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Non-viral gene therapy: Gains and challenges of non-invasive administration methods

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ABSTRACT

Gene therapy is becoming an influential part of the rapidly increasing armamentarium of biopharmaceuticals for improving health and combating diseases. Currently, three gene therapy treatments are approved by regulatory agencies. While these treatments utilize viral vectors, non-viral alternative technologies are also being developed to improve the safety profile and manufacturability of gene carrier formulations. We present an overview of gene-based therapies focusing on non-viral gene delivery systems and the genetic therapeutic tools that will further revolutionize medical treatment with primary focus on the range and development of non-invasive delivery systems for dermal, transdermal, ocular and pulmonary administrations and perspectives on other administration methods such as intranasal, oral, buccal, vaginal, rectal and otic delivery.

1. Introduction

Following almost three decades of hard work, gene therapy is starting to enter the main stream as an important part of biotherapies [1]. Gene-based medicines are part of the expanding new treatment options with biological products. According to the FDA "biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available." Important classes of biopharmaceutical compounds (genetically-engineered or biodrugs) include interferons and cytokines, blood clotting factors (erythropoietin), growth hormones/factors, hormones (insulin), enzymes, therapeutic (including monoclonal) antibodies (mAbs) and vaccines as well as nucleic acids [2]. These biodrugs, also called new biological entities or NBE, are becoming the most demanded medicines, currently representing about 10% of all prescription medicines and will make up 52% of the top 100 drug sales by 2020 (Evaluate Pharma: Pharma World Preview 2014 Outlook to 2020).

The human genome project is continuously accelerating the discovery of the genetic basis of an increasing number of diseases and the corresponding interventions for corrections. Gene therapy is one of the

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Table 1
A list of non-viral gene therapy systems used in clinical trials. (Data obtained and compiled from www.clinicaltrials.gov.) Note: Most of these leading technologies are still injectables; the proportion of non-invasive administration methods reflects the progress.

Gene delivery system	Product/formulation	Therapeutic gene	Indication being evaluated for	Administration	Trial phase	Status (active includes studies in progress)	Clinical trial reference number	Study first received
Liposome	DOTAP:Chol-fus1	Fus1 DNA plasmid	Non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)	Intravenous	Phase I	Completed	NCT00059605	2003
			Non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)	Intravenous	Phase II	Active	NCT01455389	2011
	DC-Chol Liposome	EGFR DNA plasmid	Advanced oral squamous cell carcinoma	Intratumoral	Phase I	Completed	NCT00009841	2001
	pGT-1 DMIRE/DOPE Liposome	pGT-1 DNA plasmid	Cystic fibrosis	Nasal	Phase I	Completed	NCT00004471	1999
	SGT-53	P53 DNA plasmid	Solid tumor	Intravenous	Phase I	Active	NCT00470613	2007
	Transferrin receptor-targeted (TfRscFv) cationic liposome		Children with refractory or recurrent solid tumor	Intravenous	Phase I	Active	NCT02354547	2014
			Glioblastoma	Intravenous	Phase II	Active	NCT02340156	2014
			Metastatic pancreatic cancer	Intravenous	Phase II	Active	NCT02340117	2014
	DOTMA/Cholesterol [Ratio 1:0.5(−/+)]	Interleukin-2 DNA plasmid	Stage III or IV head and neck cancer; squamous cell carcinoma of the head and neck	Intratumoral	Phase II	Completed	NCT00006033	2000
	pGM169/GL67A[GL67A/DOPE/DMPE/PEG]	CTFR DNA plasmid	Cystic fibrosis	Nasal	Phase II	Active	NCT01621867	2012
	siRNA-EphA2-DOPC	EphA2 siRNA	Advanced cancer — solid tumor	Intravenous	Phase I	Active	NCT01591356	2012
	TKM-08,301	PLK1 siRNA	Neuroendocrine tumors, adrenocortical carcinoma	Intravenous	Phase I	Active	NCT01262235	2010
	ND-L02-S20201	HSp47 SiRNA	Fibrotic diseases	Intravenous	Phase I	Completed	NCT01858935	2013
	ALN-PCS02	PCSK9 siRNA	Elevated LDL-cholesterol	Intravenous	Phase I	Completed	NCT01437059	2011
	Patisiran	TTR siRNA	Transthyretin (TTR) amyloidosis	Intravenous	Phase I	Completed	NCT01148953	2010
	ALN-TTR02		Transthyretin (TTR) amyloidosis	Intravenous	Phase I	Completed	NCT01559077	2012
			Transthyretin (TTR) amyloidosis (Japanese patient only)	Intravenous	Phase I	Completed	NCT02053454	2014
			Transthyretin (TTR) mediated amyloidosis	Intravenous	Phase II	Completed	NCT01617967	2012
			Transthyretin (TTR) mediated amyloidosis	Intravenous	Phase II	Active	NCT01961921	2013
			Transthyretin (TTR) mediated familial amyloidotic polyneuropathy (FAP)	Intravenous	Phase III	Active	NCT01960348	2013
	Revusiran	TTRSC siRNA	Transthyretin (TTR) cardiac amyloidosis	Subcutaneous	Phase I	Completed	NCT01814839	2013
	ALN-TTRSC		Transthyretin (TTR) cardiac amyloidosis	Subcutaneous	Phase II	Completed	NCT01981837	2013
			Transthyretin (TTR) cardiac amyloidosis	Subcutaneous	Phase II	Active	NCT02292186	2014
			Transthyretin (TTR) mediated familial amyloidotic cardiomyopathy (FAC)	Subcutaneous	Phase III	Active	NCT02319005	2014
	Atu027	PKN3 siRNA	Advanced solid tumor	Intravenous	Phase I	Active	NCT00938574	2009
			Advanced pancreatic cancer	Intravenous	Phase I/II	Active	NCT01808638	2013
	Pbi-shRNA STMN1	STMN1 shRNA	Advanced/metastatic cancer	Intratumoral	Phase I	Active	NCT01505153	2012
	GNELipoplex (DNA plasmid/ DOTAP/ Cholesterol)	GNE1 DNA plasmid	Muscular dystrophy	Intravenous	Phase I	Unknown	-	-
Polymer	CYL-02/polyethylenimine	Sst2 dck::umk-DNA plasmid	Advanced pancreatic adenocarcinoma	Intratumoral	Phase I	Completed	NCT01274455	2010
	DTA-H19/PEI	DT-A-H19 DNA plasmid	Superficial bladder cancer	Intravesical	Phase II	Active	NCT00595088	2008
	EGEN-001 [IL-12 plasmid DNA/PEG-PEI-cholesterol]	IL-12 DNA plasmid	Ovarian neoplasm	Intraperitoneal	Phase I	Complete	NCT00473954	2007
			Persistent ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer	Intraperitoneal	Phase I	Active	NCT01489371	2011
			Colorectal cancer	Intraperitoneal	Phase I/II	Active	NCT01300858	2011