FNLAC Ad Hoc Working Group Report: NCI RAS Initiative Evaluation Team (RIET)

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History of RAS Initiative

- RAS Initiative was launched in 2013 to explore in detail the biology of oncogenic RAS and to discover therapeutic approaches for this previously “undruggable” target, with the ultimate goal of developing new drugs.
- The RAS Initiative began by addressing critical knowledge gaps that had impeded the exploitation of RAS as a drug target, and significant investments in structural biology, biochemistry and biophysics, chemical screening.
- A 5-year renewal for FY18-22 built on this success with two broad scientific goals being pursued: a. to develop small molecules that bind directly to KRAS and block its function, and advance these towards clinical evaluation, and b. to determine how KRAS proteins interact with plasma membranes and how they activate RAF kinases.

Basis of Committee Review

- Writeup provided by the RAS Initiative
- Site visit by committee January 24-25

Important Accomplishments of the RAS Initiative for this Cycle

- **RAS G12C inhibitor that binds both GTP and GDP bound forms** expected to enter clinical trials in the coming year. These inhibitors could have unique effects relative to agents currently in clinical trials
- **RAS/PI3Ka protein-protein interaction inhibitor** expected to enter clinical trials in the coming year. Novel approach overcomes hyperglycemia observed with current PI3Ka inhibitors.
- The **outstanding protein production capabilities, biochemical studies, and structural biology** are obvious strengths of the group. This has resulted in critical structural insights into RAS function and the ability to develop assays for inhibitor discovery and development.

Important Accomplishments of the RAS Initiative for this Cycle

- The review committee was **extraordinarily impressed with the Frederick National Lab personnel working on the RAS Initiative**. They clearly demonstrated technical excellence, commitment to the project, deep knowledge of the field, and the ability to execute in this highly multi-disciplinary effort. They are to be commended for their outstanding work.

RAS Initiative Research Projects

- RAS Initiative reagents and analytics
- Targeting the RAS:PI3Kα interaction with molecular breakers
- Development of dual KRAS ON/OFF inhibitors
- Construction and screening of a novel disulfide tethering library
- RAS activation of RAF kinase
- RAS in membranes
- Structure and function of the SHOC2-MRAS-PP1C (SMP) complex
- Neurofibromin (NF1) biochemistry and structural biology
- KRAS Alleles

RAS Initiative Interactions with Community

- Collaborations
- Contractor Cooperative Research and Development Agreements (cCRADAs)
- RAS reagent distribution.
- RAS interactome
- RAS Synthetic Lethal Network (RSLN)
- Ras Initiative Symposia
- Training

RAS Initiative Future Plans

- Development of pan-KRAS inhibitors
- Targeting other small GTPases (NRAS, RAC1)
- Biochemistry and structural biology of signaling complexes
- RAS activation of RAF (ADMIRRAL)
- Second-generation disulfide tethering
- Top-down proteomic analysis of RAS proteoforms from malignant cell line

Future of the RAS Initiative

Committee recommends consideration of the following points as NCI makes plans for the future of the RAS Initiative:

1. It is critical to view this program in terms of the generous support by the NCI (Direct costs of 10.5M/year supporting 73 FTE), how long they have been going at this (over a decade), the productivity of the group with regards to novel discoveries, papers, and compounds moving to the clinic, and likelihood that this work could not be completed by start-ups, big pharma, and academia.
2. While critically contributing to generating interest and commitment to the field, the Initiative has not led the field in drugging RAS, which started with seminal discoveries conducted in laboratories in academia and industry, leading to the FDA approvals of two novel inhibitors, which are now used to treat lung cancer, with eight new inhibitors in clinical trials.

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Committee recommends consideration of the following points as NCI makes plans for the future of the RAS Initiative:

3. The RAS initiative is not the only entity pursing the development of additional KRAS inhibitors; there are others in preclinical development and clinical trials, including inhibitors targeting the more common KRAS mutants G12V and G12D.
4. There seem to be diffuse objectives for the teams, and a better delineation of critical goals would be needed for future success. Need to focus on unique capabilities of FNL that do not overlap with extramural and/or pharma efforts and to have well-defined go/no go decision points.
5. There is a need for increased transparency with the community at large as to how projects are transitioned to specific commercial entities.

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Committee recommends consideration of the following points as NCI makes plans for the future of the RAS Initiative:

6. It is important to delineate a process to ensure wide distribution of Compounds and know-how to the external community, including the recently developed cysteine tethering library, which could be of tremendous utility for the community at large.

7. Publication output has been moderate, 75 papers attributed to the RAS Initiative, ~32 first or last authored by the 10 RAS Initiative research leaders (3 papers/team leader/5 years). There have been few high-impact discoveries published, just 4 primary research papers in very high impact journals (IF ~20 or better: Science, Mol Cell, Cancer Discovery, and Nat Struct Mol Biol) that are suggestive of discoveries of wide appeal.

Future of the RAS Initiative

Based on the points delineated above, there were two views of the future of the RAS Initiative articulated by members of the committee:

a. **For some members of the committee, the assessment is that the program should continue** as the results have been outstanding and there is a high likelihood that important contributions will continue to be made. However, even for this group of committee members, there is a clear view that the RAS Initiative needs to evolve and operate differently going forward.

b. **For other members of the committee**, there is a sense that with substantial pharma investment now in RAS as a target, the goals of the RAS Initiative have been largely met and **it is time for a phased sunsetting of the program** to make the extraordinary capabilities of the FNL available for other efforts.

Future of the RAS Initiative

For those on the committee favoring a continuation of the RAS Initiative, the following recommendations were made:

1. There is a need for the RAS Initiative Team to **focus on things that only this group can effectively tackle**, not efforts that are, or will, be carried out by the extramural community and/or pharma.
    a. assess whether projects meet that uniqueness criteria and clear go/no go decision points
    b. constitute an advisory board in a manner such that they make objective assessments about projects based on uniqueness and progress
2. There is a need to **make reagents developed in this Initiative broadly available** to the research community (compounds, disulfide tethering library).
3. There is a need for **greater transparency with the community at large** on the process for engaging with pharma via the cCRADA mechanism.
4. There is a need to **engage the extramural community to take advantage** of the outstanding biochemistry and structural biology findings to guide relevant functional studies of RAS.