F ***VEGF Trap in Cancer Trials Today, and VelociGene coupled with VelocImmune for Drug Targets of Tomorrow***

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The concept that tumors can be controlled by directly targeting their vascular supply has finally come of age. Clinical trials using a humanized monoclonal antibody that blocks VEGF have demonstrated exciting efficacy in cancer patients, as well as in vascular eye diseases that can lead to blindness. However, data suggests that these current regimens may not provide for complete VEGF inhibition, and thus that the maximum therapeutic potential of VEGF blockade has not yet been achieved. We have engineered a very potent, high affinity VEGF blocker, termed the "VEGF Trap". The VEGF Trap has performed impressively in extensive animal studies of cancer and eye diseases, and initial clinical trials appear promising. The VEGF Trap may provide for the opportunity to explore the potential of more complete VEGF blockade in cancer, as well as the opportunity for even longer-interval dosing regimens in eye diseases.

Following up on the success of VEGF as an anti-angiogenesis target, we have attempted to identify and validate additional targets in this field, particularly ones that might have combination effects with VEGF blockade, or might still be active in settings resistant to VEGF blockade. These efforts resulted in the discovery of new families of requisite angiogenic growth factors, including the Angiopoietins and Ephrins, as well as the development of new high-throughput genetic technologies to rapidly test and validate targets of interest. These latter technologies, termed VelociGene and VelociMouse, allow for an unprecedented rate of generation of Knockouts, KnockIns and Transgenics – easily industrializable and scaleable to thousands per year. These approaches involve rapid manipulation of very large pieces of DNA - hundreds of kilobases in size – with enormous flexibility, allowing the production of custom mutations with nucleotide precision, deletions of very large size, reporter knock-ins, transgenic over-expression, as well as conditional and complex alleles. Exploitation of VelociGene and VelociMouse technologies for the purpose of identifying new targets in angiogenesis will be described. I will also describe how we exploited these technologies to "humanize" megabase-sized portions of the mouse immune system to generate *VelocImmune* mice, which may provide for a powerful new way to exploit the mouse so as to generate fully human therapeutic antibodies against targets of interest.