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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
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

• JCV causes brain disease (PML) in immunosuppressed patients
Kidney Damage After Solid Organ Transplantation
Market Landscape (US)

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

- BKV Viremia: 6,200 (20%)
- Nephropathy: 2,480 (8%)
- Graft Loss: 1,550 (5%)

- Each day, four US kidney transplant recipients lose their graft due to BKV
Current treatment costs attributable to BKV
$700 Million
Neutralizing Antibodies Are Protective

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

Peretti et al, 2018 *Cell Host & Microbe*
Case Study – BKV nephropathy
Case Study – BKV nephropathy

- BKV-IV “hitchhiked” in the donor kidney
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.
Excellent Immunogenicity in Monkeys

- Polyomavirus VLPs induce protective neutralizing antibody responses in monkeys after a single dose.
US Market Landscape (Post-Transplant Nephropathy)

Current treatment costs attributable to BKV
$700 Million

BKV vaccine
$10k? x 30k patients
$300? Million
Anything less than $700!!!
The Path to Market (Post-Transplant Kidney Damage)

2019

GMP VLPs

- GMP development ($5m through CRO)
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)

2019-2020

GMP VLPs

Phase 1/2

- Trial: vaccinate 96 patients on kidney transplant wait-list
- Standard monitoring for viremia, 24 weeks
• The polyomavirus VLP vaccine is eligible for the FDA’s Expedited Programs for Serious Conditions. This allows post-marketing confirmation of efficacy
Brain Disease (PML) in immunosuppression
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

<table>
<thead>
<tr>
<th>Rank</th>
<th>Tradename</th>
<th>Generic</th>
<th>2016 sales ($b)</th>
<th>FDA-reported PML cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Humira</td>
<td>adalimumab</td>
<td>16</td>
<td>83</td>
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<tr>
<td>2</td>
<td>Sovaldi/Harvoni</td>
<td>sofosbuvir</td>
<td>9</td>
<td>1</td>
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<tr>
<td>3</td>
<td>Enbrel</td>
<td>etanercept</td>
<td>9</td>
<td>73</td>
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<tr>
<td>4</td>
<td>Rituxan</td>
<td>rituximab</td>
<td>9</td>
<td>413</td>
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<tr>
<td>5</td>
<td>Remicade</td>
<td>infliximab</td>
<td>8</td>
<td>113</td>
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**PML black box warning**
# Other Drugs with Black Box PML Warning

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<tr>
<td>Tysabri</td>
<td>natalizumab</td>
<td>2</td>
<td>4332</td>
</tr>
<tr>
<td>Raptiva</td>
<td>efalizumab</td>
<td>0</td>
<td>27</td>
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<tr>
<td>Myfortic</td>
<td>mycophenolic acid</td>
<td>0.09</td>
<td>13</td>
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About a third of MS patients who want Tysabri are turned away due to PML risk stratification.
## Other Drugs with Black Box PML Warning

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Source: 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

<table>
<thead>
<tr>
<th>NIH Ref. No.: E-168-2011</th>
<th>2A</th>
<th>3B</th>
<th>55F</th>
<th>265S</th>
<th>267F</th>
<th>G-CN1</th>
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<tbody>
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<td>4.7*</td>
<td>4.1*</td>
<td>6.2*</td>
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<td>5.0*</td>
<td>4.2</td>
<td></td>
<td></td>
<td></td>
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<td>5.4*</td>
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Neutralizing “blind spot” effect

2A! 3B! 55F! 265S! 267F! G-CN1!
PML: A Lack of Neutralizing Antibodies

PML Patient 5029 (Progressor)

- June 95: 5029 wt virus
- Aug 95: 5029 wt virus
- July 96: 5029 wt virus

PML Patient 5040 (Survivor)

- Aug 96: wt virus
- Jan 97: 5040 PML mutant
- July 04: wt virus
- Jan 05: 5040 PML mutant

Patient gained the ability to neutralize

PML Diagnosis

NIH Ref. No.: E-168-2011
• Multivalent BKV-Ib, II, IV, JCV VLP vaccine: good immunogenicity in monkeys
The Path to Market (PML)

2019-2020

GMP VLPs

Phase 1/2

- Trial: vaccinate 24 PML patients.
  Monitor PML progression rate relative to 12 control PML patients
This intervention is eligible for FDA’s Expedited Programs for Serious Conditions. This allows post-marketing confirmation of efficacy (e.g., Tysabri-treated patients).
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
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
For More Information:

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Email: changke@mail.nih.gov  

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