The Emerging Role of Nucleic Acid Therapeutics: Resuscitating Cardiovascular Drug Development with Disruptive Therapies

April 14th, 2020
mrice@cellohealth.com
Cello Health BioConsulting: Who We Are

♦ Cello Health BioConsulting is a knowledge-based consultancy deeply rooted in science; we often evaluate early stage programs before much, if any, clinical data is available. In the biopharma world, we are known for our “unconventional insight” – forward thinking, independent, objective strategic advice across all therapeutic areas.

♦ Cello Health BioConsulting provides strategic advice for corporate growth and partnering strategies, disease area selection, indication prioritization, opportunity search and evaluation, opportunity and landscape assessment, valuation and forecasting, early market access strategy and early value profile development.

♦ Cello Health BioConsulting has a strong and broad network of leaders and influencers across biotech and pharma, which provides a deep understanding of next wave issues, the competitive and market landscapes, and keeps us well-informed and ahead of industry trends.
CHBC Rare Disease and Advanced Therapeutics Practice
Experience & Expertise

Rare Disease and Advanced Therapeutics (ADVTX)

Unique Experience and Insights

• RARE DISEASES and ADVANCED THERAPEUTICS platforms cross all therapeutic areas.
• Specialist in evaluating, prioritizing and valuing therapeutic platforms for rare monogenetic and multifactorial disorders.
• Conventional small molecule, biologic and nucleic acid therapeutics
• Gene transfer, editing, cell systems towards
• Guide R&D investment from preclinical through proof of concept, eventual regulatory approval and market launch into new therapeutics markets
• Disruption of mature markets such as hemophilia, oncology and through regenerative medicines.

Practice Leaders:
Michael Rice, Principal
Brent Osborne, PhD, Senior Consultant
EMAIL: CHBCADVTX@cellohealth.com

Sample Project Work

• ½ projects involve rare genetically defined tumors (targeted SMI, mAbs and Adoptive Cellular Therapies, Oncolytic viruses, etc.)
• The other half is distributed across hundreds of rare non-malignant diseases evaluating the potential of conventional therapeutics and gene/cell therapies across hundreds of monogenetic diseases.
• We have provided independent assessments and strategic advice for virtually every vector, payload strategy and enabling technologies and devices.
• We have established core domain resources on such diseases and platforms which is leveraged for client sponsored research.
Unique Experience and Insights

• CARDIOVASCULAR DISEASE has historically been one of our largest areas of business. We have provided independent assessments and strategic advice for hundreds of development-stage conventional and regenerative therapies, and interventional devices.

• METABOLIC DISEASES: We have performed hundreds of opportunity assessments of products for diabetes, obesity and associated endocrine disorders.

Sample Project Work

• Evaluation of therapeutic approaches to: Dyslipidemia, Atherosclerosis / CAD, Genetically defined lipid disorders, Regenerative Medicine, Heart Failure, Dysrhythmia/A-Fib, ACS / Myocardial Infarction, Hypertension, Peripheral Vascular Disease, Thrombosis and Restenosis, Reperfusion Injury, CV related Metabolic Disorders

• Specific metabolic targets in which CHBC has amassed substantial knowledge include: GLP-1 mimetics, SGLT2 inhibitors, DPPIV inhibitors, PCSK9 antibodies, HDL mimetics, and others.

Practice Leaders:
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Brent Osborne, PhD, Senior Consultant
Ed Saltzman, Executive Chairman
Save The Date! May 5th-6th Cancer Progress is going Virtual!

Please remember to save the dates May 5th and 6th while we continue to plan for a Virtual Cancer Progress Conference.

As we make our final plans to run this virtually, we will continue to update our website and send additional information as soon as it becomes available.

Stay safe and look forward to meeting virtually!

Since 1989, Cancer Progress is the only oncology conference that invites a discussion of scientific progress within the context of development, regulatory, clinical, commercial and investment perspectives in two days of interactive dialogue. Pivotal topics, frank discussions, vigorous debate, lively audience participation and generous networking throughout the meeting during breaks, luncheons, reception and dinner combine to make this a highly impactful conference.

Our 31st Annual Meeting on May 5-6, 2020 will provide an unsurpassed learning experience for participants in quality of information, coverage of issues, and value of professional contacts. The quality of the speaking faculty is a major contributor to the popularity and value of this conference.

www.cancerprogressycellohealth.com
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Arrowhead Pharmaceuticals

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miRagen

Barry S. Ticho, MD, PhD, FACC
Chief Medical Officer
Stoke Therapeutics
RNA Therapeutics Landscape
Nucleic Acids Therapeutics Provide a Conventional Drug-Like Advancement Towards Enabling Genotypic Modulation of Disease Pathophysiology

| Drug delivery, formulation and enabling platforms: technology (non-viral and viral) improvements in biodistribution, PK and PD, and devices |
|---|---|---|---|
| Phenotypic | Genotypic |
| 1980s | 1990s | 2000s |
| Peptides and Protein Therapeutics | Antibodies | Nucleic Acids | Gene Correction & Augmentation | Cell Therapy & Regenerative Med |
| • Plasma/tissue derived proteins | • Plasma Polyclonal Igs | • Immune Modulators | • Viral vectors | • Autologous/allo-geneic cell therapy |
| • Recombinant Proteins | • Monoclonal antibodies | • Antisense Oligonucleotides | – Retro/ | • Other cells: |
| – Clotting factors | • mAB fragments | • Exon skipping | – Lentiviral | – e.g. ES, IPS |
| – Cytokines | • Scaffolds | • RNAi (siRNA, saRNA, shRNA) | – Adv, AAV | • Mitochondrial transfer |
| – Hormones | • Darpins | • mRNA | • Non-viral | • Devices |
| – Growth factors | • Intrabodies | • miRNA | – Plasmids/ | – Encapsulation |
| • Peptides | • Diabodies | • IncRNA | – Fragments | – Scaffolds |
| • Enzyme Replacement | • Bispecific mABs | • Aptamers | • Gene editing with | – Implants |
| • Protein Degraders | • Bispecific T-Cell Engagers | • Ribozymes | Meganuclease | – Micro-organisms |
| | | | – Zinc Fingers | – Aphaeresis |
Oligonucleotide Therapeutics Have Long Held Promise, But Only Recently Are Gaining Significant Traction

Oligonucleotide Therapeutics: product of nearly 40 years of research and development.

- Steady incremental improvements have addressed multiple technological hurdles.
  - Duration of action, potency, toxicity (local and systemic), specific tissue delivery
- Approvals limited to rare populations and not yet translated to broad clinical cohorts
- Inclisiran and earlier stage antisense and RNAi drugs targeted for CVD
Progress in Oligonucleotide Based Drugs Enabled by DNA/RNA Chemical Modifications, Delivery Technology, Target/Indications Selection and Engineering to Fine Tune Therapeutic Index

- These consist of base modifications, sugar modifications, internucleoside linkage modifications, and conjugates of small and large molecules to essentially every position of a dinucleotide.
- Key formulations and conjugate strategies used in later stage clinical trials to enhance delivery.

https://doi.org/10.1016/j.cmet.2018.03.004
Leading Nucleic Acid Therapeutic Developers Have Deep Pipelines Leveraging Diverse Platforms

<table>
<thead>
<tr>
<th>Company</th>
<th>Lead NAT Candidate Status</th>
<th>Therapeutic Area*</th>
<th>Therapeutic Modality</th>
<th>Number of Programs in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ionis Pharmaceuticals</td>
<td>Marketed</td>
<td>Cardiovascular, Metabolic</td>
<td>ASO</td>
<td>46</td>
</tr>
<tr>
<td>2. WaVe Life Sciences</td>
<td>Phase 2/3</td>
<td>Neuromuscular</td>
<td>ASO</td>
<td>23</td>
</tr>
<tr>
<td>3. Alnylam Pharmaceuticals</td>
<td>Marketed</td>
<td>Metabolic</td>
<td>siRNA</td>
<td>21</td>
</tr>
<tr>
<td>4. ProQR Therapeutics</td>
<td>Phase 3</td>
<td>Sensory</td>
<td>ASO</td>
<td>17</td>
</tr>
<tr>
<td>5. Sarepta Therapeutics</td>
<td>Marketed</td>
<td>Neuromuscular</td>
<td>ASO</td>
<td>16</td>
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<tr>
<td>6. Dicerna Pharmaceuticals</td>
<td>Phase 3</td>
<td>Metabolic</td>
<td>siRNA</td>
<td>14</td>
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<tr>
<td>7. Biogen</td>
<td>Marketed</td>
<td>Neuromuscular</td>
<td>ASO</td>
<td>11</td>
</tr>
<tr>
<td>7. Quark Pharmaceuticals</td>
<td>Phase 3</td>
<td>Sensory</td>
<td>siRNA</td>
<td>11</td>
</tr>
<tr>
<td>8. OliPass</td>
<td>Phase 1</td>
<td>Neurology</td>
<td>ASO</td>
<td>8</td>
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<tr>
<td>9. Ribomic</td>
<td>Preclinical</td>
<td>Autoimmune/inflammatory</td>
<td>Aptamer</td>
<td>7</td>
</tr>
<tr>
<td>9. Silence Therapeutics</td>
<td>Phase 1</td>
<td>Hematology</td>
<td>siRNA</td>
<td>7</td>
</tr>
<tr>
<td>10. Arrowhead Pharmaceuticals</td>
<td>Phase 3</td>
<td>Hepatology</td>
<td>siRNA</td>
<td>6</td>
</tr>
<tr>
<td>10. AstraZeneca</td>
<td>Phase 2</td>
<td>Cardiovascular</td>
<td>mRNA</td>
<td>6</td>
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<tr>
<td>10. Idera Pharmaceuticals</td>
<td>Preclinical</td>
<td>Cardiovascular, Autoimmune/Inflammatory</td>
<td>ASO</td>
<td>6</td>
</tr>
<tr>
<td>10. Sylentis</td>
<td>Phase 3</td>
<td>Sensory</td>
<td>siRNA</td>
<td>6</td>
</tr>
</tbody>
</table>

Adis Insight, Clarivate Analytics Cortellis, *Note: Therapeutic area of lead candidate.
>100 Clinical Stage NAT Drugs Mainly Pursuing Neurology, Sensory and Cardiometabolic Disorders: *Half at P2 POC Value Inflection – 25 in Late Stage Development*

**NAT by Phase** *(n=458)*

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>383</td>
<td>84.0</td>
</tr>
<tr>
<td>Phase 1</td>
<td>13</td>
<td>2.9</td>
</tr>
<tr>
<td>Phase 2</td>
<td>12</td>
<td>2.6</td>
</tr>
<tr>
<td>Phase 3</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>PR/Registered</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Marketed</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**NAT by Therapeutic Area** *(n=465)**

- Neurology: 91
- Sensory: 57
- Neuromuscular: 55
- Autoimmune/Inflammatory: 52
- Cardiovascular: 47
- Metabolic: 29
- Hepatology: 27
- Dermatology: 25
- Respiratory: 25
- Unspecified: 10
- Hematology: 9
- Renal: 6
- Musculoskeletal: 4
- Rheumatology: 3
- Endocrine: 3
- Multisystem: 1
- Other: 1

*Note: Oncology and infectious disease indications have been excluded. *Note: Phase 1/2 agents are grouped with Phase 2, Phase 2/3 agents are grouped with Phase 3; **Note: Agents with multiple lead indications in different therapeutic areas were counted in each therapeutic area.*
CVD NAT Pipeline Biased Towards mRNA Knockdown (ASO/siRNA) – Competing with mAbs For Validated Targets Expressed in Liver and Creating New Markets for Novel Targets

Cardiovascular NAT by Lead Indication (n=53*)
- Lipid metabolism
- Hypertension
- Unspecified CVD
- Cardiac failure
- Vascular disease
- Ischemia
- Myocardial infarction
- Stroke
- Clotting/Thrombosis
- Atherosclerosis
- Hereditary angioedema
- Restenosis

Cardiovascular NAT by Modality (n=45)
- Antisense oligonucleotide
- siRNA
- Aptamer
- Undisclosed/Unspecified/Other
- miRNA
- mRNA

Cardiovascular NAT by Target (n=45)
- undisclosed
- PCG50
- Apol1
- AT1
- ANGPT1
- Apoe8
- ADAM1
- Chymase
- ENO1
- Factor XI
- Glycoprotein
- mnr1.2
- mnr1.8
- mnr2.7A
- MTP
- PKN
- SMURF1
- TLR4
- TTR

*Note: Assets with multiple lead indications were double-counted;
Pivotal Year for NAT Drugs as Numerous Products Grow the Rare Disease Market Beyond Rare Neuromuscular Disorders and Proteinopathies Setting Stage for Broader CVD Indications

Top 20 Nucleic Acid Therapeutic Products by WW Sales (2019 – 2024E)

Antisense/RNAi in development for CV indications

EvaluatePharma
Oligonucleotide Deals 2013-2020 (Based on Total Deal Value) indicate Upward Trend in Value

2013-2020 Nucleic Acid Therapy Total Deal Value and Number of Deals by Year (n=137, $M)

*Note: Number of deals includes deals with disclosed and undisclosed values
Upfront Payments and Overall Deal Size Increasing With Cumulative Validation of Modality

<table>
<thead>
<tr>
<th>Year</th>
<th>Company</th>
<th>Deal Type</th>
<th>Upfront Cash</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Medco (Licensor) Alnylam</td>
<td>Development and commercialization license</td>
<td>$25M</td>
<td>TMC took an exclusive global license to Alnylam’s RNAi candidates that block PCSK9.</td>
</tr>
<tr>
<td>2016</td>
<td>Amgen (Licensor) Arrowhead</td>
<td>Development and commercialization license</td>
<td>$35M</td>
<td>Amgen received exclusive license option to RNAi ARC-LPA program.</td>
</tr>
<tr>
<td>2017</td>
<td>Novartis (Licensor) Ionis/Akcea</td>
<td>Collaborative research and product license option</td>
<td>$75M</td>
<td>Agreement between Akcea and Novartis to develop and commercialize AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx.</td>
</tr>
<tr>
<td>2019</td>
<td>Novartis (Licensor) Ionis/Akcea</td>
<td>Option to license exercised</td>
<td>$150M</td>
<td>Novartis took option to license ASO TQJ230 and test in a P3 cardiovascular outcomes trial.</td>
</tr>
<tr>
<td>2019</td>
<td>Pfizer (Licensor) Ionis/Akcea</td>
<td>Development and commercialization license</td>
<td>$250M</td>
<td>Ionis and Pfizer entered into a worldwide exclusive licensing agreement for antisense therapy AKCEA-ANGPTL3-LRx.</td>
</tr>
</tbody>
</table>

BCIQ: Medco/Alnylam (2013); Amgen/Arrowhead (2016); Novartis/Akcea-Ionis (2017); Novartis/Akcea-Ionis (2019); Pfizer/Akcea-Ionis (2019)

Inclisiran is a long-acting, synthetic siRNA directed against PCSK9, which is conjugated to triantennary N-acetylgalactosamine carbohydrates (GalNAc) that bind to asialoglycoprotein receptors expressed on hepatocytes, leading to the uptake of inclisiran.

Pivotal data demonstrate that twice annual dosing of inclisiran provides similar efficacy as biweekly/monthly mABs Repatha and Praluent. ~50% reduction in LDL-C on top of maximal tolerated statins. AEs similar to mABs.

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**How Does Inclisiran Work?**

1. Typical liver cell without inclisiran

2. What happens in the liver when inclisiran is present

Inclisiran is a GalNAc-modified siRNA that inhibits production of PCSK9 in the liver. Conjugation of siRNA to N-acetylgalactosamine (GalNAc) allows for liver-specific targeting. GalNAc binds to the asialoglycoprotein receptor (ASGPR), which is highly expressed on the surface of hepatocytes, resulting in rapid endocytosis. Once internalized, inclisiran binds PCSK9 mRNA, and promotes degradation of the transcript by the RISC complex, thereby preventing synthesis of PCSK9 protein. The resulting decrease in circulating PCSK9 leads to higher expression of LDL receptors in the liver and consequently lower LDL-C levels in the blood.

Adapted from Clinical Trial Service Unit (CTSU), Oxford University and Novartis AG Investor Relations

siRNA = small interfering RNA, RISC = RNA-Induced Silencing Complex

N Engl J Med. 2020 Mar 18, PMID: 32187462
Novartis has a challenge in front of itself to leverage Inclisiran’s differentiating qualities and lessons learned from less than stellar launches of the mABs to justify their $9.7B investment.

Twice annual “vaccine-like” dosing schedule may be enough differentiation for payers to strongly consider making inclisiran a preferred therapy in the hypercholesterolemia space.

Recent analysis suggests Novartis will push for a physician-administered ‘buy and bill’ model, which they argue will improve compliance and thus real-world outcomes, compared to self-administered mAbs.

Novartis is expected to launch inclisiran at a price below the ICER recommended price for PCSK9 antibodies and provide a unique contractual guarantee between manufacturer, physicians and payers to ensure compliance and offset costs on CV events. However, with ongoing outcomes trial not set to readout until 2024, we may have to wait for full MACE data before truly knowing how disruptive this new therapy and healthcare delivery model will be.
### Nucleic Acid Therapeutics Off to a Strong Start in 2020 with Recent Deal Trajectory

<table>
<thead>
<tr>
<th>Date</th>
<th>News Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>MARCH 2020</td>
<td><strong>Evox Therapeutics and Takeda Sign Multi-target Rare Disease Collaboration</strong></td>
</tr>
<tr>
<td></td>
<td>Collaboration focuses on developing novel protein replacement and mRNA therapies and explores the targeted delivery of these payloads using Evox’s proprietary exosome technology. Partnership encompasses up to five rare disease targets, including Evox’s Niemann-Pick Type C programme, with Takeda assuming responsibility for its clinical development.</td>
</tr>
<tr>
<td>MARCH 2020</td>
<td><strong>AstraZeneca Joins RNAi Mix, Pledging $80M to Silence Therapeutics</strong></td>
</tr>
<tr>
<td>APRIL 2020</td>
<td><strong>Alnylam and Dicerna Form RNAi Therapeutics Collaboration on Alpha-1 Antitrypsin Deficiency-Associated Liver Disease and Complete Cross-License Agreement for Primary Hyperoxaluria Programs</strong></td>
</tr>
<tr>
<td>APRIL 2020</td>
<td><strong>Blackstone and Alnylam Enter Into $2 Billion Strategic Financing Collaboration to Accelerate the Advancement of RNAi Therapeutics</strong></td>
</tr>
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</table>
Versatility of Nucleic Acid Therapeutics
Panel Discussion

The Emerging Role of Nucleic Acid Therapeutics: Resuscitating Cardiovascular Drug Development with Disruptive Therapies

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Barry S. Ticho, MD, PhD, FACC
Chief Medical Officer
Stoke Therapeutics
Versatility of Nucleic Acid Therapeutics: mRNA Degradation and Down-Regulation Approaches – ASOs and siRNA

- Antisense oligonucleotides can modulate gene expression through two different mechanisms based on post-hybridization events

- siRNA binds with Argonaute (Ago) to form an RNA-induced silencing complex (RISC). The RISC binds the complementary sequence of the target mRNA and degrades it. The components of complex can be recycled, leading to extended efficacy


e.g. fomivirsen

e.g. mipomersen

e.g. patisiran
Versatility of Nucleic Acid Therapeutics: mRNA Augmentation and Up-Regulation Using Oligonucleotides

- mRNA therapies harness the natural translation abilities of the cell to make the corresponding protein

**DNA** → **mRNA** → **Protein**

- Antisense therapies can also upregulate protein production via Exon Skipping and splice modifiers

**A** Duchenne muscular dystrophy - DMD

- Pre-mRNA Delletion of exon 50 → mRNA Reading frame disrupted
- 48 49 50 51 52 → truncated and non-functional dystrophin

**B** Spinal muscular atrophy – SMN2

- Pre-mRNA ISS prevents exon 7 inclusion → 90% of mRNA missing exon 7 → no protein
- 5 6 7 ISS 8 → Only 10% of mRNA Complete → 10% of functional protein

Versatility of Nucleic Acid Therapeutics:
VEGF-A mRNA may have therapeutic potential for regenerative angiogenesis

- AstraZeneca and Moderna are developing intracoronary VEGF-A mRNA for Myocardial Infarction and Heart failure
- VEGF-A is a potent angiogenic factor that promotes growth of blood vessels
- Preclinical data suggests that expression of VEGF-A in ischemic heart tissue could increase blood flow and partially restore cardiac function

Versatility of Nucleic Acid Therapeutics:
miRNAs functions in RNA silencing and post-transcriptional regulation of gene expression

- microRNAs are short (approximately 20-25 nucleotides long), single-stranded RNA molecules that regulate gene expression and play a vital role in influencing the pathways responsible for many disease processes, including cardiovascular disease and fibrosis.
- microRNAs function by preventing the translation of messenger RNAs into proteins and/or by triggering degradation of these messenger RNAs.
- Studies have shown that microRNA gene regulation is often not a decisive on and off switch but a subtle function that fine-tunes cellular phenotypes that becomes more pronounced during stress or disease conditions.
- microRNAs can be modulated with chemically synthesized oligonucleotides by either decreasing the activity (anti-miRs or inhibitors) or increasing the levels (pro-miRs or mimics) of expressed microRNAs.
- These modulators can then directly affect the protein expression of the specific microRNA’s targets. Typically, in laboratory settings, microRNA mimics are introduced as double stranded oligonucleotides and inhibitors are introduced as single strand oligonucleotides.

Miragen Website; http://www.miragen.com/mirorna-platform/
Versatility of Nucleic Acid Therapeutics: Gene Editing Toolbox and Potential CVD Applications

https://www.nature.com/articles/s41467-018-04252-2.pdf; Verve Therapeutics Website
Panel Discussion
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