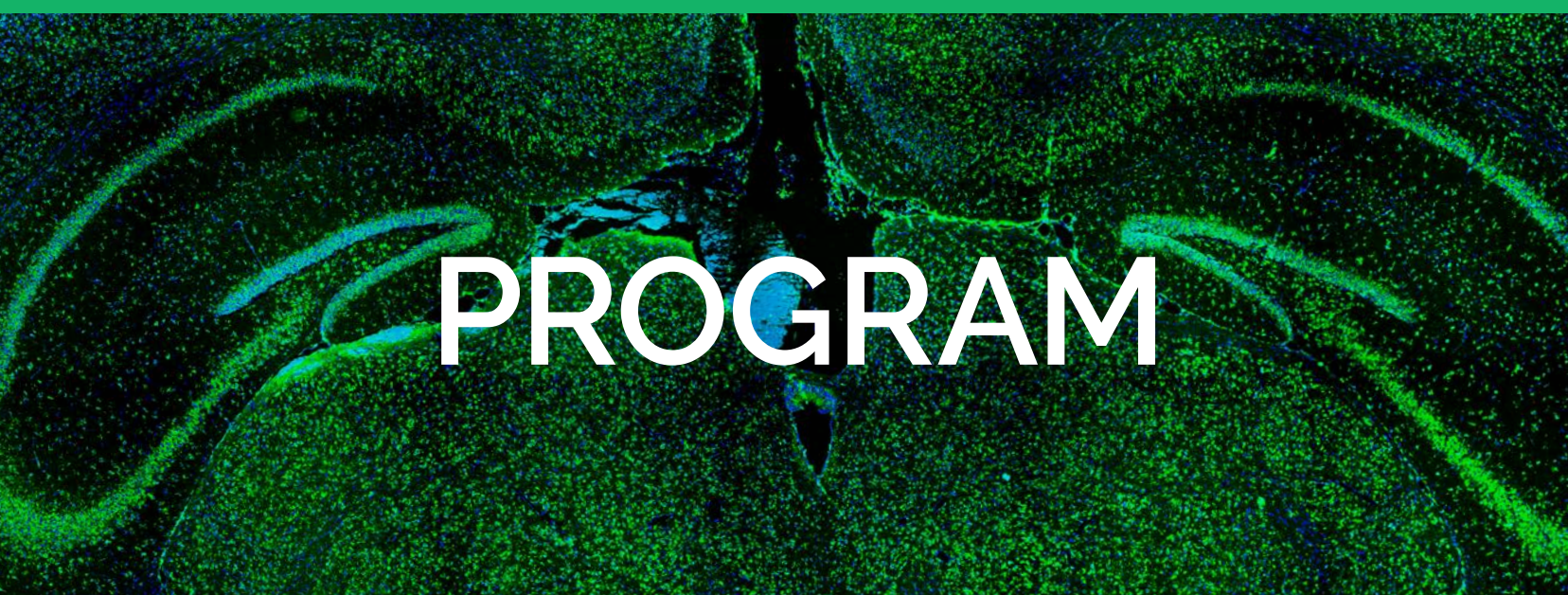
RNA Therapeutics Institute

UMass Chan MEDICAL SCHOOL

RNA Therapeutics: From Concept to Clinic



PROGRAM

JUNE 25-27, 2025

UMass Chan Medical School, Worcester, MA

#RNATx2025

@RTI-UMassChan.bsky.social

Dear Friends and Colleagues,

Welcome to the RNA Therapeutics Institute's seventh annual symposium, *RNA Therapeutics: From Concept to Clinic* at UMass Chan Medical School in Worcester, MA.

Throughout the latter half of the 20th century, RNA was thought mainly to intermediate between DNA and protein. Over the last three decades, that view has given way to the understanding that RNA plays rich and complex roles previously ascribed only to proteins. From ncRNAs to RNAi, from CRISPR to circular RNAs, we have witnessed astonishing discoveries and equally amazing translation of these breakthroughs to therapies. We are delighted to feature speakers whose fascination with RNA biology has inspired them to explore the possibilities of harnessing RNA to create therapeutics.

For those of you attending in person, welcome to the RTI and UMass Chan! We are thrilled to have you on campus. For those of you attending virtually, we are happy for you to join us from where you are and we hope that you'll be able to attend in person in the future.

To stimulate dialogue, we've included time in the program for discussion during our welcome reception on Wednesday evening, and after each talk, as well as during the poster sessions, lunches, and our ChemGenes-sponsored RNATx party at Top of the Town on Thursday evening. The scientific sessions and posters, drawn from our international call for abstracts, offer a taste of the newest work in the field and provide new opportunities to forge collaborations with current and future thought-leaders in the RNA community.

We would like to thank everyone who has worked diligently to create this symposium, particularly the talented staff at the RTI. We especially thank our speakers for their enthusiastic participation. Finally, we are most grateful to our sponsors and exhibitors for their generous support.

Sincerely,

Phillip D. Zamore, Ph.D.
Angela Messmer-Blust, Ph.D.
RNA Therapeutics Institute
UMass Chan Medical School

Symposium Co-Organizers

RNA Therapeutics: From Concept to Clinic

Contents:

Cover Image: This figure shows delivery of 100 nmol ASO (anti-ASO antibody, green) via intracerebroventricular injection, coronal hippocampus section (DAPI, blue). Image acquired by Mike Moazami, Jon Watts Lab, RTI, UMass Chan Medical School.

Signage: All of the microscopy images on symposium signage and VFairs virtual platform were taken here at UMass Chan Medical School by the Gao, Grigorieff, Grunwald, Khvorova, Korostelev, Mello, Pazour, Watts, Xue, and Zamore labs.

On-Site Information

IN-PERSON VENUE
UMass Chan Medical School
Albert Sherman Center (ASC or AS)
368 Plantation Street
Worcester, MA, 01605 USA

ONLINE VENUE
RNATx2025.vfairs.com

REGISTRATION

Dates	Times	Location
Wednesday, June 25 *(career workshop attendees must register by 12:45pm)*	10:00am–4:00pm EST	Albert Sherman Center, 1st Floor Lobby
Thursday, June 26	7:30–9:00am EST	Albert Sherman Center, 1st Floor Lobby

The registration desk will be open for queries, mother's room badges, and registration throughout the conference. After Thursday morning, the registration/help desk will be located outside of the Albert Sherman Center (ASC) auditorium.

Please write your name in your program booklet and do not leave either your program unattended at the symposium (for example, on your seat in the meeting room during breaks). Unfortunately, replacements for lost programs are not available.

CAREER WORKSHOP & SCIENTIFIC SESSIONS LOCATIONS

Session	Location	Room
Career Workshop: Wednesday, June 25	Paul J. Dimare Center, 1st floor	Conference Room
Welcome Reception: Wednesday, June 25	Paul J. Dimare Center, 1st and 2nd floors	Foyer and Terrace Areas
Keynote and Scientific Sessions: Wednesday, June 25 Thursday, June 26 Friday, June 27	Albert Sherman Center, 2nd and 3rd Floors (balcony entrance on 3rd floor) Overflow: 4th floor, ASC	Auditorium: ASC2.2102 Overflow Room: Faculty Conference Room & ASC4-2072
Poster Sessions and Exhibitions: June 25–27	Medical School Building	Medical School Lobbies Faculty Conference Room
Breakfasts and Lunches: June 25–27	Albert Sherman Center, 1st floor	Multi-Purpose Room
Refreshment Breaks: June 26–27	Medical School Building	Medical School Lobbies

BREAKFAST, LUNCH, REFRESHMENTS, WELCOME RECEPTION, AND RNATx PARTY

Catering Arrangements	Dates	Times
Welcome Reception	Wednesday, June 25	4:30–6:00pm EST
Breakfast	Thursday, June 26 Friday, June 27	Thursday 7:45–8:45am EST Friday 7:45–8:55am EST
Lunch	Thursday, June 26 Friday, June 27	Please see the full program
Refreshment Breaks	Thursday, June 26 Friday, June 27	Please see the full program
RNATx Party at the Top of the Tower *(You must have tickets; pick up at registration/help desk)*	Thursday, June 26	Shuttles will arrive on campus and begin to board at 5:45pm on North Road. Dinner will be served from 6:00–8:30pm. Shuttles will start returning to campus and hotels at 8pm until 9:30pm.

SPEAKERS

All oral presenters are reminded to be in the Albert Sherman Auditorium ASC2.2102 **no later than 30 minutes before the start of the session** in order to meet with the session chair and finalize the setup of presentation visuals.

EXHIBITORS

We are excited to welcome our exhibitors who generously support this meeting. Please take the time to visit them during the refreshment breaks and poster sessions in the Medical School Lobbies and Faculty Conference Room.

PARKING

Please look for event parking signage when arriving to the UMass Chan Campus. Parking will be available in the Biotech II lot with free valet or at the Beechwood Hotel for those guests staying at the hotel. There is also limited parking in the South Street Garage on a first come, first served basis.

RNATx PARTY at the Top of the Tower

The symposium dinner and party will take place on Thursday, June 26th from 6:00pm to approximately 9:30pm at the Top of the Tower. Dress is casual. Shuttles will be available to transport guests from the 3rd floor of the Albert Sherman Center on North Road at 5:45pm. Your dinner ticket can be picked up at the registration/help desk. Please make sure that you bring the ticket with you.

Top of the Tower
https://topofthetowerworcester.com/
446 Main Street, downtown Worcester, Massachusetts
Dinner & drinks will be served.

POSTER SESSIONS

Poster Session	Pin Up Time	Session Date	Time	Take Down
Even Posters (and P15)	Wednesday, June 25 10:00am–3:00pm	Thursday, June 26	1:45–3:30pm	Friday, June 27 by 3:00pm
Odd Posters	Wednesday, June 25 10:00am–3:00pm	Friday, June 27	1:15 – 2:45pm	Friday, June 27 by 3:00pm

*NOTE: **All posters may stay up for the duration of the symposium.** Any posters remaining after the take-down time has passed will be removed by the organizers and recycled.

SHUTTLE SCHEDULE

Date	Time	Location Pick-up	Drop-off/Pick-up
Wednesday, June 25	10:00am–4:00pm	Biotech II, Third Road by the Lazare Research Building (LRB)	Biotech II, Beechwood
Wednesday, June 25	5:30–6:15pm	Third Road by the Lazare Research Building (LRB)	Biotech II, Beechwood
Thursday, June 26	7:30–10:00am	Beechwood, Biotech II	Biotech II, Third Road/LRB
	5:15–5:45pm	Biotech II, Third Road/LRB	Biotech II, Beechwood
	5:45–6:30pm	Biotech II, North Road, 3rd Floor ASC entrance	Biotech II, Top of the Tower
	8:00–10:00pm	Biotech II, Top of the Tower	Biotech II, Beechwood, & Third Road/LRB
Friday, June 27	7:30–9:00am	Beechwood, Biotech II	Biotech II, Third Road/LRB
	5:30 – 6:30pm	Biotech II, Third Road/LRB	Biotech II, Beechwood

*NOTE: Shuttle schedule times may change slightly; changes will be communicated via registration desk and housekeeping slides.

PROGRAM

Any last-minute changes to the program will be made within the app, printed and found at the registration desk, and indicated on the housekeeping slides in the Albert Sherman Auditorium.

IN-PERSON ATTENDEES NOTICE OF PHOTOGRAPHY

Please be aware that by attending the 2025 RNA Therapeutics: From Concept to Clinic Conference, you are entering an area where photography, audio, and video recording may occur. By entering the symposium, you consent to your voice, name, and/or likeness being used, without payment or royalties, in photography and film in all media, whether now known or hereafter devised, for eternity, and you release UMass Chan Medical School, the RNA Therapeutics Institute, its successors, assigns, and licenses from any liability whatsoever of any nature. *If you do not want to be photographed, please tell the professional photographer this with your name.*

ABSTRACTS
To save paper, abstracts are available via a secure online link, on the app, and on the virtual platform.
PDF Abstract Link: **https://go.umassmed.edu/2025-RNATx-abstract-book**

WIFI
WiFi is available free of charge on the UMass Chan Medical School Campus. Go to your settings and Join "UMASSMED-GUEST"; a screen will pop up with terms and conditions of use. You will need to "ACCEPT" to connect. Please see the registration desk for any questions.

SOCIAL MEDIA
Official symposium hashtag: **#RNATx2025**
Bluesky Account: **@rti-umasschan.bsky.social**

Symposium platform: **RNATx2025.vfairs.com**
Symposium website: **www.rnatherapeutics.org**

The organizers encourage attendees to post about the remarkable science they experience at the meeting. Please respect the following rules in your posts and tweets:
1. Be polite and respectful of others.
2. Never post/tweet about unpublished data.
3. Be respectful of those presenters that ask attendees to refrain from tweeting content from talks and posters.
4. If you're enjoying the conference, share it with your social media network!
5. Take some photos with your lab and share them with the symposium hashtag: **#RNATx2025**!

CONFERENCE APP
Please scan this QR code or use the link below on your mobile phone to access to our online conference app. The app contains access to the digital program, program book, abstract book, and you can stream the conference from the app.
https://qrco.de/RNATx25

CONFERENCE HARASSMENT POLICY
2025 RNATx is dedicated to providing a harassment-free conference experience for everyone, regardless of gender, gender identity and expression, sexual orientation, disability, physical appearance, body size, race, age or religion. We do not tolerate harassment of conference participants in any form. Sexual language and imagery is not appropriate for any conference venue, including talks. Conference participants violating these rules may be expelled from the conference (without a refund) at the discretion of the conference organizers. Our anti-harassment policy and how to report any violations can be found at: **https://qrco.de/bg0C3n**

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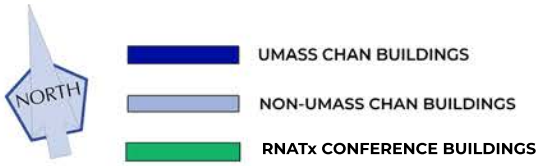

2025 RNA Therapeutics Symposium

June 25: **Career Workshop**, Paul J. Dimare Center
Welcome Reception, Paul J. Dimare Center

June 25-27: **Registration**, 1st floor, Albert Sherman Center (ASC) **Scientific Sessions**, 2nd Floor, Auditorium, ASC

June 26: Shuttle Pick up and Drop Off for **Top of the Tower, RNATx Party**, Third Rd.

June 25-27: **Poster Sessions & Exhibitors**, Medical School Building Lobbies

Symposium Parking: Biotech II Parking lot

TO I-190
PLANTATION ST. GARAGE
EMPLOYEE PARKING
PLANTATION STREET
BIOTECH 5
BIOTECH 4
ANDERSON HOUSE
TO WORCESTER RECOVERY CENTER
UNIVERSITY COMMONS
BIOTECH 2
MERCADANTE FUNERAL HOME
NORTH ROAD
FACILITIES LOT
BIOTECH 3
CLOCKTOWER DRIVE
LIBRARY LOT
POWER PLANT
ALBERT SHERMAN CENTER
MEDICAL SCHOOL BUILDING
CLINICAL LOT
STATE LOT
LAKE AVE NORTH
BIO 3 PARKING
367 PLANTATION ST.
INNOVATION DRIVE
WEST GARAGE, EMPLOYEE PARKING
PAUL J. DIMARE CENTER
QUAD 1
UMASS MEMORIAL MEDICAL CENTER
HELIPAD
BIOTECH 1
THIRD ROAD
LAZARE RESEARCH BUILDING
QUAD 2
VALET
BENEDICT BLDG.
HP LOT
SOUTH ROAD
Beechwood Hotel
RESEARCH DRIVE
U.S. ARMY RESERVE
LOWER PINE TREE LOT
QUAD 3
AMBULATORY CARE CENTER
SOUTH GARAGE
PATIENTS & VISITORS
VA BUILDING
VA PARKING LOT
DMH CENTRAL MASS.
PAUL T. LEAHY CENTER
UPPER PINE TREE LOT
QUAD 4
VA PARKING LOT
SHAW BUILDING
TO SHREWSBURY
BELMONT STREET (ROUTE 9)
TO DOWNTOWN WORCESTER

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*Virtual exhibitors only

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ScienceLIVE Educational Outreach Program Contributions

Generous contributions to the ScienceLIVE Outreach Program made by:

CHEMGENES

Wednesday, June 25, 2025

10:00am–2:30pm	**Registration | Albert Sherman Center (ASC) Lobby**
1:00–2:30pm	**Career Workshop** | Paul J. DiMare Center Conference Room | *Sponsored by Lathrop GPM (Pre-registration required)*
2:40–2:45pm	Welcome and Introduction, **Phillip D. Zamore**, *HHMI, RTI, UMass Chan Medical School* | ASC2.2102 Auditorium and Online
2:45–3:30pm	**Regulation of Exogenous RNAs: From Viral RNAs to mRNA Therapeutics** **Keynote: V. Narry Kim,** *Seoul National University*
3:40–4:15pm	**Poster Flash Talks |** ASC2.2102 Auditorium and Online *Session Chair: Theodore Carrigan-Broda, RTI, UMass Chan*
4:15–6:00pm	**RNATx Kickoff & Welcome Reception |** Paul J. DiMare Center 1st and 2nd Floor Foyer Areas and 2nd Floor Terrace

Thursday, June 26, 2025

7:45–8:50am	**Registration and Continental Breakfast,** *sponsored by **Alnylam*** | ASC Lobby and Multipurpose Room
8:50–8:55am	Welcome and Introduction, **Phillip D. Zamore**, *HHMI, RTI, UMass Chan Medical School*
	Session I: The Long and the Short of ncRNAs | ASC2.2102 Auditorium and Online *Session Chairs: Samantha Ho & Haoyang Cheng, RTI, UMass Chan*
8:55–9:20am	**MicroRNA-Mediated Gene Regulation in Animal Development** **Victor Ambros,** *UMass Chan Medical School*
9:25–9:50am	**Conserved Roles of miRNAs in Development** **Luisa Cochella,** *Johns Hopkins School of Medicine*
9:55–10:20am	**Investigating the Structure-Function Relationships of Noncoding RNAs** **Alisha "Jonesy" Jones,** *New York University*
10:25–10:35am	**Evidence for Mutator Component-Independent piRNA Silencing in C. elegans** **Wendy Tan**, *RTI, UMass Chan Medical School*
ON DEMAND	**Short Talks**
10:40–11:10am	**Networking & Coffee Break** | Medical School Lobbies, *Sponsored by **AbbVie***
	Session II: RNA Structure and Mechanism | ASC2.2102 Auditorium and Online *Session Chairs: William Cruz & Min Zhang, RTI, UMass Chan*
11:15–11:40am	**From Noise to Signal: Studying the Efficiency of mRNA Splicing** **Athma Pai,** *RTI, UMass Chan Medical School*
11:45–12:10pm	**tRNA Modifications & Codon-Biased Translation in Cancer** **Richard I. Gregory**, *UMass Chan Medical School*
12:15–12:25pm	**Cell Surface glycoRNA Biology** **Ryan Flynn,** *Boston Children's Hospital*, *Harvard Medical School*
12:30–12:40pm	**Uncovering the Postfertilization Regulatory Mechanisms Required for Intergenerational Epigenetic Inheritance in Mice** **Grace Lee,** *University of Pennsylvania*
12:45–1:45pm	**Lunch |** ASC Multipurpose Room (MPR), *sponsored by **Alloy Therapeutics***
1:45–3:30pm	**Poster Session I (Even Posters) *sponsored by ChemGenes* & Exhibit Hall** | Medical School Lobbies & Online
	Session III: RNA Technologies | ASC2.2102 Auditorium and Online *Session Chairs: Marina Krykbaeva & Valeria Sanabria, RTI, UMass Chan*
3:30–3:55pm	**Cross-Kingdom RNA Communication & RNA-Based Innovative Strategies for Crop-Protection** **Hailing Jin**, *UC Riverside*
4:00–4:25pm	**Ancient RNA - Possibilities and Limitations** **Marc Friedländer,** *Stockholm University*
4:30–4:40pm	**irCLIP-RNP and Re-CLIP Reveal Patterns of Dynamic Protein Assemblies on RNA** **Luca Ducoli**, *Stanford University*
4:45–4:55pm	**Mime-seq 2.0: Cell-Specific Sequencing of microRNAs From Mammalian Tissues and Organs** **Ariane Mandlbauer**, *Johns Hopkins University*
5:00–5:10pm	**Deep Generative Models Generate mRNA Sequences With Enhanced Translational Capacity and Stability** **He Zhang,** *Raina Biosciences*

6:00pm	**2025 RNATx Party at the Top of the Tower, ticket required** *Sponsored by ChemGenes*

Friday, June 27, 2025

7:45–8:45am	**Registration and Continental Breakfast** *sponsored by* ***City Therapeutics*** | ASC Lobby and MPR
	Session IV: ASOs, Delivery, and Cancer Therapeutics | ASC2.2102 *Session Chairs: Thomas Ormsby & Matt Yee, RTI, UMass Chan*
8:45–9:10am	**Development of SORT Lipid Nanoparticles (LNPs) for Genome Correction of Disease-Causing Mutations** **Daniel J. Siegwar**t, *UT Southwestern*
9:15–9:40am	**Gain and Loss of RBP Functions a Cancer-Associated Mutation** **Daniel Dominguez**, *UNC School of Medicine*
9:40–9:50am	**Mirror-Image Nucleic Acids as Advanced Molecular Therapies** **Wen Zhang**, *Indiana University School of Medicine*
9:55–10:20am	**The Basic and Applied Biology of Exosomes in Cancer** **Raghu Kalluri,** *MD Anderson Cancer Center*
10:20–10:50am	**Networking and Coffee Break** *sponsored by* ***CAMP4*** **|** Medical School Lobbies
	Session V: Editing | ASC2.2102 *Session Chairs: Anis Barati & Daniel MacVeigh-Fierro, RTI, UMass Chan*
10:55–11:20am	**Development and Characterization of Precision Genome Editing Tools** **Alexis Komor,** *University of California, Berkeley*
11:25–11:35am	**Applying AIMer-Based RNA Editing Technology to Nonsense Mutation Correction in the CNS and Lung** **Genliang Lu**, *Wave Life Sciences*
11:40–11:50am	**Prime Editing-Mediated Conversion of an Endogenous tRNA Gene Into a Suppressor tRNA for Disease-Agnostic Therapeutic Genome Editing** **Sarah Pierce,** *Broad Institute*
11:55–12:05pm	**Mechanistic Insights Into CRISPR-Associated Transposons and Implications for Programmable Gene Insertion** **Leifu Chang,** *Purdue University*
12:10–12:20pm	**Developing Bespoke Gene Editing Treatments for Patients With Carbamoyl Phosphate Synthetase 1 (CPS1) Deficiency in Real Time: Successes and Challenges** **Xiao Wang,** *University of Pennsylvania*
ON DEMAND	**Short Talks**
12:25–1:15pm	**Lunch,** *sponsored by* ***Eli Lilly & Co.*** | ASC Multipurpose Room (MPR)
1:15–2:45 pm	**Poster Session II (Odd Posters),** ***sponsored by ChemGenes*** **and Exhibit Hall** | Medical School Lobbies
	Session VI: Translating Discoveries | ASC2.2102 *Session Chairs: Annie Collins & Emily Knox, RTI, UMass Chan*
2:45–3:10pm	**Receptor Mediated Targeted Delivery to Proximal Tubules in Kidney** **Alfica Sehgal,** *Judo Bio*
3:15–3:25pm	**MicroRNA-21 is a Potential Therapeutic Agent Targeting Tgfbi and Mitigating High-Fat-Diet-Induced Liver Disease and Cancer** **Urmila Jagtap,** *Beth Israel Deaconess Medical Center, Harvard Medical School*
3:30–3:55pm	**Cancer Genes Beyond Chromosomes** **Howard Chang**, *Amgen*
4:00–4:10pm	**Advancing an Intrathecal Divalent siRNA for Prion Disease as an Investigator-Initiated Program** **Eric Vallabh Minikel,** *Broad Institute*
4:15–4:25pm	**RSwitch-enabled Gene Therapy to Fine Tune Frataxin Expression for the Treatment of Friedrich's Ataxia** **Jon Dempersmier,** *Rgenta Therapeutics*
4:30–4:40pm	**Unlocking the Full Potential of RNAi Therapeutics with LEAD™** **Chunyang Zhang,** *Sanegene Bio*
4:45–5:30pm	**Biomimetic Chemistry of RNA Therapeutics** **Keynote: Mano Manoharan,** *Alnylam Pharmaceuticals*
5:35pm	**Closing Remarks, Awards, and THANK YOU!**

POSTER PROGRAM

Posters are located in the Medical School Building Lobby and Faculty Conference Room. **Even Posters** and **P15** will be presented in **session I, Thursday, June 26,** and **Odd Posters** will be presented in **session II, Friday, June 27**. All posters will remain up throughout the symposium, both in-person and online; additional virtual posters (**VP1, VP2, VP3, VP4, VP70,** and **VP90**) will be online only. Posters **P1, P2, P3, P4, P5, P54, P55, P56, P78, P84, P96, P97, P98, P99, P132, P133, P134,** and **P138** are presenting flash talks Wednesday, June 25th at 3:40pm.

***Poster Flash Talk; **Late Breaking or Changed to Virtual Poster**

Poster	Authors	Title
***P1**	**Eraj Khokhar,** Kaitlyn Brokaw, Ayush Kumar, Nida Javeed, Zachary Kartje, Ezequiel Calvo, Marina Krykbaeva, Jonathan Watts, and Athma Pai	Splicing Fidelity Influences the Fate of mRNA Molecules
***P2**	**Humberto Ochoa**, Daniel Durning, Siyuan Dai, and Craig Mello	A Guide RNA-Deficient Argonaute Reveals Spatial Coupling of Nuclear piRNA Transcription and Perinuclear Processing in C. elegans
***P3**	**Harleen Saini**, Jiuchun Zhang, and Danesh Moazed	Genetic Compensation in β-actin Mutants Occurs Independently of Mutant mRNA Decay
***P4**	**Anastasios Vourekas**, Abd-El Monsif A. Shawky, Allison Scarboro, Mahmoud Dondeti, Josef Mick, Kenneth Avanzino, Constantine A. Simintiras, and Maria Hatzoglou	DDX3X Acts as a Selective Dual-Switch Regulator of mRNA Translation in Acute ER Stress
***P5**	**Tianxiong Yu**, William Theurkauf, Zhiping Weng, Jeremy Luban, Keith Chappell, Michaela Blyton, Birgit Koppetsch, Samantha Ho, and Milky Abajorga	The piRNA Pathway Response to Retroviral Invasion in Wild Koalas
P6	**Ayca Bagci** and Phillip D. Zamore	Developing Tools To Understand piRNA Precursor Trafficking
P7	**Shannon Bailey**, Amena Arif, Phillip D. Zamore, and Karina Jouravleva	How Does GTSF1 Accelerate Target RNA Cleavage by PIWI-Clade Argonaute Proteins?
P8	**Adriano Biasini**, Sam Hildebrand, Anastasia Khvorova, Phillip D. Zamore	Comprehensive Capture and Termini Identification of Small Noncoding RNAs
P9	**Hannah Brown**, Haik Varderesian, Sara Keane, and Sean Ryder	The Mex-3 3' Untranslated Region is Essential for Reproduction During Temperature Stress
P10	**Ezequiel Calvo-Roitberg**, Adam Hedger, Jonathan Watts, and Athma Pai	Kinetic Barcoding: A Novel Tool To Estimate Multi-Temporal RNA Biogenesis Kinetics
P11	**Katharine Cecchini,** Nandagopal Ajaykumar, Ayca Bagci, and Phillip D. Zamore	Mammalian Pachytene piRNAs Persist in Evolution Because Target Cleavage by a Tiny Minority of piRNAs Improves Sperm Fitness
P13	**Peren Coskun** and Sean Ryder	The Post-Transcriptional Regulation Mechanism and Functional Importance of a Key Maternal mRNA, glp-1
P14	**Daniel Durning**, Humberto Ochoa, Takao Ishidate, and Craig Mello	ZNFX-1 Plays a Surprisingly Complex Role in Propagating Epigenetic States Across Generations
P15	**Johan Girgenrath** and Craig Mello	Regulation of Cell-Fate Specification via the SUMOylation of Chromodomain Protein MRG-1
P16	**Saumya Gupta**, Andrew Berglund, and John Cleary	Characterization of MBNL1 RNA Binding Protein Domains that are Important for Regulating Alternative Splicing
P17	**Ravi Kumar Gutti**	Developmental Megakaryocytopoiesis: A Study on Novel Role of Clinically Significant non-coding RNA in Understanding Neonatal Thrombocytopenia
P18	**Samantha Ho,** Sara Keane, Chan Zhou, Yujie Chen and Wenwen Fang	A Novel Approach to Identify Double Stranded RNA using a Mouse Oocyte-specific Dicer Isoform
P19	**Seong Hyeon Hong,** Katarine Cecchini, and Phillip D. Zamore	On the Origin of piRNAs: How Do Germ Cells Know Which Transcripts Make piRNAs?
P20	**Mikhail Klenov**	Piwi and piRNA Repress Transcription of Aberrant rRNA Genes

Poster	Authors	Title
P21	**Yongjin Lee,** Adriano Biasini, Cindy Tipping, and Phillip D. Zamore	Loss of the Integrator and Nuclear Exosome Targeting Complexes Disrupts Oogenesis and Causes the Emergence of Atypical Transcripts in Drosophila
P22	**Jesse Lehman** and Athma Pai	Temporal Regulation of mRNA Biogenesis in Immune Responses
P23	**Michael McGurk**, David McWatters, and Christopher Burge	KATMAP: Inferring splicing factor activity and regulatory targets from knockdown data
P24	**Sharon Noronha**, Asli Ertekin, Francesca Massi, and Sean Ryder	Mutation of Arginine-Rich Sequence in oma-1 Causes Novel Phenotypes
P25	**Juan Rodrigo Patiño-Mercau**, Giulia Gaggi, Lucrezia Rinaldi, Marta Borchiellini, Mailin Li, Simone Ummarino, Davide D'Onghia, Alexander K. Ebralidze, Daniel G Tenen, and Annalisa Di Ruscio	Studying Small Activating RNAs' Molecular Mechanisms
P26	**Cole Pero** and Craig Mello	TOFU-7 Facilitates Mitochondrial Coordination of piRNA Processing in C. elegans
P27	**Andrew Petti,** Felix Raimundo, Jill Moore, and Wen Xue	RiboSlip is a Machine Learning Model That Can Predict Ribosomal Frameshifts in Human and Viral Genes
P28	**Paolo Pigini**, Huilin Xu, Hannah Lindmeier, and Yan Ji	Defining the Landscape of Poison Exon Splicing Events in the Human Brain: Implications for Neurodevelopmental and Neurodegenerative Disorders
P29	**Mukulika Ray**, Julia Zaborowsky, Pranav Mahableshwarkar, Smriti Vaidyanathan, Jasmine Shum, Annie Huang, Isabelle Pilo, Victoria Chen, Sarah Gunasekera, Megan Carlson, Nicolas Fawzi, and Erica Larschan	Transcription Factor and RNA Binding Proteins Targeting RNA Splicing at the Right Genomic Location
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KEYNOTE ABSTRACTS

Regulation of exogenous RNAs: From viral RNAs to mRNA therapeutics

V. Narry Kim
Seoul National University

RNAs of external origin, such as viral RNAs and therapeutic mRNAs, rely on cellular machinery for entry and translation while facing cellular barriers that restrict their functions. Thus, for developing effective antivirals and RNA therapeutics, it is important to understand how cells deal with RNAs. In this presentation, I will discuss two recent studies exploring the regulatory mechanisms of exogenous RNAs.

In the first part, I will talk about our studies on viral RNA regulation. Using massively parallel reporter assays of viral genomic segments, we discovered hundreds of RNA elements that control RNA stability and translation. Investigation of their mechanisms provides new insights into the regulation of both viral and cellular RNAs. Moreover, RNA enhancers identified in this study drastically improve mRNA therapeutics by blocking deadenylation and promoting translation. This research creates a valuable resource while highlighting the potential of viral genomes for biological discovery and therapeutic development.

Second, I will present our recent results from genome-wide screens of *in vitro*-transcribed (IVT) mRNAs encapsulated in lipid nanoparticles (LNPs), from which we identified key cellular factors that impact mRNA therapeutics. By comparing mRNAs with and without N1-methylpseudouridine modification, we also uncovered the mechanism by which this modification enhances protein production from IVT mRNAs. Our study provides a comprehensive map of cellular pathways regulating exogenous mRNAs, offering insights for improving RNA therapeutics.

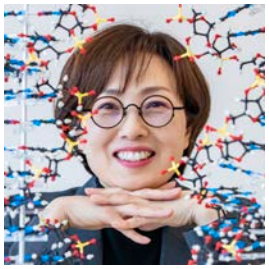
Biomimetic Chemistry of RNA Therapeutics

Muthiah Manoharan
Alnylam Pharmaceuticals

According to Professor Ronald Breslow, “biomimetic chemistry” is new chemistry inspired by the principles used by Nature. Synthetic small interfering RNAs (siRNAs) are potent inhibitors of gene expression. These molecules are perfect examples of biomimetic chemistry as synthetic siRNAs act through the natural RNA interference (RNAi) pathway. To deliver therapeutic siRNAs into human liver, we developed approaches that include chemical modification of the siRNAs and either lipid nanoparticle (LNP) formulation or multivalent N-acetylgalactosamine (GalNAc) conjugation, making possible intravenous and subcutaneous administration, respectively. The design of chemical modifications of siRNAs to enable favorable Argonaute2 (Ago2) recognition as well as both delivery strategies rely on biomimetics. The LNP approach is based on the endogenous Apo-E ligand /LDL receptor process. Conjugation of the GalNAc ligand to an siRNA mediates it uptake into liver hepatocytes through the asialoglycoprotein receptor. Using these strategies five approved RNAi therapeutics have emerged from Alnylam. We have also used lipid conjugates for CNS delivery of therapeutic siRNAs.

This presentation will cover the chemical biology of RNA therapeutics including the chemical modifications and motifs used in each RNA strand to ensure uptake into cells of the targeted tissue, Ago2 recognition, silencing efficiency, metabolic stability, and safety.

KEYNOTE BIOGRAPHIES



V. Narry Kim, Ph.D.
Director, Center for RNA Research
Institute for Basic Science & Seoul National University

Dr. Narry Kim is a Professor in the School of Biological Sciences at Seoul National University and a founding Director of the RNA Research Center at Institute for Basic Science (IBS). Kim graduated from Seoul National University in 1992 and received her Ph.D. in 1998 from the University of Oxford where she studied lentiviruses and gene delivery. For postdoctoral training, she joined the Gideon Dreyfuss lab at the University of Pennsylvania to study mRNA surveillance. Kim moved back to Seoul National University in 2001 to set up her own group and has been investigating how genes are regulated at the RNA level.

The Kim lab delineated the microRNA pathway, identified key factors including DROSHA, and revealed their action mechanisms and structures. Her group also uncovered the roles of noncanonical RNA tailing such as uridylation and mixed tailing in the control of microRNAs, mRNAs, and viral RNAs. She is a recipient of the L'Oreal-UNESCO Women in Science Award, the Hoam Prize, and the Asan Prize; was elected members of KAS, NAS, EMBO, and the Royal Society; and serves on the editorial boards of Science, Cell, Molecular Cell, GD, and EMBO J.

Muthiah 'Mano' Manoharan, Ph.D.
Senior Vice President of Drug Innovation, Distinguished Research Scientist
Alnylam

Dr. Muthiah (Mano) Manoharan serves as the Senior Vice President of Drug Innovation, a Scientific Advisory Board Member, and a Distinguished Research Scientist at Alnylam Pharmaceuticals, Cambridge, Massachusetts. In 2003, he was the founding chemist hired at Alnylam as the Head of the Drug Discovery. He and his team pioneered the discovery and development of numerous chemical modifications, GalNAc conjugation chemistry, lipid conjugates (the first in vivo demonstration of RNAi in 2004) and Lipid Nanoparticles (LNP) delivery platform that made RNA interference-based human therapeutics possible.

Prior to joining Alnylam, he worked at Isis (Ionis) Pharmaceuticals in the field of antisense oligonucleotides. He is an author of more than 250 publications (more than 70,000 Google Scholar citations with an h-index of 123 and an i10-index of 452) and over 500 abstracts, as well as an inventor of over 300 issued U.S. patents.

Among the numerous awards Dr. Manoharan has earned, two are worth pointing out: He is the winner of the Lifetime Achievement Award of the Oligonucleotide Therapeutics Society (OTS, 2019), and has been honored with the Professor Ronald Breslow Biomimetic Chemistry National award by the American Chemistry for the year 2024.

Dr. Manoharan was born in Madurai, Tamil Nadu, India and received his B.Sc. and M.Sc. degrees in chemistry at the American College, Madurai, India. He earned his Ph.D. in chemistry at the University of North Carolina, Chapel Hill, (Professor Ernest L. Eliel) and learned the field of oligonucleotides at Yale University and University of Maryland as a post-doctoral research associate (Professor John A. Gerlt).

LIVE, IN-PERSON SHORT TALK ABSTRACTS

Evidence for Mutator component-independent piRNA silencing in C. elegans.

Wendy Tan and Craig Mello
RTI, UMass Chan Medical School, Worcester, MA, USA

Despite deep conservation of the piRNA pathway components and their well-established importance in fertility and genome defense, piRNA pathway silencing strategies diverge drastically across the animal kingdom. In the Caenorhabditis elegans germline, the PIWI homologue PRG-1 is thought to recruit the Mutator complex to piRNA targets to trigger mass production of 22G secondary siRNAs that associate with worm-specific WAGO Argonautes to carry out target silencing. However, germline transcriptomic analyses of prg-1 and Mutator component rde-3 or mut-16 mutants reveal that roughly half of genes upregulated in prg-1 animals are unaffected by Mutator complex loss. Therefore, we propose that PRG-1 can directly silence some piRNA targets using an as-yet undescribed Mutator-independent mechanism. We demonstrate that a novel piRNA-sensitive transgene reporter is targeted by Mutator-dependent and -independent piRNA silencing mechanisms. Unlike the canonical C. elegans piRNA pathway, Mutator-independent piRNA silencing does not trigger mass small RNA generation. Surprisingly, Mutator-independent piRNA silencing does not require PRG-1 catalytic activity and persists transgenerationally for a few generations after prg-1(+) activity is removed. This putative pathway requires nrde-2, a conserved protein first characterized as a nuclear silencing factor, but not other known WAGO nuclear silencing components such as hrde-1 and nrde-3. Furthermore, we have identified putative endogenous targets of Mutator-independent piRNA silencing via gonadal RNA sequencing and RNA FISH. Collectively, these data demonstrate that PRG-1 can directly silence mRNAs through an epigenetic mechanism independent of the Mutator complex. Future work will focus on validating putative endogenous targets and identifying additional cis and trans components of the novel Mutator-independent piRNA silencing pathway.

Cell surface glycoRNA biology

Ryan Flynn
Boston Children's Hospital, Boston, MA, USA

Glycans modify lipids and proteins to mediate inter- and intramolecular interactions across all domains of life. RNA is not thought to be a major target of glycosylation. Here, we challenge this view with evidence that mammals use RNA as a third scaffold for glycosylation. Using chemical and biochemical approaches, we found that conserved small noncoding RNAs bear sialylated glycans. These “glycoRNAs” were present in multiple cell types and mammalian species, in cultured cells, and in vivo. GlycoRNA assembly depends on canonical N-glycan biosynthetic machinery and results in structures enriched in sialic acid and fucose. Analysis of living cells revealed that the majority of glycoRNAs were present on the cell surface and can interact with anti-dsRNA antibodies and members of the Siglec receptor family. New chemical tools and insights into the molecular nature of glycoRNAs will be presented. Specifically, details surrounding the observation that RNA binding proteins are common members of cell surface proteomes will be explored, the genetic basis of this clustering discussed, and the functional relevance of glycoRNA-csRBP clusters on growth factor signaling (e.g. the activity of VEGF-A in angiogenesis) presented.

Uncovering the postfertilization regulatory mechanisms required for intergenerational epigenetic inheritance in mice

Grace Lee, Natalie Trigg, and Colin Conine
University of Pennsylvania, Philadelphia, PA, USA

In nearly all physiological contexts, microRNAs (miRNAs) play an important role in posttranscriptional gene regulation. miRNAs in the male germline are uniquely positioned to transfer non-genetically heritable information from one generation to the next. Sperm acquire a subset of miRNAs during epididymal transit, which are critical for embryonic viability. Moreover, sperm miRNA profiles are dynamically modulated by environmental factors and linked to altered progeny phenotypes. While studies have shown that microinjection of specific miRNAs into wildtype embryos can recapitulate paternally induced phenotypes, the precise molecular mechanisms remain unclear. To dissect the role of sperm-derived miRNAs in early embryonic gene regulation, I am using parthenogenetically activated mouse eggs to undergo preimplantation development to study the isolated effects of specific sperm miRNAs. Here, I demonstrate that microinjection of physiologically relevant concentrations of individual sperm miRNAs cause reproducible, dose-dependent effects on gene expression throughout early embryonic development. Furthermore, I show that specific miRNAs in mature sperm are protected by treatment with a single-stranded RNA specific RNase, demonstrating that mature sperm contribute double-stranded miRNAs to the embryo. These data provide a potential mechanism and direct evidence that sperm miRNAs, at endogenous levels, can significantly alter developmental gene expression patterns. Altogether, my results establish parthenotes as a model for studying miRNA-driven gene regulation in early development and offer mechanistic insight into how dysregulation of sperm miRNAs can impact embryonic development and transgenerational inheritance.

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irCLIP-RNP and Re-CLIP reveal patterns of dynamic protein assemblies on RNA

Luca Ducoli, Brian Zarnegar, Douglas Porter, Robin Meyers, Weili Miao, Nick Riley, Suhas Srinivasan, Leandra Jackrazi, Yen-Yu Yang, Zhouxian Li, Yinsheng Wang, Carolyn Bertozzi, Ryan Flynn, and Paul Khavari
Stanford University, Stanford, CA, USA

RNA binding proteins (RBPs) control varied processes, including RNA splicing, stability, transport, and translation. Dysfunctional RNA-RBP interactions contribute to the pathogenesis of human disease, however, characterizing the nature and dynamics of multiprotein assemblies on RNA has been challenging. To address this, non-isotopic ligation-based ultraviolet crosslinking immunoprecipitation was combined with mass spectrometry (irCLIP-RNP) to identify RNA-dependent associated proteins (RDAPs) co-bound to RNA with any RBP of interest. irCLIP-RNP defined landscapes of multimeric protein assemblies on RNA, uncovering previously unknown patterns of RBP-RNA associations, including cell-type-selective combinatorial relationships between RDAPs and primary RBPs. irCLIP-RNP also defined dynamic RDAP remodeling in response to epidermal growth factor (EGF), uncovering EGF-induced recruitment of UPF1 adjacent to HNRNPC to effect splicing surveillance of cell proliferation mRNAs. To identify the RNAs simultaneously co-bound by multiple studied RBPs, a sequential immunoprecipitation irCLIP (Re-CLIP) method was also developed. Re-CLIP confirmed binding relationships seen in irCLIP-RNP and identified HNRNPC and UPF1 RBP co-binding on RND3 and DDX3X mRNAs. irCLIP-RNP and Re-CLIP provide a framework to identify and characterize dynamic RNA-protein assemblies in living cells.

Mime-seq 2.0: Cell-specific sequencing of microRNAs from mammalian tissues and organs

Ariane Mandlbauer, Qiong Sun, Niko Popitsch, Miroslava Spanova, Stefan Ameres, Jingkui Wang, Tanja Schwickert, Meinrad Busslinger, and Luisa Cochella

The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Many microRNAs are expressed with high cell type specificity, with some being limited to rare cell types that can be embedded in complex tissues. However, most microRNA profiling in mammals has been done at the tissue or organ level as isolating enough material for sequencing from rare cell types is challenging, and single cell small RNA sequencing protocols are currently not sufficiently efficient. To overcome this limitation, we had previously developed a technique called miRNome by methylation dependent sequencing (mime-seq) that enables high-resolution assessment of cell-type specific microRNAs in specific cell types within a tissue. Our approach involved methylation of cell-type specific microRNAs by transgenic expression of a small RNA methyltransferase, followed by methylation-selective small RNA sequencing from total RNA.

We initially established mime-seq in C. elegans and D. melanogaster using a methyltransferase from Arabidopsis thaliana, AtHEN1, which efficiently methylated microRNAs in worms and flies. Intriguingly, we found that AtHEN1 is unable to methylate microRNAs in mouse or human cell lines. To overcome possible differences in substrate availability in mammals, I engineered a chimeric methyltransferase. Tethering this enzyme to Argonaute protein allows efficient methylation of microRNAs in cultured mammalian cells and in vivo, in mice.

To allow for conditional expression of the chimeric methyltransferase, we generated a mouse line in which the methyltransferase contains a Lox-STOP cassette. Combination with cell-specific Cre recombinase lines enables specific expression in cells of interest. We validated the use of this mouse model by profiling microRNAs from B cells and bone marrow plasma cells. We expect that this will be a useful resource for the small RNA community to access microRNAs in spatiotemporally restricted or rare cell population in a sensitive and specific manner.

Deep generative models generate mRNA sequences with enhanced translational capacity and stability

He Zhang, He Zhang, Hailong Liu, Haoran Huang, Jia Wang, Yan Qin, Zhiyuan Xun, Timothy Lu
Raina Biosciences Inc, Cambridge, MA, USA

Although mRNA COVID-19 vaccines have been successful, expanding mRNA therapeutics to other indications remains a key focus. However, achieving stronger and more durable protein expression is essential for their success. Our study presents GEMORNA, a deep generative model for mRNA sequence design which leverages recent advancements in generative AI to innovate the field of mRNA engineering. Facilitating Transformer architectures tailored for mRNA coding sequences (CDSs) and untranslated regions (UTRs), GEMORNA built up RNA language models enriched with gene evolutionary information. Within this framework, designing a CDS for a given protein is analogous to translating a sentence from one language to another, while creating a UTR resembles composing a poem. Compared to mRNA sequences derived from natural genes, our method provides an efficient way for de novo generation of a diverse and extensive pool of mRNA candidates from a prohibitively large design space. Unlike current traditional mRNA optimization methods, our approach is data-driven and free from pre-defined human-design objectives, making it particularly well-suited for mRNA design, where the complete set of influencing factors and underlying cellular mechanisms remains only partially understood. Compared to prior RNA language models developed primarily for predictive tasks, GEMORNA is specifically designed to directly generate high-quality mRNA elements. To our best knowledge, GEMORNA represents the first generative model tailored for the design of full-length mRNAs.

The effectiveness of GEMORNA-generated sequences was confirmed through extensive in vitro and in vivo experiments. We compared GEMORNA-designed CDSs, UTRs, and full-length mRNAs to widely used natural, algorithm-optimized, and commercial controls. Notably, GEMORNA-generated mRNA sequences demonstrate substantial improvements in both expression levels and durability, including a 41-fold increase in firefly luciferase expression compared to an optimized sequence, a significant enhancement in anti-COVID antibody titers in mice compared to BNT162b2, and a 15-fold increase in human erythropoietin (hEPO) expression in vivo. These experiments incorporated m1Ψ nucleotide modification, a key feature of marketed mRNA drugs. Beyond linear mRNAs, GEMORNA's versatility extends to circular mRNA design, which facilitated a 121-fold increase in hEPO expression in vivo than a systematically optimized benchmark. We also created circular mRNAs with substantial improvements in expression levels, durability and anti-tumor cell cytotoxicity in mRNA-transduced CAR-T cells compared with a patented benchmark.

In conclusion, our generative AI-based model constitutes a novel and efficacious strategy for mRNA sequence design, with the potential to notably advance the development of mRNA vaccines and therapeutics.

Mirror-image Nucleic Acids as Advanced Molecular Therapies

Wen Zhang

Indiana University School of Medicine, Indianapolis, IN, USA

Nucleic acids can adopt diverse three-dimensional structures to selectively bind physiological targets, making them powerful tools for disease treatment. Advances in biotechnology have driven rapid progress in this field; however, clinical applications of nucleic acid therapeutics remain hindered by key challenges, including rapid degradation by ubiquitous nucleases and unintended RNA-protein interactions that may lead to off-target toxicity. To overcome these limitations, we have developed a chemically modified mirror-image nucleic acids (L-DNA/L-RNA) with enhanced stability and therapeutic potential. Unlike natural nucleic acids, L-nucleic acids are resistant to nuclease degradation due to its opposite chirality, resulting in a greatly extended half-life in vivo. By introducing additional chemical modifications into the backbone, we have further enhanced its thermal and structural stability, leveraging the rigidity of L-ribose and improving its drug-like properties. We demonstrate two major applications of this engineered L- nucleic acids platform:

1. Advanced Mirror-Image Aptamer Selection – Using this chemically modified L-RNA, we have successfully isolated aptamers targeting critical disease-related RNA elements, paving the way for novel antiviral strategies.

2. L-RNA Nanoparticle for Targeted Therapy – We have constructed a novel L-RNA-based nanoparticle capable of delivering multiple chemotherapeutic and gene therapy agents to cancer cells with high specificity. This nanoparticle exhibits enhanced bioavailability, stability, and targeted drug delivery, offering a promising approach for effective cancer treatment.

Our findings highlight the potential of chemically modified mirror-image RNA in both fundamental research and translational medicine, bridging the gap from bench to bedside in the treatment of complex diseases.

Applying AIMer-based RNA editing technology to nonsense mutation correction in the CNS and lung

Genliang Lu, Chikdu Shivalila, Christopher Acker, Ian Harding, Megan Cannon, Jigar Desai, Alyse Faraone, Jack Godfrey, Naoki Iwamoto, Pachamuthu Kandasamy, Tomomi Kawamoto, Jake Metterville, Prashant Monian, Erin Purcell-Estabrook, Stephany Standley, Jesse Turner, Hailin Yang, Ryan Yordanoff, Hui Yu, Michael Byrne, and Chandra Vargeese

Wave Life Science, Cambridge, MA, USA

AIMers are short, chemically modified oligonucleotides that engage endogenous adenosine deaminase acting on RNA (ADAR) enzymes to induce highly efficient and specific A-to-I RNA base editing. Recently, we described the optimization of AIMer design to increase the potency and target space capabilities of RNA editing and demonstrated the impact of this design in mouse liver. However, achieving highly efficient RNA editing in vivo remains challenging in extrahepatic tissues. Here, we report the development of AIMers for application to either the central nervous system (CNS) or the lung. We demonstrate correction of nonsense mutations and protein restoration in the mouse CNS in vivo and in human lung cells in vitro. In the CNS, we designed AIMers to edit MECP2 R168X, the most frequent nonsense mutation causing Rett Syndrome (RTT), a rare neurodevelopmental disorder. In mouse neuronal cell lines, MECP2 AIMers direct significant RNA editing and restore Mecp2 protein expression. We next investigated whether AIMers can support Mecp2 editing in the mouse CNS in vivo. We delivered AIMers via neonatal intracerebroventricular (ICV) administration to transgenic mice expressing human ADAR-p110 and Mecp2R168X. Six weeks after a single dose, we observed up to 15% Mecp2 RNA editing and Mecp2 protein restoration to 33% of wild-type levels in whole brains of male mice. For application in the lung, we developed AIMer technology using the Ugp2 transcript as a surrogate target. A single dose of Ugp2 AIMers supported 50% Ugp2 mRNA editing in the lung in mice. To assess AIMer activity against a clinically relevant target, we investigated whether AIMers could be applied to correct the W1282X nonsense mutation in CFTR mRNA, which causes cystic fibrosis, a multi-organ disease that ultimately leads to respiratory failure. These optimized AIMers are designed to convert the premature stop codon to wild-type tryptophan, promoting transcript stabilization and protein expression. In human bronchial epithelial cells expressing CFTRW1282X, AIMers directed up to 75% CFTR mRNA editing, resulting in a 3-fold increase in transcript expression and expression of up to 50% of wild-type CFTR protein levels. Together, these preclinical investigations lay the foundation for the development of AIMers as potential RNA medicines to treat diseases impacting extrahepatic tissues that are driven by nonsense mutations.

Prime Editing-Mediated Conversion of an Endogenous tRNA Gene Into a Suppressor tRNA for Disease-Agnostic Therapeutic Genome Editing

Sarah Pierce, Steven Erwood, Keyede Oye, Meirui An, Aditya Raguram, Davis Seelig, Mark Osborn, and David Liu

Broad Institute of MIT and Harvard, Cambridge, MA, USA

Precise genome editing technologies such as base and prime editing can correct most pathogenic human gene variants, but their widespread clinical application is limited by the large effort needed to develop each therapeutic agent, which typically treats patients with a specific mutation. Suppressor tRNAs (sup-tRNAs) offer a more general strategy to address diseases caused by premature stop codons. Existing therapeutic sup-tRNA approaches, however, show modest potency, require overexpression that can perturb global translation, or require repeated administration. Here, we present a strategy to rescue nonsense mutations in a disease-agnostic manner by using prime editing to convert a dispensable endogenous tRNA into an optimized sup-tRNA. Through iterative screening to investigate thousands of variants of all 418 high-confidence human tRNA genes, we identified endogenous tRNAs with the strongest potential to serve as sup-tRNAs, discovered variants of these tRNAs that greatly increase nonsense suppression potency, and developed prime editing agents that efficiently install these optimized sup-tRNAs at individual endogenous tRNA loci in human or mouse cells. A single prime editor resulting from these efforts supports the permanent, efficient readthrough of premature termination codons in human cell models of Batten disease, Tay-Sachs disease, Niemann-Pick disease type C1, and cystic fibrosis. In vivo delivery of a single prime editor programmed to convert an endogenous mouse tRNA into an optimized suppressor tRNA rescued a premature stop codon in a mouse reporter gene, and extensively rescued disease pathology in a mouse model of Hurler syndrome. Our findings suggest the potential of disease-agnostic therapeutic genome editing approaches that require the development of only a single composition of matter to treat diverse genetic diseases.

Mechanistic Insights Into CRISPR-Associated Transposons and Implications for Programmable Gene Insertion

Leifu Chang, Shukun Wang, Romana Siddique, Mark Hall, and Phoebe Rice

Purdue University, West Lafayette, IN, USA

CRISPR-associated transposons (CASTs) combine RNA-guided targeting with transposition machinery, enabling precise, large-scale genome engineering. I will discuss our recent mechanistic studies of the Type I-B CAST system while comparing it with other characterized systems including Type I-F3, Type V-K, and the prototypical Tn7. The discussion will highlight how CASTs are built in a modular fashion, consisting of three functional modules: 1) Target DNA recognition, 2) TnsC-mediated coupling, and 3) TnsA/TnsB transposases. Through cryo-EM structural analysis, we have revealed how Cascade-induced conformational changes in Cas6 prime TniQ recruitment, and how TniQ's N-terminal domain binds to the TnsC spiral heptamer. We will also present insights on the transpososome assembly and the direct role of TnsC in transpososome formation. A comparative analysis of RNA-guided versus TnsD-guided targeting pathways will be discussed. These structural insights enable rational engineering of CAST components, increasing the translational potential of CASTs in programmable gene insertion.

Developing Bespoke Gene Editing Treatments for Patients with Carbamoyl Phosphate Synthetase 1 (CPS1) Deficiency in Real Time: Successes and Challenges

Xiao Wang, Sarah Grandinette, Anne Berry, Taylor Hudson, Kevin Briseno, Petros Giannikopoulos, Fyodor Urnov, Rebecca Ahrens-Nicklas, and Kiran Musunuru

University of Pennsylvania, Philadelphia, PA, USA

CPS1 deficiency is the most severe urea cycle disorder, caused by CPS1 mutations resulting in life-threatening hyperammonemia and encephalopathy in newborns. Liver transplantation, typically not an option until about 1 year of age, is the only curative treatment, and it has substantial morbidity while requiring lifelong immunosuppression. We are establishing a workflow to develop corrective editing treatments for N-of-1 patients with rare metabolic diseases such as CPS1 deficiency within a few months of birth. For two patients recently born with CPS1 deficiency—the first with a CPS1 c:1003C>T (Q335X) variant, the second with a CPS1 c.2339G>A (R780H) variant, both potentially addressable with adenine base editors (ABEs)—we initiated the workflow immediately after receiving genetic testing results.

We used HuH-7 hepatocytes transduced with lentiviruses bearing a CPS1 variant, along with wild-type CPS1 sequences and "control" PAH P281L and R408W variants (related to phenylketonuria, for which humanized mouse models exist and published curative mRNA-lipid nanoparticles [LNP] base-editing therapies efficiently correct the variants in the liver in vivo), to perform calibrated assessments of in vitro editing efficiencies and predictions of in vivo editing efficiencies. Within one month after the Q335X patient's birth, we screened PAM-altered ABEs with various guide RNAs (gRNAs) and identified a highly efficient, optimized ABE/gRNA solution for Q335X. A similarly rapid screen with the R780H variant failed to identify an efficient ABE/gRNA solution, due to challenging sequence context.

Within two months of birth, we generated founder mice with either the Q335X variant in the endogenous Cps1 locus (humanized mice) or the Q335X variant sequence in the Rosa26 safe harbor locus. Progeny of these mice are being used to test an mRNA-LNP therapy delivering the optimized ABE/gRNA solution. In parallel, we performed patient-specific off-target analyses of the ABE/gRNA solution, combining CHANGE-seq-BE performed with genomic DNA from the patient's cells with variant-aware ABE-ONE-seq using an oligonucleotide library bioinformatically designed against the patient's genome.

Our ultimate goal is to streamline this entire workflow so as to generate sufficiently comprehensive on-target and off-target data, within a few months after a patient's birth, to obtain immediate regulatory clearance to treat the patient with the bespoke mRNA-LNP therapy—thus empowering a platform approach to gene editing for numerous diseases. For CPS1 patients, this approach would provide effective, durable treatments long before liver transplantation is feasible, forestalling irreversible neurological damage and early death.

MicroRNA-21 is a Potential Therapeutic Agent Targeting Tgfbi and Mitigating High-Fat-Diet-Induced Liver Disease and Cancer

Urmila Jagtap, Anan Quan, Yuho Ono, Jonathan Lee, Alice Rodrigues, Kylie Shen, Sergei Manakov, Gyongyi Sazbo, Imad Nasser, and Frank Slack

Beth Israel Deaconess Medical Center, Boston, MA, USA

Liver disease, including hepatocellular carcinoma (HCC), is a major global health concern, claiming approximately 2 million lives worldwide annually, yet curative treatments remain elusive. MicroRNAs are a class of small non-coding RNA molecules that play various roles in liver-related functions, such as glucose metabolism, fatty acid uptake, insulin regulation, inflammation, and detoxification. In this study, we aimed to investigate the role of microRNA- 21-5p (miR-21) in progressive liver disease within the context of a Western high-fat diet, and offering potential therapeutic insights.

We have created a comprehensive, high-fat diet-based model of liver disease in mice that recapitulates the clinical stages observed in human patients, ranging from metabolic syndrome to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) to HCC. 3-week-old WT (B6/129SF2/J) and miR-21 KO (B6;129S6-Mir21atm1YolilJ) mice were injected with 25mg/kg of diethyl-nitrosamine by intraperitoneal injections and were fed on either a normal chow or high-fat-diet – without additional choline, (HFD) till 32-weeks of age.

Biochemical, histological, and molecular analyses revealed that, while WT mice fed on HFD developed symptoms of progressive liver disease over time as expected, interestingly, as the severity of liver disease increased, miR-21 levels were significantly downregulated, suggesting an inverse correlation between the two. At the same time, the whole-body miR-21 knockout mice showed exacerbated phenotypes, including obesity, hepatomegaly, hyperglycemia, insulin resistance, steatosis, fibrosis, and HCC, suggesting the protective function of miR-21. In synergy to this, the combination of miR-21 deficiency and a high-fat diet triggered an accelerated cascade of liver damage, progressing rapidly from simple steatosis to HCC, indicating additive toxic effects on the liver pathology and functions. Using the in-vivo and in-vitro techniques, we show that miR-21 exerts these functions by directly targeting Transforming growth factor beta-induced (Tgfbi) – a gene also known to be significantly upregulated and a potential oncogene in HCC, and the fibrosis related genes downstream of it. Most notably, our study showed that the administration of miR-21 mimic in predeveloped liver disease-bearing WT mice effectively improves insulin sensitivity, steatosis, fibrosis, Tgfbi expression and tumor burden in HFD conditions.

Together, our findings demonstrate that miR-21 has protective functions in the broad spectrum of high-fat diet-based, progressive liver disease and cancer, thus offering insights into the multifaceted interplay between genetic predisposition and environmental factors in liver disease progression to HCC. At the same time our study also underscores the potential of miR-21 mimic as a viable therapeutic option for the prevention and treatment of liver.

Advancing an Intrathecal Divalent siRNA for Prion Disease as an Investigator-Initiated Program

Eric Vallabh Minikel

Broad Institute of MIT and Harvard, Cambridge, MA, USA

PrP lowering is a deeply validated therapeutic hypothesis in prion disease but has only reached its first clinical test with the fully enrolled PrProfile Phase I trial of an antisense oligonucleotide, ION717, against PrP in symptomatic prion disease patients (NCT06153966). In animals, lowering PrP by 50% triples survival time after prion infection but does not indefinitely prevent disease, indicating that deeper PrP lowering is desirable.

We set out to develop divalent siRNA against PrP as a new therapeutic for prion disease. Using a moderately potent tool compound against the mouse PrP gene, we determined that PrP lowering by this modality is effective against prion disease just as with ASOs or genetic deletion of one copy of the PrP gene. By screening in cells and in a new humanized mouse model, we identified a highly potent divalent siRNA targeted to the human PrP sequence, capable of lowering PrP to as little as 17% residual in a whole mouse brain hemisphere after a single dose and of yielding pharmacologic activity for 6 months. The median effective dose (ED50) was determined to be between 5 and 18 μg across mouse 6 brain regions. We determined that the non-matched 3' antisense tail and the use of the extended nucleic acid (exNA) modification both contribute to the potency of our compound.

Without a commercial sponsor, we sought a path to develop our divalent siRNA as an investigator-initiated program. As we are a Research IND (not commercial) but are a novel modality (not a 2'MOE ASO) and a rare but not ultra-rare indication (not N-of-1), we navigated a novel space in the regulatory framework for first-in-human oligonucleotide trials. Advice from FDA in a pre-IND meeting informed the exact study designs required for our GLP toxicology studies and the CMC requirements for our Drug Product. Leveraging NIH Ultra-rare Gene-based Therapy (URGenT) and philanthropic funds we completed manufacturing, rodent and large animal GLP toxicology, pharmacokinetic analyses, drug-drug interactions, and genotoxicity studies, and submitted an IND in February 2025. We are seeking to a Phase I trial in N=15 patients. Data and lessons learned from the full battery of IND-enabling studies and regulatory engagement will be presented.

RSwitch-enabled Gene Therapy to Fine Tune Frataxin Expression for the Treatment of Friedrich's Ataxia

Jon Dempersmier, Mariam Elhawary, Ian McLachlan, Kai Li, Diane Hamann, Chris Yates, Travis Wager, Simon Xi, and Samuel Hasson

Rgenta Therapeutics, Woburn, MA, USA

While the next generation of engineered AAV capsids have shown incredible promise with improved delivery and tropism, transgene control features could be used to further improve the safety and tractability of gene therapy. To this end, Rgenta has developed a platform for imparting gene therapy vectors with regulation via orally bioavailable small molecules. These DNA-encoded elements, called RSwitches, can be selectively modulated by synthetic small molecules, called RDrugs, in a dose-dependent manner. Tailored to interact with each RSwitch, the RDrugs direct specific pre-mRNA splicing events needed for therapeutic payload production. This technology confers temporal control of transgene expression creating therapeutic opportunities for a variety of gene therapy applications.

Gene therapy for Friedrich's Ataxia (FA) is a prime use case for exogenous regulation of transgenes. FA is an autosomal recessive disorder where repeat expansion drives loss of expression of the Frataxin gene (FXN). Frataxin loss inhibits iron-sulfur (Fe-S) cluster biogenesis leading to mitochondrial dysfunction and cell death. FA patients experience debilitating symptoms brought on by neurodegeneration and cardiomyopathy. While constitutive replacement of FXN by AAV vectors has shown promise in animal models, multiple studies have demonstrated the cardiotoxic effects of Frataxin overexpression. RSwitch control of an FXN transgene could facilitate safe and efficacious levels of gene rescue while maximizing tissue transduction coverage in the heart.

To test this hypothesis, we have optimized an RSwitch-regulated FXN transgene; a process aided by massively parallel sequence library screening and deep learning-driven design. Successive rounds of in vitro engineering yielded a system that displays highly dynamic Frataxin expression, dose-responsive to a brain-penetrant RDrug, Cp7. Complementation of Frataxin loss to WT levels occurs at single-digit nanomolar levels of Cp7 in cultured cells. When integrated into an AAV vector, the RSwitch performs similarly, providing functional Frataxin protein to transduced cells in response to Cp7. Dose-range finding studies in MCK-Cre cardiac models of FA demonstrate the relationship between Cp7 daily dose and steady-state levels of Frataxin in mouse tissues. We are now pursuing an efficacy study in MCK-Cre mice to demonstrate how sustained RDrug Cp7 dosing after systemic AAV administration: 1) maintains non-toxic levels of exogenous Frataxin expressed in the mouse heart and 2) rescues the morbidity that the mice develop at ~10 weeks of age. Success in this study will illustrate the potential for RSwitch to improve the safety and clinical success of gene replacement therapies for diseases such as FA.

Unlocking the Full Potential of RNAi Therapeutics with LEAD™

Chunyang Zhang, Peng Zhang, and Shiyu Wang
Sanegene Bio USA Inc., Boston, MA, USA

RNAi medicines represent a powerful modality for diverse unmet medical needs, including metabolic and autoimmune diseases. Novel drug delivery technologies and chemistries are required to fully realize the potential of systemically administered RNAi products. In this presentation, we will describe LEAD™ (Ligand and Enhancer Assisted Delivery) platform, developed by SanegeneBio to combine advanced clinically validated nucleic acid chemistries with receptor-mediated delivery to cell types of therapeutic relevance. The LEAD™ concept incorporates tissue-selective ligands paired with tailored enhancers, to achieve desired pharmaceutical properties and enable well-tolerated infrequent self-administered subcutaneous dosing regimens. LEAD™ ligands and enhancers are synthetic chemical moieties which are covalently conjugated to the RNAi payload. Pharmacodynamic modeling in rodents and primates has demonstrated potent and durable mRNA silencing in skeletal and cardiac myocytes, adipose tissue, liver, central and peripheral nervous system, and immune cell subpopulations in multiple compartments.

Leveraging our ability to deliver to the major metabolic organs, we have applied LEAD™ technology to develop new obesity and cardiometabolic therapeutics. INHBE and ALK7 are genetically validated obesity targets expressed primarily in hepatocytes and adipocytes, respectively. In multiple preclinical models including nonhuman primates, LEAD™ siRNAs targeting INHBE or ALK7 enable deep and durable silencing, significant body weight reduction, preservation of lean mass, and yield promising results as monotherapies or in combination with semaglutide. Additionally, we have identified cardiometabolic RNAi targets with first-in-class potential. We propose that advanced targeted RNAi medicines have the potential to become a central component of obesity therapy, and will positively impact human health across diverse disease states.

ON-DEMAND SHORT TALK ABSTRACTS

Going Nuclear: Improved Antisense Oligonucleotide Activity Through Conjugation With a Nuclear Importer

Disha Kashyapa, Thomas Milne, and Michael Booth
University of Oxford

Antisense oligonucleotides (ASOs) are a promising class of therapeutics designed to modulate gene expression. Both key mechanisms of action for ASOs operate in the nucleus: splice-switching ASOs modify pre-mRNA, processed in the nucleus, and mRNA-degrading ASOs require RNase H, an enzyme predominantly active in the nucleus. Therefore, to achieve maximal efficacy, ASOs require efficient nuclear delivery. Current ASO therapeutics shuttle in and out of the nucleus inefficiently. In this work, we have synthesised ASO conjugates for active nuclear import, by covalent conjugation with a potent small-molecule nuclear importer, (+)-JQ1. (+)-JQ1 is a well-characterised high-affinity binder for members of the BET bromodomain family of proteins and was recently shown to transport cytoplasmic proteins into the nucleus. Our (+)-JQ1-ASO conjugates outperformed their unmodified counterparts for both splice-switching and mRNA knockdown in the nucleus, at all concentrations tested. In particular, we improved the performance of Oblimersen, a BCL-2 ASO drug that failed phase-III clinical trials, showing that this therapeutic may merit re-evaluation. This work shows that the covalent modification of ASOs with a small-molecule nuclear importer can significantly improve target engagement and pave the way for more effective therapeutics.

Oligonucleotide Therapeutic Patenting Strategies

Michael J. Spellberg
Lathrop GPM, Boston, MA, USA

Oligonucleotide-based compounds, such as siRNAs and ASOs, are potent, safe, and specific therapeutics. Used for the treatment of all manner of human diseases, oligonucleotide compositions, treatment methods, and platform technologies continue to be innovated at public research centers, small biotechs, and global pharmaceutical companies. Thus, there is a continued need by oligonucleotide researchers to patent their innovations.

This talk will describe the biggest obstacles in securing patent protection for oligonucleotide therapies today, including strategic approaches to improve patentability and strengthen claims, and the impact of recent court decisions on patent eligibility.

SPEAKER BIOGRAPHIES

Victor Ambros, Ph.D.
2024 Nobel Laureate
Principal Investigator, Silverman Professor of Natural Sciences
Program in Molecular Medicine, UMass Chan Medical School

Victor Ambros earned his undergraduate degree in 1975, his doctorate in 1979 and completed his postdoctoral fellowship in 1983, all at the Massachusetts Institute of Technology. During graduate school, he worked with David Baltimore, PhD, a co-recipient of the 1975 Nobel Prize in Physiology or Medicine for discoveries related to the interaction between tumor viruses and genetic material of the cell. In Dr. Baltimore's lab, Ambros studied the poliovirus genome structure and replication. Ambros then conducted his postdoctoral research in the lab of H. Robert Horvitz, who shared the 2002 Nobel Prize in Physiology or Medicine for his research related to genetic regulation of organ development and programmed cell death. Ambros' research in Dr. Horvitz's lab focused on genetic pathways that directed the developmental timing in C. elegans. After Ambros completed his fellowship, he continued his research as a faculty member at Harvard University (1984-1992), Dartmouth College and Dartmouth Medical School (1992-2008), and the University of Massachusetts Chan Medical School (2008-present).

Ambros was elected to the National Academy of Sciences in 2007 and the American Academy of Arts & Sciences in 2011. He has received numerous honors for his scientific achievements including the Lasker Award and the Gairdner Foundation International Award in 2008; the Dr. Paul Janssen Award for Biomedical Research in 2012; the Keio Medical Science Award in 2013; the Wolf Prize, Gruber Genetics Prize and Breakthrough Prize in Life Sciences (shared) in 2014; and the Prize in Developmental Biology from the March of Dimes (shared) in 2016. Ambros was awarded the 2024 Nobel Prize for Physiology or Medicine for his co-discovery of microRNA, short single-stranded RNA molecules that are now understood to play critical roles in post-transcriptional gene regulation.

In 2008, H. Scott Silverman and his father Jeffrey L. Silverman endowed the Silverman Chair in Natural Sciences at the University of Massachusetts Chan Medical School to honor Ambros. The endowment symbolizes the Silvermans' enthusiasm for Ambros' work and comes from a longtime friendship formed in 1997 when the younger Silverman completed his honors research thesis under Ambros' guidance at Dartmouth College.

Howard Chang, Ph.D.
Senior Vice President, Research and Chief Scientific Officer
Amgen

Dr. Howard Y. Chang is senior vice president, Global Research, and chief scientific officer. He is responsible for leading all aspects of discovery research at Amgen. Prior to joining Amgen, Dr. Chang led a research laboratory at Stanford University focused on deciphering regulatory information in the human genome for disease diagnosis and therapy. A physician-scientist and board-certified dermatologist, he served as Professor of Dermatology, Genetics, and Pathology at Stanford and Investigator of the Howard Hughes Medical Institute.

Dr. Chang is the winner of the Albany Prize, Lurie Prize in Biomedical Sciences, and NAS Award in Molecular Biology for discoveries of regulatory RNAs. He is an elected member of the National Academy of Sciences, National Academy of Medicine, and American Academy of Arts and Sciences. He is a serial entrepreneur having founded five biotech companies.

Dr. Chang holds a M.D. from Harvard Medical School, a Ph.D. in Biology from MIT, and an A.B. in Biochemical Sciences from Harvard University.

Luisa Coachella, Ph.D.
Associate Professor, Department of Molecular Biology and Genetics
The Johns Hopkins University School of Medicine

Dr. Luisa Cochella grew up in Buenos Aires, Argentina. She obtained her Licenciatura (B.S.-Masters equivalent) in Biology from the Universidad de Buenos Aires and her PhD from Johns Hopkins University in Baltimore, where she conducted her thesis work in the lab of Dr. Rachel Green. For her postdoc, Luisa moved from studying fundamental aspects of protein synthesis, to using the worm C. elegans as a genetic system to study cell differentiation and development in the lab of Dr. Oliver Hobert at Columbia University in New York. Combining these two diverse trainings, Luisa started her independent group at the IMP in Vienna, Austria in 2013, with the goal to understand the basic gene regulatory mechanisms that drive the development of a multicellular organism. In 2021 the Cochella lab moved to Johns Hopkins School of Medicine, Department of Molecular Biology and Genetics. A large part of the Cochella lab focuses on the functions of microRNAs in animal development.

Luisa has been awarded an ERC Starting Grant, an NSF Career Award, she was an EMBO Young Investigator and was awarded the Elisa Izaurralde Award from the RNA Society in 2022.

Daniel Dominguez, Ph.D.
Assistant Professor, Pharmacology,
Member, Lineberger Comprehensive Cancer Center
UNC School of Medicine

Dr. Daniel Dominguez is an Assistant Professor in the Department of Pharmacology at the University of North Carolina at Chapel Hill. He earned his PhD at UNC Chapel Hill and completed postdoctoral training with Dr. Chris Burge at MIT.

His research focuses on RNA biology and gene regulation, particularly in the context of cancer and neurodegenerative disease. The Dominguez Lab investigates the molecular mechanisms of RNA-protein interactions and their regulatory consequences, using a multidisciplinary approach that combines computational biology, molecular biology, high-throughput biochemical assays, and animal models.

Previous work has included developing nuanced models of RNA-binding protein (RBP) specificity, examining the functional impact of RBP mutations, exploring the evolution of RNA-protein interactions, and uncovering mechanisms of alternative splicing in cancer and cell cycle regulation. The lab's research is supported by the National Cancer Institute (NCI), the National Institute of General Medical Sciences (NIGMS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Marc Friedländer, Ph.D.
Associate Professor, Head of Quantitative RNA Biology Group
Stockholm University

Marc Friedländer undertook his undergraduate studies in bioinformatics at the University Copenhagen under the supervision of Anders Krogh and his PhD in Berlin under the supervision of Nikolaus Rajewsky - developing the miRDeep algorithm. As a PI and tenured associate professor, he has established the Quantitative RNA Biology lab at SciLifeLab/Stockholm University.

The group has recently developed agoTRIBE - the first method to experimentally map microRNA targets transcriptome-wide in single cells - and has discovered and profiled RNA fragments in historical and ancient animals, including the extinct Tasmanian tiger.

Richard I. Gregory, Ph.D.
Chair, Department of Molecular, Cell and Cancer Biology
UMass Chan Medical School

Dr. Richard I. Gregory, Ph.D. is Professor and Chair of the Department of Molecular, Cell, and Cancer Biology at UMass Chan Medical School. Prior to this he was the Department of Pediatrics Stem Cell Biology Chair in the Division of Hematology/ Oncology at Boston Children's Hospital, Professor in the Department of Biological Chemistry and Molecular Pharmacology, at Harvard Medical School (HMS), and Co-Director, of the HMS Initiative for RNA Medicine. He received a Ph.D. from Cambridge University for his research performed at the Babraham Institute. He did postdoctoral work at the Fox Chase Cancer Center and the Wistar Institute, Philadelphia. His research focuses on understanding molecular and cellular mechanisms of RNA regulation and the relevance of these pathways in stem cell biology, development, and human diseases including cancer. Most recently, his lab has been focused on the role of RNA modifications – the epitranscriptome, in cancer biology. Notably, they identified oncogenic roles for the mRNA methyltransferase (MTase) METTL3 and the tRNA MTase METTL1 in numerous cancer types. Their work is supported by an outstanding investigator award from the National Cancer Institute.

Hailing Jin, Ph.D.
Professor & Cy Mouradick Endowed Chair, Department of Microbiology & Plant Pathology, Center for Plant Cell Biology, Institute for Integrative Genome Biology
University of California, Riverside

Dr. Hailing Jin is a Cy Mouradick Chair Professor in the Department of Microbiology & Plant Pathology at the University of California, Riverside, USA. Her research focuses on the roles of RNAs, epigenetics, and antimicrobial peptides in plant-microbe interactions, with the aim of developing innovative and eco-friendly strategies for crop protection against fungal and bacterial pathogens. Her lab discovered cross-kingdom RNA communication between plants and pathogens. They have also demonstrated the crucial role of extracellular vesicles in this process. Additionally, her lab found that many fungal pathogens can efficiently take up RNAs and vesicles from the environment, providing the essential basis for the development of spray-induced gene silencing techniques for crop protection.

Dr. Jin earned her PhD from the Shanghai Institute of Plant Physiology & Ecology, Chinese Academy of Sciences, and completed her postdoctoral training at the John Innes Centre, UK and the University of California, Berkeley. She has published a total of 115 peer-reviewed papers and has an H-index of 65. Dr. Jin is a Senior Member of the National Academy of Inventors (NAI), a Fellow of the American Association for the Advancement of Science (AAAS), a Fellow of the American Academy of Microbiology (AAM), a Fellow of the American Phytopathological Society (APS), and a CIFAR Fellow of the Canadian Institute for Advanced Research. She was recognized as a Highly Cited Researcher by Web of Science. She was recently elected to National Academy of Sciences (NAS) in 2025.

Alisha 'Jonesy' Jones, Ph.D.
Assistant Professor of Chemistry, James Weldon Johnson Professor, Department of Chemistry, New York University

Dr. Alisha 'Jonesy' Jones, one of C&EN News 2024 Talented Twelve, is a James Weldon Johnson Assistant Professor of Chemistry at New York University in the Department of Chemistry. Jonesy was a postdoctoral researcher in the lab of Dr. Michael Sattler in Munich, Germany, and earned her PhD in Chemistry in the lab of Dr. Gabriele Varani at the University of Washington.

Research in the Jones Lab focuses on investigating the structural dynamics of long noncoding RNAs (lncRNAs) and how they are linked to specific biological processes. Her team deploys a combination of biophysical, biochemical, and computational techniques to study how lncRNAs transition between various structured states and how they interact with other biomolecules. Considering that lncRNAs are critical regulators of gene expression, her lab's work has the potential to increase overall knowledge regarding lncRNA structure-function relationships, and offers a starting point for therapeutically targeting lncRNAs when they are implicated in a disease.

Raghu Kalluri M.D., Ph.D.
Professor and Chair, Department of Cancer Biology, Frederick Becker Distinguished University Chair
UT MD Anderson Cancer Center

Raghu Kalluri is a Professor and Chairman of the Department of Cancer Biology at the University of Texas MD Anderson Cancer Center. He is a CPRIT Established Investigator and holds the Frederick F. Becker Distinguished University Chair of Cancer Research. Dr. Kalluri's research program is focused on innovative research to unravel how cells and their environment communicate to maintain organ health, and how such communication networks are altered in cancer and other diseases. Current areas of research in the laboratory include cancer biology and metastasis, tumor microenvironment, tissue injury and regeneration, aging, and the biology of exosomes in health and disease.

Dr. Kalluri's research is translationally focused, with an implicit mission to develop new strategies for diagnosis and therapy. To date, his discoveries have been translated into nine successful clinical studies and Phase I clinical trials for kidney diseases, fibrosis and cancer, and led to the creation of six biotechnology companies using intellectual property generated in the Kalluri laboratory. Dr. Kalluri has been recognized for his excellence in research and teaching and the Kalluri laboratory is a fertile training ground for the next generation of scientists and physician-scientists. He has mentored over 300 research trainees during the past three decades and led numerous education and training programs as Director or co-Director at both Harvard and MD Anderson Cancer Center. Training successful researchers is one of Dr. Kalluri's core commitments for which he takes immense pride.

Dr. Kalluri's research achievements have been acknowledged in the form of several distinguished awards. He received the 2015 Jacob Henle Medal for Excellence in Medicine and the 2016 Ruth Leff Siegel Award for Excellence in Pancreatic Cancer Research. Kalluri has been funded by the NIH continuously for 29 years and, in 2022, he received the prestigious NCI Outstanding Investigator Award. In 2023, he was conferred with The Dallas/Fort Worth Living Legend Faculty Achievement Award in Basic Research. Dr. Kalluri is a Fellow of the American Society for Clinical Investigation, The American Association for the Advancement of Science, and the Association of American Physicians.

Alexis C. Komor, Ph.D.
Associate Professor, Department of Chemistry and Biochemistry,
University of California, Berkeley

Alexis received her B. S. degree in chemistry from the University of California, Berkeley in December of 2008. She then joined the lab of Jacqueline K. Barton at the California Institute of Technology for her doctoral studies. While at Caltech, she worked as an NSF Graduate Research Fellow on the design, synthesis, and study of DNA mismatch-binding metal complexes and received her Ph.D. in 2014.

She pursued postdoctoral work as a Ruth L. Kirschstein NIH Postdoctoral Fellow in the laboratory of David R. Liu, where she developed base editing. Alexis joined the Department of Chemistry and Biochemistry at the University of California at San Diego in 2017, where her lab develops and applies new precision genome editing techniques to the functional genomics field.

Alexis's contributions in teaching, mentoring, and research have been recognized through many awards, including the Cottrell Scholar Award, the "Talented 12" recognition by C&EN News, an NSF Faculty Early Career Development (CAREER) award, an NIH early stage investigator Maximizing Investigators' Research Award (MIRA), and a "40 under 40" recognition in healthcare by Fortune Magazine.

Athma Pai, Ph.D.
Associate Professor
RTI, UMass Chan Medical School

Dr. Athma Pai is an RNA systems geneticist working at the interface of RNA biology, functional genomics, and computational biology. Athma received her Ph.D. in Human Genetics from the University of Chicago, completed a Jane Coffin Childs postdoctoral fellowship in the Department of Biology at MIT, and assumed her current position as an Assistant Professor in the RNA Therapeutics Institute at the University of Massachusetts Chan Medical School in January 2018. Her lab works on developing and applying methods to study the kinetics of RNA processing and understanding how various steps in RNA maturation are efficiently coordinated through the lifecycle of an RNA molecule. Her work has been recognized with professional awards and grants such as the NIH Maximizing Investigators Research Award, NSF CAREER Award, and the UMass Chan Early Career Achievement in Science and Health Award.

Alfica Sehgal, Ph.D.
Chief Scientific Officer
Judo Bio

Dr. Alfica Sehgal is the CSO of Judo Bio working on oligos for therapeutic intervention. Over the years, she has held multiple leadership positions at CAMP4 therapeutics and Alnylam Pharmaceuticals, spanning from early discovery, new target search, platform biology, improvising delivery, and leading programs to the clinic. Her experience spans rare liver diseases like Alpha-1 antitrypsin deficiency (Belcesiran), Bleeding disorders (Fitusiran); urea cycle disorders; kidney disease, neurodegenerative and neurodevelopment disorders. She graduated from Tata Institute of Fundamental Research (TIFR), Mumbai; received her post-doctoral training at Johns Hopkins and Yale University, studying lipid uptake, cholesterol and oxygen homeostasis in parasites, mammalian cells and mice. She has authored more than 60 articles and patents across various disease areas and technologies

Daniel J. Siegwart, Ph.D.
W. Ray Wallace Distinguished Chair in Molecular Oncology Research and Professor
University of Texas Southwestern Medical Center

Daniel J. Siegwart is a Professor in the Department of Biomedical Engineering, Department of Biochemistry, and the Simmons Comprehensive Cancer Center (SCCC) at the University of Texas Southwestern Medical Center. He holds the W. Ray Wallace Distinguished Chair in Molecular Oncology Research and serves as the Director of the Program in Genetic Drug Engineering, Director of the Drug Delivery Program in Biomedical Engineering, and Co-leader of the Chemistry and Cancer Program in the NCI-designated SCCC. He received a B.S. in Biochemistry from Lehigh University (2003), and a Ph.D. in Chemistry from Carnegie Mellon University (2008), studying with Professor Krzysztof Matyjaszewski.

He also studied as an NSF EAPSI Research Fellow at the University of Tokyo with Professor Kazunori Kataoka (2006). He then completed an NIH NSRA Postdoctoral Fellowship at MIT with Professor Robert Langer (2008-2012). He has received awards including a CPRIT Scholar Award, an American Cancer Society Research Scholar Award, the Young Innovator Award in Nanobiotechnology, Biomaterials Science Emerging Investigator Award, and election to the Controlled Release Society (CRS) College of Fellows and the American Institute for Medical and Biological Engineering (AIMBE) College of Fellows. His research laboratory utilizes materials chemistry to enable targeted nanoparticle delivery of genomic medicines.

Their efforts led to an understanding of the essential physical and chemical properties of synthetic carriers required for therapeutic delivery of siRNA, miRNA, tRNA, pDNA, mRNA, and gene editors. His lab has been at the forefront in the design of synthetic carriers for gene editing and has applied these technologies for correction of genetic diseases and treatment of cancer. They reported the first non-viral system for in vivo CRISPR/Cas gene editing. They developed Selective ORgan Targeting (SORT) lipid nanoparticles (LNPs), which was the first strategy for predictable tissue specific mRNA delivery and gene editing. They ultimately aspire to utilize chemistry and engineering to make a beneficial impact on human health.

SYMPOSIUM ORGANIZERS

Phillip D. Zamore, Ph.D.
Chair and Professor, RNA Therapeutics Institute, UMass Chan Medical School
Investigator, Howard Hughes Medical Institute

Phillip D. Zamore, Ph.D. has been an Investigator of the Howard Hughes Medical Institute since 2008. In 2016, he became the Chair of the RNA Therapeutics Institute, which was established at the University of Massachusetts Medical School in 2009. Dr. Zamore also is Professor of Biochemistry and Molecular Pharmacology, the department he joined in 1999, and he became the Gretchen Stone Cook Professor of Biomedical Sciences in 2005. Dr. Zamore received his A.B. (1986) and Ph.D. (1992) degrees in Biochemistry and Molecular Biology from Harvard University. He then pursued postdoctoral studies on the role of the RNA binding proteins in Drosophila development at The Whitehead Institute for Biomedical Research, in Cambridge, Massachusetts.

Dr. Zamore's laboratory studies small RNA silencing pathways in eukaryotes and prokaryotes, including RNA interference (RNAi), microRNA, and PIWI-interacting RNA pathways. Dr. Zamore and his collaborators seek to use these insights to design therapies for human diseases, including Huntington's disease. Under Dr. Zamore's mentorship, the Zamore Lab has produced dozens of researchers working at top institutions both in the United States and abroad.

In 2015, Dr. Zamore was awarded the Chancellor's Medal for Excellence in Scholarship at the University of Massachusetts Medical School. In 2023, Dr. Zamore was elected as a member to both the American Academy of Arts and Sciences and the National Academy of Sciences.

To date, Dr. Zamore has more than 170 publications and has been among the most highly cited researchers for more than a decade. He serves on the editorial boards of numerous journals and is in demand as a presenter at conferences and institutions worldwide.

Dr. Zamore holds more than 20 patents, with other applications pending; he was elected a Fellow of the National Academy of Inventors in 2014. In 2002, Dr. Zamore co-founded Alnylam Pharmaceuticals (Cambridge, MA), a publicly traded biotech company which now has more than 1000 employees and multiple drugs in clinical trials. Alnylam's first drug, ONPATTRO, a first-of-its-kind RNAi therapeutic, for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults, was approved by the FDA in 2018. In 2014, he co-founded Voyager Therapeutics in Cambridge, MA. He serves on the scientific advisory boards of Alnylam, Voyager, and ProQR.

Angela Messmer-Blust, Ph.D.
Associate Professor, RNA Therapeutics Institute
UMass Chan Medical School

Dr. Angela Messmer-Blust studied cell motility during her graduate studies at the University of Toledo where she received her PhD (2009). She began her postdoctoral research at the CardioVascular Institute at Beth Israel Deaconess Medical Center, Harvard Medical School under Jian Li investigating transcriptional regulation in diabetes and obesity. Following her postdoctoral studies, she held editorial positions at the Journal of Visualized Experiments, and later joined Cell Press as the director of scientific conferences from 2012–2017. In 2017, Dr. Messmer-Blust joined the faculty of the RNA Therapeutics Institute (RTI) as Assistant Professor and Senior Scientific Advisor. She is currently an Associate Professor in the RTI and continues her work developing and directing departmental initiatives including the annual RNA Therapeutics symposium, Maraganore Early Independence Fellows Program, RNA Therapeutics and Biology graduate program, and educational outreach in the Worcester area. In 2021, she received the Boston Celtics Foundation's 'Heroes Among Us' award for her work in leading the creation of Emma RNA Saves the Day, a coloring book explaining the science behind the mRNA vaccines. In 2022, she was awarded the inaugural Oligonucleotide Therapeutics Society (OTS) Science Outreach Award for her efforts in leading the Emma RNA coloring book project.

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RNA Therapeutics Institute

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Save the dates

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