膠原病JC 2021.9.22 by Dr. 大村

Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus

Richard Furie,[1] Victoria P. Werth,[2] Joseph F. Merola,[3] Lauren Stevenson,[4] Taylor L. Reynolds,[4] Himanshu Naik,[4] Wenting Wang,[4] Romy Christmann,[4] Agnes Gardet,[4] Alex Pellerin,[4] Stefan Hamann,[4] Pavan Auluck,[4] Catherine Barbey,[4] Parul Gulati,[4] Dania Rabah,[4] and Nathalie Franchimont[4]

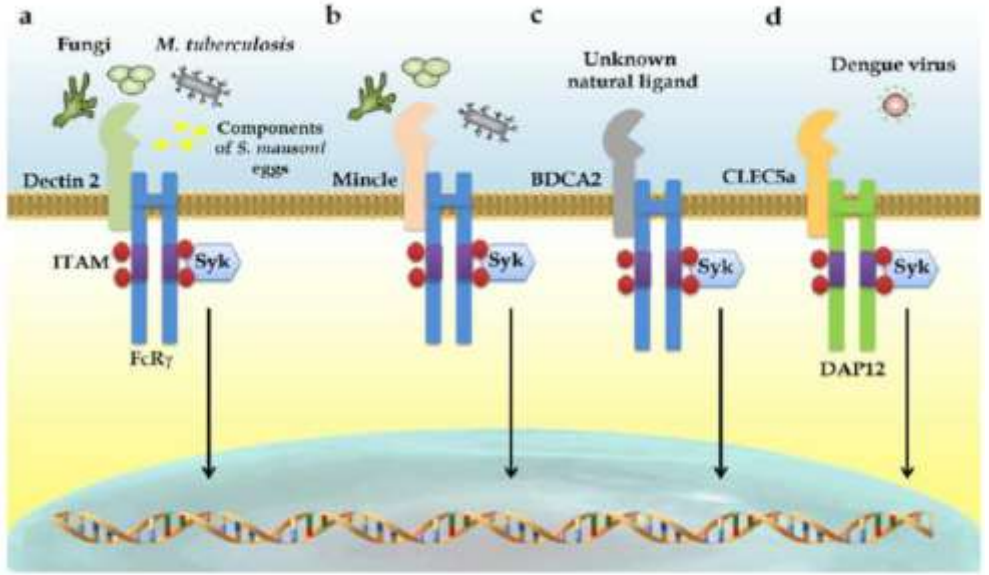
J. Clin Invest. 2019;129(3):1359-1371

論文を選んだ理由：**当院で間もなく開始されるSLE治験薬**のphase I結果であるため。
また、間もなく保険承認されるSLE治療薬Anifrolumab（抗type I IFN-R抗体）と作用機序が重なるため

BDCA2とは

plasmacytoid Dendritic Cell (pDC)上の特異抗原

C-type lectinのひとつ。ligand不明。



Signaling through ITAM-coupled C-type lectin receptors. Dectin-2, Mincle and BDCA2 do not contain defined signaling motifs in their cytoplasmic tail being incapable of inducing intracellular signaling on their own. Following ligand binding, these receptors associate with FcR leading to recruitment of Syk and subsequent activation of downstream signaling cascades (black arrows). CLEC5a also lacks a citoplasmatic catalytic domain. Recognition of Dengue virions by CLEC5a, results in the association and phosphorylation of DAP12, leading to recruitment of Syk and activation of Syk-dependent downstream signaling.

Bruno Miguel Neves　Protein Kinases www.intech.open

Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus

Richard Furie,[1] Victoria P. Werth,[2] Joseph F. Merola,[3] Lauren Stevenson,[4] Taylor L. Reynolds,[4] Himanshu Naik,[4] Wenting Wang,[4] Romy Christmann,[4] Agnes Gardet,[4] Alex Pellerin,[4] Stefan Hamann,[4] Pavan Auluck,[4] Catherine Barbey,[4] Parul Gulati,[4] Dania Rabah,[4] and Nathalie Franchimont[4]

J. Clin Invest. 2019;129(3):1359-1371

Part 2

P: 活動性皮疹(+)のSLE
E: BDCA2抗体/placebo投与
C: 健常人
O: CLASI-A score

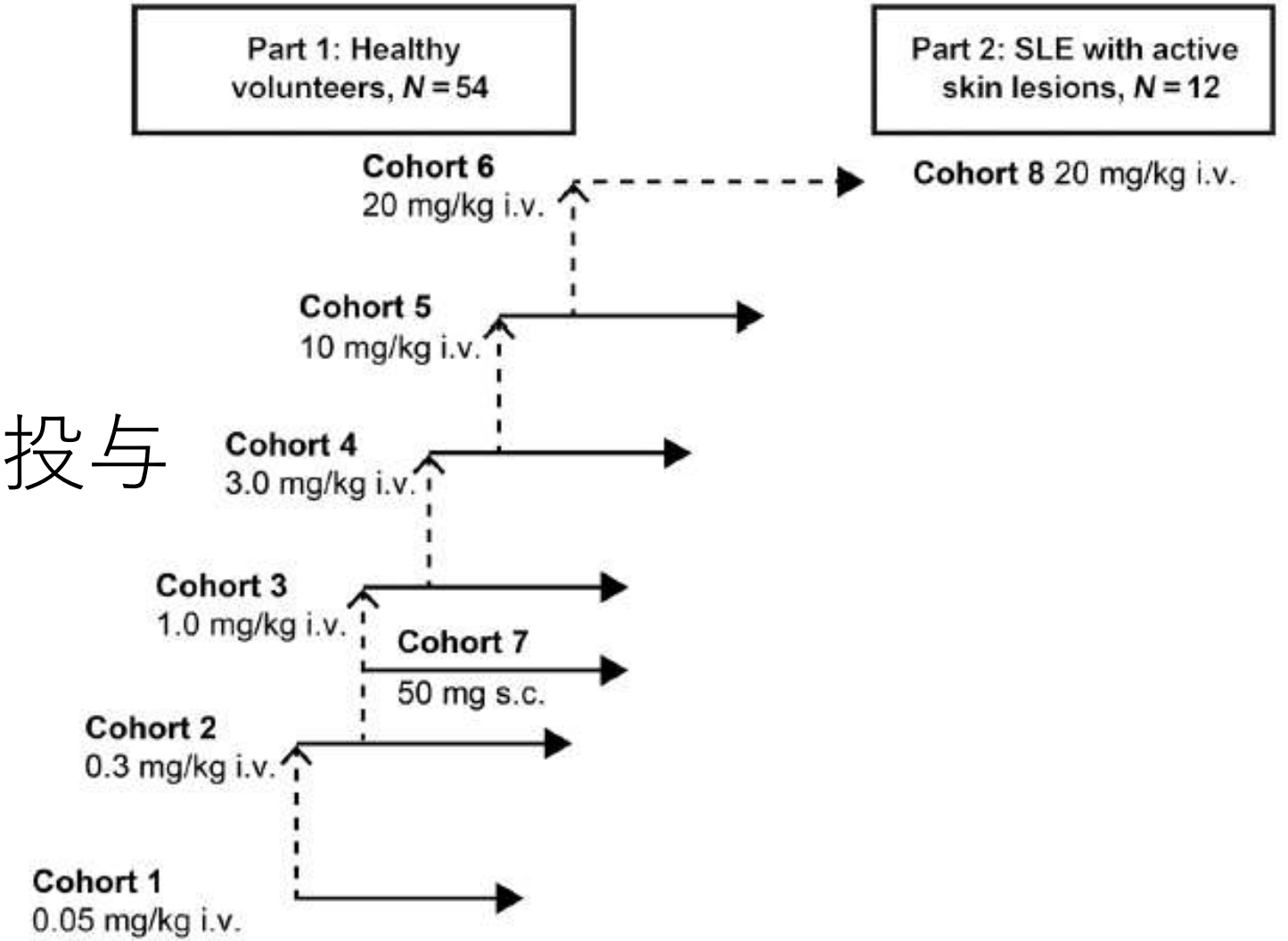


Figure 1. Study design. Single ascending dose in the HV cohorts and single dose in the SLE cohort.

Part 1. 健常者のBackground（省略します）

Table 1. Baseline characteristics of study participants: study part 1, HV

Characteristic	Pooled placebo (*n* = 16)	Pooled BIIB059 (*n* = 38)	Overall (*n* = 54)
Completed study, *n* (%)	14 (87.5)	36 (94.7)	50 (92.6)
Age, yr, mean (SD)	38.1 (11.7)	34.4 (10.6)	35.5 (10.9)
Female sex, *n* (%)	6 (38)	17 (45)	23 (43)
Race, *n* (%)			
Black/African American	4 (25)	12 (32)	16 (30)
White	10 (63)	22 (58)	32 (59)
Asian	–	1 (3)	1 (2)
American Indian/Alaskan native	–	1 (3)	1 (2)
Other	2 (13)	2 (5)	4 (7)
Body weight, kg, mean (SD)	79.9 (13.3)	73.3 (10.6)	75.2 (11.7)
Body mass index, kg/m^2, mean (SD)	25.9 (2.9)	24.1 (2.9)	24.7 (3.0)

Part 2. SLE患者のBackground

Table 2. Baseline characteristics of study participants: study part 2, patients with SLE

Characteristic	Placebo (*n* = 4)	BIIB059 (*n* = 8)	Overall (*n* = 12)
Completed study, *n* (%)	3 (75)	8 (100)	11 (92)
Age, yr, mean (SD)	43.3 (13.3)	41.1 (12.6)	41.8 (12.3)
Female sex, *n* (%)	4 (100)	8 (100)	12 (100)
Race, *n* (%)			
Black/African American	2 (50)	1 (13)	3 (25)
White	2 (50)	6 (75)	8 (67)
Asian	0	0	0
American Indian/Alaskan native	0	0	0
Other	0	1 (13)	1 (8)
Body weight, kg, mean (SD)	73.6 (14.5)	68.9 (9.8)	70.5 (11.2)
Body mass index, kg/m^2, mean (SD)	27.0 (6.9)	24.6 (3.2)	25.4 (4.6)
CLE classification (A/S/C)[A]	0/2/2	4/1/3	4/3/5
CLASI-A score, mean (SD)	16.3 (19.2)	10.4 (5.4)	12.3 (11.3)
SLEDAI-2K score mean (SD)	7.5 (3.4)	5.9 (4.7)	6.4 (4.2)

Table 2. Baseline characteristics of study participants: study part 2, patients with SLE

Characteristic	Placebo (*n* = 4)	BIIB059 (*n* = 8)	Overall (*n* = 12)
Antinuclear Ab, *n* (%)	4 (100)	8 (100)	12 (100)
Anti-dsDNA	0	1 (13)	1 (8)
Anti-Smith	0	2 (25)	2 (17)
Anti-SSA	2 (50)	7 (88)	9 (75)
Anti-SSB	0	1 (13)	1 (8)
Anti-RNP	2 (50)	5 (63)	7 (58)
Concomitant medications, *n* (%)			
Antimalarials[B]	1 (25)	2 (25)	3 (25)
Azathioprine	0	0	0
Methotrexate	0	1 (13)	1 (8)
Topical steroids	0	0	0
Oral corticosteroids[C]	0	2 (25)	1 (17)

CLASI (cutaneous lupus erythematosus disease area and severity index)とは

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

Extent

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 … absent 1 … scarring 2 … severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Albrecht J et al., J Invest Dermatol 125:889 –894, 2005

CLASI
続き

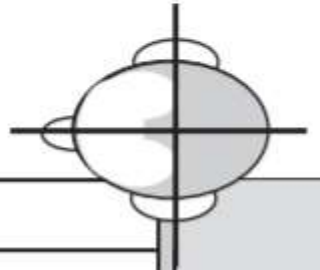
Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient … tick appropriate box)
☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains) ☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days/as reported by patient)	
1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

CLASI-A score

Total Activity Score
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

有害事象

Table 3. Safety summary: study part 2, patients with SLE

Subjects, *n* (%)	Placebo	BIIB059
Dosed	4	8
With any AE	3 (75)	7 (88)
Moderate event	2 (50)	4 (50)
Severe event	1 (25)	1 (13)
Related event	1 (25)	1 (13)
Serious event/related serious event	0/0	1 (13)
Discontinuation/withdrawal due to event	0/0	0/0

治験薬の血中濃度推移（単回投与）（省略します）

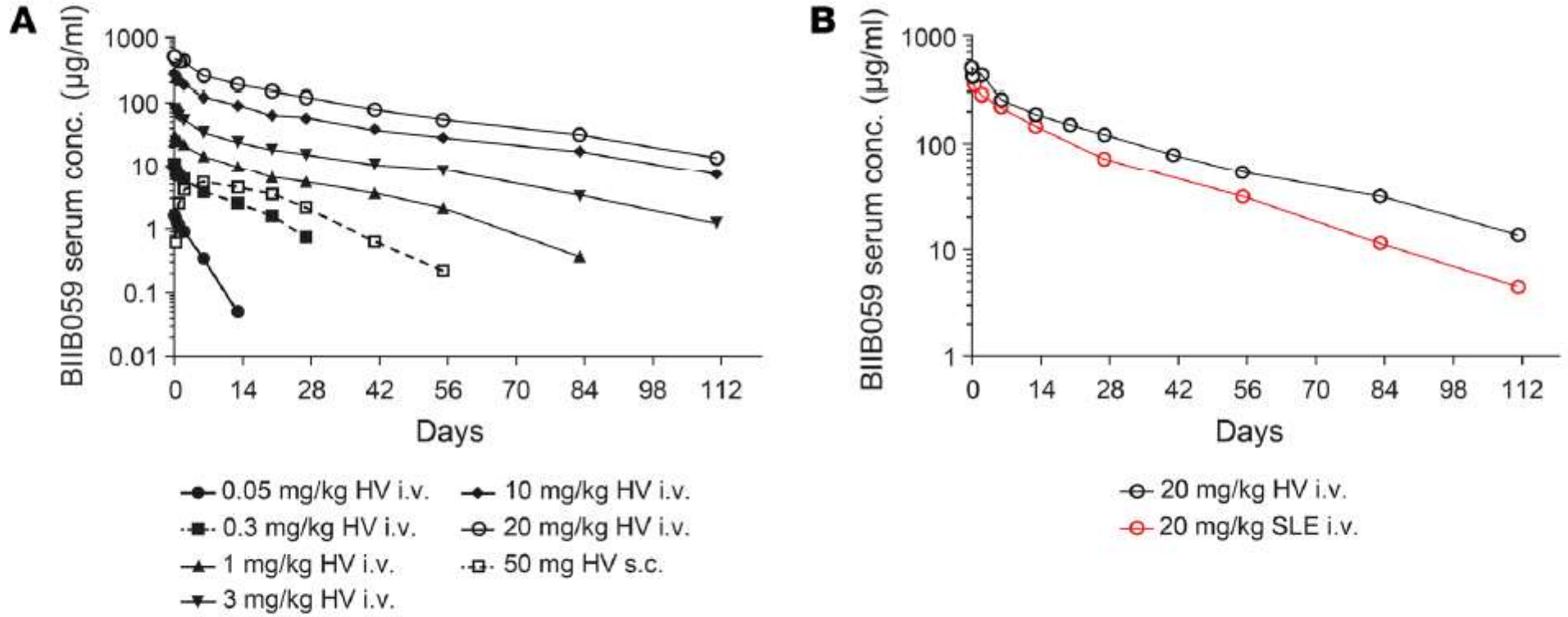


Figure 2. BIIB059 PK profile in HV and a cohort of patients with SLE with active cutaneous lupus. BIIB059 serum levels were measured using ELISA. (**A**) PK of single ascending dose of BIIB059 in HV (*n* = 38) and (**B**) PK of 20 mg/kg BIIB059 in HV (black line) (*n* = 6) and patients with SLE (red line) (*n* = 8). Arithmetic mean values are represented. conc., concentrations.

治験薬の薬効動態（PK）(省略します)

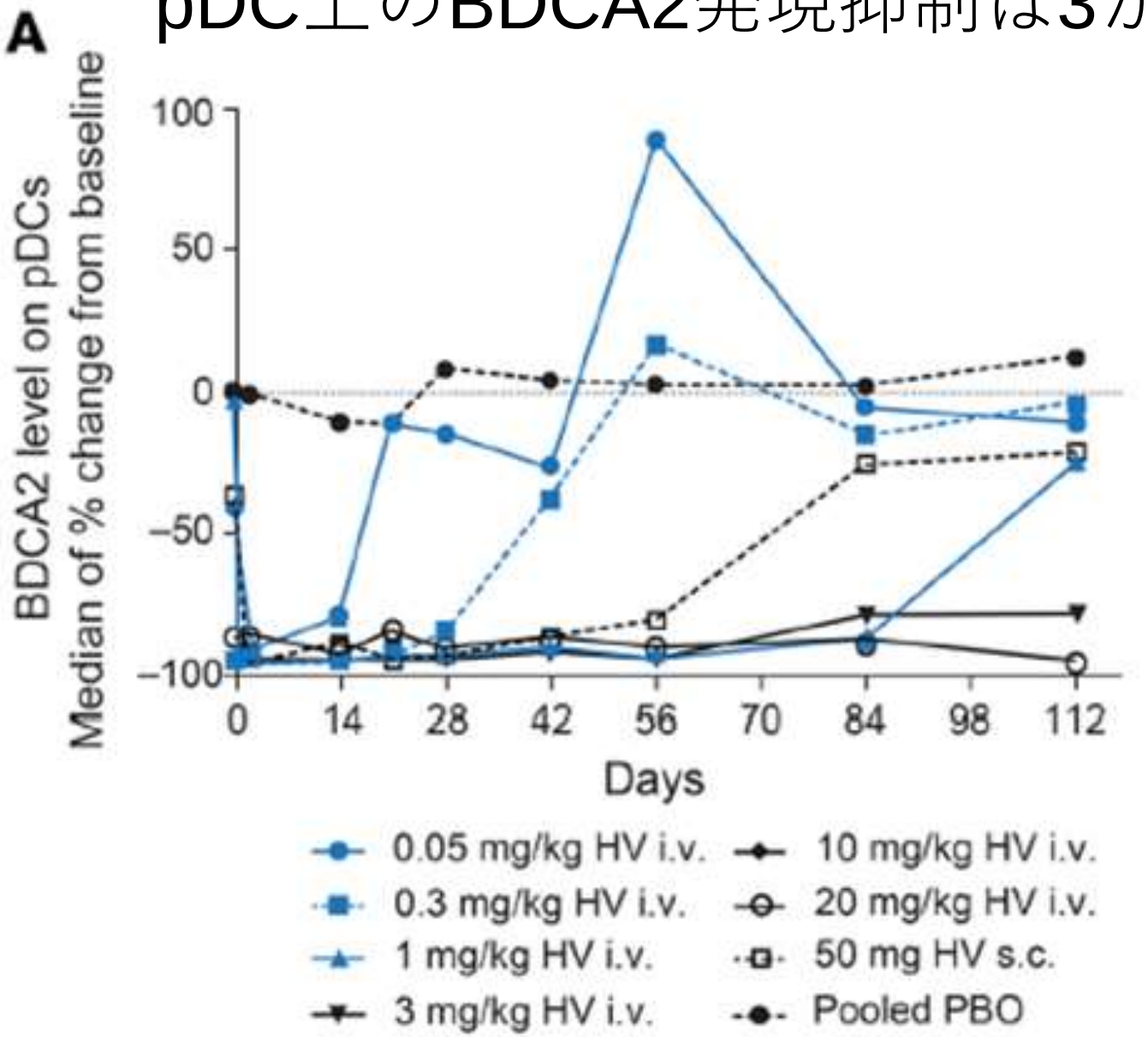
Table 4. PK parameters

	HV							Patients with SLE
Variable, mean (% CV)	0.05 mg/kg i.v.	0.3 mg/kg i.v.	1 mg/kg i.v.	3 mg/kg i.v.	10 mg/kg i.v.	20 mg/kg i.v.	50 mg s.c.	20 mg/kg i.v.
AUC_t, µg/ml/hr	119 (50.8)	1865 (36.8)	10246 (21.2)	30758 (30.2)	111535 (21.9)	225560 (17.8)	3013 (32.5)	158191.8 (36)
AUC_∞, µg/ml/hr	229 (NC)	2188 (45.5)	11105 (21.3)	32056 (31.6)	121191 (21.1)	246903 (13.3)	3508 (27.5)	162499.4 (37)
C_{max}, µg/ml	1.68 (9.8)	10.9 (25.4)	31.7 (11.7)	82.5 (12.1)	280 (23)	603 (10.6)	5.56 (16.1)	473 (31.6)
t_{max}, hours	NA	NA	NA	NA	NA	NA	144	NA
$t_{1/2}$, days	3.5 (27)	8.5 (38.8)	16.8 (34)	18.6 (47.4)	27.3 (20.3)	27.2 (14.6)	11.8 (36.3)	18.1 (40.8)

CV, coevfficient of variation; NC, not calculated.

治験薬の薬効動態（PK) 薬力学（PD)

pDC上のBDCA2発現抑制は3か月以上続く



治験薬の薬効動態（PK）薬力学（PD）（Fig.3B-D省略します）

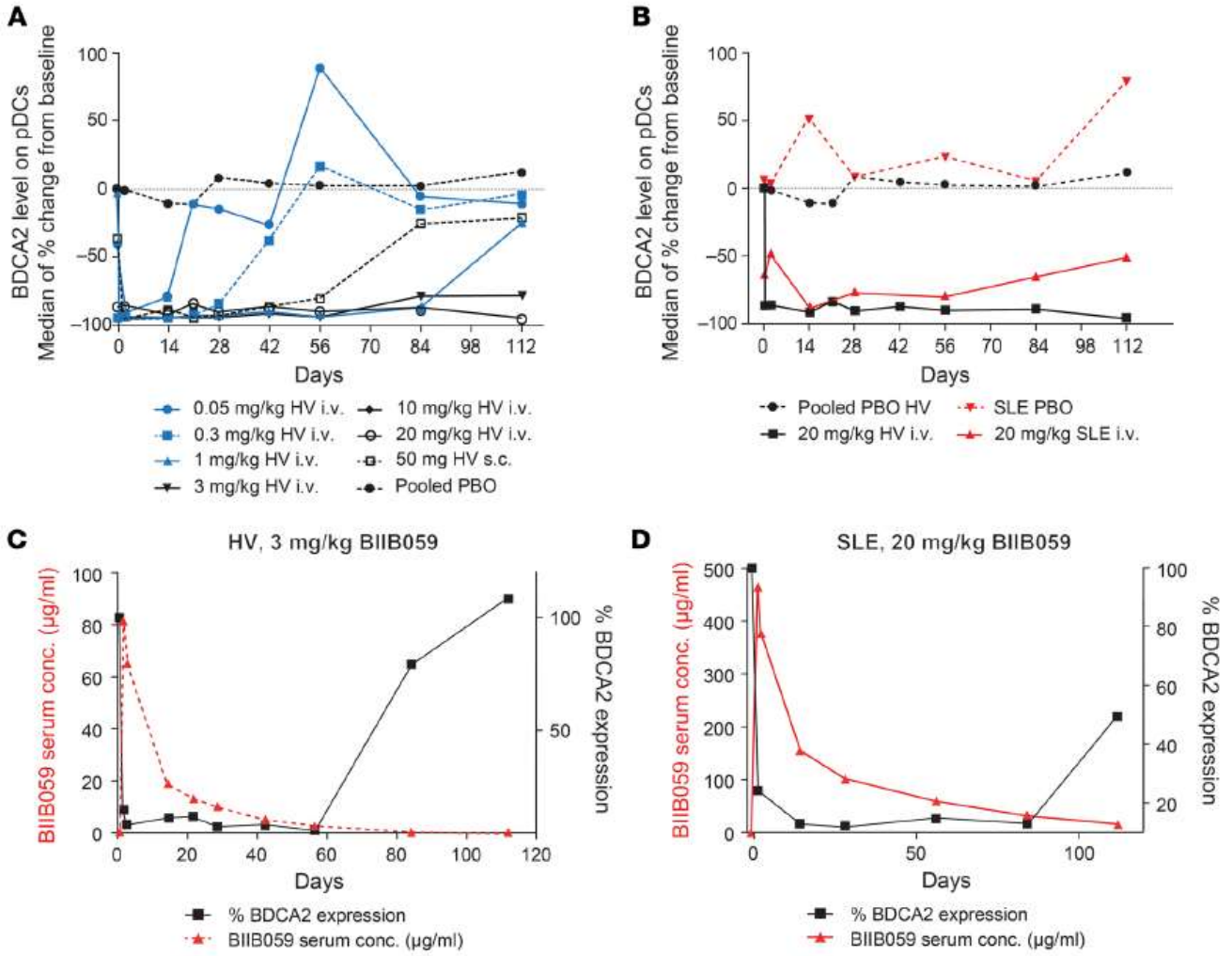
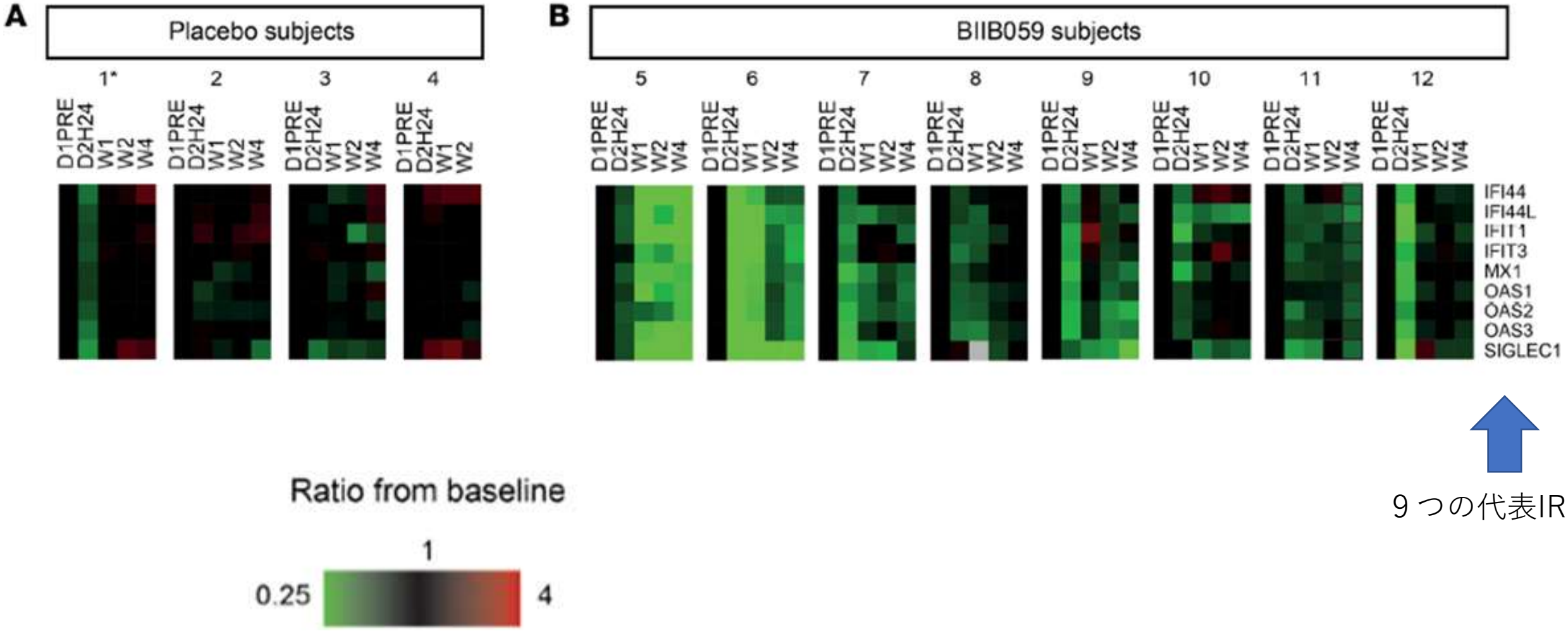


Figure 3. BIIB059 demonstrates PK and PD correlations in both HV and a cohort of patients with SLE. (**A** and **B**) BDCA2 levels on pDCs as the median percentage change in BDCA2 levels normalized to baseline level in HV placebo (PBO) cohort (n = 16), HV BIIB059-treated cohort (n = 38), SLE PBO (n = 4), SLE BIIB059-treated cohort (n = 8). Fluorescent-labeled noncrossblocking anti-BDCA2 mAb (2D6) was used to label surface BDCA2 on the pDC population ($CD123^+$ $HLA\text{-}DR^+$) in whole blood using flow cytometry. (**C** and **D**) PK/PD relationship between BIIB059 serum concentrations (red triangles, left axis) and BDCA2 expression on pDCs (black squares, right axis, normalized to baseline levels). Panel **C** depicts a representative HV from the 3 mg/kg dose group (n = 6). Panel **D** depicts a representative patient with SLE (20 mg/kg) (n = 8).

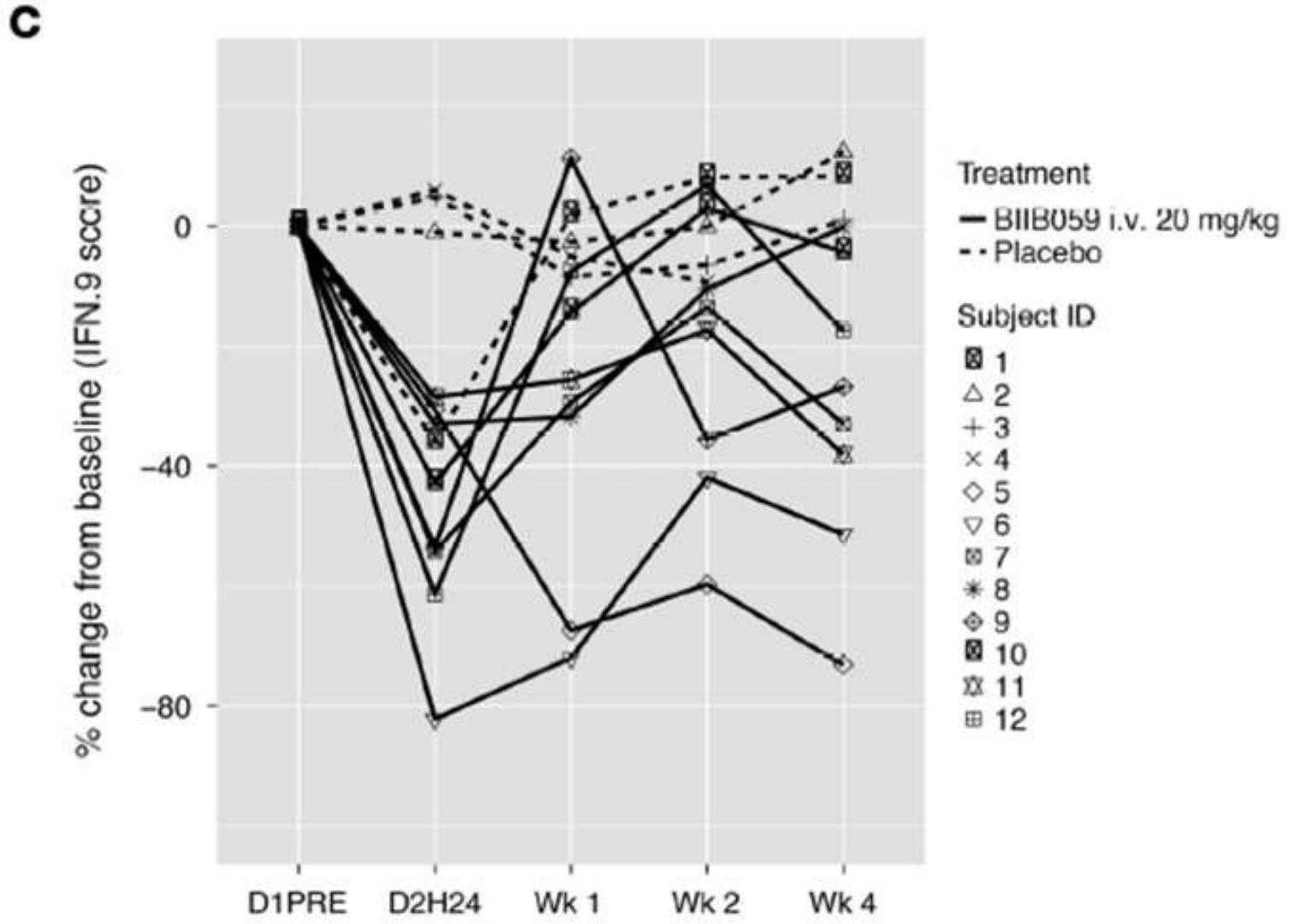
末梢血Interferon Regulated Genes (IRG)の動き



9つの代表IRG

Figure 4. Single dose of BIIB059 in patients with SLE dampens the expression of IRG in whole blood. Whole blood was collected in PAXgene Blood RNA Tubes. After RNA isolation, the expression of IRG was analyzed using the Fluidigm BioMark HD System. The ratio from baseline is shown for (**A**) placebo and (**B**) BIIB059 treatment of patients with SLE (**C**). Percentage change from baseline of the IFN score based on the 9 IRGs in individual patients.
*Subject 1 initiated steroid treatment during the study.

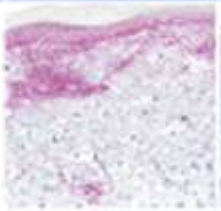
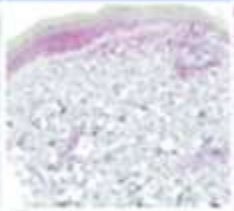
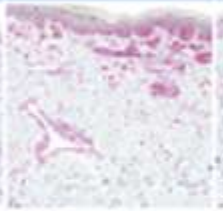
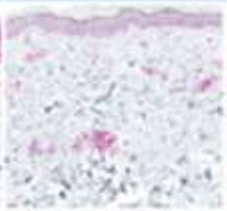
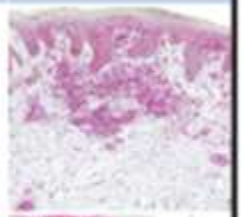
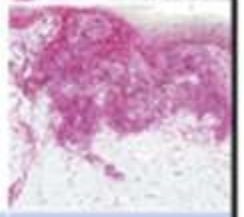
末梢血Interferon Regulated Genes (IRG)の動き



IFN関連蛋白（MxA)の発現とCLASI-Aスコアの変化

抗BDCA2抗体投与患者8例

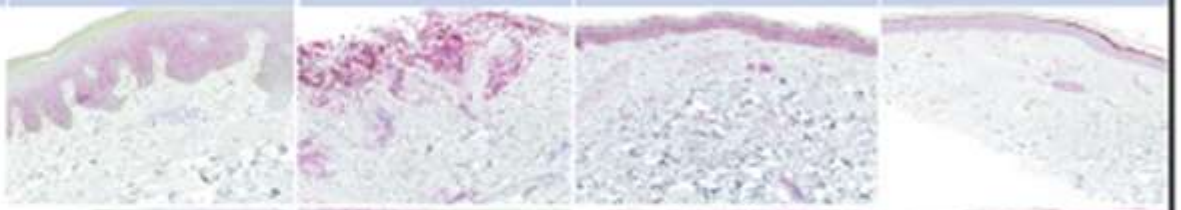
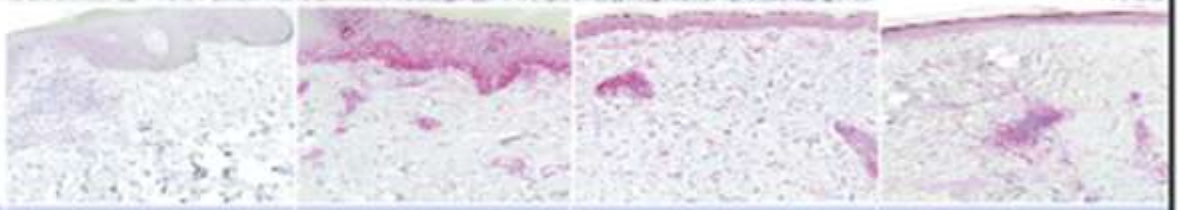
B

	Timepoint	Subject / CLE Subtype: 5 SCLE	6 ACLE	7 ACLE	8 DLE	9 ACLE	10 ACLE	11 DLE	12 DLE
MxA area Epidermis	Day −1 Week 4	58.4% 0.1%	1.2% 0.4%	21.0% 2.2%	34.3% 1.0%	23.1% 2.4%	26.4% 3.6%	ND ND	57.5% 78.4%
MxA histology	Day −1							ND	
	Week 4							ND	
CLASI-A score	Day −1 Week 4 Week 12	9 0 0	5 0 0	6 2 4	10 6 6	14 8 2	18 8 7	4 5 4	17 15 18
CLASI response		R	R	R	R	R	R	NR	NR

IFN関連蛋白（MxA)の発現とCLASI-Aスコアの変化

プラセボ投与患者4例

A

	Timepoint	Subject / CLE Subtype			
		1* SCLE	2 DLE	3 SCLE/DLE	4 DLE
MxA area Epidermis	Day −1	9.1%	54.3%	41.6%	17.3%
	Week 4	0.1%	29.4%	54.7%	45.1%
MxA histology	Day −1				
	Week 4				
CLASI-A score	Day −1	45	7	5	8
	Week 4	26	7	4	9
	Week 12	4	ND	8	7
CLASI response		R	NR	NR	NR

＊ 1の患者は途中でステロイド治療を開始された

IFN関連蛋白（MxA)の発現とCLASI-Aスコアの変化

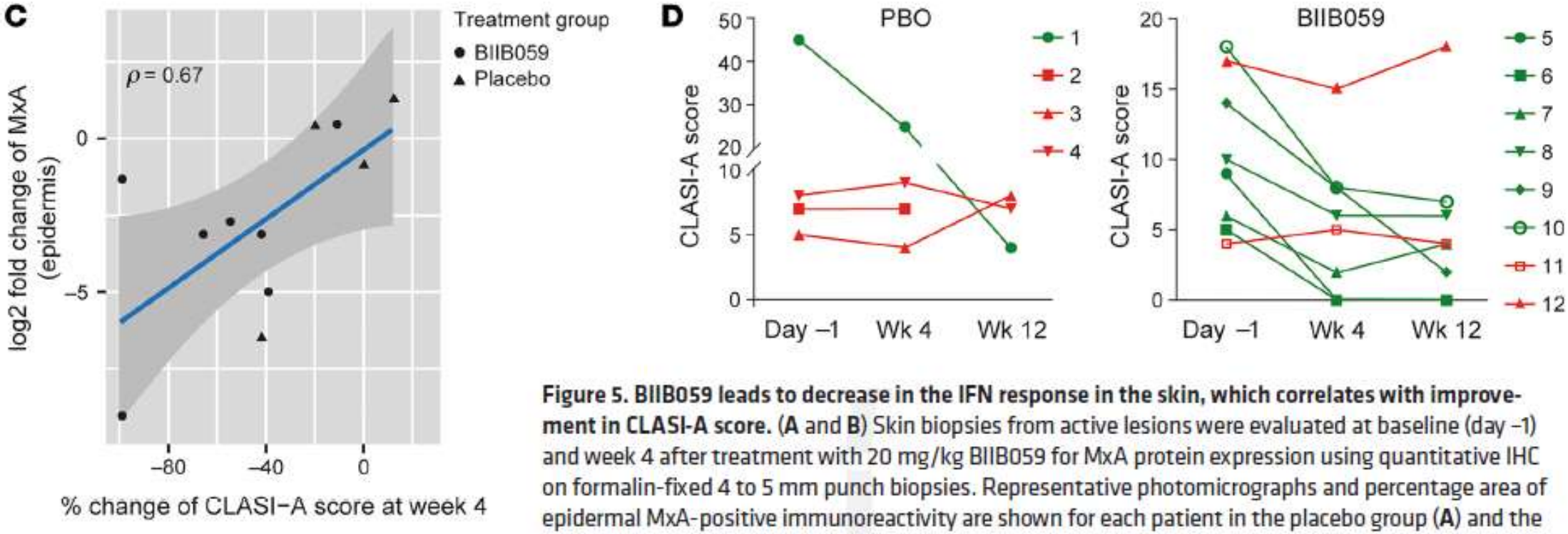
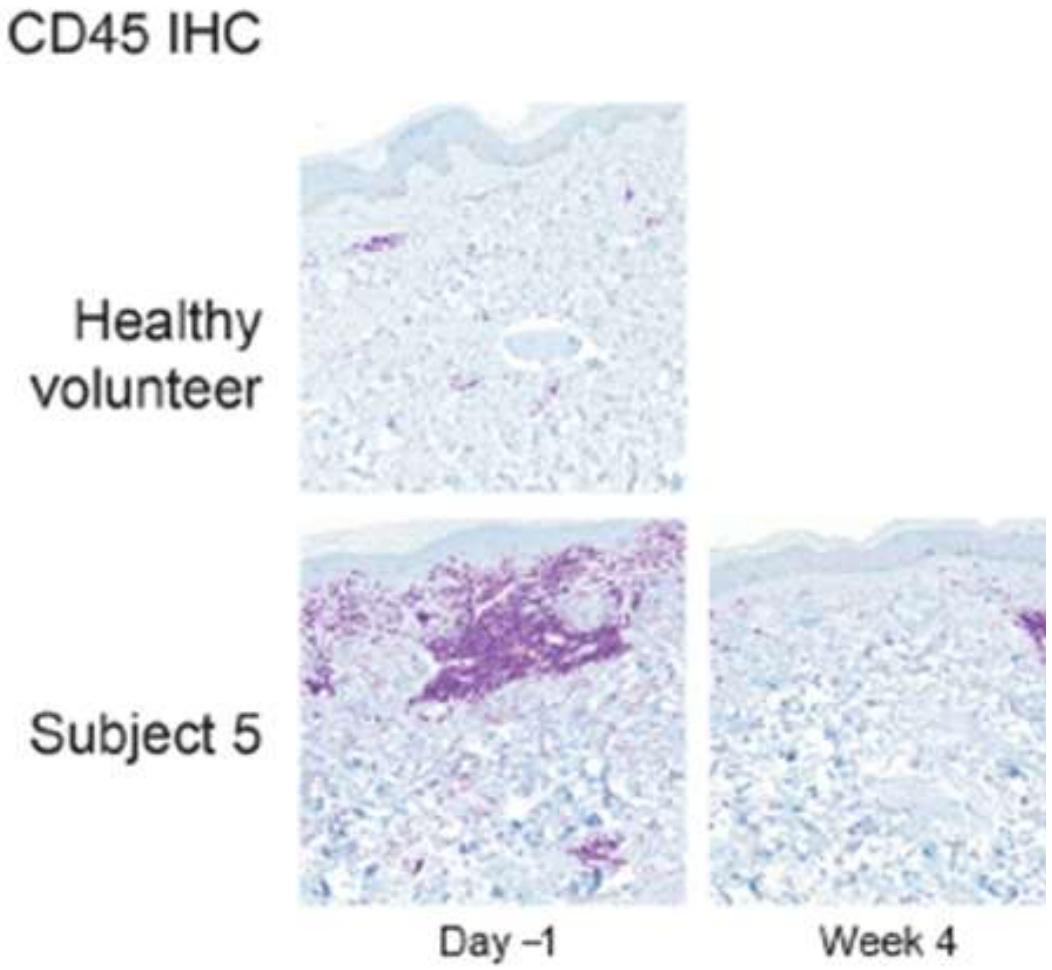
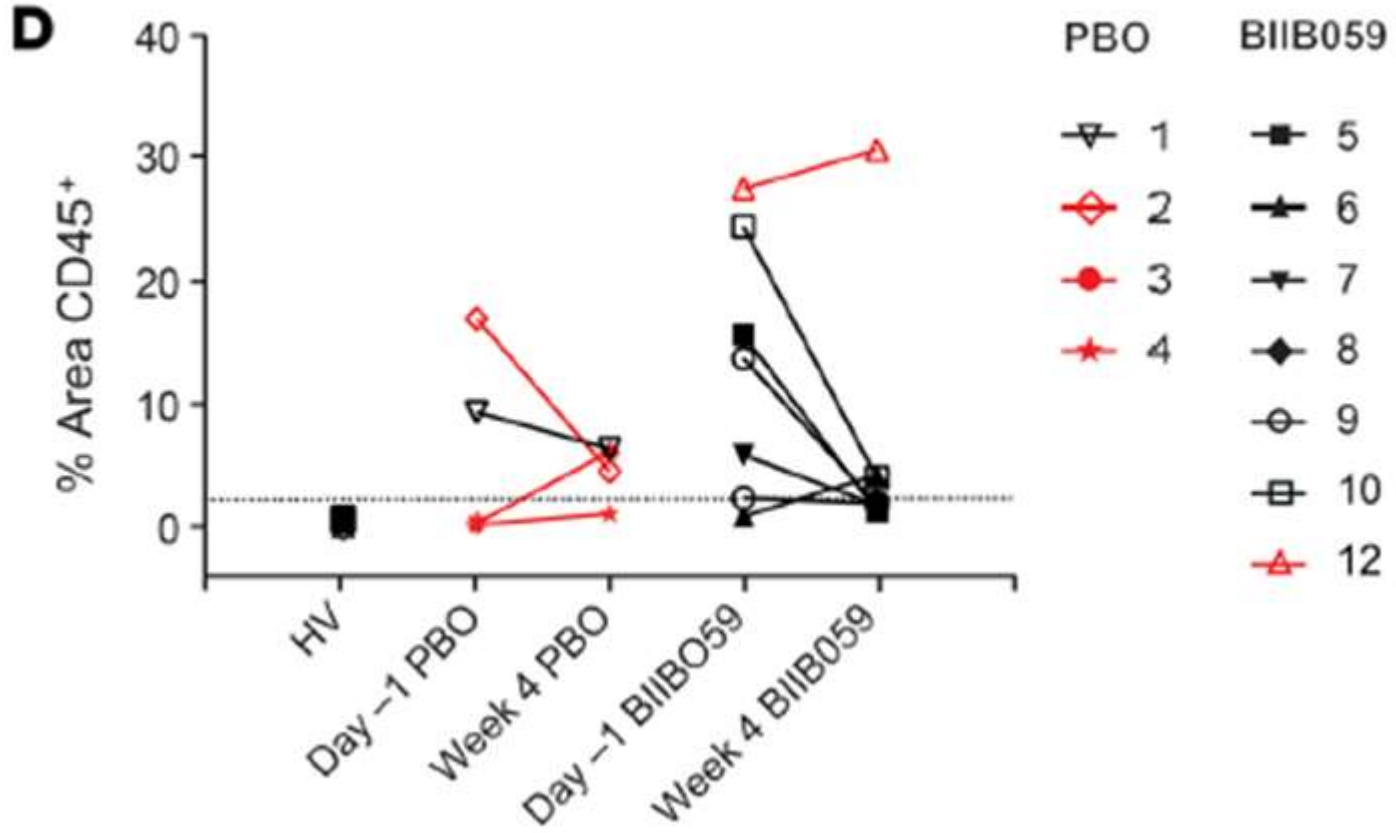


Figure 5. BIIB059 leads to decrease in the IFN response in the skin, which correlates with improvement in CLASI-A score. (**A** and **B**) Skin biopsies from active lesions were evaluated at baseline (day −1) and week 4 after treatment with 20 mg/kg BIIB059 for MxA protein expression using quantitative IHC on formalin-fixed 4 to 5 mm punch biopsies. Representative photomicrographs and percentage area of epidermal MxA-positive immunoreactivity are shown for each patient in the placebo group (**A**) and the BIIB059-treated group (**B**). CLASI-A scores were evaluated at day −1, week 4, and week 12 after treatment for placebo-treated (**A**) and BIIB059-treated (**B**) patients with SLE. Response is defined as a 4 or more point reduction from baseline in CLASI-A score at week 4 and/or week 12. Responders are depicted in green, nonresponders in red. (**C**) Correlation plot of percentage change in MxA expression from baseline and percentage CLASI-A score change from baseline for all patients (placebo treated, circles; BIIB059 treated, triangles). (**D**) CLASI-A response over time; CLASI-A responders are depicted in green, nonresponders in red. *Subject 1 initiated steroid treatment during the study. ACLE, acute CLE; DLE, discoid lupus erythematosus; ND, not determined; NR, no response; R, response; SCLE, subacute CLE.

* 1の患者は途中でステロイド治療を開始された

血球細胞（CD45+)の治療前後の変化





まとめ

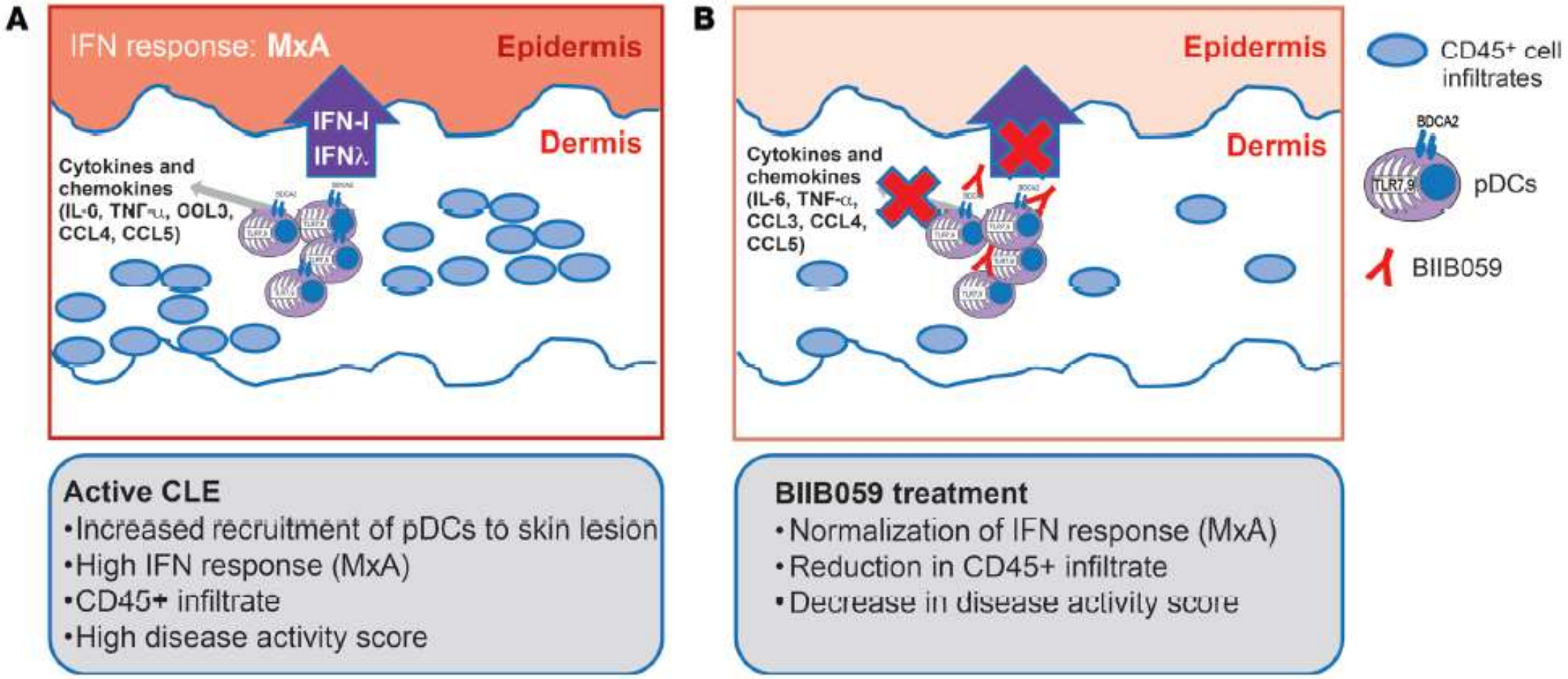
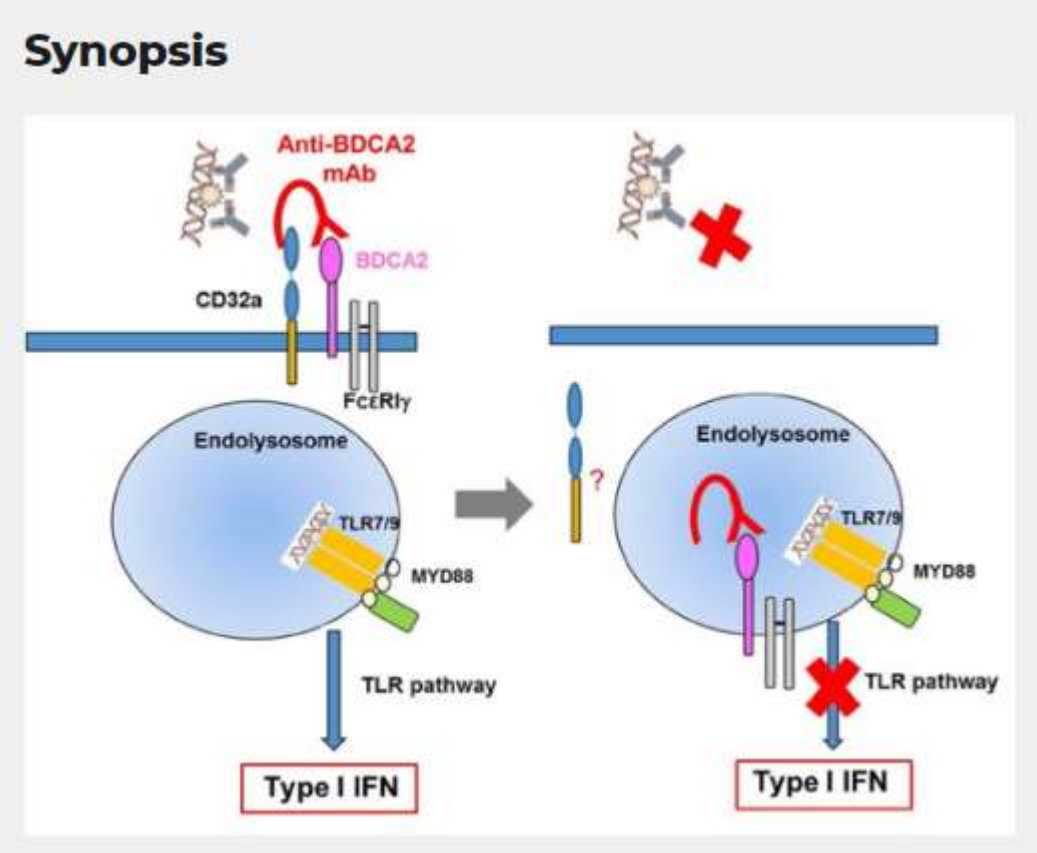


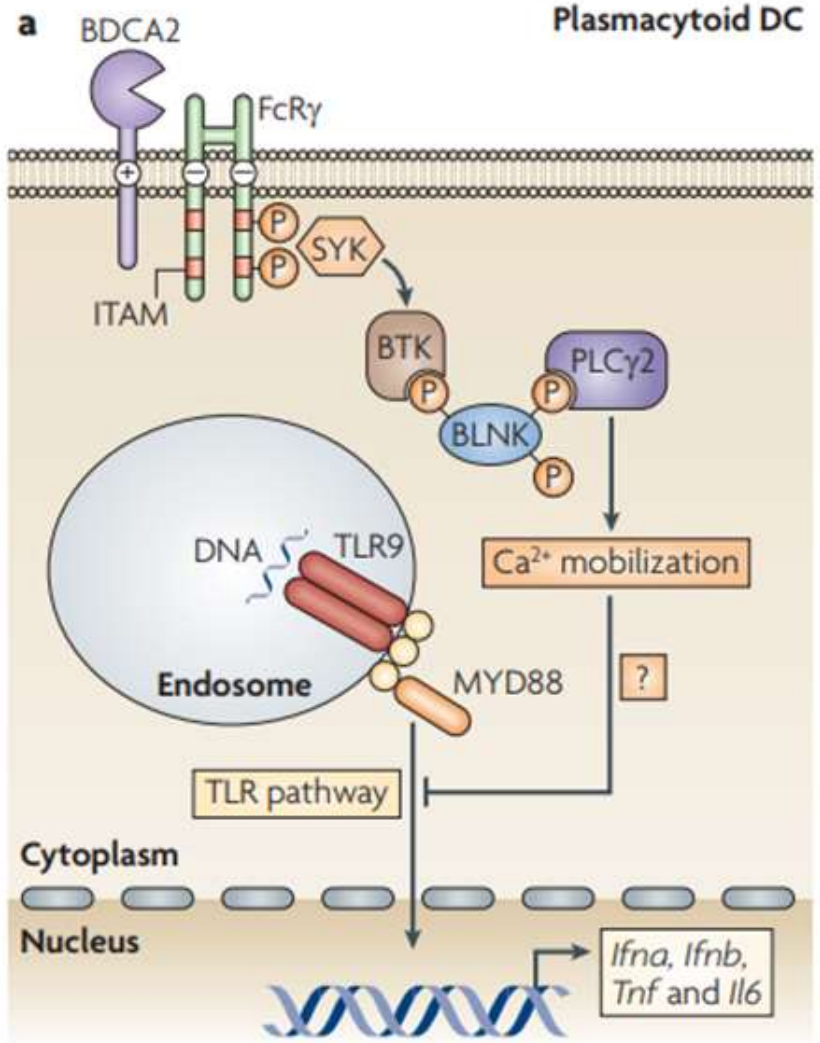
Figure 7. Model of BIIB059 mechanism of action in CLE. (**A**) In CLE, pDCs accumulate in skin lesions and produce IFN-I and IFN-λ (large arrow), as detected by the upregulation of the IFN-responsive protein MxA in the epidermis. pDCs also secrete a broad range of cytokines and chemokines, which in addition to IFN-I, may support the recruitment of inflammatory cells into the lesions (depicted by $CD45^+$ cells). (**B**) Treatment with BIIB059 leads to the functional inhibition of pDCs and the dampening of IFN-I and likely other inflammatory mediators, resulting in decreased MxA expression, reduction in immune cellular infiltrates, and amelioration of disease activity in CLE lesions.

Discussion (1)

・これまでのスタディから、BIIB059はBDCA2に結合した後、BDCA2と共に急速に細胞内に取り込まれ、エンドソーム（TLR7/9シグナルで重要）内にとどまり、IFN signalを抑制する。



Pellerin A EMBO Mol Med 2015; 7: 464



Geijtenbeek TBH. Nat Rev Immunol; 2009: 465

Discussion (2)

・過去のサルを用いたスタディから、BIIB059はpDC数には影響しない。
・ヒトを用いたスタディではBIIB059は一時的にpDC数を低下させる。
　=> mainな作用機序ではなさそう

・BIIB059の主な作用機序はinhibitory receptorであるBDCA2と結合することでpDCの反応を抑制することである（？）

・今回の結果はCLEではpDCがtype I IFNのmain producerであることを明らかにした。実際、pDCは浸潤細胞の5-10%を占めるとされる。

・今回、BIIB059はpDCからのすべてのサイトカインとケモカインを抑制することを示した。Type III IFNも。

・今回、実薬群に2人のnon-responderがいた理由はわからない。IRGの抑制自体が何故かできていなかった。

・SLEの他の症状に対する効果は今回は全く不明。