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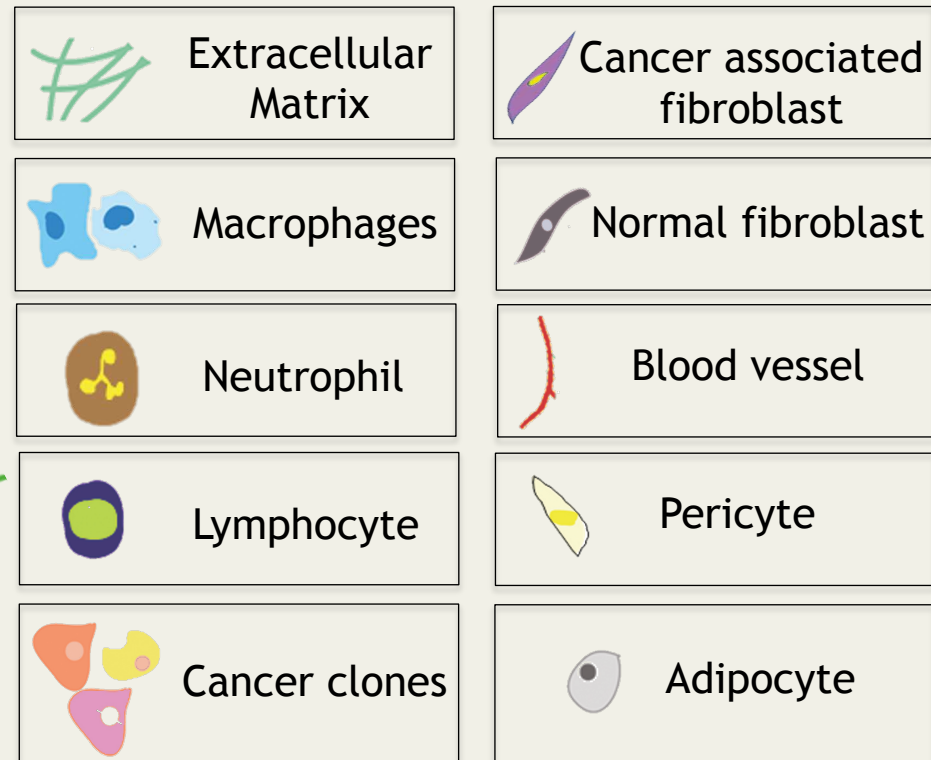
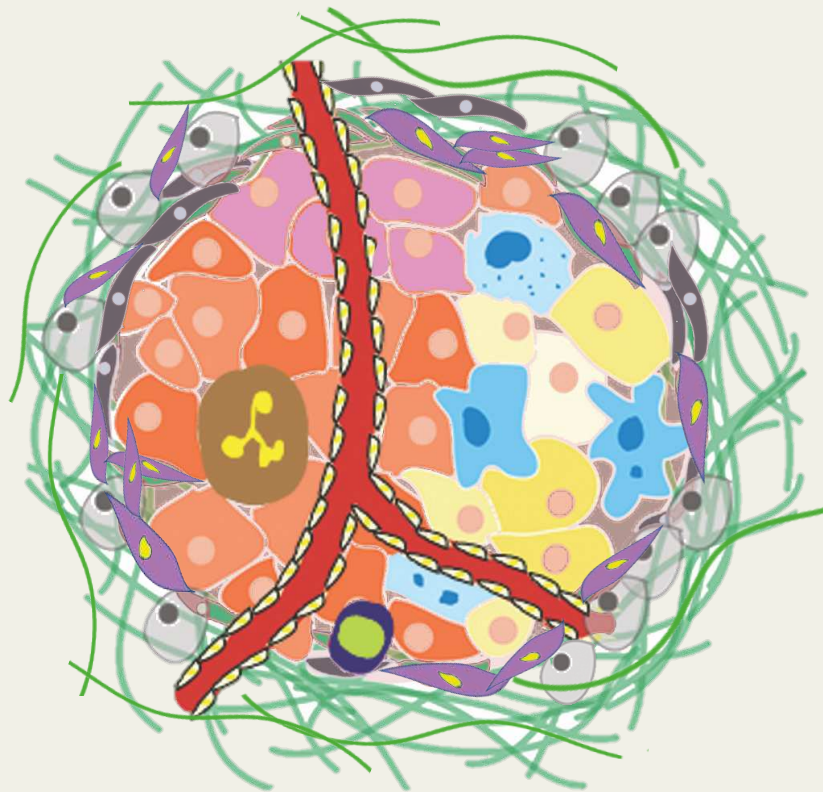


FIGURE 1: THE COMPLEXITY OF THE TUMOUR MICROENVIRONMENT: PRIMARY BREAST TUMOURS CONSIST NOT ONLY OF HETEROGENOUS NEOPLASTIC CELLS, BUT ALSO SURROUNDING STROMA (OR TUMOR MICROENVIRONMENT) INCLUDING IMMUNE CELLS, EXTRACELLULAR MATRIX COMPONENT, CANCER ASSOCIATED FIBROBLAST, BLOOD VESSELS AND CANCER ASSO-CIATED ADIPOCYTES INTERACTING TO SUPPORT TUMOUR DEVELOPMENT.

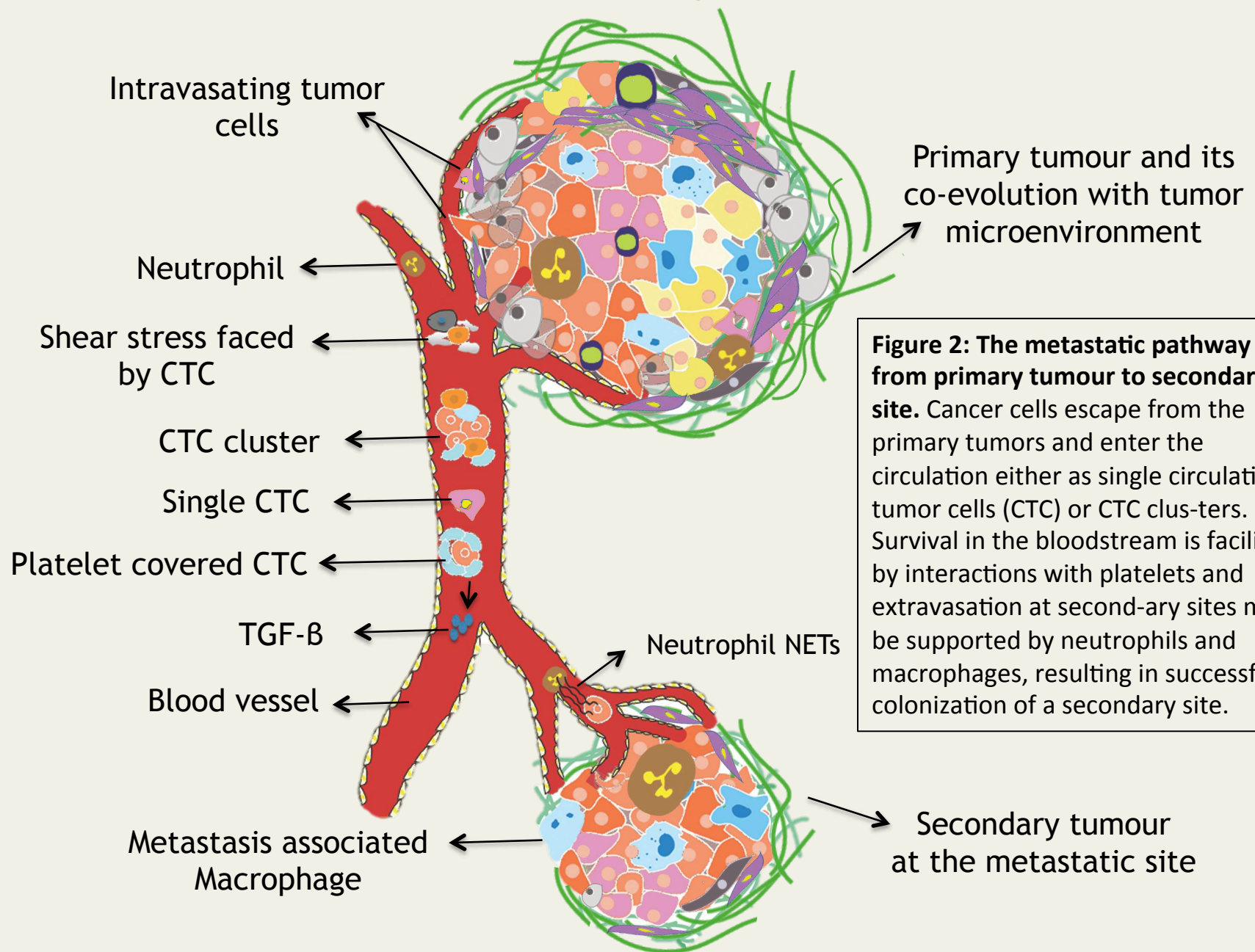


Figure 2: The metastatic pathway – from primary tumour to secondary site. Cancer cells escape from the primary tumors and enter the circulation either as single circulating tumor cells (CTC) or CTC clusters. Survival in the bloodstream is facilitated by interactions with platelets and extravasation at secondary sites may be supported by neutrophils and macrophages, resulting in successful colonization of a secondary site.

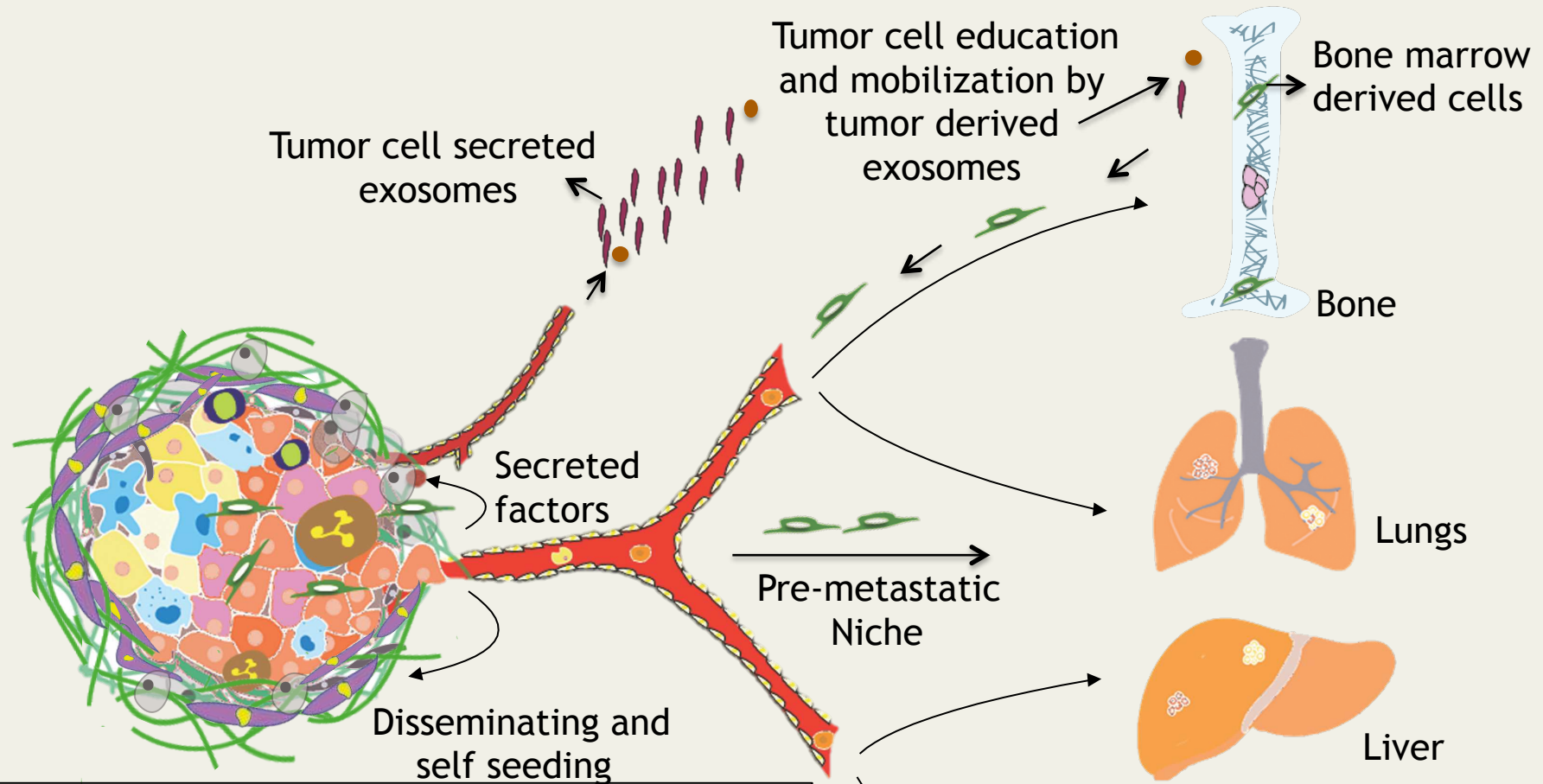


Figure 3: Metastatic progression: Tumour cells shed into circulation migrate to various organs. There is accumulating evidence that signals secreted by the cells from the primary tumor (including exosomes) mobilize bone marrow-derived cells that are recruited organs such as lungs and brain to create a pre-metastatic niche prior to the arrival of disseminated cancer cells. The interaction between bone marrow derived cells within the primary tumor enhances the growth, survival, mobility and invasive metastatic capacity of the tumor cells via paracrine interactions. Disseminated tumor cells can also return to the original primary tumor site and promote its growth and further metastatic spread in a process termed “self seeding”.