"Collaboration 4 Cure (C4C)"

3rd Call for Proposals from San Diego Alzheimer's Researchers: Alzheimer's San Diego, in partnership with the Salk Institute (Salk), Sanford Burnham Prebys Medical Discovery Institute (SBP), the Scripps Research Institute (Scripps), University of California, San Diego (UCSD), and the J. Craig Venter Institute (Venter), are seeking proposals for the locally funded and managed "Collaboration 4 Cure (C4C)", an innovative program to harvest the best research ideas and put them on a translational path towards effective therapies of Alzheimer's disease by partnering them with the existing local drug discovery infrastructure at SBP and Scripps. The C4C program will primarily award investigators the drug discovery capabilities and services of the *Conrad Prebys* Center for Chemical Genomics at SBP through contracts managed by Alzheimer's San Diego.

Background: Collaboration 4 Cure is a ground-breaking initiative now in it's third year, led by Alzheimer's San Diego, the City and County of San Diego, and San Diego's premier research institutes to come together and combine resources to accelerate research drug discovery projects to find a cure for Alzheimer's disease right here in San Diego. The funding goal for the C4C is $7 million over the next five years. San Diego has a uniquely dynamic, entrepreneurial and creative science and technology heritage, with a track record of achievement in the creation, commercialization and sustainment of disruptive technologies emanating from its medical science-based companies and leading research institutes and universities. C4C is an innovative collaborative partnership amongst Alzheimer's San Diego and five institutions, the Salk, SBP Discovery, Scripps, UCSD, and the Venter, to provide access to world-class translational drug discovery infrastructure and expertise for collaborative, open-source, pre-competitive, early-stage research towards identifying and validating starting points for the development of new therapeutic small molecule agents that can progress to the clinical treatment for Alzheimer's disease and related dementias.

Disclaimer: In late 2015, the Board of the San Diego/Imperial Chapter of the Alzheimer's Association® decided to separate from the National Alzheimer's Association® and Alzheimer's San Diego, an independent local organization was formed in order to best serve those affected by Alzheimer's and dementia in San Diego by ensuring a local governing board with local decision-making and that funds raised in San Diego remain in San Diego. Therefore, Alzheimer's San Diego is **NOT** affiliated with the Alzheimer's Association®, the Alzheimer's Association® San Diego/Imperial Chapter, the Alzheimer's Drug Discovery Foundation, the Alzheimer's Foundation of America (AFA) or the Bright Focus Foundation.

General Considerations:

Projects of interest will be those that benefit from the development and optimization of high-throughput screening (HTS) assay(s), assay automation, and synthetic chemistry capabilities. Successful awardees will be provided access to the assay development & HTS teams at SBP or Scripps' technology cores to enable the development of screens through access to their drug discovery infrastructure. These efforts will culminate in a preliminary HTS data package, to include a pilot screen that demonstrates robustness and operating characteristics of the developed assay, and articulation of a cascade of follow-up assays needed to identify a valid "hit" compound. Projects that successfully achieve a robust "preliminary HTS data" package may be considered in subsequent years of this program for advancement through hit confirmation and validation to the screening of large chemical libraries of compounds. In parallel, it is anticipated that successful projects with robust HTS data packages may be used for joint applications to additional/alternate sources of funding, (e.g. for HTS screening of large chemical collections or the 370,000 NIH Molecular Libraries Small Molecules Repository (MLSMR) compounds through the NIH PAR-14-284 RFA or additional grants from other agencies and foundations).

Important Deadlines: Letters of Intent (LOI) must be received by 5:00 PM Pacific Time on October 16. 2017. LOIs will not be accepted after this date. No exceptions will be made. Letters of intent (LOI) are submitted directly to C4C@Alzsd.org with the subject line "***C4C LOI submission"***.

For those invited from their LOIs to submit a full proposal, these applications must be received by 5:00 PM Pacific Time on December 22, 2017. Scientific and technical review will be conducted between December 22, 2017 – January 19, 2018. The C4C program will make final announcements of selected recipients no later than January 22, 2018.

Important Deadlines Summary for this program are:

August 18, 2017	Letter of Intent (LOI) Opens
Monday, October 16, 2017	LOI deadline
Monday, November 6, 2017	Full applications invited
Friday, December 22, 2017	Full applications due
Dec 22, 2017 – Jan 19,2018	Review Period for full applications
January 22, 2018	Anticipated award notifications

Eligibility: *Both academic, non-profit and small businesses with primary operations in San Diego are eligible*. The C4C program is open to any principal investigator holding a faculty appointment at any accredited, greater San Diego area-based University, academic institution, hospital, medical practice or not-for-profit medical or life sciences research institution, inclusive of stakeholder institutes: Salk, SBP, Scripps, UCSD, and the Venter. All applicants will be required to obtain institutional endorsement of their research application from their respective home institutions. In addition, small business enterprise organizations (as defined by the Small Business Administration (SBA) Table of Small Business Size Standards under NAICS Codes 325412, 541711 and 541712 and also meet NIH SBIR/STTR Eligibility Criteria) are eligible to apply. Small businesses must submit documentation of net assets and annual earnings for consideration during the letter of intent process.

IMPORTANT: *Consultation with either the SBP or Scripps Drug Discovery centers is encouraged in developing the LOI.*

Application Procedures: Both letters of intent (LOI) and invited applications are submitted directly to the Alzheimer's San Diego contact email for this program: C4C@Alzsd.org with the subject line "***C4C LOI submission" or "C4C Invited Application submission"***.

The LOI will consist of a two (2) page (8.5" x 11", 0.5" margins all around, 11-pt ARIAL font) that should ideally address the following:

- Background/Rationale – why the target important, indication, genetics, proof of concept and citations
- Preliminary Data – that verify (1) target modulation yields the desired phenotype and (2) technical feasibility of assays (robust, reproducible & scalable). Provide primary lab generated data and/or use/cite figures from key publication(s); embedded figures should be legible with legends in 8-pt ARIAL font)
- Experimental plans (approach, assay concept, format and cascade of hit progression assays)
- Readiness of homegrown reagents for the assay & follow-up cascade (necessary reagents created and qualified for stability, storage, freeze-thaw, performance, availability and scalable process for production.

In addition, the applicant may include up to two (2) reference documents (in PDF format) to support their LOI. Each reference document may only include one paper, abstract or other documentation. Multiple references combined into one (1) PDF will not be accepted. LOIs will be evaluated and select investigators will be invited

to submit full applications. Additional information regarding review evaluation for LOIs and applications is included in "Review Process" section below.

LOI Review Process: Letters of Intent (LOI) will be reviewed by a Joint Review & Operations Committee (JROC) comprising representatives from the Alzheimer's San Diego, representatives of San Diego Drug Discovery Consortium stakeholder institution, The criteria on which projects will evaluated are listed below with an emphasis on collaborative, translational research:

- Plausibility of the project based on known biology of proposed target and therapeutic agent for Alzheimer's disease or related dementias.
- Status of intellectual property, "competition", freedom-to-operate or prior art of a process or reagent.
- Appropriateness of target for chemical modulation ("druggability") and pre- or clinical proof-of-concept (POC) studies.
- Technical feasibility of the project proposed, including the readiness of investigator-created reagents and current benchtop assays for screening.

Outcomes of LOI review: After review, of the LOIs, applicants will receive 1 of 3 notification letters:

1) **Non-responsiveness** – with some feedback of deficits from
2) **Invitation to submit a full proposal** – these should be a 5-pages and include elements of the LOI with more specific details about:
   - Research plan with clear and explicit definition of the hit progression cascade (including a flow chart of assays, go/no-go criteria, expected number of compounds, and clear definition of responsible party for each assay)
   - Rationale and purpose for each secondary and tertiary assay on compounds that advance to that stage
   - Availability of purchase, or path to scale up & produce key reagent(s) for the project (engineered or base cell lines, purified proteins, enzymes, antibodies) and estimates of their costs and time to delivery
   - In cases where the applicant's lab is the only available source of key reagent(s) and/or key secondary (2°) and tertiary (3°) assay, a brief budget (total funds) and budget justification (table), with timelines for deliverables (see **"Available Funding"** below)
   - Applicants are expected to develop the research plan in consultation with either SBP or Scripps with input in feasibility. They will develop a 1-page quotation for services and cost of materials, and time to achieve each milestone: (1) reagent transfer and scale up, (2) 1° and 2° assay developed and validated w/ pilot HTS (5K), (3) hit confirmation & validation from initial pilot hits through 1° and 2° by (SBP or Scripps) which will be part of the application.

   These full applications will be reviewed by the JROC supplemented with 2-3 external reviewers from local biotech or pharmaceutical companies.
3) **"Seed Supplementation" towards assay feasibility** – LOI with robust meritorious target validation and rationale data/citations but lack robust technical assay feasibility may be invited for discussion to define a path to purchase or develop key qualified assay reagent(s) that would allow the first demonstration of the intended 1st primary and secondary assay(s) that could be miniaturized and scaled for HTS. These could be for example engineered or base cell lines, purified proteins, enzymes, antibodies, custom signal generation & detection reagents. This supplementation could take the form of (1) direct purchase commercial of reagents or services by C4C agents on behalf and delivery to investigators, (2) access to SBP or Scripps Drug Discovery centers infrastructure and expertise to perform key reagent generation or assay development activities, or (3) if reagents are unique to the investigator, with approval investigator's mentor and investigator's institutional policies total funds of up to $15,000 in the form of a "contract" to the investigators (not a research grant) for time/milestone

driven delivery the final product and use in assay development. Awardees who successfully develop robust feasibility data as judged by a JROC review will be subsequently invited to submit a full proposal for award without re-submission of an LOI "off cycle" of the LOI deadline.

Available Funding: The primary purpose of the C4C program is to provide access to early drug discovery capabilities rather than direct transfer of funds to individual investigator laboratories. Award will provide services to investigators in the form of early drug discovery capabilities and is not a direct funding mechanism for individual investigator laboratories. Successful applicants will partner with, and obtain access to resources and services of the Sanford Burnham or Scripps drug discovery centers including assay automation, HTS, and synthetic chemistry capabilities, which can be applied to the discovery and development of innovative first-in-class compounds that have the potential to be developed into therapeutics. The funds will be administered by the Alzheimer's San Diego and use to remit against approved quotes for services to these partnered centers.

In very specialized cases, with approval of the Joint Steering Committee limited funds may be made available to a PI's laboratory to enable, for example, production of unique critical reagents or key assays or services that only the PI's laboratory can perform. Investigator will submit invoices against pre-appoved service quotes. Please note that the C4C program is a unique funding opportunity that provides access to resources or specific supplemental funding to achieve drug discovery and translational critical path items and is NOT meant to replace or augment existing research grants directed towards basic research or to recruit new research personnel, launch major new research directions, fund general operating support for the lab or to purchase equipment.

Mechanism of award, reporting requirements and allowable costs: The mechanism of the award is to provide access to early drug discovery capabilities rather than direct transfer of funds to individual investigator laboratories. It is expected that successful applicants will confer bi-monthly or as needed with the project team and JROC to reach milestones submitted in final project plans. Continuation of the funding during the project's duration is contingent upon review of the scientific progress towards milestones and spending during JROC meetings. In such cases, where project have reached a scientific or technical impasse, the unspent, non-invoiced funds may be redeployed to other projects in the overall C4C portfolio upon recommendation by the JROC and approval by the JSC. PI of such defunded or terminated projects may wish to reapply if they are able to demonstrate the prior impasse has been overcome (technically or new research) and that novelty and relevance are still maintained.

Budget and Duration: For this first year, the C4C program anticipates funding multiple awards with service quotations of $35,000 - $65,000 for each project, depending on assay complexity. Duration of awards is one (1) year and contingent upon attainment of specific milestones. In future years, it is envisioned that projects that successfully achieve a robust preliminary HTS data package may be advanced for funding of larger scale HTS, (10,000-75,000 compounds), followed by hit confirmation, validation and expansion in the subsequent year (year 2), through an expedited, competitive review. It is expected that the robust and complete data obtained by this additional funding will serve as a "preliminary data" packet to support submission of an NIH R01 "HTS grant" or become drug discovery HTS aim of a larger program grant. The relevant portions of the Research Plan of a submitted R01 will suffice as the final scientific report of the project to the JROC and JSC.

Confidentiality: Consistent with the Alzheimer's San Diego policies, members of all committees will not share the information provided by applicants through the registration and application process except with directors, officers and/or representatives of stakeholder institutions, as deemed necessary. Nonetheless, applicants should not provide confidential information, such as chemical structures, at the LOI stage.

Materials and Data Sharing: Awarded applicants will be required to provide necessary, unique reagents that

are not commercially available and necessary for their proposal, such as cells expressing recombinant enzymes/proteins, primary and secondary antibodies, tagged peptide substrates, and available positive controls (e.g., a known inhibitor of the target) to the partnered translational partners (SBP or Scripps) under an MTA for the purposes of this C4C pre-competitive program.

Intellectual Property: All pre-existing intellectual property will remain the exclusive property of the party that created it prior to or independent of the funded research. During the term of the funding period, new inventions will be subject to Alzheimer's San Diego's Patent Policy existing with or to be signed with the grantee institutions at time of award.

For more information about any of the grant schemes or the application process, please contact the Alzheimer's San Diego at C4C@alz.org and your email will be directed to the scientific and program staff, who will respond by email or phone within 2-3 days.