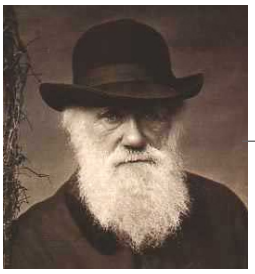
ICR The Institute of Cancer Research



Centre for Evolution and Cancer

'Nothing in biology makes sense except in the light of evolution'

T. Dobzhansky, 1973

Centre for Evolution and Cancer
The Institute of Cancer Research, London
Brookes Lawley Building
15 Cotswold Road
London SM2 5NG
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January 2016

Evolution by natural selection is the foundation law of biology. We shouldn't be surprised therefore that it has great relevance to cancer. The idea that cancer is fundamentally a process of somatic cell evolution was first advocated in the 1970s. Since then, the concept has been validated and greatly elaborated, highlighting the striking parallels with Darwinian evolution by natural selection in ecosystems. Cancer genomics has provided detailed genetic descriptions and technologies for interrogating single cells and multi-regional small biopsies, revealing space-time genetic diversification of cancer cells and allowing us to infer clonal phylogenies, or evolutionary history. It's a striking fact that every patient's cancer has an individually unique and variegated clonal architecture and evolutionary trajectory.

This represents a paradigm shift with major implications for the way we think about the fundamental biology of cancer, the emergence of drug resistance and our attempt to control it. This also applies to evolutionary considerations of why humans are so vulnerable to cancer. Evolutionary biology isn't a sub-topic of cancer sciences - it is a conceptual framework for everything in cancer.

In recognition of this important development and the research opportunities it provides, The Institute of Cancer Research, London established a Centre for Evolution and Cancer in 2013. Its overarching objective is to assemble a multi-disciplinary team of investigators that will interrogate cancer afresh using evolutionary principles derived from ecology, enabled by state-of-the-art cellular, genomic and bioinformatic technologies. Our objectives include the following:

- To provide an evolutionary logic for vulnerability to cancer in ageing humans and inherent variation in risk between individuals.

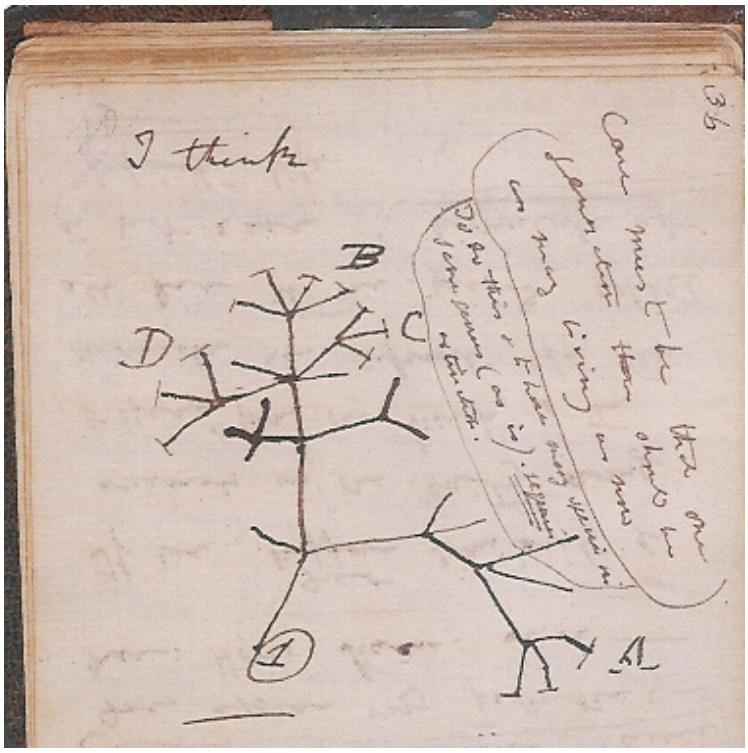
- To optimise technologies for in depth analysis of clonal architectures and dynamics in cancer.

- To integrate cancer genomics, clonal evolution with ecosystem and therapeutic selective pressures.

- To develop quantitative evolutionary parameters of cancer clones and their microenvironments that are predictive of future progression of disease or the emergence of drug resistance.

Our long term aspiration is to help resolve the challenge of how best to thwart the evolutionary resilience of cancer in order to reduce the burden of cancer on society.

The Centre is supported by a Strategic Award from the Wellcome Trust.



From Darwin's Transmutation notebook B, 1837

Centre for Evolution and Cancer

Professor Mel Greaves*	Founding Director
Dr Carlo Maley	Visiting Scientist and Associate Director
Dr Marco Gerlinger*	
Dr Andrea Sottoriva*	
Dr Yinyin Yuan*	
Professor Chris Jones*	
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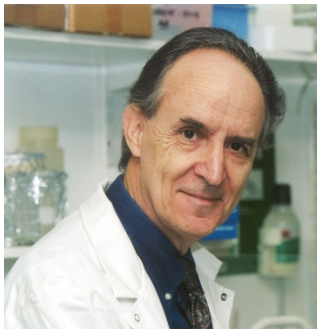
Scientific Advisory Board: to follow.



Professor Mel Greaves PhD FRS

Evolutionary Biology of Leukaemia

Mel Greaves trained in evolutionary biology and zoology (BSc) and immunology (PhD) at University College London and at the Karolinska Institute in Stockholm before focusing his research on cancer and leukaemia in the mid-1970s at the Imperial Cancer Research Fund in London. In 1984, he established the Centre for Cell and Molecular Biology of Leukaemia at The Institute of Cancer Research (ICR). In 2013, he founded the ICR Centre for Evolution and Cancer.

Research focus:

My laboratory has a longstanding interest in uncovering the natural history, evolutionary biology and causation of childhood leukaemia. We have used twins with concordant leukaemia, archived neonatal blood spots and frozen cord blood to trace back the origins of leukaemia to its earliest stages and its initiating lesions. We use single cell genetics and xeno-transplantation to determine clonal architecture, phylogeny and the genetic diversity of stem cells. In collaboration with epidemiologists, we have pursued an evolutionary 'mismatch' hypothesis that explains the role of infections in triggering childhood leukaemia.

Key publications:

Greaves M (2015) Evolutionary determinants of cancer. Cancer Disc, 5: 806-820.

Greaves M (2014) Was skin cancer a selective force for black pigmentation in early hominin evolution? Proc R Soc B, 281: 20132955.

Greaves M (2014) An evolutionary foundation for cancer control. World Cancer Report 2014 (eds Stewart BW, Wild CP). International Agency for Research on Cancer (IARC), Lyon, pp 337-345.

Greaves M (2013) Cancer stem cells as 'units of selection'. Evol Appl, 6: 102-108.

Potter NE, *et al* (2013) Single-cell mutational profiling and clonal phylogeny in cancer. Genome Res, 23: 2115-2125.

Greaves M, Maley CC (2012) Clonal evolution in cancer. Nature, 481: 306-313.

Anderson K, *et al* (2011) Genetic variegation of clonal architecture and propagating cells in leukaemia. Nature, 469: 356-361.

Greaves M (2007) Darwinian medicine: a case for cancer. Nat Rev Cancer, 7: 213-221.

Greaves M (2006) Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer, 6: 193-203.

Greaves M (2000) Cancer. The Evolutionary Legacy. Oxford University Press, Oxford.

Dr Carlo Maley PhD

Evolution Biology of Cancer

Carlo Maley has formal training in evolutionary biology (University of Oxford), computational biology (MIT) and cancer biology (University of New Mexico and Fred Hutchinson Cancer Research Center).

Research focus:

My lab focuses on three areas: the evolutionary dynamics of neoplastic progression, the evolution of therapeutic resistance, and the evolution of cancer suppression in large, long-lived animals such as elephants and whales. We are both trying to measure these phenomena and to intervene in them to slow down or prevent cancer and its recurrence after therapy.

Key publications:

Abegglen LM, *et al* (2015) Potential mechanisms for cancer resistance in elephants and comparative cellular response to DNA damage in humans. JAMA, 314: 1850-1860.

Andor N, *et al* (2015) Pan-cancer analysis of the extent and consequences of intra-tumor heterogeneity. Nat Med, advanced online publication, doi: 10.1038/nm.3984.

Kostadinov RL, *et al* (2013) NSAIDs modulate clonal evolution in Barrett's esophagus. PLoS Genet, 9: e1003553.

Greaves M, Maley CC (2012) Clonal evolution in cancer. Nature. 481: 306-313.

Maley CC, *et al* (2006) Genetic clonal diversity predicts progression to esophageal adenocarcinoma. Nature Genet, 38: 468-473.

Dr Marco Gerlinger MRCP PhD

Translational Oncogenomics

Marco Gerlinger trained in medicine and cancer biology in Munich, followed by clinical appointments in Zurich and London. He undertook postdoctoral training in cancer immunotherapy in Zurich and in biomarker and drug target discovery at the London Research Institute. He leads the Translational Oncogenomics Team at the ICR and is an honorary consultant in medical oncology at The Royal Marsden NHS Foundation Trust, where he specialises in the treatment of urological and gastrointestinal cancers.

Research focus:

My research group investigates the relevance of genetic and non-genetic intra-tumour heterogeneity for cancer progression and the development of drug resistance. We interrogate cancer specimens with high-throughput genomic and functional assays to understand how therapy re-shapes cancer genomic landscapes and to understand the rules and molecular drivers of cancer evolution. A further area of interest is the identification of therapeutic vulnerabilities of drug-resistant cancer clones through *in vitro* models.

Our research should lead to novel genomic technologies to track cancer evolution minimally invasively and to therapeutic approaches to prevent the evolution of drug resistance. Integrating these therapeutic strategies with precision genomic tracking technologies should lead to the next generation of personalised cancer therapies and improve the outcomes of patients with metastatic cancers.

Key publications:

Gulati S, *et al* (2014) Systematic Evaluation of the Prognostic Impact and Intratumour Heterogeneity of Clear Cell Renal Carcinoma Biomarkers. Eur Urol, doi: 10.1016/j.eururo.2014.06.053.

Gerlinger M, *et al* (2014) Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing. Nat Genet, 46: 225-233.

Gerlinger M, *et al* (2012) Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med, 366: 883-892.

Gerlinger M, *et al* (2012) Genome-wide RNA interference analysis of renal carcinoma survival regulators identifies MCT4 as a Warburg effect metabolic target. J Pathol, 227: 146-156.

Yap TA, *et al* (2012) Intratumor heterogeneity: seeing the wood for the trees. Sci Transl Med, 4: 127ps10.

Gerlinger M, Swanton C (2010) How Darwinian models inform therapeutic failure initiated by clonal heterogeneity in cancer medicine. Br J Cancer, 103: 1139-1143.

Dr Andrea Sottoriva PhD

Evolutionary Genomics and Modelling

Andrea Sottoriva has a background in computer science (BSc from the University of Bologna, Italy) and computational modelling (MSc from the University of Amsterdam, the Netherlands). He trained in computational physics at the National Institute for Nuclear and High-Energy Physics (NIKHEF) in the Netherlands and at CERN in Switzerland. During his masters, he became interested in computational and mathematical approaches to cancer and then completed his PhD in cancer genomics and modelling at the CR-UK Cancer Research Institute in Cambridge.

Research focus:

In my team we focus on the integration of cancer genomic data with theoretical frameworks based on tumour evolution. We use a range of genomic techniques to generate patient-specific molecular profiles and use mathematical and computational models to perform measurements and quantitative predictions on human malignancies. This rigorous characterisation of tumour evolutionary dynamics has the objective of understanding how tumours grow, disseminate and recur in a patient. We aim at using the dynamics we discover to make clinically relevant predictions that will aid the design of personalised treatments.

Key publications:

Williams M, *et al* (2016) Identification of neutral tumor evolution across cancer types. Nat Genet, 48: 238-244.

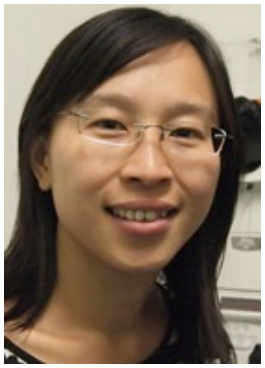
Sottoriva A, *et al* (2015) A Big Bang model of human colorectal tumor growth. Nat Genet, 47: 209-16.

Vermeulen L, *et al* (2013) Defining stem cell dynamics in models of intestinal tumour initiation. Science, 342: 995-998.

Sottoriva A, *et al* (2013) Intra-tumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. Proc Natl Acad Sci USA, 110: 4009-4014.

Sottoriva A, *et al* (2013) Single-molecule genomic data delineate patient-specific tumor profiles and cancer stem cell organization. Cancer Res, 73: 41-49.

Sottoriva A, Vermeulen L, Tavaré S (2011) Modeling evolutionary dynamics of epigenetic mutations in hierarchically organized tumors. PLoS Comput Biol, 7 (5).



Dr Yinyin Yuan PhD

Computational Pathology and Integrative Genomics

Trained as a computer scientist, Yinyin Yuan completed her BSc degree at the University of Science and Technology of China, before obtaining her MSc and PhD at the University of Warwick. At Warwick she became interested in studying genetic regulation in plant disease by adapting statistical analysis tools originally developed for other disciplines such as economics. Her postdoctoral research at the CRUK Cancer Institute in Cambridge involved characterisation of the molecular landscape of breast cancer. She joined the ICR in 2012 as the leader of the Computational Pathology and Integrative Genomics team.

Research focus:

My lab develops computational approaches to study the spatial variability of tumours and the synergistic interactions between cancer genetics and the tumour microenvironment. Our approaches combine techniques from diverse disciplines including computer science image analysis, spatial statistics and molecular pathology. Our goals are to deliver scientific and clinical advances through integrative modelling of intra-tumour heterogeneity, to foster new developments of statistical applications in pathology, and to develop objective methodologies for directing cancer therapeutic strategies.

Key publications:

Natrajan R, *et al* (2016) Microenvironmental heterogeneity parallels breast cancer progression: a histology-genomics integration analysis. PLoS Med, 13(2): e1001961.

Nawaz S, Heindl A, Koelble K, Yuan Y (2015) Beyond immune density: critical role of spatial heterogeneity in estrogen receptor-negative breast cancer. Mod Pathol, 28: 766-777.

Yuan Y *et al* (2012) Quantitative image analysis of cellular heterogeneity in breast tumors complements genomic profiling. Science Transl Med, 4: 157ra143.

Curtis C, *et al* (2012) The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature, 486: 346-352.

Yuan Y, Savage RS, Markowetz F (2011) Patient-specific data fusion defines prognostic cancer subtypes. PLoS Computational Biol, 7: e1002227.

Yuan Y, *et al* (2011) Penalized regression elucidates aberration hotspots mediating subtype-specific transcriptional responses in breast cancer. Bioinformat, 27: 2679-2685.

Professor Chris Jones PhD

Glioma

Chris Jones attained a BSc in toxicology and pharmacology followed by a PhD from the University of London. He joined The Institute of Cancer Research in 2001 as a Senior Postdoctoral Research Fellow in the Breakthrough Toby Robins Breast Cancer Research Centre, spending two years studying myoepithelial cells and basal-like breast cancers. He established his paediatric glioma team in 2005.

Research focus:

My laboratory focuses on high-grade gliomas in children. We have identified unique genetic drivers of these tumours which illustrate previously unappreciated connections between chromatin regulation, developmental signalling and cancer. The distinct anatomical distributions of childhood tumours marked by these specific mutations suggest important differences in selective pressures between regions of the developing brain. The goals of our work are to better understand the function of these genetic alterations in the context of paediatric gliomagenesis and to use this mechanistic insight to develop novel therapies for children with these tumours. A major barrier to effective treatment is the extent of variation present within an individual patient's tumour sample. We have shown that glioblastomas harbour multiple sub-clonal populations marked by distinct, mutually exclusive genomic alterations which may vary topographically across the tumour, harbour distinct functional properties, and have differential responsiveness to therapy. We are addressing these challenges through multi-region and longitudinal sampling approaches linked to high-throughput single-cell derived functional assays and targeted re-sequencing. In this way we aim to develop a more comprehensive picture of tumour evolution and to prioritise the key molecular targets for combinatorial treatment approaches.

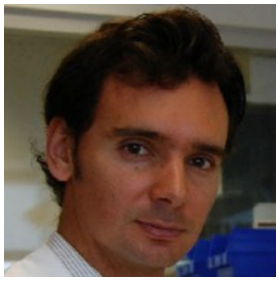
Key publications:

Taylor KR *et al* (2014) Recurrent activating ACVR1 mutations in diffuse intrinsic pontine glioma. Nature Genet, 46: 457-461.

Bjerke L, *et al* (2013) Histone H3.3 mutations drive paediatric glioblastoma through upregulation of MYCN. Cancer Discov, 3: 512-519.

Little SE, *et al* (2012) Receptor tyrosine kinase genes amplified in glioblastoma exhibit a mutual exclusivity in variable proportions reflective of individual tumor heterogeneity. Cancer Res, 72:1614-1620.]

Paugh BS, *et al* (2010) Integrated molecular genetic profiling of paediatric high grade gliomas reveals key differences with the adult disease. J Clin Oncol, 28: 3061-3068.



Dr Gerhardt Attard MD MRCP PhD

Translational Biology of Urological Cancers

Gert Attard joined the ICR in 2004, where he completed a fellowship in drug development followed by a PhD studying the molecular biology of prostate cancer. He completed his medical oncology specialist training in the Royal Marsden as an NIHR academic clinical lecturer and was appointed an honorary consultant and clinician scientist, specialising in the management of metastatic prostate cancer, in April 2013.

Research focus:

My lab focuses on metastatic prostate cancer, using functional and genomic studies to understand the evolutionary processes that lead to resistance to AR inhibition and taxane chemotherapy. By using next-generation sequencing approaches applicable to low amounts of poor quality DNA, we are interrogating sequentially collected plasma samples in order to define the temporal dynamics and spatial heterogeneity of lethal prostate cancer tumour clones. We aim to identify cancer vulnerabilities that we can exploit therapeutically and develop plasma-based assays for stratifying patients for treatment and detecting the emergence of treatment resistant clones prior to clinical manifestations of progression.

Key publications:

Romanel A, Gasi Tandefelt D, *et al* (2015) Plasma *AR* and abiraterone-resistant prostate cancer. Sci Transl Med, 7: 312re10.

Carreira S, Romanel A, Goodall J, *et al* (2014) Tumor clone dynamics in lethal prostate cancer. Sci Transl Med, 17: 254.

Richards J, *et al* (2012) Interactions of abiraterone, eplerenone and prednisolone with wild-type and mutant androgen receptor: a rationale for increasing abiraterone exposure or combining with MDV3100. Cancer Res, 72: 2176-82.

Attard G, *et al* (2009) Characterization of *ERG, PTEN* and *AR* gene status in circulating tumor cells from patients with castration-resistant prostate cancer. Cancer Res, 69: 2912-2918.

Attard G, *et al* (2009) Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. J Clin Oncol, 27: 3742-3748.

Attard G, *et al* (2008) Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer (CRPC) commonly remains hormone driven. J Clin Oncol, 26: 4563-4571.

Clark J, *et al* (2008) Complex patterns of ETS gene alteration arise during cancer development in the human prostate. Oncogene, 27:1993-2003.

Attard G, *et al* (2008) Duplication of the fusion of *TMPRSS2* to *ERG* sequences identifies fatal human prostate cancer. Oncogene, 27: 253-263.

Dr Stefano Lise PhD

Cancer Bioinformatics

Stefano Lise trained in physics at the University of Padova (Italy) and obtained a PhD in condensed matter theory from the International School for Advanced Studies (SISSA/ISAS) in Trieste (Italy). After a first post-doc at Imperial College London, he moved into bioinformatics thanks to an MRC Special Training Fellowship. He held the fellowship at University College London (UCL), working in protein and structural bioinformatics. He moved to the Wellcome Trust Centre for Human Genetics (WTCHG) in Oxford in 2010 where he developed expertise in human disease genomics and in the analysis of next generation sequencing data. He joined the ICR in 2015 as Head Bioinformatician of the Centre for Evolution and Cancer.

Research focus:

We work in collaboration with other research groups within the Centre and provide bioinformatics support to cancer research projects. Our expertise is in the analysis and interpretation of genomics data, in particular next-generation sequencing data (DNA-seq, RNA-seq, ChIP-seq, etc). We also conduct independent bioinformatics research, focused on the analysis of cancer evolution.

Key publications:

Taylor JC, *et al* (2015) Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. Nature Genet, 47: 717–726.

Conti V, *et al* (2013) Periventricular heterotopia in 6q terminal deletion syndrome: role of the C6orf70 gene. Brain, 136: 3378-3394.

Németh AH, *et al* (2013) Next generation sequencing for molecular diagnosis of neurological disorders using ataxias as a model. Brain, 136: 3106-3118.

Shanks ME, *et al* (2013) Next Generation Sequencing (NGS) as a diagnostic tool for retinal degeneration reveals a much higher detection rate in early onset disease. J Hu Genet, 21: 274–280.

Lise S, *et al* (2012) Recessive mutations in SPTBN2 implicate β-III spectrin in both cognitive and motor development. PLoS Genet, 8: e1003074.

Dr C. Athena Aktipis PhD

Cooperation and Ecology of Cancer

Athena Aktipis has a PhD in psychology from the University of Pennsylvania and completed her postdoctoral research in the Department of Ecology and Evolutionary Biology at the University of Arizona.

Research focus:

My research programme lies at the intersection of evolutionary biology and cancer biology, with a focus on the applications of cooperation theory to cancer evolution. Over the last several years I have been applying my background in cooperation theory to a number of problems in cancer biology including the evolution of metastasis, the role of tumour ecology in shaping selection pressures on cancer, and the evolution of cancer stem cells. As a theoretical biologist, my main tools are computational models that I use to test ideas, explore the conditions under which a theory should apply to cancer, and then guide experiments and clinical interventions.

Key publications:

Aktipis CA, *et al* (2013) Life history tradeoffs in cancer evolution. Nat Rev Cancer, 13: 883-892.

Aktipis CA, Nesse R (2013) Evolutionary foundations for cancer biology. Evol Appl, 6: 144-159.

Aktipis CA, Maley CC, Pepper JW (2012) Dispersal evolution in neoplasms: the role of disregulated metabolism in the evolution of cell motility. Cancer Prev Res, 5: 266-275.

Aktipis CA, *et al* (2011) Overlooking evolution: a systematic analysis of cancer relapse and therapeutic resistance research. PLoS One, 6: e26100.

Aktipis CA, Maley CC (2011) The selfish cell: cancer's emerging evolutionary paradigm. Evol Med Rev (Aug 9). http://evmedreview.com/?p=764.

POSITIONS

The Centre will have ongoing recruitment at student (PhD), post-doctoral and scientific officer (technical) level including bioinformatics posts. Anyone interested should contact Professor Mel Greaves (mel.greaves@icr.ac.uk) or individual team leaders in the Centre.