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DELHI TECHNOLOGICAL UNIVERSITY

Shahbad Daulatpur,Main Bawana Road, Delhi-42

Proforma for Submission of M.Tech. Major Project

01. Name of the Student..... Tanvika Gupta

02. Enrolment No .2K22/B10/06.....

03. Year of Admission .....2022.....

04. Programme M.Tech., Branch..BIOINFORMATICS

05. Name of Department..Department of Biotechnology

06. Admission Category i.e. Full Time/ Full Time (Sponsored)/ Part Time:.....full-Time

07. Applied as Regular/ Ex-student.....Regular.....

08. Span Period Expired on .....

09. Extension of Span Period Granted or Not Granted (if applicable).....

10.Title of Thesis/Major Project.....SARS-CoV-2 associated uveitis and its mechanism.....

11. Name of Supervisor.....Dr. Asmita Das.....

12. Result Details (Enclose Copy of Mark sheets of all semesters) :

S. No.	Semester	Passing Year	Roll No.	Marks Obtained	Max. Marks	% of Marks	Details of Back Paper Cleared (if any)
01.	1st	2022	2K22/B10/06	8	10	80	
02	2nd	2023	2K22/B10/06	8.06	10	80.6	
03	3rd	2023	2K22/B10/06	7.67	10	76.7	
04	4th (P/T only)						
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(Department of Bio Technology)

Name : TANVIKA GUPTA Roll No. : 2K22/BIO/06

Month & Year of Examination : NOVEMBER , 2022 Semester : FIRST

Subject Code	Subject Title	Credits	Credits Secured	Grade
BIO501	INTRODUCTION TO BIOINFORMATICS	4	4	A+
BIO503	ADVANCED PROTEOMICS	4	4	A
BIO5407	OMICS IN MEDICINE	4	4	A
BIO5301	DATA WAREHOUSING AND DATA MINING	3	3	B
BIO5201	OPEN AREA SEMINAR I	2	2	A+
		17	17	

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Tanvika 31/05/24

Dated : Feb 14, 2023

Date of Declaration of Result : Jan 11, 2023

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(Department of Bio Technology)

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Roll No. : 2K22/BIO/06

Month & Year of Examination : MAY , 2023

Semester : SECOND

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BIO5402	ADVANCED GENETIC ENGINEERING	4	4	B+
BIO5308	IMMUNOINFORMATICS	3	3	A+
BIO5202	OPEN AREA SEMINAR-II	2	2	A+
		17	17	

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SGPA : 8.06

Tanvika
31/05/24

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Result Declaration Date : 29-12-2023

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			3.00	4.00	2.00	3.00			
1	2K22/BIO/01	AASTHA KAUSHIK	O	O	O	A	9.5	12	
2	2K22/BIO/02	MONICA JOSHI	A	O	A	A+	8.92	12	
3	2K22/BIO/03	PRATIK	B	A+	B+	A	7.67	12	
4	2K22/BIO/05	SUNNY CHAUDHARY	C	B+	B	A	6.58	12	
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I Tanvika Gupta hereby certify that the work which is being presented in the thesis entitled "SARS-CoV-2 associated uveitis and its mechanism" in partial fulfillment of the requirements for the award of the Degree of Master of Technology, submitted in the Department of Biotechnology , Delhi Technological University is an authentic record of my own work carried out during the period from January 2024 to May, 2024 under the supervision of Dr. Asmita Das.

The matter presented in the thesis has not been submitted by me for the award of any other degree of this or any other Institute.

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Date: 31/05/24

SARS-CoV-2 associated uveitis and its mechanism

Thesis Submitted
in Partial Fulfillment of the Requirements for the
Degree of

MASTER OF TECHNOLOGY
in
BIOINFORMATICS

by

Tanvika Gupta
(Roll No. 2K22/BIO/06)

Under the Supervision of
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May, 2024

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SARS-COV-2 VACCINE ASSOCIATED UVEITIS AND ITS MECHANISM

Tanvika Gupta

Delhi Technological University, Delhi, India

ABSTRACT

The worldwide COVID-19 pandemic brought about by SARS coronavirus 2 (SARSCoV-2) caught the world by storm, halting back all global operations, and spurred rapid vaccine generation and authorization. From the time of the initial outbreak of the pandemic, 336 vaccine contenders are produced, with 32 vaccines presently approved after rigorous screenings and trials, to be used worldwide. Some of them are BNT162b2 (by Pfizer Inc) and mRNA-1273 (by Moderna) that are mRNA vaccines, Ad26.COV2.S (by Janssen Pharmaceuticals) stimulates an immune response in recipients using a adenovirus type 26 vector, BBV152 COVAXIN (by Bharat Biotech) is a whole virion inactivated vaccine, while COVISHIELD (by Serum Institute of India) is a ChAdOx1-S recombinant vaccine. Given that all the COVID-19 vaccines have been authorized for use in the time of crisis, the Centres for Disease Control and Prevention (CDC) has extended the scope of its Vaccine Adverse Event Reporting System (VAERS) that serves as a means for prior detection of possible vaccine adverse events. Consequently, despite all the careful screening methods, unusual adverse reactions were identified following the administration of different covid vaccines, such as thrombotic thrombocytopenia, Guillain-Barré syndrome, myocarditis, allergy, and many more. One such serious adverse event was an ocular illness, uveitis (a potentially blinding illness that is frequently connected with autoimmune or autoinflammatory diseases). Mechanisms like molecular mimicry, immune complex deposition, immune response against vaccine adjuvant, hyperstimulation of immune system could be the reason behind Vaccine-associated uveitis (VAU). This research thesis focuses on incidence of COVID-19 vaccine associated uveitis and trying to reason its occurrence and finding its possible mechanism.

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CHAPTER 1
INTRODUCTION

1.1. Uveitis

Uveitis is a sight-threatening disease that has traditionally been associated with inflammation of the middle layer of the eye, the uvea, which consists of iris, ciliary body, and choroid. Uveal layer is filled with blood vessels that are responsible for nourishing the eye [1]. However, recent characterization of the disease indicates that any area of the eye may have inflammation. Symptoms include redness, irritation or itchiness in the eye, pain, increased light sensitivity, change in shape of pupil, hypopyon, blurred vision or even irreversible vision loss [2]. The primary anatomical site of the inflammation in the eye determines the further classification of uveitis as: anterior, posterior, intermediate, or panuveitis.

- Anterior uveitis
  Swelling or inflammation of the uvea towards the front part of the eye, the iris, is referred as anterior uveitis. It is the most common type and appears quite abruptly. Although the symptoms might continue for weeks, it is not observed to be very serious.
- Intermediate uveitis
  It is characterized by uveal swelling in the central portion of the eye, the ciliary body and vitreous humor. Symptoms may extend from a few weeks to several years, however, intermediate uveitis tends to improve and then regress after sometime.
- Posterior uveitis
  It affects the uvea towards the rear end of the eye, the retina and the choroid. Symptoms of posterior uveitis might appear gradually and persist for several years.
- Panuveitis
  Swelling in major portion of the uvea, from front to back involving more than one anatomical zone, is called panuveitis.

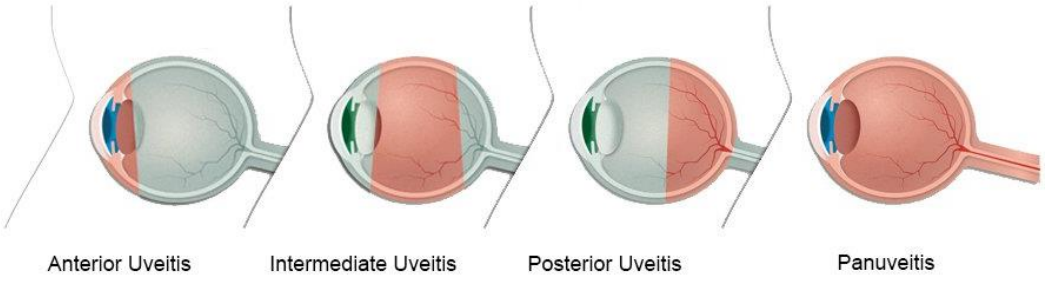


Figure 1. Types of uveitis

1.1.1. Etiology

Uveitis is quite a complex ophthalmic inflammatory illness and thus, there is no one definite cause for uveitis, there are multiple etiological elements involved. While most of the uveitis cases, about 50-70%, are idiopathic; most likely known causes include infections, systemic malfunction (like autoimmunity), injuries and/or medications/toxins [2].

- Infection- Caused by bacteria; like Mycobacterium tuberculosis (Tuberculosis), Treponema pallidum (Syphilis), Borrelia burgdorferi (Lyme disease), Leptospira species (Leptospirosis), virus; like HSV, CMV, HIV, fungus; like Candida species (Candidiasis), Aspergillus species (Aspergillosis), parasite; like Toxoplasma gondii (Toxoplasmosis) which is very common.
- Systemic processes- Caused by an underlying systemic condition leading to inflammation in the uvea, like autoimmune diseases such as Arthritis, Ankylosing Spondylitis, Behcet's Disease, VKH Syndrome, Systemic Lupus Erythematosus (SLE), Juvenile Idiopathic Arthritis (JIA), and many more.
- Injury- Some form of physical trauma leading to inflammation in uvea or retina, such as surgical procedures, accidents due to sports or chemicals.
- Medication/toxin- Drug-induced uveitis such as Rifabutin, an antibiotic used for tuberculosis or vaccine-induced such as Tetanus Toxoid (TT), BCG, MMR, etc.

Moreover, causes of uveitis also vary among different populations according to their ecological, socioeconomical, and racial differences. The distinctive climate, prevalent pathogens, and diseases of the tropical nations have an added impact on the spatial and epidemiological distribution of the disease [3].

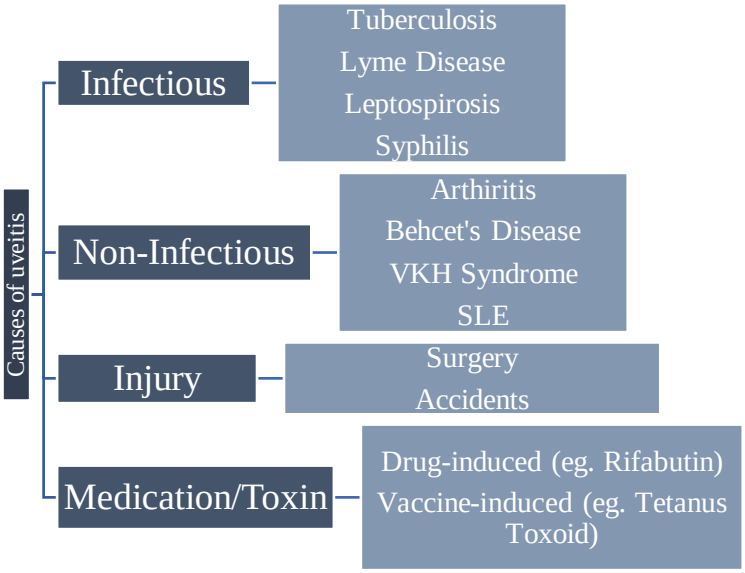


Figure 2. Schematic diagram of various etiologies of uveitis.

1.1.2. Epidemiology and risk factors

The incidence of uveitis among different populations varies due to age, gender, genetics, anatomic location of the inflammation, etiology (infectious/non-infectious), histopathology, and type of inflammation, while its prevalence varies by geographic location [4]. Uveitis accounts for over 30,000 new cases of legal blindness each year in the U.S. and that makes up for about 10-15% of all incidences of total blindness in the nation [5]. The most common form of uveitis found in general population is idiopathic anterior uveitis. In the underdeveloped world, 30-60% uveitis cases are due to infectious causes, herpes and toxoplasmosis being the two most common infectious agents [4]. According to the risk factors involved in the development of uveitis, it is widely accepted that women experience a higher incidence than males do. Smoking has also been included as a risk factor for progress of uveitis. Additionally, there is a significant link between vit. D deficiency and non-infectious uveitis.

1.1.2.1. In the U.S.

A population-based study was done by extracting data from the NHANES for the years 2009 and 2010, using 5106 people. It was found that 27 out of those, self-reported uveitis revealing a prevalence of 5.4 per 1000 individuals. The group with uveitis had an average age of 53 ± 13 years. Out of those 27 uveitis patients, 63% were found to be female and 37% were male. In 59.2% of the cases, a positive history of smoking was observed. In those diagnosed with uveitis, the breakdown of ethnicities includes 8 Hispanics, 6 African American, 10 Caucasians, and 3 Others [5].

Similarly, a retrospective study done between 1st January, 2006 to 31st December, 2007 that included about 217,061 participants, identified 874 uveitis patients. The incidence rate of uveitis was 24.9 cases per 100,000 person-years. In 2006 and 2007, the corresponding yearly prevalence rates were 57.5 and 58.0 per 100,000 individuals. Increase in incidence and prevalence due to age was observed [6].

1.1.2.2. In India

India has quite diverse in its climate, environmental conditions, flora, fauna, and microbial species across the country. However, South India has more of a tropical climate and hence, has a vast variety of prevalent pathogens and is more prone to diseases. Therefore, a large case-based study was performed using data from the patients diagnosed with uveitis from January 1996 to December 2001 in a community-based eye center of South India. A total of 11,72, 258 outpatients visited the hospital during the study period,

out of which, 9378 were identified as uveitis patients (0.8%). 81% of those 9378 patients were from the state of Tamil Nadu, 10.1%from Kerala, 7.7% from Andhra Pradesh, 1.3% from North Indian states and 0.5% from other countries. Of all the uveitis forms, anterior uveitis was found to be the most prevalent (57.4%), next to which was panuveitis (22.4%), followed by posterior (10.6%) and intermediate uveitis (9.5%). With reference to the cause of the disease, idiopathic uveitis constituted a major part (44.6%) of all 9378 patients, followed by infectious (30.5%) and non-infectious (24.9%) etiologies [7]. Correspondingly, between January 2016 and September 2017, every new patient of uveitis that visited the uvea clinic was included in a prospective qualitative study. This study's main objective was to determine the uveitis pattern at an important tertiary eye facility in central India. Approximately 30 lakh people live in the district served by this tertiary eye care facility in central India, and about 2-3 of its daily hospital-based ophthalmological outpatient appointments were found to be due to uveitis, which accounts for about 1% of their visits. 210 individuals were diagnosed with uveitis throughout the research period, consisting of 103 female patients (49.04%) and 107 male patients (50.95%). At the time of presentation, the average age was found to be 46.60 ± 11.21 years. Among the 210 patients, the most common form was found to be anterior uveitis(in 99 patients), next to which was intermediate uveitis (in 67 patients), posterior uveitis (in 27 patients) and panuveitis (in 17 patients). 101 patients were found to have idiopathic uveitis, 54 had ocular tuberculosis (TB) and 6 had toxoplasmosis as their etiology [8].

1.1.3. Diagnosis and treatment

Diagnosing uveitis involves a cumulative evaluation by an eye care professional, typically an ophthalmologist. The diagnostic process includes several steps to identify the type, cause, and severity of the inflammation. The process of diagnosis of uveitis involves several steps:

(1) Symptoms evaluation: It involves assessing the symptoms such as eye pain, redness, blurred vision, photophobia, appearance of floaters.

(2) Physical examination:

  (a) Visual Acuity Test- To measure the sharpness of vision.

  (b) Slit-Lamp Examination- A detailed examination of the anterior segment of the eye using a slip lamp to detect signs of inflammation like keratic precipitates, hypopyon, or iris nodules.

  (c) Fundoscopy- Using an ophthalmoscope to examine the posterior segment including retina, optic nerve and vitreous for signs of inflammation.

(3) Patient history:
   (a) Medical history- Patient's overall health, including any history of systemic diseases like autoimmune disease, infection, that might be linked to uveitis.
   (b) Ocular history- Any previous eye conditions like surgery or trauma.

(4) Laboratory tests:
   (a) Blood tests- To measure the levels of certain biomarkers for underlying systemic conditions like HLA-B27 for ankylosing spondylitis, ACE levels for sarcoidosis, tuberculosis screening.
   (b) Imaging- Chest X-rays or CT scans to check for sarcoidosis or tuberculosis.
   (c) Urine Tests- For diagnosing systemic diseases like Behcet's disease.

Treatment of uveitis aims to reduce inflammation, relieve pain, prevent tissue damage, and restore normal vision. Few of the treatment approaches include:

(1) Medications
   (a) Corticosteroids- Eye drops (e.g. prednisolone) for anterior uveitis, oral or IV steroids (e.g. prednisone) for posterior uveitis, periocular steroids include injections around the eye for intermediate or posterior uveitis.
   (b) Immunosuppressive Drugs- These are used when corticosteroids are insufficient or to reduce steroid dependency. E.g. methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil.
   (c) Biologic agents- To target specific components of the immune system like TNF inhibitors (infliximab, adalimumab) and interleukin inhibitors (tocilizumab).
   (d) Antibiotics/Antivirals/Antifungals- Prescribed for infectious uveitis like acyclovir for herpes viruses.
   (e) Cycloplegic agents- Eye drops to dilate the pupil and reduce pain from ciliary muscle spasms and prevent synechiae.

(2) Non-Medication Treatments
   (a) Laser therapy- Can be used for complications such as retinal neovascularization or macular edema.
   (b) Surgery- Vitrectomy (removal of the vitreous gel for severe cases of vitreous inflammation), Cataract surgery, Glaucoma surgery.

(3) Lifestyle and supportive measures- Wearing sunglasses to reduce photophobia, ensuring good hygiene in case infectious uveitis, counseling in case of chronic or recurrent uveitis.

Moreover, effective treatment of uveitis requires a personalized approach tailored to the specific type and cause of the inflammation.

1.2. Vaccine Associated Uveitis (VAU)

It is beyond any doubt that Edward Jenner's groundbreaking work of developing a smallpox vaccine in 1796 saved millions of lives. Use of vaccines to prevent various diseases has been one of the biggest achievements of public health. However, despite having many advantages, vaccinations may also have a wide range of negative consequences and adverse events. To monitor these side effects due to the administration of a vaccine, VAERS was established by the joint effort of (CDC) and the U.S. FDA [9]. Several reports of Vaccine-Associated Uveitis (VAU) have been submitted in the past decade and all the widely administered vaccines have been found to cause uveitis.

1.2.1. Previously reported VAU

Almost 290 uveitis cases linked to vaccinations were documented in a 2016 review, out of which, 199 patients were female and 77 were male with a mean age of 30 years. Some of the major vaccines that were found to be associated with uveitis infection included BCG, Brucella, Hepatitis A, Hepatitis B, HPV, Influenza, Diphtheria-Pertussis-Tetanus (DPT), Smallpox, Tetanus, Measles, Measles-Mumps-Rubella (MMR), Varicella and many more like such vaccines. The data that is available around the incidence of the disease implicate hepatitis B vaccine as the leading cause of VAU [10].

Vaccine	No. of cases
Hepatitis B	115
HPV	44
Influenza	28
BCG	21
MMR	13
Varicella	13

Table 1. Most commonly reported vaccines associated with uveitis infection in decreasing order of frequency [10].

1.2.2. Mechanism behind VAU

Even though there have been several cases of uveitis reported, the exact pathophysiology of VAU is still unknown. A number of theories have been put forth to explain this phenomenon, including immunological reaction to vaccine adjuvants, hypersensitivity due to immune-complex

deposition, and molecular mimicry resulting from a close analogy between vaccine peptide components and uveal peptides. Still, there is an alarming need to identify the relevant processes behind VAU [11].

1.2.2.1. Immune response to adjuvants

Adjuvants are the chemical compounds that improve the immune response of the host to the vaccine that is delivered. There are various categories of adjuvants used for vaccine development. The aluminum-containing adjuvant used in the hepatitis A vaccine has been implicated in inducing uveitis. Even though adding adjuvants provides an improved immune response and lowers the cost of vaccine manufacture, the data that is available indicates a possible link between vaccines that contain adjuvants and autoimmune adverse reaction due to them [11].

1.2.2.2. Deposition of antigen-antibody complexes

Antigen-antibody complex formation is a crucial part of immune response. In individuals who are healthy, mononuclear phagocytes eliminate these complexes in a timely manner. Whereas, type III hypersensitivity reactions occur due to the deposition of these immune complexes in patients with serum sickness, SLE, and reactive arthritis [12]. Deposition of these complexes within tissues triggers complement cascade and finally tissue damage. Numerous studies have demonstrated increased levels of immune complexes in the serum and aqueous humor in individuals with uveitis. In a prospective research study, high levels of serum immune complexes and complement were found in 104 individuals with uveitis [13].

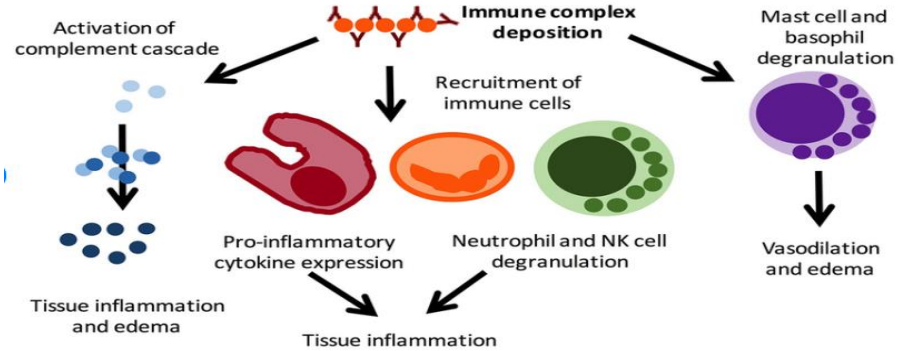


Figure 3. Tissue damage due to immune complex deposition.

1.2.2.3. Molecular mimicry

The process known as ‘molecular mimicry’ means substantial level of similarity between the foreign and host-peptides in terms of protein structure and amino acid sequence. Because of these morphologic and sequential similarities, antibody cross-reactivity may occur between self-peptides and foreign particles, causing tissue damage and autoimmunity. According to recent research, uveitis following the BCG vaccine may be caused by similarity between Mycobacterium tuberculosis peptides and antigens of the retina [14].

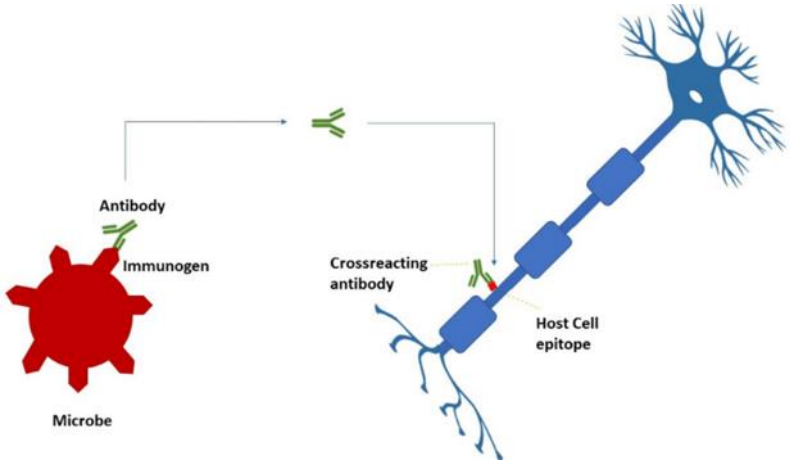


Figure 4. Molecular mimicry between the immunogen and host cell antigen.

1.3. COVID-19 and its vaccine

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus that emerged in late 2019 in Wuhan, China. It rapidly evolved into a global pandemic and presented a remarkable risk to public health worldwide. This highly contagious virus primarily spreads through respiratory droplets when an infected individual coughs, sneezes, or talks. Symptoms of COVID-19 vary largely, ranging from mild respiratory distress to severe pneumonia and multi-organ failure, particularly in older adults and those with underlying health conditions. The pandemic disrupted economies, healthcare systems, and routine life on an unprecedented scale. Scientific communities globally responded with urgency, leading to rapid vaccine development and deployment which helped in reducing the severity and spread of the disease.

1.3.1. SARS-CoV-2 and its structure

SARS-CoV-2 is a member of the coronavirus family, which causes illnesses like the common cold, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The structure

of coronavirus is integral to its property to infect and replicate within human cells.

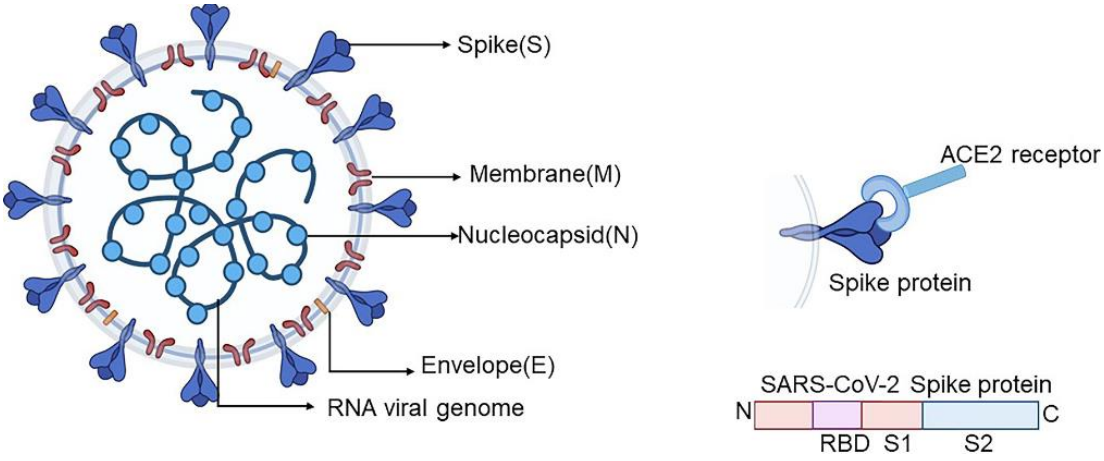


Figure 5. Structure of SARS-CoV-2 with four structural proteins: envelope protein (E), nucleocapsid protein (N), spike protein (S), and membrane protein (M). The virus enters the host cell through binding of the S protein with its receptor ACE2.

- E protein: Tiny membrane protein with ion channel activity, involved in the movement of viral particles and contributes in host's immune response modulation.
- M protein: The most abundant cytoskeletal protein that plays a crucial role viral assembly and attachment to the host cell.
- Spike Glycoprotein (S): The most prominent feature of the virus which protrudes from the viral surface and gives it a crown-like appearance. The spike protein is a trimeric protein with each monomer consisting of 2 subunits, S1 and S2. The S1 subunit has an RBD (Receptor-binding domain) that attaches to the ACE2 receptor on the host cell.
- Nucleocapsid protein (N): It packages the virus's RNA genome into a protective complex and is vital for RNA replication.
- Genome: SARS-CoV-2 has a single-stranded, positive-sense RNA genome, approximately 30,000 bases long, encoding various proteins necessary for vital replication and pathogenicity [15].

1.3.2. SARS-CoV-2 vaccine

The vaccines that are generated to fight the deadly novel coronavirus represent a major breakthrough in the effort to combat the global pandemic. A total of 336 COVID-19 vaccines were developed

worldwide in record time, out of which, 32 vaccines were approved for administration after rigorous screenings and trials, and all of the vaccines employed different technologies to stimulate the immune system. The various types of COVID-19 vaccines are as follows:

- mRNA Vaccines: Like BNT162b2 and mRNA-1273 these vaccines use a part of the mRNA of viral genome to instruct the virus to produce the spike protein on its surface. The spike protein then triggers an immune response, leading to the production of antibodies and activation of T-cells.
- Viral Vector Vaccines: Like Ad26.COV2.S that uses adenovirus vector, these vaccines use a secondary, modified, harmless virus to deliver the genetic material that codes for the coronavirus spike protein. Once inside the host, virus produces the spike protein, eliciting an immune response.
- Recombinant Vaccines: COVISHIELD (by Serum Institute of India) is a ChAdOx1-S recombinant vaccine, and likewise, these vaccines employ bacterial or yeast cells to incorporate a small piece of DNA/RNA from the pathogen, which is then administered into the host.
- Inactivated or Live Attenuated Vaccines: Like BBV152 COVAXIN (by Bharat Biotech) is a whole virion inactivated vaccine, these vaccines use a virus that has been killed (inactivated) or weakened (attenuated) so it cannot cause disease but only elicits an immune response [16].

Several clinical trials and research studies have shown that COVID-19 vaccines are highly effective at preventing symptomatic COVID-19, severe illness, and death. The widespread administration of these vaccines has been a critical component of public health strategies worldwide, aiming to achieve herd immunity and reduce the impact of COVID-19.

1.3.3. Adverse events associated with COVID-19 vaccine

Clinical trials assess the efficacy and safety of vaccines in specific populations, such as children, expectant mothers, and individuals with an underlying medical issue. Before vaccines are authorized for administration to the general population, extensive research and stringent testing are carried out to guarantee their safety and effectiveness. The CDC keeps a check on the safety of vaccines and offers advice to health providers on how to handle and record side effects [17]. But even after rigorous screenings and testing, various SARS-CoV-2 vaccines approved for public administration have been reported to cause some mild to severe side effects. There are few common side effects that are typically mild and short-lived, including pian at the injection site, redness, swelling, headache, fatigue, fever,

chills, and joint pain. However, there are some serious and irreversible adverse effects due to COVID-19 vaccine, such as:

- Myocarditis and Pericarditis:
  It refers to the inflammation of the heart muscle and the lining outside the heart. It is mostly reported in younger males after the second dose of mRNA vaccines (Pfizer-BioNTech and Moderna).
- Thrombosis:
  It is a rare condition involving blood clots in combination with low platelet counts. It is associated with adenovirus vector vaccines like Johnson & Johnson (Janssen) and AstraZeneca.
- Guillain-Barré Syndrome (GBS):
  It is a rare neurological disorder where the body's immune system attacks the nerve cells leading to damage and destruction of the tissues associated with it. It is reported very rare, associated mainly with the Janssen vaccine.
- Immune Thrombocytopenia (ITP):
  It is a condition where the immune system attacks and destroys platelets leading to increased bleeding risk.

1.4. COVID-19 vaccine and Uveitis

Among other severe side effects of COVID-19 vaccines, many cases of uveitis have been reported, which can further lead to blindness, if untreated. Several reports VAU due to COVID-19 vaccine have been found worldwide, either after the 1st dose or after the booster shot. According to the various reports, the most common uveitis causing COVID-19 vaccines, globally are BNT162b2 mRNA vaccine by Pfizer, BBIBP-CorV inactivated vaccine by Sinopharm, and in India is Covishield by Bharat Biotech. Followong are few of the many case reports of COVID-19 vaccine associated uveitis:

There have been multiple reports of uveitis infection post COVID-19 vaccination across the globe. Recently, in a 2022 study by Waseem et. al., 6 individuals with past medical history of a systemic disease experienced symptoms of uveitis after 5-14 days of COVID-19 vaccine administration in 2021. Of those 6 people, two were from India and were administered Covishield vaccine [18]. Another retrospective case study by Elsheikh et. al. described a case of an 18-year-old girl with JIA-associated anterior uveitis 5 days after the second dose of Sinopharm COVID-19 vaccine administration. The anterior chamber was shown to have hyperreflective spots optical coherence tomography, along with tiny endothelial granularities that indicated the circulating cells inside the anterior segment [19]. Similarly, five days after getting an inactivated COVID-19 vaccine shot, a fifty-year-old lady complained of bilateral impaired vision and visual distortion. She was

found to have developed bilateral posterior uveitis, as determined by auxiliary and physical examination [20]. Likewise, ocular examination of a 23-year-old male showed keratic precipitates and posterior synechiae 14 days following the booster dose of the BNT162b2 COVID-19 vaccination. He was then diagnosed with bilateral anterior uveitis [21]. In a multinational case series of uveitis incidence within 14 days after COVID-19 vaccination by Testi et. al., it was found that a total of 70 individuals experienced ocular inflammatory events after the vaccine administration, with anterior uveitis being the most common one. Most of the patients (n = 65) were managed with topical corticosteroids and their vision was not affected. However, 5 of them experienced reduced visual acuity by ≤3 lines and >3 lines [22]. A retrospective case report of 2023 by Sophia Li et. al. included 10 female patients (16 eyes) of Hong Kong to study intraocular inflammation after COVID-19 vaccine. Of the 10 individuals, 8 received Pfizer-BioNTech m RNA vaccine and were diagnosed with anterior uveitis [23]. Another retrospective observational case study by Eun Sim and Hwang described 11 cases of acute uveitis at the Sanggye Paik Hospital of Inje University of Korea, following COVID-19 vaccine [24]. In the same manner, a clinical study at a tertiary eye care centre of South India by Padmamalini et. al. in September 2023 identified 67 patients (98 eyes) with intraocular inflammatory presentation after COVID-19 vaccination. Again, anterior uveitis was found to be the most common presentation (n = 31), followed by panuveitis (n = 24) [25].

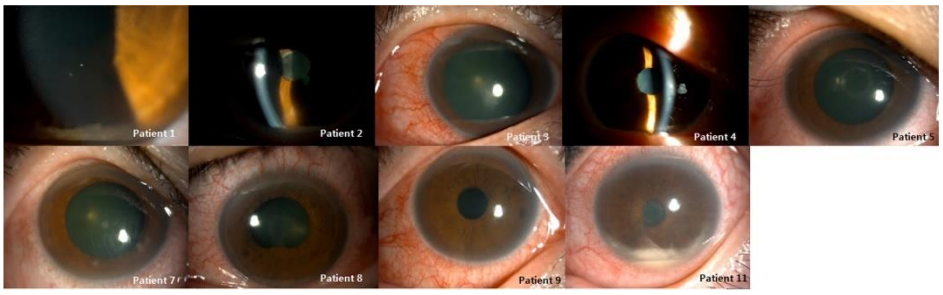


Figure 6. Acute uveitis clinical presentation in 11 patients at the University of Korea using slit-lamp photography, with all patients showing anterior chamber cells [24].

1.5. Research Objective

The objective of this research thesis is to understand the possible association between SARS-CoV-2 vaccine administration and Uveitis incidence. This study aims to identify the mechanism behind uveitis infection due to COVID-19 vaccination, thereby contributing to a deeper understanding of Vaccine-Associated Uveitis (VAU). Finding the answer to few of the questions like, "Is there any similarity between SARS-CoV-2 antigens and uveal or retinal proteins?", or "Is there an antibody cross-reactivity reaction happening between antibodies to SARS-CoV-2 antigens and uveal antigens?", can help in deciphering the basic processes behind VAU. To answer these questions, two majors approaches that we have used are:

- Approach I- Determining sequence similarity between the Spike glycoprotein of SARS-CoV-2 and some of the major uveal proteins that are known to play vital role in causing uveitis.
- Approach II- Understanding protein-protein interactions between the antibodies against SARS-CoV-2 and uveal proteins using molecular docking tools.

1.6. Literature review

As we delve into the previous literature related to COVID-19 vaccine associated uveitis, it becomes evident that the two have some sort of correlation. There are many research studies indicating some level of similarity between coronavirus proteins and human proteins. A research study by Yekbun Adiguzel on molecular mimicry between SARS-CoV-2 and human proteins demonstrated sequence similarity between a short peptide stretch of the spike protein of SARS-CoV-2 and various human proteins including Neuronal acetylcholine receptor subunit alpha-2, Phospholipid phosphatase-related protein type 2, Adenosine receptor A2b, Plasminogen receptor, Slit homolog 2 protein, Protein crumbs homolog 1, and various regions of many immunoglobulins [26]. Additionally, COVID-19 infection and its vaccine have been demonstrated to be related to autoimmunity in various research studies. In a research paper of 2020 by Vojdani et. al., cross-reactivity between the antibodies to SARS-CoV-2 proteins and tissue antigens has been described. They used human monoclonal anti-SARS-CoV-2 antibodies to 55 different human antigens and found cross-reactivity with 28 of those antigens including acetylcholine receptor, thyroid peroxidase (TPO), thyroglobulin, mitochondria M2 protein, and many more. The strongest reaction of the human spike protein antibody was found with neurofilament protein (NFP), followed by mitochondria M2, GAD-65 and nuclear antigen (NA) [27]. COVID-19 infection can lead to autoimmunity either by causing hyperstimulation of the host's immune system or by the mechanism of molecular mimicry [28].

CHAPTER 2

METHODOLOGY

2.1. Data Collection

All the proteins and ligands were downloaded from public domain databases and tools. Following is the list of all databases and online/offline tools used to carry out the research:

- PDB
- UniProt
- NCBI
- ClusPro
- BLAST
- PDB Mol* 3D viewer

The structures of some major uveal proteins including Recoverin, Cellular Retinaldehyde-Binding Protein (CRALBP), Transthyretin, Cellular Retinol-Binding Protein 1 (CRBP1), of SARS-CoV-2 spike glycoprotein, and of antibodies IgG and IgA were retrieved from PDB.

2.1.1. Recoverin

Also known as Cancer-associated retinopathy protein, recoverin (23 kDa) is a calcium-binding protein found in the photoreceptor cells of the eye. It controls phototransduction of rod and cone cells by acting as a calcium sensor and also contributes to scotopic vision. As the dim/low light induces increase in Ca2+ levels, recoverin prolongs the rhodopsin (RHO) activation in rod cells by inhibiting its phosphorylation.

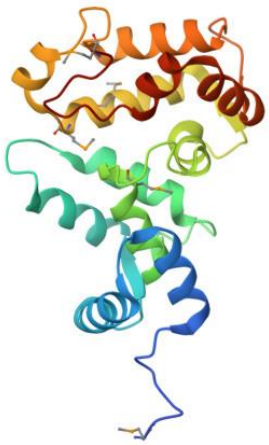


Figure 7. Crystal structure of human recoverin protein (PDBID: 2D8N)

2.1.2. Cellular Retinaldehyde-Binding Protein (CRALBP)

A 36 kDa water-soluble retinoid carrier that is important for proper functioning of both, rod and cone photoreceptors. It takes part in de novo synthesis of the retinoids from 11-trans metabolic precursors as well as the regeneration of active 11-cis-retinol and 11-cis-retinaldehyde from the inactive 11-trans products of the rhodopsin photocycle or 'visual cycle'. The visual cycle refers to the movement of retinoids between neighboring pigment epithelial cells and photoreceptors.

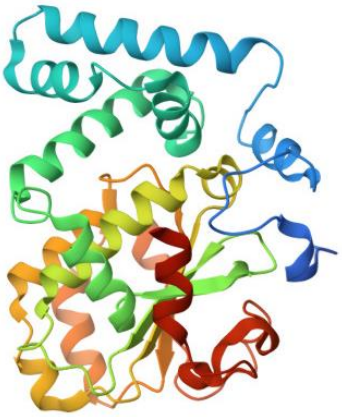


Figure 8. Crystal structure of human CRALBP (PDBID: 3HY5)

2.1.3. Transthyretin

It is a transport protein that is produced mainly in liver and retina. It is responsible for transporting retinol throughout the body. To do so, it forms a tetramer and binds retinol-binding protein. This TTR and RBP complex formation prevents the glomerular filtration and renal catabolism of the RBP molecule.

Figure 9. Crystal structure of human transthyretin protein (PDBID: 1DVQ)

2.1.4. Cellular Retinol-Binding Protein 1 (CRBP1)

It is a carrier protein for retinol and contributes in retinol absorption, storage, and retinoid homeostasis by accepting retinol from the transport protein STRA6. It also regulates the bioavailability of retinol, which helps in maintaining the differentiative form of endometrial cells, thereby, loss of CRBP1 may lead to endometrial cancer.

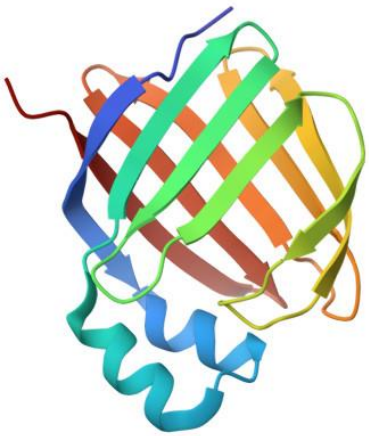


Figure 10. Crystal structure of human CRBP1 (PDBID: 5LJK)

2.1.5. SARS-CoV-2 spike protein S1

A 180 kDa glycoprotein on the surface of the virus, important for viral attachment and entry into the host cell. It helps the virus in attaching itself with the cell membrane by binding to the ACE2 host receptor. It consists of S1 and S2 subunits and a receptor-binding domain (RBD).

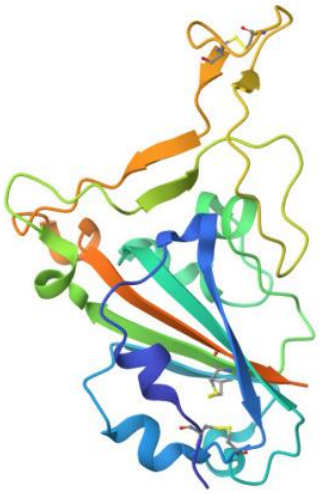
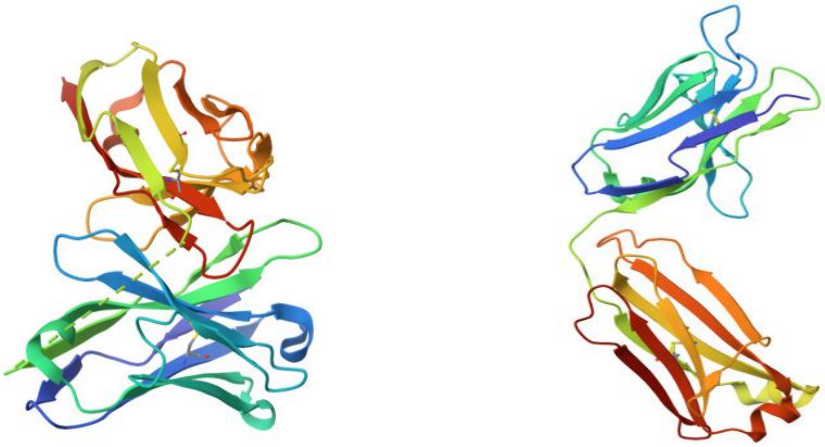


Figure 11. Crystal structure of SARS-CoV-2 spike protein S1 (PDBID: 7F15)

2.1.6. Antibodies IgG and IgA

These two immunoglobulins are involved in the primary immune response against SARS-CoV-2.



(a) (b)

Figure 12. Crystal structure of (a) IgG antibody (PDBID: 7F15)

(b) IgA Fab fragment (PDBID: 3M8O).

2.2. Data Processing

2.2.1. Approach I: Molecular Docking

Molecular docking is a computational method used to determine the architecture of two or more different molecules when linked together. Predicting the intended 3-D structures in aim of docking experiments. Based on the preferred orientation of two molecules, one may evaluate the strength of the binding affinity between the molecules using appropriate scoring systems. In this study, molecular docking was performed to understand protein-protein interactions between SARS-CoV-2 viral proteins and human uveal proteins using an online docking server called ClusPro. The resultant models were then visualized in PDB Mol* 3D viewer.

2.2.1.1. ClusPro

ClusPro (cluspro.org) is one of the popular tool used for protein-protein docking. With just two files in PDB format, the server offers a fast and almost accurate docking models. Additionally, ClusPro also offers advanced options to customize the docking experiments. One such advanced option is ‘Antibody mode,’ which was mainly used in this study.

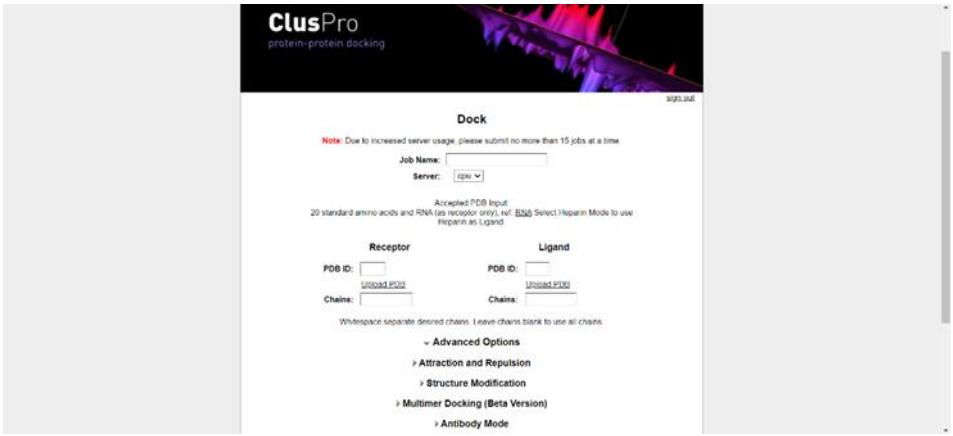


Figure 13. Homepage of ClusPro showing different advanced options.

2.2.1.2. PDB Mol* 3D viewer

It is a web server that provides user friendly interface to visualize and analyze different proteins at the same time.

2.2.2. Approach II: Sequence Similarity

At protein level, similarity in the amino acid sequence can reveal the possible link between the two proteins in terms of signal transduction and immune response. In this study, sequence similarity search was done using BLAST (Basic Local Alignment Search Tool) that gives optimal alignments of two or more sequences (nucleotide or protein). It uses BLOSUM62 as its default scoring matrix.

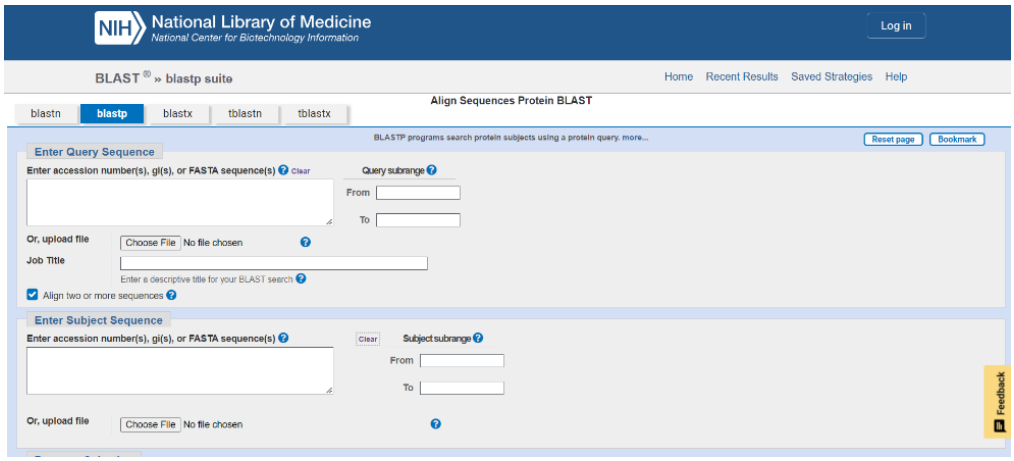


Figure 14. BLAST homepage.

CHAPTER 3

RESULTS

3.1. Approach I: Protein-Protein interactions between anti-spike protein antibody and uveal proteins by performing molecular docking using ClusPro.

3.1.1. Between recoverin and IgG antibody

After setting the appropriate docking parameters and running the query, the following model turned out to be the most stable, with the highest weighted score and lowest binding energy (-395.1) among all the 10 models that were displayed in ClusPro.

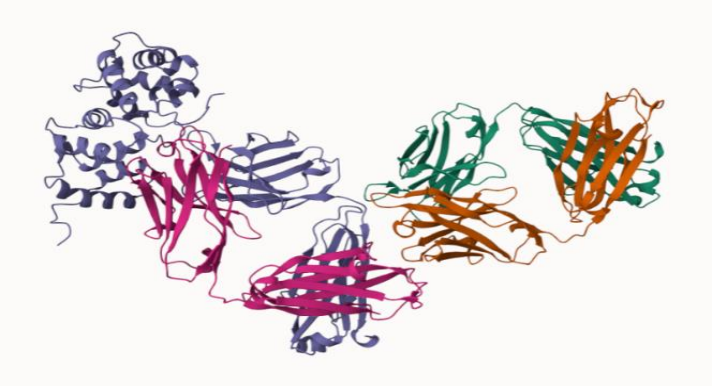


Figure 15. Molecular docking model of Recoverin and IgG antibody.

3.1.2. Between recoverin and IgA antibody

After setting the appropriate docking parameters and running the query, the following model turned out to be the most stable, with the highest weighted score and lowest binding energy (-399.0) among all the 10 models that were displayed in ClusPro.

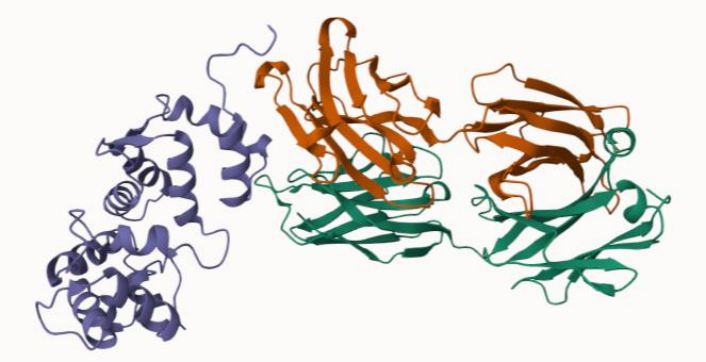


Figure 16. Molecular docking model of Recoverin and IgA antibody.

3.1.3. Between CRALBP and IgA antibody

After setting the appropriate docking parameters and running the query, the following model turned out to be the most stable, with the highest weighted score and lowest binding energy (-430.0) among all the 10 models that were displayed in ClusPro.

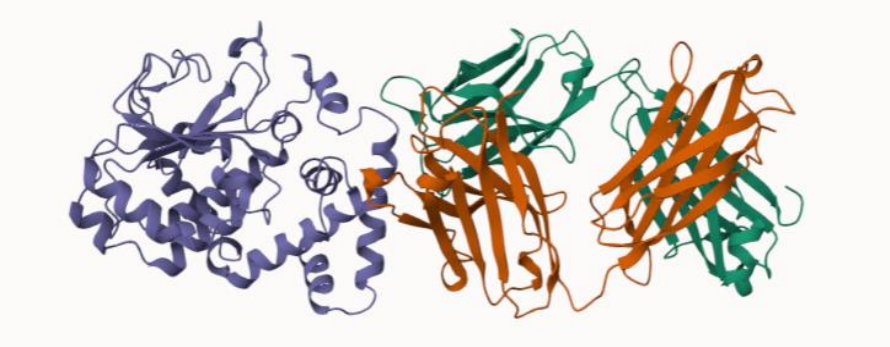


Figure 17. Molecular docking model of CRALBP and IgA antibody.

3.1.4. Between Transthyretin and IgA antibody

After setting the appropriate docking parameters and running the query, the following model turned out to be the most stable, with the highest weighted score and lowest binding energy (-240.2) among all the 10 models that were displayed in ClusPro.

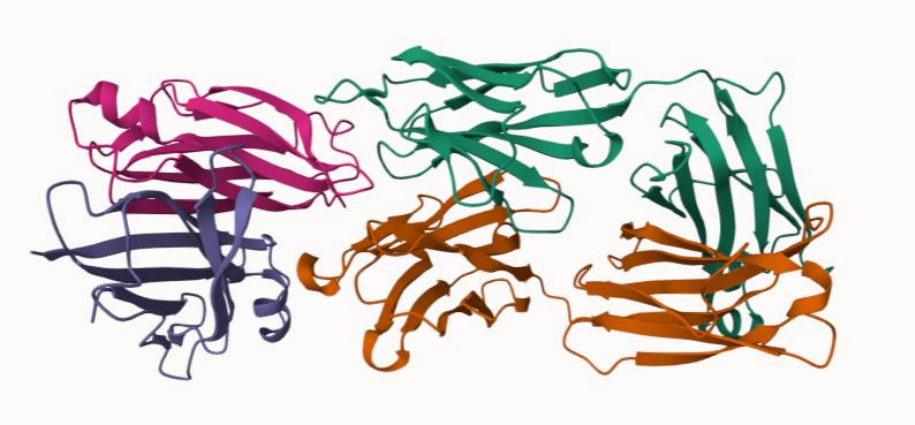


Figure 18. Molecular docking model of Transthyretin and IgA antibody.

3.1.5. Between CRBP1 and IgA antibody

After setting the appropriate docking parameters and running the query, the following model turned out to be the most stable, with the highest weighted score and lowest binding energy (-224.2) among all the 10 models that were displayed in ClusPro.

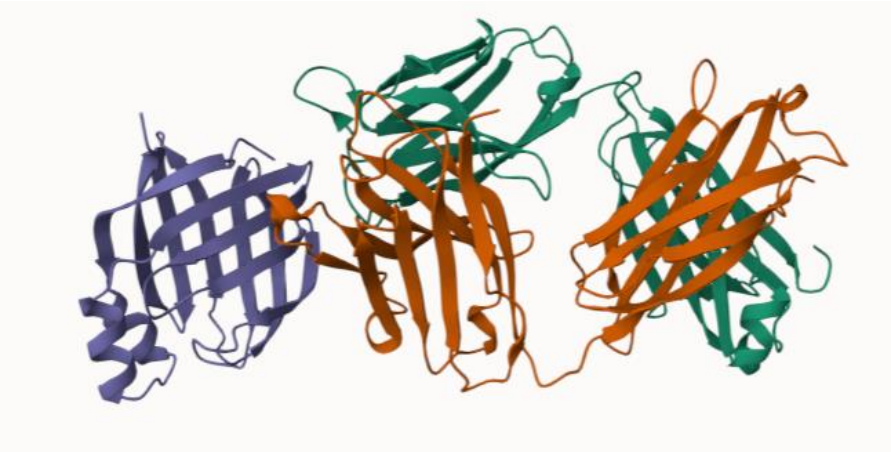


Figure 19. Molecular docking model of CRBP1 and IgA antibody.

3.1.6. Between Spike protein S1 and IgA antibody (reference model)

After setting the appropriate docking parameters and running the query, the following model turned out to be the most stable, with the highest weighted score and lowest binding energy (-480.5) among all the 10 models that were displayed in ClusPro.

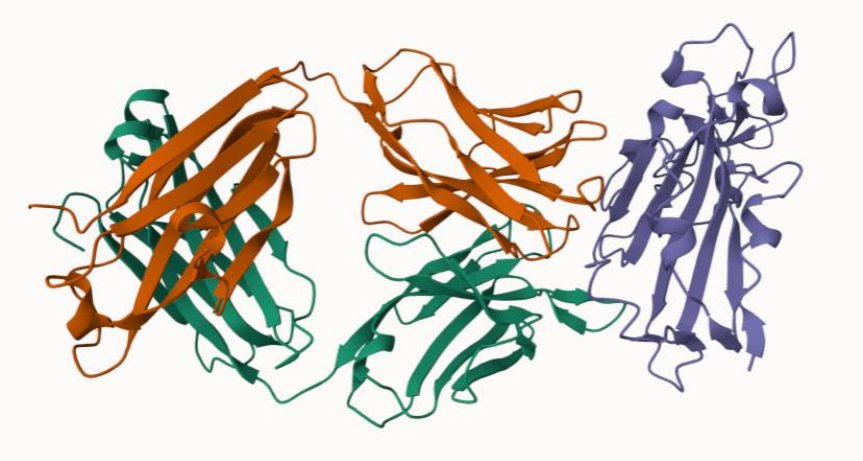


Figure 20. Molecular docking model of SARS-CoV-2 spike protein S1 and IgA antibody (reference).

3.2. Approach II: Finding sequence similarity between SARS-CoV-2 spike protein and uveal proteins using BLAST.

For this solution approach, FASTA sequence of the spike protein S1 and uveal proteins was taken from UniProt. After entering appropriate scoring parameters (BLOSUM62 matrix, Existence:11 Extension: 1 gap costs) and performing BLAST for all the proteins, only CRALBP (query sequence) came out to have some degree of alignment with spike protein (subject sequence).

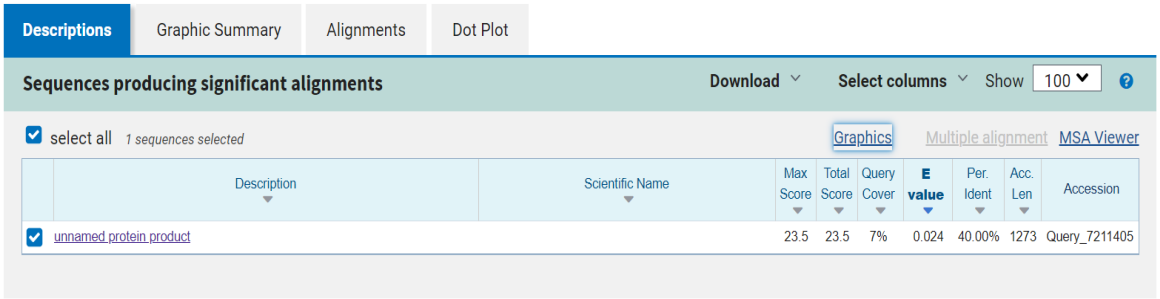


Figure 21. BLAST results of CRALBP and coronavirus spike protein showing 40% identity and 0.024 E value.

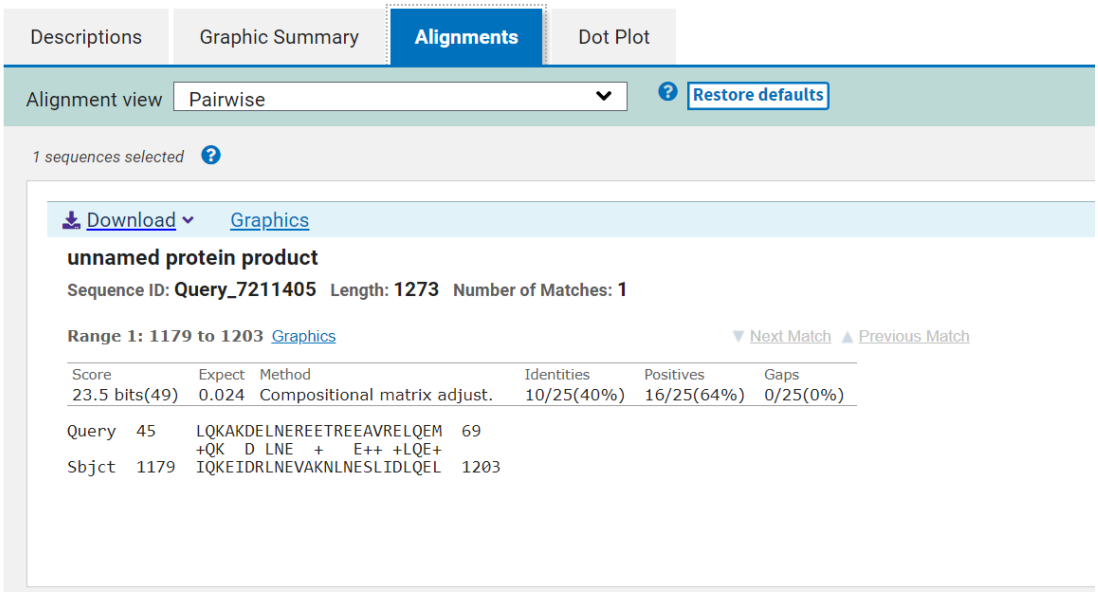


Figure 22. Showing sequence alignment between 45th and 69th amino acid positions in CRALBP with the spike protein (query sequence).

CHAPTER 4

CONCLUSION

The results of molecular docking reveal that there is some correlation between novel coronavirus spike protein and uveal proteins, Recoverin and CRALBP, as the binding energies of these two proteins and the IgA antibody came out to be the closest to that of the reference model (spike protein and IgA antibody). Therefore, it can be concluded that the proteins, Recoverin and CRALBP, may be involved the mechanism of COVID-19 vaccine associated uveitis.

The results of sequence alignment by BLAST reveal a possible connection between SARS-CoV-2 spike protein and CRALBP, as it showed 40% identity and a low E value of the resultant alignment. Therefore, it can be concluded that the cross-reactivity of antibody IgA, may be due to the sequence similarity between CRALBP and spike protein.

CHAPTER 5

DISCUSSION AND FUTURE PERSPECTIVE

The COVID-19 vaccine, undoubtedly, has proved to be a powerful asset in the fight against the deadly novel corona virus, SARS-CoV-2. However, like every solution comes with another problem with it, COVID-19 vaccines came with serious adverse effects, one of them being uveitis. Uveitis is a sight-threatening, intraocular inflammatory disease with multifactorial etiology and no cure to its chronic form, per se. The incidence of this grave disease has significantly increased after the COVID-19 vaccine administration worldwide, while the mechanism behind it is still unclear. In this research thesis, we tried to understand the mechanism behind COVID-19 vaccine associated uveitis, and in the process of doing so, we came across some interesting findings.

Molecular docking experiment of human anti-SARS-CoV-2 spike protein antibody and two major uveal proteins, Recoverin and CRALBP, gave somewhat stable models, indicating cross-reactivity between the SARS-CoV-2 antibody to the spike protein and to human uveal-antigens. Binding of spike protein antibody with the uveal protein, recoverin, would lead to the disruption of calcium sensor in the retina. Subsequently, this would affect the phototransduction of rod and cone cells which is crucial for scotopic vision, leading to sight reduction and possibly, uveitis. Likewise, CRALBP being a vital protein present in retina that transports retinoids between neighboring epithelial cells and photoreceptors, binding of spike protein antibody with CRALBP result in disturbance in retinoid transport and again possibly, uveitis. Furthermore, sequence alignment experiment of SARS-CoV-2 antibody and uveal proteins gave a significant degree of alignment between human anti-SARS-CoV-2 spike protein antibody and CRALBP, providing with the possible explanation behind the cross-reactivity between the two in previous experiment.

Both these experiments show some correlation between COVID-19 vaccine and uveitis infection. While the benefits and importance of COVID-19 vaccines certainly precede its side effects, the severity of few of those side effects cannot be ignored and shall be understood in depth to prevent the increase of their incidence and remove vaccine hesitancy. Similarly, vaccine associated adverse events due to all vaccines should be studied to improve the safety and efficacy of all vaccines.

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Summary

TANVIKA GUPTA

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Permanent residence - Delhi

Date of Birth: August 29, 1998

Want to secure a responsible career opportunity in industry to fully utilize my training and skills, while learning something new every day. Hard working, have keen attention to detail, work well under pressure.

EDUCATION

2014

SECONDARY SCHOOL EXAMINATION,
MAHARAJA AGARSAIN PUBLIC SCHOOL, CBSE, DELHI

CGPA - 8.2 (Science, Maths, English, Social Studies)

2016

SENIOR SCHOOL CERTIFICATE EXAMINATION
MAHARAJA AGARSAIN PUBLIC SCHOOL, CBSE, DELHI

75.4% (Biology, Physics, Chemistry, English)

2017

ALL INDIA BIOTECHNOLOGY COMMON ENTRANCE TEST, DPU, PUNE

Merit rank – 5

2017-21

B. TECH in MEDICAL BIOTECHNOLOGY, DPU, PUNE

GPA - 8.79 (1st semester)
8.64 (2nd semester)
8.90 (3rd semester)
8.89 (4th semester)
8.69 (5th semester)
9.50 (6th semester)
9.36 (7th semester)
10.00 (8th semester)

LAB SKILLS

Fair knowledge about lab techniques and basic instruments used in various areas of Biotechnology and Bioinformatics:

- **Protein quantification** using Spectrophotometry.
- Different microbiological media preparation, Isolation of micro-organisms from different samples, Staining of microbes, Endospore staining, Bioassay of different antibiotics, PBMC isolation, different **tissue scaffold** preparation.
- Various molecular biology techniques like **Isolation and purification of plant/microbial DNA and Plasmid DNA**, Quantification of DNA using Spectrophotometry, Restriction digestion analysis, **PCR**, **Competent cell** preparation, Transformation of cells, Preservation of cells and DNA, **DNA fingerprinting**, **Ligation** of target DNA, **Total RNA isolation**, determining **GC content** in the DNA, **Southern Analysis,**

Western Blotting, ARMS-PCR, Multiplex PCR, Chromosome Staining, Polytene chromosome staining of *Drosophila* larva, **Karyogram** preparation, fair understanding about **FISH.**

- **Culturing, breeding and study of *Drosophila melanogaster***, Studying Human **karyotype,** fair understanding about **Genetic Disorders, Dissection of *Drosophila* larva and identification of Imaginal discs.**
- **MTT assay, Clonogenic assay, Scratch assay** in cancer biology.
- Protein purification by **Gel chromatography**, **SDS-PAGE**, Paper and Thin layer chromatography, **Mass Spectrometry.**
- Widal test, Immunodiffusion assay, **Immuno-electrophoresis**, **ELISA**, Antibody purification using proteinA beads.
- Various statistical operations, **Energy minimization** and **Dynamics** of molecules using Cheminformatics.
- **Synthesis of nanoparticles** by different methods, knowledge about Clinical trials and QC/QA of drugs.
- **Growth Kinetics** study in batch culture, **Whole cell immobilization in alginate beads and blocks, Downstream processing.**

TRAININGS AND INTERNSHIPS

- Received training from **Dr. Shweta Saran** at **Department of Development Biology, Jawaharlal Lal Nehru University (JNU)**, Delhi in 2019. Learned how to develop ***Dictyostelium discoideum*** (a soil amoeba), **X-Gal staining** of lacZ gene, **cloning of a gene in a vector.** I was given the gene, *Rab7*, for cloning, which is recruited at the time of autophagy in *Dictyostelium*, in unfavorable conditions.
- Completed online course on **Molecular Biology: DNA replication and repair from MIT** on edx portal.
- Completed a dissertation project in 2021 at **CORE DIAGNOSTICS PVT. LTD.** as a part of the degree program. The project was about the diagnosis of Chronic Myeloid Leukemia using RT-PCR and FISH.
- Completed an internship at **FOOD REGULATION AND COMPLIANCE CENTRE (FRCC)** in Food and Fortification division in 2021.

CO-CURRICULAR

- Completed a 15-day **Entrepreneurship Development Programme** by **The National Institute for Entrepreneurship and Small Business Development** at Dr. D.Y. Patil Biotechnology and Bioinformatics Institute (DYPBBI), Dr. D.Y. Patil Vidyapeeth Pune, India from 28th Sept 2018 to 12th Oct 2018.
- Lead an **Online Summer activity** organized by Dr. D. Y. Patil Biotechnology and Bioinformatics Institute, Pune of **question bank preparation for GATE exam.**
- Microsoft Specialist of MS PowerPoint 2010.

EXTRA-CURRICULAR

- SPORTS AND PARTICIPATION
  - Lead the cultural team at various college events and was elected as the Cultural Secretory of the Student Council in 2019.
  - Awarded a certificate of appreciation for securing **1st and 2nd position** in **Face Painting** event on Cytosoul 2019 and 2020 respectively held at Dr. D.Y. Patil Biotechnology and Bioinformatics Institute, Pune.
- INTERESTS
  - Reading, Singing and Painting.
- LANGUAGES
  - English, Hindi.