

The NHGRI Intramural Research Program

Dan Kastner, MD, PhD

NHGRI/NIH/DHHS

February 10, 2014

Overview

- Intramural Research at the NIH
- NHGRI Intramural Vision
- NHGRI Intramural Faculty and Organization
- Scientific Accomplishments
- Evaluating NHGRI Intramural Science
 - Blue Ribbon Panel Review, 2011-12
 - Board of Scientific Counselors (BSC)
- Budget
- New Initiatives

Distinctive Features of Intramural NIH

- Institutional commitment to researchers over projects
- Quadrennial heavily retrospective review
- Long-term studies that require stable funding
- High-risk, high-reward projects that would be difficult to do with R01 funding
- Critical mass in certain areas
- Ability to “turn on a dime”
- Intellectual home for Institute Directors and extramural program staff
- Proximity to the seat of government
- Specialized resources

The NIH Clinical Center

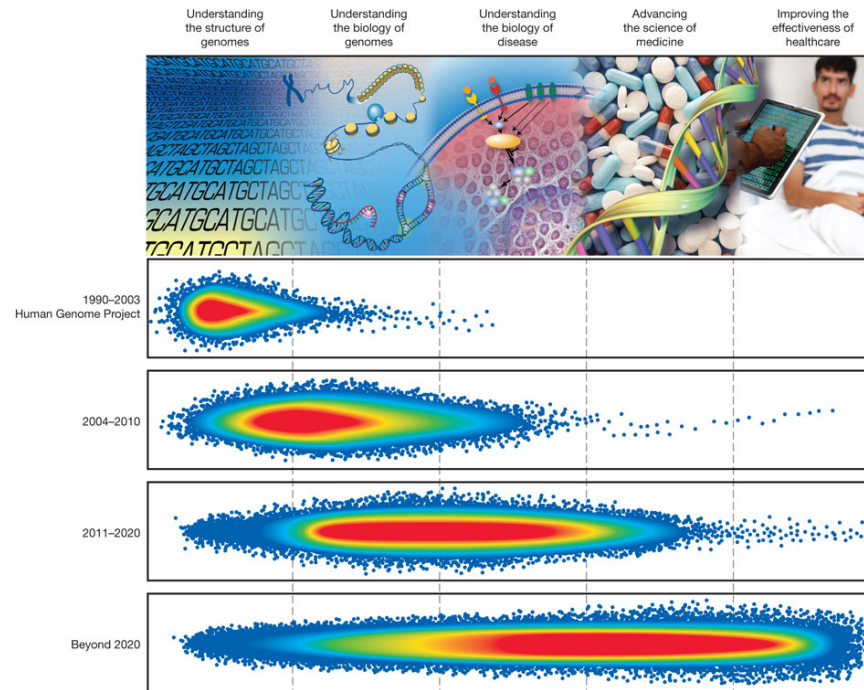


NHGRI IRP 101

NHGRI Intramural Vision Statement (2012)

- To lead the way on the NIH campus in genetics, genomics, pathophysiology, and treatment of human disease, fostering a deeper understanding of human biology
- To conduct transformative science
- To develop collaborations among basic, clinical, and social/behavioral scientists
- To take full advantage of the intramural environment
- To catalyze change across the NIH campus

Schematic representation of accomplishments across five domains of genomics research

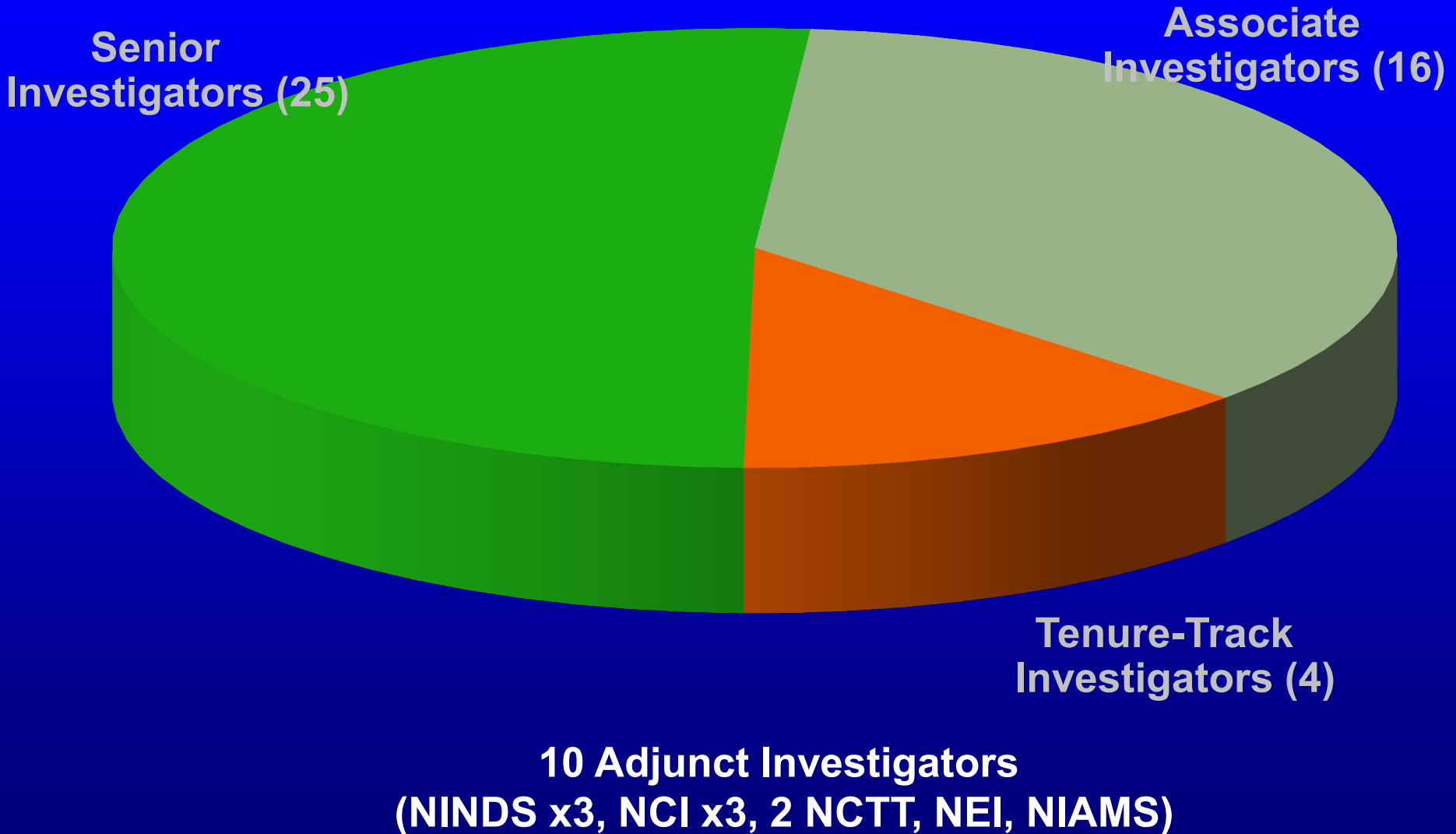


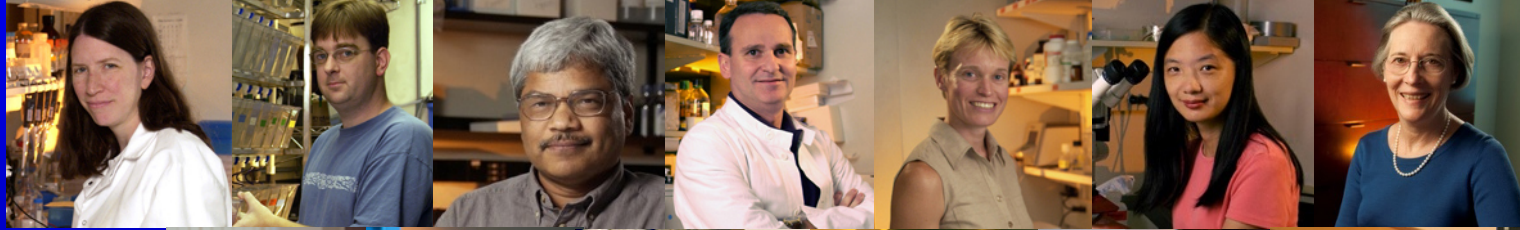
E D. Green *et al. Nature* **470**, 204-213 (2011) doi:10.1038/nature09764

nature

NHGRI Intramural Investigators

45 Investigators ('Research Faculty')





Faculty Comings and Goings

Gary Gibbons, M.D.
Director, NHLBI



Yardena Samuels, Ph.D.
Weizmann Institute,
Rehovot



2013 NHGRI Intramural Reorganization

- Goals
 - Scientific synergy
 - Career advancement
 - Succession planning
 - Genome Technology Branch reassignments with the promotion of Larry Brody to Division Director
- Three new Branches/Chiefs: Julie Segre, Pam Schwartzberg, Charles Rotimi
- Clearer delineation of the role of the Branch Chief
- Expanded Intramural Leadership Group

NHGRI Cores

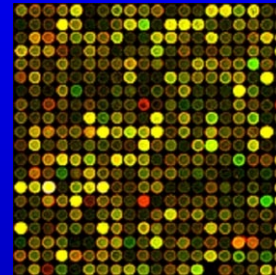
**Bioethics
Core**



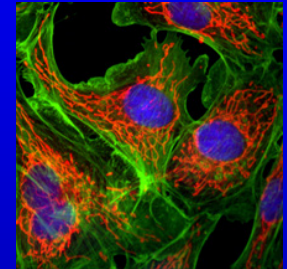
**Bioinformatics & Scientific
Programming Core**



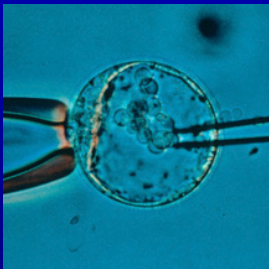
**Microarray
Core**



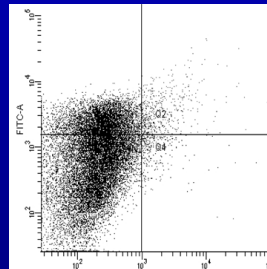
**Cytogenetics &
Microscopy Core**



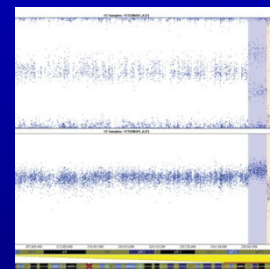
**Embryonic Stem Cell
& Transgenic Mouse Core**



**Flow Cytometry
Core**



**Genomics
Core**



**Zebrafish
Core**



NISC

- Midsized genome-sequencing center that provides next-generation DNA sequencing and sequence analysis
- Total budget ~\$7M
- Jim Mullikin, Director; staff of 36
- 1 HiSeq 2500, 4 HiSeq 2000, 3 MiSeq, 2 Roche 454, 2 Ion Torrent
- 2013: 45 Tb HiSeq output for 55 PI's in 11 Institutes

Undiagnosed Diseases Program (UDP)

- Trans-NIH Intramural initiative established (in 2008) by Bill Gahl (NHGRI Clinical Director)
- Patients with seemingly inexplicable conditions referred from throughout the US
- Comprehensive clinical and molecular genetic analysis for those patients accepted into the Program
- Discovery of heretofore unknown molecular lesions defining new genetic diseases
- Basis for the Undiagnosed Diseases Network of the Common Fund

ORIGINAL ARTICLE

A Congenital Neutrophil Defect Syndrome Associated with Mutations in *VPS45*

Thierry Vilboux, Ph.D., Atar Lev, M.Sc., May Christine V. Malicdan, M.D., Ph.D.,
Amos J. Simon, B.Sc., Päivi Järvinen, Ph.D., Tomas Racek, Ph.D., Jacek Puchalka, Ph.D.,
Raman Sood, Ph.D., Blake Carrington, B.Sc., Kevin Bishop, B.Sc.,
James Mullikin, Ph.D., Marjan Huizing, Ph.D., Ben Zion Garty, M.D., Eran Eyal, Ph.D.,
Baruch Wolach, M.D., Ronit Gavrieli, M.Sc., Amos Toren, M.D., Ph.D.,
Michalle Soudack, M.D., Osama M. Atawneh, M.D., Tatiana Babushkin, Ph.D.,
Ginette Schiby, M.D., Andrew Cullinane, Ph.D., Camila Avivi, Ph.D.,
Sylvie Polak-Charcon, Ph.D., Iris Barshack, M.D., Ninette Amariglio, Ph.D.,
Gideon Rechavi, M.D., Ph.D., Jutte van der Werff ten Bosch, M.D., Ph.D.,
Yair Anikster, M.D., Ph.D., Christoph Klein, M.D., Ph.D.,
William A. Gahl, M.D., Ph.D., and Raz Somech, M.D., Ph.D.

Opinion

VIEWPOINT

Reporting Genomic Sequencing Results
to Ordering Clinicians
Incidental, but Not Exceptional

Topographic diversity of fungal and bacterial communities in human skin

Keisha Findley¹, Julia Oh¹, Joy Yang¹, Sean Conlan¹, Clayton Deming¹, Jennifer A. Meyer¹, Deborah Schoenfeld², Effie Nomicos², Morgan Park³, NIH Intramural Sequencing Center Comparative Sequencing Program†, Heidi H. Kong^{2*} & Julia A. Segre^{1*}



Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110 δ result in T cell senescence and human immunodeficiency

Carrie L Lucas^{1,15}, Hye Sun Kuehn^{2,15}, Fang Zhao^{3,4,15}, Julie E Niemela², Elissa K Deenick^{5,6}, Umaimainthan Palendira^{5,6}, Danielle T Avery⁵, Leen Moens⁵, Jennifer L Cannons³, Matthew Biancalana¹, Jennifer Stoddard², Weiming Ouyang⁷, David M Frucht⁷, V Koneti Rao¹, T Prescott Atkinson⁸, Anahita Agharahimi^{9,10}, Ashleigh A Hussey⁹, Les R Folio¹¹, Kenneth N Olivier⁹, Thomas A Fleisher², Stefania Pittaluga¹², Steven M Holland⁹, Jeffrey I Cohen¹³, Joao B Oliveira¹⁴, Stuart G Tangye^{5,6}, Pamela L Schwartzberg³, Michael J Lenardo¹ & Gulbu Uzel⁹

ARTICLES

nature
medicine

Activation of Hedgehog signaling by loss of *GNAS* causes heterotopic ossification

Jean B Regard^{1,7}, Deepti Malhotra^{1,7}, Jelena Gvozdenovic-Jeremic¹, Michelle Josey¹, Min Chen², Lee S Weinstein², Jianming Lu³, Eileen M Shore^{4,5}, Frederick S Kaplan^{4,6} & Yingzi Yang¹

Genome-wide meta-analyses of multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia

LETTERS

A genome-wide association study identifies susceptibility loci for nonsyndromic sagittal craniosynostosis near *BMP2* and within *BBS9*

Cristina M Justice^{1,24}, Garima Yagnik^{2,24}, Yoonhee Kim¹, Inga Peter³, Ethylin Wang Jabs³, Monica Erazo³, Xiaoqian Ye³, Edmond Ainehsazan³, Lisong Shi³, Michael L Cunningham⁴, Virginia Kimonis⁵, Tony Roscioli⁶, Steven A Wall⁷, Andrew O M Wilkie^{7,8}, Joan Stoler⁹, Joan T Richtsmeier¹⁰, Yann Heuzé¹⁰, Pedro A Sanchez-Lara¹¹, Michael F Buckley¹², Charlotte M Druschel¹³, James L Mills¹⁴, Michele Caggana¹⁵, Paul A Romitti¹⁶, Denise M Kay¹⁵, Craig Senders¹⁷, Peter J Taub¹⁸, Ophir D Klein¹⁹⁻²¹, James Boggan²², Marike Zwienenberg-Lee²², Cyrill Naydenov²³, Jinho Kim², Alexander F Wilson¹ & Simeon A Boyadjiev²

A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry

RESEARCH ARTICLE SUMMARY

Integrative Annotation of Variants from 1092 Humans: Application to Cancer Genomics

Ekta Khurana, Yao Fu, Vincenza Colonna, Xinmeng Jasmine Mu, Hyun Min Kang, Tuuli Lappalainen, Andrea Sboner, Lucas Lochovsky, Jieming Chen, Arif Harmanci, Jishnu Das, Alexej Abyzov, Suganthi Balasubramanian, Kathryn Beal, Dimple Chakravarty, Daniel Challis, Yuan Chen, Declan Clarke, Laura Clarke, Fiona Cunningham, Uday S. Evani, Paul Flicek, Robert Fragoza, Erik Garrison, Richard Gibbs, Zeynep H. Gümüş, Javier Herrero, Naoki Kitabayashi, Yong Kong, Kasper Lage, Vaja Liluashvili, Steven M. Lipkin, Daniel G. MacArthur, Gabor Marth, Donna Muzny, Tune H. Pers, Graham R. S. Ritchie, Jeffrey A. Rosenfeld, Cristina Sisu, Xiaomu Wei, Michael Wilson, Yali Xue, Fuli Yu, 1000 Genomes Project Consortium, Emmanouil T. Dermitzakis, Haiyuan Yu, Mark A. Rubin, Chris Tyler-Smith,* Mark Gerstein*

Targeting proximal tubule mitochondrial dysfunction attenuates the renal disease of methylmalonic acidemia

Irini Manoli^{a,1}, Justin R. Sysol^{a,1}, Lingli Li^b, Pascal Houillier^{b,c}, Caterina Garone^{d,e}, Cindy Wang^a, Patricia M. Zerfas^f, Kristina Cusmano-Ozog^g, Sarah Young^h, Niraj S. Trivediⁱ, Jun Cheng^j, Jennifer L. Sloan^a, Randy J. Chandler^a, Mones Abu-Asab^k, Maria Tsokos^k, Abdel G. Elkahloun^l, Seymour Rosen^{m,n}, Gregory M. Enns^g, Gerard T. Berry^o, Victoria Hoffmann^f, Salvatore DiMauro^d, Jurgen Schnermann^b, and Charles P. Venditti^{a,2}

LETTERS

nature
genetics

Exome sequencing of serous endometrial tumors identifies recurrent somatic mutations in chromatin-remodeling and ubiquitin ligase complex genes

Matthieu Le Gallo^{1,10}, Andrea J O'Hara^{1,10}, Meghan L Rudd¹, Mary Ellen Urick¹, Nancy F Hansen², Nigel J O'Neil³, Jessica C Price¹, Suiyuan Zhang², Bryant M England¹, Andrew K Godwin⁴, Dennis C Sgroi^{5,6}, NIH Intramural Sequencing Center (NISC) Comparative Sequencing Program^{7,8}, Philip Hieter³, James C Mullikin^{2,8}, Maria J Merino⁹ & Daphne W Bell¹

Chromatin stretch enhancer states drive cell-specific gene regulation and harbor human disease risk variants

Stephen C. J. Parker^{a,1}, Michael L. Stitzel^{a,1}, D. Leland Taylor^a, Jose Miguel Orozco^a, Michael R. Erdos^a, Jennifer A. Akiyama^b, Kelly Lammerts van Bueren^c, Peter S. Chines^a, Narisu Narisu^a, NISC Comparative Sequencing Program^a, Brian L. Black^c, Axel Visel^{b,d}, Len A. Pennacchio^{b,d}, and Francis S. Collins^{a,2}

^aNational Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892; ^bGenomics Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720; ^cCardiovascular Research Institute, University of California, San Francisco, CA 95158; and ^dDepartment of Energy Joint Genome Institute, Walnut Creek, CA 94598

The Genome of the Ctenophore *Mnemiopsis leidyi* and Its Implications for Cell Type Evolution

Joseph F. Ryan,^{1,2} Kevin Pang,² Christine E. Schnitzler,¹ Anh-Dao Nguyen,¹ R. Travis Moreland,¹ David K. Simmons,³ Bernard J. Koch,¹ Warren R. Francis,⁴ Paul Havlak,⁵ NISC Comparative Sequencing Program,⁶ Stephen A. Smith,^{7,8} Nicholas H. Putnam,⁵ Steven H. D. Haddock,⁴ Casey W. Dunn,⁷ Tyra G. Wolfsberg,¹ James C. Mullikin,^{1,6} Mark Q. Martindale,³ Andreas D. Baxeavanis^{1*}

LETTER

OPEN

doi:10.1038/nature12228

Great ape genetic diversity and population history

ARTICLE

doi:10.1038/nature12886

The complete genome sequence of a Neanderthal from the Altai Mountains

ARTICLE

doi:10.1038/nature12053

Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus

The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca^{2+} and cAMP

Geun-Shik Lee^{1,2}, Naeha Subramanian³, Andrew I. Kim¹, Ivona Aksentijevich¹, Raphaela Goldbach-Mansky⁴, David B. Sacks⁵, Ronald N. Germain³, Daniel L. Kastner¹ & Jae Jin Chae¹

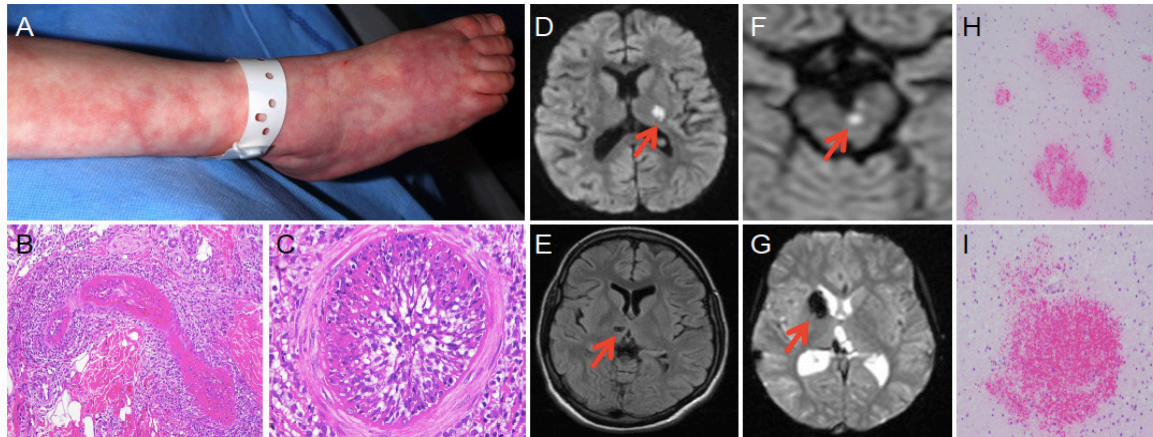
LETTERS

nature
genetics

Genome-wide association analysis identifies new susceptibility loci for Behçet's disease and epistasis between *HLA-B*51* and *ERAP1*

Yohei Kirino^{1,2,12}, George Bertisias^{1,3,12}, Yoshiaki Ishigatsubo², Nobuhisa Mizuki⁴, Ilknur Tugal-Tutkun⁵, Emire Seyahi⁶, Yilmaz Ozyazgan⁷, F Sevgi Sacli⁶, Burak Erer⁸, Hidetoshi Inoko⁹, Zeliha Emrence¹⁰, Atilla Cakar¹⁰, Neslihan Abaci¹⁰, Duran Ustek¹⁰, Colleen Satorius¹, Atsuhisa Ueda², Mitsuhiro Takeno², Yoonhee Kim¹¹, Geryl M Wood¹, Michael J Ombrello¹, Akira Meguro⁴, Ahmet Gül^{8,13}, Elaine F Remmers^{1,13} & Daniel L Kastner^{1,13}

Early-Onset Stroke and Vasculopathy Associated with Mutations in *ADA2*



Evaluating NHGRI Intramural Science

Blue Ribbon Panel Decennial Review, 2012

“The Blue Ribbon Panel concludes that the NHGRI IRP remains an outstanding research enterprise. In broad terms, this is reflected by

1)Scientific productivity . . .

2)An excellent record of educating and mentoring . . .

3)Enhancement of the broader NIH IRP through the dissemination of genomic technologies . . .

4)The development of an impressive research and clinical faculty . . .

5)The establishment of a robust research infrastructure . . .

6)A spirit of collaboration and collegiality . . .

Blue Ribbon Panel Review of the IRP Guiding Principles – Moving Forward

- Embrace a risk-taking culture
- Insist on excellence
- Continue to be a ‘change agent’ on the NIH campus and beyond
- One area of expanding need is the interpretation of the volume of genome information that is being captured and its integration with other clinical data.

NHGRI Board of Scientific Counselors

Tom Hudson, Chair (2015)

John Atkinson (2017)

Sally Camper (2016)

Sean Eddy (2014)

Sarah Gehlert (2015)

Rick Kittles (2016)

Bruce Korf (2014)

Gloria Petersen (2017)

Jerry Radich (2016)

Ontario Institute for Cancer
Research

Washington University

University of Michigan

Janelia Farm/HHMI

Washington University

U. of Illinois, Chicago

U. of Alabama, Birmingham

Mayo Clinic

Fred Hutchinson Cancer Ctr

Standards of Excellence for IRP Science

- Does the work fundamentally change the way that we think about or understand relevant areas of biomedical science?
- Through the development of new methods, does it change the way that we do science?
- For clinical research, does it change the way that we practice medicine?
- Whether clinical or basic, how would the field look if the Intramural Investigator had not been active for the last five years?
- Is the research worth studying with the special resources associated with the IRP?

Summative Ratings, 2011-2013

6 Branches, 25 faculty

- 17 Outstanding
- 1 Outstanding to Excellent
- 5 Excellent
- 2 Very Good

Budget

- FY2010 – FY2012: \$104M/yr - \$32M/yr to NIH overhead
- FY2013: \$100M - \$32M NIH overhead
- FY2014: budgeted for \$98M - overhead
- Converted from a capitated centrally supported budget model for investigators to a “bottom line” approach
- 15% across-the-board cuts since FY2010, merit-based adjustments beginning FY2015
- Actual FY2014 budget will be ~\$102.5M
- Mandated expenditures, capital expenses, bioinformatics recruits

New Initiatives

The NHGRI-Clinical Center Sequencing Project (Biesecker, Mullikin)

- NISC whole-exome sequencing on Clinical Center patients at reagent-only cost
- Further subsidized by competitive awards from the Deputy Director for Intramural Research (Michael Gottesman)
- CLIA-certified sequencing
- Return of incidental findings
- Support from Genetic Counseling Service
- 1000 exome first year pilot
- Eventual goal of expanding to all Clinical Center patients, integrated with deep phenotyping

U01 Extramural-Intramural Collaboration

- NIH-wide program to foster Clinical Center-based collaborations between extramural scientists and intramural investigators
- Projects in which patients can be extensively evaluated at the NIH, with laboratory-based investigations conducted extramurally
- \$500K/year x 3 years
- NHGRI Intramural Research Program will fund 1 new application per year
- Applications should have a strong genomics orientation to be funded by NHGRI

Immediate Challenges

- Maintaining a vibrant research enterprise in an era of flat budgets
- Funding the NIH Clinical Center
- Staying at the cutting edge of genomic technology and bioinformatics
- Catalyzing the genomic medicine in the Intramural Program
- Liberating resources for new recruitments

NIH Intramural 10-Year Planning Initiative

- Each Institute with an Intramural Program will review its IRP and develop a strategic plan
- Main question: What should the IRP look like in 10 years, and how can we get there?
- Each Institute will constitute a review committee of prominent extramural and intramural scientists
- For Institutes with a recent Blue Ribbon Panel Review, the current review may be an addendum to the BRP Review
- The review should address both scientific priorities and operational issues; Institute reports due 7/30/14
- Combined report from the Institutes transmitted to the Advisory Committee to the NIH Director (ACD) on 9/15
- ACD recommendations at 12/12/14 ACD meeting

EXCELSIOR!

