

Cover Page



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**Author:** Kazem, Siamaque

**Title:** The trichodysplasia spinulosa-associated polyomavirus : infection, pathogenesis, evolution and adaptation

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VePyV1 CaPyV JCPyV *mPyV* SA12 RacPyV GHPyV BKPyV

*BatsyV* CPyV OrAPyV1 FPyV MptV APPyV1 SqPyV LPyV CSLPyV

EPyV PRPyV1 APP<sub>g</sub>V2 KIPyV **MIRgV** PtvPyV2c OtPyV1 **STLLPyV**

MFPyV1 *KSgV09* SV40 TSPyV CoPyV1 PPPyV CPPyV HPyV12

MXPyV PtvPyV1a PDPyV EIPyV1 AtPPyV1 HaPyV (TggPyV1

CdPyV DRPyV MWPyV APyV CaPyV1 HPyV7 CHPyV MasPyV

WUPyV *HSPyVc* BPyV MCPyV OrAPyV2 MMPyV SLPyV HPyV10

**VePyV1** *CaPyV* **JCPyV** *mPyV* **SA12**

*BatPyV* **CPyV** **OraPyV1** **FPyV** **MptV** **APPy**

**EPyV** **PRPyV1** **APPyV2** **KIPyV** **MiPyV** **P**

**MFPyV1** *HPyV9* **SV40** **TSPyV** **CoPyV1**

**MPyV** **PtvPyV1a** **PDPyV** **EiPyV1** **At**

**CdPyV** **DRPyV** **MWPyV** **APyV** **CAPyV1**

**WUPyV** *HPyV6* **BPyV** **MCPyV** **OraPyV2**

## Part V

### Appendix

**PyV** **BKPyV**

**PyV** **CSLPyV**

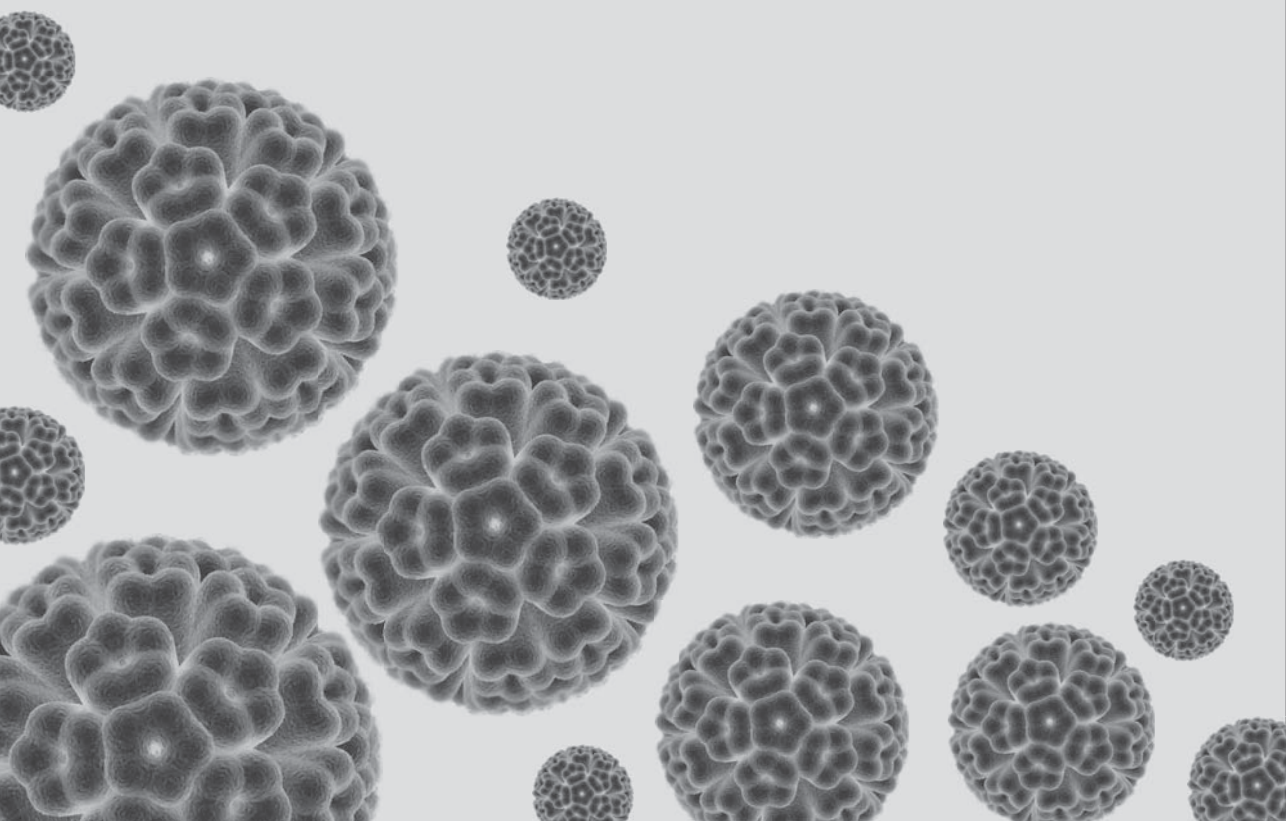
**PyV1** **STLPyV**

**PyV** **HPyV12**

**PyV** **GgPyV1**

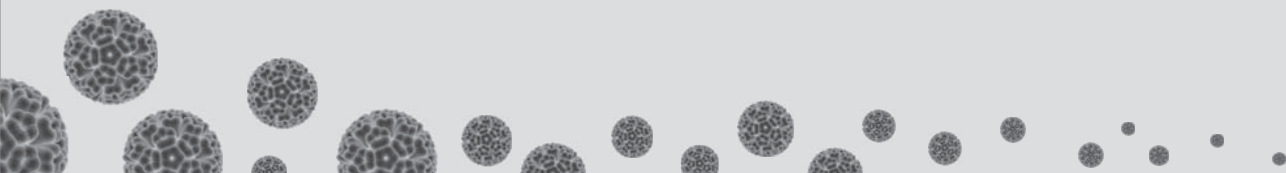
**PyV** **MasPyV**

**PyV** **HPyV10**



# Appendix 1

## List of Abbreviations



## List of Abbreviations

<b>A</b>	AelPyV	African elephant polyomavirus
	AI	Association index
	ALL	Acute lymphocytic leukemia
	ALTO	Alternate frame of the large T open reading frame
	APPyV1	Artibeus planirostris polyomavirus
	APPyV2	Artibeus planirostris polyomavirus
	APyV	Avian polyomavirus
	AtPPyV1	Ateles paniscus polyomavirus
<b>B</b>	BatPyV	Bat polyomavirus
	BKPyV	BK polyomavirus
	BPyV	Bovine polyomavirus
<b>C</b>	CAPyV1	Cebus albifrons polyomavirus
	CaPyV	Canary polyomavirus isolate
	CDK	Cyclin dependent kinases
	CdPyV	Cardioderma polyomavirus
	ChPyV	Chimpanzee polyomavirus
	CLL	Chronic lymphocytic leukemia
	COCO-VA	Codon-constrained Valine-Alanine
	CoPyV1	Chaerephon polyomavirus
	CPPyV	Carollia perspicillata polyomavirus
	CPyV	Crow polyomavirus
	CSLPyV	California sea lion polyomavirus
<b>D</b>	dsDNA	Double-stranded DNA
	DRPyV	Desmodus rotundus polyomavirus
	DS	Dataset
<b>E</b>	EiPyV1	Eidolon polyomavirus
	EM	Electron microscopy
	EPyV	Equine polyomavirus
<b>F</b>	FFPE	Formalin-fixed paraffin-embedded
	FPyV	Finch polyomavirus
	FRFR	Fresh frozen
	FUBAR	Fast unconstrained bayesian approximation

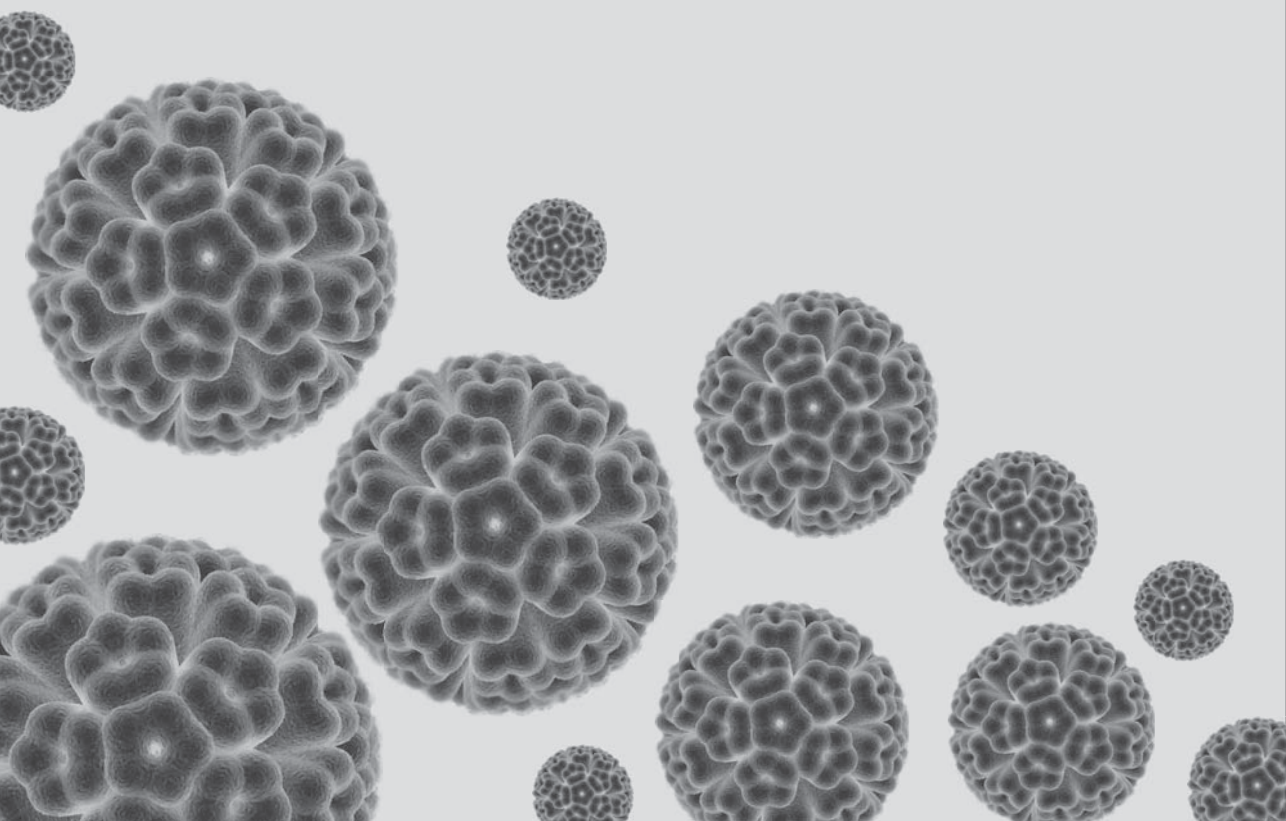
<b>G</b>	GE	Gastroenteritis
	GggPyV1	Gorilla gorilla gorilla polyomavirus
	GHPyV	Goose hemorrhagic polyomavirus
	GI-tract	Gastro-intestinal tract
	GST	Glutathione-S-transferase
<b>H</b>	HaPyV	Hamster polyomavirus
	H&E	Hematoxylin and eosin
	HPV	Human papillomavirus
	HPV16	Human papillomavirus type 16
	HPyV6	Human polyomavirus type 6
	HPyV7	Human polyomavirus type 7
	HPyV9	Human polyomavirus type 9
	HPyV10	Human polyomavirus type 10
	HPyV12	Human polyomavirus type 12
	HPyVs	Human polyomaviruses
HSF	Human Splice Finder	
<b>I</b>	ICTV	International committee on taxonomy of viruses
	IDRs	Intrinsically disordered regions
	IFA	Immunofluorescence assay
	IHC	Immunohistochemistry
	IR	Intergenic region
	IRB	Institutional review board
	IRS	Inner root sheath
<b>J</b>	JCPyV	JC polyomavirus
<b>K</b>	KIPyV	KI polyomavirus
<b>L</b>	LGN	Lupus glomerulonephritis
	LPyV	B-lymphotropic polyomavirus
	LT-antigen	Large tumor antigen
<b>M</b>	MasPyV	Mastomys polyomavirus
	MC	Maximum monophyletic clade size
	MCC	Merkel cell carcinoma
	MCMC	Markov chain monte carlo
	MCPyV	Merkel cell polyomavirus
	MDA	Multiple displacement amplification

	MFPyV1	Macaca fascicularis polyomavirus
	MiPyV	Miniopterus polyomavirus
	M&M	Material and Methods
	MMPyV	Molossus molossus polyomavirus
	MptV	Murine pneumotropic virus
	MPyV	Murine polyomavirus
	MT-antigen	Middle tumor antigen
	MWPyV	Malawi polyomavirus
	MXPyV	Mexico polyomavirus
<b>N</b>	NCCR	Non-coding control region
	NHL	Non-Hodgkin's lymphoma
	NJPyV	New Jersey polyomavirus
	NLS	Non-lesional skin
	nts	Nucleotides
<b>O</b>	OPTN	Organ procurement and transplantation network
	OraPyV1	Orang-utan polyomavirus Bornean
	OraPyV2	Orang-utan polyomavirus Sumatran
	ORF	Open reading frame
	Ortho-I	Orthopolyomavirus-I
	Ortho-II	Orthopolyomavirus-II
	OtPyV1	Otomops polyomavirus
<b>P</b>	PDPyV	Pteronotus davi polyomavirus
	PED	Pair-wise evolutionary distance
	PHK	Primary human keratinocytes
	PML	Progressive multifocal leukoencephalopathy
	PPPyV	Pteronotus parnellii polyomavirus
	PRPyV1	Piliocolobus rufomitratu polyomavirus
	PS	Parsimony score
	PtvPyV1a	Pan troglodytes verus polyomavirus
	PtvPyV2c	Pan troglodytes verus polyomavirus
<b>R</b>	RacPyV	Raccoon polyomavirus
	RB	Retinoblastoma
	RCA	Rolling-circle amplification
	RefSeq	Reference sequence
	REL	Random effect likelihood
	RF	Reading frames
	RTR	Renal transplant recipients



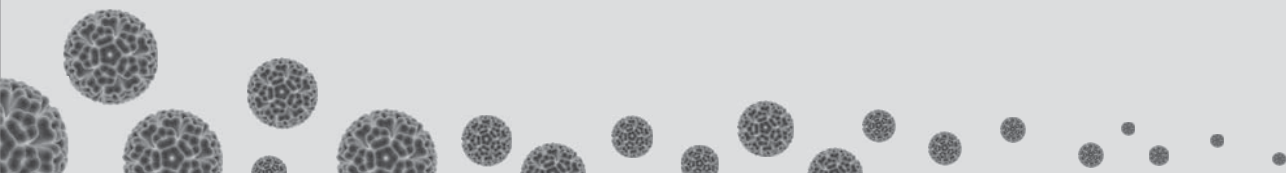
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<b>S</b>	SA12	Baboon polyomavirus 1
	SLiMs	Short linear motifs
	SLPyV	Sturnira lilium polyomavirus
	SNP	Single (di)nucleotide polymorphism
	SPED	Smallest pair-wise evolutionary distance
	SqPyV	Squirrel monkey polyomavirus
	ST-antigen	Small tumor antigen
	STLPyV	St. Louis polyomavirus
SV40	Simian virus 40	
<b>T</b>	TCHH	Trichohyalin
	TM	Transmembrane domain
	tMRCA	Time to the most recent common ancestor
	TOI	Trichodysplasia of immunosuppression
	TP	True-palindrome
	TS	Trichodysplasia spinulosa
	TSPyV	Trichodysplasia spinulosa-associated polyomavirus
	TX	Transplant patient
<b>V</b>	VATD	Viral-associated trichodysplasia of immunosuppression
	VATS	Virus associated trichodysplasia spinulosa
	VePyV1	Vervet monkey polyomavirus
	VP1	Viral capsid protein 1
	VP2	Viral capsid protein 2
	VP3	Viral capsid protein 3
<b>W</b>	WUPyV	WU polyomavirus
<b>Y</b>	ybp	Years before present



# Appendix 2

Acknowledgement



## Acknowledgements

This dissertation would obviously have not been realized without the many contributions of my fellow researchers **Els, Chris, Sander, Richard, Alexander K., Arlene, Philip, Klaus, Elena, Taylor, Lauren, Esther, John, Just, Genevieve, Louis, Sasha** and **Mariet**, who co-authored with me the published papers because of their sample collection/collaboration, technical assistance, data analyses and/or manuscript writing and editing. In addition, I am also much gratitude indebted to my two promotors, Prof. dr. **Alexander Gorbalenya** and Prof. dr. **Louis Kroes**, for the time and continuous support they have invested in me and for making this PhD candidacy possible at the department of Medical Microbiology of the Leiden University Medical Center.

My co-promotor Dr. **Mariet Feltkamp** is sincerely thanked for the freedom she gave me to explore and pursue ideas and experiments of my own, but still be critically involved, despite her activities at the department as an associate professor and clinical virologist. She always remained accessible for questions and help. After all, it was her enthusiasm, openness and clarity that ensured me to develop a preference for DNA virus research and enrolled for this PhD candidacy.

I also owe my (past-)colleagues at the department of Medical Microbiology a lot of admiration, even if it was for the many great tips, chats, notes and ideas we shared. Indispensable were also the-always-helpful secretaries and the lab managers. **Many thanks to all of you!** My gratitude will not end with these words. I will thank you repeatedly in person when we meet again.

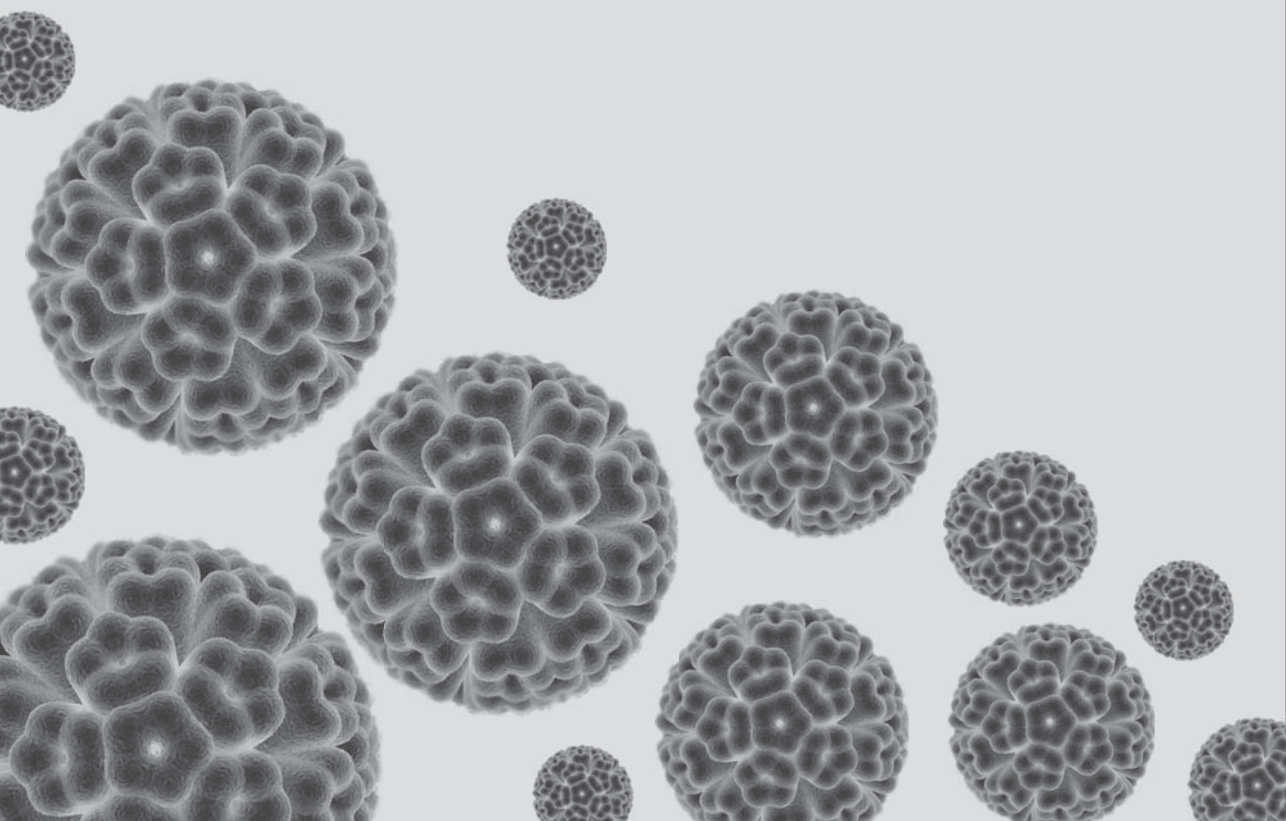
My (present-)colleagues at the **DDL Diagnostic Laboratory** are thanked for their support and help to let me adjust to a new research environment. Dr. **Wim Quint** is especially thanked for making my current position at the DDL possible.

I am all my **friends** and **family** thankful for the pleasant moments that make life enjoyable. Your unconditional support and advice have always motivated me in my career choices.

In this part, first I would like to express my sincere gratitude towards my lovely parents. Words are powerless to express my feeling for all the care and love the two of you (**Mami** and **Baba**) have given us “The Four Brothers”! Even if it meant to risk everything you had and owned, just to create and ensure a perfect environment for us to live in. You succeeded! I wish I could do this much for the two of you. You are the core of my existence. My lovely and always supportive brother **Rosbe (Rob)** is thanked unconditionally for his support and helpfulness in any way. Big-bro, you are and will always be an excellent example in my life.

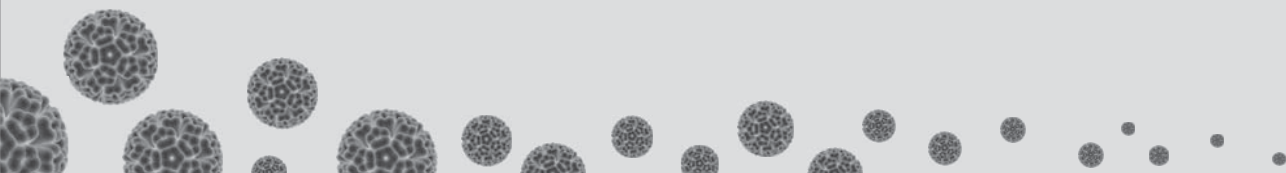
**Babak**, it is hard to find words to express how much I miss you my lovely brother. I wish we had more time to spend together and share thoughts about science. More importantly, to play again many matches of football together, the way you always won. The memories of you will always be with me, and your place in my hearth will be kept warm! Lil-bro **Dariush**, thanks for being such a wise and great brother by always helping others. Seeing your smile makes always my day. Great to always have your support at my side. In addition, special thanks are reserved for my **in-laws** for all the nice family occasions we had together and the discussions we shared about science and technology in relation to human believe in which everyone is always fully interested. Thank you for accepting me in the family!

**Beheshta (BeBe)**, my love, my better half! The moment is here. We have finalized it! I am grateful for all your support in the past years. Thank you for being at my side in the moments of happiness and in the moments of sadness. Without you, there would be less love and happiness in my life. I am also grateful for all the beautiful moments we shared and I am already thrilled about the many many many more magnificent moments that will follow. With you by my side, we can conquer the world. I Love You!



# Appendix 3

Curriculum Vitae

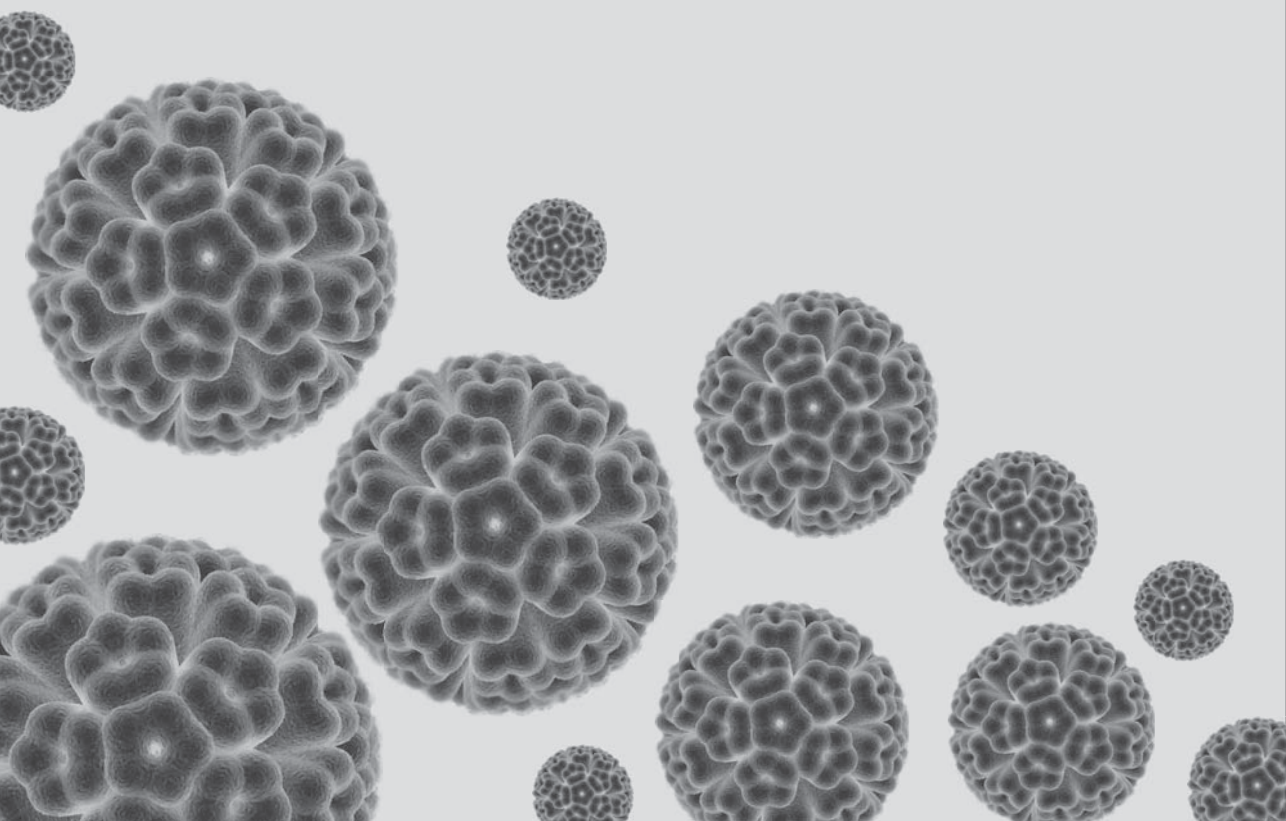






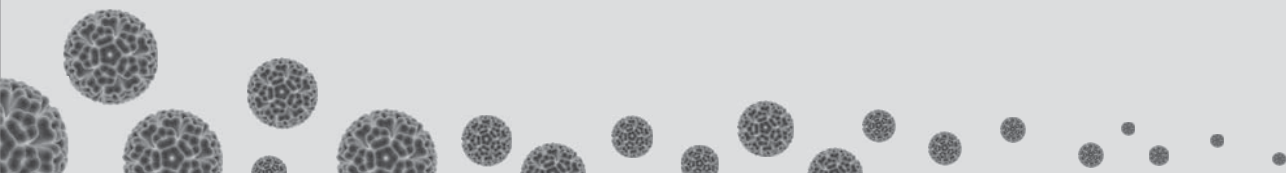
## Curriculum Vitae

**S**iamaque Kazem was born on December 23, 1982 in Kabul, Afghanistan. At the age of twelve, he arrived with his family in The Netherlands, embraced the opportunity to study and obtained his high school diploma at the Atlas College OSG West-Friesland in Hoorn, in the year 2000. One year later, he was enrolled for his Bachelor of Science (BSc) degree at the University of Applied Sciences (HSL) in Leiden, The Netherlands, where he became committed to specialize in the field of Medical Microbiology. In the final year before obtaining his BSc degree, he was trained for almost one year as an intern under supervision of Dr. Mariet Feltkamp and Dr. Linda Struijk working on the human papillomaviruses in relation to skin cancer at the Leiden University Medical Center department of Medical Microbiology. Upon graduating *cum laude* (with honor) for his BSc degree in 2006, in the same year he was admitted for his Master of Science (MSc) degree at the VU University Amsterdam aimed to specialize in (molecular) Oncology. As part of his MSc curriculum, for his minor-placement he was trained as an intern under supervision of Dr. David Noske, Dr. Gerrit Schuurhuis and Dr. Jacqueline Cloos working on Glioblastoma multiforme tumors at the VU University Medical Center departments of Neurosurgery, Hematology and Child oncology. For his major-placement, he was trained as an intern under supervision of Prof. dr. Paul van Diest and Dr. Petra van der Groep working again on brain tumors, now at the University Medical Center Utrecht department of Pathology. He graduated for his MSc degree in 2008 and in the same year, he joined again the group of Dr. Mariet Feltkamp as a junior researcher working on the human papillomaviruses in relation to skin cancer. Upon discovery of the polyomavirus TSPyV in 2010, in the same year he started his PhD studies on this virus. To obtain his PhD degree at the University of Leiden under supervision of Dr. Mariet Feltkamp, Prof. dr. Alexander Gorbalenya and Prof. dr. Louis Kroes at the Leiden University Medical Center department of Medical Microbiology section Experimental Virology, the results of his studies are put together in this dissertation. Since December 2014, Siamaque Kazem is working as a Postdoctoral Scientist in the Research and Development department of DDL Diagnostic Laboratory in Rijswijk (The Netherlands), to continue his career in the field of Molecular Oncology and Next Generation Sequencing.



# Appendix 4

List of Publications



## List of Publications

1. Van der Meijden E, **Kazem S**, Dargel CA, van Vuren N, Hensbergen PJ, Feltkamp MCW. Characterization of T-antigens, including Middle T and ALTO, expressed by the human polyomavirus associated with trichodysplasia spinulosa.  
*Submitted for publication*
2. **Kazem S**,\* Lauber C,\* van der Meijden E, Kooijman S, Kravchenko AA, Feltkamp MCW# and Gorbalenya AE.#  
Adaptation of trichodysplasia spinulosa-associated polyomavirus to the human population is mediated by middle T antigen and involves COCO-VA toggling.  
*Submitted for publication*  
*\*and # Authors than contributed equally*
3. Lauber C,\* **Kazem S**,\* Kravchenko AA, Feltkamp MCW and Gorbalenya AE.  
Interspecific adaptation by binary choice at de novo polyomavirus T antigen site through accelerated codon-constrained Val-Ala toggling within an intrinsically disordered region.  
*Nucleic Acids Research (10.1093/nar/gkv378), 2015*  
*\*Both authors contributed equally*
4. **Kazem S**, van der Meijden E, Wang RC, Rosenberg AS, Pope E, Benoit T, Fleckman P and Feltkamp MCW.  
Polyomavirus-associated trichodysplasia spinulosa involves hyperproliferation, phosphorylation of pRB and upregulation of p16 and p21.  
*PLoS ONE (9: e108947), 2014*
5. **Kazem S**, van der Meijden E and Feltkamp MCW.  
The trichodysplasia spinulosa-associated polyomavirus: virological background and clinical implications.  
*APMIS (121: 770 - 782), 2013*
6. Feltkamp MCW, **Kazem S**, van der Meijden E, Lauber C and Gorbalenya AE.  
From Stockholm to Malawi: recent developments in studying human polyomaviruses.  
*Journal of General Virology (94: 482 - 496), 2013*
7. **Kazem S**, van der Meijden E, Kooijman S, Rosenberg AS, Hughey LC, Browning JC, Sadler G, Busam K, Pope E, Benoit T, Fleckman P, de Vries E, Eekhof JA and Feltkamp MCW.  
Trichodysplasia spinulosa is characterized by active polyomavirus infection.  
*Journal of Clinical Virology (53: 225 - 230), 2012*
8. **Kazem S**, van der Meijden E, Struijk L, de Gruijl FR and Feltkamp MCW.  
Human papillomavirus 8 E6 disrupts terminal skin differentiation and prevents pro-Caspase-14 cleavage.  
*Virus Research (163: 609-616), 2012*

9. Lazic D, Hufbauer M, Zigrino P, Buchholz S, **Kazem S**, Feltkamp MCW, Mauch C, Steger G, Pfister H and Akgül B.  
Human Papillomavirus Type 8 E6 Oncogene Inhibits Transcription of the PDZ Protein Syntenin-2.  
*Journal of Virology* (86: 7943-7952), 2012
10. Kanitakis J, **Kazem S**, van der Meijden E and Feltkamp MCW.  
Absence of the trichodysplasia spinulosa-associated polyomavirus in human pilomatrixomas.  
*European Journal of Dermatology* (21: 453-454), 2011
11. Van der Meijden E, **Kazem S**, Burgers MM, Janssens R, Bouwes Bavinck JN, de Melker H and Feltkamp MCW.  
Seroprevalence of Trichodysplasia spinulosa-associated Polyomavirus.  
*Emerging Infectious Diseases* (17: 1355-1363), 2011
12. Struijk L, van der Meijden E, **Kazem S**, ter Schegget J, de Gruijl FR, Steenbergen RD and Feltkamp MCW.  
Specific betapapillomaviruses associated with squamous cell carcinoma of the skin inhibit UVB-induced apoptosis of primary human keratinocytes.  
*Journal of General Virology* (89: 2303-2314), 2008



*Fly me to the moon  
Let me play among the stars  
Let me see what spring is like on  
Jupiter and Mars*

*In other words, hold my hand  
In other words, baby, kiss me*

*Fill my heart with song  
And let me sing forever more  
You are all I long for  
All I worship and adore*

*In other words, please be true  
In other words, I love you ~ BeBe ~*

*Frank Sinatra (1964)*

