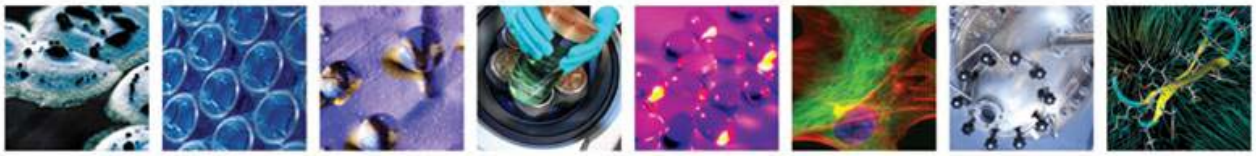

BRIC • BIOPROCESSING RESEARCH INDUSTRY CLUB

BIOPROCESSING RESEARCH INDUSTRY CLUB (BRIC) CALL FOR PROPOSALS FOR RESEARCH RELEVANT TO THE MANUFACTURE OF BIOLOGICAL MEDICINES

SUMMARY

The Bioprocessing Research Industry Club (BRIC) is a well-established, managed research programme funded by BBSRC, EPSRC and the biopharmaceutical industry, and has now entered a second phase (BRIC2). The biopharmaceutical industry already has annual sales of £61 billion ($101 billion), and seven of the top ten drugs are forecast to be of biological origin in 2016[1]. Research in many areas of bioscience and bioengineering could be relevant to this industry, e.g. biochemical engineering, protein expression, structural molecular biology, systems biology, synthetic biology, cell biology, biophysics and biochemistry.

In response to the recommendations of the BRIC Working Group Report and the BRIC1 Evaluation Report, BRIC stakeholders agreed to provide up to £10M (BBSRC £6M, EPSRC £3M, BRIC Industrial Members £1M), as part of BRIC2. Proposals to the BRIC programme for research relevant to the manufacturing of biological medicines are welcome.

It was anticipated that BRIC2 would support research projects through at least two funding calls (BRIC2/1 & 2/2) over five years. £3.7M was distributed in response to applications received to BRIC 2/1 and it is expected that, in this second call, a further £6M will be allocated.

The funding call for BRIC2/2 research projects is now open and is focused on the same research areas as BRIC 2/1 **(see Annex 1).**

Outline applications may now be submitted for Standard Research Grants (see Call Guidelines) with a closing date of 08 February 2012.

Applicants should read this document in full before formulating their ideas into a research proposal. As this programme is funded in partnership with the biopharmaceutical industry, any applications must have a strong relevance to that industry in order to fulfil the assessment criteria for strategic relevance. Applicants should seek to engage industry in the design of any proposal and to achieve this it is strongly recommended that they discuss, in confidence, their planned application with the BRIC Programme Manager (Andy Lyddiatt – al@lyddallan.co.uk), the BRIC Industrial Coordinator (Malcolm Rhodes –malcolm.rhodes@healthktn.org) or the BRIC Business Interface Manager at the BBSRC (James Phillips – James.Phillips@bbsrc.ac.uk) to ensure appropriate alignment with the BRIC2 scope and associated industrial need.

BACKGROUND

BRIC was founded in 2005 to achieve the effective translation of UK scientific and medical discoveries into the market place of biopharmaceutical manufacture and delivery, by funding innovative bioprocessing-related research.

A major goal of BRIC funding is to encourage academics active in the biological, physical and engineering sciences, and focused on the workings and products of living and physical systems, to apply their understanding of such entities to the design and operation of effective

[1] http://www.i-newswire.com/the-market-for-biopharmaceuticals/122211

bioprocesses for biopharmaceutical manufacture. This has been achieved by communicating industrial needs, and by supporting the growth of a community where collaboration with academic and industrial bioprocess engineers is encouraged.

BRIC entered a second phase in 2010, the main purpose of which is to continue the growth of the research community supported in the first phase, and to fund research that would further understanding of the science underpinning existing and future biopharmaceutical products, and the invention of new, industrially-relevant, tools to facilitate the acceleration of robust product and process development.

Biopharmaceutical products are large and complex structures (proteins, nucleic acids, viruses, cells) which require sophisticated manufacturing methods. The development phase is currently slow, expensive and complicated and, since speed to market is vital, there is a need for new tools and methods, which will contribute to accelerating development. Improved scientific understanding of the workings of relevant industrial bioprocesses (both established and planned) facilitates improved predictive design, execution, monitoring and control of intrinsically complex operations.

In recent years the early demonstration of robust manufacturability or operability, in the development of new products and processes, has become an essential quality for assessing commercial investment in scientific discoveries and inventions. Such demonstrations of manufacturability are rooted in scientific understanding of the measured characteristics and behaviour of biological products (and their production systems) in the physical and chemical environments of existing or proposed bioprocesses. These must be designed to yield biopharmaceutical products at lowest possible cost and in formulations appropriate for medical administration. Such bioprocesses differ from analogous laboratory procedures in respect of the (i) scale of operation, (ii) physico-chemical nature of handling procedures, (iii) quality-driven definition of validated operations, and (iv) precise end-product specifications which characterise safe and robust industrial manufacture and product end-use.

SCOPE OF THIS CALL

Many key scientific problems have been identified in earlier BRIC calls, and there is also now an opportunity for applicants to propose **translational projects** that would develop technologies which can provide practical solutions to these problems. **Translational projects** may build on underpinning research already carried out in earlier phases of BRIC, or other research programmes.

These technologies are likely to be of nearer term applicability in industry. However, applicants must ensure that their proposal falls within the remit of BBSRC and/or EPSRC. Research Council funding supports high quality research that is fundamental and precompetitive in nature, and encompasses basic, strategic and applied research, and technology development.

Academic research relevant to the effective manufacture of biopharmaceutical product types such as proteins, nucleic acid assemblies, viruses and cells will continue to be funded through BRIC. Research proposals addressing biologically produced **small molecules are not within the scope of this call** and will not be considered for funding. However this area of research is supported by BBSRC through other funding routes as part of its strategic priority in Industrial Biotechnology: http://www.bbsrc.ac.uk/publications/planning/strategy/priority-bioenergy.aspx

One of the aims of the BRIC programme is the funding of a balanced research portfolio which covers the broad scope that was originally envisaged when the programme first launched. Applicants are encouraged to discuss with the BRIC Programme Manager (Andy Lyddiatt) whether their proposal fits within the scope of this call, how it aligns with the priority areas

identified in the next section, and whether their proposal will contribute to the development of a more balanced BRIC research portfolio.

BRIC2/2 will continue under the same remit as previous BRIC calls in addressing two **overarching themes:**

(i) Extending an understanding of the bioscience that underpins bioprocess improvement.
(ii) Development of new enabling tools (underpinned by scientific understanding) for bioprocessing implementation.

Call Objectives

Research projects supported in BRIC2 should:

- address at least one of the six industry value drivers described in the Business Case established for BRIC 2 funding (please see below).
- enable the most promising and industrially relevant research, previously established in BRIC1 and elsewhere, to be further developed toward translation into commercial practice.
- address research challenges identified by BRIC Industrial Members.
- address the research challenges encapsulated in the Industrial Priority Areas discussed in this document.

Industrial Research Priorities

The following five Industrial Research Priorities have been identified by BRIC company members as being areas of importance:

- Bioprocessing research challenges for protein products and their host cell producers
- High-throughput bioprocess development
- Effective modelling of whole bioprocesses
- Robust and effective analytics for bioprocessing
- Bioprocessing research for cellular products

Full descriptions of these priorities are located at **Annex 1** of this document.

Applications to this call of BRIC2 must address the overarching themes of BRIC and the Call Objectives. Applicants should also seek to align their proposals with at least one of the Industrial Research Priorities in order to show industrial relevance. Proposals of a high quality that do not align with these priority areas, but have clear industrial relevance, will also be considered, but may not fulfil the assessment criteria for strategic relevance to BRIC2. Further guidance on the alignment of research proposals with industrial need should be sought from the BRIC Programme Manager (Andy Lyddiatt) and the BRIC Industrial Coordinator (Malcolm Rhodes).

BRIC2 Business Drivers

A key recommendation of the BRIC2 Working Group was that all funded projects should clearly address at least one of six business drivers judged essential to the underpinning of an ‘impact’ case for continued investment in the BRIC initiative. These were identified as:

- the considerable commercial opportunity presented by recovering and expanding the overall UK position in the growing global market for biological medicines that was worth £61 billion ($101 billion) in 2010.

- the indirect support of a major cluster of UK based high-technology companies (i.e. approximately 50 companies of all sizes developing biological medicines and about 200 other companies supplying technologies, products and services in support) many with significant growth potential.
- the creation of a vibrant and highly skilled bioprocess community of professionals that will facilitate new business start-ups, remove 'access to skills' growth constraints on existing companies, facilitate inward investment and encourage companies to stay in the UK even if they are acquired.
- the direct commercial and competitive value to existing companies from decreasing the time, cost and risk of product development.
- the reduction in capital investment magnitude and risk to existing companies coming from the ability to design intensive, modular and predictable processes that inherently embrace 'quality by design'.
- the decrease in risk of product development delays imposed by Regulatory Authority concerns about process and product integrity and reproducibility.

Guidance for Translational Projects

Applicants should consider the Technology Readiness Level (TRL) of their proposal. Translational projects submitted to this call must fall within the remit of BBSRC and/or EPSRC and should fall in TRL 4 or below. At TRL4, the critical function or proof of concept for the process or technology will have already been established and, for example, research will move towards integration of different technologies and processes at laboratory scale to establish that performance targets may be attainable and that further integrated testing in a more realistic environment would be enabled. If applicants have any questions about TRLs, they should contact the BRIC Programme Manager Andy Lydiatt at: al@lyddallan.co.uk.

Applicants may also wish to consider the Follow on Funding scheme, which provides grants for proof of concept studies leading to commercialisation studies. Further information is available at: http://www.bbsrc.ac.uk/business/commercialisation/follow-on.aspx

Translational projects could, for example, build upon previous research into the intracellular bottlenecks during expression of proteins to develop new technology for cell line development, or to nutritional approaches to improved media or nutrient feeds, to overcome these bottlenecks. The technologies are likely to be in areas such as cell culture technology, protein recovery and purification technology, glycoengineering, protein engineering, protein characterisation, protein formulation and delivery, unwanted immunogenicity. Applications in process engineering relevant to the bioprocessing of biopharmaceuticals will also help to translate the basic science already funded through BRIC into practical applications of value to industry, and therefore will be aligned with the business drivers.

GUIDELINES FOR THE CALL

In the BRIC 2/2 call applicants may apply for a Standard BRIC Research Grant. Proposals will be assessed and selected through a two-stage process. In the first stage all applicants will be asked to produce an outline proposal for assessment. The successful applicants will then be invited to submit a full proposal in the second stage.

Applicants currently holding BRIC2/1 Enabling Funds may proceed directly to the second stage and are required only to assemble a full proposal for the appropriate deadline, provided that the full proposal is linked to the Enabling Fund project. It is strongly recommended that these applicants discuss their applications with the BRIC Programme Manager at the earliest opportunity.

The objectives of the proposed research must fit within the BRIC2 scope. The science proposed must fall within the remit of BBSRC and/or EPSRC. Proposals may address more than one aspect of the BRIC2 scope, and novel approaches to the meeting of research challenges are encouraged.

Collaborative applications which bring together academic groups with relevant expertise in bioscience and engineering are strongly encouraged. In addition, in the first stage of the assessment, the BRIC Steering Group will identify research projects from the outline applications with previously unrecognised potential for collaboration that may benefit from closer cooperation or from submitting a joint application.

Applicants are asked to note that the normal BBSRC equipment guidelines that were introduced in 2011 in response to the Wakeham review on FEC, and the reduction in capital funding, will apply to this call. The guidelines are explained in detail after the following URL:
http://www.bbsrc.ac.uk/funding/news/2011/110812-new-bbsrc-equipment-guidance.aspx

ASSESSMENT

Outline applications will be assessed by the BRIC Steering Group and will not be externally reviewed. Subsequent invited full applications will be externally peer reviewed prior to final assessment by the BRIC Steering Group. Further details on assessment for all BRIC2 grants are as follows:

- The applications will be shared, in confidence, with the company members of BRIC in order to facilitate the assessment process.
- The criteria of scientific excellence and strategic relevance are given equal weight in the assessment of proposals and applications must meet both criteria to be considered fundable.
- The economic and social impact, timeliness, cost effectiveness, and potential for staff training of the project are all taken into account when judging the scientific excellence. These assessment criteria are explained in the next section.
- The Steering Group consists of 6 academic members (nominated by BBSRC and EPSRC) and 6 industrial representatives (chosen by the BRIC Industry Members).
- For assessments conducted by the Steering Group, each proposal has two Introducing Members (IMs). One IM is from academia and the other is from industry.
- The procedure for dealing with conflicts of interest (e.g. where a Steering Group member has pre-existing links to an applicant) is the same as for other BBSRC Research Committees. Conflicted individuals leave the room while the proposal is being discussed.

CRITERIA FOR ASSESSMENT

The primary criteria for assessment are the strategic relevance to BRIC2 and the quality of science proposed. It is expected that any proposal that goes on to be funded through BRIC2 will be competitive against comparable international work and will demonstrate alignment with the Club's aims. Proposals for standard research grants will be assessed against the following criteria:

- **Strategic Relevance to BRIC2**
  All applications must be within the scope of the BRIC programme and ideally should address one or more of the Industrial Research Priorities. Applications will be assessed for relevance to industry. Preference will be given to applications that demonstrate strong industrial

engagement and show a clear potential for translation into industry.

- **Scientific Excellence**
  The extent to which the proposal meets the highest international standards of current research in its field. High performance against this factor will indicate a project of the highest standard, competitive with the best activity anywhere in the world, demonstrating originality and innovative potential.
- **Economic and Social Impact**
  The extent to which the output of the research will contribute knowledge that shows direct potential for economic return or societal benefits to the UK.
- **Timeliness and Promise**
  The extent to which the proposal is particularly appropriate at the present time, or offers longer-term benefits over and above the direct value of the research.
- **Cost Effectiveness**
  The extent to which the resources requested, relative to the anticipated scientific gains, represent an attractive investment of BRIC funds.
- **Staff Training Potential of the Project**
  Where resources are requested for postdoctoral or other research staff, the extent to which the proposed project will provide research training and development opportunities of benefit both to the individual(s) employed, and to the wider science base beyond the completion of the specific project.

SPECIAL CONDITIONS

Recognising the financial support for the programme from industrial members of the Club, it should be noted that special conditions will be attached to any research grants from BRIC. A letter from the institution's technology transfer office or equivalent, acknowledging that the institution is able to accept those conditions relating to IP, will be requested at the full application stage. The conditions are as follows:

Early Access

Commercial parties are entitled to early access to results from research funded by the Club. To ensure this grant holders must:

- Give at least 28 days notice of an intention to publish, outside of the Club, results from research funded by a Club grant. The material for proposed publication should be submitted to BBSRC along with the notice of intent to publish. BBSRC will ensure a copy is distributed to each of the Commercial Parties who shall have fourteen (14) days from receipt of such copy to inform the researcher if in their view the proposed publication may:

  (i) dilute or prejudice the value of proprietary information of a Commercial Party or
  (ii) jeopardise the application for Resulting IPR protection or
  (iii) otherwise inhibit future exploitation of the results and whether a Commercial Party has an interest in exploiting those results.

- Produce annual progress reports. A form will be provided for grant holders to complete each year and grant holders will be notified in advance when the final report will be due at the end of the project.

- Attend and present the results, progress, and a final report of Club funded research at 6-monthly Club dissemination events. Grant holders will be notified of the dates and format of their presentation.

- Give advance notification of any opportunities to exploit intellectual property arising from their grant to the commercial parties.

Access to Resulting Intellectual Property Rights (IPR)

Commercial parties are entitled, if they wish, to engage in good faith negotiations with the research organisation for terms of access to the resulting IPR to allow further development or commercial exploitation of results, such access rights preferably to include the right to sublicense. This must be offered before access to resulting IPR can be offered to third parties outside the Club. An interested commercial party can exercise its option right by giving notice to the grant holder within one month of the date of receipt of notice of results or resulting IPR.

Good Faith Negotiations

Good faith negotiations would imply a willingness to reach agreement with commercial parties on the terms and conditions of a commercial licence, to desist from publishing the results or making offers to third parties while negotiation with commercial parties are ongoing and, if such agreement is not reached within a reasonable period (for example four months from the exercise of the option) that the research organisation would not seek to enter into negotiations with third parties on terms substantially more favourable to such third parties.

APPLICATION PROCEDURE

There is a 2-stage application process:

- Outline Applications will be submitted through Je-S (https://je-s.rcuk.ac.uk). Guidelines for how to apply are available on the BRIC website (http://www.bbsrc.ac.uk/bric). The closing date for outline applications is 08/02/2012.
- Successful applicants will be invited by 02/05/2012 to write a full application for submission by 26/06/2012. Applicants may not be notified about the outcome of their full proposals until 06/11/2012.
- Applicants holding BRIC 2/1 Enabling Fund grants may submit a full application after 02/05/2012 but before 26/06/2012. These applications must build upon an Enabling Fund project, and will be considered for funding alongside the invited full proposals.

ELIGIBILITY

Staff at lectureship level or above at UK Higher Education Institutions and their equivalents at Research Council institutes and Independent Research Organisations are eligible to apply.

CONTACTS

For further information please contact:

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Annex 1

INDUSTRIAL PRIORITY RESEARCH AREAS IDENTIFIED FOR BRIC2/2

Bioprocessing research challenges for protein products and their host cell producers

This priority area is concerned with the harnessing of an advanced understanding of macromolecular and cellular properties, and the quantitative documentation of their response to the challenges of current and future bioprocessing environments, to improve the design of bioprocesses for up-scaled production and recovery.

The majority of biopharmaceuticals in manufacture or development are proteinaceous in nature. Fundamental biochemical and biophysical understanding of protein form and structure is not yet sufficient to enable useful predictions of protein behaviour in physical and chemical environments that define industrial bioprocesses – both existing and projected. A key economic requirement is prediction of manufacturability of biological medicine discoveries at the earliest possible stage of development – particularly where structural variants (e.g. monoclonal antibodies engineered from a common molecular scaffold) are to be manufactured by established template bioprocesses. Issues of unexpected pharmacological or biological activity loss, increased immunogenicity, proteolytic sensitivity, molecular aggregation, insolubility and losses through surface adsorption, all arise from the effect of variable bioprocessing environments on protein 3-D structure.

Understanding of relevant protein chemistry is critical to advancing the effective expression of native, folded protein products in established and newly developed host cell lines with higher expression capabilities.

The physico-chemical impact of the environment in common unit operations of product recovery and downstream purification (e.g. centrifugation, microfiltration, selective precipitation or crystallisation, chromatography and ultrafiltration) upon the molecular integrity of protein products or impurities as process/product antagonists is poorly understood. Operational lifetimes of membrane and chromatographic media are strongly predicated upon degrees of protein fouling and the effectiveness of cleaning regimes. Proposed alternatives to chromatography such as selective precipitation, crystallisation or aqueous solvent extraction are constrained beyond laboratory demonstration by a lack of meaningful, mechanistic molecular understanding of the impact of novel bioprocessing environments upon structural integrity and potency of end-products.

Analogous arguments apply to the encouragement of work to establish an improved understanding of the response of producer cells (bacterial, lower eukaryote or animal species) to the dynamic processing environments of bioreactors, centrifuges and filters to which they are exposed. This aspect may become more important as capabilities become established in the bioprocessing of cells as products in their own right.

BRIC industrial opinion has emphasised a need for reliable predictive tools correlated with elements of protein (and gene) structure that would indicate process watch-outs in respect of manufacturability, DSP bottlenecks and costs of manufacture.

High-throughput bioprocess development

This priority area is concerned with the establishment of robust and rapidly achieved procedures by which target products (macromolecules, nanoplexes, cells) or the processes of their current or prospective manufacture, can be rapidly and credibly evaluated at an early stage with respect to practical compatibilities with industrial bioprocessing.

Automated, ultra-scaled down, high-throughput technologies are required for the rapid development and selection of productive cell lines, as well as the selection and optimisation

of other unit operations of cell processing and product recovery. For example, the rapid establishment of a 'state of manufacturability' of candidate protein targets (underpinned by clear scientific understanding) as noted above would be an extremely valuable tool in process development.

The high-throughput approach is not only applicable to existing processes (e.g. therapeutic protein production) but also emergent processes for products appearing on the horizon such as antibody fragments, complex protein assemblies, nanoplexes and cell-based therapies. It should embrace the effective integration of upstream and downstream operations of manufacture as well as the establishment of compatible solvent and excipient conditions from bioreactor through downstream recovery to product formulation. It should also include the development of analytical techniques that allow for real-time measurement of parameters in a non-invasive manner and/or with negligible analyte consumption.

Furthermore, high-throughput process development would also help facilitate *Quality by Design (QbD)* by increasing the speed and reducing the cost to reach a defined design space.

BRIC industrial opinion has emphasised a need for high-throughput screening for multi-parallel evaluations of operational conditions, comparisons of analogous unit operations, accelerated testing of intermediates and final products, and application of real-time process monitoring.

Effective modelling of whole bioprocesses

This priority area is concerned with the establishment of effective and robust models which describe (and enable critical comparison of) the various components of bioprocesses from the biosynthetic pathways which account for cellular assembly of bioproducts to the integrated operations of their production, enrichment, recovery and formulation for end-use.

There continues to be an important requirement for robust modelling procedures that are applicable to whole bioprocesses. These should exploit early data flowing from scale-down process measurements, facilitate the evaluation of alternative process routes and allow confident prediction of process component behaviours at the manufacturing scale. Improved models must be based upon, and be validated by using industrial bioprocess datasets which contemporarily are commonly limited in size and quality.

Modelling approaches that could link (i) high-throughput discovery, (ii) native product expression, (iii) optimised fermentation and (iv) downstream recovery and purification in an integrated fashion would accelerate development and reduce the need for expensive pilot studies. The capacity for such modelling approaches exists in UK academia focused upon other markets such as the chemical process industries, but is not currently widely applied to industrial bioprocessing.

It is a goal of BRIC2 to catalyse greater collaboration between appropriately active disciplines (within/without the conventional bioprocessing community) to generate highly competitive proposals in this priority research area.

BRIC industrial opinion has emphasised the urgent need for improved methods of data mining of bioprocess informatics, predictive models to link with high-throughput screening (II), and model guided decision making for R&D development programmes.

Annex 1

Robust and effective analytics for bioprocessing

This priority area is concerned with the translation of laboratory-based analytical procedures to describe the molecular, physiological and biopharmacological characteristics of target bioproducts (macromolecules, nanoplexes, cells) in the context of product and process qualities in biomanufacture.

There continues to be a need for the development of improved analytical methods and tools for the design, analysis and control of both present and future bioprocesses. The scope of these methods should embrace the extent of product structural homogeneity (for macromolecules, nanoplexes, cellular products), molecular integrity of products, functionality, stability, product and process contaminants and shelf-life evaluation.

It is highly desirable that new measurement technologies are robust enough to operate near-plant on minimal volumes of real process fluids, ideally in real-time or rapidly off-line. Given the highly regulated environment for biomanufacturing, it is also essential that the techniques selected are capable of full GMP validation.

The sensible and rapid development of a similar suite of analytic capabilities to underpin the project development of bioprocesses to manufacture cellular therapeutics remains a very urgent opportunity for research conducted under the auspices of BRIC2 (see below).

In addition, this priority area could develop analytics that could ultimately facilitate Process Analytical Technologies in production processes.

BRIC industrial opinion has emphasised the urgent need for the establishment of robust, small-volume, high-throughput analyses that can be operated at/on-line to generate credible process data suitable for product definition and predictive modelling.

Bioprocessing research for cellular products

This priority area is concerned with the translation of laboratory based procedures of cell-line development, demonstration of efficacy in chosen fields, and putative approaches to candidate production into bona fide *product manufacture and characterisation which will underpin safe practice in cellular therapies.*

Cell therapy products are currently commonly produced by larger, non-optimised versions of laboratory scale methods. More robust and practical large-scale manufacturing processes need to be developed, together with scaled down versions that facilitate predictive process evaluation and new non-invasive (or low sample consumption) analytical methods for monitoring and control.

Since the development of active cell based products is in its infancy, further research must also be conducted to define the minimum set of biological markers that can be used to define the qualities of such products for clinical use.

BRIC industrial opinion has emphasised the importance of relevant scale-up methodologies, particularly with respect to novel culture surfaces, passage technology, responses to environmental cues and purification at advanced scales. Supply chain elements in respect of capabilities for on-line measurement of product and antagonists qualities, metabolic integrities and next generation automation are also important.