ADVANCES IN EXTRACORPOREAL LIVER SUPPORT

Ram Subramanian MD,MBA

Hepatology and Critical Care

Emory University

DISCLOSURES

- Consultant: Baxter

OUTLINE

- Review the rationale for the need for extracorporeal liver support (ECLS)
- Discuss goals of ECLS in different types of liver failure
- Outline current modalities of extracorporeal liver support
- Propose future applications of liver support

Rationale for Extracorporeal Liver Support

- According to 2020 US adult liver transplant data:
  - Waitlist recipients: *11,884*
  - Transplants: *8,906*
  - Waitlist removal (death or too sick)*: 2426*
  - Rising disease acuity (MELD) at time of transplant due to organ reallocation policies

- Given above trends, strategies are required to:
  - (a) facilitate hepatic recovery *or*
  - (b) stabilize liver function on the waitlist

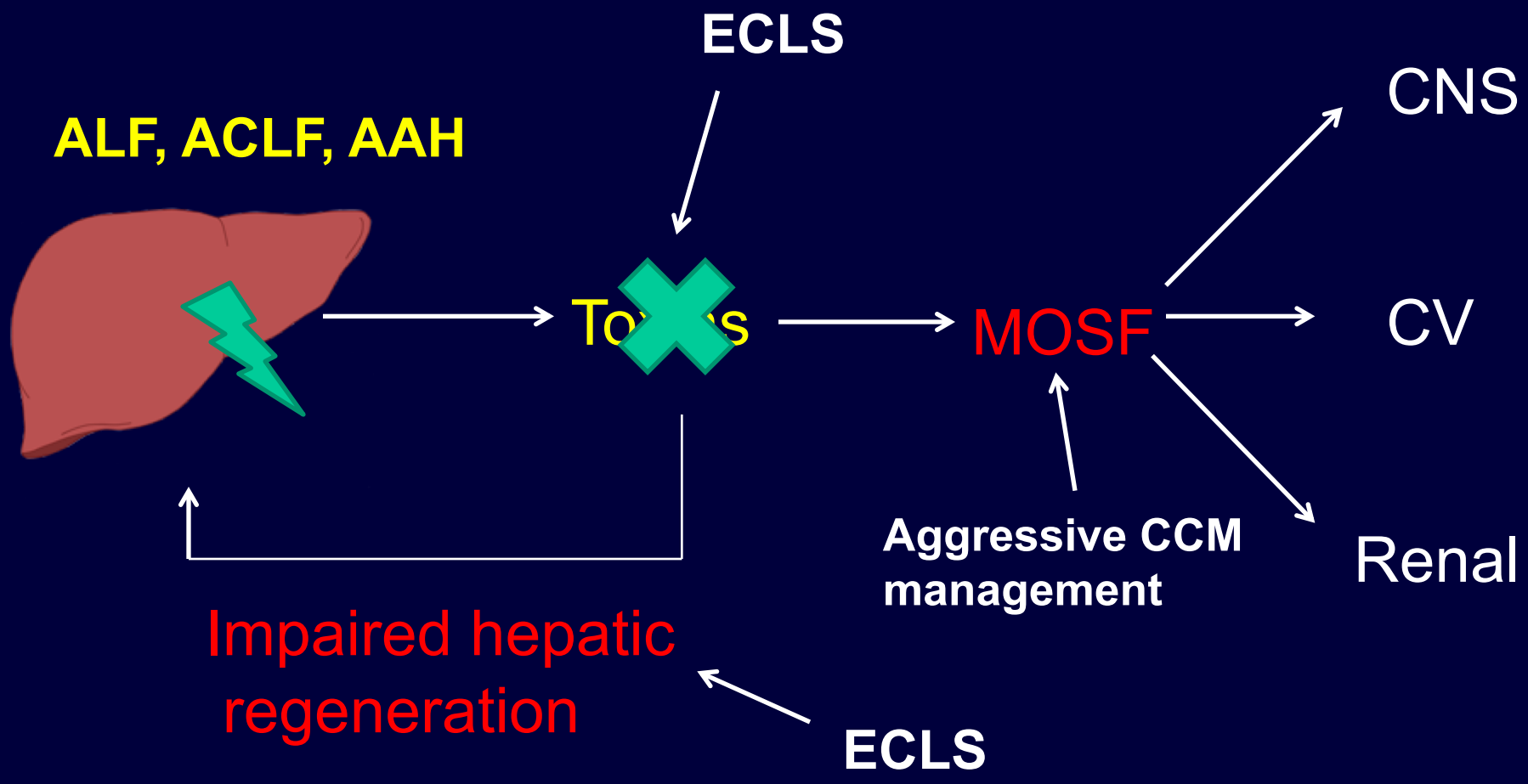
- Potential role of ECLS systems in achieving above goals

Classification of Liver Failure

- ***Acute Liver Failure:***
  - Acute hepatic dysfunction in the absence of chronic liver disease (e.g. acetaminophen overdose)
  - Potentially reversible to normal hepatic function following hepatic regeneration
  - Role of ECLS: bridge to *intrinsic hepatic recovery or LT*

- ***Acute on Chronic Liver Failure:***
  - Decompensation of prior cirrhosis (e.g. Hep C cirrhosis)
  - Resolution of acute insult does not result in resolution of underlying chronic hepatic dysfunction
  - Role of ECLS: bridge to *temporary stabilization or LT*

Mechanistic Rationale for ECLS



ECLS CATEGORIES

- 'Artificial' Liver Support:
  - No hepatocytes in extracorporeal circuit
  - Mechanism: Detoxification
  - Examples:
    - Albumin dialysis (e.g. Molecular Adsorbent Recirculating System, MARS)
    - High Volume Plasma Exchange
    - 'High Dose' CRRT

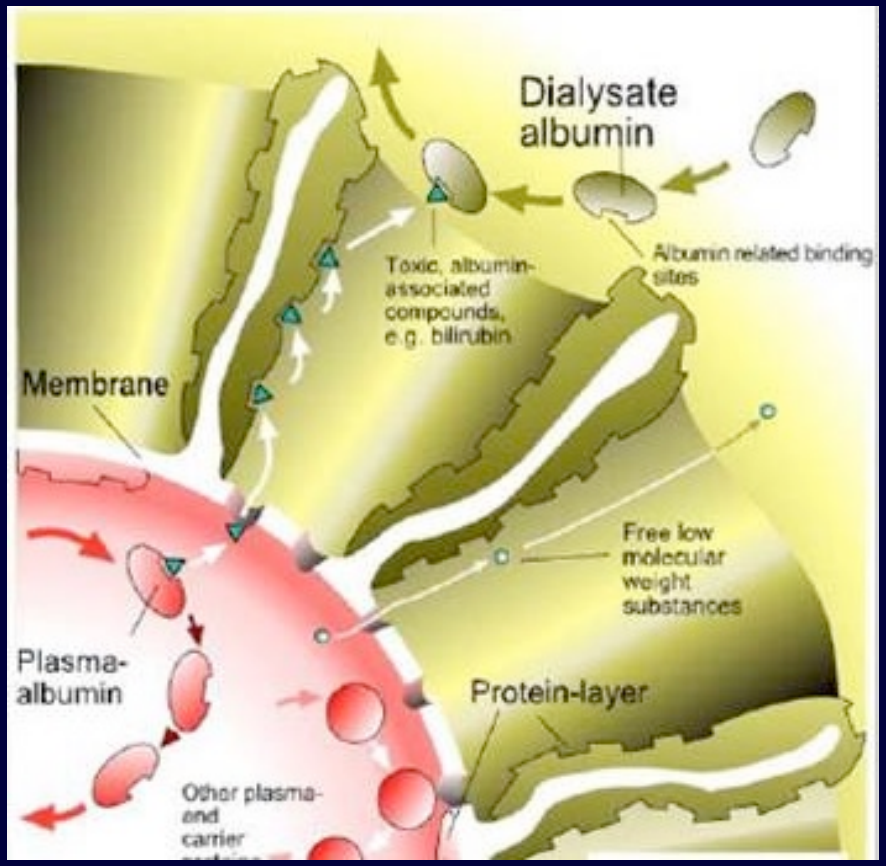
- 'Bioartificial' Liver Support:
  - Hepatocytes in extracorporeal circuit (human/ porcine)
  - Mechanism: Detoxification & Synthesis
  - Examples:
    - Extracorporeal Liver Assist Device, ELAD (human)
    - HepatAssist (porcine)

ARTIFICIAL LIVER SUPPORT:

‘MARS’ Albumin Dialysis

Principles of MARS Albumin Dialysis

- In addition to intravascular expansion, important role of albumin in binding protein bound toxins.
- In liver failure, quantitative and qualitative defects documented in serum albumin (*Jalan et al, Hep 2006*)



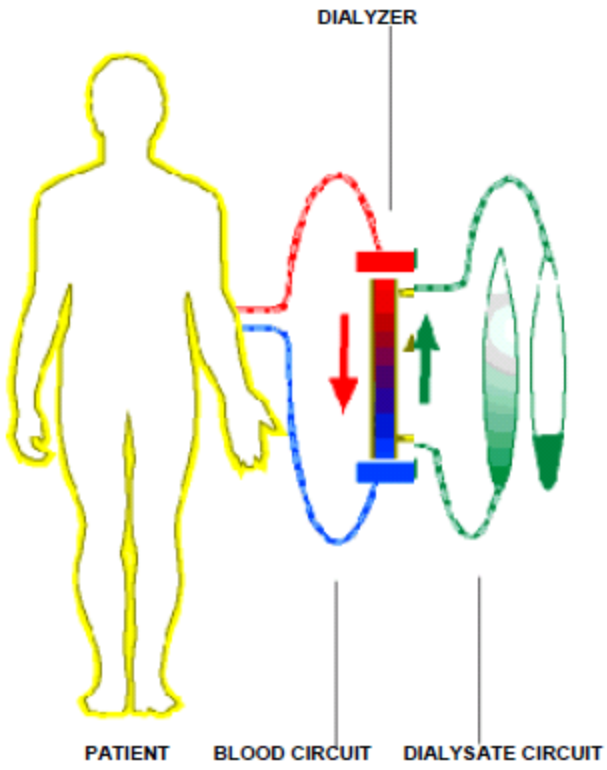
- In contrast to hemodialysis, the initial dialysate is a 16% albumin solution
- The albumin dialysate and membrane pore size (50k Da) allow the extraction of both water soluble and albumin bound toxins

Table 1. Removal of Substances During Albumin Dialysis MARS

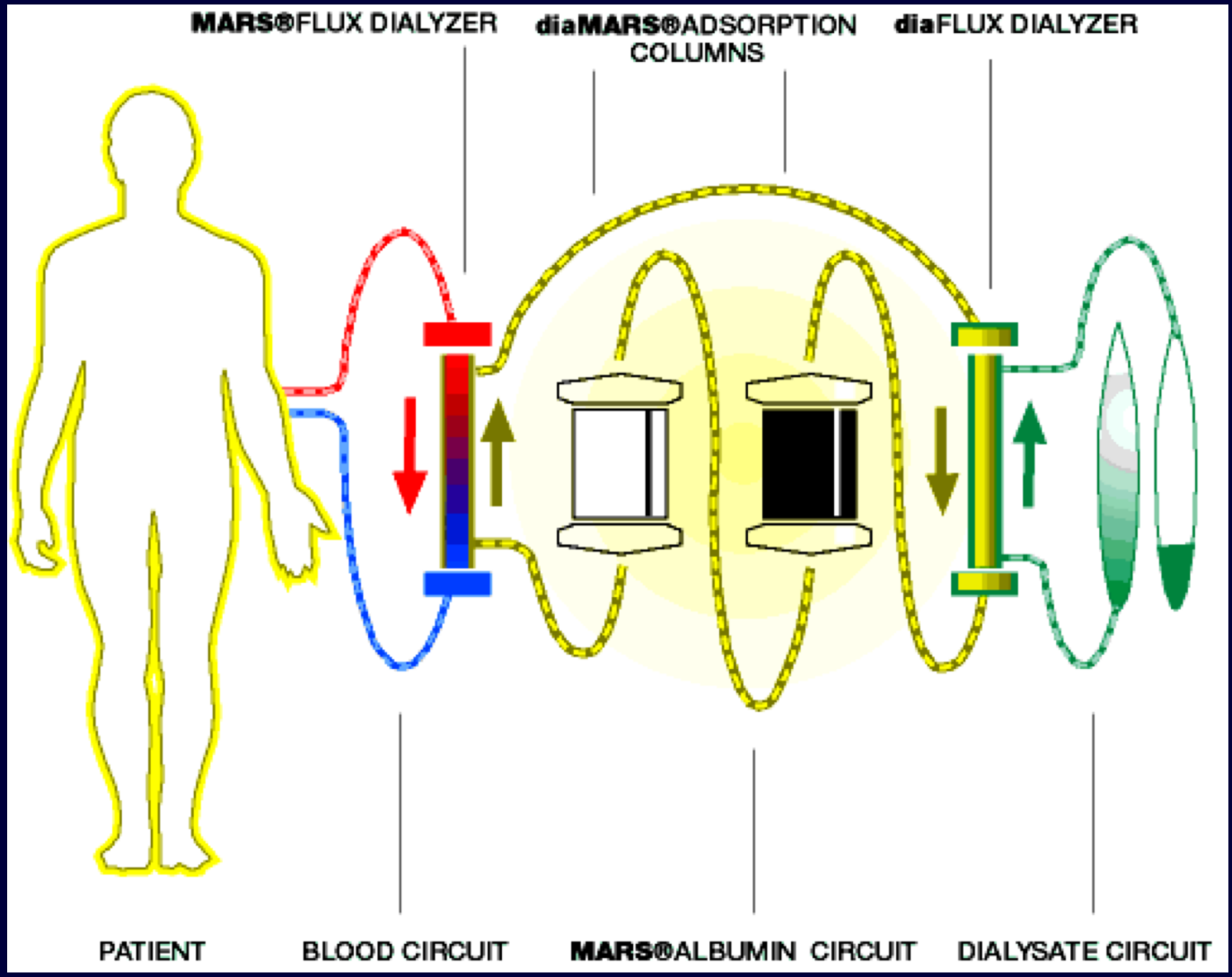
Albumin-Bound Substances	Water-Soluble Substances
Benzodiazepines*†	Ammonia
Bilirubin, conjugated	Aromatic amino acids
Bilirubin, unconjugated	Creatinine
Bile acids	Interleukin 6
Copper	Tryptophan
Furancarboxylic acid	Tumor necrosis factor alpha
Indoyxlsulfate	Urea
Middle- and short-chain fatty acids	
Nitric oxide	
Para-cresol†	
Protoporphyrin	

Mitzner SR, Stange J,Klammt S, et al: Albumin Dialysis MARS:Knowledge from 10 years of clinical investigation. *ASAIO Journal 2009*: 498-502, 2009.

Renal Replacement Therapy



MARS



- *Duration:* 8 hours of MARS therapy / day for 3-5 consecutive days.
- *Albumin dialysate:* 600 ml of 16 % albumin (400 ml of 25% albumin + 200 ml of normal saline)
- *Blood flow:* 180ml / min
- *Anticoagulation:* Heparin or citrate

Beneficial Effects of MARS(*Observational Studies*)

- Improvement of jaundice and pruritis (adult and peds (*Jain et al. JPGN 2017*))
- Improvement of hemodynamic instability (NO removal ?)
- Reduction in portal pressure
- Reduction in ICP in ALF, and *hepatic encephalopathy in ACLF* (RCT as well)
- Improvement of renal function in HRS
- *Short term (14-d) survival benefit in severe ACLF* (Gerth et al. Crit Care Med 2017, 9.5% vs 50% mortality rate)
  - *(utility of MARS as a bridge to transplant ?)*

RCTS with MARS

- Few RCTS comparing MARS to SOC have not demonstrated a survival benefit (yet)
  - *RELIEF trial* (Banares et al, Hep 2013) in ACLF adult patients (n=189) did not demonstrate a benefit on *28 d survival*
  - *FULMAR trial* (Saliba et al, Ann of Int Med 2013) in adult ALF patients (n=102) did not demonstrate a benefit on *6 mo survival* (of note, ~75% of pts in both study arms underwent transplant within 24h of enrollment)
- *Reversal of severe hepatic encephalopathy* documented in 2 RCTs (Hassenein et al. Hep 2007, Banares et al. Hep 2013)
- No increased adverse events in MARS groups compared to controls in above studies.
- No RCTs looking specifically at MARS efficacy as a bridge to transplant in ACLF and ALF

Applications of MARS

- Bridge to spontaneous recovery or transplant in ALF (*increasing use of CRRT instead*)
- Bridge to transplant in ACLF
- Treatment of Hepatic Encephalopathy in ACLF
- Treatment of cholestatic DILI
- Treatment of refractory pruritis

‘Artificial’ ECLS with High Volume Plasma Exchange (HVP)

- RCT in an ALF cohort (n=182) demonstrated a statistically significant benefit in transplant free survival (*Larsen et al. J Hepatol 2016*)

- HVP defined as an exchange of 8-12 liters FFP over ~ 9hrs, with 2.4 mean number of sessions per patient

- Primary endpoint: transplant free survival during hospital stay : *58.7% HVP, 47.8% SMT* (HR 0.56, p< 0..01). Secondary endpoints: Improvement in INR, Bili, *MAP* in HVP group.

- Current multi-center adult trial of Albumin PLEX in ACLF

‘High Dose’ CRRT in ALF

- In ALF, severity of hyperammonemia associated with worsening intracranial hypertension. (*Bernal et al. Hepatology 2007)*
- Evidence supporting efficacy of **high dose CRRT** (90ml/kg/hr dialysate;) in reversing hyperammonemia, (*Slack et al. Liver Int 2014)*
- Emerging observational data to suggest utility of CRRT in treating hyperammonemia (goal < ~100 umol/ L) to reverse ICH and improve survival. (*Cardoso et al. Hepatology 2017, Warillo et al. Crit Care Med 2020*)
- *Should hyperammonemia be an indication for CRRT independent of other conventional indications for RRT*?
- Case series in pediatric ALF combining CRRT and PLEX (*Ide et al. Ped Crit Care Med 2015*)

Case Illustration:

Combined High Dose CRRT and PLEX

(Veeramachaneni et al. Hepatology 2021)

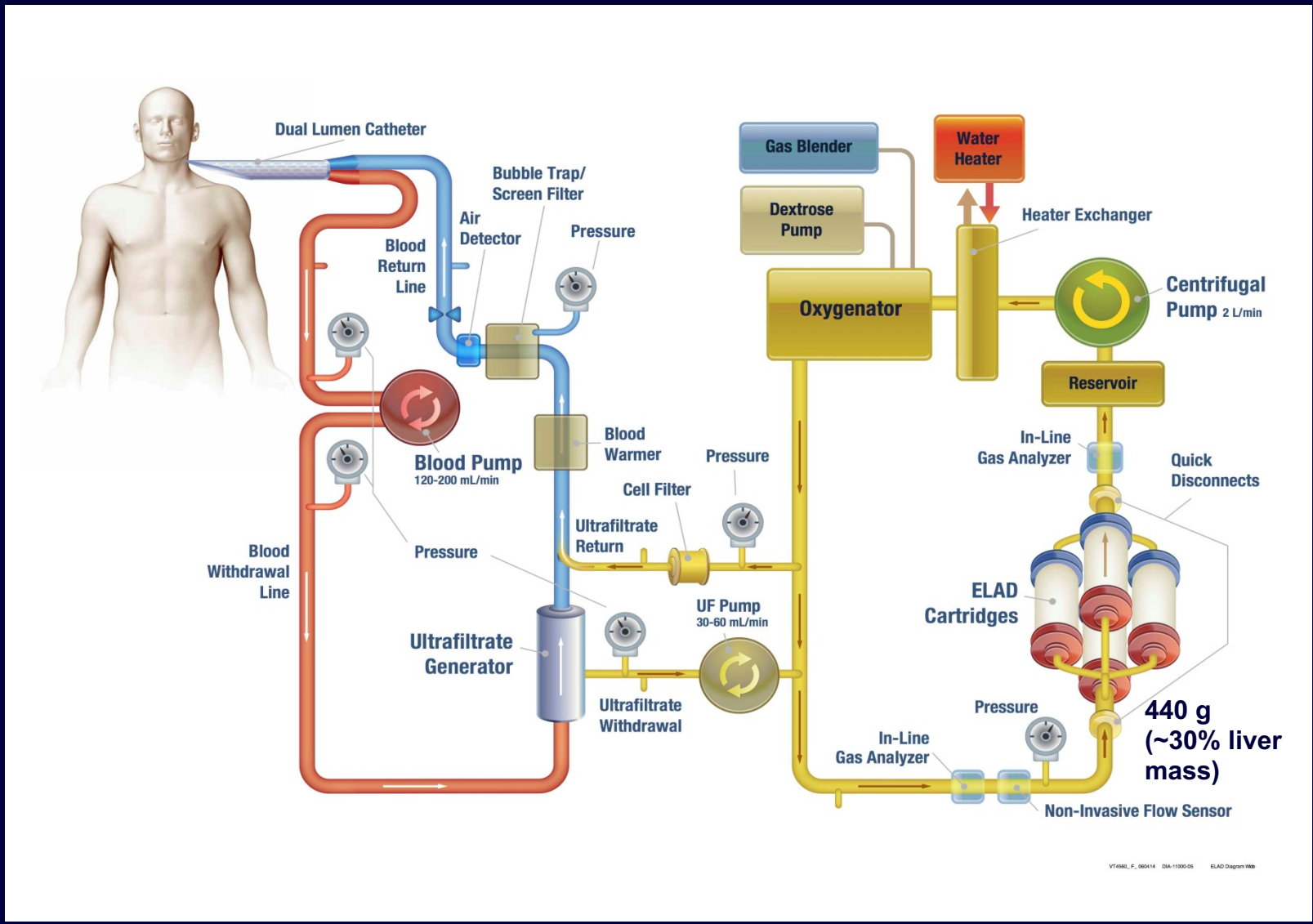
- 30 y/o F, with herbal DILI induced severe ALF, presents to OSH:
  - Neuro: G4 HE, *serum ammonia of 500 mcmol/ L*
  - CV: severe shock requiring maximal pressor support
  - Hepatic: *INR 7*, TAs ~ 10,000s, *ph 6.9*

- Emergently transferred in to Emory:
  - High dose CRRT initiated
  - PLEX co-initiated via 2nd dialysis catheter
  - Within 24 hours,
    - NH_3 < 150; pupillometry and Head CT stable
    - Correction of metabolic acidosis
    - *Dramatic improvement in shock*
  - Patient transplanted 48 hours later, with stable intraoperative and post operative course

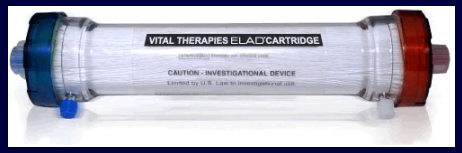
BIOARTIFICIAL LIVER SUPPORT

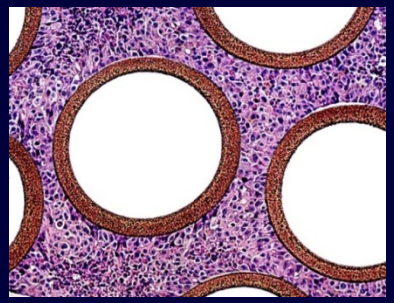
- Extracorporeal liver support systems containing hepatocytes that are aimed at providing both detoxifying and synthetic hepatic function
- Human and porcine hepatocyte based systems trialed to date, without a documented survival benefit
- Challenges of developing a bioartificial system have included maintaining hepatocyte viability and functions
- Most recent iteration using an immortalized hepatoblastoma cell line (ELAD) trialed in severe alcoholic hepatitis

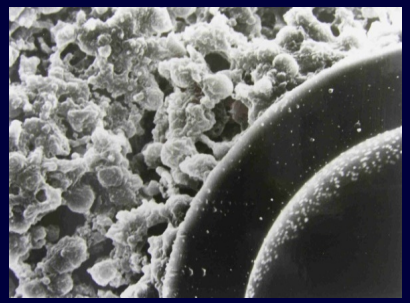
ELAD System


Dual Lumen Catheter
Bubble Trap/
Screen Filter
Air
Detector
Pressure
Blood
Return
Line
Blood Pump
120-200 mL/min
Blood
Warmer
Pressure
Cell Filter
Ultrafiltrate
Return
Blood
Withdrawal
Line
Pressure
UF Pump
30-60 mL/min
Ultrafiltrate
Generator
Ultrafiltrate
Withdrawal
Gas Blender
Water
Heater
Dextrose
Pump
Heater Exchanger
Oxygenator
Centrifugal
Pump 2 L/min
Reservoir
In-Line
Gas Analyzer
Quick
Disconnects
ELAD
Cartridges
Pressure
In-Line
Gas Analyzer
Non-Invasive Flow Sensor
440 g
(~30% liver
mass)

ELAD C3A Cells







Allogeneic Cell Therapy

- Immortalized human C3A liver hepatocytes (Subclone of HepG2 human hepatoblastoma cell line)
- C3A hepatocytes divide to fill available extra-capillary space in the cartridges
- Plasma flows through semipermeable hollow fibers (pore size 0.2 μm)
- **Bidirectional diffusion** between UF and C3A cells; Toxins processed and metabolites secreted across membrane to UF

ELAD: Hepatic Functions:

(In red – retained hepatocyte functions)

Purification, transformation and clearance:

- **Ammonia**
- **Bilirubin**
- **Amino acids**
- **Hormones**
- **Drugs**
- **Toxins**

Regulation:

- **Glucose/glycogen**
- **Cholesterol**
- Kupffer cells

Storage:

- Glucose
- Fat soluble vitamins
- Folate
- Vitamin B_{12}
- Copper
- Iron

Synthesis and secretion:

- **Albumin**
- **Clotting factors**
- **Transporter proteins**
- Cholesterol
- Bile
- **Glucose**
- **Complement**

ELAD Study:
Another failed bio-artificial liver trial

Thompson et al. Liver Transplantation 2018

- Patient population (n=203): Severe alcoholic hepatitis, MELD 18-35
- Primary endpoint: 90 day survival
- Groups: ELAD + SOC vs SOC

- Continuous treatment of ultra-filtrated plasma for up to 5 days

- Cell viability closely monitored with real-time assessment of metabolic activity (e.g. ph, O_2 and glucose consumption)

- Results: *No ELAD benefit on 90 day mortality*; no difference in adverse events

- Trend towards ELAD benefit in pre-defined subgroup of MELD < 28; subsequent study in this sub-population negative

Summary & Future Directions

- Growing evidence supporting the use of Albumin Dialysis in the management of refractory HE in decompensated cirrhosis
- Emerging role for the use of ‘high dose’ CRRT and PLEX in ALF
- In addition to survival benefit, future studies should examine the benefit of ECLS as a bridge to transplant
- Further studies may help identify the limitations of both artificial and bioartificial ECLS, with the potential for combining artificial and bioartificial systems
- The presence of MOSF in both ALF and ACLF create opportunities for coupling ECLS with other extracorporeal organ support systems