IDA SCIENCE AND TECHNOLOGY POLICY INSTITUTE

Evaluation of the National Cancer Institute (NCI) Specialized Programs of Research Excellence (SPORE)

NCI Clinical Trials and Translational Research Advisory Committee

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Analysis Methodology

- Sample set of 55 SPORE awards
  - Active any time since 2004
  - Completed at least one 5-year award cycle
- Organ site distribution
  - Brain—4
  - Breast—8
  - Gastrointestinal—5
  - Genitourinary—4
  - Head and Neck—4
  - Hematological—5
  - Lung—7
  - Ovarian—4
  - Prostate—11
  - Skin—3
- Data sources
  - Applications/progress reports for most recently completed 5-year award cycle
  - Individual discussions with SPORE PIs
  - Independent analysis of major advances

Evaluation Highlights

- Major Conclusions
- SPORE-Influenced Major Advances
- Clinical Trials
- Collaborations
- Career Development Program
- Developmental Research Program
- Flexibility Option

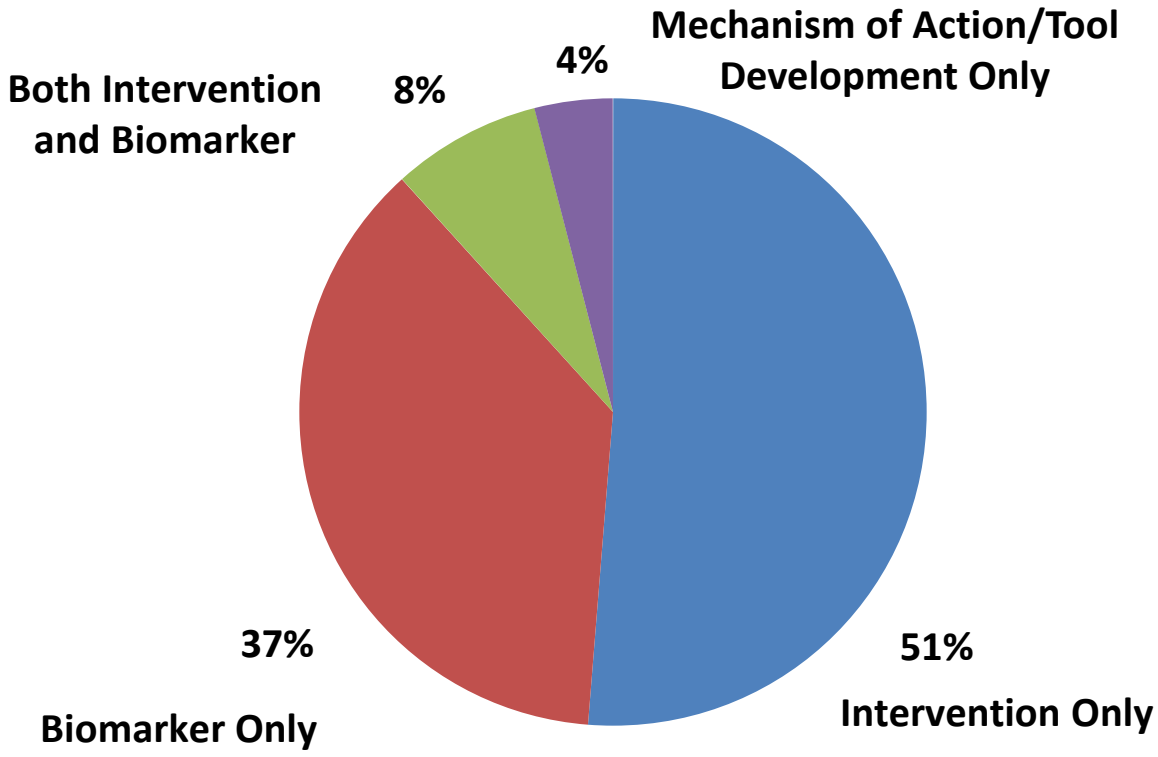
Major Conclusions

- Clear focus on early translation
- Award-related constraints to translational progress
- Success in reaching a human endpoint
- Distinct niches for SPORE research
- Key SPORE roles in building capacity for translational research

Synthesis of evidence gathered throughout the evaluation from multiple data sources

Clear Focus on Early Translation

96% of projects had a defined intervention or biomarker test development objective



Clear Focus on Early Translation

80% of intervention projects propose late-stage development activities

# of Projects	MOA[1] Only	Identify Target	Confirm Target	Develop Intervention	Clinically Test Intervention
11	■				
6		■			
3		■	■		
3		■	■		■
2		■	■	■	■
1		■		■	
2		■		■	■
8		■			■
6			■		
6			■	■	
8			■	■	■
6			■		■
16				■	
45				■	■
17					■

[1] Mechanism of Action

Clear Focus on Early Translation

90% of biomarker projects propose to identify or confirm a biomarker

# of Projects	MOA[1] Only	Identify Biomarker	Confirm Biomarker	Develop Biomarker Test	Human Testing
4	■				
40		■			
17		■	■		
2		■	■	■	
3		■	■	■	■
6		■	■		■
2		■		■	
5		■			■
10			■		
1			■	■	
6			■		■
1				■	
4					■

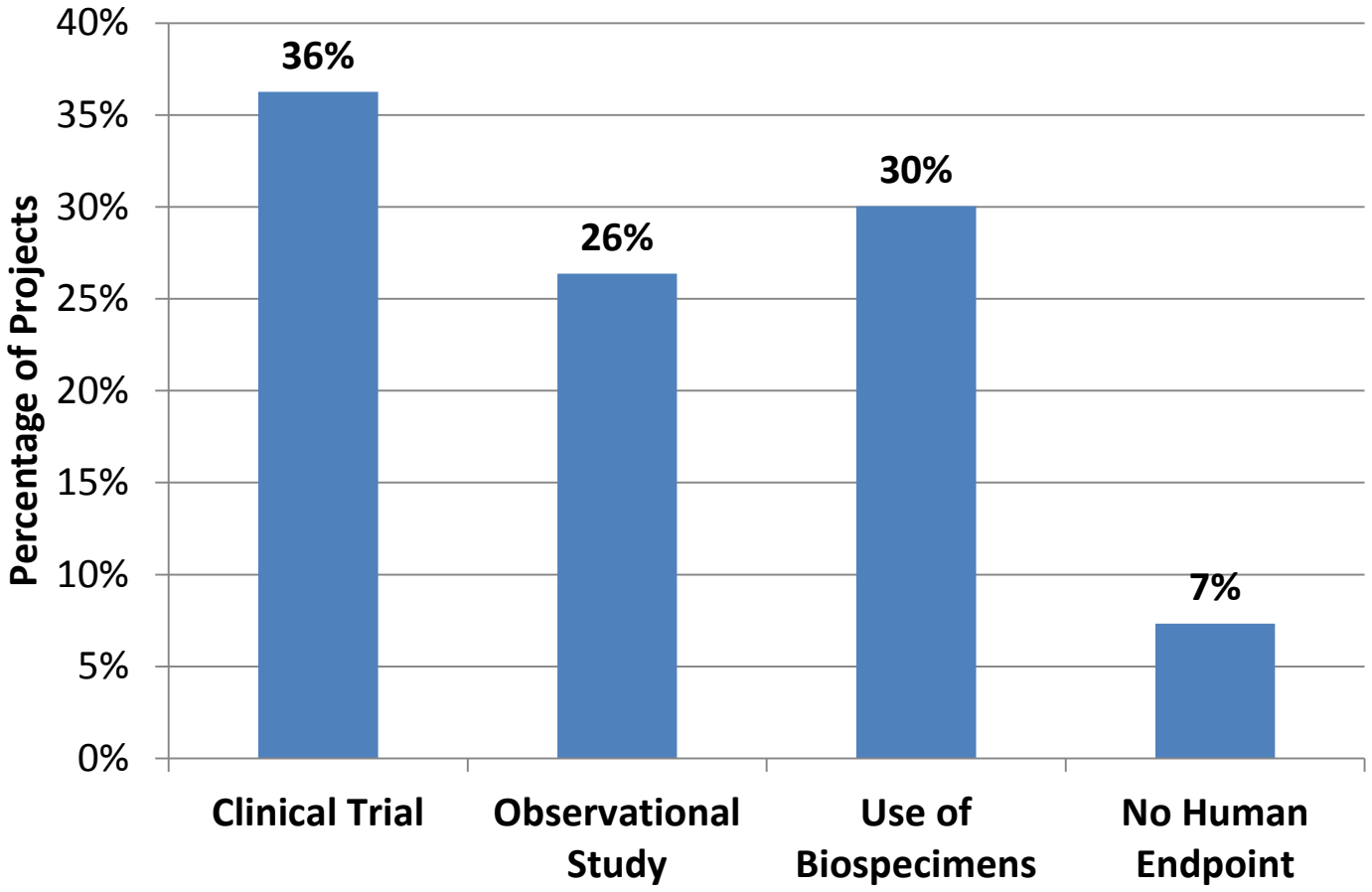
[1] Mechanism of Action

Award-Related Constraints to Translational Progress

- Primary constraint is financial
  - $200-400K annual total cost per project insufficient for most trials
  - Shortfall even greater if clinical material must be prepared
  - Non-SPORE funding required for most clinical trials and product manufacturing
  - Restricts projects to those attractive to industry, foundations, or other funders
  - Often delays progress
- Secondary constraint is time
  - Five years very short for true “bench to bedside” conversion
  - Favors projects already well advanced in development
  - May restrict pursuit of innovative, high risk ideas if can’t use subsequent award cycle to conduct human testing

Success in Reaching a Human Endpoint

93% of projects succeeded in reaching a human endpoint



Distinct Niches for SPORE Research

- Complex or risky development projects
  - Collaborative, multidisciplinary research environment encourages development of innovative ideas and approaches to difficult problems
  - Pilot projects under Developmental Research and Career Development Programs provide “proof of concept” testing for new ideas
- Creating community of translational researchers in a disease
  - Provides basic scientists avenue for moving discoveries into the clinic
  - Allows clinicians to clinically test recent scientific advances
  - Developmental Research and Career Development awards integrate new investigators into the network of research in a disease area
- Collaborative projects with industry
  - SPORE contributions: expertise, research tools, specimen resources, access to patients
  - Industry contributions: funding, drugs, drug/device development expertise

Key SPORE Roles in Building Capacity for Translational Research

- Within host institutions
  - Builds translational research core infrastructure around a specific disease (expertise, equipment, specimen services)
  - Raises profile of translational research, enhancing perceived value in academic setting
  - Facilitates collaborations and outside funding
- Within disease area
  - Creates a national community of researchers through meetings, conference calls, and research collaborations
  - Research collaborations enable clinical trials, tissue sample collection, and epidemiology studies
  - Catalyzes formation of consortia for the conduct of randomized, early phase trials

SPORE-Influenced Major Advances

- A total of 79 major advances identified
  - 24 accepted into clinical practice
  - 36 in late-phase human testing
  - 19 with broad clinical potential

- NCI selected 14 advances for further analysis
  - Discoveries and developmental steps underlying the advance
  - Role of SPORE-associated research in those discoveries and developmental steps

Selected Advances

- **Accepted into Clinical Practice**
  - Enzalutamide (MDV3100) for Late-Stage Prostate Cancer
  - Novel Agents and Regimens for Multiple Myeloma
  - Contemporary Partin Tables/Kattan Nomograms—Tools for Management of Prostate Cancer
  - Diagnostic Test for EML4-ALK Translocation in Non-Small Cell Lung Cancer (NSCLC) Patients
  - Predictive Assay for Lung Cancer Response to EGFR Tyrosine Kinase Inhibitors
  - Chromosomal 1p/19q Deletion as an Oligodendroglioma Prognostic/Predictive Marker
  - BRAF Mutation Detection and Prognostic Value in Papillary Thyroid Cancer
  - Screening and Monitoring in Endometrial Cancer and Hereditary Non-Polyposis Colorectal Cancer (HNPCC)/Lynch Syndrome

Selected Advances *(continued)*

- **Late-Phase Human Testing**
  - Difluoromethylornithine (DFMO) and Sulindac for Prevention of Colorectal Cancer
  - Heat Shock Protein Peptide Complex (HSPPC) 96 Vaccine for Brain Cancer
  - Rindopepimut (CDX-110) Vaccine for EGFR Variant III (EGFRvIII)-Expressing Glioblastoma
  - Transmembrane Protease, Serine 2 (TMPRSS2) Gene Fusions as Prostate Cancer Detection and Risk Markers
- **Broad Clinical Potential**
  - Sensitivity and Resistance to EGFR Tyrosine Kinase Inhibitors in Lung Cancer
  - Risk Factors and Disease Subtypes in Breast Cancer

Enzalutamide (MDV 3100) for Late-Stage Prostate Cancer

- Key findings
  - Castration-resistant prostate cancer xenografts overexpress functional androgen receptor (AR)
  - Increased AR levels confer resistance to anti-androgens by amplifying physiologic response to low levels of androgen
  - Increased AR levels convert prostate cancer from hormone-sensitive to hormone-refractory phenotype providing a functional AR ligand-binding domain is retained
- SPORE role (UCLA/MSKCC)
  - Novel AR antagonists with little agonist activity developed under UCLA SPORE Career Development Award
  - Phase I/II clinical trial of lead candidate MDV-3100 carried out through DoD Prostate Cancer Program Clinical Research Consortium with partial MSKCC SPORE support
  - MSKCC SPORE supported preclinical development and phase I trial of further-refined AR antagonist, ARN-509
- Current status
  - Enzalutamide (MDV-3100) FDA approved for metastatic castration-resistant prostate cancer
  - ARN-509 in phase I/II clinical trial

Chromosomal 1p/19q Deletion as an Oligodendroglioma Prognostic/Predictive Marker

- Key findings
  - Strong association between tumor 1p/19q deletions and chemosensitivity, recurrence-free survival and overall survival in anaplastic oligodendroglioma case series
  - Finding of significant association between 1p/19q deletions and prolonged overall survival extended to low-grade oligodendrogliomas
  - Robust clinical trial evidence from RTOG 9402 for association between 1p/19q deletion and chemosensitivity and survival in anaplastic oligodendroglioma
- SPORE role (Mayo)
  - Identification of an unbalanced, whole-arm translocation [t(1;19)(q10;p10)] as likely mechanism for combined deletion of 1p and 19q
- Current status
  - Predictive value of 1p/19q deletions for likely benefit of chemotherapy in patients with low-grade oligodendrogliomas noted in current NCCN Guidelines

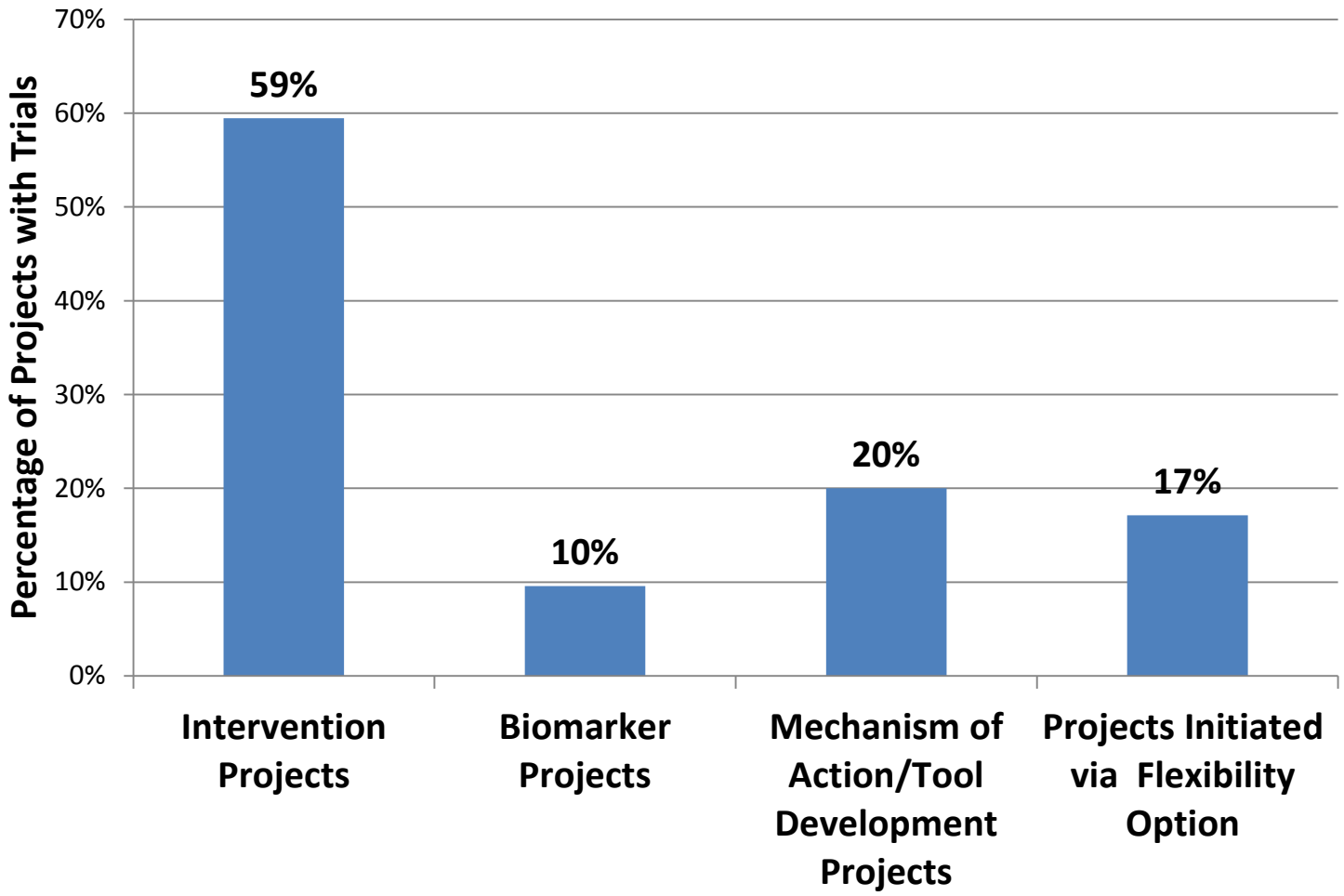
Rindopepimut (CDX-110) Vaccine for EGFRvIII-Expressing Glioblastoma

- Key findings
  - Elucidation of role of EGFR amplification and EGFR genetic variants in human gliomas, identification of EGFRvIII as the most common variant
  - Development of tumor-specific monoclonal antibodies against EGFRvIII
  - Demonstration of efficacy of EGFRvIII peptide vaccination in syngeneic tumor models
- SPORE role (Duke, UCSF and UAB)
  - Duke led phase I and phase II clinical trials
  - Duke, UCSF and UAB participating in registration trials sponsored by Celldex in front-line and recurrent glioblastoma
- Current status
  - Phase II and phase III (registration) trials are underway

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 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

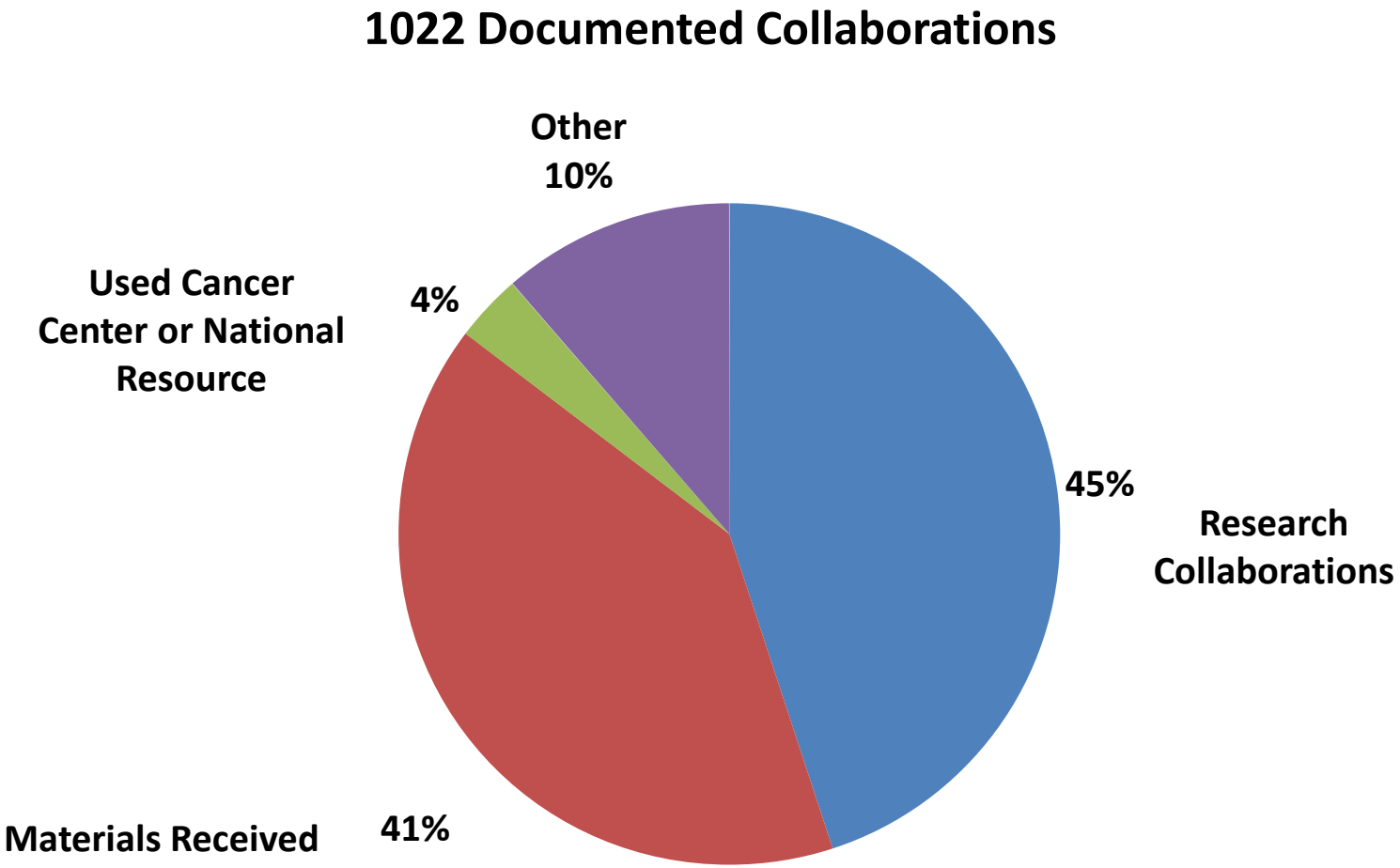
Percentage of Research Projects with One or More Clinical Trials



Phase III Trials Based on SPORE Project Results

- Eflornithine and Sulindac to prevent recurrence of high-risk adenomas and second primary colorectal cancers
  - SWOG and Cancer Prevention Pharmaceuticals, Inc.
  - Arizona GI SPORE
- Brentuximab for Hodgkin's lymphoma and T-cell lymphoma
  - Seattle Genetics
  - City of Hope Lymphoma SPORE
- Sorafenib plus carboplatin and taxol for metastatic melanoma
  - ECOG and SWOG
  - Wistar Skin SPORE

SPORE External Collaborations



Career Development Awardee Success

- 38% received subsequent NIH research funding
- 39% received promotions
- 71% are authors on a SPORE publication
  - 45% have at least one first-authored SPORE publication
- 14% are authors on 6 to 10 SPORE publications
- 15% are authors on >15 SPORE publications
  - 25 Career Development Program awardees with >30 SPORE publications

Developmental Research Project Success

- 1,618 projects funded over lifetime of awards
- 136 projects promoted to SPORE research projects
  - Represents ~20% of all research projects conducted over lifetime of these SPORE awards
- 419 projects (27%) received non-SPORE follow-on funding including 248 NIH awards

Utilization and Value of the Flexibility Option

- 51% of SPORE awards utilized the flexibility option to terminate and initiate projects
  - 13% of all research projects originally proposed by the 55 awards replaced with new projects
- Flexibility option praised by SPORE PIs as an effective management tool
  - Allows continuing focus on the most promising translational opportunities
  - Keeps investigators “on their toes” and focused on making translational progress