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Virus-like particle vaccines against BK and JC polyomaviruses

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Diana V. Pastrana, Alberto Peretti, Eileen M. Geoghegan, and Christopher B. Buck, "Virus-like particle vaccines against BK and JC polyomaviruses" in "Vaccine Technology VII", Amine Kamen, McGill University Tarit Mukhopadhyay, University College London Nathalie Garcon, Bioaster Charles Lutsch, Sanofi Pasteur Eds, ECI Symposium Series, (2018). http://dc.engconfintl.org/vt_vii/135

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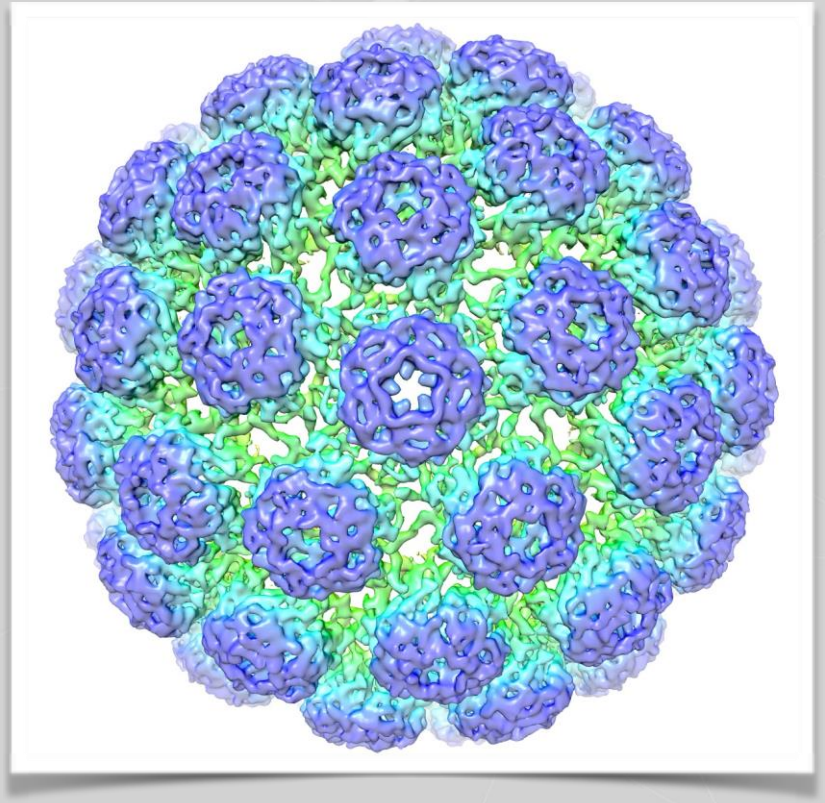
NATIONAL CANCER INSTITUTE

Virus-like particle vaccines Against BK and JC polyomaviruses

Diana V. Pastrana
Buck Lab
National Cancer Institute, NIH, USA

Human Polyomaviruses

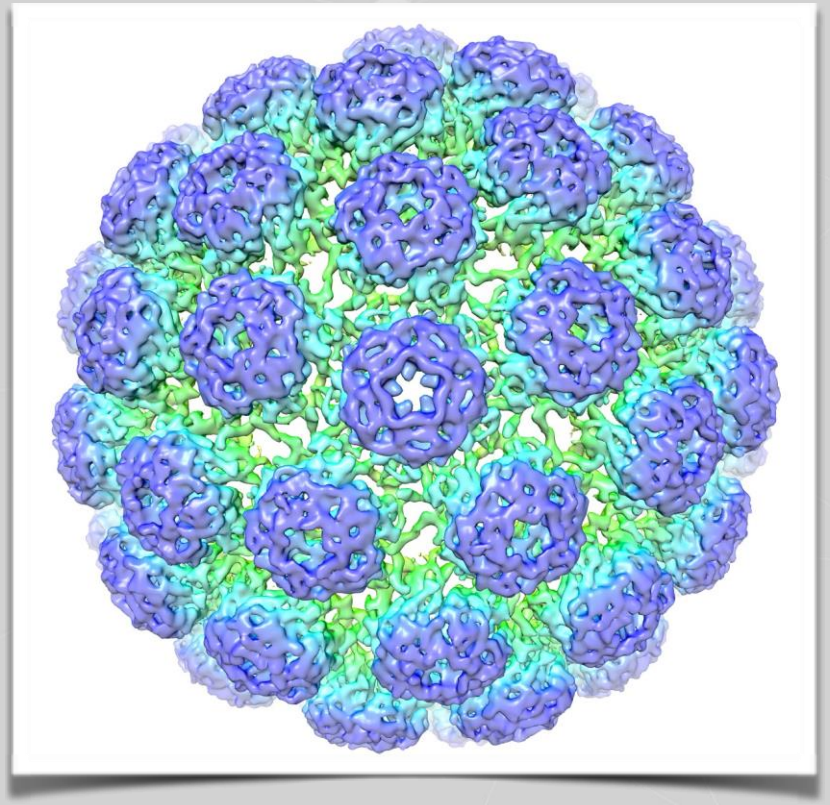
- Poly + Oma = “Many Tumors”
- 11 human polyomavirus types
- Lifelong infection is common and generally asymptomatic, but…



BK polyomavirus (BKV)

Human Polyomaviruses

- Poly + Oma = “Many Tumors”
- 11 human polyomavirus types
- Lifelong infection is common and generally asymptomatic, but…
- **BKV present in transplanted organs causes kidney and bladder damage**



BK polyomavirus (BKV)

- **JCV causes brain disease (PML) in immunosuppressed patients**

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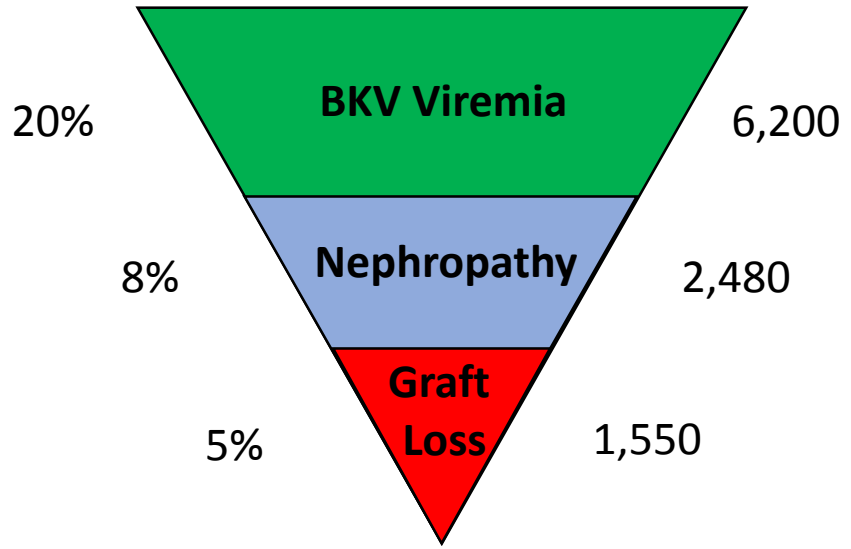
Kidney Damage After Solid Organ Transplantation

techtransfer.cancer.gov

Market Landscape (US)

Number of KTR in 2016 (US): 31,000

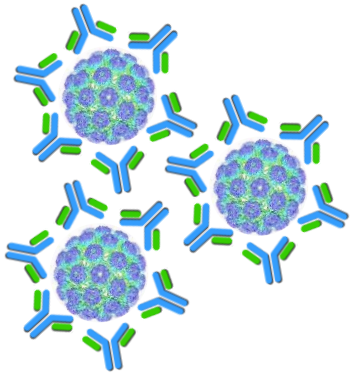


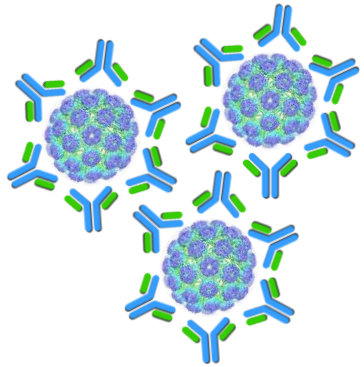
- **Each day, four US kidney transplant recipients lose their graft due to BKV**

US Market Landscape (Post-Transplant Nephropathy)

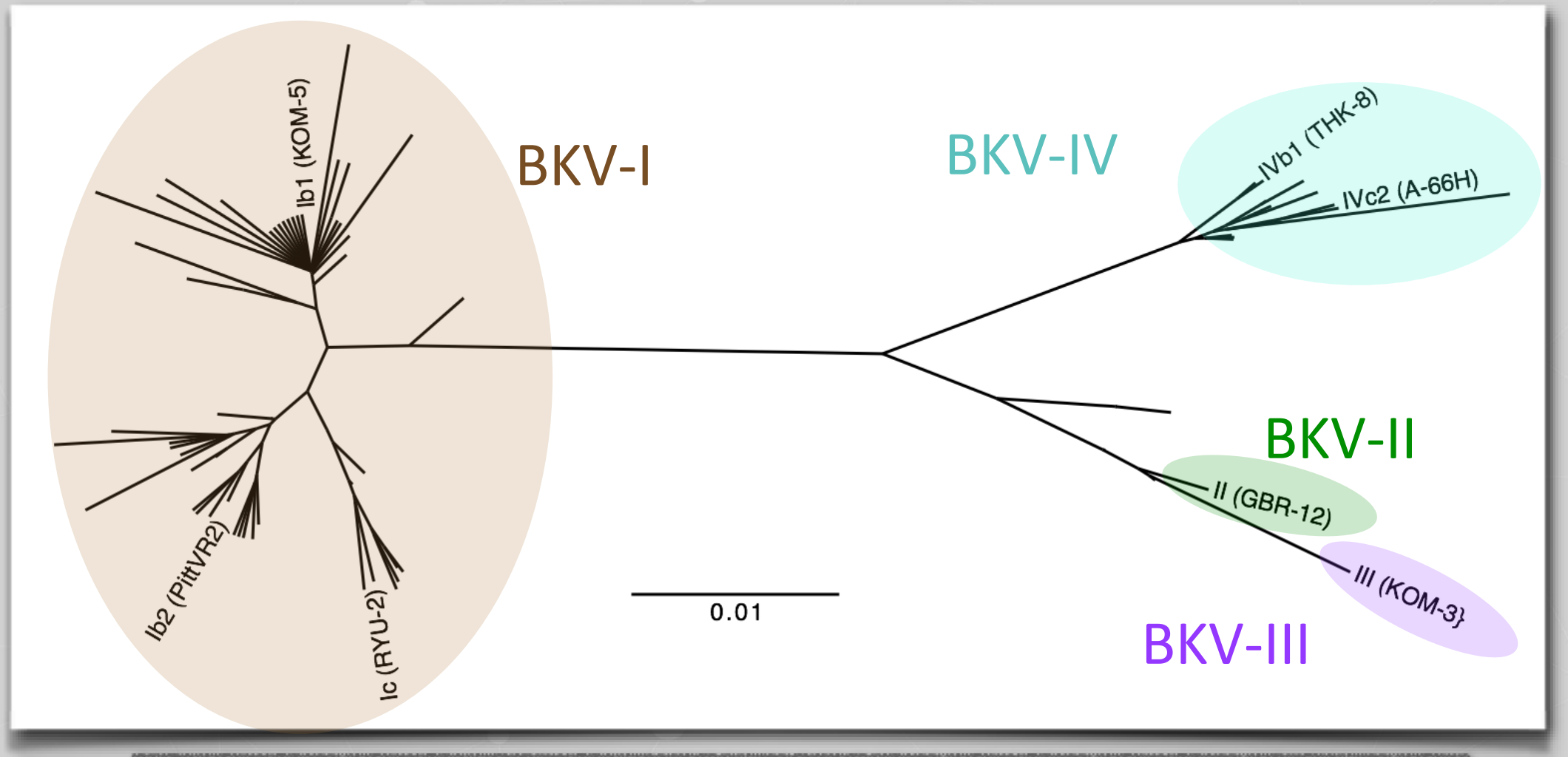
Current treatment costs attributable to BKV

$700 Million





BKV Neutralization Serotypes



Phylogenetic tree (major capsid protein VP1)

Neutralizing Antibodies Are Protective

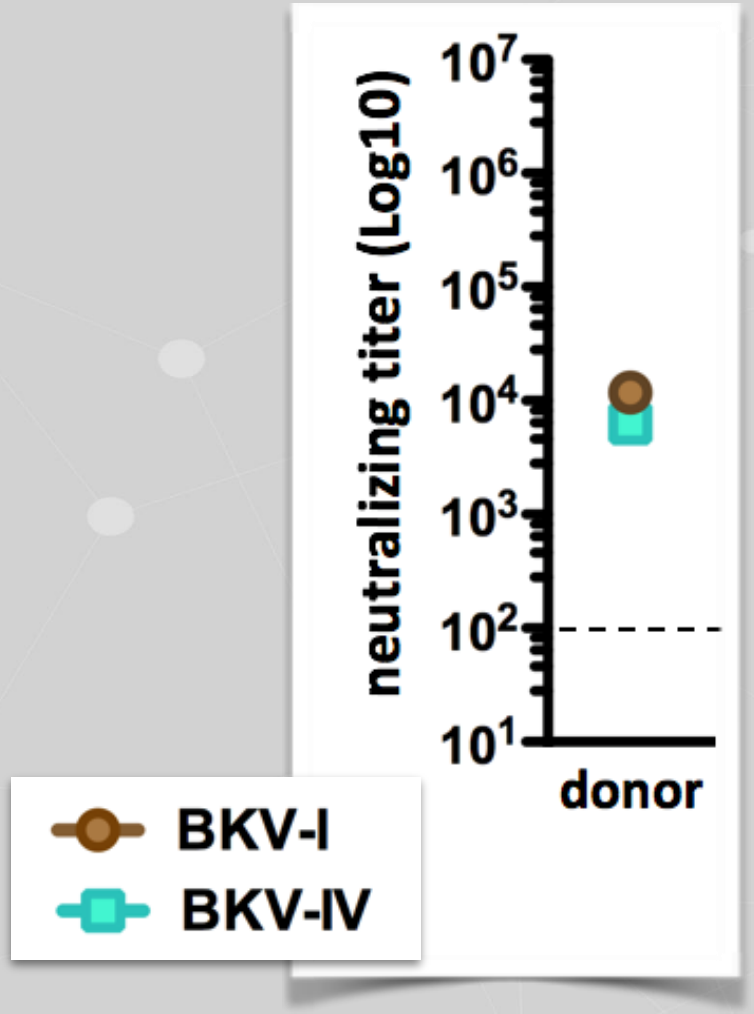
CLINICAL RESEARCH www.jasn.org

Neutralizing Antibody–Mediated Response and Risk of BK Virus–Associated Nephropathy

Morgane Solis,*† Aurélie Velay,*† Raphaël Porcher,‡ Pilar Domingo-Calap,† Eric Soulier,† Mélanie Joly,†§ Mariam Meddeb,* Wallys Kack-Kack,* Bruno Moulin,†§ Siamak Bahram,† Françoise Stoll-Keller,*† Heidi Barth,*† Sophie Caillard,†§ and Samira Fafi-Kremer*†

- "A neutralizing antibody titer against the donor's strain **<10,000** before transplant significantly associate with BKV replication after transplant"

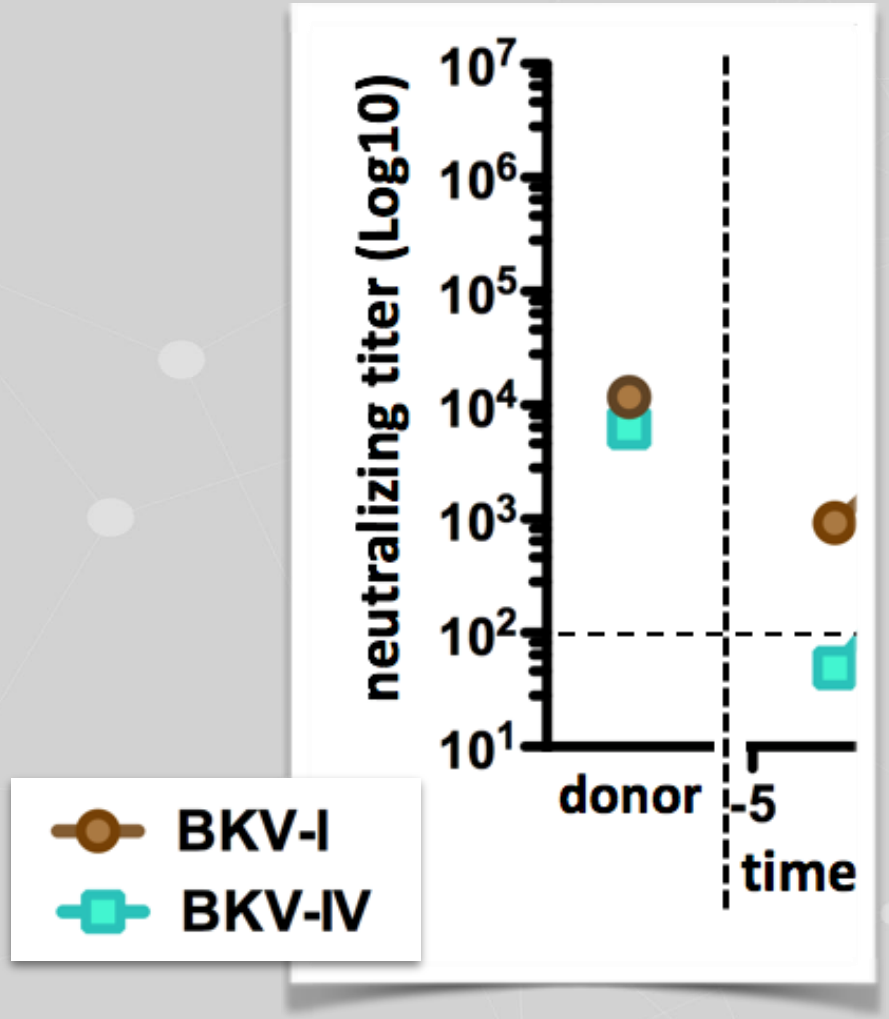
Case Study – BKV nephropathy



- Kidney donor was co-infected with BKV-I and BKV-IV

Peretti et al, 2018 *Cell Host & Microbe*

Case Study – BKV nephropathy



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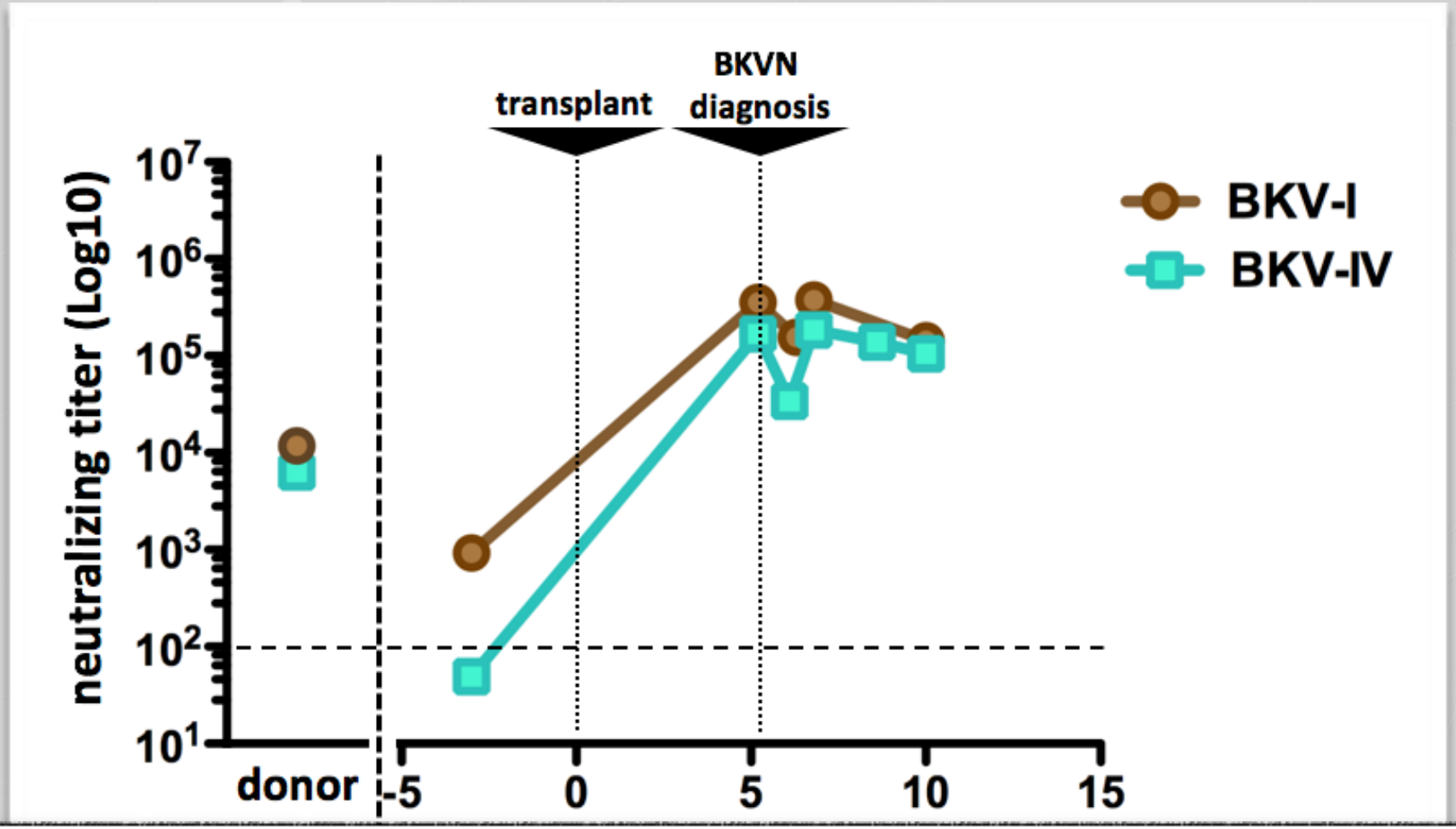
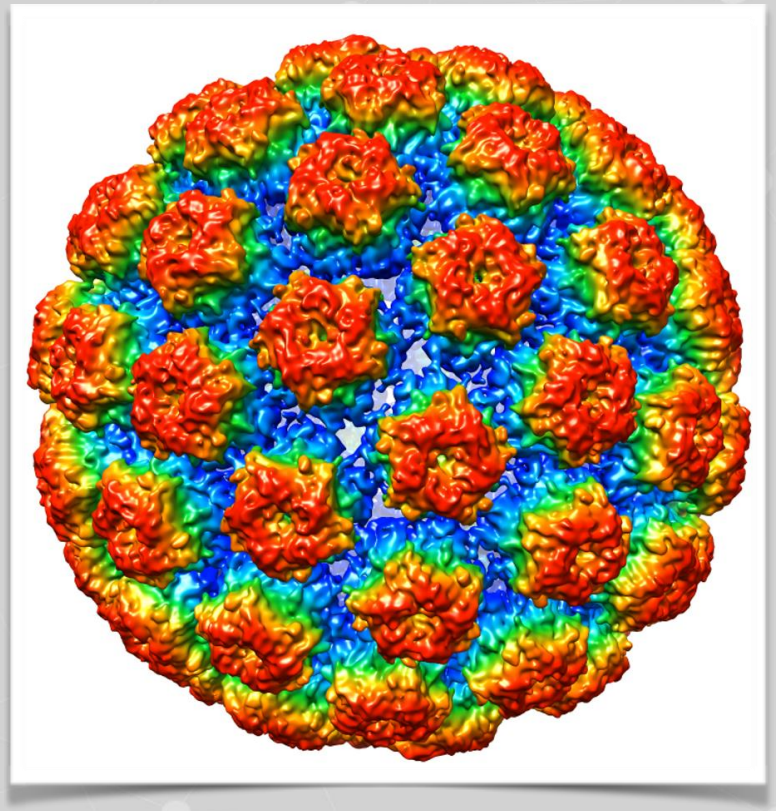
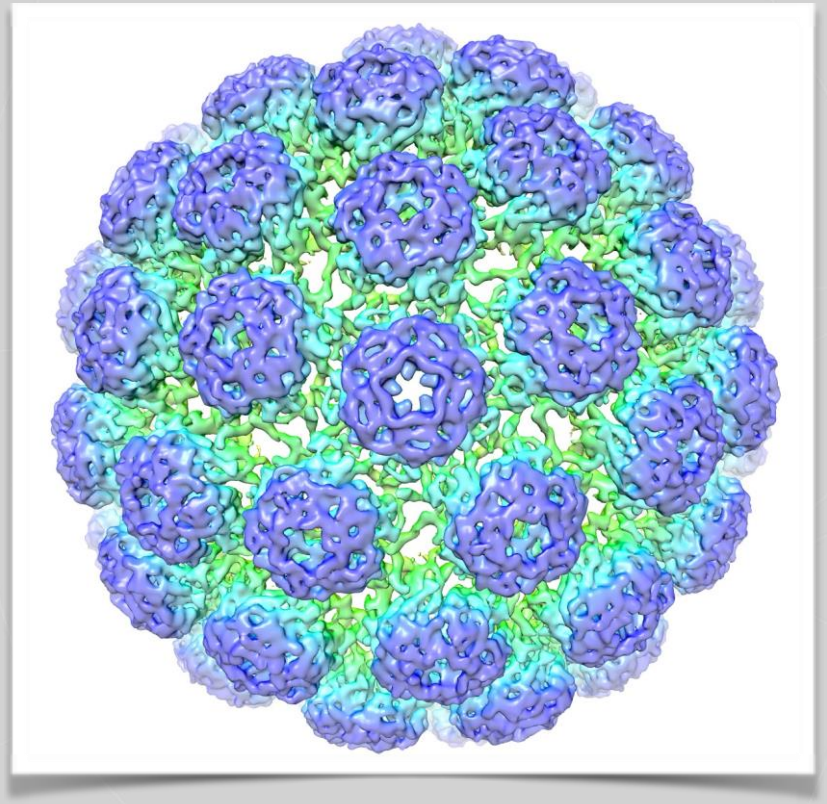


- BKV-IV "hitchhiked" in the donor kidney

Polyomaviruses Also Form VLPs



Papillomavirus

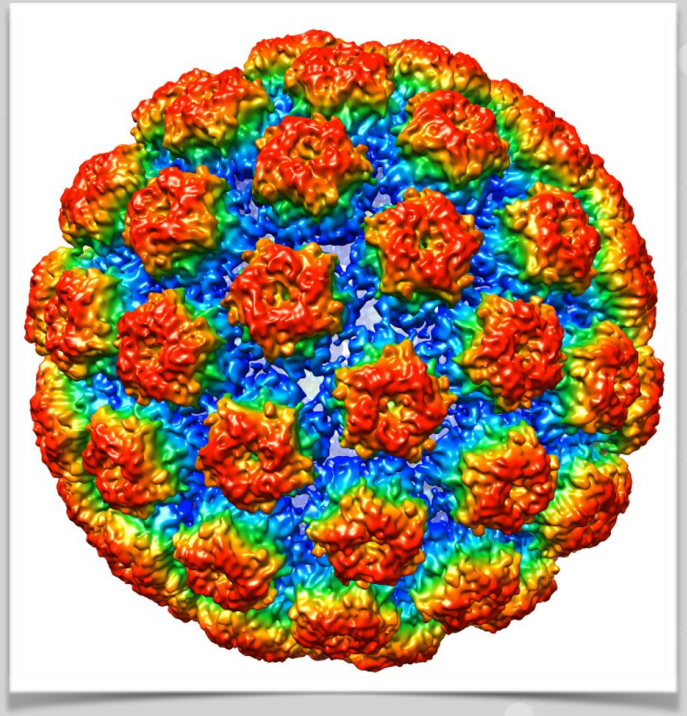


Polyomavirus

Lessons of the HPV Vaccine

- Recombinant HPV virus-like particles (VLPs) are extraordinarily effective for eliciting durable high-titer neutralizing antibody responses that effectively protect vaccinees against HPV diseases

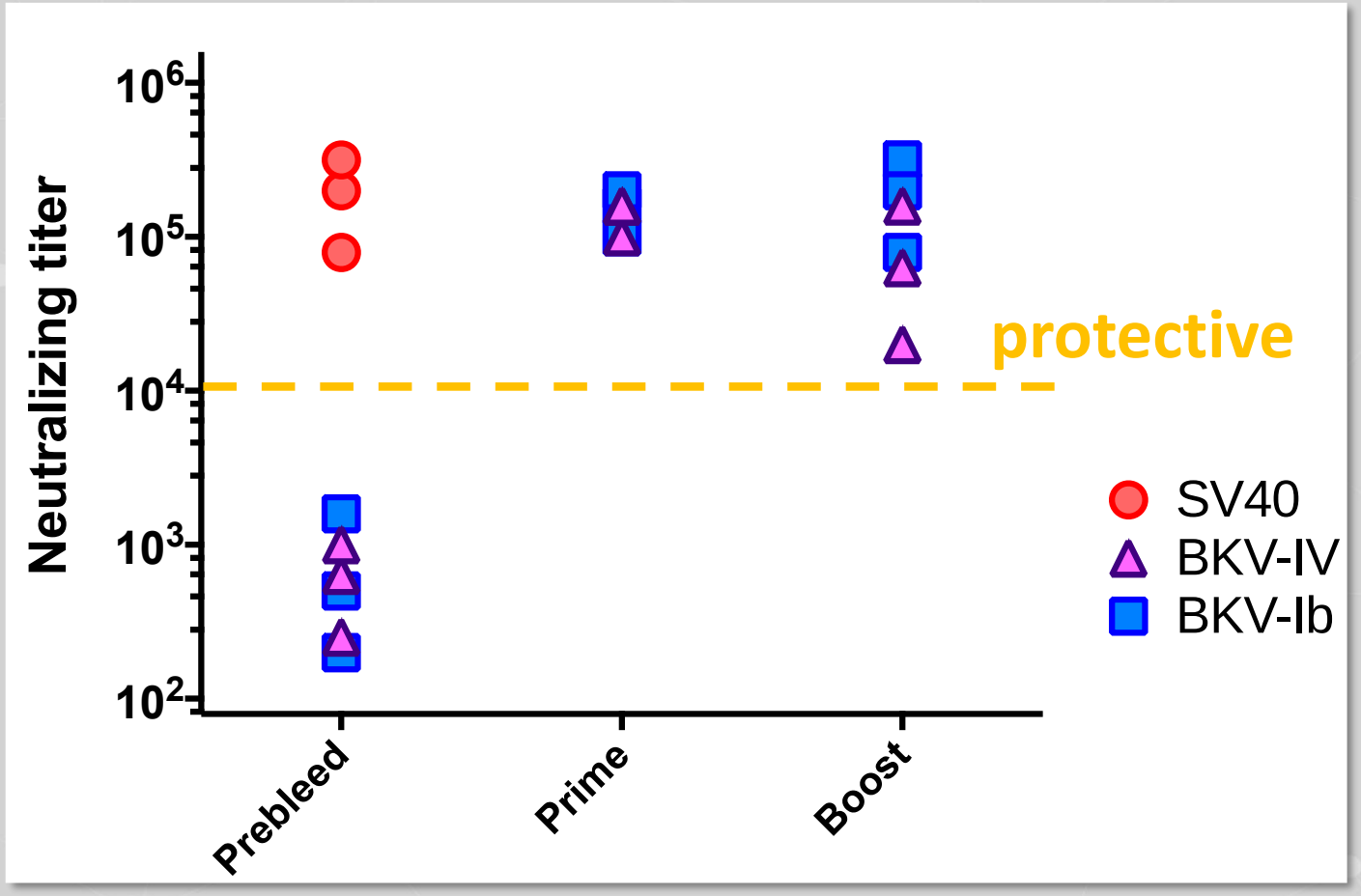
John Schiller
Doug Lowy



Papillomavirus (HPV16)

Excellent Immunogenicity in Monkeys

- **Polyomavirus VLPs induce protective neutralizing antibody responses in monkeys after a single dose**

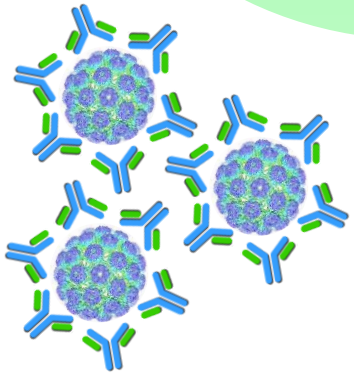


Monkeys immunized with BKV-IV VLPs

US Market Landscape (Post-Transplant Nephropathy)

Current treatment costs attributable to BKV

$700 Million



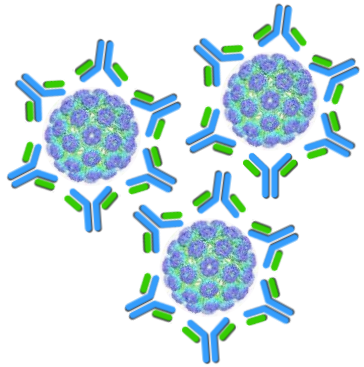
<u>BKV vaccine</u>

$10k? x 30k patients

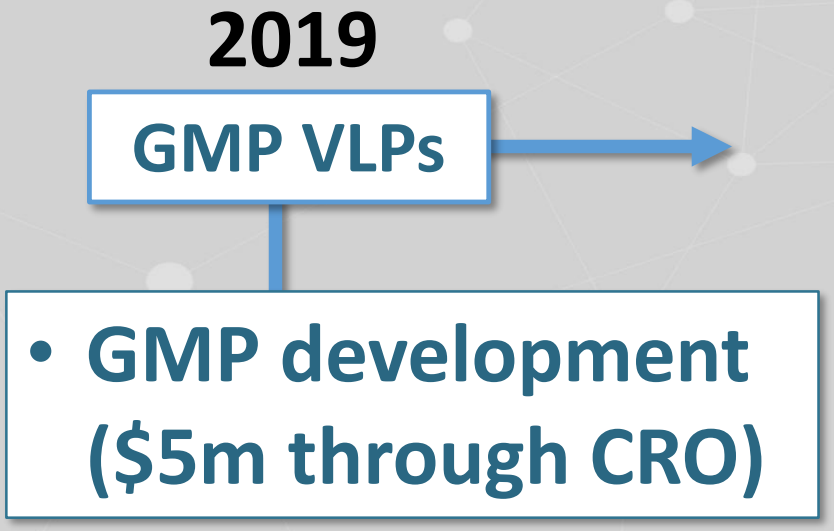
$300? Million

Anything less than

$700!!!



The Path to Market (Post-Transplant Kidney Damage)



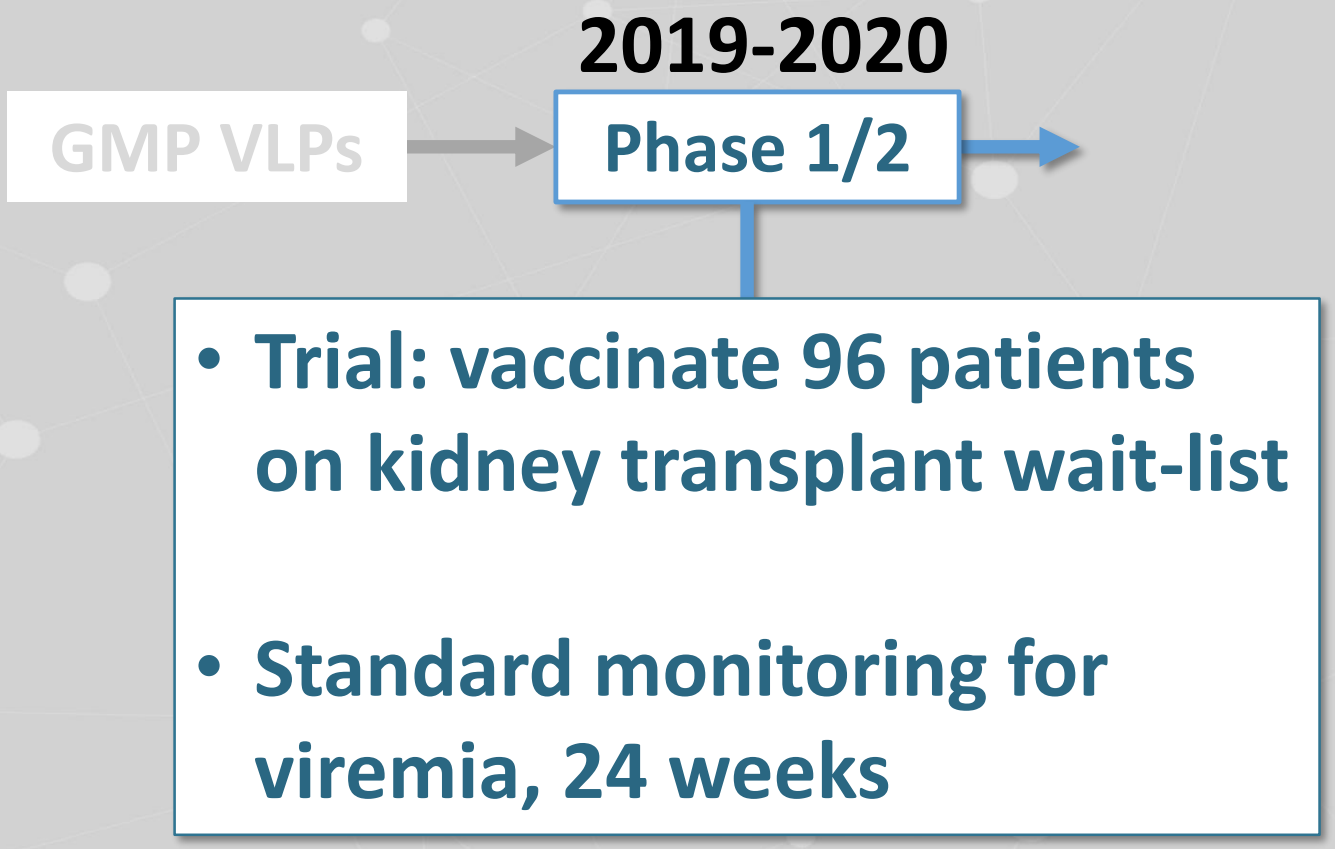
The Path to Market (Post-Transplant Kidney Damage)

2019

GMP VLPs

- **GMP development ($5m through CRO)**
- **NCI assistance (application in process)**

The Path to Market (Post-Transplant Kidney Damage)



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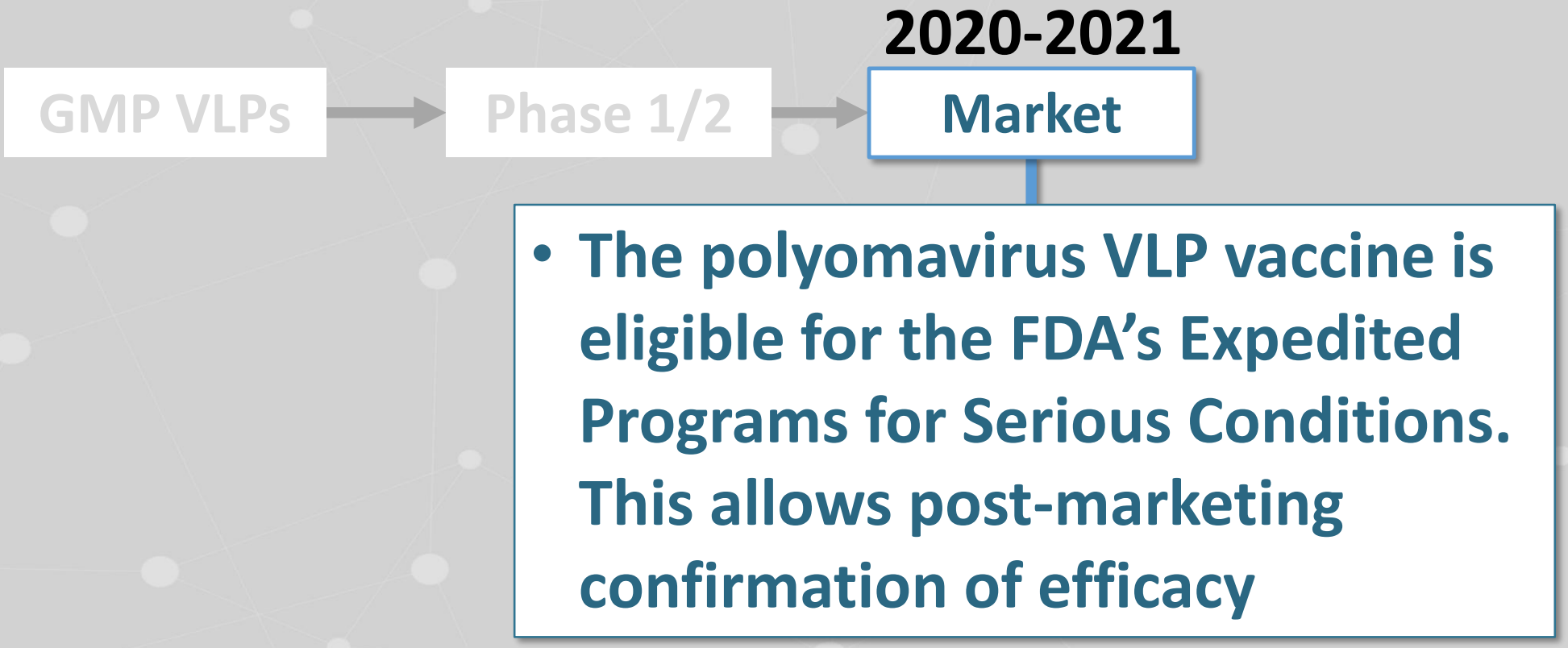

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Brain Disease (PML) in immunosuppression

Brain Disease (PML)

- **The PROBLEM:**
  - Polyomaviruses (JCV) causes a brain disease called progressive multifocal leukoencephalopathy (PML). AIDS patients and individuals taking many types of immunosuppressive therapies are at high risk

Best-Selling Drugs 2016

Rank	Tradename	Generic	2016 sales ($b)	FDA-reported PML cases
1	Humira	adalimumab	16	83
2	Sovaldi/Harvoni	sofosbuvir	9	1
3	Enbrel	etanercept	9	73
4	Rituxan	rituximab	9	413
5	Remicade	infliximab	8	113

PML black box warning

Other Drugs with Black Box PML Warning

Tradename	Generic	2016 sales ($b)	FDA-reported PML cases
Tysabri	natalizumab	2	4332
Raptiva	efalizumab	0	27
Myfortic	mycophenolic acid	0.09	13
Adcetris	brentuximab vedotin	0.07	25
Entyvio	vedolizumab	1.4	0

ehealthme.com
genengnews.com

Other Drugs with Black Box PML Warning

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		0	27
		0.09	13
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About a third of MS patients who want Tysabri are turned away due to PML risk stratification

ehealthme.com
genengnews.com

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License revoked

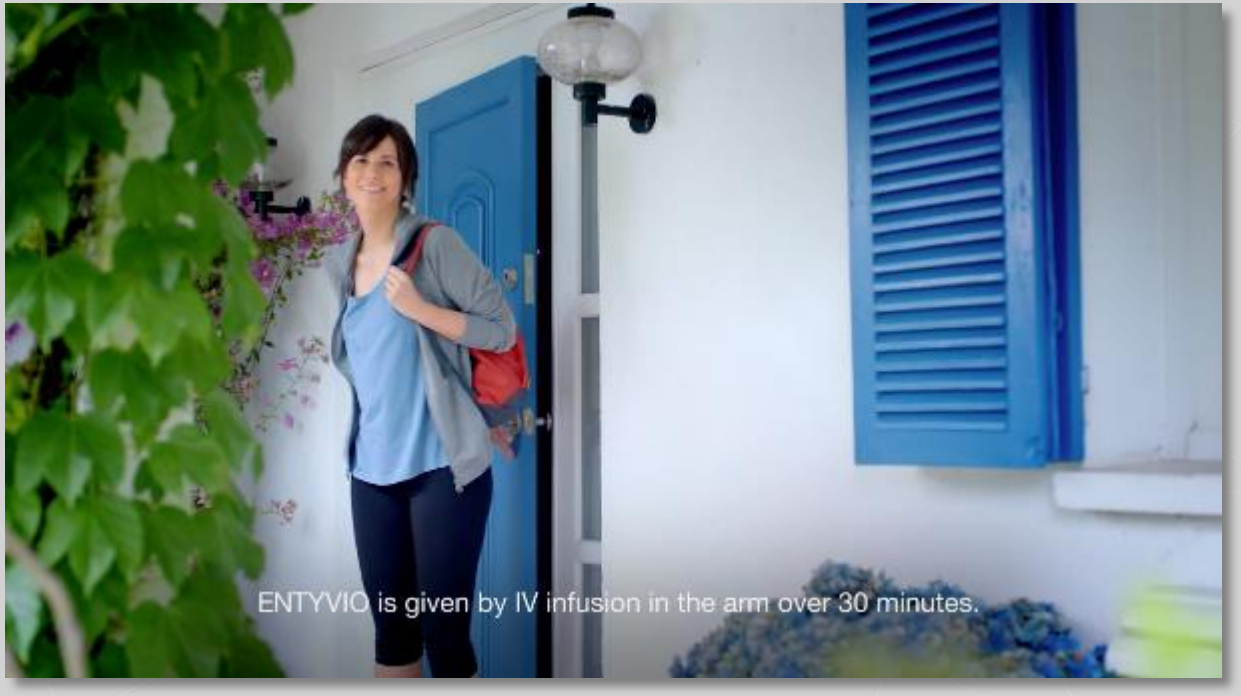
ehealthme.com
genengnews.com

PML Side-Effects Cast a Long Shadow

Entyvio TV ad: “While not reported with Entyvio, PML - a rare serious brain infection - may be possible…”

Ultimate Market

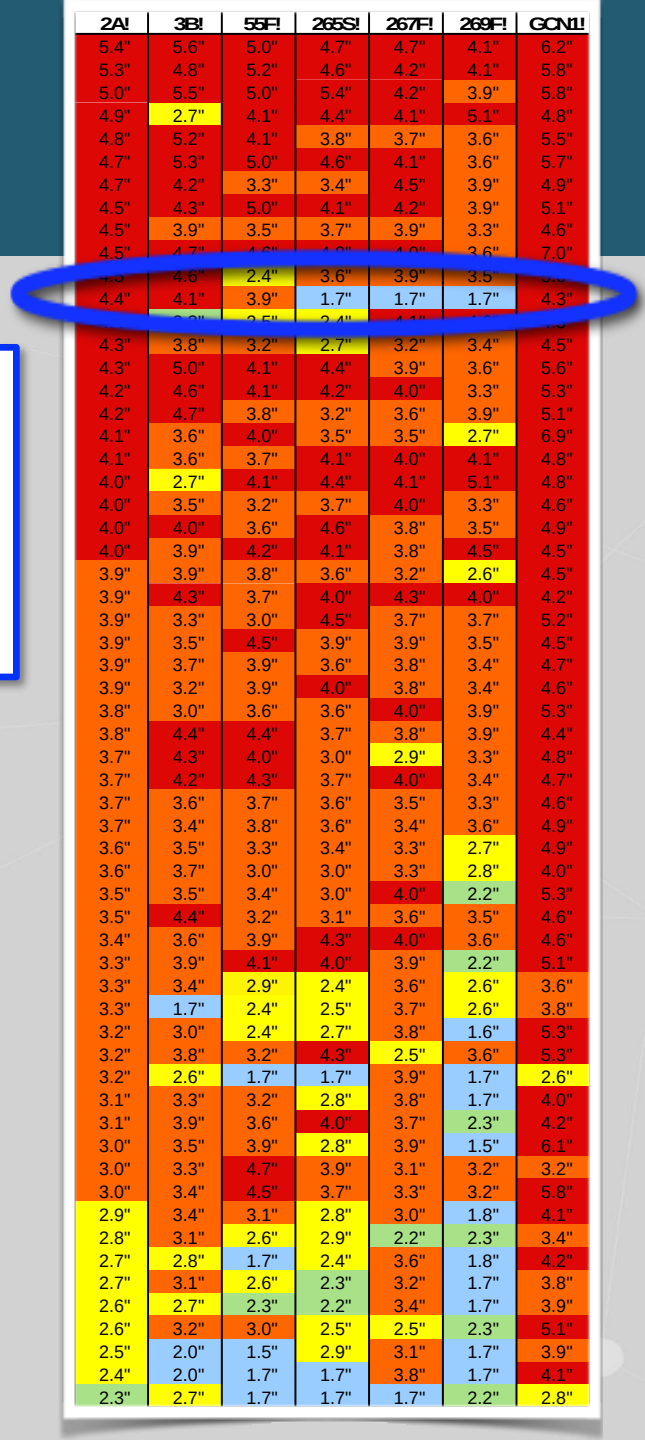
- Co-therapy for patients taking Tysabri, Rituxan, Entyvio, and many other high-grossing immunosuppressive therapies. 20-50 million Americans have autoimmune disorders treatable with these therapies
- People living with HIV



http://bioethicsbulletin.org/archive/how-many-americans-are-immunocompromised

A Lack of Neutralizing Antibodies

Some healthy adults who robustly neutralize w.t. JCV fail to neutralize some PML mutant JCVs. Neutralizing “blind spot” effect



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2.7"	2.8"	1.7"	2.4"	3.6"	1.8"	4.2"
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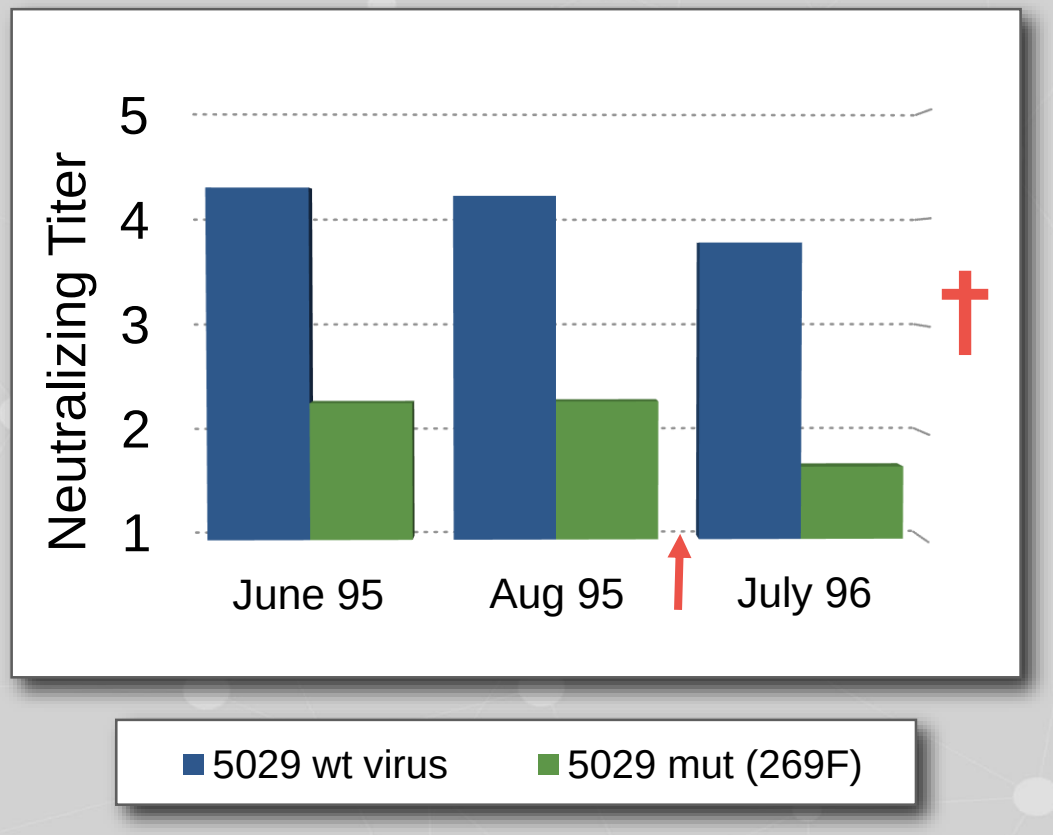
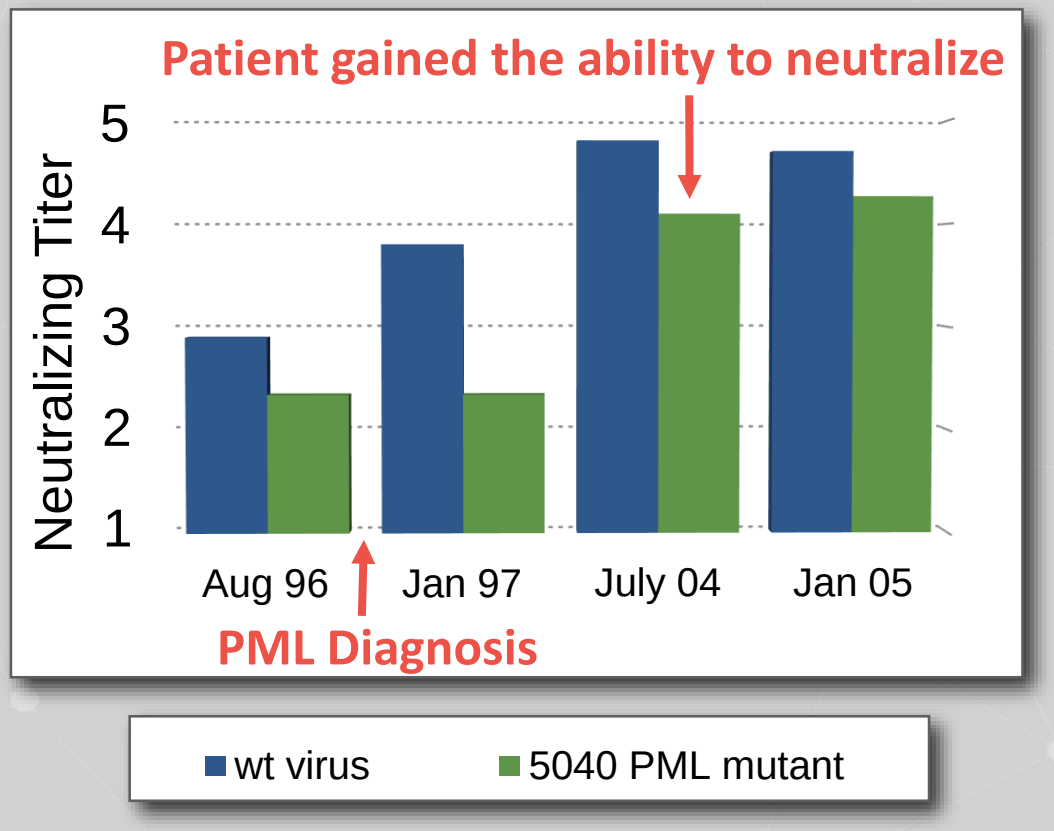
PML: A Lack of Neutralizing Antibodies

PML Patient 5029 (Progressor)



PML Patient 5040 (Survivor)



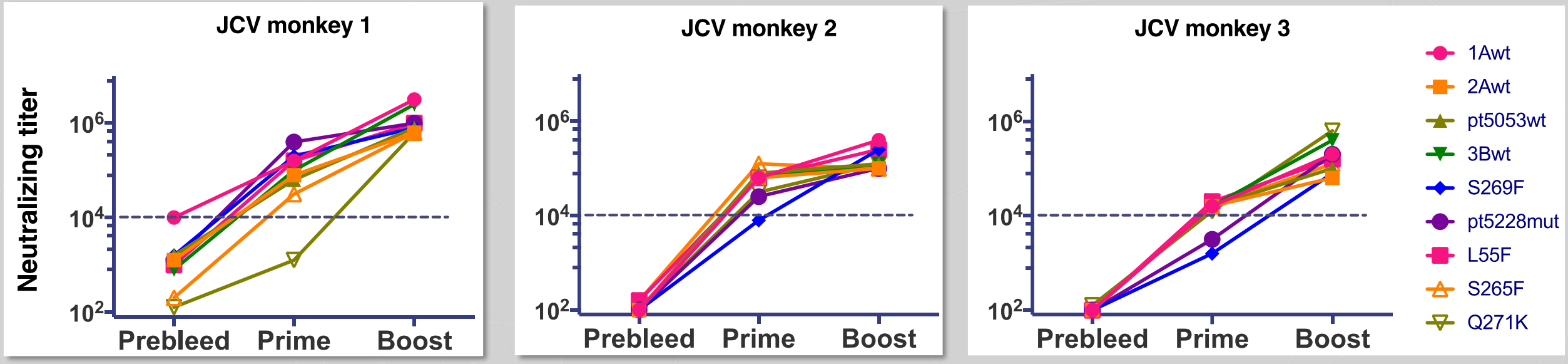
NIH Ref. No.: E-168-2011

The Path to Market (PML)

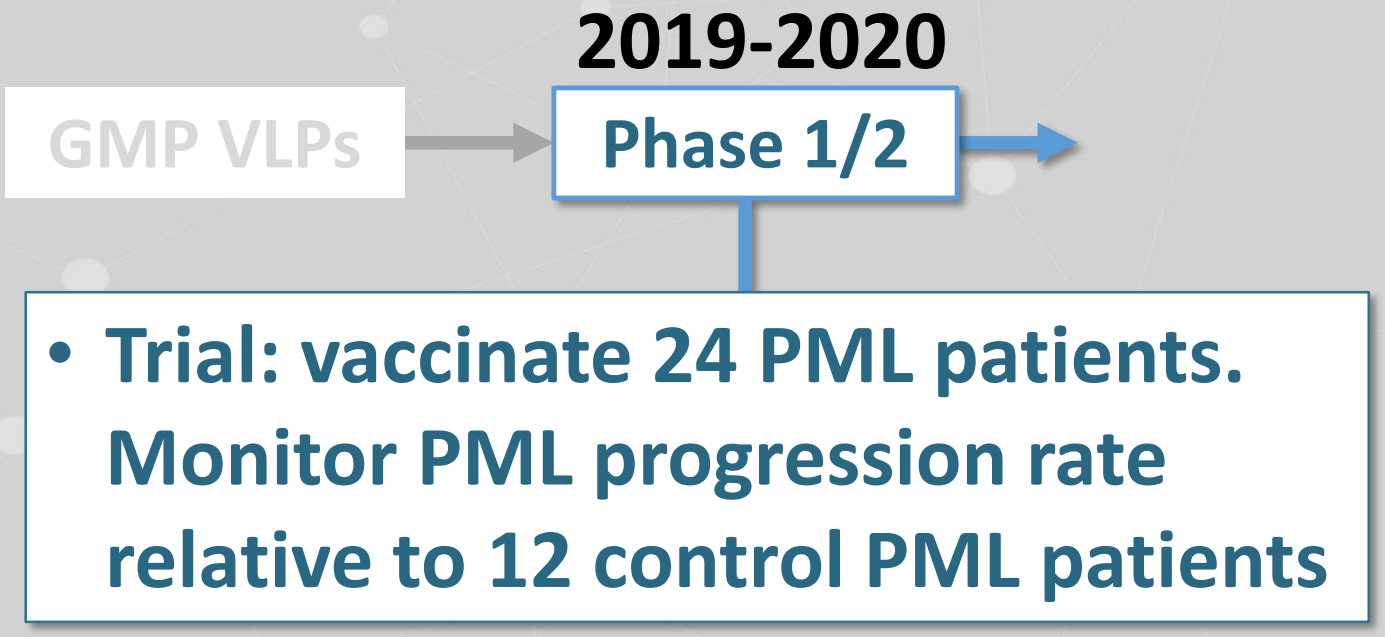
2018

GMP VLPs →

- **Multivalent BKV-Ib, II, IV, JCV VLP vaccine: good immunogenicity in monkeys**



The Path to Market (PML)



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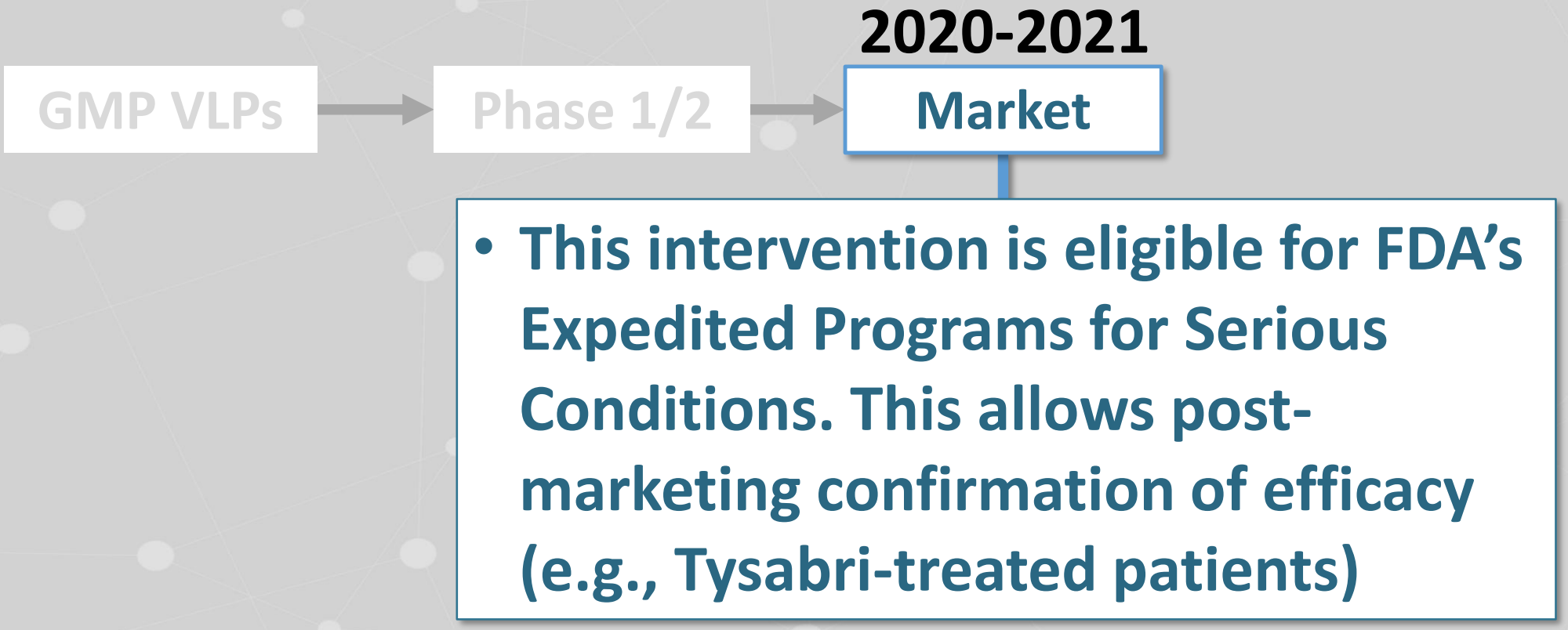

Conclusions

- **Indication 1: prevention of polyomavirus nephropathy in transplant patients. Predicted US market $600 million/year**

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- **Indication 2: prevention of bladder disease after bone marrow transplant. Predicted US market $400 million/year plus an uncertain fraction of 250,000 patients diagnosed with conditions that may require transplant**

Conclusions

- Indication 1: prevention of polyomavirus nephropathy in transplant patients. Predicted US market $600 million/year
- Indication 2: prevention of bladder disease after bone marrow transplant. Predicted US market $400 million/year plus an uncertain fraction of 250,000 patients diagnosed with conditions that may require transplant
- **Indication 3: prevention of PML side effects in individuals taking top-selling immunosuppressive therapies. $Billions**

Conclusions (continued)

- All indications are serious conditions with no currently available treatment. New FDA programs allow accelerated approval with post-marketing efficacy

- NCI has been issued patents covering these technologies. Exclusive licensing remains possible

Patent Information

Patent Status

NOTE: polyvalent BKV/JCV vaccine can protect against both kidney disease in transplant patients and PML in immuno-modulatory patients.

- Allowed Claims
  - US (14/233,582) – Method of eliciting an immune response to BKV/JCV by administering to a patient an effective amount of a trivalent BKV/JCV vaccine (BKV-Ib2, BKV-IV and JC antigens) – NIH Ref. No. E-168-2011
  - JAPAN (2014-521716) – Vaccine compositions directed to a trivalent vaccine (BKV-Ib2, BKV-IV and JC antigens) – NIH Ref. No. E-168-2011

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NIH Ref. No.: E-168-2011

NIH Ref. No.: E-549-2011