



Ichthyosis and FIRST

Common threads in my life of investigation

Leonard M. Milstone, MD





Merging Interests Make Good Bedfellows

- Retinoids
- Scale and Desquamation
- Importance of genetic diagnosis
- Keratins
- Emerging therapies
- Skin Microbiome



Pharmaceutical retinoids improve scaly skin
and are safer than vitamin A



10 y.o. with lamellar ichthyosis



Pharmaceutical retinoids improve scaly skin
and are safer than vitamin A



40.y.o. with epidermolytic ichthyosis (epidermolytic hyperkeratosis)



10.y.o. with PRP



PRP after
isotretinoin

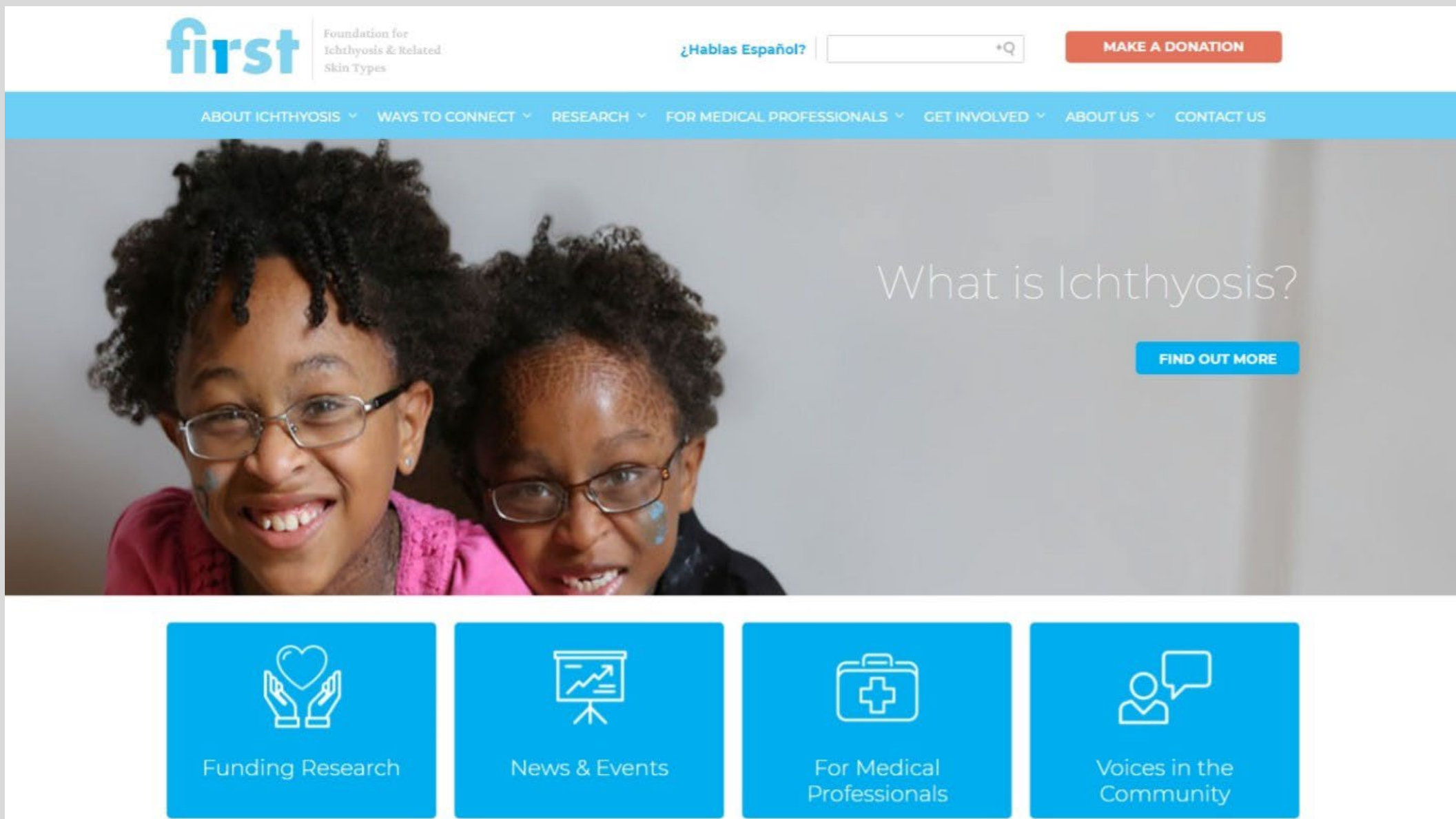


CARD14-associated papulosquamous eruption: A spectrum including features of psoriasis and pityriasis rubra pilaris

Craiglow et al. JAAD, 2018



Beginning of the Ichthyosis Foundation



The screenshot shows the homepage of the Ichthyosis Foundation. At the top left is the logo "first" in blue, followed by the text "Foundation for Ichthyosis & Related Skin Types". To the right is a language selector "¿Hablas Español?" with a search box and a "MAKE A DONATION" button. A navigation bar below contains links: "ABOUT ICHTHYOSIS", "WAYS TO CONNECT", "RESEARCH", "FOR MEDICAL PROFESSIONALS", "GET INVOLVED", "ABOUT US", and "CONTACT US". The main content area features a photograph of two young girls with ichthyosis and the text "What is Ichthyosis?" with a "FIND OUT MORE" button. At the bottom, four blue buttons with icons represent: "Funding Research" (hands holding a heart), "News & Events" (presentation board), "For Medical Professionals" (first aid kit), and "Voices in the Community" (two people talking).

first Foundation for Ichthyosis & Related Skin Types

¿Hablas Español? +Q [MAKE A DONATION](#)

[ABOUT ICHTHYOSIS](#) [WAYS TO CONNECT](#) [RESEARCH](#) [FOR MEDICAL PROFESSIONALS](#) [GET INVOLVED](#) [ABOUT US](#) [CONTACT US](#)

What is Ichthyosis?

[FIND OUT MORE](#)

[Funding Research](#) [News & Events](#) [For Medical Professionals](#) [Voices in the Community](#)





FIRST – Foundation for Ichthyosis and Related Skin Types

- A remarkable group of resilient people
- Refocused my thinking about what is important
- Critical questions for that community
- Importance of research to people with incurable disease

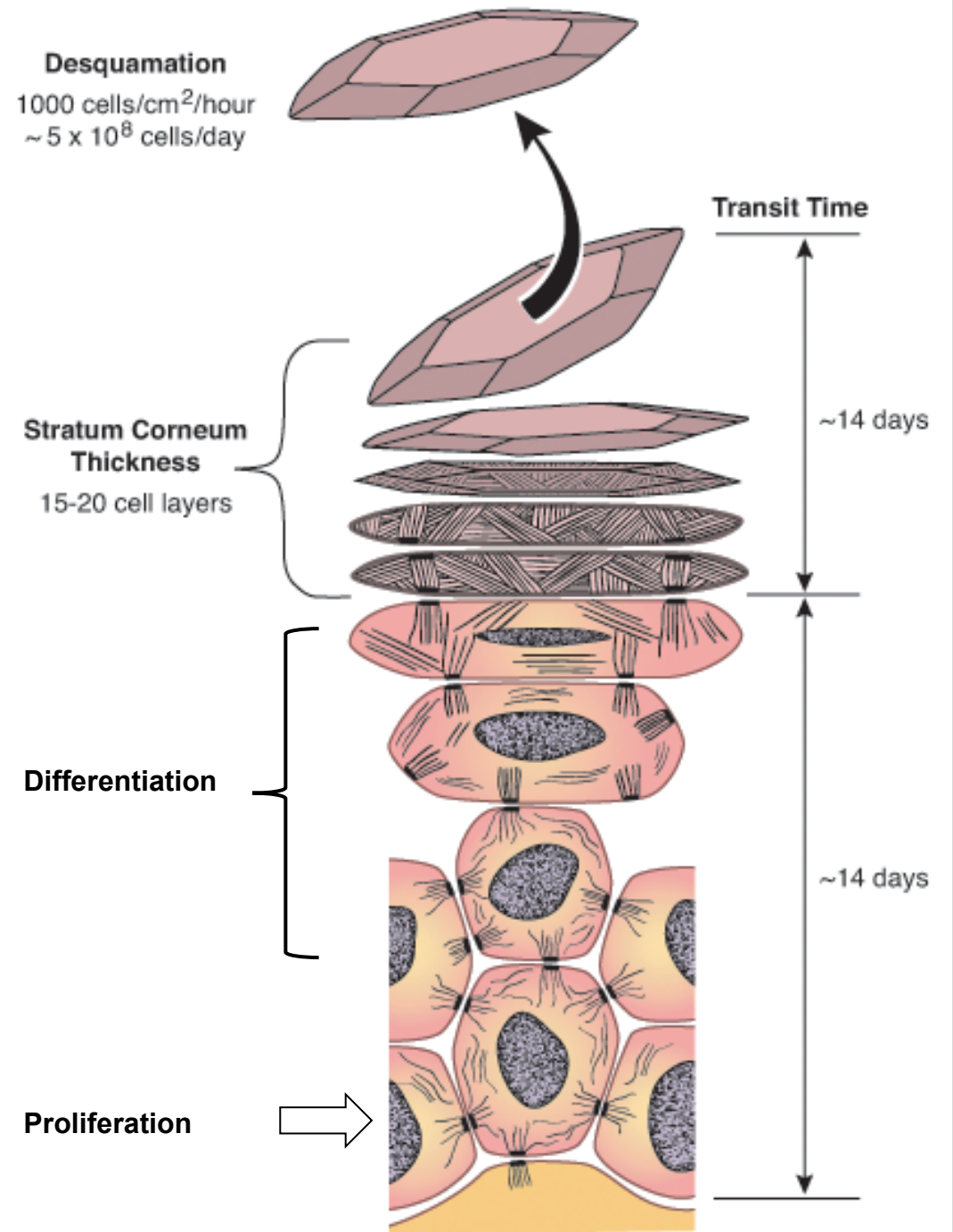




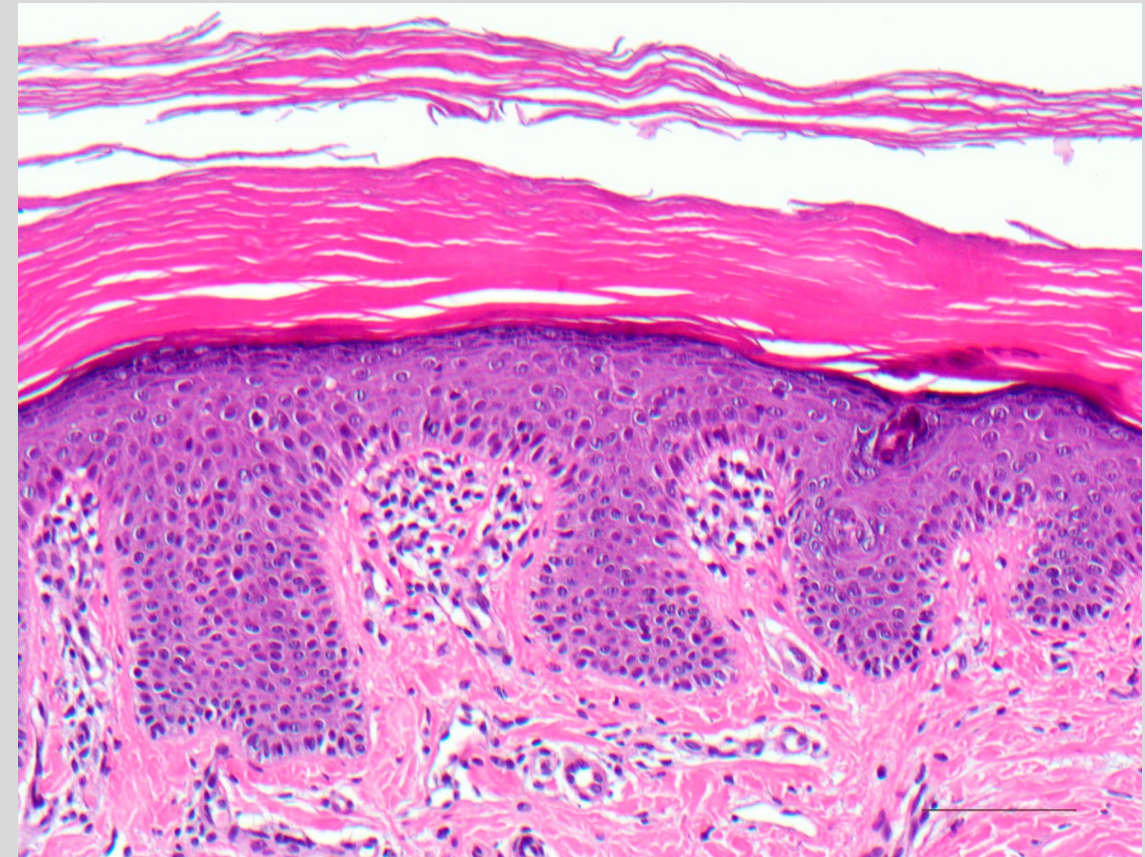
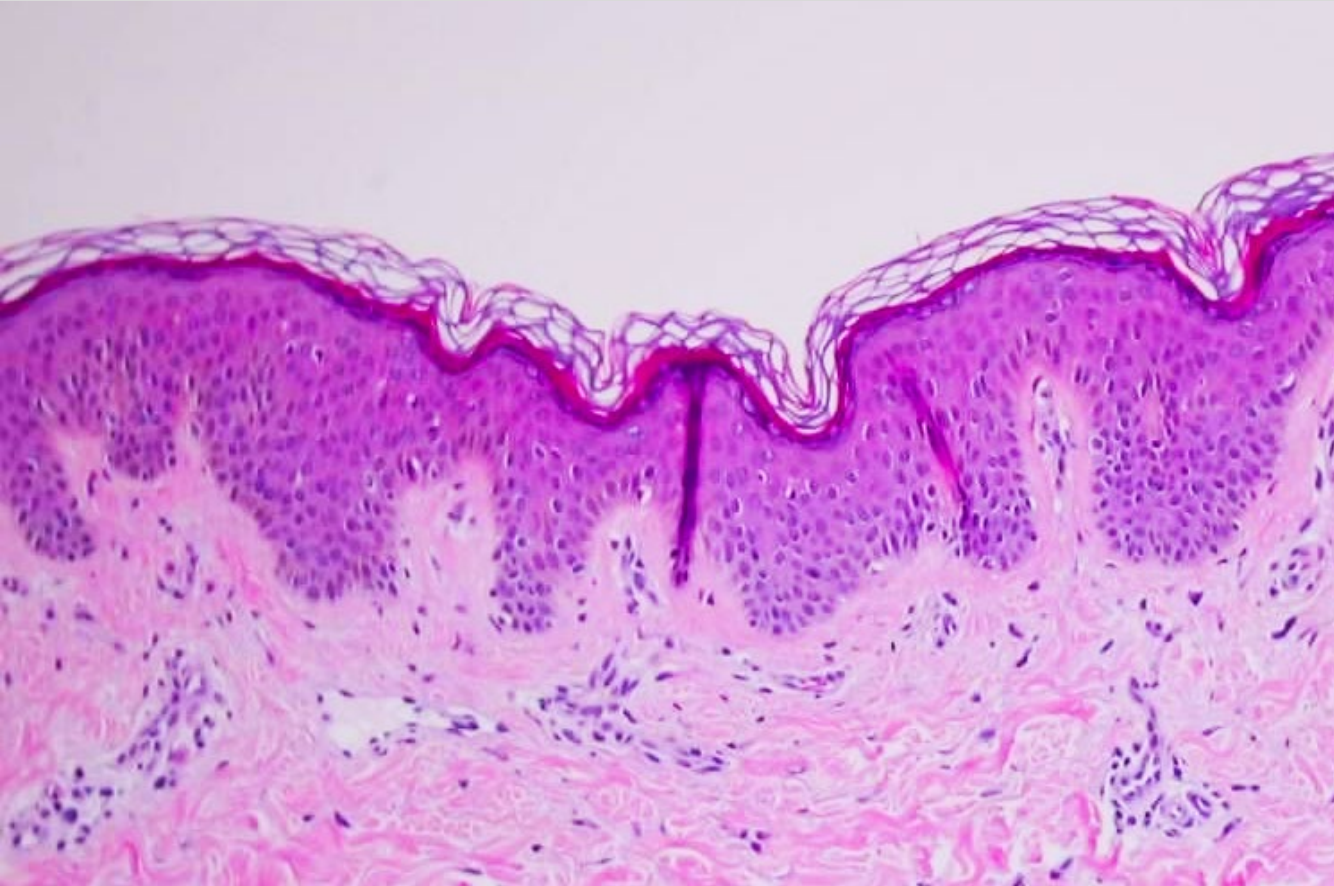
Retinoids facilitate skin shedding (desquamation)



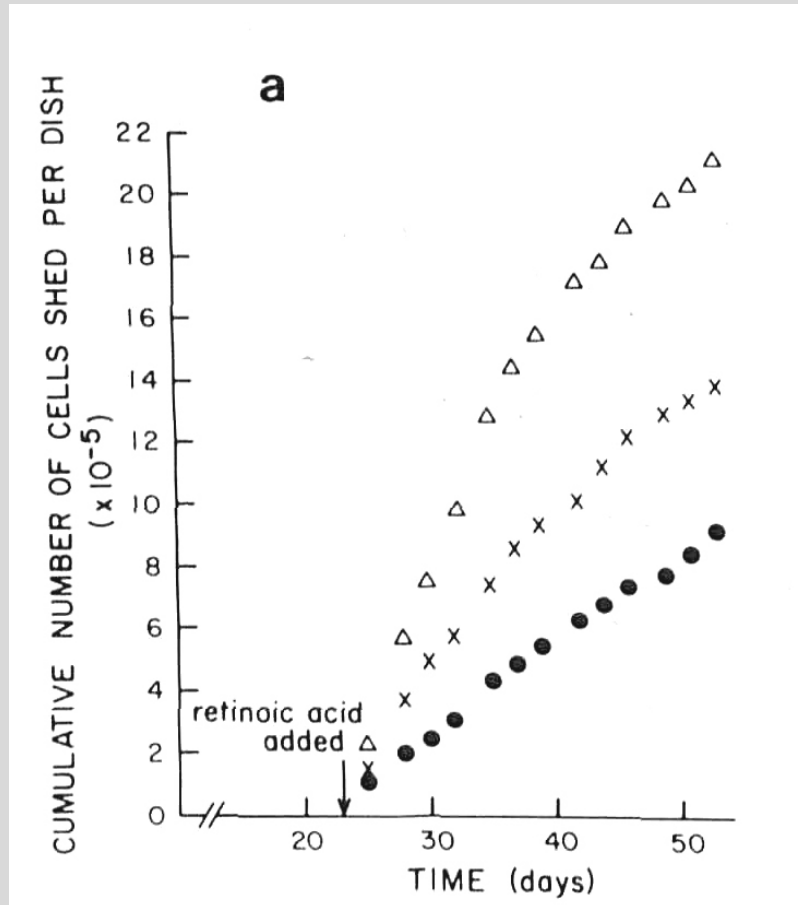
Epidermal Renewal

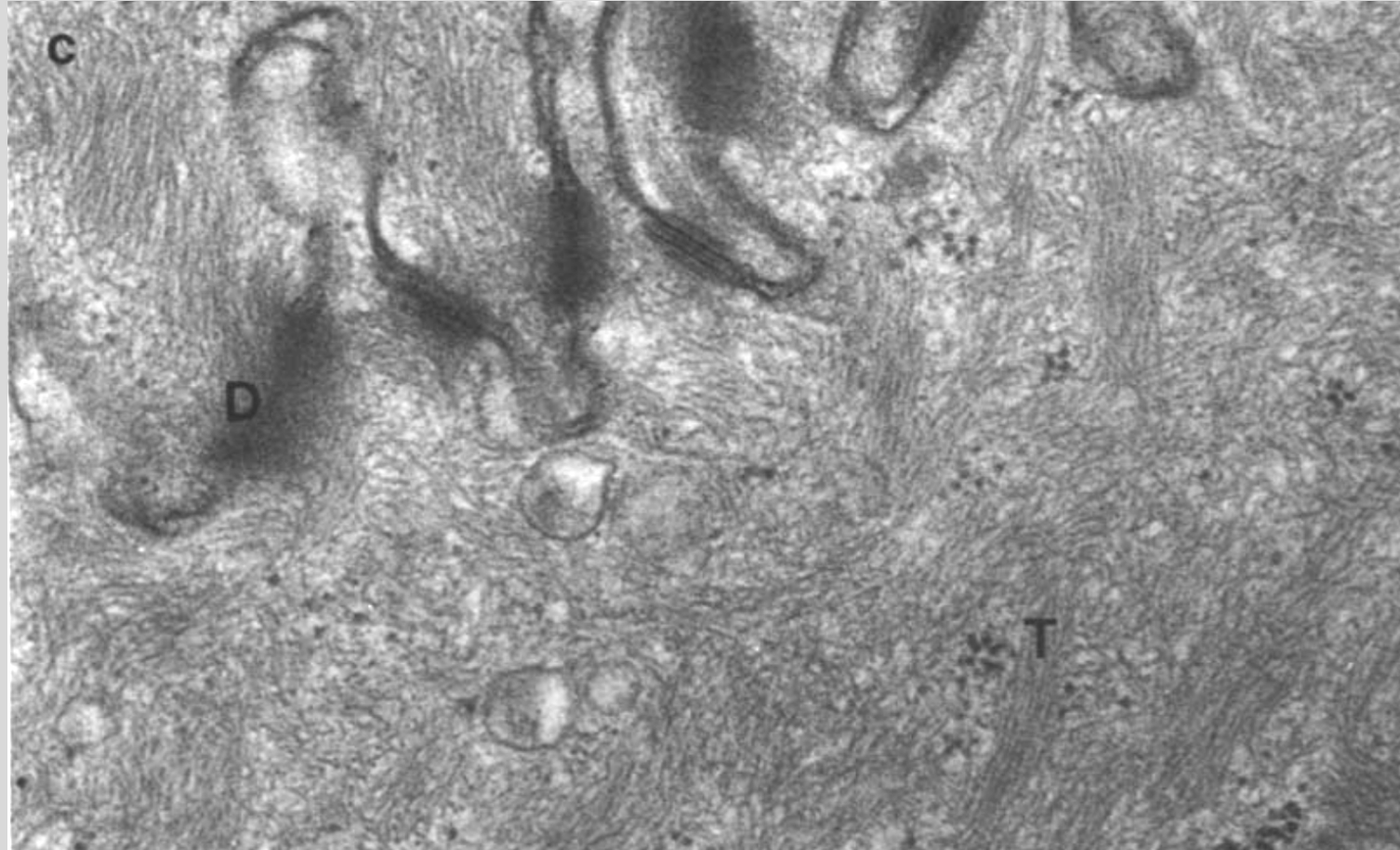


Thick stratum corneum in ichthyosis



Retinoids increase shedding from surface of confluent, stratified epithelia

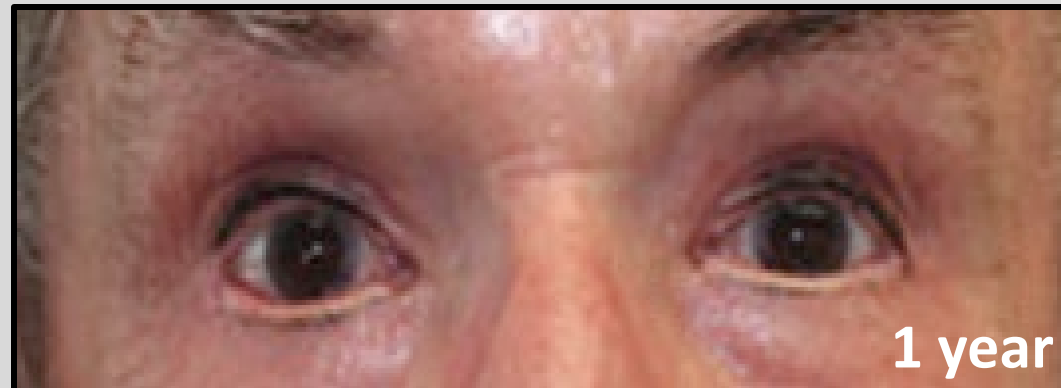
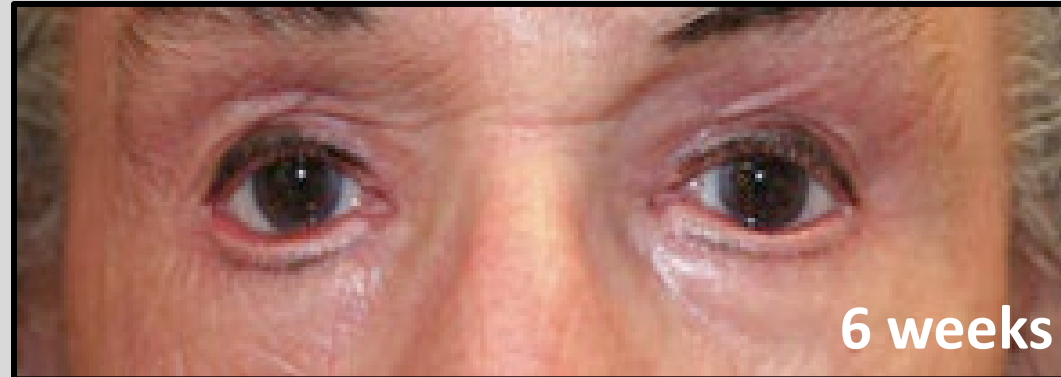
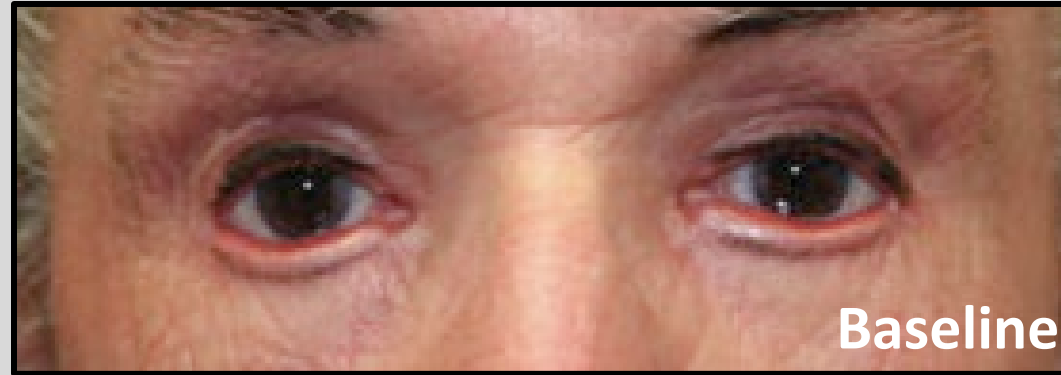




Retinoids relieve pseudoainhum



Topical Tazarotene for Ectropion

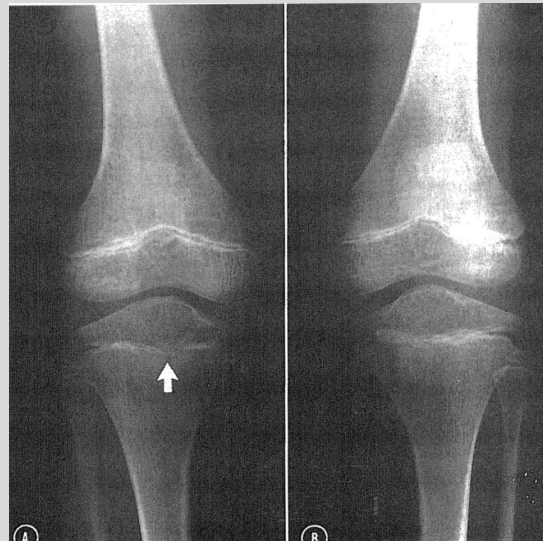


Craiglow et al
Ped Derm, 2013

Retinoid effects on bones

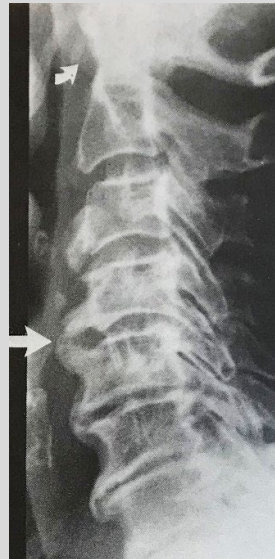
permanent

Fused Epiphyses



JAAD 7:663-666, 1982

Calcified Ligaments (DISH)

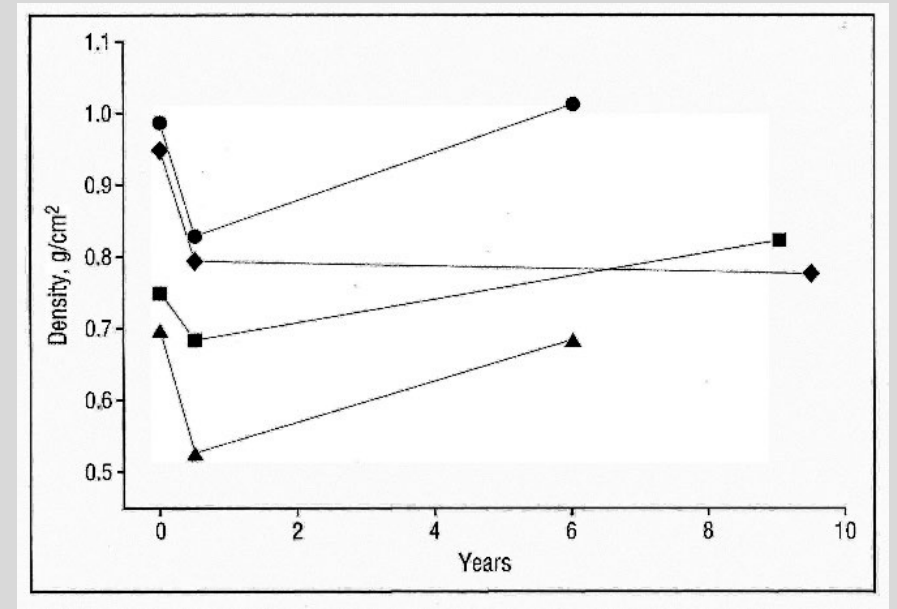


Retinoids pp 419-439 (Karger) 1984



reversible

Osteopenia



Arch Derm 138:1517, 2002



FIRST's Evolution from Advocate to Participant in Research

NIH-funded Ichthyosis Registry in Seattle - 1995-2005



KEY PERSONNEL. See instructions on Page 11. Use continuation pages as needed to provide the required information in the format shown below.

| Name | Organization | Role on Project |
|-----------------------------------|--|---------------------------|
| Leonard M. Milstone, M.D. | Yale School of Medicine | Principal Investigator |
| Amy S. Paller, M.D. | Northwestern School of Medicine | Co-Principal Investigator |
| Mary L. Williams, M.D. | University of California San Francisco | Co-Principal Investigator |
| Philip Fleckman, M.D. | University of Washington | Investigator |
| Moise Levy, M.D. | Baylor College of Medicine/Texas Children's Hospital | Investigator |
| Gabriele Richard, M.D. | Jefferson Medical College | Investigator |
| Mary Spraker, M.D. | Emory University | Investigator |
| Sherri J. Bale, Ph.D., F.A.C.M.G. | GeneDx, Inc. | Consultant |
| Mary-Margaret Chren, M.D. | University of California San Francisco | Consultant |
| Peter M. Elias, M.D. | UCSF and VA Medical Center | Consultant |
| Melvin Heyman, M.D. MPH | University of California San Francisco | Consultant |
| Karl Insogna, M.D. | Yale School of Medicine | Consultant |
| John H. Krystal, M.D. | Yale School of Medicine | Consultant |
| Jean Pickford | Foundation for Ichthyosis and Related Skin Types (F.I.R.S.T.) | Consultant |
| Gerald Sanacora, M.D., Ph.D. | Yale School of Medicine | Consultant |



FIRST's Evolution from Advocate to Participant in Research

- Ichthyosis Registry in Seattle – 1994-2012
- Consortium Grant Applications – 2003, 2013
- Grant Funding -2006
- Frontiers in Ichthyosis Meetings – 2010
- Ichthyosis Registry at Yale - 2016



2010 Frontiers in Ichthyosis Research

Incidence and Prevalence of Ichthyosis?

We need data!



Jeff Hoerle

Incidence of Moderate to Severe Ichthyosis in the United States

Table. Babies With Ichthyosis per Hundred Thousand Enrollees^a or Discharges^b

| Year | CCAЕ ^a | | | Medicaid ^a | | | HCUP ^b Total |
|---------|-------------------|--------|--------------|-----------------------|--------|--------------|-------------------------|
| | Male | Female | Total | Male | Female | Total | |
| 2000 | | | | | | | 4.03 |
| 2001 | 8.408 | 8.769 | 8.584 | 7.876 | 5.419 | 6.667 | NA |
| 2002 | 20.899 | 3.976 | 12.629 | 10.582 | 6.938 | 8.797 | NA |
| 2003 | 5.609 | 7.127 | 6.346 | 10.853 | 6.915 | 8.922 | 3.99 |
| 2004 | 6.861 | 6.343 | 6.609 | 10.659 | 8.739 | 9.718 | NA |
| 2005 | 9.427 | 3.301 | 6.440 | 12.420 | 7.963 | 10.237 | NA |
| 2006 | 10.954 | 7.727 | 9.386 | 11.277 | 8.315 | 9.829 | 5.97 |
| 2007 | 13.248 | 7.591 | 10.499 | 13.900 | 6.444 | 10.644 | NA |
| 2008 | 8.178 | 6.578 | 7.400 | 10.884 | 3.784 | 7.409 | NA |
| 2009 | 11.749 | 3.853 | 7.909 | 15.527 | 9.875 | 13.108 | 4.96 |
| 2010 | 14.828 | 5.236 | 10.171 | 19.128 | 8.136 | 13.751 | NA |
| Average | 11.005 | 5.848 | <u>8.497</u> | 11.881 | 7.371 | <u>9.721</u> | <u>4.75</u> |

Abbreviations: CCAE, Thomson Reuters MarketScan Commercial Claims and Encounter Database; HCUP, Healthcare Cost and Utilization Project KID (Kids' Inpatient Database) Databases; NA, not available.

^aEnrollees analyzed from the CCAE and Medicaid databases.

^bDischarges analyzed from the HCUP database.

Milestone, Miller, Haberman, Dickens
Arch Dermatol 148: 2012



Merle Haberman



Incidence and Prevalence of Moderate to Severe Ichthyosis in USA

6.7 cases per 100,000 births

With 4 million births per year = 270 new cases per year

With population of 330,000,000 = 22,000 total cases in USA



How FIRST Became a Driver for Genetic Diagnosis



Personal relationships developed at patient support organizations stoke drive to research



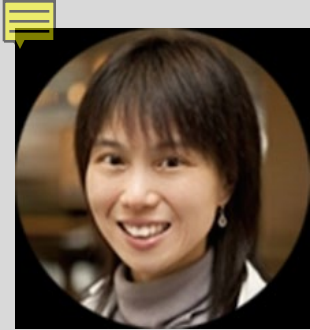




1999



2002

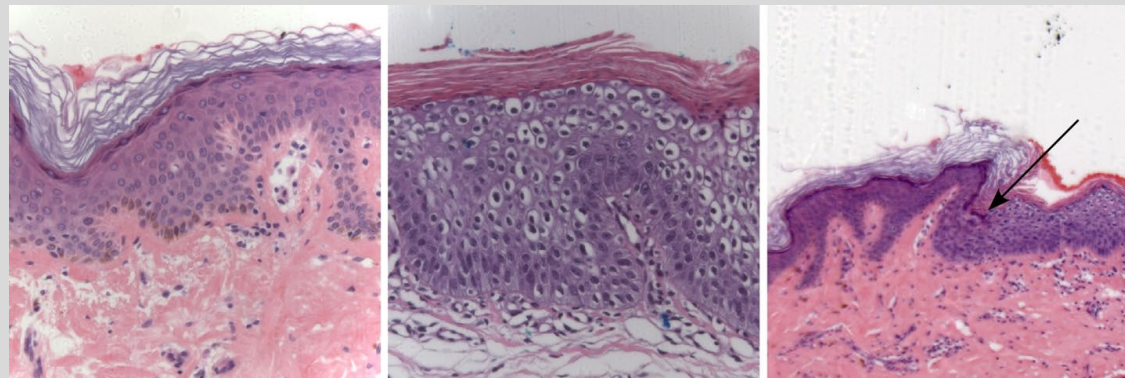


Michele Mak

Histology of white spot looks normal

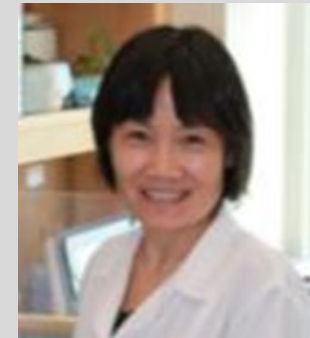


Revertant mosaicism?



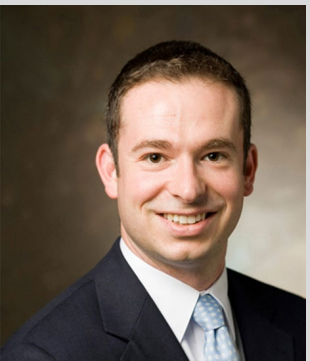
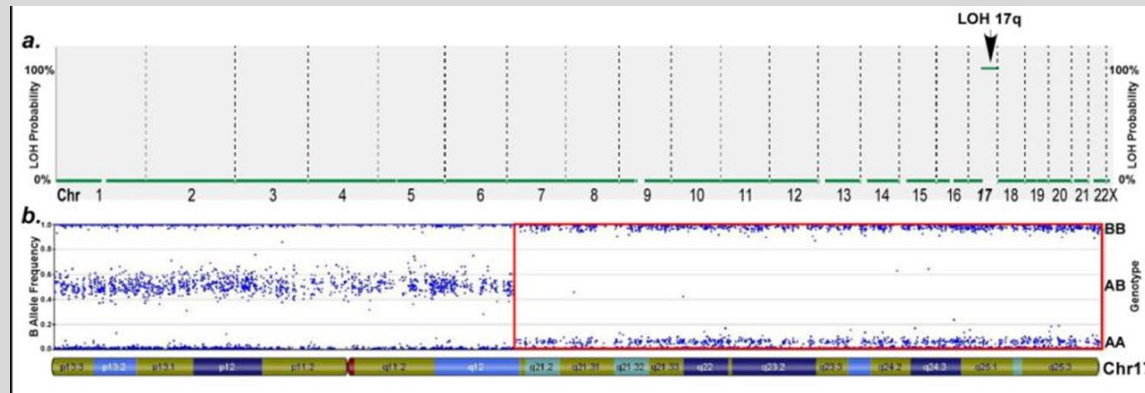
Richard Lifton

Explanation simple:
Loss of heterozygosity



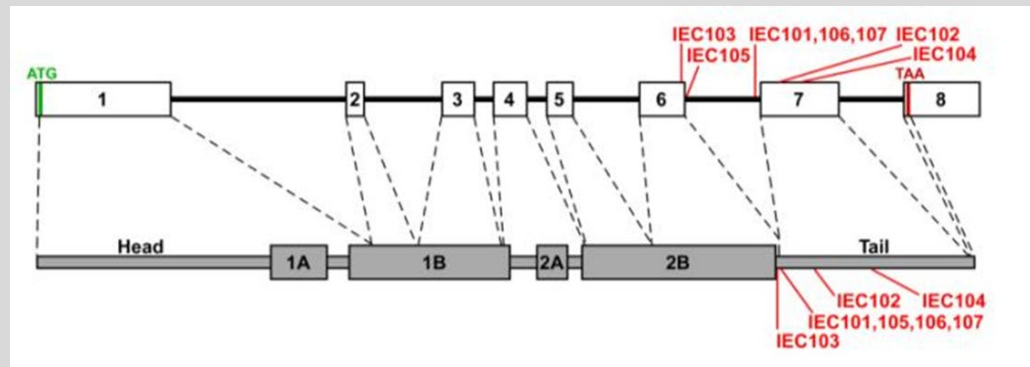
Jing Zhou

White spot keratinocytes show LOH on Chr 17



Keith Choate

Red spots have mutations in KRT 10 or KRT 1; white spots do not



Ichthyosis with confetti caused by mutations in KRT10 or KRT 1; white spots represent revertant mosaicism from mitotic recombination.
Choate et al
Science 330:94-97, 2010

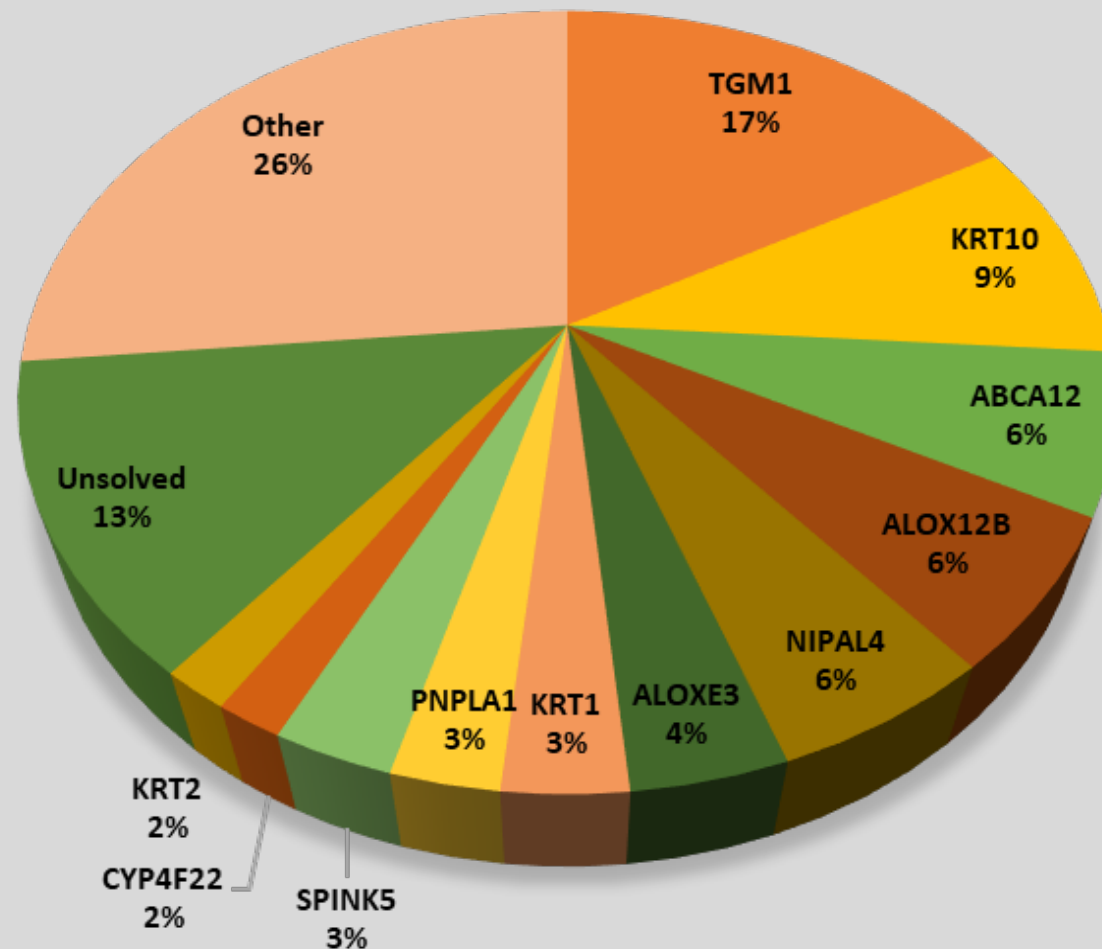
FIRST supports genetic diagnosis of ichthyosis in 1000 ichthyosis kindreds



Mike Briggs and Dave Scholl



Keith Choate



Other genotypes include *ABHD5*, *ALDH3A2*, *AP1B1*, *ASPRV1*, *ATP2A2*, *ATP2C1*, *CARD14*, *CAST*, *CDSN*, *CERS3*, *CLDN1*, *CSTA*, *DKC1*, *DSC2*, *DSG1*, *DSP*, *EBP*, *ELOV1*, *ERCC2*, *FLG*, *GJA1*, *GJB2*, *GJB3*, *GJB4*, *GJB6*, *KANK2*, *KDSR*, *KRT14*, *KRT16*, *KRT6B*, *KRT9*, *LOR*, *LSS*, *MBTPS2*, *NSDHL*, *PERP*, *POGLUT1*, *RHBDF2*, *RSP01*, *SDR9C7*, *SERPINB7*, *SLC27A4*, *SNAP29*, *SREBF1*, *ST14*, *STS*, *TGM5* and *TRPV3*.



Importance of Early Genetic Diagnosis

- Prognosis

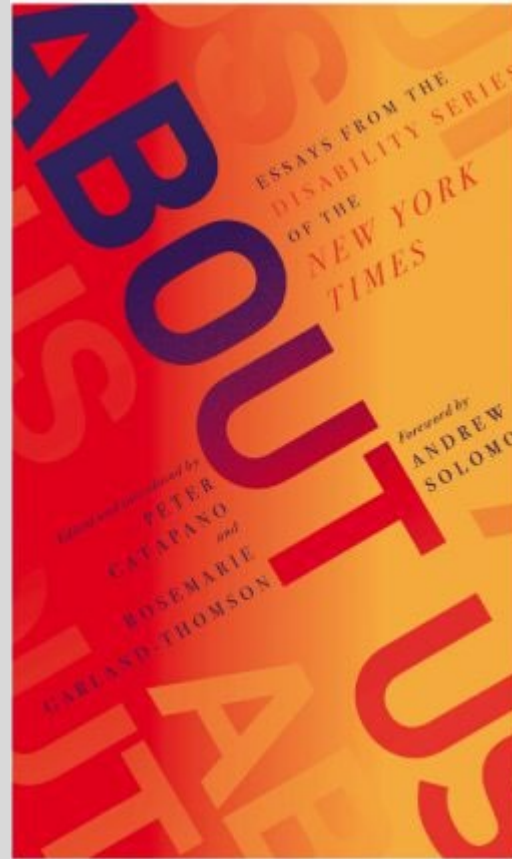
Collodion baby – TGM1 mutations





Professor Anne Kaier

Finding Refuge With the Skin I'm In
By Anne Kaier
New York Times, Aug. 24, 2016



Harlequin – ABCA12 mutations



Harlequin Ichthyosis at birth and 1 year



Why better outcomes in past 50 years?

- Critical role of St. corneum as barrier to water loss
- Hydration
- Emollients to reduce water loss
- NICUs
- Broader social acceptance of disability
and chronic disease



Are any types of ichthyosis lethal?

- Non-syndromic ichthyoses

- Collodion baby
- Harlequin

Should not be

Should not be

- Syndromic ichthyoses

- KID syndrome
- Cardio-cutaneous
- Neuro-cutaneous

Usually not; in rare cases unavoidable

Long-term prognosis guarded

Long-term prognosis guarded

Lethal Keratitis Ichthyosis Deafness (KID) syndrome

Cased by mutations in *GJB2*, coding for connexin 26 protein

Many cases worldwide; not usually lethal

All cases with A88V or G45E mutation are lethal in 1st year

No uniform cause of death

Abnormalities in many organ systems



More than keratitis, ichthyosis, and deafness:
Multisystem effects of lethal *GJB2* mutations

Lilly, et al
JAAD 80:217, 2019





Importance of Early Genetic Diagnosis

- Prognosis
- Family planning



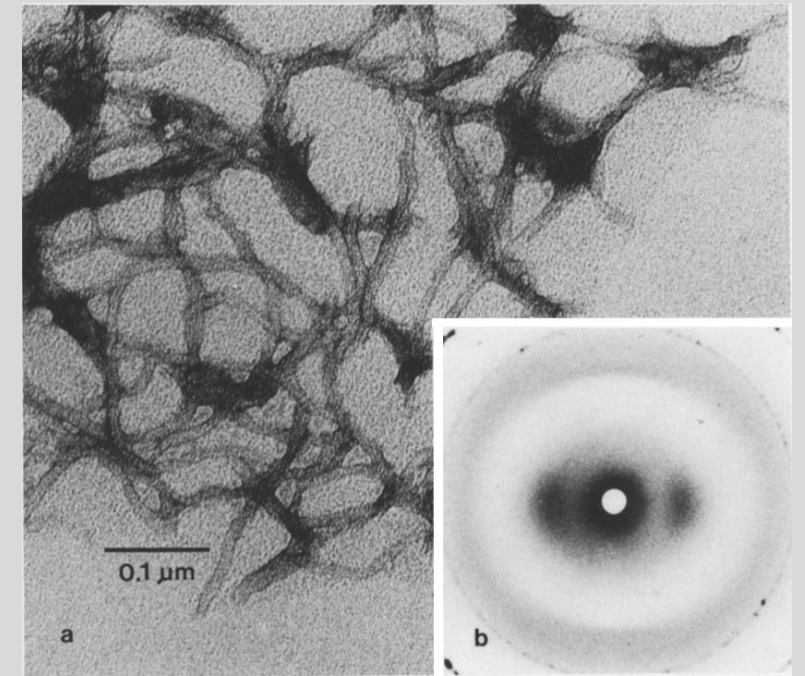
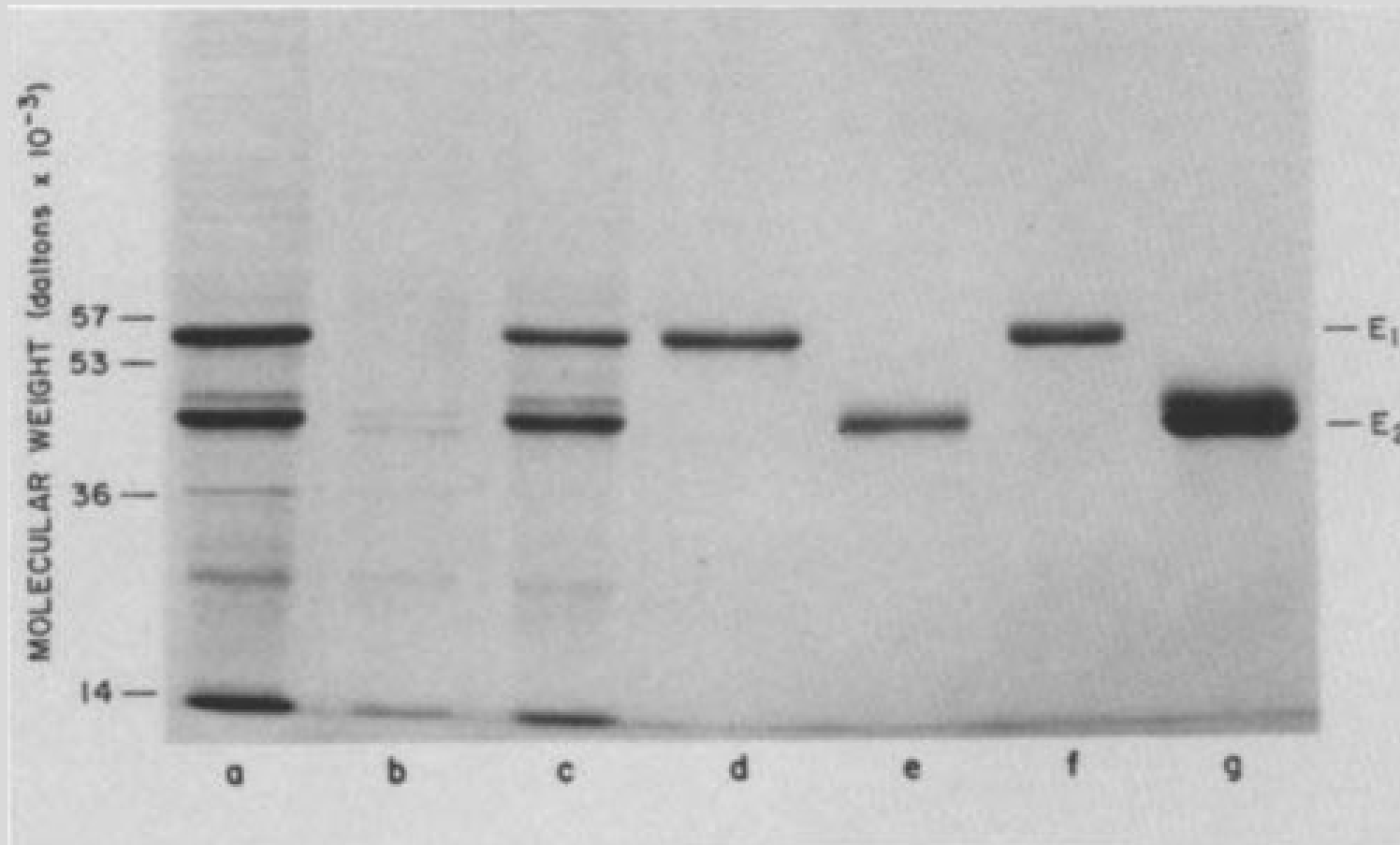
Importance of Early Genetic Diagnosis

- Prognosis
- Family planning
- Targeted therapy



FIRST Supports of Basic Research

Helps Me Revisit a Core Research Interest

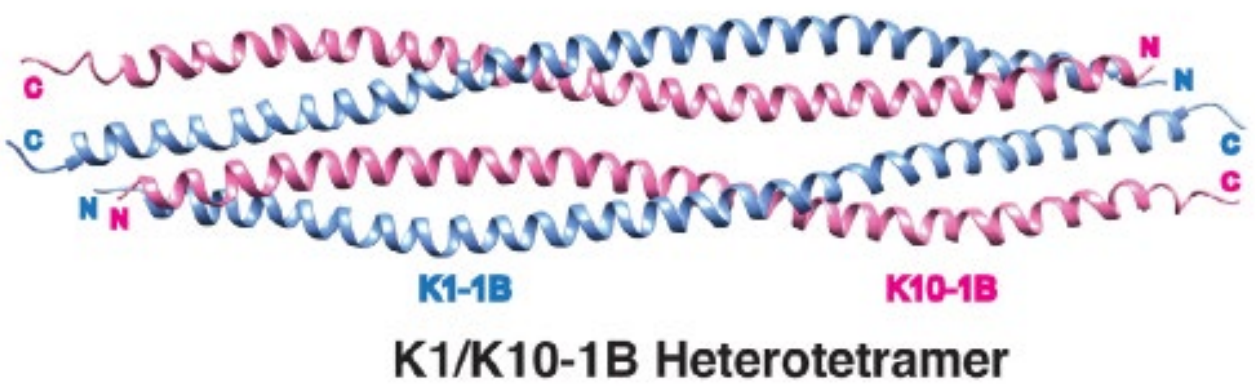


Isolation and Characterization of Two Polypeptides That Form Intermediate Filaments in Bovine Esophageal Epithelium

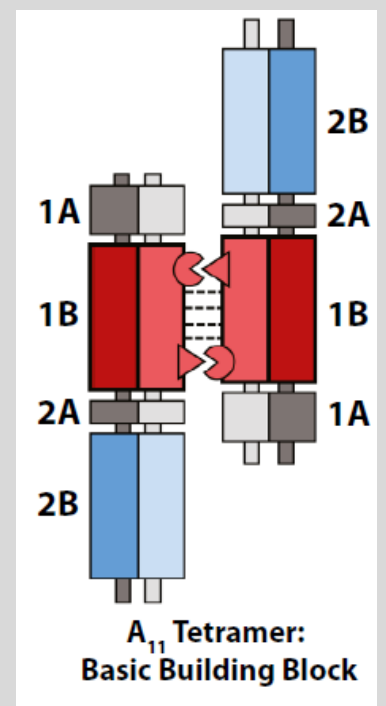
Leonard M. Milstone

THE JOURNAL OF CELL BIOLOGY 88:317-322, 1981

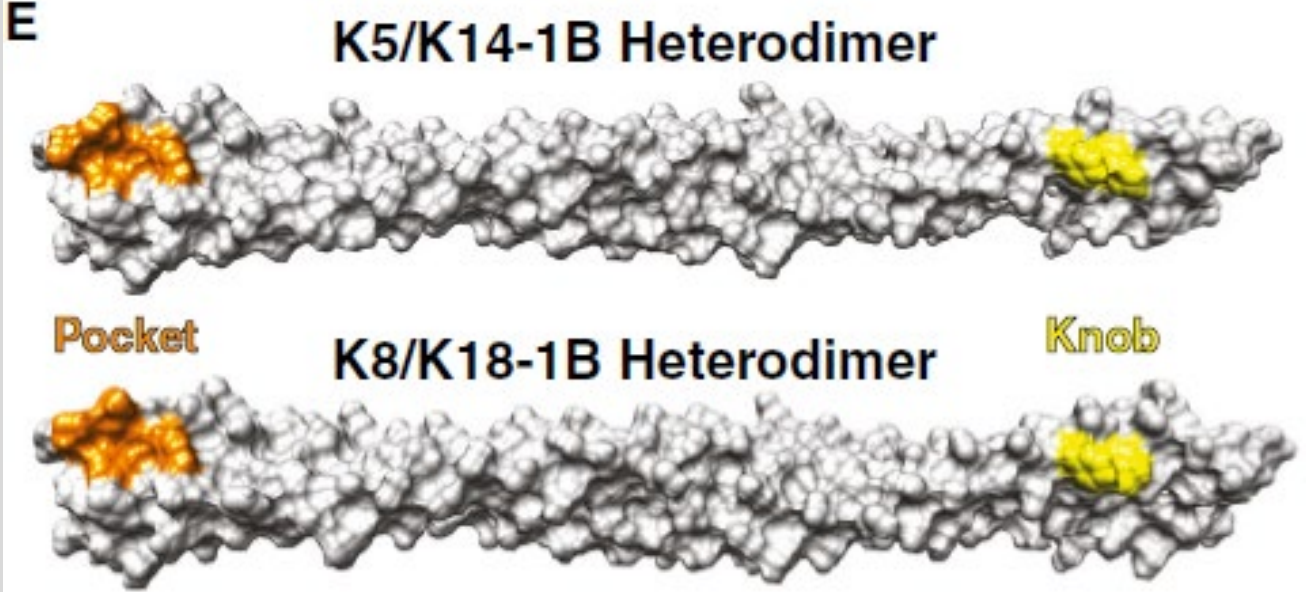
B



Anti-parallel heterodimers



E



Christopher Bunick

Human keratin 1/10-1B tetramer structures reveal a knob-pocket mechanism in intermediate filament assembly. EMBO Journal e100741, 2019

Variations in Plantar Keratoderma



K16 N125S



K16 N125S



K16 N125D



K16 L132P

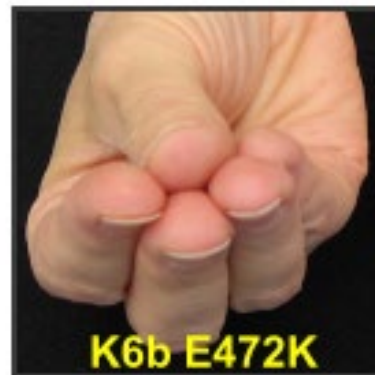


K16 L132P



Pachyonychia Congenita Project

Variations in Nail Thickness



K6b E472K



K6a N171del



K16 N125D



K16 L132P



K16 N125D



Pachyonychia Congenita Project

Targeted Therapy: siRNA Reduces Callus in Pachyonychia Congenita





Engineer bacteria to deliver therapeutic proteins to skin



TARGETS:

Ichthyosis vulgaris – Filaggrin

Netherton - LEKTI

Azim Munivar and Travis Whitfill >>>>>> Azitra



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**Our skin microbiome plays
a crucial role in human
health**



Julia Oh
Jackson Labs



Nan Ring
Yale

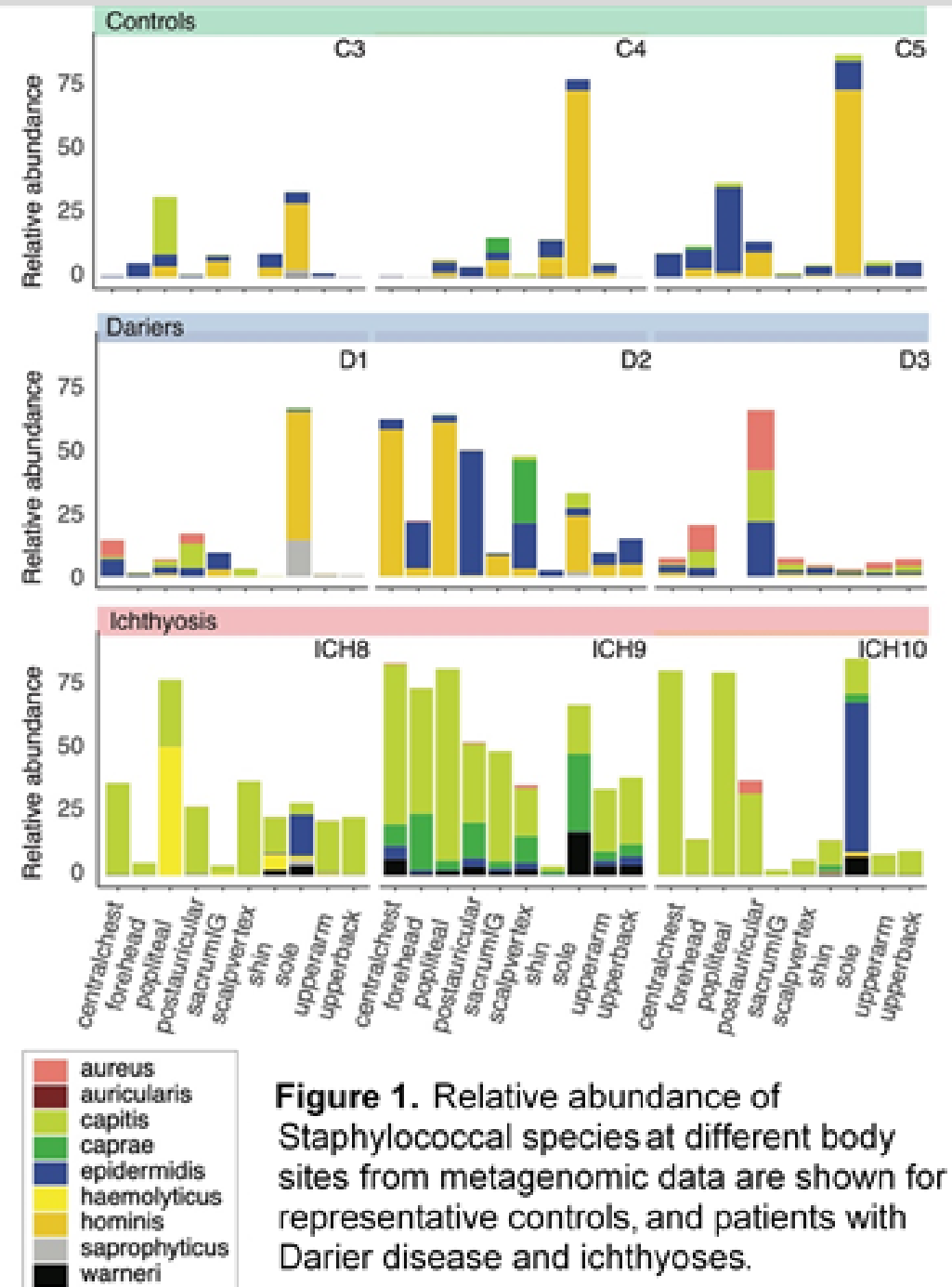


Figure 1. Relative abundance of Staphylococcal species at different body sites from metagenomic data are shown for representative controls, and patients with Darier disease and ichthyoses.



My journey and the ever-present role of FIRST

- **Retinoids**
- **Scale and Desquamation**
- **Importance of genetic diagnosis**
- **Keratins**
- **Emerging therapies**
- **Skin Microbiome**

FIRST LEADERS

Board of Directors President/Chair...

Office Executives



Rowe



McHugh



Vilas



Landwehr



Eichhorn



Snyder



Dunleavy



Rice



Phillips



Gattucio



E. Levitan



Scholl



Briggs



Hoerle



Pickford



Wenik



Evans



Pretak



Gass



Boynton







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