A new approach to R&D at GSK

Dr. Hal Barron

25 July 2018

Cautionary statement regarding forward-looking statements

This presentation may contain forward-looking statements. Forward-looking statements give the Group's current expectations or forecasts of future events. An investor can identify these statements by the fact that they do not relate strictly to historical or current facts. They use words such as 'anticipate', 'estimate', 'expect', 'intend', 'will', 'project', 'plan', 'believe', 'target' and other words and terms of similar meaning in connection with any discussion of future operating or financial performance. In particular, these include statements relating to future actions, prospective products or product approvals, future performance or results of current and anticipated products, sales efforts, expenses, the outcome of contingencies such as legal proceedings, and financial results.

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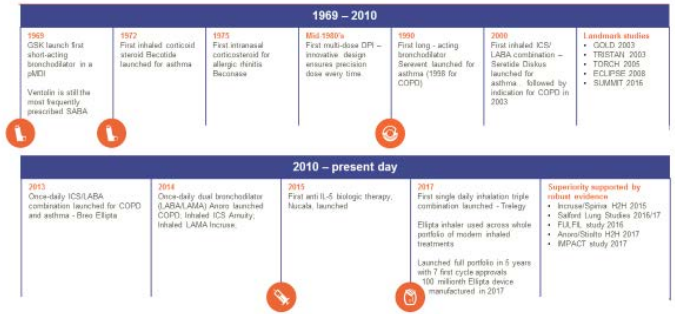
A number of adjusted measures are used to report the performance of our business, which are non IFRS measures. These measures are defined and reconciliations to the nearest IFRS measure are available in our second quarter 2018 earnings release on page 39 and Annual Report on Form 20-F for FY 2017.

All expectations and targets regarding future performance should be read together with "Assumptions related to 2018 guidance and 2016-2020 outlook" on page 40 of our second quarter 2018 earnings release.

Innovation

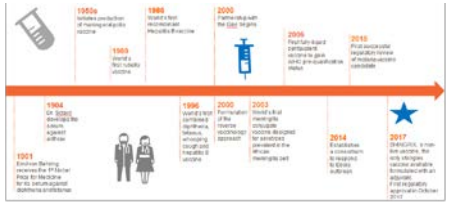
GSK has a strong presence and history of leadership in four major areas

Leadership in Respiratory Medicine



Leadership in HIV/AIDS

Leadership in Vaccines



A strong pipeline of 13 assets

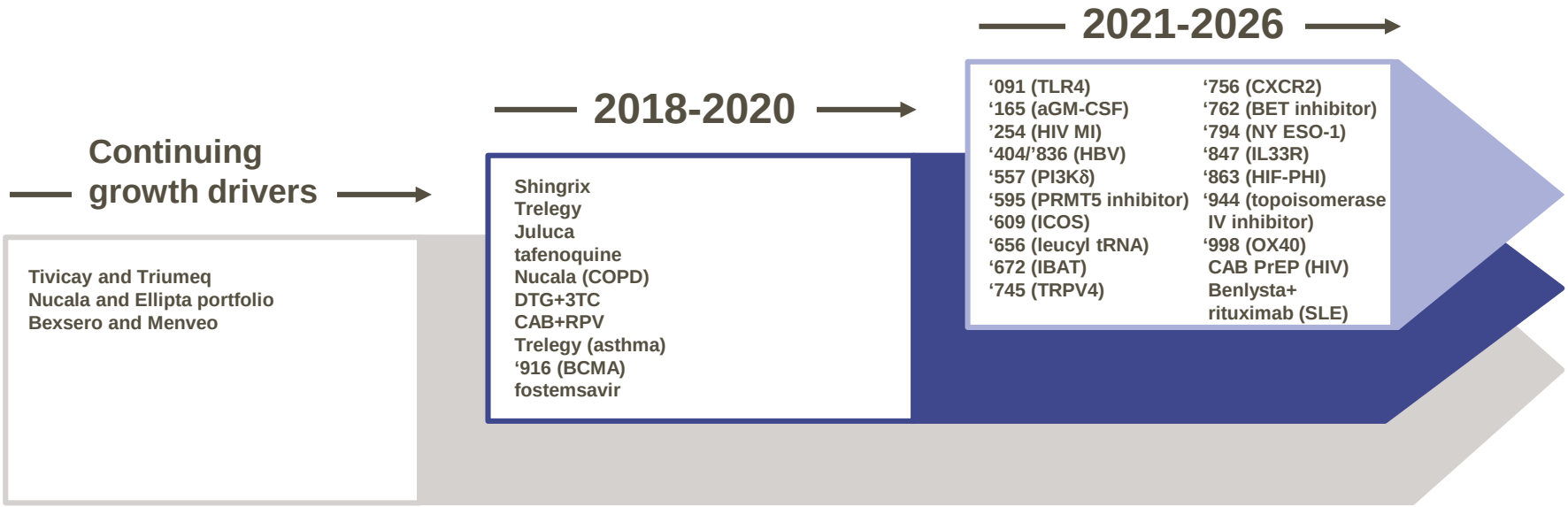
Focus on emerging fields
- Therapeutic vaccines
- Universal or one-dose vaccines
- Antimicrobial resistance

Impact on global public health
- 2 million vaccine doses per day for +160 countries
- Broad portfolio to protect throughout life (22 out of the 30 currently vaccine preventable diseases)
- Reaching ~40% of the world's children
- 1st malaria vaccine for children, recommended by WHO for phased introduction in Africa
- 17bn polio vaccine doses since 1988 to contribute to the Global Polio Eradication Initiative
- +70% of our vaccine doses go to low and middle income countries
- 850 million vaccine doses committed to Gavi at reduced prices to help protect 300 million children in the developing world by 2024

Leadership in Global Health Science and partnership

Innovation

Driving our growth outlook beyond 2020



Base business portfolio optimisation; limited exposure to patent expiries

Consumer Health power brands

Innovation

High performing businesses reinvent themselves

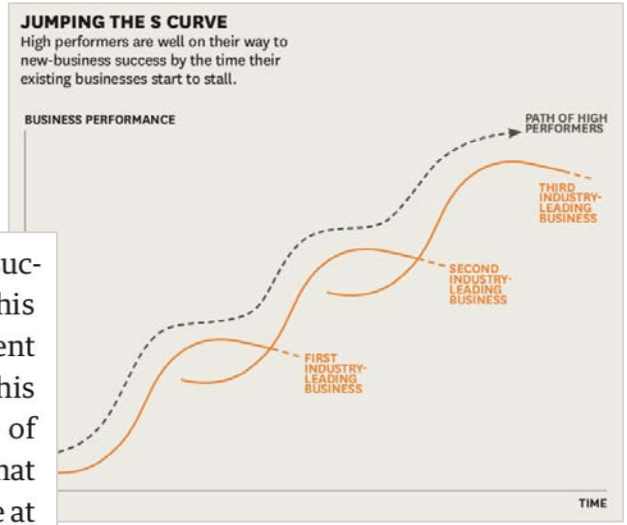
Reinvent Your Business Before It's Too Late

Watch Out for Those S Curves

by Paul Nunes and Tim Breene

80 Harvard Business Review January–February 2011

SOONER OR LATER, all businesses, even the most successful, run out of room to grow. Faced with this unpleasant reality, they are compelled to reinvent themselves periodically. The ability to pull off this difficult feat—to jump from the maturity stage of one business to the growth stage of the next—is what separates high performers from those whose time at the top is all too brief.



Source: "Reinvent your business before it's too late", Paul Nunes and Tim Breen, Harvard Business review, Jan-Feb 2011

The key is understanding what problem you are trying to solve, and what levers you have to engender the change

Science
X
Technology
X
Culture

3 Components to our new R&D approach

Science

X

Technology

X

Culture

The industry needs more innovative medicines for patients with real unmet needs.

Drugs that modulate the immune system have had profound effects on patients with many different diseases.

Our scientific understanding of the role the immune system plays in the development of human disease is rapidly advancing.

GSK has deep understanding in Immunology, with several promising medicines in the pipeline.

Innovation

Drugs that modulate the immune system have had profound effects on patients with many different diseases

Tomorrow

Neurodegeneration
Cardiovascular
Metabolic
Ophthalmology
Hepatology
Osteoarthritis
Ageing

?

2011 onwards

Immuno-oncology

KEYTRUDA, TECENTRIQ, KYMRIAH, IMFINZI, OPDIVO nivolumab, YESCARTA, YERVOY ipilimumab

1990 onwards

Autoimmune Diseases
rheumatology, lupus
IBD, psoriasis, atopic dermatitis

Respiratory

HUMIRA, Rituxan Rituximab, DUPIXENT (dupilumab) injection 300mg, Benlysta, Remicade, Cosentyx (secukinumab), Nucala, Enbrel etanercept, Xolair (omalizumab), OCREVUS, Stelara (ustekinumab), ACTEMRA tocilizumab

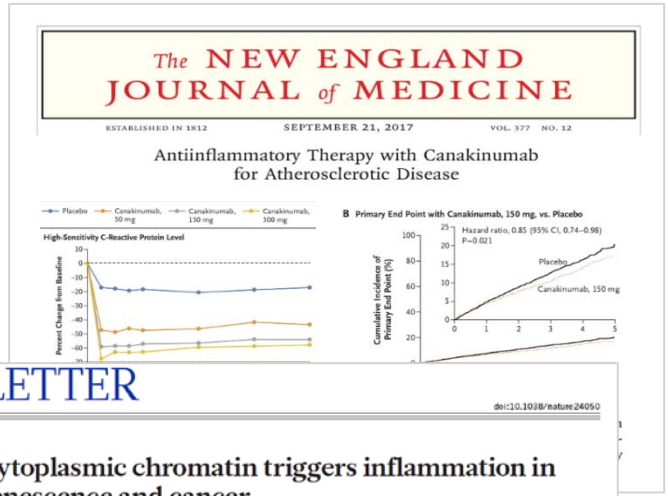
1950 onwards

Steroids

Standard of care for respiratory, MS, rheumatic disease, and many more.

Innovation

Scientific understanding of the role the immune system plays in disease is expanding


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2017 VOL. 377 NO. 12

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

LETTER

doi:10.1038/nature24050

Cytoplasmic chromatin triggers inflammation in senescence and cancer

Zhixun Dou[1], Kanad Ghosh[1], Maria Grazia Vizioli[2,3], Jiajun Zhu[1], Payel Sen[1], Kirk J. Wangensteen[4], Johayra Simithy[1,5], Yemin Lan[1], Yanping Lin[1,5], Zhuo Zhou[6], Brian C. Capell[6,7], Caiyue Xu[1], Mingang Xu[2], Julia E. Kieckhaefer[8,9], Tianying Jiang[10], Michal Shoshkes-Carmel[8,9], K. M. Ahasan Al Tanim[1], Glen N. Barber[11], John T. Seykora[7], Sarah E. Millar[7], Klaus H. Kaestner[8,9], Benjamin A. Garcia[1,5,12], Peter D. Adams[2,3,13] & Shelley L. Berger[1,8,12,14]

Once virtually ignored, microglia, the resident immune cells of the CNS, have recently taken center stage in research for their roles in CNS health and disease.

Microglia emerge as central players in brain disease

VOLUME 23 | NUMBER 9 | SEPTEMBER 2017 NATURE MEDICINE

Michael W Salter[1] & Beth Stevens[2]

There has been an explosion of new findings recently giving us insights into the nervous system (CNS) disorders. A host of new molecular tools and mouse mod implicating this enigmatic type of nervous system cell as a key player in conditi disorders such as autism to neurodegenerative disorders such as Alzheimer's di Contemporaneously, diverse roles are emerging for microglia in the healthy brai

NEURODEVELOPMENT

Complement and microglia mediate early synapse loss in Alzheimer mouse models

Soyon Hong,[1] Victoria F. Beja-Glasser,[1,*] Bianca M. Nfonoyim,[1,*] Arnaud Frouin,[1] Shaomin Li,[2] Saranya Ramakrishnan,[1] Katherine M. Merry,[1] Qiaoqiao Shi,[2] Arnon Rosenthal,[3,4,5] Ben A. Barres,[6] Cynthia A. Lemere,[2] Dennis J. Selkoe,[2,7] Beth Stevens[1,8,†]

Synapse loss in Alzheimer's disease (AD) correlates with cognitive decline. Involvement of microglia and complement in AD has been attributed to neuroinflammation, prominent late in disease. Here we show in mouse models that complement and microglia mediate synaptic loss early in AD. C1q, the initiating p complement cascade, is increased and associated wit deposition. Inhibition of C1q, C3, or the microglial com number of phagocytic microglia, as well as the extent necessary for the toxic effects of soluble β-amyloid (A hippocampal long-term potentiation. Finally, microglia material in a CR3-dependent process when exposed t these findings suggest that the complement-depende inappropri

Innate Immunity

REVIEW

The NLRP3 Inflammasome: A Sensor for Metabolic Danger?

Kate Schroder,[1,2] Rongbin Zhou,[1] Jurg Tschopp[1,*]

Interleukin-1β (IL-1β), reactive oxygen species (ROS), and thioredoxin-interacting protein (TXNIP) are all implicated in the pathogenesis of type 2 diabetes mellitus (T2DM). Here we review mechanisms directing IL-1β production and its pathogenic role in islet dysfunction during chronic hyperglycemia. In doing so, we integrate previously disparate disease-driving mechanisms for IL-1β, ROS, and TXNIP in T2DM into one unifying model in which the NLRP3 inflammasome plays a central role. The NLRP3 metabolic to the pathogenesis of

REVIEW Open Access

Neuroinflammation in Parkinson's disease and its potential as therapeutic target

Immunomodulators as adjuvants for vaccines and antimicrobial therapy

Erin F. Nicholls, Laurence Madera, and Robert E. W. Hancock

Center for Microbial Diseases and Immunity Research, University of British Columbia, Vancouver, British Columbia, Canada

Emerging targets in neuroinflammation-driven chronic pain

Innovation

Broad portfolio with strong focus in immunology

Phase 1

- **2831781* (LAG3)** ulcerative colitis
- **3008348 (aVb6 integrin antagonist)** IPF
- **3358699* (BET targeted inhibitor)** RA
- **3858279* (CCL17 antagonist)** OA
- **2636771 (PI3kb inhibitor)** cancer
- **2983559 (RIP2k inhibitor)** IBD
- **3036656* (leucyl t-RNA inhibitor)** TB
- **3640254 (HIV maturation inhibitor)** HIV
- **3511294* (IL5 LA antagonist)** asthma
- **2292767 (PI3kd inhibitor)** COPD/asthma
- **3810109* (broadly neutralizing antibody)** HIV

Phase 2

- **3196165* (GM-CSF inhibitor)** RA
- **3389404*/3228836* (HBV ASO)** HBV
- **3772847* (IL33r antagonist)** severe asthma
- **2982772 (RIP1k inhibitor)** pso/RA/UC
- **3359609* (ICOS receptor agonist)** cancer
- **3377794* (NY-ESO-1 TCR)** cancer
- **2586881* (rhACE2)** acute lung injury/PAH
- **1325756 (danirixin CXCR2 antagonist)** COPD
- **2140944 (topoisomerase IV inhibitor)** antibacterial
- **2269557 (nemiralisib PI3Kδ inhibitor)** COPD**
- **2330811 (OSM antagonist)** systemic sclerosis
- **'852*+'698* (SAP antagonist)** AL/ATTR-CM
- **2881078 (SARM)** COPD muscle weakness**
- **1795091 (TLR4 agonist)** cancer
- **2245035 (TLR7 agonist)** asthma
- **2862277 (TNFR1 antagonist)** acute lung injury
- **2798745 (TRPV4 antagonist)** cough
- **3174998* (OX40 agonist)** cancer
- **525762 (BET inhibitor)** cancer**
- **2330672 (IBAT inhibitor)** cholestatic pruritus
- **3326595* (PRMT5 inhibitor)** cancer
- **GR121619* (oxytocin)** postpartum haemorrhage

Pivotal/Registration

- **Benlysta + Rituxan** SLE**
- **cabotegravir** + rilpivirine* LA** HIV
- **D3, dolutegravir + lamivudine** HIV
- **1278863 (daprodustat HIF-PHI)** anemia
- **3684934 (fostemsavir HIV AI)** HIV
- **Nucala** COPD/HES/nasal polyps
- **Trelegy*** asthma
- **tafenoquine*** malaria***
- **Dectova* IV** influenza
- **2857916* (BCMA ADC)** multiple myeloma**

Vaccines

- **Rotavirus - Phase 3**
- **MMR - Phase 3 (US)**
- **Ebola - Phase 2**
- **Strep pneumonaie next gen - Phase 2**
- **COPD – Phase 2**
- **Hepatitis C - Phase 2**
- **Malaria next gen - Phase 2**
- **MenABCWY - Phase 2**
- **Shigella - Phase 2**
- **Tuberculosis - Phase 2**
- **RSV - Phase 2**
- **HIV - Phase 2**
- **Flu universal - Phase 1**

27

immuno-modulators in development

*In-license or other alliance relationship with third party
** Additional indications also under investigation
*** Received FDA approval 20 July 2018

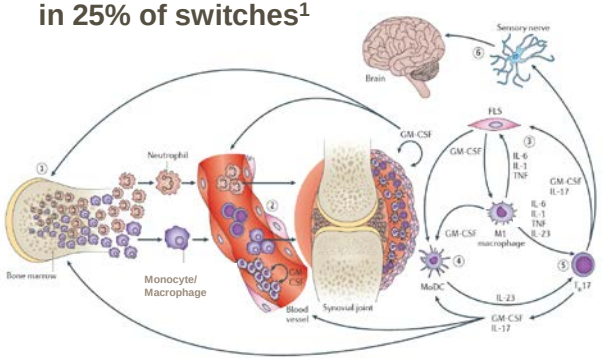
Innovation

GSK‘165 (aGM-CSF): potential for a disease modifying effect in rheumatoid arthritis (RA) with a unique impact on pain

The target	– GM-CSF is a pro-inflammatory cytokine that induces differentiation and proliferation of granulocytes and macrophages – One of the first cytokines detected in human synovial fluid from inflamed joints – Preclinical data suggests a broader range of actions than existing biologics (including a beneficial effect on pain)
The agent	– GSK’165 is a fully humanised antibody targeting anti-granulocyte macrophage colony-stimulating factor (aGM-CSF)
Current status	– Positive Phase 2b results in RA in house; clinical data to be presented at an upcoming conference – Discussions with regulators planned to advance development rapidly in RA

– **Unmet need remains in RA despite development of new classes of agent (JAK inhibitors, anti IL6):** ~50% of patients do not achieve low disease activity criteria within 12 months of aTNF treatment and ~80% do not achieve Disease Activity Score 28 (DAS28)[1]

– **Currently 45% of patients report daily pain despite treatment with targeted therapies and pain is the key driver in 25% of switches[1]**

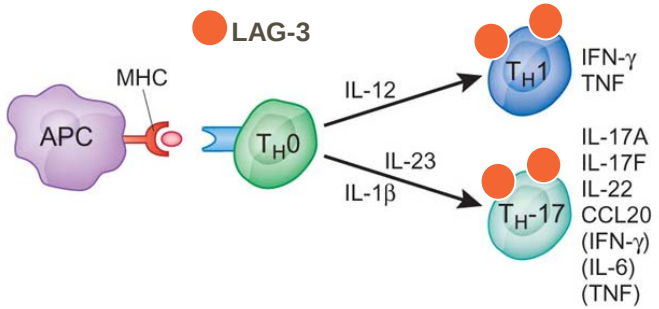


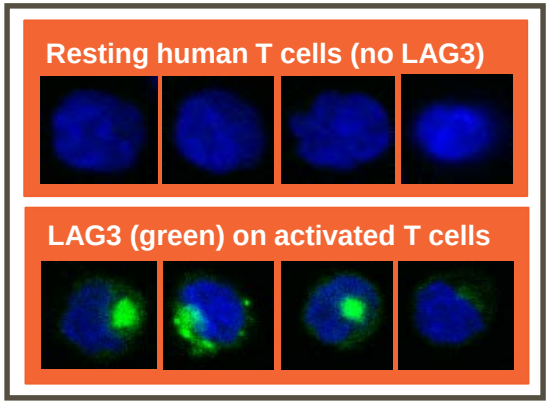
1 Targeting GM-CSF in inflammatory diseases. Ian P. Wicks & Andrew W. Roberts. Nature Reviews Rheumatology volume 12, pages 37–48 (2016)

Innovation

GSK‘781: targeting the inflammatory cascade through depletion of recently activated LAG-3+ T cells

The target	– Lymphocyte Activation Gene-3 – Marker of early T-cell activation (predominantly expressed on newly activated CD4+ & CD8+ T-cells) – Negative regulator of T-cell response
The agent	– GSK’781 is a humanised monoclonal antibody: – Specific to the Lymphocyte Activation Gene-3 (LAG-3) protein – Afucosylated to enhance ADCC
Current status	– Lead indication : ulcerative colitis – Phase 1b studies ongoing – PoC data expected 2020





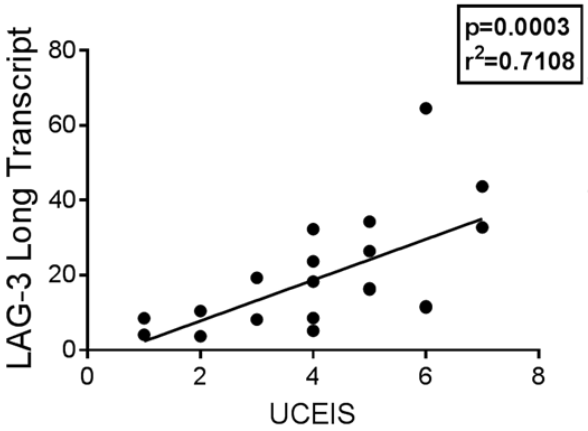
ADCC: antibody-dependent cell-mediated cytotoxicity

GSK in house data, after CD28 bead stimulation

Innovation

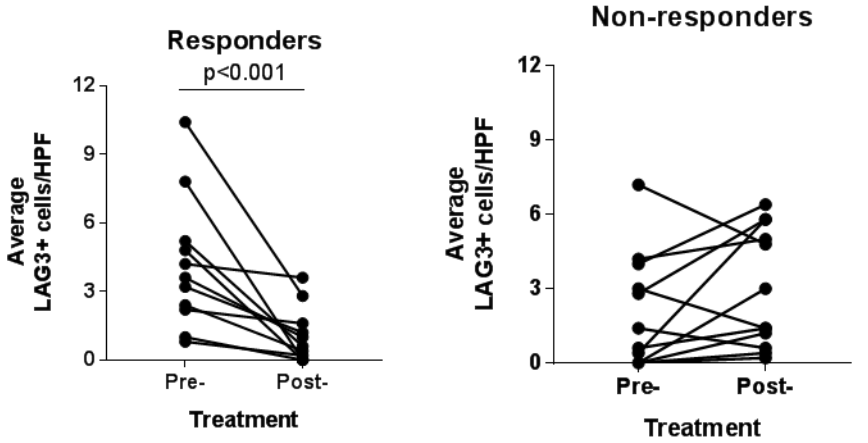
Experimental medicine studies support UC as lead indication

Gut transcript levels correlate with endoscopic index of disease activity*



* unpublished

LAG3+ cell numbers (IHC) reduce in responders but not non responders to established biologics



Slevin et al. P064, ECCO 2018

Dose dependent depletion of LAG-3 positive cells was demonstrated in FTiH/Phase 1b study

FTiH: first time in human

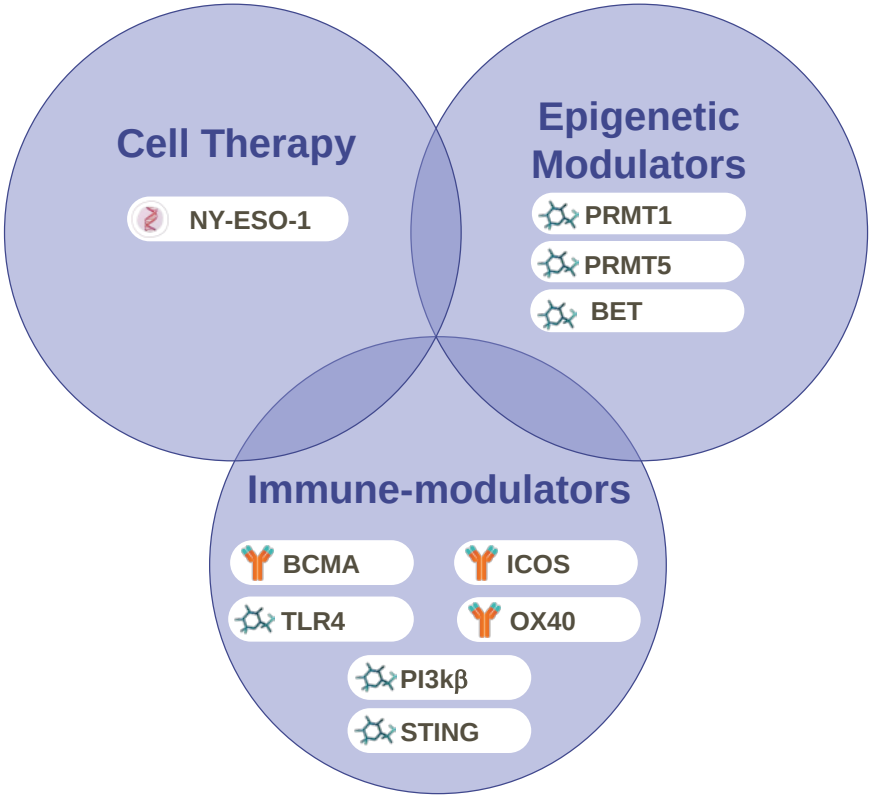
Innovation

GSK's expertise in immunology will enable success in immuno-oncology

Monoclonal Antibodies

Cellular Therapies

Synthetic/small Molecules



Innovation

GSK ‘916: First-in-class anti-BCMA ADC agent for treatment of multiple myeloma

The target	– BCMA plays a key role in plasma cell survival – It is found on the surfaces of plasma cells and is expressed on malignant plasma cells – Not expressed in healthy tissues

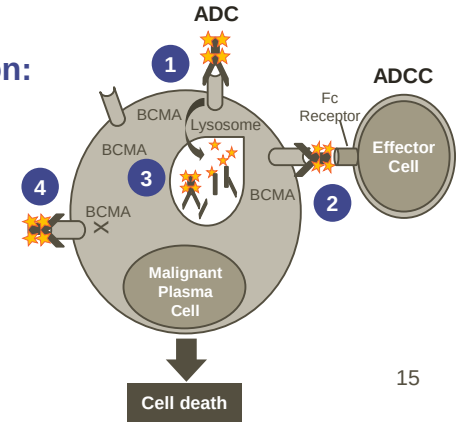
The agent	– GSK’916 is a humanised IgG1 antibody targeting BCMA (B-cell maturation antigen)
	  – Linked to the anti-mitotic agent MMAF
	  – Afucosylated to enhance ADCC

Key attributes	– New modality in multiple myeloma: first ADC – Easy and convenient to administer: 1h infusion q3w – No pre-medication required for infusion reactions – Pre-medication with steroid eye drops – New MoA enabling diverse combination – Breakthrough and PRIME designations

– **Multiple myeloma**, also known as **plasma cell myeloma**,
is a cancer of plasma cells, a type of white blood cell normally responsible for producing antibodies.
– Multiple myeloma is treatable, but generally incurable.
– Globally, multiple myeloma affected 488,000 people and resulted in 101,100 deaths in 2015.
– Without treatment, typical survival is seven months, with current treatments, survival is usually 4–5 years

Four mechanisms of action:

1. ADC mechanism
2. ADCC mechanism
3. BCMA receptor signaling inhibition
4. Immunogenic cell death

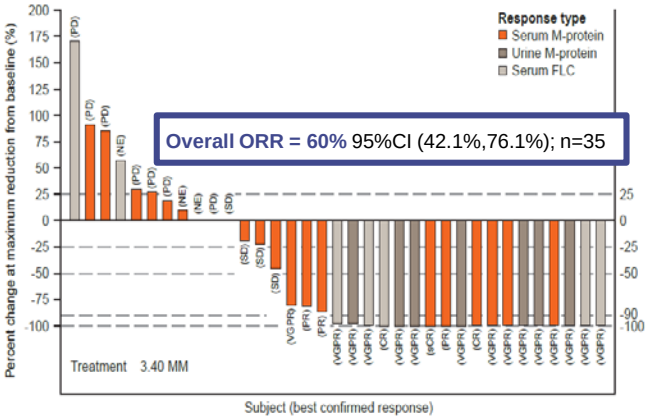


ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; MMAF, monomethyl auristatin-F

Innovation

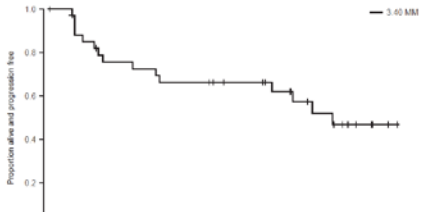
GSK'916 anti-BCMA ADC: robust single agent activity in heavily pre-treated/refractory patients

Drug, Sponsor	Line of therapy; Trial	ORR	mPFS	mOS
[1]*Kyprolis*‡ (IV), monotherapy Amgen	3L+, Single arm, N=266	23.7%	3.7m	15.6m
[2]*Darzalex*‡ (IV), monotherapy Janssen	4L+, Single arm, N=106	29.2%	3.7m	17.5m
GSK'916 (IV), monotherapy	***More than 50% of patients had ≥5 lines (40% Darzalex‡ treated), Single arm, N=35***	***60% (43% in Darzalex‡ exposed)***	***7.9m (6.8m in Darzalex‡ exposed)***	***NA***



Progression-free survival (months)

Q1 (95% CI)	2.3 (0.7, 6.8)
Median (95% CI)	**7.9 (3.1, -)**
Q3 (95% CI)	N/A



Most frequent adverse events (AEs)
- Corneal events 63%
- Thrombocytopenia 57%

Corneal events – mostly low grade (9% Gr3)
- Manageable with steroid eye drops
- Dose reductions

Hematologic AEs (including thrombocytopenia)
- Frequent in MM population due to disease

Infusion related reactions 23%
- Occur at first dose without premedication
- Manageable
- Do not recur with subsequent dose

1: Siegel et al. Blood (2012); 2: Lonial et al., Lancet (2016). GSK'916 data presented at ASH 2017;
‡Trademarks are the property of their respective owners

Innovation

GSK‘916: broad development plan initiated

First launch in 4L in 2020; 2L launch planned for 2023

Development strategy for use in:

				Study start	Est launch
4L/3L Monotherapy and combinations	DREAMM-1	pilot	relapsed/ refractory patients	‘916 monotherapy, single arm, n=73	2014	---
	DREAMM-2	pivotal	daratumumab failures	‘916 monotherapy, single arm, n=155	July 2018	2020
	DREAMM-3	pivotal	failed lenalidomide and proteasome inhibitor	‘916 monotherapy vs. PomDex, n=320	2019	2022
	DREAMM-4	pilot	relapsed/ refractory patients	‘916 + PD1 combination, single arm, n=40	4Q18	---
	DREAMM-5	platform	relapsed/ refractory patients	‘916 + novel combinations, n=245	2019	---
2L Combination with SOC	DREAMM-6	pilot	failed 1 prior therapy	‘916+LenDex OR ‘916+BorDex open label, n= 90	Q3 2018	---
	DREAMM-7	pivotal	failed 1 prior therapy	‘916+BorDex vs. Dara+BorDex, n= 478	2019	2023
	DREAMM-8	pivotal	failed 1 prior therapy	‘916+PomDex vs. PomBorDex, n= 449	2019	2024
1L Combination with novel and SOC agents	DREAMM-9	pivotal	transplant Ineligible	‘916+SoC vs SOC, n=TBC	2020	TBC
	DREAMM-10	pivotal	transplant Ineligible	‘916+novel agent vs SOC, n=TBC	2021	TBC

36k patients*

50k patients*

56k patients*

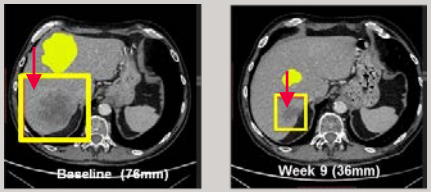
* Treatable patients in G7 (US, EU5, Japan), Kantar Health 2031 projected; 3L pts 26k, 4L 10k;~65-70% 1L MM pts undergo transplant (source IPSOS, March 2018)
SOC: standard of care

Innovation

Early stage oncology portfolio with near term data read outs

GSK'609 ICOS agonist

- humanised IgG4 anti-ICOS agonist monoclonal antibody, engineered to provide non-depleting 'best in class' agonist activity
- First-in-human trial ongoing across several cancers
- Clinical activity observed with both monotherapy and PD-1 combination (pembrolizumab)
- Several combinations to be tested in platform study starting year end 2018

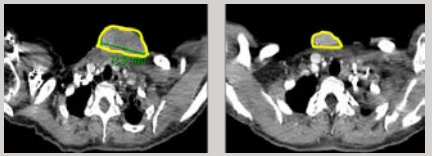


Confirmed PR in 64yr old male head & neck cancer patient

PoC anticipated 2H 2018

GSK'595 PRMT5 inhibitor

- First-in-class agent with potential broad activity across multiple haematologic and solid cancers
- Dose escalation ongoing
- PRMT5 highly expressed in cancers; high expression associates with poor survival
- Clinical responses seen in cervical cancer and adenoid cystic carcinoma (ACC)

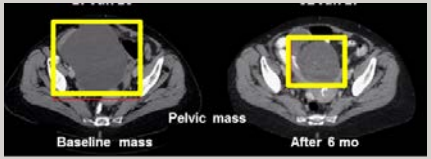


Confirmed PR in 38yr old female cervical cancer patient

PoC anticipated 2H 2019

GSK'998 OX40 agonist

- humanised, engineered IgG1 OX40 agonist mAb
- Mono and PD-1 combo dose escalation completed
- Clinical activity observed in monotherapy and PD-1 combination (pembrolizumab)
- TLR4/OX40 combo dose escalation is ongoing

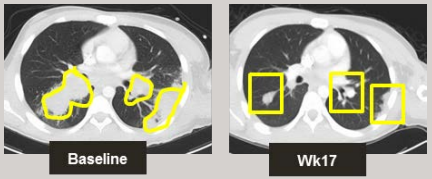


Confirmed PR in 66yr old female liposarcoma patient

PoC anticipated 2H 2020

GSK'762 BET inhibitor

- Oral epigenetic-targeted drug, being developed as a novel treatment for a broad range of solid and blood cancers
- Evidence of activity as monotherapy in NUT midline carcinoma
- Ongoing combination studies in breast and prostate cancer with read outs in 2019



Confirmed PR in 18yr old male NUT midline carcinoma patient

PoC anticipated 2H 2019

PoC: proof of concept

Science
X
Technology
X
Culture

Drug discovery and development is very risky with <10% of drugs that undergo clinical testing ultimately becoming medicines[1].

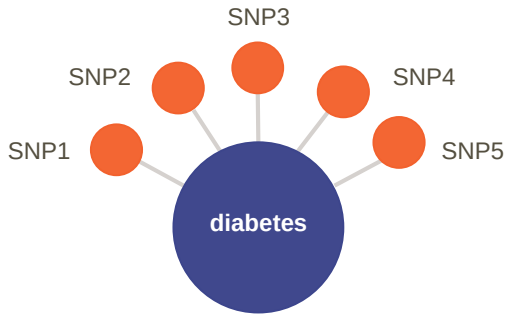
Medicines with genetic validation succeed nearly 2x more often than those without[2].

1. Parsing clinical success rates. Asher Mullard. Nature Reviews Drug Discovery June 2016
2. The support of human genetic evidence for approved drug indications. Nelson et al, Nature Genetics, 47,856-860 (2015)

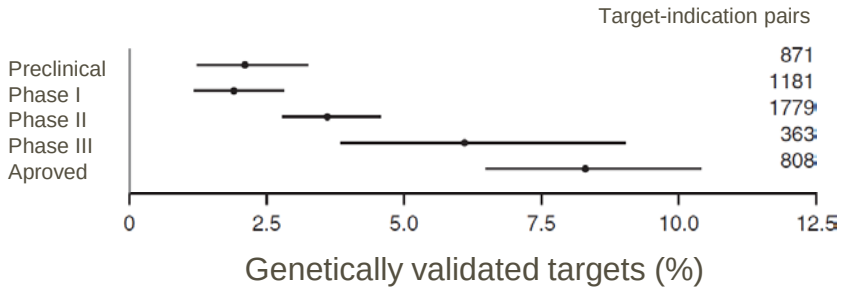
Innovation

"Genetically validated" targets have a higher probability of success[1]

GWAS focuses on diseases of interest and looks for genetic associations



Drugs with human genetic evidence nearly 2x more likely to be successful[1]



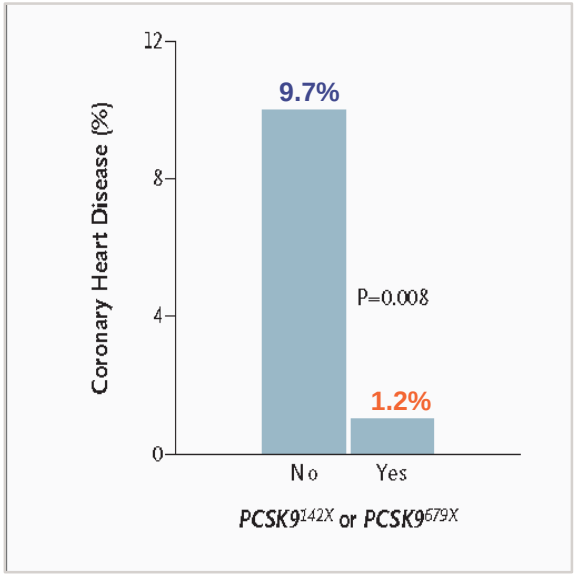
GWAS: genome-wide association study; SNP: single nucleotide polymorphism

1. Adapted from Nelson et al, Nature Genetics, 47,856-860 (2015)

Innovation

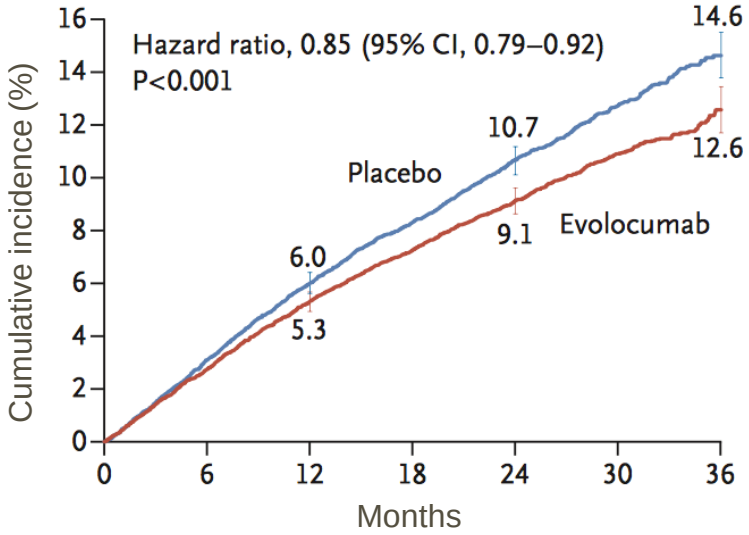
PCSK9: the power of genetically validated targets

Heterozygous carriers of PCSK9 loss-of-function alleles have lower LDL and fewer CV events



11 years for validation of genetics to be demonstrated

Evolocumab and clinical outcomes in patients with cardiovascular disease



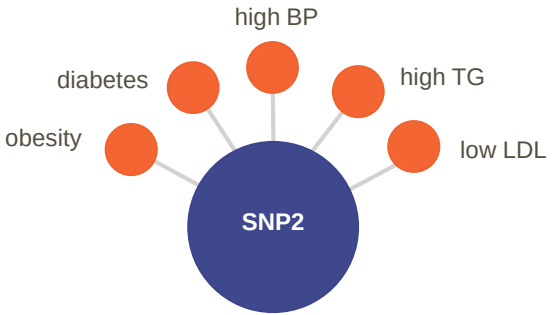
Cohen et al., N Engl J Med 2006;354:1264-72

M Sabatine et al New England Journal of Medicine March 2017

Innovation

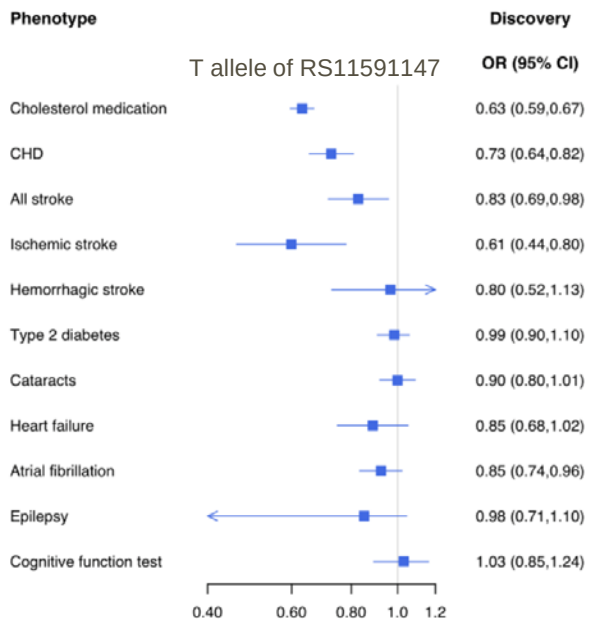
PheWAS can enable discovery of novel genetic associations

PheWAS focuses on SNP/gene of interest and looks for phenotype associations



Large-scale phenome-wide association study of *PCSK9* loss-of-function variants demonstrates protection against ischemic stroke

Abhiram S. Rao[1], Daniel Lindholm[2,3], Manuel A. Rivas[4], Joshua W. Knowles[5], Stephen B. Montgomery[6,7], Erik Ingelsson[8*]



PheWAS: phenome-wide association study
BP: blood pressure; TG: trigylcerides; LDL: low density lipoprotein

Innovation

A new approach to drug discovery is needed to make this a reality

?

2015

2017

2018

Innovation

A new approach to drug discovery is needed to make this a reality

2015

2017

2018

Innovation

A new approach to drug discovery is needed to make this a reality

Innovation

23andMe database metrics: massive engaged database

5m+ customers

>80% consent to research and recontact

1.5b+ survey questions answered

- Genotype data
- Phenotype data
- Biobanked samples
- Longitudinal data
- Ability to re-contact

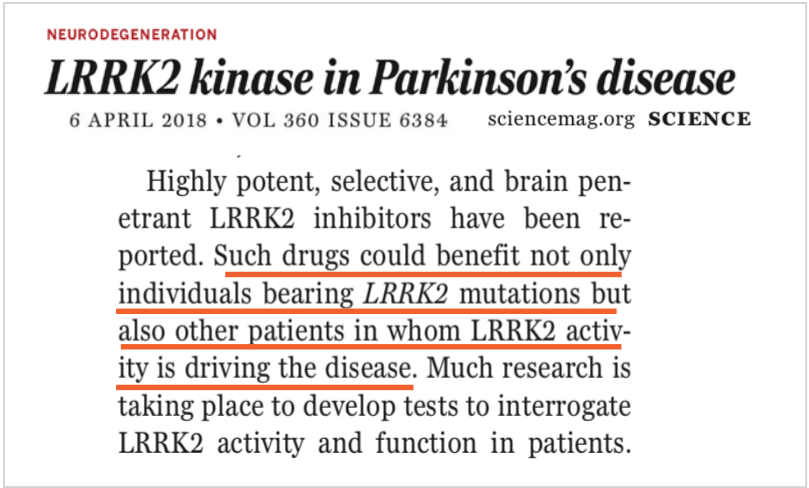
No individual will be identifiable to GSK. Continued protection of data and privacy is the highest priority for both GSK and 23andMe

Innovation

Leucine rich-repeat kinase 2 (LRRK2): a genetically validated target for Parkinson's Disease

The target	– Leucine rich-repeat kinase 2 (LRRK2) is a genetically validated target for Parkinson's disease
The agents	– GSK'984 and GSK'813 are LRRK2 kinase inhibitors – Opportunity to modify disease, while current therapies symptomatic only – Early treatment to prevent disease is possible if LRRK2 inhibition is shown to modify disease
Current status	– 2 diverse GSK molecules poised to enter the clinic in 2019 – Opportunity to accelerate

- 2nd most prevalent neurodegenerative disease
- Genetically validated targets provide an opportunity to treat earlier in the disease
- If LRRK2 inhibition benefits the rare genetically driven patients it may work in others (as in PCSK9)



NEURODEGENERATION

LRRK2 kinase in Parkinson's disease

6 APRIL 2018 • VOL 360 ISSUE 6384 sciencemag.org **SCIENCE**

Highly potent, selective, and brain penetrant LRRK2 inhibitors have been reported. Such drugs could benefit not only individuals bearing *LRRK2* mutations but also other patients in whom LRRK2 activity is driving the disease. Much research is taking place to develop tests to interrogate LRRK2 activity and function in patients.

Innovation

LRRK2 inhibitor programme: 23andMe's advantage to expedite clinical trial recruitment

Identifying eligible participants is a time intensive and costly process

In the US:
- **~1M** individuals with Parkinson's Disease
- **~135,000** LRRK2 G2019S carriers
- **~10,000-15,000** Parkinson's Disease patients who are LRRK2 G2019S carriers

Clinical trial sites would need to genotype 100 Parkinson's Disease patients to find **one** LRRK2 G2019S carrier

23andMe database currently includes:
- **>10,000** re-contactable individuals with Parkinson's Disease
- **>3,000** re-contactable LRRK2 G2019S carriers
- **>250** re-contactable LRRK2 G2019S carriers with Parkinson's Disease
- Ongoing efforts to increase and engage the LRRK2 G2919S cohort to identify newly diagnosed individuals

23andMe provides expedited and focused clinical trial recruitment
- Strategic trial site selection to maximize enrollment at each site
- Flexible and streamlined recruitment: pace recruitment appropriate to sites' ability to screen, randomize and treat participants; ability to screen on comorbidities and select inclusion criteria
- Opportunity to significantly reduce total clinical trial recruitment duration

Innovation

23andMe and GSK exclusive collaboration

- Collaboration offers scale, diversity, sustainability for advancing therapeutic programs
- Questionnaire yields unique phenotype information vs other biobanks
- Can deploy custom surveys to dive deeper into specific diseases
- Allows rapid recruitment of clinical trials based on genotype, phenotype and proximity to study centres

→

- Improved target selection (higher PoS, and safer, more effective medicines)
- Allows more efficient/effective identification and recruitment of patients for clinical studies
- Empowers patients!

PoS: probability of success

Science
X
Technology
X
Culture

Technology has been a driver of innovation in many industries, especially science and medicine.

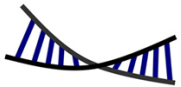
Innovation

Functional genomics: the power of gene editing to unravel biology at scale

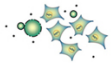
Reverse genetics (think PheWAS) is the process of going from genotype to phenotype

All experiments nature could do

Reverse genetic screens



Known gene

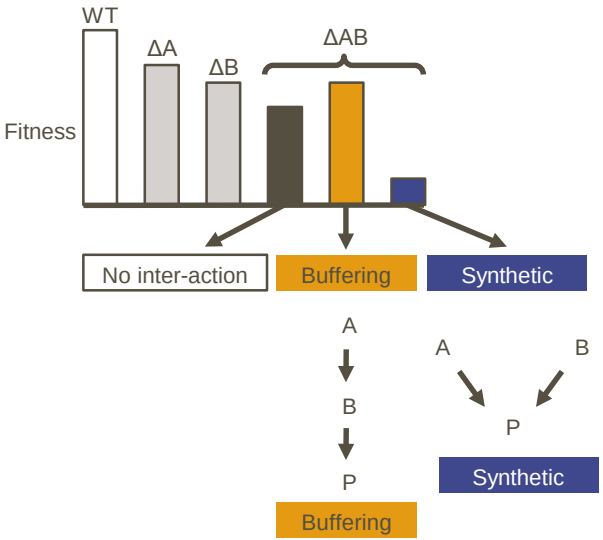


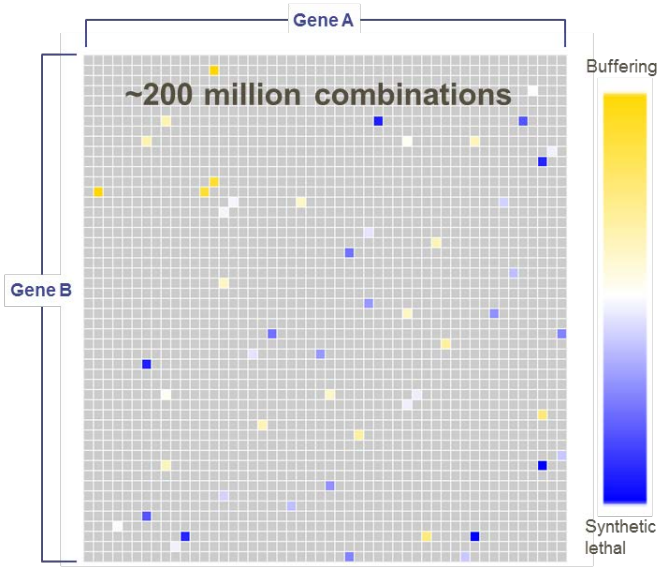
Phenotype resulting from alternative

CRISPR

Genetic interactions reveal functional relationships

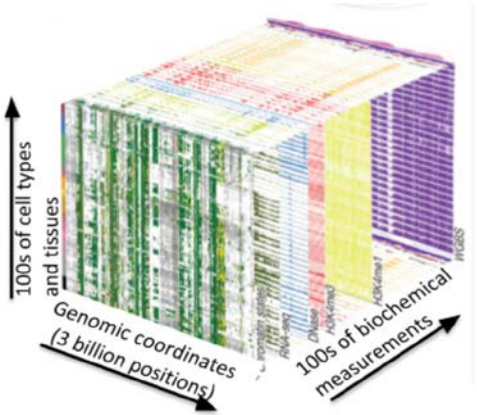
Genetic interaction maps systematically measure how the presence of one gene modulates the phenotype of another gene.





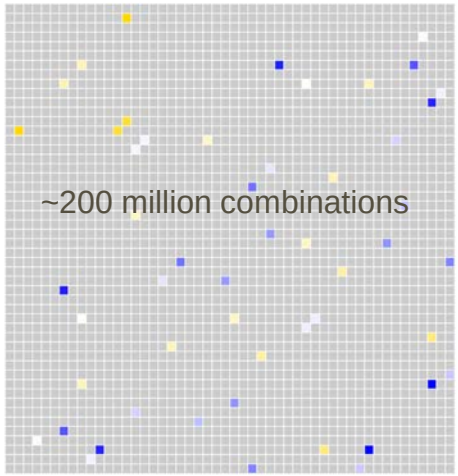
Innovation

Functional genomics (the power of gene editing) combined with machine learning will be very powerful



x

Gene x Gene



Deep learning

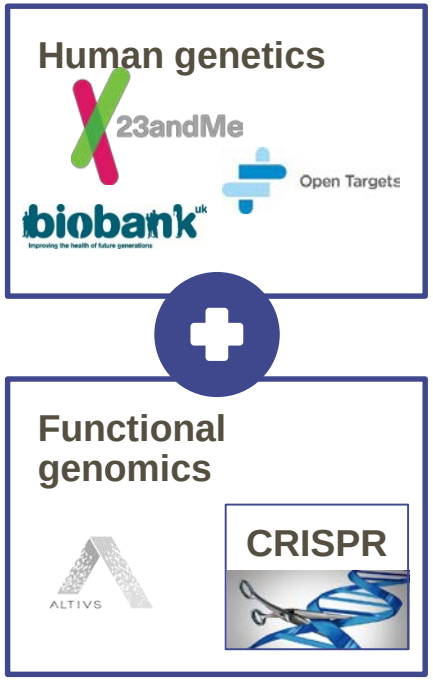
- Functional annotation of the human genome → Acceleration of drug discovery
- Prediction of disease-associated mutations → Disease diagnosis
- Liquid biopsy decomposition → Early cancer detection

cell types x genome x (gene x gene) => a lot of data points!

Innovation

Human genetics and functional genomics

Science and technology together to drive better R&D success



"Artificial Intelligence is the new electricity and is changing industry after industry."
Stanford School of Business lecture by Andrew Ng

Machine learning

Machine Learning will enable the fields of science and medicine to evolve from an era of "Big Data" to an era of "Understanding Data"

More high quality targets

Faster development

Better success rates

Innovation

Cell and Gene Therapy is a potentially disruptive technology that has the potential to transform medicine

GSK is positioned to lead the field through:

Pioneer in autologous cell therapy

- Early clinical and manufacturing expertise gained with Strimvelis*, and other rare disease candidates
  - Key: ability to scale autologous cell therapy for immuno-oncology
  - Requires automation and “close-system” manufacturing
  - Miltenyi Biotec collaboration

Patented enabling technology

- Autologous cell therapy: manual approaches to transfection (viral vector generation) and transduction have high COGS, limiting potential applicability
- Industry-wide shortage of viral vector
- GSK’s patented proprietary SCLT** technology industrializes lentivirus vector production; expected to reduce COGS 5-10-fold
- Opportunity to licence technology and leverage royalty opportunities

Strong pipeline of candidate antigens, including:

- Leading TCR-T capability, accessing solid tumours
- Access to further target antigens through partners (Adaptimmune, Miltenyi Biotec, others)
- Novel technologies to enhance activity of engineered cell products in solid cancer

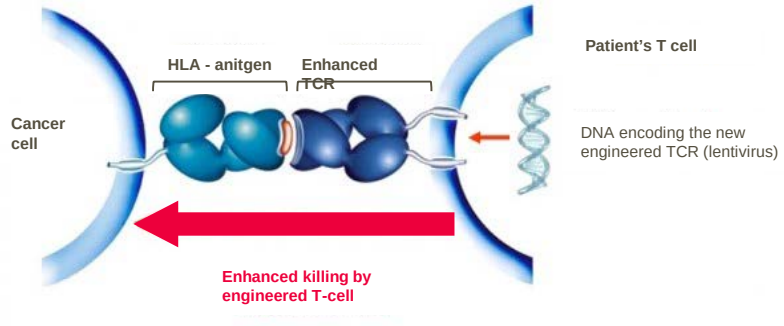
*GSK retains 19% stake in Orchard Therapeutics, focused on providing ex vivo cell therapies for rare diseases
**SCLT: Stable cell line technology

Innovation

GSK‘794: NY-ESO-1 – a potential first to market TCR-T autologous cell therapy for solid tumours

The target	– NY-ESO-1 has significant expression in several tumour types, including NSCLC, sarcoma and myeloma
The agent	– GSK’794 is a TCR-T cell therapy targeting the NY-ESO peptide – In-licensed from Adaptimmune – NY-ESO-1 provides PoC for the TCR technology and access for a portfolio of new targets – Next generation engineering will allow us to assess technologies to enhance activity and/or synergistic combinations that can be utilized across the whole portfolio
Current status	– Ongoing studies in synovial sarcoma, MRCLS, MM and NSCLC – Completed transition to GSK in July 2018

NY-ESO-1^{c259} TCR-T:
affinity-enhanced TCR enabling identification and killing of target tumor cells



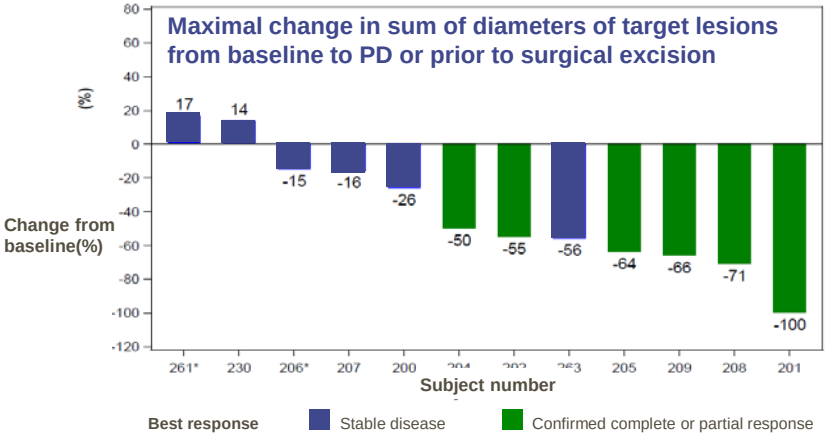
Natural NY-ESO-1 TCR K_D = 9.3μM
NY-ESO-1^{c259} TCR K_D = 0.73μM
Affinity-enhancement: enables recognising tumour antigens expressed at low levels

MRCLS: mixoid round cell liposarcoma; MM: multiple myeloma; NSCLC: non small cell lung cancer

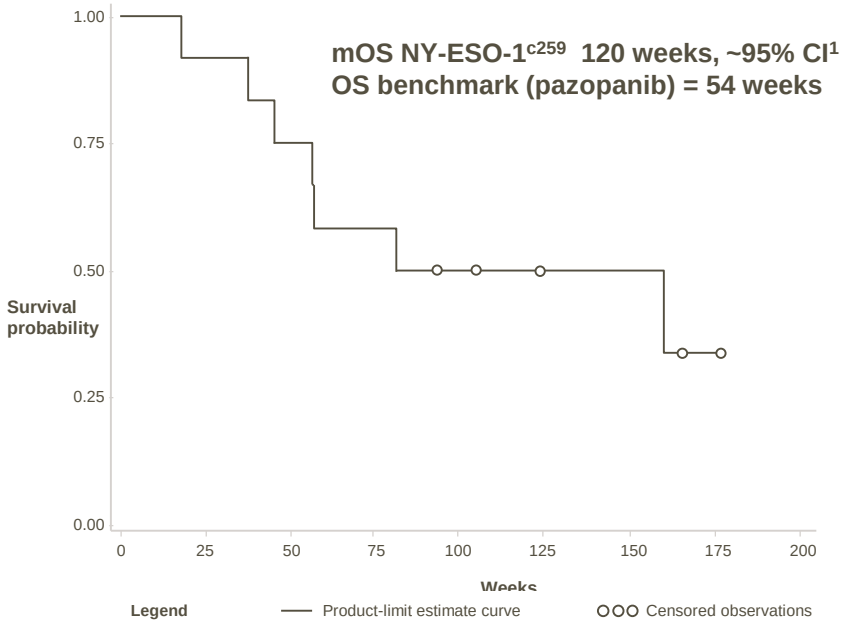
Innovation

GSK'794 NY-ESO-1c259 TCR-T is transformational in improving ORR and mOS in synovial sarcoma

- Confirmed antitumour activity in 10/12 subjects treated
- Tumour shrinkage over several months.
- Circulating NY-ESO-1c259T cells detectable in all patients and persisting >6 months in all responders
  - Central memory and stem cell memory cells that remained polyfunctional with no evidence for T cell exhaustion



Metastatic synovial sarcoma is incurable with standard therapy



1. Antitumor Activity Associated with Prolonged Persistence of Adoptively Transferred NY-ESO-1c259T Cells in Synovial Sarcoma.
P D'Angelo S et al. Cancer Discov. 2018 Jun 11. doi: 10.1158/2159-8290.CD-17-1417.

Innovation

Expanding the power of our strategy through Business Development

Therapeutic opportunities	– Targets aimed at modulating the immune system – Genetically validated targets – Targets that complement our current pipeline	**New programs that enhance our strategy**
Platforms and technologies opportunities	– Human Genetics & Functional Genomics – Immune Biology – Machine Learning & Data Analytics – Genetic & Health Databases – Cell & Gene Therapy – New/complementary therapeutic modalities	**Collaborations that amplify or leverage our capabilities**
Out-licensing opportunities	– Identify partners who can accelerate the delivery of medicines from our portfolio to patients	**Collaborations that enable us to focus on what we do best**

Science

X

Technology

X

Culture

Culture matters.
A lot!

Innovation

Culture change will drive solutions to problems that need to be fixed

Following the science	Smart risk-taking	Single accountable decision making	Focus	Outstanding people
Therapeutic area and modality agnostic approach **in research**	Incentivise people to make courageous and “smart” decisions	Consensus can kill innovation and dramatically slow down decision making	Aggressively resource your big ideas and stop other projects	Demand, develop and retain the best - outstanding talent attracts outstanding talent

Innovation

Smart risk-taking

	Good outcome	Bad outcome
Good decision	**Success** Celebrate the good decision and successful outcome	**Smart risk-taking** Needs to be celebrated to foster innovation
Bad decision	**Lucky!** Do not celebrate - luck is not a strategy	**A learning opportunity**

Innovation

Focus: prioritisation is critical

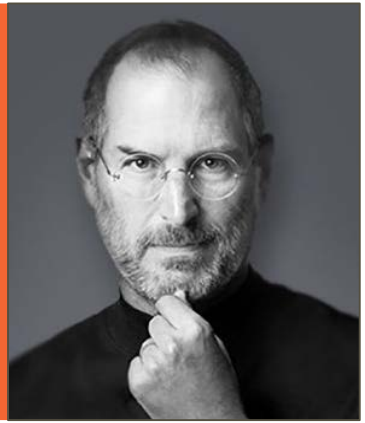
"More organizations die of indigestion than starvation."

David Packard

Simplify. ~~Simplify~~. ~~Simplify~~.

"I'm as proud of many of the things we haven't done as the things we have done. Innovation is saying no to a thousand things."

Steve Jobs



Innovation

Refocusing to reinvest

65

Decisions made to terminate, partner or divest programmessince April 2017*

42

programmes were in clinical phase, and the remainder were preclinical

>400 FTEs

re-allocated to priority programmes

*Includes transfer of Rare Disease assets to Orchard Therapeutics (announced April 2018) and divestment of dermatology asset tapinarof to Dermavant Sciences (announced July 2018)
FTE: full time employee

Innovation

Upcoming milestones that will inform our progress

	2H 2018	1H 2019	2H 2019	1H 2020	2H 2020
Submission	**dolutegravir+lamivudine (D3)** HIV	**fostemsavir** (attachment inhibitor) HIV	**Trelegy** asthma		**mepolizumab** HES
		cabotegravir+rilpivirine HIV treatment	**GSK'916 (BCMA)** 4L MM monotherapy		**mepolizumab** NP
					GSK'944 (gepotidacin) antibacterial
Pivotal data	**dolutegravir+lamivudine (D3)** HIV	**Trelegy** asthma	**GSK'916 (BCMA)** 4L MM monotherapy	**mepolizumab** HES	**belimumab+rituximab** SLE
	cabotegravir+rilpivirine HIV treatment			**mepolizumab** NP	**GSK'944 (gepotidacin)** antibacterial
					cabotegravir HIV PrEP
					GSK'863 (daprodustat) anemia
PoC data	**GSK'609 (ICOS)** cancer therapy	**GSK'294 (IL5 LA antagonist)** asthma	**GSK'254 (maturation inhibitor)** HIV	**GSK'811 (oncostatin M)** SSc	**GSK'109 (bNAb N6LS)** HIV
		GSK'772 (RIP1 kinase) RA	**GSK'745 (TRPV4)** cough	**belimumab+rituximab** Sjogren's syndrome	**GSK'781 (LAG3)** UC
		GSK'847 (IL33R) severe asthma	**GSK'595 (PRMT5)** cancer monotherapy	**GSK'078 (SARM)** COPD muscle weakness	**GSK'348 (avb6)** IPF
		GSK'881 (ACE2) PAH	**GSK'762 (BET inh)** mCRPC and ER+ breast combo therapy	**GSK'794 (NY-ESO)** NSCLC mono/combo therapy	**GSK'771 (PI3kb)** cancer combo therapy
		GSK'404 (HBV ASO) hepatitis B	**GSK'656 (leucyl t-RNA)** tuberculosis	**GSK'916 (BCMA)** 2L MM combo therapy	**GSK'091 (TLR4)** cancer combo therapy
		GSK'772 (RIP1 kinase) UC	**GSK'762 (BET inh)** hem malignancies monotherapy		**GSK'998 (OX40)** cancer combo therapy
					GSK'916 (BCMA) 1L MM combo therapy

HES: hypereosinophilic syndrome; IPF: idiopathic pulmonary fibrosis;MM: multiple myeloma; NP: Nasal polyposis; PAH: pulmonary arterial hypertension; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SSc: systemic sclerosis; UC: ulcerative colitis;

Innovation

New R&D approach will support the development of current clinical portfolio

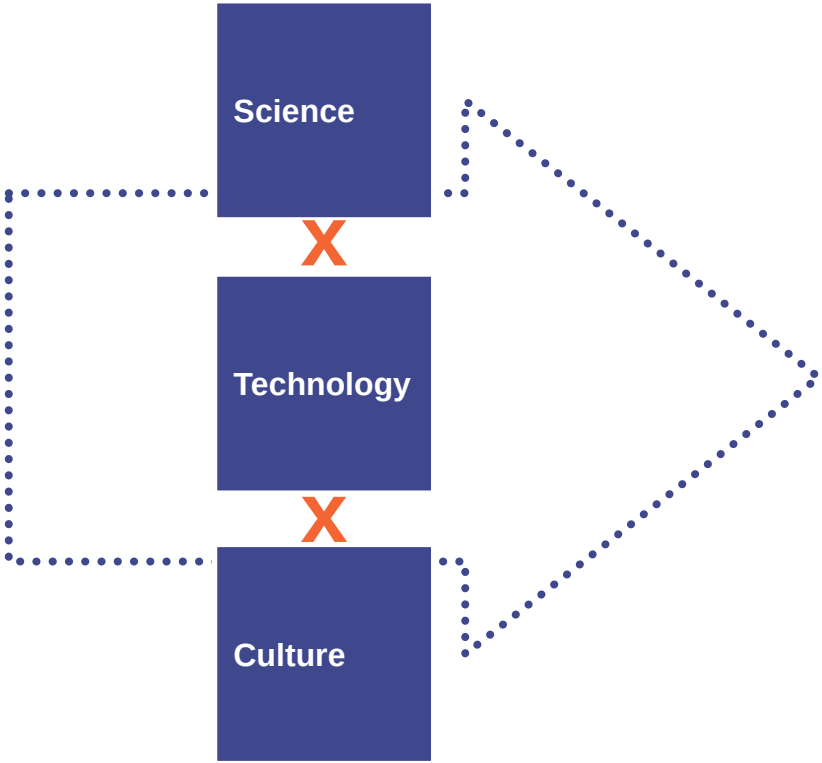
From

Spend spread thinly across too many programmes ("shots on goal" strategy)

Consensus-driven decision making

R&D/Commercial silos

Limited Business Development activity



To

Backing the best assets, and removing those that don't look promising

Culture of accountability where smart risk-taking and courageous decisions are made by individuals **and** rewarded

Robust governance model with scientific peer review, commercial input and data-driven decisions

Leveraging Business Development to optimise our portfolio

Science x Technology x Culture

We will seek to understand how the immune system causes disease in a therapeutic area agnostic manner and use human genetics to generate new targets and direct our focus

We will invest in advanced technologies (such as functional genomics, machine learning and cell therapy) to leverage this science

We will create a culture that incentivises courageous and smart risk-taking, ensures clarity of decision-making and hires and retains outstanding people

- High quality targets with higher success rates
- Faster development more life-cycle options
- Transformative therapies

Science

X

Technology

X

Culture

=

Next generation of medicines for patients

Thank you

Q&A panel

Axel Hoos
Oncology Therapy Area

Kim Smith
Global Research and Medical Strategy, ViiV

Gijs van den Brink
Immunoinflammation R&D

Emmanuel Hanon
R&D Vaccines

John Lepore
R&D Pipeline

Kevin Sin
R&D Pharmaceuticals Business Development

Kate Knobil
Chief Medical Officer

Tony Wood
Platform Tech & Science

Pauline Williams
Global Health