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The New Antibodies Revolutionizing Medicine

by Melanie Senior

Nucleic acid-based therapies are poised to revolutionize medicine – just as antibodies did thirty years ago.

While most biotechs struggle amid a prolonged funding winter, one group is doing just fine. We are not talking about artificial intelligence. Several start-ups working on nucleic acid-based therapies – a sprawling category that includes several flavors of RNA, anti-sense oligonucleotides (ASOs), aptamers (short single stranded oligonucleotides) and gene-edited cell and gene therapies – are raising bigger-than-average rounds. Four of the top five private financings in 2023 have been companies working on RNA, gene editing or manufacturing. ReNAgade Therapeutics and Orbital Therapeutics each pulled in over $250m; this year's biggest round yet brought ElevateBio, with its suite of gene- and cell-editing tools, more than $400m.

These groups are competing for dominance in a field of medicine whose scope, impact and value is being compared to that of therapeutic antibodies. Nucleic acid-based therapies, which harness genetic material – DNA and RNA – to treat or prevent disease, is "the next set of modalities that will change what medicines look like," says Amit Munshi, CEO of ReNAgade, drawing a parallel between these therapies today and antibodies in the early 2000s. Antibodies are now worth over $300bn and include two of the top-selling drugs of all time, *AbbVie Inc.*'s recently genericized auto-immune drug Humira (adalimumab) and *Merck & Co., Inc.*'s cancer behemoth Keytruda (pembrolizumab). And they are still growing, as antibody-drug-conjugates (ADCs), bispecific antibodies, fragments and nanobodies enter the mix.

Nucleic acid-based therapies' transformative potential comes from a vastly bigger set of potential targets (including intracellular targets), more precise targeting mechanisms and more efficient development. Conventional small and large molecule drugs can only access a tiny proportion of disease-relevant proteins. Nucleic acid-based therapies, including RNA (the most versatile), work upstream to control which proteins – and how much of them – are produced in

the first place. RNA has many forms and functions besides messenger RNA (mRNA), the protein-production template thrust into the limelight by *Moderna, Inc.* and *BioNTech SE*/*Pfizer Inc.*'s successful COVID-19 vaccines. It can also tune gene expression. Small-interfering (si) RNAs can silence or destroy mRNA transcripts, and scientists have recently uncovered that RNA can also bind gene-regulating transcription factors. RNA can be catalyst, cell defence mechanism, and can even fold into 3D protein-binding structures, like traditional drugs. Furthermore, since RNA binds in a highly specific, predictable fashion via Watson Crick base-pairing, RNA-based medicines can be designed and produced faster and more efficiently than large and small molecules.

"In 10-15 years' time, RNA-based modalities will be the largest category out there," predicts Ansbert Gadicke, managing partner at MPM BioImpact, founder of ReNAgade and founding investor at *ElevateBio, LLC*. John Leonard, president and CEO of gene editing firm *Intellia Therapeutics, Inc.*, hails a "new era of medicine."

Niche For Now…

We are not there yet: most first-generation nucleic acid-based medicines treat rare, genetically defined disorders. *Ionis Pharmaceuticals, Inc.*/*Biogen, Inc.*'s and *Sarepta Therapeutics, Inc.*'s respective antisense oligonucleotides Spinraza (nusinersen) and Amondys (casimersen) for Duchenne's muscular dystrophy, *Alnylam Pharmaceuticals Inc.*'s RNA interference-based drugs such as Onpattro (patisiran) for hereditary transthyretin amyloidosis, Iveric Bio/Astellas' RNA aptamer avacincaptad pegol (Izervay) for geographic atrophy, an advanced form of age-related macular degeneration, and the 14 approved gene therapies treat rare conditions from beta thalassemia to spinal muscular atrophy/cerebral adrenoleukodystrophy.

No mRNA-based therapeutic has yet been approved.

But the scope and versatility of these categories is expanding as tools and knowledge progress. In just the last few months, there have been several important way-markers in the journey toward more widespread precision-designed medicines, some offering one-time – or much less frequently administered – treatments.

On November 16, *Vertex Pharmaceuticals Incorporated*'s/*CRISPR Therapeutics AG*' Casgevy (exagamglogene autotemcel) became the first CRISPR-edited therapy ever to be approved, for sickle cell disease and transfusion-dependent beta thalassemia. CRISPR-Cas9, a revolutionary gene editing technology uncovered barely a decade ago, uses a guide RNA molecule to direct molecular 'scissors' that can cut specific genes. In this case, a nick to the BCL11A gene enables re-activation of fetal hemoglobin production, radically improving outcomes for patients who lack functioning adult hemoglobin. Regulators were concerned about potentially harmful 'off-target' gene editing, though Vertex's analyses of such effects persuaded them that benefit outweighed risk.

Casgevy is a complex therapy: patients' hematopoetic stem cells must be extracted, edited *ex-vivo* and re-infused. Sickle cell disease is rare, even though it is one of most common genetic conditions. But as Timothy Opler, managing director at Stifel, notes in his weekly biopharma market update, "the exa-cel approval is about much more than a new drug for sickle cell." Casgevy is the first drug made from editing human DNA, rather than silencing genes, as in RNA interference, or altering how genes are 'read' by messenger RNA, as antisense oligonucleotide drugs such as Sarepta's Amondys do.

In vivo gene-editing approaches are not far behind: in October, Intellia Therapeutics received US FDA approval to begin Phase III trials of its *in vivo* CRISPR-edited ATTR amyloidosis with cardiomyopathy candidate, marking regulators' growing comfort with gene-editing. Other recent CRISPR-related advances allow individual DNA 'letters' – nucleotides – to be swapped in or out to control disease. Verve Therapeutics in November announced the first human data for its single base-pair edited drug candidate Verve-101, which deactivates the PCSK9 gene that controls 'bad' low-density lipoprotein cholesterol. The treatment uses CRISPR-Cas machinery including a guide RNA and mRNA to replace an adenine base with a guanine base in the PCSK9 gene sequence, turning off the gene and helping reduce LDL levels.

While most gene-editing approaches – including CRISPR – tend to cut DNA, some are more focused on 'pasting': Flagship-backed Tessera Therapeutics' gene writing technology uses RNA to write new or corrected therapeutic messages into the genome. It claims to be able to insert entire functional genes or bits of genes, using technology based on naturally occurring 'mobile genetic elements' that can re-arrange genes. The company in May 2023 presented preclinical proof-of-concept data across three rare diseases including SCD.

… But Going Mainstream

RNA-based modalities are now being investigated for more prevalent conditions. Programs for hypertension, high cholesterol, obesity, non-alcoholic steatohepatitis (NASH), Alzheimer's and Parkinson's disease all now feature in RNA and gene-editing pipelines – including at big pharma. (Novartis' RNAi drug Leqvio (inclisiran) is already approved for high cholesterol.)

Larger players are starting to buy into RNA and gene-editing based technologies – just as they did into antibodies two decades ago. Roche's July 2023 licensing of Alnylam's RNA interference-based hypertension candidate zilbesiran was one this year's biggest partnerships, worth $310m up-front; Eli Lilly paid a similar amount in upfront cash and equity this year for rights to *Verve Therapeutics, Inc.*'s base-edited gene therapies for atherosclerotic cardiovascular diseases. (Also see "*Eyebrows Raised As Roche Inks Cardiovascular Pact With Alnylam*" - Scrip, 24 Jul, 2023.)

The combined annual value of nucleic-acid focused deals and partnerships almost trebled from $15bn to $40bn in the five years to 2022, according to Evaluate Pharma. Other notable transactions include, in 2021, Novo Nordisk's $3.3bn purchase of RNAi-focused *Dicerna*

Pharmaceuticals, Inc., spanning chronic liver disease, NASH, type 2 diabetes and obesity, and Sanofi's $3.2bn acquisition of mRNA therapeutics company Translate Bio, looking to take that technology into immunology and oncology. (Also see "*RNAi Returns To Spotlight As Novo Nordisk Swoops For Dicerna*" - Scrip, 18 Nov, 2021.) (Also see "*Sanofi Goes All The Way In mRNA With Translate Bio Buy*" - Scrip, 3 Aug, 2021.)

"We've reached a pivotal moment where RNA medicines are poised to make a broad impact in the clinic," write University of Würzburg scientists Anke Sparmann and Jörg Vogel in the *September European Molecular Biology Organization (EMBO) Journal*.

The combined value of RNA- and DNA-based drugs is currently about $10bn. But by 2028, just 10 years after the first RNAi drug approval, Alnylam's Onpattro, it will hit over $60bn, according to Evaluate (*see Exhibit 1*).

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Solving Delivery

There have been setbacks. Several companies backed out of RNAi in 2016 after Alnylam halted a Phase III trial due to patient deaths. A cautious FDA has paused several gene editing programs, and gene therapy, too, like any new technology, has had ups and downs.

Chemical modifications have made RNA-based medicines more stable, potent and long-lasting (unmodified RNA has a short half-life). But their "giant limitation" remains delivery, says Munshi. Two key problems are getting RNA into cells, and getting into cells beyond the liver. RNA and DNA are hydrophilic and cannot cross hydrophobic cell walls without protection; they also face highly evolved cellular defence mechanisms designed to rebuff invaders. That is why RNA-based drugs are often packaged within lipid nanoparticles (LNP) – as for the COVID-19 vaccines – or conjugated with lipid molecules or sugars. (Gene therapies are usually packaged into adeno-associated or other modified virus carriers.) But LNPs' fatty packaging means most RNA medicines go straight to the liver, where they bind to the cholesterol carrier apolipoprotein-E (APO-E). "When you coat LNPs with lipids, the body views it as a low-density lipoprotein (LDL) particle," explains ReNAgade chief scientific officer Peter Smith, a veteran of Alnylam and Moderna.

The liver is an appropriate target for many diseases, but not all. ReNAgade is among those investigating different LNP coatings and electrical charge profiles, and different conjugation molecules, to direct binding to other cell types. It recently reported preclinical data showing successful mRNA delivery to mouse hematopoietic stem cells using a proprietary LNP,

potentially opening up treatments for larger blood and auto-immune conditions. Alnylam and partner Regeneron are using C16 lipid conjugates to deliver RNAi targeting amyloid precursor protein to the central nervous system, as a potential treatment for Alzheimer's disease and cerebral amyloid angiopathy. Munich-headquartered Ethris is using cationic (positively charged) lipidoids to deliver nebulized mRNA-based medicines directly to the lung. One of its lead mRNA candidates encodes type III interferon and is designed to reduce a range of viral asthma exacerbations by activating the innate immune system; another contains instructions for a ciliary motility protein required to clear airways and which misfunctions in patients with primary ciliary dyskinesia.

Immunogenicity is another hurdle facing RNA based medicines. Modifications to increase RNA stability and mRNA translation efficiency (how much protein is expressed), can trigger the host immune system. So can LNPs and other carriers.

Orna Therapeutics, Inc.'s circular RNA seeks to overcome these challenges – and more. Its one-step method for synthesizing large circular RNA – dubbed 'oRNA' – results in longer-lasting RNA (there are no 'ends' for degradation enzymes to attack) and does not require chemical modifications. This makes it less likely to trigger an immune reaction, and significantly cheaper to manufacture in large quantities. The format also generates 10-to-100-fold higher expression rates and is easy to package into LNPs, according to MPM's Gadicke. (Orna has a joint venture with ReNAgade and a collaboration with Merck & Co.) Flagship-backed Laronde (now part of Sail Biomedicines), ARCH Ventures-backed Orbital Therapeutics (which raised $270m in an April 2023 Series A) and Sweden's Circio Holdings ASA are among others working on circular RNAs.

Other biotechs are refining related modalities. Germany's *Secarna Pharmaceuticals*, for example, designs next-generation antisense oligonucleotides with higher target affinity and potency and lower immunogenicity, thanks to its "locked nucleic acid" (LNA)plus technology. Chemical modifications "lock" nucleotides into a high affinity conformation which is also more resistant to degradation. Using bioinformatics to rapidly screen and select optimal ASO candidates, Secarna has built an early pipeline of oncology and inflammation candidates, including an ASO targeting the checkpoint inhibitor programmed death-ligand 1 (PD-L1). Secarna's *ASOs have shown pre-clinical activity across several tissue and organ types beyond the liver, including blood, lung and CNS, where it has a research collaboration with Denali Therapeutics. The ASOs may also be combined* with conventional checkpoint inhibitors or other immune-modulating drugs to improve their activity, according to chief business officer Konstantin Petropoulos. Barcelona, Spain-based start-up *SpliceBio, S.L.*, meanwhile, is expanding the scope of gene therapies using a novel protein splicing system. The technology, based around engineered linker proteins called inteins, allows therapeutic genes too large to package into a single AAV vector to be split into two separate AAVs, and for the full-length protein to be reliably reconstituted inside the cell. (Also see "*SpliceBio CEO: The Route From US Academic To Spanish Gene Tech Entrepreneur*" - In Vivo, 17 Oct, 2023.)

Which modality works best will depend on the disease challenge in question. In some cases that may be a gene-silencing ASO or siRNA, in others it could be mRNA or gene-edited cells. That is why companies like ReNAgade are assembling the biggest possible toolbox and trying to reach as many tissue-types as possible. "You need the right tool at the right time for the right disease," says Munshi. "It may be to silence, edit, insert or interfere."

For Munshi, the obstacles facing RNA-based medicines are no different to those faced by antibodies. "I can literally hear the same conversations [around delivery, manufacturing and immunogenicity] about antibodies in the 1990s as we're having today." The challenges look hard in the moment, and it's not clear who the winners will be. Yet, zooming out, these efforts and investments are beginning to "completely change how we see medicine."

Bigger Than Antibodies?

The early impact of these approaches could include making cell therapies cheaper and less burdensome on patients and health systems. Orna is using its circular mRNA to deliver chimeric antigen receptor (CAR) instructions to T cells *in vivo* via what could be a handful of weekly injections, rather than the months-long cell extraction and re-infusion process required today for CAR-T cell therapies such as Novartis' Kymriah (tisagenlecleucel) or Gilead's Yescarta (axicabtagene ciloleucel). "*In vivo* gene editing is what we're most excited about," says Gadicke. Autologous cell therapies and CRISPR/Vertex's Casgevy breakthrough are great first steps, but "imagine a one-off cure for sickle cell disease."

As gene editing and RNA-based technologies progress and converge – including with adjacent capabilities across data science – they will continue to accelerate the scope and accessibility of genetic-based medicines.

The result could be a revolution in the therapy landscape "even bigger and faster" than that brought about by antibodies, according to Gadicke. Antibodies have many strengths, but they cannot get inside cells, and do not create new cellular functions. RNA-based modalities penetrate cells and enable drug developers to replace, repair or bring entirely new functions to them, such as adding a particular antigen receptor to T cells. And they can be "designed cheaply and quickly on a laptop."

The huge dollar value of antibody-based drugs stems in part from their high price tags relative to small molecules. The US Inflation Reduction Act recently made antibodies more attractive still by allowing longer exclusivity periods for biologic drugs than for small molecules before price controls kick in for top-selling Medicare products. Different RNA-based medicines may sit either side of that 'biologic; vs, 'chemical' line: Alnylam's siRNAs and other short fragments are classed as small molecules, while 'long' RNA – including coding mRNA – are not. Hence, long term, "our main focus will be on long RNA," says Gadicke, referring to ReNAgade and Orna. Clearly the legislation's impact on portfolio decision-making is not limited to late-stage pipelines.

Ultimately Gadicke sees these therapies being priced in line with antibodies. That is a bargain if the alternative is a $500,000 *ex vivo* cell therapy, but a significant cost burden if these medicines do become the dominant modality. Commercial challenges facing new RNA-based and gene-edited drugs – including how to price eventual one-time cures – remain to be addressed. But their potential is undisputed.