



# Development of Personalized Therapeutics Using Neo7logix<sup>®</sup> Precision Profiling for Progressive CNS Inflammation And Autoimmune Disease

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## Abstract

In this study, we aimed to develop the personalized therapy using Neo7logix precision profiling for progressive CNS inflammation and autoimmune disease. The brief data has been shown in this publication.

**Key words:** Personalized Therapeutics, Neo7logix<sup>®</sup>, CNS Inflammation Autoimmune Disease

## Patient medical history

Patient is a > 50 year old female with CNS Syring, neuronal inflammation and autoimmune autoantibody reactivity. She has a history of progressive intermittent seizures, fluid leakage from ears, eyes, nose and throat and progressive global fatigue and weakness.

## Suppressing autoimmunity by reverse vaccination

Neo7Logix Precision-Based Immuno-Molecular Augmentation (PBIMA) approach can facilitate naïve T cells either to induce deletion of naïve T cells specific for the peptides composing the vaccine or induce differentiation of T cells with regulatory properties. These regulatory T-cells have the potential to inhibit pathogenic inflammatory (Th1) memory T cells and exert linked suppression by

blocking the differentiation of naïve T cells that recognize self-antigens released because of tissue damage via epitope spreading. PBIMA can also directly at the level of memory T cells promote energy and cause clone deletion. Targeted immunosuppression is used to deactivate immune system attacking patient organs in case of autoimmune disease. This deactivation must be aimed against possible protein targets for auto-antibodies or memory T-cells developed in patients with autoimmune disorders. Autoantibody targets can be proteins secreted by organs under attack or plasma membrane proteins in affected tissue cells. Autoimmunity can develop due to the appearance of cryptic epitopes during tissue damage. Such cryptic epitopes are hidden from T-reg education in thymus and therefore have the ability to activate immune response when they become exposed during tissue damage. Search for potential auto-antibody targets begins with analysis of patient genotype measured by WES to find proteins encoded by homozygous alleles. List of homozygous proteins is then compared with the list of proteins linked in scientific literature to autoimmune diseases related to patient condition. Proteins with patient allele that was linked to patient autoimmune condition in scientific literature are ranked higher.

To induce targeted immune-suppression, peptides are calculated from self-antigen sequences and then administered into patient in the presence of known physiological immune-suppressors such as

## Significance | Cancer Immunotherapy data

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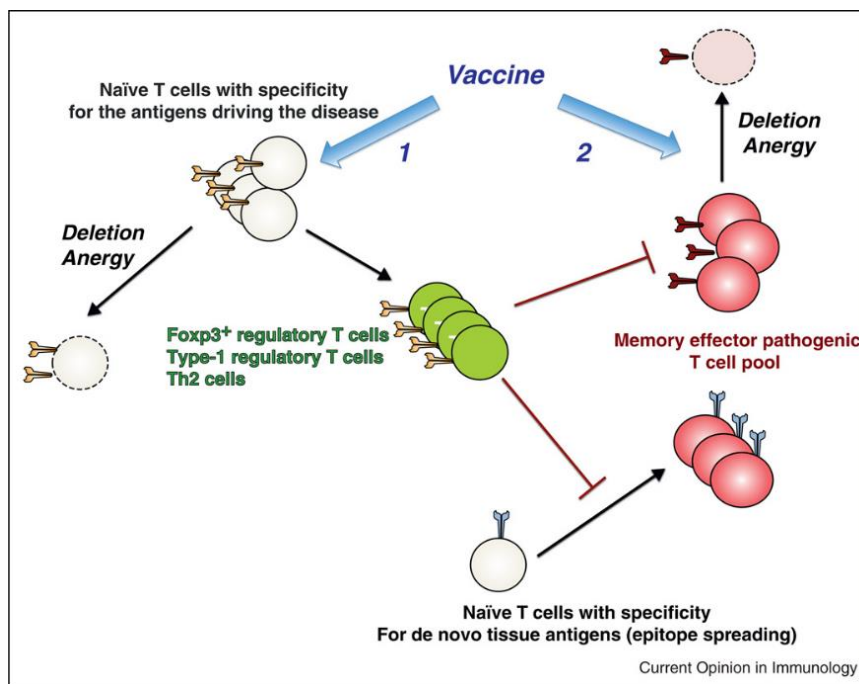


Figure 1: Suppressing autoimmunity by reverse vaccination

cytokine IL10 or CD25<sup>+</sup> regulatory T-lymphocytes isolated from patient blood and proliferated *in vitro* prior to vaccinations. This ensures production of soluble MHC molecules bound to peptides from vaccine [8]. Such soluble MHC molecules down-regulate memory T-cells and B-cells activated in patients with autoimmune condition directly or through intramolecular epitope spreading to cryptic determinants.

Finding potential autoantigens in patient

We focused on two pathological processes in the patient:

- 1) Spontaneous cerebrospinal fluid (CSF) leaks
- 2) Demyelination and breakdown of blood-brain barrier symptoms

Demyelination symptoms were considered secondary to CSF leaks and caused by CSF material inducing autoimmune reaction in the patient. CSF leaks can be due to recessive genetic predisposition for weak dura mater. We excluded intracranial hypertension as possible cause of CSF leaks because of patient history. Structural dura mater weakness may be further exacerbated by developed later in life autoimmune reactivity towards structural components of dural mater due to leaking into CSF.

Identification of genetic alleles predisposing patient to autoimmune disease

List of dbSNP rs identifiers containing patient homozygous alleles from whole genome sequencing (WES) was imported into Pathway Studio. Figure 2 shows homozygous genetic variants (GVs) linked to autoimmune disease in the literature and identified in Pathway Studio knowledgebase.

Finding proteins linked to demyelinating disorders that predispose patient to autoimmune disease and secreted into CSF

Proteins containing alleles predisposing patient to autoimmune disease were checked for the links to demyelinating disorders. Three genes IL6R, IL6ST, TNFRSF1B were found to have alleles predisposing patient to autoimmune disorder, involved in demyelination, and expressed on the surface of astrocytes. Astrocytes are cells responsible for building myelin layer around neurons which structural integrity is necessary for healthy blood-brain barrier. In demyelinating and psychiatric disorders astrocytes are under attack of patient's immune system.

Finding structural proteins of dura mater

To identify genes that may predispose patient to structural weakness in dura mater we found "dura mater" entity in Pathway Studio knowledgebase and then found 143 proteins linked to it with CellExpression relation type. All proteins were inspected to select extracellular matrix (ECM) proteins contributing to dura mater structural strength. Figure 2 shows the Extracellular matrix proteins expressed in dura mater.

To find more structural proteins from dura mater that may contribute to CFS leak we searched for diseases predisposing patients to CSF leaks. For this, we found "spontaneous cerebrospinal fluid leak" disease entity in Pathway Studio database and then found all diseases linked to it in Pathway Studio knowledge graph. Manual inspection of all 17 diseases revealed that CSF leaks can be caused by intracranial hypertension. CSF leaks can be also associated with three connective tissue disorders: Ehlers-Danlos syndrome, cervical spondylosis, and

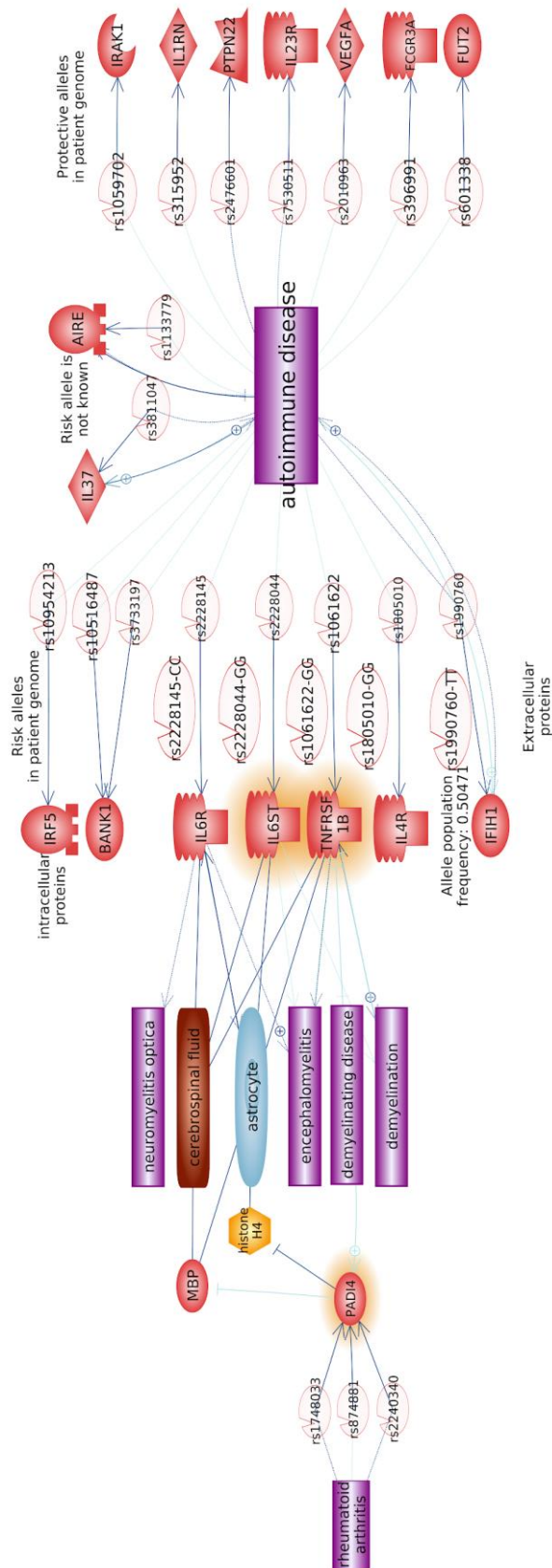


Figure 2. Genes with genotypes predisposing patient to autoimmune disease and their links to demyelinating disorders. Proteins found in patient urine are shown by orange highlight

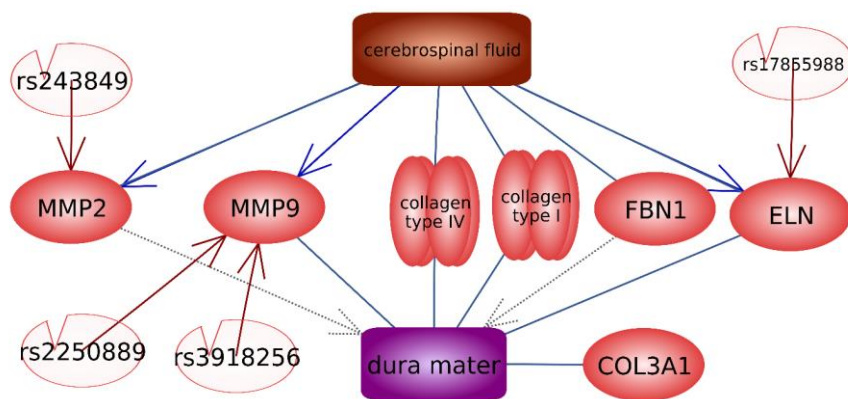


Figure 3. Extracellular matrix proteins expressed in dura mater. (GV homozygous in patient’s genome are linked to dura mater structural proteins.)

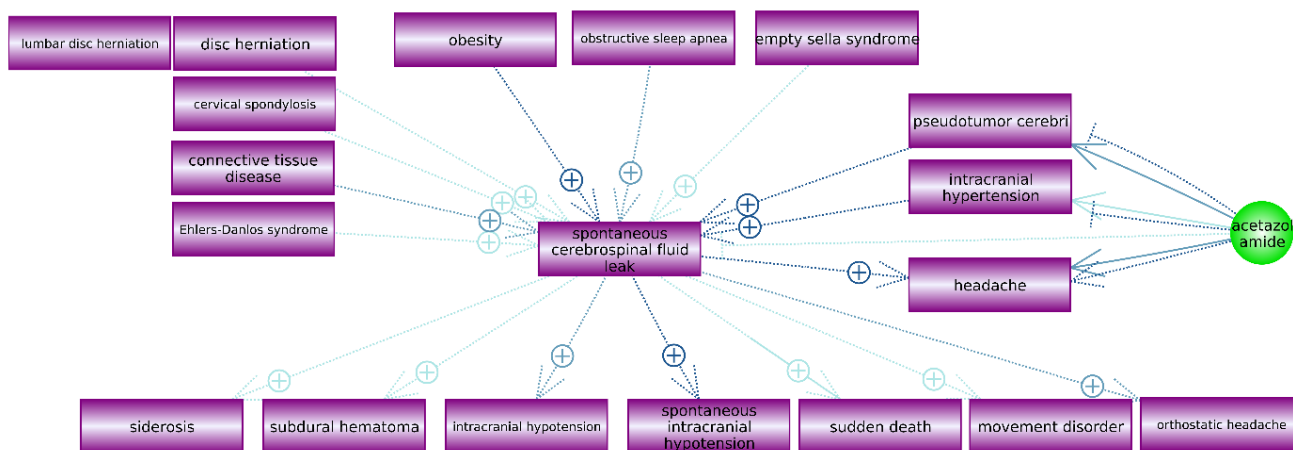


Figure 4. Diseases linked to spontaneous CFS leaks in Pathway Studio Knowledge-Base

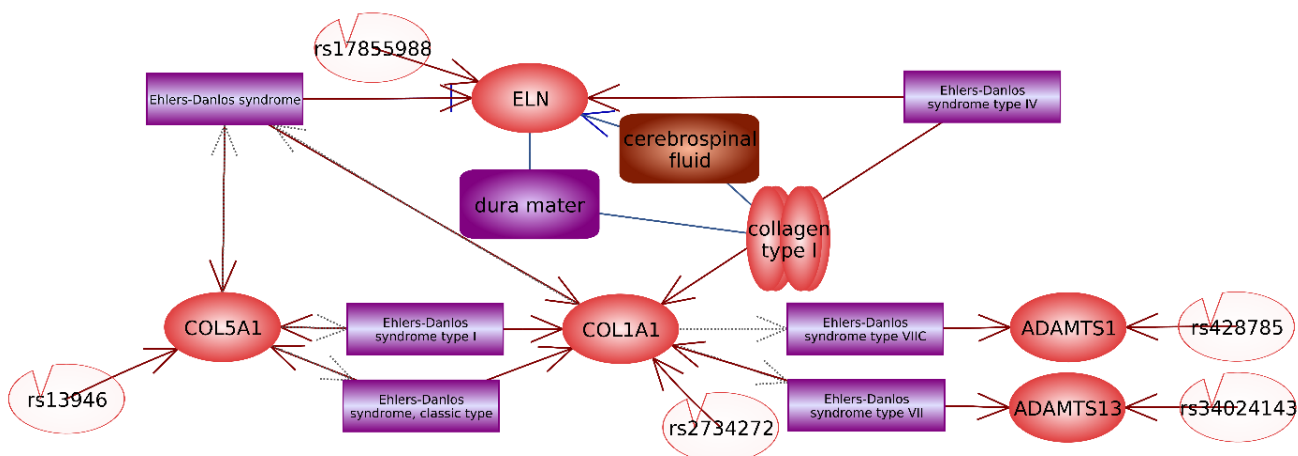


Figure 5. Proteins linked to Ehlers-Danlos syndrome that are homozygous in patient’s genome.

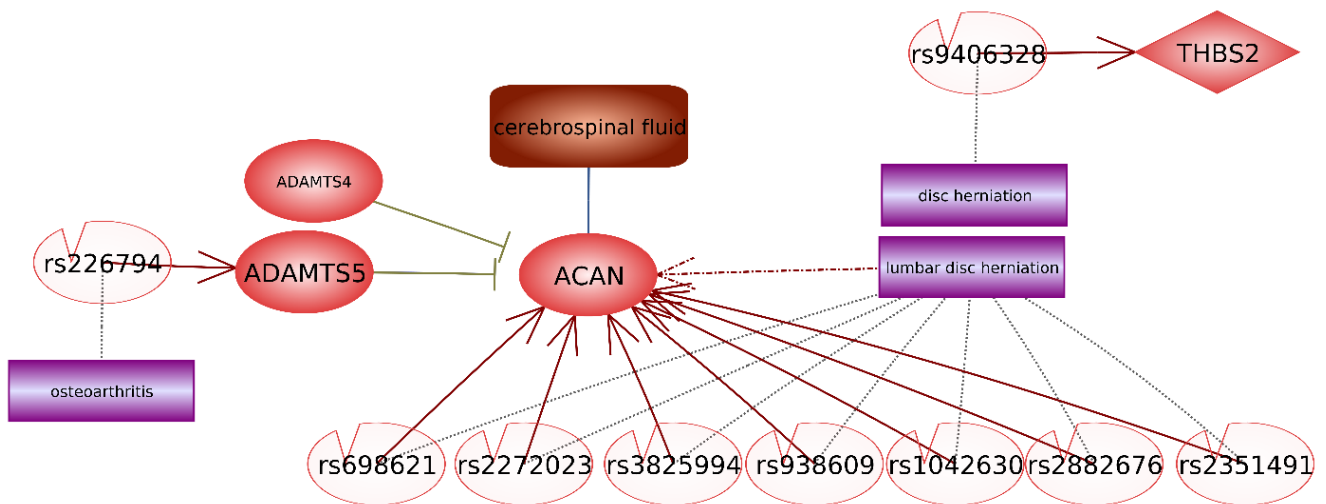


Figure 6. Proteins linked to disk herniation that are homozygous in patient’s genome.

Table 1. Homozygous proteins selected for epitope calculation

Protein	Localization	Diseases linked
IL6R	Plasma membrane, CSF, astrocytes	Demyelination, autoimmunity
IL6ST	Plasma membrane, CSF, astrocytes	Demyelination, autoimmunity
TNFRSF1B	Plasma membrane, CSF, astrocytes	Demyelination, autoimmunity
IL4R	Plasma membrane, soluble receptor	autoimmunity
IFIH1	Plasma membrane, intracellular	autoimmunity
COL1A1	Dura mater, CSF	Autoimmunity, Ehlers-Danlos syndrome
COL3A1	Dura mater, CSF	Autoimmunity
COL4A1	Dura mater, CSF	Autoimmunity
COL5A1	Dura mater, CSF	Autoimmunity, Ehlers-Danlos syndrome
FBN1	Dura mater, CSF	Autoimmunity
ELN	Dura mater, CSF	Autoimmunity, Ehlers-Danlos syndrome
ACAN	Dura mater, CSF	Autoimmunity, disk herniation

Table 2. Epitopes calculated using IEDB software and used for reverse vaccination

Table 3. Drugs recommended to patient based on combined analysis of genome and disease etiology.

Protein target	Drug	Symptom
MMP2		
MMP9		
ADAMTS1		
ADAMTS4		
ADAMTS5		
ADAMTS13		

disc herniation. Figure 4 shows Diseases linked to spontaneous CFS leaks in Pathway Studio Knowledge-Base.

We then identified structural ECM proteins linked to three connective tissue genetic disorders related to CSF leaks. Figure 5 shows Proteins linked to Ehlers-Danlos syndrome that are homozygous in patient’s genome. Table 1 shows Epitope selection for reverse vaccine.

Epitope calculation

Extracellular region sequences for proteins in Table 1 were submitted to [IEDB on-line software](#) along with patient HLA types to predict epitopes.

Selection of protein using urine proteomics.

Data not shown

Reverse vaccination protocol.

Data not shown

Drug therapy recommendations.

Data shown in table 1

Author Contribution

Acknowledgment

Competing financial interests

The author(s) declare no competing financial interests.

References

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