The John A. Moran Eye Center 2011 Visualizing Vision
John A. Moran Eye Center Research Areas

- Molecular Disease Mechanisms
- Cellular Disease Mechanisms
- Systems Disease Mechanisms
- Translational science
- Molecular Therapeutics
- Systems Therapeutics
• The Vision Institute
• 21 NIH grants (18 JMEC, Vision Core)
• 20 research investigators (16 JMEC)
• New commercialization ventures
• New therapeutic ventures
Macular Disease

- Gregory Hageman
  John Moran Presidential Professor
  Director, Center for Translational Research
  Immune disease and AMD

- Margaret DeAngelis
  Associate Professor of Ophthalmology
  AMD Genetics

- Mary Elizabeth Hartnett
  Professor of Ophthalmology
  Angiogenesis, ROP & AMD

- Yingbin Fu
  Assistant Professor of Ophthalmology
  Animal Models of AMD
Monica Vetter
Adjunct Professor of Ophthalmology
George & Lorna Winder Professor of Neuroscience
Chair of Neurobiology & Anatomy
Retinogenesis & glaucoma

Edward M. Levine
Associate Professor of Ophthalmology
Retinal neurogenesis

Chi-Bin Chien
Adjunct Professor of Ophthalmology
Retinal pathfinding in the brain

Sabine Fuhrmann
Associate Professor of Ophthalmology
Ocular & RPE histogenesis
Vision & Disease
Sunlight
Spectral Light

- **Radio** (> 1 m)
- **Microwave** (10 mm)
- **Infrared** (1 μm)
- **Visible** (700-400 nm)
- **Ultraviolet** (100 nm)
- **X-ray** (1 nm)
- **γ Ray** (10 pm)

- "hot light" breaks molecules
- "soft light" moves electrons
- "hard light" breaks atomic bonds

Amaj add 6
Light Switches
Light Switches

OFF

ON

Light Switches
Photoreceptors

Diagram showing anatomical structures labeled with abbreviations: r, ro, cos, el, my, OLM, k, c, sp, ax, ped.
The Challenge of Wiring
Vision by day and night
The Retinal Sensor Array
The Retinal Processor Array
Wiring is too complex for conventional neurobiology.

The relatively simple human retina contains ≈70 kinds of neurons, each with at least 10 different partners.

Over 397 billion unique networks could be built from this collection of cells.

Analyzing them all to find the right one would take over 1 billion years. Analyzing only 1% would take 10 million years.

How can we discover the true wiring of the retina? The new technology of connectomics.
Interlude
Scientific Genealogy
THE GENEALOGY OF THE MARC LAB

21st Century

11th Century

The Genealogy of the Marc Lab
All of these scientific endeavors were “solo”

After 9 centuries, science has changed at last

Collaborations and alliances are critical to future advances
Connectomics is too complex for one lab
THE RETINAL CONNECTOME COLLABORATION

University of Utah, John A. Moran Eye Center: Marc, Jones
University of Utah, SCI Institute: Whitaker, Tasdizen
University of Colorado / Boulder: Mastronarde
University California / Santa Barbara: Manjunath, Fisher, Lewis
University of Texas / Houston: Marshak
Japan Electron-Optical Ltd, Tokyo, Japan
THE UTAH RETINAL CONNECTOME
Building Real Networks

Robert Marc
Scott Laurizten
Carl Watt
Bryan Jones
Shoeb Mohammed
James Anderson

Moran Eye Center
University of Utah

Disclosure
REM is a principal of
Signature Immunologics, Inc.

NIH EY02576, EY015128, EY14800
NIH EB005832, NSF 0941717
Signature Immunologics
The Thome Foundation
Research to Prevent Blindness
A connectome is a complete diagram of a neural system.
**Connectomics Methods**

**Harvest**
- Section Volume:
  - 401 sections
  - 370 data sections
  - 342 TEM sections
  - 28 CMP sections

**Synaptic imaging**
- 2.18 nm resolution
- SerialEM
- 5000 tiles/day
- Storage ≈ 50TB

**CMP: N-dimensional molecular tagging**
- AGB
- asp
- glu
- gly
- GTH
- gln
- arg
- tau
- GABA

**Autobuild**
**IRIS transforms**

**Navigate & Annotate**
- **Viking**
- Browser
- HTTP
- WSDL
- XML data
- SQL
CONNECTOMICS METHODS

Visualize
- TEM overview
- TEM synaptic view

Mine
- Circuit Viz: Adjacency Matrix
- Structure Viz: Statistics & Topology
Connectome Economics

Drive Capacity per $US

- 10 GB
- 1 GB
- 100 MB
- 10 MB
- 1 MB
- 100 KB
- 10 KB
- 1 KB

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First consumer terabyte drive
Now you can get our disk systems within 30 days ARO at the industry's lowest prices:

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Sunnyvale, California 94086
(408) 732-1600, Fax 546-658

* OEM prices 40-69 systems.
Connectomes
AII CROSSOVER
> 50 crossover subnetworks involve the AII cell

AII :: CROSSOVER
AII :: LONG CONTROL LOOPS :: AI CELLS

AII AC 476
AI AC 591

ribbon

gap junction

wf cBC 491

1000 nm
Biomorphic Networks
The future of computing
Blindness is too complex for one lab
THE RP THERAPEUTICS COLLABORATION

University of Utah: Marc, Jones, Baehr, Krizaj, Tian
Nagoya University, Japan: Kondo
University of Southern California: Sampath
University of Houston: Frishman
EOS Corporation, Los Angeles, CA: Horsager
Spiral Genomics, Berkeley, CA: Greenberg
Retinal Remodeling in the Tg P347L Rabbit, a Large-Eye Model of Retinal Degeneration

Jones, Kondo, Terasaki, Watt, Rapp, Anderson, Lin, Shaw, Yang, & Marc  JCN 2011

NIH EY015128, NIH EY02576, NIH EY014800, RPB (2), Thome Memorial Foundation, Moran Tiger Team Translational Medicine Award & the Ministry of Health, Labor and Welfare, Japan
Optogenetics

Inserting light sensitive genes into cells
CONE NETWORK

- Layer 1: photoreceptors
- Layer 2: bipolar cells
- Layer 3: bipolar-amacrine networks
- Layer 3: ganglion cells
CONE NETWORK + RODS

Layer 1 photoreceptors

Layer 2 bipolar cells

Layer 3 bipolar-amacrine networks

Layer 3 ganglion cells

r

S

color

hue

pupil

OFF blue

ON blue

OFF alpha

OFF beta

ON-OFF DS

ON DS

LED

ON beta

square

delay

bandpass

motion

contrast

pitch-yaw

roll

edges

contrast

fast

slow

wide

narrow

narrow

wide

slow

fast

La yer 1 photoreceptors

La yer 2 bipolar cells

La yer 3 bipolar-amacrine networks

La yer 3 ganglion cells

r

S

FULL ROD CONE NETWORK

Layer 1.5 AII amacrine cells
Layer 1 photoreceptors
Layer 2 bipolar cells
Layer 3 bipolar-amacrine networks
Layer 3 ganglion cells
RETNITIS PIGMENTOSA

Layer 1.5
AII amacrine cells

Layer 2
bipolar cells

Layer 3
bipolar-amacrine networks

Layer 3
ganglion cells
OPTOGENETICS TARGETS    GANGLION CELLS

Layer 1.5 AII amacrine cells
Layer 2 bipolar cells
Layer 3 bipolar-amacrine networks
Layer 3 ganglion cells

AII AC

motion pitch-yaw roll

fast slow wide narrow narrow wide slow fast

delay

square bandpass


OFF alpha OFF beta ON-OFF DS ON DS LED ON beta

hue pupil

OFF blue ON blue
OPTOGENETICS TARGETS ON BIPOLAR CELLS

Layer 1.5 AII amacrine cells

Layer 2 bipolar cells

Layer 3 bipolar-amacrine networks

Layer 3 ganglion cells
OPTOGENETICS TARGETS  AII AMACRINE CELLS

Layer 1.5
AII amacrine cells

Layer 2
bipolar cells

Layer 3
bipolar-amacrine networks

Layer 3
ganglion cells

- Hue
- Pupil
- Motion
- Contrast
- Pitch-yaw
- Roll
- Edges
- Contrast

Off
- Blue

On
- Blue

Off
- Alpha

Off
- Beta

On-Off
- DS

On
- DS

LED
- On

Beta
- On

Blue
- Off

Alpha
- Off
University of Utah: Marc, Jones, Baehr, Krizaj, Tian
Nagoya University, Japan: Kondo
University of Southern California: Sampath
University of Houston: Frishman
EOS Corporation, Los Angeles, CA: Horsager
Spiral Genomics, Berkeley, CA: Greenberg