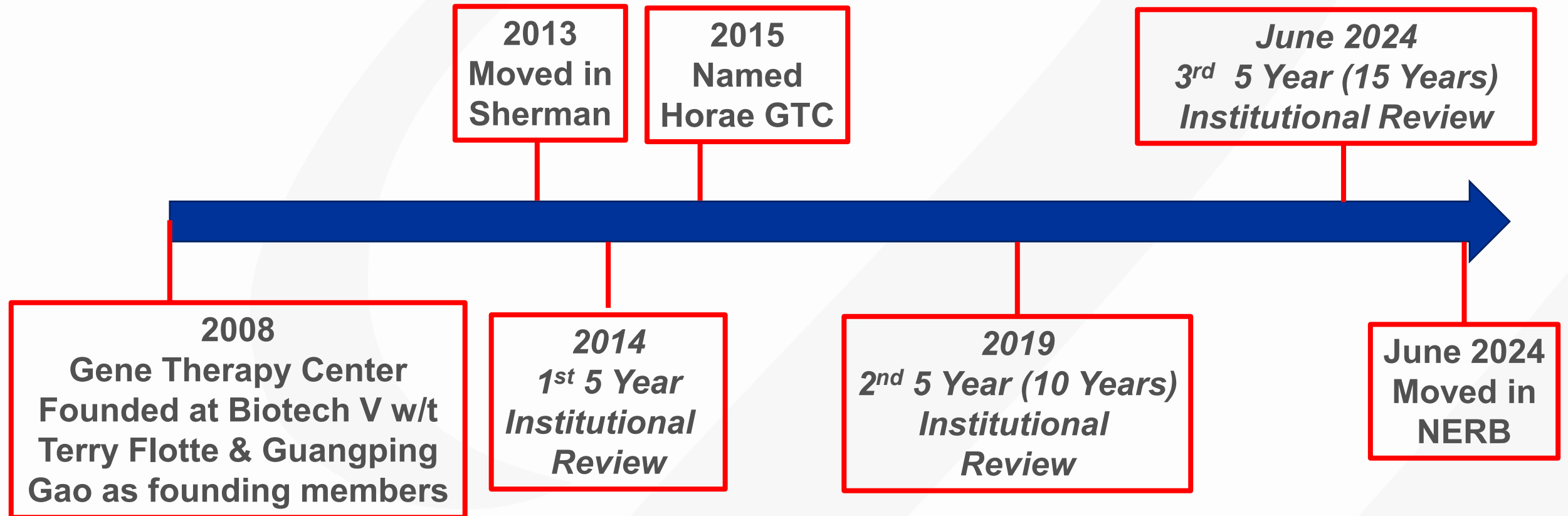


A Request for Elevating *Horae Gene Therapy Center to Department of Genetic & Cellular Medicine*

- **Guangping Gao, PhD, Executive council, 11/21/2024**



HORAE GTC HISTORY & MILESTONES



HORAE GTC CURRENT FACULTY, TRAINEE AND STAFF

➤ Faculty members	20
➤ Interns, graduate and postdoc trainees	48
➤ Research staff	54
➤ Administrative staff	6

Total: 128

HORAE GTC CURRENT FACULTY & RESEARCH PROGRAMS

Tenured faculty (5)



**Terry Flotte, MD
Prof**



**G Gao, PhD
Prof & Director**



**Jen Adair, PhD
Prof & Assoc Director**



**Miguel Esteves, PhD
Assoc Prof**



**Jae Shim, PhD
Assoc Prof**

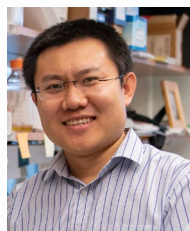
Tenure Track (7)



**Heather GradEdwards
VMD.PhD, Asst Prof**



**Allison Keeler
PhD, Asst Prof**



**Dan Wang
PhD, Asst Prof**



**Phil Tai
PhD, Asst Prof**



**Guocai Zhong
PhD, Asst Prof**



**Qinglan Ling
PhD, AsstProf**



**Dominic Gessler
MD.PhD, Asst Prof**

Research Track (8)



**Rob Kotin
PhD, Aff Prof**



**Jun Xie
PhD, AssocProf**



**Sylvain Cecchini
PhD, Assoc Prof**



**Alisha Gruntman
VMD.PhD, Asst Prof**



**Rita Batista
PhD, Instr**



**Toloo Taghian
PhD, Instr**



**Mohan Parsi
PhD, Instr**



**Hector Benatti
VMD. PhD, Instr**

INNOVATIVE INTERDISCIPLINARY SCIENCE IS THE MAIN DRIVE FOR HGTC RAPID GROWTH

- Human genetic diseases and pathomechanisms
- Animal modeling and translational science in large animals
- DNA and RNA virus biology and vectorology (Ad, AAV & Lenti)
- Gene and genetically modified Cell Therapy platform Technologies
- Gene Therapy immunology and host interactions
- Vector manufacturing & characterization platform technologies
- Pre-clinical proof-of-concept and clinical gene therapies

PIs & RESEARCH PROGRAMS

<u>PI(s)</u>	<u>Primary Research Area</u>	<u>Gene Tx Products in pipeline</u>	<u>Academic Department</u>
Flotte	AAV biology, preclinical & clinical gene therapies, gene therapy immunology	<i>A1ATD, FAOD, Cockayne Syndrome, DMD</i>	Pediatrics
Adair	Lentivirus vectorology, genetic modified cell therapy, Car-T, gene editing	Cancer, Sickle cell anemia	Medicine
Esteves	CNS & neuromuscular gene therapy, capsid engineering	<i>Dravet, Rett, SPAST, GM1, GM2, LGMD2g, GNAO1, LMNA, TNNT1, NF1</i>	Neurology
Shim	Gene therapy for skeletal disorders	<i>Gene therapies for arthritis, FOP-ACVR1, Bone fracture & graft defects</i>	Medicine
Guangping Gao	Gene Therapy in general, vector engineering and platform technologies	<i>Canavan, GM3S, AxD, H-ABC, 4HLCN, MSUD, SMA, ALS</i>	MAPs
GrayEdwards	CNS gene therapy, large animal modeling	<i>Sialidosis-NEU1, GM1, GM2, MSUD</i>	Radiology
Keeler	Gene Therapy and gene therapy immunology	<i>FAOP, AAVCar T cells, gene therapy immunology</i>	Pediatrics
Wang	Gene editing & replacement Tx, stRNA Tx, animal modeling, AAV production platform technologies	<i>Hurler, Pitt-Hopkins, NGly1, FoxG1, MSUD, Dysferlinopathy, AARS2D</i>	RNA Therapeutics Inst
Tai	Vector innovation, development, & engineering, Bioinformatics	<i>Novel vectors & QC pipeline, AMD, Glaucoma</i>	MAPs
Zhong	RNA switches for temporally regulatable gene delivery	<i>Ribozyme on- & Aptazyme off- switches for regulated gene therapy</i>	RNA Therapeutics Inst
Ling	Gene Therapy for neurological mitochondrial disorders	<i>MTATP6-related mitochondrial disease, SURF1-&TACO1-related Leigh Syndrome</i>	MAPs
Gessler	Neuro-metabolome, neuro-energetics, CNS Gene therapy	<i>Canavan, AxD, CoX20D</i>	Neurosurgery
Xie	Vector biology, capsid engineering, vector development, gene therapy	<i>H-ABC, 4HLCN, AxD, SMA, ALS</i>	MAPs
Cecchini	Gene Therapy vector process development and large-scale manufacturing	<i>Production of toxicology lots for GM2 gene therapy</i>	MAPs
Gruntman	Respiratory biology and Gene therapy	<i>A1ATD</i>	Pediatrics
Kotin	AAV evolution & vector integration safe harbor	<i>HIV vaccine</i>	MAPs
Batista	CNS gene therapy	<i>Stroke, TTR Alzheimer's disease</i>	Neurology
Taghian	CNS gene therapy, neuroimaging, animal modeling	<i>UBA5 disorder</i>	Radiology
Parsi	AAV evolution & vector integration safe harbor	<i>HIV vaccine</i>	MAPs
Benatti	Gene delivery to the CNS and animal modeling	<i>CNS disorders</i>	MAPs.

UMASS CHAN GENE TX PIPELINE

- 14 DISEASE CATEGORIES AND 42 DRUGS IN DEVELOPMENT

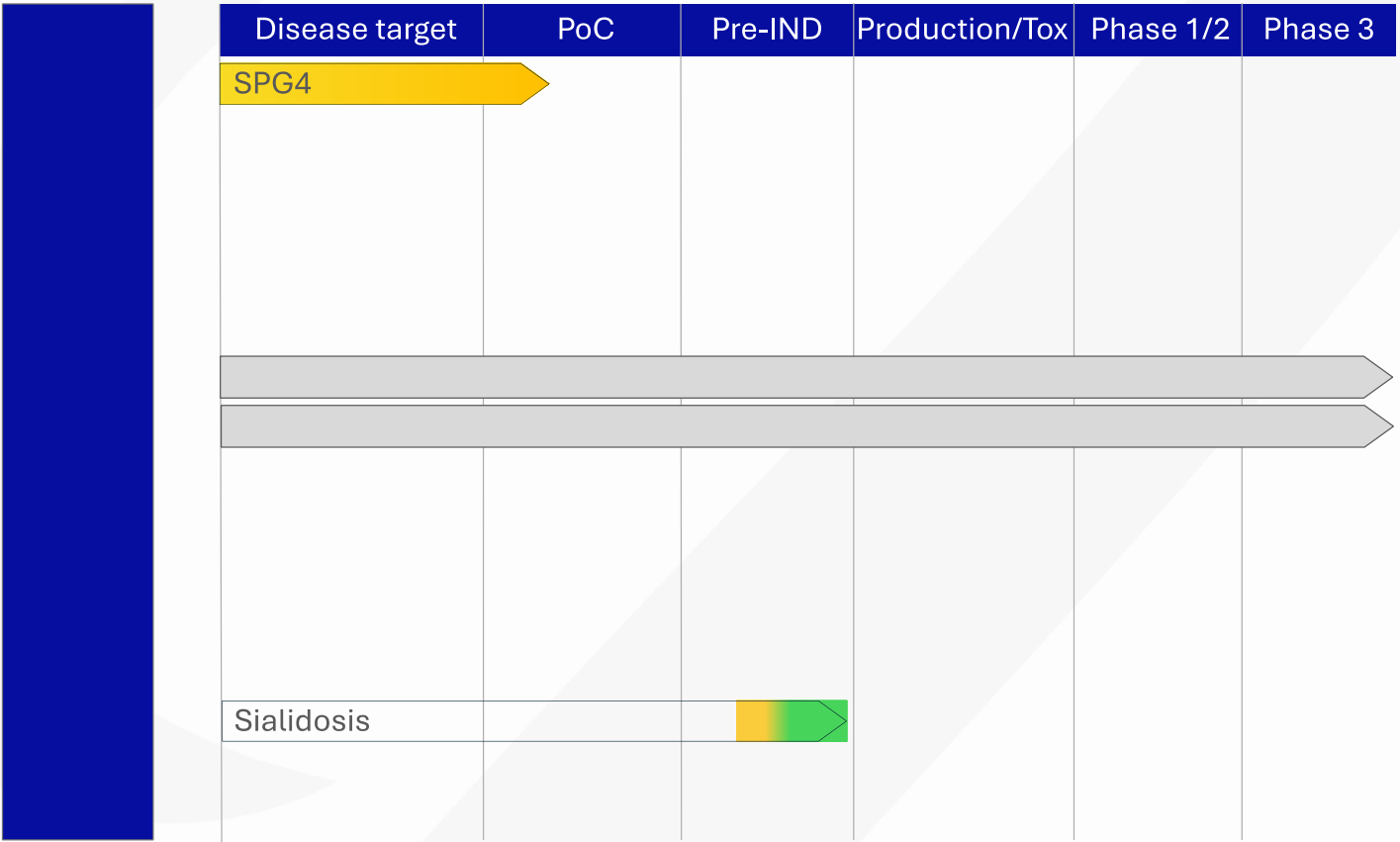
- 14 DISEASE CATEGORIES AND 42 DRUGS IN DEVELOPMENT											Type of Disorder	Disease	Target Gene(s)	Therapeutic Strategy	Preclinical Proof-of-Concept	UMMS PIs	
Type of Disorder	Disease	Target Gene(s)	Therapeutic Strategy	Preclinical Proof-of-Concept	UMMS PIs	Type of Disorder	Disease	Target Gene(s)	Therapeutic Strategy	Preclinical Proof-of-Concept	UMMS PIs	Neurological/ Epileptic	Cockayne Syndrome	ERCC8	AAV gene replacement	Mice	Batista and Sena-Esteves
Cardiovascular Disease	Atrial Fibrillation	KCNH2 and CX43	AAV gene addition	Pigs	Donahue and Tai	Metabolic Diseases	Cytochrome C Oxidase Deficiency	COX20	AAV gene replacement	Mice	Gessler, Gao		Dravet Syndrome	SCN1A	AAV gene replacement	Mice	Sena-Esteves and Wolfe
Connective Tissue Disorder	Dermatosp araxis Ehlers Danlos Syndrome	ADAMTS2	AAV gene replacement	Mice	Gray-Edwards		Leigh Syndrome	SURF1	AAV gene replacement	Mice, patient-derived iPSCs	Ling		GNAO1-related neurodevelop mental disorder	GNAO1	AAV gene replacement	Mice	Sena-Esteves
Infectious Diseases	HIV infection	N/A	Neutralizing antibodies AAV gene addition	NHPs	Xie and Gao		Maple Syrup Urine Disease	BCKDHA and BCKDHB	AAV gene replacement	Mice, cows, patient-derived iPSCs	J. Wang, D. Wang, Strauss, Gray-Edwards, Gao		Hypomyelinati on with Atrophy of the Basal Ganglia and Cerebellum (H-ABC)	TUBB4a	AAV gene silencing AAV gene replacement AAV gene editing	Mice	Xie, Gao
Leukodystrophie s	Aicardi-Goutières Syndrome (AGS)	ADAR1 and others	AAV gene silencing AAV gene replacement	Mice	Xie, Gao		Mucopolipidosis IV	COLN1	AAV gene replacement	Mice	Sena-Esteves/ Gray-Edwards		Neurofibromat osis	NF1	AAV gene replacement	Mice, pigs	Sena-Esteves
	Alexander Disease (AxD)	GFAP	AAV gene silencing	Mice, rats	Xie, Gao		Sialidosis	NEU1	AAV gene replacement	Mice, sheep (planned)	Gray-Edwards		Rett Syndrome UBA5 Deficiency	MECP2	AAV gene replacement	Mice	Sena-Esteves
	Canavan Disease	ASPA	AAV gene replacement	Mice	Gessler, Tai, Gao		VLCAD Deficiency	VLCAD	AAV gene replacement	Mice	Keeler/Flotte		UBA5	UBA5	AAV gene replacement	Mice	Taghian
Liver Diseases	Acetamino phen-Induced Acute Liver Failure	miR-375 and others	AAV gene silencing siRNA	Mice	Xie, Gao		Myopathy	Nemaline myopathy	TNNT1	AAV gene replacement	Mice and sheep ongoing		Edwards/ Sena-Esteves	Hereditary and Sensory Autonomic Neuropathy Type 1	SPTLC1	ASO knockdown	Mice
	Alagille Syndrome (ALGS)	SOX4	AAV gene silencing	Mice	Xie, Gao	TK2 deficiency		TK2	AAV gene replacement	Mice	Xie and Gao		Autoimmune Uveitis		N/A	CAR Treg therapy	Mice
Lysosomal Storage Disorders	Galactosial idosis	CTSA	AAV gene replacement	Mice	Gray-Edwards	Neurodegenerativ e Diseases		Hereditary Amyotrophic Lateral Sclerosis (ALS)	C9orf72	ASO knockdown	Mice, sheep, NHPs, 1 human		Brown	Glaucoma	RhoA and sFasL	AAV gene knockdown AAV gene addition	Mice
	GM1 Gangliosid osis	GLB1	AAV gene replacement	Mice, cats, NHPs, human Phase I/III complete	Sena-Esteves and Gray-Edwards		SOD1 ALS	SOD1	AAV artificial miRNA silencing	Mice, NHPs, 2 humans	Brown, Flotte, Gao, Sena-Esteves	Wet AMD	VEGF		AAV gene addition	Mice	Lin, Punzo, Tai, Xie, Gao
	GM2 Gangliosid oses (Tay-Sachs and Sandhoff Disease)	HEXA and HEXB	AAV gene replacement	Mice, cats, sheep, NHPs, human Phase I/III complete	Sena-Esteves/ Gray-Edwards		Bivalent siRNA	Mice	Brown, Khvorova	Alpha-1 Antitrypsin Deficiency	A1AT		AAV gene augmentation AAV gene replacement/knockd own		Mice and ferrets	Flotte, Gruntman	
	GM3 Synthase Deficiency	ST3GAL5	AAV gene replacement	Mice, patient-derived iPSCs	Gao, Strauss, Wang, Tai,		AAV gene silencing	Mice	Xie		Surfactant B Deficiency	proSFTPB	AAV gene addition	Mice	Gruntman, Flotte		
	Hypomyeli nating Leukodystro phy (POLR3-HLD)	POLR3b	AAV gene replacement	Mice	Xie, Gao		Spastic Paraplegia Type 4	SPG4	AAV silencing with gene replacement	Mice, cow (planned)	Sena-Esteves/ Gray-Edwards	Fibrodysplasia Ossificans Progressiva	ACVR1	AAV or siRNA gene silencing	Humanized mice, patient-derived iPSCs	Shim	
							Spinal Muscular Atrophy (SMA)	SMN1	AAV gene replacement	Mice	Xie, Gao		Fibrodysplasia Ossificans Progressiva	ACVR1	AAV or siRNA gene silencing	Humanized mice, patient-derived iPSCs	Shim
							Sporadic ALS	STMN2	ASO knockdown	Rats, 1 human	Brown		Osteogenesis Imperfecta	COL1A1 and COL1A2	AAV gene replacement or editing	Mice	Shim
								ATXN2 and others	AAV gene silencing AAV gene replacement	Mice	Xie						

FIRST-IN-HUMAN GENE THERAPY CLINICAL TRIALS AT UMASS CHAN PRIMARILY LED BY TERRY FLOTTE (7 TOTAL)

Vector	Years	Description
AAV1-AAT	2006–2017	Nine Alpha-1 Antitrypsin Deficiency patients were treated in a Phase I trial and a Phase IIa 5-year follow up.
AAV2-RPE65	2007–present	Eight patients were treated in a Phase I trial and two patients were treated in a Phase I/II trial for Leber Congenital Amaurosis.
AAV2-sFlt1	2009–2014	Two patients were treated for AMD.
AAVrh10-antiSOD1miR	2019–2020	Patients with familial ALS caused by <i>SOD1</i> mutations.
AAVrh8-HexA/HexB	2018–2024	Nine patients with Tay-Sachs/Sandhoff disease were treated in a Phase I/II trial and two patients were treated in an expanded access trial.
AAV9-dCas9/VP64-DMD	2022	N of 1 trial for a DMD patient treated with a custom-designed CRISPR therapy.
AAV9-Bi_HexA-HexB	2024 (planned)	N of 1 trial, then 12 patients with Tay-Sachs/Sandhoff Disease.

Treated during this 5-year review period

AAV GENE THERAPY PIPELINE AT *TRANSLATIONAL INSTITUTE OF MOLECULAR THERAPEUTICS* LED BY MIGUEL ESTEVES



HORAE GTC PRODUCTIVITIES IN TRAINING, RESEARCH & INNOVATION

HGTC TRAINEE AWARDS FROM ASGTC IN THE PAST 5 YEARS

- CURRENT TRAINEES **48**

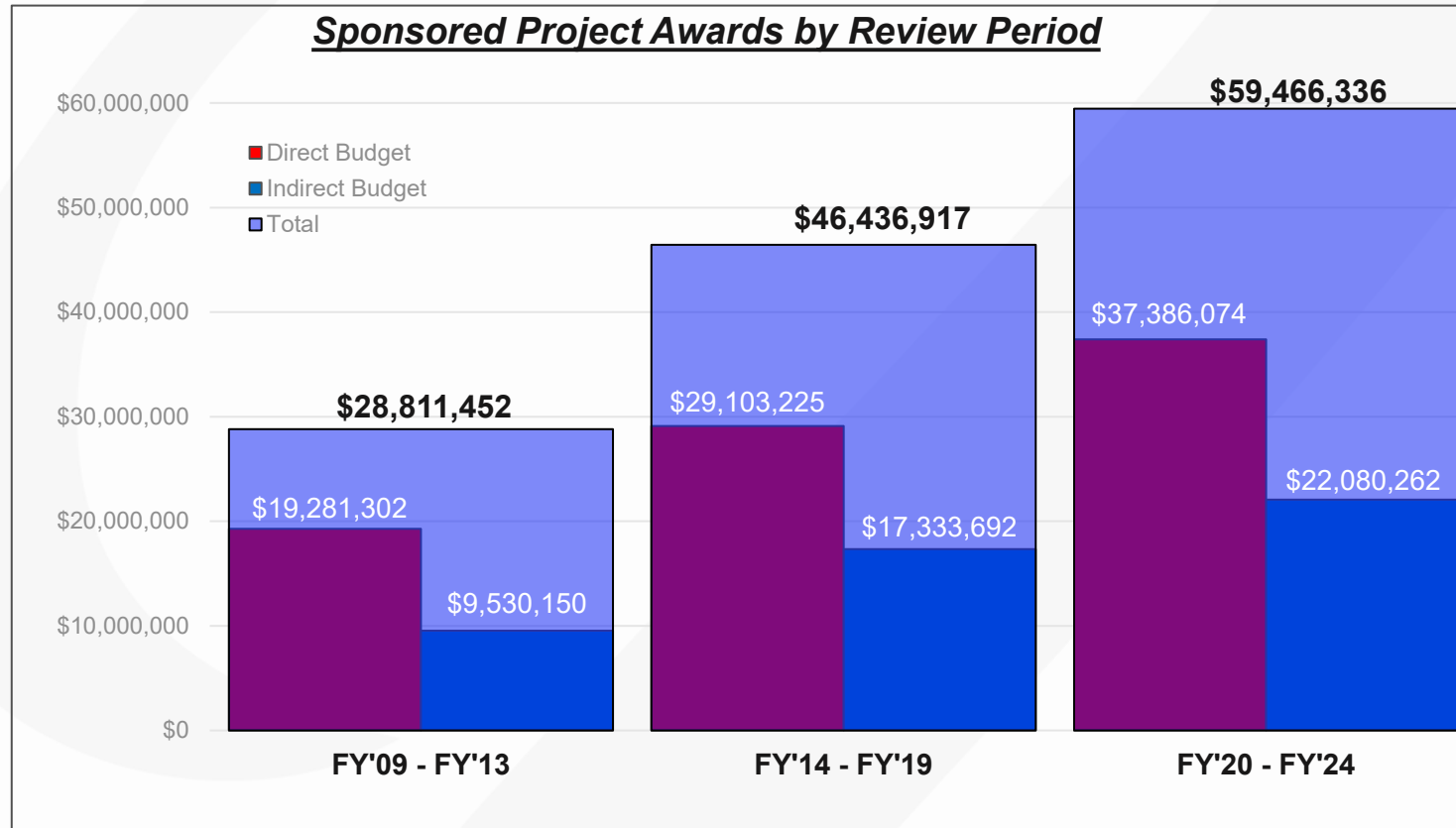
	2020	2021	2022	2023	2024	Totals
Career Development Award	0	1	0	2	0	3
Travel Award	4	*	5	10	9	28
Excellence in Research Award	1	2	2	1	4	10
Outstanding Poster Award	0	0	3	1	**	4

*No Travel Awards were given in 2021 because the meeting was held virtually due to the COVID-19 pandemic.

**Not yet selected.

HGTC GRANT AWARDS/REVENUES

- A 30% INCREASE IN THE PAST 5 YEARS WITH \$135 MILLIONS TOTAL PLUS \$43 MILLION PATENT LICENSURE REVENUE IN THE PAST 15 YEARS



HGTC PUBLICATIONS IN THE PAST 5 YEARS

Year	Total Manuscripts Published	Peer Reviewed	Non-Peer Reviewed	Books/ Chapters
2019 (May–Dec)	24	21	3	2
2020	61	52	9	0
2021	53	40	13	0
2022	54	46	8	1
2023	46	36	10	0
2024 (Jan–Apr)	15	14	1	3
Totals	253	209	44	6

HGTC PATENTS IN THE PAST 5 YEARS

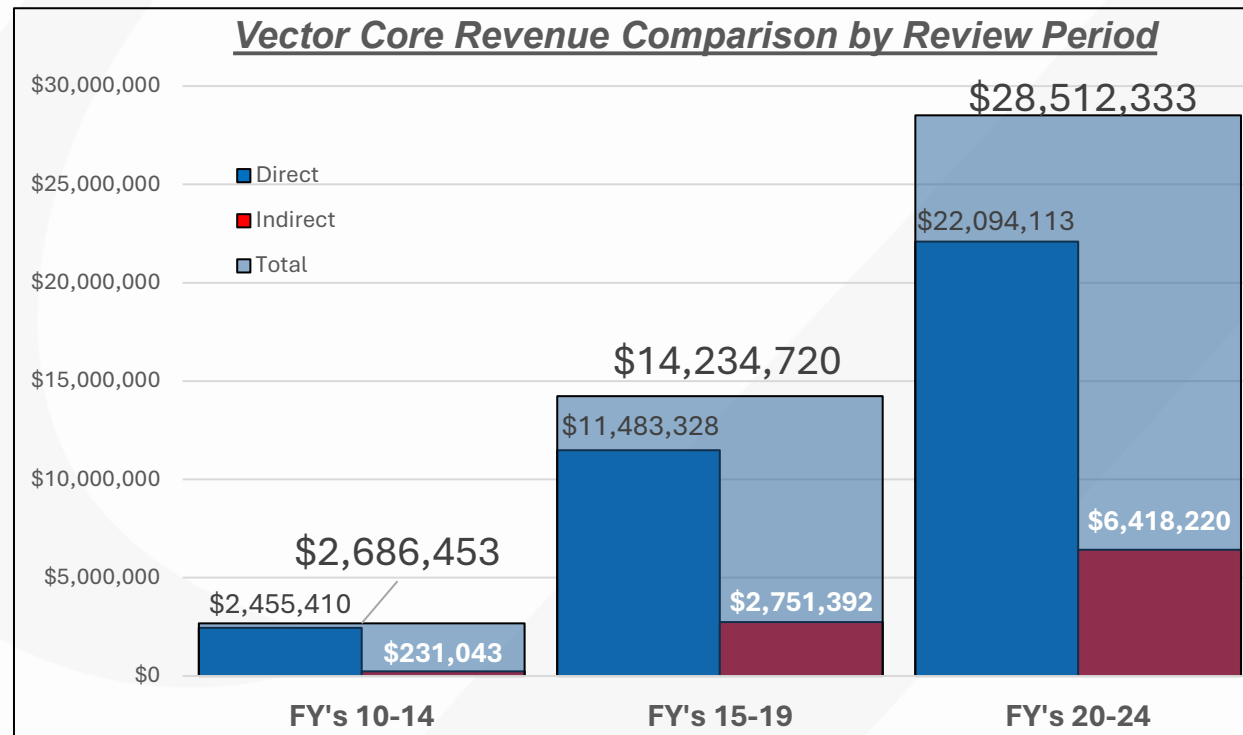
Name	Total Patents	Patents Issued	Patents Pending
Dominic Gessler	1	0	1
Guangping Gao	294	97	197
Allison Keeler-Klunk	2	0	2
Jae-Hyuck Shim	12	12	0
Toloo Taghian	14	2	12
Phil Tai	7	7	0
Dan Wang	10	0	10
Jiaming Wang	4	3	1
Jun Xie	15	0	15
Guocai Zhong	2	0	2
Totals (some duplicate)	361	114	232

RESEARCH INSTITUTES AND RESEARCH SERVICE CORES RUN BY HGTC PIs

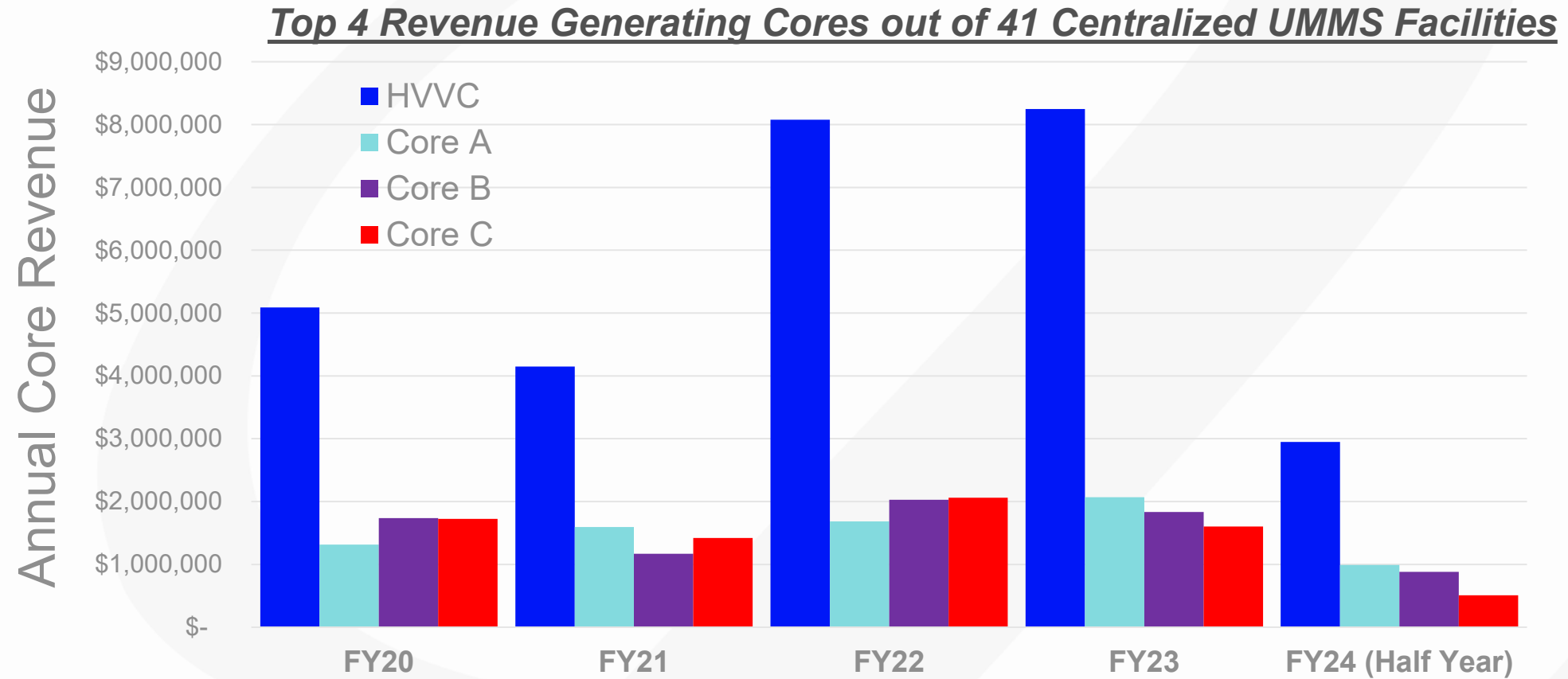
- *Translation Institute of Molecular Therapeutics* directed by Miguel Esteves
- *Li Weibo Research Institute of Rare Diseases* directed by Guangping Gao
- Research Service Cores
 - *Respiratory Biology Core* to be set up by Alisha Gruntman
 - *Transgenic Animal Core* directed by Heather Grayedwards
 - *Viral Vector Cores*
 - *Research Vector Core* directed by Jun Xie & Guangping Gao
 - *Large Scale Vector Manufacturing Core* directed by Sylvain Cecchini & Guangping Gao

HGTC VIRAL VECTOR CORE (NON-SUBSIDIZED CORE) REVENUE

- Doubled in past five years with \$45 million total revenue since funded 15 years ago
- Impacted by recent Biotech/Biopharma contractions
- Started advertisement for the first time to expand the client base



PERFORMANCE OF HOARE VECTOR CORE IN PAST 5 YEARS



DEPARTMENT OF *GENETIC AND CELLULAR MEDICINE*

WOULD ALLOW US TO

- Grow and better support our faculty
- Expand and strengthen our Interdisciplinary Science
- Promote science and technology innovations
- Increase & diversify grant awards, licensing and core revenues
- Develop gene therapy-focused training programs & funding resources to train scientist and clinician-scientists as future leaders for gene and cell therapy innovation and clinical translation
- Increase opportunities for research collaborations and engagement among faculty members and trainees

Thank You!

Questions?



UMass Chan
MEDICAL SCHOOL