

Novel MOA: RNA as a Target and a Therapeutic



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Moderator:

Mike Rice, MS, MBA, Senior Consultant, Defined Health

Panelists:

- *Andreas G. Bader, PhD*, VP, Translational R&D, Mirna Therapeutics
- *Bob Brown, PhD*, Chief Scientific Officer and Senior Vice President, Dicerna
- *Carlo M. Croce, MD*, Distinguished University Professor, The John W. Wolfe Chair in Human Cancer Genetics, The Ohio State University
- *Nigel Horscroft, D.Phil*, Director, Alliance Management, CureVac AG
- *Steven M. Kelsey, MD, FRCP, FRCPATH*, President, Onkaido Therapeutics

Scope of Panel: RNA as a Target and Therapeutic in Oncology

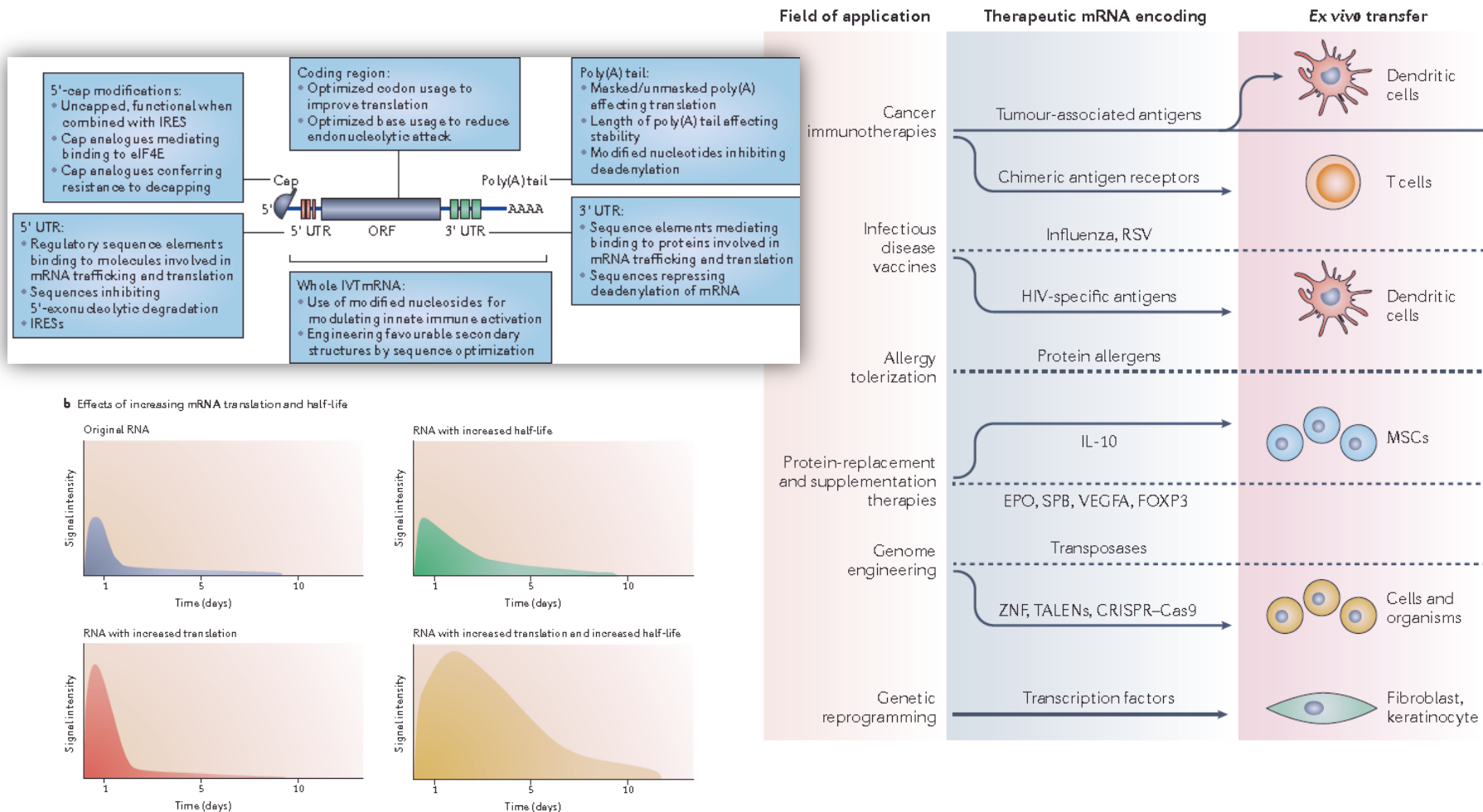
- microRNA (miRNA)
 - Prognostic biomarker
 - Therapeutic target
 - Augmentation: miRNA mimetics
 - Inhibition: Anti-miRNA, Decoys
- RNAi (DsiRNA/siRNA, snRNA)
 - Knockdown of gene expression as drugs for previously undruggable targets
- Messenger RNA (mRNA)
 - Alternate delivery of therapeutic proteins, vaccines, mAbs, etc.
 - Transient augmentation of therapeutic proteins and peptides as drugs for previously undruggable targets
 - Immuno-Oncology – TAA, Neoepitopes, etc.
- Nucleic acid delivery and targeting strategies
 - Chemical modifications, nanoparticles and gene therapy

Nucleic Acid Technologies in The Continuum of Biologic Therapeutics Platforms

Therapeutic Interventions

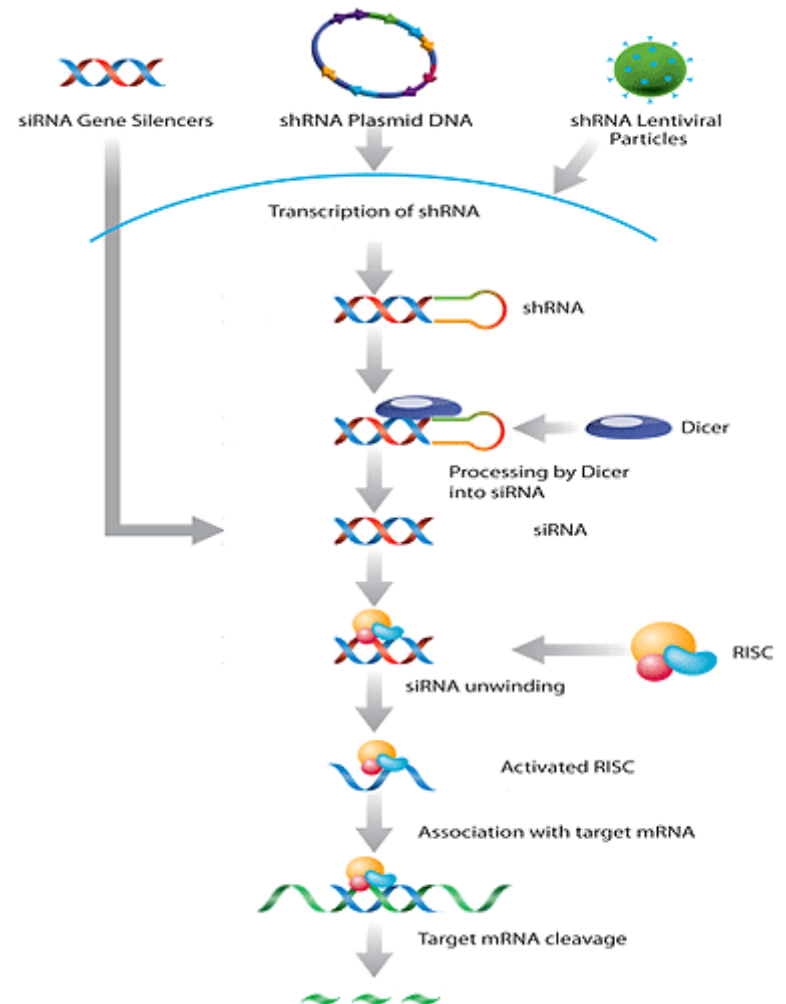
Small Molecule Modulators	Protein Augmentation	Antibodies	Nucleic Acids	Gene Correction & Augmentation	Cell Therapy / Regen Med
<ul style="list-style-type: none"> • Immune Modulators • SMIs • Chaperones • Substrate Reduction • Transcription / Translation enhancers • Epigenetics 	<ul style="list-style-type: none"> • Plasma/tissue derived proteins • Recombinant Proteins <ul style="list-style-type: none"> – Clotting factors – Cytokines – Hormones – Growth factors • Enzyme Replacement 	<ul style="list-style-type: none"> • Plasma derived Polyclonal Igs • Monoclonal antibodies • mAB fragments • Scaffolds • Intrabodies 	<ul style="list-style-type: none"> • Antisense • mRNA • RNAi /siRNA • miRNA • Toll modulators • Aptamers • Ribozyme • Exon skipping 	<ul style="list-style-type: none"> • Viral vectors <ul style="list-style-type: none"> – Retro/ – Lentiviral – AdV – AAV • Non-viral <ul style="list-style-type: none"> – Plasmids/ – Fragments • Gene editing with Meganucleases <ul style="list-style-type: none"> – Zinc Fingers – TALENS – CRISPR/Cas9 	<ul style="list-style-type: none"> • Autologous and allogeneic BMT/Cell therapy • Other cell sources: e.g. ES, iPS • Devices <ul style="list-style-type: none"> – Encapsulation – Scaffolds – Implants – Micro-organs – Aphaeresis

mRNA Augmentation is a Broadly Applicable Therapeutic Platform for Cancer and Other Disorders

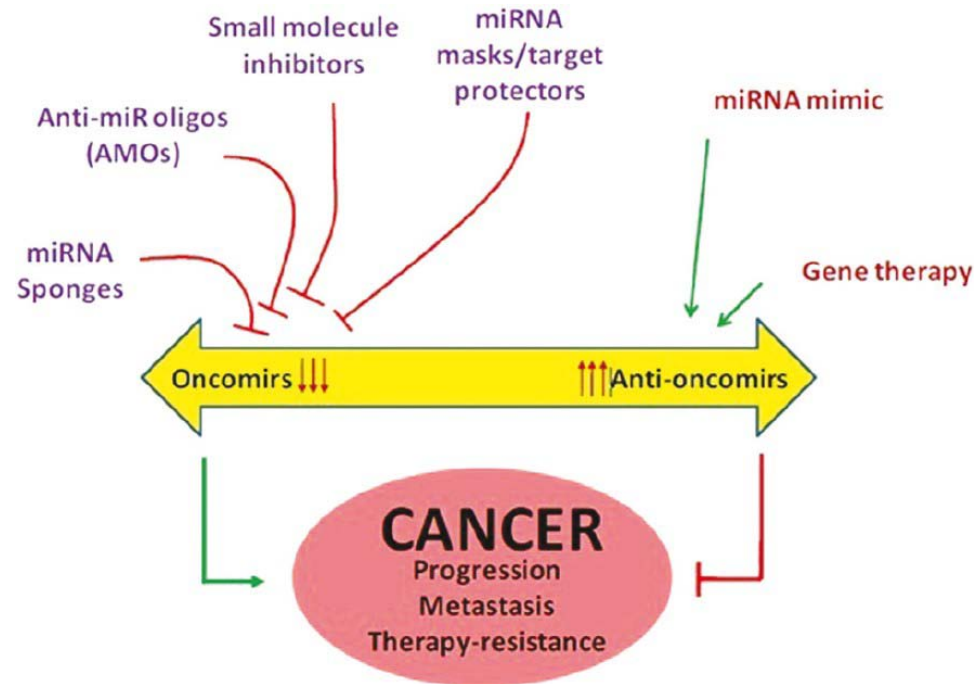


siRNA (and miRNA) Provides a Way to Specifically Inhibit Intractable Targets

- **siRNA:** dsRNA is exogenously introduced and is processed by Dicer into siRNA which is loaded into the RISC.
- AGO2, which is a component of RISC, cleaves the passenger strand of siRNA.
- The guide strand then guides the active RISC to the target mRNA.
- The full complementary binding between the guide strand of siRNA and the target mRNA leads to the cleavage of mRNA.
- Many clinical stage siRNA based drugs are targeting long known, but intractable targets:
 - Myc
 - P53
 - KRAS
 - BCR-ABL
 - Beta Catenin
 - PLK1
 - PKN3
 - RRM2



miRNA Mimetics and anti-miRNAs Can Modulate Multiple Oncogenic Pathways

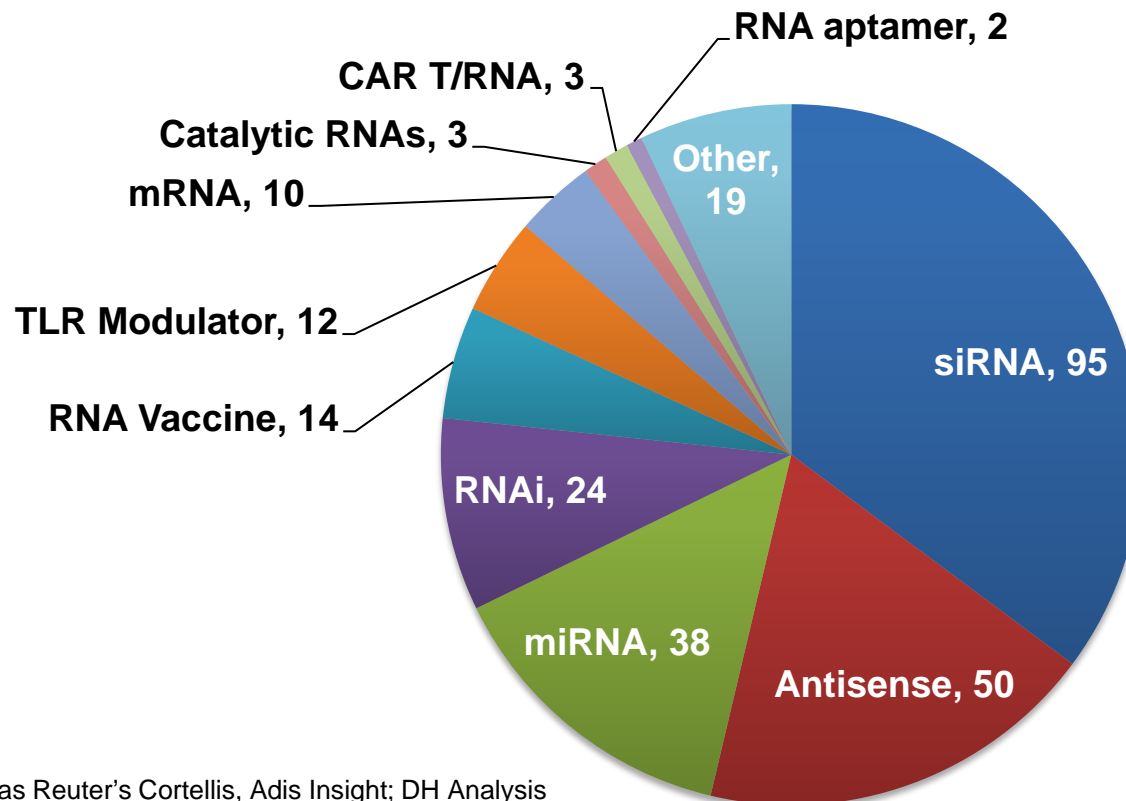


- miRNAs control multiple pathways for which one microRNA mimic can regulate numerous oncogenes across multiple cancer pathways and immune evasion pathways.
- Inhibiting the function of oncomirs by use of anti-miR oligonucleotides (AMOs), small molecule inhibitors, miRNA sponges and miRNA masks/target protectors, and promoting the activity of anti-oncomirs through gene therapy or delivery of miRNA mimics can serve as novel therapeutic options against cancer.

Majority of RNA Drugs in Development Lead to Message Knockdown

- Emerging approaches augment endogenous mRNA levels or express synthetic constructs (TAAs, CARs) designed to induce antitumor immune response

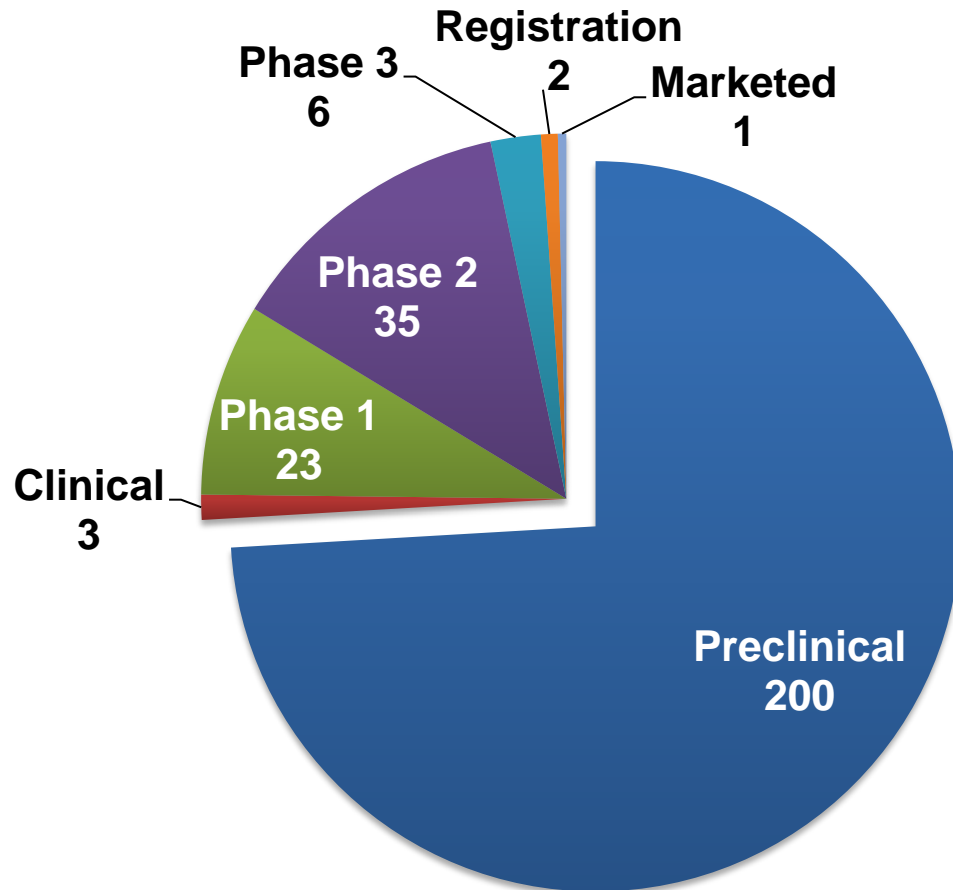
Preclinical and clinical Stage RNA Pipeline



Thomas Reuter's Cortellis, Adis Insight; DH Analysis
Cancer Progress by Defined Health
New York, NY | March 8 - 9, 2016

1 Marketed RNA CVD Drug: >50 in Development Across All Therapeutic Areas

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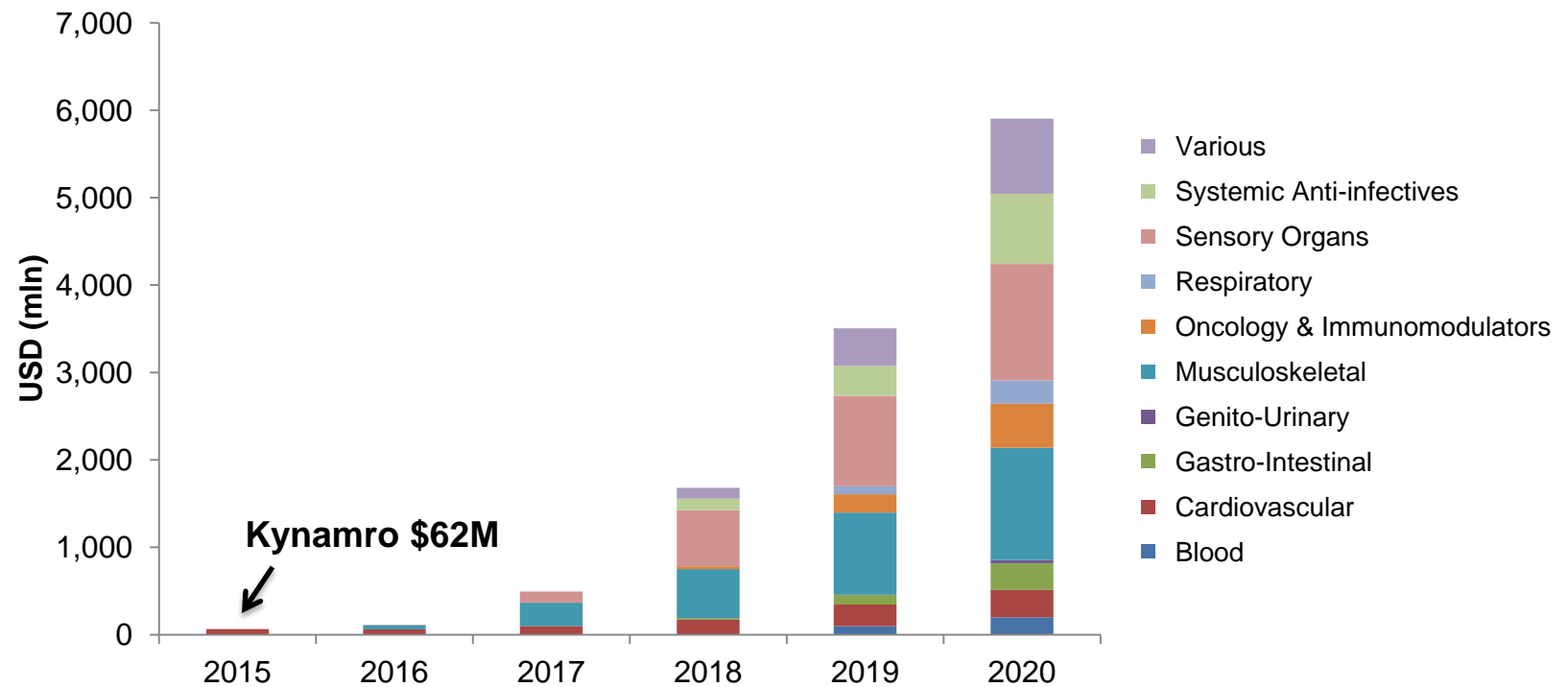
DefinedHealth
unconventional insight



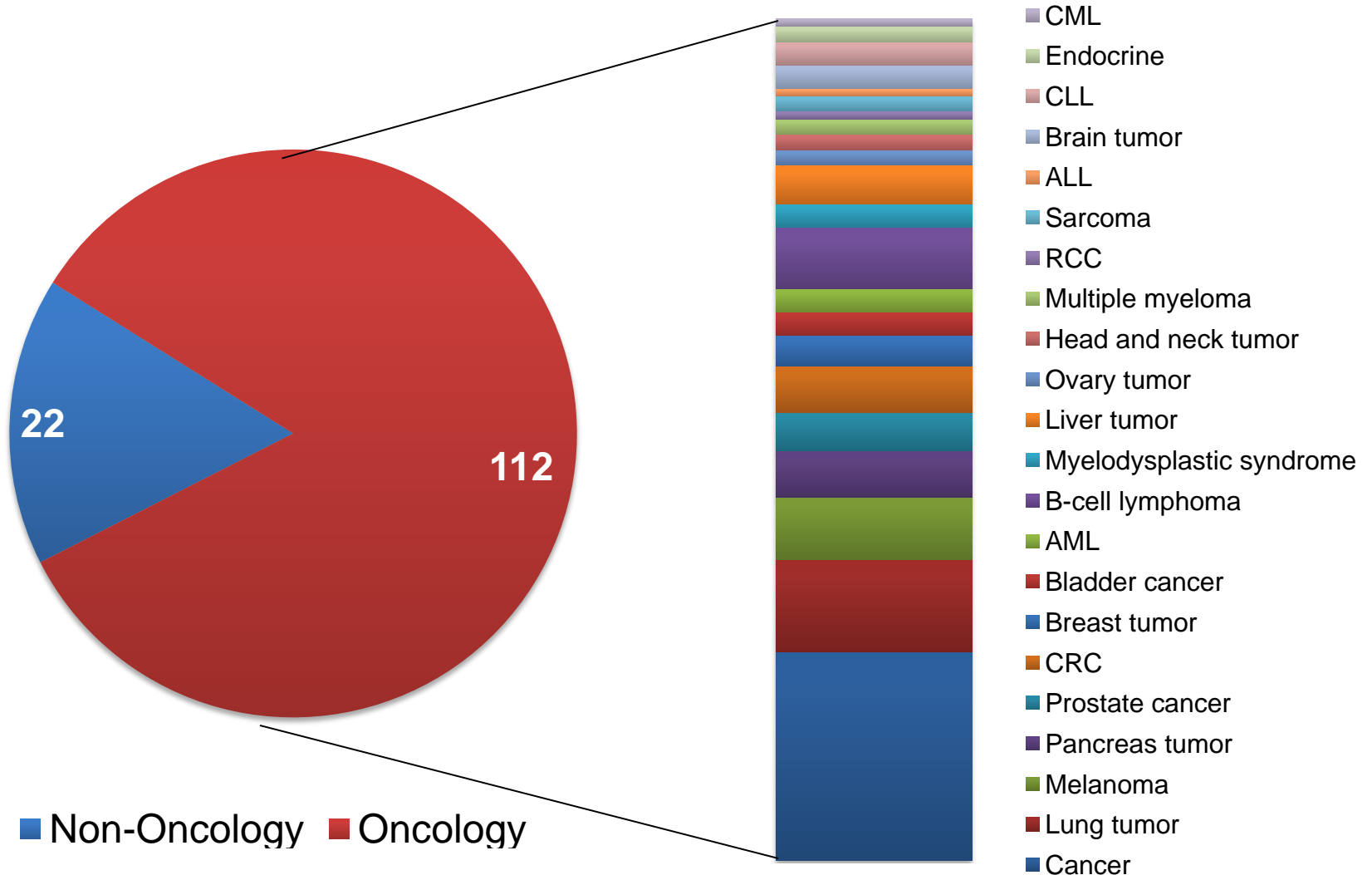
Global Sales Forecasts of DNA/RNA Therapeutics

- Oncology Makes up 6% of DNA/RNA Therapeutic Sales in 2019 and 9% of Sales in 2020

WW Sales of DNA/RNA Therapeutics



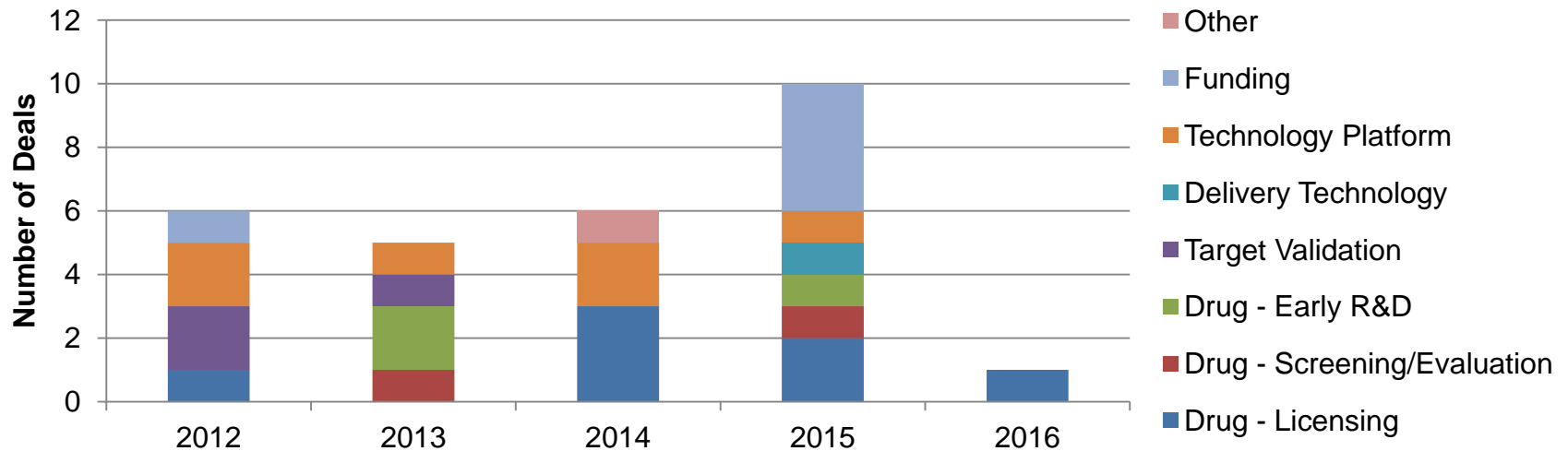
RNA Therapeutics by Therapeutic Area (Clinical)



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Recent Deals Have Been Centered Around RNA based Drug Licensing and Collaborations to Gain Access to Technologies

RNA Technology Deal Activity by Type



Deal Value

Principal Company	Partner Company	Product/Platform	Upfront	Milestones
Rosetta Genomics Ltd	Mirna Therapeutics Inc	MRX-34	\$1.6 M	Potential payments
BioNTech AG	Sanofi	Five immunotherapies: synthetic mRNAs	\$60 M	\$300 M per product
CureVac GmbH	Boehringer Ingelheim Corp	CV-9202	\$48 M	\$590 M
ModeRNA Therapeutics	Onkaido	Company creation	\$20 M capital	--
Horizon Discovery Group plc	AstraZeneca plc	Identification/validation of novel targets	Undisclosed	\$88 M

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