NCI Specialized Programs of Research Excellence (SPORE)

Translational Research Program (TRP)
Division of Cancer Treatment and Diagnosis (DCTD)
National Cancer Institute (NCI)
National Institutes of Health (NIH)
Website: trp.cancer.gov

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2018 NCI IMAT PI Meeting

NIH NATIONAL CANCER INSTITUTE

November 29, 2018

The Birth of Specialized Programs of Research Excellence

The **Specialized Programs of Research Excellence** (**SPORE**) is a *translational research program* established in 1992 by the National Cancer Institute in response to the Congressional mandate to integrate laboratory and clinical investigations for the rapid translation of basic scientific discoveries into clinical application.

Excerpt from 1992 Senate Report

The Committee believes that breast cancer research must be a top priority for the National Cancer Institute. Of the $40,000,000 the Committee has provided for research on cancers affecting women, the Committee directs that not less than $30,000,000 be available for breast cancer research. Of this total, $20,000,000 is to be available for basic breast cancer research to understand the cause and find a cure for breast cancer, and $10,000,000 is to be used to establish up to six specialized breast cancer research centers. The Committee urges that the centers be established through the P–50 grant mechanism that links laboratory studies with clinical research to rapidly translate basic scientific discoveries in breast cancer into clinical medicine. The grantee institution receiving the award must make a major commitment to support a comprehensive, interdisciplinary approach to breast cancer research that will integrate basic research, etiology, diagnosis, prevention, clinical applications, training, and quality-of-life issues. The Committee also urges NCI to ensure that the centers encourage cutting edge and innovative research; provide training for young researchers; attract qualified scientists who previously have not been given the opportunity to concentrate their talents on breast cancer research; and expedite the translation of research advances from the laboratory to the patient.

The Committee urges the establishment of up to six specialized programs of research excellence [SPORE] through the P50 grant mechanism that links laboratory studies with clinical research to rapidly translate basic scientific discoveries in breast cancer into clinical medicine. The grantee institution receiving the award must make a major commitment to support pilot interdisciplinary collaborative projects in addition to career development.

By its participation in the trans-NIH healthy women's study, the NCI will explore whether reducing fat intake lowers the risk of developing breast, colorectal, and other cancers in addition to cardiovascular disease. The NCI will begin a 3-year feasibility study to determine effective ways to promote dietary change among minority and less educated women by restricting their fat intake. The tumor suppressive effects of tamoxifen will be assessed in a randomized clinical trial that will enroll women at high risk for devel-

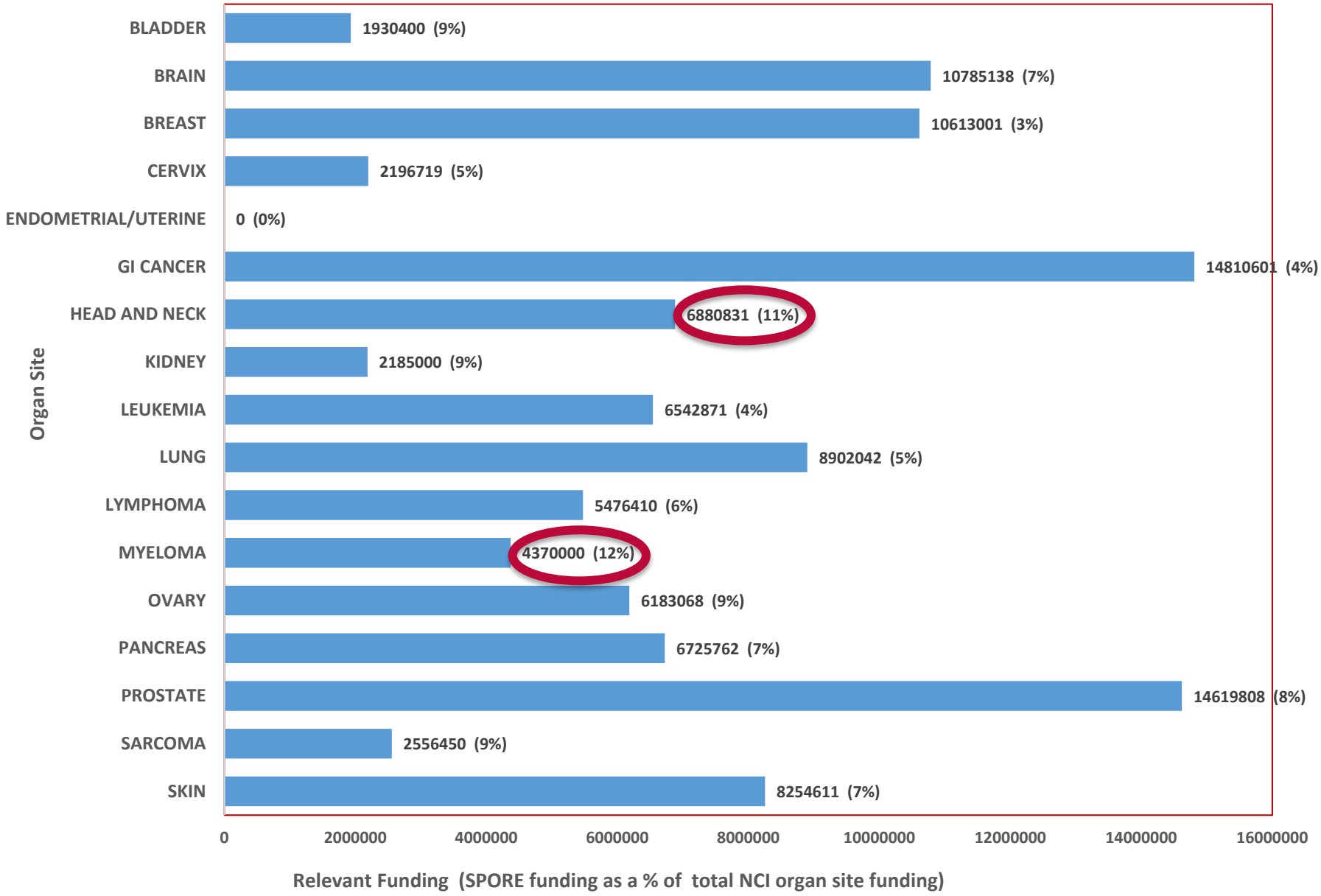
SPORE Program (1992-2018)

Number of Grants

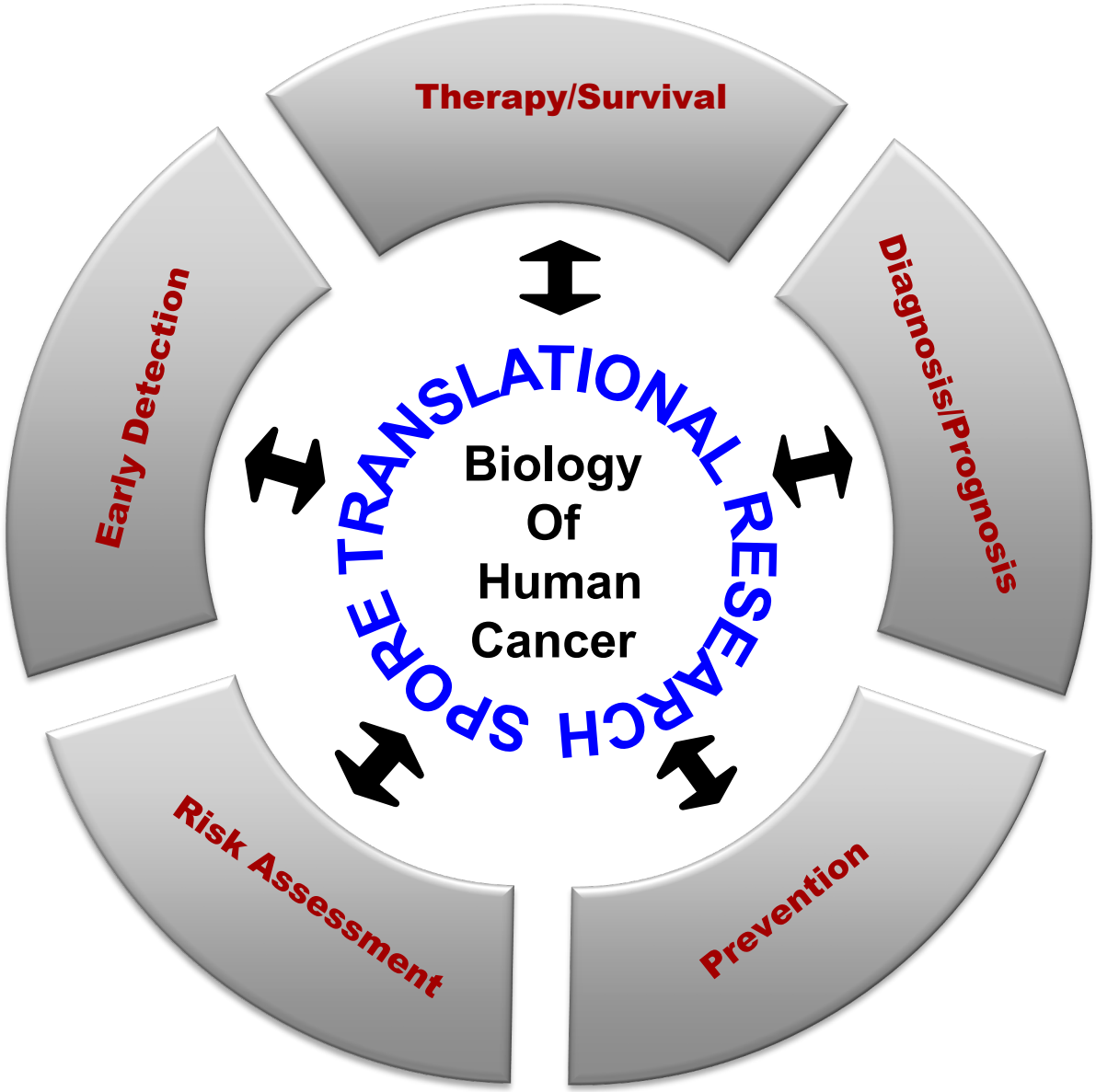
	1992-95	1996-98	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Breast	4	6	6	9	9	9	9	10	8	10	11	10	10	8	6	6	5	6	5	5	4	3
Prostate	2	3	3	4	8	11	11	11	11	8	7	7	9	9	8	5	6	6	7	8	9	7
Lung	2	3	3	3	6	6	7	7	7	5	6	6	7	7	7	6	2	3	4	3	3	3
Gastrointestinal	1	2	2	2	2	4	4	5	4	4	5	5	5	6	7	4	5	5	4	3	2	2
Ovary			4	4	4	4	4	5	4	4	4	4	4	4	4	4	5	2	2	2	3	4
Bladder					1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1
Skin					1	2	2	3	3	3	3	5	3	4	3	4	4	5	4	4	3	2
Brain						2	2	4	4	4	3	4	2	2	4	3	5	5	5	4	5	4
Head & Neck						3	3	4	4	4	3	5	4	5	5	4	2	2	2	3	2	2
Lymphoma						2	2	3	3	3	3	4	4	4	5	4	3	3	3	3	3	4
Endometrial							1	1	1	1	1	0	1	2	2	1	1	1	0	1	1	1
Cervical							1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Kidney							1	1	1	1	1	0	1	1	1	1	1	0	1	2	2	2
Leukemia							1	1	1	1	1	1	2	2	2	2	3	2	2	2	3	3
Myeloma							1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	1
Pancreas							3	3	3	3	3	2	2	3	3	3	1	3	2	3	3	3
Sarcoma														1	1	2	2	2	1	1	0	1
Thyroid																	1	2	2	2	2	1
Neuroendocrine																			1	1	1	1
Pediatrics/RAS																			1	1	1	1
Liver																						1
Total Programs*	9	14	18	22	31	44	53	61	57	54	54	55	57	62	61	53	49	49	50	52	50	48
Annual Budget	20M	30M	39M	48M	68M	112M	126M	135M	133M	125M	121M	123M	128M	134M	122M	116M	106M	106M	106M	106M	106M	109.2M

*** Excluding grants receiving interim funding**

FY2015 Relevant Funding for Organ Site Specific SPORE



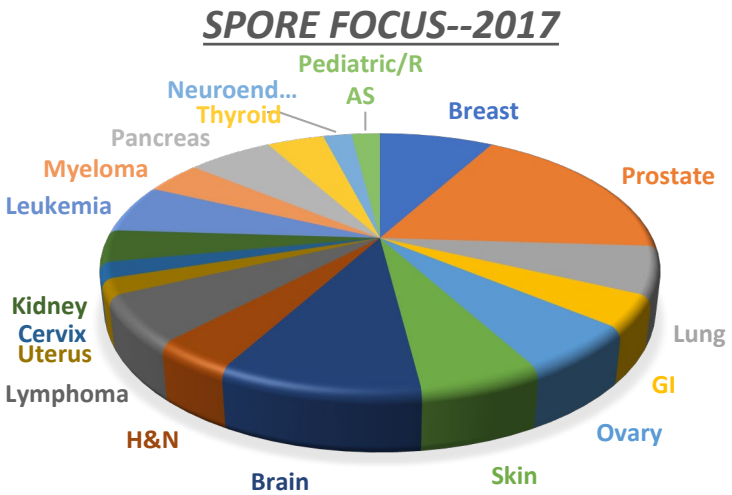
Bi-Directional Translational Research

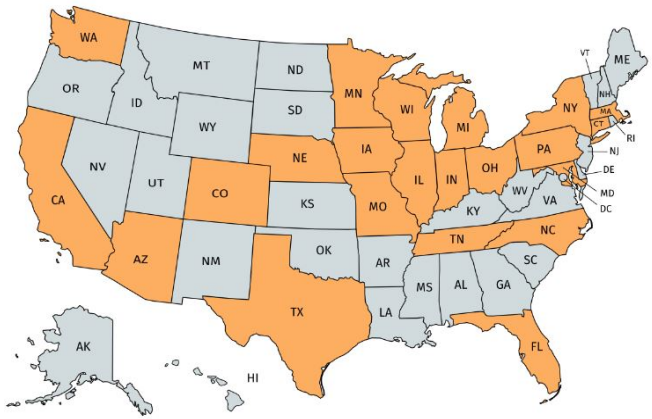


SPOREs: Unique Aspects and Distribution

- All scientific projects must be translational and have a human endpoint within 5 years.
- Team approach; at least one basic and one clinical/applied science co-leader must head each project.
- Flexibility to terminate projects and to add projects within funding period. This allows the PI to move rapidly to refocus research based upon new knowledge and opportunities in the field.
- Scientific focus: organ-specific; group of related cancers; cancers related by common pathway alteration or cross-cutting theme
- Career Enhancement Program: not a training program. Allows basic and clinical scientists to become involved in translational research.
- Developmental Research Program for cutting-edge pilot studies, high risk/high payoff studies, and initiation of collaborations;
- Biospecimens/Pathology CORE is required: a source of research specimen and analytic services. SPOREs must share specimens among other SPOREs and with the general scientific community, when appropriate. Many R01s depend upon biospecimen resources in SPOREs.
- SPOREs must collaborate.
- Involve input from patient advocates.

In 2017:
50 funded SPOREs
22 States
32 Institutions





What is a Human Endpoint?

- **At least one of the following types of human endpoints should be proposed in each SPORE research project:**
  - **Early phase clinical trials of new investigational drugs (INDs) and biologics, experimental procedures, medical devices, or combinations thereof**
  - **Early phase clinical trials of new combinations or new uses of the FDA-approved agents and devices**
  - **Discovery and development of biomarkers, only when measurements are made in human biospecimens, or directly in human subjects**
  - **Laboratory studies using clinical materials that lead to new clinical hypotheses (reverse translation)**
  - **Population, behavioral, or psychosocial studies, when these studies address mechanistic aspects of the biology of the disease**
  - ***IND-directed toxicological studies conducted following a pre-IND meeting with the FDA in which the plan proposed by the investigators is acceptable to the FDA**
- **Cell lines, organoids, xenografts, or patient-derived xenografts (PDX) using primary human tumors are not sufficient as human endpoints**

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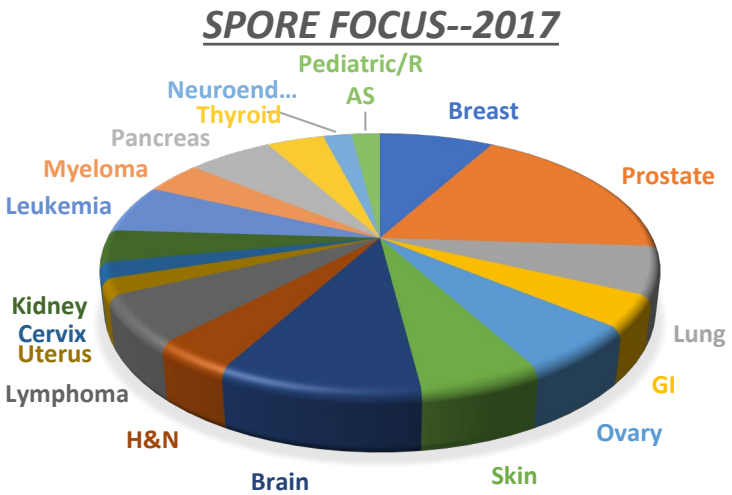
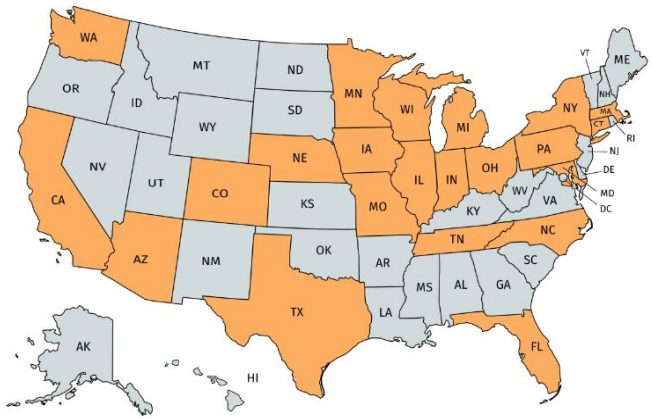




SPORE Eligibility

- **Minimum Research Base:** Four investigators with a significant role in a SPORE (as project co-leader, core director, or SPORE Director) must have an independently funded peer-reviewed grant or serve as an overall/site chairperson on an active NCI-sponsored clinical trial.

SPORE Budget

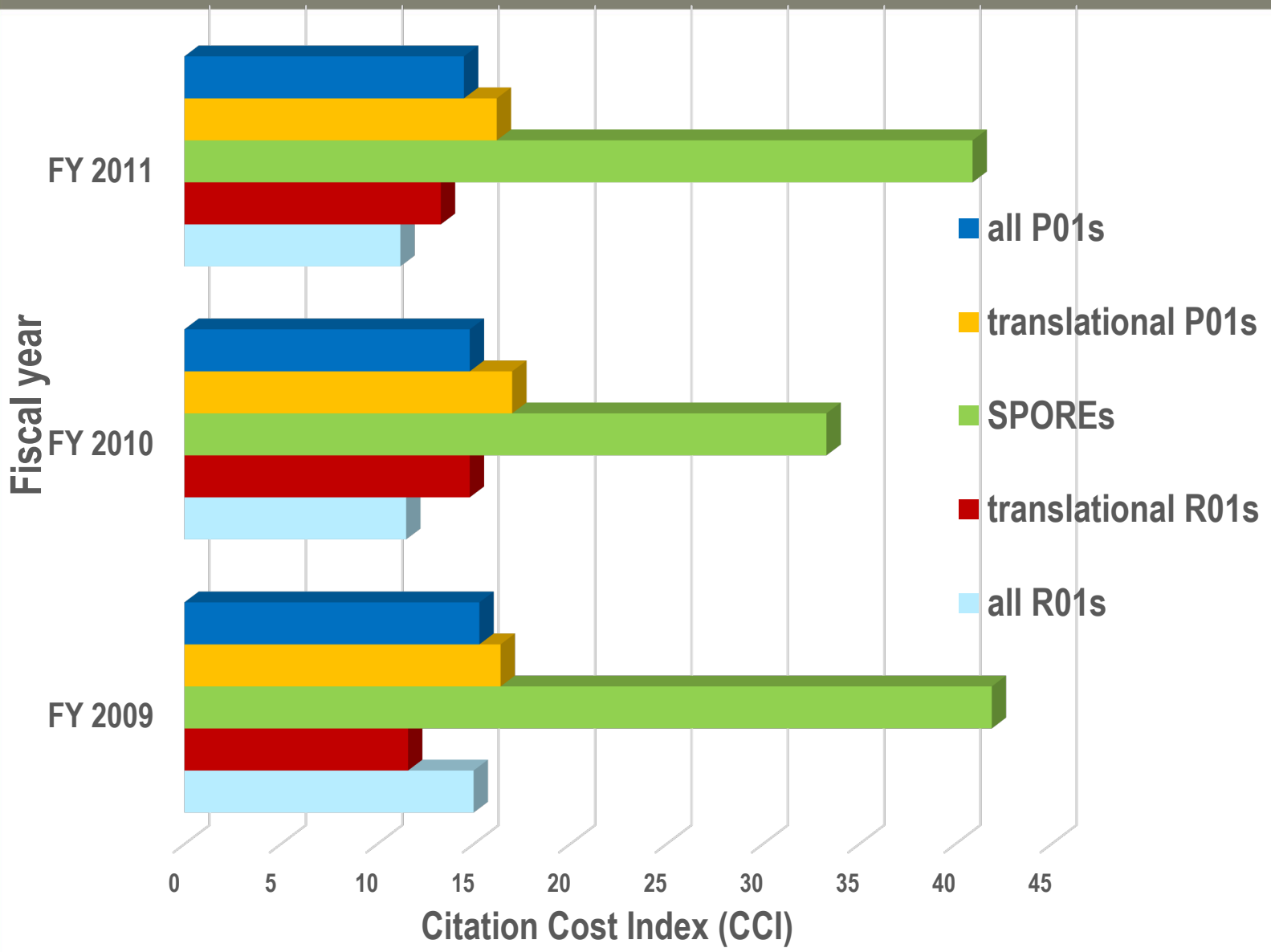
- Up to $1.4M direct cost/year if no EPPS* project is proposed
- Up to $1.52M direct cost/year if one or more EPPS projects are included

* Early Detection, Prevention, or Population Science (EPPS)

SPORE Highlights

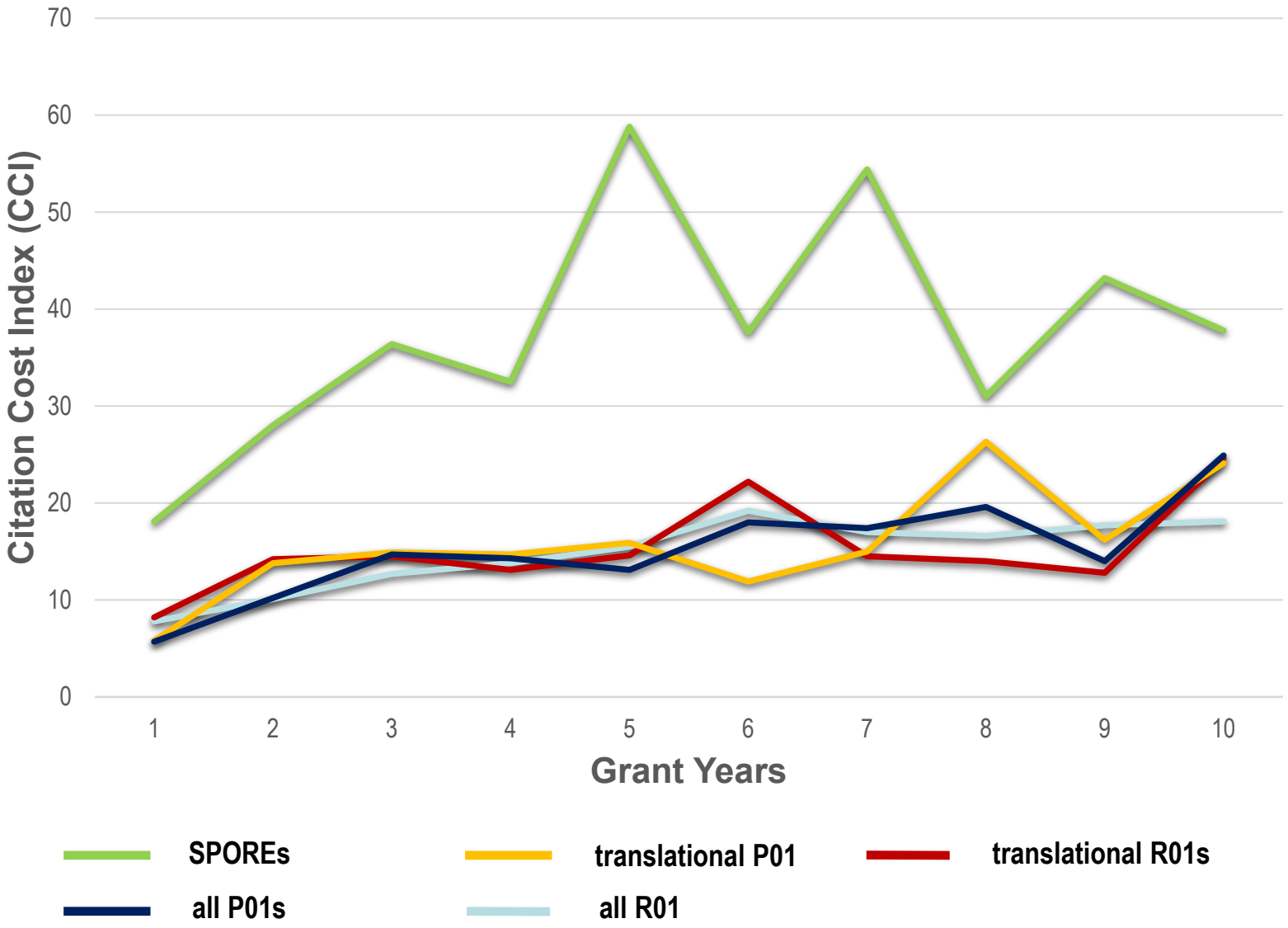
National Cancer Institute

Citation Productivity by FY



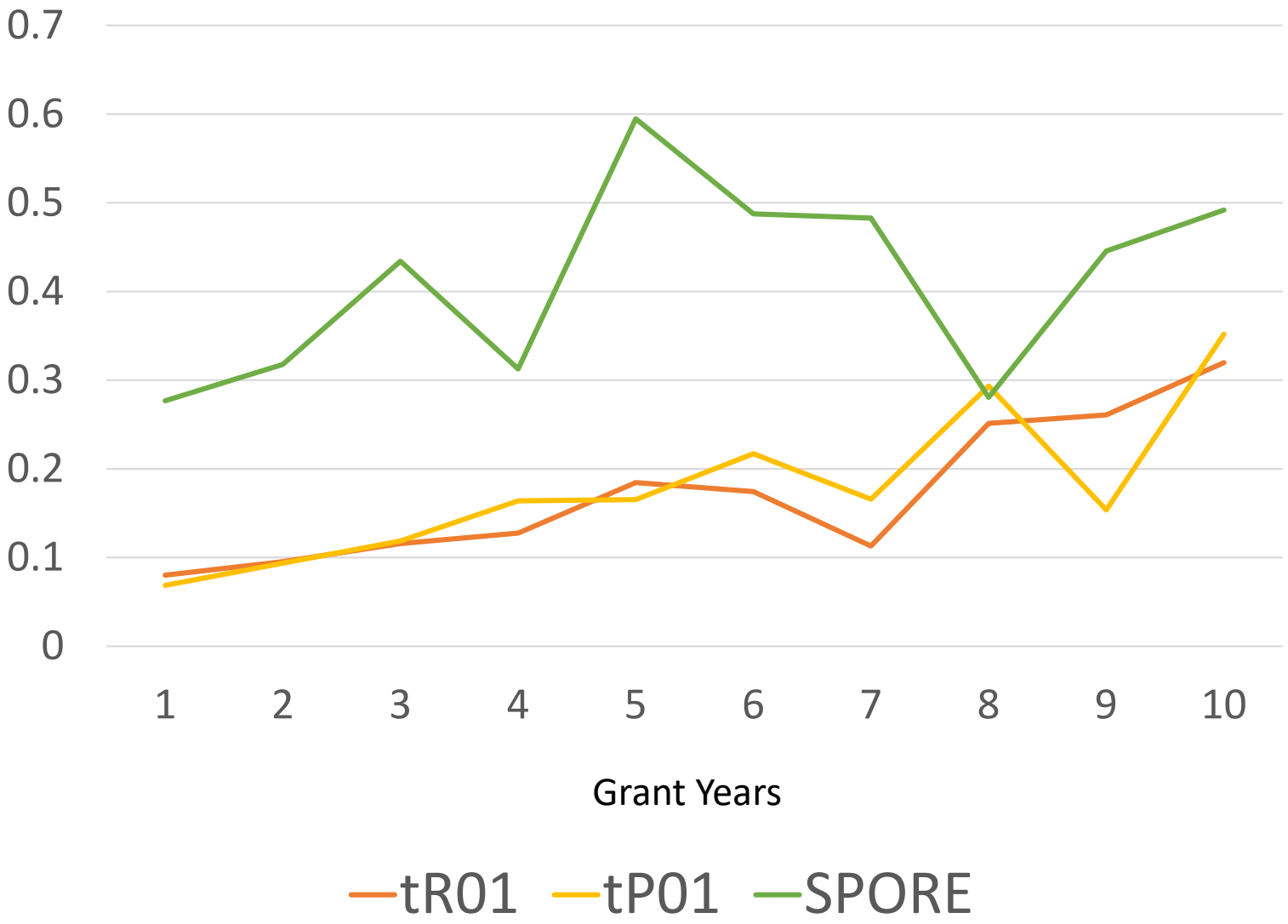
National Cancer Institute

Citation Productivity by Grant Support Years

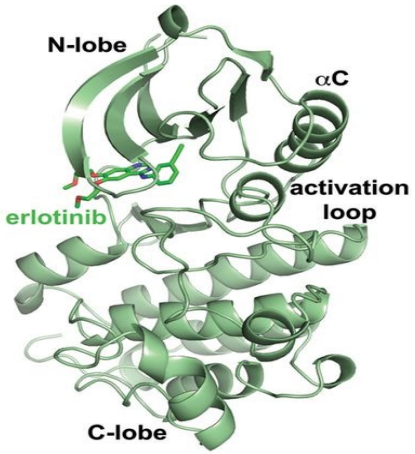


National Cancer Institute

Cited by Clinical Papers per $100K



Sensitivity and Resistance to EGFR Tyrosine Kinase Inhibitors in Lung Cancer



- Key findings
  - Association of EGFR gene mutations with response to gefitinib and erlotinib
  - Association of secondary EGFR point mutation (T790M) with emergence of resistance to gefitinib and erlotinib
- SPORE role (DF/HCC)
  - MGH/DFCI/HMS work on EGFR gene mutations and gefitinib sensitivity
  - DFCI work on the association of the T790M mutation with gefitinib resistance
- Current status
  - Extensive body of ongoing research exploring genomic and other determinants of sensitivity and resistance to EGFR tyrosine kinase inhibitors
  - NCCN guidelines for NSCLC recommend adenocarcinoma EGFR mutation testing
  - Several laboratory-developed EGFR mutant tests are available as commercial or hospital lab services

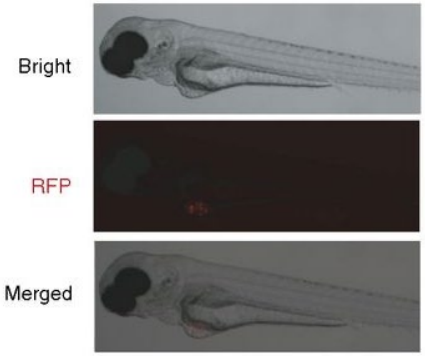
SPORE Advances in Cancer Treatment

FDA-approved or Breakthrough Therapy Designated Agents with SPORE Contribution (past 15 years)

- Regorafenib in GIST
- Decitabine in myelodysplastic syndrome
- Ibrutinib and Idelalisib in CLL
- Rituximab +Fludarabine in CLL
- Vincristine Sulfate Liposome in ALL
- Lenalidomide and Pomalidomide in myeloma
- Erlotinib and Afatinib in $EGFR^+$ NSCLC
- Crizotinib in ALK^+ NSCLC (FISH test)
- Ceritinib in ALK, RET, or ROS^+ NSCLC (FISH test)
- Abiraterone Acetate and Enzalutamide in castration-resistant prostate cancer
- Olaratumab in soft tissue sarcoma
- Larotrectinib in TRK fusion gene $^+$ tumors
- PVS-RIPO (re-engineered poliovirus) in GBM

Significant SPORE Accomplishments from 2016 : 1130 papers were published in 2016

- **Basic/Translational Science:**
  - **Myeloma SPORE—DFCI/HCC: Kenneth Anderson "A clinically relevant in vivo zebrafish model of human multiple myeloma to study preclinical therapeutic efficacy"** ***Blood 128, 2016, 249***

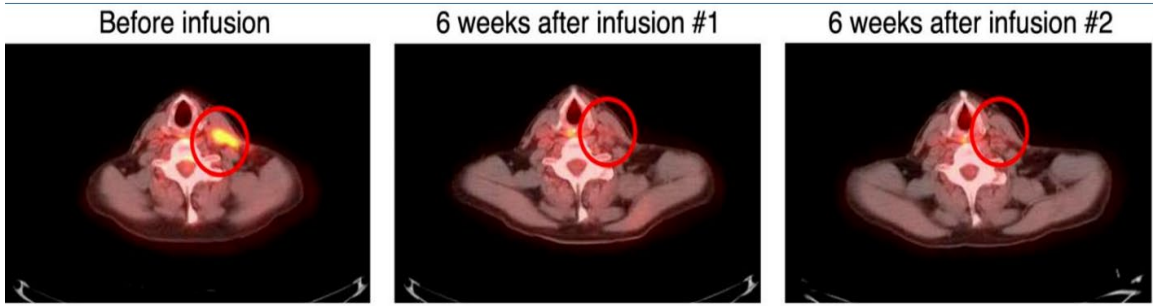


- ***Use of cell lines demonstrated cell growth in zebrafish embryos and showed that addition of anti-MM drugs to embryo water would inhibit cell growth of the drug-sensitive cells, but not that of the drug-resistant cells. Using primary cells from newly diagnosed and relapsed/refractory MM patients, they showed that engraftment of these patient-derived cells was similar to that of the cell lines. Newly diagnosed patient cells were sensitive to bortezomib and lenalidomide in the model, but cells from patients who had been resistant to these drugs were also resistant in the zebrafish model. This model potentially can be used for preclinical drug screening on a small number of patient cells (10^5) within a short period of time. PDX models are difficult for this disease.***

Significant SPORE Accomplishments from 2016 (continued)

- **Clinical Science:**
  - **Lymphoma SPORE—Baylor College of Medicine: Helen Heslop/Malcolm Brenner "Responses with T lymphocytes targeting malignancy-associated κ light chains"** ***J Clin Investig 126, 2016, 2588***
    - ***Autologous T cells expressing CD19-directed chimeric antigen receptors have shown activity in patients with lymphoma in an MHC-independent fashion, but long-term persistence is required for sustained responses and this leads to B cell aplasia and hypogammaglobulinemia. This group generated a CAR-T that is specific for the κ light chain on malignant B cells and spares normal B cells that express the λ light chain. In vitro cytotoxicity against κ+ targets was demonstrated.***
    - ***In a Phase I trial (NCT00881920) of 16 patients with relapsed/refractory κ+ NHL, CLL, or MM treated with κ -CAR-T cells, κ -CAR-T expansion peaked at 1-2 weeks and remained detectable for at least 6 weeks. Two patients (NHL) achieved a CR; 1 reached a PR; 4 (MM) had stable disease lasting 2-17 months. No toxicities were observed that were attributable to κ-CAR-Ts.***

This follicular lymphoma patient has been without evidence of disease for almost 3 years



Current examples of new technologies in therapy development used by SPOREs

- Oncofetal Glycosaminoglycans as Molecular Targets in Prostate Cancer – *malarial rVAR2-Drug Conjugate (VDC886) to target oncofetal chondroitin sulfate-expressing prostate cancer cells (P50CA097186)*
- L1 Capsomeres as a Next Generation Preventive HPV Vaccine – *subunit HPV vaccine composed of "capsomeric" subunits of the virus-like particles that can be manufactured at an affordable cost (P50CA098252)*
- An *in situ* Patient-Specific Chemo-Immunotherapy for Skin Cancers – *new in situ patient-specific microneedle array chemo-immunotherapy technology that delivers a chemotherapeutic agent to promote immunogenic cell death and a potent adjuvant (P50CA121973)*
- Monitoring metabolism in GBM using hyperpolarized C-13 imaging and H-1 MRSI – *H-1 MR spectroscopic imaging; hyperpolarized C-13 imaging, a novel technology for monitoring dynamic changes in the magnitude and rate of conversion of pyruvate to its metabolic products (P50CA097257)*
- Engineered T Cell Therapy for Melanoma – *electroporated T cells that express optimized mRNA CARs targeting c-Met in melanoma (P50CA174523)*

TRP Team

trp.cancer.gov

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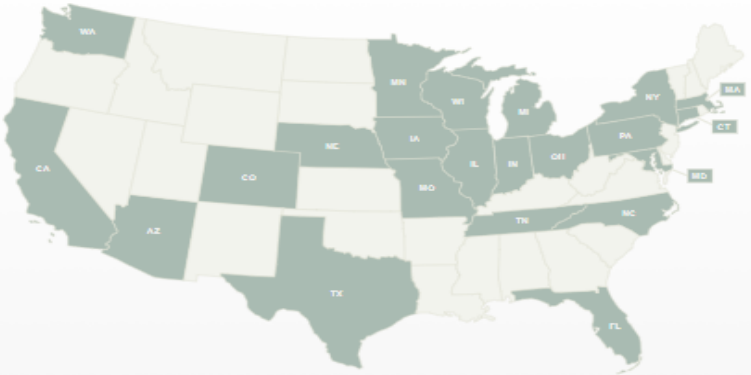
Welcome to the Translational Research Program (TRP)

The Translational Research Program (TRP) is the home of the SPOREs — the Specialized Programs of Research Excellence — a cornerstone of NCI's efforts to promote collaborative, interdisciplinary translational cancer research. SPORE grants involve both basic and clinical/applied scientists working together and support projects that will result in new and diverse approaches to the prevention, early detection, diagnosis and treatment of human cancers.

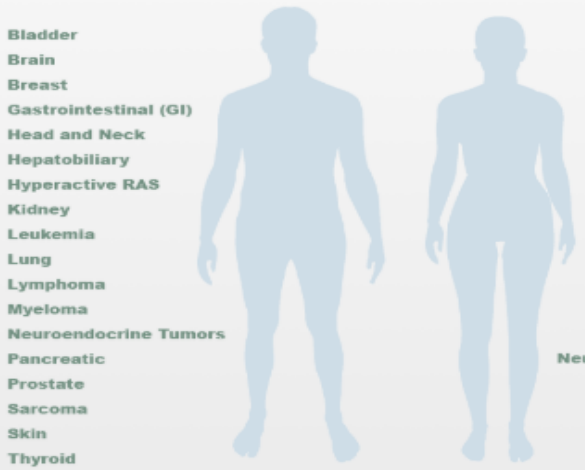
Each SPORE is focused on a specific organ site, such as breast or lung cancer, a group of highly related cancers, such as gastrointestinal cancers and sarcomas, or a common pathway or theme that ties together the cancers under study. SPOREs are designed to enable the rapid and efficient movement of basic scientific findings into clinical settings, as well as to determine the biological basis for observations made in individuals with cancer or in populations at risk for cancer. SPOREs are required to reach a human end-point within the 5-year funding period. Over twenty organ sites, systems, and pathway-specific themes are represented in the SPORE portfolio, including: bladder, brain, breast, cervical, endometrial, gastrointestinal, head and neck, hepatobiliary, kidney, leukemia, lung, lymphoma, myeloma, neuroendocrine, ovarian, pancreatic, prostate, sarcoma, skin, thyroid, and hyperactive RAS tumors.

The program is open to additional organ system or pathway-related translational research, including research in less common cancers. The objective for all SPOREs is to reduce cancer incidence and mortality and to improve survival and quality of life for cancer patients. SPOREs encourage the advice of patient advocates in SPORE activities. Prospective applicants are encouraged to contact TRP Officials for advice prior to submission. The current Program Announcement for submitting applications is https://grants.nih.gov/grants/guide/pa-files/PAR-18-313.html.

SPOREs by State



SPOREs by Organ Location



Thank you!

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