*Production Assistance for Cellular Therapies*

**Educational Web Seminar**

"Challenges and Problem-Solving in Cell Therapy Product Development"

**Thursday, September 25, 2014**

12:00 PM – 1:30 PM ET

---

**Speakers**

**Ann Leen, PhD**
Associate Professor, Department of Pediatrics
Center for Cell and Gene Therapy
Baylor College of Medicine

**Claudio Brunstein, MD, PhD**
Associate Professor
University of Minnesota

**Derek Hei, PhD**
Director
Waisman Biomanufacturing
University of Wisconsin-Madison

Today’s web seminar presentation slides are available publicly at [www.pactgroup.net](http://www.pactgroup.net)

---

**Faculty Disclosure**

The Accreditation Council for Continuing Medical Education (ACCME) is the governing body that accredits AABB to provide continuing medical education credits for physicians. In accordance with the ACCME Standards for Commercial Support, AABB implemented mechanisms, prior to the planning and implementation of this CME/CE activity, to identify and resolve conflicts of interest for all individuals in a position to control content of this CME/CE activity.

---

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Disclosure</th>
<th>Nature of Relationship</th>
<th>Membership-Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Leen, PhD</td>
<td>None</td>
<td>Speaker</td>
<td>N/A</td>
</tr>
<tr>
<td>Claudio Brunstein, MD, PhD</td>
<td>None</td>
<td>Speaker</td>
<td>N/A</td>
</tr>
<tr>
<td>David Lyons</td>
<td>None</td>
<td>Planning Committee PACT Staff</td>
<td>N/A</td>
</tr>
<tr>
<td>Matt Brine</td>
<td>None</td>
<td>Planning Committee PACT Staff</td>
<td>N/A</td>
</tr>
<tr>
<td>Laura Brunswick</td>
<td>None</td>
<td>Planning Committee PACT Staff</td>
<td>N/A</td>
</tr>
<tr>
<td>Holly Baughman</td>
<td>None</td>
<td>Planning Committee PACT Staff</td>
<td>N/A</td>
</tr>
<tr>
<td>Sharon McFadden</td>
<td>None</td>
<td>AABB Staff</td>
<td>N/A</td>
</tr>
<tr>
<td>Kari Elder</td>
<td>None</td>
<td>AABB Staff</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Description

In this web seminar, speakers will discuss manufacturing challenges faced in various points along the development pathway of a cellular therapy clinical product. Challenges will be highlighted in both the pre-clinical aspects of process development and in the evolution of preparing a product for use in clinical trials. Speakers will share challenges and successes encountered with products they were involved with developing.

Disclaimer

Inclusion of companies in this web seminar does not indicate endorsement by either the speakers or PACT, nor is it meant to imply that their products or services are superior to those of other companies.

Virus-specific T cells post-transplant
Viral infections post-transplant

• 40% deaths after alternative donor transplant due to viral infections

• Antiviral drugs
  – Costly
  – Significant side effects
  – Often ineffective

• Alternative - Adoptive T cell transfer

Adoptive T cell transfer

1. Blood draw
2. SCT donor
3. Blood draw
4. SCT donor
5. T cells

Adoptive T cell transfer
Immunotherapy for viral infections

- Virus-specific T cells as prophylaxis and treatment
  - EBV
  - Adv/EBV (bivirus)
  - Adv/EBV/CMV (trivirus)
**Trivirus VST generation**

PBMC → EBV LCL → Ad5f35pp65 transduced EBV LCL

**Clinical Outcome Summary – Donor-specific setting**

- *In vitro* expanded donor-derived virus-specific T cells targeting Adv, EBV, CMV
  - Safe
  - Reconstituted antiviral immunity for EBV, CMV and Adv
  - Effective in clearing disease
  - Considerable expansion in vivo

Leen et al, Nat Med. 2006
Leen et al, Blood. 2009

**Problems**

SCT donor → Blood draw → T cells → Antigen Specificity → T-cell product generation → Infusion → SCT recipient

1. T-cell product generation
2. Blood draw
3. T cells
4. Infusion
Problems

Addressing Problem #1

Manufacturing limitations

- Reduce cost
- Reduce complexity
Reduce cost: Replace virus/vector with peptides

EBV LCL
Ad5f35pp65

Overlap peptide libraries
Reduce cost:
Replace virus/vector with peptides

EBV LCL → Overlapping peptide libraries
Ad5f35pp65

Target antigens
- EBV- EBNA1, LMP2, BZLF1
- CMV- IE1, pp65
- Adv- Hexon, Penton
- BK- Large T, VP1
- HHV6- U11, U14, U90

Addressing Problem #2

Manufacturing limitations
- Reduce cost – peptides
- Reduce complexity

Complexity

<table>
<thead>
<tr>
<th>Day</th>
<th>Event</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>CTL initiation</td>
<td>2.4 x 10⁷</td>
</tr>
<tr>
<td>9</td>
<td>restim</td>
<td>2 x 10⁷</td>
</tr>
<tr>
<td>12</td>
<td>IL2 feed</td>
<td>6 x 10²</td>
</tr>
<tr>
<td>16 – harvest and reseed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>split + IL2 feed</td>
<td>1.2 x 10³</td>
</tr>
<tr>
<td>23</td>
<td>harvest and reseed</td>
<td>3.6 x 10⁴</td>
</tr>
<tr>
<td>27</td>
<td>split + IL2 feed</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>harvest/freeze</td>
<td></td>
</tr>
</tbody>
</table>
Reduce complexity:
Simplifying Production using G-Rex devices

- Gas permeable membrane allows CO₂/O₂ exchange
- Supports cell growth with large volumes of media
- Reduces feeding frequency and manipulation
- No rocking or stirring

Superior expansion of VSTs in G-Rex vs 24w plate

Production time halved

Bajgain et al, Mol Therapy Methods and Clinical Development, 2014

Solutions

Manufacturing limitations

- Reduce cost – peptides ✓
- Reduce complexity – G-Rex ✓
Solutions

**Manufacturing limitations**

- Reduce cost – peptides √
- Reduce complexity – G-Rex √

Will they work?

Rapidly generated T cell lines targeting 5 viruses (ARMS)

Patients infused

- 11 pts infused on study:
  - 4 pts: 5x10^6/m^2 (DL1)
  - 4 pts: 1x10^7/m^2 (DL2)
  - 3 pts: 2x10^7/m^2 (DL3)
- No dose limiting toxicity
  - 1 Grade II skin GvHD (improved with topical steroids)
- 3 infused prophylactically
  - All remained infection-free for at least 3 months
- 8 pts had active infections
### 8 pts treated for infections

<table>
<thead>
<tr>
<th>Patient with</th>
<th>AdV</th>
<th>CMV</th>
<th>EBV</th>
<th>BKV</th>
<th>HHV6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 virus</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>2 viruses</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>3 viruses</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>4 viruses</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
8 pts treated for infections

<table>
<thead>
<tr>
<th>Patient with</th>
<th>AdV</th>
<th>CMV</th>
<th>EBV</th>
<th>BKV</th>
<th>HHV6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 virus</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>2 viruses</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 viruses</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 viruses</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Clinical response - Pt with EBV-PTLD

Clinical response - Pt with EBV-PTLD
Outcomes

- **Complete response:** (√)
  - viral load to the normal range
  - resolution of clinical signs/symptoms

- **Partial response:** (PR)
  - >50% reduction in viral load
### 94% Response Rate

<table>
<thead>
<tr>
<th>Patient with</th>
<th>Adv</th>
<th>CMV</th>
<th>EBV</th>
<th>BKV</th>
<th>HHV6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 virus</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>2 viruses</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3 viruses</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>4 viruses</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>PR</td>
<td>✓</td>
</tr>
</tbody>
</table>

### Old vs New

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Rapid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>Adv, EBV, CMV</td>
<td>Adv, EBV, CMV, BK, HHV6</td>
</tr>
<tr>
<td>Blood vol.</td>
<td>60ml</td>
<td>20ml</td>
</tr>
<tr>
<td>Cells</td>
<td>LCL, CTL</td>
<td>CTL</td>
</tr>
<tr>
<td>Time</td>
<td>56-84 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Cell #</td>
<td>200x10⁶</td>
<td>390x10⁶</td>
</tr>
</tbody>
</table>

Adoptive T cell transfer

1. Blood draw
2. Antigen Specificity
3. T-cell product generation
4. Infusion

Adoptive T cell transfer

1. Blood draw
2. Antigen Specificity
3. T-cell product generation
4. Infusion

Adoptive T cell transfer

1. Blood draw
2. Antigen Specificity
3. T-cell product generation
4. Infusion
Addressing Problem #2

- Investigate the therapeutic benefit of 3rd party T cells

Assess whether banked virus-specific T cells (VSTs) produced clinical benefit in partially HLA-matched 3rd party recipients

3rd party T cells - “Off the shelf”

Blood donor

A1, A24; B8, 18; DR1, 15
3rd party T cells - “Off the shelf”

Blood donor → Trivirus VST

EBV activity – B8, DR1
CMV activity – A24
A1, A24; B8, 18; DR1, 15

Blood donor → Trivirus VST

EBV activity – B8, DR1
CMV activity – A24
A1, A24; B8, 18; DR1, 15

Blood donor → Trivirus VST

EBV activity – B8, DR1
CMV activity – A24
A1, A24; B8, 18; DR1, 15

Blood donor → Trivirus VST

EBV activity – B8, DR1
CMV activity – A24
A1, A24; B8, 18; DR1, 15
Clinical protocol

• Treatment of refractory EBV, CMV, or AdV
• Patients receive $2 \times 10^7$ VSTs/m$^2$
• If partial response may receive additional doses at 2+ weekly intervals

Patients Treated on Study

• 50 patients infused – 45 evaluable
  – 19 received VSTs for CMV
  – 17 received VSTs for Adv
  – 9 received VSTs for EBV

74% Overall Response Rate

74% - CMV
67% - EBV
79% - Adv

CR/PR based on infection

Days post-VST

PACT Project 00014/64/88

Leen et al Blood 2013
**Where we started**

- **Donor-derived VSTs**
  - Safe
  - Effective
  - Costly
  - Complex
  - Time consuming
  - Biohazards
  - Limited breadth

**Where we are now**

- **Donor-derived VSTs**
  - Safe
  - Effective
  - Costly
  - Complex
  - Time consuming
  - Biohazards
  - Limited breadth

- **3rd party VSTs**
  - Safe
  - Effective
  - Rapid
  - Simple
  - Scalable
  - Broad spectrum

**Where we are now**

- **Peptides**
  - G-Rex
Thanks!

Funding: NO Program Project Grant, NHLBI Somatic Cell Therapy Center, Lymphoma SPORE, Leukemia and Lymphoma Society Specialized Center of Research, Doris Duke Distinguished Clinical Scientist Award, PACT

Question

What are the major obstacle(s) limiting the commercialization of cell therapy products?

(a) Lack of IP/patents
(b) Lack of interest from industry partners/investors
(c) Complexity of preparing personalized therapies
(d) Manufacturing limitations (e.g., scale up issues)
(e) Other
Dr. Claudio Brunstein’s presentation will not be publicly available.

Considerations for cGMP Production of Patient-Specific Cell Therapeutics – A PACT Case Study

Derek J. Hei, Ph.D.
Director, Waisman Biomanufacturing
University of Wisconsin

September 25, 2014

Challenges for Patient-Specific Cell Therapeutics

- Autologous or allogeneic cell therapeutics with patient-specific donor (not “off-the-shelf” therapy)
- Manufacturing cost – cost of goods, Quality Control testing, cleanroom time
- Scale-up vs. scale-out
- Manufacturing logistics – timing, QC testing
- Patient/donor variability and impact on manufacturing process
- In some cases repeat dosing is highly desirable – increased cost
**PACT Project Overview**

- **Proposed clinical trial** -
  - PI – Dr. Ken DeSantes, UW Carbone Cancer Center
  - Neuroblastoma – relapsed/refractory in pediatric patients
  - Haploidentical NK cells from KIR-mismatched parent
  - hu14.18-IL2 immunocytokine - humanized anti-GD2 mAb linked to IL-2 (Osenga et al., Clin Cancer Res 2006; 12(8):1750)
  - Goal – multiple doses, preferably from single manufacturing process

- **Initial proposed target dose** –
  - 1E6 NK cells/kg escalate to 1E8 NK cells/kg
  - Potential for up to 4 doses per patient
  - Requires up to 2.8E10 CD56+ cells for 70 kg patient
  - T cell reduction is critical < 5E4 CD3+ cells/kg

- Ex-vivo expansion of NK cells using K562-mbIL15-41BBL feeder cells (Campana et al., Cancer Res 2006; 66(9):4010-7)

**Natural Killer Cells**

- Cytotoxic lymphocytes that are active against cells infected with viruses and intracellular pathogens
- NK cell killing determined by inhibitory and stimulatory ligands expressed by malignant and infected cells including lack of MHC expression
- Currently under evaluation as therapy against a wide range of cancers including AML, ALL, NSCLC, multiple myeloma
- CD56+ CD3- cells comprising 5-20% of circulating monocytes
- Potential sources –
  - PBMCs from Apheresis with immunomagnetic selection (CD56+ / CD3-), IL-2/IL-15 activation
  - Ex vivo expansion using stimulatory "feeder" cells (K562-mbIL15-41BBL)

**NK Cell Manufacturing Process**

1. **Donor Apheresis**
2. **K562 Irradiation**
3. **PBMC Isolation**
4. **CD3 Depletion (CliniMACS)**
5. **K562 Irradiation**
6. **Bioreactor Expansion (11 days)**
7. **QC Testing/Release**

- Z1-23 day manufacturing process
- Quality Control testing logistics for K562-IRR intermediate
- Goal to produce 3-4 doses/patient
Potential Improvements to NK Cell Manufacturing Process

- K562-mbIL15-41BBL production and testing
  - Ability to produce irradiated, cryopreserved cells that retain function in NK cell expansion?
  - Ability to scale-up K562-IRR production

- NK cell expansion -
  - Ability to produce multiple doses in a bioreactor?
  - Ability to cryopreserve NK cell product and maintain function

K562 Expansion and Irradiation

- Processing logistics —
  - Require 10:1 K562:CD56+ cells for NK expansion – >2E9 K562s/run
  - Expansion time for K562 cell line is approximately 2 weeks
  - QC testing for release of K562-IRR cells – time and money

- K562-mbIL15-41BBL cell banks
  - Master Cell Bank provided by Baylor PACT facility
  - Produced Working Cell Bank under cGMP
  - Adventitious agent testing

- K562-IRR production process
  - Expand K562 WCB in suspension culture – spinner flasks, bioreactor
  - Harvest and irradiate (100 Gy)
  - Cryopreservation – demonstrated acceptable recovery and function of cryopreserved K562-IRR for NK cell expansion
  - Final dose – 1E7 cells/mL, 200 mL RPMI-1640 + 20% FBS + 10% DMSO
  - Is the process scalable?
K562-mbIL15-41BBL Suspension Culture

- Maximum density for late-logarithmic growth = 1.5E6/mL
- Expansion from spinner flasks to 50L Single-Use Bioreactor (SUB)
- Projected yield = 15-20 bags at 2E9 K562 cells/bag
- Cleanroom time savings = 25-35 weeks/year

K562-mbIL15-41BBL Harvest and Recovery

- Hollow fiber TFF system (0.65 μm)
- Sterile, completely closed single-use system
- Three pump system – fed batch with permeate flow control
- 10X volume reduction, < 1 hour, > 95% recovery

K562 Expansion and Irradiation

- Advantages of irradiated/cryopreserved K562 cells
  - Cells can be thawed for immediate expansion of NK cells
  - Decreased cleanroom time and overall process cost – 25-35 weeks/yr
  - Decreased QC testing requirements due to increased batch size
  - Improved consistency in K562 cells

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Method</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Endotoxin</td>
<td>Kinetic chromogenic LAL</td>
<td>&lt; 5 EU/mL</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>PTC method (direct and indirect culture)</td>
<td>No contamination detected</td>
</tr>
<tr>
<td>Sterility Test</td>
<td>21 CFR 10.32</td>
<td>No contamination detected</td>
</tr>
<tr>
<td>Post-thaw viable cell recovery</td>
<td>Trypan Blue</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Residual unirradiated K562 cells</td>
<td>Cell Proliferation assay</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td></td>
<td>(Beckman Cell Proliferation assay)</td>
<td></td>
</tr>
</tbody>
</table>

K562-mbIL15-41BBL Expansion and Recovery

- Hollow fiber TFF system (0.65 μm)
- Sterile, completely closed single-use system
- Three pump system – fed batch with permeate flow control
- 10X volume reduction, < 1 hour, > 95% recovery
Overview of NK Cell Manufacturing Process

- 11 day manufacturing process
- Cryopreserved K562-IRR intermediate with full QC testing
- Goal to produce 3-4 doses/patient

Potential Improvements to NK Cell Manufacturing Process

- K562-mbL15-41BBL production and testing
  - Ability to produce irradiated, cryopreserved cells that retain function in NK cell expansion?
  - Ability to scale-up K562-IRR production

- NK cell expansion -
  - Ability to produce multiple doses in a bioreactor?
  - Ability to cryopreserve NK cell product and maintain function
**NK Cell Expansion Process**

- **Apheresis unit** – 4-8E8 PBMCs, 5-20% NK cells
- **NK expansion in Wave 20 Bioreactor**
  - 10:1 K562:NK cells (irradiated, cryopreserved)
  - XVivo 10/AB serum, 100 U/mL hIL-2
  - 60-150X expansion over 11 days
- **NK harvest** – Cobe, TFF
- **CD3 depletion** - CliniMACS
- **Release first dose as fresh NK cells**
- **Cryopreserve additional 3 doses of NK cells**
  - Goal: 1E6 NK/kg escalate to 1E8/kg, up to 4 doses per patient
  - 2E7 cells/mL, 100-350 mL dose
- **Can NK cells be cryopreserved and maintain viability and activity?**

---

**Cytotoxicity is Maintained in Expanded NK Cells**

*Maximum Lysis based on 51Cr release using Cetrimide Detergent*

Kimberly A. McDowell MD, PhD
Department of Pediatrics
Division of Hematology, Oncology and Bone Marrow Transplant

---

**Cryopreservation of Expanded NK Cells**

- NK cells cryopreserved following expansion in Wave bioreactor at 2.0x10^7 cells/mL
- 1 fresh dose, 3 cryopreserved doses
- Two cryopreservation media evaluated in initial PD studies
  - Initial viable cell recovery >80%, delayed onset cell death
  - Plasmalyte + 5% HSA + 5% DMSO 18-30% recovery
  - BioLife Solutions Cryostor CS5 Medium 45-55% recovery
- **Process Qualification trials (N=3)**
  - 40% human AB serum, 50% Plasmalyte, 10% DMSO (Dean Lee, MDACC)
  - Viable NK recovery > 90% post thaw and wash
  - Cell washing process qualified
Neuroblastoma cell line
CHLA21
Melanoma cell line
M21

Cytotoxicity Testing of Cryopreserved NK Cells

Cytotoxicity of NK cell resistant cell lines
Melanoma cell line
M21
Neuroblastoma cell line

Cytotoxicity of NK cell sensitive cell line
CML cell line
K562

Ab = hu14.18K322A (100 ng/ml)
IL2 = Interleukin 2 (100 units/ml)
4 hour 51Cr assay

Process Qualification Trials
- Process Qualification trials – demonstrate process reproducibility and impact of donor variability
- NK cell expansion in Wave bioreactor
  - 1.3 – 6.0 E10 NK cells
  - 30-200 fold expansion
- ClinMACS CD3 depletion
  - < 0.1% residual T cells
  - > 87% CD56+ CD3- cells
- Thaw/wash qualification studies
  - Validate process – sterility, endotoxin, viable cell recovery
  - Stability study performed out to 6 months on frozen NK cells
- Donor variability – still a challenge
  - In-process testing to predict final process outcome
  - Process adjustments based on in-process tests?

Conclusions
- For autologous/patient-specific cell therapeutics it is critical to address manufacturing logistics, scale-out, and manufacturing cost issues early in development
- Donor/patient variability will continue to be a challenge – in-process testing and process adjustments are key in addressing this issue
- QC testing logistics on final fresh and thawed/washed product should be addressed along with shipping and post-thaw processing issues
Special Thanks To…

Waisman Biomanufacturing

Bryan Atkinson  Diana Drier  Ross Meyers  Carl Ross  Natalie Russell  Josh Sotos  Tim Sparks  Megan Stone  Kari Throston
Chris Bartley  Heather Dunn  Carl Ross  Natalie Russell  Josh Sotos  Tim Sparks  Megan Stone  Kari Throston
Jaime Bollon Michael Hainstock  Jen Jauquet  Tim Sparks  Janice Boyer  Bill Kreamer  Kari Throston  Diana Drier  Heather Dunn  Carl Ross  Natalie Russell  Josh Sotos  Tim Sparks  Megan Stone  Kari Throston
Neehar Bhatia  Rebecca Ertel  Heinemeyer  Diana Drier  Heather Dunn
Janice Boyer  Bill Kreamer  Kari Throston
Paula Brisco  Laurie Larson  Rebecca Ertel  Heinemeyer
Lisa Burdette  Connor Lyons  Diana Drier  Heather Dunn
Brian Dattilo  Eric Mauer  Tim Sparks

UW PACT Team

Peiman Hematti, Deb Bloom, Jaehyup Kim
Amish Raval, John Centanni, Eric Schmuck
Tim Hacker, Jill Koch
Marlowe Eldridge, Ruedi Braun

UW Carbone Cancer Center

Ken De Santes, MD
Paul Sondel, MD, PhD
Kim McDowell, MD, PhD

Q & A Session

“Challenges and Problem-Solving in Cell Therapy Product Development”

Speaker Contact Email

Ann Leen
amleen@txch.org

Claudio Brunstein
bruns072@umn.edu

Derek Hei
hei@waisman.wisc.edu
Web Seminar Presentation Slides

Today’s web seminar presentation slides and presentation slides from previous web seminars are available publicly at www.pactgroup.net

Select Education → PACT Web Seminars

---

CE Credit

The activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of AABB and PACT. AABB is accredited by the ACCME to provide continuing medical education for physicians (Provider number 0000381). AABB designates this educational activity for a maximum of 1.5 hours of Category 1 credit toward the AMA Physician Recognition Award. Each physician should claim those credits that he/she actually spent in the activity.

California Clinical Laboratory Personnel

AABB is approved by the California Board of Clinical Laboratory Personnel, Provider number 50-4261-1, as a provider of continuing education programs for California-licensed clinical laboratory personnel. AABB designates this educational activity for a maximum of 1.5 contact hours.

Florida Clinical Laboratory Personnel

AABB is approved by the Florida Board of Clinical Laboratory Personnel, Provider number 50-4261-1, as a provider of continuing education programs for Florida-licensed clinical laboratory personnel. AABB designates this educational activity for a maximum of 1.5 contact hours.

California Nurses

AABB is approved by the California Board of Registered Nursing, Provider Number 4341, as a provider of continuing nursing education programs. AABB designates this event for a maximum of 1.8 contact hours.

General Attendees

Administrators, nurses (other than California-licensed nurses), clinical laboratory personnel (other than California- and Florida-licensed personnel), and other health-care professionals may receive a certificate of attendance for participation in this event. This certificate verifies the attendance at the event.

---

Interested in obtaining CE credit for attending this web seminar?

Each attendee must:

Sign and fax roster to 240–306–2527

Complete the online survey

https://www.surveymonkey.com/s/pact_webinar_challenges_problem_solving_ct_pd

(Survey link above is embedded in the reminder email sent 09/24/14)

Note: Please complete within 48 hrs of the web seminar
**AABB Live Learning Center**

After the web seminar, attendees will receive an email from AABB regarding the CME/CE certificates for this event. The email will include instructions on how to print your CME/CE certificate for the web seminar.

To access the Live Learning Center, visit: www.aabb.org>Professional Development>Live Learning Center

Please note that attendees signing the sign-in sheet is AABB’s way of verifying attendance at the event.

---

**Thank you for attending!**

To register for updates on upcoming web seminars, workshops, and PACT attended meetings visit us on the web at: www.pactgroup.net