Ad5-based gene transfer vectors and oncolytic viruses are the most frequently used vector type in clinical trials up to date. However, early vector-blood interactions impose significant barriers for the systemic I.V. delivery of this vector type and limit a broad clinical success. Even in the absence of adaptive immunity, Ad5-based particles become quickly opsonized by different blood proteins, are scavenged by macrophages, and sequestered to non-target sites. The presentation will provide an overview over the most important early vector-blood interactions and present chemical strategies to overcome the barriers. A special emphasis will be put on combined genetic and chemical modifications developed in the Kreppel lab.