CTRad Scoping Workshop for CRUK Grand Challenge
Wednesday 25 February 2015 – London

Introduction

At the end of 2014 Cancer Research UK (CRUK) launched the idea of a Grand Challenge, with funding of up to £20m over five years to fund a key question in cancer research. CRUK will be holding two 'Big Think' meetings, the first of which was to take place in London two days after CTRad's Idea Scoping Workshop. The second will take place on 20 March in Edinburgh. CTRad considered it potentially useful to discuss ideas that might be appropriate for the Grand Challenge.

The primary objective of CTRad's Scoping Workshop was to provide ideas that CTRad could specifically feed into the CRUK Big Think process. A secondary objective was to bring people together as a community and to allow discussion of topics which might subsequently be developed into smaller projects or programme collaborative proposals.

Structure of the Day

The introduction to the workshop concentrated on the scale and scope of the Grand Challenge idea, including the need for a project which could realistically be completed within five years, and of scope both wide enough to represent a Grand Challenge but small enough to be achievable with £20m; it also needs to be within the specified 5-year timeframe. The group clearly supported the notion of keeping discussions of projects within this envelope of scale, scope and time frame.

More than 40 members of CTRad and additional invited research colleagues attended the workshop, with support from the CTRad Secretariat.

Five separate breakout discussion groups were arranged, in two sessions, so that each delegate would be able to go to two of the sessions. Each of the breakout discussion groups was facilitated by two CTRad members. The discussion groups were as follows:

<u>Breakout session 1</u>

Group A: Radiation & Drugs, Immunotherapy and Molecular Radiotherapy
Group B: Imaging & Radiotherapy
Group C: Interface of Radiotherapy (including SABR) with Surgery & Site Specific Cross Cutting Topics

<u>Breakout session 2</u>

Group D: Data, New Technologies (e.g. PBT, MR Linac) & Mathematical Modelling
Group E: Biology, Biomarkers & Theragnostics

The afternoon session concentrated on feedback from the individual discussion groups and then a synthesis and distillation of the discussions.

Output from Breakout Discussions

Key points from the breakout discussions are presented below. These are not intended to represent the full discussion that took place, which was animated, collaborative and wide-ranging in all of the groups. Throughout the discussions, the scope and constraints of the Grand Challenge were borne in mind and delegates tried hard to pitch the scale of the discussions and proposals accordingly.

A. Radiation & Drugs, Immunotherapy and Molecular Radiotherapy

There was a clear view that clinical trials would need to be used to evaluate newer concepts and combinations. There were opportunities to optimise models of radiation, drug interactions and molecular radiotherapy, which would be of value. There is a clear need to optimise combinations of treatments, particularly including radiotherapy, and this area is considered to have considerable potential scope. The potential importance of radiotherapy to cause tumour damage leading to release of tumour antigens which are able provoke an immune response was discussed within this group. Overall, the notion of using radiotherapy as an immune modulator was considered a very real opportunity for future development.

Discussions in this group also highlighted some key visionary concepts. It should be possible to collect tumour tissue and blood samples from patients, as well as imaging data sets and outcome data, which could and should be stored in an appropriate data base system. Such a resource would be capable of answering many different questions. There was a clear interest in promoting the individualisation of treatment, including radiotherapy, whilst also emphasising that radiotherapy is already the most individualised of the non-surgical treatment options for cancer.

B. Imaging & Radiotherapy

There are considerable opportunities for using advances in imaging to improve treatment, particularly radiotherapy, but not only confined to radiotherapy. Imaging should be developed further to characterise anatomy, biology and function. In particular, the need to define the margin of the tumour and tumour spread was emphasised. Methods to correlate imaging with tumour biology, so as to 'image the biology' should also be a key area for development. Imaging the tumour during a course of radiotherapy and developing methods to predict response (i) before radiotherapy as an adjunct to decision making about the combination of modalities, (ii) during radiotherapy, and (iii) after treatment, are all areas of considerable interest. Molecular imaging is an area ripe for further development.

With the advent of computing capacity to analyse large amounts of data, it was suggested that retrospective analysis of imaging datasets from large-scale radiotherapy clinical trials would be likely to be yield valuable information, but to do this, imaging data would have to be collected together. Such a collection might form an 'imaging biobank' that would be a valuable resource for researchers.

The group discussed an objective of being able to shift treatment intent for patients from a purely palliative expectation into a category of potentially curative intent. This would be most likely to be possible in patients with oligometastatic disease, where radiotherapy would form an important part of tumour control, but systemic therapies would also be vital.

C. Interface of radiotherapy including SABR with surgery, & site-specific cross-cutting topics

The group discussed that clinical trials would be a focus under this topic. Work is required on hypoxia and the tumour microenvironment in general. New combinations of treatments and treatment modalities need to be developed. Further development of pre-clinical models could be very valuable.

Many clinical trials currently have relatively stringent inclusion criteria. A very large number of patients do not fit into clinical trials and the inclusion of such patients in properly conducted studies would have considerable importance for the patient population and would be likely to yield important scientific data.

Tumour types of lung, oesophagus and glioblastoma were specifically discussed although no specific Grand Challenge ideas were proposed for the individual tumours. These nevertheless represent important tumour types with considerable research interest.

D. Data, New Technologies & Mathematical Modelling

This group also discussed the importance of having clinical trials which would be open to all patients, without conventional inclusion and exclusion criteria. The importance of patient-reported outcomes was also agreed.

This group discussed the importance of data, which had become an important theme for the whole day.

There was a specific discussion about how to identify the gross tumour volume for the purposes of contouring. The margins used for the clinical target volume (CTV) are largely historical, but success or failure of tumour control really depends on the biology, which is not currently understood, as well as the physical (dose) CTV margin. There is certainly a dilemma in whether we can refine CTV margins for a population of patients if we do not understand the biology of the tumour at an individual level. Using computational techniques to appraise CTV margins would nevertheless be valuable, but requires large scale data collection and analysis. There are also legal aspects of consent for the use of imaging which would need to be considered, particularly in order not to lose important subgroups of patients who might fail to give consent.

There was some discussion of developing models of normal tissue complication probability (NTCP) since it is this that defines dose. Better models might allow individual NTCP calculations to define a dose for individual patients.

It could be worth considering developing a phone application to allow patients to return PROM information.

The group suggested the idea that ‘everyone counts’ as both the scientific approach and a promotional one.

E. Biology, Biomarkers & Theragnostics

The group endorsed the idea of trying to increase five year survival by 20%. Individualised treatment even for patients with metastatic spread should be a key

objective, achievable by individualising radiotherapy and chemo-radiotherapy. This group also discussed issues about collecting imaging, radiotherapy dose data and biological data, which would represent a 'big data' project. Standardisation of assays for biomarkers was also discussed. Further development of mathematical models and also pre-clinical models was proposed.

Some specific discussion took place on the idea of putting detector chips into tumours and the possibility of measuring key metabolic changes in real time, to provide feedback during radiotherapy, was discussed. Such development would hinge upon the size of a detector.

Whole Group Discussion

The second part of the afternoon session allowed presentation of each of the five group discussions and this was followed by an overall group discussion, particularly focussed on what ideas could and should be proposed as Grand Challenges.

General Discussion

As part of that discussion, several key points were made:

1. It should be emphasised that radiotherapy is already a highly individualised treatment option;
2. Radiotherapy already contributes substantially to local control, but if it can be developed as an immune modulator then it has the potential to contribute to the control of metastatic disease;
3. Imaging is a critical element for decision making in radiotherapy, at all stages of the patient pathway;
4. There is considerable scope for improving radiotherapy drug combinations, and an excellent existing research infrastructure, not only in the form of CTRad, but also in the RaDCom initiative, developed together with CRUK.

Headline statements

There was some discussion about possible promotional strap lines to promote a proposal, including:

1. Curing the incurable.
2. Turning cancers on themselves.
3. Get it right first time.
4. Using the microenvironment to increase cure rates.

Conclusions

The group discussion suggested two key topics as potential Grand Challenges.

CTRad Grand Challenge ideas

1. Exploiting tumour biology and the host microenvironment for effective therapy. This would include the use of radiotherapy as an immune stimulant.
2. Curing the incurable – translating palliation to cure for patients with oligometastatic disease.

Post-script

Both of these specific ideas were fed into the CRUK Grand Challenge Big Think meeting two days after our Scoping Workshop.

National Cancer Research Institute
Clinical and Translational Radiotherapy Research Working Group (CTRad) CRUK Grand Challenge idea scoping workshop

Wednesday 25 February 2015
Brewer & Smith Room, Mary Ward House, 5-7 Tavistock Place, London WC1H 9SN
10:00am – 3:45pm

AGENDA

9:30am	*Registration and refreshments*	
10:00am	Welcome and introduction	Neil Burnet
10:30am	Breakout discussion Group **A**: Radiation and drugs, immunotherapy and molecular radiotherapy Group **B**: Imaging and radiotherapy Group **C**: Interface of radiotherapy (including SABR) with surgery and site specific cross-cutting topics	*Group facilitators:* Anthony Chalmers, Kaye Williams Ricky Sharma, Richard Adams David Sebag-Montefiore, Corinne Faivre-Finn
11:30am	*Tea and coffee (grab and go)*	
11:35am	Breakout discussion Group **D**: Data, new technologies (e.g. PBT, MR linac) and mathematical modelling Group **E**: Biology, biomarkers and theragnostics	*Group facilitators:* Ran Mackay, John Staffurth Tracy Robson, Catharine West
12:35pm	*Lunch*	
1:15pm	Discussion of themes and links from group discussions	Neil Burnet
1:45pm	Scale and scope of Grand Challenge, fitting in of linked topics	Neil Burnet
2:45pm	*Tea and coffee*	
3:00pm	Summary, mechanism of feedback to CRUK, proposals and next steps	Neil Burnet
3:45pm	*Close*	

The NCRI CTRad initiative is funded by

CTRad CRUK Grand Challenge idea scoping workshop - attendees

Richard	Adams
Angela	Baker
Luc	Bidaut
Francesca	Buffa
Helen	Bulbeck
Neil	Burnet
Sue	Campbell
Anthony	Chalmers
Catharine	Clark
Adrian	Crellin
Nicola	Curtin
Phil	Evans
Corinne	Faivre-Finn
Glenn	Flux
Emma	Hall
Susan	Harden
Tom	Haswell
Maria	Hawkins
Ann	Henry
Alan	Hounsell
Kate	Law
Ranald	Mackay
Stewart	Martin
Tim	Maughan
Philip	Mayles
Gillies	McKenna
Helen	McNair
Alan	Melcher
Elizabeth	Miles
James	O'Connor
Alf	Oliver
Melanie	Powell
Kevin	Prise
Tracy	Robson
David	Sebag-Montefiore
Ricky	Sharma
John	Staffurth
Hilary	Stobart
Ian	Stratford
Gillian	Tozer
Frank	van den Heuvel
Catharine	West
Gillian	Whitfield
Kaye	Williams