Identifying Common, Unmet Needs in Biosciences – An Interpretive Synopsis[1]

It is evident across the entire biosphere that consideration of measurements of substances without adequate consideration of the environment or milieu in which the substances exist and act predisposes to misinterpretation of their importance or function in biological processes and in the biosphere. The complexity of the substances that are to be measured, the likely multiplicity of their functions in conjunction with other biological substances and in organisms that than the organisms used for any particular investigation, imposes requirements for the quality of their measurement and characterization that are far greater than measurements carried out on simpler substances. The fact that biological substances participate in complex chemical pathways (metabolic processes) implies that inadequate quality of measurement results can and probably will provide misleading data and erroneous interpretation. Measurement of single substances in biological processes in which many components interact is now recognized to be inadequate to their intended use and thus methods for simultaneous measurement of many substances is necessary to reduce the likelihood of misinterpretation or inadvertent misuse of the measurement results. Measurement results must be of an appropriate quality to avoid their contributing to unintended consequences that might have been anticipatable were the measurements sufficient to their intended uses. Because measurement results obtained from different analytical methods and from different biological systems must be comparable if the information inherent in the measurements is to be realized, the presentation of data must enable easy access and facilitate correlation and hypothesis testing. Easily accessible common data formats specifications will be necessary if the goals for acquiring the aforementioned data rer to be achieved and the benefits that the measurement can provide actually realized.

[1] The members of the panel invited to make presentations in this session were chosen to represent diverse disciplines and perspectives ranging from basic research to the application of contemporary analytical methods to everyday problems such as water pollution. None of the speakers were informed in advance of “points” that might be made by other speakers in the session.

Synopses – By Speaker

Yamamoto – Perception of biology as qualitative and descriptive may mask its dependence on quantitative measurements that underpin the evaluation of qualitative descriptions (models) of biological processes and systems. Methods and measurements that provided the basis for progress in molecular biology (genomics) have provided impetus to advance from component characterization to characterization of assemblies of macromolecules that interact in order to produce the properties of cells that we associate with living entities and distinguish them from individual macromolecules. An opportunity for a structural biology of the cell can be envisioned that might include a molecule positioning system (MPS) analogous to a GPS system for navigation. Such a system might enable tracking of molecules over space and time within the cell. Methods that enable counting individual molecules within the cell, observing the interactions between and among these molecules and the consequent possibility of identifying molecular phenotypes could provide a leap forward in the development of biology at a molecular level.

If this vision of a structural biology of the cell is to be realizable, we require capabilities for organizing and maintaining the data from which new information about intracellular processes can be obtained. Interoperability of devices that make the measurements to provide the source data, database structures and access to data within these databases must be designed and provided so that knowledge can be readily derived from the data. Software must be designed to that it can serve as a platform for querying the databases and the databases must be open so that data across biological systems, laboratories and investigators can be accessed, compared, correlated and models derived and tested from the data present in them.

The requirement for open database structures goes beyond characterization of the cell and is needed for making information available from clinical data and physician's notes so that insights can be derived from common observations even though such observations might be anecdotal – but discoverable as common anecdotes. Templates for recording

observations that aid in promoting the acquisition and recording of reliably comparable data may enable greater use and insights to be derived from data now available and continuing to accumulate. Currently such data are not as widely available as it could be to basic researchers and clinical investigators. NIST as a non-regulatory agency that serves its constituents by providing standards may be the best positioned organization to develop and promote the development of acceptable standards for data structures and means of access to data with broad acceptability and utility.

Hudson – relationships between genetic mutations and/or polymorphisms and diseases although unambiguously established when interpreted as if they are necessarily singly significant may mislead. Molecular genetic measurements in the absence of comparable information about mutations that could provide compensating changes in the organism can generate unnecessary anxiety and/or action that have substantial adverse consequences. Ambiguity is inadequacy and can create and promote inference and interpretation that causes damage. Genetic marker laboratory testing occupies an unusual position among diagnostics tests because of the differences in their regulation. Commonly, traditional laboratory diagnostics are reviewed for evidence of safety and efficacy from clinical trial data or from their substantial equivalence to tests already on the market. Genetic tests are more "loosely" regulated and their quality assured via laboratory conformity to general guidelines. Although the traditional regulation is used for some genetic tests, it is not applied to tests developed in the laboratories that are using their own "home brew" tests. Although a few control materials and calibrators are available from the Centers for Disease Control and Prevention, materials are not available in sufficient amounts to support proficiency testing for all laboratories and genetic tests that are currently in use. Quality assurance via proficiency testing, when it exists, is principally voluntary and provided through professional scientific organizations with interests in genetic testing. Cross instrument platform and reagent comparisons that can validate the test results and generate confidence in the measurements, independent of considerations of inference from valid results are needed, but not generally available.

Reid[2] – recognition of biodiversity of a magnitude previously unimagined requires that many contemporary approaches to antibiotic development may need to be greatly modified, if not abandoned entirely. Methods and reference materials by which to distinguish among the members of the microbial communities and measure their differences and distinguishing properties must be developed if we are to be able to assess their significance as symbiotic microbes or as pathogens and the circumstances and situations in which the same organism might play either of these roles. Consequences of encountering microbes for eliciting immunity, immune tolerance or intolerance to products that might be produced by such previously unrecognized organisms may be crucial to understanding and curing or ameliorating conditions such as food allergy and resistance to such organisms and toxins produced by them. The sheer magnitude of the number of such organisms and their evolution requires measurement methods and standards that may be similar to the massively parallel processing methods required for some computations to be capable of providing the data and information which we will require to cope with such biodiversity. Measurement methods and standards (reference materials) capable of permitting a distinction between risks and benefits of members of microbial communities and the destruction of all members when only a few are pathogenic are needed. The extremely large number of organisms in the microbiome make realizing this goal very difficult and expensive, however, because of the symbiotic relationships can be beneficial as well as pathogenic, improved health of the human may depend on being able to achieve this goal.

Reijo Pera – progression from stimulation of ovulation to successful pregnancy is characterized by stages in which large losses (lack of success) in going from one step to the next indicate that our knowledge of the critical requirements for success is clearly lacking. Methods and reference materials when the relevant molecules are identified will be necessary for the development of an understanding of the molecular events that accompany cell fusion, cell division, cell implantation, cell differentiation and the molecular decision-making processes that produce pluripotent versus committed cells

[2] *I have not done justice to the presentation, but I have found myself to be unable to summarize the points regarding the existence of microbes already resistant to antibiotics and the consequences of antibiotic use that may foster selection of the resistant forms in an intelligible way.*

during embryonic development. Knowledge to enable achieving efficient in vitro fertilization leading to successful pregnancy can be advanced when measurements enable distinguishing between viable and unviable early stage embryos. "Natural" programming of embryonic stem cells has been "imitated" by induction of pluripotency in other cells; demonstration of the equivalence of these two groups of cells although very promising, is limited by the large number of possible differences and the likelihood that the significance of these differences may be missed because of our limited ability for identifying the most informative measurements to be made and methods for making the measurements. Of very grave concern is the current necessity of making measurements of particular differentiating cells without them being in contact and communication with other cells that are normally present in the developing organism and in mutual communication. Realization of the potential benefits of stem cell therapies

Discussion comments – in addition to molecules within the cell, the production of these molecules cannot be overlooked or ignored. Single cell metabolomics may be sources of insight that by comparison with multicellular systems, e.g. during the early stages of cell differentiation could provide clues to the nature and consequences of cell-cell interaction already recognized, but for which the molecular agents and their actions are only inferred. Differentiation into endo, meso and ectoderm during embryogenesis although long described requires measurement methods and then reference materials if the molecules that produce such differentiation can be identified and their actions and functions describable and understood.

Petsko – Unintended consequences – disasters that arise because of failure to recognize or acknowledge risks or relationships that may be ascribable to discipline-linked ignorance. Anticipatable effects thus arise that complicate and may doom noble, but ill considered. "scientific" ventures. Such ignorance or conscious avoidance of potential adverse consequences can lead to disastrous consequences; examples are abundant. Even if evidence for potential adverse consequences is recognized, decision making that is based on or depends on measurements of inadequate quality will be confounded and/or delayed because bad data enables and even fosters counterproductive debate. One

situation, oversimplification in assessment of the requirements for achieving apparently simple goals that involve the use of microorganisms as bioreactors exemplifies the danger of inadequate or otherwise limited information. The evident inadequacy of modification of four genes to produce a chemical intermediate was clear when 26genes were finally determined to be required to enable the organism to produce the intermediate because of unrecognized control mechanisms involved in the organisms metabolic pathways. In complex biological systems, selective consideration without regard to interactions between and among macromolecular components in particular predisposes to invalid inferences and inadequate or inappropriate actions. Although scientific and technical considerations are commonly made, they cannot be made without consideration of the economics of the processes, interventions and assumed benefits. Can NIST act as the agent for the identification measurement needs and the provider of reference materials reduce the frequency of intended consequences? Perhaps because of its mission and acceptance within the scientific and industrial community it may be the only governmental agency with the stature to do so.

Pierce – water treatment produces its own chemical modifications that results in substances for which the toxicity and adverse effects are unknown. Even when the primary substances used in water treatment are considered, the disinfection byproducts are inadequately identified and even when know, inadequately measured and their effects evaluated. Methods for identification, quantification at concentrations low enough to provide adequate evidence for presence and amount are not in widespread use although they may be available and used by others. Methods currently in use may be inadequate to the task of identification and quantification of disinfection by products. The ramifications of inadequate testing extend to all aspects of agriculture, animal and plant production, food safety and pollution of the soil and water upon which agriculture depends. Without technologies currently in use in other scientific disciplines being applied to water and agriculture in all of its aspects, progress in improving these vital resources and our food supply will remain seriously hampered and handicapped.

Pierce – manufacturing biological materials such as vaccines and other biologically derived therapeutics will not progress at the needed pace unless nondestructive measurement methods can be developed and applied to bioprocessing. The principal challenges to biomanufacturing arise not from limited research success, but from the complexity involved in transferring a bench scale process to commercial, large scale production. The ability to test at intermediate stages, the rapid identification of contaminants that will require subsequent removal and more efficient separation methods for removing contaminating substances from biomanufactured materials and verifying the adequacy of their removal are needed.

Shen – replacement of petroleum by hydrocarbon fuels derived from replenishable plant materials is handicapped by its current competition for raw materials that are also used for food. Algae offer an alternative with great promise because they can grow on simple carbon sources such as CO_2 and under appropriate conditions convert CO_2 from sources such as flue gas into lipid materials that may subsequently be used to produce biodiesel fuel. Genetically engineering the algae to carry out these processes efficiently and cost effectively constitute the current challenge. Multiple and multiplex measurement of the ability of engineered algae requires the development or tailoring of methods and the development of reference materials for key steps in the processes if work on different algal species and engineered variants are to be accurately compared. Selection of variants that are capable and sustainable is a formidable task. Optimization that will be required to go from the bench top to the bioreactor ponds depends on accuracy of measurement because of the many variables that can be expected to require monitoring and/or control. Progress in replacing petroleum with biohydrocarbons will not occur at the speed necessary without measurement standards to assure comparability of data across species and between laboratories.

Wall – Evaluation of new drugs in animals is mandated by law, however, animal models have been shown to be poor predictors of safety and efficacy. Replacement of animal models with cell based models will require appropriate measurements of multiple effects on the cells if cells are to replace animals. As with similar considerations of systems

biology, the ability to measure relevant substances will require the identification of what is appropriate to measure and then to measure it accurately so that results can be compared across test systems. Agriculture in the future will depend on transgenic organisms, for economic reasons related to yields, resistance to disease and ability to tolerate growing conditions that may be anything but optimal. The creation of suitable transgenic species currently rests on both scientific bases and art developed through experience. The success in creating transgenic organisms efficiently and that are appropriate for their desired characteristics rests on being able to efficiently make measurement that inform with respect to gene and metabolic regulation of the key steps in engineered pathways.

Spence – the safety of the food supply is crucial to the nation. Safety can be conceived as protection of the production of animal and plant foods as well as in the identification and elimination of pathogenic microorganisms that can contaminate foods. Because both plant and animal foodstuff processing occurs in facilities in which the conditions are dictated by the environments in which animals and plants are raised, processed and packaged, testing for disease and the presence of infectious agents must be performed under conditions very different from the general laboratory environment. Rapid, simple and specific tests are needed if the highest degree of safety is to be possible. Methods and many more calibration materials for the pathogens encountered in these environments are needed. All tests must be robust and suitable for the meat and produce processing environments and ideally use a common platform.

Discussion Comments – (I have none because I didn't take notes and my memory bank(s) have been erases….).

Several measurement barriers were identified by the speakers in this session as common across all areas of biological science investigation and science application.

Inadequacies in our ability to conveniently share information across disciplines as the result of database structural incompatibilities were commonly cited as a serious barrier to information exchange. The absence of interoperability in respect to data transfer between instrument platforms is one example of such inadequacy. Another example is the inflexibility of data structures to accommodate new information or previously overlooked information that needs to be incorporated into existing databases.

A general lack of familiarity of the utility of measurement science in assuring the quality of laboratory measurement results was observed throughout this meeting thus indicating a need for education in principles of measurement. Standardization, but not metrological traceability are concepts unknown outside the metrology community.

Inadequate assurance of the quality of the data upon which decisions and recommendations can be made exists because of the absence of reference materials suitable for use in measurements extending from assessment of water quality to genetic markers for disease. Quality assurance procedures that are outside the current regulatory structure for genetic marker tests used in medical diagnosis, creates a situation that does not result in confidence of the comparability or accuracy of these tests. Test quality has not kept pace with new developments to the extent that confidence in the measurement results is unsatisfactory. It was also evident that measurements that ignore the environment or milieu in which biological processes and reactions occur can provide data that mislead rather than inform – a consequence of the need for measurements that can be made in situ with the accuracy of measurements previously made only after preparation of samples that destroys the information that is only available from in situ measurements.

The need for noninvasive measurements, particularly for cells was noted in several contexts. MRI, CAT and PET scanning were mentioned as potential types of technologies

that might be adaptable to measurements of single cells. Examples of applicability are in embryogenesis and single cell toxicology studies.

Technologies that have been developed and are currently used in medical diagnostic testing environments need to be made available to laboratories in which more routine testing is employed; an example is water quality testing and soils testing. Some of the impediments are economic, but others are the result of the absence of methods and reference materials suitable for use in these application areas. Testing for microbial contamination of water is too frequently performed by methods that permit one only to be able to say that the water was too safe two days ago rather than is its unsafe or safe now as is needed

It is now apparent that the traditional uses of animal models for assessment of risk and efficacy in the evaluation of new drugs are unsatisfactory, particularly when more specifically targeted therapeutic agents are being evaluated. Misleading results may arise from inadequate specificity of conventional methods and may result in risks not being identified or efficacy missed. Single cell procedures that can be more suitable are hampered by inadequate sensitivity or the absence of calibration materials to assure the validity of such measurements.

The absence of technologies suitable to meet the need for noninvasive measurements on systems such as embryonic development severely impede progress in assessing the likelihood of successful in vitro fertilization Similarly, technologies capable of acting like global positioning systems for intracellular structures could provide advantages for evaluating the effects of both toxic substances and potential therapeutic drugs on cells If such technologies were to be developed many of the impediments now identified with animal testing and limited traditional methods are potentially overcome

Advancement is limited conceptually by measurement of what we know how to measure, rather than what we believe could be more informative if only it were measurable with the specificity and accuracy required to provide a basis for making recommendations and

decisions. Inadequacies in data and information availability and in the formats in which the data are stored pose serious, even threatening risks when the data are intended to be used for making decisions. These deficiencies predispose to unintended consequences that need to be anticipated and might if the relevant information was available and accessible.

The opportunity to rapidly exploit sources for hydrocarbon energy substitutes is hampered by the need for measurement methods that can be efficiently applied to systems such as engineered algae that are capable of converting carbon dioxide from flue gases into biofuels. High throughput methods for evaluating the diversity of algal species, the broad variation in conditions that are encountered because of the diversity of feedstuffs used to produce biohydrocarbons are needed if rapid progress is to be made.

Achieving the goals is impossible in the absence of resources comparable to the complexity of these goals. Our speakers highlighted a previously unrecognized disparity between NIST's mandates and its budgetary allocations.

Closing the Gap Morning Session

Keith Yamamoto – University of California San Francisco Medical School

Quantification and Integration in Biomedical Research. Or Measurements and Standards: emerging, needed, overlooked and resisted.

In the past bioscience was pretty simple:
- Microbiology – taxonomy
- Cell Biology
- Molecular Biology – light vs dark gel bands

Then came "omics"
Quantitative work in parallel, sometimes done under the radar but now more prominent and driving qualitative models.

Some tools have been really advantageous:
Optical tweezers, laser temperature jump and H-exchange, NMR rapid kinetics of protein folding, x-ray crystallography and NMR.for biological mechanisms for drug design and development, and tandem mass spectrometry for post translational protein processing epigenetics.

All of these technologies have helped drive quantitative biology.

Quantitative work is driving qualitative models.
There is an increase in resolution and scale of quantitation:
- Raise opportunities but have the challenge of integration

Relationships enhance richness of information
Increase need and value of measurement of standards and bench;marks.

Relationships change the value of the information.

What areas do we need to be working in to derive information in new ways?

Measurements and standards have different needs in different fields.

Microarray Quality Control Project led by FDA with 150 investigators.
There was about 80 -90% correspondence across platforms.
There is a need for standard reference tools, analysis software, platform comparison benchmarking and network building tools.

Synthetic Biology
- Need standard conditions for measuring activities of various components.
- Need standard sets of parts with predictable relative activities under several conditions, or don't cook it.

Clinical Research
-need better data and standard databases (common coding conventions) for comparison and statistical analyses.
-need standard template methods for collecting and portraying components of clinical care
–need standard replacement for medical record notes – currently doctors write their notes by hand and this information is lost forever.

Medical Informatics – medical devices
-need standards for device interoperability
-companies are resistant to have their equipment talk to other companies' equipment
-need to coordinate readouts to standard databases.

Opportunities to extend integration

Develop a "structural biology of a cell" to relate stochastically and to regulation.
Measure the number, size and distribution of protein complexes and aggregates.
Measure and track properties of cancer cells within population of normal cells
Define multiple molecular phenotypes of cells to determine molecular networks that predict complex behavior such as disease, drug response, etc.

Kathy Hudson – Johns Hopkins University

Currently there are 1300 genetic tests ranging from being able to detect disease diagnostics to reproduction tests.

You can now get parts of your genome or your entire genome sequenced. Companies like Navigenics and DeCode Me will do this for a fee.

The costs of sequencing are reduced as the speed of sequencing has increased.

You can carry this information with you but the accuracy of tests is very important.

Kate mentioned that there are three different levels of accuracy – analytical validity, clinical validity, and clinical utility. The use of these tests are for the improvement of health outcomes.

Lab development tests and test 'kits' difference is key to the level of regulatory oversight.
There is inequality across genetic testing industry.
Standards must address both QA and QC, and record keeping facilities.
Congress passed law in 1988 on proficiency testing but the focus is more on education than enforcement.

The website on CLIA has not been updated for a year.

Legislation by Senator's Obama and Kennedy was passed to do proficiency testing for genetic tests. CMS argued against new proficiency testing regulation, citing the absence of proficiency testing materials program.

NIST could fill in the gap by providing valuable standard reference materials for the most frequently performed tests or for the most frequently used methods.

Ann Reid – Greater Appreciation of Microbiology being in Control – NAS - NRC

New science of metagenomics. Treating infectious diseases in a world that is loaded with microorganisms.

There is a need for tools and standards to characterize these microbial communities that will lead to a transformation to how we think about life as well as how we deal with disease.

Your body contains 10 times more microbes than human cells.

Immunity may be highly affected by the microbial biome in your gut.

NIAD had a goal to develop an antibiotic that could treat any pathogen or boost your immune system. Called Gorillacillin or immunebooster.

Antibiotic resistance is ancient, ubiquitous and easily shared. What we need to go after is an antibiotic that is activated only in the presence of immune system damage signals.

How do antibiotics interact with our immune system since they also attack healthy biota in our intestines that are responsible for a healthy immune system?

Our individual microbiomes have variability and we know very little about the differences between an older and younger person's microbiome. Neither do we know how the microbial community interacts with the host.

We need to focus on functional metagenomics.

Renee Reijo Pera - Embryonic stem cells

Stem cells can make new stem cells or differentiate into many types of cells – they are cells that can make a decision. It is a molecular Passover event!

When the egg and sperm meet, they erase the genetic programs they each had and reset to that of an embryo. There is little or no transcription until day 3. Differentiation starts at day 5.

World wide there are 475 embryonic stem cell lines. Each embryonic stem cell can form ecto, meso and endoderm cells. There is a program, that we have yet to unravel, that allows fate to be determined. Humans have 216 different cell types.

Reprogramming somatic cells or redirecting them only can be done by frogs and mice.

Stem cells have the biggest impact in reproduction and fertility research.
400,000 embryos are discarded each year.

What is the regulatory fact that turns on the gene activation at day 3? Is it cell division or time?

Embryo is not merely cell division.

We have been treating cancer wrong since it has now been documented that there are cancer cell lines.

Don't know if we are using the right medium to grow embryos or not.

We need better molecular imaging that is not invasive to the embryos. WE need tools for measuring life style and environmental effects. We need to measure precisely genetic changes and measurement of chemical output of enzymatic pathways in a time dependent manner.

Quiescent cells – resistant to antibiotics – why? Perhaps we should study the normal state of cells – that is a resting state rather than metabolically active states which may be coloring our interpretation of data since for the most parts cells are quiescent. Therefore we need a standard reference for what is a quiescent cell.

We also need to balkanize disease and this is too limited of a perception to make any advances. An example is patients with Parkinson's Disease never get cancer but have a 10 times greater incidence of melanomas.

We need to rethink the process of how we study disease. What the roadmap could and should have done but did not. (not sure of what roadmap Greg is talking about here)

Have to have an end goal of what a cell type is – lot's of mistakes in the media we use.

When is a gene off or on – need a standard definition here and profile of on off activities.

How many proteins are in an embryonic cell – don't know.
How do you diagnose what a cell is?
How do you validate the models we use?

There is a big push and big need for 3 D biology research.

Closing the Gap Afternoon Session

Greg Petsko – Australia had a problem with cane beetle. Imported cane toads from Africa. But the cane toads ate everything in site and took over. They are poisonous. Now Australia has both a cane beetle and can toad problem. The law of unintended consequences – if you don't know what you are doing, the risks will outweigh the benefits.

We have a climate crisis – producing adverse events as a result of the industrial revolution. Dump iron into ocean; get algal blooms to eat up CO_2. – DC folks call it geo-engineering.

Would need a set of measurements to do something this stupid.

Rachel Carson – one of the un-intended outcomes of getting rid of mosquitoes with DDT is West Nile Virus.

Measurements are normally run in disciplines but we need measurements where disciplines cross.

Genetic factors and environmental factors – impact.

We do not understand the interplay of the individual genetic background and the environment.

Need measurements to tell us how these two factors correlate with each other.
Trend is not destiny.

DuPont wanted to use bacteria to make a polymer for durable clothing. The bacteria lacked three genes to do it. How much money and time did it take to introduce the genes to make the polymer – 7 years, 26 genes and 100 million dollars.

More than half of the genes in a microbe were introduced from the outside. Yersina pestis – is lethal to people because it picked up the gene for tyrosine transferase.

We can't do biomanufacturing until we know how microbes react to gene inserts.

No one on the panel with economics. All that we are discussing will have gross impact on economics within society. Some of the standards we set and measurements we make, should be set also for the economists as well as the scientists.

What questions get asked? What measurements will be needed?

Pickett Scientific = slide rule. HP and Texas Instruments simultaneously invented the calculator. They are still in the business. Seeing what you do in limited terms, is stagnation.

NIST has the responsibility of asking questions as well. Engage the scientific community but also ask within the institution.

Synthetic biology is one of those things you have to wait to see what happens.

We need people who can think broadly in this field just not about applications. Avoid from being Evil Kenival – it is a stunt and you are left in the end with nothing but other than how clever the investigator is.

Who will guard the guards themselves? We will have the best oversight if we ourselves come up with the guidelines.

We need to be proactive in what people are afraid of before the government gets involved. The public is educable.

George Pierce

Three environmental issues – drinking water, drinking water disinfection and bioremediation.

People in water do not talk to people in soils and vice versa.

New chemicals are introduced into our water supply putting water under a lot of stress.

Drinking water processes – aging infrastructure, increasing knowledge regarding Disinfectants By Products, impacts on lakes, reservoirs, groundwater, marine environment.

There is no treatment for water that does not have a by-product.

We are in stage 2 regulation of DBPs. Choramination – make iodo-compounds. If you do combinations, you can create a whole wrath of chemicals.

Trying to catalog chemicals produced. – How do you measure them, standardize them across the nation? We do not know what the toxicology and epidemiology is of these compounds?

We do not know if you are at risk or your children's children.

Applications of standards – NPDES Point source, or non-point source – all will require more robust screening.

Risk based treatment options – these are needed but we don't know what we are treating. If the background is different, the chemical byproducts will be different.

What is entering the water stream? Caffeine, DEET, antibiotics, hormones, disinfection breakdown product, etc.

Despite the success of superfund site restoration efforts, the clean-up and restoration of legacy groundwater pollution lags far behind.

Funding of remediation R & D has not received the attention matched by the intent of the environmental legislation.

General shift in education focus away from remediation to process wastes, pollution prevention and public health related issues.

Is bioremediation cost effective? This is the wrong question.

Successful bioremediation is characterized by
Achieves desired results in a timely manner, is reliable and efficient, economically and competitive with other treatment technologies.

Much of bioremediation R& D has focused only on potential for archiving degradation and has not addressed what it takes to be successful.

There is also a social community aspect to bioremediation.

IT is more expensive to do bioremediation than pollution prevention.

<u>George Pierce – Bio-manufacturing</u>

Major issue is making large amount of doses in a reliable timely manner.

Recombinant vaccines – characterization is a real issue
Have to develop appropriate standards, need both product and process standards.

Aluminum is the only certified adjuvant. If you use anything else, it becomes part of your product.

You have to determine and understand the product during manufacturing.

How much information do you need to identify your product?

The approved anthrax vaccine was actually developed in 1960.

There is a certain amount of integration between process and product standards.

Have to know what you have before you ship it out and determine it during manufacturing.

Factors to consider when producing biologically active macromolecules
-separation of recombinant proteins from host proteins
-Protein denaturation / renaturation / refolding
-aggregation/interaction of proteins
-Removal of nucleic acids
-Endo-toxin(s)
-Etc. – it is all inter-related.

If you change one thing in the process, you change everything.

The last natural vaccine that came out was flu mist – all the work done in the late 1970s but it took many years for safety, product id, scale up etc.

<u>Feng – marine biofuels and global climate change</u>

Major biofuel types – vegetable oils, ethanol, biogas (methane)

Ethanol produces less energy than gasoline, and has a corrosive effect.

Biofuels could end up damaging the natural world rather than saving it from global warming – Jeffrey Needly – BBC news.

Algae – 20g/m2/day, with 50% oil –much higher than other forms of biofuels.

Challenges for microalgae

Flue gas can be toxic to algae
High CO_2 influx could decrease pH quickly
Waste water may contain contaminants.

AT COMB, test existing culture collections for their tolerance of desired treatments
Do HTP screening to select strains

Algae grown on flue gases grow twice as fast – don't know why.

Measurements

Composition of flue gas
Maximum level of flue gas charge
Composition and function of other microbes
Sustainability of algal species
Cost of such an integrated system

Bob Wall - Transgenic animals

Measurements – genotype to phenotype
Standards – animal models
Technical Challenges – genetically modified organisms

Measure what we should – DNA –mRNA – protein

We measure these because we can

Tool building vs. measure what we can conundrum.

He wants animals as standards – use them to verify efficacy of drugs because of the analogy to the target organisms.

WE need animal models when it is ethically inappropriate to study the real thing and it is required by law.

Nuremberg Code – animal dose studies are a prerequisite to human clinical trials.

Do animal fulfill their promise –yes and no depending upon the question.

As a biomedical predictive tool – not so well

92% of preclinical studies fail to predict an adverse clinical outcome.

All human clinical trials must be preceded by at least 2 successful animal studies.

Need a better system.
Why are they failing –inappropriate experimental design, environmental differences, health status differences, maybe animal models are not a good analog.

Better control of transgenes

Technical challenges – genetically modified organism are an inevitable part of agriculture's future. So we better get it right. What is broken? The transgene

We currently build transgene partly on art. We do not understand genetic control of phenotype lacking and therefore the transgene behavior is unpredictable.

The control site of insertion into genome is lacking. So is this a real problem> Is there a good genomic site for transgenes?
You can only measure about 10% of the transgene that was inserted. Heterochromtin is more important than we thought.

Another problem is a lack of control of tempora and spatial expression patterns.

How does gene regulation work?
Can we borrow it or do we have to invent it anew?

We are limited to one gene at a time. We need to be able to build pathways and need stoichiometric control of multicistronic elements. Don't know how the liver or muscles would react.

Measurements – measure the right thing genotype to phenotype
Standards, animal models are not meeting our needs
Challenges – genetically modified organisms – need to control the transgenes in a more sophisticated manner.

Joe Spence – Human Nutrition BARC

Food and Agriculture

Animal and plant production and protection
Food safety, nutrition, product quality.
Environmental and natural resources

6-8 B chickens in the USA at any one time, so we need HTP screening tools to catch any disease.

We are exposed to our environment via the food we eat. Diet and nutrition is extremely important. Harmful contaminants at all stages of food supply.

NIST role:

Detection and measurement

Too few reference materials and do not cover all commodity areas
Standardized or official methods of measurements – the matrix matters so the difference in how you measure things counts. Geographical influence. Using folic acid technology that dates back to the 1940's.
Robust methods
Multiplex method – if you had a specific food reference and measure for specific virus or toxin. At USDA they measure over 700 foods for nutritional value. Need standards and methods that could measure many things in one sample.

New technologies:
Nanotechnology
Non-destructive spectroscopy
Proteomics
Bioinformatics
Gene Expression

Epigenetics
DNA repair.

We can now see what is going on in cells.

Joe is very interested in diet quality. He feels there is influence from food on DNA repair.

Roadblocks

Resources, mission space and customer needs and priorities

NIST can not stop work on what is it currently doing. Have to balance the resource and prioritize what you work on.

NIST could function as a referee or act as the driving force to get the right group to come together and work on these projects.

Who speaks for whom? Everyone has there own priority. Who is ultimately going to set those priorities? There will be unmet needs unless the right people speak up.