Immuno-Inflammation

Immuno-Inflammation areas of focus

Immune modulation to alter disease course, induce and sustain remission

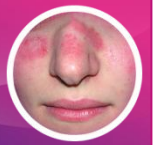
Rheumatoid Arthritis (RA)

- Circa 5.3m RA patients in G7 countries[1]
- Aging demographics a major driver of market growth
- Highly debilitating; associated with higher mortality & progression to other serious conditions
- Significant medical needs for remission-inducing therapies & for patients resistant to current standard of care

Osteoarthritis (OA)

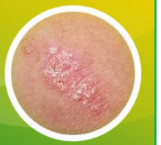
- Circa 72m OA patients in G7 countries; largest proportion of musculoskeletal diseases[2,3]
- Aging demographics a major driver of market growth
- Major opportunity for a disease-modifying therapy
- Immune modulation offers opportunity to move from only alleviating symptoms of "wear and tear"

Systemic Lupus Erythematosis (SLE)



- Prevalence: 40 -100 out of 100,000 [4]; 9/10 sufferers are women in their 20s & 30s[4]
- Chronic disease with poor QoL, involving musculoskeletal, haematological, cutaneous & renal systems
- Mortality rate 3x higher than the general population, and 10x higher in under 40[5]
- Benlysta IV - 1st drug approved for SLE in 50 years (2011)

Other immune-mediated diseases

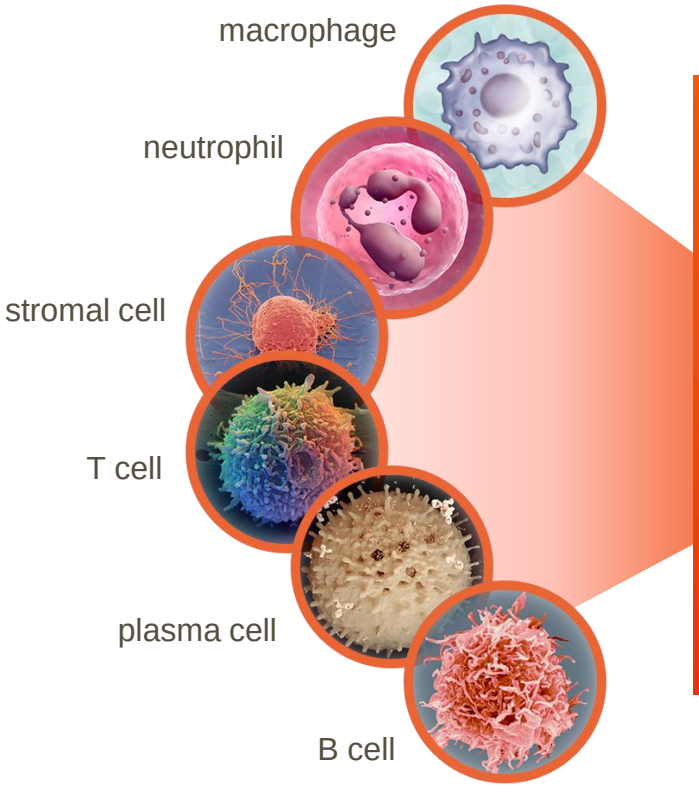


- Mechanisms are relevant for mainstream diseases e.g psoriasis, Crohn's disease & ulcerative colitis
- Opportunities exist to treat less common disease e.g. primary Sjögren's syndrome, systemic sclerosis & myasthenia gravis

[1] Decision Base Rheumatoid Arthritis 2015 ; [2] World Health Organisation 2010; [3] Decision Resources OA Pain 2012; [4] Danchenko N *et al*. Epidemiology of SLE: a comparison of worldwide disease burden. Lupus 2006; 15:308–318 [5] Bernatsky S, Boivin JF, Joseph L, *et al*. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006; 54:2550–2557.; * Decision resources 2013 estimate

Immuno-Inflammation R&D strategy:

From symptomatic benefit to sustainable remission



GSK Pipeline

Targeted Biologicals

Targeted Small Molecules

Targeting Resistant Disease

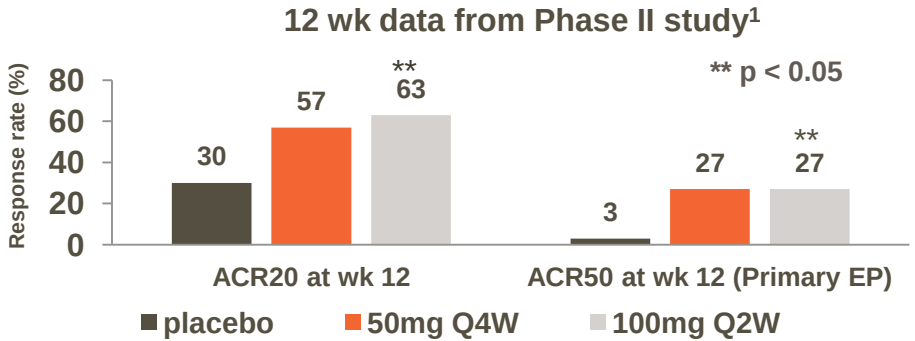
Early Intervention & Remission Induction

sirukumab: rheumatoid arthritis

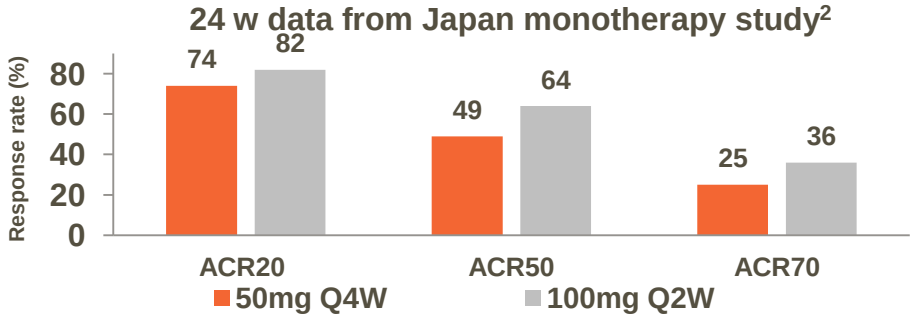
The anti-IL-6 class is the fastest growing of the biologicals in RA

- Collaboration with Janssen Biologics (Ireland)
- Low frequency sc dosing potential (monthly)
- Targets the cytokine
- Efficacy demonstrated in Phase II; consistent safety profile across doses
- >3000 patients in studies to date
- Phase III interim read-out, full read out expected by year end 2015
- Indication expansion: Phase III in Giant Cell Arteritis started screening. Phase II in asthma start in 2016

Status:	RA: Phase III
Indications:	RA (lead), GCA, asthma
Planned Filing:	RA 2016



[1]adapted from Smolen et al 2014 Ann Rheum Dis 73 (9)

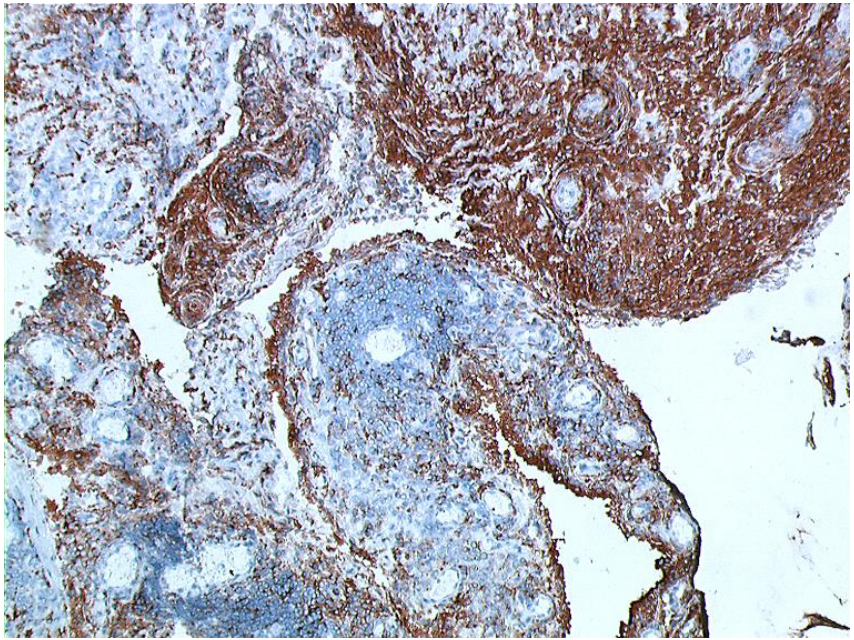


[2] ACR 2015 abstract #1672

Clinical improvement in RA is consistently associated with decreased macrophage infiltration

- Activated macrophages are abundantly expressed in early RA synovial tissue, representing the predominant cell type
- Reduction in macrophage infiltration correlates with improvement in disease activity scores[1,2]
- Macrophage is a primary cause of tissue destruction and affects many other cell types
- GM-CSF is important in every step of macrophage production and infiltration in the tissues

GM-CSF plays a key role in activation of macrophages at the site of injury or inflammation



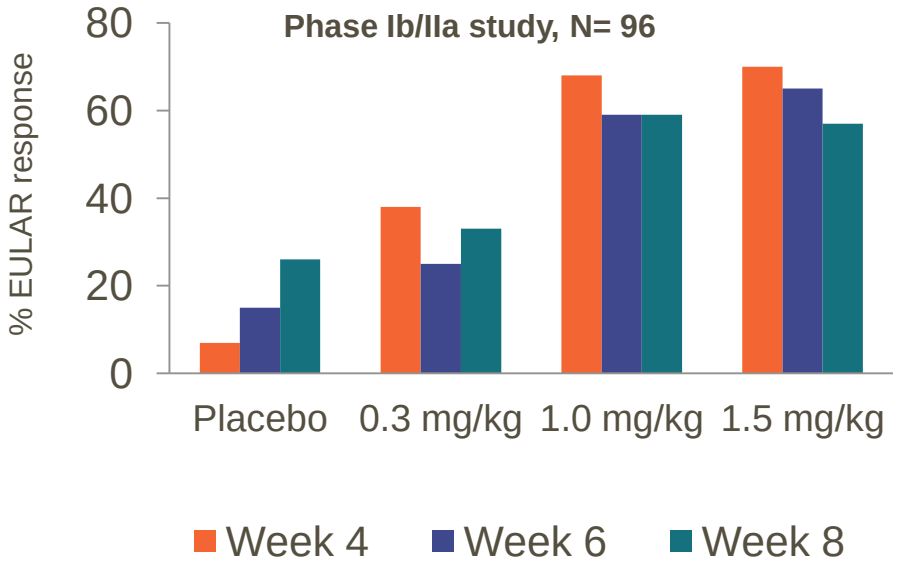
[1] Boumans MJ, *et al*. Arthritis Rheum. 2011;63:3187-94.
[2] Bresnihan B, *et al*. J Rheumatol 2009;36:1800-2.

GSK3196165 – aGM-CSF, targets key effector cells in RA

Aiming to induce remission in early rheumatoid arthritis

- In-licensed from MorphoSys AG
- Good magnitude of effect with fast onset of action and long duration post treatment
- Effect size appears similar or greater than anti-TNF
- Targeting the macrophage in early RA
- Potential for early use to induce remission
- BAROQUE (RA Phase IIb) ongoing. Initial clinical read-out 2016

% EULAR good/moderate response at 4 weeks: Rapid onset of action



Behrens, *et al*. Ann Rheum Dis. 2015;74:1058-64

Status:	Phase IIb
Indication:	Rheumatoid Arthritis
Planned Filing:	2021-2025

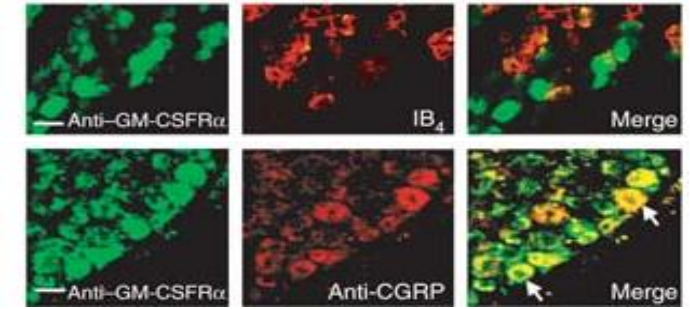
GSK3196165: Potential for disease modification & analgesic activity in hand osteoarthritis (HOA)

- The macrophage is a mediator of tissue destruction in OA
- aGM-CSF is effective in animal models of OA
- aGM-CSF rapidly reduces pain (through effect on nerves) in animal models of OA
- Hand OA presents unique clinical development path
- Phase II to start in 2016

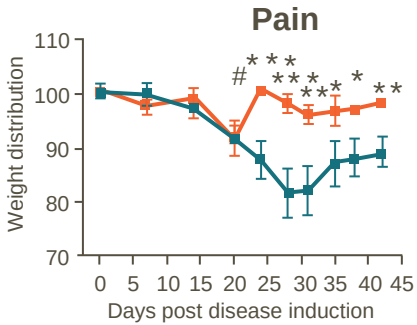
Status:	Phase II start 2016
Indication:	Hand OA
Planned Filing:	2021-2025

GSK3196165 in-licensed from MorphoSys AG

GM-CSF receptor expression on primary afferent nerve fibres in mouse tibial bone and periosteal nerves



M Schweizerhof *et al*. Nature Medicine 2009;15:802-807



* p<0.05,
** p<0.01,
*** p<0.001,
control vs. anti-GM CSF # p<0.0001, control and anti-GM-CSF vs. t=0 readings

Cook *et al*. Arthritis Res Ther. 2012;14:R199

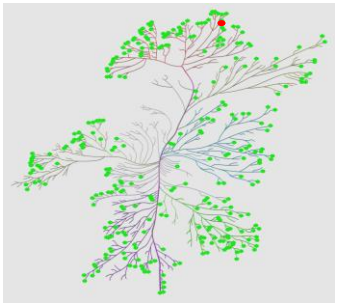
GSK2982772: RIP1 kinase inhibitor in the clinic

"a key regulator of inflammation, apoptosis and necroptosis, RIP1 is positioned at a strategic crossroads of multiple signalling nodes in the innate immune response".[1]

- New class, oral therapeutic
- World leading internal team
- Anti-TNF effect with additional protection against effects of cell death
- GSK2982772 well tolerated at all doses with robust target inhibition achieved
- Exquisite kinase selectivity
- Multiple potential indications

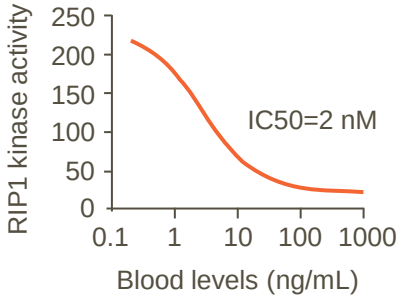
Status:	Phase I
Indications:	Rheumatoid arthritis, Psoriasis, Ulcerative Colitis
Planned Filing:	2021-2025

Kinome plot



GSK2982772 -most selective ATP competitive kinase inhibitor to advance into man

RIP1 kinase inhibition achieved in the clinic



Molecular Cell

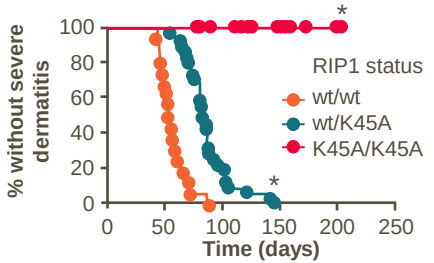
"NF-κB-Independent Role of IKKα/IKKβ in Preventing RIPK1 Kinase-Dependent Apoptotic and Necroptotic Cell Death during TNF Signaling"

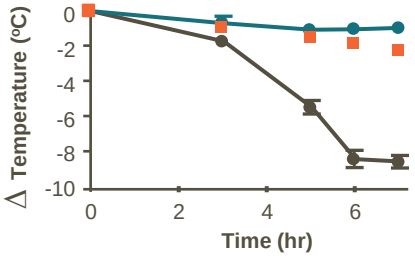
Authors: Yves Dondelinger, Sandrine Jouan-Lanhouet, Tatyana Divert, Emilie Theatre, John Bertin, Peter J. Cough, Piero Giansanti, Albert J.R. Heck, Emmanuel Dejardin, Peter Vandenabeele, Mathieu J.M. Bertrand

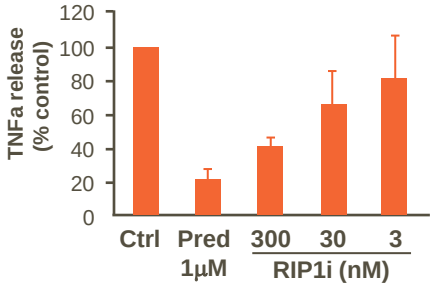
[1]Ofengeim & Yuan. Nat Rev Mol Cell Biol. 2013;14:727-36

GSK2982772: studies in three indications to start in 2016

Key target, compelling target, compelling pre-clinical data







Blocks severe skin inflammation[1]

Prevents against TNF induced shock[1]

Inhibits TNF production in human gut from Crohn's[2]

Clinical Studies

- rheumatoid arthritis
- ulcerative colitis
- psoriasis

Three Phase II clinical studies to progress in parallel mid-2016

Plans in place to rapidly deliver clinical validation in 2017

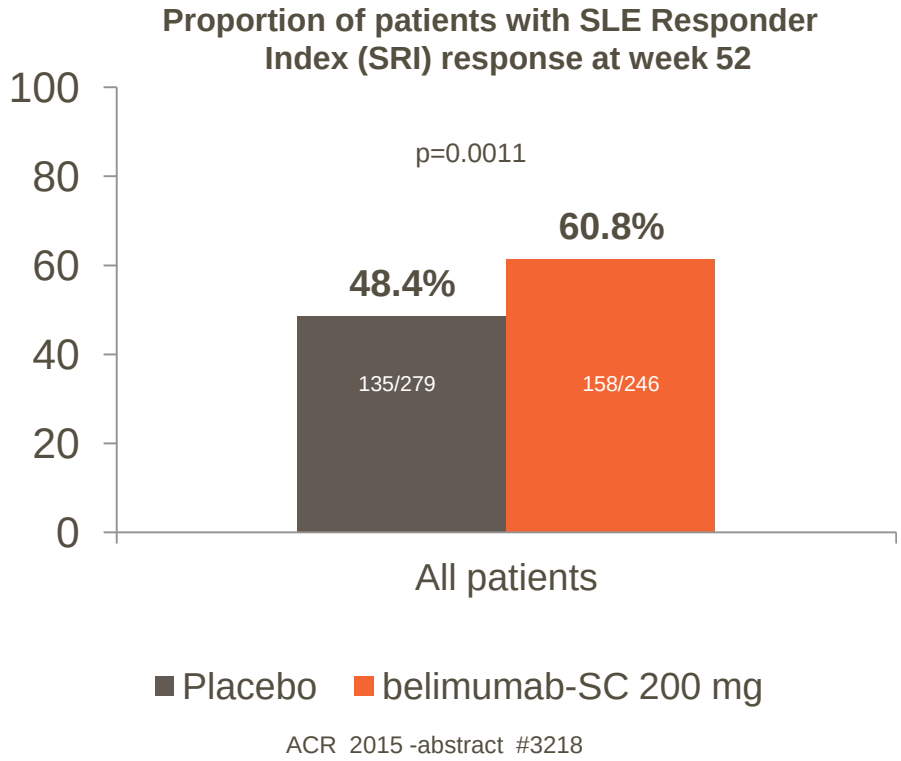
Filing: 2021 - 2025

[1]Berger *et al*. J Immunol. 2014;192:5476-80
[2]GSK, data on file.

Benlysta™ (belimumab):

3rd consecutive positive pivotal study – new data

- Benlysta – the only medicine to treat systemic lupus erythematosus (SLE) to have succeeded in Phase III. Three other medicines have failed.
- Improvement in time to first severe flare (HR 0.5 p< 0.0003) – flare is the major driver of disease progression.
- Trend for reduction in corticosteroid use seen again (p=0.07). Further evaluation ongoing.
- Subcutaneous weekly medicine.
- 9 ongoing studies, including subgroups in SLE and other indications.

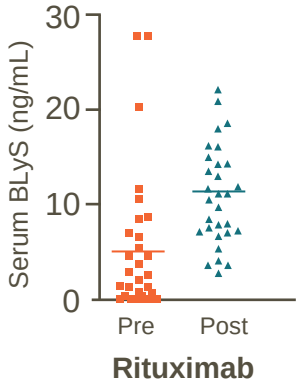


ACR 2015 -abstract #3218

Status:	IV approved 2011
Indication:	SLE
Planned Filing:	SC file Q4 2015/Q1 2016

Translating clinical experience into a new hypothesis: Phase II experimental study to start 2016

- After B-cell depletion with aCD20, BLyS levels increase
- BLyS drives persistence and re-population with auto-immune B-cells
- Benlysta suppresses BLyS
- Single patient case report suggests complete and persistent response in patient treated with aCD20 + Benlysta

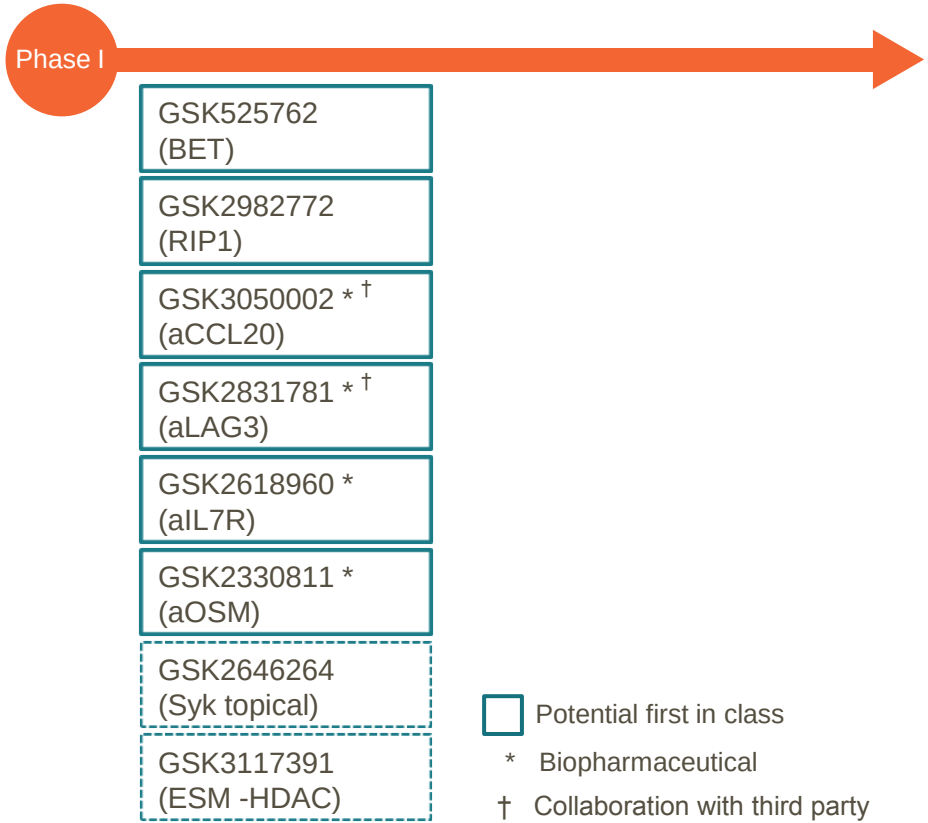


CASE REPORT

De Vita, Clin Exp Rheum. 2014;32, 490-494

- Severe, refractory Sjögren's syndrome, parotid B-cell lymphoma and cryoglobulinaemic vasculitis
- Failed several immunosuppressants, plasma exchange & surgical therapy as well as Benlysta alone and rituximab alone
- Dramatic response to combination including complete and persistent regression of lymphoma

Early Immuno-Inflammation clinical phase pipeline with multiple first in class assets



- Multiple first in class assets
- Eight key disease mechanisms
- Four biologicals
- Smart clinical development programmes to get early data read-outs

Four “first in class” antibodies in the clinic: GSK2618960

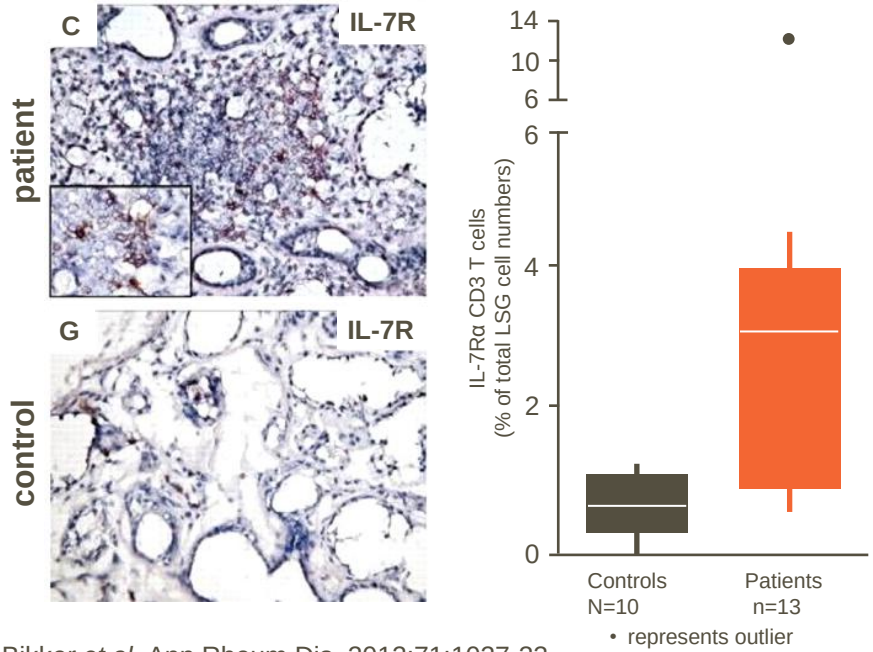
Anti-IL-7R antibody

“First in class” treatment for Sjögren’s syndrome

- IL-7R inhibition affects pathogenic T cell survival, reducing cytokine and auto-antibody production
- IL-7 promotes Sjögren’s-like syndrome in animal models[1]
- Potential for disease modification by prevention of salivary and lacrimal gland destruction
- Phase I study in healthy volunteers completed - well tolerated

Status: Phase II start 2016
Planned Filing: 2021-2025

Ectopic lymphoid tissue and increased IL-7R$^+$ cells in salivary glands of patients with Sjögren’s syndrome



Bikker *et al*. Ann Rheum Dis. 2012;71:1027-33.

1. Jin *et al*. Arthritis.Rhematol. 2013;65:2132-2142

Four “first in class” antibodies in the clinic: GSK3050002

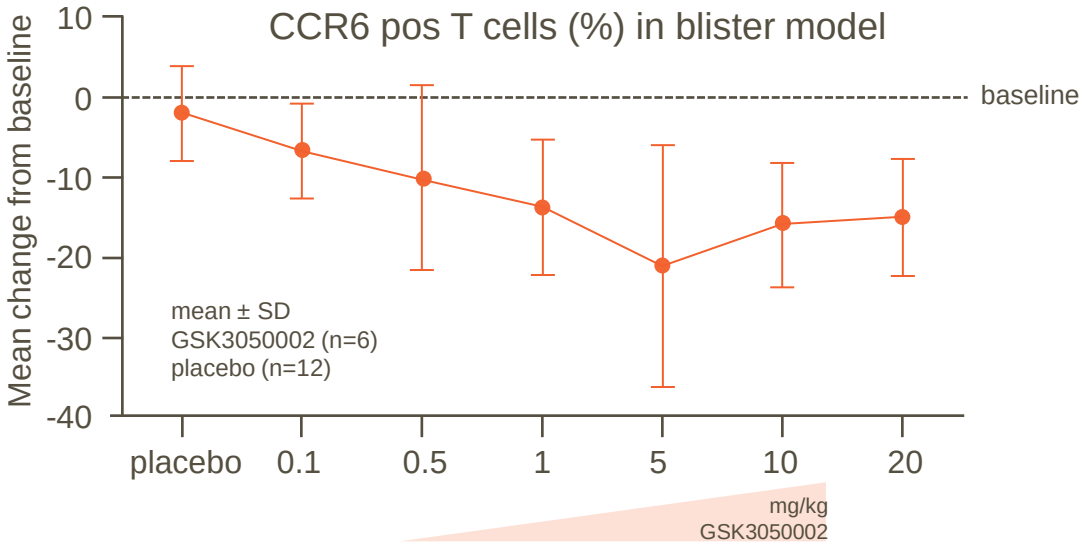
Anti-CCL20 antibody
Collaboration with Morphotek / Eisai

“First in class” treatment for psoriatic arthritis

- Unique MOA - CCL20 inhibition blocks recruitment of pathogenic immune cells - single receptor
- Potential to perturb chronic inflammation & reduce disease activity – applicability in multiple diseases
- Inhibits CCR6+ T cells migration into inflamed tissue in humans *in vivo*

Status: Phase II start 2016
Planned Filing: 2021-2025

Anti CCL20 prevents CCR6+ cells migration into inflamed blister in humans *in vivo*



GSK, data on file. GSK3050002 in experimental medicine study (200784)

- Selective inhibition (CCR6 +ve cells only)
- Dose dependency

Four “first in class” antibodies in the clinic: GSK2831781

Cell depleting anti-LAG3 antibody

Collaboration with Prima BioMed

“First in class” treatment for T-cell driven II indications

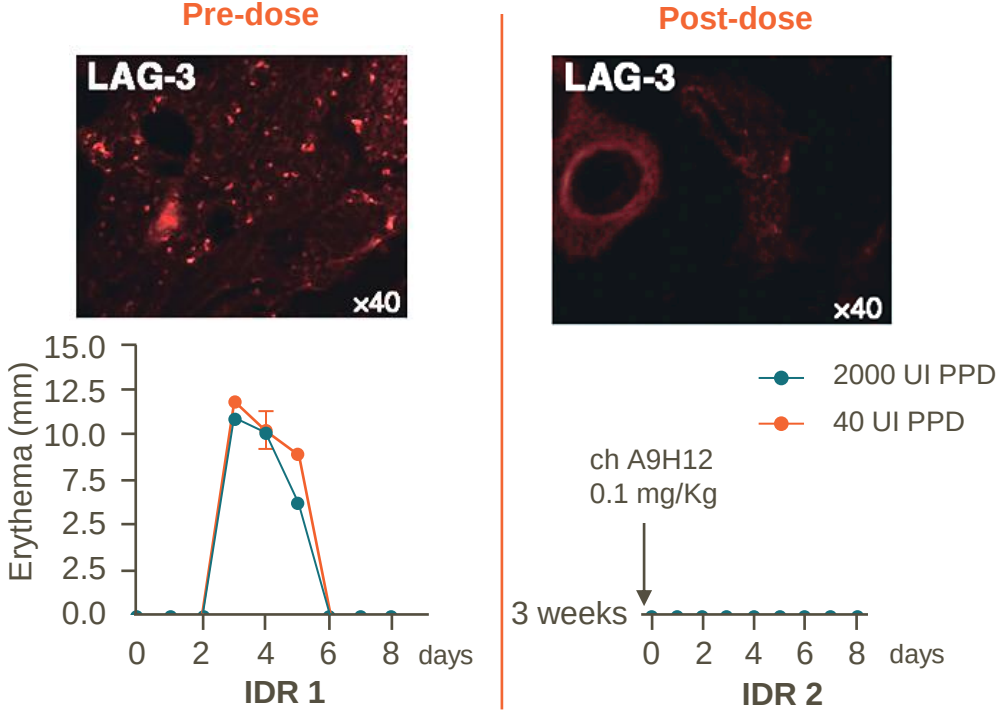
- Unique MOA – a-LAG3 depletes recently activated, “pathogenic” T cells
- Potential for long term disease remission in multiple T cell-driven indications

Status: Phase I ongoing
Planned Filing: 2021-2025

Targeted depletion of LAG-3 T-cells with an antibody (A9H12) suppresses the immune reaction to the tuberculin antigen

Depletion of LAG-3 T-cells at challenge site ...

..results in suppression in the skin reaction



Poirier *et al*. Clin Exp Immunol. 2011;164:265-74.

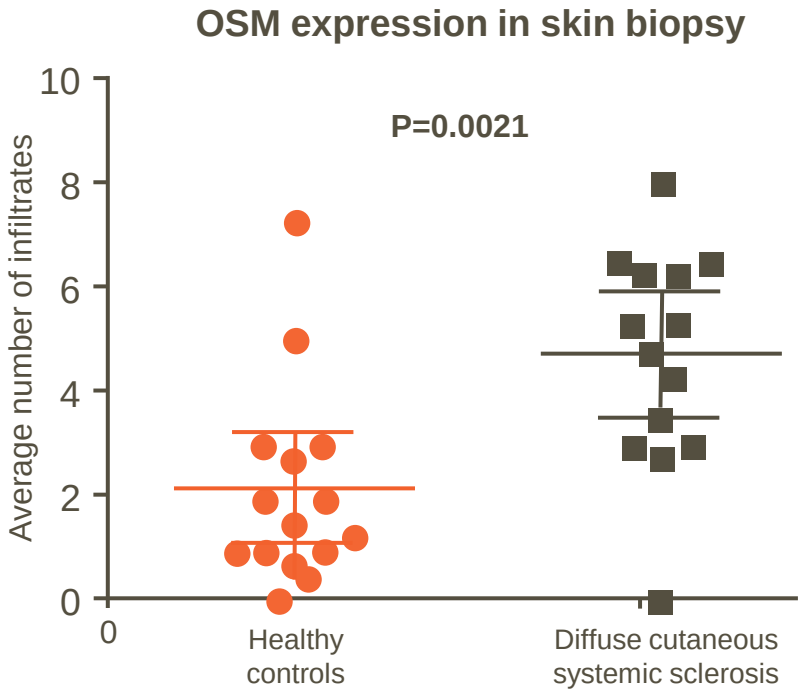
Four “first in class” antibodies in the clinic: GSK2330811

Anti-OSM antibody

“First in class” treatment for systemic sclerosis

- Systemic sclerosis patients have increased OSM serum levels and upregulated OSM and OSM-related genes in skin biopsies (data at ACR)
- Inhibition of OSM signalling is expected to reduce inflammation, vascular dysregulation and fibrosis

Status: Phase I ongoing
Planned Filing: 2021-2025



ACR 2015, abstract #1914

Four “first in class” antibodies in the clinic

All expected to progress to PhII in 2016

Anti-IL-7R antibody

“First in class” treatment for Sjögren’s syndrome

- IL-7R inhibition affects pathogenic T cell survival, reducing cytokine and auto-antibody production
- IL-7 promotes Sjögren’s syndrome in animal models
- Potential for disease modification by prevention of salivary and lacrimal gland destruction
- Phase I study in healthy volunteers completed - well tolerated

Status: Phase II start 2016
Planned Filing: 2021-2025

Anti-CCL20 antibody

Collaboration with Morphotek / Eisai

“First in class” treatment for psoriatic arthritis

- Unique MOA - CCL20 inhibition blocks recruitment of pathogenic immune cells - single receptor
- Potential to perturb chronic inflammation & reduce disease activity – applicability in multiple diseases
- Inhibits CCR6+ T cells migration into inflamed tissue in humans *in vivo*

Status: Phase II start 2016
Planned Filing: 2021-2025

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- Systemic sclerosis patients have increased OSM serum levels and upregulated OSM and OSM-related genes in skin biopsies (data at ACR)
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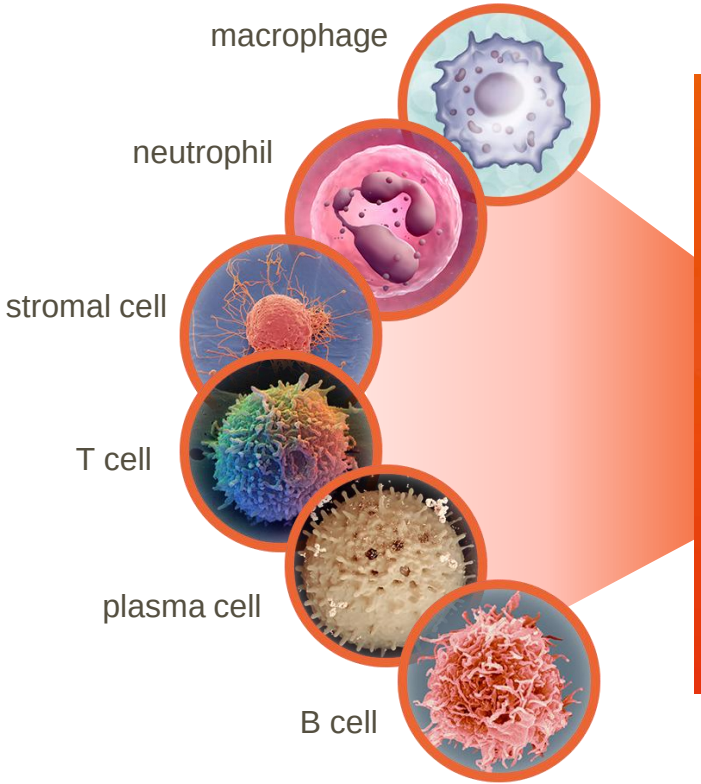
Status: Phase I ongoing
Planned Filing: 2021-2025

Immuno-Inflammation R&D strategy:

From symptomatic benefit to sustainable remission



GSK Pipeline

Targeted Biologicals

- Benlysta
- sirukumab
- Anti-GM-CSF
- Anti-IL-7
- Anti-LAG3
- Anti-CCL20
- Anti-OSM

Targeted Small Molecules

- RIP1
- I-BET

Targeting Resistant Disease

- RIP1
- I-BET
- Anti-IL-7
- Anti-LAG3
- Anti-CCL20
- Anti-OSM

Early Intervention & Remission Induction

- Anti-GM-CSF
- RIP1
- Anti-CCL20
- Anti-LAG3

Oncology

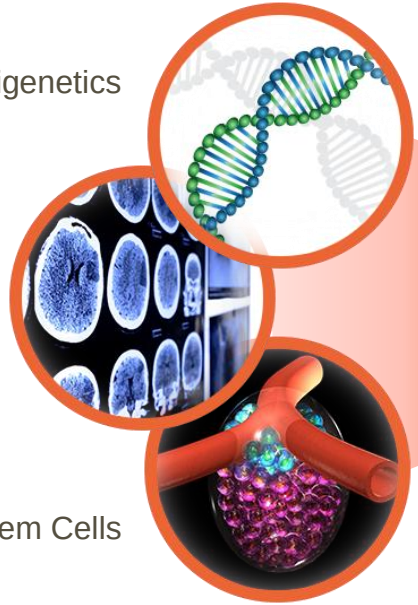
Oncology R&D strategy

Focusing on 3 areas fundamental to oncology

Cancer Epigenetics

Immuno-Oncology

Cancer Stem Cells



GSK Pipeline

Long-Term Survival & Cures

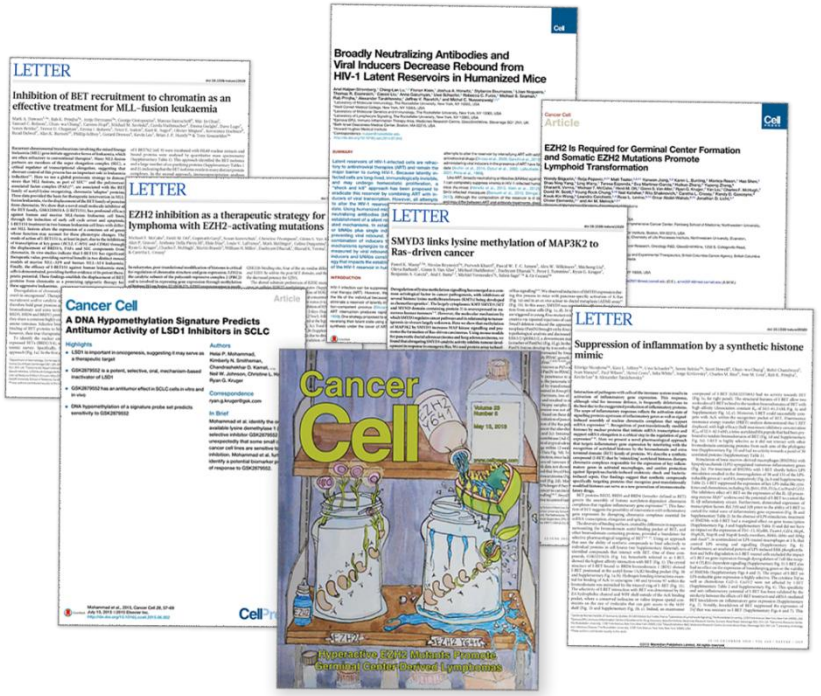
Reprogram Cancer Cells

Stimulate Anti-Tumour Immunity

First in Class Medicines & Combination Therapy

GSK Epigenetics: an early commitment with a pipeline now at the forefront of industry

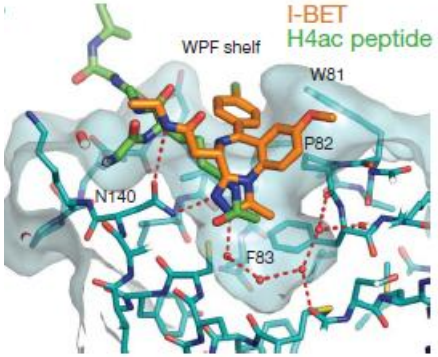
- World-leading science in epigenetics since 2008
- Team has published 9 papers in *Nature* & *Cell*
- World-leading academic collaborations
- Strategic collaborations with biotech



GSK525762: potential first in class BET inhibitor

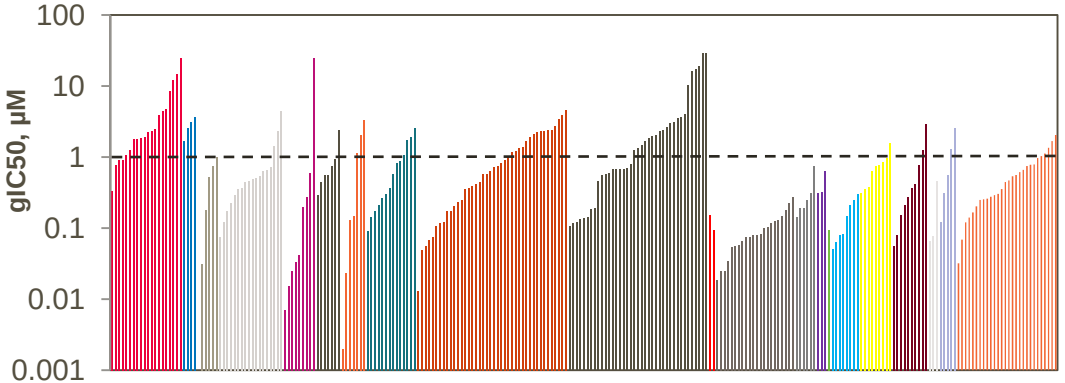
Potential for broad activity

- GSK525762 blocks binding of BET family proteins (BRD2, 3 and 4) to transcriptional mediators changing gene expression including suppressing oncogene expression
- Potential use in many potential indications
- Broad activity in preclinical cell line models
- PoC opportunity in NUT midline carcinoma (NMC)
- Rare and rapidly lethal cancer caused by chromosomal translocation involving BET target (NUT gene and either BRD3, BRD4, or NSD3 (which binds BRD4) gene)



Nature 2010;468:1119-1123

Status:	Phase I
Indications:	Solid Tumours, Heme Malignancies
Filing:	2018



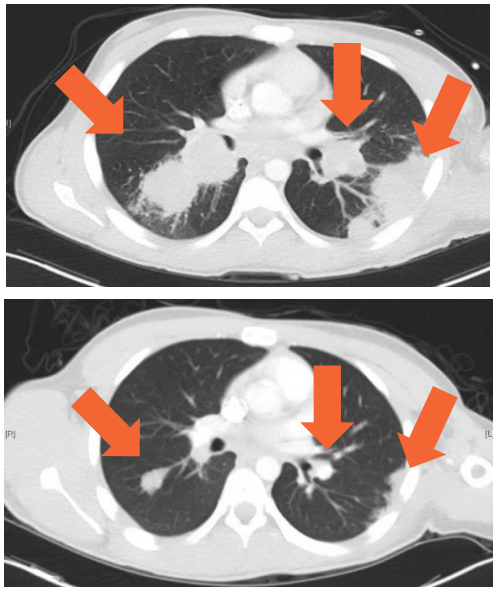
Preclinical data show activity of GSK525762 in many cancer types (gIC50 < 1 µM)

GSK525762: early evidence of potential clinical benefit

Potential new treatment for rapidly lethal cancer

- Responses observed in NUT midline carcinoma
  - 6 patients treated at 60-100 mg QD with 4 Partial Responses
- Solid tumour studies underway across multiple tumour types;
  - 36 patients enrolled across CRC, NMC, CRPC, SCLC, BC & MM
- Haematological studies underway; partial responses seen in AML
  - 20 patients enrolled cross AML, NHL & MM

GSK525762 active in NMC, a very difficult to treat cancer



Chest CT of patient with NMC treated with GSK525762: ~ 90 % reduction in tumour volume at week 16

GSK, data on file.

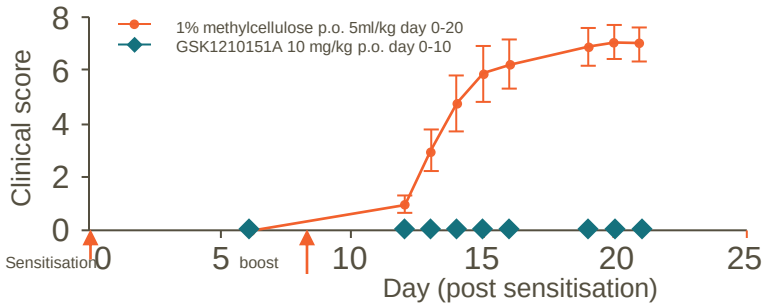
GSK525762: potential to treat and reset disease in rheumatoid arthritis: *Extensive preclinical data package for BET inhibition*

- GSK525762 interferes with stromal cells driving autonomous disease progression in RA
- Profound cytokine, chemokine and immunoglobulin inhibition in human macrophages[1] and RA patient samples and biopsies
- Modulation of macrophage[1], osteoclast[2] and Th17 cell types
- Profound inhibition of disease in multiple RA preclinical models[2]
- Rebalances gene expression in RA stromal cells (decreased cytokines, chemokines, metalloproteases, elevated protease inhibitors[3, 4]

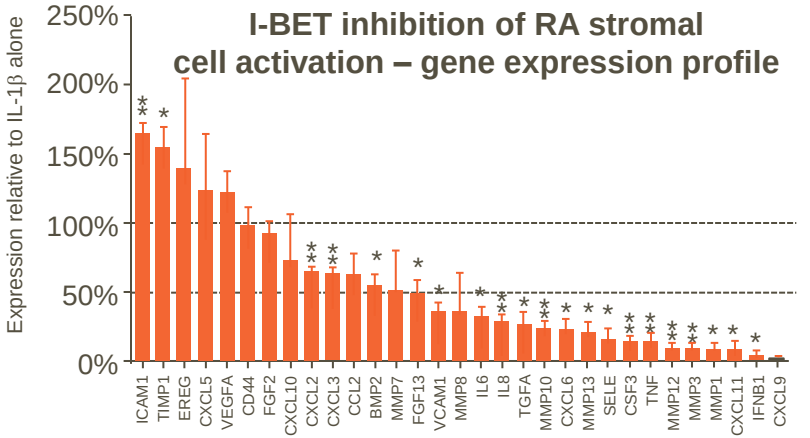
1.Chan *et al*. 2014 EJ Imm., 2. Park-Min *et al*. 2014 NatCom,
3. Xiao *et al.* 2015 Rheumatology, 4. Klein *et al.* 2014 ARD

Status:	Phase II start 2016
Indication:	Therapy Resistant RA
Planned Filing:	2021-2025

I-BET resets disease in rat collagen-induced arthritis



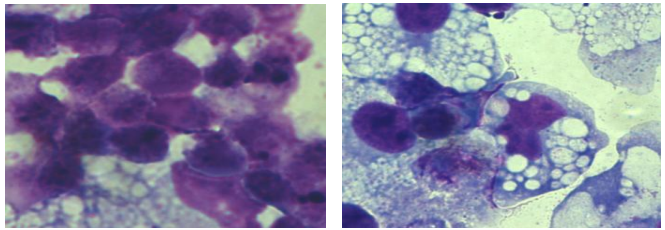
I-BET inhibition of RA stromal cell activation – gene expression profile



GSK2879552 LSD1 inhibitor: Early signal of efficacy in SCLC

- Preclinical data give reason to believe
- Clinical studies ongoing in Small Cell Lung Cancer and Acute Myeloid Leukaemia
- Signal of significant progression-free survival for some patients

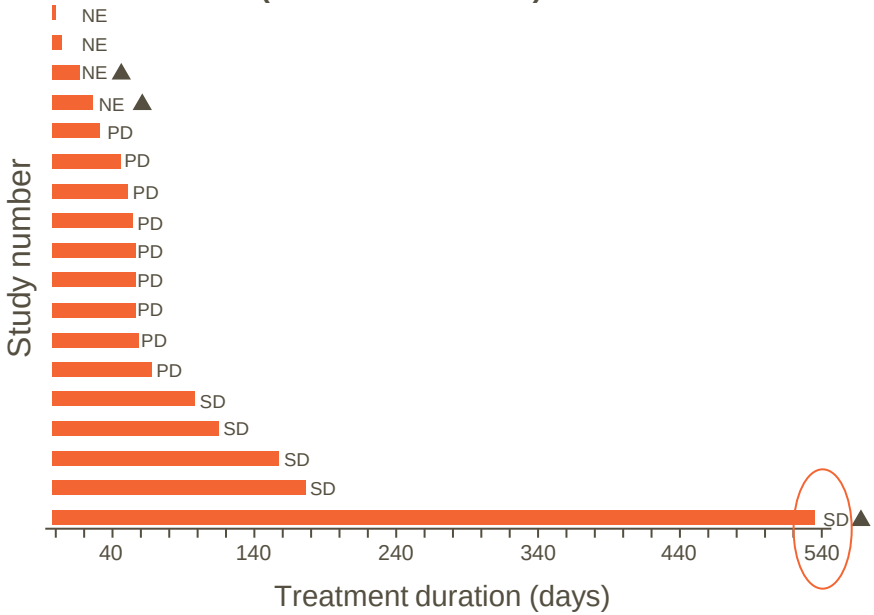
Untreated **10 nM GSK552**



MLL-AF9 mouse derived leukemia cells treated for 6 days *in vitro*

Status:	Phase I
Indications:	AML, SCLC
Planned Filing:	2020

Plot of duration of treatment (days) with Tumour Response (RECIST 1.1 criteria) SCLC



Best confirmed response –PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, NE: Not Evaluable
Triangles indicate ongoing subjects

GSK, data on file.

Immuno-Oncology: NY-ESO T-Cell Therapy

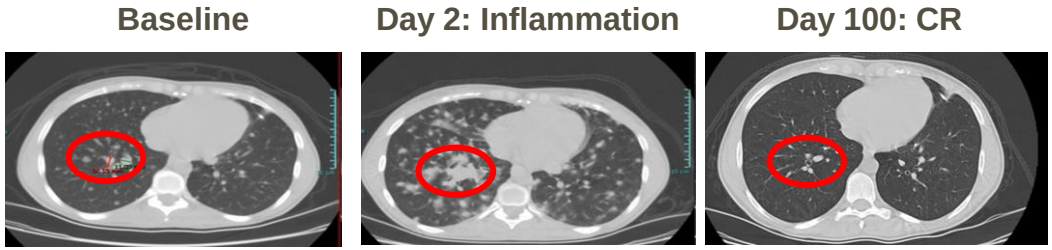
- TCR T-cell therapy
- 50% ORR seen in sarcoma
- Ongoing studies in ovarian and other solid tumours and haematological malignancies
- Planned studies in combination with checkpoint modulators
- Collaboration with Adaptimmune

Status:	Phase I/II
Indications:	NY-ESO-1 positive Cancers: Sarcoma, Myeloma, NSCLC, Melanoma, Ovarian Cancer

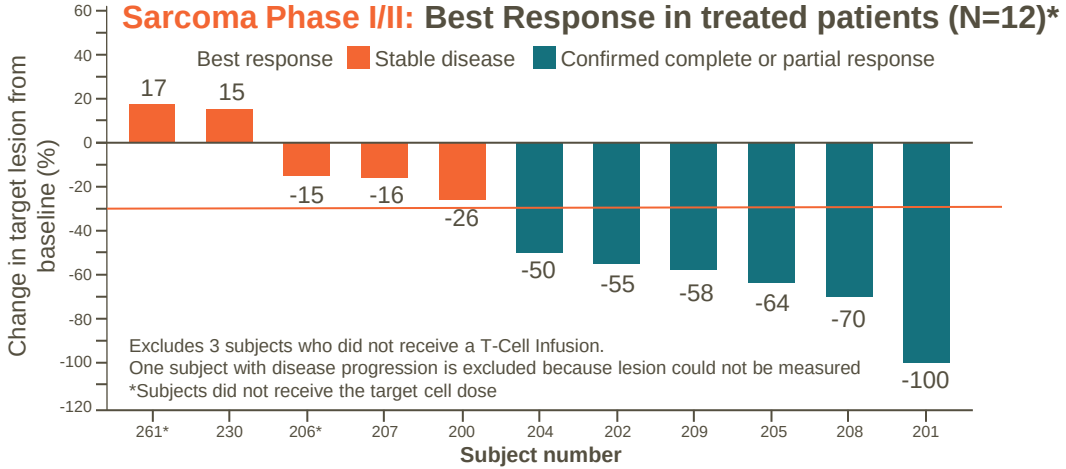
Filing strategy to be agreed with Adaptimmune

Note: GSK3377794 subject to exercise of option by GSK

Sarcoma Phase I/II: Individual patient complete response (CR)



Sarcoma Phase I/II: Best Response in treated patients (N=12)*

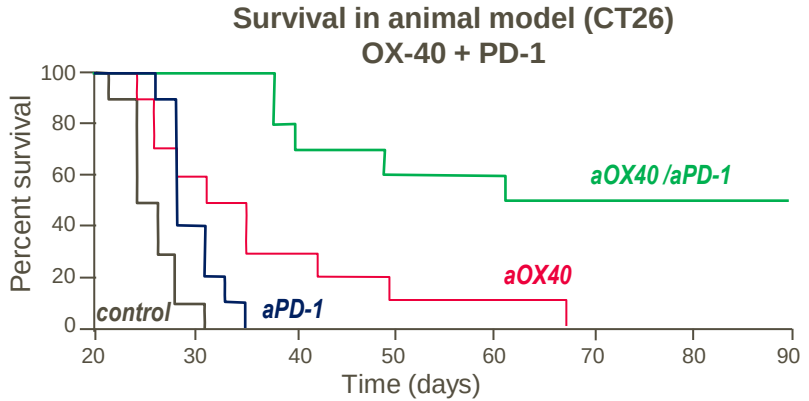


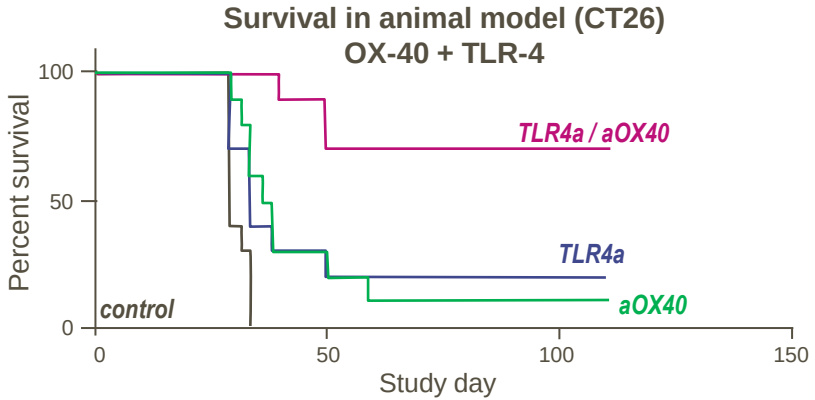
GSK, data on file.

Immuno-Oncology: GSK3174998 OX40 agonist mAb

- GSK3174998 is one of four humanised OX-40s in clinic
- Dual mechanism: enhancing effector T-cell and suppressing T-regs
- Phase I Study started in eight cancers
- Combination with Merck PD1 in 2016
- Combination with GSK TLR4 in 2017
- Collaboration with MD Anderson

Status:	Phase I
Indications:	Solid tumours, Heme Malignancies
Planned Filing:	2020





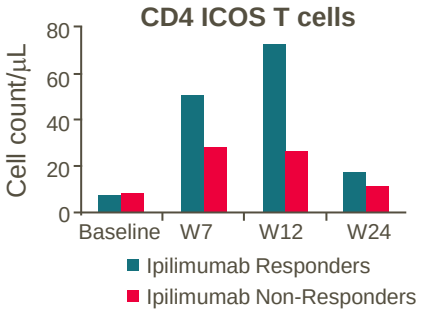
GSK, data on file.

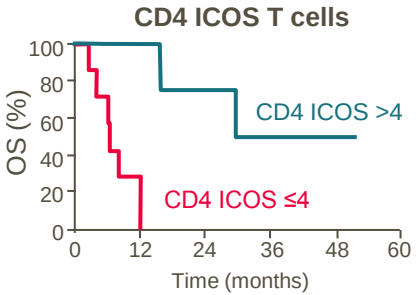
Immuno-Oncology: GSK3359609 first-in-class ICOS agonist antibody

- Universal mechanism across multiple cancers
- Patient selection biomarker
- Enhances T-cells associated with survival
- Use after CTLA-4 and PD-1 in unresponsive or refractory patients
- Possible anchor for use in combinations
- Collaboration with INSERM

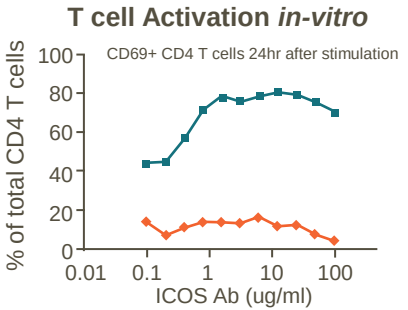
Status:	Phase I start Q1 2016
Indications:	Solid tumours, Heme Malignancies
Planned Filing:	2020

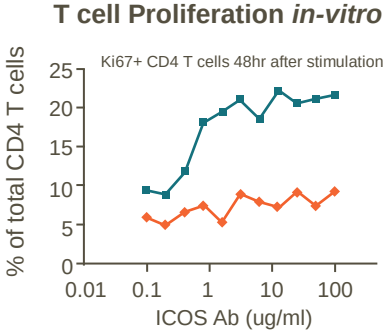
ICOS in ipilimumab-treated patients





GSK3359609



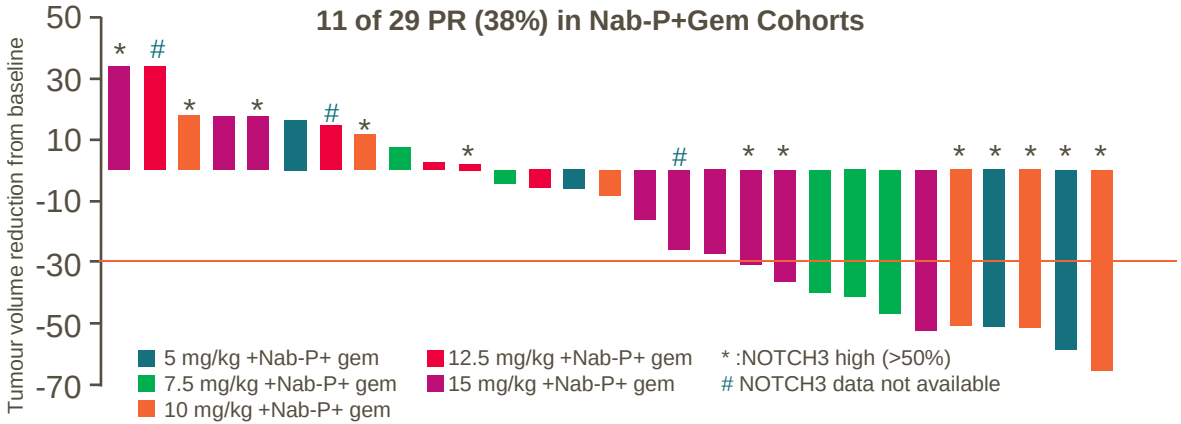


DiGiacomo, Clin Immunol Immunother 2013

Cancer Stem Cells: tarextumab (anti-Notch 2/3)

- Inhibition of Notch 2/3 Receptors in cancer stem cells
- Phase Ib: Overall response rate of 38%
- Ongoing randomised Phase II studies in pancreatic cancer and SCLC
- Phase II read-out 2016
- Collaboration with OncoMed

ALPINE (Phase Ib) Pancreatic Cancer:
gemcitabine/Abraxane* + tarextumab
Dose range: TRXT from 5 to 15mg/kg Q2W



Attractive signal over 23% ORR of Gem/Abraxane SOC in hard-to-treat cancer

O'Reilly *et al*. 2015 Gastrointestinal Cancer Symposium

Status:	Phase II
Indications:	Pancreatic cancer and Small Cell Lung Cancer
Planned Filing:	2020

Note: tarextumab subject to exercise of option by GSK
*Abraxane is a trademark of Abraxis Bioscience LLC

Oncology R&D strategy

Focusing on 3 areas fundamental to oncology

Cancer Epigenetics

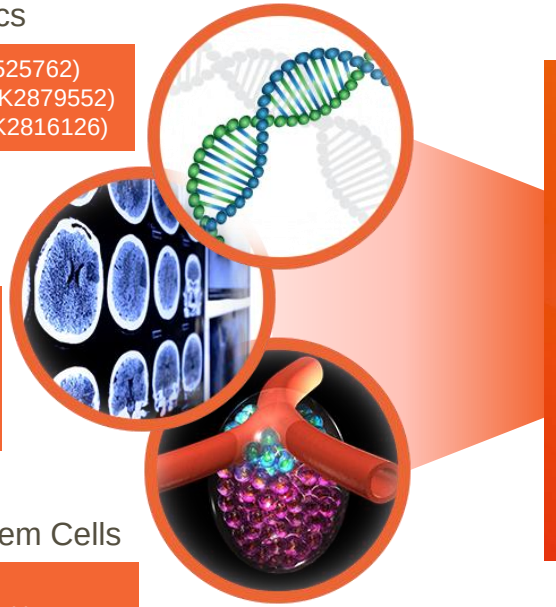
- BET inhibitor (GSK525762)
- LSD-1 inhibitor (GSK2879552)
- EZH2 inhibitor (GSK2816126)

Immuno-Oncology

- NY-ESO-1 TCR-T
- OX40 agonist (GSK3174998)
- ICOS agonist
- TLR4 agonist

Cancer Stem Cells

- Notch2/3 (tarextumab)
- Notch1 (brontictuzumab)



GSK Pipeline

Long-Term Survival & Cures

- Epigenetics
- Immuno-oncology
- Stem cells

Reprogram Cancer Cells

- Epigenetics

Stimulate Anti-tumour Immunity

- Immuno-oncology

First in Class Medicines & Combination Therapy

- Epigenetics
- Immuno-oncology
- Stem cells

Oncology – Pipeline snapshot

BET inhibitor (GSK525762)	*Solid tumours, Heme Malignancies*
LSD-1 inhibitor (GSK2879552)	*AML, SCLC*
EZH2 inhibitor (GSK2816126)	*Solid tumours, Heme Malignancies*
PRMT5 inhibitor (GSK3326595) †	*Solid tumours, Lymphoma*
Novel small molecule targets (X6)	
NY-ESO-1 TCR-T †	*Sarcoma, Multiple Myeloma, NSCLC, Ovarian, Melanoma*
OX40 agonist (GSK3174998) †	*Solid tumours, Heme Malignancies*
ICOS agonist (GSK3359609) †	
TLR4 agonist (GSK1795091)	
CAR-T and TCR-T targets (x6)	
Novel small molecule targets (x2)	
ImmTacs (x4) †	
mAb-dAbs and dual-specific Abs (x5)	
Notch2/3 (tarextumab) †	*Pancreatic, SCLC*
Notch1 (brontictuzumab) †	*Solid tumours, Heme Malignancies*
BCMA ADC (GSK2857916)	*Multiple Myeloma*
FGF Ligand Trap (GSK3052230) †	*Mesothelioma, NSCLC*

- Epigenetics
- Immuno-Oncology
- Stem Cells
- Other targeted therapies

† Collaboration with a third party.

Assets profiled at R&D day by planned filing date

See www.gsk.com for full clinical pipeline

2014 to 2017: 6 NMEs & 5 PLEs

Nucala (mepolizumab) *IL-5 mAb* **Severe Asthma**	sirukumab *IL-6 mAb* **Rheumatoid Arthritis**
mepolizumab *IL-5 mAb* **COPD**	GSK2696273 *Ex-vivo stem CGT* **ADA-SCID**
mepolizumab *IL-5 mAb* **EGPA**	GSK2696274 *Ex-vivo stem CGT* **Metachromatic Leukodystrophy**
fluticasone furoate+vilanterol +umeclidinium *ICS/LABA/LAMA* **COPD**	GSK2696275 *Ex-vivo stem CGT* **Wiscott-Aldrich Syndrome**
dolutegravir + rilpivirine *Integrase inhibitor + NNRTI* **HIV**	GSK2998728† *TTR production inhibitor* **FAP**
Benlysta Subcutaneous *BLyS mAb* **SLE**	

2018 to 2020: 10 NMEs & 5 PLEs

mepolizumab *IL-5 mAb* **Nasal Polyposis**	tarextumab† *Notch 2/3 mAb* **Pancreatic Cancer, SCLC**	GSK2398852+ GSK2315698 *SAP mAb + SAP depleter* **Amyloidosis**
mepolizumab *IL-5 mAb* **HES**	GSK525762 *BET inhibitor* **Solid Tumours, Haematological Malignancies**	GSK2998728† *TTR production inhibitor* **TTR Cardiomyopathy**
dolutegravir + lamivudine FDC *Integrase inhibitor+NRTI* **HIV**	GSK2879552 *LSD1 inhibitor* **Acute Myeloid Leukaemia, SCLC**	daprodustat* *Prolyl hydroxylase inhibitor* **Anaemia of CKD**
cabotegravir *Long acting integrase inhibitor* **HIV, HIV PrEP**	GSK3174998 *OX40 agonist mAb* **Solid tumours, Haematological Malignancies**	
gepotidacin *Type 2 topoisomerase inhibitor* **Bacterial Inf.**	GSK3377794†# *NY-ESO-1 TCR* **Sarcoma, Mult. Myel., Melanoma Ovarian, NSCLC**	
sirukumab *IL-6 mAb* **Giant Cell Arteritis**	GSK3359609 *ICOS agonist mAb* **Solid tumours, Haematological Malignancies**	

2021 to 2025: 17 NMEs & 5 PLEs

sirukumab *IL-6 mAb* **Severe Asthma**	GSK3008348 *Alpha V beta 6 integrin antagonist* **IPF**	GSK525762 *BET inhibitor* **Therapy Resistant RA**	GSK3196165 *GM-CSF mAb* **RA, OA**
danirixin *CXCR2 antagonist* **COPD**	*Long acting IL-5 mAb (NBE)* **Asthma, Others**	GSK2330811 *OSM mAb* **Systemic Sclerosis**	GSK2696277†^ *Ex-vivo stem CGT* **Beta Thalassemia**
GSK2269557 *PI3 kinase delta inhibitor* **COPD, Asthma**	*IL5/13 bispecific antibody* **Asthma**	GSK2618960 *IL-7 receptor mAb* **Sjogren's Syndrome**	daprodustat* *Prolyl hydroxylase inhibitor (topical)* **Wound Healing**
GSK2862277 *TNFR1 dAb* **Acute Lung Injury**	GSK2878175 *NS5B inhibitor* **HCV**	GSK2831781 *LAG-3 mAb* **Autoimmune Diseases**	mepolizumab *IL-5 mAb* **Severe Atopic Dermatitis**
GSK2245035 *TLR7 agonist* **Asthma**	GSK3228836† *Antisense oligonucleotide* **HBV**	GSK2982772 *RIP1 kinase inhibitor* **Psoriasis, RA, UC**	
GSK3191812 *TSLP dAb* **Asthma**	belimumab + CD20 *BLyS+CD20* **Sjogren's Syndrome**	GSK3050002 *CCL20 mAb* **Psoriatic Arthritis**	

- Respiratory
- HIV / Infectious Diseases
- Immuno-Inflammation
- Oncology
- Rare Diseases
- Other

† Subject to exercise of option
# Subject to collaborator agreement
^ EU filing
* USAN, INN approval pending

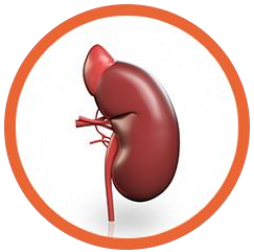
Rare Diseases

Amyloidosis and Cell and Gene Therapy

Amyloidosis: a complex protein deposition disease process with ~50% mortality at 3 years

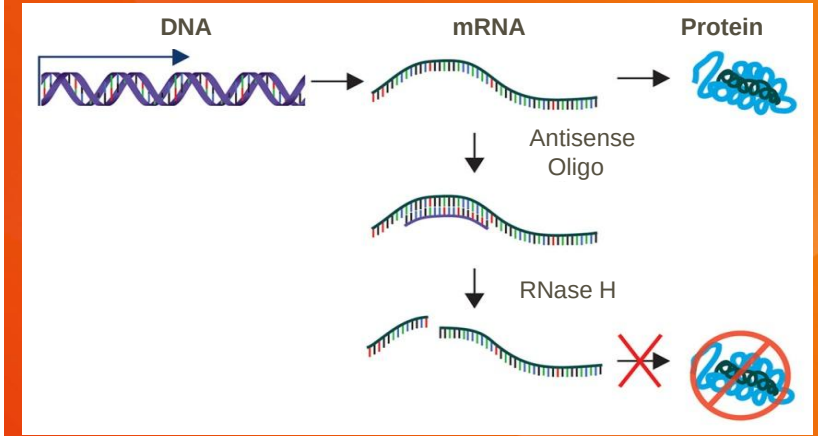
- AL amyloidosis – monoclonal immunoglobulin light chains (plasma cell dyscrasia) (~70% of all cases)
- ATTR amyloidosis – hereditary disease caused by variant transthyretin (TTR) protein
  – acquired disease caused by wild type TTR (senile amyloidosis)
- AA amyloidosis – complication of chronic inflammation or infection
- **Implication in other disease states**. Growing recognition of its importance

Accumulation of amyloid deposits damages vital organs causing disease

Peripheral / visceral nerves	Kidney	Heart	Liver
			
TTR	**AA, AL, TTR**	**AL, TTR**	**AL, AA**

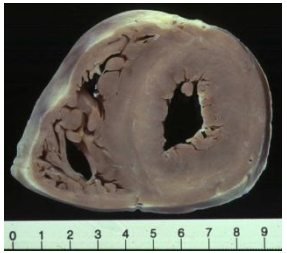
Two fundamental approaches to treatment: prevent amyloid formation and remove amyloid deposits

"Gene silencing" by antisense oligonucleotide

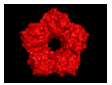


- **Knockdown of TTR gene prevents production of mutant and wild type TTR protein**
- **Prevents formation of amyloid deposits in vital organs**
- **GSK2998728 in collaboration with Isis Pharmaceuticals**

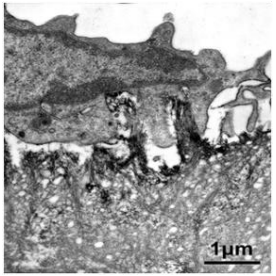
Removal of amyloid deposits by macrophage-mediated clearance



Serum amyloid P component (SAP) in blood and all amyloid deposits



SAP removed from plasma by GSK SAP depleter but still decorates deposits in organs



Anti-SAP mAb can then target SAP in amyloid deposits

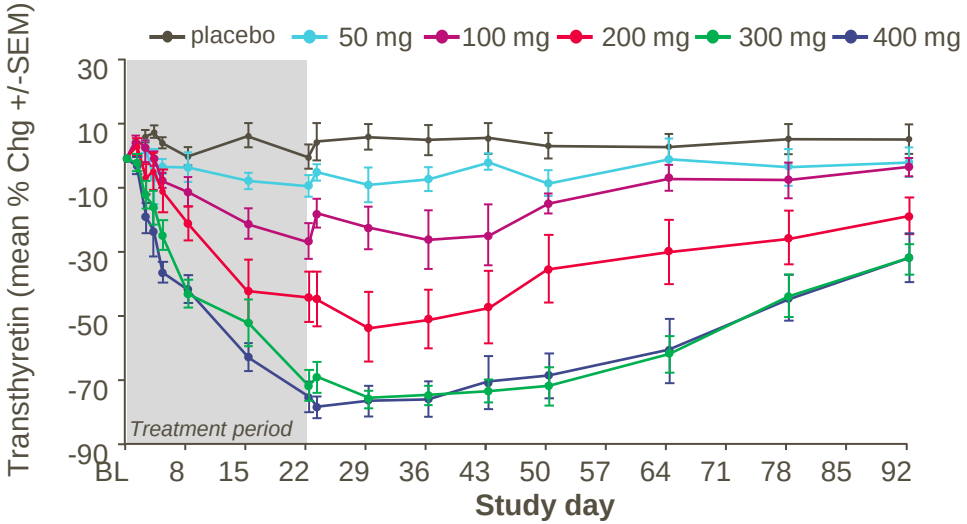
Antibody binding triggers amyloid clearance by macrophages

Organ function is restored

GSK2998728 RNA targeted transthyretin (TTR) knockdown

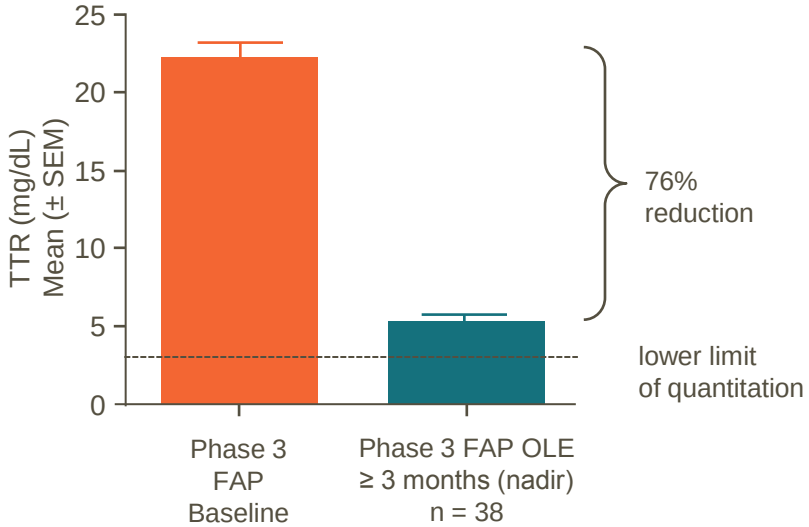
~80% TTR knockdown

Mean change - Time profile following 3 loading doses week 1, then 1 weekly dose (n=65; healthy volunteers)



TTR reductions observed in Phase III FAP open label extension

Mean max TTR reduction = 76%
Max TTR reduction = 92%



Status:	Phase III
Indication:	Familial amyloid polyneuropathy (FAP); Familial and wild-type amyloid cardiomyopathy (TTR CM)
Filing:	2017 (FAP), 2020 (TTR CM)

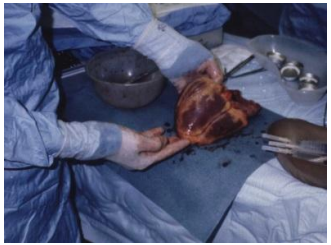
GSK: data on file

Note: GSK2998728 is a collaboration with Isis Pharmaceuticals and subject to exercise of option by GSK

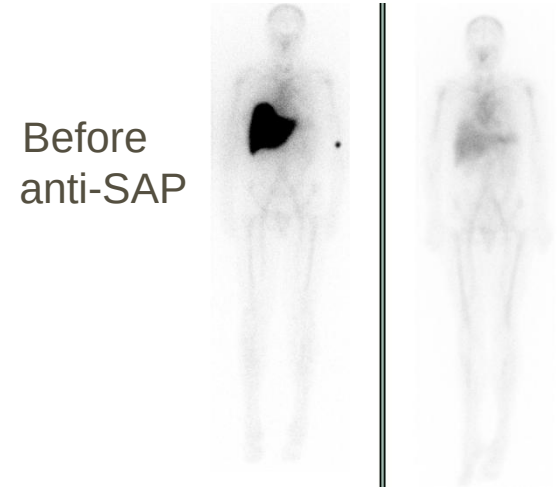
Ackermann et al. International Symposium on Amyloidosis. 2012, poster #0P73

CPHPC + Anti-SAP mAb for systemic amyloidosis

- Directly targets amyloid deposits that cause disease
- Proof of concept in systemic amyloidosis
  - Regression of amyloid in liver, kidney, spleen, etc
- Potential for accelerated approval
- US breakthrough status application planned
- Use in cardiac AL and ATTR amyloidosis
- Example of academic partnership model
- Collaboration with Pentraxin



Reason to believe – amyloid imaging



Liver ECV (median normal 29%)	36.0	29.0
Liver Stiffness (median normal 5.3 kPa)	5.7	2.8
% of tracer in liver	61.1	17.4

Therapeutic clearance of amyloid by antibodies to serum amyloid P component

Richards *et al*. N Engl J Med 2015; 373:1106-1114

Amyloidosis: a comprehensive R&D approach

- Similar prevalence to Pulmonary Arterial Hypertension
  - Approximately 30,000 cases but currently under-diagnosed
- Fundamental mechanism in diverse but medically important disease states
- GSK approaches address both removal of existing deposits and prevention of accumulation
- World class expertise – ability to maximise the opportunity from our leadership position
  - Oral SAP depleter/ anti fibril approaches

GSK's dual approach to amyloidosis

1. "Gene silencing" by antisense oligonucleotide

TTR to prevent formation of amyloid deposits in vital organs

2. Removal of amyloid deposits by macrophage-mediated clearance

Anti-SAP mAb to target SAP in amyloid deposits

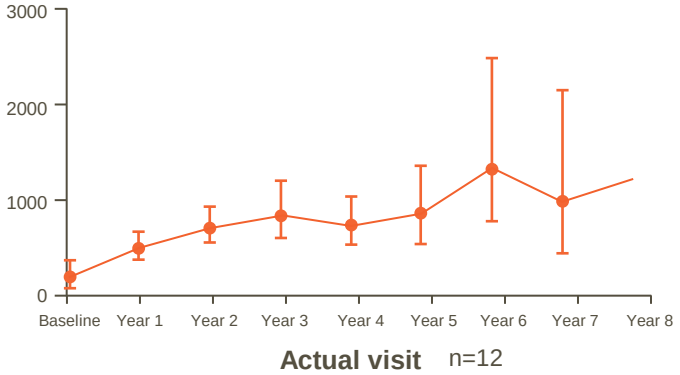
GSK2696273 for adenosine deaminase severe combined immunodeficiency: 100% survival at median 7 year follow up

Severe Combined Immuno-Deficiency (SCID)

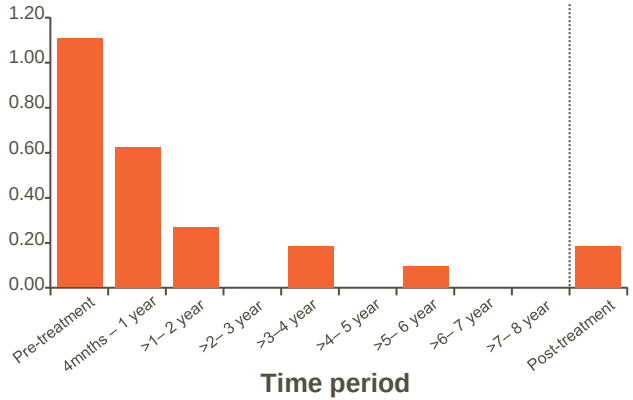
- Fatal
- Life-threatening opportunistic infections

Status:	Filed in Europe
Indication:	ADA SCID
Planned Filing:	US filing 2017

Increased T cell count



Reduced infections



GSK2696273 is a collaboration with Telethon and Ospedale San Raffaele

Cicalese *et al*. ESID 2015, poster #0779.

Gene therapy works in different monogenic diseases

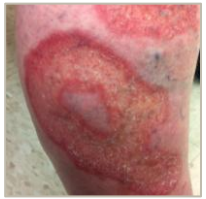
Innovative collaboration with Telethon and Ospedale San Raffaele

- World first *ex vivo* autologous stem cell gene therapy filed
- Filing strategy agreed for 2 more
- Beta thalassaemia study started
- Building GSK platform capability in cell and gene therapy. New alliances and internal platform build
- Cell gene therapy approaches in oncology and potentially other areas. IP estate and know-how accumulating

Pipeline of products

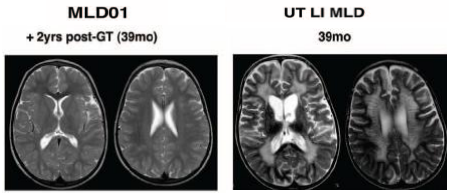
- ADA SCID [a]
- Metachromatic Leukodystrophy [a]
- Wiskott-Aldrich Syndrome [a]
- Beta thalassemia [b]
- MPS1 [b]
- Chronic Granulomatous disease [b]
- Globoid Cell Leukodystrophy [b]

[a] Licensed from Telethon and Ospedale San Raffaele
[b] GSK holds an option to license programme from Telethon and Ospedale San Raffaele



Wiskott-Aldrich Syndrome (WAS)

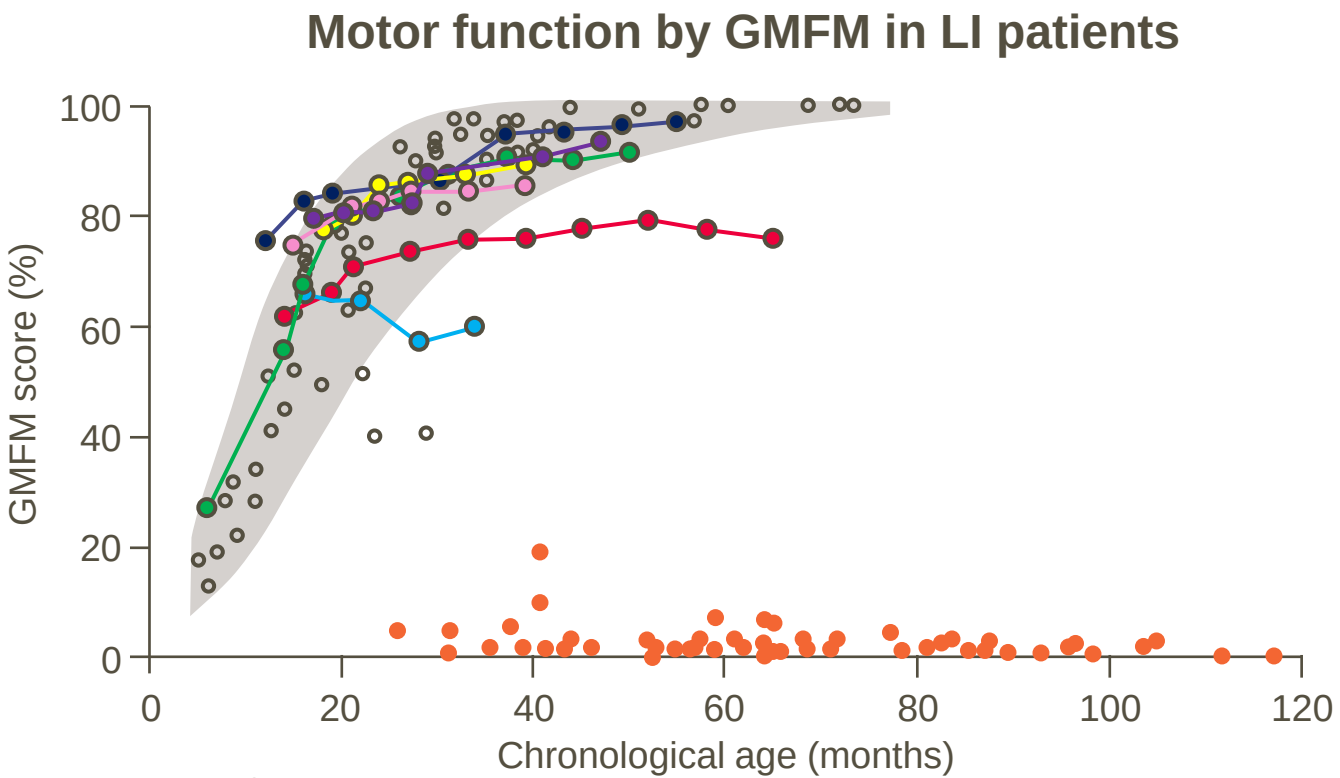
- Thrombocytopenia
- Infections
- Autoimmune disease
- Lymphoma



Metachromatic Leukodystrophy (MLD)

- Fatal
- Rapid loss in cognitive & motor function, followed by death

Cell Gene Therapy clinical effect in MLD



Biffi *et al*. ESCGT 2015 presentation

Introducing our experts

GSK's leading scientists in immuno-inflammation, cancer research, amyloidosis and CGT

Paul-Peter Tak

Senior Vice President,
Head Immuno-
Inflammation (II) TAU

Ravi Rao

Vice President, Medicines
Development Leader &
Head Unit Physician II

John Bertin

Vice President,
Head Pattern Recognition
Receptor DPU

Axel Hoos

Vice President, Head
of Immuno-Oncology

Chris Carpenter

Vice President, Head
Cancer Epigenetics DPU

Duncan Richards

Vice President, Head Academic
DPU

Sven Kili

Vice President, Development
Head for Gene Therapy

Assets profiled at R&D day by planned filing date

See www.gsk.com for full clinical pipeline

2014 to 2017: 6 NMEs & 5 PLEs

Nucala (mepolizumab) *IL-5 mAb* **Severe Asthma**	sirukumab *IL-6 mAb* **Rheumatoid Arthritis**
mepolizumab *IL-5 mAb* **COPD**	GSK2696273 *Ex-vivo stem CGT* **ADA-SCID**
mepolizumab *IL-5 mAb* **EGPA**	GSK2696274 *Ex-vivo stem CGT* **Metachromatic Leukodystrophy**
fluticasone furoate+vilanterol +umeclidinium *ICS/LABA/LAMA* **COPD**	GSK2696275 *Ex-vivo stem CGT* **Wiscott-Aldrich Syndrome**
dolutegravir + rilpivirine *Integrase inhibitor + NNRTI* **HIV**	GSK2998728† *TTR production inhibitor* **FAP**
Benlysta Subcutaneous *BLyS mAb* **SLE**	

2018 to 2020: 10 NMEs & 5 PLEs

mepolizumab *IL-5 mAb* **Nasal Polyposis**	tarextumab† *Notch 2/3 mAb* **Pancreatic Cancer, SCLC**	GSK2398852+ GSK2315698 *SAP mAb + SAP depleter* **Amyloidosis**
mepolizumab *IL-5 mAb* **HES**	GSK525762 *BET inhibitor* **Solid Tumours, Haematological Malignancies**	GSK2998728† *TTR production inhibitor* **TTR Cardiomyopathy**
dolutegravir + lamivudine FDC *Integrase inhibitor+NRTI* **HIV**	GSK2879552 *LSD1 inhibitor* **Acute Myeloid Leukaemia, SCLC**	daprodustat* *Prolyl hydroxylase inhibitor* **Anaemia of CKD**
cabotegravir *Long acting integrase inhibitor* **HIV, HIV PrEP**	GSK3174998 *OX40 agonist mAb* **Solid tumours, Haematological Malignancies**	
gepotidacin *Type 2 topoisomerase inhibitor* **Bacterial Inf.**	GSK3377794†# *NY-ESO-1 TCR* **Sarcoma, Mult. Myel., Melanoma Ovarian, NSCLC**	
sirukumab *IL-6 mAb* **Giant Cell Arteritis**	GSK3359609 *ICOS agonist mAb* **Solid tumours, Haematological Malignancies**	

2021 to 2025: 17 NMEs & 5 PLEs

sirukumab *IL-6 mAb* **Severe Asthma**	GSK3008348 *Alpha V beta 6 integrin antagonist* **IPF**	GSK525762 *BET inhibitor* **Therapy Resistant RA**	GSK3196165 *GM-CSF mAb* **RA, OA**
danirixin *CXCR2 antagonist* **COPD**	*Long acting IL-5 mAb (NBE)* **Asthma, Others**	GSK2330811 *OSM mAb* **Systemic Sclerosis**	GSK2696277†^ *Ex-vivo stem CGT* **Beta Thalassemia**
GSK2269557 *PI3 kinase delta inhibitor* **COPD, Asthma**	*IL5/13 bispecific antibody* **Asthma**	GSK2618960 *IL-7 receptor mAb* **Sjogren's Syndrome**	daprodustat* *Prolyl hydroxylase inhibitor (topical)* **Wound Healing**
GSK2862277 *TNFR1 dAb* **Acute Lung Injury**	GSK2878175 *NS5B inhibitor* **HCV**	GSK2831781 *LAG-3 mAb* **Autoimmune Diseases**	mepolizumab *IL-5 mAb* **Severe Atopic Dermatitis**
GSK2245035 *TLR7 agonist* **Asthma**	GSK3228836† *Antisense oligonucleotide* **HBV**	GSK2982772 *RIP1 kinase inhibitor* **Psoriasis, RA, UC**	
GSK3191812 *TSLP dAb* **Asthma**	belimumab + CD20 *BLyS+CD20* **Sjogren's Syndrome**	GSK3050002 *CCL20 mAb* **Psoriatic Arthritis**	

- Respiratory
- HIV / Infectious Diseases
- Immuno-Inflammation
- Oncology
- Rare Diseases
- Other

† Subject to exercise of option
# Subject to collaborator agreement
^ EU filing
* USAN, INN approval pending

Q&A