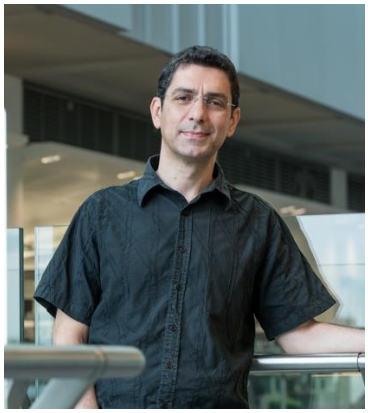
Name	GEORGE KASSIOTIS
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2005



Career History

2000- 2005: Post-doctoral scientist, Molecular Immunology, MRC National Institute for Medical Research, London, UK
2005- 2011: Programme leader-track, Immunoregulation, MRC National Institute for Medical Research, London, UK
2011- 2015: Programme leader, Immunoregulation, MRC National Institute for Medical Research, London, UK
2015- present: date Senior Group Leader, Retroviral Immunology, the Francis Crick Institute, London, UK

Major Awards, Honours and Prizes

1997: Short-term EMBO fellowship, European Molecular Biology Organization (EMBO)
1998: Young Investigator Award, European League Against Rheumatism (EULAR)
2012: Non-Resident Ordinary Member, Medical Research Club, London, UK
2018: Sir David Cooksey Prize in Translation, The Francis Crick Institute, London, UK

Membership of external committees, editorial boards, review panels, SABs etc

2016 – date Supervisor, Wellcome Trust Clinical PhD Programme - Imperial Immunity, Inflammation, Infection and Informatics (4i)
2015 – date Cancer Immunology Expert Review Panel, Cancer Research UK
2016 – date MRC-CRUK Cancer Immunology and Immunotherapy Advisory Group
2020 – date The Children and Young People's Cancer Innovation Award Expert Review Panel, Cancer Research UK
2020 – date Cancer Grand Challenges workshop member, Cancer Research UK
2016 – date Genome Editing Mice for Medicine (GEMM) Review Panel, Harwell, MRC, UK

Lab Name	***Retroviral Immunology Laboratory***

Research programme and achievements

In the last five years, we explored basic aspects of viral disease pathogenesis, the viral and host characteristics that determine the outcome of infection and the quality of the immune response that can afford immune protection to viral infection. At the same time, we initiated work on the role of endogenous retroviruses, particularly in cancer.
We have been focusing on CD4 T helper (Th) cells, the central orchestrators of the immune response, which we study in a mouse model for infection with murine leukaemia virus (MLV), a mouse retrovirus. The immune interplay between MLVs and their natural host involves the numerous MLVs that have invaded the murine germline and are part of the enormous constellation of endogenous retroviruses (ERVs). Consequently, we have begun investigating the impact of ERVs on host physiology and pathology, separately in mice and humans, given the phylogenetic divergence between their ERVs.
We have been able to establish unique experimental systems, which offered novel insights into these key questions. Notable findings include the following:

- The unexpected impact of vaccine vectors on the quality, as well as the magnitude of the CD4 T cell response.
- The rules governing clonal selection of CD4 T cells during the antigen-specific response, particularly the decisive role of B cells.
- The distinctive transcriptional profile, at the single-cell level, of the enigmatic CD4 T cell subset with granzyme-mediated cytotoxic potential.
- The influence of host exposure to unrelated pathogens and commensals on genome-wide ERV transcriptional activity.
- The discovery of transmissible retroviruses resurrected from defective ERVs and their control by host immunity.

We pay particular attention to the interaction between the immune system and chronic retroviral infections, as well as the vast number of ERVs and other retroelements. We first described the complex interplay between immune stimulation by symbiotic or pathogenic microbes, the genome-wide activity of ERVs in the murine host, and immune competence. Immune reactivity to retained viral properties of ERVs ('viral mimicry hypothesis') has now become an area of intense investigation by several groups. We have also generated the bioinformatics tools for probing the transcriptional patterns of ERVs, both in mice and humans.
We also demonstrated the surprising finding that not only is adaptive immunity to ERVs possible to induce, it also critical to prevent ERV 'resurrection'. We uncovered how immunological tolerance to ERVs can be broken, in order to elicit effective anti-ERV immunity. Although autoimmune in nature, we further showed that anti-ERV responses can be used in the protection against tumours, taking advantage of transcriptional ERV induction in transformed cells.
Our most recent work focuses on the transcriptional patterns of human endogenous retroelements, with the recent description of a pan-cancer *de novo* transcript assembly. This laid the foundations for further study of the impact of human endogenous retroelements in molecular and cellular functions in health and disease.
Identification and targeting of ERV-encoded antigens required knowledge of particular ERV proviruses or ERV overlapping transcripts specifically expressed in diverse cancer types. We developed methodology to interrogate RNA-seq data, uncovering characteristic associations between ERVs and all major cancer types. This included investigation of the effect of epigenetic anti-cancer drugs, such as 5-Azacitidine, on ERV expression, with particular emphasis on myelodysplastic syndrome and acute myeloid leukaemia. The discovery of ERV-encoded cancer-specific antigens has led to the creation of a Crick spin-out company, Enara Bio (formerly ERVAXX).
Over the next few years, we will make full use of the pan-cancer *de novo* transcriptome assembly to pinpoint cases of retroelement onco-exaptation, the co-option of endogenous retroelements in the oncogenic process. We have identified over 20 candidate onco-exaptation events in diverse cancer types, which we will validate functionally in *in vitro* and *in vivo* preclinical models. We will further develop and use *in vivo* mouse cancer models expressing human HLA, where human cancer-specific antigens, encoded by

human endogenous retroelements, can be assessed for immunogenicity and anti-tumour immunity.
In the past six months, we have been studying COVID-19, developing research and diagnostic serology assays. We demonstrated protective pre-existing immunity to SARS-CoV-2 from seasonal coronavirus exposure, a finding that attracted considerable attention, and our ERV work identified a novel ACE2 isoform, responsible for the interferon inducibility wrongly attributed to the canonical form, a result which questioned the efficacy of interferon treatment in COVID-19. Although the level of our long-term commitment to COVID-19-related work is currently difficult to decide, we will continue at least part of this work, particularly the research into cross-reactive and cross-protective HCoV antibodies that could be the bases of a pan-coronavirus vaccine.

Research outputs

Merkenschlager, J., Eksmond, U., Danelli, L., Attig, J., Young, G. R., Nowosad, C., Tolar, P. & Kassiotis, G. (2019) *MHC class II cell-autonomously regulates self-renewal and differentiation of normal and malignant B cells*. Blood 133, 1108-1118. DOI: 10.1182/blood-2018-11-885467
A recent example of our interest in basic immunology with ramifications for cancer. We described a role for the best-studied immune molecule, MHC II, that extends beyond its immunological function to cell-intrinsic regulation of stemness and differentiation. This provides an alternative interpretation of the frequent loss of MHC II during tumour evolution.

Attig, J., Young, G. R., Hosie, L., Perkins, D., Encheva-Yokoya, V., Stoye, J. P., Snijders, A. P., Ternette, N. & Kassiotis, G. (2019) *LTR retroelement expansion of the human cancer transcriptome and immunopeptidome revealed by de novo transcript assembly*. *Genome Res* 29, 1578-1590. DOI: 10.1101/gr.248922.119
We assembled and disseminated the most complete, to date, transcriptome with a focus on transcripts initiated by or overlapping with endogenous retroelements. This assembly doubles the number of known transcripts and forms the basis for in-depth analysis of retroelement studies in health and disease, particularly in cancer. It also provided unconventional targets for novel cancer vaccines that are being developed by Enara Bio.

Kazachenka, A., Young, G. R., Attig, J., Kordella, C., Lamprianidou, E., Zoulia, E., Vrachiolias, G., Papoutselis, M., Bernard, E., Papaemmanuil, E., Kotsianidis, I. & Kassiotis, G. (2019) *Epigenetic therapy of myelodysplastic syndromes connects to cellular differentiation independently of endogenous retroelement derepression*. Genome Med 11, 86. DOI: 10.1186/s13073-019-0707-x
We extended our work on endogenous retroelement deregulation in cancer, particularly in bone marrow cancers treated with epigenetic drugs, thought to work through reactivation of these elements (the viral mimicry hypothesis). We described a *de novo* transcript assembly of bone marrow cancers which uncovered alternative splicing as the main determinant of the response to epigenetic drugs.

Ng, K. W., Attig, J., Young, G. R., Ottina, E., Papamichos, S. I., Kotsianidis, I. & Kassiotis, G. (2019) *Soluble PD-L1 generated by endogenous retroelement exaptation is a receptor antagonist*. Elife 8. DOI: 10.7554/eLife.50256
We used our transcript assembly to discover a novel form of PD-L1 with receptor antagonist function, created through exaptation of a normally intronic retroelement, with significant implications for immunity, autoimmunity and cancer immunotherapy.

Ng, K. W., Faulkner, N., Cornish, G. H., Rosa, A., Harvey, R., Hussain, S., Ulferts, R., Earl, C., Wrobel, A., Benton, D., Roustan, C., Bolland, W., Thompson, R., Agua-Doce, A., Hobson, P., Heaney, J., Rickman, H., Paraskevopoulou, S., Houlihan, C. F.,

Thomson, K., Sanchez, E., Brealey, D., Shin, G. Y., Spyer, M. J., Joshi, D., O'Reilly, N., Walker, P. A., Kjaer, S., Riddell, A., Moore, C., Jebson, B. R., Wilkinson, M. G. L., Marshall, L. R., Rosser, E. C., Radziszewska, A., Peckham, H., Ciurtin, C., Wedderburn, L. R., Beale, R., Swanton, C., Gandhi, S., Stockinger, B., McCauley, J., Gamblin, S., McCoy, L. E., Cherepanov, P., Nastouli, E. & Kassiotis, G.(2020) ***Pre-existing and de novo humoral immunity to SARS-CoV-2 in humans*****. Science 370:1339-1343 DOI: 10.1126/science.abe1107**

An example of our work on COVID-19 and of the flexible and collaborative nature of the Crick, involving several labs within the Crick and our collaborating universities and university hospitals. In this work, we described the discovery of pre-existing binding and neutralising antibodies against SARS-CoV-2 in uninfected and unexposed individuals. These antibodies, likely induced by exposure to seasonal coronaviruses, are present in a small percent of adults but in the majority of children, consistent with the relative sparing of the latter from the severe form of COVID-19.