# Revolutions and Resolutions– Some Perspectives for 2008

*Christopher Joneckis, Ph.D.*
*Center For Biologics Evaluation and Research*
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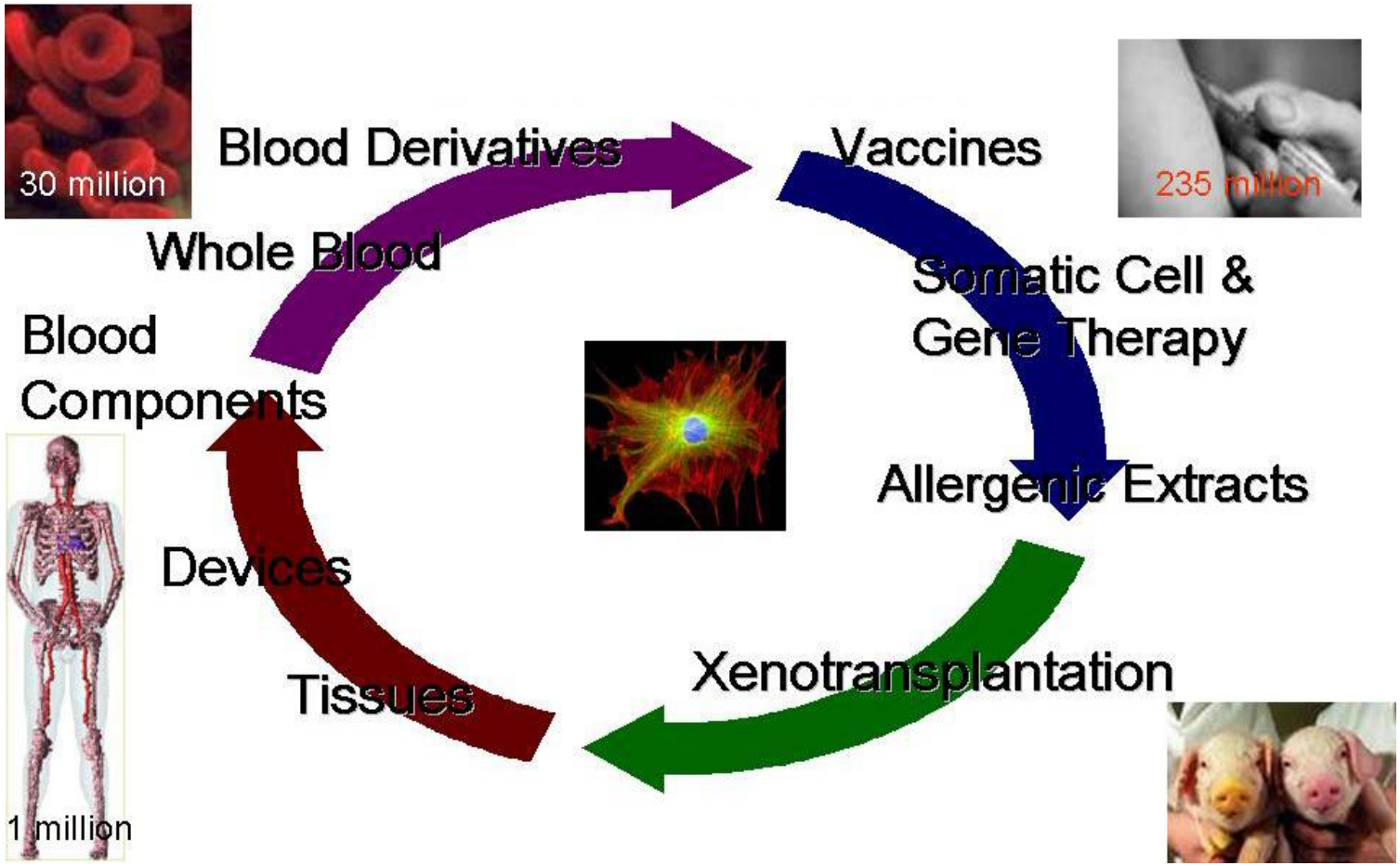
# Critical Products for Public Health, National Preparedness & 21st Century Medicine



- ***Change and excitement***
- ***Some major directions/thoughts***
- ***Strive to envision and seek opportunities – not fight them***
- ***Though much is possible, nothing is simple…yet***
- ***Enabling – collaboratively and globally – early and throughout development and manufacturing***
- ***Common goals – improve US and global health***

# Change and Excitement – Just a Few Examples

- Targeted and Personalized Medicine
- Repair or replace, not just treat - stem cells, gene therapy, tissue engineering
- Prevention, primary and secondary, including cancer
- Global and Public Health – increased needs and valuation
- Large Databases for Safety and Utility

# 1- Hit The Target

# Right Target in Right Person – Biomarkers – Critical Path

- Biomarkers can help identify promising (or risky) pathways, leads, responses, dosing etc.
- Goal – more effective/safer therapy, more efficient and less costly development
- *What's not simple*
  - Most biomarkers not surrogates – but still can be useful – right patient/right drug
  - Business models, costs
  - Pathway targets/actions may also be good
    - There is probably some reason that you name it (gene, protein, polymorphism) is there, and it is possible that even the most targeted therapy will mess something up
      - » Examples – TNF and infection, cox-2

# Resolutions

- FDA promoting biomarker research, validation
- Biomarker Consortium - FNIH-NIH-FDA-Academia-Industry collaboration
- OBQI - FDA/NIH/NCI/CMS collaboration
- Pharmacogenomic safety
  - *CBER biologics genomics initiative*
- Pandemic, anthrax correlates
- Critical Path Research (CBER – biomarkers on stem cells, cell substrate quality, vaccine, adjuvant and blood product efficacy and toxicity)

# Role of Science and Critical Path

- **CBER reviewers and research-reviewers identify solutions to product development challenges**
  - expert in biological product evaluation AND standard scientific disciplines
  - " Big Picture" - rapidly identify successes, failures, and missed opportunities across whole classes of exciting and innovative products
  - work for the American Public w/o conflicts and play a convening and coordinating role for scientific needs across sponsors
  - collaborative & Leveraging: internal and external resources
  - focus is unique: research managed to identify solutions to product development challenges
- Creating efficient, high quality regulatory pathways where there are none
- Applying 21st Century science to improve efficiency and predictability of established regulatory pathways

# FY08 Research Priorities - 1*

- Improve or develop new methods to measure and augment biological product **safety and efficacy.**
- Evaluate, develop, integrate **novel scientific technologies** to improve biologics product regulatory pathways, availability, quality.
- Facilitate the development of new biological products for **high priority public health threats**, including pandemic influenza, emerging infectious diseases, and agents of bioterrorism.

**Developed by CBER's Research Leadership Council*

# FY08 Research Priorities - 2

- Improve clinical trial design and evaluation, including **adaptive design** approaches
- Develop formal **risk management and risk assessment** approaches
- Enhance **safety surveillance** by developing improved analytical tools and accessing large databases (CDC, Medicare, etc)

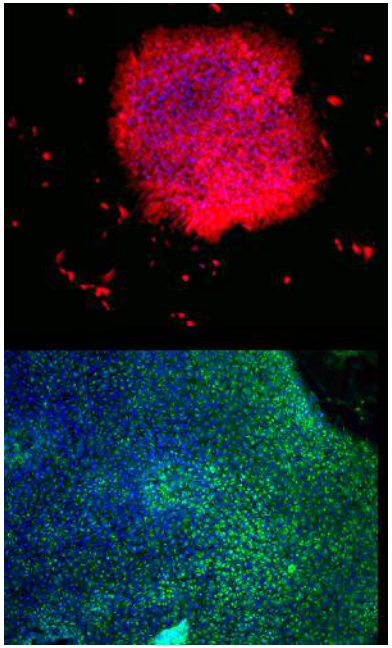
# Biomarkers - Genomics/Microarray: Application to Cellular & GeneTherapy

- Ability to assess quality of cell substrates
  - Identification of genes signatures as biomarkers for quality of cell products (e.g., confluence status, comparabilty)
- Biomarkers for biological product characterization ( purity, identity, potency)
  - rapid detection and identification of viral and bacterial pathogens
- Identification of unique product characteristics linking to clinical outcome - good or bad

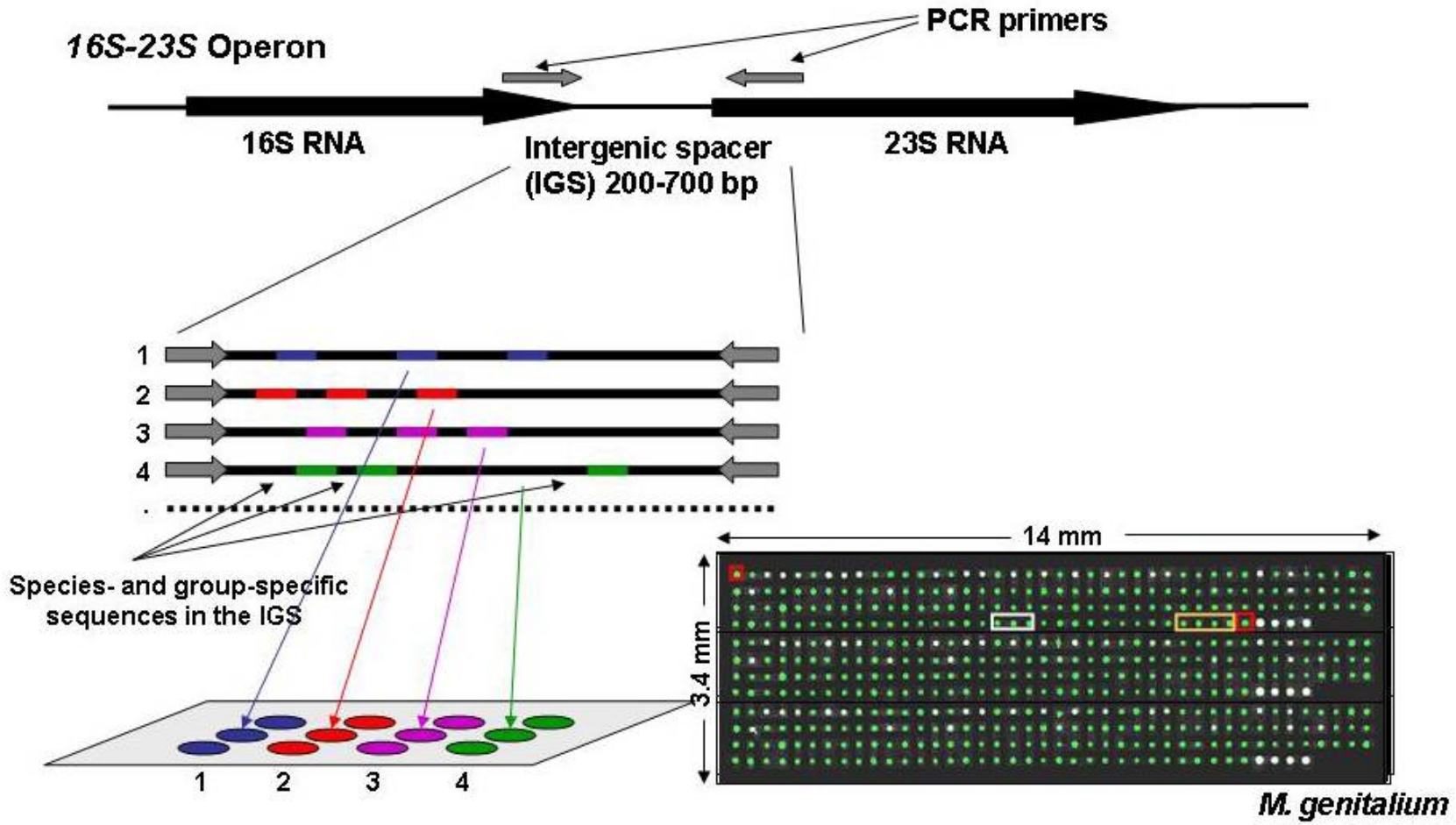
# Characterization of Stem Cell Therapies by Genomics/Microarray

In collaboration with NIH, Academia and Industry, CBER scientists developed a method and identified gene biomarkers expressed in several stem cell lines

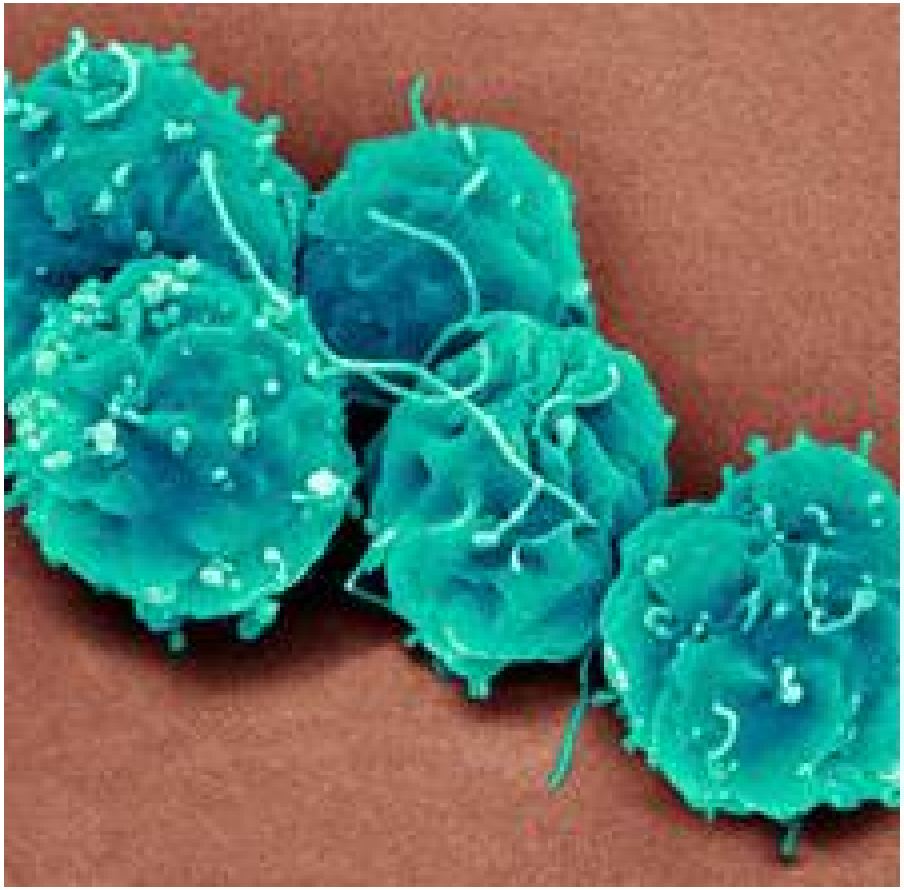
Ongoing communications with stakeholders to develop standards to compare results across different platforms and across different clinical sites



# Genomics/Microarray: Application to Mycoplasma Detection

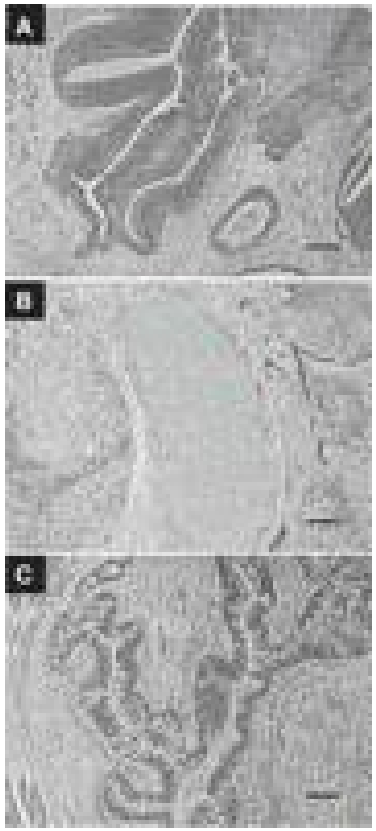


# 2 - Repair/replace! - New Sources of Stem Cells



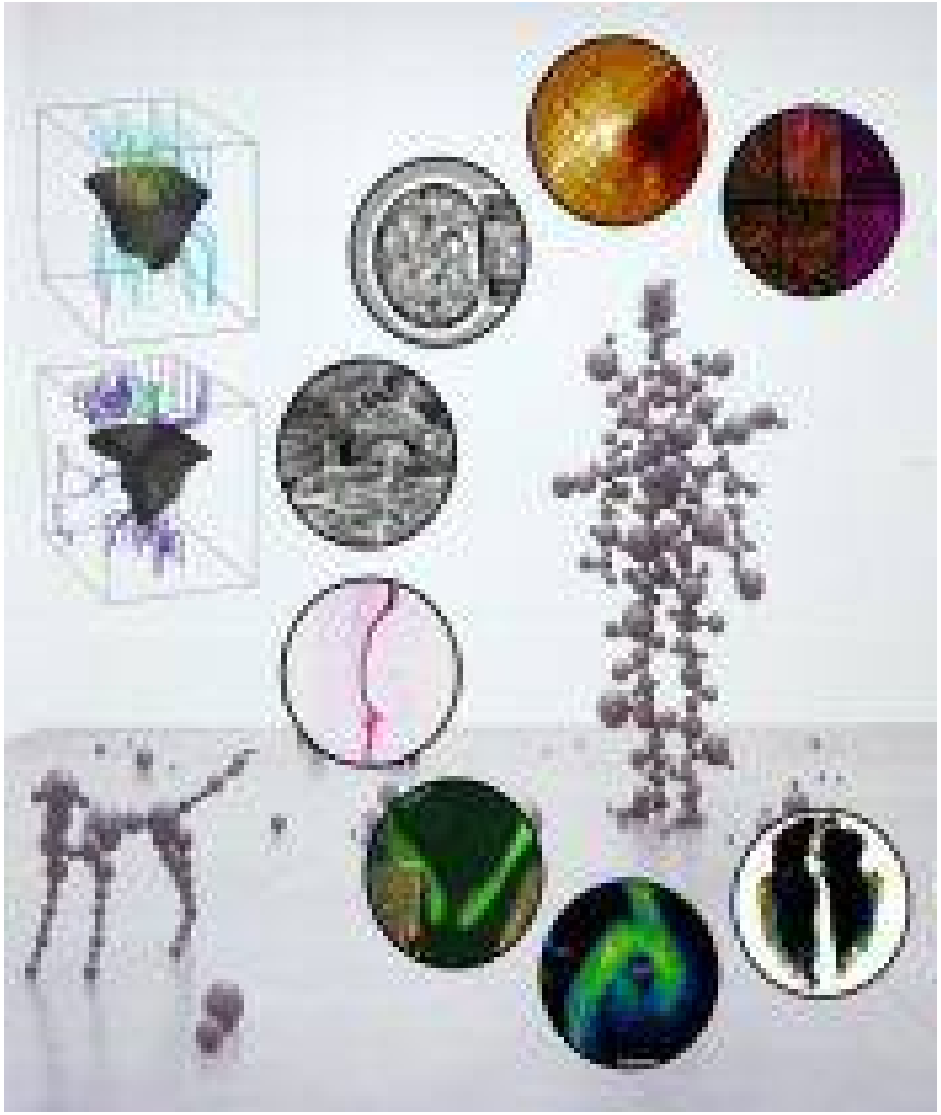
*Development of Human cloned Blastocysts Following Somatic Cell Nuclear Transfer (SCNT) with Adult Fibroblasts – French et al, Stem Cells, 2008*

# Or…Reprogram

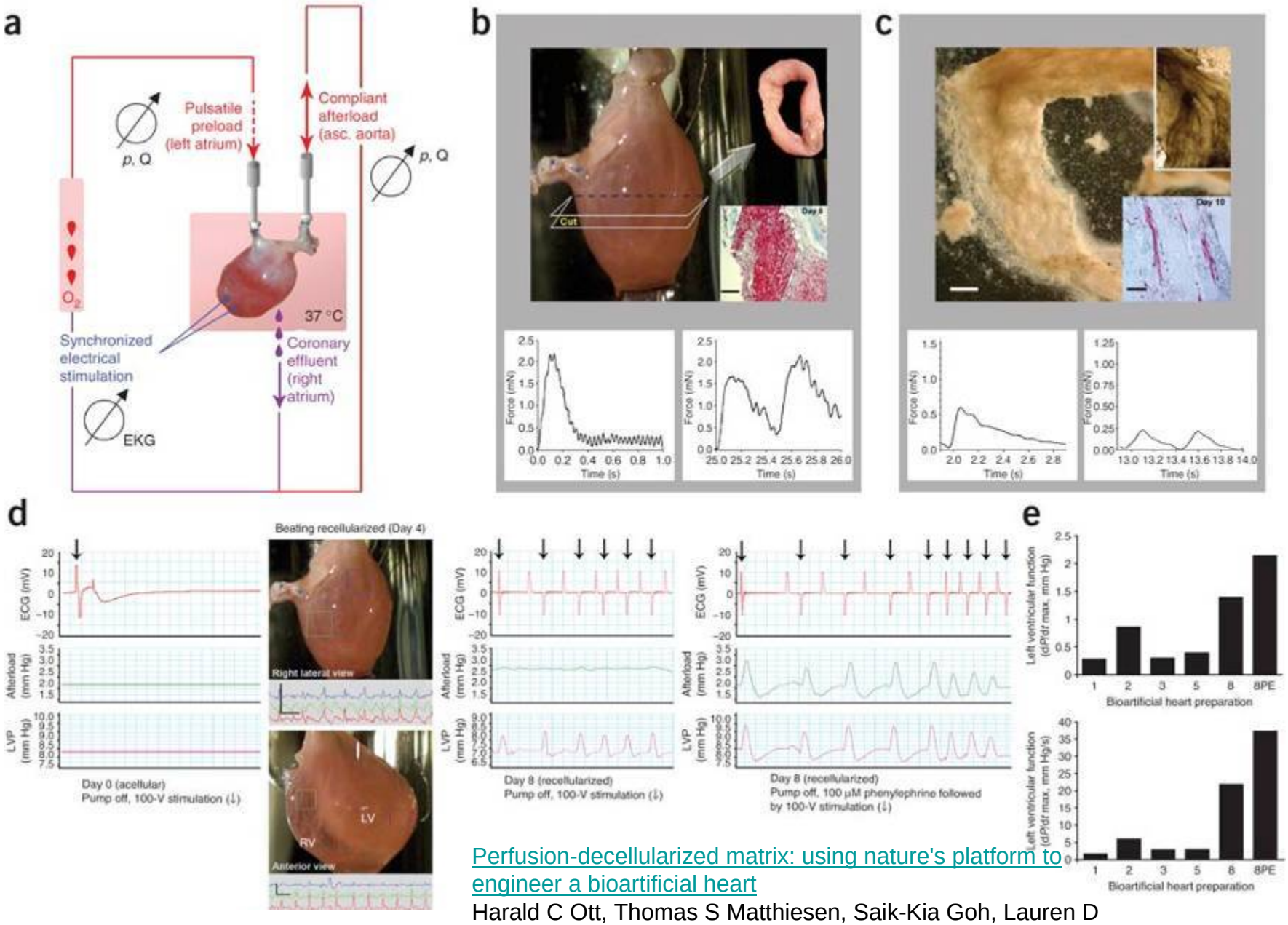



**Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells** Junying Yu, Maxim A. Vodyanik, Kim Smuga-Otto, Jessica Antosiewicz-Bourget, Jennifer L. Frane, Shulan Tian, Jeff Nie, Gudrun A. Jonsdottir, Victor Ruotti, Ron Stewart, Igor I. Slukvin, and James A. Thomson *Science* December 2007

# or…Remake the Target – Bioengineered Heart Valve



*OR A NEW HEART???*




[Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart]

Harald C Ott, Thomas S Matthiesen, Saik-Kia Goh, Lauren D Black, Stefan M Kren, Theoden I Netoff & Doris A Taylor

***Nature Medicine*** 13 January 2008

# *What's Not Simple?*

- Fate/oncogenesis of genes/cells/tissues
- Differentiation/functionality/regulation
- Host environmental effects on new cells/tissues, functionality, survival
- Boundaries, ethics, unforeseen risks?
- Resolutions:
  - proactive workshops, AC's to define issues/pathways, study designs etc.
    - examples – cell scaffolding, islet, cartilage, cardiac cell Rx, MATES, discussion of ESC science issues
  - Collaborative CP science – e.g. NTP study

# Enabling New Technologies: Approaches and Resolutions

- We will continue to enable and develop our:
  - Science base: nurture, sustain, collaborate
  - Multidisciplinary & Integrated review & inspection teams
  - Life cycle approach – multidisciplinary safety teams, risk assessment/risk based approaches in manufacturing, compliance and for regulatory decisions
  - Early and continued interactions with sponsors: include manufacturing and product characterization
  - Interaction with 3rd party standards organisations
  - Open to new approaches, tools, your help!

# Participation in Standards Development Organizations

- FDA Standards Policy
- In 2007
  - ~100 staff participated in ~75 stds development activities with ~30 organisations in all product areas
- Organizations include:
  - Accredited voluntary consensus standards organizations (e.g., ASTM, ISO, HL-7)
  - Industry, Trade Groups (e.g., ISCT, AABB, AATB )
  - International (e.g., ICH, GHTF, WHO/ECBS, PAHO, NIBSC, PEI, TGA)
- ASTM Subcommittee on Cell Signaling (F04.46)
  - Accurate and quantitative measurements of cell signaling biomarkers, aided by reference materials and standards
  - Global impact on scientific understanding,  R&D, QA/ QC

# FDAs Bioinformatics

- Centralization of information management and many information systems across FDA
- Electronic environment – advantages & challenges
- Sensitivities – e.g., transition time, small entities, participation of users
- Standards development crucial– ICH, HL-7
- Ensuring capability for 21st technologies –
  - Designing for scientific computing

# 3 - Prevent or Intervene Early

- Classic vaccine strategy
  - Revolutions – prevention of cervical, hepatocellular cancers
- Increased interest in early use of therapeutics
- *What's not simple?*
  - Scientific challenges (e.g. malaria, TB, cancer immunology)
  - Duration and cost of large, prolonged clinical trials, other market issues
  - Potential risks to healthy
- Resolutions: cancer vaccine workshops, adjuvant science, new biomarkers, initiatives for prevention

# 4 - Globalization and Public Health -Needs and Opportunities

- Humanitarian needs and value
- Disease threats global, no boundaries
  - Pandemic flu, HIV, malaria, TB (including drug resistance) – I'd get a safe TB vaccine
  - And don't forget - diseases of 'progress' – emerging threats as nations develop
- Manufacturing, knowledge *and regulation* are global
- *Needs, markets and opportunities are global*

# *What's Not Simple*

- Markets – uncertain or 'insufficient'
- Examples in US and globally
  - Uncertainty – emerging diseases, bioterrorism
  - Insufficient – segmented - blood diagnostics, antibiotics especially for resistant organisms
  - Value to public health and preparedness not directly economically linked – incentives/push/pull
  - But recent successes with vaccine industry
- Delivery systems and sustainability
- Resolutions: Intense FDA/CBER input and support for BioShield/BARDA and influenza projects, other priority public health projects (e.g. WNV) – global leadership, information sharing, quality, scientific and regulatory collaboration and convergence
- Challenges - with increasing collaboration, increasing demands upon CBER resources

# Resolutions - Global Harmonization & Collaboration: Examples

- Emerging Threat Preparedness - Leadership FDA/WHO/Health Canada Pandemic Regulators
- WHO and WHO Collaborating Center, PAHO
  - ECBS, SAGE, GCVS, influenza, xeno and gene therapy
  - Regulatory capacity building/assistance
- Blood: GCBS leadership, WHO “Circle of Regulators”
- ICH (including GT) , PIC-S, ICDRA
- Information sharing + support global product development plans/coordinated regulation
  - EMEA, HC, TGA, PEI, others
- CBER Global Vaccine Initiative
  - Consultation, standards, CP science, reg. capacity
  - MVI, Gates, TB, PATH, meningitis, etc.

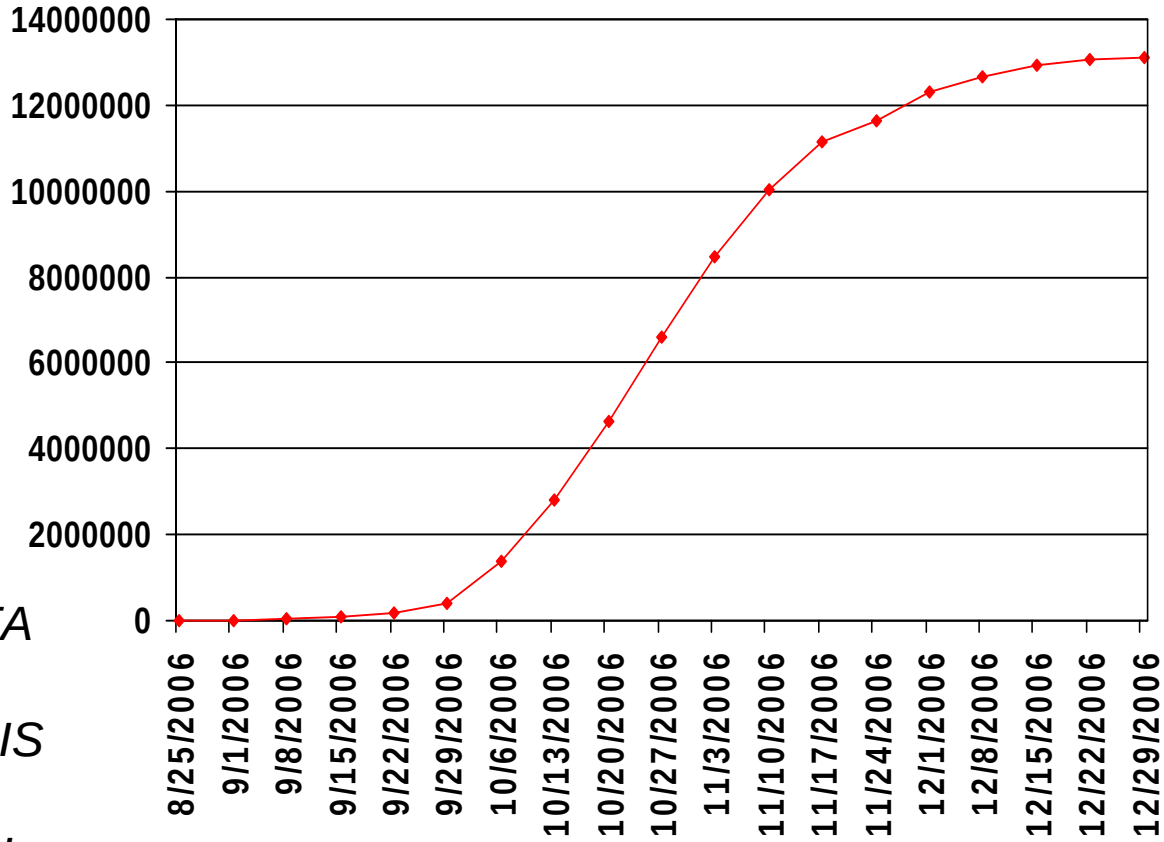
# Safety and Value: New Approaches

- *Safety* is not absolute: need for transparency and better, early communication, “risk literacy”
  - Benefits & risks both considered
  - Patient & consumer trust/confidence
- CBER multidisciplinary teams
  - Increased use of large datasets
  - Consistent with IOM, FDAAA
- *Value* of improved safety approaches will be rewarded
  - Prevention, improved therapies, not marginal gains
  - Challenges in measurement:
    - Should consider not just value to health systems but also
    - To individual and…..*to public welfare, society and health*
    - Large datasets can help with some of this, as well

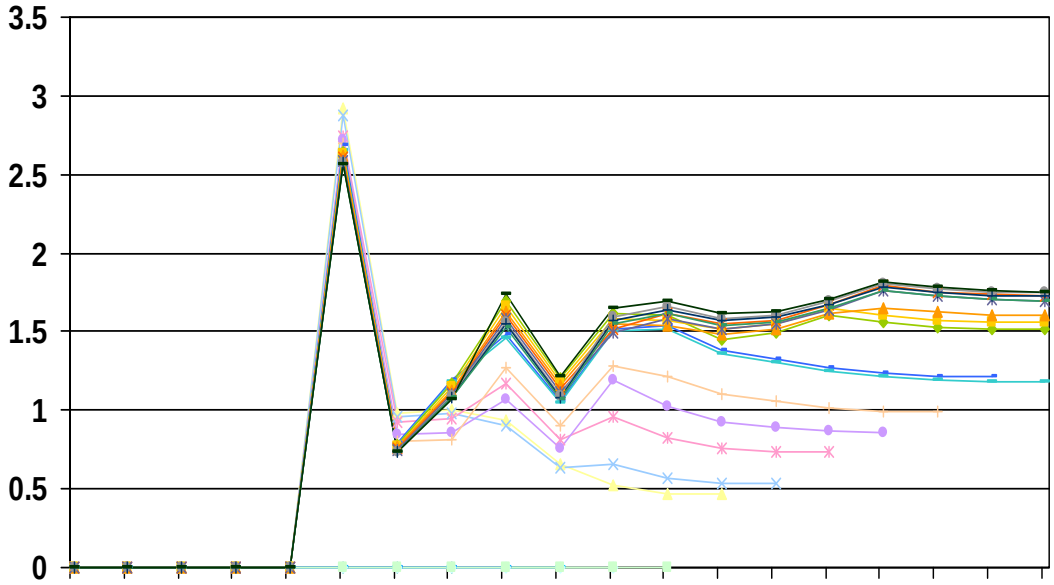
# CBER's Safety Teams

- **Tissue (2004), Blood (2006), Vaccine (2007)**
  - **Multidisciplinary and collaborative – each includes product, manufacturing, safety, clinical, compliance, and communication experts – all share common data**
  - **Meet at least monthly, IOD participates, entire team also meets quarterly with Center Director/Deputy – can be immediately convened in any emerging/urgent situation**
  - **Structured interfaces with ORA, CDC, others as appropriate**
- **Goals/accomplishments:**
  - **Proactively and rapidly identify and address significant ongoing and emergent safety issues**
  - **Serve as focus for developing and implementing longer term priorities, innovative practices and collaborations, and quality improvement**
  - **Enhance internal and external communication and collaboration (including public, rest of FDA, CDC, HRSA, international/WHO etc.)**

*FDA/CBER DATA USING CMS – RAPID ANALYSIS OF GBS AND SEASONAL FLU VACCINE - 2006*




DOSES




GBS rates

# *What's Not Simple?*

- Quality and format of data from health systems – variable at best
- Analytic tools and approaches not yet up to data quantity and variability
  - Clusters – false positives
  - Lack of background rates
  - Confounding is abounding
- Communication of risk and of uncertainty
- Resolutions – partnerships e.g. FDA/RUF
  - CBER: Data Analytic Unit, CDC VSD, CMS, VA, DMSS, enhanced early communication
- HHS Sentenial Initiatives

# Knowledge, Risk, & Oversight

- Increasing complexity results in increasing unknowns – applicable in many areas
- **Effective Understanding for Appropriate Regulation**
  - Scientific foundation will need to be established and effectively communicated
  - Risk will have to be appropriately assessed, managed and communicated
  - Product Quality & Safety will need appropriate oversight
- Early and continued interactions with sponsors/ manufacturers and integration of review and CGMP issues has proven beneficial, particularly when **complex and/or innovative technologies** are proposed in facilitating product development and improvement

# “Risk Literacy”

- Risk literacy – difficult and non-intuitive to understand risk and causal association statistically vs. individually
- There are risks in conveying uncertainties, including potential decreased use of safe product, public health consequence if vaccine
- Major behavioral science, educational system and risk communication science needs (FDA AC)

# 2008 CBER Priorities

- ***Pandemic/emerging threat preparedness***
- ***Enhance product safety and confidence***
  - ***Interdisciplinary safety teams, FDAAA, new sources and approaches to data, better communication***
- ***Improve manufacturing and product quality***
  - ***Risk based and preventive compliance, product testing, assay, standards development, CMC QS***
- ***Innovative, safe, effective products to patients***
  - ***Critical Path, Tissue Engineering Team, Blood Cell Preservation, Genomics, Research Management***
- ***Strengthen human and organizational resources***
  - ***Recruitment, succession planning, continual process improvement system, staff competencies &training***
- ***Global public health and globalization***
  - ***Products for public health needs, Global Vaccine Initiative, product and supply chain quality/availability, harmonization and collaboration***

# Thank you!

- ***We are poised for and embrace many revolutions and changes***
- ***Value will be rewarded and includes, but is not limited to, safety, effectiveness and quality***
- ***Collaboration and best science essential – work together ahead of curve***
- ***Challenge us and yourselves!***
- ***We will work with stakeholders to go from "good to great"***
- ***Individual, global and public health can and must benefit***

***www.fda.gov/cber***

**Contact** OCTMA@CBER.FDA.GOV 301-827-1800

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