Efficacy and Mechanism Evaluation Programme

Closing date: 1:00 pm, 28th August 2019 (two stage – Stage 1 to Stage 2)

Epigenetics

Applications are sought for research to evaluate the use of epigenetic biomarkers for the detection, diagnosis, or establishing the prognosis of a disease or condition.

Areas of interest include, but are not limited to:

- evaluations of therapies and management strategies guided by assessment of epigenetic markers for the treatment of disease
- the use of epigenetic markers as a screening tool in a selected or general population

Clinical validation of existing biomarkers (i.e. studies of biomarkers that have already undergone initial validation and shown signal strength and specificity) is within the scope of this call but early validation and the discovery of novel biomarkers is excluded.

Applicants may wish to consider the role of epigenetic biomarkers within the context of a P4 (predictive, preventative, personalized and participatory) systems medicine approach.

Applications for phase 2b studies of modest size and cost are encouraged.

Applicants are encouraged to consider opportunities to embed the testing of mechanistic hypotheses within the main study. Also of interest are standalone studies of the mechanisms underpinning interventions (investigational or control) used in existing CSO- and NIHR-funded trials, although applications in this area should refer to the EME Mechanisms of Action of Healthcare Interventions call.

Applications are expected to set out programmes of work which may contain distinct stages. It is expected that the initial stages of the study will, if successful, lead onto a full evaluative clinical study or trial, which is in the remit of the EME Programme. This study must also be included and clearly specified within the application. Clinical trials embedded within the programme of work must be large enough to detect a meaningful effect.

Applications to this call may include initial stages such as:

- The limited steps needed to progress the development of an intervention to a stage suitable for use in an accredited clinical service;
- Prospective clinical work or retrospective research utilising existing big data or clinical samples to inform the main study;
- Pilot or feasibility studies.

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As a rough guide it is expected that these initial stages will be complete within the first 18 months of the project and must not contribute more than 25% to the total cost or duration of the project.

Applicants will need to make a strong case for the future importance of the intervention through providing a measurable positive impact on health, innovation or future wealth creation and for the ultimate benefit of individual patients’ or the wider NHS. Applicants should read the details of the EME remit at https://www.nihr.ac.uk/eme

Supporting information

This background section provides further information to support applicants for this call. It is intended to summarise what prompted the call, including examples of relevant technologies that are currently in development. It was researched and written on the basis of information from a search of relevant sources and databases, and in consultation with a number of experts in the field.

Epigenetics is the study of heritable changes in gene expression that are not caused by changes in the DNA sequence. The ‘epigenome’ is the cellular machinery that switches genes ‘on’ or ‘off’, allowing stem cells to differentiate into different cell types. Epigenetic regulation occurs via three main mechanisms; DNA methylation (adding methyl groups to DNA), histone modification (the proteins that package the DNA into chromatin) and non-coding RNAs (not translated into protein). DNA methylation within the promoter or regulatory regions of a gene causes gene silencing because the methyl group physically blocks the binding of transcription factors and recruits proteins involved in gene silencing. The histone proteins undergo covalent modifications including acetylation and methylation, which alters the configuration of the chromatin to be either more open or condensed. This in turn leads to gene activation or silencing, respectively. Non-coding RNAs, for example microRNAs (miRNAs), cause gene silencing by binding to their target messenger RNA (mRNA) thereby inducing degradation or chromatin condensation.

Whilst epigenetic changes are required for normal development and health, dysregulation of the three mechanisms that contribute to epigenetic alterations can cause abnormal gene activation or silencing. Various publications have highlighted cancer, neurological disease, cardiovascular disease and autoimmune disease as those having epigenetic dysregulation. Gene specific hypermethylation occurs in the promoter regions (specifically in CpG islands) of tumour suppressor genes, and genes responsible for cell cycle regulation and DNA repair. This leads to gene silencing of these ‘protective’ genes and tumour growth. Hypomethylation leads to increased activation of specific genes, a phenomenon that occurs in cancer, cardiovascular disease and autoimmune disease. Aberrant histone modifications such as hypoacetylation have been associated with neurological disorders. Non-coding RNAs, specifically miRNAs, are essential for the normal function of the nervous system and there is growing evidence that their dysregulation is important in the development of neurological disease.

The epigenome is dynamic and influenced by many biological and environmental factors throughout the life course. Therefore, interventions such as nutrition, particularly in prenatal and postnatal life, can improve later health. For example, a healthy diet and exercise before and during pregnancy decreases the risk of gestational diabetes mellitus, improving both maternal and fetal outcomes.

Epigenetic dysregulation often precedes disease pathology and therefore can be used as a diagnostic and prognostic biomarker to indicate disease risk, disease classification, disease progression and guide treatment management. This would identify those patients at increased risk of a particular disease, who may benefit from intervention or a targeted therapy. An example is the measurement of methyl guanine methyl transferase (MGMT) promoter
methylation in high-grade glioma specimens to inform prognosis and guide treatment (see NICE guidance).

Epigenetic therapy is the use of drugs that modify epigenetic mechanisms in order to treat disease. Histone deacetylase inhibitors (HDACi) and DNA methyltransferase inhibitors (DNMTi) are clinically approved for the epigenetic therapy of different types of cancer (see figure 1). An example is Azacitidine or Vidaza, a DNMTi, which is used in the treatment of acute myeloid leukaemia (see NICE guidance). Many more 'epidrugs' are at the preclinical and clinical trial stage for the treatment of cancerous and non-cancerous disease including neurological disease. Multiple epigenetic aberrations can be present in diseased tissue and the cell can develop resistance, suggesting that combination epigenetic therapies may be beneficial.

Because so many diseases involve epigenetic dysregulation, understanding how these epigenetic processes are regulated will aid the discovery of biomarkers and the development of more targeted and effective therapies. The use of epigenetics as a screening tool in a readily available tissue, for example blood or urine, could replace the need for invasive and costly tests thereby improving the quality of life for the patient and a potential cost saving to the NHS.
The EME Remit and Epigenetics

Relevant research activity includes the use of epigenetic changes as biomarkers for prediction, diagnosis, prognosis and disease progression, epigenetic therapies for the treatment of disease and the control of environmental factors in early life to improve later health (for example, nutrition in pregnancy).

Early-phase studies focussed on biomarker discovery are not within remit for EME and may be better suited to earlier funding programmes, such as the MRC Boards, while early phase (Phase 1/2a) biomarker validation studies should be directed to the MRC Developmental Pathway Funding Scheme (DPFS).

Examples of research that might be within remit for EME under this scope include:

1. **Evaluating an epigenetic biomarker for the detection, diagnosis and prognosis of a disease or condition, e.g.**
   * [NCT02336074:](#) Research In Viral Eradication of HIV Reservoirs (RIVER). A two-arm, phase 2 RCT to determine the effect on latent HIV reservoir levels using combination antiretroviral therapy alongside the class II HDACi Vorinostat (Active, UK)

2. **Evaluating the mechanism of epigenetic therapies for the treatment of a disease or condition, e.g.**
- EME project **14/209/13**: SAVER - Sodium Valproate (SV) for Epigenetic Reprogramming in the Management of High Risk Oral Epithelial Dysplasia (OED). SV inhibits histone deacetylase activity and epigenetic changes potentially occur in OED. A phase 2, RCT to establish clinical activity of SV as chemopreventive therapy in high-risk OED, and determine if progression is reduced by epigenetic reprogramming (Active).
- **NCT03761511**: Study of the Efficacy and Safety of Nicotinamide in Patients With Friedreich Ataxia (NICOFA). The frataxin gene (FXN) is silenced at the chromatin level by the formation of heterochromatin. A proof-of-concept study showed that FXN levels can be increased using the class III HDACi nicotinamide. A phase 2, RCT to provide clinical evidence for the efficacy and safety of nicotinamide in patients with Friedreich’s ataxia (Active, Germany). A pre-award has been given by the EME programme for the UK arm of this multi-centre study (**17/90/01**).

3. **Novel interventions for the control of environmental factors that can improve later health e.g.**
- **NCT02786875**: Diet, Exercise and Vitamin D in Breast Cancer Recurrence (DEDiCa). A phase 3, randomised parallel assignment trial to determine if the high intensity program is more efficacious than the lower intensity program in reducing breast cancer recurrence and improving cancer-related epigenetic markers (Active, Italy)

**References**