**Final publishable summary report**

**The TuMIC Consortium**

1. The address of the project public website:

**http://www.umm.uni-heidelberg.de/inst/cbtm/mbio/tumic/**

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Description: tumiclogo3

1. Project logo

1. List of all beneficiaries with the corresponding contact names

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**Executive summary**.

At the outset of the TuMIC project, it was clear that our concept of the process of metastasis is inadequate and needs to be revised. In the TuMIC project we aimed to use novel experimental approaches to integrate newly emerging principles and ideas such as cancer stem cells and metastatic niches with the different hypotheses that have until now tried to explain the process of metastasis. Specifically we wanted to understand how cancer stem cells (CSCs) behave in and contribute to metastasis, and how networks and pathways that are known to regulate metastasis affect their properties. Further objectives were to determine how a permissive niche microenvironment for metastasis formation is established in given organs, how this contributes to determining patterns of metastasis, and how these microenvironments interact with cancer stem cells. We also set out to perform preclinical studies that build on TuMIC findings with the aim of developing novel anti-cancer therapies.

Our data link CSC properties with metastatic proclivity. For example, a stem cell marker was shown to be functionally required for metastasis of squamous cell carcinomas. Furthermore, a gene expression signature specific to breast cancer CSCs proved to be a robust and reliable indicator of poor prognosis for breast cancer patients. Several lines of evidence we produced link the epithelial-mesenchymal transition (EMT) with CSC properties and metastasis, and the underlying transcriptional regulatory mechanisms have been elucidated. For example, a gene expression signature induced by an EMT-inducing transcriptional regulator proven to be a potent indicator of poor prognosis in breast cancer.

We have made important progress in understanding how the formation of metastatic niches is regulated. The S100 family member S100A4 has emerged from our work as a central regulator of metastatic niche formation, acting to create an inflammatory milieu that constitutes a pivotal component of the metastatic niche, as well as suppressing expression of factors in metastatic niches that counteract metastatic formation. Other factors such as VEGF-C, CCL2 and the c-Kit/KitL axis have arisen from our research as other factors that positively regulate niche formation. Together our data functionally demonstrate the importance of CD11b+ bone marrow-derived cells in the metastastic niche, and also validate the metastatic niche as a therapeutic target for inhibition of metastasis. We also found that EMT endows tumor cells with stemness properties that is associated with angiogenesis induction that is in turn required for metastasis formation, consistent with the notion that CSCs can functionally interact with the metastatic niche by inducing angiogenesis.

Based on these findings we have set up high throughput screens, developed inhibitory antibodies and rationally designed novel compounds with the aim of therapeutically applying our result to the treatment of cancer patients. Novel inhibitors of EMT have been discovered, and several ways of inhibiting metastatic niche formation have been identified. Ongoing studies beyond the lifetime of the TuMIC funding period will develop these promising preclinical approaches to the point where clinical trials can be started.

To ensure that the findings of the TuMIC project has maximum impact, we have engaged in a number of dissemination and exploitation activities, including scientific publications, organization and participation in conferences, intellectual property protection in the form of patents, and establishment of a project website. We have been actively involved in technology transfer, and have extensively interacted with EU-funded consortia and other key stakeholders.