BEATING CANCER WITH CRUK

Tim Hudson, Research Engagement Manager

Friday 2 October, 2019

CANCER RESEARCH UK

Together we will beat cancer

Image credit: LRI EM

WHAT WE'LL COVER

- Introduction to CRUK
- What do we do?
- How do we fund research?
- Our research
- Our strategy
- Our achievements
- Cancer Grand Challenges

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INTRODUCTION TO CANCER RESEARCH UK

CANCER RESEARCH UK

We're the world's largest charity dedicated to saving lives through research
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Our vision is to bring forward the day when all cancers are cured

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Cancer Research UK formed from the merger of two cancer organisations in 2002

Imperial Cancer Research Fund

the cancer research campaign

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Now, we are the largest charitable funder of cancer research in the world
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Cancer is not a single disease, there are over 200 different types
Over 360,000 people are diagnosed each year in the UK
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1 in 2
people born after 1960 in the UK will be diagnosed with cancer in their lifetime
But cancer survival is improving and has **doubled** in the last 40 years
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9 out of 10 donations are under £10
CANCER RESEARCH UK
Find out more at cruk.org
or call our hotline on
0870 60 20 40
PLEASE DONATE TODAY
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Together
we will
beat cancer
CANCER
RESEARCH
UK

WHAT DO WE DO?

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We focus on areas with the greatest potential to beat cancer

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OUR STRATEGY

OUR CORE EXPERTISE SPANS

PREVENT

DIAGNOSE

TREAT

OPTIMISE

STRATEGIC PRIORITIES INCLUDE CANCERS OF UNMET NEED

LUNG

OESOPHAGEAL

PANCREATIC

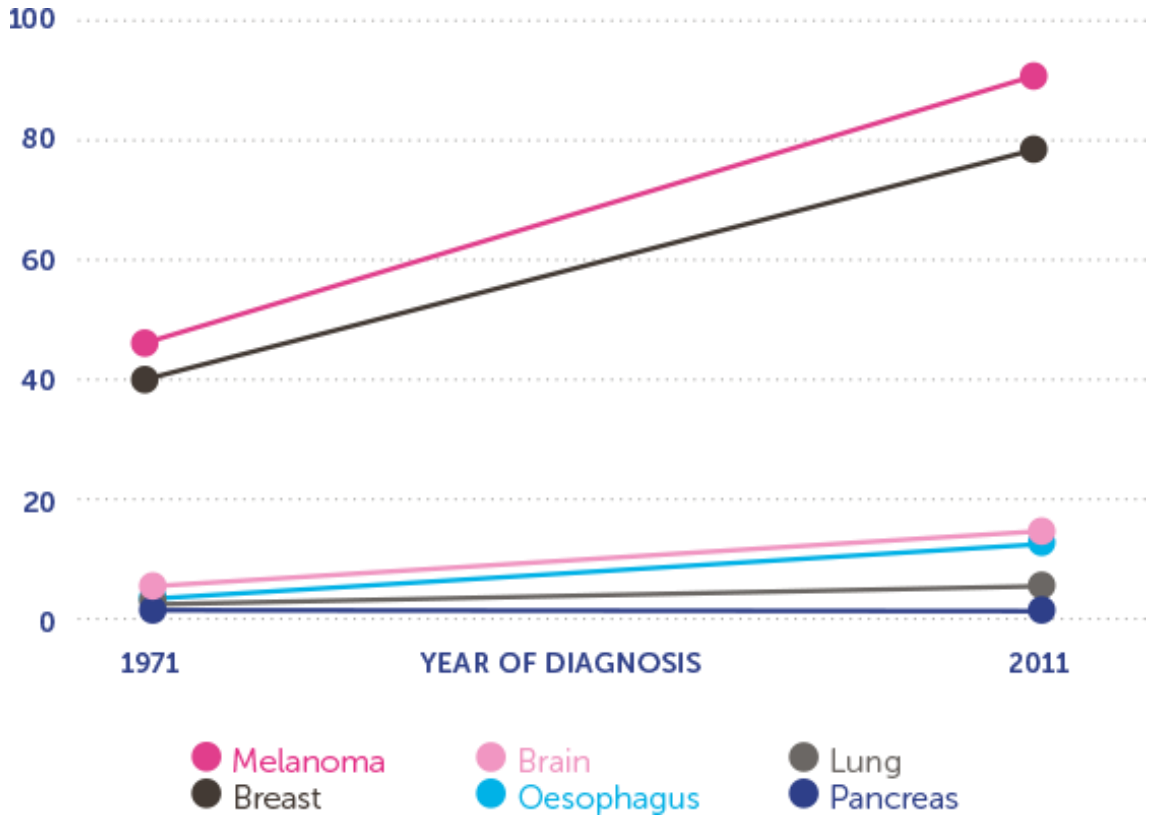
BRAIN

UNMET NEED

TACKLING HARD-TO-TREAT CANCERS

CANCERS OF UNMET NEED

10 YEAR NET INCREASE SURVIVAL (%)



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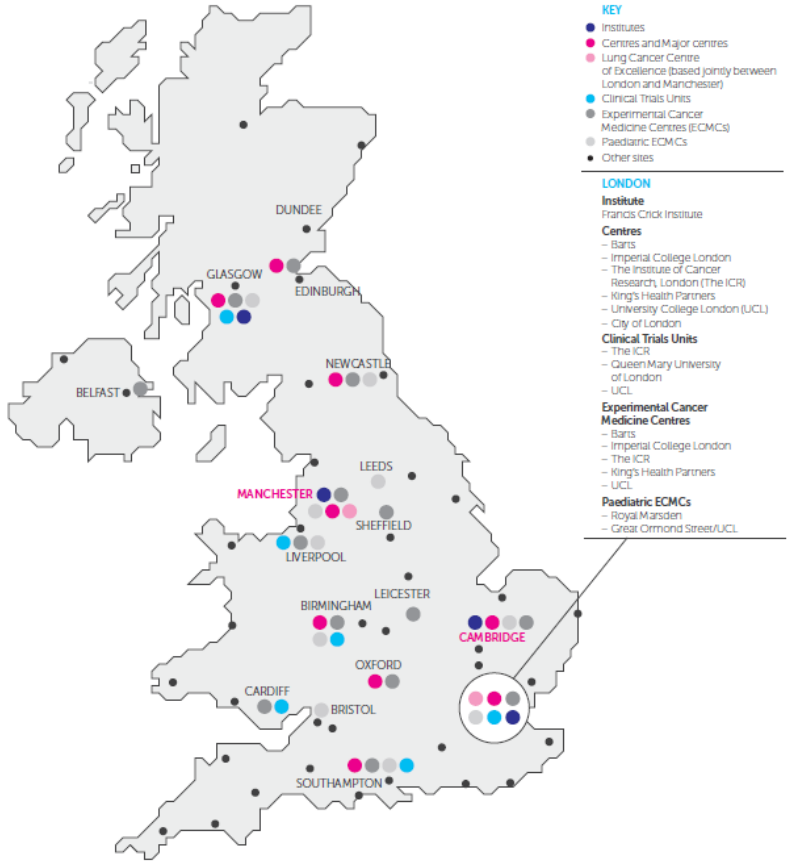

KEY

- Institutes
- Centres and Major centres
- Lung Cancer Centre of Excellence (based jointly between London and Manchester)
- Clinical Trials Units
- Experimental Cancer Medicine Centres (ECMCs)
- Paediatric ECMCs
- Other sites

LONDON

Institute
Francis Crick Institute

Centres
- Barts
- Imperial College London
- The Institute of Cancer Research, London (The ICR)
- King's Health Partners
- University College London (UCL)
- City of London

Clinical Trials Units
- The ICR
- Queen Mary University of London
- UCL

Experimental Cancer Medicine Centres
- Barts
- Imperial College London
- The ICR
- King's Health Partners
- UCL

Paediatric ECMCs
- Royal Marsden
- Great Ormond Street/UCL

OUR WORLD-CLASS RESEARCH NETWORK

4	14	8	18	4	11
Institutes	Centres	Clinical Trials Units	ECMCs	Drug Discovery Units	Paediatric ECMCs

We fund over 4,000 scientists, doctors and nurses

RESEARCH UK

Our institutes ensure that our researchers have everything they need to help beat cancer in one building
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CRUK Beatson Institute, Glasgow
the Beatson

Francis Crick Institute, London

CRUK Manchester Institute

CRUK Cambridge Institute
CANCER RESEARCH UK

We worked with
5 other world-leading
research organisations
to build the Francis
Crick Institute

© The Wellcome Trust

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RESEARCH
UK

THE
FRANCIS
CRICK
INSTITUTE
Over
1,600
outstanding
scientists
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UK

At our 15 research centres, we work closely with universities, NHS trusts, government, industry and other charities
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And our 18 Experimental Cancer Medicine Centres (ECMCs) help to bring new treatments to the clinic
Whatman
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I VOLUNTEERS
BEATING CANCER SOONER
OUR RESEARCH STRATEGY
I VOLUNTEERING
BECOME A CANCER CAMPAIGNS AMBASSADOR FOR SCOTLAND
BECOME A CANCER CAMPAIGNS AMBASSADOR FOR THE SOUTH EAST
BECOME A CANCER CAMPAIGNS AMBASSADOR FOR THE SOUTH WEST
BEATING CANCER SOONER
OUR STRATEGY HIGHLIGHTS
Our nurses provide support and information about cancer online and over the phone
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We keep cancer high on the political agenda

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HOW DO WE FUND RESEARCH?

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How do we decide what research to fund?

1. Our scientific executive board set aside money for each major area of research

2. Researchers apply for funding

3. Expert funding committees decide which projects to fund

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What do our funding committees look for?

Backed up by evidence?

Will it benefit patients?

Is it ethical?

Good research team?

Is it achievable?

Is it new?

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OUR RESEARCH STRATEGY

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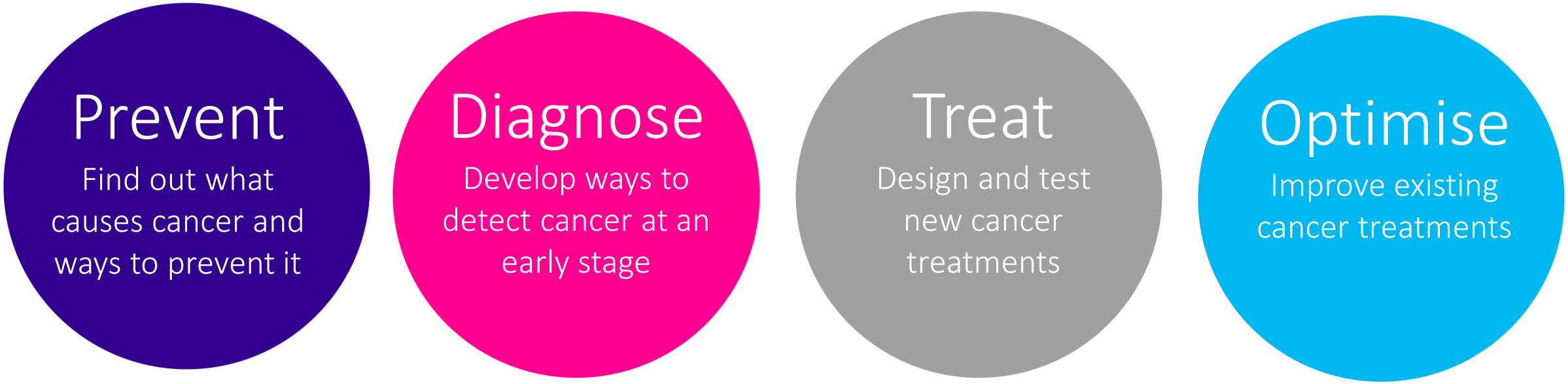
OUR RESEARCH STRATEGY



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PREVENT

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Together we will beat cancer

Having no children

Facebook

Bottling up emotions

Biscuits

Soup

Candle-lit dinn

4 IN 10 CANCERS CAN BE PREVENTED

Broken heart

Left-Handedness

Gardens

Internet

Chocolate

Large Heads

Crayons

Long Fingers

Broccoli

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ENGLISH BREAKFASTS

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GETTING OLD

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CANDLES

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Prevent

Finding out what causes cancer and developing ways to prevent it

Around
4 in 10
cases of cancer in the UK could be prevented

Smoking is the largest cause of cancer in the UK, accounting for

15%

of all cancer cases.

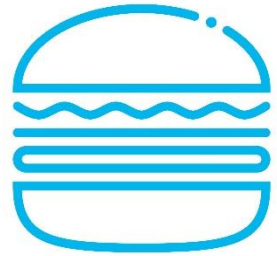
Prevent

Reducing people's risk of developing cancer

Personalised approaches to prevention and screening

Prevention research

Health awareness campaigns



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PREVENT

Reducing people's risk of developing cancer

Cervical cancer interventions

Dr Jo Waller
University College London

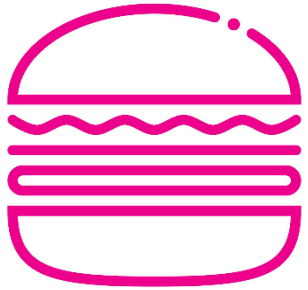
Dr Jo Waller is investigating why some people don't participate in cervical cancer interventions (such as HPV vaccination); and how to encourage participation in these initiatives.

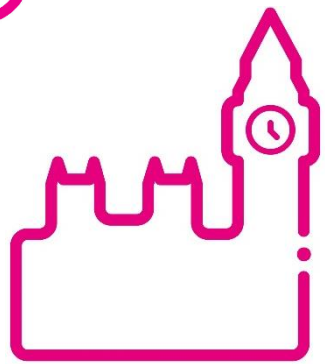
Prevent

Reducing people's risk of developing cancer

Watershed for junk food ads

We're calling for a ban on TV and online adverts for food high in fat, sugar and salt before 9pm will help protect children from exposure to marketing for junk food.





Obesity is the second biggest cause of cancer in the UK.

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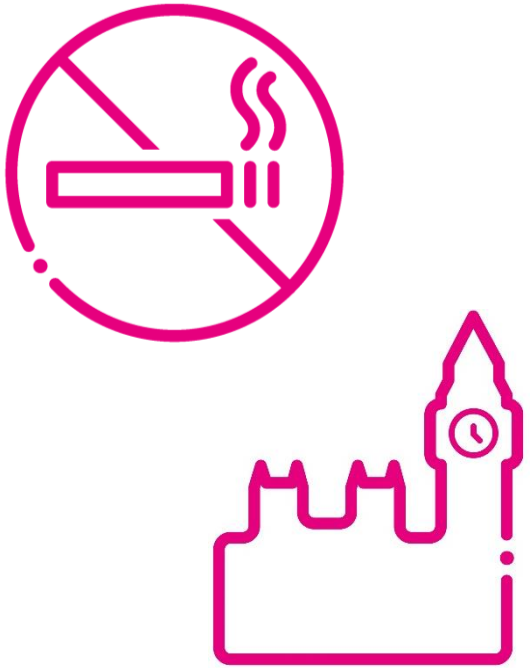
Prevent

Reducing people's risk of developing cancer

Smokefree by 2030



Cuts to public health budgets mean vital stop smoking services are under threat.

We're calling on the UK Government to provide increased and sustainable public health funding.

We're calling for the English and Welsh Governments to adopt a **smokefree by 2030** target.

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WHAT IS A TOBACCO LEVY?

The Government can pass a law

To force tobacco companies to pay £500 million out of their profits to the Government

This is equivalent to 1 penny per cigarette they sell in the UK

The Government will then give this money to fund Stop Smoking Services and advertising campaigns

Which will help the 2/3 of smokers who want to kick the habit for good

ACT RIGHT NOW

LET'S BEAT CANCER SOONER
Take action right now at cruk.org/big-tobacco-cough-up

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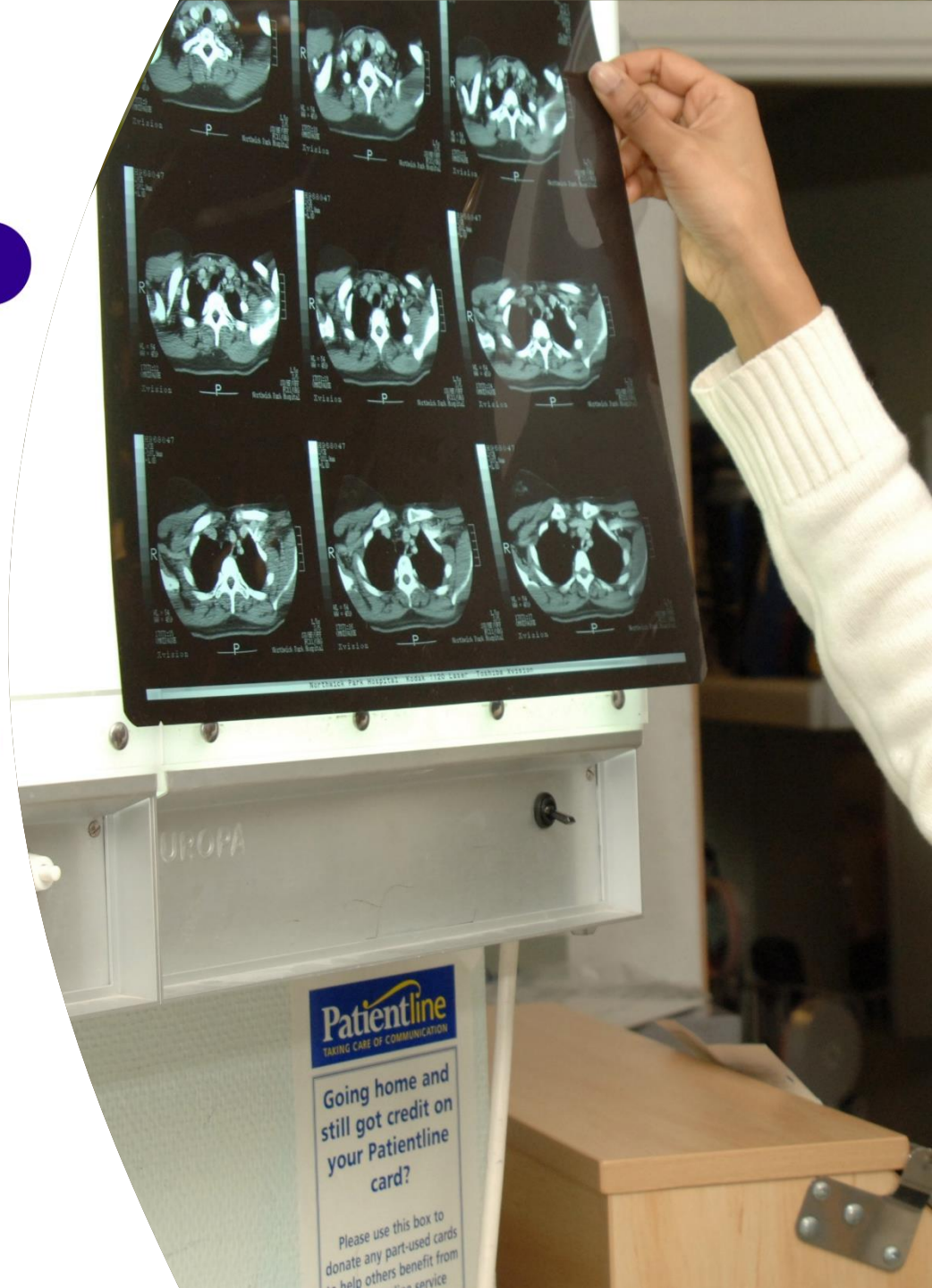
DIAGNOSE



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Together we will beat cancer

Diagnose

Developing ways to detect cancer earlier, when it's more likely to be treated successfully

When diagnosed at the earliest stage (stage 1), more than

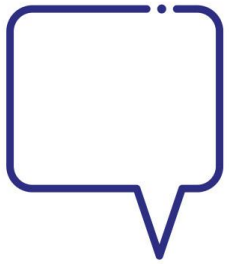
9 in 10

people with bowel cancer will survive their disease for five years or more

Diagnose

Developing ways to detect cancer earlier, when it's more likely to be treated successfully

Campaign to fill vacant NHS diagnostic posts



Help to diagnose more people at an earlier stage

Develop more effective screening tests

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Diagnose

Developing ways to detect cancer earlier, when treatment is more likely to be successful

Thinking outside the box to detect bowel cancer earlier

Combined new approaches with existing screening tests to identify people at risk of bowel cancer

Professor Chris Probert is looking for clues in the gases released from stool samples to develop a simple, non-invasive bowel cancer test

Professor Chris Probert
University of Liverpool

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DIAGNOSIS

DIAGNOSING CANCERS AT AN EARLIER STAGE

NATIONAL CANCER SCREENING PROGRAMMES

3

THE UK HAS
3 SCREENING PROGRAMMES

1. It's estimated that Breast Screening reduces the number of deaths from breast cancer by about 1,300 a year in the UK

2. Cervical Screening is one of the most effective cancer prevention measures ever implemented, and cervical cancer death rates have decreased by 72% in the UK since the late 1970s.

3. Bowel Screening saves lives. It aims to prevent and detect cancer at an early stage when treatment is more likely to work.

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DIAGNOSIS

DIAGNOSING CANCERS AT AN EARLIER STAGE

DIAGNOSE BOWEL CANCER EARLIER THROUGH SCREENING

MORE THAN

9 IN 10

BOWEL CANCER PATIENTS WILL SURVIVE THEIR DISEASE FOR 5 YEARS OR MORE IF DIAGNOSED AT THE **EARLIEST STAGE,** COMPARED **TO**

1 IN 10

WHEN DIAGNOSED AT THE LATEST STAGE

BOWEL SCREENING IS THE BEST WAY TO DIAGNOSE BOWEL CANCER EARLY

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DIAGNOSIS

DIAGNOSING CANCERS AT AN EARLIER STAGE

BEST3 TRIAL: DIAGNOSING BARRETT'S OESOPHAGUS – A RISK FACTOR FOR OESOPHAGEAL CANCER

THE TEAM HAVE DEVELOPED A TEST CALLED THE 'CYTOSPONGE' – A NIFTY, SPONGE-ON-A-STRING CELL COLLECTION DEVICE

Professor Rebecca Fitzgerald
University of Cambridge

BY MAKING BARRETT'S OESOPHAGUS EASIER TO DIAGNOSE, DOCTORS CAN INTERVENE AT AN EARLY STAGE, BEFORE IT DEVELOPS INTO OESOPHAGEAL CANCER

SEE HOW THE CYTOSPONGE WORKS

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TREAT

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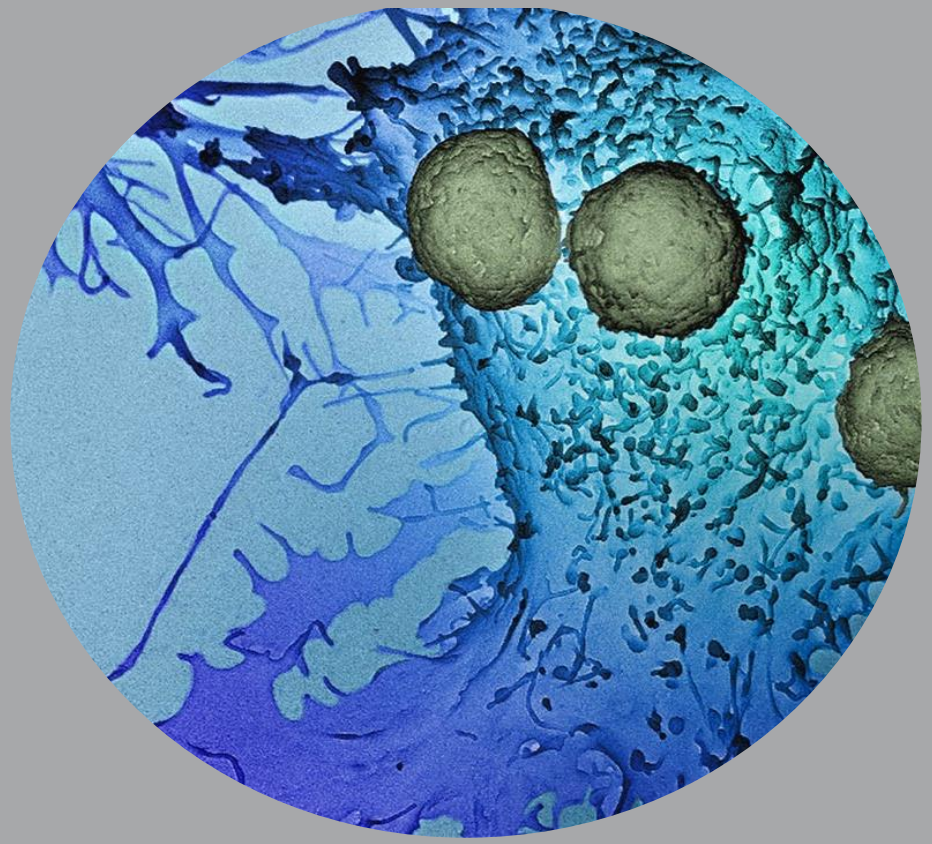
TREAT

DEVELOPING AND TESTING NEW CANCER TREATMENTS



NEW AVENUES OF RESEARCH COULD SAVE MORE LIVES

DELIVERING
MORE EFFECTIVE NEW TREATMENTS
WILL REQUIRE NEW PERSPECTIVES, MECHANISMS & METHODS

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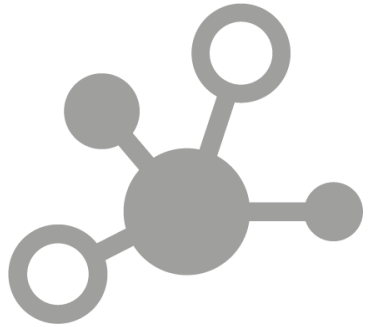
TREAT

DEVELOPING & TESTING NEW CANCER TREATMENTS

DEVELOPING AND TESTING NEW CANCER TREATMENTS

LEAD INNOVATION IN RADIOTHERAPY AND SURGERY

DISCOVER AND DEVELOP NEW THERAPEUTICS



FOCUS ON TARGETING COMMONLY MUTATED CANCER GENES

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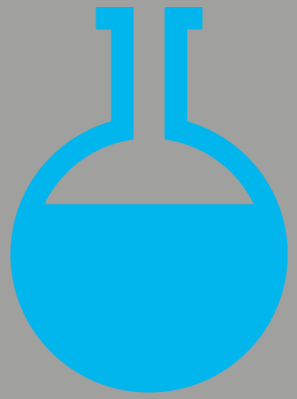
TREAT

DEVELOPING & TESTING NEW CANCER TREATMENTS

CURRENT TREATMENTS AVAILABLE



TARGETED THERAPIES home in on specific genetic weaknesses of certain cancer cells

CHEMOTHERAPY AND RADIOTHERAPY stop cancer cells from growing and dividing

IMMUNOTHERAPY turns the immune system against cancer

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TREAT

DEVELOPING & TESTING NEW CANCER TREATMENTS

RADIOTHERAPY & SURGERY

OF ALL CANCER PATIENTS, ALMOST

3 IN 10

WILL HAVE

RADIOTHERAPY

AS A PRIMARY TREATMENT

RECENT ADVANCE: STEREOTACTIC ABLATIVE RADIOTHERAPY

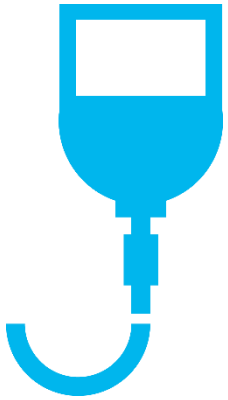
OF ALL CANCER PATIENTS, ALMOST

5 IN 10

WILL HAVE

SURGICAL INTERVENTION

AS A PRIMARY TREATMENT



THE FUTURE: LESS INVASIVE APPROACHES AND THE USE OF ADVANCED IMAGING

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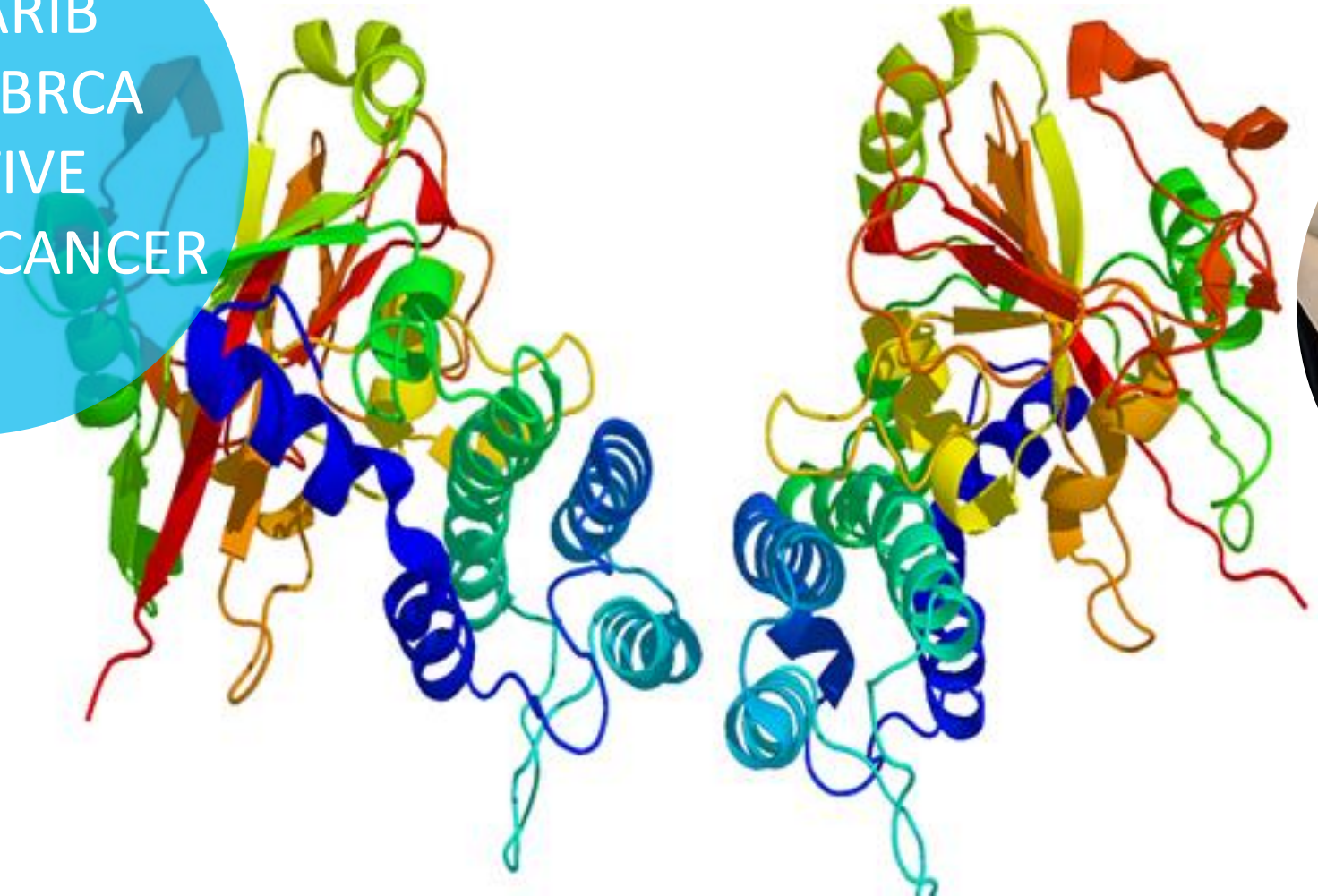
NEW THERAPEUTICS

OLAPARIB TREATS BRCA POSITIVE OVARIAN CANCER



"I am optimistic that research will help turn cancer into more of a manageable disease"

Professor Ruth Plummer
Newcastle University

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TREAT

DEVELOPING & TESTING NEW CANCER TREATMENTS

NATIONAL LUNG MATRIX TRIAL

The world's largest ever clinical trial for non small cell lung cancer is matching treatments to patients based on genetic changes in their cancer

THE STUDY IS PAVING THE WAY FOR MORE EFFICIENT AND EFFECTIVE CLINICAL TRIALS

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OPTIMISE

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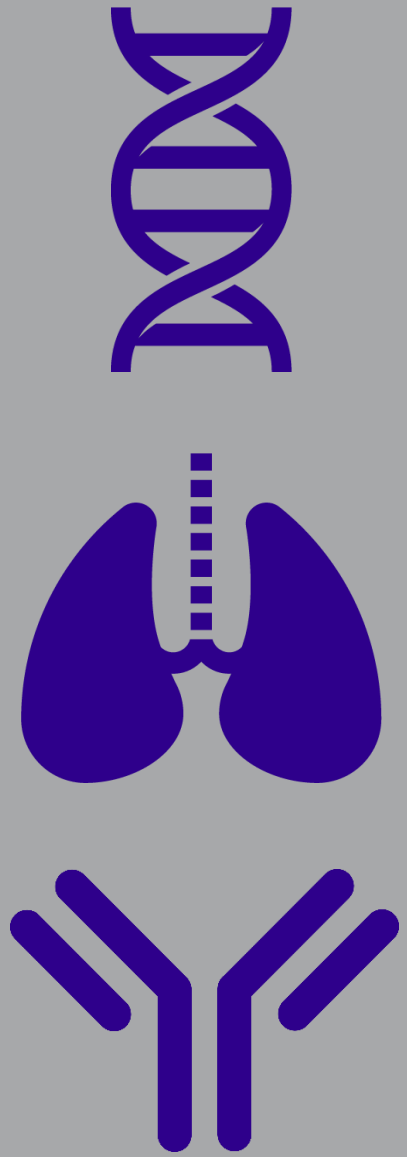
OPTIMISE TREATMENTS

IMPROVING EXISTING CANCER TREATMENTS

WE NEED TO
MAKE EXISTING
CANCER
TREATMENTS
MORE EFFECTIVE



WE NEED TO
HARNESS OUR UNDERSTANDING
OF HOW EVERY PATIENT AND THEIR CANCER IS
DIFFERENT TO
IDENTIFY THOSE MOST LIKELY TO BENEFIT
FROM TREATMENTS

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OPTIMISE TREATMENTS

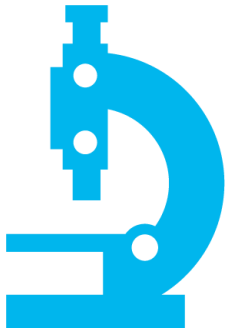
IMPROVING EXISTING CANCER TREATMENTS

IMPROVING EXISTING CANCER TREATMENTS

TAILOR TREATMENTS TO THE INDIVIDUAL

ADVANCE OUR UNDERSTANDING OF TUMOUR EVOLUTION

DEVELOP NEW COMBINATION TREATMENTS



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PERSONALISED MEDICINE

TAILORING TREATMENTS TO THE INDIVIDUAL

CANCER VARIES BETWEEN DIFFERENT PEOPLE. AND EVEN IN AN INDIVIDUAL PATIENT, THE CANCER CAN CHANGE OVER TIME.

PERSONLISED MEDICINE MATCHES PATIENTS TO TREATMENTS BASED ON THE BIOLOGY OF THEIR CANCER

JUST AS EACH FINGERPRINTS IS DIFFERENT – SO IS EACH PERSON'S CANCER

"PERSONALISED MEDICINE IS THE MOST EXCITING CHANGE IN CANCER TREATMENT SINCE THE INVENTION OF CHEMOTHERAPY"

PROFESSOR PETER JOHNSON,
CHIEF CLINICIAN,
CANCER RESEARCH UK

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PRECISION -Panc

PERSONALISED MEDICINE

TAILORING TREATMENTS TO THE INDIVIDUAL

It is predicted that 5 in every 100 people with pancreatic cancer can expect to survive their disease for more than 10 years in England and Wales

Professor Andrew Biankin
University of Glasgow, Beatson Institute

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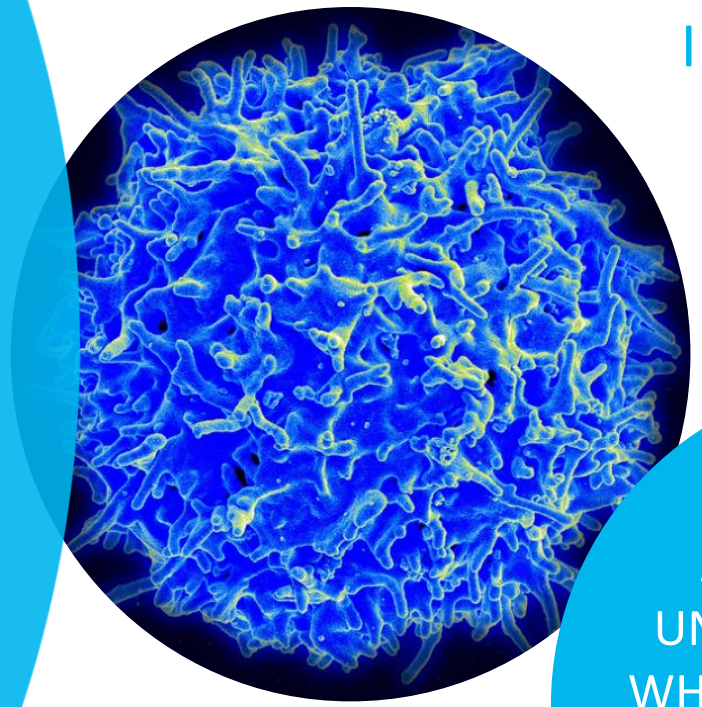
Tracking Cancer Evolution through Therapy

TUMOUR EVOLUTION: TRACERx

ANALYSING HOW LUNG CANCER CHANGES OVER TIME



ADDING TO OUR UNDERSTANDING OF WHY PEOPLE RESPOND DIFFERENTLY TO TREATMENTS

CRUK'S SINGLE LARGEST INVESTMENT IN LUNG CANCER RESEARCH

Professor Charles Swanton
Francis Crick Institute

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STAMPEDE: testing new combination treatments

Finding the right treatment combination for men with prostate cancer

Professor Nick James
Institute of Cancer Research, London

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OUR ACHIEVEMENTS

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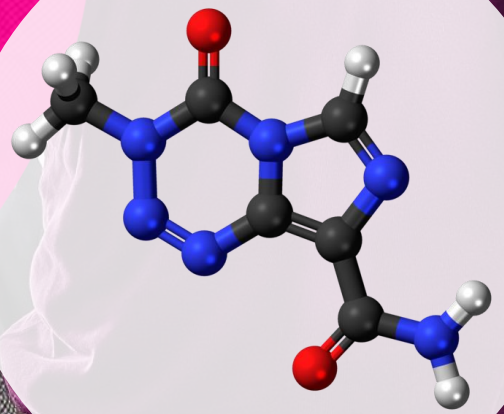
Our scientists across the UK worked together to develop temozolomide.

It’s now used to treat brain tumours worldwide



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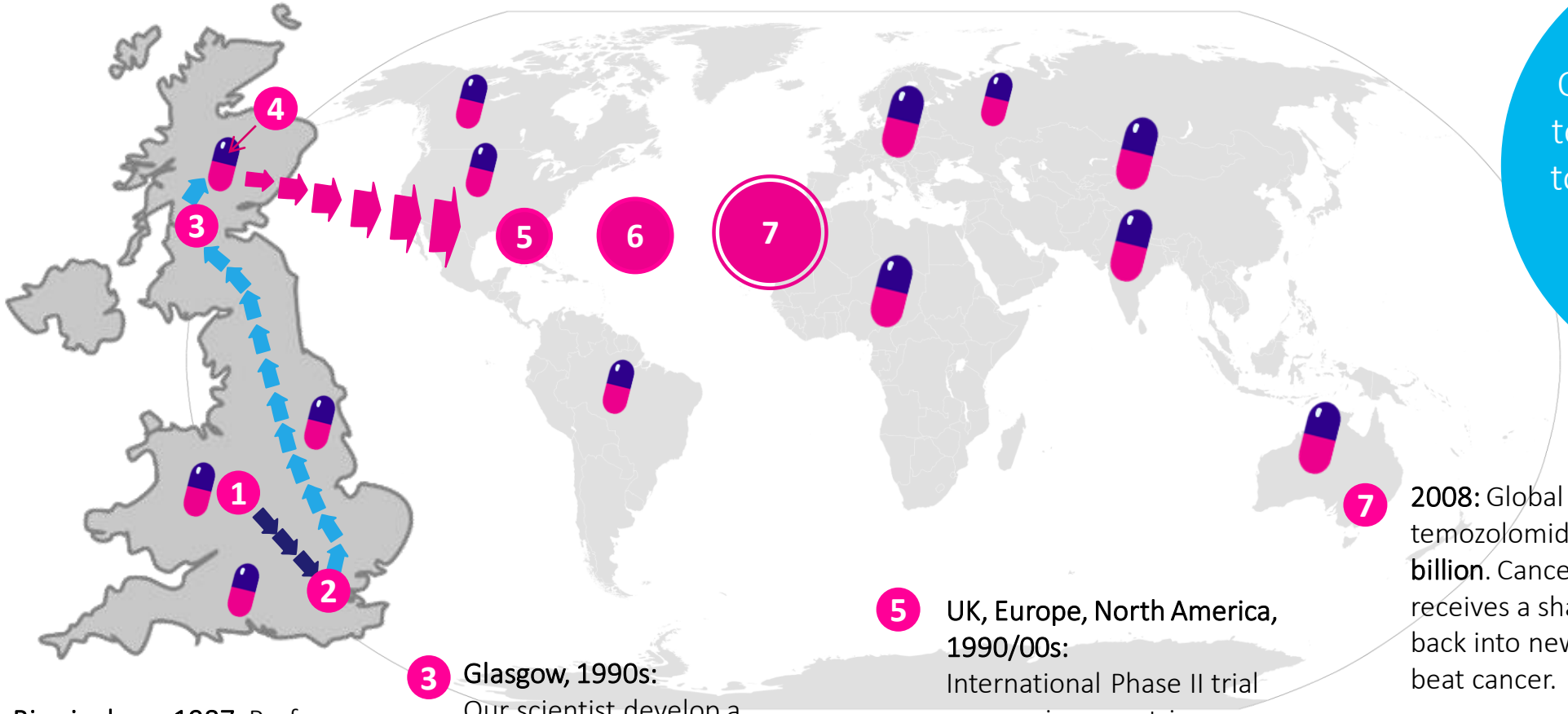
Temozolomide: a global success story



Our scientists continue to investigate new ways to use temozolomide to treat other types of cancer

1 **Birmingham, 1987:** Professor Malcolm Stevens develops temozolomide.

2 **London, 1980/90s:** Phase I clinical trials show promising results.

3 **Glasgow, 1990s:** Our scientist develop a method to mass produce the drug in capsule form.

4 **Across UK, 1990s:** Phase II clinical trials test effectiveness and toxicity of temozolomide.

5 **UK, Europe, North America, 1990/00s:** International Phase II trial across nine countries.

6 **Europe, Canada, Australia, 2000s:** Large Phase III trial involving patients from 15 countries. Confirms benefit of using drug for glioblastoma patients.

7 **2008:** Global sales of temozolomide reach **$1 billion**. Cancer Research UK receives a share which is put back into new research to beat cancer.

Thousands of people with brain tumours now benefit from temozolomide treatment

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And our researchers have contributed to most of the top cancer drugs

Aromasin

Gemzar

Femara

Avastin

Tamoxifen

Erbitux

Cisplatin

Carboplatin

Herceptin

Olaparib

Tarceva

Oxaliplatin

Gefitinib

Temozolomide

Zoladex

Anastrozole

Taxotere

CANCER RESEARCH UK

We currently support over 150 active clinical trials.
On average, over 8,000 patients are recruited to our treatment trials each year
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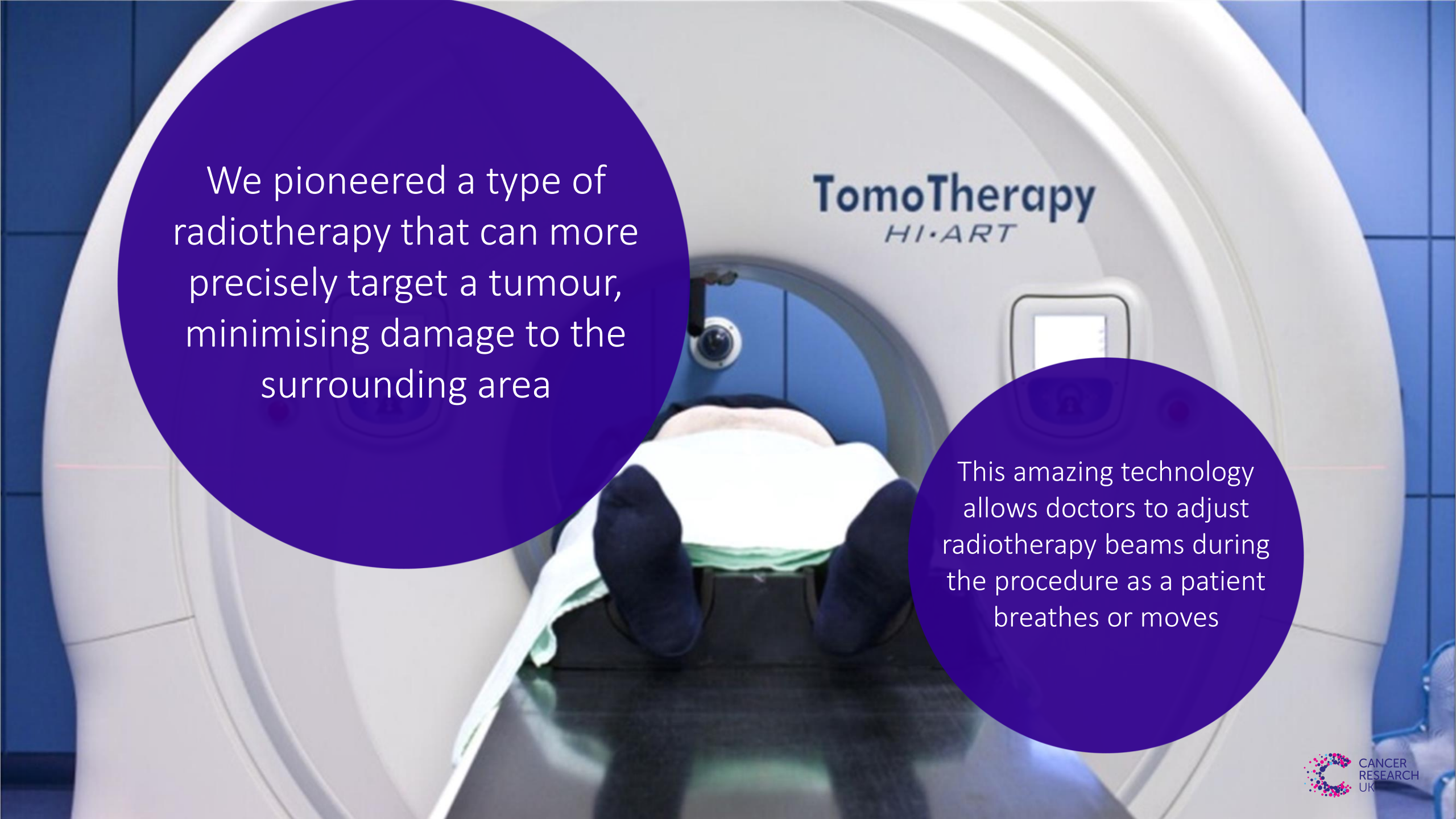

We pioneered a type of radiotherapy that can more precisely target a tumour, minimising damage to the surrounding area

This amazing technology allows doctors to adjust radiotherapy beams during the procedure as a patient breathes or moves

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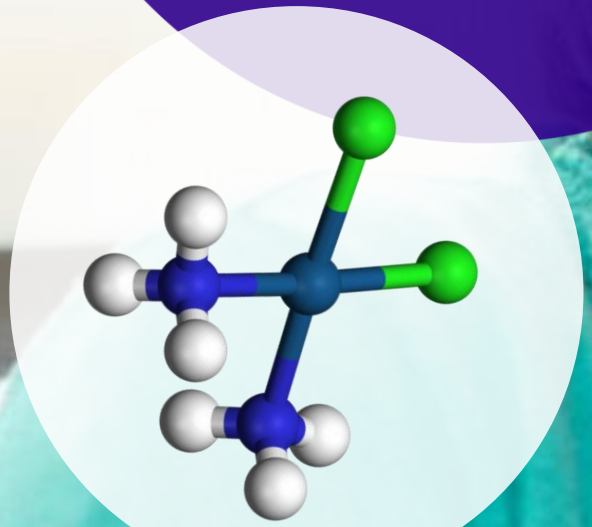
We helped to develop cisplatin – a drug that transformed the treatment of testicular cancer



'It is predicted that around 9 in 10 of men diagnosed with testicular cancer in England survive their disease for 10 or more years

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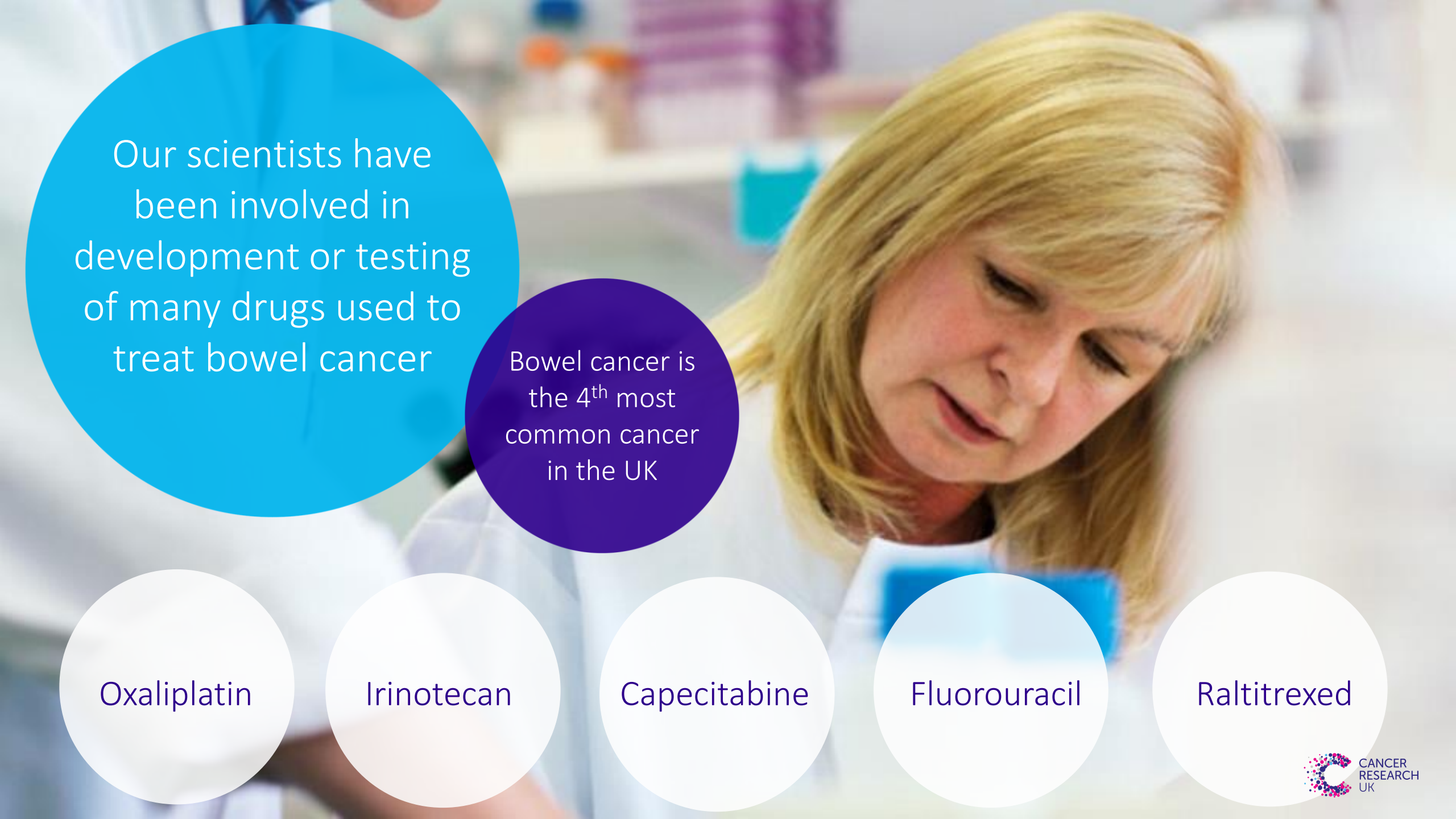
Our scientists discovered carboplatin, a kinder version of cisplatin and one of the most successful cancer drugs ever developed

CANCER RESEARCH UK



Our scientists have been involved in development or testing of many drugs used to treat bowel cancer

Bowel cancer is the 4th most common cancer in the UK

Oxaliplatin

Irinotecan

Capecitabine

Fluorouracil

Raltitrexed

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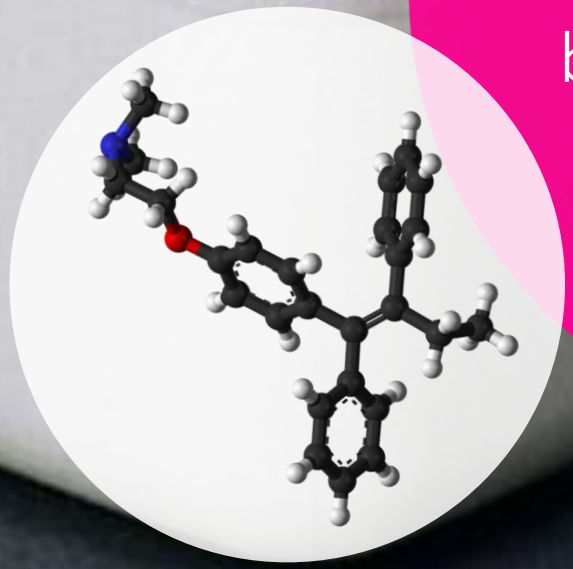
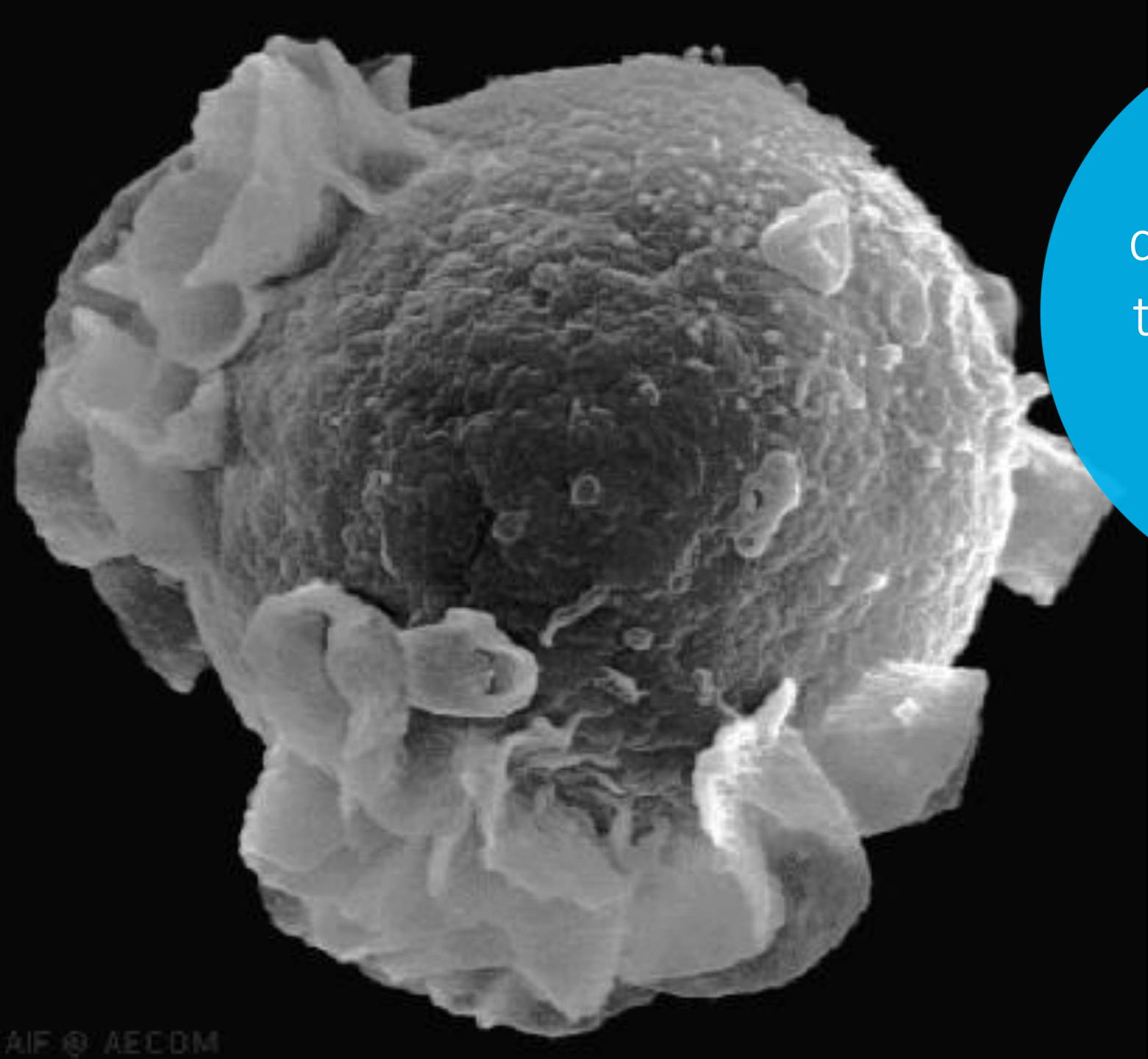
No other research organisation has done more to improve the lives of women with breast cancer in the UK
It is predicted that around 3 in 4 women in England survive their breast cancer for 10 years or more'
Our research helped us to discover more about HRT and its links with cancer, through the Million Women Study
CANCER RESEARCH UK

Our scientists helped to find out how tamoxifen could benefit women with breast cancer



CANCER RESEARCH UK

We were involved in the development and testing of some of the drugs that have had the biggest impact on lung cancer
Cisplatin
Carboplatin
Pemetrexed
Etoposide
CANCER RESEARCH UK



Our scientists discovered EBV, the first human virus that can cause cancer

paving the way for the development of vaccines against cancer, such as the HPV vaccine for cervical cancer

CANCER RESEARCH UK

In the 1970s
more than a third of
children with cancer
survived their disease…
now, it’s around three
quarters
The CRUK children’s
cancer trials team in
Birmingham coordinates
groundbreaking trials
across the UK
CANCER
RESEARCH
UK

We played a key role in setting up the International Rare Cancers Initiative

We've joined forces with research groups around the world to boost the number of clinical trials for rare cancers

CANCER RESEARCH UK

Cancer Grand Challenges

Overview

September 2020

CANCER GRAND CHALLENGES

CANCER RESEARCH UK

NIH NATIONAL CANCER INSTITUTE

TRANSFORMING GLOBAL CANCER RESEARCH

- Cancer Grand Challenges (CGC) is a global funding platform created to solve the toughest problems in cancer research. Co-founded through a partnership between Cancer Research UK and the National Cancer Institute that launched in 2020
- CGC is challenge-led problem solving on a scale beyond traditional funding routes – challenges are set from the ground-up through consultation with the research and advocacy community
- Whole process overseen by eminent scientific committee with input from our advocacy panel

THE FUNDING OPPORTUNITY:

- £20 ($25) million awards + £30,000 ($40,000) seed funding for shortlisted teams to build their proposal

- 2 staged-application process: expression of interested followed by full application for shortlisted teams.

- International teams - including collaborators from commercial entities can apply

- Encouraging multidisciplinary approaches - researchers from all disciplines can apply

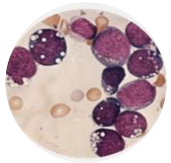
NEW CHALLENGES REVEALED AND OPENING FOR EXPRESSIONS OF INTEREST:
14 October 2020

PREVIOUS CHALLENGES

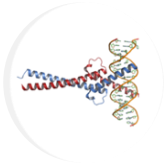
7 CHALLENGES SET IN ROUND 1

PREVENTION VACCINES
Develop vaccines to prevent non-viral cancers

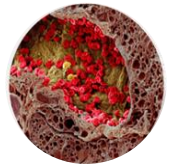
LETHAL VS NON-LETHAL
Distinguish between lethal cancers which need treating, and non-lethal cancers that don't



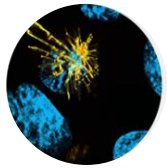
EBV CANCERS
Eradicate EBV-induced cancers from the world



TARGETING MYC
Develop innovative approaches to target the cancer super-controller MYC



3D TUMOUR MAPPING
Map the molecular & cellular tumour microenvironment in order to define new targets for therapy and prognosis

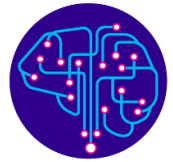


BIOLOGICAL MARCOMOLECULES
Deliver biologically active macromolecules to any & all cells in the body

UNUSUAL PATTERN MUTATIONS
Discover how unusual patterns of mutation are induced by different cancer-causing events

8 CHALLENGES SET IN ROUND 2

TREATMENT REGIMENS
Define mechanistic rules for combinatorial treatments to overcome resistance and avoid toxicity



ARTIFICIAL INTELLIGENCE
Detect cancer earlier by interrogating medical and non-medical data sets using machine and deep-learning

CANCER CAUSES
Determine the mechanisms that "cause" cancer without known mutagenesis, such as obesity, in order to devise novel interventions

MICROBIOTA
Improve treatment responses by manipulating the composition and status of the microbiota

LETHAL VS NON-LETHAL
Distinguish between lethal cancers which need treating, and non-lethal cancers that don't

DORMANCY
Identify and target tumour cells that remain dormant for many years after seemingly effective treatment

TUMOUR VACCINOLOGY
Create novel tumour vaccinology approaches that establish or enhance successful immune responses beyond what is revealed by current checkpoint therapy

TISSUE SPECIFICITY
Devise approaches to prevent or treat cancer based on mechanisms that determine tissue specificity of some cancer genes

SCIENTIFIC PORTFOLIO

TEAM ROSETTA - £16/ 5 YR

GB

- STUDYING TUMOUR METABOLISM FROM EVERY ANGLE
- Led by Josephine BUNCH, 10 investigators & 2 patient advocates

TEAM SPECIFICANCER - £20/ 5 YR

NL GB US

- MAP OF CANCER DRIVERS & THEIR SPECIFICITY TO DIFFERENT TISSUES
- Led by Steve ELLEDGE, 10 investigators & 3 patient advocates

The Mark Foundation for Cancer Research

TEAM MUTOGRAPHS - £20/ 5 YR

GB US FR

- IDENTIFYING PREVENTABLE CAUSES OF CANCER
- Led by Mike STRATTON, 6 investigators & 2 patient advocates

TEAM STORMING - £20/ 5 YR

CA GB US

- DEVELOP NEW OPTIONS TO TREAT AND PREVENT INFLAMMATION INDUCED CANCER
- Led by Thea Tlsty, 10 investigators & 5 patient advocates

TEAM IMAXT - £20/ 6 YR

GB US CA CH IE

- CREATING VIRTUAL REALITY MAPS OF TUMOURS
- Led by Greg HANNON, 14 investigators & 2 patient advocates

OPTIMISTICC - £20/ 5 YR

GB US CA NL ES

- INVESTIGATE THE MICROBIOME'S IMPACT ON TREATMENT IN COLORECTAL CANCER
- Led by Matt MEYERSON & Wendy GARRETT, 13 investigators & 8 patient advocate

TEAM PRECISION - £15/ 5 YR

NL GB US

- PREVENTING UNNECESSARY BREAST CANCER TREATMENT
- Led by Jelle WESSELING, 13 investigators & 5 patient advocates

DUTCH CANCER SOCIETY

CANCER GRAND CHALLENGES

CANCER RESEARCH UK

NIH NATIONAL CANCER INSTITUTE

ROSETTA TEAM

STUDYING TUMOUR METABOLISM FROM EVERY ANGLE

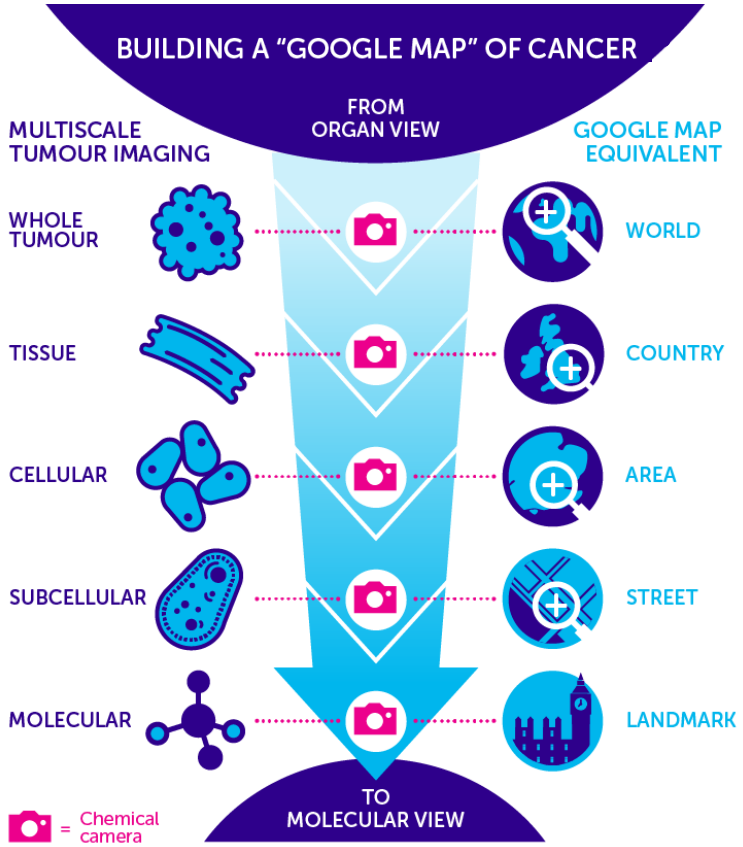
PROF. JOSEPHINE BUNCH
NPL, United Kingdom

10 investigators
2 patient advocates

UK

Breast, bowel, pancreatic & brain

£16m



MUTOGRAPHS TEAM

IDENTIFYING PREVENTABLE CAUSES OF CANCER

PROF. SIR MIKE STRATTON
Wellcome Trust Sanger Institute, United Kingdom

6 investigators
2 patient advocates

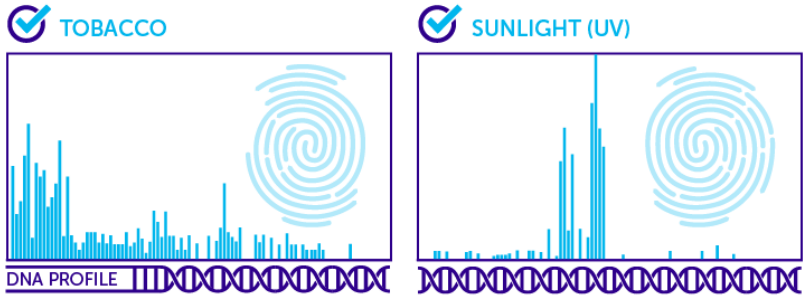
France
UK
USA

Bladder, bowel, kidney, liver, lung, oesophageal & pancreatic

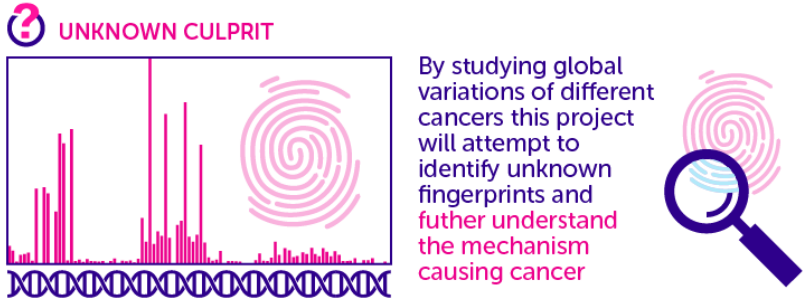
£20m

Cancer causing chemicals leave identifiable scars (like fingerprints) on damaged DNA

SOME OF THOSE FINGERPRINTS HAVE BEEN IDENTIFIED



BUT OVER 50% OF RECOGNISED FINGERPRINTS ARE UNKNOWN



By studying global variations of different cancers this project will attempt to identify unknown fingerprints and futher understand the mechanism causing cancer

IMAXT TEAM

CREATING VIRTUAL REALITY TUMOUR MAPS

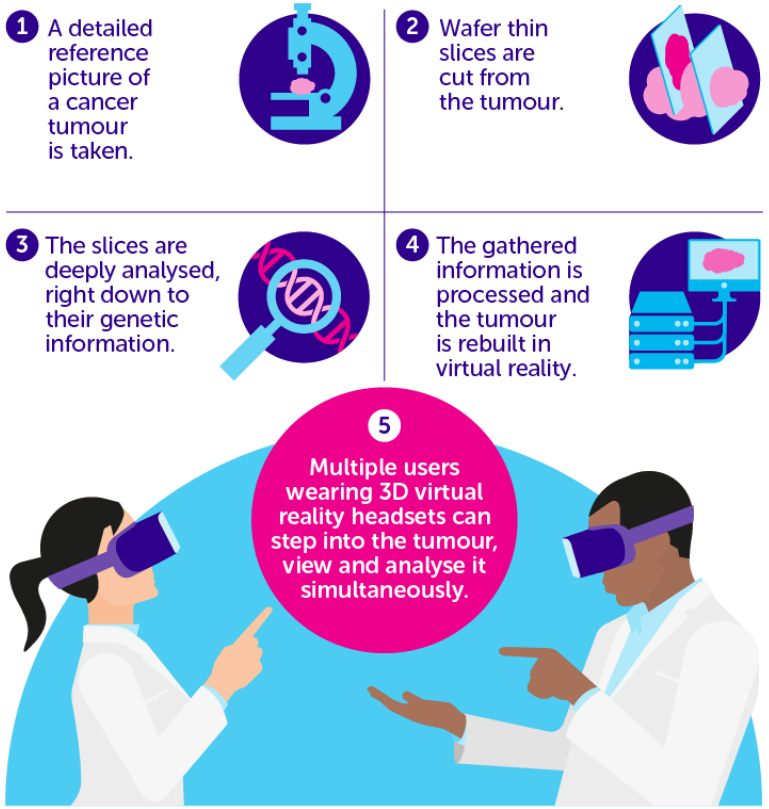
PROF. GREG HANNON
CRUK Cambridge Institute,
United Kingdom

14 investigators
2 patient advocates

Canada
Republic of Ireland
Switzerland
UK
USA

Breast

£20m



PRECISION TEAM

PREVENTING UNNECESSARY BREAST CANCER TREATMENT

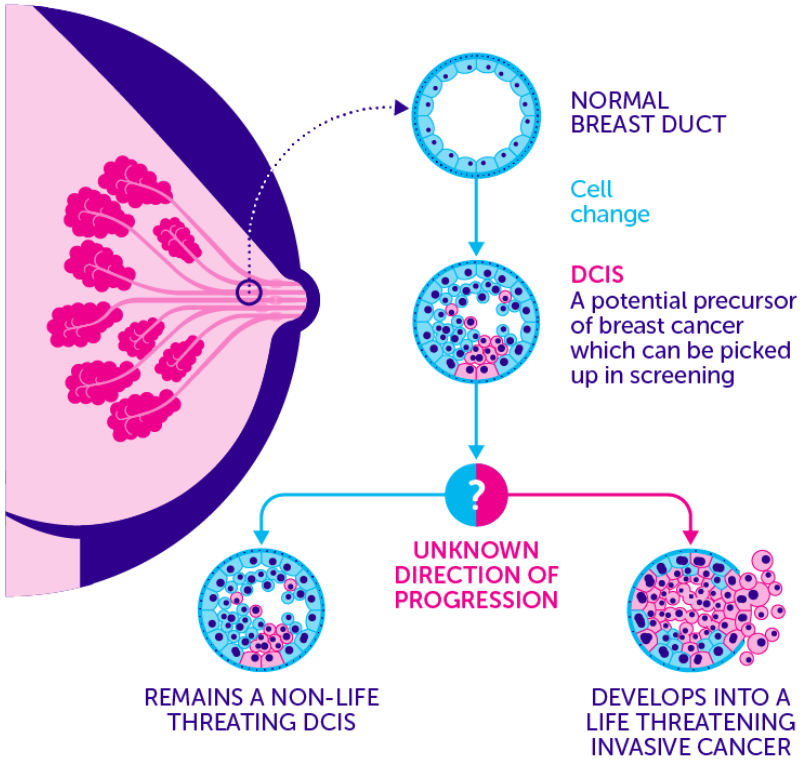
PROF. JELLE WESSELING
NKI, The Netherlands

13 investigators
5 patient advocates

The Netherlands
UK
USA

Breast

£15m



This project aims to understand which DCIS will develop into life threatening cancer and which will not. This could ultimately save some women from unnecessary cancer treatment.

SPECIFICANCER TEAM

GENERATE A COMPREHENSIVE MAP OF CANCER DRIVERS AND THEIR SPECIFICITY TO DIFFERENT TISSUES

PROF. STEVE ELLEDGE
Brigham and Women's Hospital, Harvard Medical School, USA

10 investigators
3 patient advocates

The Netherlands
UK
USA

Bowel, pancreatic, breast, lung, skin, kidney & brain

£19m

STORMING CANCER TEAM

DEVELOP NEW OPTIONS TO TREAT AND PREVENT INFLAMMATION INDUCED CANCER IN HIGH-RISK PATIENTS

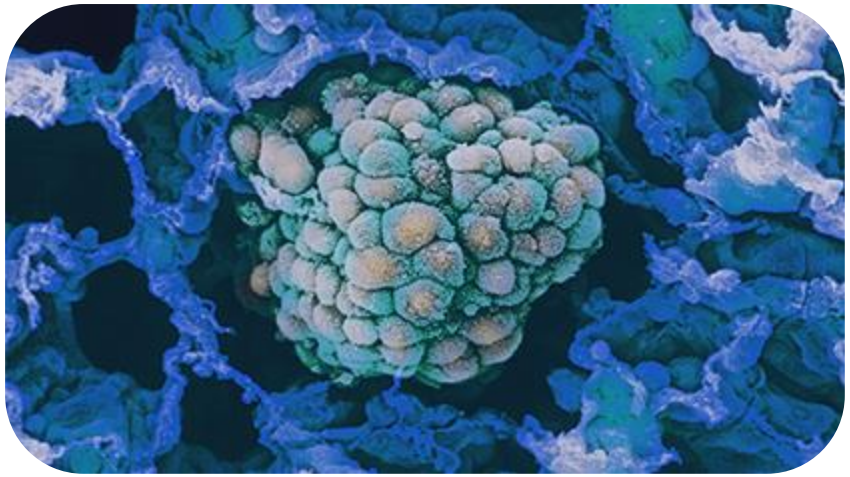
PROF. THEA TLSTY
UCSF, USA

10 investigators
5 patient advocates

Canada
Israel
UK
USA

Bowel,
oesophageal,
stomach & lung

£20m



OPTIMISTICC TEAM

OPPORTUNITY TO INVESTIGATE THE MICROBIOME'S IMPACT ON AND TREATMENT OF COLORECTAL CANCER

PROF. WENDY GARRETT
Harvard T.H. Chan School of Public Health, USA

PROF. MATTHEW MEYERSON
Dana-Farber Cancer Institute, USA

13 investigators
8 patient advocates

Canada
Spain
The Netherlands
UK
USA

Bowel

£20m

THANK YOU

Tim Hudson,
Research Engagement Manager
tim.hudson@cancer.org.uk
@CRUKresearch

CANCER RESEARCH UK