

# Guidance for applicants to the MRC/AZ Centre for Lead Discovery Initiative

## Contents

	<b>Page</b>
Scope of the Initiative .....	2
Background .....	2
Funding Available .....	2
Post-award Scheduling .....	3
Application Process and Assessment .....	4
Intellectual Property .....	5
Requisite Assays and Minimum Requirements .....	6
How to apply .....	9
Completing the Application Form .....	9

## Scope of the Initiative

The MRC/AZ Centre for Lead Discovery (CLD) aims to support academic researchers in discovering potential starting points for small molecule therapeutic approaches. Academic researchers will benefit from unprecedented access to over two million molecules in AstraZeneca's compound library, as well as its state-of-the-art high throughput screening facilities. A clear line-of-sight to therapeutic use will be required to secure funding.

The primary and secondary assays required for screening will need to be ready or near-ready for use and scalable; only limited funds for further assay development or refinement will be available. If suitable hits are identified, applicants will subsequently, be able to seek funding for hit-to-lead development from MRC by making an application through the MRC's Development Pathway Funding Scheme.

Outputs from the screening cascade will include all 'hits' statistical information on the hit rates from the screen and an associated data package on the 'hits' from up to 3 chemical series giving an indication of:

- Potency
- Selectivity (vs pre-agreed targets)
- Preliminary Structure Activity Relationship - SAR,
- Activity in a cellular assay
- Preliminary PK/DMPK

## Background

'Classical' development of new investigational medicinal products (IMPs) has been based on the manufacture of active chemical substances (drugs), and accounts for approximately 90% of the drugs available for treatment of medical conditions today. High throughput screening is a tool that has been used by big Pharma for decades to search for small molecule starting points for their internal R&D pipeline projects

The AstraZeneca-MRC UK Centre for Lead Discovery will form a unique cornerstone for academic and industrial drug discovery projects by supplying access to state-of-the-art high throughput screening (HTS) infrastructure. Access to advanced compound management, screening robotics and assay technology which do not exist in academia and will provide a valuable opportunity to the UK academics to instigate drug discovery projects.

AstraZeneca has carefully curated a collection of ~2 Million compounds within its corporate HTS collection. This full collection is available for screening within this scheme, if suitable assays are derived, providing the same opportunity for academic projects as for AstraZeneca's internal R&D projects, thereby maximising the chance of the academics identifying tractable hits which could be advanced into chemistry development programmes.

## Funding Available

The MRC will provide funding to support up to 5-10 projects per year with the competition initially running annually. As capacity is limited, projects will be prioritised for funding and for timeslots within the facility. If further assay development is required this may impact on the timeframe for HTS. All applications will be shared with AstraZeneca following the competitions closing date.

AstraZeneca may offer to fund a project, at this point in the process, in its entirety if, based on the application, it considers that route to be the most appropriate funding mechanism for an 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**

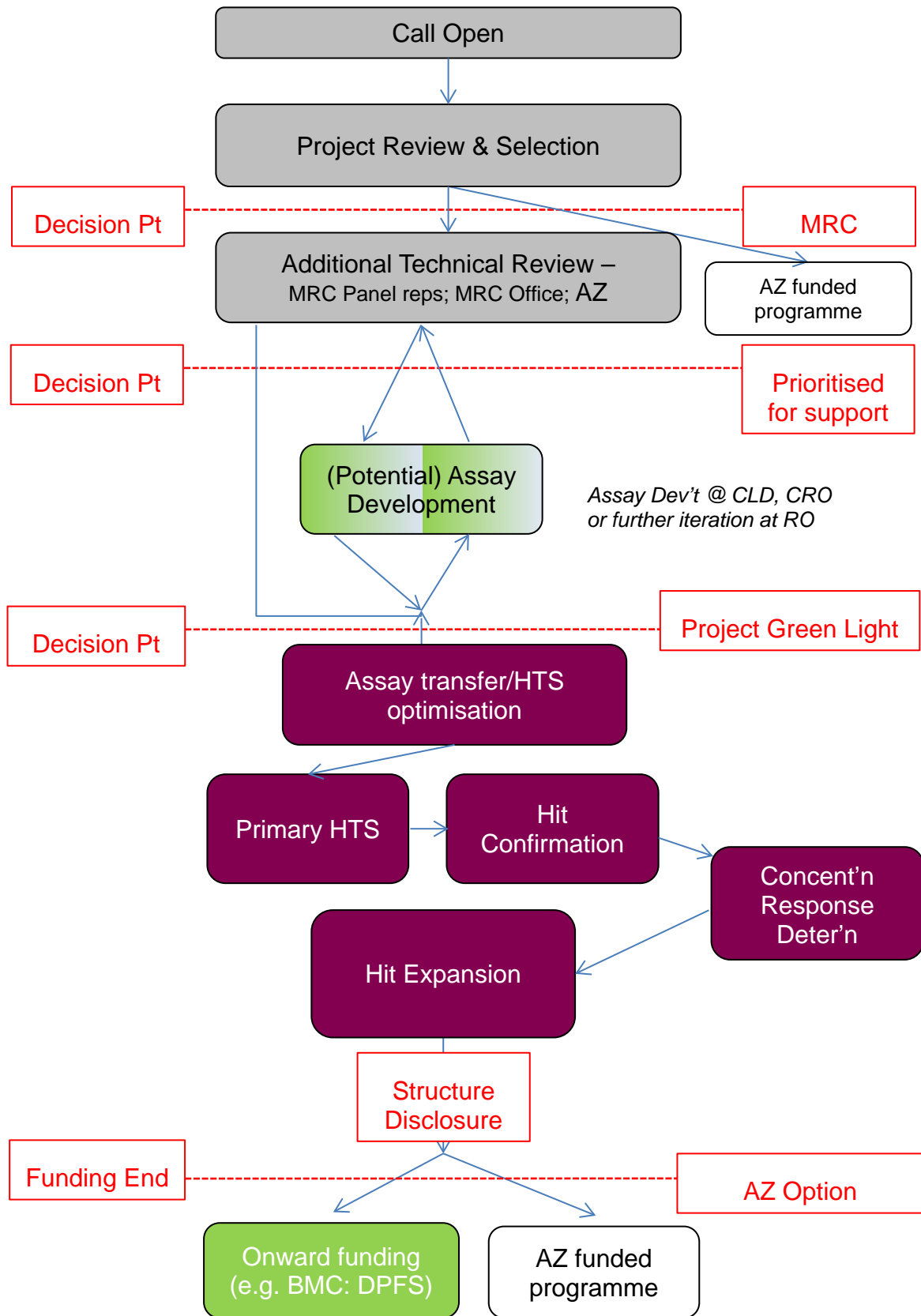
Assay transfer and high-throughput screening activities will be conducted at the AstraZeneca facility in Alderley Park (Cheshire), prior to the relocation to the Cambridge Biomedical Campus in 2019, with costs met by MRC; typically, applicants will not be able to request costs associated with this component of the project.

The MRC Panel, in consultation with technical input from AstraZeneca, may agree to provide funding to support assay optimisation prior to transfer to the CLD. If this work is conducted within the RO, AstraZeneca will nominate a contact to provide advice and enable transition into the CLD.

Limited costs from MRC may also be provided for re-synthesis of tool compounds arising from the screen, additional in-vitro selectivity data and preliminary in-vivo PK. Costs will be limited and the studies will need to be delivered and reported on within a 3 month window.

**Note that, the less well developed the assay, and the more work that is required prior to transfer to the CLD, the less competitive the proposal will be.**

# Application and Assessment Process



Applications will be assessed and prioritised for funding by the MRC with AZ providing guidance to confirm that projects are technically feasible, that there are no 3<sup>rd</sup> party agreements that would prevent AZ from undertaking the project and no equivalent HTS campaign has been conducted internally by AZ or as part of AZ's open innovation project.

An MRC Panel will consider all applications against the criteria outlined below. The Panel will, independent of AZ 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**

- 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, responsible for assessing what, if any assay optimisation work needs to be conducted prior to transfer to AZ. Applicants may be required to provide further information in advance of this sub-Panel, and to potentially join by telephone. AZ will provide a point of contact to applicants to enable efficient transfer to the Centre for Lead Discovery.

### **Intellectual Property**

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

AZ will have the first right to negotiate for an exclusive licence to any arising and relevant background IP. AZ can declare an interest (in writing) in exercising their option at any point in the project and up to 6 months after the project end. If AZ do not exercise their option or are unable to agree terms, any jointly generated IP will be assigned to the HEI at the relevant period with AZ signing away any claim over exploitation or profit.

## Requisite Assays and Minimum Requirements

In order to apply for funding, an assay suitable for high-throughput screening against the target of interest must be available (either through the investigators work or commercially) or at an advanced stage of development. Assays suitable for hit-confirmation, specificity and or key selectivity must have been developed or be in the process of development.

### Primary Screening Assay

The primary screening assay will need to be compatible to a 384 well plate format and will typically comprise an assay which fulfils the guidelines below. It is envisioned that where possible HTS campaigns will be conducted in 1536 well format

### Assay quality and reproducibility

Due to the large number of tests to be performed in high throughput screening there is a requirement for a high quality assay that is able to identify with a high degree of confidence compounds that are 'hits' at the target of interest. Prior to screen optimisation and automation development, all assays developed for single point screening should fulfil the following principles of acceptable criteria.

### Why is this important

Your HTS campaign will involve the single test of up to 2 million compounds. Imagine if you tested a compound twice, on day 1 a compound produced a result of 40% and on day 2 only 20%, if the cut-off for the assay was set at 30%, then on day 1 your compound would be determined as a hit, and on day 2 it would not be selected. This can impact in 2 ways,

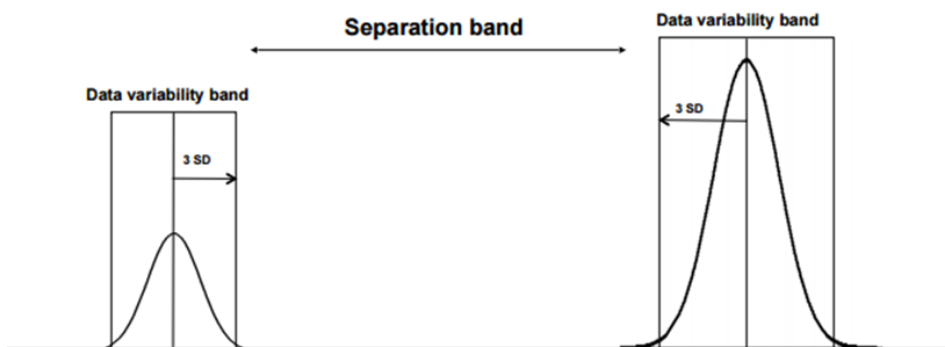
- 1) If this compound isn't active, then on day 1 it has been selected as a false positive, whilst this would ultimately be detected in confirmation studies, if the campaign has a high false positive hit rate, then you may end up with too many hits to efficiently run XC<sub>50</sub> confirmation assays on.
- 2) If this compound is active, then on day 2 it was not selected, and you end up with a false negative, its ability to be detected may be lost. This 'hit' may have ended up as the best starting point for a lead optimisation programme, but will now never be reported.

### DMSO Tolerability

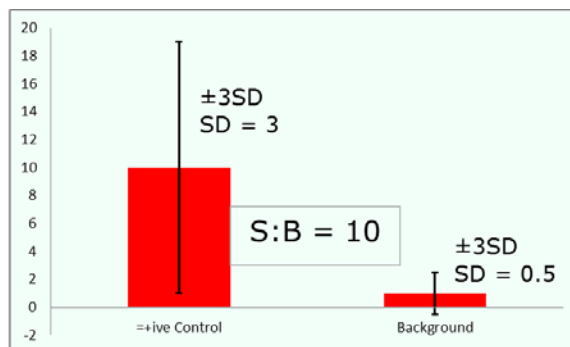
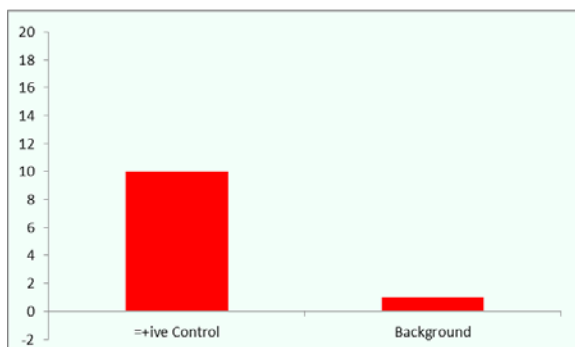
Test compounds are stored in 100% DMSO, so assays should be run in the absence of test compounds, in the presence of a range of DMSO concentrations, to ensure that the assays are compatible with a DMSO concentration  $\geq 10\%$ .

### Assay performance

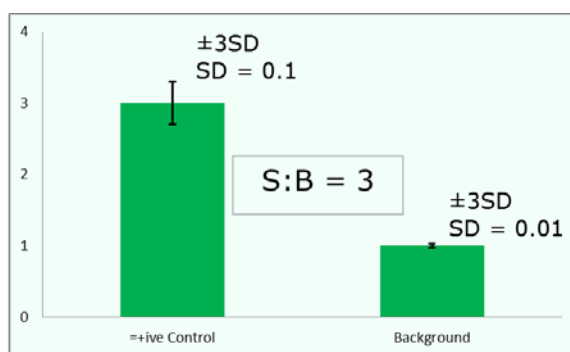
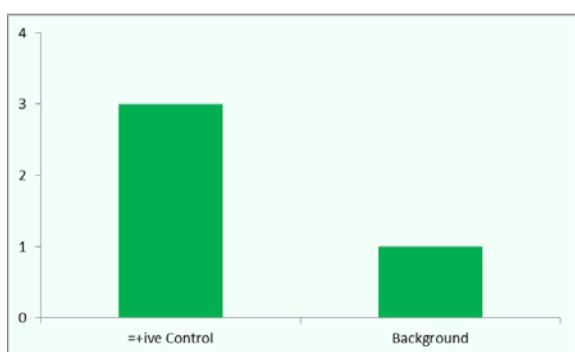
The signal to background (S:B) of an assay is the difference between the reading in the absence of a test compound and the reading obtained with a known control compound. Assays should target a S:B > 3. However the difference between the mean Signal and Mean background is not sufficient to confirm the quality of the assay and neither is an assay with a very large S:B.



Assuming that your response is normally distributed, if you run the assay lots of times there is a 99% probability that your result will be within 3 Standard Deviations of the mean, if there is a lot of variability in the background and control readings, then even a 10 fold S:B may result in a high probability of overlap. (see below)



If the variability is small then an assay even with a small S:B of 3 may be better (see below).



These statistical measures work well if the data is normally distributed and there are very few extreme outliers, however the purpose of an HTS is to discover outliers and mean and standard deviation can become an inaccurate measure.

So it is more come to determine 'Robust' measures based on the median and Robust Standard Deviations (RSD) which is less sensitive to the influence of outliers. A RSD is defined as the Median Absolute Deviation (MAD) \* 1.483. The MAD can be calculated by determining the median of individual well values minus the median of all well values.

Assay performance data should be generated across at least 10 plates, with a minimum of 16 wells each for max, mid, min controls. A Robust Z' should be calculated using the formula

$$RZ' = 1 - \frac{3 \times \text{Background RSD} + 3 \times \text{Positive control RSD}}{\text{Median positive Control} - \text{Median Background}}$$

The average result across at least 10 plates should be  $\geq 0.5$ , and <10% of all plates should have an RZ' less than 0.4

#### Pharmacology of Standard Compounds

If a tool compound exists that shows activity in the primary assay (this can be non-selective), then applicants should provide pXC<sub>50</sub> data from at least 3 separate experiments. Results from multiple tests should be  $\pm 0.3$  log units.

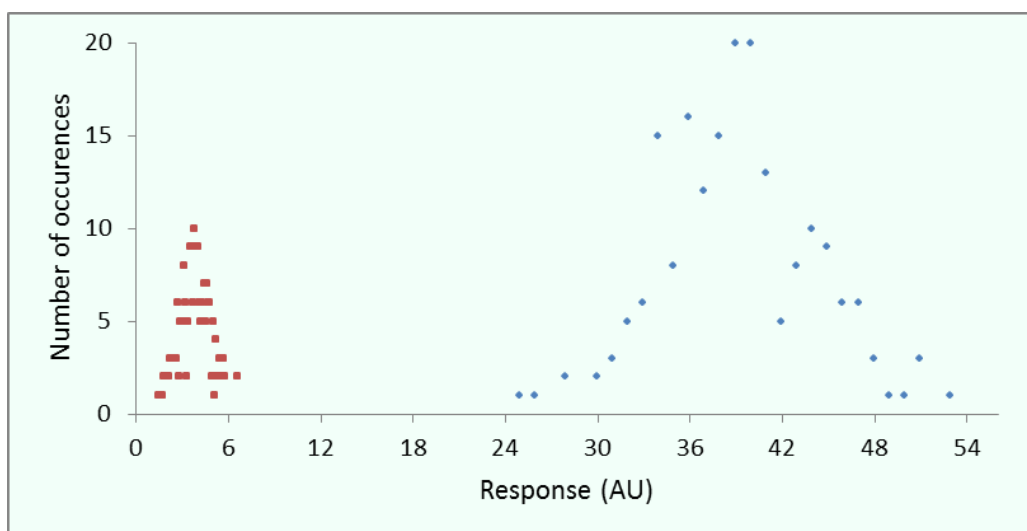
#### Secondary Assays

Secondary assays are used to confirm that 'hits' from the primary screening assays are valid eg not false positives and to determine key factors for onward development such as

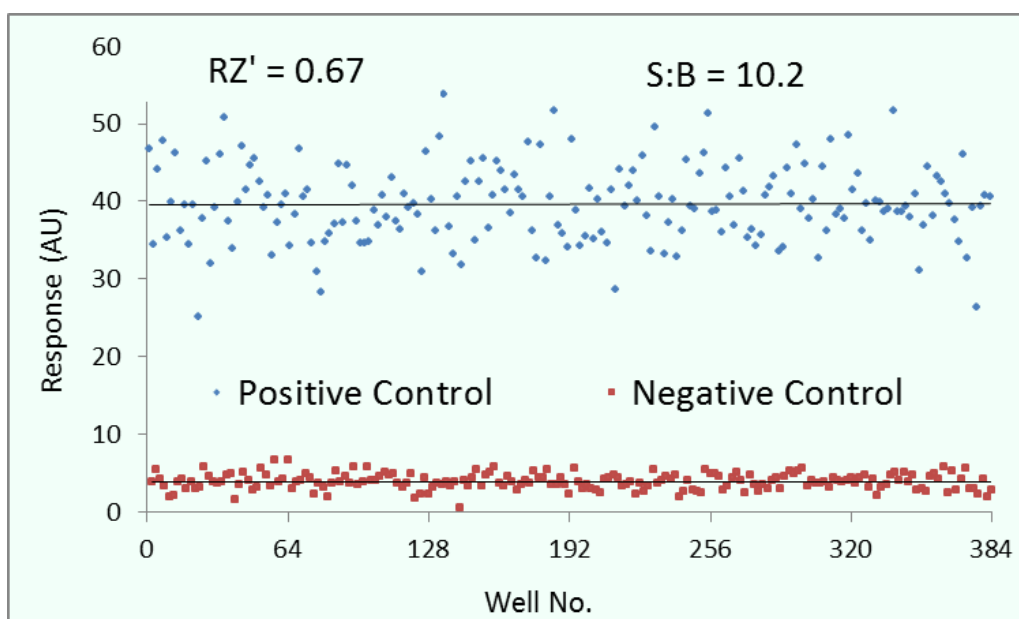
specificity and/or key selectivity relative to members of the same protein family, isoforms etc. The nature of the secondary assays will be specific to the target and should not be generic.

#### Supporting data

If available, assay performance data should be presented as a Robust Gaussian plot (see below)



and/or a scatter plot for the Z' factor measurement (see below)



#### Further Reading

NIH Centre for Clinical Excellence Guidance for Assay Development and HTS  
[http://hts.ku.edu/sites/hts.drupal.ku.edu/files/docs/NCGC\\_Assay\\_Guidance\\_Manual.pdf](http://hts.ku.edu/sites/hts.drupal.ku.edu/files/docs/NCGC_Assay_Guidance_Manual.pdf)

A Review of High Throughput screening for Drug discovery  
<http://www.combichemistry.com/articles/htscreening.pdf>



## 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. It will be the applicant's responsibility to ensure that no a priori information is contained in these sections which could affect the future exploitation

- 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 AZ Centre for Lead Discovery Oct 2018**

## Completing the Application Form

### *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/AZ Centre for Lead Discovery 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 detail the associated requested costs (see Funding Available and Post-award Scheduling see page 2 & 3). Assay transfer and high-throughput screening activities will be conducted at the AstraZeneca facility with costs met by MRC; typically, applicants will*

not be able to request costs associated with generation of HTS quality assay materials. Costs relating to post-screen activities, should not be included in the application.

## **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 the 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 therapeutic, how it would be used clinically etc; an example is shown below.

<b>4.6 Therapeutic Product Profile</b>	
<b>Target name</b>	Salt Inducible Kinase 2 (SIK2)
<b>Target type</b> <i>Eg. soluble cytokine, cell surface protein</i>	A serine/threonine kinase of the CAMKL family and related to AMPK.
<b>Mechanism of Action</b> <i>Eg. agonist, antagonist</i>	Selective and potent inhibitors of SIK2
<b>Proposed therapeutic use</b> <i>Eg. disease, subpopulation etc</i>	Prevention of tumour reoccurrence in Ovarian Cancer patients
<b>Route of administration and dosing frequency</b> <i>Eg. IV/sub-cut ; daily/weekly; acute/chronic</i>	Daily Oral administration, as single agent or adjunct to standard of care.

Note that applicants are encouraged to provide up to 2 pages of supplementary data (at the end of the form) 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 - 5.4**

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 (see page 7).

### **5.5 Identify and justify any resources requested by the academic research organisation. Indicate if any resources are not readily to hand?**

Note that justification for any requested costs should be provided in the Justification of Resource.

## **Section 6: Downstream Development**

### **6.1 Outline the subsequent application to MRC (or other funders)**

To further develop any hits. 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 on the [Lambert model agreements](#) for preclinical studies with AZ committing them to giving AZ 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 AZ.
- 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)