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Could RAS Inhibition Create a Transient Window for Tumor-Antigen Cross-Presentation in Pancreatic Cancer?

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To Editor,

Recent RAS inhibitors have challenged the view that oncogenic RAS is not druggable in pancreatic cancer. Daraxonrasib, an oral RAS(ON) multi-selective inhibitor, has produced clinically meaningful responses in previously treated pancreatic ductal adenocarcinoma (PDAC).[1] These findings establish the therapeutic relevance of suppressing active RAS signaling, but they do not demonstrate immune reprogramming. Tumor regression may result from cytostasis, apoptosis, or loss of RAS-dependent survival without immunogenic cell death, antigen cross-presentation, or durable immune memory.[2]

Preclinical evidence nevertheless suggests that RAS inhibition can alter tumor–immune interactions in PDAC. RAS(ON) multi-selective inhibition produced rapid regressions in immunocompetent models, reduced suppressive myeloid populations, increased intratumoral T cells, and required T cells and conventional dendritic cells for maximal depth and durability of response. This provides a PDAC-specific basis for investigating immune consequences of RAS suppression, while leaving the responsible mechanism unresolved.[3]

We propose a restricted, testable hypothesis: daraxonrasib-induced tumor remodeling may create a transient interval during which endogenous tumor antigens become more accessible to dendritic cells, and a properly formulated QS-21-containing adjuvant may increase the probability that these antigens are cross-presented to $CD8^+$ T cells.[4] The novelty is not a nonspecific combination of a RAS inhibitor and an adjuvant, but a temporally coordinated sequence built around a measurable “cross-presentation window.”

The proposed sequence contains three separable steps. First, RAS inhibition must generate immunologically relevant tumor material. Suppression of RAF–MEK–ERK and PI3K–AKT–mTOR signaling can reduce proliferative and anabolic output, impair stress adaptation, and induce tumor-cell death.[5] However, loss of viability alone is insufficient. Immunogenic remodeling should be evaluated through surface calreticulin, extracellular ATP, HMGB1 release, and changes in tumor-cell MHC class I expression.[6] Calreticulin may promote phagocytic uptake, ATP can signal through purinergic pathways, and HMGB1 can support innate sensing; none of these markers alone proves productive immunity.[7]

RAS inhibition may also alter antigen presentation independently of cell death.

PDAC cells can reduce surface MHC-I through autophagy-mediated lysosomal degradation, thereby limiting recognition by cytotoxic T cells.[8] Because blockade of RAS–MAPK signaling can modify autophagic dependence and cellular stress, daraxonrasib could increase, decrease, or leave unchanged the abundance and diversity of displayed peptides.[9] The direction must therefore be measured using surface MHC-I, β2-microglobulin, TAP1/TAP2, immunoproteasome components, and, where feasible, immunopeptidomics. Tumor shrinkage without increased antigen release or peptide–MHC-I display would weaken the hypothesis.

Second, released antigen must reach competent dendritic cells. This is a major limitation in PDAC, where dense stroma, suppressive macrophages and myeloid-derived suppressor cells, deficient dendritic-cell function, and T-cell exclusion can interrupt the cancer-immunity cycle. Conventional type 1 dendritic cells are particularly relevant because they acquire cell-associated material, migrate through CCR7-dependent pathways, and cross-present antigen to $CD8^+$ T cells. Dendritic-cell paucity itself can impair immune surveillance in pancreatic cancer.[10] Thus, increased antigen availability cannot be assumed to overcome stromal or myeloid barriers.

Third, acquired antigen must be preserved and cross-presented. Internalized proteins ordinarily enter acidified endolysosomal compartments and may be destroyed. In cytosolic cross-presentation, a fraction of antigen escapes into the cytosol, undergoes proteasomal processing, and generates peptides transported by TAP1/TAP2 for loading onto MHC-I. Stable priming additionally requires CD80/CD86-mediated co-stimulation and cytokine instruction; peptide display alone may produce abortive activation or tolerance.

QS-21 is relevant only as an experimental adjuvant intended to support this step. Studies in human dendritic cells indicate cholesterol-dependent QS-21 uptake, lysosomal destabilization, Syk activation, and cathepsin-B-dependent inflammatory signaling. Saponin-based systems can also promote cytosolic antigen access and cross-presentation.[11] However, these observations derive mainly from defined vaccine formulations and antigens. They do not show that QS-21 will cross-present heterogeneous endogenous PDAC antigens.

Formulation and colocalization are therefore central. Free QS-21 has membrane-lytic and hemolytic potential, whereas cholesterol-containing liposomal or particulate formulations can limit unbound saponin and control distribution. The dendritic cell exposed to QS-21 must also be the cell that acquired tumor antigen.[12]

Systemic administration cannot guarantee this overlap; local delivery may improve colocalization but can independently cause tissue injury and antigen release. Empty-formulation and sham-injection controls are therefore necessary.

The proposed window should be identified pharmacodynamically rather than assigned arbitrarily. Serial sampling after daraxonrasib should measure phosphorylated ERK suppression, calreticulin exposure, ATP and HMGB1 release, tumor-antigen uptake by $XCR1^+$ cDC1 cells, dendritic-cell migration to tumor-draining lymph nodes, and peptide–MHC-I display. QS-21-containing formulation should then be tested simultaneously and at prespecified delays after RAS inhibition. A true temporal effect would require one sequential schedule to outperform both monotherapies, the simultaneous combination, and alternative delays at matched cumulative exposure.

A concise preclinical study could use an immunocompetent orthotopic Kras/Trp53-mutant PDAC model, with confirmation in a second syngeneic or autochthonous model. Groups should include vehicle, daraxonrasib alone, formulated QS-21 alone, empty formulation, simultaneous treatment, and sequential schedules. A traceable

model-antigen arm could sensitively assess uptake and cross-presentation, but principal findings should be reproduced in parental tumors to avoid dependence on artificial immunogenicity.

Early endpoints should separate direct tumor effects from immune effects: tumor growth, phosphorylated ERK, apoptosis, calreticulin, ATP, HMGB1, MHC-I, antigen-bearing cDC1 cells, peptide–MHC-I complexes, CD80/CD86, CCR7, IL-12, and tumor-specific $CD8^+$ expansion, clonality, interferon-γ, granzyme B, and killing capacity. CD8 depletion and Batf3 deficiency or selective cDC1 depletion should test mechanistic dependence. Loss of the sequential advantage after either intervention would support a cDC1–CD8 cross-presentation mechanism; preserved efficacy would favor direct cytotoxicity or other immune pathways.

Safety must be assessed with body weight, blood counts, hepatic and renal chemistry, cytokines, plasma free hemoglobin, haptoglobin, bilirubin, complement activation, injection-site injury, and organ histology. Standard chemotherapy or checkpoint blockade should not be included until the independent efficacy and toxicity of each component are defined.

Alternative outcomes must be treated explicitly. RAS inhibition may cause non-immunogenic regression, reduce MHC-I, or release antigens that undergo complete lysosomal degradation.[13]

QS-21 may produce nonspecific inflammation without tumor-specific $CD8^+$ expansion, and stromal exclusion may prevent primed cells from reaching tumor nests.[14] Equivalent activity across schedules would argue against a discrete window.

Immune memory should be claimed only after treatment withdrawal and tumor rechallenge. Protection against the parental tumor, but not an unrelated tumor, together with re-expansion of tumor-specific clonotypes, would support antigen-specific memory. Failure of rechallenge protection would indicate that initial regression did not generate durable adaptive immunity.

This hypothesis does not justify clinical administration of daraxonrasib with QS-21. It defines a biomarker-guided preclinical question: can RAS inhibition create a temporary antigen-accessible state, and can spatially and temporally coordinated QS-21 formulation convert that state into cDC1-dependent cross-presentation and durable $CD8^+$ immunity? Confirmation would require sequential superiority, increased peptide–MHC-I display, cDC1 and CD8 dependence, acceptable toxicity, and protection after treatment-free rechallenge.

Author Contributions

Maher Akl: Conceptualization; development of the original hypothesis and scientific novelty; mechanistic framework development; methodology; investigation; interpretation of the scientific literature; design of the proposed preclinical study; writing original draft; writing review and editing; and final approval of the manuscript.

Abdelrahman Ahya M. Ali: Literature search; evidence collection; reference screening; literature curation; critical review of the mechanistic framework; writing review and editing; and final approval of the manuscript.

Khalid Saeed Sadoon Hamad: Literature search; evidence collection; reference verification; literature curation; critical review of the manuscript; writing review and editing; and final approval of the manuscript.

Amr Ahmed: Supervision; scientific oversight; critical evaluation of the hypothesis; validation of the proposed conceptual and experimental framework; writing review and editing; and final approval of the manuscript.

All authors have read and approved the final version of the manuscript and agree to be accountable for the accuracy and integrity of the work.

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Competing Interests

The authors declare that they have no financial or non-financial competing interests.

Data Availability

No new datasets were generated or analyzed in this work. This letter presents a mechanistic hypothesis based exclusively on previously published scientific evidence.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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