PML Consortium

Research Activities

25 July 2011

EMA

London

Need for a Consortium

- PML is a rare, but serious and potentially fatal, infection of the brain, usually associated with immunosuppressed states, also seen with some immunomodulatory and immunosuppressive treatments.

- A knowledge base with sufficient number of patients is needed to identify risk factors and improve management of PML.

- Because PML occurs so rarely, efforts will be accelerated through collaboration. No single company, research center, or agency can effectively obtain sufficient data to conduct research on its own.

- Thus, there is a need for a cooperative effort to achieve this goal.

Vision and Mission

Vision

The Consortium aims to find methods to predict, prevent and treat PML.

Mission

Perform research to reduce occurrence, morbidity and mortality of PML through:

- Multi-company, not-for-profit, collaborative approach
- Shared strategy, investment, data acquisition & analysis and communication
- Multi-year commitment from member organizations

PML Consortium

Organization

Board of Directors (*two members from each company*)

Working groups: Communications, Regulatory Affairs, Clinical, Research

Advisory Board *(Chair David Clifford + six members*)

Member Companies

Current:	Biogen Idec, Bristol Myers Squibb, Elan, Pfizer, Roche
Prospective:	Open to new members
Secretariat:	Drinker Biddle & Reath, provides legal (including antitrust), scientific, project management, and administrative support.

Research and Clinical Activities

2010-2011

Research and Clinical Activities

A staged collaboration

- Ongoing:
  - Creation of a clinical database
  - Establishment of a repository of samples available for Consortium-sponsored research
  - Funding Academic Collaborative Research Network
- Future plans under consideration:
  - Clinical validation of risk stratification assays
  - Clinical evaluation of emerging PML therapeutics

Member companies will also continue independent research efforts to mitigate, cure, or stratify the risk of PML.

A Shared Clinical Database and Sample Repository Have Been Established

- A Consortium model allows us to pool resources to gather clinical data and samples from PML patients.
  - This is a top priority of the Consortium -
- Shared clinical database contains relevant data associated with confirmed PML cases:
  - Demographic
  - Clinical
  - Brain imaging
- Clinical database will be linked to a Consortium sample repository
- Access will be determined according to scientific question. The exact process is being established.

A Shared Clinical Database and Sample Repository Have Been Established (cont.)

- Sample Repository:
  - Member companies are sharing best practices for sample acquisition, shipping and storage
  - Consortium is developing a process for sharing and prioritizing use of samples

Academic Collaborative Research Network

- In mid- 2010, the Consortium agreed to create a Collaborative Research Network.
- Through this network, the Consortium will fund research in the academic community to fill gaps in our knowledge of PML.
  - Basic biology of JC Virus and pathogenesis of PML
  - Immune responses to JCV associated with PML development
  - Viral changes associated with PML
  - Animal models of PML
- To foster collaboration, awardees will participate in regular JCV/PML discussion forums and symposia.
- The Consortium has developed a framework to implement the research network (legal, financial, and operational aspects).

Academic Collaborative Research Network: Current and Future Grants

Consortium Research Initiatives	
Infectivity of mutant viral strains	Virology
Screen a wide sampling of tissue types from cadavers as potential viral reservoirs	
Use murine polyomavirus as an animal model of PML-like disease	Animal Models
Develop a mouse model of JCV infection (humanized kidney and immune system)	

Areas of Continuing Interest & Future Grants	
CD4+ and CD8+ T cell and B cell responses to JCV	Host Immune Function
PML pathogenesis	
JCV mutations, infectivity & PML	Virology
JCV latency – tissues & cell types	
Animal models of PML	Animal Models

Current Projects

Develop a mouse model of peripheral JCV infection.

- Use engrafted human kidney cells to establish a JCV infection in the mouse to study viral pathogenesis.

Use murine polyoma virus (PyV) as a model for PML.

- Generate PyV variants that mimic the pathogenic forms of JCV to study the tropism, replication and spread of the virus.

Use in vitro systems to study JCV infectivity and replication.

- Generate JC virus found in brain isolates from PML patients and use primary human glial cells from different donors to explore the role of JCV mutations in infectivity and replication.

Determine sites of JCV infection.

- Tissues from fresh human cadavers will be assayed for JCV DNA by PCR.
- JCV from positive samples will be sequenced and in situ hybridization will be used to look for active replication.

Activities of the Academic Collaborative Research Network

- Annual Symposia for Grantees
  - April 2010
  - June 2011
- Small Working Groups
  - Immune function testing for PML prediction – Nov 1-2, 2010, Boston USA
  - Genetic approaches to identifying PML susceptibility loci – March 2011, Boston USA
  - Immune response to viral infections of the CNS Fall 2011.

Near-Term Research Priorities

- Continued population of the clinical database
- Continued collection of samples
- Continuation of research efforts and symposia
- Funding of new grants (RFP Fall 2011).

Further information can be obtained through the consortium:
pmlconsortium@dbr.com

Questions?

BACKUPS

Consortium Advisory Board

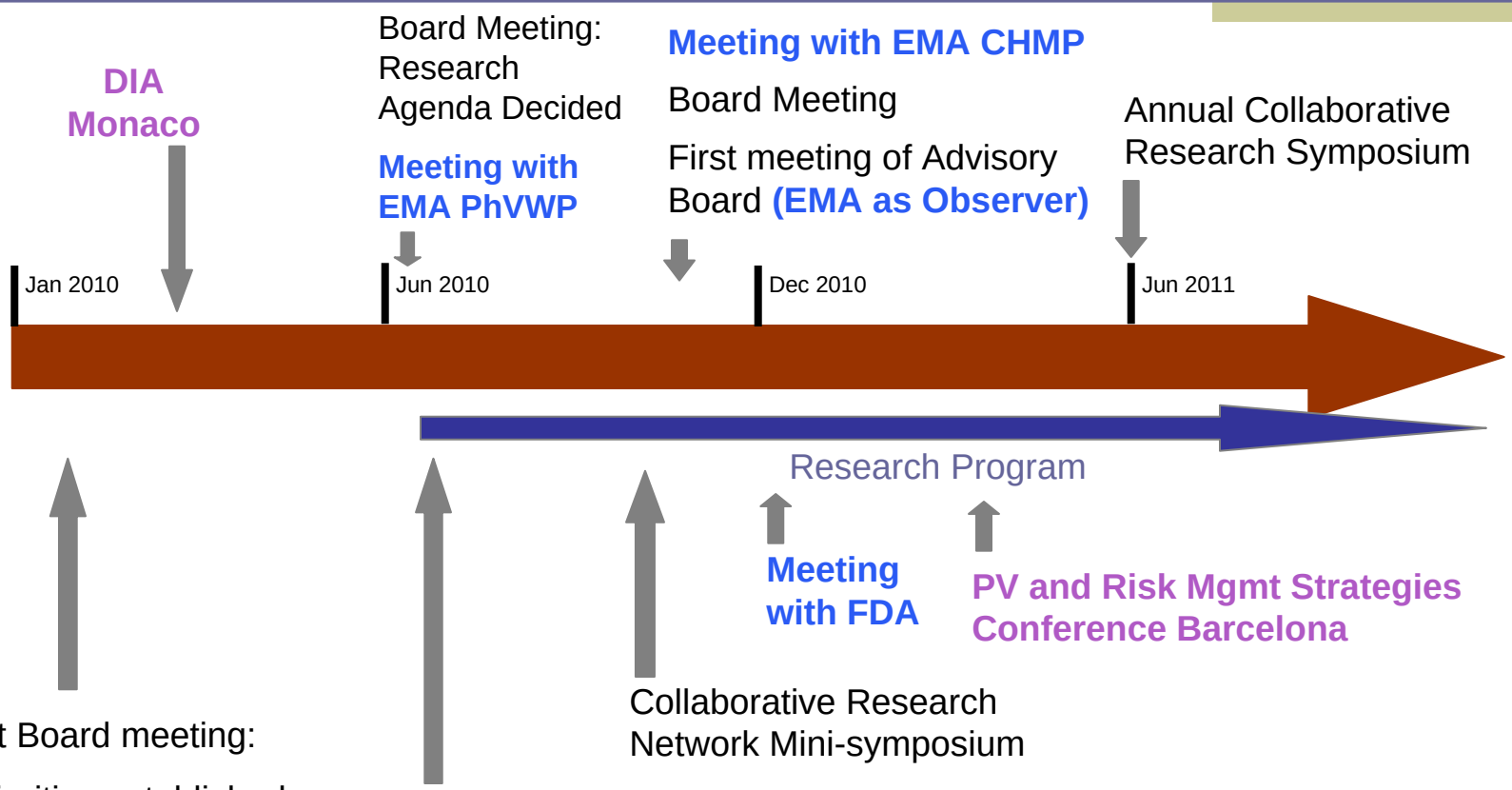
Responsibilities

- The Advisory Board will meet with the Board of Directors on a semi-annual basis.
  - First meeting held in November 2010.
- The remit of the Advisory Board is to:
  - Represent the interests of the recipients of the Consortium's work, including patients, physicians, and the scientific community;
  - Provide feedback and advice on all Consortium activities;
  - Provide insight into advancements in the scientific and medical communities; and
  - Assist the Consortium in disseminating information about PML, in collaboration with the Consortium's Working Groups.

Key Accomplishments in 2010/2011

- Consortium established as a legal entity
- Agreement on funding
- Creation of Advisory Board
- Agreement on content and vendors for clinical database
- Initiated development of processes for sample collection, banking and storage
- Agreement to create Academic Collaborative Research Network
- Academic Collaborative Research Network symposia held

Timeline of Activities



1st Board meeting:

Priorities established

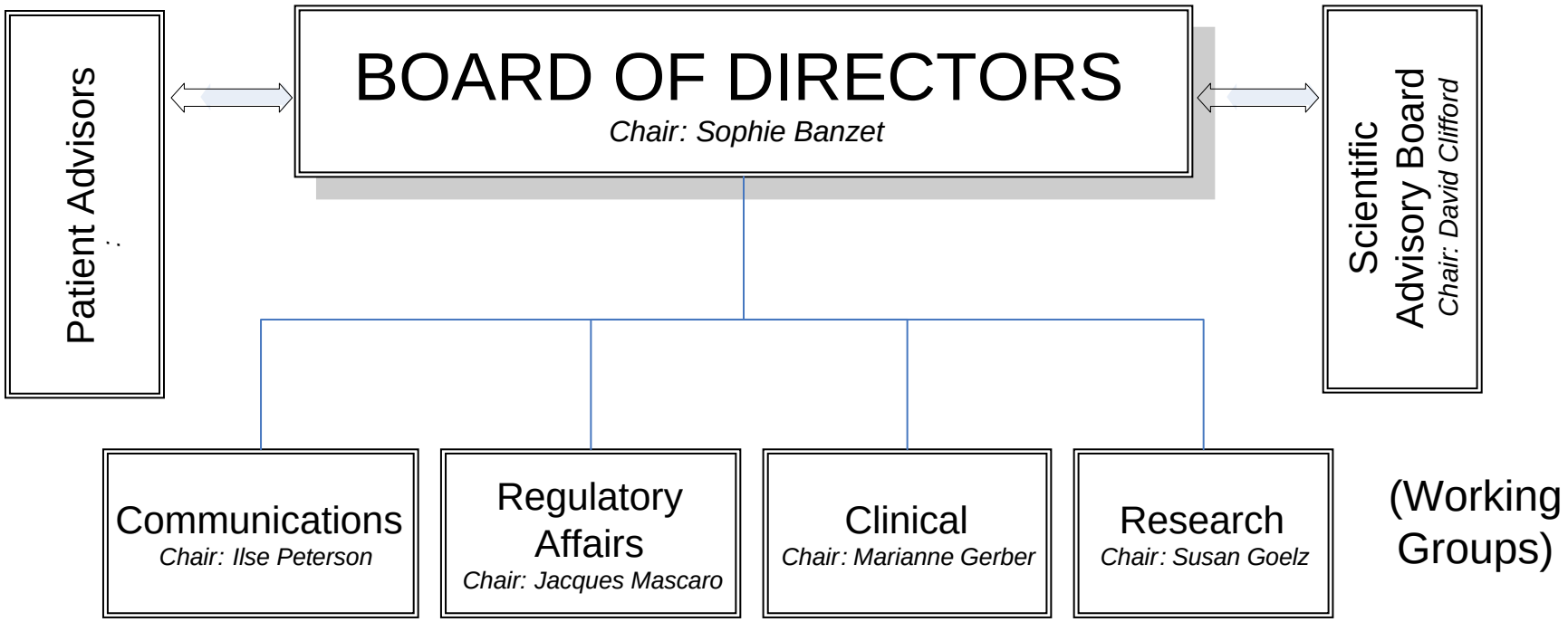
Working Groups Populated

Research activities initiated:

Agreement to fund Academic Collaborative Research Network

Agreement to establish Virtual Sample Bank & Clinical Database

PML Consortium



Secretariat (Drinker Biddle & Reath) provides legal (including antitrust), scientific, project management, and administrative support.

Consortium Advisory Board

Composition

- David Clifford, Chair, Washington University School of Medicine
- Eugene Major, National Institutes of Health
- John Seeger, Harvard Medical School
- Alessandro Sette, La Jolla Institute of Allergy and Immunology
- Kenneth Tyler, University of Colorado School of Medicine
- Thomas Weber, University of Hamburg
- Monica Vinhas, EMA Observer