

Center for Neuroscience and Regenerative Medicine

Programmatic Oversight Committee

August 11, 2010



A Catalyst For Brain Injury Research



CNRM

Director, Dr. Regina Armstrong (USU)
Co-Director, Dr. Walter Koroshetz (NIH)

Administrative
Executive Manager
Corey Hastings (USU)

Henry M. Jackson
Foundation
(Nadine Shewell, Dir PM)

Diagnostics
Smirniotopoulos
Bluemke

Rehabilitation
Pasquina
Chan

Neuroprotection
McCabe
Hallenbeck

**Neuro-
regeneration**
Symes
Frank

Neuroplasticity
Juliano
Grafman

Biomarkers
Cox
Dionne

CNRM External Research Interactions I

Faculty Candidate Visits

Related Research Teams (seminars and/or leadership discussions)

- Claudia Robertson (Mission Connect, Texas consortium)
- Arthur Kellermann and Donald Stein (ProTECT progesterone clinical trials)
- John Russell, Joachim Cohen and George Muschler (AFIRM, Pittsburgh, Rutgers and Cleveland Clinic)
- James Stuhmiller (L-3/Jaycor) (hosted with USU Dept of Surgery)
- Howard Federoff (Georgetown; TBI consortium agreement in process)
- Alan Fadan (UMD Shock Trauma)
- Jim Ecklund (Inova Fairfax)
- Defense Medical and Environmental Research Institute (Singapore)
- DVBIC and NICOE for NCA military effort interactions

Conferences hosted

- CNRM Federal TBI research portfolio conference (Sept 17, 2008)
- CNRM Annual retreat (Apr 19, 2010)
- IBMISPS (May 24-27, 2010) at USUHS (COL Mike Roy, CNRM staffing)

CNRM External Research Interactions II

- **CNRM Director as invited presenter:**
 - HJF Board of Advisors
 - Institute of Medicine Board on Health Sciences Policy
 - HJF Center for Private-Public Partnerships
 - Society for Neuroscience Public Advocacy Forum
- **CNRM Director as invited attendee:**
 - National Football League TBI conference
 - Defense Health Program TBI/PH Portfolio Review
- **Public Engagement Group**
 - In planning
- **Media Interviews**
 - Pentagon Channel, U.S. Medicine magazine, Maryland magazine, NIH CC Newsletter, USU and HJF annual reports

CNRM

Diagnosis and
Imaging

Biomarkers

Neuro-
protection
and Models

Neuro-
Regeneration

Neuro-
Plasticity

Rehabilitation
and
Evaluation

Informatics

Clinical
Biomarkers

Pre-Clinical
Surgery

Neuro-
pathology

Microscopy

Patient
Recruitment

Human
Imaging

Pre-Clinical
Behavior

Patient
Phenotyping

Image
Processing

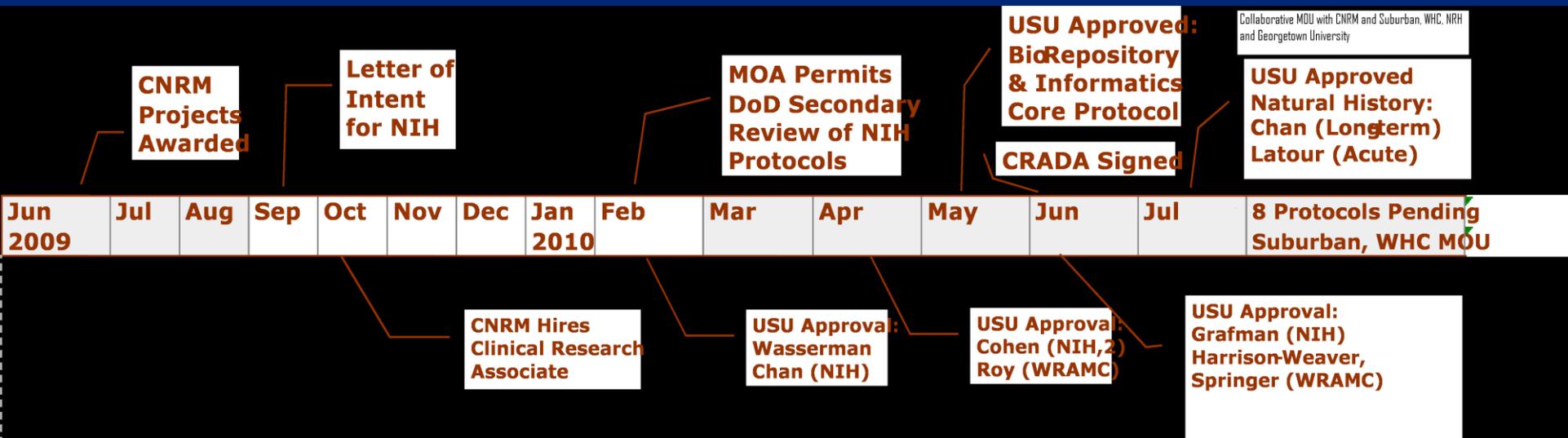
Translational
Imaging

Human Studies in CNRM

The focus of this initiative is an intramural start-up for the study of blast injury to the brain and post traumatic stress by studying actual combat casualties cared for at Walter Reed Army Medical Center and the National Naval Medical Center and using sophisticated neuroimaging technology at the National Institute of Health's Clinical Center.

Clinical Operations & Protocol Development: Timeline

- DOD / NIH MOA signed February, 2010 establishing regulatory framework for DOD review of NIH approved protocols
- Recent progress in protocol approval - 11 USU (Sponsor) approved human use protocols in last 120 days at NIH, WRAMC and USU and agreements underway at Suburban, WHC



CNRM Clinical Core Update

- Three cores support patient studies:
 - Human Imaging, Phenotyping, and Recruitment
 - CNRM core leaders and HJF staff, administrative core, and PIs collaborate on Clinical Operations and Protocol Development
- Three cores providing samples and data processing storage, and analytics:
 - Clinical Biomarkers, Informatics, Image Processing

Human Imaging Core

(PI: Jim Smirniotopoulos, M.D., USU, David Bluemke, M.D., Ph.D, CC/NIH)

The overarching goal of the core is to provide imaging support for basic and translational TBI research.

Components at the NIH Clinical Center

MRI: Siemens Verio 3T scanner (large bore), 32 channel head coil

PET / CT: (Pictured)

MRI / PET: Fully integrated MRI/ PET, 3T

Personnel: two technicians & a senior scientist.



Patient Phenotyping

(PI: Leighton Chan, M.D., CC/NIH, Rehabilitation Program Leader: COL Paul Pasquina, WRAMC)

The phenotyping core is responsible for determining the phenotypic expression of the entire spectrum of TBI, including patients who display evidence of overlap symptoms related to both TBI and PTSD.

- Assessments of the entire spectrum of patients in CNRM studies (natural history/screening protocol)
- Integrate with Cores and Projects
- Active at both NIH & WRAMC



CNRM Renovated Phenotyping Facility at NIH CC

Patient Recruitment

PI: Raymond Dionne, DDS, Ph.D., NINR/NIH

The recruitment core will integrate subject recruitment into one administrative activity, use personnel and resources more effectively and minimize the burden on TBI subjects.

Task Definition

- 25 total military and civilian clinical projects that will require human subjects (estimated 1400 to 2500)
- Two primary means of participating study support:
 - (A) Direct staff support to CNRM studies in recruitment strategy and implementation;
 - (B) A CNRM Recruitment Core database and associated web screening protocol to recruit and pre-screen patients for allocation to CNRM studies

Clinical Biomarkers Core

(Core PI: Raymond Dionne, DDS, Ph.D., NINR/NIH, Repository Protocol PI: Brian Cox, Ph.D., USU)

The purpose of the Clinical Biomarkers Core is the development of a biospecimen repository for the receipt, cataloging, storage and distribution of biospecimens from persons subjected to traumatic brain injury or related conditions, and appropriate control subjects.



CNRM Leased Space & Biorepository - Rockville

Informatics Core

(PI: Yang Fann, Ph.D., NINDS/NIH)

The overarching goal of the Informatics Core is to provide support for basic and translational TBI research to have storage, access, and analysis of data sets generated within CNRM projects.

Milestones

- Protocol establishing de-identified CNRM database approved 5/2010
- Military and civilian electronic data capture systems in user testing phases
- Core Director hired (9/2009) and Steering Cmte Established

Image Processing Core

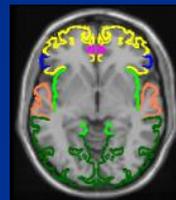
(PI: John Butman, M.D., Ph.D., CC/NIH)

The Image Processing Core will support standardization and processing of imaging data across CNRM projects.

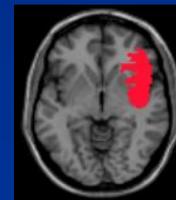
Milestones

- Director, Dr. Dzung Pham, hired 3/2010 with extensive experience in brain image analysis algorithms – establishing faculty status at USU
- Currently testing core developed anonymization software, Extensible Neuroimaging Archive Toolkit and modification of pulse sequences

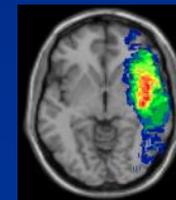
Image Processing Example:
Coregistration across patients and
registration to atlas space



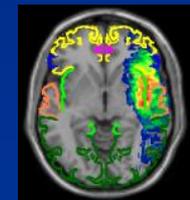
Atlas



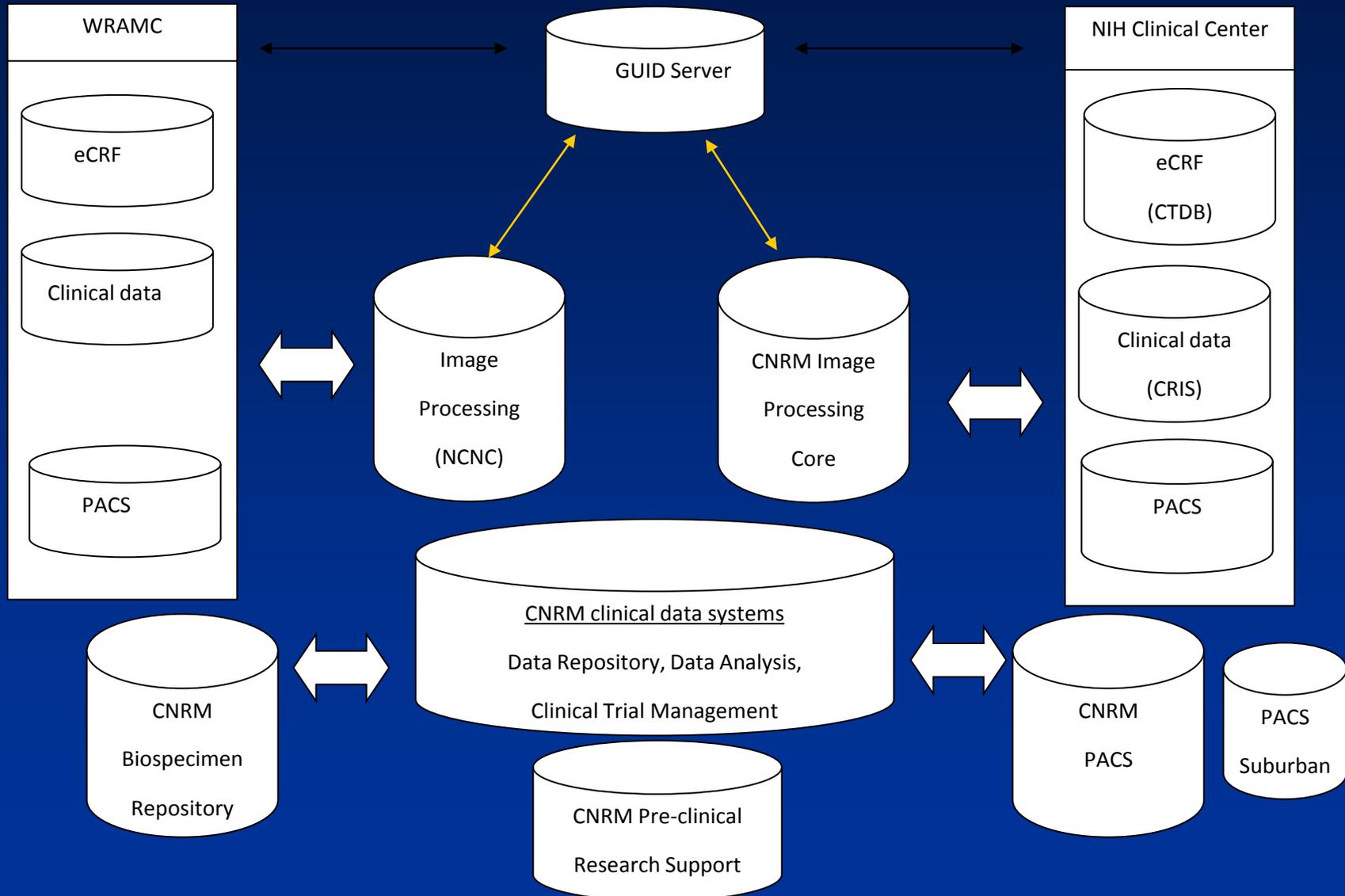
one
patient
lesion



10
patients
lesions



Integrated Clinical, Pre-clinical and Translational Data Management



CNRM Pre-clinical Core Functions - Integrated, Longitudinal Analyses

Behavior

MR/PET/CT

TBI injury

CCI

LFP

HIFU

(BOP)

Behavior

MR/PET/CT

Slice preps:

Electrophysiology

Multiphoton Microscopy

Behavior

MR/PET/CT

Fixed tissues:

Multiphoton Confocal

Stereology

Neuropathology

(rodent-human)

TBI Models in Use

PI: Joe McCabe, Ph.D., USU

- Controlled Cortical Impact - CCI (2 in core; 1 NIH NINDS; 1 NIH NIBIB) - focal and diffuse injury, scalable
- Lateral Fluid Percussion – LFP (1 in core)
 - diffuse axonal injury
- High Intensity Focused Ultrasound – HIFU (1 in core)
 - being developed as primary blast energy wave
- Blast Over Pressure – BOP (WRAIR)
- Several stress models in use across labs
- Repeat injury models being developed

Behavioral Assessments Available

PI: Joe McCabe, Ph.D., USU

- Neurobehavioral scale (forelimb flexion, circling with spontaneous ambulation)
- Open field, Elevated plus maze, Acoustic startle
- Light/dark box, conditioned place preference
- Morris water maze, Barnes maze, Elevated plus maze
- Hole board test
- Sociability chambers, Activity chambers
- Rota-rod
- Beam walk, Parallel rod floor
- Grip strength and wire hanging
- Olfactory habituation/dishabituation
- Saccharin preference test
- Hot/cold plate
- Other assessments – discuss with staff



Translational Imaging

PI: Reed Selwyn Ph.D., USU

- Bruker 7T MRI (20 cm bore)
- MicroPET with MicroCT
- Image Processing



Microscopy/Neuropathology

PI: Sharon Juliano, Ph.D., USU/ Regina Armstrong, Ph.D. USU

- Multiphoton confocal with electrophysiology
- Histology processes (paraffin, stains)
- Slide digitizing (USU and AFIP)
- Unbiased stereological quantification



CNRM – Building a Center Culture

1. Small group **internal discussions** within Programs.
2. Directors/Leaders serving as “**Research Navigators**” to foster science connections.
3. Programs to host **outside high profile speakers** to present seminars and participate in group discussions of targeted research topics of interest across CNRM Programs.
 - Dr. Arnold Kriegstein will be hosted by Neuroregeneration
4. Access to CNRM **core research resources**
5. Structure of CNRM **funding opportunities** (fellowships, collaborative projects)
6. Infrastructure to develop **external research opportunities** (collaborative grant submissions, commercial interactions, academic and private partnerships)