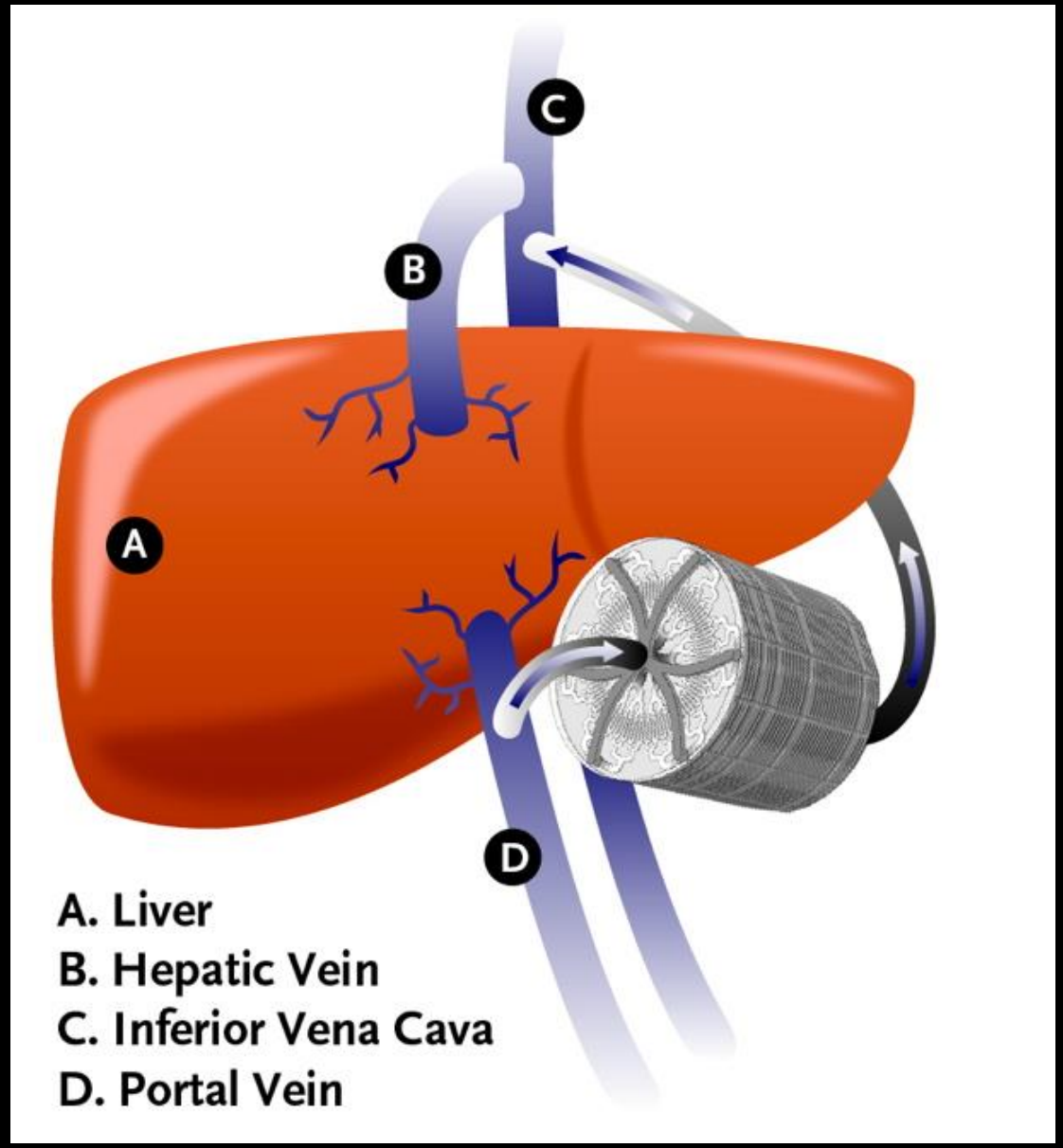


Bio Artificial Liver

Prajapati Hiral

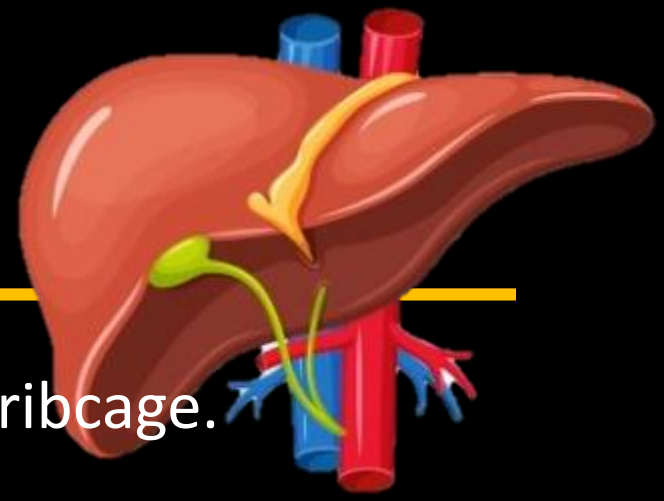
CONTENTS

- Introduction
- Liver and its functions
- Liver Diseases
- History of BAL
- Bio-artificial Liver Systems
- Treatments
- Bioreactor Designs
- Advantages
- Disadvantages
- Future Challenges

INTRODUCTION

- The liver, a one of the most complex organs in the body and the hardest to replace.
- It removes toxins from the blood and manufactures more than 1,000 proteins, metabolites and other vital substances.
- A bio-artificial liver has a two-part chamber—patient's blood on one side, live animal (rabbit) cells suspended in a solution on the other—with a semipermeable membrane in between. As toxins from the blood pass through the membrane, the animal cells metabolize them and send the resulting proteins and other good things back to the other side.
- Because the animal cells never come into direct contact with human blood, the chances of infection or rejection are minimized.

LIVER AND ITS FUNCTIONS



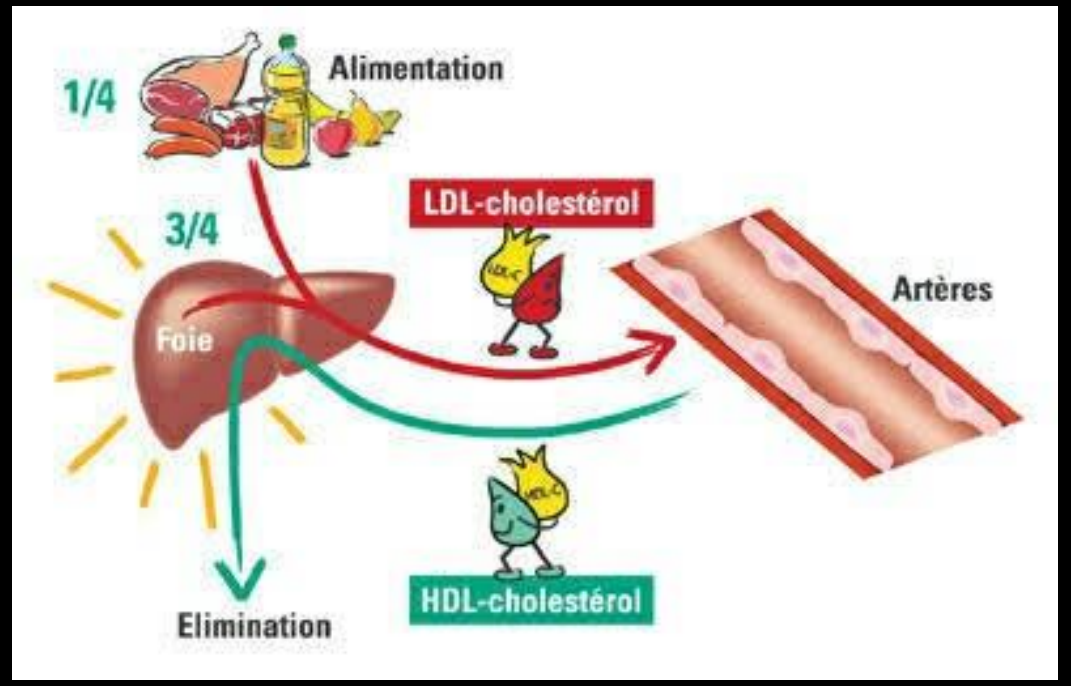
- Located in the right upper abdomen, just underneath the ribcage.
- Liver is responsible for cleaning the blood.
- The liver produces bile that aids in the digestion of fats. It also helps maintain the right level of blood sugar in the body.
- Liver cells are organized into units called lobules, each with their own blood supply.
- One of the liver’s many jobs is to process and purify the blood, removing alcohol and any toxins, including byproducts of medication.
- With the help of vitamin K, the liver produces proteins that help the blood to clot. In addition, this organ works to break down old or damaged blood cells.

LIVER DISEASES

- **Fascioliasis:** This is caused by the parasitic invasion of a parasitic worm known as a liver fluke. Fascioliasis is considered a tropical disease.
- **Cirrhosis:** This sees scar tissue replace liver cells in a process known as fibrosis. This condition can be caused by a number of factors, including toxins, alcohol, and **Hepatitis**.
- **Hepatitis:** Hepatitis is the name given to a general infection of the liver, and viruses, toxins, or an autoimmune response can cause it. It is characterized by an inflamed liver.

LIVER DISEASES

- **Alcoholic liver disease**
- **Primary sclerosing cholangitis (PSC):** PSC is a serious inflammatory disease of the bile ducts that results in their destruction.
- **Fatty liver disease:** This usually occurs alongside obesity or alcohol abuse.
- **Gilbert's syndrome:** This is a genetic disorder.
- **Liver cancer:** The most common types of liver cancer are hepatocellular carcinoma and cholangiocarcinoma.



HISTORY OF BAL

- Dr. Kenneth Matsumara, a world-renowned scientist, has developed a device called a bioartificial liver. In 1987, Matsumura (at ALIN Foundation) reported the first application of a BAL support system in a patient. And later this invention was consider as the invention of the year by Time magazine in 2001.
- Dr. Kenneth Matsumura took a completely different approach to developing an artificial liver. Instead of trying to design all the complexities that perform each of the liver's functions, he designed a device that uses liver cells grown in culture.
- Because the device contains both biological and manufactured components, it is called a “bio-artificial liver” A patient's blood circulates through this bio-artificial liver, where a unique synthetic membrane separates it from the animal cells.

BIOARTIFICIAL LIVER SYSTEMS

- Acute liver failure (ALF) is a disease with a high mortality. Standard therapy at present is liver transplantation. Liver transplantation is hampered by the increasing shortage of organ donors, resulting in high incidence of patients with ALF dying on the transplantation waiting list.
- Among a variety of liver assist therapies, BAL therapy is marked as the most promising solution to bridge ALF patients to liver transplantation or to liver regeneration, because several BAL systems showed significant survival improvement in animal ALF studies. Until today, clinical application of 11 different BAL systems has been reported.

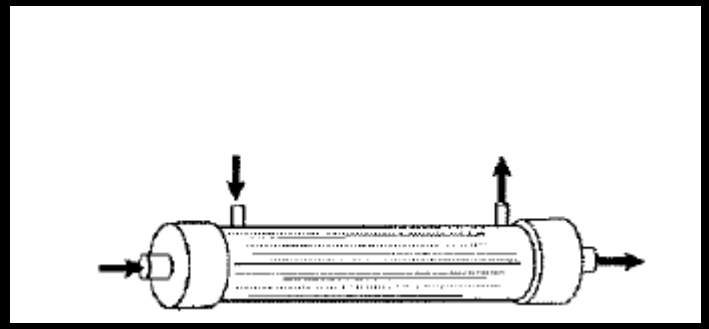
TREATMENTS

- Bioartifical liver, in this system patient blood or plasma is pumped into bioreactors which are hollow fiber devices seeded on the dialysate side with freshly isolated or cryopreserved porcine hepatocytes or transformed human hepatoma cell line.
- CELLULAR COMPONENT OF BIOARTIFICIAL LIVER DEVICES
- The full complement of cellular functions required in BAL devices to effect positive clinical outcomes has not been determined. To address this problem, surrogate markers of each class of liver-specific functions typically are characterized including: synthetic, metabolic, detoxification (phase I and II pathways), and biliary excretion.

TREATMENTS (CONTINUE)

- STABILIZATION OF PRIMARY HEPATOCYTE PHENOTYPE
- Although primary hepatocytes represent the most direct approach to replacing liver function in hepatic failure, they are anchorage-dependent cells and notoriously difficult to maintain in vitro. When enzymatically isolated from the liver and cultured in monolayer or suspension cultures, they rapidly lose adult liver morphology and differentiated functions.
- Finally, liver-specific functions are stabilized in hepatocytes that are cocultured with nonparenchymal cells.
- Modifications such as hormonally defined media55,67 and addition of low concentrations of dimethyl sulfoxide68 or dexamethasone69 are known to help stabilize hepatocyte morphology, survival, and liver-specific functions.

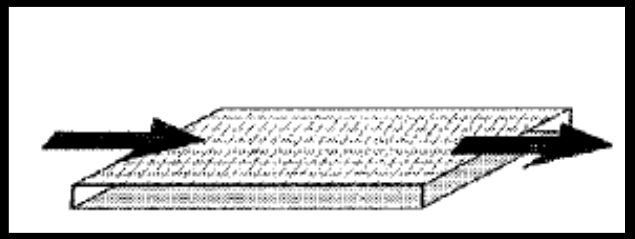
BIOREACTOR DESIGNS - HOLLOW FIBER



Hollow Fiber

- Extracapillary cryopreserved cells on microcarriers
- C3A cells cultured in extracapillary space
- Multicompartmental interwoven fibers with extracapillary seeding and oxygenation
- Cells entrapped in contracted gel in interlumenal space.
- Cells entrapped in collagen gel in extracapillary space.
- Tricompartmental coaxial hollow fibers.
- Extracapillary seeding with in-line oxygenation.
- Dialysis against circulating hepatocytes
- Spirally-wound fabric scaffold and integrated hollow fiber oxygenation

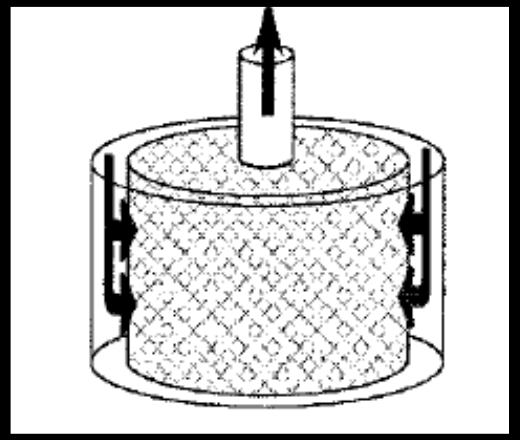
BIOREACTOR DESIGNS - FLAT PLATE AND MONOLAYER



Flat Plate and Monolayer

- Dialysis against cell suspension
- Flat membrane reactor with cell in sandwich culture.
- Stacked plates of monolayer culture.
- Stacked plate reactor with monolayer culture
- Monolayer coculture with membrane oxygenation
- Collagen gel sandwich culture bioreactor

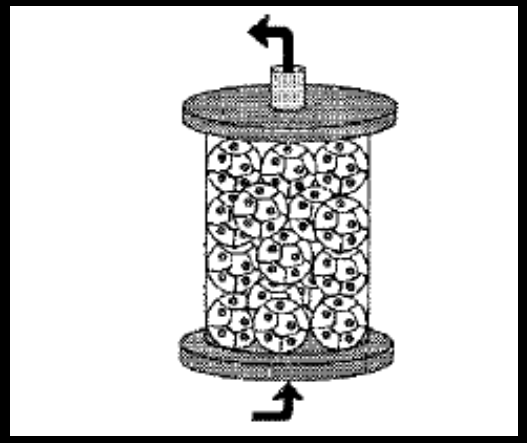
BIOREACTOR DESIGNS - PERFUSED BEDS/SCAFFOLDS



Perfused Beds/Scaffolds

- Radial flow through packed bed, cells on glass microcarriers.
- Microchanneled polyurethane packed bed with spheroids.
- Polyvinyl resin cubes seeded with cells in a packed bed.
- Murine cell line on porous carriers in packed-bed
- Radial flow through polyester fabric cellscaffold

BIOREACTOR DESIGNS - ENCAPSULATION AND SUSPENSION



Encapsulation and Suspension

- Encapsulation:
  - Spouted bed perfusion with encapsulated spheroids
  - Fluidized bed of alginate encapsulated cells
  - Encapsulated spheroids in perfusion chamber
  - Multicomponent capsules containing rabbit hepatocytes
  - Entrapped aggregates in glass bead packed bed
  - Hydrogel entrapped cells on rotating disks with perfusion
- Suspension:
  - Perfusion chamber with membrane isolated cell and charcoal suspension
  - Cell suspension with a centralized spinning filter

REGULATION AND SAFETY

- Current devices are being regulated as drugs through the Center for Biologics and Evaluation Research of the Food and Drug Administration.
- Hybrid devices are being developed by a consensusbased group at the American Society of Testing and Materials in conjunction with other organizations such as the International Standards Organization.

REGULATION AND SAFETY

- The safety concerns for BAL devices are similar to those for other cellular therapies and include immune reactions to foreign antigens, xenozoonosis, and escape of tumorigenic cells.
- The design of clinical trials for BAL devices has proven to be very challenging for a number of reasons. First, the course of liver failure is variable and etiology dependent. Animal models using hepatotoxins, ischemia, obstruction, or hepatectomy each have had limited predictive ability.

ADVANTAGES

- Chances of survival for burn patients.
- Artificial Skin seals the wound preventing fluid and bacteria from entering thought the wound.
- The fear of Stigmatization of the patient is eliminated.
- It performs metabolic functions in addition to detoxification.
- BAL therapy is marked as the most promising solution to bridge to liver transplantation or to liver regeneration.

DISADVANTAGES

- Risk of infection and rejection by the patient.
- Lack of vascularization to the implanted skin or skin cells can lead to the cell death which provide a breeding ground for bacteria.
- Loss of sensitivity.
- Cut of blood supply.
- Artificial skins are very expensive.

FUTURE CHALLENGES

- Research in cell sources/viability, bioreactor design, filtering techniques, packaging for implantable devices.
- Should provide at least 10% of liver functioning.
- Limited volume of bioreactor.
- Hepatocytes and plasma have very different physiochemical properties.
- Hepatocytes cells undergo a lot of stress inside of bio-artificial liver.

Thank you !!!