ICR The Institute of Cancer Research

Post Doctoral Training Fellow: Functional Genomics - Epigenetic mechanisms of immunotherapy resistance

Candidate Information

February 2025

About the role

Project focus: Epigenetic and transcriptional regulation of neoadjuvant immunotherapy resistance in triple negative breast cancer.

The role will work collaboratively together with a dedicated computational biologist working on the analysis of the single cell and spatial data generated from the wider project goals.

Triple negative breast cancer (TNBC) is an aggressive form of breast cancer characterised by high levels of molecular heterogeneity that underpin its high recurrence rate after neoadjuvant immunotherapy and chemotherapy. There is an unmet clinical need to identify the molecular events that underpin this process and how they evolve over time. Moreover, identifying biomarkers that will aid in predicting which patients will relapse are much needed.

We are seeking a highly motivated collaborative Post Doctoral Training Fellow for a collaborative project supervised by Dr. Rachael Natrajan and co-mentored by Dr. Esther Arwert to lead on the biological and mechanistic insights into the evolutionary dynamics of the epigenetic sub-clonal evolution of response to neoadjuvant immunotherapy and chemotherapy in TNBC *in vivo* mouse models using using high

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throughput cellular tracking coupled with single cell sequencing and functional genomic screening approaches. These will be linked to single cell epigenetic profiling from TNBC patient samples.

The candidate will perform experimental work to identify epigenetic regulators of neoadjuvant immunotherapy and chemotherapy resistance in TNBC and assess the implications of novel biology using innovative *in vivo* models and developing genetic screening approaches *in vitro* and *in vivo*.

You should possess a PhD in biology, biochemistry, genetics or other associated subjects and have an excellent track record in biomedical research and experience in cell and molecular biology. Experience with *in vitro* and *in vivo* cancer models is essential.

This position will be offered on a fixed-term 3 year contract. Starting salary is based on previous Post Doctoral experience, in the range £45,600 - £49,350 p.a. inclusive.

About the teams

The Functional Genomics laboratory headed by Dr. Rachael Natrajan is a multidisciplinary dynamic reserch group with the mission to develop new treatment strategies for breast cancers resistant to standard of care therapies. The lab uses state of the art molecular profiling such as single cell sequencing and spatial genomic profiling on patient samples throughout disease progression to understand the molecular evolution of breast cancer and response to targeted therapies. Together with molecular barcoding strategies in patient derived, syngeneic and GEMM models, mechanistic hypotheses are evaluated *in vitro* and *in vivo* and candidate biomarkers or therapeutic options are tested pre-clinically that informs the design of proof of concept clinical trials or drug discovery programmes. We have made novel advances into the understanding of genomic alterations both at bulk and single cell level and their impact on breast cancer in different contexts and how to target these effectively (including Bland et al Nature Genetics 2023 PMID: 37524790; Peck et al Cancer Res 2021 PMID:33509944; Inayatullah et al PMID: 38480932 PMID: 24240700; Natrajan et al PLOS Medicine 2015 PMID: 26881778, Maguire et al 2016 PMID: 27512948; Naidoo et al 2017 MCT PMID:29133620).

The Functional Tumour Immunology laboratory, led by Dr. Esther Arwert, focusses on uncovering tumour microenvironmental mechanisms that drive immune escape and therapy resistance, using cutting-edge technology and sophisticated mouse models, to investigate

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how the tumour microenvironment modulates antigen-specific T cell responses.

As part of the ICR's Centre for Cancer Evolution and Translational Immunotherapy Initiatives, we collaborate across disciplines to understand the evolutionary mechanisms of therapy resistance and accelerate the development of more effective, targeted therapies for breast cancer.

The candidate will benefit from close interactions with the other teams within the Centre and the ICR

https://www.icr.ac.uk/our-research/research-divisions/division-of-breast-cancer-research

The teams sit within the Breast Cancer Now Toby Robins Research Centre, within the Division of Breast Cancer Research at The Institute of Cancer Research which is the first centre in the UK entirely devoted to breast cancer research. Our goal is to advance research into the causes, diagnosis and treatment of breast cancer. It is located in state-of-the-art laboratory space, with excellent core facilities and is funded through a long term renewable programme grant from Breast Cancer Now. The Centre is Directed by Clinician Scientist Professor Andrew Tutt, Professor Chris Lord is Deputy Director of the Centre. Our Breast Cancer Research Centre was awarded the 2022 AACR Team Science award with our breast cancer clinical partners in the ICR's CTSU clinical trial unit and Royal Marsden Hospital, and also received recognition in an award to the ICR for the 2023 Queen's Anniversary Prize for transforming lives through world-leading breast cancer research.

About our organisation

The Institute of Cancer Research, London, is one of the world's most influential cancer research institutions with an outstanding track record of achievement dating back more than 100 years. Our mission is to make the discoveries that defeat cancer.

As well as being one of the UK's leading higher education institutions in research quality and impact, the ICR is consistently ranked as one of the world's most successful for industry collaboration. As a member institution of the University of Lonon, we also provide postgraduate higher education of international distinction.

We are also a charity and rely on the support of partner organisations, funders, donors and the general public.

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Our values

The ICR has a highly skilled and committed workforce, with a wide variety of roles, each requiring different skills. But whether you work as a researcher, or work as part of our corporate team, your work and behaviour is underpinned by these six values. They are what bring us together as one team - as 'One ICR'.

Pursuing excellence

We aspire to excellence in everything we do, and aim to be leaders in our field.

Acting with Integrity

We promote an open and honest environment that gives credit and acknowledges mistakes, so that our actions stand up to scrutiny.

Valuing all our people

We value the contribution of all our people, help them reach their full potential, and treat everyone with kindness and respect.

Working together

We collaborate with colleagues and partners to bring together different skills, resources and perspectives.

Leading innovation

We do things differently in ways that no one else has done before, and share the expertise and learning we gain.

Making a difference

We all play our part, doing a little bit more, a little bit better, to help improve the lives of people with cancer.

Our values set out how each of us at the ICR, works together to meet our mission – to make the discoveries that defeat cancer. *They summarise our desired behaviours, attitudes and culture – how we value one another and how we take pride in the work we do, to deliver impact for people with cancer and their loved ones."*

Professor Kristian Helin
Chief Executive

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Job description

Department / division:	Functional Genomics Breast Cancer Reseasrch Division
Pay grade / staff group:	Post Doctoral Training Fellow
Hours / duration:	Full time (35 hours per week), Monday to Friday. Fixed term contract for 3 years
Reports to:	Dr Rachael Natrajan
Main purpose of the job:	To lead on the functional assessment of the epigenetic and transcriptional regulation of neoadjuvant immunotherapy resistance in triple negative breast cancer in order to generate new biological insights.

Duties and responsibilities:

To develop and lead on projects in the teams aimed at investigating the epigenetic and transcriptional regulation of neoadjuvant immunotherapy and chemotherapy resistance in triple negative breast cancer, including:

- Modelling of cancer using immune competent, patient derived and organoid models using lineage tracing and single cell readouts
- Designing and implementing *in vivo* epigenetic CRISPR screening approaches using immune competent models
- Evaluation of immune response using single cell and spatial approaches
- Immunofluorescence and *in situ* hybridization techniques
- High throughput DNA sequencing library preparation
- The successful candidate must be capable of performing bioinformatic tasks which will allow them to collaborate and communicate with bioinformaticians in the analysis of data and interpret the analyses performed
- To work under the supervision of the line manager and to consult where appropriate
- To take an interest in the relevant scientific literature and attend relevant user group meetings
- Comply with COSHH and Risk Assessment documentation including biological containment for the project
- When required, be able to provide basic costing for individual studies
- Work to deadlines and manage time efficiently
- Perform data analyses ready for publication and/ or presentation at national and international meetings

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- To generate publication-quality figures and figure legends for scientific publications, grant applications, scientific reports etc.
- Retrieve and interrogate appropriate published data in the field of the research project and apply this to future work

General

- All staff must ensure that they familiarise themselves with and adhere to any ICR policies that are relevant to their work and that all personal and sensitive personal data is treated with the utmost confidentiality and in line with the General Data Protection Regulations
- Any other duties that are consistent with the nature and grade of the post that may be required.
- To work in accordance with the ICR's Values.
- To promote a safe, healthy and fair environment for people to work, where bullying and harassment will not be tolerated.

Workforce Agreement for Postdoctoral Training Fellows

The ICR has a workforce agreement stating that there is a maximum duration of employment of 7 years including pre-ICR PDTF Experience.

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Person specification

Education and Knowledge

PhD in molecular or cellular biology (or equivalent qualification)	Essential**
Knowledge of sub-clonal heterogeneity and evolution in cancer	Essential
Knowledge of molecular biology	Essential
Strong track record of biomedical research	Essential
Knowledge of cancer biology	Essential
Knowledge of bioinformatics	Essential
Knowledge of the use of cancer *in vivo* models	Essential
Knowledge of cancer immunology	Desirable
Knowledge of single cell sequencing methodologies	Desirable

as a minimum requirement candidates must have submitted their thesis by the start date of their employment and awarded their PhD within the six month probationary period.

Skills

Proven ability ability to design, implement and interpret experiments	Essential
Proven ability to organise and prioritise workload and to meet deadlines under considerable pressure	Essential
Ability to work effectively under pressure whilst maintaining accuracy	Essential
Demonstrable excellent written and oral communication skills, including the ability to write scientific manuscripts	Essential
Proven ability to rapidy learn new technquies and a strong commitment to learn new research technologies	Essential
Results-orientated; adaptable approach to answering scientific experiments	Essential
Good presentation skills including the ability to present data at regular project meetings and at scientific meetings nationally and internationally	Essential
Ability to develop, support and train team members	Essential
High degree of technical expertise in molecular and cell biology techniques	Essential
Good negotiation skills	Essential
Good interpersonal skills with the ability to establish effective working relationships	Essential

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Experience

Considerable experience in modeling of cancer using immune competent, patient derived xenograft and organoid systems including genetic manipulation these	Essential
Considerable experience in cell culture, including high-throughput genetic CRISPR screens, lineage tracing and drug screening approaches	Essential
Experience in target identification and validation	Essential
Experience in cell and molecular biology (such as cloning, western blot, immunofluorescence staining and imaging etc.)	Essential
Experience with single cell sequencing and data interpretation	Desirable
Experience handling patient clinical material	Desirable
Authorships in peer-reviewed literature illustrating each of the above	Essential
Experience in managing laboratory research of others, including, technicians, clinical fellows and PhD students	Essential
Experience in the drafting, submission and revision of peer reviewed research manuscripts	Essential
Experience in managing research projects between multiple partners, including both internal and external collaborators	Essential
Experience in target identification and validation	Desirable

General

Flexibility to work, efficiently and effectively, independently or as part of a team	Essential
Computer literate	Essential
Proven ability to work with limited supervision	Essential
To take interest in the relevant scientific literature	Essential

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Benefits

We offer a fantastic working environment, great opportunities for career development and the chance to make a real difference to defeat cancer. We aim to recruit and develop the best – the most outstanding scientists and clinicians, and the most talented professional and administrative staff.

The annual leave entitlement for full time employees is 28 days per annum on joining. This will increase by a further day after 2 years' and 5 years' service.

Staff membership to the Universities Superannuation Scheme (USS) is available. The USS is a defined benefit scheme and provides a highly competitive pension scheme with robust benefits. The rate of contributions is determined by USS and details of the costs and benefits of this scheme can be found on their website. If staff are transferring from the NHS, they can opt to remain members of the NHS Pension Scheme.

We offer a range of family friendly benefits such as flexible working, a parents' group, and a maternity mentoring scheme. Other great benefits include interest free loans for discounted season tickets for travel and bicycle purchases, access to the NHS discounts website, a free and confidential Employee Assistance Programme which offers a range of well-being, financial and legal advice services, two staff restaurants, and access to a gym and sporting facilities at our Sutton site.

Further information

You may contact Dr Rachael Natrajan for further information by emailing rachael.natrajan@icr.ac.uk This job description is a reflection of the current position and is subject to review and alteration in detail and emphasis in the light of future changes or development.