

XVIVO



***World's first
and only
incubator
designed for
explant and
implant cell
cultures***

New Incubation System

Our new Xvivo Incubation System changes everything for people growing cells in the dish. It's a new concept in incubators and is designed to dramatically increase your ability to grow and manipulate the most demanding and important cultures of all: explants and implants.

It combines many advanced features into one integrated package. It can control more variables and can control them over a wider range, automatically changing them at precise times to accomplish things never before possible. Multiple independent incubation chambers can do different things at the same time.

The chambers are integrated with a super clean gloved workspace to avoid contamination. Workspace conditions can duplicate conditions inside any incubation chamber to avoid disturbance while being handled.

The Xvivo system is modular and scalable to exactly fit the needs and budgets of most labs. Grow and manipulate cells in open-dish culture (flasks, petri plates, multi-wells) like never before...way beyond what all other incubators can do.

- stem cells
- engineered cells
- embryoids
- transgenics
- expansions
- transplants
- biopsies
- etc.

***Take open-dish
passive-vessel
cell culture
(flasks, plates,
multi-wells,
bags)
to the next
phase.***



Dynamic Optimization

If you can keep up with your cells, you can do more with them. Cell cultures are dynamic entities. They grow. They differentiate. They are never static.

Yet, standard incubators have nothing but static conditions. You get one concentration of CO₂, one temperature, and if you're lucky, one concentration of O₂.

As cell culture becomes more and more sophisticated, there's a point where conventional incubators with static conditions are going to be severely limited. Static incubators cannot keep up with dynamic cultures.

The Xvivo system is different. It offers high performance dynamic control (pat. pending) of multiple variables simultaneously (O₂, CO₂, NO, CO, and temperature). Instead of static conditions, you can program it to automatically change any variable (or all variables) any time you want. Virtually any dynamic can be accommodated. Now you *can* keep up with your cells.

Grow Explants Better

You can grow them better. For example, primary cultures initially do best in a low oxygen gas phase. But as they grow and cell population density expands, the consumption of oxygen goes up. In a static incubator you can't adapt to the change, and the oxygen is consumed until the cells are under oxygen deprivation.

Xvivo is different. It compensates. It can raise the oxygen concentration over the course of the culture to keep up with the consumption. The result? More cells. Healthier cells. Any cell expansion will probably do better with a ramp up in oxygen!

Prepare Implants Better

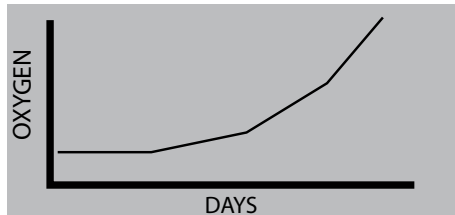
You can manipulate them better too. For example, hypoxia preconditioning stands to make cellular implants much more robust.

The Xvivo system can help you develop your conditioning protocols, and then run them day in and day out. Standard incubators can't do that.

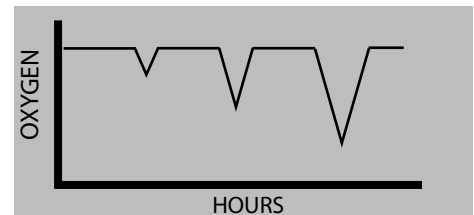
No Comparison

Conventional static incubators make you adapt your cultures to the limitations of the incubator. The Xvivo system allows you to adapt to a wide range of different culture-specific needs...at the same time.

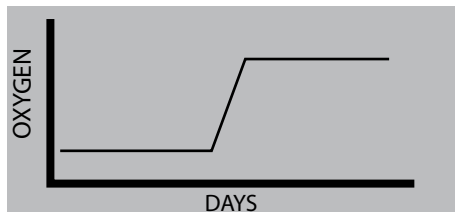
HIGH PERFORMANCE



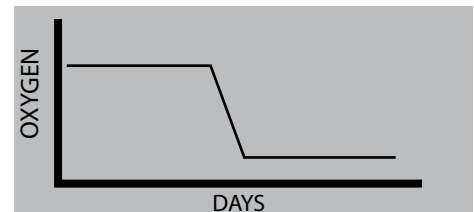
EXPANSION PROTOCOL: Primary cultures and other low cell population density do best under low oxygen gas phase when they start, but when they grow, they are bound to need more. You can design any ramp you want in oxygen, and consistently repeat it with a click of the mouse.



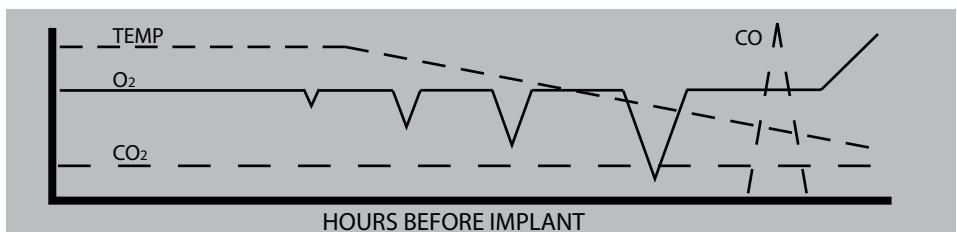
HYPOXIA PRECONDITIONING PROTOCOL: Cells *in vitro* destined for *in vivo* may be better prepared for their hypoxic journey if they get a little taste of it first. Implants need all the help they can get. You can design and consistently repeat any frequency and any amplitude with the click of the mouse.



DIFFERENTIATION INDUCTION PROTOCOL: Induce stem cell transition from proliferation to differentiation at any point in the culture by raising oxygen. Rise in oxygen can signal your cells they are entering a new place in the body or in their development.



WOUND PRIMING PROTOCOL: Elicit wound response in tissue repair cell cultures before they are placed in the wound. Upregulate inflammation phenotype. Upregulate angiogenic phenotype. Priming may result in faster healing. You can design and consistently repeat any rate of drop and any depth of drop with the click of the mouse.



HYPOTHETICAL PROTOCOL: To illustrate the unprecedented power of dynamic multi-variable optimization, imagine you have a transgenic cell population to be implanted. You use the last few hours before implantation to prepare it. You know the cells are going to better survive the time between the dish and the body if their metabolism slows down, so you program the temperature to gradually cool the cells just before they leave the incubator. You know your cells are going to be hypoxic for their first few days in the body, so you program the O₂ for a series of acute hypoxic episodes in the last hours before implantation to precondition them, then at the last moment make the O₂ rise to saturate their media just before they leave the incubator. You also know they will handle the stress a lot better if you can upregulate their stress response, so you program a short burst of CO just before they leave the incubator. As usual, you program the CO₂ concentration to stay constant while the other variables are manipulated up and down.

INTEGRATION



XVIVO SYSTEM integrates multiple high performance incubators with clean hood and glove chamber for advanced, high value, open-dish cell cultures.



TECHNICIANS work with cultures safely inside clean hood/glove chamber, and are never exposed to cultures. Of course, cultures are never exposed to technicians either.



DEDICATED INCUBATION CHAMBERS One per culture. This maximizes your ability to grow and manipulate different cultures. No culture mix ups. No cross contamination.



INCUBATION is only part of cell culture. Handling is the other. Incubators all open only into clean controlled atmosphere of gloved workspace. This eliminates moving cultures to clean hood for handling. It also eliminates any disruption to conditions that affect cultures.



WORKSPACE GAS PHASE is cleaned 24 hours a day by UV sterilization, HEPA filtration, activated carbon adsorption, mild ionization, and dessication. This eliminates many trips to clean hood.



PASS THROUGH CHAMBER is a port into and out of the glove workspace. Materials and supplies can be moved in and out without disturbing the conditions in the workspace in front of the incubators. So can cell cultures. The pass through is designed to fit a transport chamber perfectly, so you can open and close it from inside the workspace undisturbed.

New Bio-active Gases

Standard cell culture incubators control CO₂ and temperature, and if you're lucky, oxygen. Even then, you'll only get oxygen control over a limited range. Usually, they can't even reach the lower physiological ranges.

Xvivo system is different. It controls O₂ over the full 0.1-99.9 % range. It can also control NO and CO. These bio-active gases stand to play an important role in many areas. Manipulating phenotype or gene expression may help in preparing cultures for implant. No other incubators allow you to use these important new bio-active gases.

Multiple Independent Chambers Per Incubator

Conventional static incubators are usually monoliths, with many different cultures incubated in the same big chamber, under the same conditions, at the same time. Plates from different cultures can get mixed up together. A small contamination can be devastating. One contaminated culture can quickly and easily spread to all the other cultures in the incubator.

Xvivo is different. It can be configured with any number of chambers. Each individual culture can be incubated in its own dedicated chamber. Each culture is isolated from all other cultures. This unique design has many advantages over conventional monolithic incubators.

First of all, it allows you to adapt to the different needs of each different culture. Each chamber is fully independent of all others, so you can control different conditions in each, without affecting any other cultures. No two cultures ever have to be in the same space at the same time. This means culture mix ups are much less likely. Chance of cross contamination between cultures is also minimized.

Clean Hood Is Built Around Incubators

No longer will you have to carry your cultures back and forth from the incubator to the clean hood. That's what you have to do with standard incubators.

Standard incubators open into the room. You take your cells out of the incubator, and carry them through the lab to the clean hood where you handle them. When you're done, you take them back to the incubator. The travel, of course, takes valuable time.

What's worse, the trip increases chance of contamination from room air, and from the people carrying the cultures. The Xvivo system is different. Your clean workspace is integrated with and envelopes the incubators. All incubation chambers open only into a sealed glove chamber whose gas phase is constantly circulated through a cleaner where it's cleaned 24 hours a day via UV sterilization, HEPA filtration, activated carbon scrubbing, mild ionization, and dessication.

Your cells never see the room. Nor do they ever have to venture into the same space as a "germy" human technician. Of course, humans are never in the same space as "germy" cultures either.

UNINTERRUPTIBLE OPTIMIZATION

Cultures inside standard conventional incubators are disrupted everytime the door is opened. Air rushes in. O₂ concentration goes toward 21%. CO₂ concentration goes toward 0%. Temperature goes toward room temperature. Regardless of what was being controlled inside the incubator, conditions are temporarily disrupted, on a regular basis. Sometimes dozens of times a day.

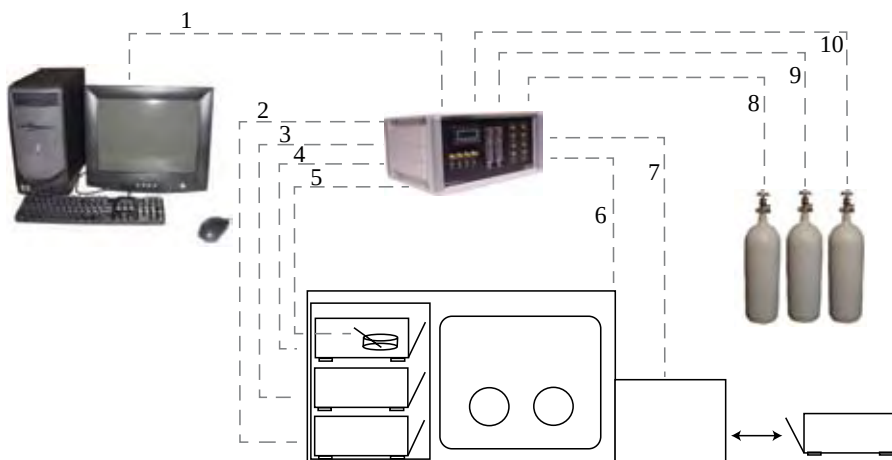
The disruption is even bigger when cultures are removed from the incubator and taken to the hood. These disruptions are now known to be a big handicap with oxygen. Even a brief exposure to room air oxygen levels in a hypoxic culture can immediately turn off hypoxia upregulated genes that took hours to induce. This is significant because manipulating oxygen regulated genes stands to play a big role in preconditioning of implants.

What about disruptions in pH due to CO₂ disruptions? What about the temperature disruptions? Here there's currently less worry, but intuitively, it can't be good. As cell culture becomes more and more sophisticated, this will become dogma. Face it, conventional incubators condemn your cultures to frequent and possibly severe bouts of suboptimal conditions.

The Xvivo system is different. You control the same variables in the workspace as in the incubators. Incubators open only into controlled environment of gloved workspace. Glove chamber is prepared before incubator is opened, to exactly the same O₂, CO₂, NO, CO, and temperature as that inside the incubator.



SCHEMATIC



1. PC provides familiar, convenient interface, security access, and datalogs everything. PC accessories allow you to operate system from any remote location via modem, network, or internet.

2. Controller controls wide range of conditions in first cell culture chamber (temperature, CO₂, O₂, CO, NO). Conditions can be different in each chamber. Conditions can be static or dynamic.

3. Controller controls different conditions in second independent chamber.

4. Controller controls third chamber. Unlimited chambers can be added and integrated.

5. Controller can interface special custom accessories such as liquid sensors in media, timed aliquots of liquid infused into media, fiber optic spectrometry, etc.

6. Controller duplicates conditions of glove workspace to each different incubator just before it is opened. Optimal conditions need never be disturbed. Workspace atmosphere is constantly HEPA filtered, UV sterilized, activated carbon adsorbed, and dehumidified to levels less than those that support bacterial proliferation.

7. Controller adapts conditions of pass-through chamber to glove box so conditions in glove box are not affected by moving things in and out.

8. Nitrogen is used to push down oxygen and carbon dioxide.

9. Oxygen is used to push up oxygen.

10. Carbon dioxide is used to push up carbon dioxide.

11. Transport chambers are part of the system. They can transport cultures uninterrupted and be opened uninterrupted inside glove workspace.

Then when incubator is opened, there will be no disruption to cells. They can be removed from the incubator and remain under optimal conditions. Nor will there be any disruption to the cultures left inside the incubator.

If the next incubator to be opened has different conditions, the workspace is simply preset to those new conditions before that incubator is opened. Other accessories include transport chambers and media conditioners.

UNINTERRUPTIBLE TRANSPORT

Transport chambers are designed to fit into pass-through chamber of glove box. They open inside glove chamber to uninterrupted conditions. They allow you to transport cultures without interruption as well.

UNINTERRUPTED FEEDING

Media conditioners can equilibrate fresh culture media to same conditions as incubator and workspace before you let it contact cells.

MODULARITY MAKES IT SCALABLE

You can configure your system with any number of independent incubation chambers. Simply scale the number of chambers to the number of different cultures you'll need to incubate simultaneously.

Chambers range in size, so you can also scale the size of the chamber to the size of the culture. All modules fit together with all other modules. Modules that integrate also maximize your flexibility.

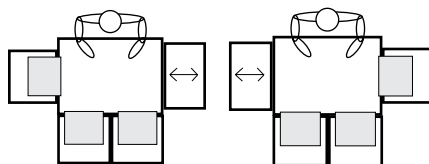
MODULARITY MAKES IT FLEXIBLE

There are infinite combinations. Modularity means you can satisfy your particular needs. You can adapt the equipment if those needs change. You can expand your equipment as necessary. You can change directions as necessary. All your previous investments stay intact. Everything works together.

MODULARITY MAKES IT AFFORDABLE.

Since system is scalable from small to large, there's probably a configuration that fits your lab and fits your budget. Clear upgrade paths are ready when you are. Regardless of how much capacity you need, you can meet it. No matter how big it gets. Nothing compares.

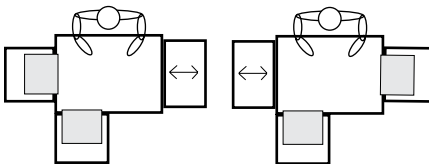
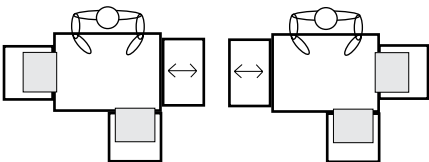
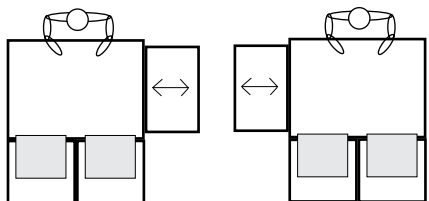
CONFIGURATIONS



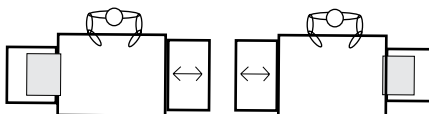
SINGLE USER-TRIPLE STACK Each glove chamber can only be a workspace for one technician at a time if all the incubators possible are installed. Each workspace can have up to three incubator stacks of chambers. Each workspace has to have a pass-thru chamber (represented by arrow). Two "full boat" configurations are possible, mirror images of each other. Criteria for which depends on your lab space. Is it good for pass-thru access on the left or right of gloves?



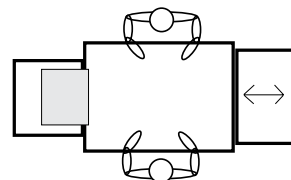
INSIDE LOOK at a 12 chamber system shows the 3 stacks of incubation chambers. Here all incubators are one size. You can choose the sizes you want. Any combination that will fit. We have several different sizes.



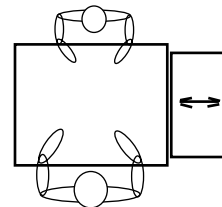
SINGLE USER-DOUBLE STACK There are 6 different ways to configure a system with 2 incubator stacks. One is likely to fit any lab.



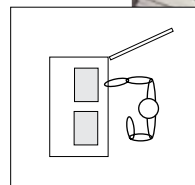
SINGLE USER-SINGLE STACK Only consideration is which side will have access for the pass-through.



DOUBLE USER-SINGLE STACK Two people can use it at the same time. Working independently or together.



DOUBLE USER-NO STACK You can get glove workspaces without resident incubation chambers. Options range from just O₂ control to O₂, CO₂, NO, CO, temperature control, and any combination in between. Air cleaning is also an option, just like it is on the resident chamber systems.



INCUBATION CHAMBERS don't have to be in our glove workspace chamber. Here a 10 chamber system is located in a big thermal incubator.

GMP FEATURES

GMP MEANS "QUALITY"

Good Manufacturing Practices are guidelines for producing a high quality cell product. Regulatory agencies require you to produce your cells under cGMP to assure patient safety if you plan on using them for therapy.

Quality means two things. First it means a highly reproducible and consistent end-product. Second it means a product free of microbial and particulate contaminants. Xvivo System was designed for GMP from the start. In both cases, it raises the bar.

CLOSED SYSTEM MAXIMIZES CONSISTENCY

A tightly controlled and reproducible production process is the formula for consistent high quality cell product. Xvivo System is the only commercially available incubation system designed for uninterrupted conditions.

Cultures are never exposed to ambient room conditions. They experience none of the suboptimal transients that normally occur between the incubator and the hood, or between the incubator and the microscope, or between the hood and the centrifuge. Uninterrupted optimum conditions throughout the production process generates a higher quality cell product. It is always going to be considered a better GMP than frequent uncontrolled exposures to suboptimal conditions.

CLOSED SYSTEM MINIMIZES CONTAMINATION

The Xvivo System totally isolates cells inside aseptic mini-environment. They are never exposed to the room, and more importantly, they are never exposed to the people in the room. A closed system gives you better security against contamination than any walk-in cleanroom ever can. It is always going to be considered a better GMP to have cells totally isolated from technicians than to have cells in the same space as technicians.

DEDICATED CULTURE CHAMBERS ELIMINATE CROSS CONTAMINATION

Dedicating each incubation chamber to just one culture, and never allowing two cultures to be in the same space at the same time, is always going to be considered a better GMP than culturing two different cultures in the same incubator at the same time.

ENTRY/EXIT CONTROL

All doors in and out can open into an external clean hood. Hoods provide staging area and external workspace for surface decontamination, removal of protective overwrap, or general aseptic preps before items go into the system.

All gas and liquid ports can be double filtered with aseptic connectors. It is much easier to control what gets into a small isolation cabinet than what gets into a big walk-in clean room.

The better the control over what gets into the manufacturing space, the better the GMP.

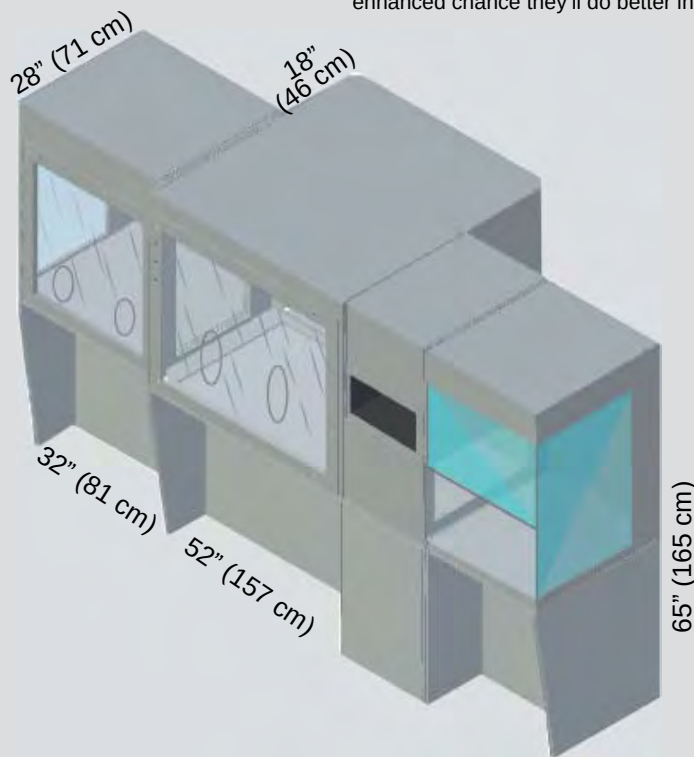
AUTOMATION

Numerous automated routines can be built in to sterilize or decontaminate (in place) any specific individual chamber or group of chambers, or items passing into or out of the system, or between any two stages of the process. These routines can run regularly on schedule, after each culture, or as needed.

STEM CELL WORK-STATION

Embryonic stem cell cultures require frequent microscopic examination. This Xvivo system configuration has a side chamber that holds a microscope with access to the microscope through gloves and an eyepiece. Cells can be removed from their incubator, processed in the workspace, and easily placed inside the adjacent microscope chamber, close to the microscope. At the microscope chamber you can place

the cultures on the stage and view them without interruption in any conditions. The microscope stays in the clean controlled atmosphere all the time. The result is a greatly reduced chance of contamination by avoiding a trip across the room from the incubator to the microscope. If your cells aren't shocked by temperature drop, or alkalinity shock, or oxygen shock, then there is a greatly enhanced chance they'll do better in the dish.



1. MICROSCOPE CHAMBER - Any microscope can be fitted into this side chamber. Has same atmosphere as workspace.
2. WORKSPACE GLOVE CHAMBER - This is where your cultures are handled and manipulated. Workspace atmosphere can replicate conditions inside any incubator before that incubator is opened. Cultures brought into workspace experience no disturbance in optimum conditions.
3. PASS-THROUGH CHAMBER - Air lock through which all items pass into and out of the system. Equilibrates to atmosphere of workspace before pass-through is opened into workspace. Avoids disruption of workspace atmosphere.
4. LAMINAR FLOW OR SAFETY HOOD - Envelopes outer door of pass-through chamber to eliminate any chance of airborne contamination entering.
5. INCUBATORS - High performance incubators for user-defined stem cell differentiation and proliferation protocols. Cell line expansions under control of dynamic profiling conditions.

ACCESSORY CHAMBERS

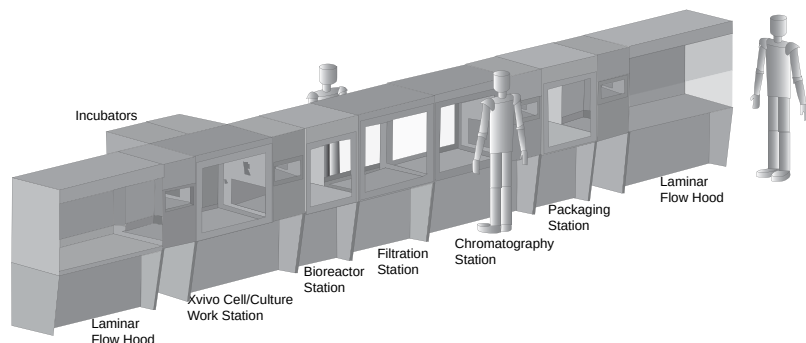


INVERTED MICROSCOPE INSIDE XVIVO MICROSCOPE CHAMBER Microscope chamber can house virtually any microscope. Cultures can be removed from incubators and placed directly in contiguous microscope chamber. Conditions in microscope chamber are controlled exactly the same as in workspace. Atmosphere in microscope chamber is also cleaned 24/7 along with workspace atmosphere. Cultures can be viewed with no disruption in temperature, pH, O₂, or CO₂. Cultures never have to risk exposure to room air in order to be viewed. Dry atmosphere in Xvivo microscope chamber is more hospitable for microscopes and inhospitable for microbes than humidified atmospheres.

High velocity gas showers, log displacement of "used atmospheres" with sterile filtered gases, spray washdowns with disinfectant, fumigation protocols with VHP, ozone, chlorine dioxide, formaldehyde, etc. all can be automated and even integrated together. Automated pressure cascades can be established along any set of contiguous chambers, and changed or redirected to anywhere within the system instantly. Automated ventilation protocols, both re-circulating and exhausting, can be built anywhere into the system, and similarly, changed or redirected to any other set of chambers within the system in an instant.

Even doors, and access ports, and lights, and process equipment can be automated as standard operating procedures. Decreasing chance for human error increases quality. Anything you can do in a cleanroom, you can do easier and cheaper in an isolation system like the Xvivo. Some GMPs you just can't do in a big open walk-in cleanroom with people in it, but you can in an Xvivo System.

CYTO-MANUFACTURING



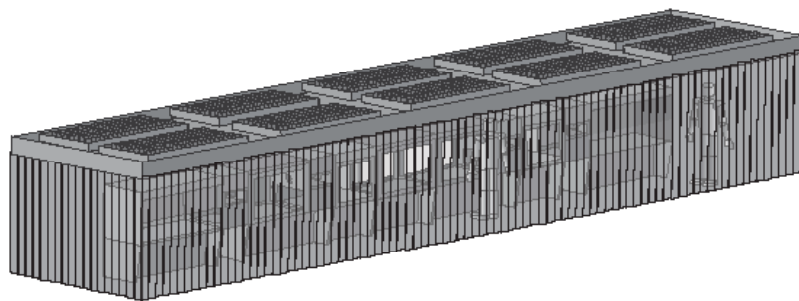
COMPLETELY CLOSED-SYSTEM PRODUCTION LINE

Cells are produced in a series of modular integrated interconnected chambers. Entire set of instruments and processing tools are arranged inside modules according to the final process sequence. Cells and supplies enter on one end, waste is expelled aseptically along the way, and cell product emerges at the opposite end. One advantage over traditional bricks-and-mortar, walk-in cleanrooms is that the process can be developed anywhere. Then when it is time for cGMP certification, surround it with or move it to a Class 100,000 (ISO 8, GMP Class C) cleanzone.

DOCUMENTATION

Along with automation comes real-time monitoring, alarming, and documentation of bioburden, particulates, vapors etc. Complete batch process variables can also be routinely documented for quality auditing of each culture. User access and electronic records and electronic signatures in compliance with FDA 21CFR Part 11 can be designed in from the start or added later. The better the documentation, the better the GMP.

CYTO-MANUFACTURING



GMP PRODUCTION FOR PHASE 1 CLINICAL TRIALS

Cell manufacturing process can be debugged, optimized, and characterised during translational research phase. Once production process is validated, cell production mini-facility can be converted to GMP by simply surrounding it in minimally classified space. Surrounded by Class 100,000 (ISO 8) cleanspace, isolators meet regs. Modular softwall clean rooms can be constructed around isolators for ISO 8. Any production line can be fitted. Any room can be fitted. Or system can be moved to cleanroom, down the hall, or across the ocean.

MAKES GMP EASIER AND MORE ECONOMICAL

Not only are GMPs in the Xvivo System superior to traditional cleanrooms, but meeting GMP regulations with Xvivo System should be easier and more economical. Traditional bricks-and-mortar cleanrooms are prohibitively expensive for many. The Xvivo System is much more economical.

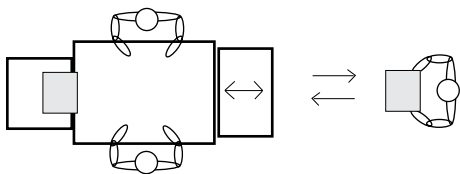
It can evolve along with your research, and fit practically any existing facility. Translational phase of development can be perfected, and then scaled up or moved as needed, on a pay-as-you-go basis, with much less risk. Now anyone can produce top quality cells for therapy.

TRANSPORT

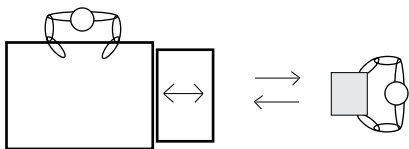
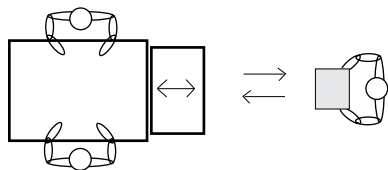
MOBILE CULTURES

Cultures need to travel sometimes. Possibly they need to travel to or from the vivarium or operating room, or some other lab. When traveling, they need to travel in comfort and safety. Xvivo system has been designed to provide for transporting cell cultures undisturbed across the lab, down the hall, up the elevator, or across the street.

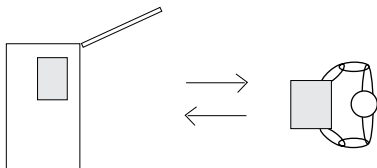
Transport chambers fit into the pass-through chamber. Once the pass-through is equilibrated with the workspace, the chamber can be opened without disturbance. The cells can be removed and manipulated. They are then returned to the mobile chamber, and removed and transported to a remote location. Or they can be incubated in one of the resident incubation chambers.



TRANSPORT CHAMBERS can be used with any of the Xvivo resident incubation chamber systems. They can transport cultures that are resident, or they can transport non-resident cultures for temporary handling only



TRANSPORT CHAMBERS can be used with glove workspace chambers with no resident incubators.



TRANSPORT CHAMBERS can be used as incubation chambers if fitted with controllers and placed inside thermal incubators or CO2 incubators



TRANSPORT CHAMBERS are designed for moving cultures without disturbing conditions inside. They are light enough to carry and balance on one hand.



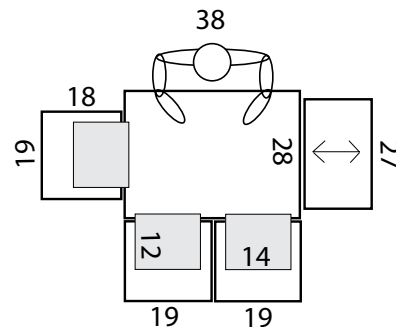
PASS THROUGH CHAMBER of all our gloved workspace chambers are designed to be a perfect fit for the transport chambers. Three sizes will fit.



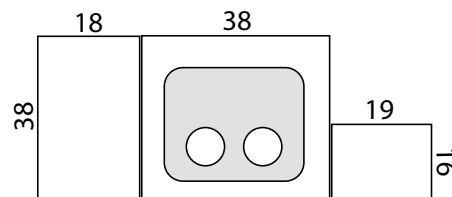
TRANSPORT CHAMBERS open into the workspace and can stay in the pass through chamber, out of the way, while the technician opens it and accesses the cultures. Slide out trays help access.

DIMS

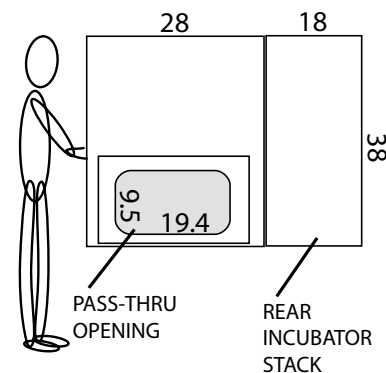
TOP VIEW



FRONT VIEW



END VIEW



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**"We make biological atmospheres,
and make them work for you"**

Since 1982 we've been making unique tools for bio medical scientists. Our tools help you manipulate and control biologically active gases (O₂, CO₂, NO, CO, O₃, H₂S, etc.) in both *in vitro* and *in vivo* applications. We build controllers, chambers, partial systems, and complete systems. We can even "soup up" any existing third party equipment. If necessary, we can customize to exactly fit your needs. We guarantee solutions.

CUSTOM GLOVE WORKSPACE CHAMBERS can be built for all sorts of other cell processing equipment, such as microscopes, cell sorters, centrifuges, electroporators, gene guns, irradiators, etc. to receive transport chambers.

