Cloning and Transgenesis

Hermonat, Clon Transgen 2015, 4:1
DOI: 10.4172/2168-9849.1000e115

Editorial Open Access

Waking the Sleeping Giant: Gene Therapy in Decline?

Paul L Hermonat*

Central Arkansas Veterans Healthcare System, Little Rock, AR 72205, USA

***Corresponding author:** Paul L Hermonat, Central Arkansas Veterans Healthcare System, 4300 West 7th St., Little Rock, AR 72205-548, USA, Tel: 501-940-7034; Fax: 501-257-4821; E-mail: Paul.Hermonat@va.gov

Rec date: Dec 30 2014; **Acc date:** Dec 31 2014; **Pub date:** Jan 8 2015

Abstract

A search of the literature shows that overall interest in gene therapy, as indicated by publication numbers, has been on a slow decline for over a decade, since the year 2000. In spite of this the stunning potential of gene therapy to revolutionize modern medicine remains unfulfilled. The bottleneck of NIH funding for basic research and lack of means to enter into the clinical trials pipeline (toxicology and Phase I-III clinical trials) strongly limits advancements in gene therapy-based medical breakthroughs. Within the declining general field, publications on adeno-associated virus (AAV) - and lentivirus-based gene delivery continue to rise and offer some hope for the future.

Introduction, Results and Discussion

The promise and potential of gene therapy to positively impact our health is very high as its goal is to use endogenous human genes as medicines to treat and cure a wide variety of diseases. There are many diseases, both major and minor, which remain unbowed by modern small molecule drugs and present day standards of care. Cardiovascular disease and cancer are two of these, and they remain our biggest killers. No other area of medical research can provide for so many new treatment approaches as gene therapy. The vast number of possible gene therapy "drugs" is, in fact, greater than the actual number of human genes, as these genes, and their encoded products, can be modified or customized to give enhanced activities beyond that of the natural, endogenous, wild type genes. The choice of transcriptional promoter to use also gives important refinements in treatments [1].

Opposed to this potential, as shown in Figure 1, I was surprised to discover that there is an actual overall decline in the topic of gene therapy as indicated by searching PubMed. This decline in gene therapy also likely reflects, and may be due to, the overall decline in NIH funding. Yet the gene therapy field remains a "giant" in regards to it's almost certain payoffs for advancing improvements in human quality of life and extension of life.

There are presently three major virus types that are being used for gene therapy in humans (Table 1). These include recombinant adeno-associated virus (AAV) [1-6], retrovirus/lentivirus (Lenti) [7-10] and adenovirus (Ad) [11-13]. These are described in Table 1, and all of these have shown their usefulness and power since the pioneer years of 1983-1984. But there are obvious differences.

Adeno-associated virus (AAV) has a number of advantages and continues to grow in popularity and use as shown in Figure 2A. It is safe, a BSL1 agent, and does not cause inflammation, rarely causes integration into the germ line, and induces a limited immune response. AAV also displays long term stability whether as an integrated or episomal provirus. AAV2-based gene expression has been shown to be maintained for many months, as long as ten years, in our and others' laboratories [1,4-6]. There is also a plethora of AAV capsid types which can be used to customize their uptake in liver, lungs, kidney, blood vessels, and other sites with a single intravenous injection.

Retroviruses require chromosomal integration for their life cycle and are known to integrate into the germ line [14]. A very unfortunate development with retrovirus use was the development of cancer in a group of pediatric patients undergoing retroviral gene therapy in France [15]. Retrovirus integrated provirus resulting from transduction is also notorious for being inactivated, having their transgene expression eliminated, while used in vivo. In contrast, the lentiviral retroviruses, a subset of retroviruses, are proving to be superior to the earlier Moloney murine leukemia virus-based vectors, however it is unclear if these disadvantage with their use are only reduced and not eliminated by the use of lentiviral vectors. So the use of lentivirus is giving new life to the retroviral gene therapy field and this is strongly shown in Figure 2B.

Viral Vector use in clinical trials and approved standard of care **Data from clinlcaltrials.gov**						
Virus	**Total**	**Complted**	**Active**	**Permanent chrom Int**	**Adverse reactions**	**Approved stnd of care**
AAV	13	4	9	Yes/sometimes	None	Yes (Europe)
Lenti	40	34	6	Yes	Yes (death)	No
Adeno	62	30	22	No	Yes (cancer)	No

Table 1: Major vector use in clinical trials and approved standard of care. These data are from www.clinical trials.gov and from the public record. AAV is the only fully approved vector for regular therapeutic use (Europe).

Ad is a highly useful vector for laboratory use and may be useful for certain clinical applications. But Ad can cause quite significant inflammation, and a decade ago a patient died in a gene therapy trial at the University of Pennsylvania in likely due to adenovirus-mediated

inflammatory processes [16]. Further, adenovirus usually induces only a short term expression of transgenes; usually the expression lasts about three weeks post-infection. In any case, the use of adenovirus is clearly on the decline and may be partially responsible for the overall decline of gene therapy studies, as shown in Figure 2C.

Going back to Figure 1, while the popularity and validation of AAV and lentivirus-based gene therapy, are increasing, it remains that the overall research base and interest in gene therapy is in decline. Moreover, the two major mistakes [15,16] in retroviral and adenoviral clinical trials have not been repeated and are now events over ten years in the past. It is noteworthy that the initiation of the decline in gene therapy publications appears to correlate with those two events. Yet the continued decline in gene therapy effort remains in the face of the stunning potential that gene therapy has towards altering the health care industry for the better. Lack of increases in NIH funding for basic research in gene therapy is likely one cause.

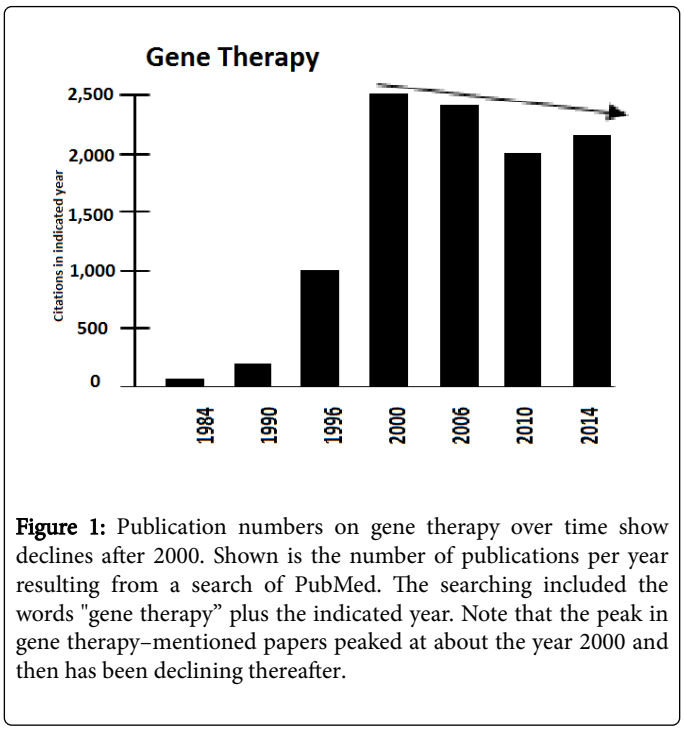

Figure 1: Publication numbers on gene therapy over time show declines after 2000. Shown is the number of publications per year resulting from a search of PubMed. The searching included the words "gene therapy" plus the indicated year. Note that the peak in gene therapy–mentioned papers peaked at about the year 2000 and then has been declining thereafter.

This specific issue can be readily fixed by those in charge of prioritizing funding. Perhaps even more serious is the lack of ways for promising gene therapy results to enter into clinical trials. Private company participation is now a requirement to pay the high cost of gene therapy development (toxicology and Phase I-III clinical trials). While the number of such companies who have this interest is increasing, these numbers remain modest and their resources are limited. One idea to address this issue is for the NIH to partner with industry in identifying those promising approaches and to bring them forward into those important next steps. It is true that the SBIR and STTR funding mechanisms are in place and serve this purpose, but they seem rather inadequate in the level of support and expertise that they can provide for gene therapy protocol development. In any case, if this situation remains, it strongly limits advancements in gene therapy-based medical breakthroughs.

I envision that many diseases can be better addressed through gene therapy than present standards of care. I'm sure many others see this as well. Therefore, can't we address these limiting factors in the near term to drive the health care industry towards higher efficacy, ultimately lower cost, and higher quality of life for patients that the gene therapy approach can provide?

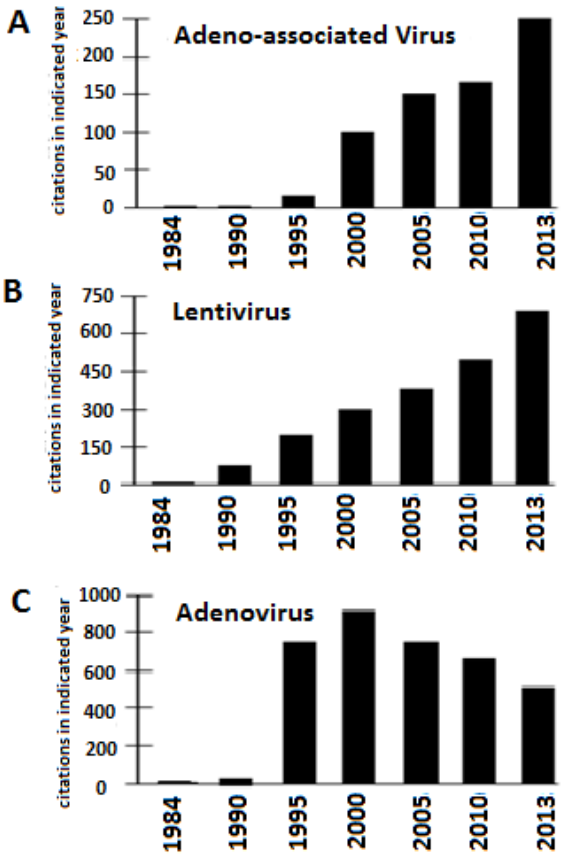

Figure 2: (A) Use of viral vectors. PubMed search of numbers of papers on various viral vectors over time. A shows paper numbers on AAV-based gene therapy per indicated year. (B) Shows paper numbers on lentiviral-based gene therapy per indicated year. These paper numbers may be inflated by the use of other vectors used to inhibit lentiviruses themselves by gene therapy. (C) Shows paper numbers on adenovirus-based gene therapy per indicated year.

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