Project proposal with Chemical Biology Consortium Sweden

Instructions: Project proposals are uploaded directly as a **pdf file** into Anubis in the open call for larger CBCS project support. All material is considered confidential, and access is restricted to a limited group of CBCS Project Review Committee members and CBCS personnel under conditions of confidentiality, solely for the purpose of evaluating the proposed research.

The scope of the collaborative CBCS projects varies significantly and the different project types require different competencies from CBCS. To ensure that we can deliver support to prioritized projects, we categorize the project proposals as either of the types 1-5 below.

**(1) Assay Development project**

An example may include assay design, plate formatting, and assay optimization. This project type is applicable when:

* no suitable compounds are available for biological studies and an assay that meets the general screening requirements is not yet ready
* compounds are available but need optimization for biological/preclinical studies and an assay that meets the general optimization requirements is not yet ready

For assay development projects approved by PRC and that run successfully according to a pre-agreed project plan between CBCS and the PI, the following screening campaign (project type 2) or chemistry activities (project type 5) will not require a new PRC proposal.

**(2) Screening project**

A typical example includes assay transfer efforts followed by the completion of a screening campaign, including hit confirmation and the first follow-up studies to characterize the value of identified hits. This activity can also include virtual screening campaigns based on primary screening data or other ligand-based virtual screening approaches, structure-based screening, as well as fragment-based screening techniques. For studies further investigating the identified hits including the synthesis of hits and new analogs, or establishment of structure-activity relationship a new PRC proposal will be required. This project type is applicable when:

* no suitable compounds are available for the described biological studies and an assay that meets general screening requirements as listed in the technical feasibility section is available
* a crystal structure of the target protein exists and there are no suitable compounds for the described biological studies
* no suitable compounds are available for the described biological studies but ligands for the protein target are known

If the general screening requirements are not met, you should also apply for an assay development project (project type 1).

**(3) Target identification/mode of action project**

This type of project typically follows a phenotypic screening campaign, and the main goal is to understand the molecular targets or mode of action of a compound or hit series. Techniques used for these projects are often multidisciplinary and can include Cell Painting, CRISPR screening, and proteomics-based approaches. This type of project is applicable when:

* a hit compound has been sufficiently validated, e.g. demonstrates efficacy in dose-response studies, and is not ruled out counter screens
* the compound is sufficiently cell penetrable for downstream studies
* in the ideal scenario an inactive close analogue of the hit compound has been identified

In some cases, it may be desirable to establish a structure-activity relationship for the series of compounds before the identification of the target/MOA. Choose an Enabling Chemistry (type 5 project) as well.

**(4) Compound or disease profiling project**

This type of project includes the profiling of disease models against libraries of compounds in functional precision medicine studies, as well as Cell Painting studies. This type of project is applicable when:

* Characterized disease models exist
* Relevant compound libraries exist

If the general optimization/SAR requirements are not met, you should also apply for an assay development project (project type 1).

**(5) Enabling chemistry project**

A typical example includes optimization activities post a screening campaign or otherwise identified small molecule modulators. More specifically, the request to optimize or modify compounds to suit the needs of the investigator may require activities such as structure-activity relationship (SAR) studies, *in silico* and/or *in vitro* physicochemical or pharmacokinetic characterization, and the various *in vitro* pharmaceutical profiling tests available. This can also include in silico hit expansion and lead optimization studies. This project type is applicable when:

* no suitable compounds are available for the described biological or preclinical studies
* an assay that meets the general optimization/SAR requirements as listed in the technical feasibility section is available
* if desired, data for in silico hit expansion can be delivered

If the general optimization/SAR requirements are not met, you should also apply for an assay development project (project type 1).

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| --- | --- |
| Date of Submission | Click here to enter a date. |
| Principal Investigator |       |
| Primary Affiliation |        |
| Application for project type (1-5) |       |

Title of proposal

Abstract (max 750 characters)

Background and expected scientific impact (please be as concise as possible, max 3 pages)

(1) What scientific need does the proposed project address?

Click here to enter text.

(2) Concisely describe what makes your approach unique. Briefly explain the underlying biology of the proposed research and what the expected outcome of the collaboration with CBCS is. Include references.

Click here to enter text.

(3) Describe the broader impact of the proposed study (biological/chemical novelty and applications of potential discoveries) and include any emerging data supporting this. Add relevant literature references, figures, tables and define abbreviations.

Click here to enter text.

(4) Are small molecule tools already available for the current purpose? Ensure you have made a detailed search. Add relevant literature references.

Click here to enter text.

(5) Describe how new or optimized compounds can be used to increase the basic understanding of the biological system and why existing compounds, when available, cannot be used for this research purpose. (Note: This section may not be relevant for functional precision medicine and Cell Painting projects).

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(6) If the project concerns the study of a specific target or pathway for which there are currently no small molecule tools available, has this target or pathway been previously modulated by other means than small molecules (e.g. genetic methods)?

Click here to enter text.

 (7) Are there already disease models in place for functional precision medicine studies or Cell Painting projects? Please describe their disease relevance and characterization.

Click here to enter text.

(8) Does your project require an ethical permit, an addendum to the existing ethical permit, or a material transfer agreement?

Click here to enter text.

**Technical description and feasibility (max 3 pages)**

Most chemical biology projects are based on an assay (a primary screening assay, a SAR driving assay, or an otherwise needed method) used to initially assess the value of provided small molecules. Information on the development and current status of this assay and planned follow-up activities for the project is needed to estimate the resources required to carry out and publish the proposed work. For chemistry proposals including SAR studies, the assay must have a dynamic range, *i.e.* is sensitive enough, to rank small molecules with potencies of different orders of magnitude.

**Questions for project types 1-4.**

*Assay Development, Screening, Target ID/MoA, or Compound/disease profiling projects.*

(9) Give a detailed technical description of the assay and outline the successive steps. Describe the format of the assay (96- or 384-well plate format or another non-plate-based format). Include information on available positive and negative controls and describe their biological relevance.

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(10) Do you have a suggestion on what compound library/libraries to screen?

Click here to enter text.

(11) List the availability, source (in-house production or commercial), and estimated costs of the reagents needed to perform a screening campaign of the number of compounds stated in *question (10).*

Click here to enter text.

(12) Show all current experimental data illustrating the performance of the assay: relevant controls, Z’ factor (for a screen project Z’>0.5 is desirable), signal to background ratio, DMSO tolerance, reagent stability, and plate edge effects.[[1]](#footnote-1) If your assay is at a stage where this is not applicable please explain what steps are lacking. For functional precision medicine assays characterization of disease relevance or plans for these studies are necessary.

Click here to enter text.

(13) Describe the availability and current status (up and running/under construction/at the planning stage) of an appropriate counter assay[[2]](#footnote-2) and an assay with an orthogonal readout.[[3]](#footnote-3)

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(14) Describe the availability and status of additional secondary assays such as selectivity assays, cellular assays, and in vivo models (if applicable to your project).

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(15) If in silico studies like virtual screening are planned describe steps and available data (e.g. crystal structure).

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**Questions for project type 5**

*Enabling chemistry (must include a description of the SAR-driven assay)*

(16) Describe the chemical series including identification, validation studies, and intended sites for modification.

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(17) Give a detailed technical description of the intended SAR driving assay or alternative method for compound testing. Outline the successive steps, and describe the assay format. Include information on available controls/reference compounds and describe their biological relevance.

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(18) Present experimental data with the intended reference compound demonstrating a dose-response experiment (n=3 with a minimum of 7 points) tested at a minimum of two independent occasions.

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(19) Have several compounds with different potencies been tested in the SAR driving assay?

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(20) Suggest secondary assays such as selectivity assays, cellular assays, and *in vivo* models (if applicable to your project) and describe the current status (up and running/under construction/at the planning stage). For assays not available in your lab, please describe plans for accessing them (via other research infrastructures or else).

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(21) Describe any available plans (if applicable) for pharmaceutical property profiling?

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(22) If in silico studies are planned describe steps and available data (eg crystal structure).

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**Project plan (max 2 pages)**

(23) What are the short and long-term goals of the proposed project?

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(24) Please consult CBCS personnel to provide information on the proposed research project plan by listing activities and potential milestones in the table below (Table 1). Add all activities relevant to reaching publication. For each activity, disclose the tentative time required, which aspects of the project require input/resources from CBCS, and the current availability of different types of resources (human, financial, and instrumentation). All technical/scientific details relating to each activity and milestone should be provided in the section on technical feasibility (see above).

**Table 1. Summary of all project activities to reach publication**

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| --- | --- | --- | --- |
| Project activity*E.g.,* assay development, assay transfer, assay optimization, assay validation, screening, hit confirmation, enabling chemistry, efficacy models, in vivo studies, *etc.* | Time (months)a | Responsibleb | Resourcesc |
| **Human***(e.g.,* postdoc or Ph.D. student) | **Financial**(Secured or unsecured) | **Instrument**(Available in-house, yes or no) |
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| (a) Estimated time for a full-time employee to complete these activities; (b) Indicate who will be primarily responsible for resourcing the activity (CBCS, PI, co-PI, CRO, etc.); (c) Please specify PI resources as human: *e.g.* postdoc or Ph.D. student/financial: secured or unsecured/instrument: available in-house yes or no. |

(25) Propose at least one stop/go decision point relating to any uncertainties concerning the technical feasibility as described above.

Click here to enter text.

(26) Have you contacted CBCS personnel and discussed the proposal and project plan in detail (required for submission)? Specify CBCS node and person.

Click here to enter text.

**Publication strategy (max 1 page)**

(27) Chemical biology projects are complex and often require significant validation steps including multiple model systems and detailed mechanism of action studies. Please detail the steps to gather this information for your project to ensure the identification of a robust small-molecule tool. This includes a publication strategy and potential intellectual property interests if applicable. Suggest a tentative journal of publication for a successful project and disclose which aspects of a draft manuscript that require input/resources from CBCS and comment on the importance of these efforts. The publication plan will often determine the requirements for validation of tool compounds, eg if animal models are necessary.

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# Additional Comments

(Please enter any additional comments you see fit to clarify your proposal)

1. If you are not familiar with these terms, please see e.g. the Assay guidelines manual [Internet], available from: https://www.ncbi.nlm.nih.gov/books/NBK53196/ (Sittampalam GS, Coussens NP, Brimacombe K, et al., editors. Bethesda (MD): Eli Lilly & Company and the National Center for Advancing Translational Sciences; 2004-), or contact CBCS personnel for assistance. [↑](#footnote-ref-1)
2. The purpose of a counter assay is to identify compounds that interfere with the read-out in the primary assay by *e.g.* auto-fluorescence. A counter assay can also be used to identify compounds with undesirable properties such as cytotoxicity. [↑](#footnote-ref-2)
3. An orthogonal assay is generally performed using a different read-out than that applied in the primary assay to further eliminate false positive compounds from the screen. [↑](#footnote-ref-3)