Memorial Sloan Kettering Cancer Center

Re: 2024-2025 IHPBA Kenneth Warren Fellowship, 6-month Interim Report

Dear IHPBA Research Committee,

I am deeply honored and sincerely grateful for granting me the 2024-2025 IHPBA Kenneth Warren Fellowship, providing me the extraordinary opportunity to pursue my research project at Memorial Sloan Kettering Cancer Center (MSKCC). Under the invaluable mentorship of Dr. William R. Jarnagin, Chief of the HPB Service, and the scientific guidance of Dr. Andrea Ventura, Director of The Andrea Ventura Lab (Cancer Biology and Genetics Program), this experience has already proven to be a tremendously enriching and transformative milestone in my career.

Since November 2024, I have been working as a Research Fellow in the Department of Surgery, HPB Service, at MSKCC. My primary research project focuses on:

- **Investigating the role of extrachromosomal circular DNA (ecDNA) in hepatobiliary tumors**

Despite ecDNA being increasingly recognized as a crucial driver of oncogene amplification in several aggressive human cancers, its role in hepatobiliary malignancies remains largely unexplored. Our translational project aims to assess the prevalence and biological significance of ecDNA-mediated oncogene amplifications in hepatobiliary cancers, with the broader goal of enhancing our understanding of intra-tumoral heterogeneity, treatment response variability, and patient prognosis.

After promptly obtaining IRB approval, I leveraged the vast biobank and genomic resources available at MSKCC. The institution has extensively characterized the mutational and genomic landscape of hepatobiliary tumors using the MSK-IMPACT platform, a targeted next-generation sequencing assay. However, while MSK-IMPACT is highly sensitive in detecting genomic alterations, it cannot directly identify ecDNA. To overcome this, we utilized a novel bioinformatic ecDNA-diagnostic tool – ECS (ecDNA Solution) – available at MSKCC through the Berger Lab. This algorithm can distinguish oncogenic amplifications occurring on ecDNA vs. chromosomal DNA from clinical-grade NGS data, making it the first clinically applicable assay for ecDNA detection using standard sequencing platforms. Using this tool, we screened 2,501 tumor samples from 2,337 patients (including HCC, intrahepatic and extrahepatic cholangiocarcinoma, gallbladder cancer, and mixed HCC-ICC histologies). We observed that 15.5–17.1% of these tumors harbored oncogenic focal amplifications likely mediated by ecDNA. Notably, mixed HCC-ICC histologies showed a significantly higher ecDNA prevalence (38.5%). Gene-specific analyses revealed distinct patterns: CCND1, FGF3/4/19 were enriched in HCC, whereas ERBB2, KRAS, and EGFR were more frequently amplified via ecDNA in cholangiocarcinoma and gallbladder cancers. Amplification metrics (total copy number and segment size) were consistent with ecDNA biology: ECS-positive events typically had a segment size <5 megabases (Mb) and copy number >20, while chromosomal amplifications exhibited a mild inverse correlation between copy number and segment size, possibly reflecting constraints of chromosomal architecture.

Our next steps include validation of these findings through fluorescence in situ hybridization (FISH) using gene-specific probes on a subset of tissue samples. Additionally, I am collecting clinical, demographic, pathologic,

and outcome data from prospectively maintained institutional databases to investigate correlations between ecDNA features and patient outcomes.

Beyond this main project, I have actively contributed to several clinical research studies, including:

- **Hepatic artery infusional (HAI) chemotherapy in unresectable locally advanced intrahepatic cholangiocarcinoma**

MSK has long been a pioneer in hepatic arterial infusion pump (HAIP) chemotherapy, having led the development, validation, and clinical adoption of this liver-directed approach. Building on this legacy, I led an individual patient data pooled analysis evaluating hepatic arterial infusion pump chemotherapy in liver-confined iCCA. The study demonstrated unprecedented survival rates (3-year OS: 29%; 5-year OS: 15%) – a dramatic improvement over systemic chemotherapy alone (3-year OS: 2.8%). I had the honor of presenting these results at AHPBA 2025 in Miami.

- **International trends in management of intrahepatic cholangiocarcinoma**

Retrospective, multicenter international study that analyzes the management of liver-confined intrahepatic cholangiocarcinoma, including multifocal tumors and lymph node metastasis, across centers in North America, Europe, and Japan. The aim is to describe international variability in presentation, management, and outcomes by stage over time.

- **Radiomics and IPMN progression to malignancy**

A pilot study evaluating the role of radiomic features in predicting malignant transformation in intraductal papillary mucinous neoplasms (IPMN).

I've also been fortunate to collaborate on several impactful studies, including:

- A multimodal machine learning model integrating clinical, genomic, pathologic, and radiomic data to enhance outcome prediction in intrahepatic cholangiocarcinoma.
- A study evaluating liver transplant eligibility in patients with liver-confined unresectable iCCA, analyzing the proportion of patients who meet proposed criteria and their management/outcomes.
- The pancreatic cyst surveillance database (>2000 patients): Our first analysis showed that IPMNs ≥3 cm without other high-risk features may be safely monitored with minimal risk of malignancy. The results were published in the Journal of the American College of Surgeons (Choubey AP et al., 2025).

In parallel with my research, I have been fully immersed in the MSKCC academic ecosystem, regularly attending Grand Rounds, Surgical Oncology Conferences, and HPB service meetings, which have tremendously enhanced my clinical acumen in HPB surgery.

At the halfway point of my fellowship, I can confidently say this experience has exceeded all expectations – both scientifically and personally. The opportunity to work alongside world-class mentors such as Dr. Jarnagin and Dr. Ventura, and within a dynamic, resource-rich institution like MSKCC, is deeply shaping my future as a surgeon-scientist.

I am incredibly grateful to the IHPBA Research Committee for making this journey possible and I look forward to sharing the complete results of my project at the IHPBA 2026 Congress in Singapore.

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With sincere appreciation,

Remo Alessandris

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