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.

- Intervention Only: 51%
- Biomarker Only: 37%
- Both Intervention and Biomarker: 8%
- Mechanism of Action/Tool Development Only: 4%
### Clear Focus on Early Translation

80% of intervention projects propose late-stage development activities

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<thead>
<tr>
<th># of Projects</th>
<th>MOA(^1) Only</th>
<th>Identify Target</th>
<th>Confirm Target</th>
<th>Develop Intervention</th>
<th>Clinically Test Intervention</th>
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\(^1\) Mechanism of Action
### Clear Focus on Early Translation

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

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<th># of Projects</th>
<th>MOA(^1) Only</th>
<th>Identify Biomarker</th>
<th>Confirm Biomarker</th>
<th>Develop Biomarker Test</th>
<th>Human Testing</th>
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\(^1\) 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

<table>
<thead>
<tr>
<th>Percentage of Projects</th>
<th>Clinical Trial</th>
<th>Observational Study</th>
<th>Use of Biospecimens</th>
<th>No Human Endpoint</th>
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<td>36%</td>
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<td>26%</td>
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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

- Intervention Projects: 59%
- Biomarker Projects: 10%
- Mechanism of Action/Tool Development Projects: 20%
- Projects Initiated via Flexibility Option: 17%
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

1022 Documented Collaborations

- Research Collaborations: 45%
- Materials Received: 41%
- Used Cancer Center or National Resource: 4%
- Other: 10%

Total: 100%
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