Cancer Target Discovery and Development (CTD^2) Network Virtual Symposium

March 19, 2026

EXECUTIVE SUMMARY

Overview

The Cancer Target Discovery and Development (CTD²) Network is an NCI-funded functional genomics initiative that is bridging the gap between large-scale genomic datasets and the underlying etiology of cancer development, progression, and metastasis.

On March 19, 2026, CTD^2 Network investigators held a virtual, public symposium of recent advances in functional genomics and CTD^2 Network research progress. During the meeting, researchers shared functional systems biology studies of tumor heterogeneity, treatment resistance in cancer, and the preclinical development of new therapeutic strategies.

Symposium Goals:

- Highlight and promote CTD² Network science
- Foster interactions between CTD² Network investigators and the cancer research community
- Support CTD² program-specific opportunities and collaborations

NCI Director Opening Keynote Presentation

The symposium began with a keynote talk by the NCI Director, Dr. Anthony Letai. He emphasized stability at NCI, underscored that NCI's mission remains unchanged, and said, "NCI remains on solid footing, with stable funding and continued momentum."

Dr. Letai highlighted functional precision medicine as a priority area, describing efforts to use patient tumor samples to directly assess drug sensitivities, identify vulnerabilities, and support the development of companion diagnostics through broadly accessible research resources.

He also outlined NCI's alignment with NIH's initiative to reduce animal use in research by prioritizing human-based methods.

In addition, he pointed to the NIH Standardized Organoid Modeling Center as a key national resource to improve reproducibility, scale organoid technologies, and accelerate clinical translation.

Dr. Letai also identified cancer vaccines as a promising area for preventing relapse in hard-to-treat cancers and described an FNIH & NCI partnership to speed up the development of therapeutic cancer vaccines.

Session 1: Cancer Biology

The first session of the symposium focused on cancer biology advances of the CTD^2 Network.

Dr. Michael McManus opened the scientific sessions by reflecting on the history of the CTD^2 Network and underscoring an evolving challenge for the consortium: cancer is a systems-level disease shaped by interactions among tumor, immune, stromal, and tissue-resident cells.

He then described collaborative work decoding peptide– Major Histocompatibility Complex (MHC):T Cell Receptor (TCR) recognition as a central language of immune surveillance and cancer cell recognition. As part of this research, his team developed the Relay barcode platform, which uses engineered peptide–MHC-coated virus-like particles linked to stable circular RNA barcodes to convert binding events into sequencing-readable outputs. This approach is designed to support pooled, large-scale mapping of peptide presentation and TCR specificity across millions of peptides and diverse Human leukocyte Antigen (HLA) alleles. When combined with single-cell sequencing, this technology can identify cell identity, cell state, and pMHC:TCR pairing. This new approach has important implications for neoantigen discovery, immunotherapy development, and studies of immune escape.

Investigators from the MD Anderson CTD2 Project shared their work on modeling and understanding microsatellite-stable (MSS) colorectal cancer (CRC). Dr. Ron DePinho presented genetically engineered mouse models that recapitulate key features of human colorectal cancer (CRC) progression. He shared how these models revealed mechanisms brought about by chromosomal instability (CIN) or oncogenic KRAS activation accelerates CRC initiation and reshapes the tumor immune microenvironment. Dr. DePinho also discussed chemopreventive and therapeutic targets in CRC based on preclinical CTD2 studies. In addition, Dr. Chaohao Li showed that CIN drives ligand-receptor interactions that promote myeloid suppressor activity in MSS-CRC. Both presentations provided pharmacological proof-of-concept that CIN-induced immune suppressive mechanisms are targetable and demonstrated that such mechanisms are present in human MSS-CRC with high CIN levels.

In summary, the session shared advances in measurement tools needed to map cell–cell recognition at scale and mechanistic insights that reveal actionable vulnerabilities in difficult-to-treat MSS-CRC. The studies may, ultimately, inform biomarker development and the design of anti-cancer treatment strategies.

Session 2: Precision Oncology

The second session of the symposium focused on progress in precision oncology by the CTD^2 Network. The talks during this part of the meeting showed how CTD²-supported research is advancing the design of clinically relevant models of tumor heterogeneity and the identification of personalized therapeutic vulnerabilities.

Dr. Chris Kemp presented a translational advance in functional precision oncology using the PARIS/Cure First platform, which combines patient-derived organoids, whole-exome sequencing, and high-throughput drug sensitivity testing to generate ranked therapeutic reports. In the Profiling Ovarian Cancers to Improve Personalized Therapy (PROSPERITY) study, patient-derived organoids largely retained the driver alterations and broader genomic features of

ovarian tumors. Dr. Kemp also showed that drug sensitivity is conserved during tumor evolution and metastatic spread but varies between patients. He also shared data and a case study that suggests this approach can identify clinically meaningful treatment options and may predict patient responses.

Systems biology studies by the Columbia University CTD^2 Project focused on defining tumor cell states and their therapeutic dependencies at single-cell resolution. Dr. Luca Zanella revealed distinct state-specific Master Regulators (MRs) in Isocitrate dehydrogenase (IDH)-mutant gliomas. He also presented OncoTreat modeling that predicted drugs that invert the concerted activity of MR proteins in the malignant glioma states. Dr. Melania Franchini shared a single-cell atlas of Desmoplastic Small Round Cell Tumors (DSRCT) patient samples. Protein activity analysis identified two tumor transcriptional programs: State A characterized by epithelial-mesenchymal transition (EMT) and inflammatory signaling, as well as State B characterized by proliferative and secretory features. She shared that OncoTarget analysis identified actionable vulnerabilities in DSRCT tumor cell states based on their MRs. Dr. Franchini also presented OncoTreat analysis, which identified proteasome inhibitors as promising therapeutic candidates for DSCRT. Future directions for these studies include experimental validation of predicted therapeutic targets and drugs.

Dr. Tugba Yildiran Ozmen presented her work on improving functional assessment of homologous recombination (HR) deficiency in patient samples. She shared the MAP-HR (Machine-learning Assisted Profiling of Homologous Recombination) platform that uses automated image analysis and machine learning to quantify cell cycle states, HR repair, double strand breaks, and nuclear localization per nucleus. This approach enables precise HR status analysis. It appears well suited to capture spatial heterogeneity in HR status, with potential applications in selecting patients for PARP inhibitor-based or rational combination therapies.

The studies presented in this session illustrated progress towards mechanism-informed precision oncology strategies that can better account for tumor heterogeneity, cancer evolution, cellular state diversity, and dynamic drug responses.

Session 3: Technology Enablement

The third session of the symposium focused on the development and application of new technologies that enable advances in functional cancer genomics, including CRISPR-based perturbation screening, circulating biomarker technologies, and epitranscriptomic analysis.

Dr. Brian Brown shared his studies of immunotherapy resistance in pancreatic cancer using Perturb-map (a spatial functional genomics method). His team identified important mediators of immune evasion and immunosuppressive programs, thereby contributing to immunotherapy resistance. Complementary preclinical studies further showed that targeting tumor-associated macrophages with engineered CAR T cells can selectively localize to tumors, reprogram the macrophage compartment, recruit endogenous T cells, and convert immunologically “cold” tumors to “hot” microenvironments.

Dr. Natalia Moskal described the ExoRelay platform for tracking cell-derived exosomes and cellular identity over time using stable circular RNA barcodes. Pilot data in melanoma models suggests feasibility of this new system for detecting tumor-associated signals in blood.

Dr. Yining Zhao shared a pan-cancer analysis of m6A RNA modifications and the generation of a methylation atlas across TCGA tumors. He showed that somatic mutations can lead to measurable loss or gain of m6A marks. These findings suggest that some somatic variants may function as epitranscriptomic neomorphic mutations and reveal the importance of evaluating mutation consequences at both the protein and RNA regulatory levels.

Dr. Chenchu Lin presented the genetic modeling of drug responses through a CRISPR/enCas12a multiplexed perturbation platform. Her team in the Traver Hart Lab developed the PharmaKO library (a focused in4mer-based screening resource covering 223 oncology drugs) and tested it across cancer cell lines. Dr. Lin showed that multiplexed target perturbation provided performance comparable to Cas9 for single-target drugs while improving concordance between genetic sensitivity profiles and observed drug responses, particularly for agents acting through paralogous or multi-gene target relationships. Additionally, application of the platform in patient-derived xenograft and organoid settings demonstrated its potential to prioritize candidate therapies, validate vulnerabilities, and identify resistance mechanisms.

Collectively, this session highlighted emerging technologies in functional cancer genomics aimed at improving the understanding and treatment of cancer.

Session 4: Computational Biology

In the last session of the symposium, CTD^2 investigators shared computational biology approaches to improve target discovery, prioritize tractable therapeutic hypotheses, and enable broader clinical translation.

Dr. Traver Hart shared the development of scalable approaches for identifying synthetic lethal interactions. This work addressed a central barrier in the field—the enormous combinatorial search space of gene pairs—by using network-guided gene selection to concentrate screening on biologically coherent functional modules rather than genome-wide exhaustive testing. Dr. Hart also presented new analytical and simulation tools, including GRAPE and Synulator, to improve interpretation and benchmarking of pairwise genetic interaction data. These resources support a more efficient framework for detecting context-dependent synthetic lethalities in oncogenic pathways.

Dr. Yue Zhang presented modular AI-based drug response models. These models were trained on Cancer Therapeutics Response Portal (CTRP) datasets and evaluated using Genomics of Drug Sensitivity in Cancer (GDSC), PRISM: Profiling Relative Inhibition Simultaneously in Mixtures, Beat AML, and PROSPERITY datasets. These models demonstrated predictive capability for new drug responses in cancer cell lines. Potential applications for these types of AI models include predicting potential novel drugs in particular cancer types and predicting personalized drug responses for specific drugs.

Dr. Qingnan Liang introduced S-FLARE (Spatial Feature Learning for Anchored Reference-guided Embedding) for the accurate and scalable inference of unmeasured features in spatial

proteomics data using scRNA-seq references. Benchmarking results indicated improved performance over existing integration methods. Dr. Liang also shared that S-FLARE enables better cell type annotation.

Dr. Andrea Califano described a network-based “quantum cancer therapy” framework centered on master regulator (MR) proteins and tumor checkpoint modules. Potential applications of this framework include functional mutation interpretation, drug mechanism analysis, and single-cell therapeutic prioritization in tumors. Dr. Califano also shared some of his CTD^2 cross-network collaborative projects that are investigating chromosomal instability MRs in colorectal cancer and tumor microenvironment remodeling in pancreatic cancer liver metastases.

The final session showcased computational biology approaches across the CTD^2 Network that aim to improve the identification of context-specific vulnerabilities in cancer, predict treatment responses more accurately, enhance the understanding of tumor cell types/states, and support actionable precision oncology strategies.

Conclusion

Overall, the 2026 CTD² Network Virtual Symposium shared advances in functional cancer genomics, including mechanistic insights related to cancer-associated alterations, therapeutic vulnerabilities, and preclinical therapeutic candidates. Across cancer biology, precision oncology, technology development, and computational biology, CTD² investigators presented complementary strategies that are improving the ability to model tumor heterogeneity, define resistance mechanisms, identify actionable targets, and prioritize therapies using patient-relevant systems. The work highlighted the strength of the Network’s collaborative and multidisciplinary structure, which enables integration of experimental and computational methods. Moving forward, the program aims to continue to improve the understanding of how mutations affect downstream functions within cellular pathways, to identify new therapeutic targets and develop strategies to overcome treatment resistance, and to preclinically design optimal combination therapies.