Prometheus Unbound: From Myth to the Clinical Reality of Organ Regeneration

Michael Hufford, PhD
Co-Founder & CEO
LyGenesis, Inc.
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Our vision is being led by an experienced, world-class management team

CEO: MICHAEL HUFFORD, PHD

- **Drug development**: P1-P3 trials, FDA lead on pre-INDs, multiple INDs, EOP2 meetings, approved NDAs
- 3x **Co-Founder / C-level** biotech exec (NQ Oncology, e-Nicotine Technology, Harm Reduction Tx)
- **Exits**: Cypress Bio (NMEs) $255M to Royalty Pharma; VP, Corp. & Clinical Development at Cypress Bioscience (NMEs) – Sr Clinical Team Leader at Amylin Pharmaceuticals – eventual $5.3B to BMS

CSO: ERIC LAGASSE, PHARMD, PHD

- World **leader in ectopic transplantation research**
- **Director**, Liver Stem Cell Program at StemCells Inc.
- **Associate Professor** of Pathology, **Director** of Cancer Stem Cell Center at McGowan Institute for Regenerative Medicine, University of Pittsburgh

AMYLIN

Cypress BIOSCIENCE, INC.

HARM REDUCTION THERAPEUTICS

McGowan Institute for Regenerative Medicine

STEMCELLS

Stanford MEDICINE

CMO: PAULO FONTES, MD, FACS

- Leading **transplant surgeon**: cell transplantation, transplant immunology & multi-organ transplantation
- Conducted 2 **clinical trials** (26 pancreatic islet transplants, 350 bone marrow transplants)
- Extensive experience in ce**ll isolation, sorting,** culture and cryopreservation
- Directed **Liver Transplant Program**, Starzl Transplant Institute for almost a decade,
- **Oversaw 1,500 liver transplant** procedures, providing for 10,000 patients
- Extensive scientific contributions with more than 250 publications Consecutive DOD grants for limb transplantation
- Active **biotech entrepreneur**: 7 patents, 3x founder. Director of life science foundation

UPMC LIFE CHANGING MEDICINE

UPMC | TRANSPLANT SERVICES

McGowan Institute for Regenerative Medicine

VirTech Bio

WVUMedicine

LYGENESIS

Investment thesis highlights

Allogeneic cells engrafted into lymph nodes to generate functioning ectopic organ

Positive small and large animal data confirm ability to grow ectopic liver, pancreas, kidney, and thymus tissue… this technology could deliver an end to organ shortages for transplants

Lead cell therapy program starting Phase 2a at Harvard's MGH in patients with End Stage Liver Disease (ESLD)

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Liver program IND-enabled on $7M

Low COGS at $15k/liver treating a dozen patients

Commercially scalable, bolt on to any GMP cell processing facility

Management Team has deep experience with fundraising, M&A, FDA (approved INDs and NDAs), and deep translational and clinical medicine expertise

We aim to operate at the forefront of organ regeneration and transplantation science

1 Donated Organ
Treats Only 1 Patient

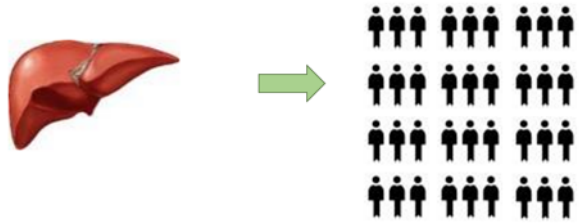
Thousand die each year awaiting organ transplants

Standard of Care

Major Surgery

Sickest patients ineligible and extremely costly procedure

1 Donated Organ
Treats Up to 75 patients



LYGENESIS

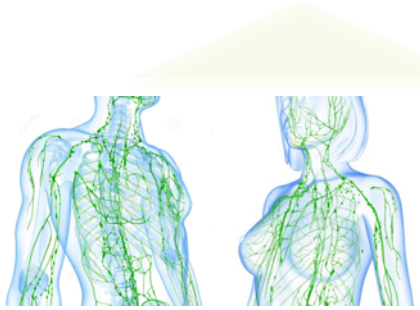
Our Approach

Minor surgery

Endoscopic ultrasound procedure (EUS)

Our organ regeneration platform scales across a wide range of disease indications

Lymph Node



Liver

Thymus

Kidneys

Pancreas

Target Indications

- ESLD
- NASH-related fibrosis
- Multiple orphan indications (e.g., single enzyme deficiencies like PKU, Maple syrup urine disease)

- Aging
- Cancers
- Auto-immune diseases
- Inflammatory diseases
- Tolerance (Organ transplant)
- Pediatric thymectomy post neonatal cardiac surgery

- End stage renal disease

- Type 1 diabetes
- Chronic pancreatitis

LyGenesis

LyGenesis's tissue regeneration programs will provide life-changing benefit to patients with debilitating chronic conditions

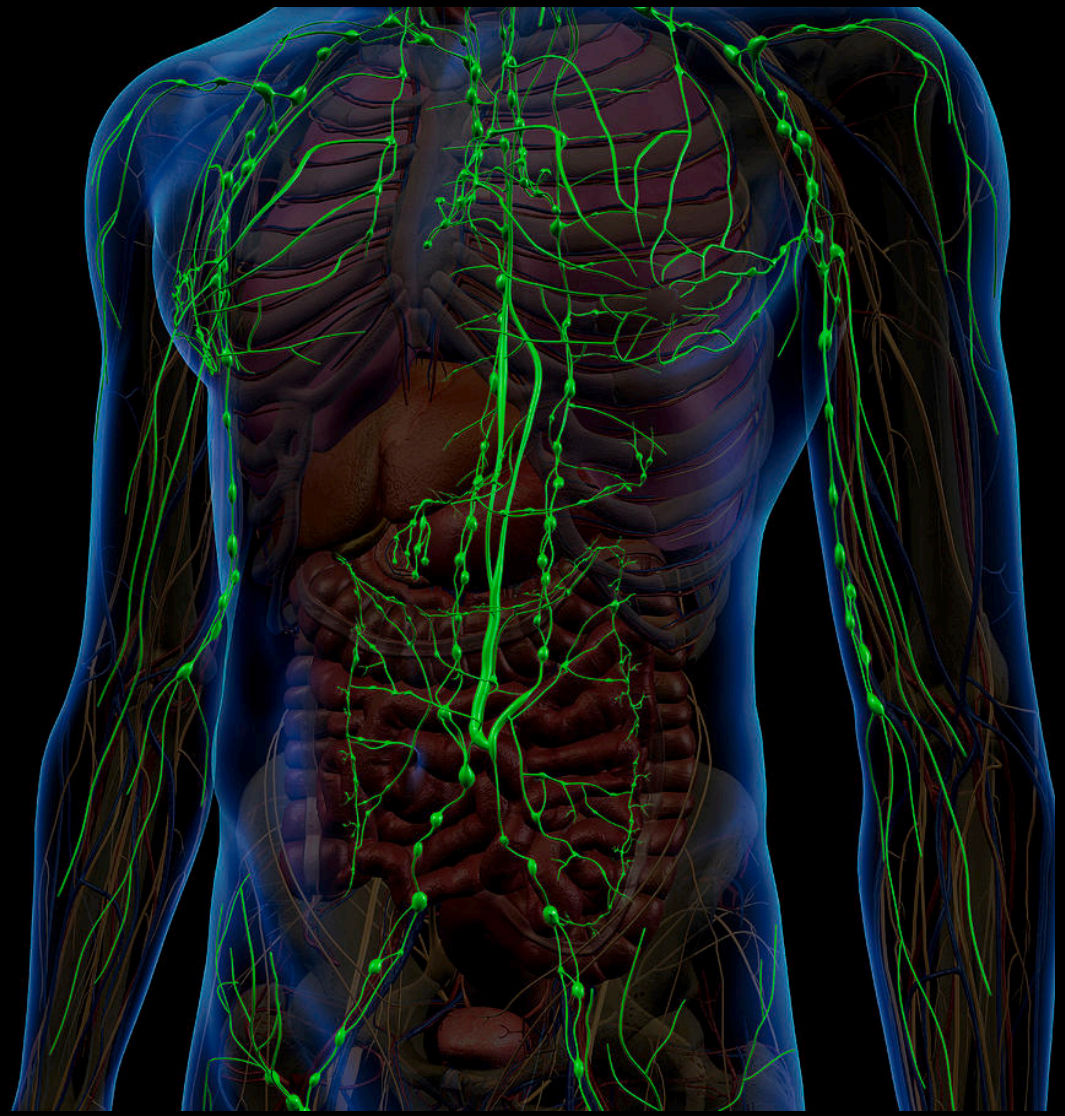
- In the **US alone:**
  - 164 people die daily from liver disease
  - 125,000 people begin treatment annually for End-stage kidney disease (ESKD)
  - 240 dialysis patients die each day
  - 725,000 are on dialysis or living with a kidney transplant
  - CDC- **34M** people currently have diabetes ; **88M** people with prediabetes

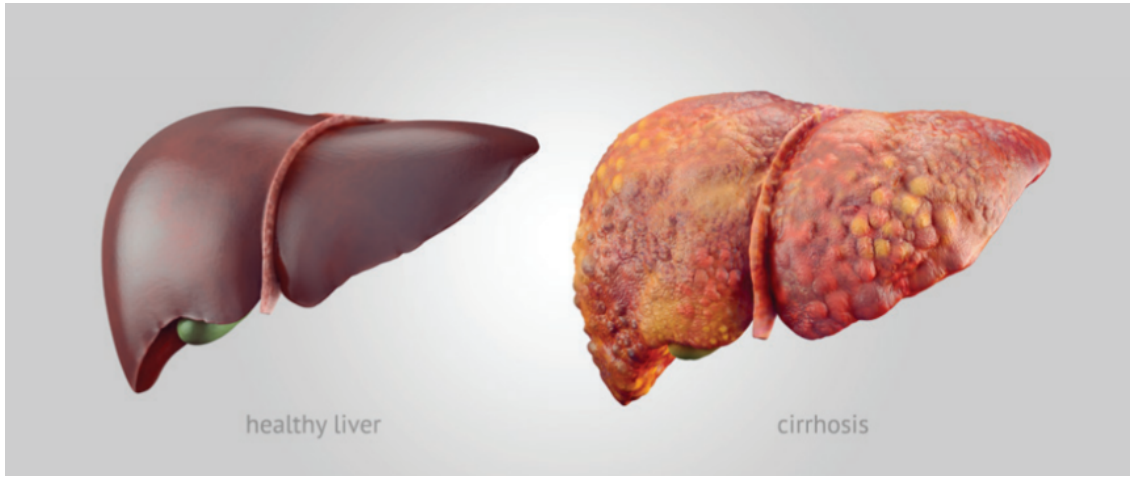
Worldwide

Disease	Incidence (millions)	Mortality (millions)
Liver	**844**	**2**
Renal	**850**	**10**
Diabetes	**422**	**2**
Pulmonary	**650**	**6**
Cardiovascular	**540**	**18**

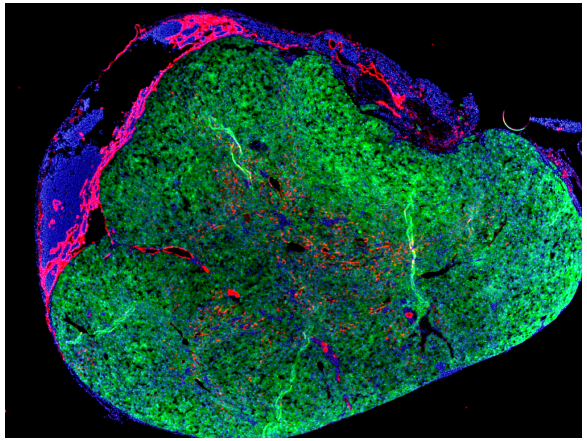
1.CDC: Chronic Kidney Initiative https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html
2.Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ 2018;362:k2817
3. CDC: Chronic Liver and Cirrhosis https://www.cdc.gov/nchs/fastats/liver-disease.htm
4. CDC: Diabetes in the U.S https://www.cdc.gov/diabetes/library/socialmedia/infographics/diabetes.html

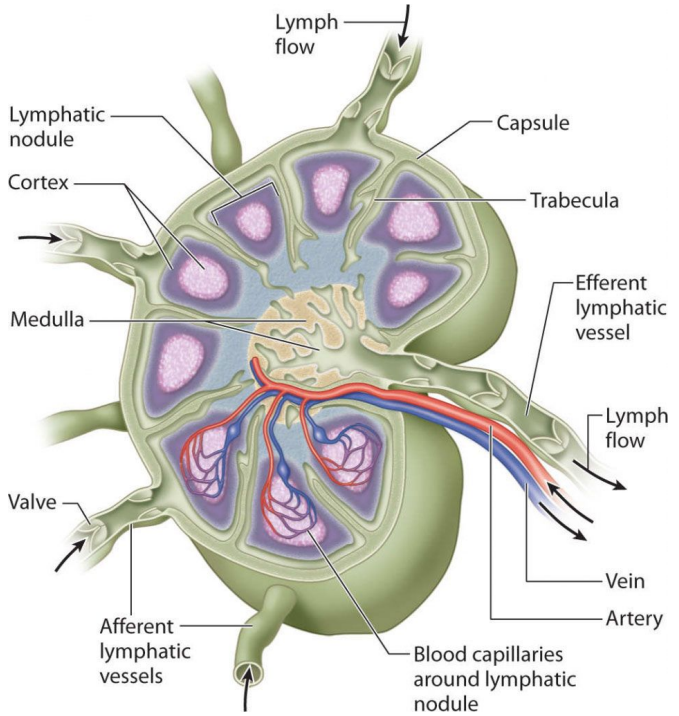
BMJ Journals





LyGenesis

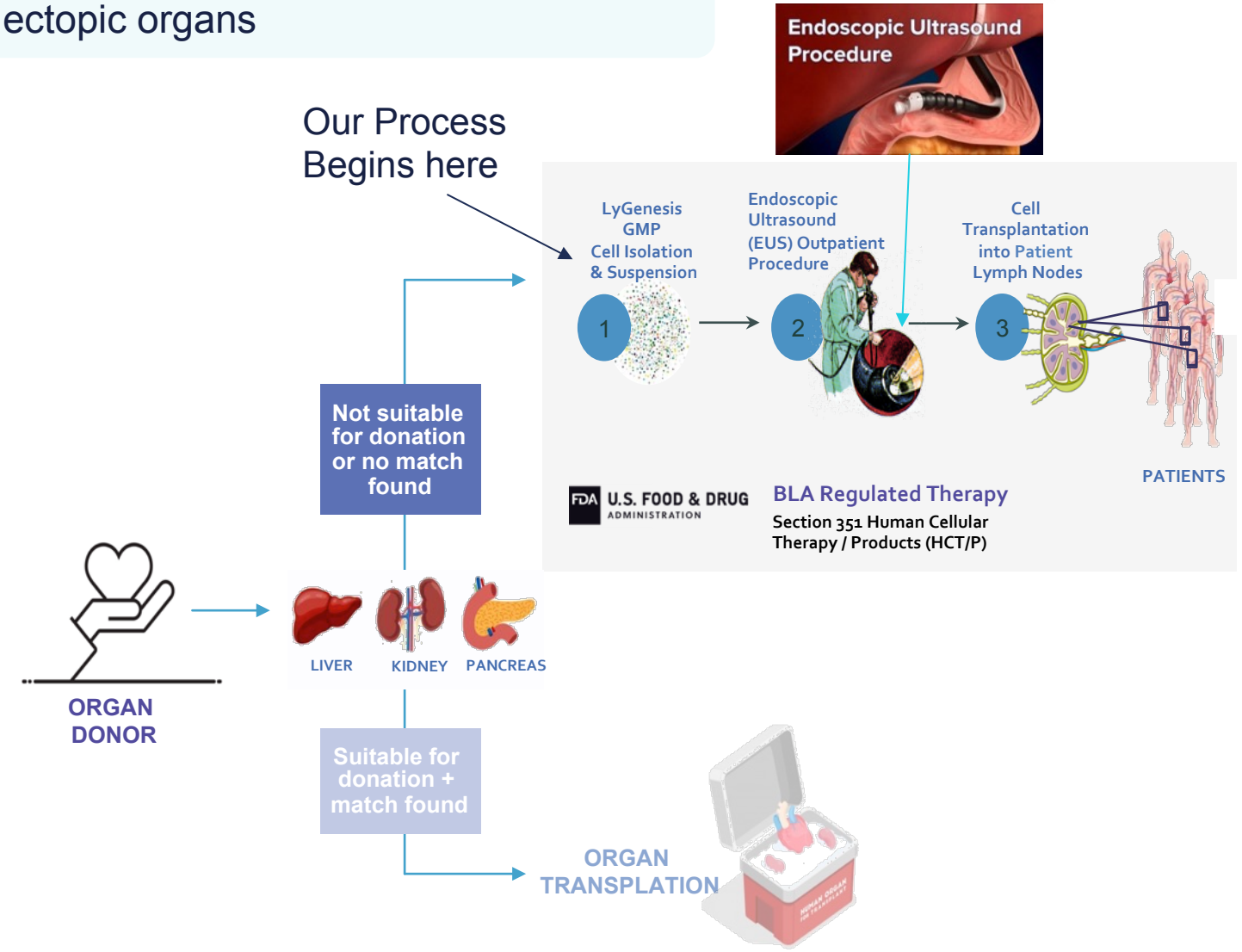




Lymph Node

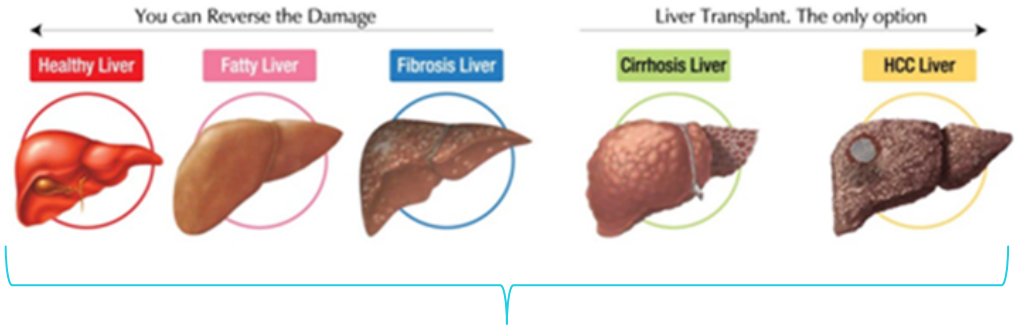
We engraft allogeneic cells into lymph nodes using outpatient endoscopic ultrasound (EUS) to generate functional ectopic organs

- Functional organs exert life-saving effects in multiple small and large animal pre-clinical studies
- Positive animal data show ability to grow ectopic liver, pancreas, kidney, and thymus tissue
- **1** donated liver can generate organs for up to **75** patients
- Lead cell therapy program starting Phase 2a at Harvard's MGH in patients with end stage liver disease (ESLD) in 4Q2021



Organ utilization trends show major opportunities for hepatocyte isolation

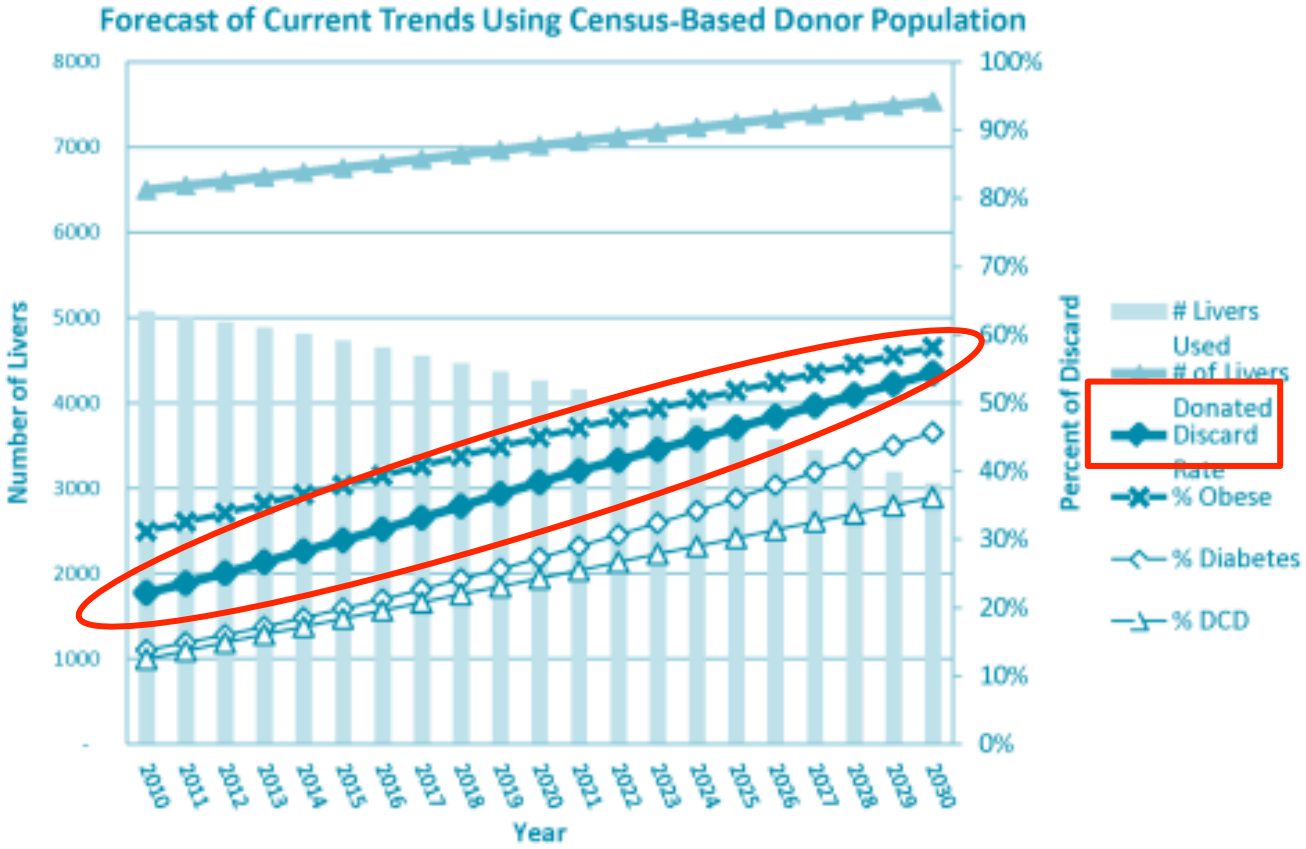
LyGenesis provides a transformative and scalable breakthrough approach to treatment



Thousands of organs available for transplant are never matched, so they are discarded

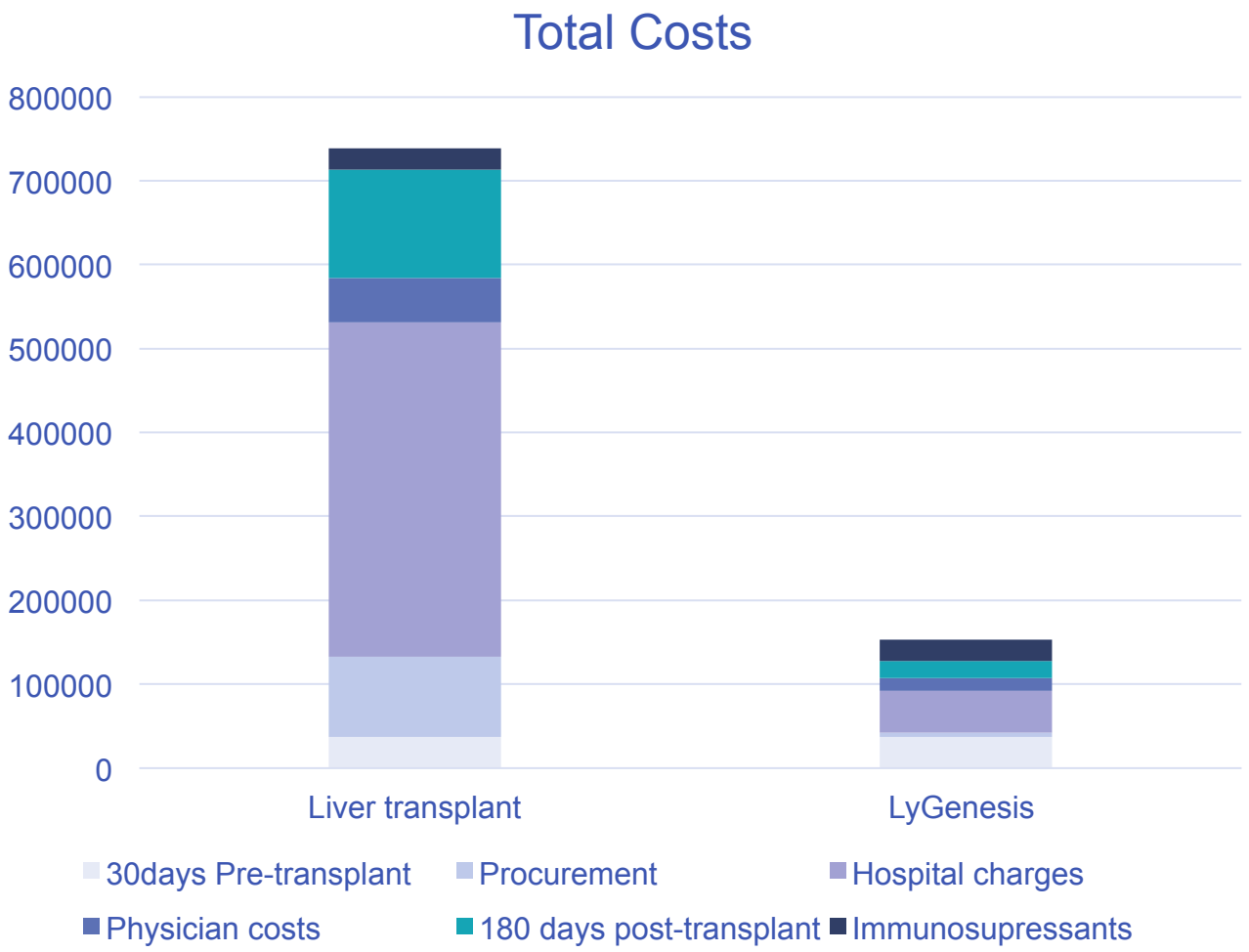
Our technology enables each liver to treat dozens of patients

- Each liver comprises billions of hepatocytes
- Our technology injects 50-250M hepatocytes into 1-5 lymph nodes
- <$15k costs per liver, applicable to multiple livers
- Existing GMP cell processing labs further reduces COGS
- Engraftment relies on endoscopic ultrasound (EUS), safe and inexpensive



Orman SE et al. *Liver Transplantation* 2015; **21**:1040-50

Low COGS, Slots into Any Existing GMP Cell Processing Facility



Low COGS – High Pricing Headroom

COSTS:

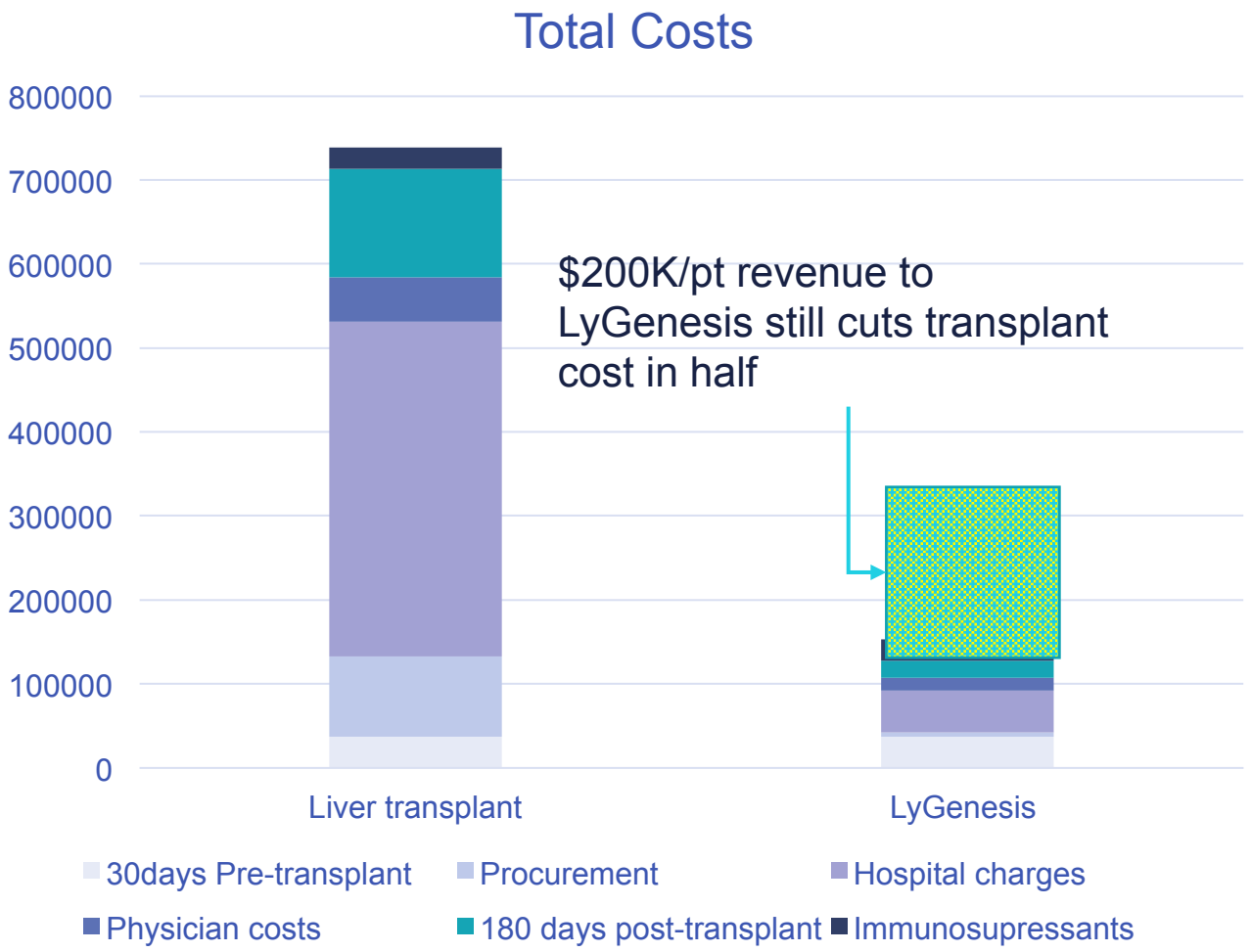
- Transplant procedure: $500K+ vs. LyGenesis EUS: $15K
- <$10K in reagents to process 1 liver, which can treat dozens of patients
- Using organs not otherwise matched for transplant, helps Organ Procurement Organizations lower their discard rates

RAPID GMP PROCESSING:

- Use **any existing GMP cell processing facility** – requires 10’ of bench space + hood
- Takes 2 FTEs ~6 hours to prepare for engraftment

Milliman Research report: 2014 U.S. Organ and Tissue Transplantation Cost estimates & Discussion

Low COGS, Slots into Any Existing GMP Cell Processing Facility



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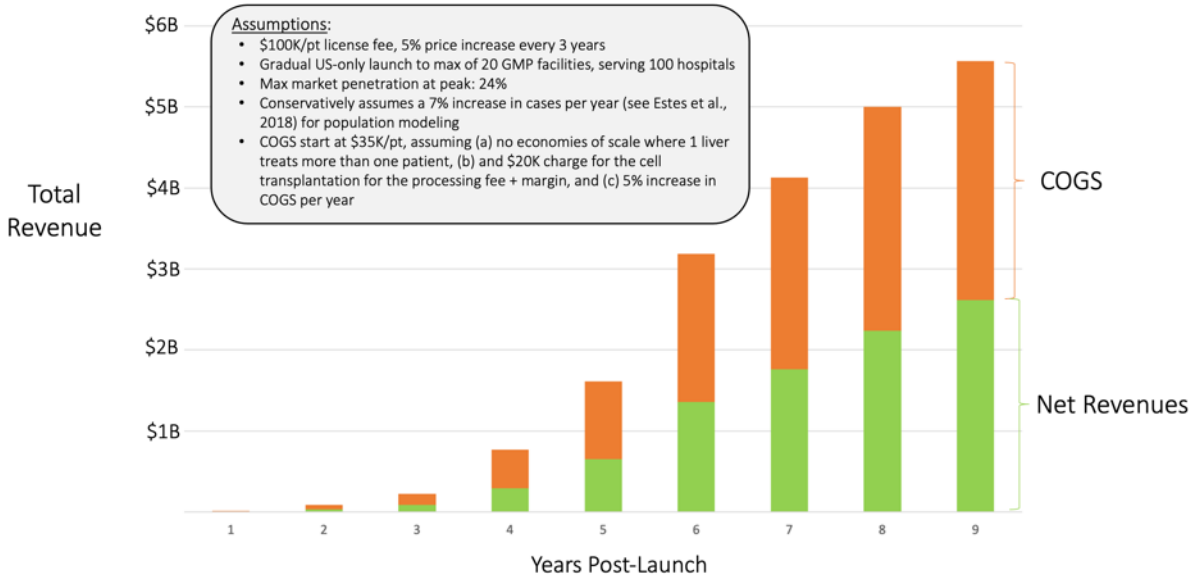
Low COGS, Commercially Scalable with Bolt-On Cell Processing to Existing GMP facilities

Licensing model enables rollout to existing GMP cell processing facilities servicing multiple hospitals without a large salesforce



Low COGS

- <$10K in reagents required to process the donated liver into multiple batches of cells ready to be engrafted
- Outpatient EUS engraftment procedure (CPT 43232) billed at <$2K[1]

Commercially Scalable

- 20 sites are responsible for the majority of liver transplants today[2], making the licensing model to these top centers and other hospitals in the geographic region tractable and cost-effective
- Our cell processing easily bolts onto existing GMP cell processing facilities

Well-Protected

- Issued US patent through mid-2030s, multiple PCTs pending
- Section 351 HCT/Ps require BLAs = 12 years exclusivity post-approval
- FDA and US courts have consistently taken the position that HCT/Ps are not merely "the practice of medicine" and are subject to FDA regulation – including requiring a BLA and all CMC requirements (21 C.F.R. § 1271(a)(4)(ii))[3]

[1] e.g., https://www.cookmedical.com/wp-content/uploads/2019/12/RG_ESC_50099_RF_202001.pdf
[2] https://optn.transplant.hrsa.gov/data/view-data-reports/build-advanced/#
[3] See U.S. v. Regenerative Sciences, LLC, 741 F.3d 1314 (D.C. Cir. 2014)

We can leverage our organ regeneration platform across several disease indications; our pipeline is varied and progressing quickly

	Pre-Clinical			Clinical			
Program ***Indication***	**Discovery/ Lead Optimization**	**Small Animal**	**Large Animal**	**Phase I**	**Phase II**	**Phase III**	**FDA Approval**
Liver *ESLD*	✓	✓	✓	Skip per FDA	FPI: 4Q2021		
Thymus *Multiple indications*	✓	POC complete					
Kidney *ESRD*	✓	POC complete					
Pancreas *T1DM*	✓	POC complete					

Liver program: FPFV expected 4Q 2021

Pre-clinical studies: Our studies in small and large animal models demonstrate successful regeneration of functional tissue

Mouse Model of Tyrosinemia Type I (Fah -/-)

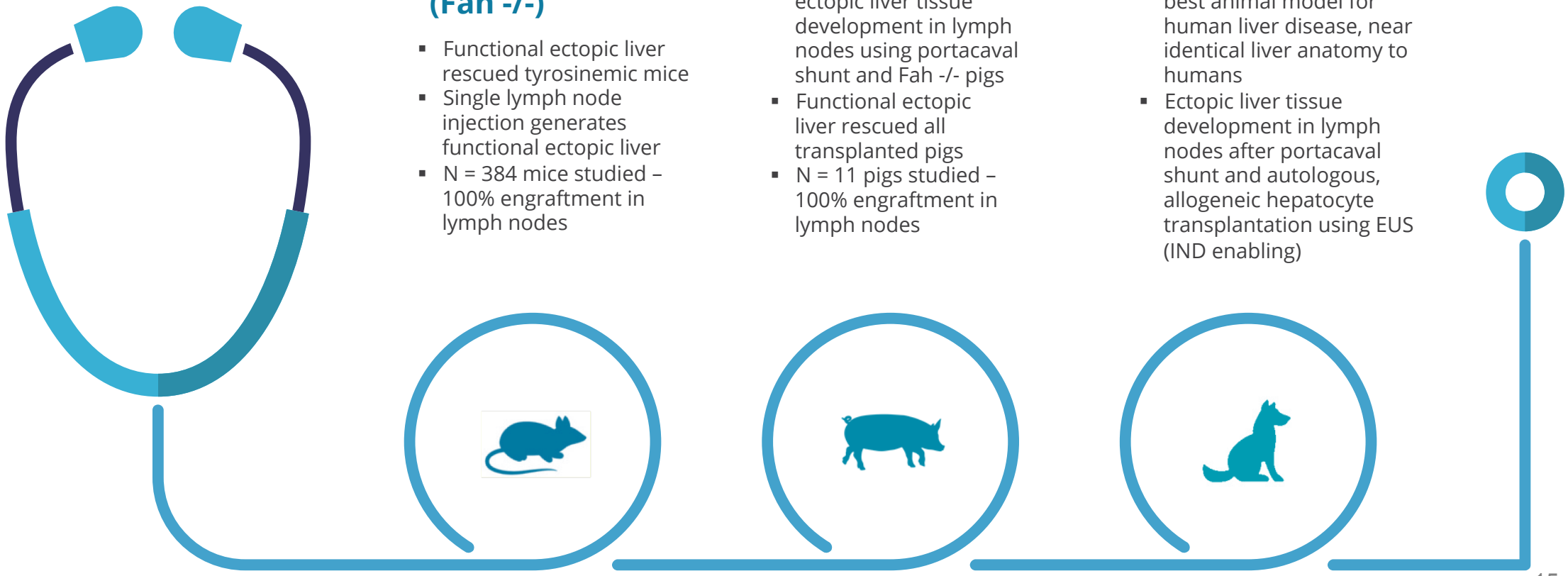
- Functional ectopic liver rescued tyrosinemic mice
- Single lymph node injection generates functional ectopic liver
- N = 384 mice studied – 100% engraftment in lymph nodes

Swine

- Replicate studies showing ectopic liver tissue development in lymph nodes using portacaval shunt and Fah -/- pigs
- Functional ectopic liver rescued all transplanted pigs
- N = 11 pigs studied – 100% engraftment in lymph nodes

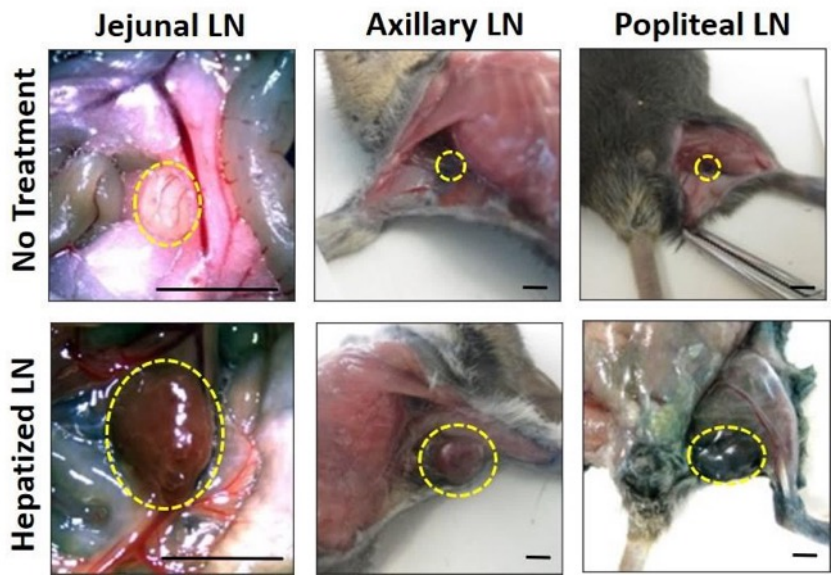
Canine

- Pioneered late 1950s, best animal model for human liver disease, near identical liver anatomy to humans
- Ectopic liver tissue development in lymph nodes after portacaval shunt and autologous, allogeneic hepatocyte transplantation using EUS (IND enabling)

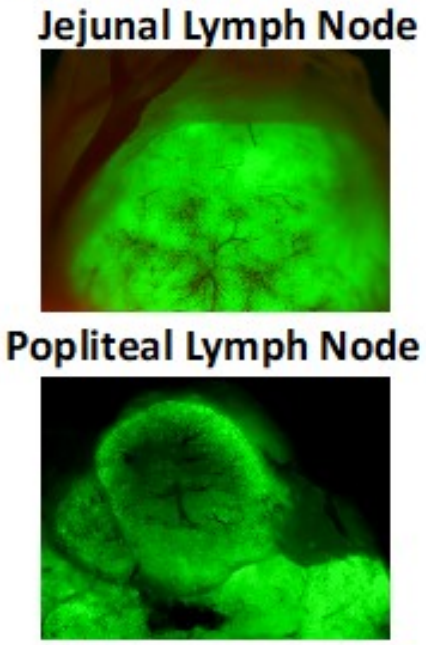


Developing Functional Hepatic Tissue:
POC for generation of functional ectopic liver in mouse lymph nodes

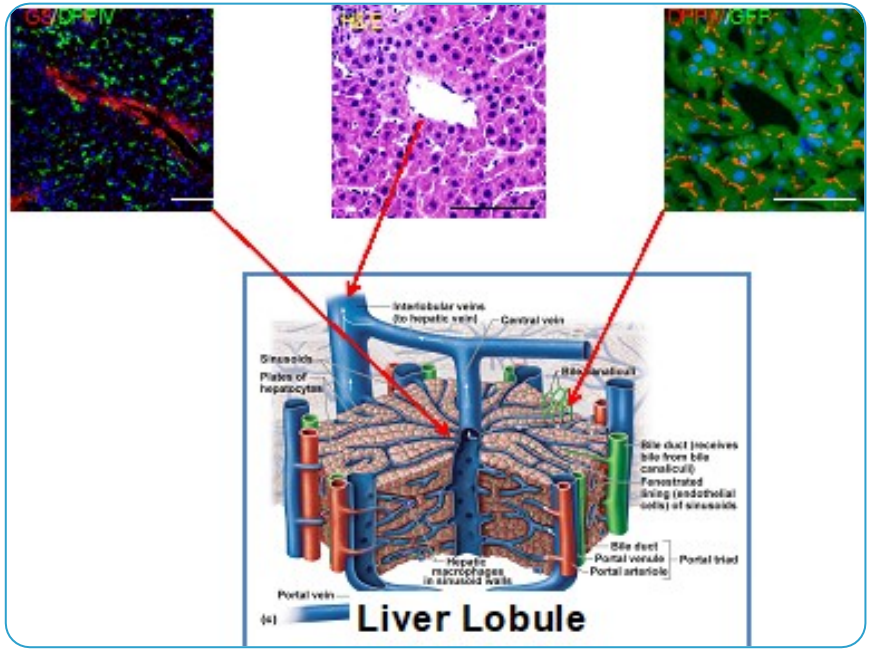
Single LN Injection Generates Ectopic Liver Tissue in Fah$^{-/-}$ Mice 10 Weeks after Transplantation



Auxiliary Liver Regeneration by Direct Injection into:



Auxiliary Liver Cellular Anatomy



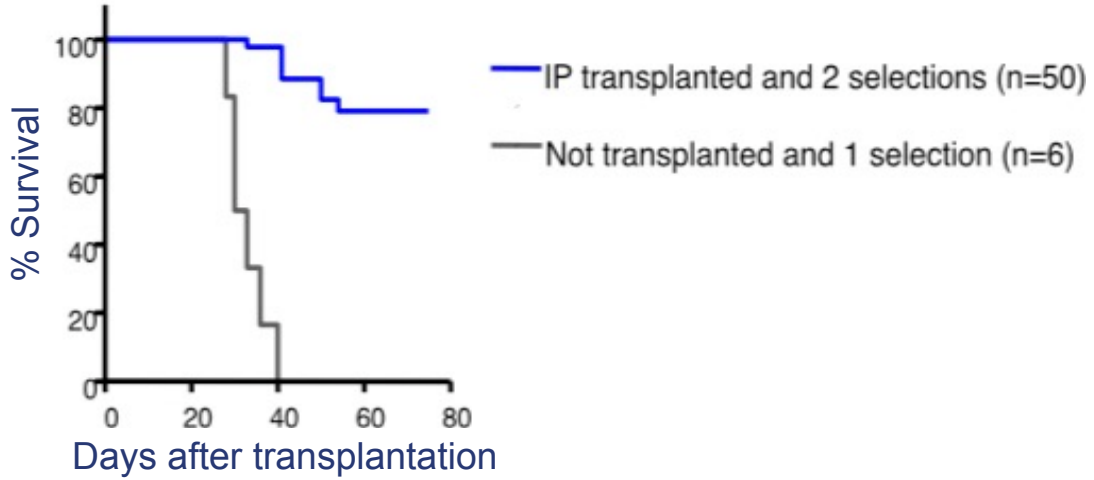
nature biotechnology

- Komori J, Boone L, DeWard A, Hoppo T, Lagasse E.
- Nat Biotechnol. 2012 Oct;30(10):976-83

Hepatocytes engrafted into LNs consistently produce functional tissue

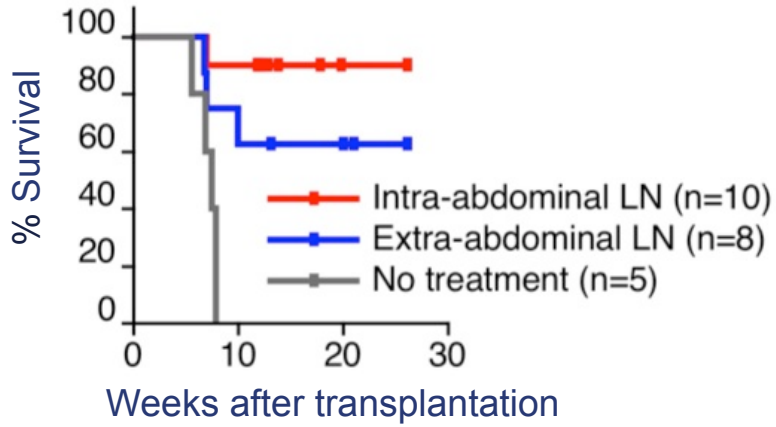
Hepatocytes generate *functional Liver tissue as life-saving therapeutics*

LYG-LIV-001 Study
Survival post hepatocyte transplantation



Kaplan-Meier survival curves of Fah−/− mice transplanted by intraperitoneal injection and compared to mice given no treatment

LYG-LIV-002 Study
Survival by Type of hepatocyte transplantatio



Kaplan-Meier survival curves of Fah−/− mice transplanted in intra- and extra-abdominal lymph nodes compared to mice given no treatment

nature biotechnology

- Komori J, Boone L, DeWard A, Hoppo T, Lagasse E.
- Nat Biotechnol. 2012 Oct;30(10):976-83

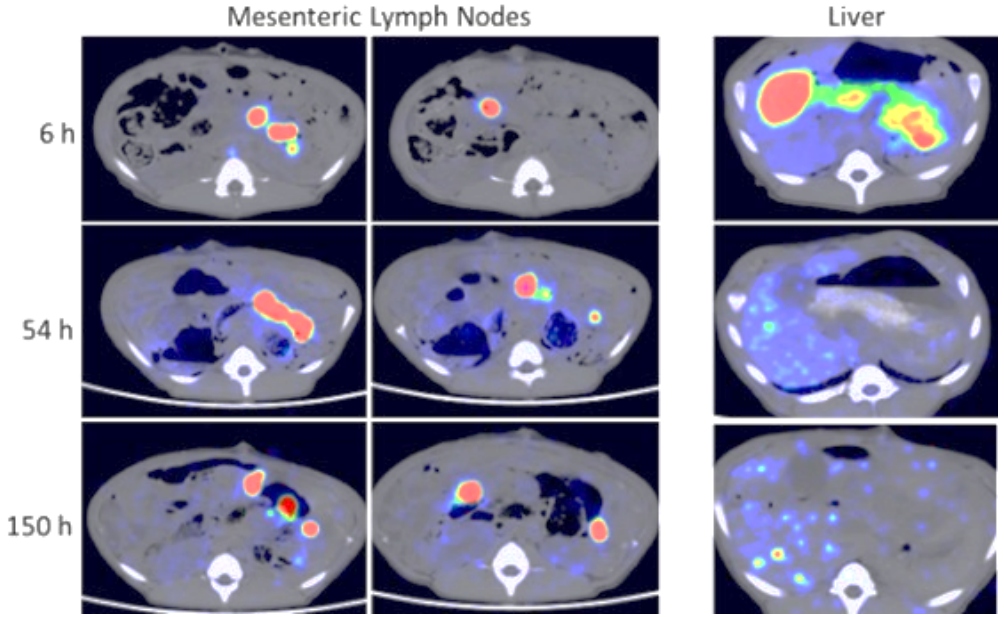
Ectopic Liver Tissue in Tyrosinemic Pig Lymph Nodes: Positive, Functional Engraftment through 6-Months

Porcine LYG-LIV-002 study

Molecular Therapy
Methods & Clinical Development
Original Article

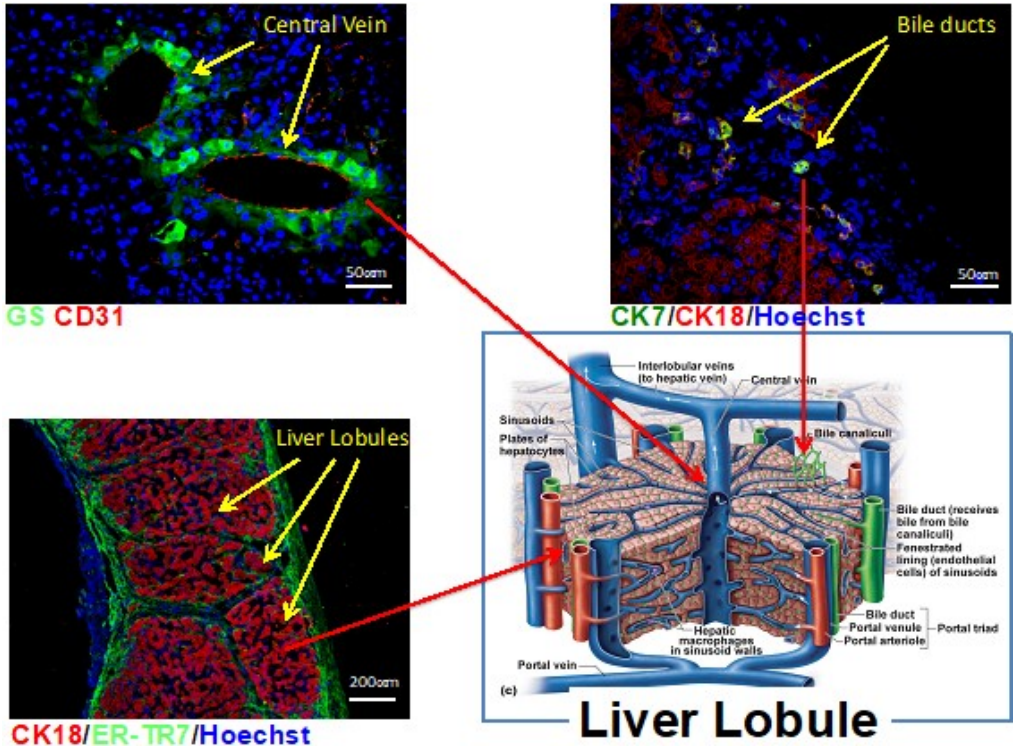
Ex Vivo Cell Therapy by Ectopic Hepatocyte Transplantation Treats the Porcine Tyrosinemia Model of Acute Liver Failure

Tyrosinemic Model (Fah$^{-/-}$) of Liver



PET-CT images of ^{89}Zr-labeled hepatocytes at 6, 54, and 150 h post-transplantation into pig mesenteric lymph nodes

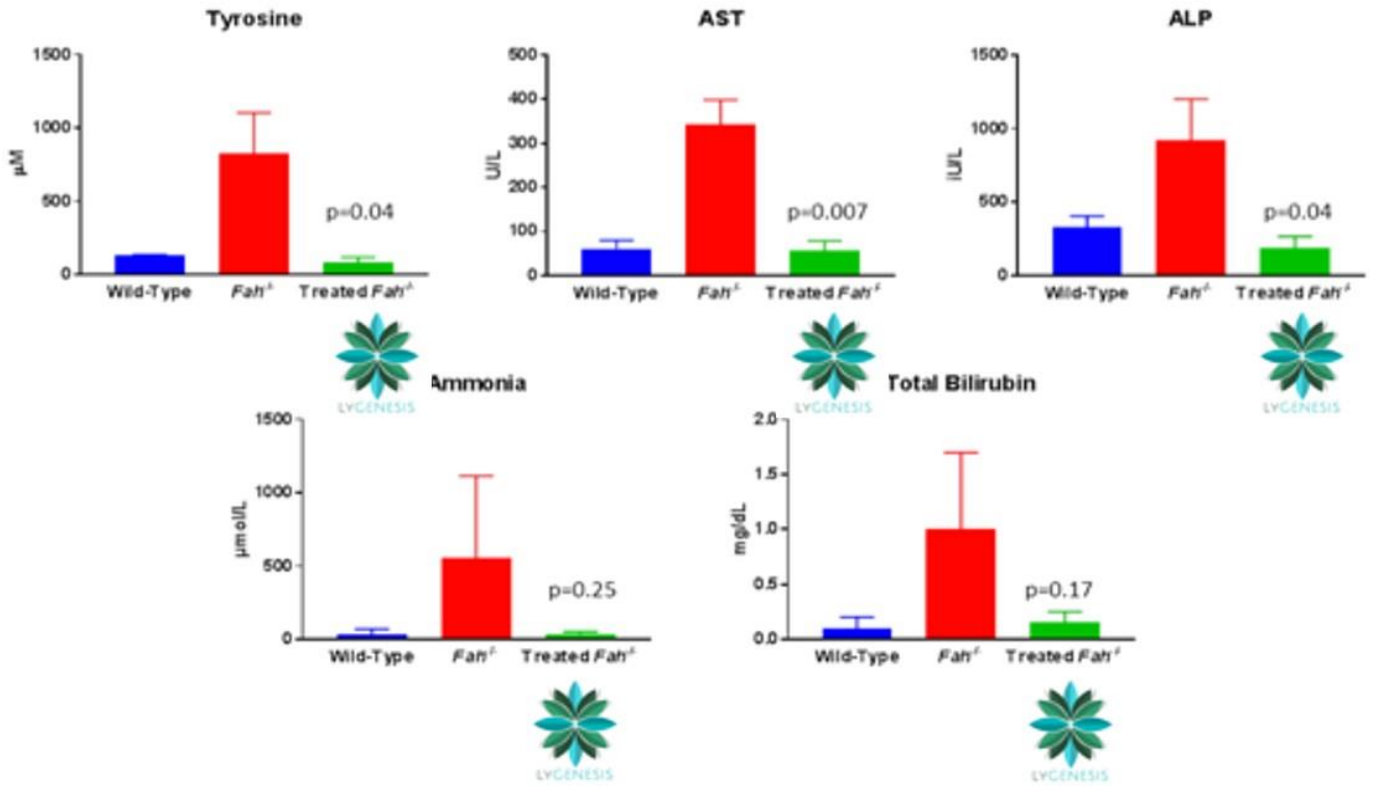
Auxiliary Liver Cellular Anatomy



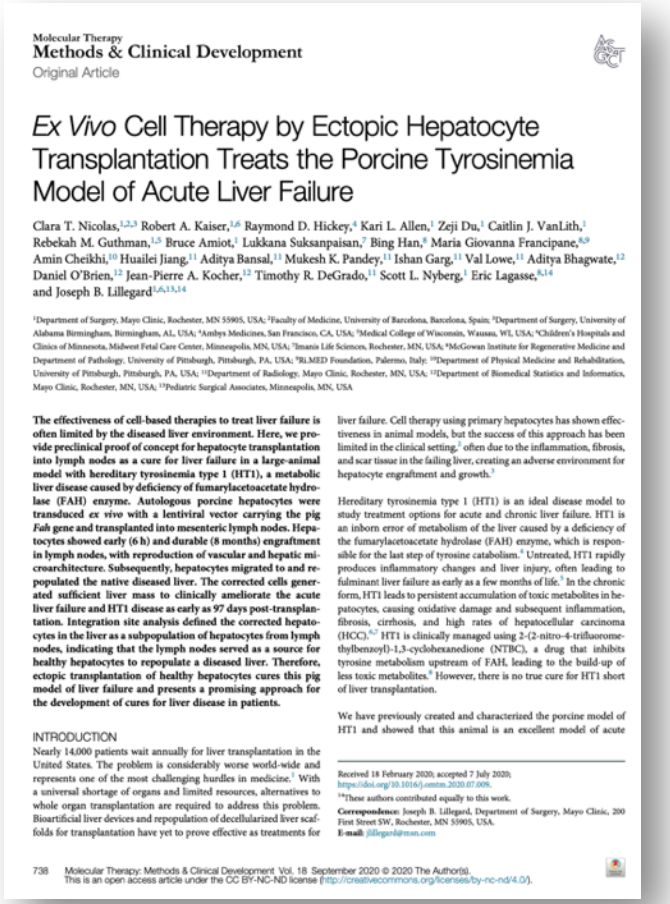
Ectopic Liver Tissue in Tyrosinemic Pig Lymph Nodes Rescues Animals from Otherwise Fatal Liver Disease

Porcine LYG-LIV-002 study

Restoration of liver function in all tyrosinemic pigs transplanted



Normalization of tyrosine, aspartate aminotransferase (AST), alkaline phosphatase (ALP), ammonia, and total bilirubin levels at the time of euthanization in all animals. Wild type are control pig, Fah-/- are tyrosinemic pig and treated Fah-/- are tyrosinemic previously transplanted with hepatocytes into lymph nodes.



Molecular Therapy
Methods & Clinical Development
Original Article

Ex Vivo Cell Therapy by Ectopic Hepatocyte Transplantation Treats the Porcine Tyrosinemia Model of Acute Liver Failure

Clara T. Nicolas,[1,2,3] Robert A. Kaiser,[1,6] Raymond D. Hickey,[4] Kari L. Allen,[1] Zeji Du,[1] Caitlin J. VanLith,[1] Rebekah M. Guthman,[1,5] Bruce Amiot,[1] Lukkana Suksanpaisan,[7] Bing Han,[8] Maria Giovanna Francipane,[8,9] Amin Cheikhi,[10] Huailei Jiang,[11] Aditya Bansal,[11] Mukesh K. Pandey,[11] Ishan Garg,[11] Val Lowe,[11] Aditya Bhagwate,[12] Daniel O'Brien,[12] Jean-Pierre A. Kocher,[12] Timothy R. DeGrado,[11] Scott L. Nyberg,[1] Eric Lagasse,[8,14] and Joseph B. Lillegard[1,6,13,14]

[1]Department of Surgery, Mayo Clinic, Rochester, MN 55905, USA; [2]Faculty of Medicine, University of Barcelona, Barcelona, Spain; [3]Department of Surgery, University of Alabama Birmingham, Birmingham, AL, USA; [4]Ambys Medicines, San Francisco, CA, USA; [5]Medical College of Wisconsin, Wausau, WI, USA; [6]Children's Hospitals and Clinics of Minnesota, Midwest Fetal Care Center, Minneapolis, MN, USA; [7]Imanis Life Sciences, Rochester, MN, USA; [8]McGowan Institute for Regenerative Medicine and Department of Pathology, University of Pittsburgh, Pittsburgh, PA, USA; [9]RiMED Foundation, Palermo, Italy; [10]Department of Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, PA, USA; [11]Department of Radiology, Mayo Clinic, Rochester, MN, USA; [12]Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA; [13]Pediatric Surgical Associates, Minneapolis, MN, USA

The effectiveness of cell-based therapies to treat liver failure is often limited by the diseased liver environment. Here, we provide preclinical proof of concept for hepatocyte transplantation into lymph nodes as a cure for liver failure in a large-animal model with hereditary tyrosinemia type 1 (HT1), a metabolic liver disease caused by deficiency of fumarylacetoacetate hydrolase (FAH) enzyme. Autologous porcine hepatocytes were transduced *ex vivo* with a lentiviral vector carrying the pig *Fah* gene and transplanted into mesenteric lymph nodes. Hepatocytes showed early (6 h) and durable (8 months) engraftment in lymph nodes, with reproduction of vascular and hepatic microarchitecture. Subsequently, hepatocytes migrated to and repopulated the native diseased liver. The corrected cells generated sufficient liver mass to clinically ameliorate the acute liver failure and HT1 disease as early as 97 days post-transplantation. Integration site analysis defined the corrected hepatocytes in the liver as a subpopulation of hepatocytes from lymph nodes, indicating that the lymph nodes served as a source for healthy hepatocytes to repopulate a diseased liver. Therefore, ectopic transplantation of healthy hepatocytes cures this pig model of liver failure and presents a promising approach for the development of cures for liver disease in patients.

INTRODUCTION

Nearly 14,000 patients wait annually for liver transplantation in the United States. The problem is considerably worse world-wide and represents one of the most challenging hurdles in medicine.[1] With a universal shortage of organs and limited resources, alternatives to whole organ transplantation are required to address this problem. Bioartificial liver devices and repopulation of decellularized liver scaffolds for transplantation have yet to prove effective as treatments for liver failure. Cell therapy using primary hepatocytes has shown effectiveness in animal models, but the success of this approach has been limited in the clinical setting,[2] often due to the inflammation, fibrosis, and scar tissue in the failing liver, creating an adverse environment for hepatocyte engraftment and growth.[3]

Hereditary tyrosinemia type 1 (HT1) is an ideal disease model to study treatment options for acute and chronic liver failure. HT1 is an inborn error of metabolism of the liver caused by a deficiency of the fumarylacetoacetate hydrolase (FAH) enzyme, which is responsible for the last step of tyrosine catabolism.[3] Untreated, HT1 rapidly produces inflammatory changes and liver injury, often leading to fulminant liver failure as early as a few months of life.[3] In the chronic form, HT1 leads to persistent accumulation of toxic metabolites in hepatocytes, causing oxidative damage and subsequent inflammation, fibrosis, cirrhosis, and high rates of hepatocellular carcinoma (HCC).[4,7] HT1 is clinically managed using 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC), a drug that inhibits tyrosine metabolism upstream of FAH, leading to the build-up of less toxic metabolites.[8] However, there is no true cure for HT1 short of liver transplantation.

We have previously created and characterized the porcine model of HT1 and showed that this animal is an excellent model of acute

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[*]These authors contributed equally to this work.

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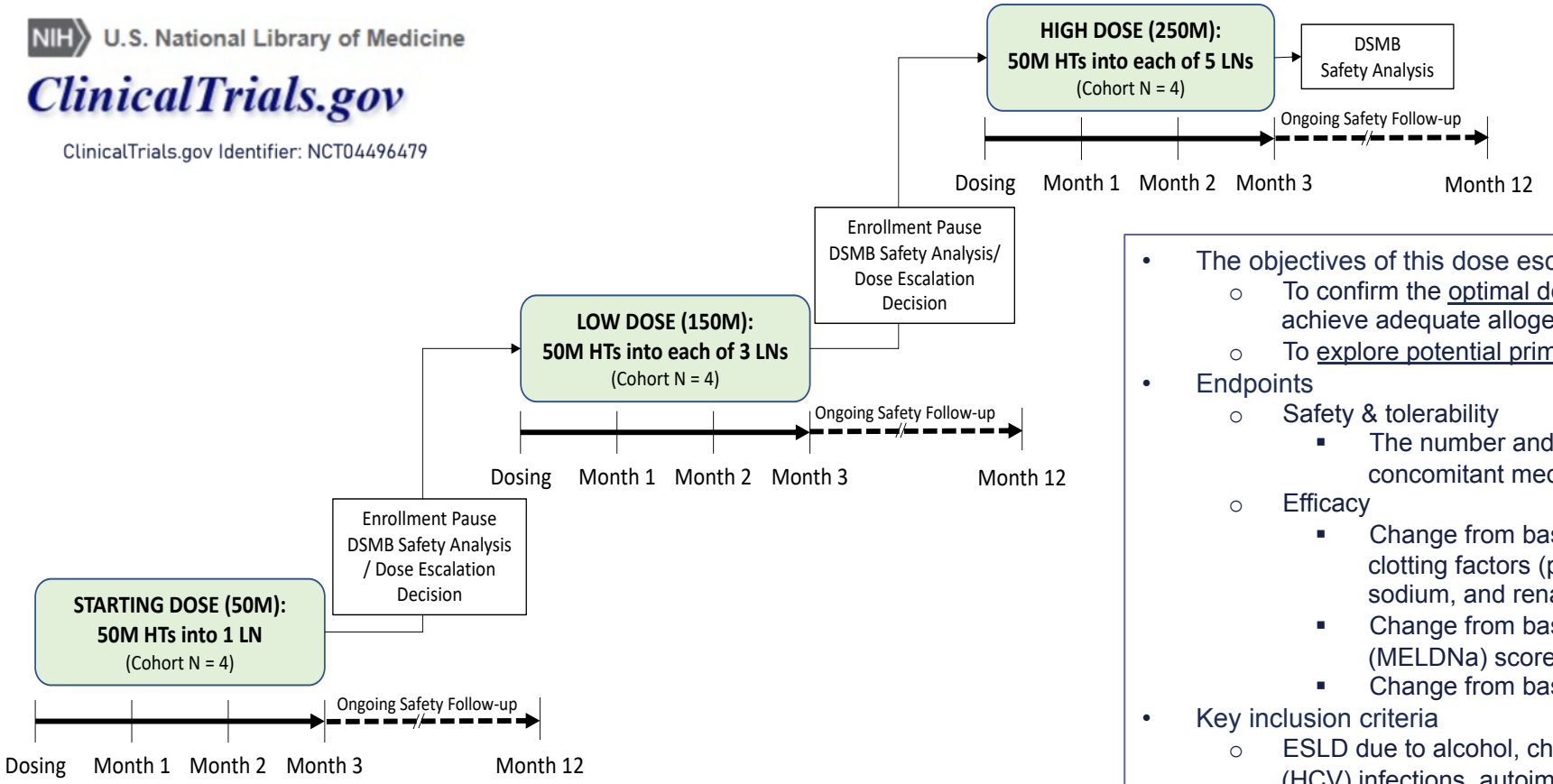
LyGenesis: Phase 2a trial at Harvard's MGH

This is an open-label Phase 2a (first-in-human for patients with end stage liver disease (ESLD) who have been declined for liver transplantation) dose escalation study involving 3 cohorts of 4 patients (n=12) – 20 month timeline

NIH U.S. National Library of Medicine

ClinicalTrials.gov

ClinicalTrials.gov Identifier: NCT04496479



HT = hepatocyte
LN = lymph node

- The objectives of this dose escalation study are:
  - To confirm the optimal dose of transplanted hepatocytes (HTs) to safely achieve adequate allogeneic hepatocyte engraftment
  - To explore potential primary and secondary endpoints for Phase 2b trial
- Endpoints
  - Safety & tolerability
    - The number and severity of AEs, summaries of clinical laboratory data, concomitant medication use, and vital signs
  - Efficacy
    - Change from baseline in total serum bilirubin, venous ammonia, clotting factors (prothrombin time, international normalized ratio), sodium, and renal function (blood urea nitrogen, creatinine)
    - Change from baseline in Model for End-stage Liver Disease-Sodium (MELDNa) score
    - Change from baseline in Child-Turcotte-Pugh score
- Key inclusion criteria
  - ESLD due to alcohol, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, autoimmune hepatitis, primary sclerosis cholangitis, primary biliary cirrhosis (cholangitis), cirrhosis as the result of Wilson disease, hemochromatosis, sarcoidosis and alpha 1 antitrypsin deficiency, cryptogenic cirrhosis and nonalcoholic steatohepatitis cirrhosis
  - MELD-Na score >10 and <25 at screening

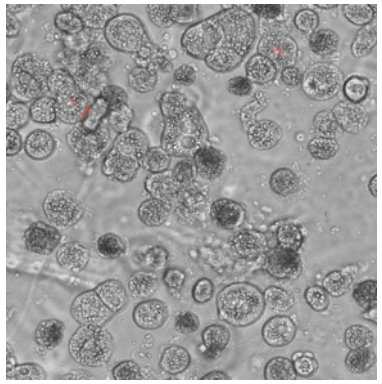
If necessity is the mother of invention, discontent is the father of progress

-- David Rockefeller

Orphan Pediatric Indication for Inborn Errors of Metabolism

New technology for the treatment of Maple Syrup Urine Disease (MSUD)

- MSUD is regarded as **one of the most significant and serious inborn errors of metabolism**
  - MSUD is a pan-ethnic disorder with an incidence in the general population of 1:185,000 newborns
    - Georgia population 1:84,000 newborns
    - Ashkenazi Jewish population 1:51,000 newborns
    - Mennonites of Pennsylvania population (1:176) newborns
- Clinical profile
  - Birth: lethargy, hypotonia
  - Low BCAA diet required for life
  - **Untreated = brain injury within days, death in 1 year**
- Standard of care
  - With early treatment, lifetime dietary adherence, close to normal IQ possible
  - **Full liver transplant** cures metabolic issues, at cost of surgical risk, immunosuppression and risk of post-transplantation lymphoproliferative disease (PTLD)



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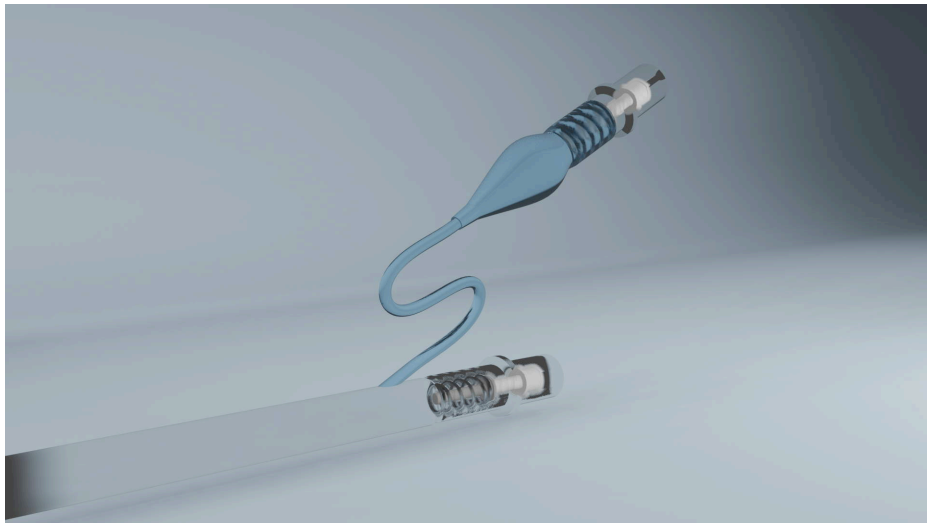

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High volume infusions (>100 ml) of a thermoregulated gel containing PLGA nanoparticles of hepatic growth factors for delayed release

LyGenesis owns the IPs for this new technique, which involves composition of matter for the new Hydrogel/Nanoparticles combination (Patent Application filed by WSGR, July 29, 2021)

We can leverage our organ regeneration platform across several disease indications; our pipeline is varied and progressing quickly

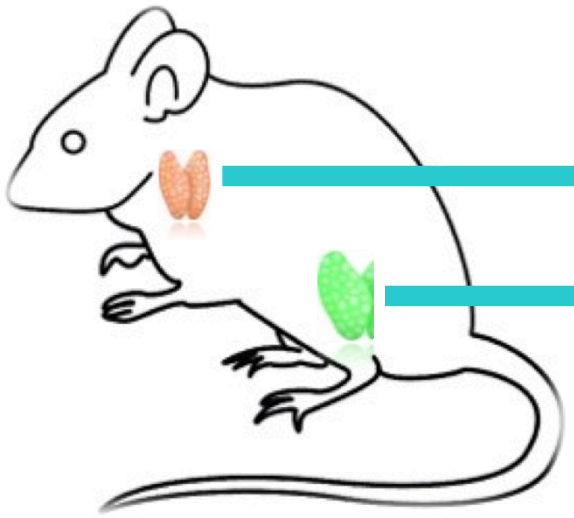
	Pre-Clinical			Clinical			
Program ***Indication***	**Discovery/ Lead Optimization**	**Small Animal**	**Large Animal**	**Phase I**	**Phase II**	**Phase III**	**FDA Approval**
Liver *ESLD*	✓	✓	✓	Skip per FDA	FPI: 4Q2021		
Thymus *Multiple indications*	✓	POC complete					
Kidney *ESRD*	✓	POC complete					
Pancreas *T1DM*	✓	POC complete					

Liver program: FPFV expected 4Q 2021

Development of ectopic thymus with T-Cell development in a lymph node: Proof of Concept

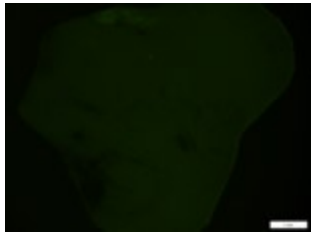
LYG-THY-01.01 study

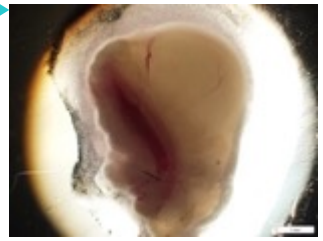
LyGenesis can generate a functional ectopic thymus for anti-aging

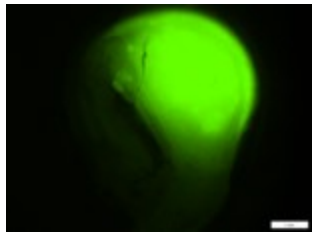


C57Bl/6 Mouse with additional Ectopic C57Bl/6 GFP+ Thymus in LN

Native Thymus

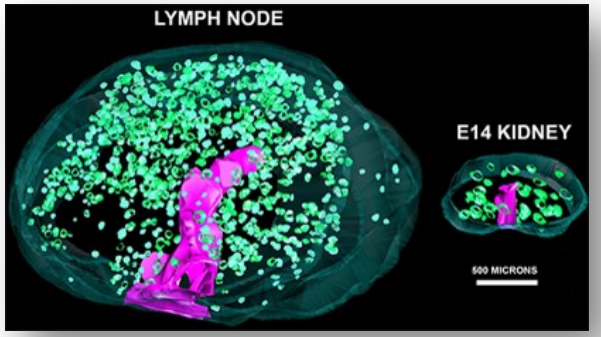




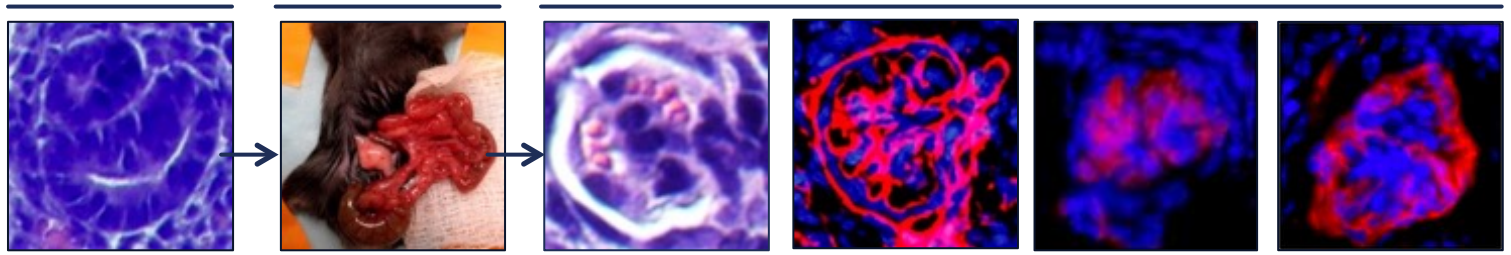


Ectopic Thymus

Replicating kidney in lymph node: Molecular characterization of renal tissue

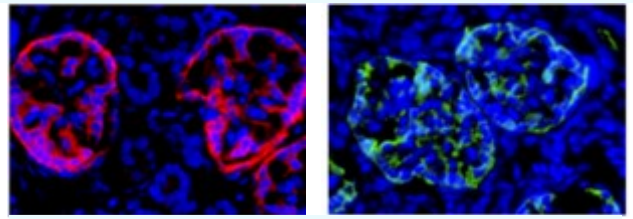


3D reconstructions show significant growth and proper spatial orientation of kidney renal corpuscle in 3-week grafts. Capsule (light green), nephron structures (green), and collecting system (purple)

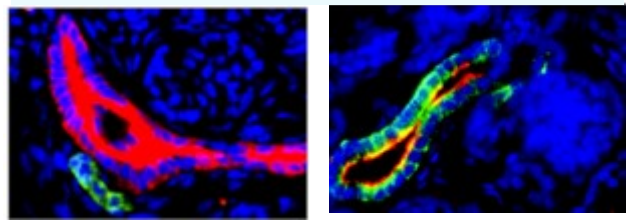


Mouse kidney in a lymph node

Nephron's renal corpuscle/glomerulus



Nephron's proximal/distal tubules



Human kidney in a mouse lymph node

- Francipane MG, Han B, Oxburgh L, Sims–Lucas S, Li Z, Lagasse E. Kidney–in–a–lymph node: A novel organogenesis assay to model human renal development and test nephron progenitor cell fates. J Tissue Eng Regen Med. 2019;13:1724–1731. https://doi.org/10.1002/term.2924.
- Francipane, Maria Giovanna, Bing Han, Leif Oxburgh, Sunder Sims-Lucas, Zhongwei Li and Eric Lagasse. Kidney-in-a-lymph node: a novel organogenesis assay to model human renal development and test nephron progenitor cell fates. Journal of tissue engineering and regenerative medicine (2019). https://doi.org/10.1002/term.2924.

Replicating the pancreas in lymph node:
Pancreatic Islets for Type 1 Diabetes

Patient without insulin-producing beta cells

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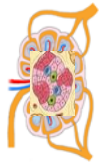
Pancreatic Islets



Lymph Node

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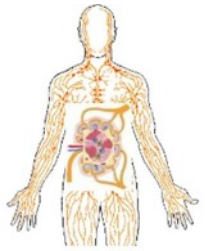

Patient with normoglycemia

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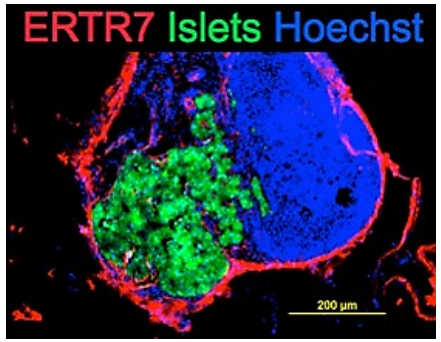
Applications in Type 1 Diabetes



Pancreatic islets engrafted In lymph node

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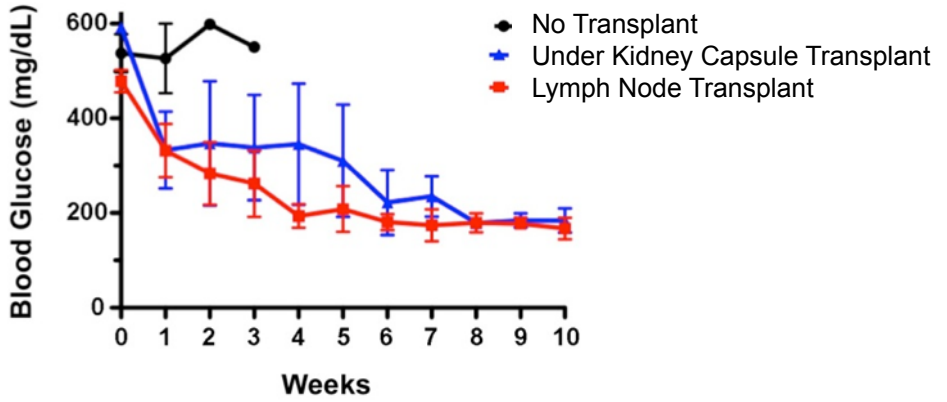

Function of pancreatic islets in lymph node

- Average blood glucose concentrations in diabetic recipient mice over course of 10 weeks after transplantation of islets into jejunal lymph nodes.
- Data are presented as means ± s.e.m.

Summary

Compelling cell therapy platform solving critical unmet need for organ transplantation

- Ability to manufacture new organs at low COGS using endoscopic ultrasound could completely eliminate the chronic shortage of transplant organs and tissue worldwide
- This cell therapy can save countless lives and radically improve patients' quality of life

Core indication – end stage liver disease – is sufficient on its own to found a major company, but other organ types are significant call options

- Ability to generate functioning ectopic pancreas signals promising therapy for T1DM
- Thymus (aging, cancer, auto-immune disorders) and kidney (end stage renal disease) additional promising indications

Existing + filed IP provides deep moat – together with management team and current valuation, investment opportunity is compelling

- Issued and pending IP on use of lymph nodes as bioreactors for organogenesis
- Worldwide IP in prosecution on use of endoscopic ultrasound to engraft cell therapy into lymph nodes