3rd International Conference and Exhibition on Clinical & Cellular Immunology

Elena Gavrilova



Application of drugs based on release-active antibodies as immunotherapy agents

OOO “NPF “Materia Medica Holding”,
Moscow, Russia

Monoclonal antibodies approved for therapeutic use

Licensed therapeutic mAbs

Scientific name	Trade name	Origin and isotype	Target	Licensed indication(s) and year of first approval-region
Capromab pendetide	Prostascint	Murine IgG1	PSA[a]	Diagnostic imaging (1996-US)
Muronomab-CD3	Orthoclone OKT3	Murine IgG2a	CD3	Transplant rejection (1992-US)
Tositumumab iodine|131	Bexxar	Murine IgG2	CD20	NHL[b] (2003-US)
Ibritumomab tiuxetan	Zevalin	Murine IgG1	CD23	NHL (2002-US, 2004-EU)
Basiliximab	Simulect	Chimeric IgG1	CD25	Prophylaxis for transplant rejection (1998-US)
Brentuximab vedotin	Adcetris	Chimeric IgG1	CD30 ADC[c]	ALCL[d] and Hodgkin lymphoma (2011-US)
Catumaxomab	Removab	Chimeric IgG2a/b	CD3, EpCAM[e]	Malignant ascites (2009-EU)
Cetuximab	Erbitux	Chimeric IgG1	EGFR[f]	Colorectal, head and neck cancer (2004-US, EU)
Infliximab	Remicade	Chimeric IgG1	TNF[g]	RA[h], ankylosing spondylitis, Crohn's disease, ulcerative colitis (1998-US, 1999-EU)
Rituximab	Rituxan, MabThera	Chimeric IgG1	CD20	B cell non-Hodgkin lymphoma (1997-US, 1998-EU)
Alemtuzumab	Campath, MabCampath	Humanized IgG1	CD52	B-CLL[i] (2001-US)
Bevacizumab	Avastin	Humanized IgG1	VEGF[j]	Colorectal, lung, breast cancer (2004-US, 2005-EU)
Daclizumab	Zenapax	Humanized IgG1	CD2[illegible]	Prophylaxis for transplant rejection (1997-US, 1999-EU (withdrawn 2009))
Eculizumab	Soliris	Humanized IgG2/4	Comp[illegible] factor 5	Paroxysmal nocturnal haemoglobinuria, atypical haemolytic-uremic syndrome (2007-US)
Efalizumab	Raptiva	Humanized IgG1	CD11a	Psoriasis (2003-US (withdrawn 2009))
Gentuzumab ozogamcin	Mylotarg	Humanized IgG4	CD33 ADC	Leukemia (2000-US)
Natalizumab	Tysabri	Humanized IgG4	$\alpha_4\beta_1$ integrin	Multiple sclerosis (2004-US, 2006-EU)
Omalizumab	Xolair	Humanized IgG1	IgE	Severe asthma (2003-US, 2005-EU)
Palivizumab	Synagis	Humanized IgG1	RSV[k] F protein	Prevention of RSV infection in neonates (1998-US)
Ranibizumab	Lucentis	Humanized IgG1	VEGF	Macular degeneration (2006-US, 2007-EU)
Tocilizumab	Actemra, Roactemra	Humanized IgG1	IL-6R[l]	Castleman's syndrome, RA (2010-US, 2009-EU)
Trastuzumab	Herceptin	Humanized IgG1	HER-2[m]	HER-2 positive breast cancer (1998-US)
Adalimumab	Humira	Human IgG1	TNF	RA, Crohn's disease, plaque psoriasis (2002-US, 2003-EU)
Belimumab	Benlysta	Human IgG1	BLys[n]	Systemic lupus erythematosus
Canakinumab	Ilaris	Human IgG1	IL-1β[o]	Muckle-Wells syndrome (US, EU-2009)
Denosumab	Prolia, Xgeva	Human IgG2	RANKL[p]	Osteoporosis, bone metastasis (2009-US, EU)
Golimumab	Simponi	Human IgG1	TNF	RA, psoriatic arthritis, ankylosing spondylitis (2009-US, EU)
Ipilimumab	Yervoy	Human IgG1	CTLA4[q]	Advanced melanoma (2011-US, EU)
Ofatumumab	Arzerra	Human IgG1	CD20	CLL (2009-US, 2010-EU)
Panitumumab	Vectibix	Human IgG2	EGFR	Colorectal cancer (2007-US, EU)
Ustekinumab	Stelara	Human IgG1	IL-12p40[r]	Plaque psoriasis (2009-US, EU)
Pertuzumab	Perjeta	Humanized IgG1	HER-2[m]	HER-2 positive breast cancer (2012-US)

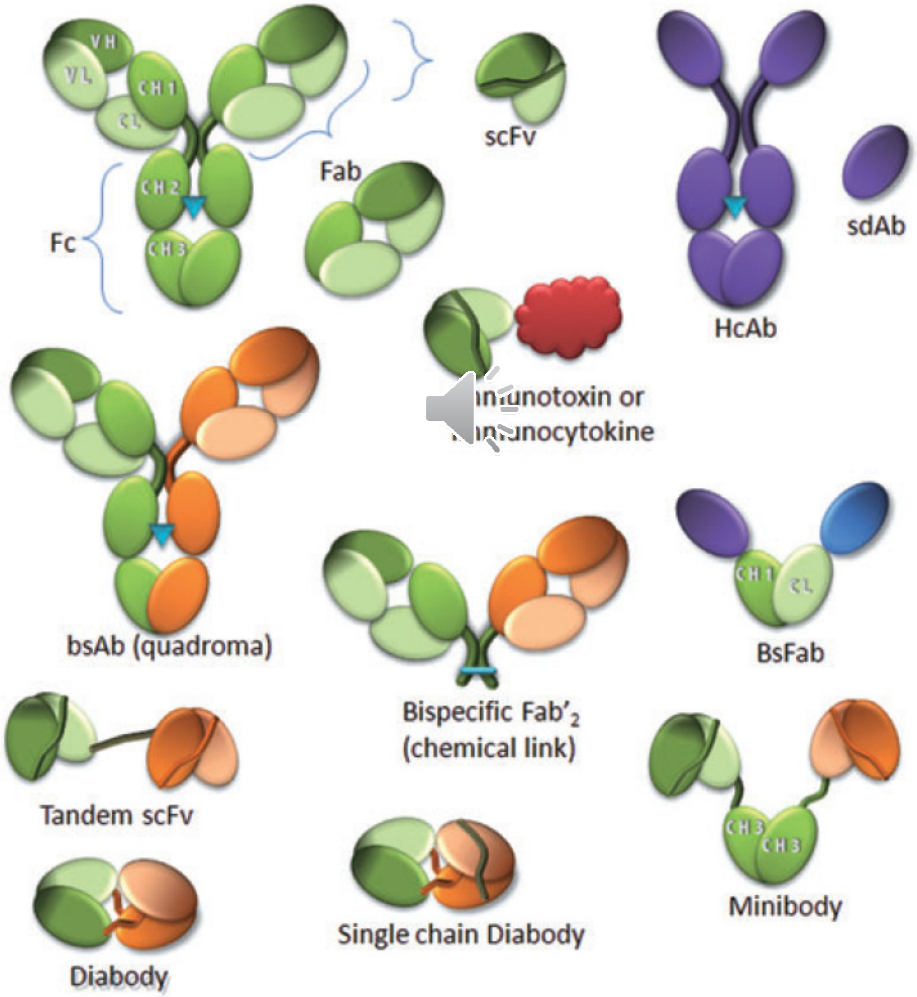
Buss NAPS et all// Current Opinion in Pharmacology, 2012

Limitations in mAbs-based therapies

Attributes	Description
Production	• Safety of biological material used • Potential cancer risk in case of EBV introduction • Generating stoichiometric amounts of heavy and light chains • Glycosylation profile
Cost	• Production cost is 300-500 million euros • Annual cost of therapy is U[illegible] 100 000 per patient
Pharmacokinetics	• Rapid elimination of mAbs • Non-linear PK and PD profile • Effect of demographic variables on mAbs PK • Tissue penetration properties
Route of administration	• Intra-venous infusions
Safety	• Immunogenicity • Side-effects

H. Samaranayake et al, Annals of Medicine, 2009

Antibodies engineering to safety and efficacy increase

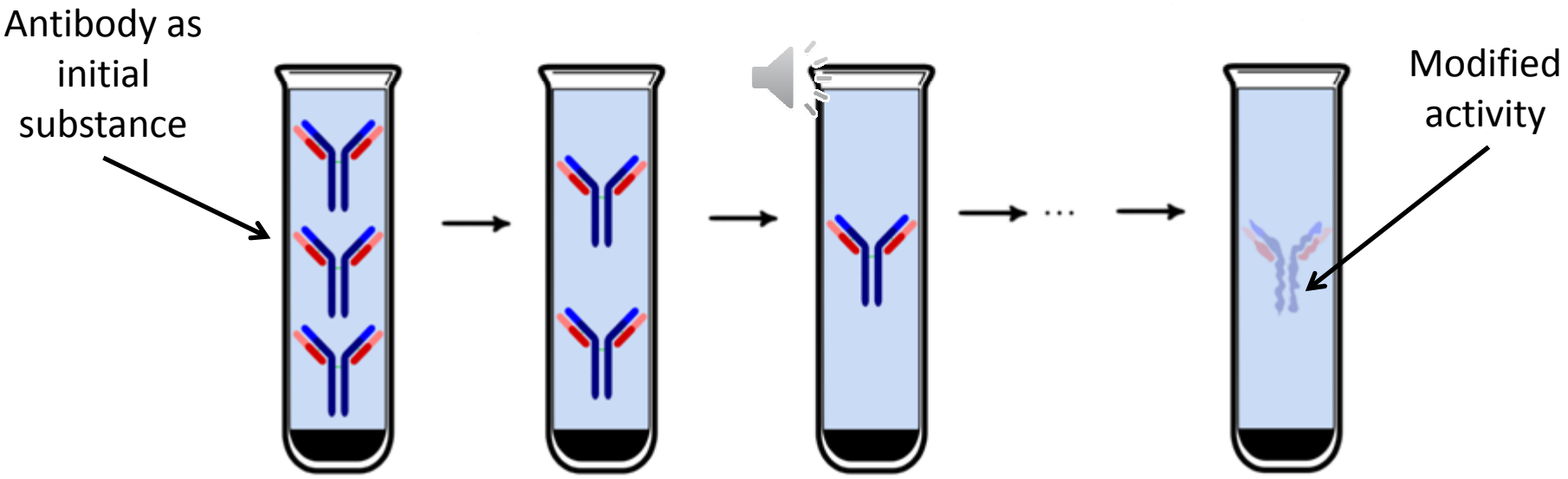


P. Chames et al, British Journal of Pharmacology, 2009

Release-active antibodies

Method: A combination of multiple rounds of consequent decrease in the substance's initial concentration and physical treatment

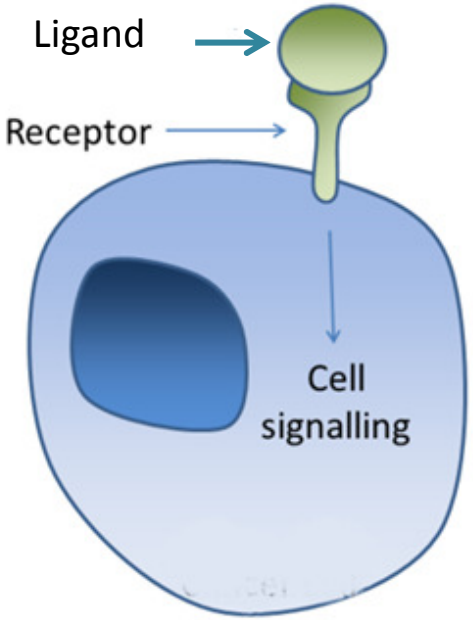
Substance: Rabbit polyclonal antibodies to different targets
Level of Abs concentration reduction: 10^{24}



The technology was discovered d by **Prof. Dr. Oleg Epstein** (Epstein O.I., 1999, Epstein O.I. et al, Usp. Fiziol. Nauk, 2013).

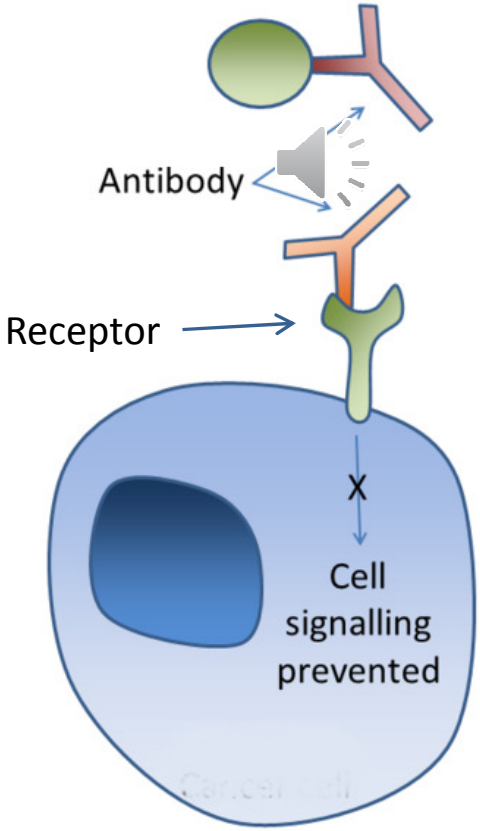
Ligand-receptor binding

Regular process



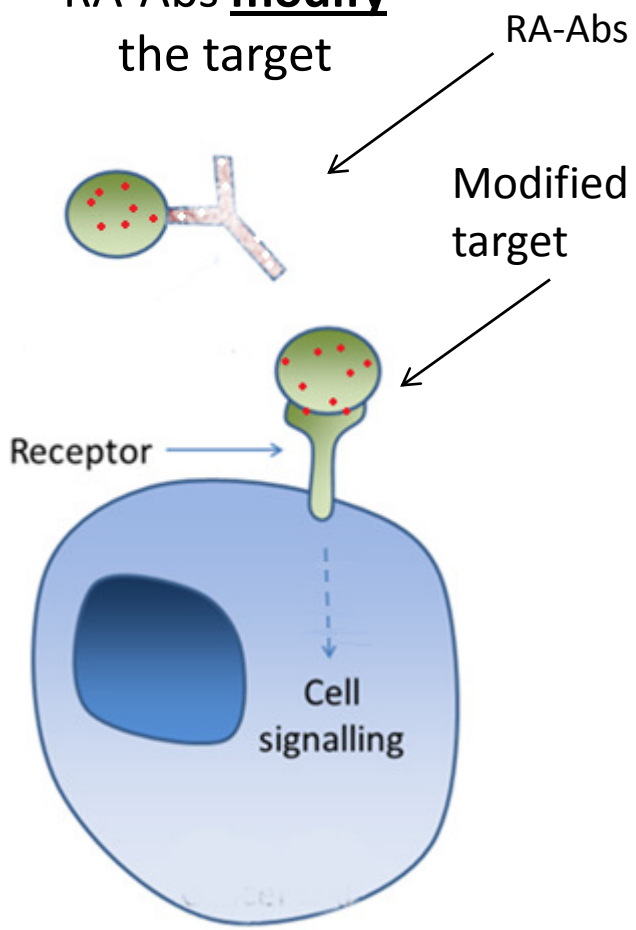
How monoclonal antibodies work?

mAbs **neutralize** the targets



How release-active antibodies work?

RA-Abs **modify** the target



Study of influence RA of Ab to IFNγ on interferon-gamma by NMR

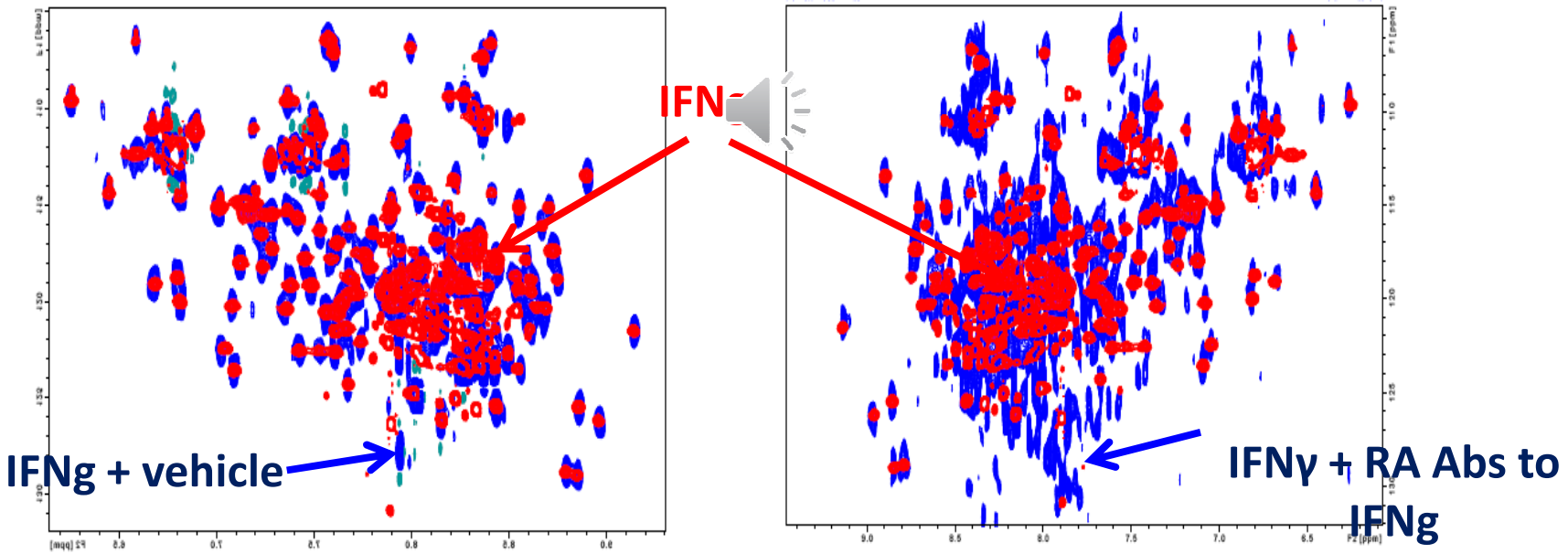
Preclinical site: Department of Structural Biology University of Pittsburgh School of Medicine (USA)

Design: ^{5}N-^{1}H-HSQC spectra of IFN-γ in absence (colored in blue) and present of RA of Ab to IFN-γ or placebo (colored in red)

2D HSQC Spectrum of IFNg

IFNg + placebo

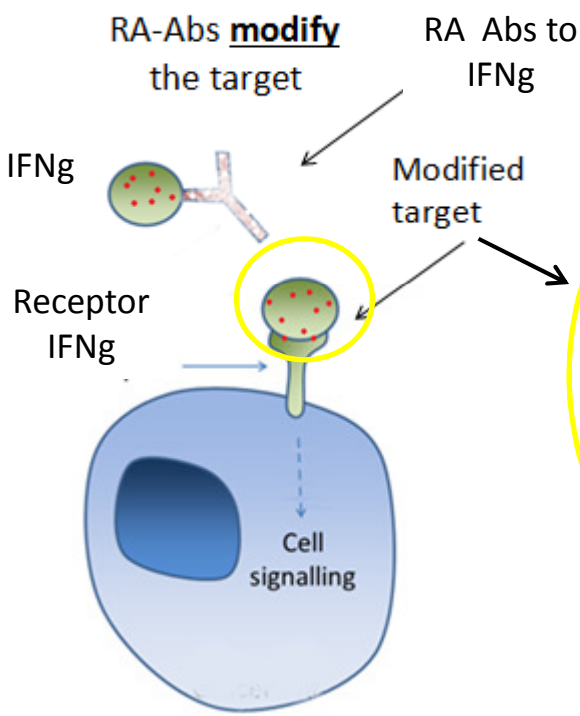
IFNg + RA of Ab to IFNg

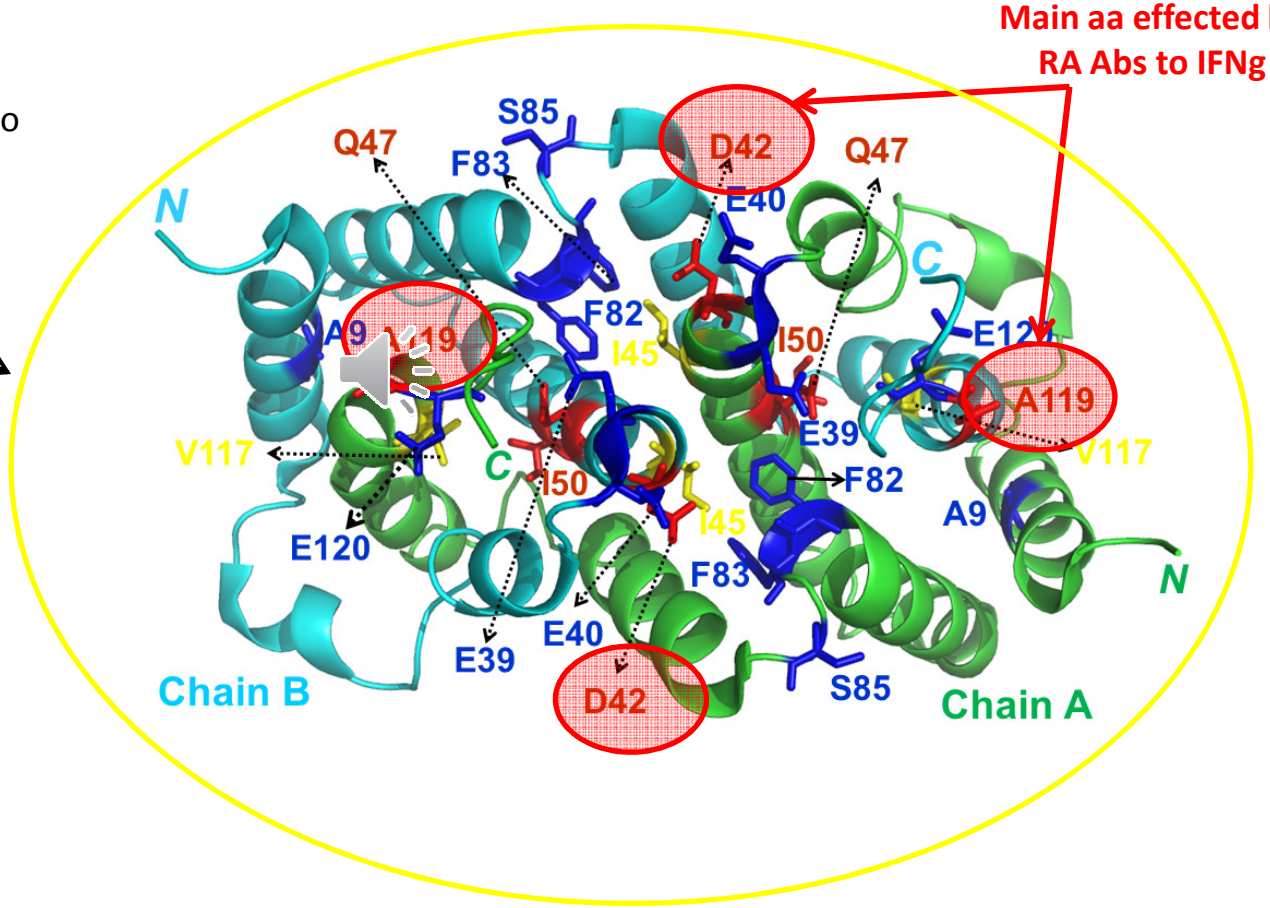


Conclusion: Addition of concentrated RA of Abs to IFNγ causes specific chemical shift changes in two-dimensional ^{1}H,^{15}N-HSQC spectra of ^{15}N-labeled IFNg, located primarily at the IFNg dimer interface

Study of influence RA of Ab to IFNγ on interferon-gamma

Site: Department of Structural Biology University of Pittsburgh School of Medicine (USA)



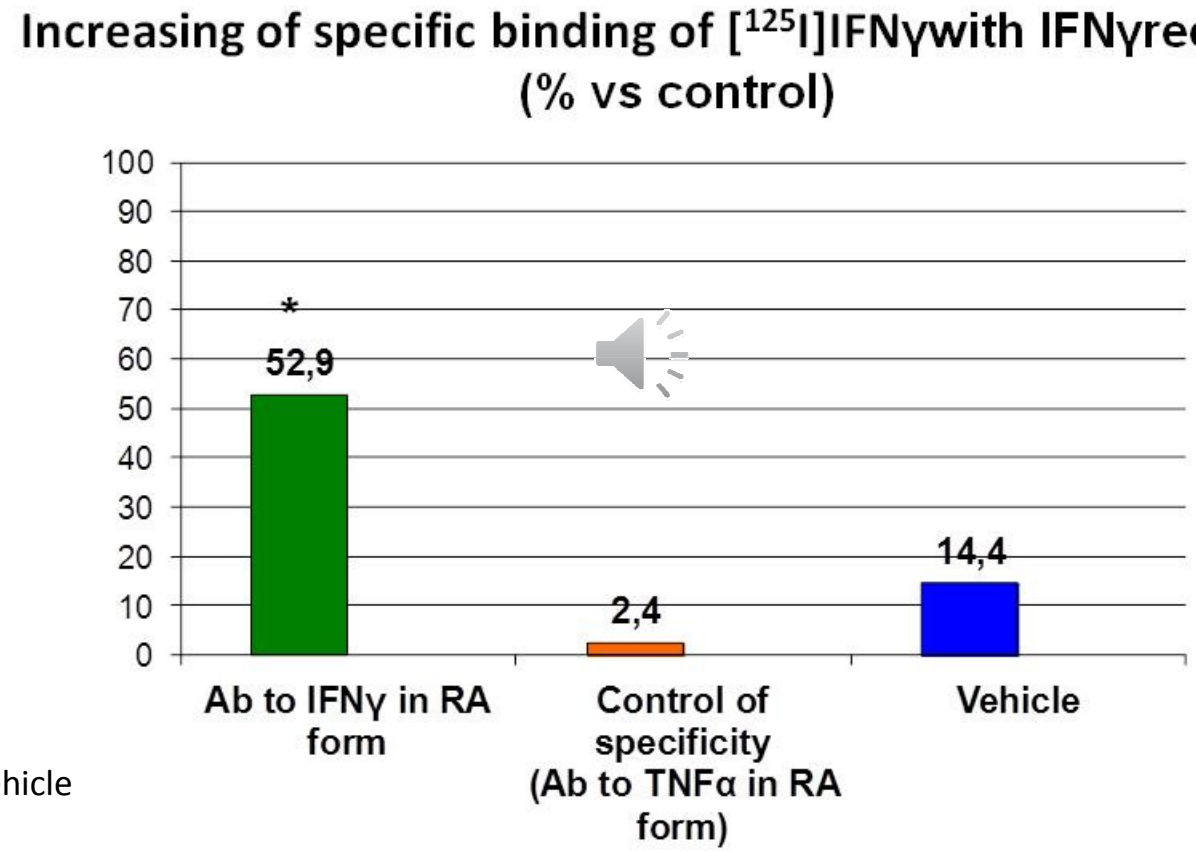


Conclusion: The interferon-gamma sites which affected by Anaferon for children were founded

Study of influence RA of Ab to IFNγ on interferon-gamma

Site: Euroscreen (Belgium)

Assay: Radioligand binding assay



*p< 0.05 vs vehicle

Conclusion: RA Abs to IFN gamma significantly increase the specific binding of IFNg with IFNg receptor

List of main Materia Medica drugs based on RA antibodies

	Product	Lead Indications	Target
	Propoten-100	Alcoholism	S-100 protein
	Anaferon	Influenza, upper respiratory infections	IFNγ
	Anaferon for children	Influenza, upper respiratory infections	IFNγ
	Impaza	Erectile Dysfunction	NO sythase
	Arthrofon	Rheumatoid arthritis	TNFα
	Tenoten	Anxiety/ Depression, other CNS disorders	S100 protein
	Afala	First and second stage BPH	PSA
	Tenoten for children	Anxiety, Depression, Attention Deficit Disorder	S100 protein
	Dietressa	Obesity	CB1 receptor
	Colofort	Inflammatory Bowel Syndrome	Histamine, S100 protein, TNFα
	Brizantin	Cigarette Smoking	CB1 receptor, S100 protein

Manufacture

AB Biotechnology facility, UK







Materia Medica Holding facility, RF







Antigen production:
Recombinant protein production

↓

Immunization of SPF rabbits and antiserum preparation

↓

Affinity purified antibodies preparation:
Delipidization of antiserum
Viral inactivation stages
Affinity chromatography

↓

Rabbit polyclonal affinity purified antibodies – Drug Substance

↓

Preparation of Drug Substance release-active dilutions

↓

Preparation of Drug Product dosage form

↓

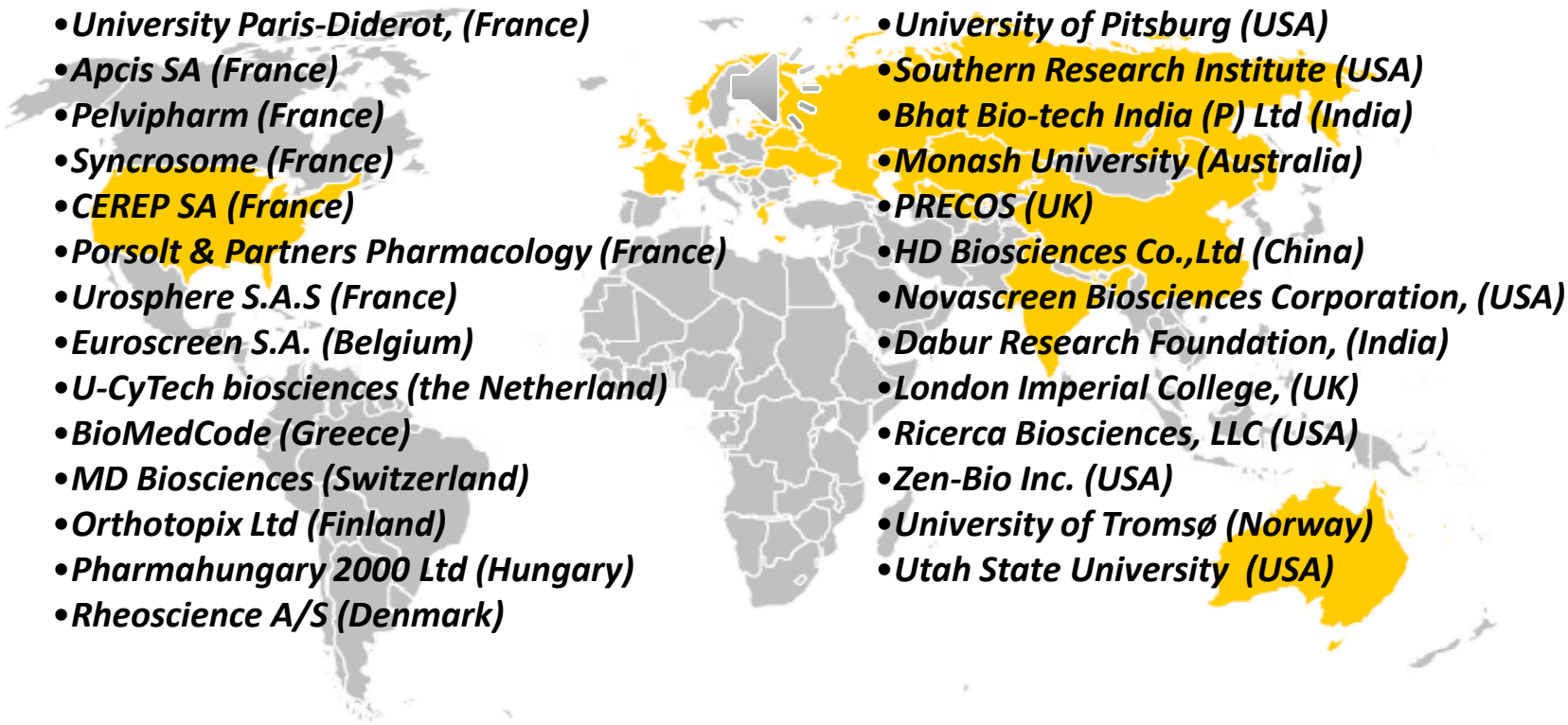
Orodispersible tablets

RA antibodies-based drugs preclinical studies

- Toxicological studies
- Pharmacological activity studies
- Mechanism of action studies

✓Well planned and controlled
✓Performing in accordance with current requirement
✓Performed by world leading research institutions and CRO

Main European collaborators of Materia Medica



- ***University Paris-Diderot, (France)***
- ***Apcis SA (France)***
- ***Pelvipharm (France)***
- ***Syncrosome (France)***
- ***CEREP SA (France)***
- ***Porsolt & Partners Pharmacology (France)***
- ***Urosphere S.A.S (France)***
- ***Euroscreen S.A. (Belgium)***
- ***U-CyTech biosciences (the Netherland)***
- ***BioMedCode (Greece)***
- ***MD Biosciences (Switzerland)***
- ***Orthotopix Ltd (Finland)***
- ***Pharmahungary 2000 Ltd (Hungary)***
- ***Rheoscience A/S (Denmark)***
- ***University of Pitsburg (USA)***
- ***Southern Research Institute (USA)***
- ***Bhat Bio-tech India (P) Ltd (India)***
- ***Monash University (Australia)***
- ***PRECOS (UK)***
- ***HD Biosciences Co.,Ltd (China)***
- ***Novascreen Biosciences Corporation, (USA)***
- ***Dabur Research Foundation, (India)***
- ***London Imperial College, (UK)***
- ***Ricerca Biosciences, LLC (USA)***
- ***Zen-Bio Inc. (USA)***
- ***University of Tromsø (Norway)***
- ***Utah State University (USA)***

RA antibodies-based drugs clinical studies

Clinical sites location:

- ✓ Russian Federation
- ✓ Commonwealth of Independent States
- ✓ Asia

Number of clinical sites:

> 100, one-site and multi-central studies

Design of studies:

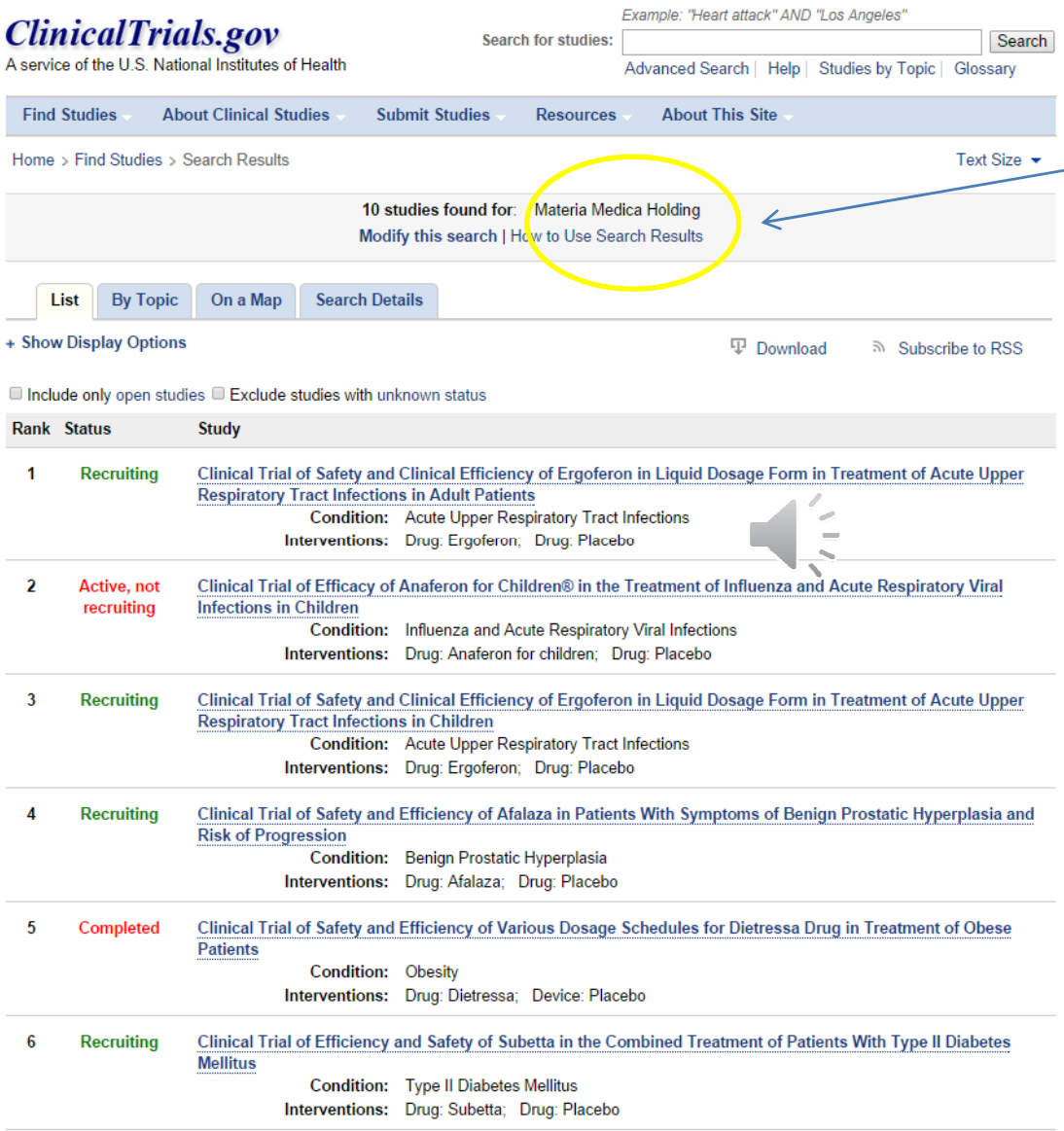
Double Blind Randomized Placebo Control or Comparative

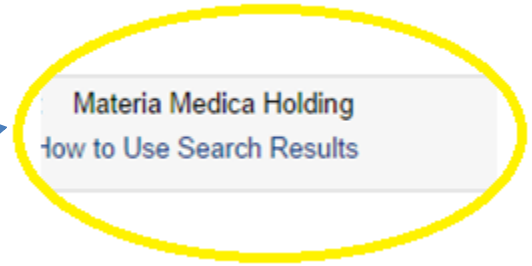
Number of patients enrolled:

Abou[illegible]30 000

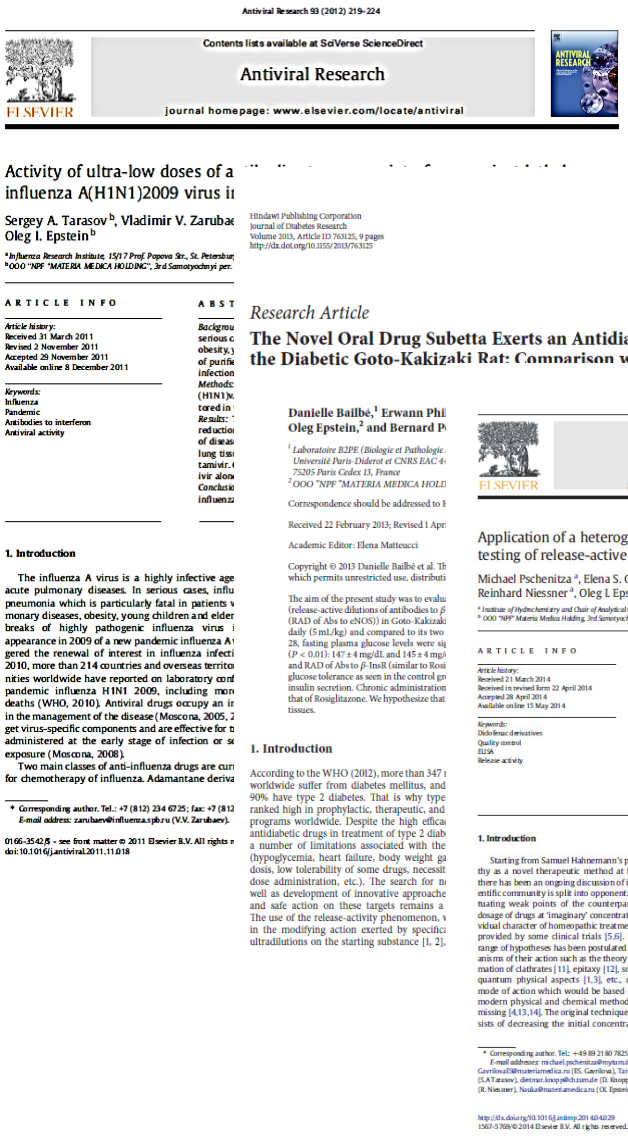


RA antibodies-based drugs clinical studies





Publications



Antiviral Research 93 (2012) 219–224

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Activity of ultra-low doses of a
influenza A(H1N1)2009 virus i

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Antibodies to interferon
Antiviral activity

ABST

Backgrou
serious c
obesity, y
of purifi
infection
Methods:
(H1N1)v
tored in
Results:
reduction
of diseas
lung tiss
tamivir, (
ivir alon
Conclusio
influenza

1. Introduction

The influenza A virus is a highly infective age
acute pulmonary diseases. In serious cases, influ
pneumonia which is particularly fatal in patients v
monary diseases, obesity, young children and elder
breaks of highly pathogenic influenza virus i
appearance in 2009 of a new pandemic influenza A
gered the renewal of interest in influenza infecti
2010, more than 214 countries and overseas territo
nities worldwide have reported on laboratory conf
pandemic influenza H1N1 2009, including mor
deaths (WHO, 2010). Antiviral drugs occupy an ir
in the management of the disease (Moscona, 2005, 2
get virus-specific components and are effective for t
administered at the early stage of infection or s
exposure (Moscona, 2008).

Two main classes of anti-influenza drugs are cur
for chemotherapy of influenza. Adamantane deriva

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E-mail address: zarubaev@influenza.spb.ru (V.V. Zarubaev).

0166-3542/$ - see front matter © 2011 Elsevier B.V. All rights r
doi:10.1016/j.antiviral.2011.11.018

Hindawi Publishing Corporation
Journal of Diabetes Research
Volume 2013, Article ID 763125, 9 pages
http://dx.doi.org/10.1155/2013/763125

Research Article

The Novel Oral Drug Subetta Exerts an Antidiabetic Effect in the Diabetic Goto-Kakizaki Rat: Comparison with Rosiglitazone

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Oleg Epstein,[2] and Bernard P

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75205 Paris Cedex 13, France
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Received 22 February 2013; Revised 1 Apr

Academic Editor: Elena Matteucci

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which permits unrestricted use, distributi

The aim of the present study was to evalu
(release-active dilutions of antibodies to β
(RAD of Abs to eNOS)) in Goto-Kakizaki
daily (5 mL/kg) and compared to its two
28, fasting plasma glucose levels were sig
($P < 0.01$): 147 ± 4 mg/dL and 145 ± 4 mg/
and RAD of Abs to β-InsR (similar to Rosi
glucose tolerance as seen in the control gr
insulin secretion. Chronic administration
that of Rosiglitazone. We hypothesize that
tissues.

1. Introduction

According to the WHO (2012), more than 347
worldwide suffer from diabetes mellitus, and
90% have type 2 diabetes. That is why type
ranked high in prophylactic, therapeutic, and
programs worldwide. Despite the high efficac
antidiabetic drugs in treatment of type 2 diab
a number of limitations associated with the
(hypoglycemia, heart failure, body weight ga
dosis, low tolerability of some drugs, necessit
dose administration, etc.). The search for n
well as development of innovative approache
and safe action on these targets remains a
The use of the release-activity phenomenon,
in the modifying action exerted by specific
ultradilutions on the starting substance [1, 2],

Hindawi

International Immunopharmacology 21 (2014) 225–230

Contents lists available at ScienceDirect

International Immunopharmacology

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Application of a heterogeneous immunoassay for the quality con
testing of release-active forms of diclofenac

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Reinhard Niessner [a], Oleg I. Epstein [b]

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Quality control
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Release activity

ABSTRACT

We report on a specially designed diclofenac-ELISA for the determinatio
active forms of diclofenac in lactose dissolved in water solutions accor
blind experiments. In accordance with the objective of this project, a r
to determine the optimal ELISA conditions for detecting potential modi
diclofenac depending on their ability to affect the binding of diclofenac t
the diclofenac antibodies were previously incubated with manufactu
release-active forms of diclofenac or placebo. For comparison of the samp
sities were chosen. For statistic analysis, Student's two-sample t-test an
extremely low concentrations of diclofenac of 0.01, 0.05 and 0.1 ng m
assay performance. The source of diclofenac used for standard solut
could be important as the source of diclofenac for release active form o
the ELISA appeared to be suitable for the detection of the modifying eff
toward the pharmaceutical substance in vitro.

1. Introduction

Starting from Samuel Hahnemann's pioneering work on homeopa-
thy as a novel therapeutic method at the end of the 18th century,
there has been an ongoing discussion of its reasonability [1–4]. The sci-
entific community is split into opponents and proponents, each accen-
tuating weak points of the counterpart, such as those relating to
dosage of drugs at 'imaginary' concentrations or contempt for the indi-
vidual character of homeopathic treatment, or results of meta-analysis
provided by some clinical trials [5,6]. Despite the fact that a wide
range of hypotheses has been postulated to justify and elucidate mech-
anisms of their action such as the theory of water memory [7–10], for-
mation of clathrates [11], epitaxy [12], some hypotheses basing on the
quantum physical aspects [1,3], etc., convincing evidence for this
mode of action which would be based on rational studies involving
modern physical and chemical methods is, although desirable, still
missing [4,13,14]. The original technique to prepare the remedies con-
sists of decreasing the initial concentration of a drug substance by
multiple consecutive dilution or gr
the 1990s, another concept called
was introduced, which is based o
'release-active' (RA) forms of sub
ceutical substance during their co
The efficacy of such RA therapeuti
biological (antibodies, cytokine,
phenazepam, etc.) compounds a
One of the chemical substances
The ability of RA form of diclofen
cy and improve its safety has be
in-vitro and in-vivo studies [1
anti-inflammatory activity achieve
suggest possible reduction in the d
tice which may be useful to ach
well-known gastric toxicities such
rhage [22–24]. Despite this fact, ho
RA forms is currently on the agenda
for quality control is ongoing. Gen
tested for the detection of high d
evaluate either some of its prop
Among the examples of the first c
nance [25,26], flux calorimetry, con
vanic cell electrode potential [8,27

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INT. J. TISSUE REACT. XXVII(1) 15-21 (2005)

A RANDOMIZED, OPEN-LABEL, COMPARATIVE, 6-MONTH TRIAL OF ORAL ULTRA-LOW DOSES OF ANTIBODIES TO TUMOR NECROSIS FACTOR-α AND DICLOFENAC IN RHEUMATOID ARTHRITIS

DUGINA J.L.,[1] PETROV V.I.,[2] BABAYEVA A.R.,[2] MARTYUSHEV-POKLAD A.V.,[1] TCHEREVKOVA E.V.,[2] EPSTEIN O.I.,[1] SERGEEVA S.A.[1]

ussian Federation.

el drug approved by the Russian
s study was to assess clinical effi-
andomized, open-label, compara-
; mean disease duration 10 years)
). RA signs and symptoms as well
and at months 1, 3 and 6. Most
toms by the end of the study. The
roup, 57% of the patients achieved
h 6 versus 20% of those receiving
ikine levels significantly decreased
nd no changes in cytokine profile.
d no adverse effects and the over-
4 tablets daily) was able to sustain
n is a safe and effective treatment

herapeutic agents for rheumatoid
vailable, better patient outcomes
and a good safety profile are still

© 2005 Bioscience Edipint Inc.

Drug Watch

ow doses of

uld be to achieve clinical
lity. Arthrofoon modifies
is factor-α (TNF-α). The
ecause it does not produce
treatment with arthrofoon
rected to the 28-year-old
early RA. The strategy of
two years was confirmed
regression in patient with

is

hrofoon under the tongue
h a maintenance dose of
ment or combination of
wo years). The treatment
loon as a newer drug for

vith initial diagnosis of
s a clinical study for early
gy of the Orenburg State
y). Pharm companied of
s, elbows, knees, ankles
r for 20 minutes with no
l two weeks ago. Before
had history of chicken
l of azithromycin by her
he disease activity score
ic activity). The results
ding were positive (two
st for rheumatoid factor

aken into consideration
imesulide (Nise of Dr.
[, India) 100 mg twice a

with reactive arthritis
odies (immunoglobulins
Ureaplasma urealyticum
respectively). No atypical

OPEN ACCESS Freely available online

PLOS ONE

Novel Approach to Activity Evaluation for Release-Active Forms of Anti-Interferon-Gamma Antibodies Based on Enzyme-Linked Immunoassay

lena S. Gavrilova[1]*, Sergey A. Bobrovnik[2], Gordon Sherriff[3], Andrey A. Myslivets[1], Sergey A. Tarasov[1], Oleg I. Epstein[1]

1 OOO "NPF "MATERIA MEDICA HOLDING", Moscow, Russian Federation, 2 Department of Molecular Immunology, Palladin Institute of Biochemistry of the National Academy of Sciences of Ukraine, Kiev, Ukraine, 3 Ab Biotechnology Limited, Penicuik, United Kingdom

Abstract

Selection of a suitable assay to measure the activity of drug agents based on release-active forms of anti-interferon-gamma antibodies (RA forms of Abs) is an important step forward in the investigation of such agents. In this study, the enzyme-linked immunosorbent assay was utilized to examine the effect of RA forms of Abs specific for human interferon gamma on the interaction between monoclonal anti-interferon gamma antibodies and recombinant human interferon gamma. The experimental data and the results obtained by using relevant mathematical analysis showed that such RA forms of Abs are able to modulate the monoclonal antibody interaction with both soluble and immobilized (to the assay plate well) interferon gamma. These data demonstrated the importance of using relatively low concentrations of both soluble and plate-immobilized interferon gamma to detect the effects of RA forms of Abs to interferon gamma on the binding of monoclonal antibodies to interferon gamma. It has been suggested that the observed influence of RA forms of Abs on 'antibody-antigen' interaction could be used to detect and analyze the activity of drugs containing RA forms of Abs.

Citation: Gavrilova ES, Bobrovnik SA, Sherriff G, Myslivets AA, Tarasov SA, et al. (2014) Novel Approach to Activity Evaluation for Release-Active Forms of Anti-Interferon-Gamma Antibodies Based on Enzyme-Linked Immunoassay. PLoS ONE 9(5): e97017. doi:10.1371/journal.pone.0097017

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Introduction

Antibody-based drugs are widely available among marketed medicinal products. To date, approximately 30 commercial therapeutic monoclonal antibodies (mAbs) are available for sale in the USA and Europe [1]. However, despite the success of these therapeutics, the use of antibody-based agents remains challenging [2,3] and considerable efforts at designing and modifying antibody-containing pharmaceuticals or antibody derivatives are ongoing. An example of this is the using of antibody fragments or the production of fusion proteins by coupling antibody fragments to toxins or cytokines [4–6]. Another approach to overcome the obstacles associated with the use of mAbs are the attempts to facilitate qualitative penetration of antibodies into the cell by means of microinjections, electroporation etc. [7,8].

In the last decade, a number of publications devoted to the so-called "release-active forms of drugs" have appeared [9–18]. It was observed that during the process of decreasing the initial concentration of a drug substance by multiple consecutive dilution or grinding (trituration) with lactose that the end products of such a process have physicochemical and biological properties which are different from the initial substance properties [11–14]. The main feature of these release-active forms is their ability to exert a modifying influence on the starting material. Several drugs based on release-active antibodies have already been introduced into clinical practice and have a pro-antigen nature of action, caused by a direct modifying effect of these drugs on the appropriate antigen.

One of the most studied substances used for the preparation of antibody-containing RA drugs is the anti-IFN-gamma antibody. The efficacy and safety of drugs containing RA forms of Abs to interferon gamma have been extensively studied in various experimental models as well as in clinical studies [17–23]. It was shown during these studies that RA forms of Abs change the conformation and binding affinity of interferon gamma (IFN-gamma), demonstrated by changes in antigen-antibody interaction. Therefore, an enzyme-linked immunosorbent assay (ELISA) seems to be one of the most appropriate techniques for quality control of RA-based medicines. The purpose of the present study was to develop an ELISA that could permit detection of RA forms of Abs to IFN-gamma. The study involved a number of experiments to evaluate the applicability of the ELISA assay and determine the optimal conditions for the detection of the modulatory effect produced by RA forms of Abs to IFN-gamma, based on their ability to impact the specific binding of antibodies to interferon gamma.

RA Abs to be discussed:

RA Abs to IFN-gamma (IFNg)

IFN-gamma is a cytokine with antiviral and antiparasitic activities, inhibiting the proliferation of a number of cells.

RA Abs to S-100 protein (S100)

S-100 protein is a Ca^{2+}-binding neuropeptide which play an important role in appearance of depression, anxiety etc.

RA Abs to endothelial NO synthase (eNOS)

Endothelial NO synthase is an enzyme catalyzing the production of nitric oxide. This enzyme is one of the responsible for appearance of sexual motivation.

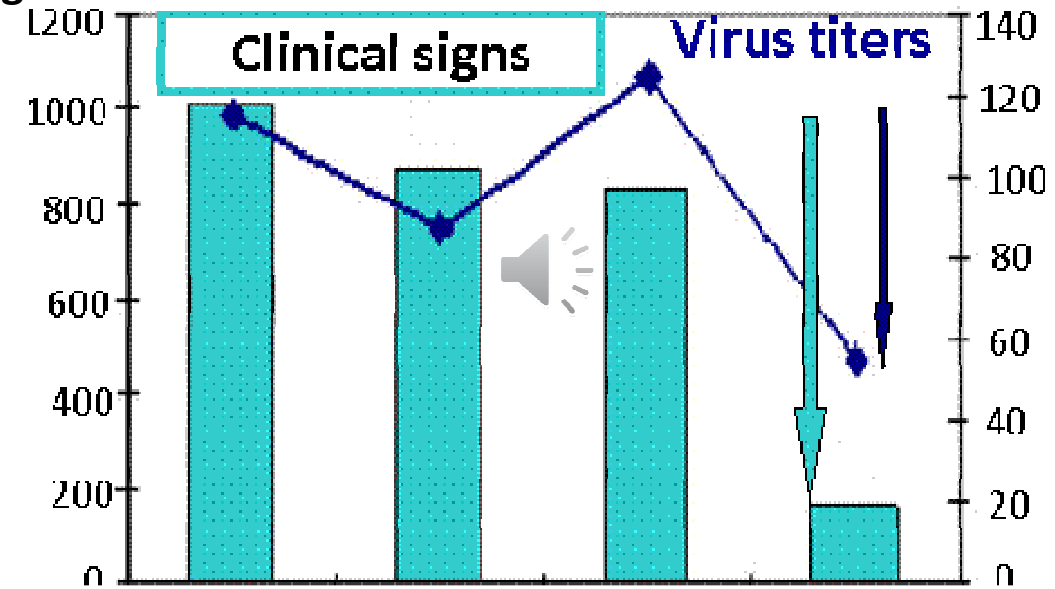
Efficacy of RA of Abs to interferon-gamma (IFNg): Antiviral activity against DNA-viral infections

Preclinical site: Research institute for epidemiology and microbiology (Russia)

Model: genital herpes (herpes simplex virus strain type 2) in guinea pigs

Points of clinical signs

Lg of virus titers

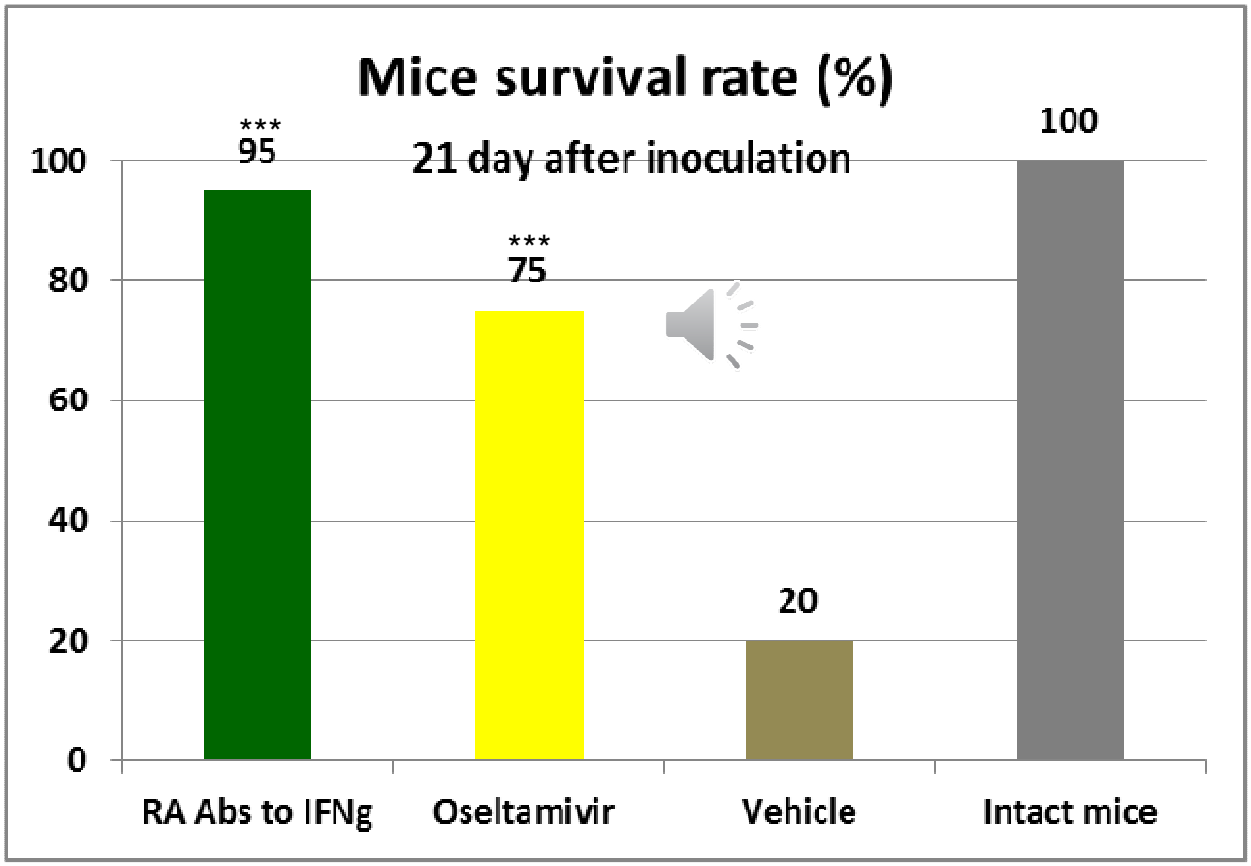


Conclusion: ***There were decreases of the virus titer and points of a clinical signs in RA Abs to IFNg group in comparison with control and reference standard group***

Epstein O.I., Vestnik MAN RS, 2008

Efficacy of RA Abs to IFNg: antiviral activity against RNA-viral infections

Preclinical site: APcis S.A. (France)
Virus: influenza A/Equine/2/Miami/1/63 (H3N8)



*** p<0.001 vs control

Conclusion: ***Survival rate in RA Abs to IFNg group was comparable to Oseltamivir group***

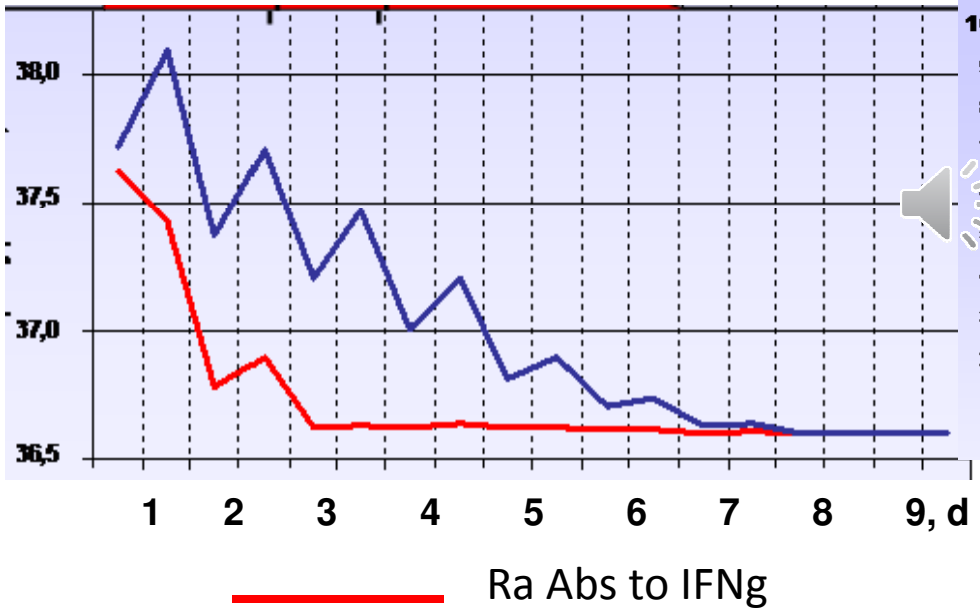
Submitted for publication

Clinical studies of RA Abs to IFNg
Antiviral activity against DNA-viral infection

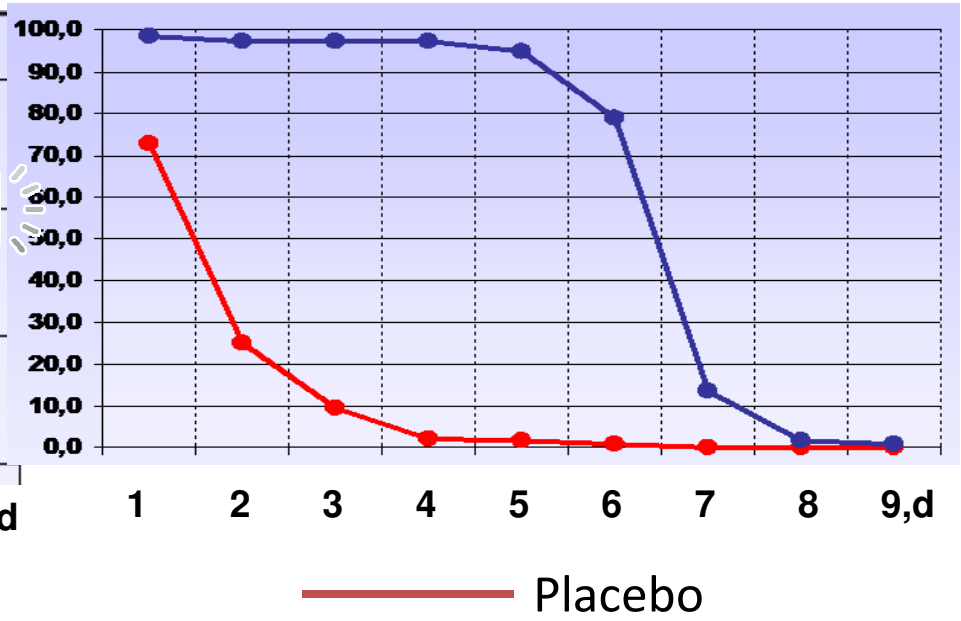
Site: Tomsk Institute of pharmacology (Russia)

Design: Randomized double blind placebo-controlled in 236 patients (1-18 y.o.) with chickenpox

The duration of fever



Percent of patients with itch



Ra Abs to IFNg

Placebo

<u>Conclusion:</u> Administration of Ra Abs to IFNg reduced the duration of fever at 2.7 days, the time of appearance of new lesions - 3.3 days, itch - 4.2 days.

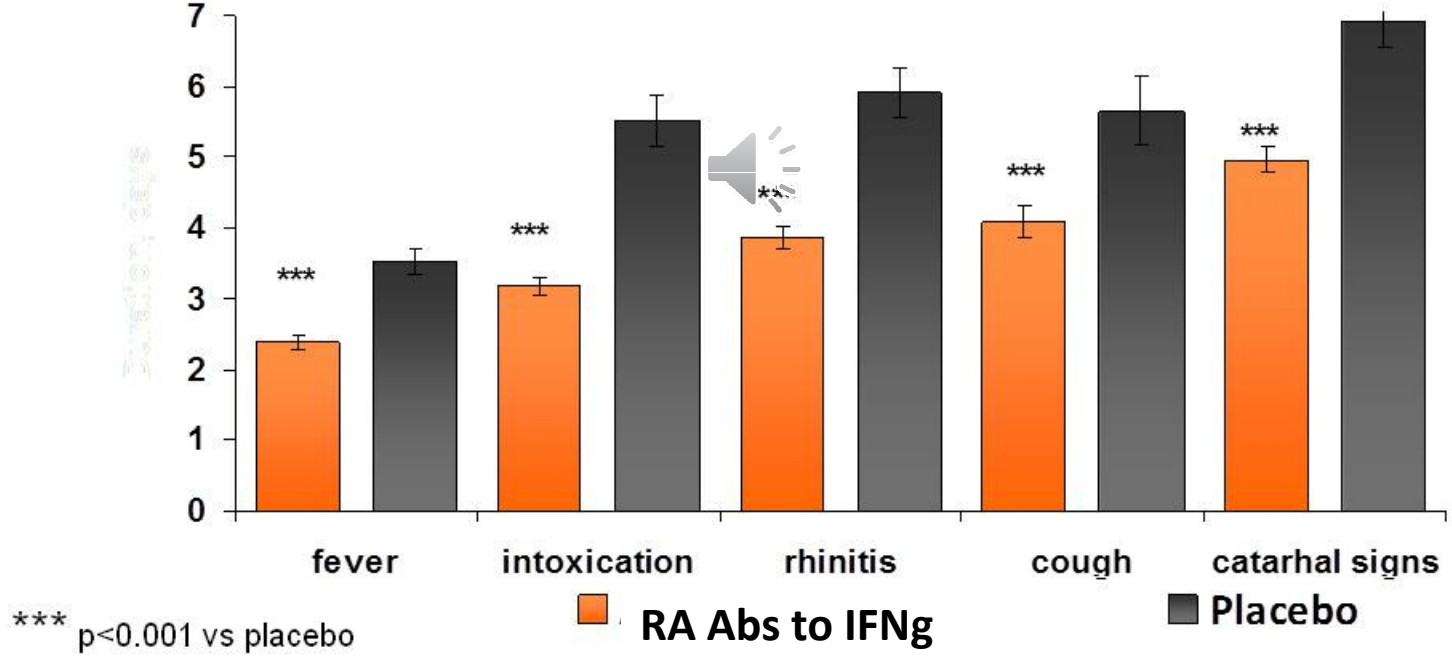
Kudin M.V. et al, CHILDREN INFECTIONS, 2007

Clinical studies of RA Abs to IFNg
Antiviral activity against RNA-viral infections

Site: Influenza institute (Russia); Russian State Medical University (Russia)

Design: Randomized double blind placebo-controlled in 255 patients (0.5 – 14 y.o.) with upper respiratory viral infections

Duration of major clinical signs (days)



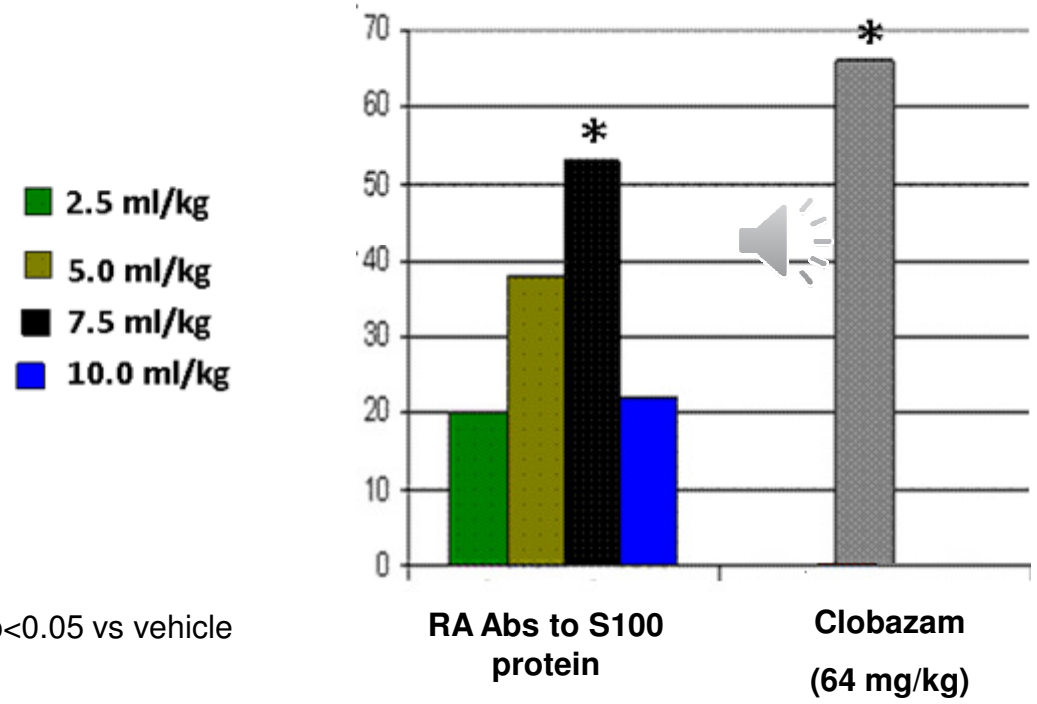
Conclusion: ***Administration of RA Abs to IFNg significantly reduced the duration of clinical signs in comparison with placebo***

Efficacy of RA Abs to S-100 protein: anxiolytic activity

Preclinical site: Porsolt & Partners Pharmacology (France)

Model: Vogel conflict test

Number of shocks (% vs vehicle)



* p<0.05 vs vehicle

Conclusion: ***There are significant increase in a numbers of shocks in RA Abs to S-100 group in comparison with vehicle***

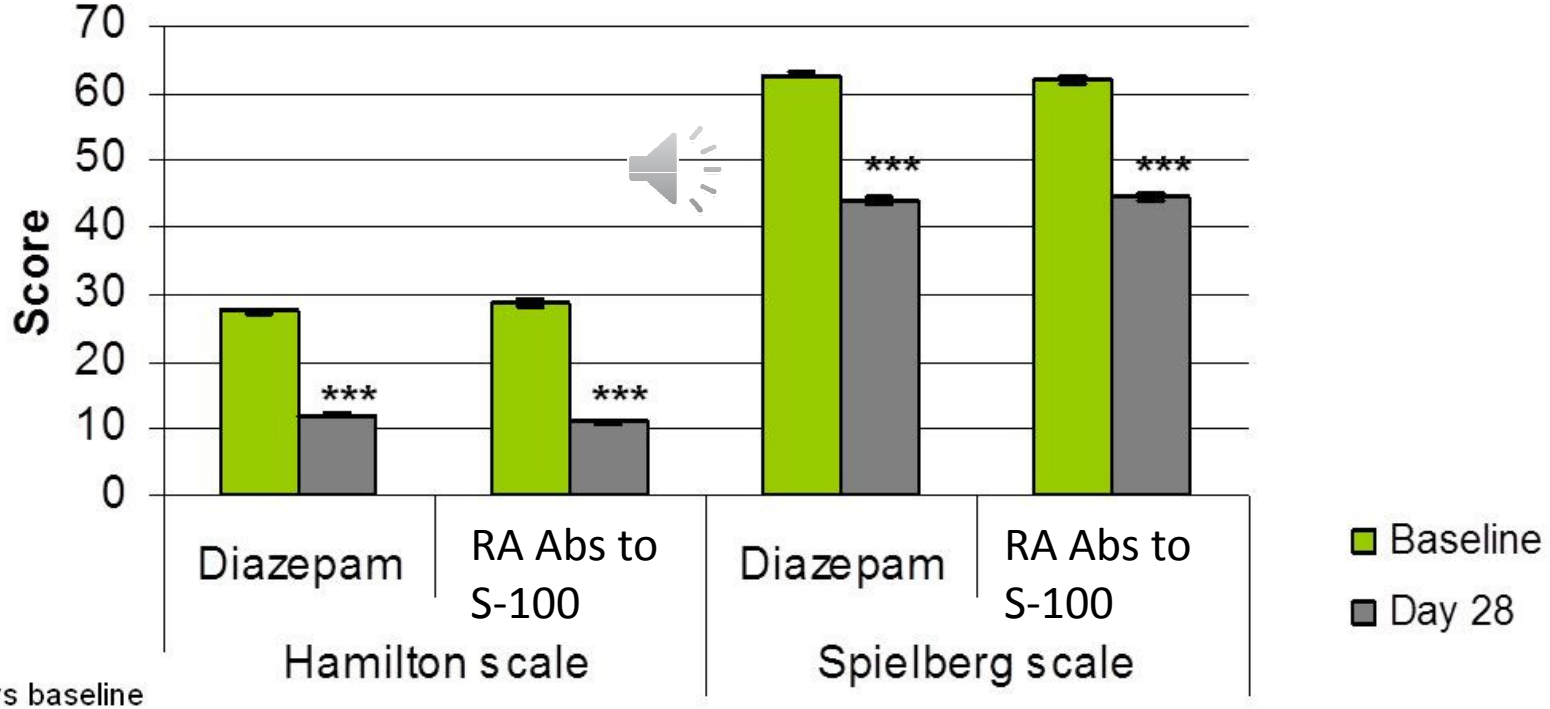
Castagne V., et al //JPP, 2008

Clinical studies of RA Abs to S-100 protein: anxiolytic activity

Sites: Four Russian clinical sites

Design: Randomized clinical study in 247 patients (18 – 65 y.o.) with anxiety disorders in comparison with diazepam

Clinical signs assessed by scales



*** p<0.001 vs baseline

Conclusion: ***Anxiolytic activity of RA Abs to S-100 is close to one of Diazepam***

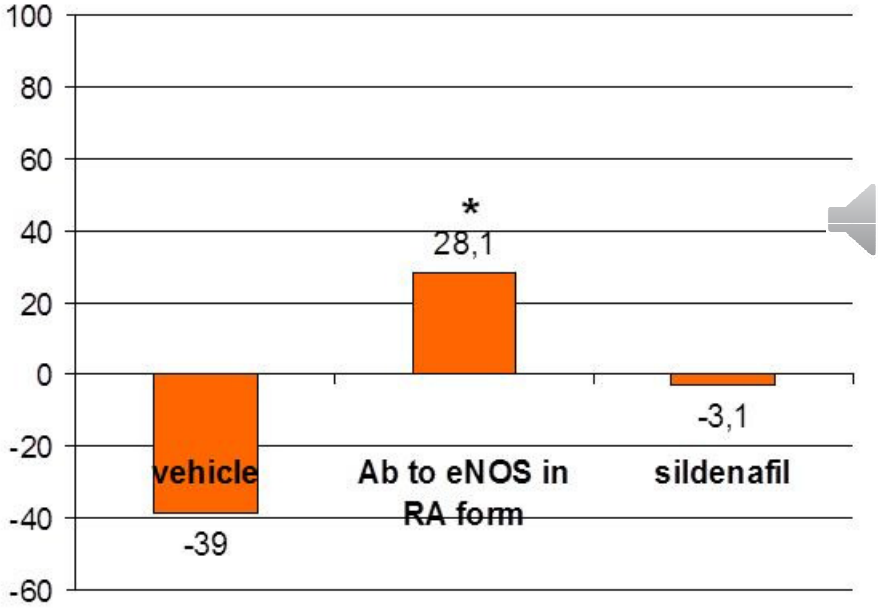
Martyushev-Poklad A, et al //The Practitioner 2006

Efficacy of RA Abs to endothelial NO-synthase (eNOS): sexual activity

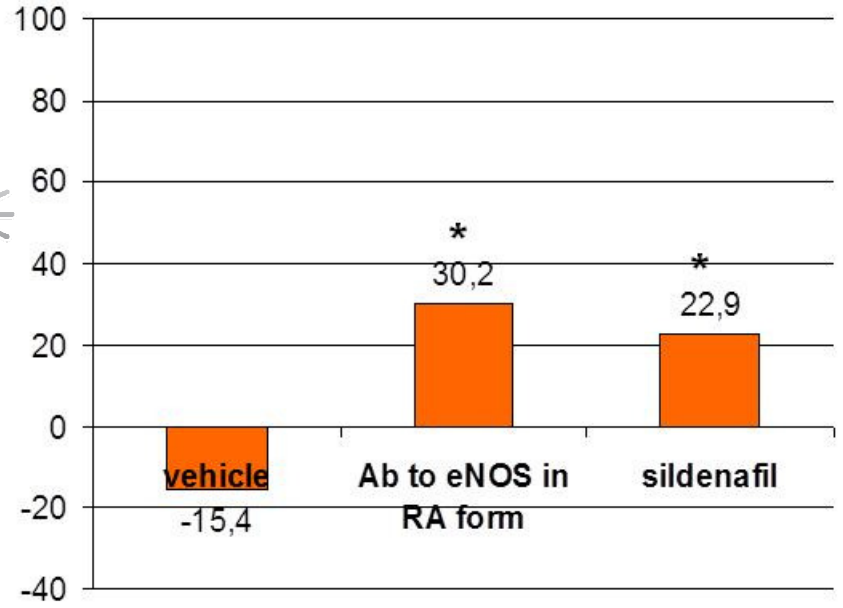
Preclinical Site: University of Tromsoe (Norway)

Model: assessment of sexual activity of Fischer 344 rats

Change in preference score on day 28 of treatment (% vs baseline)



Change in intromission ration on day 28 of treatment (% vs baseline)



* p<0.05 vs vehicle

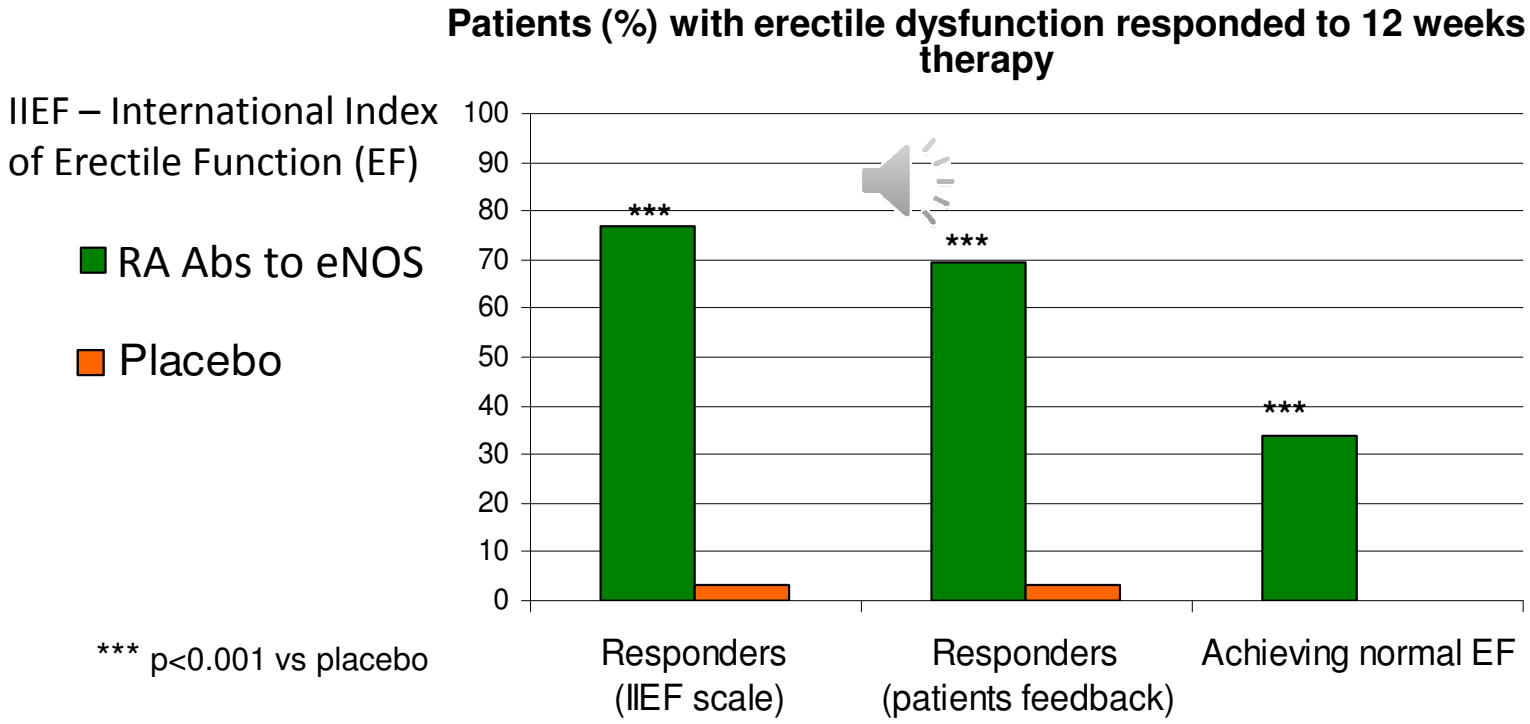
***Conclusion:* Sexual activity of rats increased after receiving of RA Abs to eNOS in comparison with sildenafil and vehicle group**

Chu X and Agmo A,// Pharmacol Biochem Be, *2008*

Clinical studies of RA Abs to eNOS: patients with erectile disfunction

Sites: Four Russian clinical sites

Design: Randomized double blind placebo-controlled clinical trial in 169 patients (18 – 70 y.o.) with erectile disfunction



*** p<0.001 vs placebo

Conclusion: ***There is an significant activity of RA Abs to eNOS in comparison to placebo***

Tarasov S.A. et al //Signatura, 2007

Toxicological studies

Experimental sites:

- Research Institute of Pharmacology (Tomsk, Russia),
- Volgograd State Medical University (Volgograd, Russia)

Studies:

- Single-dose (acute)toxicity study
- General toxicity study
- Cumulation studies
- Study of mutagenic properties
- Study of allergenic properties
- Study of reproductive toxicity
- Study of postnatal development

Experimental animals:

- mice,
- rabbits,
- guinea pigs,
- rats (including sexually immature and infant)

Route of administration:

- oral
- intraperitoneal
- subcutaneous

Conclusion:

No toxic effects of RA Abs have been revealed exerts positive effect on lactating females (general condition, body weight gain) and postnatal development (facilitates cognition process and memory trace reproduction)

Drugs safety assessment in clinic studies

Sources of data

Safety assessment of the drugs during the clinical studies:

1. The assessment in the course of every planned visit via questioning of patients
2. the assessment of vital functions:
3. the assessment of main laboratory rangers:
   - ✓clinical blood analysis
   - ✓clinical urine analysis
   - ✓biochemical markers

Data from regulatory bodies of countries where the drugs have been registered (15 countries) on adverse events associated with the drug use

Spontaneous reports on adverse events

Reports in international press on adverse events associated with the drug use

Conclusion

✓ The available data indicates no adverse events associated with the drug use

Main advantages of RA Ab as therapeutic agents

Key Advantages

- High safety: has been used for 14 years and in ~100 mln patients
- High efficacy: demonstrated in clinical studies conducted

(the same or even better than that of the reference drugs)

- Oral use
- Possibility to combine with other medicinal drugs
- Low price
- Platform to rapidly screen and develop new drugs

Medical Benefits

- ➢ Long-term use possible
- ➢ Use in pediatric practice
- ➢ Use in patients with concomitant diseases
- ➢ Use for disease prophylaxis

Future prospects

- ○Platform to rapidly screen and develop new drugs
- ○Possibility of testing a plenty of different targets

Thank you for your attention!



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