



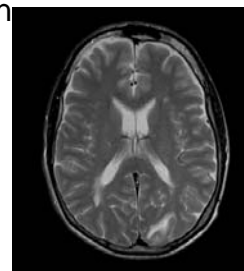
Discovery and Development of PML treatments

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JC Virus and The Risk of PML

- PML is a rare disease of CNS that occurs in patients immunosuppressed and in patients taking certain immunomodulatory drugs
- JCV is the etiologic agent of PML
- JCV is a common infection in the human population
- JCV associated with PML has undergone genetic changes relative to archetype (kidney-derived) virus
- The pathogenesis of PML remains poorly understood



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Pillars of JCV/PML Research



Biogen Idec has a comprehensive research program integrating knowledge and resources

- internal research programs
- worldwide academic collaborations
- participation in the PML Consortium

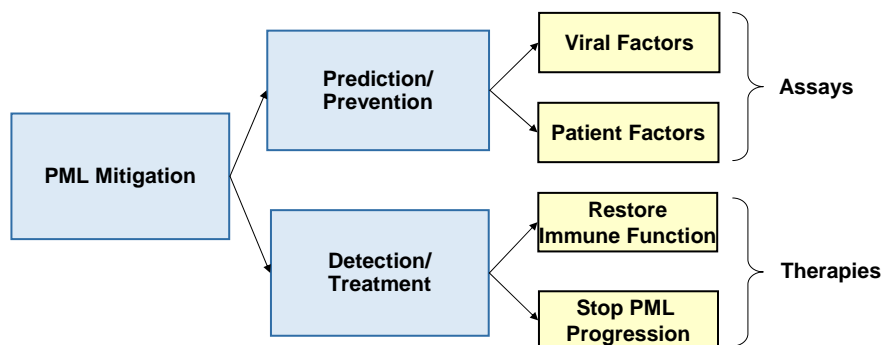
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Goals of PML Research at Biogen Idec

Provide physician's and patients with tools to:

- Assess the risk of PML
- Diagnose PML early
- Improve PML outcomes



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Basic Biology Questions

Research on JCV/PML is challenging

- Relevant cell culture systems; difficulty to grow pathogenic forms of JCV
- No animal model
- What is the reservoir(s)?
- Circumstances supporting transmission to the brain is not known
- When/how do mutant virus strains arise

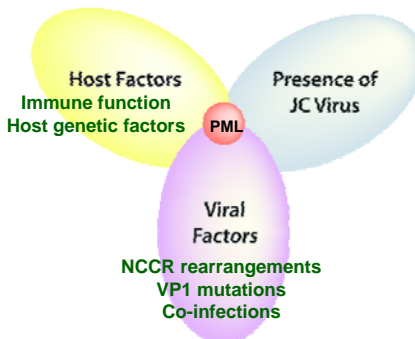


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Present Status of Risk Stratification Knowledge with Tysabri-associated PML

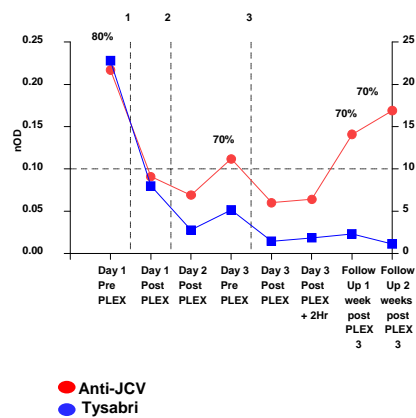
- Duration of Tysabri treatment more than 2 years
- Prior Immunosuppressant Use
- Exposed to JCV (Anti-JCV positive)



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Current Standard of Care for Tysabri-associated PML



The majority of patients who developed PML in the post-marketing setting received plasma exchange (PLEX) and/or immunoadsorption (IA) to accelerate removal of TYSABRI

IRIS has occurred after discontinuation or removal (by PLEX) of Tysabri

IRIS has occurred within days to several weeks (steroids). Indicates reconstitution of cellular immune response

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Efforts and Trials in JCV/PML Treatment

Immune Modulators	Marketed drugs for other indications	Broad spectrum antivirals	Related to JCV lifecycle
IFN-α •Results Inconclusive	Cytarabine •no effect on mortality	Cidofovir •no specific effect on mortality	5HT_{2a} Inhibitors •In vitro data difficult to reproduce, no proven efficacy
IL-7; IL-2 •No clinical data, no proven efficacy	Mefloquine •no effect on JCV load in CSF or clinical endpoints	CMX001 •no proven efficacy	

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Challenges for JCV/PML Drug Development

- **Preclinical –Limited tools**

- No robust inhibition assay for PMLgenic strains
- No in vivo POC before moving into patients
- Dose estimations be based on in vitro data, assumptions about BBB penetration

- **Clinical - Challenging indication**

- Acute, life-threatening infection with undefined window for intervention
- Variability of disease course depending on underlying condition, status of immune reconstitution, IRIS, and standard-of-care
- Rarity of disease affects feasibility and design of clinical trials
 - Limited patients across broad geographic region
 - Logistical challenges associated with pre-identification of sites and protocol approvals

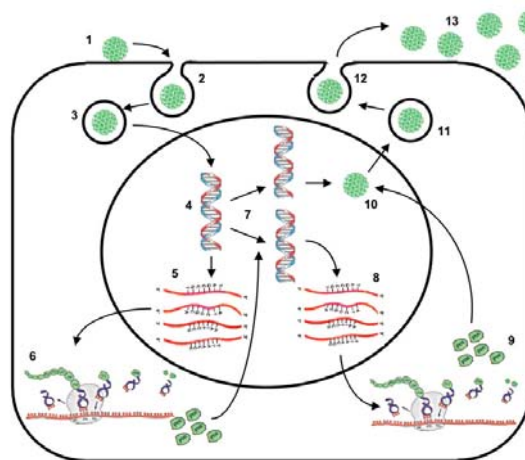
- **Regulatory – no established path for approval**

- No established endpoints or precedents for registrational trial

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Multiple Steps of the JC Lifecycle are Potential Targets for Drug Discovery



Successes in Antivirals

Entry: HIV (host) RSV (MoAb)

Uncoating: Influenza

Protein Processing: HIV
HCV

Genome Replication:
HIV, CMV, HSV, HBV

Maturation/Egress:
Influenza

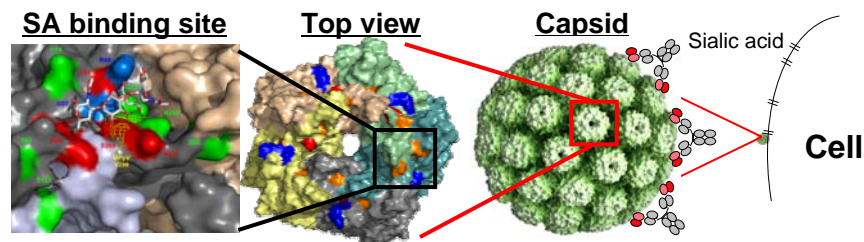
Approaches to Discover Antiviral Drugs

- Small molecule screens for target-based enzymatic activity
- Small molecule screens for target-based cellular reporter assays
- Phenotypic infectivity screens
- Monoclonal antibody discovery for exposed virion proteins, cellular receptors, intact virions

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Anti-JCV Neutralizing Antibody as a Potential Therapeutic Agent



Molecular Hypothesis

A high affinity/potency anti-JCV neutralizing monoclonal antibody, at sufficient concentration in the brain of a PML patient, will slow viral spread and reduce viral burden in the CNS

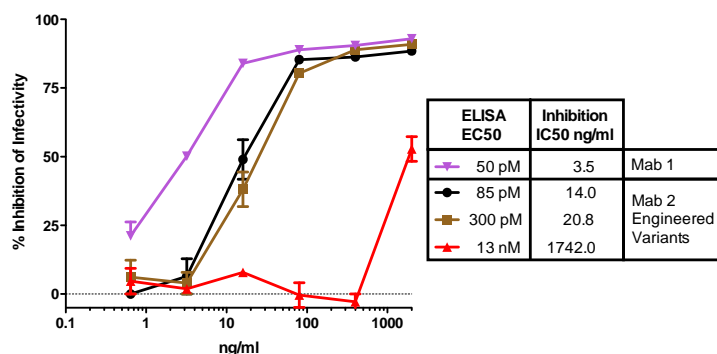
Therapeutic Hypothesis

Slowing JC-viral replication during PML, until the immune system is restored and normal immune function clears the virus, will reduce neurological damage and improve PML prognosis

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Anti-JCV Neutralizing Antibody as a Potential Therapeutic Agent

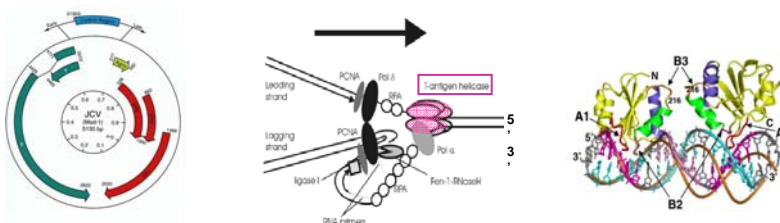


- A collection of fully human neutralizing MoAbs with excellent biochemical properties has been developed
- Affinity threshold for inhibition, potentially different for each antibody class
- Mechanism of action can impact potency
- Must neutralize viral mutants

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T Ag as a Potential Target for Small Molecule Therapy



Molecular Hypothesis

The helicase or ATPase activities of T Ag may be targets for small molecule inhibitors. Inhibition of these activities of T Ag will block virus replication.

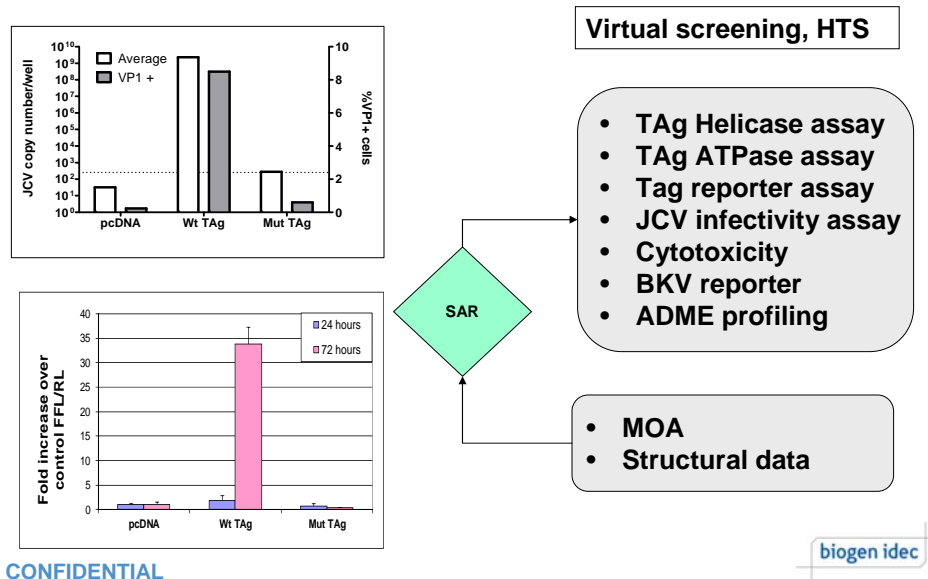
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T Ag Target Validation and Flow Chart



Summary of JCV/PML Therapy

- Biogen Idec is committed to comprehensive, collaborative research program for PML, although both biological and clinical challenges exist for identifying and advancing new therapies
- Currently, immune reconstitution remains the standard approach in the treatment of PML
 - Active drug removal for agents such as Tysabri
- Ongoing efforts continue with broad spectrum antivirals
- Specific anti-JCV therapy is targeted to identify potential therapeutic agents
 - Biogen is currently working on two novel JCV treatment options
- Significant challenges exist with regard to clinical trial design and logistics
- Addressing these challenges is a global problem
 - Requires focused concerted effort
 - Consortia of academia and industry
 - Guidance from regulatory agencies

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