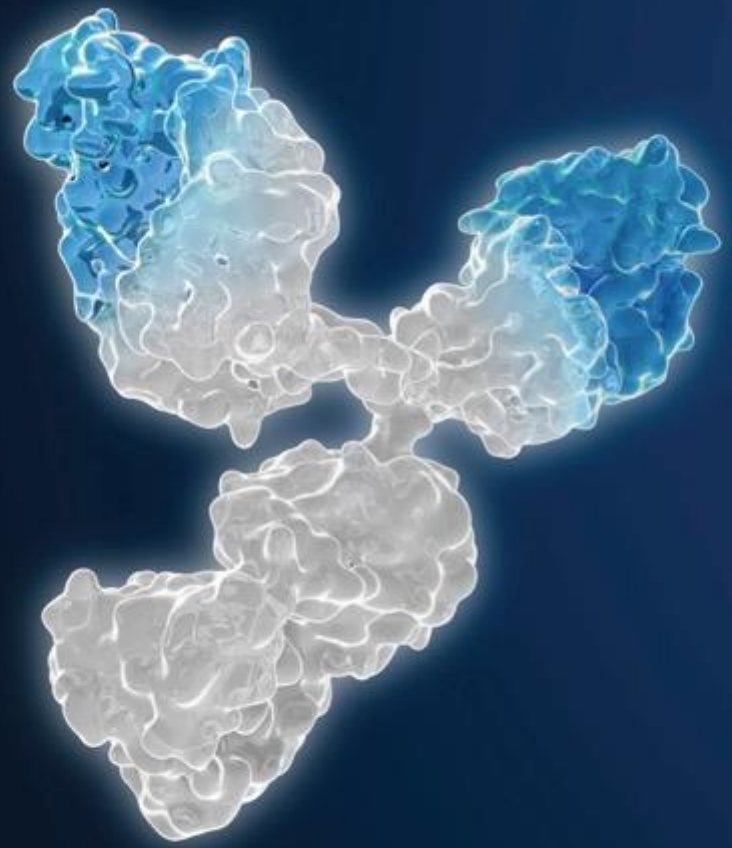


EARLY CLINICAL DEVELOPMENT OF BIOLOGICS: HOW TO APPROACH SAFETY AND PHARMACODYNAMICS

MEAGAN O'BRIEN, MD

DIRECTOR, EARLY CLINICAL DEVELOPMENT & EXPERIMENTAL SCIENCES

REGENERON

SCIENCE TO MEDICINE®

OUTLINE

- Early clinical development overview
- Safety in Early Clinical Development of Biologics
- Pharmacodynamics in Early Clinical Development of Biologics

KEY POINTS

- Clinical dose of biologics is highly informed by pre-clinical studies
  - Use in vitro, in vivo studies to target clinical dose
  - As compared to small molecules, PK may be more predictable with less differences based on gender/weight/age
  - Minimal drug interactions
- Safety is generally target/mechanism related
- Use of genetically validated targets and objective endpoints informed by biology can provide meaningful pharmacodynamic data in relatively small studies

BIOLOGICAL PRODUCTS INCLUDE A WIDE RANGE OF PRODUCTS ISOLATED FROM A VARIETY OF NATURAL SOURCES

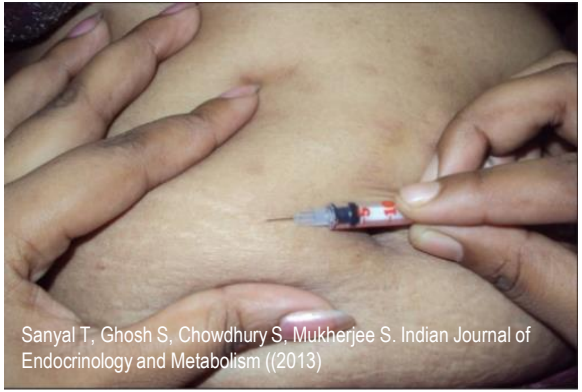
BLOOD + BLOOD COMPONENTS

Pinnaro P, Soriani A, D'Alessio D, Giordano C, Foddai ML, Pinzi V, Strigari L. Journal of Experimental & Clinical Cancer Research: CR (2011)

TISSUES

Anand J, Singh SK, Antoun DG, Cohn WE, Frazier OH, Mallidi HR. Bio research international (2015)

RECOMBINANT THERAPEUTIC PROTEINS



Sanyal T, Ghosh S, Chowdhury S, Mukherjee S. Indian Journal of Endocrinology and Metabolism ((2013)

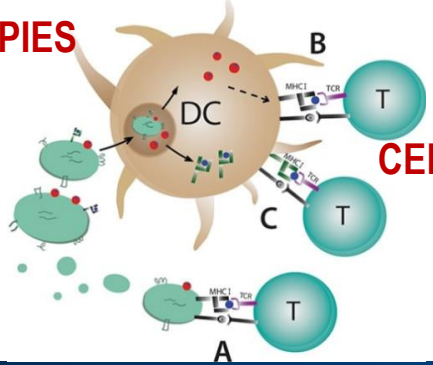
VACCINES

ALLERGY IMMUNOTHERAPY

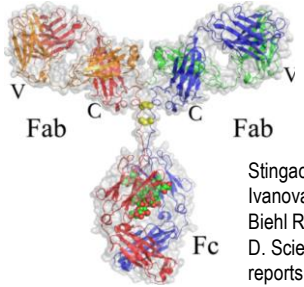
Sedwick C. PLoS biology (2012)

RNA THERAPIES

CELL THERAPY



ANTIBODIES



Stingaciu LR, Ivanova O, Ohi M, Biehl R, Richter D. Scientific reports (2016)

BIOLOGICS DIFFER FROM SMALL MOLECULES IN KEY WAYS

	Small Molecules	Biologics
Molecular weight	<500 Da	150 kDa
Administration	Oral preferred	SC or IV or IM
Distribution	High volume of distribution	Vascular/interstitial fluids
Half life	Short(dosed daily or mult. times aday)	Long (dosed by week/month)
Toxicity	Off target and on target	Highly specific mostly on target
Excretion	Kidney and liver	Recycled through FcRn receptor
Target	Both intracellular and surface targets	Membrane proteins or soluble proteins in circulation
Drug-drug interaction	Expected and need to be investigated for CYP P450 and transporter interactions	Rarely observed
PK/PD	Short acting, in line with PK properties	Long acting PD effect and direct impact on PK. PK/PD are mechanistically linked
Immunogenicity	Not commonly observed	Expected/needs to be monitored

OPTIMIZATION OF EARLY CLINICAL DEVELOPMENT STRATEGIES BRING INNOVATIVE MEDICINES TO PATIENTS WHO NEED THEM

Discovery and Pre-Clinical Research Partners

- Identify drug targets using genomics approaches, in vitro, ex vivo, animal models
- Pre-clinical work is optimized to determine mechanism of action, PD, safety, projected efficacious dose
- Precision medicine and Clinical Experimental Sciences studies to optimize selection of patient populations, study design, PD endpoints
- PK, toxicology, biology studies in relevant in vitro and in vivo models determine safety parameters for drug dosing in human studies

Phase 1 First in Human Studies (FIH: Healthy volunteers vs. Patients)

- Safety + tolerability in human subjects
- PK: how the drug is absorbed, metabolized, and excreted
- Pharmacodynamic profile

Phase 2 Studies

- Safety + tolerability in human subjects
- Pharmacodynamics and Efficacy (clinical vs surrogate endpoints)
- Exploratory endpoints: inform biology, future study design, future targets
- Dose ranging

Phase 3 Studies

- Clinical Efficacy for regulatory approval

KEY QUESTIONS IN EARLY DEVELOPMENT (FIRST-IN-HUMAN THROUGH PROOF OF CONCEPT)

- Is the biologic sufficiently safe and well tolerated to permit further testing?
- Pharmacokinetics – behavior of the biologic- suitable behavior for long-term testing?
- Is the biologic having the intended pharmacological effects that are likely to translate to benefit?
  - Confirm the biology observed in animals or through human genetics
  - Show activity in disease indications that have high unmet need
    - Endpoints should relate in some way to ultimate benefit
  - Differentiation: is the biologic likely to work as well or better than standard of care?
- Dose and patient selection
  - Can we identify a viable dose range suitable for further exploration in late development?
  - Can we identify patient segments that may get more benefit from the drug?

SAFETY

REGENERON

NEW EMA GUIDANCE (2018) OUTLINES STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN AND EARLY CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS

TeGenero 1412 Trial – FIH (UK – 2006)

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

SUMMARY

Six healthy young male volunteers at a contract research organization were enrolled in the first phase 1 clinical trial of TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes after receiving a single intravenous dose of the drug, all six volunteers had a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension. Within 12 to 16 hours after infusion, they became critically ill, with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. Severe and unexpected depletion of lymphocytes and monocytes occurred within 24 hours after infusion. All six patients were transferred to the care of the authors at

- *EMA issued a guideline on how to mitigate risks for high-risk molecules (released in 2007)*

BIA 10-2474 Trial – FIH/MD (France – 2016)

Report by the Temporary Specialist Scientific Committee (TSSC), "FAAH (*Fatty Acid Amide Hydrolase*)", on the causes of the accident during a Phase 1 clinical trial in Rennes in January 2016.

9.1. Clinical symptoms

The first volunteer was hospitalised in the evening of 10 January 2016, day of the fifth administration of the investigational product. Two other volunteers were hospitalised on 11 January (day of the sixth administration), two others on 12 January (day after the last administration) and the last volunteer on 13 January, therefore two days after the last administration.

The main clinical symptoms observed were:

- headaches, in all five volunteers, very severe in one but not occurring as a thunder clap headache,
- cerebellar syndrome in three volunteers,
- consciousness disorders (in three volunteers) ranging from sedation to coma (deceased volunteer),
- memory impairment in two volunteers.

Other symptoms were only noted once: diplopia, paraesthesia of the thighs, and hemiparesis with "tremor" of one side of the body, without pyramidal syndrome, spine pain and stiffness.

The initial clinical picture worsened in three volunteers. The first subject hospitalised progressed to brain death three days after onset of the symptoms. The clinical picture worsened in the other two over three to four days before stabilising (over two to three

- *EMA revisited the high-risk molecule guideline (released 01 Feb 2018)*

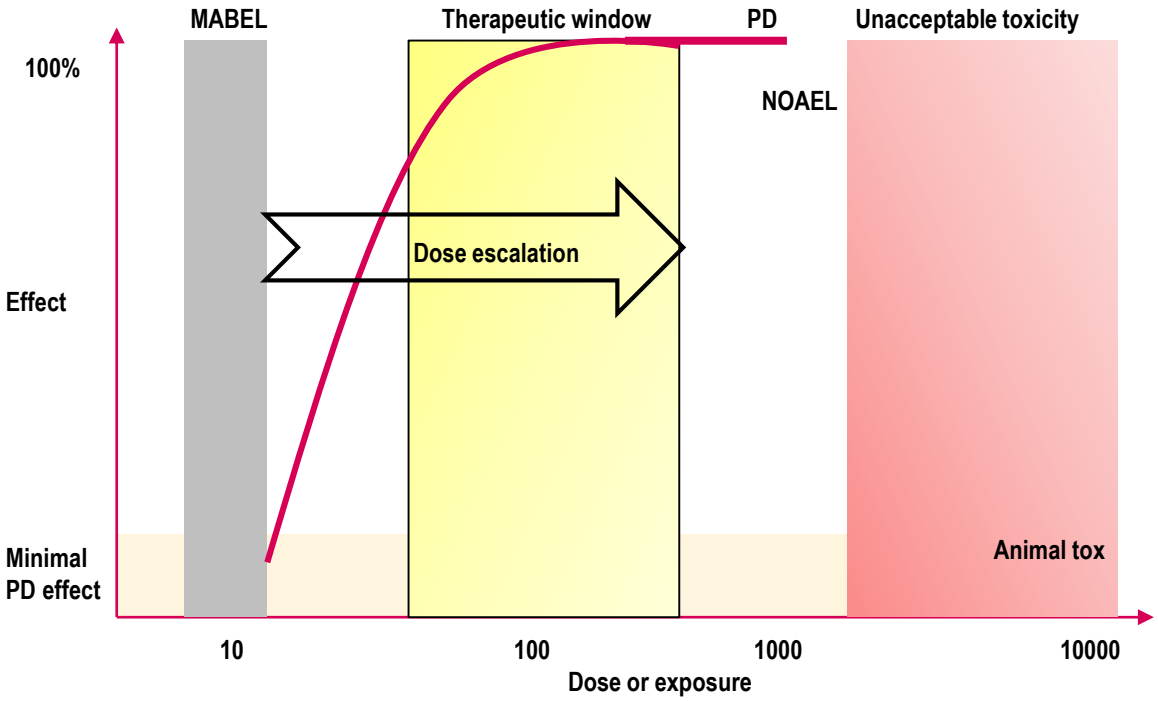
FOLLOWING THE TEGENERO 1412 TRIAL(UK – 2006) *EMA ISSUED A GUIDELINE ON HOW TO MITIGATE RISKS FOR HIGH-RISK MOLECULES IN FIH STUDIES (RELEASED IN 2007)*

- In 2006, a phase 1 clinical study was conducted for a CD28 superagonist antibody TGN1412 in human volunteers
- After very first infusion of a dose 500 times smaller than that found safe in animal studies, all six human volunteers receiving 0.1 mg/kg faced life-threatening conditions involving multiorgan failure for which they were moved to intensive care unit
- Historical experience with other anti–T cell mAbs and data available to TeGenero prior to the Phase 1 trial suggested that first-dose reactions were likely to occur at the FIH dose
- Preclinical studies conducted for TGN1412 did not predict a cytokine storm, as was also true for OKT3 and HuM291, both of which cause intense cytokine release in humans
- The absence of CRS-like findings in monkeys and rats should not have been unexpected, as there was also considerable phylogenetic variation in species sensitivity to cytokine-releasing stimuli
- **GUIDANCE**:
  - First in human trials of potent biological molecules should include initial testing on a sentinel number of human volunteers before administration of drug to a greater number of human volunteers.
  - Adoption of a pharmacologically based method of establishing the FIH starting dose(MABEL), rather than traditional toxicology-based algorithms (NOAEL) for new molecules that target the immune system via a novel mechanism

FOLLOWING BIA 10-2474 TRIAL – FIH/MD (FRANCE – 2016) EMA UPDATED GUIDELINES ON HOW TO MITIGATE RISKS FOR HIGH-RISK MOLECULES IN FIH STUDIES (RELEASED IN 2018)

- In 2016, a phase 1 clinical study with secondary endpoints to investigate neuropathic pain was conducted for a fatty acid amide hydrolase (FAAH) inhibitor in human volunteers, in which serious adverse events occurred affecting 5 participants of hemorrhagic and necrotic brain lesions, including one death
- Randomized double blind single ascending dose of BIA 10-2474: at 0.25, 1.25, 2.5, 5.0, 10, 20, 40 and 100 mg, with the possibility of additional groups to be added if no maximal tolerated dose was reached
- In the multiple dose ascending part, the doses were 2.5, 5.0, 10, 20 and 50 mg BIA 10-2474, each to be given once per day for 10 days to groups of 8 volunteers (3:1 randomised). The severe adverse events were observed in the 50 mg dose group
- BIA 10-2474 showed non-linear pharmacokinetics at doses between 40–100 mg (that is, the molecule appeared to be accumulating at higher doses) and that most likely the elimination mechanism had become saturated
- Dosing at 50 mg daily was - each day - <u>40 times more than required to achieve complete inhibition</u>, and in practice this dose level resulted in accumulation
- **GUIDANCE**:
  - Strategies for mitigating and managing risks, including principles on the calculation of the starting dose to be used in humans, the subsequent dose escalations, the criteria for maximum dose and the conduct of the trial inclusive of multiple parts.

MABEL AND NOAEL ARE USED FOR MODELING HUMAN EXPOSURES TO ASSURE THE FIRST DOSE WILL NOT CAUSE TOXICITY IN HUMANS



- **MABEL** (minimal anticipated biological effect level), **PAD** (pharmacologically active dose) and/or **ATD** anticipated therapeutic dose range
  - All in vitro and in vivo studies, including in human tissues if feasible, is used to determine in humans
  - MABEL, PAD and/or ATD should consider target binding and receptor occupancy studies in vitro in target cells from human and the relevant animal species and exposures at pharmacological doses in the relevant animal species
- **NOAEL** (no observed adverse effect level)
  - Determined in the non-clinical safety studies (pre-clinical toxicology)
  - Performed in the most relevant animal models available
  - Used for estimation of an equivalent exposure for humans
  - Estimation for human dosing based on modelling by applying an appropriate scaling factors to adjust for body surface area among different species
- **Safety factor**
  - NOAEL- or the MABEL-derived human equivalence dose can be reduced further by applying the safety factor, a number by which the calculated human equivalence dose is divided to increase the assurance that the first dose will not cause toxicity in humans.

Liu. Protein Cell 2018

NEW EMA GUIDANCE OUTLINES STARTING DOSE CONSIDERATIONS

CAREFUL DOSING SELECTION

Healthy volunteers: Use MABEL, PAD or NOAEL AND use a safety factor

- Safety factor: informed based on novelty, PD (irreversible, long lasting findings, shape of dose-response curve), relevance of animal models, characteristics of safety findings, other uncertainties

Patients: Similar consideration as above HOWEVER

- if not acceptable to start substantially lower than PAD ⇨ include justification to start higher (+ inform trial subjects)
- Consider (potential) differences between HV and patients (e.g. PK, target distribution)

NEW EMA GUIDANCE OUTLINES DOSE ESCALATION STRATEGIES

- **Target dose**
  - based on pre-clinical data
    - in vitro
    - in vivo (relevant animal model)
    - PK/PD modeling data
- **Dose escalation**
  - Pre-specify maximum number of cohorts
  - Pre-specify dose levels and estimate exposure/potential AE
  - Pre-specify maximum fold increase in dose/exposure from cohort to cohort

- **Considerations when moving from single to multiple dosing** (e.g. combined protocols):
  - Maximum duration of dosing to be stated in protocol
  - Expected exposure (C_{max}, $AUC_{0-\infty}$) should be have been covered in preceding parts/trials
  - Higher exposure in multiple ascending dose is possible PROVIDED this option is pre-specified, rational given and anticipated exposure still remains below a particular, justified maximum exposure

SAFETY CONSIDERATIONS WHEN THE MEDICINAL PRODUCT IS A BIOLOGIC

Antibodies and protein therapeutics

- hypersensitivity reactions
- Immunogenicity
- Target mediated AEs

RNA (aptamer/chemically modified RNA, antisense oligonucleotide/DNA, siRNA, delivery systems/lipid nanoparticle)

- Immunogenicity
- Liver toxicity: Lipid nanoparticles (encapsulate mRNA)
- Target mediated AEs (potential long term effects)

T cell therapy (e.g. chimeric antigen receptor [CAR] T cell therapy)

- Hypersensitivity reactions
- Cytokine release syndrome
- Cytopenias
- Hypogammaglobulinemia
- Serious infections
- Neurological toxicities
- Target mediated AEs (tumor lysis syndrome)

PHARMACODYNAMICS

REGENERON

PHARMACODYNAMIC AND EFFICACY MEASURES ARE DETERMINED BY THE THERAPEUTIC TARGET AND BY THE DISEASE

PD measures should be informed by biology and may be simple or complex. In small early studies objective measures are critical:

- **Simple**
  - Pharmacokinetics
  - Blood test for cholesterol
  - LDH
  - Blood glucose
  - Patient reported Outcome (symptoms, signs) (subjective)
  - Physical exam findings (skin, weight)
- **Complex**
  - Imaging(PET, MRI, CT)
  - Biomarkers (Biochemical, nucleic-acid based (e.g. RNA sequencing/expression), physiological, functional, histopathological)
  - Provocative testing (e.g. allergy challenges, food challenges)
  - Acquisition of relevant tissues through biopsy when feasible
  - Clinical responses (assessment criteria depending on the disease)

INTEGRATION OF PHARMACODYNAMIC ENDPOINTS INFORMS UPON CLINICAL DEVELOPMENT STRATEGIES: EXAMPLES FROM REGENERON

PHASE 1

CEMIPLIMAB*
PD-1 Antibody | Cancer

REGN1979
CD20xCD3 Antibody | Cancer

CEMIPLIMAB* + REGN1979
PD-1 Antibody + CD20xCD3 Antibody | Cancer

REGN3767
LAG-3 Antibody | Cancer

CEMIPLIMAB* + REGN3767
PD-1 Antibody + LAG-3 Antibody | Cancer

REGN4018*
MUC16xCD3 Antibody | Cancer

CEMIPLIMAB* + REGN4018*
PD-1 Antibody + CD20xCD3 Antibody | Cancer

REGN4659
CTLA4 Antibody | Cancer

REGN5458*
BCMAxCD3 Antibody
Cancer

REGN1908-1909
Fel d 1 Antibody | Cat allergy

REGN-EB3
Ebola Virus Antibody
Ebola virus infection

REGN3048-3051
Middle Eastern Respiratory Coronavirus Antibody
MERS-CoV infection

POZELIMAB
C5 Antibody
Paroxysmal nocturnal hemoglobinuria

GARETOSMAB + TREVOGRUMAB
Activin A Antibody + GDF8 Antibody
Muscle-wasting diseases

REGN4461
LEPR Antibody
Lipodystrophy and obesity

REGN5069
GFRα3 antibody | Pain

PHASE 2

CEMIPLIMAB*
PD-1 Antibody
Basal cell carcinoma (BCC)

DUPILUMAB*
IL-4R Antibody
Grass allergy, peanut allergy

SARILUMAB*
IL-6R Antibody
Polyarticular-course juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis

EVINACUMAB
ANGPTL-3 Antibody
Refractory hypercholesterolemia (both HeFH and non-FH), severe hypertriglyceridemia

GARETOSMAB
Activin A Antibody
Fibrodysplasia Ossificans Progressiva (FOP)

REGN3500*
IL-33 Antibody | Asthma, chronic obstructive pulmonary disease (COPD)

PHASE 3

AFLIBERCEPT
VEGF-Trap | Non-proliferative diabetic retinopathy (NPDR) without DME

ALIROCUMAB*
PCSK9 Antibody
Homozygous familial hypercholesterolemia (HoFH) in adults and pediatrics, heterozygous familial hypercholesterolemia in pediatrics

CEMIPLIMAB*
PD-1 Antibody
Non-small cell lung cancer, cervical cancer

DUPILUMAB*
IL-4R Antibody | Atopic dermatitis in pediatrics and adolescents, asthma in pediatric, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic esophagitis

SARILUMAB*
IL-6R Antibody
Polymyalgia rheumatica, giant cell arteritis

EVINACUMAB
ANGPTL-3 Antibody
Homozygous familial hypercholesterolemia (HoFH)

FASINUMAB†
NGF Antibody
Chronic pain from osteoarthritis of the knee or hip

This graphic displays pipeline drug candidates currently undergoing clinical testing in a variety of diseases. The safety and efficacy of these drug candidates have not been fully evaluated by any regulatory authorities for the indications described in this section.

IMMUNOLOGY & INFLAMMATORY DISEASES | CARDIOVASCULAR/ METABOLIC DISEASES | ONCOLOGY | INFECTIOUS DISEASES | OPHTHALMOLOGY | PAIN | RARE DISEASES

*IN COLLABORATION WITH SANOFI
† IN COLLABORATION WITH TEVA AND MITSUBISHI TANABE

25

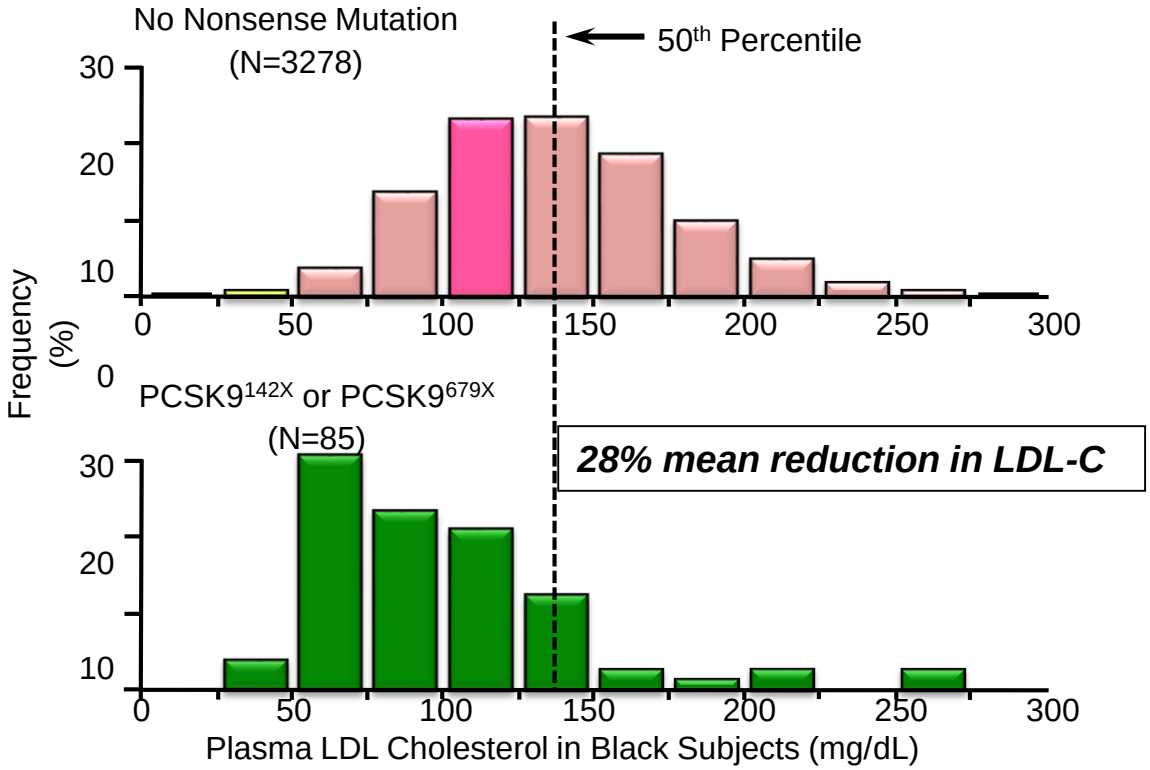
CASE 1

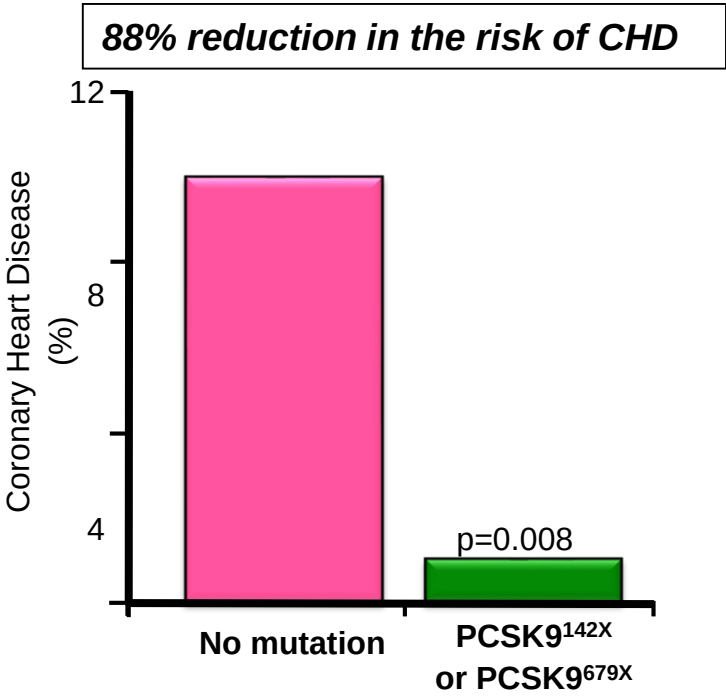
PCSK9 ANTIBODY:

- FOUNDATIONAL GENETICS & BIOLOGY ARE USED TO DEVELOP TARGETED THERAPIES

- PD: PK AND LDL-C IN EARLY CLINICAL STUDIES

PATIENTS WITH LOSS OF FUNCTION VARIANTS IN PCSK9 HAVE LOWER LDL-C AND REDUCED RISK OF HEART DISEASE

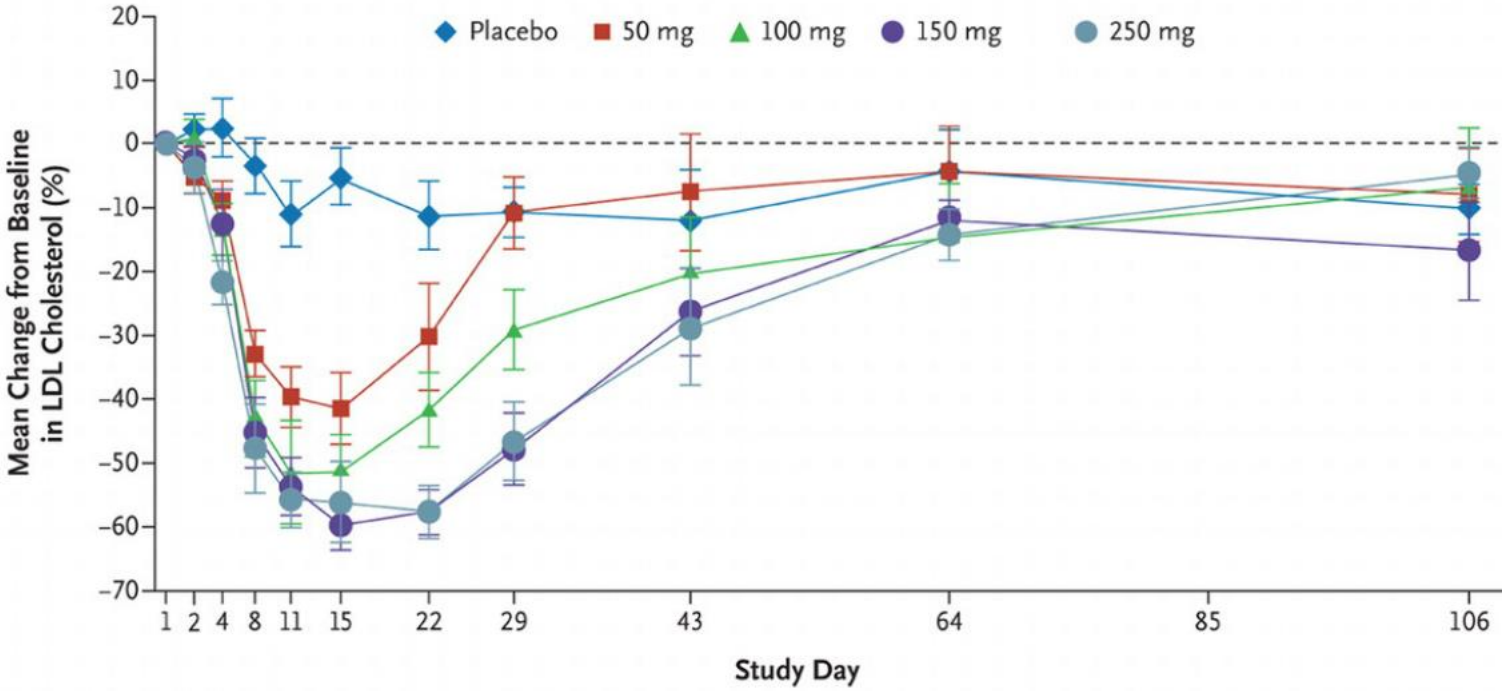




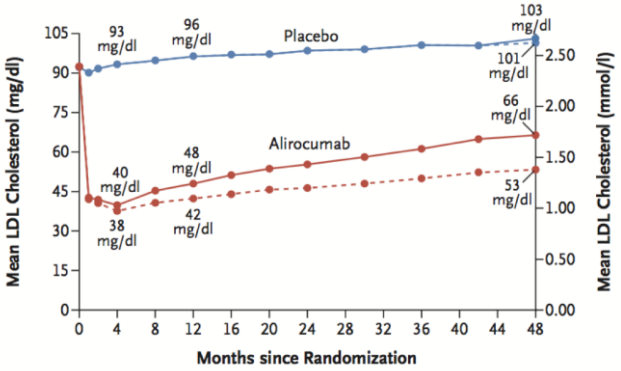
REGENERON

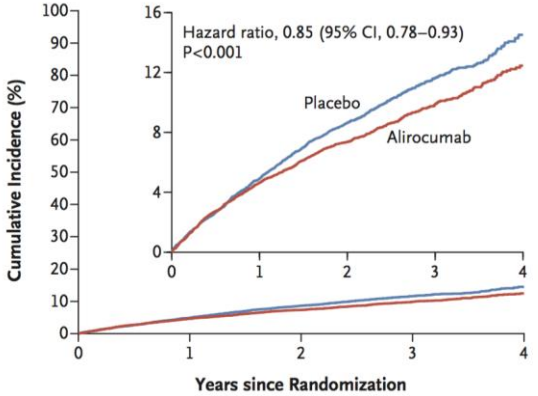
Cohen JC. *N Engl J Med* 2006

REGENERON DEVELOPED ALIROCUMAB (ANTI-PCSK9): EARLY STUDIES CORROBORATED THE BIOLOGY- SINGLE DOSES PROVIDED ROBUST REDUCTIONS IN LDL-C

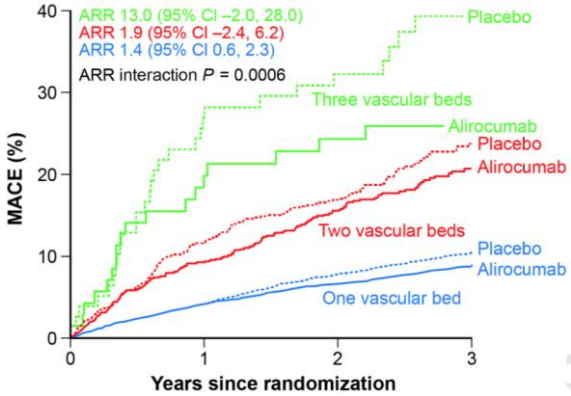


ODYSSEY STUDY: ALIROCUMAB EVERY 2 WEEKS REDUCED MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH A HISTORY OF CARDIOVASCULAR DISEASE





No. at Risk					
Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653



J Am Coll Cardiol. 2019 Feb 5;73(4):387-396
J Am Coll Cardiol. 2019 Mar 12 pii: S0735-1097(19)33921-X. doi: 10.1016/j.jacc.2019.03.013. [Epub ahead of print]

CASE 2

IL4 RECEPTOR-ALPHA ANTIBODY:

- BIOLOGY USED TO DEVELOP TARGETED THERAPIES

- PD: PK, TARC, AND CLINICAL RESPONSES IN EARLY CLINICAL STUDIES

DUPILUMAB (ANTI-IL-4R) WAS DEVELOPED AS A TREATMENT FOR ALLERGIC DISEASES: INHIBITION OF IL4 RECEPTOR BLOCKS IL4 AND IL13 SIGNALING

- IL-4 and IL-13 activity is mediated via IL-4 Receptor-alpha (IL-4R)

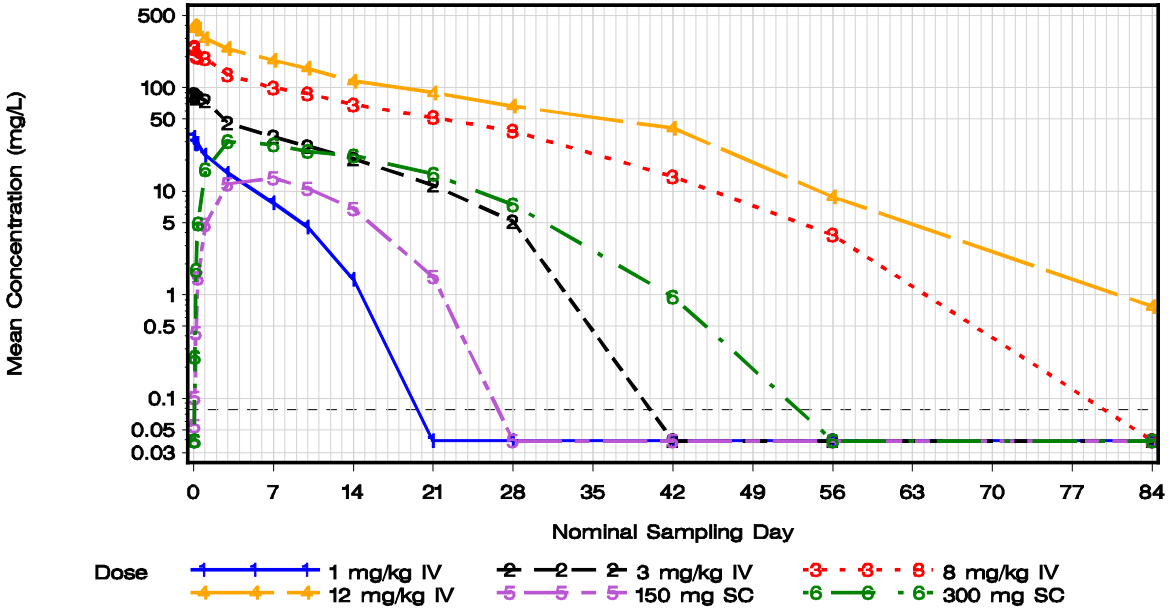
- These cytokines have a putative role in mediating Type 2 and allergic inflammation
  - Initiate and propagate T helper cell- 2 (TH2) differentiation
  - Induce Type 2 cytokine production
  - Ig class switching to IgE subtype
  - Eosinophilic trafficking

- Atopic Dermatitis has very high Thymus and Activation Regulated Chemokine (TARC) levels, a downstream indicator of Type 2 inflammation
  - Inhibition of IL-4R led to decrease in TARC

- Asthma is associated with lung eosinophilia
  - Inhibition of IL-4R attenuated airway inflammation in preclinical models of asthma (multiple published reports)

PK AND PD ARE MECHANISTICALLY LINKED WITH THERAPEUTIC ANTIBODIES

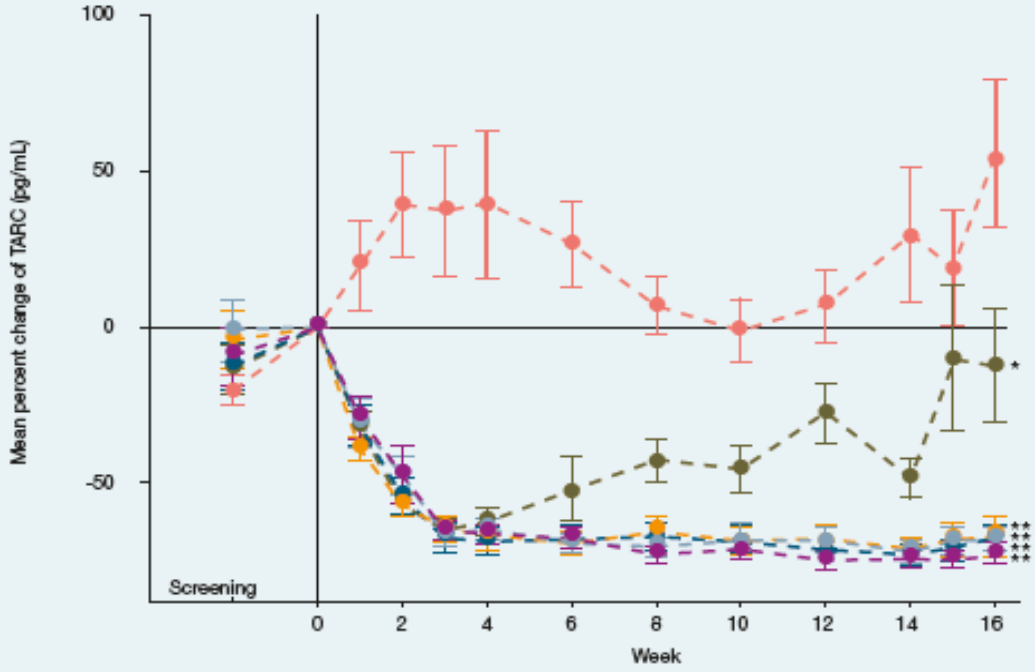
Dupilumab: target dose levels that show linear kinetics with target saturation



Clearance of therapeutic mAb

- Nonspecific clearance
  - via pinocytosis (FcRn), dose independent as clinical doses fall far below endogenous IgG (10g/mL)
  - Via proteolysis in the liver and reticuloendothelial system
- Target mediated clearance
  - via elimination through it's antigen-specific interactions
  - Target-mediated clearance decreases with the saturation of the target, which in turn is dependent on dose. At and above the saturation dose level, the target-mediated clearance becomes insignificant
- Other factors
  - antibody properties (hydrophobicity, charge, glycosylation patterns)
  - inter- subject variability (disease status, body size, genetic polymorphisms, concomitant medication, comorbidities, etc)
  - immune-mediated

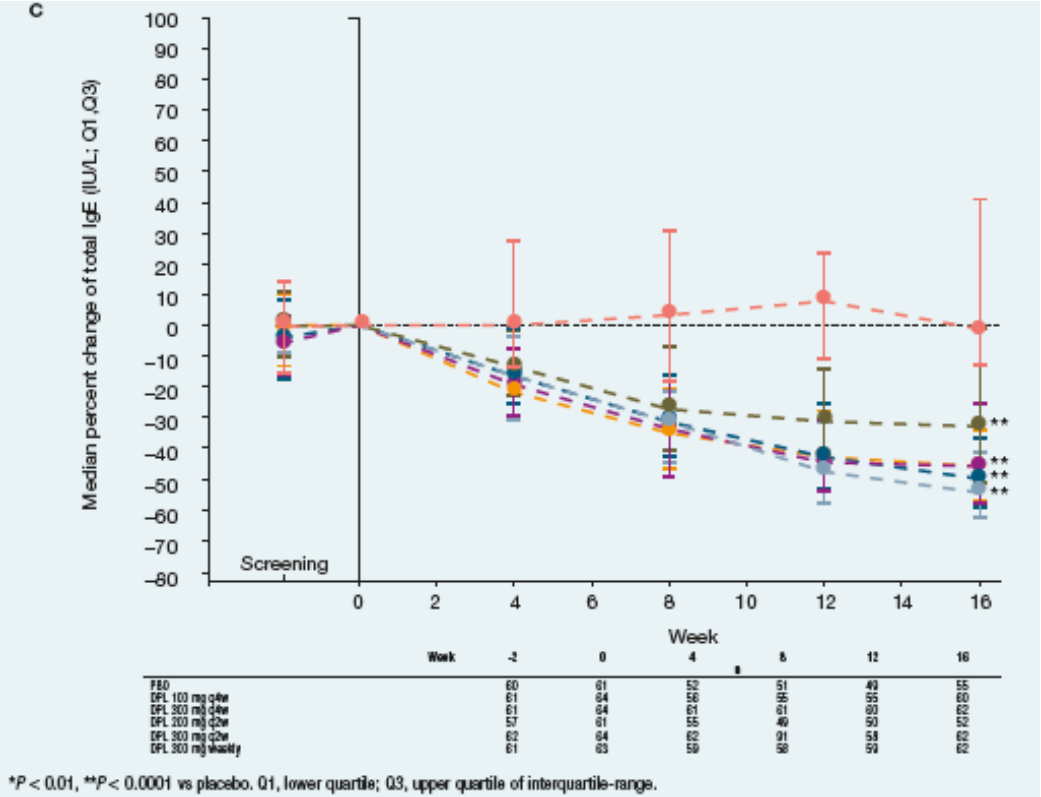
SIGNIFICANT SUPPRESSION OF TARC WAS OBSERVED IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS AFTER 4 WEEKS OF DUPILUMAB TREATMENT



Week	-2	0	1	2	3	4	6	8	10	12	14	15	16
							n						
PBO	62	61	60	58	59	58	53	53	51	50	49	49	54
DPL 100 mg q4w	65	65	64	64	63	61	61	43	56	56	55	57	61
DPL 300 mg q4w	64	65	64	62	65	65	65	62	64	64	61	62	62
DPL 200 mg q2w	61	61	60	60	57	56	53	52	50	50	50	47	52
DPL 300 mg q2w	63	64	61	62	61	62	61	60	61	62	58	57	61
DPL 300 mg weekly	62	64	60	60	61	59	59	59	58	60	58	58	61

- PBO weekly
- DPL 100 mg q4w
- DPL 300 mg q4w
- DPL 200 mg q2w
- DPL 300 mg q2w
- DPL 300 mg weekly

SIGNIFICANT SUPPRESSION (~50%) OF TOTAL IGE WAS OBSERVED IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS AFTER 16 WEEKS OF DUPILUMAB

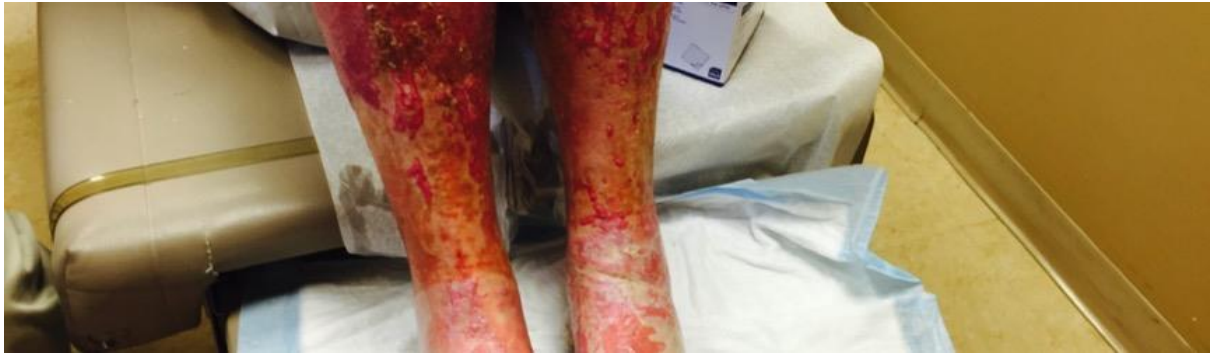


Week	-2	0	4	8	12	16
PBO	60	61	52	51	49	55
DPL 100 mg q4w	61	64	58	55	55	60
DPL 300 mg q4w	61	64	61	61	60	62
DPL 200 mg q2w	57	61	55	49	50	52
DPL 300 mg q2w	62	64	62	61	58	62
DPL 300 mg weekly	61	63	59	58	59	62

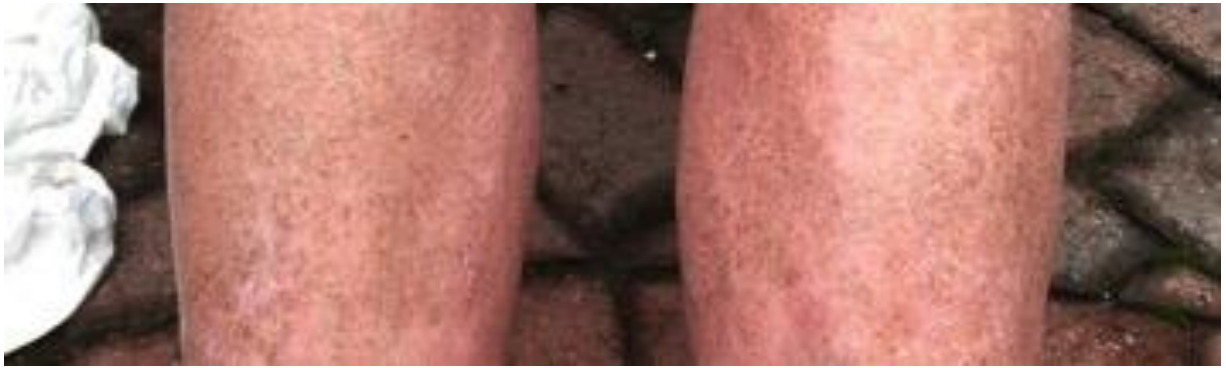
*$P < 0.01$, **$P < 0.0001$ vs placebo. Q1, lower quartile; Q3, upper quartile of interquartile-range.

DUPILUMAB IN ATOPIC DERMATITIS AFTER JUST A FEW DOSES- TRUE THERAPEUTIC BENEFIT

BEFORE



AFTER



CASE 3

FEL D 1 ANTIBODY COCKTAIL:

- BIOLOGY USED TO DEVELOP TARGETED THERAPIES

- PD: PK, TITRATION SKIN PRICK TEST AND NASAL ALLERGEN CHALLENGE RESPONSES IN EARLY CLINICAL STUDIES

ALLERGY IMMUNOTHERAPY CAUSES ALLERGEN-SPECIFIC BLOCKING ANTIBODIES TO FORM IN THE BODY, WHICH MAY REDUCE ALLERGIC SYMPTOMS UPON ALLERGEN EXPOSURE: LET'S JUST MAKE THE BLOCKING ANTIBODIES AND SKIP THE SHOTS!

Cat-specific IgG4

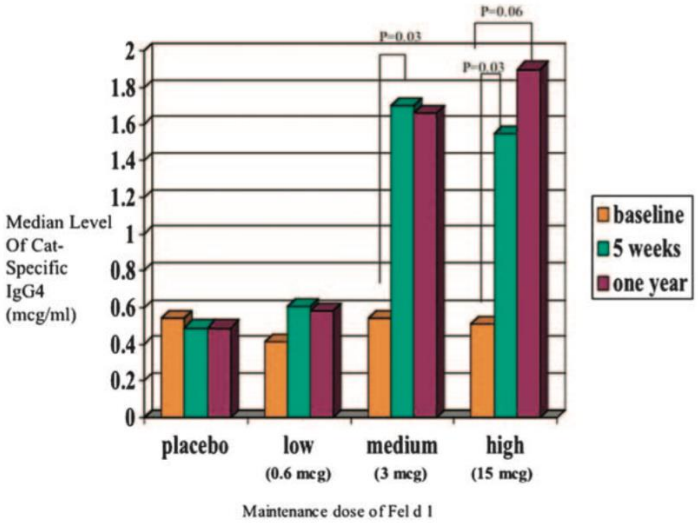


FIG 3. Median levels of cat-specific IgG4 (μg/mL) at baseline, after 5 weeks, and after 1 year of immunotherapy. The overall dose effect at 5 weeks is significant ($P = .004$), as are the changes with 3 and 15 μg ($P = .03$). After 1 year, the overall dose effect is significant ($P = .003$).

Total Nasal Symptom Score

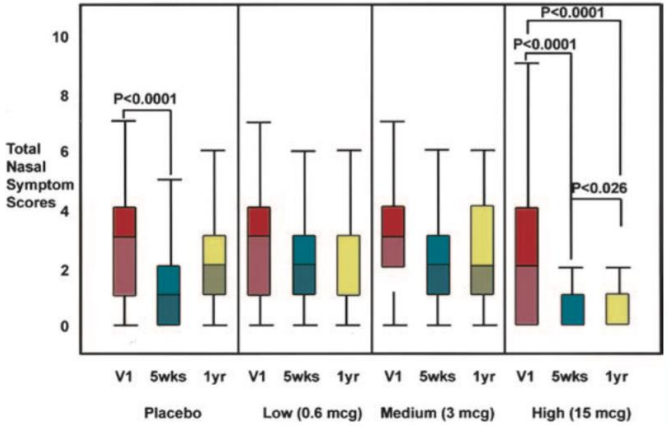


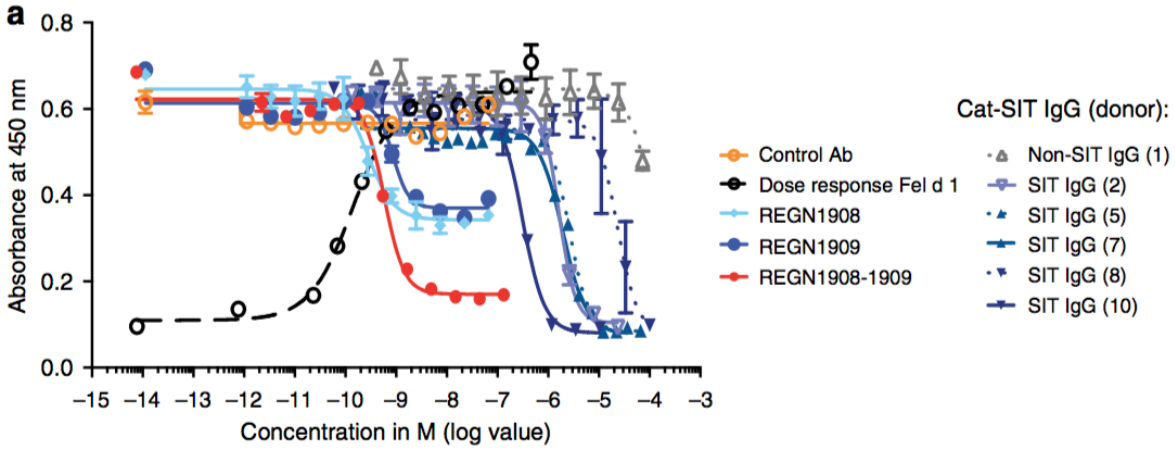
FIG 1. Total early symptom scores from all doses during titrated nasal challenge at baseline *(V1)*, after 5 weeks, and after 1 year of immunotherapy. The *bottom and top edges of the box* are located at the 25th and 75th percentiles. The *center horizontal line* is the median. The *bottom and top end of the whiskers* show the 20th and 80th percentiles. A significant dose-response relationship exists between increasing dose and decreasing symptoms at 5 weeks ($P < .0001$) and 1 year ($P < .0001$).

7 subjects per arm

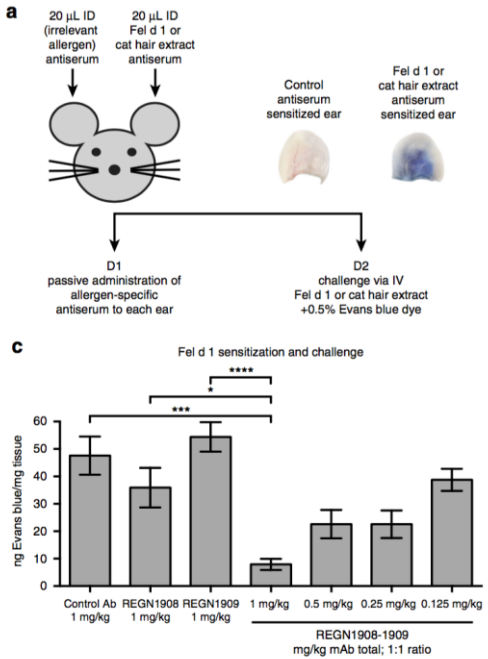
Nanda A, O'Conner M, Anand M, Dreskin SC, Zhang L, Hines B, Lane D, Wheat W, Routes JM, Sawyer R, Rosenwasser LJ, Nelson HS. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. J. Allergy Clin. Immunol. 2004 Dec;114(6):1339-44.

ANTI-FEL D 1 IS A COCKTAIL OF 2 MONOCLONAL ANTIBODIES 1908-1909 THAT BIND THE MAJOR CAT ALLERGEN FEL D 1

REGN1908–1909 blocks Fel d 1 binding to polyclonal Fel d 1-specific IgE more efficiently than natural IgGs from specific immunotherapy (SIT) patients



REGN1908–1909 inhibits Fel d 1-induced mast cell degranulation in vivo in the passive cutaneous anaphylaxis (PCA) mouse model

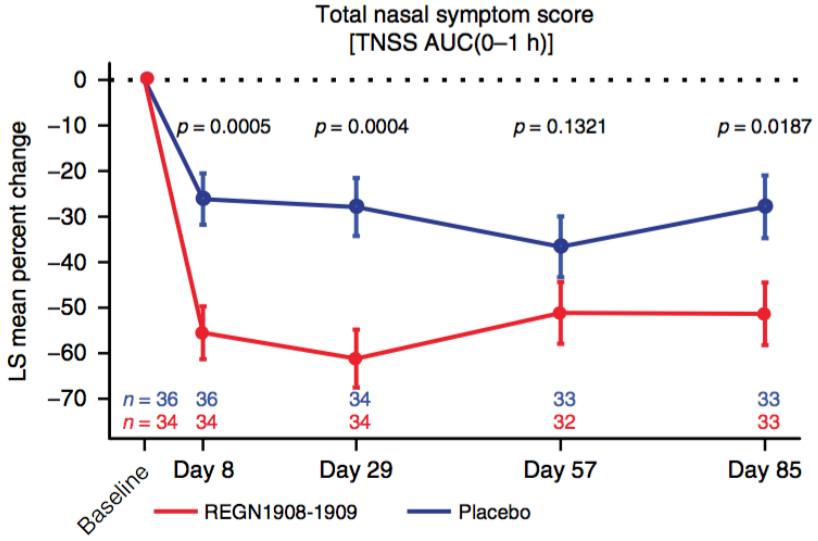


REGENERON

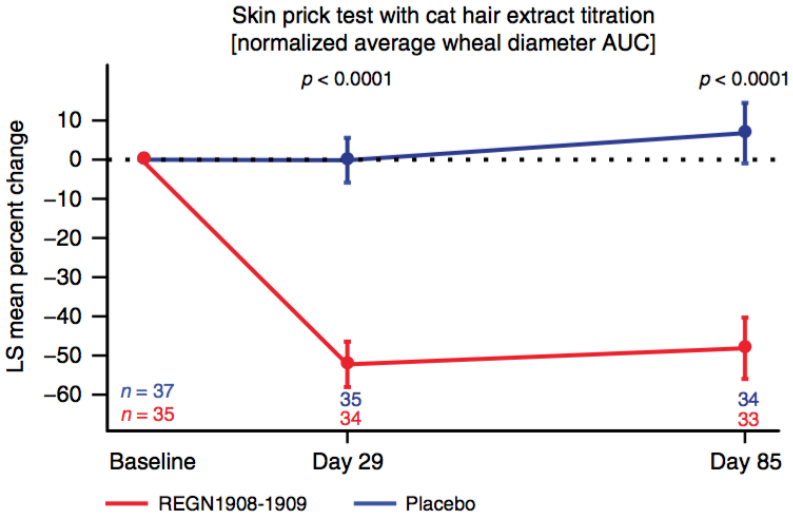
Orengo JM, Radin AR, Kamat V, Badithe A, Ben LH, Bennett BL, Zhong S, Birchard D, Limnander A, Rafique A, Bautista J, Kostic A, Newell D, Duan X, Franklin MC, Olson W, Lipsich L, Stahl N, Papadopoulos NJ, Murphy AJ, Yancopoulos GD. Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement . Nature Communications2018 Apr 12;9(1):1421

ANTI-FEL D 1 (REGN 1908-1909) BLOCKS ACTIVATION OF THE ALLERGIC IMMUNE SYSTEM BY THE ALLERGEN

Total Nasal Symptom Score after a Nasal Allergen Challenge



Skin Prick Test with Cat Allergen



Orengo JM, Radin AR, Kamat V, Badithe A, Ben LH, Bennett BL, Zhong S, Birchard D, Limnander A, Rafique A, Bautista J, Kostic A, Newell D, Duan X, Franklin MC, Olson W, Lipsich L, Stahl N, Papadopoulos NJ, Murphy AJ, Yancopoulos GD. Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement . Nature Communications2018 Apr 12;9(1):1421

CASE 4

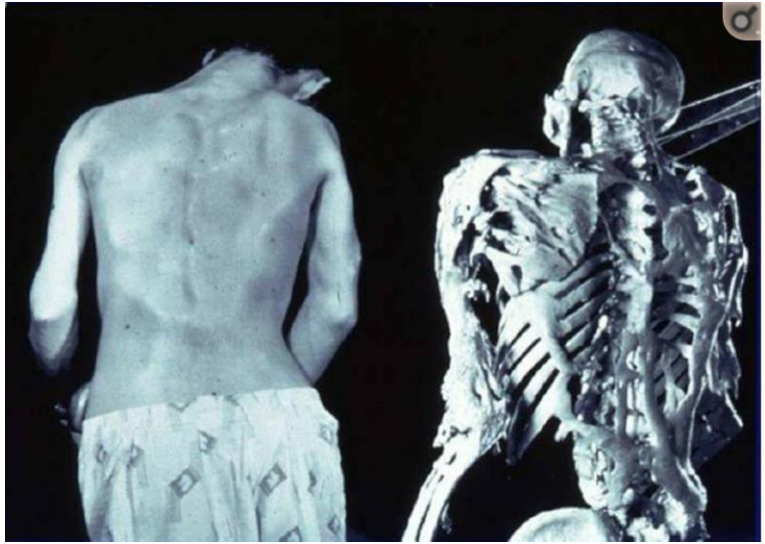
ACTIVIN A ANTIBODY:

- FOUNDATIONAL GENETICS AND BIOLOGY USED TO DEVELOP TARGETED THERAPIES

- PD: PK, NOVEL IMAGING IN EARLY CLINICAL STUDIES

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP) IS CAUSED BY A MUTATION IN ACVR1 GENE THAT CAUSES HETEROTOPIC OSSIFICATION

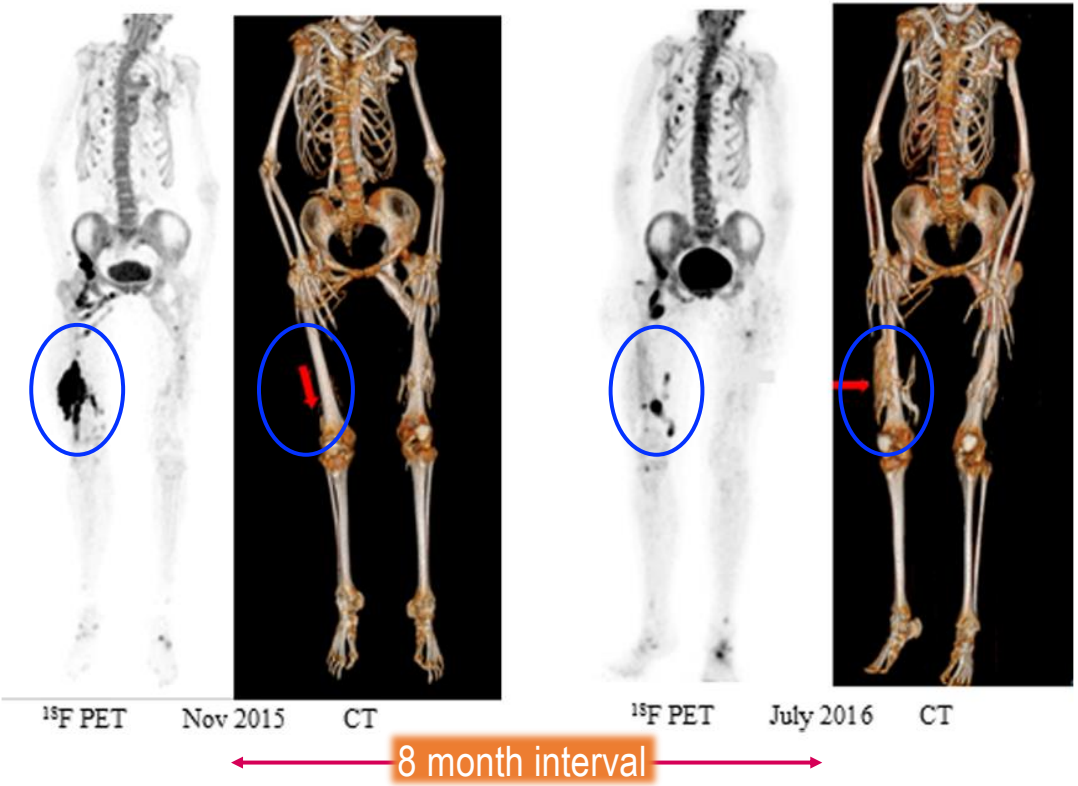
- Disorder in which skeletal muscle and connective tissue such as tendons and ligaments, are gradually replaced by bone (ossified).
- Trauma, such as a fall or invasive medical procedure, or a viral illness may trigger episodes of muscle swelling and inflammation (myositis), resulting in permanent bone growth in the injured area.
- FOP is almost always caused by missense mutations in the cytoplasmic domain of the type 1 bone morphogenetic protein (BMP) receptor Activin A receptor type 1 (ACVR1) gene and is inherited in an autosomal dominant manner
- Activin A (BMP family member that normally antagonizes BMP signaling via ACVR1) is perceived by mutant ACVR1 as an agonist
- Inhibition of Activin A by a monoclonal antibody completely abrogates HO in FOP mouse models -> REGENERON developed an anti-Activin A mAb for human use = GARETOSMAB



Shafritz AB, Shore EM, Gannon FH, Zasloff MA, Taub R, Muenke M, Kaplan FS.
Overexpression of an osteogenic morphogen in fibrodysplasia ossificans progressiva (FOP) N Engl J Med. 1996;335:555–561

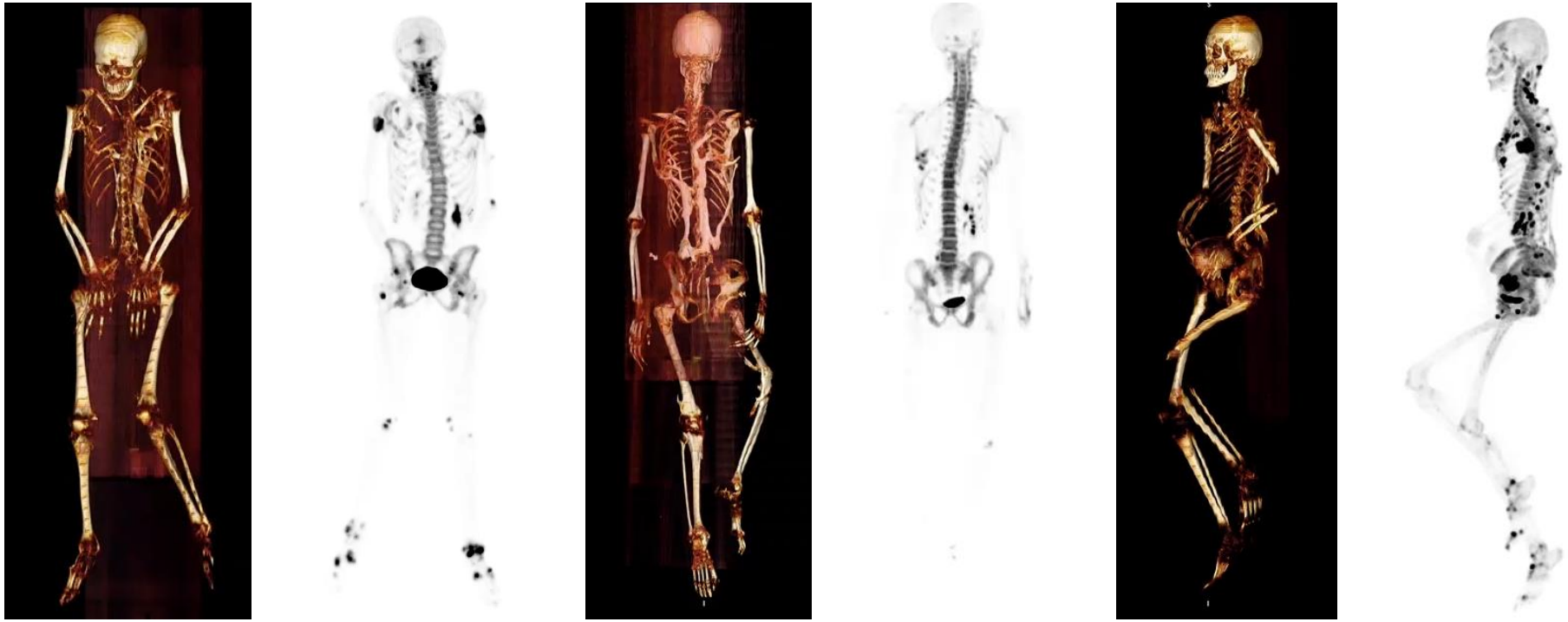
NOVEL IMAGING CAN BE USED AS A PD MARKER IN EARLY STUDIES OF FOP TREATMENT: HIGH 18F-NAF POSITRON EMISSION TOMOGRAPHY (PET) SIGNAL PRECEDES HETEROTOPIC OSSIFICATION IN PATIENTS WITH FOP

- 18F-NaF is taken up more by bone that is growing/remodeling
- Emerging data in FOP patients show some HO sites as 18F-NaF hot spots in PET images
- Some time later (weeks to months) new HO bone forms where there used to be high 18F-NaF PET signal, and can be seen by X-ray CT
- Old/mature HO bone shows 18F-NaF similar to normal skeleton, indicating that it is no longer growing as fast.
- 18F-NaF PET and X-ray CT can be used to track **which HO lesions are growing**, and whether **treatment is having an effect on HO bone growth** rate



E.M.W. Eekhoff, et al., [18F]NaF PET/CT scan as an early marker of heterotopic ossification in fibrodysplasia ossificans progressiva, Bone (2017).

BASELINE 18F-NAF PET IMAGES REVEAL FOCI OF HO FORMATION



KEY POINTS

- Clinical dose of biologics is highly informed by pre-clinical studies
- Safety is generally target/mechanism related
- Use of genetically validated targets and objective endpoints informed by biology can provide meaningful pharmacodynamic data in relatively small studies