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Virus-like particle vaccines against BK and JC polyomaviruses

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Virus-like particle vaccines Against BK and JC polyomaviruses

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



techtransfer.cancer.gov

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



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)



BKV Neutralization Serotypes



NIH Ref. No.: E-168-2011

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



Peretti et al, 2018 Cell Host & Microbe

Case Study – BKV nephropathy



Case Study – BKV nephropathy



11

Polyomaviruses Also Form VLPs



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



Papillomavirus (HPV16)

John Schiller Doug Lowy

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)



BKV vaccine \$10k? x 30k patients \$300? Million Anything less than \$700!!!



The Path to Market (Post-Transplant Kidney Damage)



• GMP development (\$5m through CRO)

The Path to Market (Post-Transplant Kidney Damage)



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



NATIONAL CANCER INSTITUTE

DCTD Division of Cancer Treatment & Diagnosis CCR Center for Cancer Research

NExT NCI Experimental Therapeutics Program



The Path to Market (Post-Transplant Kidney Damage)



- Trial: vaccinate 96 patients on kidney transplant wait-list
- Standard monitoring for viremia, 24 weeks

The Path to Market (Post-Transplant Nephropathy)





Brain Disease (PML) in immunosuppression



techtransfer.cancer.gov

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

ehealthme.com genengnews.com 22

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 ²³

Other Drugs with Black Box PML Warning

				FDA-reported PML
Trad	ename	Generic	2016 sales (\$b)	cases
Tysa	bri	natalizumab	2	4332
About a	third o	f MS patients who	0	27
want Ty	sabri ar	re turned away due		
to PML	risk stra	atification	0.09	13
Adce	etris	brentuximab vedotin	0.07	25
Enty	vio	vedolizumab	1.4	0
				ehealthme.co

genengnews.com ²⁴

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	myco License revoke	ed 0.09	13
Adcetris	brentuximab vedotin	0.07	25
Entyvio	vedolizumab	1.4	0 abaalth maraa

ehealthme.com genengnews.com ²⁵

PML Side-Effects Cast a Long Shadow



Entyvio TV ad: "While not reported with Entyvio, PML - a rare serious brain infection may be possible..."

ENTYVIO is given by IV infusion in the arm over 30 minutes.

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-immunocompromised27

A Lack of <u>Neutralizing</u> Antibodies

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

4.9" $2.7"$ 4.1" $3.4"$ $3.7"$ $3.6"$ $5.5"$ 4.7" $5.2"$ $4.1"$ $3.6"$ $5.7"$ $3.7"$ $3.6"$ $5.7"$ 4.7" $4.2"$ $3.3"$ $3.4"$ $4.5"$ $3.9"$ $4.9"$ 4.5" $4.3"$ $5.0"$ $4.1"$ $4.2"$ $3.9"$ $5.7"$ 4.5" $4.3"$ $5.0"$ $4.1"$ $4.2"$ $3.9"$ $5.7"$ 4.4" $4.1"$ $3.9"$ $3.2"$ $3.4"$ $4.6"$ $7.0"$ 4.3" $3.8"$ $3.2"$ $2.4"$ $1.7"$ $1.7"$ $4.2"$ $4.0"$ $3.5"$ $5.6"$ 4.2" $4.6"$ $4.1"$ $4.4"$ $4.0"$ $3.5"$ $5.5"$ $2.7"$ $6.9"$ 4.1" $3.6"$ $3.2"$ $3.5"$ $3.5"$ $2.7"$ $4.8"$ $4.0"$ $3.5"$ $4.5"$ 4.0" $3.5"$ $3.2"$ $3.5"$ $4.5"$ $3.9"$ $5.1"$ $4.1"$ $4.8"$ $4.5"$ $3.9"$ $3.5"$ $4.5"$		5.0"	5.5"	5.0"	5.4"	4.2	3.9	5.8	
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4.0" 3.5" 3.2" 3.7" 4.0" 3.3" 4.6" 4.0" 3.9" 4.2" 4.1" 3.8" 3.5" 4.9" 4.0" 3.9" 4.2" 4.1" 3.8" 3.5" 4.5" 3.9" 3.9" 3.8" 3.6" 3.2" 2.6" 4.5" 3.9" 3.3" 3.0" 4.5" 3.7" 3.7" 3.7" 5.2" 3.9" 3.5" 4.5" 3.9" 3.6" 3.8" 3.4" 4.6" 3.9" 3.7" 3.9" 3.6" 3.8" 3.4" 4.6" 3.9" 3.2" 3.9" 3.6" 3.8" 3.4" 4.6" 3.8" 3.4" 4.4" 3.7" 3.8" 3.9" 4.4" 3.7" 4.3" 4.0" 3.0" 2.9" 3.3" 4.4" 3.7" 4.3" 3.6" 3.4" 3.6" 3.4" 3.6" 3.4" 3.7" 3.4" 3.6" 3.4" 3.3" 2.7" 4.9" 3.6" 3.6" 3.5" </td <td></td> <td>4.0"</td> <td>2.7"</td> <td>4.1</td> <td>4.4"</td> <td>4.1"</td> <td>5.1"</td> <td>4.8"</td> <td></td>		4.0"	2.7"	4.1	4.4"	4.1"	5.1"	4.8"	
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		3.9"	4.3"	3.7"	4.0"	4.3"	4.0"	4.2"	
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$\begin{array}{cccccccccccccccccccccccccccccccccccc$		3.8	3.0	3.6	3.6	4.0"	3.9"	5.3	
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$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		3.5"	3.5"	3.4"	3.0"	4.0"	2 2"	5.3"	
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		3.3	0.4	4.1	4.0	3.9	2.2	0.1	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		3.3	3.4	2.9"	2.4"	3.6	2.6	3.6	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		3.3"	1.7"	2.4"	2.5"	3.7"	2.6"	3.8"	
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		3.2"	3.8"	3.2"	4.3"	2.5"	3.6"	5.3"	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		3.2"	2.6"	1.7"	1.7"	3.9"	1.7"	2.6"	
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$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		3.1"	3.9"	3.6"	4.0"	3.7"	2.3"	4.2"	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		3.0"	3.5"	3.9"	2.8"	3.9"	1.5"	6.1"	
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		2.0"	3.4"	3.4"	2.0"	3.0"	1.0"	1.1"	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		2.9	0.4	3.T	2.0	3.0	1.0	4.1	
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2.5" 2.0" 1.5" 2.9" 3.1" 1.7" 3.9" 2.4" 2.0" 1.7" 1.7" 3.8" 1.7" 4.1" 2.3" 2.7" 1.7" 1.7" 1.7" 2.2" 2.8"		2.6"	3.2"	3.0"	2.5"	2.5"	2.3"	5.1"	
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2.3" 2.7" 1.7" 1.7" 2.2" 2.8"		2.4"	2.0"	1.7"	1.7"	3.8"	1.7"	4.1"	
		2.3"	2.7"	1.7"	1.7"	1.7"	2,2"	2.8"	

PML: A Lack of Neutralizing Antibodies

PML Patient 5029 (Progressor)



PML Patient 5040 (Survivor)



The Path to Market (PML)



The Path to Market (PML)



• Trial: vaccinate 24 PML patients. Monitor PML progression rate relative to 12 control PML patients

The Path to Market (PML)



Conclusions

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

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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 <u>both</u> 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 <u>JC</u> antigens) – NIH Ref. No. E-168-2011
 - JAPAN (2014-521716) Vaccine compositions directed to a trivalent vaccine (BKV-Ib2, BKV-IV and <u>JC</u> antigens) – NIH Ref. No. E-168-2011

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NIH Ref. No.: E-168-2011 NIH Ref. No.: E-549-2011