RNA-Targeted Novel Drug Modalities

Based on RNA Editing, Epitranscriptomics, Direct RNA Targeting, Splicing Modulation, Translation Regulation, lncRNA & regRNA Targeting & More:

a landscape analysis of technologies, targets, business and financing from an industry perspective

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Previously, the Company followed the FDA's recommendation and collected, using newer technologies via procedures and methods that the Company designed, dystrophin data in a new study, Study 045, and announced the results of Study 045 in February 2021. Study 045 **did not meet its pre-specified primary endpoint.**

Translarna net product revenues were $ 236 million for the full year 2021, compared to $ 191.9 million for the full year 2020. These results were driven by treatment of new patients, continued high compliance, and geographic expansion (Press Release Feb 22, 2022). Translarna sales in the nine-month period ended on September 30, 2022 were US$ 232.8 mln. Full year 2022 sales are expected to be about US$ 310 mln.

3.1.1 Companies

The key corporate data characterizing the six companies active in the field of mRNA translation regulation are summarized in Tables 1a and 1b and presented in alphabetical order by company name. Detailed company profiles can be found in the following section "Company Profiles" of this chapter.

Table 1a: Key Corporate Characteristics of Translation Regulator Companies

Company	**Anima Biotech**	**Ceptur Therapeutics**	**eFFECTOR Therapeutics**
Location(s)	Bernardsville, NJ, USA; Israel	Hillsborough, NJ, USA; New York; Copenhagen	San Diego, CA, USA
Founding Year	2014	2021	2012
Technology	mRNA Lightning	U1 Adaptor Technology	Selective Translation Regulator Inhibitors (STRIs)
Source of Technology	University of Pennsylvania	Silagene & Rutgers University, New York	University of California, San Francisco
Private/Public (market cap)	Private	Private	Public (market cap of $ 22 mln)
Total Funds Raised (US$ mln)	180	75	US$ 247.5 mln
No. of Employees	58	13	25
Collaboration Agreement Partner	Eli Lilly; Takeda Pharmaceutical	No	Pfizer
No of Pipeline Projects	18 (mostly discovery stage)	3	2 clinical, 1 preclinical
Highest R&D Phase	Preclinical	Preclinical	II

Cap, capitalization

Table 12: Financing of mRNA Splicing Modifier Companies

Company	Technology	Round (Year)	Amount (US$)	Investors
Chordia Therapeutics	RNA Maturation Process Modifiers	Series A (11/2017)	JPY 1.2 bln	Takeda Pharmaceutical Co, Kyoto University Innovation Capital ("KYOTO-iCAP", Mitsubishi UFJ capital and SMBC venture capital
		Series B (03/2019)	JPY 3.0 bln	KYOTO-iCAP, JAFCO, Shinsei Capital Partners, Mitsubishi UFJ Capital, SMBC Venture Capital, Nippon Venture Capital
		Series C (5/2022)	JPY 4.0 bln	Japan Growth Capital Investment Corp., UTokyo Innovation Platform Co., MEDIPAL Innovation Fund, Shinsei Capital Partners, Ltd., Nippon Venture Capital Co., Ltd., and others
Envisagenics	SpliceCore	Seed (11/2017)	2.35 mln	Third Kind Venture Capital (3KVC), Cosine, LLC (NYC biotech investors), Dolby Family Ventures, Dynamk Capital, NY Empire State Development (ESD), SV Angel.
		Series A (09/2021)	19.2 mln	Red Cell Partners. Microsoft's M12, Madrona Venture Group, Third Kind Venture Capital, Dynamk Capital, Empire State Development's VC arm, New York Ventures.
Panorama Medicine	PAN-ACEA	Seed 1 (04/2019)	3.7 mln	WI Harper Group, Delian Capital, Zhen Fund
Rgenta Therapeutics	Proprietary platform	Seed (04/2020)	20 mln	Boehringer Ingelheim Venture Fund, Matrix Partners China, Kaitai Capital, Legend Star Fund
		Seed 2 (05/2021)	18 mln	Lilly Asia Venture (LAV), Vivo Capital, Kaitai
		Equity (02/2022)	8.9 mln	Not disclosed
Skyhawk Therapeutics	SkySTAR	Seed (01/2018)	8 mln	Tim Disney, the Duke of Bedford, Alexandria Venture Investments, & others
		Equity (06/2018)	40 mln	Alexandria Venture Invest., GreatPoint Ventures, ShangPharma Innovation and Agent Capital, Tim Disney, the Duke of Bedford, the Reilly Family and others
		Equity (09/2021)	133 mln	Fidelity Mgt & Res Co., GreatPoint Ventures, Rock Springs Capital & others
Stoke Therapeutics	TANGO	Series A (01/2018)	40 mln	Apple Tree Partners (ATP)
		Series B (10/2018)	90 mln	RTW Investments, ATP, RA Capital Mgt, Cormorant Asset Mgt, Perceptive Advisors, Janus Henderson Investors, Redmile Group, Sphera Funds Mgt, Alexandria Venture Investments
		IPO (06/2019)	163.3 mln	NASDAQ

Table 17: Stoke Therapeutics' Pipeline of Antisense Oligonucleotides for Protein Upregulation

Product Name	Target / Mechanism of Action	Class of Compound	Company	Indication	R&D Stage
STK-001	To increase SCN1A mRNA expression and Nav1.1 protein levels	Antisense oligo-nucleotide (ASO)	Stoke Therapeutics	Dravet syndrome (epilepsy)	Ib/II
STK-002	Decrease in non-productive OPA1 mRNA and increase in OPA1 protein	TANGO antisense oligo-nucleotide (ASO)	Stoke Therapeutics	Autosomal dominant optic atrophy (ADOA)	0
SYNGAP1 TANGO	Decrease in non-productive SYNGAP1 mRNA and increase in SynGAP protein	TANGO antisense oligo-nucleotide (ASO)	Stoke Therapeutics & Acadia Phar-maceuticals	SYNGAP1 syndrome	Res
MECP2 TANGO	Decrease in non-productive MECP2 mRNA and increase in correspond-ing protein	TANGO antisense oligo-nucleotide (ASO)	Stoke Therapeutics & Acadia Phar-maceuticals	Rett syndrome	Res

Stoke's first compound, **STK-001**, is in clinical testing for the treatment of Dravet syndrome, a severe and progressive genetic epilepsy. Stoke believes that STK-001, a proprietary antisense oligonucleotide (ASO), has the potential to be the first disease-modifying therapy to address the genetic cause of Dravet syndrome. STK-001 is designed to upregulate $Na_V1.1$ protein expression by leveraging the non-mutant (wild-type) copy of the *SCN1A* gene to restore physiological $Na_V1.1$ levels, thereby reducing both occurrence of seizures and significant non-seizure comorbidities. Stoke has generated preclinical data demonstrating proof-of-mechanism and proof-of-concept for STK-001. The MONARCH study is a Phase 1/2a open-label study of children and adolescents ages 2 to 18 who have an established diagnosis of Dravet syndrome and have evidence of a genetic mutation in the SCN1A gene. The ADMIRAL study is a Phase 1/2a open-label study of children and adolescents ages 2 to <18 who have an established diagnosis of Dravet syndrome and have evidence of a genetic mutation in the *SCN1A* gene. The primary objectives for the study are to assess the safety and tolerability of multiple doses of STK-001, as well as to determine the pharmacokinetics in

Ascidian developed a designer RNA discovery screening engine which enables high-throughput and non-biased lead optimization of RNA editing molecules. The screening platform has a capacity to test thousands of molecules in human cell culture and pre-clinical animal models.

Table 19: Key Features of Technologies in mRNA Trans-Splicing

Company	Technology	Features	Lead Compound
Ascidian Therapeutics	RNA Exon Editing	Precise post-transriptional editing of genes, resulting in full length functional proteins	ABCA4 retinopathy
Rznomics	Ribozyme Trans-Splicing Technology	RNA replacement enzyme (Ribozyme) delivered by AAV: high target specificity and efficacy, target accuracy & minimal off-target ability	RZ001
ViGeneron	vgAAV REVeRT	Novel engineered AAV capsids Reconstition via mRNA trans-splicing using dual vector approach for large genes	VG801

The core platform technology of Rznomics is based on a RNA replacement enzyme called Tetrahymena Group I ‘trans–splicing ribozyme’, which can edit target RNAs through simultaneous destruction and repair (and/or reprograming) to yield the desired therapeutic RNAs, thus selectively inducing therapeutic gene activity in cells expressing the target RNAs. Trans-splicing ribozymes are RNA-based catalysts capable of splicing RNA sequences from one transcript specifically into a separate target transcript. In doing so, a chimeric mRNA can be produced. Specificity is achieved by a specific RNA-sensing riboswitch and efficacy is achieved by dual function of RNA-cleavage & transgene induction.

Rznomics is partnering with CEVEC Pharmaceuticals for use of the CAP® Technology for the manufacturing of adenoviruses for gene therapy applications. CAP® Technology for the manufacturing of adenoviruses for gene therapy applications.

REVeRT, Reconstitution via mRNA trans-splicing, is ViGeneron’s next generation vector platform for transfer of large genes. Messenger RNA (mRNA) splicing is a very efficient cellular process for the seamless ligation of adjacent protein coding sequences, thereby enabling the formation of a functional gene product. REVeRT was developed to overcome the limited genome capacity of AAVs (<5Kb). REVeRT is the dual AAV vector technology

consist of a tandem array of 2-30 PPR motifs, each of which aligns to one nucleotide in the RNA target. The amino acid side chains at two or three specific positions in each motif confer nucleotide specificity in a predictable and programmable manner. Thus, PPR proteins appear to provide an extremely promising opportunity to create custom RNA-binding proteins with tailored specificity.

PPRs are known to play important roles in RNA processing, RNA editing, and translational regulation. Recent studies on the RNA recognition mode of PPR proteins revealed that one PPR motif interacts with one nucleotide. In addition, it was revealed that amino acids at three specific positions in a single motif serve to specify its binding base. Thus, mutation of these amino acids can cause a modification of the binding specificity of PPR motifs. Indeed, the engineered PPR motifs fused with various effector domains are shown to bind to and manipulate RNAs in a controlled manner (Imai, 2018).

EditForce has put a major effort into creating its own proprietary PPR editing tools for versatile editing of RNA molecules at the genomic scale, called “transcriptome editing.” This enables free research and implementation without the added legal risk down the road. Once perfected, PPR can edit not only DNA (like CRISPR), but also the RNA. This is a significant improvement because roughly 15% of all human diseases are caused by RNA splicing defects. Its technology platform, EditForce claims, has another advantage over CRISPR: PPR is free of patent disputes and licensing fees that often come with the application of CRISPR genome editing tools.

In a joint study of EditForce with the company’s scientific co-founder Professor Takahiro Nakamura, Kyushu University, they realized the world's first RNA-editing technology that enables RNA-editing bases to be changed from "U" to "C," and demonstrated that this technology works even in human cells (Ichinose, 2022). Currently, genome-editing technology has been developed rapidly, but the development of editing technology for RNA sequences remains limited. Especially as regards a single base substitution, technologies have been established to substitute "C" with "U" and "A" with "G," but the substitution of other bases is yet to be realized.

The study clarified the mechanism of RNA editing in plants to substitute "U" with "C. Base-editing technologies can be applied to the treatment of diseases caused by a single mutation, and "U-to-C" RNA-editing technology of the study opens up the possibility to edit mutations which could not have been the target with the existing technologies.

Partnering

In June 2020, AstraZeneca entered a collaboration agreement with Accent Therapeutics to discover, develop and commercialise transformative therapeutics targeting RNA-modifying proteins (RMPs) for the treatment of cancer (Press Release June 04, 2020). This collaboration focuses on targeting RMPs, proteins that control many aspects of RNA biology and represents a new approach for addressing the process disruptions that can lead to cancer and can cause resistance to medicines. It combines AstraZeneca's industry leading expertise bringing forward novel oncology medicines with Accent's expertise as a leader in the biology, target identification and drug discovery of RMP-targeting therapies.

Accent is responsible for research and development activities for a nominated preclinical program through to the end of Phase I clinical trials. Following completion of Phase I, AstraZeneca will lead development and commercialization activities for the program, with Accent having the option to jointly develop and commercialize with AstraZeneca in the US. AstraZeneca will also have the exclusive option to license worldwide rights to two further preclinical discovery programs, for which Accent will conduct certain preclinical activities.

Accent received an upfront payment of $ 55 mln and in the event that Accent elects to jointly develop the nominated program, is eligible to receive up to $1.1 billion in additional success-based payments across all programs in the form of option fees and milestone payments, as well as tiered royalties on net sales ranging from mid-single digit to low-double digits (Accent Therapeutics PR June 04, 2020) . In the event Accent opts into co-developing and co-commercializing the nominated program, profits and losses will be split in the US.

In October 2021, Ipsen and Accent Therapeutics signed an exclusive worldwide-collaboration agreement to research, develop, manufacture, and commercialize Accent's pre-clinical stage METTL3 program (Press Release Oct 18, 2021).

RNA modifying proteins (RMPs) are an emerging target class that control multiple aspects of RNA biology and represent a new approach for the potential treatment of various cancers. METTL3 is an RMP that has been validated pre-clinically as a novel therapeutic target for acute myeloid leukemia (AML). This collaboration combines Accent's expertise in RMP-targeting therapeutics with Ipsen's capabilities and proven track record in Oncology medicine development and commercialization.

Ipsen will pay up to $ 446 mln, comprising upfront payment as well as pre-clinical, clinical, regulatory, and sales-based milestone payments, plus tiered sales royalties ranging from mid-single digits to low-double digits.

8.4 Drug Candidate Profile

8.4.1 CMP-SCN; CO-3527

CAMP4 Therapeutics expects to enter the clinic with its lead candidate **CMP-SCN** to treat Dravet syndrome by mid-2023. Loss of function of the **SCN1A** gene leads to disease in the majority of Dravet Syndrome patients. The majority of Dravet syndrome patients are haploinsufficient for SCN1A. CAMP4's therapeutic strategy is to increase the expression of the wild-type allele to restore function.

CAMP4's candidate molecule, CMP-SCN, is designed to directly upregulate endogenous gene expression of SCN1A by targeting Natural Antisense Transcripts (NAT), a subset of regulatory RNAs ("regRNAs") that control mRNA transcription. Importantly, CMP-SCN targets the SCN1A-NAT that is expressed stably from birth to adulthood in order to achieve a consistent therapeutic effect irrespective of patient's age (Press Release Dec 03, 2021).

CAMP4 Therapeutics presented in vivo proof-of-concept data demonstrating the potential therapeutic utility of its lead **oligonucleotide** candidate for the treatment of Dravet Syndrome, a form of severe genetic epilepsy. CMP-SCN resulted in increased SCN1A mRNA expression both in vitro and in vivo. In a mouse disease model, treatment with a SCN1A NAT-targeting ASO led to an increase in SCN1A expression by 25%, which was accompanied by an approximately 70% decrease in the number, frequency, amplitude and duration of seizures. In CAMP4's recent non-human primate study, a low dose of CMP- SCN increased SCN1A protein expression 1.5-2 fold across multiple regions of the brain (Giagtzoglou, 2021).

CMP-SCN readily distributes into cynomolgus monkey CNS tissues, without evidence of adverse histomorphologic effects at the studied dose levels and dosing frequency (Brynczka, 2022).

RegRNAs act as gene-specific rheostats that can finely modulate gene expression upstream of mRNA transcription. CAMP4 applies its RNA Actuating Platform™ comprised of extensive proprietary epigenomic and transcriptomic data to map the regulatory genome and pinpoint regRNAs and the genes they control. Oligonucleotide drug candidates, or RNA Actuators™, are then screened and designed to precisely and potently engage gene-specific regRNA targets, but not to excessive levels that might generate toxicity. This approach is applicable to any genetic disease whereby even small increases in gene output can lead to meaningful therapeutic outcomes.