2018

Strategic Review of CRUK's Investment in Radiation Biology and Radiation Oncology

PANEL REPORT

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EXECUTIVE SUMMARY

Radiotherapy is a mainstay of current cancer treatment. How we improve radiotherapy treatment based on both physical and biological aspects is a key research priority for Cancer Research UK (CRUK)[1]. The organisation invests in radiation biology and radiation oncology research through a combination of a core-funded Institute, infrastructure grants and response mode project, programme and trial grants, as well as supporting initiatives seeking to build capacity or overcome barriers to research in this field. A major review of radiation biology and radiation oncology research in the UK was last carried out in 2003 by the National Cancer Research Institute (NCRI), which was followed up by a rapid review in 2008. The output of the 2003 review led to the establishment of the CRUK/MRC Oxford Institute for Radiation Oncology, and the output of the 2008 update led to the creation of the Clinical & Translational Radiotherapy Research Working Group (CTRad).

In recognition of the importance of radiation biology and radiation oncology (RB&RO) to CRUK's research strategy, this current, independent review was commissioned by the Charity's Research Committee (RC). As a community, we have a unique opportunity afforded by recent investment not only across the NHS in improved radiotherapy infrastructure, but also significant national investment in state of the art technologies such as proton therapy. Based on these developments in the field, the RC tasked this Review Panel with the question 'How should CRUK structure its investments in radiation oncology and radiobiology research in the future'.

The overall conclusion of this Review Panel is that whilst there has been significant progress since the NCRI reviews of 2003 and 2008, current levels of research funding from CRUK (~5% of research spend) to support RB&RO research is less than would be expected in the context of its clinical importance, curative potential, and the current unanswered questions, including how to combine radiotherapy with other approaches (including targeted therapies and immune manipulation) and understanding the potential benefits of particle treatments (protons and heavier ions/or particles). In light of this conclusion, we have agreed the following recommendations for CRUK to consider in developing its approach for RB&RO:

1. CRUK needs to more clearly articulate that RB&RO research is a priority, and signal an ambition to grow investment into this important research field;
2. CRUK should proactively convene the research community to develop a detailed strategy for RB&RO research which must include the key research questions in the field and must consider how to optimise translation of scientific discoveries to deliver patient benefit;
3. Specific research expertise in RB&RO research should be incorporated into all CRUK funding committees so that they have the expertise to develop committee remits and assess grant applications;
4. There is an important role for a critical mass of core-funded investigators in RB&RO research at one or more locations, as investment of this nature has allowed the UK to start to regain effective capability in this area following a period of decline;
5. CRUK should develop a well-coordinated network of Centres of Excellence in RB&RO research that has cutting-edge facilities for translational and clinical research and aligns with recent infrastructure developments in the NHS;
6. Centres of Excellence should capitalise on local research strengths and develop unique research programmes, but must also complement each other and work together to form a national network that has the capability to deliver research across a broad range of themes and key research questions, and has a clear ambition to improve patient outcomes;

[1] CRUK, Beating Cancer Sooner – Our Research Strategy

7. Centres of Excellence should be expected to play a leading role in training the next generation of RB&RO researchers, particularly clinician scientists, and CRUK should explore partnership opportunities to implement innovative training programmes across the network;
8. A programme of activities to further build the UK RB&RO community should be developed and implemented, potentially including events and workshops, and importantly, mechanisms introduced to facilitate and incentivise collaborations between discovery and clinical scientists, and with full-time clinical oncologists in the NHS;
9. A partnership strategy for RB&RO research, covering national, international, commercial and non-commercial opportunities, should be developed in order to leverage opportunities for further research investment and access to experimental drugs, tools and technologies;
10. The absence of any specific questions orientated to RB&RO research in CRUK's Grand Challenge initiative is a missed opportunity and the charity is encouraged to address this in future Grand Challenge rounds;
11. The development of a national particle research facility would potentially transform RB&RO research in the UK, therefore CRUK should consider how to convene the national debate around this issue.

Professor Patrick Maxwell, DPhil FRCP FMedSci,

Chair of the Independent Review Panel

Regius Professor of Physic & Head of the School of Clinical Medicine

University of Cambridge

BACKGROUND TO THE REVIEW

The last comprehensive review of Radiation Biology and Radiation Oncology (RB&RO) research in the UK was undertaken by the National Cancer Research Institute (NCRI) in 2003. This review was commissioned based on growing concerns on the overall sustainability of the field of RB&RO in the UK. Following the review, a number of crucial steps were undertaken to address the highlighted concerns, most notably the major investment in establishing the CRUK/MRC Oxford Institute for Radiation Oncology. Since 2003, several relevant reviews have been undertaken[2][3] by stakeholders in this field in the UK, including a 2008 update by the NCRI[4] which led to the creation of the Clinical & Translational Radiotherapy Research Working Group (CTRad) in 2009. However, until the recent publication of CTRad's Strategic Vision 2018-2021[5] these have not been primarily research focused.

Given that radiotherapy is a mainstay of treatment for cancer patients, the field of RB&RO remains a key focus area for CRUK. It supports research through a combination of infrastructure grants and response mode project, programme and trial grants, as well as supporting initiatives seeking to build capacity or overcome barriers to research in this field. In light of the importance of RB&RO to the Charity mission, CRUK's Research Committee (RC) requested this Panel undertake an independent review of CRUK's investment and strategy in the field of RB&RO, addressing the question ''How should CRUK structure its investments in radiation oncology and radiobiology research in the future'. Full membership of the Review Panel can be found in Appendix 1 and the agreed terms of reference in Appendix 2.

As a research community, there is an important opportunity to capitalise on recent investment not only in updated clinical radiotherapy infrastructure with the NHS, but also major national investment in state-of-the-art clinical technologies such as stereotactic ablative radiotherapy (SABR), proton therapy and magnetic resonance linear accelerator (MR-Linac) systems at locations across the UK. As a result, this Panel welcomes CRUK's decision to consider how best to support, sustain and grow the RB&RO research community in the UK in the future.

[2] Royal College of Radiologists, Clinical Oncology – The Future Shape of the Speciality

[3] Cancer Taskforce, Achieving World Class Cancer Outcomes – A Strategy for England 2015-2020

[4] National Cancer Research Institute, Radiotherapy Rapid Review 2008

[5] Clinical and Translational Research Working Group, Strategic Vision 2018-2021

REVIEW METHODOLOGY:

REVIEW PANEL AND WORKSHOPS

This independent strategic review was coordinated by the Chair, Professor Patrick Maxwell, with operational support from members of the Research and Innovation Directorate at CRUK. Broadly the review was divided into 2 phases, each with an associated workshop for the Panel:

1. Landscaping – What are the major research priorities in the field of RB&RO?
2. Recommendations – How should CRUK best support the field of RB&RO?

EXTERNAL CONSULTATION

This Panel concluded that consultation with the community would be valuable as part of the review; therefore key stakeholder organisations and institutions were contacted for a written submission as part of the landscaping phase. This included leading UK host institutions in the field (including the CRUK Centres and Institutes), major academic funders in the UK, organisations responsible for training and development, leading international cancer research organisations and relevant commercial partners. A full list of the stakeholders contacted can be found in Appendix 3. Responders were asked to provide a single coordinated response from their institution, although no format or word limit was required. 6 sub-questions were provided to guide the submissions and these can be found in Appendix 3. Responses were evaluated by all members of this Review Panel and informed the discussions that took place during the workshops.

INTERNAL PORTFOLIO REVIEW

To inform our discussion on how best to support the field of RB&RO in the future, CRUK undertook a portfolio review to evaluate the amount of funding currently provided to researchers in the field of RB&RO (both by CRUK and the other NCRI partners). This included details of the individual funding mechanisms being utilised by researchers from the field of RB&RO when applying to CRUK. A summary of this data is provided in Appendix 4 of this report.

KEY RECOMMENDATIONS

RECOMMENDATION 1: CRUK NEEDS TO MORE CLEARLY ARTICULATE THAT RB&RO RESEARCH IS A PRIORITY, AND SIGNAL AN AMBITION TO GROW INVESTMENT INTO THIS IMPORTANT RESEARCH FIELD;

This Panel recognise that CRUK has played a pivotal role in the growth and development of RB&RO research in the UK since the publication of the 2003 NCRI report. Notably, we consider that the establishment of the CRUK/MRC Oxford Institute for Radiation Oncology has met a number of important objectives. This level of investment in a critical mass is important in ensuring that the community perceive that RB&RO research is a strategic focus for CRUK. The Institute under the leadership of Professor Gillies McKenna has increased both the international profile and competitiveness of the field of RB&RO in the UK. We consider it important to also acknowledge the role of the NCRI partners in support of the establishment of CTRad.

However, we note that the current CRUK Research Strategy published in 2014 highlights that the focus is the "continued growth in radiobiology and radiotherapy research through the CRUK/MRC Oxford Institute for Radiation Oncology". It is the opinion of this Panel that this may create a perception within the UK community that CRUK does not consider RB&RO research a priority more broadly. Perhaps as a consequence we note the low number of CRUK Centres highlighting RB&RO research as a priority theme as part of the recent call, resulting in a considerable missed opportunity to build the underpinning national infrastructure to support the field. This Panel considers that clear articulation of priority areas as part of significant infrastructure calls, such as the CRUK Centre call, has a major effect on the themes developed by the associated leadership teams in their applications.

As an example, we would highlight the extremely exciting developments related to cancers of unmet need (lung, pancreatic, oesophageal and brain). CRUK has consistently communicated these tumour types to be priority areas for future investment. We consider this to have been highly successful in influencing leadership across the country to build the infrastructure and recruit and develop new talent to research these tumour types where there has been little progress in clinical outcome for many years. This underpinning infrastructure investment will no doubt have a significant long-term benefit for research in these tumour types, which have often struggled to attract funding via traditional competitive funding routes, and ultimately deliver significant patient impact. We consider a similar ambition to develop RB&RO could be transformative.

RECOMMENDATION 2: CRUK SHOULD PROACTIVELY CONVENE THE RESEARCH COMMUNITY TO DEVELOP A DETAILED STRATEGY FOR RB&RO RESEARCH WHICH MUST INCLUDE THE KEY RESEARCH QUESTIONS IN THE FIELD AND MUST CONSIDER HOW TO OPTIMISE TRANSLATION OF SCIENTIFIC DISCOVERIES TO DELIVER PATIENT BENEFIT;

It is the opinion of the Panel that given the importance and breadth of the field, CRUK should consider developing a clear strategy specifically for RB&RO research, covering discovery through to clinical sciences. We encourage CRUK to engage expertise from disciplines such as the physical sciences and engineering in developing this strategy, which should address the translation of scientific discoveries to deliver clinical impact.

As part of our review, key organisations and institutions were invited to submit priority areas for the field. These responses were consolidated by the Review Panel during the first workshop to identify common research themes which are presented in Appendix 4. In this section, we briefly discuss several of these priority areas. While we acknowledge that these are not exhaustive, they represent a summary of this Panel's discussions and would serve as a starting point with which to engage the wider community.

DISCOVERY RESEARCH:

The Panel noted that CRUK supports a broad range of world-leading research relevant to RB&RO including, but not limited to, genomic integrity (including DNA damage repair), hypoxia, tumour microenvironment, evolution of therapeutic resistance, immunology and imaging which can underpin future research and translational developments. However, we noted that rarely was response to radiation a key driver, which we consider a significant missed opportunity given the strength of the UK cancer research community in many of these areas. Mechanisms by which to forge such collaborations are discussed elsewhere in this report.

It was the opinion of this Panel that understanding the biological response to radiation remains a key priority, and is essential in order to maximise the therapeutic response while minimising the significant toxicities associated with radiotherapy. Furthermore, given that the availability and uptake of particle therapies, including protons and heavy ions, will continue to increase, we consider that understanding the difference in biological response between radiation modalities is key to harnessing the promise of these technologies. This understanding will be necessary to both design rational combination approaches, and to ensure the adoption of these promising technologies is appropriate and evidence based.

In alignment with this, both this Panel and responders to the consultation note that there would be a significant utility in developing novel models, particularly to study long-term toxicity associated with radiotherapy. However, this Panel is also of the opinion that there remains a significant opportunity to address important questions utilising existing preclinical models, for example in the study of the influence of tumour genetics on response or exploring combination approaches and synthetic lethality.

CLINICAL RESEARCH THEMES:

In was the opinion of this Panel that personalisation of radiotherapy has progressed significantly more slowly than for systemic therapeutics. Developing surrogate markers will be essential, particularly for novel drug-radiotherapy combinations where there is a risk that associated toxicities may be increased. We note that historically a barrier has been validation and clinical adoption of such approaches. An example is MRE11 for stratification of therapy in bladder cancer, which has struggled in clinical adoption, and hypoxia where despite significant conceptual advances from many groups, the community has failed to deliver a definitive trial. It is our opinion that the community must shift to designing prospective trials with sufficient power to validate biomarker endpoints, rather than relying on retrospective analysis.

Late toxicity is highlighted as a crucial area for future studies in the field of RB&RO, particularly given the introduction of novel radiotherapy approaches and that therapy is now multi-modality for the majority of patients receiving radiotherapy. Again, developing surrogate markers will be important. As toxicity remains a major hurdle for engaging pharmaceutical partners, the community must address these concerns as a priority. Given that clinical oncologists are trained in both radiotherapy and systemic therapeutics, the UK is well placed to lead on the trial of novel radiotherapy-drug combinations.

Introducing effective adaptive therapy and real-time treatment planning are highlighted as a recurring theme amongst the community. Given the continued improvement of imaging technologies, as well as installation of MR-LINAC platforms in the UK, this will continue to be a priority area. We note that development and validation of intra-therapy biomarkers of response will be essential to deliver patient impact in this area. Furthermore, there is significant interest in artificial intelligence (AI) which has considerable potential in this area. We note that there are opportunities to develop highly enabling partnerships in this space that would leverage not only funding, but also expertise and access to technology for the community. The coordinated approach and data collection that is possible across the NHS would make the UK an attractive location for such studies.

RECOMMENDATION 3: SPECIFIC RESEARCH EXPERTISE IN RB&RO RESEARCH SHOULD BE INCORPORATED INTO ALL CRUK FUNDING COMMITTEES SO THAT THEY HAVE THE EXPERTISE TO DEVELOP COMMITTEE REMITS AND ASSESS GRANT APPLICATIONS;

CRUK has a comprehensive suite of opportunities to fund discovery and clinical research. That said, this Panel considers it important that the individual remits of each of the committees be clarified in the context of RB&RO research. The Panel would also like to emphasise that much RB&RO research is translational in nature and that available funding opportunities need to reflect this. During our discussion, a miscommunication of the remit of the Clinical Research Committee was highlighted, namely that the recently published CRUK Clinical Research Statement of Intent was perceived to exclude toxicity/tolerability-driven trials. Given many of the technological developments in recent years aim to reduce toxicity associated with radiotherapy, this is viewed as a key issue. We recommend that this be reviewed as a priority by CRUK, to ensure researchers are not discouraged from applying with toxicity driven proposals for radiotherapy or radiotherapy-drug combinations.

While the idea of forming a stand-alone 'Radiation Research Committee' was discussed, it is not clear to this Panel that this is warranted at present. That said, CRUK currently has dedicated Committees for both drug discovery and drug development, and a similar case could be made for the field of RB&RO. In the view of this Panel, the priority should be to ensure that the current funding committees have sufficient expertise to assess grant applications in the field of RB&RO research. The audit performed as part of this review suggests that some may lack sufficient expertise in the field of RB&RO. While we appreciate the difficulty in ensuring representation and balance across fields, RB&RO research has a number of special challenges, such as high infrastructure costs and dependency on multidisciplinary expertise. As a result, this Panel recommends having appropriate international experts, who are familiar with the priorities and challenges for the field, to ensure grants are properly reviewed and the potential patient impact appreciated.

RECOMMENDATION 4: THERE IS AN IMPORTANT ROLE FOR A CRITICAL MASS OF CORE-FUNDED INVESTIGATORS IN RB&RO RESEARCH AT ONE OR MORE LOCATIONS, AS INVESTMENT OF THIS NATURE HAS ALLOWED THE UK TO START TO REGAIN EFFECTIVE CAPABILITY IN THIS AREA FOLLOWING A PERIOD OF DECLINE;

It is the opinion of this Panel that the establishment of the CRUK Oxford Institute for Radiation Oncology in partnership with the MRC was a significant national achievement, and has contributed to the reinvigoration of RB&RO research in the UK. Furthermore, the Institute has dramatically increased the profile of the country's RB&RO research in the UK and internationally. We acknowledge the role of CRUK, the MRC and the leadership of Professor Gillies McKenna in establishing the Institute and its continued development.

This Panel considers it essential that there is continued support from CRUK for a critical mass of core-funded RB&RO research in one or more locations and that any such investment will only realise its full potential if it is effectively supported by its host institution. In our view, this type of investment provides the long-term support necessary to establish the appropriate multidisciplinary faculty to have significant impact in the field of RB&RO, including but not limited to radiation physicists, engineers, cancer discovery researchers and clinical oncologists. However, not all of this necessary research base can be supported by individual funders such as CRUK and the MRC in isolation. Therefore, there is a need for significant long-term commitment from any host institution, university and NHS trust in establishing the necessary faculty and underpinning infrastructure.

RECOMMENDATION 5: CRUK SHOULD DEVELOP A WELL-COORDINATED NETWORK OF CENTRES OF EXCELLENCE IN RB&RO RESEARCH THAT HAS CUTTING-EDGE FACILITIES FOR TRANSLATIONAL AND CLINICAL RESEARCH AND ALIGNS WITH RECENT INFRASTRUCTURE DEVELOPMENTS IN THE NHS;

There is currently a unique opportunity to capitalise on recent national developments including the impending availability of proton therapy and national MR-Linac platforms. Furthermore, the NHS has recently made significant investment in updating clinical radiotherapy infrastructure in addition to these novel technologies. Given that these platforms have dedicated research capability, this is an exciting time for the field of RB&RO, as the UK community will have access to internationally competitive infrastructure which has been lacking.

As a result of the above, the Panel concluded that CRUK's investment strategy should not focus RB&RO research on one location in isolation. While the appropriate number of Centres for the UK would need to be established, we highlight the network model established in Germany for RB&RO research, which includes 8 Centres each with the critical mass of expertise required to deliver high impact research. This is a world-leading example of how to establish the necessary multidisciplinary expertise necessary to carry out practice changing research in this collaborative field.

While specific recommendations on the development and implementation of such a network is beyond the scope of this review, we suggest that this could involve a competitive national call involving the CRUK Centres and other nationally leading locations. A network would include core-funded hubs with significant critical mass, but there should also be the opportunity to include small centres with particular expertise. It is our opinion that a competitive call would have the advantage of leveraging further investment from host locations and partners committed to the field of RB&RO and drawing in additional faculty from other disciplines at these Centres. However, we acknowledge that for such an approach to be successful additional investment is likely to be required to establish the network.

RECOMMENDATION 6: CENTRES OF EXCELLENCE SHOULD CAPITALISE ON LOCAL RESEARCH STRENGTHS AND DEVELOP UNIQUE RESEARCH PROGRAMMES, BUT MUST ALSO COMPLEMENT EACH OTHER AND WORK TOGETHER TO FORM A NATIONAL NETWORK THAT HAS THE CAPABILITY TO DELIVER RESEARCH ACROSS A BROAD RANGE OF THEMES AND KEY RESEARCH QUESTIONS, AND HAS A CLEAR AMBITION TO IMPROVE PATIENT OUTCOMES;

As noted elsewhere in this report, it is the belief of this Panel that for the further development of an internationally competitive RB&RO network in the UK, it will be necessary to integrate multiple fields of research. Examples discussed include, but are not limited to, genomic integrity, hypoxia, tumour microenvironment and immunology, imaging, radiation physics and drug discovery/development. It is our recommendation that if Centres of Excellence were to be implemented for RB&RO research, these should be strongly encouraged to develop unique research programmes, capitalising on local research strengths.

For a distributed model of Centres of Excellence to be successful, it would be essential that they are tasked with building a collaborative leadership network, which capitalises on the individual expertise of each Centre, to cover the breadth of this field, and build on the success of CTRad in creating and supporting radiotherapy research in the UK. Within this overall national network, we envisage sub-networks linking Centres with complementary expertise in areas of discovery, clinical sciences technologies and platforms. The challenge of developing and managing such a network is not underestimated by this Panel, but we consider this will be crucial to maximise utilisation of infrastructure and potential impact of the research.

As an example of such collaboration we cite the CRUK Advanced Radiotherapy Technologies Network consortium (ARTNET), funded via a CRUK Network Accelerator Award. This consortium highlights a model that could be replicated by a Centres Network, and beyond, to forge further national and international collaborations and link researchers working on similar challenges in the RB&RO community. Furthermore, we believe such a collaborative and networked approach will be necessary to ensure evidence based clinical adoption of developments in the field.

RECOMMENDATION 7: CENTRES OF EXCELLENCE SHOULD BE EXPECTED TO PLAY A LEADING ROLE IN TRAINING THE NEXT GENERATION OF RB&RO RESEARCHERS, PARTICULARLY CLINICIAN SCIENTISTS, AND CRUK SHOULD EXPLORE PARTNERSHIP OPPORTUNITIES TO IMPLEMENT INNOVATIVE TRAINING PROGRAMMES ACROSS THE NETWORK;

We agree that a significant risk to the future of RB&RO research in the UK is the low number of clinical (radiation) oncologists that progress within the clinical academic career track. That said, we wish to highlight that research funders should not consider it to be a failure if academically trained clinical oncologists focus on clinical duties, as the period of research is a significant benefit for the training of these clinicians. Whilst we acknowledge that this is a significant problem across many medical specialities, we consider the issue to be particularly acute in clinical oncology due to the training schedule and clinical workload. We recognise that CRUK is currently in the process of reviewing its support for clinical training, which will involve input from key members of the clinical oncology community.

From the data presented to this Panel we note that the CRUK Oxford Centre is responsible for most CRUK studentships specifically allocated to RB&RO research, and we regard this as a very valuable contribution. However, we consider it unrealistic to expect one CRUK Centre to drive the coordinated training effort that is required nationally to ensure the sustainability of this field. Furthermore, the number of fellowship applications in this field to CRUK (clinical and non-clinical) is worryingly low; and there are very few fellows with a significant research focus on RB&RO outside Oxford. If CRUK were to establish a Centres of Excellence model in RB&RO research, this Panel strongly encourages CRUK to task Centres to develop innovative, nationally-coordinated training and mentorship programmes, capitalising on the breadth of research strengths across the network. This should form part of both the competitive review process for the establishment of the Centres, but also the ongoing assessment for those that are successfully awarded.

In discussing alternative funding opportunities for training for RB&RO, we considered dedicated CRUK Centre Network Accelerator Award funding to be a viable route that has been successfully utilised in other fields of research. Furthermore, it is the opinion of this Panel that CRUK should explore potential partnership opportunities to leverage additional support for a dedicated training programme. In particular we highlight that the Royal College of Radiologists should be invited to be involved in the development of such an approach.

RECOMMENDATION 8: A PROGRAMME OF ACTIVITIES TO FURTHER BUILD THE UK RB&RO COMMUNITY SHOULD BE DEVELOPED AND IMPLEMENTED, POTENTIALLY INCLUDING EVENTS AND WORKSHOPS, AND IMPORTANTLY, MECHANISMS INTRODUCED TO FACILITATE AND INCENTIVISE COLLABORATIONS BETWEEN DISCOVERY AND CLINICAL SCIENTISTS, AND WITH FULL-TIME CLINICAL ONCOLOGISTS IN THE NHS;

This Panel acknowledges the important role that CTRad plays nationally in coordinating the RB&RO research community. While we consider it important that CTRad continues this role, we conclude that CRUK could also play a more active part in the development of the community and fostering collaboration.

To encourage the community to build new links we recommend that CRUK consider organising dedicated workshops and meetings bringing together key opinion leaders in relevant fields of research, as well as ensuring that RB&RO research features more prominently across CRUKs existing high-profile research events. It is the opinion of this Panel that CRUK should consider innovative mechanisms to facilitate new collaboration. In this regard the Panel notes with interest the model of the CRUK multidisciplinary project awards, which specifically require collaboration across disciplines. Such an approach could be used to enable CRUK's discovery scientists to focus on clinically relevant questions in collaboration with clinical (radiation) oncologists and could have a significant impact on the overall quality of RB&RO research in the UK.

We note that the approaches outlined above represent a partnership opportunity, as demonstrated by CRUK's existing partnership with Arthritis UK to facilitate sandpit workshops in immunology or co-funding of the multidisciplinary project awards in collaboration with the EPSRC. This would not only leverage investment, but provides access to relevant research communities, which may not traditionally consider CRUK funding, e.g. physical sciences and engineering.

RECOMMENDATION 9: A PARTNERSHIP STRATEGY FOR RB&RO RESEARCH, COVERING NATIONAL, INTERNATIONAL, COMMERCIAL AND NON-COMMERCIAL OPPORTUNITIES, REQUIRES TO BE DEVELOPED IN ORDER TO LEVERAGE OPPORTUNITIES FOR FURTHER RESEARCH INVESTMENT AND ACCESS TO EXPERIMENTAL DRUGS, TOOLS AND TECHNOLOGIES;

Key to the continued development of the field of RB&RO will be the establishment of strategic partnerships both nationally and internationally. We acknowledge that CRUK has had considerable success in forming such partnerships, both with other not-for-profit organisations and the commercial sector. However, we note that few have been established with a focus on RB&RO research, which is a considerable missed opportunity. For example, whilst historically it might have been the case that the pharmaceutical industry has shown limited interest in RB&RO research, this is now changing (as illustrated by the recent Nature Reviews Clinical Oncology publication by CTRad and a number of major pharmaceutical companies[6]).

It is the opinion of this Panel that to successfully address the research themes highlighted in this report, it will be essential for CRUK to develop a coordinated strategy for partnership. If executed correctly this could leverage both investment and enable the community to access resources such as experimental tools, technologies and drugs. We consider that this will be key if the UK is to be world-leading in this field. In particular, partnership between the major technology suppliers and academia has been historically limited. CRUK's national and international profile could be used to convene the necessary organisations to establish such strategic partnerships for the UK research community.

RECOMMENDATION 10: THE ABSENCE OF ANY SPECIFIC QUESTIONS ORIENTATED TO RB&RO RESEARCH IN CRUK'S GRAND CHALLENGE INITIATIVE IS A MISSED OPPORTUNITY AND THE CHARITY IS ENCOURAGED TO ADDRESS THIS IN FUTURE GRAND CHALLENGE ROUNDS;

This Panel considers that the CRUK Grand Challenge initiative is an extremely exciting development, which has energised the international research community to address some of the major questions in cancer research. By pioneering the approach and providing significant, long term funding, CRUK has enabled establishment of the necessary collaborative and multidisciplinary teams.

Given the overall importance of radiotherapy to the clinical treatment of cancer, we consider it disappointing that neither of the initial two rounds have featured challenges relating to radiation oncology. This Panel believes this is a missed opportunity to foster the development of a national and international collaborative network, which would be highly enabling. This could have significant long-term benefits beyond the scope of the original award, not only increasing the profile of RB&RO research in the UK but also signalling CRUK's commitment to the field. Moreover, the high-profile nature of a Grand Challenge represents a significant opportunity to develop strategic partnerships with international funders or commercial organisations.

In support of the above, it is the opinion of this Panel that CRUK should consider appointing a key opinion leader from the field of RB&RO to the Grand Challenge Advisory Panel. While it is acknowledged that ensuring

[6] Clinical development of new drug–radiotherapy combinations – Nature Reviews Clinical Oncology volume 13, pages 627–642 (2016)

representation from all fields of research is difficult, we consider the lack of RB&RO expertise a significant omission given the scope of this field.

As part of this review process, Panel members were asked to consider potential Grand Challenge questions for future rounds as well as discuss these with other key opinion leaders in the field. Patient stratification and optimisation of radiotherapy for specific patient populations is highlighted as an area that would benefit from this type of large scale, multidisciplinary and collaborative approach.

RECOMMENDATION 11: THE DEVELOPMENT OF A NATIONAL PARTICLE RESEARCH FACILITY WOULD POTENTIALLY TRANSFORM RB&RO RESEARCH IN THE UK, THEREFORE CRUK SHOULD CONSIDER HOW TO CONVENE THE NATIONAL DEBATE AROUND THIS ISSUE.

The recent £250M investment in two state-of-the-art proton facilities in the UK is a significant development. Based within a clinical and academic framework, these facilities have the capability to deliver both clinical and fundamental underpinning research. However, despite the presence of internationally recognised expertise in physics, accelerator design and engineering, disappointingly, there are currently no plans for a UK particle clinical research facility. Given the significant research and technological challenges around the delivery of proton therapy, such as whether protons or other particles (e.g. carbon, helium or lithium) represent the 'optimum' profile for cancer treatment, this Panel believe there is significant opportunity to develop such a capability in the UK.

While we recognise that the creation of a facility, capable of the necessary engineering innovation, is beyond the scope of CRUK funding we consider that CRUK could demonstrate leadership by convening national funders around this issue. Given the multidisciplinary nature of this endeavour we believe that a partnership between multiple research councils and UKRI, CRUK and the Department for Health, would be appropriate. Furthermore, given the scale of investment necessary we believe central government should have a stake in such a high-profile programme, which could place the UK at the forefront of this key area of biomedical, engineering and physics research.

Acknowledging that the specific scope of this programme would require further careful consideration and input from the research community, we propose that a potential framework could be structured around four key research strands. These strands would be linked through a formal network of academic centres each bringing complimentary expertise and resource to the programme, including links to existing NHS proton facilities and associated research infrastructure. The facility should be co-located with a major NHS cancer centre, research excellence in RB&RO, academic physics institution and with associated radiobiology infrastructure including animal research capability.

Potential scope for each research strand is as follows: (1) To deliver new technologies in accelerator, gantry, beam delivery and imaging design for different particles. This could involve development of "demonstrator facilities" which could be used for 2D and 3D radiobiology, zoomorphic and anthropomorphic phantoms and pre-clinical research, prior to development of clinical systems. (2) Construction and commissioning of a single facility able to deliver carbon and helium (at a minimum), to be a focus for clinical physics, engineering, radiobiology and in time, clinical research. This should have capability to apply new technologies developed from strand 1 and have capacity for experiments to be conducted at clinical energies with interrupting patient treatment. (3) To develop an integrated resource including data, tissue and blood samples, before, during and after treatment to include clinical outcomes, PROs and data from smart devices. Techniques from astronomy, particle physics and AI could be used to mine these data sets to enable economic indicators of clinical and technical/commercial viability to be evaluated. (4) Support and delivery of Clinical trials and studies via standard funding routes.

APPENDIX 1: REVIEW PANEL MEMBERSHIP

Professor Patrick Maxwell (Chair)	University of Cambridge
Professor Michael Baumann	German Cancer Research Center (DKFZ), Heidelberg
Professor Rob Bristow[7]	University of Manchester
Professor Anthony Chalmers	University of Glasgow
Professor Adrian Crellin	University of Leeds
Professor Anna Dubrovska	TU Dresden / HZDR
Professor Gerard Evan	University of Cambridge
Professor Alec Kimmelman	New York University

Note that CRUK staff provided secretariat support to the Review Panel, and prepared various briefing materials but did not directly contribute to the discussions

Dr Nathan Richardson, Head of Molecular and Cellular Medicines at the Medical Research Council, attended workshop two as an observer.

[7] Attended the first workshop only

APPENDIX 2: REVIEW TERMS OF REFERENCE

CRUK's Scientific Executive Board and Research Committee agreed the following terms of reference for this independent review.

THE FOLLOWING ARE TO BE INCLUDED WITHIN THE SCOPE OF THE REVIEW, WHERE AVAILABLE:

- Likely emerging areas in radiation oncology/biology in the next 10-15 years;
- Appraisal of CRUK radiation biology and oncology strategic funding in the past 10 years (source: CRUK committee data, scientific milestone reports and quinquennial reviews);
- Appraisal of CRUK fellowships and training funding in radiation biology and oncology in the past 10 years (source: CRUK committee data);
- Appraisal of CRUK response mode project, programme and trial funding in radiation biology and oncology across all CRUK schemes in the past 10 years (source: CRUK committee data);
- Appraisal of NCRI partners' relative contributions to radiation biology and oncology funding in the past 10 years, and CRUK's contribution within this context (source: NCRI CaRD data package);
- Appraisal of CRUK-led commercial partnerships in radiation biology and oncology in the past 10 years (source: CRT/ strategic partnerships data);
- Appraisal of the state of discovery, translational and clinical research within the UK, including strengths, weaknesses, opportunities and gaps (source: consultations with UK and international experts);
- Appraisal of barriers to radiation biology and oncology research that relate to, or could be influenced by, research funding – for example, suitability of funding schemes, distribution or format of infrastructure funding (source: consultations with UK and international experts).

THE FOLLOWING ARE CONSIDERED TO BE BEYOND THE SCOPE OF THIS REVIEW:

- Performance review of individual CRUK grants in radiation biology and oncology (these are covered by existing governance structures);
- The function of the Radiotherapy Trials Quality Assurance (RTTQA) programme (this is supported by top-sliced NIHR funds and although there have been recent concerns about RTTQA capacity being a factor in trial setup delay, this is considered to be an NIHR responsibility);
- Implementation of new radiotherapy techniques/equipment within the NHS (this was previously under the remit of a national radiotherapy implementation group (NRIG) within DH and while in latter years there has not been a dedicated group and clinical trials do facilitate best practice implementation, delivery itself remains an NHS-led issue);
- The progress review of CTRad and a decision around CRUK's future financial contribution to this;
- Assessment of barriers to radiation biology and oncology research that *do not* relate to, nor can be reasonably influenced by, research funding investments – for example, NHS equipment, medical physics career pathways, regulatory hurdles. (These have periodically been reviewed by CTRad or other parties, and can be referenced where helpful rather than repeating existing work).

APPENDIX 3: EXTERNAL STAKEHOLDER CONSULTATION

A written submission, addressing the questions below, was requested by the Chair of the Review Panel from the following institutions or organisations. Those highlighted in bold responded to this request.

1. What are the key discovery science questions in the field of radiation biology and physics?
2. What are the major challenges and research questions in clinical and translational radiation oncology?
3. What are the emerging technologies and methodologies likely to have major impact the field over the next 10 years?
4. How will the research workforce in UK radiation oncology need to develop over the next 10 years to achieve the necessary critical mass to remain internationally competitive?
5. What are the critical infrastructure and capital investments necessary over the next 10 years in order for the UK to be/ continue to be world-leading in this field?
6. Where are the top radiation oncology centres internationally and what makes their programmes cutting-edge? What can the UK learn from these centres?

CRUK CENTRES AND INSTITUTES
- **CRUK Beatson Institute**
- **CRUK Cambridge Institute**
- **CRUK Manchester Institute**
- **Francis Crick Institute**
- **Oxford Institute for Radiation Oncology**
- **CRUK Barts Centre**
- CRUK Birmingham Centre
- **CRUK Cambridge Major Centre**
- **CRUK Edinburgh Centre**
- **CRUK Glasgow Centre**
- **CRUK Imperial College London Centre**
- **CRUK Institute of Cancer Research Centre**
- **CRUK King's Health Partners Centre**
- **CRUK Manchester Major Centre**
- **CRUK Newcastle Centre**
- **CRUK Oxford Centre**
- CRUK Southampton Centre
- **CRUK University College London Centre**

OTHER LEADING UK ACADEMIC INSTITUTIONS
- University of Bristol
- **Queen's University Belfast**
- **University of Cardiff**
- University of Dundee
- **University of Leeds**
- **University of Leicester**
- University of Liverpool
- **University of Surrey**
- University of Sussex
- University of Warwick

UK ACADEMIC FUNDERS
- **Medical Research Council**
- Wellcome Trust
- National Institute for Health Research

TRAINING AND WORKFORCE
- **The Royal College of Radiologists**
- NIHR Trainees Coordinating Centre
- Health Education England
- General Medical Council
- National Clinical Director for Cancer

INTERNATIONAL ORGANISATIONS:
- National Cancer Institute
- American Association for Cancer Research
- European Society for Medical Oncology
- **European Organisation for Research and Treatment of Cancer**
- European Society for Radiotherapy and Oncology

COMMERCIAL PARTNERS:
- Pfizer
- AstraZeneca
- Merck
- Astex
- Vertex
- Eli Lilly and Company
- Genentech
- GSK
- Novartis
- Elekta
- Phillips
- Siemens Healthcare
- Varian
- J&J
- **Advanced Oncotherapy**
- **Proton Partners International**

APPENDIX 4: SUMMARY OF KEY RESEARCH THEMES IN DISCOVERY AND CLINICAL RESEARCH

KEY DISCOVERY SCIENCE THEMES:

1. Differences in biological response of tumour and non-malignant cells to ionising radiation and the mechanisms governing the resulting cell fate.
2. Signatures of cellular damage induced by alternative particle and photon radiation sources, and the differences in biological response to these therapeutic approaches.
3. Biological mechanisms underlying the inherent radio-resistance or sensitivity of different tumour types observed clinically.
4. Evolution of secondary resistance to radiotherapy and the mechanisms driving the tolerance to the resulting DNA damage.
5. Influence of tumour subtype on response to radiotherapy (e.g. genetics, genomics or transcriptomic) and the mechanisms driving these differences.
6. Radiation response at the tissue rather than cellular level, including the contribution of the tumour versus normal stroma.
7. Influence of the baseline and activated immune response during radiotherapy and the mechanism governing this effect on efficacy.
8. Validation of existing in vivo models for studying response and resistance to radiotherapy approaches preclinically.
9. Development of novel preclinical models to study the long-term toxicity associated with radiotherapy in the clinic.
10. Identification and validation of novel opportunities to exploit synthetic lethality arising from tumour genetics or novel drug-radiotherapy combinations.

KEY CLINICAL SCIENCE THEMES:

1. Identification, validation and clinical implementation of predictive biomarkers to enable stratification and personalisation of radiotherapy or radiotherapy-drug combinations.
2. Design of clinical trials with sufficient power for biomarker endpoints, rather than retrospective sample analysis.
3. Development of surrogate markers of late toxicity to enable potential mitigation strategies to be explored.
4. Hypothesis driven combination trials of novel therapeutics, such as DNA repair inhibitors or immunotherapy, with radiotherapy modalities.
5. Optimisation of imaging (e.g. PET or MRI) to enable adaption to change in anatomy, physiology and metastatic spread.
6. Development of intra-therapy biomarkers of the stress response to ionising radiation or radio-resistance to enable adaptive treatment planning.
7. Investigation of artificial intelligence as a tool to enable personalisation of radiotherapy, decision making for combination approaches and adaptive treatment planning.

APPENDIX 5: INVESTMENT IN RB&RO BY CRUK AND THE NCRI PARTNERS

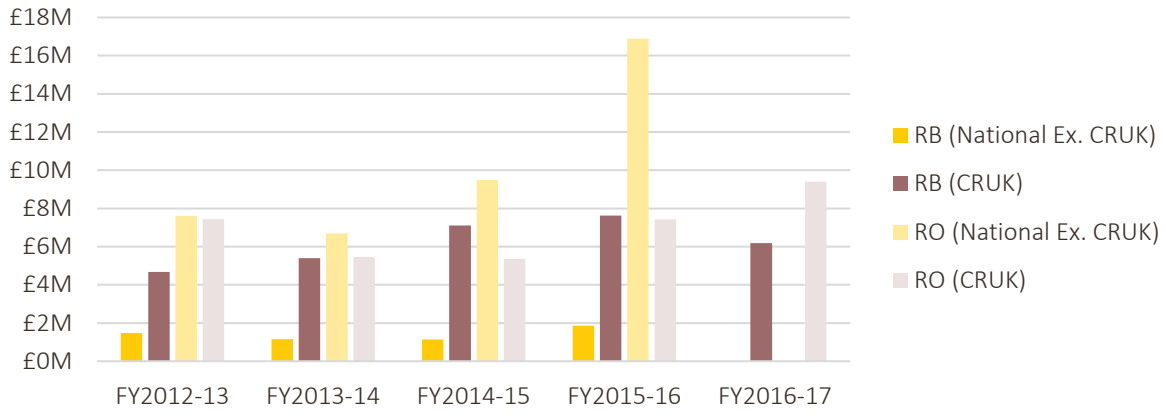

Figure 1. National (total NCRI, excluding CRUK) and CRUK spend in RB&RO. FY2016-17 NCRI data unavailable

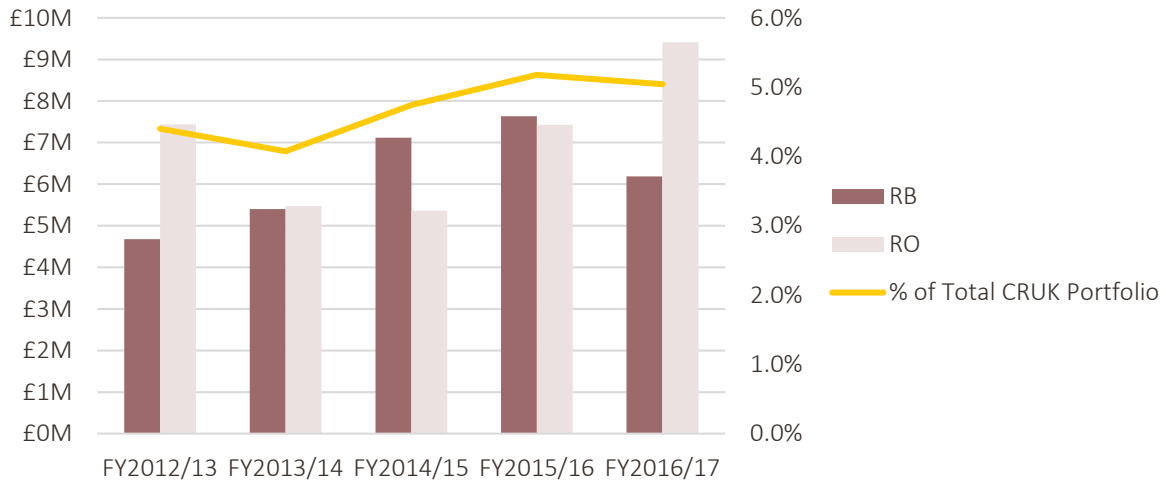

Figure 2. CRUK spend in RB&RO, and proportion of RB&RO spend of total CRUK research spend

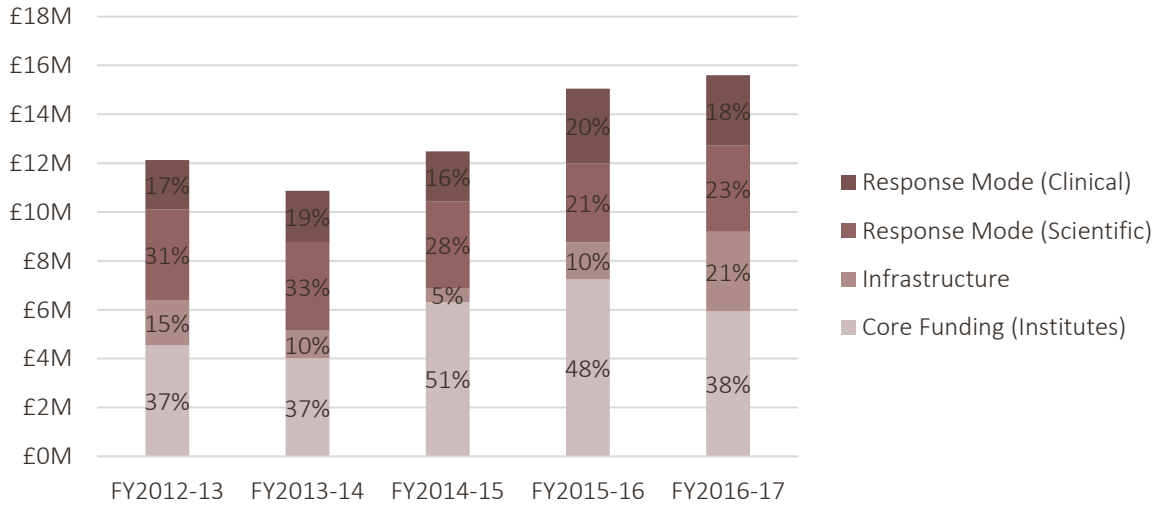

Figure 3. CRUK spend by funding type