CLINICAL INNOVATION: Fair & Effective Incentives for New Uses of Established Drugs

Examples of Clinical Success

Moderator: Brian Cordery *Bristows LLP*

Presenters:

- **Francois Houyez** *Director of Treatment Info & Access Policy Advisor at EURORDIS and patient activist*
- **Prof. Michelle Petri** *Director, Hopkins Lupus Cohort*

Panellist:

- **Dr Bruce Bloom** *CEO, Cures within Reach*

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RARE DISEASES EUROPE

BACK TO THE FUTURE: AUTHORISING THALIDOMIDE FOR HUMAN USE… AGAIN!

Second Medical Uses Conference

François Houÿez

8 & 9 February 2018, Washington DC

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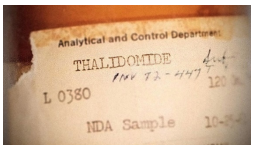
Thalidomide first life 1957-1962



- 12,000 Thalidomide babies were born - 8,000 Thalidomide babies survived
- ***At the time of Thalidomide' development, scientists did not believe any drug taken by a pregnant woman could pass across the placental barrier and harm the developing foetus***
  - Heaton, C. A. (1994). The Chemical Industry. Springer. pp. 40. ISBN 0751400181
- Many of the 8,000 are still alive today – they are in their late 50's and early 60's
- Spectrum of malformations (besides limbs): absence of ears, deafness, defects of eye and facial muscles, malformations of heart, bowel, uterus, and gallbladder

EDRIC
AN ORGANISATION FOR PEOPLE AFFECTED BY DYSMELIA

DysNet
The Online Dysmelia Community

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Second medical use: a striking observation made in 1964 | Jacob Sheskin, Hansen Leper Hospital in Jerusalem

- He prescribed thalidomide as a sleeping pill to a patient suffering from leprosy
  - Not only could the patient sleep, but with significant improvements in his scars and pain
  - Within three days the leprosy had gone and skin lesions healed
  - At treatment stop: all lesions reappeared
- WHO confirmed a total remission of the disease in 99% of thousands of lepers he treated in 52 countries
- Years later: proposed in diseases with inflammation or immunology problems: psoriasis, sarcoidosis, lupus, Behcet's syndrome, AIDS …
- Approved for leprosy by FDA in 1998

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Third medical use of thalidomide: multiple myeloma

- 1994: Dr Robert D'Amato (Harvard Med School) discovered thalidomide was a potent inhibitor of new blood vessel growth (angiogenesis)
- The sister of a myeloma patient presented to Dr Bart Barlogie in Little Rock, Arkansas, in the late 1990s
  - She had read on thalidomide and its anti-angiogenic properties
  - She forced Dr Barlogie to administer thalidomide to her brother
- First case of successful thalidomide use in MM in a subject with otherwise resistant disease

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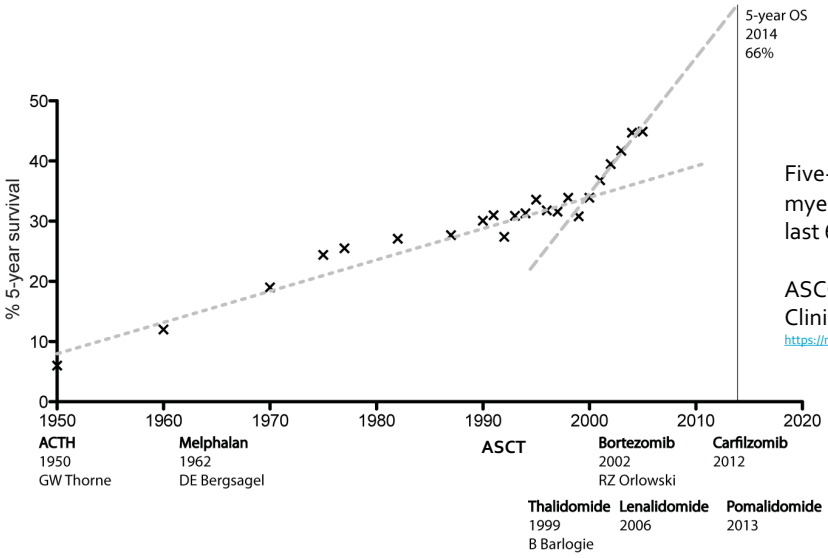

Five-year relative survival of multiple myeloma patients in the U.S. over the last 65 years

ASCO 2014, Dr. Leif Bergsagel, Mayo Clinic
https://meetinglibrary.asco.org/record/89162/edbook#fulltext

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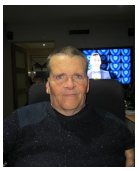
2001: 5 entities obtained orphan drug designation for Thalidomide to treat MM in the EU

- Obtained orphan drug designation
  - Laphal (pharmaceutical company, France)
  - Pharmacie Centrale des Hôpitaux (Central pharmacy of Paris University hospitals, France)
  - Kendle International ltd. (Consultant, United Kingdom)
  - Chemie Grünenthal (pharmaceutical company and originator manufacturer, Germany)
  - Pharmion, (pharmaceutical company, USA), designation on 9/07/2001
- Of which two submitted a marketing authorisation application in 2002:
  - Pharmion
  - Laphal (later acquired by Pharmion)

Immediate controversy "Thalidomide never again"



- **20 January 2003: victims of Thalidomide opposed to Thalidomide**
  - Press conference in front of EMA byThalidomide UK Freddie Astbury with EURORDIS
- ***"We never thought that this drug would come back. It seems to be coming back to haunt us."***
- EMA called for series of meetings with Multiple Myeloma patients and victims of thalidomide in 2003-2004 to discuss the proposed risk management plan
  - ***How to avoid any new accident if thalidomide is back on the market?***
  - ***Should we aim at tolerance o?***
  - ***Should MAH provide funds to secure financial support to future thalidomide victims? Or would the MAH be protected by European Commission's approval?***

EMA: blockage

- MM patients rejected the STEPS programme as not respecting their privacy, as over demanding, disproportionate, as inadequate, as practically impossible to comply with
  - As did EU lawyers in some Member States (obstruction to the profession of medical doctors and pharmacists…)
  - Among many questions: legal value of a consent form for an authorised product?
- Victims rejected the idea that Thalidomide could be authorised again, even with the STEPS programme
- EMA was listening (experts and an army of lawyers) but ill-at-ease to decide
- Then EURORDIS came with the solution…

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Three EURORDIS initiatives at the EMA 13/01/2004

Invited Dr Wijermans and Prof Moreau (independent investigators) to present clinical trials results on Thalidomide efficacy in Multiple Myeloma

- CHMP rapporteurs could not disclose the information (confidential, belonged to Pharmion, only safety and teratogenicity data could be presented)
- Yet, victims needed to know which benefits for MM patients to make their mind

EURORDIS asked all EMA staff and CHMP experts to leave the room

- To have only patients and victims in the room, for a singular dialogue

And asked all organisations to disclose their financial interests with Pharmion (no precedent at EMA – no framework for the interaction with patients)

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21 April 2004: EURORDIS expressed the voice of patients at a CHMP meeting

- *… No pharmaceutical company should be given the right to invade patients' privacy by investigating the patient's sexual activity monthly, or imposing the patient to call a computer assisted phone line to record health related information…*
- *When asked to explain thalidomide price increase at an EMA hearing 12 November 2003, Pharmion Vice-President explained, "**the increase is solely explained by the cost of the STEPS programme**" (MA minutes of the hearing)*
  - *(in response to concerns at European Parliament and in Member States that the Orphan Drug regulation translated for Thalidomide into a monopoly of a US based industry over European pharmaceutical groups with an important drug price increase (+380%) and clinical development publicly funded)*

Thalidomide price	France (ATU), Laphal	Pharmion Fra, Dnk, Aus
	50mg: 2.74 €	50 mg: 12 €
	100 mg: 4.75 €	100 mg: 22.8 €

May 2004: Pharmion withdrew its marketing application

- Pharmion failed to convince Celgene that the STEPS programme could not be accepted in the EU
- Celgene refused the Pregnancy Prevention Programme as proposed by patients and victims

June 2004, EURORDIS General Assembly, Cork
Ilse Hein, MM patient, explains the situation, and Pharmion is given the floor to respond

Relaunching the dialogue

- 17 January 2005: EURORDIS wrote to Pharmion denouncing the grey market Pharmion was perpetuating in the EU (no MA: absence of evidence-based medical practice)
- 20 January 2005: reply from Pharmion, OK to meet
- 21 June 2006: EURORDIS organised a round table with 20 participants:

Multiple Myeloma Patients	Victims	Pharmion	European Commission	Healthcare professionals
• Lia Van Ginneken, Netherlands • Doris Mayerböck, Austria • Morgane Yvon, France • Johan Creemers, Belgium • Peter Randlov, Denmark	• Margaret Hogg, United Kingdom • Bjorn Hakansson, Norway	• Pat Mahaffy, CEO • Alan Newlands, Director Regulatory Europe • Gillian Ivers-Read, VP Clinical and Regulatory • Selma Boussen, Medical Director	• Peter Arlett, Pharmaceuticals Unit	• Mary Ann de Vries, Apotheekzorg, The Netherlands • Prof Werner Linkesch, Univ. Graz, Austria • Prof Philippe Moreau, Univ. Nantes, France

EMA	National Authority (France)	Lawyer	Moderator (EURORDIS)
• Myriam Chapelin, pre-authorisation unit	• Dr Chantal Belorgey, Afssaps France	• Jean-Luc Laffineur, law firm, Belgium	• Yann Le Cam • François Houÿez

- Where Pharmion started to change their position, moving away from the STEPS programme

Thalidomide Clinical efficacy was demonstrated by clinical trials conducted by other sponsors than Celgene or Pharmion

Table 11: Summary of design and population characteristics of the studies included in the submission

Characteristic	MP + Thalidomide		Dex + Thalidomide	
	IFM 99-06	GISMM2001 (publication)	THAL-MM-003	E1A00
Design	International, multicenter, randomized, open-label, controlled, Phase III (pivotal)	Multicenter, randomized, open-label, controlled, Phase III	International, multicenter, randomized, double-blind, placebo-controlled, Phase III (pivotal)	Multicenter, randomized, open-label, controlled Phase III
Population	≥ 65 to ≤ 75 years (or < 65 but not eligible for treatment intensification protocol with bone marrow suppression conditioning), stage II or III per DS (stage I if high progressive potential), and no prior treatment for MM 447 pts randomized	> 65 years with DS stage II or III MM (younger if unable to undergo transplantation) 255 pts randomized	≥ 18 years with diagnosis of MM, DS stage II or III, and no prior treatment with systemic antimyeloma therapy (prior radiotherapy okay) 470 pts randomized	≥ 18 years with recent diagnosis of MM, no prior treatment 207 pts randomized

Abbreviations: Dex: dexamethasone; DS: Durie and Salmon classification [32]; MM: multiple myeloma ; MP: melphalan/prednisone.

Thalidomide European Public Assessment Report Summary EMA 2008

- IFM 99-06 sponsored by the Intergroupe Français du Myélome (NIH NCT00367185)
- GISMM2001 by Gruppo Italiano per lo Studio del Mieloma Multiplo (NCT00232934)
- E1A00 by the National Cancer Institute (NIH NCT00033332)
- THAL-MM-003 by Celgene but for a withdrawn indication

Phase III

IFM 99-06: 2000-2005

GISMM: 2002-2010

E1A00: 2002-2006

Thal MM 2003: 2003-2006

EU
5 competitors
in starting blocks

Victims and
MM patients
meet at EMA

Pharmion
withdrew
application

2001 2002 | 2003-4 | 2004 | 2006 | 2007

Pharmion
Laphal
Authorisation
Application

Victims and
MM patients
agreed on a
pregnancy
prevention
programme

EURORDIS
arbitration
meeting
(June)

Pharmion
2e MAA and
authorisation

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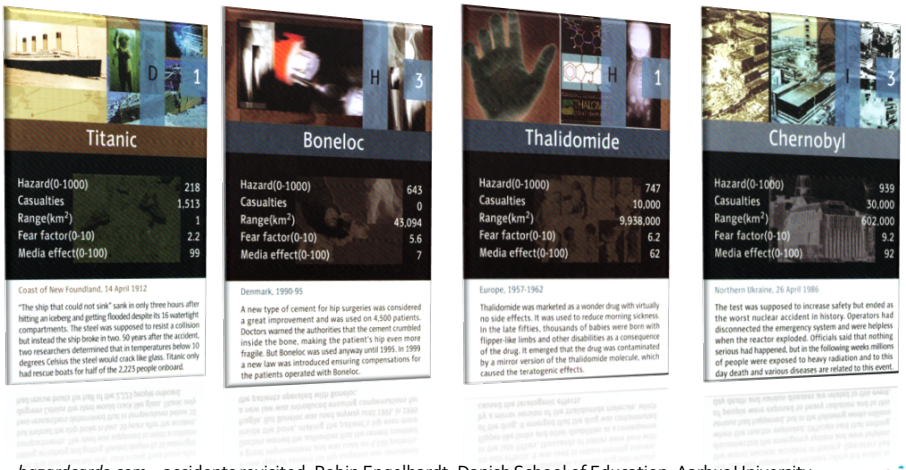
Nowadays: Thalidomide as a reference for the education of the public about risks



hazardcards.com – accidents revisited. Robin Engelhardt, Danish School of Education, Aarhus University

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- A second life for a medicine you would never have thought could come back
- Key role of patients in initial research
- Even greater role of patients in regulatory / Risk Management Plan, and of the victims
- 10 years after its re-use: no accident in the EU. Off-label use: 19-25%*. A drug now regulated with success

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Thank you for your attention.

François Houÿez

Director of Treatment Information and Access

francois.houyez@eurordis.org

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EURORDIS, the European Organisation for Rare Diseases

- Founded in 1997 to support the adoption of the Orphan Medicinal Products Regulation
- Rarity: fewer than 5/10,000 citizens or 230,000 patients in the EU (all RD: 3-4% of EU pop)
- Some 6,000 rare diseases, of which 1,200 with more than 5 published cases
- 779 member patient organisations, 726 in Europe (1,000 + rare diseases represented)
- 69 countries (28 EU Member States)
- Outreach to over 2,400 patient groups
- 40+ staff members in Paris (HQ), Brussels, Barcelona, London, Geneva, Belgrade
- 130+ volunteers

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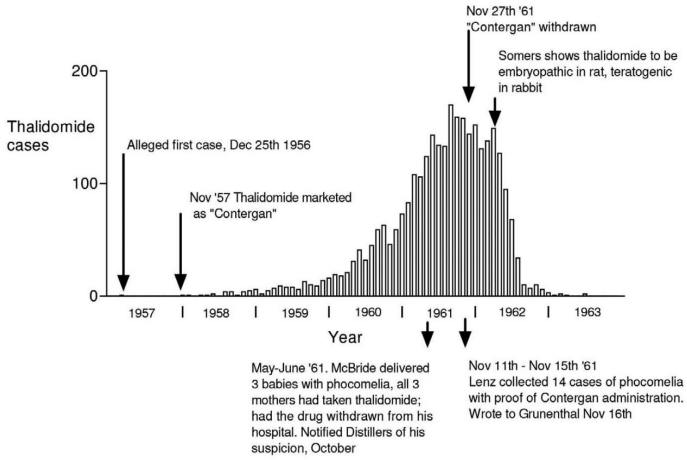
1956-1962
Thalidomide, one of the biggest medical tragedies of modern times



Botting, Jack Howard. "18. The History of Thalidomide". *Animals and Medicine : The Contribution of Animal Experiments to the Control of Disease.* By Botting. Cambridge : Open Book Publishers, 2015. (pp. 183-198) Web. <http://books.openedition.org/obp/1991>

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Pharmion agreement with Celgene (US)

- Pharmion had exclusive rights to use the "STEPS" programme marketed by Celgene in the US: "System for Thalidomide Education and Prescribing Safety"
  - Counselled by physician, educational materials
  - Registration of patient, informed consent
  - Negative blood pregnancy test: Initial, then monthly
  - 2 methods of contraception at the same time (median age of patients > 63 years)
  - Monthly telephone surveys to explain all about the sexual activity to computerised system
  - Prescription limited to one month supply
  - STEPS for prescribing physicians and pharmacists: control of medical practice and operation of the pharmacovigilance system by the MAH, no longer by pharmacovigilance experts
- STEPS was enormous, costly, complex, intrusive, minimising health professionals' responsibilities
- The "phantasmagorical illusion of safety"

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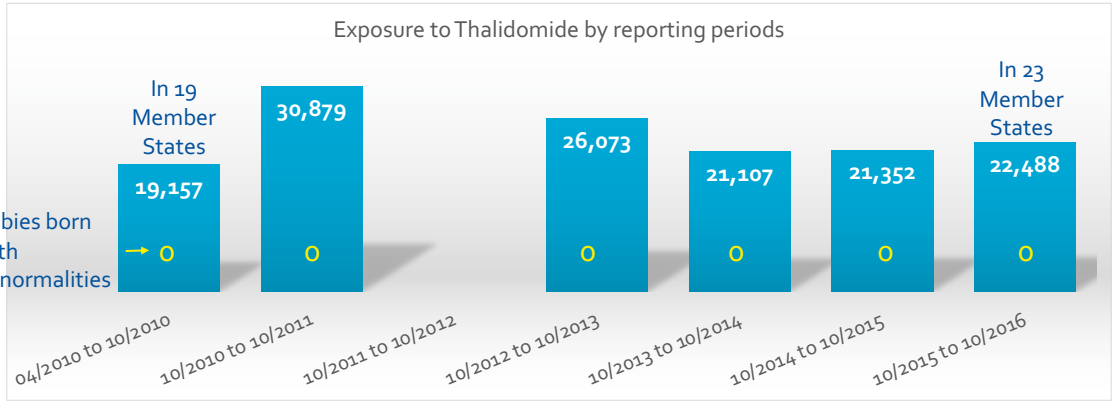
Worldwide exposure to thalidomide by reporting period

(off-label use* 19% to 25% of patients exposed to thalidomide)
Source: EMA PSURs. Data prior to April 2010 unavailable as considered as commercially confidential



*: mainly for systemic lupus erythematosus, myelodysplastic syndrome, myelofibrosis, Crohn's disease, neurodermatitis, brain neoplasm and Behcet's syndrome or first line to treat multiple myeloma

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Early signal
Dr Mc Bride

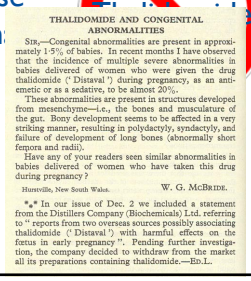
Leprosy

Anticancer properties

Research in MM

1956 1961 1962 1964 1994 1998

First use in hum



THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1-5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (" Distaval ") during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. McBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (" Distaval ") with harmful effects on the foetus in early pregnancy ". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

34 years

FDA APPROVAL

Leprosy

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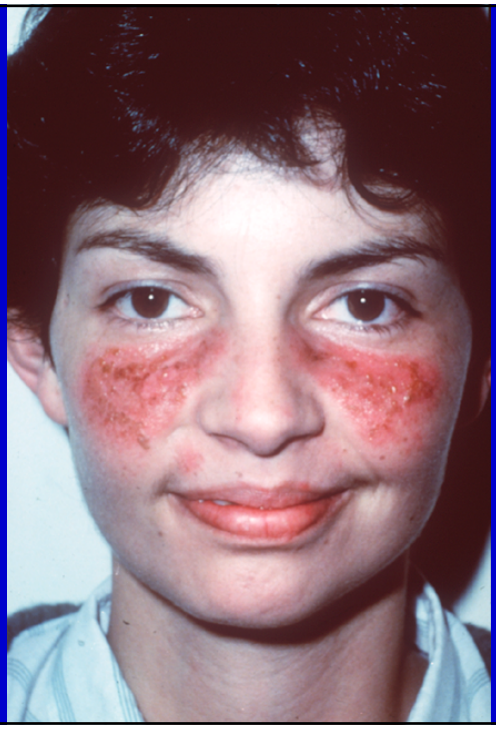
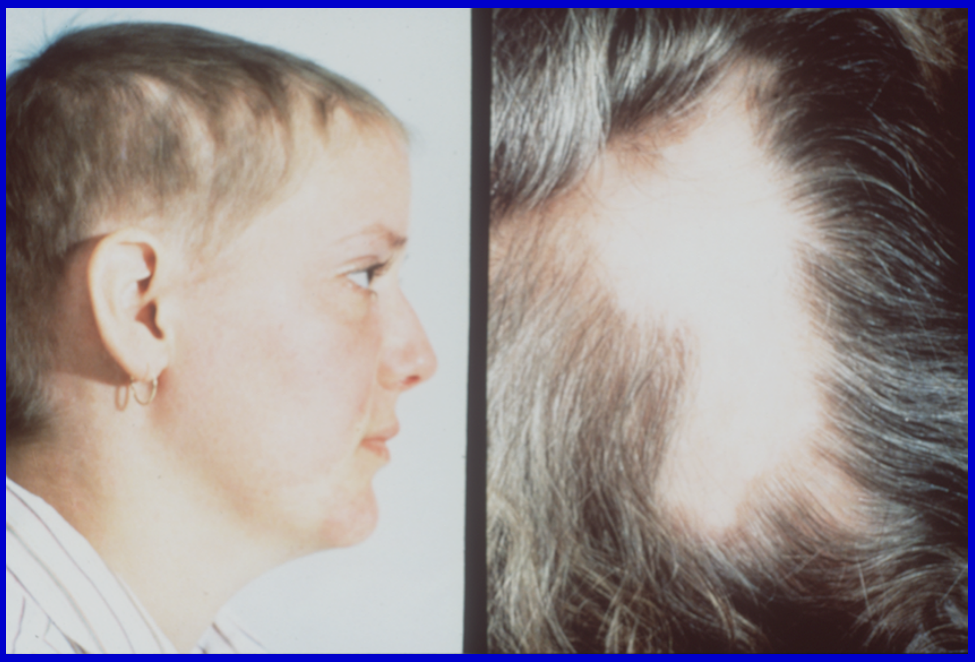
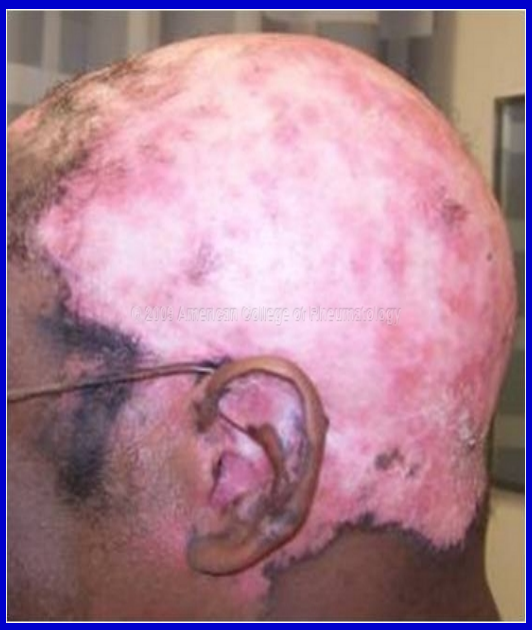
Examples of Clinical Success in SLE

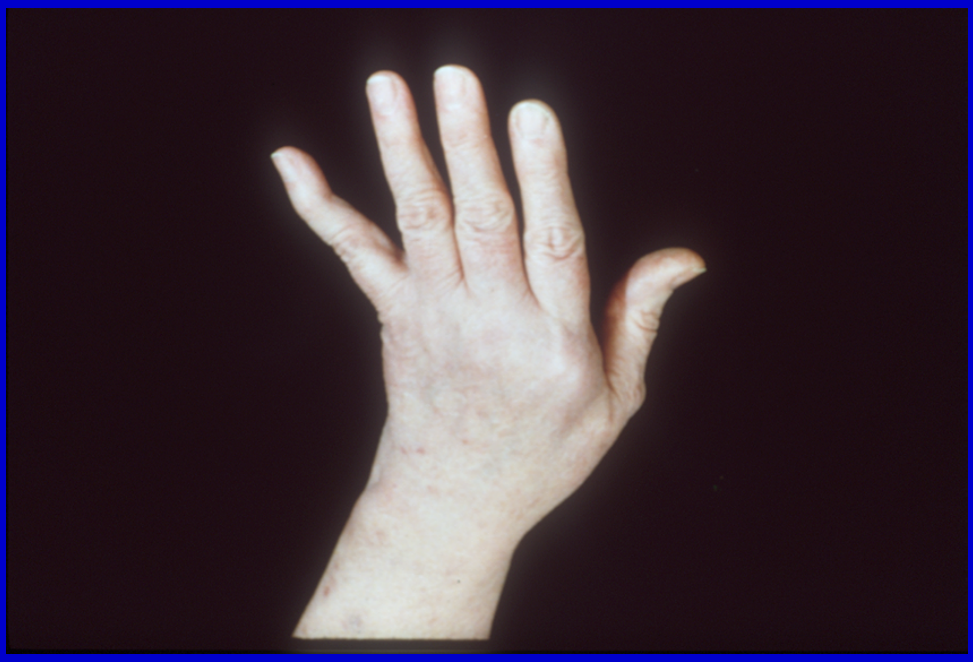
Michelle Petri, MD, MPH
Professor of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, Maryland

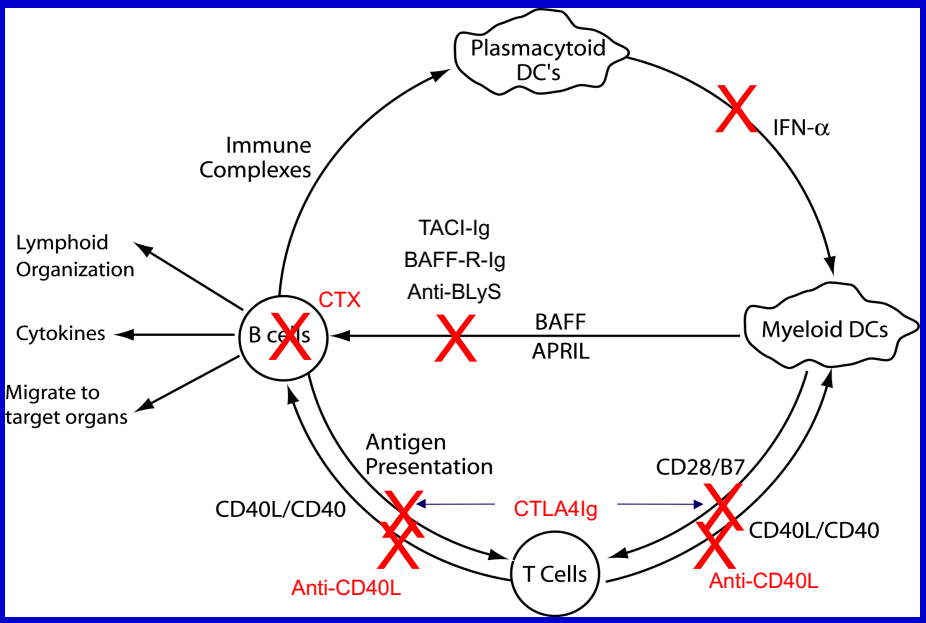
Recognize It When You See It











M. Ramanujam and A. Davidson. Arthritis Research and Therapy. 2004. 6:197-202.

Current Treatment Approaches

First Treatment Was An Accident!

Hydroxychloroquine Should Be Background Therapy in All SLE Patients

- Reduction in flares
  Canadian Hydroxychloroquine Study Group. N Engl J Med. 1991;324:150-4.
- Reduction in organ damage
  Fessler BJ, et al. Arthritis Rheum. 2005;52(5):1473-80.
- Reduction in lipids
  Petri M. Lupus. 1996;5(Suppl. 1):S16-S22.
  Wallace DJ, et al. Am J Med. 1990;89:322-6.
- Reduction in thrombosis
  Pierangeli SS, Harris EN. Lupus. 1996;5(5):451-5.
  Petri M. Curr Rheumatol Rep. 2011;13:77–80
- Triples mycophenolate response in lupus nephritis
  Kasitanon N, et al. Lupus. 2006;15(6):366-70.
- Improvement in survival
  Alarcon GS, et al. Arthritis Rheum 2005;52:S726.
  Ruiz-Irastorza G, et al. Lupus 2005;14:220.

The second treatment was “borrowed” from rheumatoid arthritis (it won a Nobel Prize for Dr. Hench).

Effect of Prednisone on Organ Damage

Adjusting for Confounding by Indication Due to SLE Disease Activity

Prednisone Average Dose	Hazard Ratio
> 0-6 mg/day	1.16
> 6-12 mg/day	1.50
>12-18 mg/day	1.64
> 18 mg/day	2.51

Thamer M, et al. *J Rheumatol*. 2009;36:560–564.

Prednisone Itself Increases the Risk of Cardiovascular Events

Prednisone use	Observed number of CVE	Rate of events/1000 person years	Age-adjusted rate ratios (95% CI)	P value
Never taken	22	13.3	1.0 (reference group)	
		Currently taking		
1-9 mg/d	32	12.3	1.3 (0.8, 2.0)	.31
10-19 mg/d	**31**	**20.2**	**2.4 (1.5, 3.8)**	**.0002**
20+mg/d	**25**	**35.4**	**5.1 (3.1,8.4)**	**<.0001**
		Cumulative past dose		
<3650 mg[1]	14	9.9	0.9 (0.4,1.6)	.56
3650-10,950 mg[2]	26	13.8	1.2 (0.7, 2.2)	.49
10,950-36,499 mg[3]	41	12.8	1.1 (0.6, 1.8)	.83
36,500+[4]	**30**	**25.3**	**2.2 (1.2,3.7)**	**.0066**

1. 3650 mg equals 10 mg/day for 1 year, or an equivalent cumulative exposure; 2. 1-3 years with 10 mg/day or an equivalent cumulative exposure; 3. 3-10 years with 10 mg/day or an equivalent cumulative exposure; 4.10+ years with 10 mg/day or an equivalent cumulative exposure; CVE=cardiovascular events

Magder LS, Petri M. *Am J Epidem.* 176:708-19, 2012.

The Next Treatments
Were All Borrowed

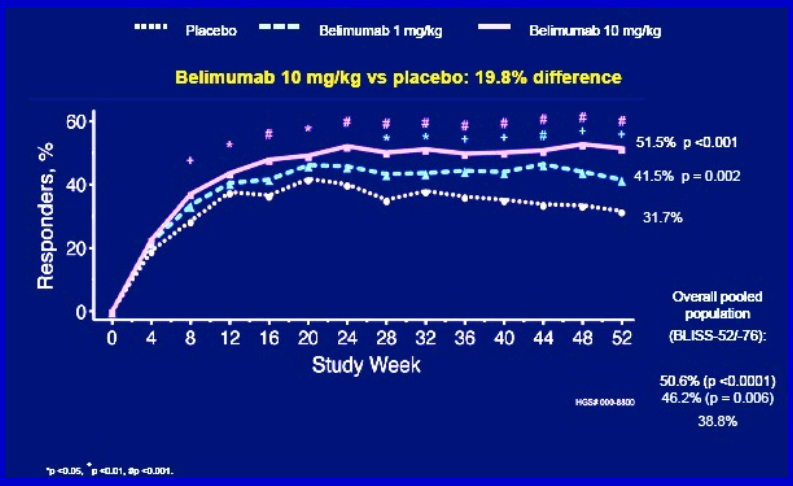
Immunosuppressive Approaches

- Drugs
  - Mycophenolate mofetil* (borrowed from transplant)
  - Methotrexate (borrowed from RA)
  - Azathioprine (borrowed from transplant)
- Biologics
  - Rituximab§ (borrowed from Oncology and RA)

*Chan TM, et al. *N Engl J Med*. 2000;343:1156–1162; Ginzler E, et al. Arthritis Rheum. 2003;48(9, Suppl.):S647.; Contreras G, et al. N Engl J Med 2004;350(10):971-80.
§Leandro MJ, et al. *Arthritis Rheum*. 2002;46:2673–2677.

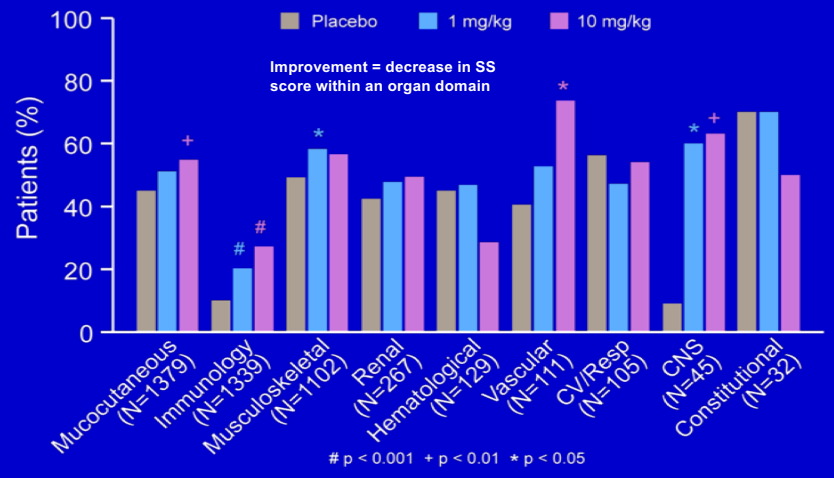
Finally, a Designer Treatment for Lupus!

The Subgroup with BOTH High Anti-dsDNA and Low Complement is About 20% More Likely to Respond to Belimumab



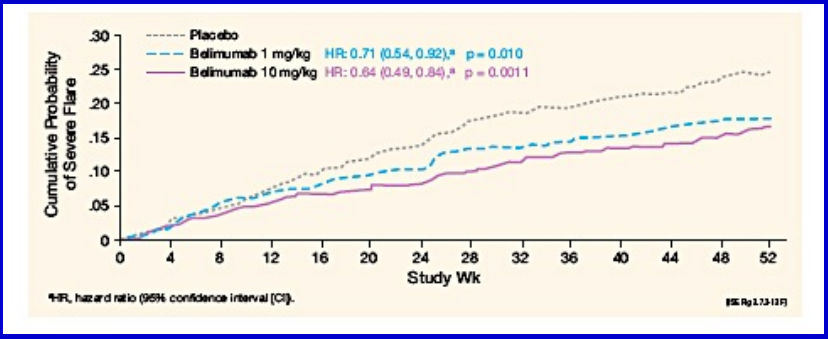
van Vollenhoven RF, et al. Presented at EULAR 2011; May 25-28, 2011; London, UK

A Post-hoc Analysis Shows the Organ Systems that Respond to Belimumab



Manzi S, et al. Ann Rheum Dis, 2012. [May Epub ahead of print, doi: 10.1136/annrheumdis-2011-200831].

Belimumab Reduced Severe Flares



Cervera R, et al. Presented at EULAR 2011: Annual European Congress of Rheumatology; May 25–28, 2011; London, UK

Seven Year Followup on Belimumab

- Open label 296 patients
- SLE Responder Index
  - Year 2 – 57%
  - Year 7 – 65%
- Anti-dsDNA 40-60%↓
- Prednisone 50-55%↓

Ginzler EM, et al. J Rheumatol. 2014;41:300-7

Drug Repositioning in SLE: An Innovative Approach

- Initiative of the Lupus Research Alliance begun in 2013.
- Used crowd-sourcing and literature mining to generate a large number of drug candidates from the list of compounds approved by the FDA (~1200 for 6800 indications).
- Prioritized list using the Combined Lupus Treatment Scoring (CoLTs) system. Score based on:
  - Scientific rationale
  - Pre-clinical experience in lupus mice/human cells
  - Clinical experience in autoimmunity
  - Drug properties
  - Safety profile, including adverse events
- High priority candidates validated through "Big Data" analysis of gene-expression data.

Grammer AC, et al. *Lupus* 25:1150-1170, 2016.

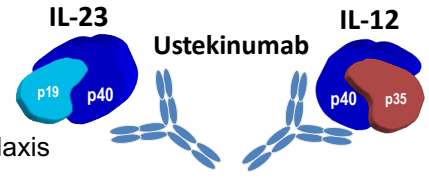
Candidate Drugs for Repositioning Into Lupus (CoLTs Score)

- Standard of Care
  - Belimumab (5)
  - Azathioprine (5)
  - Hydroxychloroquine (5)
  - Statins (3)
  - Quinacrine (7)
  - Rituximab (4)
- Candidate Drugs
  - Ustekinumab (10)
  - Autologous HSCT (5)
  - Bortezomib (6)

Grammer AC, et al. *Lupus* 25:1150-1170, 2016.

Ustekinumab Background

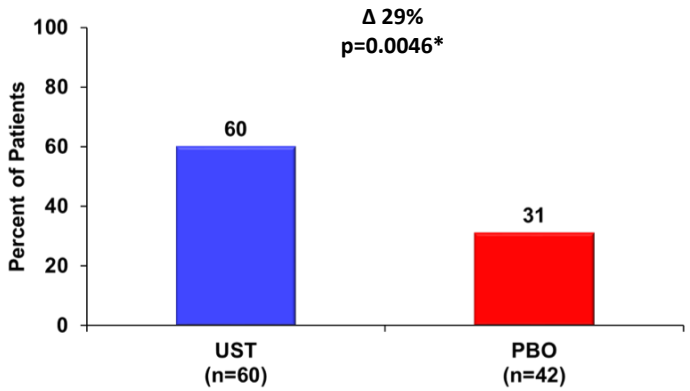
- Ustekinumab (UST) is a monoclonal antibody that blocks the shared p40 subunit of the cytokines IL-12 and IL-23
- UST is approved for the treatment of patients with:
  1. Moderate to severe plaque psoriasis
  2. Active psoriatic arthritis
  3. Moderate to severe Crohn's disease
  4. Adolescent (aged ≥12 years) moderate to severe plaque psoriasis
- The safety profile of UST is well established
  - As of December, 2016 >777,000 PYs exposure to UST
- Warnings and Precautions
  - Serious infections including TB
  - Malignancy risk in animals, not in humans
  - Hypersensitivity including anaphylaxis



*Ustekinumab is currently not indicated for SLE

Ustekinumab investigator's brochure; Florek, et al. *Br J Dermatol*. 2017.
FDA Label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761044lbl.pdf

UST Exhibited a Statistically Significant Improvement in SRI-4 Response at Wk 24 Compared to PBO: Primary Endpoint Analysis



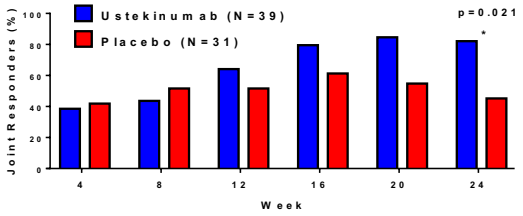
*p-value calculated by logistic regression with baseline SLEDAI, baseline SLE medication use, and race as covariates. Pre-specified analysis with α level 0.10.

Modified ITT analysis with treatment failures, dropouts, and missing data considered to be non-responders.

9 discontinued in PBO arm vs. 4 in the UST arm.

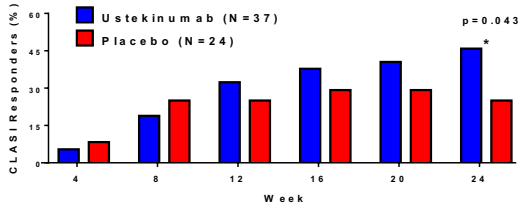
UST Demonstrated Greater Proportions of Patients with Improvement in Joint and Mucocutaneous Disease Compared to PBO

Post Hoc Exploratory Analysis



69% of Study Population with ≥4 Active Joints at BL

Responder defined as ≥50% improvement from baseline



60% of Study Population with CLASI activity score ≥4 at BL

Responder defined as ≥50% improvement from baseline

*p-value based upon logistic regression with treatment group, baseline SLEDAI, baseline medication use for SLE and race as covariates.
Modified ITT analysis with treatment failures, dropouts, and missing data considered to be non-responders.

El Greco – *St. Sebastian* (Prado)