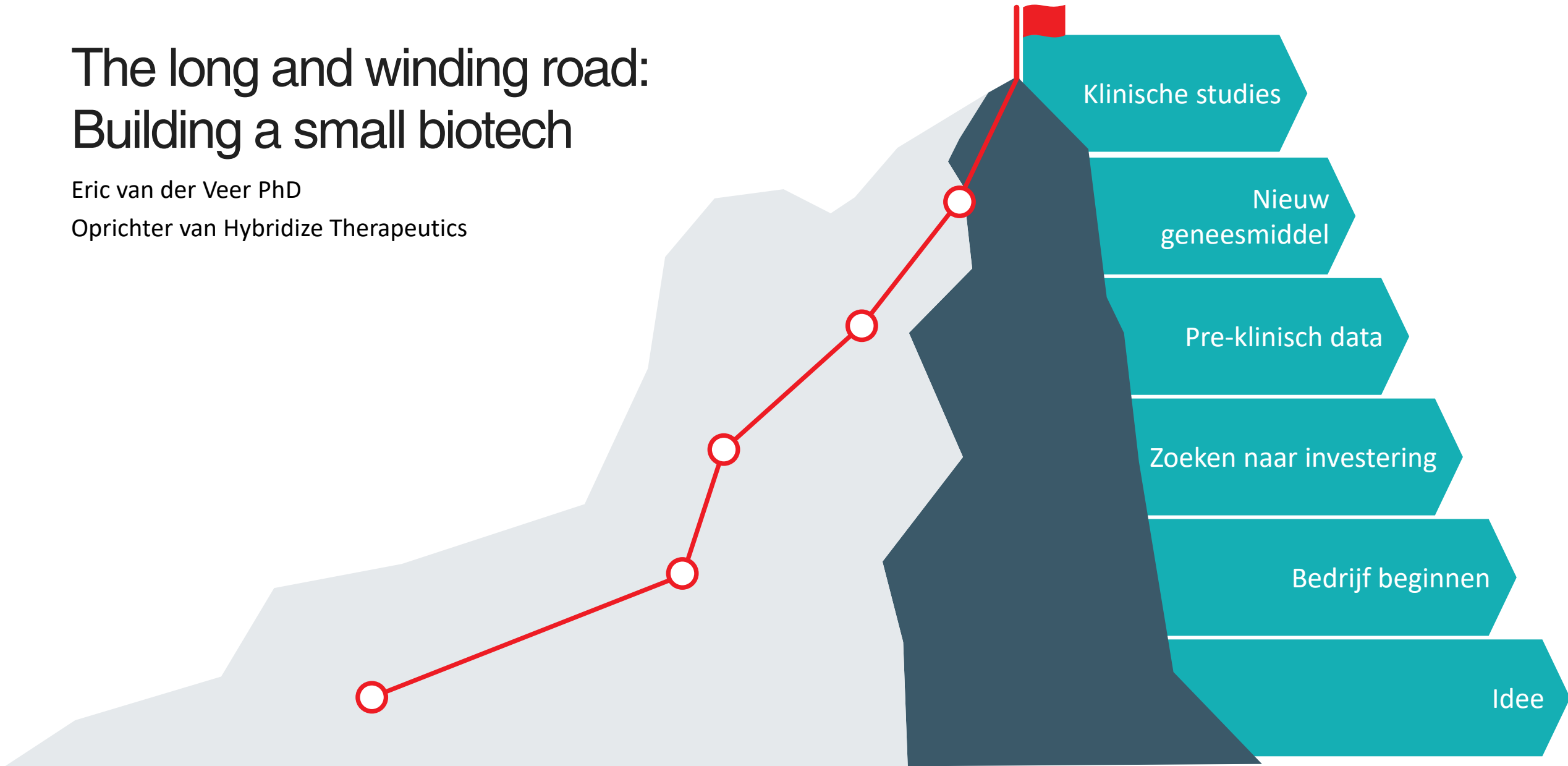


The long and winding road: Building a small biotech

Eric van der Veer PhD

Oprichter van Hybridize Therapeutics

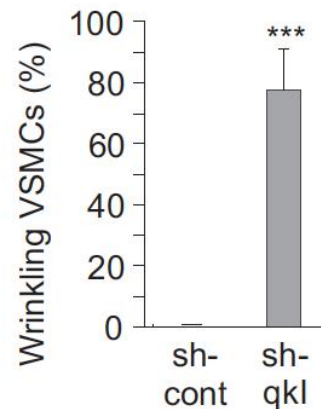
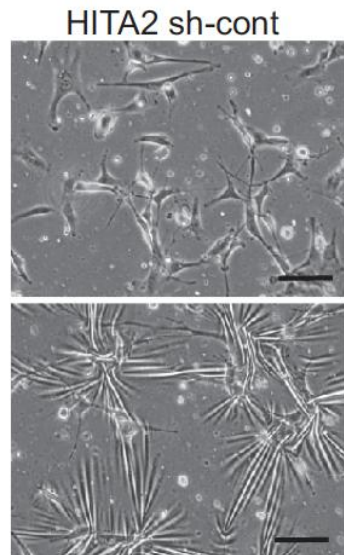


11 jaar fundamentele onderzoek naar een eiwit met de mooie naam “Quaking”



Cellular Biology

Quaking, an RNA-Binding Protein, Is a Critical Regulator of Vascular Smooth Muscle Cell Phenotype



van der Veer, E.P. et al., 2013



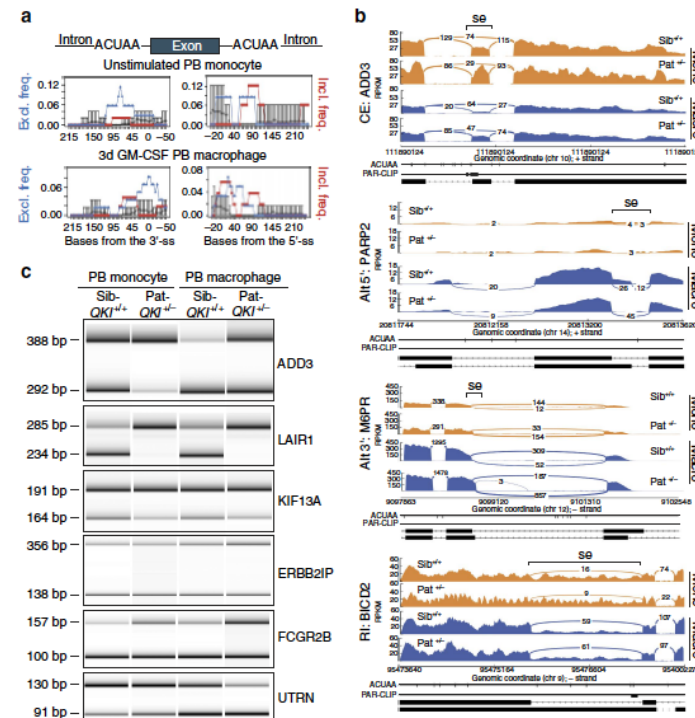
ARTICLE

Received 17 Jun 2015 | Accepted 26 Jan 2016 | Published 31 Mar 2016

DOI: 10.1038/ncomms10846

OPEN

Quaking promotes monocyte differentiation into pro-atherogenic macrophages by controlling pre-mRNA splicing and gene expression



de Bruin, R.G., et al., 2016

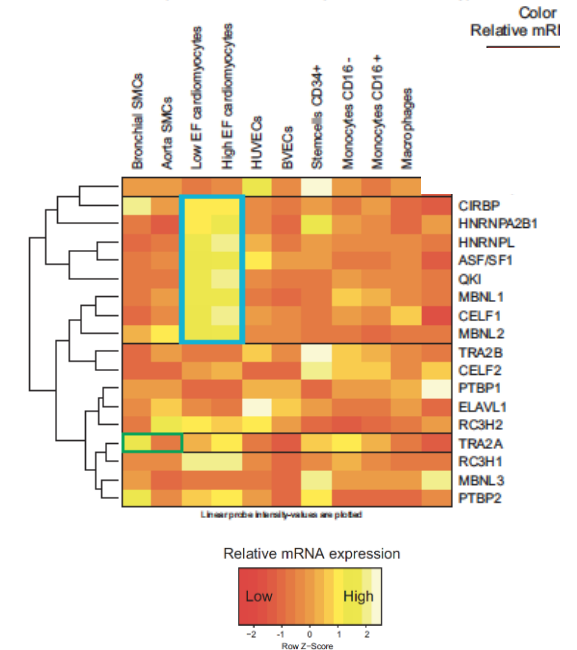
European Heart Journal



European Heart Journal (2016) 0, 1–13
doi:10.1093/eurheartj/ehw567

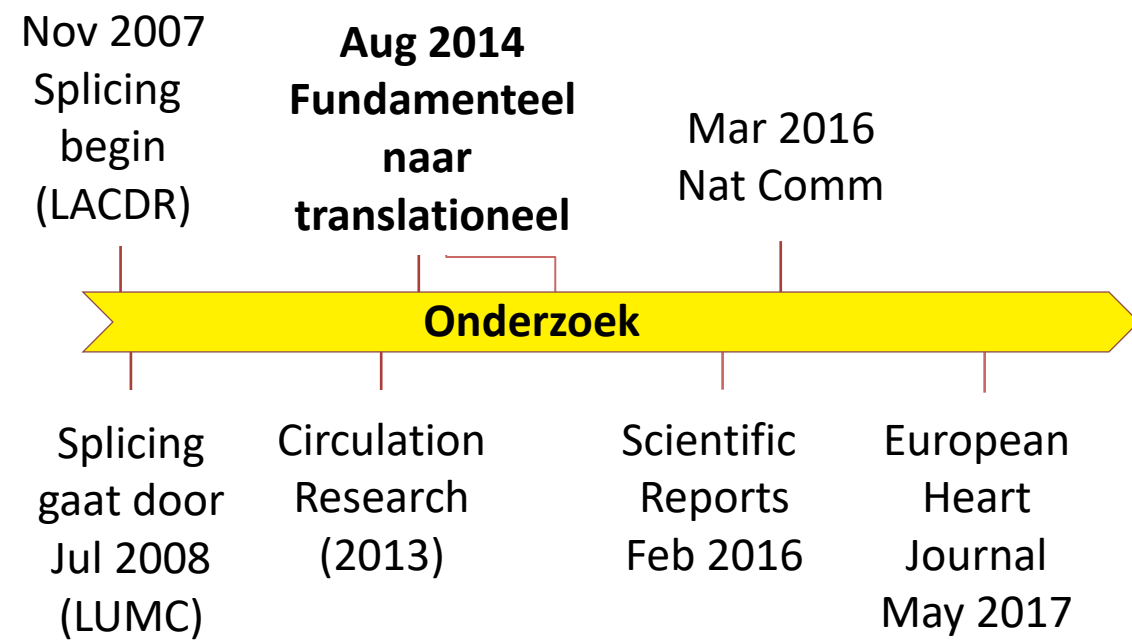
Emerging roles for RNA-binding proteins as effectors and regulators of cardiovascular disease

Relative expression of RBPs compared to other cell types



de Bruin, R.G., et al., 2016

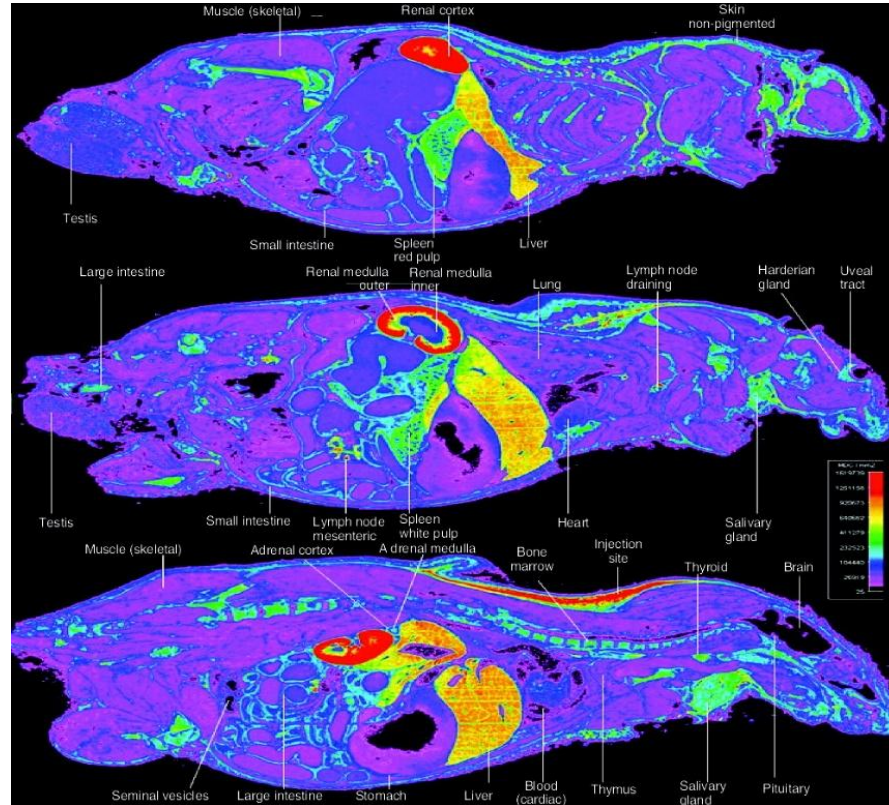
Prof. Ton Rabelink
(Nierziekten, LUMC)



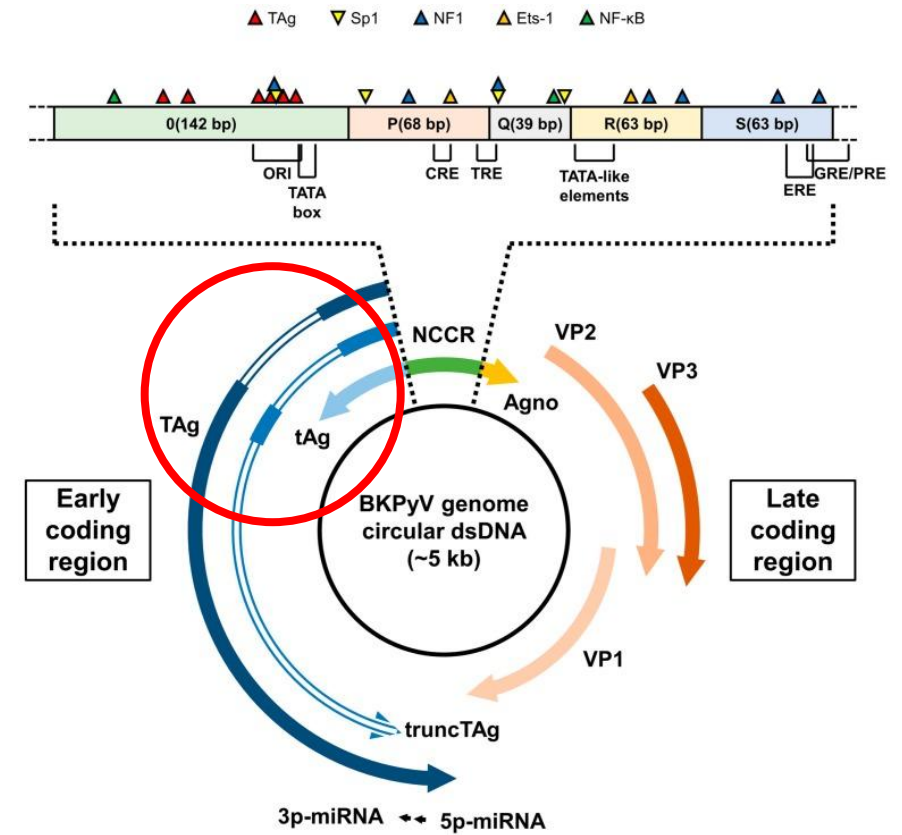
Eureka: Nieuwe ideeën moeten van ver (en dichtbij) komen!



☁ Leiden ☁

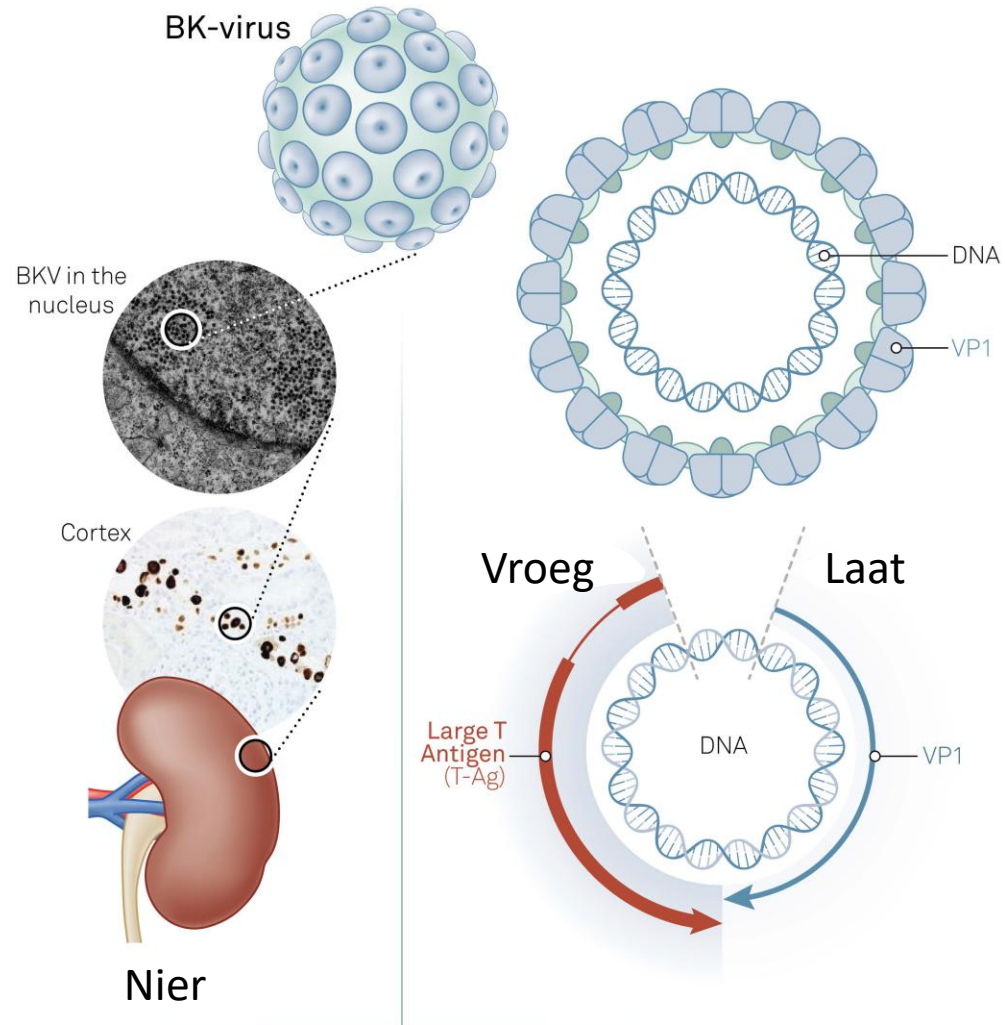


☀ Californie ☀

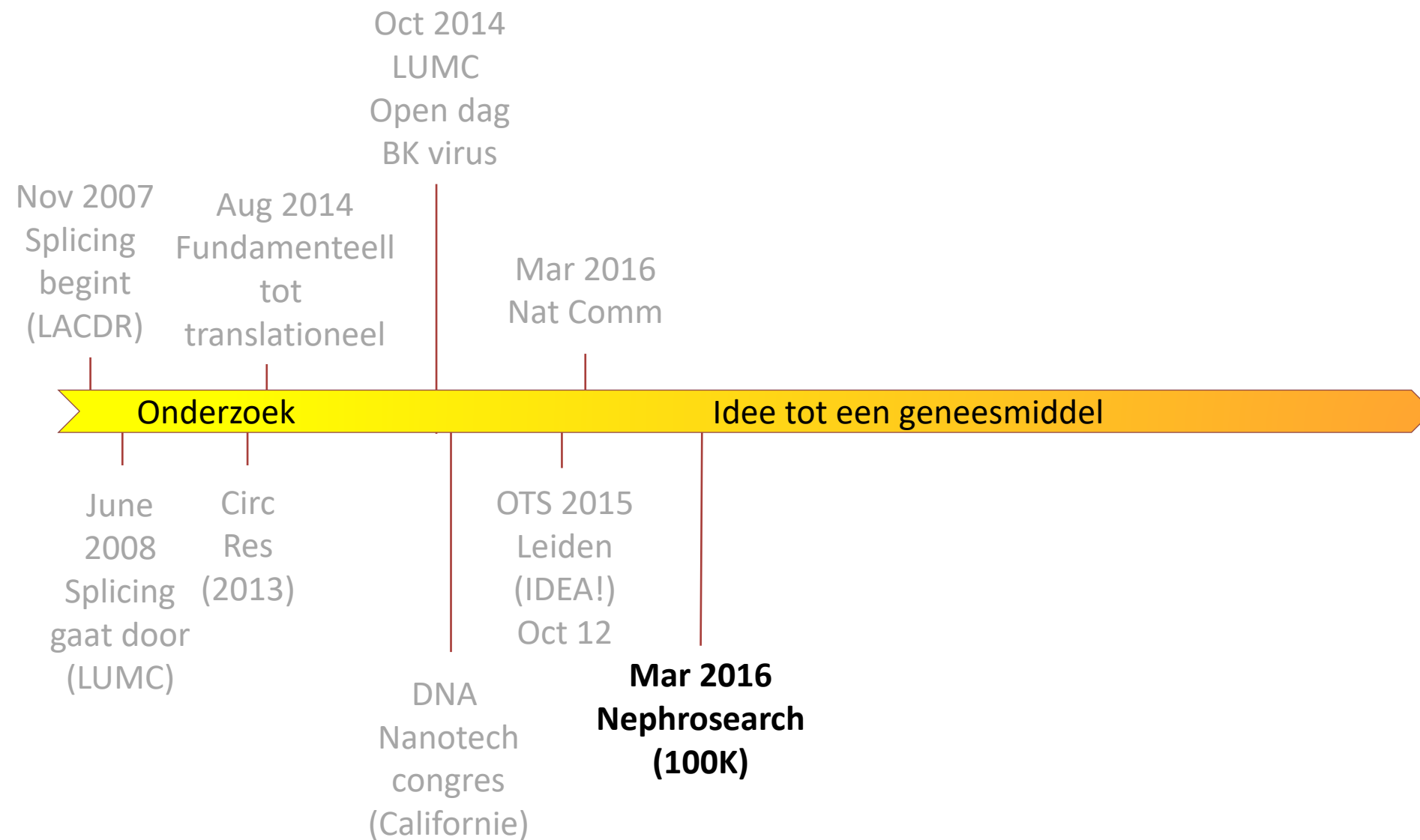


☁ Leiden ☁

Remmen van BK virus: Sleuteleiwit uitschakelen voor virus vermindering

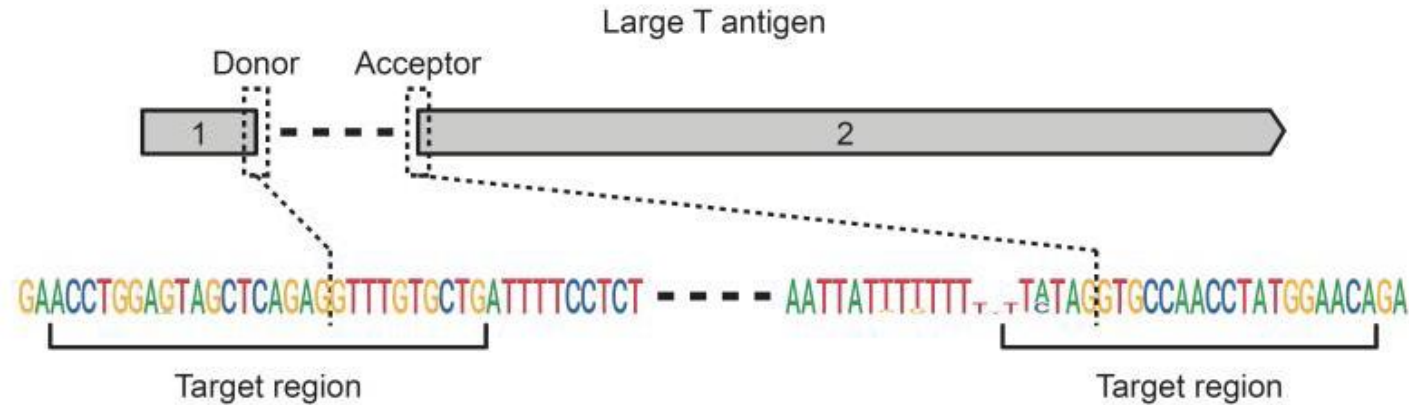


Sources: 1) Helle et al. 2017. Biology of the BKPyV: An Update. Viruses MDPI, 2) Saade et al. 2020. BK virus infection in allogeneic hematopoietic cell transplantation. Journal of Infection

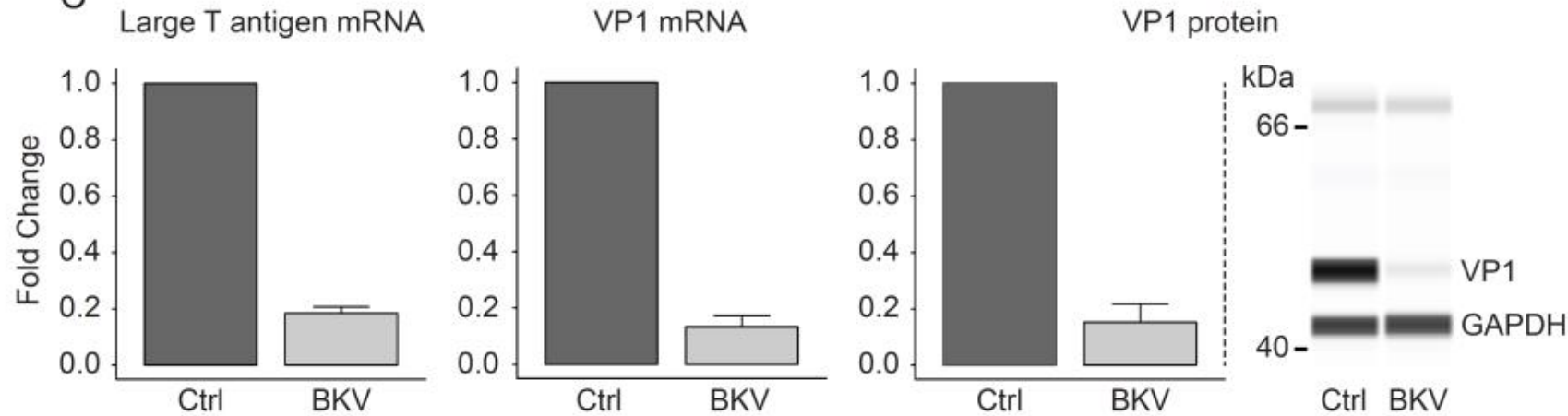


Remmen van BK virus: Sleuteleiwit uitschakelen voor virus vermindering

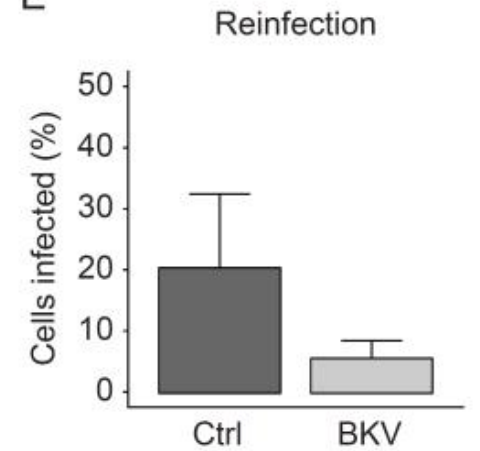
B



C



E



Wat heb je nodig om een geneesmiddel te ontwikkelen: GELD!

DUTCH KIDNEY FOUNDATION

Application form
Call Innovation Grant
Version 8 December 2015

Dutch Kidney Foundation
Nierstichting
+31 (0) 35 697 8011
subsidie@nierstichting.nl

Project code: _____

This code will be assigned by the DKF after receiving your application.

Application date: 17 March, 2016

1. Title: **A novel, RNA-based anti-viral approach to limit BK virus propagation during immunosuppressive therapy following kidney transplantation**

2. Applicant

Name (M/F)	Dr. Eric P. van der Veer (M)/ Prof. dr. A.J. van Zonneveld
Institute & Department	Leiden University Medical Center; Internal Medicine (Nephrology)
<u>Address:</u>	
Name Institute, Department	Leiden University Medical Center
Room number	Department of Internal Medicine (Nephrology, C7.36)
Street name	Albinusdreef 2
Postal code, Town/City	2300 RC, Leiden
Country	The Netherlands
Telephone	+71 5268135
E-mail	e.p.van_der_veer@lumc.nl

3. Project

Expected start date	1 September, 2016
Expected end date	1 September, 2017
Duration in months	12 months
Proposed DKF budget	100,000 €

Sections

- I. General Information
- II. Description
- III. Research Environment
- IV. Patient Perspective
- V. Impact
- VI. Knowledge Transfer, Implementation and Follow-up
- VII. Financial Issues
- VIII. Signatures

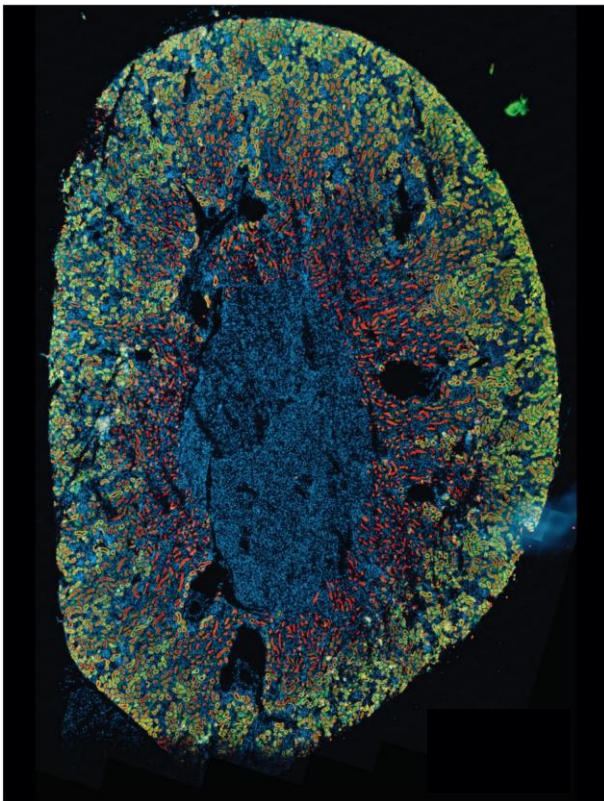


100K€



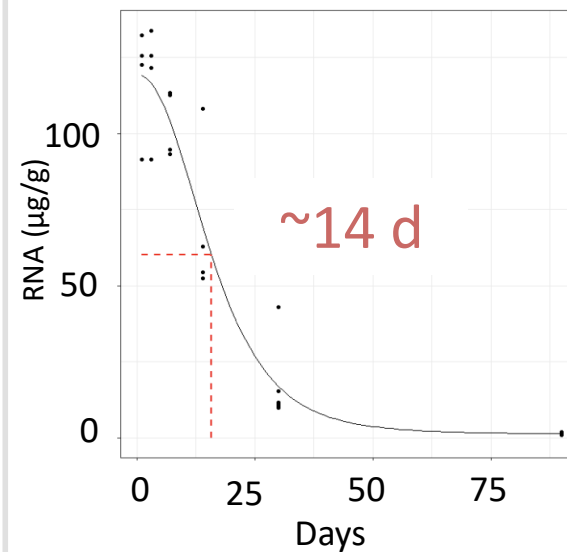
RNA therapeutics & de nier: Ze komen, blijven en werken daar

1. Distributie



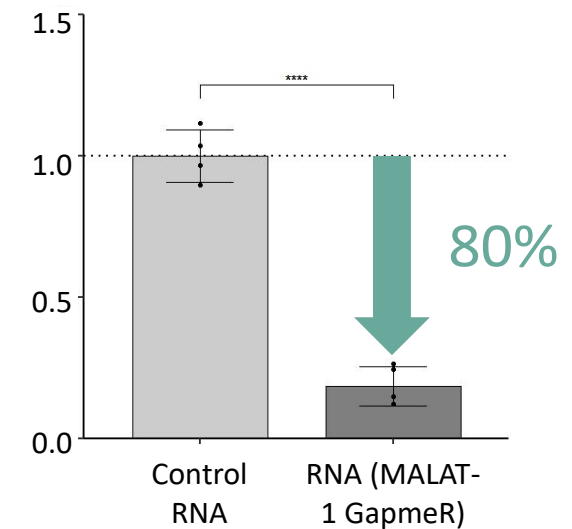
2. Stabiliteit

Metabolite stability in mouse kidney cortex (Half life ~16 d)



3. Effectiviteit

MALAT-1 expression in mouse kidney (after 24h)



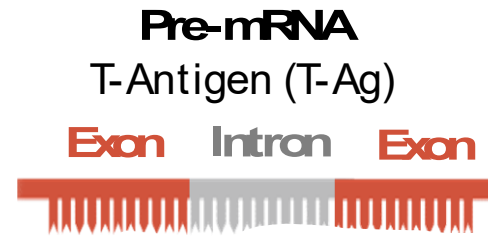
Waar begin je: Veel literatuur lezen en bioinformatica toepassen

13 oligonucleotides across the viral pre-mRNA string were developed and screened

First tests in HK-2 human cell lines showed **3 lead candidates**

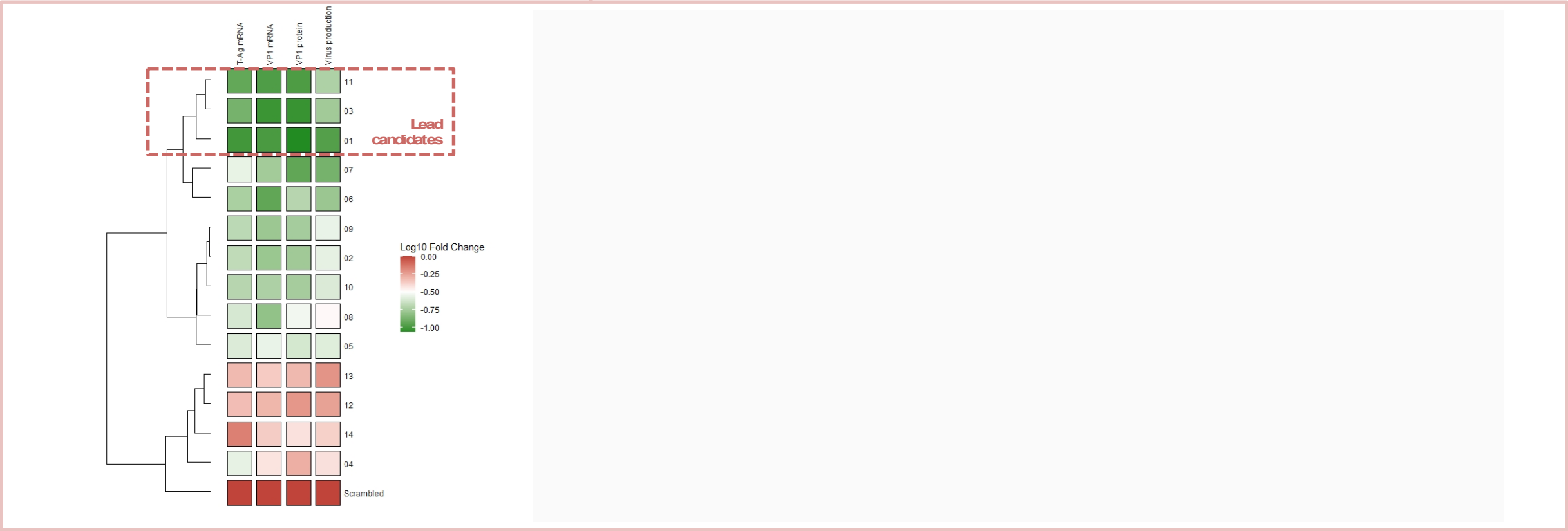
Further tests in PTEC (primary kidney cells) **validated efficacy**

Final tests to select the **lead compound are almost finished**



Deze dingen heten:
ASOs 😂

Eerste tests van ons idee: Cel-gebaseerd activiteit metingen van ASOs



Een therapie ontwikkelen: Het leren van een nieuwe vak(gebied)



Leids Universitair
Medisch Centrum

Onze visie

Toen & Nu

English

Regeneratieve Geneeskunde

Het LUMC staat als innovator voor de verbetering van de gezondheidszorg en de gezondheid van mensen door regeneratieve geneeskunde. Regeneratieve geneeskunde is één van onze drie maatschappelijke speerpunten.



Regeneratieve geneeskunde

Visie en toekomstperspectief

[Lees meer](#)



Samenwerkingen



Faciliteiten



Valorisatie

Alvleesklier

Bloed

Darm & lever

Eierstok

Hart

Long

Nier

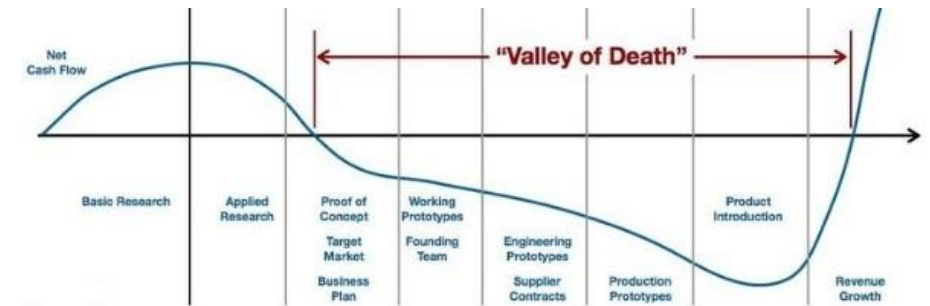
Oog

Oor

Zenuw, spier & hersenen



Leiden Regenerative Medicine Platform



- Identificeer nieuwe projecten
- Assisteer met IP bescherming
- Samenwerken met LURIS (LUMC BD)
- Bedenk kritieke experimenten
- Uitlicenseer opties (incl. partners)
- Identificeer investeerders
- **Ontwikkel Hybridize**

Intellectuele eigendom en valorisatie: Stappen die nodig zijn om een geneesmiddel te ontwikkelen

Belangrijke momenten:

- **November, 2017:** Begonnen als bedrijfsontwikkelaar (LRMP)
- **March, 2018:** Provisioneel octrooi aangevraagd
EPO commentaar: Innovatieve nieuwe aanpak – meer bewijs nodig
- **March 2018:** Deelname aan Health-Holland Venture Challenge
- **March, 2019:** Definitief indiening van octrooi
Aanvullende bewijs voor geneesmiddel en nieuwe geneesmiddelen
- **Februari, 2023:** Nieuw patent ingediend met nieuw BKV-remmende geneesmiddelen
- Tot op de dag van vandaag, constant vragen aan het beantwoorden over ons geneesmiddel

European Patent Office
80000 MUNICH
GERMANY

Questions about this communication?
Contact Customer Services at www.epo.org/contact

V.O.
P.O. Box 87930
Carnegieplein 5
2500 DH Den Haag
PAYS-BAS

Date: 06.08.18

Reference P112760EP00	Application No./Patent No. 18159797.2 - 1111
--------------------------	---

Applicant/Inventor
Academisch Ziekenhuis Leiden h.o.d.n. LUMC

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the European search report (R. 61 EPC) or the partial European search report/ declaration of no search (R. 63 EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☒ 0 additional set(s) of copies of such documents is (are) enclosed as well.

The following have been approved:

☒ Abstract ☒ Title

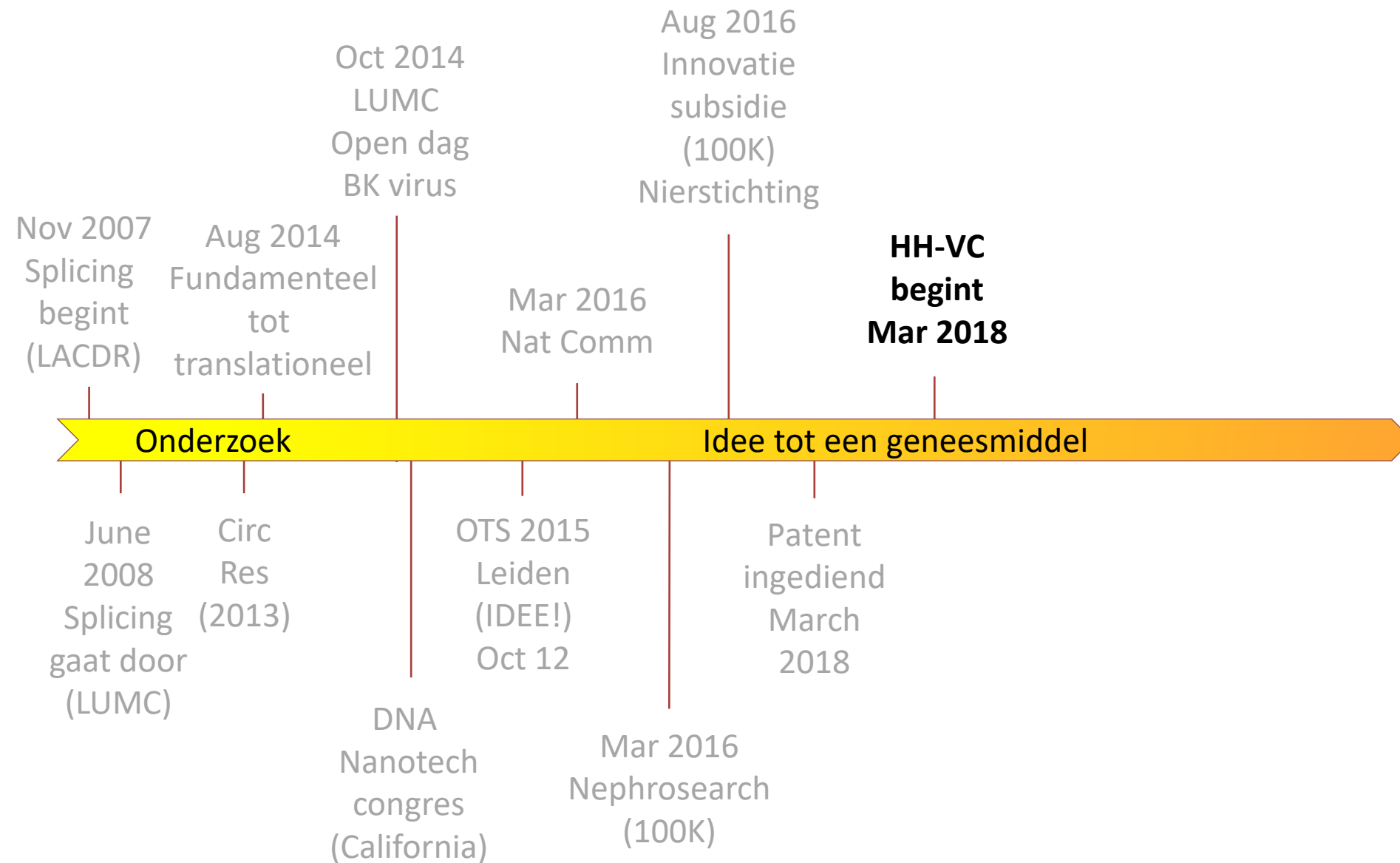
☐ The Abstract was modified and the definitive text is attached to this communication.

The following figure(s) will be published together with the abstract:

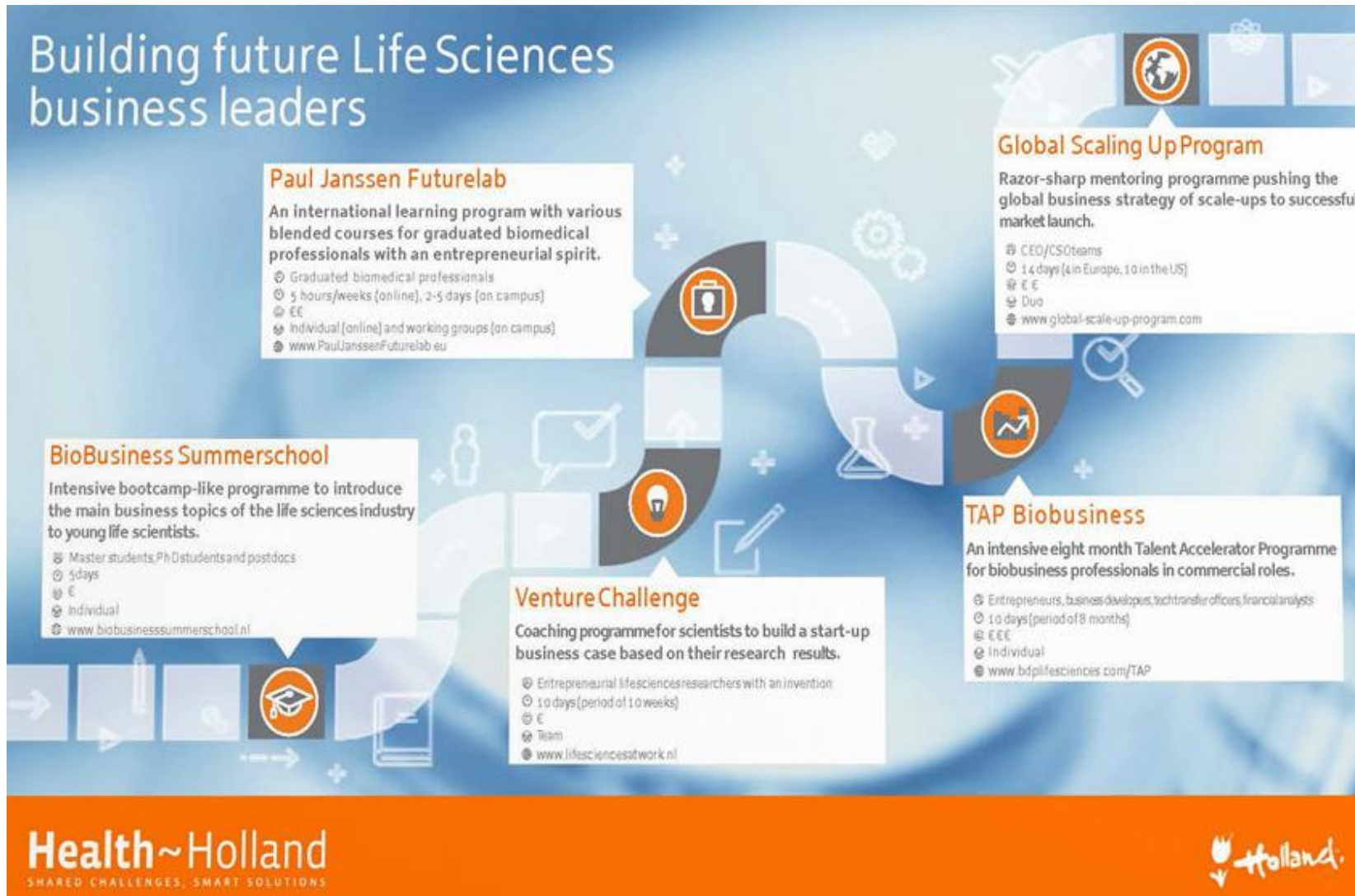
Refund of search fee
If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

Should you wish to further prosecute this application in the examination phase, your attention is drawn to the provisions of Rule 70a EPC. An invitation to respond to the extended European search report will be issued once the date of publication of the European search report has been mentioned in the European Patent Bulletin (R. 69(1), R. 70(2) EPC).

EP0 Form 1507N 06.12 page 1 of 1



HH Venture Challenge: De 'business-kant' van een idee tot een geneesmiddel



Hanna Groen • 1st
Programme Coordinator bij Health~Holland
Leiden, South Holland Province, Netherlands

[Message](#) [More...](#)



Chretien
Herben



Math
Kohnen

Wat heb je nodig om een geneesmiddel te ontwikkelen: GELD!

DUTCH KIDNEY FOUNDATION

Application form
Call Innovation Grant
Version 8 December 2015

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Institute & Department Leiden University Medical Center; Internal Medicine (Nephrology)
Address:
Name Institute, Department Leiden University Medical Center
Room number Department of Internal Medicine (Nephrology, C7.36)
Street name Albinusdreef 2
Postal code, Town/City 2300 RC, Leiden
Country The Netherlands
Telephone +71 5268135
E-mail e.p.van_der_veer@lumc.nl

3. Project

Expected start date 1 September, 2016
Expected end date 1 September, 2017
Duration in months 12 months
Proposed DKF budget 100,000 €

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- I. General Information
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- VI. Knowledge Transfer, Implementation and Follow-up
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- VIII. Signatures

100K€



Application date: 2 September, 2018

Title: **BK-away: A novel, RNA-based anti-viral approach to limit BKV propagation during immunosuppressive therapy following kidney transplantation**

Acronym: BK-away

Applicant, Principal Investigator

Name (M/F)	Eric P van der Veer
Position	Assistant Professor
Name of organization,	Leiden University Medical Center
Department	Internal Medicine (Nephrology)
Address: Name Institute, Department Room number Street name Postal code, Town/City	Leiden University Medical Center Department of Internal Medicine (Nephrology) Room K5.40 Albinusdreef 2 2300RC, Leiden
Telephone	+31 715262500
Email	e.p.van_der_veer@lumc.nl
Researcher Identification (e.g. ResearcherID, ORCID)	https://orcid.org/0000-0002-4324-0181 http://www.eindhovenlaboratory.com/medewerkers/eric-van-der-veer-phd/

Project

Expected start date (ultimately 31-08-2019)	01-04-2019		
Expected end date (ultimately 31-08-2023)	31-03-2023		
Duration in months (max. 48)	48		
	In cash	In kind	Total Percentage
Proposed total budget	€ 925.000	€ 116.250	€ 1.041.250 100%
DKF contribution	€ 250.000	-	€ 250.000
PPS-Allowance	€ 400.000	-	€ 400.000
Contribution private enterprises	€ 275.000	-	(min. 25%)
Contributions Knowledge Institutes	-	€ 116.250	(min. 10%)
Contribution other private parties (if applicable)	-	-	-

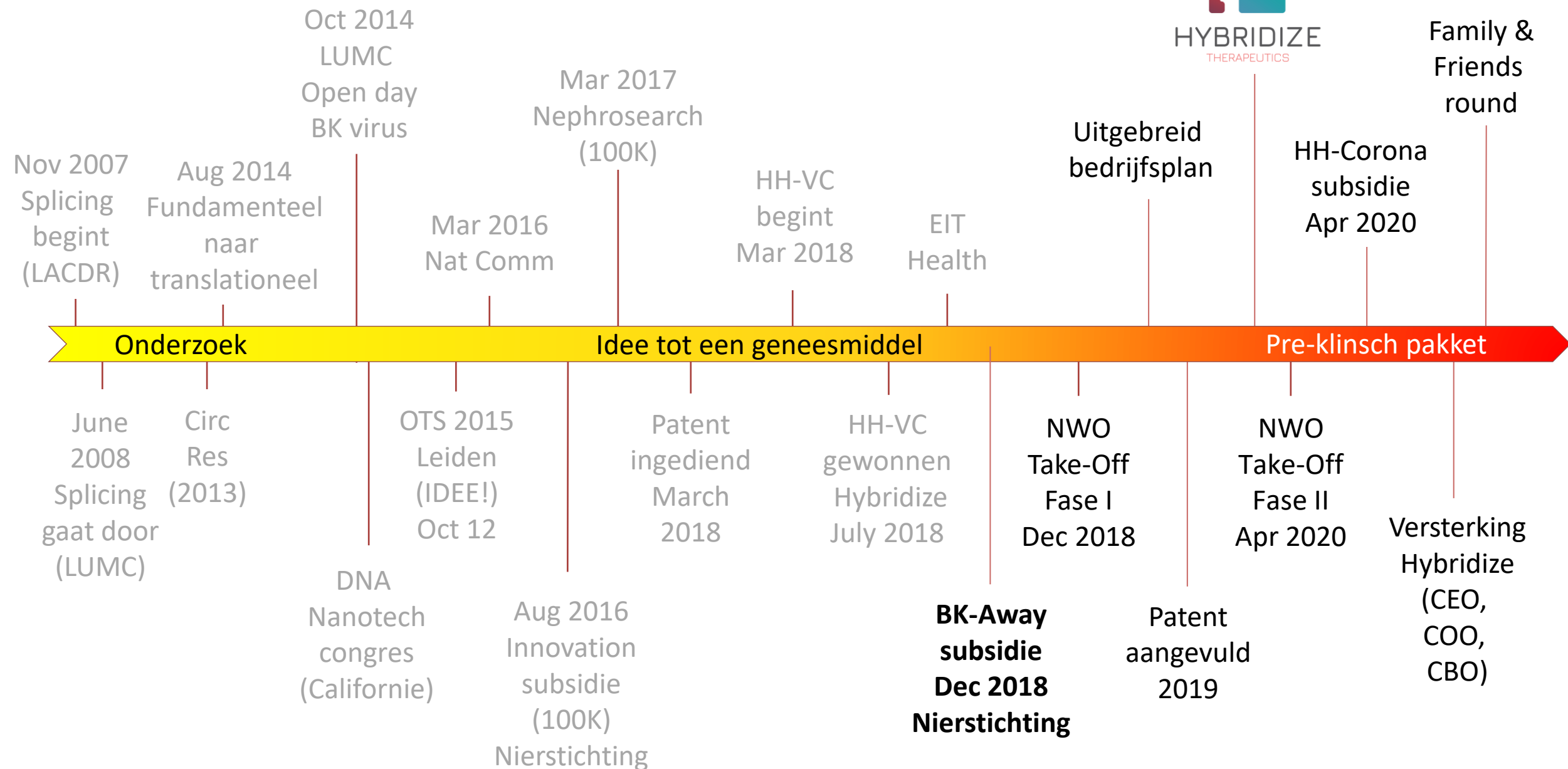
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- VI. Impact and Valorization
- VII. Financial Issues
- VIII. Signatures

1,04M€



HYBRIDIZE
THERAPEUTICS



Wanneer je denkt dat je er bent...: Geneesmiddel nog verder verbeteren!

Strategic Advisory Board



Onno vd Stolpe
(ex-CEO)

Galápagos



Dr. Dinko Valerio
(ex-CEO & Founder)

Crucell



Dr. John Maraganore
(ex-CEO)

Alnylam
PHARMACEUTICALS



Daniel de Boer
(CEO)

ProQR THERAPEUTICS



Dr. James Shannon
(ex-CMO)

gsk
GlaxoSmithKline



Dr. Andre Hoekema
(CBO)

Galápagos



Alison Lawton
(ex-CEO)

Kaleido
BIOSCIENCES



MD Michael Hodges
(ex-CMO)

amplyx

Scientific Advisory Board



Dr. Annemieke Aartsma-
Rus
(Prof. Human Genetics)

Leids Universitair
Medisch Centrum



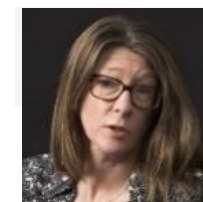
Dr. A.J. van Zonneveld
(Prof. Exp. Vascular Medicine)

Leids Universitair
Medisch Centrum



Dr. Troels Koch
(ex-CTO)

santaris
pharma a/s
RNA Medicines for the 21st Century



Dr. Mariet Feltkamp
(As. Prof. Med. Virology)

Leids Universitair
Medisch Centrum



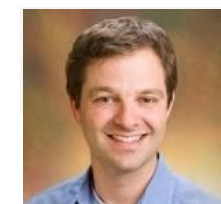
Dr. Gerard Platenburg
(CIO)

ProQR THERAPEUTICS



Dr. Volker Nickleit
(Prof. Nephropathology)

UNC



Dr. Ben Laskin
(As. Prof. Pediatrics)

Washington University in St. Louis
SCHOOL OF MEDICINE

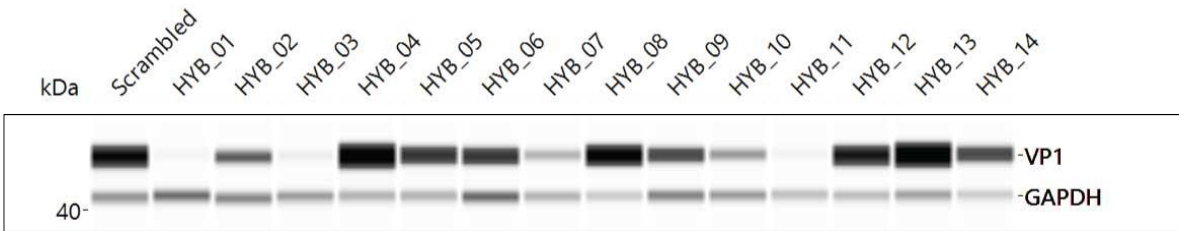
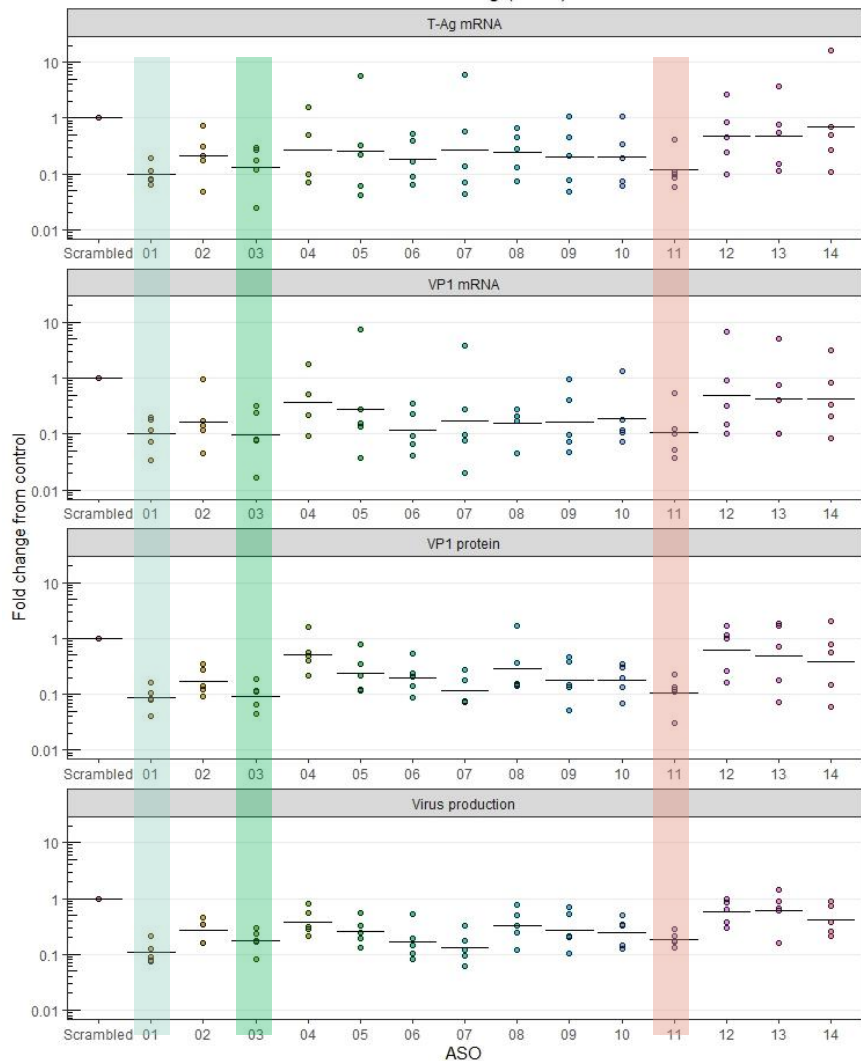


Dr. Jaap Jan Boelens
(Chief HSCT)

Memorial Sloan Kettering
Cancer Center

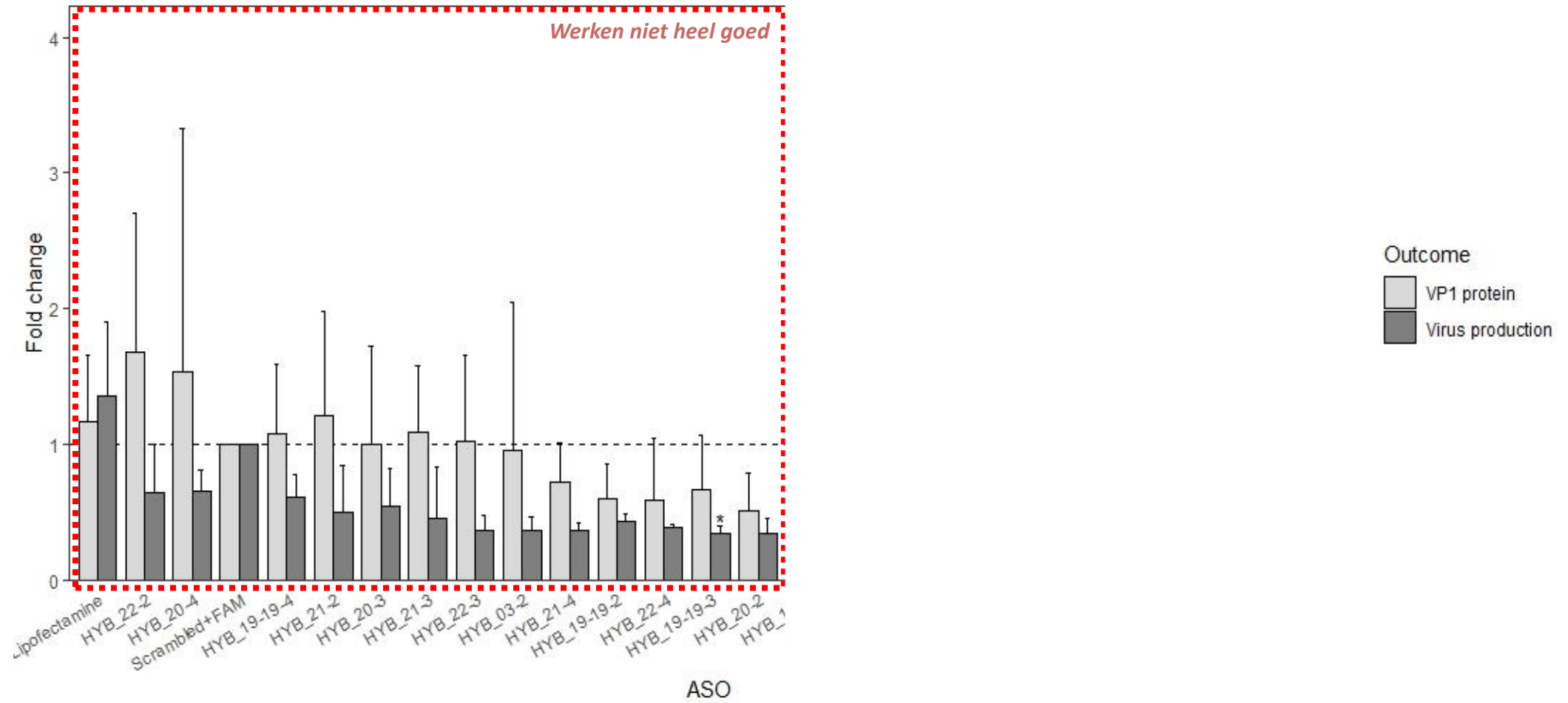
Poging 2 voor verbetering: Terug naar de computer en nieuwe testen van ASOs

Jurrien Prins Janneke Kouwenberg Anouk Spruit Lizanne Daleman



ASO	Mean reduction compared to scrambled control (%)			
	T-Ag mRNA	VP1 mRNA	VP1 protein	Viral DNA
Scrambled	-	-	-	-
HYB_01	90.2	89.8	91.4	89.2
HYB_03	86.8	90.5	90.7	82.6
HYB_11	88.3	89.5	89.6	81.2
HYB_14	30.1	56.8	62.1	57.9

Nog verder sleutelen: De zoektocht naar maximale remming van BK virus



Heel belangrijk: Bewijs dat je geneesmiddel werkt zoals je denkt dat het werkt!



*pRP cells constitutively express the BKV early coding region mRNA as these mouse fibroblasts have been stably transformed with the BKV early coding region DNA. This is evidenced by abundant expression of the large T (product 1) and small t antigen mRNAs (product 3) (Negrini, M. et al., Cancer Research, 1992)

Geld: De constant zoektocht naar investeerders!

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Version 8 December 2015

Dutch Kidney Foundation
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Telephone +71 5268135
E-mail e.p.van_der_veer@lumc.nl

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1

100K€



Application date: 2 September, 2018

Title: **BK-away: A novel, RNA-based anti-viral approach to limit BKV propagation during immunosuppressive therapy following kidney transplantation**

Acronym: BK-away

Applicant, Principal Investigator

Name (M/F)	Eric P van der Veer
Position	Assistant Professor
Name of organization,	Leiden University Medical Center
Department	Internal Medicine (Nephrology)
Address: Name Institute, Department Room number Street name Postal code, Town/City	Leiden University Medical Center Department of Internal Medicine (Nephrology) Room K5.40 Albinusdreef 2 2300RC, Leiden
Telephone	+31 715262500
Email	e.p.van_der_veer@lumc.nl
Researcher Identification (e.g. ResearcherID, ORCID)	https://orcid.org/0000-0002-4324-0181 http://www.eindhovenlaboratory.com/medewerkers/eric-van-der-veer-phd/

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1,04M€



AiCuris: Een geweldige partner om mee samen ons geneesmiddel naar de patient te brengen

AiCuris and Hybridize sign licence agreement for BK virus therapy

According to the agreement, Hybridize is eligible to receive upfront, milestone and royalty payments from AiCuris.

February 10, 2022

Share <



Hybridize's BKV programme is based on a new RNA-based treatment approach. Credit: © Hybridize Therapeutics.



Vervolg traject na uitlicenseren: Vele stappen naar klinische studies

Program
Kidney virus



Een frisse wind: Een nieuwe locatie om verder te groeien

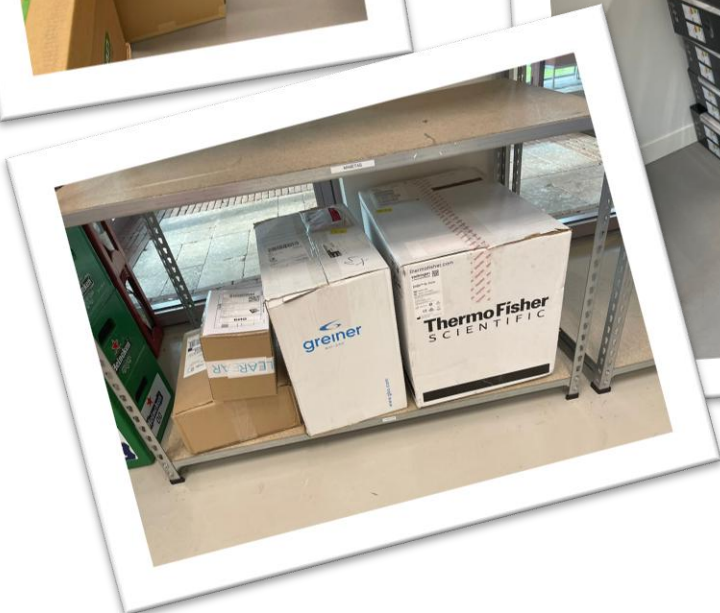
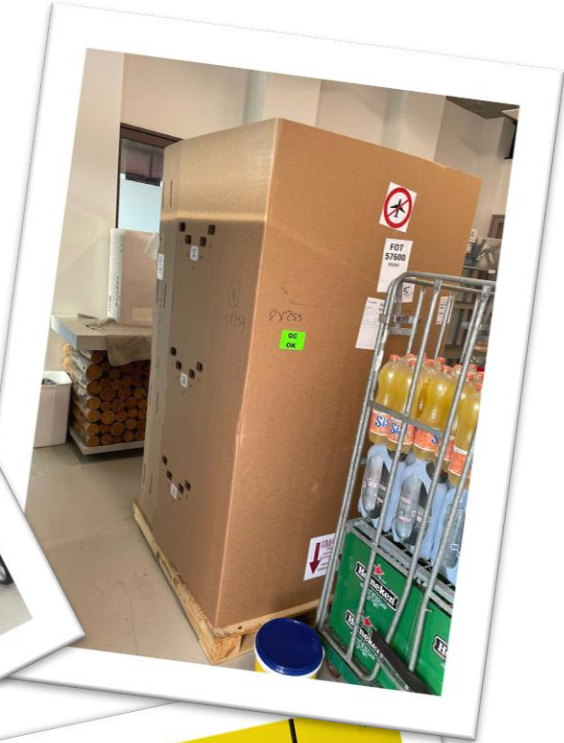
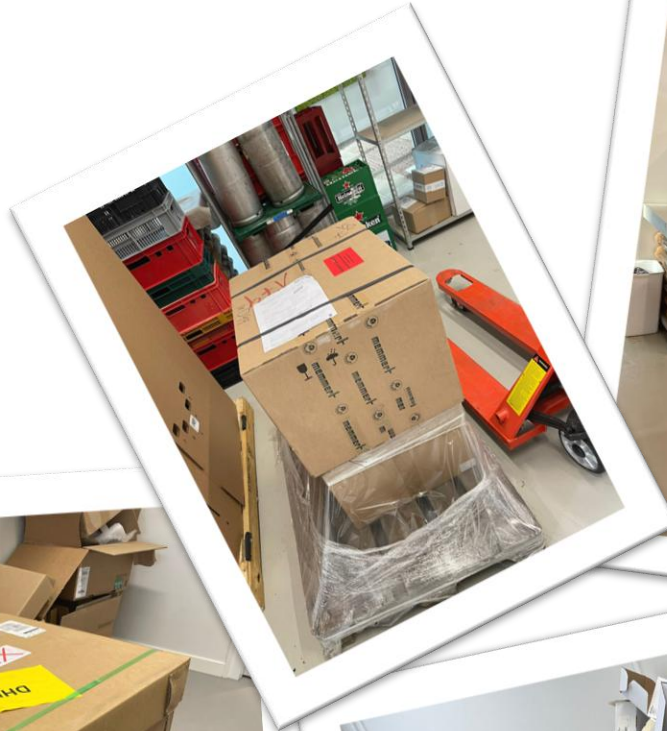
LUMC



Biopartner 5



Dozen, dozen, en meer dozen...en vertraging!



Complexe omschakeling: Van 'Academisch Onderzoek' naar 'Pharma deugdelijkheid'

New team

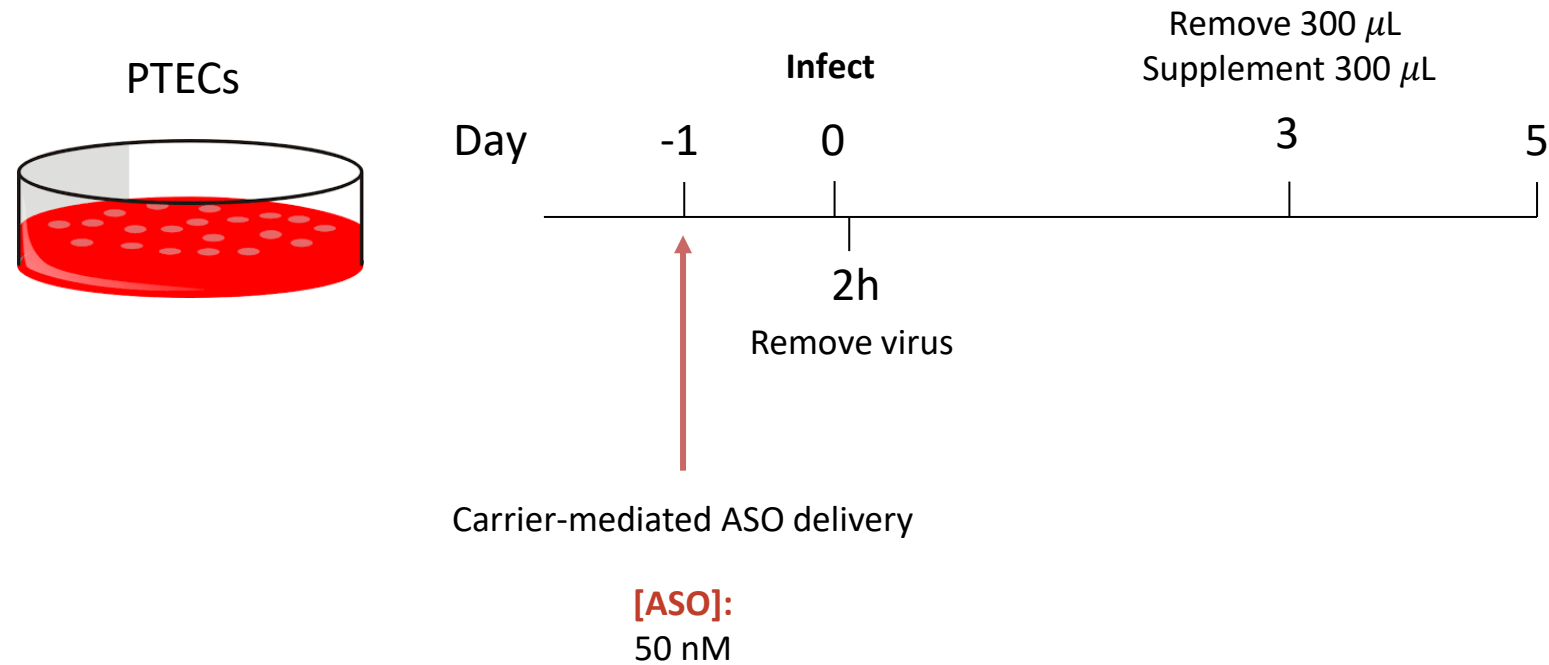


 Jurrien Prins

New partner



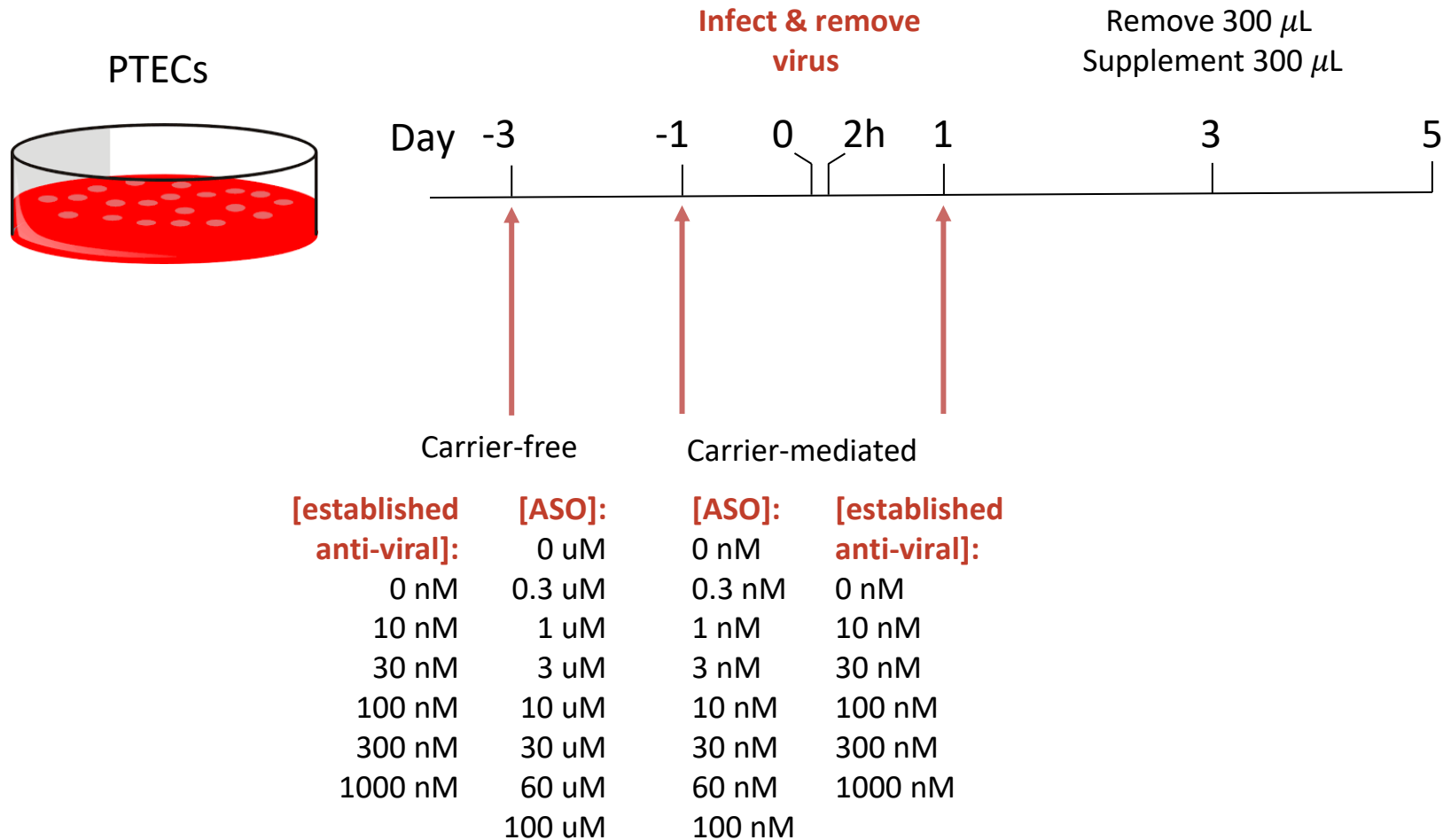
Academisch experimenten: Bewijs genereren dat ons geneesmiddel werkt



Activity readouts:

1. Protein -> VP1 expression
2. Virus DNA
3. Infectious virus (our method)

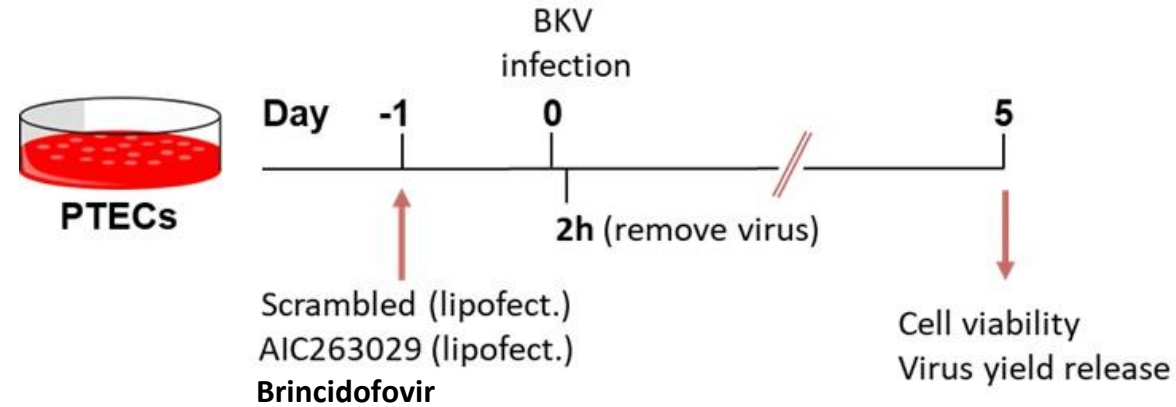
Pharma experimenten: Uitvoerig bewijs genereren dat het geneesmiddel werkt



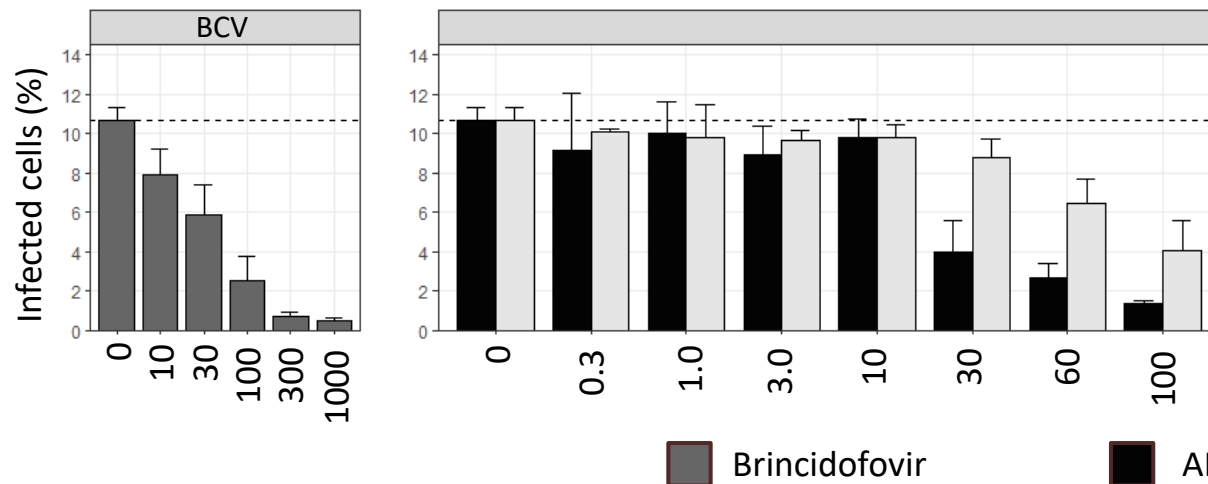
Activity readouts:

1. HELISA -> intracellular [ASO]
2. Cell viability
3. Protein -> VP1 expression
4. Virus DNA
5. Infectious virus

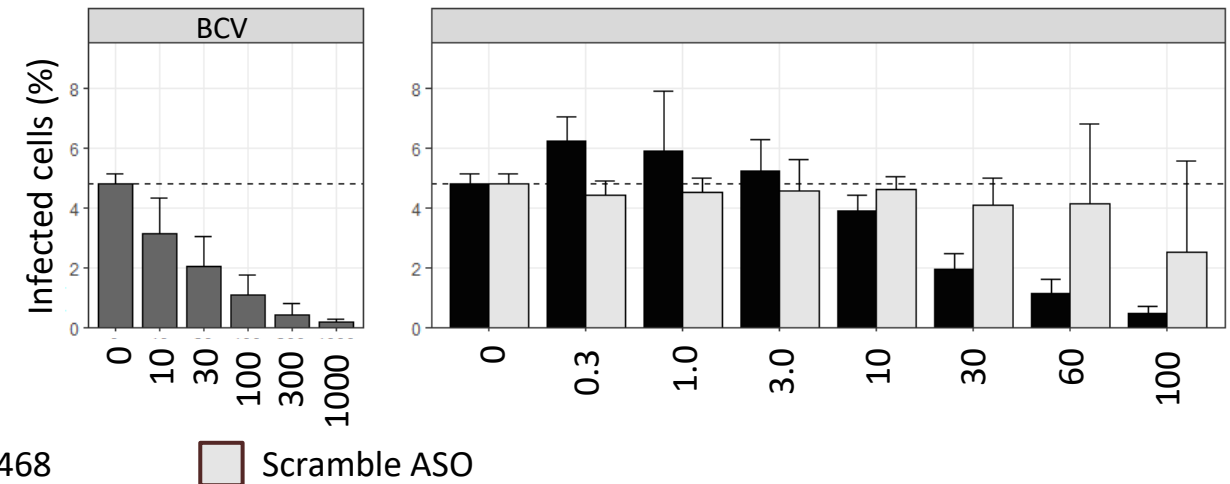
Complexe omschakeling: Van 'Academisch Onderzoek' naar 'Pharma deugdelijkheid'



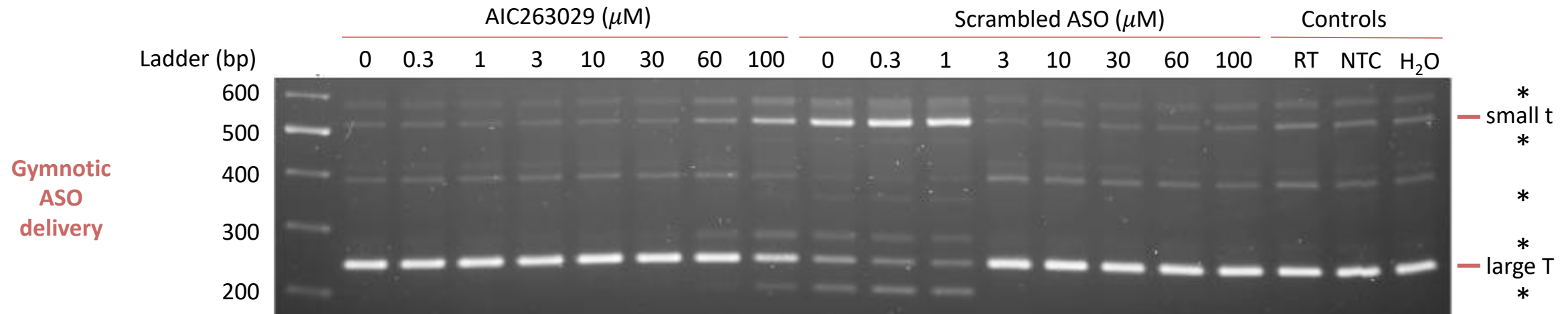
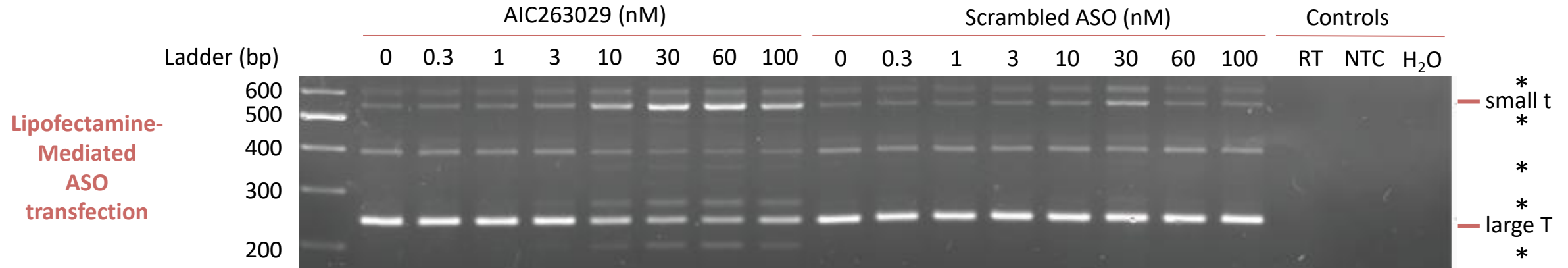
Large T Antigen positive cells (biological n=5)



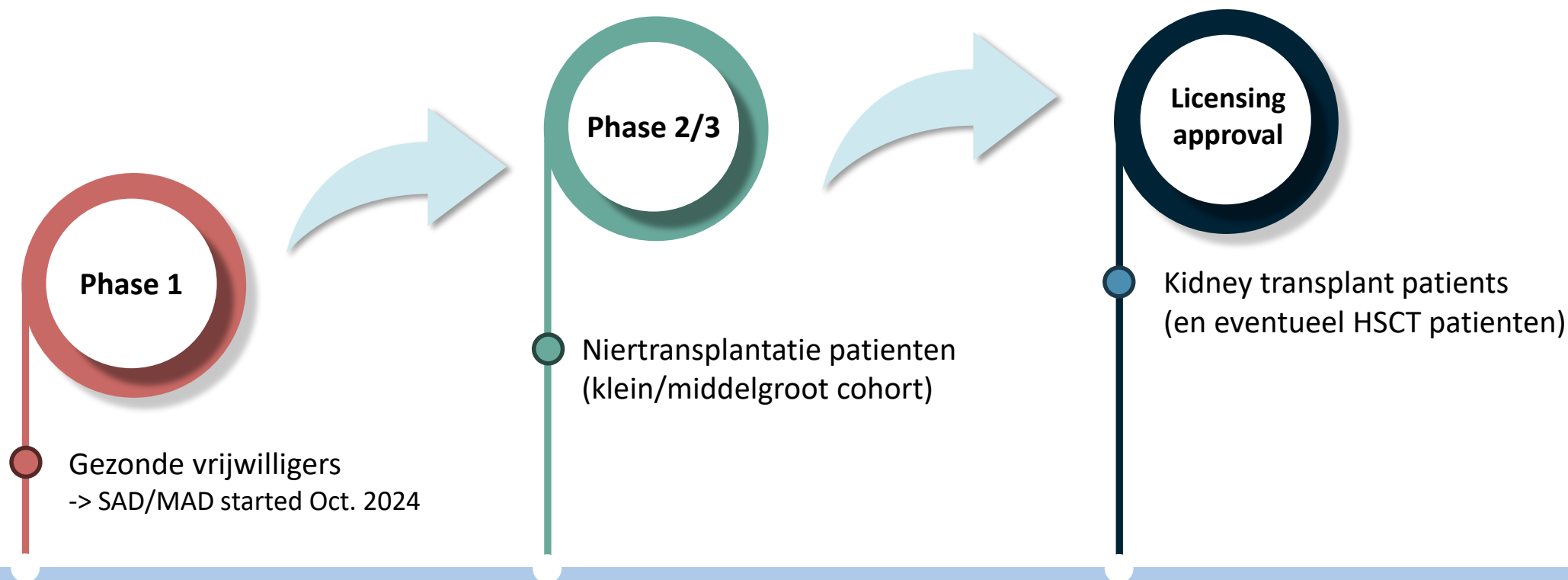
VP1 positive cells (biological n=5)



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Klinisch Programma en perspectief



Klinisch: Toekomst: Fase 1 klinische studie in Oktober 2024 gestart
Fase 2 / 3 studies in niertransplantatie patienten worden gepland

Een waardevolle reis: Een idee is een geneesmiddel geworden

1. **Durf:** Anders te denken
2. **Durf:** Een uitstap te maken wat geen garantie voor de toekomst met zich meebrengt
3. **Durf:** Alles op alles te zetten om een doel voor ogen te realiseren
4. **Droom:** Dat patienten nooit meer last hebben van BK virus na een niertransplantatie

Ons team (2024):

Hybridize leadership team



Eline van Beest
(CEO)



Dr. Eric vd Veer
(CIO & Founder)



Prof. Dr. Tim Johnson
(CSO)



Alex Mentink
(Chief of Staff / BD)



Dr. Jessica Sipkens
(COO)



Dr. Miranda de Jager
(Head of CMC)



Patricia Biasutto
(Head of Translational Science)



Hybridize lab team



Dr. Falk Wachowius
(Sr. Scientist)



Barbara Cambi
(Scientist)



Iris van Wissen
(Researcher)



Chaja Hudepol
(Researcher)



Jurrien Prins
(Scientist)



Dr. Rob de Jong
(Principal technician)



Janneke Kouwenberg
(Researcher)



Loes Wiersma
(Scientist)



Een zeer grote dank aan onze 'Partner' and 'VRIENDEN' bij AiCuris



- Larry Edwards (Chief Executive Officer)
- Cynthia Wat (Chief Operating Officer)
- Jacques Dumas (Chief Scientific Officer)
- Holger Zimmermann (Chief Research and Development Officer)
- Tamara Pfaff (Head of Pre-Clinical Development)
- Peter Lischka (Senior Director Virology)
- Susanne Bonsmann (Associate Director – Laboratory Head Pharmacokinetics)
- Marouane Zarrouk (BKV Project Lead)
- Andreas Kühbacher (Senior Manager Innovation and Alliance)
- Silvia Riffel-Friedrich (Head of Regulatory Affairs)
- Helmut Buschmann (Head of CMC)
- Dr. Alexander Birkmann (Head of Project, Portfolio Management and Strategy)
- Sabrina Kuttruff-Coqui (Chief Financial Officer)
- and many more...