MetasTx
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Keeping cancer in its place: overcoming metastasis

Metastatic cancer remains one of oncology's most stubborn problems. MetasTx is developing a first-in-class small-molecule therapy against a unique target that inhibits cancer's ability to metastasize.

Most progress in cancer outcomes over recent decades has been driven by earlier detection and diagnosis, combined with therapies that slow the growth of early-stage cancers. However, much less progress has been made in combating metastasis—the ability of cancer cells to migrate to different parts of the body and establish new tumors. Metastasis remains the primary cause of cancer mortality, accounting for 90% of cancer deaths.

MetasTx, an early-stage biotech headquartered in Basking Ridge, New Jersey, is tackling the problem of metastatic cancer head-on with a pipeline of novel therapies developed to stop metastasis in its tracks. With a leadership team combining decades of immersion in cancer biology and drug delivery technology, and extensive experience creating value in biotech start-ups, MetasTx has its sights firmly set on the most challenging problem in oncology.

MetasTx has created an anti-metastasis platform based around the small molecule IPA-3, a highly selective allosteric inhibitor of group 1 p21-activated kinases (PAK1). This is a family of conserved non-receptor serine/threonine kinases that integrate a number of signaling pathways essential for normal cell proliferation, survival and motility.

Group 1 PAKs also have an established role in cancer biology, especially the cellular and cytoskeletal changes that drive metastasis. In particular, group 1 PAKs function downstream of two GTPases, Rac and CDC42, which are necessary for cells to form the lamellipodia and filopodia that enable a cell to change shape and move. Once activated by Rac and CDC42, the group 1 PAKs phosphorylate several proteins, including β-catenin, MEK1, Raf-1 and AKT, which drive many processes in cellular proliferation, survival and directional motility (Fig. 1).

Crucially, the changes in cytoskeletal structure and shape induced by the activation of group 1 PAKs enable the epithelial-to-mesenchymal transition (EMT), which is a critical step enabling cells to migrate, invade and establish themselves as new tumors in distant tissues. These collective skills define metastatic cancers.

MetasTx's therapies are designed to inhibit these pro-metastatic processes. In animal models, IPA-3 has been demonstrated by MetasTx co-founders Brian Cummings and Somanath Shenoy to inhibit EMT and prevent metastases to other organs[1], with few effects on other cellular functions and a consequent reduction in side effects.

Taking the lead with MTX-101

Unfortunately, IPA-3 is unstable in the bloodstream, so it cannot be delivered as a naked small molecule.

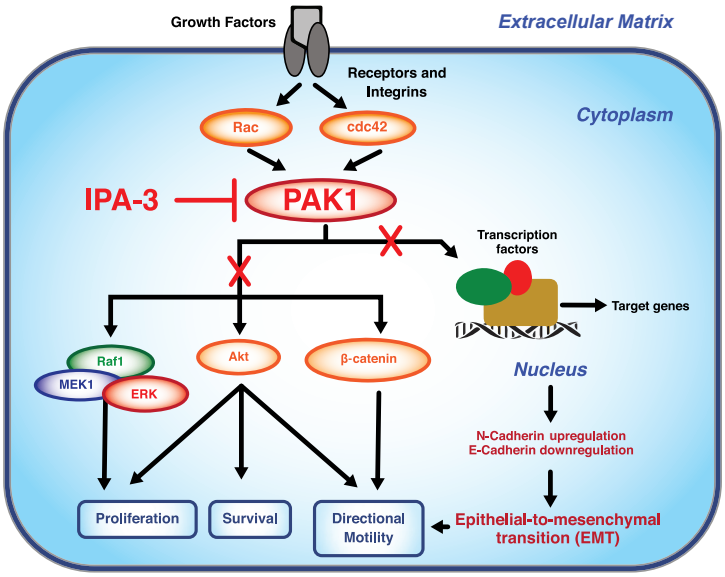

Fig. 1 | IPA-3 and the prevention of metastasis. PAK1 is activated by growth factors and integrins to promote cellular function. IPA-3 selectively inhibits PAK1, leading to the downregulation of pathways that drive cellular proliferation, survival and directional motility by preventing the loss of E-cadherin and increase in N-cadherin that characterize the epithelial-to-mesenchymal transition.

MetasTx has circumvented this problem with its lead candidate, MTX-101, a proprietary liposomal formulation of IPA-3 that shields the active ingredient from enzymatic degradation in the blood. In addition, the inclusion of polyethylene glycol (PEG) in the liposomal layer turns the nanoparticles into 'stealth liposomes' that go undetected by the reticuloendothelial systems, which ordinarily clear particles such as immune complexes and bacteria from blood and tissues. Finally, because the blood vessels that feed growing tumors typically have leaky walls and are more permeable than normal blood vessels, MTX-101 nanoparticles selectively aggregate in tumor sites—a phenomenon known as the enhanced permeability and retention effect.

MTX-101 is currently being developed for the treatment of prostate cancer and is close to beginning investigational new drug (IND)-enabling studies. MetasTx selected prostate cancer as a target indication partly because of the unmet clinical need for androgen-sparing treatments in this cancer, but also because PAK1 is expressed at high levels in prostate cancer and in precancerous prostatic hyperplasia. In mouse models of prostate cancer, MTX-101 delivered twice a week reduced tumor growth, lung metastases, bone remodeling, and tissue loss induced by the presence of metastatic cancer cells in the bone.

Further opportunities

Beyond the MTX-101 program, MetasTx is also investigating a range of novel compounds with a similar mechanism of action to IPA-3 that are stable in the blood and can be delivered without the need for a liposomal delivery vehicle. As these programs develop, and as the MTX-101 program matures, these novel forms of PAK1 inhibitors will be explored in other cancers.

Looking to the future, MetasTx envisions a number of potential value-creating exit points when the pipeline assets mature and are ready for clinical-stage development. The company welcomes discussions with investors and potential strategic partners who want to become part of the journey to reach these inflection points.

1. Verma, A. et al. *Oncol. Lett.* **20**, 179 (2020).

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