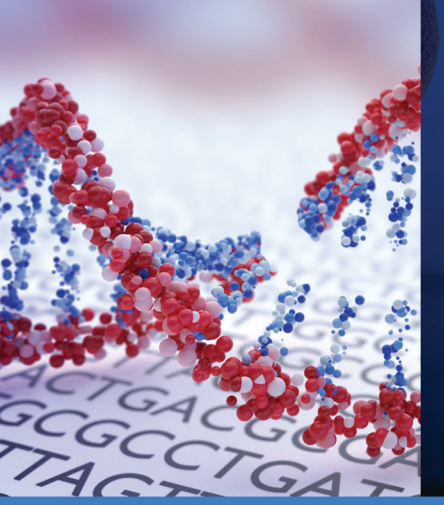


On the Transformative Potential of **Advanced Therapeutics in Rare Disease**

With the US Food and Drug Administration (FDA) approval of the first gene and cell therapy drugs last year, the broad class of Advanced Therapeutics (ADVTX) are primed to become progressively important in rare disease treatment algorithms and evolve into standard-of-care (SoC) therapies. Such approaches will be especially impactful to patients with genetically driven pathologies as therapeutic intervention transforms from phenotypic management to genotypic correction of the underlying deficiencies. The use of these novel therapeutic platforms will become an increasingly practical and attractive strategy for targeting rare and monogenetic disorders. In many cases, ADVTX may represent more efficacious and convenient solutions for patients than established conventional chronically administered small molecules and biologic drugs.

ADVTX Are Novel Medicines Based on Genes, Tissues, or Cells

Gene Therapy delivers nucleic acid payloads to control or repair gene expression at the DNA level. The following therapeutic strategies are currently being explored:

- **Gene Augmentation:** Delivery of functioning gene to complement inherited loss of function mutations (applicable to recessive alleles)
- **Gene Editing:** Repair/modification of a patient's genome by insertion, deletion, or site directed modification of mutated DNA (applicable to recessive mutations, but also dominant gain of function mutations)
- **Gene Knockdown:** Inhibition of detrimental gene expression (applicable to dominant negative mutation)

The Promise of ADVTX

The transformative promise of ADVTX is to offer the remarkable potential of a one-time curative treatment for patients with genetically driven rare disease, in many cases providing a lifesaving long-term survival advantage or dramatically improved quality of life (QoL), activities of daily living,

CONTRIBUTORS

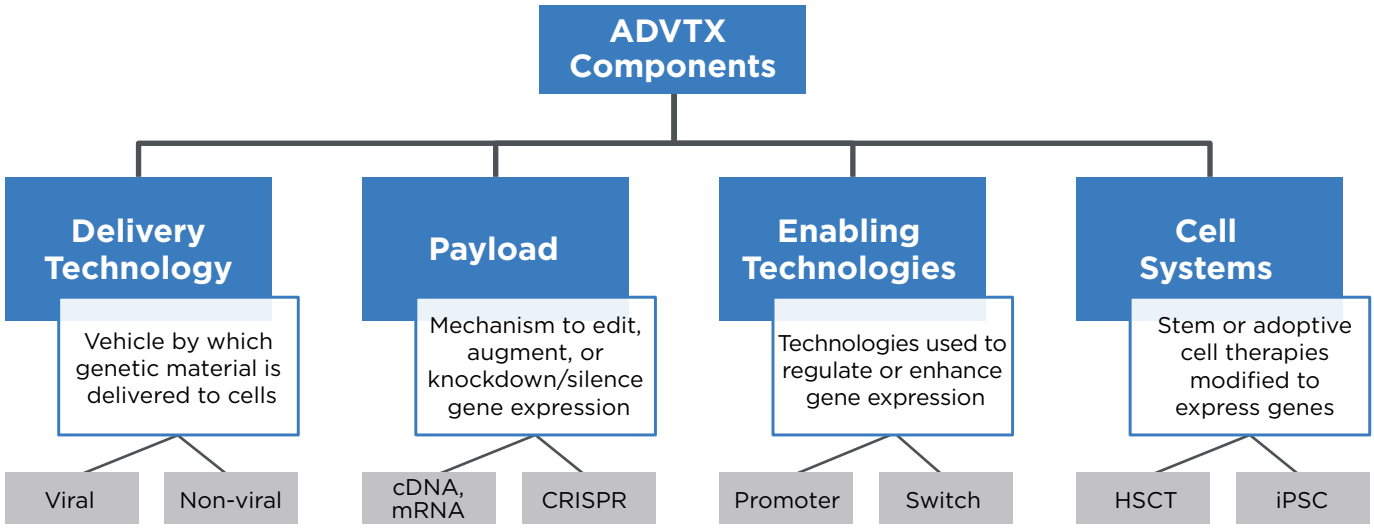
Brent W. Osborne, PhD
Senior Consultant

Akash Katakam
Senior Research Analyst

Michael C. Rice, MS, MBA
Principal
Rare Disease Practice Lead
Advanced Therapeutics Practice Lead

and avoidance of expensive conventional chronic medical treatment. Today, many patients who suffer the sequelae of rare disease are managed on a complex SoC that provides merely palliative relief. Management often requires lifestyle modifications, dietary limitations, and restricted physical activity coupled with a complex treatment regimen of symptomatic pharmacotherapies. This is a burdensome process that can confer severe QoL impacts for both patients and caregivers. In rare disease areas where there are approved conventional disease modifying medicines such as protein replacement therapy and substrate reduction, chaperone, and/or other small molecule strategies, ADVTX platforms present a significant threat to individual commercial drug franchises and are poised to disrupt entire therapeutic classes.

The Major Components of ADVTX Are More Complex Than Conventional Therapeutics



Note: CRISPR = clustered regularly interspaced short palindromic repeats; HSCT = hematopoietic stem cell transplantation; iPSC = induced pluripotent stem cell

Validation of ADVTX Platforms

As increasing evidence is established validating the efficacy, durability, and safety profile for certain adeno-associated viral (AAV) and lentiviral gene transfer vectors, therapeutic development is accelerating for additional diseases using these established platforms. However, despite the transformative potential of ADVTX, enthusiasm across rare disease communities has been tempered as setbacks have occurred with both novel platforms and specific disease applications using the more validated AAV and lentiviral vectors. For example:

- Sangamo Therapeutics' Zinc Finger Nuclease program in MPS-II (*SB-913*) highlights the challenges with *in vivo* gene editing and suggests that this approach is still nascent and not yet ready for prime time. Sangamo has demonstrated proof of concept via liver biopsy that gene integration is possible; however, their approach has thus far failed to show therapeutic levels of iduronate 2-sulfatase (IDS) expression (i.e., no measurable increase in plasma IDS activity, nor measurable reduction in urinary glycosaminoglycans).

- AVROBIO's *ex vivo* lentiviral program in Fabry disease (*AVR-RD-01*) has been plagued by decreasing vector copy number after initial dosing, causing some to wonder if a continued decline will lead to α-galactosidase A (AGA) expression falling below therapeutic levels. AVROBIO executives are beginning to posit that vector copy number appears to be stabilizing and a recent analysis reports several patients having stable levels of AGA above the diagnostic range with associated reductions in substrate and metabolite levels. Additionally, at least 1 *AVR-RD-01*-treated patient is reported to have to suspended SoC treatment with enzyme replacement therapy.

Company	Mkt Cap	Asset:Indication	Modality	Phase	Partners
Sanofi	$111.7B	*Fitusiran*:Hemophilia A and B	RNAi	P3	Alnylam
Biogen	$64.5B	*Spinraza*:SMA	Antisense	Mkt	Ionis
		BIIB087:X-linked Retinoschisis	AAV	P2	AGTC
		BIIB080:Alzheimer's	Antisense	P1	Ionis
Shire/Takeda	$61B	*SHP654*:Hemophilia A	AAV	P1/2	Chatham Therapeutics
Vertex	$44.8B	*CTX001*: Beta-thalassemia	HSC	P1	CRISPR Therapeutics
		CFTR-mRNA: Cystic Fibrosis	mRNA	PC	
Alexion	$27.5B	*Unnamed*:Unnamed	Unknown	PC	Dicerna
Biomarin	$17.2B	*BMN 270*:Hemophilia A	AAV	P3	-
		BMN 307:PKU	AAV	PC	-
Alnylam	$8.7B	*Onpattro*: ATTR amyloidosis	RNAi	Mkt	-
Ultragenyx	$2.7B	*DTX301*:OTC deficiency	AAV	P1	Dimension Therapeutics
		DTX401:GSD type 1a	AAV	P1	
Amicus	$2.1B	*CLN6 gene therapy*:Batten	AAV	P2	Celenex
		AAV gene therapy: Niemann-Pick C	AAV	PC	
		AAV gene therapy:Wolman	AAV	PC	
GW Pharmaceuticals	$62B	-	-	-	-
Recordati	$7.0B	-	-	-	-
Horizon Pharma	$4.5B	-	-	-	-
Retrophin	$0.9B	-	-	-	-

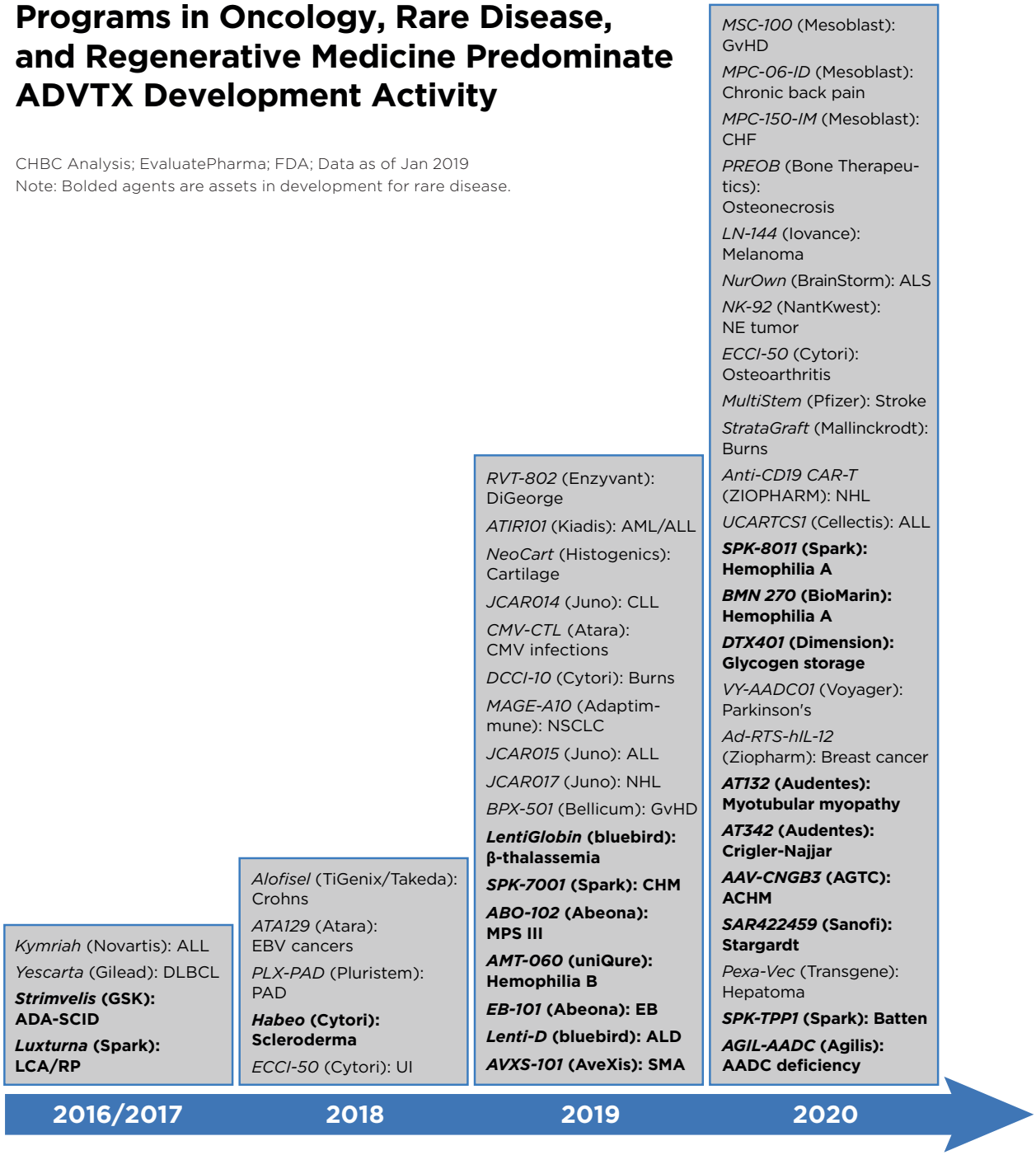
Note: RNAi = RNA interference; Antisense = antisense oligonucleotide; Data as of February 2019

Near-term Impact of ADVTX

Gene and cell therapies are already having a disruptive impact across several rare, genetically driven diseases, with a few approved and recently filed products, as well as several late stage assets with encouraging clinical data. Patients are seeking enrollment in these paradigm-shifting trials, demanding to participate in active treatment arms in higher dose escalation cohorts challenging the ethics of clinical trials design. The FDA is preparing for a significant influx of new ADVTX activity, with some estimating upwards of 200 annual IND filings by 2020 and an expected 10 to 20 ADVTX approvals per year by 2025.

Programs in Oncology, Rare Disease, and Regenerative Medicine Predominate ADVTX Development Activity

CHBC Analysis; EvaluatePharma; FDA; Data as of Jan 2019
Note: Bolded agents are assets in development for rare disease.



Approximate Approval Timelines From Anticipated FDA PDUFA Dates

ADVTX Are Already Improving the SoC Across the Landscape of Several Rare, Genetically Driven Diseases

Spark Therapeutics' *Luxturna*: FDA-approved (December 2017) and marketed for patients confirmed to have a rare form of inherited vision loss: biallelic *RPE65* mutation-associated retinal dystrophy. *Luxturna* was the first US-approved gene therapy and alters progression of vision loss in patients who may otherwise be blind for life. While treatment with *Luxturna* does not restore visual acuity to normal levels, it does retard the progressive loss of vision inherent to the pathology of the disease. Interestingly, a novel clinical endpoint called multi-luminance mobility test (MLMT) was built into in clinical studies of *Luxturna*. MLMT was designed to assess a patient's ability to navigate in varying levels of light, including low light, and is intended to evaluate a real-world consequence of living with this form of retinal dystrophy. *Luxturna*-treated patients showed a mean improvement in MLMT score which was sustained for greater than 12 months, suggesting that some QoL improvements may accompany *Luxturna's* ability to slow disease progression. While MLMT is novel and has not yet been correlated to outcomes in the real world, this case highlights the FDA's willingness to work with developers in designing unique trial designs for ADVTX in rare disease populations.

AveXis' *Zolgensma* (previously *AVXS-101*): Gene therapy under priority review (December 2018) as a potential one-time treatment for type 1 spinal muscular atrophy (SMA1). A final regulatory decision anticipated in May 2019. SMA is a genetically defined neuromuscular disease resulting from a mutation in the *SMN1* gene. This genetic lesion leads to a loss of motor neurons, progressive muscle weakness, movement deficiencies, and paralysis. If untreated, mechanical ventilation is required and most patients succumb to the disease by the age of 2. SMA patients do have an approved therapy that can improve symptoms (Biogen's *Spinraza*); however, this treatment requires chronic intrathecal dosing every 4 months, and a return to relatively normal muscle function is not achieved. *Zolgensma* offers the promise of a single-dose treatment with curative potential for SMA1 patients by providing a functional copy of the mutated *SMN1* gene. Results from pivotal studies were highly encouraging with most patients avoiding the need for mechanical ventilation, and the majority being able to sit upright unassisted for an extended period of time, a remarkable achievement given outcomes with current SoC. The SMA community is optimistic for an imminent FDA approval and in the long-term durable benefits of *Zolgensma*.

Where is the Next Disruption in Rare Disease SoC Likely to Happen?

Hemophilia and its large, mature clotting factor replacement market may soon be disrupted by late stage ADVTX programs. Hemophilia is a clotting factor deficiency caused by mutations in either the *F8* or *F9* genes, resulting in low expression of *factors VIII* or *IX*, respectively. Hemophilia patients lack the ability for normal clot formation, causing even minor bleeds or bruises to have potentially life-threatening consequences. On-demand and prophylactic factor replacement therapy consisting of an intravenous infusion of clotting *factor VIII* is the current SoC for hemophilia A (*factor VIII* deficiency), with several long-acting recombinant versions having recently entered the market. Despite advances in the field of replacement therapies, significant unmet need remains, as illustrated by a high frequency of breakthrough bleeds and factor augmentation required even for less severe incidents (e.g., falling down). Several ADVTX for hemophilia have demonstrated clinical proof of concept and are continuing to advance through the clinic. BioMarin has emerged with the leading approach in hemophilia A with *BMN 270* (*Valoctocogene roxaparvovec*), a virally delivered *factor VIII*-encoding gene with the aim of a single administration providing a long-lasting increase in *factor VIII* expression. If successful, BioMarin is poised to eliminate the need for hemophilia A patients to receive

"It's so important for new developments to keep happening. My son is on his fourth port and will need another as his veins are too terrible to go into every day. The idea that a product wouldn't really require factor VIII replacement would be tremendous. This would give him his life back and that would be amazing!"

– parent of hemophilia patient

chronic factor replacements by maintaining consistent *factor VIII* expression levels and eliminating the need for supplemental infusions. With an accelerated approval filing decision anticipated in the second half of 2019, the hemophilia community may soon have a transformational therapy in their treatment armamentarium. Patients and caregivers will then have to decide which treatment approach is best. Historically, there has been a lot of hesitancy on the patient side toward switching treatments, even for improved efficacy and greater convenience.

"I would be hesitant to switch over to a new brand that I have never heard of or that it's not known in the hemophilia industry."

– hemophilia patient

Sickle cell disease (SCD) may also be one of the next rare diseases to benefit from the promise of ADVTX. SCD is a hemoglobinopathy that manifests in a collection of overlapping clinical syndromes resulting from mutations in the *HBB* gene, which encodes for β-globin. Mutated β-globin perturbs the hemoglobin complex under hypoxic conditions leading to distorted, sickle-shaped red blood cells (RBCs) that die prematurely, thus leading to anemia. Additional SCD complications include aggregation of sickle RBCs, which can cause vaso-occlusive crisis, widespread pain, acute chest syndrome, stroke, fibrosis, end-organ failure, and death. Presently, the only potentially curative treatment is allogeneic HSCT (matched sibling donor allo-HSCT); however, this approach is rarely used due to donor-recipient eligibility challenges and overall risks of the procedure. bluebirdbio's *LentiGlobin* program is aiming to bring a broadly effective, durable treatment option to the SCD community. Currently in phase 3 development for β-thalassemia (a hemoglobinopathy affected by mutations in the same gene) and in phase 1/2 for SCD, *LentiGlobin* is a therapy that uses lentiviral-transduced version of a patient's own CD34+ hematopoietic stem cells to deliver a functional copy of the β-globin-encoding *HBB* gene. An NDA submission to the FDA for β-thalassemia is expected by the end of 2019, with the phase 1/2 proof-of-concept study in SCD positioned for a data read-out in early 2021. But again, despite the enthusiasm, patients and caregivers maintain a sense of caution as they consider receiving treatment with these new ADVTX modalities and their, as of yet, undefined long-term therapeutic durability and safety profiles.

"...by phase 2 we can look at the adverse events from phase 1 and ask, 'am I willing to put up with this?'"

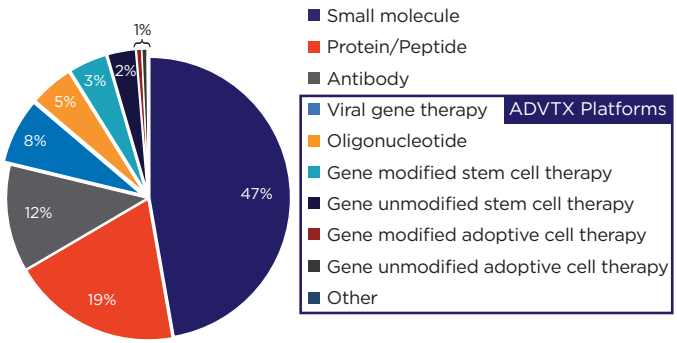
– SCD patient

> ***"The risk cannot be greater than the reward because we already go through so much."***
>
> – SCD patient

Concluding Remarks

The transformative potential of ADVTX has attracted increasing interest from drug developers. Several hundred agents are presently in clinical development for rare diseases (exclusive of oncology indications), 20% of which can be classified as being an advanced therapeutic modality. This number is expected to increase, leading to additional pressures on target product profiles and the commercial potential of conventional medical therapies. However, given the breadth of rare disease, white space is still significant, leaving ample opportunities for new drug development in relatively uncompetitive disease areas. **Companies that have built rare disease franchises comprised of conventional therapeutics are advised to evaluate the ever-growing and emerging ADVTX landscape as a real threat to their portfolios. Developers of conventional rare disease therapies are further advised to consider ADVTX as potential growth opportunities as these new platforms become derisked and gain acceptance among healthcare providers and patients.**

WW Clinical-stage Rare Disease Pipeline by Therapeutic Modality*



CHBC Analysis; Cortellis Clarivate Analytics; Data as of January 2019
*Exclusive of infectious disease and cancer indications
**Other includes microbiome/bacterial replacement agents

Unique Challenges Exist to Sustain Growth Beyond the Life Cycle of Initial ADVTX Products

While the curative potential of many ADVTX programs offers patients real hope for transformative improvements in QoL, the single-dose, one-time therapy model places additional constraints on the ability of biopharma to sustain revenue growth in disease areas where their patients are cured and don't require chronic therapy. Initial uptake into the prevalent pool is soon tempered once the bolus of symptomatic patients is cured. Future sales come from only very few numbers of incident patients entering treatment pool. Thus, it is recommended to establish novel up-front pricing strategies and continue to build diversified pipelines in order to maintain a relevant footprint in rare disease and ensure sustainability. Furthermore, given the relative immaturity of the space, biopharmas will face a myriad of new challenges if they are to successfully navigate the development, regulatory, and commercial landscapes.

Rare Disease Companies, Whether or Not Already Invested in Novel Therapeutic Modalities, Will Face Unique Business Challenges as They Consider the Transformative Potential of ADVTX

- Refinement of rare disease franchise strategy
- Evaluation of novel platforms and technologies
- Assessment of threat novel ADVTX platforms pose to conventional therapeutic franchises
- Identification and prioritization of white space opportunities within genetic disease landscape
- Elucidation of rare disease patient journey and real-world QoL issues
- Communication of value story to stakeholders: patients, physicians, and payers
- Integration of new expertise and processes within organization
- Execution of launch strategy of ADVTX in an environment of established SoC

CELLO HEALTH

For more information on how to unlock the potential of rare disease assets, contact the Cello Health team.

CELLO HEALTH CONSULTING

STEVE MATHER
President

smather@cellohealth.com
Cell: +44 774 267 2225

CELLO HEALTH BioCONSULTING

MICHAEL C. RICE
Principal
Rare Disease Practice Lead
Advanced Therapeutics Practice Lead

mrice@cellohealth.com
Ph: 973 805 5001 x5249

CELLO HEALTH COMMUNICATIONS

SUZANN SCHILLER
Executive Vice President,
Strategic Collaborations

sschiller@cellohealth.com
Ph: 215 504 5082 x103

CELLO HEALTH INSIGHT

ANGELA WHEELER
President, USA

awheeler@cellohealth.com
Ph: 847 983 3686

Philadelphia ■ Boston ■ New York ■ Chicago ■ San Francisco ■ London ■ Farnham

www.cellohealth.com

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