Biologics

Biologic drugs with focus on allergy and asthma

Sachsska barn- och ungdomssjukhuset

En del av Södersjukhuset

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Conflicts of interest and funding

I have received lecture fees from: **Novartis** and **Thermo Fisher Scientific**

My research funding does not imply any conflicts of interest but I would like to take this opportunity to thank my funders:

- Stockholm City Council
- Sachs´s Children and Youth Hospital Swedish Asthma and Allergy association
- Hesselman´s Foundation
- Frimurare Barnhuset Foundation (Freemasons of Sweden)
- Konsul Th C Bergh foundation
- Research grant in memory of Kerstin Hejdenberg
- The Samariten Foundation
- Her Royal Highness Crown Princess Lovisa research fund
- Mjölkdroppen Foundation
- Åke Wiberg Foundation and
- Torsten Söderberg foundation
- EAACI
- SFFA
- Swedish Medical Association (Stockholm section)

- Biologic drugs
- Biologic drugs in asthma
- Biologic drugs (omalizumab) in food allergy

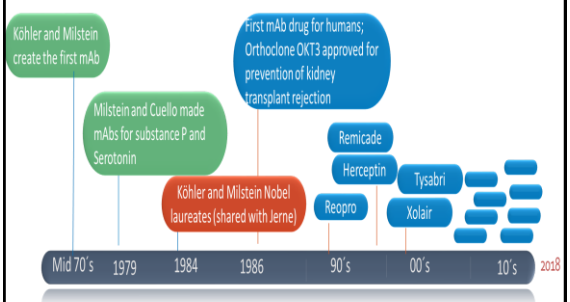
Biopharmaceuticals

Biologic drugs = Biological medicinal products

- EU-definition: "a protein or nucleic acid–based pharmaceutical substance used for therapeutic or *in vivo* diagnostic purposes, which is produced by means other than direct extraction from a native (non-engineered) biological source"
- Monoclonal antibodies mAb
  omalizumab, infliximab….
- Genetically engineered proteins
  Anakinra, etanercept…

(Re)defining biopharmaceutical Rader R Nature Biotech 2008

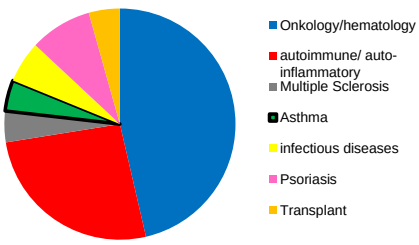
History



Liu J. The history of mAb…Ann Med Surg 2014

>70 approved mAbs today

Distribution of mAbs per main indication



Non-approved mAb

- Several hundreds of registered non-approved mAb
- Mostly for malignancies
- But also for
  - → Migraine
  - → Infections (gram-neg sepsis, S. Aureus, Influenza, rabies-prophylaxis)
  - → Sciatica
  - → Diabetes type 1
  - → Alzheimer´s disease
  - → Non-alcoholic Steatohepatitis (NASH)
  - → .....

Pharmacodynamics

- Bind cell-surface receptors
  - → Alters intracellular signaling and cytokine production
  - → Alter cell adhesion/migration
- Bind malignant/infected cells→ helping immune system in clearing out malignant cells. **Radioactive mAb!**
- Inhibition of circulating molecules like cytokines, immunoglobulins
- Antidotes: Bind toxins or drugs

What about the strange names?

All have a prefix: just a made up name

ipilimumab

All have the –mab suffix = Monoclo[illegible]ti-body

obinutuzumab

rituximab

What is in-betwe[illegible]des information about: target/indication and origin

abciximab

omalizumab

ustekinumab

palivizumab

mepolizumab

Rituximab or ri-tu-xi-mab

	Target
-l(i)-	Immune system
-*tox(a)*-	Toxin
-*t(u)*-	Tumor
-*v(i)*-	Virus
	Source of mab
-o-	Mouse
-i-	primate
-u-	human
-xi-	chimer
-zu-	humanized

Omalizumab
Oma-li-zu-mab

Palivisumab
Pali-vi-su-mab

Trastuzumab
Tras-tu-zu-mab

Obiltoxaximab
Obil-toxa-xi-mab

Approved mAb in asthma and allergy

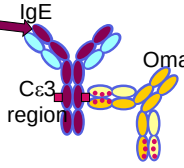
Generic	Name	Indication	Type	Effect
omalizumab	Xolair, 2003	Asthma, chronic spont urticaria	Anti-IgE	↓ IgE-ab ↓FcεRI
mepolizumab	Nucala 2015	eosinophilic asthma (adults)	Anti-IL 5	↓IL-5 stimulation of eosinophils→ ↓ production/ survival
reslizumab	Cinqair 2016	eosinophilic asthma (adults)	Anti-IL 5	↓ IL-5 stimulation of eosinophils→ ↓ production/ survival
dupilumab	Dupixent 2017	Atopic dermatitis (adults)	Anti-IL 4/13 receptor	↓ Interleukin 4 and 13 signaling

Hugo Farne. Anti-IL5 therapies for asthma. Cochrane Systematic review sept 2017

mAb targeting IgE

Generic	Trade-name	Year Appr.	Indication(s)	Type	Effect
Omalizumab	**Xolair**	**2003**	**Asthma, Chronic spont. urtic.**	**Anti-IgE**	**↓ IgE-ab ↓FcεRI**
Ligelizumab	----------	No	?	Anti-IgE	More potent than omalizumab

Antigen-binding region of IgE



Binds constant part of free IgE→ non allergen specific blocking of IgE to FcεRI interaction

Arm J.P Pharmakinetics, pharmacodynamics...Ligelizumab, a novel high affinity anti IgE... Clin Exp All 2014

Omalizumab for asthma in adults and children.

Rebecca Normansell et al. 2014

	OR	95% CI	Absolute risk reduction
Exacerbations *During week 16-60 of omalizumab*	**0.55**	0.42-0-6	**10 %** Placebo 26%, Omalizumab 16%
Hospitalization *During week 16-60 of omalizumab*	**0.16**	0.06-0.42	**2.5 %** Placebo 3 %, Omalizumab 0.5 %
Complete steroid withdrawal within 6~months	**2.5**	2-3.13	**19 %** Placebo 21 %, Omalizumab 40%
Daily inh. corticosteroid dose	-118 µg (minus 84 ug to minus 154 µg)		

Safe and no reports of anti-drug antibody development

Omalizumab; shortcomings in asthma

- No significant difference in discontinuation of oral corticosteroids!
- Little or no effect on lung function
- High IgE or body weight might disqualify from treatment
- **Cost-effectiveness?**

Normansell R et al. Omalizumab for asthma in adults and children. Cochrane Syst rev. 2014

Tianwen Lai et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. Scientific reports 2015

Cost-effectiveness

- There is no definitive cut-off for when a drug is considered cost-effective. UK guidelines ~ € 20k → 100k depending on disease

Author/year/country	Patients	Cost per QUALY	Author's Conclusion
Brown / 2007 /Canada	Uncontrolled severe asthma	€ 821.000	Cost effective
Wu / 2007 / USA	Severe persistent asthma	€ 821.000	Not cost-effective for most patients
Dewilde / 2006 / Swed	Uncontr. severe asthma	€ 56.000	May be cost-effective
Dal Negro / 2011 / Italy	Severe and resistant asthma	€ 26.000	Positive effects justifies price

Why is omalizumab not effective sometimes?

→Is the asthma IgE-driven?
→Unknown reasons
→Doses are individualized; can they still be to low?

- Since omalizumab does not remove all IgE; patients with a high proportion of disease-relevant s-IgE might not respond to treatment

  The size of the disease relevant IgE-ab fraction in relation to total-IgE predicts the efficacy of anti-IgE (Xolair) treatment. Johansson S.G.O, Nopp A et al. Allergy 2009

"Anti-IgE 2.0"

Generic	name	Indication	Type	Effect
Omalizumab	Xolair	Asthma,spont. urtic.	Anti-IgE	↓ IgE-ab, ↓FcεRI
Ligelizumab	**-------**	**Asthma?**	**Anti-IgE**	**More potent than omalizumab**

Ligelizumab vs. omalizumab (mild asthma) effect on allergen induced bronchial reactivity

Median PC_{15} increased 16-fold in ligelizumab vs. 5-fold in omalizumab (p=0.1).

Treating food allergies with omalizumab
RCTs have shown

Tolerated dose is significantly increased in omalizumab vs. placebo at food challenges or initiation of oral immunotherapy (OIT).

Sampson H. JACI 2011, MacGinnitie AJ. JACI 2017

Omalizumab-treated patients reach maintenance dose faster in OIT
Wood RA JACI 2015 , MacGinnitie AJ

Significantly reduced number of adverse events. *Wood RA*

No significant difference in primary outcomes: maintained desensitization post omalizumab discontinuation or after OIT is paused for weeks-months

Other types of AIT: omalizumab decrease adverse events and facilitate initiation in pollen and venom subcutaneous immunotherapy. Larenas-Linnemann D. JACI 2014

Successful management of severe cow's milk allergy with omalizumab treatment and CD-sens monitoring.

Nilsson C, Nordvall L, Johansson S.G.O, Nopp A. Asia Pac Allergy 2014

Case series with 5 patients

All patients had previously had very severe reactions to small amounts of milk with at least one of the following symptoms; apnea, unconsciousness, cyanosis

- After 16 weeks on omalizumab basophil allergen threshold sensitivity (CD-sens) was assessed and 4/5 patients´ basophils were not reacting to milk any longer
- The last patient´s dose was doubled
- Oral food challenge after suppression of basophil sensitivity
- The patients tolerated 50-450 ml of milk after omalizumab

FASTX

Food Allergen Suppression Therapy during protection with omalizumab (xolair)

Treating severe peanut allergy by combining peanut oral immunotherapy with omalizumab

Monitor and guide treatment with Basophil allergen threshold sensitivity analysis (CD-Sens)

FASTX

- 23 adolescents, 12-19 years, with severe peanut allergy

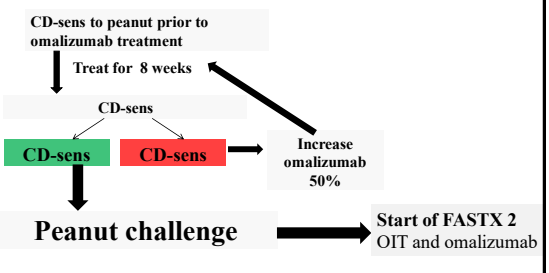
Anaphylaxis to peanut within 5 years n=9	Anaphylaxis/impending anaphylaxis at OFC n=14

Peanut s-IgE: median 86 kU_A/l range(35-350)
Ara h 2 s-IgE: median 58 kU_A/l range (16-220)

- Omalizumab
  Dose based on body weight and IgE level (as for asthma)
  Patients requiring a higher omalizumab dose than 600mg/2 weeks were not included

FASTX

Study design FASTX 1



FASTX

Individually dosed omalizumab; an effective treatment for severe peanut allergy.
Brandström J, Vetander M, Kalm F, Lilja G, Sundqvist A-C, Johansson S.G.O, Nilsson C & Nopp A. Clin Exp Allergy 2016

Results; omalizumab dosing

- Start dose: 150 mg to 1050 mg/4 week
- 8/23 patients turned negative in CD-sens after asthma dose of omalizumab for 8 weeks → Food Challenge
- The other 15 (65%) continued with 50% dose increments every 8th week until basophils were suppressed

FASTX

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Peanut challenge after omalizumab

- Median peanut dose 10 g (range 3.3-10). Mean 8 g
- 19/23 (83%) had no objective symptoms
  3 mild rhinitis and 1 perioral erythema
- Among the 14 patients who were challenged twice (inclusion and exit); tolerated peanut dose increased 50-fold (median)

Brandstrom J et al. Clin Exp All 2016

FASTX

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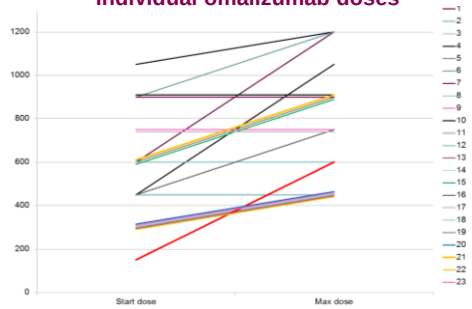
Individual omalizumab doses



Could you tell from the start: who will need a higher dose?

FASTX

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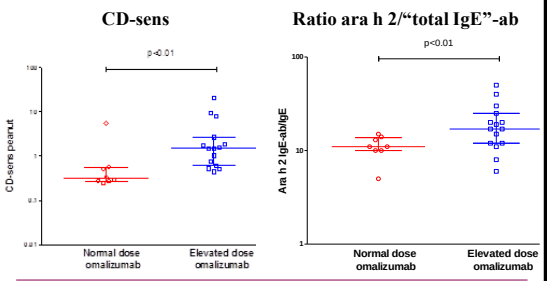
Indicators of need of increased anti-IgE



Brandstrom J et al. Clin Exp All 2016

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Summary

- Biologic drugs have played a very important part in medicine over the last two decades
- Many new mAbs, for many different diseases are currently going through clinical trials
- Main limitation is the high cost: Are mAbs cost-effective?
  → Probably if we select patients carefully
- We need improved diagnostic markers for patient selection

Acknowledgements

Karolinska Institutet

Sachs´s children and youth Hospital
Caroline Nilsson *main supervisor*
Mirja Vetander *co-supervisor*
Ann-Charlotte Sundqvist
Gunnar Lilja *co-supervisor*
Nurses and doctors at allergy dept.
Carina Wallén
Staff at Sachs´ research center
Stefan Johansson *PhD-student mentor*
Anna-Karin Edstedt-Bonamy
Susanne Glaumann
Erik Melén
Bodil Schiller
Fredrik Stenius

KI Södersjukhuset
Hans Järnbert Pettersson

KI immunology and allergy unit
Anna Nopp *co-supervisor*
Gunnar Johansson
Frida Kalm
Zekiye Cansu

KI dept of clinical epidemiology
Björn Pasternak
Gabriella Bröms

Karolinska Trial Alliance
Lotta Mazouch *study monitor FASTX*

Stockholm University
Eva Sverremark Ekström
Claudia Queiroz (now at KI)

A special thanks to all patients at Sachs´s children's hospital participating in our clinical studies and their parents