**Bispecific Antibody in Prostate Cancer Metastasis**

**Ananya Chopra ’27**

Metastasized prostate cancer is one of the most difficult forms of cancer to treat. This means the cancer cells have spread from their original location to another part of the body through the bloodstream or the lymphatic system. These cells can then form new tumors in places like the bones or lymph nodes, but also other organs.

Once prostate cancer becomes metastatic, it is often resistant to common treatments like chemotherapy, immunotherapy, and radiation. Because of its complex biology, it is usually incurable at this stage. According to the American Cancer Society, the five-year survival rate for patients with metastatic prostate cancer is only 30%, compared to the 98% five-year survival rate for all prostate cancer patients. While there are several treatment strategies that address the spread of the disease, they often have limited success, especially due to the ability of advanced-stage cancer cells to evade immune surveillance, ie. hide from the immune system.

Because of this, patients with metastatic (or stage IV) prostate cancer typically shift from a treatment regimen that aims to eliminate the cancer to a treatment plan that focuses on managing symptoms and improving the patient’s quality of life.

However, recent research at the Mathew Lab at Tufts Medical Center gives new hope to future patients and families. The lab investigates epithelial-stromal interactions, or the way that cancer cells communicate with each other and the supportive tissue around them, to understand how prostate cancer spreads. Their work has identified two target integrins, αv and α5, as implicated in the metastatic cascade, the series of steps through which prostate cancer cells form metastases (Connell et al., 2020). The lab developed a bispecific antibody, a type of antibody that

simultaneously targets two different molecules, αv and α5, which has shown promising early results (Joshi, Ren, & Mathew, 2020).

The investigative process at the lab began with a foundational understanding of the tumor microenvironment (TME), which refers to the surrounding environment where the tumor grows, including blood vessels, cells, and other components. They particularly focused on interactions between epithelial cancer cells, the cells that make up organ linings, and the surrounding stromal components. In prostate cancer, cells called fibroblasts, which are part of the stroma and normally help repair tissue, can help cancer cells break away, move, and facilitate metastatic progression. In essence, stroma fibroblasts help create a permissive niche, or a supportive environment, for cancer cells to detach, migrate, and colonize distant organs.

Integrins are transmembrane protein receptors embedded in cell membranes, which help cells stick to the extracellular matrix. Integrins αv and α5 specifically are responsible for cell adhesion and signaling, and they bind to the extracellular matrix proteins. In prostate cancer, though, they are believed to modulate the adhesion, migration, and invasion properties of cancer cells within the TME (Connell et al., 2020). The lab used immunohistochemical and immunofluorescence staining (techniques that help visualize where and how much of a protein is present in tissues) to compare integrin expression levels between primary and metastatic prostate tumor samples. These experiments revealed an upregulation (or an increase) of both αv and α5 in metastatic tumors (Joshi, Ren, & Mathew, 2020). When these cancer cells were co-cultured with cancer-associated fibroblasts, a marked increase in integrin-mediated signaling pathways was observed (Connell et al., 2020). Some of these pathways included FAK and Src, which promote motility and invasion, or the ability of cancer cells to spread into new tissues (Connell et al., 2020).

The lab used siRNA-mediated knockdowns (a method for turning off specific genes) and small-molecule inhibitors (drugs that block certain proteins) to selectively disrupt αv and α5 integrin function in prostate cancer cells. This impaired the ability of cancer cells to adhere to the proteins fibronectin and vitronectin, which provide structural support in the ECM. This disruption reduced their invasive potential, or their ability to move and spread to other areas (Joshi et al., 2017).

To test this in a living system, the lab used xenograft models, experiments where human cancer cells are implanted into mice to study cancer. These mice were used to test the potential of integrin blockade, which stops the integrin proteins from functioning in its entirety, in a living system. Prostate cancer cells, pre-treated with integrin inhibitors, were implanted into immunocompromised mice, which are mice with weakened immune systems, so that they would not reject the tumor and could not fight off the cancer. These mice displayed reduced tumor burden, meaning smaller tumors, and fewer metastatic lesions, especially in bone and lymph nodes, which are common targets of metastatic prostate cancer (Joshi et al., 2025). These findings further highlighted the clinical relevance of targeting integrins to suppress metastatic dissemination.

A significant component of the lab's work also focused on exploring the downstream effects of integrin signaling. Transcriptomic analyses (RNA-seq), a method of studying the genes that are "on" or "off" in cells, revealed that integrin activation modulated the expression of several genes involved in three key functions. The first of these was EMT (epithelial-mesenchymal transition), which is responsible for driving the transformation of epithelial cells into more mobile and invasive mesenchymal cells. It also showed the involvement of immune evasion genes, which occur due to mutations and allow pathogens,

cancer cells, or other foreign agents to avoid detection and destruction by the host's immune system. Finally, angiogenesis genes, responsible for regulating the formation of new blood vessels from existing ones, were also implicated due to the function of these integrins (Joshi et al., 2025).

The team identified potential co-targets that could enhance the efficacy of integrin inhibition. For example, targeting TGF-β signaling mediators and matrix metalloproteinases (MMPs), molecules that help cancer cells remodel their environment, made the treatment more effective. The lab has collaborated with other partners to explore drug development strategies that optimize integrin-targeting compounds. Early-stage results suggest that combination therapies, particularly those that integrate immunotherapy with integrin inhibition, seem promising in overcoming disease resistance (Joshi et al., 2025).

The 2025 study provided strong evidence that integrin inhibition could work in conjunction with immune-based therapies. The bispecific antibody they developed not only disrupted tumor-intrinsic signaling (through the Myc and AP pathways), but it also reprogrammed the cancer cells to become more immunogenic, or recognizable to the immune system (Joshi et al., 2025).

When prostate cancer cells were treated with the bispecific α5β1/αv antibody, researchers saw increased activity in immune-related pathways, especially those involving Type I and Type II interferons (Joshi et al., 2025). These are important molecules that help kickstart immune responses. The treatment also boosted the release of cytokines, which are small proteins that act as chemical messengers for immune responses and inflammation, especially CXCL10 and CCL5 (Joshi et al., 2025). These cytokines recruit natural killer (NK) cells, which destroy tumor cells;

macrophages, which perform phagocytosis; and dendritic cells, which process and present antigens to initiate adaptive immune responses, into the TME (Joshi et al., 2025).

In xenographic models, this resulted in NK cell-mediated tumor elimination and reversal of immune evasion, outcomes rarely achieved in advanced prostate cancer. Because of these results, the authors proposed that future approaches could integrate the bispecific antibody with immune checkpoint inhibitors, a type of immunotherapy used in other cancers. This combined approach could offer a new way to overcome treatment resistance in metastatic prostate cancer (Joshi et al., 2025). In fact, tests of the bispecific antibody in xenographic models led to complete tumor regression in 50% of mice with DU-145 tumors and 38% of those with PC-3 tumors, which are two common prostate cancer cell lines (Joshi et al., 2025). These results show early but exciting potential for improving outcomes in patients with advanced disease.

The lab's work shows a significant shift in our understanding of prostate cancer metastasis. Through the identification of the role of αv and α5 integrins in tumor progression, immune evasion, and metastatic spread, there are opportunities for the development of new targeted therapies, such as bispecific antibodies (Joshi, Ren, & Mathew, 2020). These therapies might not only slow down or stop cancer from spreading, but they could also help the immune system fight back. This potential treatment also offers hope for the application of similar principles in other types of cancer regulated by similar pathways. If successful, this approach could provide hope for the future of prostate cancer treatment, where patients with advanced disease might no longer be met with limited options and grim statistics, but with targeted, immune-activating strategies that could massively improve their prognosis.

## References

Connell B, Kopach P, Ren W, Joshi R, Naber S, Zhou M, Mathew P. Aberrant integrin αv and α5 expression in prostate adenocarcinomas and bone-metastases is consistent with a bone-colonizing phenotype. Transl Androl Urol. 2020;9(4):1630–1638. https://doi.org/10.21037/tau-19-763

Joshi R, Goihberg E, Ren W, Pilichowska M, Mathew P. Proteolytic fragments of fibronectin function as matrikines driving the chemotactic affinity of prostate cancer cells to human bone marrow mesenchymal stromal cells via the α5β1 integrin. Cell Adh Migr. 2017;11(4):305–315. https://doi.org/10.1080/19336918.2016.1212139

Joshi R, Ren W, Mathew P. A bispecific antibody targeting the αv and α5β1 integrins induces integrin degradation in prostate cancer cells and is superior to monospecific antibodies. Mol Cancer Res. 2020;18(1):27–32. https://doi.org/10.1158/1541-7786.MCR-19-0442

Joshi R, Zhou M, Lin JH, Song F, Fein D, Morrissey C, Hu K, Poltorak A, Mathew P. *A novel bispecific integrin α5β1/αv antibody reprograms the Myc-regulated basal phenotype of prostate cancer with natural killer cell–mediated tumor elimination.* Mol Cancer Res. 2025. https://doi.org/10.1158/1541-7786.MCR-25-0104