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**AURKA targeting: a NEAT approach to halt myeloma**

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**Contributions**

Conceptualization, Antonio Giovanni Solimando (AGS); methodology, AGS and Cirino Botta (CB); writing - original draft preparation, AGS and CB; writing - review and editing, AGS and CB. AGS and CB have read and agreed to the published version of the manuscript.

Multiple myeloma (MM) remains a formidable clinical challenge, characterized by its heterogeneous nature and complex pathogenesis. Despite advances in treatment, disease relapses often thwart long-term control, necessitating the development of novel targeted therapeutic strategies[1]. Long non-coding RNA (lncRNA) have emerged as key players in the regulation of various biological processes, including those involved in the mitotic spindle. They are implicated in the pathogenesis of MM by influencing cell proliferation, apoptosis, invasion, and therapeutic resistance[2]. However, the complex network of lncRNAs makes this field sketchily explored.

In this groundbreaking issue of *Haematologica*, Puccio et al.[3] delve into the regulatory interaction between the lncRNA NEAT1 and the serine/threonine kinase AURKA, shedding light on their roles in promoting MM cell viability.

Through a comprehensive multi-omics, transcriptomic, computational, and functional analyses, the study demonstrates that NEAT1 modulates gene networks involved in cytoskeleton dynamics and mitosis by regulating key effectors such as AURKA and TPX2.

Disruption of NEAT1 leads to impaired mitotic spindle assembly[4], while inhibition of AURKA hinders chromosome segregation, establishing their coordinated roles in maintaining genomic integrity. Excitingly, the combination of NEAT1 silencing and AURKA inhibition exhibits enhanced cytotoxic effects in vitro, suggesting a potential synthetic lethality approach[3] (Figure 1).

AURKA plays a crucial role in MM pathogenesis by controlling cell cycle checkpoints but targeting it alone may be circumvented through feedback activation of redundant signaling pathways. The findings provide a strong rationale for combinatorial targeting, as NEAT1 depletion blocks compensatory pathways while AURKA inhibition eliminates proliferative capacity[3].

The identified AURKA inhibitors, alisertib, and AURKA inhibitor I, have demonstrated manageable safety profiles in phase I clinical trials in multiple myeloma, supporting their translation into clinical applications[5]. Leveraging established agents with emerging RNA-targeting modalities could expedite the clinical implementation of this research. Importantly, precision targeting of intra-clonal vulnerabilities may prove valuable against aggressive and treatment-resistant disease phenotype.

In view of this, the translational relevance of this discovery is underscored by the correlation of NEAT1 and AURKA co-expression with a poorer prognosis in MM patients, independent of risk stratification models, thus identifying a population of patients with functional high-risk features[3].

From the clinical standpoint, Puccio et al. mention a critical link between AURKA expression and other high-risk MM phenotypes, marked by specific genetic aberrations, namely 1q gain/amplification, 17p deletion, and MYC/MAF translocations[3]. Previously, Den Hollander et al., have discovered that MYC oncoproteins specifically drive Aurora A/B kinases in B-cell lymphoproliferative disorders, with Aurora inhibition showing promise in MYC-driven models[6]. These findings position AURKA as a key therapeutic target, particularly in high-risk MM, and offer hope for effective strategies across a spectrum of malignancies.

In their research Puccio et al. employed human AMO-1, NCI-H929 and MM1.S human myeloma cell lines[3], which are derived from pleural, peritoneal extramedullary effusions and peripheral blood, respectively. This biological model recapitulates the enhanced proliferative properties of MM: the enhanced pro-angiogenic property[7] as well as the dynamic and context-dependent interplay with the bone marrow microenvironment conspire to the intrinsic boosted mitotic propensity, the disease progression and dissemination[8]. The NEAT1-AURKA axis offers a promising target in this context, as its disruption could address the unique challenges posed by halting unexplored biological circuitries pinpointing to proliferative aggressive disease.

Moreover, it got even more interesting, as it is evident that genomic stability in MM can be severely compromised[9]. Nonetheless, strategies that efficiently target the dysfunctional spindle-assembly process are scanty. Thus, delving into the regulation of mitosis in MM, it's noteworthy to highlight that the actors on the scene of mitotic process regulation in MM are sparse. Intriguingly, Favasuli et al. showed that inhibiting DIS3 with specific gapmers produced a phenotype akin to that observed in studies on NEAT1[10]. DIS3 gene is mutated in approximately 10% of MM patients and DIS3 expression can be influenced by monosomy 13 and del(13q)[10]. When DIS3 dysfunction is combined with an impaired spindle-assembly checkpoint, cells may advance through the cell cycle without accurate chromosome separation, resulting in the generation of aneuploid cells, which can facilitate the progression of myeloma[10]. The potential crosstalk between NEAT1, DIS3, AURKA and the mitotic control in MM remains a fascinating area that requires further exploration.

Overall, the identified NEAT1-AURKA regulatory axis offers a promising avenue for precision targeting, providing opportunities to disrupt interconnected survival dependencies. By developing optimized regimens that combine AURKA inhibitors with targeted NEAT1 silencing, researchers can potentially achieve enhanced selectivity and overcome the resistance mechanisms. Further investigations into NEAT1 isoforms and downstream effectors may reveal additional intervention achille's heel within these regulatory pathways. While exploring the impact on tumor-associated cells and immune surveillance novel opportunities for integrating immunotherapy can be uncovered[1].

Nonetheless, despite of their potential as biomarkers and therapeutic targets, our understanding of lncRNAs and mitotic spindle targeting in MM is still limited. The complexity of lncRNA regulatory networks and the need for large-scale studies hinder their immediate application. Further research is required to elucidate the synergistic effects of multiple lncRNAs and their interactions with other signaling pathways and proteins, which will enhance our knowledge of MM and potentially lead to more effective treatments.

A particular mention should be reserved for the approach chosen to functionally validate the results[3]. This methodology not only identifies promising therapeutic targets but also introduces a valuable platform for the study of non-coding molecules. By assaying numerous pathways simultaneously, this holistic approach is essential for identifying more effective and less toxic cancer therapies, paving the way for rapid translation into clinical practice.

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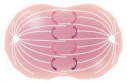
**Figure 1**. The figure elucidates the novel therapeutic strategy aimed at inhibiting NEAT1 and AURKA to potentially counteract myeloma progression. Disruption of the M/G1 checkpoint prevents the proper assembly of chromatids on the mitotic spindle, thereby arresting MM cell division. Intervention at the G1/S checkpoint impedes the activation of growth factors and organelle production, curtailing cell growth. The inhibition of AURKA's function in mitosis compromises spindle assembly and chromosome segregation[3]. Furthermore, perturbation of the G2/M checkpoint impairs DNA damage repair mechanisms, culminating in the apoptosis of MM cells. This dual-targeting modality represents a significant advancement in the treatment of MM, exploiting the pro-survival and pro-oncogenic properties of NEAT1[4] and AURKA[3].



## M/G1 Checkpoint

**Pass**
- Equal distribution of chromosomes between new daughter cells

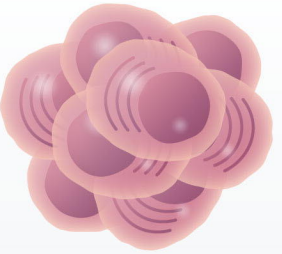
**Fail**
- Chromatids are not properly assembled on mitotic spindle

**AURKA**
- Plays a role in mitotic progression and ensures proper spindle assembly and chromosome segregation

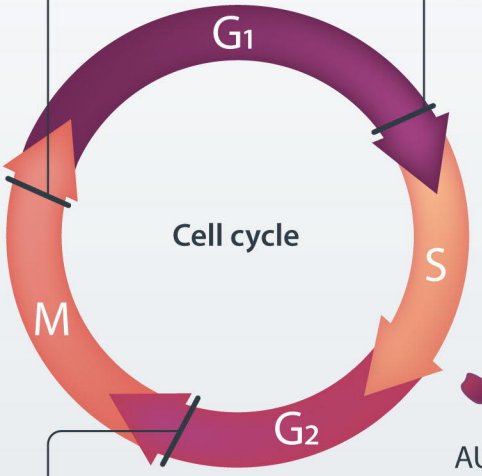
## G2/M Checkpoint

**Pass**
- Completely replicated genome
- Large cell volume
- NEAT1 and paraspeckles increase in DNA damage repair

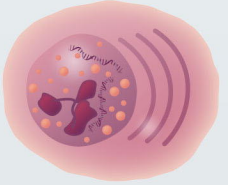
**Fail**
- DNA damage



Myeloma progression




Myeloma cell



## G1/S Checkpoint

**Pass**
- Sufficient number of organelles
- Growth factors activation

**Fail**
- Presence of TGF-β proliferation inhibitor
- ATP deficiency

MM cell death

AURKA

Paraspeckles

NEAT1

Pro survival, cell division and pro-oncogenic advantages: MM proliferation