ＷＨＯ（世界保健機関）が、２４日までに「子宮頸がんワクチンは安全」とする声明を再び出しました。

子宮頸がんワクチンの副反応をめぐっては、日本だけでなく、フランスやデンマークなど、世界各国で報告されていて、調査や研究が行われていますが、ＷＨＯの「ワクチン安全性諮問委員会」は、「接種のリスクがあったとしても、とても小さく、がんを予防する効果のほうが高い」としています。

また、接種の推奨を一時中止している日本については、「若い女性をがんの危険にさらしている」と指摘しています。（24日18:14）

Physiological effects of chronic adoministration of C. aromatica or 6-MITC for bone marrow suppression by anti-tumor agents.

Significant growths of B220+B cells and CD11c+dendritic cells in Peyer`s Patches, which are located in large intestine.

Including productions of IgA and anti-bacteria peptides for mucosal immunity in large intestine.

Physiological effect of intramuscular injection of Cervarix on central nervous system (CNS), especially Hippocampus.

Auto-antibody productions in serum drived from NF-κBp50-null mice with intramuscular injection of Cervarix.

Future research policy to solve the physiological effects of chronic adoministration of C. aromatica or 6-MITC.

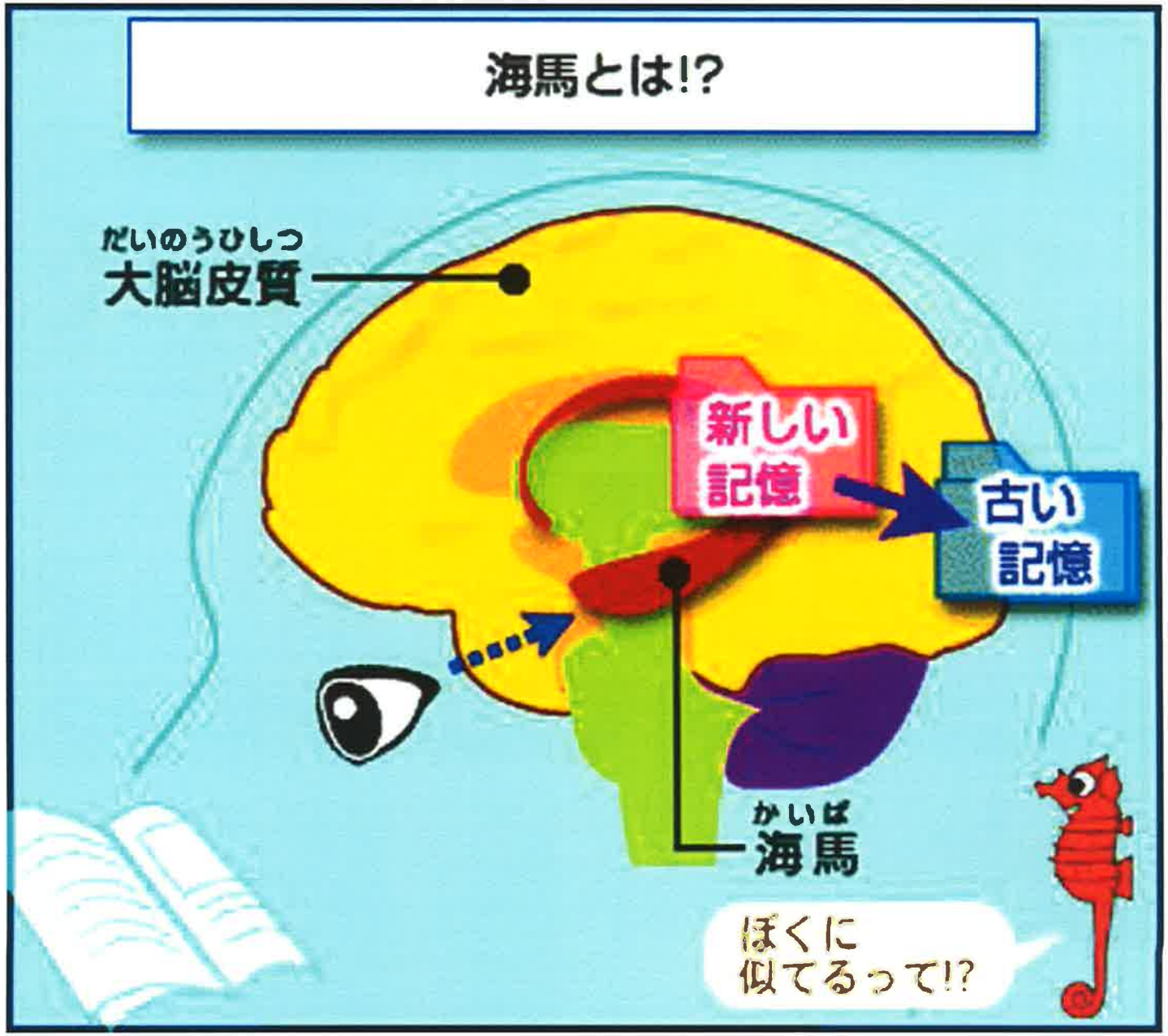
02. 23. 2015

Cervarixの中枢神経「海馬」への影響：

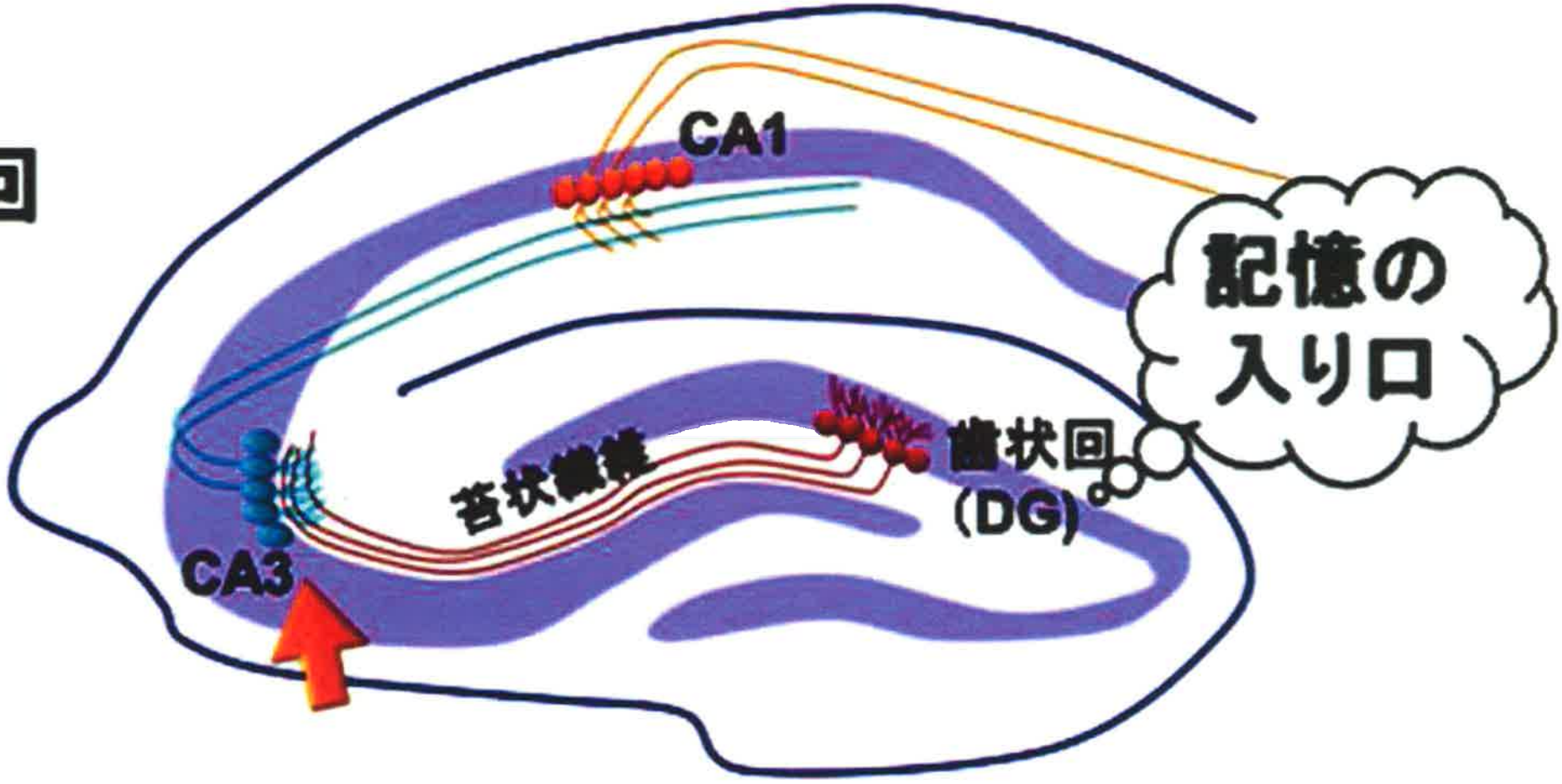
①患者の多くに線維筋痛症にほとんどない「物忘れなどの高次脳機能障害」が起きている。

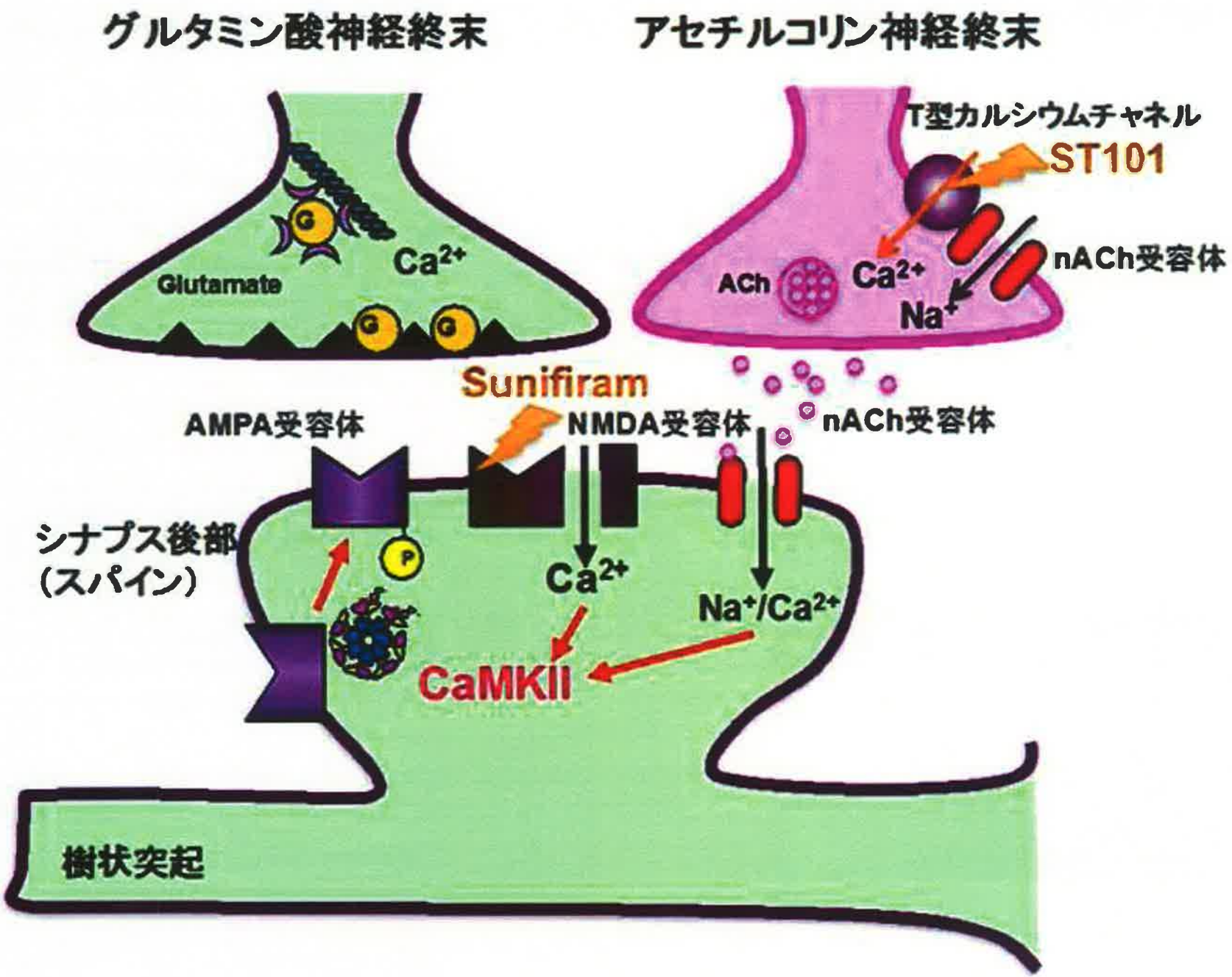
②患者の多くで、神経伝達に必須なグルタミン受容体の１つであるNMDA受容体に対する抗体(自己抗体)が認められている。

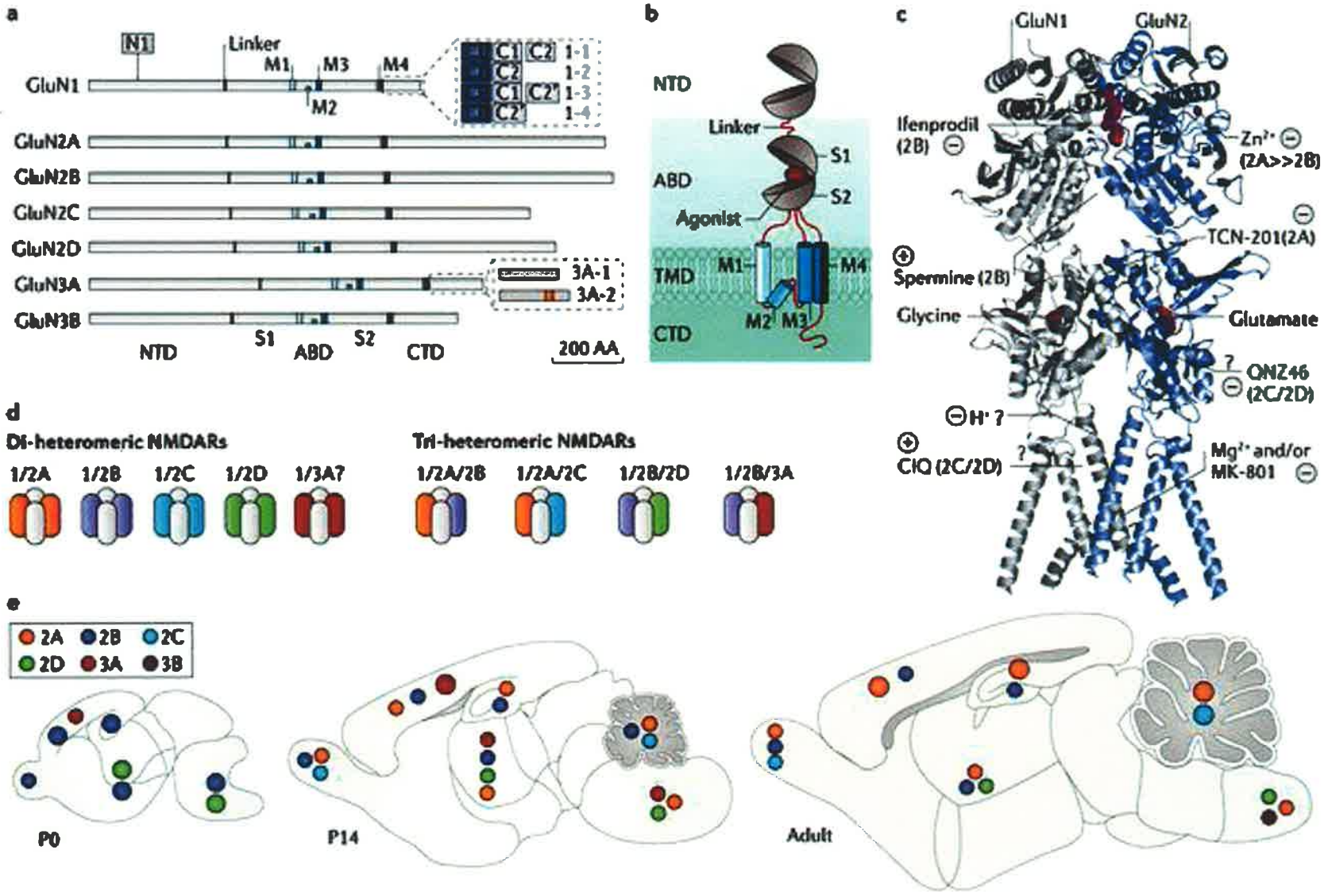
①と②の臨床所見から、NMDA受容体を中心とした神経回路で構成されいる中枢神経、特に、記憶の中枢を担っている「海馬」ついてFocusを絞って検討を行っています。


海馬とは!?
だいのうひしつ
大脳皮質
新しい
記憶
古い
記憶
かいば
海馬
ぼくに
似てるって!?

歯状回
↓
CA3
↓
CA1




グルタミン酸神経終末
アセチルコリン神経終末
T型カルシウムチャネル
ST101
nACh受容体
Glutamate
Ca2+
ACh
Ca2+
Na+
Sunifiram
AMPA受容体
NMDA受容体
nACh受容体
シナプス後部
(スパイン)
P
Ca2+
Na+/Ca2+
CaMKII
樹状突起


a
N1
Linker
M1
M3
M4
M2
GluN1
C1
C2
1-1
1-2
1-3
1-4
GluN2A
GluN2B
GluN2C
GluN2D
GluN3A
GluN3B
3A-1
3A-2
NTD
S1
ABD
S2
CTD
200 AA
b
NTD
Linker
S1
S2
ABD
Agonist
TMD
M1
M4
M2
M3
CTD
c
GluN1
GluN2
Ifenprodil (2B)
Zn2+ (2A>>2B)
TCN-201(2A)
Spermine (2B)
Glycine
Glutamate
?
QNZ46 (2C/2D)
H+ ?
ClQ (2C/2D)
?
Mg2+ and/or MK-801
d
Di-heteromeric NMDARs
1/2A
1/2B
1/2C
1/2D
1/3A?
Tri-heteromeric NMDARs
1/2A/2B
1/2A/2C
1/2B/2D
1/2B/3A
e
2A
2B
2C
2D
3A
3B
P0
P14
Adult

Cell. 1995 Jan 27;80(2):321-30.

Targeted disruption of the p50 subunit of NF-kappa B leads to multifocal defects in immune responses.

Sha WC[1], Liou HC, Tuomanen EI, Baltimore D.

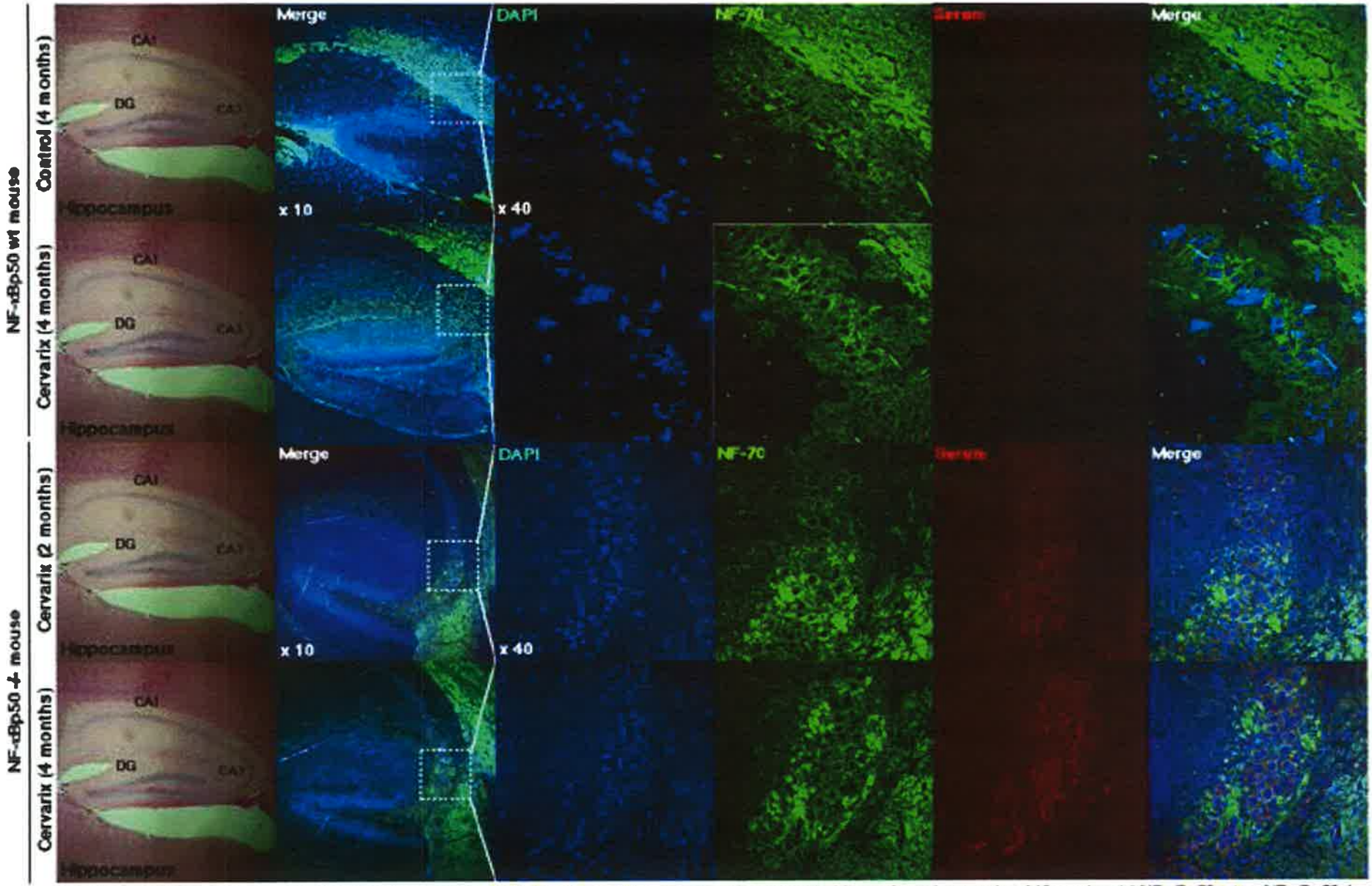
Author information

Abstract

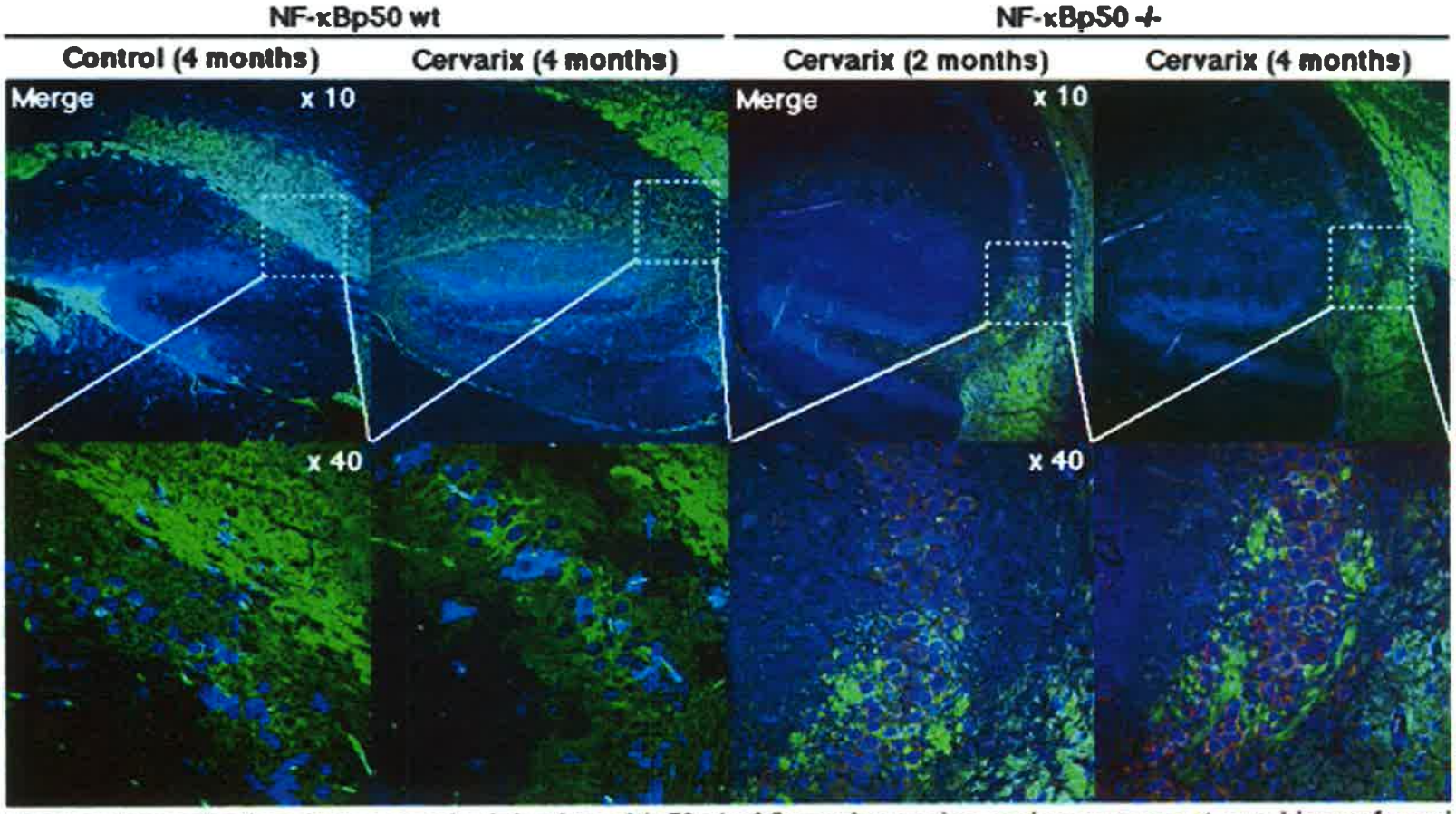
NF-kappa B, a heterodimeric transcription factor composed of p50 and p65 subunits, can be activated in many cell types and is thought to regulate a wide variety of genes involved in immune function and development. Mice lacking the p50 subunit of NF-kappa B show no developmental abnormalities, but exhibit multifocal defects in immune responses involving B lymphocytes and nonspecific responses to infection. B cells do not proliferate in response to bacterial lipopolysaccharide and are defective in basal and specific antibody production. Mice lacking p50 are unable effectively to clear L. monocytogenes and are more susceptible to infection with S. pneumoniae, but are more resistant to infection with murine encephalomyocarditis virus. These data support the role of NF-kappa B as a vital transcription factor for both specific and nonspecific immune responses, but do not indicate a developmental role for the factor.

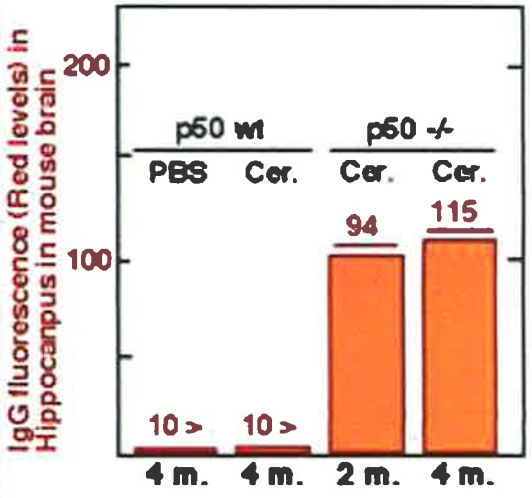
autoimmunity-like disease

PMID: 7834752 [PubMed - indexed for MEDLINE]



Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50 wt or NF-κBp50-/- mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 06, 2014. At 30 days after 1st shot of Cervarix vaccine, Intramascular injection with 50 μl of Cervarix vaccine was performed at April 3rd, 2014. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies.
Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml. Immunofluorescence analysis of Neurofilament-70 (NF-70, a major component of the neuronal cytoskeleton of neuronal cells), mouse IgG (autoantibody in serum, which was corrected from immunized BALB/c mouse with Cervarix vaccine at May 3rd, 2014, July 1st, 2014) in normal BALB/c mouse brain tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of brain tissue section: brain, especially hippocampus of BALB/c mouse with α-Neurofilament-70 (NF-70)-m Ab conjugated with Alexa488 (SIGMA-Aldrich), α-mouse IgG-pAb-conjugated with Alexa 549 (eBioscience, Inc.) and DAPI (Vector Laboratories, Inc.) was performed at February 07 - 08, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at February 09, 2015.





Control (tap water)
C. aromatica (2 mg/day)
6-MITC (150mg/day)

Z stack:
Image Dim. z; 16 μm
Sections ; 50 sections

Neurofilament-70 (NF-70)
IgG (autoantibody)
DAPI

Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50 wt or NF-κBp50-/- mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine, Intramascular injection with 50 μl of Cervarix vaccine was parformed at April 3rd, 2014. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies.
Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml. Immunofluorescence analysis of Neurofilament-70 (NF-70, a major component of the neuronal cytoskeleton of neuronal cells), mouse IgG (autoantibody in serum, which was corrected from immunized BALB/c mouse with Cervarix vaccine at May 3rd, 2014, July 1st, 2014) in normal BALB/c mouse brain tissue, detail is indicated in the supplementary information.
Immunofluorescence analysis of brain tissue section: brain, especially hippocampus of BALB/c mouse with α-Neurofilament-70 (NF-70)-m Ab conjugated with Alexa488 (SIGMA-Aldrich), α-mouse IgG-pAb-conjugated with Alexa 549 (eBioscience, Inc.) and DAPI (Vector Laboratories, Inc.) was performed at February 07 - 08, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at February 09, 2015.

Physiological significance of chronic adoministration of C. aromatica and 6-MITC in metabolism and tumour immunity.

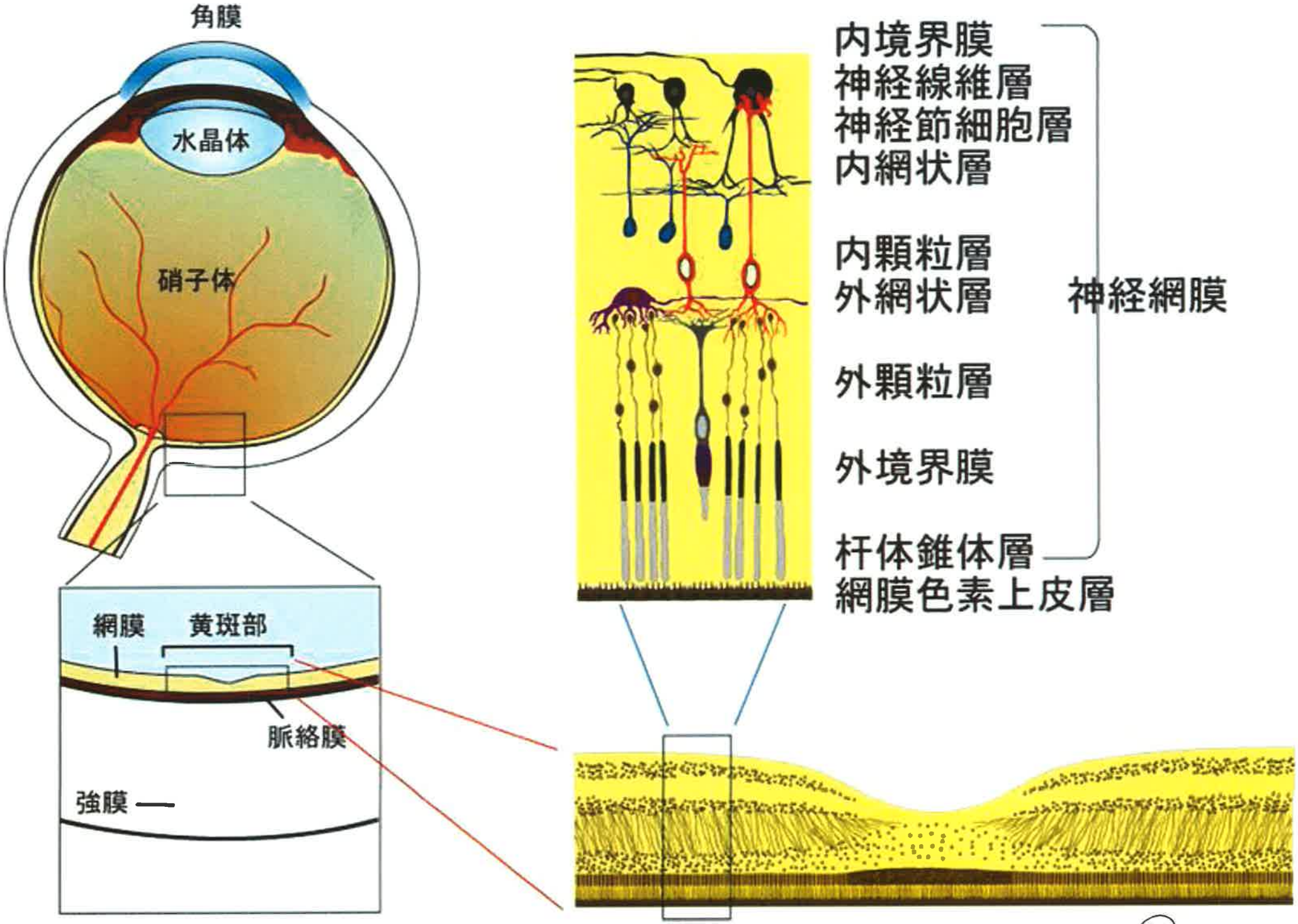
The physiological effects of chronic adoministration of C. aromatica or 6-MITC in Redox regulation, Tiol products in serum.

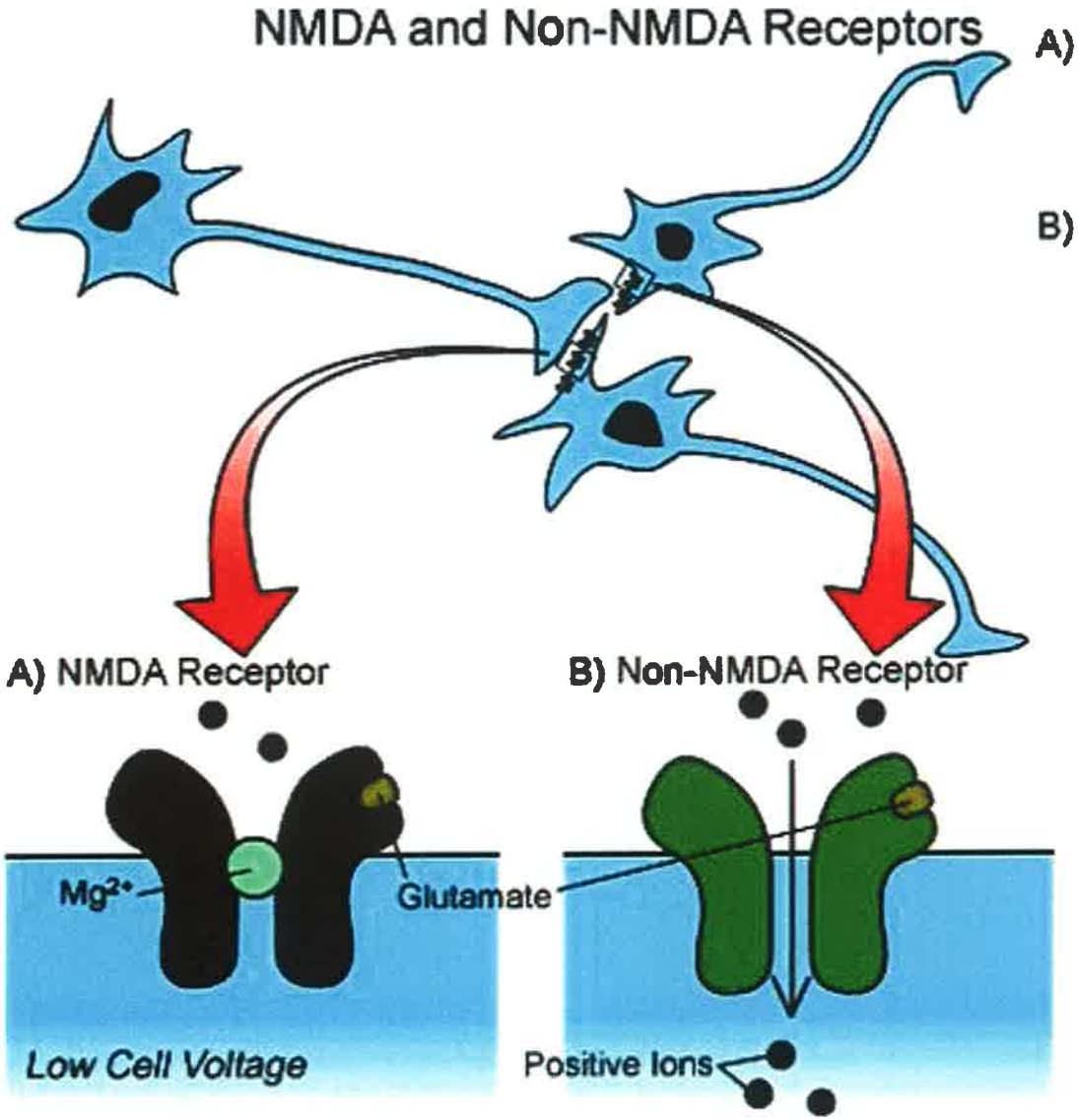
Biological function of chronic adoministration of C. aromatica or 6-MITC on tumourigenesis of syngenenic grafting with Lewis lung carcinoma.

Physiological effect of intramuscular injection of Cervarix on central nervous system (CNS) and abnomal lymphocyte progration.

Production of autoantibody in serum of NF-κBp50-null mice with intramuscular injection of Cervarix.

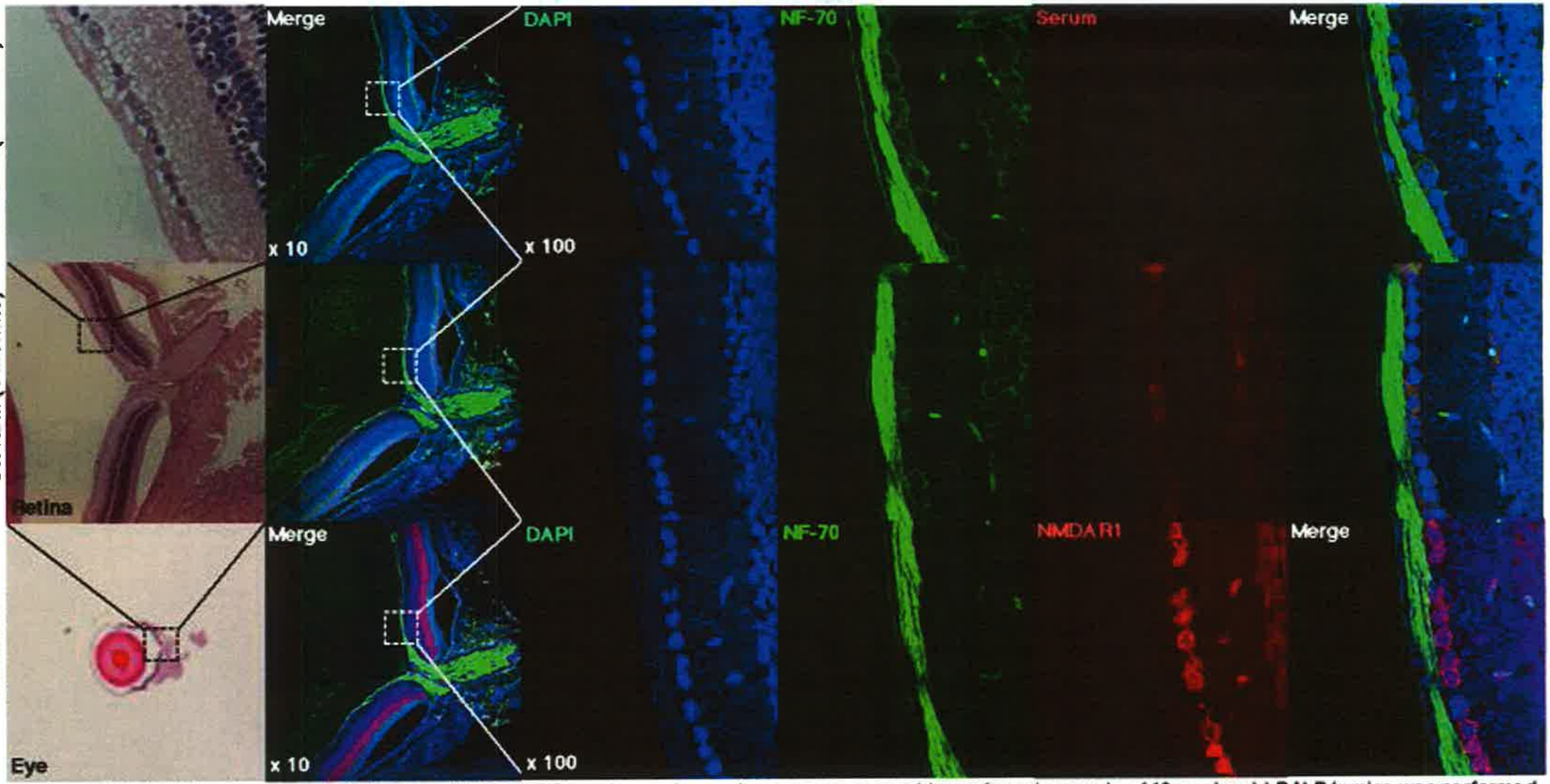
Observation of B cell lymphoma in NF-κBp50-null mice with intramuscular injection of Cervarix.


角膜
水晶体
硝子体
網膜
黄斑部
脈絡膜
強膜
内境界膜
神経線維層
神経節細胞層
内網状層
内顆粒層
外網状層
外顆粒層
外境界膜
杆体錐体層
網膜色素上皮層
神経網膜



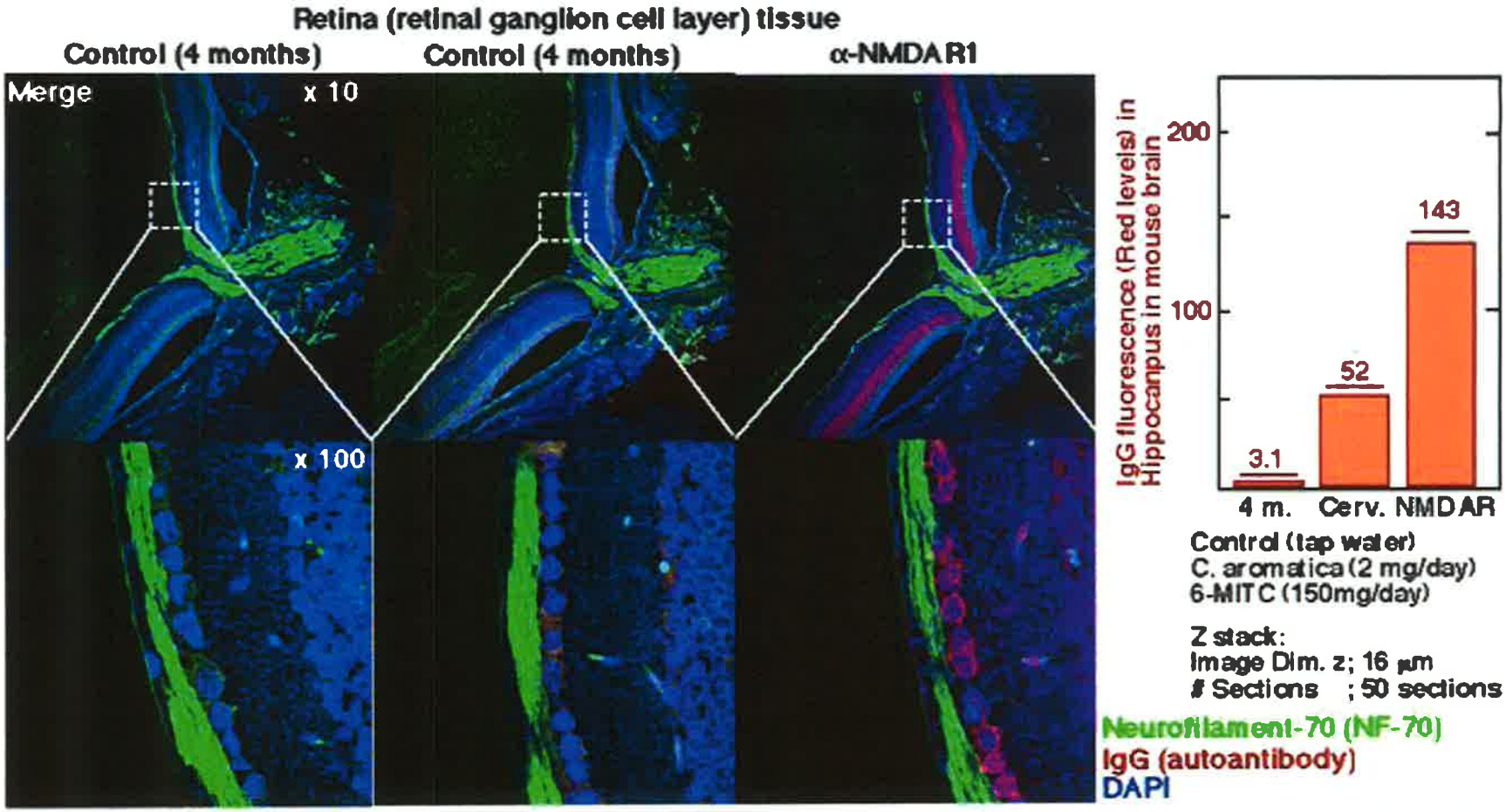
A) The NMDA receptor is usually blocked by the Mg^{2+} ion. Positive ions are unable to rush in even if glutamate binds to NMDA unless the Mg^{2+} ion is removed by an increase in the cell voltage.

B) The non-NMDA receptor opens as soon as glutamate binds to it. Opening of the non-NMDA receptor allows the entry of positive ions into the cell.

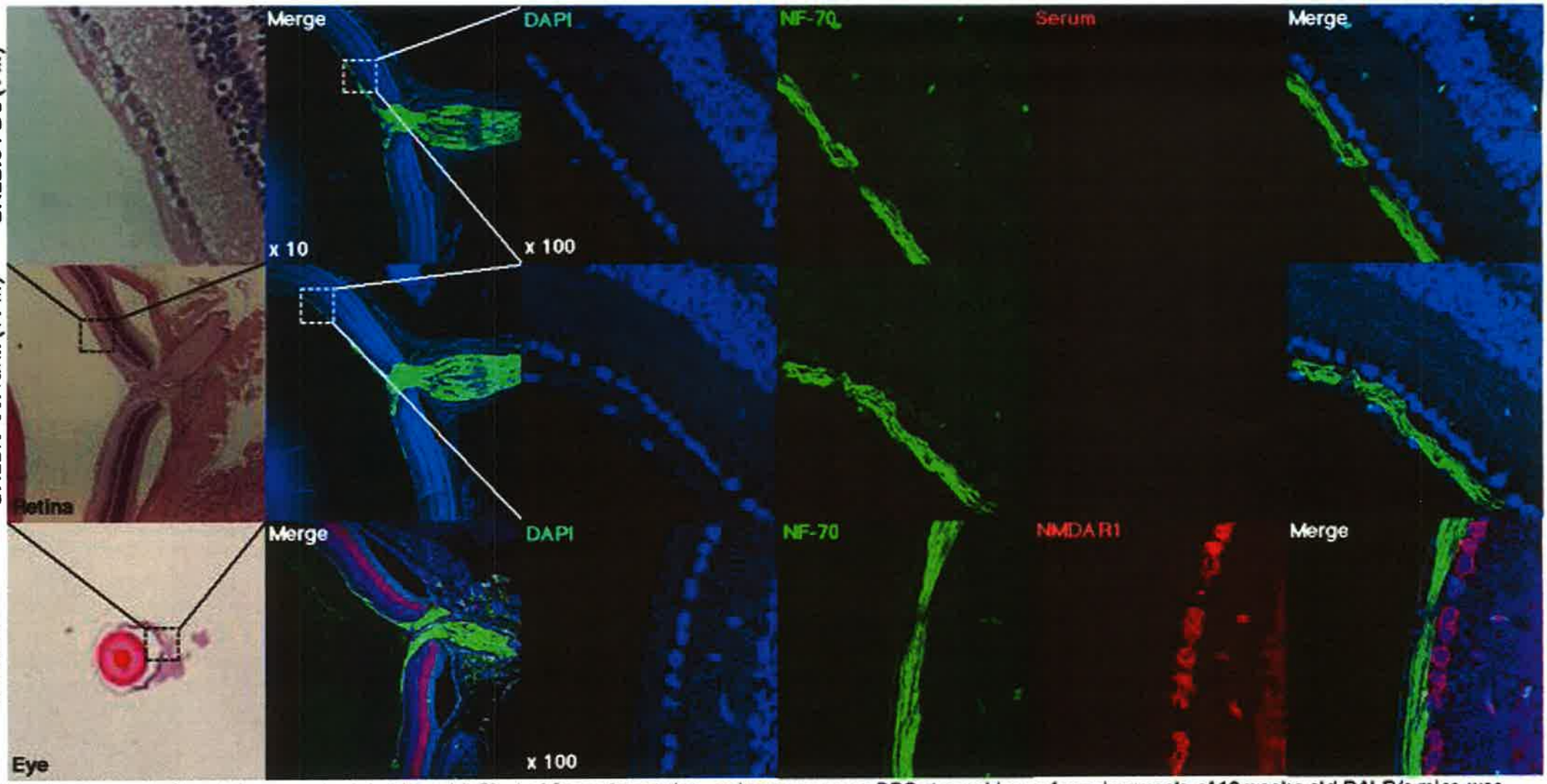


Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine as immunogen at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine, Intramascular injection with 50 μl of Cervarix vaccine was parformed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies.

Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml. Immunofluorescence analysis of Neurofilament-70 (NF-70, *a major component of the neuronal cytoskeleton of* neuronal cells), NMDA receptor 1 (NMDAR1, glutamate receptor, controlling synaptic plasticity and memory function), mouse IgG (autoantibody in serum, which was corrected from immunized BALB/c mouse with Cervarix vaccine at May 3rd, 2014, July 1st, 2014) in normal BALB/c mouse retina tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of retina tissue section: retina, retinal ganglion cell layer of BALB/c mouse with α-Neurofilament-70 (NF-70)-pAb conjugated with Alexa488 (SIGMA-Aldrich), α-mouse NMDAR1-mAb conjugated with Alexa 549 (eBioscience, Inc.), α-mouse IgG-pAb-conjugated with Alexa 549 (eBioscience, Inc.) and DAPI (Vector Laboratories, Inc.) was performed at August 05 - 06. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at August 07, 2014.

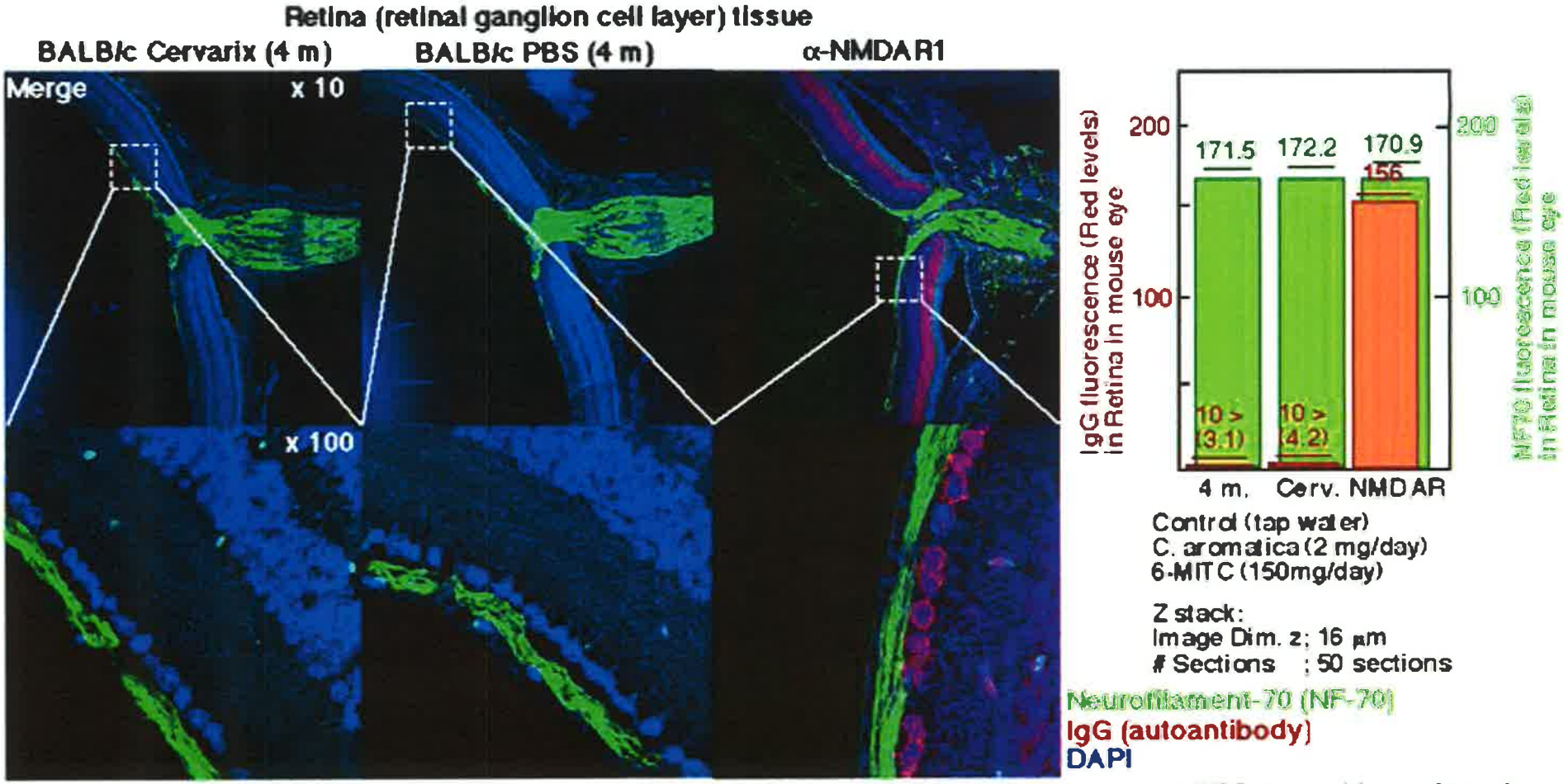


Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine as immunogen at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine, Intramascular injection with 50 μl of Cervarix vaccine was parformed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies.
Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.
Immunofluorescence analysis of Neurofilament-70 (NF-70, a major component of the neuronal cytoskeleton of neuronal cells), NMDA receptor 1 (NMDAR1, glutamate receptor, controlling synaptic plasticity and memory function), mouse IgG (autoantibody in serum, which was corrected from immunized BALB/c mouse with Cervarix vaccine at May 3rd, 2014, July 1st, 2014) in normal BALB/c mouse retina tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of retina tissue section: retina, retinal ganglion cell layer of BALB/c mouse with α-Neurofilament-70 (NF-70)-pAb conjugated with Alexa488 (SIGMA-Aldrich), α-mouse NMDAR1-mAb conjugated with Alexa 549 (eBioscience, Inc.), α-mouse IgG-pAb-conjugated with Alexa 549 (eBioscience, Inc.) and DAPI (Vector Laboratories, Inc.) was performed at August 05 - 06. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at August 07, 2014.

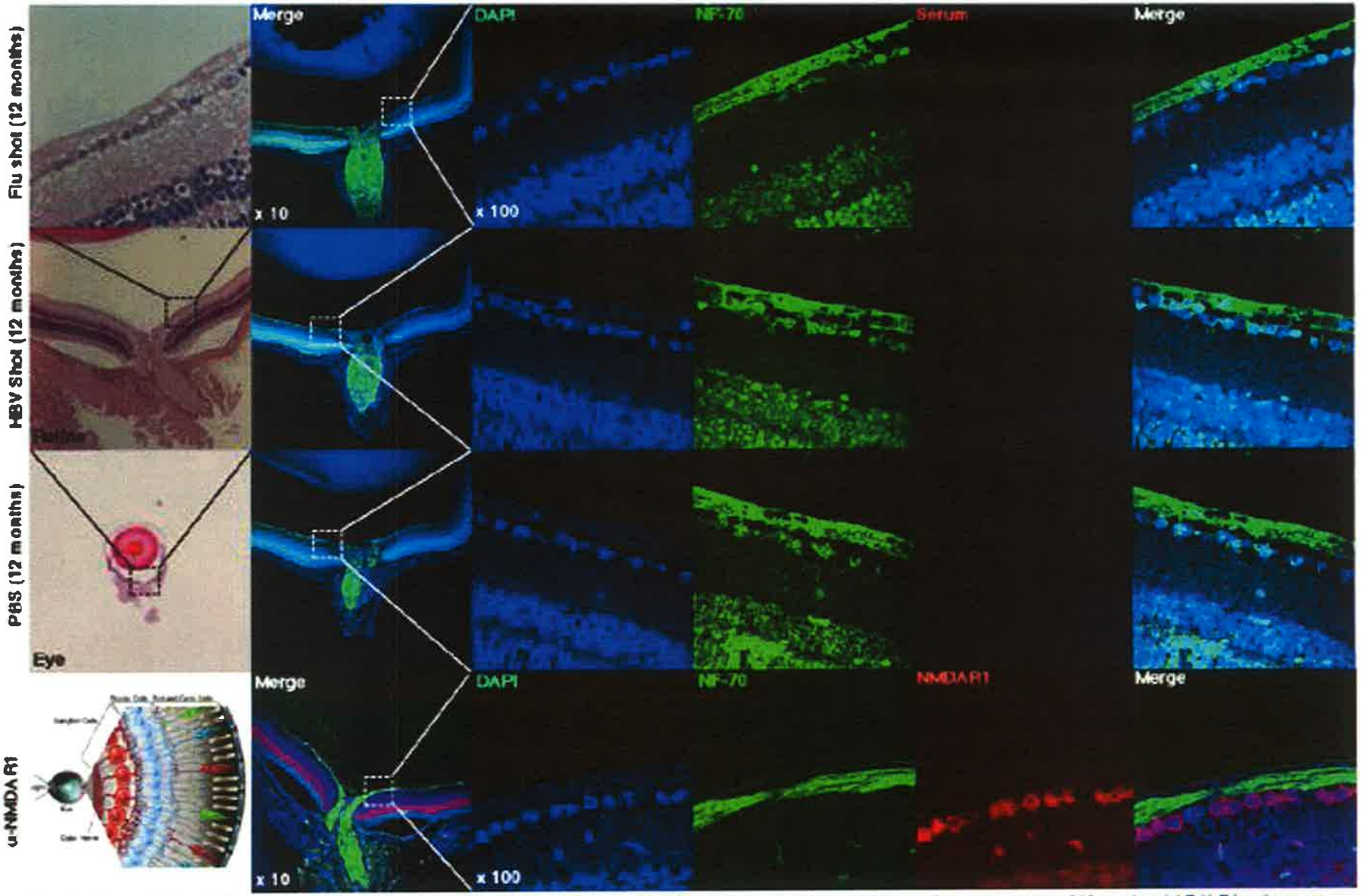


Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine as immunogen or PBS at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine or PBS, Intramascular injection with 50 μl of Cervarix vaccine was parformed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies.

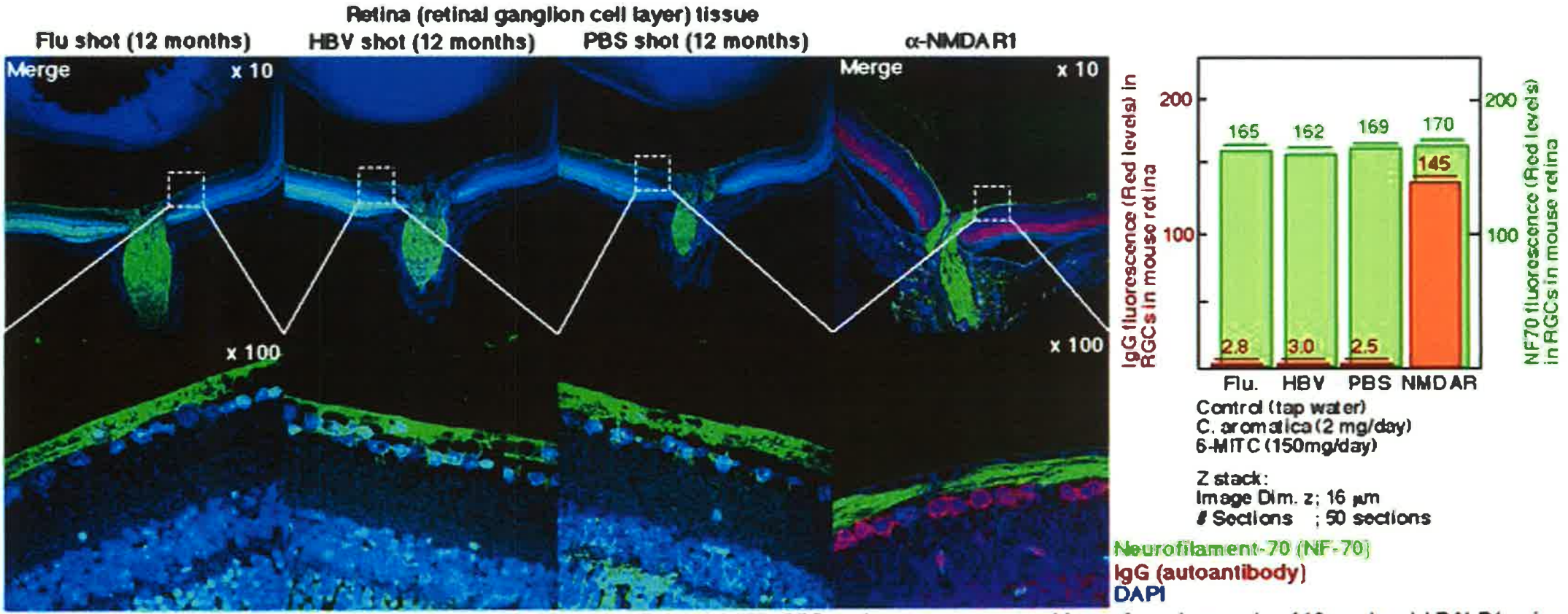
Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml. Immunofluorescence analysis of Neurofilament-70 (NF-70, a major component of the neuronal cytoskeleton of neuronal cells), NMDA receptor 1 (NMDAR1, glutamate receptor, controlling synaptic plasticity and memory function), mouse IgG (autoantibody in serum, which was corrected from immunized BALB/c mouse with Cervarix vaccine at May 3rd, 2014, July 1st, 2014) in normal BALB/c mouse retina tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of retina tissue section: retina, retinal ganglion cell layer of BALB/c mouse with α-Neurofilament-70 (NF-70)-pAb conjugated with Alexa488 (SIGMA-Aldrich), α-mouse NMDAR1-mAb conjugated with Alexa 549 (eBioscience, Inc.), α-mouse IgG-pAb-conjugated with Alexa 549 (eBioscience, Inc.) and DAPI (Vector Laboratories, Inc.) was performed at Marcht 24 - 25,2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at March 25, 2015.



Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine as immunogen or PBS at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine or PBS, Intramascular injection with 50 μl of Cervarix vaccine was parformed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies.
Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml. Immunofluorescence analysis of Neurofilament-70 (NF-70, a major component of the neuronal cytoskeleton of neuronal cells), NMDA receptor 1 (NMDAR1, glutamate receptor, controlling synaptic plasticity and memory function), mouse IgG (autoantibody in serum, which was corrected from immunized BALB/c mouse with Cervarix vaccine at May 3rd, 2014, July 1st, 2014) in normal BALB/c mouse retina tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of retina tissue section: retina, retinal ganglion cell layer of BALB/c mouse with α-Neurofilament-70 (NF-70)-pAb conjugated with Alexa488 (SIGMA-Aldrich), α-mouse NMDAR1-mAb conjugated with Alexa 549 (eBioscience, Inc.), α-mouse IgG-pAb-conjugated with Alexa 549 (eBioscience, Inc.) and DAPI (Vector Laboratories, Inc.) was performed at Marcht 24 - 25,2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at March 25, 2015.



Vaccine immunization: Intramascular injection with 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Flu, HBV vaccine or PBS as control March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and pathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.
Immunofluorescence analysis of Neurofilament-70 (NF-70, a major component of the neuronal cytoskeleton of neuronal cells), NMDA receptor 1 (NMDAR1, glutamate receptor, controlling synaptic plasticity and memory function), mouse IgG (autoantibody in serum, which was corrected from immunized BALB/c mouse with Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) in normal BALB/c mouse retina tissue, detail is indicated in the supplementary information.
Immunofluorescence analysis of retina tissue section: retina, retinal ganglion cell layer of BALB/c mouse with αNeurofilament-70 (NF-70) pAb conjugated with Alexa488 (SIGMA-Aldrich), α-mouse NMDAR1-mAb conjugated with Alexa 549 (eBioscience, Inc.), α-mouse IgG pAb-conjugated with Alexa 549 (eBioscience, Inc.) and DAPI (Vector Laboratories, Inc.) was performed at May 18 - 19, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co., Ltd. Fukui Japan) at May 20, 2015.



Vaccine immunization: Intramascular injection with 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Flu, HBV vaccine or PBS as control: March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and pathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml. Immunofluorescence analysis of Neurofilament-70 (NF-70, a major component of the neuronal cytoskeleton of neuronal cells), NMDA receptor 1 (NMDAR1, glutamate receptor, controlling synaptic plasticity and memory function), mouse IgG (autoantibody in serum, which was corrected from immunized BALB/c mouse with Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) in normal BALB/c mouse retina tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of retina tissue section: retina, retinal ganglion cell layer of BALB/c mouse with α-Neurofilament-70 (NF-70)-pAb conjugated with Alexa488 (SIGMA-Aldrich), α-mouse NMDAR1-mAb conjugated with Alexa 549 (eBioscience, Inc.), α-mouse IgG-pAb-conjugated with Alexa 549 (eBioscience, Inc.) and DAPI (Vector Laboratories, Inc.) was performed at May 18 - 19, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at May 20, 2015.

Physiological effects of chronic adoministration of C. aromatica or 6-MITC for bone marrow suppression by anti-tumor agents.

Total counts of Bonmarrow-derived Neutrophil granulocytes (CD32+) under injection of CDDP with or without C. aromatica or 6-MITC.

Physiological effect of intramuscular injection of Cervarix on central nervous system (CNS) in comparison with Flu shot and HBV vacctine.

Production of autoantibody, especially anti-ganglioside GM1 IgG in serum of NF-κBp50-null mice with intramuscular injection of Cervarix.

12. 28. 2015

子宮頸がんワクチン接種関連　自己免疫脳症の病態と治療

鹿児島大学　神経内科・老年病学
代表　　髙嶋 博
荒田 仁、岡田敬史、髙畑克徳、牧 美充、吉村道由、
東 桂子、松浦英治

鹿児島大学神経内科では、以前から線維筋痛症や心因性と診断された麻痺や疼痛、不随意運動を呈する症例の中に、多くの自己免疫脳症患者が混在していることを認識し、治療を行ってきた。

これらは慢性経過で、び漫性に中枢神経が侵される、橋本脳症がその中心となるが、未知の自己抗体も多い。

これらの自己免疫脳症は通常の神経症候学では、つじつまが合わないことが多く、専門医でも誤って心因性に原因をもとめることも多い。

当科においては、子宮頸がんワクチン関連脳症は、症候学的にも自己免疫脳症としてなんらの矛盾もみとめないものであり、免疫学的な治療例を紹介する。

2013年～2014年に鹿児島大学を受診した子宮頸がんワクチン接種後の神経障害発症患者10名の臨床像

患者		薬剤の種類	発症までの期間	神経症状
case1	15歳 F	サーバリックス®	5ヶ月	記憶障害、立ちくらみ、右上肢運動障害
case2	14歳 F	ガーダシル®	1ヶ月	記憶障害、退行傾向、歩行時のふらつき
case3	18歳 F	サーバリックス®	1ヶ月	記憶障害、計算力低下、異常感覚
case4	19歳 F	サーバリックス®	1ヶ月	てんかん 発作（笑い発作　脳波異常有り）
case5	15歳 F	ガーダシル®	1ヶ月	発作性せん妄、記憶障害、発汗低下、尿閉 、歩行不能
case6	18歳 F	サーバリックス®	4ヶ月	記憶障害、立ち眩み、眼振
case7	14歳 F	サーバリックス®	6ヶ月	両下肢痛、頭痛
case8	15歳 F	サーバリックス®	1ヶ月	不随意運動 発汗障害、便秘
case9	17歳 F	サーバリックス®	2ヶ月	発作性せん妄、発汗障害、右上肢両下肢運動障害、歩行不能
case10	15歳 F	サーバリックス	ヶ月	理解力低下、発作性せん妄

記憶障害、運動障害、計算力低下、てんかん発作、または発作性せん妄、不随意運動
尿閉、 疼痛、 頭痛など全国の報告と同様の症状

自己免疫脳症の中枢神経の症状と考えられた。

自己抗体と治療

	患者	薬剤の種類	発症までの期間	運動症状	非運動症状	AChR抗ガングリオニック抗体	抗ガングリオシド抗体	治療効果	
								ステロイド	免疫吸着
case1	15		3			(-)			
case2	14歳	サーバリックス	5ヶ月	右上肢運動障害	記憶障害　立ちくらみ		IgMGM1(+)	やや改善	
case3	18歳	ガーダシル	1ヶ月	歩行時のふらつき	記憶障害、退行傾向	(-)	(-)	やや改善	
case4	19歳	サーバリックス	1ヶ月		記憶障害、計算力低下 異常感覚	α3+　β4+	(-)	効果なし	
case5	15歳	サーバリックス	1ヶ月		てんかん発作	(-)	IgMGM1(+) IgMGalNAc-GD1A(+)		効果なし
case6	18歳	ガーダシル	1ヶ月	両下肢脱力 歩行不能	発作性せん妄 記憶障害 発汗低下　尿閉	(-)	(-)	効果なし	効果あり
case7	14歳	サーバリックス	4ヶ月		記憶障害　立ち眩み 眼振　不安発作	(-)	IgMGM3(+)	効果なし	効果なし
case8	15歳	サーバリックス	6ヶ月		両下肢痛	(-)	IgMGM1(+) IgMGalNAc-GD1A(+)		効果なし
case9	17歳	サーバリックス	1ヶ月		不随意運動 発汗障害　便秘	α3+　β4+	IgMGM1(+)		
case10	15歳	サーバリックス	2ヶ月	右上肢、両下肢脱力 歩行不能	発作性せん妄 発汗障害	(-)	IgMGM1(+)	効果なし	効果あり
					理解力低下　性格変化 退行　てんかん様発作			効果なし	やや改善

抗ガングリオニックコンジュゲートアセチルコリンレセプター抗体検査　川棚医療センター　中根氏による
抗ガングリオシド抗体検査　近畿大学神経内科楠教授による

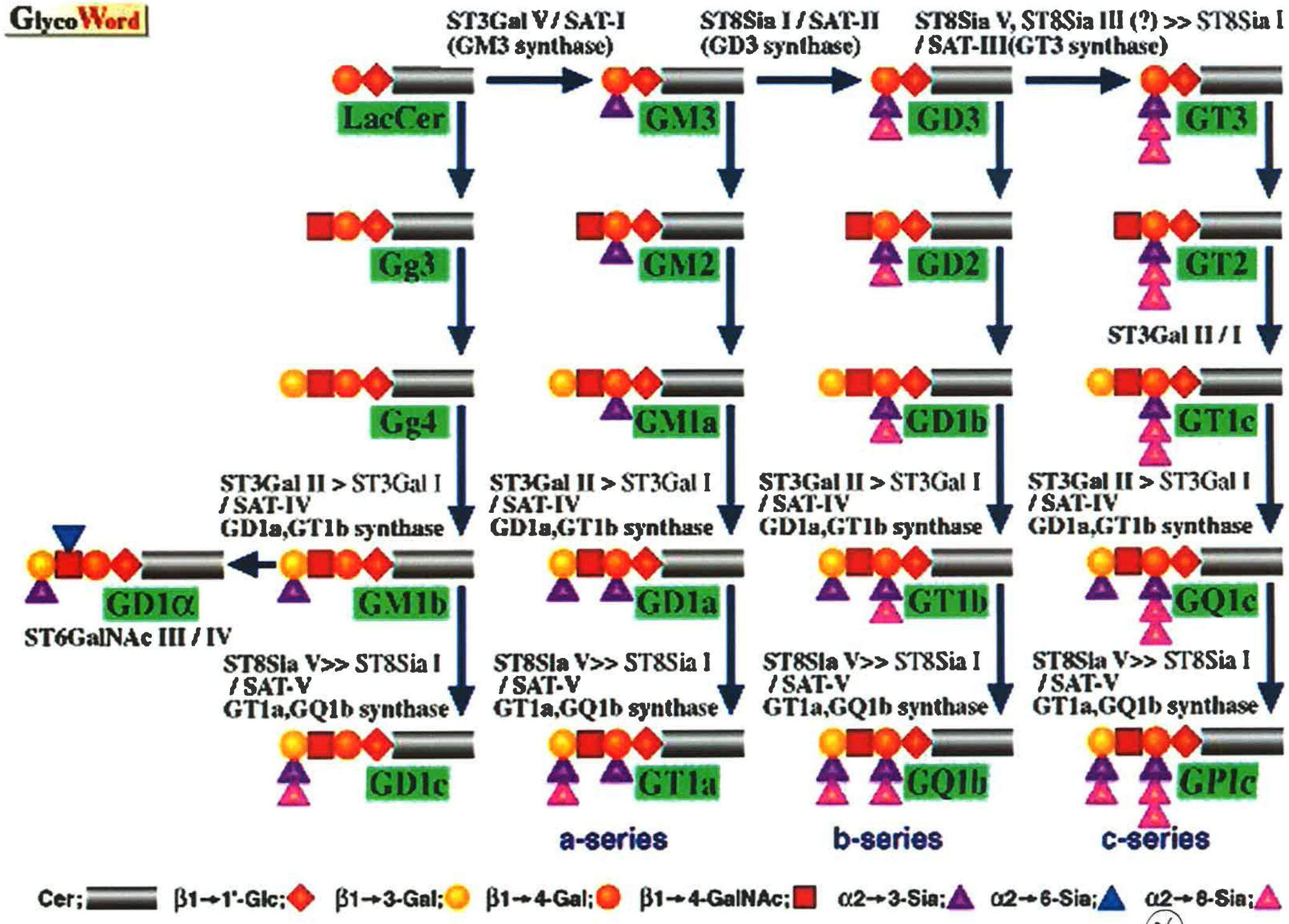
まとめ

- 子宮頸がんワクチン関連脳症は、自己免疫機序で起こっており、免疫吸着療法に反応する

- 症状が一度寛解しても再燃する例が多く、有効な維持療法を開発する必要がある
  （高額な免疫抑制剤の使用に費用の補助が必要）

- 病態を理解できる施設での継続した診療が不可欠であるため、全国的な治療ネットワークの構築が必要である

品名	活性	CAS	包装	商品コード
Ganglioside GM1, Sodium Salt (bovine brain)	カルシウム恒常性を制御するニューロンの細胞膜を構成する，主なアシル酸糖脂質。	37758-47-7	1 mg	AG-CN2-9000-M001
			5 mg	AG-CN2-9000-M005
			10 mg	AG-CN2-9000-M010
Ganglioside GM2, Sodium Salt (bovine brain)	神経系に極微量存在する構成要素。テイ-サックス病およびサンドホフ病患者の脳に蓄積する。	19600-01-2	1 mg	AG-CN2-9001-M001
Ganglioside GM3, Sodium Salt (bovine brain)	哺乳動物において最も多く存在するガングリオシド。上皮細胞の増殖や，インスリンレセプターの活性を阻害する。	54827-14-4	1 mg	AG-CN2-9002-M001
Ganglioside GD1a, Disodium Salt (bovine brain)	神経系に存在する主要なガングリオシド。増殖細胞のマーカー。	12707-58-3	1 mg	AG-CN2-9003-M001
			5 mg	AG-CN2-9003-M005
Ganglioside GD1b, Disodium Salt (bovine brain)	破傷風毒素レセプターおよびボツリヌス毒素レセプターとして機能すると考えられている。	19553-76-5	1 mg	AG-CN2-9004-M001
Ganglioside GD3, Disodium Salt (bovine brain)	カルシウムイオン濃度の上昇を必要とせずに，ミトコンドリアにおける透過性遷移(MPT)を誘導し，Fas介在性アポトーシスを引き起こす。	62010-37-1	500 ug	AG-CN2-9005-C500
			1 mg	AG-CN2-9005-M001
Ganglioside GT1b, Trisodium Salt (bovine brain)	ボツリヌス毒素や破傷風毒素と結合し，グルタミン酸による神経毒性を防ぐ。	59247-13-1	1 mg	AG-CN2-9006-M001
			5 mg	AG-CN2-9006-M005
Ganglioside GQ1b, Tetrasodium Salt (bovine brain)	ヒト神経芽腫細胞の神経分化を促進する。	68652-37-9	100 ug	AG-CN2-9007-C100
			500 ug	AG-CN2-9007-C500
Asialo-Ganglioside GM1	細胞上のGanglioside GM1へのコレラ毒素の結合を阻害しない。	71012-19-6	500 ug	AG-CN2-9008-C500
			1 mg	AG-CN2-9008-M001
Asialo-Ganglioside GM2	テイ-サックス病およびサンドホフ病の患者に存在する主要な神経ガングリオシド。	35960-33-9	100 ug	AG-CN2-9009-C100


GlycoWord
ST3Gal V / SAT-I
(GM3 synthase)
ST8Sia I / SAT-II
(GD3 synthase)
ST8Sia V, ST8Sia III (?) >> ST8Sia I
/ SAT-III(GT3 synthase)
LacCer
GM3
GD3
GT3
Gg3
GM2
GD2
GT2
ST3Gal II / I
Gg4
GM1a
GD1b
GT1c
ST3Gal II > ST3Gal I
/ SAT-IV
GD1a,GT1b synthase
ST3Gal II > ST3Gal I
/ SAT-IV
GD1a,GT1b synthase
ST3Gal II > ST3Gal I
/ SAT-IV
GD1a,GT1b synthase
ST3Gal II > ST3Gal I
/ SAT-IV
GD1a,GT1b synthase
GD1α
GM1b
GD1a
GT1b
GQ1c
ST6GalNAc III / IV
ST8Sia V>> ST8Sia I
/ SAT-V
GT1a,GQ1b synthase
ST8Sia V>> ST8Sia I
/ SAT-V
GT1a,GQ1b synthase
ST8Sia V>> ST8Sia I
/ SAT-V
GT1a,GQ1b synthase
ST8Sia V>> ST8Sia I
/ SAT-V
GT1a,GQ1b synthase
GD1c
GT1a
GQ1b
GP1c
a-series
b-series
c-series
Cer;
β1→1'-Glc;
β1→3-Gal;
β1→4-Gal;
β1→4-GalNAc;
α2→3-Sia;
α2→6-Sia;
α2→8-Sia;

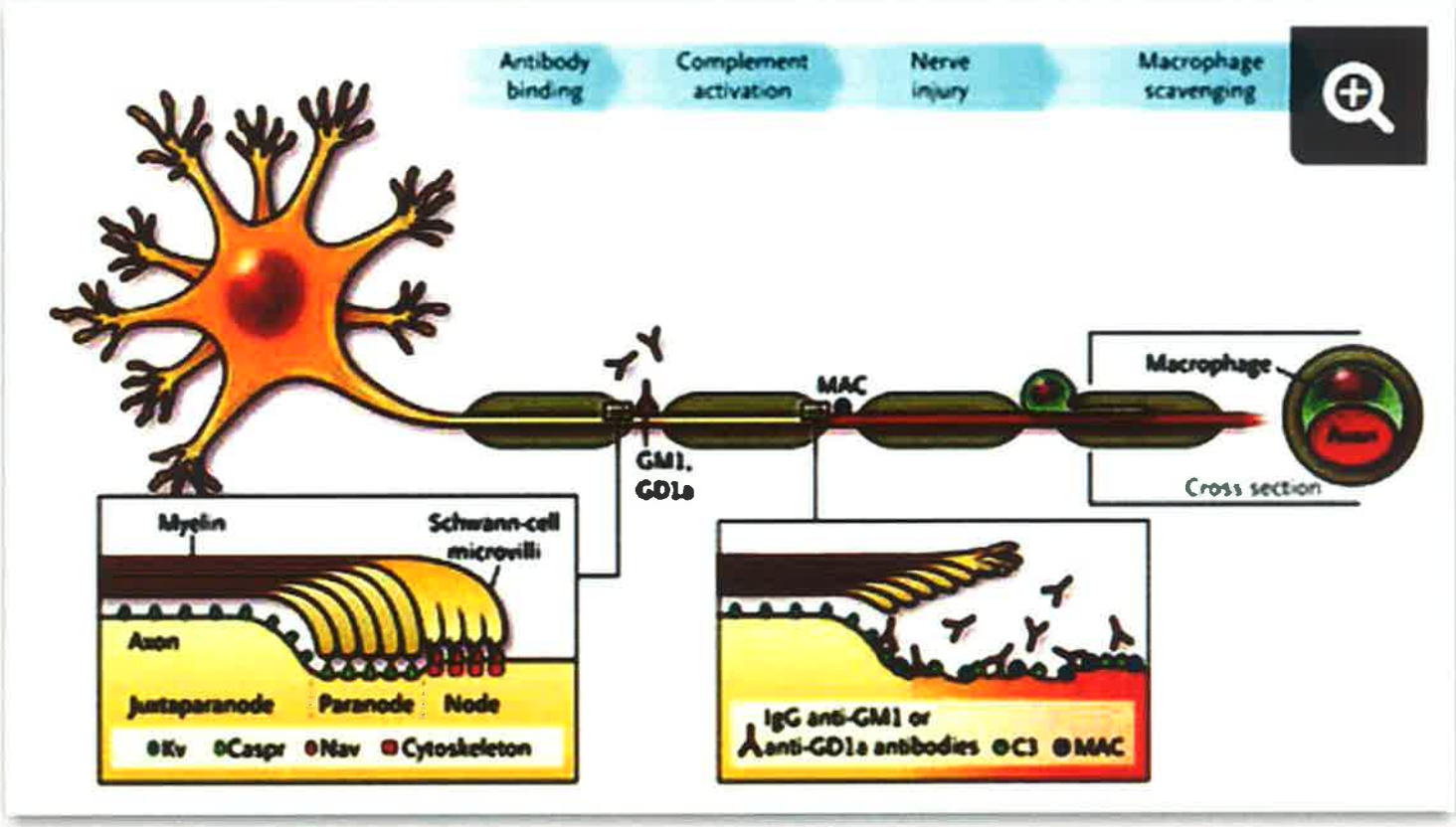
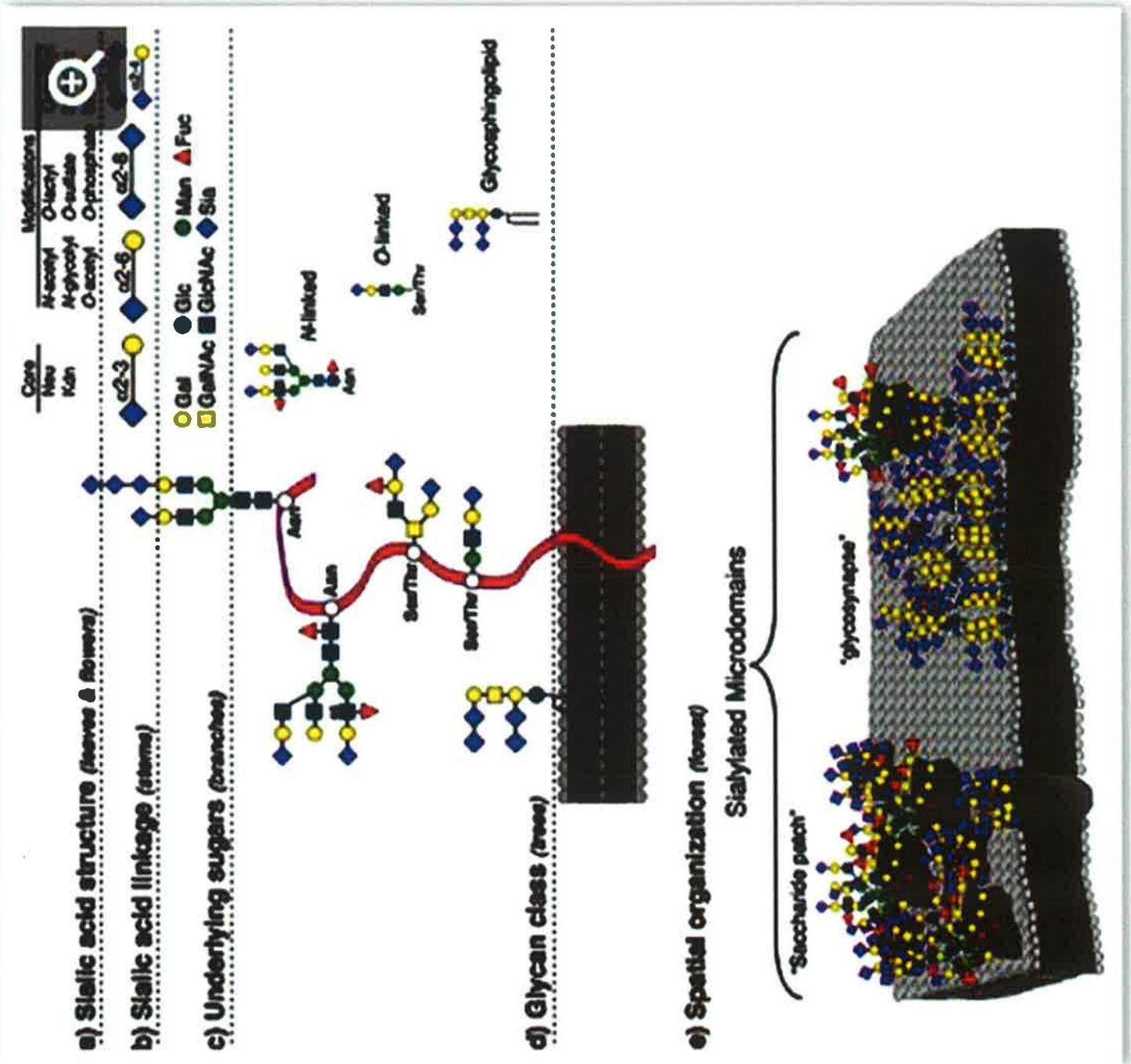


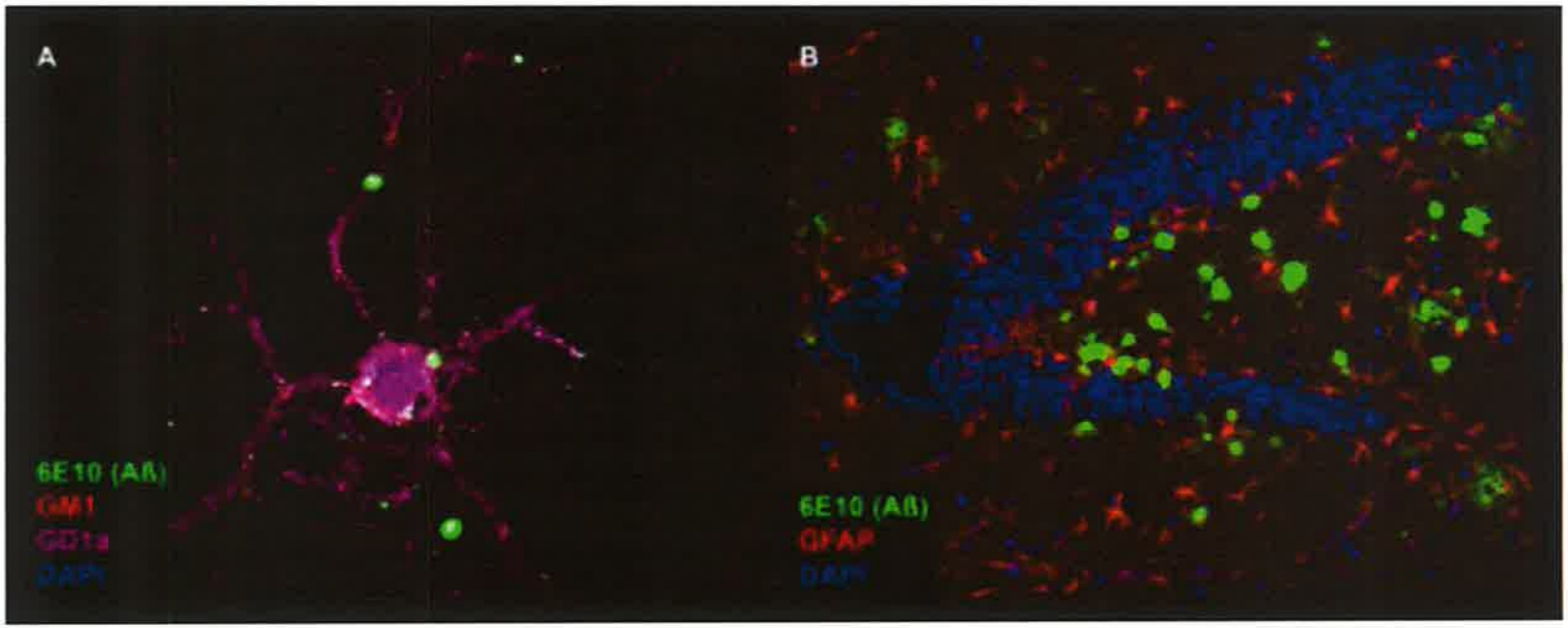
FIGURE 26. **Download figure | Open in new tab | Download powerpoint**

Immunopathogenesis of the AMAN form of Guillain-Barré syndrome. Gangliosides GM1 and GD1a are strongly expressed at nodes of Ranvier, where the voltage-gated sodium (Nav) channels are localized. Anti-GM1 or anti-GD1a antibodies bind to the nodal axolemma, leading to formation of the complement membrane attack complex (MAC). This results in the disappearance of Nav clusters and the detachment of paranodal myelin, which can lead to nerve-conduction failure and muscle weakness. Axonal degeneration may follow at a later stage. Macrophages subsequently invade from the nodes into the periaxonal space, scavenging the injured axons. [Adapted from Yuki and Hartung (**577**), with permission from Massachusetts Medical Society.]

FIGURE 3. Download figure | Open in new tab | Download powerpoint

Hierarchical levels of sialome complexity. The sialome can be analyzed at the following complexity levels. *A*: sialic acid core and core modifications: esterification (with various groups), *O*-methylation, lactonization, or lactamization yielding >50 different structures. *B*: linkage to the underlying sugar (four major and many minor linkages). *C*: identity and arrangement of the underlying sugars that can also be further modified by fucosylation or sulfation. *D*: glycan class (*N*-linked, *O*-linked, or glycosphingolipids). *E*: spatial organization of the Sia in sialylated microdomains, which have been referred to as "clustered saccharide patches" (509) or "the glycosynapse" (182). Gal, galactose (Gal), GalNAc, *N*-acetylgalactosamine; Glc, glucose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Sia, sialic acid; Fuc, fucose; Asn, asparagine; Ser, serine; Thr, threonine. [Adapted from Cohen and Varki (86), with permission from Mary Ann Liebert, Inc.]





A: Primary hippocampal neuron stained for 6E10 (amyloid ß) and gangliosides GM1, GD1a and DAPI.
B: Dentate gyrus of an AD mouse model stained for 6E10 (amyloid ß), GFAP (glial cells) and DAPI.

Cell. 1995 Jan 27;80(2):321-30.

Targeted disruption of the p50 subunit of NF-kappa B leads to multifocal defects in immune responses.

Sha WC[1], Liou HC, Tuomanen EI, Baltimore D.

Author information

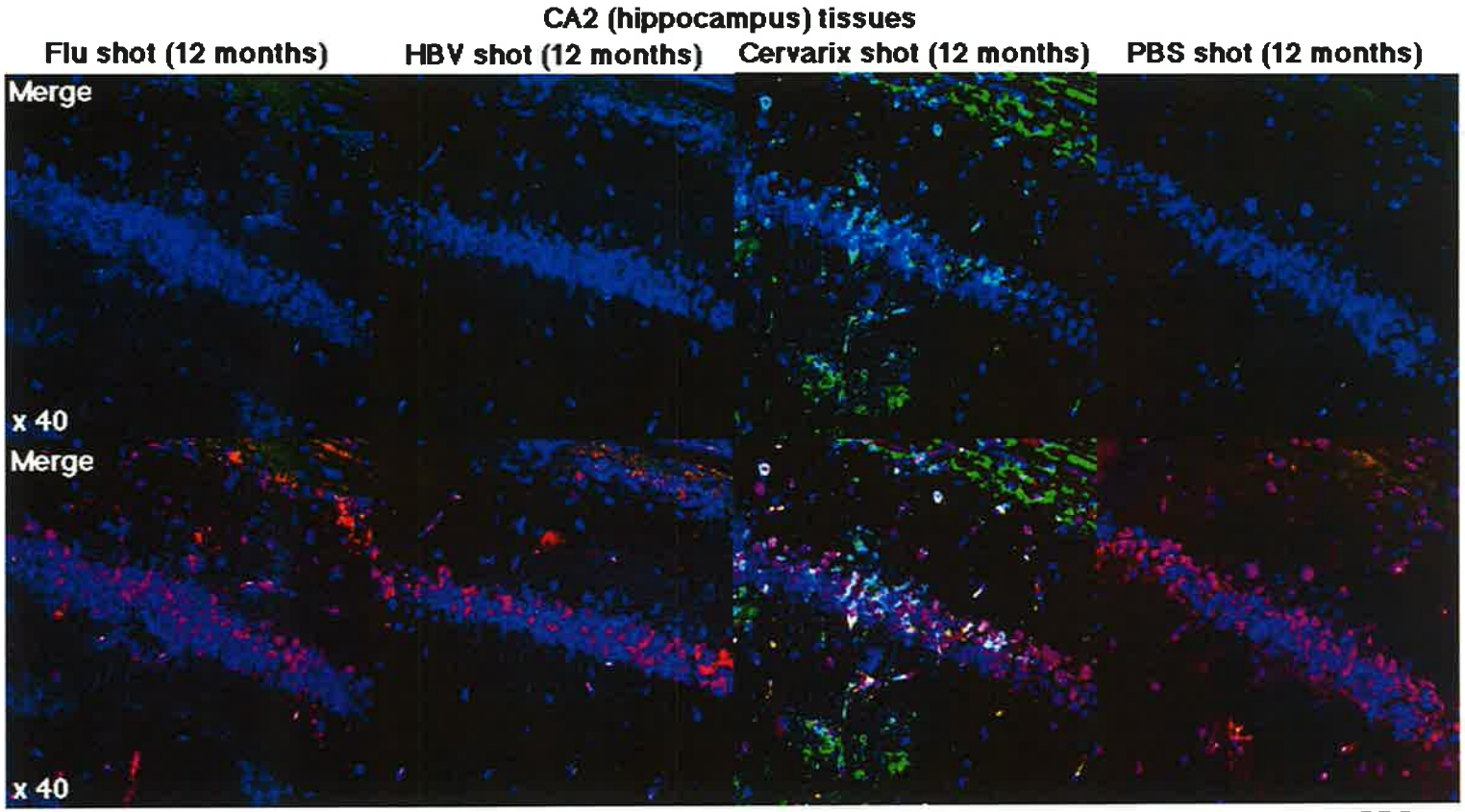
Abstract

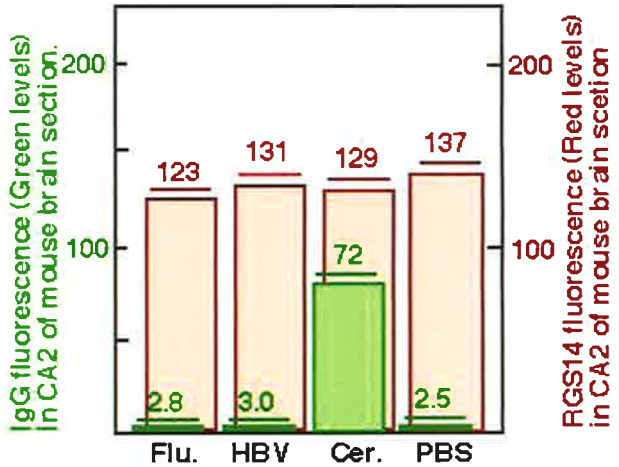
NF-kappa B, a heterodimeric transcription factor composed of p50 and p65 subunits, can be activated in many cell types and is thought to regulate a wide variety of genes involved in immune function and development. Mice lacking the p50 subunit of NF-kappa B show no developmental abnormalities, but exhibit multifocal defects in immune responses involving B lymphocytes and nonspecific responses to infection. B cells do not proliferate in response to bacterial lipopolysaccharide and are defective in basal and specific antibody production. Mice lacking p50 are unable effectively to clear L. monocytogenes and are more susceptible to infection with S. pneumoniae, but are more resistant to infection with murine encephalomyocarditis virus. These data support the role of NF-kappa B as a vital transcription factor for both specific and nonspecific immune responses, but do not indicate a developmental role for the factor.

autoimmunity-like disease

PMID: 7834752 [PubMed - indexed for MEDLINE]

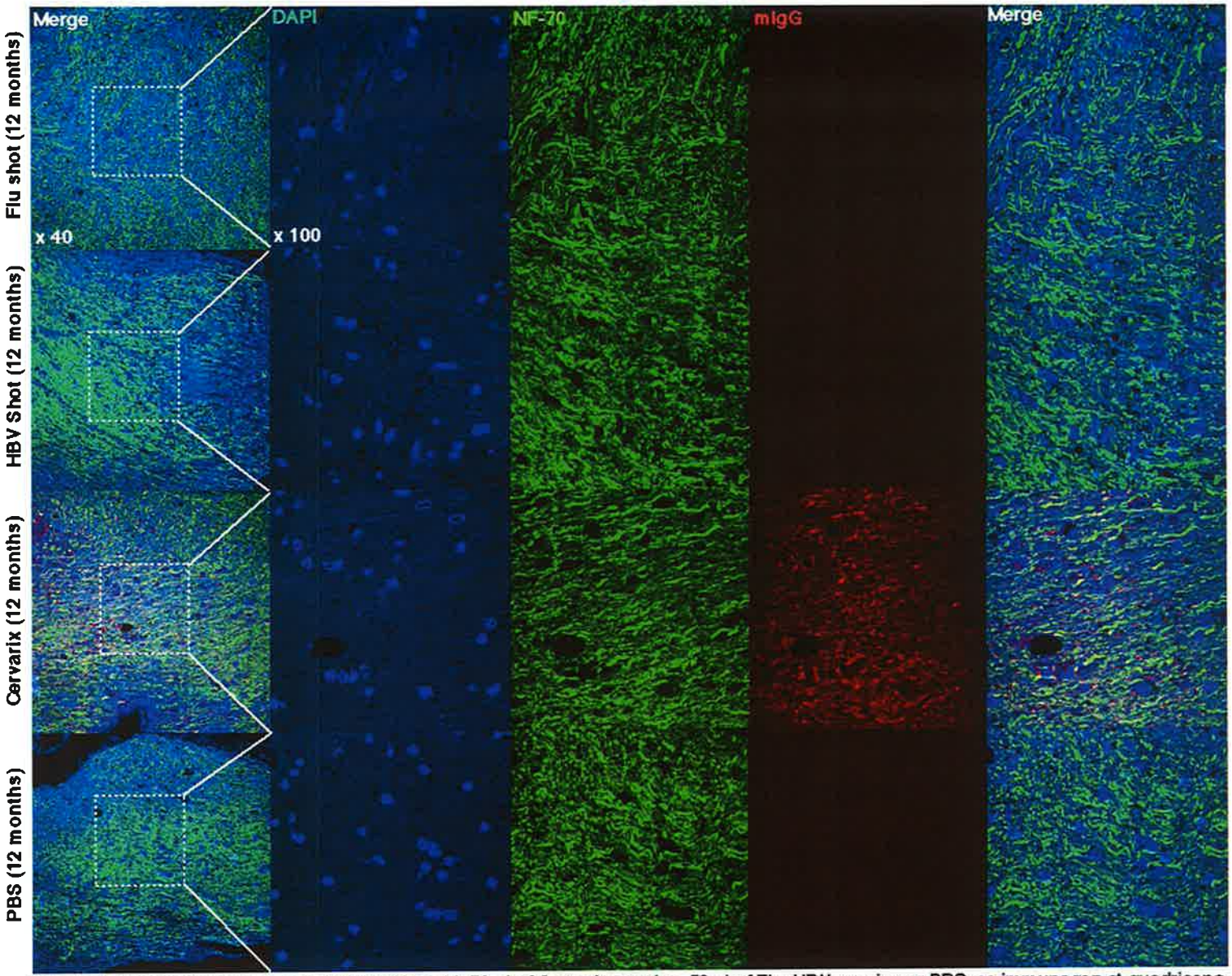
Vaccine Immunization: Intramascular injection with 50 μl of Cervarix vaccine, 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50-deficient mice was performed for immunological studies: Date of 1st shot of Flu, HBV vaccine or PBS as control: March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Cervarix vaccine, Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and pathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.
Immunofluorescence analysis of RGS14 (Regulator of G-protein signaling 14, Conversely RGS14 is enriched in CA2 pyramidal neurons), mouse IgG (autoantibody in serum, which was corrected from immunized NF-κBp50-deficient mouse with Cervarix, Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) in normal BALB/c mouse retina tissue, detail is indicated in the supplementary information.
Immunofluorescence analysis of brain section: Brain sections of BALB/c mice with α-mouse IgG conjugated with Alexa488 (SIGMA-Aldrich), and α-mouse RGS14-pAb conjugated with Alexa 549 (eBioscience, Inc.), and DAPI (Vector Laboratories, Inc.) was performed at November 08 - 09, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at May 20, 2015.





Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine, 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50-deficient mice was performed for immunological sudies; Date of 1st shot of Flu, HBV vaccine or PBS as control: March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Cervarix vaccine, Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and pathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.

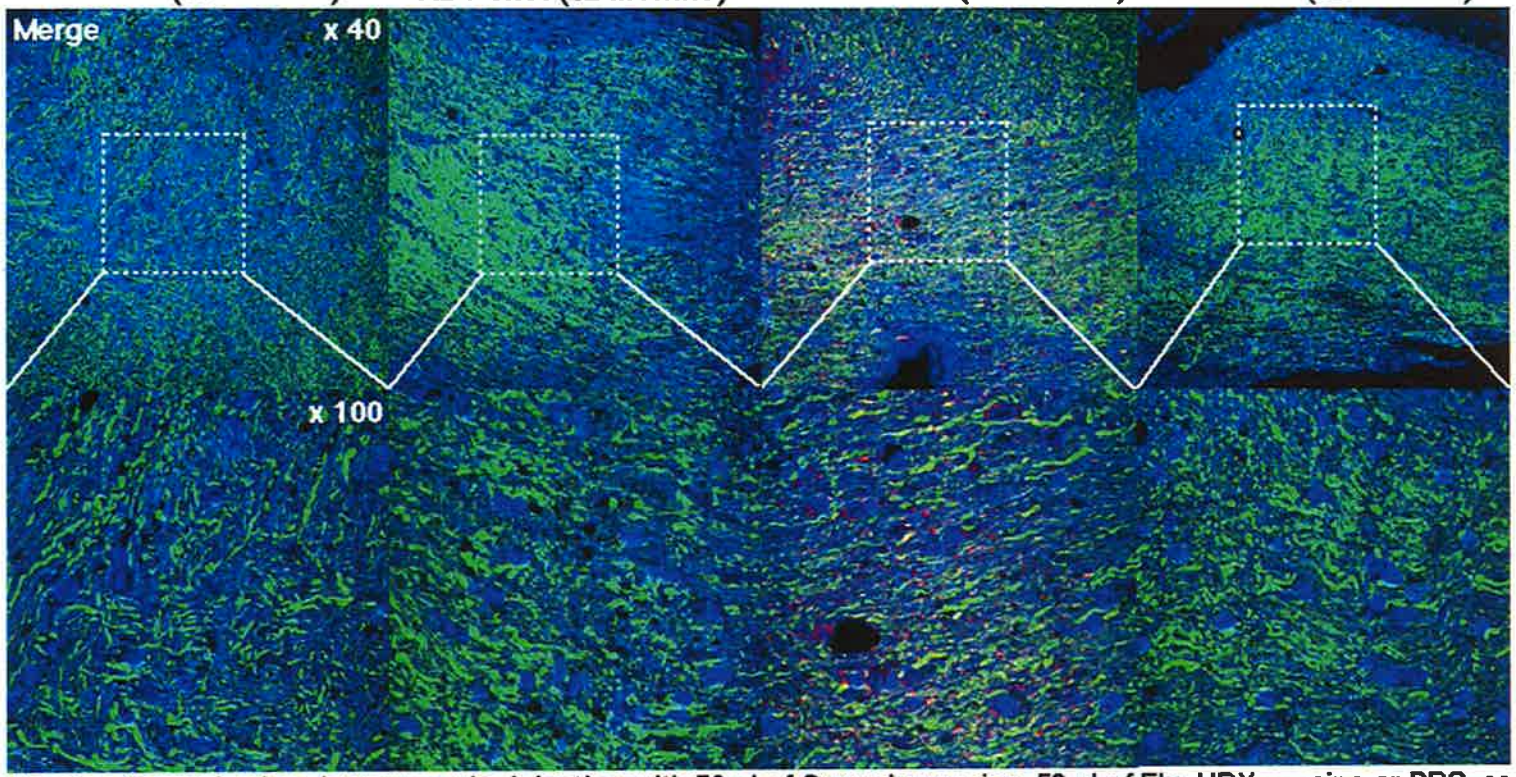
Immunofluorescence analysis of RGS14 (Regulator of G-protein signaling 14, Conversely RGS14 is enriched in CA2 pyramidal neurons), mouse IgG (autoantibody in serum, which was corrected from immunized NF-κBp50-deficient mouse with Cervarix, Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) in normal BALB/c mouse retina tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of brain section: Brain sections of BALB/c mice with α-mouse IgG conjugated with Alexa488 (SIGMA-Aldrich), and α-mouse RGS14-pAb conjugated with Alexa 549 (eBioscience, Inc.), and DAPI (Vector Laboratories, Inc.) was performed at November 08 - 09, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at May 20, 2015.

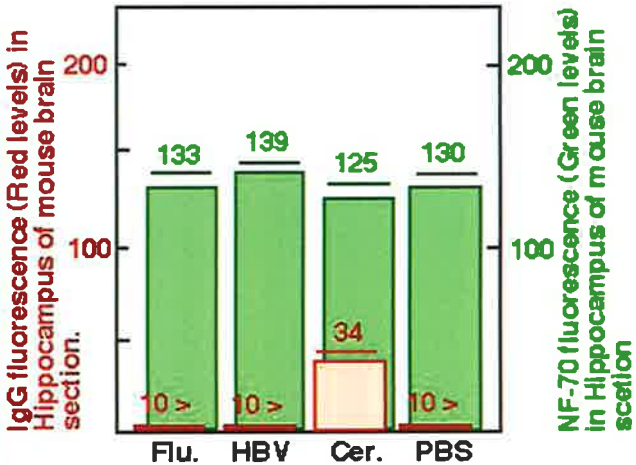


Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine, 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50-deficient mice was performed for immunological sudies; Date of 1st shot of Flu, HBV vaccine or PBS as control: March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Cervarix vaccine, Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and pathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.
Immunofluorescence analysis of NF-70 (Neurofilament-70, Neurofilaments (NF) are the 10 nanometer or intermediate filaments found in nwurons), mouse IgG (autoantibody in serum, which was corrected from immunized NF-κBp50-deficient mouse with Cervarix, Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) in normal human brain tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of brain section: Human Brain sections (US Biomax-Normal Brain Tissue Array, Biomax US) with α-mouse IgG conjugated with Alexa 548 (SIGMA-Aldrich), and α-mouse NF-70-pAb conjugated with Alexa 488 (eBioscience, Inc.), and DAPI (Vector Laboratories, Inc.) was performed at November 24 - 25, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at November 26, 2015.

Human hippocampus tissues

Flu shot (12 months) | HBV shot (12 months) | Cervarix shot (12 months) | PBS shot (12 months)





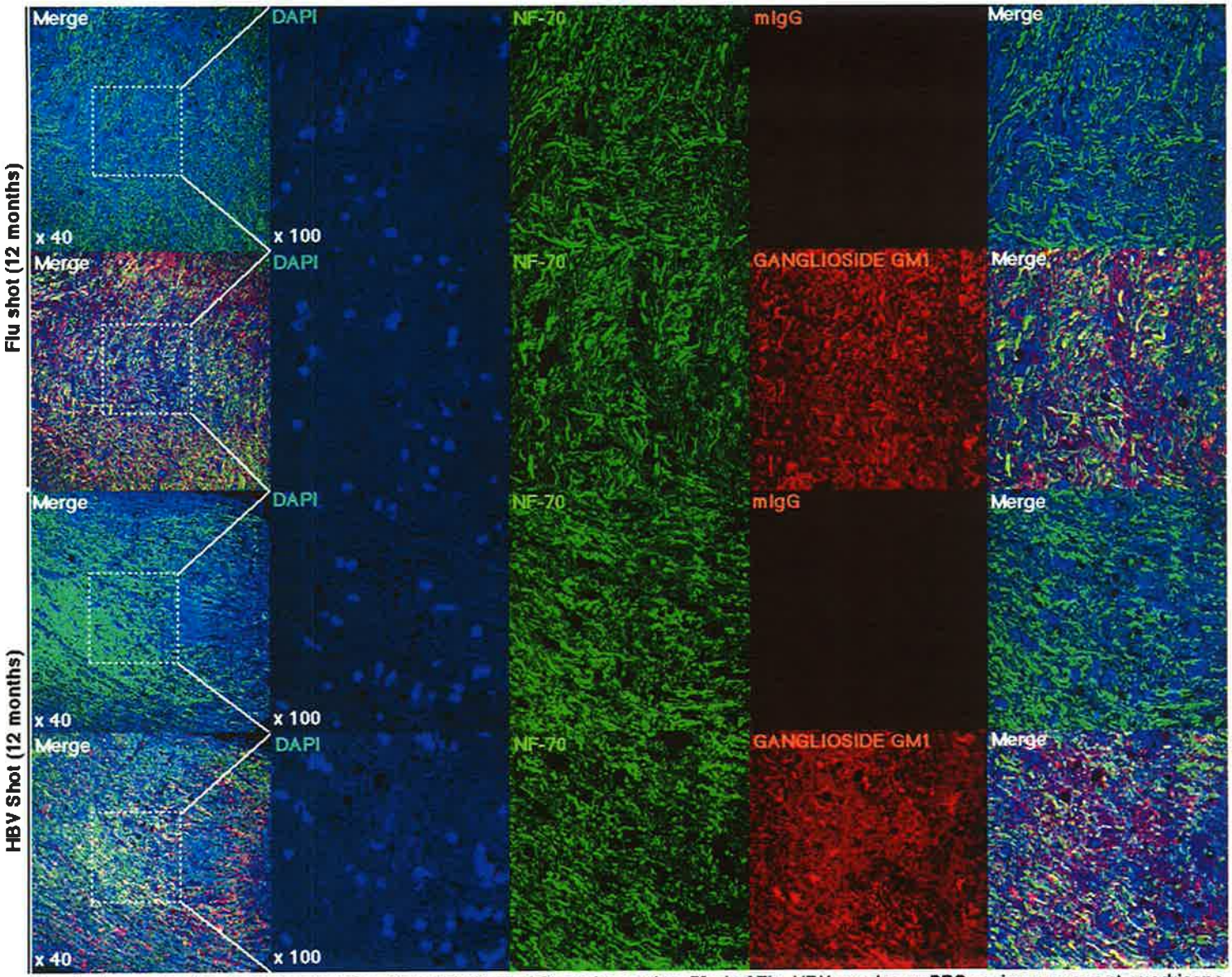
Control (tap water)
C. aromatica (2 mg/day)
6-MITC (150mg/day)

Z stack:
Image Dim. z; 16 μm
Sections ; 50 sections

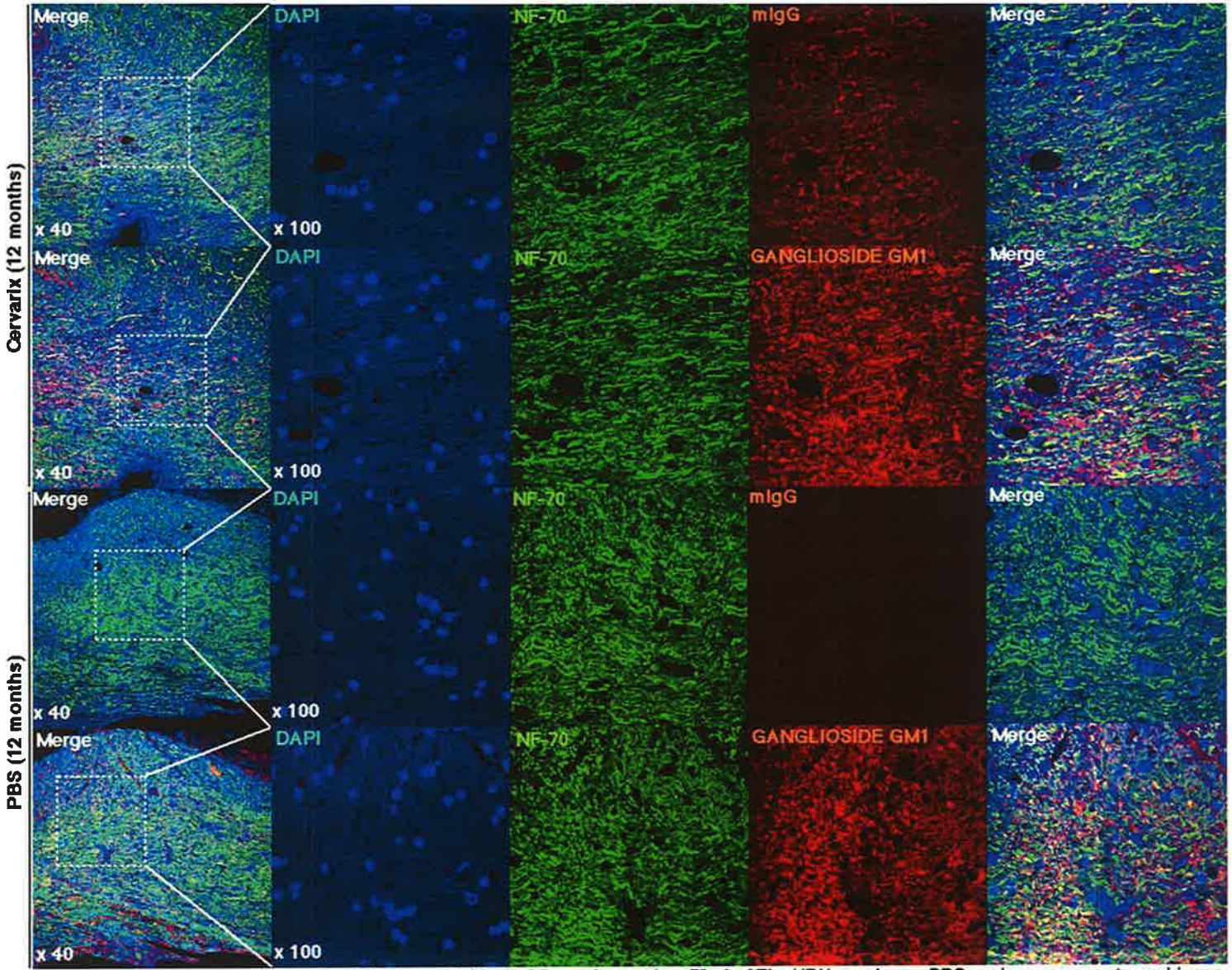
NF-70 (Neurofilament-70)
Mouse IgG
DAPI

Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine, 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50-deficient mice was performed for immunological sudies; Date of 1st shot of Flu, HBV vaccine or PBS as control: March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Cervarix vaccine, Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and pathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.

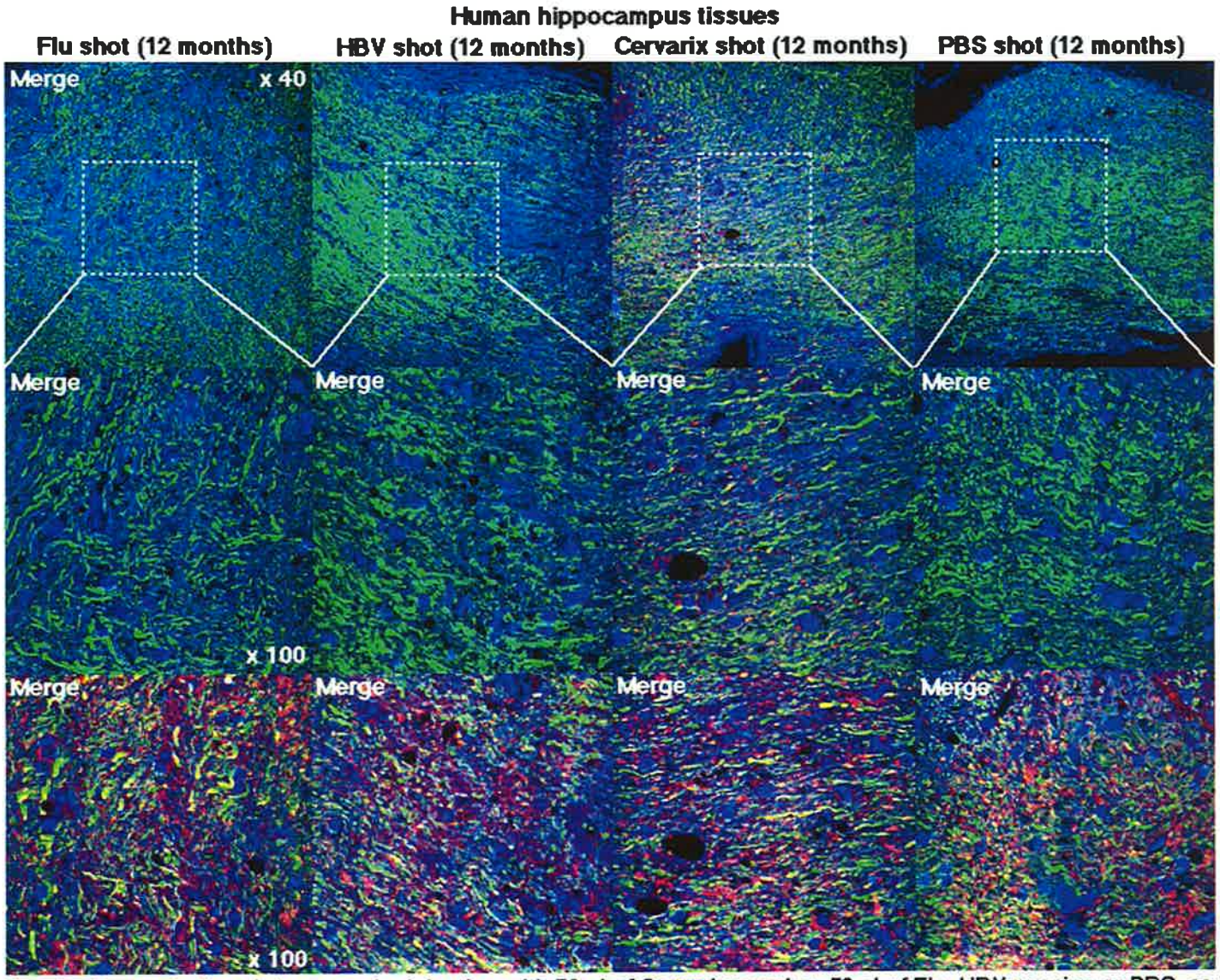
Immunofluorescence analysis of NF-70 (Neurofilament-70, Neurofilaments (NF) are the 10 nanometer or intermediate filaments found in nwurons), mouse IgG (autoantibody in serum, which was corrected from immunized NF-κBp50-deficient mouse with Cervarix, Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) in normal human brain tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of brain section: Human Brain sections (US Biomax-Normal Brain Tissue Array, Biomax US) with α-mouse IgG conjugated with Alexa 548 (SIGMA-Aldrich), and α-mouse NF-70-pAb conjugated with Alexa 488 (eBioscience, Inc.), and DAPI (Vector Laboratories, Inc.) was performed at November 24 - 25, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at November 26, 2015.

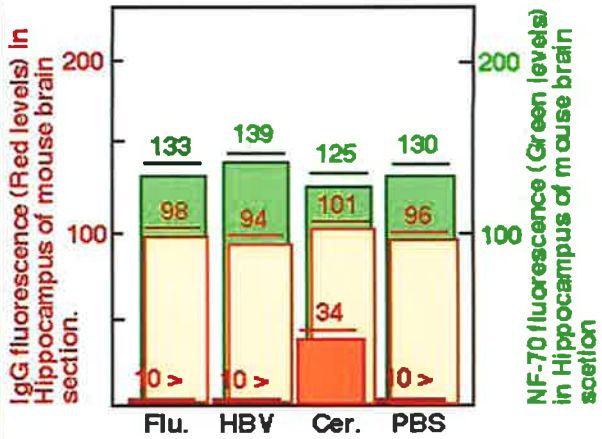


Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine, 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50-deficient mice was performed for immunological sudies; Date of 1st shot of Flu, HBV vaccine or PBS as control: March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Cervarix vaccine, Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and pathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.
Immunofluorescence analysis of NF-70 (Neurofilament-70, Neurofilaments (NF) are the 10 nanometer or intermediate filaments found in nwurons), GANGLIOSIDE GM1 and mouse IgG (autoantibody in serum, which was corrected from immunized NF-κBp50-deficient mouse with Cervarix, Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) in normal human brain tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of brain section: Human Brain sections (US Biomax-Normal Brain Tissue Array, Biomax US) with GANGLIOSIDE GM1 conjugated with Alexa 548 (SIGMA-Aldrich) or α-mouse IgG conjugated with Alexa 548 (SIGMA-Aldrich), and α-mouse NF-70-pAb conjugated with Alexa 488 (eBioscience, Inc.), and DAPI (Vector Laboratories, Inc.) was performed at November 24 - 25, and November 30 - December 1, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at November 26, and December 2, 2015.



Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine, 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50-deficient mice was performed for immunological sudies; Date of 1st shot of Flu, HBV vaccine or PBS as control: March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Cervarix vaccine, Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and pathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucus in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.
Immunofluorescence analysis of NF-70 (Neurofilament-70, Neurofilaments (NF) are the 10 nanometer or intermediate filaments found in nwurons), GANGLIOSIDE GM1 and mouse IgG (autoantibody in serum, which was corrected from immunized NF-κBp50-deficient mouse with Cervarix, Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) in normal human brain tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of brain section: Human Brain sections (US Biomax-Normal Brain Tissue Array, Biomax US) with GANGLIOSIDE GM1 conjugated with Alexa 548 (SIGMA-Aldrich) or α-mouse IgG conjugated with Alexa 548 (SIGMA-Aldrich), and α-mouse NF-70-pAb conjugated with Alexa 488 (eBioscience, Inc.), and DAPI (Vector Laboratories, Inc.) was performed at November 24 - 25, and November 30 - December 1, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at November 26, and December 2, 2015.





Control (tap water)
C. aromatica (2 mg/day)
6-MITC (150mg/day)

Z stack:
Image Dim. z; 16 μm
Sections ; 50 sections

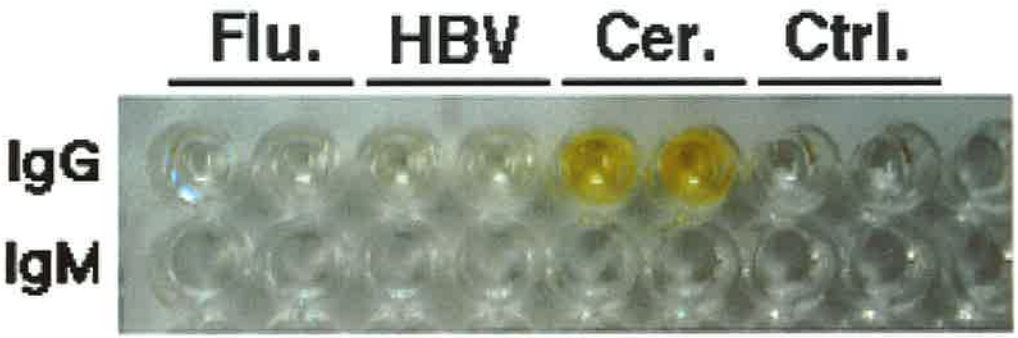
NF-70 (Neurofilament-70)
Mouse IgG
DAPI

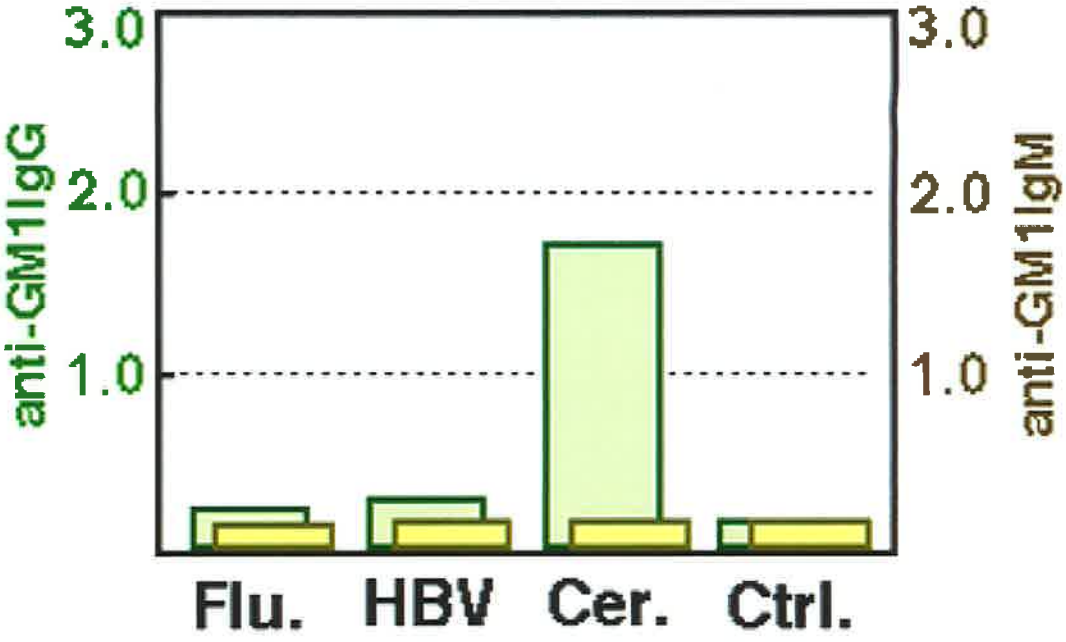
NF-70 (Neurofilament-70)
GANGLIOSIDE GM1
DAPI

Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine, 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50-deficient mice was performed for immunological sudies; Date of 1st shot of Flu, HBV vaccine or PBS as control: March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Cervarix vaccine, Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and biopathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucusal fluid in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.

Immunofluorescence analysis of NF-70 (Neurofilament-70, Neurofilaments (NF) are the 10 nanometer or intermediate filaments found in nwurons), GANGLIOSIDE GM1 and mouse IgG (autoantibody in serum, which was corrected from immunized NF-κBp50-deficient mouse with Cervarix, Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) in normal human brain tissue, detail is indicated in the supplementary information. Immunofluorescence analysis of brain section: Human Brain sections (US Biomax-Normal Brain Tissue Array, Biomax US) with α-GANGLIOSIDE GM1 conjugated with Alexa 548 (SIGMA-Aldrich) or α-mouse IgG conjugated with Alexa 548 (SIGMA-Aldrich), and α-mouse NF-70-pAb conjugated with Alexa 488 (eBioscience, Inc.), and DAPI (Vector Laboratories, Inc.) was performed at November 24 - 25, and November 30 - December 1, 2015. Quantitative analysis was performed using WinROOF Ver6.3.0 software (Mitani Co,. Ltd. Fukui Japan) at November 26, and December 2, 2015.

	Flu.	HBV	Cer.	Ctrl.
GM1 IgG IgM	0.23 0.17	0.32 0.21	1.73 0.19	0.18 0.20





Vaccine immunization: Intramascular injection with 50 μl of Cervarix vaccine, 50 μl of Flu, HBV vaccine or PBS as immunogen at quadriceps femoris muscle of 10 weeks old-NF-κBp50-deficient mice was performed for immunological sudies; Date of 1st shot of Flu, HBV vaccine or PBS as control: March 05, 2014. At 30 days after 1st shot of Flu, HBV vaccine or PBS. At 2 times, 2 months, 4 months and 12 months after date of 1st shot of Cervarix vaccine, Flu, HBV vaccine or PBS, the serum were collected from all immunized mice for immunological examinations and biopathological studies. Average of mouse serum IgA concentration in adult mouse, 3.15 ~ 5.38 μg/ml, average of IgA concentration in adult mouse mucusal fluid in 12 mg/ml. Avberage of mouse serum IgG concentration in adult mouse, 3.0 ~ 10.0 mg/ml.

Immunological analysis of anti-GANGLIOSIDE GM1 mouse IgG or mouse IgM (autoantibody in serum, which was corrected from immunized NF-κBp50-deficient mouse with Cervarix, Flu, HBV vaccine or PBS at May 3rd, 2014, July 1st, 2014, May 14, 2015) using GANGLIOSIDE GM1 ELISA with anti-IgG AP or anti-IgM AP, detail is indicated in the supplementary information (GM1 IgG E-3, Shino Test, Tokyo, Japan). 0.4 >; Negative, 1.0 >; False Positive, 1.0 <; Positive. Quantitative analysis was performed at December 22, 2015.

Physiological significance of chronic adoministration of C. aromatica and 6-MITC in metabolism and tumour immunity.

The physiological effects of chronic adoministration of C. aromatica or 6-MITC in Redox regulation, Tiol products in serum.

Biological function of chronic adoministration of C. aromatica or 6-MITC on tumourigenesis of syngenenic grafting with Lewis lung carcinoma.

Physiological effect of intramuscular injection of Cervarix on central nervous system (CNS) and abnomal lymphocyte progration.

Production of autoantibody in serum of NF-κBp50-null mice with intramuscular injection of Cervarix.

Observation of B cell lymphoma in NF-κBp50-null mice with intramuscular injection of Cervarix.

表I　3,4-BP 1000γ 投与による
経時的白血病発生率

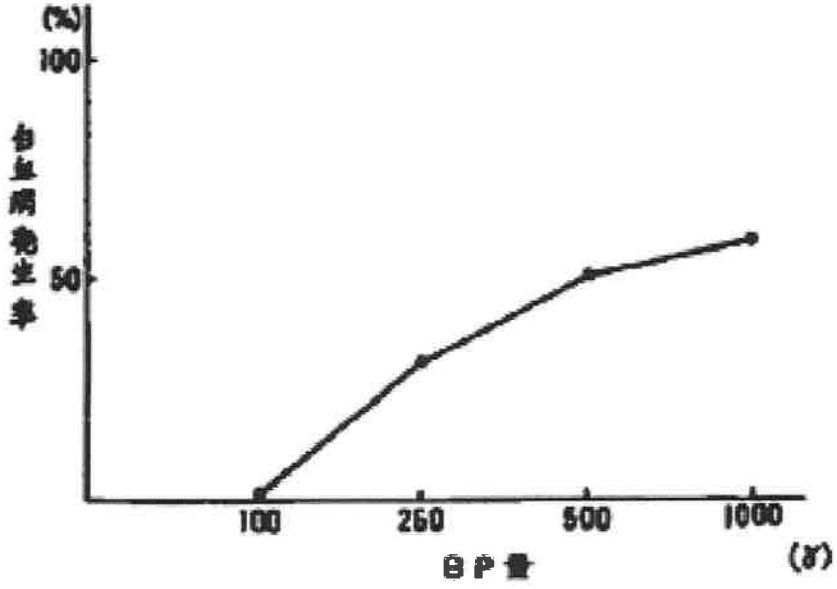
BP投与日月数 ＼ マウス匹数	実験マウス	白血病マウス	白血病発生率（%）
1.0	6＜♂3 ♀3	0	0
1.5	8＜♂3 ♀5	1＜♂0 ♀1	13
2.0	10＜♂5 ♀5	7＜♂4 ♀3	70
2.5	13＜♂8 ♀5	10＜♂7 ♀3	77
3.0	9＜♂4 ♀5	8＜♂3 ♀5	89

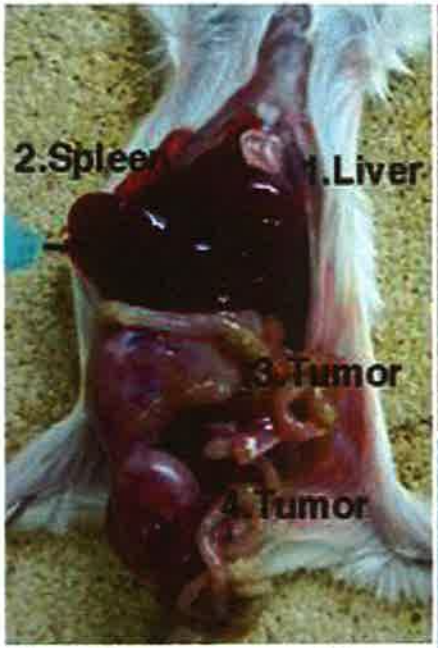
表II　3,4-BP 1000γ，500γ，250γ，100γ
投与による白血病の発生率

BP量（γ） ＼ マウス匹数	実験マウス	白血病マウス	白血病発生率（%）	生存期間（日）
1000	46＜♂23 ♀23	26＜♂14 ♀12	57	59～95
500	12＜♂7 ♀5	6＜♂3 ♀3	50	72～142
250	10＜♂5 ♀5	3＜♂2 ♀1	30	95～123
100	10＜♂5 ♀5	0	0	200以上

永森　発癌性物質の新生児マウス注射による白血病の発症機序に関する研究, p147-171.

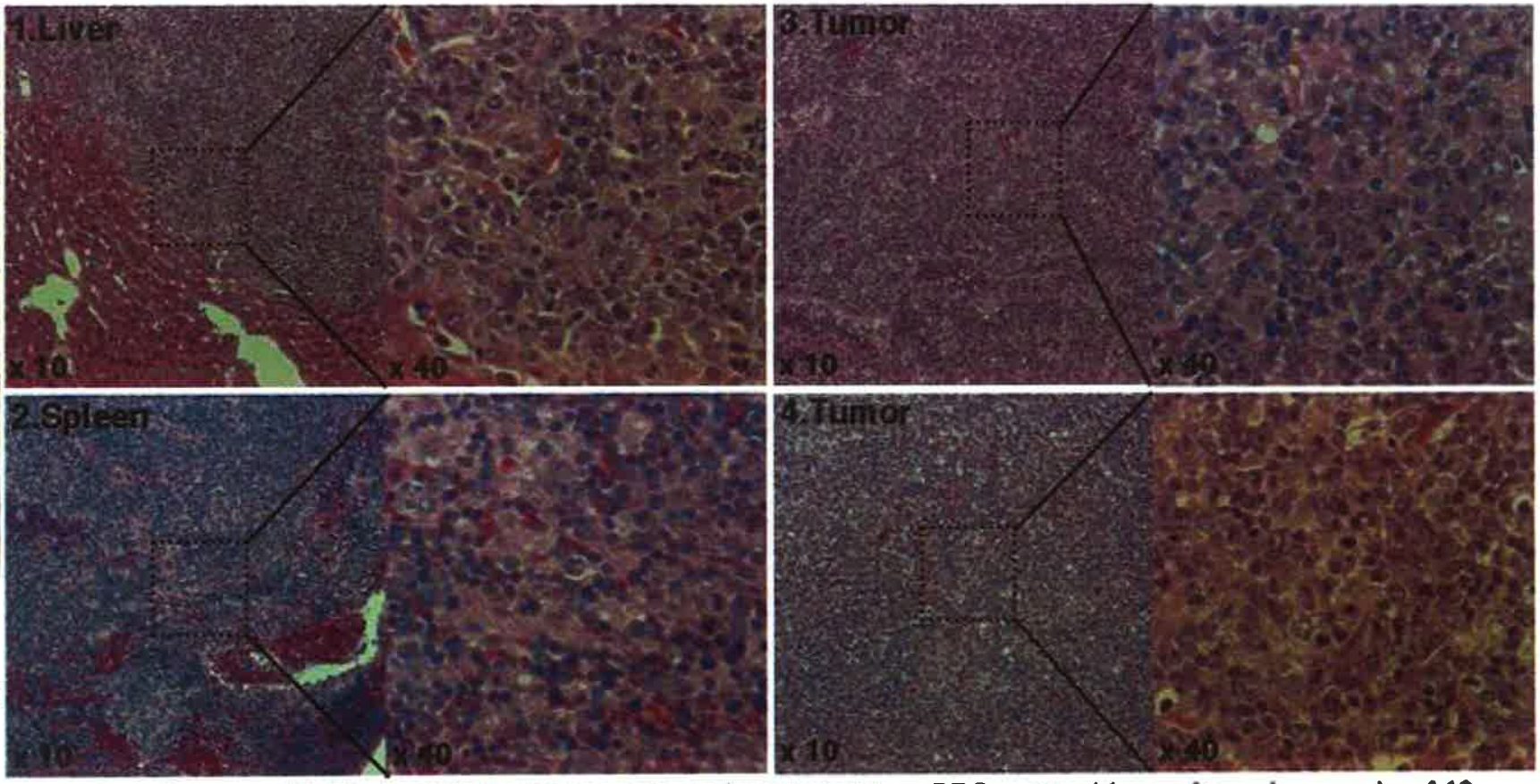
図2　BP 各 Dosis による白血病発生率



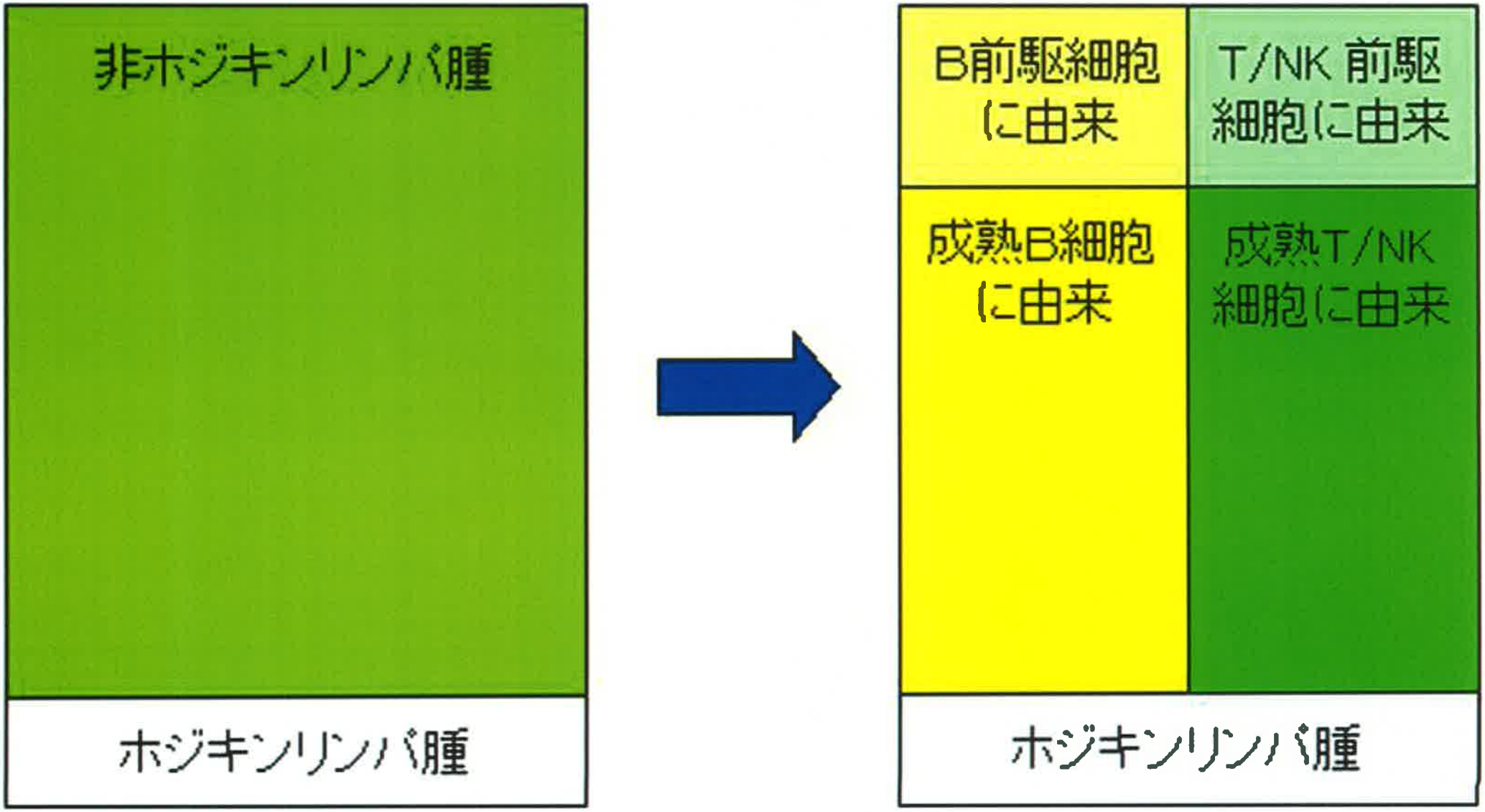


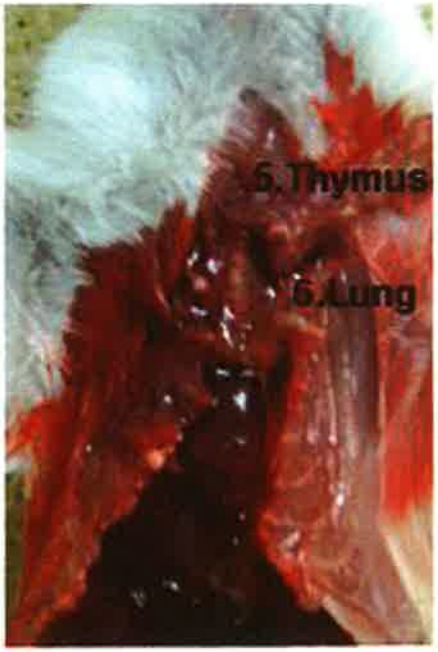
#1 to #7 Tissues are obtained from BALB/c immunized with Cervarix 50 μL.

Lymph node is obtained from normal BALB/c mouse.



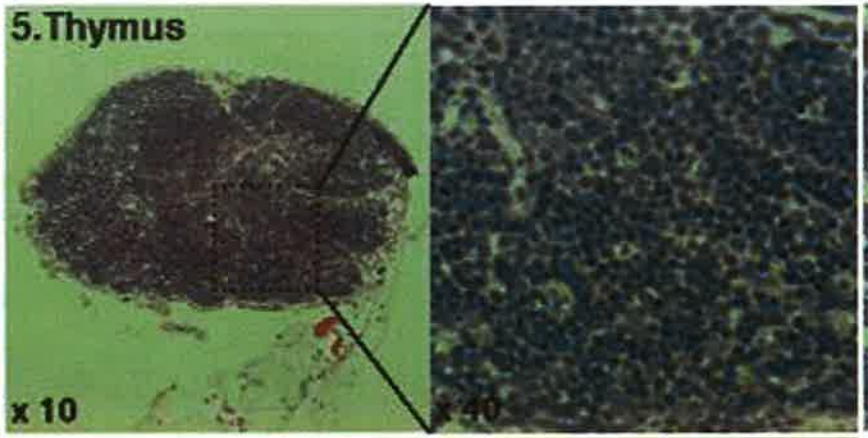
Vaccine immunization: Intramascular injection with 50 μL of Cervarix vaccine as immunogen or PBS at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine or PBS, Intramascular injection with 50 μl of Cervarix vaccine was parformed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies. All immunized BALB/c mice were sacrificed for immunological studies and pathological examinations at 27 March, 2015.

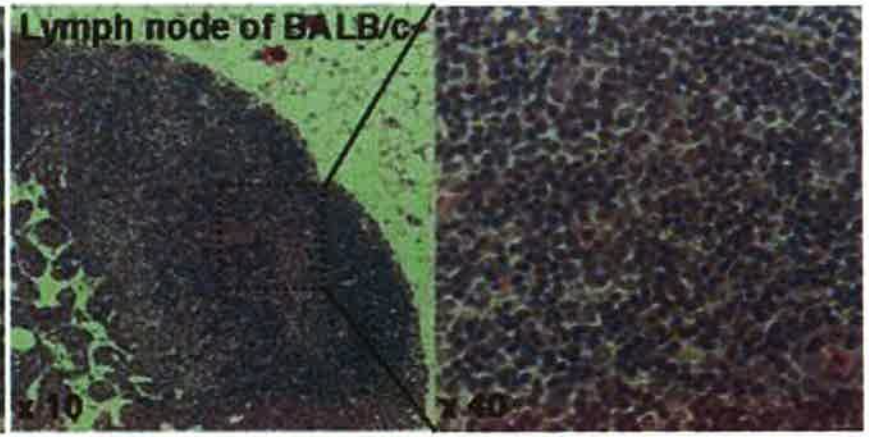

非ホジキンリンパ腫
ホジキンリンパ腫
B前駆細胞に由来
T/NK 前駆細胞に由来
成熟B細胞に由来
成熟T/NK細胞に由来
ホジキンリンパ腫

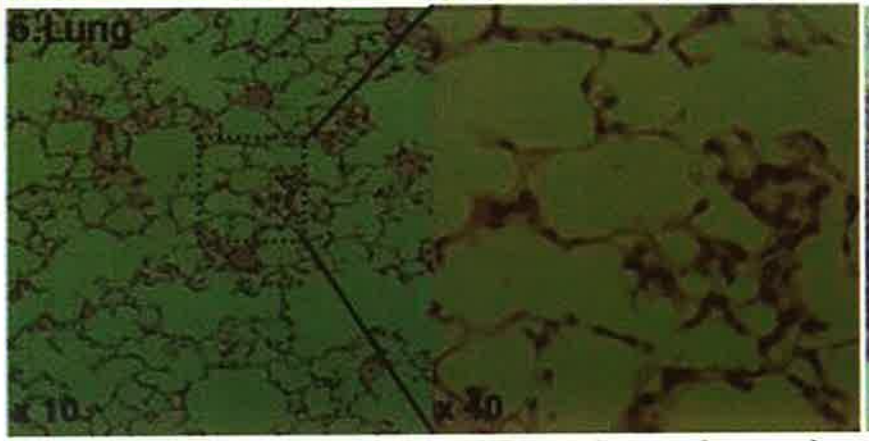


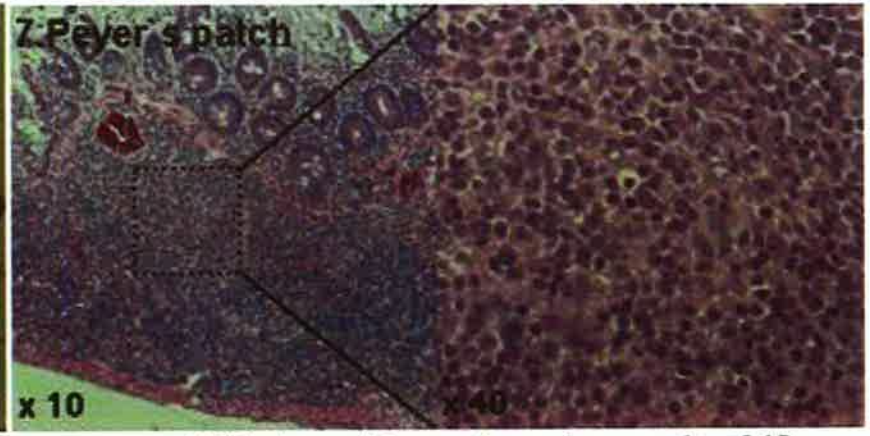
#1 to #7 Tissues are obtained from BALB/c immunized with Cervarix 50 μL.

Lymph node is obtained from normal BALB/c mouse.





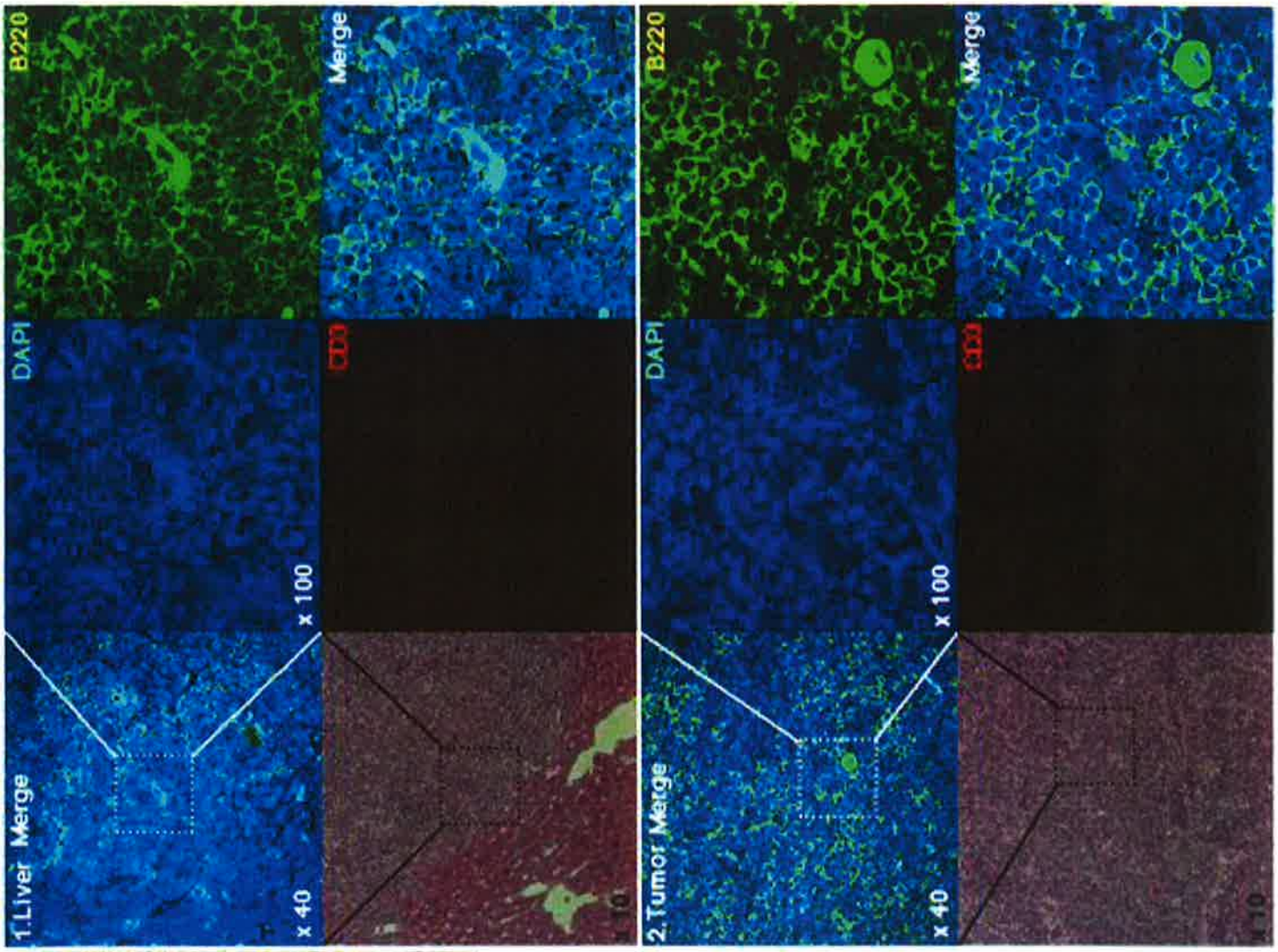




Vaccine immunization: Intramascular injection with 50 μL of Cervarix vaccine as immunogen or PBS at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine or PBS, Intramascular injection with 50 μl of Cervarix vaccine was parformed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies. All immunized BALB/c mice were sacrificed for immunological studies and pathological examinations at 27 March, 2015.

Vaccine immunization: Intramascular injection with 50 µL of Cervarix vaccine as immunogen or PBS at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine or PBS, Intramascular injection with 50 µl of Cervarix vaccine was performed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies. All immunized BALB/c mice were sacrificed for immunological studies and pathological examinations at 27 March, 2015.

Immunofluorescence analysis of B220 (surface marker for mouse B cells) and CD3 (surface karker for common T cells) in tissues derived from BALB/c nu/nu mice, which were xenografted with A2780 cells. Immunofluorescence analysis with sections of tumors and several tissues with Alexa 546-conjugated anti-CD3-mAb (Species: react with mouse T cells; Pharmingen), and Alexa 488-conjugatd B220 (Species: react with mouse surface biomarker for mouse B cells; Pharmingen) and DAPI (Vector Laboratories, Inc.) was performed at April 15-16, 2015.

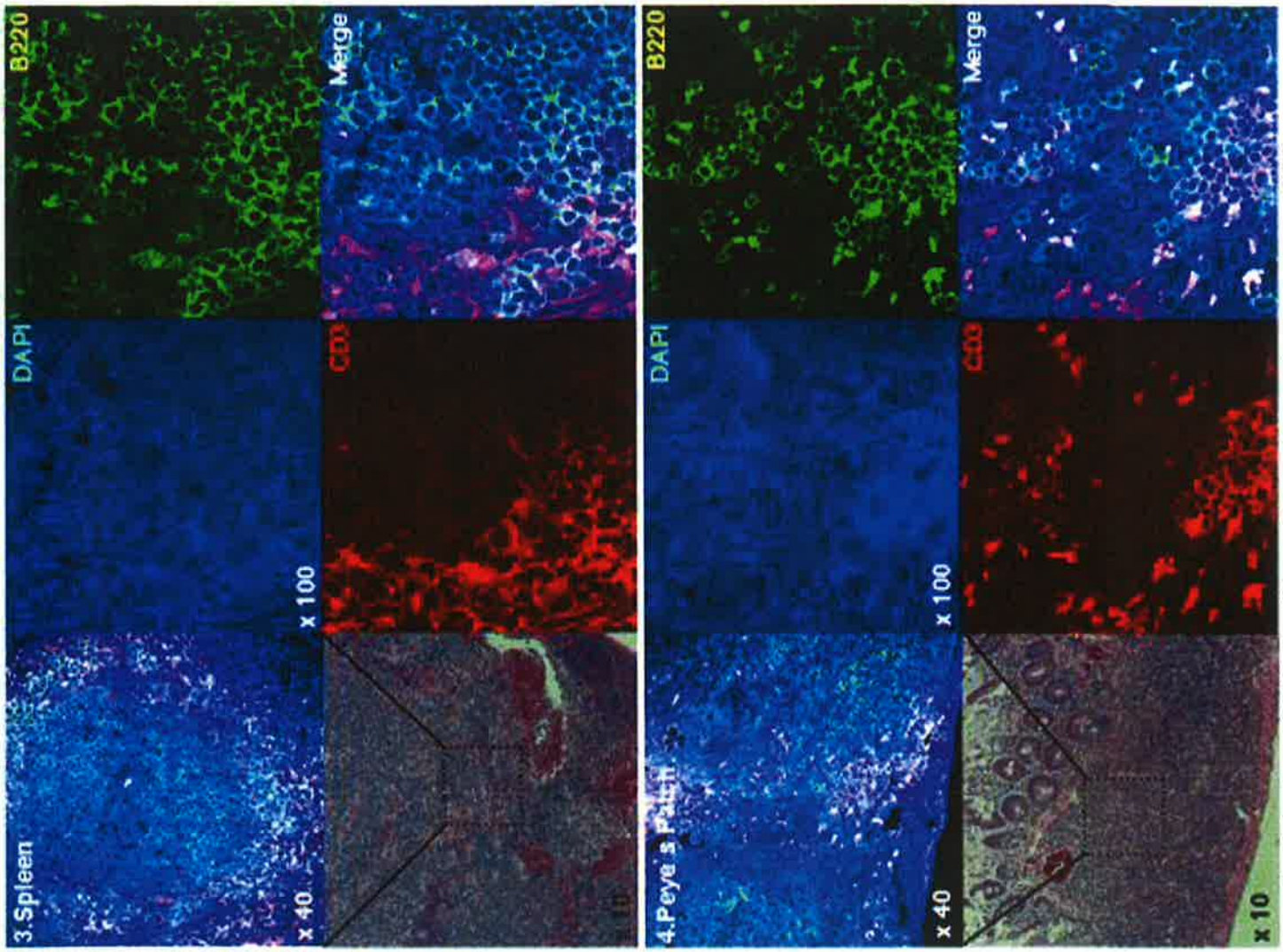


#1 to #7 Tissues are obtained from BALB/c immunized with Cervarix 50 µL.

Lymph node is obtained from normal BALB/c mouse.

Vaccine immunization: Intramascular injection with 50 µL of Cervarix vaccine as immunogen or PBS at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine or PBS, Intramascular injection with 50 µl of Cervarix vaccine was parformed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies. All immunized BALB/c mice were sacrificed for immunological studies and pathological examinations at 27 March, 2015.

Immunofluorescence analysis of B220 (surface marker for mouse B cells) and CD3 (surface karker for common T cells) in tissus derived from BALB/c nu/nu mice, which were xenografted with A2780 cells. Immunofluorescence analysis with sections of tumors and several tissues with Alexa 546-conjugated anti-CD3-mAb (Species: react with mouse T cells; Pharmingen), and Alexa 488-conjugatd B220 (Species: react with mouse surface biomarker for mouse B cells; Pharmingen) and DAPI (Vector Laboratories, Inc.) was performed at April 15-16, 2015.

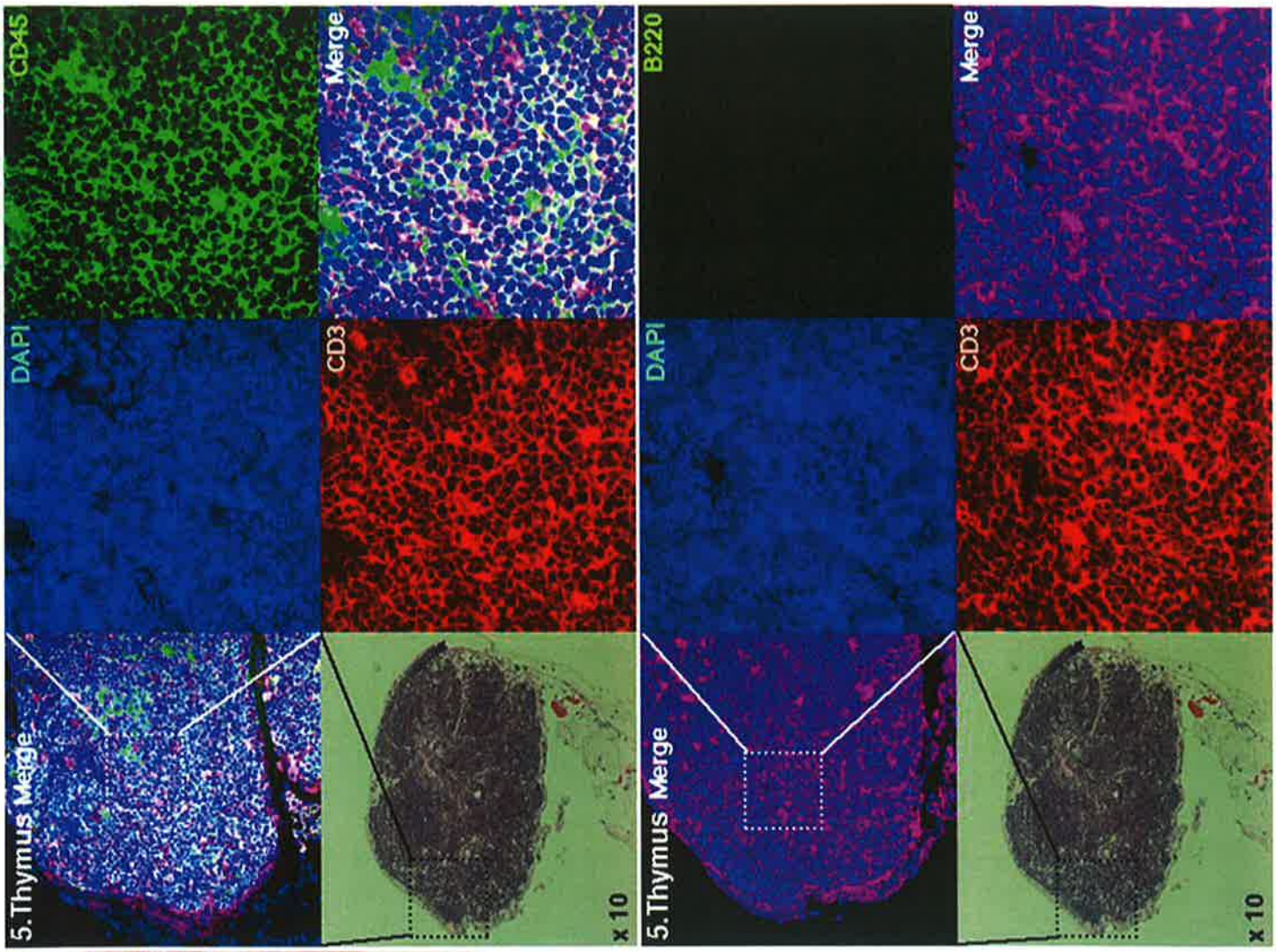


#1 to #7 Tissues are obtained from BALB/c immunized with Cervarix 50 µL.

Lymph node is obtained from normal BALB/c mouse.

Vaccine immunization: Intramascular injection with 50 μL of Cervarix vaccine as immunogen or PBS at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine or PBS, Intramascular injection with 50 μl of Cervarix vaccine was parformed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies. All immunized BALB/c mice were sacrificed for immunological studies and pathological examinations at 27 March, 2015.

Immunofluorescence analysis of B220 (surface marker for mouse B cells) and CD3 (surface karker for common T cells) in tissues derived from BALB/c nu/nu mice, which were xenografted with A2780 cells. Immunofluorescence analysis with sections of tumors and several tissues with Alexa 546-conjugated anti-CD3-mAb (Species: react with mouse T cells; Pharmingen), and Alexa 488-conjugatd B220 (Species: react with mouse surface biomarker for mouse B cells; Pharmingen) and DAPI (Vector Laboratories, Inc.) was performed at April 21-22, 2015.

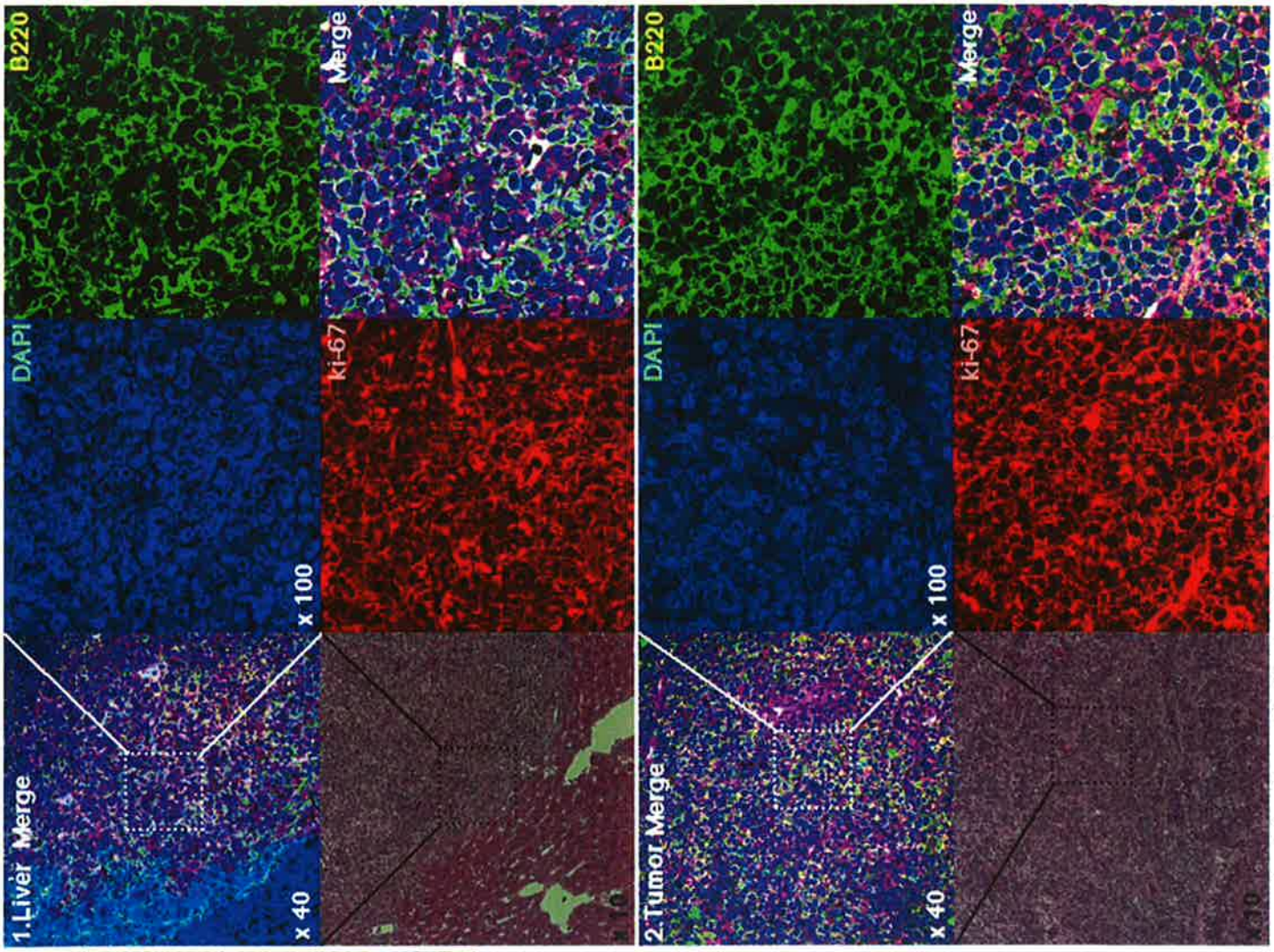


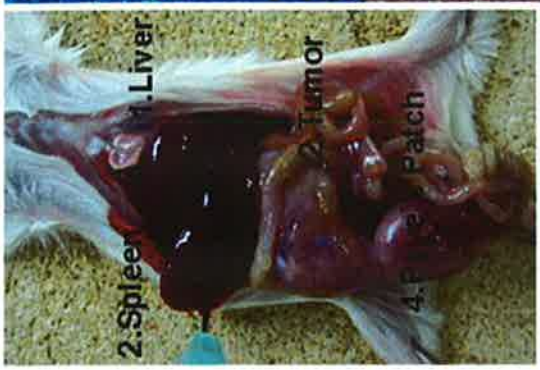
#1 to #7 Tissues are obtained from BALB/c immunized with Cervarix 50 μL.

Lymph node is obtained from normal BALB/c mouse.

Vaccine immunization: Intramascular injection with 50 μL of Cervarix vaccine as immunogen or PBS at quadriceps femoris muscle of 10 weeks old-BALB/c mice was performed for immunological sudies; Date of 1st shot of Cervarix vaccine: March 05, 2014. At 30 days after 1st shot of Cervarix vaccine or PBS, Intramascular injection with 50 μl of Cervarix vaccine was parformed at April 3rd, 20-14. At 2 times, 2 months and 4 months after date of 1st shot of Cervarix vaccine, the serum were collected from all immunized mice for immunological examinations and pathological studies. All immunized BALB/c mice were sacrificed for immunological studies and pathological examinations at 27 March, 2015.

Immunofluorescence analysis of B220 (surface marker for mouse B cells) and ki-67 (biokarker for growing cells) in tissues derived from BALB/c nu/nu mice, which were xenografted with A2780 cells. Immunofluorescence analysis with sections of tumors and several tissues with Alexa 546-conjugated anti-ki-67-mAb (Species: react with growing cells; Pharmingen), and Alexa 488-conjugatd B220 (Species: react with mouse surface biomarker for mouse B cells; Pharmingen) and DAPI (Vector Laboratories, Inc.) was performed at April 17-18, 2015.





#1 to #7 Tissues are obtained from BALB/c immunized with Cervarix 50 μL.

Lymph node is obtained from normal BALB/c mouse.