Alteration of lipids and the transcription of lipid-related genes in Imatinib-treated CML

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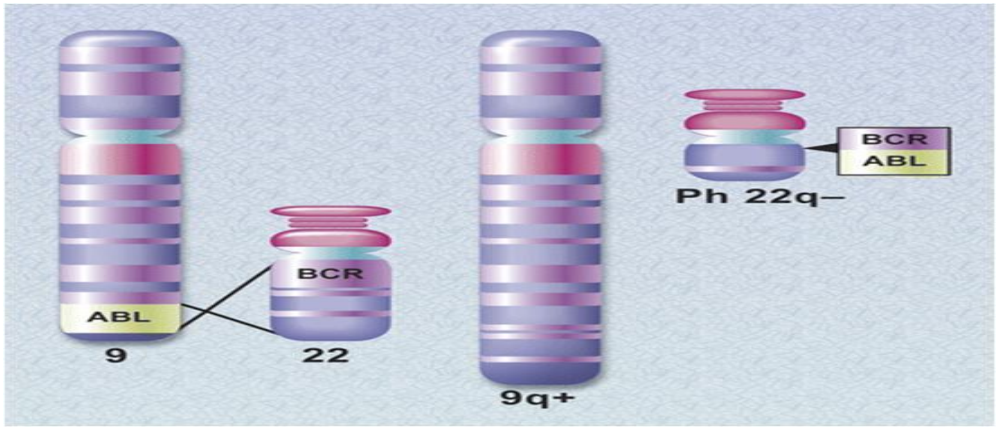
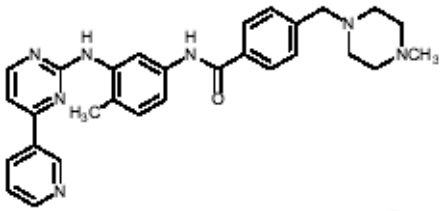
CML
Chronic Myeloid Leukemia

- Clonal myeloproliferative neoplasm
- Philadelphia chromosome
- BCR/ABL1 tyrosine kinase

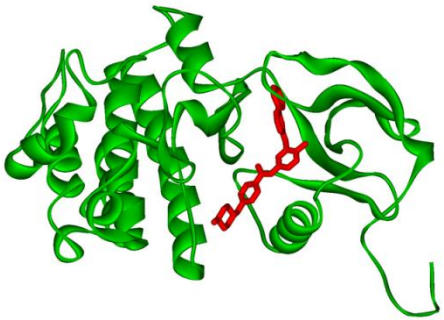


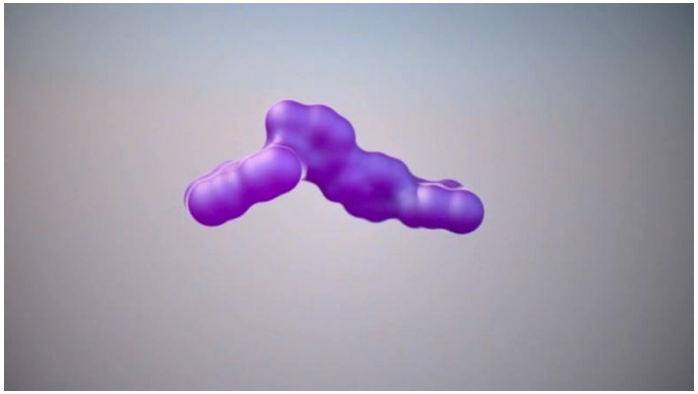
Imatinib

X-Ray Structure of Abl-Tk/STI-571 (1IEP)



STI-571(a.k.a. imatinib or Gleevec®)





Imatinib

Metabolic effects

Imatinib and Regression of Type 2 Diabetes

TO THE EDITOR: We report the case of a nulliparous, 70-year-old woman with long-standing type 2 diabetes mellitus who had regression of the disease during treatment of chronic myeloid leukemia with imatinib, an antineoplastic agent. Type 2 diabetes mellitus was diagnosed when the patient was 62 years of age and weighed 60 kg (body-mass index [the weight in kilograms divided by the square of the height in meters], 24.2) She was treated with diet for one year, oral agents for four years, and insulin thereafter. After the detection of leukocytosis and immature myeloid cells in the blood, chronic myeloid leukemia was diagnosed (in March 2004) and treatment with imatinib (400 mg per day) was initiated. Hematologic remission was documented two months later. During treatment with imatinib, the patient's blood glucose level progressively declined, and insulin doses were titrated down. Insulin treatment was discontinued in June 2004. In July 2004, a standard oral glucose-tolerance test revealed the following plasma glucose values:

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PNAS

Tyrosine kinase inhibitors reverse type 1 diabetes in nonobes

Cédric Louvet[a], Gregory
Arthur Weiss[c,1], and Jeff

[a]Diabetes Center and the Depar
Medicine and the Howard Hugh

www.pnas.org/cgi/doi/10.1073/

Imatinib Attenuates Diabetes-Associated Atherosclerosis

Markus Lassila, Terri J. Allen, Zemin Cao, Vicki Thallas, Karin A. Jandeleit-Dahm, Riccardo Candido, Mark E. Cooper

Objective—Diabetes is associated with accelerated atherosclerosis, the major factor contributing to increased mortality and morbidity in the diabetic population. The molecular mechanisms by which diabetes promotes atherosclerosis are not fully understood. Platelet-derived growth factor has been shown to play a major role in the pathology of vascular diseases, but whether it plays a role in atherosclerosis associated with diabetes remains unknown. The aims of this study were to assess whether platelet-derived growth factor–dependent pathways are involved in the development of diabetes-induced atherosclerosis and to determine the effects of platelet-derived growth factor receptor antagonism on this disorder.

Methods and Results—Diabetes was induced by injection of streptozotocin in 6-week-old apolipoprotein E knockout mice. Diabetic animals received treatment with a tyrosine kinase inhibitor that inhibits platelet-derived growth factor action, imatinib (STI-571, 10 mg/kg per day), or no treatment for 20 weeks. Nondiabetic apolipoprotein E knockout mice served as controls. Induction of diabetes was associated with a 5-fold increase in plaque area in association with an increase in aortic platelet-derived growth factor-B expression and platelet-derived growth factor-β receptor phosphorylation as well as other prosclerotic and proinflammatory cytokines. Imatinib treatment prevented the development of atherosclerotic lesions and diabetes-induced inflammatory cytokine overexpression in the aorta.

Conclusions—Tyrosine kinase inhibition with imatinib appears to be a novel therapeutic option to retard the development of atherosclerosis, specifically in the context of diabetes. (***Arterioscler Thromb Vasc Biol.*** **2004;24:935-942.)**

The NEW ENGLAND JOURNAL of MEDICINE

Imatinib and Hyperlipidemia

N ENGL J MED 353;25 DECEMBER 22, 2005

Table 1. Plasma Lipid Levels in Nine Patients Receiving Imatinib Therapy.*

Patient	Underlying Disease	At Diagnosis	Day 30 of Imatinib Therapy	Last Follow-up	
				Value	Mo from Starting Imatinib
		mg per deciliter			
Patient 1	HES				30
Cholesterol		223	183	185	
Triglyceride		154	64	75	
Patient 2	CML				27
Cholesterol		282	181	174	
Triglyceride		230	126	130	
Patient 3	CML				27
Cholesterol		293	160	162	
Triglyceride		230	126	128	
Patient 4	CML				25
Cholesterol		240	187	174	
Triglyceride		93	41	52	
Patient 5	HES				18
Cholesterol		250	260	257	
Triglyceride		230	240	245	
Patient 6	HES				17
Cholesterol		233	174	165	
Triglyceride		368	138	152	
Patient 7	CML				17
Cholesterol		229	179	184	
Triglyceride		145	81	97	
Patient 8	CML				14
Cholesterol		249	160	158	
Triglyceride		144	150	148	
Patient 9	CML				4
Cholesterol		284	182	165	
Triglyceride		150	127	115	

NEJM

Study pitfalls

- Small study group (n=9)
- Heterogeneous cohort
- Limited lipid-profile
- No statistical analysis
- No *in-vitro* study

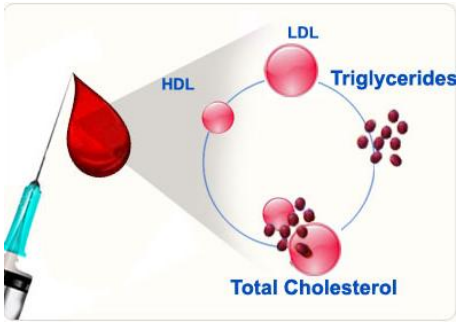
Study aim

To confirm Imatinib beneficial lipid effect in a larger-scale group of CML patients

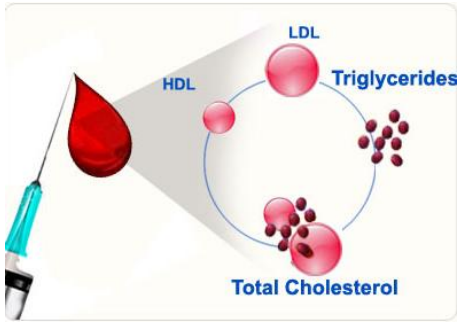
Study Cohort

- 40 CML patients
- January 2005 - March 2015
- 3m of imatinib treatment

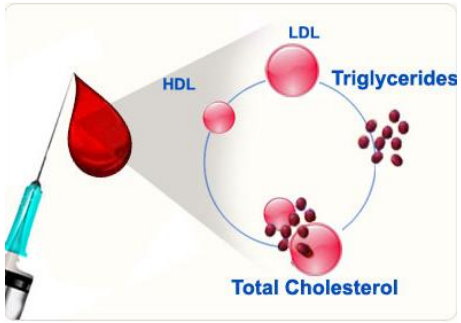
Retrospective Follow-up



Baseline



3-12 months



>12 months

Before
Imatinib

After
Imatinib

RESULTS

Patient data

- 55% male
- Mean age 67.3
- Median time from diagnosis to imatinib –1m
- 47.5% prior treatment with statins

Imatinib improves lipid profile

Baseline:

	Sex	Age	T. Ch	Tg	HDL	LDL	Non HDL
#1	M	68	213.0	265.0	43.0	117.0	127.8
#2	F	57	195.0	144.0	39.0	127.0	98.2
#3	F	55	218.0	170.0	44.0	140.0	119.2
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
#38	F	80	213.0	149.0	54.0	129.0	159.0
#39	M	68	204.0	184.0	59.0	108.0	96.0
#40	M	55	172.7	114.0	46.0	102.1	72.0
Avg.			**175.6**	**172.0**	**40.2**	**100.5**	**135.4**

3-12 months:

	Sex	Age	T. Ch	Tg	HDL	LDL	Non HDL
#1	M	68	202.3	258.0	42.0	104.3	160.3
#2	F	57	119.0	107.0	42.0	56.7	77.0
#3	F	55	205.0	116.0	41.0	140.8	164.0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
#38	F	80	203.9	89.0	74.0	110.9	129.9
#39	M	68	161.0	147.0	50.0	82.0	111.0
#40	M	55	133.0	74.0	44.0	74.0	89.0
Avg.			**157.3**	**127.8**	**47.5**	**83.8**	**109.8**
T-test			**0.0302**	**0.0016**	**0.0023**	**0.0144**	**0.0012**

Imatinib improves lipid profile

Baseline:

	Sex	Age	T. Ch	Tg	HDL	LDL	Non HDL
#1	M	68	213.0	265.0	43.0	117.0	127.8
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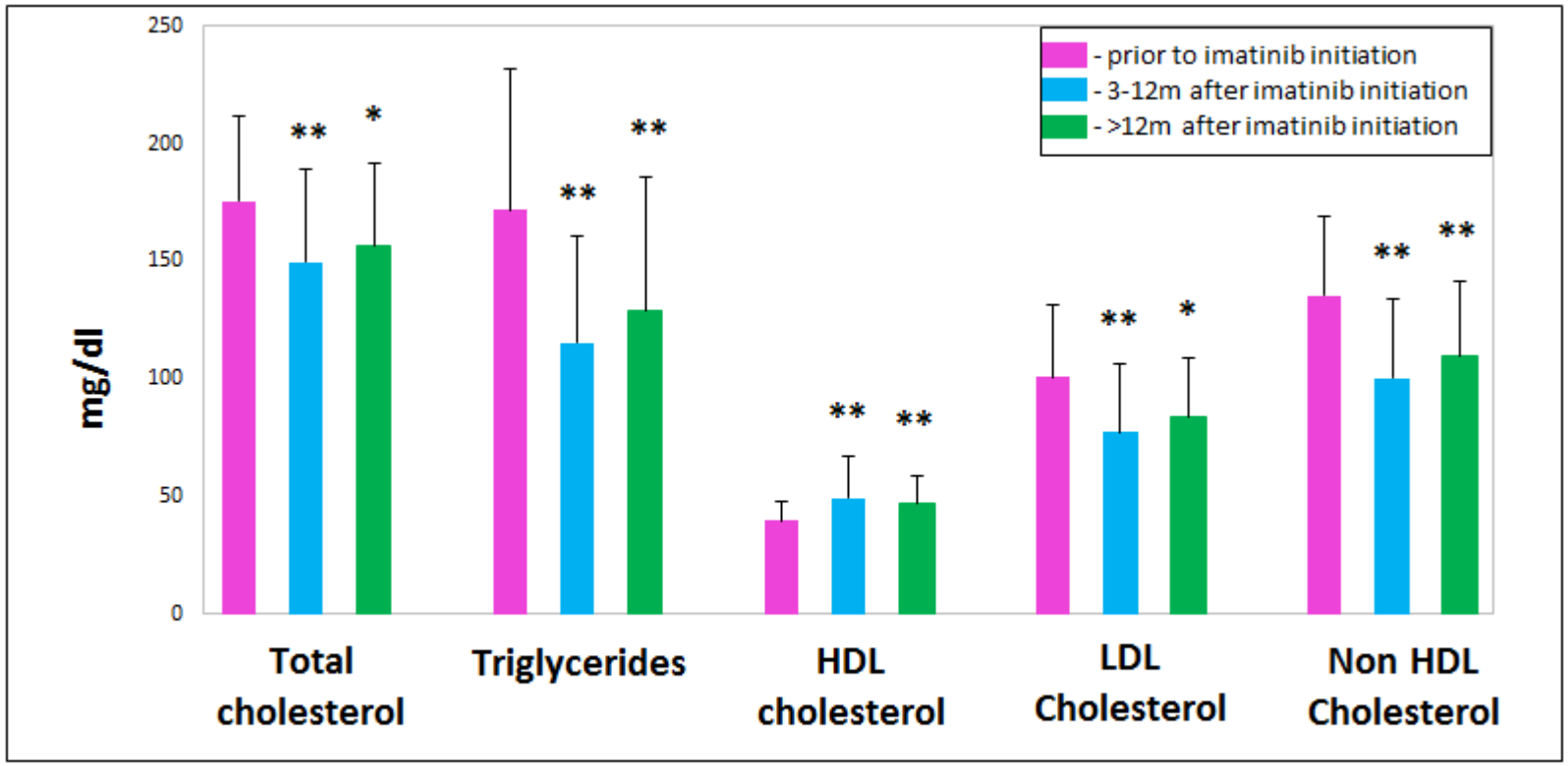
Avg.			**175.6**	**172.0**	**40.2**	**100.5**	**135.4**

>12 months:

	Sex	Age	T. Ch	Tg	HDL	LDL	Non HDL
#1	M	68	209.0	171.0	47.0	127.8	162.0
#2	F	57	152.0	79.0	38.0	98.2	114.0
#3	F	55	187.0	134.0	41.0	119.2	146.0
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
#38	F	80	204.3	89.0	73.0	112.5	131.3
#39	M	68	177.0	138.0	53.0	96.0	124.0
#40	M	55	131.0	82.0	43.0	72.0	88.0
Avg.			**150.0**	**111.9**	**50.1**	**77.6**	**99.8**
T-test			**0.005**	**4.7E-06**	**0.002**	**0.002**	**2.4E-05**

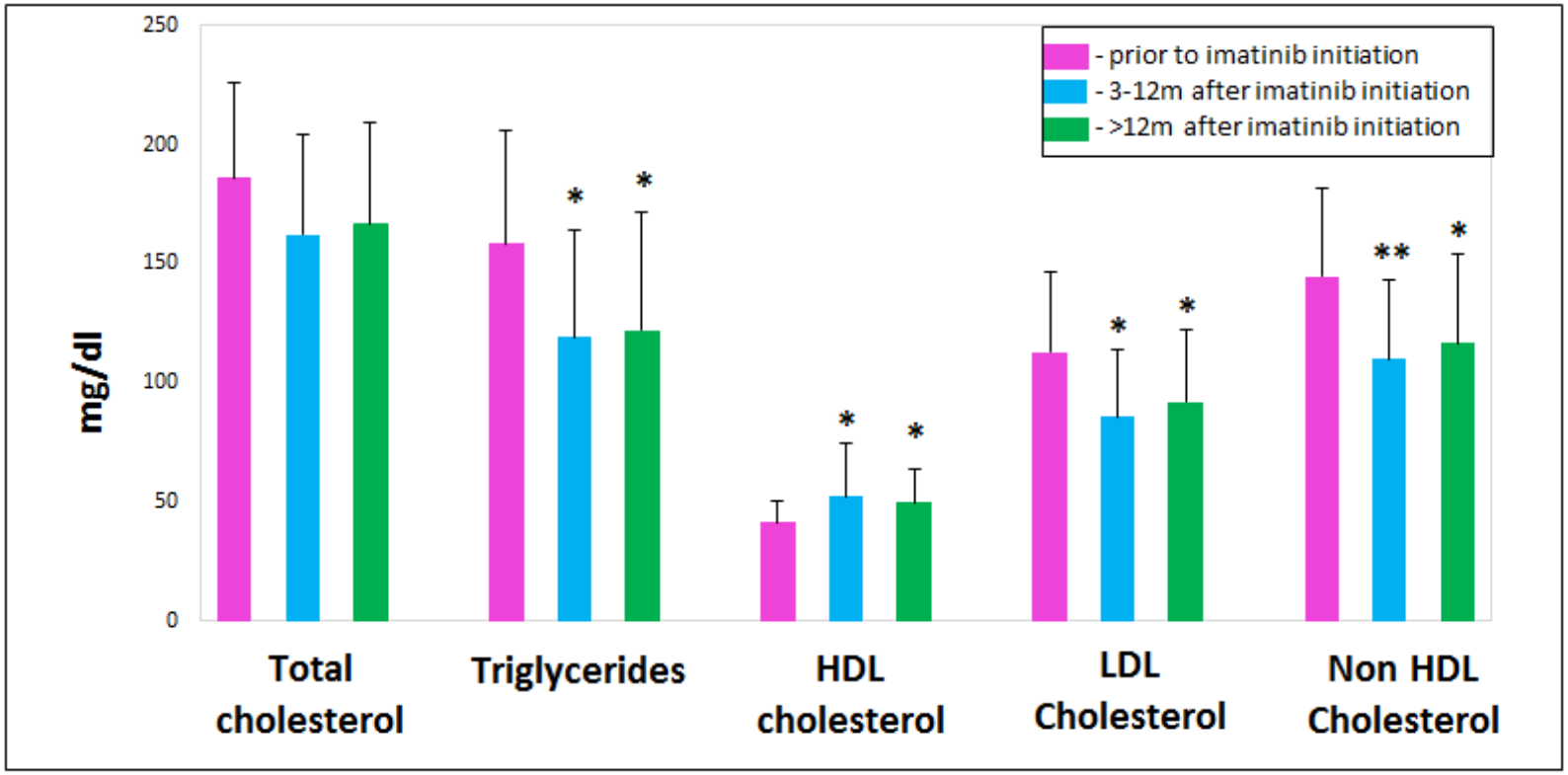
Imatinib improves lipid profile

All patients



Imatinib improves lipid profile

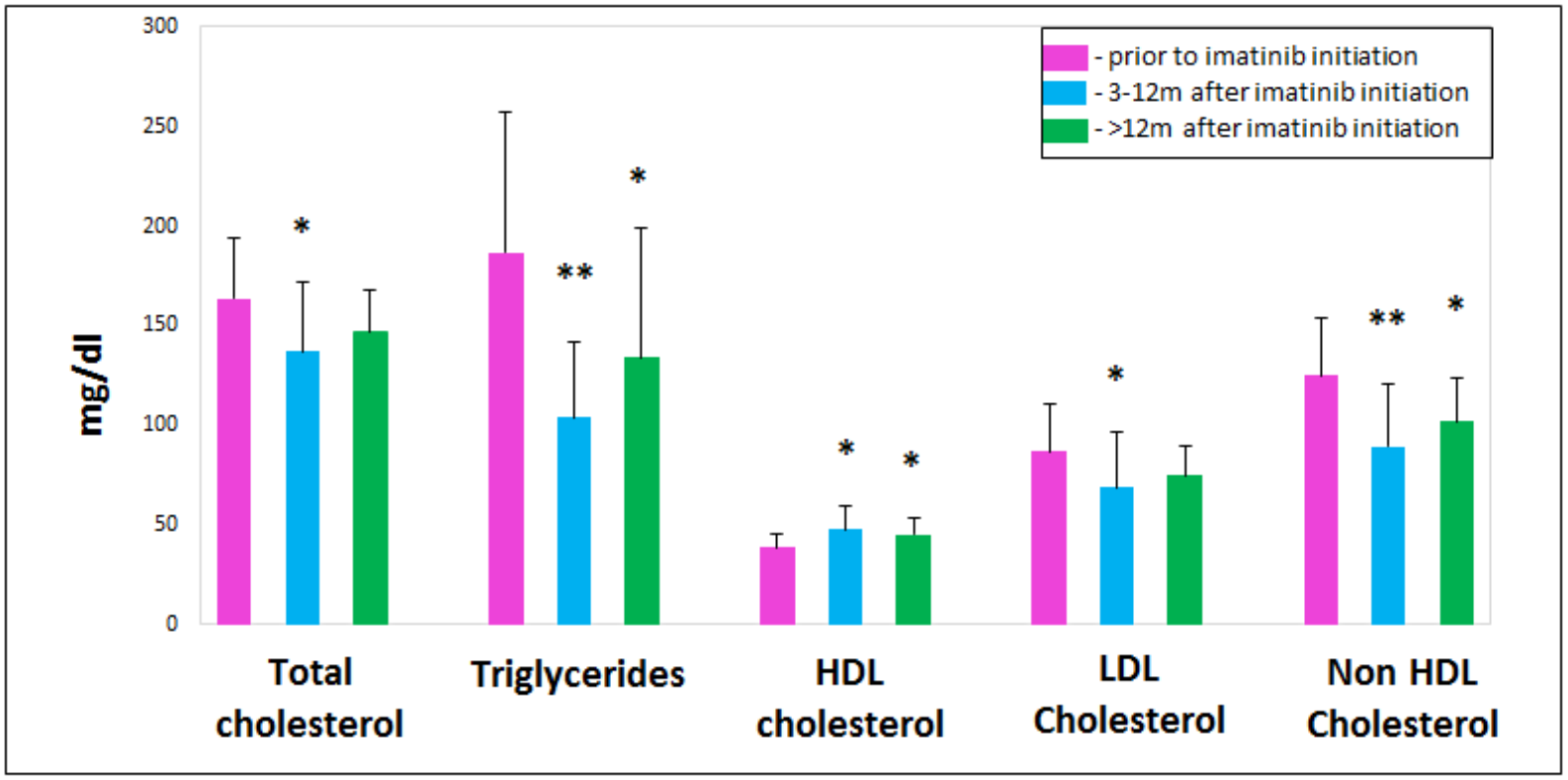
No statins



Lipid profile without statins, n=21

Imatinib improves lipid profile

With statins



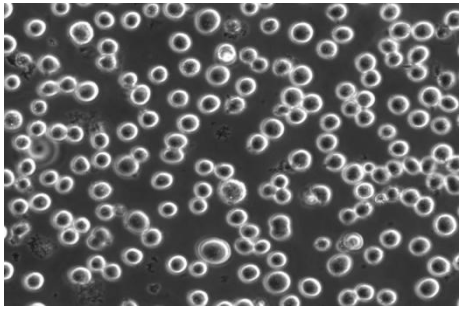
Lipid profile with statins, n=19

Study aim

To study *in vitro* the mechanism of Imatinib-lipid-effect in CML

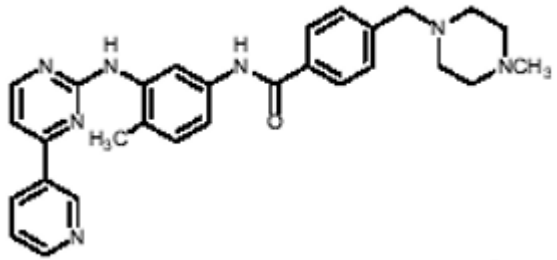
CML model

In vitro



K-562

+

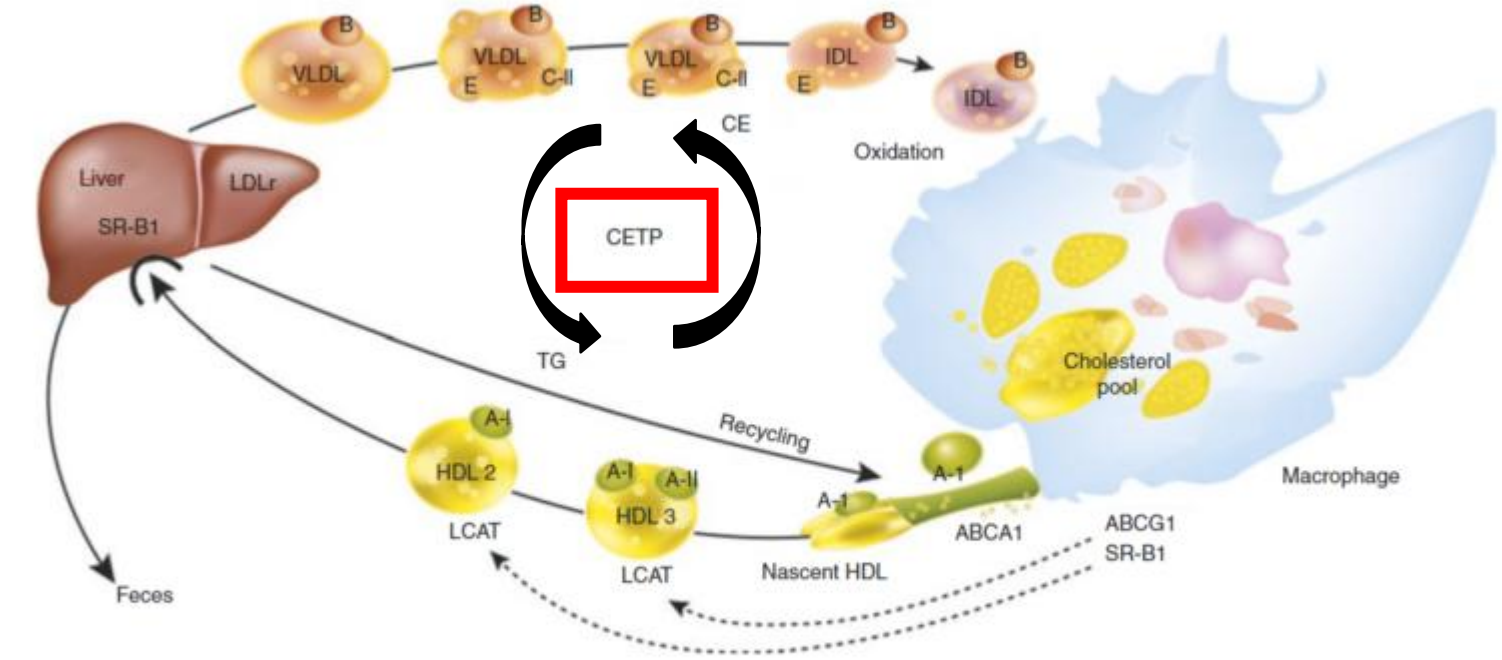


Imatinib

24h
48h
72h
96h

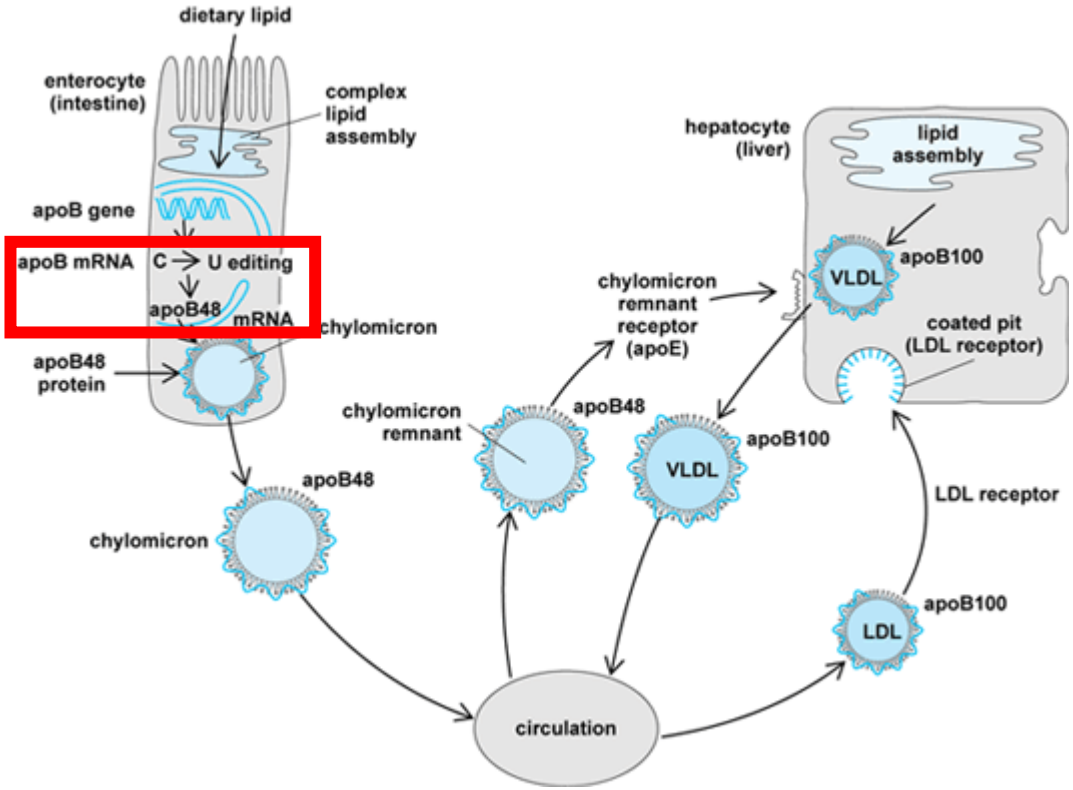
Lipid-related
genes transcription

CETP

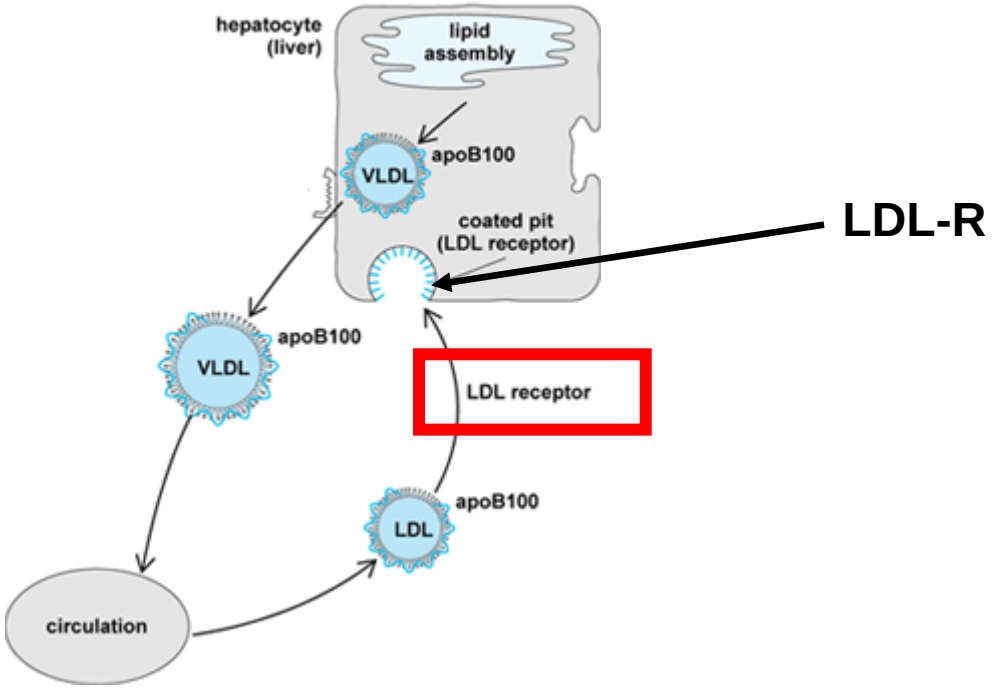

B
VLDL
VLDL
E
C-II
VLDL
IDL
IDL
CE
Oxidation
Liver
LDLr
SR-B1
CETP
TG
Recycling
Cholesterol
pool
Macrophage
A-I
HDL 2
LCAT
A-I
A-II
HDL 3
LCAT
A-I
A-I
Nascent HDL
ABCA1
ABCG1
SR-B1
Feces

Apobec1

Apobec1 →



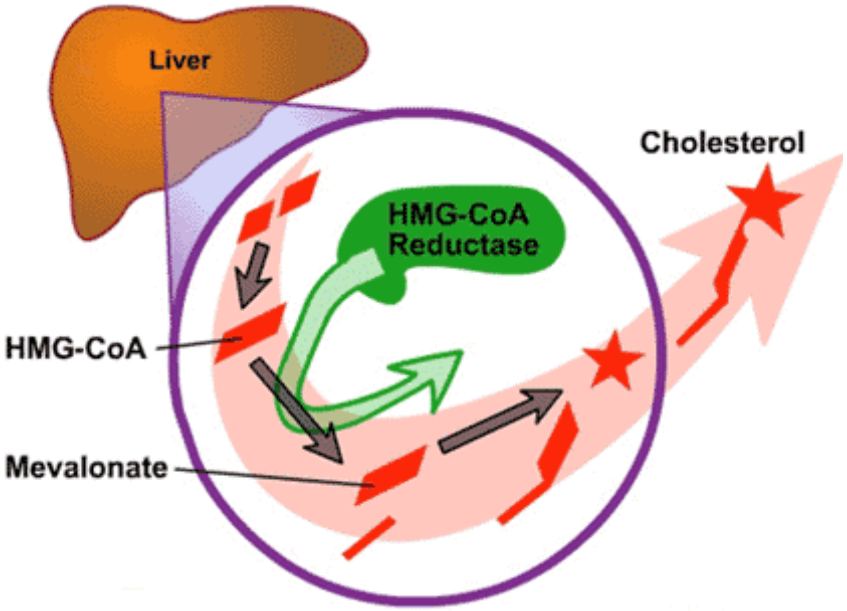
LDL Receptor



כללית מעל 100 שנה
הכי טובה למשפחה

מרכז רפואי מאיר
מסונף לפקולטה לרפואה, אוניברסיטת תל אביב

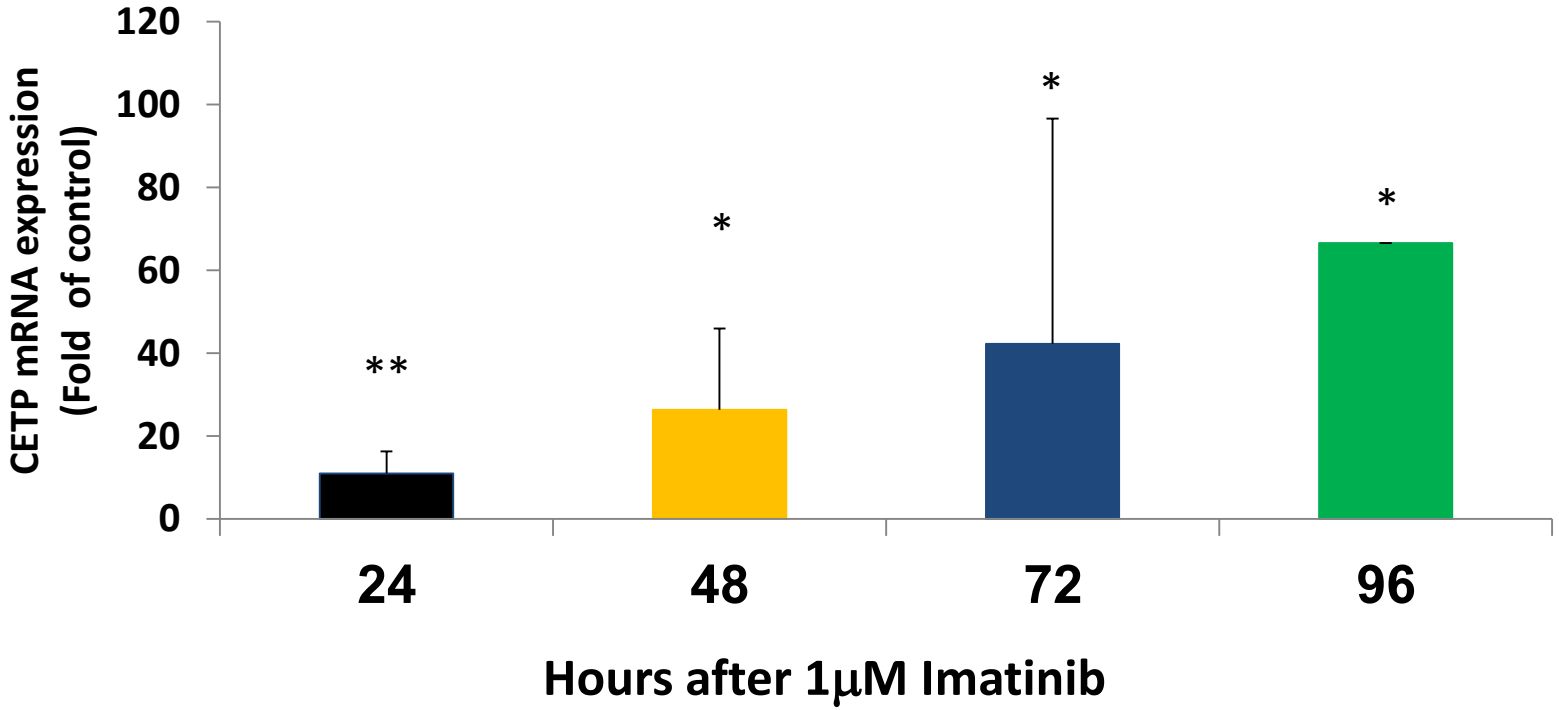
HMGcoAR



RESULTS

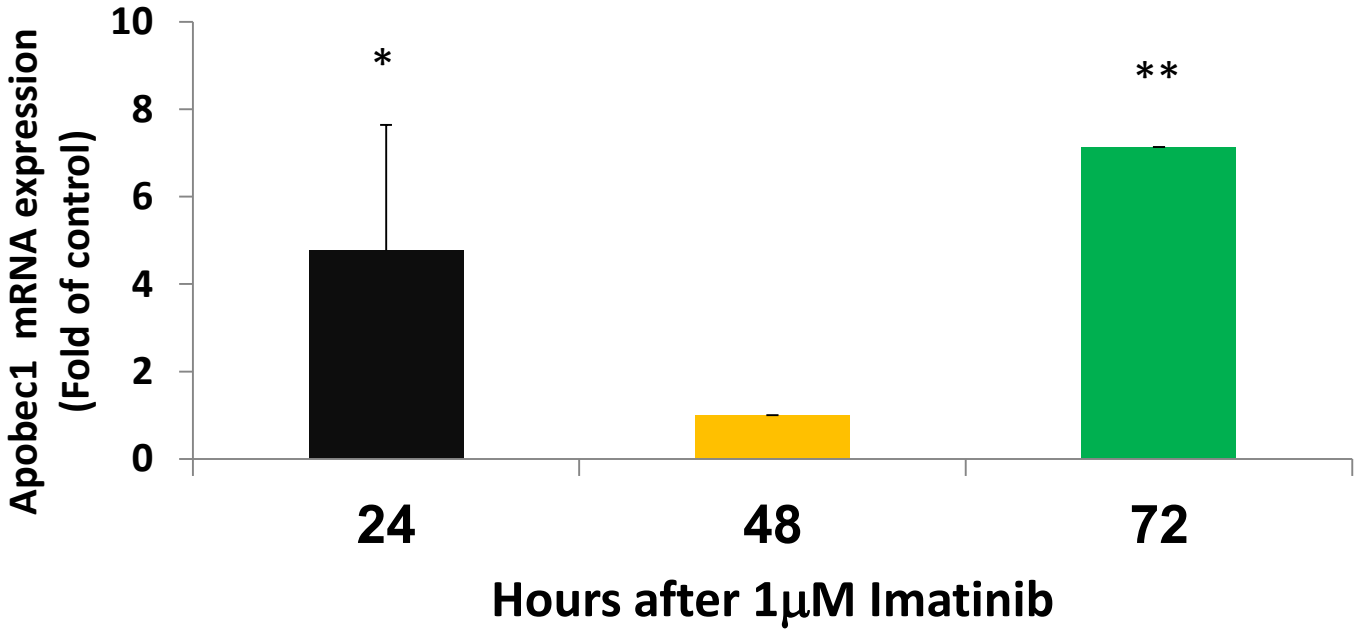
Imatinib

Induces CETP mRNA



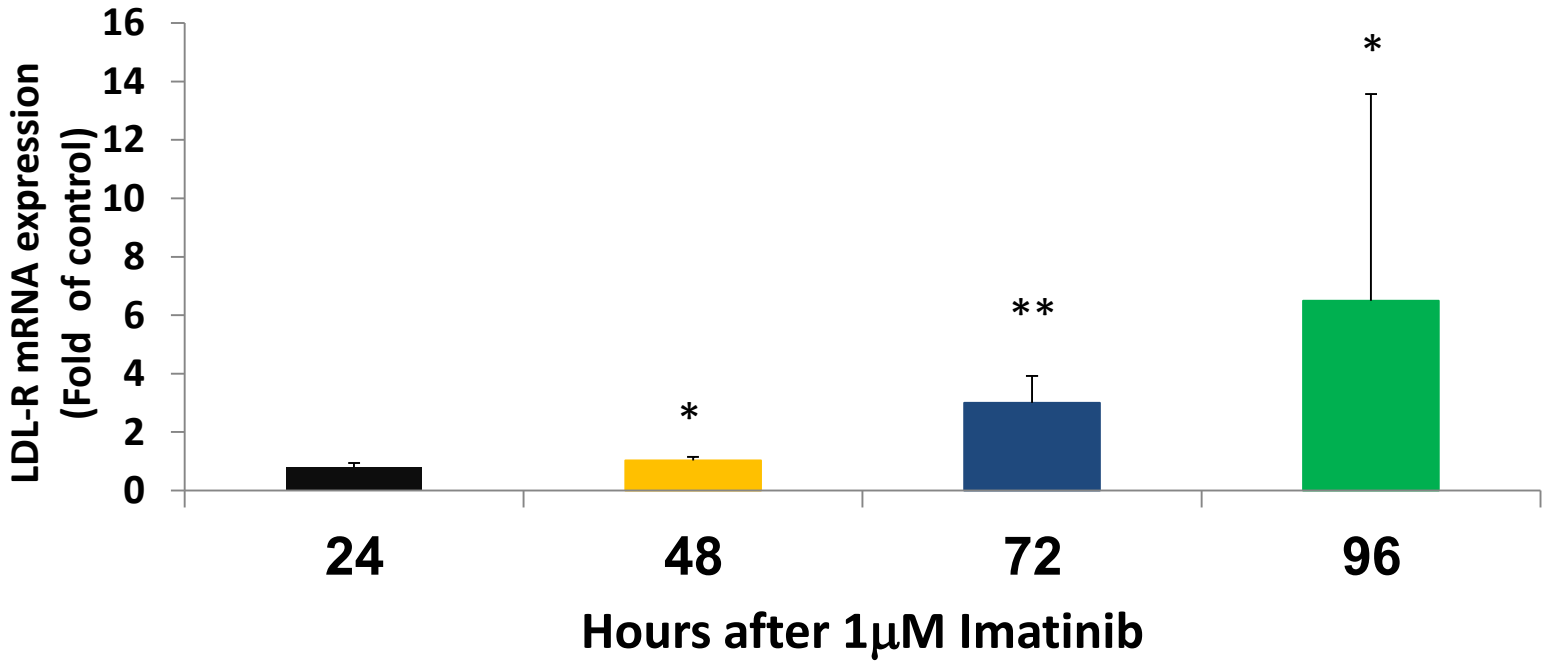
Imatinib

Induces apobec-1 mRNA



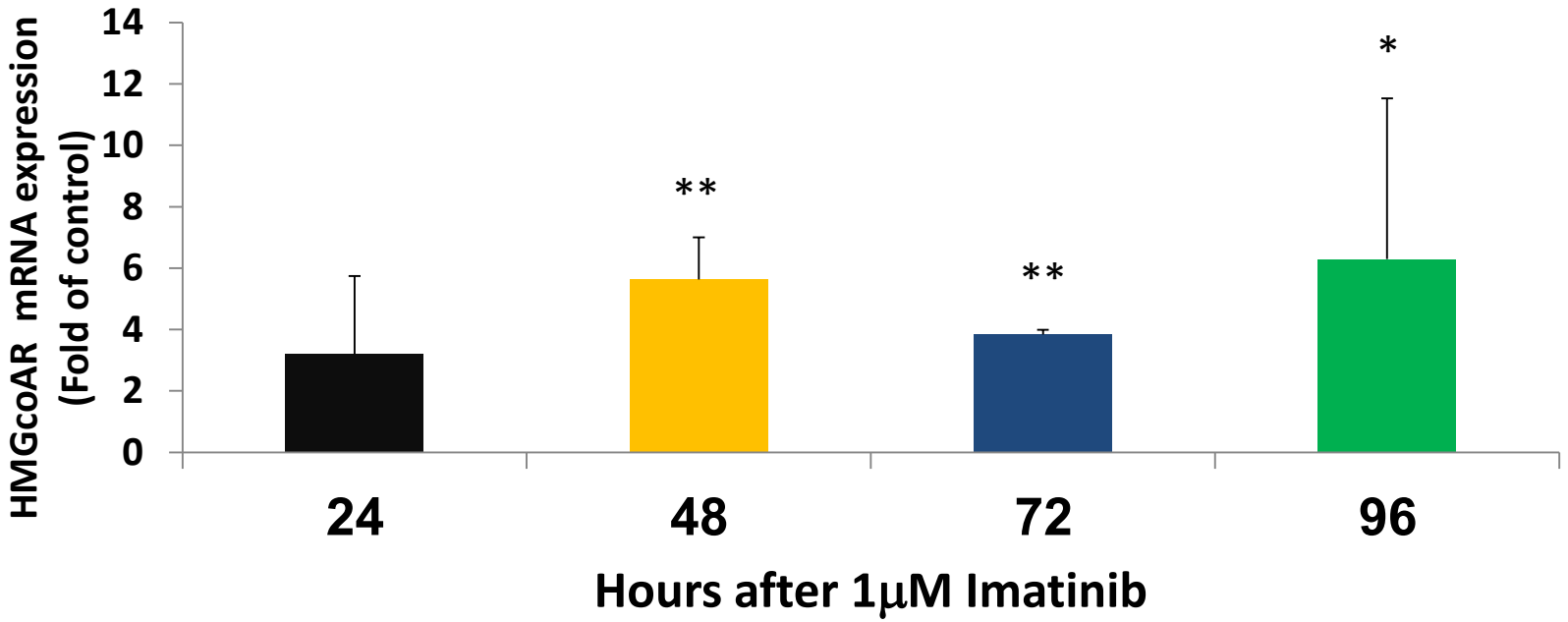
Imatinib

Induces LDL-R mRNA



Imatinib

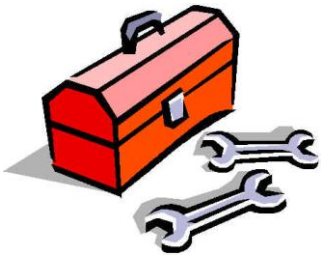
Induces HMGcoAR mRNA

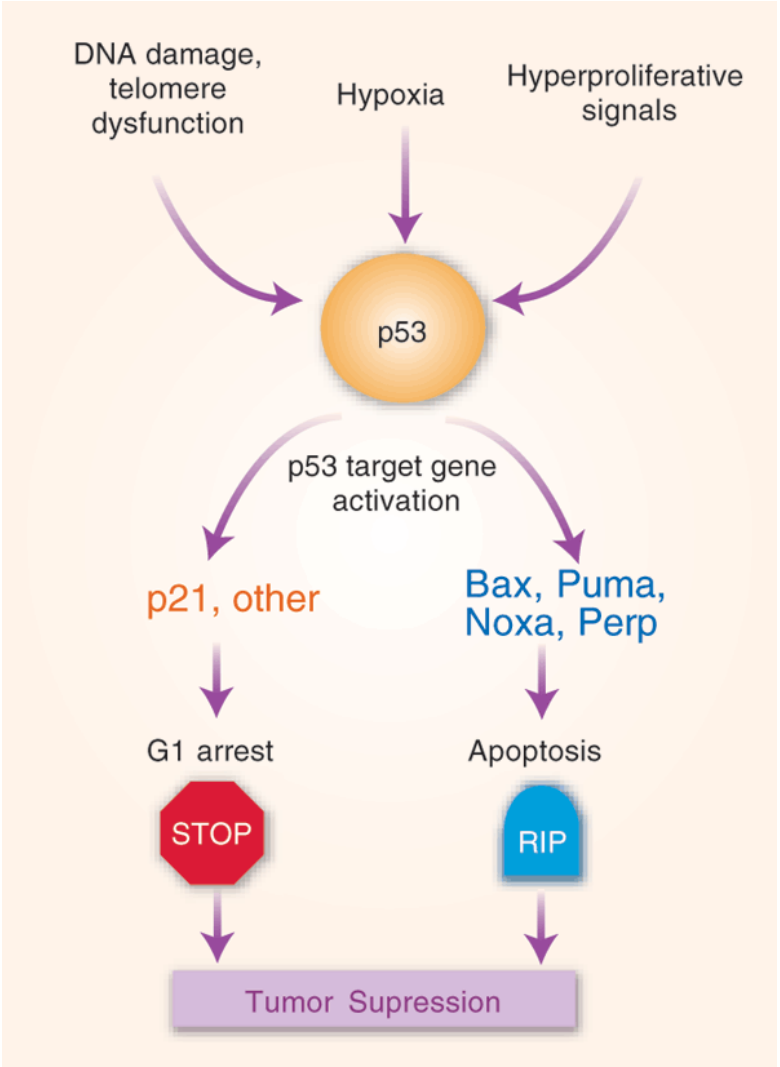


How are lipid-genes regulated by imatinib?

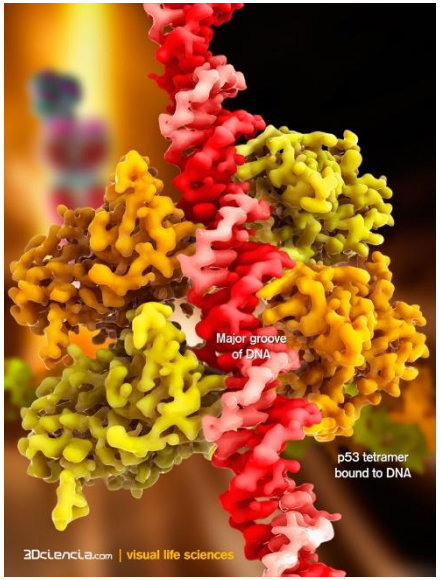
p53

Master Gene





p53 regulated genes



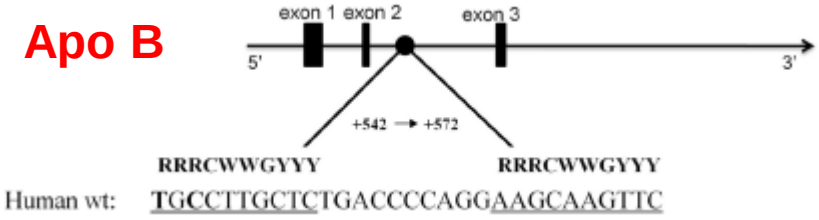
SHEBA MEDICAL CENTER

Novel p53 regulated genes

מרכז הסרטן
Cancer Center

Apobec-1

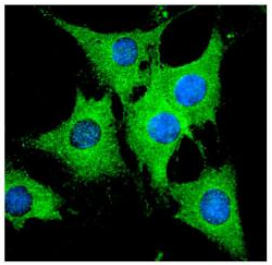
Apo B

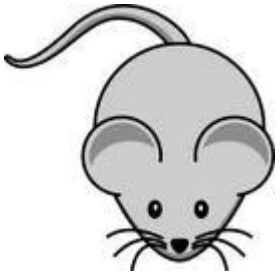


SHEBA MEDICAL CENTER

Novel p53 regulated genes

מרכז הסרטן
Cancer Center





REPORT

Cell Cycle 9:18, 3761-3770; September 15, 2010; © 2010 Landes Bioscience

apoB and apobec1, two genes key to lipid metabolism, are transcriptionally regulated by p53

Osnat Ashur-Fabian,[1,2,†,*] Adi Har-Zahav,[1,2,†] Aviv Shaish,[2,3] Hila Wiener Amram,[1,2] Ofer Margalit,[1,2,4] Orly Weizer-Stern,[1,2] Dan Dominissini,[1,2] Dror Harats,[2,3] Ninette Amariglio[1,2] and Gideon Rechavi[1,2]

SHEBA MEDICAL CENTER

Novel p53 regulated genes

מרכז הסרטן
Cancer Center

Gene name	% response element score	Genomic location
Apobec1	92.47%	Promoter
Apo B	91.2%	Intron 2
LDL receptor	86.29%	Promoter
HMGCoA R	83%	Promoter
LRP1	89.1%	Promoter
Apo E	83.56%	Promoter
Apo A1	85.38	Promoter
Apo C-I (VLDL)	83%	Promoter
LCAT	83.4%	Promoter
Apo B48 receptor	88%	Promoter
Apo A2	86%-Two sites	Promoter
Apo A4	81-85%-Two sites	Promoter

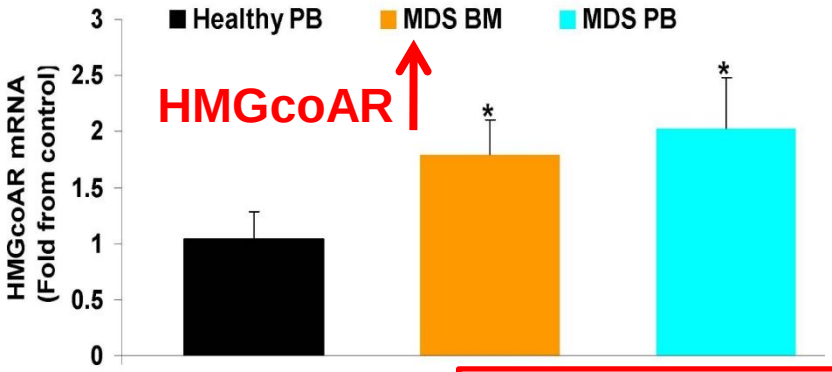
ELSEVIER

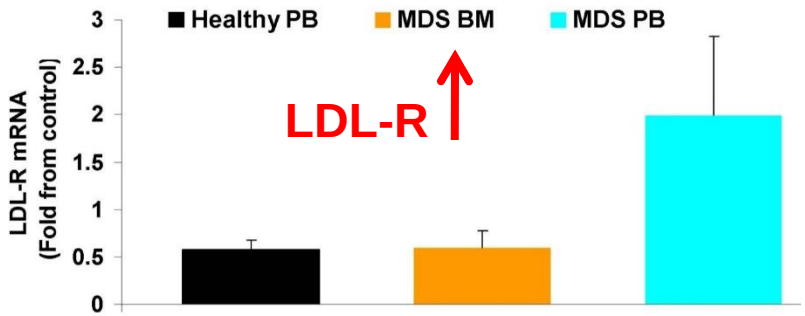
Experimental Hematology

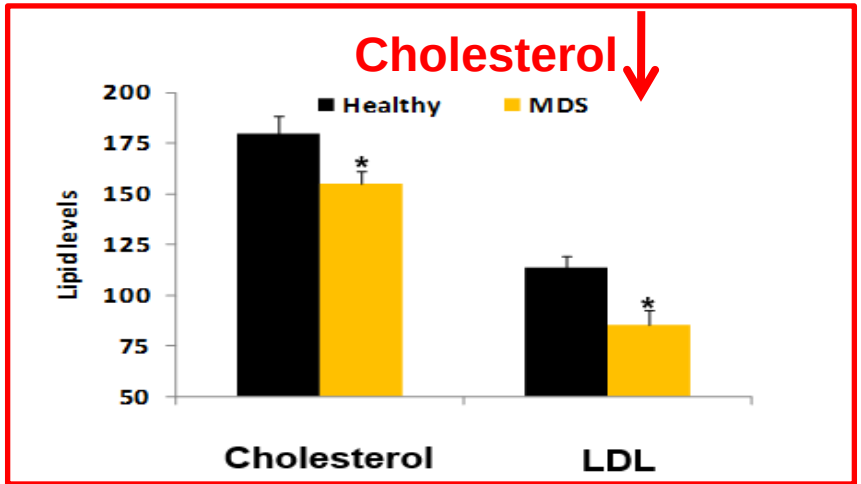
Experimental Hematology 2012;40:540–547

Alteration of lipids and the transcription of lipid-related genes in myelodysplastic syndromes via a TP53-related pathway

Martin H. Ellis[a,b], Lior Baraf[a], Aviv Shaish[c], Adi Har-Zahav[b,d], Dror Harats[b,c], and Osnat Ashur-Fabian[a,c]

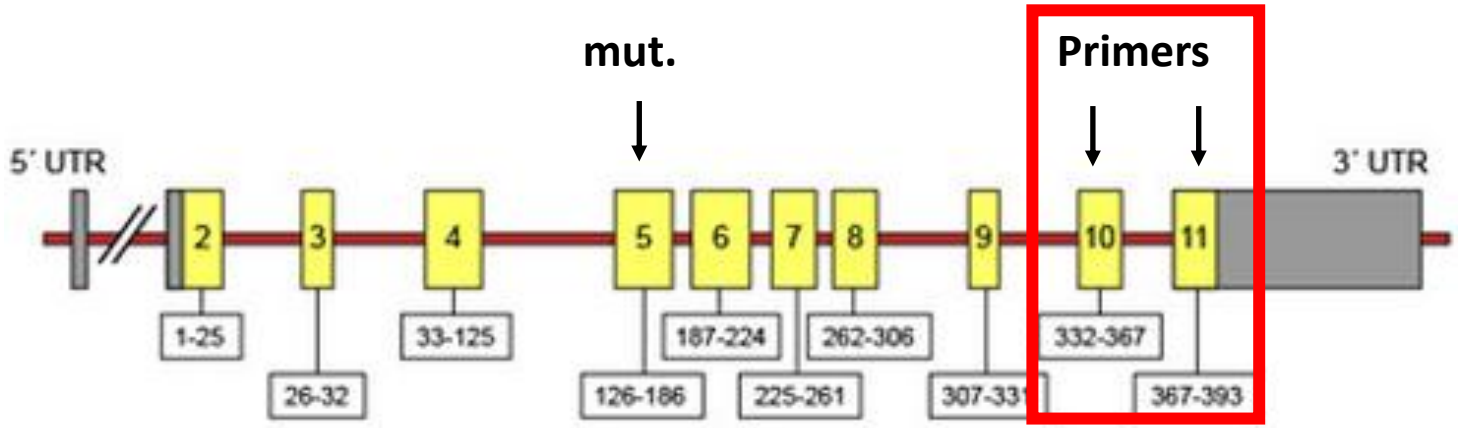




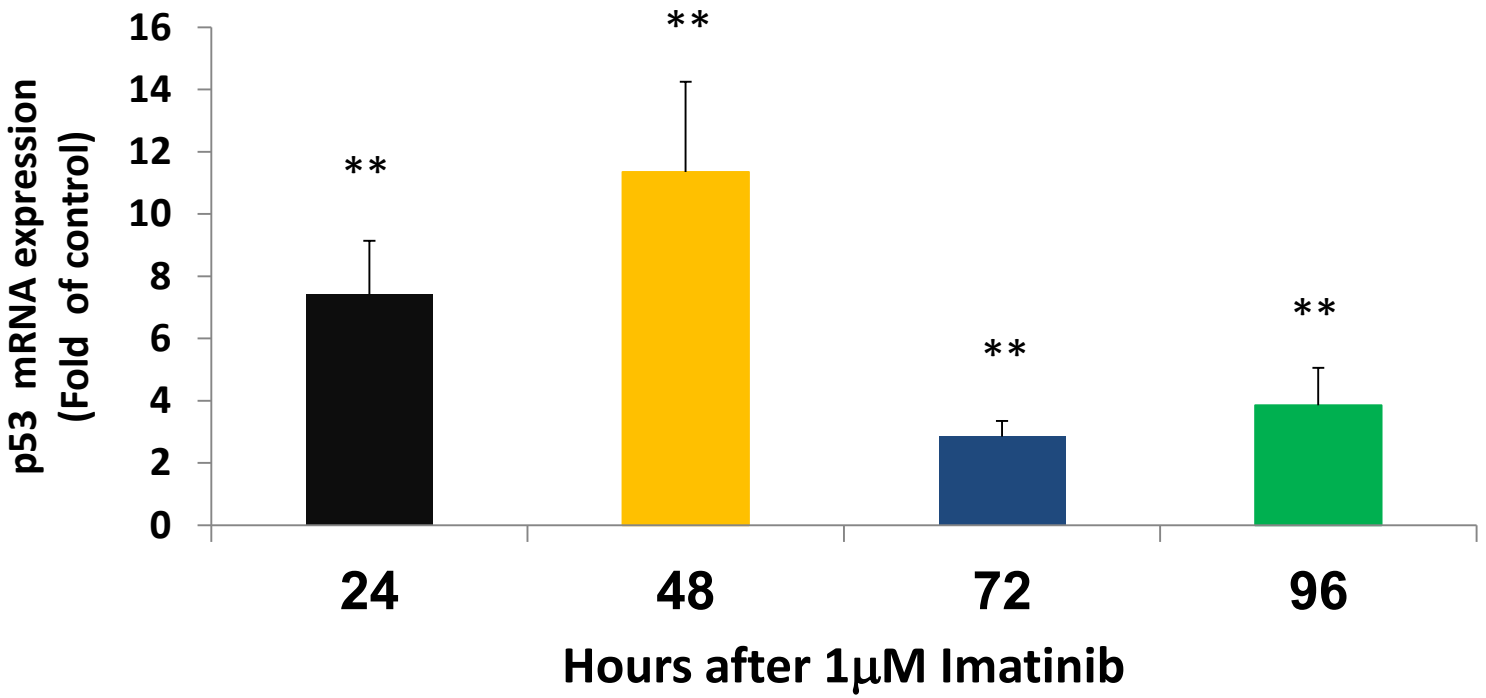


Is the lipid-genes expression in K-562 p53-mediated?

p53 mutation in K-562

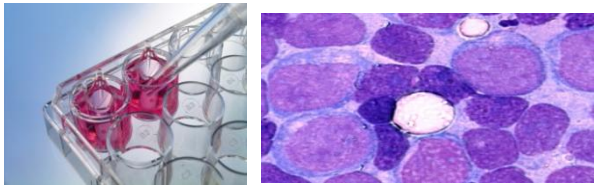


p53 is induced by imatinib



CML

In vitro



K562 (blast crisis)
no p53 expression

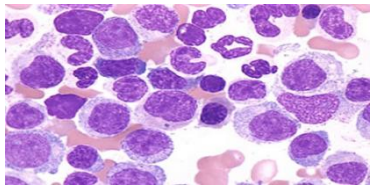
Imatinib

p63/73
expression?

↑ "lipid clearance genes" expression

CML

Patients



Chronic phase CML
Wild type p53

↓

Imatinib

↓

↑ p53 expression

↓

↑ "lipid clearance genes" expression

↓

Favorable lipid profile

Summary

- A favorable lipid profile with Imatinib in CML patients
- Imatinib induces lipid-clearing-genes in vitro

Future plans

CML patients

- To prove the imatinib-lipid molecular association in cells collected before/after Imatinib
- To asses p53 regulation
- To assess new generation TKI's effect

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