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A potential mechanism to improve targeted immuno-therapies and immune-cell / tumour cell interaction

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Monoclonal antibodies are emerging as an important component of cancer treatment regimes. However, clinical outcomes can be unpredictable and the biological determinants of antibody therapy sensitivity remain unknown. For example, it is unclear why a patient, whose tumour over-expresses the Epidermal Growth Factor Receptor (EGFR), does not respond to therapeutic antibodies directed against EGFR. We have developed a novel imaging method that allows ex-vivo examination and quantification of ligand-induced endocytosis of EGFR in non-dissociated human squamous cell carcinoma (SCC). Using confocal, three dimensional structured illumination microscopy (3D-SIM) and multi-parametric fluorescence activated cell sorting (FACS) analysis we have demonstrated that receptor trafficking influences antibody-dependent cellular cytotoxicity and that blocking receptor trafficking can enhance anti-EGFR antibody (Cetuximab)-induced SCC tumour cell death by ADCC in Cetuximab-insensitive SCC cells. Using different classes of endocytosis inhibitors we are able to demonstrate that ADCC increase occurs only when the surface EGFR is clustered and this presents a new model for targeted therapy.

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Modelling the potential impact of gonococcal vaccines

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Gonorrhoea, one of the most common sexually transmitted infections worldwide, can lead to serious sequelae, including infertility and increased HIV transmission. Recently, untreatable, multidrug-resistant *Neisseria gonorrhoeae* strains have been reported. In the absence of new antibiotics, and given the speed with which resistance has emerged to all previously used antibiotics, development of a vaccine would be the ideal solution to this public health emergency. Understanding the desired characteristics, target population, and expected impact of an anti-gonococcal vaccine is essential to facilitate vaccine design, assessment, and implementation. The modelling presented herein aims to fill these conceptual gaps and inform future gonococcal vaccine development.

Using an individual-based, epidemiological simulation model, gonococcal prevalence was simulated in a heterosexual population of 100,000 individuals (with a ~1.7% prevalence rate) after the introduction of vaccines with varied efficacy (10-100%) and duration of protection (2.5-20 years).

Model simulations predicted that gonococcal prevalence could be reduced by, at least, 90% after 20 years, if all 13-year-olds were given a vaccine with 50% efficacy that does not wane. A comparable reduction in prevalence could be achieved by a vaccine with 100% efficacy that wanes after 7.5 years. A 40% reduction in prevalence would be achieved with a non-waning vaccine of just 20% efficacy.

A vaccine of moderate efficacy and duration could have a substantive impact on gonococcal prevalence and disease sequelae, if coverage is high and protection lasts over the highest risk period (i.e. most sexual partner change) among youths.