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

- Guangping Gao, PhD, Faculty council, November 7, 2024

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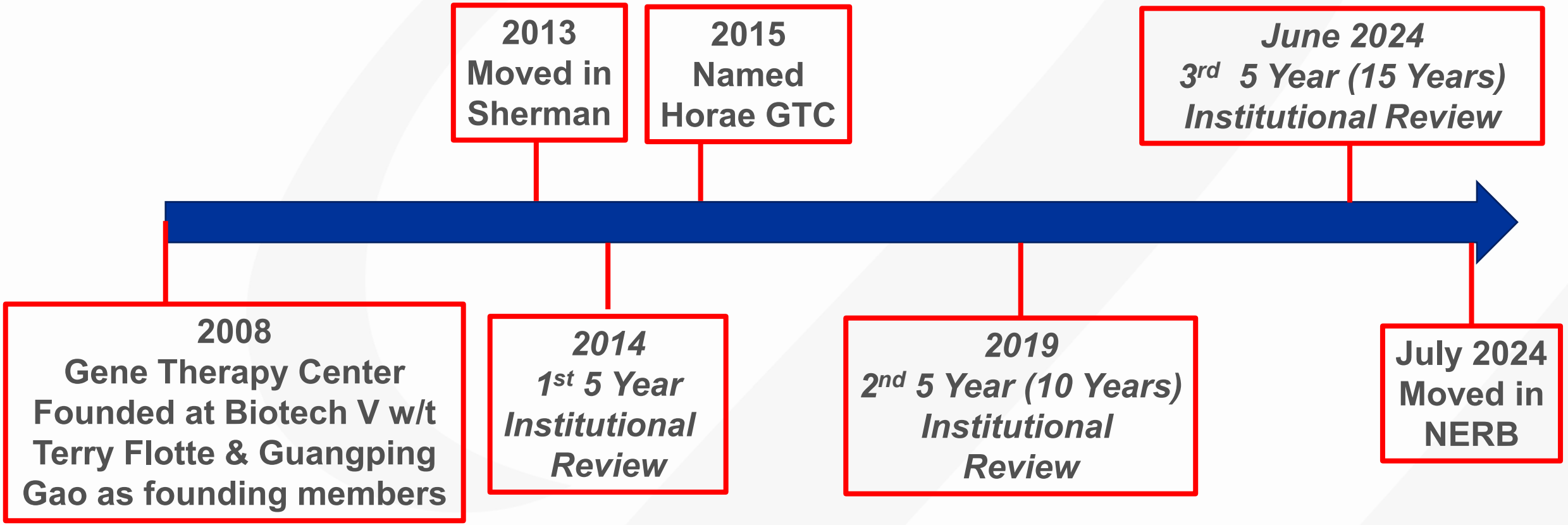
HORAE GENE THERAPY CENTER

HORAE GTC HISTORY & MILESTONES



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HORAE GTC CURRENT FACULTY, TRAINEE AND STAFF

➢ Faculty members	20
➢ Interns, graduate and postdoc trainees	48
➢ Research staff	54
➢ Administrative staff	6
Total:	**128**

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HORAE GTC CURRENT FACULTY & RESEARCH PROGRAMS

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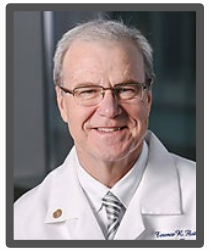
Tenured faculty (5)



Terry Flotte, MD
Prof

G Gao, PhD
Prof & Director

Jen Adair, PhD
Prof & Assoc Director

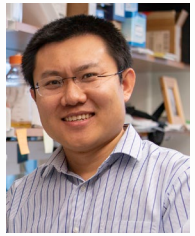
Miguel Esteves, PhD
Assoc Prof

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

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PIs & Research Programs

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

UMass Chan Gene Tx Pipeline

- 14 disease categories and 42 drugs in development

Type of Disorder	Disease	Target Gene(s)	Therapeutic Strategy	Preclinical Proof-of-Concept	UMMS PIs
Cardiovascular Disease	Atrial Fibrillation	KCNH2 and CX43	AAV gene addition	Pigs	Donahue and Tai
Connective Tissue Disorder	Dermatosparaxis Ehlers Danlos Syndrome	ADAMTS2	AAV gene replacement	Mice	Gray-Edwards
Infectious Diseases	HIV infection	N/A	Neutralizing antibodies AAV gene addition	NHPs	Xie and Gao
Leukodystrophies	Aicardi-Goutières Syndrome (AGS)	ADAR1 and others	AAV gene silencing AAV gene replacement	Mice	Xie, Gao
	Alexander Disease (AxD)	GFAP	AAV gene silencing	Mice, rats	Xie, Gao
	Canavan Disease	ASPA	AAV gene replacement	Mice	Gessler, Tai, Gao
Liver Diseases	Acetaminophen-Induced Acute Liver Failure	miR-375 and others	AAV gene silencing siRNA	Mice	Xie, Gao
	Alagille Syndrome (ALGS)	SOX4	AAV gene silencing	Mice	Xie, Gao
Lysosomal Storage Disorders	Galactosialidosis	CTSA	AAV gene replacement	Mice	Gray-Edwards
	GM1 Gangliosidosis	GLB1	AAV gene replacement	Mice, cats, NHPs, human Phase I/II complete	Sena-Esteves and Gray-Edwards
	GM2 Gangliosidoses (Tay-Sachs and Sandhoff Disease)	HEXA and HEXB	AAV gene replacement	Mice, cats, sheep, NHPs, human Phase I/II complete	Sena-Esteves/ Gray-Edwards
	GM3 Synthase Deficiency	ST3GAL5	AAV gene replacement	Mice, patient-derived iPSCs	Gao, Strauss, Wang, Tai,
	Hypomyelinating Leukodystrophy (POLR3-HLD)	POLR3b	AAV gene replacement	Mice	Xie, Gao

Type of Disorder	Disease	Target Gene(s)	Therapeutic Strategy	Preclinical Proof-of-Concept	UMMS PIs
Metabolic Diseases	Cytochrome C Oxidase Deficiency	COX20	AAV gene replacement	Mice	Gessler, Gao
	Leigh Syndrome	SURF1	AAV gene replacement	Mice, patient-derived iPSCs	Ling
	Maple Syrup Urine Disease	BCKDHA and BCKDHB	AAV gene replacement	Mice, cows, patient-derived iPSCs	J. Wang, D. Wang, Strauss, Gray-Edwards, Gao
	Mucolipidosis IV	COLN1	AAV gene replacement	Mice	Sena-Esteves/ Gray-Edwards
	Sialidosis	NEU1	AAV gene replacement	Mice, sheep (planned)	Gray-Edwards
	VLCAD Deficiency	VLCAD	AAV gene replacement	Mice	Keeler/Flotte
Myopathy	Nemaline myopathy	TNNT1	AAV gene replacement	Mice and sheep ongoing	Edwards/ Sena-Esteves
	TK2 deficiency	TK2	AAV gene replacement	Mice	Xie and Gao
Neurodegenerative Diseases	Hereditary Amyotrophic Lateral Sclerosis (ALS)	C9orf72	ASO knockdown	Mice, sheep, NHPs, 1 human	Brown
	SOD1 ALS	SOD1	AAV artificial miRNA silencing	Mice, NHPs, 2 humans	Brown, Flotte, Gao, Sena-Esteves
			Bivalent siRNA	Mice	Brown, Khvorova
			AAV gene silencing	Mice	Xie
	Spastic Paraplegia Type 4	SPG4	AAV silencing with gene replacement	Mice, cow (planned)	Sena-Esteves/ Gray-Edwards
	Spinal Muscular Atrophy (SMA)	SMN1	AAV gene replacement	Mice	Xie, Gao
	Sporadic ALS	STMN2	ASO knockdown	Rats, 1 human	Brown
		ATXN2 and others	AAV gene silencing AAV gene replacement	Mice	Xie

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
	Dravet Syndrome	SCN1A	AAV gene replacement	Mice	Sena-Esteves and Wolfe
	GNAO1-related neurodevelopmental disorder	GNAO1	AAV gene replacement	Mice	Sena-Esteves
	Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum (H-ABC)	TUBB4a	AAV gene silencing AAV gene replacement AAV gene editing	Mice	Xie, Gao
	Neurofibromatosis	NF1	AAV gene replacement	Mice, pigs	Sena-Esteves
	Rett Syndrome	MECP2	AAV gene replacement	Mice	Sena-Esteves
	UBA5 Deficiency	UBA5	AAV gene replacement	Mice	Taghian
Neuropathy	Hereditary and Sensory Autonomic Neuropathy Type 1	SPTLC1	ASO knockdown	Mice	Brown, Watts
Ocular Diseases	Autoimmune Uveitis	N/A	CAR Treg therapy	Mice	Keeler, Darren Lee
	Glaucoma	RhoA and sFasL	AAV gene knockdown AAV gene addition	Mice	Keeler, Gregory-Ksander, Lin, Rothstein, Tian, Xie, Tai, Gao
	Wet AMD	VEGF	AAV gene addition	Mice	Lin, Punzo, Tai, Xie, Gao
Pulmonary Diseases	Alpha-1 Antitrypsin Deficiency	A1AT	AAV gene augmentation AAV gene replacement/knockdown	Mice and ferrets	Flotte, Gruntman
	Surfactant B Deficiency	proSFTPB	AAV gene addition	Mice	Gruntman, Flotte
Skeletal Diseases	Fibrodysplasia Ossificans Progressiva	ACVR1	AAV or siRNA gene silencing	Humanized mice, patient-derived iPSCs	Shim
	Fibrodysplasia Ossificans Progressiva	ACVR1	AAV or siRNA gene silencing	Humanized mice, patient-derived iPSCs	Shim
	Osteogenesis Imperfecta	COL1A1 and COL1A2	AAV gene replacement or editing	Mice	Shim

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 *SOD1* 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 trail 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

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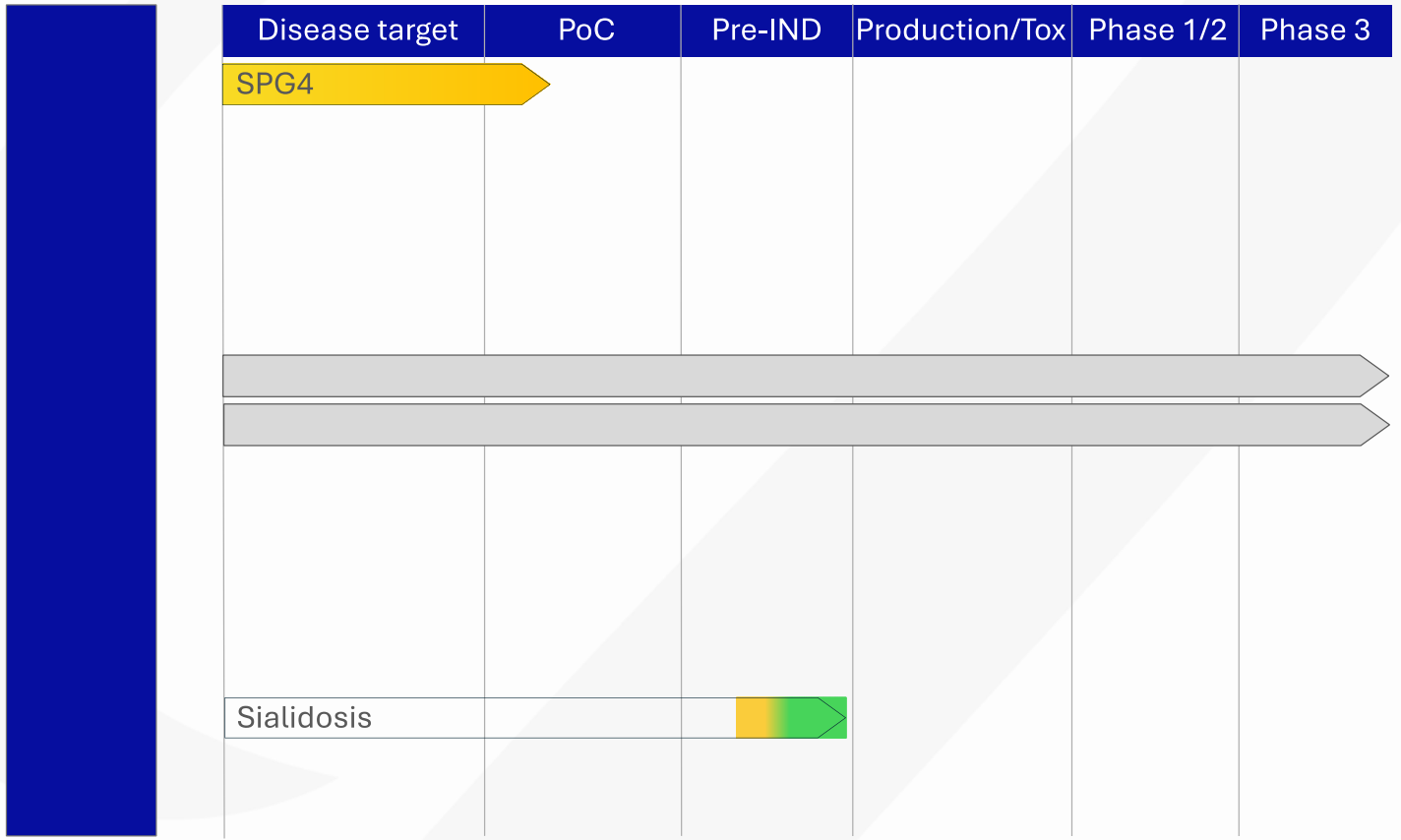
AAV Gene Therapy Pipeline at *Translational Institute of Molecular Therapeutics* led by Miguel Esteves



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HORAE GTC PRODUCTIVITIES IN TRAINING, RESEARCH & INNOVATION

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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.

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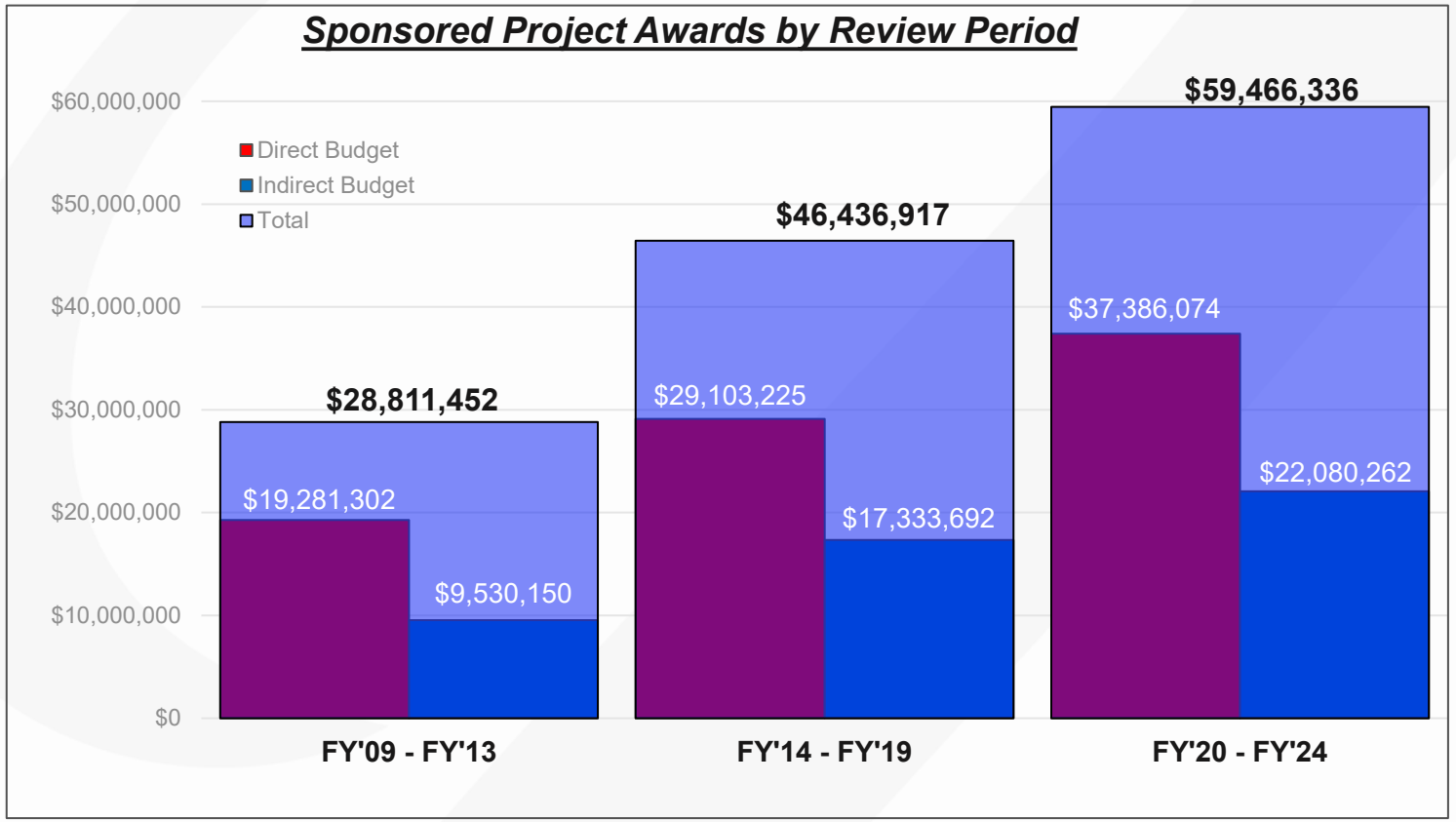
HGTC Grant Awards/Revenues

- A 30% increase in the past 5 years with $135 millions total
Plus $43 million patent licensure revenue in the past 15 years



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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**

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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**

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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

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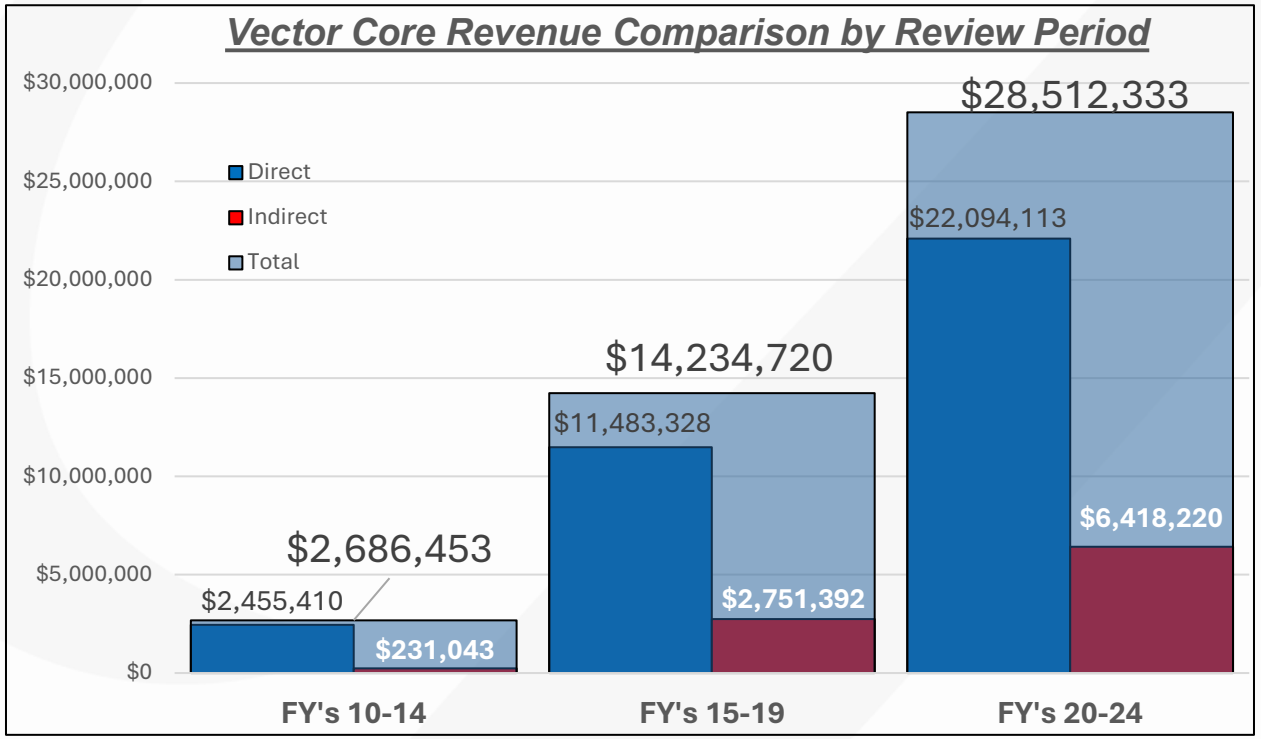
HGTC Viral Vector Core (*non-subsidized Core*) Revenue

- *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*



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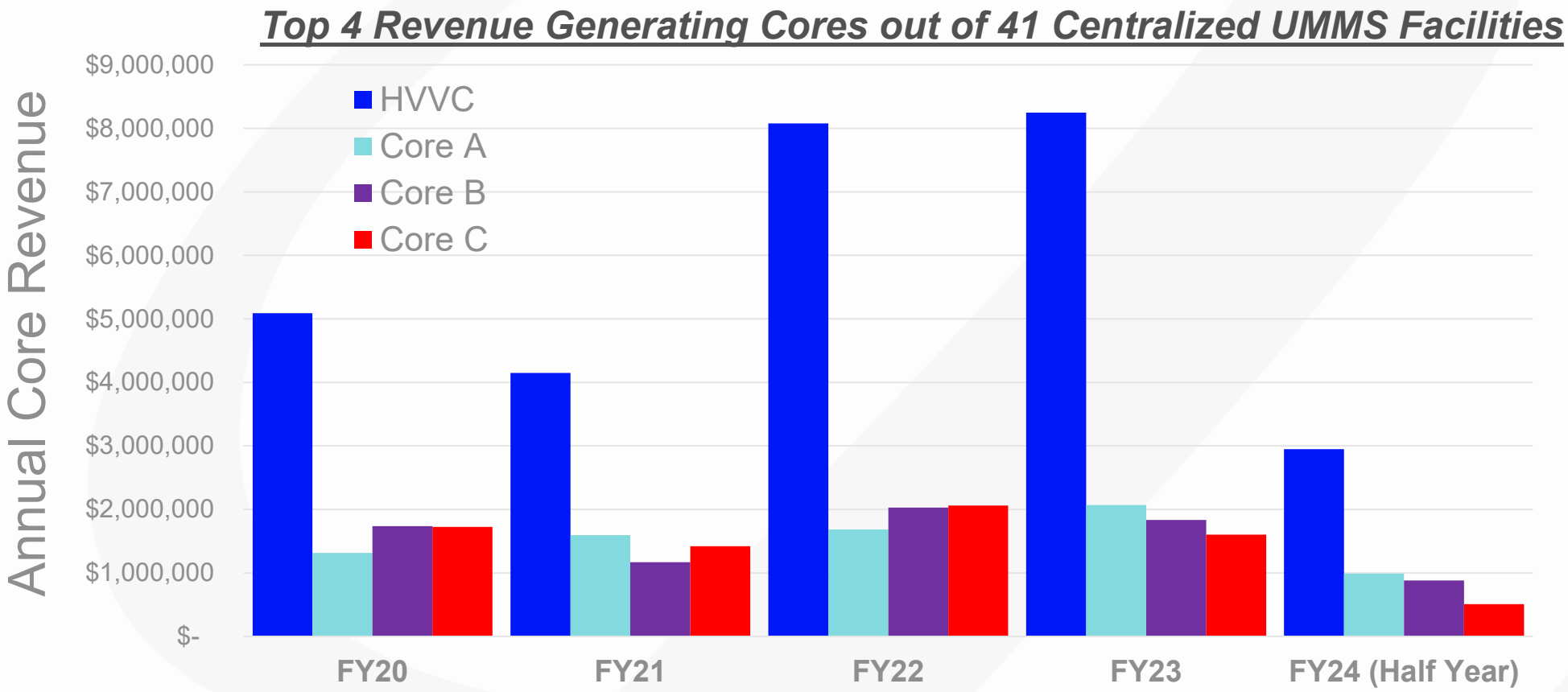
Performance of Hoare Vector Core in past 5 years



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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

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Thank You!

Questions?

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