ICTR-PHE 2014

Uniting physics, biology and medicine for better healthcare

The REQUITE project: validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects

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REQUITE

Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality-of-Life in Cancer Survivors

SEVENTH FRAMEWORK PROGRAMME

The REQUITE project: validating predictive models and biomarkers of radiotherapy toxicity to reduce side-effects

Nothing to disclosure

BACKGROUND

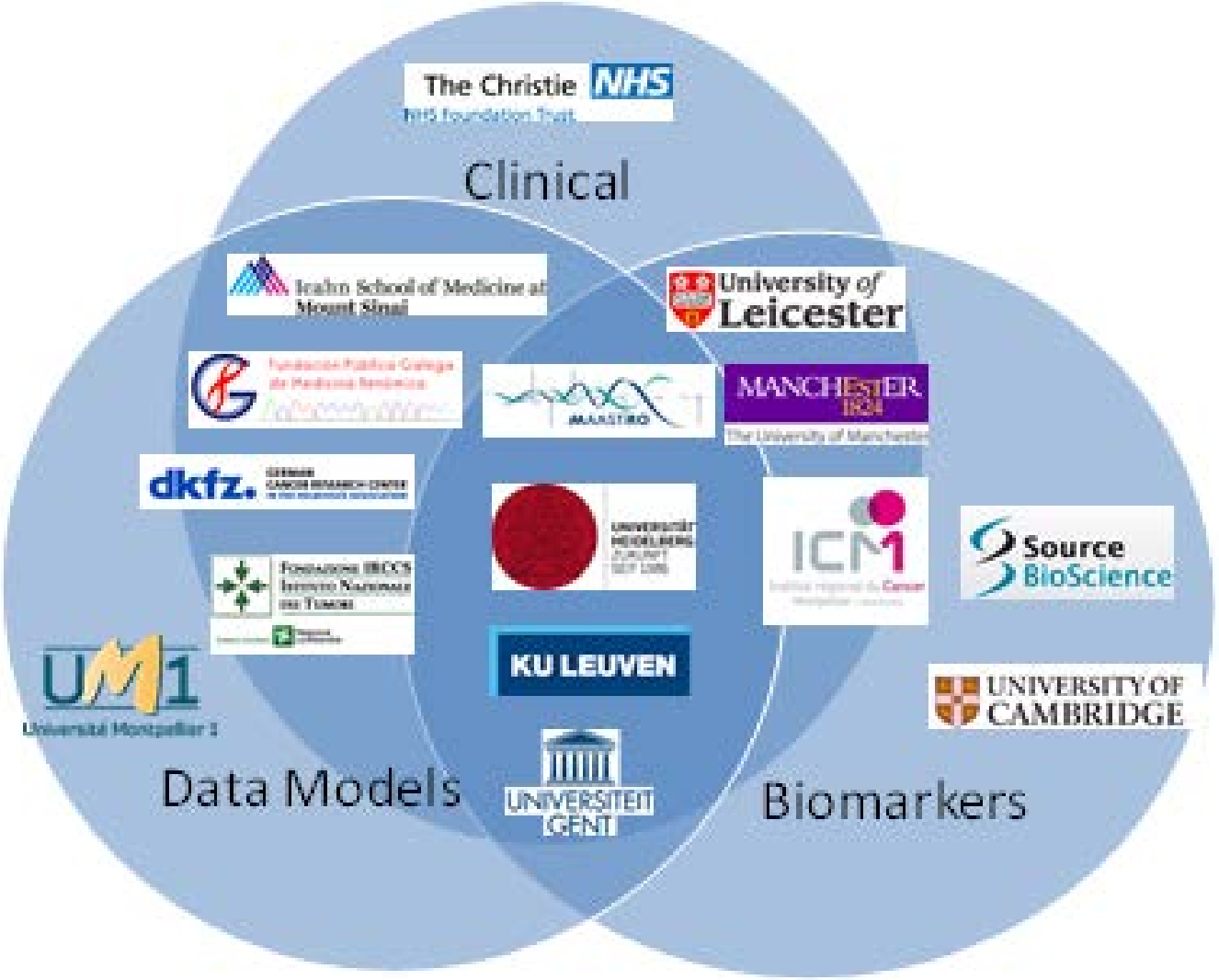
- Recently the first replicated genetic associations for adverse reactions to radiotherapy have been reported.
- These will help to build predictive statistical models for optimising radiotherapy delivery or interventions to alleviate the side effects.
- It is now timely to start a project that aims to validate known predictors of adverse reactions and develop the statistical models to become clinically useful.

The REQUITE project is a European Union funded FP7 project that aims to do this.

OBJECTIVES

1. Perform a multi-centre, cohort study collecting: blood samples, epidemiology and treatment data, longitudinal side-effect and QOL data (before and after treatment, years 1 & 2)
2. Produce a centralised biobank of DNA from 5,300 patients and a centralised data management system
3. Validate published biomarkers of radiosensitivity – genetic and apoptosis assays
4. Validate clinical predictors of radiotherapy toxicity in breast, prostate and lung cancer and incorporate biomarker data.
5. Design interventional trials to reduce long-term side-effects.
6. Provide a resource for dissemination and exploitation to the radiotherapy community.

PARTNERS


The Christie NHS
NHS Foundation Trust
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University of Leicester
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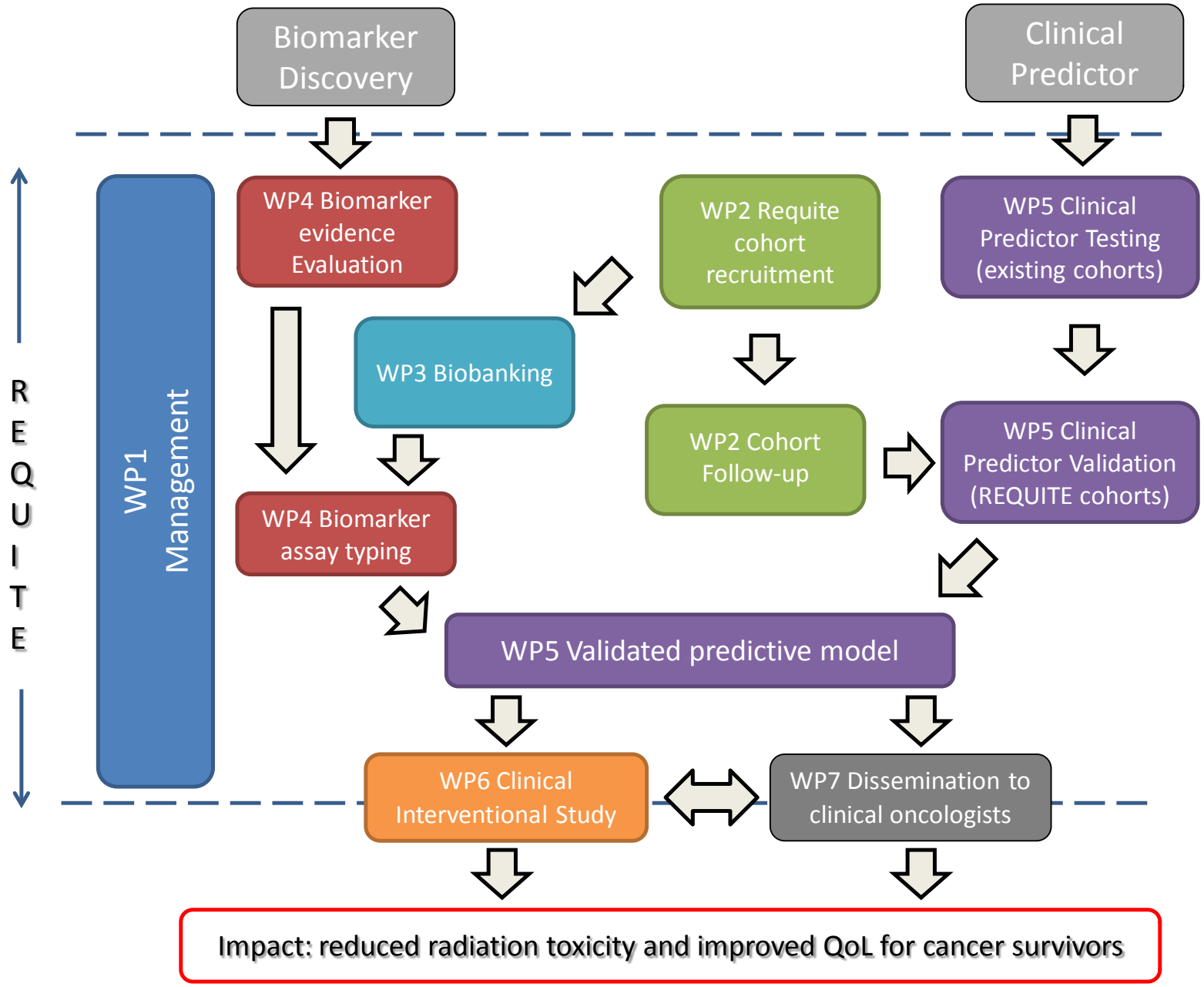
MANCHESTER 1824
The University of Manchester
dkfz.
ICM
Source BioScience
KU LEUVEN
UM1
Universitat Montpellier 1
UNIVERSITY OF CAMBRIDGE
Data Models
UNIVERSITEIT GENT
Biomarkers

Time scale

Project start	Oct 2013
Recruitment start	Apr 2014
Recruitment ends	Mar 2016
Follow-up ends	Mar 2018
Project complete	Sep 2018


Biomarker Discovery
Clinical Predictor
REQUITE
WP1 Management
WP4 Biomarker evidence Evaluation
WP2 Requite cohort recruitment
WP5 Clinical Predictor Testing (existing cohorts)
WP3 Biobanking
WP2 Cohort Follow-up
WP5 Clinical Predictor Validation (REQUITE cohorts)
WP4 Biomarker assay typing
WP5 Validated predictive model
WP6 Clinical Interventional Study
WP7 Dissemination to clinical oncologists
Impact: reduced radiation toxicity and improved QoL for cancer survivors

REQUITE PROSPECTIVE OBSERVATIONAL TRIAL

REQUITE prospective cohort

Country	Cohort	Breast	Prostate	Lung	Total
Belgium	UGENT	300	200	100	**500**
Belgium	KULEUVEN	500	150	200	**850**
France	UMONT	500	0	300	**800**
Germany	DKFZ	400	400	0	**800**
Italy	INT	100	200	80	**380**
Spain	FPGMX	100	350	120	**570**
UK	CNFT	0	200	200	**400**
UK	ULEIC	300	200	100	**600**
USA	MSSN	0	400	0	**400**
Total	REQUITE	**2,100**	**2,100**	**1,100**	**5,300**

ENDPOINTS

PRIMARY ENDPOINTS	• Change in breast appearance at 24 months following start of radiotherapy (breast) • Rectal bleeding at 24 months following start of radiotherapy (prostate) • Dyspnea/ breathlessness at 12 months following start of radiotherapy (lung)
SECONDARY ENDPOINTS	• Other toxicity endpoints including but not limited to: fibrosis, induration and vascular changes (breast); rectal incontinence, urinary toxicity and erectile dysfunction (prostate); dysphagia and oesophagitis (lung) • Quality of life • Maximum grade of toxicity during follow-up period

BIOMARKERS

All 5,300 samples will be genotyped for SNPs or CNVs with evidence for association with radiotherapy toxicity.

1,800 samples will be assayed for radiation-induced lymphocyte apoptosis using FACS analysis.

REQUITE
VALIDATION OF AVAILABLE MODELS

Tumour	n	Toxicity endpoints	Predictive variables	Ref
Breast	1010	Overall radiosensitivity (STAT score): breast shrinkage, telangiectasia, oedema, pigmentation, pain and skin oversensitivity	Breast volume, surgical specimen weight, dosimetry, radiation boost, post-operative infection, smoking, diabetes, chemotherapy, age	Barnett 2011
Breast	3,624	Fibrosis	Dose, chemotherapy	Collette 2008
Prostate	718	Rectal bleeding	EUD, surgery, presence of haemorrhoids, use of anticoagulants, androgen deprivation	Tomatis 2012
Prostate	718	Rectal bleeding, faecal incontinence	Prior surgery, dose-volume, haemorrhoids, antihypertensive medication	Valdagni 2012
Prostate	669	Rectal bleeding, faecal incontinence	DVH, Prior surgery	Rancati 2011
Prostate	586	Longitudinal fecal incontinence	Dose-volume, previous bowel disease, previous abdominal/pelvic surgery, and the use of antihypertensive	Fiorino 2011
Prostate	322	Nocturia	Radical prostatectomy, pre-treatment nocturia	De Langhe 2012
Prostate	512	Rectal bleeding, faecal incontinence	Prior surgery, cardiac history, diabetes	Defraene 2012
Lung	141	Pneumonitis	MLD, smoking status, SNPs	Tucker 2013
Lung	836	Pneumonitis	V20, chemotherapy, age	Palma 2013
Lung	324	Pneumonitis	MLD, tumour volume	Bradley 2007
Lung	219	Pneumonitis	D35, maximum dose, tumour location	Hope 2006

CURRENT STATUS OF THE PROJECT (1/2)

- ✓ External Advisory, Patient Advisory and Ethics Review Groups were established
- ✓ Final version of trial protocol was submitted to ethics in USA, UK, Italy, Spain and Germany
- ✓ CRFs have been finalised and the first version of the database is ready for testing
- ✓ Patient reported outcome (PRO) questionnaires have been translated into each language, and back translations completed to check for consistency
- ✓ PRO questionnaires are being tested in each country as a validation exercise to check that the questions are not difficult, confusing or upsetting to patients

CURRENT STATUS OF THE PROJECT (2/2)

- ✓ The Informed Consent Form (ICF) and Patient Information Sheet have been finalised
- ✓ The website is under construction (www.requite.eu) and the dissemination manager is developing content for both the health professional and patient sections of the website
- ✓ The Centre for Integrated Genomic Medical Research (CIGMR) is assembling the bar-coded blood sample kits for distribution.

CONCLUSIONS

The REQUITE project will develop and validate statistical models incorporating biomarker data to predict radiotherapy adverse reactions. Future interventional trials will use these models to help optimise radiotherapy.

The project encourages collaborations that add value to the project, including additional datasets for validating clinical models.

Email for enquiries: requite@manchester.ac.uk

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Thank you to the REQUITE collaboration

and

Thank you for your kind attention!

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Grant Agreement No. 601826