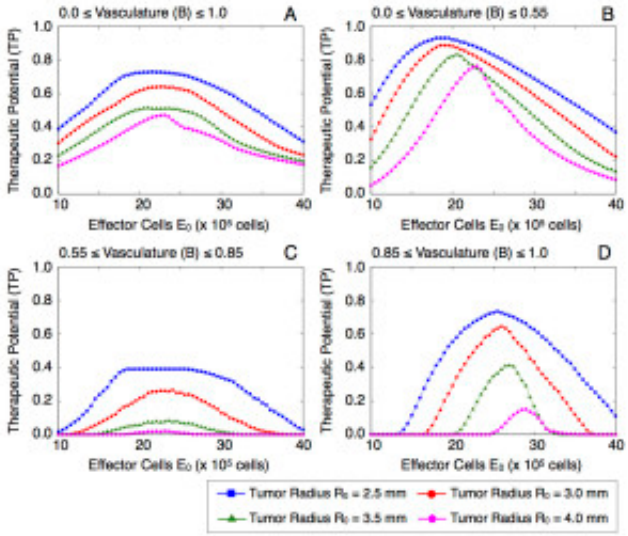
Combinatorial cancer therapies: too many “good guys” don’t do always good!

“?????? ???????” (Metron ariston) is an ancient Greek phrase, attribute to Cleobulus (6th century BC), one of the Seven Sages of Antiquity, and is translated, as “Moderation is the best”. This was meant to be applied to all aspects of life, good or bad. In the fight against tumor (bad guys) our body uses its own “good guys”, the immune cells. Immune cells infiltrate into the tumor bulk via a vasculature network, a network of blood vessels originally induced by cancer cells for their own feeding. Recently, the emerging field of Onco-immunology is focusing on the development of immunotherapies against tumor growth. Two of the dominant ideas are: (i) to “train”, in the lab, as many as possible effective “good guys”, i.e. immune cells, and implant them at tumor’s vicinity, and (ii) improve their infiltration within the tumor bulk via a process called *vasculature normalization*.

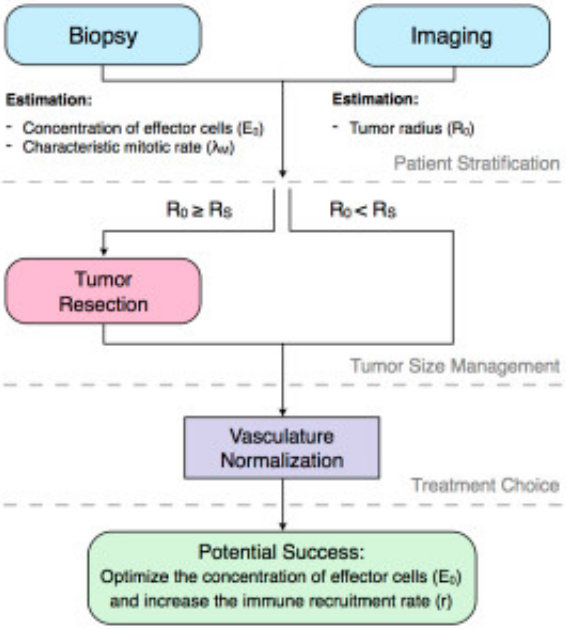


Therapeutic potential dependence on tumor vasculature (B) and immune cell concentration (E_0)

Although applying these therapeutic strategies standalone sounds promising, it does not guarantee tumor control. And what about their combination? Mathematical/computational modeling allows us to understand how potential combinations of immune-stimulation and vascular modulations can lead to an effective therapy design that can be subsequently experimentally tested.

Our model analysis has shown that there is an *optimal* number of immune cells that confer the best result, in terms of tumor control. A large amount of externally administrated immune cells (effectors) induces a large initial decrease of tumor bulk. However, this signals the immune system to send less effector cells against the tumor, since there are already enough. In turn, the tumor has

the chance to regrow faster than the recruitment of new immune cells. Intuitively, one could draw an analogy between hitting a spring (tumor) with a hammer or a maul (hammer weight=immune cell concentration). Our goal is to control spring length by successive hits. After an initial hammer blow the spring contracts but we can be fast enough to raise the hammer and hit again.



Theory-driven treatment proposal for non-invasive tumors.

Hitting with a maul, we might succeed a much larger spring contraction but lifting the maul can be much slower than the spring extension, allowing the latter to reach its maximum length. Although for tumors there is no size limitation, apart the hosting organ size, but there exists a *critical tumor size* where larger tumors cannot be anymore controlled by the immune system. Thus, the immune response should be strong but also fast enough to catch up tumor relapse before reaching its critical size, i.e. implying uncontrollable tumor growth.

And here comes the catch: if the functionality of tumor-induced vasculature is very good or very bad then this optimal dosage of immune cells can be really effective. However, killing tumor's feeding network (vascular) might sound positive, but it has been proven that tumors under starvation become more aggressive and tumor cells start invading elsewhere – first stage of metastasis. Instead one should keep the tumor "happy" by improving the functionality of its feeding network by means of vasculature normalization therapy techniques. Then applying an optimized immune-stimulation therapy, we can expect tumor's long-term control.

Publication

Cancer therapeutic potential of combinatorial immuno- and vasomodulatory interventions.
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