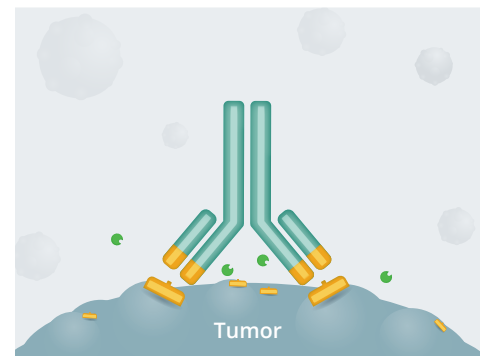
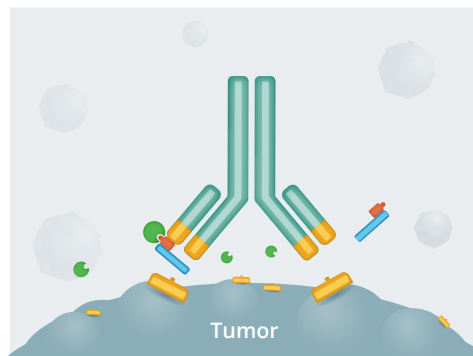
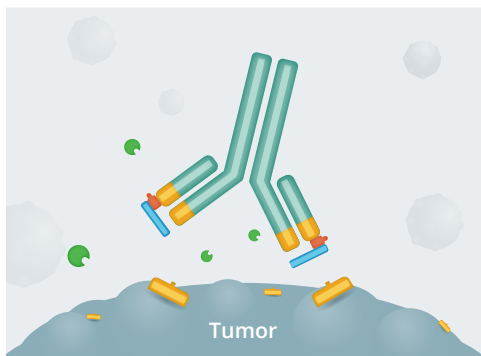
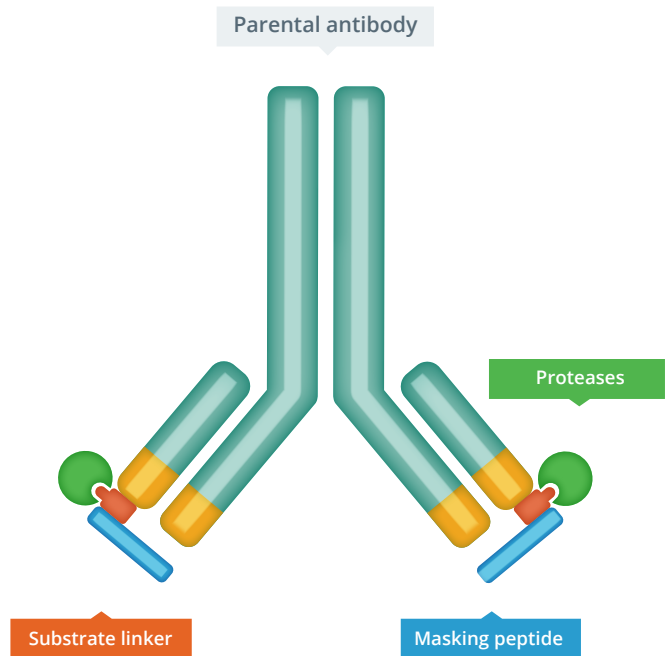


## PROTEASE BIOLOGY

Probody® therapeutics are designed to exploit the unique conditions of the tumor microenvironment to more effectively localize treatment to the tumor, while limiting activity in healthy tissues. These novel therapies take advantage of high levels of protease activity that are unique to the tumor microenvironment. A Probody therapeutic consists of three components: an anti-cancer antibody, a mask for the antibody and protease-cleavable linker, which tethers the mask to the antibody. Probody therapeutics are produced as a single protein by standard antibody production methodology. The mask is a peptide designed to disguise the active binding site of the antibody to prevent the therapeutic binding to the target present on healthy tissue.

When Probody therapeutics enters the tumor, they encounter proteases—enzymes that cleave proteins and have increased activity in the tumor microenvironment. The proteases in the tumor cleave the linker, removing the mask and activating the antibody to bind to the target, potentially turning the disease against itself.



Proteases play an essential role in many aspects of normal physiology, such as digestion of food in the gastrointestinal tract, wound healing and metabolic function. However, uncontrolled protease activity can lead to destruction of essential proteins and tissues. Therefore, proteases are normally very tightly regulated by redundant mechanisms, with only small amounts of extracellular protease activity being detectable in healthy tissues.

In contrast, it has been well documented that proteases are not only present, but also activated, in virtually all types of tumors, playing a key role in tumor growth, invasion and metastasis. Probody therapeutics are designed to be activated in this protease-rich tumor microenvironment, but not in healthy tissue where proteases are under tight control.

## PROTEASE BIOLOGY

- Upregulated protease activity is a hallmark of all cancers
- Protease activity is tightly controlled in healthy tissues

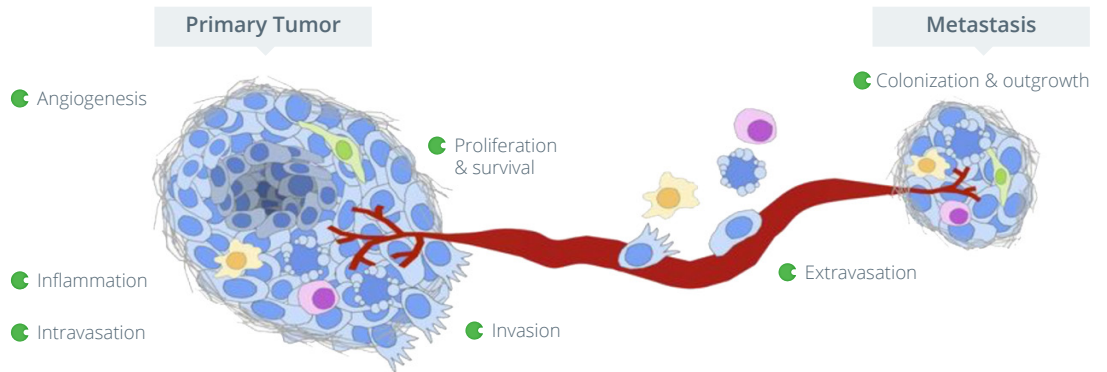
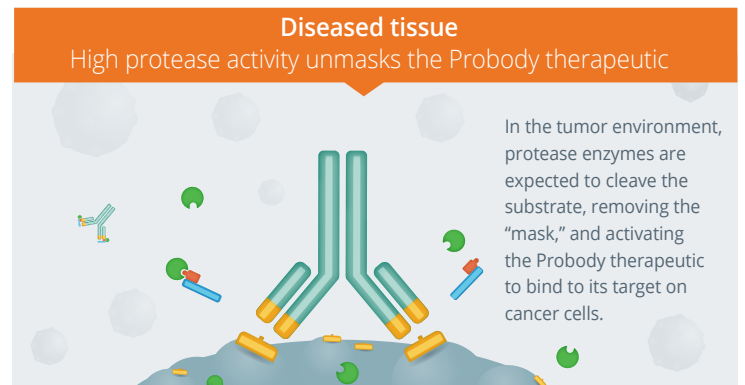
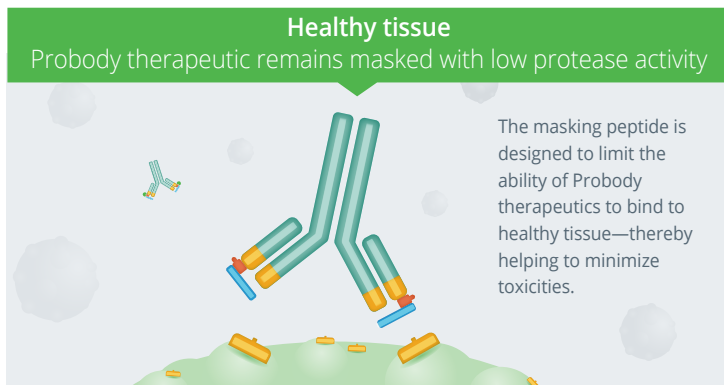


Figure 1: Sevenich and Joyce, *Genes and Development* (2014), and reproduced with permission from Prof. Johanna Joyce, Ludwig Institute for Cancer Research, University of Lausanne, Switzerland.



CytomX and its partners have demonstrated applicability of the Probody platform across more than 15 targets in multiple monoclonal antibody modalities, including cancer immunotherapy, antibody drug conjugates and T cell engaging bispecifics, with emerging application in CAR-based cellular therapies.

The protease-cleavable linkers have been designed so that any one of a number of activated proteases can cleave them. Using this approach, CytomX believes Probody therapeutics can be cleaved

and activated by at least one protease across a large number of tumors. The company has generated *in vivo* efficacy data in dozens of human tumor models in mice and *ex vivo* data from hundreds of human tumor explants to suggest that our Probody therapeutics can be activated across a broad set of tumors. The company is now assessing the first Probody therapeutics in human clinical trials.



Figure 2: Imaging active matriptase by Aaron M. LeBeau, Minhee Lee, Stephanie T. Murphy, Byron C. Hann, Robert S. Warren, Romelyn Delos Santos, John Kurhanewicz, Samir M. Hanash, Henry F. VanBrocklin, Charles S. Craik. *PNAS* Jan 2013, 110 (1) 93-98; DOI: 10.1073/pnas.1218694110