



Wolfgang-Stille-Preis 2020:

„Restriction of HIV-1 Escape by a Highly Broad and Potent Neutralizing Antibody“ Cell 2020

Dr. Dr. Philipp Schommers, Uniklinik Köln

08.10.2021

Conflict of Interest

Patent filed for antibody 1-18 (EP 19212986.4)

Conflict of Interest

Patent filed for antibody 1-18 (EP 19212986.4)

Antikörper-vermittelte Immuntherapie



Antikörper-vermittelte Immuntherapie



Emil
von Behring

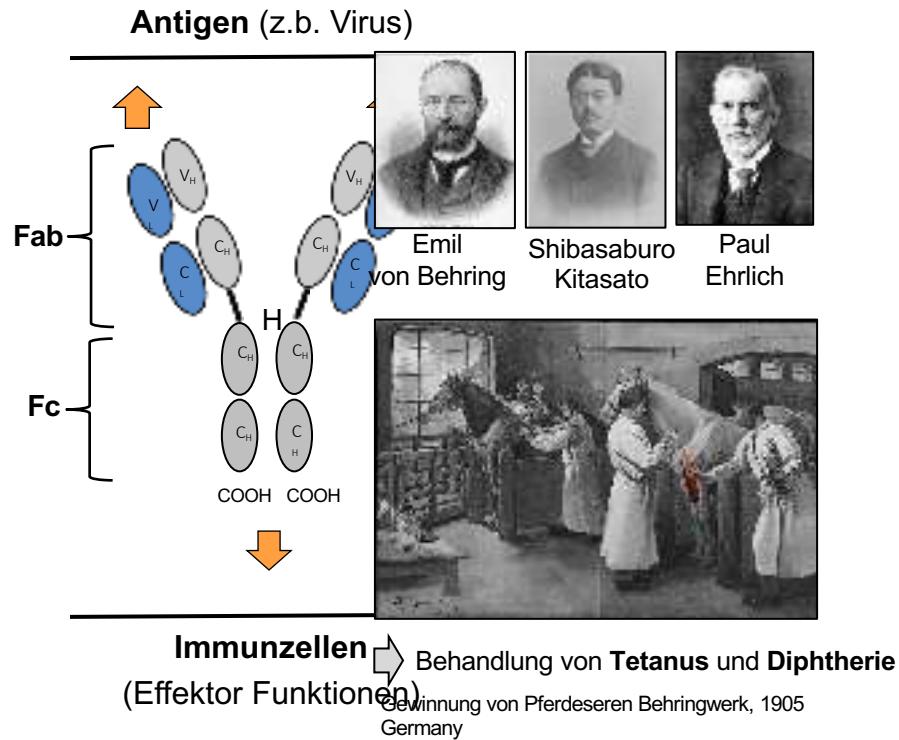


Shibasaburo
Kitasato

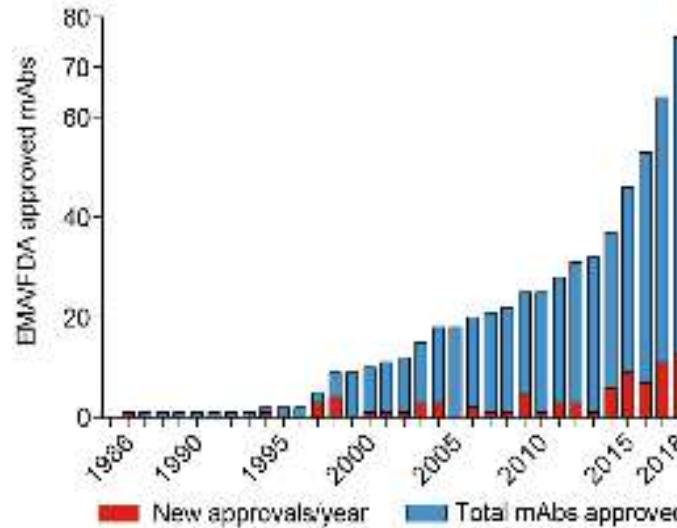
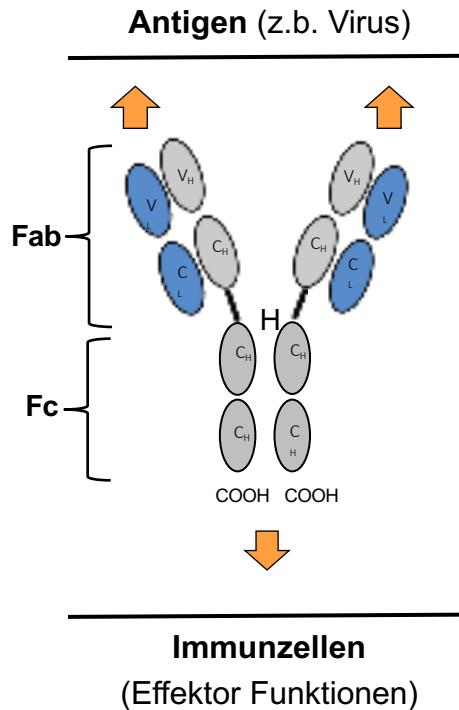


Paul
Ehrlich

Antikörper-vermittelte Immuntherapie

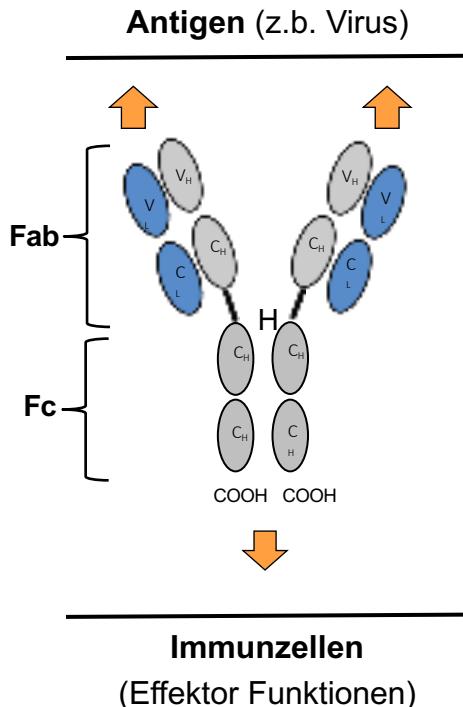


Antikörper-vermittelte Immuntherapie



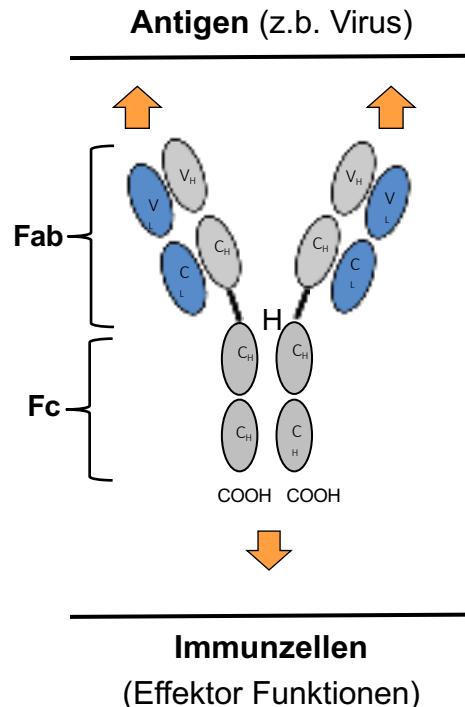
Antikörper-vermittelte Immuntherapie

Durch EMA/FDA zugelassene monoklonale Antikörper

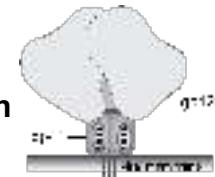


- Metabolische Erkrankungen
 - Neurologie
 - Dermatologie
 - Onkologie/
Hämatologie
 - Rheumatologie
-
- A pie chart illustrating the distribution of approved monoclonal antibodies across different therapeutic areas. The largest slice is blue, representing Metabolische Erkrankungen, Neurologie, Dermatologie, and Onkologie/Hämatologie combined. A smaller red slice represents Rheumatologie. The list of approved drugs below the chart includes several entries from the red slice.
- Pavalizumab (anti-RSV), 1998
 - Raxibacumab (Anti-*B. anthracis*), 2012
 - Obiltoximab (Anti-*B. anthracis*), 2016
 - Bezlotoxumab (Anti-*C. difficile*), 2016
 - Ibalizumab (anti-CD4; HIV), 2018
 - mAb114 (anti-Ebola), 2019
 - Bamlanivimab (anti-SARS-CoV-2), 2020
 - REGN-EB3 (anti-Ebola), 2020

Antikörper-vermittelte Immuntherapie



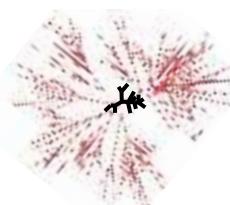
Komplexer Aufbau und
Viele **Glycosilierungen**



Wenige **Envelope-
Spikes**



Genetische Variation

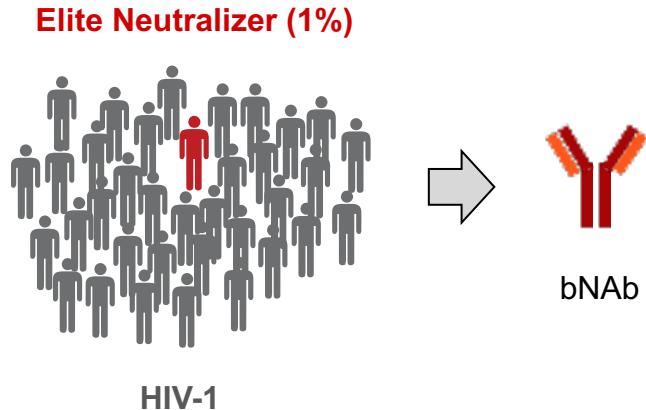


HIV-1; Influenza A

Was wird benötigt für eine effektive Antikörpertherapie?

Breit neutralisierende Antikörper

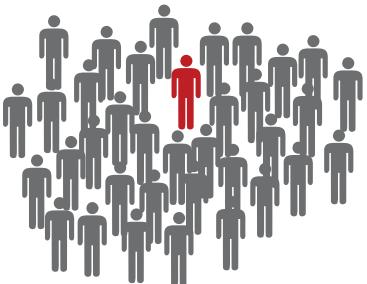
Breit neutralisierende Antikörper



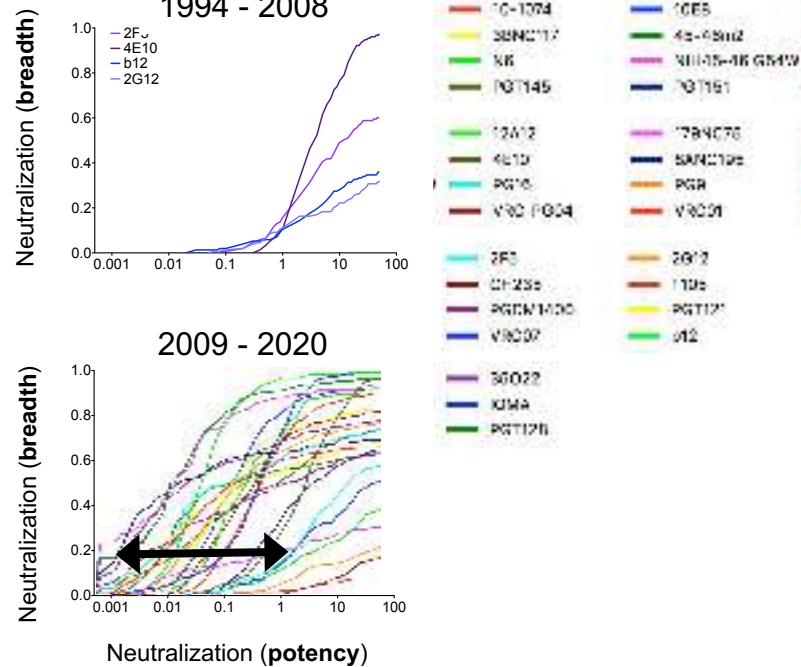
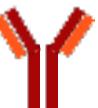
Scheid *et al.*, Science 2011; Walker *et al.*, Science 2009; Wu *et al.*, Science 2010; Corti *et al.*, Plos One 2010; Diskin *et al.*, Science 2011; Walker *et al.*, Nature 2011; Mouquet *et al.*, PNAS 2012; Klein *et al.*, J Exp Med 2012, Huang *et al.*, Nature 2012; Bonsignori *et al.*, J. Virol 2012; Rudicell *et al.*, J Virol. 2014; Huang *et al.*, Immunity 2016; Kwon *et al.*, J Virol 2016; Doria-Rose *et al.*, J Virol 2016; Xu *et al.*, Science 2017.

Breit neutralisierende Antikörper

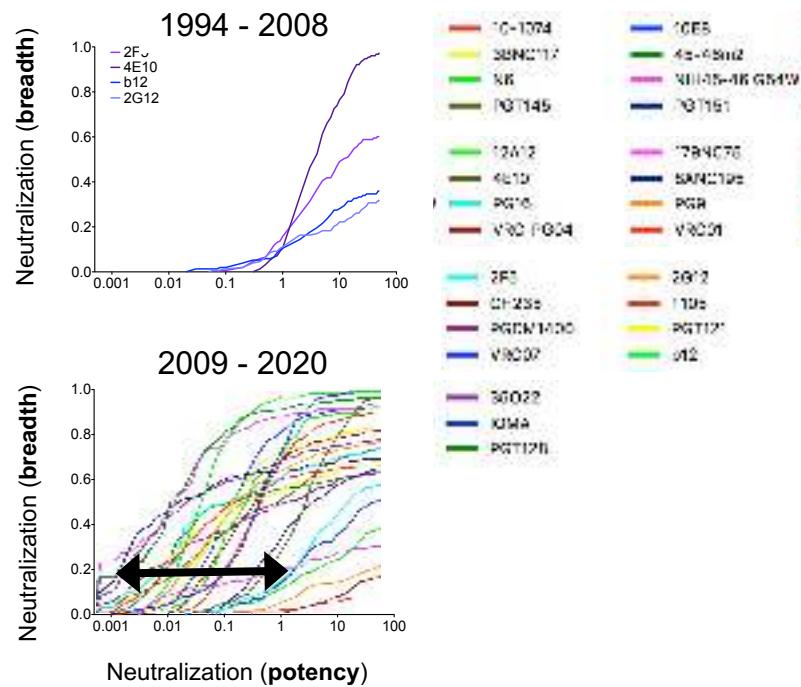
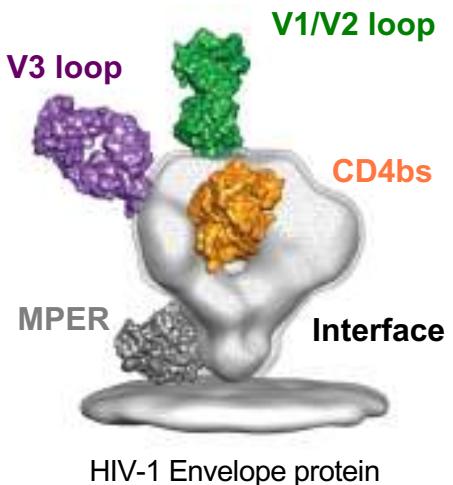
Elite Neutralizer (1%)



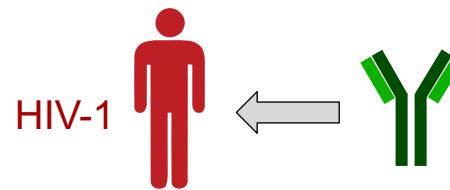
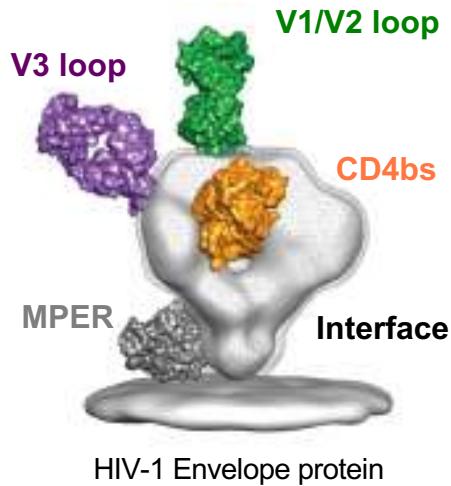
HIV-1



Breit neutralisierende Antikörper

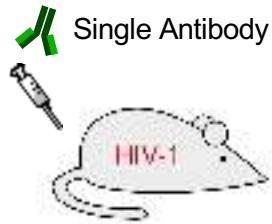


Breit neutralisierende Antikörper



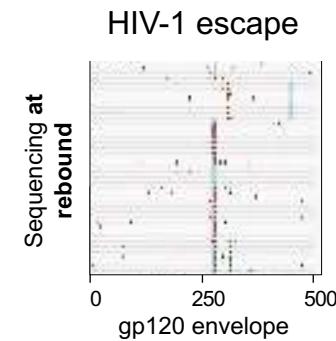
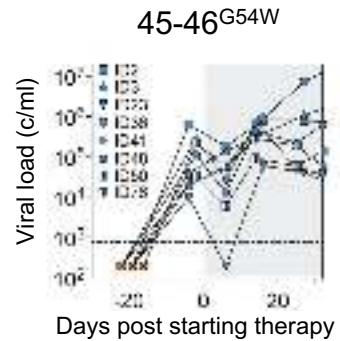
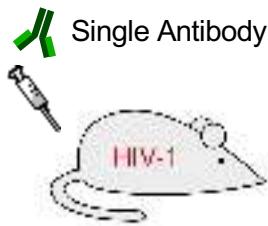
Breit neutralisierende Antikörper in humanisierten Mäusen

Single bNAbs



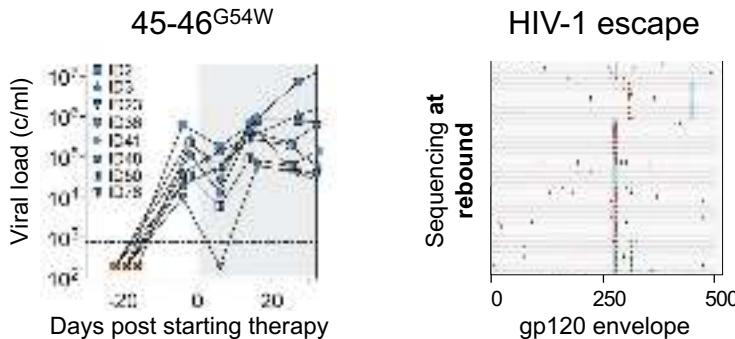
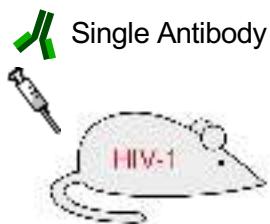
Breit neutralisierende Antikörper in humanisierten Mäusen

Single bNAbs

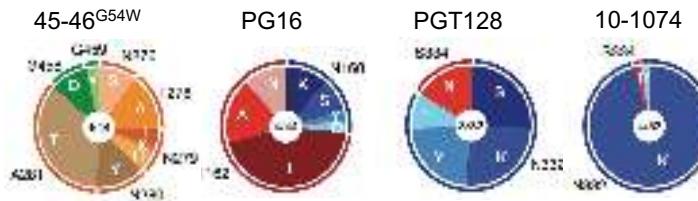


Breit neutralisierende Antikörper in humanisierten Mäusen

Single bNAbs

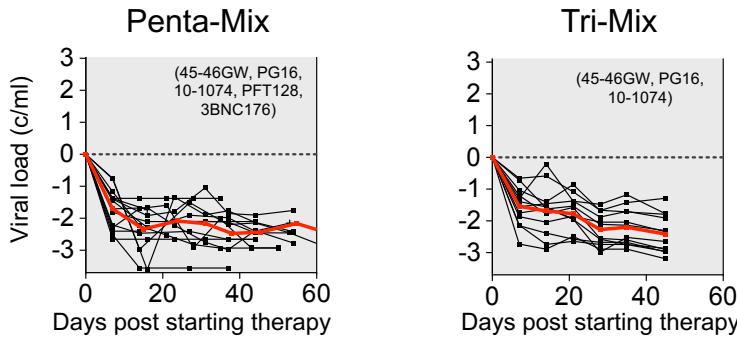
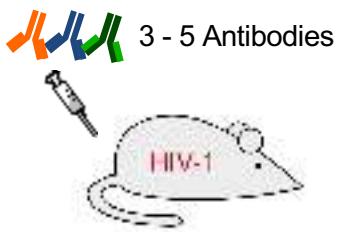


HIV-1 escape



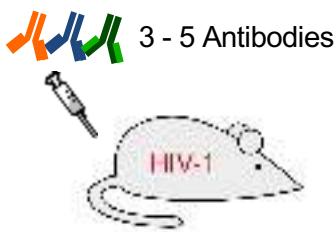
Breit neutralisierende Antikörper in humanisierten Mäusen

Kombination



Breit neutralisierende Antikörper in humanisierten Mäusen

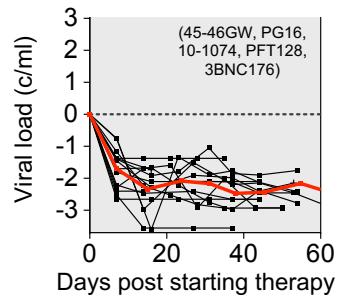
Kombination



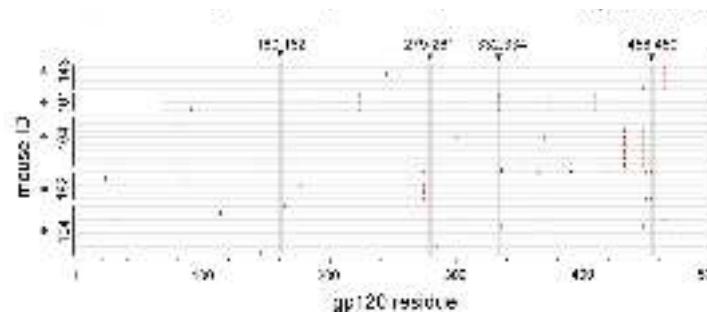
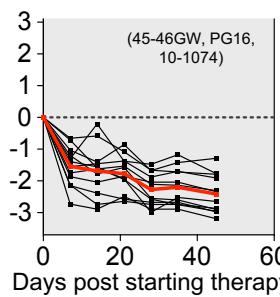
3 - 5 Antibodies

No
HIV-1 escape

Penta-Mix

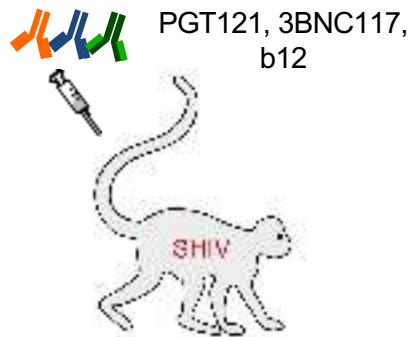


Tri-Mix



Breit neutralisierende Antikörper in Primaten

Kombination

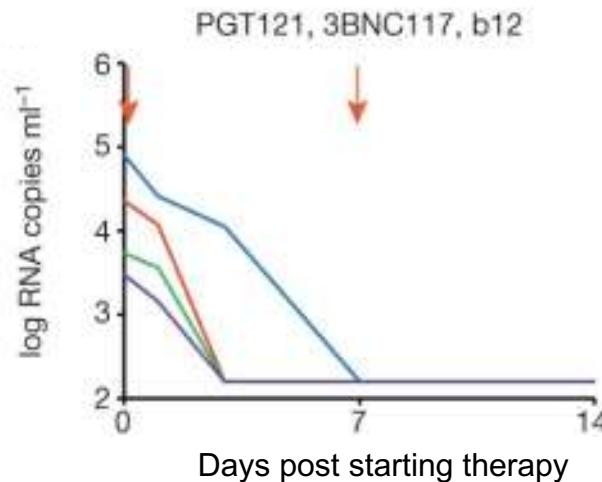


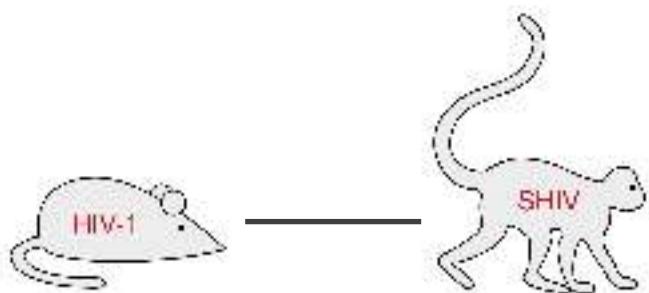
Breit neutralisierende Antikörper in Primaten

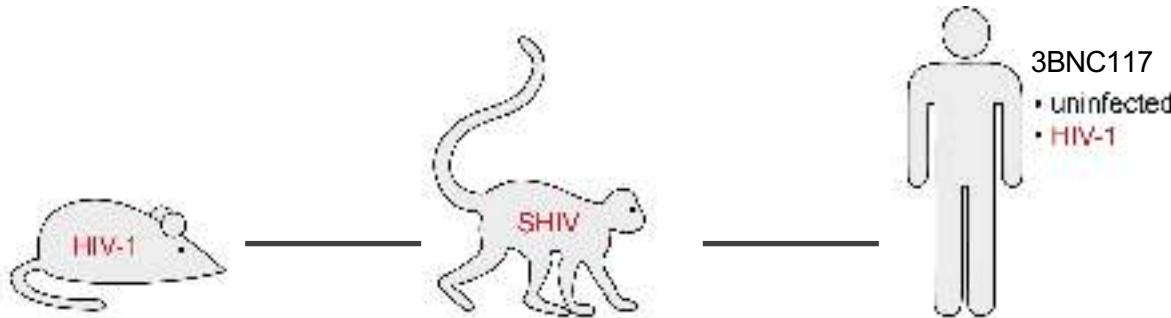
Kombination



Tri-Mix



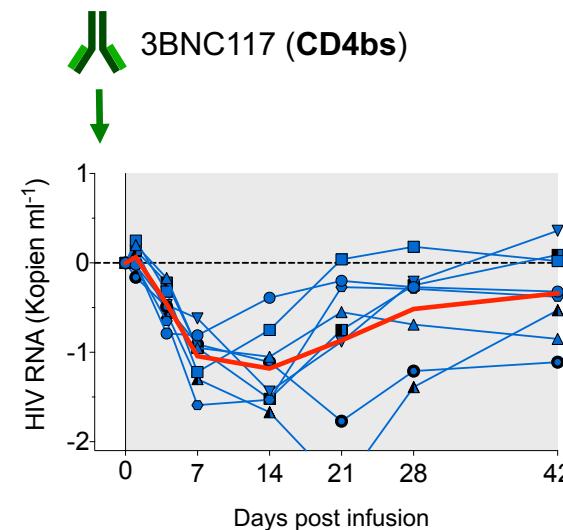
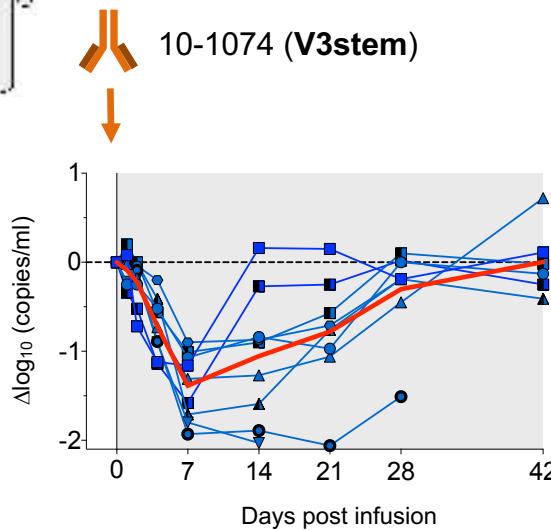




Klinische Testung von breit neutralisierenden Antikörpern



Antivirale Aktivität in Patienten

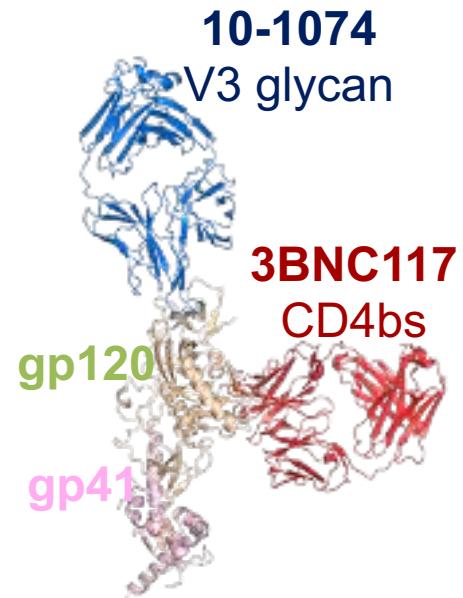


Drop Viral load
1,52 log (1.0 – 2.1)

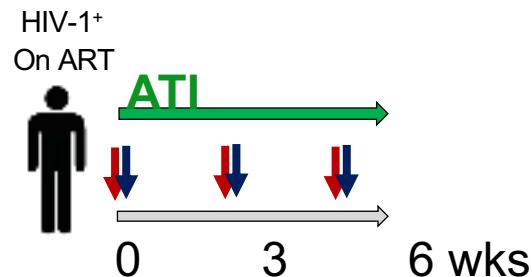
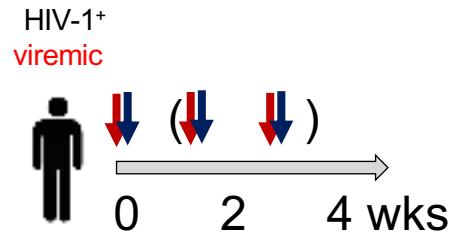
Drop Viral load
1,48 log (0.8 – 2.5)

Kombinationstherapien

Nicht-überlappende Epitope

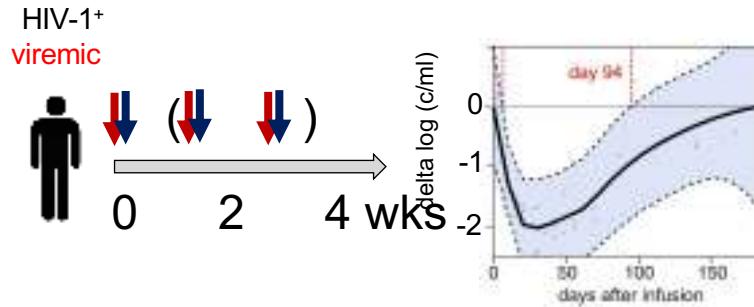


Kombinationstherapien

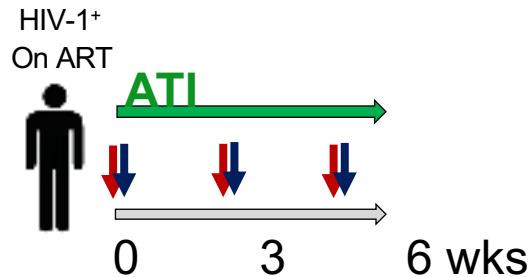


Bar-On* and Gruell*, *et al.*, Nat. Med., 2018;
Mendoza* and Gruell*, *et al.*, Nature, 2018

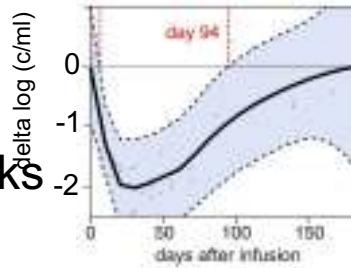
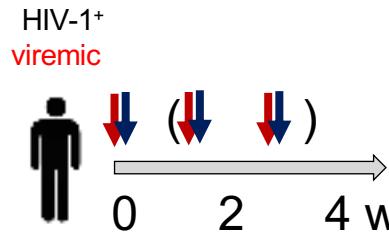
Kombinationstherapien



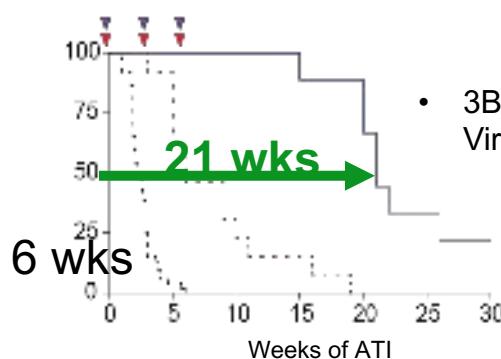
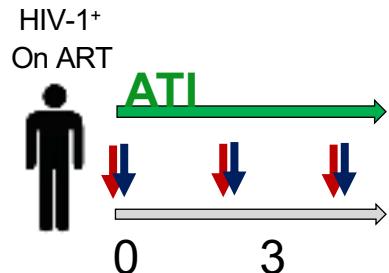
- Kombination supprimiert Viruslast ohne Entstehung von Resistzenzen



Kombinationstherapien

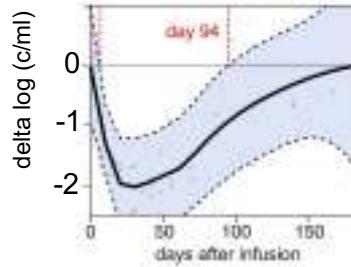
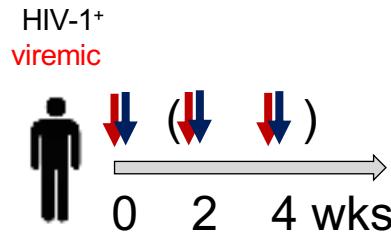


- Kombination supprimiert Viruslast ohne Entstehung von Resistzenzen

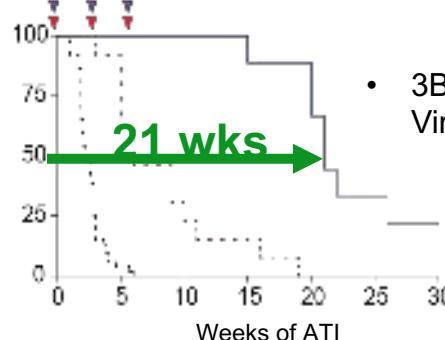
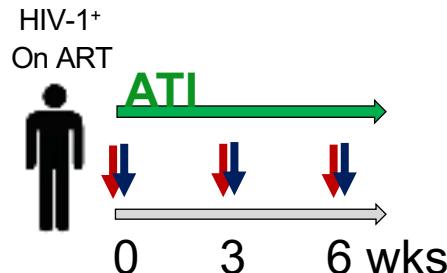


- 3BNC117/10-1074 erhält Virussuppression

Kombinationstherapien



- Kombination supprimiert Viruslast ohne Entstehung von Resistzenzen

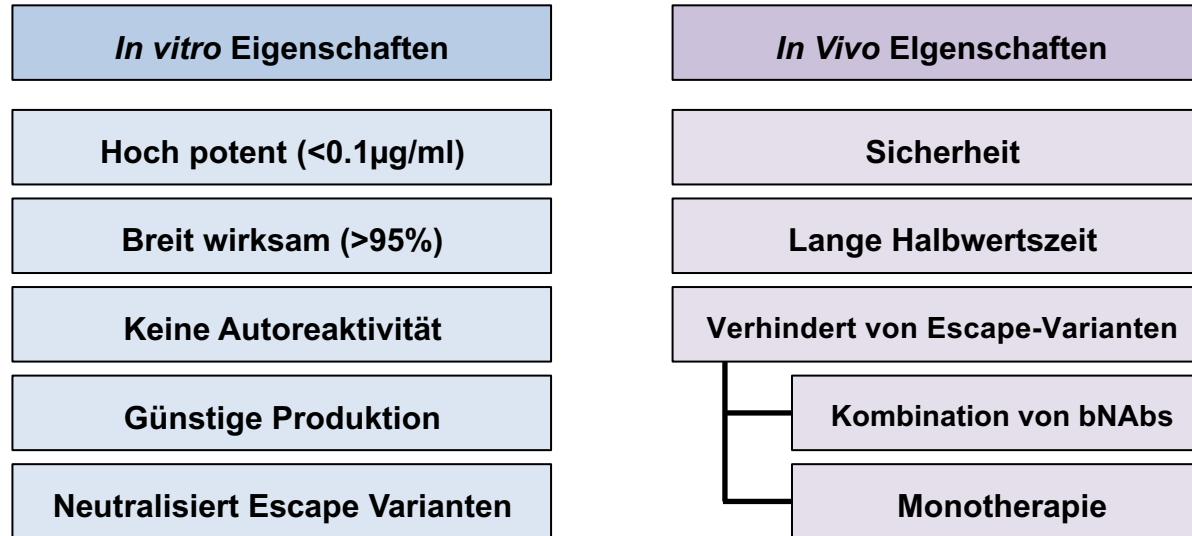


- 3BNC117/10-1074 erhält
Virussuppression

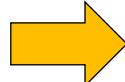
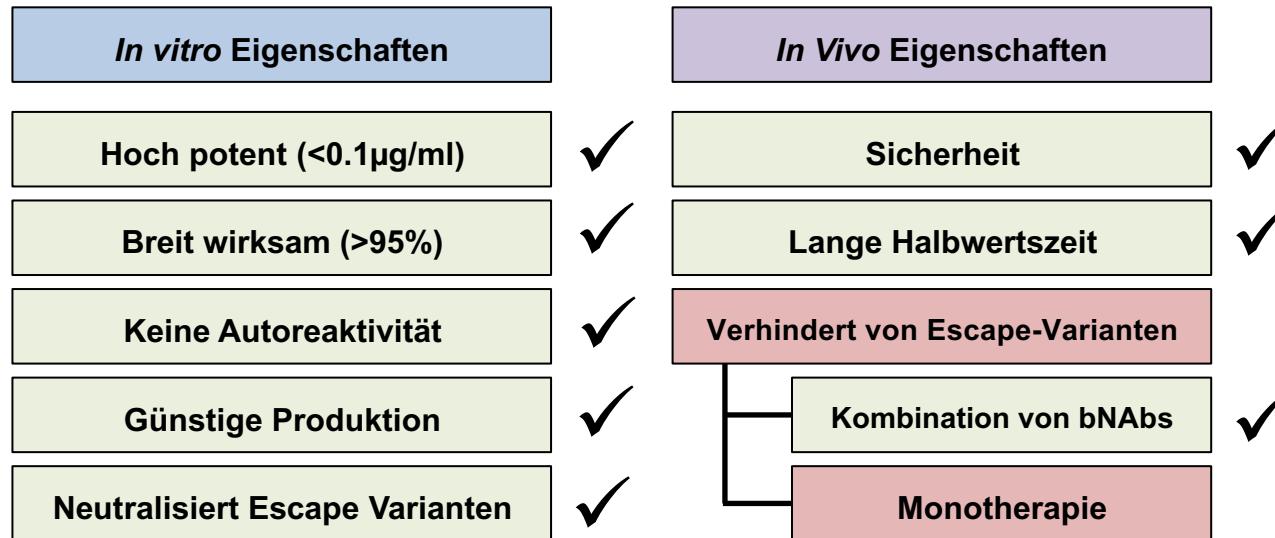
10-1074/3BNC117 Kombination limiert viralen Escape

Bar-On* and Gruell*, et al., Nat. Med., 2018;
Mendoza* and Gruell*, et al., Nature, 2018

Gewünschte Eigenschaften von bNAbs



Gewünschte Eigenschaften von bNAbs

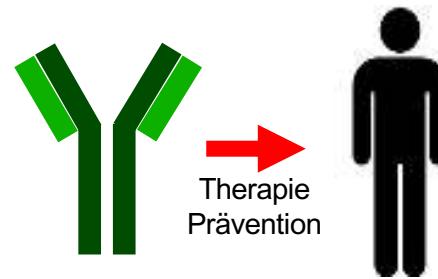
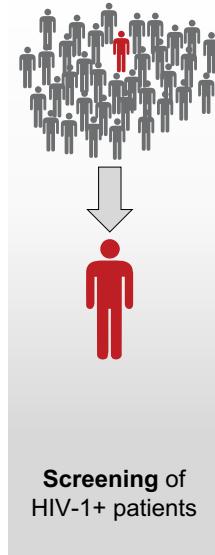


- bNAbs mit **gewünschten Eigenschaften** schon vorhanden
- Nur **wenige** vereinen **alle** Eigenschaften
- Kein Antikörper verhindert **Fluchtmutationen**

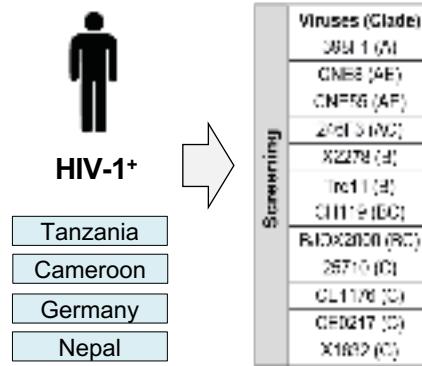
Daher werden dringend noch **neue Antikörper** benötigt

Pipeline zur Identifizierung neuer Antikörper

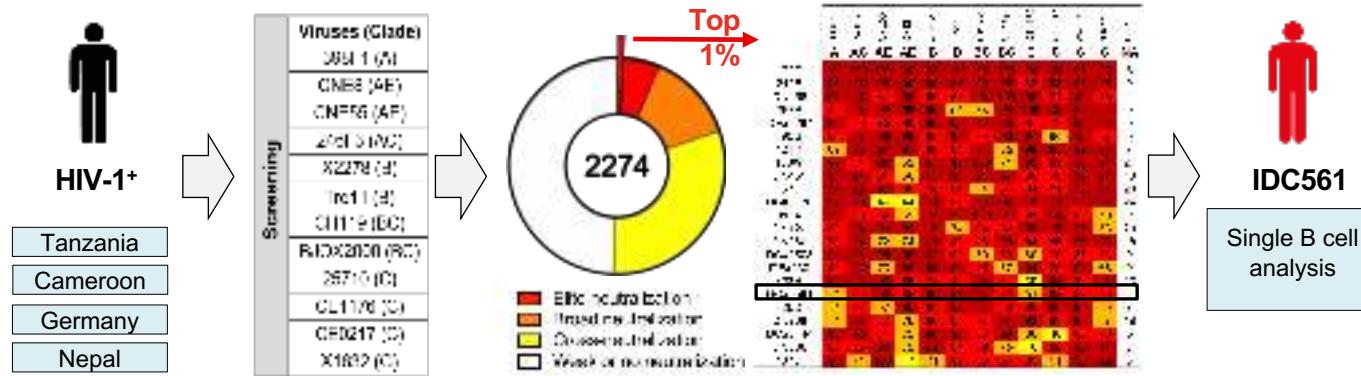
Pipeline zur Identifizierung neuer Antikörper



Identification of elite neutralizer IDC561



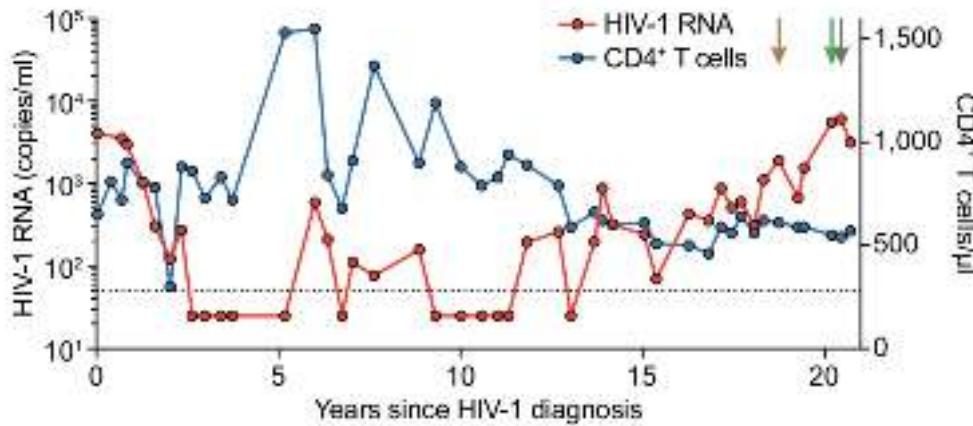
Identifizierung von Elite Neutralizer IDC561



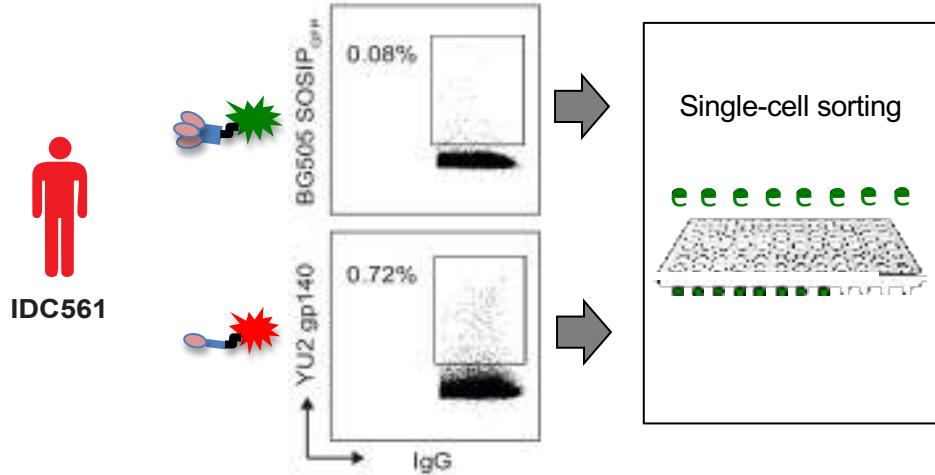
Identifizierung von Elite Neutralizer IDC561



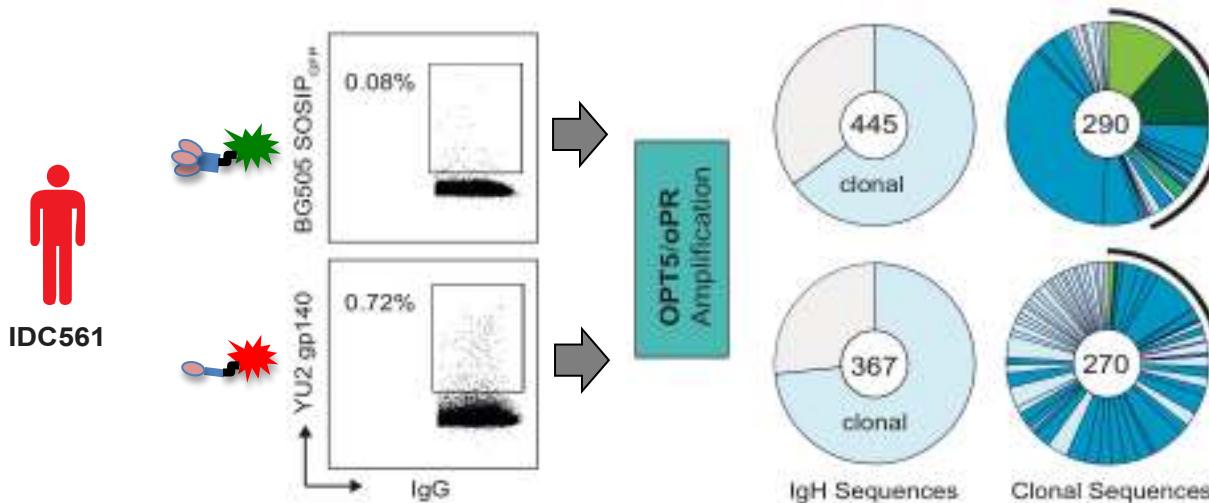
IDC561



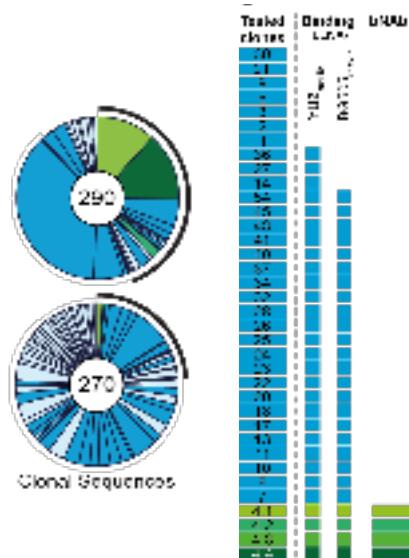
Identifizierung des neuen bNAbs 1-18



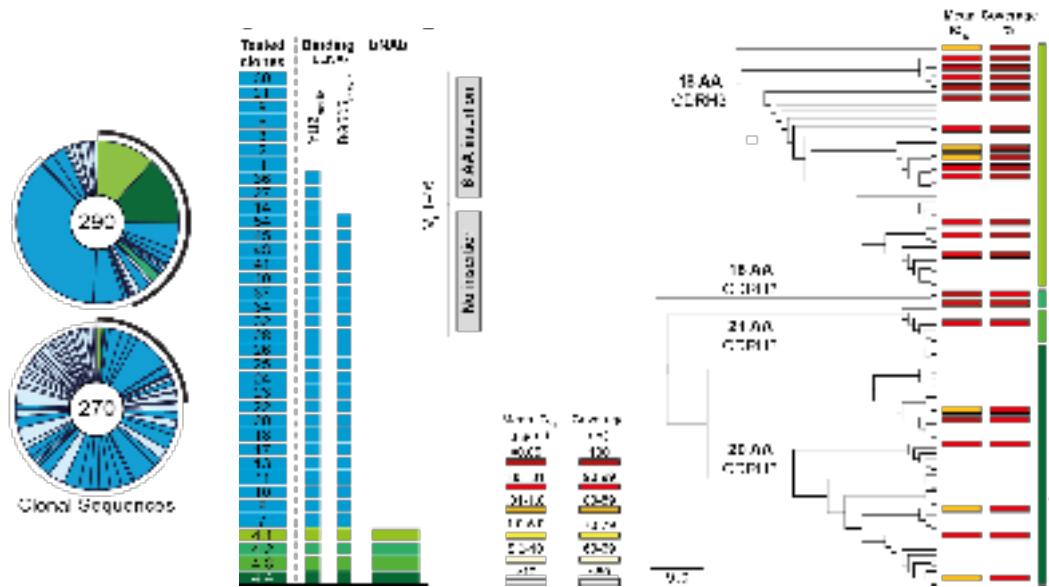
Identifizierung des neuen bNAbs 1-18



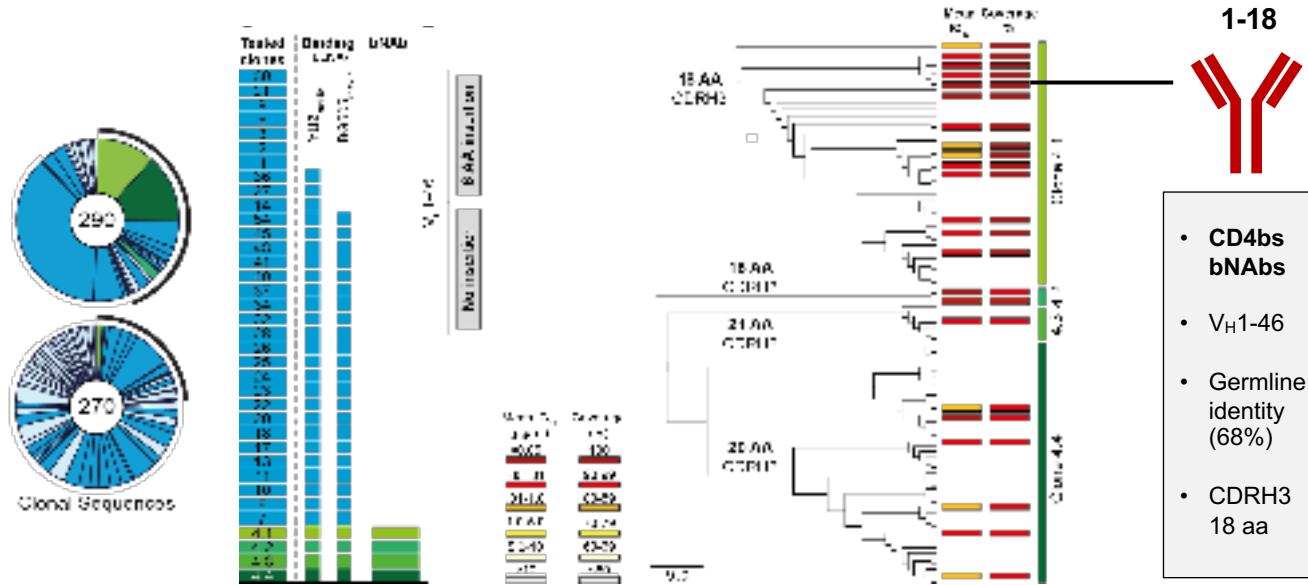
Identifizierung des neuen bNAbs 1-18



Identifizierung des neuen bNAbs 1-18



Identifizierung des neuen bNAbs 1-18



bNAb 1-18 *in vitro*

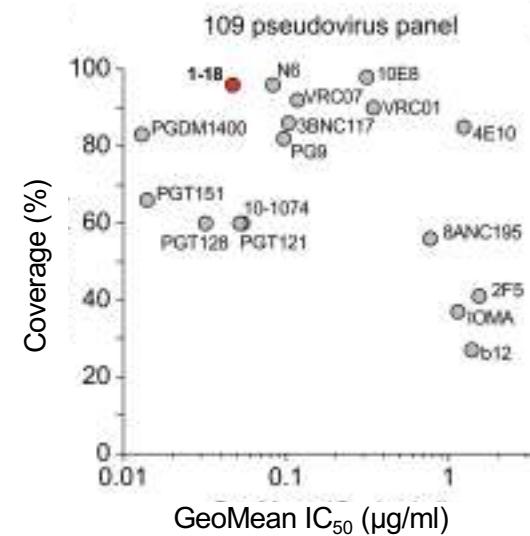
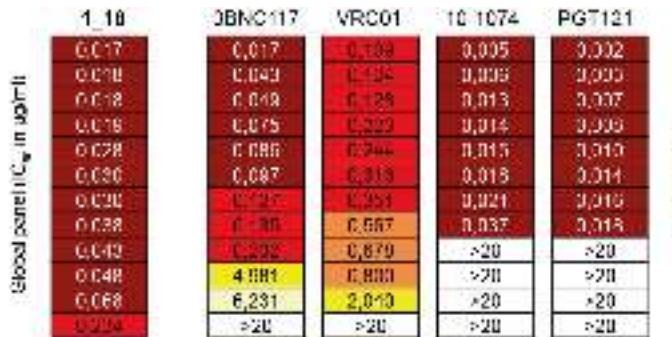
Blood panel (C _v in µg/ml)	1_18
	0,017
	0,018
	0,018
	0,018
	0,028
	0,030
	0,030
	0,038
	0,042
	0,048
	0,068
	0,990

bNAb 1-18 *in vitro*

Blood panel (C ₉ in µg/ml)	1_18	2BNC117	VRC01	10_1074	PGT121
0,017	0,017	0,019	0,005	0,002	
0,018	0,049	0,194	0,009	0,000	
0,018	0,019	0,128	0,013	0,007	
0,019	0,075	0,502	0,014	0,009	
0,028	0,086	0,246	0,015	0,010	
0,030	0,097	0,313	0,018	0,011	
0,036	0,225	0,259	0,021	0,016	
0,038	0,186	0,687	0,037	0,018	
0,042	0,292	0,879	>20	>20	
0,048	4,081	0,800	>20	>20	
0,068	6,231	2,010	>20	>20	
0,993	>20	>20	>20	>20	

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8333033/

bNAb 1-18 *in vitro*



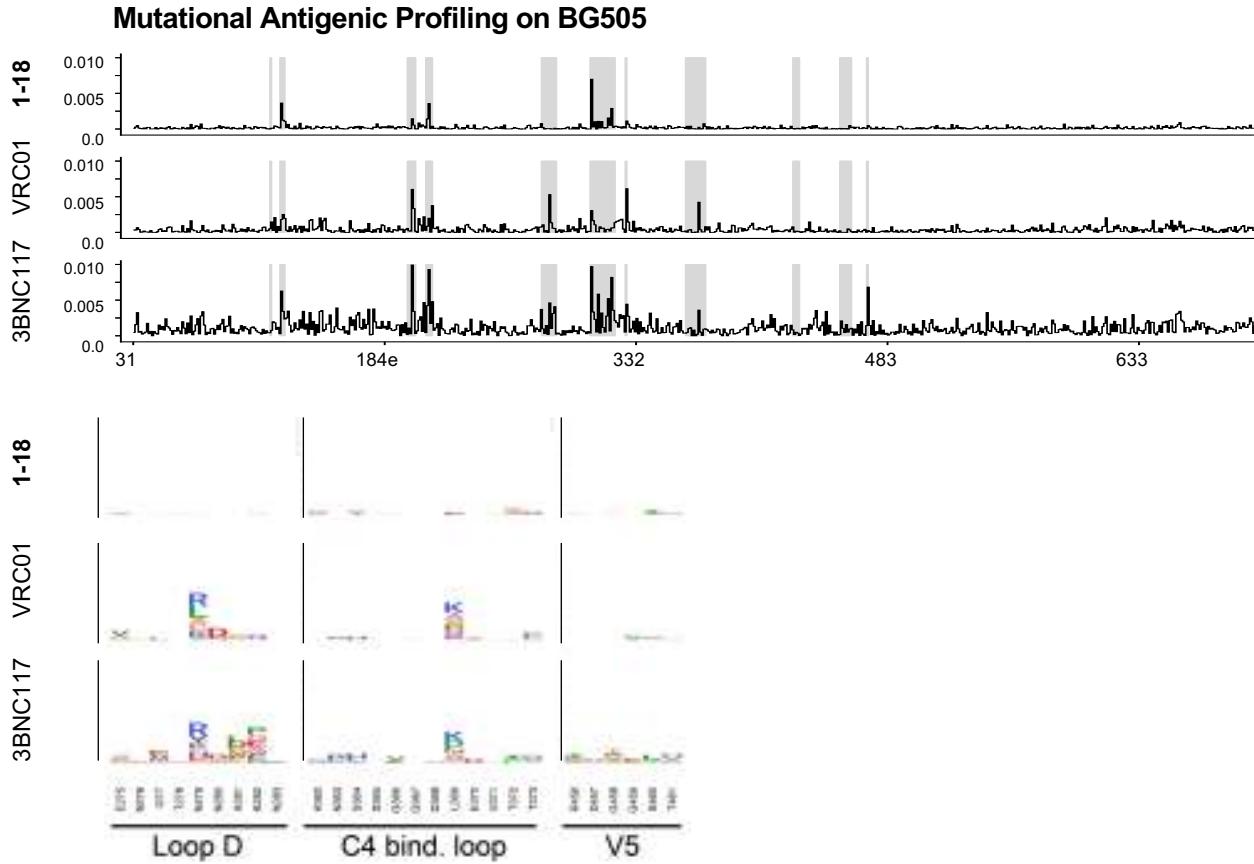
bNAb 1-18 *in vitro*

		SANC117	VRC01	N6	SANC191	SANC196	10-1074	PGT128	PD1B1460	PG16
YU2 wild type IC ₅₀ (nM)		0.029	0.107	0.047	0.256	0.491	0.232	0.090	0.387	0.125
Neutralization fold-change relative to YU2 wild type										
Y2 Loop	E1C2K	0.88	0.64	0.72	1.75	0.87	0.48	1.80	0.30	0.46
	N1E6K	0.59	0.54	0.50	0.54	0.41	0.38	0.76	>5.0	>20.0
	N1N9T	0.66	0.63	0.47	0.71	0.77	0.41	1.46	>6.5	>20.0
	T16S1	0.82	0.50	0.72	0.93	0.97	0.38	0.84	>8.5	>20.0
	T16N	0.45	0.48	0.49	0.88	0.88	0.44	1.48	>8.5	>20.0
Loop D	N276D	0.37	0.36	0.78	0.11	>5.1	0.40	1.80	0.87	1.87
	T278K	0.35	0.32	0.18	>5.1	1.45	1.43	1.01	1.29	
	T278A	0.26	0.31	0.30	0.18	>5.1	0.33	1.45	1.12	1.39
	T278I	0.28	0.31	0.26	0.22	>5.1	1.34	1.28	1.31	1.42
	N279K	>5.0	>23.4	0.74	>5.0	1.86	0.33	0.38	0.38	0.73
	N279H	1.17	0.52	0.40	0.48	1.00	0.36	0.31	0.44	0.78
	N280Y	0.81	>23.4	0.32	>5.0	0.35	0.16	0.08	0.18	0.43
	A281T	0.52	>23.4	15.17	0.68	0.70	0.28	0.16	0.37	0.48
	T278A-A281T	0.52	>23.4	>5.0	0.38	>5.1	1.44	0.23	0.57	0.74
	N285S	0.82	0.61	0.77	0.73	0.97	0.38	1.35	0.57	1.18
V3 Loop	N301D	0.17	0.28	0.34	0.43	1.24	0.87	>51.3	0.76	2.05
	N112K	0.41	0.35	0.28	0.37	0.32	>10.8	>51.3	0.27	0.70
	N332S	0.52	0.41	0.80	1.14	0.88	0.50	>51.3	0.51	1.28
	N332Y	0.69	0.42	0.68	0.85	1.12	>10.8	>51.3	0.62	0.99
	S334D	0.78	1.32	0.81	1.25	0.70	>10.8	>51.3	0.41	1.10
	S334N	0.48	0.48	0.68	0.89	0.90	>10.8	>51.3	0.48	0.76
	G360E	0.2	0.41	0.24	0.27	0.25	0.46	0.14	0.26	0.61
Patches	N385L	0.49	0.93	0.24	0.71	0.80	0.17	0.19	0.31	0.70
	E71M	0.62	0.63	0.64	0.68	0.64	0.76	0.34	0.30	0.73
	E429K	1.10	1.02	0.83	0.82	0.98	0.72	0.50	1.48	1.00
	N440Q	0.93	0.65	1.00	1.41	1.92	0.57	1.26	1.27	1.25
	G458D	2.76	0.97	0.51	>5.0	0.88	0.86	0.26	0.38	0.70
Patch Loop	G459D	0.77	0.70	0.78	0.59	0.64	0.41	0.28	0.40	0.54
	G471R	0.76	1.05	0.80	>5.0	0.82	0.44	0.14	0.74	0.80

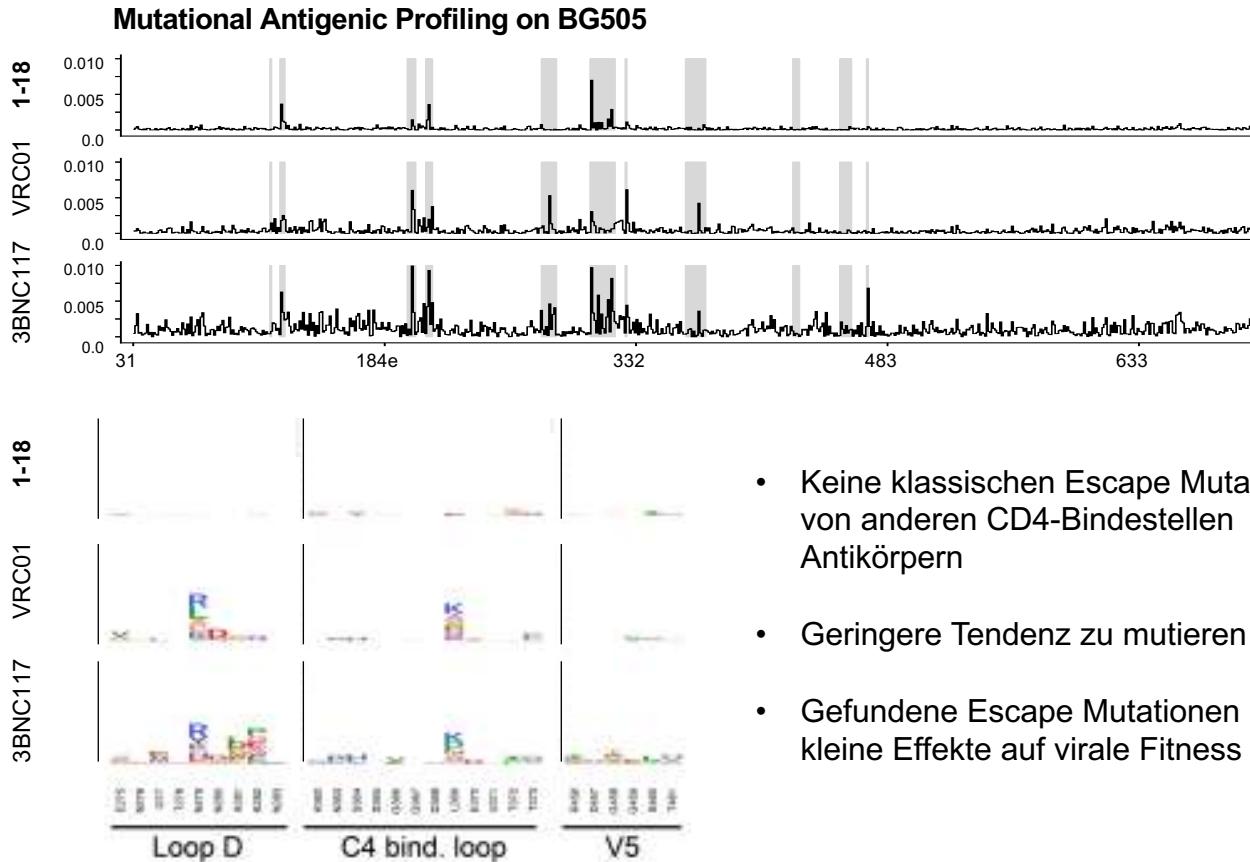
bNAb 1-18 *in vitro*

		1-18	gBNC117	VRC01	N6	BANC131	BANC186	10-1074	PGT128	PD101460	PG16
YU2 wild type IC ₅₀ (nM)		0.019	0.029	0.107	0.047	0.256	0.491	0.232	0.090	0.387	0.125
Neutralization fold-change relative to YU2 wild type											
Y2 Loop	E1C2K	0.88	0.88	0.64	0.72	1.75	0.87	0.48	1.80	0.30	0.46
	N1E6K	0.47	0.39	0.54	0.37	0.54	0.41	0.38	0.75	>6.6	>20.0
	N1N8H	0.32	0.36	0.53	0.47	0.71	0.77	0.41	1.46	>6.6	>20.0
	T16S1	0.84	0.82	0.50	0.72	0.93	0.97	0.38	0.84	>8.5	>20.0
	T16N	0.83	0.45	0.48	0.49	0.88	0.88	0.44	1.48	>8.5	>20.0
Loop D	N276D	0.16	0.37	0.36	0.78	0.11	>5.1	0.40	1.80	0.87	1.87
	T278K	0.21	0.37	0.35	0.32	0.18	>5.1	1.45	1.43	1.01	1.29
	T278K	0.15	0.26	0.31	0.30	0.18	>5.1	0.33	1.45	1.12	1.39
	T278I	0.26	0.29	0.31	0.26	0.22	>5.1	1.34	1.29	1.31	1.42
	N279K	0.30	>5.1	>23.4	0.74	>5.1	1.86	0.33	0.38	0.38	0.73
	N279H	0.32	1.17	0.52	0.40	0.48	1.00	0.36	0.31	0.44	0.78
	N280Y	0.26	0.81	>23.4	0.32	>5.1	0.35	0.16	0.08	0.16	0.43
	A281I	2.21	>5.1	>23.4	15.17	0.68	0.70	0.28	0.16	0.37	0.46
	T278A-A281T	1.84	>5.1	>23.4	>5.1	0.83	>5.1	1.44	0.23	0.57	0.74
Y3 Loop	N385S	0.88	0.82	0.61	0.77	0.73	0.97	0.38	1.35	0.57	1.18
	N3C1D	0.17	0.28	0.34	0.43	0.43	1.24	0.87	>11.3	0.76	2.05
	N112K	0.83	0.47	0.35	0.28	0.37	0.32	>10.8	>11.3	0.27	0.70
	N332S	0.53	0.52	0.41	0.80	1.14	0.88	0.89	>11.3	0.51	1.28
	N332Y	0.58	0.69	0.42	0.68	0.85	1.72	>10.8	>11.3	0.62	0.99
	S334D	0.58	0.79	1.32	0.81	1.25	0.70	>10.8	>11.3	0.41	1.10
	S334N	0.42	0.48	0.48	0.68	0.89	0.90	>10.8	>11.3	0.48	0.76
CDR H4	G360E	0.07	0.21	0.41	0.24	0.27	0.25	0.46	0.14	0.26	0.61
	N385L	0.07	0.49	0.30	0.24	0.71	0.80	0.17	0.19	0.31	0.70
	D71M	0.08	0.63	0.64	0.68	0.64	0.76	0.34	0.30	0.30	0.73
Patches	E429K	0.47	1.10	1.02	0.83	0.82	0.98	0.72	0.50	1.48	1.00
	N448Q	0.58	0.93	0.65	1.00	1.41	1.92	0.57	1.26	1.27	1.25
	G458D	0.21	2.76	0.97	0.51	>5.1	0.88	0.88	0.26	0.26	0.70
	G458D	0.39	0.79	0.70	0.78	0.59	0.64	0.41	0.28	0.40	0.54
	G471R	0.53	0.76	1.05	0.80	>5.1	0.82	0.44	0.14	0.74	0.80

bNAb 1-18 *in vitro*

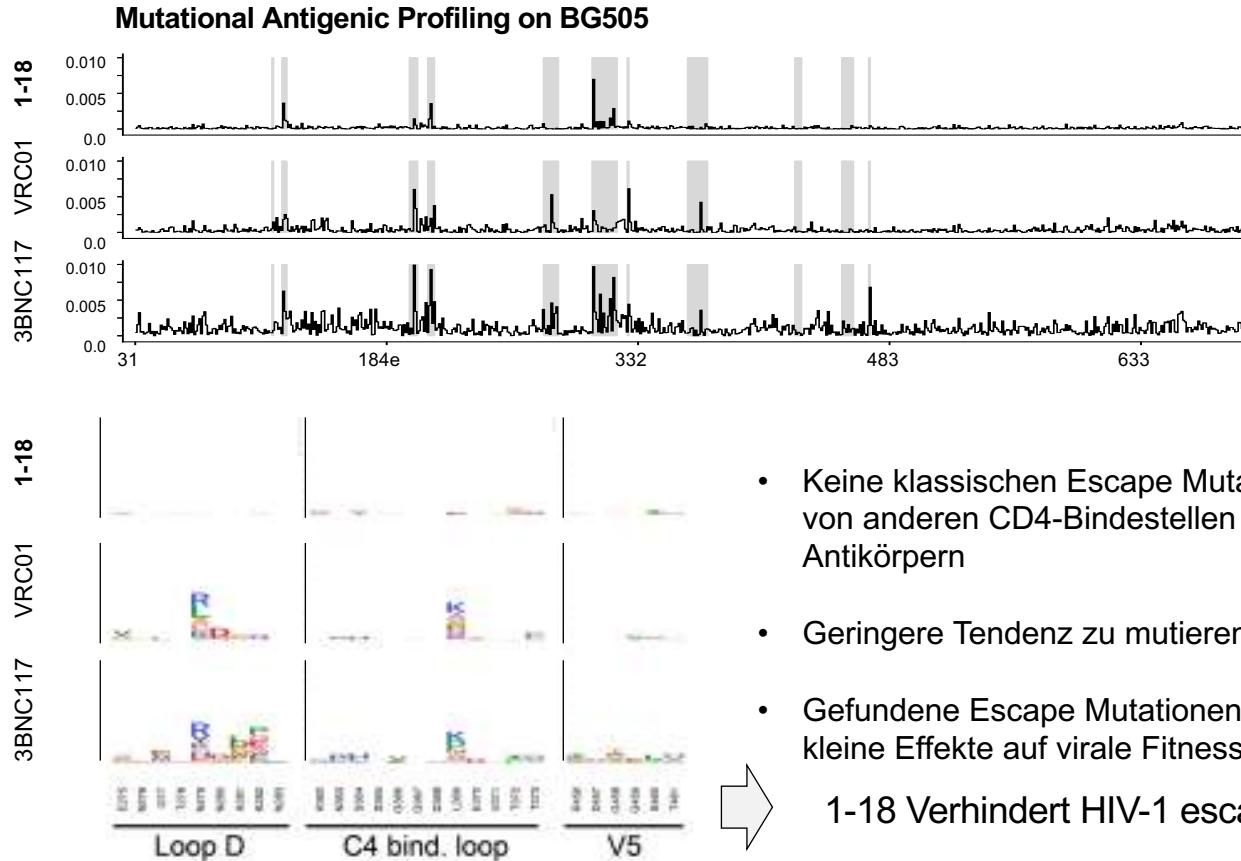


bNAb 1-18 *in vitro*

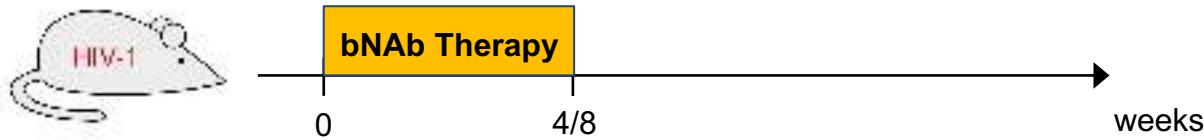


- Keine klassischen Escape Mutationen von anderen CD4-Bindestellen Antikörpern
 - Geringere Tendenz zu mutieren
 - Gefundene Escape Mutationen nur kleine Effekte auf virale Fitness

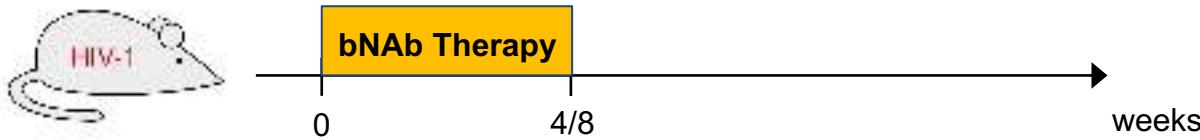
bNAb 1-18 *in vitro*



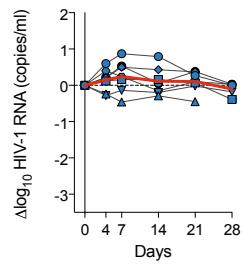
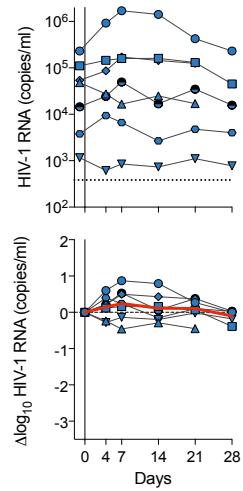
bNAb 1-18 *in vivo*



bNAb 1-18 *in vivo*



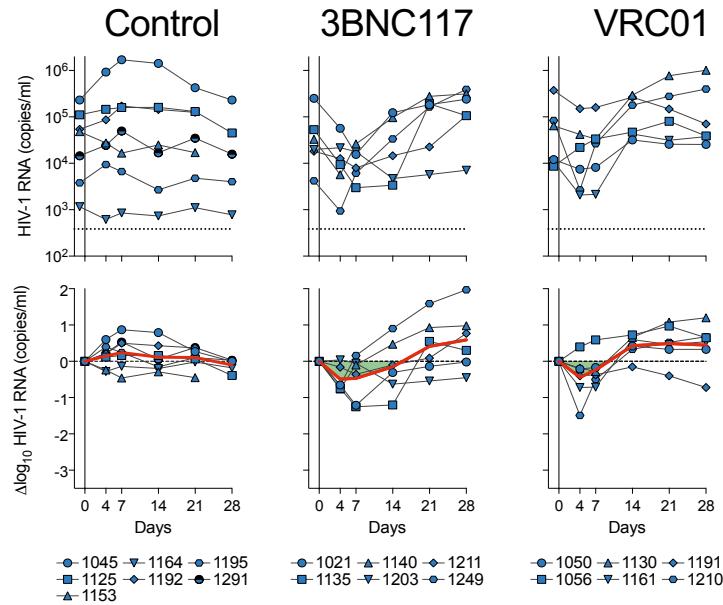
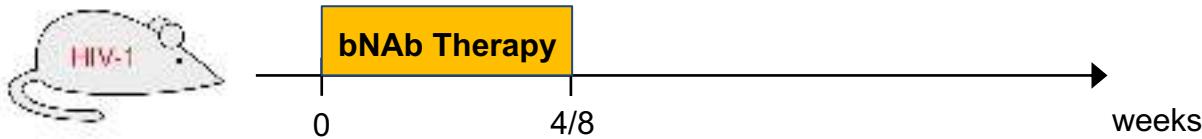
Control



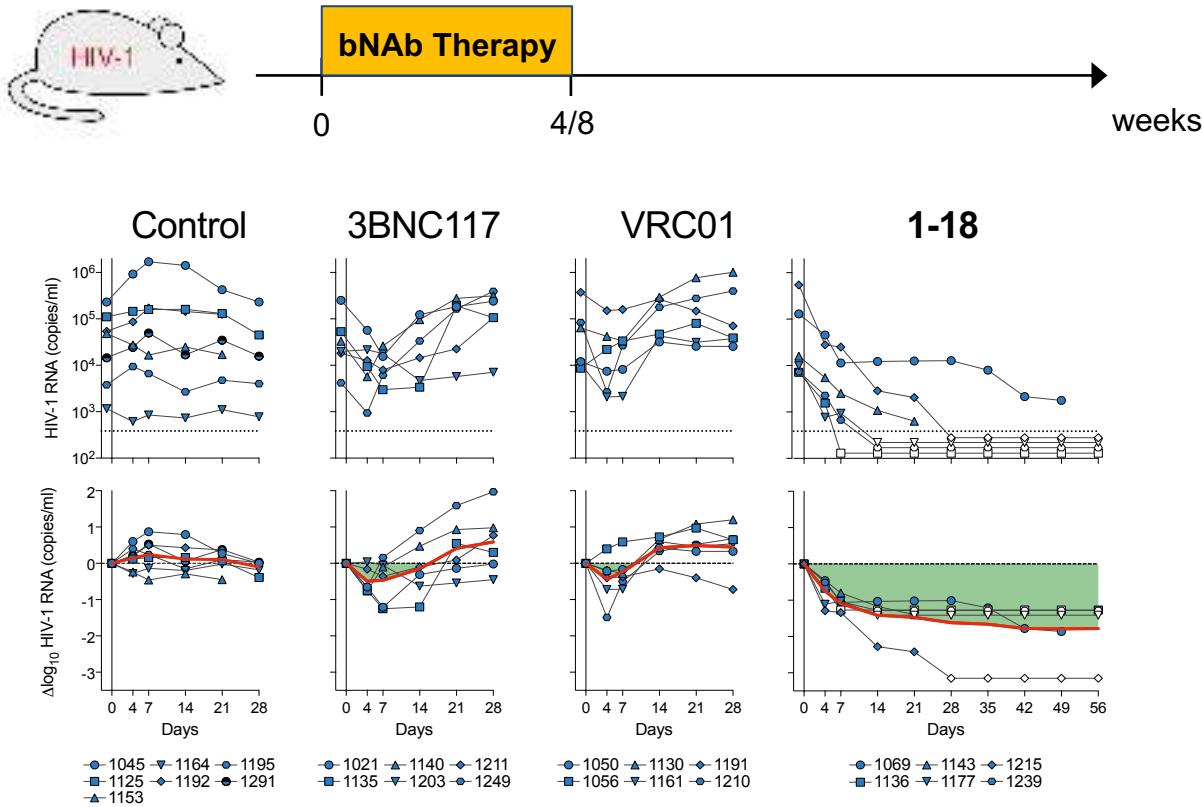
Legend:

- 1045 ▽ 1164 ○ 1195
- 1125 □ 1192 ● 1291
- ▲ 1153

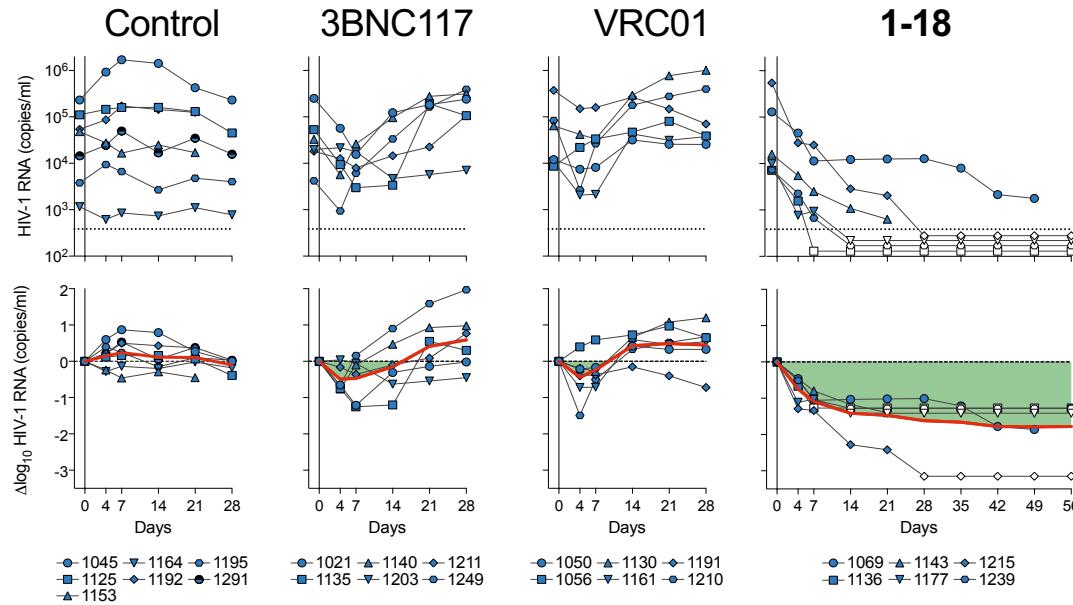
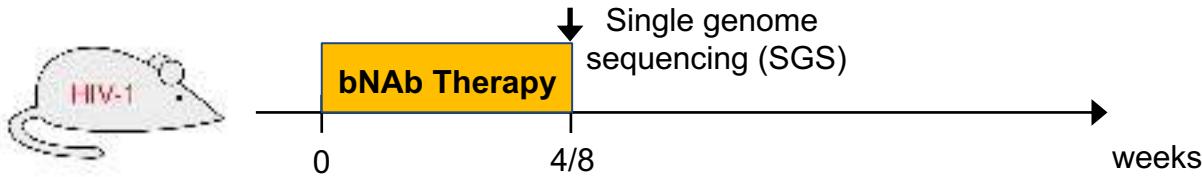
bNAb 1-18 *in vivo*



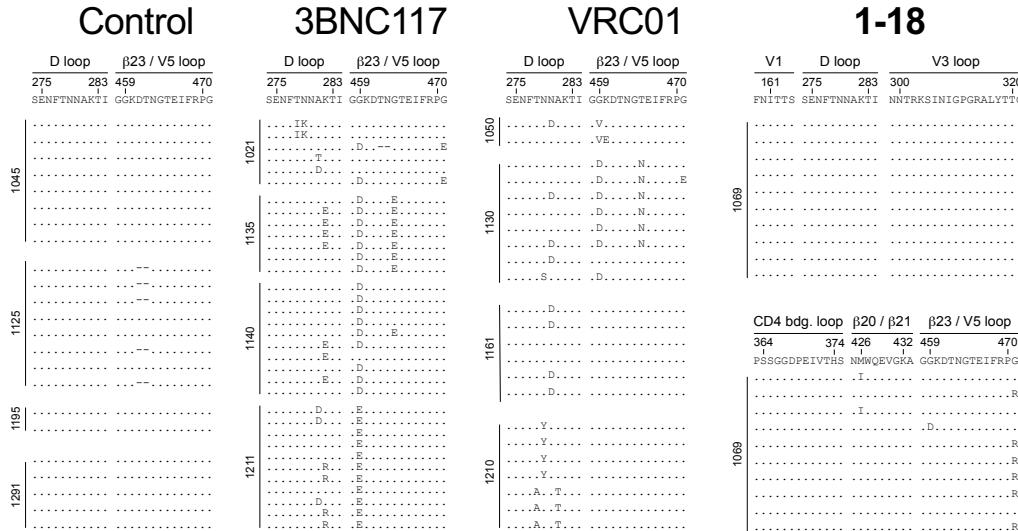
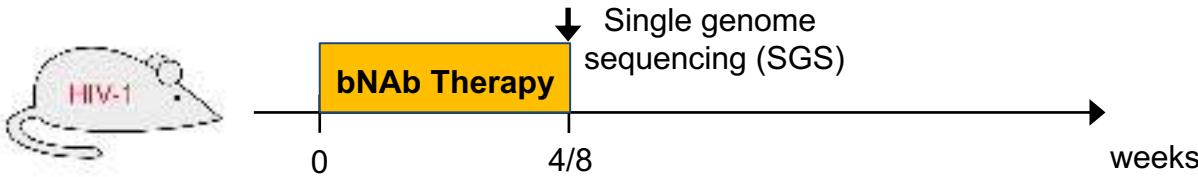
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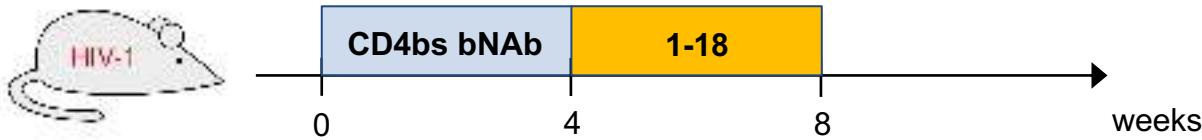
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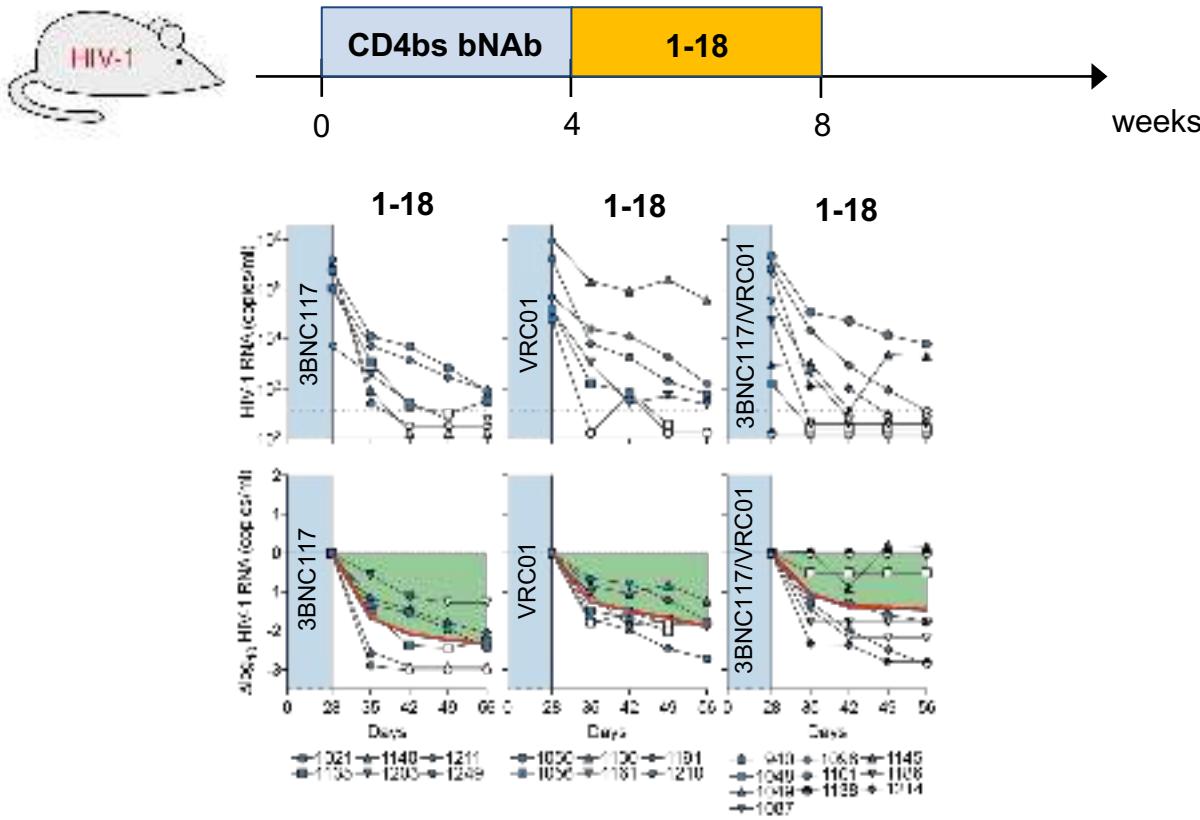
bNAb 1-18 *in vivo*



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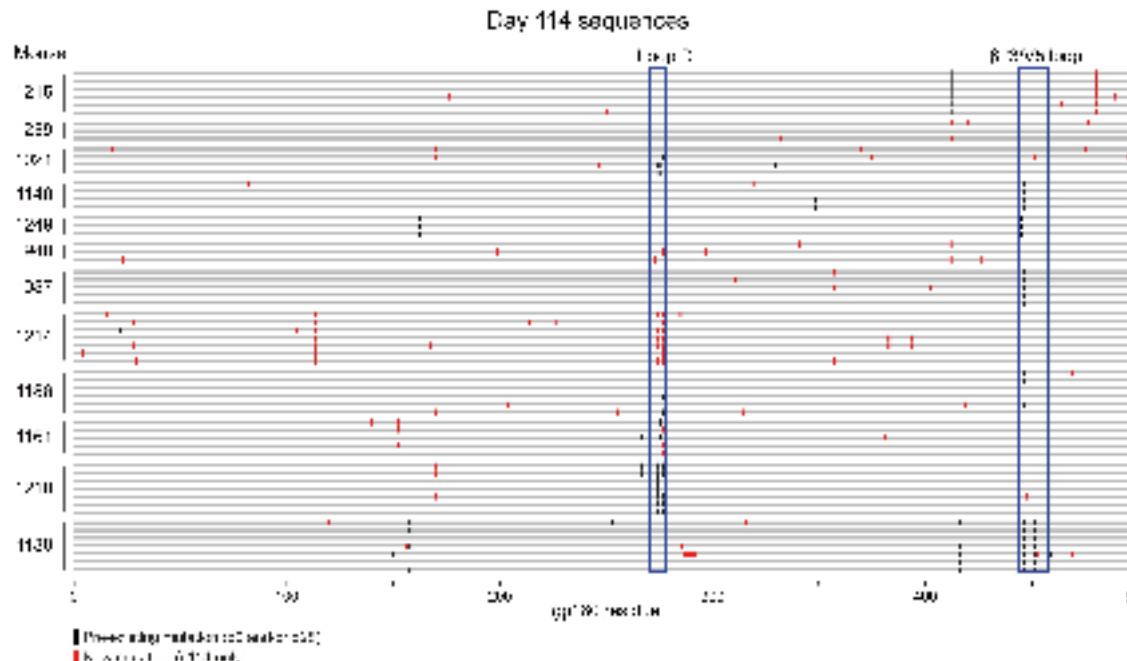
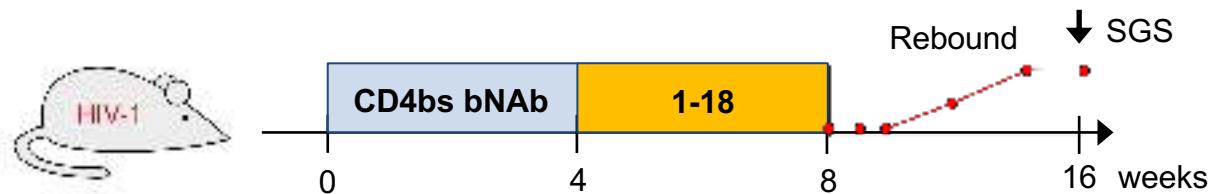
bNAb 1-18 *in vivo*



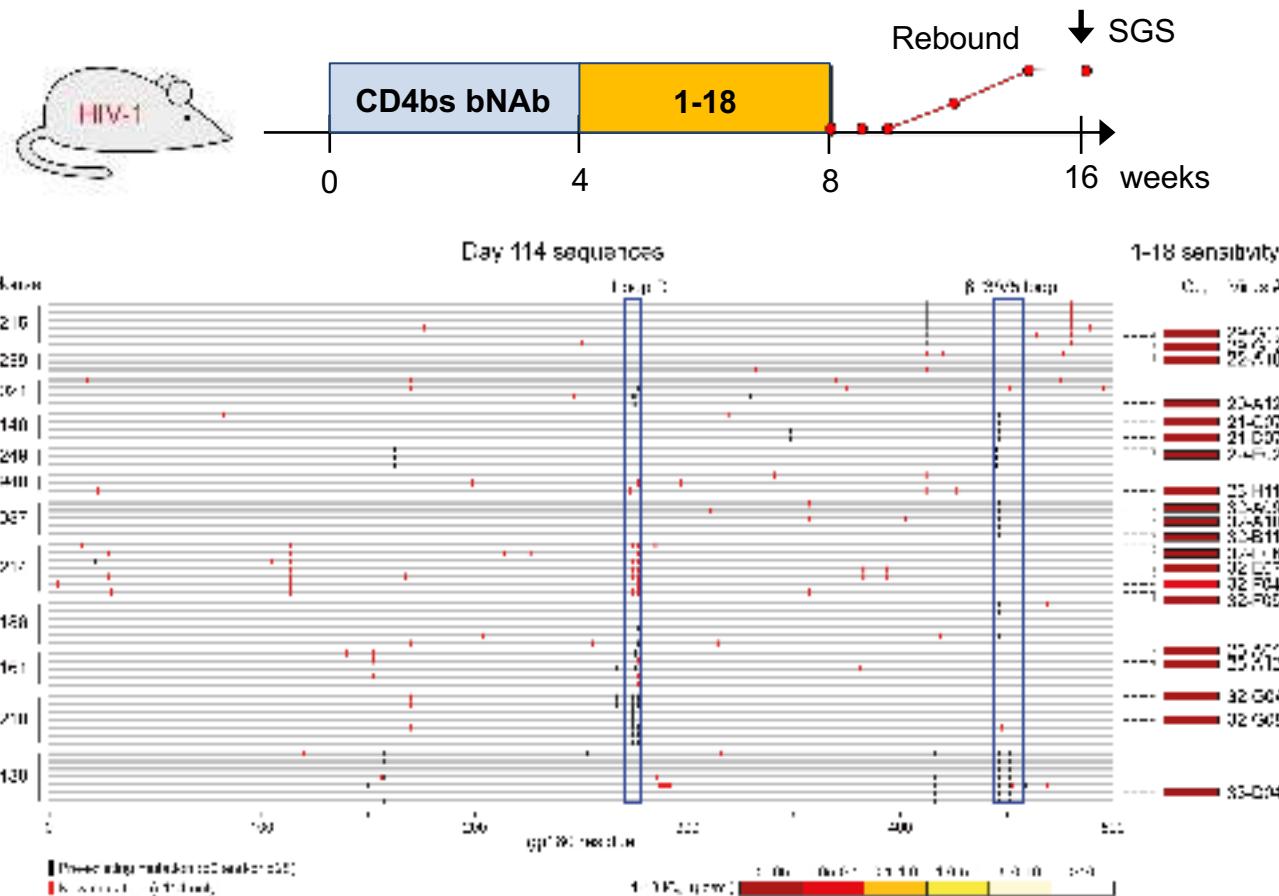
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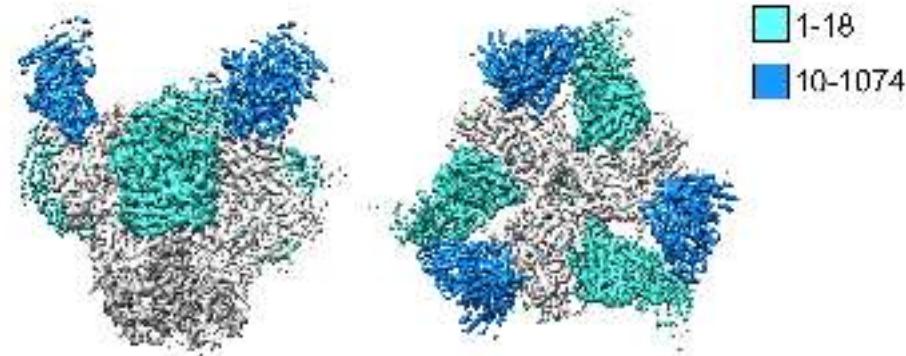
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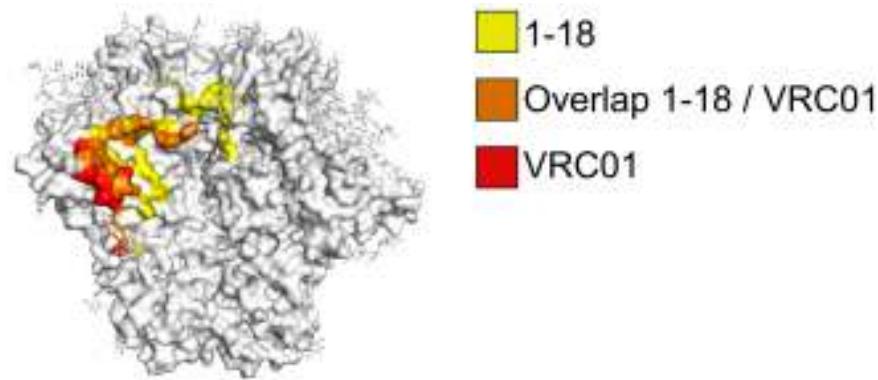
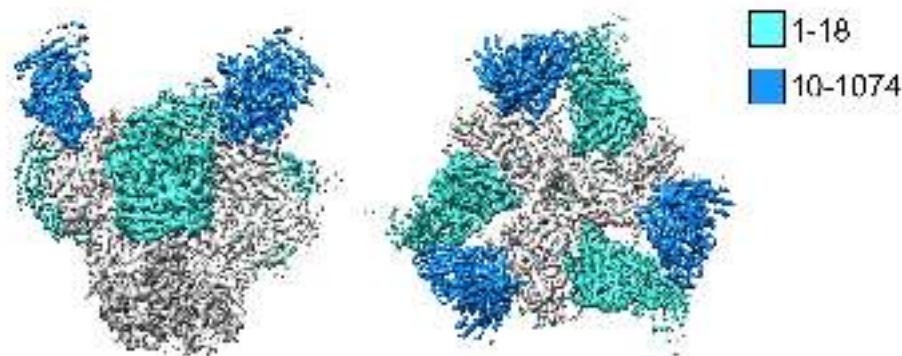
bNAb 1-18 *in vivo*



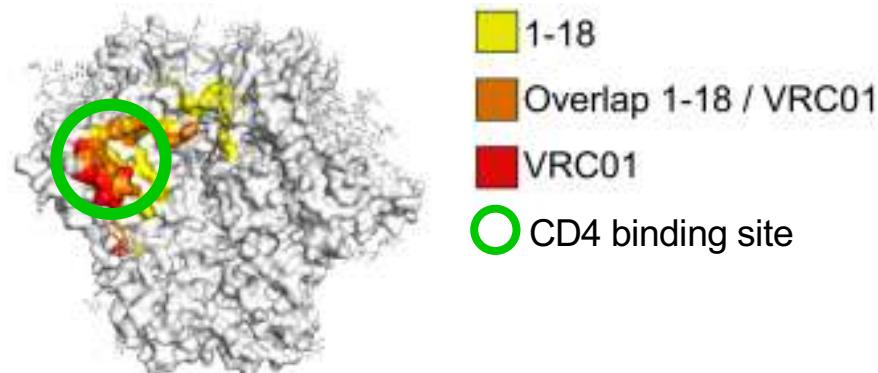
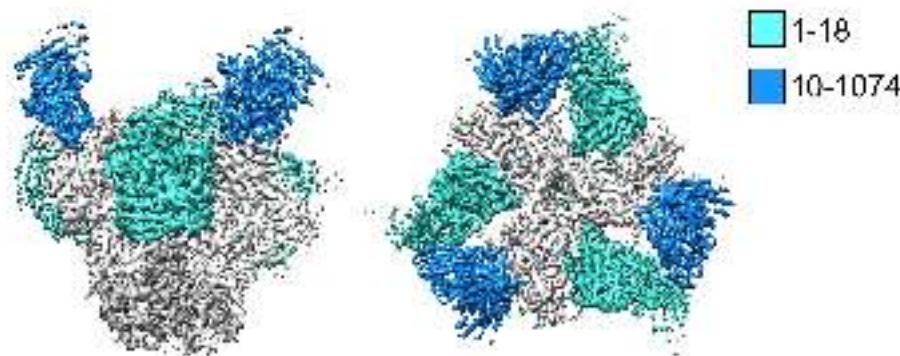
Cryo-EM von 1-18



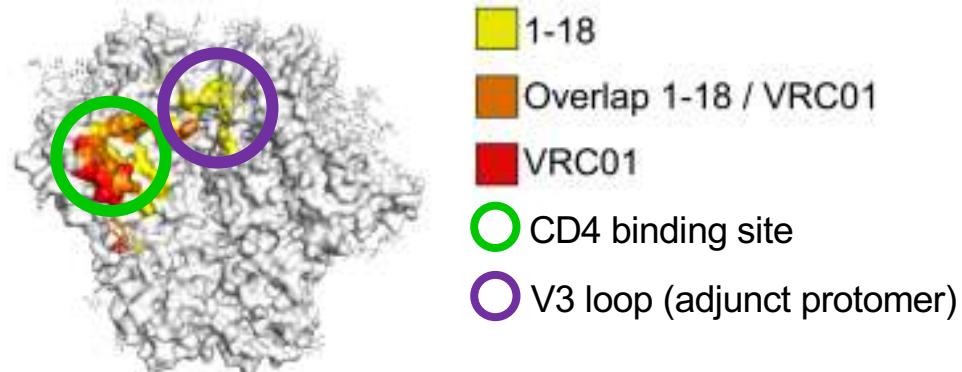
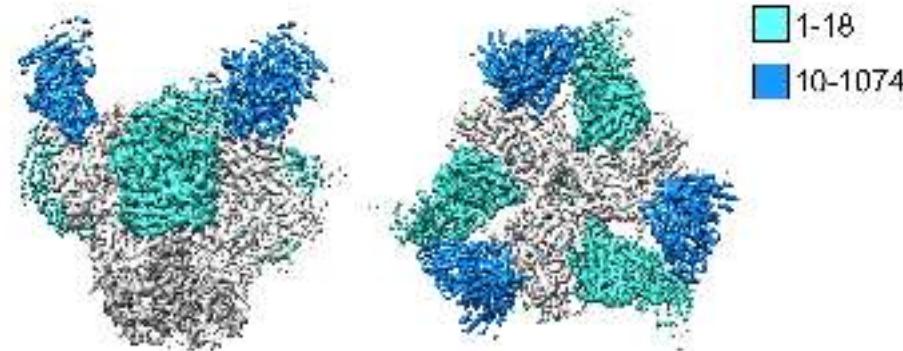
Cryo-EM von 1-18



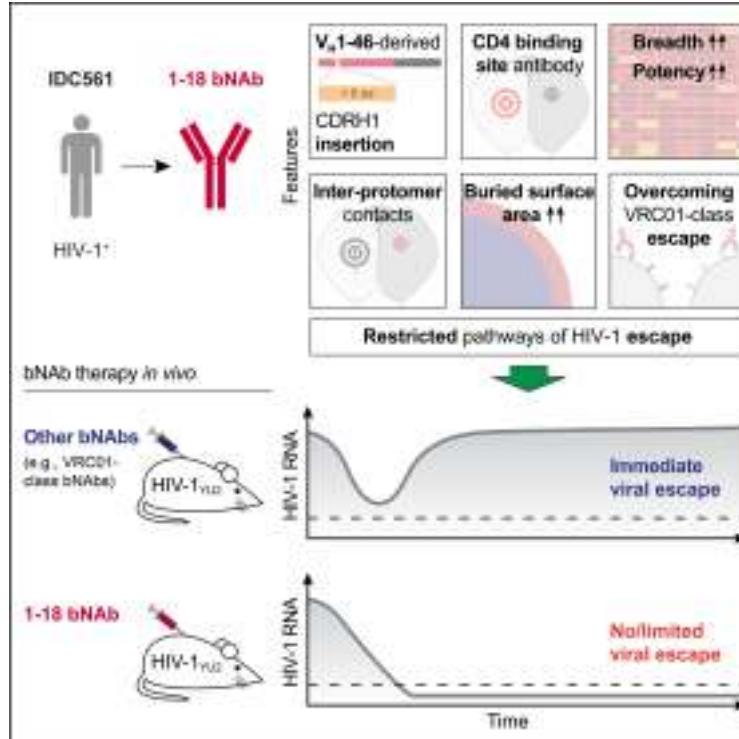
Cryo-EM von 1-18



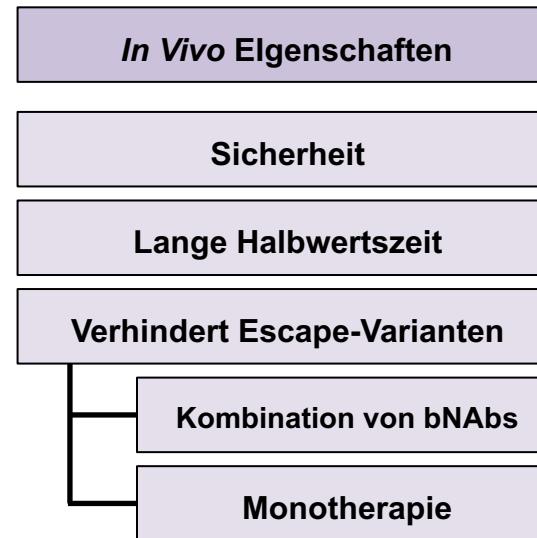
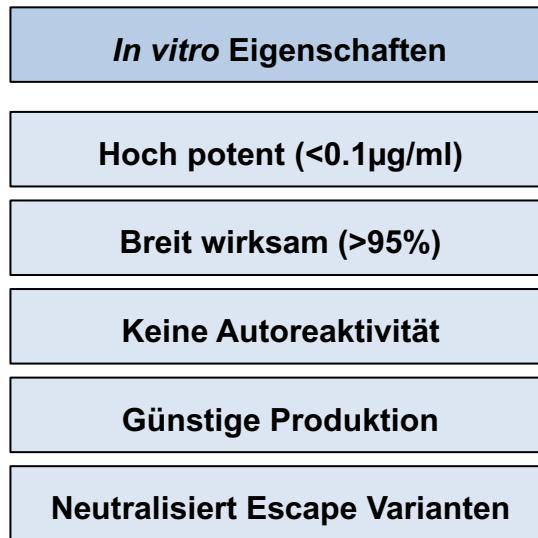
Cryo-EM von 1-18



Eigenschaften von 1-18



Eigenschaften von 1-18



Eigenschaften von 1-18

In vitro Eigenschaften

GeoMean IC₅₀ 0.048 µg/ml

Breit wirksam (>95%)

Keine Autoreaktivität

Günstige Produktion

Neutralisiert Escape Varianten

In Vivo Eigenschaften

Sicherheit

Lange Halbwertszeit

Verhindert Escape-Varianten

Kombination von bNAbs

Monotherapie



Eigenschaften von 1-18

In vitro Eigenschaften

GeoMean IC₅₀ 0.048 µg/ml

Neutralisiert 97% der Isolate

Keine Autoreaktivität

Günstige Produktion

Neutralisiert Escape Varianten

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In Vivo Eigenschaften

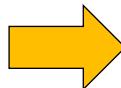
“Sicher” im Mausmodell

Lange Halbwertszeit

Verhindert Escape-Varianten

Kombination von bNAbs

Monotherapie



1-18 als vielversprechender Kandidat für klinischen Einsatz

Vielen Dank für ihre Aufmerksamkeit!

Vielen Dank für ihre Aufmerksamkeit!

Und vielen Dank an die PEG für die Verleihung des
Wolfgang-Stille-Wissenschaftspreis!

