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NEWS AND COMMENTARY

Topical treatment for oral cancers

Winners and losers and oncolytic adenoviruses: who should be down in the mouth?

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It is an important sign of maturity for any new class of anti-cancer therapies when the centre of gravity of research shifts from simply cataloguing new candidate agents to critically appraising their relative strengths and weaknesses in head-to-head comparisons. In classical drug discovery programs, the process of target selection and subsequent lead identification and optimization from libraries of related compounds is an essential prerequisite for efficient preclinical testing and selection of a frontrunner that will subsequently be evaluated in the clinic.[1] In the pharmaceutical industry, go/no-go decisions and attrition of suboptimal compounds are a way of life. In addition, drug developers will also consider which route of clinical administration is most likely to yield therapeutic efficacy and will concentrate their effort on certain classes of agents for these specific indications.

Unfortunately, the classical drug discovery approach has seldom been replicated by those working with oncolytic viruses. In part, this may be due to difficulties in generating large libraries of agents with subtle genetic variations for systematic testing, but it also reflects the partisan nature of the research/commercial environment. Understandably, competing groups may be wary of their agent being found wanting in direct comparisons with others and may, therefore, avoid conducting such analyses.[2] This is wasteful in terms of research resources and may lead to suboptimal agents reaching the clinic with little chance of success.

Therefore, it is refreshing to see in this issue that van Zeeburg *et al*.[3] have adopted the approach of comparing and contrasting different oncolytic adenoviruses with a view to assessing them for use as topical agents in patients with oral cancers. In regard to the issue of selecting the best agent for future investigation, the authors compared the activities of 11 different oncolytic adenoviruses in normal, pre-malignant and frankly malignant cell lines. The viruses, chosen on the basis of six different modifications to enhance selectivity and three to increase potency, represent the current state-of-the-art in engineered oncolytic adenoviruses and include a number of agents with past pedigree or future credentials for candidacy for clinical testing. A particular strength of the current work is the derivation of indices of relative potency and selectivity of the various engineered adenoviral species. Importantly, wild-type adenovirus serotype 5 (Ad5) was used as a reference and demonstrated striking activity against normal keratinocytes at levels exceeding those seen in any of the tumour cell lines. Reassuringly, a number of engineered adenoviruses showed oncolytic potentials that were equal to or greater than Ad5, but often with significantly less collateral damage in keratinocytes or fibroblasts. However, only two of the 11 candidates demonstrated ratios of selectivity for cancer cells versus keratinocytes of more than 10-fold. Worryingly, many of the engineered, so-called oncolytic, adenoviruses showed selective cytotoxicity to normal, rather than cancer, cells. By choosing a number of common themes in adenoviral genetic engineering, the authors were able to highlight potentially advantageous and disadvantageous properties of the viruses they tested: cyclic RGD modifications in the fibre capsid protein were associated with better anti-tumour selectivity, while E1A Δ24 deletion or complex manipulation of the E1 region appeared to be associated with the opposite phenotype. From their studies, the clear winner is a conditionally replication-competent adenovirus with an RGD-modified fibre capsid protein in which the survivin promoter drives E1A expression.

Clearly, the results of studies such as these must be considered in light of the clinical scenario under evaluation and should not be taken as generally applicable across all tumour models. The investigators' choice of tumour model addresses an important clinical problem. Squamous cell cancers of the head and neck (SCCHNs) represent a huge global disease burden, with the largest group comprising tumours that affect the mucosa of the mouth. Despite receiving optimal treatment (surgery for early-stage disease and surgery plus post-operative radiotherapy/chemoradiotherapy for late-stage disease), patients remain at risk from the twin perils of local recurrence and/or second primary cancers.[4] The former represents failure to eradicate all of the original cancer cells within the primary tumour, and its occurrence carries an extremely poor prognosis by virtue of the relative resistance of recurrent disease to standard anti-cancer therapies. The latter arises from chronic mucosal exposure to tobacco products and alcohol and subsequent 'field cancerization' such that pre-malignant changes accumulate in the epithelium.[5] These field changes are associated with the development of synchronous or metachronous tumours in the mouth or in the rest of the upper aerodigestive tract. Second (and third) primary tumours pose difficult management problems, not least of all because many patients have previously undergone extensive surgery and may have received maximal doses of radiotherapy/chemoradiotherapy. As a consequence, treatment of metachronous tumours is often associated with very severe functional and cosmetic damage. Clearly, effective strategies to prevent local recurrence and to eradicate pre-malignant epithelial lesions would be a major breakthrough in the treatment of SCCHN. In this regard, the current report offers encouraging

signs for the potential value of topical oncolytic virotherapy for oral cancers. However, this optimism must be tempered by the knowledge that their *in vitro* experimental system does not faithfully recapitulate the architecture of the oral mucosa. In addition, it is not yet clear how accurately detailed *in vitro* analyses such as this will model the *in vivo* situation. Clearly, further studies addressing these deficiencies will be required, but it is encouraging that van Zeeburg *et al*. have taken the first steps along this path.

Finally, we must hope that this study will serve as a stimulus to others to conduct studies testing the relative potency and selectivity of viruses that are candidates for use in specific clinical situations. By mirroring the practices of our colleagues in drug discovery programs, we have an opportunity to drive the selection of increasingly effective virotherapeutics for application across a broad range of clinical indications.

Conflict of interest

The author declares no conflict of interest. ■

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