February 25, 2014 Type C FDA Meeting

Copaxone® (glatiramer acetate injection) 20mg/ml

Teva Pharmaceutical Industries, Ltd

Presentation Outline

- ❑ **Introduction**
- ❑ **Clinical Perspective**
- ❑ **Comparison** Between Purported Generics and Copaxone
- ❑ **Regulatory considerations**
- ❑ **Expert opinion:** Dr. Lawrence Steinman
- ❑ **Summary**

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Purpose and Attendees

Purpose of Meeting: to present scientific data on Copaxone's complexity and mode-of-action in consideration of **evidentiary standards** for follow-on products

Name	Title
Michael Hayden, M.D., Ph.D	President of Global R&D and CSO, Teva
Volker Knappertz, M.D., D.M.Sc.	VP, Head of MS Global Clinical Development, Teva
James Ottinger	SVP, Regulatory Affairs, Teva
Dennis Ahern	Sr. Director, CNS & Oncology Regulatory Affairs, Teva
Mike Nicholas, Ph.D	VP, Specialty Life Cycle Initiatives Global R&D, Teva
Valerie Mulligan	Sr. Director, CMC, Regulatory Affairs
Vera Weinstein, Ph.D	Director, Scientific Affairs, Teva
Iris Grossman, Ph.D	Sr. Director, Global Head of Personalized Medicine & Pharmacogenomics, Teva
Lawrence Steinman, M.D.	Prof. Neurology & Neurological Sciences, Stanford School of Medicine
Ben Zeskind, Ph.D., M.B.A.	CEO, Immuneering Corporation
Nick Fleischer, Ph.D.	VP, The Weinberg Group

Copaxone (glatiramer acetate for injection)

- **Approval and Access:**
  - Approved in the U.S. since **1996**
  - Indicated for **relapsing forms of multiple sclerosis**
  - **Identical** formulation in **57 countries worldwide**
- **Manufacturing:**
  - Proprietary manufacturing process **ensures antigen homology**

Regulatory and Scientific Issues

- **Complex mixture formulation,** where differences in composition could confer **different biological activity**
- Locally acting, rendering **pharmacokinetics irrelevant**
- **Lack of validated biomarkers**
- **Immunogenic potential**
- The **risk** of approval of a generic to Copaxone is **compromised efficacy and safety**

Teva's Position

- There is **no replacement** for **adequate, well-controlled clinical trials** for assuring that a generic to Copaxone will be a safe and effective alternative for treating MS patients
- Why would **concerns** around characterization of a generic to Copaxone be **less than for biosimilars**, most of which **are far better understood and less complex than Copaxone?**

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Copaxone Efficacy Profile

Annual Relapse Rate (ARR)

(Treatment effect compared to placebo, N>2,500)

Study	Copaxone dose	Risk Ratio [95% CI]	P value	Reference
9001	20mg QD	**0.72 [0.56, 0.93]**	0.007	Johnson, 1995
9003	20mg QD	**0.68 [0.49, 0.94]**	0.012	Comi, 2001
CONFIRM	20mg QD	**0.72 [0.55, 0.92]**	0.01	Fox, 2012
GALA	40mg TIW	**0.66 [0.54, 0.80]**	<0.0001	Khan, 2013

Copaxone Efficacy Profile is CONSISTENT

Consistent ARR effects

Active comparator trials

Study	Copaxone 20mg qd ARR	Comparator	Comparator ARR	P value	Reference
REGARD	**0.29**	IFNβ-1a 44 µg TIW	0.30	0.828	Mikol, 2008
BECOME	**0.33**	IFNβ-1b 250µg QOD	0.37	0.68	Cadavid, 2009
BEYOND	**0.34**	IFNβ-1b 250 µg QOD IFNβ-1b 500 µg QOD	0.36 0.33	0.79 0.42	O'Connor, 2009
FORTE	**0.33**	Copaxone 40mg QD	0.35	0.486	Comi, 2011
COMBIRX*	**0.23**	IFNβ-1a 30µg QWK Copaxone + IFNβ-1a	0.32 0.23	0.008 0.44	Lublin, 2013

** NIH-funded*

Well-Established Safety Profile

Copaxone has a **favorable** safety profile with approximately **2,000,000 patient-years exposure**

Label Information		
Adverse events occurring >3% more frequently on Copaxone compared to placebo	• Injection site reactions • Vasodilatation • Dyspnea • Rash • Chest pain	• Edema • Palpitations • Lymphadenopathy • Nausea
Warnings and precautions	• Immediate post-injection reaction • Chest pain • Lipoatrophy and skin necrosis • Potential effects on immune response	
Pregnancy	Category B	

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Comparing Copaxone to Purported Generics

Physicochemical Properties

Copaxone: Physicochemical Characterization

- Characterization of **fragmented** products compared to the **entire mixture**
- **Similarities** are observed between Copaxone and purported generics, particularly when using common non-specific analytical methods
- **Differences** are observed between Copaxone and purported generics in **key elements of Copaxone's physicochemical properties: composition, size and charge distribution**

Copaxone: Fragments vs. the Entire Mixture

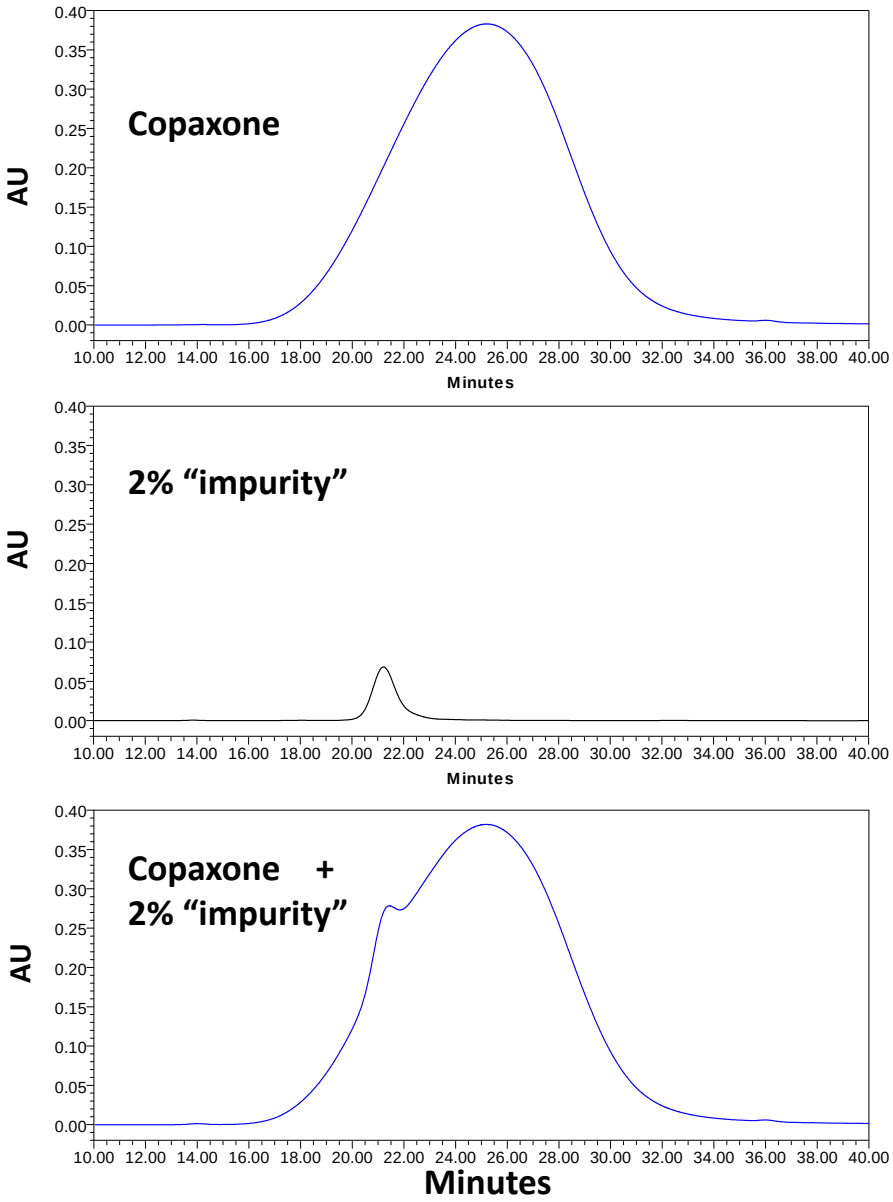
- Characterization of **fragmented** products compared to the **entire mixture**

- **Similarities** are observed between Copaxone and purported generics, particularly when using common non-specific analytical methods

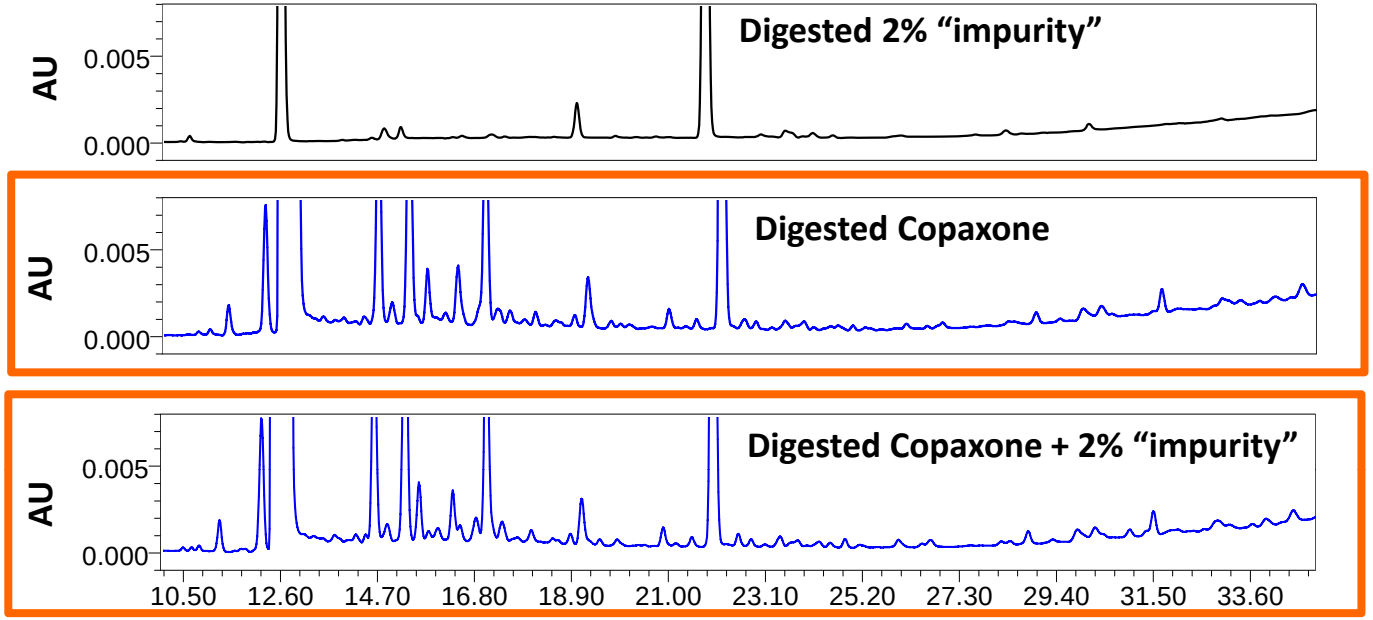
- **Differences** are observed between Copaxone and purported generics in **key elements of Copaxone's physicochemical properties: composition, size and charge distribution**

Sensitivity to Impurities in the Intact Form

- Size Exclusion Chromatography of the intact form **detects "impurity"** in a Copaxone mixture
- **"Impurity"** – a foreign peptide comprising the **same amino acids** in the **same ratio**



Insensitivity to Impurities in the Fragmented Form



- Enzymatic hydrolysis Reverse-Phase High-performance liquid chromatography (RP-HPLC) of the same mixtures detected **no difference between pure and contaminated** Copaxone

Conclusion:

- Methodologies based on analysis of **fragmented forms** are **not sufficient** for assessing small differences in quality and physicochemistry

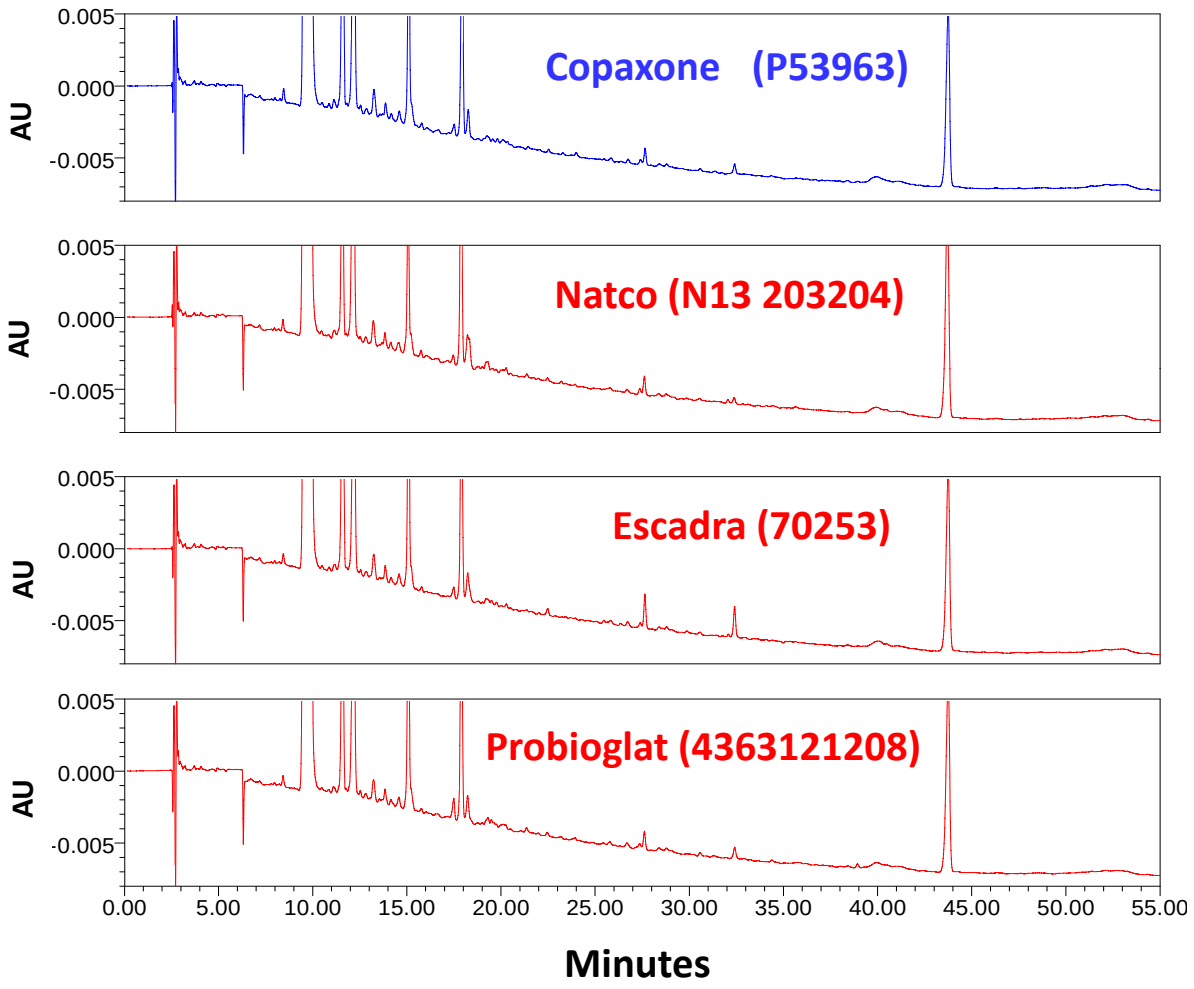
Purported Generics Analyzed Physicochemically

Compound	**Company/ Product**	**Market**
Copaxone *glatiramer acetate (GA)*	Teva	57 countries worldwide
Glatimer *Purported generic GA*	Natco	India
Probioglat *Purported generic GA*	Probiomed	Mexico
Escadra *Purported generic GA*	Raffo	Argentina

Purported generics to Copaxone under review in the US were publically requested without success

Peptide Maps by RP-HPLC

Upon enzymatic digestion and RP-HPLC **no significant difference** observed between Copaxone and different purported generics



Physicochemical Similarities

Similarities are observed between Copaxone and purported generics, particularly when using common non-specific analytical methods

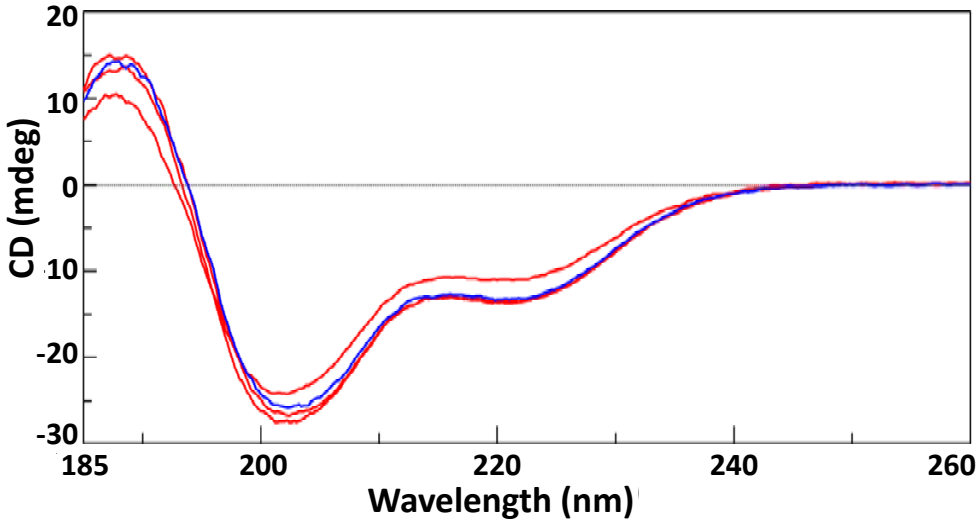
Similarities of Copaxone & Purported Generics

0.129-0.153 L-glutamic acid
0.392-0.462 L-alanine
0.086-0.100 L-tyrosine
0.300-0.374 L-lysine

Copaxone Natco Escadra Probioglat

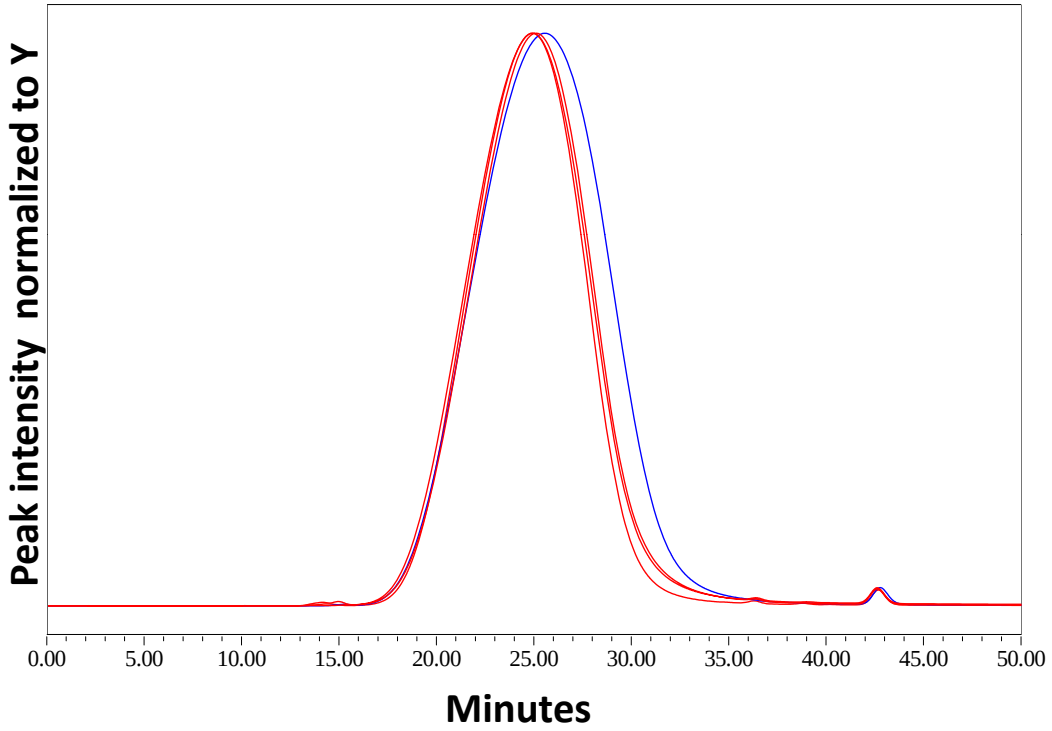
- **Basic composition**: the same amino acid ratio composition in Copaxone and purported generics

- **Higher order structure** by Circular Dichroism (CD) appears similar for Copaxone overlaid by Natco, Escadra and Probioglat



Molecular Weight Distribution by SEC

- **Hydrodynamic size of the constituents**: molecular weight distribution by Size Exclusion Chromatography (SEC) appears similar for Copaxone overlaid by Natco, Escadra and Probioglat

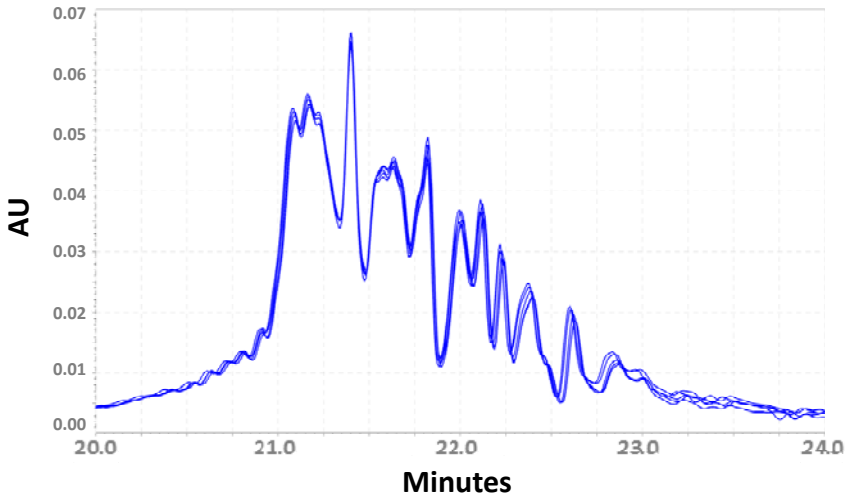


Physicochemical Differences

Differences are observed between Copaxone and purported generics in **key elements of** Copaxone's physicochemical properties: **composition, size and charge distribution**

Consistent Charge Distribution of Copaxone Lots

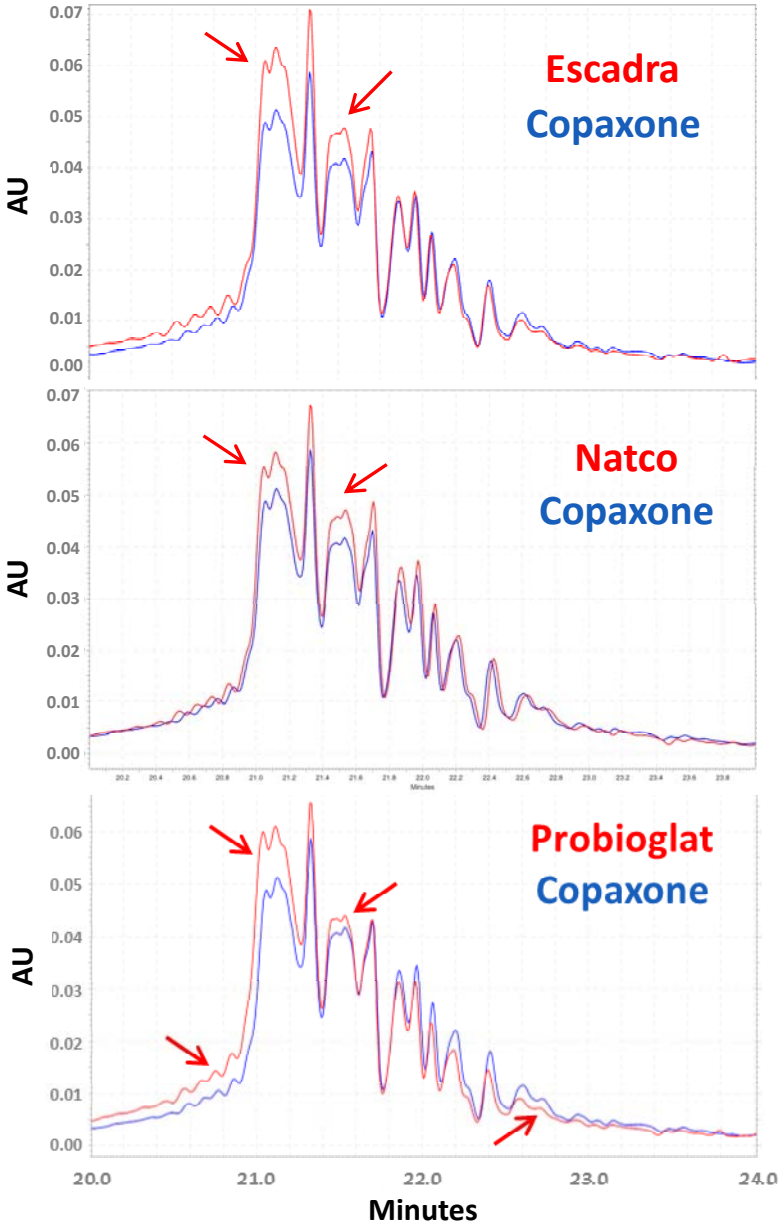
- **Charge distribution pattern** of **5** randomly chosen Copaxone batches shows **tight consistency** based on capillary electrophoresis (CE)



Charge Distribution of Purported Generics

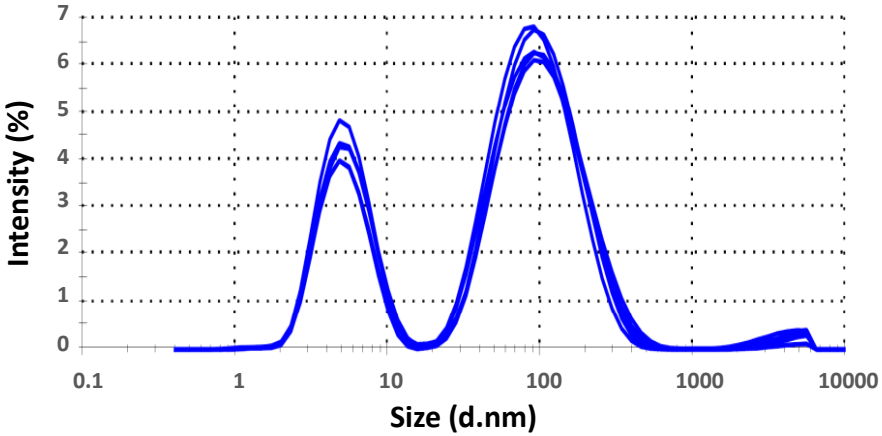
- **Distribution pattern** from capillary electrophoresis (CE) is **different for each glatiramoid**, demonstrated by Copaxone overlaid on Natco, Escadra and Probioglat

- Differences in **charge distribution (composition)** are highlighted by **red** arrows



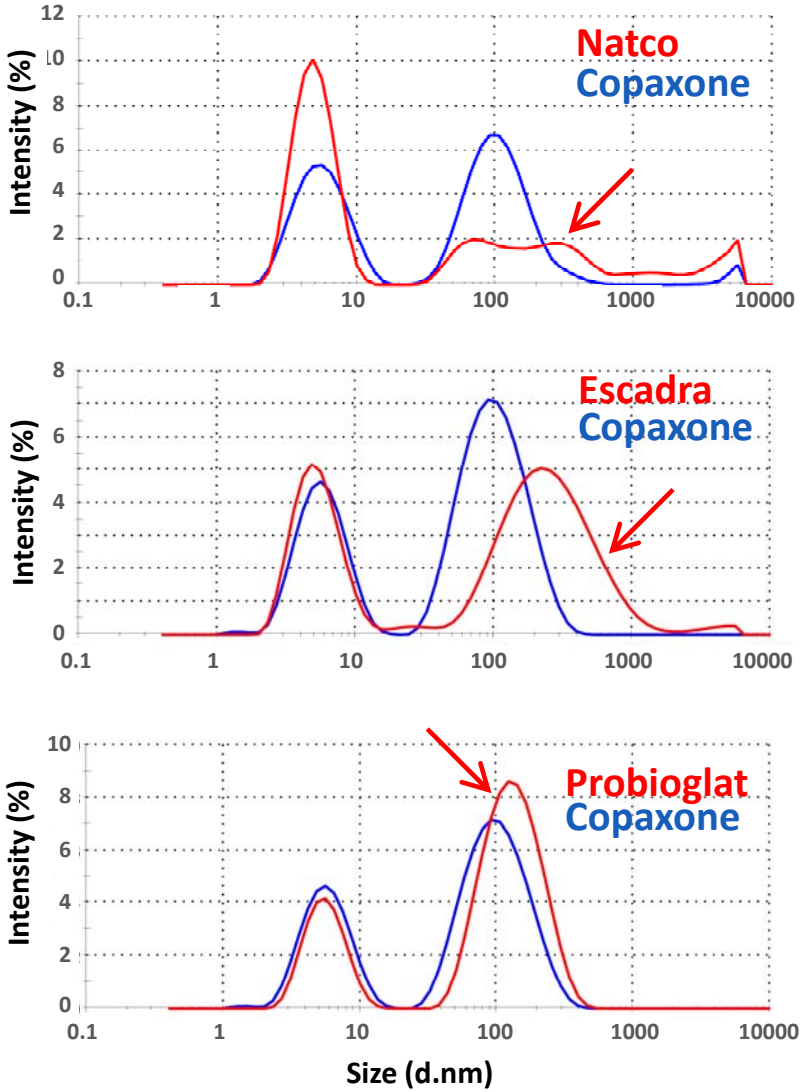
Particle Size Distribution of Copaxone Lots

- Analysis of **10** randomly chosen Copaxone batches shows **minimal size differences** by Dynamic Light Scattering (DLS)



Particle Size Distribution of Purported Generics

- **Difference in aggregate size** in colloidal solutions of Copaxone and purported generics as detected by DLS



Cutting-Edge Higher Information Content Methods

- **Ion Mobility Mass Spectrometry (IMMS)** is a well established, robust technology routinely used to analyze proteins/peptides
- **Ion mobility** separates isomeric peptides that chromatographic techniques cannot *(e.g., liquid chromatography, capillary electrophoresis)*
- *HDMS Compare software* (Waters), unveiled **mid-2012:** detects and visualizes **differences between apparently identical samples**
- **Key analytical tool** used in characterization of biologics

Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars

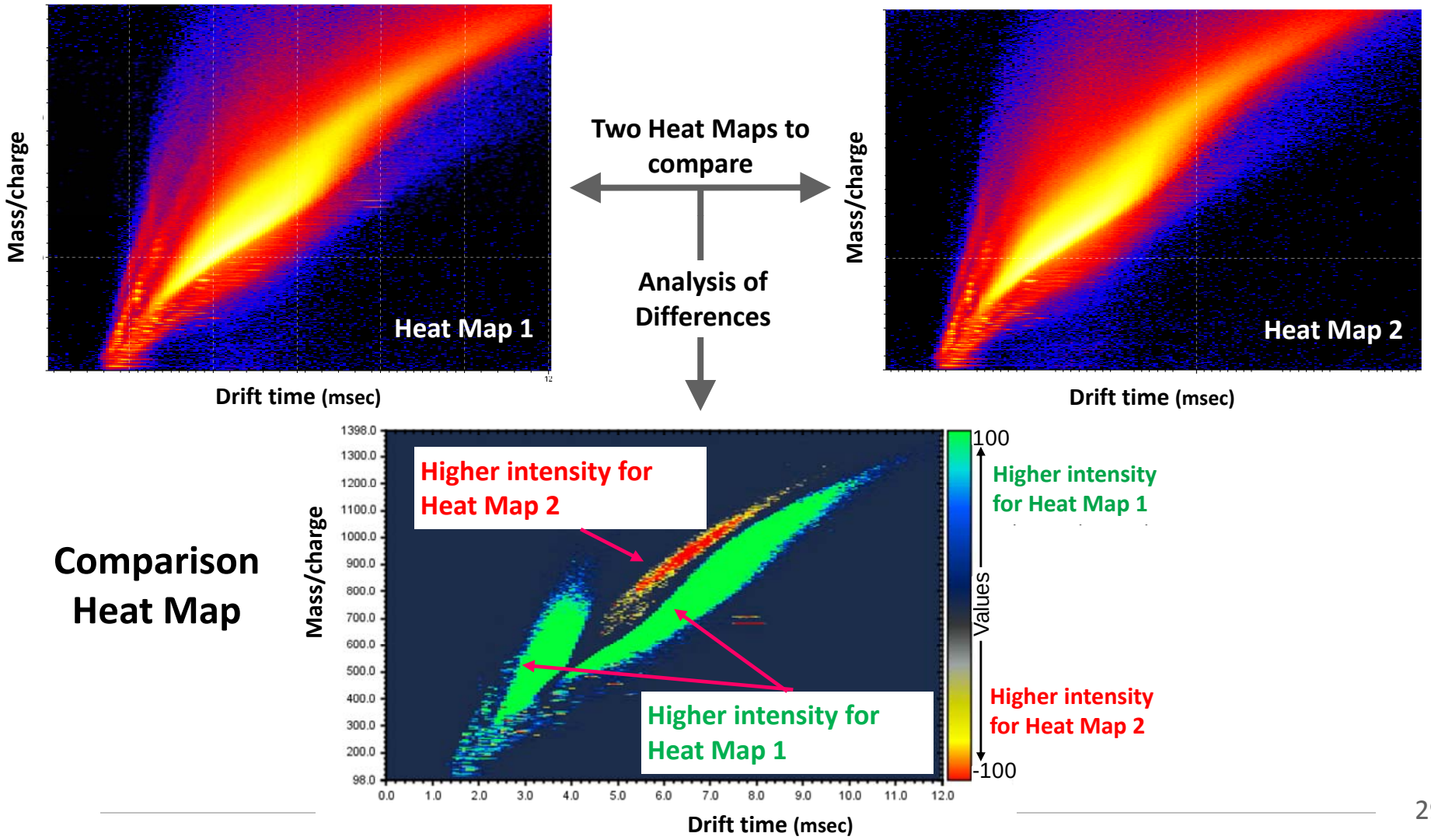
Steven A. Berkowitz[1], John R. Engen[2], Jeffrey R. Mazzeo[3] and Graham B. Jones[2]

2012, 11: 527-540

nature REVIEWS DRUG DISCOVERY

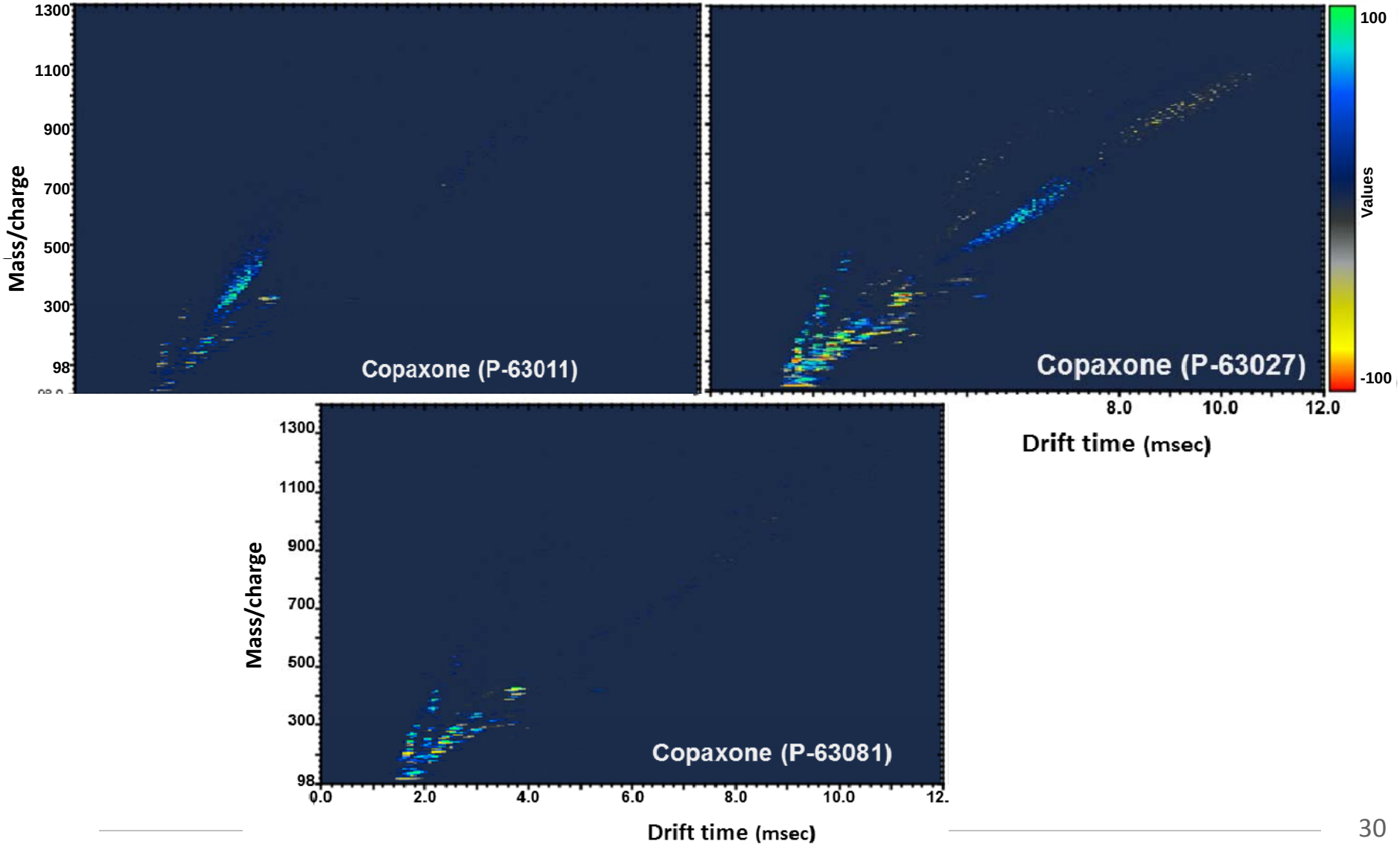
Comparing Heat Maps to Identify Differences

The *HDMS Compare Software* evaluates **each pixel** from two Heat Maps and calculates differences



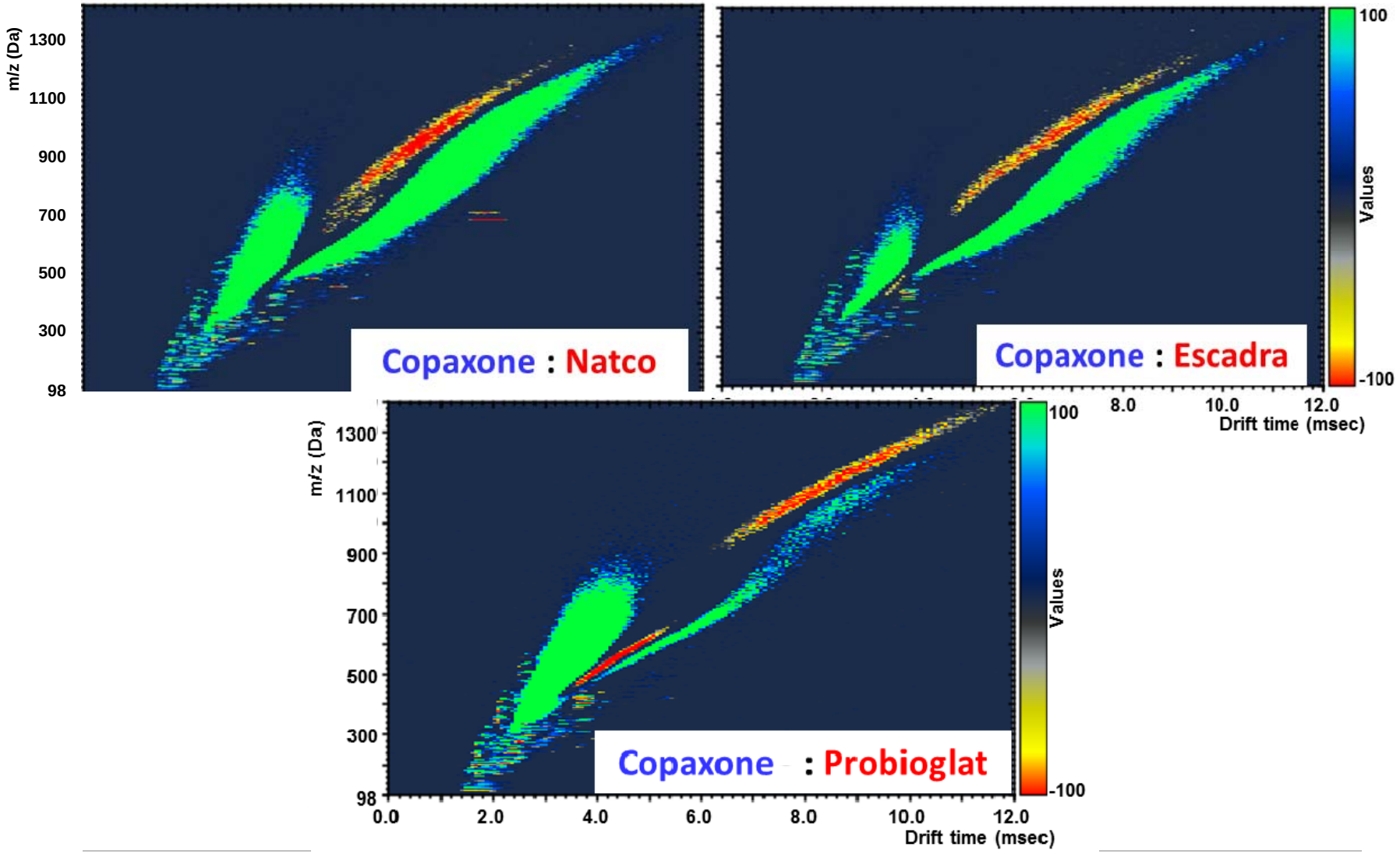
Copaxone Lot Variability is Minimal

Copaxone (P-53961) compared to 3 Copaxone Lots

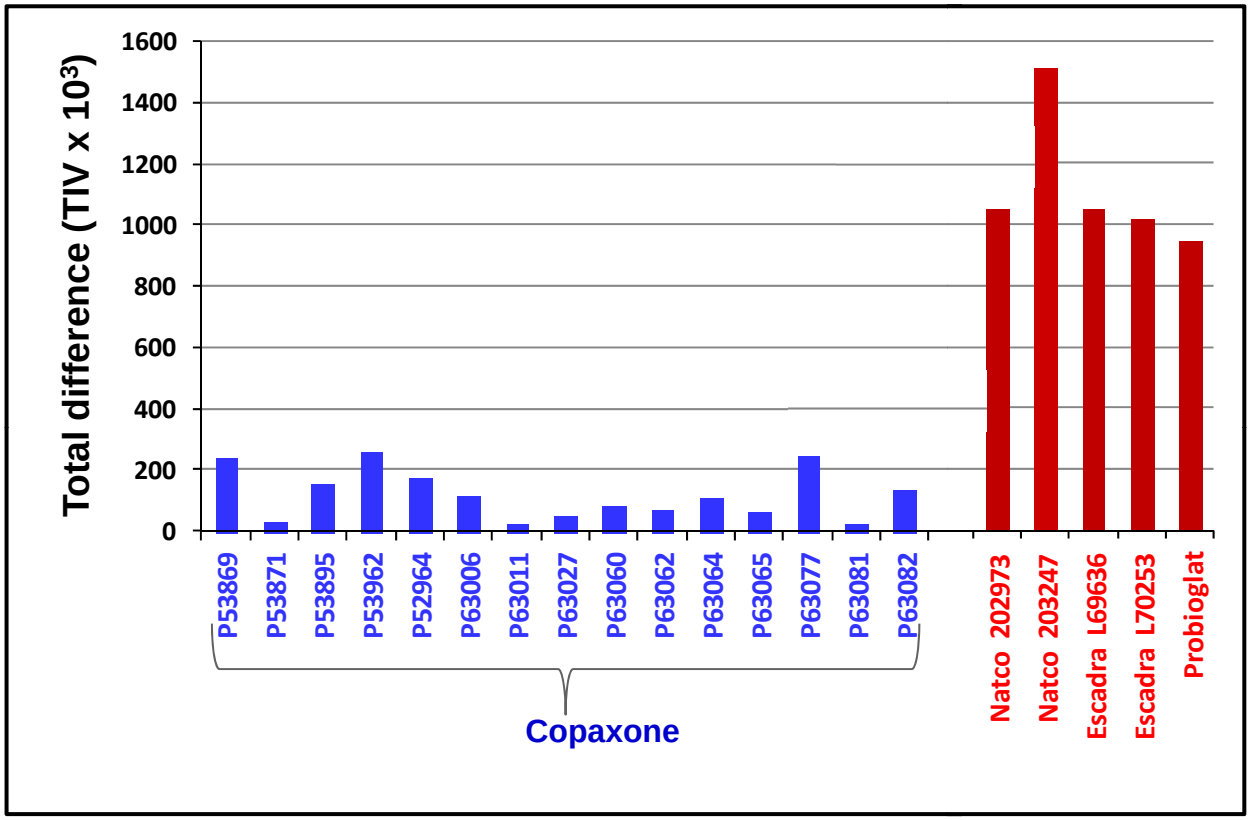


Profound Differences Copaxone vs. Purported Generics

Copaxone (P-53961) versus 3 Generics - (4 injections each)



Total Intensity Value Comparison



Conclusions:

- IMMS results indicate a **combination of differences** between Copaxone and purported generics in **amino acid sequence, size, charge and shape** of the product

Summary: Physicochemical Analysis

- Copaxone is a **highly consistent** complex product manufactured by TEVA's proprietary process

- **Differences can be overlooked** when investigating fragmented peptides
  - **Direct comparison** of fragmented purported generics to market reference Copaxone is therefore **not informative**
  - Meaningful comparison can best be established **in the intact state**

Conclusions

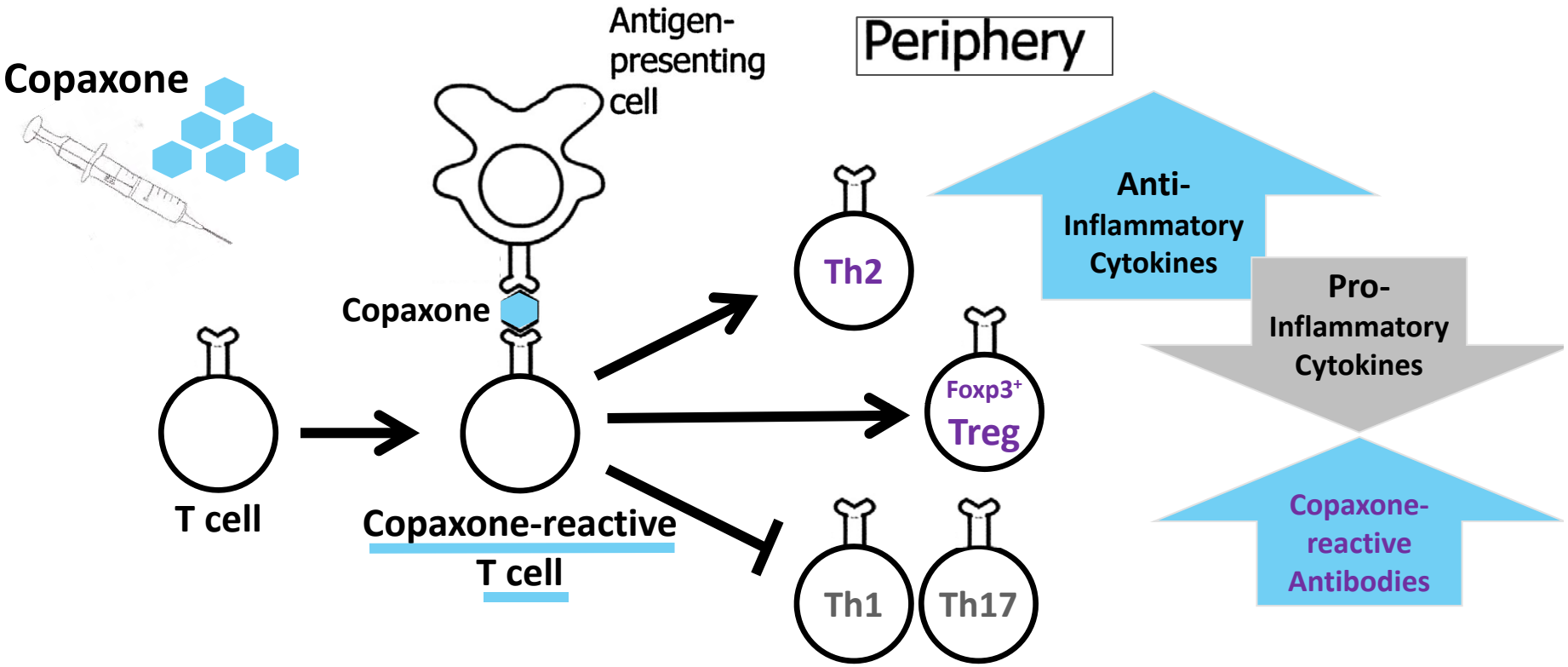
- **Reverse engineering** of Copaxone from fragmented structures does **not capture** the intact complex material and its **pharmaceutical properties**

- The specific set of methods that can capture overall bioequivalence, correlating with efficacy and safety, **has yet to be defined**

Comparing Copaxone & Purported Generics

Gene Expression Analysis

Antigenicity of Copaxone is Critical to its Function



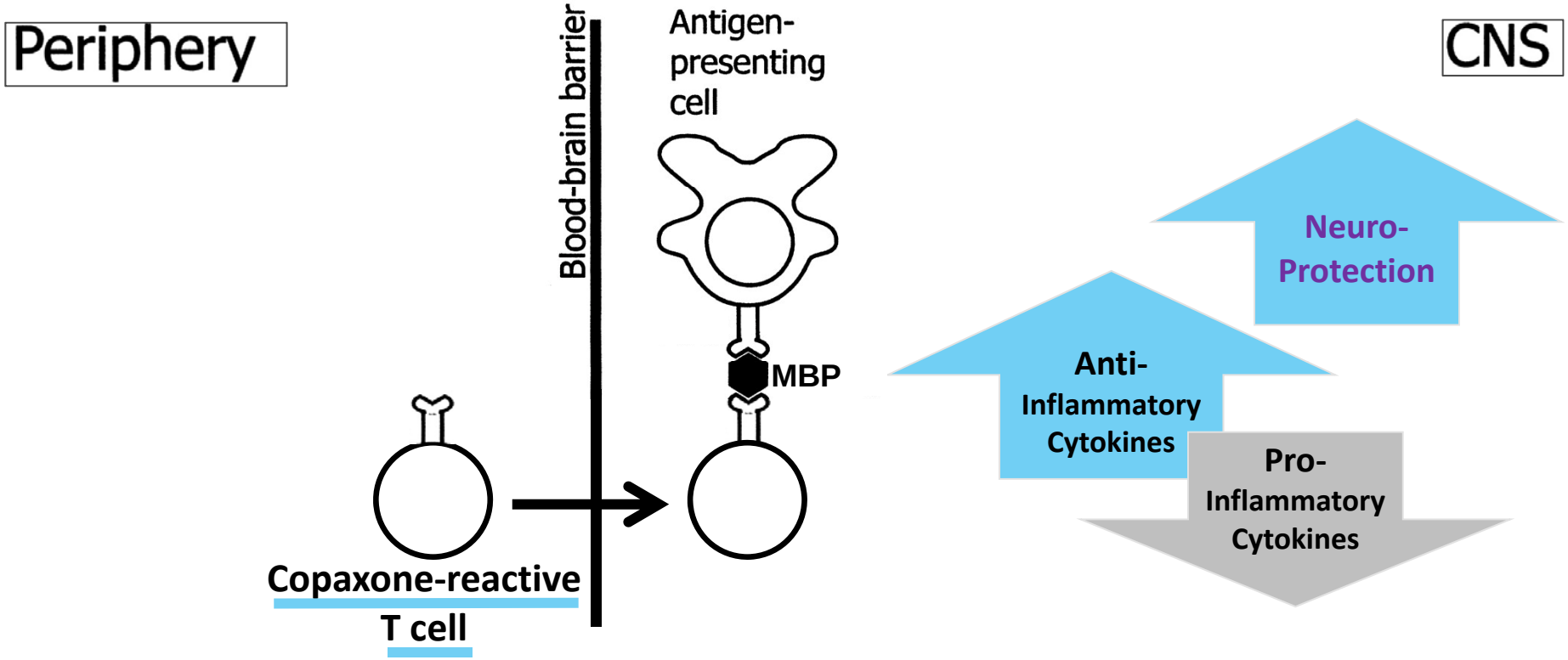
- Copaxone is an **antigen** that binds to antigen presenting cells (APCs), inducing a specific shift from pro-inflammatory (Th1/Th17) to **anti-inflammatory Th2, regulatory T (Foxp3$^+$ Treg)**, and B cells

- Copaxone also induces non-neutralizing, **Copaxone-reactive specific antibodies** that are associated with clinical response**

TCR = T-cell receptor. **Treg** = regulatory T cell. **Th** = T helper cell. **Foxp3** = Forkhead box P3 transcription factor.

Figure modified based on Hohlfeld,& Wekerle, *PNAS* (2004). *Farina et al, *J Neuroimmunol* (2002); Brenner et al, *J NeuroImmunol* (2001)

Current Understanding of MoA in the CNS

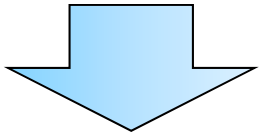


- **Copaxone-reactive Th2 and Foxp3+ Treg cells migrate into the CNS** and cross react with Myelin Basic Protein (MBP) and other autoantigens, inducing secretion of **anti-inflammatory cytokines**
- Copaxone induces secretion of neurotrophic factors (e.g. BDNF, NT-3, NT-4)

Figure modified based on Hohlfeld,& Wekerle, *PNAS* (2004)

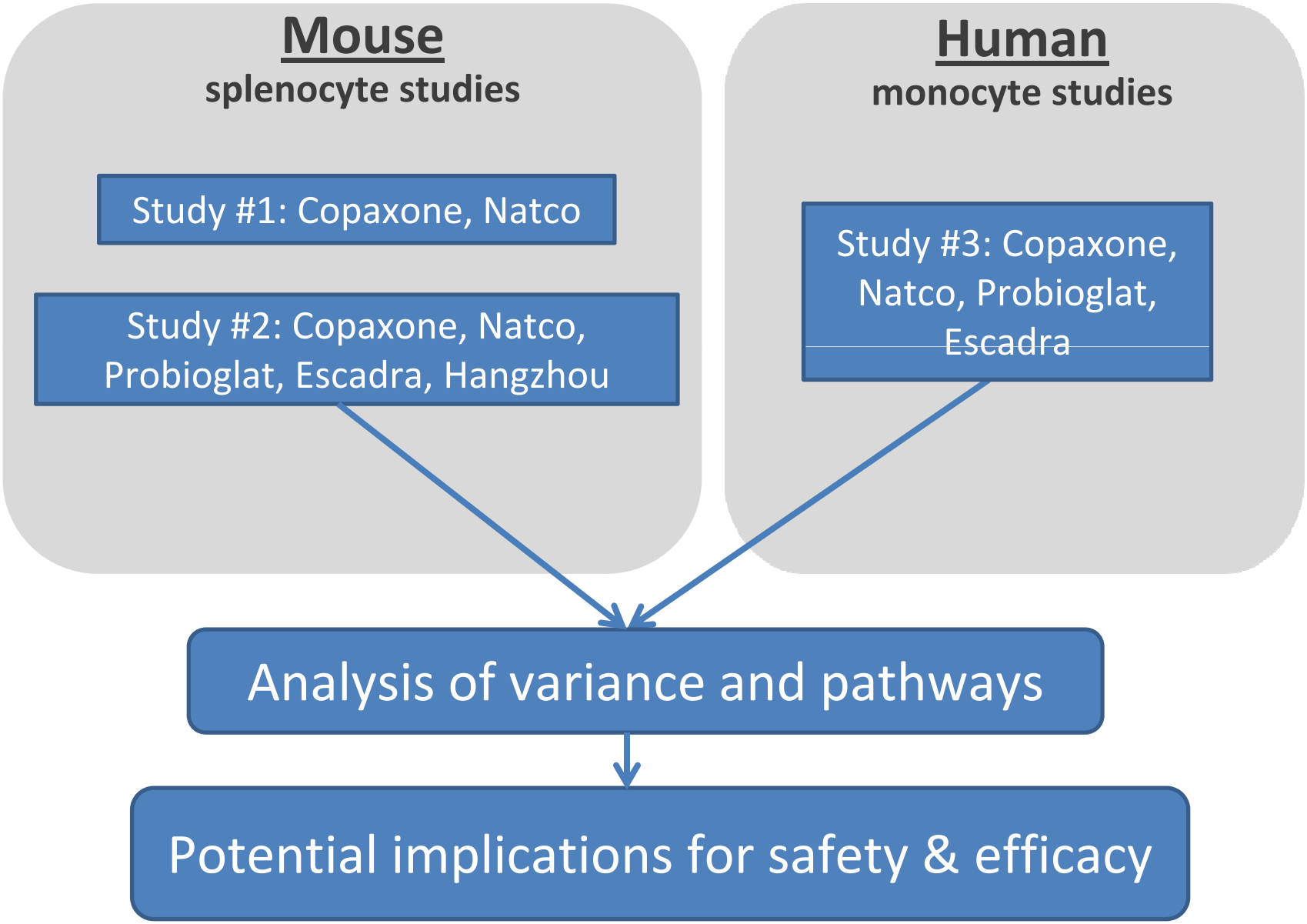
Copaxone Gene Expression Studies: Rationale

Traditional biological characterization methods, (e.g. ELISA, secreted cytokine screens), are **insufficient** to fully characterize Copaxone's **mode of action**

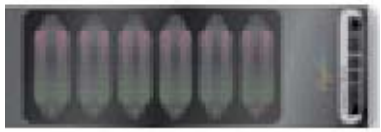


Gene expression arrays provide a **broader and more comprehensive analysis** of pathways modulated by Copaxone, helping to elucidate its **functional effects**

Experimental Roadmap: Mouse & Human Studies



State-of-the-Art Gene Expression Arrays



Mouse

splenocyte studies

Illumina MouseWG-6 v2.0 chip: 45,000+ transcripts

We used the most "up-to-date content for mouse whole-genome expression profiling"
[Illumina.com, February 2014]

Human

monocyte studies

Affymetrix U133 plus 2.0 chip: 47,000+ transcripts

We used the "most comprehensive whole human genome expression array …"
[Affymetrix.com, February 2014]

Independent State-of-the-Art Data Analysis

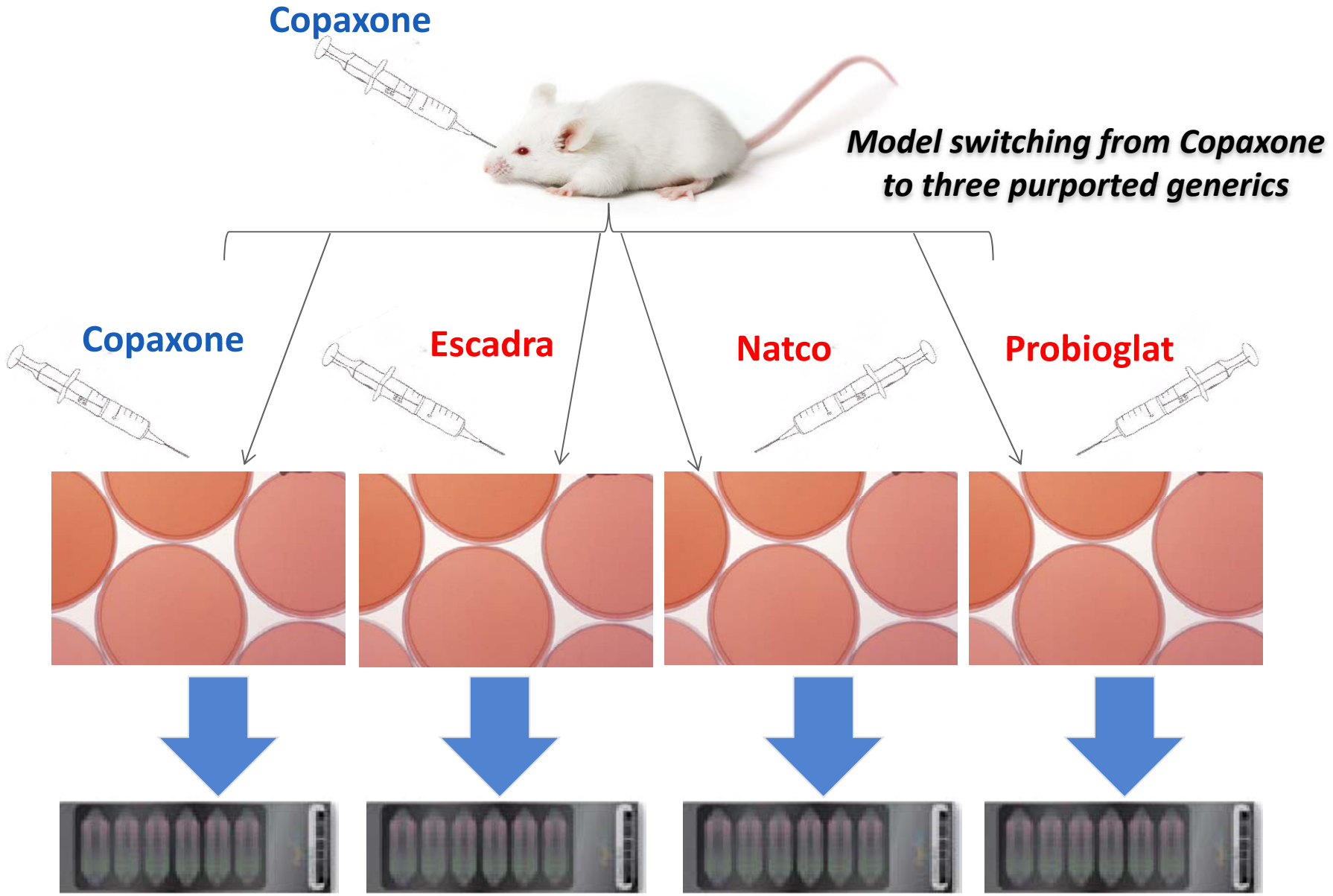
- **Immuneering provides independent, advanced data analysis services to many leading pharmaceutical companies including Teva**

- Immuneering specializes in analyzing gene expression and genomic data to identify key **biological mechanisms**

Immuneering's Team and Advisory Board

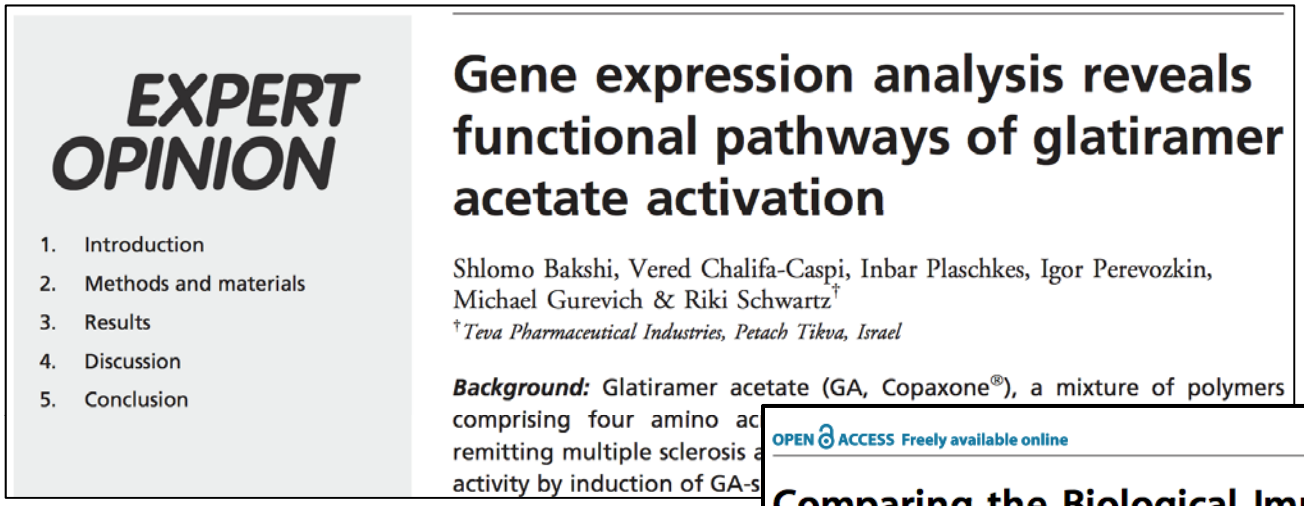
- *Immuneering's team has PhD and/or postdoctoral training from:*
  - **MIT**
  - **Johns Hopkins**
  - **Broad Institute of MIT and Harvard**
  - **Massachusetts General Hospital**
- *Immuneering's scientific advisory board includes:*
  - **Prof. Doug Lauffenburger, MIT** Biological Engineering Department Head
  - **Prof. Maxim Artyomov, Washington University in St. Louis** Department of Pathology and Immunology
  - **Prof. Neda Bagheri, Northwestern University** Chemical and Biological Engineering

Design of Mouse Splenocyte Studies



[Image sources: The Jackson Laboratory, Teva, Illumina]

Peer Reviewed Publications Summarizing Study #1



EXPERT OPINION

1. Introduction
2. Methods and materials
3. Results
4. Discussion
5. Conclusion

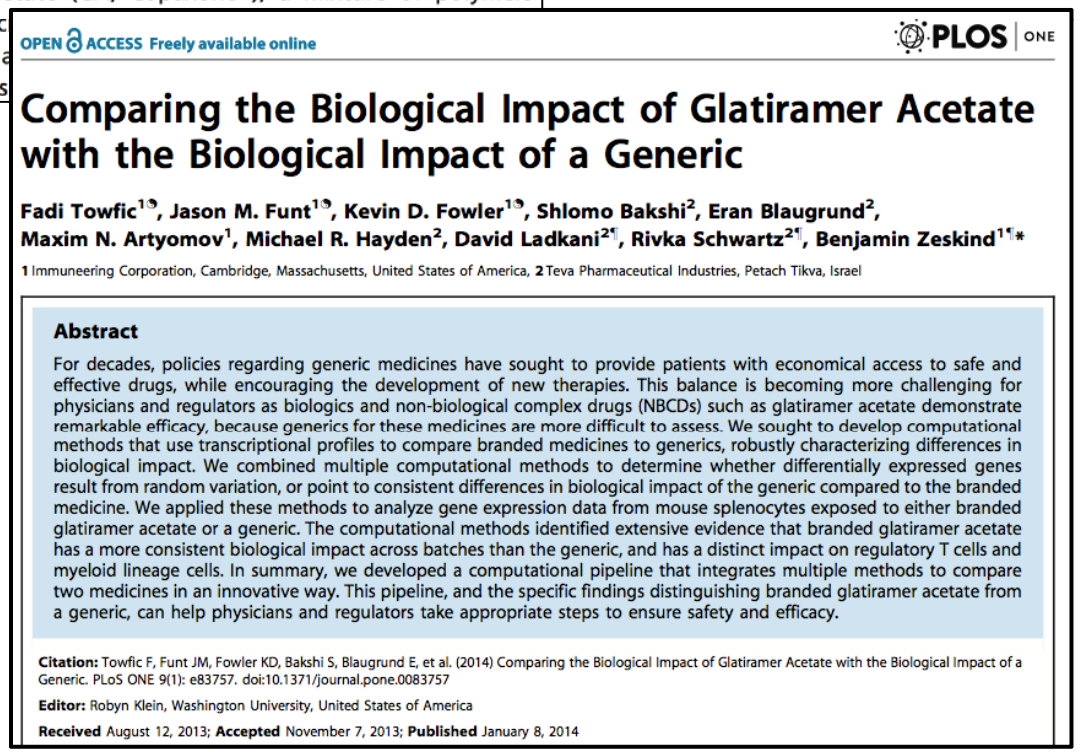
Gene expression analysis reveals functional pathways of glatiramer acetate activation

Shlomo Bakshi, Vered Chalifa-Caspi, Inbar Plaschkes, Igor Perevozkin, Michael Gurevich & Riki Schwartz†

†*Teva Pharmaceutical Industries, Petach Tikva, Israel*

Background: Glatiramer acetate (GA, Copaxone®), a mixture of polymers comprising four amino ac
remitting multiple sclerosis a
activity by induction of GA-s

Expert Opin Ther Targets, 17(4):351-362 (2013)



OPEN ACCESS Freely available online

PLOS ONE

Comparing the Biological Impact of Glatiramer Acetate with the Biological Impact of a Generic

Fadi Towfic[1☯], Jason M. Funt[1☯], Kevin D. Fowler[1☯], Shlomo Bakshi[2], Eran Blaugrund[2], Maxim N. Artyomov[1], Michael R. Hayden[2], David Ladkani[2¶], Rivka Schwartz[2¶], Benjamin Zeskind[1¶*]

1 Immuneering Corporation, Cambridge, Massachusetts, United States of America, **2** Teva Pharmaceutical Industries, Petach Tikva, Israel

Abstract

For decades, policies regarding generic medicines have sought to provide patients with economical access to safe and effective drugs, while encouraging the development of new therapies. This balance is becoming more challenging for physicians and regulators as biologics and non-biological complex drugs (NBCDs) such as glatiramer acetate demonstrate remarkable efficacy, because generics for these medicines are more difficult to assess. We sought to develop computational methods that use transcriptional profiles to compare branded medicines to generics, robustly characterizing differences in biological impact. We combined multiple computational methods to determine whether differentially expressed genes result from random variation, or point to consistent differences in biological impact of the generic compared to the branded medicine. We applied these methods to analyze gene expression data from mouse splenocytes exposed to either branded glatiramer acetate or a generic. The computational methods identified extensive evidence that branded glatiramer acetate has a more consistent biological impact across batches than the generic, and has a distinct impact on regulatory T cells and myeloid lineage cells. In summary, we developed a computational pipeline that integrates multiple methods to compare two medicines in an innovative way. This pipeline, and the specific findings distinguishing branded glatiramer acetate from a generic, can help physicians and regulators take appropriate steps to ensure safety and efficacy.

Citation: Towfic F, Funt JM, Fowler KD, Bakshi S, Blaugrund E, et al. (2014) Comparing the Biological Impact of Glatiramer Acetate with the Biological Impact of a Generic. PLoS ONE 9(1): e83757. doi:10.1371/journal.pone.0083757

Editor: Robyn Klein, Washington University, United States of America

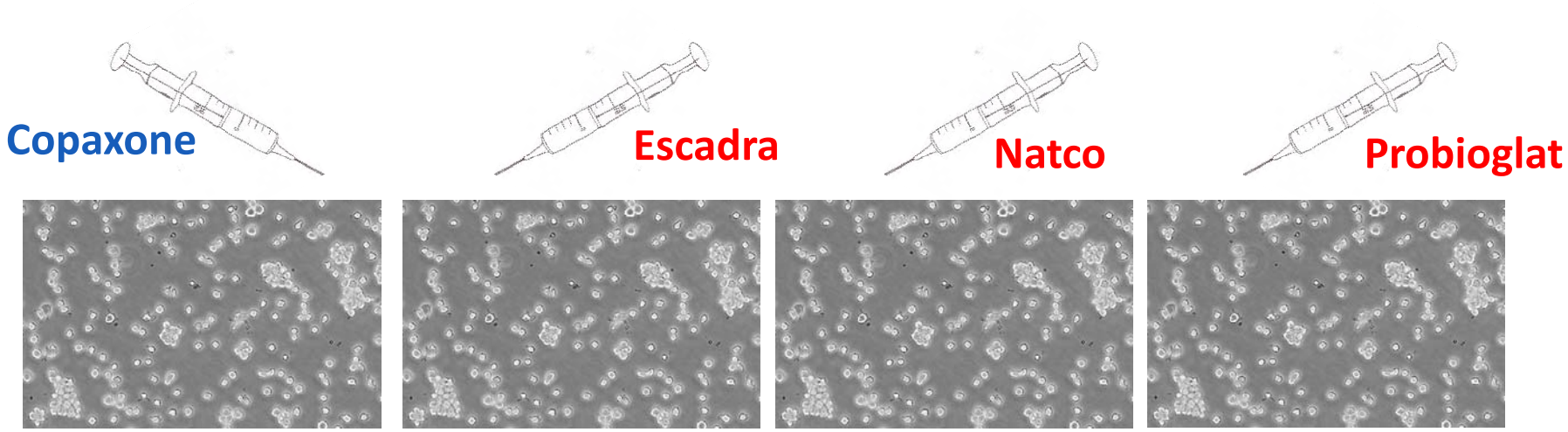
Received August 12, 2013; **Accepted** November 7, 2013; **Published** January 8, 2014

PLoS ONE, 9(1): e83757 (2014)

Design of Human Monocytes Study (THP-1)

Study Copaxone's MOA using human monocytes (THP-1 cell line)

Model impact of purported generics on human monocytes (THP-1 cell line)

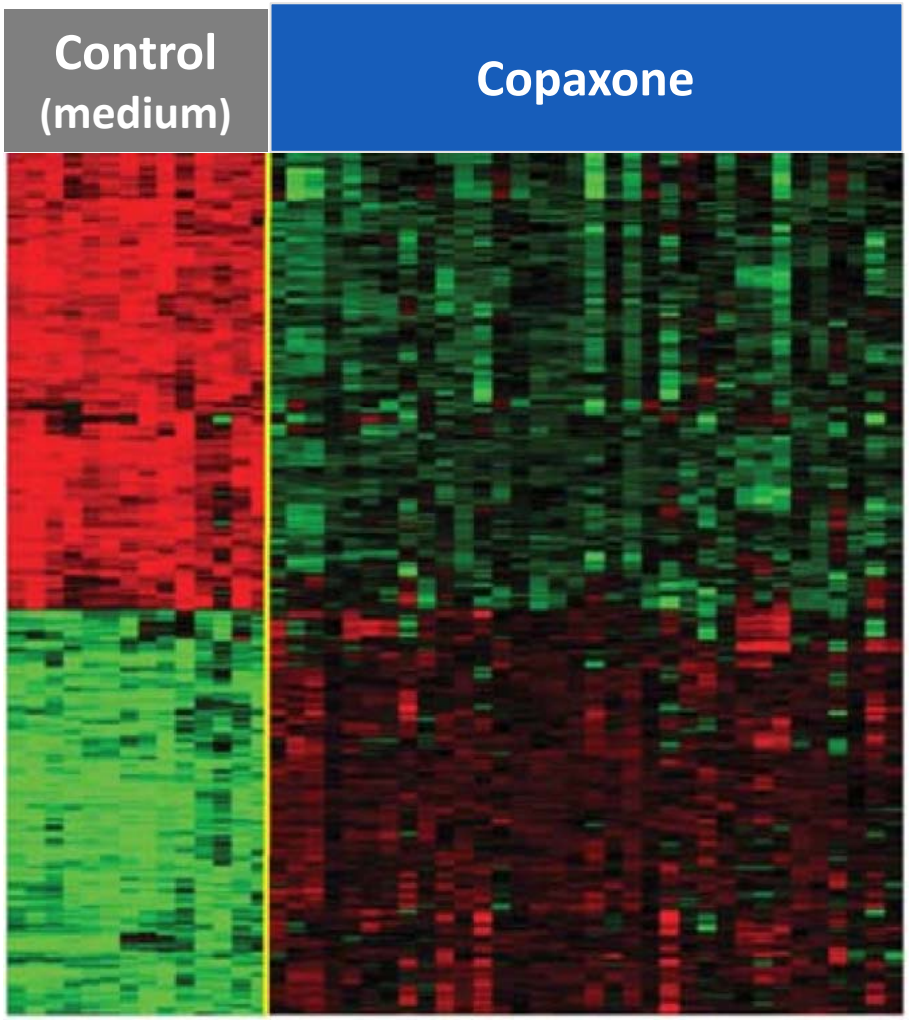


RNA extracted and mRNA array tested 6, 12 and 24 hours post treatment

[Image sources: ATCC, Affymetrix]

Affymetrix U133 plus 2.0 chips: 47,000+ transcripts

Copaxone Significantly Impacts 1,400+ Genes



Genes downregulated by Copaxone

Genes upregulated by Copaxone

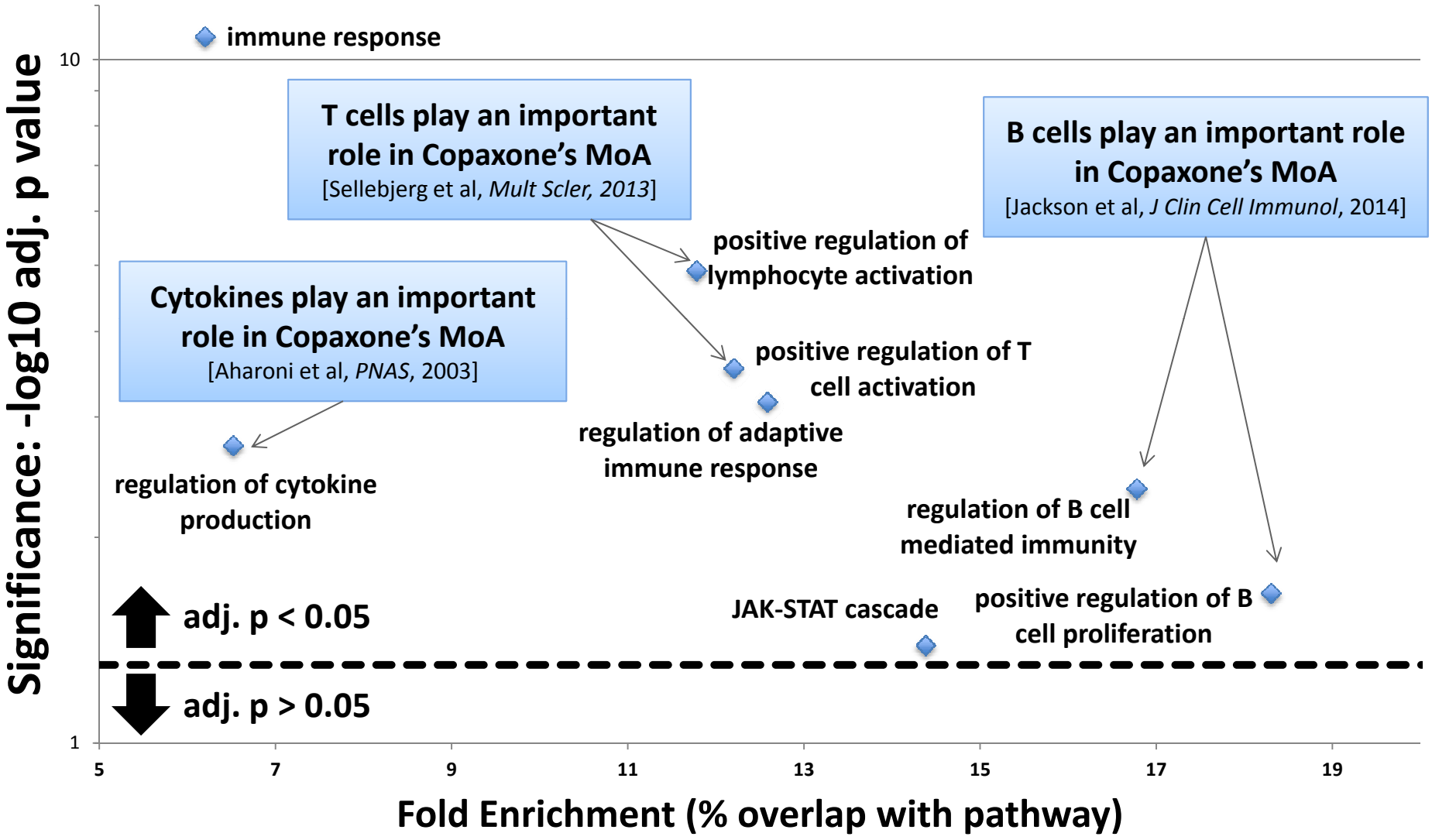
Copaxone: 34 samples
Control: 15 samples

Samples (columns)

[Bakshi et al, 2013,
Expert Opin Ther Targets, Fig. 2A]

Color = z-scored expression = -2  **+2**

Copaxone Significantly Impacts 100+ Pathways



Study #1: LIMMA analysis of Copaxone compared to medium, processed using NIH DAVID enrichment. Plot shows a subset of all significant pathways.

Published Evaluation Method (a Momenta Patent)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2008 (24.12.2008)

PCT

(10) International Publication Number
WO 2008/157697 A2

(54) Title: COPOLYMER ASSAY

(71) Applicant *(for all designated States except US)*: MOMENTA PHARMACEUTICALS, INC. [US/US]; 675

Chemokines	IP10	MCP1	MDC	I309	IL-8	MIP1α	RANTES	TARC
Cytokines	IFNγ	IL-6	IL1β	IL-10	IL12p70	TNFα		
Receptors/Proteases	ICAM1	MMP2	TNFR1	TNFR2	TIMP1	MMP9		

Additional proteins noted in patent: ITAC, MIG, TNF-α, IL-1, IL-2, IL-4, IL-13, IL-17, IL-18, IL-23, LTA

A panel of proteins reported by Momenta as a Biological assay for Copaxone

Gene Expression of Proteins in Momenta's Patent

	Natco	Escadra
IFNG*		
IL6*		
IL1B		
IL10		
IL12p70		
TNF alpha		
ICAM1		
MMP2		
TNFR1		
TNFR2		
TIMP1		
MMP9		
IP10*		
MCP1		
MDC*		
I309*		
IL8		
MIP1A		
RANTES		
TARC*		
ITAC*		
MIG*		
IL1A*		
IL2*		
IL4*		
IL13*		
IL17A*		
IL17B*		
IL17C*		
IL17D*		
IL17F*		
IL18		
IL23		
LTA*		

Adj. p < 0.05 compared with Copaxone

Adj. p > 0.05 compared with Copaxone

NO significant differences from Copaxone

Study #3: human monocytes

**probeset called absent*

Gene Expression of Proteins in Momenta's Patent

	Natco	Escadra
IFNG*		
IL6*		
IL1B		
IL10		
IL12p70		
TNF alpha		
ICAM1		
MMP2		
TNFR1		
TNFR2		
TIMP1		
MMP9		
IP10*		
MCP1		
MDC*		
I309*		
IL8		
MIP1A		
RANTES		
TARC*		
ITAC*		
MIG*		
IL1A*		
IL2*		
IL4*		
IL13*		
IL17A*		
IL17B*		
IL17C*		
IL17D*		
IL17F*		
IL18		
IL23		
LTA*		

*probeset called absent

Adj. p < 0.05 compared with Copaxone

Adj. p > 0.05 compared with Copaxone

CD44 is the receptor for Hyaluronan which accumulates in demyelinated lesions
[Back et al, *Nature Medicine*, 2005]

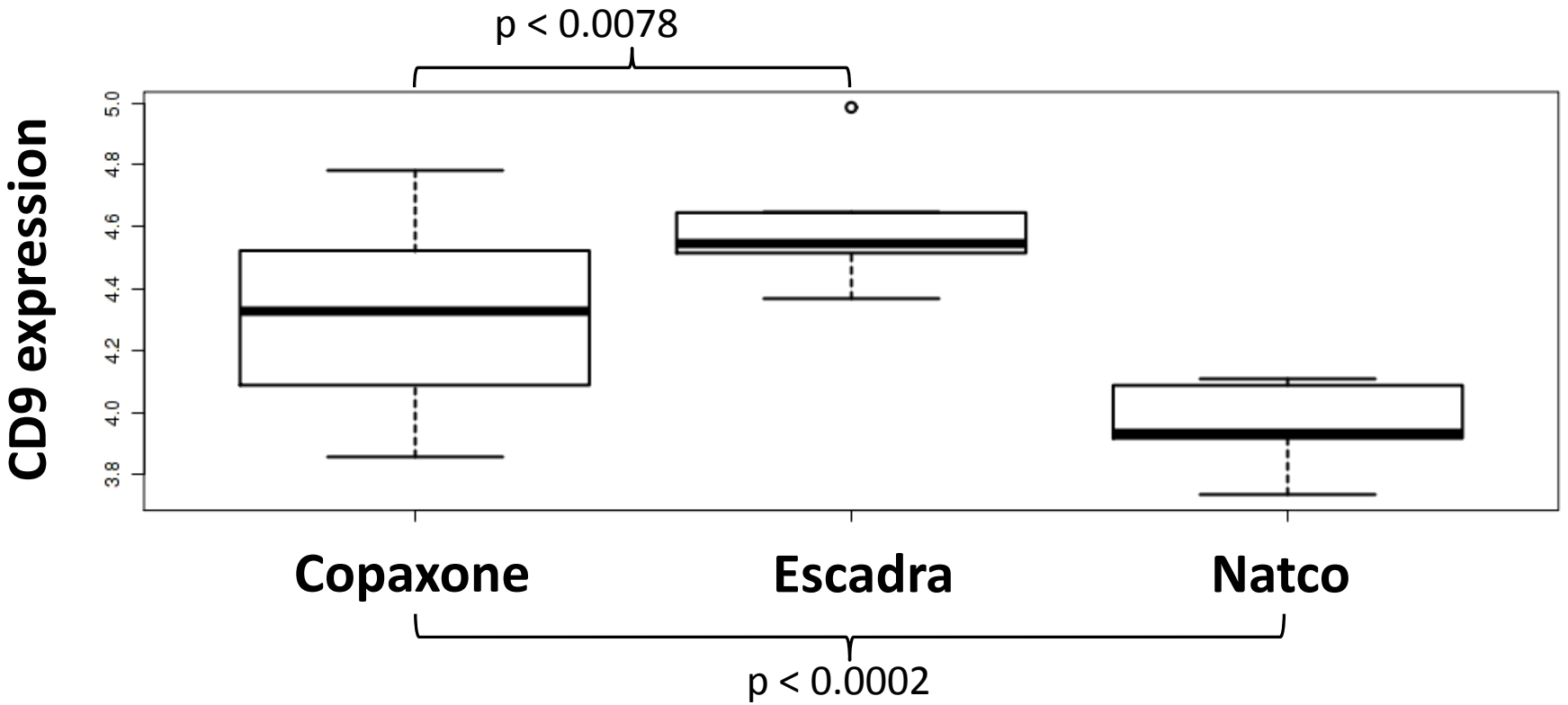
CD9 is a component of myelin and a marker of myelinogenic progenitor cells
[Sim et al, *Nature Biotechnology*, 2011]

	Natco	Escadra
ANXA1		
ARRB2		
BEAN		
BIN1		
BIN1		
C13ORF31		
C14ORF10		
C1ORF51		
C1ORF63		
C1ORF63		
CBR4		
CD36		
CD44		
CD44		
CD44		
CD44		
CD9		
CFP		
COL6A1		
CRIP2		
DAB2		
EPB41		
Fam119a		
FGR		
FOXO3B		
GATA2		
HSD11B1		
HSPD1P6		
KIAA0907		
LOC100506233		
LOC387790		

	Natco	Escadra
MCM6		
MMP1		
MPEG1		
MS4A4A		
MTSS1		
MYB		
OLIG1		
PCMTD1		
PLD1		
PPP4R2		
PRDM1		
RBM6		
SNX27		
SOD2		
STATH		
STK4		
STX7		
TAF15		
TARP		
TIA1		
TMF1		
TREM1		
TRGC2		
TRGC2		
TRGC2		
TXNDC11		
UBN2		
ZCCHC7		

Study #3: human monocytes

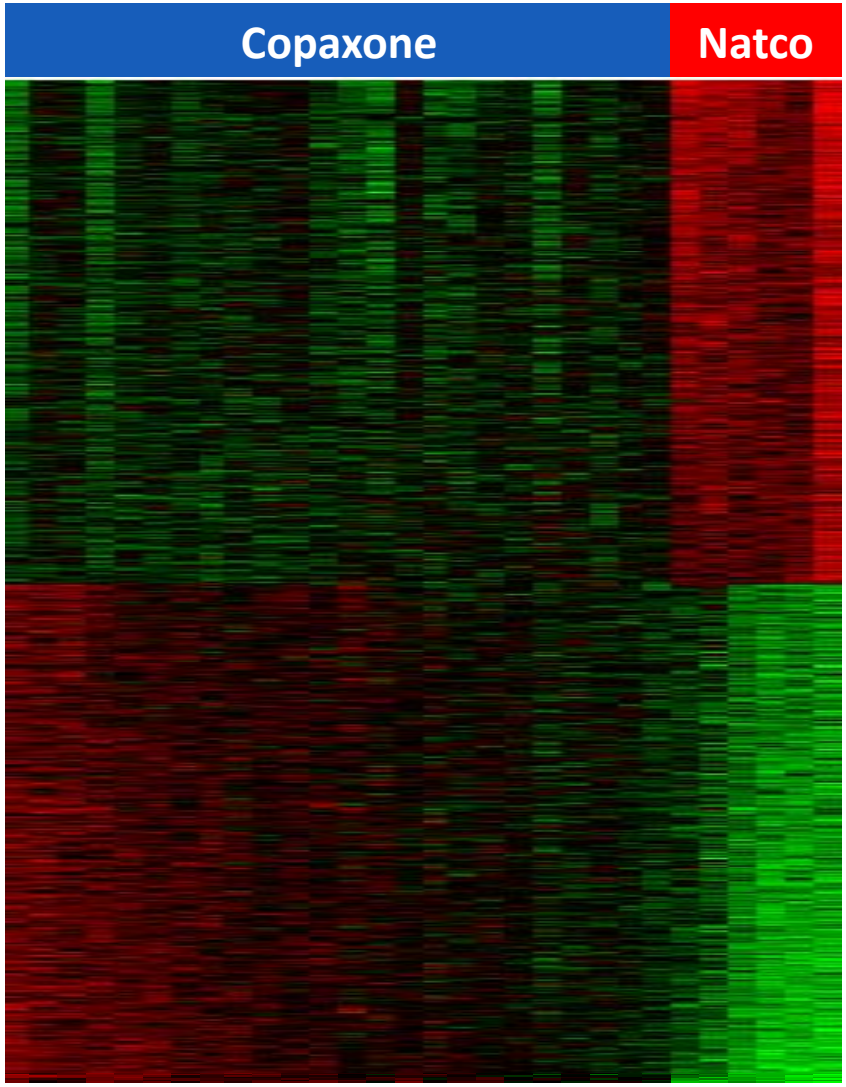
Confirmation of CD9 Expression by qRT-PCR



- **Two different purported generics show opposite effects for a critical myelin marker**

Data is based on **6 biological samples** with **15 technical replicates** and normalization to the house keeping gene, GAPDH

Differences in Many Genes: Natco Comparison



Genes
(rows)

Samples
(columns)

Genes
upregulated by
Natco compared
with Copaxone

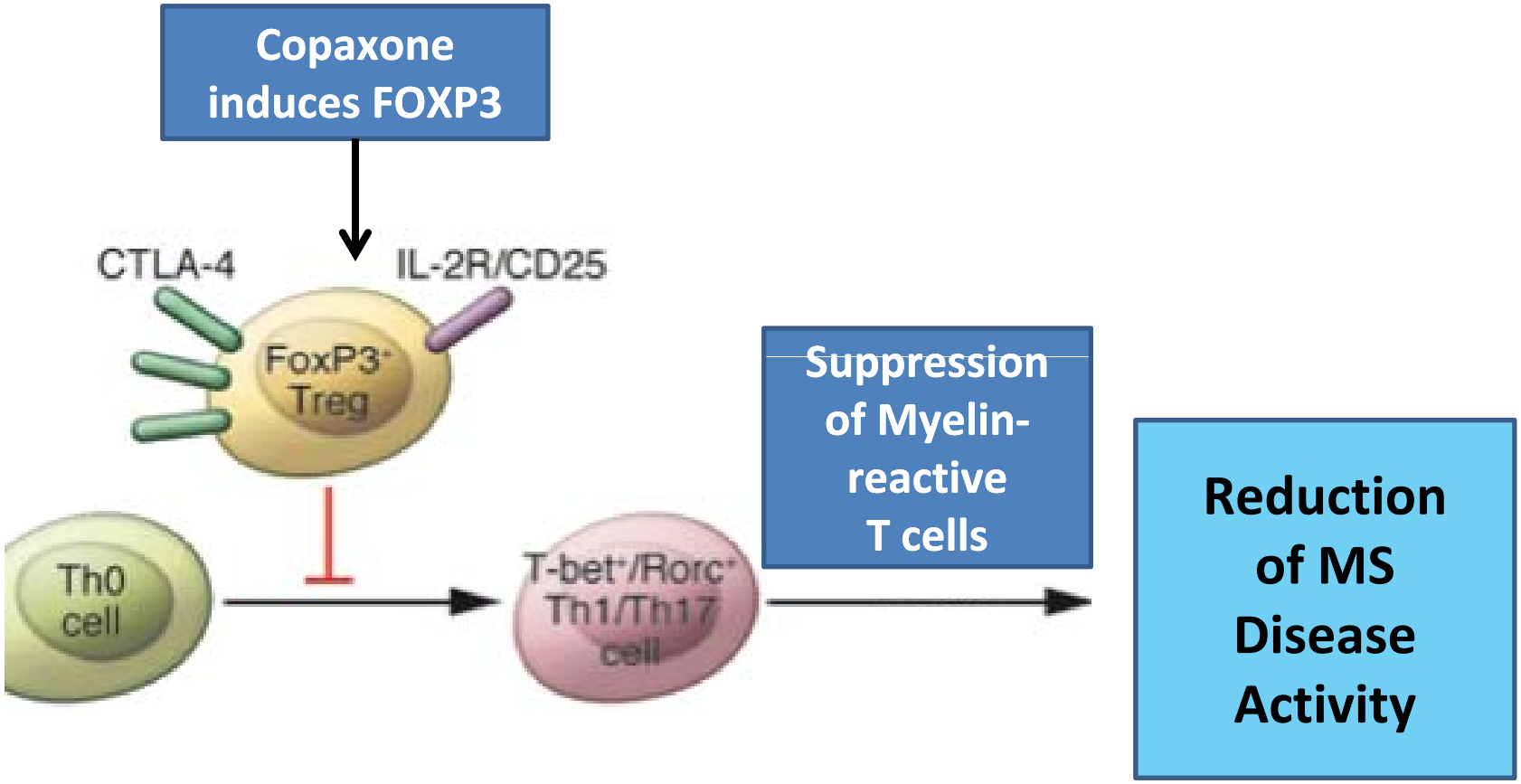
Genes
downregulated by
Natco compared
with Copaxone

Color =
z-scored expression =

-2 0 +2

Study #3: human monocytes

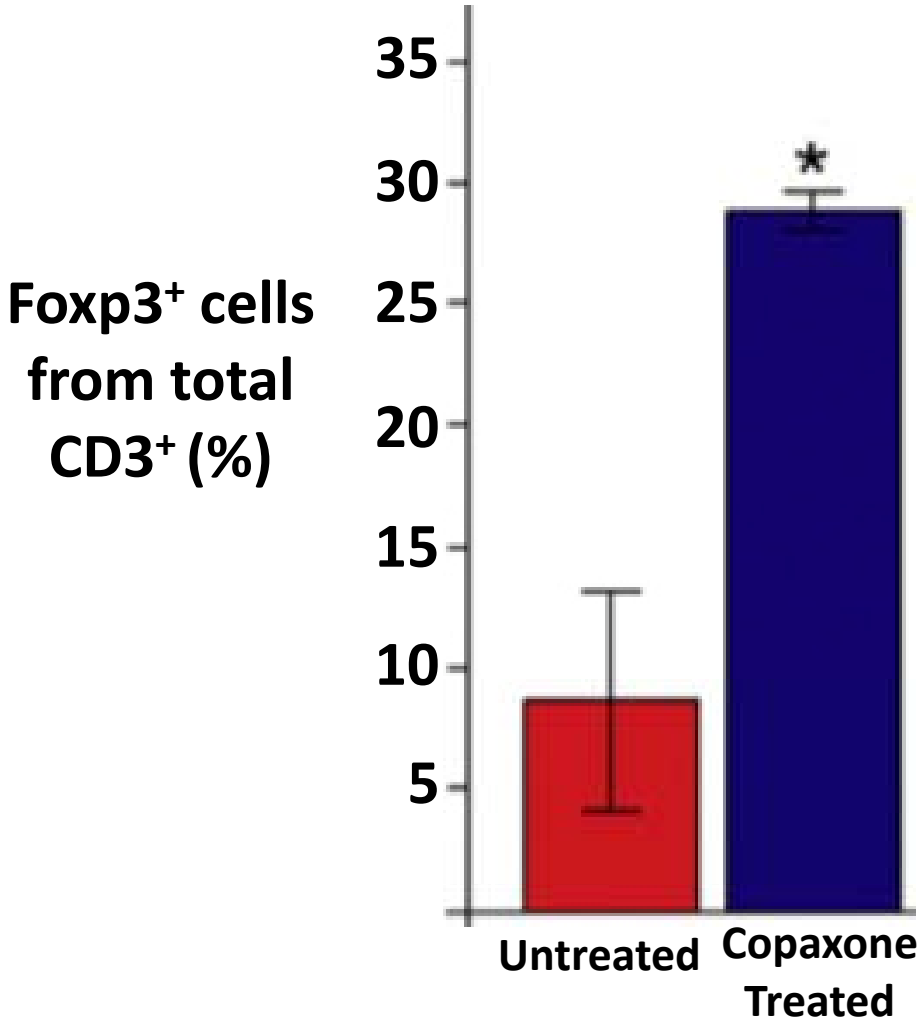
FoxP3+ Tregs Suppress Myelin-Reactive T Cells



Adapted from: Nylander and Hafler, 2012, *Journal of Clinical Investigation*

Copaxone Induces Treg Marker FOXP3

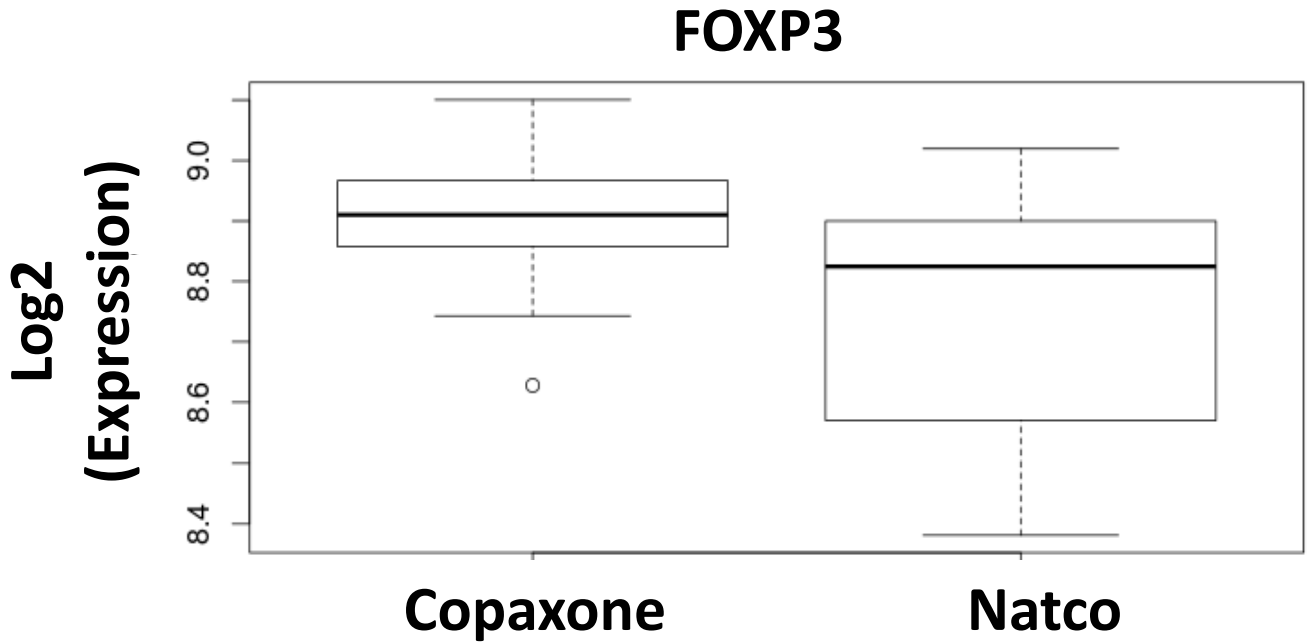
FOXP3 induction was reported as important for **Treg activation**



*** p < 0.05**
Mouse studies described in [Aharoni at al, 2010]

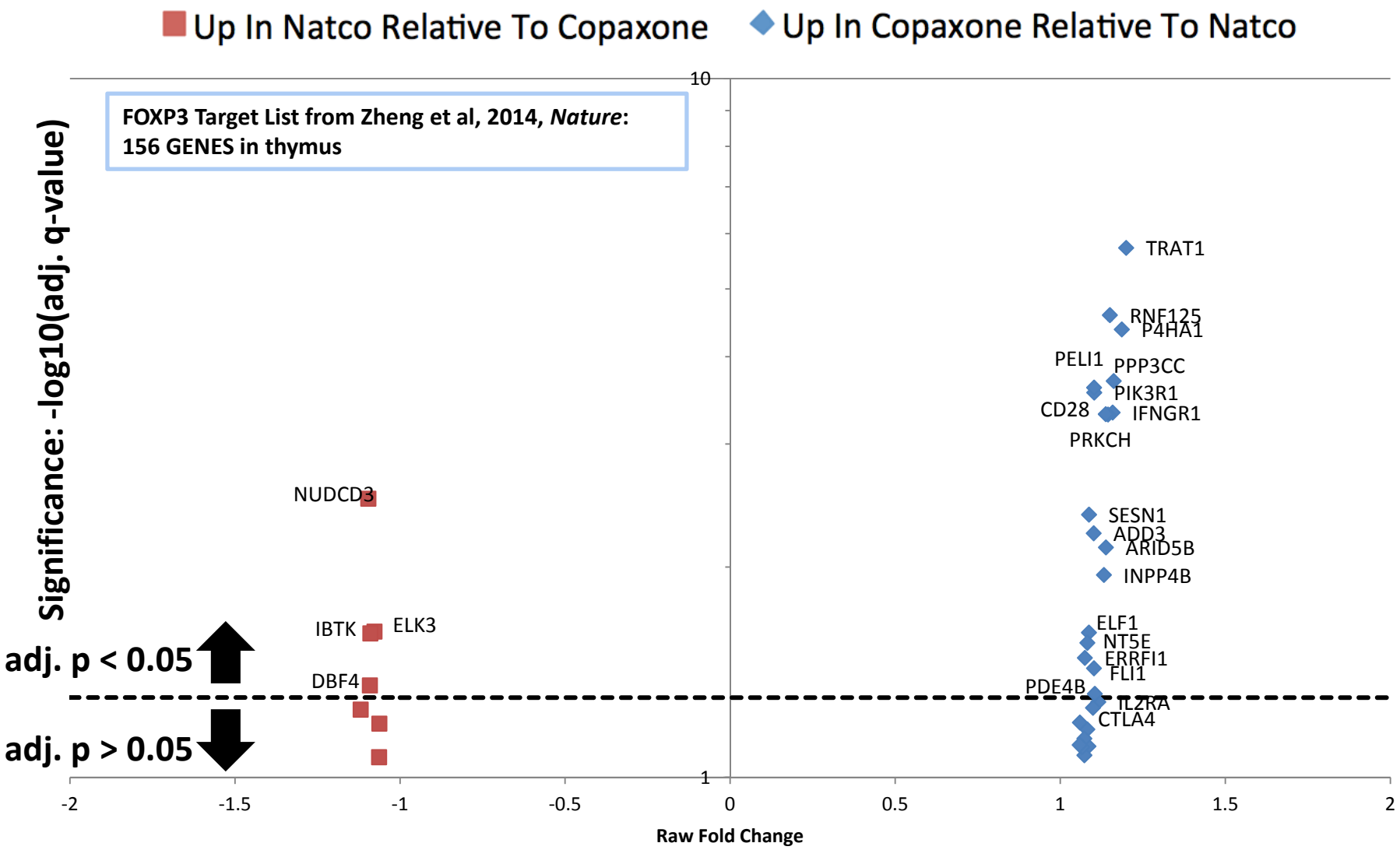
Copaxone Induces FOXP3 More Effectively

- Copaxone induces **higher levels** of *FOXP3* than Natco,
  adj p = 1.4 x 10^{-3} by ANOVA



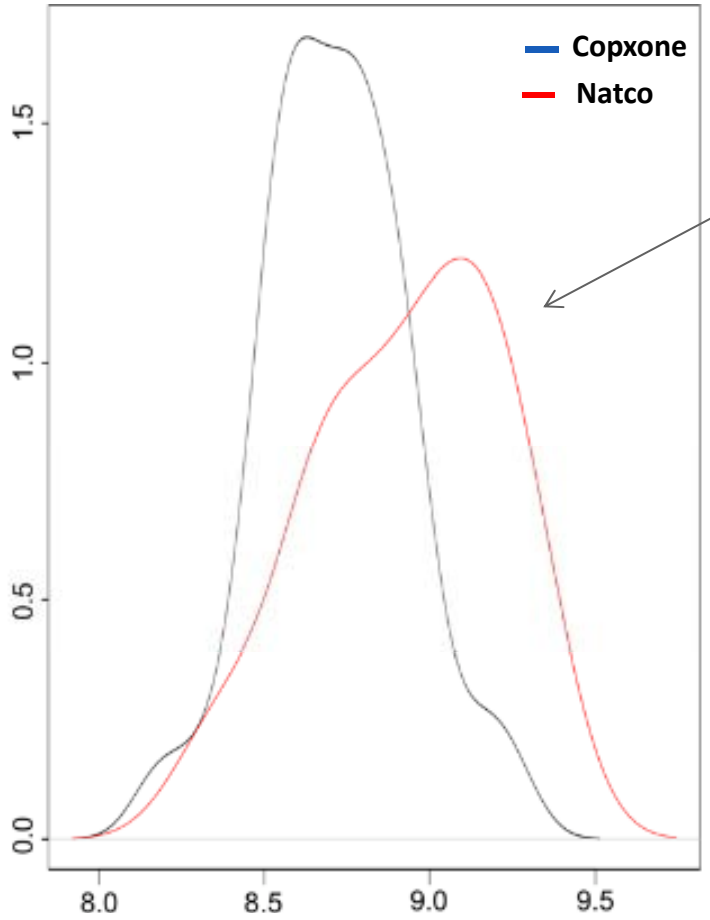
- Copaxone induces FOXP3 **4.17-times more consistently** than Natco
  (Copaxone: 34 samples from 30 batches; Natco: 11 samples from 5 batches)

Copaxone Upregulates FOXP3 Targets More than Natco



Gene Set Enrichment Analysis (GSEA): Subramanian et al, 2005, *PNAS*, Results: Towfic et al, 2014, *PLOS ONE*

Natco Induces More CD14 than Copaxone



Higher CD14 expression levels in Natco treated samples

Adj. p = 0.0203
ANOVA: CD14 for Copaxone compared with Natco

Study #1
mouse splenocytes

[Towfic et al, 2014, *PLOS ONE*, Fig 4A]

- LPS response pathway genes are **significantly enriched** among genes upregulated by **Natco**: **adj. p = 4.96 x 10^{-6}**

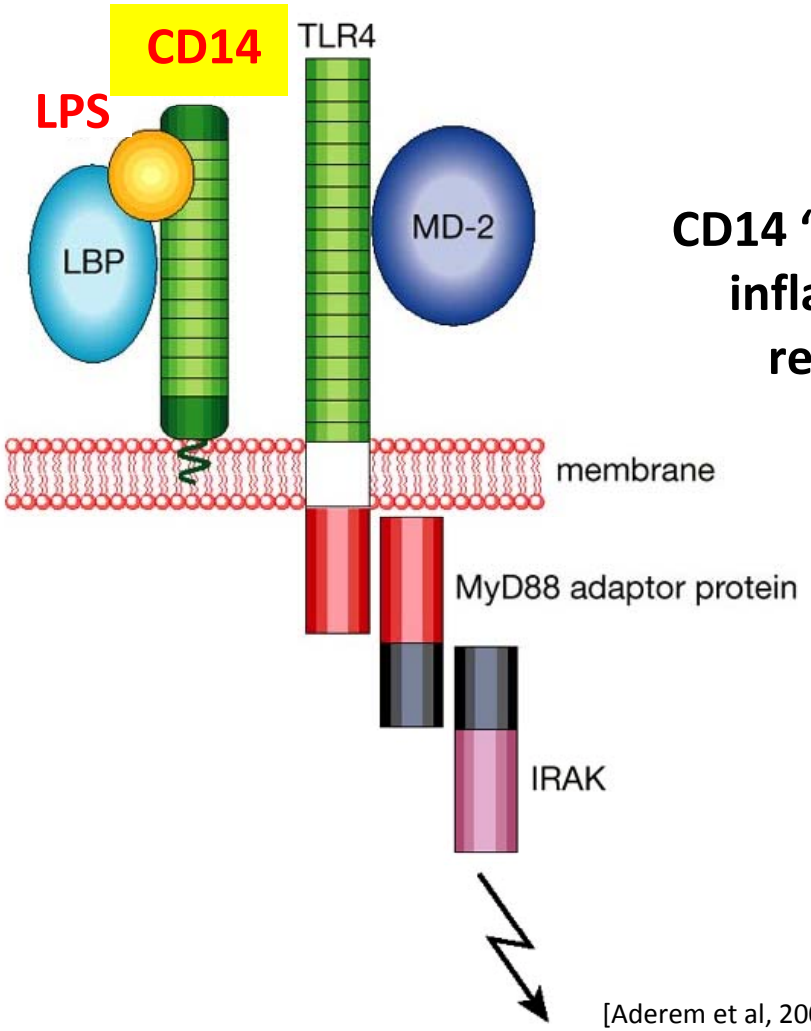
CD14: Key Monocyte Inflammation Marker

"CD14 is expressed in abundance on the surface of mature <u>monocytes</u> and in trace amounts on granulocytes, but not on other hematopoietic cells"

[Simmons et al, 1989, *Blood*]

Monocytes may serve as "prominent contributors" to neuroinflammation in multiple sclerosis

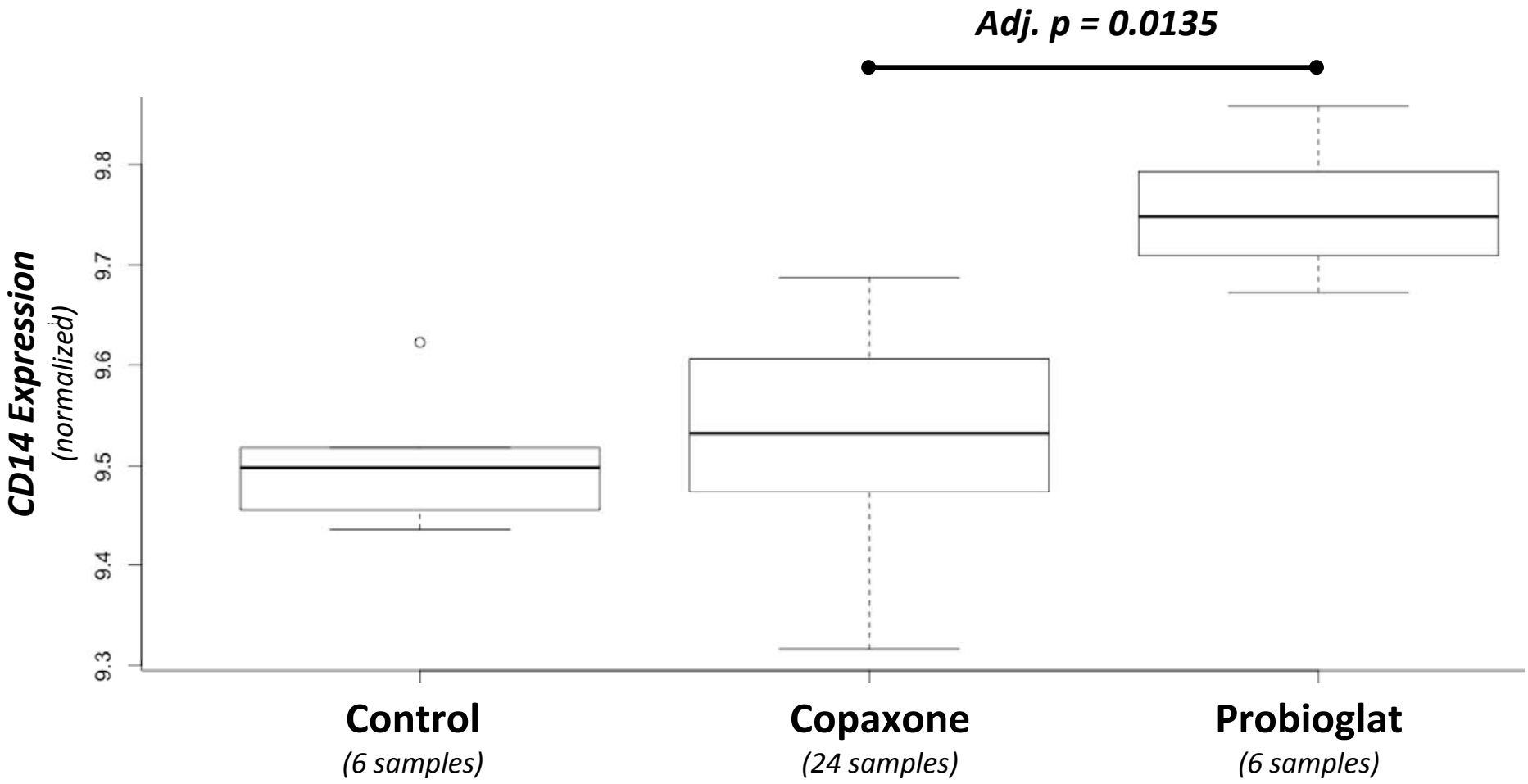
[Bar-Or et al, 2003, *Brain*]



[Aderem et al, 2000, *Nature*]

CD14 "enhances inflammatory response"

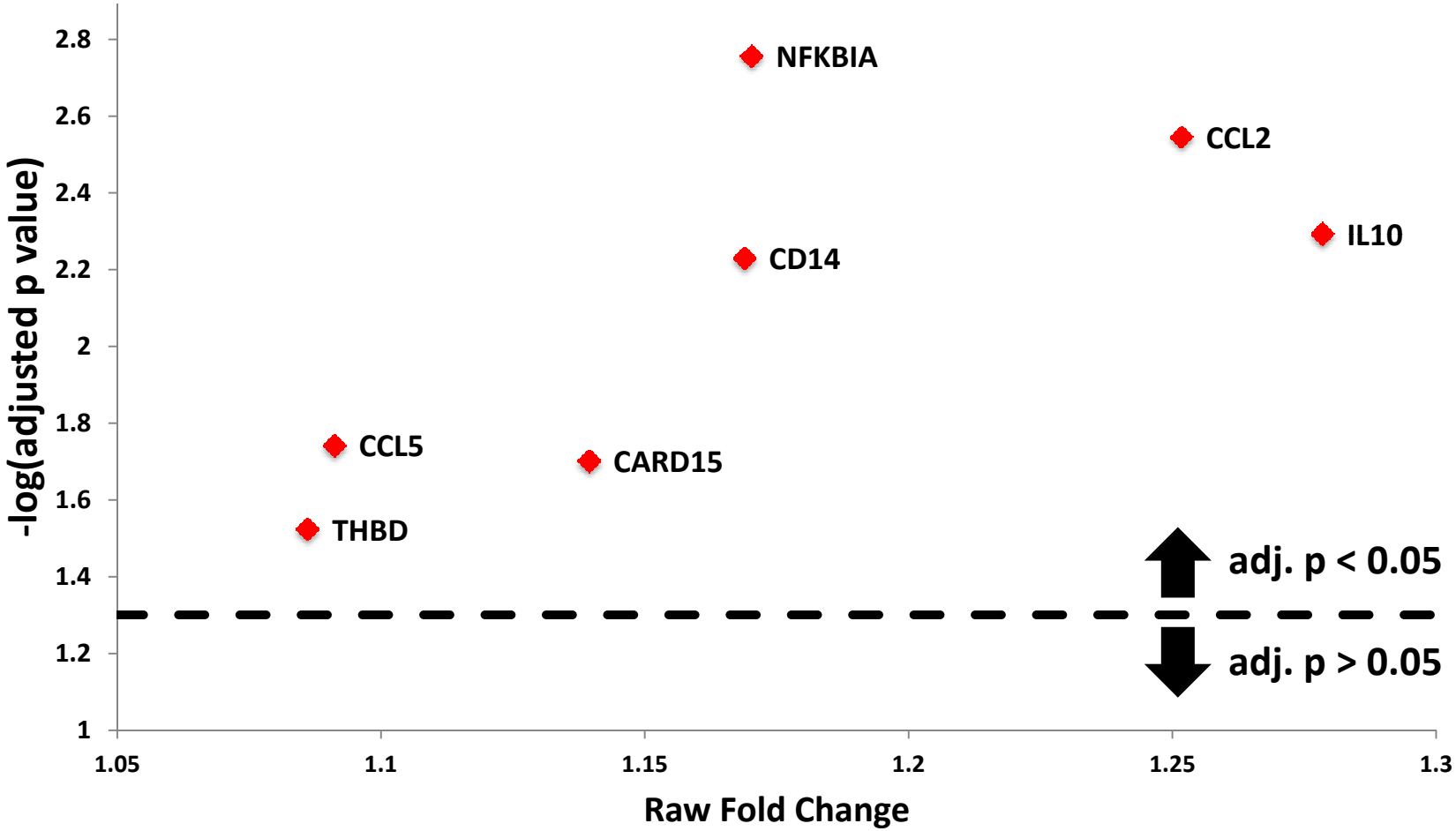
Probioglat Induces More CD14 than Copaxone



Study #3
human monocytes

Probioglat Significantly Upregulates Inflammation

- Significant enrichment for this pro-inflammatory response pathway among genes **upregulated** by **Probioglat**: **adj. p = 2.86 x 10^{-3}**



Study #3 (human monocytes): LIMMA analysis of Copaxone compared with Probioglat, processed using NIH DAVID enrichment
NOD = nucleotide-binding oligomerization domain; LPS = lipopolysaccharide

Pro-inflammatory Concerns: Probioglat Clinical Events?

- Probioglat was launched in Mexico **January 2013**
- Hospital la Raza (Mexico City) follows 232 MS patients regularly
- This is **one of the three biggest hospitals of the IMSS** (*Instituto Mexicano de Seguro Social*), 65 patients are treated with both **Probioglat** and **Copaxone** since January 2013:
  - **Increase in injection site reactions**, painful local reactions, erythema and diffuse flush, pruritus and chest pain (consistent with Immediate Post Injection Reaction), confirmed by Health Care Providers (HCP)
  - **>50% of the patients** experienced a relapse within 2-4 months of switch
  - **Relapse related hospitalizations increased 200%** in 2013

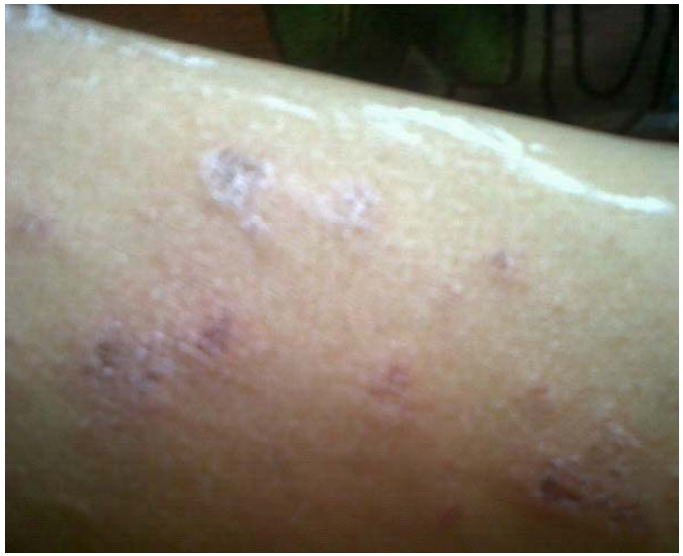
Probioglat: Patient Reported Events in Mexico

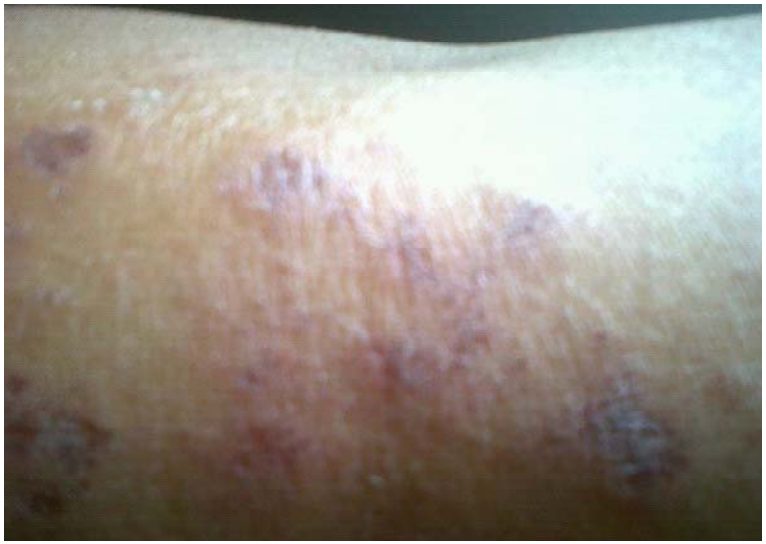
- Patients reported their complaints in the **local media**

http://www.televisaregional.com/aguascalientes/noticias/IMSS-da-medicamento-generico-que-afecta-a-pacientes-con-esclerosis-235464281.html

http://www.radiogrupo.com.mx/index.php/local-movil/34-principales-locales/12519-imss-les-cambio-medicamento-por-uno-generico-y-pacientes-empeoraron-su-salud

- Example of **pictures** anonymously shared by some of these patients:





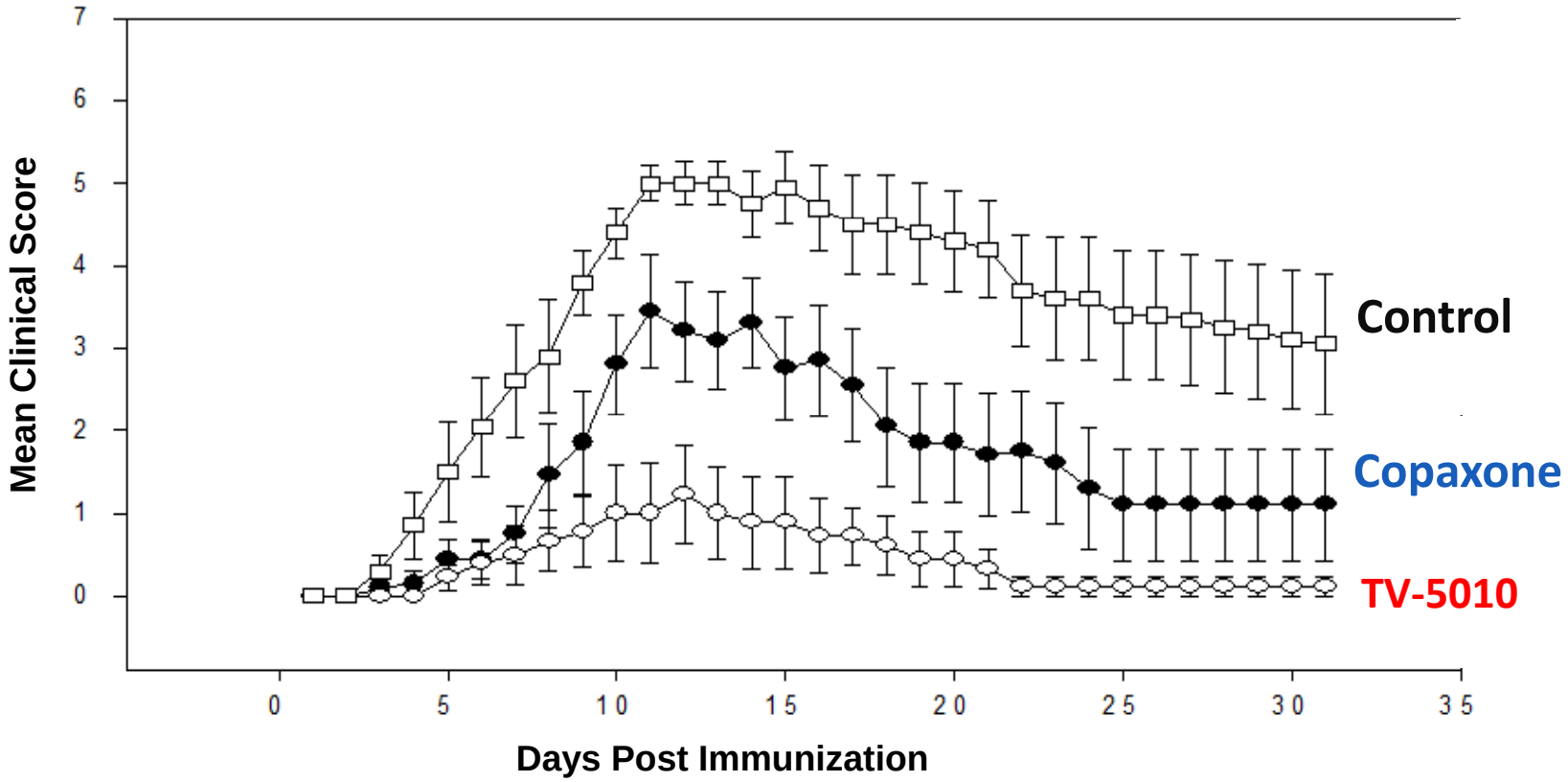
Implications of Gene Expression Findings

- Gene expression data **corroborates the very complex mechanism of action of Copaxone**
- **Key differences** between Copaxone and purported generics are **undetectable** by characterization methods that only measure a few proteins
- Purported generics with **significantly altered gene expression profiles** affecting key immunological pathways **cannot be assumed** to have the same efficacy and safety properties as Copaxone
- The gene expression properties presented raise concern that purported generic products **may not be clinically and biologically equivalent to Copaxone**

TV-5010 Developed by Teva as NME

- Produced by a **small change** in the Copaxone **manufacturing process**
- **Similar** to Copaxone in **amino-acid ratio**, **physical properties**, shares **same mode of action**
- TV-5010 was identified by **Copaxone-specific antibodies**, indicating that they share similar B cell epitopes, and likely similar mechanism of action
- TV-5010 showed similar or **better efficacy** profile in pre-clinical studies compared to Copaxone

TV-5010 More Effective in Blocking EAE



Experimental Allergic Encephalomyelitis (EAE) was induced by injection of Myelin Oligodendrocyte Glycoprotein (MOG) to C57BL female mice

Blocking is defined as reduced incidence of clinical signs and disease severity post injection

TV-5010 Favorable Short-Term Safety Profile

- **No toxicological** changes observed in **short-term toxicity** studies (13 weeks) in Sprague Dawley rats
- **Extrapolated** favorable toxicity profile due to **similarity to Copaxone**

Led to the conduct of two phase II studies in MS patients

- **Good general safety and tolerability** demonstrated in the two small, 9-months clinical trials (De Stefano et al. 2009)

However…

TV-5010: Unfavorable Long-Term Toxicity Profile

Monkeys
(52 weeks)

- Injection site reactions (**ISR**)
- **Death**

Rats
(26 weeks)

- **Fibrosis** in liver
- **Nephropathy**
- **ISR**
- **Death**

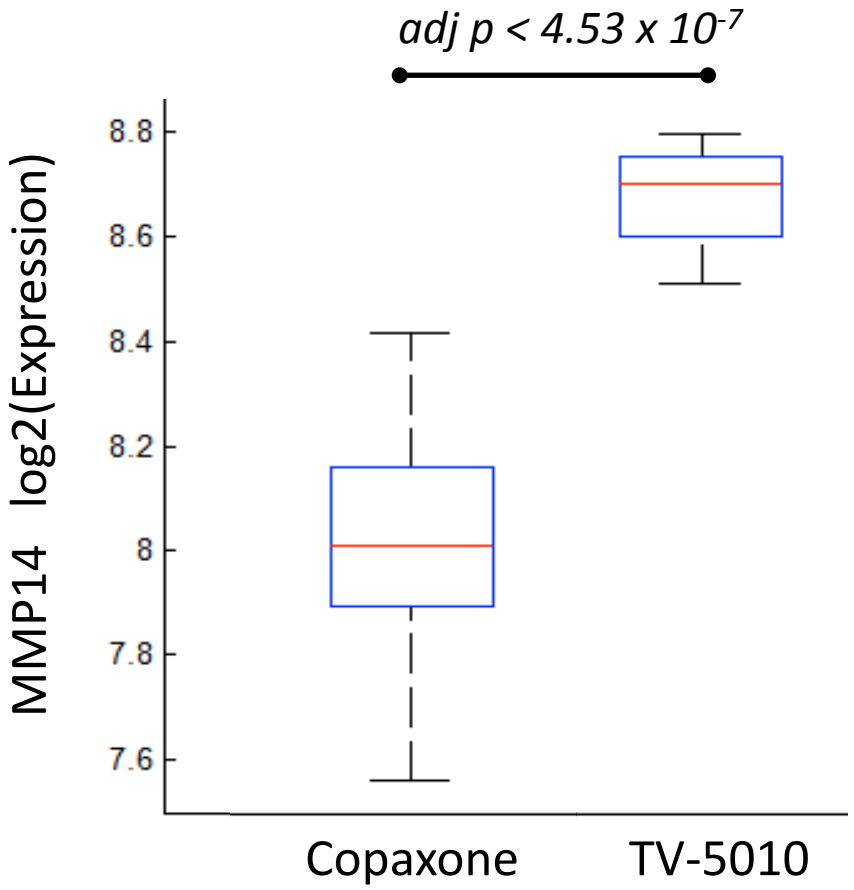
- **Long-term preclinical toxicity** studies revealed marked toxicological findings (Ramot et al. 2012)
- The program was terminated due to **concern for patient safety** (Varkony et al. 2009)

Conclusions

- **A small change** in the manufacturing process can lead to an **unpredictable** and concerning outcome (**toxicity**)
- The immune system is **extremely sensitive** to changes in the **antigenic nature of Copaxone**

Gene Expression Data Predicts Toxicity in Animals

MMP14 is a top-ranked gene distinguishing TV-5010 from Copaxone



TV-5010: Increased Expression of Profibrotic MMP14

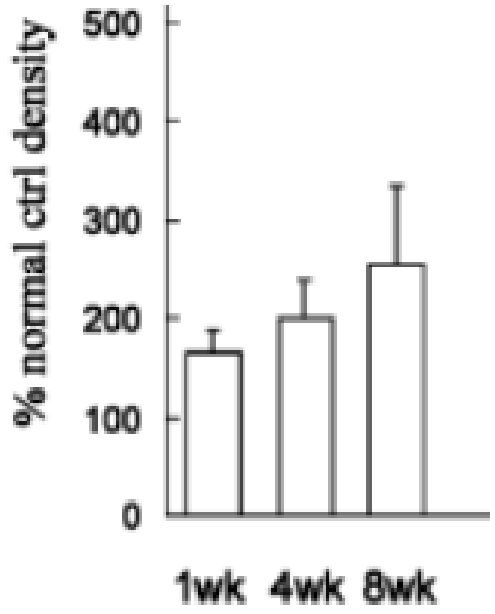
Gene expression data correlates with clinical safety findings

"**MMP-14**, which may **promote fibrosis** via up-regulated TGF-β signaling ..." [Bailey et al, 2012]

"both MMP-2 and **MMP-14** become **highly expressed in liver during fibrogenesis in rats ...**" [Zhou et al, 2004]

"in a mouse model of age-related **dermal fibrosis ... MMP14 activity** and TGFβ bioavailability are **chronically elevated ...**" [Sounni et al, 2010]

MMP14 levels increase >250% as fibrosis is induced in rats



[Zhou et al, 2004]

Presentation Outline

- ❑ **Introduction**
- ❑ **Clinical Perspective**
- ❑ **Comparison** Between Purported Generics and Copaxone
- ❑ **Regulatory considerations**
- ❑ **Expert opinion:** Dr. Lawrence Steinman
- ❑ **Summary**

A Concentrated Formulation of Copaxone

- Teva proposed to market a **concentrated** formulation (20mg in 0.5ml vs 1ml) of Copaxone to **reduce pain on injection**

- **Division of Neurology Products Complete Response** *(Ref ID #2881241, 12/21/2010):*

  - Decision: "**an adequate and well controlled efficacy study** will be needed to **support efficacy** of this new formulation", even though the *only change* was the **decrease in diluent**

  - Rationale: "The uncertainty about the glatiramer acetate mechanism of action, and the fact that **some of the effect** may be related to the **activation of lymphocytes in the periphery**, raise questions about a possible impact of a higher concentration/lower volume formulation on the **safety and efficacy of the product**. "

Comparing Concentrated to Original Copaxone

Drug Development	Copaxone (20mg / 1ml)	Copaxone (20mg / 0.5ml)
CMC		
• Starting material	**Proprietary**	**Same**
• Manufacturing process ensuring antigen homology	**Proprietary**	**Same**
• Drug Product	**Original**	**Same, concentrated**
Immunogenicity testing	**Yes**	**Same**
Clinical Studies	**Required**	**Required**

Comparing Copaxone Formulations to Purported Generics

Drug Development	Copaxone (20mg / 1ml)	Copaxone (20mg / 0.5ml)	Purported Generics (20mg / 1ml)
CMC • Starting material	Proprietary	Same	Different
• Manufacturing process ensuring antigen homology	Proprietary	Same	Different
• Drug Product	Original	Same, concentrated	Different
Immunogenicity testing	Yes	Same	Not conducted in patients
Clinical Studies	Required	Required	Should be required

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Independent Advisory Board, 16 January 2014

February 6, 2014

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Dear Dr. Woodcock,

We are writing to you as Multiple Sclerosis experts that reviewed gene expression data on Copaxone, published by Teva in *PLOS ONE* (2014) and in *Expert Opinion in Therapeutic Targets* (2013), and presented to us in detail (16 January, 2014). Our independent overall conclusion is that there is insufficient evidence to assure that the tested generic glatiramer acetate (PG-GA) products will show the same level of clinical efficacy and safety as Copaxone. We therefore **urge the FDA to require manufacturers of candidate PG-GA products to conduct clinical trials with clinically relevant primary endpoints, in order to prove that these products are efficacious and safe**.

Recently, the gene expression data was presented to the four of us at an Advisory Board meeting organized by Teva Pharmaceuticals, where we had the opportunity to review the data independently. Gene expression arrays were analyzed using state-of-the-art methods to: (1) Characterize batch-to-batch variability for each product and identify regulated transcripts; (2) Identify transcripts that differ in response to each tested product; and (3) Investigate the pathways associated with those transcripts in (1) and (2), and determine their potential clinical implications.

Following the day-long scientific discussion, our **unanimous view** is that:

I. The data presented is based on a complementary set of well-designed experiments, expertly analyzed with appropriate and robust methodologies;

II. While some similarities exist, the findings unequivocally reveal differences in gene expression patterns induced by different GA products, particularly as relates to specific immunological pathways known to be involved in Copaxone's mode-of-action; and

III. These subtle changes in regulation and activation of affected pathways may translate into clinical outcomes different from those consistently experienced with Copaxone.

Larry Steinman, M.D., Stanford School of Medicine

Sergio Baranzini, Ph.D., University of California, San Francisco

Timothy Vollmer, M.D., University of Colorado School of Medicine

Jorge Oksenberg, Ph.D., University of California, San Francisco

Advisory Board's Unanimous View

- The genomic data presented to the Advisory Board is based on "**well-designed experiments**, **expertly** analyzed and robust"
- "While some similarities exist, the findings **unequivocally reveal differences**"
- "These subtle changes in regulation and activation of affected pathways **may translate into clinical outcomes different** from those consistently experienced with Copaxone."
- **Conclusion**: "We **strongly recommend** that FDA require manufacturers of candidate generic products of Copaxone to conduct **clinical trials with clinically relevant primary endpoints** to ensure that **efficacy and safety equivalence** is demonstrated to ensure a quality product to treat multiple sclerosis patients."

Providing Safe and Effective Therapeutic Options

- **Immunological modulators** such as Copaxone affect a delicate balance between pro-inflammatory and anti-inflammatory processes, as well as neurodegenerative and neuroprotective pathways

- **Risk** of altered efficacy or safety is thus significant

- Experience in the clinic is based on **consistent and reliable** overall efficacy and safety profile of Copaxone as a **first-line therapy**

- Introduction of purported generics with **uncertain clinical profile** will shift medical decisions toward second line therapies and **increased risks to patients**

Predicting Safety and Efficacy

- Current laboratory assays, including those practiced in own institution, are **insufficient to guarantee equivalence** in clinical effect
- EAE and other model systems are useful for potency characterization but have proven **misleading as predictors of clinical efficacy or safety**
- Information on **clinical outcomes** with purported generics will be valuable for clinicians to **assess safety and efficacy**

Experimental Allergic Encephalomyelitis (EAE)

- Widely used **animal model** of MS, utilized for testing candidate compounds for **efficacy in MS. First developed 1931**
- Inflammation and demyelination are induced in the CNS by **infiltrating activated T-cells**
- **No evidence for clinical safety or infection risk** can be derived. For example no hint of PML when Natalizumab developed
- Due to **lack of predictability**, results in EAE **cannot be used** to directly compare Copaxone and purported generics to claim sameness
- "…. there are **many discrepancies between the pathology of EAE and MS**. Therefore, extrapolations must be made with **caution** when **predicting** what might happen in MS, based on results obtained in the EAE model." *[L. Steinman, Neuron, 1999]*

EAE Not Predictive of Efficacy or Safety in MS

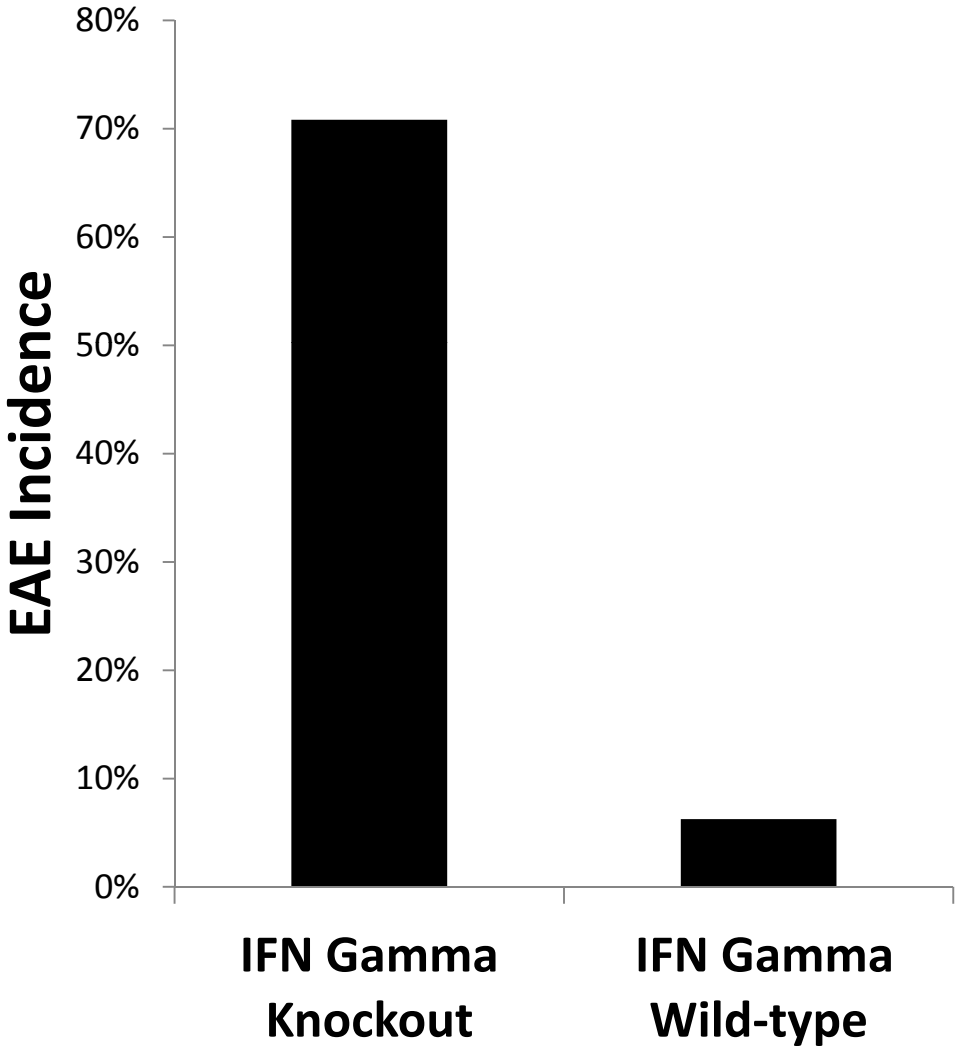
- Despite **positive effects in EAE**, many compounds failed in human, in some cases **even exacerbated the disease**

[L. Steinman, *Neuron*, 1999; Constantinescu et al BMJ 2011]

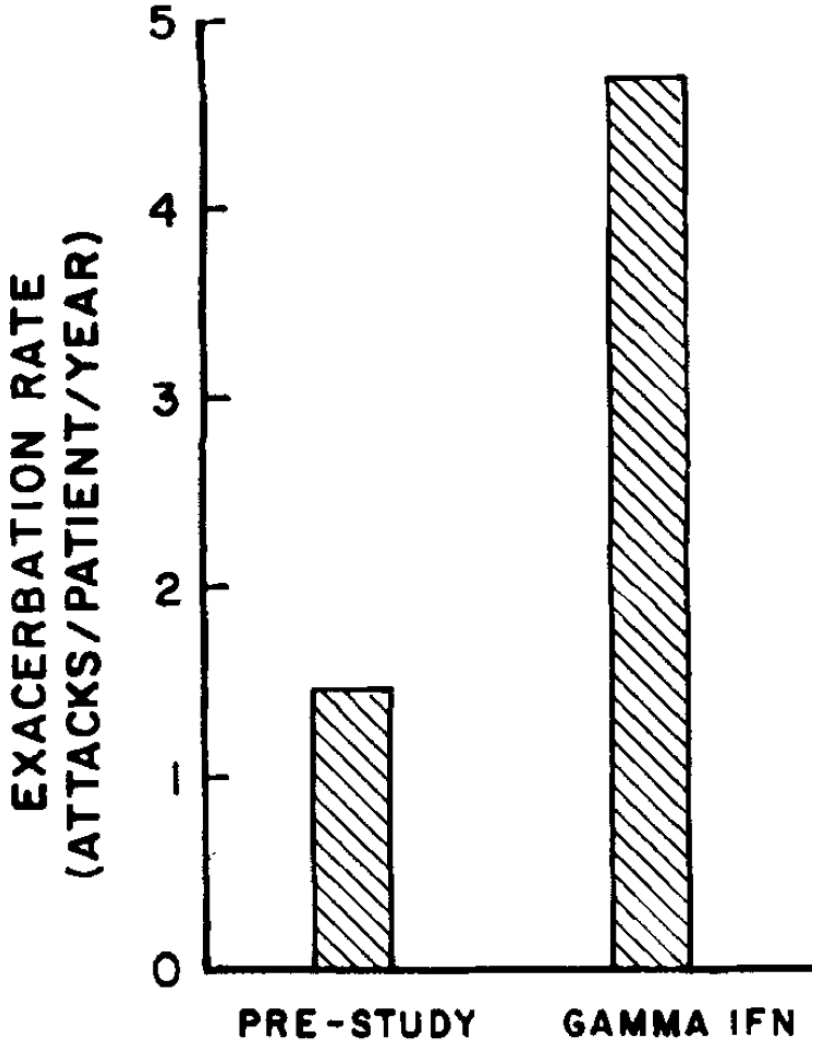
Therapy	EAE effect	MS effect
IFN-γ	*Effective*	*Worsens*
anti-TNFα Mab	*Effective*	*Worsens*
TNFα receptors blockers	*Effective*	*Worsens*
MBP altered peptide ligands	*Effective*	*Toxicity*
oral MBP	*Effective*	*Failed*
IL-10	*Effective*	*Failed*
TGFβ	*Effective*	*Failed*
anti-IL12p40	*Effective*	*Failed*

- Due to **lack of predictability**, results in EAE **cannot be used** to directly compare Copaxone and purported generics for sameness

IFNγ Confers Resistance to EAE, Exacerbates MS



Data from: [Krakowski et al, *Eur. J. Immunol*, 1996]



[Panitch et al, *Neurology*, 1987]

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Conclusions

- For the past **18 years** the Risk/Benefit profile of Copaxone has been favorable
- MS patients **depend** on its **consistent efficacy**, as well as **low adverse event** profile for **decades of chronic treatment**
- Lack of a fully characterized molecular target / validated surrogate for outcomes render approval of a generic based **solely** on *in vitro* characterization **uncertain for assuring efficacy and safety**
- A contemporary clinical trial to confirm the safety and efficacy of the generic would **address this uncertainty**

Synthon Phase 3 Trial

- Synthon is conducting a **Phase 3 trial** to satisfy **EU requirements** for approval of its generic to Copaxone
- Worldwide enrollment, including the US, ~750
- Copaxone vs. Synthon's GTR vs. Placebo
- **Primary Outcome**: Cumulative Gd+ lesions at month 7-9
- Estimated completion **imminent**

ClinicalTrials.gov Identifier: NCT01489254

Questions for Consideration

- Given data on characterization presented today, can it be concluded that purported generics are **really the same as Copaxone**?

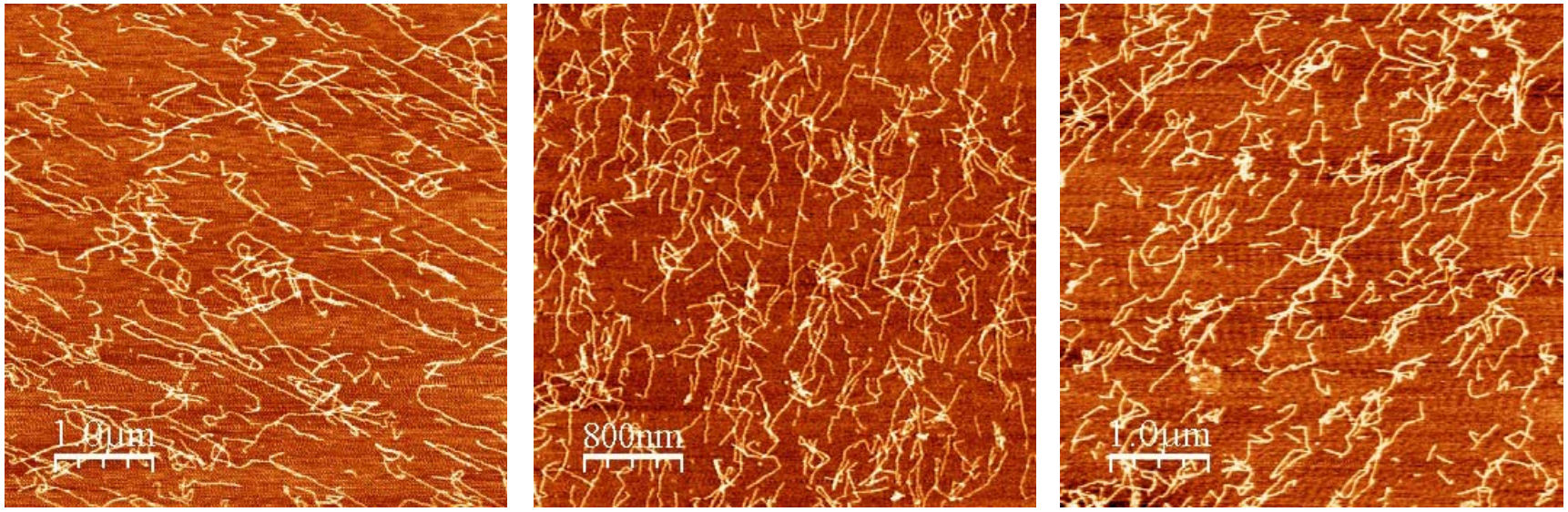
- Why would **concerns** around characterization of follow-on Copaxone products be less than for **biosimilars**, most of which are far better understood and less complex than Copaxone?

- Teva believes the only approach to showing therapeutic equivalence is by conducting **clinical trials**

BACK-UP SLIDES

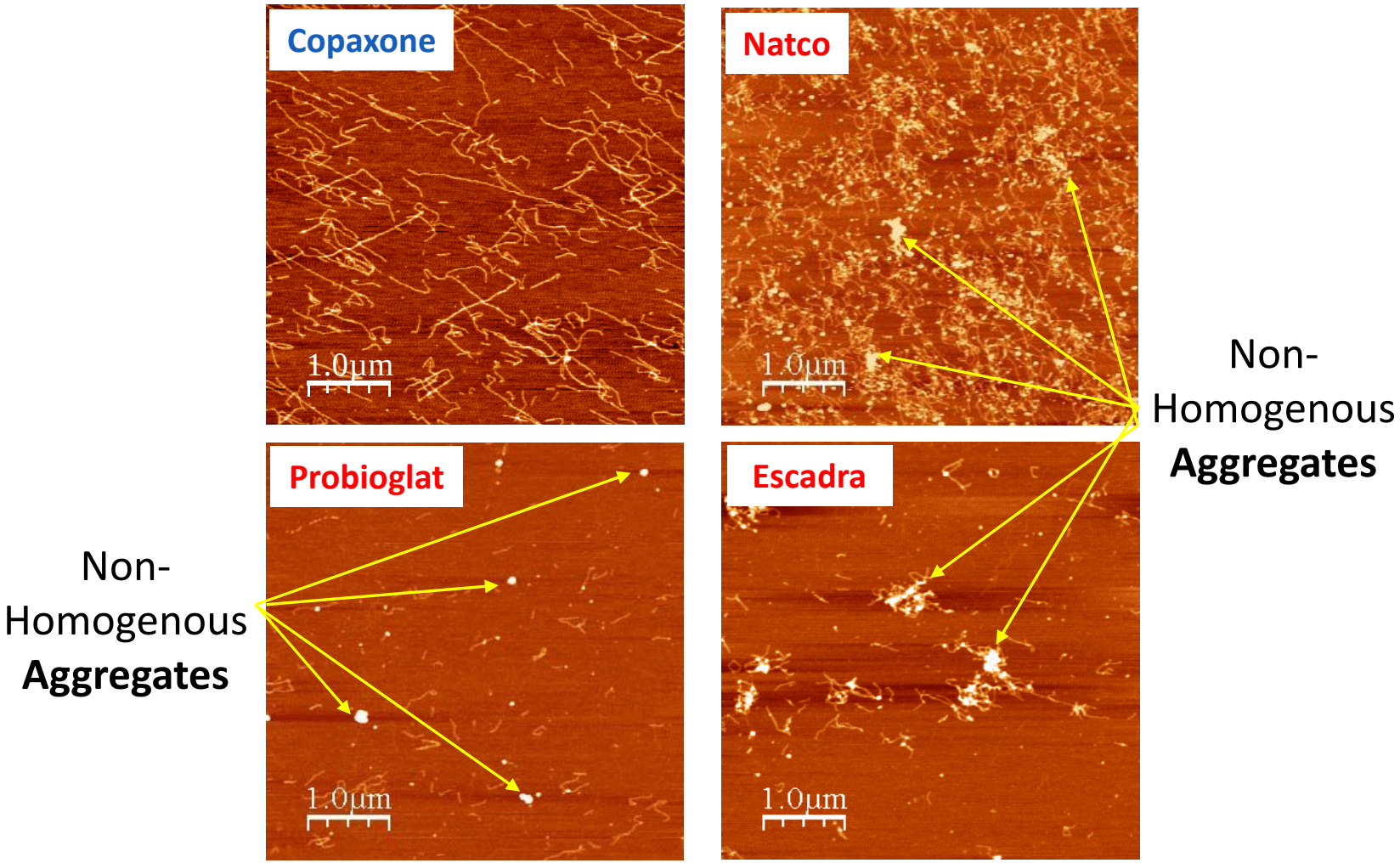
Copaxone Morphology by Atomic Force Microscopy

Morphology of aggregates: different batches of Copaxone analyzed by Atomic Force Microscopy (AFM) show **consistent linear folded structures** (strings)



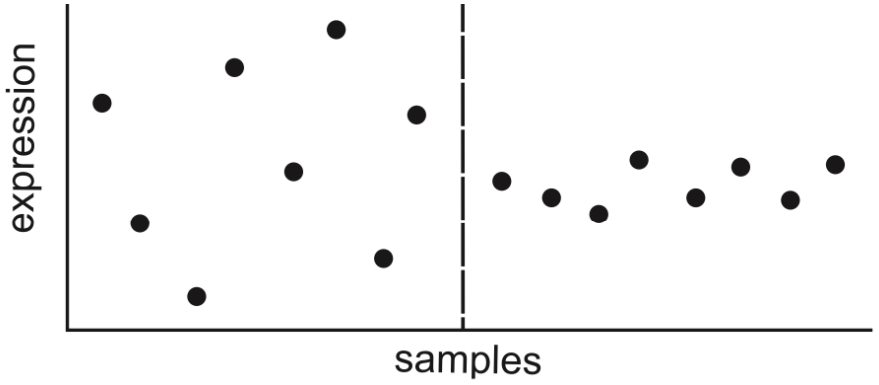
Morphology Analysis: Differences in Composition

Large globular aggregates present in purported generics



Natco's Variability 4 Fold Higher than Copaxone

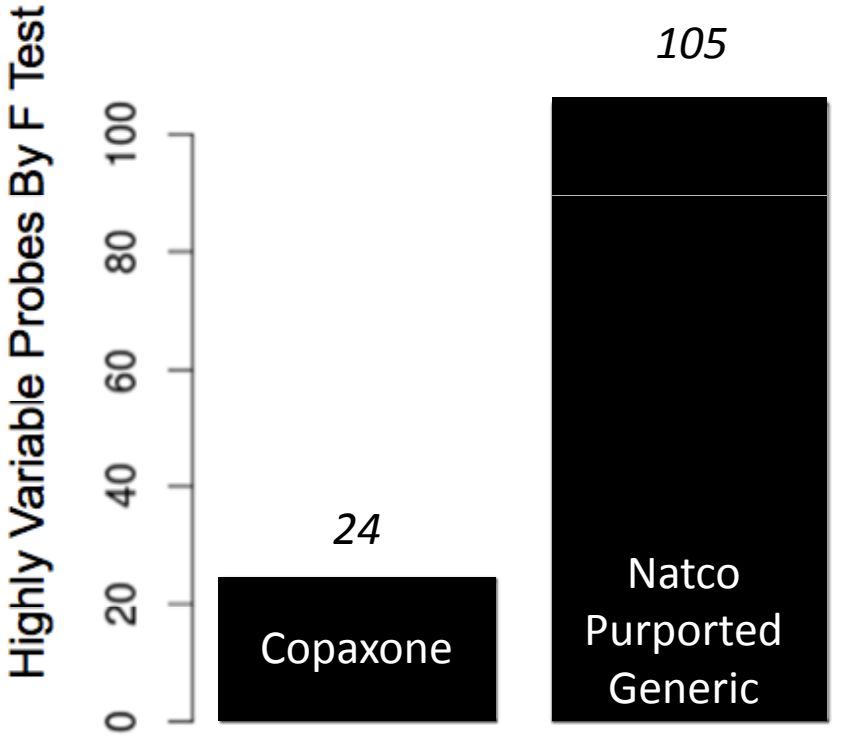
F-test for differential variability analysis



$$f = \frac{s_1^2}{s_2^2} = \frac{\text{variance}_{Natco}}{\text{variance}_{Copaxone}}$$

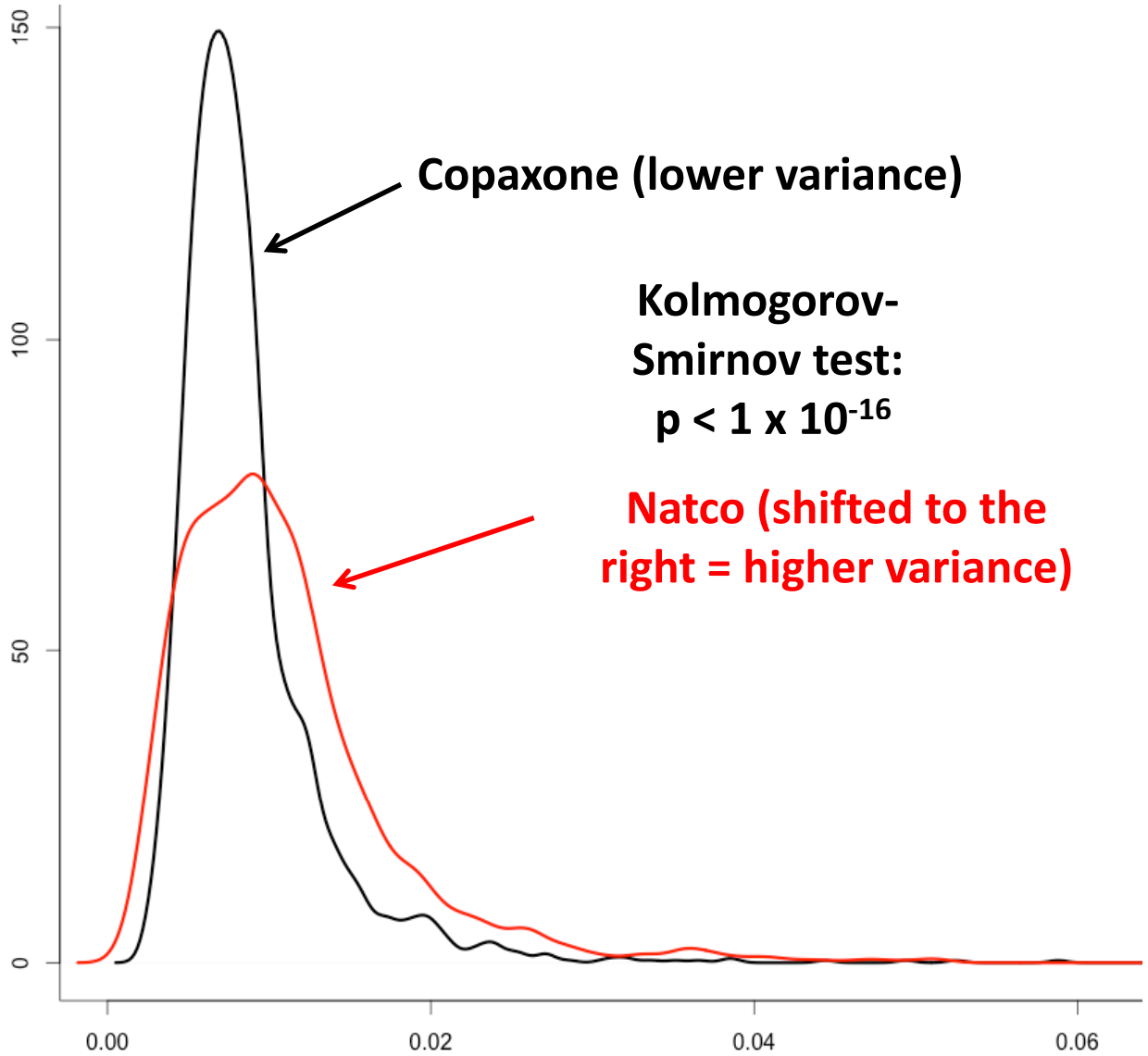
[Ho et al, 2008, *Bioinformatics*,]

Number of probes found to be highly variable across batches



Among probes with significant variability relative to medium
[Towfic et al, 2014, *PLOS ONE*, Fig. 1A]

Natco Induces Higher Variance than Copaxone



Among probes with significant variability relative to medium [Towfic et al, 2014, *PLOS ONE*]