New treatment options for the deadliest of cancers

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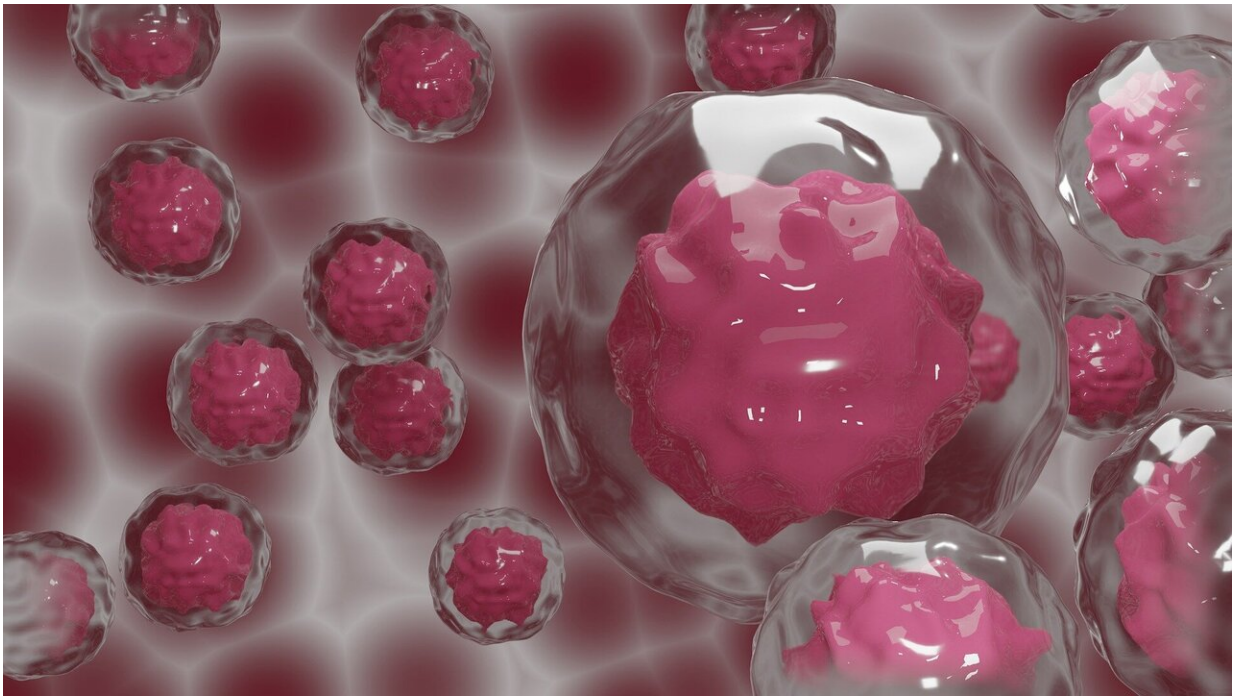

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A new way to target a mutant protein which can cause the deadliest of cancers in humans has been uncovered by scientists at the University of Leeds.The mutated form of the RAS protein has been referred to as the "Death Star" because of its ability to resist treatments and is found in 96% of pancreatic cancers and 54% of colorectal cancers.

RAS is a protein important for health but in its mutated form it can be switched on for longer, leading to the growth of tumors.

One drug has already been approved for treatment but it can only tackle a small subset of the total number of cancers driven by RAS.

Now a team from the University of Leeds' School of Molecular and Cellular Biology has gone further and found a new way to target the protein to pave the way for a greater range of treatments for more patients.

Lead author of the report, Dr. Darren Tomlinson, of the Astbury Centre for Structural and Molecular Biology, said: "The RAS protein has been referred to as the Death Star with good reason and that's because it's spherical and impenetrable, essentially preventing drugs binding and inhibiting it. We've identified a further chink in the Death Star that can be used to develop new drugs beyond the ones already in development."

The researchers used the School of Molecular and Cellular Biology's own patented Affimer biotechnology platform to pinpoint druggable "pockets" on the protein to allow effective treatment to take place.

The study was funded by the Wellcome Trust, the Medical Research Council, the Technology Strategy Board and Avacta and is published today (30 June 2021) in the journal, *Nature Communications.*

Dr. Tomlinson added: "This work opens up the door for the hundreds of other disease targets. We could effectively probe any protein involved in any disease for druggable pockets in the future."

Co-first author of the report and Ph.D. student, Amy Turner, from the School of Molecular and Cellular Biology, said: "Because it causes 20-30% of all known cancers, RAS really is the Holy Grail of

therapeutic targets. The fact that it has previously been termed 'undruggable' has allowed us to demonstrate the huge impact that our Affimer technology can have when it comes to treating challenging pathologies. We have already identified small molecules that bind to RAS, so it will be very exciting to be involved in developing these over the next few years."

The researchers say work on expanding more ways to target RAS is still in its early stages but they believe their discovery could lead to new treatments, putting Leeds at the forefront of the fight against cancer.

More information: Katarzyna Z. Haza et al, RAS-inhibiting biologics identify and probe druggable pockets including an SII-α3 allosteric site, *Nature Communications* (2021). DOI: 10.1038/s41467-021-24316-0

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