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Dorian Mcilroy, M. Hohnemann, Y. Verres, C. Peltier, F. Halary, et al.. Neutralization escape in kidney transplant recipients with persistent BK polyomavirus replication. Réunion du Labex IGO, Apr 2018, Nantes, France. inserm-02160211

HAL Id: inserm-02160211

<https://inserm.hal.science/inserm-02160211v1>

Submitted on 19 Jun 2019

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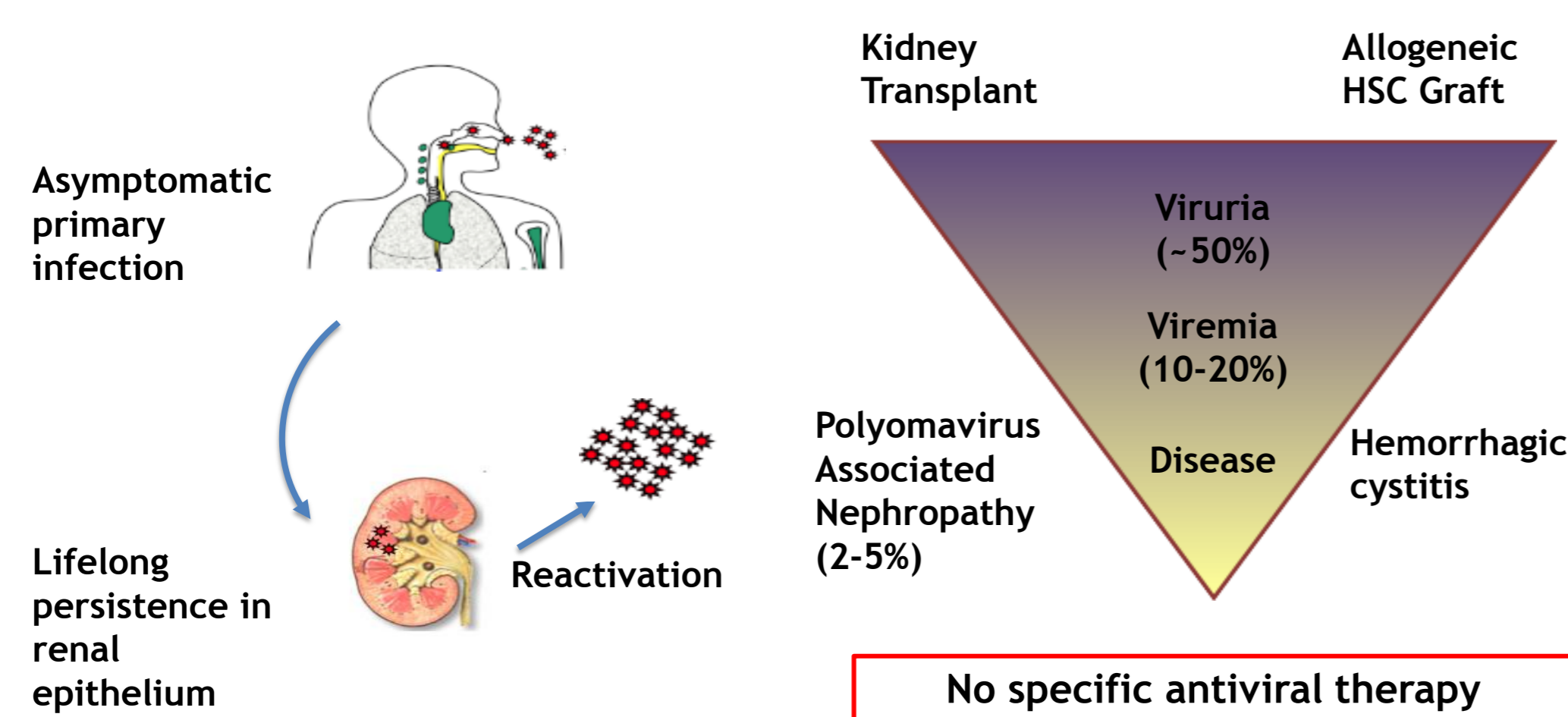
Neutralization escape in kidney transplant recipients with persistent BK polyomavirus replication

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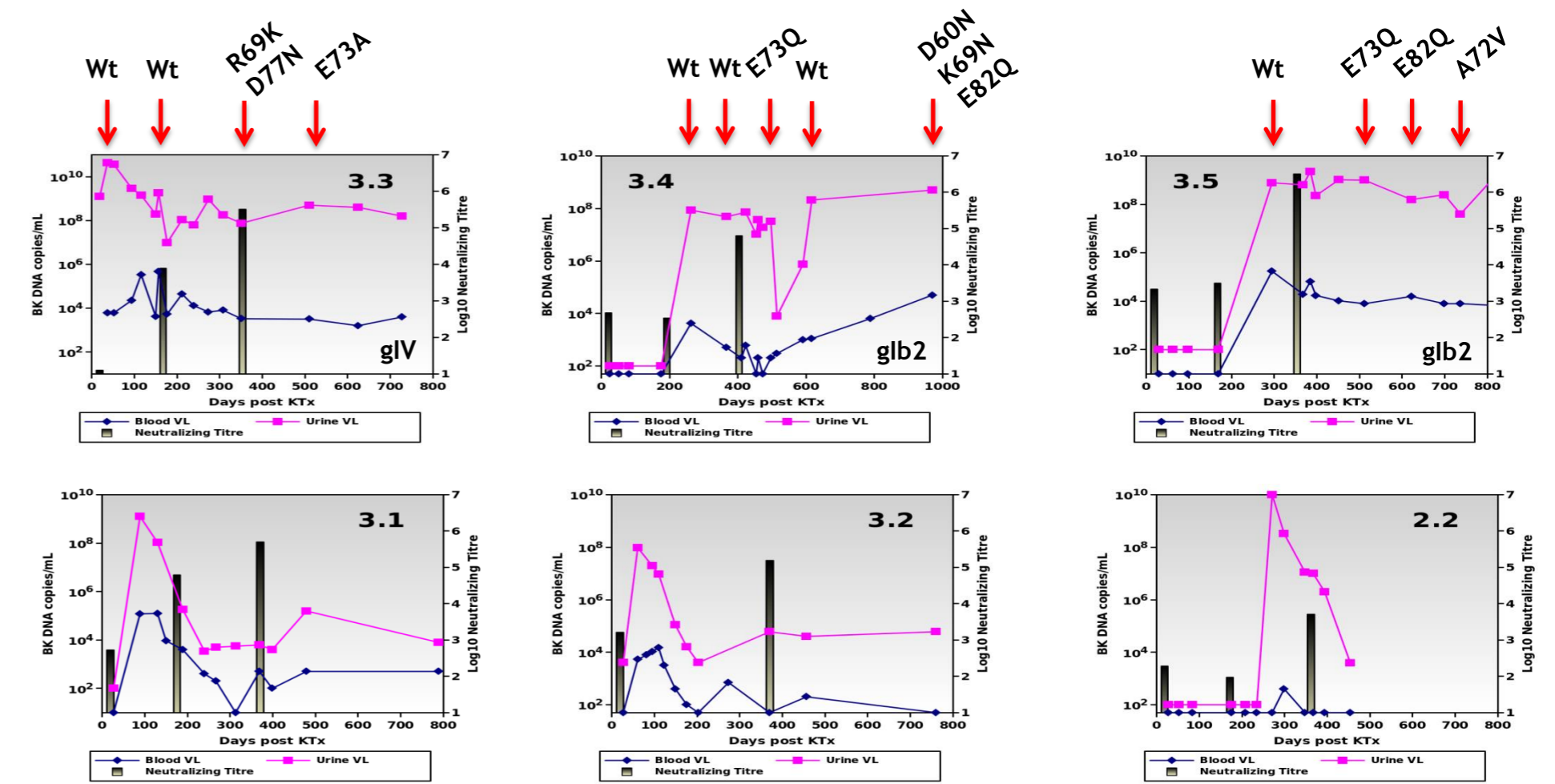
1. Introduction

The BK polyomavirus (BKPyV) infects more than 80% of the adult population in Europe. The virus persists in a latent state in the kidney and active replication is only seen in immunosuppressed individuals, such as kidney transplant (KTx) recipients, in whom BKPyV reactivation is associated with interstitial nephropathy and allograft dysfunction.



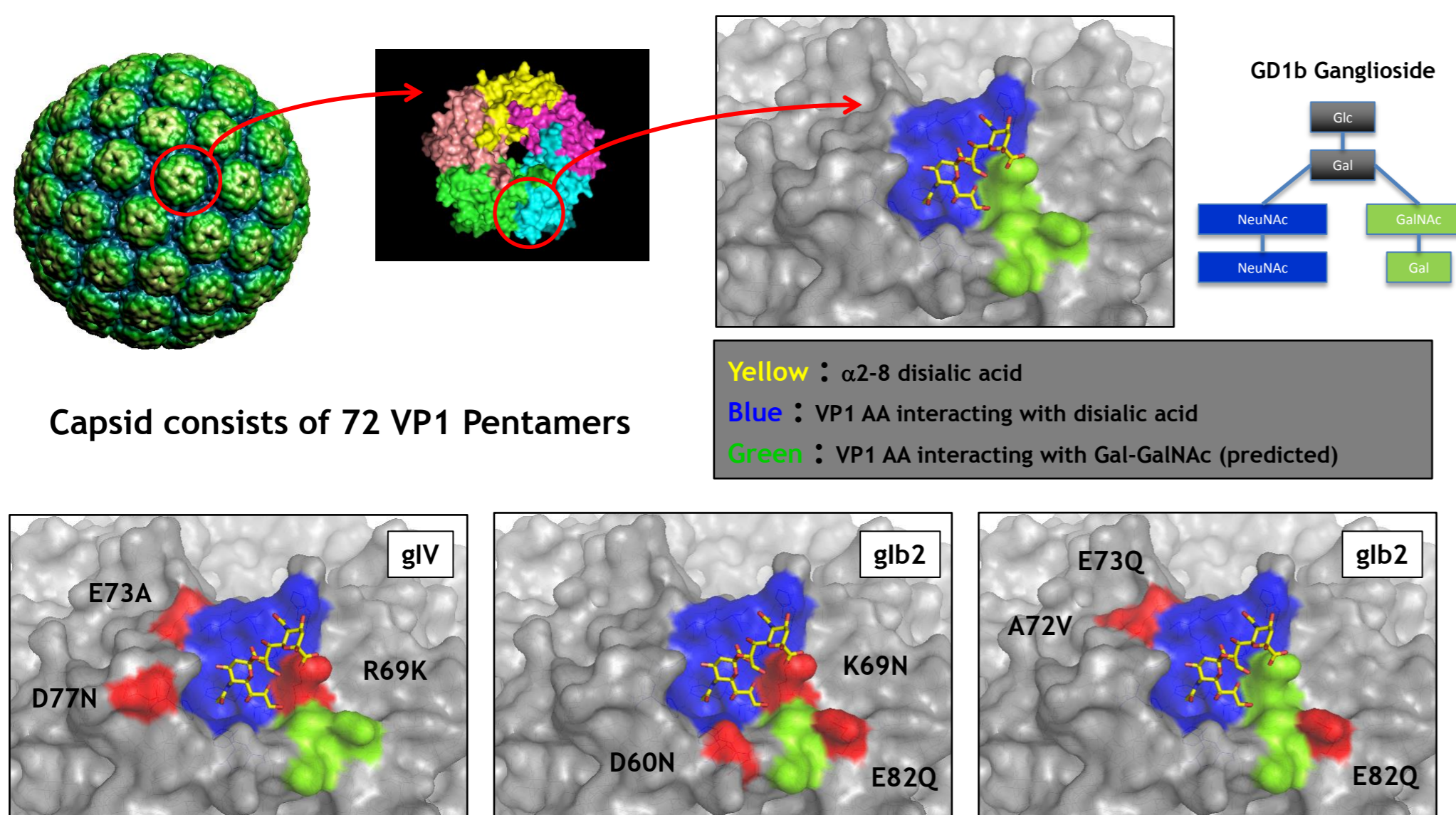
2. VP1 gene evolution in KTx patients

Non-synonymous VP1 mutations accumulate over time in patients with persistent viremia despite the presence of a robust humoral response



No VP1 mutations found by Sanger sequencing in urine of patients who controlled BKPyV reactivation

3. Location of VP1 mutations on BKPyV capsid



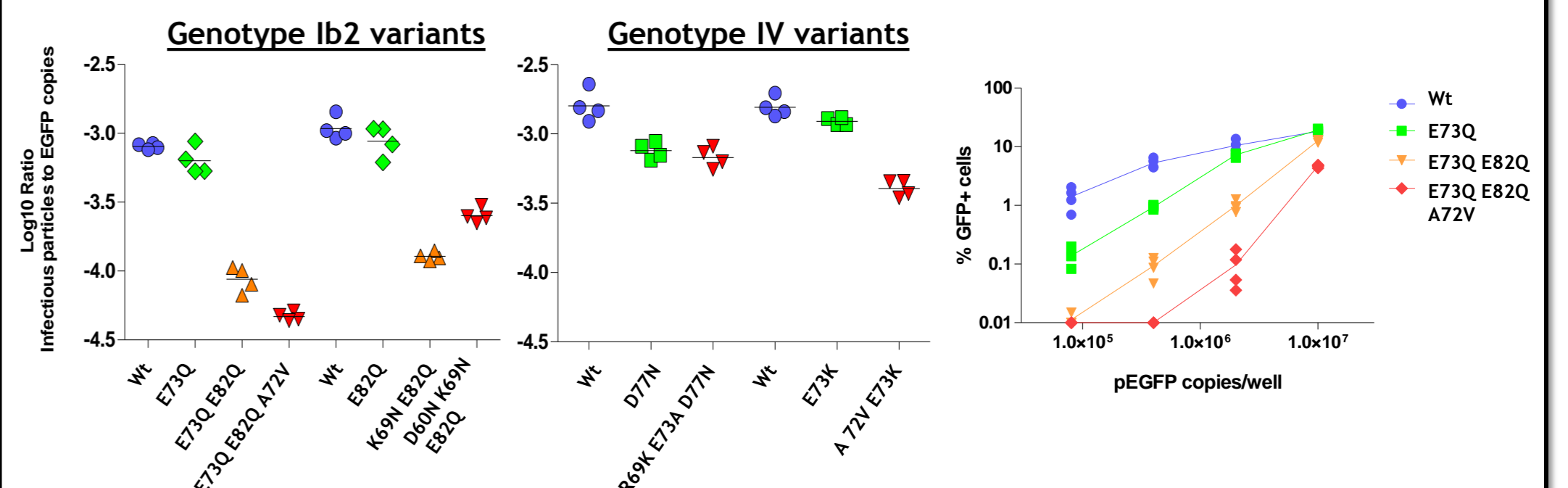
VP1 mutations cluster on the external surface of the capsid proximal to the receptor binding site

4. Effects of VP1 mutations on infectivity

Pseudotype production of different VP1 variants:

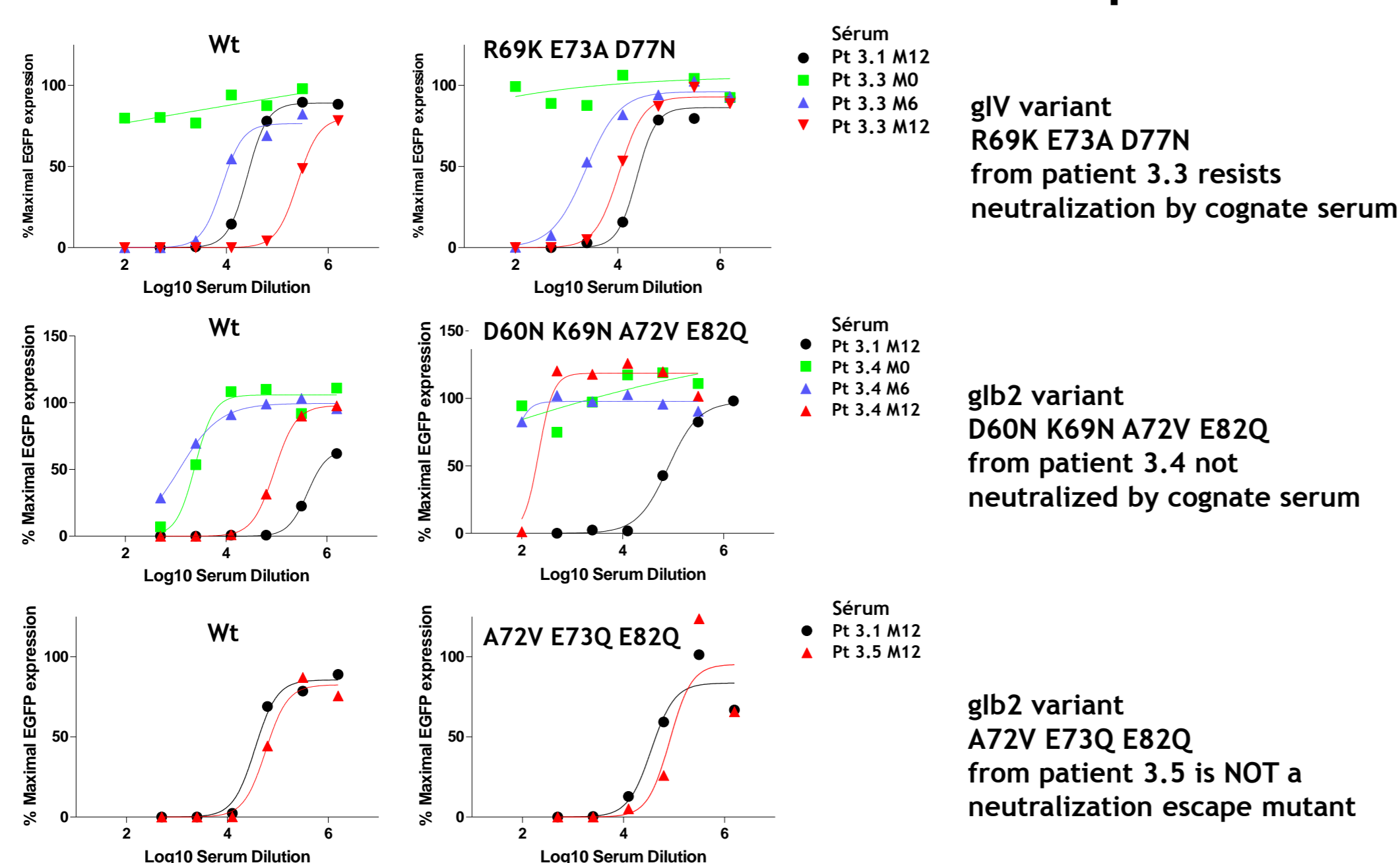
- Mutagenesis to generate panel of VP1 variants
- Co-transfect into 293TT cells with VP2, VP3 and EGFP
- Extract and purify on Optiprep gradient
- Quantify by qPCR - number of pEGFP copies/ μ L
- Test pseudotype infectivity in 293TT cells

Name	Time	Sequence
AEE	M9	⁷¹ SAENDFSSDSPERKM
AQE	M17	⁷¹ SAQNDFFSSDSPERKM
AQQ	M21	⁷¹ SAQNDFFSSDSPQRKM
VQQ	M24	⁷¹ SVQNDFFSSDSPQRKM



VP1 mutations reduce the ability of genotype I and genotype IV capsid proteins to mediate entry into 293TT cells

5. VP1 mutations and neutralization escape



6. Conclusions

Evolution of VP1 is consistently observed in KTx recipients with sustained viremia and viremia. Non-synonymous VP1 mutations reduce the efficacy of entry into 293TT cells mediated by both genotype I and genotype IV VP1 proteins.

In addition, clear neutralization escape from cognate serum was observed in one patient with glb2 infection (3.4), and one patient with glV infection (3.3). Both of these variants were neutralized as effectively as wild-type VP1 by serum from patient 3.1 who had successfully resolved post-KTx BKPyV viremia. These results indicate that the humoral response against BKPyV in KTx recipients is heterogeneous, since some patients develop a narrow neutralizing response that is vulnerable to neutralization escape mutants. They suggest that neutralization escape contributes to the persistence of BKPyV replication in patients with durably high viral loads.

Nevertheless data from patient 3.5 indicate that lower infectivity in 293TT cells is not always accompanied by neutralization escape. One possible explanation is that the VP1 variant observed in this patient was associated with a modification of viral tropism.