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# Bioinformatics as a Tool to Identify Infectious Disease Pathogen Peptide Sequences as Targets for Antibody Engineering

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Additional information is available at the end of the chapter

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#### Abstract

Bioinformatics is an interdisciplinary field of information technology for understanding biological data from genome to protein. It includes a combination of fields of science, computer science, statistics, mathematics, and engineering to analyze, interpret and derive biological data. This chapter describes how to use Bioinformatics to identify pathogen virulence factor peptide sequence similarities in human nerve tissue proteins and for evaluation as antibody engineering target peptides.

Keywords: bioinformatics, infectious diseases, peptide, recombinant antibody

### 1. Introduction

Bioinformatics is the application of techniques derived from disciplines such as applied mathematics, computer science, and statistics to analyze and interpret biological data. In this chapter, you will learn how to use bioinformatic techniques to identify pathogen virulence factor (VF) peptide sequence similarities to human nerve tissue proteins and then how to identify target peptides that could form the basis for engineering recombinant antibodies. Also, wet experiments could be conducted on the identified overlapping sequences to help us to single out target antibodies to be tested for tissue culture studies [1, 2]. The most ideal targeted peptide sequences for antibody engineering are those physiologically relevant, easy to access, and comprise amino acid sequence regions which have high specificity in pathogenic steps and reduced amino acid string length.



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### 1.1. Bioinformatics and its role in peptide discovery

The accessibility to the extensive genomic and proteomic databases and the availability of tools to compare and evaluate the information have given rise to a new interdisciplinary field that combines biology and computer science [3]. Bioinformatics conceptualizes physical and chemical biology in terms of macromolecules and then applies "informatics" techniques (derived from disciplines such as applied mathematics, computer science, and statistics) to assimilate and organize the information associated with these molecules, on a large scale [4]. Bioinformatics is an exciting and exploratory method for peptide discovery in antibody engineering and development of antimicrobial therapies and vaccination strategies [5].

There is significantly growing evidence that a number of neurodegenerative diseases are a result of the association of host cell proteins with viral and bacterial infectious agents [6]. When pathogenic micro organisms such as bacteria, viruses, parasites, or fungi cause an infectious disease, there are many molecular interactions between the host-pathogen proteins and host peptides [7] through all the stages of the disease whether incubation, prodromal illness, decline, and convalescence. There is much experimental evidence identifying the virulence factors (VF) of pathogen and host components such as receptors and tissue-specific proteins [8, 9]. Though the pathogenic pathway of the infectious agent in various host tissues is unknown, many of these processes are suspected to be attributable to the yet undiscovered role of molecular mimics identified in pathogenic microorganisms and its corresponding host tissue proteins. The sequence and structural similarities between the pathogenic VF protein and nerve peptides could impact either directly or indirectly the pathogenesis of the infectious disease [10–12]. It could contribute to molecular mimicry, steric hindrance, receptor binding, cell signaling, and autoantibody production events (involved in neuro degeneration) in the host.

Leprosy patients with peripheral nerve damage develop autoimmunity to myelin P0 (nerve protein). The above conclusion was drawn by gathering known scientific evidence that are as follows: (1) labeling and binding studies found that *Mycobacterium leprae* (bacterium causing leprosy) binds to myelin P0 [13]; (2) clinical studies confirmed the production of autoantibodies as a response of the bacterium to interact with myelin P0 [14, 15]; and (3) bioinformatics searches identified sequences and structural similarities between *M. leprae* and the immunoglobulin regions of myelin P0 [16].

Identification of molecular mimics in pathogen-host peptide sequences is one approach to identify target peptides for antibody engineering. There are about 180 extensive biological databases to retrieve information on sequence and functional aspects of biological molecules. The updated list is available in Nucleic Acids Research [17].

### 1.2. The use of bioinformatics in identifying sequence similarities

This section teaches you how to conduct a search for proteins present in a target host, how to obtain its amino acid sequence/s from the existing databases, how to compare the sequence/s of the host protein to that of the pathogen protein, and finally how to interpret the results based on existing evidential data. In our case study, we identify the virulence factor peptide

sequence similarities of a few selected infectious agents with human nerve tissue proteins for selecting peptides to engineer antipeptide antibodies which recognizes corresponding host/ viral proteins.

#### 1.2.1. Selection of nerve proteins

63 proteins were extracted from the Human Protein Atlas Database that were enriched and enhanced in the nervous tissue as observed by immunehistochemistry (**Figure 1**).

To conduct a search for human proteins in the nervous tissue, access the website (www.proteinatlas.org), enter the tissue of study (e.g. nervous tissue) into the search box provided and click on search.

Manual protein selection was carried out based on their tissue expression (enriched and enhanced) and also on immunohistochemistry evidence (Figure 2).

The list of selected proteins are as follows: agrin (AGRN\_HUMAN, O00468), calbindin (CALB1\_HUMAN, P05937), n-chimaerin (CHIN\_HUMAN, P15882), secretogranin-2 (SCG2\_HUMAN, P13521), neuromodulin (NEUM\_HUMAN, P17677), kinesin (KIFC1\_HUMAN, Q9BW19), tau (TAU\_HUMAN, P10636), 2',3'-cyclic-nucleotide 3'-phosphodiesterase (CN37\_HUMAN, P09543), myelin-associated glycoprotein (MAG\_HUMAN, P20916), myelin P0 (MYP0\_HUMAN, P25189), myelin P2 (MYP2\_HUMAN, P02689), oligodendrocyte-myelin

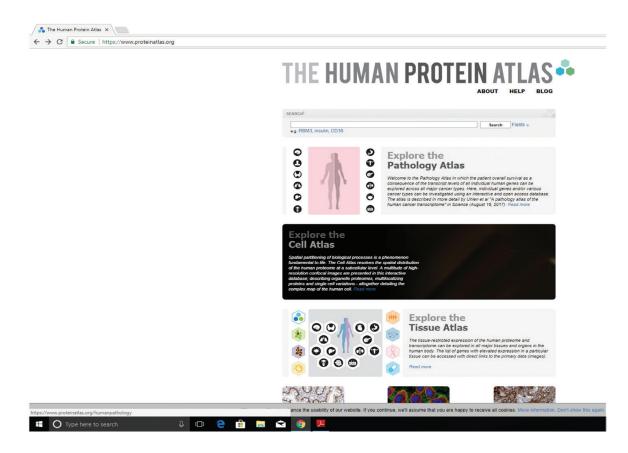


Figure 1. Conducting a search on the Human Protein Atlas Database.

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G	Gene	Gene description	x Protein class x	Tissue Cell	Pathology	Subcellular location x	RNA tissue category x
c	ONTER	Ciliary neurotrophic factor receptor	Plasma proteins Predicted membrane proteins Predicted secreted proteins			Golgi apparatus	Tissue enhanced
N	NTRK2	Neurotrophic tyrosine klnase, receptor, type 2	Cancer-related genes Disease related genes Enzymes Plasma proteins Potential drug targets Predicted membrane proteins			Cytosol	Tissue enhanced
ĸ	L6ST	Interleukin 6 signal transducer	Cancer-related genes Candidate cardiovascular disease gene CD markers Plasma proteins Predicted membrane proteins Predicted secreted proteins			Golgi apparatus Plasma membrane	Expressed in all
c	CLCF1	Cardiotrophin-like cytokine factor 1	Disease related genes Predicted secreted proteins			Nuclear bodies Vesicles	Tissue enhanced
c	ONTE	Ciliary neurotrophic factor	Cancer-related genes Plasma proteins Predicted intracellular proteins		1 Car	Vesicles	Tissue enhanced
R	RAPGEF2	Rap guanine nucleotide exchange factor (GEF) 2	Predicted intracellular proteins	RNA		Nucleoplasm Centrosome	Expressed in all
L	lifR	Leukemia inhibitory factor receptor alpha	Cancer-related genes CD markers Disease related genes Plasma proteins Predicted membrane proteins Predicted secreted proteins			Nuclear speckles Golgi apparatus	Mixed
B	BDNF	Bran-derived neurotrophic factor	Cancer-related genes Disease related genes Plasma proteins Predicted intracellular proteins Predicted membrane proteins Predicted serviced proteins	*		Nuclear speckles Mitochondria	Tissue enhanced
			Cancer-related genes FDA approved drug targets		*	Nuclearlasm	

Figure 2. Conducting an advanced search on the Human Protein Atlas Database.

glycoprotein (OMGP\_HUMAN, P23515), brain-derived neurotrophic factor (BDNF\_HUMAN, P23560), ciliary neurotrophic factor (CNTF\_HUMAN, P26441), neurotrophin-3 (NTF3\_ HUMAN, P20783), beta-nerve growth factor (NGF\_HUMAN, P01138), nestin (NEST\_HUMAN, P48681), neurofilament heavy polypeptide (NFH\_HUMAN, P12036), neurogranin (NEUG\_ HUMAN, Q92686), voltage-dependent T-type calcium channel subunit alpha-1G (CAC1G\_HUMAN, O43497), hippocalcin (HPCL1\_HUMAN, P37235), neurocalcin-delta (NCALD\_HUMAN, P61601), recoverin (RECO\_HUMAN, P35243), bombesin receptor subtype-3 (BRS3\_HUMAN, P32247), kininogen-1/bradykinin (KNG1\_HUMAN, P01042), calcitonin (CALC\_HUMAN, P01258), cholecystokinin (CCKN\_HUMAN, P06307), galanin peptides (GALA\_HUMAN, P22466), pro-neuropeptide Y (NPY\_HUMAN, P01303), neurotensin/neuromedin N (NEUT\_HUMAN, P30990), protein S100-B (S100B\_HUMAN, P04271), synapsin-1 (SYN1\_HUMAN, P17600), probable tubulin polyglutamylase (TTLL1\_HUMAN, O95922), myelin basic protein (MBP\_HUMAN, P02686), protein phosphatase 1 regulatory subunit 1B (PPR1B\_HUMAN, Q9UD71), Arf-GAP with GTPase, ANK repeat and PH domain-containing protein 2 (AGAP2\_HUMAN, Q99490), cathepsin L2 (CATL2\_HUMAN, O60911), D(1A) dopamine receptor (DRD1\_HUMAN, P21728), BDNF/NT-3 growth factors receptor (NTRK2\_HUMAN, Q16620), melanoma-associated antigen E1 (MAGE1\_HUMAN, Q9HCI5), microtubule-associated protein 6 (MAP6\_HUMAN, Q96JE9), protocadherin alpha-12 (PCDAC\_HUMAN, Q9UN75), carboxypeptidase E (CBPE\_HUMAN, P16870), Down syndrome cell adhesion molecule (DSCAM\_HUMAN, O60469), dyslexia-associated protein KIAA0319 (K0319\_HUMAN, Q5VV43), uncharacterized protein KIAA1211-like (K121L\_HUMAN, Q6NV74), microtubule-associated protein 1B (MAP1B\_HUMAN, P46821), neuronal calcium sensor 1 (NCS1\_HUMAN, P62166), neurofilament light polypeptide (NFL\_HUMAN, P07196), receptor expression-enhancing protein 2 (REEP2\_HUMAN, Q9BRK0), secretogranin-3 (SCG3\_HUMAN, Q8WXD2), ubiquitin carboxyl-terminal hydrolase iso-zyme L1 (UCHL\_HUMAN, P09936), galactosylgalactosylxylosylprotein 3-beta-glucurono-syltransferase 1 (B3GA1\_HUMAN, Q9P2W7), beta-1,4 N-acetylgalactosaminyltransferase 1 (B4GN1\_HUMAN, Q00973), caprin-2 (CAPR2\_HUMAN, Q6IMN6), dopamine beta-hydroxylase (DOPO\_HUMAN, P09172), FAM81A (FA81A\_HUMAN, Q8TBF8), mitogen-activated protein kinase 10 (MK10\_HUMAN, P53779), N-terminal EF-hand calcium-binding protein 1 (NECA1\_HUMAN, Q8N987), neuroligin-3 (NLGN3\_HUMAN, Q9NZ94), protein kinase C and casein kinase substrate in neurons protein 1 (PACN1\_HUMAN, Q9NZ94), sodium channel protein type 7 subunit alpha (SCN7A\_HUMAN, Q01118), and clathrin coat assembly AP180 (AP180\_HUMAN, 060641). The biological accepts of the proteins have been derived from the information presented in UniProt database for each protein [18–20].

### 1.2.2. Retrieving FASTA formats

FASTA formats for each of the above proteins were retrieved from NCBI PubMed. The FASTA format is a text-based format obtained from the PubMed search and represents either nucleo-tide sequences or peptide sequences (**Figure 3**).

Upon accessing the website, select the database in which the search is to be conducted (e.g. Protein). Type the name of the protein and its species in brackets into the search text box provided (e.g. Agrin (*Homo sapiens*)) and click on the search button.

The protein with the highest number of amino acids is chosen. Click on the hyperlinked protein to access its gene bank. Upon reaching the gene bank of the selected protein, click on the hyperlinked *FASTA* (**Figures 4**, **5** and **6**).

Obtain the FASTA format by copying all the information (Starting from the > symbol).

### 1.2.3. Arranging the FASTA formats

All the FASTA formats of the human proteins are saved in a sequence on Microsoft Notepad (**Figure 7**).

### 1.2.4. Running the BLAST

Pathogen-protein mimics, nerve protein sequences were BLAST (Basic Local Alignment Search Tool; Version 2.7.1; e-value ≤0.01) [21] against a pathogen genome (**Figure 8**).

Access the BLAST website at https://blast.ncbi.nlm.nih.gov/Blast.cgi and click on Protein (Protein~Protein) BLAST. The FASTA formats of 63 nerve proteins were copied and pasted from the notepad into the text box provided. Enter the species of the organism against which the blast has to be performed/the sequence comparison has to be carried out specifying its Tax ID (**Figure 8**).

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Figure 3. Conducting a search on the PubMed database.

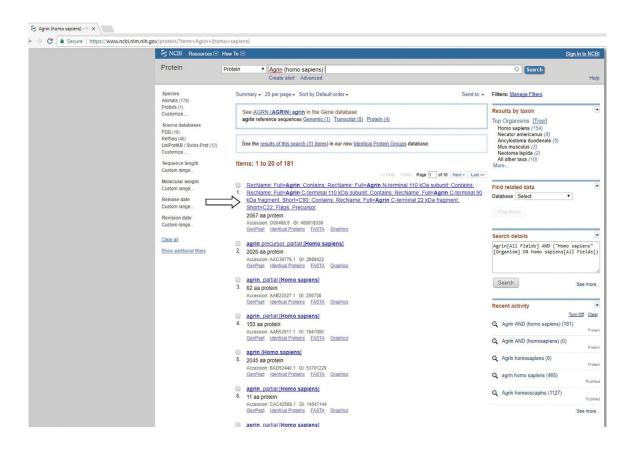


Figure 4. List of available sequenced protein information.

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Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;	Articles about the AGRN gene
Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo. PFFFFMF 1	C-terminal agrin fragment (CAF) reflects renal function in patients suffering from [Clin Lab. 2015]
REFERENCE 1 AUTHORS Kato,S., Ohtoko,K., Ohtake,H. and Kimura,T.	Serum levels of C-terminal agrin fragment (CAF)
TITLE Vector-capping: a simple method for preparing a high-quality full-length cDNA library	are associated with sarcope [Exp Gerontol. 2014]
JOURNAL DNA Res. 12 (1), 53-62 (2005)	Agrin mutations lead to a congenital myasthenic
PUBMED <u>16106752</u> REFERENCE 2 (residues 1 to 2045)	syndrome with distal muscle weaknr [Brain. 2014]
AUTHORS Kato,S.	See all
TITLE Direct Submission JOURNAL Submitted (27-SEP-2004) Contact:Seishi Kato National Rehabilitation	
Center for Persons with Disabilities, Research Institute,	Pathways for the AGRN gene
Department of Rehabilitation Engineering; 4-1 Namiki, Tokorozawa, Saitama 359-8555, Japan	ECM-receptor interaction
COMMENT For cDNA clones and library availability, please contact RIKEN	Defective B3GALT6 causes EDSP2 and
BioResource Center. E-mail: dnabank@brc.riken.jp	SEMDJL1
URL:http://dna.brc.riken.jp/	NCAM1 interactions
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Figure 5. Gene information of agrin.

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		AGRN gene (NG_016346.1).	) for the
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Figure 6. FASTA format of agrin.

 ■ FASTA seq of Human nerve proteins - Notepad

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 MAGRSHPCI,PRILLUWACV,DEGAGTCPERALERREEAMV/LIGTVEETLINDPY

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 PCPVIPARKIELMU,BUSINRTITURILEVECPCVEDROFTETPVDPTPADAREMULCEG

 PCREPARAGENERKERDERCONCOMPORTERIEVERSTOCSOBADRAGENDERGULISR

 PACARQEIN/FKKEDGPCDPCQGALPDPSRSCRVIIPRTRRPEMLLRPESCPARQADYCGDD

 GATYERIOCVMRRSGAARGLULQVISGOGUTYSSACELEATACTLGRUGZEARGENCONCOGC

 RFGALECALETATICKVPSECVLQVPSCSDGVTYSSACELEATACTLGRUGZEARGENCOGC

 RRFGALECALETATICRUPSECVLQVPSCSDGVTYSSACELEATACTLGRUGZEARGENCE

 TCGDAVCLAFGAVCSAGQUCYPRECHPPREPVCGSDGVTYSSACELEATACTLGQUTEAR

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 AGPCEQAEGASSCSSCREGODECQEQUTELCSCRPFVAPLPPIAPLAQTPVCCQQUITA

 AGPCEQAELAPSTHPTSASVITTPGLLLSQALPAPPGALLPAASSTANSQTTPP

 SSERTASVRRTIVWVLTVPPTAFASSVITTPGLLLSQALPAPPGALLPAASSTANSQTTPP

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 SSEGLEPTTASVRRTIVWVLTWPUTTPEASSVDVSLISQVAKTANAPTREPPTTPPP

 SSSEGLEQUESSAFCOPUNCHAGASCRESSLISSTSDDISCHELSGGS

#### Figure 7. FASTA formats of the 63 proteins in sequence.

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BLAST®	Home Recent Results
	Basic Local Alignment Search Tool BLAST finds regions of similarity between biological sequences. The program compares nucleotide or protein sequences to sequence databases and calculates the statistical significance. Learn more
	Web BLAST           Image: State of the stat
	BLAST Genomes Enter organism common name, scientific name, or tax id Search
	Human Mouse Rat Microbes
	Standalone and API BLAST Download BLAST Ger BLAST and executables Ger BLAST databases and executables Ger BLAST databases and executables Use BLAST from your application Use BLAST an instance at a cloud provider
	Specialized searches

Figure 8. BLAST home page.

The pathogen genome sequences that were compared with the human nerve proteins are as follows: HIV (Tax ID: 11,676), Polio (Tax ID: 138,950), Japanese Encephalitis (Tax ID:64,320), *M. leprae* (Tax ID: 1769), Human herpes virus 1 (Tax ID: 10,298), Human herpes virus 2 (Tax ID: 10,310), Rabies virus (Tax ID: 11,292), Zika virus (Tax ID: 64,320), Corona virus (Tax ID: 11,118), Varicella zoster virus (Tax ID: 10,335).

Select program PSI BLAST as the BLAST algorithm for a more position-sensitive search. It looks deeper into the database to best match to your query. Click on the BLAST button and wait for the results. Take screen shots of your result and also download the provided excel format (**Figure 9**).

The output of the BLAST identified the significant peptide sequence similarities between the human protein and its pathogenic counterpart **Figure 10**. These peptide sequence similarities are identified by amino acid positions, in which amino acids exist in single-letter codes. The BLAST provides us with the number of sequence similarities between the pathogenic genomic sequence and its host proteins. It also identifies viral counterpart peptides and the region of similarity on the host proteins.

Further interpretations of the results can be made by referring to the Uniprot database to obtain the biological and functional aspects of the host and the pathogen proteins (**Figures 11** and **12**).

### 1.2.5. Ascribing a biological role and application

The results show a number of sequence similarities existing between host proteins and various pathogen proteins. The maximum number of peptide sequence similarities were found between host protein caprin-2 which had 495 similarities with polio; neurogranin had 230

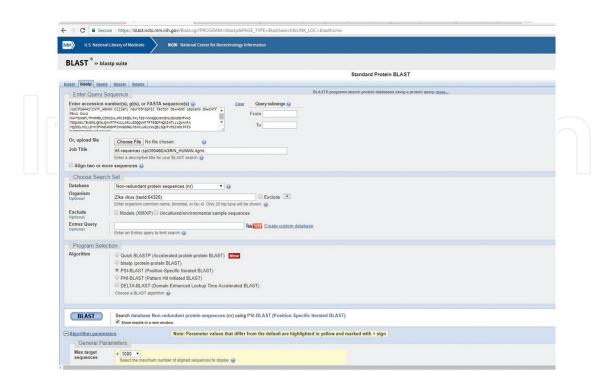


Figure 9. BLAST search.

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() Your search is limited to records that include: Zika virus (taxid:64320) ▷ Full Entrez Query		
Edit and Resubmit Save Search Strategies > Formatting options > Download		You The How to read this page Blast report description
Job title: sp 000468 AGRIN_HUMAN Agrin OS=Homo sapiens	PSI blast Iteration 1	
Results for: 11cl/Duery_278137 sp/000488/AGRIN_HUMAN Agrin OS=Homo sapiens GN=AGRN PE=1 SV=5(2087aa)	• 0	
RID 059CHV0D015 (Expires on 11-09 13:34 pm)		
Query ID IclQuery_278137 Description spl004668(AURU, HUMAN Aprin 05+Homo sapiens GN=AGRN PE=1 SV=5 Molecule type amin acid Query Length 2067	Database Name pdb Description 108 protein database Program EL/STP 2.7.1+ » <u>Otation</u>	
Other reports: » Search Summary (Texonomy resorts) [Distance tree of results] [Multiple alignment]  Graphic Summary	New Analyze your query with <u>SmartBLAST</u>	
	Distribution of the top 5 Blast Hits on 5 subject sequences 🕢 Mouse over to see the title, click to show alignments	
	Color key for alignment scores           <40	
Descriptions		
Run PSI-Blast iteration 2 with max 500 Go		

Figure 10. BLAST results of nerve proteins showing similarity to pathogen proteins.

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BLAST Align Retrieve/ID mapping	Destide caseb		Help Cor	
			Help Cor	pma
UniProtKB - O00	0468 (AGRIN	_HUMAN)	🖀 Basi	iske
Display	SLAST Align	🔂 Format 🚔 Add to basket 🖉 History	Help video Dther tutorials and v	1 vie
Entry	Protein Agrin			
Publications	Gene AGRM			
Feature viewer	Organism Homo			
Feature table				
All N	None Status 🐕 Re	viewed - Annotation score: ***** - Experimental evidence at protein level <sup>1</sup>		
Function	Function			
Names & Taxonomy	Function			-
Subcellular location		ulfate basal lamina glycoprotein that plays a central role in the formation and the maintenance of the neuromuscular junction (NMJ) and directs key events in postsynapt		
Pathology & Biotech		ex that induces the phosphorylation and activation of MUSK. The activation of MUSK in myotubes induces the formation of NMJ by regulating different processes including the postsynaptic membrane. Calcium ions are required for maximal AChR clustering. AGRN function in neurons is highly regulated by alternative splicing, glycan binding		
PTM / Processing	calcium ion homeost	asis in neurons, specifically by inducing an increase in cytoplasmic calcium ions. Functions differentially in the central nervous system (CIIS) by inhibiting the alphay-subh 5 synapses. This secreted isoform forms a bridge, after release from motor neurons, to basal lamina through binding laminin via the NtA domain.		
<ul> <li>Expression</li> <li>Interaction</li> </ul>	Isoform 2: transmen the action of Rho-far	tbrane form that is the predominate form in neurons of the brain, induces dendritic filopodia and synapse formation in mature hippocampal neurons in large part due to ti nily GTPases.	te attached glycosaminoglycan chains	6 8
Structure		and isoform 5: neuron-specific (z+) isoforms that contain C-terminal insertions of 8-19 AA are potent activators of AChR clustering. Isoform 5, agrin (z+8), containing th o the neuronal ACRN, the muscle-specific kinase MUSK and LRP4, a member of the LDL receptor family. The splicing		ple
Family & Domains		m 6: lack any 'z' insert, are muscle-specific and may be involved in endothelial cell differentiation.		
Sequences (7)		kDa subunit: is involved in regulation of neurite outgrowth probably due to the presence of the glycosaminogican (GAG) side chains of heparan and chondroitin sulfate a in modulation of prowth factor signaling (by similarity) . If similarity I 2 Diblications -	ttached to the Ser/Thr- and Gly/Ser-rid	ric
Similar proteins	Agrin C-terminal 22 filopodia.	Da fragment: this released fragment is important for agrin signaling and to exert a maximal dendritic filopodia-inducing effect. All 'z' splice variants (z+) of this fragment	also show an increase in the number	ro
Cross-references	Miscellaneous			
Entry information		agments may be used as a biomarker for sarcopenia, age-related progressive loss of skeletal muscle. 91 Publication -		
Miscellaneous	Sites	adiunture una ne anna as a anautarunt nei aarooberust ada reastro krodi anne on a gyelena unastro <u>e 1 Lenuranni e</u>		
Тор	Feature key	Position(s) Description Actions	Graphical view Let	ep
	Site <sup>1</sup>	1250 Alternative splice site to produce 'x' isoforms @ By similarity		-
	Site	1751 Alternative splice site to produce 'V isoforms' & By similarity		
	Site <sup>1</sup>	1862 Critical for cleavage by neurotrypsin @ By similarity	1	
	Site <sup>1</sup>	1888 Alternative splice site to produce 'z' isoforms 🛛 🛛 🕹 By similarity		
	Site <sup>1</sup>	1892 Highly important for the agrin receptor complex activity of the 'z(8)' insert # By similarity		

Figure 11. UniProtKB screenshot showing the biological and functional data of the human protein.

Bioinformatics as a Tool to Identify Infectious Disease Pathogen Peptide Sequences as Targets... 287 http://dx.doi.org/10.5772/intechopen.71011

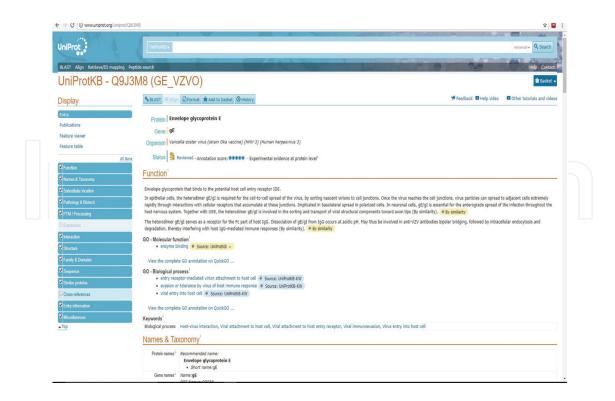


Figure 12. Uniprot screenshot showing the biological and functional data of the viral protein.

similarities with HHV2; secretogranin-3 had 221 similarities with Japanese encephalitis; agrin had 212 similarities with varicella; caprin-2 had 198 similarities with rabies virus; galanin peptides had 87 similarities with Zika virus; kinesin had 54 similarities with HIV; neurofilament heavy polypeptide had 46 similarities with corona virus; neurogranin had 39 similarities with HHV1; and 2',3'-cyclic-nucleotide 3'-phosphodiesterase had 21 similarities with *M. leprae*.

This method identifies significant virulent factors which have sequence similarities to human nerve tissue proteins. The nerve proteins that exhibited sequence similarities with four or more pathogenic virulent factors are displayed in **Table 1**. All 63 proteins are found to have sequence similarities with *M. leprae* proteins.

Agrin is a heparin sulphate basal lamina glycoprotein with a molecular mass of 217,232 Da. It plays a central role in the formation and maintenance of the neuromuscular junction. It is known to direct events in postsynaptic differentiation. Agrin also induces the phosphorylation and activation of muscle-specific kinase (MUSK), the clustering of Acetyl choline esterase receptor (AChR) in the postsynaptic membrane, regulates calcium ion homeostasis in neurons, and is involved in regulation of neuritis outgrowth [22, 23].

### 1.2.6. HHV3 peptide similarity to human protein agrin

Agrin UniProtKB-O00468 (AGRIN\_HUMAN) (AA position 1269–1326) (**Figure 13**) has a similarity to membrane glycoprotein C (Sequence ID: AEW88711.1 AA Position 43–122) of the varicella zoster virus UniProtKB-Q9J3M8 (GE\_VZVO) which by its similarity has the

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Antibody Engineering	

S. No	Query No.	Proteins	HIV	Polio	JE	HHV 1	HHV 2	M. leprae	Corona	Zika	Rabies	Vericella
1	O00468	Agrin	0	0	4	0	0	6	1	0	1	212
<u>)</u>	P17677	Neuromodulin	1	1	0	1	3	6	28	1	0	75
3	Q9BW19	Kinesin	54	1	0	0	0	9	0	0	0	0
Ł	P10636	Tau protein	0	1	0	0	14	5	9	0	0	19
5	P25189	Myelin protein P0	2	0	0	1	22	7	1	0	0	0
,	P23515	Oligodendrocyte-myelin glycoprotein	0	2	0	1	0	9	0	0	1	23
7	P48681	Nestin	0	0	3	2	0	8	2	30	0	22
3	P04271	Protein S100-B	0	26	0	2	11	7	0	0	0	12
)	P17600	Synapsin-1	0	1	7	11	2	13	0	0	5	0
0	P02686	Myelin basic protein	0	0	0	0	2	9	4	3	0	5
.1	Q16620	BDNF/NT-3 growth factors receptor	0	0	0	23	8	11	0	0	1	15
2	Q5VV43	Dyslexia-associated protein KIAA0319	0	0	0	37	21	5	5	_0	2	1
.3	P07196	Neurofilament light polypeptide	0	0	0	1	1	2	4	0	0	77
4	Q8WXD2	Secretogranin-3	3	5	221	0	10	8	0	0	9	0
.5	Q00973	Beta-1,4 N-acetylgalactosaminyltransferase 1	1	29	0	1	2	8	0	0	0	0

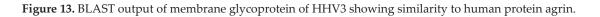
Table 1. Sequence similarities of human nerve tissue proteins with human virulent factors. Multiple alignments obtained in a single BLAST search could result in identities of the amino acids or substitutions of the amino acids in the same peptide region.

### Alignments

membrane glycoprotein C [Human alphaherpesvirus 3] Sequence ID: AEW88711.1 Length: 520 Number of Matches: 2 Range 1: 43 to 122

45.4 bit	s(106)	2e-05()	Composition-based stats.	29/80(36%)	37/80(46%)	6/80(7%)	
Feature	S:						
Query	1269		ASRLPSSAVTPRAPHPSHTSQPV				1326
Sbjct	43		ASR P AV P + V ASRKPDPAVAPTSAASRKPDPAV	A T + TR+P		R+P PA SRKPDPAA	102

Query 1327 Q----OPPKPCDSQPCFHGG 1342 OPP ++ C HGG Sbjct 103 NTQHSQPPFLYENIQCVHGG 122



potential to bind to the tissue cell receptor. Experimental evidence in epithelial cells shows that the hetero demonization of viral receptors could spread the virus by sorting nascent virion to nerve tissue cell junctions. The virus particles can spread to adjacent cells through interactions with cellular receptors at these cell junctions. The virus at cell junctions spreads extremely rapidly into the tissues [24, 25]. Sequence mimics of agrin to the varicella membrane glycoprotein could have an effect on either viral entry into host cell, evasion or on tolerance of host immune response to the virus and virion attachment to the host cell. These similarities in peptide regions warrant further exploration to understand pathogenesis and to identify target peptides for antibody engineering [26].

### 1.2.7. Poliovirus and rabies virus peptide similarities to human protein caprin-2

Caprin-2UniProtKB-Q6IMN6 (CAPR2\_HUMAN) is a protein of molecular mass 68,429 Da. The structure of caprin-2 was found to be similar to the polio and rabies viruses. Caprin-2 (AA position: 136–176) has a similarity to the polyprotein of polio virus UniProtKB–E0WCG5 (E0WCG5\_9ENTO) (polyprotein sequence ID: ACZ05040.1 AA position: 1994–2070) (**Figures 14** and **15**). Caprin-2 (AA position: 13–54) also has a similarity to the phosphoprotein of rabies virus UniProtKB-Q80JL8 (Q80JL8\_9RHAB) (phosphoprotein sequence ID: AAO60615.1 AA position 76–110) (**Figure 15**). Caprin-2 has a significant role in influencing phosphorylation of the Wnt-signaling pathways (PubMed:18,762,581) [27]. Caprin-2 also facilitates LRP6 phosphorylation by CDK14/CCNY during G2/M stage of the cell cycle, which may potentiate cells for transport or translation of mRNAs, modulate the expression of neuronal proteins involved in synaptic plasticity [28], while simultaneously influencing cell cycle signaling and regulation of viral transcription and replication [29, 30].

## Alignments

polyprotein [Human poliovirus 1] Sequence ID: ACZ05040.1 Length: 2209 Number of Matches: 1 Range 1: 1994 to 2070

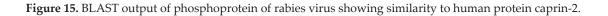
Score	Expect	Method		Identities	Positives	Gaps	Frame	
30.4 bits(6	7) 1.7()	Compositional m	natrix adjust.	22/77(29%)	32/77(41%)	19/77(24%)		$\cap$
Features:								
Query 13		KLKLED' KL LE D'			Y		176	
Sbjct 19		KLVLEKIGFGDRVD	Y D L HL YIDYLNHSHHLYI	+++ V+ KNKIYCVKGGM	IPSGCSGTSIF	+++NL NSMINNLII	2053	
Query 17	7 AKEL	QKTFSGLSLDLLK KT+ G+ LD LK	193					
Sbjct 20	54 RTLL	LKTYKGIDLDHLK	2070					

Figure 14. BLAST output of polyprotein of poliovirus showing similarity to human protein caprin-2.

1.2.8. Mycobacterium leprae peptide similarity to 2', 3'-cyclic-nucleotide 3'-phosphodiesterase

2', 3'-cyclic-nucleotide 3'-phosphodiesterase UniProtKB-P09543 (CN37\_HUMAN) is a protein of molecular mass 47,579 Da. 2', 3'-cyclic-nucleotide 3'-phosphodiesterase (sequence ID: WP\_010908292.1 AA position 191–261) has a similarity to thiamin pyrophosphokinase of *M. leprae* UniProtKB A0A197SEI9 (A0A197SEI9\_MYCLR) (AA position: 170–2166) (**Figure 16**) 2', 3'-cyclic-nucleotide 3'-phosphodiesterase is involved in RNA metabolism of the myelinating cell, CN37 (2', 3'-cyclic-nucleotide 3'-phosphodiesterase) is the one of the most abundant myelin protein in nervous system. The sequence similarities identified could impact cell signaling and also regulate energy metabolism [31].

phosphoprotein, partial [Rabies lyssavirus] Sequence ID: AAO60615.1 Length: 116 Number of Matches: 1 Range 1: 76 to 110									
Score	Expect	Method	Identities	Positives	Gaps	Frame			
29.3 bits(6	4) 1.4()	Compositional matrix adjust.	14/42(33%)	25/42(59%)	7/42(16%)				
Features:									
	EL TOVE	KSLREWSRLSREVIAWLCPSSPNFI		54					
Query 1			+NFP PP SS	24					



thiamin pyrophosphokinase [Mycobacterium leprae]

Sequence ID: WP	010908292.1	Length: 393	Number of Matches:	1
-----------------	-------------	-------------	--------------------	---

Score		Expect	Method		Identities	Positives	Gaps	Frame
28.5 bits	s(62)	0.70()	Composition	al matrix adjust.	24/75(32%)	33/75(44%)	17/75(22%)	6
Features	s:							
Query	170		KLKPGLEKDF	LPLYFGWFLTKKS	SETLRKAG		EELGNH	216
Sbjct	191			QPVLVGVSGG				246
Query	217	KAFKKE	LRQFVPGDE	231				
Sbjct	247	WLPAD	PG E	261				

**Figure 16.** BLAST output of thiamin pyrophosphate of *Mycobacterium leprae* showing similarity to human protein 2', 3'-cyclic-nucleotide 3'-phosphodiesterase.

#### 1.2.9. Zika virus peptide similarity to human protein galanin

Galanin peptide UniProtKB-P22466 (GALA\_HUMAN) is a protein of molecular mass 13,302 Da. Galanin (AA position 53–99 position) has a similarity to polyprotein envelope protein E of Zika virus UniProtKB-Q73880 (Q73880\_9HIV1) sequence ID: ARB07952.1 (AA position: 729–765) (**Figure 17**). Galanin is involved in the smooth muscle contraction of the gastrointestinal and genitourinary tract, regulation of growth hormone release, modulation of insulin release, and might also be involved in the control of adrenal secretion [32]. The envelope protein E of the Zika virus is responsible for binding to host cell surface receptors and mediating fusion between viral and cellular membranes. It is synthesized in the endoplasmic

	n, partial [Z					
	e ID: ARB0 729 to 765	7952.1 Length: 1939 Number of	Matches: 1			
Score	Expec	t Method	Identities	Positives	Gaps	Frame
24.3 bits	51) 2.2()	Compositional matrix adjust.	14/47(30%)	23/47(48%)	10/47(21%)	
Features						
Query	SFSD	NGLTSKRELRPEDDMKPGSFDRSIP		SFLHL 99 S H+		
	29 SFRA					

Figure 17. BLAST output of polyprotein of Zika virus showing similarity to human Galanin peptide.

reticulum with protein prM and forms a heterodimer. Galanin's similarity with the ZIKA polypeptide could subsequently affect neural regulation of muscle function and play a role in immune evasion pathogenesis and viral replication [33].

### 1.2.10. HIV 1 peptide similarity to human kinesin-like protein

Kinesin-like protein KIFC1 UniProtKB-Q9BW19 (KIFC1\_HUMAN) is a protein of molecular mass 73,748 Da. Kinesin-like protein (AA position: 411–470) has a similarity to HIV virus envelope glycoprotein UniProtKB-D6QPK9 (D6QPK9\_9HIV1) sequence ID:ADG63850.1 (AA position:270–387)(**Figure 18**). KIFC1 along with microtubules contributes to movement of endocytic vesicles. These similarities could affect viral attachment to the host cell, membrane fusion, and entry into the cell and the nucleus [34, 35].

### 1.2.11. Corona virus peptide similarity to human neurofilament heavy polypeptide

Neurofilament heavy polypeptide UniProtKB-P12036 (NFH\_HUMAN) is a protein of molecular mass 112,479 Da. Neurofilament heavy polypeptide (AA position: 819–872) has a similarity to ORF1a UniProtKB-A0A0F6SKM6 (A0A0F6SKM6\_9GAMC) of Corona virus sequence ID: AKF17723.1 (AA positions: 890 –1031) (**Figure 19**) neurofilament of the nerve tissue usually contain three intermediate filament proteins: L, M, and H (NFH-human) which is involved in the maintenance of neuronal caliber. NFH-H has an important function in axon maturation. These similarities could affect viral replication, protein processing, and could generate autoantibody production [36, 37].

#### 1.2.12. HHV 1 and HHV 2 peptide similarity to human protein neurogranin

Neurogranin UniProtKB-Q92686 (NEUG\_HUMAN) is a protein of molecular mass 7618 Da. The structure of neurogranin at identical regions has a similarity to envelope glycoprotein M of

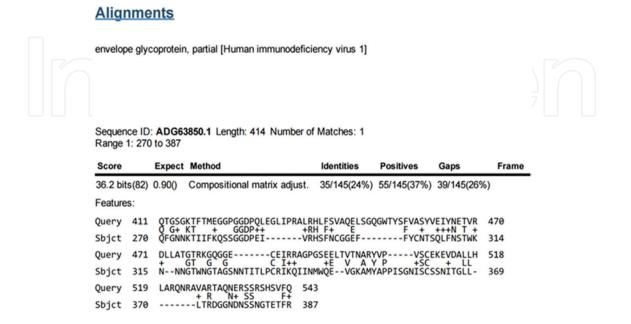


Figure 18. BLAST output of envelope glycoprotein of HIV 1 showing similarity to human kinesin-like protein.

### Alignments

Score	Exp	ect Met	hod	Identities	Positives	Gaps	Frame
79.3 bits(*	194) 2e-1	40 Con	nposition-based stat	s. 58/155(37%)	78/155(50%)	26/155(16%)	
Features:							
Query 8			SPVKEEEKPQEVKVKE	PPKKAEEE	KAPATPKTEEK		872
. ,	EP	K+E K	SPVKEEEKPQEVKVKE EE+KP+E V+ PQKVEEQKPKETPVET	P P+K EE+	K TP	CDSKKEEAPK E PK	872 939
Sbjct 8	890 ETP	KEETQK	EE+KP+E V+ PQKVEEQKPKETPVET EEKKEPAVEKPKES	P P+K EE+ PKEETQKPQKVEEQ KVEAKKEEAEDKKK	K TP KPKETPV VPTPEKEA	E PK ETPK -PAKVEVKED	
Sbjct 8 Query 8	890 ETP 873 KEA +E	K+E K KEETQK	EE+KP+E V+ PQKVEEQKPKETPVET	P P+K EE+ PKEETQKPQKVEEQ KVEAKKEEAEDKKK + +K E + K+	K TP KPKETPV VPTPEKEA P TP++E	PAKVEVKED P KV E+	939

Figure 19. BLAST output of ORF1 of corona virus showing similarity to human neurofilament heavy polypeptide.

HHV1 and envelope glycoprotein M of HHV2 at partially overlapping positions. Neurogranin (AA position: 38–63) has a similarity to the envelope glycoprotein M of HHV1(UniProtKB-A0A181ZHE7 (A0A181ZHE7\_HHV11) (sequence ID: SBO07578.1 AA position: 347–376) (**Figure 20**). Neurogranin (AA position: 38–64) also has a similarity to the envelope glycoprotein M of HHV2 (UniProtKB-A0A0Y0R357 (A0A0Y0R357\_HHV2)) (sequence ID: AMB66044.1 AA position 389–416) (**Figure 21**). Neurogranin functions as a signaling messenger, a substrate for protein kinase C and has affinity to calmodulin in the absence of calcium. These similarities

Alignments									
Envelope glycoprotein M [Herpes simplex virus (type 1 / strain 17)] Sequence ID: SB007578.1 Length: 455 Number of Matches: 1 Range 1: 347 to 376									
Score Expect Method Identities Positives Gaps Frame									
Score	Expect	Method	Identities	Positives	Gaps	Frame			
Score 27.7 bits(60)	Expect 0.11()	Method Composition-based stats.	Identities 13/30(43%)	Positives 16/30(53%)	Gaps 4/30(13%)	Frame	ı		
						Frame			

Figure 20. BLAST output of envelope glycoprotein of HHV 1 showing similarity to human protein neurogranin.

of HHV1 & 2 with neurogranin could have an interaction with viral transport into the host cell Golgi network and subsequently to the host nucleus [38].

#### 1.2.13. JE 2 peptide similarity to human protein secretogranin-3

Secretogranin-3 UniProtKB-Q8WXD2 (SCG3\_HUMAN) is a protein of molecular mass 53,005 Da. Secretogranin-3 (AA position: 139–190) has a similarity to the polyprotein of Japanese encephalitis virus (UniProtKB-G3LHD8 (G3LHD8\_9FLAV) (sequence ID: SBO07578.1 AA position: 2744 to (**Figure 22**). Secretogranin-3 is a member of the chromogranin/secretogranin

## Alignments

envelope glycoprotein M [Human alphaherpesvirus 2] Sequence ID: AMB66044.1 Length: 491 Number of Matches: 1 Range 1: 389 to 416

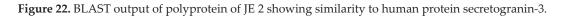
Score		Expect	Method	Identities	Positives	Gaps	Frame
29.3 bits	s(64)	0.024()	Composition-based stats.	13/28(46%)	18/28(64%)	1/28(3%)	
Features	S:						
Query	38	RGHMARKKIKSGERG-RKGPGPGGPGGA R H A ++++S RG R+G PG PG A		64			
Sbjct	389		RVRSSMRGSRRGGPPGDPGYA	416			

Figure 21. BLAST output of envelope glycoprotein of human alpha herpes virus 2 showing similarity to human protein neurogranin.

### Alignments

polyprotein [Japanese encephalitis virus] Sequence ID: AE072439.1 Length: 3432 Number of Matches: 1 Range 1: 2744 to 2833

Score	Exp	ect Meth	od	Identities	Positives	Gaps	Frame
29.3 bits(	64) 0.77	() Com	position-based stats.	21/90(23%)	45/90(50%)	9/90(10%)	
Features:							
Query 1			EDIVHKIAARIYEEND				190
Sbjct 2			GNVVHAVNMTSQVLLGRM			+ + H+ + SKGEVHSNQ	2803
Query 1	.91 DE	VAEVLOKL	ISKEANNYEEDPNKP-TSW + A + +DP P +W				
Sbjct 2	2804 EK	IKKRIQKL	KEEFATTWHKDPEHPYRT	VT 2833			



family of neuroendocrine secretory proteins comprising a number of significant cellular functions. In an experimental mouse model, autoimmunity with secretogranin was associated with encephalitis [39]. These similarities identified in the host-pathogen could affect neuro endocrine secretory protein release and autoimmunity.

### 2. Creating a schematic model

The sequence similarities in agrin, caprin-2,2',3'-cyclic-nucleotide 3'-phosphodiesterase, galanin peptide, kinesin-like protein, neurofilament heavy polypeptide, neurogranin and secreto-granin-3 with its corresponding pathogenic peptide/s could have a number of cellular-level implications which include alternations in receptor binding, signaling/synaptic transmission, metabolic alteration, inflammation, resulting in autoimmunity and consequently neuropathy (**Figure 23**) [11, 40].

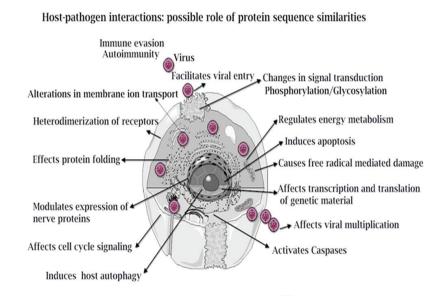


Figure 23. A model for the modes of host-pathogen interaction and possible intracellular regulation of metabolic activities.

### 3. Conclusion

In conclusion, it is important to conduct bioinformatic searches and design wet experiments with the objective of identifying a vast number of functionally significant peptides for further comparison and study. Bioinformatic search tools and various available databases are to be extensively explored to rapidly develop possible neuroprotective or pathogenic peptide sequences. These peptides can be further explored as targets to generate recombinant antibodies. This exercise can also be used to develop an efficacious and safe vaccine against pathogens that demonstrate no autoimmune cross-reactions. It can also contribute to design peptide/drug molecules to neutralize the effects of neurotoxins. Bioinformatics is the key to open the door of understanding medical and biological processes in the future.

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