Galápagos

First selective JAK1 inhibitor: GLPG0634 from hit to Proof of Concept

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Protein Kinase 2012
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GLPG0634
The 1st selective JAK1 inhibitor

- Introduction
- Target identification
- Hit finding to PCC
- Clinical development
  - Phase I
  - Phase II Proof of Concept

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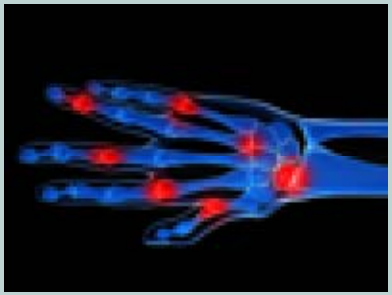
Rheumatoid arthritis (RA)
A global health issue

Disease facts

- Inflammation & destruction of joints
- Affects ~1% of population
- Typically diagnosed age 40-60
- 2-3 times more prevalent in women



Current treatments

- First line: steroids, methotrexate (MTX)
- Second line: disease-modifying biologics
  - TNFα blockers (Enbrel®, Remicade®, Humira®)
  - IL-6 (Actemra®), B & T-cells (Rituxan®, Orencia®)
  - effective in 50-60% of MTX non-responders

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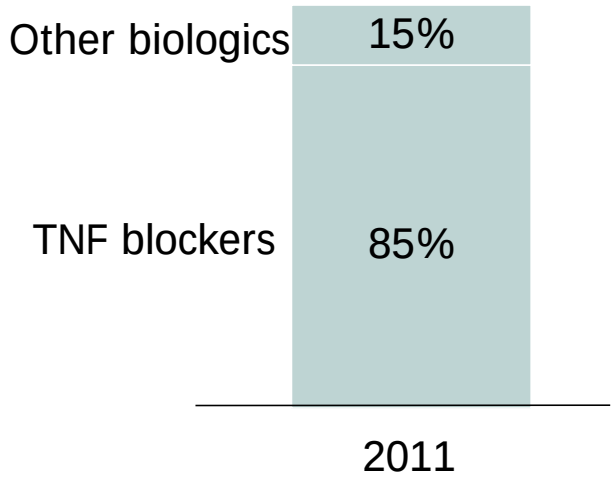
New wave of RA oral therapies

Small molecule drugs in development for RA

- Easier to use (oral administration)
- Lower cost of goods
- Comparable efficacy & safety profile to biologics



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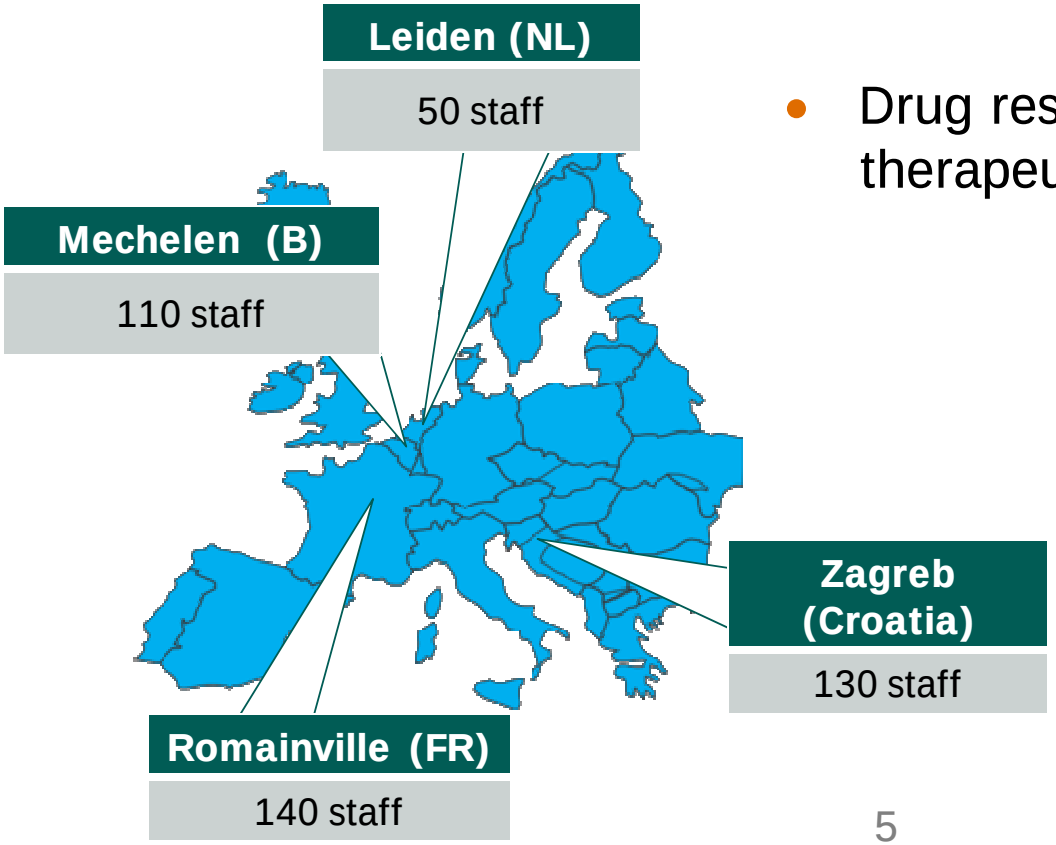
Galapagos: a leader in European biotech

- One of the largest biotech pipelines in Europe
- > 800 staff in pharmacology/biology, chemistry and drug development
- 400 staff fee-for-service organization in UK: discovery research activities



- Drug research & development in various therapeutic areas throughout Europe

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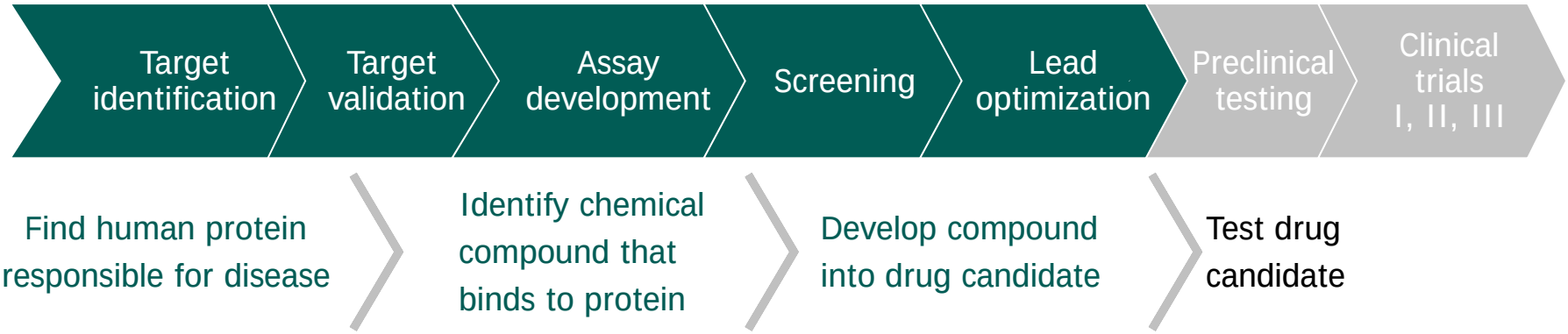
Galapagos approach
From protein to drug



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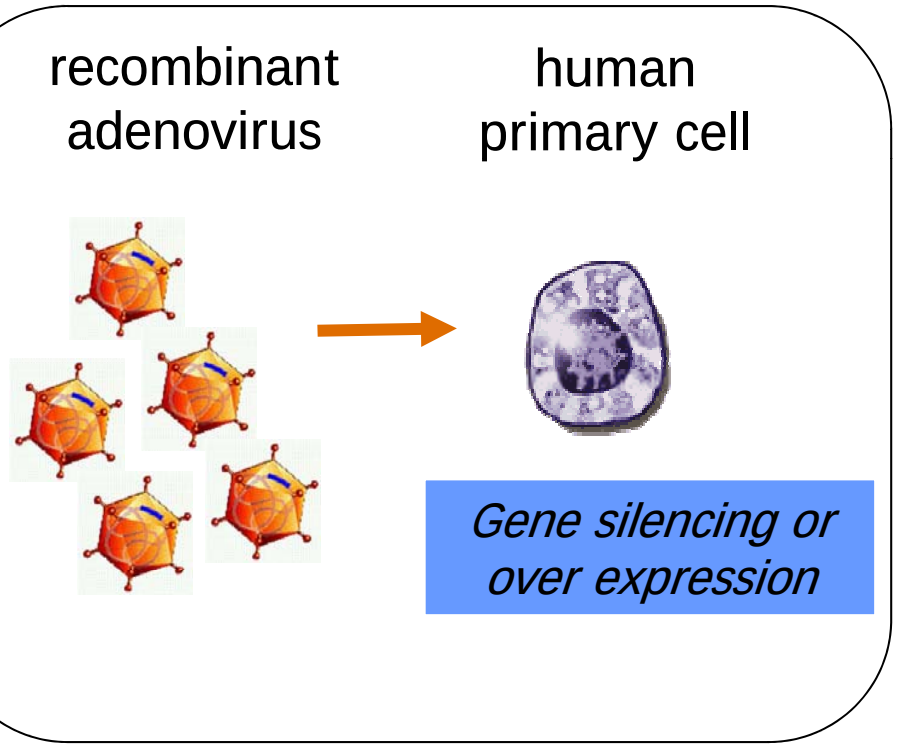
Technology
Adenoviral technology



- Changes in cell health monitored via functional readouts
- 20-25 validated targets per screen
- IP on target and compound

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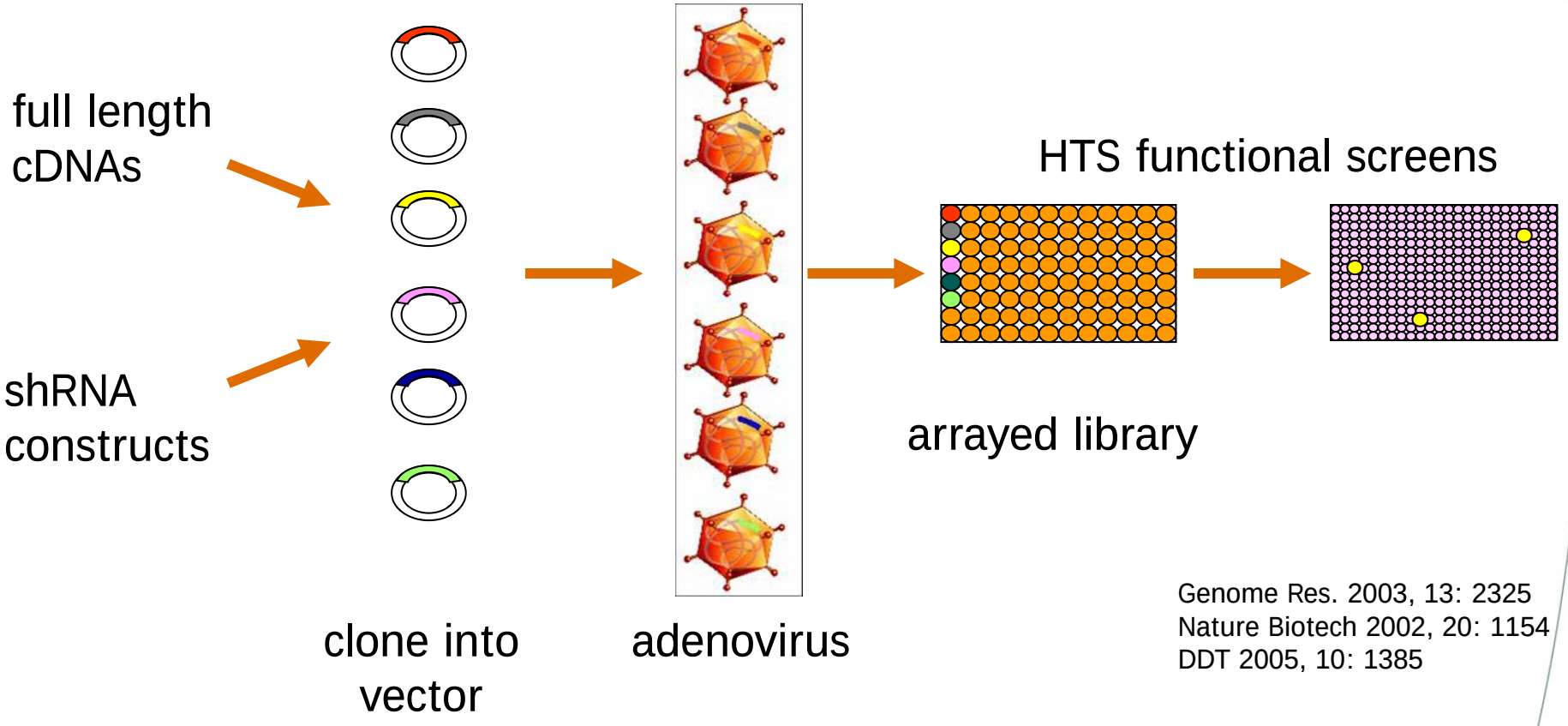
Technology

Arrayed adenoviral libraries for KI and KD



Genome Res. 2003, 13: 2325
Nature Biotech 2002, 20: 1154
DDT 2005, 10: 1385

JAK1 was identified using this technology

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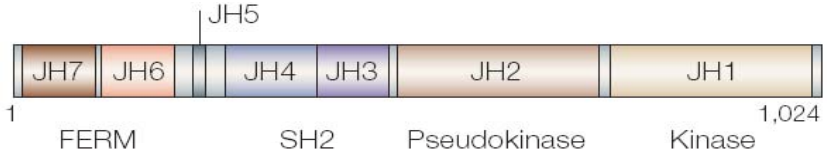
JAK family

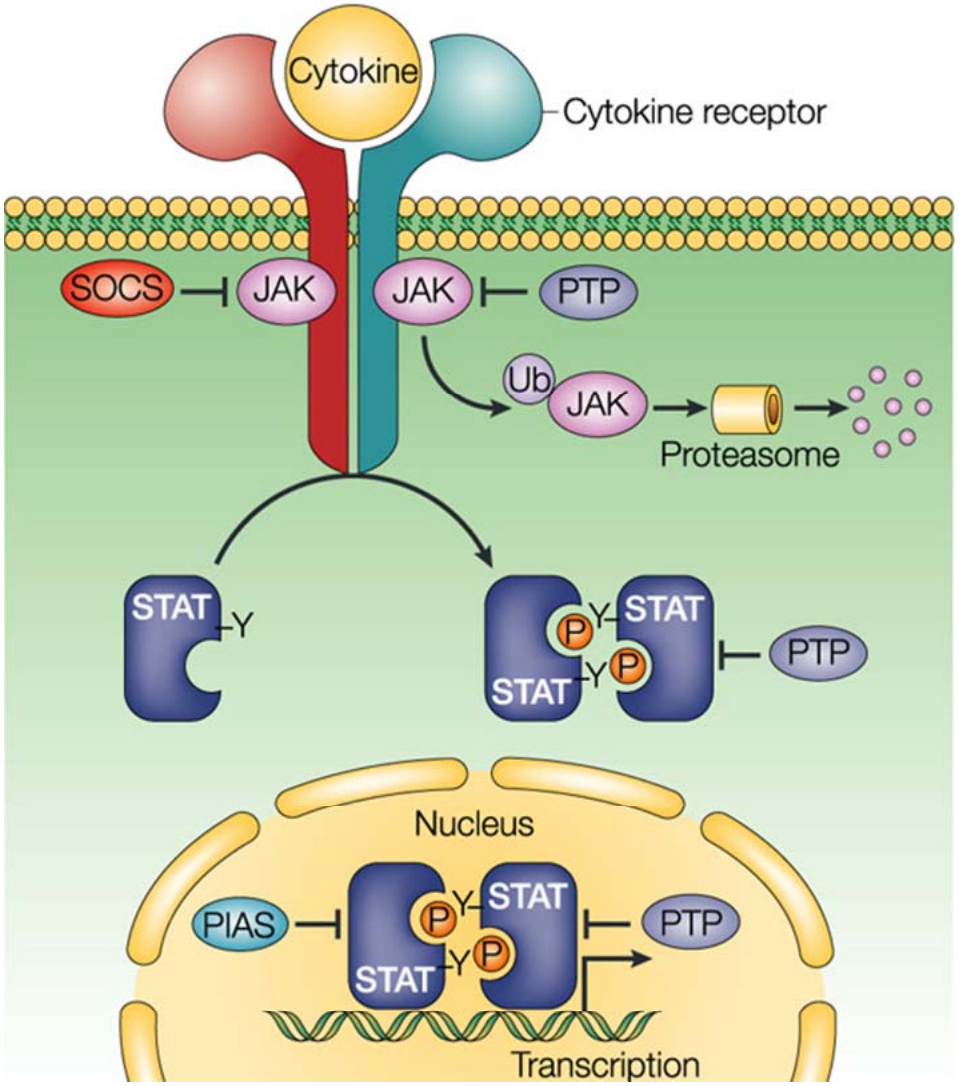


O'Shea JJ et al., 2004; Nat Rev Drug Discov 3, 555

- 4 family members: JAK1, JAK2, JAK3, TYK2
- Cytoplasmic tyrosine kinases
- Serve as intracellular signal transducers for many cytokines, hormones
  - interleukins, interferons, EPO, GH, OSM, LIF,...

JAK	Cytokines	Phenotype of mouse knockout
JAK1	Gp130 cytokine, type I IFN, IFN-γ, and βc cytokines, γc cytokines	Perinatally lethal; neurological defects and SCID
JAK2	EPO, TPO, PRL, GH, IFN-γ and IL-12	Embryonically lethal; defective erythropoiesis
JAK3	γc cytokines	SCID
TYK2	Gp130 cytokines, typeI IFNs, IL-12 and IL-23	Modest viral susceptibility, reduced IL-12 response and resistance to arthritis induction

JAK-STAT signalling



Ke Shuai & Bin Liu, Nature Reviews Immunology 3, 900-911

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JAK inhibitors in development for RA

Three JAK inhibitors have shown clinical efficacy in RA

- rapid onset, 30-50% improvement in ACR20 over placebo
- *tofacitinib* and VX-509 administered twice-daily

RA clinical candidate	JAK inhibition profile	Phase
tofacitinib	JAK3>JAK1>JAK2	Filed
INCB28050 *baricitinib*	JAK1=JAK2	Phase II
VX-509	JAK3	Phase II

Different selectivity profile = opportunity to differentiate JAK inhibitors

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Balancing safety and efficacy

Lessons from 24 weeks of *tofacitinib* in Phase II

	placebo	5 mg bid	10 mg bid	15 mg bid
N=	59	49	61	57
ACR20 (%)	25.4	51.0	65.6	66.7
ACR50 (%)	10.2	34.7	44.3	54.4
ACR70 (%)	6.8	20.4	37.7	33.3

tofacitinib 24-week Phase II study

- significant, dose-dependent improvements in ACR20/50/70 response rates[1]
- dose selection (5 mg, 10 mg bid) for Phase III studies based on efficacy data and safety: incidence of (severe) anemia, at doses of 10 mg bid and higher[2]
- anemia is JAK2-driven side effect, apparent within 2 weeks[1]

Potential to increase efficacy by minimizing JAK2 side effects

1 Fleischmann et al/Kremer et al. ACR presentation (2009).
2 Riese et al. Best Pract & Res Clin Rheum 24 (2010) 513-526.

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Hit finding overview

JAK1 biochemical assay

Primary screen: 9,510 compounds (10 µM, single dose)
90%: focused kinase collection

↓ Overall hit rate: 5.6%

Rescreen, D/R testing

↓ 161 actives

Spec panel – Cell tox

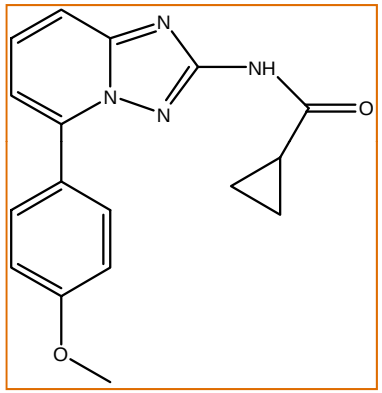
↓ Cpd QC

JAK/STAT cellular assays

↓

SAR identified > H2L

Best hit:



hJAK1 IC_{50} = 65 ± 18 nM

hJAK2 IC_{50} = 168 ± 7 nM

hJAK3 IC_{50} = 675 ± 174 nM

hTYK2 IC_{50} = 783 ± 148 nM

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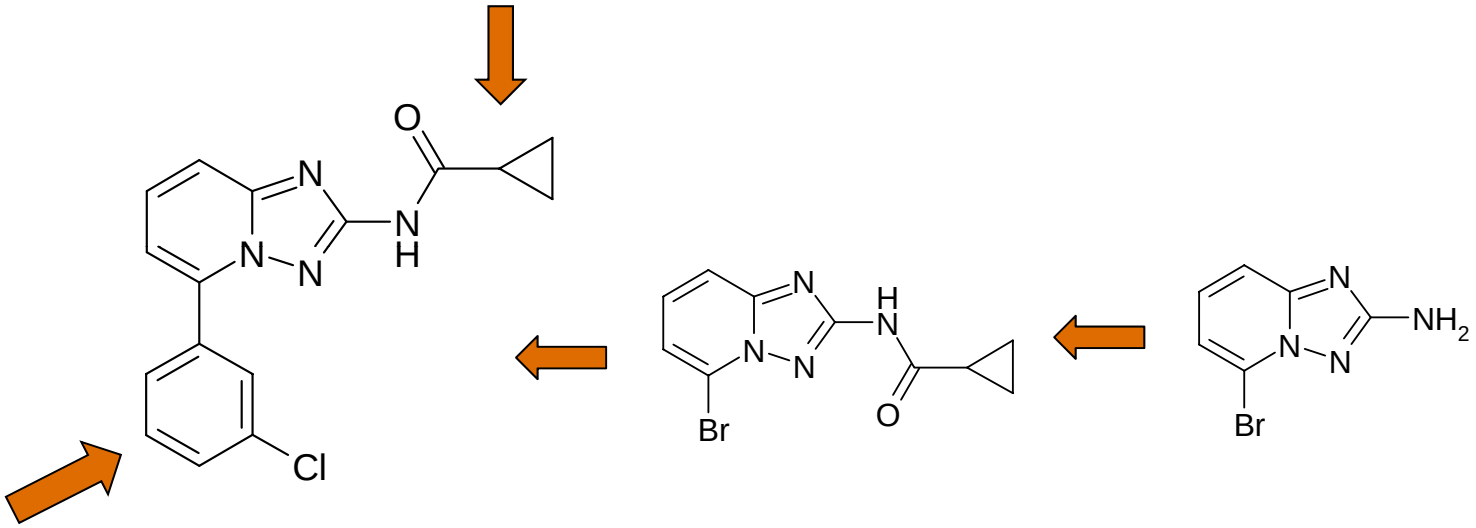
From H2L to LO

Hit

Investigation on position 2



SAR of the phenyl was developed

hJAK1 IC_{50}, 110 nM

Start at easy point, diversify to large variety of compounds to understand the SAR of the series

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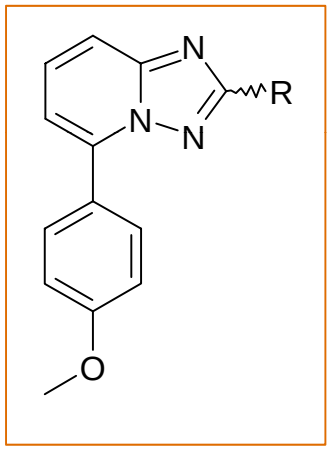
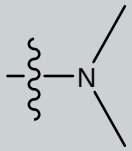
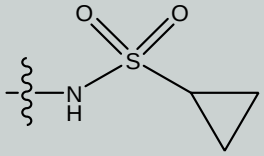
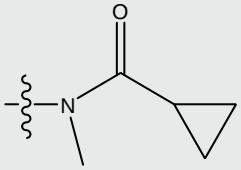
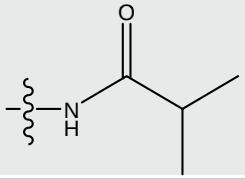
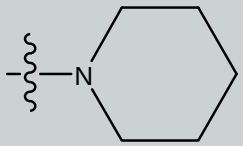
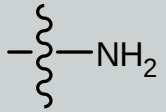
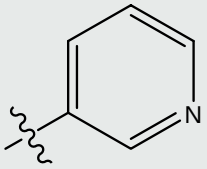
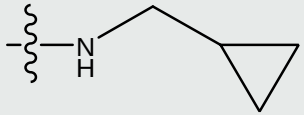
Exploration in position 2



R	JAK1 IC_{50} (nM)	R	JAK1 IC_{50} (nM)
	>10,000		5,740
	>10,000		>10,000
	>10,000		2,270
	>10,000		>10,000

Replacement of the cyclopropyl-amide on the 2-position was not tolerated

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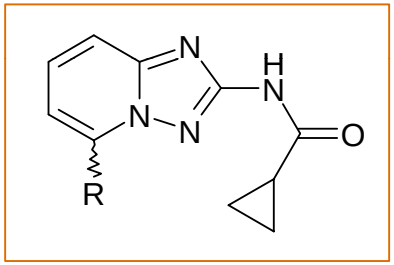
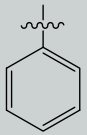
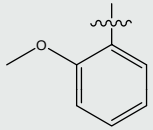
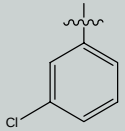
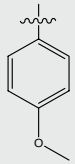
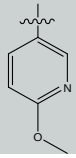
Phenyl substitution improvement



Substitution R	JAK1 IC_{50} (nM)	JAK2 IC_{50} (nM)	JAK3 IC_{50} (nM)	TYK2 IC_{50} (nM)
	180	564	1,790	1,767
	361	925	1,142	3,877
	110	188	1,155	587
	65	168	675	783
	528	980	2,857	7,049

The *para*-position of the phenyl was tolerant to wide range of substitutions

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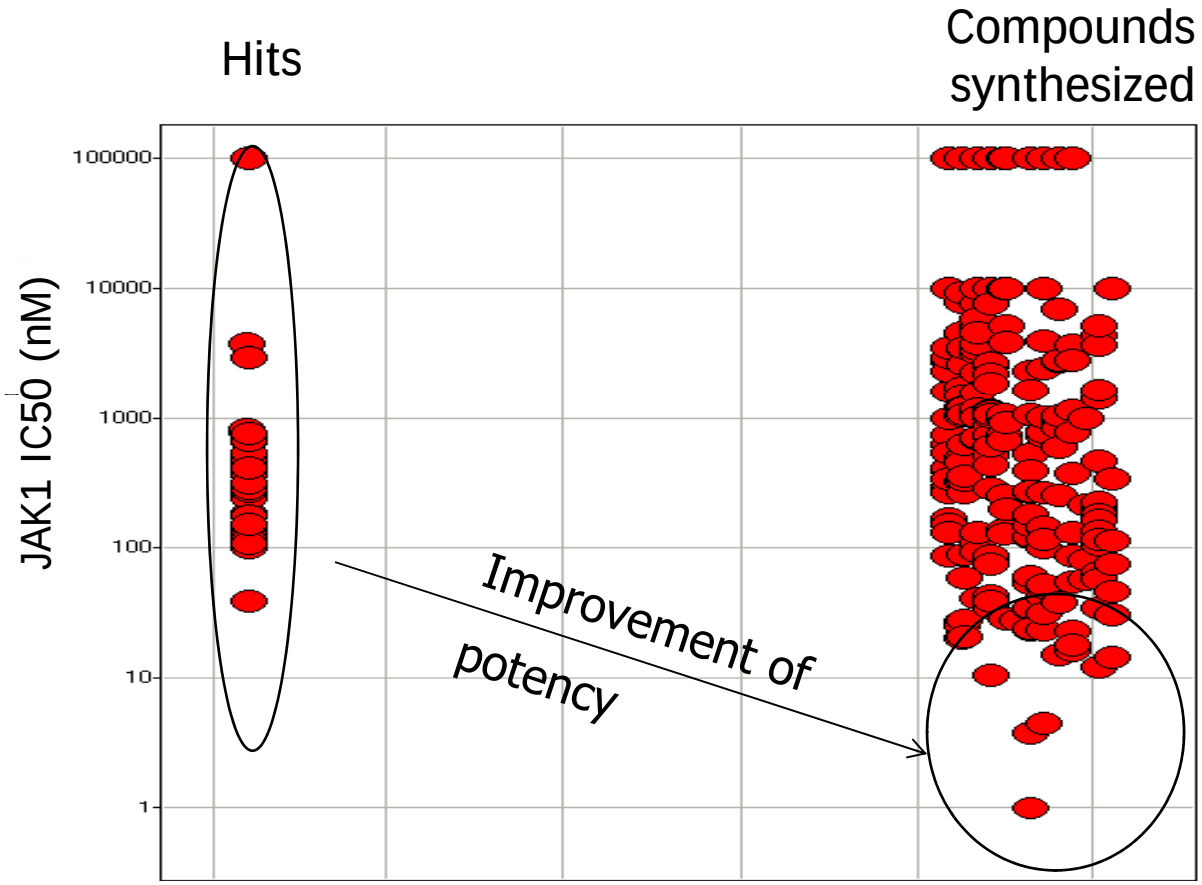
Lead optimisation

SAR



Drive towards potent JAK1 compounds

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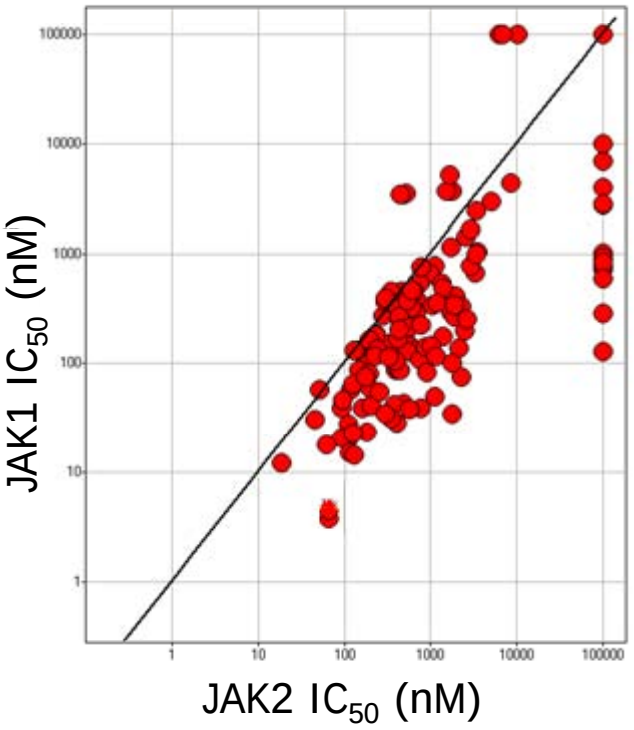
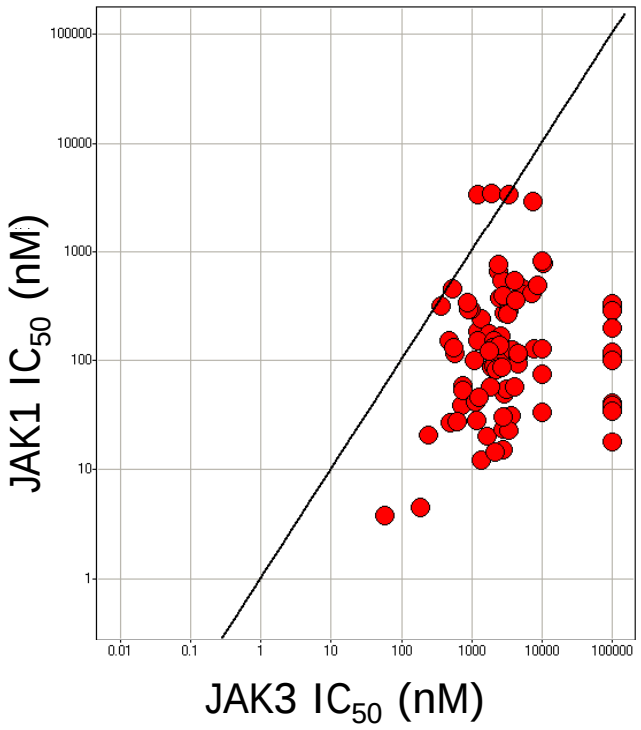
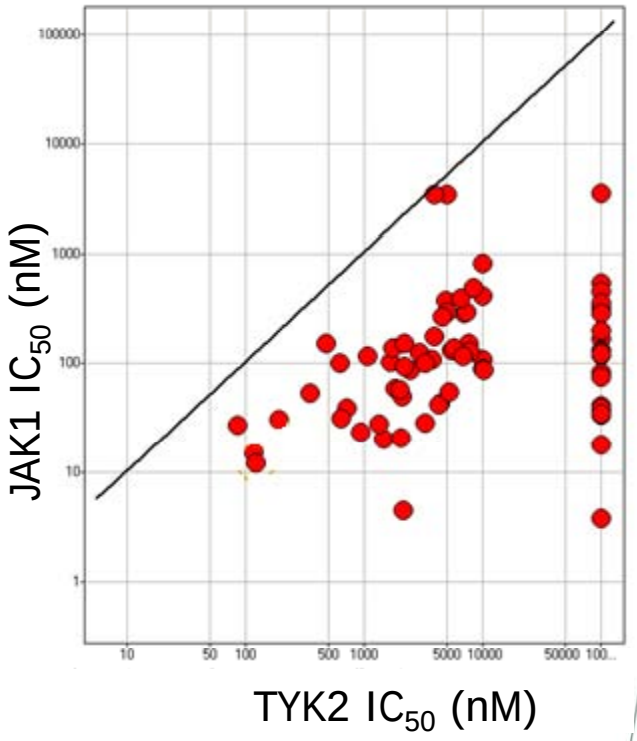
Lead optimisation
Biochemical selectivity







The series was made selective towards JAK1

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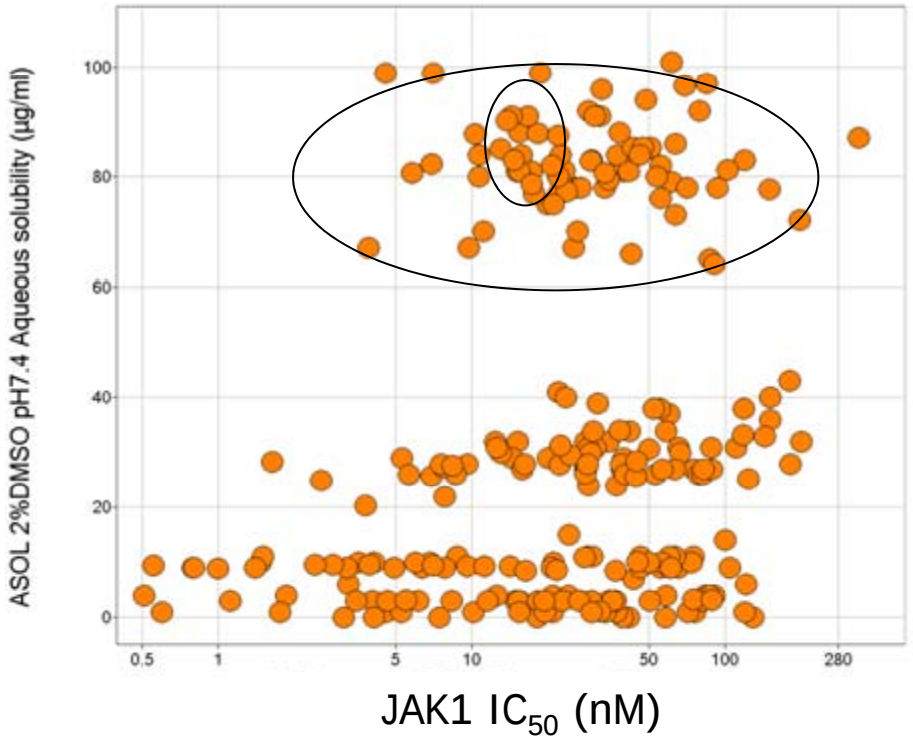
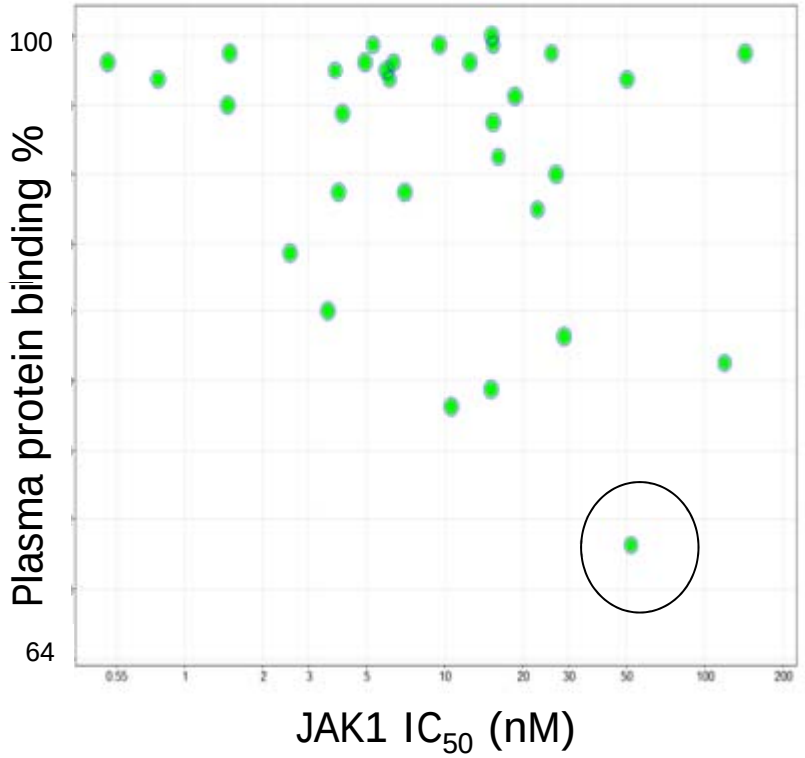
Lead optimization

ADME analysis





ADME analysis of main series led to sub-series: good solubility, low PPB
Further optimization resulted in GLPG0634

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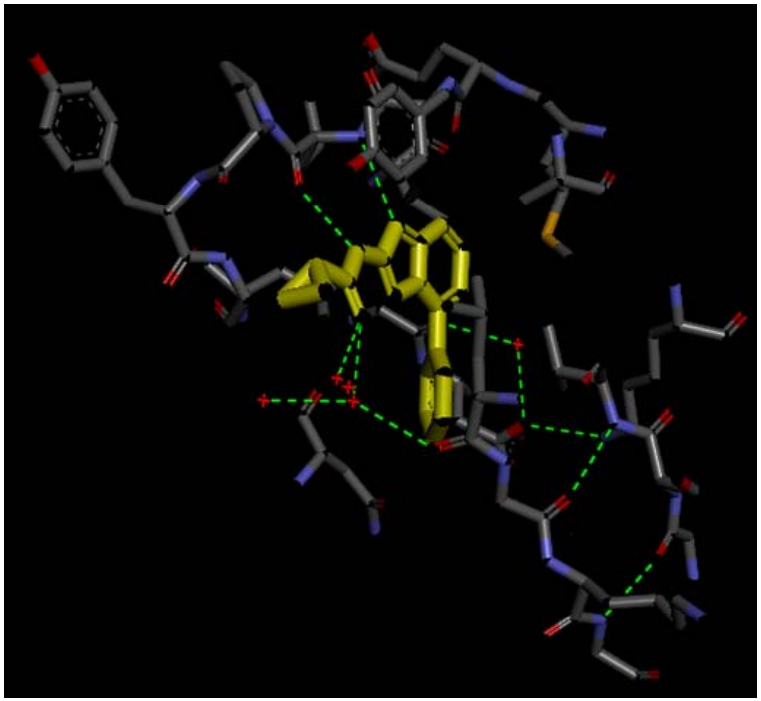
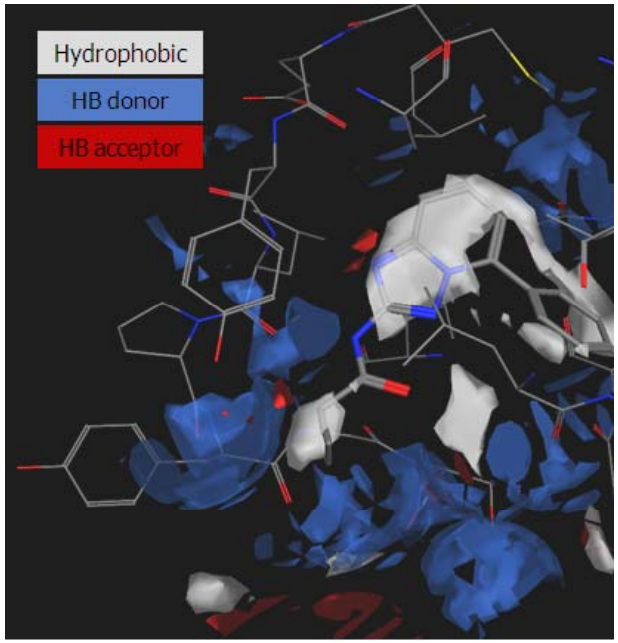
Crystal structure of JAK2

Triazolo-pyridine series docked in JAK2 crystal structure

Nitrogen atom of the scaffold and of cyclopropylamide of the series interact with the hinge





Cyclopropyl group locates in favorable hydrophobic pocket

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GLPG0634 inhibits JAK1

JAK selectivity

Potencies of compounds in biochemical assays*

Compound	JAK1 IC_{50}, nM	JAK2 IC_{50}, nM	JAK3 IC_{50}, nM	TYK2 IC_{50}, nM
GLPG0634	10	28	810	116
tofacitinib	1.3	1.9	0.2	23
INCB28050	5.9	5.7	>400	53

* Biochemical assays by fluorescence read-out show higher potencies than prior radioactive assays.

JAK1 selectivity ratios of compounds in biochemical assays

Compound	JAK2/JAK1 ratio	JAK3/JAK1 ratio	TYK2/JAK1 ratio
GLPG0634	2.8	81	11.6
tofacitinib	1.5	0.2	17.7
INCB28050	1.0	60	9.0

GLPG0634 shows good selectivity over JAK3 and TYK2

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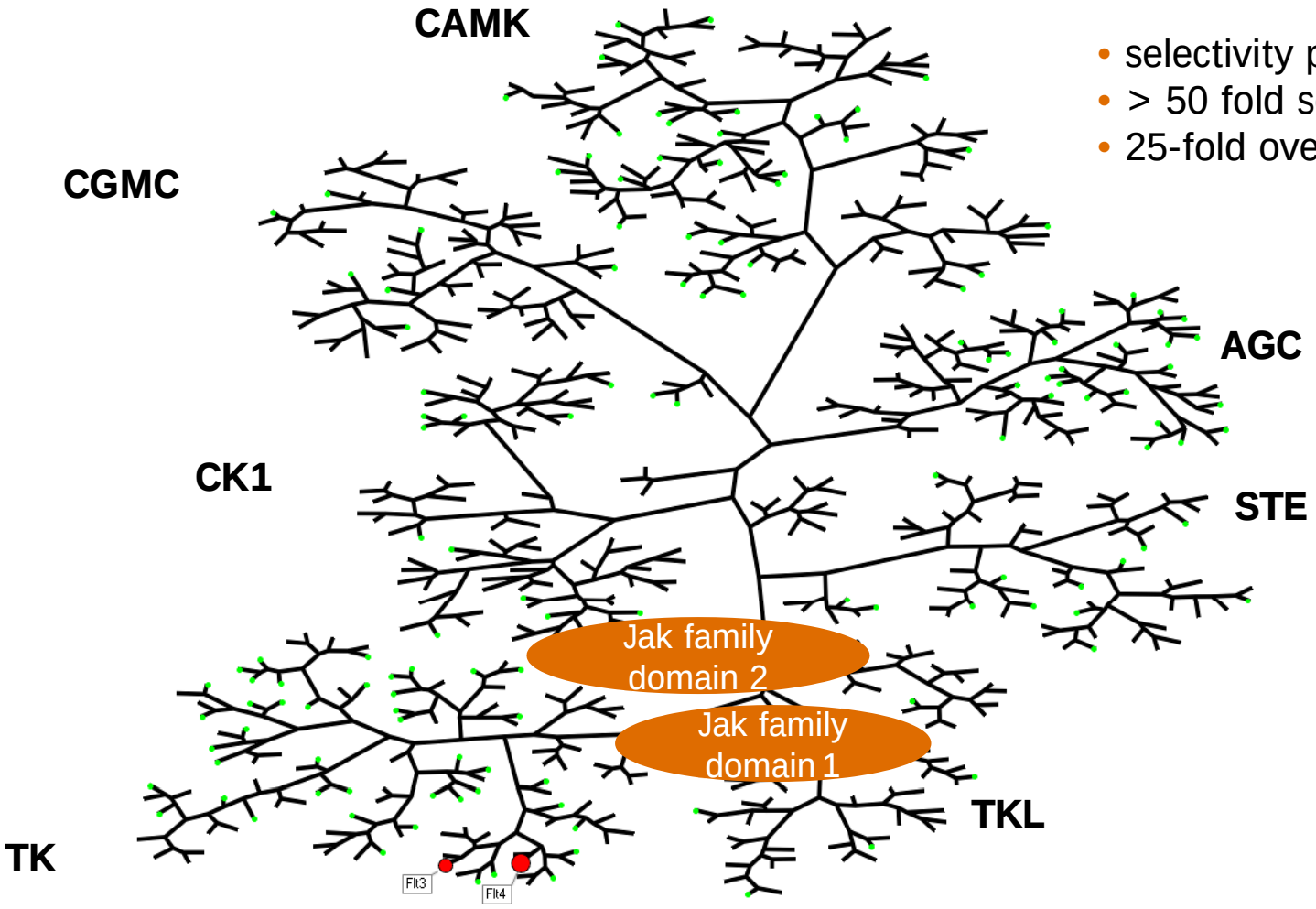
GLPG0634 inhibits JAK1

High selectivity towards 150 kinase-panel



- selectivity panel upstate GLPG0634
- > 50 fold selective over 175 kinases
- 25-fold over FLT3, FLT4 and CSF1R

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GLPG0634 inhibits JAK1

High selectivity for JAK1 over JAK2 in cellular assays

JAKs involved	Cell type	Trigger	Read-out	pIC_{50} ± SEM	**IC_{50} (nM)**	n
JAK1-JAK3	THP-1	IL-4	pSTAT6	6.75 ± 0.06	154; 203	2
JAK1-JAK3	NK-92	IL-2	pSTAT5	6.46 ± 0.12	148; 757; 367	3
TYK2-JAK1	U2OS	IFNαB2	pSTAT1	6.33 ± 0.03	494;436	2
JAK1-JAK2	HeLa	OSM	STAT1 reporter	6.01 ± 0.07	1,045	4
JAK1-JAK2	U2OS	IFNγ	pSTAT1	5.45	3,364	1
JAK2	TF-1	IL-3	pSTAT5	5.45	3,524	1
JAK2	BaF3	IL-3	proliferation	5.34 ± 0.04	4,546	3
JAK2	UT7-EPO	EPO	pSTAT5	>5	>10,000	2
JAK2	22Rv1	PRL	pSTAT5	>5	>10,000	2

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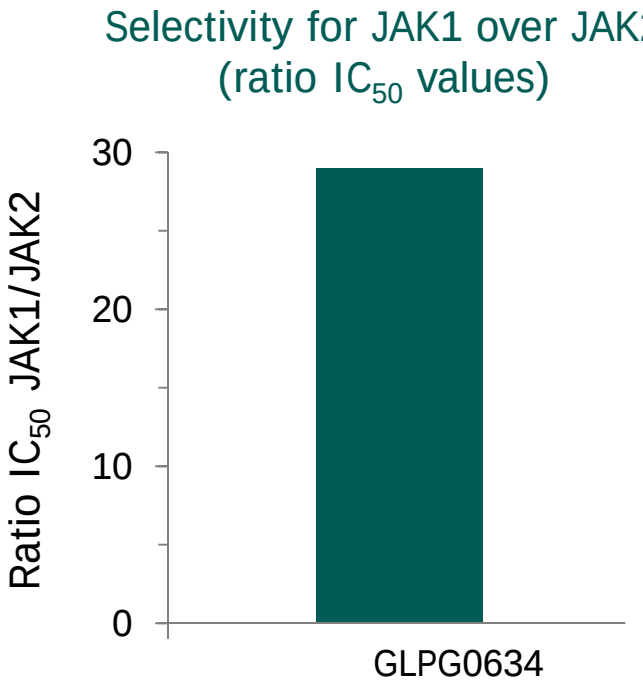
GLPG0634 inhibits JAK1

High selectivity for JAK1 over JAK2 in human blood

Preclinical JAK profiling in human whole blood assay



	Assay	IC_{50} (nM)
JAK1	IL6/pSTAT1	600
JAK2	GM-CSF/pSTAT5	17,500

rhIL-6: 10 ng/mL; pSTAT1 in $CD4^+$ leucocytes by FACS
rhGM-CSF: 20 pg/mL; pSTAT5 in $CD33^+$ leucocytes

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Animal pharmacokinetics for GLPG0634

Vehicle MC 0.5% (v/v)		C_{max} (ng/mL)	Tmax (h)	$AUC_{0\text{-}24h}$ (ng.h/mL)	$T_{1/2}$ (h)	Cl (L/h/kg)	V_{ss} (L/kg)	F (%)
rat	IV 1 mg/kg	1,407		739	1.6	1.4	1.8	
	PO 5 mg/kg	310	2.2	1,681	3.9			45
dog	IV 1 mg/kg	1,143		4,098	7.5	0.25	1.7	
	PO 5 mg/kg	1,807	1.5	13,908	5.2			67

GLPG0634 was well exposed in rodent and non-rodent species using 0.5% methylcellulose as vehicle

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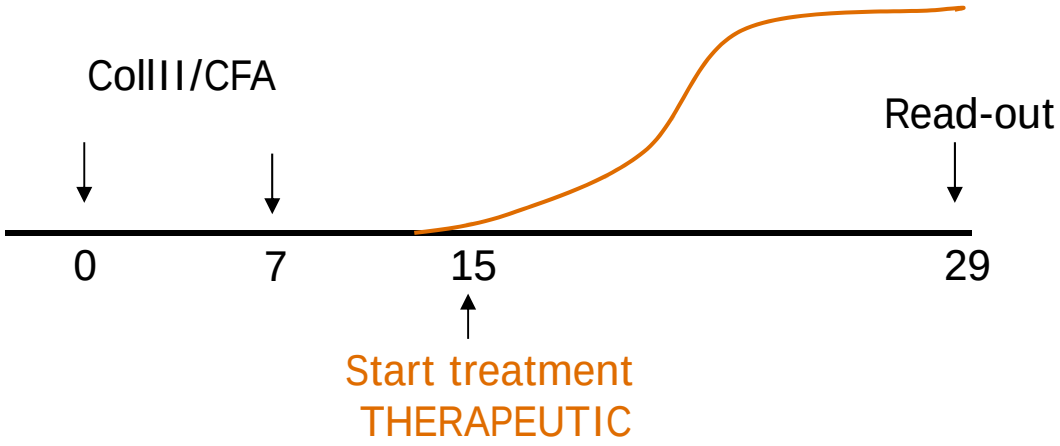
Collagen-induced arthritis rat model

- Injection of hererologous type II collagen in susceptible rat strain
- Boost injection with Coll II at day 0 and 7
- Treatment day 15
- Read-out until day 29



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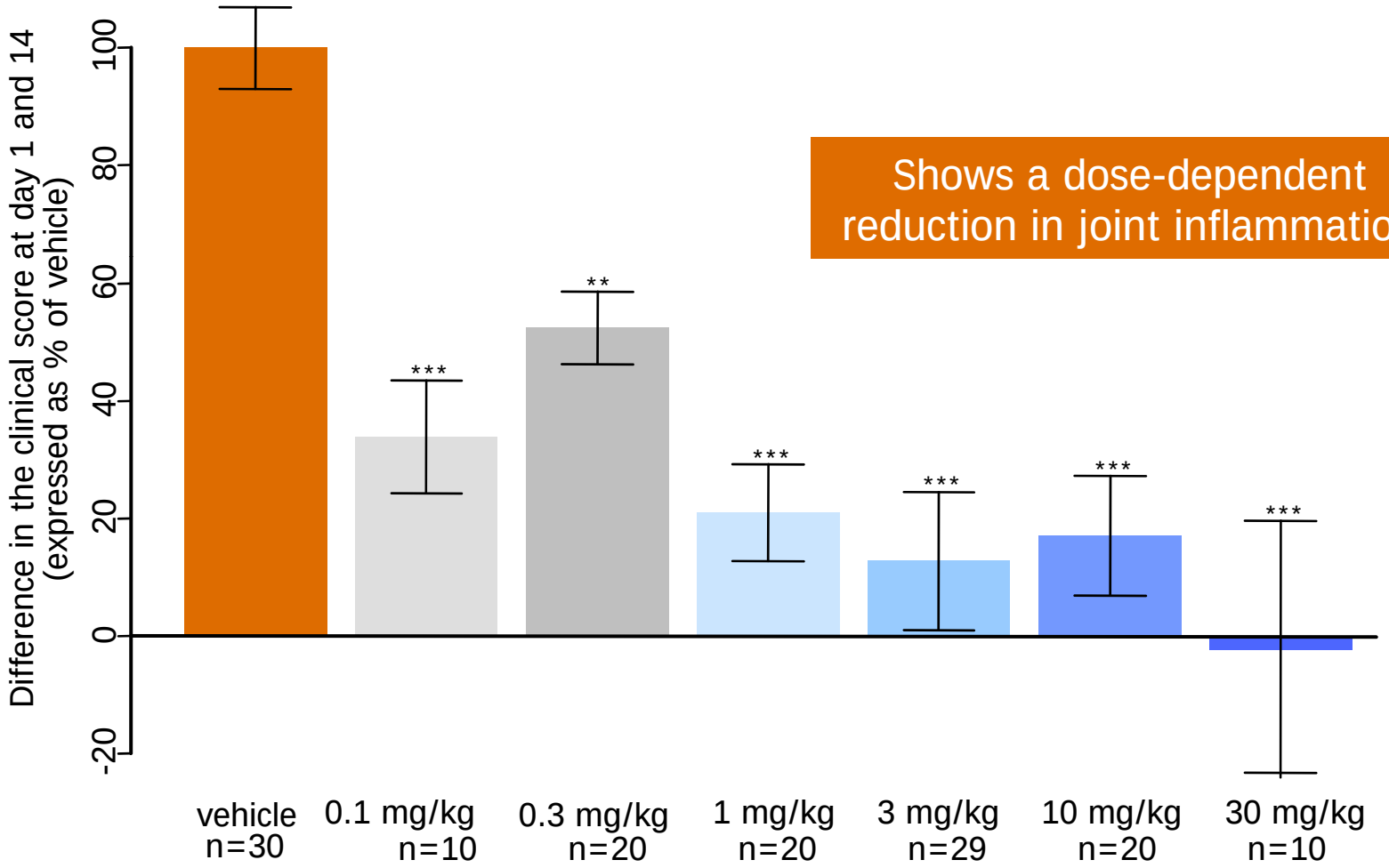
Therapeutic CIA rat model
GLPG0634



Shows a dose-dependent reduction in joint inflammation

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Conclusion lead optimization

- GLPG0634 is a selective JAK1 inhibitor
  - JAK1 biochemical potency IC_{50} ~10 nM
  - human whole blood assay and cellular models show selectivity for JAK1 over JAK2
- Highly potent in therapeutic CIA animal model

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GLPG0634
The 1st selective JAK1 inhibitor

- Introduction
- Target identification
- Hit finding to PCC
- Clinical development
  - Phase I
  - Phase II Proof of Concept

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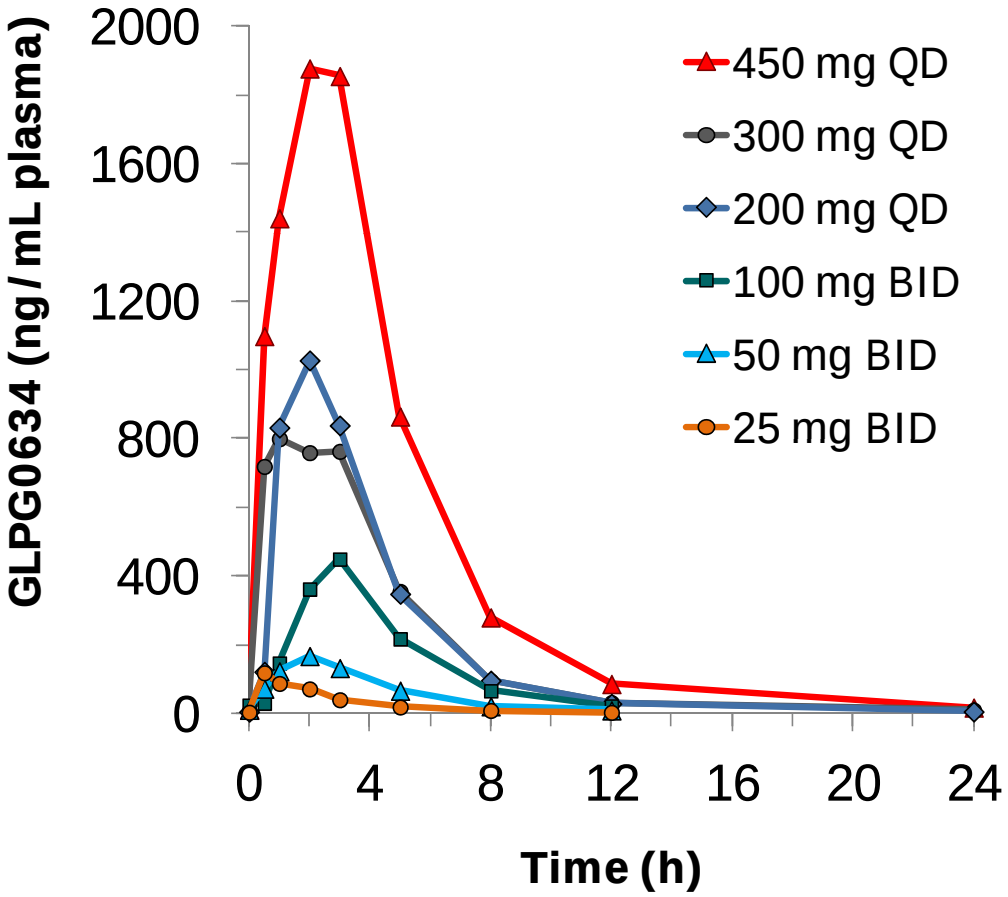
Phase I
Trial design and safety

- Ascending single dosing and Multiple dosing
  - 48 healthy volunteers: 6 subjects per groups received GLPG0634 and 2 placebo
- Safety: adverse events were mild and transient in nature.
  - headaches and abdominal discomfort (including loose stools) were reported in more than one subject, over all dose groups and including placebo
  - no changes in hematology parameters (including reticulocytes)
  - no changes in blood biochemistry (including cholesterol)
  - no signal in cardiovascular safety or vital signs

GLPG0634 clinical pharmacokinetics

Healthy volunteers



- Dose proportional PK
- Low variability (CV < 20%)
- Half life: 5-8 hours
- No food effect on capsule formulation
- Plasma exposure ≥ 50 mg
  - exceeds effective exposure in rat CIA
  - exceeds cellular IC_{50}

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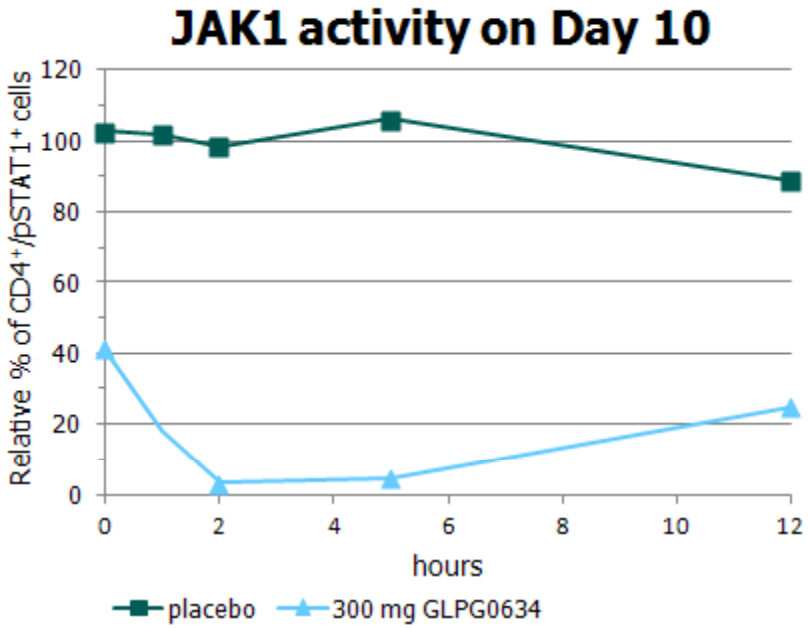
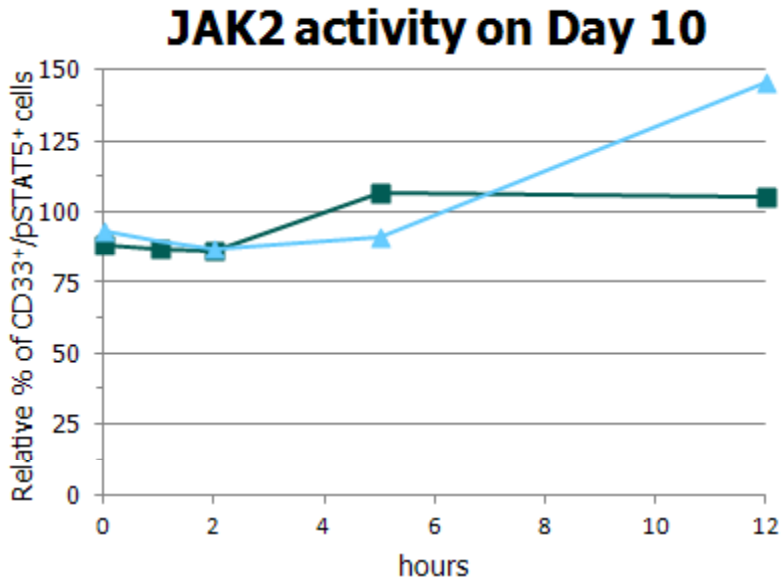
GLPG0634 has a unique JAK profile

JAK1 and JAK2 measured in whole blood from Phase I healthy volunteers

- JAK1 (IL-6/pSTAT1) compared to JAK2 (GM-CSF/pSTAT5)





GLPG0634 is a selective JAK1 inhibitor

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Conclusion Phase I

- GLPG0634 is well tolerated in the pharmacological active dose range, with no effects on hematology or other safety markers following 10 days dosing in healthy volunteers
- Good oral pharmacokinetics and biomarker PK/PD support a once-daily oral dosing regimen
- Results support the initiation of a Phase II trial in rheumatoid arthritis patients

GLPG0634
The 1st selective JAK1 inhibitor

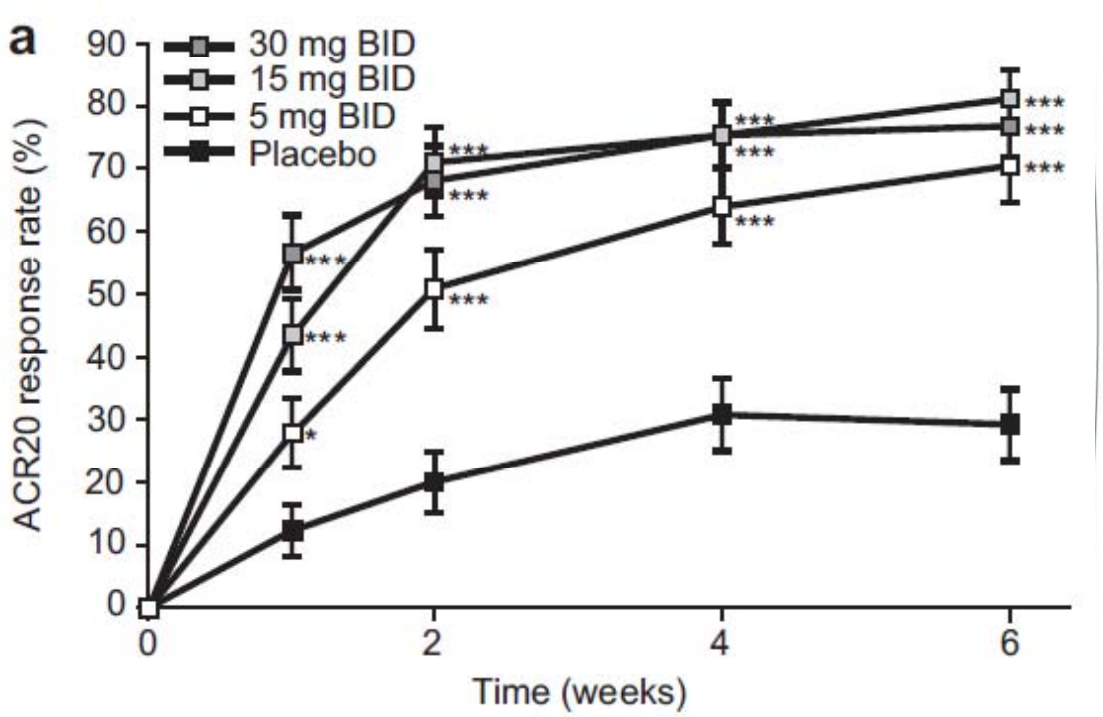
- Introduction
- Target identification
- Hit finding to PCC
- Clinical development
  - Phase I
  - Phase II Proof of Concept

Galápagos

Phase II: Why only a 4 week trial?

tofacitinib monotherapy in active RA

- Rheumatoid arthritis patients failing prior DMARD (n=264)
- Dose dependent efficacy
  - ➢ short-term efficacy (4 weeks) is maintained long-term (2 year)
- Safety and tolerability
  - ➢ infections
  - ➢ lipid elevations
  - ➢ transaminase increased
  - ➢ anemia
  - ➢ neutropenia



Ref: Kremer et Al. Arthritis & Rheumatism, 7, 2009, 1895
Riese et Al. Best Practice & Research Clinical Rheumatology, 24, 2010, 513

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GLPG0634 Phase II PoC
Trial design

- Randomized, double-blind, placebo-controlled study in Moldova
- 36 RA patients with insufficient response to MTX, naïve to biologics
  - 4 week treatment, oral dosing
  - 200 mg QD *vs.* 100 mg BID *vs.* placebo
  - all on MTX (mean: 12 mg/week), with stable low-dose steroids/NSAIDs
  - patients randomized to 12 per group
    - similar demographics (mean age 49 years, 11 females per group)
- All 36 patients completed 4 weeks of treatment

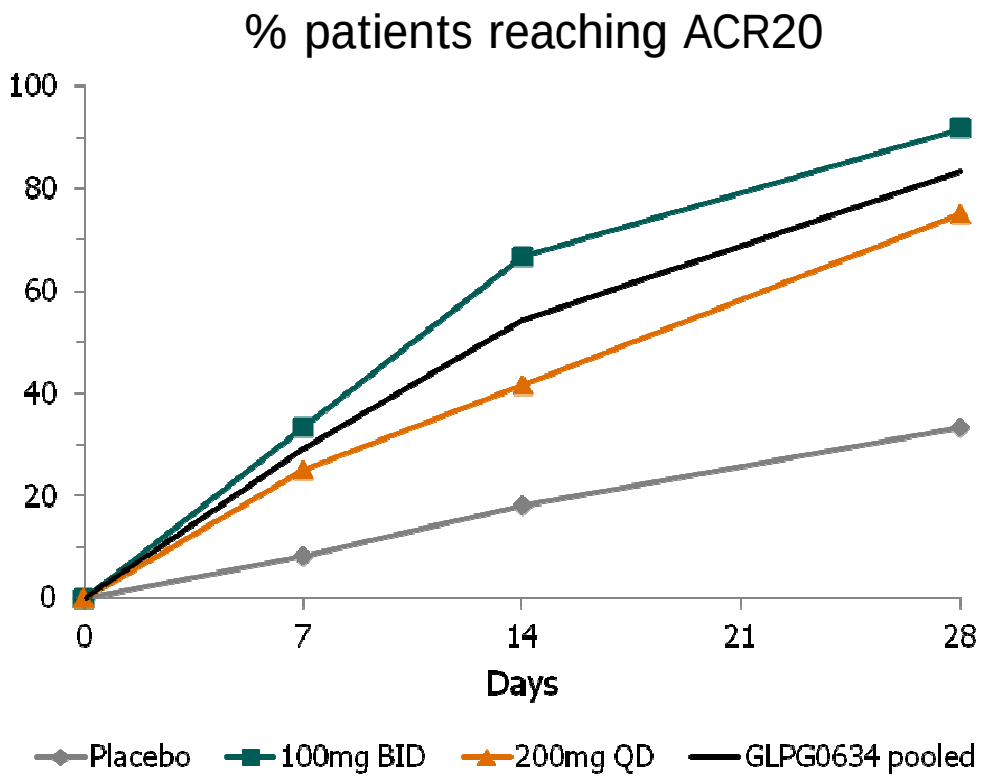
Designed to give rapid evaluation of efficacy at high dose

Baseline patient characteristics

	Placebo n=12	GLPG0634 100 mg BID n=12	GLPG0634 200 mg QD n=12
RA diagnosis (years)	5.6	9.7	7.5
Use of steroids	2	4	4
Use of NSAIDS	11	10	6
CRP at baseline (mg/L)	34.9	21.3	40.5
DAS28	6.3	6.7	6.4

GLPG0634 efficacy: ACR20

- Achieved primary endpoint
- ACR20 scores at Day 28: 42-58% improvement over placebo



GLPG0634 is highly efficacious with rapid onset of action

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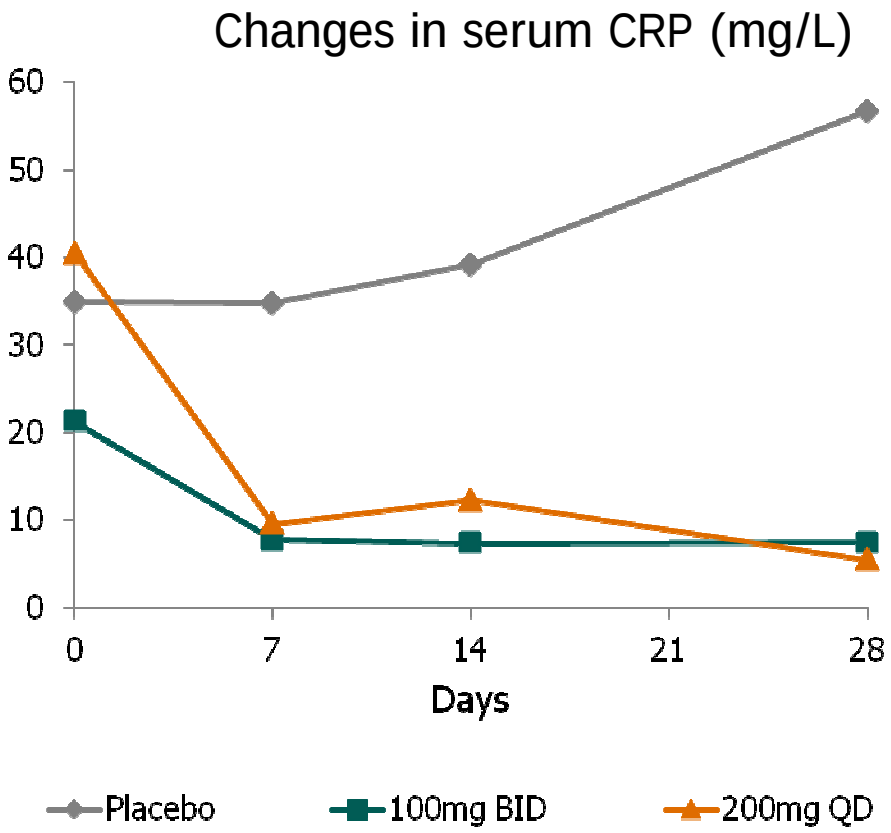
GLPG0634 efficacy: C-reactive protein

- CRP: inflammation biomarker
- GLPG0634 treatment induces a rapid and lasting decrease in serum CRP to near-normal levels



GLPG0634 is highly efficacious with rapid onset of action

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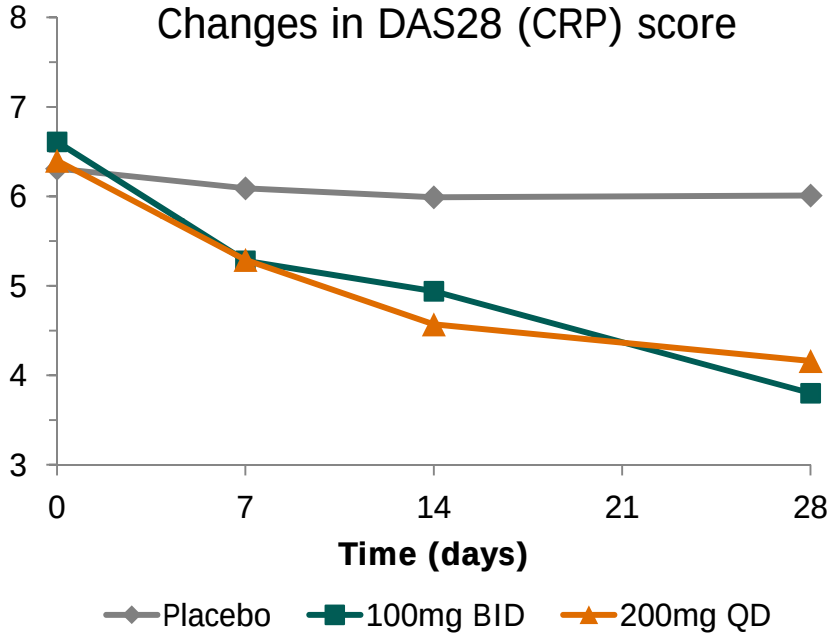
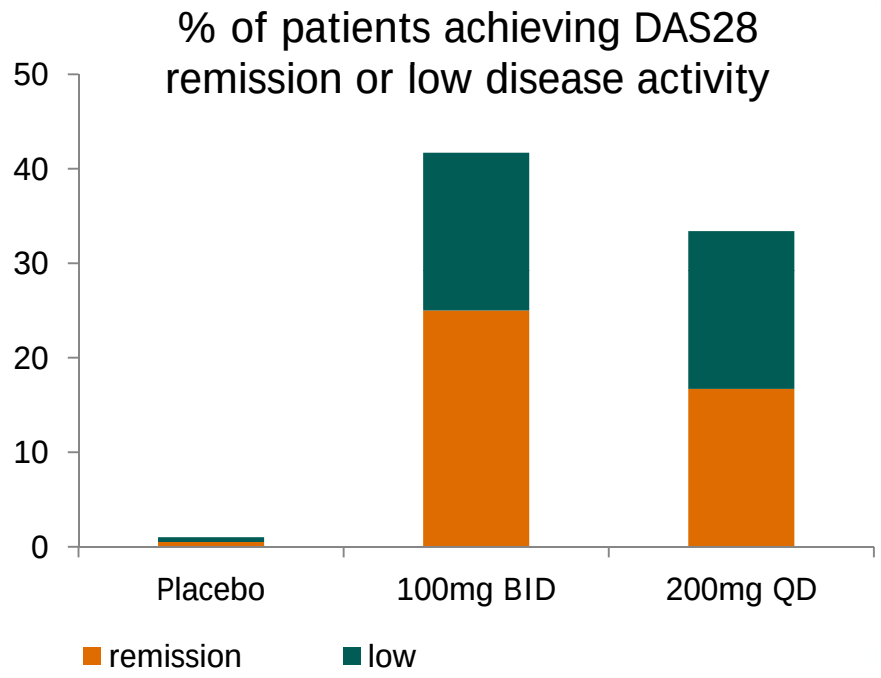
GLPG0634 efficacy
DAS28





GLPG0634 is highly efficacious with rapid onset of action

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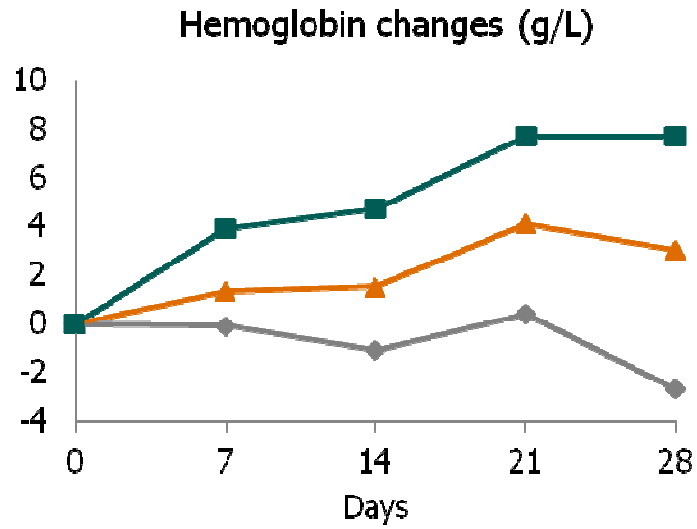
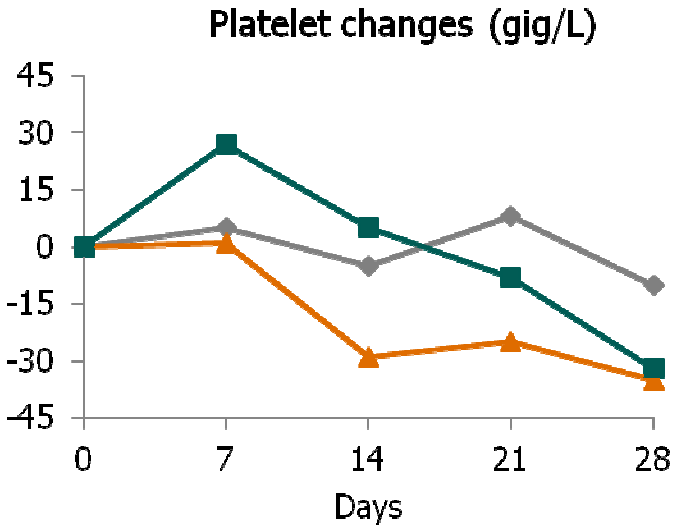
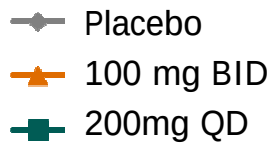
GLPG0634 safety findings

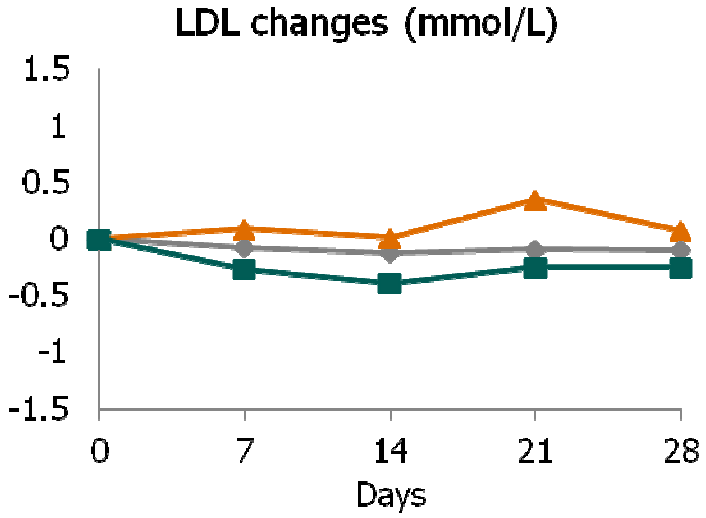
Any treatment-related AE	Placebo n=12	GLPG0634 100 mg BID n=12	GLPG0634 200 mg QD n=12
None	8	10	9
Nausea		2	2
Abdominal discomfort			1
Abdominal pain		1	
Asthenia (weakness)	2		
Fatigue	1		
Dysgeusia (abnormal taste)			1
Headache	1	1	
Somnolence (drowsiness)			1

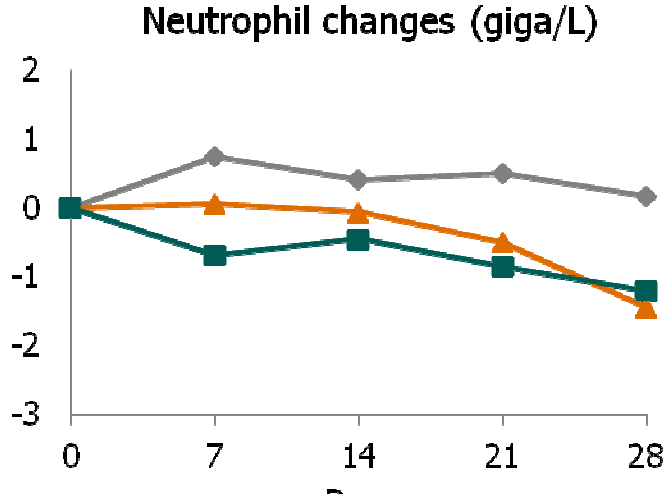
GLPG0634 safety











GLPG0634 safety summary

- Safe and well-tolerated
  - no SAEs on GLPG0634 treatment
  - few patients reported side-effects
  - neither anemia nor increase in LDL
  - modest decrease in neutrophils and platelets
  - no effects on blood pressure

Conclusion
GLPG0634 a potential best in class

- Hit finding to PCC
  - Triazolopyridine identified as JAK1 inhibitors by HTS screening
  - Identification of subseries that offer a balance of ADME properties and potency
- GLPG0634 has a unique profile
  - a selective JAK1 inhibitor in biological systems
  - active in preclinical models of arthritis
  - well tolerated in a wide dose range in Phase I
  - PK/PD profile consistent with once daily dosing
- Proof-of-Concept in rheumatoid arthritis patients achieved
  - 4 weeks treatment at 200 mg/day on top of failing MTX

THANK YOU

Questions?