PAR Concept: Clinical Characterization of Cancer Therapy-Induced Adverse Sequelae and Mechanism-Based Interventional Strategies

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Background

- Cancer treatment can result in acute, chronic, and/or progressive toxicities
  - Adverse effects often persist after completion of therapy or develop as late effects
- Cancer survivorship and adverse effects will significantly increase in the next couple of decades
- Little is known about the rates of adverse events related to new therapies
- Development of biomarkers and/or mitigation or prevention strategies are limited by:
  - Lack of mechanistic understanding of adverse events
  - Lack of accurate reporting and archiving of adverse event data
  - Difficulties in objectively measuring treatment-related toxic effects
  - Insufficient characterization of the clinical phenotypes
  - Insufficient studies validating pre-clinical biomarkers in the clinical setting

Purpose of the PAR (R01, Clinical Trials Optional)

- Support preclinical and clinical research projects which seek to:
  1. Clinically characterize adverse sequelae
  2. Translate the mechanistic understanding into therapeutic approaches to prevent or minimize the development of long-term sequelae
  3. Identify mechanisms of new therapy-induced adverse sequelae

- Applications should prospectively identify the specific adverse effects and/or cluster of effects under evaluation

- Collaborations between clinical and non-clinical investigators are encouraged to couple the mechanistic knowledge with the clinical phenotype

- Emphasis should be on translating mechanistic knowledge into approaches or interventions to prevent or mitigate adverse sequelae

Provocative Questions

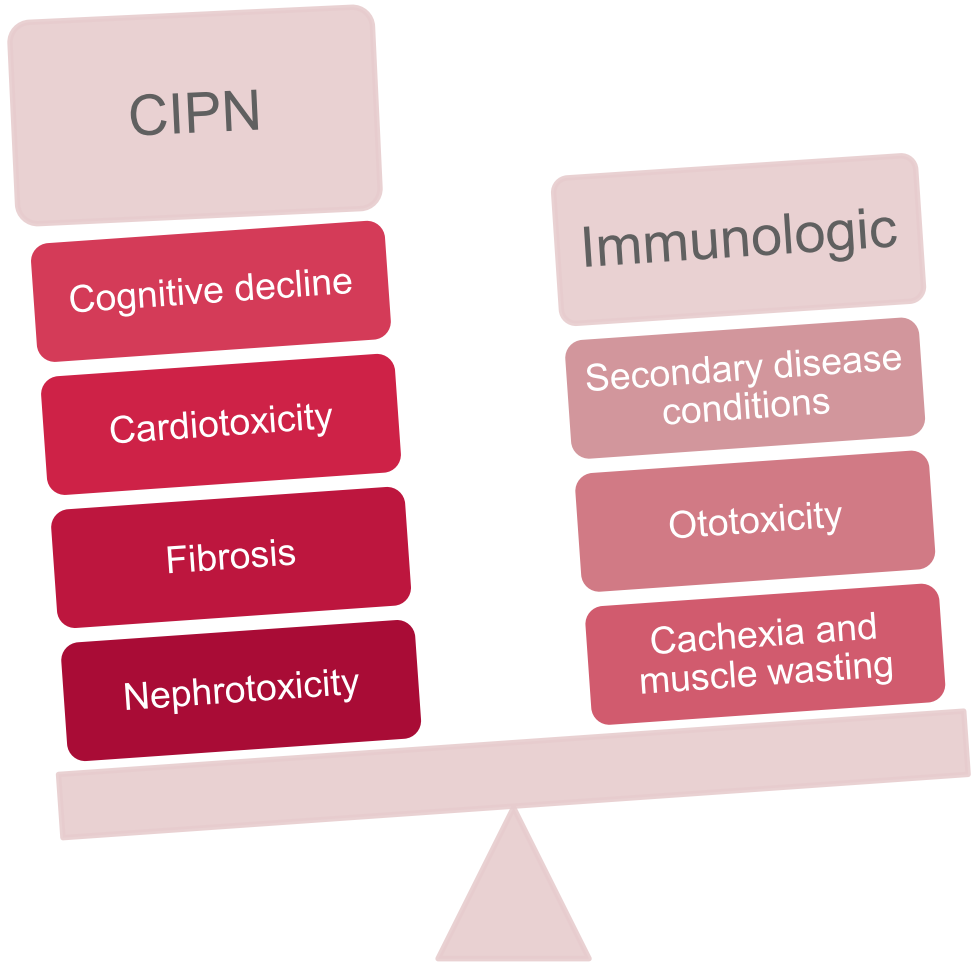
- 2015 RFA: PQ 9 had highest number of applications submitted to the NCI
- 2017 RFA: PQ 9 was re-issued as PQ12 due to popularity and success
- Applications were mechanistic studies primarily in preclinical models
- Specific peer review panels are required for related PQ

2015 Provocative Questions RFA- PQ9

What are the molecular and/or cellular mechanisms that underlie the development of cancer therapy-induced severe adverse sequalae?

	Round1		Round2		Round3		Round4		Overall		
	Apps	Funded	Apps	Funded	Apps	Funded	Apps	Funded	Apps	Funded	SuccessRate
PQ1	15	4	25	6	26	5	29	2	95	17	17.9%
PQ2	14	0	11	2	15	3	17	2	57	7	12.3%
PQ3	16	3	24	4	25	4	35	4	100	15	15.0%
PQ4	4	0	6	2	8	0	7	0	25	2	8.0%
PQ5	16	4	15	3	28	5	24	2	83	14	16.9%
PQ6	5	1	10	1	18	3	11	1	44	6	13.6%
PQ7	5	2	8	0	3	1	11	2	27	5	18.5%
PQ8	10	1	7	1	13	1	13	0	43	3	7.0%
PQ9	23	4	24	7	42	4	37	5	126	20	15.9%
PQ10	4	1	8	1	12	3	10	1	34	6	17.6%
PQ11	12	1	12	1	15	0	26	1	65	3	4.6%
PQ12	2	0	7	0	5	1	3	0	17	1	5.9%

Provocative Questions



Provocative Questions RFA

- Daohong Zhou- 1R01CA219836-01
- Hypothesis: Senescent cells primarily initiate and drive the progression of radiation induced pulmonary fibrosis (RIPF)
  - Clearance of senescent cells prevents and reverse RIPF
  - Development of a safe senolytic drug for treatment of RIPF

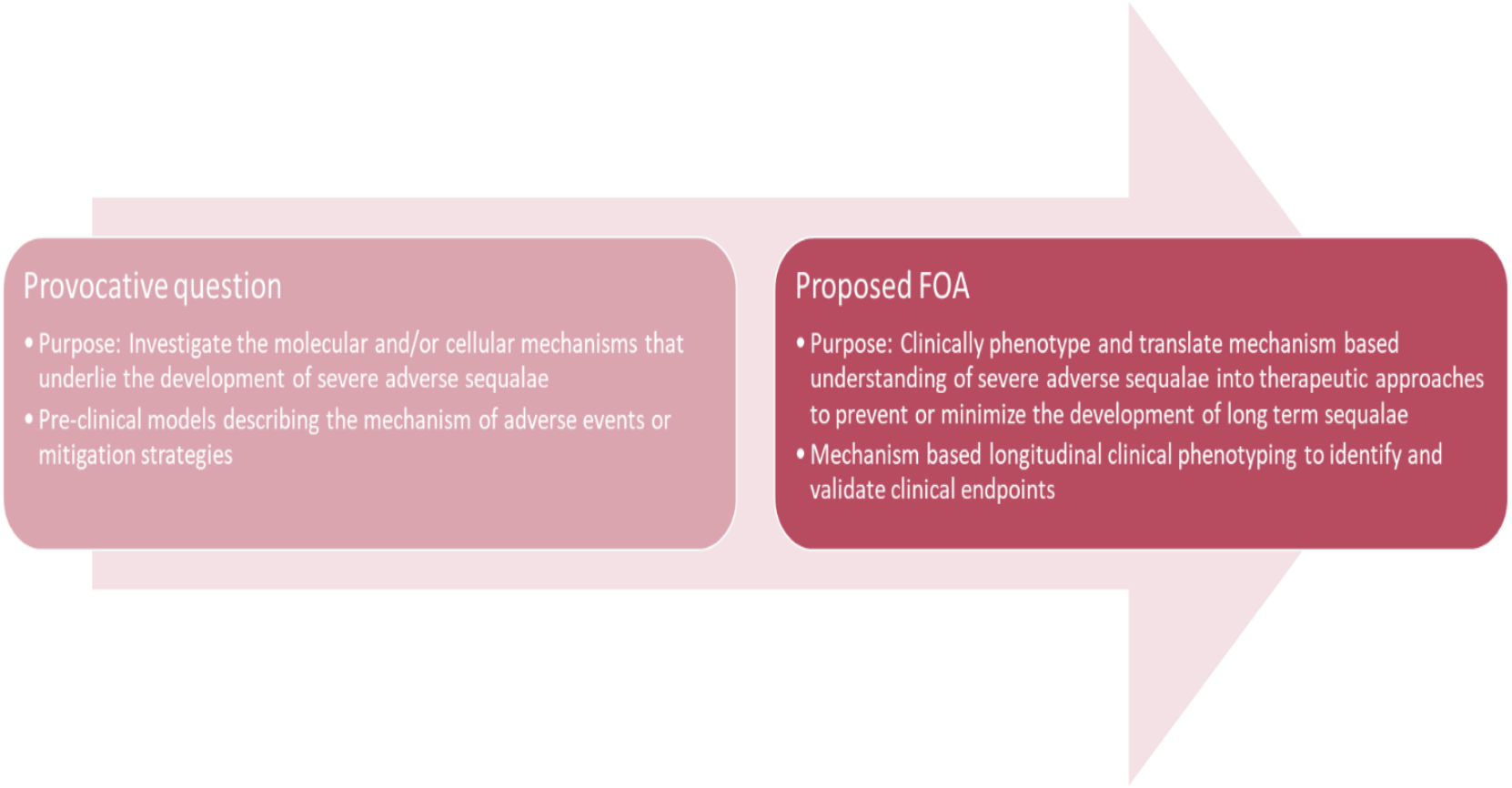
- Next step:
  - Pre-clinical studies of the newly developed senolytic drug

Provocative Questions RFA

- Maryam Lustberg and Shuiying Hu- R01CA238946-01
- Hypothesis: Targeted inhibition of OATP1B1 function with nilotinib will specifically affect accumulation of paclitaxel in peripheral nerves and affect its downstream toxic effects.
  - Adaptive dose selection to define the lowest intermittent dose of nilotinib producing statistically significant inhibition of OATP1B1
  - Placebo controlled, double blind, randomized Phase 2 clinical trial involving patients with early stage breast cancer eligible to receive weekly paclitaxel

- Next step:
  - Clinical characterization of CIPN phenotype
  - Phase 3 trial

Translating the Provocative Questions



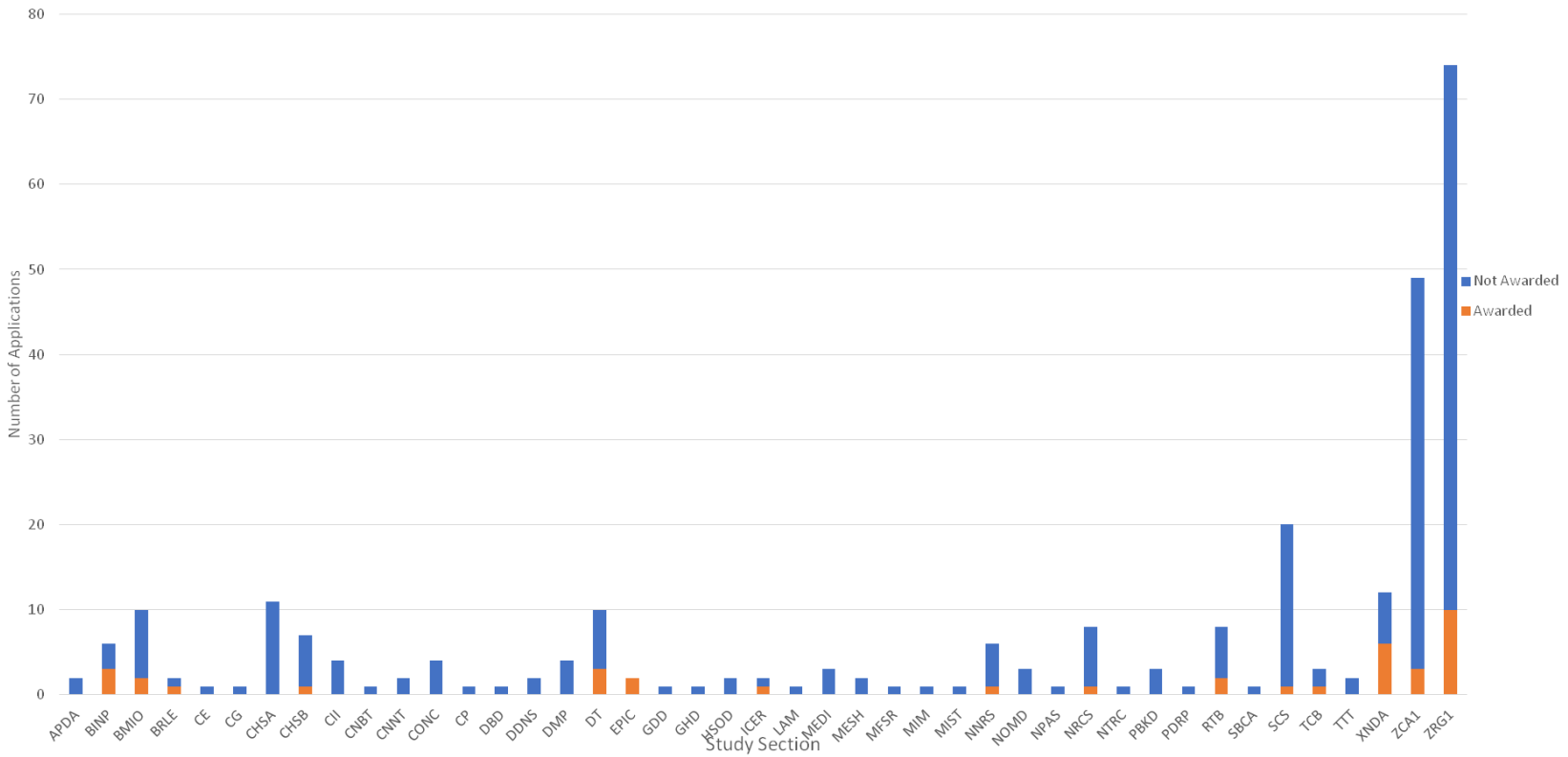
Relevance to NCI

- DCTD
  - Develop and validate new clinical endpoints and biomarkers that can be used in clinical trials
  - New drug development for the prevention or mitigation of long term adverse sequelae
- DCP
  - Develop novel agents for evaluation in toxicity mitigation trials
  - Validate endpoints for use in toxicity mitigation clinical trials
  - Clinical phenotyping of adverse effects, particularly clusters of effects
- DCCPS
  - Clinical phenotyping for improved toxicity capture in population studies
  - Translation of new endpoints and biomarkers to improve quality of life in cancer survivors
- DCB
  - Develop model systems to study the regulation of immune responses affected by cancer therapies leading to adverse sequelae

Rationale for PAR Issuance

- Stimulate clinical and translational research related to adverse-effects with strong mechanistic underpinnings that:
  - Go beyond single adverse-effects to look at clusters of effects
  - Address newly identified adverse-effects related to treatment
  - Characterize clinical phenotypes of adverse-effects
  - Evaluate and/or validate new biomarkers
  - Evaluate the trajectory of chronic or progressive adverse-effects and their relationship with cancer treatments and other comorbid conditions
  - Develop intervention strategies
- Applications that evaluate clinical characteristics and mechanisms of adverse sequelae tend to be poorly reviewed in NIH standing study sections (which lack expertise in treatment relative adverse effects)

NCI Portfolio Analysis- 2015 to 2018



Justification for PAR Issuance

- Translate mechanistic findings from the Provocative Questions
  - Enabled the research community to study basic mechanisms in the PQ
  - Created an environment in which these grants could be properly evaluated
  - Research community poised to translate the mechanistic findings

Justification for PAR Issuance

- Leveraging NCI investment to:

    1. Clinically characterize adverse sequelae
    2. Translate the mechanistic understanding into therapeutic approaches to prevent or minimize the development of long-term sequelae
    3. Identify mechanisms of new therapy-induced adverse sequelae

- Specific review panels are critical
    - Disease specific experts
    - Clinicians (Medical Oncology, Radiation Oncology)
    - Epidemiologists
    - Basic scientists
    - Pharmacologists
    - Biostatisticians
    - Toxicologists

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