International project provides definitive data on how key cancer drugs work

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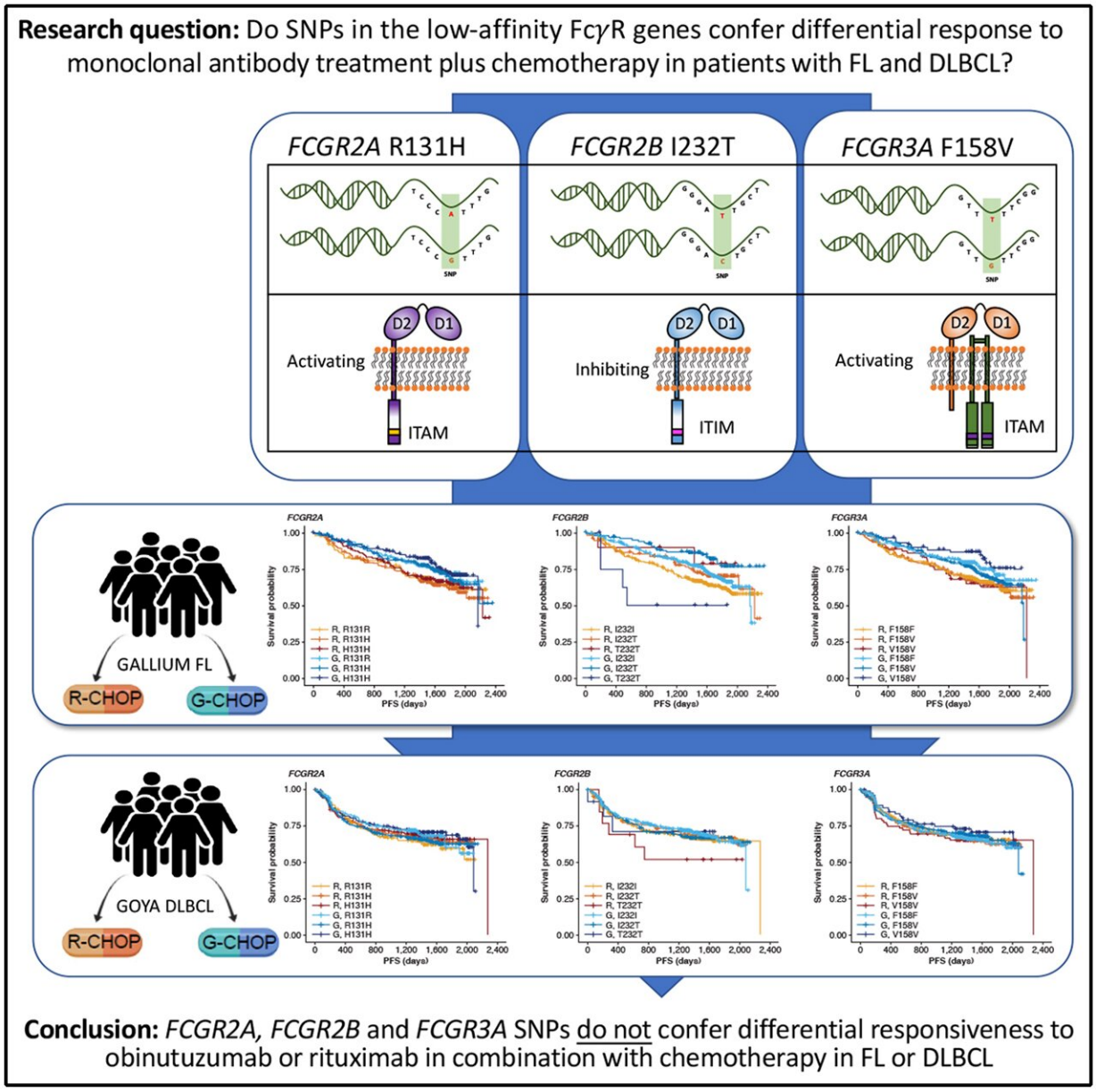

Graphical abstract. Credit: DOI: 10.1182/bloodadvances.2020003985

Scientists in Cancer Sciences have published findings of their research into how two important antibody drugs work and why they sometimes fail in some patients.

Working with researchers and clinicians across 11 academic institutions, eight countries and alongside colleagues in Industry the team examined patient specimens and clinical trial data from 1000's of patients to assess the importance of immune cell molecules called Fc gamma receptors (FCGRs) in the therapeutic efficacy of two antibody drugs, rituximab and obinutuzumab. Over the last decade these two antibodies have become the mainstay of many treatments for lymphoma and more recently autoimmune disorders such as rheumatoid arthritis and multiple sclerosis.

However, not all patients respond and it has long remained speculation as to why this is the case. In one hypothesis, researchers speculated whether inherited genetic differences in FCGRs, might explain this difference. These single genetic changes, known as single nucleotide polymorphisms (SNPs) are known to be present throughout the population and can impact antibody binding. It was also speculated as to whether the same effect would be seen with rituximab as with obinutuzumab, as through antibody engineering obinutuzumab binds much more tightly to several FCGRs.

The new study, published in the American Society of Hematology journal *Blood Advances* shows that these SNPs do not impact the therapeutic success of either antibody in either diffuse B cell lymphoma (DLBCL) or follicular lymphoma.

Professor Jon Strefford of the University of Southampton, who led this aspect of the work, said "This work is the culmination of five years of research, performed in close collaboration with our commercial partners. We have been able to demonstrate, in by far the most conclusive manner to date, that key SNPs in the FCGR genes do not influence the clinical outcome of patients with lymphoma treated with anti-CD20 antibodies, most notably whether an individual will develop aggressive disease despite treatment. This research will allow future studies to investigate other aspects of FCGR biology, helping us to understand why certain patients respond to these treatments whilst facilitating the development of the next generation of anti-CD20 therapies."

A second hypothesis for why certain lymphoma patients may not respond effectively is due to the increased levels of another FCGR, FCGR2B, on the surface of the lymphoma cells. In earlier pre-clinical work the University of Southampton team including Dr. Sean Lim, Professor Stephen Beers, Professor Martin Glennie and Professor Mark Cragg had observed that the FCGR2B could cause the rituximab antibody to be lost from the cell surfaces but that obinutuzumab was not effected in the same way.

In the second paper published in *Blood Advances*, the team assessed this hypothesis in multiple clinical studies of DLBCL, including the GOYA trial of over 1200 patients—measuring the expression of the FCGR2B on the tumor and assessing its impact on clinical efficacy with rituximab or obinutuzumab.

In all four clinical cohorts examined the authors saw evidence of the ability of high levels of FCGR2B on the tumor to prevent rituximab efficacy, independent of other established prognostic biomarkers. Moreover, in the GOYA trial they showed that obinutuzumab was not impacted in the same way, indicating this different antibody could more successfully treat patients with high FCGR2B on their tumor cells.

Professor Cragg who led this aspect of the work said "It is very satisfying to follow this work from initial lab studies in 2011 all the way through to clinical validation of the findings 10 years later. This finding may help to identify patients who would benefit most from different antibody treatments."

More information: Jonathan C. Strefford et al, Single-nucleotide Fcγ receptor polymorphisms do not impact obinutuzumab/rituximab outcome in patients with lymphoma, *Blood Advances* (2021). DOI: 10.1182/bloodadvances.2020003985

Malgorzata Nowicka et al, Prognostic significance of FCGR2B expression for the response of DLBCL patients to rituximab or obinutuzumab treatment, *Blood Advances* (2021). DOI: 10.1182/bloodadvances.2021004770

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