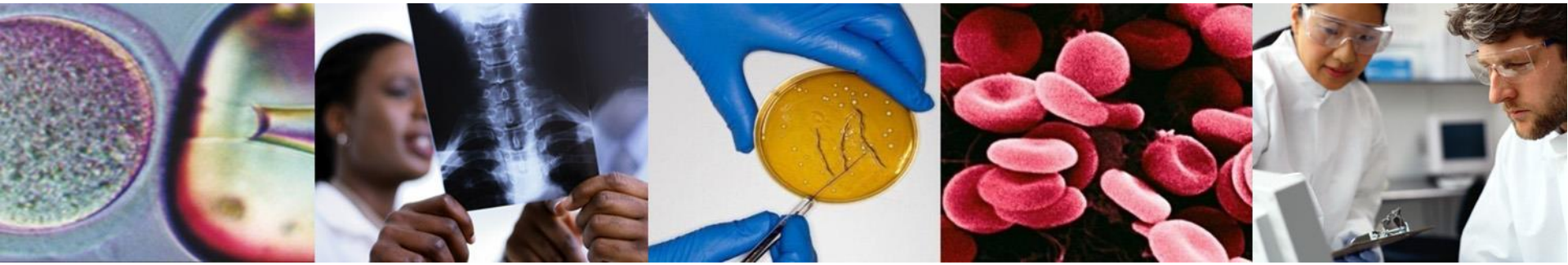


MRC Translational Funding

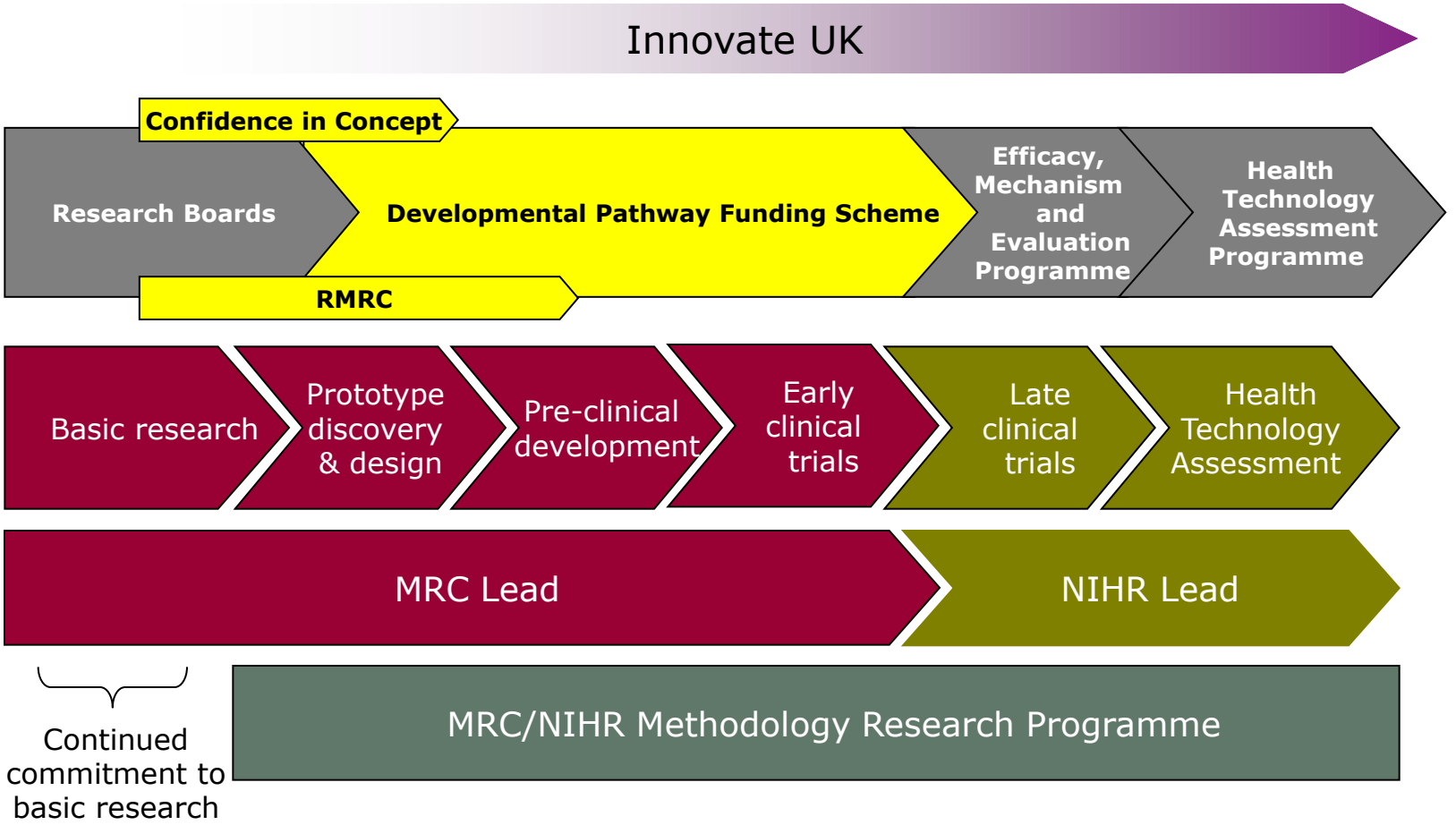
Charlotte Durkin– University of Manchester – 31st January 2018

Medical Research Council

MRC: Leading & Partnering Research

- Encourage and support high-quality research with the aim of improving human health
- Produce skilled researchers
- Advance and disseminate knowledge and technology to improve the quality of life and economic competitiveness in the UK and worldwide.
- Promote dialogue with the public about medical research.

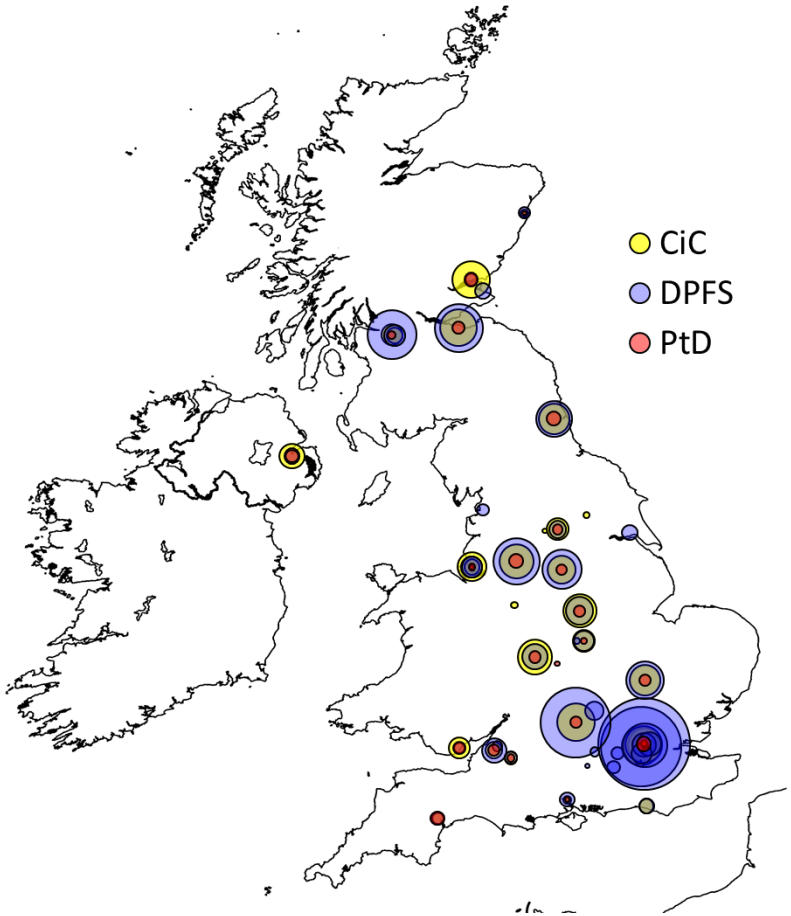
Core Translational Research Funding



BBSRC & EPSRC

Medical Charities

Translational spending since 2012/13



Confidence in Concept

The aim is to accelerate the transition from discovery science to translational research i.e. to get projects to the point where they are well placed to seek funding for development (e.g. through DPFS)

- Institutional awards of up to £0.84m over 24 months
- Awards are intended to support multiple projects covering preliminary work or feasibility studies; projects decided by university.
- Projects should be tightly defined, typically £50-100k in cost and lasting 6-12months

Proximity to Discovery

- Institutional awards of up to £250k
- Promotion of academic-industry interactions.
- supports 'people exchange' partnerships between academia and industry, to enhance skills, knowledge and understanding.

Impacts of CiC

- **£53.4 M** awarded since 2012
- **£75.6M** of leveraged/match funding
- **1051** projects supported
- **980** industry interactions
- **£461.1M** of follow on funding secured
- **123** patents awarded
- **834** papers published
- **34** spin out companies created
- On average every pound spent by MRC through CiC returns **£8** of further funding

Manchester CiC & P2D Awards

- 2012 - £7.5m distributed to 14 universities (29 applications)
  - Manchester: **£500k**
- 2013 - £10.5m distributed to 22 universities (33 applications)
  - Manchester: **£700k**
- 2014 - £10.2m distributed to 20 universities (24 applications)
  - Manchester: **£700k** + £200k P2D
- 2015 - £11.6m distributed to 21 universities (29 applications)
  - Manchester: **£600k** + £250k P2D
- 2016 - £13.7m distributed to 28 universities (33 applications)
  - Manchester: **£672k** + £150k P2D
- 2017 - £16.5m distributed to 27 universities (29 applications)
  - Manchester tbc

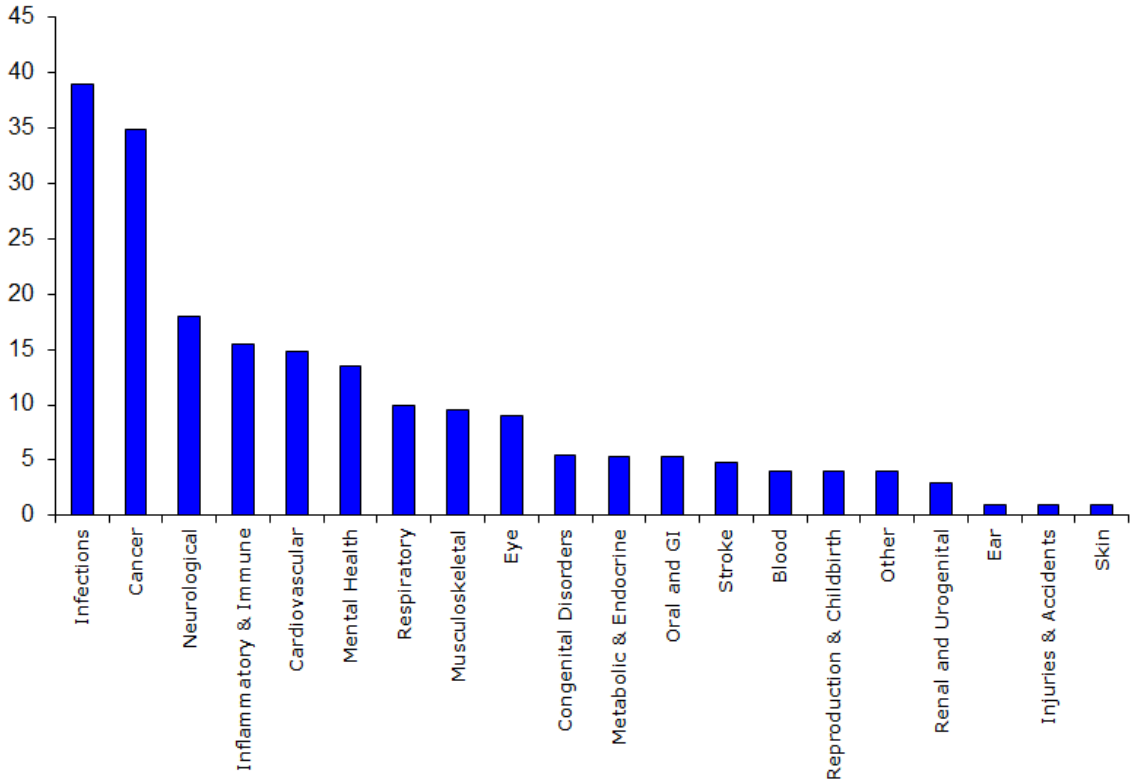
BMC: DPFS

- The cornerstone of the MRC's Translational Strategy: http://www.mrc.ac.uk/funding/browse/developmental-pathway-funding-scheme/
- ~£30m/year, rolling deadline every four months

- Not just 'Translational Research Grants'
  - Projects are goal oriented and milestone-based;
  - This allows MRC to provide a long-term commitment to inherently risky projects;
  - Ongoing reporting helps MRC develop a strong evidence base on outcomes
  - Investigators are required to submit
    - Quarterly reports, to inform MRC of project progress,
    - Milestone reports, to secure continued support
  - **Projects are not considered as isolated entities, but must sit on a translational pathway**

DPFS Portfolio

As of now, 231 projects have been supported through DPFS, ranging from pre-clinical studies to early phase trials with a total commitment of more than £227.6m including:



161 therapeutic interventions including:

- 40 small molecule
- 46 biologics (antibodies, proteins etc.)
- 14 drug other
- 23 genetic therapies
- 12 cell therapies
- 18 medical devices
- 7 psychological interventions

22 vaccines

40 diagnostics

13 others

Note some proposals involve multiple approaches and may be counted twice

BMC:DPFS

In remit:

- Development and pre-clinical testing of novel therapeutic entities, devices and diagnostics through to early-phase clinical studies (P1 to P2a)
- "Repurposing" clinical studies – existing therapies in new indications
- Pre-clinical development and early clinical testing of novel regenerative medicine therapies. (*Regenerative Medicine Research Committee will consider CIC type proposals* (£2m/year, deadlines 3 times/year)).

Out of remit:

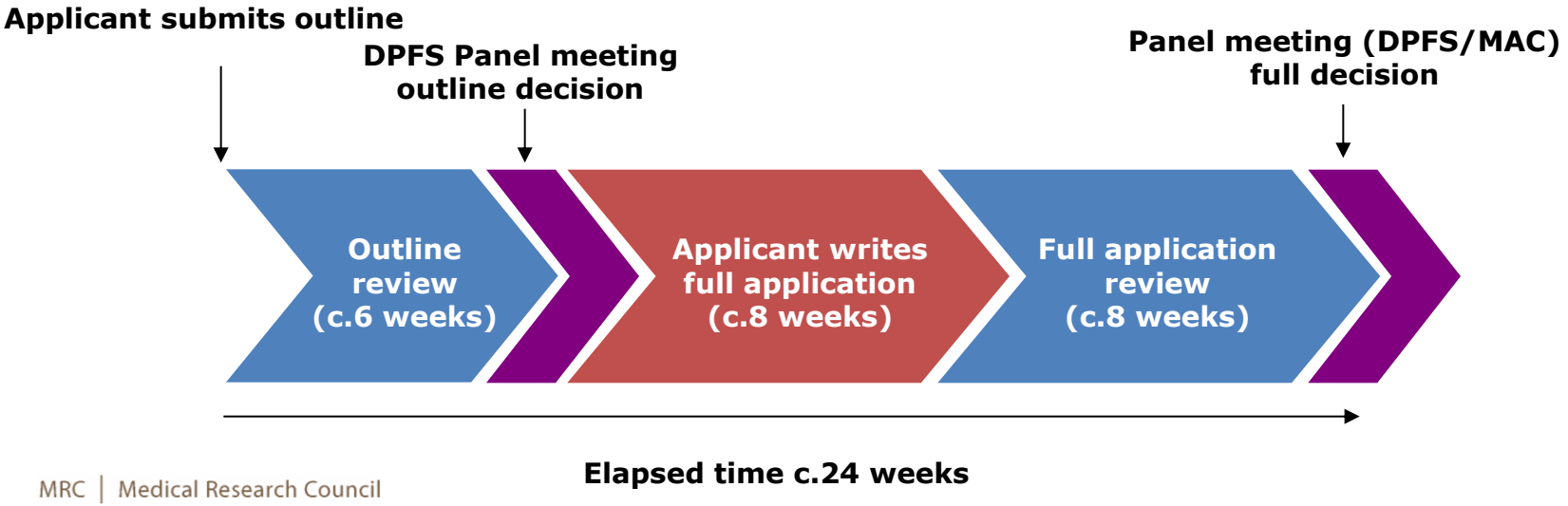
- Discovery science including mechanistic studies and biomarker identification (MRC research boards)
- Technology development where not aligned to a medical/clinical developmental plan (likely BBSRC or EPSRC remit)
- Phase 2b and 3 clinical trials & trials of non-novel agent-disease combinations (NIHR)

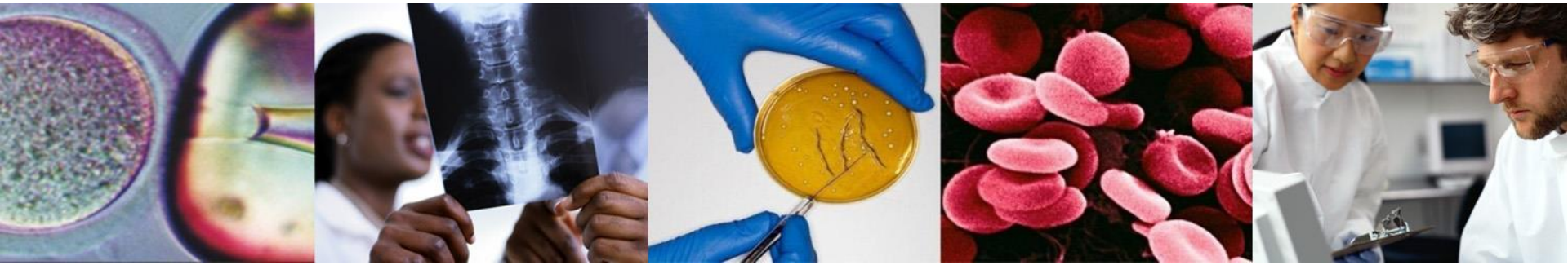
BMC: DPFS application process

- Two step decision process
  - Outline application: DPFS Panel review
  - Full Application: Expert referee and Panel review (DPFS or MAC)

- Full stage applicants have six months in which to submit their application i.e. can skip a meeting

- Budget is ~£30M per year





Tips for Successful Applications

Assessment Criteria

- **Need:** What is the need the proposal aims to help address?
- **Rationale:** What is the rationale for the proposed solution?
- **Deliverability:** Is the proposed development plan realistic? Does it offer good value-for-money? Does the team have access to the necessary assets to deliver the plan?
- **Intellectual Property:** Is there an appropriate intellectual property strategy in place to optimise the chances of downstream funding/partnering?

Need

- In addition to describing the clinical problem your work will address, you should indicate:
  - Where in the clinical pathway will your work be relevant?
  - What value will be added **relative to current best practise**?
  - Don’t forget to consider economics and feasibility
- Be specific and avoid catchy headline figures
- Focus on the need for your specific product/intervention

Need (Competition and market)

- **Clearly identify your competitors** – why is your solution better?
  - Consider both related and unrelated avenues of work relevant to your condition of interest;
  - Consider the potential impact of competitors doing well or poorly;
  - Concentrate on benefits not features;
  - Provide evidence or references to support your chosen approach;
- Economics
  - In the long-term, will there be uptake of your work?
  - If the cost is higher than for competing solutions, the need for extra spending will need to be justified;
    - Consider the role of NICE where appropriate.

Rationale

- Why will your solution work?
  - Ensure you provide sufficient data for the translational stage of your proposal
    - Proposals will be rejected if evidence for current status is lacking
  - If you are proposing a medicinal chemistry programme you will need to complete the supplementary documentation and detail chemical structures
  - Include quantitative analysis where appropriate
  - In addition to the Case for Support, you can upload 2 pages of supporting figures and data tables (5 at full stage)

Target Product Profile – Linking Need to Rationale

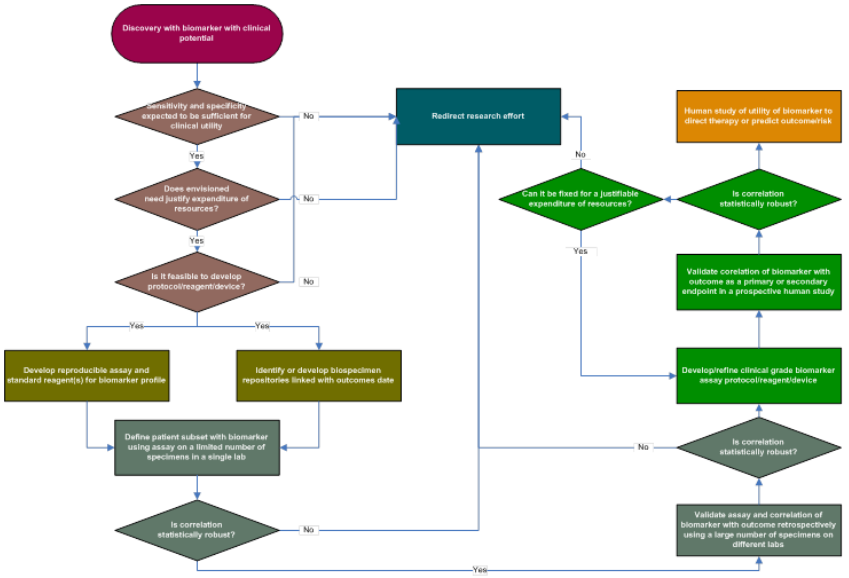
- What –
  - what you hope your product/solution will look like
  - the essential attributes of a clinically (and potentially commercially) successful product, which can form the basis of a development plan
  - at the early stages in the development process the TPP is a bit of a wish list but, over time, it will come to define the product
- Why –
  - provide focus to your planning and give success criteria
  - allows for development of clear achievable milestones
  - useful as a regulatory affairs tool
  - provides the basis for discussions on commercial investment/exploitation

Deliverability

- **Consider inclusion of a project manager post**
  - MRC will meet appropriate project management costs
- Manage the risks across the duration of the project
  - Too many uncertainties associated with any given step may reduce confidence in overall feasibility
- Don’t be overly ambitious in your timelines
- Include the right expertise; clinical, statistical etc.
- Show that you have access to the right facilities, e.g. GMP
- If you are planning a drug discovery programme:
  - Seek advice on the size of your screen and consider iterative development: SAR and PK/PD analysis to inform chemistry

Developmental Pathways

- Translational research is complex
- You will not know the exact route your project will take but you need to be able to show how you will decide how you will get to your desired outcome

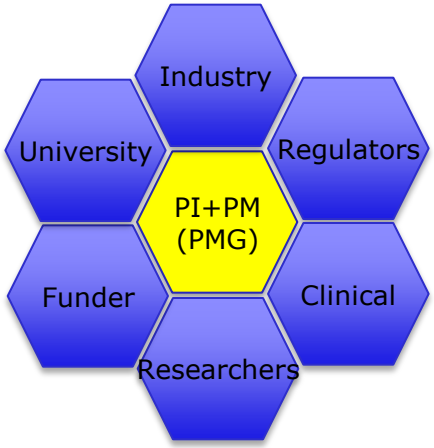


- You may wish to graphically represent your plan by schematic flowcharts that capture relevant contingencies, decision points, and interdependencies

* CCR Special Focus: The Translational Research Working Group Developmental Pathways: Introduction and Overview
Ernest T. Hawk, Lynn M. Matrisian, William G. Nelson, Gary S. Dorfman, Lisa Stevens, Jennifer Kwok, Jaye Viner, Judith Hautala, and Oren Grad
Clin Cancer Res September 15, 2008 14:5664-5671

Proposal details: Project team

- Team work is essential;
- PI is the natural team leader but may not be ideally positioned for day-to-day project management;
- All team members should have clear roles
- Team management: regular meetings, agenda, minutes and actions;
- Reporting: regular reporting to MRC;
- Risk management;
- Monitor (particularly outsourced work!);
- Aware of IP status and competitors.



Milestones & Monitoring

- Milestones are a key feature of BMC proposals
  - They encourage MRC Panel to support high risk proposals.
  - Milestones should be positioned at points of key risk or decision within a project
  - Should reflect key go/no-go decision points on the path to long-term goals.

- Milestones must be SMART
  - Specific, Measurable, Achievable, Relevant, Timely

- Milestones are a very common weakness in proposals

- Funded projects are required to report Quarterly and may be stopped if they fail to meet pre-agreed Milestone criteria.

IP common mistakes and associated risks

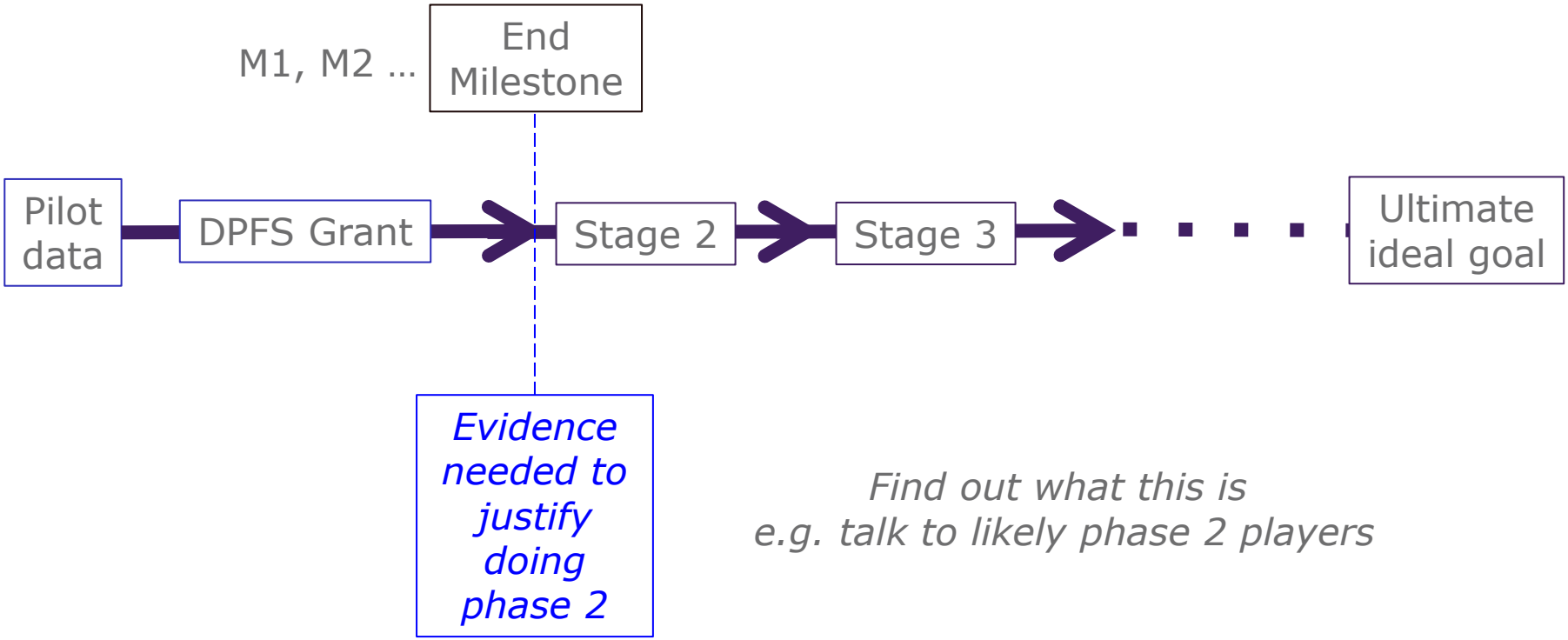
- Include detail of the current IP situation and the strategy for development and protection

  - **Exploitability:** Describe any potential limitations or risks to exploitation of your work. The Panel will be reluctant to support projects where the translational pathway is not clear.

  - **Early spinout:** Carefully consider the costs and benefits of forming a spinout company. If this is done during the grant lifetime and the spinout receives external support, the project may cease to be eligible for MRC support.

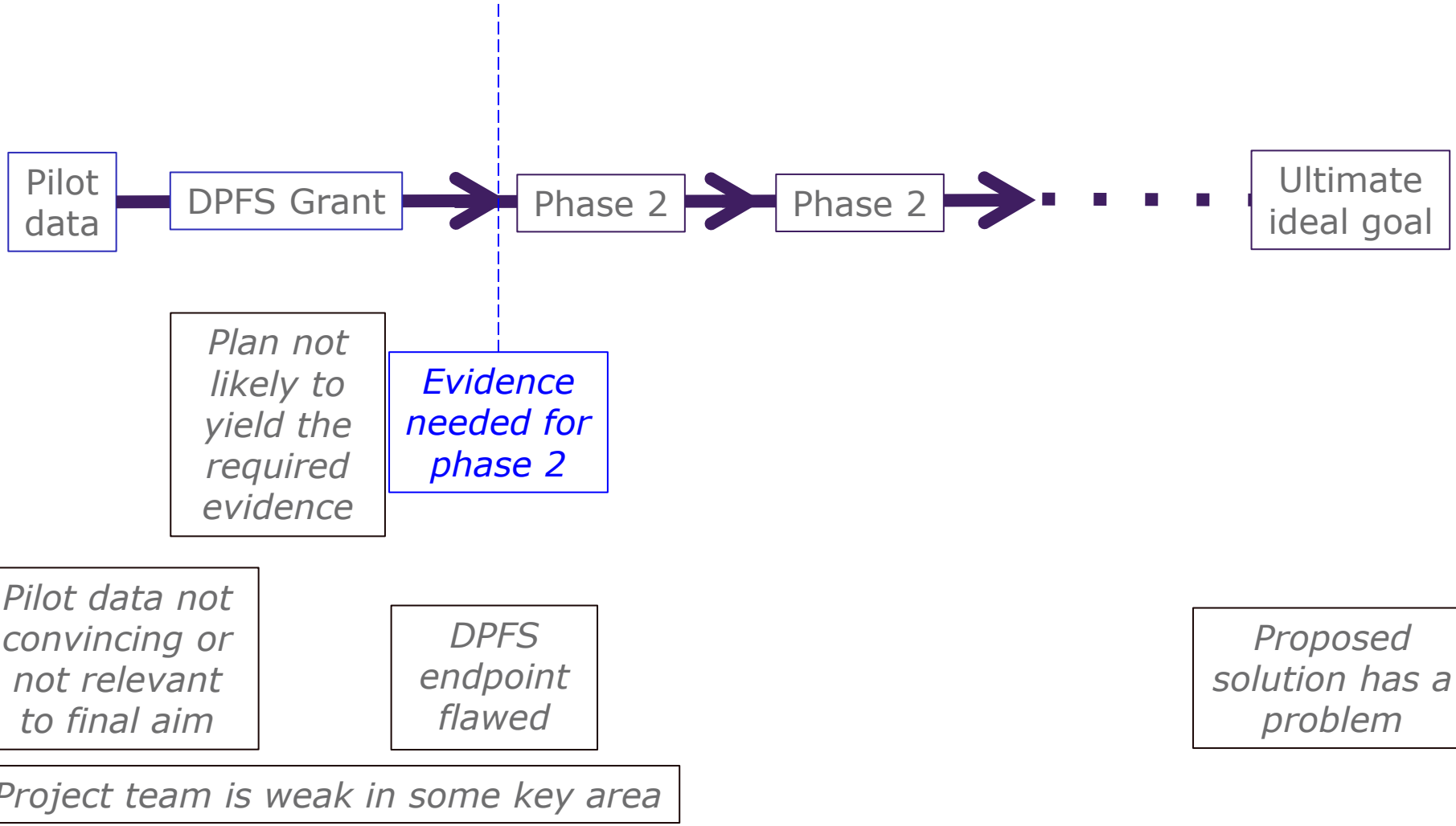
  - **Premature licensing:** If the output of your work is licensed prior to the project end, the project may cease to be eligible for MRC support.

Pathway



DPFS project aim: to get the evidence needed to justify doing for stage 2?
What are the tasks needed to get to the aim?
What resources, particularly what team, is needed?

Common failure modes



Being Successful…

Plan well & be realistic

- Don’t be over-optimistic! A complex study will roll out slower than you think.
- Agreements and authorisations will take time.
- Ensure you engage appropriate expertise early.

Consult

- Draw on experienced colleagues, research office, research Panel members and funding officials
- Learn from “failure” and feedback (<20% of proposals may be funded)

MRC Industry Collaboration Agreements (MICA)

- Encouraging and supporting collaborative research projects between academic and industry researchers
  - Ensure that you provide details of the IP distribution agreements between academic and industrial parties
- Key feature: **Flexibility**
  - The level and nature of industry contribution can vary – minimum amount will depend on IP arrangements and research stage (basic or applied)
  - Companies of any size can participate
  - Applies to all MRC funding and fellowship schemes
- Agreement between partners forms part of application – this may take months of negotiation.
- For DPFS, MICA forms are only required at Full stage, but an overview should be provided at Outline

MRC Industry Collaboration Agreements (MICA)

- MICA proposals are assessed in parallel with other proposals and the quality of the proposal is of primary importance.

- Questions that may apply particularly to MICA proposals are:
  - Would MRC funding support work that would otherwise not be undertaken at the required quality level or timescale?
  - Is the project truly collaborative and intellectually led by the academic PI?
  - Is there long-term freedom to operate?
  - Are the IP distribution arrangements within the MICA rules?
    - http://www.mrc.ac.uk/Fundingopportunities/Grants/MICA/Specification/index.htm

What makes an exciting proposal? (My view)

- Addresses a clear need or niche (doesn't have to be 'big' but must be significant)
- A clear, logical, evidence-based rationale with few 'leaps of faith'
- New or exciting (& well though out) use of technology [much rarer than you might imagine]

and/or

- Something previously overlooked but subsequently very logical (obvious?)
- Clear and well thought through plan, addressing all relevant questions and risks in a logical order and taking account of 'route to market'

Preparing your application

Need

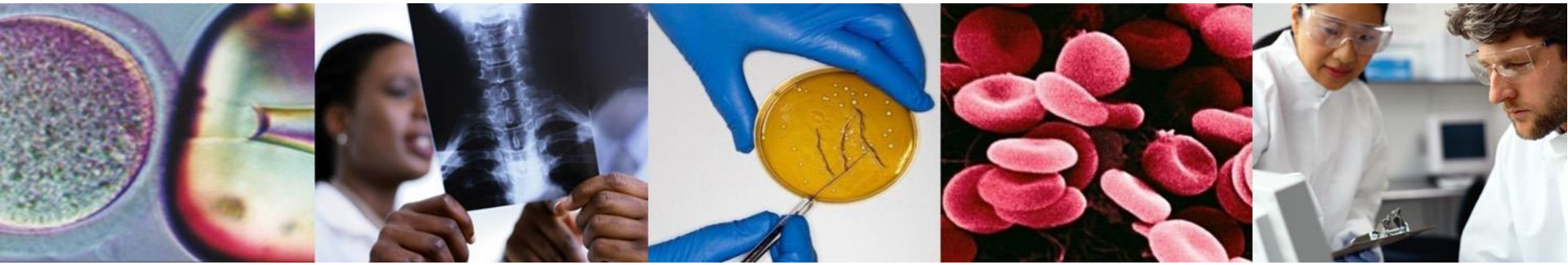
Deliverability

IP

Rationale

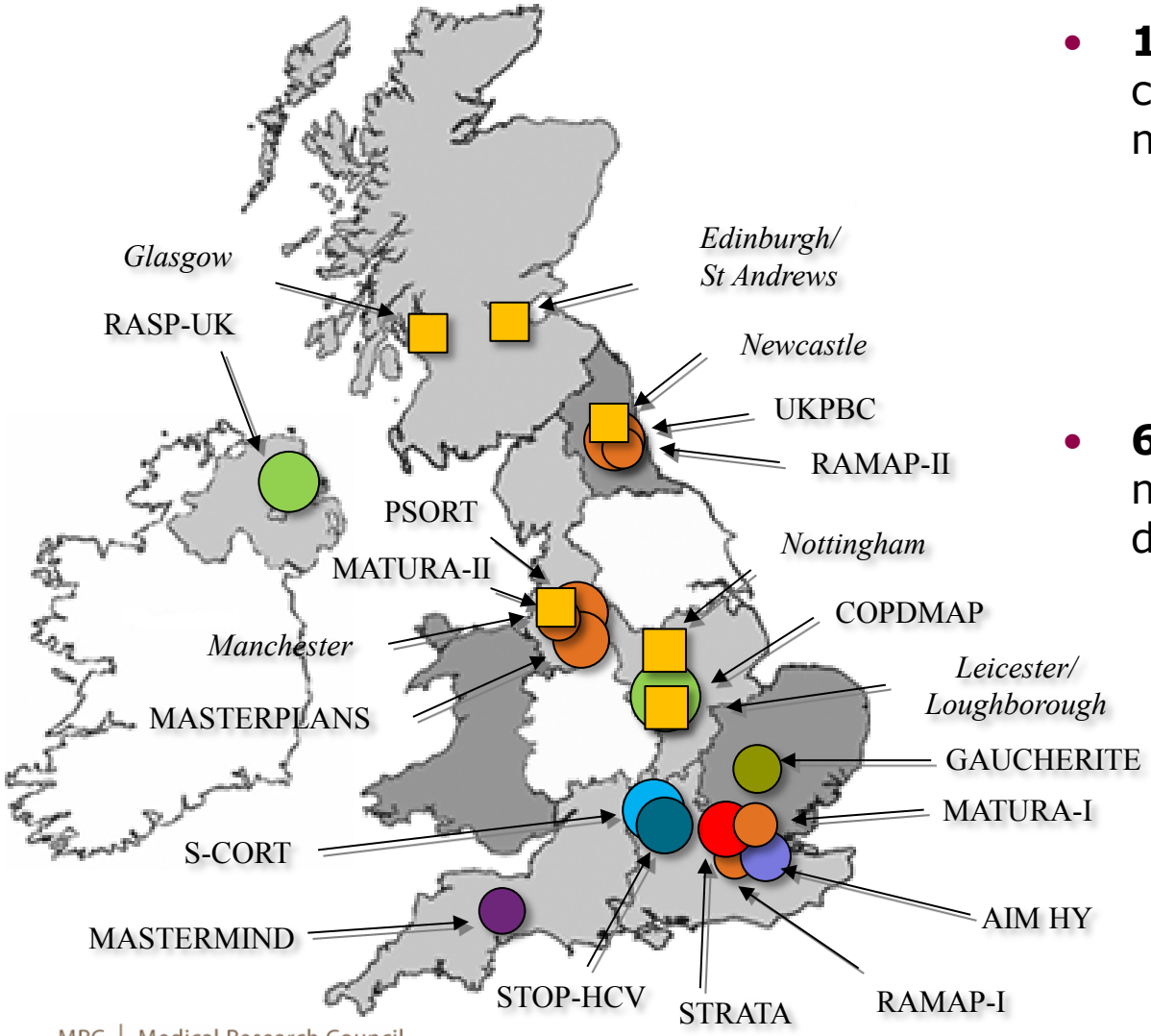
Downstream Support

An application will only be as strong as its weakest link

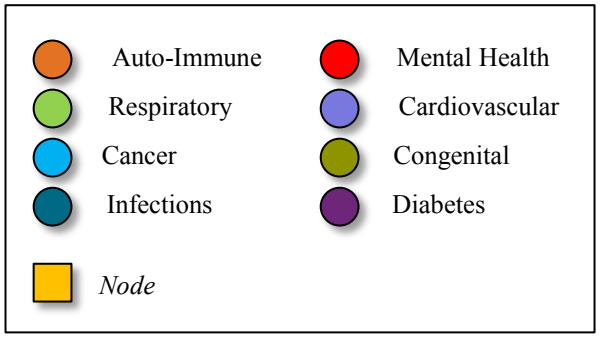


MRC Translational Strategic Initiatives

MRC Stratified Medicine Consortia and MRC/EPSRC Molecular Pathology Nodes



- **13** internationally competitive stratified medicine discovery engines
  - Total c.£60m
  - 3 charity co-funders (CRUK, ARUK, BHF)
  - 32 academic and 51 commercial partners
- **6** centres of innovative molecular diagnostic test development
  - Total c.£16m
  - 8 academic and 21 commercial partners



AMR Target Discovery and Validation

A £4 million call under **Global Challenges Research Fund** to stimulate development of new antibacterials for use in LMICs

Antibacterial drug discovery is challenging

- keeping the drugs in the bugs
- fast mutation rate
- toxicity to the host.

Promising candidates fail because of low efficacy or safety, due to a **lack of understanding** and **validation** of the biological target.

Funding available for **consortia** that can demonstrate the relevant skills (basic bacteriology, computational biology, chemical biology etc.) and capabilities to manage a complex, multidisciplinary programme of work.

The following strategies will be considered:

- Methods to find new antibacterial targets e.g. discovery platforms, data mining, genetics.
- Improved mechanistic understanding of new targets, the major systems targeted by existing antibiotics and mechanisms of resistance.
- Approaches to revisit, refine or redesign existing or failed antibiotics
- New approaches to screening e.g. new methods, assays, cell lines, clinical isolates.
- New animal challenge models, to understand and investigate pharmacology, PK/PD and bioavailability etc.
- New treatment approaches e.g. targeting the host, antibody therapies etc.

Therapeutic Target Validation in Mental Health call coming soon in 2018/19

MRC / Industry Asset Sharing 2017

- Researchers can use industry compounds in experimental medicine studies to understand disease mechanisms and explore treatment opportunities
- 68 compounds, with at least 21 CNS-penetrant, across 61 mechanisms of action

MRC/AstraZeneca Centre for Lead Discovery

- Access to AstraZeneca's ~2m screening collection and technology platforms to discover therapeutically-relevant small molecules
- MRC-funded scientists alongside AZ researchers, working on MRC selected projects.
- Two pilot studies instigated in collaboration with LMB
  - Identification of small molecule inhibitors using biochemical assay (1536 well format – 1 million compounds)
  - Identification of small molecule inhibitors and activators using a cell based assay (384 well format – 400k compounds)




MRC/UCB antibody discovery initiative

- Access to UCB's innovative technology platform
  - novel platform technology capable of sampling the immune repertoire through culturing B-cell pools,
  - identifying wells containing binders
  - identifying antigen specific B-cells within wells of interest.
  - Single cell PCR and gene cloning to generate constructs for the expression of recombinant antibodies of the desired specificity
  - Suitable for the identification of rare functional antibodies
  - Suitable for humanisation to obtain therapeutic antibodies or for surrogate anti-rodent antibodies as tool

EMINENT network

- The Experimental Medicine Initiative to Explore New Therapies;
- The MRC, GlaxoSmithKline and five UK universities collaborating to crack difficult disease areas;
- Investigation of fundamental biological mechanisms responsible for a range of inflammatory diseases → accelerating the development of innovative treatments;
- Up to £8m over five years matched with GSK in-kind contributions;
- Coordinated by UCL, bringing together teams of researchers initially from the Universities of Cambridge, Glasgow, Newcastle, Imperial College London and UCL, with GSK researchers;

Contacts

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- Gene and cell therapies, vaccines and physical therapies

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