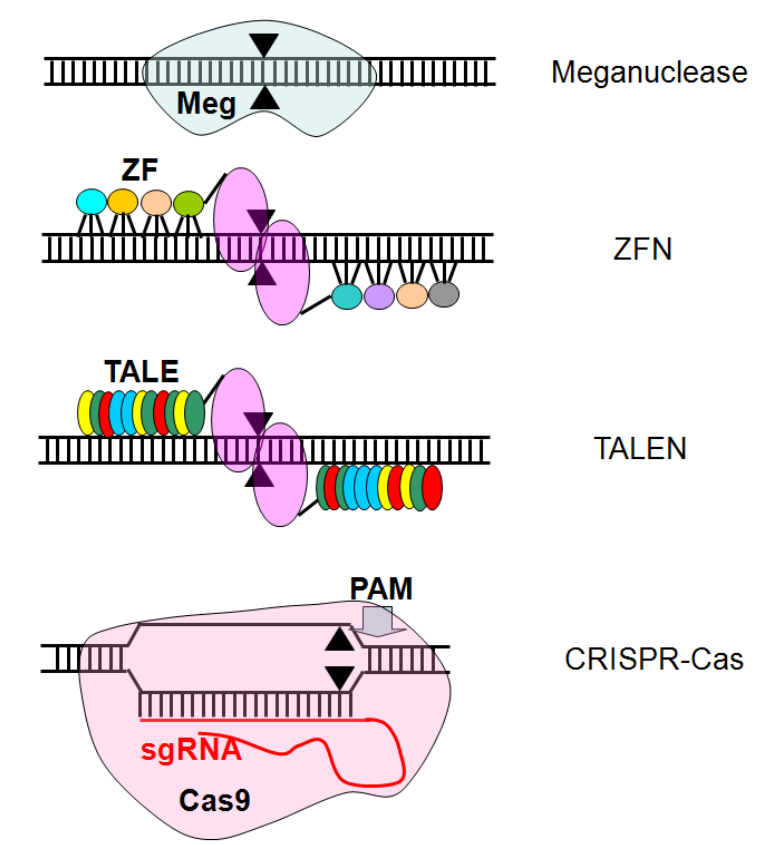
Evaluating the performance of a cell counting method for **relative accuracy and precision**:
Experimental design and statistical analysis





Sumona Sarkar

Gene Editing: assuring comparability in results through assay qualification, consistent reporting and benchmarking



NIST-led consortium in partnership with the Standards Coordinating Body

- Compare existing assays
- Define minimum metadata to report
- Design benchmark materials
- Compare informatics platforms

Samantha Maragh

Assuring comparability and confidence in measurement

- Interlaboratory studies
- Design of Experiment
- Testing assumptions
- Traceability to a reference material
- Statistical models
- Assay qualification
- Consistent reporting

Assuring comparability and confidence in measurement

Challenge	Risk
Can involve significant effort	Data are not reliable, results and conclusions are not correct, bad decisions are made

Can mitigate the challenge through community efforts

Standards development organizations (ISO, ASTM)
Standards Coordinating Body (SCB)
Workshops, white papers, data sharing

The need for comparability and confidence in measurement is critical for data sharing

Today: Hypothesis → Data collection → Analysis

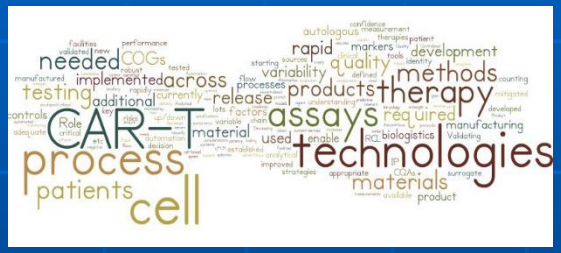
With bigger datasets: Data collection → Analysis → Hypothesis

Data sharing could profoundly change biology

Address very large parameter space
Generate new hypotheses
Expose rare events
Expose patterns
Indicate what is important to measure

NIST Workshops on RMAT Measurements

Strategies to achieve measurement assurance for cell therapy products
May 11-12, 2015; NIST



NIST Workshop on Measurement Challenges for CAR-T Biomanufacturing January, 2016; IBBR

NIST National Institute of Standards and Technology U.S. Department of Commerce

AMERICAN SOCIETY of GENE & CELL THERAPY

Microsoft

editas MEDICINE

Genome Editing Standards Workshop
NIST Hosted, ASGCT partnered May 2016

- ***NIST-FDA Cell Counting Workshop: Sharing practices in cell counting measurements*** April 10, 2017; NIST Gaithersburg, MD
- ***NIST-FDA Flow Cytometry Workshop*** Oct 2017, NIST Gaithersburg, MD

Thank You