Renewal of RFA: Consortium on Translational Research in Early Detection of Liver Cancer

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Purpose

Approval for the renewal of the **NCI Translational Liver Cancer (TLC)** initiative that was established in 2018 to advance translational research focused on the early detection of liver cancer.

Background

Senate Committee on Appropriations in 2015 stated –

“the Committee encourages NCI to continue to support liver cancer research across its portfolio, including research focused on the development of biomarkers to serve as early detection markers of cancer to offer the prospect of improved outcomes.”

Viral Hepatitis: Federal Implementation Plan (2021-2025)

Strategy 2.4.3 Improve and validate tools for earlier detection of hepatocellular carcinoma, such as improved liver imaging and blood and urine tests.

Action Step	Timeframe	Federal Partners	Nonfederal Partners	Indicators	Funding Mechanism
Continue to support a multicenter U.S. Translational Liver Cancer Consortium, which is charged with developing a large clinical network to conduct advanced translational research on the early detection, diagnosis, clinical management, prevention, and treatment of liver cancer in patients with chronic liver disease who are at high risk for this highly fatal malignancy.	2021-2025	NIH/NCI		6	

External Evaluation of TLC Consortium

*"**Two important conclusions** can be made regarding the progress of the TLC. Firstly, **the direction of the TLC remains extremely relevant**, in fact, perhaps more timely today than ever. **HCC incidence continues to increase, in the U.S.**, and **early detection** remains the best way to assure the **most beneficial outcome** possible. **Secondly**, regarding progress, they key questions asked of this consortium is if the 'whole is greater than the sum of its parts'. We believe the answer is yes. This **consortium** brings together an **outstanding group of investigators** who, as a result of the consortium, are **achieving goals that out be difficult or impossible otherwise**."*

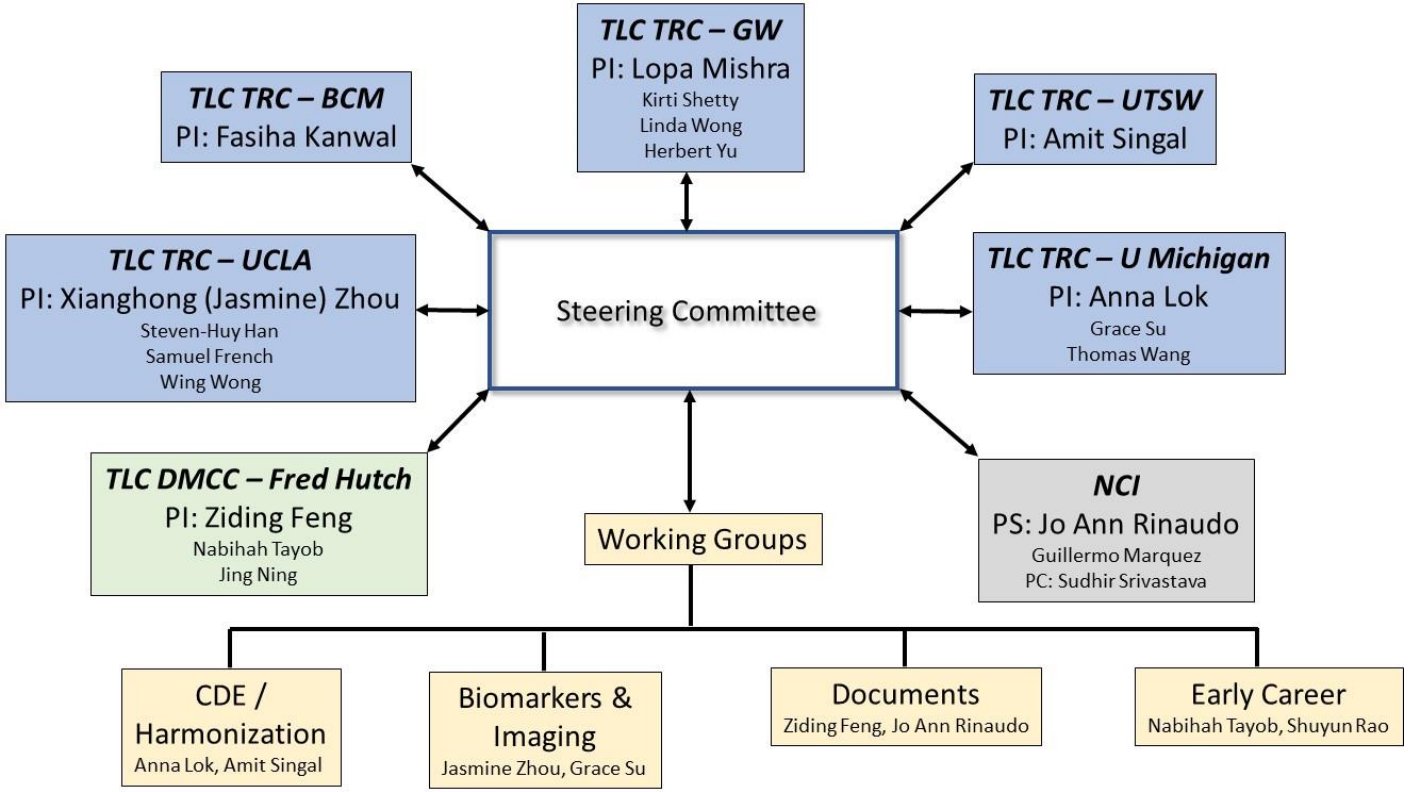
Future Directions/Recommendations

- Expand/support Phase 3 biomarker studies (longitudinal studies to detect pre-clinical HCC)
- Expand cohorts (HBV, ALD, NASH, HIV co-infections) and ensure racial and ethnic diversity
- Additional partnerships and collaborations to accelerate biomarker identification
- Encourage more trans-TLC studies
- Increase TLC resources/funding

Research Objectives of the Reissued RFA

- Longitudinal collection and analysis of samples and/or images from cirrhotic patients with LR3/LR4 nodules to determine the likely progression to liver cancer within a defined period of time (e.g., 1-2 years)
- Integration of imaging approaches with biomarkers
- Identifying and/or validating biomarkers for HCC arising from different etiologies (e.g., viral and NASH, or ALD) and diverse populations to address health disparities.
- Supplementing cohorts of cirrhotic patients, with biospecimens, to study risk for liver cancer associated with viral infections (HCV or HBV), NASH, or ALD.

Current TLC Organizational Structure



Major Accomplishments: Scientific Advances

Risk Assessment	
Study	***Results***
Prognostic Liver Secretome Signature (PLSec) (Site: UTSW)	Risk stratification biomarkers are an unmet need to improve the feasibility and cost-effectiveness of HCC screening in cirrhosis patients. An 8 serum-based signature (plus AFP) was used on a longitudinal liver cirrhosis/HCC reference set for prediction of long-term HCC risk. Signature distinguished patients at high-risk from low-risk patients. (Serum-based signature - **VCAM-1**; **IGFBP-7**; **gp130**; **matrilysin**; **IL-6**; **CCL-21**; **angiogenin**; **protein S**; and **AFP**)
Polygenic Risk Score (PRS) (Site: Baylor)	Large, multiethnic cohort of cirrhosis patients, PRS developed was associated with HCC risk. Variants examined - **PNPLA3** (patatin-like phospholipase domain containing 3), **MBOAT7** (membrane bound O-acyltransferase domain containing 7), **TM6SF2** (transmembrane 6 superfamily member 2), **NCAN** (neurocan), and **PPP1R3B** (Protein Phosphatase 1 Regulatory Subunit 3B).

Major Accomplishments of TLC

Improved Surveillance	
EMR (Site: U Michigan)	Electronic medical record best practice advisory (BPA) for HCC surveillance has been developed, implemented, and evaluated.
Imaging (Sites: U Michigan / UTSW)	Abbreviated MRI (aMRI) is more accurate than ultrasound to detect HCC at an early stage. Potential for aMRI as a surveillance tool in selected patients.
Early Detection of HCC	
cfDNA (Site: UCLA)	A novel cfDNA methylome sequencing assay (methylation signals, fragment size, CNV) and a computational platform. Hypermethylated markers achieved the best performance for differentiating liver cancer from cirrhosis.
Proteomic Profiles (Site: GW)	Decrease in TGF-β receptor subunit 2 (TGFBR2) among HCC samples versus cirrhosis samples. A subset of cirrhosis presented an HCC-like pattern; currently following these patients to see if they develop HCC.

24 Publications

Future Consortium Collaborative Projects

Major unmet need is the ability to differentiate whether an indeterminate nodule identified during HCC screening is benign or malignant. Indeterminate nodules (LR3/LR4 lesions) are found in ~20% patients undergoing HCC screening. Current guidelines recommend these nodules to be evaluated by surveillance (CT or MRI) or biopsy until HCC diagnosis.

Project Goals

- A retrospective and prospective study will leverage the diverse (race/ethnicity and etiologies) population of cirrhosis patients at the clinical centers.

- A combination of clinical, blood-based biomarkers, and image-based biomarkers are being used to (1) determine the risk of HCC among patients with cirrhosis and indeterminate nodules found during HCC screening, and (2) detect HCC earlier (at or shortly after initial detection of indeterminate nodules).

Rationale for Reissue of RFA and Cooperative Agreement

- TLC consortium has established the infrastructure and resources for collaborations.

- Consortium developed two major collaborative projects on indeterminate liver nodules. These studies require recruitment of sufficient patients, collection of biospecimens and imaging, and address health disparities. No single site has resources to achieve these goals.

- Collaborations with other consortia and programs can bring additional resources to the Translation Liver Consortium (e.g. NCI – EDRN (HEDS); NCI- HCCEC; NIDDK research (Liver Cirrhosis Network); and Texas HCC Consortium.

The cooperative agreement mechanism will allow NCI program staff to guide and support the research to facilitate meeting the goal to improve the early detection of liver cancer.

Current Portfolio Analysis

- FY 2020, NCI invested $130M* in liver cancer research.
- Majority funds supported research on tumor biology, infectious diseases, and community cancer control/outreach and therapy.
- NCI funded Research Portfolio on liver cancer and early detection or risk or surveillance listed approximately $6M in relevant funding, (including $4M for the TLC sites).

*https://report.nih.gov/funding/categorical-spending#/

U01 / U24 Awards

Funding:	$5M / year
Anticipated Number of Awards:	Up to 6
▪ Clinical Centers (U01)	Up to 5 U01 ($880K total cost/site)
▪ Coordinating Center (U24)	1 U24 ($600K total cost)
Length of Award:	5 Years

Support for Renewal Request: Summary

- Significant clinical impact of current studies
- Established virtual biorepository and building future cohorts
- Experienced and accomplished investigators
- Associate Membership for establishing collaborations and assistance for Early Career Investigators
- Strong endorsement from the External Evaluation Committee

Thank you.

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