What’s New in Pediatric Dermatology?
The Pediatric Dermatology Research Alliance: PeDRA

• Collaborative research network of >200 pediatric dermatology investigators from ~130 institutions that was initiated in 2012
• Conduit for bench and clinical research: providing power for studies of rare diseases and high severity common diseases
• 5 disease specific working groups: 50 collaborative studies
  • Birthmarks and procedures
  • Genetic skin disorders
  • Skin tumors and reactions to cancer therapy (STARC)
  • Inflammatory skin diseases
  • Neonatal skin
• 6 studies published to date
• First pan-PeDRA study about to start: Burden of stigma in pediatric skin disease

http://pediatricresearch.org
7 year old boy with junctional EB and LAMB3 mutations

Infection exacerbated EB and he was hospitalized with 60% complete skin loss without response to therapy

Phase I/II clinical trial

- 4 mm punch biopsy from nonblistered skin inguinal area
- Full-length LAMB3 gene introduced under control of Moloney leukemia virus retroviral vector

Hirsch et al. Nature 2017;551:327
Regeneration of the entire human epidermis using transgenic stem cells

Tobias Hirsch1, Tobias Rothoerft2, Norbert Teig3, Johanna W. Bauer4, Grazzella Pellegrini5,6, Laura De Rosa6, Davide Scaglione6, Julia Reichelt7, Alfred Klaussegger7, Daniela Kneiss7, Oriana Romano7, Alessia Seccone Seconetti8, Roberta Conti9, Elena Enzo9, Irene Jurman9, Sonia Carulli9, Frank Jacobsen9, Thomas Luecke9, Marcus Lehnhardt9, Melanie Fischer10, Maximilian Kueckelhaus10, Daniela Quaglini10, Michele Mongante10, Silvio Bicciato10, Sergio Bondanza9, & Michele De Luca10

*Nature* 2017;551:327-

- Transgenic epidermal grafts covered all denuded areas (0.85 m²)
- Touch up grafts for other areas during next few months to restore in total 80% total BSA
- Demonstration of laminin 332 deposition at all sites tested
- Sustained by long-lived stem cells (detected as holoclones)
- As of this past week, “not a single blister in the transplanted areas” at 2.8 years after transplantation

What about recombinant protein?

- X-linked Hypohidrotic ectodermal dysplasia from ectodysplasin (EDA) deficiency
  - Studies in mouse and dog models of HED suggest the value of recombinant Eda therapy
  - Some evidence of effect even when given in early postnatal period (as well as in utero)

- Phase 2 study of 2-14 d/o HED-affected male newborns given Fc-EDA fusion protein 3 or 10 mg/kg/dose twice weekly (5 doses); total 6 babies
  - No effect........(NCT01775462)

Recombinant fusion protein

- Delivery to amniotic cavity of 100 mg/kg fetal weight Fc-EDA at 26 wks in 3 affected babies (and again at 31 wks in 2 dizygotic twins); diagnosis prenatally by genetics and ultrasound
  - Fetal uptake through gut Fc receptors

- Normal sweat gland density/function
- Normal salivation
- Good development of tooth germs
- Did not develop hair (too late?)
Somatic and germline mutations leading to vascular and lymphatic malformations
Newly recognized somatic mutations of RAS-ERK pathway

- CM-AVM2: Germline heterozygous loss-of-function mutations in EPHB4 leads to capillary malformation-arteriovenous malformation type 2
- Lesions as “second hit”

- Features of CM-AVM1 (RASA1): Port-wine/telangiectasia/AVM
- Fewer fast-flow/intracranial lesions than in RASA1 CM-AVM1
- Likely almost 2x more common than CM-AVM1 and underdiagnosed

Amyere et al. Circulation 2017;136:1037
Blue rubber bleb nevus syndrome/BRBN

- Single venous malformations: most due to TEK/TIE2 mutations (L914F) + 20% PIK3CA

- BRBN have **two mutations** on the **same allele** of TEK (cis, esp T1105N-T1106P) in all lesions that activate TIE2 pathway; no mutations found in blood

Soblet et al. JID 2017;137:207
Systematic review of systemic sirolomus:
- Most common for lymphangiommas > capillary-lymphatic-venous > venolymphatic

Therapeutic value of inhibition of mTORC1 pathway
- Start with 0.8 mg/m²/dose twice daily with serum 12 hour trough levels (10-15 ng/ml) to guide dosing
- Six month course: 47/57 (83%) had partial response with 3 patients stable and 7 patients progressing

Significant improvement in quality of life
27% had some toxicity, esp blood/bone marrow, some GI

Macrocytic lymphangiomia
Kaposi’s hemangioendothelioma

Streichowsky et al. Laryngoscope 2018;128:269
Adams et al. Pediatrics 2016;137:e20153257
Topical rapamycin/sirolimus for microcystic lymphangiomas

- Flattens, reduces oozing and bleeding (0.1-1%) – but not in all patients
- Risk: irritation

Garcia-Montero et al. Pediatrics 2017;139:e20162105

Le Sage et al. Pediatr Derm 2018;35:472
Therapeutic value of inhibition of mTOR pathway

- **Blue rubber bleb nevi: Sirolimus (mTOR)**

- **PIK3CA-related overgrowth syndrome: PIK3CA inhibitor**


Venot et al. Nature 2018;558:540
Mosaic and somatic mutations of the RAS-ERK pathway leading to vascular malformations

- Mosaic activating variants in KRAS, NRAS, BRAF and MAP2K1 lead to vascular malformations, especially high-flow

- In zebrafish models, expression of BRAF^{V600E} in endothelial cells led to disordered vessel formation

- Vemurafenib improved blood flow

Al-Olabi et al. JCI 2018;128:1496
MEK inhibitor for CMN

• 7 year old girl with giant congenital melanocytic nevus from BRAF activation

• Intractable, debilitating pain and pruritus with chronic insomnia and anxiety

• Marked response to trametinib: sleeping through night with improved behavior and off pain meds

• MRI findings show near resolution of deep invasion and improvement in associated neurocutaneous melanosis

Courtesy of Drs. Jennifer Day, Adnan Mir, and Nnenna Agim, UTSW, presented SPD, July, 2018
Based on understanding underlying pathogenesis of disease, are there other disorders for which targeted therapy could be used?

- Dupilumab for atopic dermatitis (pedi in trials)

Wide array of choices for subcutaneously injected biologics for treating psoriasis

Targeting pathways for inflammatory diseases
CARD14-associated papulosquamous eruption (CAPE)

- 15 kindreds with heterozygous CARD14 mutations
- Variably called pityriasis rubra pilaris, plaque psoriasis, erythrodermic psoriasis with pustules, or even CIE ichthyosis
  - 80% with palmoplantar keratoderma
  - 40% with follicular-based papules/islands of sparing
- 87% with onset in first year of life
- Facial involvement prominent (cheeks, ears)
- Sometimes patterning
• Often recalcitrant to Mtx, TNF inhibitors, retinoids

• Activating mutations in CARD14 drive IL-23/Th17 signaling

• Of 6 treated with ustekinumab, 5 experienced nearly complete clearance

Craiglow et al. JAAD 2018 Mar 1 [Epub ahead of print]
Finally... skin/blood molecular profiles of ichthyosis: 3 papers

- **RT-PCR of skin: 21 patients**
  
  An IL-17–dominant immune profile is shared across the major orphan forms of ichthyosis  
  JACI 2017;139:152

  Amy S. Paller, MD, MS, a, Yael Renert-Yuval, MD, b, Maria Supran, MPH, a Hitokazu Esaki, MD, b,d Margaux Oliva, BA, b, Thy Nhat Huynh, MD, a, Benjamin Ungar, BA, a Norma Kunjpravat, MD, a Rivka Friedland, MD, a Xiangyu Peng, MSc, b Xiuzhong Zheng, MSc, c Yeriel D. Estrada, BSc, c James G. Krueger, MD, PhD, a Keith A. Choate, a Mayte Suarez-Farinas, PhD, b,d and Emma Guttmann-Yassky, MD, PhD d

- **Gene array of skin: 29 patients**
  
  Ichthyosis molecular fingerprinting shows profound T_{H}17 skewing and a unique barrier genomic signature  
  JACI May 24 2018 [Epub]

  Kunal Malik, MD, a,b, Helen He, BS, a,b, Thy Nhat Huynh, MD, a, Gary Tran, MD, a Kelly Mueller, BS, a Kristina Doytcheva, MS, a Yael Renert-Yuval, MD, b Tali Czarnowicki, MD, MS, a,d Shai Magidi, MS, a Margaret Chou, BA, a Yeriel D. Estrada, BSc, a Huei-Chi Wen, MD, PhD, a Xiangyu Peng, MS, a Hui Xu, MS, a Xiuzhong Zheng, MSc, c James G. Krueger, MD, PhD, a Amy S. Paller, MD, MS, a, and Emma Guttmann-Yassky, MD, PhD d

- **Blood flow studies: 47 patients**
  
  The Major Orphan Forms of Ichthyosis Are Characterized by Systemic T-Cell Activation and Th-17/Tc-17/Th-22/Tc-22 Polarization in Blood  
  JID April 14 2018 [Epub]

  Tali Czarnowicki1,2, Helen He1, Alexandra Leonard1, Kunal Malik1,2, Shai Magidi3, Stephanie Rangel1, Krishna Patel1, Kara Ramsey2, Morgan Murphy2, Teresa Song2, Yeriel Estrada1, Hue-Chi Wen1, James G. Krueger2, Emma Guttmann-Yassky1,2,3, and Amy S. Paller1,2
Shared ichthyosis profile in skin resembles that of psoriasis

**Differences among ichthyoses**

- ie, lipid metabolism genes markedly abnormal in LI, near normal EI; higher IL-23 in CIE and NS

**Flow studies on blood**

- CLA+ cells: high expression of IL-17A, IL-22 and IL-9 (highest in NS)
- IL-17A/-9 higher than either AD/Pso
- IL-22 higher than Pso, less than AD
Is the high expression of Th17 pathway merely a response to increase the antimicrobial innate immune defense in the face of epidermal barrier impairment in ichthyosis?

Does the IL-17 skewing drive the inflammation and scaling of ichthyosis, as for psoriasis?

Could targeted therapies for psoriasis treat ichthyosis?
Erythrokeratodermia with cardiomyopathy (DSP mutation)

Treated with ustekinumab

Followup pictures are 16 weeks

Continues to be almost clear more than a year after initiation: life-changing

- First clinical trial of targeted psoriasis therapy for ichthyosis
  ....... with more to come
Thanks for your attention