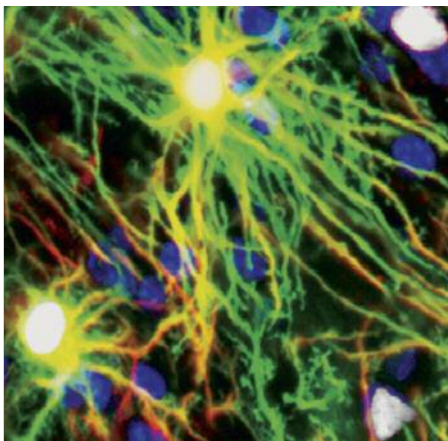


Upstate Stem Cell cGMP Facility



Accelerating early-phase clinical trials

The University of Rochester Medical Center (URMC) has recently constructed and commissioned a new cGMP (current Good Manufacturing Practice) facility, the Upstate Stem Cell cGMP Facility (USCGF), for the manufacture of stem cell and monoclonal antibody products for early-phase clinical trials.

The USCGF is part of the URMC Stem Cell and Regenerative Medicine Institute and only one of a handful of academic cell-based cGMP facilities in the country. There are more than 40 labs at URMC working with stem cells in fields such as neurological disorders, cancer, cardiovascular disease, and musculoskeletal disorders. These labs employ more than 260 scientists and technicians and collectively have more than \$80 million in active research projects.

The USCGF is designed as a multi-use cGMP manufacturing and testing facility with the goal of accelerating “first-in-man” early-phase clinical studies with the following capabilities:

- Development of clinical-scale manufacturing processes;
- Development of analytical methods for product characterization and release;
- GMP manufacturing and in-process testing of clinical-grade materials;
- Quality Control release testing of final product.

The facility is open and available for contract manufacturing and testing services to academic and private sector scientists. The USCGF was created with support from New York State Stem Cell Science (NYSTEM) and is located on the main URMC campus in Rochester, NY.



“This facility represents the key bridge to early stage trials in humans and will enable us to move forward with studies in a wide range of conditions, including efforts to repair CNS damage, re-grow bone and cartilage, and even target cancer stem cells.” — Mark Noble, Ph.D.



Why cGMP?

The FDA Code of Federal Regulations requires that products intended for human use are safe, pure, and effective.

- GMP regulations and guidance provide for a “Quality Approach” to manufacturing and testing with the goal of eliminating or minimizing contamination, cross-contamination, mix-ups, and errors in order to protect human patients.
- The FDA reviews submitted Investigative New Drug (IND) applications in order to determine whether the product to be used in the investigation has the identity, quality, purity, strength and potency necessary to ensure the safety of the subjects in proposed Phase 1 studies.



Design characteristics

The USCGF is a multi-use facility, with high flexibility and versatility designed with the goal of eliminating or minimizing contamination and/or cross-contamination of manufactured materials to ensure product safety.

In addition to multiple segregated HEPA-filtered manufacturing labs, the facility also contains process development, testing, and support space. Controlled environment design features include the following:

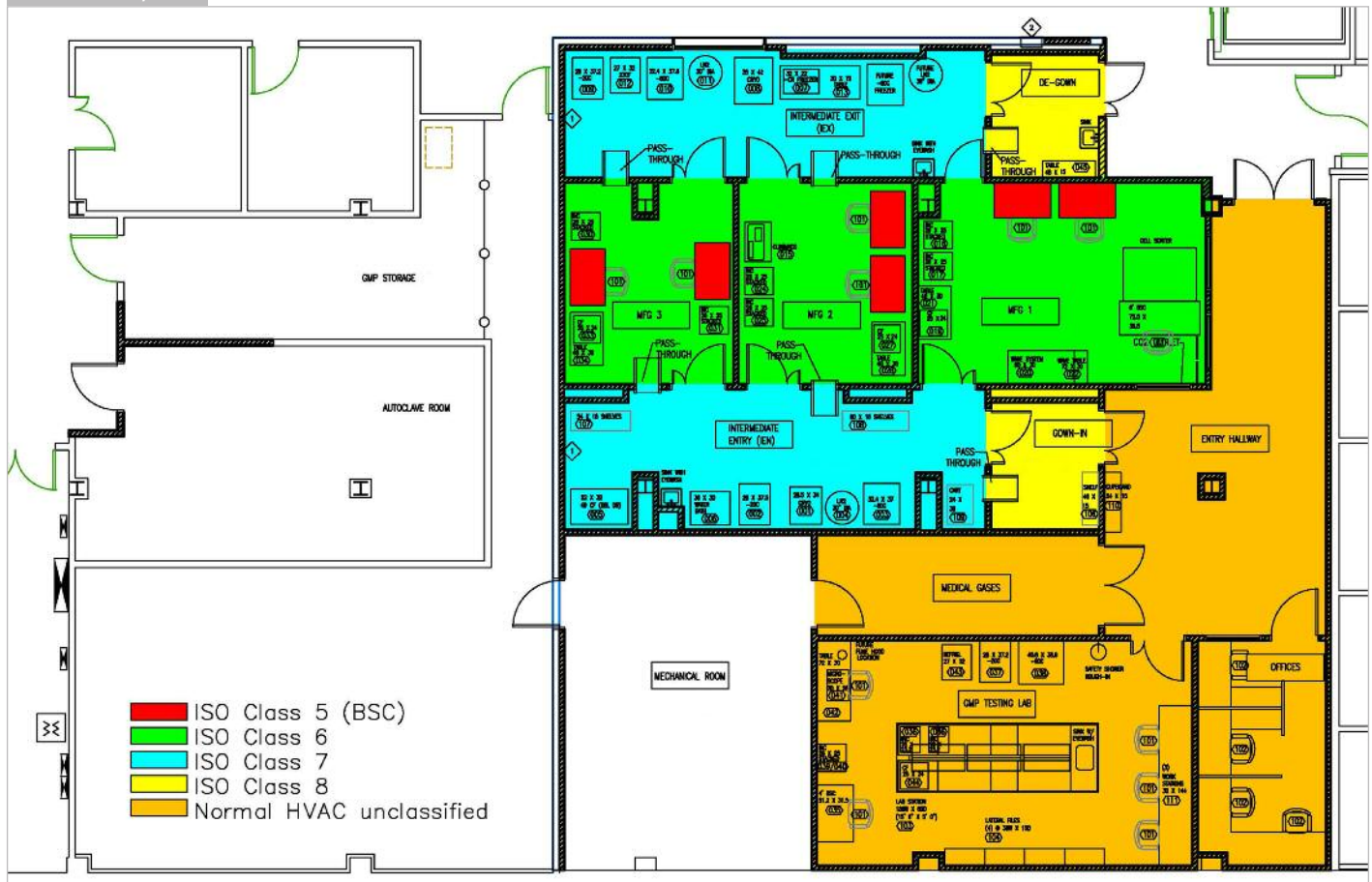
- Redundant air handling systems providing clean-room air classification and quality from Class 100,000 (ISO 8) to Class 100 (ISO 5);
- Pressure differentials of 0.05" w.c. between adjacent rooms with up to 60 air changes/hour;
- Rigorous control of room temperature, pressure and relative humidity;
- Unidirectional flow of personnel, raw materials, product, and waste;
- Easily cleanable surfaces with floors, walls, and ceilings constructed with minimal seams and ledges; use of easy to clean gel-coat wall polymers, epoxy coated floors, and stainless steel surfaces; and moveable equipment and work surfaces.

The USCGF has successfully completed a Type C meeting with the FDA in which the facility design, intent of use, operational flow, and quality management system were reviewed in detail.



“We selected the USCGF to create clinical grade Retinal Pigment Epithelial Stem Cell lines for future clinical applications. The staff is highly experienced and knowledgeable and respond rapidly to our questions – they are part of our team!” – Sally Temple, Ph.D.

USCGF Layout



“This facility is a boon to researchers across the state. It will specifically help accelerate our lab’s work in multiple sclerosis and other neurological disorders by enabling us to generate cell lines suitable for early phase clinical studies.” – Steven A. Goldman, M.D., Ph.D.



Production process capabilities

The USCGF was designed and outfitted with process capabilities for the GMP manufacture of early-phase clinical trial materials including stem cell therapy products as well as monoclonal antibodies to be used either for reagents in stem cell purification or as therapeutic proteins. Production capabilities and facility flow are as follows:

- Entrance into the facility is through a Class 100,000 (ISO Class 8) Gown-in area;
- The subsequent Class 10,000 (ISO Class 7) Intermediate Entry (INE) contains cryogenic liquid N₂ storage, -80°C and -20°C freezer space and refrigerator space for the storage and staging of raw materials and reagents released for GMP production;
- The INE provides access to 3 manufacturing labs, each with its own HEPA filtered HVAC unit operating independently and providing Class 1,000 (ISO Class 6) air. Each manufacturing lab (MFG) also contains biosafety cabinets, dual chamber incubators, centrifuges, a microscope, and work surfaces. In addition, MFG-1 is outfitted with a WAVE bioreactor, a microfiltration / ultrafiltration system, and a downstream purification system to support the production of monoclonal antibodies under GMP, at a 1–10 gram scale;
- Exit from the manufacturing rooms is through a Class 10,000 (ISO Class 7) Intermediate Exit (INX) equipped with a cryogenic liquid N₂ storage, -80°C and -20°C freezer space, a liquid N₂ controlled rate freezer, and refrigerator space for the storage of process intermediates as well as final manufactured product;
- Exit from the facility is through a Class 100,000 (ISO Class 8) De-gown Room.

Analytical testing capabilities

The Quality Control (QC) analytical testing lab is a dedicated area equipped with cell culture capabilities, as well as extensive analytical instrumentation and methodologies. A number of analytical capabilities are in place for the characterization of both stem cell products as well as therapeutic protein molecules. In addition, the USCGF has access to the Core Facilities at URM C that includes flow cytometry, functional genomics, proteomics, and more. Established partnerships with external contract research organizations (CROs) are also leveraged to increase the analytical testing capabilities.

Pre-clinical study capabilities

The URM C staff can also provide training, support, and quality oversight for Good Laboratory Practice (GLP) compliant pre-clinical studies.



Quality management system

The USCGF has established a GMP-compliant Quality System which consists of an organizational structure with policies, procedures, processes, and resources needed to implement a quality management approach for the manufacturing and testing of clinical trial materials. Elements of the Quality System include:

- Good documentation practices;
- Document control system;
- Change control;
- Validation support;
- Personnel training program;
- Supplier qualification;
- Raw materials & product inventory management;
- Internal and external auditing;
- Oversight of Environmental Monitoring Program;
- Oversight of manufacturing, Quality Control testing, and product release.



Current projects

The USCGF has been contracted to produce clinical grade stem cells for two major consortium grants that have been funded by the NYSTEM.

- The first is directed by **Sally Temple, Ph.D.** of the Neural Stem Cell Institute in Albany, and seeks to use retinal stem cells to treat age-related macular degeneration.
- The second is led by **Burk Jubelt, M.D.** of Upstate Medical University in Syracuse and **Steve Goldman, M.D., Ph.D.** of URM, and will use glial stem cells to treat multiple sclerosis.

In addition, several programs are underway at the USCGF:

- **Mark Noble, Ph.D.** and **Christopher Pröschel, Ph.D.** with URM are studying:
 - Tissue-derived glial-restricted precursor cells for central nervous system injury.
- **Edward Schwarz, Ph.D.** with URM is studying:
 - Bone marrow-derived mesenchymal stem cells for bone repair;
 - Therapeutic monoclonal antibody for MRSA infections associated with total joint replacement.

Contact us!

For those considering contract manufacturing and testing of early-phase clinical materials, we invite you to visit and/or audit our facility. Please contact us for additional information or to schedule a visit.



Facility leadership

The facility is directed by **Michael J. Fiske, M.S.**, who has more than a decade of clinical-scale cGMP experience as the former Manager of GMP Production and Analytical Services at Wyeth Vaccines and Director of GMP Clinical Production for Genencor International.

The facility director also has significant experience managing Quality Assurance functions, validation, technology transfer, GMP process development, analytical method development and validation, as well as interactions with regulatory agencies. The facility also has access to expert scientific advisors at URMIC including former FDA personnel, who can help with the preparation of funding proposals and grant applications, and provide additional guidance on regulatory issues.



585.276.6208 Michael J. Fiske, M.S.

www.urmc.rochester.edu/upstate-stem-cell-facility



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