Maintaining Excellence in a High Volume Academic Cell Therapy Production Facility

Optimization of Space Utilization, Operations, Scheduling and Staffing

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The Clinical Cell and Vaccine Production Facility (CVPF)

The Clinical Cell and Vaccine Production Facility (CVPF) is a FACT accredited resource at the University of Pennsylvania in Philadelphia, PA, USA. CVPF has a 25 year record of novel and first-in-human cell and gene therapy clinical trials.

CVPF is integrated with research, process development and correlative studies laboratories, quality control, quality assurance, clinical operations and monitoring, apheresis facilities and infusion sites at Penn.

CVPF
Clinical Cell & Vaccine Production Facility
University of Pennsylvania

CVPF Mission

Enable bench-to-bedside translational research by transforming research insights into novel cellular therapies

Primary Operational Goals:

1. Increase Production Capacity
2. Increase Efficiency
3. Reduce Costs
4. Improve Staff Recruitment & Retention
5. Reduce Time-To-Proficiency for Trainees

Donald L. Siegel, Director
Bruce L. Levine, Founding Director

The Clinical Cell and Vaccine Production Facility (CVPF)

A High Volume Academic Cell therapy Production Facility

CVPF has two clean room facilities within which cellular immunotherapy products are manufactured at Penn. The Center for Advanced Cellular Therapies (CACT) is in the Perelman Center for Advanced Medicine and the Ravdin facility is in the Hospital of the University of Pennsylvania.

15 total cell processing suites • Bioreactor "Nursery" Automation Room • Cell therapy products manufactured in support of >20 currently open clinical trials • Support >15 currently open IND applications

20 Years of Academic and Industry Collaborations

WRAMC/NNMC • Univ. Maryland • Univ. Minnesota • Moffitt Cancer Center • MD Anderson Cancer Center • UCSF • Boston Children's • MSKCC • Cincinnati Children's • Univ. Wisconsin • Univ. Michigan • Univ. Utah • Univ. Minnesota • Children's Mercy • Stanford • Cell Genesys • Xcyte Therapies • Virxsys • Adaptimmune • Lentigen • Sangamo • ImmunoCellular Therapeutics • Takara • Maxcyte • Novartis • Cognate Bioservices • Progenitor Cell Therapies • Tmunity Therapeutics • Carisma Therapeutics • Cabaletta Bio

Cell Processing Expertise

Apheresis processing and cryopreservation • Ex-vivo T cell activation and expansion • Formulation of infusion products • Dendritic cell vaccine production • Gene modification • Gene editing

First – In – Human Clinical Trials

1st Trial of CAR T Cells • 1st Trial of Lentiviral Transduced Cells • 1st Trial of Genome Edited Cells • 1st Trial of Lentiviral transduced TCR T Cells in Cancer • 1st Trial of RNA Electroporated CAR T Cells in Cancer • 1st Trial of Lentiviral Transduced CAR T Cells in Cancer • 1st Global Trial of CAR T Cells • 1st FDA Approved Gene Therapy (Kymriah™) • 1st in U.S. Trial of CRISPR-edited CAR T Cells

Quality Expertise

Quality Control Methods and Development • Method Validation • Quality Assurance • Regulatory Compliance

Staff Recruitment, Training and Retention

Step 01

The staffing model of an academic cell therapy facility plays a crucial role in its success. High rates of employee turnover can impede forward progress of programmatic initiatives; yet staff recruitment, retention and training continue to be a challenge for academic manufacturing facilities. CVPF joined forces with University Leadership to develop a Career Advancement Track for cell therapy technologists.

What is the Career Advancement Track?

Previously, there was no clear path to retain and reward top performers on the team. In order to grow professionally, senior technologists would find new opportunities with competing industry establishments.

To improve retention a novel, metrics-based approach was developed to establish criteria for employee advancement (see **Figure 1** for abbreviated version). Involving Human Resources and University Leadership was critical to getting the program started. In addition to a defined path of career progression, the track introduced more competitive compensation for technologists in line with market value.

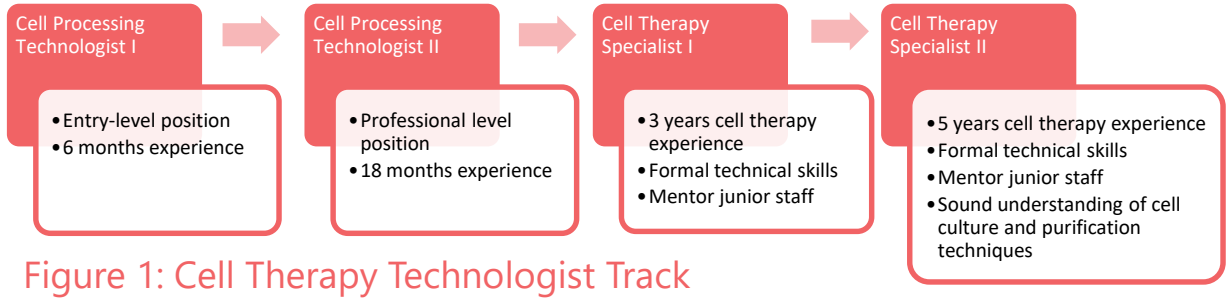


Figure 1: Cell Therapy Technologist Track

A highly productive team can accelerate progress on programmatic initiatives.

Highly trained technologists in the field of cell and gene therapy are a vital resource. They are hard to find and hard to keep. Each time you lose a valuable employee to a competitor, a new cycle of recruitment and training begins. Staying on this "hamster wheel" creates a constant uphill battle to make process improvements and initiate new studies.

Employee retention should be an operational priority.
High morale improves productivity. A new position posting is a need-based objective. **Career progression should be merit-based, not need-based**.

Strong incentives facilitate recruitment.
Clear deliverables for advancement and more competitive wages **attracts top talent**.

Staff Recruitment, Training and Retention.

Step 01

A robust training program stimulates increased productivity, improves retention and drives employee satisfaction.

CVPF developed a structured training program to improve quality, compliance and capacity outputs. In addition, further refinements resulted in an Accelerated Training Program with a reduction in time-to-proficiency (TTP) by > 8 weeks.

- Reduced TTP
- Combined skill & knowledge
- Improved training records
- Consistency in training

Figure 2: Training Program Goals and Benefits

Training Program Success

Program Structure

Reduced TTP with accelerated training • Clear goals & expectations • Established milestones & red flags

Dedicated Training Space

Cost reduction with use of non-GMP materials • Standardized training calendar • Low-stress learning environment

Dedicated Training Personnel

Progress tracking • Metrics evaluation • Improved compliance • Continuous improvement of curricula, aids & program

Re-Designed Curricula

Re-designed curricula • Lesson plans • Boot-camp style basic training for beginners • Focused learning for specialized processes • Training Aids (Slides/Videos/Work Instructions)

Step
02

Clean Room Space Utilization

CVPF developed a clean room space utilization model to increase production capacity.

In our previous model a product occupied a single processing room for the length of manufacture. We introduced a new model (see **Figure 4**) with the implementation of a "nursery" for expansion of multiple products in a single space in conjunction with space re-configuration to maximize facility efficiency.

Clean Room Space Utilization Model

Improved Processing Room Layout

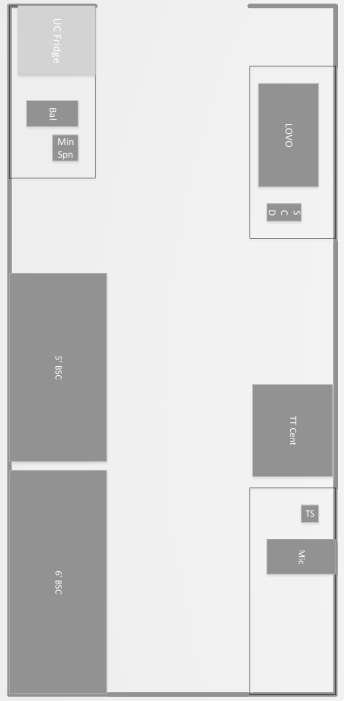
Minimal changes were made to the existing room layout. With operator input, the location of critical processing equipment in the room was evaluated. Changes were made to achieve a more intuitive design layout that better harmonized with the flow of cell processing activity (see **Figure 3**).

Bioreactor "Nursery"

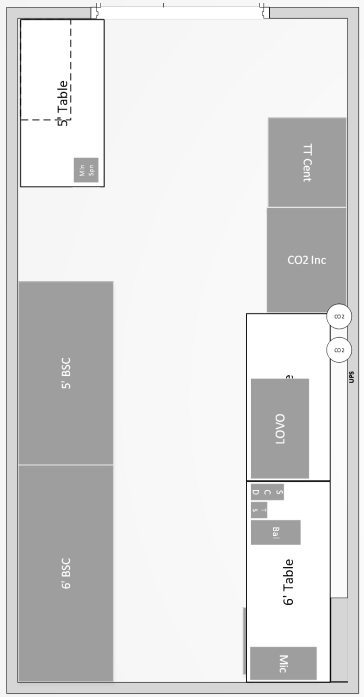
A bioreactor automation room was brought online to accommodate the ex vivo expansion of multiple cell therapy products in a single space. The products in the "nursery" share biosafety cabinet space and small portable equipment so that maintenance activities can be completed by one or two teams. Appropriate quality measures are in place to ensure product identity and prevent product mix-up.

Step 02

Figure 3: Improved Processing Room Layout

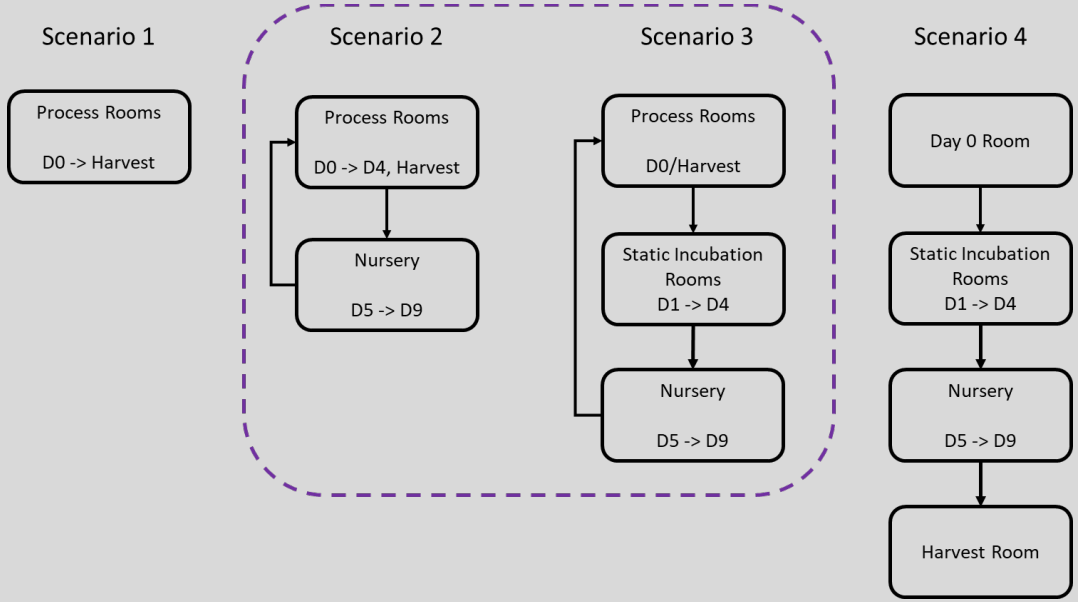


At left: Processing room layout required operators to continuously move back and forth throughout the processing room to access equipment. Small equipment was often relocated to different surfaces throughout the room as needed.



At right: Modification allowed operators to remain stationary while processing in the biosafety cabinets (BSC). Tables were relocated behind the BSCs to house small equipment frequently used by operators. Additional table space was made available in the room for ease of documentation.

Figure 4: Cleanroom Space Utilization Model



Scenario 1 represents the previous model where one product occupied a single room for the duration of the culture; the nursery was not in use. Scenarios 2 – 4 were considered and all included use of the nursery. In Scenario 4 culture initiation happened in one room, static incubation in another and harvest in another. It was quickly ruled out because simulations indicated that it would reduce current capacity due to restrictions on equipment and space. Scenarios 2 and 3 were both piloted and Scenario 2 was selected as the best fit. The equipment needs for culture initiation and harvest overlap such that one room design accommodate both processes. The separate static incubation room (Scenario 3) was undesirable as it increased the number of times products relocated and made prep, documentation and facility cleaning unnecessarily complicated. Scenario 2 has been successfully implemented and has dramatically increased maximum production capacity.

Step
03

Resource Management Systems

CVPF utilizes paper batch record documentation systems. Raw materials, critical reagents and equipment records are all maintained by paper as well. In order to appropriately expand our production capacity, we recently adopted electronic laboratory information management systems (LIMS) for more **efficient material storage and inventory solutions**.

Our experience with industry collaborators has allowed us to integrate practical material storage and inventory solutions. We've developed tactics and systems to maximize use of existing university resources for the growing needs of a cell therapy manufacturing facility. These approaches have reduced waste, standardized inventory thresholds and reduced overall cost. We are also in the process of evaluating vendor partners for the implementation of a Manufacturing Execution System (MES).

Electronic inventory systems
CVPF has leveraged available LIMS resources within the University (e.g. LabVantage) to better track materials usage and trend inventory thresholds.

Implementation of Kitting
CVPF uses kits to prepare for cell processing activity (e.g. culture initiation, culture harvest) The use of kits reduces material storage needs in the cleanroom and allows for better inventory control via lot sequestration and inventory tracking.

Step
04

Standardized Production Schedule

CVPF adopted the use of a resource management and scheduling software tool several years ago. After reviewing several vendor options, Visual Planning (© Stilog, IST) was selected due to it's flexible design and ease-of-use.

A primary constraint to efficiency in CVPF was unpredictability in the production schedule. Many activities precede a scheduled processing event including staff schedules, preparation of materials and reagents and readying of rooms and equipment.

However, due to the unpredictability of patient status, cancellations, postponements and new date requests occurred often. While clinically understandable, the lack of structure imposed a significant challenge for CVPF as the manufacturing facility.

A standardized approach brought much needed stability and structure to the production schedule.

Fresh apheresis as a source material was the primary challenge for CVPF. Creating more flexibility around source material and start dates gave CVPF control of the production schedule and reduced the number of unfilled slots.

Frozen Starts

Schedule control and redundancy was attained by implementing a frozen start production model. CVPF secured recurring bed space in the on-site apheresis unit for use by the clinical trial units. Apheresis collection slots were then aligned with CVPF available processing slots. CVPF staff process and freeze the apheresis products to keep in our inventory for future manufacture.

Standardized Schedule

Frozen starts provides structure to the schedule. By eliminating the variable availability of source material, CVPF was able to schedule culture starts and harvests using a standardized format. A fixed schedule created efficiency that resulted in significant productivity advantages (see **Figure 6**).

Standardized Production Schedule

Step 04

Figure 6: Standardized Production Schedule

The example schedule at left is a screenshot from Visual Planning. Schedule production slots are indicated by green bars; dark green boxes indicate culture harvests, yellow boxes show apheresis collection & processing slots and red boxes reference facility cleaning and maintenance activity.

Culture Start

Frozen products are thawed for culture initiation on Mondays or Tuesdays only.

Culture Harvest

A 9-10 manufacturing process leads to culture harvests occurring on Wednesdays or Thursdays of the following week.

Apheresis Processing

Dedicated beds scheduled in the apheresis unit on Wednesdays and Thursdays leads to next day apheresis processing and cryopreservation on Thursdays and Fridays.

Step
04

Standardized Production Schedule

The benefits of the standardized production slot model are remarkable.

Efficient scheduling
Coordination of staff schedule, sample transport, environmental monitoring, facility cleaning, equipment maintenance, QC testing, batch record preparation, review and product release are improved.

Maximize facility efficiency
Production task scheduling and capacity projections are improved. In addition, fewer pieces of equipment are required with built-in redundancy.

Improve resource management
Inventory management is simplified with a standardized production schedule; material needs are anticipated with regularity.

Increase production capacity
These changes combined with a cleanroom utilization model enabled an increase in maximum capacity by over 40%.

Reduce unfilled slot rate
Having apheresis products in the freezer provides flexibility to backfill slots that are unexpectedly cancelled or postponed.

Improve effort tracking
Visual Planning simplifies tracking effort in all functional groups, trending product release and monitoring key performance indicators.

A Whole New World…
The Impact of COVID-19 on Operations

Step 05

CVPF took early and immediate action to ensure the continued delivery of patient products. The University has deemed the clinical trials we support as essential and we are onsite to manufacture immunotherapy products. A phased re-introduction plan is scheduled to start in the coming weeks.

Maintain Production
CVPF immediately reduced capacity in order to limit interpersonal interactions and avoid a total shutdown. We immediately identified alternatives in the supply chain to prevent production interruption due to unavailability of at-risk / critical materials.

Ensure Continued Operation
CVPF leadership identified alternative options and assignments for staff to work remotely. "Staffing to demand" was implemented to prevent interruption of work on ongoing projects including engineering runs, validations and other billable activity.

Maintain Staff Safety
CVPF paired staff to work in teams that were maintained throughout the entire closure period to reduce exposure risk and trace potential at-risk personnel in the event of an exposure. CVPF implemented the use of masks before government mandate to promote staff well-being. Provide reassurance and reduce exposure risk.

Phased Return
CVPF will continue to provide masks for staff use on-site. Staffing-to-demand will continue with a steady ramp-up towards normal activity. The number of occupants in shared spaces (e.g. café) is reduced and spaces will be regularly cleaned by hospital staff.

Reduce Risk of Exposure
CVPF follows social distancing guidelines to facilitate physical separation on-site and arranged no-contact transfers for sample transfers, apheresis transport and infusion product release.

How has COVID-19 impacted your work?
Log onto the LPC's *Laboratory Life Line* forum to open the discussion! (Hint: Use the link at the end of this presentation)

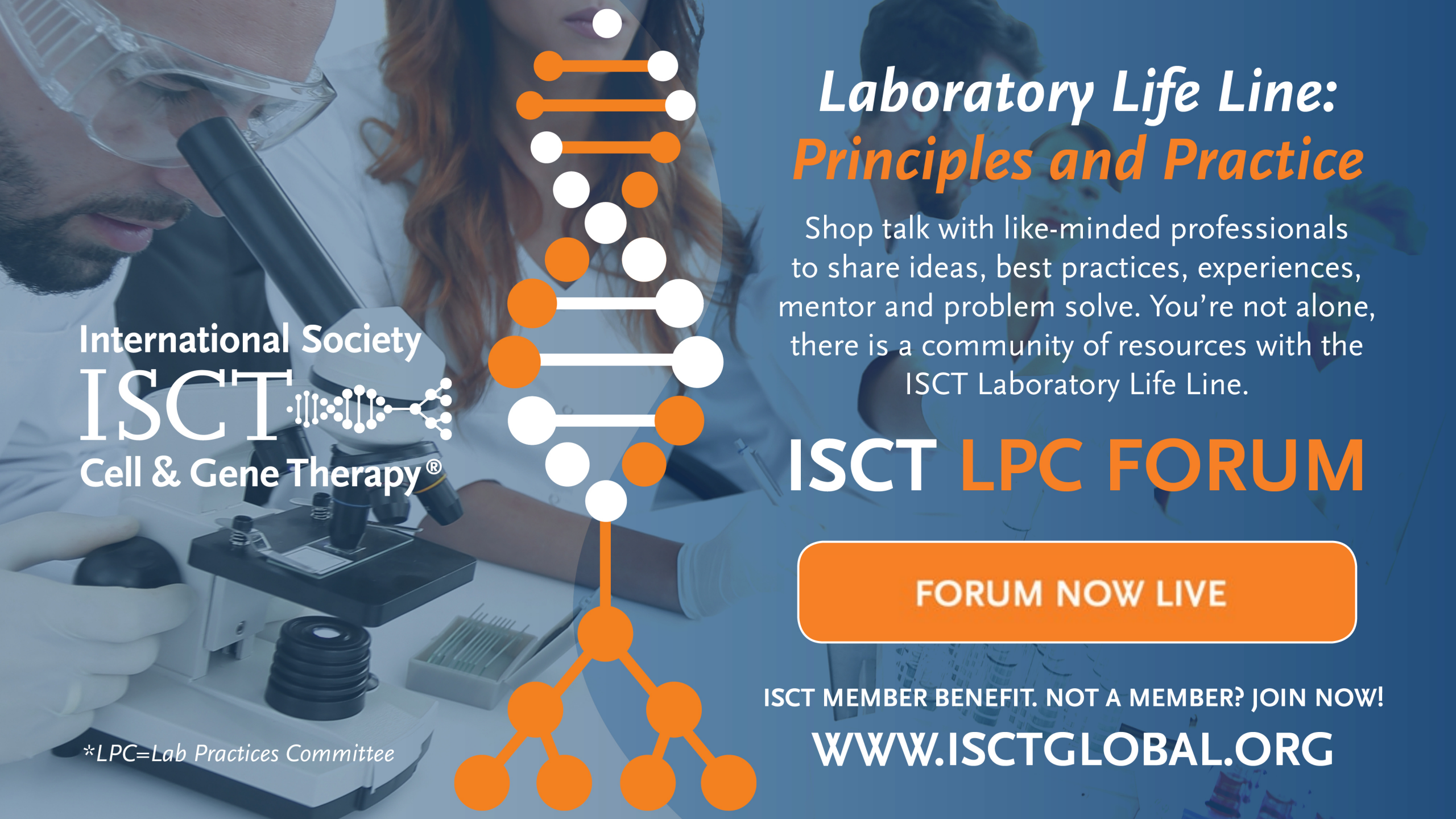
These techniques for increased productivity coupled with improved training methods and staff retention initiatives can be adopted by academic cell therapy facilities to optimize staffing, reduce costs and increase efficiencies, thereby increasing production capacity and patient clinical trial enrollment.

Images from inside CACT

Have a question?
Want to share a suggestion?

Do you have a question or want to share your expertise? The Lab Practices Committee *Laboratory Life Line* forum is a great way to get in touch with your network for insight, collaboration and help! **Click on the link in the next slide to start or join a discussion in the forum.**

I'd love to hear how you approach training at your facility, how you manage tasks and schedules and in what ways COVID-19 has helped you to get more creative in your operational solutions. Hope to see you there!



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