An Emerging RNAi Oncology Company
Defeating Cancer by *Delivering* on the Promise of RNAi

Executive Summary
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Michael Dudley, CEO and Co-Founder
Tel: 857-301-6857
Email: michael.dudley@transcodetherapeutics.com

Defeating Cancer by *Delivering* on the Promise of RNAi

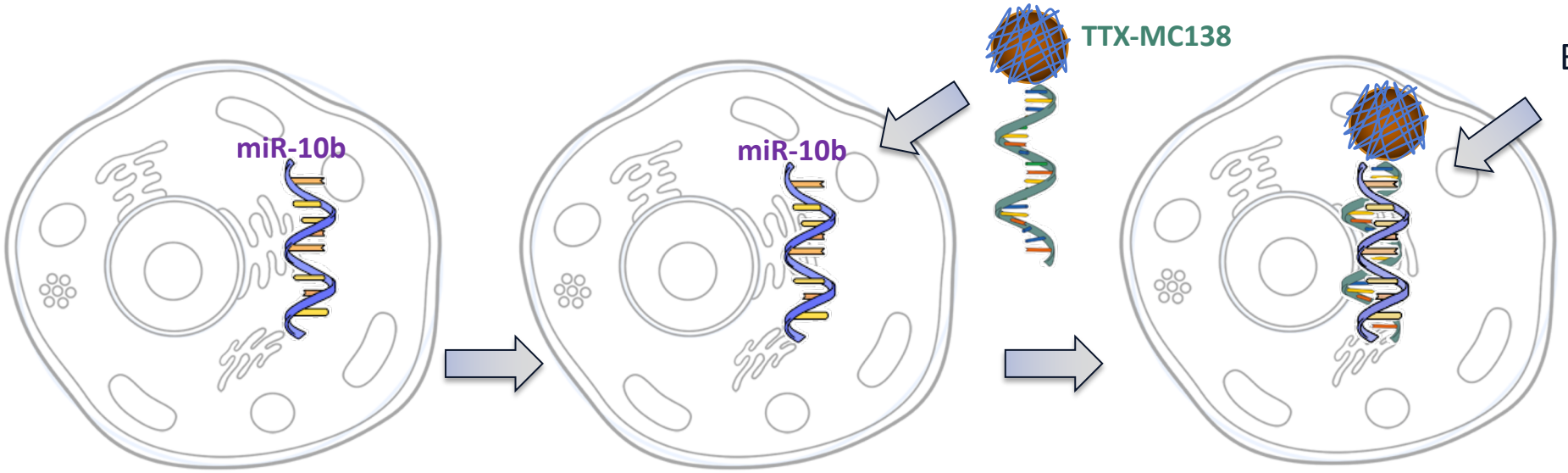
Value Proposition	• Lead candidate therapeutic – ***TTX-MC138 - Eliminates metastasis*** in animals with no toxicity • Broad applicability across 18 different tumor types • Provides durable regression with no recurrence of disease • Optimized delivery system overcomes previous delivery challenges by competitors • Broad IP portfolio
Relevant Target	• Initial target - ***microRNA-10b (miR-10b) - responsible for migration, invasion and viability of metastatic tumor cells*** • Validated by leading researchers - over 150 publications demonstrate strong association of miR-10b and metastasis
Unmet Clinical Need	• ***90% of cancer deaths are due to metastasis*** *(i.e.,* the spread of cancer from the primary site to a distant site) • Current treatments mainly target primary tumors
Market Opportunity	• Global metastatic cancer treatment market anticipated to be $98 billion by 2025 • Limited number of companies targeting metastasis • Significant return on investment potential

Staged Funding Opens Multiple Exit Windows

How Does TTX-MC138 Eliminate Metastasis?

miR-10b responsible for migration, invasion and metastatic tumor cell viability

TTX-MC138 is delivered inside metastatic tumor cells and binds to miR-10b



Binding inhibits miR-10b and inactivates it

Resulting in metastatic cell death

Metastatic tumor cell

RNAi – Inhibiting Gene Expression - A Multibillion Dollar Market Potential

Unique Features of RNAi as a Therapeutic Modality:

Druggable targets

- Any gene can be targeted - unlike antibodies or small molecules

Modular in design

- Design based on the complementarity to the gene of interest
- Rational and straightforward drug design

Potency

- RNAi mechanism is catalytic - Single therapeutic molecule can destroy hundreds of copies of a disease-causing gene
- Nominal amounts of drug required to achieve a powerful therapeutic effect
- Acts upstream of modern medicines; blocks the expression of disease-causing antigens vs. interfering with their function

"RNAi Got Its Sexy Back"- John Maraganore, CEO of Alnylam

Alnylam

- *Onpattro* first-of-its-kind RNAi therapeutic for the treatment of hATTR, a rare, inherited, rapidly progressive life-threatening disease
- *Onpattro* revenues for Q4 & 2019 were $56M & $166M
- Alnylam shares up by 62% in 2019

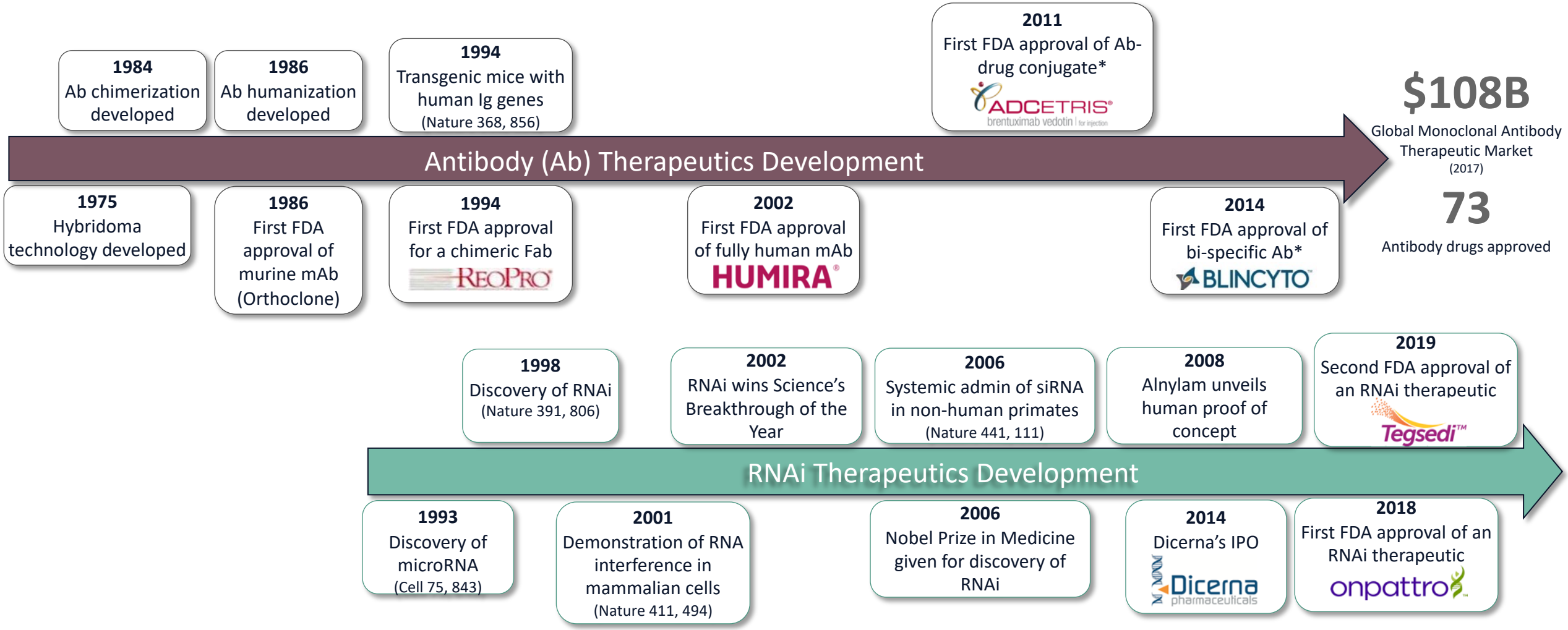
Novartis

- Novartis buys Medicines Co. in $9.7B to obtain RNAi cholesterol drug, *inclisiran* (Nov 2019)
- Treatment with *inclisiran* reduced cholesterol levels by half among individuals already taking statins

Arrowhead

- Arrowhead Pharmaceuticals Inc. - $3.7B Agreement with Janssen (Oct 2018)
- Current valuation $4.2 Billion

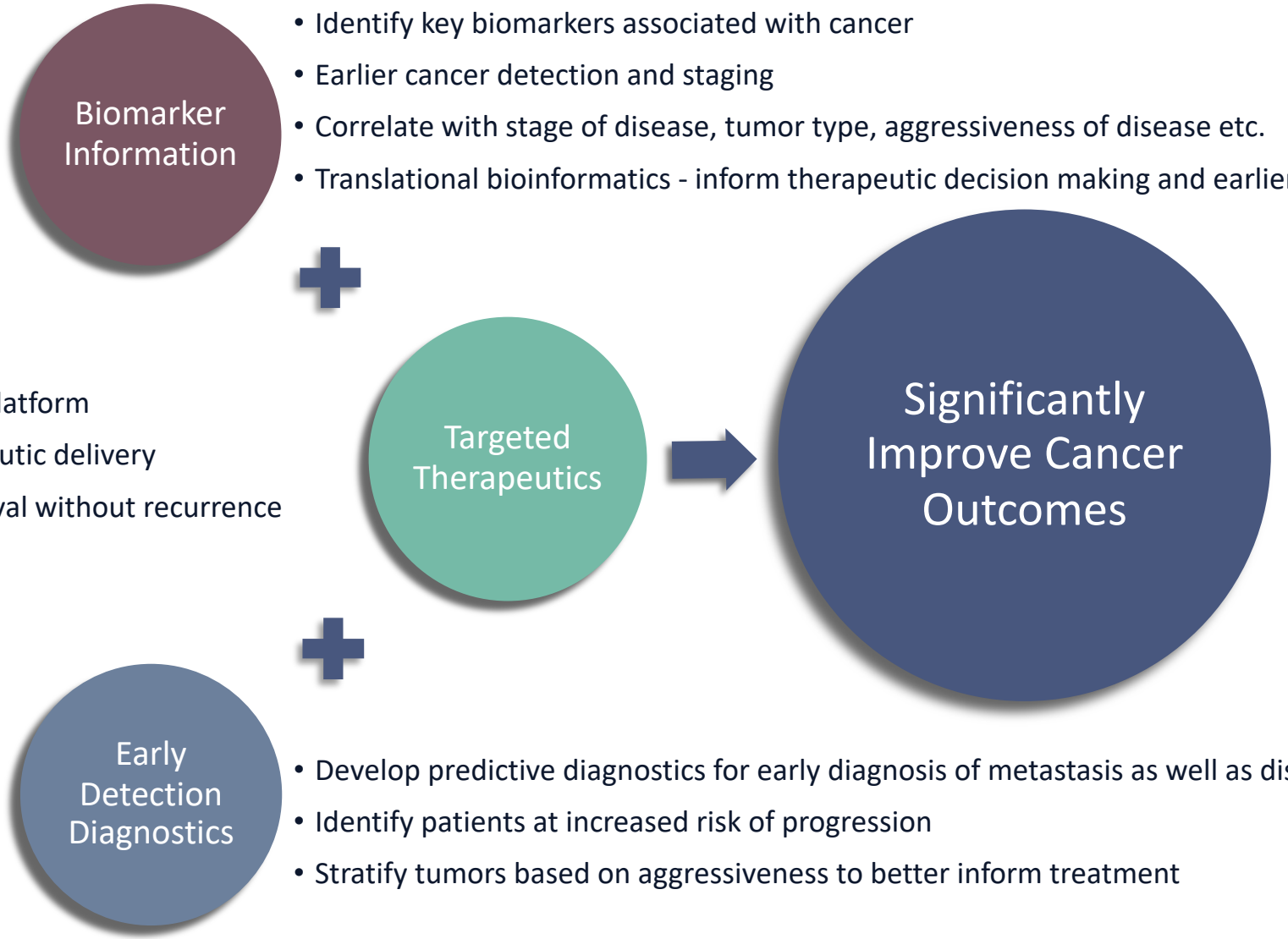
Next Generation Medicines: Adoption of Novel Technologies Takes Time



Market Potential Unlocked for RNAi Therapeutics

Source: Frontiers in Immunology 2017, Adv Ther 2017, Chemical & Engineering News, Science, Pharma Manufacturing, Zion, *first approval for one that remains marketed, Mylotarge was pulled from the market in 2010

Improve Cancer Outcomes in Late Stage Disease



microRNA-10b (miR-10b) is a Unique, Well Documented Biomarker

Clinical Evidence Demonstrated in >150 Publications:

Biomarker of Metastasis

- Positive expression associated with ***tumor cell migration and invasion***
- ***Marker of local & distant metastasis*** (based on organ of origin)

Linked to Higher Cancer Risk Poor Survival Outcomes

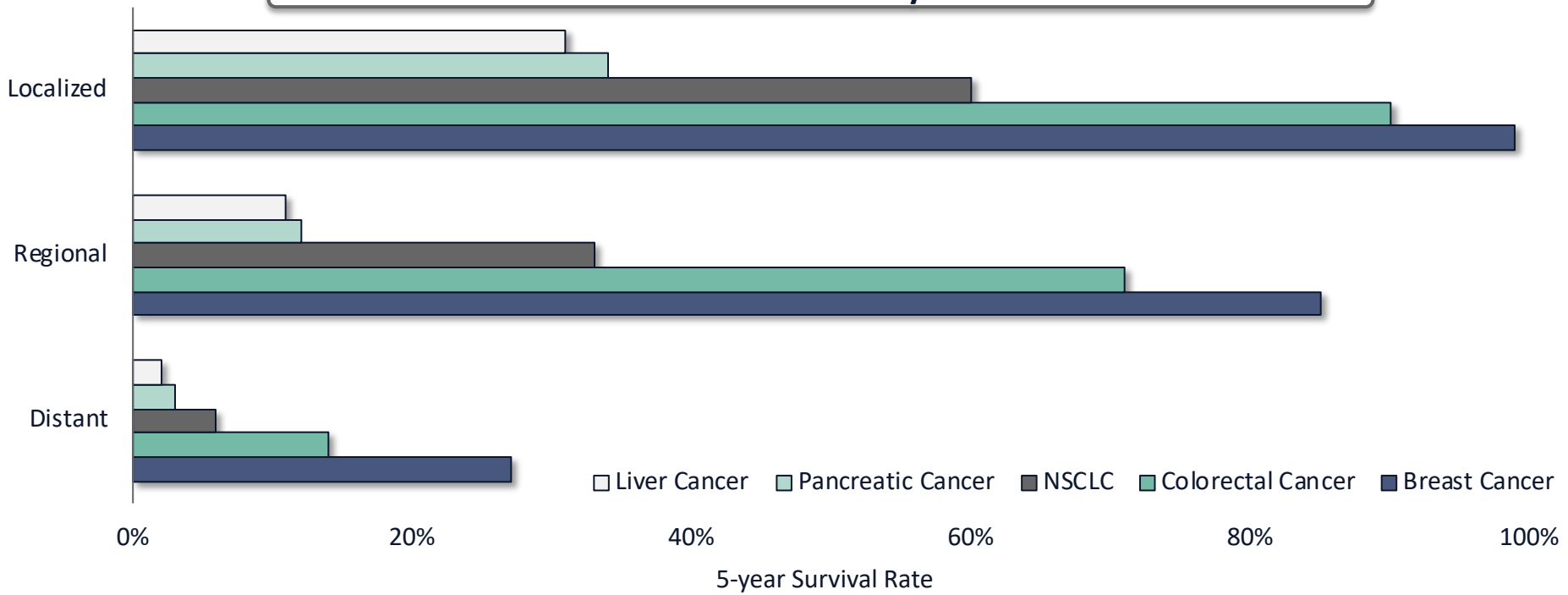
- Carcinogenesis, presence of cancer
- Poor overall-survival (OS) in patients especially in late-stage disease
- Linked to aggressiveness of disease

Linked to Progression in Multiple Cancer Types

- Breast
- Pancreatic
- Non-small cell lung
- Gastric
- Hepatocellular
- Ovarian
- Colorectal
- Glioma
- Prostate
- Esophageal, and more

Metastasis Treatment: Deficiency in the Oncology Market

Metastatic Cancer Reduces 5-year Survival Rate



Segment Overview

- Metastatic cells are anatomically, biologically & physiologically distinct from cells found in the primary tumors allowing them to travel & seed a new site
- All current therapeutic modalities developed to target the primary site or elicit an immune response

Novel Treatments Targeting Metastasis are Crucial

90%

of Cancer Deaths Due to Metastasis

$98B

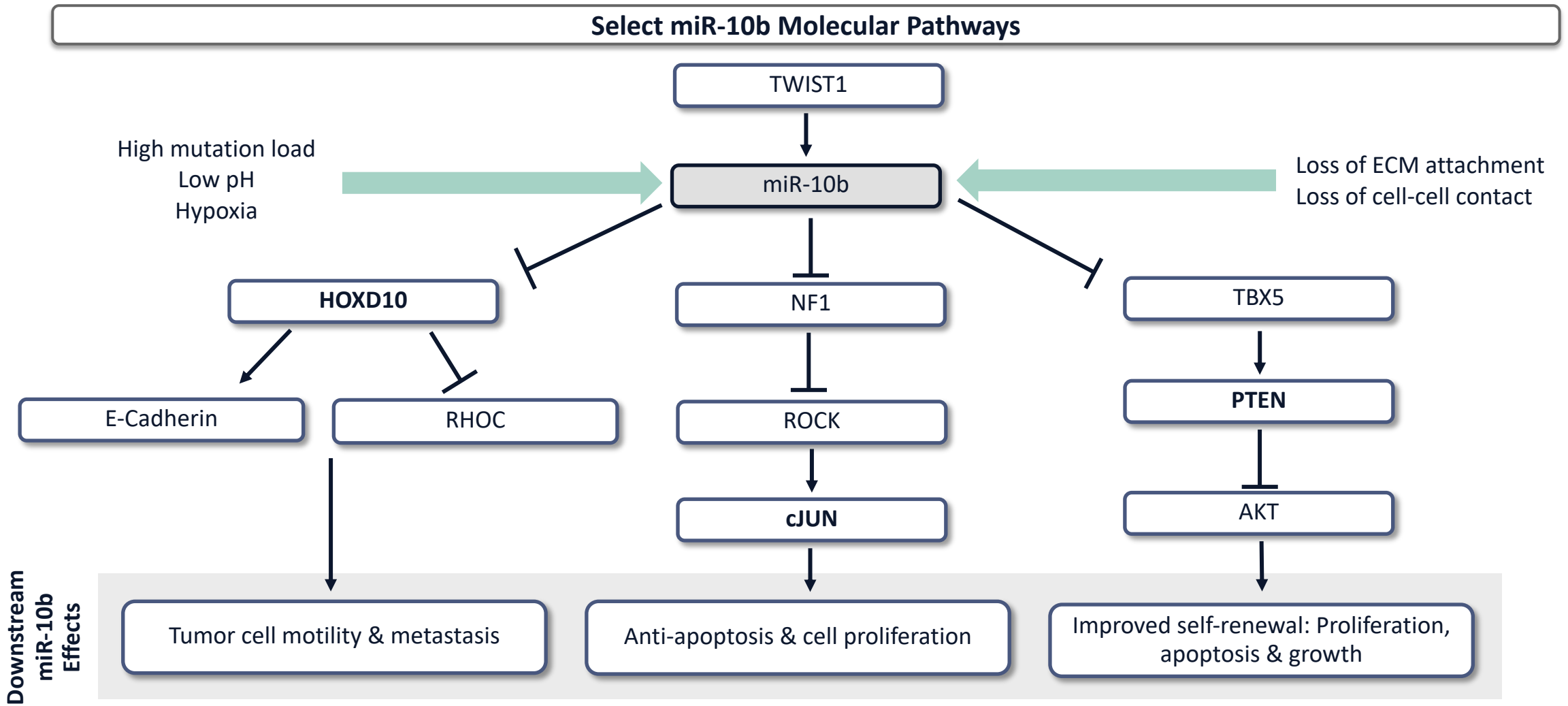
Global Metastatic Cancer Treatment Market
By 2025

7.7%

CAGR
Global Metastatic Cancer Treatment Market
(2017- 2025)

Source: ACS, BIS Research

Pleiotropic Effects of miR-10b Driving Metastasis



Sources: Am J Cancer Res 2018, Oncotarget 2016, Protein Cell 2011, Oncoimmunology 2013, PLoS ONE 2019, Can Res 2013

Unique Tumor Cell Delivery Technology via Hemodynamic and Metabolic Targeting

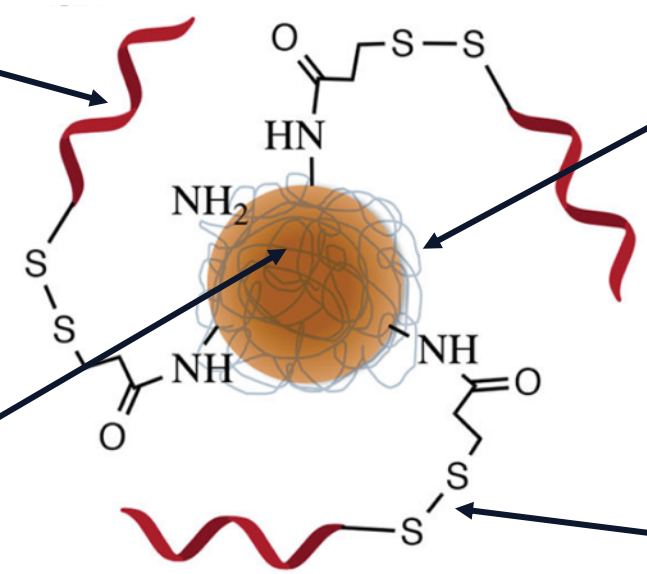
TTX-xx Structure

RNAi-targeted nucleic acid:

- Designed to improve binding affinity & stability while reducing immunogenicity

Iron Oxide Nanoparticle Platform:

- 23.5 ± 3.5 nm nanoparticles avoid kidney clearance & effectively deliver the oligo to the tumor cells
- Superparamagnetic properties allows for quantitative non-invasive imaging via MRI & measurement of drug bioavailability during treatment
- Objective measurement of response
- Vast amount of clinical use



Dextran Coating:

- Creates steric hindrance by blocking large nuclease proteins from gaining access to oligo
- Charge improves cell uptake

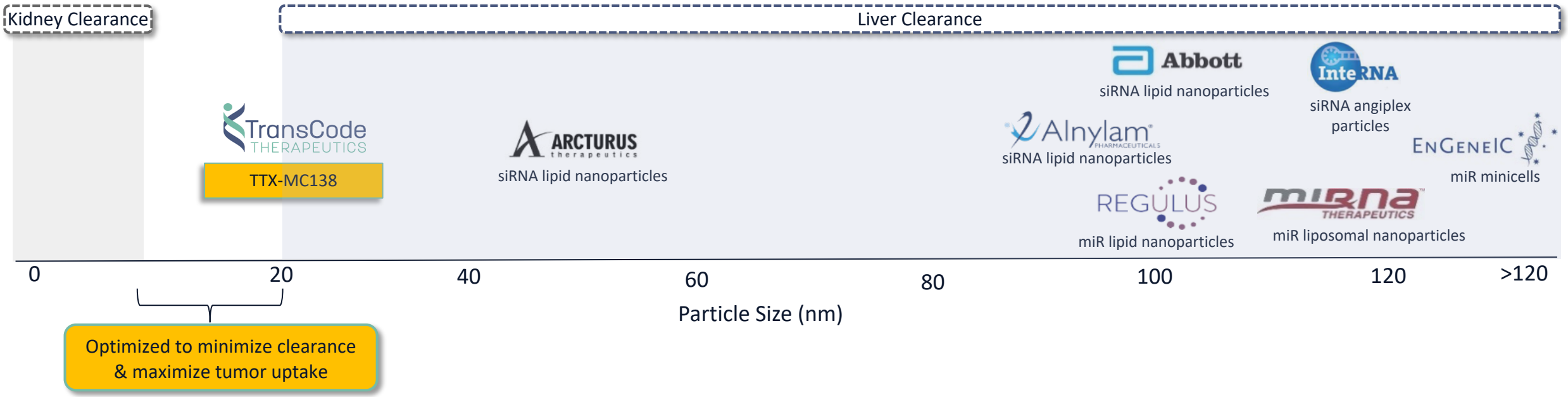
Disulfide bond:

- Covalently attaches oligo to the amino-dextran
- Cleaved within tumor cell

Delivery with Enhanced Binding Affinity & Stability

Unique Particle Size Coupled with Exceptional Safety

Select miR/siRNA Nanoparticle Competition



Competition & Differentiation Summary

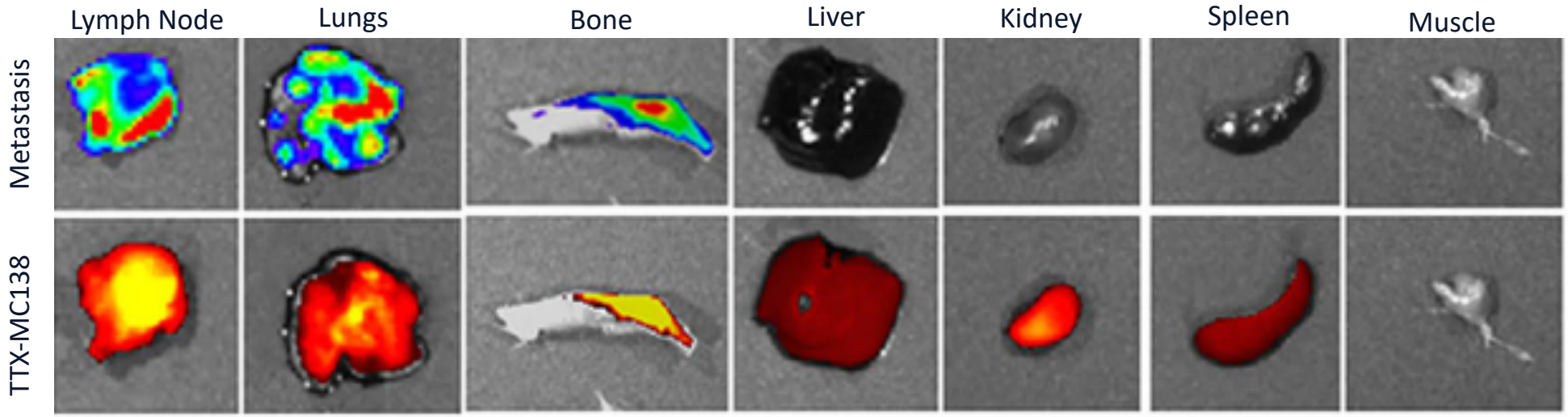
- Delivery system particle size allows for a long circulation time & efficient accumulation in the tumor while minimizing kidney & liver clearance
- Competitors' lipid nanoparticles carry a risk of immunogenicity that is avoided with TransCode's iron oxide particles
  - Iron oxide nanoparticles verified safe after decades of use as an imaging agent & FDA-approved treatment for iron deficiency anemia
- Dextran coating results in a positive zeta potential improving stability and tumor cell uptake

TransCode's Nanoparticle Optimized for Delivery to Metastases

Source: J Nano Res 2014, J Drug Targeting 2012, Alnylam presentation, Molecular Therapy-Nucleic Acids 2016, Nature Communications 2018, Molecular Therapy 2018, Int J Pharmaceut 2014, Analytical Chem 2013, Large Molecular Therapeutics 2017, Current Pharma Design 2015, Radiology 2018

Effective Delivery to Metastatic Sites

Demonstrated Delivery to Metastatic Sites



Study Results

- Drug accumulated in distant metastatic organs & the foci of nanodrug accumulation co-localized with the metastatic lesion
- Organs that were free of metastases but accumulated TTX-MC138 included the liver, spleen & kidney
- Muscle did not show evidence of TTX-MC138 accumulation, as anticipated as it has a relatively hypopermeable vasculature

***In vivo* Delivery Confirmed**

Source: Scientific Reports | 7:45060 | DOI: 10.1038/srep45060, Can Res 2015

Clinical Feasibility of Delivery to Metastases

White Arrows in images point to brain metastases in a patient with pancreatic cancer. Accumulation of the nanoparticles is visualized as darkening on magnetic resonance images.

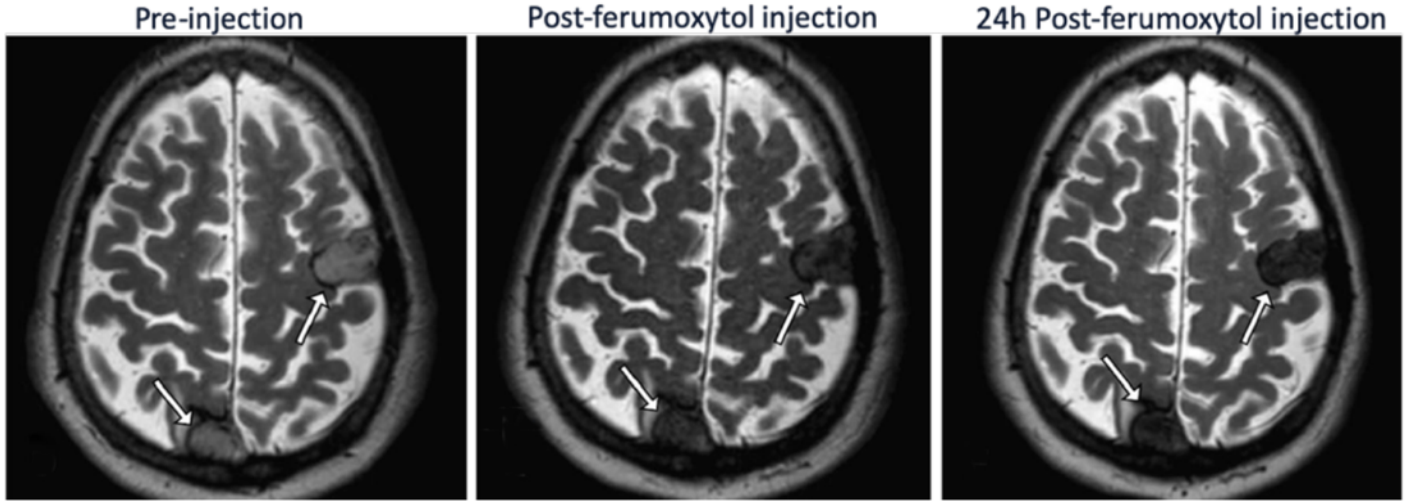
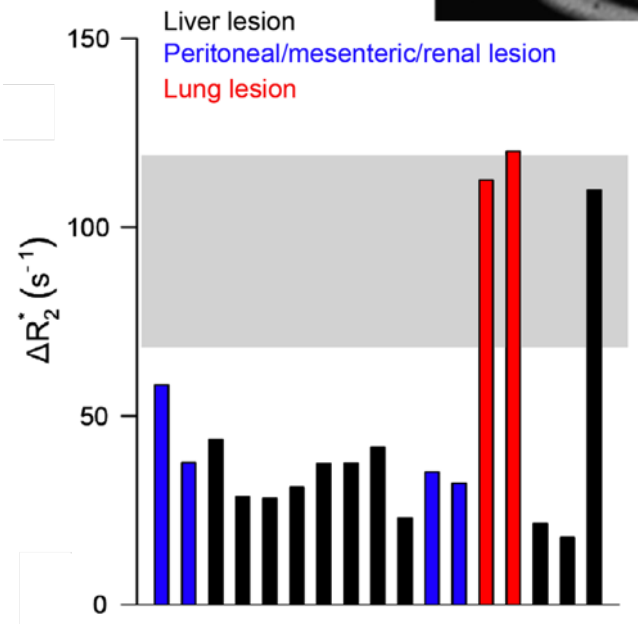
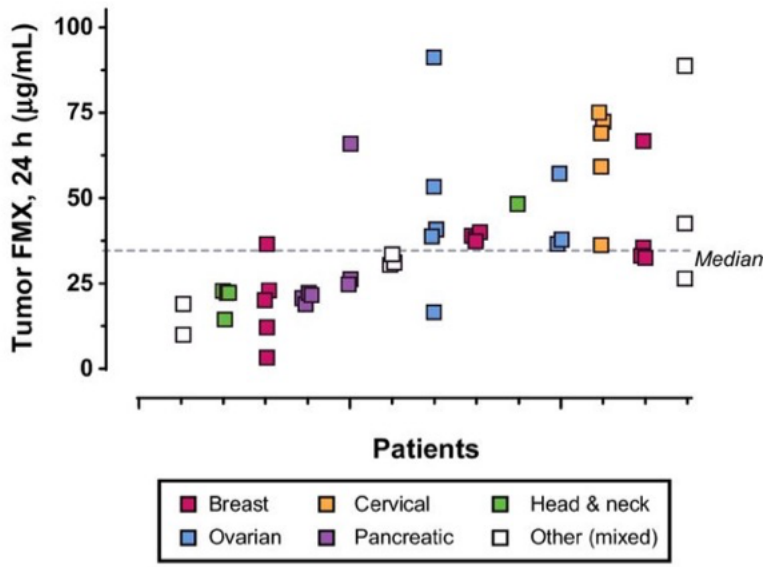


Image-Guidance Delivery Benefits:

- Optimize dose/schedule during clinical trials
- Predictive response during treatment



Delivery to liver, peritoneal, and lung metastases



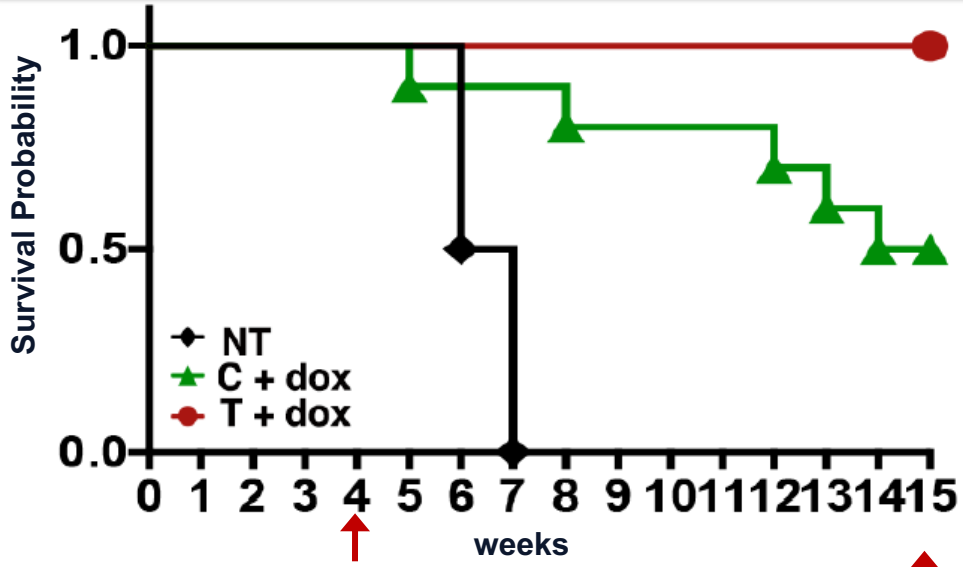
Delivery to multiple solid cancers

Concentration in metastatic lesions equivalent to 2.5µM of oligo

Sources: Hamilton et al, J Neurooncol 2016; Fredrickson et al, MRM 2017; Ramanathan et al, 2017 Clin Cancer Res

Pre-Clinical Survival Benefit Demonstrated in Multiple TNBC Models

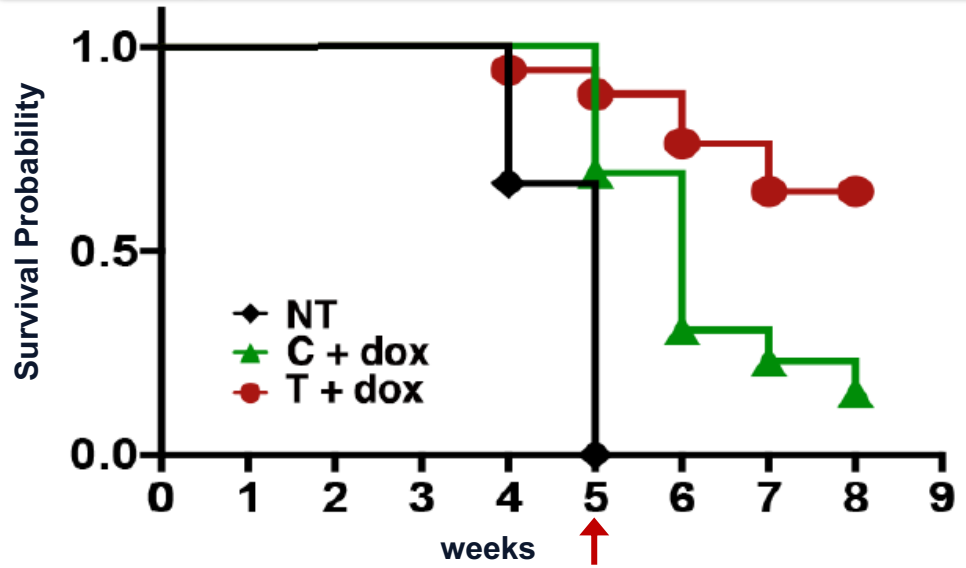
Stage II/III Metastatic TNBC Murine Model



NT: No therapy, C: Control (Irrelevant oligo), T: TTX-MC138, dox: doxorubicin; Therapy stopped

- **Study Design:** NIH III nude mice were implanted orthotopically with MDA-MBA-231-luc-D3H2LN
  - Treatment stopped after evidence of no metastatic cell presence
- **Results:** TTX-MC138 improves survival via eliminating pre-existing local metastases

Stage IV Metastatic TNBC Murine Model



NT: No therapy, C: Control (Irrelevant oligo), T: TTX-MC138, dox: doxorubicin; Therapy stopped

- **Study Design**: Balb/c mice were implanted orthotopically with 4T1-Red-Fluc cells
  - Treatment stopped after evidence of no metastatic cell presence
- **Results**: TTX-MC138 improves survival via eliminating pre-existing distant metastases

Following Cessation of Therapy, No Recurrence or Toxicity Observed

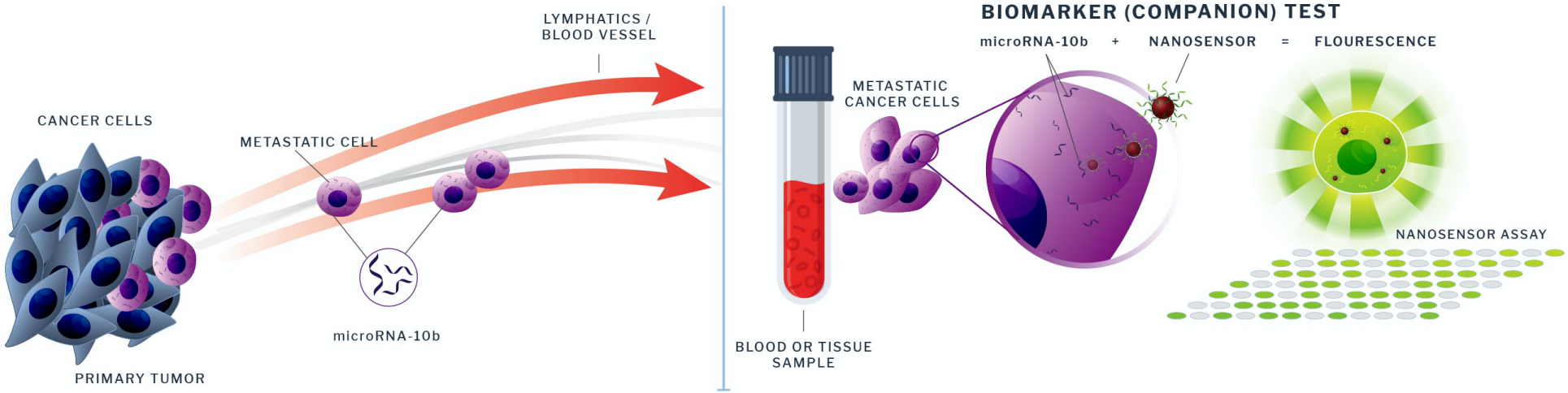
Sources: Can Res 2015, Sci Report 2017

Biomarker Opportunity – Early Detection Reduces Mortality

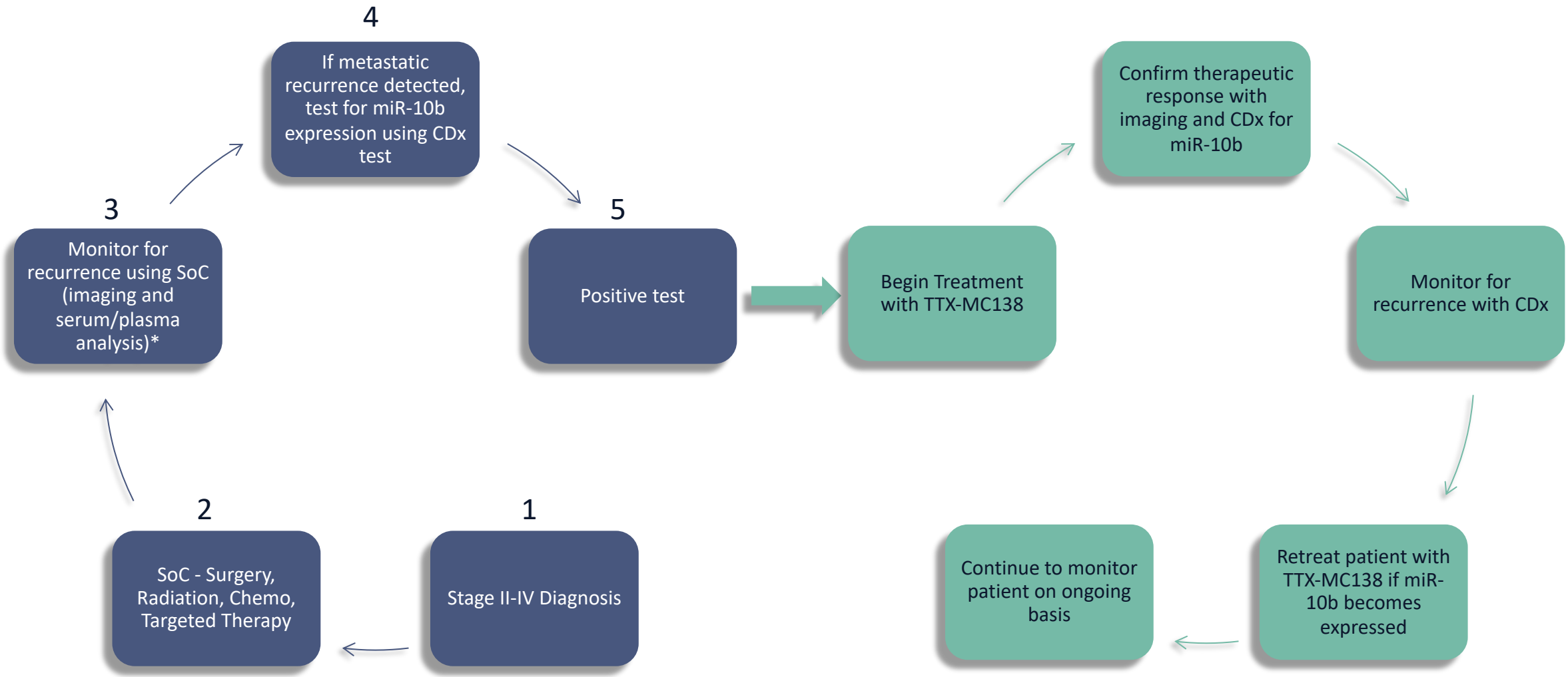
Predictive Biomarker with Capability of microRNA Profiling

Expression of microRNA-10b can be used as a diagnostic biomarker to detect the presence of metastasis as well as a biomarker to predict overall survival and disease-free survival in cancer.

- TransCode's predictive biomarker nanosensor has the unique capability of microRNA profiling in intact live cells and tissues.
- The fluorescent read-out generated by the nanosensor is highly specific and has nanomolar sensitivity.



Utility of CDx in Therapeutic Treatment with TTX-MC138



* SoC plasma analysis such as CA15-3, CA19-9, CEA or PSA test, depending on the type of cancer

Therapeutic Pipeline

Drug Candidate	Target	Disease Indication	Discovery	Preclinical	Phase 0	Phase 1	Phase 2	Key Anticipated Milestone
TTX-MC138 (Lead Candidate)	microRNA-10b	Breast Cancer						eIND FIM study IND enabling studies
		Glioblastoma (GBM)						Animal study 2020
		NSCL cancer						
		Pancreatic Cancer						
		Colorectal Cancer						
		Hepatocellular Cancer						
TTX-siLin28b	Lin28b	Pancreatic Cancer						
TTX-MC710	microRNA-710	Breast Cancer						Animal study 2020
TTX-siPD1	PD-L1	Pancreatic Cancer						Additional animal studies 2020
Small molecule inhibitors	microRNA - xxx	Breast Cancer & others						Testing small molecules

Intellectual Property Portfolio

Title	Patent #	Status	Date of Filing	Geography	Target(s)	Indications	Owner	Description
Nanoparticle Intellectual Property								
Amine Terminated Dextran Coated Iron Particles and their Functionalization	62/943,927	Provisional Filed	12/5/19	PCT to be filed	Target agnostic	Delivery vehicle	MGH	Nanoparticle formulation composition and synthesis methods
Therapeutics Intellectual Property								
Therapeutic Nanoparticles & Methods of the Use Thereof	9,763,891	Granted	7/19/12	U.S.	miR-10b	Metastatic cancer	MGH	Composition and method (antagomir linked to nanoparticle)
	9,629,812	Granted	8/1/14	U.S.	miR-10b	Metastatic cancer	MGH	Composition and method (antagomir linked to nanoparticle)
	10,463,627	Granted	9/8/17	U.S.	miR-10b	Metastatic cancer	MGH	Composition and method (antagomir linked to nanoparticle)
Therapeutic microRNA Compositions and Uses	62/941,121	Provisional Filed	11/27/19	PCT/US	miR-710	Metastatic cancer	MGH	Composition and method (miR mimic linked to nanoparticle)
Sentinel Nanoparticles for the Treatment of Multiple Cancers	62/922,581	Provisional Filed	8/16/19	PCT to be filed	Multiple	Multiple cancer types	TransCode	Composition and methods for targeting and treatment of multiple cancers using different delivery methods
Compositions and Methods for Immune Checkpoint Inhibition	PCT/US 2019/050003	Application	9/6/19	PCT/US	PD-L1	Cancer	MGH	TTX-siRNA targeting immune checkpoint molecule PD-L1 for treatment of cancer
Agents & Methods for Treating Pancreatic Cancer	15/563,248	TransCode adding to license	9/29/17	Intend to file PCT	SIRT6	PDAC	MGH	Composition and method targeting LIN28b inhibitor using TTX nanoparticle delivery system
TransCode Diagnostics Intellectual Property								
miRNA Profiling Composition & Methods of Use	10,086,093	Granted	2/26/14	U.S.	Any microRNA	Cancer	MGH	Diagnostic assay for detection of microRNAs in tissue & blood
	2961386	Granted	2/26/14	E.P.	Any microRNA	Cancer	MGH	Diagnostic assay for detection of microRNAs in tissue & blood

2020 Financing Requirements

TransCode 2020 financing requirements:

- Seed Round $3.7M*
- Complete First-in-Man study
- Scaleup manufacturing of DP
- Begin pre-IND enabling studies

* $1.2M Already secured

Seed Round Use of Proceeds		
Expense	**Description**	**2020 Financing**
Clinical Development	• Exploratory IND Study (eIND) • Pre-IND Studies	$1,500,000
Legal/Patents	• Legal • Patent Expenses	$ 200,000
Advanced CMC	• Drug Substance Manufacturing • Drug Product Manufacturing	$1,450,000
Company Operations	• Salaries, benefits, rent, consultants	$ 550,000
		$3.7M

Clear Pathway To Disrupt Cancer Treatment Market

Seek Partnership

Exit Window

Exit Window

Exit Window

Month 11

Milestones

- cGMP Drug Substance/Product Manufacturing
- FIM – eIND study
- Begin Pre-IND Enabling Studies

charles river
Avecia
LUBRIZOL LIFE SCIENCE

$3.7M

Month 22

Milestones

- Complete Pre-IND Studies + Toxicity Studies
- **IND Obtained**

charles river
Avecia
LUBRIZOL LIFE SCIENCE

$11.0M

Month 24

Milestones

- Phase 1a Dose escalation
- **POC in humans** (in initial patients treated)

PRECISION FOR MEDICINE

$14.2M

Month 36

Milestones

- Phase II enrollment
- Complete Phase II
- **POC in Multiple tumor types**

PRECISION FOR MEDICINE

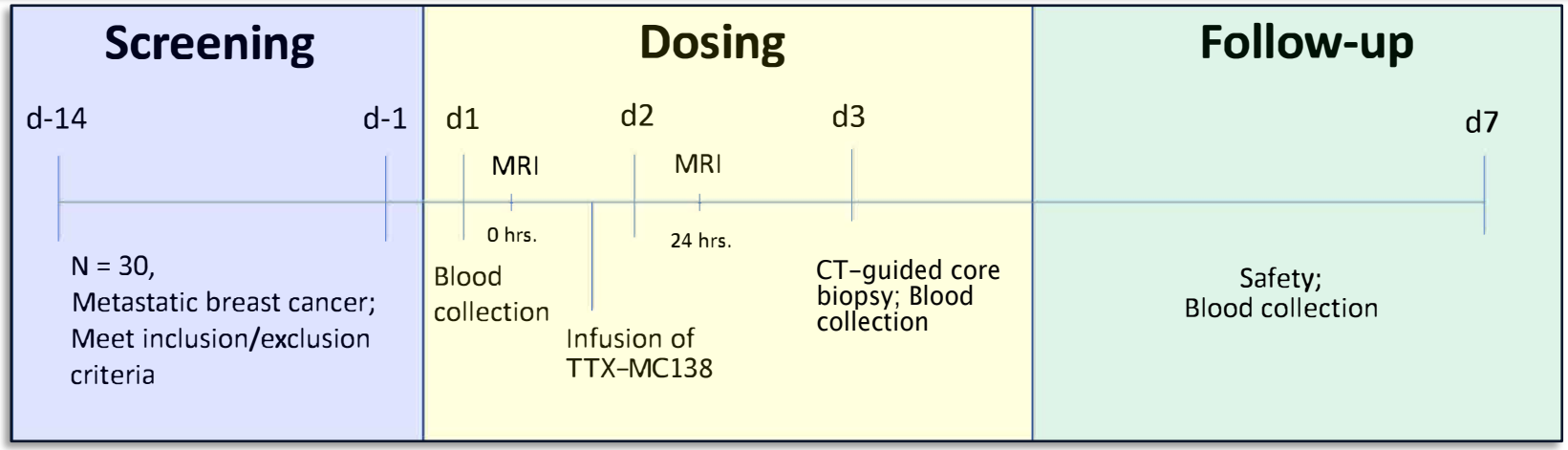
$34.0M

Cumulative

Value-Generating Milestones Create Multiple Liquidity Opportunities

Proof of Mechanism with Exploratory Investigational New Drug (EIND)

Phase 0 eIND Study Design



Study Summary

- Clinical objective: Delivery of TTX-MC138 to the intended target in humans
  - MRI pre and post therapy to visualize delivery to intended target
  - Measure microRNA-10b expression in patient serum pre and post therapy to determine successful target engagement
- Validate proof of delivery to target with MRI and histology
- Validate inhibition of microRNA-10b measuring HOXD10
- Single investigator study – Termeer Center – Dr. Dejan Juric
- 30 patients – 3 cohorts of 10 patients each - Stage IV Breast Cancer
  - Group 1 – 2.0mg/kg; Group 2 – 5.0mg/kg; Group 3 – 7.0mg/kg

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Clinical Assessment of Therapeutic Delivery in Humans to Drive Value Inflection

Phase 1 Trial Design

Study Design

Screening

Abbreviated Criteria
- microRNA-10b expression in serum
- Stage IV with primary tumor resected

Phase 1a

Escalation
Solid tumors (not otherwise specified)
3+3 dose escalation for MED & MTD

N=36 (3-6 subjects per dose)

Phase 1b

Expansion
All-comers that meet inclusion criteria
Expansion at MED dose

N=25

Study Summary

- Phase 1a objective: Dose finding & safety assessment
  - Secondary objectives: Confirm delivery to tumor site via MRI imaging & pharmacokinetics, microRNA-10b inhibition measured by qRT-PCR
- Phase 1b objective: Determine clinical response rate according to RECIST
  - Secondary objectives: ORR according to investigator's assessment, duration of response, safety and additional pharmacokinetic & pharmacodynamic evaluations
- 3 sites recruiting, including Mass General
- Follow up: 6 months

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Clinical Trial Design Assesses Safety & Determines Dose with Indication of Efficacy

Phase 2 Trial Design

Study Design

Screening | **Treatment** | **Follow up**

Abbreviated Criteria
- microRNA-10b expression in serum
- Stage IV with primary tumor resected

Treatment Cycles
Using MED identified in Phase I – basket trial with adaptive design
3 cohorts: breast cancer (n=18), colorectal (n=18), other solid tumors (n=25)

N=61

Follow up
12 months off-therapy

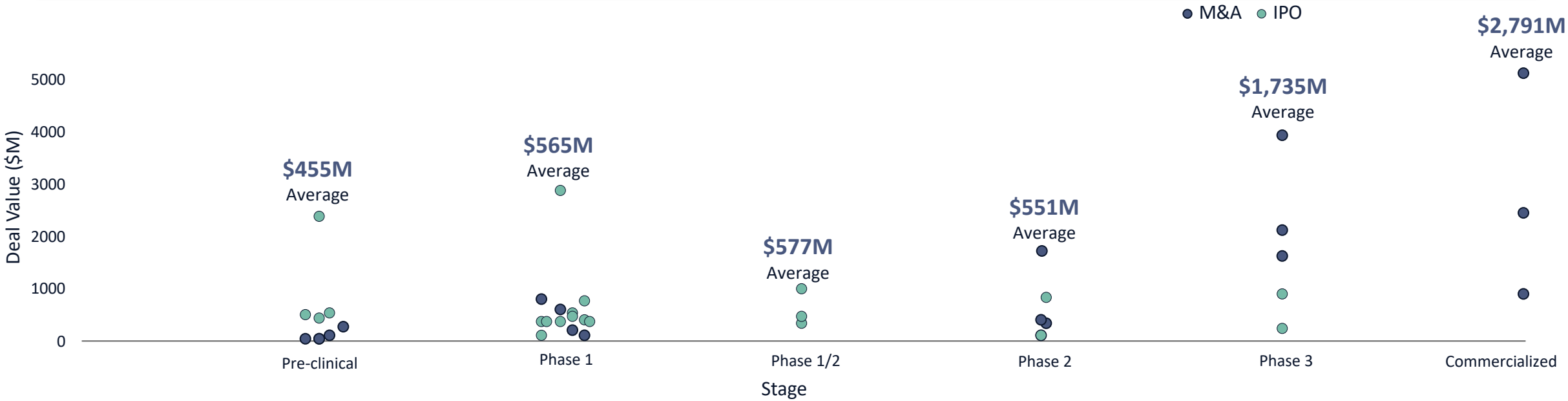
Study Summary

- Single-arm, open-label study, multi-center trial
- Malignancies most likely to show response in Phase I: breast cancer & colorectal
- Primary Endpoint: Best overall response rate as assessed by an independent review committee (RECIST, version 1.1)
- Secondary Endpoints: Duration of response, progression free survival, overall survival
- Patients treated until progression, follow up 12 months off-therapy

Clinical Trial Design based on Precedent

Oncology Assets Demonstrate High Return on Investment

Recent Oncology Deals



Deals from: 01/2018-03/2019, IPO deal value is market cap @ IPO, Large outliers Celgene, Impact Biosciences, Moderna & Loxo Removed

Exit Landscape Overview

- Large oncology exits happen during early stages
  - Average oncology Phase I deal value: $565M
- TransCode plans to seek an early partnership to add third-party validation & expand bench strength
- Substantial return on investment potential for oncology M&As & IPOs
  - Average M&A exit return is 10×, average IPO return is 2.5× (calculated at time of IPO)

Active Landscape for Early M&As & IPOs

Source: Pitchbook, company press releases

Current Management Team

	Name	Role	Experience	Education
	Michael Dudley	Co-Founder CEO & Director	• An entrepreneurial senior executive with over 35 years of with diversified industry experience within the biopharma industry and multiple medical device markets • Experienced in operations, finance, manufacturing, strategic planning & analysis, & P&L management • Has guided dozens of medical products through the FDA & CE mark approval processes	• BS in Biology from Kent State University
	Anna Moore, PhD	Co-Founder	• Professor of Radiology and Physiology; Director, Precision Health Program and Assistant Dean, College of Human Medicine at Michigan State University • 27 + years at Harvard Medical School/MGH, Professor of Radiology and Director of the Molecular Imaging Laboratory at the Martinos Center for Biomedical Imaging at MGH • International leader in targeted cancer imaging and image-guided drug delivery in cancer	• PhD in Bioorganic Chemistry from the Russian Academy of Sciences, Moscow, Russia
	Zdravka Medarova, PhD	Co-Founder, VP Drug Discovery	• Associate Professor of Radiology at Harvard Medical School • Developed core nanodelivery platform & identified microRNA-10b as a promising therapeutic target • Multiple publications in high-impact journals such as Cancer Research, Nature Medicine, Oncogene, & Scientific Reports	• BA in pre-medicine from the University of Southern Maine • PhD in Genetics from the University of New Hampshire
	Thomas Fitzgerald, MBA	CFO & Director	• Extensive CFO and investment banking experience • Led major turnaround of Velico Medical, Inc. when Velico had only six weeks of cash • CFO of other life sciences companies • Founding Managing Director of Leerink Partners Investment Banking group	• AB in Economics from Stanford University • MBA from the Harvard University Graduate School of Business Administration
	Oliver Steinbach, PhD	VP Clinical and Regulatory Affairs	• 20 + years leading preclinical and clinical R&D in pharma, diagnostics, medical technology. • PHILIPS: clinical research in Healthcare North America; molecular medicine in Global Innovation. ALTANA Pharma: preclinical drug development oncology and inflammation. • Managing interdisciplinary academic, commercial and international consortia & alliances	• PhD in Biochemistry from the University of Tuebingen & Max-Planck-Institute of Development Biology
	Judy Carmody, PhD	VP Operations	• 20+ years of experience providing consulting services in CMC and Clinical Operations, Quality, Validation and Analytical Development for Biologics, Small molecules, and DNA therapeutics • Founder and Principal Consultant of Carmody Quality Solutions, LLC • Previous Director of CMC and QbD at Vertex Pharmaceuticals	• M.A. in Analytical Chemistry from Clark University • Ph.D. in Analytical Chemistry from Clark University

Significant Expertise Added Through Active Advisory Board

Keith Flaherty, MD
Director of Clinical Research, MGH & Professor of Medicine, Harvard Medical School

- Clinical Oncologist; Past Dir. of the Termeer Center for Targeted Therapies, MGH
- >200 publications & principal investigator on several clinical trials, including vemurafenib; Member of BOD of Clovis Oncology and Checkmate Pharmaceuticals

George Calin, MD, PhD
Professor of Experimental Therapeutics & Co-Director of RNAi & Non-coding RNA Center, MD Anderson Cancer Center

- Studies miRNAs in cancer initiation & progression
- Named one of the most highly cited researchers by Thomson Reuters

Dmitry Samarsky, PhD
CTO, Sirnaomics

- Pioneer and internationally recognized expert in the field of RNAi therapeutics
- Held roles at Sequitur (acquired by Invitrogen), Dharmacon (now part of GE), RXi Pharmaceuticals, RiboBio & Silence Therapeutics

G. Susan Srivatsa, PhD
Founder and President of ElixinPharma

- World leading expert in strategic regulatory support in CMC for preclinical and clinical stage companies
- 27+ years experience development and regulatory support for oligonucleotide therapeutics, including multiple drug approvals in US and Europe

Betsabeh Madani Hermann, MBA
Partner, Advantary LLC

- Bringing globally impactful products and services from ideation and strategy throughout various stages of launch, partnership, growth, and implementation
- Expertise includes defining market requirements, creating build/buy/partner growth strategies

Jerome M. Lewis, MBA, PhD
Nanoparticle Consultant

- Pioneer in developing iron oxide nanoparticles used as contrast agents for magnetic resonance imaging
- Co-Inventor of 3 FDA approved nanoparticle formulations used to treat millions of patients with iron deficiency anemia

Jack Henneman, JD
Partner SparkMed Advisors
Director Aprea Therapeutics; R1 RCM; Seaspine

- Former CFO, NewLink Genetics & Integra LifeSciences Holdings Corp
- Led Integra's business development function & responsible for the more than 40 acquisitions & alliances

Raghu Kalluri, MD, PhD
Chairman & Professor of Cancer Biology & Director of the Metastasis Research Ctr, MD Anderson Cancer Ctr

- Previous Chief of the Division of Matrix Biology & Professor of Medicine at HMS
- Scientific Founder – Codiak Biosciences

Philippe Calais, PhD
Director, TransCode Therapeutics, Inc.

- 30+ years of biotech & pharma industry experience
- Former President & CEO of Isarna Therapeutics, developer of oligonucleotide therapeutics
- Previous President & CEO of Univalor & Ambrilia Biopharma

Unique Opportunity to Change the Future of Cancer Treatment

Focus on Elimination of Metastasis	• Focused on ***elimination of metastasis*** resulting in progression free survival without recurrence • Goal of improving treatment outcomes in patients with late stage cancer • Lead candidate therapeutic affects *only metastatic tumor cells* (**no toxicity in animal studies**)
Clear Regulatory Path & IP	• Potential to receive *breakthrough designation & expedited review by FDA* • **Received written guidance from FDA March 2020 on proposed eIND study supporting number of patients and dosing** • Expanded IP portfolio: Composition of matter & methods of use protected
Validated Targets	• Initial target - ***miR-10b - responsible for migration, invasion and viability of metastatic tumor cells*** • miR-10b substantiated by leading researchers – over 150 publications correlate miR-10b expression and metastasis
Translational Relevance	• TTX-MC138 - First in-class therapeutic – capable of treating multiple tumor types known to metastasize • ***Image-guided Delivery-system - backbone of therapeutic pipeline*** • Potential for use in combination with standard of care treatment modalities • Potential for blockbuster drug - Transforming the treatment of cancer
Investment Opportunity	• Seed Round - $3.7M - Convertible Note converts at valuation discount to Series A Preferred • Investment by RNAi Industry executive of $1.0M - Feb. 2020

Creating the Next Cancer Treatment Paradigm