Guidance for applicants to the MRC/UCB Antibody Discovery Initiative

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Scope of the Initiative

The MRC/UCB antibody initiative aims to support academic researchers seeking to develop antibody-based therapeutic approaches by enabling generation of novel antibodies suitable for use in models of disease. A clear line-of-sight to therapeutic use will be required to secure funding.

Antibodies will be generated by providing access to UCB's antibody discovery platform (see below). Following production of the antibodies, MRC will provide a modest amount of funding to support a (set of) proof-of-concept experiment(s) to enable the applicants to generate data that will enable them to seek follow-on funding through the MRC's Development Pathway Funding Scheme, or elsewhere.

Background

UCB has developed a novel platform technology capable of sampling the immune repertoire through culturing B-cell pools, identifying wells containing binders, further characterising binders through carefully selected functional assays and then identifying antigen specific B-cells within wells of interest. Single cell PCR and gene cloning is then used to generate constructs for the expression of recombinant antibodies of the desired specificity. The technology is suited to identifying rare functional antibodies within an immune repertoire and suitable for humanisation to obtain therapeutic antibodies or for surrogate anti-rodent antibodies as tools. Several of the early steps in the process have been automated to increase the capacity, the speed and the consistency of the process. More details and background on the automated system can be viewed here: https://www.youtube.com/watch?v=QfShgQ_x_vA

Careful choice of immunogens is necessary to generate a robust immune response to the desired antigen/epitope. Discriminatory functional assays, ideally compatible with the B-cell supernatant, are necessary to identify functional antibodies of the required potency.

Funding Available

The MRC will provide funding to support up to 3-5 projects per year with the competition running once per year, initially for a 5 year period. As capacity is limited, projects will be prioritised for funding and for timeslots within the facility. Accordingly, the timeframe for commencement of the studies conducted within the RO using the discovered antibodies will vary although the expectation is around 9-12 months post award. If further assay development is required this timeframe could be extended.

UCB may offer to fund a project in its entirety if, based on the application, it considers that route to be the most appropriate funding mechanism for that individual study. In such cases, these will be taken forward through direct collaboration with the company without any further MRC involvement. Applicants who do not wish to accept this offer may continue to seek MRC support through the initiative.

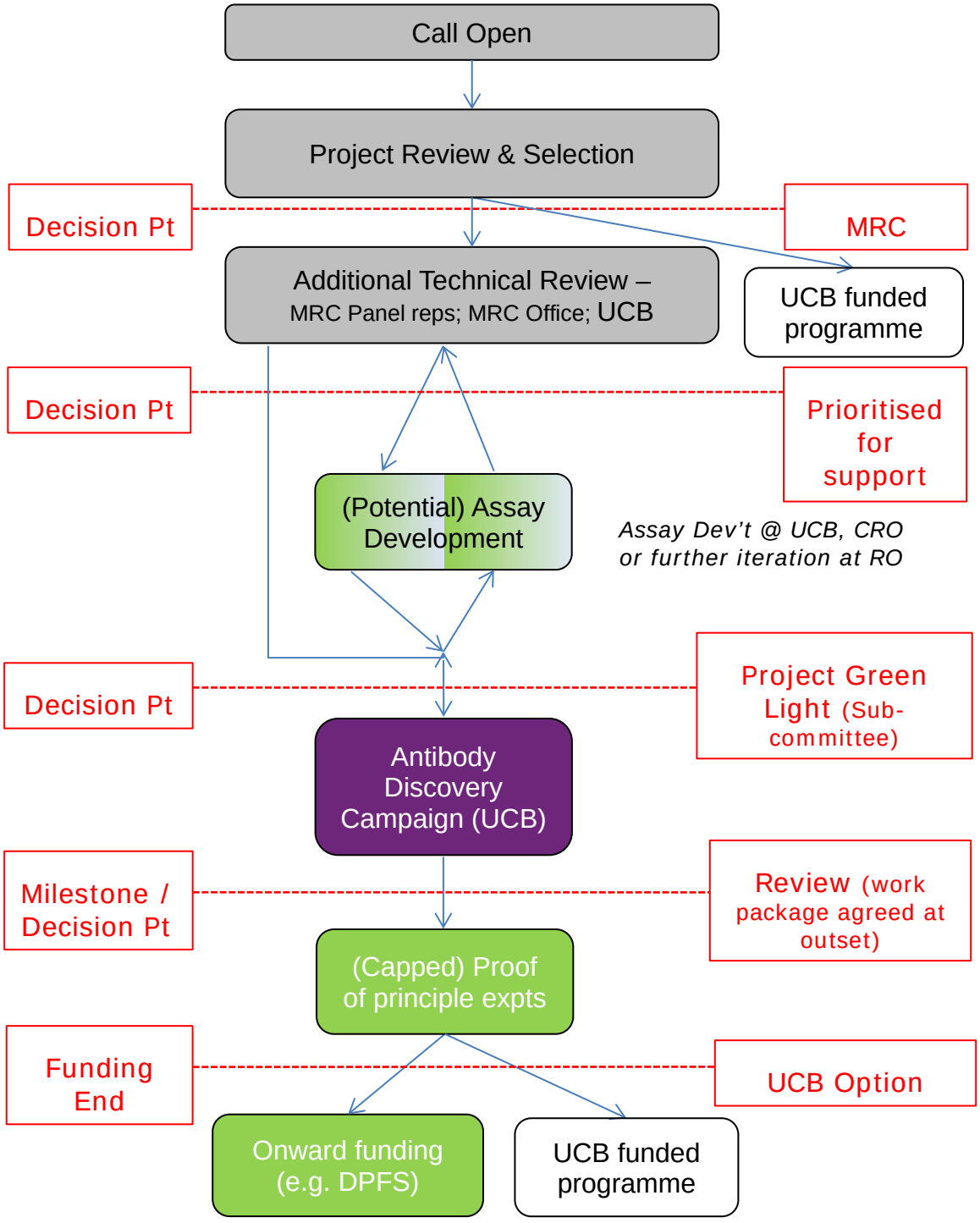
Post-award Scheduling

The antibody discovery and production activities will be conducted at the UCB facility in Slough, UK with costs met by MRC; applicants will not be able to request costs associated with this component of the project. Applicants can request costs from MRC to conduct proof of concept experiments with the generated antibodies. Costs will be limited and the studies will need to be delivered and reported on within a 6 month window. The MRC Panel, in consultation with technical input from UCB, may agree to provide funding

to support assay optimisation prior to transfer to the UCB antibody platform. If this work is conducted within the RO, UCB will nominate a contact to provide advice and enable transition to the UCB facility.

Note. The less well developed the immunogen and/or assays are and the more work that is required prior to transfer to the UCB antibody platform, the less competitive the proposal will be.

Application Process and Assessment



Applications will be assessed and prioritised for funding by the MRC, via a bespoke expert Panel including members of MRC's DPFS Panel, MRC's Research Boards and external experts, with UCB only providing guidance to confirm that projects are technically feasible, that there are no 3rd party agreements that would prevent UCB from undertaking the project, and that no equivalent antibody exists within the UCB pipeline or commercially.

The Panel will consider all applications against the criteria outlined below. The Panel will, independent of UCB input, determine the applications that merit support and rank them by order of priority.

Need

- Does the identified need exist?
- Would meeting this need significantly reduce disease burden and/or provide a valuable commercial opportunity and/or alleviate an important development bottleneck?
- If the need is not significant now, will it become so in the future?
- Is the need met or unmet? If unmet, will it likely be unmet at the time that the proposed solution is in place?
- Has the applicant identified the key competing solutions and their status or are you aware of other similar or complementary research underway elsewhere?
- Has the applicant identified the key competitive advantages of their proposed solution?
- How likely is it that the proposed solution, if achieved, would be widely adopted?

Rationale

- Is there a good medical/scientific rationale for the project?
- Is there a reasonable body of evidence to support the proposed rationale?

Deliverability

- Is the approach technically feasible and is there a reasonable prospect of generating a functional antibody to the proposed target
- If successful, will the proposal make a significant contribution demonstrating proof of principle that the approach could meet the identified need?
- If successful, will it achieve an endpoint that has a reasonable chance of attracting any required additional investment?
- Are upstream or downstream development hurdles surmountable?

If modifications to the approach or provision of additional data would potentially make a re-application worthy of support, declined applications may receive 'Positive Feedback'.

Please note that the decision of the Panel is final and will not be open to appeal and the MRC reserves the right to amend the application process.

Applications will be supported in order of priority, taking into account the view of a subsequent technical review sub-Panel. Applicants may be required to provide further information in advance of this Panel, and to potentially join by telephone.

Intellectual Property

All projects funded under this initiative will be collaborative studies between academic researchers and UCB. The investigators will work under a collaborative research agreement, jointly signed by the HEI and UCB, based closely on the Lambert Agreement for preclinical studies. Release of funds will be contingent on receipt of the signed agreement by MRC.

UCB will have an option and first right to negotiate for an exclusive licence to any arising project intellectual property owned by the HEI.

Requisite Assays and Minimum Requirements

In order to apply for funding, an immunogen must either be available (through the investigator's work or commercially) or there must be a route to immunogen production (see below). Assays suitable for antibody selection, specifically antigen binding and ideally also functional activity, should also either be developed or there should be clear ideas of how they can be developed.

Immunogen

Protein and peptide immunogens can both be appropriate depending on the requirement. Peptides are conjugated to appropriate carriers (e.g. Ova, KLH, BSA). Protein antigens will need to be of a certain purity (>90% by SDS-PAGE), have low levels of aggregate (<5%) and must have low endotoxin level (ideally <1EU/mg). For membrane proteins another option is to immunise with syngeneic cells expressing the protein in the cell membrane (UCB has experience and can offer advice on this option).

The species from which the immunogen is derived is an important consideration. Normally rabbits (or rodents) will be used to generate antibodies, so information on the percentage identity of the target antibody, between the immunised and 'target' species (e.g.rabbit:human, mouse:human), and between the human:cyno proteins, must be included. The requirement for cross-species reactivity of the selected antibody should be noted (eg mouse / cyno / human) in the application form.

Antigen binding Assay

The antigen binding assay is used to identify wells containing B-cells secreting antigen-specific antibodies; supernatant from the identified wells can then be further interrogated to identify functional antibodies. The antigen binding assay will typically comprise an homogenous, fluorescence-based binding assay, requiring biotinylated soluble purified protein (or peptide) coated onto a streptavidin/superavidin bead (approx. 1mg will support a typical screening campaign but it is dependent on assay sensitivity). Alternatively, a cell line or transiently transfected cell expressing the target of interest can be used. Other capture systems (eg Fc capture) or alternative binding assays formats can be used, e.g. ELISA or FACS.

It will be important to demonstrate that the antibodies bind to natively produced protein, or at least to known active protein, rather than just recombinant tagged forms. The use of such a secondary binding assay is encouraged.

Functional Activity Assay

An *in vitro* assay of functional activity is required to identify wells containing secreted antibodies with the particular desired functionality. It is advisable to consider more than one type of functional assay and whether an assay cascade is appropriate. The nature of the functional assay depends very much on the biology of the interaction being modified and cannot be generic. UCB can offer advice on assay development at technical review.

The precise approach will depend on whether the assay is compatible with B-cell supernatant, transient supernatant (HEK-293-conditioned media) or purified antibody samples.

- If compatible with B-cell supernatant, the assay will be performed at UCB – expectation is to screen ~ 10 x 96-well master plates (1000 samples). Expect ≤100ng/ml specific mAb per culture well. B-cells will be isolated from positive wells, variable region genes will be cloned and recombinant antibody generated for further characterisation.
- If not compatible with the B-cell supernatant but compatible with transient culture supernatant following recombinant expression, the assay can be performed either at UCB or at the academic lab. Numbers are limited by the requirement to isolate B-cells, clone genes and express recombinantly at small scale – 20-100 samples. Expect ~ 10-100µg/ml mAb.
- If the assay requires purified material, it can be performed either at UCB or at the academic lab. Numbers are limited by small-scale purification requirement - 10-50 samples, at ~ 100µg/ml.

If a functional assay cannot be used, there may be the option of using an epitope binning/cross-blocking approach to identify a small panel of antibodies to different epitopes on the protein surface. However, this is an inefficient, resource rich and time consuming process and would not be considered to be a preferred option.

How to apply

Please note that sharing information and knowledge about MRC's research grants is central to the MRC's mission. The following details from successful applications will be made publically available via the MRC or Gateway to Research websites:

- Project Title
- Technical Summary
- Lay summary
- Impact Summary
- Grant holders
- Host institution
- Value and duration of award

To submit an application, the applicant must complete the Case for Support Form and submit as a PDF, along with all other documents via the Research Council's Joint electronic Submission (Je-S) System.

Je-S selections for applications:

- Council: **MRC**.
- Document Type: **Standard Proposal.**
- Scheme: **Research Grant**
- Call/Type/Mode: **MRC UCB Antibody Discovery Initiative Oct 2018**

Completing the Application

The proposal form

The proposal form provides a summary of the whole project. Some of the sections overlap with mandatory attachments, with the attachments providing the additional detail required for the decision-making purposes.
Guidance is available through the Je-S help text provided for each section

Case for Support

A pdf under document type Case for Support should be uploaded using 'The MRC/UCB Antibody Discovery Initiative Case for Support Form'. Guidance on how to complete this form can be found below:

Section 1: Project Summary

1.1 Title:
Please provide a concise title for your proposal.

1.2 Technical Summary:
Please provide a summary of the need you are seeking to address, your proposed solution, the rationale for why your proposed solution is likely to meet the targeted need and your development plan. Both the title and technical summary should be non-confidential, as they will be used, if you are successful at the outline stage, in project review.

1.3 Project Duration and Cost:
Please outline the proposed duration of the proof of concept studies with the discovered antibodies to be conducted at the RO and detail the associated requested costs (see Requisite Assays and Minimum Requirements *see page 2).*

Section 2: Investigator Details
See MRC Applicant's Handbook for definitions and further information

Section 3: Host Institute Technology Transfer Office Contact
The MRC would normally expect the host institute TTO to assist in the preparation of application and expects the TTO to play an active role in maintaining and exploiting intellectual property generated by successful applications. Accordingly, the MRC requests that the contact details for a relevant member of the R.O.'s TTO team be provided.

Section 4: Need and Approach

Please refer to the application assessment criteria outlined above. The table in Section 4.6 should be completed to show the properties of the desired antibody-based therapy, how it would be used clinically etc; an example is shown below.

4.6 Therapeutic Product Profile	
Target name	TNF
Target type ***Eg. soluble cytokine, cell surface protein***	Soluble cytokine and cell surface molecule. Inflammatory mediator
Mechanism of Action ***Eg. agonist, antagonist***	Antagonism – blocking TNF signalling by preventing interaction with receptor
Proposed therapeutic use ***Eg. disease, subpopulation etc***	TNF mediated inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, Crohn's disease
Route of administration and dosing frequency ***Eg. IV/sub-cut ; daily/weekly; acute/chronic***	Sub-cutaneous administration; 4-week dosing interval; chronic use

Note that applicants are encouraged to provide up to 2 pages of supplementary data (Supporting data attachment) to support their application. This can be used to explain rationale underpinning the approach of an antibody-based therapeutic.

Section 5: Project Status and Plan

5.1 What is the current status of the project?

Outline the current status of the project, how it has progressed to date and, if applicable, what attempts have been made to generate antibodies previously. Note if any external organisations have been involved.

Questions 5.2 - 5.5

Immunogen and assays will be discussed in detail during the technical review stage but it is important to include an outline of the status of the assays available / envisaged. For further information see Requisite Assays and Minimum Requirements *(pages 5-6). An example of completed Section 5.2 is shown below.*

5.2 Antibody Generation (for pre-clinical PoC studies)	
Desired mAb characteristics ***Eg species, affinity, epitope***	Rabbit anti human antibody cross-reacting with primate (cyno) TNF. Sub nM affinity - Desirable. Any epitope resulting in blocking.
Immunogen sequence identity ***mouse:human*** ***rabbit:human*** ***mouse:rabbit*** ***human:cyno***	Mouse:human 79% Rabbit human 72% Rabbit:mouse 78% Human:cyno 97%

5.6 Describe the key proof of principle experiment with the generated antibodies that will enable further funding to be applied for.

Outline what studies will be performed with the discovered antibody and their significance in terms of demonstrating the feasibility and impact of your approach. Note that studies, particularly those involving animals, will need to be appropriately designed and powered.

On completion of the screening and selection of a lead antibody, typically 250 – 500 mg of antibody will be prepared for further testing. Where animal studies are involved, applicants must provide details of proposed dosing and give confidence that ethical approval could be obtained.

5.7 Identify and justify the skills and resources needed to deliver the immediate and downstream plan.
Note that justification for requested costs is provided in the Justification of Resource.

Section 6: Downstream Development
6.1 Outline the subsequent application to MRC (or other funders)
to further develop the antibody as a therapy. Include two-three key progression milestones (one being the project end). For each milestone set out the success criteria that will be used to ascertain whether the milestone has been met.

Milestone success criteria should be SMART (ie quantifiable) and detail any Go/No go criteria (failure to meet which will result in early termination of the project). For all projects, it is advisable to structure the project so that the critical question(s) are addressed as early as possible in the plan.

For the final milestone, the criteria should reflect outcomes that would represent successful prosecution of the project and be reflective of the data that will enable onward prosecution of exploitation of the project. Analysis only, planning or write-up focused milestones will not be considered acceptable.

Section 7: Intellectual Property (IP)
Note that applicants must have freedom to operate and exploitation must not be restricted by any existing third party agreements. To participate in the initiative, applicants will need to enter into an agreement based closely on the Lambert model agreements for preclinical studies with UCB, committing them to giving UCB first right to negotiate for any arising IP.

Other Attachments:

*Select **Add New Attachment:** Applicants will need to submit, as attachments via JeS, pdf versions of:*

- *An optional but advised document of supporting figures and data tables (under document type Supporting Data - no more than **2 x A4 pages** Arial 11 point);*
- *A signed letter of support from the TTO, or equivalent, indicating the role they have played in developing the application and they will play in supporting the project on an on-going basis (under document type 'Letter of Support' - no more than **2 x A4 pages** Arial 11 point);*
- *Justification for Resources, please refer to the Je-S help pages for further information and guidance on Justification for Resources requirements (under document type 'Justification for Resources' - no more than **2 x A4 pages** Arial 11 point). Due to the nature of this call, it is anticipated that requested PI time will be limited, with no PI time required during the execution of the work at UCB.*
- *A CV for the Principal Investigator, any Co-Investigators and named individual research staff, please refer to the Applicants handbook for further information on CV requirements (under document type 'CV' - no more than **2 x A4 pages** Arial 11 point).*
- *A Publications list for the Principal Investigator, any Co-Investigators and Named individual research staff, please refer to the Applicants handbook for further information on publication requirements (under document type 'Publications' - no more than **1 x A4 pages** Arial 11 point)*