Vectorized antibodies by in vivo expression of DNA or RNA: a competitive business, stakeholder, technology and pipeline analysis from an industry perspective

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manufacturing plant in the Banwol Campus with capacity for 100 mln doses per year. Both powder and solution forms are stable at room temperature (>12 months).

WuXi AppTec is a global company with operations across Asia, Europe, and North America, WuXi AppTec provides a broad portfolio of R&D and manufacturing services. WuXi AppTec provides a comprehensive platform to support the discovery of mRNA drugs. WuXi's services include mRNA design and production, assessment of mRNA delivery systems, in vitro evaluation, and determination of in vivo efficacy and biodistribution after intravenous and intratumoral administration. The company showcased the anti-tumor properties of a mRNA-encoded CD3-EpCAM bispecific antibody (BsAb) and a mRNA-encoded IL-12 protein.

3.6 Partnerships with Licensing and Collaboration Agreements for Vectorized Antibodies

Commercial partnerships for vectorized antibodies include typical licensing agreements, e.g. between REGENXBIO and AbbVie, as well as technology collaborations in which one partner contributes vectorization technology and the other antibody technology, e.g. Transgene and BioInvent. Table 8 summarizes the partnering agreements which also includes one partial asset acquisition. It is noteworthy that at present only one Big Pharma company (AbbVie) has licensed rights to a vectorized antibody.

Table 8a: Partnerships of Pharma/Biotech and Companies with Vectorized Antibody Technologies

Pharma / Biotech	Technology Partner	Vectorized Antibody Technology	Year of Start / Status	Goals & Terms
AbbVie	RREGENXBIO	AAV8	2021 /ongoing	RGX-314 for retinal diseases; global rights for $ 370 mln upfront + max $ 1.38 bln mile-stones + profit share / royalties
AstraZeneca	Inovio Phar-maceuticals & academia	pDNA + EP by Cellectra device	2020 / ongoing	Public-private partnership spon-sored by US gvt to develop anti-SARS-CoV-2-specific DMAbs
BioInvent	Transgene	Oncolytic Copenhagen Vaccinia Virus	2017 / ongoing	Co-Co partnership with shared costs & profits
CRBio	ImmVira	Attenuated on-colytic HSV-1	2022 / ongoing	Co-development of oncolytic virus for glioblastoma in China
De Novo Biotherapeutics	NuclixBio	Circular RNA + LNP	2022 / ?	Joint development of bispecific NK cell engager antibody
Junshi Bioscience	ImmoRNA	mRNA + delivery vehicle	2021 / stand by	Joint venture to develop mRNA + delivery vehicles in the fields of tumors, infectious & rare diseases

existing investor Pureos BioVentures committing new funds to support the Phase I study of PST-611 and enable preparation for a Phase IIa clinical trial (Press Release Feb 13, 2025). PST-611 is a non-viral vectorized therapy for the treatment of dry age-related macular degeneration (AMD)/geographic atrophy (GA), expressing human transferrin, a highly potent iron regulator.

The Series A financing remains open to new investors, to provide funds to support PST-611 Phase IIa clinical trial preparation and implementation, as well as the development of PulseSight's wider portfolio of non-viral vectorized therapies including **PST-809**, a therapy for wet AMD that comprises a dual-gene plasmid encoding for a potent anti-VEGF (aflibercept), together with decorin, an anti-angiogenic and anti-fibrotic native protein.

PulseSight has a unique approach to the administration of disease-modifying genes through its proprietary electro-transfection technology. Already validated in the clinic for safety and delivery, this non-viral delivery platform delivers DNA plasmids encoding therapeutic proteins into the ciliary muscle to safely and sustainably treat major eye diseases. The company's technology and therapeutic applications are covered by an IP portfolio of 11 patent families, with 90 granted patents.

Technology

Eyevensys is developing non-viral gene therapies for ophthalmic diseases. The company has developed an **Electrotransfection System**, novel medical devices that use electroporation to deliver proprietary **DNA plasmids** encoding therapeutic proteins to the ciliary muscle of the eye. The Eyevensys technology turns the eye into a biofactory, allowing the ciliary muscle to produce the therapeutic protein. The secreted protein reaches the back of the eye, including the retina and choroid.

Ciliary Electrotransfection & DNA Plasmids

The company's technology is a non-viral gene therapy ocular drug delivery platform that uses a two-part Electrotransfection System, including a proprietary Ocular Device and Electrical Pulse Generator, that delivers DNA plasmids encoding therapeutic proteins into the ciliary muscle. This turns the eye into a biofactory, allowing the ciliary muscle to produce the therapeutic protein. The secreted protein reaches the back of the eye, including the retina and choroid.

R100 has the capacity to cross vitreoretinal barriers and transduce all regions and layers of the retina following intravitreal injection. 4DMT has completed discovery programs targeting a diverse array of tissue types including various retinal cell types, heart and skeletal muscle tissues, different lung cell types, liver, brain, dorsal root ganglia, and synovial joints, resulting in hundreds of unique and proprietary customized and evolved vectors. The company's upstream manufacturing step involves triple plasmid transfections in an adherent **HEK293** mammalian production cell line.

Adverum Biotechnologies utilizes the AAV.7m8 capsid as a key platform for intravitreal (IVT) delivery. This engineered variant, derived from natural AAV2, was developed through directed evolution for its ability to transduce neural retinal cells upon IVT administration. AAV.7m8 has exhibited the capability to cross the inner limiting membrane in the retina, a hurdle for naturally occurring AAV serotypes and demonstrated widespread transduction of the retina. Retinal transduction is primarily located in the macula, or central retina, and retinal periphery. The companies lead product candidate ixo-vec is produced in the **baculovirus** expression system in Sf9 cells where two baculoviruses were used.

Avirmax Biopharma is developing ocular gene therapies. Lead candidates are using a proprietary novel capsid AAV2.N54. AAV2.N54 was developed through capsid engineering and showed significantly improved tropism to the macular retina over wildtype serotypes and AAV2.7m8 in mice, rabbits, pigs, and non-human primates and had the ability to detarget the ciliary body. AAV2.N54 was identified through multi-species screening in mice, pigs, rabbits, and monkeys. The Saf AAV manufacturing platform employs a closed AAV production system using a virus-free Sf-9 cell culture inoculated with recombinant **baculoviruses**.

Capsida Biotherapeutics is developing engineered AAV capsids that can effectively cross the blood-brain barrier (BBB) while minimizing off-target transduction. Capsida applied its high-throughput, non-human primate (NHP)-based AAV engineering platform for the directed evolution of an AAV9 capsid library and has generated capsids that overcome the limitations of these early gene therapy approaches. Capsida has developed engineered capsids that transduce >70% of neurons brainwide, generating a significantly increased therapeutic index. Capsida manufacturing capabilities are based on a **HEK 293** platform.

antibody selectively binds toxic TDP-43 aggregates and clears them from the cytoplasm. Subsequently, it restores the essential function of TDP-43 in the nucleus. VTx-002 is currently in the pre-clinical testing phase. The company prepares to submit an investigational new drug (IND) application for its lead candidate, VTx-002, for sporadic amyotrophic lateral sclerosis (ALS) before the end of 2025 and enter clinical development in 2026 (Press Release Apr 01, 2025). The Company has recently received favorable FDA feedback regarding the sufficiency of the pre-clinical data package, CMC requirements, and the proposed clinical protocol (Press Release Dec 16, 2024).

TAR-DNA binding protein-43 (TDP-43) is necessary for the correct processing and transport of multiple mRNA's that are essential for neuronal survival. Cytoplasmic mis-localized, misfolded or aggregated TDP-43 has been implicated in the pathogenesis of >97% of ALS patients. VectorY has confirmed that iPS-derived ALS motor neurons exhibit TDP-43 pathology. The Company has developed a library of single-chain variable fragments (scFv), named 'VecTabs', which are designed to exclusively bind to the misfolded, toxic TDP-43, while leaving the native TDP-43 functional. New data show that TDP-43-targeting intracellular VecTabs can effectively clear (large) TDP-43 aggregates from U2OS cells. In addition, iPS-derived ALS motor neurons were efficiently transduced with AAV to express TDP-43 VecTabs in a dose-dependent manner (Press Release June 02, 2022).

Duarte et al. (2022) presented that VectorY has developed a therapeutic strategy for ALS of AAV5-delivered scFv's (Vectorized Transformative Antibodies, VecTabs®) expressed as an intrabody targeting aggregated TDP-43 (α-TDP-43 VecTab). Induced pluripotent stem cells, derived from ALS patients, were combined with microfluidics for modelling ALS phenotypes as a screening platform for scFv efficacy. Pathological ALS hallmarks such as protein aggregation, impaired mitochondrial function and neurotoxicity were evaluated in advanced *in-vitro* models. Furthermore, they investigated the potential of scFv therapy in recovering gene expression changes in ALS, which are known to contribute to disease phenotypes. VecTabsVR effectively reduced intracellular TDP-43 aggregates, improved mitochondrial function, and reversed neuronal toxicity in ALS motor neurons (MNs).

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