The Role of Epithelial-Mesenchymal Transition in Cancer Progression and Metastasis

Compiled by:

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

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KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

Summary

Epithelial-Mesenchymal Transition (EMT) is a crucial biological process that is pathologically co-opted by cancer cells to drive tumor progression and metastasis. While EMT has vital roles in normal physiological processes like embryogenesis and wound healing, a distinct pathological form (Type III EMT) allows malignant cells to lose their epithelial characteristics and acquire the migratory and invasive properties of mesenchymal cells. This cellular transformation is a critical facilitator of metastasis, enabling cancer cells to invade from the primary tumor, survive in circulation, and disseminate to distant sites. Upon arrival, the cells must undergo a reverse transition, Mesenchymal-Epithelial Transition (MET), to proliferate and establish a new tumor. The dynamic and reversible nature of this process, known as Epithelial-Mesenchymal Plasticity, is a key driver of tumor heterogeneity. Beyond metastasis, EMT serves as a master program that contributes to several key hallmarks of advanced cancer, including therapeutic resistance to chemotherapy and radiotherapy, and immune evasion. While targeting EMT represents a promising therapeutic strategy, its complexity and essential role in normal body functions present significant challenges that will require highly specific and well-timed interventions to avoid off-target toxicity.

Part 1. Introduction: Defining EMT and its Dual Nature

Epithelial-Mesenchymal Transition (EMT) is a fundamental biological process characterized by a profound shift in cellular phenotype. During this transition, epithelial cells, which are typically stationary and organized in sheets, lose their distinct cell polarity and cell-cell adhesion, and subsequently acquire the migratory and invasive properties of mesenchymal cells.[www] This process involves a comprehensive reprogramming of gene expression, which results in the downregulation of epithelial markers and the corresponding upregulation of mesenchymal markers.[www] EMT is not an irreversible, one-way process; it is a highly dynamic and plastic state that can be reversed through a process known as Mesenchymal-Epithelial Transition (MET).[www]

The physiological significance of EMT is highlighted by its essential role in numerous normal life activities, a fact that stands in stark contrast to its pathological role in disease. To better categorize these diverse functions, EMT has been classified into three distinct types:

- **Type I EMT:** This category encompasses the processes that occur during embryogenesis and organ development.[www] For example, Type I EMT is crucial for events such as gastrulation, neural crest formation, and heart development.[www] This type of EMT is tightly regulated, non-inflammatory, and serves to create new organs and tissues.[www]
- **Type II EMT:** This is a process associated with tissue repair, wound healing, and organ fibrosis.[www] Similar to Type I, it is a reversible process vital for regeneration and is a natural response to tissue damage.[www]
- **Type III EMT:** This is the pathological form of the process and is the central focus of cancer biology research.[www] In this context, the latent embryonic EMT program is aberrantly reactivated, or "hijacked," by malignant cells.[www] This pathological activation is a key determinant of tumor progression and confers a range of malignant traits that align with multiple hallmarks of cancer, including metastasis, therapeutic resistance, and immune evasion.[www]

The distinction between these EMT types is critically important for understanding the challenges of developing targeted cancer therapies. Any therapeutic strategy designed to inhibit EMT in a pathological context must be highly specific to Type III EMT to avoid interfering with the fundamental, life-sustaining physiological processes of Type I and Type II EMT, such as wound healing and tissue repair.[www] This need for selectivity represents a major theme in the development of EMT-targeting

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

therapies, as it balances the potential for therapeutic benefit with the risk of severe off-target toxicity.

Part 2. Core Mechanisms of Epithelial-Mesenchymal Transition

The transition from a stable epithelial phenotype to a mobile mesenchymal one is governed by a complex and tightly regulated network of cellular, molecular, and genetic changes. These transformations move beyond simple morphological alterations to encompass a fundamental reprogramming of cellular function.

2.1 Cellular and Morphological Transformations

A hallmark of the EMT is the profound change in cell structure and organization. Epithelial cells, which are typically arranged in a monolayer and connected by stable intercellular junctions, lose their apical-basal polarity and their cell-cell adhesion.[www] This process involves the dissolution of various junction structures, including adherens junctions and tight junctions.[www] This structural disorganization is a multi-stage process that slowly modifies the architecture and functional capacities of epithelial cells, enabling them to detach from their neighbors and the extracellular matrix (ECM).[www]

Concurrently, the cytoskeleton undergoes a dramatic reorganization to facilitate this new, migratory behavior. The cell's morphology changes from a cuboidal or columnar epithelial shape to a more elongated, spindle-like mesenchymal form.[www] This reorganization includes the elongation of pseudopodia, which enables directional motility and cell movement.[www] The newly formed mesenchymal cytoskeleton, specifically the vimentin intermediate filaments, provides mechanical integrity to the cell, allowing it to withstand the physical stresses encountered during migration and to squeeze through narrow spaces.[www]

2.2 Key Molecular Markers and the EMT Continuum

The morphological changes of EMT are driven by a reciprocal change in the expression of key molecular markers. The loss of epithelial characteristics is most notably defined by the downregulation of E-cadherin, a critical component of adherens junctions.[www] E-cadherin functions as a tumor suppressor protein, and its loss is an early and well-established event in EMT that is strongly associated with cancer metastasis.[www] The loss of E-cadherin is not merely a passive consequence of EMT; it is a profound causal trigger for the entire metastatic cascade. Research has shown that the loss of E-cadherin protein, independent of simple cellular disaggregation, is sufficient to induce EMT, confer metastatic ability on non-metastatic breast cancer cells, and activate a range of downstream transcriptional pathways.[www] The liberation of proteins from E-cadherin's cytoplasmic tail appears to be a critical signaling event that activates these malignant properties. As epithelial markers are repressed, a corresponding set of mesenchymal markers are upregulated. Key examples include N-cadherin, fibronectin, and vimentin.[www] The coordinated loss of E-cadherin and gain of N-cadherin is a hallmark of EMT.[www] Vimentin, a Type III intermediate filament, is considered a canonical biomarker of Type III EMT.[www] However, it is more than just an indicator; it is an active functional player. As a cytoskeletal protein, vimentin supports the cell's mechanical integrity during migration and is also involved in the DNA repair system, helping cells survive DNA damage and resist apoptosis during migration and therapeutic stress.[www]

A crucial aspect of EMT is that it is not a simple, binary "on-off" switch. Cancer cells frequently exist in an "intermediate" or "hybrid" state, expressing a mix of both epithelial and mesenchymal characteristics.[www] This state, sometimes referred to as "Epithelial-Mesenchymal Plasticity," confers a high degree of cellular plasticity and heterogeneity.[www] This phenotypic diversity is a key factor in tumor

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

progression and the development of therapeutic resistance.

2.3 Master Regulators: The EMT Transcription Factor Network

The molecular machinery that orchestrates these changes is centered on a family of master regulators known as EMT-inducing transcription factors (EMT-TFs).[www] The core drivers of the EMT program belong to the Snail, Slug (SNAI1/2), ZEB (ZEB1/2), and Twist (TWIST1/2) protein families.[www] These TFs coordinate the repression of epithelial genes and the induction of mesenchymal genes, often controlling the expression of both.[www]

- **Snail and Slug:** These are key repressors of E-cadherin expression and play crucial roles in cancer progression, therapeutic resistance, and cellular invasion.[www] Snail, in particular, has been shown to directly control the expression of cancer stem cell markers like Nanog, establishing a molecular link between EMT and stemness.[www]
- **Twist:** As a basic helix-loop-helix transcription factor, Twist is activated by a variety of upstream signaling pathways, including Wnt, Akt, and Ras.[www] It actively upregulates N-cadherin while downregulating E-cadherin, which are considered the hallmarks of EMT.[www] Twist also plays a significant role in promoting angiogenesis and protecting cancer cells from apoptotic cell death.[www]
- **ZEB1 and ZEB2:** These transcription factors form a mutually inhibitory feedback loop with the microRNA family, miR-200. The repression of the miR-200 family results in the upregulation of ZEB1 and ZEB2, which in turn promotes EMT progression.[www]

These transcription factors do not act in isolation; they cooperate and often regulate the expression of one another, forming a complex and redundant regulatory network.[www] For example, Snail can act as an upstream regulator, inducing the expression of Slug, ZEB1, and Twist1.[www]

The complexity of EMT regulation extends beyond the transcription factors to include post-transcriptional and epigenetic mechanisms. The differential splicing of nascent RNAs into mRNAs, as well as the regulation by non-coding microRNAs (miRNAs), adds another layer of control.[www] These mechanisms highlight that targeting the EMT program may require strategies that go beyond simple transcriptional repression, perhaps by restoring the expression of key miRNAs that are repressed during the transition.

Table 1. Key EMT Transcription Factors and their Functions.

Transcription Factor	*Protein Family*	*Primary Function*	*Downstream Effects*	*Upstream Regulators*
Snail/Slug	Zinc-finger	Represses epithelial genes, especially E-cadherin	Promotes invasion, therapeutic resistance, and stemness; controls Nanog expression	TGF-β, Wnt
Twist	Basic helix-loop-helix	Represses E-cadherin, activates N-cadherin	Promotes angiogenesis, protects from apoptosis, and contributes to chromosomal instability	Akt, Ras, Wnt, STAT3, MAPK
ZEB1/ZEB2	Zinc-finger, E-box-binding	Represses epithelial genes	Drives EMT progression, forms a feedback loop with miR-200 family	TGF-β, Wnt; miR-200 downregulation

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

FOXC1/FOXC2	Forkhead box	Induces EMT	Correlates with poor patient survival and aggressive breast cancer subtypes	Not specified

2.4 Regulatory Signaling Pathways

The EMT program is initiated and controlled by multiple intracellular signaling pathways that respond to cues from the extracellular environment.[www] Among these, the **Transforming Growth Factor-β (TGF-β) pathway** is a predominant inducer of EMT.[www] TGF-β signals through a complex of type I and type II receptors, activating SMAD proteins and non-SMAD pathways, which leads to the expression of EMT-TFs and the repression of epithelial markers.[www] The **Wnt/β-catenin pathway** is another crucial regulator, promoting the transcription of EMT-associated proteins such as Snail, Slug, and vimentin.[www] Other pathways, including **Hedgehog, Notch, and PI3K/Akt**, also play a significant role in orchestrating the EMT program.[www]

Part 3. EMT in the Metastatic Cascade

Metastasis is a complex, highly inefficient, but deadly process responsible for the vast majority of cancer-related mortality.[www] EMT is a critical and necessary program that facilitates several key steps of this metastatic cascade, enabling tumor cells to disseminate from a primary site and colonize a distant organ.[www]

3.1 Invasion from the Primary Tumor

The first step in metastasis is the invasion of cancer cells from the primary tumor into the surrounding stroma.[www] The EMT program provides the critical invasive phenotype necessary for this process.[www] The loss of cell-cell adhesion, coupled with the acquisition of a motile, spindle-like morphology, allows individual cells or small clusters of cells to break free from the epithelial tumor mass.[www] These cells then digest and migrate through the surrounding extracellular matrix (ECM), a process facilitated by the reorganization of the cytoskeleton and the secretion of enzymes such as matrix metalloproteinases (MMPs).[www] This ability to become migratory and invasive is a prerequisite for dissemination.[www]

3.2 Dissemination and Survival in Circulation

Once cancer cells have invaded the surrounding tissue, they must gain access to the circulatory system to travel to distant sites. EMT-activated cells acquire the ability to enter the bloodstream, where they become circulating tumor cells (CTCs).[www] The mesenchymal phenotype conferred by EMT is crucial for these cells to survive the harsh conditions of the circulatory system. This includes resistance to apoptosis, a form of programmed cell death that occurs when cells lose contact with the ECM, a phenomenon known as anoikis.[www]

3.3 The Crucial Role of MET in Colonization

While EMT is essential for invasion and dissemination, it is not a terminal state. The notion that EMT alone is sufficient for successful metastasis has been challenged by evidence showing that it may even be detrimental for metastatic colonization.[www] Upon arriving at a distant site, the disseminated tumor cells need to undergo a reversed transition, Mesenchymal-Epithelial Transition (MET), to recover some epithelial characteristics and proliferate to form a new tumor.[www] This is a necessary step for metastatic colonization and the

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

establishment of macrometastases, as the epithelial phenotype is better suited for proliferation and integration into the new tissue microenvironment.[www]

The process is therefore a dynamic, reversible cycle, which is often referred to as Epithelial-Mesenchymal Plasticity (EMP).[www] The cells use EMT for movement and MET for settlement. This dynamic plasticity is a far more accurate and nuanced view than a simple one-way transition and is critical for understanding tumor heterogeneity and metastatic progression.[www] The existence of this reversible cycle suggests that therapeutic strategies must consider both transitions. Inhibiting EMT could prevent initial dissemination, while inhibiting MET could prevent colonization at distant sites, highlighting the complexity of targeting this process.

Part 4. EMT's Deep Interplay with the Tumor Microenvironment

The progression of cancer is not solely driven by changes within the tumor cells themselves; it is a complex process of co-evolution between the malignant cells and their surrounding environment.[www] This ecosystem, known as the tumor microenvironment (TME), is a "heterocellular ecosystem" comprising immune cells, fibroblasts, endothelial cells, and the extracellular matrix (ECM).[www] The relationship between EMT and the TME is not a simple cause-and-effect interaction; it is a self-reinforcing, bidirectional feedback loop.

4.1 The TME as an EMT Inducer

The TME provides a permissive state that can initiate the EMT program in cancer cells, a concept that aligns with Paget's "seed and soil" theory.[www] EMT is not a spontaneous event; it is initiated by various signals from the TME.[www] Key inducing signals include:

- **Growth Factors and Cytokines:** Signals such as transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and Wnt are crucial inducers of EMT.[www]
- **Hypoxia:** Low oxygen levels within the tumor, a common feature of solid tumors, can act as a trigger for EMT.[www]
- **Extracellular Matrix (ECM):** The ECM provides both structural and biochemical support, and signals from its components can initiate and reinforce the EMT program.[www]

4.2 EMT as a TME Remodeler

In a reciprocal manner, EMT-activated tumor cells do not just passively respond to the TME; they actively remodel it to create a more hospitable and pro-tumorigenic milieu.[www] This is a crucial feedback mechanism that accelerates cancer progression. EMT-reprogrammed tumor cells acquire an enhanced paracrine signaling capacity, enabling them to communicate with and influence neighboring cells via secreted mediators.[www]

- **Secreted Mediators:** EMT cells secrete a variety of soluble factors. They promote angiogenesis by releasing pro-angiogenic factors like vascular endothelial growth factor (VEGF) and fibroblast growth factors (FGFs).[www] They also secrete immunosuppressive cytokines and chemokines (e.g., CXCL1/2, IL−8, CCL2), which recruit immunosuppressive immune cells like myeloid-derived suppressor cells (MDSCs) and macrophages (Mφ).[www]
- **Differentiation into CAFs:** In an even more direct form of remodeling, cells undergoing EMT can differentiate into cancer-associated fibroblasts (CAFs), which become functional constituents of the TME.[www] These CAFs, in turn, can further support tumor growth, creating a self-reinforcing feedback loop where the tumor cells and the TME mutually adapt and reinforce each other's malignant properties. This understanding has profound implications for therapeutic strategies, suggesting that targeting either the tumor cell's EMT program or the TME's ability to support it could be effective.

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

Part 5. EMT's Contribution to the Hallmarks of Advanced Cancer

The pathological activation of EMT in cancer confers a suite of malignant traits that are central to the development of a fully developed tumor. The process is not an isolated event but a central nexus that links multiple, seemingly disparate hallmarks of cancer, providing a unifying mechanism for metastasis, stemness, therapeutic resistance, and immune evasion.[www]

5.1 Acquisition of Cancer Stem Cell (CSC) Properties

EMT is directly linked to the generation of cancer stem cells (CSCs), a subpopulation of cells with the ability to self-renew and differentiate into various cancer cell types.[www] Cells that undergo EMT can acquire stem cell-like characteristics, which contributes to tumor recurrence, intratumor heterogeneity, and the ability to initiate new tumors at distant metastatic sites.[www] This connection is established at a molecular level, as EMT-TFs such as Snail have been shown to directly control the expression of stemness genes like Nanog, Bmi-1, and CD44.[www]

5.2 Mechanisms of Therapeutic Resistance

EMT is a major contributor to resistance to various cancer treatments, including chemotherapy, radiotherapy, and targeted therapies.[www] The general mechanisms by which EMT confers resistance include:

- **Increased Drug Efflux:** EMT can alter the expression of multidrug-resistance (MDR) efflux transporters, which leads to increased drug efflux and decreased drug uptake.[www]
- **Slow Cell Proliferation:** Cells in an EMT state often exhibit a low proliferative rate.[www] This makes them less susceptible to cell cycle-dependent chemotherapies that primarily target rapidly dividing cells.[www]
- **Avoidance of Apoptosis:** EMT confers anti-apoptotic properties, protecting cells from programmed cell death induced by therapies.[www] The EMT-TFs and associated signaling pathways protect cells from apoptosis, allowing them to survive conditions of stress in the primary tumor.[www]
- **Chromatin Remodeling:** EMT-TFs can drive chromatin remodeling, contributing to a therapy-resistant phenotype.[www]

Table 2: EMT-Driven Mechanisms of Therapeutic Resistance.

Type of Therapy	*Specific EMT-Related Mechanism*	*Molecular Players*
Chemotherapy	Increased drug efflux; slow cell proliferation; anti-apoptotic signaling	MDR efflux transporters, p21, anti-apoptotic proteins like Bcl-2
Radiotherapy	Anti-apoptotic signaling; enhanced DNA damage repair	Vimentin, ATM kinase, Snail, anti-apoptotic proteins
Targeted Therapy	Activation of redundant pathways; acquisition of stem cell properties	EMT-TFs, cancer stem cell markers (CD44, Nanog), alternative signaling pathways

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

Immunotherapy	Downregulation of antigens; upregulation of immune checkpoints; immunosuppressive TME	MHC molecules, tumor-associated antigens, PD-L1, TGF-β, CXCL1/2

5.3 Strategies for Immune Evasion

EMT enhances the ability of cancer cells to evade detection and destruction by the immune system.[www] Key mechanisms by which EMT promotes immune evasion include:

- **Downregulation of Antigens:** EMT can downregulate the expression of Major Histocompatibility Complex (MHC) molecules and tumor-associated antigens, making the cancer cells less recognizable to immune cells.[www]
- **Upregulation of Immune Checkpoint Molecules:** The EMT program promotes the upregulation of immune checkpoint proteins like PD-L1, which can inhibit T-cell activation and cytotoxicity.[www] EMT-induced expression of PD-L1 is linked to increased sensitivity to PD-1 inhibitors in some lung cancer models, a point of significant clinical interest.[www]
- **Secreted Immunosuppressive Factors:** As discussed previously, EMT-activated cells secrete cytokines and chemokines that create an immunosuppressive TME, further protecting them from immune attack.[www]

The interconnectedness of these effects means that EMT is a master program that orchestrates a constellation of malignant behaviors. The generation of a CSC population is directly linked to therapeutic resistance and recurrence, while the remodeling of the TME to be immunosuppressive directly facilitates immune evasion. Targeting EMT therefore has the potential for a cascading therapeutic effect, impacting multiple hallmarks of cancer simultaneously.

Part 6. Targeting EMT for Therapeutic Intervention

The central role of EMT in cancer progression, metastasis, and therapeutic resistance has made it a promising target for novel therapeutic strategies.[www] The rationale for targeting EMT is twofold: to prevent or reverse the transition of epithelial cells to a mesenchymal state, thereby reducing tumor aggressiveness and metastasis, and to enhance the efficacy of existing cancer treatments by overcoming resistance.[www]

6.1 Emerging Therapeutic Strategies

Several emerging strategies are being explored to modulate the EMT program:

- **Small Molecule Inhibitors:** These agents target key EMT-related signaling pathways, which are often involved in both EMT and other aspects of cancer biology.[www]
  - **TGF-β Pathway:** Galunisertib, a TGF-β receptor I inhibitor, has shown promise in inhibiting EMT and metastasis in breast cancer models.[www]
  - **Wnt/β-catenin Pathway:** The inhibitor PRI-724 is being investigated for its ability to inhibit EMT and cancer stem cell self-renewal in colorectal cancer models.[www]
  - **PI3K/Akt Pathway:** Idelalisib is an inhibitor being explored for lymphoma and other cancers, and it has been shown that combining it with a TGF-β inhibitor can block EMT in breast cancer models.[www]
- **RNA-Based Therapies:** These therapies, including siRNA and microRNA (miRNA) mimics, are being developed to modulate the expression of EMT-regulating genes. For example, siRNA-mediated knockdown of Snail has been shown to inhibit EMT and metastasis in breast cancer models, while the use of miR-200c mimics has been shown to inhibit EMT and CSC self-renewal in ovarian cancer models.[www]
- **Immunotherapies:** Immunotherapies can

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

exploit EMT-related vulnerabilities. For instance, EMT-induced expression of PD-L1 can be a vulnerability that is targeted by PD-1 inhibitors in some lung cancer models.[www]

Table 3: Emerging Therapeutic Strategies Targeting EMT.

Therapeutic Strategy	Target	Example Drug/Agent	Cancer Type	Mechanism of Action
Small Molecule Inhibitor	TGF-β receptor I	Galunisertib	Breast cancer	Inhibits EMT signaling and metastasis
Small Molecule Inhibitor	Wnt/β-catenin	PRI-724	Colorectal cancer	Inhibits EMT and cancer stem cell self-renewal
Small Molecule Inhibitor	PI3Kδ	Idelalisib	Lymphoma	Inhibits EMT signaling and proliferation
RNA-based Therapy	Snail	siRNA for Snail	Breas cancer	Gene knockdown to inhibit EMT and metastasis
RNA-based Therapy	miR-200c	miR-200c mimic	Ovarian cancer	Restores repression of EMT-TFs
Immunotherapy	PD-L1	PD-1 inhibitors	Lung cancer	Blocks immune checkpoint to restore T-cell activity

6.2 Challenges and Future Directions

Despite the promise, several significant challenges must be addressed for EMT-targeting therapies to succeed.

- **Complexity and Heterogeneity:** The EMT program is highly complex, involving multiple redundant molecular pathways and a spectrum of cellular states (the EMT continuum).[www] The coexistence of different EMT states within a single tumor increases intratumor heterogeneity, making a single-target approach difficult and often insufficient.[www]
- **Off-Target Toxicity:** Given the essential roles of Type I and Type II EMT in physiological processes like wound healing and embryogenesis, there is a significant risk of off-target toxicity.[www] Therapies must be designed to selectively target the pathological Type III EMT while sparing normal, healthy cells.
- **Combination Therapies:** The most promising therapeutic strategy is a combination approach that addresses the redundancy and plasticity of the EMT network.[www] For example, combining a TGF-β inhibitor with a PI3K inhibitor has been shown to have synergistic effects in inhibiting EMT and metastasis in breast cancer models.[www]
- **Context-Specificity:** The timing and context of therapeutic intervention are critical. Since EMT can play opposite roles at different stages of the metastatic cascade (e.g., promoting dissemination but potentially hindering colonization), interventions must be carefully timed and evaluated to avoid unintended consequences.[www]

Part 7. Conclusion: Looking Ahead

The pathological activation of the Epithelial-

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com

Mesenchymal Transition program is a central driver of cancer progression, orchestrating the key events of invasion, dissemination, metastatic colonization, and the acquisition of a suite of malignant hallmarks, including cancer stemness, therapeutic resistance, and immune evasion. The understanding of EMT has evolved from a simple binary transition to a more nuanced view of a reversible, plastic process with a spectrum of intermediate and hybrid states. This plasticity is a fundamental cause of tumor heterogeneity and a major challenge in developing effective treatments.

Future research must focus on overcoming the inherent complexities of the EMT program. This includes discerning the precise role of EMT at different stages of the metastatic cascade to optimize therapeutic timing, developing highly selective therapies that target Type III EMT without affecting vital physiological functions, and investigating the potential of combination therapies to address the redundancy and plasticity of the underlying signaling networks. Ultimately, leveraging EMT-related biomarkers for prognostic purposes and to predict patient response to treatment holds immense potential for improving clinical outcomes and finally addressing the lethal process of metastasis.

KaMoZo Biologics, LLC
Nashville, TN, USA
info@kmzbio.com