LASKER/IRRF
Initiative for Innovation in Vision Science

2012
JANELIA FARM RESEARCH CAMPUS
HOWARD HUGHES MEDICAL INSTITUTE
The second Lasker/IRRF Initiative convened at the Janelia Farm Research Campus of the Howard Hughes Medical Institute in Ashburn, VA and consisted of formal presentations by newly invited speakers on new projects, ideas or collaborations, and target sessions. Additional presentations by Paul Sieving, M.D., Ph.D., of the National Eye Institute and Nelson Spruston, Jr., Ph.D., Scientific Program Director and Group Leader of the Janelia Farm Research Campus were also highlights of the meeting.

A special presentation was given by Lloyd M. Aiello, M.D., who attended a historic meeting almost 50 years ago at the Airlie House in Warrenton, VA. He was part of a group of distinguished experts from all over the world who convened for a Symposium on the Treatment of Diabetic Retinopathy. Organized by the U.S. Public Health Service, it was considered innovative for the time. Several initiatives came from that meeting including a standard system for classifying diabetic retinopathy based on severity and extent of the lesions – which has been modified over the years. It also opened doors for treatment by laser photocoagulation. These ground-breaking ideas led to several clinical trials concerning the diagnosis and treatment of diabetic retinopathy during the next two decades.

Dr. Lloyd M. Aiello presented an overview of the changes that have taken place in the field of diabetic retinopathy since that meeting, while Lloyd P. Aiello, M.D., Ph.D., spoke about changes in diabetic eye care since 1990 and emphasized the role of laser photocoagulation and VEGF.
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Keynote Speakers

Airlie House

Robert N. Frank, Keynote Speaker
Lloyd M. Aiello, Keynote Speaker
Lloyd P. Aiello, Keynote Speaker
Larry A. Donoso
The Airlie Conference Center consisting of the Airlie House and Environmental Studies celebrated fifty years in 2011. The Center was established as an Island of Thought, much like the Lasker/IRRF Initiative. It was founded by Dr. Murdock Head and has been the home to many other national and international meetings of historic significance. Its first conference, Challenge for the Minds of Men, laid the groundwork for many actions as the Civil Rights Movement,
The Doctors Aiello and Beetham: One Family and the History for the Treatment of Diabetic Retinopathy

Introduction by Bob Frank

Lloyd M. Aiello presented a comprehensive review on the history of diabetes spanning some 3,500 years. The discovery of insulin in 1921 by Banting and Best made it a disease you could live with. The Airlie House meeting in 1968 set new standards to reach and was the forerunner of clinical trials which led to outcomes as basis for evaluating clinical medical care including laser photocoagulation. Based on these foundations by many leading experts in the field, pituitary ablation as a treatment was essentially stopped; visual prognosis after pregnancy in patients with diabetic retinopathy was significantly enhanced. Overall, the treatment of this condition from these beginnings showed extraordinary results. As M. Aiello put it - Standing on the shoulders of giants included many famous ophthalmologists, whom we all know, but the real giants were the participants in research and study coordinators.

“By 2030, in order to evaluate one diabetic patient per year almost 5 Million eyes per day will need to be evaluated!”

Lloyd P. Aiello spoke about changes from 1990 onward with a focus not only on new therapies including anti-growth factors and angiogenesis, but also the staggering economies of scale. By 2030 there will be approximately 450 million diabetics worldwide. He emphasized the need for the awareness of the condition, optimized therapies, risk assessment, networks, multidisciplinary approaches and new drugs to treat the condition that may be individualized and based on predictable risk factors known at the time of the clinical examination.

White House Conference on Mental Retardation in conjunction with the Kennedy Foundation, the North Atlantic Treaty Organization and the United Nations Educational, Scientific and Cultural Organization) and the American College of Surgeons. It also established the Statesmen in Medicine Award. In 1968 it hosted the Symposium on Diabetic Retinopathy. (Breanna Detwiler of the Airlie Center provided archival material including photographs of the Airlie House circa 1968.)
A Unity of Purpose…


Keynote Speakers
Moderator – Bob Frank
Lloyd M. Aiello
The road traveled with Airlie colleagues and patients: Beyond blindness - our memories are our realities.

Lloyd P. Aiello
Following in their footsteps: The road from laser to VEGF, and beyond - how the past quarter century may inform the next.

SESSION 1
Moderator - Bob Frank
Alan Bird
Diabetic retinopathy in the absence of ischaemia.

Robert A. Linsenmeier
Some gaps in understanding the elevation of VEGF.

Donald G. Puro
Role of microvascular ion channels.

Bruce A. Berkowitz
Translational imaging of diabetes-evoked retinal cell pathobiology in vivo.

SESSION 2
Moderator – Lloyd P. Aiello
Tim Kern
New approaches to understand diabetic retinopathy.

Usha Chakravarthy
Diabetic macular edema - is it a different entity to diabetic retinopathy?

Arup Das
Diabetic macular edema - potential targets beyond VEGF.

SESSION 3
Moderator - Tony Adamis
Tom Gardner
Diabetic retinopathy - a rose by any other name.

Marcus Bease, Jr.
Neuroretinal dysfunction predicting clinical retinopathy.
Gregory Jackson
A framework for the validation of a clinical trial endpoint for non-proliferative diabetic retinopathy.

SESSION 4
Moderator - Usha Chakravarthy
David Hicks
Diet-induced diabetic retinopathy in a diurnal cone-rich rodent.

Paula Dore-Duffy
Role of the pericyte on brain microvascular function.

SESSION 5
Moderator – John Dowling
Tim Kern and Kris Palczewski
Role of photoreceptors in the pathogenesis of diabetic retinopathy.

Tailoi Chan-Ling, Susanne Mohr, Steve Abcouwer, and Maria Grant
CCR2+ monocytes in the pathogenesis of diabetic retinopathy.

Special Presentation
Paul Sieving
Research update of the National Eye Institute.

Airlie House, front (top) and rear (right) views.
### Targeted Sessions

#### TS1 Role of Glucose and Oxygen

**Co-Chairs Tim Kern and Jena Steinle**

- Abouver
- Arden
- Connaughton
- D'Amore
- Hammes
- Kowluru

**GOALS**

1. Characterize what pathology constitutes early DR in T1DM and T2DM to explain discrepancy in outcomes for the same pathological processes.
2. Provide input into time points needed for relevant comparisons to be made to test hypotheses in animal models.
3. Develop animal models to explain role of oxygen in DR and the mechanism of beneficial oxygen therapy and laser photocoagulation effects in patients.
4. Determine if glucose is sufficient to explain observed pathology in DR or lipids/fatty acids involved to explain why DR can continue to progress even when glucose is under good control.

#### TS2 Early Signs of Diabetic Retinopathy

**Co-Chairs Tom Gardner and Francesca Cordeiro**

- Caldwell
- Chan-Ling
- Friedlander
- Fujimoto
- Hicks
- Klein, B

**GOALS**

2. Obtain natural histories of young diabetics who do not have comorbidities that could confound the clinical picture.
3. Determine the earliest change(s) induced by diabetes.
4. Determine if any early changes are useful as sensitive markers of disease progression.
5. Determine if retinal dysfunction is the result of several events occurring in parallel or a single event driving the other events.
6. Determine the early adaptive response in diabetes useful in slowing the progression of diabetic retinopathy.

#### TS3 Genetics and Environmental Susceptibility

**Co-Chairs Usha Chakravarthy - Susanne Mohr**

- Bird
- Busik
- Donoso
- Dore-Duffy
- Frank
- Grant
- Iyengar

- King
- Klein, R
- Puro
- Shima
- Swaroop
- Scribe: George Murphy

**GOALS**

1. Critically review the role of genetics in the development and progression of DR.
2. How can clinical DR phenotypes potentially mask genetic associations.
3. What is the current knowledge on environment and epigenetic factors in the development of DR.
4. Formulate short to medium term research themes.
5. Investigate existing promising genetic markers in DR.

#### TS4 Present and Proposed Approaches

**Co-Chairs Lloyd P. Aiello and Jennifer Sun**

- Adamis
- Bearse
- Berkowitz
- Chew
- Das
- Duh

- Fitzke
- Jackson
- Palczewski
- Sadda
- Smith
- Scribe: John Lillvis

**GOALS**

1. Develop safe therapies with expanded efficacy.
2. Scalable to larger populations and amenable to underserved populations.
3. Minimally or non-invasive, and inexpensive.
4. Improved and shorter prediction of clinical validation.
5. Target more fundamental mechanisms.
6. Longer duration of action and easily administered.
Where Have We Been? What Do We Need To Do? How Do We Get There?

**TS5 Pathogenesis**

**Co-Chairs Tony Adamis and David Shima**

- Abcouwer
- Aiello
- Berkowitz
- Caldwell
- Chakravarthy
- Das
- Kern
- Mohr
- Penn
- Schlingemann
- Zhang
- Scribe: Alex Veenstra

**GOALS**

1. Establish differences between patients who respond to VEGF therapy in several doses and those that do not. Limit genetic analysis to inflammation.
2. Determine if edema is intercellular or extracellular.
3. Extend data on VEGF concentrations in animal models past 3 months.
4. Request access to data from companies testing novel compounds for other indications to determine if there is an effect on DR in a subset of participants that are diabetic.
5. Compare treatment of peripheral edema with different anti-VEGF compounds regarding neural damage.

**TS6 Diagnostic Methods**

**Co-Chairs Larry A. Donoso and James Fujimoto**

- Bearse
- Berkowitz
- Chan-Ling
- Connaughton
- Cordeiro
- Gardner
- Hicks
- Jackson
- Linskemeier
- Lorenti
- Max Stem-Presenter
- Penn
- Palczewski
- Puro
- Steinle
- Stitt
- Zhuo
- John Lillvis-Presenter

**GOALS**

1. Develop structural and functional imaging techniques that can be applied in vivo to animal models and can potentially be translated to humans.
2. Develop and validate new tests of visual structure and function tests that can detect early neovascularization that look outside the fovea (moving away from acuity). Functional mapping correlation to imaging results.
3. Create 2 to 5 clinical testing sites with standardized tests to conduct cross-sectional and longitudinal studies of patients with early stage diabetes (T1DM).

**TS7 Epidemiology and Unusual Cohorts**

**Co-Chairs Barbara Klein and Julia Busik**

- Arden
- Bird
- Chew
- Iyengar
- King
- Klein, R
- Ma
- Sadda
- Smith
- Sun
- George Murphy-Presenter

**GOALS**

1. Examine accepted and novel risk factors for retinopathy/macular edema in inception cohorts of Type1 and Type2. Include interaction of environmental/personal risk factors. Possible interactions with genetic risk factors.
2. Investigate new risk factors and interactions with known risk factors over time in established cohorts.
3. Collaboration/consortium with existing cohorts to examine uncommon exposures and therapeutic regimens on changes in incidence/progression of retinopathy and macular edema.
4. Examine unique cohorts including patients with bariatric surgery; extreme calorie restriction; for protection of disease and patients with retinal degenerations to investigate role of decreased oxidant environment on disease progression.

**TS8 Vascular and Retinal Repair**

**Co-Chairs Bob Frank and Renu Kowluru**

- D'Amore
- Dore-Duffy
- Duh
- Friedlander
- Lutty
- Hammes
- Grant
- Palczewski
- Puro
- Steinle
- Stitt
- Zhuo
- John Lillvis-Presenter

**GOALS**

1. Further evaluate the advantages and disadvantages of the various animal models of DR and how they can be exploited for maximal relevance to human DR.
2. Explore more fully the changes seen in the Psammomys obesus rodent model of DR regarding relevance to other forms of retinal degenerations including humans.
3. Further define the role of pericytes as targets for the treatment of DR.
AT THIS YEAR’S INITIATIVE four scribes were present. Scribes are researchers in training who show exceptional ability to analyze and understand research related to the eye while at the same time continue to work on advanced degrees related to Vision Science. The Scribes are an important part of the Initiative and their involvement is greatly appreciated by all.

John Lillvis is an M.D.-Ph.D. student at Wayne State University School of Medicine. Max Stem, M.D. is a research fellow at the W.K. Kellogg Eye Center in Ann Arbor, Michigan. Alex Veenstra is a graduate student at Case Western Reserve University in Cleveland, OH. George Murphy is a medical student at the Queen’s University in Belfast, Northern Ireland.

SPECIAL PRESENTATION

Nelson Spruston, Ph.D.
HHMI Janelia Farm Research Campus

Nelson Spruston, Ph.D., the Scientific Program Director and a Group Leader of the Janelia Farm Research Campus, described the internal workings of the Campus. He emphasized how projects are undertaken by a small group of scientists who collaborate and interface with other small groups that are necessary to complete the project, including investigators from outside the Janelia Campus. The aims and groups can shift as necessary in order to best achieve the objectives of the goal. It is a multidisciplinary concept reminiscent of the approach taken by the Lasker/IRRF Initiative.

Spruston's main interest is in neural circuits and how it relates to memory. Specifically he is involved in unraveling how single dendritic cells receive, process and transmit signals to other cells. It is not a simple process since this complex "internet" may be involved with many thousands of inputs to unravel and transmit. Ultimately it is all aimed at understanding cognition and behavior and how it relates to memory.
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Kate Chapman, Project Manager

Invited Guest
Paul Sieving, M.D., Ph.D.
National Eye Institute

Observer
Teresa L.Z. Jones, M.D.
National Institute of Diabetes and Digestive and Kidney Disease

Scribes
John Lillvis
George Murphy
Max Stern, M.D.
Alex Veenstra
The meeting at Janelia Farm was nothing short of amazing. I typically leave a small meeting with one or two legitimate action items that may or may not lead to new experiments. Over the last three days, I wrote down so many ideas for new projects I eventually quit counting them. I also initiated two new collaborations with other attendees...all of these things aimed at the goals that came from the final session. In my view, this is the way to move the field forward...with deliberation from the outset and with guiding information about where there is or isn’t consensus thinking. Thank you so much for your roles in developing the program and format and in managing the discussion.

...the concept of this meeting was to bring together a diverse group of scientists who would address research related to the retina from many different perspectives. I believe this is one of the best meetings of this kind anywhere.

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