SPOTLIGHT ON GENETICS

Making waves in genomics

The big data of omics research and advanced imaging technology are being combined to understand, diagnose and treat disease.

"Building personalised medicine is as much about images as it is about omics. By combining the two, we can really move towards precision medicine for individuals."

Gabriel Krestin, Erasmus University Medical Centre in Rotterdam, the Netherlands

THE LONG-ACCEPTED narrative that radiation merely kills cells and damages DNA is officially a thing of the past, according to Gillian Tozer, from the Department of Oncology at Sheffield University in the UK. There has been much progress in radiation biology since X-rays were first used to treat cancer a few years after their discovery in 1895. After decades of steady progress, radiation development has reached an accelerating phase as the rapid accumulation of molecular and genomic information has given birth to the field of radiogenomics, which means different things in varying contexts.

Cancer radiogenomics

Coined in the early 2000s, the term was initially used by cancer physicians to describe the use of features of a patient's genome to predict their responses to radiation therapy across many types of cancer. More than 50% of cancer patients receive radiation therapy at some stage of their treatment, and the first focus of associated genomics research was to identify common genetic variations, such as single nucleotide polymorphisms (SNPs), that influence a patient's likelihood of developing toxicity to the therapy.

But, scientists are learning of the effects of such treatment beyond toxicity. Radiation can induce gene expression, alter signalling pathways and affect the blood supply to a tissue. This effect of radiation on a tumour's vasculature is Tozer's particular expertise. "A key question in the field is how radiotherapy can best be combined with specific drugs, such as those developed to inhibit blood vessel growth or function," she says.

Tozer says that this broadening of scope has brought radiation-biology research out of a slump. "The funding situation has been up and down over the years, but it's picked up in the past decade or so."

The Medical Research Council (MRC) in the UK, for example, is particularly encouraging grant applications in radiation oncology and biology. This is opening opportunities for new and existing researchers, such as at the Oxford Institute for Radiation Oncology and Biology, a joint initiative of Cancer Research UK and the MRC, which opened in 2008.

In 2009, the UK's National Cancer Research Institute (NCRI) also set up CTRad, a working group of clinicians and scientists focused on enhancing radiation research in the UK and for developing radiotherapy-related clinical trials.

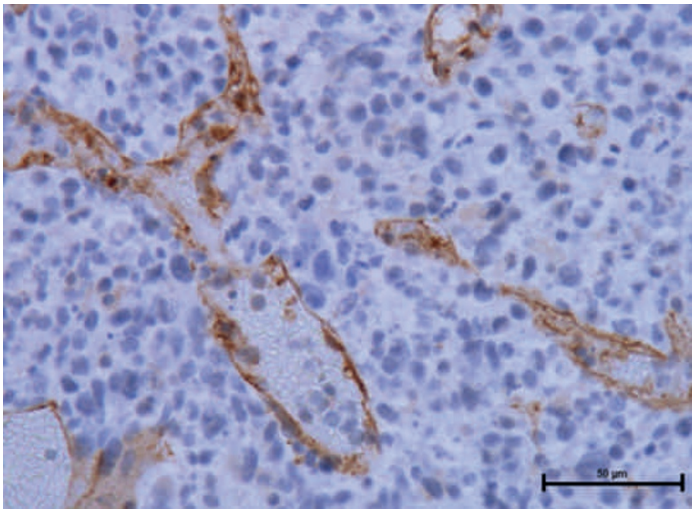
In the USA, the Radiogenomics Consortium was established in 2009 and now involves more than 150 researchers across 19 countries. The main aim of the group is to identify common genetic variations, associated with radiation toxicity. The consortium also facilitates international collaborations by sharing data and specimens, develops standards for radiogenomics research and encourages meta-analyses of relevant studies.

The resurgence of interest in radiation biology is leading to immediate improvements for patients as well as enhanced understanding of basic biology. In particular, using real-time imaging during radiation therapy allows more accurate targeting of the radiation and determination of changes in tumour size or exact position of an organ.

Information and imaging

The newer and more widely used interpretation of the term radiogenomics is the interface of imaging with radiation biology: linking information from the booming 'omics' sciences — genomics, transcriptomics and proteomics — with medical imaging in all its forms, from magnetic resonance imaging (MRI) through to X-ray computerised tomography (CT) scans. The primary aim is to identify image characteristics, or biomarkers, that can be used to diagnose and treat conditions including neurodegeneration, cardiovascular disease, arthritis and cancer. It is hoped that such biomarkers will reduce the necessity for tissue biopsies, allowing more rapid and frequent monitoring of a disease.

To identify image biomarkers, researchers look for associations between image features — such as tissue morphology, texture or density — and molecular or genetic characteristics, for example the expression of proteins that indicate a specific tumour type or that are predictive of a patient's prognosis or response to a treatment. Gabriel Krestin from the Erasmus University Medical Centre in Rotterdam in the Netherlands says that scientists have long believed there was much more information to be



Irradiated mouse tumour with damaged cells (blue) and disrupted layers of endothelial cells (brown) that line all blood vessels.

GILLIAN TOZER

gleaned from images than what meets the eye, and the underlying biological reasons for particular tissue characteristics are starting to become clear. For instance, we now know that certain image features can be associated with a tumour's aggression or can point to tissue hypoxia, a frequent tumour characteristic that not only alters responses to radiation and other therapies, but may also promote metastasis of the cancer cells.

Making these associations is not straightforward. "We can get 120 or more imaging descriptions of a tumour," says Krestin. The large volume of information is incredibly useful, but it turns what was once a highly qualitative science into a highly quantitative one. Scientists who are familiar with 'big data' are stepping in to help.

One such researcher is Olivier Gevaert at Stanford University in California. The Belgian started his career at the KU Leuven, using Bayesian networks to model omics data and predict diagnosis, prognosis or therapy responses in cancer patients. In 2009 he moved to Stanford to work in their radiology department as part of their Integrative Cancer Biology Program. "I started linking their imaging expertise with my work on omics data," he says. Now, he describes his lab's work as 'multiscale data fusion'. "We consider a tumour on a molecular level, looking at gene expression, copy number, epigenetic patterns. We look at it on a cellular level, using pathology techniques such as staining, and we look at it on a tissue level, using medical imaging. And then we try to integrate all of that information."

"You need at least a desire to be able to understand some of the language of the other scientists you'll be working with"

Gillian Tozer, Sheffield University

Radiogenomics research is highly collaborative, involving scientists with backgrounds in radiology, molecular biology, genomics, informatics and imaging analysis. It has taken a while for this expertise to start to come together, and Gevaert estimates that the field is five to ten years behind genomics in certain respects. For example, journals often don't require imaging data to be published in the same way that genomics data are.

"We used to have very few datasets with both imaging and molecular data from the same tumour sample," says Gevaert. But momentum is building and leading to increased awareness of the value of such matched samples. A catalyst for the field has been The Cancer Imaging Archive (TCIA), an ever-growing collection of cancer-related medical images to which researchers around the world have free access. A main goal of the archive, which is curated by the Cancer Imaging Program of the US National Cancer Institute (NCI), is to gather clinical diagnostic images that match patient cases for which there is genomic information available as part of The Cancer Genome Atlas. The TCGA project, initiated in 2006 and sponsored by NCI and the National Human Genome Research Institute, is collating genomic information on more than 20 cancer types from source institutions across the US, and these data are also freely available.

It is hoped that generating large databases of data from many individuals will eventually lead to care which is much more patient specific. "Building personalised medicine is as much about images as it is about omics," says Krestin. "By combining the two, we can really move towards precision medicine for individuals."

Although the main focus of imaging genomics research has been in cancer thus far, researchers are using the same concepts to study other diseases. For example, combining knowledge of medical images and genetic information might help predict an individual's risk of developing Alzheimer's disease. And right at the cutting edge of the field of radiogenomics is the idea that radiation might be used to modulate gene expression (**see Natural nanoparticles**).

Researchers interested in this fast-moving field should approach it with an open mind. "You need at least a desire to be able to understand some of the language of the other scientists you'll be working with," says Tozer. Somehow, the statistics and cell biology of omics, the physics of radiation biology and imaging, and the clinician's experience of treating individual patients need to come together. But radiogenomics is a relatively young field and it has had a highly collaborative start. "People talk about fields becoming interdisciplinary, but we always have been," says Krestin. "You could say it's in our genes."

This content was commissioned and edited by the Naturejobs editor

Natural nanoparticles

The technique of optogenetics, in which light-sensitive proteins are used to regulate the activity of specific neurons, has been a game-changer in neuroscience research. But the process requires a light source to be implanted into the brain of experimental animals. Jeffrey Friedman at Rockefeller University in New York and his colleague Sarah Stanley, now at Mount Sinai Hospital, are trying to accomplish the same goal in a non-invasive manner. His lab is pioneering a technique that relies on natural nanoparticles — specifically, ferritin, protein particles that store iron within cells. These can heat up in response to low-frequency radio waves.

The group have created a modified gene that encodes ferritin expressed close to a heat-activated ion channel in the cell membrane. Opening this channel causes calcium ions to move into the cell. The researchers then added a gene that expresses insulin in a calcium-dependent manner. By expressing this combined gene construct in mice, using either stem cells or a lentivirus, and then exposing the mice to radio waves or a magnetic field, they could induce the ferritin nanoparticles to move such that the ion channel opened and insulin expression was switched on.

This proof-of-principle experiment was published in *Nature Medicine* in December 2014. Friedman says he's excited about adapting the approach to other scenarios. "We're now exploring the utility of the method to control neural activity," he says. Much further down the track, the technique might be used for long-term modulation of neural activity in humans, such as to treat severe metabolic disease or Parkinson's. But alongside all the biological challenges is a more technical hurdle. "For the mice experiments, we use a commercial welding apparatus to create the radio waves," says Friedman. This is where engineers join the radiogenomics field. Several stakeholders, including personnel from Google, are already developing small and safe devices to generate radio waves for medical use.

ZACK VEILLEUX

Jeffrey Friedman and Sarah Stanley.

TOUCHLIGHT GENETICS

Touchlight Genetics Ltd is pioneering the development of innovative technologies and products in the field of nucleic acids. Our in vitro DNA amplification technology leads the way for the production of high quality synthetic DNA suitable for both therapeutic and synthetic biology applications.

Currently located in Leatherhead, Surrey, the company will be moving to state of the art, custom-built, laboratories in Hampton, West London in Summer 2015. This is an exciting opportunity to join a young dynamic biotech company working at the forefront of DNA research and development.

Further details about the company and the skills requirements for each of these roles can be found at **www.touchlightgenetics.com**

Salaries will be commensurate with experience, other benefits include performance related bonuses and a company pension scheme.

Apply for these roles by emailing a CV and tailored cover letter (in pdf format) to jobs@touchlightgenetics.com clearly stating the position and reference number of the role you are applying for. Applicants must be eligible to work in the UK.

Closing date for applications 19th June 2015.

No Agencies please.

CORE TECHNOLOGY RESEARCH POSITIONS

Research Scientist - Process Enhancement TGL- 001/15

Our current in vitro process utilises a DNA polymerase and a protelomerase to produce dbDNA™ at very high yields. We continue to develop and improve our process both in terms of DNA production, process efficiency, and product purification. We are looking for one Research Scientist to continue the development and optimisation of Touchlight Genetics' propriety process for DNA amplification to increase efficiency and reduce waste. In particular the enhancement of yield through automation using our proprietary DNA synthesis machine will be a major responsibility of the role. Leveraging this learning into the design of innovative research kits for in vitro DNA production will follow.

Research Scientist - in vitro DNA Replication TGL-002/15

Touchlight is currently developing new methods of DNA amplification using novel techniques. This will be used not only for the production of our standard closed linear dbDNA™ cassette but will allow us to amplify new and unique DNA structures with enhanced properties. The successful applicant will develop new in vitro amplification methods to fully utilise this new platform technology. This work will involve identifying proteins required for this process and optimisation of new amplification systems.

▲ **Essential qualifications for the above two positions: Educated to PhD level, you will have relevant experience in molecular biology, protein biochemistry and / or enzyme kinetics.**

RESEARCH POSITIONS

Research Scientist - Molecular Biology TGL-003/15

The successful applicant will play an important role in the characterisation of dbDNA™ and its output in various cell based assays including, but not restricted to, reporter gene evaluation and fluorescence imaging. The ability of dbDNA™ to traverse the cell membrane, its efficiency in transcription and the stability of the constructs inside cells are all parameters which affect the efficacy of DNA therapies. Given Touchlight's interest in genetic therapies and biomanufacturing, understanding the performance of these products in vitro and in vivo will be a major responsibility of this position.

Research Scientist - Cell Biology TGL-004/15

This job requires an innovative and flexible Cell Biologist to expand our tissue culture, transfection and formulation capabilities with an emphasis on human therapeutics. The successful applicant must be prepared to be highly flexible and able to explore and develop new systems for the in vitro assessment of DNA transfection output.

▲ **Essential qualifications for the above two positions: You will possess a Degree or PhD in Molecular Biology / Virology / Cell Biology / Immunology or a related discipline and 2-5 years experience, preferably in an industrial setting. Experience in virology, gene therapy or cell therapy highly desirable.**

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MRC Harwell

Programme Leader Position

MRC Harwell is a leading international centre for mouse genetics and genomics with a focus on developing and utilising mouse models to decipher and elucidate mechanisms of disease. Funded by the UK Medical Research Council, the campus comprises the Mammalian Genetics Unit (MGU) and Mary Lyon Centre (MLC). MRC Harwell conducts research into numerous aspects of mouse genetics, from development to ageing (see www.har.mrc.ac.uk). It is also a member of the International Mouse Phenotyping Consortium (IMPC), a large-scale collaborative effort to phenotype a knockout mouse for every gene in the genome. MRC Harwell has excellent facilities and extensive expertise in mouse functional genomics that enable us to provide a multitude of facilities and services for the scientific community, including mutagenesis and phenotyping techniques, mouse lines and genetic archives.

The MGU plans to establish two new research groupings over the coming year and welcomes applications for Programme Leader positions from outstanding researchers with an internationally leading track record of research, exemplified by a substantial record of high impact publications, a proven ability to attract research funding and experience in leading a research team.

Applicants will have a major interest in using mouse genetics to undertake investigations into the mechanisms of disease, be able to deliver a world-leading research programme and to sustain and advance the international reputation of the Unit. The successful applicants will also play a role in the senior team leading the strategic development of MGU and be expected to be able to articulate a strong and dynamic vision of their future research and its interactions with and impact on human and clinical genetics.

MRC Harwell will be interested to receive proposals from candidates with interests in diverse areas of disease or biological research, as well as explore the synergies with existing research programmes (see www.har.mrc.ac.uk). We will also be happy to consider joint appointments that would involve for example the candidate holding a position at MRC Harwell alongside an appointment at a relevant medical school, HEI or research institute. This is a tenured appointment with core funding including a number of research posts.

Starting salary will be in the range of (£44,314 - £99,999).

Applications should include a covering letter and full CV, an outline of current research interests (1 page) and a proposal for future research (up to 2 pages), together with the names and addresses of three professional referees who can be contacted prior to interview. The Director of the MGU, Professor Steve Brown, will be happy to receive enquiries and applications from interested applicants. (s.brown@har.mrc.ac.uk).

Closing date 25 June 2015.

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EMBL

The European Molecular Biology Laboratory offers a highly collaborative, uniquely international culture. It fosters top quality, interdisciplinary research by promoting a vibrant environment consisting of young independent research groups with access to outstanding graduate students and postdoctoral fellows. Significant core funding and limited teaching responsibilities allow EMBL group leaders to undertake ambitious, farsighted research programmes and provide a scientific environment that is particularly attractive for researchers with families.

Group Leader / Team Leader Genome Biology and Proteomics

at EMBL Heidelberg, Germany

The European Molecular Biology Laboratory (EMBL) is renowned for its innovative, interdisciplinary research conducted in an open, international culture. The Headquarters is located in Heidelberg (Germany), with additional sites in Grenoble (France), Hamburg (Germany), Hinxton (UK) and Monterotondo (Italy).

The Genome Biology Unit studies all aspects of how the genome gives rise to phenotype. It is a highly interdisciplinary department, including groups with expertise in genomics, proteomics, computer science, microfluidics and chemistry, which provides a collaborative and supportive environment to perform cutting edge research. The research focusses on dissecting fundamental principles of how different layers of molecular information (DNA, RNA, Protein, Metabolites) are regulated and interconnected to give rise to diverse phenotypes.

We are looking for outstanding candidates in proteomics and biological mass spectrometry. The position involves running an independent research group within the Genome Biology Unit, developing and applying cutting edge mass spectrometry approaches. We particularly encourage candidates with interests in chromatin biology, regulation of gene expression, posttranslational protein modifications, quantitative or dynamic proteomics or any aspect linking genotype to phenotype. EMBL has an excellent proteomic core facility that provides mass spectrometry service to biological research groups. In addition to running a research group, the position also involves managing this facility and ensuring that the technologies it offers remain at the cutting edge.

EMBL is an inclusive, equal opportunity employer offering attractive conditions and benefits appropriate to an international research organisation with a very collegial and family friendly atmosphere. The remuneration package comprises from a competitive salary, a comprehensive pension scheme, medical, educational and other social benefits, as well as financial support for relocation and installation, including family, and the availability of an excellent child care facility on campus.

Please apply online through **www.embl.org/jobs** and include a cover letter, CV and a concise description of research interests and future research plans. Please also arrange for 3 letters of recommendation to be emailed to **references@embl.de** at the latest by 28 June 2015.

Interviews are planned for September 2015.

Further information about the position can be obtained from the Head of Unit Eileen Furlong (**eileen.furlong@embl.de**).

An initial contract of 5 years will be offered to the successful candidate. This is foreseen to be extended to a maximum of 9 years, subject to an external review.

Further details on Group Leader appointments can be found under **www.embl.org/gl_faq**.

www.embl.org

W262234R

National Cancer Institute

CENTER FOR CANCER RESEARCH

CHIEF, RNA BIOLOGY LABORATORY
CENTER FOR CANCER RESEARCH
NATIONAL CANCER INSTITUTE - FREDERICK, MARYLAND
NATIONAL INSTITUTES OF HEALTH
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Application Deadline: June 15, 2015

NCI is seeking an outstanding, internationally recognized scientist to serve as Chief of the RNA Biology Laboratory (RBL) in the Center for Cancer Research (CCR). The position, which is the equivalent of an academic Department Chair, is the key component of a major initiative to expand CCR's RNA Biology research at the NCI. The RBL Chief will play leading roles in developing an integrated program in RNA Biology and in the CCR RNA Initiative. In addition, the RBL Chief will direct an extensive individual research program at the Frederick campus which will complement and augment CCR expertise in chromosome biology, immunology, HIV/AIDS, cancer biology and molecular oncology, areas in which Centers of Excellence have been established. Supported with stable financial resources, the RBL will have access to a wide array of intellectual and technological assets, including high-quality technology cores dedicated to protein chemistry, natural products chemistry, biophysics, mass spectrometry, imaging, microscopy, proteomics and genomics, bioinformatics/bio-statistics, and flow cytometry, in addition to clinical support.

The National Cancer Institute (NCI) is part of the National Institutes of Health (NIH) in the Department of Health and Human Services (DHHS), a federal government agency. CCR is the largest component of the NCI Intramural Research Program, providing an environment conducive to advancing translational research and collaborative interactions through investigator-initiated and interdisciplinary team science. Additional information on CCR research priorities can be found at: http://ccr.cancer.gov.

In addition to a Ph.D., M.D./Ph.D., or equivalent doctoral degree in a relevant discipline, applicants should possess outstanding communication skills and documented leadership experience. Tenured faculty or industrial scientists of equivalent rank with a demonstrated commitment to RNA Biology should apply. Salary will be commensurate with experience and accomplishments. Applications should include a description of research interests and leadership philosophy, career synopsis, and current curriculum vitae with complete bibliography.

Review of applications will begin on or about June 15, but applications will be accepted until the position is filled. Send applications to **Dr. Janelle Cortner, RNA Biology Laboratory Search Committee, National Cancer Institute Building 428/46, PO Box B, Frederick MD 21702, or by email to CCR_RNA_Biology@mail.nih.gov**

DHHS, NIH and NCI are Equal Opportunity Employers

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

NW261826R

Assistant/Associate Professor
Department of Pediatric Ophthalmology
Cincinnati Children's Hospital Medical Center

Pediatric Ophthalmology at Cincinnati Children's Hospital is a vibrant division that combines high-level clinical and research programs. We are seeking a world-class tenure track Assistant or Associate Professor to join the Visual Systems Group, the research wing of Pediatric Ophthalmology. Candidates must have completed a postdoctoral training period, published high quality and original work, and hold an MD, PhD, or MD/PhD degree. The successful candidate may be a full-time researcher or may combine research with clinical practice.

Pediatric Ophthalmology has a strong interest in recruiting a researcher in the field of ocular genetics, but will consider any high-quality candidate working in a field that has a connection to vision science. To learn more about Pediatric Ophthalmology and the Visual Systems Group, please visit http://www.cincinnatichildrens.org/research/divisions/o/ophthalmology/default/

Pediatric Ophthalmology is a division of the Department of Ophthalmology at the University of Cincinnati College of Medicine.

Interested candidates should send curriculum vitae and letter of interest to:
Erica Mason
Cincinnati Children's Hospital Medical Center
Erica.Mason@cchmc.org

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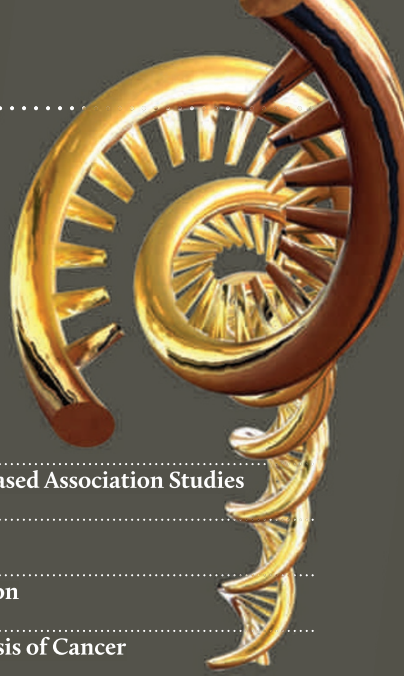

Conferences

Pharmacogenetics and Stratified Medicine
14 January

Biomarkers for Brain Disorders: Challenges and Opportunities
1–3 February

The Challenge of Chronic Pain
11–13 March NEW FOR 2015

Innate Immune Memory
18–20 March NEW FOR 2015

The Biology of Regenerative Medicines
22–24 April

Genomics of Rare Disease: Beyond the Exome
29 April–1 May

Applied Bioinformatics and Public Health Microbiology
6–8 May

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2–5 September

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16–19 September

Infectious Disease Genomics
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18–23 January

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11–17 July

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28–30 January

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EMBL-EBI-Wellcome Trust Workshop on In Silico Systems Biology
7–12 June

Genetics, Breeding and Welfare of Laboratory Mice
16–19 June

EMBL-EBI-Wellcome Trust Summer School in Bioinformatics
22–26 June

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6 –11 December

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1–6 February (San José, Costa Rica)

Malaria Experimental Genetics
15–20 March (Bangkok, Thailand)

Genomic Epidemiology in Africa
21–26 June (Durban, South Africa)

Molecular Approaches to Clinical Microbiology in Africa
19–25 September (Nairobi, Kenya)

Working with Pathogen Genomes
30 November–4 December (Montevideo, Uruguay)

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