Microbiome-Targeted Intervention Cancer Network (MTCN)

Concept Proposal (New RFA:U19 Clinical Trial Optional and RFP: N01)

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Primary sponsor: DCTD. Co-sponsor: DCB

Trans-NIH Microbiome-Targeted Intervention Cancer/Other Diseases Clinical Network Working Group (MTDCN WG) and inputs from others
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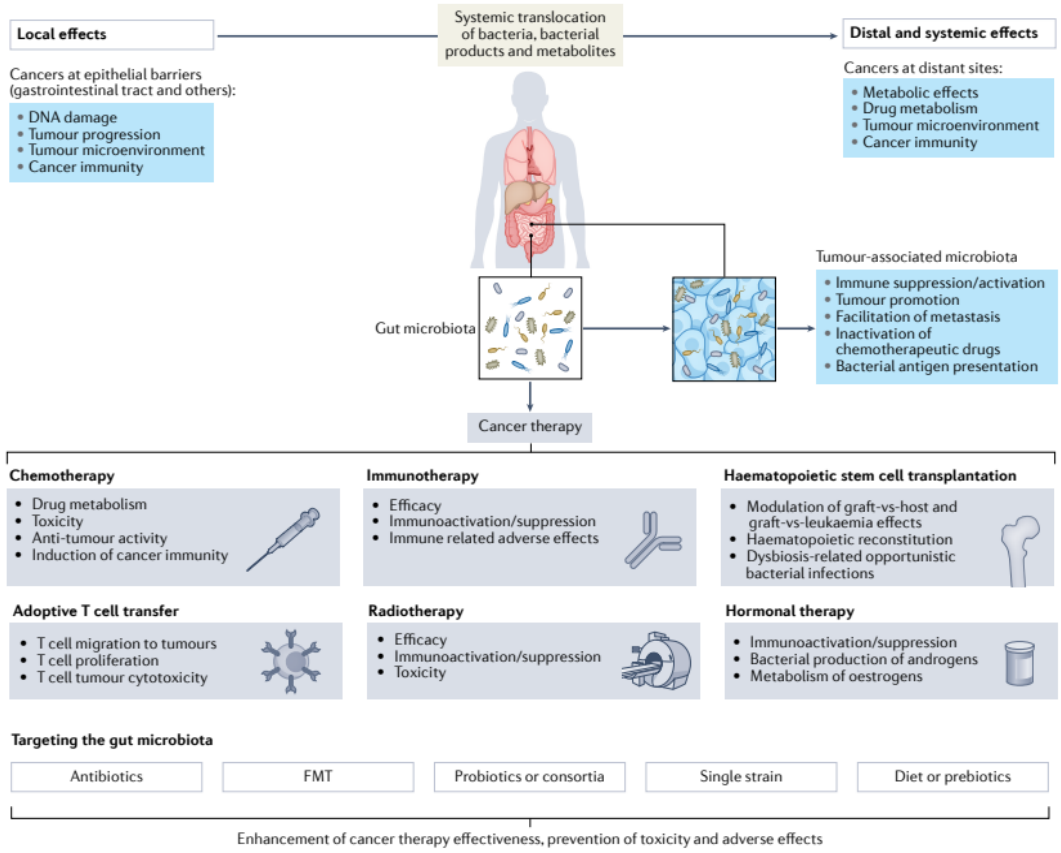
Background

➢ Targeting the Gut Microbiota for Cancer Therapy



Ref: Miriam R. Fernandes, Poonam Aggarwal, Raquel G. F. Costa, Alicia M. Cole & Giorgio Trinchieri. Nature Reviews Cancer volume 22, pages 703–722 (2022) https://www.nature.com/articles/s41568-022-00513-x

➢ Challenges and Opportunities in Translating Microbiome Research to Cancer Therapies

Challenges:

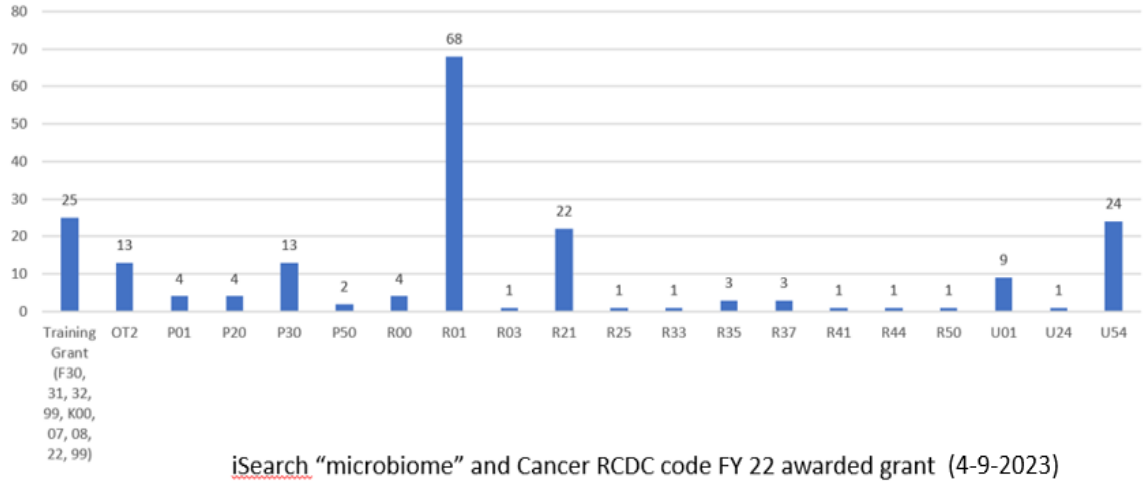
1) Clinical trial: phase 1 or 2 trials of Fecal Microbiota transplantation (FMT) and defined-microbial consortia are underway in US and internationally with various designs, but lack of correlative mechanistic studies
2) FMT: optimal donor selection, composition variations, long-term safety, and biomarkers for patient stratification
3) Defined-microbial consortia: beneficial bacterial species correlated with therapy outcomes are different between labs/cohorts varies

Opportunities:

1) Several pilot FMT trials showed safety & improved immunotherapy response rate and colitis. Need larger trials
2) Optimize clinical trials, paired with bidirectional human relevant mechanistic research in a coordinated network
3) Build Human Cancer Immunotherapy Fecal Microbiome Atlas and national FMT registry
4) Research variables: lifestyle (e.g., diet); antibiotics and medication; health conditions (e.g., periodontitis, obesity); and experimental, biological, social, geographical and environmental factors, etc.

FY 22 NCI Microbiome Portfolio Analysis

➢ NCI FY 22 Awarded 201 Projects (183 grants)

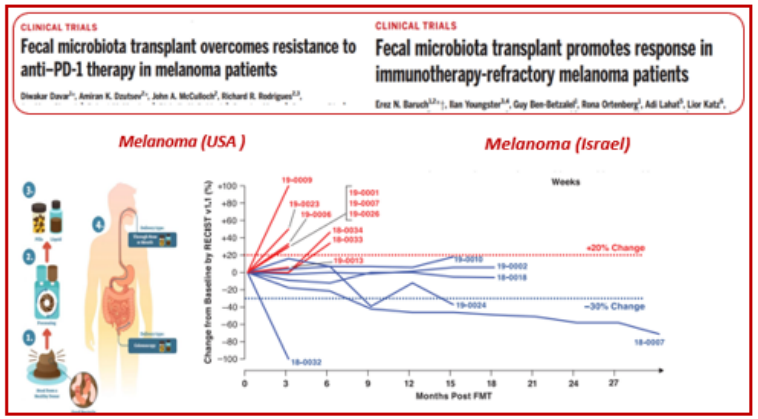


iSearch "microbiome" and Cancer RCDC code FY 22 awarded grant (4-9-2023)

Only Funded 2 Microbiome-based Cancer Therapeutic Trials

- ***FY18: R01CA222203***
  "*Fecal Microbiota Transplant and PD-1 blockade in Melanoma"*
- ***FY22: U01 CA268806***
  "*Therapy with fecal microbiota transplantation and immune checkpoint blockade for solid tumors" (Melanoma, Lung, HPV+ solid tumor).*

First-in-Human Positive Pilot Trial



Science 371, 2021

➢ Scientific/Clinical Needs

1) Insufficient representation of clinical trials in the NCI microbiome portfolio. Small trial and need optimization.
2) Various assays/tools in microbiome measurement and data analysis.
3) Prospective correlative cohort analyses are mostly from 1 site/location, statistical powered for 1 race (white).
4) Most studies are correlative analyses, preclinical mechanistic studies and casual testing in mice using FMT.
5) Limitation of preclinical models for translation to trials.
6) **NCI Needs To:**

   (A) Stimulate clinical testing of causal effect of microbiome on cancer therapy as potential therapeutics in network-based coordinated centers to foster collaboration and human relevant mechanism-based optimization.

   (B) Ensure racial diversity in human microbiome research to improve rigor and reduce disparity in cancer care.

   (C) Centralize standardization and investigate variables.

Purpose and Goals of RFA U19 and RFP N01

- **Purpose:**

  To timely accelerate innovative early-stage clinical testing of microbiome-targeted cancer intervention to improve immunotherapy in a transdisciplinary "Microbiome-Targeted Intervention Cancer Network" (MTCN) through U19 "Microbiome Research and Clinical Trial Centers" (MTCC) and N01 "Microbiome Clinical Network Coordinating Center" (MTCNC).

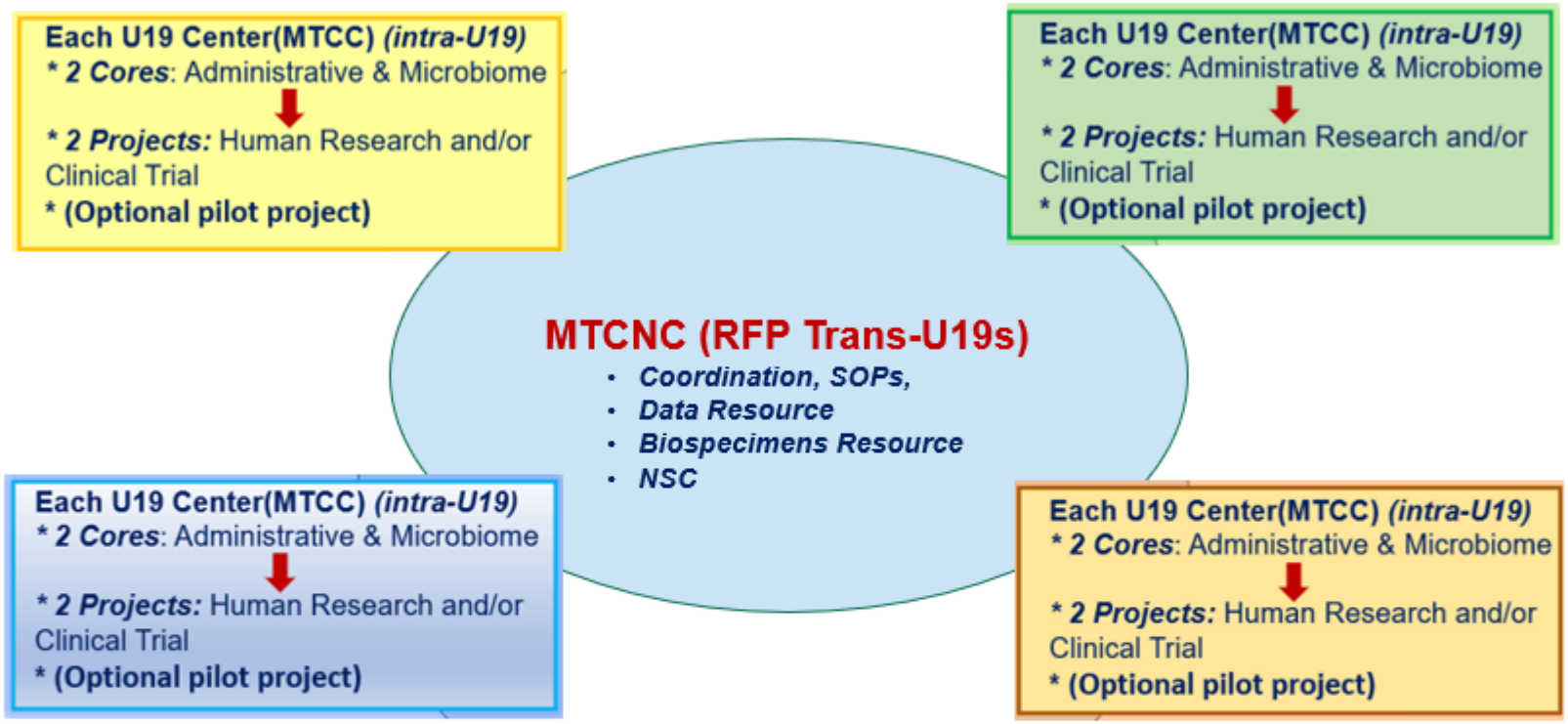
- **The overall specific goals:**

  - **(U19) (1)** develop optimal FMT or defined-microbial consortia products for early phase (*1/2, or 2*) clinical trials of safety and efficacy to overcome immunotherapy resistance and alleviate therapeutic-induced adverse events. **(2)** conduct bidirectional human relevant mechanistic studies to inform trial design.
  - **(N01) (1) Administrative core**: coordinate across U19 centers, **(2) Microbiome core**: **(a)** harmonize and standardize the procedures/protocols for optimizing FMT and defined-microbial consortia products, and clinical trial design, **(b)** coordinate and standardize microbiome measurement, centralize bioinformatics, and database infrastructure, establish one FMT Cancer National Registry and one Human Cancer Immunotherapy Fecal Microbiome Atlas, and **(c)** establish one fecal repository biobank resource including characterization (e.g. multi-omics, animal model testing, and inoculum) for distribution to academic research community and private-public partnership.

- **The priority of microbiome-targeted interventions**:

  FMT or defined-microbial consortia for enhancing immune checkpoint inhibitor and CAR T therapies.

Structure Outline of MTCN (MTCC & MTCNC)



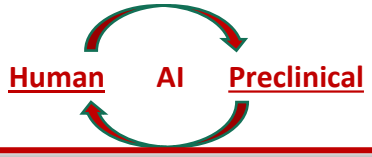
- **MTCN:** Microbiome-targeted Intervention Cancer Network
- **MTCC:** U19 Microbiome Research and Clinical Trial Centers (Intra-U19)
- **MTCNC:** RFP Microbiome Clinical Network Coordinating Center (Trans-U19s)
- **NSC:** Network Steering Committee

- **At least two U19 centers conduct clinical trial**
- **All U19s conduct human study**
- **Co-PI U19s with one basic cancer researcher and one clinical researcher**

Network Steering Committee:

- U19 PIs, NCI, NIH staff and NCI funded R01 PIs
- Monthly meeting
- Annual meeting

The Examples of Priority Topics and Projects



1. **Each center Must conduct at least one of the following human projects**:

   1) Develop fecal microbiota or defined-microbial consortia products and obtain FDA IND approval , and/or,

   2) Conduct FMT or defined-consortia early phase trials, e.g., primary end point of response or adverse event.

2. **Must investigate gut microbial compositions and functions through multi-omics** measurements (16S rRNA, metagenomic, metatranscriptomic and metabolomics).

3. **Must assess immunological biomarkers** associated with therapy response, resistance and adverse event.

4. **Must investigate variables to inform Optimization of trial design:** e.g., healthy or responder FMT donors; product preparation; selection of defined-microbial formula; engraftment; dosing; timing; antibiotics/medication; health conditions; lifestyle; biological factors including sex, age, genetic/ genetic ancestry; social, geographical and environmental factors; and interaction of microbiota between gut and tumor, or other tissues/organs etc..

5. **Immune-microbiome modulation through pre/probiotics as one of the aims or projects is encouraged.**

6. **Required multiple components,** bidirectional human relevant preclinical studies. AI is encouraged.

7. **Required 2 races** in each cohort study: White, Black, Hispanic, Asian, and Native Hawaiian/Pacific Islander.

8. **Needs strong preliminary data**, e.g., expanding research, or already have fecal/consortia products.

Justification RFA & RFP, & Cooperative Agreement Mechanism (U)

- **RFA and RFP:**

  1) Unmet scientific need for optimizing proof-of-concept clinical trial to better inform future larger randomized phase 2 or 3 trials.
  2) Lack of NCI funding in clinical trials and coordinated clinical research center.
  3) Quickly attract transdisciplinary teams into a collaborative network with a single receipt date, specific responsiveness and specific review criteria.
  4) RFP would better serve the consortium and the community in the long run to enhance timely data and biological resource sharing and distribution.

- **U Funding Mechanism (network and synergy):**

  To enhance rigor and reproducibility through harmonization and standardization in a coordinated muti-center network.

  1) Substantial NCI/NIH program staff involvement in steering committee to provide programmatic inputs and to rapidly address common goals, challenges and opportunities and to foster collaboration and timely share resources among awardees.
  2) NCI/NIH program staff provide information on availability of other relevant NCI/NIH resources.
  3) Collaborations can be further established post-award across centers.

Budget

Funding Mechanism	No. of Awards	Funding Level	Recommended Total Costs
RFA U19	4	Each award max. $1.1 M DC	$7.5 M (First year)
RFP N01	1	$1.0 M TC	
			Total for the program $37.5 M (5 years)

Evaluation Criteria

- **Microbiome Research and Clinical Trial Center (MTCC) (RFA U19):**
  1) Conducted clinical trial and obtained FDA's IND approval for FMT and/or defined-microbial consortia.
  2) Standardized protocol and procedure for optimal FMT and/or defined-microbial consortia clinical trial design.
  3) Advanced scientific knowledges of variables (e.g. antibiotics/medication, health conditions, biological, sex, lifestyle, race, geographic, environmental and social factors, and interaction of microbiota between gut and tumor or other tissues/organs).
  4) Transformed understanding of gut microbiome impact on immunotherapy outcomes with rigor and precision.
  5) Established new collaborative transdisciplinary teams for future clinical trial.
  6) Data and results will timely inform the rationale for future larger randomized phase 2 or 3 clinical trial.
  7) Improved health disparity in cancer microbiome research.

- **Microbiome Clinical Coordinating Center (MTCNC) (RFP N01):**
  1) Advanced cancer immunotherapy and microbiome research for a broad scientific community through sharing two comprehensive gut microbiome clinical databases and one biological fecal resource.
  2) Established scientific and administrative infrastructure for timely coordinating multi-centers microbiome-targeted cancer therapeutic clinical research and private-public partnership.
  3) Standardized experimental measuments and advanced computation biology.

Incorporating BSA Reviewers Comments in RFA/RFP

(Reviewers: Drs. Nelson Chao, Cornelia Ulrich, Richard Zellars)

1) Intervention priorities are FMT or defined-microbial consortia. Pre/probiotics can be included (slide #4 & 6).
2) Transdisciplinary team including epidemiologist (epidemiology/preclinical/clinical) would be also appropriate.
3) Include sex in variable research.
4) To reduce overhead, RFP will combine cores into 2: “administrative core” and “microbiome core” (slide #4).
5) RFP funds:
    a) given expensive clinical trial, RFP will provide measurements for 16S rRNA and 3 types of -omics up to certain amount (e.g. 300 samples/year) for clinical trial U19 with justification and NCI pre-approval.
    b) Proteomics is not required for all U19s. NCI MTCN working group will make plans for RFP providing services for proteomic assays with the inputs from MTCN network steering committee after award.
6) Disparity and diversity requirements:
    a) Trial with > 1 statistical powered race will be considered as priority in funding, but no requirement > 1 site.
    b) Evaluating gut microbiome from cohorts of cancer patients treated with immunotherapy is required to be powered adequately for 2 different races; and include at least 2 locations, with 3 locations preferred.

Thank You!

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