

Merck Research Laboratories – Discovery Biologics (MRL DB) SSF Emerging Discovery Science (SEEDS) Program

Bringing together the most promising academic research with Merck R&D capabilities to validate and advance emerging therapeutic targets, pathways and technologies that show potential relevance to treat human disease.

About Us

Merck Research Laboratories (MRL), the arm of Merck & Co., Inc. focused on discovering and developing therapies to improve patients' lives, has expanded its discovery capabilities in South San Francisco (SSF) by opening a new, cutting-edge research facility.

The new nine-story, multi-disciplinary discovery research hub, accommodates more than 300 scientists and support research spanning exploratory biology through early clinical development. The building was custom designed with an open atmosphere that encourages collaboration and team work. The site also boasts a large auditorium to provide space for nearby academics, scientists and entrepreneurs to convene and engage in scientific dialogue.

About the MRL SEEDS Program

The MRL SEEDS program is a new MRL SSF initiative seeking research collaborations with academic researchers to advance the most innovative discoveries for therapeutic targets, pathways and technologies. The targeted institutions are 3 of the premiere San Francisco Bay Area universities: **Stanford University, the University of California, Berkeley and the University of California, San Francisco**. The MRL SEEDS program and subsequent collaborations underscore the importance of industry and academic interactions in the early discovery space.

The MRL SEEDS program was launched last year with initial focus on the Cardio-Renal-Metabolic-Ophthalmic (CRMO) therapeutic areas. In a second wave, we are asking for project ideas in areas related to the discovery of biotherapeutics that will fulfill the mission of Discovery Biologics (DB).

As a first step in a potential collaboration, ideas for proposed projects should be submitted for evaluation by the Scientific Review Committee (SRC) comprised of Scientists from Discovery Biologics (DB). Ideas are to be submitted in the form of a brief **non-confidential pre-proposal form by May 15, 2020**. Pre-proposals will be evaluated for selection for full proposal development as a 1-year pilot program (up to \$125,000 USD in direct costs plus institutional indirect costs) based on recommendations by MRL DB SEEDS SRC. 1-year pilot programs have the potential opportunity for extension at the discretion of the MRL DB SEEDS program SRC.

At the discretion of Merck, MRL Scientists will work closely with investigators to make available relevant capabilities and technologies that will enhance the success of the joint research program. As part of the full proposal development process, scientists from MRL will engage with lead investigators to ensure expertise and capabilities of both parties are incorporated into the project plan as applicable.

To define the current research areas of interest and/or specific challenges to address, Merck has published four Active Requests for Proposals (RFPs) in Section 3 of this document.

MRL DB SEEDS Research Project Proposals

Who can apply?

MRL DB SEEDS program RFPs are open to researchers at the following universities collocated in the San Francisco Bay Area with our MRL DB SSF Discovery Hub: **Stanford University, the University of California, Berkeley and the University of California, San Francisco.**

Why apply?

The MRL DB SEEDS program is an effort to jointly advance high-quality science. All proposals submitted will be reviewed for scientific merit, tractability for drug discovery and alignment with the published areas of interest. The strongest proposals with the most compelling cases to experimentally address areas of significant medical benefit will be considered for funding, collaboration and/or sharing of Merck's R&D capabilities.

1. Getting Started

Review the current active MRL DB SEEDS program RFPs (Section 3). To respond to an RFP please complete the pre-proposal form. The pre-proposal form includes the required elements for completing and submitting your initial 1-2 page response.

Requirements for Submitting a Pre-proposal Form

A pre-proposal form is a brief 1-2 page non-confidential summary of your project proposal that should provide sufficient information for a pre-review by the MRL DB SEEDS Scientific Review Committee. If the pre-proposal is of interest to MRL, you will be notified that your pre-proposal has been selected. As required, you may be contacted by an MRL DB SEEDS program representative for clarification of the pre-proposal or further discussion of the concept. A full project proposal and plan will be developed by the applicant or may be co-developed with Merck's Scientists and the applicant.

A pre-proposal must not contain any confidential information. Merck will not be responsible for the confidentiality of any information that is included in the pre-proposal.

A detailed view of the request for proposal process can be found in the RFP Process section (Section 4).

Submission of a full proposal does not imply or guarantee approval. Financial and/or reagent support is contingent upon full execution of a contract between Merck and the academic institution in accordance with standard practices and terms for sponsored research agreements.

2. MRL DB SEEDS Contact Information (Summer 2020)

To learn more or to ask a question, please contact the Merck DB SEEDS Program at daniel.huang@merck.com

3. MRL DB SEEDS: Summer 2020 – Discovery Biologics Active Requests for Proposals

The current MRL DB SEEDS Requests for Proposals (RFPs) are described below. All proposals submitted will be reviewed for scientific merit and tractability for drug discovery. The strongest proposals with the most compelling cases to experimentally address areas of significant medical benefit will be considered for funding, collaboration and/or sharing of MRL capabilities.

▪ **DB-RFP-01: Antibody Transport Across the Cell Membrane**

Antibodies have been widely shown to be an effective therapeutic modality for targeting proteins. However, the limited ability of antibodies to penetrate the cell membrane has largely restricted their use to targeting extracellular proteins. We are seeking proposals for projects that will study new mechanisms (other than endocytosis) for transporting antibodies across cell membranes in order to gain access to intracellular protein targets.

▪ **DB-RFP-02: Identification of Tumor Cell Surface Markers through Serum Proteome Measurements**

Overexpressed cell surface proteins can be used to preferentially eradicate cancer cells with modalities such as antibodies, peptides and small molecules and respective drug conjugates. New and more specific cancer cell surface markers are urgently needed. Patient derived tissue samples are hard to obtain but blood samples are readily available. This begs the question whether and under which circumstances tumor cell surface markers can be identified indirectly from quantitative measurements of the serum proteome? Is the concentration of circulating shed tumor cell surface proteins, for example, an accurate reflection of the density of these proteins on the tumor cell surface? We are seeking proposals aimed at investigating these questions. Proposals on how to use serum proteome measurements to quantitatively monitor changes of the tumor cell surface proteome during preclinical drug-treatment studies are also welcome.

▪ **DB-RFP-03: High-throughput Techniques for Isolating Antibodies from Immunized B-cell Repertoires**

Many approaches are currently being used to isolate antibodies from immunized animals for use as both reagents and therapeutics. While established protocols like hybridoma fusion and B-cell cloning have been shown to effectively identify antibody candidates, they typically only sample a small fraction of the immunized B-cell repertoire. The use of these more standard approaches can limit the diversity of antibody candidate pools and can be challenging to apply to more difficult targets. We are seeking proposals for projects that explore the use of high-throughput technologies such as microfluidics and next generation sequencing that will more efficiently and thoroughly analyze the immunized B-cell repertoire from different species. Technologies that are compatible with difficult targets, such as GPCRs, are of particular interest.

▪ **DB-RFP-04: Novel Sequence Motifs to Engineer into Antibody CDR-H3 to Generate Unique Paratopes in Anti-viral Antibodies**

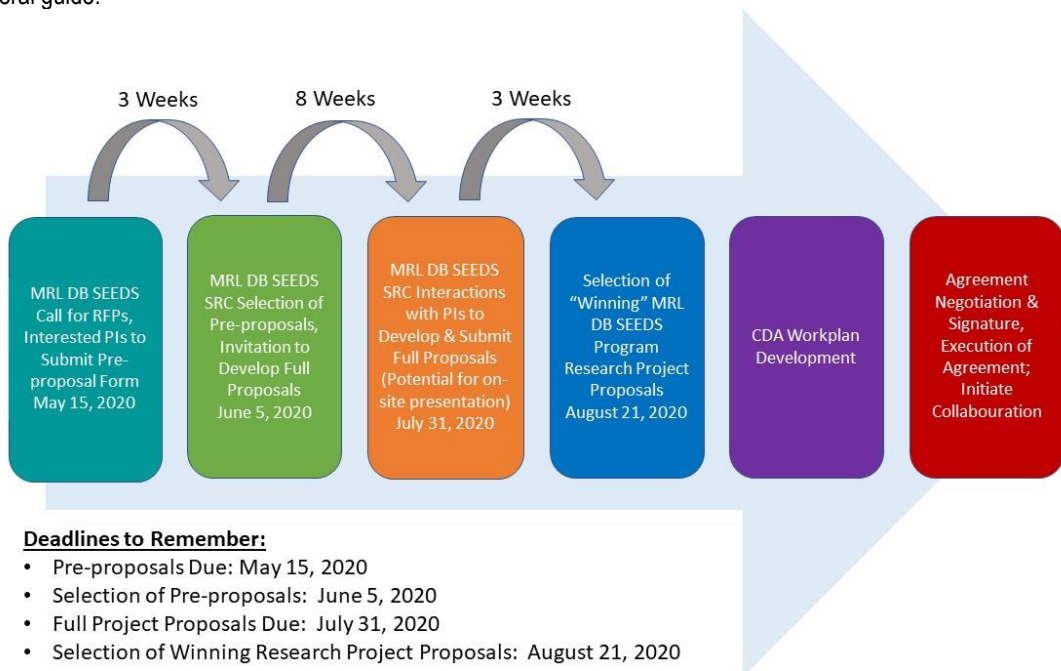
Antibodies from humans and rodents generate complementarity determining regions (CDRs) that typically form relatively flat binding surfaces to interact with targets of interest. An exception to this is the presence of a Cys-Xn-Cys motif in CDRs which have been identified in a number of potent neutralizing anti-viral antibodies suggesting a possible role of this unique paratope structure in binding to more difficult to reach epitopes that traditional antibodies may not be able to. Since CDR-H3 is the most permissive to accommodate structural flexibility, we are seeking novel and stable sequence motifs or structured peptides to engineer into an antibody CDR-H3 to generate unique paratopes to extend the scope of molecular recognition for antibodies.

- **DB-RFP-05: Glycan-targeting Bispecific Antibodies in Enhanced Tumor Selectivity**

Merck's Biologics Discovery department is exploring new modalities in therapeutic antibody engineering. Biologics is using these modalities to bridge the gap between the well-known target biology of Oncology, Immunology, and Neurosciences, with novel targeting biology of glycosciences. We seek to bring new understanding to the significance of glycobiology as a tumor targeting modality by exploring the diversity of glycans across unique tumor profiles, understanding the co-expression of specific glycans or glyco-modifications with well-known tumor antigens or check-point inhibitors, and evaluating the efficacy of a bi-specific targeting approach, bridging glycobiology and oncology, to enhance therapeutic efficacy and broaden patient populations that receive benefit from our drugs.

4. MRL DB SEEDS: Request for Proposal (RFP) Process

The MRL DB SEEDS RFP process involves several steps illustrated in the diagram below. The timeline outlined below is meant as a general guide.



 Confidential

MRL DB SEEDS: Frequently Asked Questions

Questions and responses are divided by each phase of the MRL DB SEEDS program. To learn more or to ask a question, please contact the Merck SEEDS Program daniel.huang@merck.com. Your disclosure of information does not grant you any ownership interest in future Merck company inventions.

Submissions

1. Is there any flexibility regarding the identified Active Request for Proposal statements (DB-RFP 01 - 05)? If so, how is this determined and who might an investigator speak to about this?

The vast majority of funded requests for proposals will fall within the Active Request for Proposal descriptions; However, the MRL DB SEEDS SRC may consider proposals outside the defined problem statements if they are scientifically relevant. Before submitting a proposal that is outside the published Active Request for Proposals, it is best to contact the Merck SEEDS Program daniel.huang@merck.com to bring any requests to the attention of the MRL DB SEEDS SRC.

2. Is there someone within Merck I can speak with to see if there is interest in my study idea (before submission of a pre-proposal form) or in case I have any questions in preparing the pre-proposal?

Yes. Please contact the Merck SEEDS Program at daniel.huang@merck.com

3. How do I submit a proposal?

Review Section 3, MRL DB SEEDS: Active Requests for Proposals and submit a completed pre-proposal form to the Merck SEEDS Program at daniel.huang@merck.com by May 15, 2020.

4. What is the difference between a pre-proposal and a full proposal?

A pre-proposal is a brief 1-2 pages form outlining a non-confidential summary of your proposal that will be reviewed by the MRL DB SEEDS SRC. The pre-proposal will provide sufficient information for a pre-review of your proposal. Therefore, if the pre-proposal is rejected, requestors will not have spent a significant amount of time developing the proposal. If the pre-proposal is found to be of interest, the SRC will request a full proposal for further review. The SRC also may potentially contact the requestor for additional information and/or to co-develop the full proposal with the requestor. Full proposals may or may not be accepted for approval and therefore are not guaranteed funding. As part of the full proposal, there may be a request from the MRL DB SEEDS SRC for an optional onsite presentation at the MRL campus in South San Francisco, CA.

5. Who should I contact if I need information regarding the MRL DB SEEDS program?

Please contact the Merck SEEDS Program at daniel.huang@merck.com

6. Will Merck contribute any capabilities to the project?

Access to specific capabilities will be discussed and agreed upon for accepted proposals as part of the discussions and workplan development process after acceptance of the pre-proposal.

7. Will Merck contribute any funding to the project?

Funding for approved collaborative 1-year pilot research projects is anticipated (up to \$125,000 in direct costs plus institutional indirect costs) in order to facilitate execution of the agreed upon specific aims of the project in the principal investigator's laboratory or at a third-party establishment. The amount of funding will be project-specific and will be discussed and agreed upon for accepted proposals as part of the discussions and work plan development process after acceptance of the pre-proposal. Our goal is to enable the specific aims of the selected proposals.

8. How should I manage and communicate confidential information?

Only non-confidential information should be included in the pre-proposal form. If your pre-proposal is selected to develop a full proposal requiring disclosure of confidential information, please contact the Merck SEEDS Program at daniel.huang@merck.com so that a Confidential Disclosure Agreement (CDA) can be put in place to protect any confidential information.

Review & Decision

9. Who reviews the applications?

A Scientific Review Committee (SRC) comprised of Merck Research Laboratories Scientists will review all proposals.

10. What does Merck expect from investigators submitting a pre-proposal?

The MRL DB SEEDS program funds proposals of scientific interest that can be conducted professionally and within the agreed timeline. Our expectations: 1) to receive a well-written pre-proposal that is scientifically relevant and concise; 2) that investigators demonstrate the ability to conduct a study within the agreed timelines; 3) that, if approved, investigators agree to provide quarterly status updates and a final report of manuscript quality; 4) that part or all of the results generated during the collaboration are disseminated in peer-reviewed publications.

11. What can investigators expect from Merck?

Prompt and courteous response to submitted pre-proposals or full proposals; 2) thorough scientific review of the pre-proposal and proposal; 3) timely decision on acceptance or rejection; 4) confidentiality of information under a Confidential Disclosure Agreement (CDA) if requested by applicant.

12. What scientific points are considered when assessing a submitted protocol?

The following scientific points are considered: 1) the study is aligned with the published Active RFP statements; 2) the specific aims answer the scientific/medical questions with a well-organized study plan 3) a data analysis plan is included with the full proposal and work plan.

13. If there are questions regarding the pre-proposal, will I have a chance to address them prior to a final decision being made?

Yes. If your pre-proposal is not rejected and questions arise or clarifications are needed, you have the option of interacting with the MRL DB SEEDS SRC before a full proposal and work plan are completed.

Contract Negotiations and Terms

14. How much will my lab be awarded if my full proposal is selected for collaboration?

After a sponsored research agreement is executed between Merck and the academic institution, in accordance with standard practices and terms, Merck will fund up to \$125,000 USD in direct costs for a 1-year pilot program plus institutional indirect costs.

15. What are the terms of the sponsored research agreement between Merck and the academic institution if my full proposal is selected for funding?

Once your full proposal is selected for contract negotiation and funding, a Merck Discovery Transactions Manager will contact the academic institution's Technology Transfer Office to negotiate a sponsored research agreement in accordance with established and reasonable practices and terms. Financial and/or reagent support of a full proposal is contingent upon execution of a contract between Merck and the academic institution.