# Autoimmune and Paraneoplastic Neurological Syndromes

Pavel Štourač

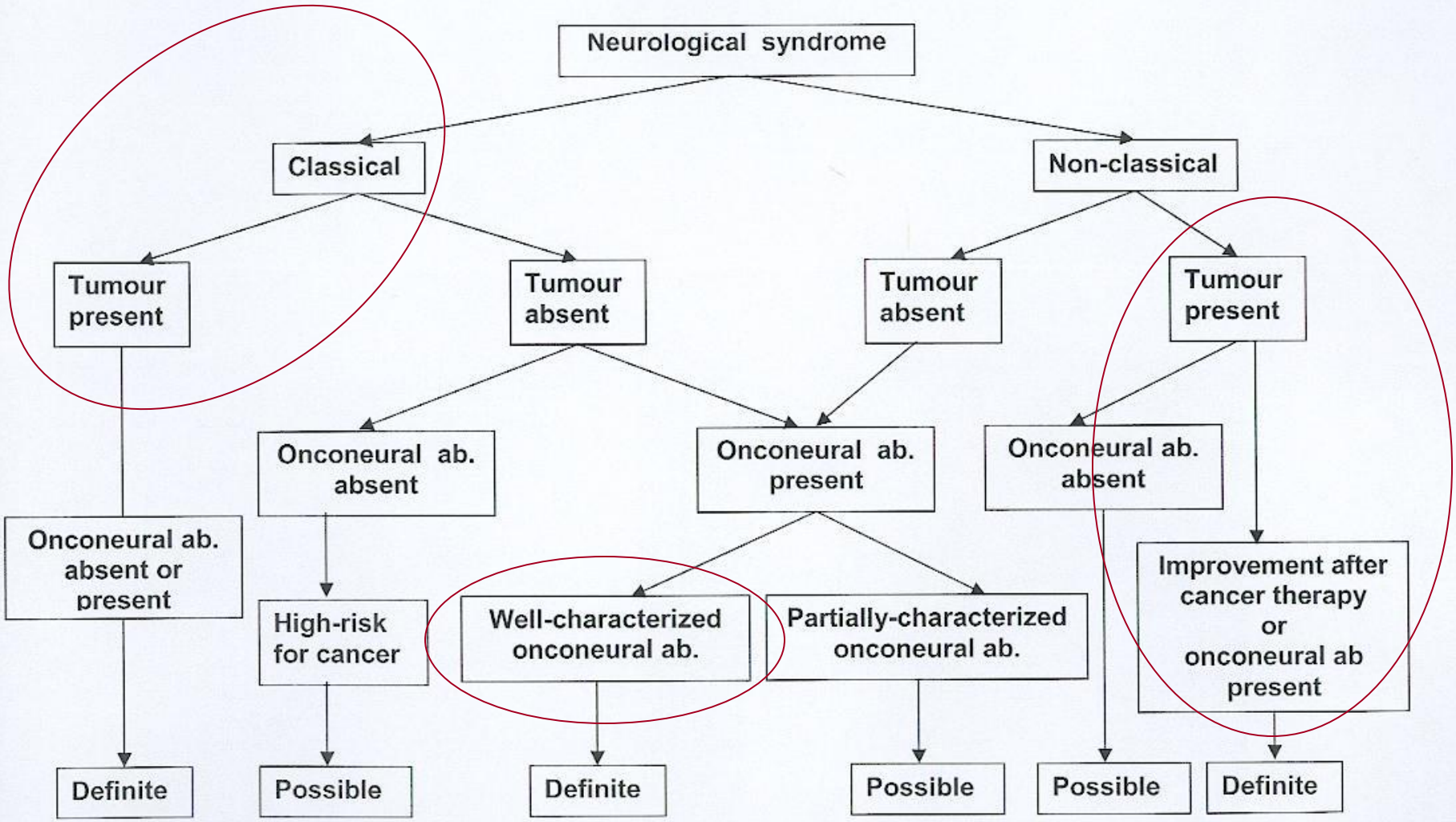
Department of Neurology
University Hospital, Masaryk University
Brno, Czech Republic

FAKULTNÍ NEMOCNICE BRNO

UNIVERSITAS MASARYKIANA BRUNENSIS

# Classical and non-classical paraneoplastic syndromes

| Classical syndrome | Non-classical syndrome |
|---|---|
| **Central nervous system** | |
| Encephalomyelitis | Brainstem encephalitis |
| Limbic encephalitis | Optic neuritis |
| Subacute cerebellar degeneration | Myelitis/necrotizing myelopathy |
| Opsoclonus–myoclonus syndrome | Stiff-person syndrome and variants |
| **Peripheral nervous system** | |
| Subacute sensory neuronopathy | Distal-symmetric sensorimotor neuropathy |
| Chronic intestinal pseudo-obstruction | Polyradiculoneuropathy (acute/chronic) |
| | Multiplex mononeuropathy |
| | Pure autonomic neuropathies |
| Neuromuscular junction and muscle | |
| Lambert–Eaton myasthenic syndrome | Myasthenia gravis |
| Dermatomyositis | Neuromyotonia |

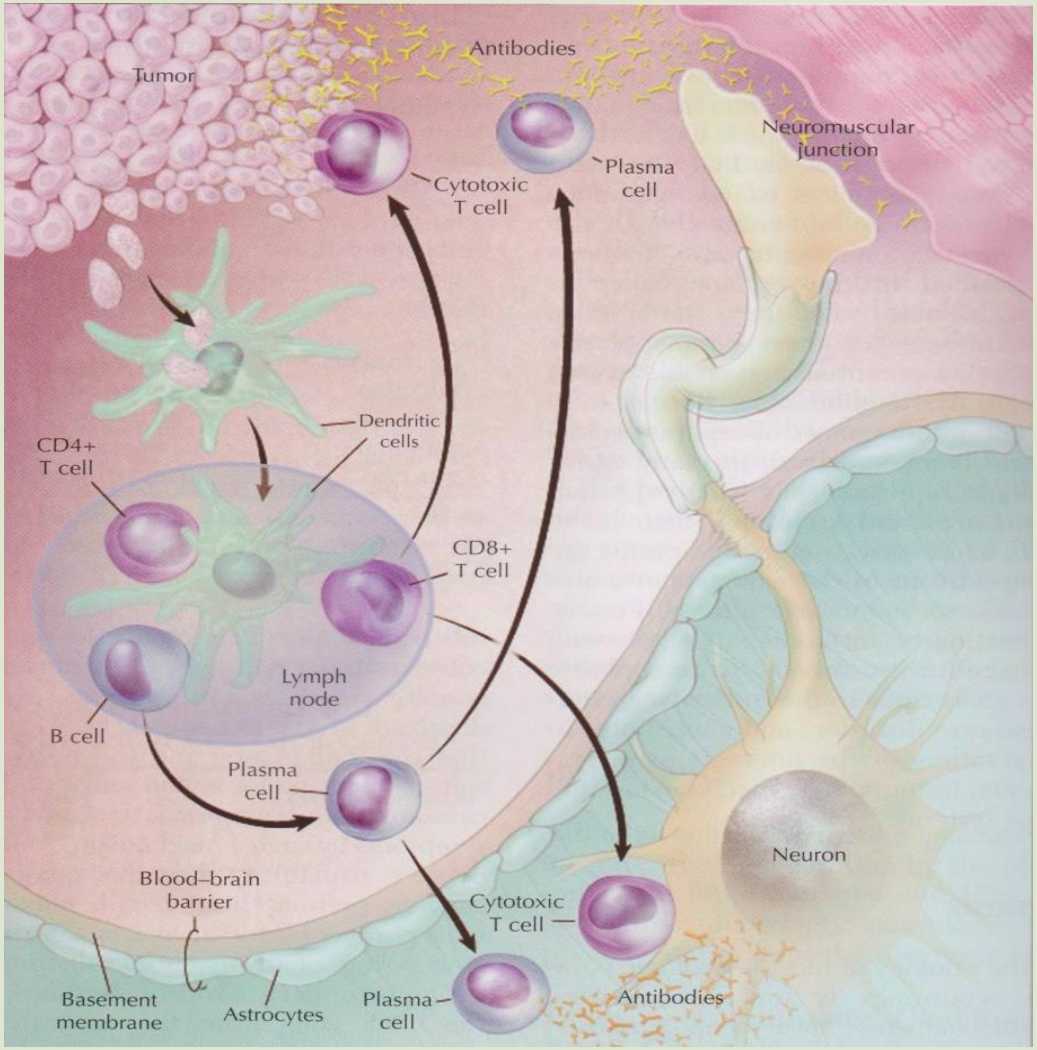

Neurological syndrome
Classical
Non-classical
Tumour present
Tumour absent
Tumour absent
Tumour present
Onconeural ab. absent
Onconeural ab. present
Onconeural ab. absent
Onconeural ab. absent or present
High-risk for cancer
Well-characterized onconeural ab.
Partially-characterized onconeural ab.
Improvement after cancer therapy or onconeural ab present
Definite
Possible
Definite
Possible
Possible
Definite

JNNP 2004

# Well-characterized onconeural antibodies found in paraneoplastic syndromes

| **Antibody** | **Associated syndromes and symptomes** | **Most common tumours** |
|---|---|---|
| Anti-Hu (ANNA-1) | Encephalomyelitis, limbic encephalitis, cerebellar degeneration, brain stem encephalitis, multi-segmental myelitis, sensory neuronopathy, sensory motor neuropathy, autonomic neuropathy | Lung cancer (85%), mostly SCLC, neuroblastoma, prostate carcinoma |
| Anti-Yo (PCA-1) | Paraneoplastic cerebellar degeneration | Ovarian, breast cancer |
| Anti-CV2/CRMP5 | Encephalomyelitis, polyneuropathy, optic neuritis, limbic encephalitis, choreatic syndromes, cerebellar degeneration | SCLS, thymoma |
| Anti-Ta/Ma2 | Limbic encephalitis, rhombencephalitis, male>>female | Testicular cancer |
| Anti-Ri (ANNA-2) | Opsoclonus-myoclonus syndrome, rhombencephalitis, cerebellar degeneration, myelitis, jaw dystonia, laryngospasm | Breast, ovarian carcinoma, SCLC |
| Anti-amphiphysin | Stiff-person syndrome, limbic encephalitis, , rhombencephalitis, cerebellar degeneration, polyneuropathy | Breast cancer, SCLC |
| Anti-recoverin | Retinopathy | SCLC |
| Anti-Tr (DNER) | Paraneoplastic cerebellar degeneration | Hodgkin |

# Pathophysiology of paraneoplastic neurological syndromes




*N Engl J Med 2003; 349:1543-1554*

# Antibodies against neural surface antigens

- Probably pathogenic
- Good response to immunotherapy
- Do not indicate if syndrome is paraneoplastic

| Antibody | Syndrome | % cancer | Cancer Type |
|---|---|---|---|
| NMDAR | Encephalitis | 50 | Ovarian teratoma |
| AMPAR | LE | 60 | Breast; SCLC |
| GABA(B)R | LE | 70 | SCLC |
| mGluR5 | LE | 100? | Hodgkin |
| CASPR2 | Morvan/LE | 50/0 | Thymoma |
| LGI1 | LE | 0 | - |
| GlycineR | PERM | <1? | - |
| DPPX | Encephalitis | 0 | - |
| GABAaR | Encephalitis | 0? | - |

**PERM:progressive encephalomyelitis/rigidity/myoclonus;**

**LE: limbic encephalitis; SCLC: small cell lung cancer**

# Paraneoplastic syndromes of the CNS and relevant well-characterized onconeural or neuronal cell-surface antibodies

| **Syndrome** | **Relevant antibodies** |
|---|---|
| Subacute cerebellar degeneration<br>25% | Hu, Yo, CV2/CRMP5, Ri, Tr, amphiphysin, VGCC |
| Encephalomyelitis<br>6% | Hu, CV2/CRMP5, amphiphysin |
| Limbic encephalitis<br>10% | Hu, Ma2, GABA(b)-, AMPA-, mGluR5, |
| Opsoclonus-myoclonus syndrome (adults)<br>2% | Ri |
| Retinopathy<br>1% | CV2/CRMP5, recoverin |
| Stiff-person syndrome<br>1% | Amphiphysin, |
| Chorea | CV2 |
| Encephalitis | NMDAR |

# Recommended tumour screening (Titulaer *et al.)*

| **Tumour** | **Diagnostics** | | |
|---|---|---|---|
| | **Primary** | **Secondary** | **Tertiary** |
| Lung cancer | Thoracic CT (80-85%), thoracic MRI | FDG-PET or FDG-PET/CT | Bronchoscopy/EB-US, possibly needle biopsy and/or mediastinoscopy |
| Thymoma | Thoracic CT (75-90%), thoracic MRI | FDG-PET or FDG-PET/CT | |
| Breast cancer | Mammography (80%), ultrasound | Breast MRI | |
| Ovarian carcinoma | Ultrasound (69-90%) + CA-125 | Pelvic and abdominal CT | FDG-PET |
| Ovarian teratoma | Ultrasound (69-90%) | MRI (93-98%) | Thoracic CT (extra-pelvic teratomas) |
| Testicular cancer | Ultrasound (72%) + β-HCG, AFP | Pelvic/abdominal CT (76%), abdominal MRI | Possibly FDG-PET (malignant teratomas) |
| Lymphoma | Thoracic/abdominal CT, ultrasound | FDG-PET or FDG-PET/CT | |
| Skin tumours (Merkel-cell carcinoma) | Dermatological examination, biopsy | | |

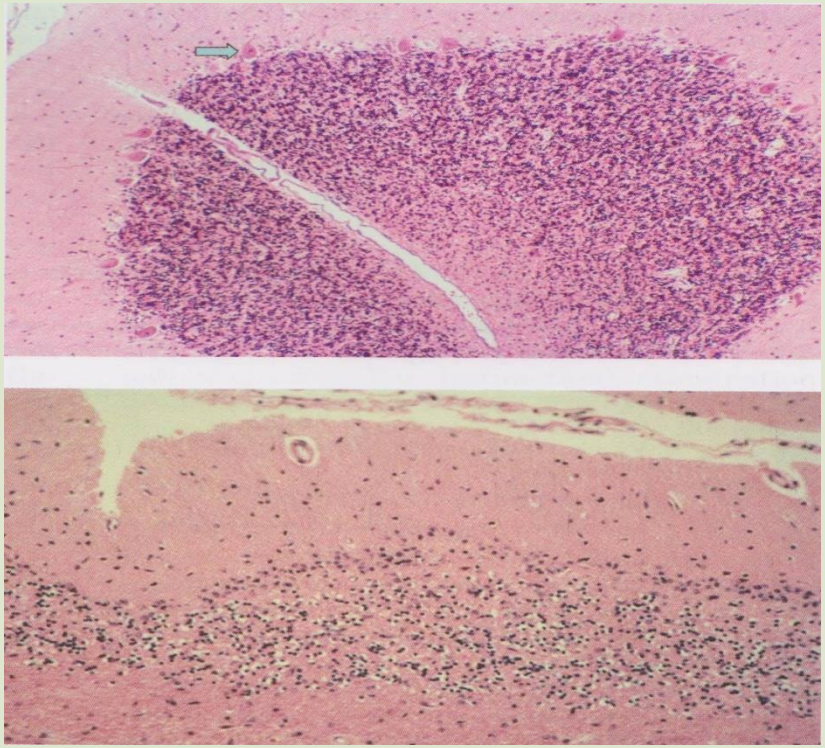
# Paraneoplastic cerebellar degeneration - the most common PS syndrome of the CNS

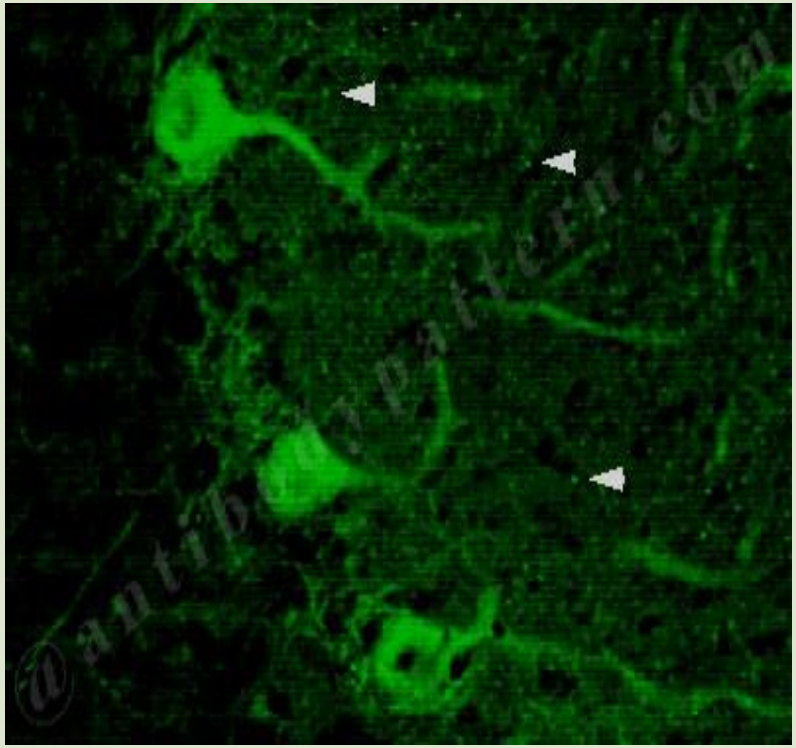
- MRI - normal, late phase - cerebellar atrophy
- CSF - pleocytosis, oligoclonal IgG bands - 60%
- anti - Yo (PCA-1) antibodies (gynaecological malignancy)
- anti - Hu (ANNA-1)/VGCC antibodies (SCLC)
- CV2/CRMP5 - (SCLC)
- anti - Tr antibodies (Hodgkin´s lymphoma) - **newly discovered antigen delta notch - like epidermal growth factor related receptor (DNER)**
- anti - Ri antibodies (breast and lung cancer) + POM
- amphiphysin, Zic4, mGluR1,VGCC

a) normal cerebellar structure - Purkinje cells, stratum granulare
b) PCD - the absence of Purkinje cells and reduced granular layer of cerebellum
c) indirect immunofluorescence with positive anti -Yo antibodies

a

b





c

# New antibodies and paraneoplastic cerebellar degeneration

- single cases and small series cases:

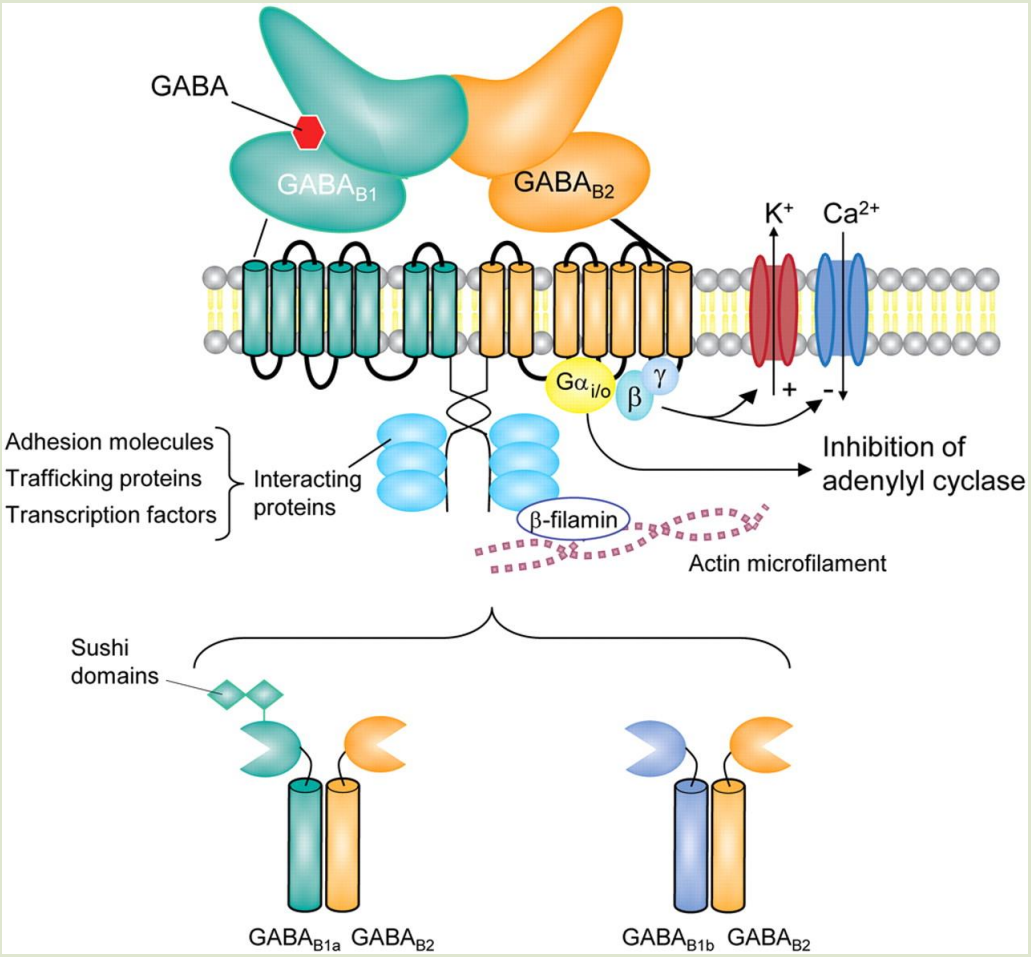
✓ anti - protein kinase Cγ/PCD/adenocarcinoma
✓ anti - RhoGTPase - activating protein 26/PCD/ovarian cancer
✓ anti-CARP7/melanoma
✓ idiopathic cerebellitis - associated:
  – VGKC complex antibodies, GAD, mGluR1 and Homer 3

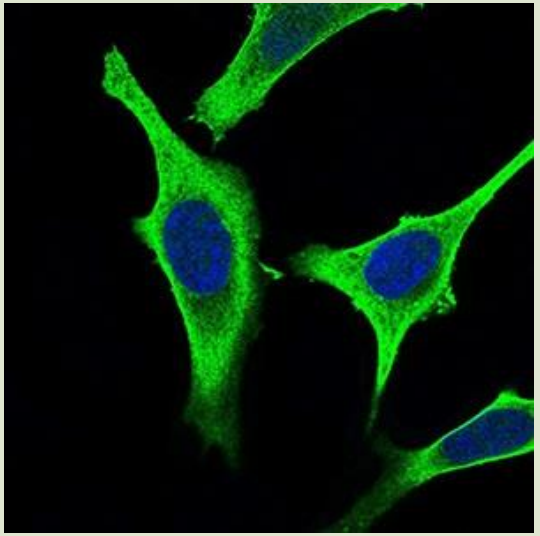
# Anti-GABA(B)receptor antibodies and PNS

- antibodies to the **GABA(B)** receptor *GABA(B1)* and *GABA(B2*) receptor subunits - an inhibitory receptor
- antibodies against a neuronal cell - surface antigen
- limbic encephalitis with seizures; limbic dysfunction (MRI, EEG)
- 15 pts suspected  from paraneoplastic or immune - mediated encephalitis
- **7pts had tumours; 5pts SCLC**; 7pts non - neuronal Abs
- 9 pts from 10 pts who received immunological or cancer therapy had improved
- **50-80% of paraneoplastic origin**
- Res: treatable condition associated with seizures and SCLC

*Lancaster E. , Lancet neurol 2010; (9):67-76*

# GABA (B) receptor



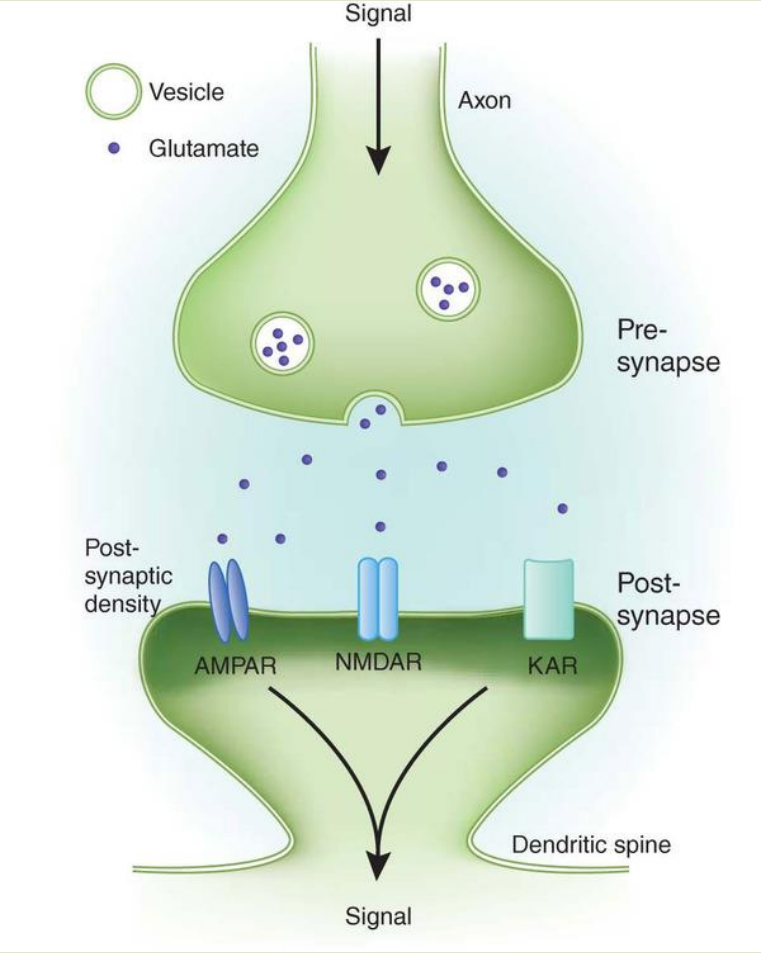



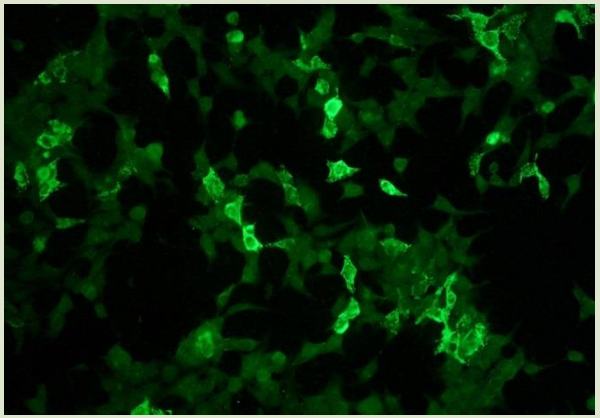
Immunofluorescent analysis of HeLa cells labeling GABA B Receptor 2 with ab181736 at 1/200 (green). Blue: DRAQ5 fluorescent DNA dye.

# Anti-NMDA receptor antibodies and PNS

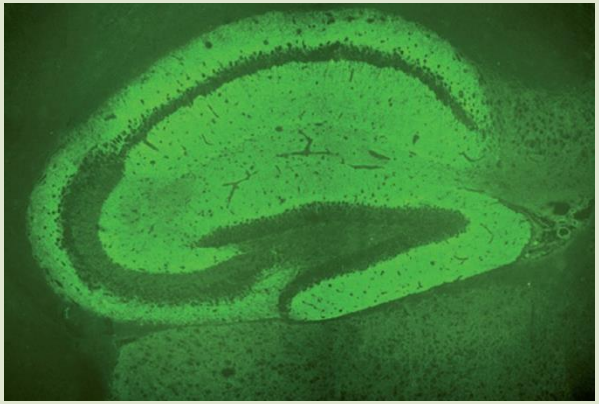
- glutamate (inotropic) excitatory receptors:
- N-methyl-D-aspartate (**NMDA**) receptor (4 subunits; two NR1 and two NR2)
- (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA receptor)
- kainate receptor
- metabotropic  glutamate receptor (**mGluR**) coupled with G protein
- both glutamate and glycine binds to and open ion channel
- paraneoplastic antibodies react with **NR1 subunit** in NMDAR receptor and downregulate NMDA receptors

# NMDA receptor



NMDAR antibodies determined using commercially available NR1 transfected cells.



Fluorescence of the hippocampus (neuropil staining)

*http://imgsoup.com*

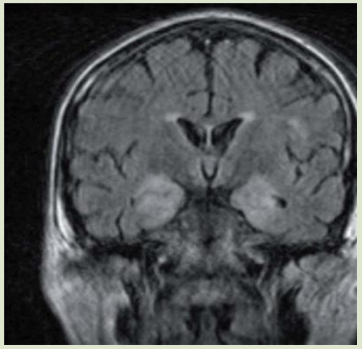
*www.birmingham.ac.uk*

# Anti-NMDA receptor antibodies and PNS

- clinical manifestation
- cortico-subcortical encephalopathy
- psychiatric symptoms; behavioral and cognitive disorders, paranoia, delusions, hallucinations
- involuntary movements; orofacial dyskinesias, choreoathetoid dystonia, increased muscle tone
- vegetative symptoms; cardiac dysrhytmia,blood pressure instability,hyperhidrosis, dysthermia,sialorhea, ileus ,central hypoventilation
- seizures; generalized, focal and also atypical
- reduction in consciousness, unconsciousness, arteficial ventilation and ICU

# Anti-NMDA receptor antibodies and PNS

- **association with tumours: ≤ 50% mostly ovarian teratomas,endocrine tumour, SCLC**
- Diagnosis:



✓ EEG slow and epileptic activity (100% pts)

✓ abnormal brain MRI scan (55%)

✓ CSF abnormalities; (100 %) lymphocytic pleocytosis, increased protein concentration and oligoclonal IgG bands

- potentially  treatable disorder, not always
- refractory  cases treatment - cyclophosphamide, rituximab

# Anti-AMPA receptor antibodies and PNS

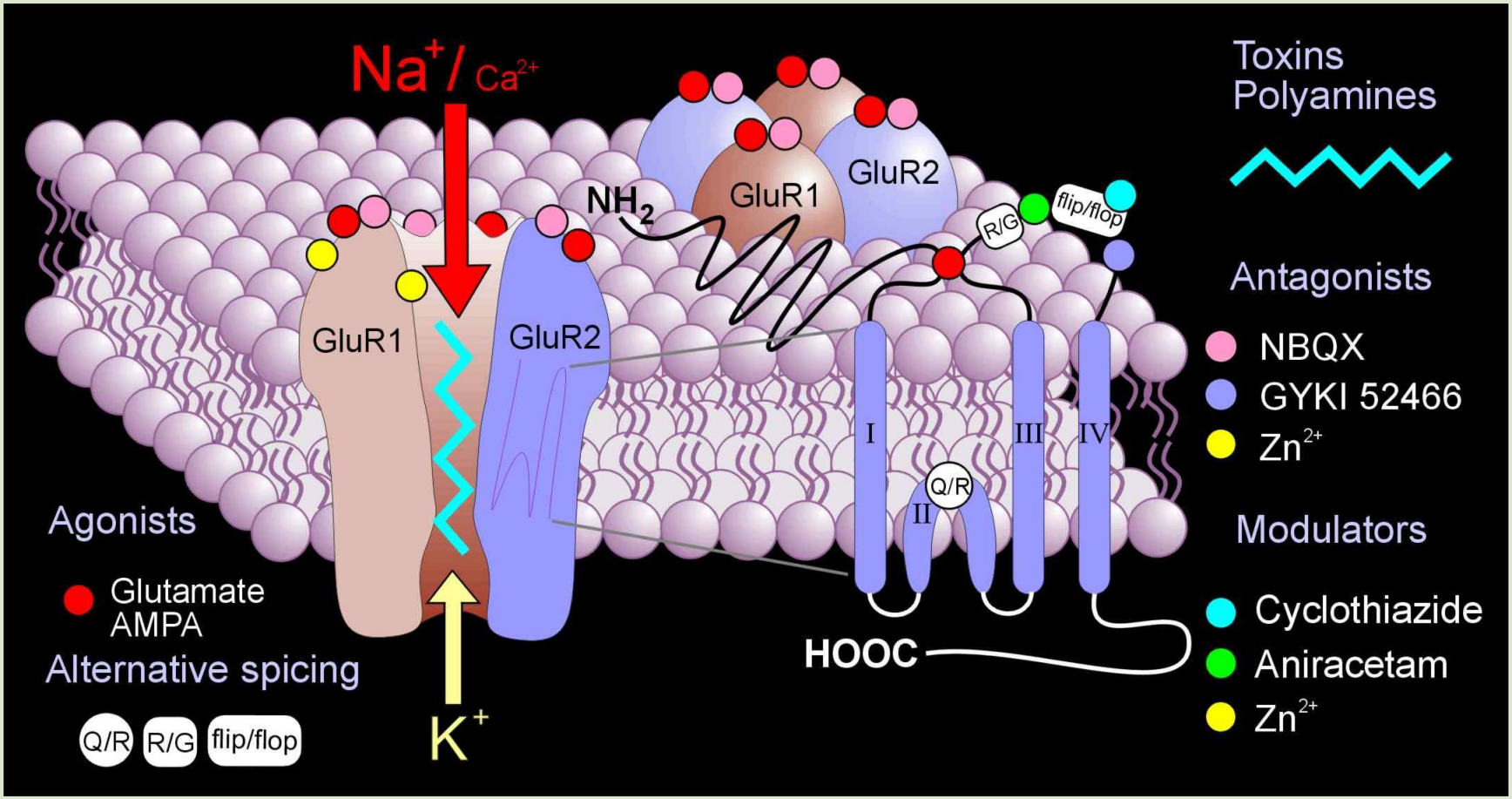
- antibodies against the GluR1/GluR2 subunit of AMPA
- clinical manifestations
- limbic encephalitis, i.e. amnesia, seizures, psychosis
- **in 67% (70-75%) paraneoplastic origin - thymoma, lung, breast, ovary**
- abnormal MRI 85%

*Bataller et al.,2010; Titulaer et al. 2014*

- antibodies against mGluR1
- **paraneoplastic cerebellar degeneration (2 pts)**

*Sillevits-Smitt,2000*

# AMPA receptor

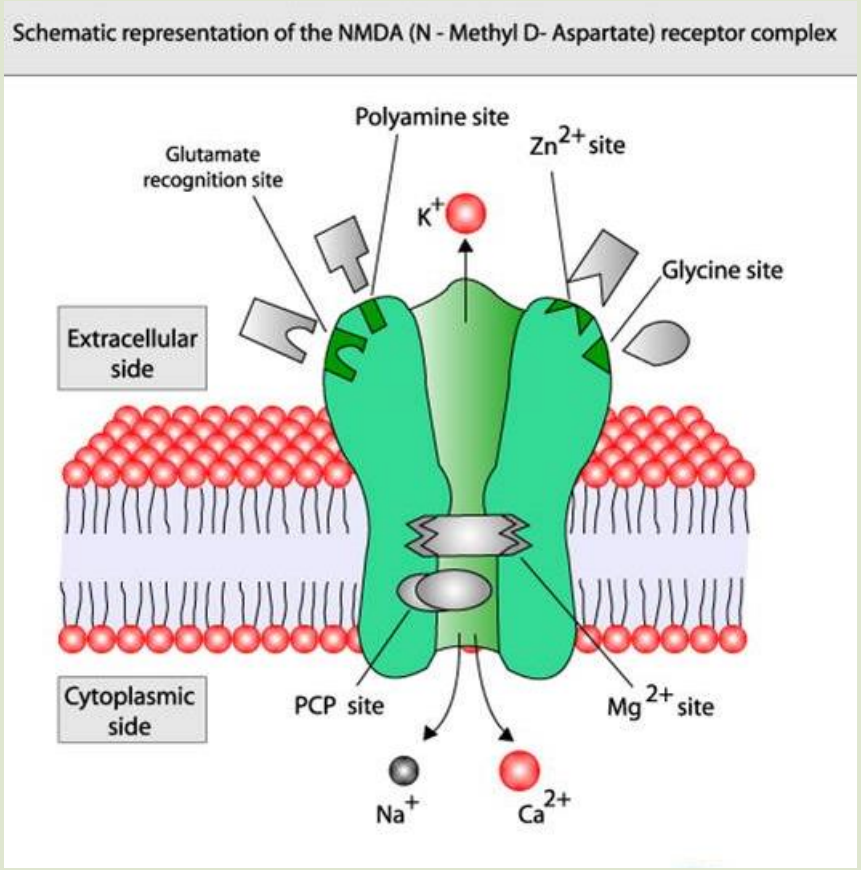



http://wiki.bioguider.com

# Anti-glycine receptor antibodies and PNS

- glycine is an inhibitory neurotransmitter in CNS
- member of superfamily of inotropic receptors
- PERM syndrome - progressive encephalomyelitis, rigidity and myoclonus
- cognitive and brainstem  disturbance,  seizures
- lung cancer, thymoma
- typically non-paraneoplastic syndrome

# Glycine receptor




*http://www.brown.edu*

# Anti-VGKC antibodies and PNS

- voltage gated potassium channels complexes:
- LGI1 = leucine-rich glioma inactivated 1 (70% of VGKC)
- CASPR 2 = conctactin associated protein 2 (20% of VGKC)
- Contactin 2  (10% of VGKC)
- Cell based assay for detection of LGI1, CASPR 2, Contactin 2
- Radioimmunoassay for VGKC complex antibodies

# Anti-VGKC antibodies reacting with hippocampal tissue (A) and superficial (membrane) structures of neuron (B)

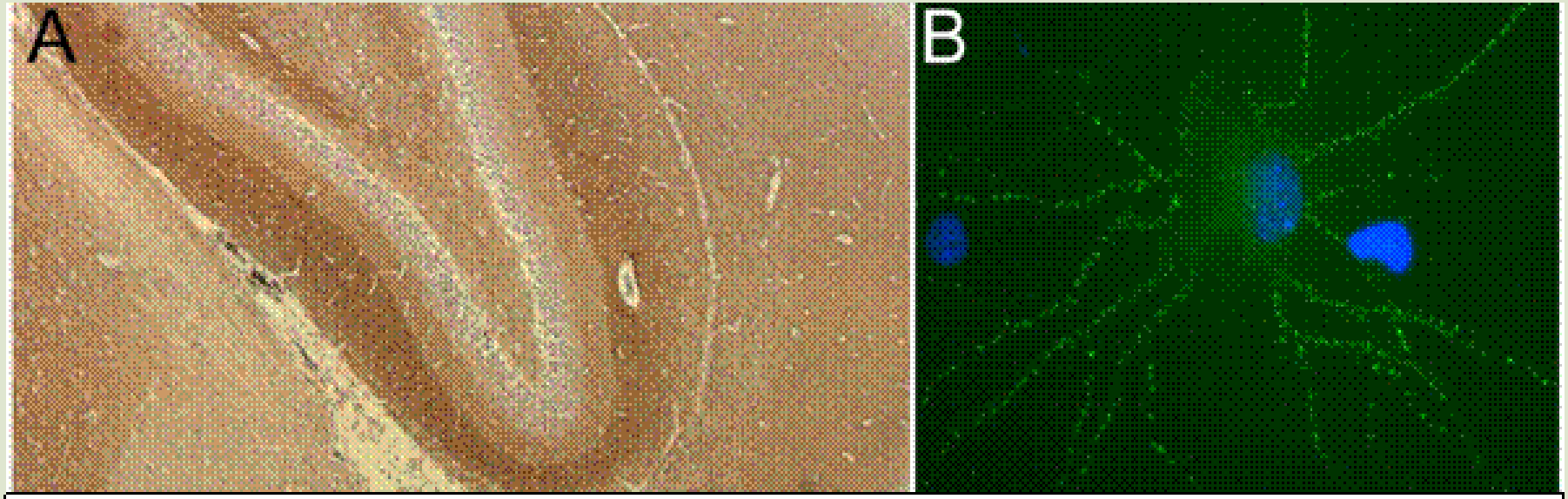
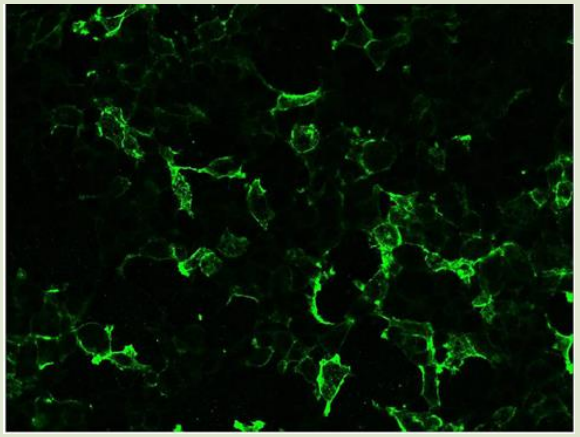



**Figure 2**: Antibodies to voltage-gated potassium channels (VGKC).
The picture on the left shows the VGKC antibodies reacting with brain tissue (hippocampus). The reactivity is shown as diffuse brown staining.
The picture on the right shows the VGKC antibodies reacting with the cell surface of a live neuron. The reactivity is shown as a dot like labeling of the "tree-like" processes of the neurons.

# Antibodies against LGI1 and PNS

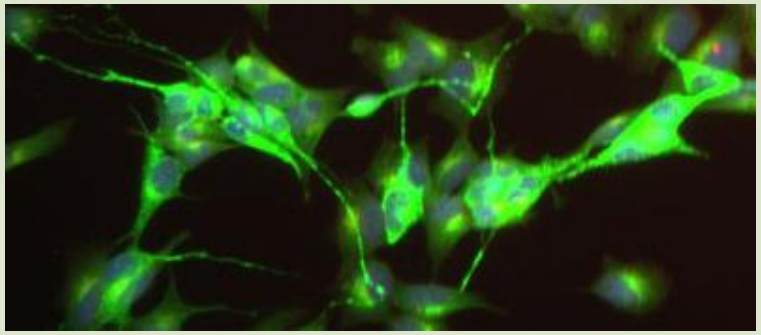
- antibodies against LGI1 leucine rich glioma inactivated 1
- clinical manifestation:
  limbic encephalitis, amnesia, epileptic seizures, psychiatric manifestations, faciobrachial dystonic seizures, myoclonus, dysautonomia
- **paraneoplastic origin**: thymoma, thyroid gland cancer, SCLC ovarian teratoma, kidney cell carcinoma
  paraneoplastic origin **rare 0-10 %**

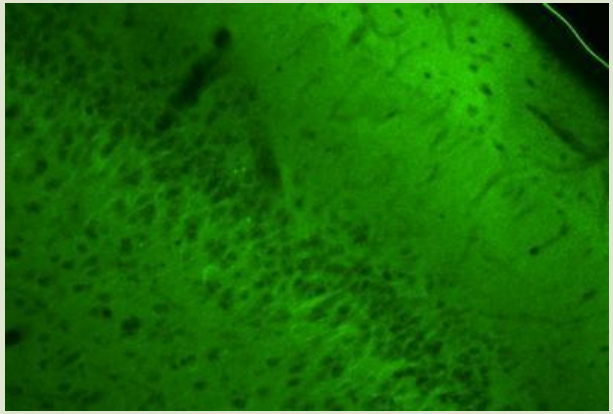


*http://en-journal.org*

# Antibodies against CASPR2 and PNS

- CASPR2 - contactin- associated protein 2
- clinical manifestation: limbic encephalitis, Morvan syndrome, neuromyotonia, confusion, memory disorders, dysautonomia and neuronal hyperexcitability
- paraneoplastic origin  0-35 %
- associated tumours: thymoma, endometrial cancer





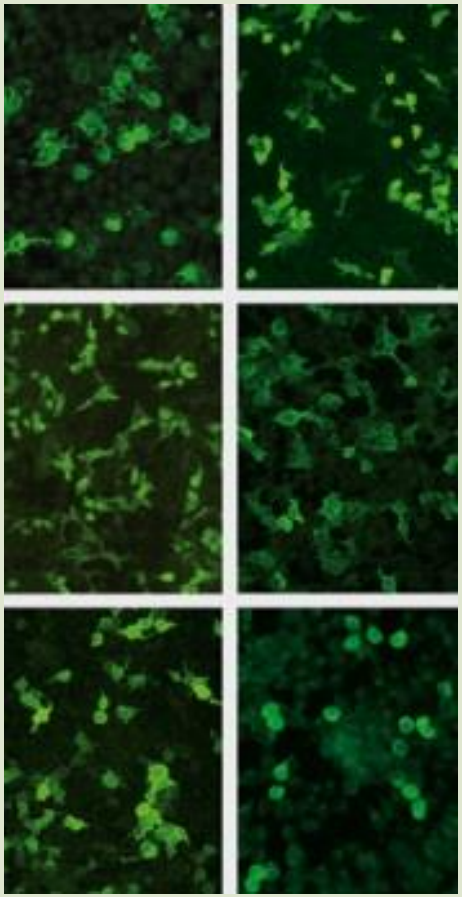
Transfected cells and tissue substrate

*www.abcam.com*

# IIFT: Autoimmune Encephalitis Mosaic 1

NMDAR

CASPR2



AMPAR1

LGI1

AMPAR2

GABA(B)R

EUROIMMUN

# Limbic encephalitis

- classified as „**new classical paraneoplastic syndrome**“
- clinical pattern: epileptic seizures, short - term memory deficit, behavioral and psychiatric disturbances
- minor involvement of other areas of nervous system
- associated with onconeural antibodies: Hu, Ma2, CV2/CRMP5, Ri, amphiphysin
- associated with neuronal cell surface antibodies: NMDAR, LGI1, CASPR2, GABA(B)R, AMPAR, mGluR5, GlyR
- associated tumours: lung cancer, SCLC, breast and ovarian cancer, testicular cancer, lymphoma, thymomas

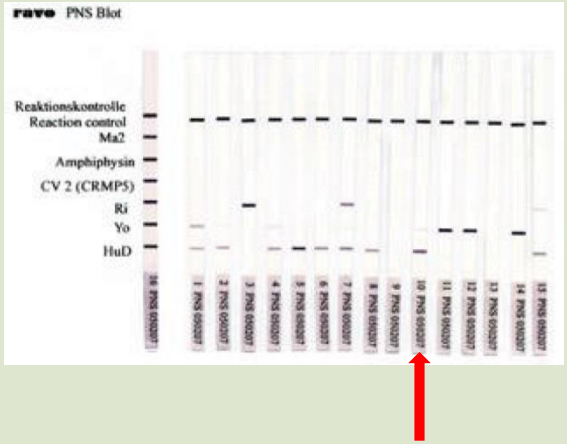
# Limbic encephalitis

- Hodgkin lymphoma and limbic encephalitis (Ophelia syndrome)
- treatment outcome more favorable with synaptic and cell-surface antibodies
- treatment outcome worse  in syndromes with onconeural antibodies

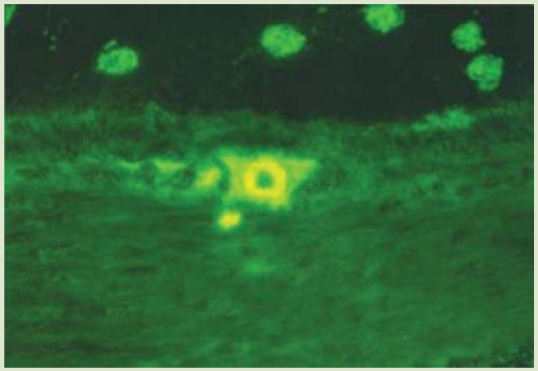
# Case Report

- The patient (male) presented at age 48 with diplopia, nystagmus, dysphagia,nausea and vertigo of subacute course in May 1998. Cerebellar symptoms and mild paresis of the left arm developed some weeks later reaching the plateau phase. Anti-Hu antibodies were repeatedly **positive** by immunoblot and indirect immunofluorescence
- Repeated MR scan showed mild atrophia of vermis cerebellum and repeated PET (positron emission tomography) did not revealed any tumour for 22 years , now
- The patient´s mobility is very limited and most of time patient is wheelchairbound
- Antibody positive (anti-Hu) patient with brainstem encephalitis/cerebellar syndrome of possible paraneoplastic origin **keeps alive the hypothesis that the tumour could be discovered later beyond the 5 years arbitrary period**
- Alternatively the tumour was removed by immune response. The persistent neurological deficit is probably a scar caused by an immune system attack during the oncogenesis

# Case Report




Immunoblot anti-Hu positive patient is on the position No.10



Indirect immunofluorescence of anti-Hu antibodies in plexus myentericus of mouse tissue

# Treatment of paraneoplastic neurological syndromes

Tumour therapy

- elimination of tumour tissue is beneficial i.e. recovery or stabilization
- longer survival (PCD)
- NMDAR encephalitis (teratoma) lesser risk of relapse
- treatment according to the current oncological guidelines
- no specific guidelines for PNS
- tumour therapy initiate as soon as possible

# Treatment of paraneoplastic neurological syndromes

Immunotherapy

- syndromes with onconeural antibodies - low level evidence for efficacy
- no clear consensus about the type of immunosupression:

✓1.line: steroids, plasmapheresis, IVIG, immunoadsorption

✓2.line: cyclophosphamide, azathioprine, methotrexate,cyclosporin A, tacrolimus, mycophenolate mofetile

- NMDAR encephalitis (LGI1, CASPR2,GABA(b),AMPAR)

✓1.line: steroids, IVIG and plasmapheresis

✓2.line: cyclophosphamide, rituximab or both