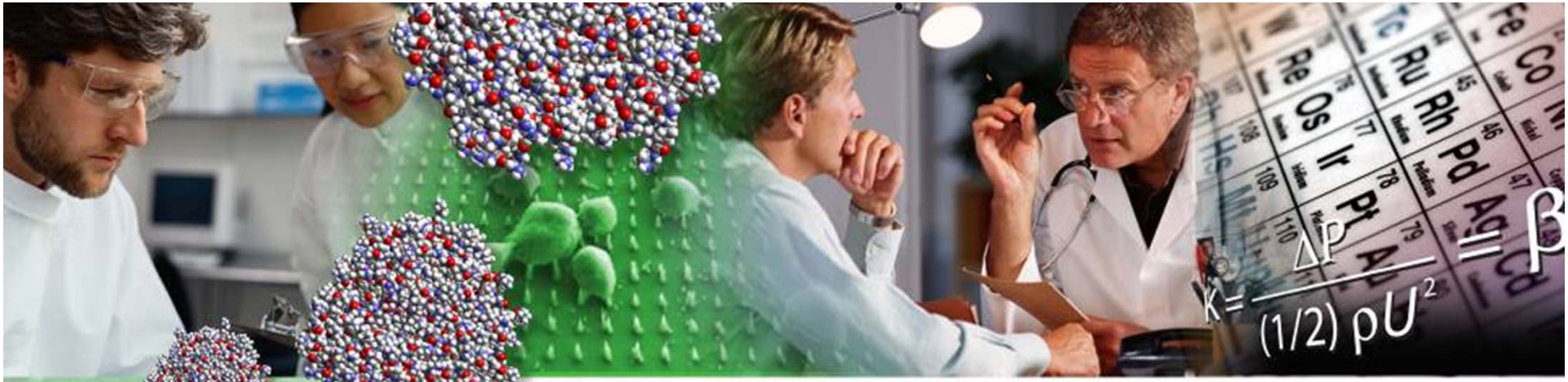


NCI Alliance for Nanotechnology in Cancer RFA Re-issuance

Program Summary and Responses to Subcommittee Questions

Piotr Grodzinski, Ph.D.
Board of Scientific Advisors Meeting
November 6, 2008

Alliance for Nanotechnology in Cancer (ANC) Current Program and Re-issuance

NCI Alliance for Nanotechnology in Cancer

Current ANC Model

- **Oncology applications of nanotechnology require multi-disciplinary approaches involving both technology developers and users to facilitate the process of innovation and development**
- **ANC is a milestone driven program which leverages innovation in nanodevices and nanomaterials for cancer applications. The ANC awards were made in 2005.**
  - **8 Centers of Cancer Nanotechnology Excellence (CCNEs)**
  - **12 Cancer Nanotechnology Platform Partnerships (CNPPs)**
  - **11 F32 and F33 Fellowship Awards**
  - **4 IGERT Training Awards (jointly with NSF)**
  - **Nanotechnology Characterization Laboratory (NCL)**

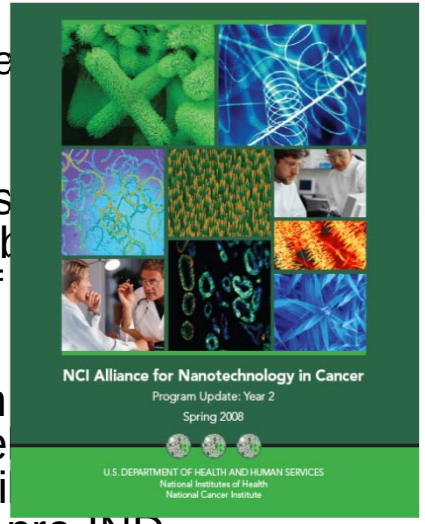
Reissuance

- **The reissuance will fund the established successful and integrated model of the centers (CCNEs), platforms (CNPPs), and training programs**
- **Centers will consist of 3-5 interactive/synergistic clinically relevant research projects in at least two different tumor types**
- **The program will increase its focus on complete technology solutions through collaborations within and among centers and platforms, and among centers and complementary groups within the community.**

Summary of Key Accomplishments

NCI Alliance for Nanotechnology in Cancer

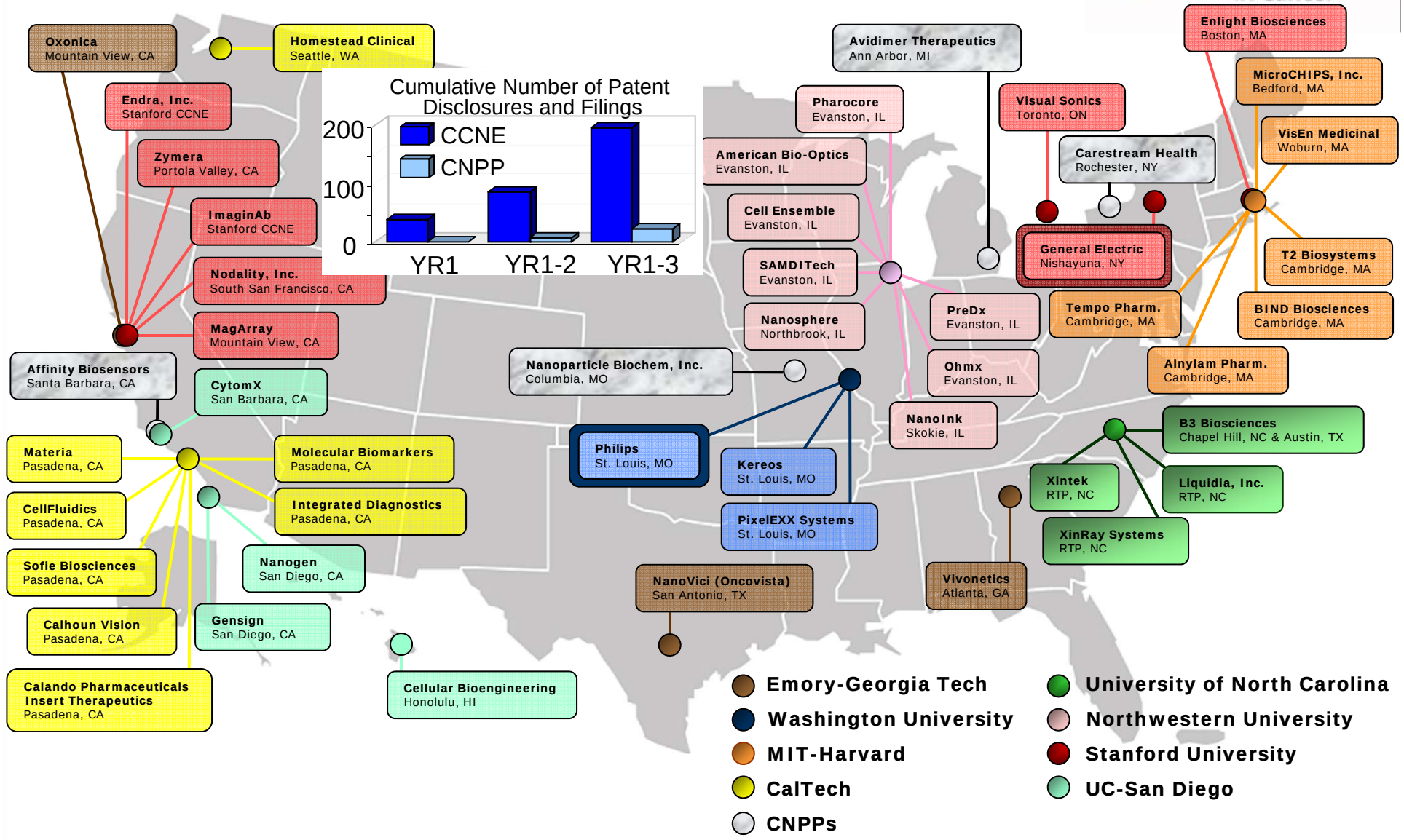
- **Building the nano-oncology community** – established well operating multi-disciplinary teams around scientific focus areas of the program
  - Met or exceeded program goals of the Cancer Nanotechnology Plan
  - Established Nanotech Characterization Lab (NCL) for nano-materials characterization
  - Established ties to the divisions to address current and future scientific opportunities and needs for the cancer nanotechnology field
  - Held 3 Strategic Nanotechnology Workshops to outline needs of the fie



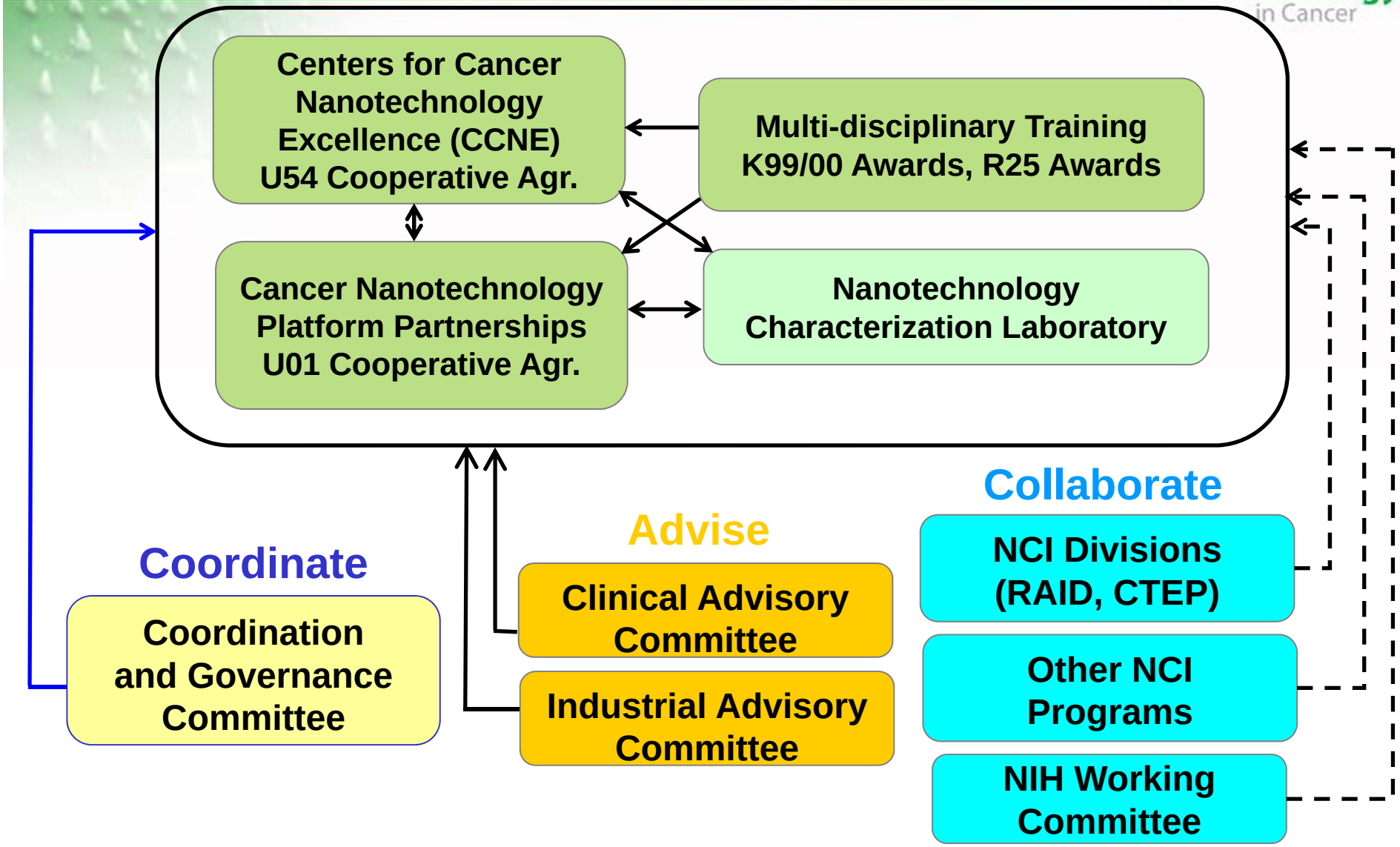
- **Scientific output** – over 600 peer-reviewed journal papers publis impact factor ~7. Even if 1st year of the program is discounted, pub is over 470. Increasing collaborations support growing number of publications
- **Clinical translation** – 50 companies associated with the program diagnostics and therapy; 24 were formed in the last 3 years. Deve intellectual property portfolio – over 200 disclosures and patents fi last two years). Several companies entered clinical tri discussions with FDA
- **Leveraged funding** – investigators received numerou reviewed government sources, philanthropy, industry,

Completing the Technology Development Pipeline - Partnerships with Industry

NCI Alliance for Nanotechnology in Cancer



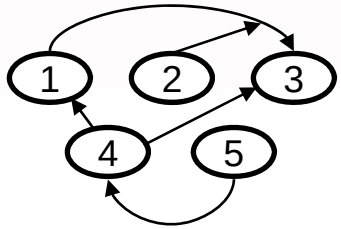
NCI Alliance for Nanotechnology in Cancer – Re-issuance - Organizational Structure



Program Re-issuance Model

NCI Alliance for Nanotechnology in Cancer

- Focus on complete technology solutions leveraging collaborative efforts within the centers, among different centers, and among centers and platforms
- Each center will consist of 3-5 interactive and synergistic research projects relying on nanotechnology-based devices and materials and having a clinical utility in at least two different tumor types.



- Develop interactive projects which can be integrated to improve overall development - results of one project provides input into other projects and draws on a broader range of expertise across the centers and the Alliance
- Further strengthen interactions among the PIs - development of integrated teams with different scientific expertise and responsibilities
- Promote a mix of projects with different levels of maturity and risk

- Require multiple PIs representing oncology/cancer biology, nanotechnology., engineering, etc.
- Require CCNE association with NCI-designated Cancer Centers and for-profit organizations for technology commercialization
- Facilitate closer interaction of centers and platforms
- Revamp training program and establish training centers
- Establish joint Alliance Challenge projects: 5 - 10% of budget set-aside.

BSA Subcommittee Questions

NCI Alliance for Nanotechnology in Cancer

1. **What is the relationship and appropriate balance between platforms and centers?**
2. **Is emphasis going to be on more technology development or pre-clinical studies?**
3. **How and when will the translational part be done?**
4. **How will this project interact/integrate with the Translational Research Working Group recommendations?**
5. **Since the platform projects were initially supported as R01s, why the conversion to cooperative agreements?**
6. **What are Grand Challenge projects? Who is going to conceive and communicate the Grand Challenge? Why 10 percent?**
7. **What does it mean that the centers are expected to focus on complete solutions? How is complete solution defined?**
8. **Various strategies are proposed to get clinicians interested. Why not assemble a group of clinicians to help provide insight, i.e., a clinical advisory committee? If not an advisory committee, would consideration be given to convening a clinical advisory group on a project by project basis to get input?**
9. **Address proposed expansion of training component and indicate why it is important to do this.**

Balance Between CCNEs and CNPPs – Q 1 and 5

NCI Alliance for Nanotechnology in Cancer

- ANC program is designed as an integrated network of Centers for Cancer Nanotechnology Excellence (CCNEs, U54) and Cancer Nanotechnology Platform Partnership (CNPPs, R01) and supportive trans-disciplinary training mechanisms
- CCNEs represent a network of multi-disciplinary hubs consisting of suite of projects and shared resources (e.g., mouse models, nanofabrication, toxicology). The CCNEs undertake a number of projects ranging from early pilots to advanced development – all of which have the potential to mature toward clinical utility in cancer
- CNPPs are focused on the maturation and translation of cutting-edge science and nanotechnology platforms. CNPPs are topically focused projects which require substantial collaborative development – bridge to the CCNEs. For example: 1) Katti (CNPP), Gambhir (CCNE); 2) Manalis (CNPP), Mallick (CCNE)
- CNPPs represent a “pipeline” of innovative nanotechnologies leveraging collaborations with the CCNEs. For example, the availability of shared resources is key to advancing the technologies deriving from the CNPPs. In turn, the CCNEs have early access to promising advanced technologies that can benefit their overall mission and focus
- Active management via cooperative agreement (i.e., U-mechanism) provides for very effective oversight and operational effectiveness of projects in the Alliance (CCNEs are U54s). The investigators, who were interviewed during the course of the external program evaluation, praised involvement of NCI program staff and close communication with the institute during the course of the program. Thus, we propose converting CNPPs from R01 to U01 mechanism

Examples of Collaborative Efforts – CCNEs and CNPPs

Project PI	PI Affiliation	Collaborating PI(s)	Collaborating PI(s) Affiliation	Collaboration Summary
Paras Prasad	SUNY/Buffalo CNPP	Allan Oseroff	Roswell Park CNPP	Application of organically modified silica (ORMOSIL) nanoparticles in cancer photodynamic therapy.
James Heath	Caltech /UCLA CCNE	Scott Manalis	MIT CNPP	Integration of DEAL technology with SMR nanosensor platform to increase capture efficiency of relevant cancer
Gregory Lanza	Washington U. CCNE	James Baker	U. of Mich CNPP	Facilitate targeted imaging studies examining neovasculature in tumor mouse models.
Michael Sailor	UCSD CCNE	Jan Schnitzer James Baker	SKCC CNPP U. of Mich CNPP	Develop RGP dendrimer constructs for a combined nano-based technology for targeted therapeutics and diagnostics.
Al Charest	MIT/Harvard CCNE	Miqin Zhang	U. of Wash CCNP	Transfer of unique brain tumor mouse model system for MR imaging studies of targeted nanoparticle system.
Sangeeta Bhatia	MIT/Harvard CCNE	Scott Manalis	MIT CNPP	Integrate protease-triggered nanoparticles system with SMR nanosensor platform to detect protease activity in various
Scott Manalis	MIT CNPP	Kattesh Katti	U. of Missouri CNPP	Test gum-arabic coated gold nanoparticles as functional probes for SMR nanosensor platform.
Miqin Zhang	U. of Wash CNPP	Chun Li	M.D. Anderson CNPP	Evaluate pharmacokinetic and bio-distribution of multifunctional nanoparticles in mouse models.
Douglas Hanahan	UCSF CNPP	Ralph Weissleder	MIT/Harvard CCNE	Synthesis of phage-peptide targeted nanoparticles for SPECT imaging of cancer.
Douglas Hanahan	UCSF CNPP	Leland Chung	Emory/GT CCNE	Targeted imaging of novel pancreatic cancer mouse models for detection of metastatic lesions.
Leland Chung	Emory/GT CCNE	Miqin Zhang	U. of Wash CNPP	Use of CTX nanoparticles for MR imaging detection of prostate metastasis cancer.
Leland Chung	Emory/GT CCNE	Kattesh Katti	U. of Missouri CNPP	BBN targeted nanoparticles for imaging of metastatic prostate cancer.
Shawn Chen	Stanford CCNE	Miqin Zhang	U. of Wash CNPP	Evaluate biodistribution VEGF targeted PET nano-imaging agent
Sam Gambhir	Stanford CCNE	Kattesh Katti	U. of Missouri CNPP	Development of biocompatible gold nanoparticles for use as Raman molecular imaging agents
Brian Kay	UNC CCNE	Scott Manalis	MIT CNPP	Develop SMR nanosensor platform-based detection assay using based on Ankyrin repeat proteins for Her2.
Parag Mallick	Stanford CCNE	Scott Manalis	MIT CNPP	Single cell growth monitor for classifying therapeutic response using SMR nanosensor platform.
Tayyaba Hasan	Mass Gen CNPP	Mansoor Amiji	Northeastern CNPP	Nanomaterial design for PDT in cancer and subsequent evaluation and optimization of PD and PK properties.

Balance of Technology Dev and Translation Q 2 and 3

NCI Alliance for Nanotechnology in Cancer

- Alliance will continue to embrace technology development and will further increase the numbers of project that represent strong candidates for clinical translation
- Translation of the technology will be pursued through the academic medical center/cancer center that is working as part of a specific project(s) and/or spin-off companies established through licensing of the technologies developed in the program
- Technology scale-up and early clinical trials pursued based on the technology developed in the program will become part of the NCI's overall drug and diagnostics development strategy. NCI will provide input to and support of these activities through its various programs: NCL, RAID, CTEP and grant programs for clinical development and early phase trials (e.g., phase 0 and phase I)

Alignment with TRWG Recommendations – Q 4

NCI Alliance for Nanotechnology in Cancer

- Alliance adopted several of TRWG core ideas, even before group's final report and recommendations were issued in June 2007:
  - Alliance is U54 milestone driven program (**C1**)
  - The Alliance network consists of CCNE resources that are shared across the network (**C2**)
  - The NCL and Alliance working groups are establishing standardization and uniform baseline measurements for various nanotechnologies (**B5, C3**)
  - The Multidisciplinary Training and Team Development Program is actively developing a 'translational research workforce' for the cancer community (**C6**)
  - Active grant management scheme allows for guidance and modification of milestones to focus the investigator's research and advance new opportunities (**B1**)
  - NCI program staff has worked closely with the SBIR Development Center to assist Alliance investigators in seeking commercial avenues to enable translational opportunities (**B4**)
  - Within the program re-issuance, 5 - 10% set-aside for the Alliance Challenge projects will allow for several other TRWG recommendations to be addressed (**B2, B3**).

Alliance Challenge Projects – Q 6

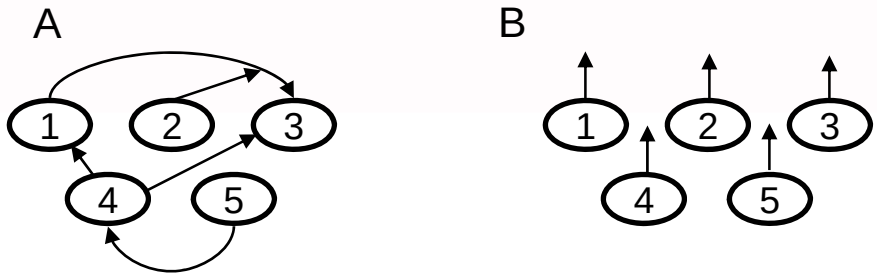
NCI Alliance for Nanotechnology in Cancer

- Current issuance of the ANC program recognizes and supports the advantage of science and technology development through multi-disciplinary team work. However, a "lesson learned" is that the current program does not provide dedicated resources to undertake more comprehensive trans-ANC targeted projects in over-arching areas such as critical diagnostics or drug delivery.
- Alliance Challenge Projects will provide resources and a mechanism to enable groups of Alliance investigators representing several CCNEs – or combinations of CCNEs and CNPPs – to leverage their specific capabilities through integrated teams and projects to address specific challenges
- Suggestions for Alliance Challenge Projects can come from several sources: investigators, NCI program staff and advisory committees. The final selection will be made by the Coordinating and Governance Committee in consultation with the Clinical Advisory Committee. Projects will be chosen based on their scientific merit; technical feasibility; and ultimate translational impact
- 5 - 10% set-aside request to support these innovative efforts will enable the ANC to undertake a sufficient number of projects to develop a portfolio of high and moderate risk projects - and engage broad participation
- The Alliance Challenge projects will be funded for 12-24 months and will require involvement of collaborative teams that engage at least two (preferably more) funded institutions from CCNEs and CNPPs.

CCNE – Project Portfolio
"Complete Solution" Concept – Q 7

NCI Alliance for Nanotechnology in Cancer

- Current issuance of the program demonstrated unequivocally the value of technology development in the environment of multi-disciplinary teams, which could leverage collaborative efforts within the centers, among centers and platforms, and among centers and other groups within the community
- CCNE projects can be (**A**) interactive and rely upon each other for overall development (projects are elements which come together as pieces of a larger initiative); or (**B**) independent and working on innovative ideas representing different areas of cancer research and not necessarily related



- Multi-disciplinary teams united through integrated projects are proving to be more effective in moving technology forward. This model allows for 1) the results of one project to enable other projects and to draw on a broader range of expertise across the center and Alliance, 2) strengthening of interactions among the PIs and leading to the development of integrated teams with different scientific responsibilities, 3) promoting a mix of projects with different levels of maturity and risk
- The integrated, "complete solution" concept is deemed to 1) be highly effective in technology development and translation, 2) emphasize the importance of cross-center validation of the technology platforms developed and implemented by the different centers, 3) provide for centers to become more specialized and effective.

Training Rationale – Q 9

NCI Alliance for Nanotechnology in Cancer

- Cross-disciplinary training is paramount to further development of cancer nanotechnology. Current program RFA for F32 awards (postdoctoral trainees) and F33 awards (senior fellows) prompted an increase in the total number of meritorious nanotechnology-directed F32 and F33 applications within NCI. The large pool of students participating in the current Alliance program, including a significant fraction of foreign nationals (who could not be supported by F32/F33 mechanism), calls for more training initiatives and alternate training mechanisms
- Instead of individual awards, we propose:
  - R25 mechanism which funds training centers where an experience mentor could oversee a group of young trainees (both students and post-docs) working on different projects in a multidisciplinary environment
  - K99/00 program which provides young cancer nanotechnology investigator with sufficient resources to firmly establish his/her research career. After being mentored at the early stage of the award, he/she enters an independent research stage. In addition, K99/00 mechanism allows for applications from foreign nationals (large and critical post-doctoral pool in nanotechnology research).

Summary

NCI Alliance for Nanotechnology in Cancer

- **Current program has been highly successful in:**
  - Establishing multi-disciplinary community in cancer nanotechnology
  - Establishing an infrastructure for continuous development of this field
  - Proving effectiveness of the team science model demonstrating high productivity - outstanding scientific output (publications and patents)
  - Creating viable commercial outlet through industrial partnerships and formation of the companies
- **Continuity of the program will assure:**
  - Further development of cancer nanotechnology center/platform infrastructure
  - Increased engagement of engineers and physical scientists in future innovation and close collaborations between oncology and nanotechnology communities
  - Training of the cadre of multi-disciplinary experts who will benefit the field in the future
  - Engagement of NCI divisions into nanotechnology-based development of preventive, diagnostic, and therapeutic solutions
  - Strengthening of cooperative agreement program management models.