大阪大学
THE UNIVERSITY OF OSAKA

CMC STRATEGY FORUM
ADVANCING BIOPHARMACEUTICAL DEVELOPMENT
JAPAN 2025

December 8th, 2025
13:30-13:50

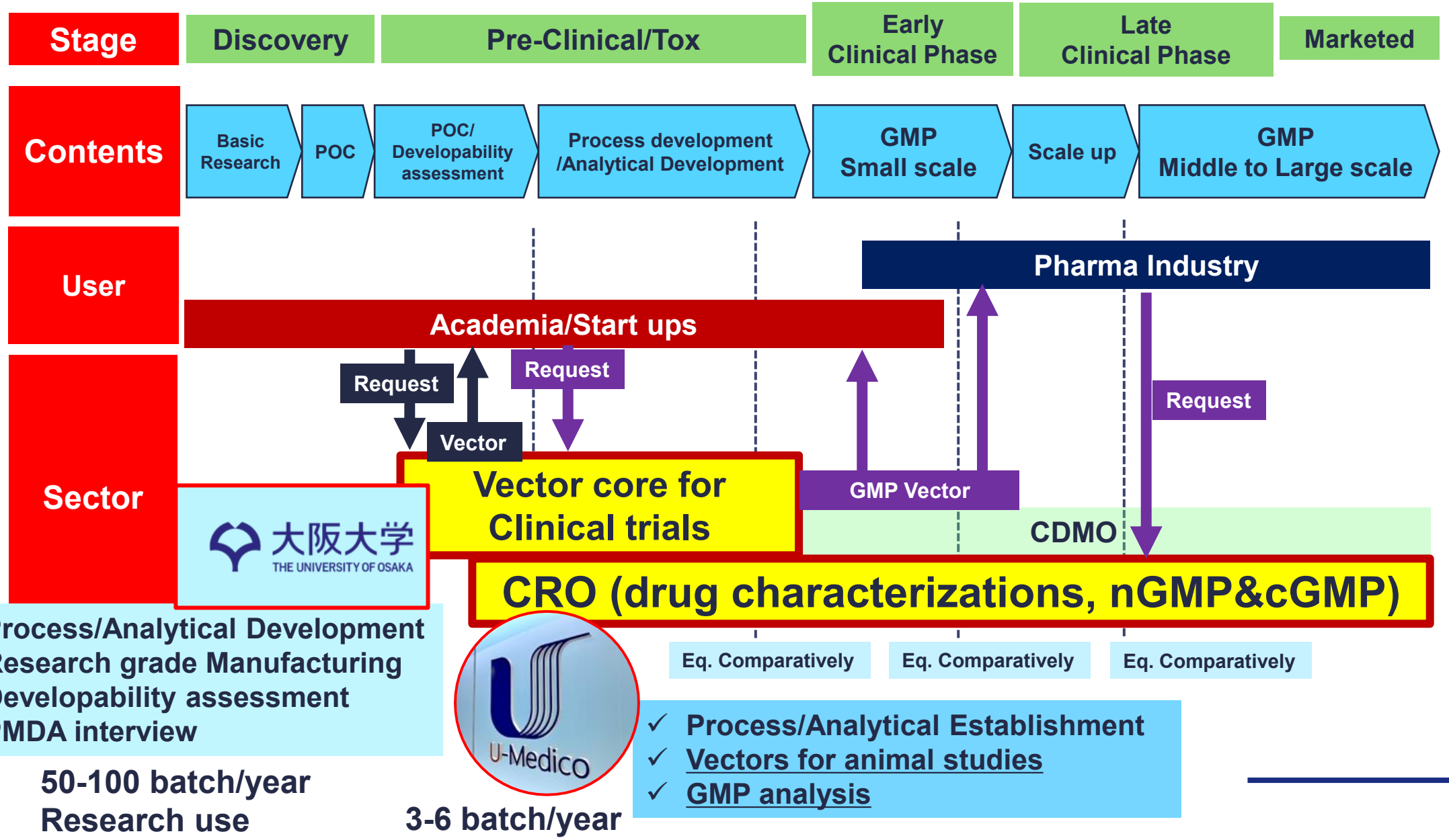
rAAV as a Heterogeneous Particle Ensemble: Current Understanding of Its Quality Attributes

Department of Biotechnology,
Graduate School of Engineering,
The University of Osaka
Susumu Uchiyama

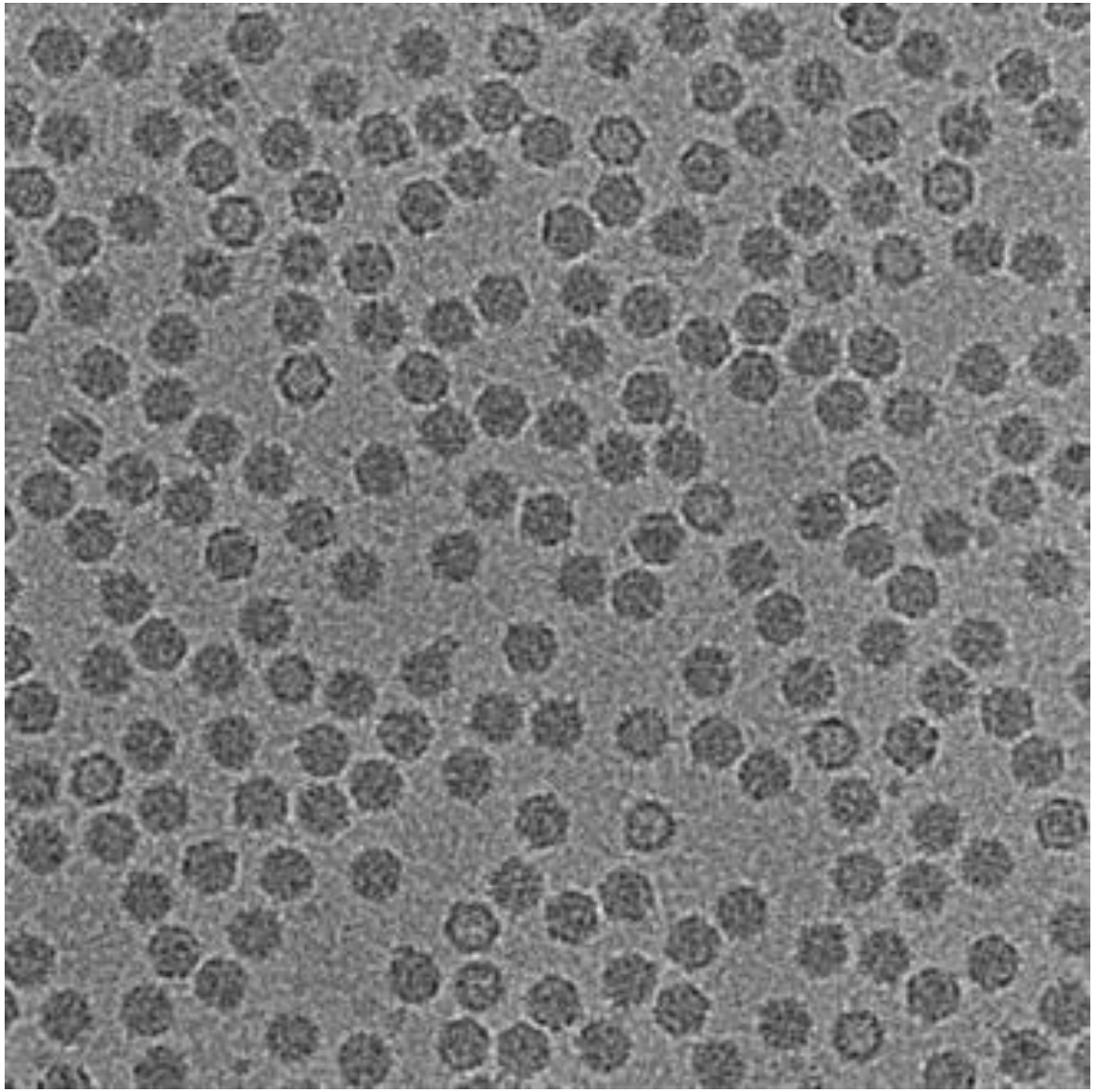
COI disclosure

Susumu Uchiyama is a founder and CSO of U-Medico. Inc.
Susumu Uchiyama is a member of expert committee of USP.
The opinions expressed are the speaker’s own and do not represent the views of USP.

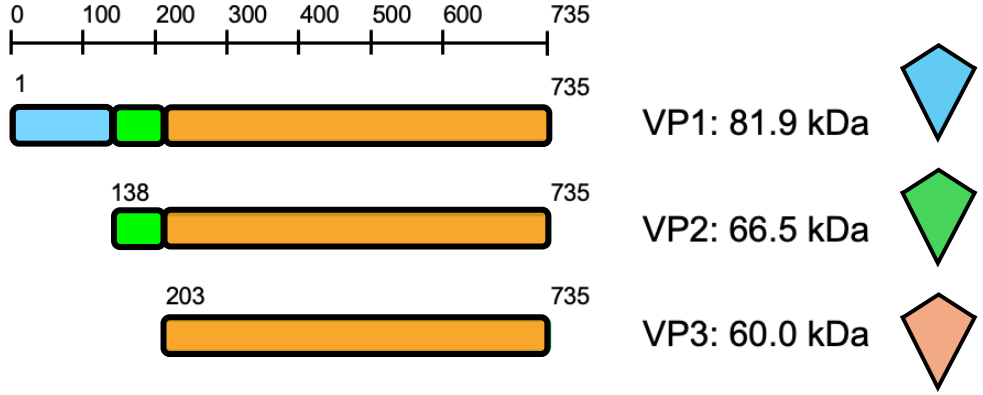
For the success of Gene Therapy



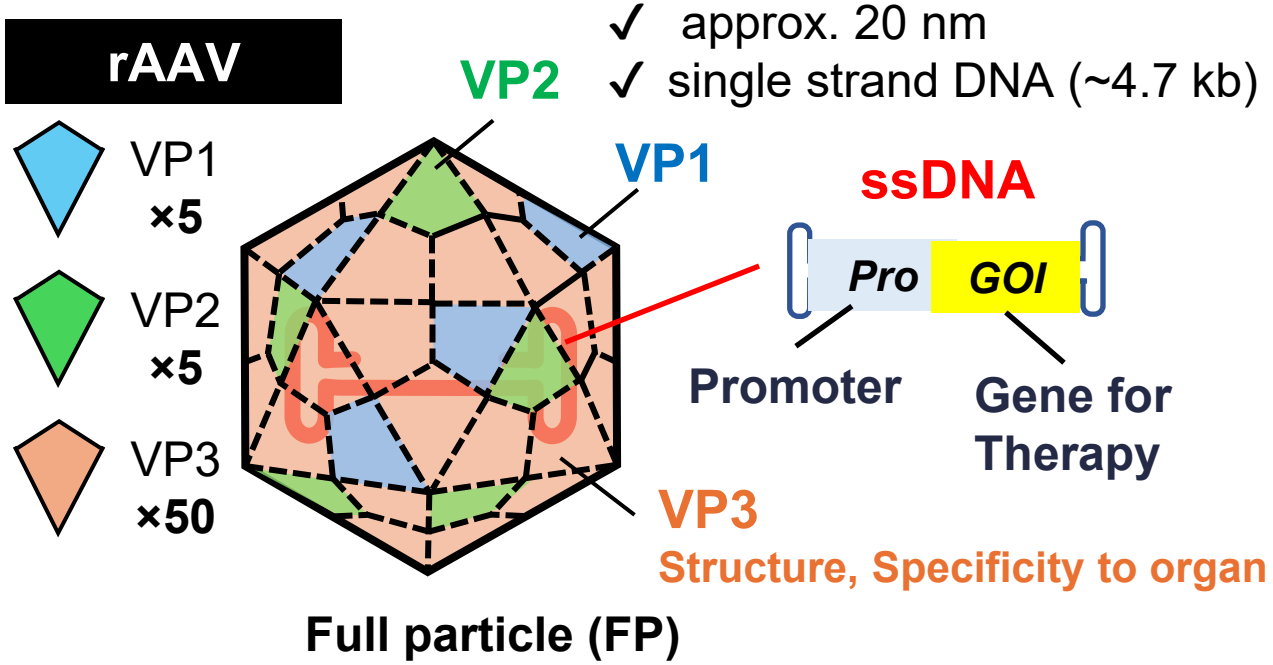
Recombinant adeno-associated virus: rAAV



Nishiumi et al., *J. Pharm. Sci.* 2024

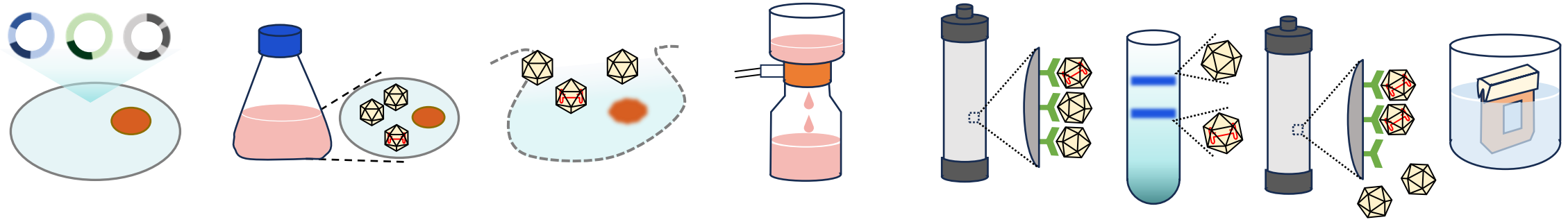


- ✓ icosahedral
- ✓ approx. 20 nm
- ✓ single strand DNA (~4.7 kb)



Manufacturing process of rAAV and analytical Challenges

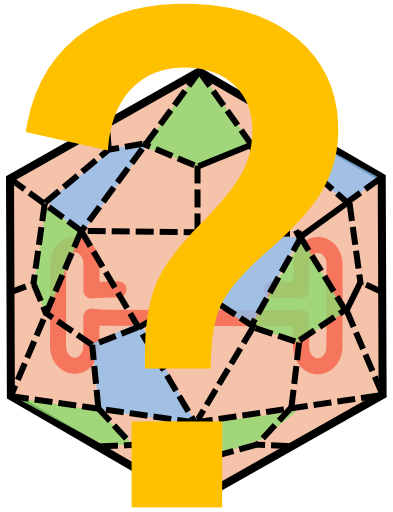
Upstream processes | **Downstream processes**



Cell culture → Transfection → Cell harvest → Cell Lysis → Filtration → Affinity chromatography → Separation of FPs and EPs → Dialysis and concentration

Variation of Produced rAAV particles

Purification is challenging
Impurity analysis is required



1L Culture 0.1 mg (10^{13} particles)
60kg/person => $5x10^{13}$ vg
=> 30L Culture（0.5M USD)

QAs of rAAV and evaluation methods

Attribute category	Quality attribute	Method	Comment
Identity	Genome	PCR	dPCR no standard, better CV than qPCR
		CGE	Genome size needs to be confirmed
		NGS	Short read or Long read
	Capsid	CE-SDS	+ VP ratio
		SDS-PAGE	Need standard
		ELISA	Mutant AAV is difficult, Ab dependent
		WB	Need standard, Ab dependent
		LC-MS	Intact MS
		LC-MS/MS	Sequence + PTM + chemical mod
		MALDI-MS	Newly added
Titer	Genome	PCR	ITR lead to higher value than GOI
	Capsid	ELISA	Total particle number
		UV-Abs	Assumption: only F and E
		AEX	Assumption: only F and E with no PTM
		SEC	Assumption: only F and E
		AUC	Reliable

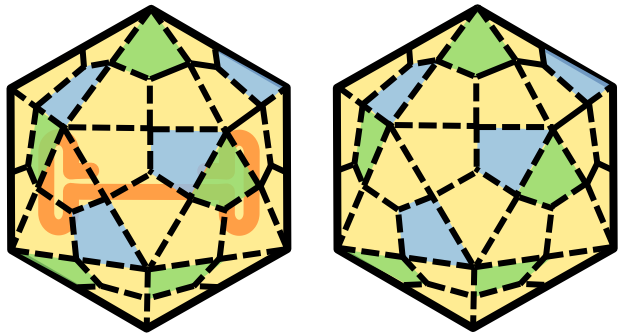
Attribute category	Quality attribute	Method	Comment
Purity	Genome	PCR	Multiple primer dPCR
		CGE	Suitable for lot-to-lot variation
		NGS	Identify sequences
	Capsid	CE-SDS	Suitable for lot-to-lot variation
		SDS-PAGE	Need standard
		ELISA	Need standard, Ab dependent
	F/E	UV	Assumption: only F and E
		ELISA/PCR	Assumption: only F and E
		AEX	Assumption: only F and E with no PTM
		SEC-MALS	Assumption: only F and E
		Cryo TEM	Assumption: only F and E
		Mass Photometry	Assumption: only F and E, PP > component number needs to be defined as prior knowledge
	F/E/PP/OP	AUC	Gold standard, base line separation
		CD-MS	Base line separation, careful parameter settings
	Aggregation	DLS	Qualitative
		SEC	Most commonly used
		AUC	Alternative candidate to SEC

Attribute category	Quality attribute	Method	Comment
Potency and Biological Activity	In vitro expression	ELISA	Need Ab for GOI protein
		WB	Need Ab for GOI protein
		FCM	Need Ab for GOI protein
		PCR	RT-PCR, need specific primer
		NGS	Advanced
	Transduction efficiency	TCID50	Independent of GOI, but not reflect actual in vivo situation
		FCM	Need Ab for GOI protein

Key points:

QAs analysis using orthogonal methods

Assessment of Full and Empty Particles



ARTICLE

Empty virions in AAV8 vector preparations reduce transduction efficiency and may cause total viral particle dose-limiting side effects

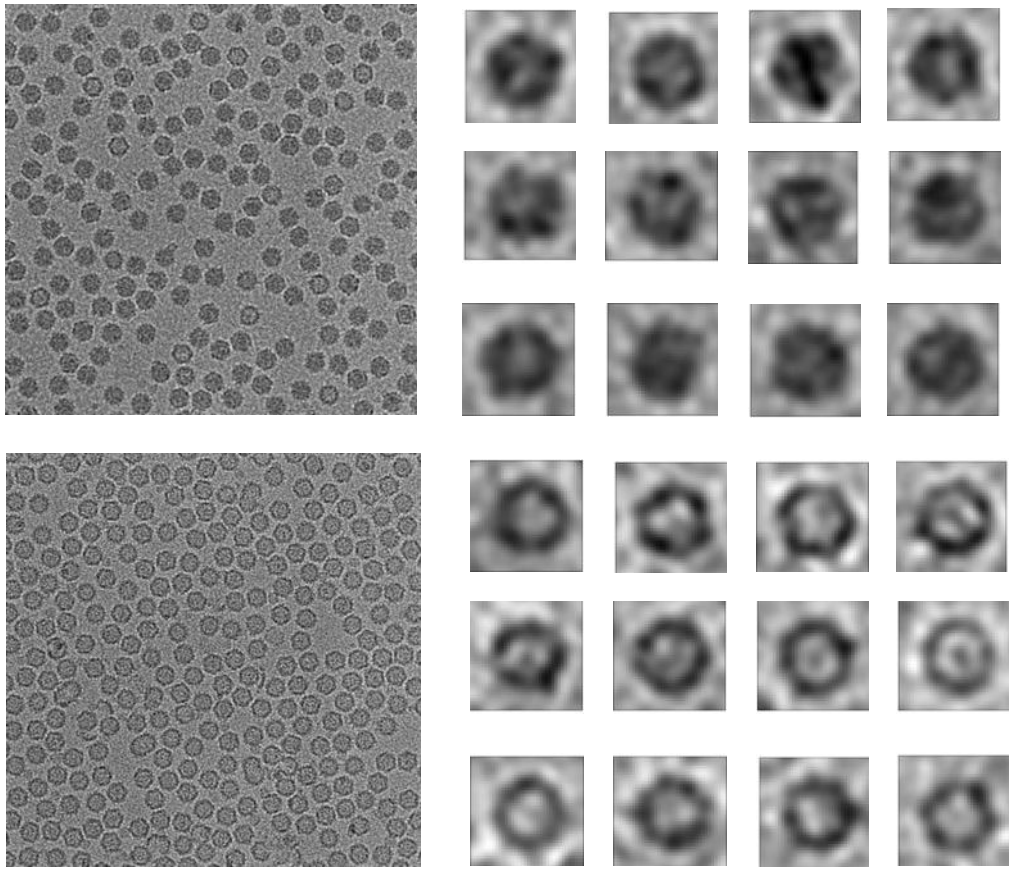
Kai Gao[1,2], Mengxin Li[1,3,4], Li Zhong[1,3,5], Qin Su[1,3], Jia Li[1,4], Shaoyong Li[1,4], Ran He[1,3], Yu Zhang[1,6], Gregory Hendricks[7], Junzhi Wang[2] and Guangping Gao[1,3,4,8]

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Guidance for Industry

iii. Physicochemical and Biologic Properties (3.2.P.2.2.3)

In your IND you should describe the parameters relevant to the performance of the DP, (or reference relevant DS sections, if appropriate). These parameters include physicochemical or biological properties of the product (e.g., dosing units, genotypic or phenotypic variation, particle number and size, aggregation state, infectivity, specific activity (ratio of infectious to non-infectious particles or full to empty particles), biological activity or



Nishiumi et al., *J. Pharm. Sci.* 2024

MW-SV-AUC, Band Sedimentation AUC (BS-AUC):small volume AUC, DGE-AUC separation based on buoyant density

MW-SV-AUC


Journal of Pharmaceutical Sciences 110 (2021) 3375–3384

Contents lists available at ScienceDirect

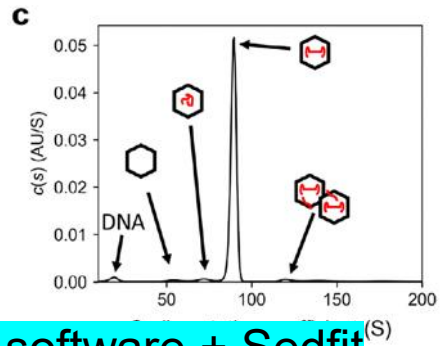
Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutical Biotechnology

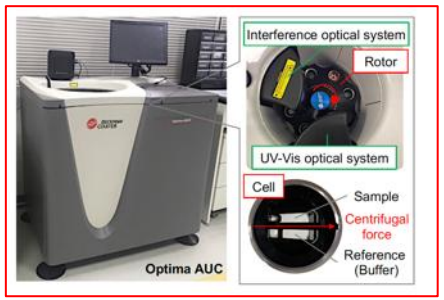
Comprehensive Size Distribution and Composition Analysis of Adeno-Associated Virus Vector by Multiwavelength Sedimentation Velocity Analytical Ultracentrifugation

Takahiro Maruno[a], Kaede Usami[a], Kentaro Ishii[a], Tetsuo Torisu[a], Susumu Uchiyama[a,b,*]



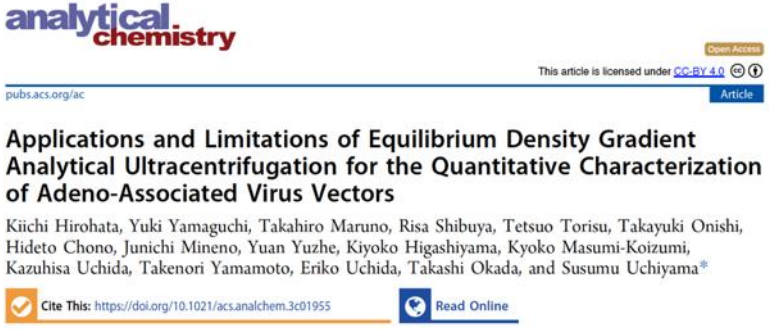
cGMP

In house software + Sedfit



DGE-AUC

Buoyant density based separation


analytical chemistry

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Article

Applications and Limitations of Equilibrium Density Gradient Analytical Ultracentrifugation for the Quantitative Characterization of Adeno-Associated Virus Vectors

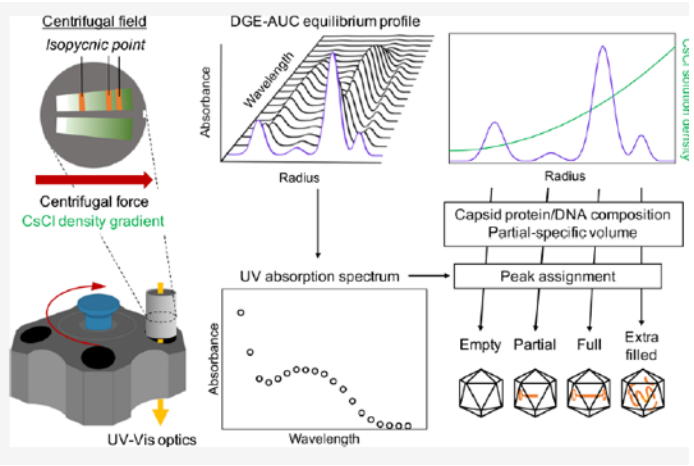
Kiichi Hirohata, Yuki Yamaguchi, Takahiro Maruno, Risa Shibuya, Tetsuo Torisu, Takayuki Onishi, Hideto Chono, Junichi Mineno, Yuan Yuzhe, Kiyoko Higashiyama, Kyoko Masumi-Koizumi, Kazuhisa Uchida, Takenori Yamamoto, Eriko Uchida, Takashi Okada, and Susumu Uchiyama*

Cite This: https://doi.org/10.1021/acs.analchem.3c01955

Read Online

S-value (Mw + shape) based separation

FP/EP/PP/OP/freeDNA



BS-AUC

Band Sedimentation AUC :
Vinograd J, et al., PNAS1963


Journal of Pharmaceutical Sciences 112 (2023) 937–946

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

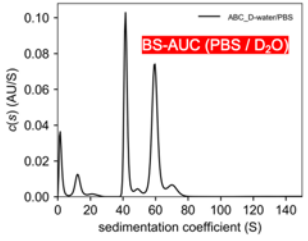
journal homepage: www.jpharmsci.org

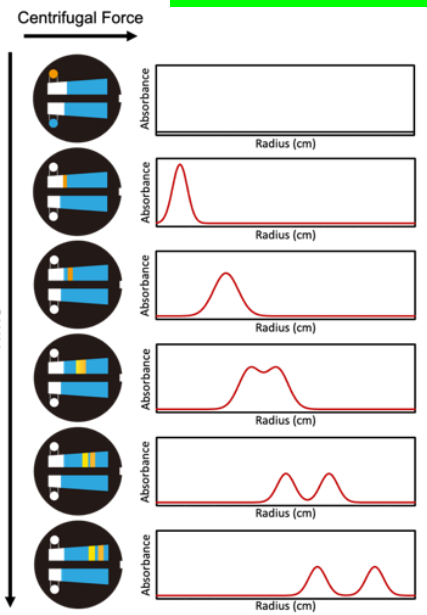
Pharmaceutical Biotechnology

Size Distribution Analysis of the Adeno-Associated Virus Vector by the *c*(*s*) Analysis of Band Sedimentation Analytical Ultracentrifugation with Multiwavelength Detection

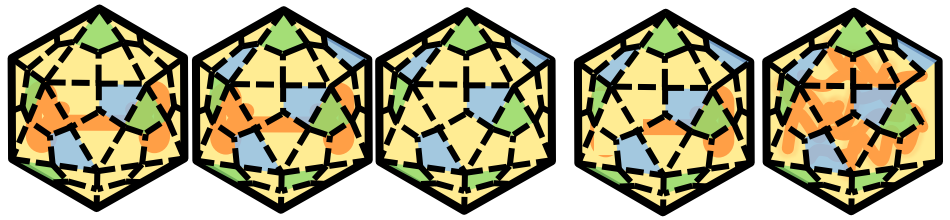
Takahiro Maruno[a,b], Kentaro Ishii[a], Tetsuo Torisu[a], Susumu Uchiyama[a,*]

[a] Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan
[b] U-Medico Inc., 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan



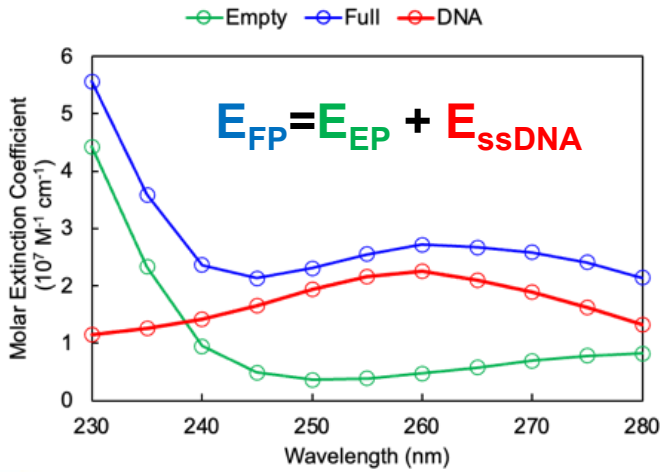


AUC with 10^{10} vg sample



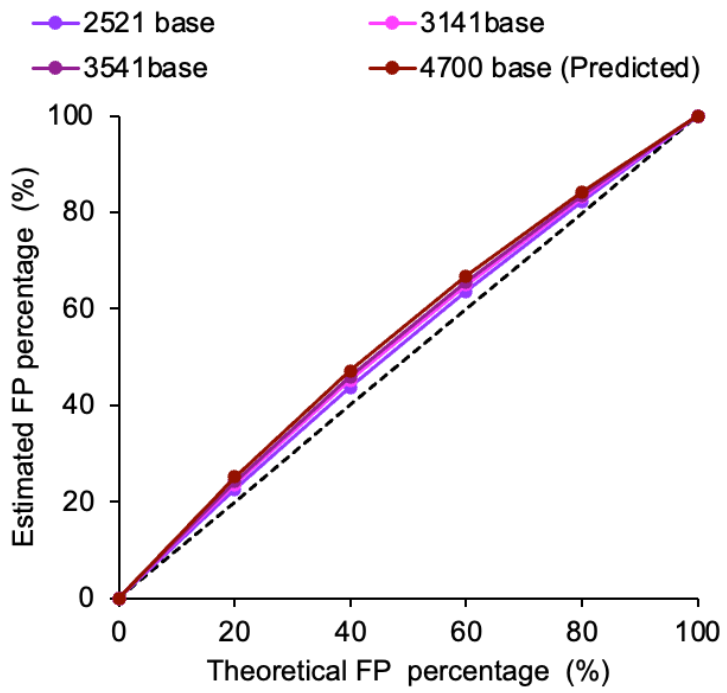
Maruno T, et al., J Pharm Sci. 112, 937-946 (2023).

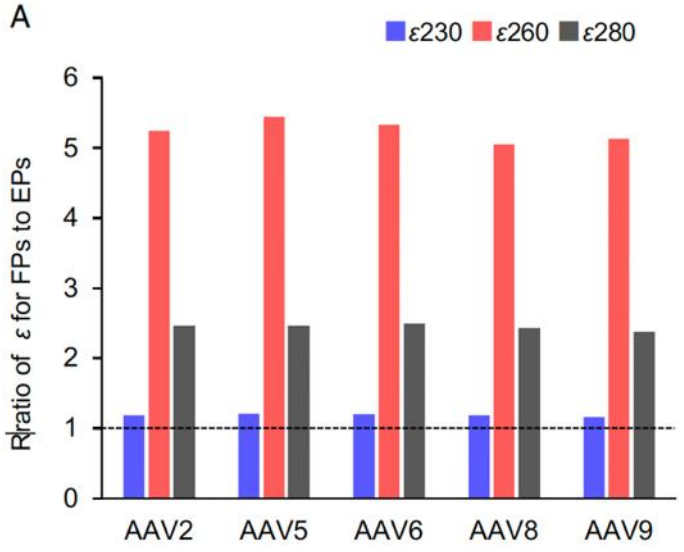
Correct extinction coefficient is essential for reliable quantification
The difference in the ε values for EPs and FPs in various serotypes



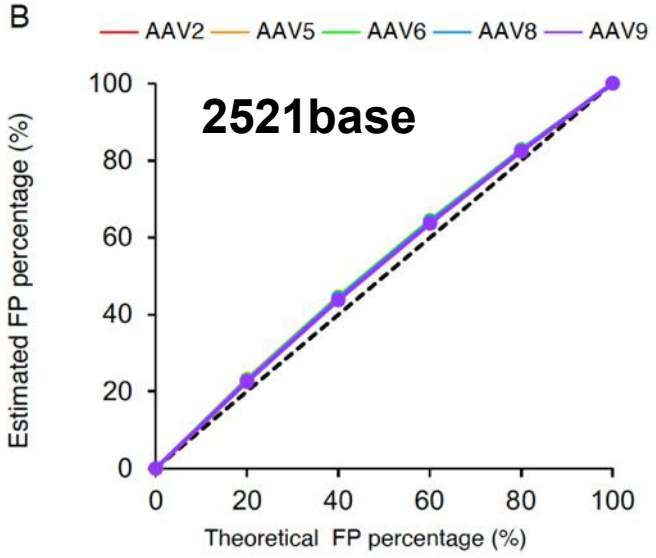
Maruno T, et al., J Pharm Sci. 2022

When $E_{FP}=E_{EP}$
FPs is more overestimated as ssDNA length longer





When $E_{FP}=E_{EP}$
FPs is overestimated



✓ **On average, FP values were 5.2-, 2.4-, and 1.2-fold higher than those of EPs at 260, 280, and 230 nm, respectively.**

Yamaguchi et al., ***Submitted***

Encapsidated genome analysis by CD-MS, CD-MS high energy mode

analytical chemistry

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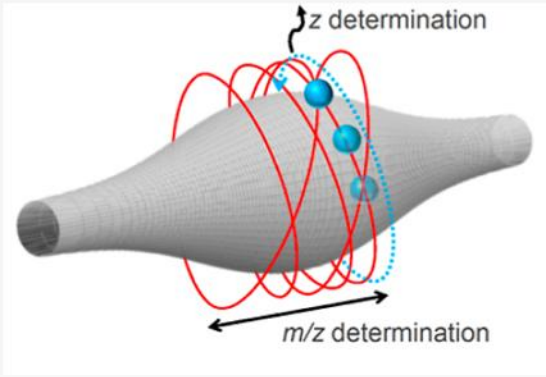
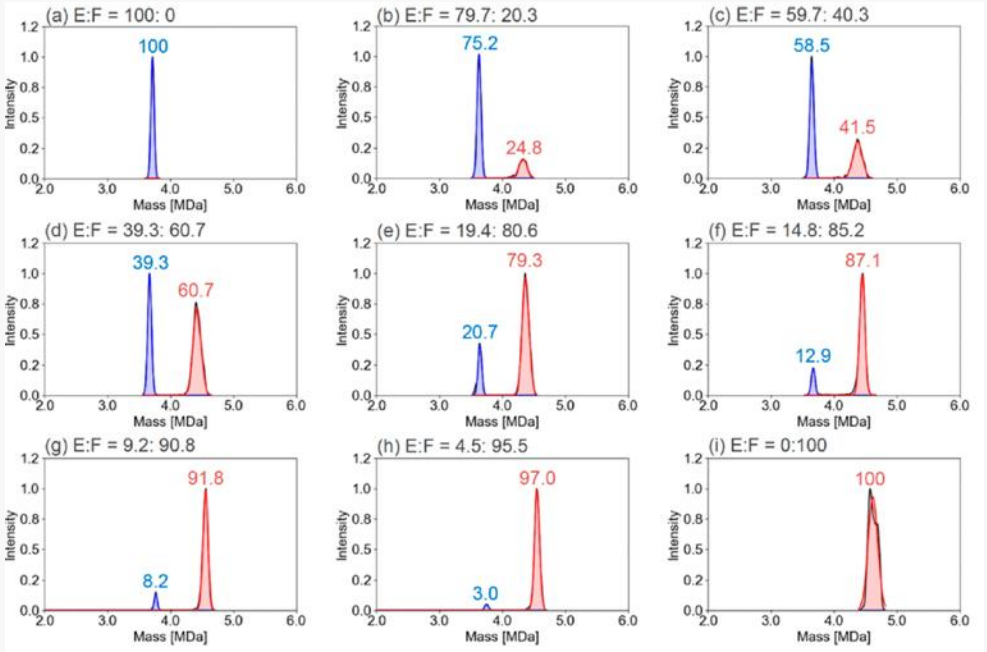
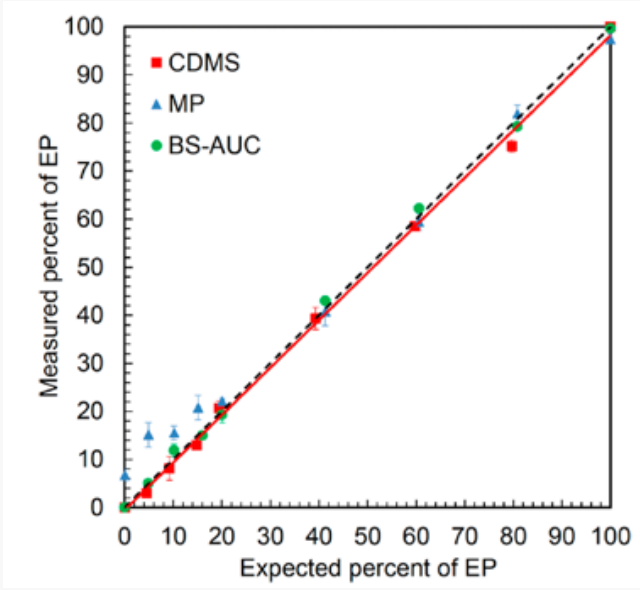
Article

Multimass Analysis of Adeno-Associated Virus Vectors by Orbitrap-Based Charge Detection Mass Spectrometry

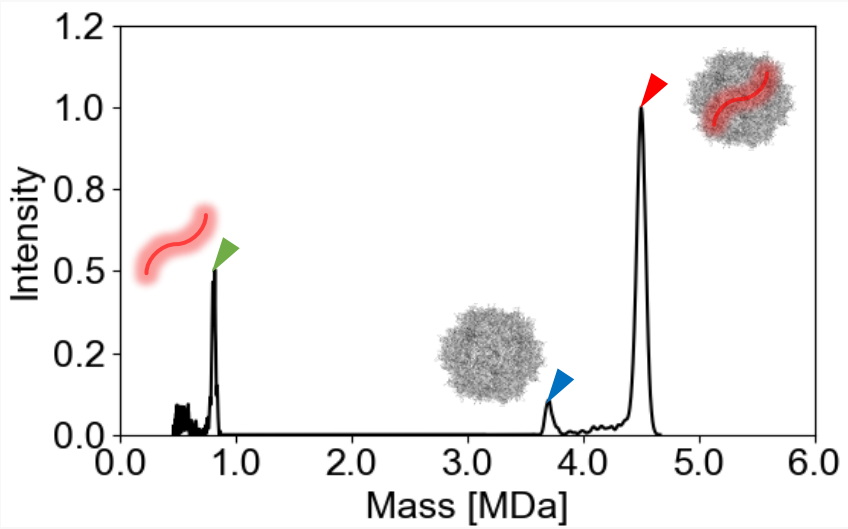
Ryoji Nakatsuka, Yuki Yamaguchi, Kiichi Hirohata, Saki Shimojo, Makoto Murakami, Mark Allen Vergara Rocafort, Yasuo Tsunaka, Mitsuko Fukuhara, Tetsuo Torisu, and Susumu Uchiyama*





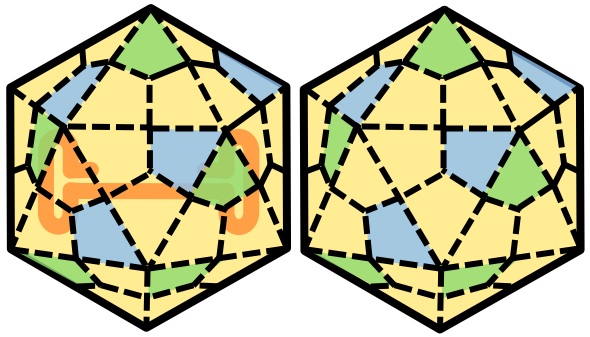


CDMS analysis with capsid disassembly in MS



Nakatsuka et al., 2024

DirectMP F/E determination in Cell Lysate



analytical chemistry

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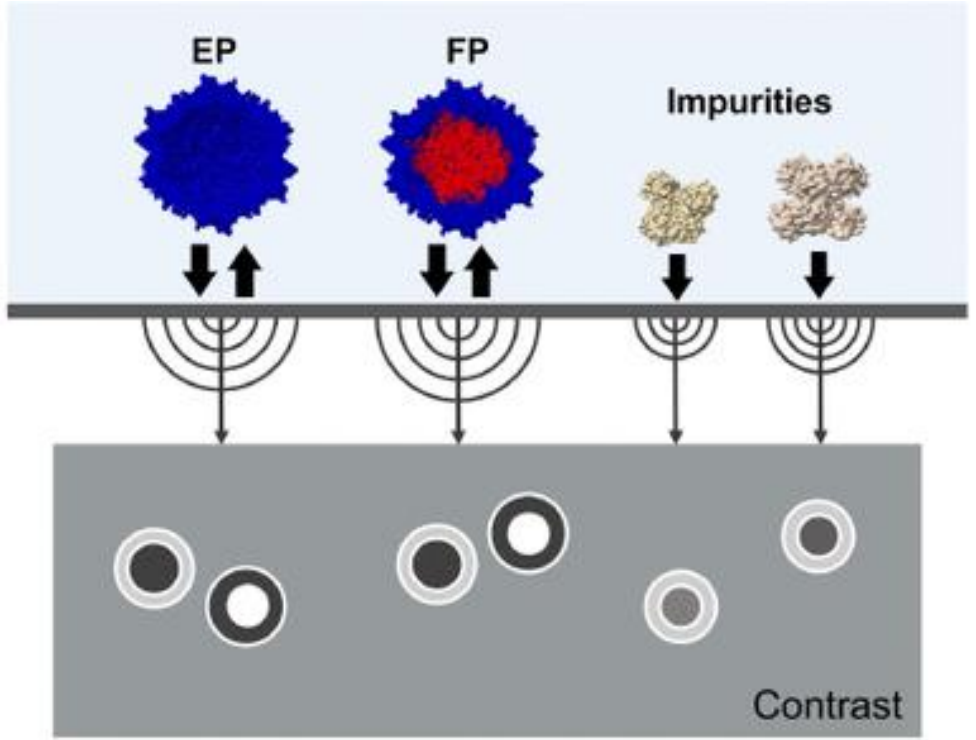
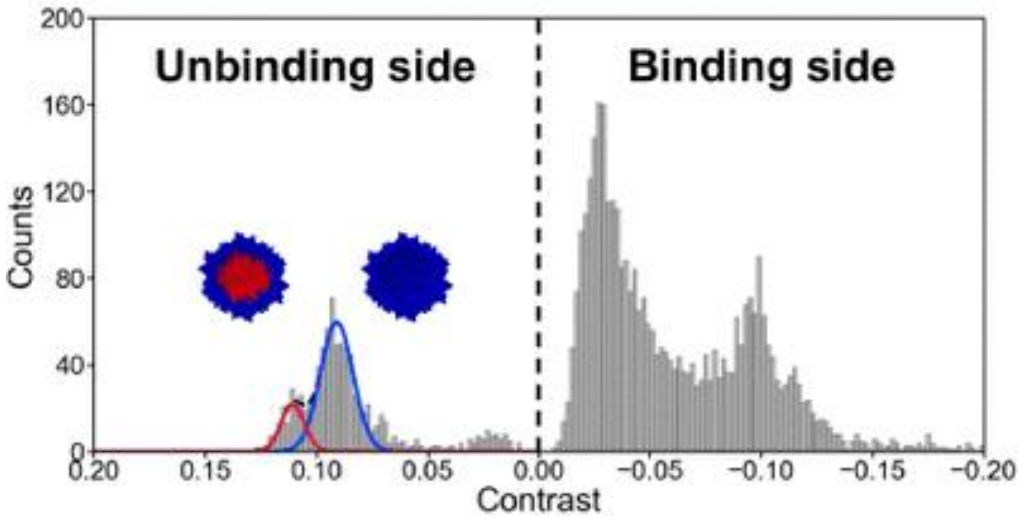
Article

Direct Identification and Quantification of Recombinant Adeno-Associated Virus in Crude Cell Lysate and Conditioned Medium by Mass Photometry

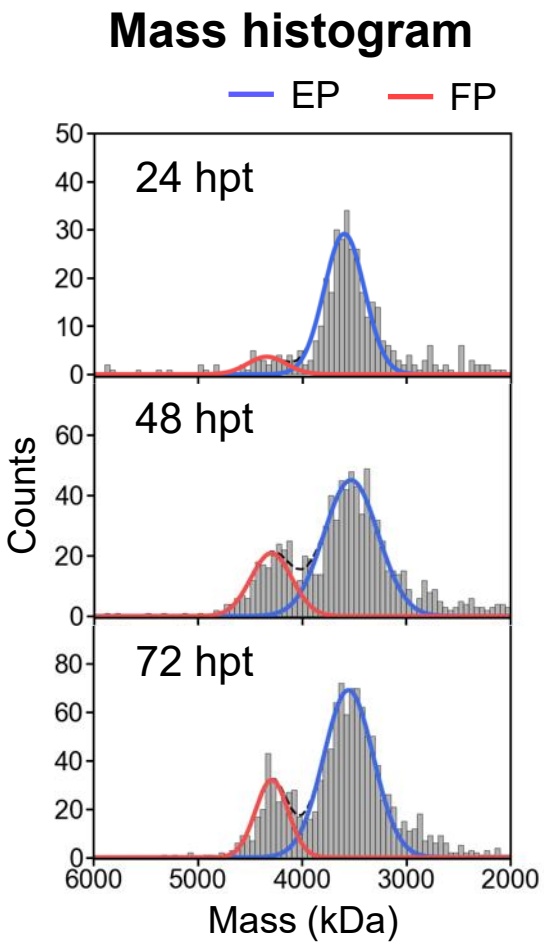
Yuki Yamaguchi,[#] Saki Shimojo,[#] Risa Shibuya, Karin Bandoh, Aoba Matsushita, Mitsuko Fukuhara, Yasuo Tsunaka, Tetsuo Torisu, and Susumu Uchiyama[*]

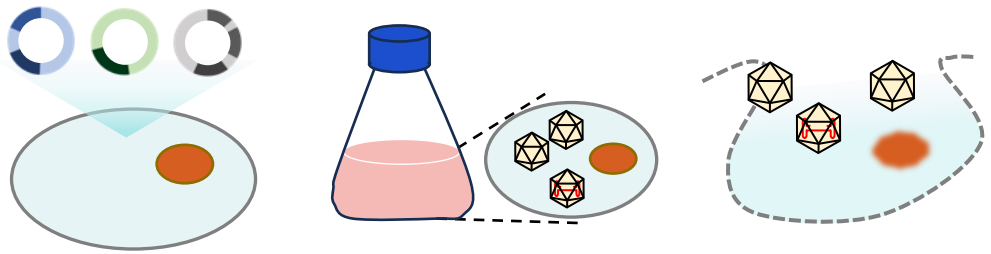


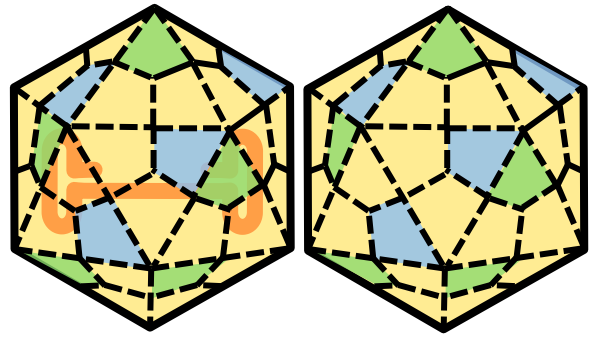


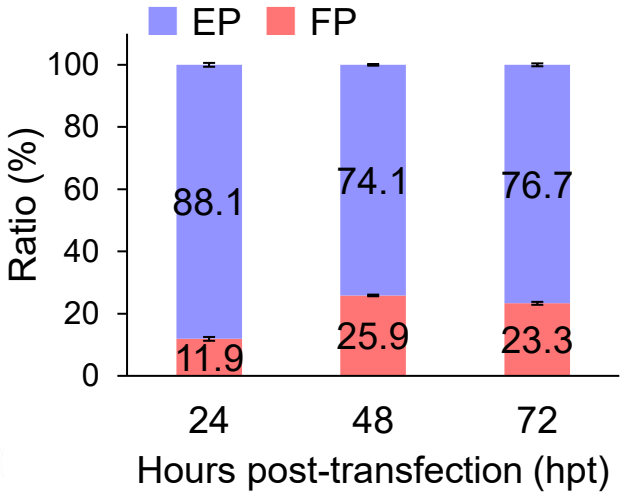
Yamaguchi et al., *Anal. Chem.* 2025

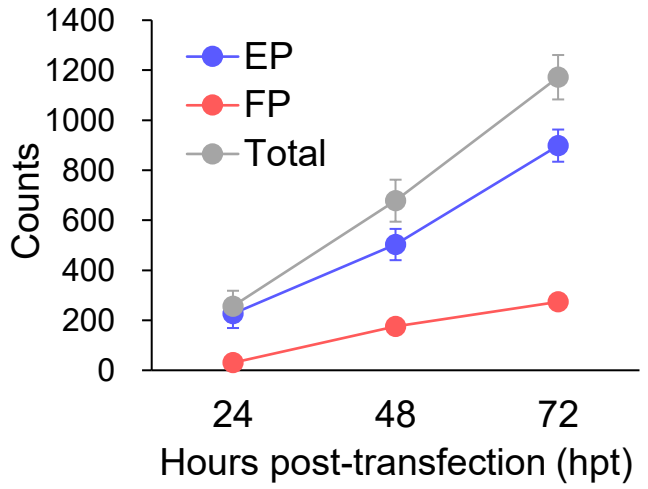
DirectMP F/E determination in Cell Lysate Process development

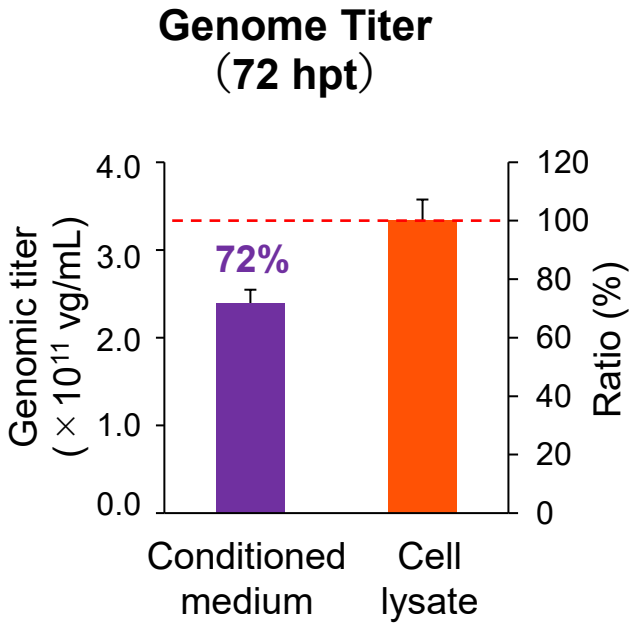








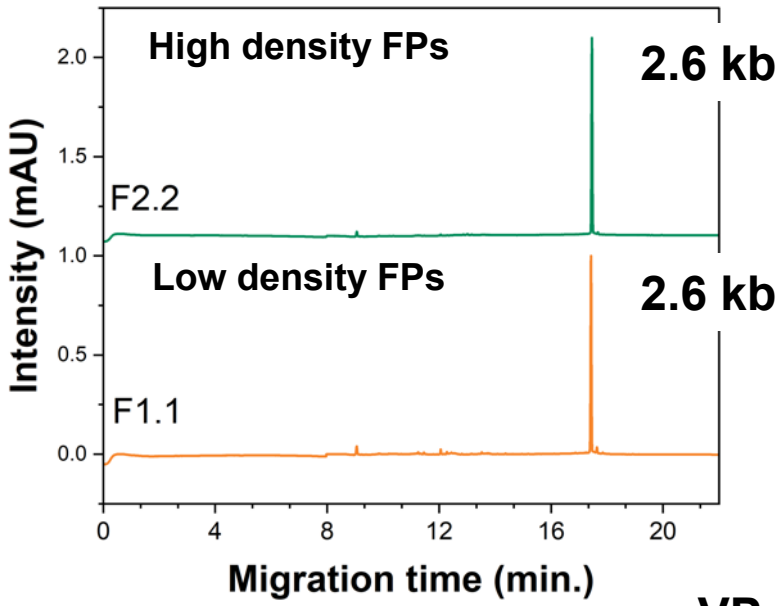




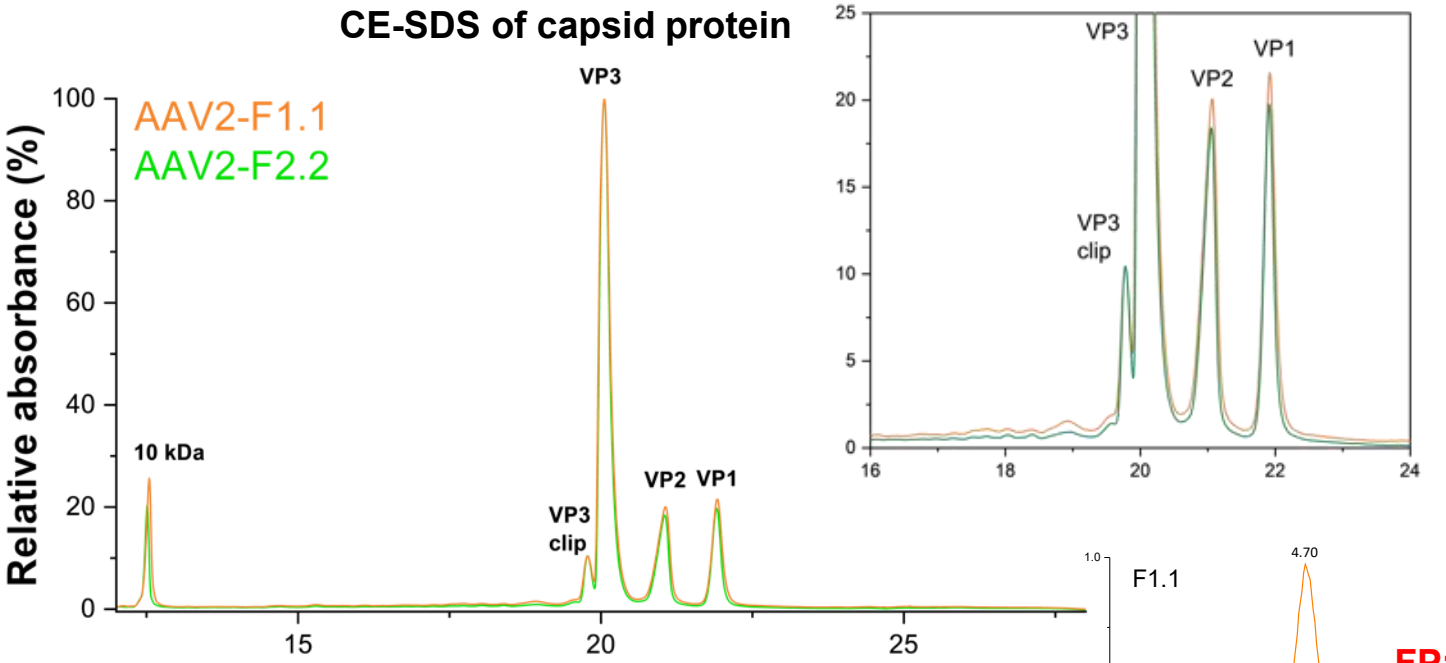
Yamaguchi et al., *Anal. Chem.* 2025

Physicochemical characterization of F1.1 and F2.2 particles

Evaluation of encapsulated DNA



CE-SDS of capsid protein



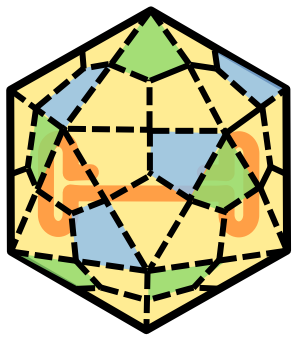
EP

FP1

FP2

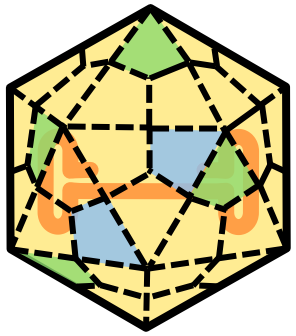
VP stoichiometric ratio

FP1
VP1: 6
VP2: 8
VP3: 46



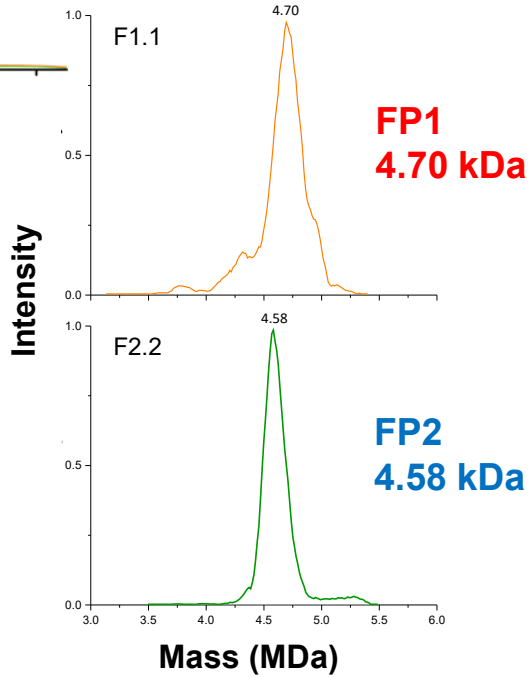
Low density FPs
Higher transgene expression

FP2
VP1: 5
VP2: 7
VP3: 48



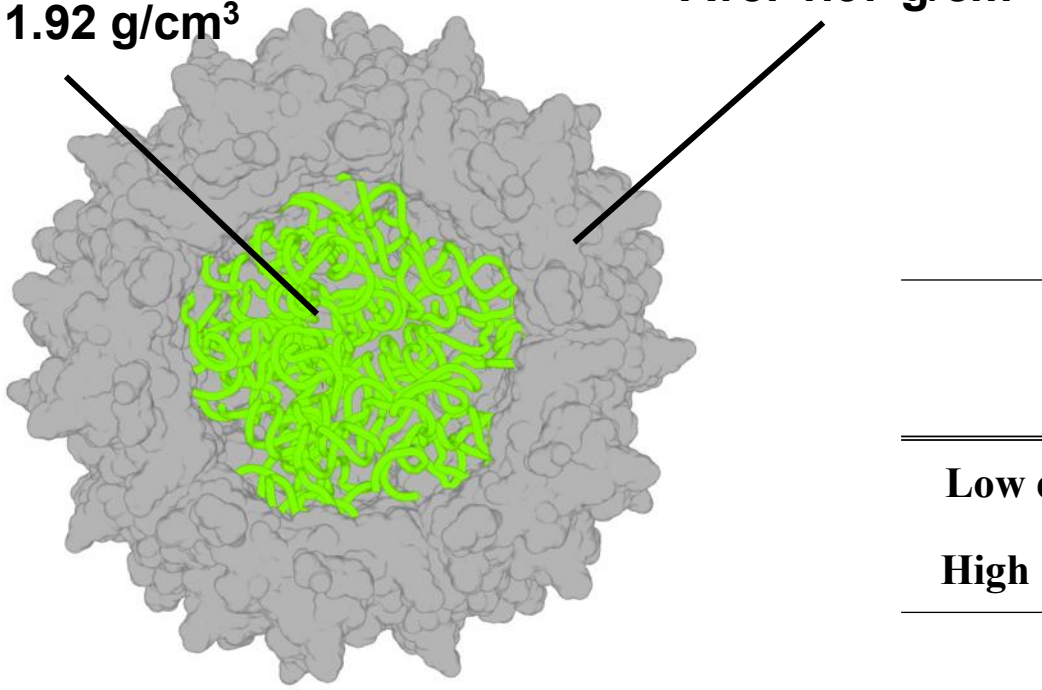
High density FPs
Lower transgene expression

Waters ELIT CDMS



Ohnishi et al., *Mol. Ther. Meth. Clin. Dev.* (2023)

Cause of difference in buoyant density



$$\rho_{rAAV} = \frac{(\rho_{protein} V_{capsid} + \rho_{nucleic\ acid} V_{DNA})}{V_{capsid} + V_{DNA}}$$

	Calculated density from VP ratio by CGE (g/cm^3)		Experimental buoyant density (g/cm^3)	
Low density (F1.1)	1.462	0.001 g/cm^3	1.352	0.009 g/cm^3
High density (F2.2)	1.463		1.361	

Hydration change/ion binding may enhance the difference

Ohnishi et al., *Mol. Ther. Meth. Clin. Dev.* (2023)

Elucidation of the correlation between VP stoichiometry and transduction efficacy

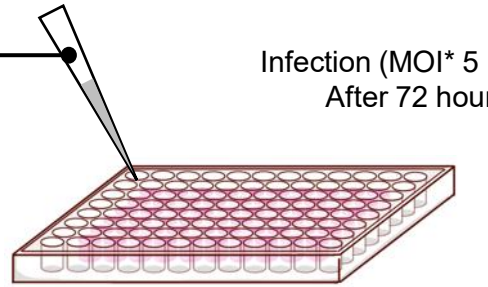
Each AAV vector with EGFP gene in GOI

Bulk

F1
Low density

F2
High density

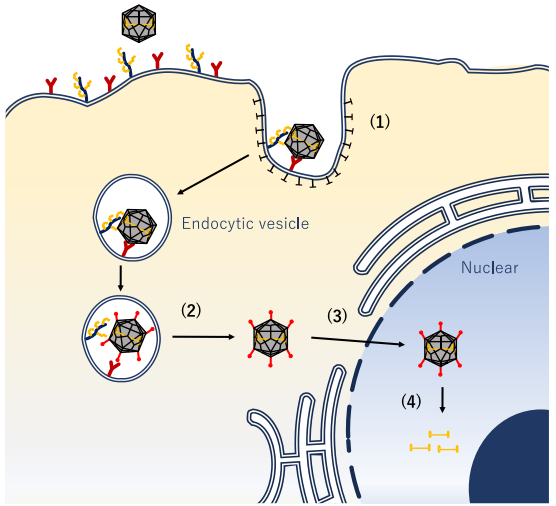
GOI : Gene Of Interest

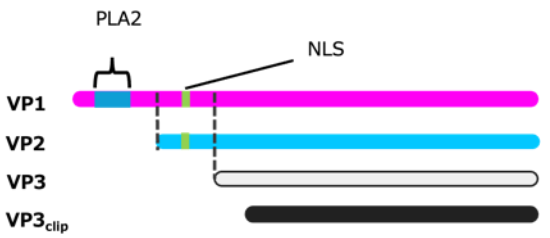


Infection (MOI* 5 points)
After 72 hours

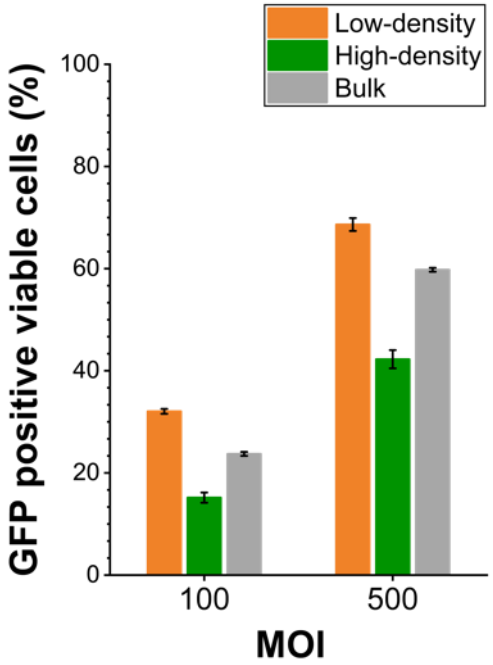
HeLa CELLS

Evaluation of gene transfer rate by fluorescence-activated cell sorter (FACS)





*MOI (Multiplicity of infection) = virus / cells

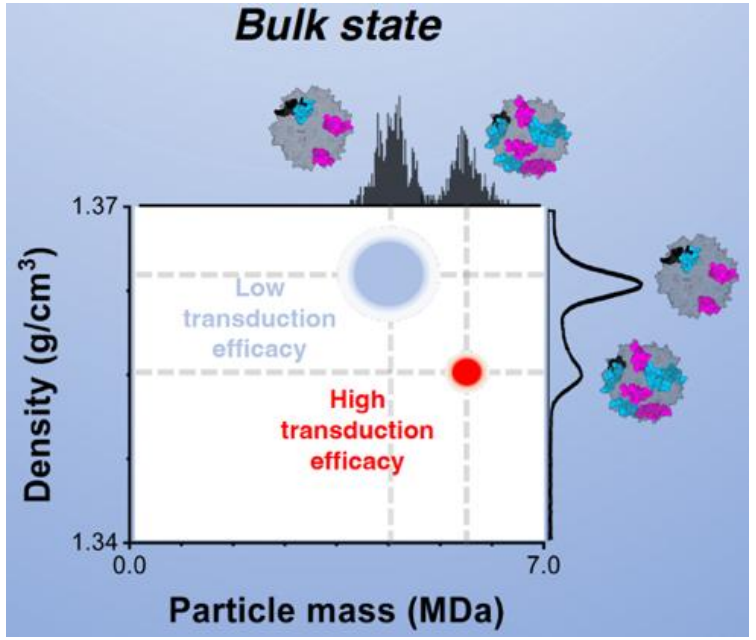


The infectivity of Low density AAV is 23.9% ~26.4% higher than that of High density AAV

Molecular Therapy
Methods & Clinical Development
Original Article

Enhancement of recombinant adeno-associated virus activity by improved stoichiometry and homogeneity of capsid protein assembly

Takayuki Onishi,[1] Michika Nonaka,[1] Takahiro Maruno,[1,2] Yuki Yamaguchi,[1] Mitsuko Fukuhara,[1,2] Tetsuo Torisu,[1] Masaharu Maeda,[3] Susan Abbatiello,[4] Anisha Haris,[4] Keith Richardson,[5] Kevin Giles,[4] Steve Preece,[5] Noriko Yamano-Adachi,[1] Takeshi Omasa,[1] and Susumu Uchiyama[1]

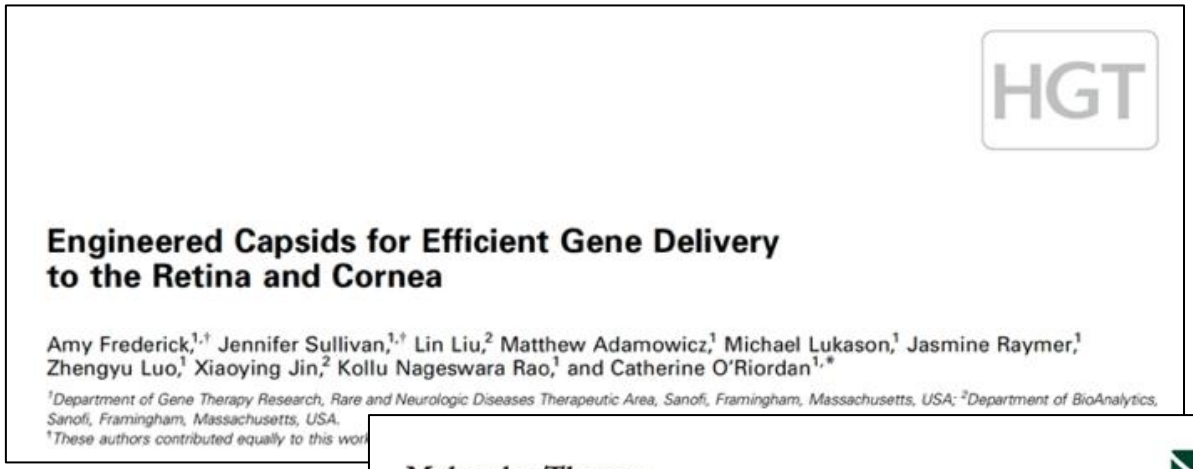


Ohnishi et al., *Mol. Ther. Meth. Clin. Dev.* (2023)

Glycosylation of rAAV

Recent Publications of Glycosylation of AAV

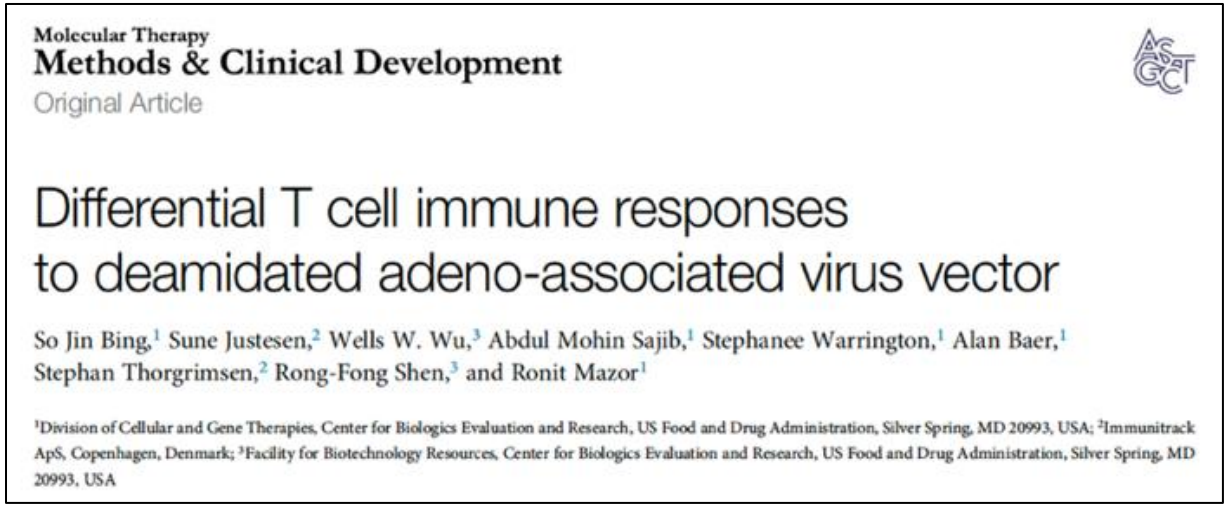
(1) 2019 Mary et al, *Mol. Pharm.*
(2) 2019 Mary et al, *FEBS*
(3) 2018 Aloor et al, *Viruses*
(4) 2020 Rumachik et al, *Mol. Ther. Meth. Clin. Dev.*
(5) 2024 Xie et al, *Glycobiology*


HGT

Engineered Capsids for Efficient Gene Delivery to the Retina and Cornea

Amy Frederick,[1,†] Jennifer Sullivan,[1,†] Lin Liu,[2] Matthew Adamowicz,[1] Michael Lukason,[1] Jasmine Raymer,[1] Zhengyu Luo,[1] Xiaoying Jin,[2] Kollu Nageswara Rao,[1] and Catherine O'Riordan[1,*]

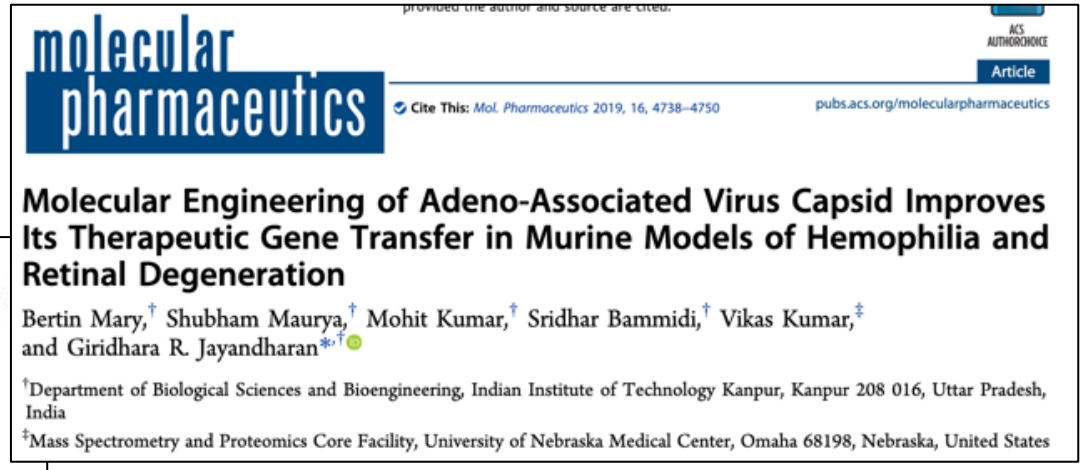
[1]Department of Gene Therapy Research, Rare and Neurologic Diseases Therapeutic Area, Sanofi, Framingham, Massachusetts, USA; [2]Department of BioAnalytics, Sanofi, Framingham, Massachusetts, USA.
[†]These authors contributed equally to this work


Molecular Therapy
Methods & Clinical Development
Original Article

Differential T cell immune responses to deamidated adeno-associated virus vector

So Jin Bing,[1] Sune Justesen,[2] Wells W. Wu,[3] Abdul Mohin Sajib,[1] Stephanee Warrington,[1] Alan Baer,[1] Stephan Thorgrimsen,[2] Rong-Fong Shen,[3] and Ronit Mazor[1]

[1]Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993, USA; [2]Immunitrack ApS, Copenhagen, Denmark; [3]Facility for Biotechnology Resources, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993, USA


molecular pharmaceutics

ACS AUTHORCHOICE
Article

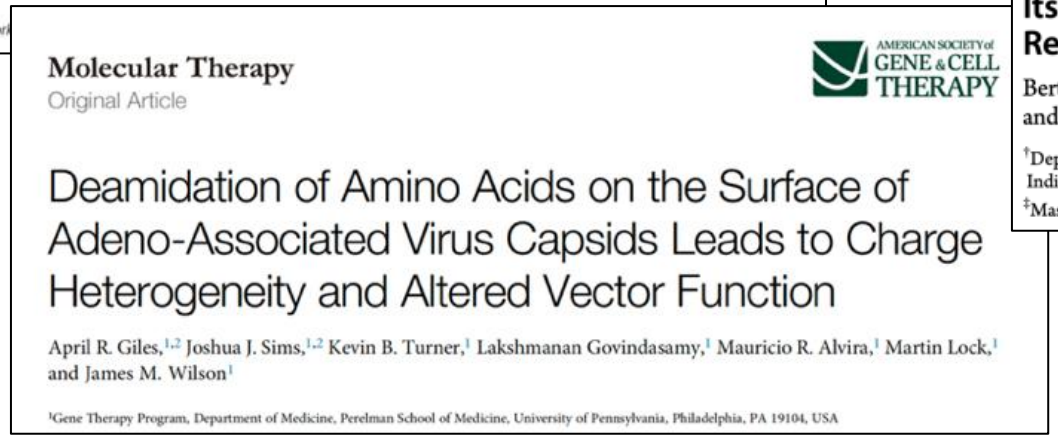
Cite This: Mol. Pharmaceutics 2019, 16, 4738−4750

pubs.acs.org/molecularpharmaceutics

Molecular Engineering of Adeno-Associated Virus Capsid Improves Its Therapeutic Gene Transfer in Murine Models of Hemophilia and Retinal Degeneration

Bertin Mary,[†] Shubham Maurya,[†] Mohit Kumar,[†] Sridhar Bammidi,[†] Vikas Kumar,[‡] and Giridhara R. Jayandharan[*,†]

[†]Department of Biological Sciences and Bioengineering, Indian Institute of Technology Kanpur, Kanpur 208 016, Uttar Pradesh, India
[‡]Mass Spectrometry and Proteomics Core Facility, University of Nebraska Medical Center, Omaha 68198, Nebraska, United States


Molecular Therapy
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

Deamidation of Amino Acids on the Surface of Adeno-Associated Virus Capsids Leads to Charge Heterogeneity and Altered Vector Function

April R. Giles,[1,2] Joshua J. Sims,[1,2] Kevin B. Turner,[1] Lakshmanan Govindasamy,[1] Mauricio R. Alvira,[1] Martin Lock,[1] and James M. Wilson[1]

[1]Gene Therapy Program, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

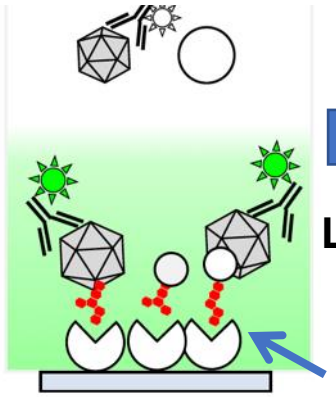
Glycosylation of rAAV: Lectin trap + LC-MS/MS

Molecular Therapy
Methods & Clinical Development
Original Article

Glycosylation of recombinant adeno-associated virus serotype 6

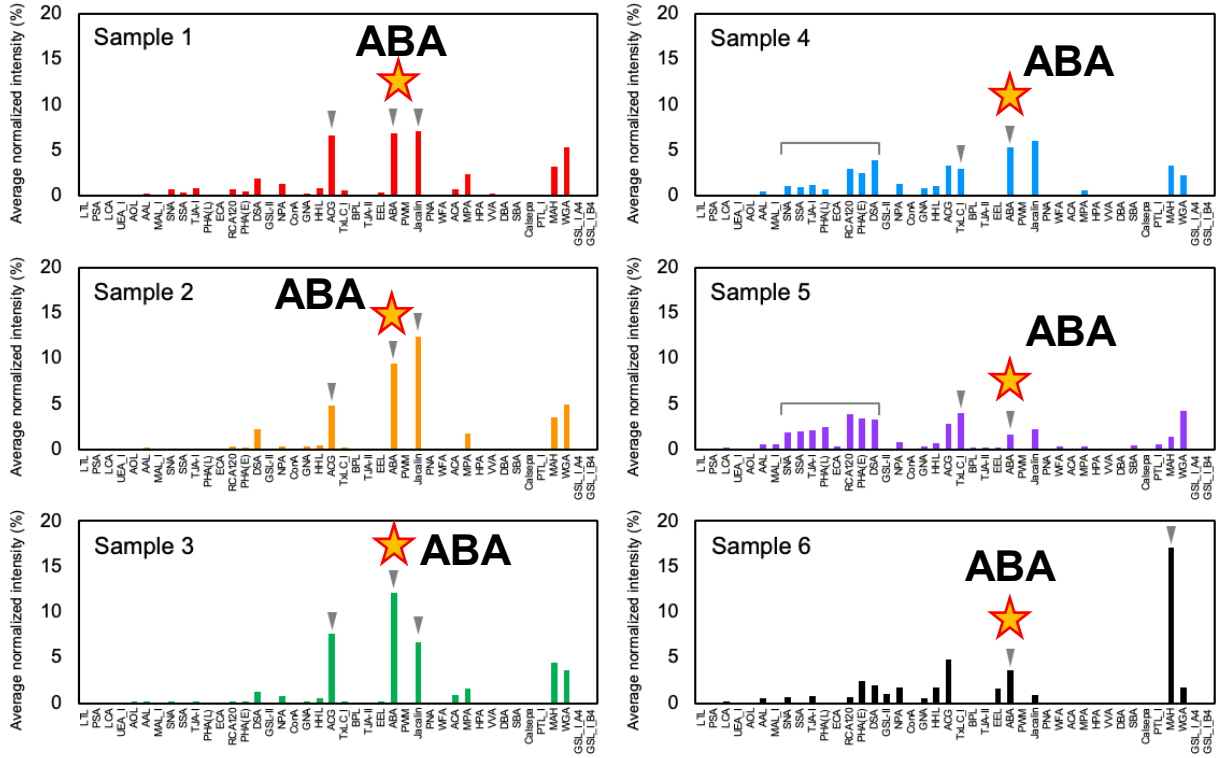
Yuki Yamaguchi,[1] Kentaro Ishii,[1] Sachiko Koizumi,[2,3] Hiroaki Sakaue,[4] Takahiro Maruno,[1,5] Mitsuko Fukuhara,[1,5] Risa Shibuya,[1] Yasuo Tsunaka,[1] Aoba Matsushita,[1] Karin Bandoh,[1] Tetsuo Torisu,[1] Chie Murata-Kishimoto,[2] Azusa Tomioka,[4] Saho Mizukado,[4] Hiroyuki Kaji,[6] Yuji Kashiwakura,[7,8] Tsukasa Ohmori,[7,8] Atsushi Kuno,[4] and Susumu Uchiyama[1]

Name	Cell type	Affinity
Sample 1	Adherent	Yes
Sample 2	Adherent	Yes
Sample 3	Adherent	Yes
Sample 4	Adherent	No
Sample 5	Adherent	No
Sample 6	Suspension	Yes

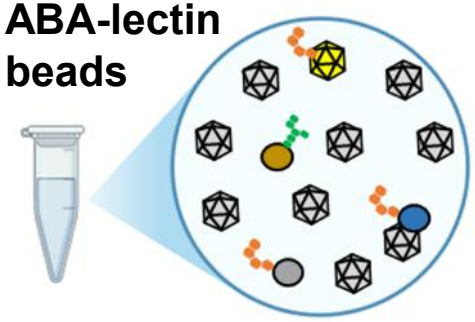


Lectin array detection

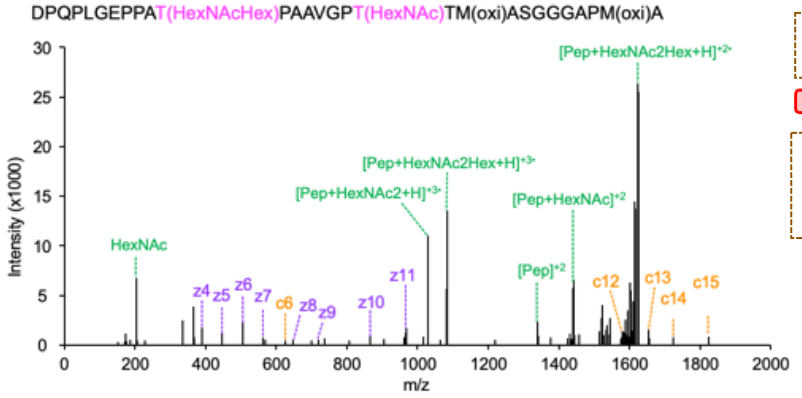
Lectin

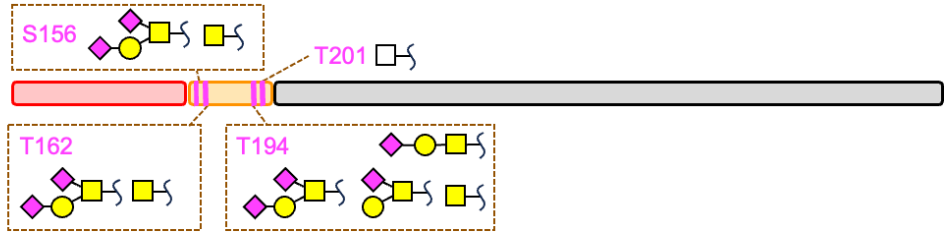


ABA-lectin beads



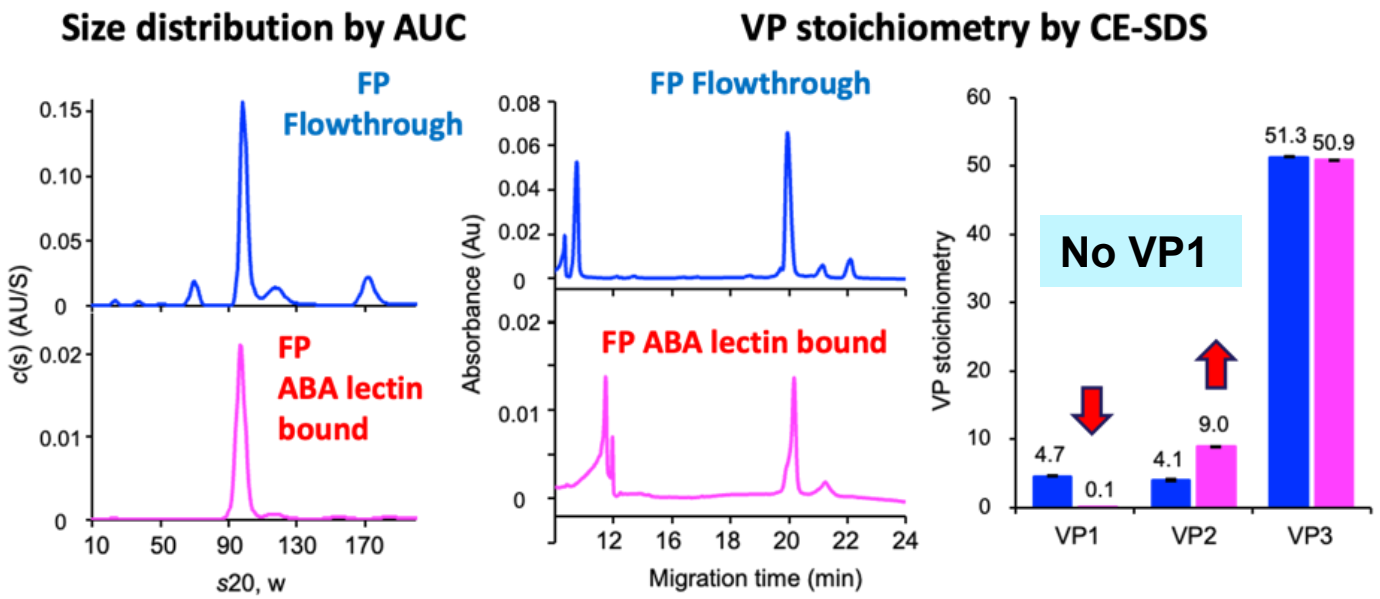
Capture + LC-MS/MS

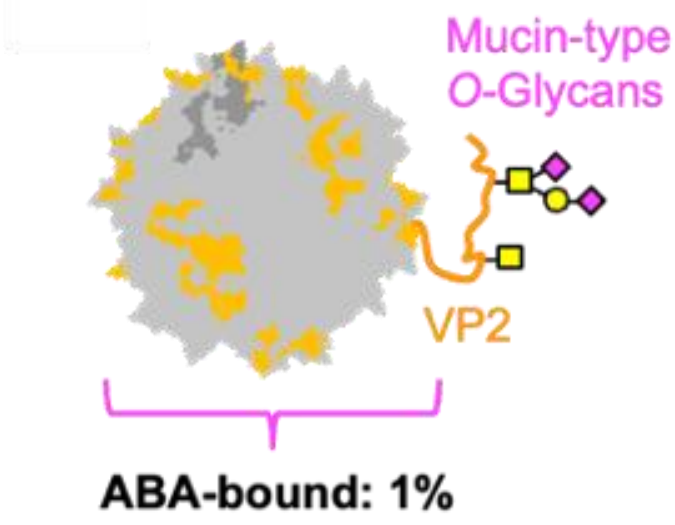


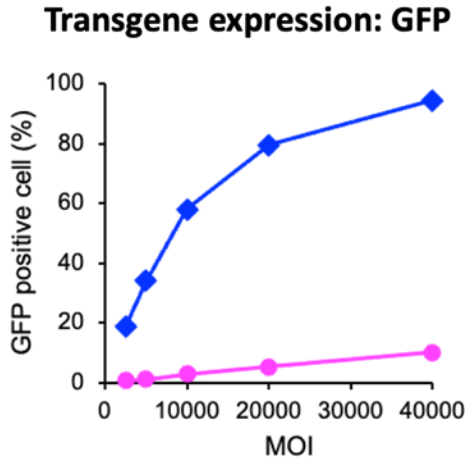


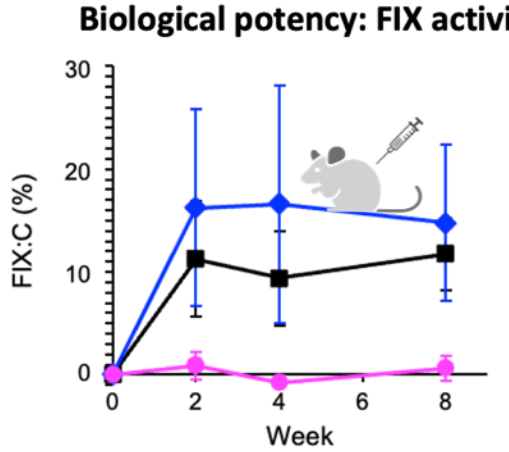
S and T at VP2 is *O*-glycosylated

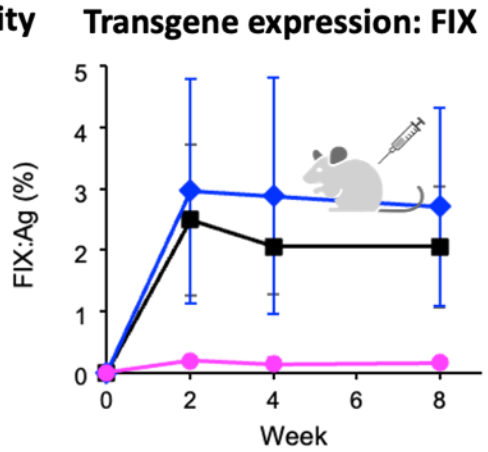
Characterization of O-Glycosylated rAAV

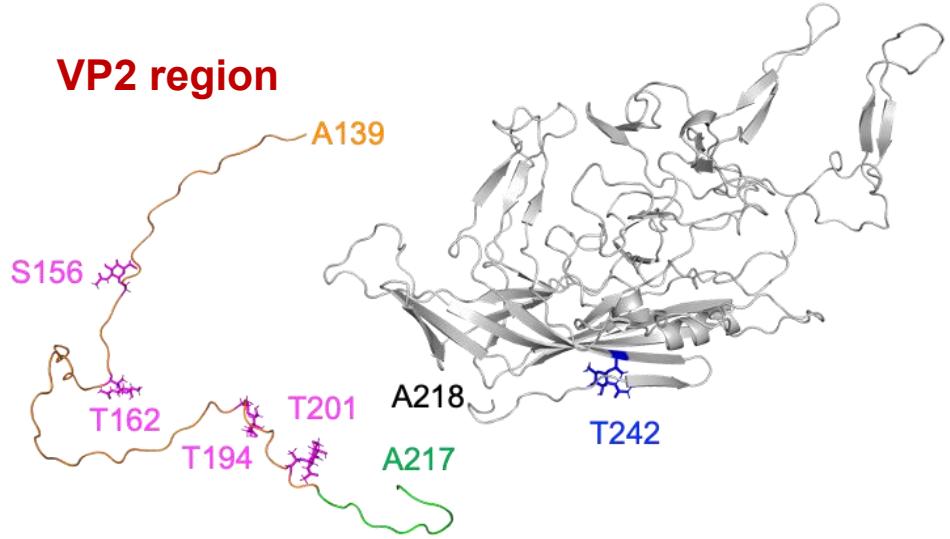












Glycosylation of VP2 region ➔ No VP1 ➔ Loss of function

Yamaguchi et al., *Mol. Ther. Meth. Clin. Dev.* (2024)

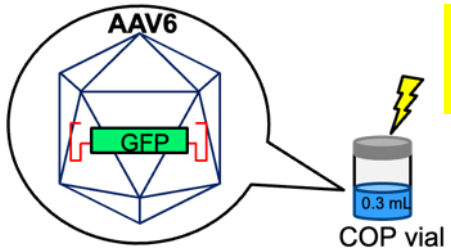
Photo-degradation (DNA and capsid protein)

Modification (DNA degradation) by Light irradiation (Photostability test (ICH))

Molecular Therapy
Methods & Clinical Development
Original Article

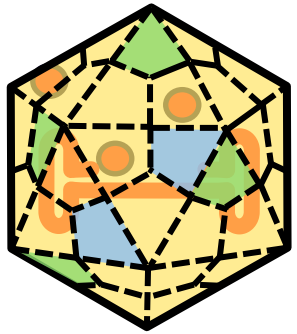
Physicochemical and biological impacts of light stress on adeno-associated virus serotype 6

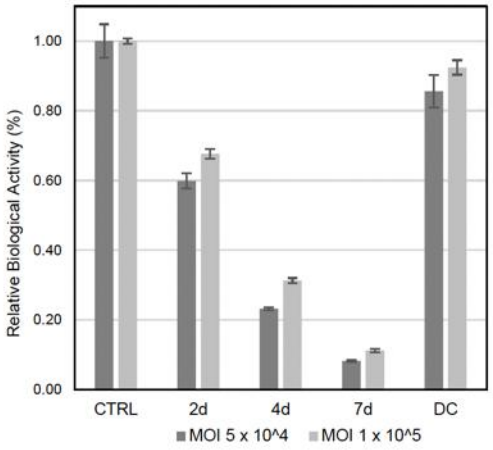
Rie Takino,[1,2] Yuki Yamaguchi,[2] Takahiro Maruno,[2] Ekaputra Ramadhani,[2] Misaki Furukawa,[2] Tetsuo Torisu,[2] and Susumu Uchiyama[2,3]



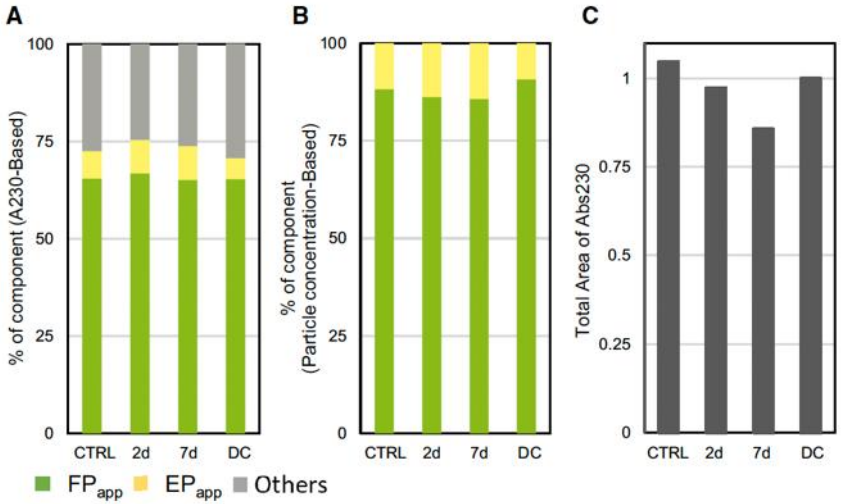
1.11 x 10^{13} vg/mL

ICH Option 1 conditions using D65

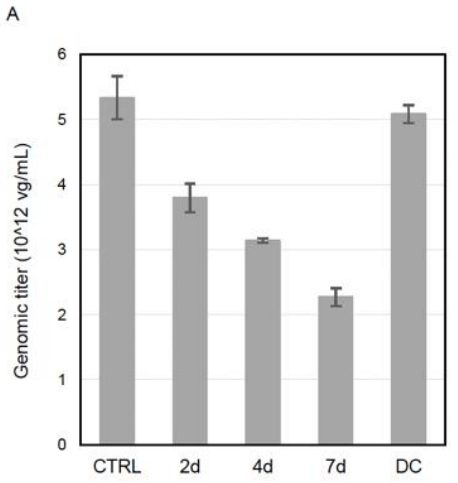


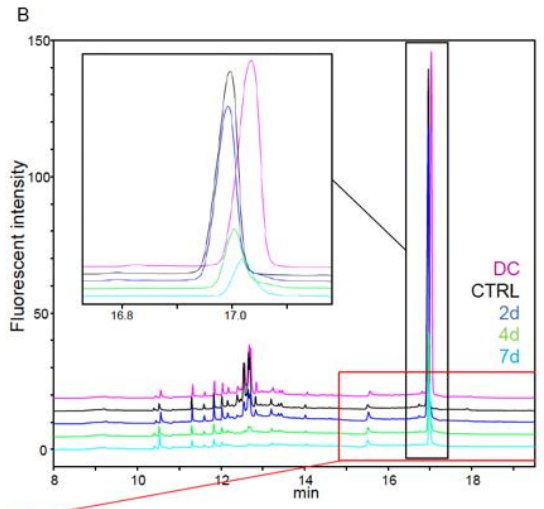


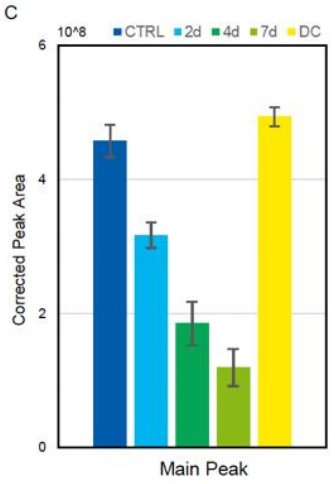
90% activity loss after 7 days

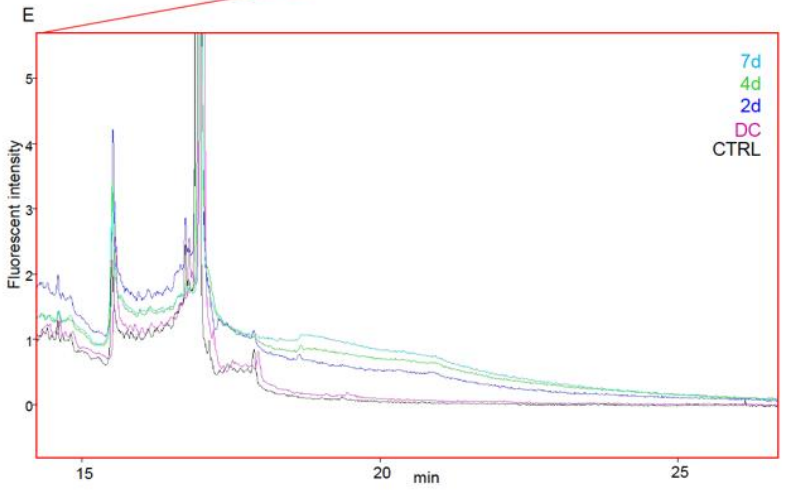


F/E ratio unchanged, 20% FP loss





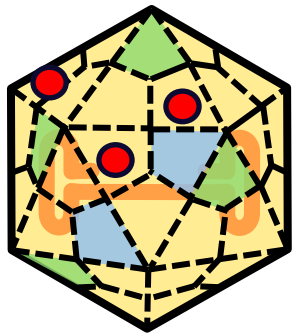




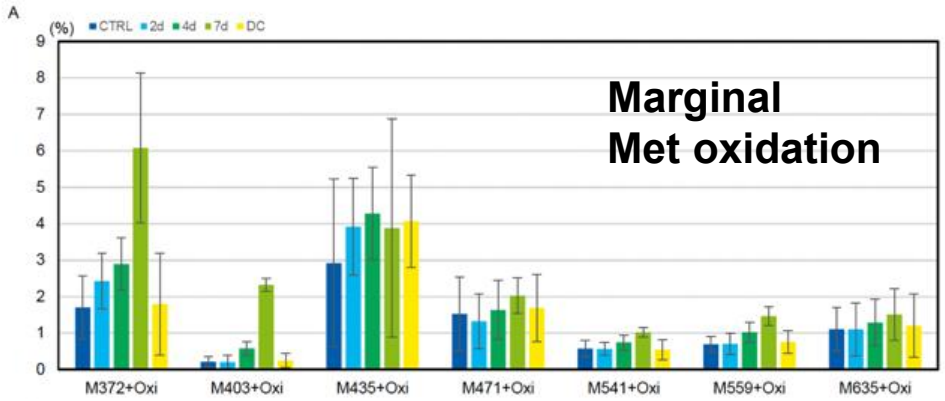
80% main DNA loss

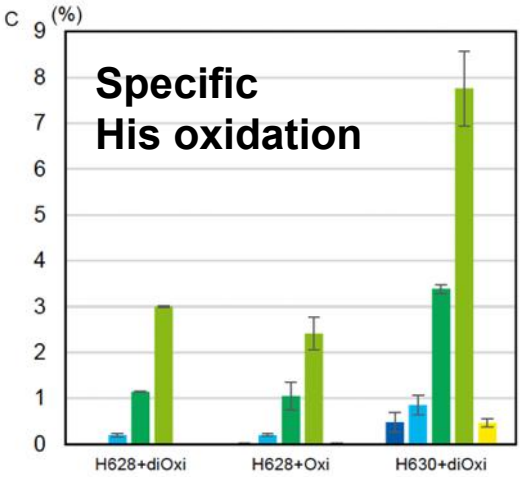
Takino et al., *Mol. Ther. Meth. Clin. Dev.* (2024)

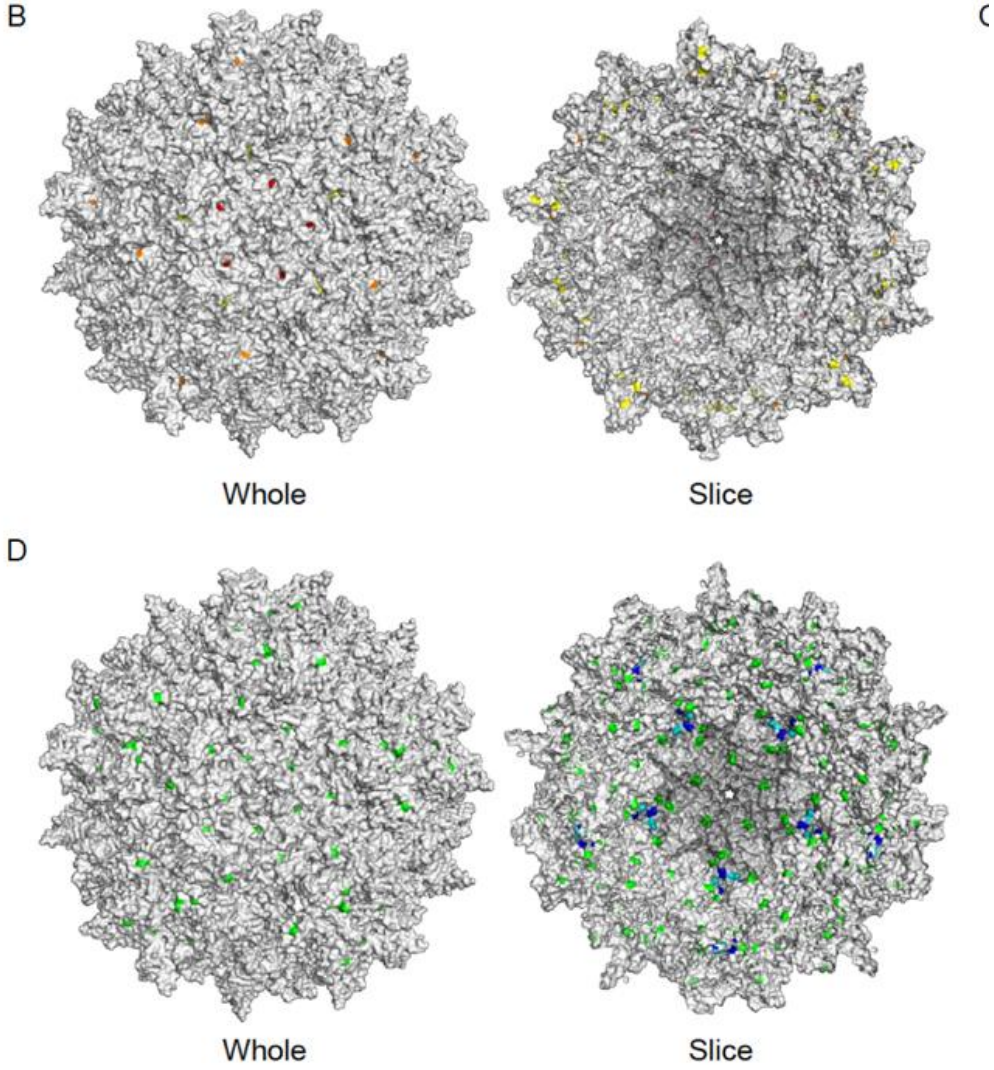
Photo-degradation (DNA and capsid protein)



Modification
(Oxidation)
by
Light irradiation
(Photostability test)



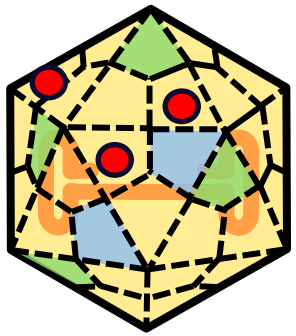




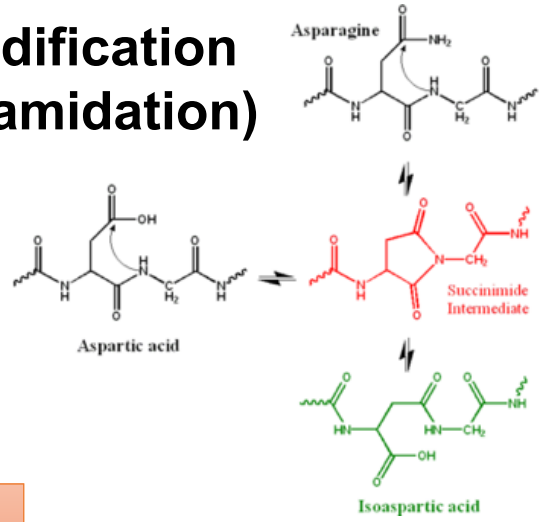
Oxidation of His628 and His630 close to ssDNA

Takino et al., *Mol. Ther. Meth. Clin. Dev.* (2024)

Deamidation of VPs



Modification (Deamidation)



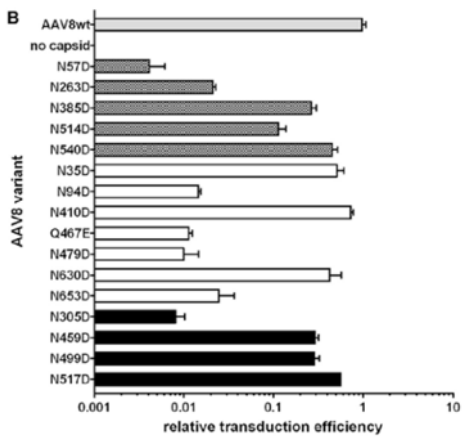
Relation to potency

Molecular Therapy
Original Article

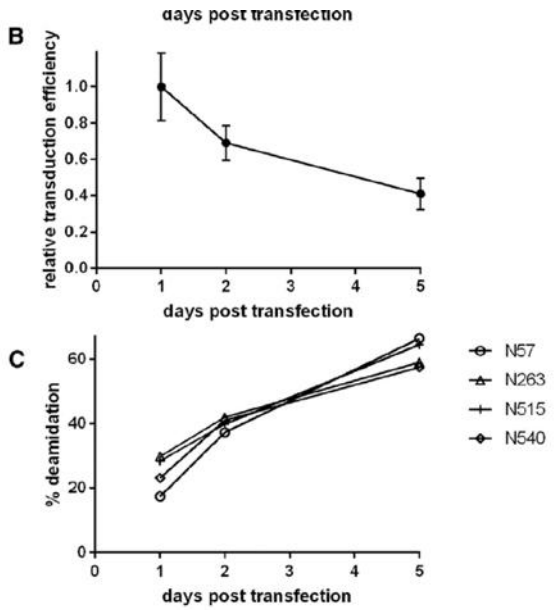
Deamidation of Amino Acids on the Surface of Adeno-Associated Virus Capsids Leads to Charge Heterogeneity and Altered Vector Function

April R. Giles,[1,2] Joshua J. Sims,[1,2] Kevin B. Turner,[1] Lakshmanan Govindasamy,[1] Mauricio R. Alvira,[1] Martin Lock,[1] and James M. Wilson[1]

[1]Gene Therapy Program, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA



Molecular Therapy Vol. 26 No 12 December 2018



T Cell mediated immune response

FDA U.S. FOOD & DRUG ADMINISTRATION

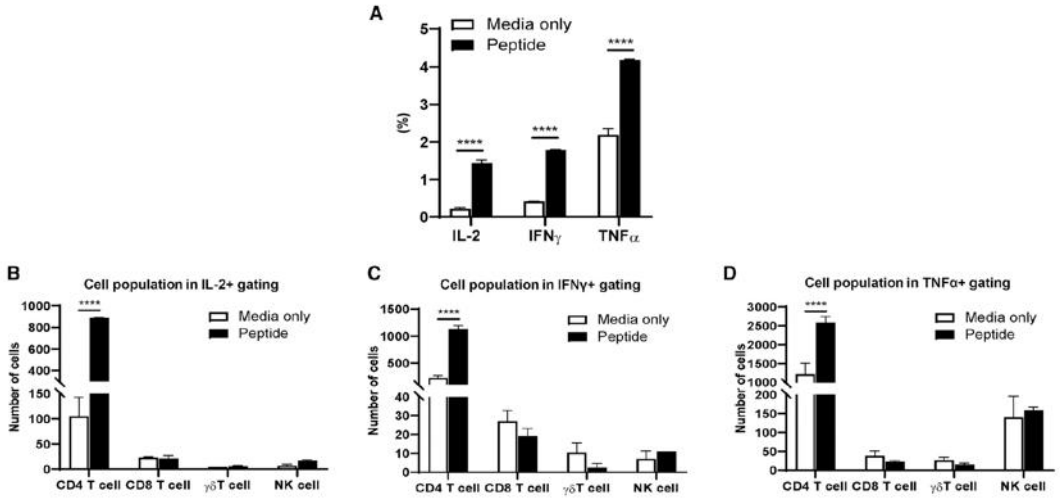
Identification and elimination of helper and cytotoxic T cell epitopes in AAV9

Molecular Therapy
Methods & Clinical Development
Original Article

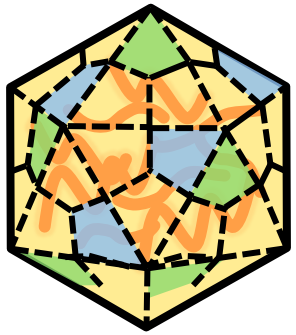
Differential T cell immune responses to deamidated adeno-associated virus vector

So Jin Bing,[1] Sune Justesen,[2] Wells W. Wu,[3] Abdul Mohin Sajib,[1] Stephanee Warrington,[1] Alan Baer,[1] Stephan Thorgrimsen,[2] Rong-Fong Shen,[3] and Ronit Mazor[1]

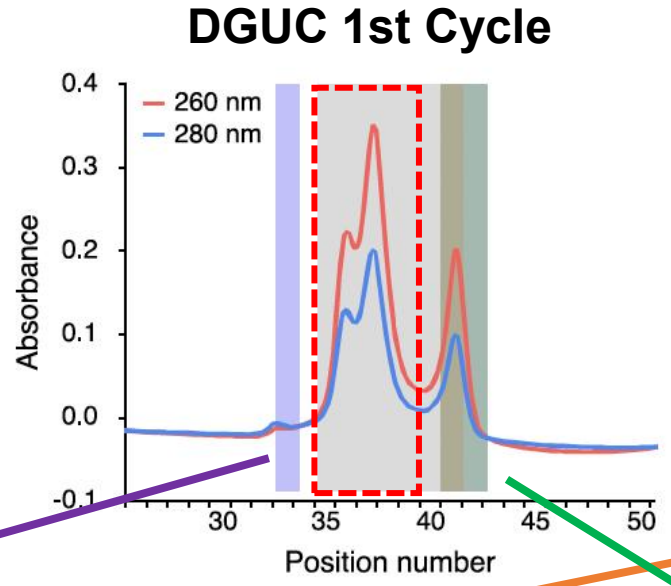
[1]Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993, USA; [2]Immunitrack ApS, Copenhagen, Denmark; [3]Facility for Biotechnology Resources, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993, USA

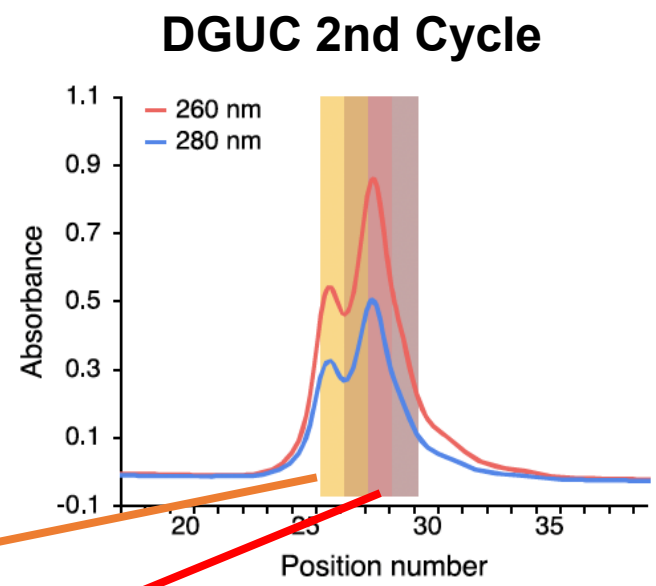


DNA size variation



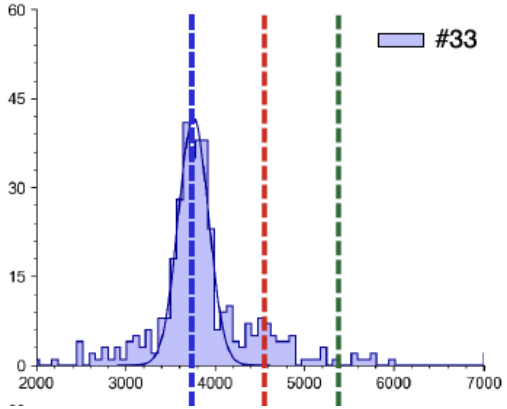
Over-packaged (OP)



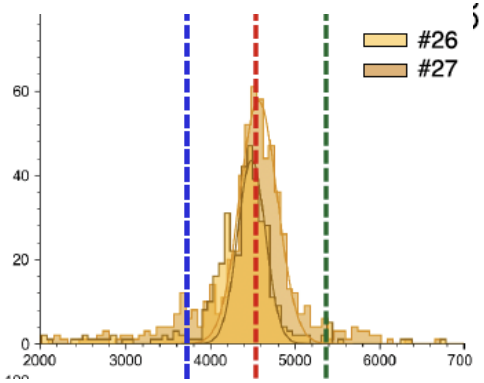


EP

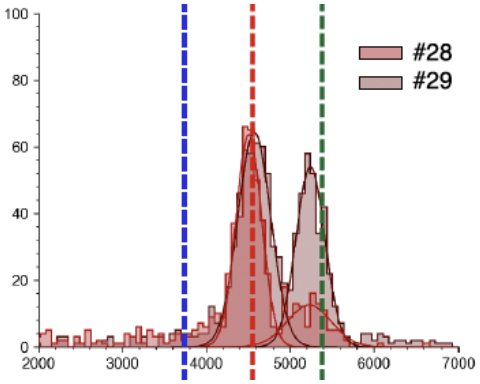
3.7 kDa



4.5 kDa FP

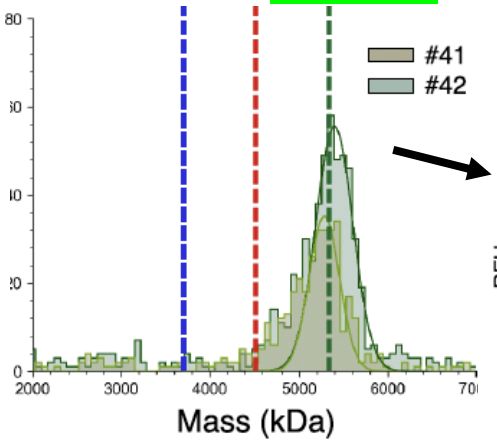


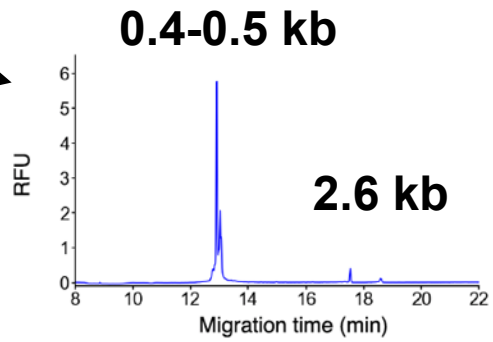
FP 4.5 kDa 5.4 kDa



OP

5.4 kDa OP





Maruno et al., *Mol. Ther. Meth. Clin. Dev.* 33(4) Dec. 2025

Variation of QAs among Lots/Batch

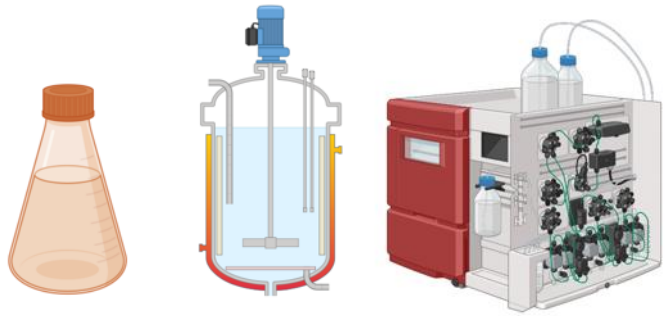
Molecular Therapy
Methods & Clinical Development
Original Article

Variation of VP2 stoichiometry and deamidation of VP1 during production and their impacts on the transduction efficiency of AAV vectors

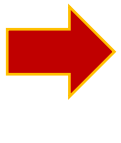
Takahiro Maruno,[1,2] Mitsuko Fukuhara,[1,2] Yasuo Tsunaka,[2] Aoba Matsushita,[2] Kiichi Hirohata,[2] Karin Bandoh,[2] Megumi Onaka,[1] Risa Shibuya,[2] Yuki Yamaguchi,[2] Haruka Nishiumi,[2] Yoshiki Nagashima,[3] Daisuke Higo,[3] Toshie Kuwahara,[2] Tomoko Ueno,[2] Masaharu Maeda,[4] Guirong Kanai-Bai,[2] Noriko Yamano-Adachi,[2] Tetsuo Torisu,[2] Takeshi Omasa,[2] and Susumu Uchiyama[2]

Table 1. Summary of conditions in the upstream process

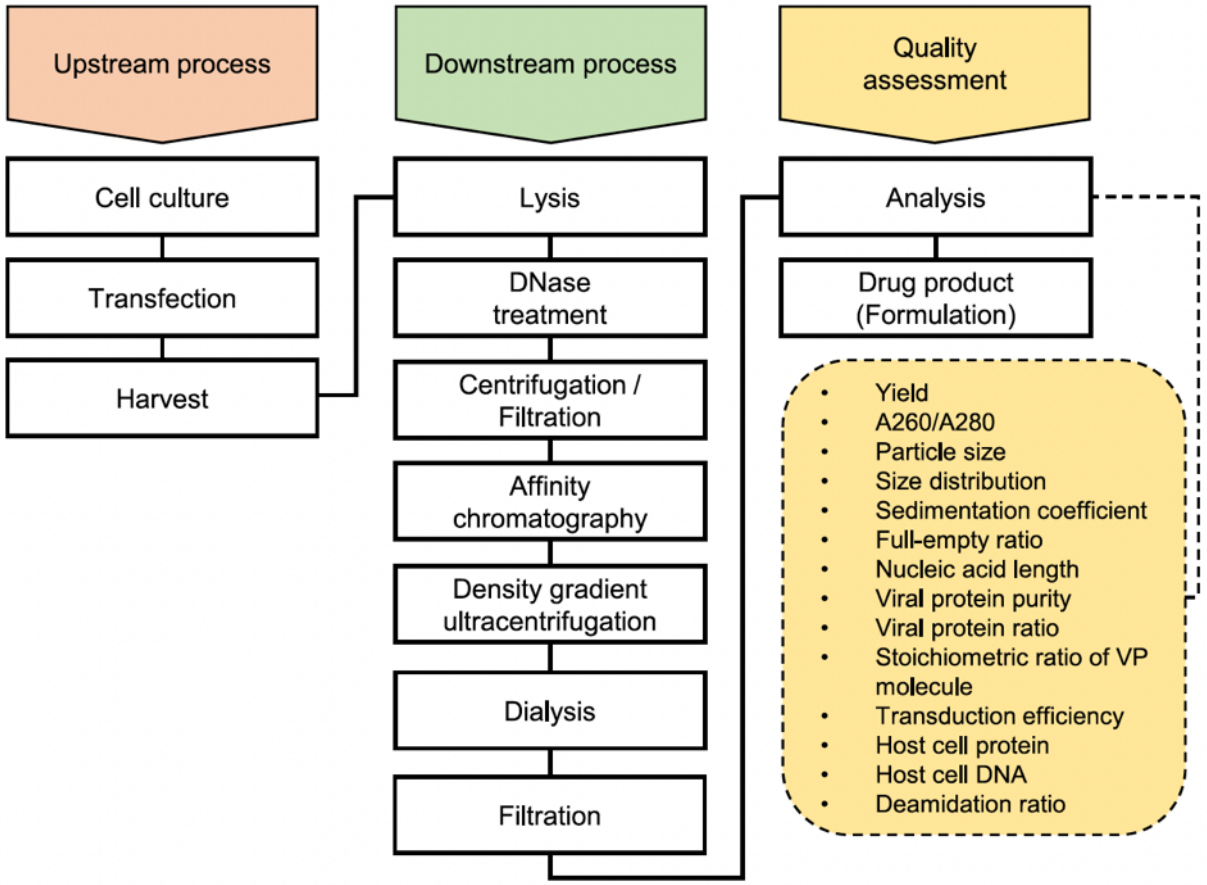
Product No.	Batch	Culture	Culture volume (L)	Transfection reagent	Harvest after transfection (days)	Purified volume (L)
1	A	1 L flask	0.2	FectoVIR-AAV	4	0.2
2						
3						
4						
5	B	2 L flask	1			
6						
7						
8	C	2 L bioreactor				
9						
10						



10 Products (Culture + Purification)



Variation in 14 QAs



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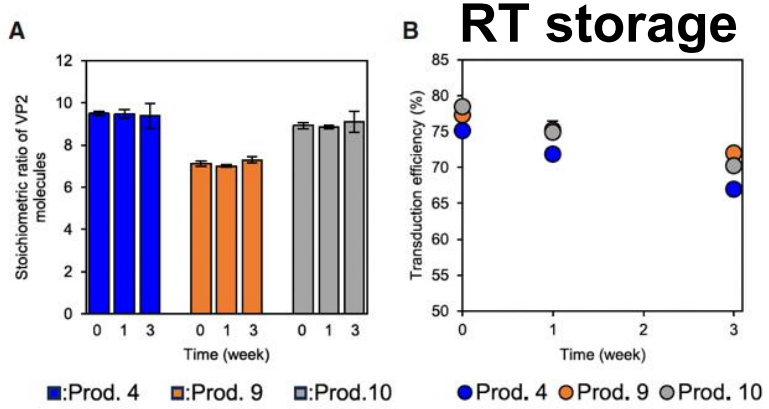
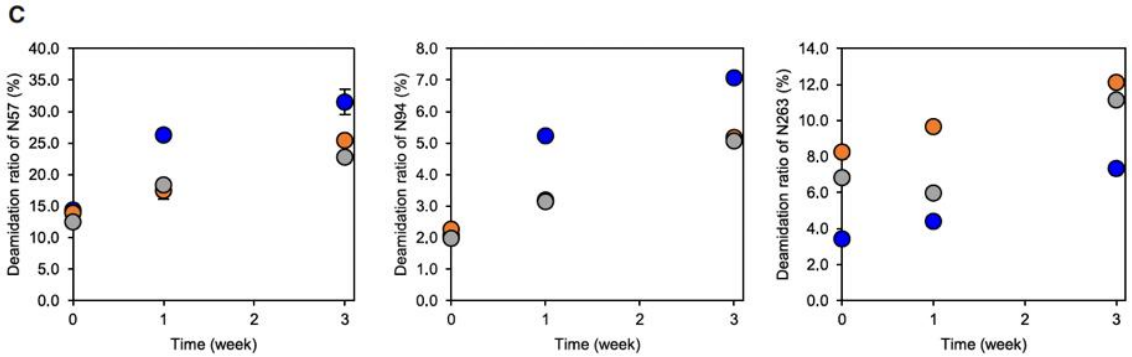
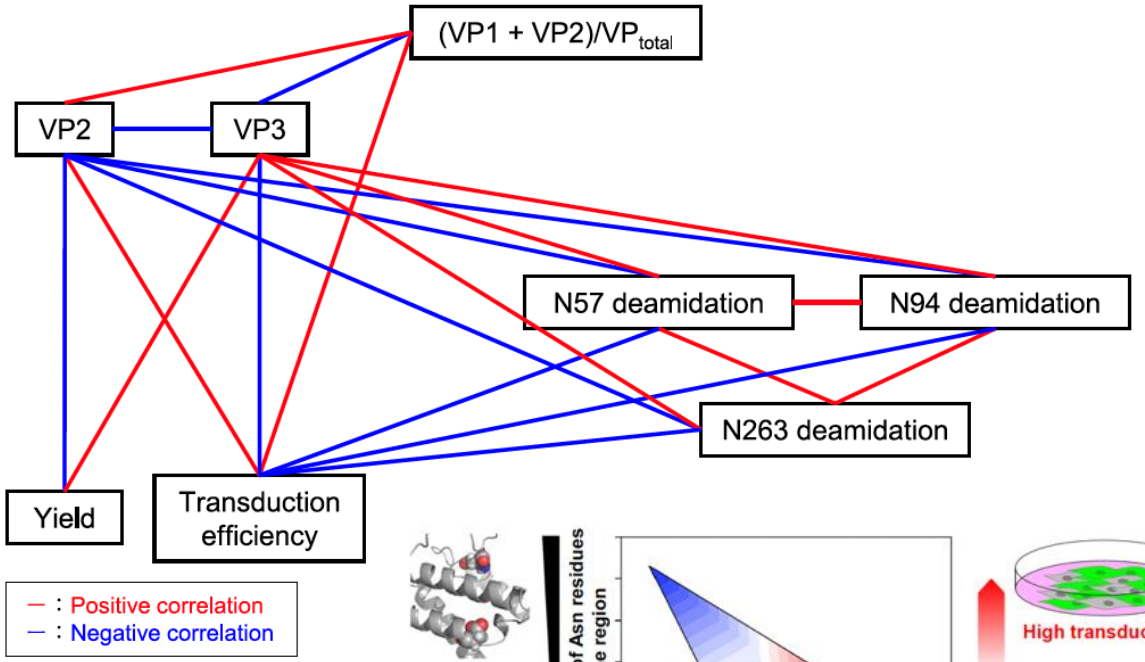
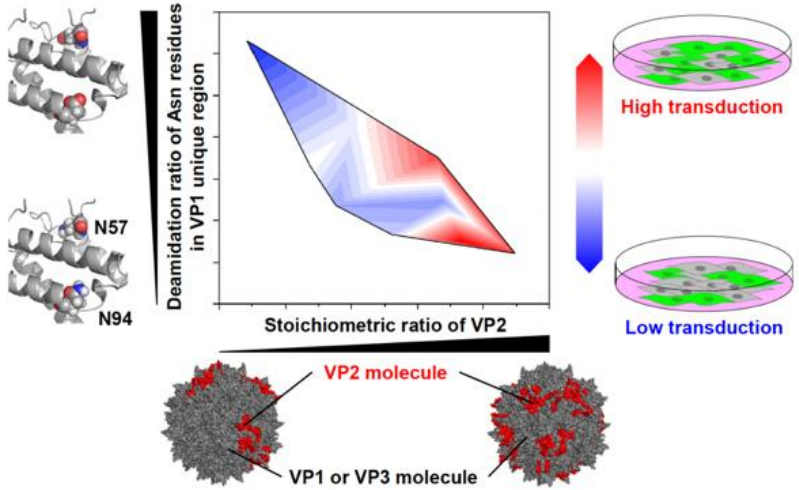
Deamidation of VP1 (N57 and N94) and VP2 level is related to biological activities

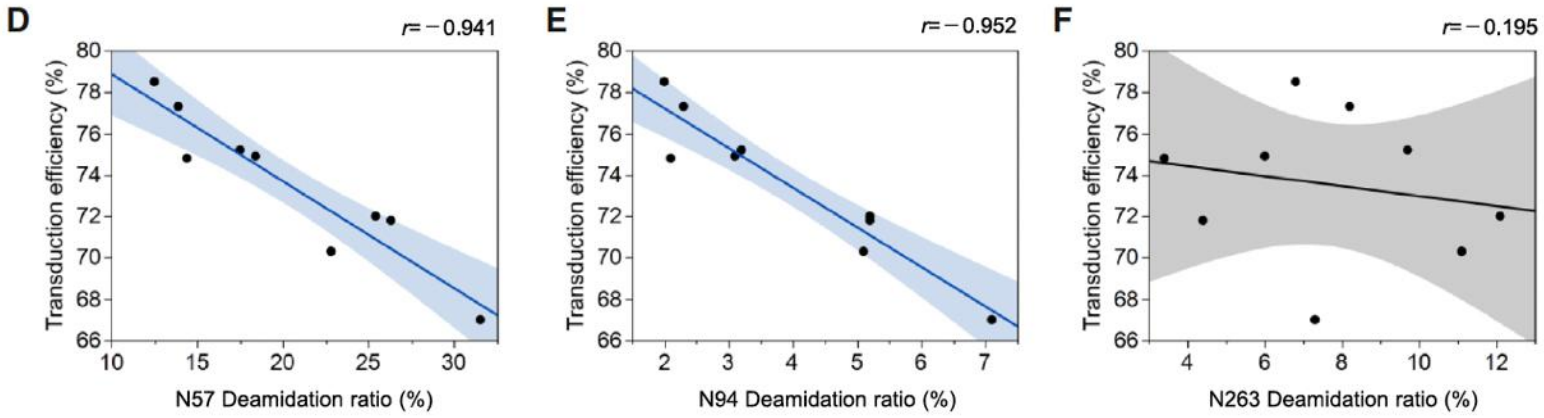
RT storage











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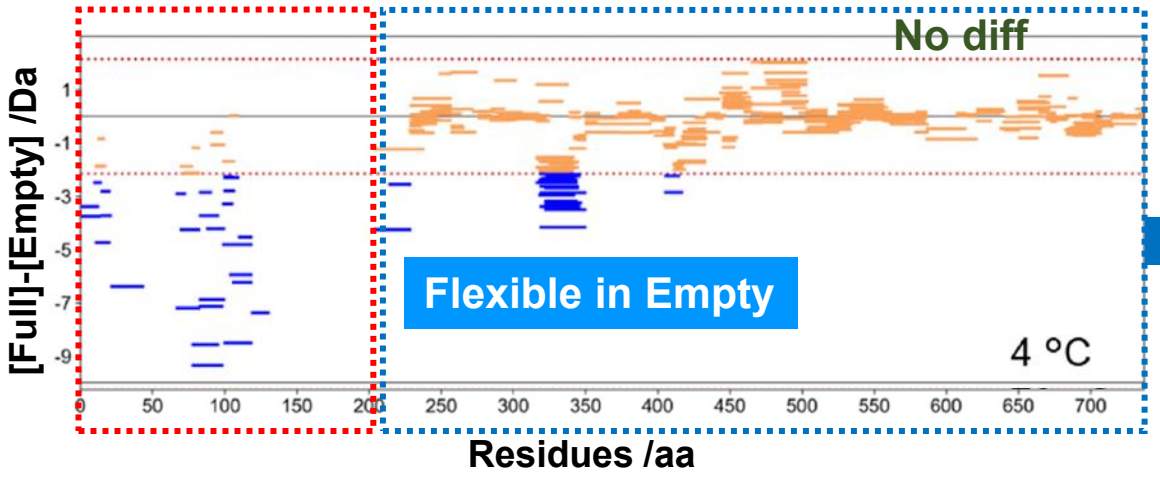
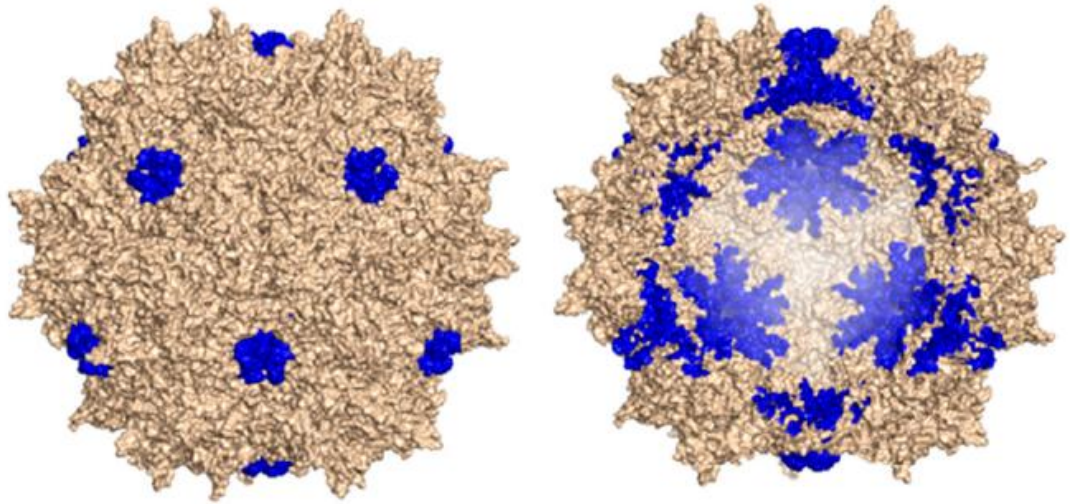
Capsid structure of FP and EP is different

H/D exchange rate difference between full and empty





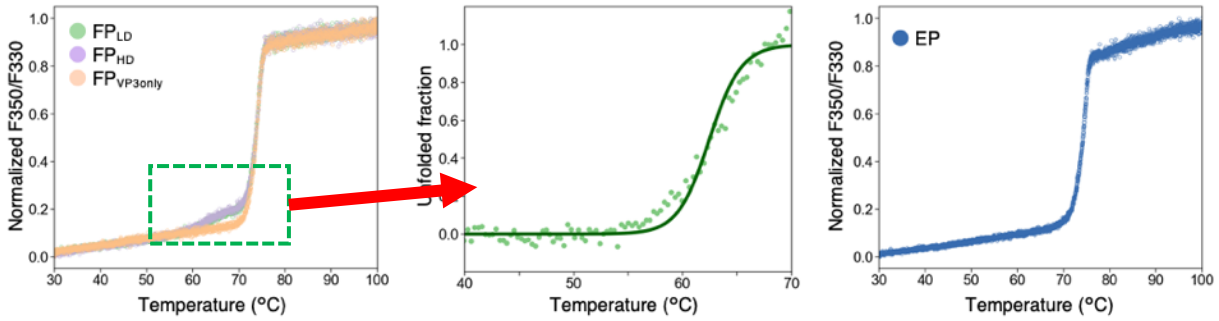
Outside surface

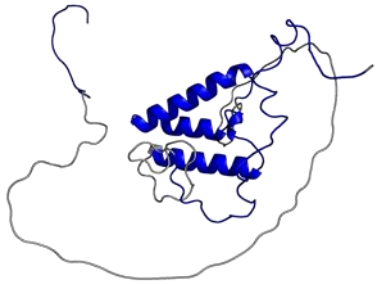
Inner surface

Higher H/D ratio
In Empty

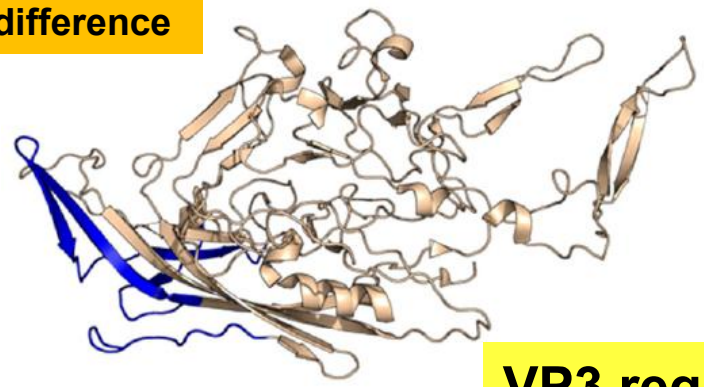
No difference

Temperature dependence of F350/F330 Ex. 280nm





VP1/2 region



VP3 region

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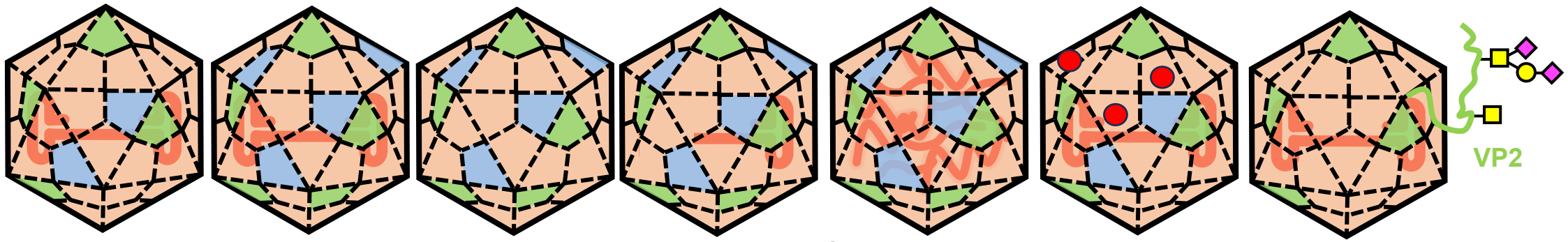
Ikeda et al, *Viruses* (2024)

rAAV as a Heterogeneous Particle Ensemble



Species

Full particle (FP)

Empty (EP)

Partial (PP)

Over-packaged (OP)

Modification

Sub-species

VP variation

VP variation

DNA length variation

Chemical

Glycosylation

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