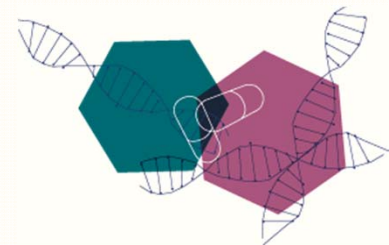
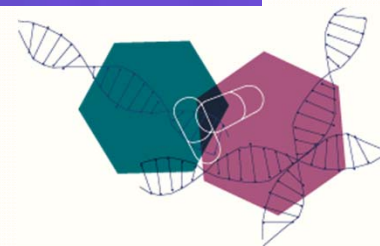
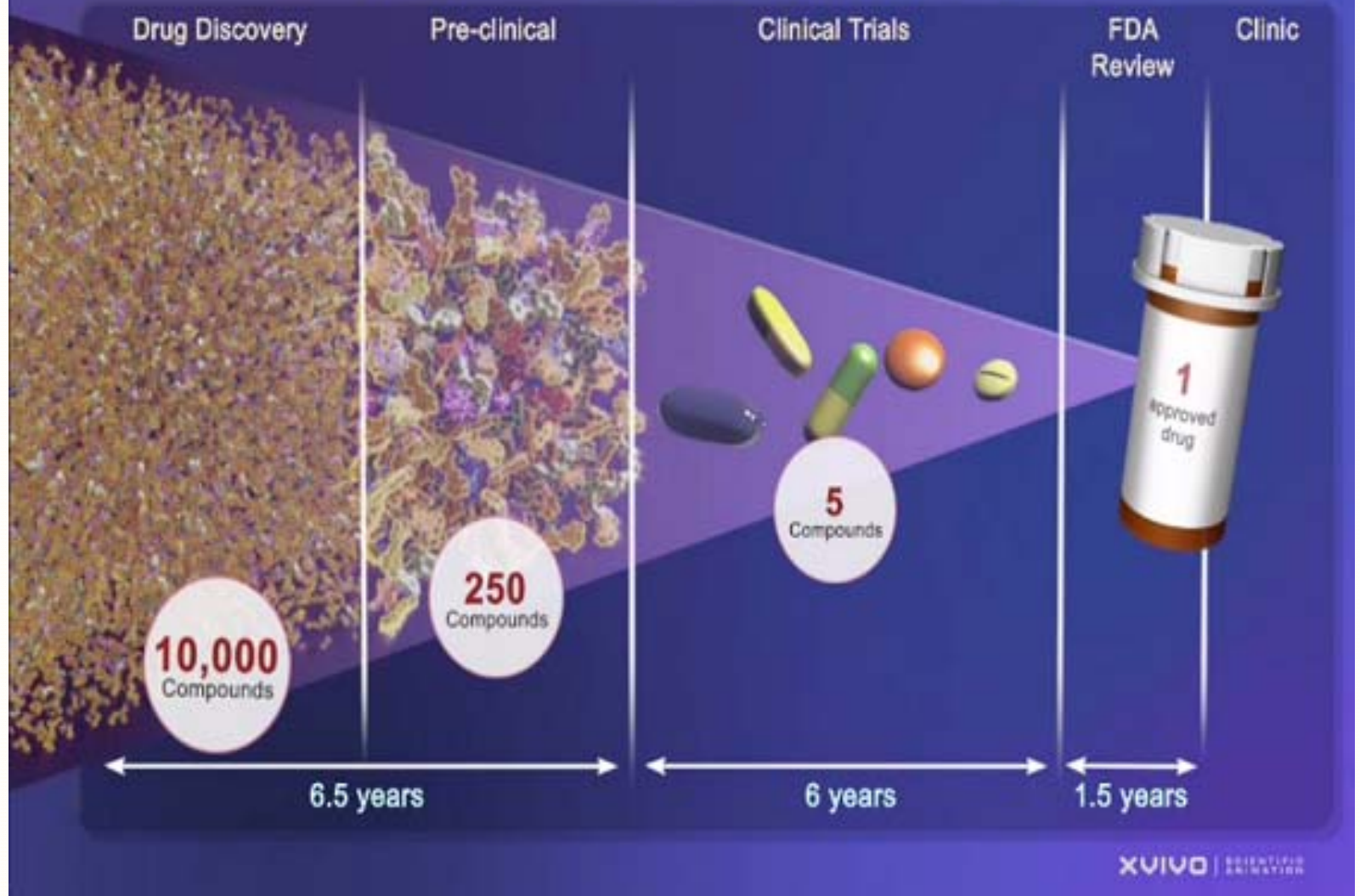


NIH - Industry Pilot Program:

*Discovering New Therapeutic
Uses for Existing Molecules*



Therapeutic Development Pipeline



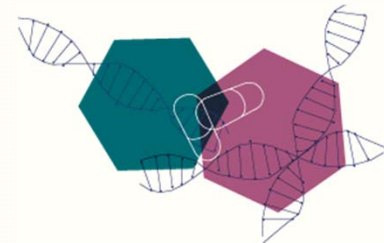
NCATS: Therapeutics Discovery Pilot

Goal:

To identify new therapeutic uses of proprietary compounds and biologics across a broad range of human diseases in areas of medical need.

The pilot initiative will:

- Match candidate Agents from 8 pharmaceutical partners with innovative ideas for new indications from the biomedical research community.
 - **NIH provides:** template Collaborative Research Agreements (CRAs) and Confidential Disclosure Agreements (CDAs), FOAs, review, funding, and oversight
 - **Pharmaceutical partners provide:** compounds, biologics, in kind support, and pertinent data
 - **Academic researchers provide:** deep understanding of disease biology, new concepts to test, and access to appropriate patient populations

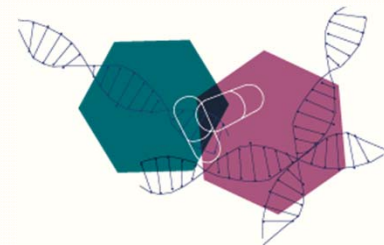


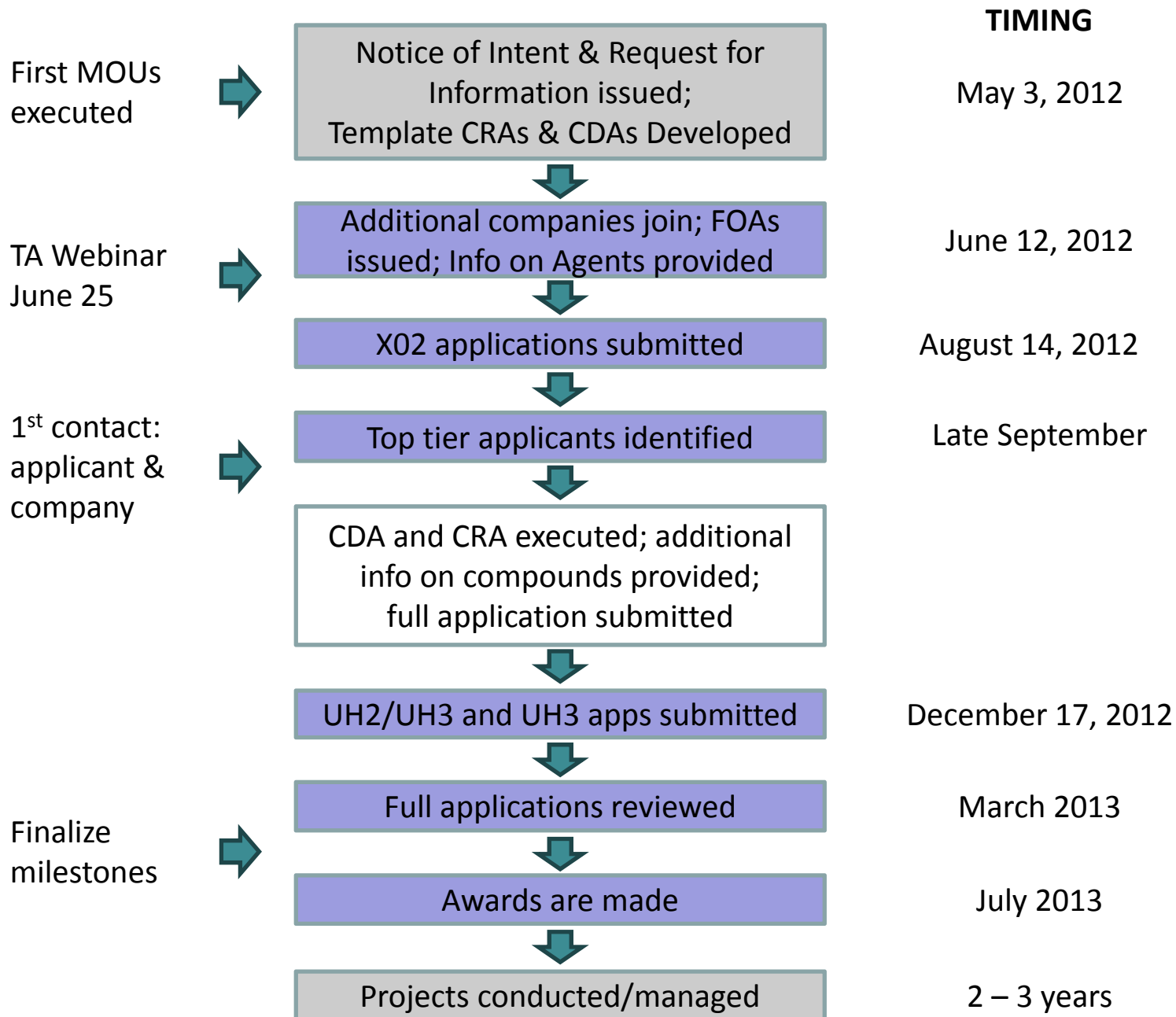
NCATS: Therapeutics Discovery Pilot

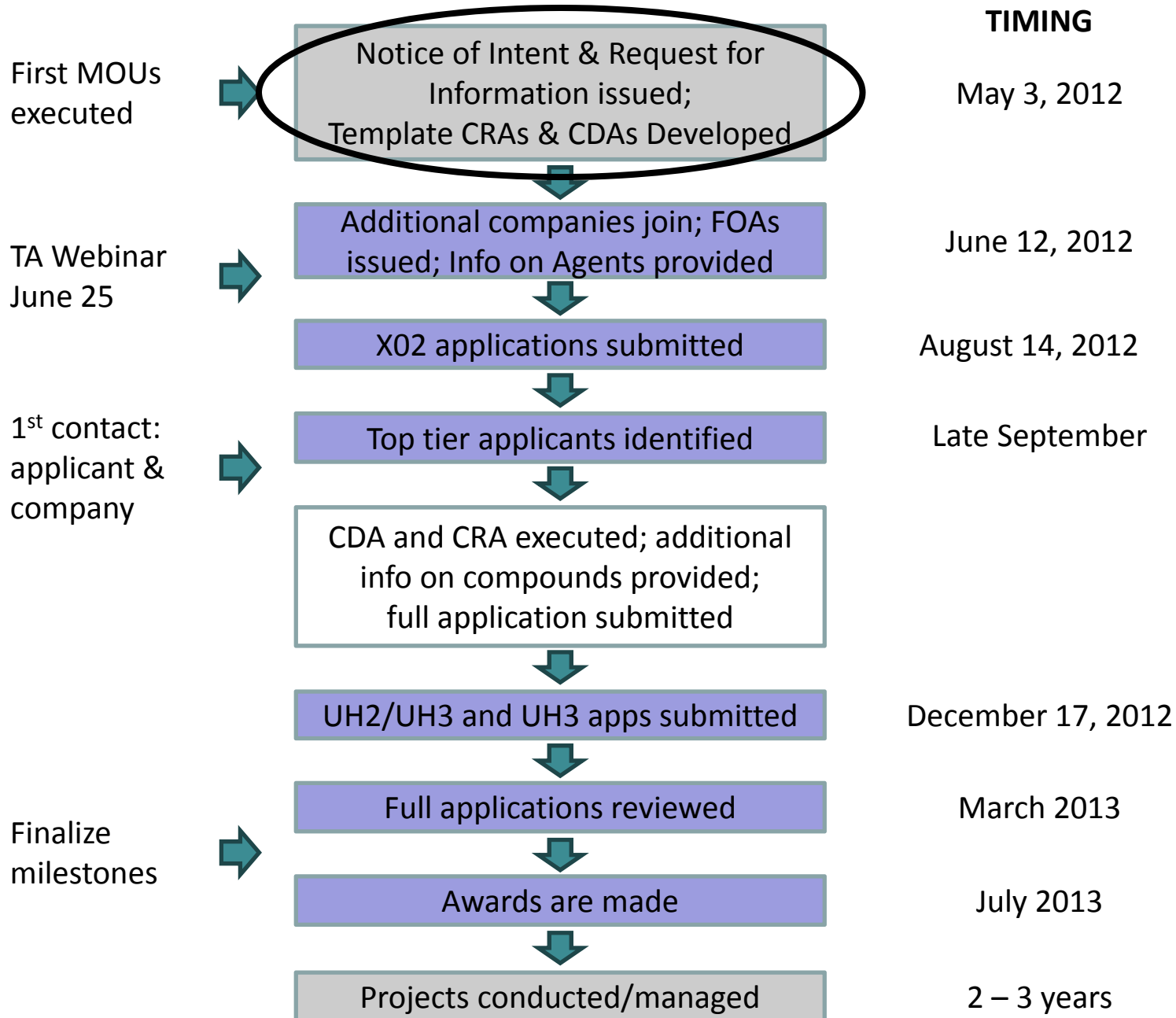
58 Agents made available for this pilot program by 8 pharmaceutical company partners*

- Abbott
- AstraZeneca
- Bristol-Myers Squibb Company
- Eli Lilly and Company
- GlaxoSmithKline
- Janssen Pharmaceutical Research and Development, LLC
- Pfizer
- Sanofi

**listed alphabetically*

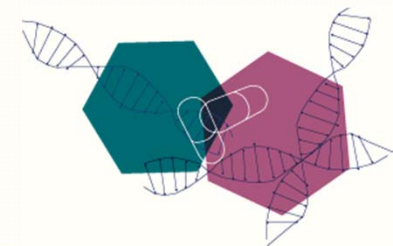
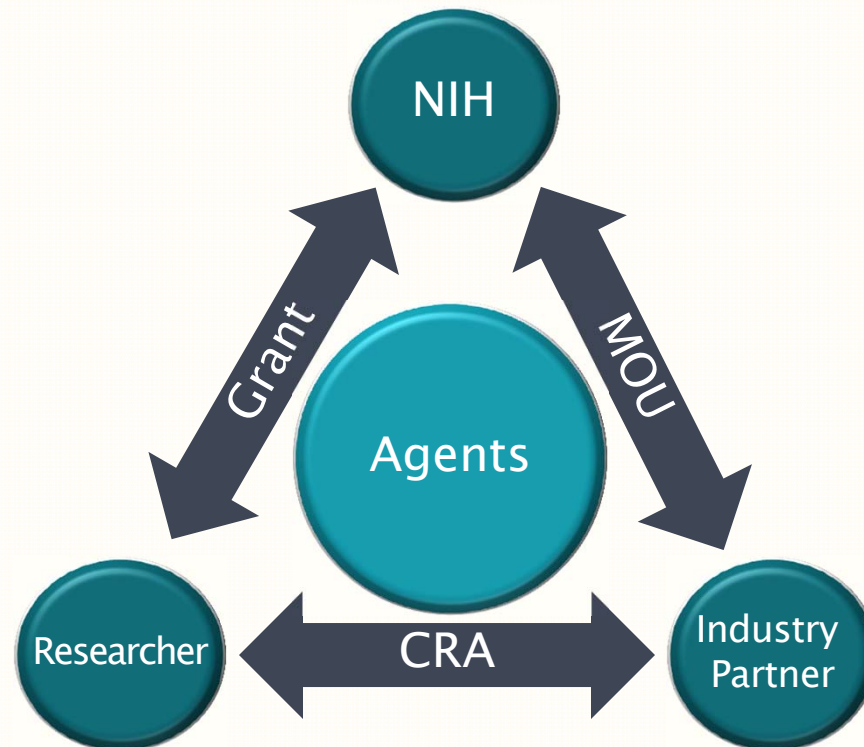






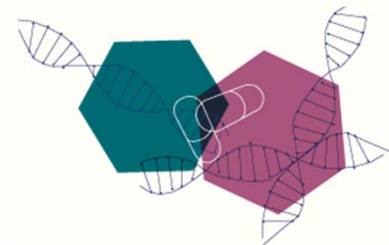
NCATS: Therapeutics Discovery Pilot

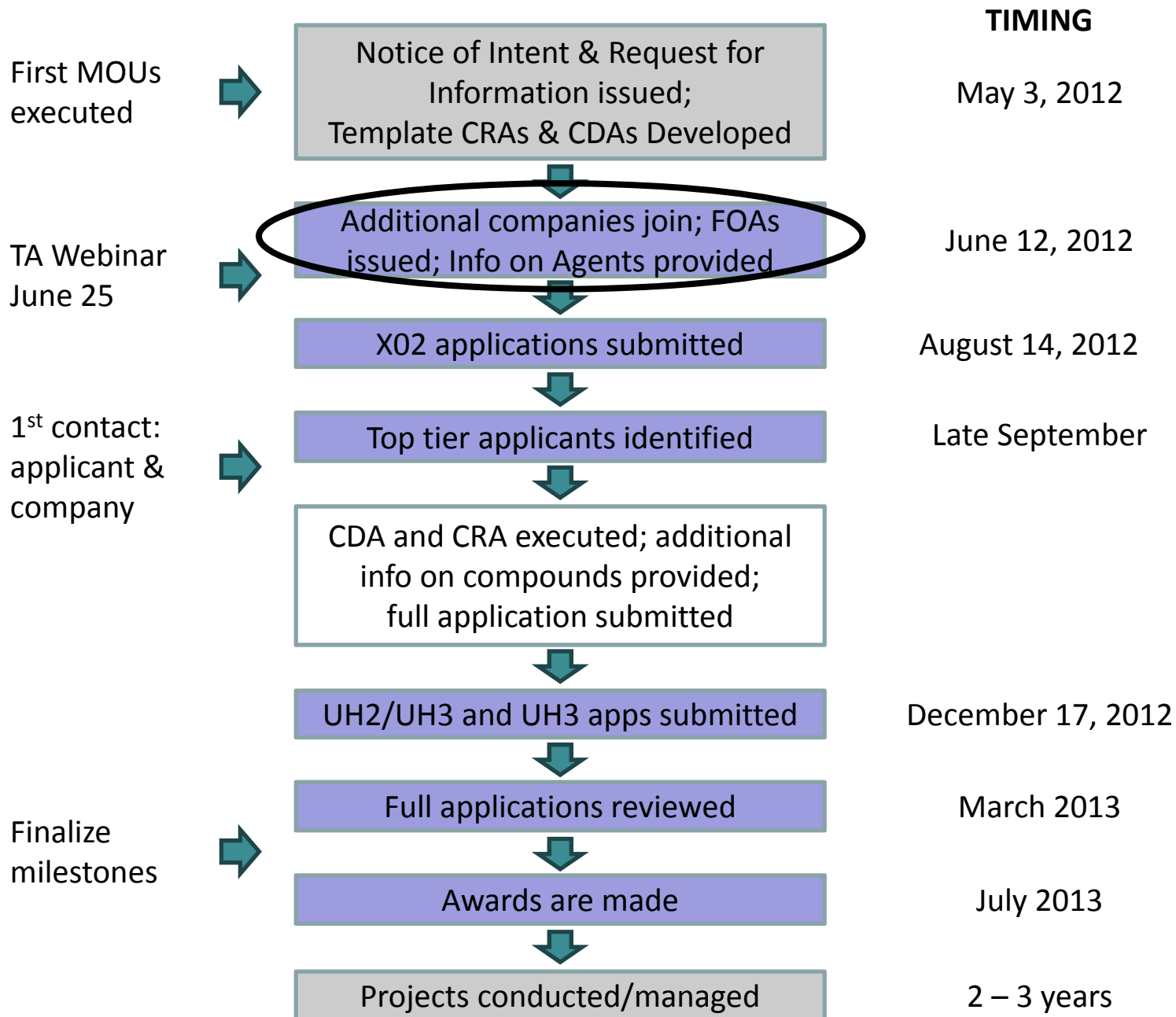
- Template agreements - reduce time, cost, and effort



Criteria for Agents Included in the Pilot

- Well-characterized against mechanism of action (MoA), selectivity
- Undergone significant R&D, including some human studies
- Most have been in Phase I or Phase II for original indication(s)
- Suitable PK to explore mechanism
- Most are ready for Phase IIa studies for unexplored new uses
- Safety profile understood
- Company's commitment to supplying material





Sample from the Table of Compounds and Biologics

Code Number & Link to More Information	Mechanism of Action	Original Development Indication(s)	Route of Administration Formulation Available (CNS Penetrant [†])
AVE5530 canosimibe	Acyl-coenzyme A:cholesterol O-acyltransferase (ACAT) inhibitor Cholesterol absorption inhibitor	Hypercholesterolemia	Oral
SSR149744C celivarone	Anti-arrhythmic, Vaughan Williams Class I to IV	Maintenance of sinus rhythm in atrial fibrillation patients Prevention of shocks and major clinical outcomes in patients with implanted cardiac defibrillator	Oral
PF-05416266 senicapoc (ICA-17043)	Calcium-activated potassium channel blocker (KCa3.1), intermediate-conductance	Sickle cell disease Asthma	Oral
ABT-639	Calcium channel, voltage-gated (Cav3.2, T-type) blocker	Pain	Oral (Yes)
CP-945598 otnabant	Cannabinoid receptor 1 (CB1) antagonist	Obesity	Oral (Yes)
LY2828360	Cannabinoid receptor 2 (CB2) agonist	Osteoarthritis pain	Oral (Yes)
AZD1981	Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2)/prostaglandin D2 (DP2) receptor antagonist	Asthma Chronic obstructive pulmonary disease	Oral
SSR150106	Chemokine receptor antagonist (TNF α release)	Rheumatoid arthritis pain	Oral
AZD2423	Chemokine (C-C motif) receptor 2 (CCR2) antagonist	Chronic obstructive pulmonary disease	Oral

<http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/directory.html>

Sample from the Table of Compounds and Biologics

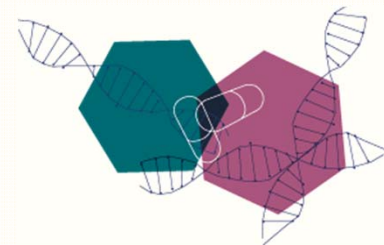
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<http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/directory.html>

AstraZeneca	AZD2423
Mechanism of Action	Chemokine (C-C motif) Receptor 2 (CCR2) antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=59 http://www.ncbi.nlm.nih.gov/gene/729230
Overview	<p>AZD2423 is a potent orally bioavailable non-competitive, negative allosteric modulator of the CCR2 chemokine receptor. CCR2 is a receptor for monocyte chemoattractant protein MCP-1 (CCL2) and the closely related proteins MCP-2 (CCL8), MCP-3 (CCL7), and MCP-4 (CCL13). Human CCR2 exists as two forms, CCR2a and CCR2b, which differ at their C-termini by alternative splicing. Evidence obtained from studies on leukocytes suggests that MCP-1 binds preferentially to CCR2 and mediates monocyte chemotaxis. Studies have implicated MCP-1-mediated monocyte infiltration in pain and a range of inflammatory diseases. AZD2423 has been developed for the oral treatment of neuropathic pain and chronic obstructive pulmonary disease (COPD).</p> <p>In pre-clinical studies, AZD2423 inhibited MCP-1 induced calcium mobilization and chemotaxis of THP-1 cell line with an IC₅₀ of 4 nM. The AZD2423 affinity for CCR2 in human whole blood, measuring MCP-1 induced L-selectin shedding from monocytes, was the same. AZD2423 is highly selective (> 500-fold) for CCR2. AZD2423 demonstrated robust analgesia in two rodent models of neuropathic pain and a pain model of joint destruction against heat, mechanical and weight-bearing endpoints. A significant (> 500-fold) drop-off in potency was observed for several pre-clinical species (rat, mouse, dog, marmoset). Consequently several tool compounds have been used for most <i>in vivo</i> pharmacology studies; a tool CCR2 antagonist inhibited neuronal excitability in rat neuropathic models to heat, mechanical and electrical stimuli either via systemic administration or via administration directly to the spinal cord.</p>
Safety/tolerability	<p>A comprehensive safety assessment package has been performed on AZD2423 including pivotal reproductive toxicity studies and general toxicity studies of 6 month duration in rat and dog. Identified target organs for toxicity are liver and cardiovascular function.</p> <p>In healthy volunteers, AZD2423 has been studied at single doses of up to 600 mg and in multiple ascending doses of up to 300 mg once daily for up to 14 days. Gastrointestinal side effects, (nausea and vomiting), determined a single dose MTD of 300 mg and multiple dose MTD of 150 mg. In patients (COPD and neuropathic pain) multiple doses up to 150 mg (pain) and 100 mg (COPD) for 28 days have been generally well tolerated.</p>
Additional Information	AZD2423 has been studied in several Phase 2a studies. Doses of up to 150 mg for 4 weeks have been tested examining its potential effects in pain and COPD. In the COPD study, treatment with AZD2423 (100 mg) was associated with a decrease in the number of monocytes in peripheral blood. This effect was observed within 1 week after start of treatment, was sustained over the 4-week treatment period, and is consistent with the mechanism of action, as was the observed increase in CCL2, the endogenous ligand.
Suitable for and exclusions	<p>Reproductive toxicity studies support the inclusion of women of child-bearing potential in clinical studies, provided that pregnancy is prevented using a reliable form of contraception. Mycobacterium tuberculosis screening should be performed to exclude patients with latent tuberculosis until more information has been gained on the potential risk with CCR2-antagonists regarding host defense.</p> <p>Proposals for studies in COPD, ophthalmology or dermatology are not of interest.</p>
Clinical trials	http://clinicaltrials.gov/ct2/results?term=AZD2423
Publications	None

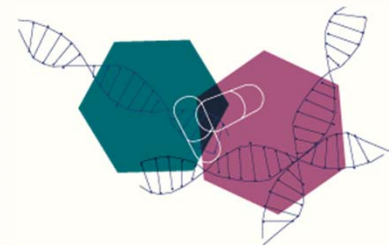
Before writing the X02 pre-application

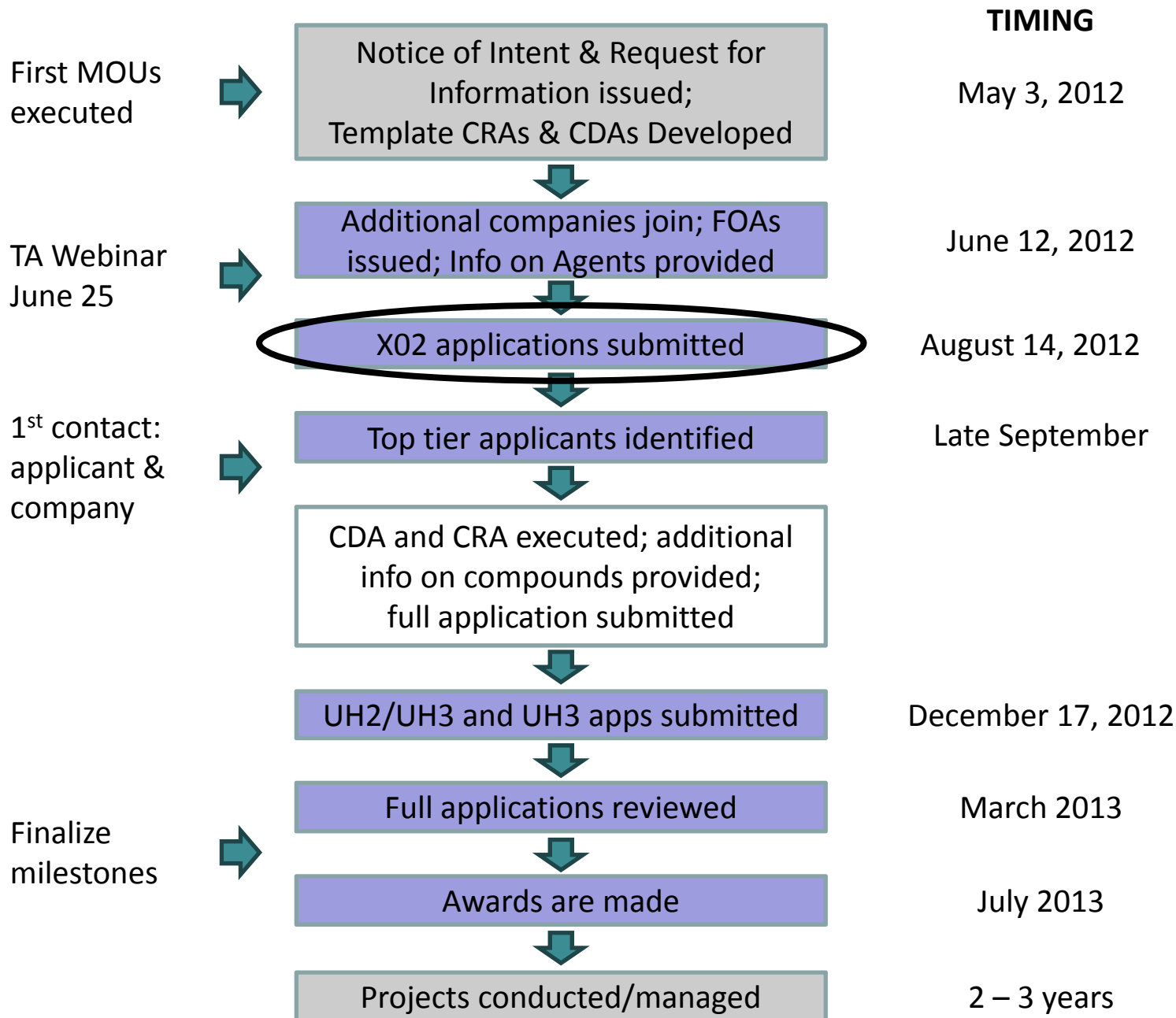
- Investigators are strongly encouraged to consult with the appropriate office (e.g. technology transfer office) to consider the willingness of the institution to agree to the conditions in the appropriate CRA for the selected Agent.
- Application with multiple PI's from more than one institution: each institution will need to demonstrate access to the Agent and data. It is recommended that appropriate offices within each institution be consulted for willingness to agree to the conditions in the appropriate CRA.
- All template agreements are posted on the NCATS website.



Letter of Intent (LOI)

- Due to the NIH by July 14, 2012
- Assists NIH prepare for review of applications
- Not binding
- Will not be provided to reviewers
- Will not factor into review of the application
- The LOI should be sent by email to:
Therapeutics.Discovery@nih.gov



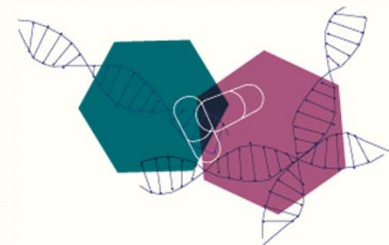


Structure of the Research Strategy of the X02 pre-application – up to 6 pages

- Background and Significance
- Preliminary studies

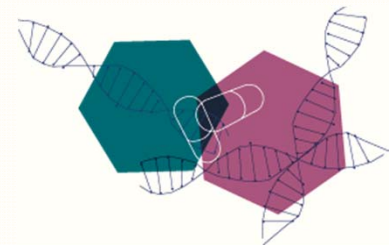
For example, in vitro or in vivo evidence that the target/pathway is involved in the disease

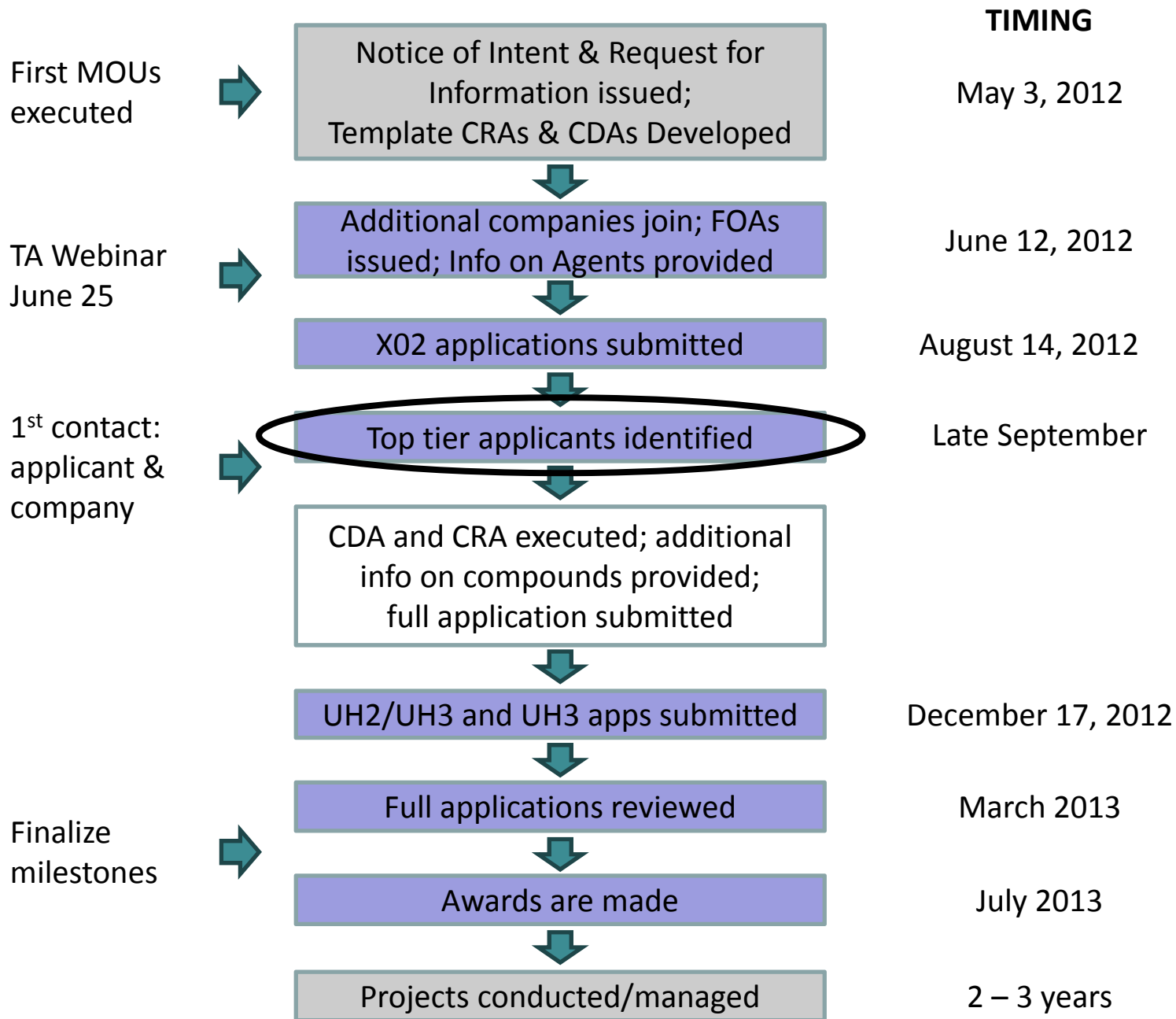
- Approach
 - Should include timeline, go/no go decision points and milestones, and a plan for expedited Institutional Review Board approval.
- Administration and Management



The following should NOT be included in the X02 pre-application

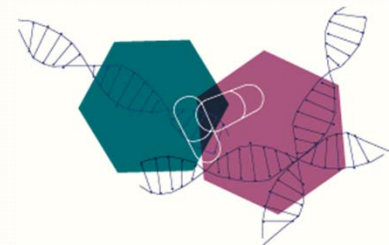
- Specific Aims page
- Resource Sharing Plan
- Human Subjects section – even if human subjects are involved
- Vertebrate Animal section – even if animals are involved
- Consortium/Contractual arrangements attachment
- Budget
- Appendices





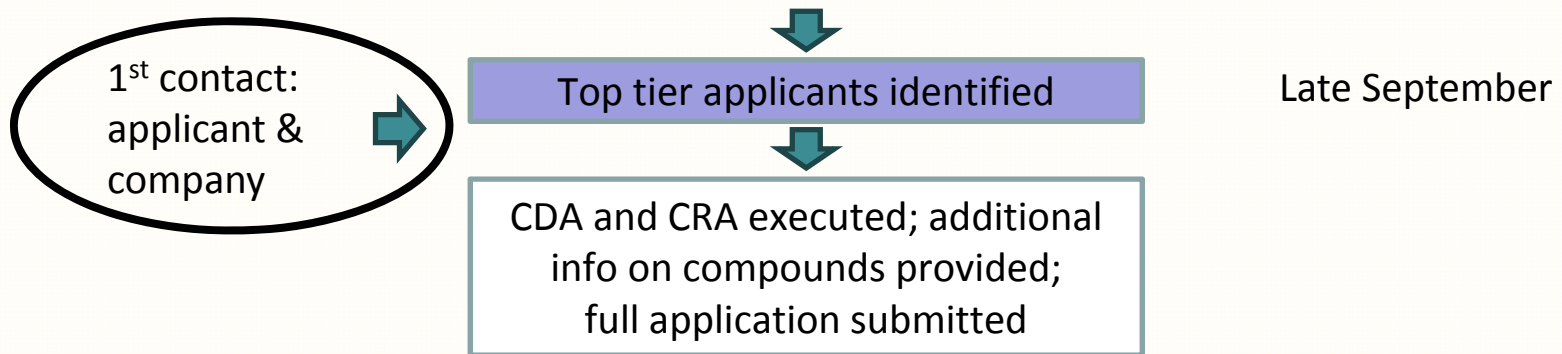
Evaluation of X02 pre-applications

- NIH review conducted by external panel of experts
- Pharmaceutical partner personnel do not participate in any way
- Applications will be scored
- Scored criteria: Significance, Investigators, Approach and Environment
- Summary statements will be made available

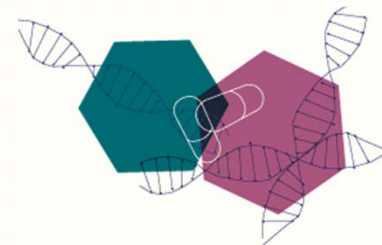


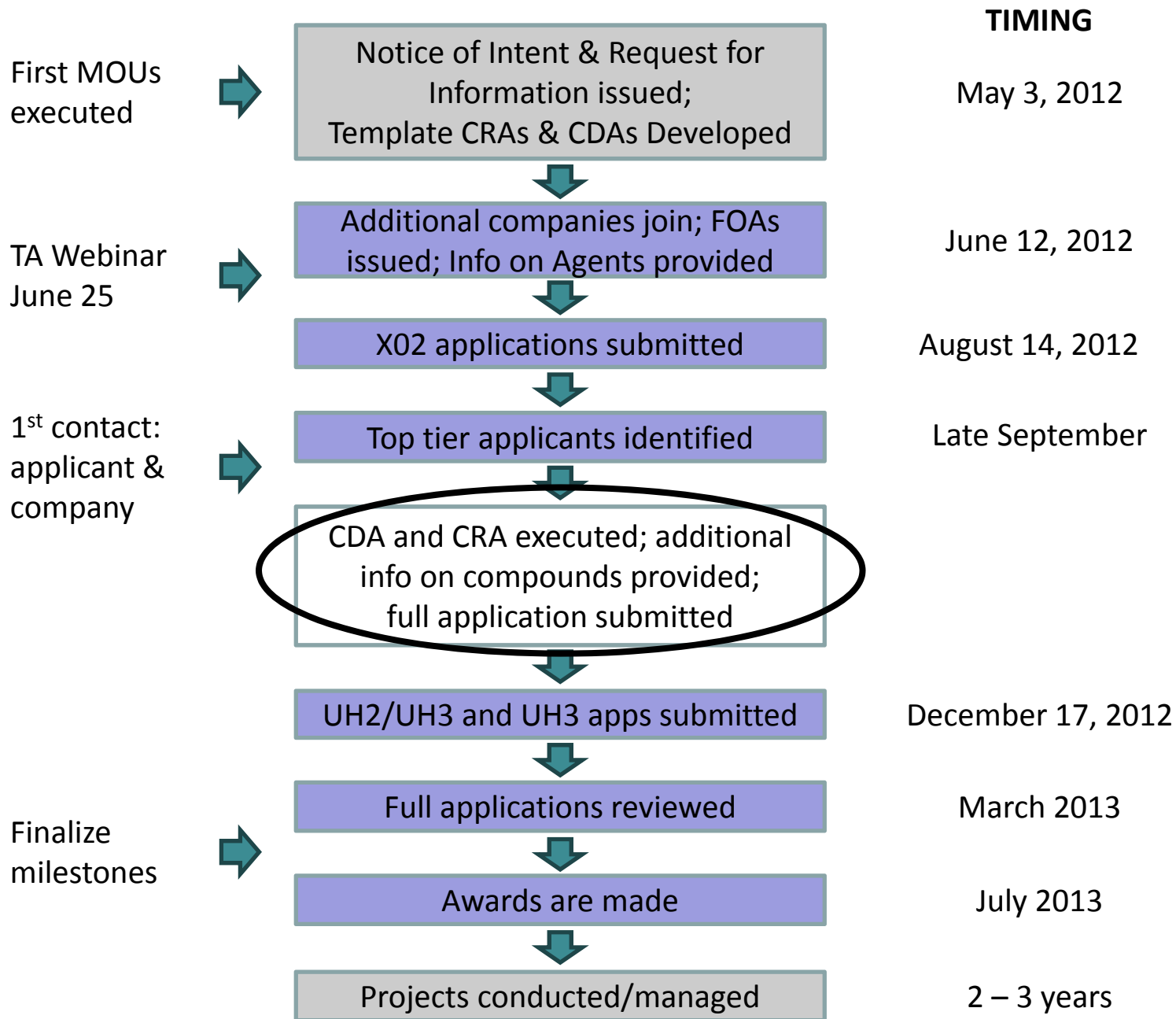
Top tier applications identified

- Successful applicants will receive notification of the contingent opportunity* to submit a UH2/UH3 or UH3
- Notification will include contact information for the pharmaceutical partner



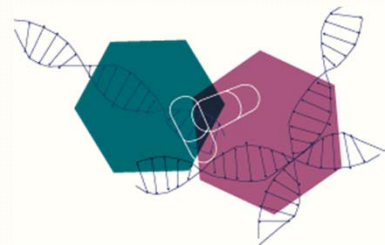
*Opportunity to submit a UH2/UH3 or UH3 application is contingent upon pharmaceutical company partner agreement to provide compound

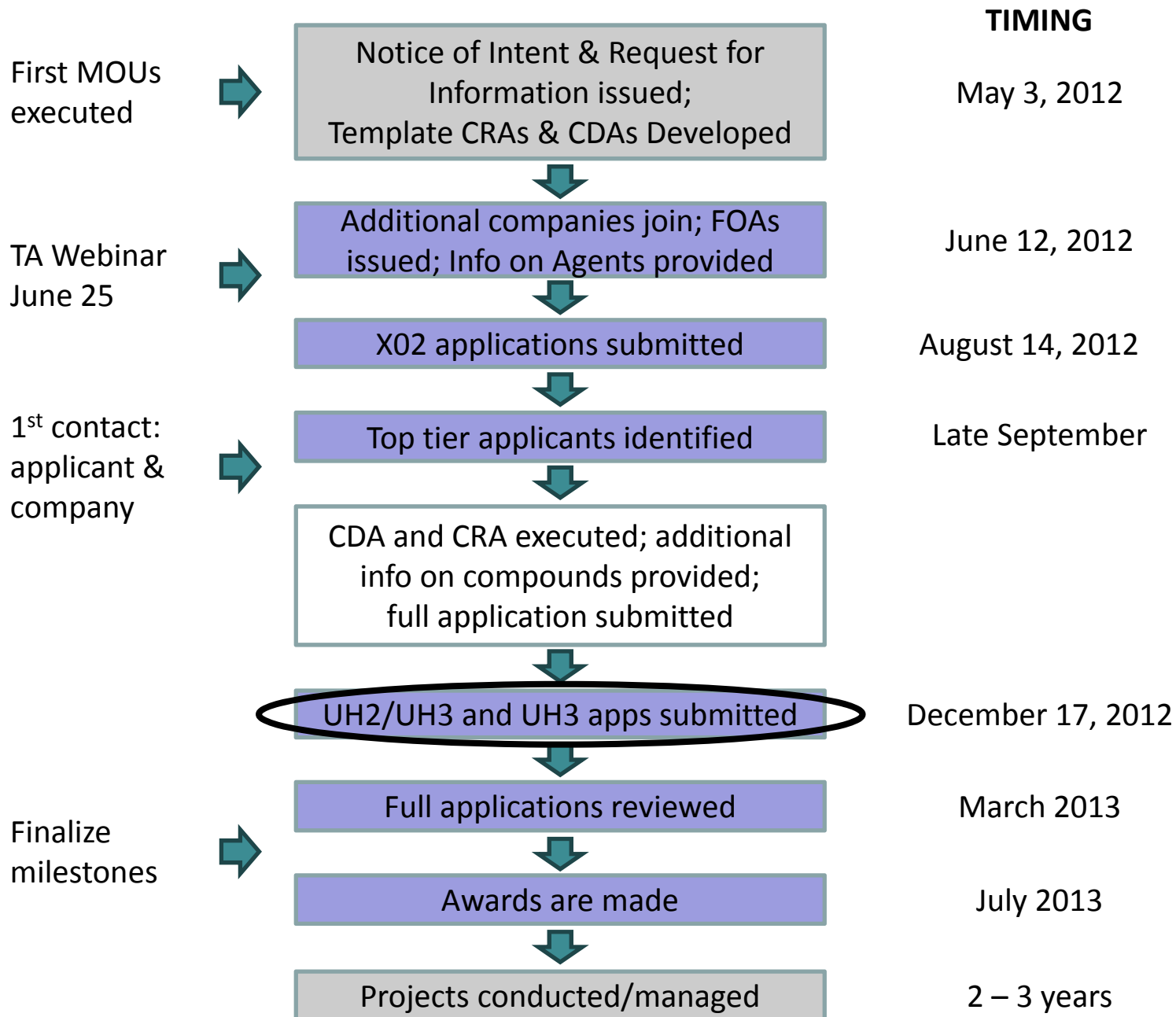




Confidential Disclosure Agreement (CDA)

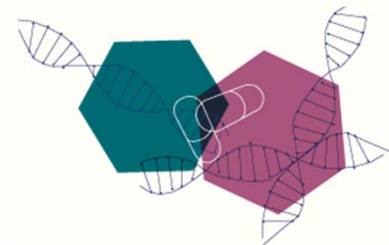
- Executed by pharmaceutical company authorized signing official, if pharma partner agrees to engage on the project
- Executed by the applicant institution authorized signing official
- Enables the parties to share confidential and proprietary information about the Agent to prepare a full application for RFA-TR-12-004 or RFA-TR-12-005





UH3 vs UH2/UH3 Application

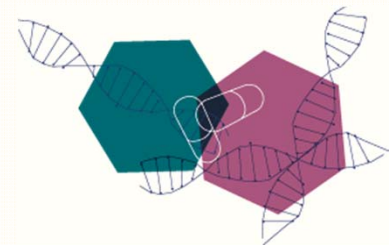
- Investigator will decide whether to submit a UH3 or UH2/UH3 application based on the existing data on the Agent as it relates to the proposed new therapeutic use.
- UH3 supports implementation of proof of concept Phase IIa trials (no feasibility studies needed).
- UH2/UH3 supports a two-stage approach, including feasibility studies (pre-clinical or Phase Ib trials) prior to a proof of concept Phase IIa trial.



UH2 – pre-clinical and/or Phase Ib clinical trials

- Pre-clinical studies should assess validity of the Agent for the new indication.
- Animal studies, if proposed, should be tied to go/no go decisions to test the Agent in a Phase Ib trial.
- Discuss how data from UH2 will be assessed to determine the risk/benefit of the Agent to patients.
- Discuss plans for IND filing and expedited Institutional Review Board approval.
- For this program, Phase Ib trials are defined as:

Studies usually conducted in the target patient population to establish feasibility (e.g., target engagement, pharmacodynamics/ pharmacokinetics (PD/PK), optimal dosing of the Agent) for a Phase IIa proof of concept trial.

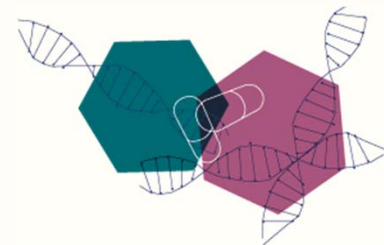


UH3 - Phase IIa clinical trials

- For this program, Phase IIa proof of concept trials are defined as:

Studies designed to explore new hypotheses and to assess whether the Agent demonstrates an early signal of efficacy in the targeted patient population, typically 150 subjects or less. In addition to clinical benefit, Phase IIa trials also include assessments of safety, tolerability, and PD/PK response of the Agent.

- Provide a clear description of the timeline, interim milestones and go/no go decision points.
- Provide detailed quantitative criteria by which milestone achievement will be assessed.
- Provide detailed timeline for attainment of milestones



Structure of Research Strategy

UH2/UH3

UH2 – up to 12 pages

- Background
- Preliminary Studies
- Approach for the UH2
- Milestones and Timeline for UH2

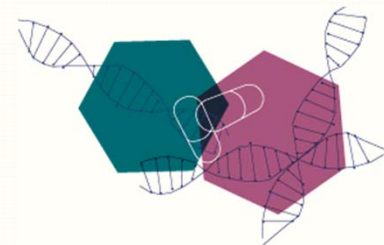
UH3 – up to 12 pages

- Approach for UH3
- Milestones and Timeline for UH3
- Future Plans

UH3 only

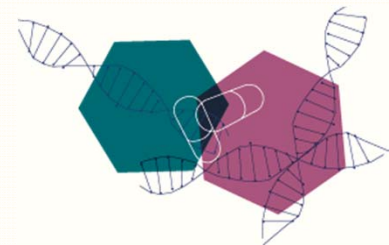
Up to 12 pages

- Background
- Preliminary Studies
- Approach
- Milestones and Timeline
- Future Plans



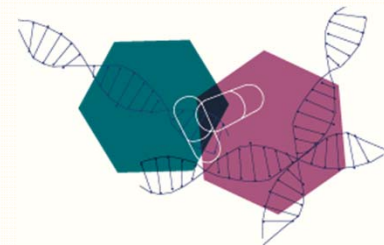
Milestones and Timeline

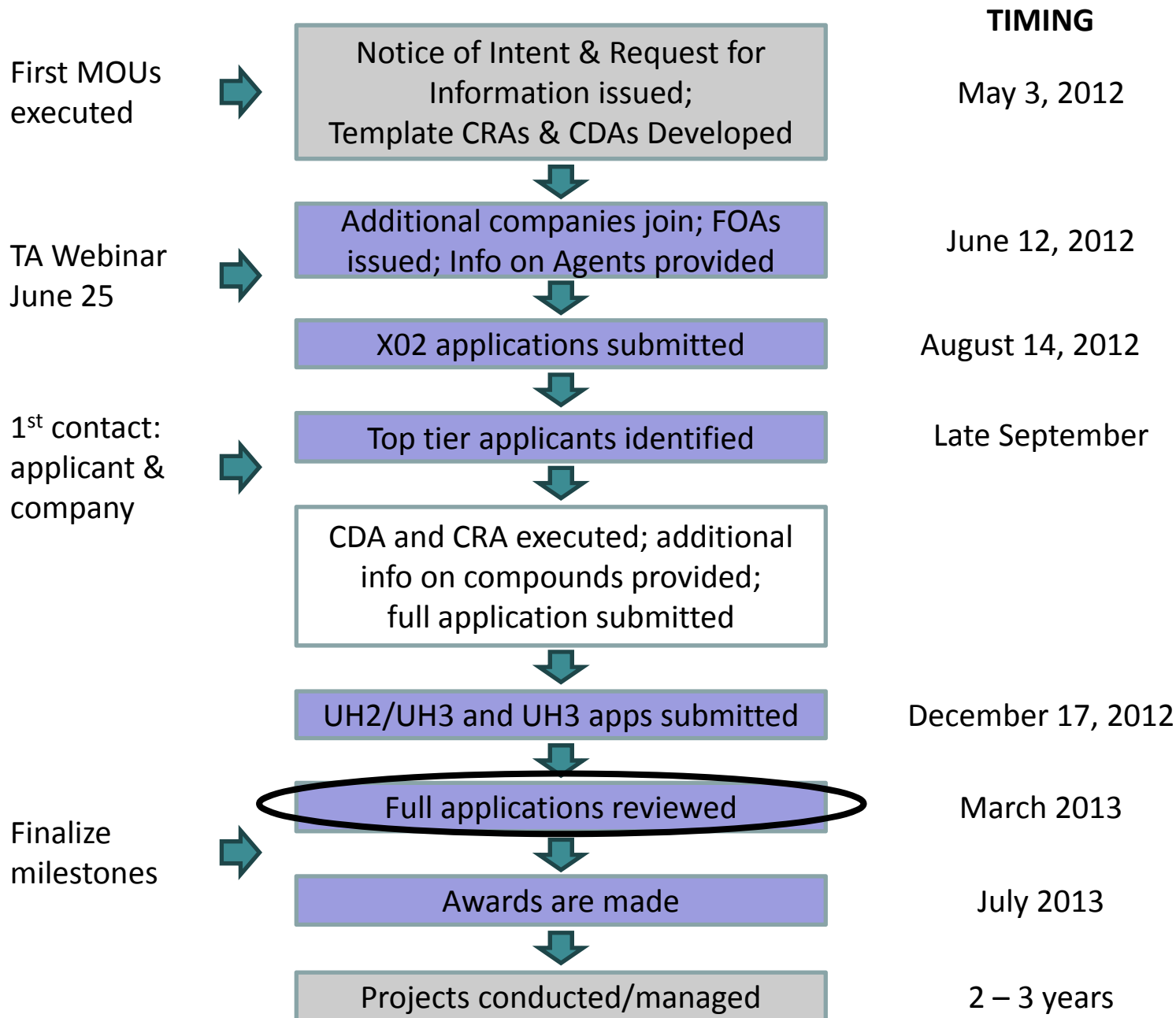
- Included within the 12-page Research Strategy of the UH2 and within the 12-page Research Strategy of the UH3
- Will be part of the Additional Review Criteria
- Will factor into the overall score
 - See *Section V. Application Review Information* of the FOA
- Additional guidance is provided in the FOA
 - See *Section IV. Application and Submission Information*
 - *Part 2 Content and Form of Application Submission*
 - *Part 6 Other Submission Requirements and Information*



Collaborative Research Agreement

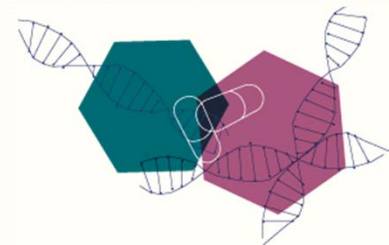
- A letter of support from the pharmaceutical company partner must be included in the UH2/UH3 or UH3 application documenting that the applicant(s) will have access to the Agent and associated data needed for conducting the proposed pre-clinical and/or clinical studies contingent on the NIH making an award.
- A CRA should be executed before the UH2/UH3 or UH3 application is submitted to the NIH.
- A copy of the Collaborative Research Agreement should not be submitted with the NIH application.

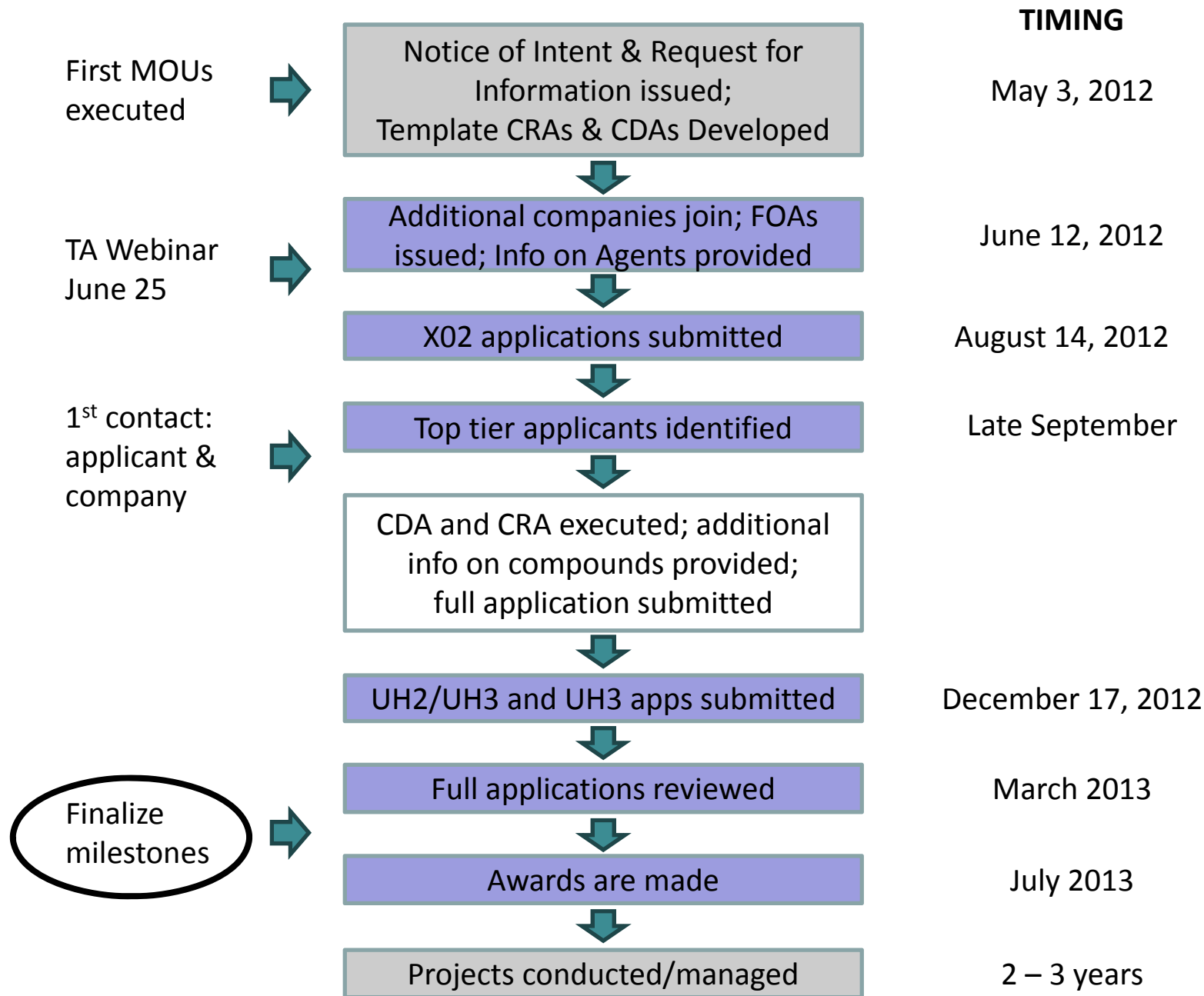




Review of the UH2/UH3 and UH3 applications

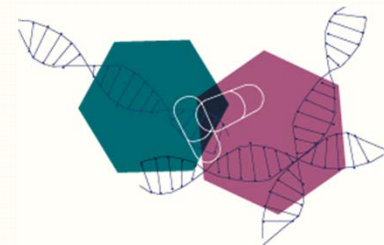
- Pharmaceutical company partners will not participate in any way.
- Applications will receive a score and summary statement.
- *Additional Review Criteria* including the Milestones and Timeline will be factored into the overall score of an application.





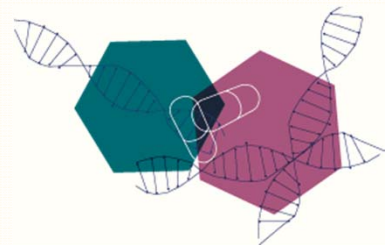
Staged (UH2/UH3)

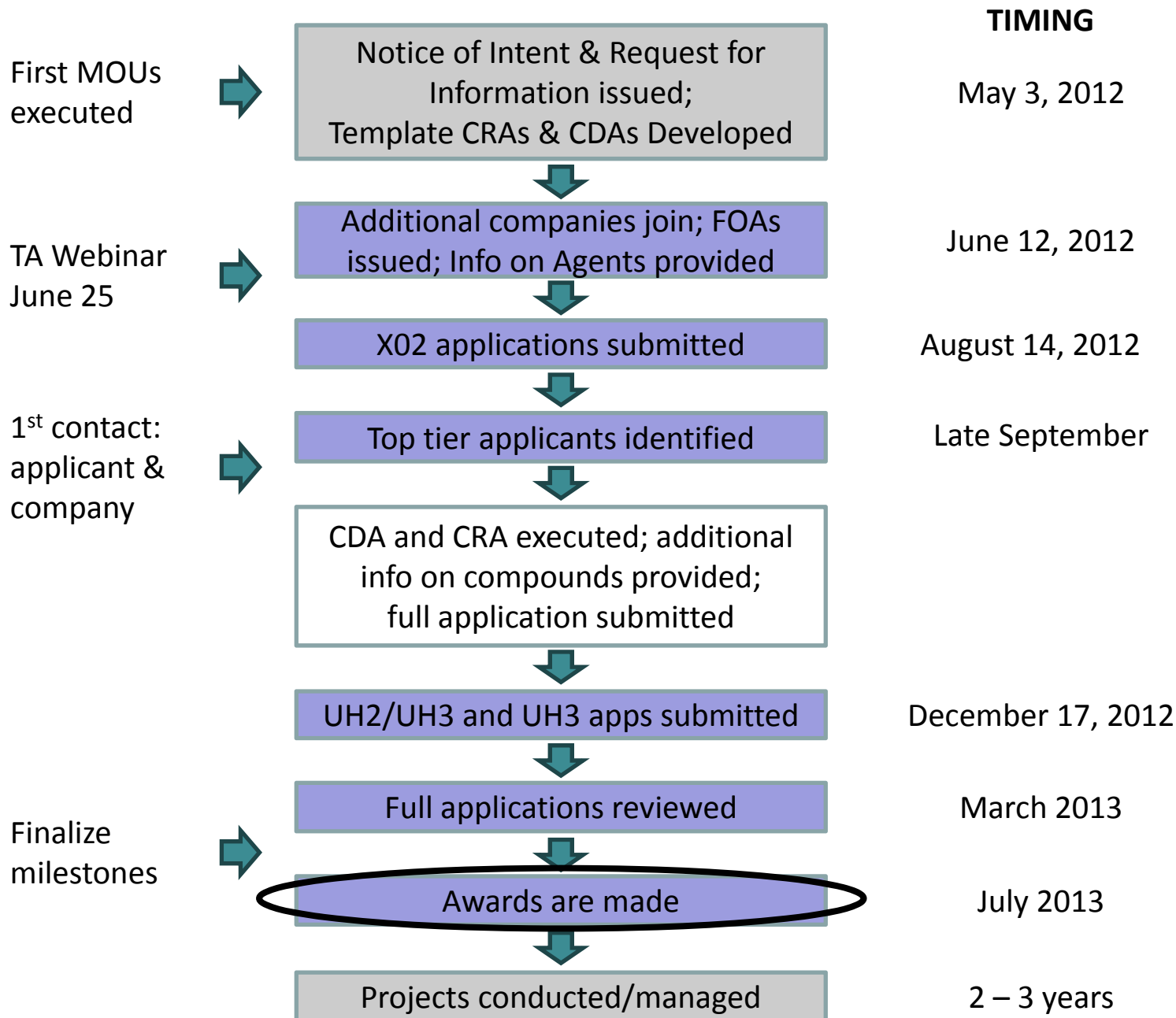
- Prior to funding, the Program Official will contact the applicant to discuss the UH2 and UH3 milestones and any potential changes.
- The Program Official and the applicant will agree on a final set of UH2 milestones.
- These milestones will be specified in the Notice of Award and will be the basis for judging successful completion of the UH2 stage and progress towards interim milestones in the UH3 stage.
- The Program Official will be responsible for determining if the awardee has met the milestones and feasibility requirements for transition from the UH2 to the UH3 stage.
- The Program Official reserves the right to obtain periodic external peer review and recommend reviewers for an assessment of progress and achievement of milestones.



Receipt of a UH2 award does not guarantee transition to a UH3 award

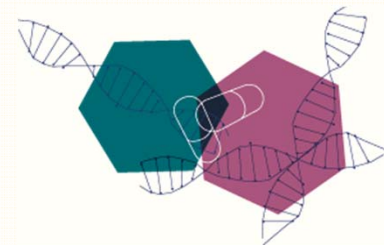
Finalized milestones will be specified in the Notice of Award and will be the basis for judging the successful completion of the work proposed in the UH2 stage and progress towards interim milestones in the UH3 stage.



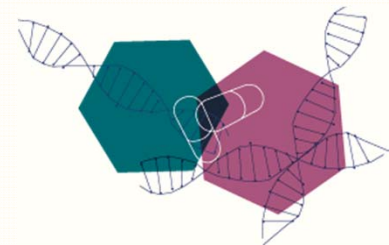


NIH Cooperative Agreements “U” Awards

- Awardee has primary responsibility for the project
- NIH Project Scientist will have substantial involvement, including participation in weekly project meetings
- NIH Program Official will be responsible for normal scientific and programmatic stewardship of the award
- Each project will have a Steering Committee (SC)
 - PD/PI(s) and designated key personnel
 - Pharmaceutical company collaborator, *ex officio*
 - NIH Project Scientist and Program Official
 - External Scientists (invited by the PD/PI in consultation with other SC members)

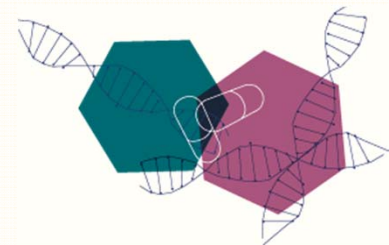


Frequently Asked Questions



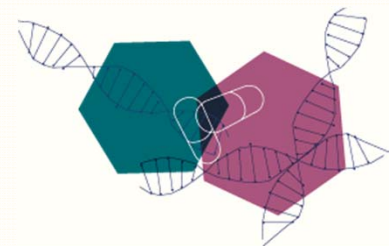
Can an investigator submit an application requesting the collection of molecules for pre-clinical studies, including screening?

No. However, applicant organizations may submit more than one application, provided that each application is scientifically distinct. Institute or Center contacts can assist in addressing questions related to proposed new therapeutic uses of other potential molecules that might be of interest in specific disease areas.



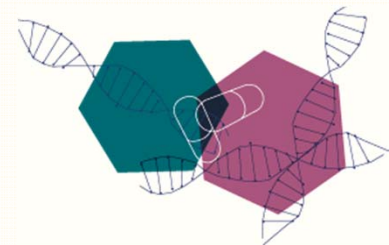
There is more than one compound with the same target/mechanism of action on the list of Agents. Do I need to choose one in particular when I submit my X02 application?

No. In some cases, there will be sufficient information in the one-page summaries for applicants to choose the most appropriate molecule for the proposed study. In cases where the information provided on the NCATS website is not sufficient for an applicant to choose, he or she may simply identify the target/mechanism of action in the X02 application. X02 applicants who are notified of the contingent opportunity to submit a UH2/UH3 or UH3 application will be provided contact information for each of the relevant pharmaceutical companies to execute a Confidential Disclosure Agreement (CDA) and obtain additional information on the compounds with similar MoA. The UH2/UH3 or UH3 application must identify a specific molecule in order to be responsive.



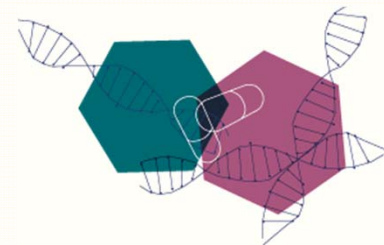
Are applicants required to use the template Collaborative Research Agreements posted on the NCATS website?

Use of the template agreements is not required. However, UH2/UH3 and UH3 applications submitted without evidence of access to and ability to work with the Agents, such as evidence that a CRA or equivalent document has been executed, will be deemed non-responsive and will not be accepted for review.



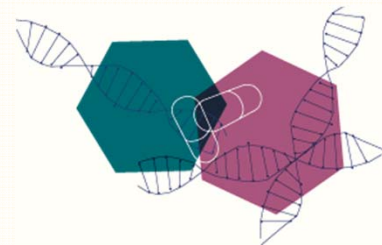
What is the total budget limit for each application and how many applications does NCATS plan to fund?

Application budgets are not limited, but need to reflect actual needs of the proposed project. NCATS will commit up to \$20 million in Fiscal Year 2013 to fund six to eight UH2/UH3 or UH3 awards in response to [RFA-TR-12-004](#) and [RFA-TR-12-005](#). Future year amounts will depend on availability of funds. Note that an applicant with a successful X02 should not apply for both the UH2/UH3 and UH3. There should be just one cooperative agreement application per successful X02. The decision of whether to submit a UH2/UH3 or a UH3 application will be that of the applicant.



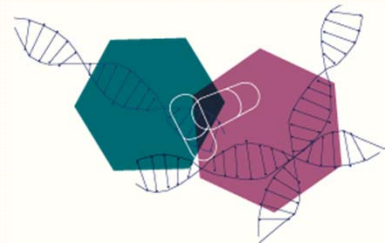
Are proposed new uses for the Therapeutics Discovery program Agents limited to stand-alone interventions?

No, this is not limited. The program supports clinical studies/trials to develop new uses of the molecules as stand-alone interventions or as proposed add-on treatments if there is no evidence of drug-drug interactions with the standard-of-care treatment. However, the pharmaceutical partners will not provide standard-of-care therapeutics.



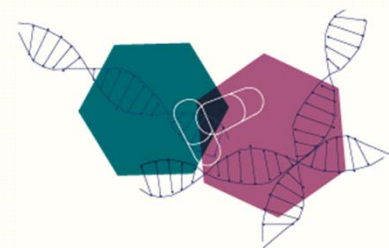
Would strategies that could improve delivery or bioavailability of the Agents be appropriate for this program?

New formulations or delivery strategies would be outside the scope of this program.



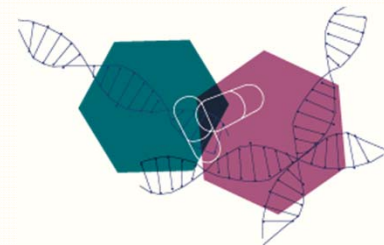
Can an applicant propose to test a combination of Agents on the list for a single indication?

For this pilot, applicants should focus on one molecule to develop biological evidence for the proposed new use. The initiative focuses on proof-of-concept trials with pre-clinical studies as needed to strengthen the biological evidence for the proposed new use.



Intellectual Property

- Pharmaceutical companies will retain the IP of their molecules
- Research partners will own any IP they discover through the research project, subject to certain licensing obligations to the pharmaceutical company that provided the molecule
- Researchers will be able to publish the results of their work



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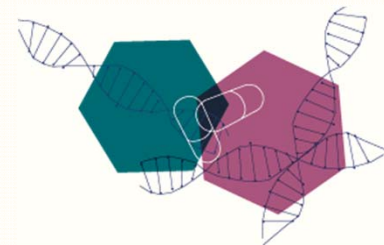
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Thank you!

If you have questions after the webinar, please email them to:

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Also see the Frequently Asked Questions posted at:

<http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutics-faq.html>

