Cardiff School of Chemistry

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Microwaves and Heterocycles: New Methodology and Chemotherapeutic Opportunities

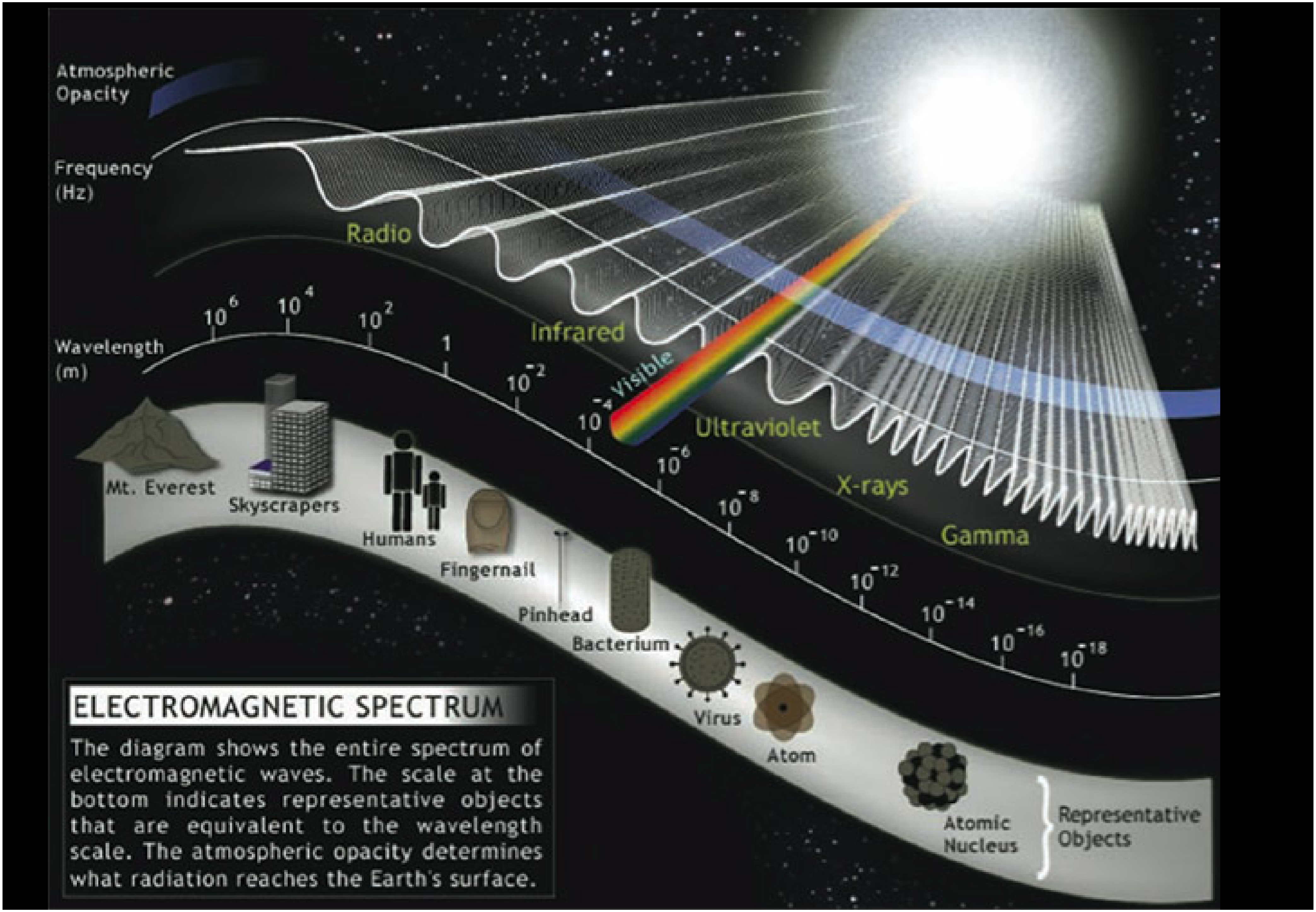
Mark C Bagley

Biotage

29th–31st July 2008
Application of Modern Tools in Organic Synthesis
Edinburgh University Summer Programme

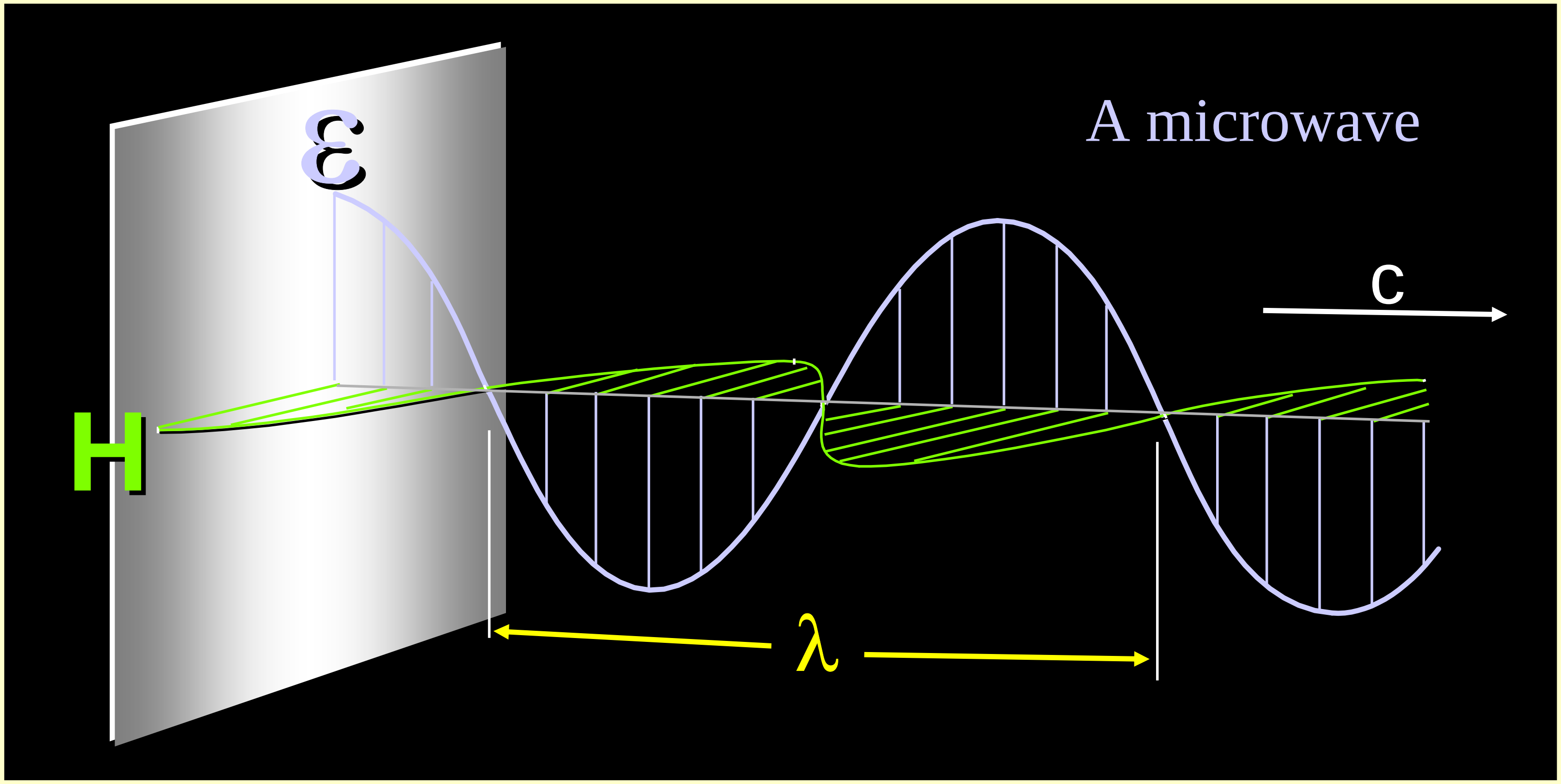
CARDIFF UNIVERSITY PRIFYSGOL CAERDYDD

Cardiff Institute of Tissue Engineering and Repair



Atmospheric Opacity
Frequency (Hz)
Wavelength (m)
Radio
Infrared
Visible
Ultraviolet
X-rays
Gamma
10^6
10^4
10^2
1
10^{-2}
10^{-4}
10^{-6}
10^{-8}
10^{-10}
10^{-12}
10^{-14}
10^{-16}
10^{-18}
Mt. Everest
Skyscrapers
Humans
Fingernail
Pinhead
Bacterium
Virus
Atom
Atomic Nucleus
Representative Objects
ELECTROMAGNETIC SPECTRUM
The diagram shows the entire spectrum of electromagnetic waves. The scale at the bottom indicates representative objects that are equivalent to the wavelength scale. The atmospheric opacity determines what radiation reaches the Earth's surface.

How do microwaves cause rapid heating?



ε = electric field

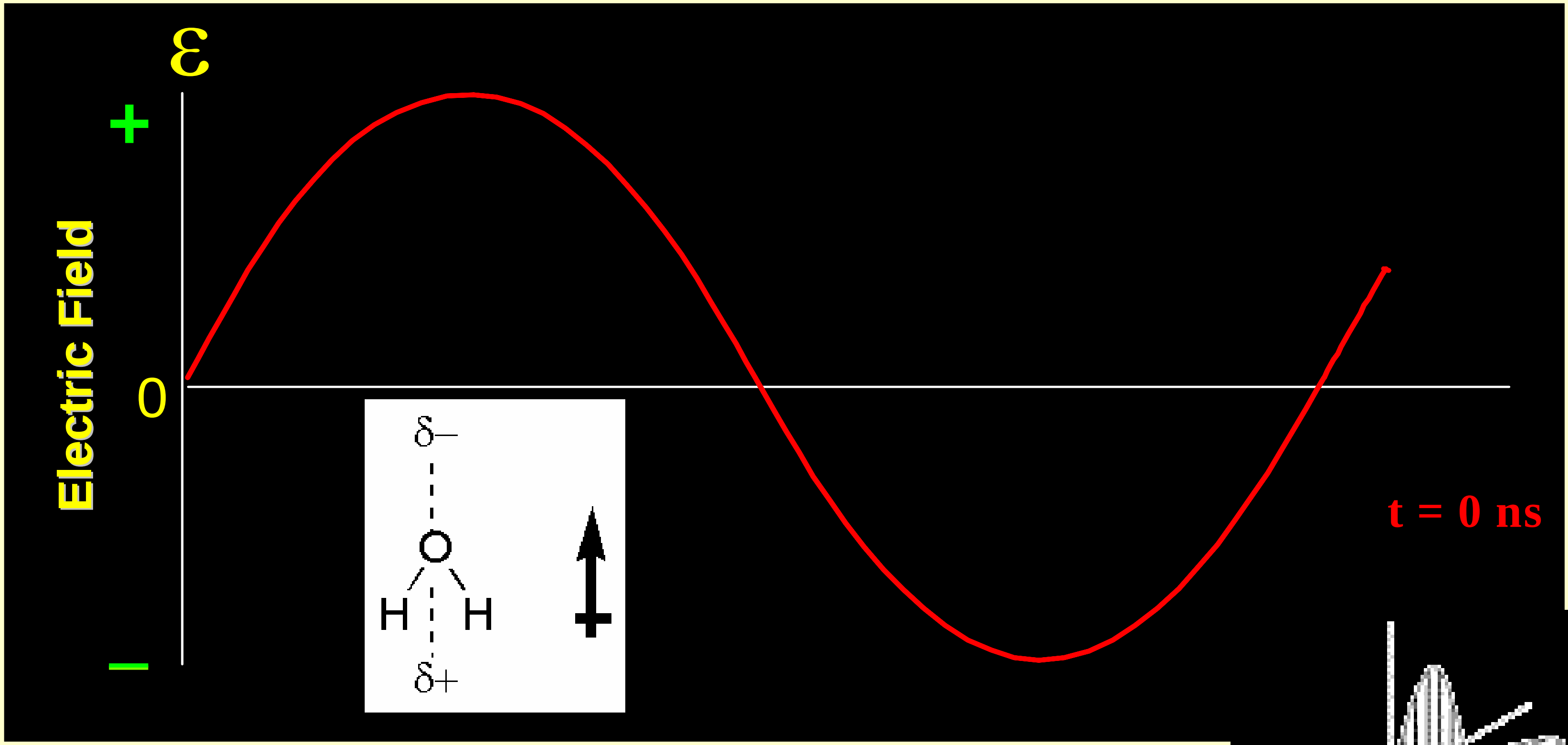
H = magnetic field

λ = wavelength (12.2 cm for 2450 MHz)

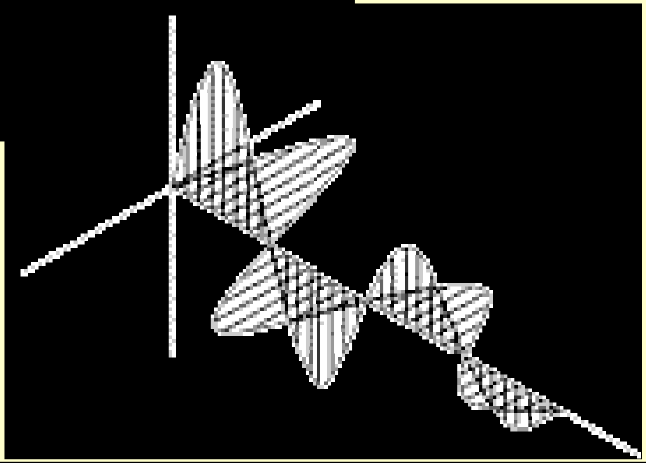
c = speed of light (300,000 km/s)

How do microwaves cause rapid heating?

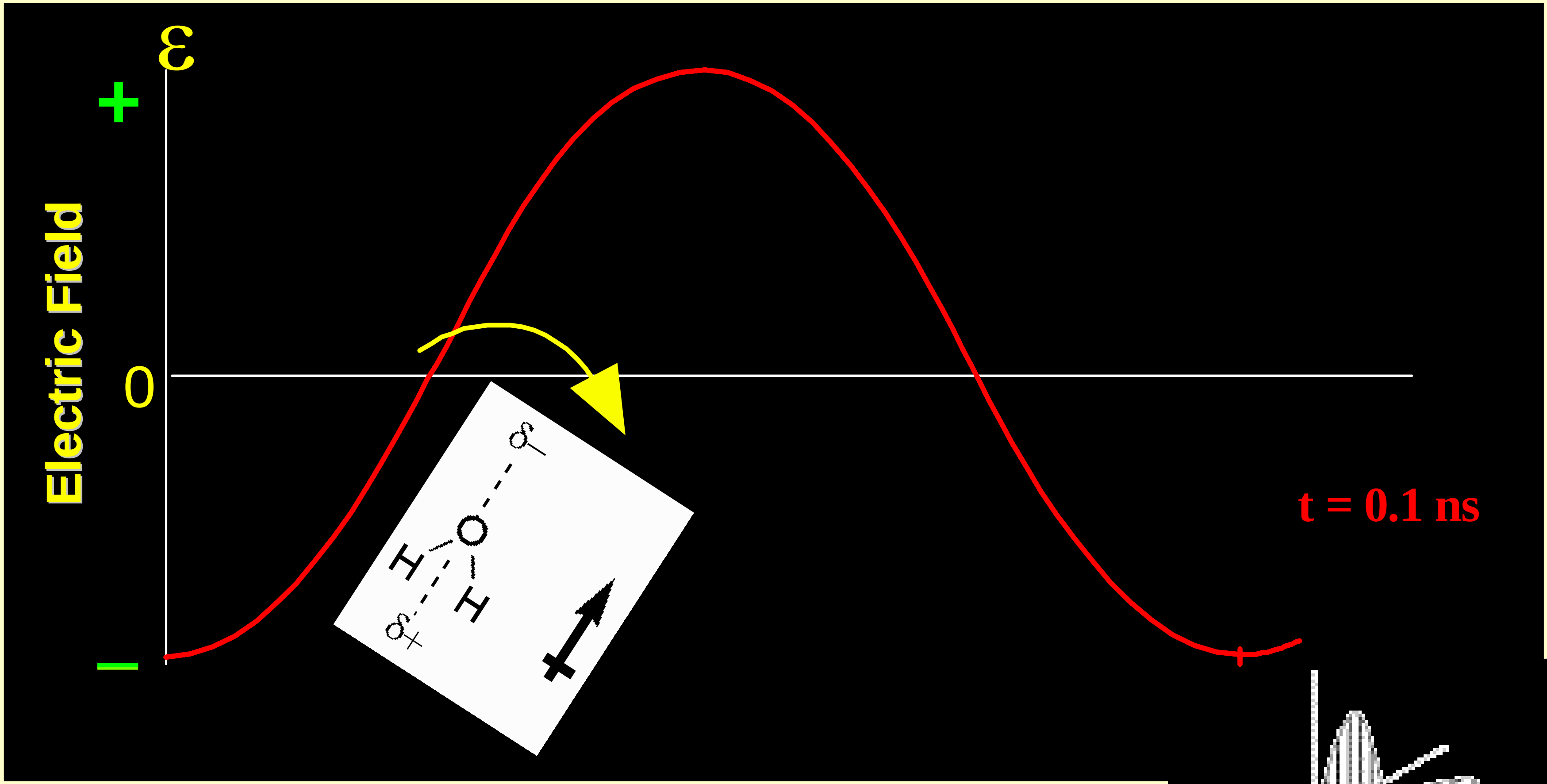
The microwave electric field interacts with the dipole of the water molecule

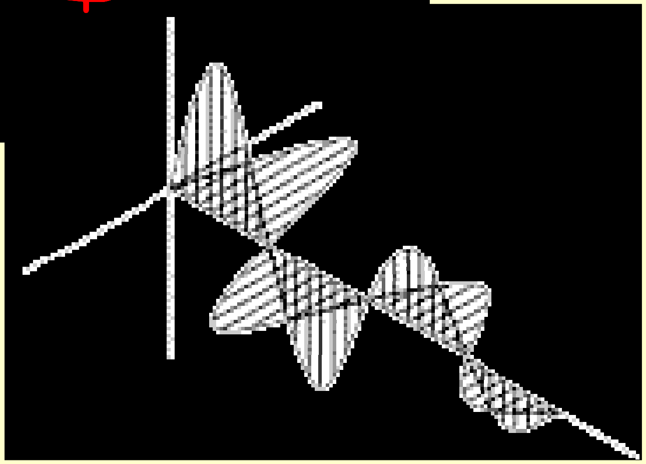


The dipole is aligned with the field at t = 0 ns
but then the field rapidly oscillates



How do microwaves cause rapid heating?





The dipole moment rotates in an attempt to follow the field

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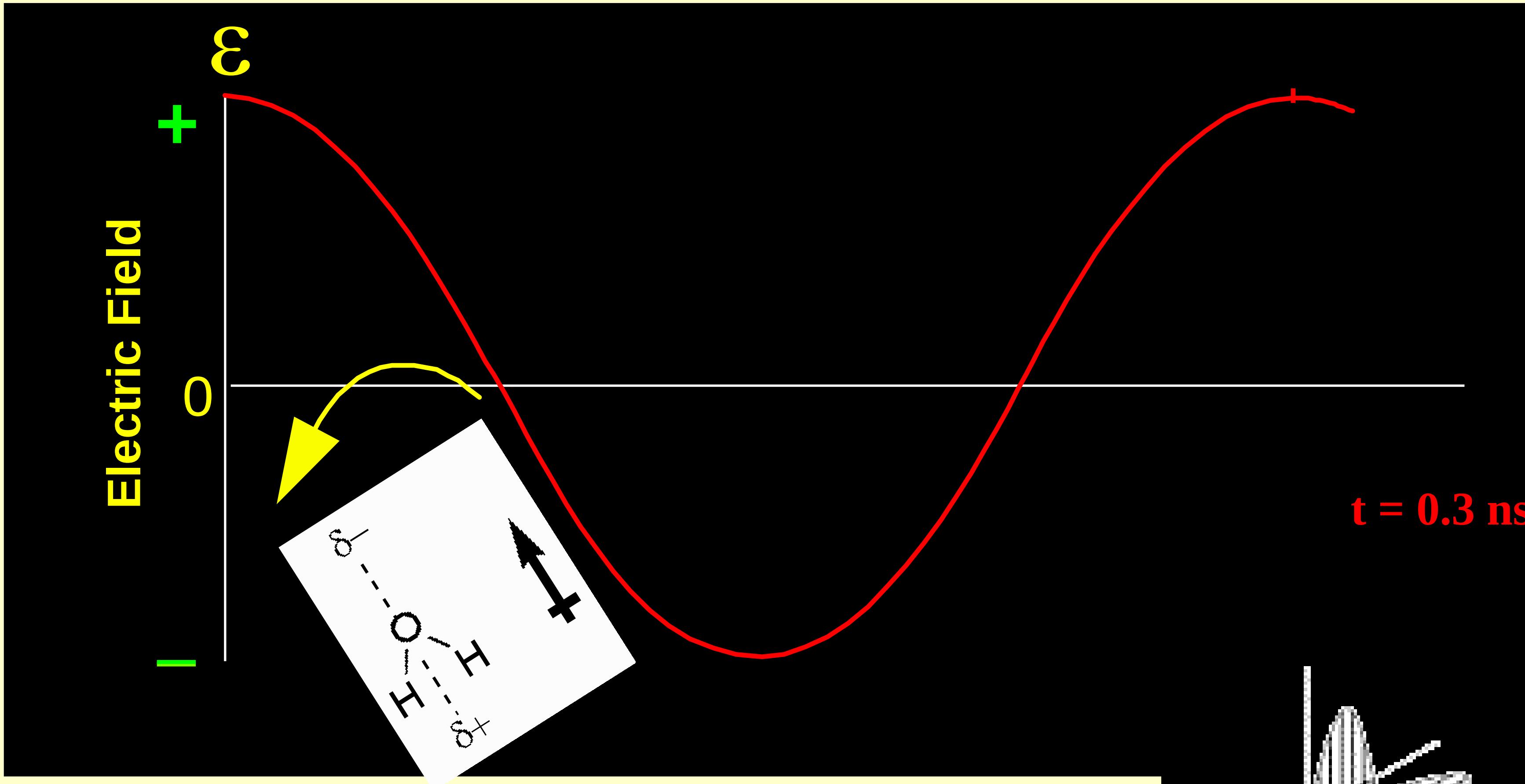
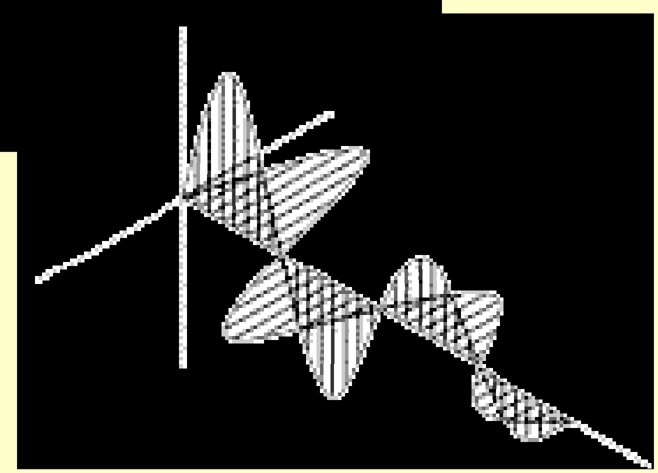
How do microwaves cause rapid heating?





The dipole rotates in the opposite direction an attempt to follow the field

Dielectric Heating Mechanism

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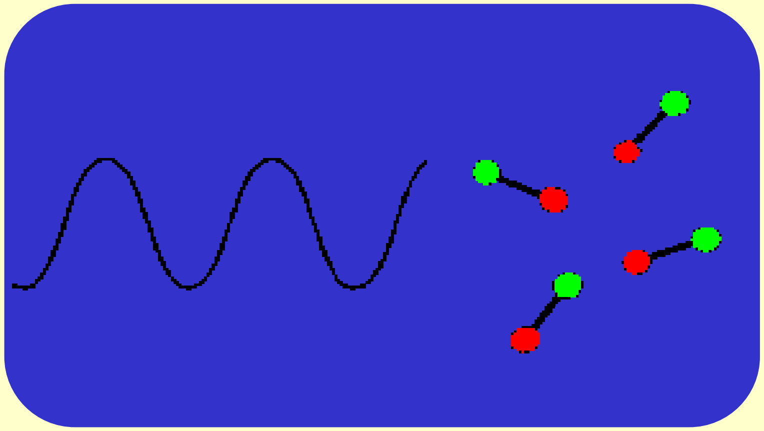
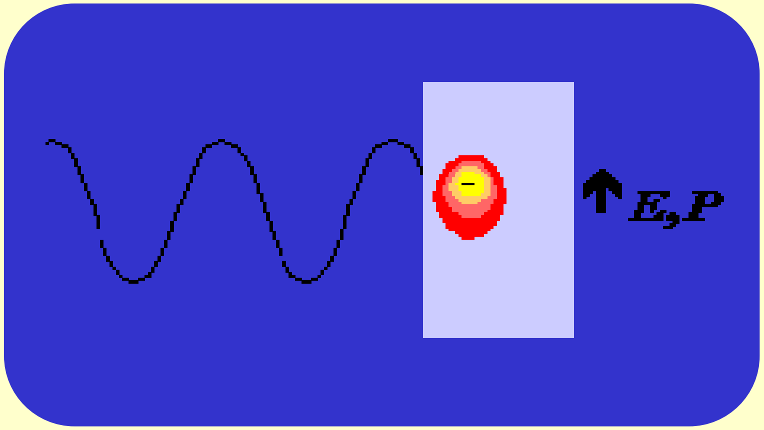
DIPOLE ROTATION

- Polar molecules rotate to attempt to align dipole with the rapidly oscillating electric field



IONIC CONDUCTION

- Ions move to attempt to align with the rapidly oscillating electric field



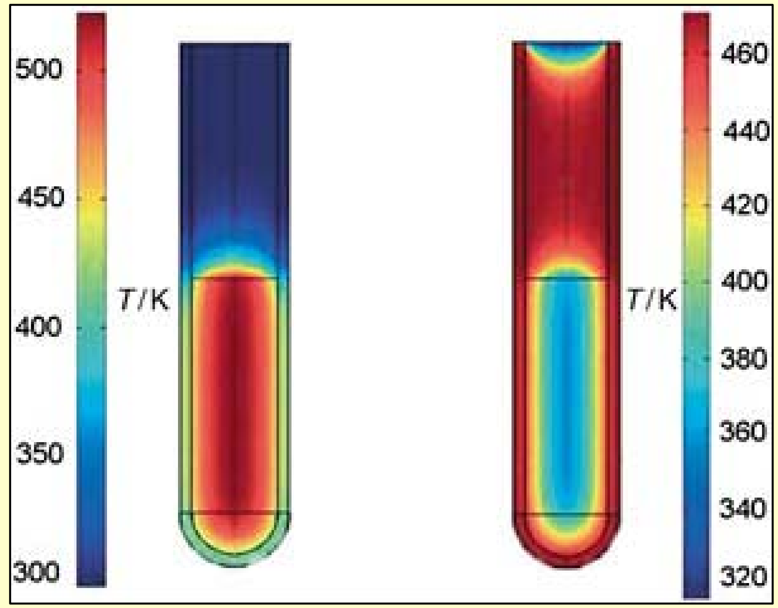
Energy is lost in the form of heat through molecular friction and dielectric loss

Mingos, D. M. P. *et al. Chem. Soc. Rev.* **1991**, *20*, 1; *Chem. Soc. Rev.* **1998**, *27*, 213

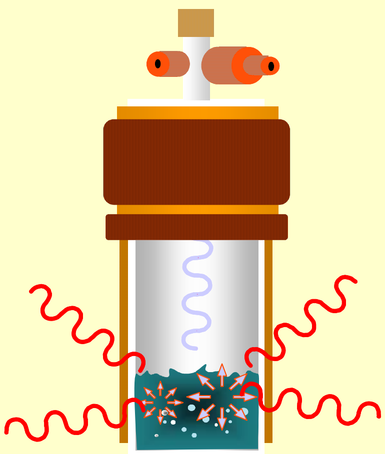
Dielectric Heating Mechanism

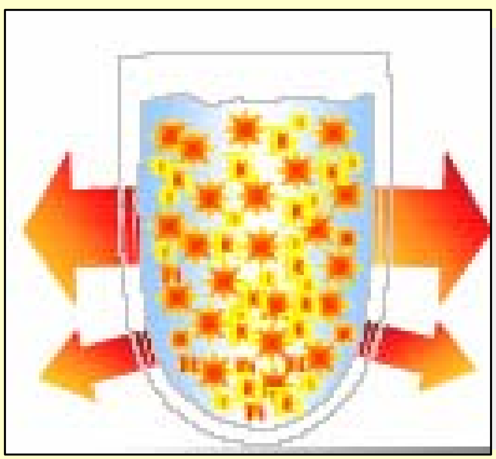
Inverted temperature gradients in microwave versus oil-bath heating:

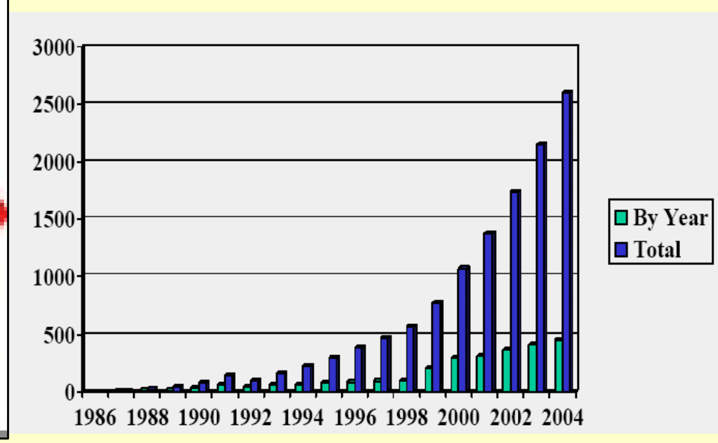
Microwave irradiation raises the temperature of the whole volume simultaneously (bulk heating) whereas the oil-heated tube heats in contact with the vessel wall first.

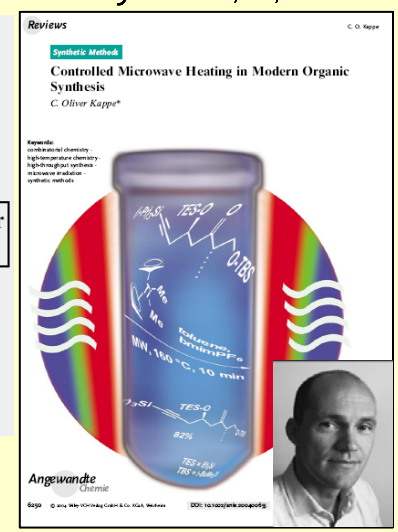


Schanche, J.-S. *Mol. Diversity* **2003**, *7*, 293.









For review see: Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

Advantages of microwave heating

Direct transfer of energy by dielectric heating

Sealed vessel heating

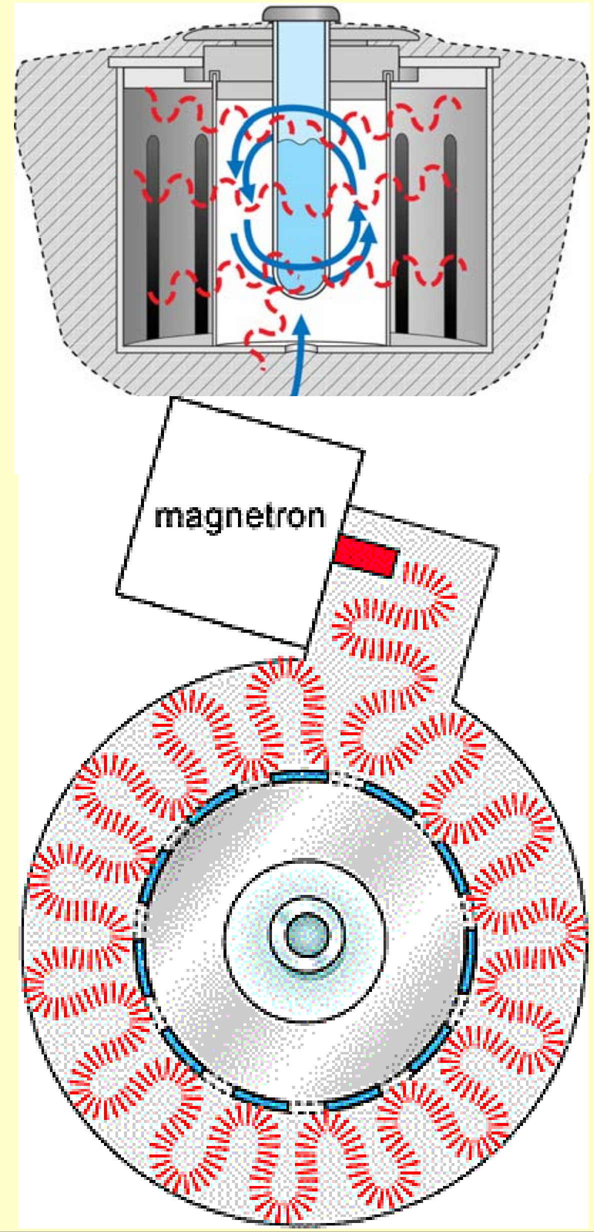
Rapid energy transfer: ns timeframe

Instant on/off energy control: 0.1 ms control

Relatively large energy transfer: 1.25 kcal/s

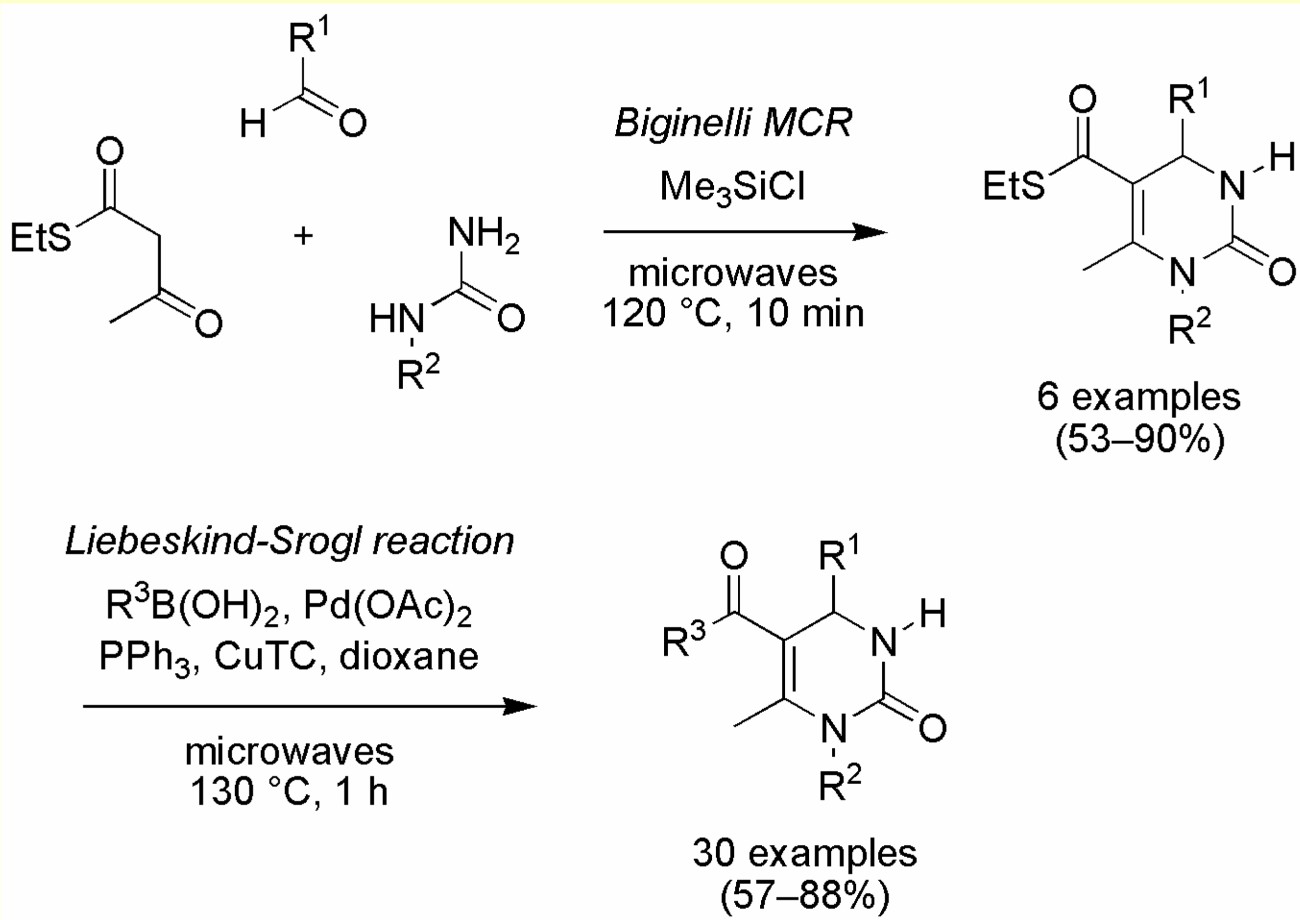
Selective coupling with irradiation

Reproducible procedures that are readily automated



What are microwaves good for?

Automated Library Synthesis



Kappe, C. O. *et al. J. Comb. Chem.* **2007**, *9*, 415.

Microwave dielectric heating in synthetic organic chemistry
Kappe, C. O. *Chem. Soc Rev.* **2008**, *37*, 1127-1139.

TUTORIAL REVIEW www.rsc.org/csr | Chemical Society Reviews

Microwave dielectric heating in synthetic organic chemistry

C. Oliver Kappe*

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First described more than two decades ago, microwave-assisted organic synthesis has matured from a laboratory curiosity to an established technique that today is heavily used in both academia and industry. One of the most valuable advantages of using controlled microwave dielectric heating for chemical synthesis is the dramatic reduction in reaction times: from days and hours to minutes and seconds. As will be explained in this *tutorial review*, there are many more good reasons why organic chemists are nowadays incorporating dedicated microwave reactors into their daily work routine.

1. Introduction. Microwave theory

In an ideal world, chemical transformations occur at room temperature, reach full conversion within a few minutes, and provide quantitative isolated product yields. The reality, however, is quite different. Many synthetically relevant processes necessitate an elevated temperature regime in order to proceed, with reaction times of several hours or even days to drive a reaction to completion not being uncommon. Until recently, heating reaction mixtures on a laboratory scale was typically performed using isomantles, oil baths or hot plates applying a reflux set-up where the reaction temperature is controlled by the boiling point of the solvent. This traditional form of heating is a rather slow and inefficient method for transferring energy into a reaction mixture, since it depends on convection currents and on the thermal conductivity of the various materials that must be penetrated, and often results in the temperature of the reaction vessel being higher than that of the reaction mixture.

Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, Graz, A-8010, Austria. E-mail: oliver.kappe@uni-graz.at

C. Oliver Kappe received his undergraduate and graduate education at the University of Graz under Professor Gert Kollenz. After periods of postdoctoral research work with Professor Curt Wentrup at the University of Queensland and with Professor Albert Padwa at Emory University, he moved back to the University of Graz in 1996 to start his independent academic career. In 1999 he became Associate Professor and in 2006 was appointed Director of the Christian Doppler Laboratory for Microwave Chemistry at the University of Graz.

In contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the molecules that are present in the reaction mixture.[1,2] Microwave irradiation triggers heating by two main mechanisms—dipolar polarization and ionic conduction. Whereas the dipoles in the reaction mixture (for example the polar solvent molecules) are involved in the dipolar polarization effect, the charged particles in a sample (usually ions) are affected by ionic conduction. When irradiated at microwave frequencies, the dipoles or ions of the sample align in the applied electric field. As the applied field oscillates, the dipole or ion field attempts to realign itself with the alternating electric field and, in the process, energy is lost in the form of heat through molecular friction and dielectric loss.[1–3] The ability of a specific material or solvent to convert microwave energy into heat at a given frequency and temperature is determined by the so-called loss tangent ($\tan \delta$) and in general a reaction medium with a high $\tan \delta$ at the standard operating frequency of a microwave synthesis reactor (2.45 GHz) is required for good absorption and, consequently, for efficient heating (Table 1).[1–3]

For low absorbing solvents, polar additives such as ionic liquids or passive heating elements made out of strongly microwave absorbing materials can be added to otherwise low absorbing reaction mixtures in order to increase the absorbance level of the medium.[4] Since the reaction vessels employed in microwave chemistry are made out of essentially microwave transparent materials such as glass or Teflon ($\tan \delta < 0.01$), only the reaction mixture—not the reaction vessel—is heated.

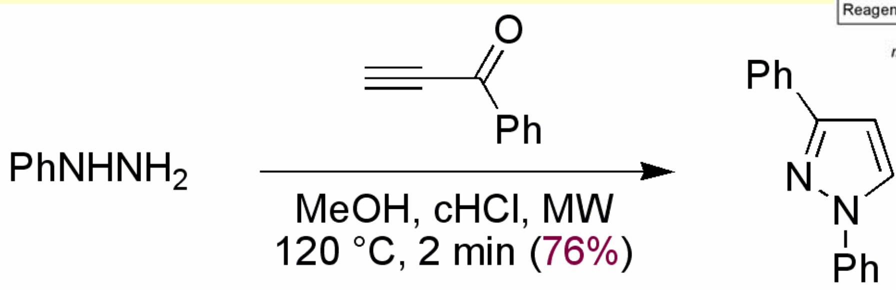
The use of microwave heating in organic synthesis was introduced in 1986 by the groups of Gedye and Giguere/Majetich.[5] Although many of the early pioneering experiments in microwave-assisted synthesis have been carried out in domestic microwave ovens, the trend since the year 2001 undoubtedly is to use dedicated microwave reactors specifically designed for synthetic applications (controlled microwave synthesis).[3] These instruments feature built-in magnetic stirrers, direct temperature control of the reaction mixture with the aid of internal fiber-optic probes or external infrared sensors, and software that enables on-line temperature/pressure control by regulation of microwave power output.[2,3]

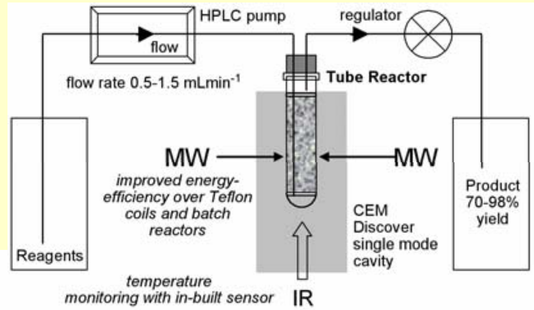
What are microwaves good for?

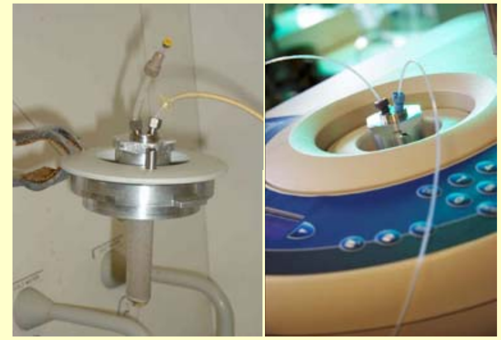
Automated Library Synthesis

<u>Shortening Reaction Times</u>

1)







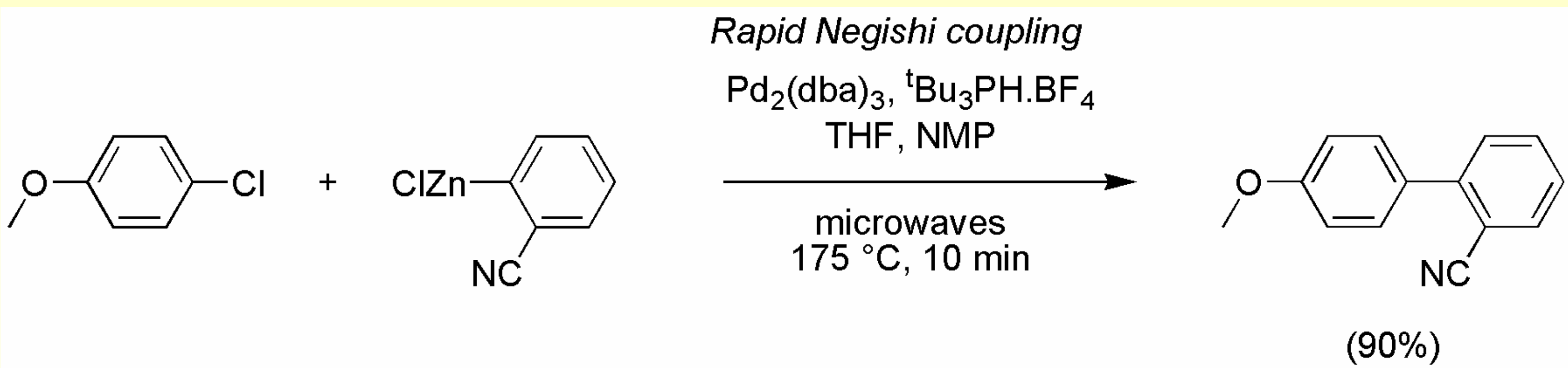
Pyrazole formation

cf reflux, 15 h (76%)
conductive heating

10 mL Flow Cell
CEM Discover®
Flow rate 1.5 ml/min
(**84%**)

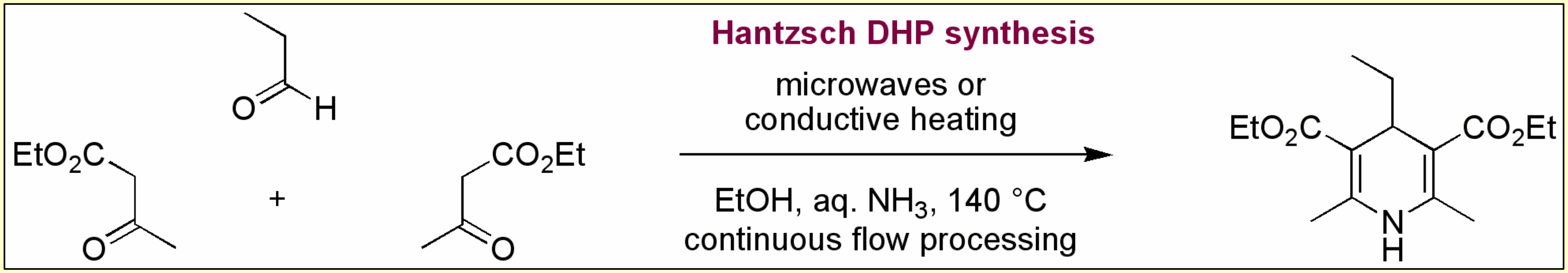
Bagley, M. C. *et al*. *Synlett* **2007**, 704-708.
with M.C. Lubinu, R. Wood, C. Mason, *J. Org. Chem.* **2005**, *70*, 7003-7006.

2)



Walla, P.; Kappe, C. O. *Chem. Commun.* **2004**, 564.

What are microwaves good for?



Other technology is available for carrying out reactions above the solvent bp:

CEM Discover®
10 min (68%)

Uniqsis FlowSyn
0.5 ml/min, 10 min (65%)

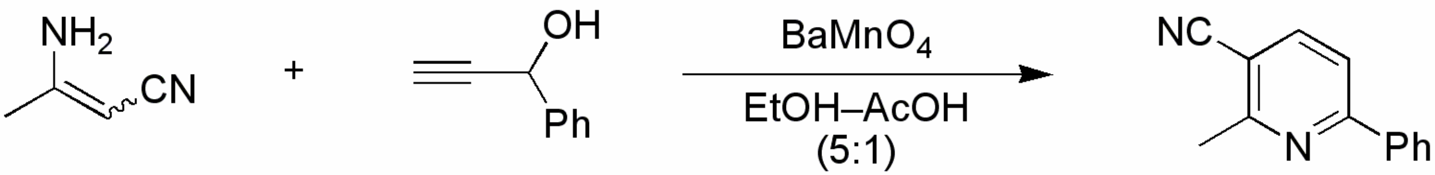
Outcome comparable

What are microwaves good for?

Automated Library Synthesis

Shortening Reaction Times

<u>Optimizing Reaction Conditions</u>



tandem oxidation
Bohlmann–Rahtz

1	80 °C, 18 h, conductive heating	30%
2	80 °C, 45 min, conductive heating	0%
3	100 °C, 45 min, microwaves	31%
4	150 °C, 45 min, microwaves	54%
5	170 °C, 45 min, microwaves	61%
6	170 °C, 60 min, microwaves	57%
7	170 °C, 25 min, microwaves	40%

For account of the Bohlmann-Rahtz reaction, see: Bagley, M. C. *et al.* *Synlett* **2007**, 2459–2482.

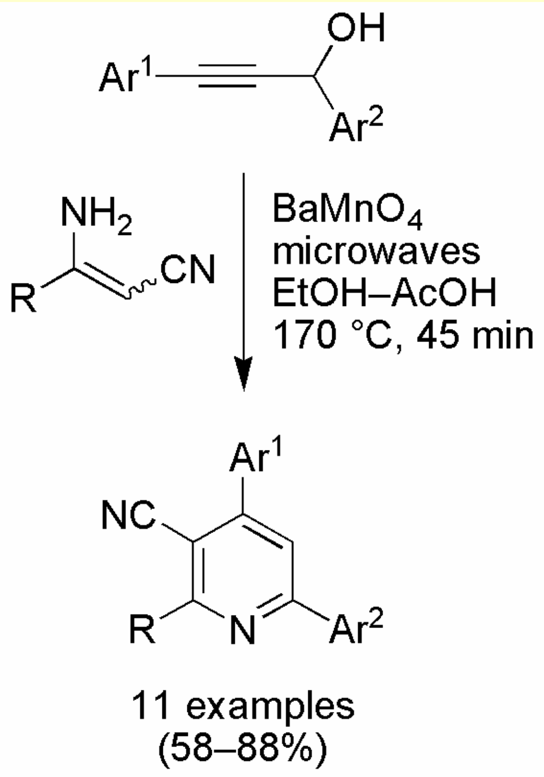
What are microwaves good for?

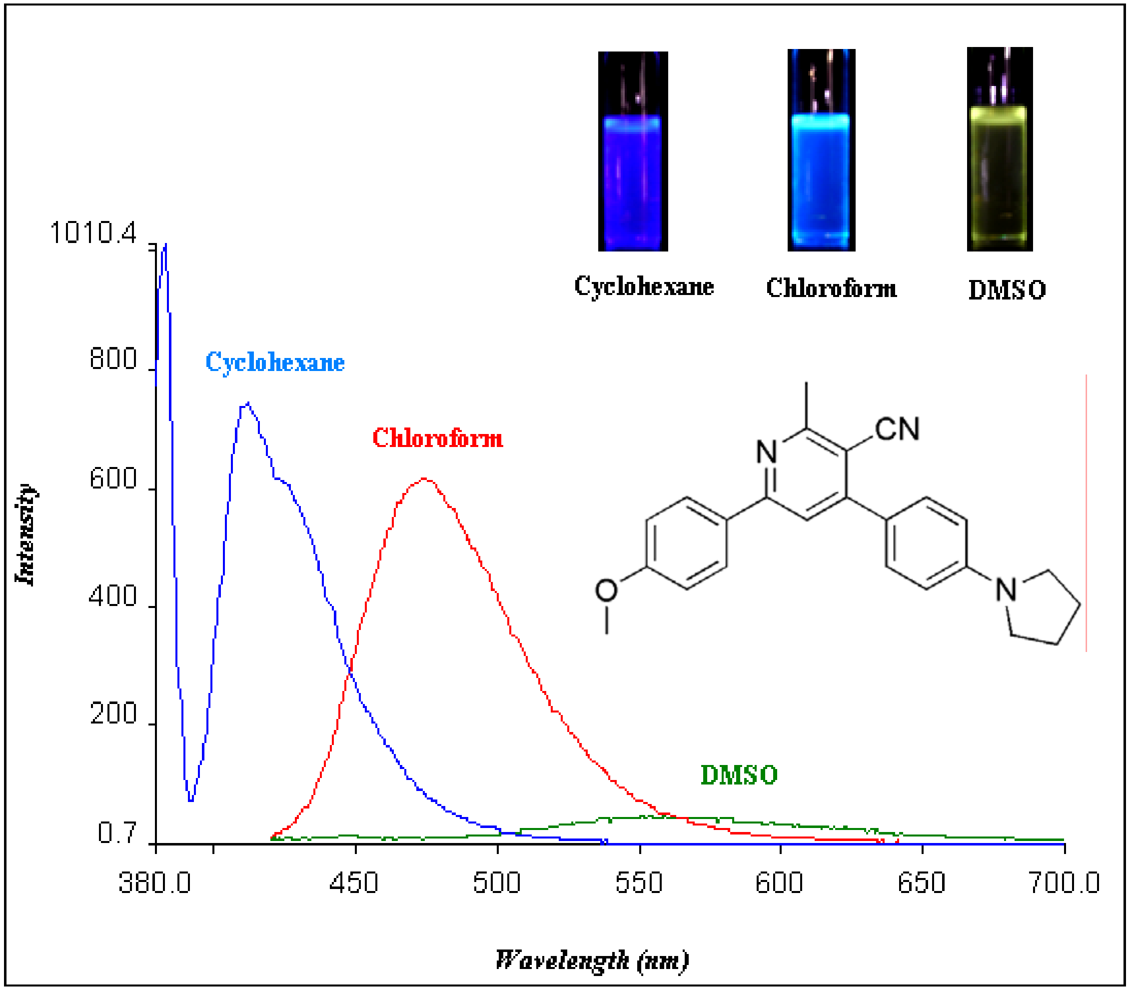
Automated Library Synthesis

Shortening Reaction Times

Optimizing Reaction Conditions

Screening Reaction Scope





What are microwaves good for?

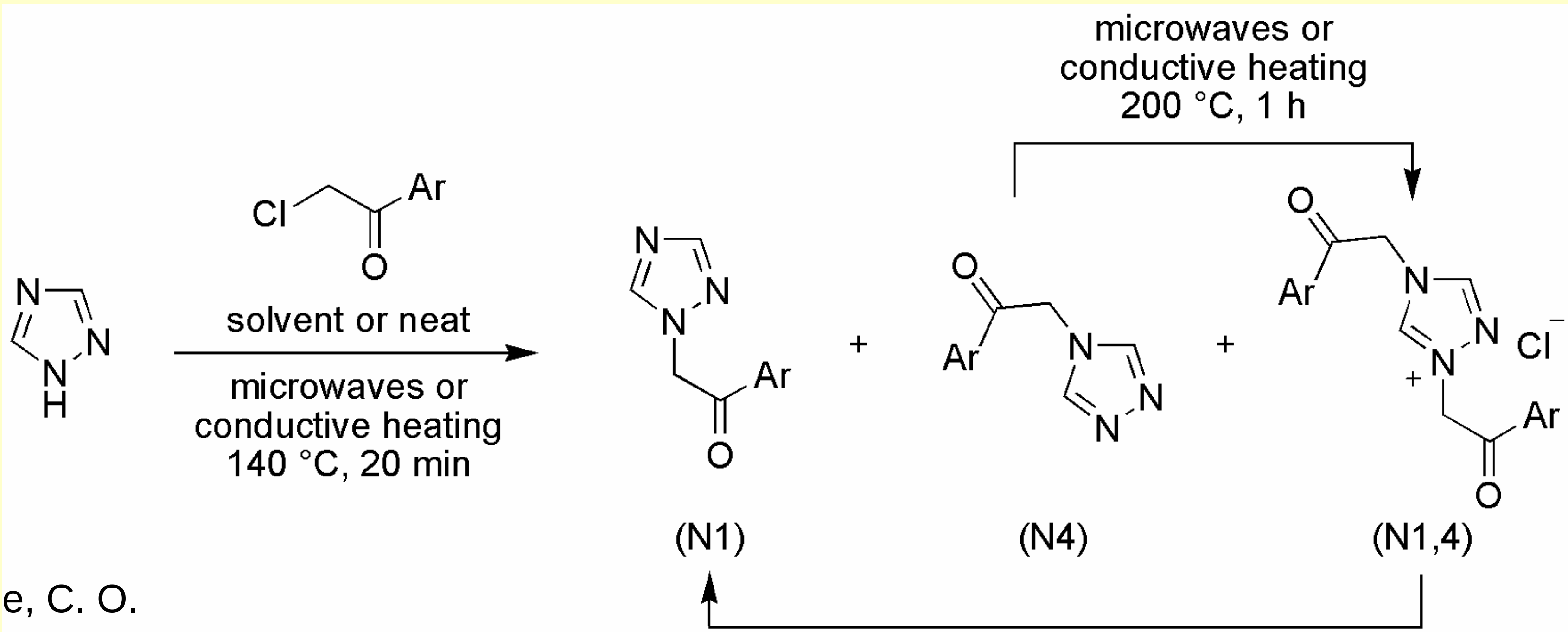
Automated Library Synthesis

Shortening Reaction Times

Screening and Optimizing Reaction Conditions

Improving Yields (minimizing wall effects, rapid heating and cooling)

Altering Product Distributions and Reaction Selectivity



Kappe, C. O.
Chem. Soc Rev. **2008**, *37*, 1127-1139.

What are microwaves good for?

Automated Library Synthesis

Shortening Reaction Times

Screening and Optimizing Reaction Conditions

Improving Yields (minimizing wall effects, rapid heating and cooling)

Altering Product Distributions and Reaction Selectivity

Which Reactions in Heteroaromatic Chemistry?

Synthesis: cyclocondensation reactions

Synthesis: multicomponent reactions

S_NAr reactions

Cross-coupling reactions

Functional group interconversion

Thermodynamic control

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What are the outstanding issues?

Can we scale up reactions readily from mg to kg to tonnes?

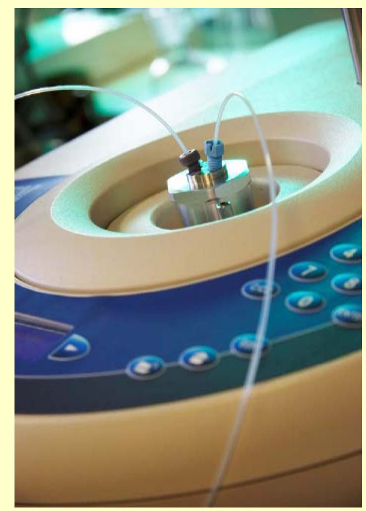
Can we monitor microwave-assisted reactions?

Do we have robust methods for all useful transformations?

Can we combine microwave heating with other technologies?

What reactions are only possible with microwave heating?

Are there any specific or non-thermal microwave effects?



What can progeroid syndromes tell us about human ageing?

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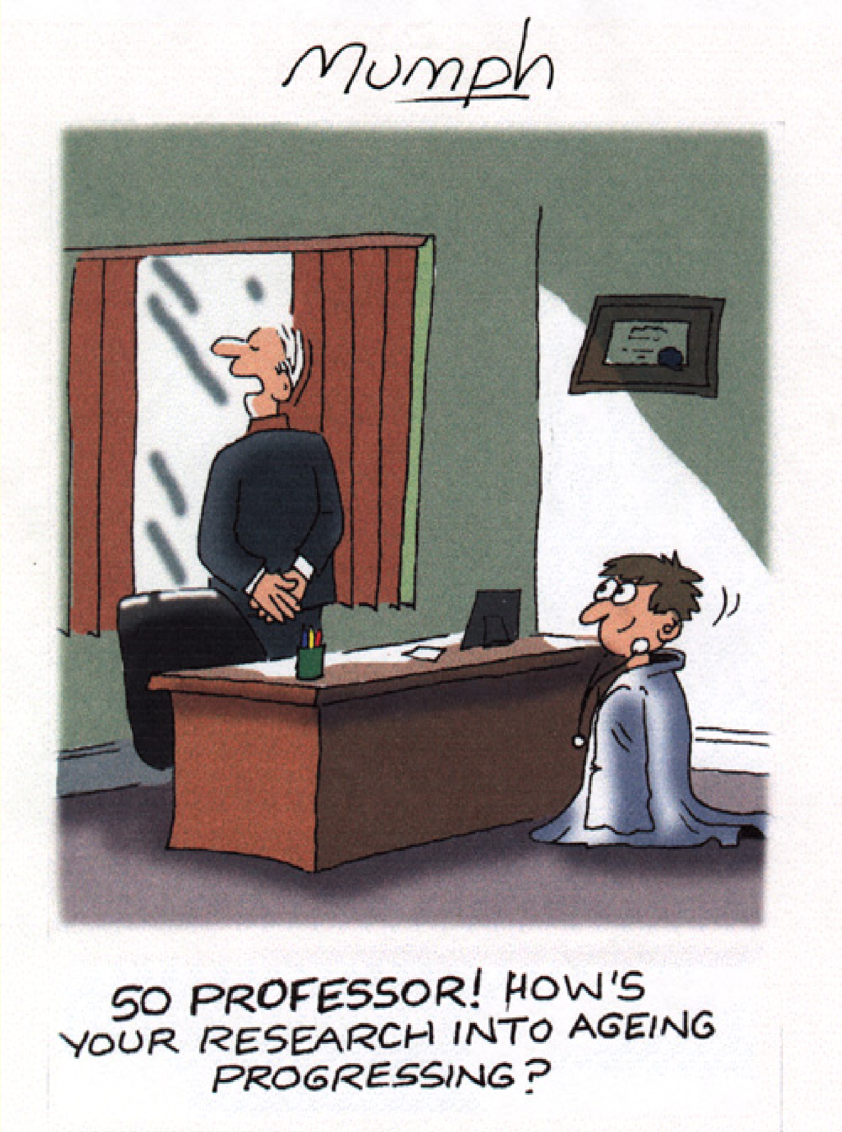
Ageing:

The universal, progressive, and intrinsic accumulation of deleterious changes.

Why are we bothered about ageing?

The physiological effectiveness of an organism is compromised, ultimately leading to death.

What causes it?



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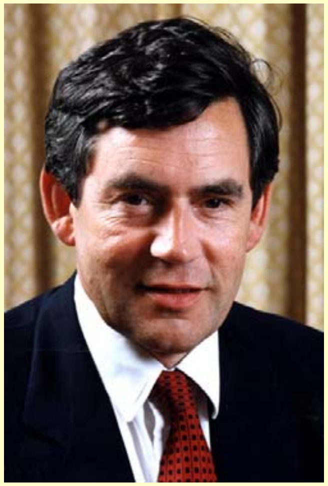
Is there a link between stress and ageing?



7th Oct 07

3rd May 08

What can progeroid syndromes tell us about human ageing?

Ageing:

The universal, progressive, and intrinsic accumulation of deleterious changes.

Why are we bothered about ageing?

The physiological effectiveness of an organism is compromised, ultimately leading to death.

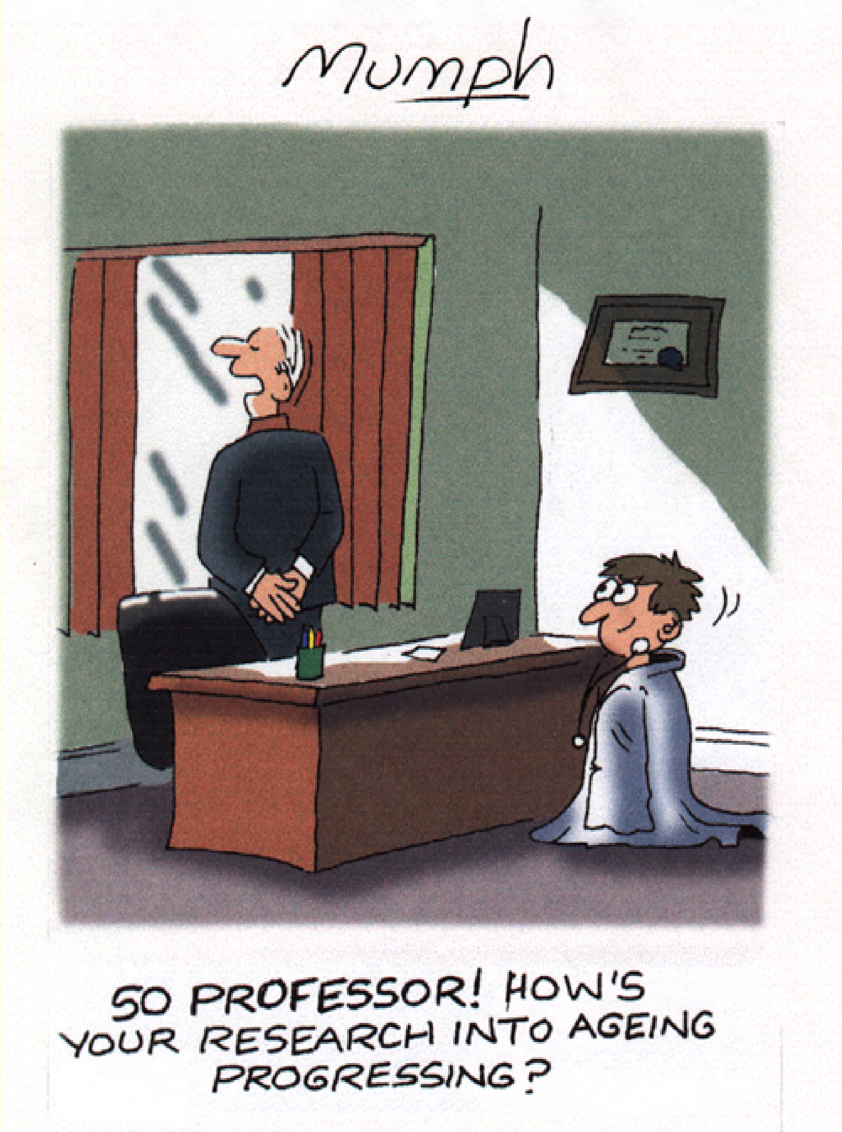
What causes it?

How can we understand it?

Manipulate it!

Model species vs. human genetic diseases

Universal vs. species-specific



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Discovery of Werner Syndrome

Aus der Königlichen Augenklinik zu Kiel.

Über

Katarakt in Verbindung mit Sklerodermie.

Inaugural-Dissertation

zur Erlangung der Doktorwürde

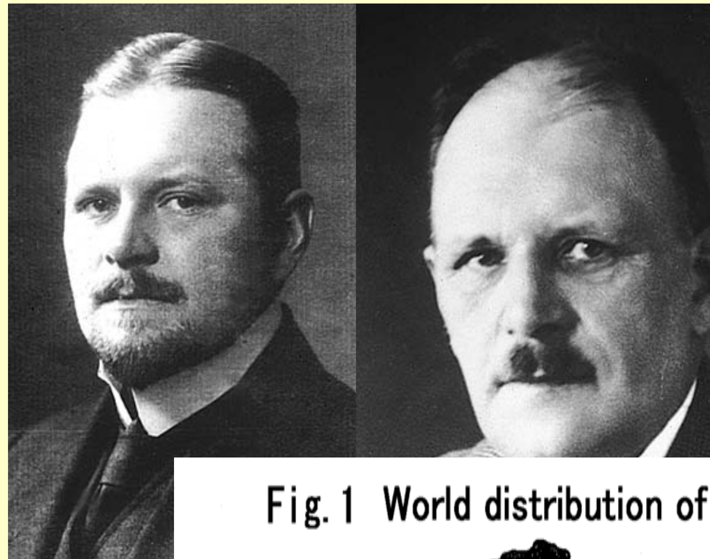
der medizinischen Fakultät
der Königl. Christian-Albrechts-Universität zu Kiel

vorgelegt von

Otto Werner,
approb. Arzt aus Kiel.

Kiel 1904.
Druck von Schmidt & Klaunig.

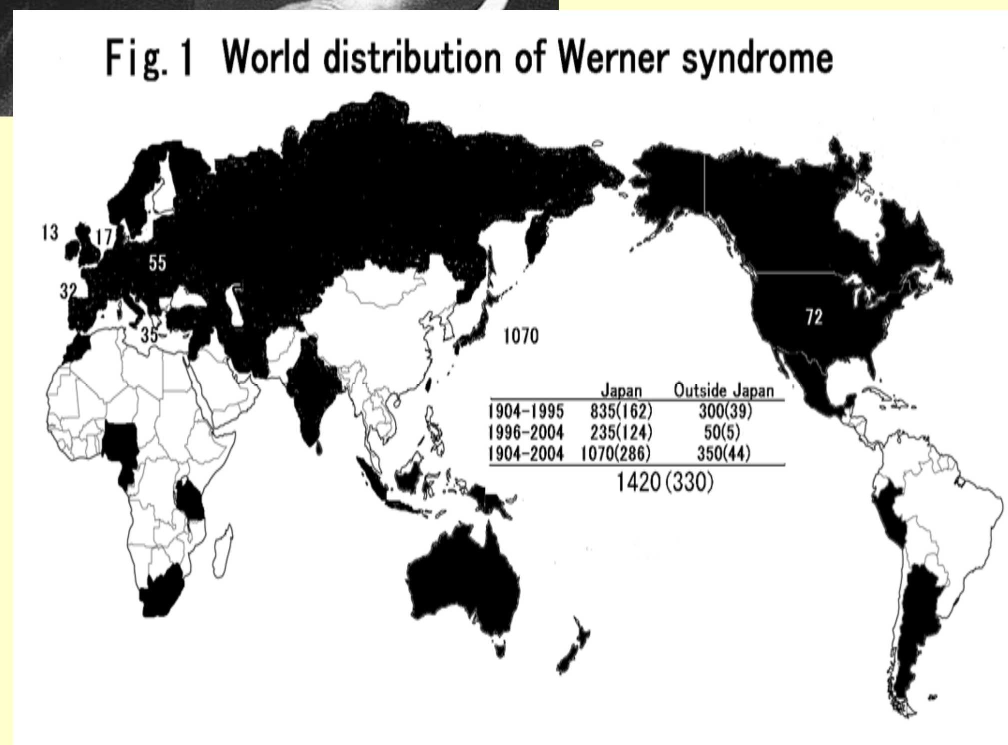
Dissertation, Kiel University, 1904

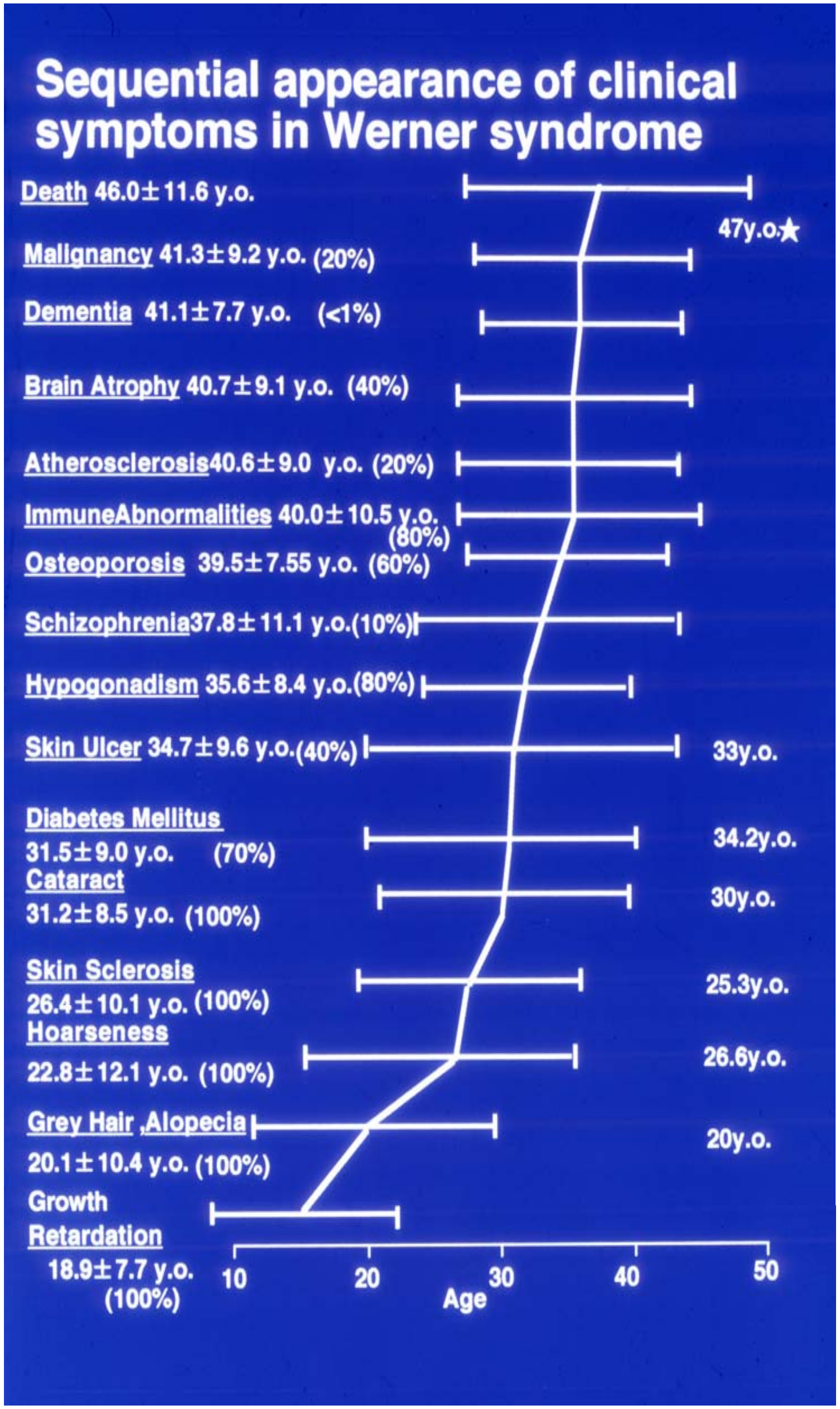


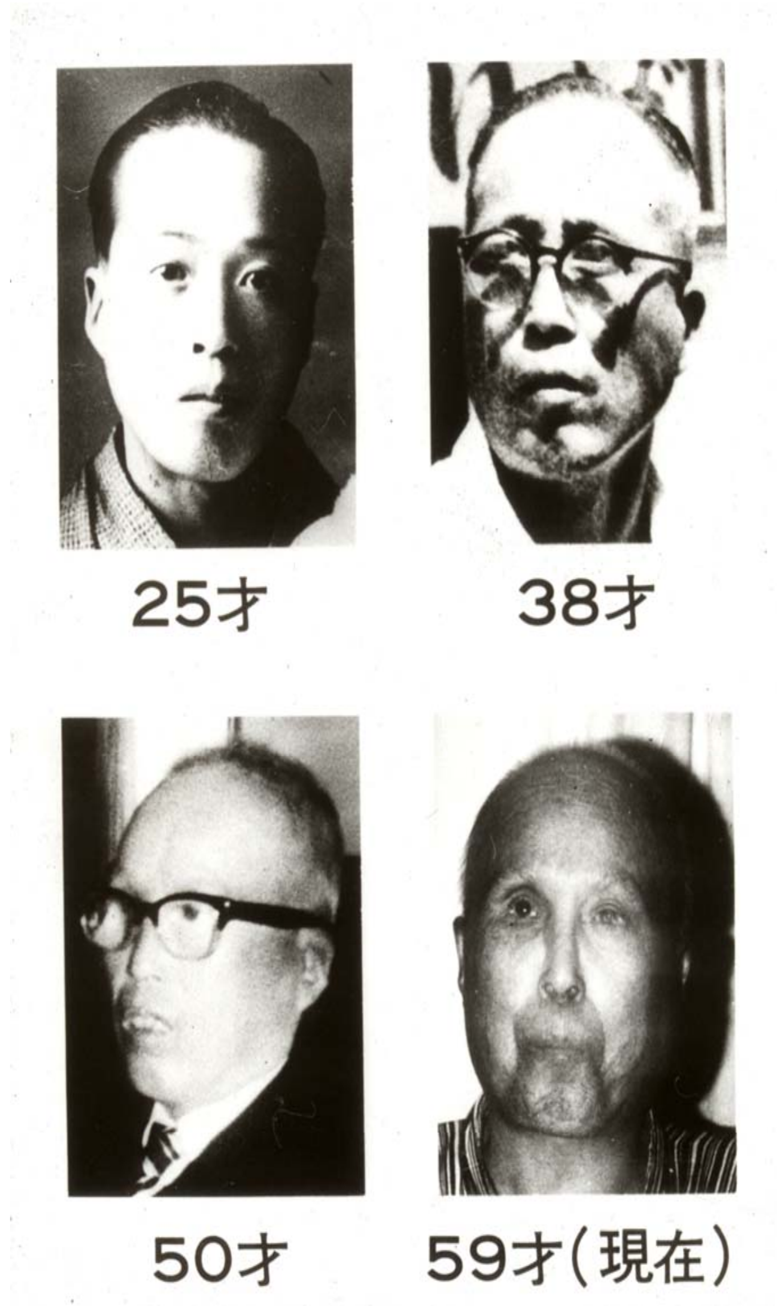
Charles W. Otto Werner

German physician

(1879–1936)







Courtesy of Makoto Goto, Toin University of Yokohama

Clinical symptoms: atrophic/sclerotic skin

Courtesy of Atsushi Hatamochi MD, Dokkyo University School of Medicine

Clinical symptoms: ulceration, calcification and sarcomas

Courtesy of Atsushi Hatamochi MD, Dokkyo University School of Medicine

Calcification

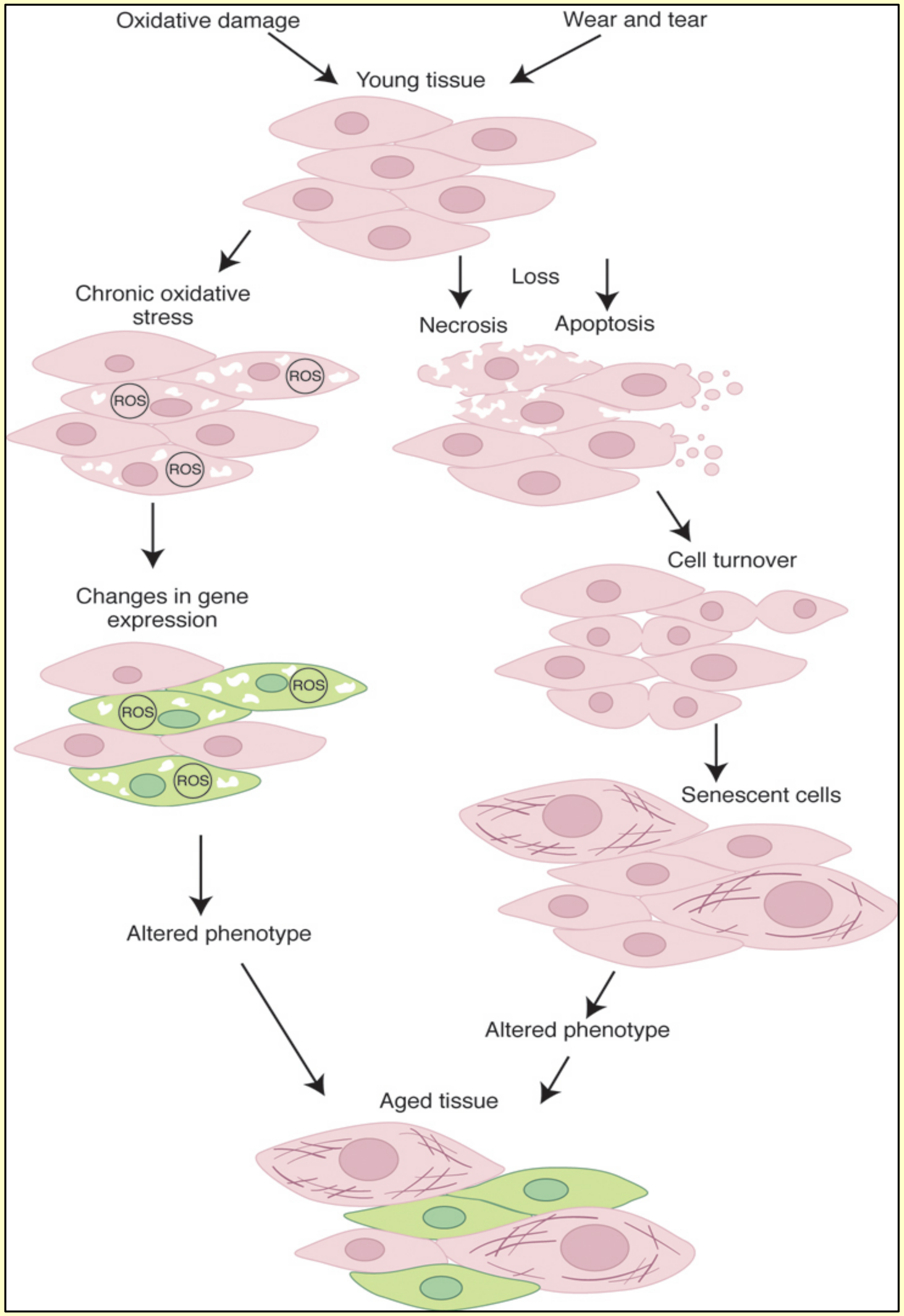
Ulceration

Sarcomas

Senescence as an Ageing Mechanism

How could senescent cells produce ageing bodies?

Dysdifferentiation hypothesis of ageing



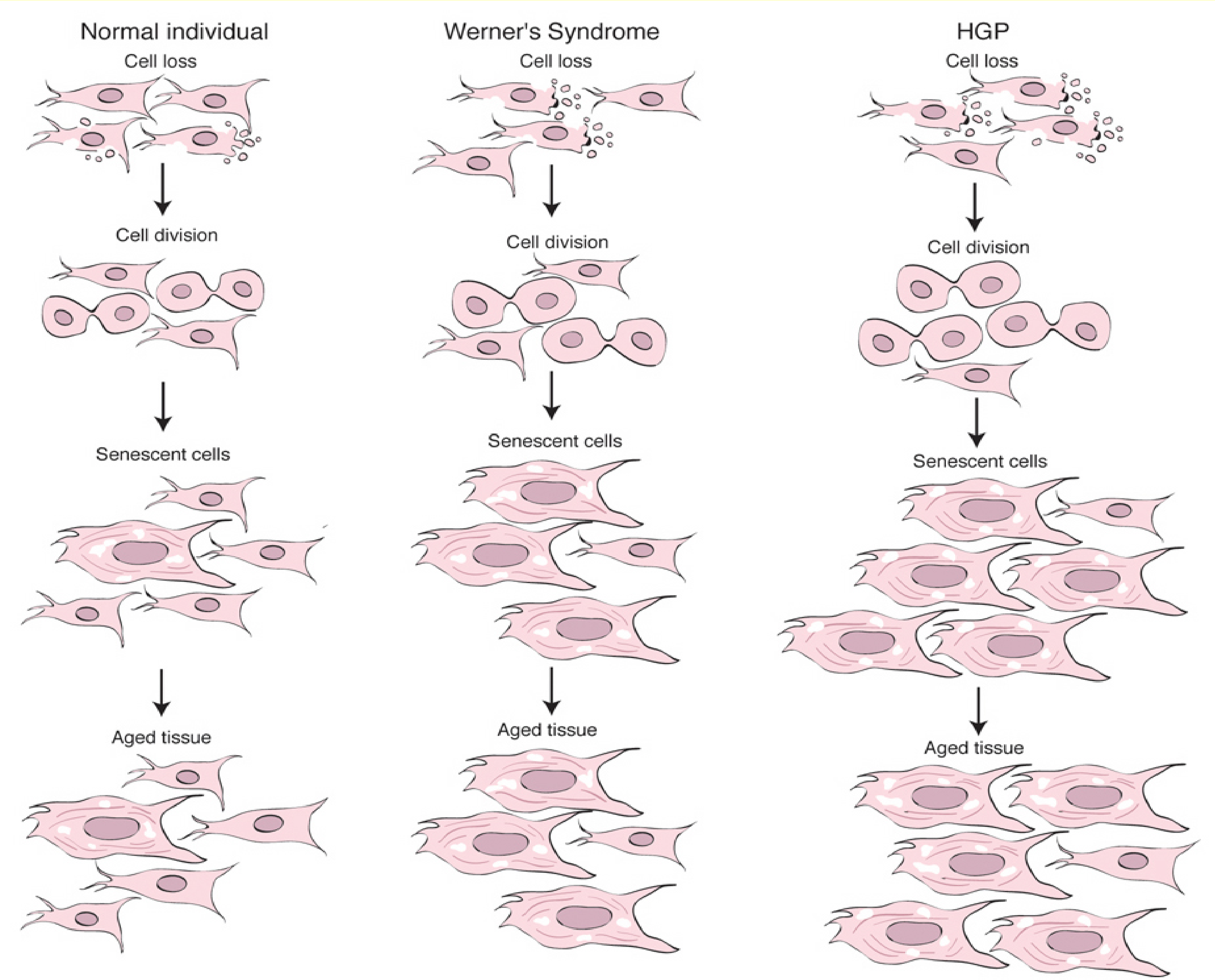
Kipling *et al.* (2004) Science 305: 1426-31

Replicative senescence hypothesis of ageing

Do senescent cells exist in bodies?
e.g. Li *et al.* (1997) *Invest. Ophthalmol. Vis. Sci.* 38: 100-7, Herbig *et al* (2006) *Science* 311 (5765)**:** 1257

Can senescent cells exert degenerative effects?
(Funk *et al.* (2000) *Exp. Cell Res.* 258:270-8, Minamino, T. *et al.* (2003) *Circulation* 108: 2264-2269)

Accelerated Ageing in Progeroid Syndromes



Kipling *et al.* (2004) Science 305: 1426-31

Cell loss

Cells divide to replace

Senescent cells build up

This leads to aged tissue

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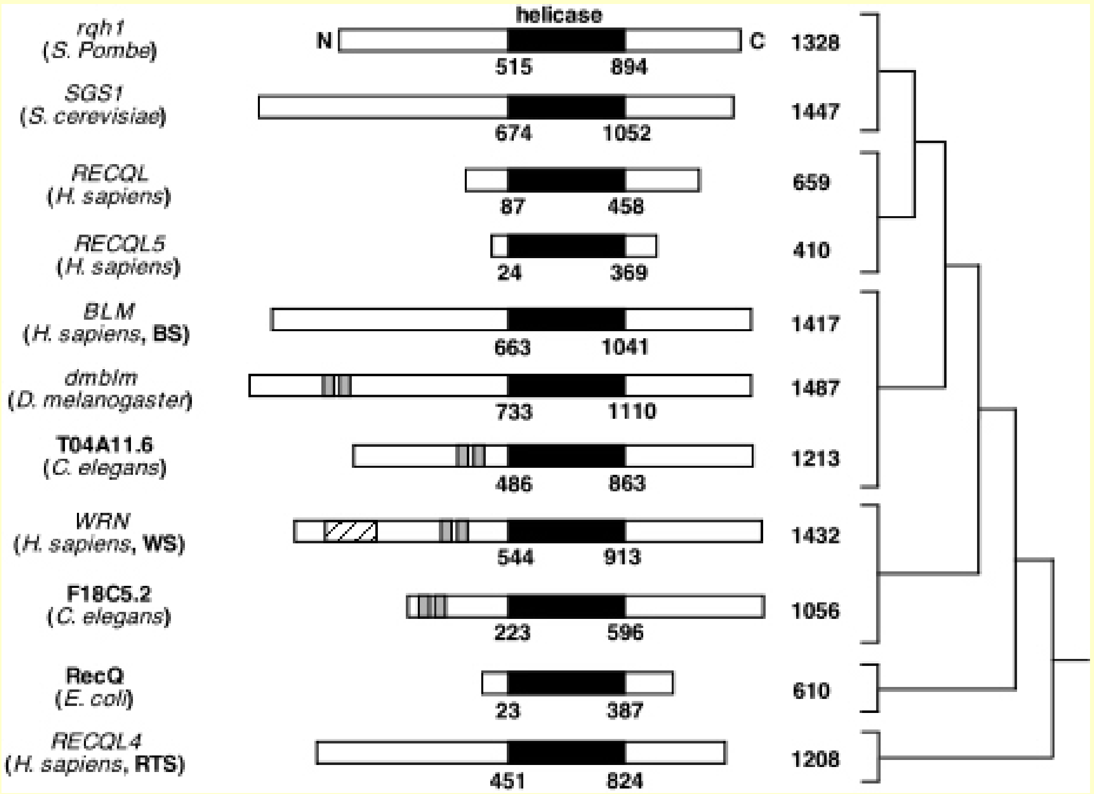
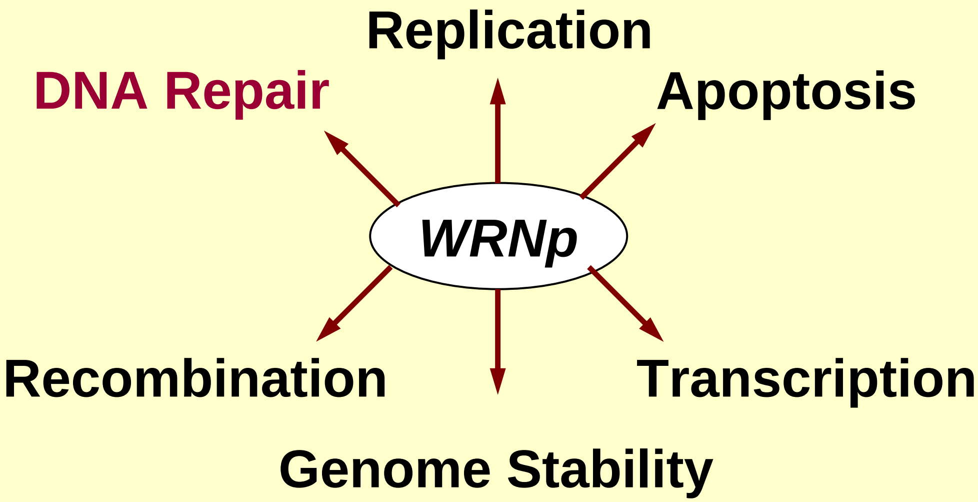
WS is caused by *WRN* mutations...



- ***WRN*** **encodes protein** ***WRNp***
- ***WRNp*** **is homologous to the RecQ helicase of** ***E. coli***
- ***WRNp*** **contains both a helicase and nuclease unit**
- **WS is caused by assorted mutations in** ***WRN***

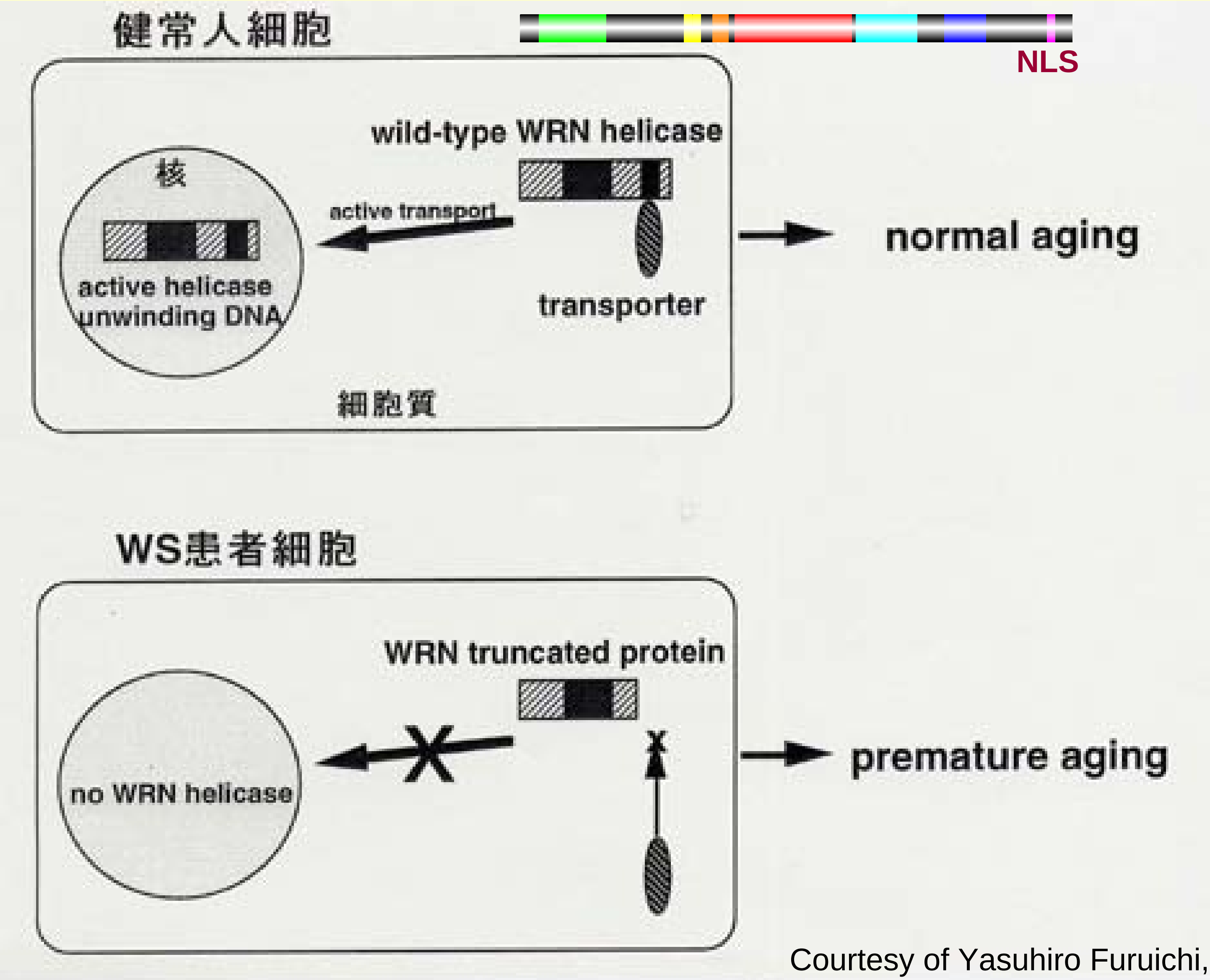
WRNp **plays a vital role in cellular processes by interacting with DNA**

...which cause loss of function



- *WRNp* is one of five helicases in the human genome
- Helicases open up the double strand of DNA
- **Of this family, only *WRNp* couples a helicase and an exonuclease function**
- Nucleases degrade one or both of the DNA strands
- **WRN-exo belongs to a family of nucleases involved in maintaining genomic integrity**

...as mutant peptides are truncated



WRNp helps to bind, unwind and process disrupted forks in DNA replication to prevent their collapse

Lack of *WRNp* results in DNA replication stalling and causes problems with DNA repair

Courtesy of Yasuhiro Furuichi, GeneCare Research Institute

Linking the Genetic Basis and Phenotype

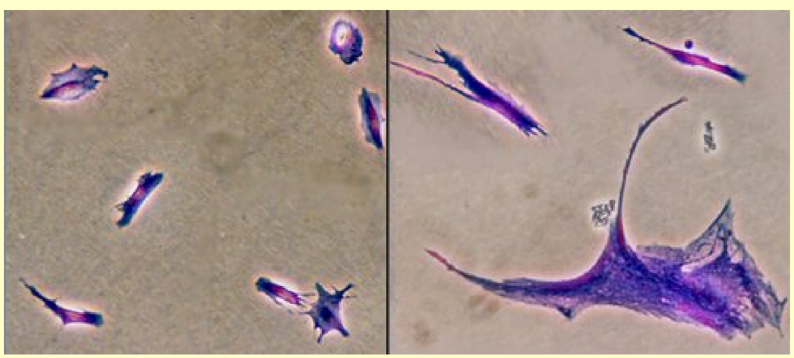
What links stalled replication with accelerated ageing?

- **WS cells in culture have:**

  Shortened replicative lifespan (15-20 PD)

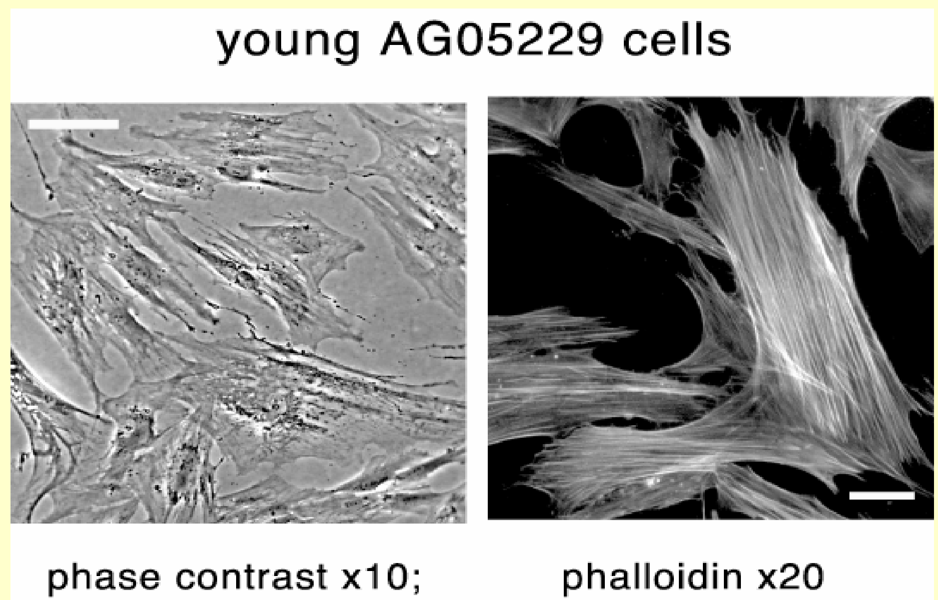
  Slow growth rate, elongated cell cycle, senescent morphology of aged normal fibroblasts

- **Premature ageing is consistent with accelerated replicative senescence that is independent of telomere erosion**



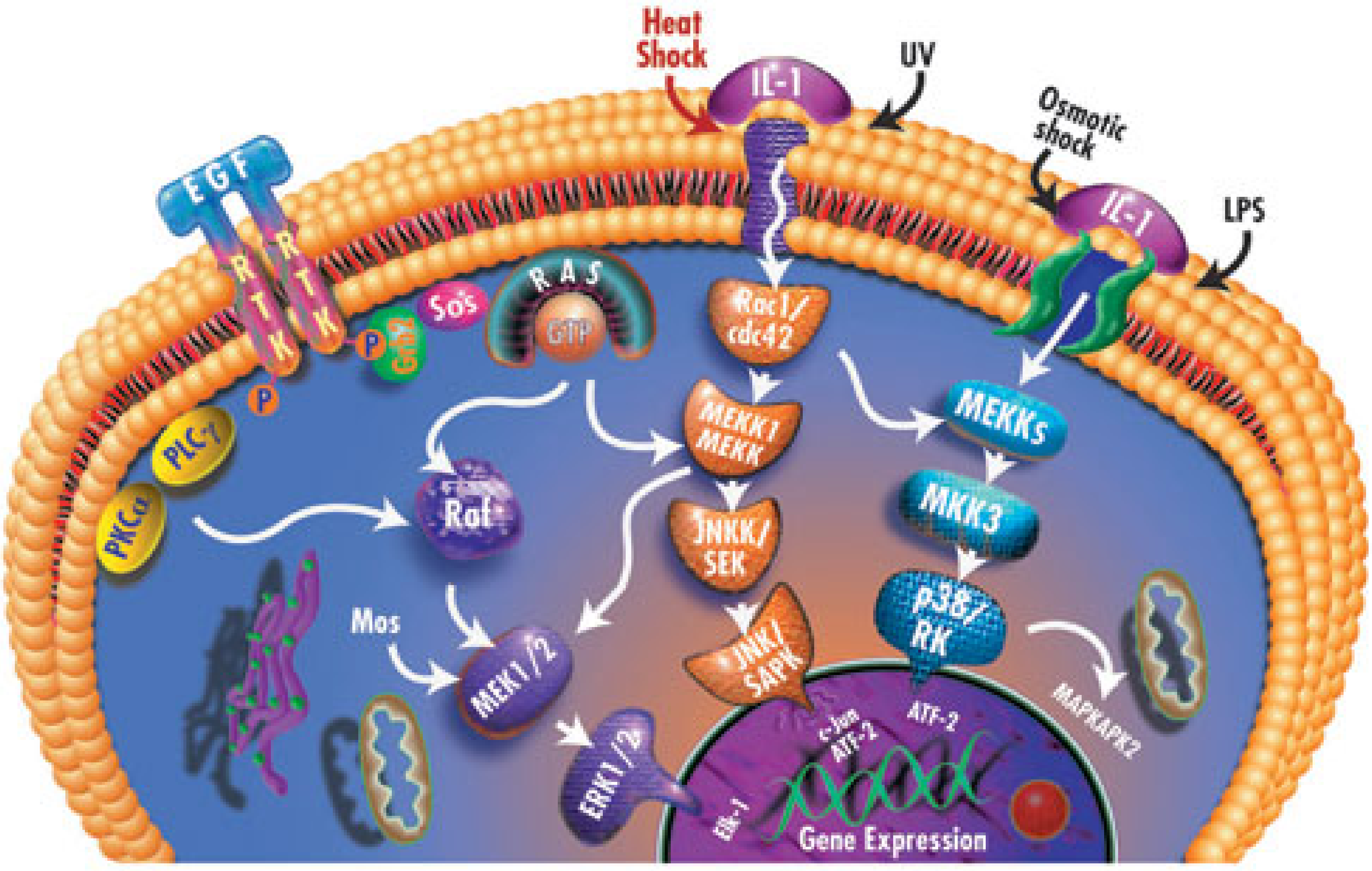
Young Senescent

Davis, T.; Wyllie, F. S.; Rokicki, M. J.; Bagley, M. C.; Kipling, D. *Ann. N. Y. Acad. Sci.* **2007**, *1100*, 455

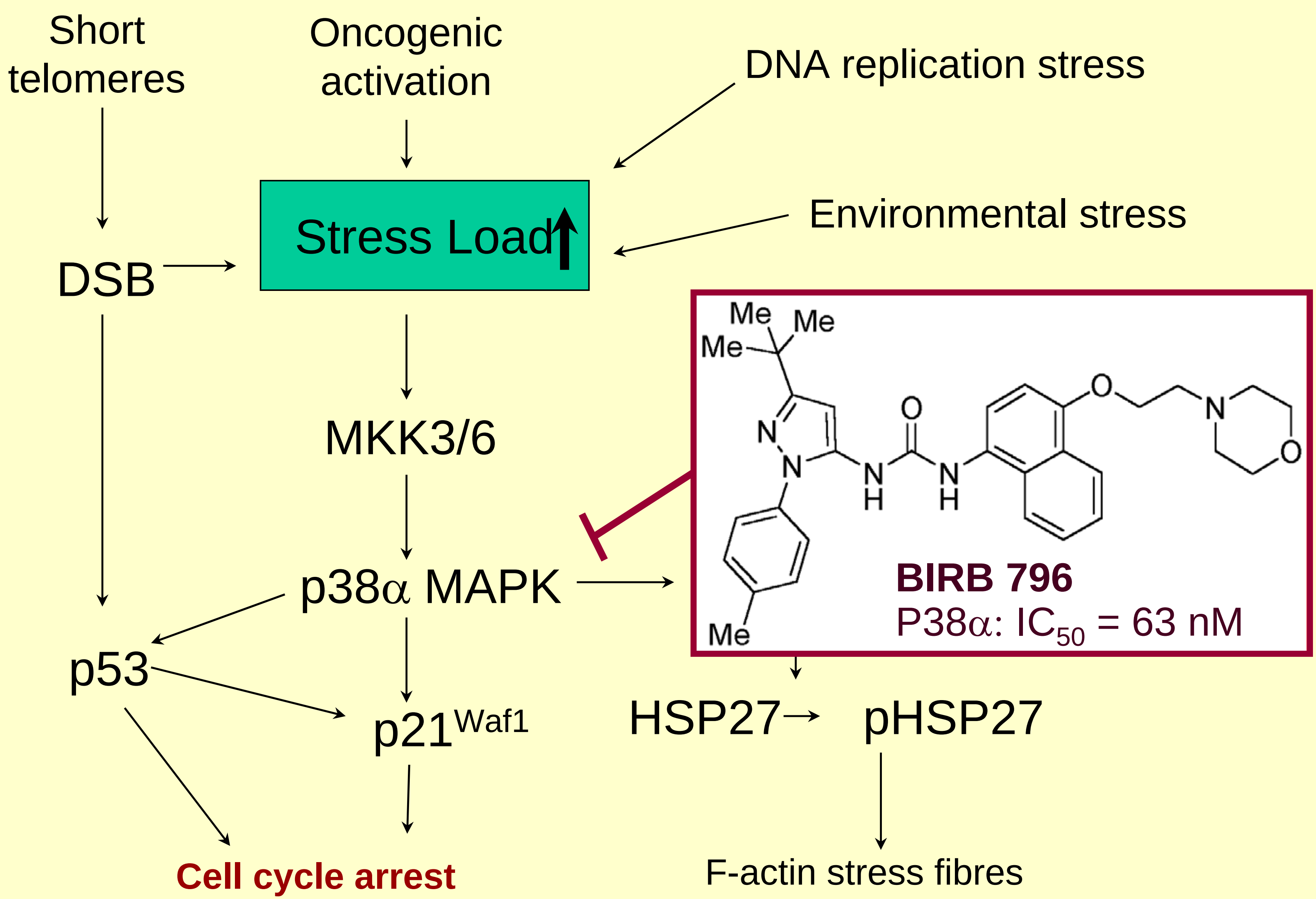


Stress Induced Growth Arrest

Environmental stress causes premature senescence by signal transduction



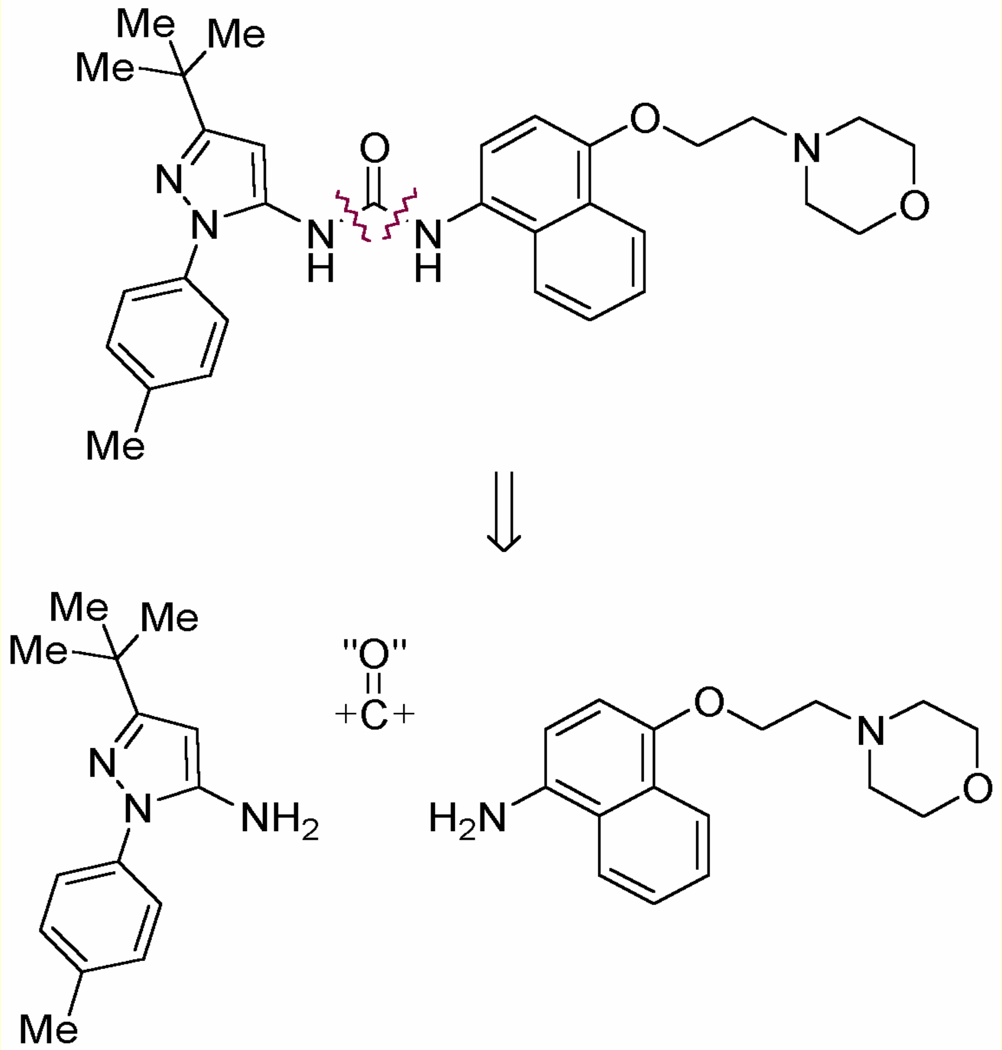
Growth Arrest Pathways



Disconnective Scheme for BIRB 796

BIRB 796

N-pyrazole urea



5-Aminopyrazole

4-Aminonaphth-1-ol

Synthetic needs:

- Convergent
- High purity
- Rapid
- Efficient
- **MICROWAVE**

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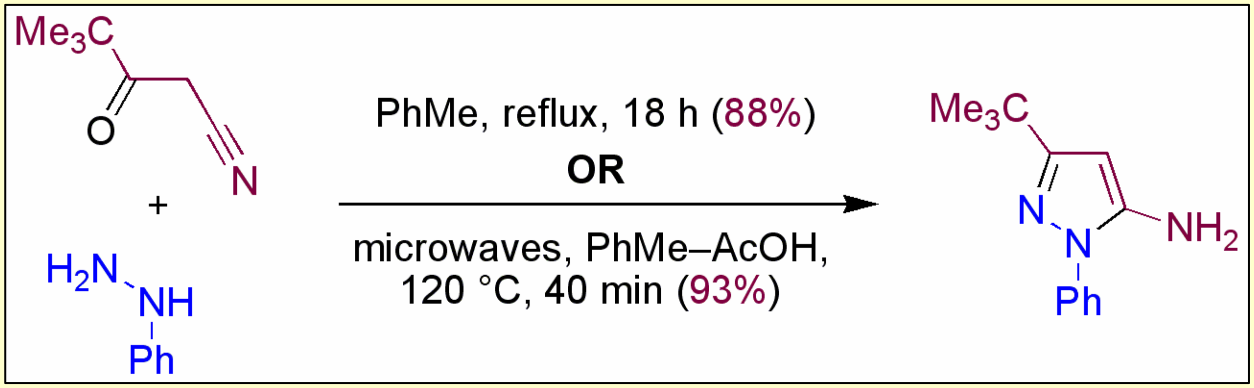
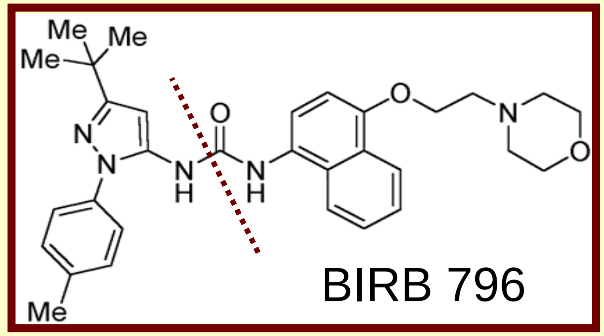
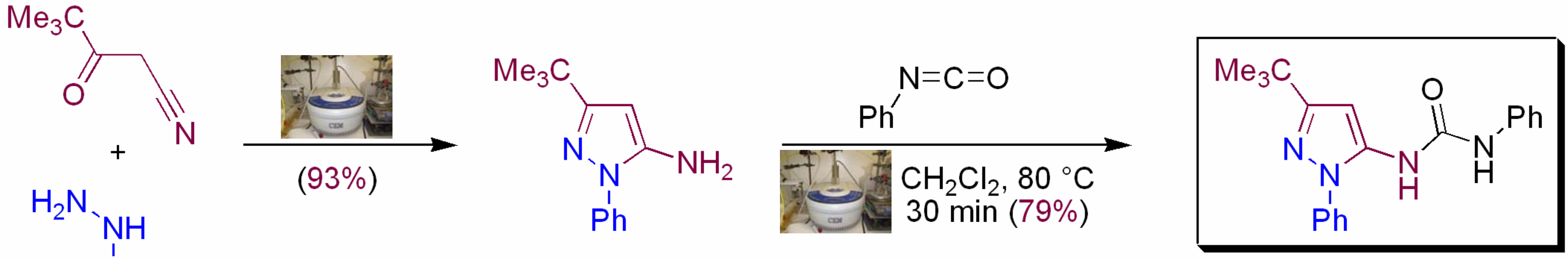
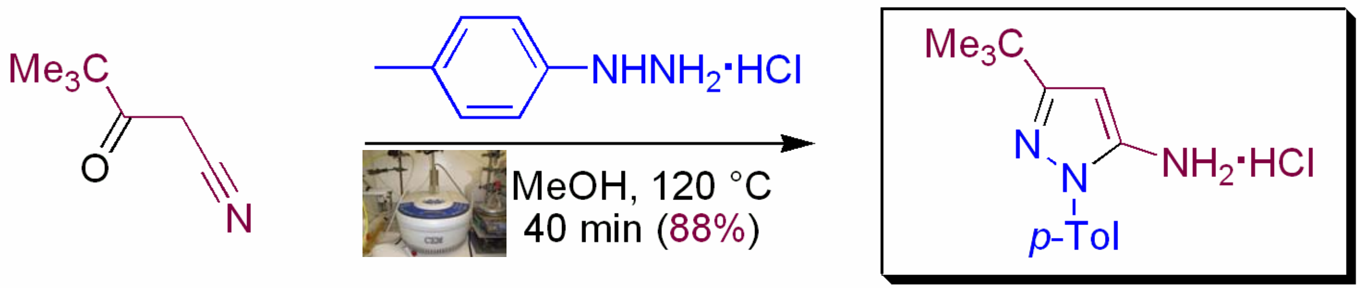
Synthesis of BIRB 796 Building Block







Analogue of BIRB 796



5-aminopyrazole
building block for BIRB 796

 Bagley, M. C.; Davis, T.; Dix, M. C.; Widdowson, C. S.; Kipling, D. *Org. Biomol. Chem.* **2006**, *4*, 4158.

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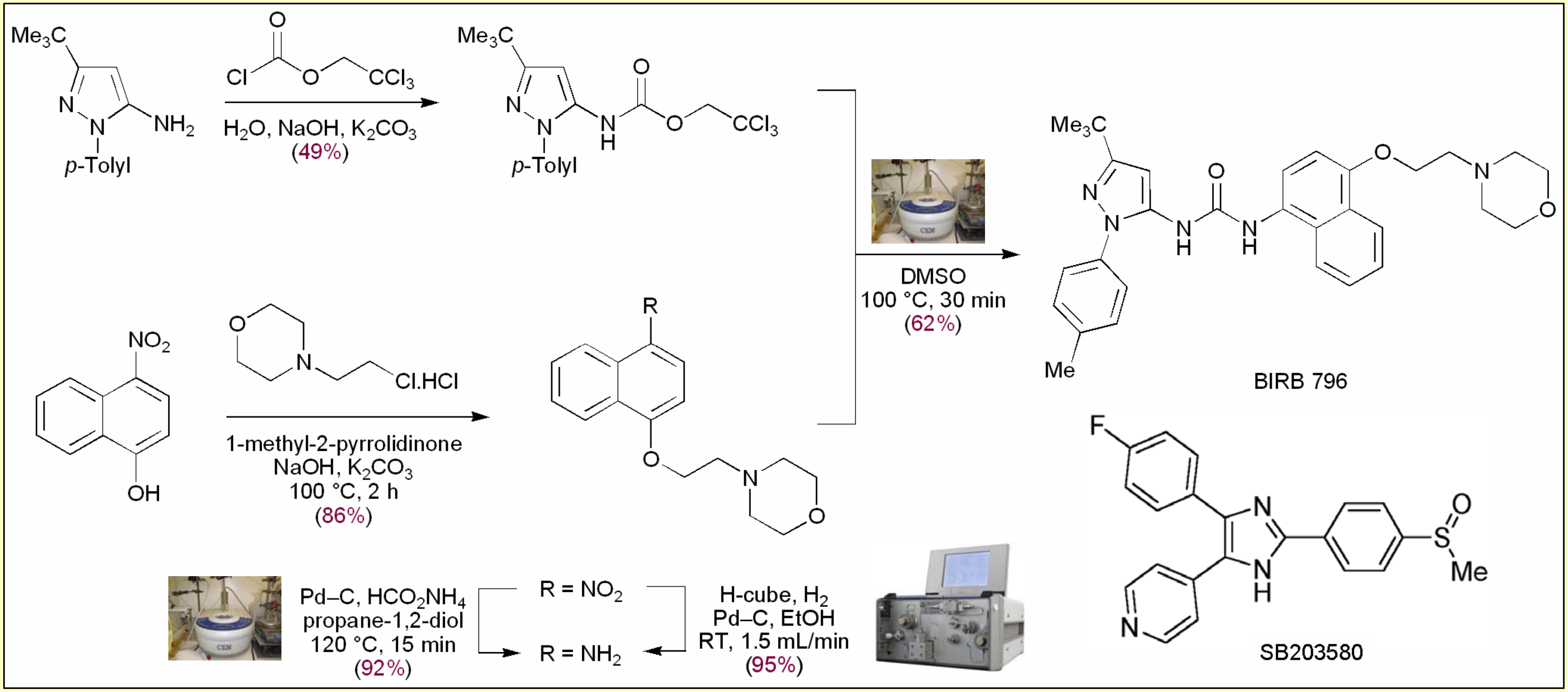
Synthesis of BIRB 796



Bagley, M. C.; Davis, T.; Dix, M. C.;
Widdowson, C. S.; Kipling, D.
Org. Biomol. Chem. **2006**, *4*, 4158.

bbsrc
biotechnology and biological sciences research council

School of Chemistry

Biological Studies: BIRB 796

FINDINGS

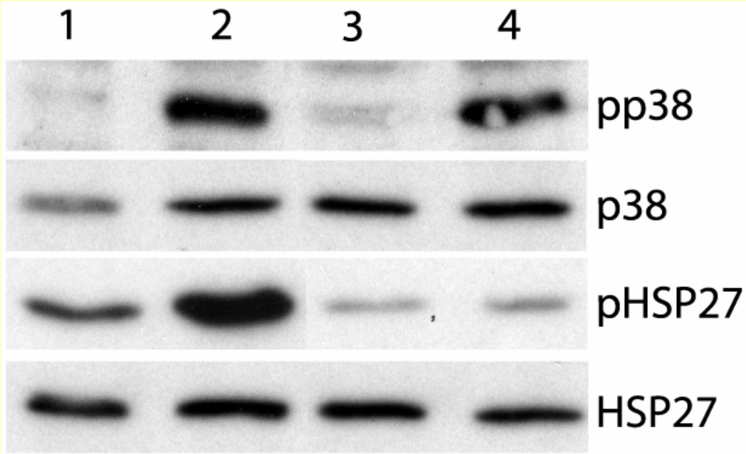
- Immuno-detection of pp38 and pHSP27 demonstrates that both SB203580 and BIRB 796 inhibit signal transduction through p38α in WS cells
- Both inhibitors rescue the growth rate of WS cells on daily treatment, restoring replicative life span

HYPOTHESIS

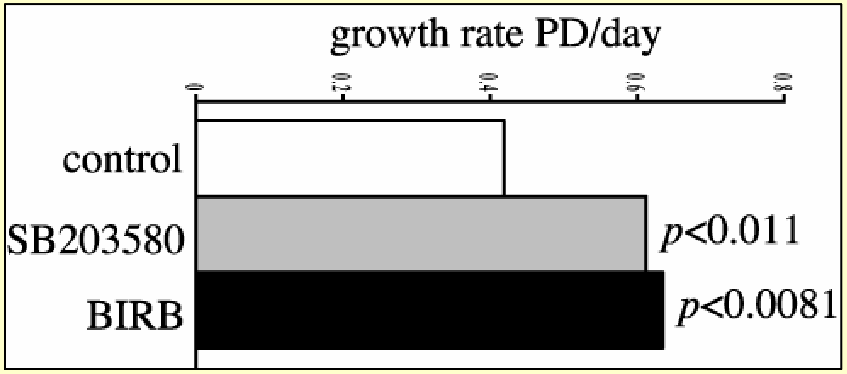
- We propose the mode of action is by inhibition of p38α signal transduction
- **BUT** the inhibition of other kinases may contribute to activity

TEST

Inhibitors with different selectivity profile



Key:
1=WS cells
2=WS cells + Anisomycin (A)
3=WS cells + A + 10µM BIRB 796
4=WS cells + A + 10µM SB203580

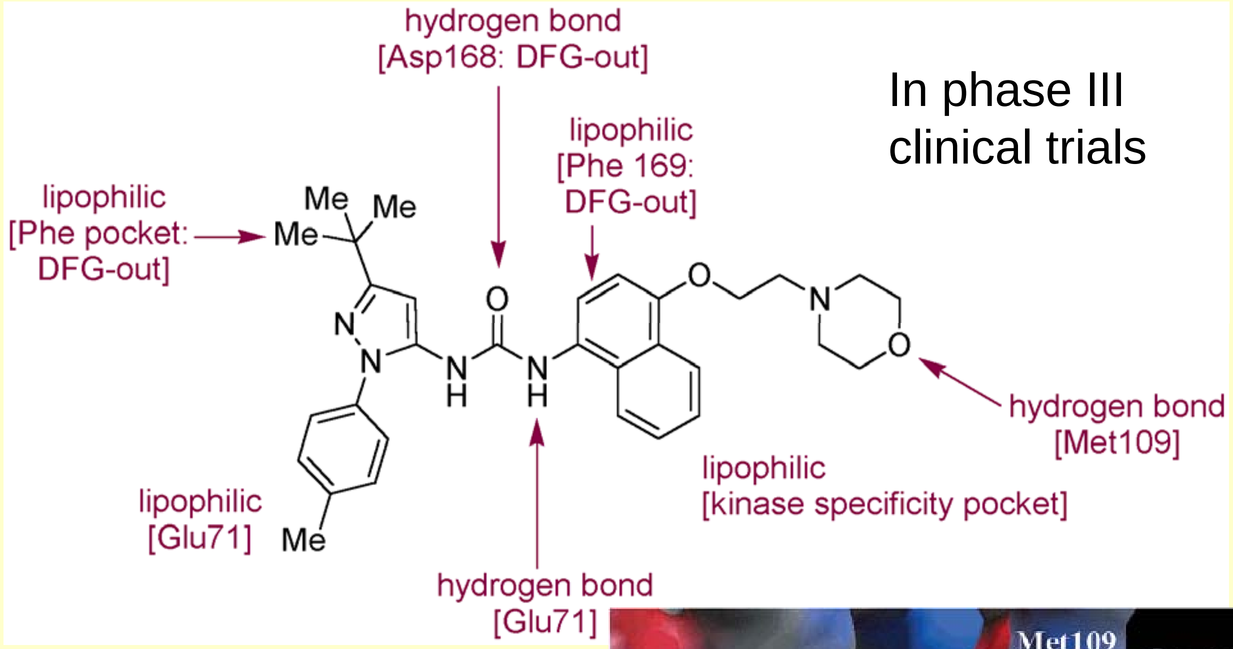


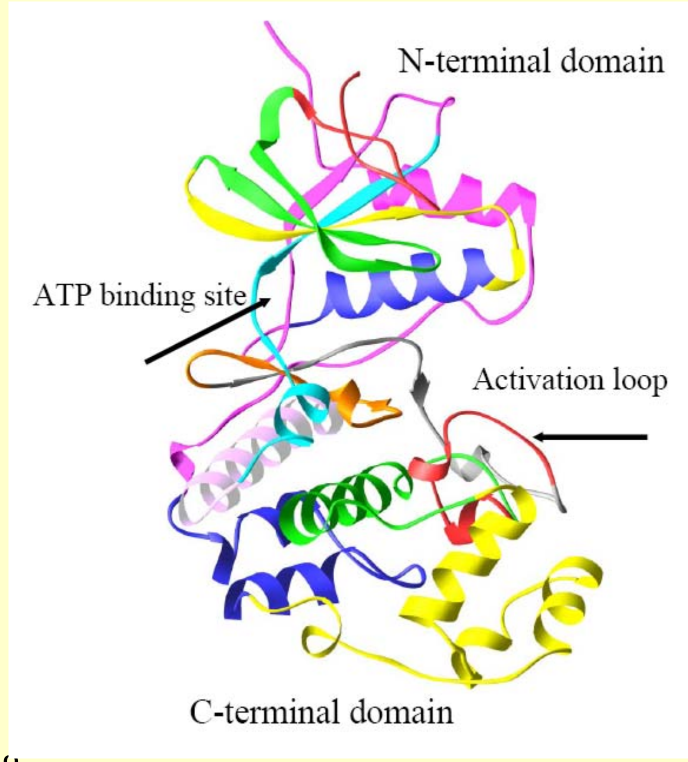
Bagley, M. C.; Davis, T.; Dix, M. C.; Widdowson, C. S.; Kipling, D. *Org. Biomol. Chem.* **2006**, *4*, 4158.

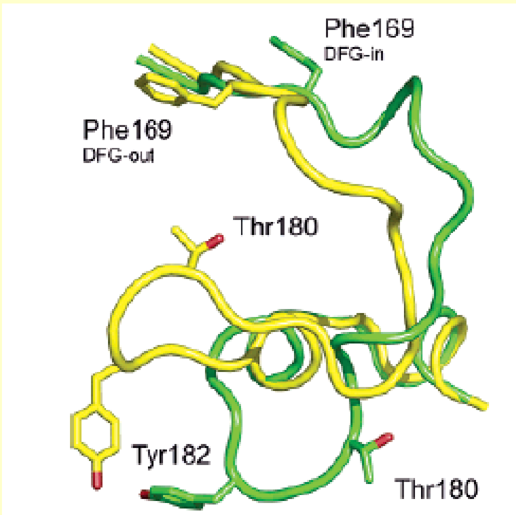
BIRB 796: Key Interactions with P38α

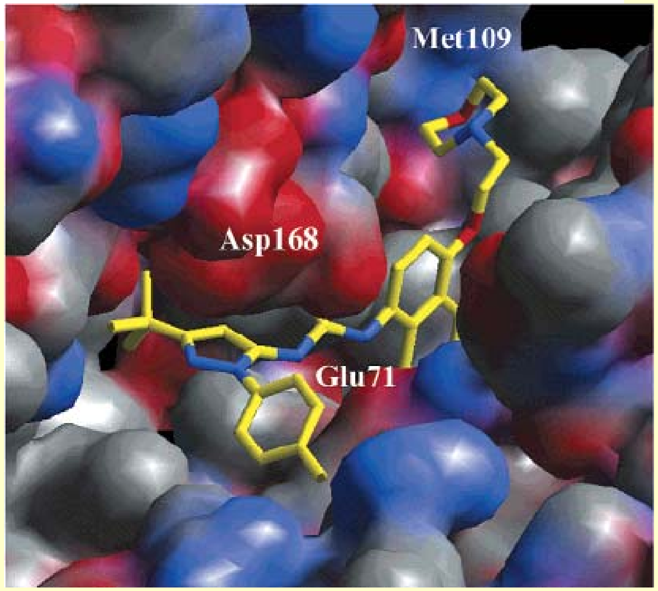
Formation of the allosteric binding site requires conformational change of the activation loop, DFG-out (Asp168-Phe169-Gly170)

In phase III clinical trials

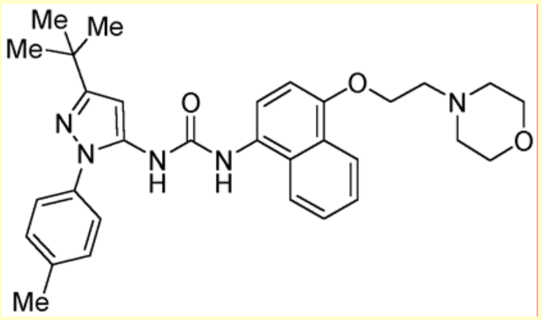






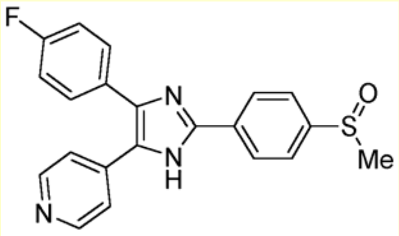


Selectivity of P38α Kinase Inhibitors



DNA replication stress

Stress Load ↑



MKK3/6

BIRB 796
SB203580

MKK4/7

p38α MAPK

MK2/3

p53

JNK

p21[Waf1]

HSP27 → pHSP27

Growth arrest

Growth arrest

F-actin stress

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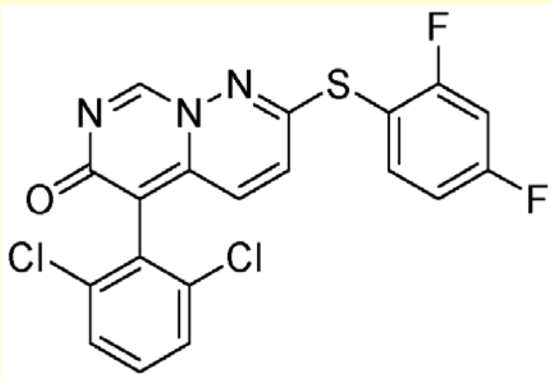
Confirming the Role of P38α Signalling

VX-745: p38α IC_{50} 10 nM



DNA replication stress

Stress Load ↑

MKK3/6

VX-745

MKK4/7

p38α MAPK

MK2/3

p53

JNK

$p21^{Waf1}$

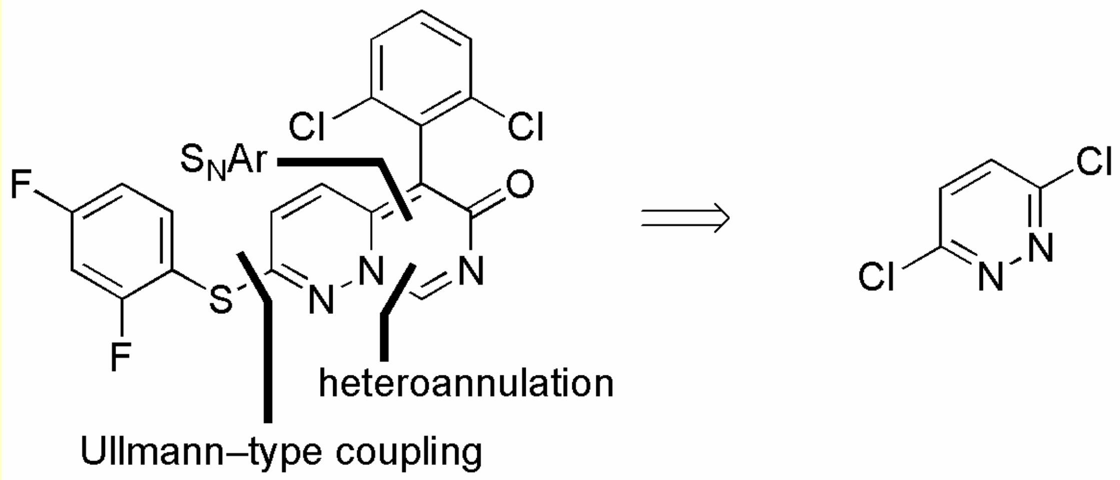
HSP27 → pHSP27

Growth arrest

Growth arrest

F-actin stress

Vertex's P38α Inhibitor VX-745

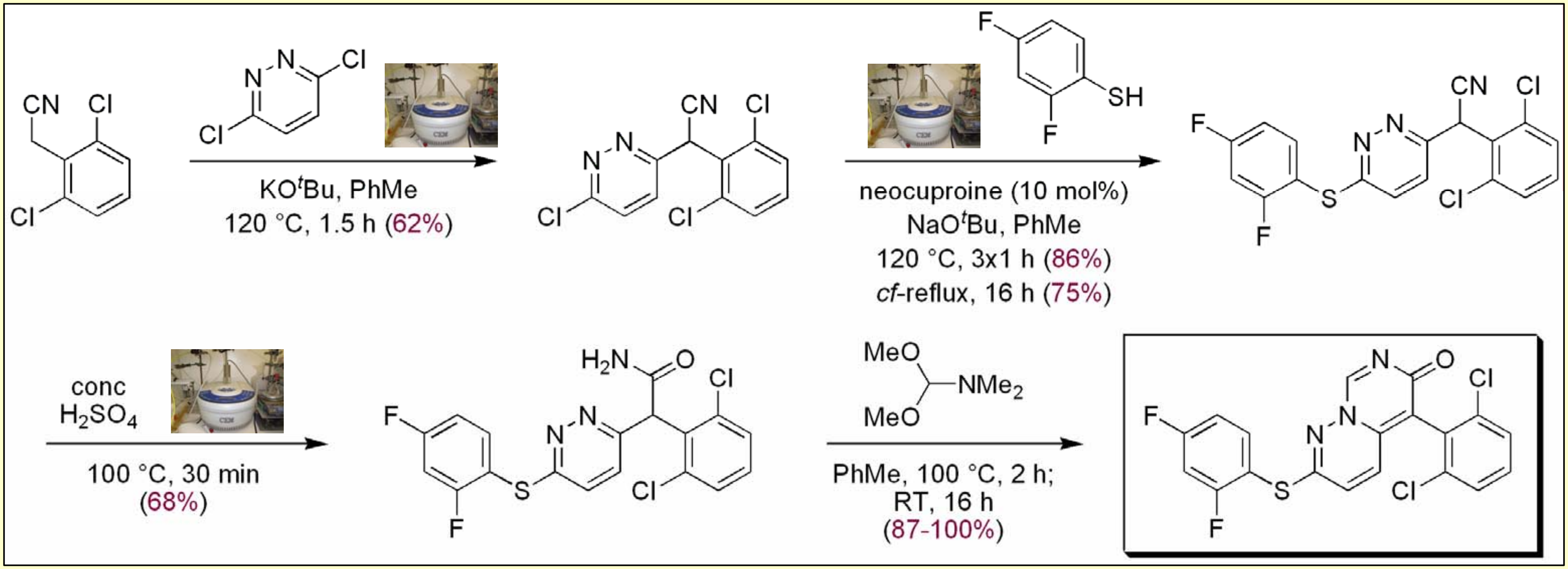


BINDING AND CLINICAL DATA

- 1000-fold selectivity over closely-related kinases including JNK1-3
- Novel binding mode to the ATP site via H-bond to Met 109
- Produced significantly higher ACR20 response rates *vs.* placebo (43% vs. 8%) in 12 week human trial of rheumatoid arthritis patients
- Drug was suspended following adverse neurological effects in dogs

 Bagley, M. C.; Davis, T.; Dix, M. C.; Rokicki, M.; Kipling, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5107.

Synthesis of VX-745



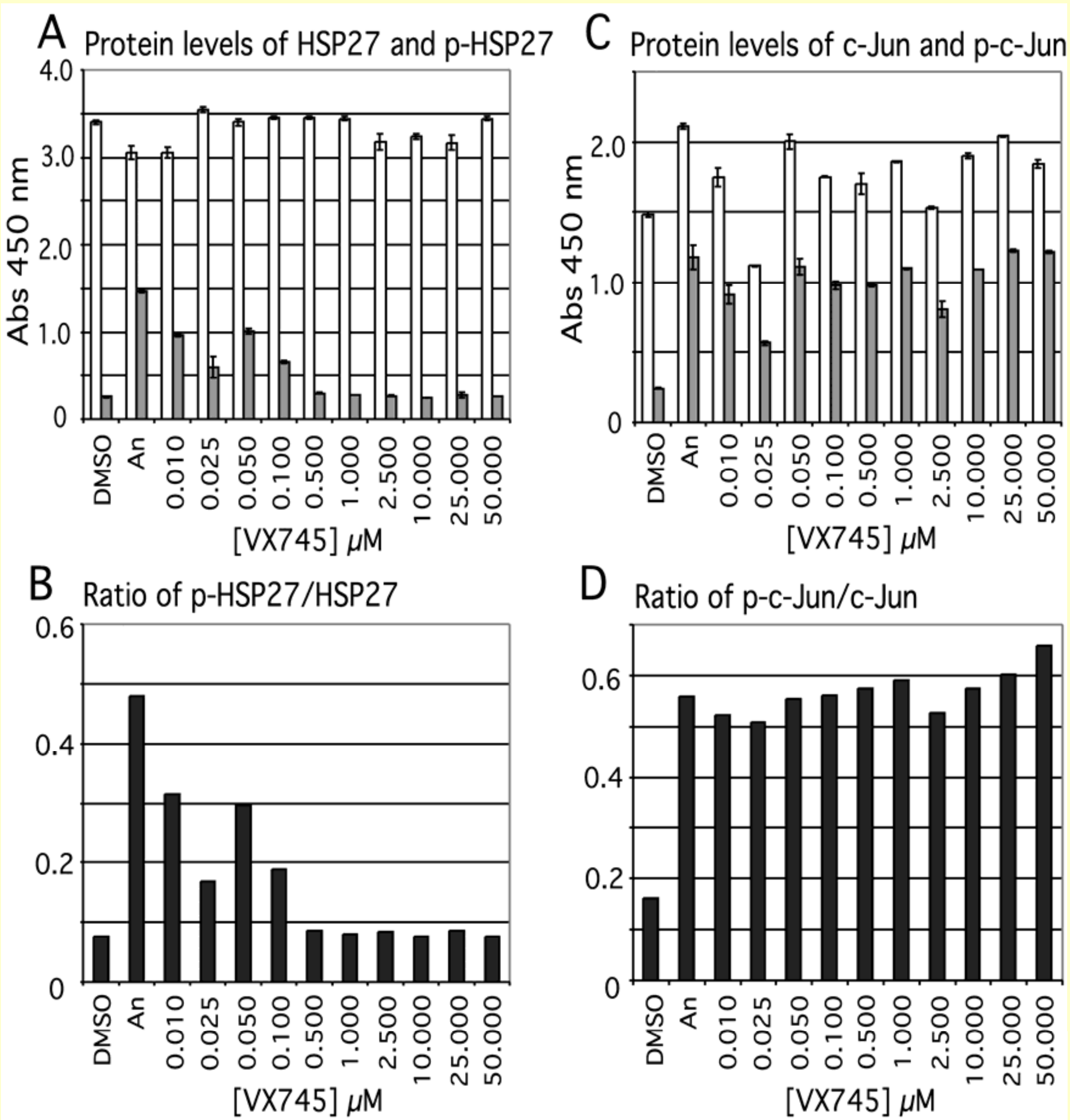
With microwave heating:

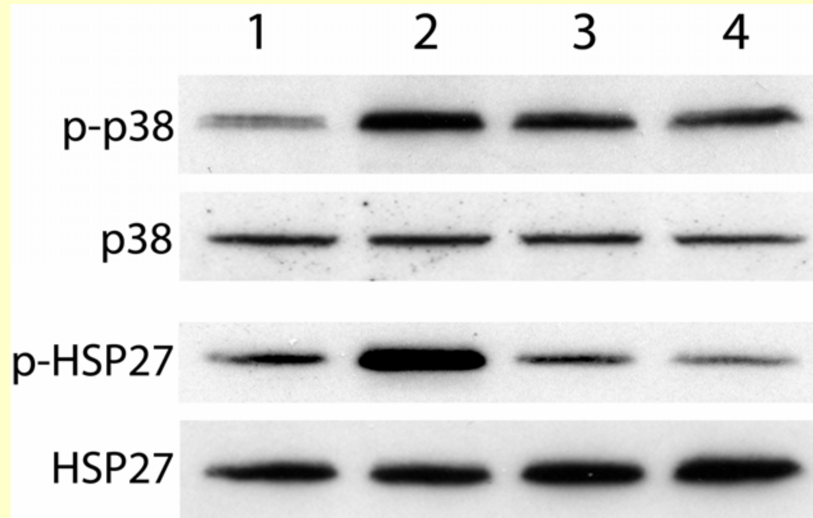
- **Yields similar <u>but</u> reaction times reduced and purification simplified**

Microwave mediated C-S bond formation: Wu, Y.-J.; He, H. *Synlett* **2003**, 1789**.**
Reviews: <u>Cu catalyzed C-S bond formation</u>: Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.
<u>Pd catalyzed C-S bond formation</u>: Prim, D. *et al. Tetrahedron* **2002**, *58*, 2041.

 Bagley, M. C.; Davis, T.; Dix, M. C.; Rokicki, M.; Kipling, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5107.

Evaluating VX-745 in WS cells





KEY

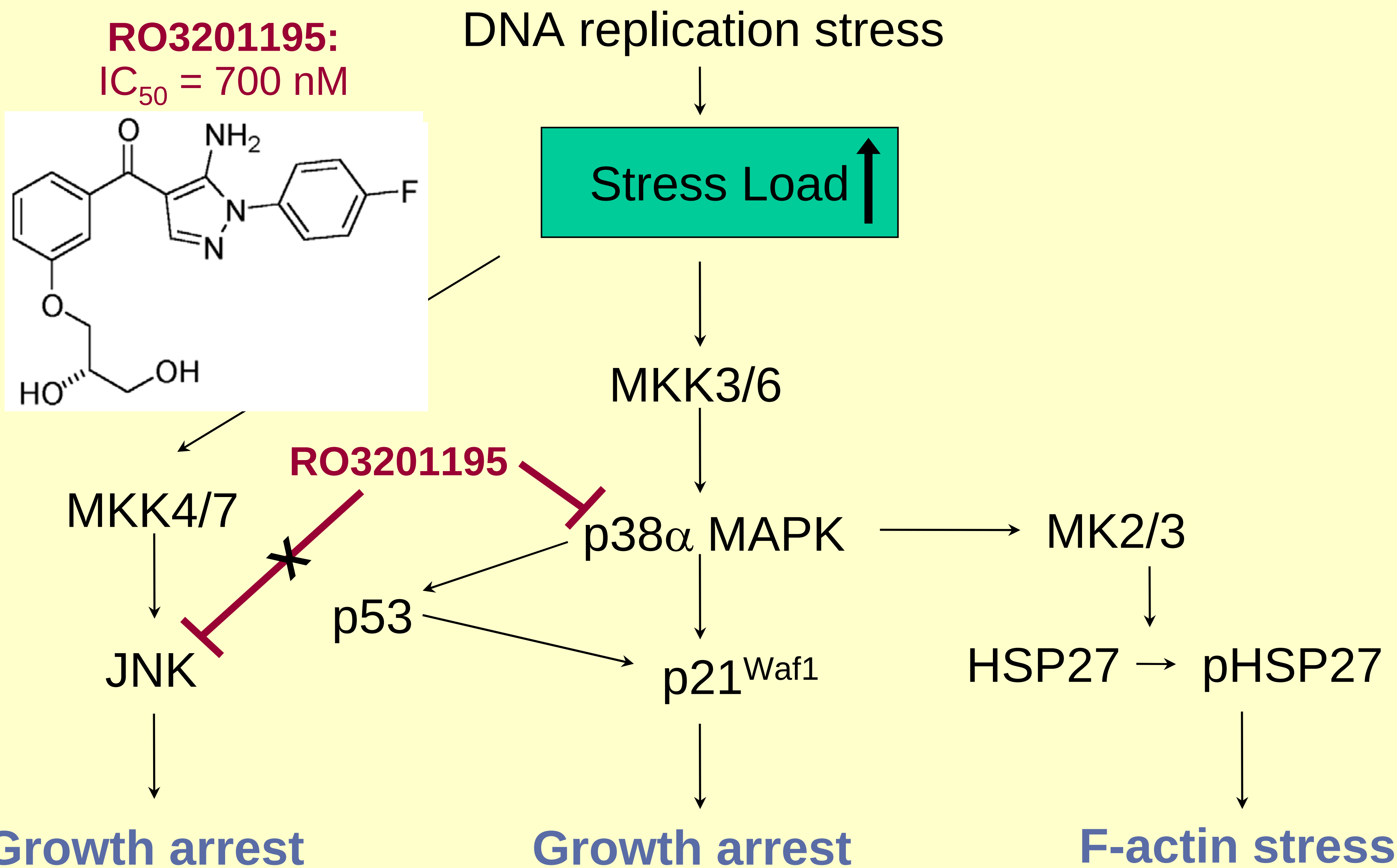
Lane 1: WS cells

Lane 2: WS cells + anisomycin

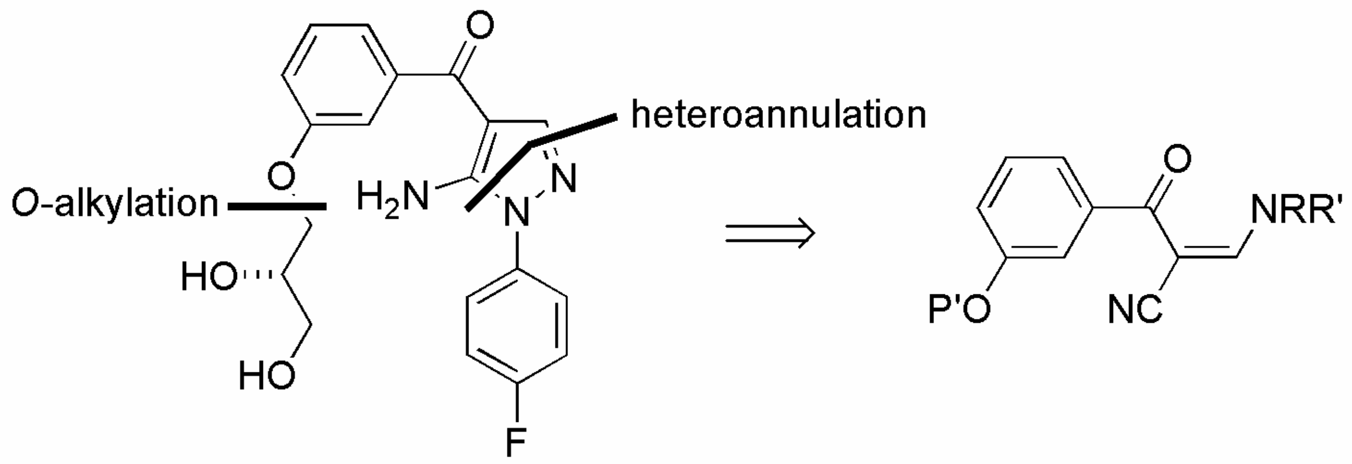
Lane 3: WS cells + anisomycin + 1.0 μM VX-745

Lane 4: WS cells + anisomycin + 2.5 μM SB203580

Confirming the Role of P38α Signalling



Roche's P38α Inhibitor RO3201195



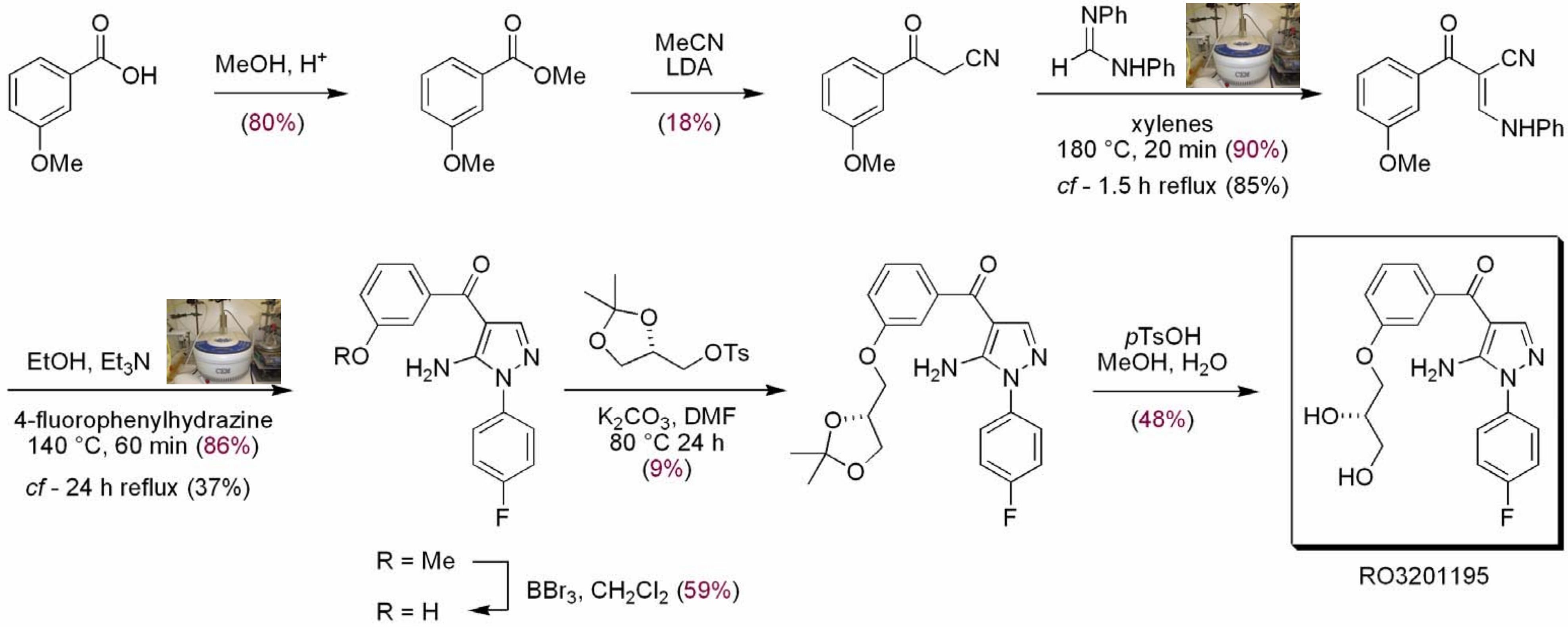
BINDING AND CLINICAL DATA

- High selectivity in 105 kinase panel showing (only PDGFRβ and GAK).
- Binds in ATP pocket (to both p38 and pp38) with unique H-bond to Thr 106
- Significantly inhibited IL-1β production in 28 day placebo controlled human trial

Goldstein, D. M.; Alfredson, T.; Bertrand, J.; Browner, M. F.; Clifford, K.; Dalrymple, S. A.; Dunn, J.; Freire–Moar, J.; Harris, S.; Labadie, S. S.; La Fargue, J.; Lapierre, J. M.; Larrabee, S.; Li, F.; Papp, E.; McWeeney, D.; Ramesha, C.; Roberts, R.; Rotstein, D.; San Pablo, B.; Sjogren, E. B.; So, O.–Y.; Talamas, F. X.; Tao, W.; Trejo, A.; Villasenor, A.; Welch, M.; Welch, T.; Weller, P.; Whiteley, P. E.; Young, K.; Zipfel, S. *J. Med. Chem.* **2006**, *49*, 1562.

Synthesis of RO3201195

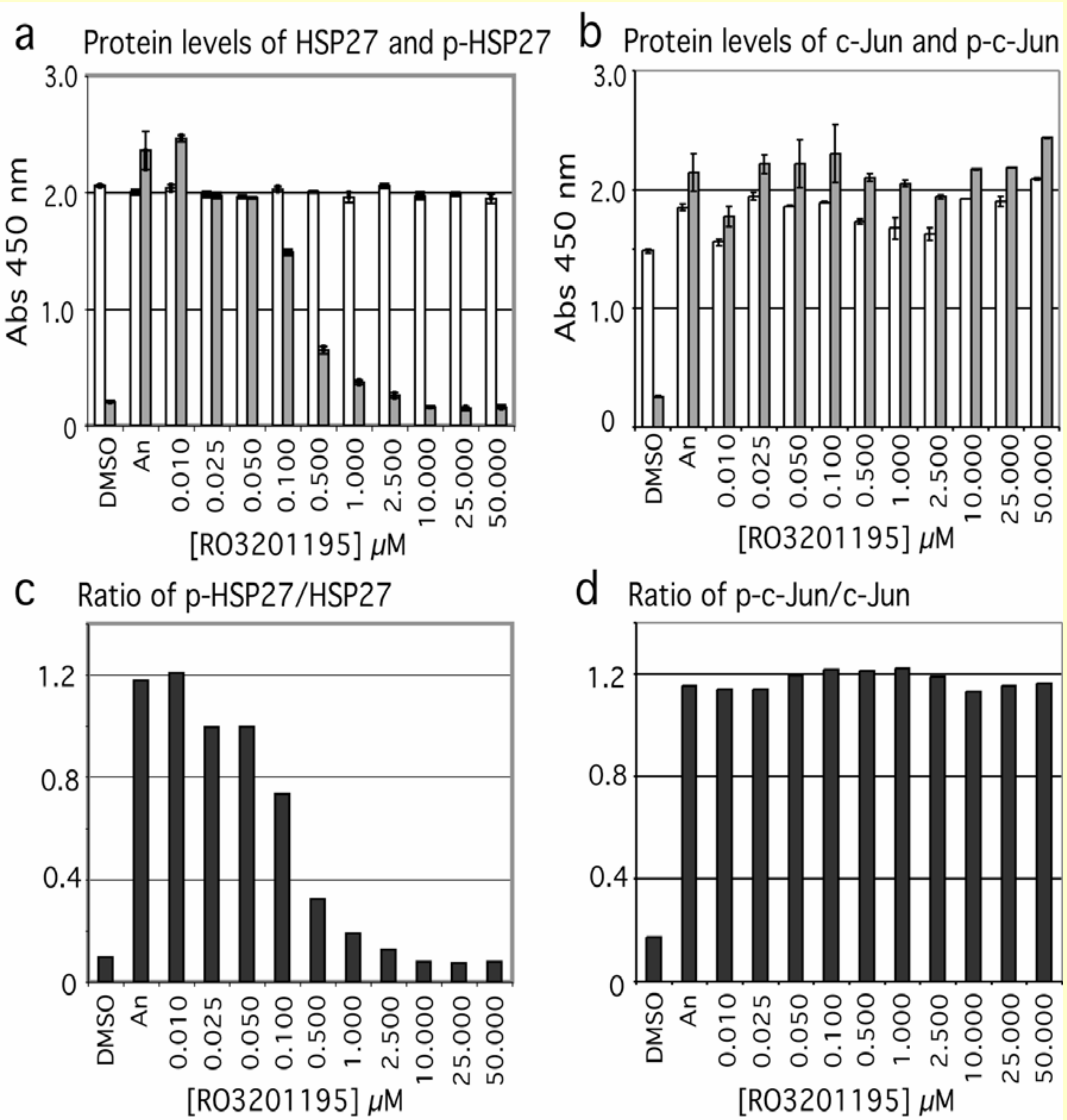
Microwave heating results in:
- Reaction times significantly reduced for 2 key steps
- Yield of pyrazolyl ketone formation improved dramatically

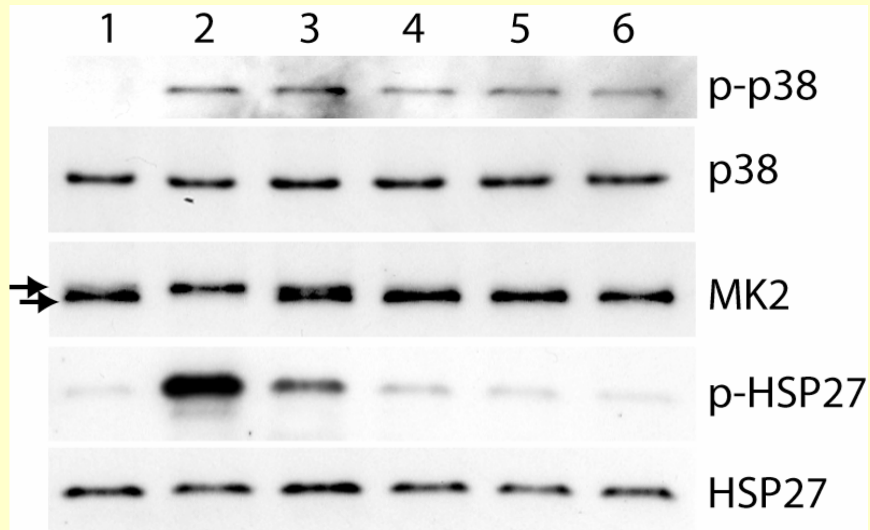


Bagley, M. C.; Davis, T.; Dix, M. C.; Murziani, P. G. S.; Rokicki, M.; Kipling, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3745.

School of Chemistry

Evaluation of RO321195 in WS cells





KEY

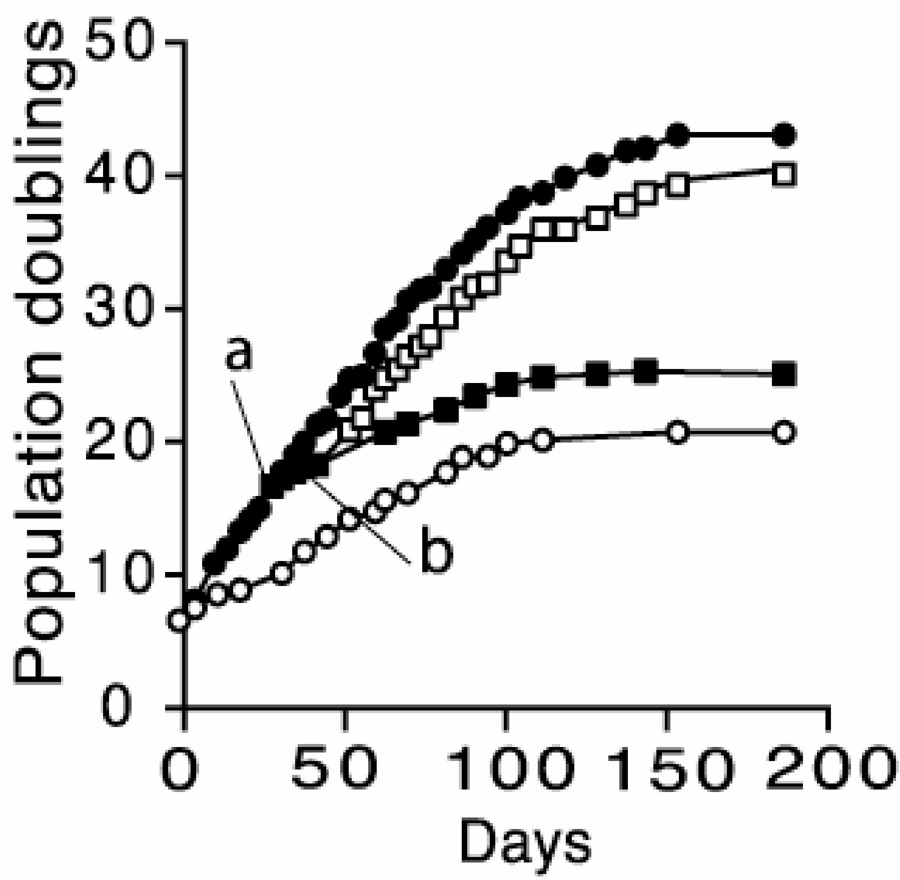
Lane 1: hTERT-imm. WS cells

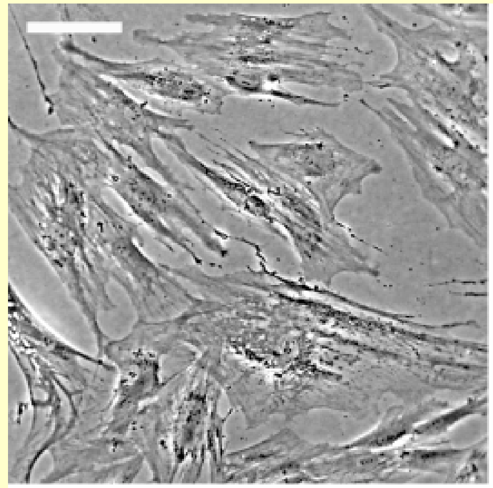
Lane 2: WS + anisomycin (A)

Lanes 3-5: WS + A + 2.5 (3), 10 (4) or 25 (5) μM RO3201195

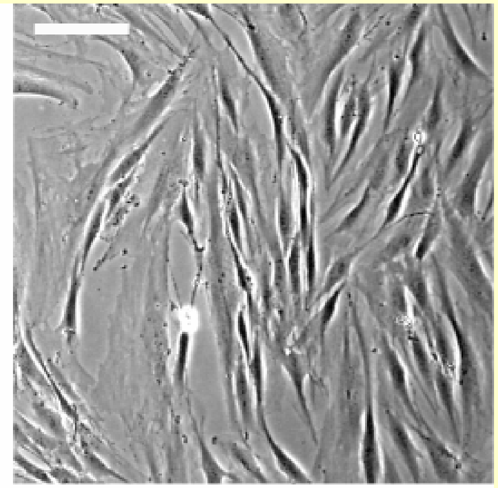
Lane 6: WS + anisomycin + 2.5 μM SB203580

Blocking the p38α Stress Response

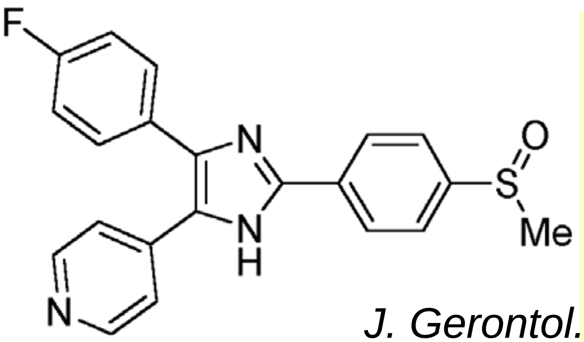




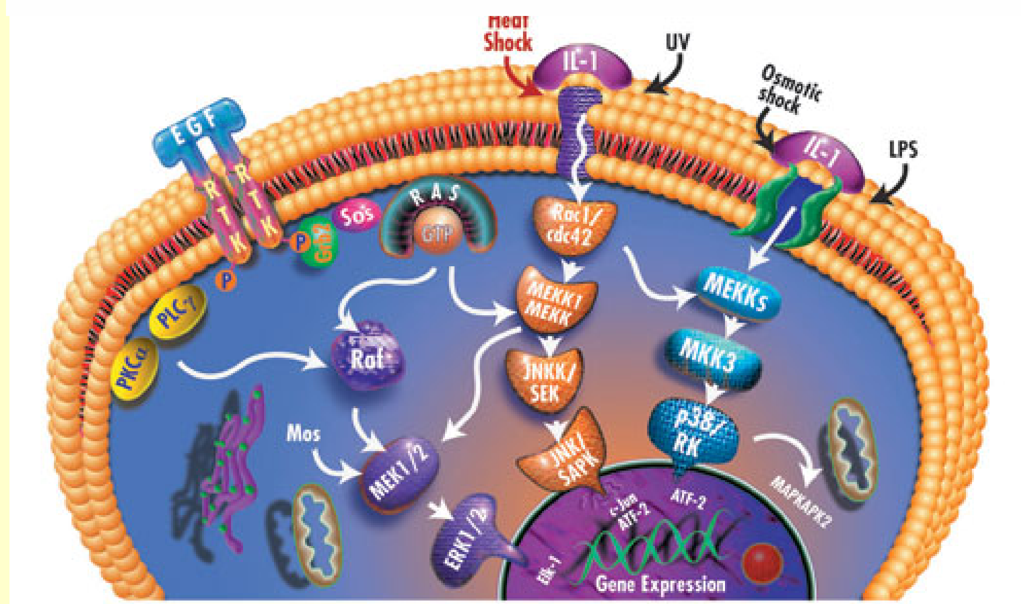
young control
AG05229 cells



young SB203580 treated
AG05229 cells



SB203580



J. Gerontol. **2005**, *60A*, 1386.

Treating age-related diseases: can we manipulate the main risk factor?

CARDIFF UNIVERSITY

<u>Relevance to normal ageing</u>

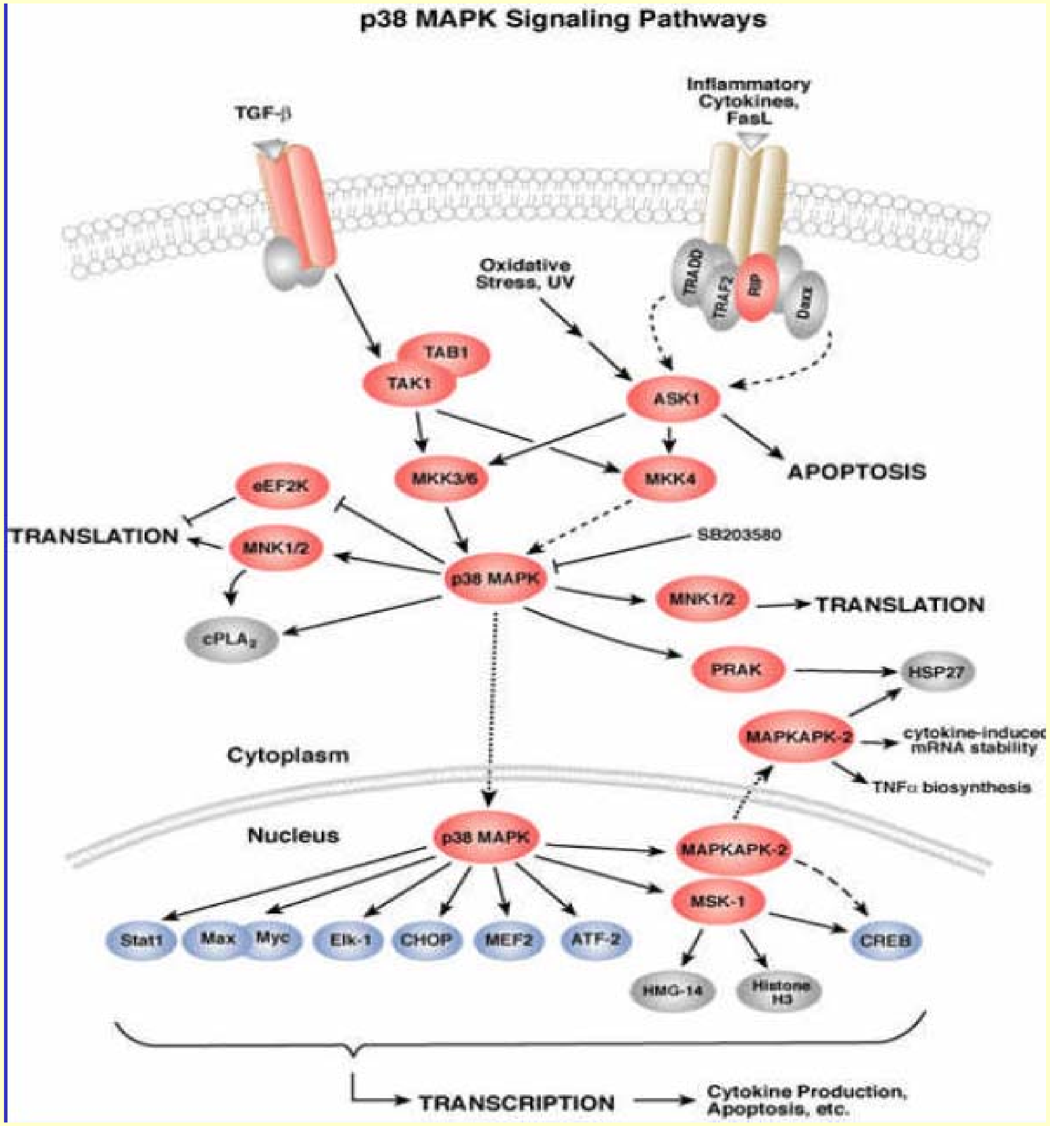
There are environmental and clinical factors (such as cancer, infection, periodontal disease, stress) that can activate p38 in normal individuals.

This could link extrinsic lifecourse factors with a fundamental mechanism of ageing

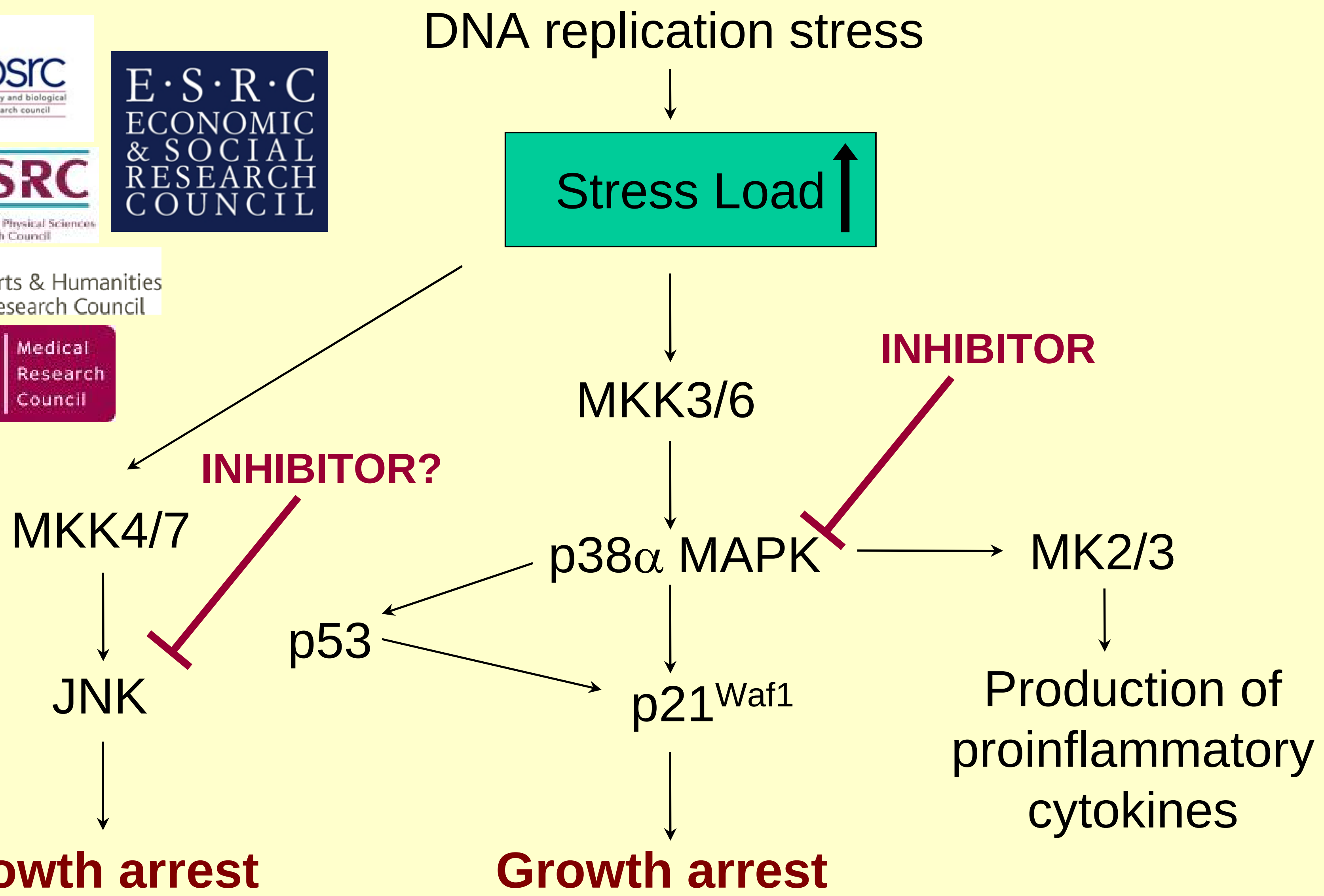
<u>Problems with using p38 inhibitors</u>

P38 is a major cellular signalling 'hub' and regulates a very large number of downstream pathways.

Its nodal role perhaps explains toxicity/side effect issues



Treating age-related disease: can we manipulate the main risk factor?



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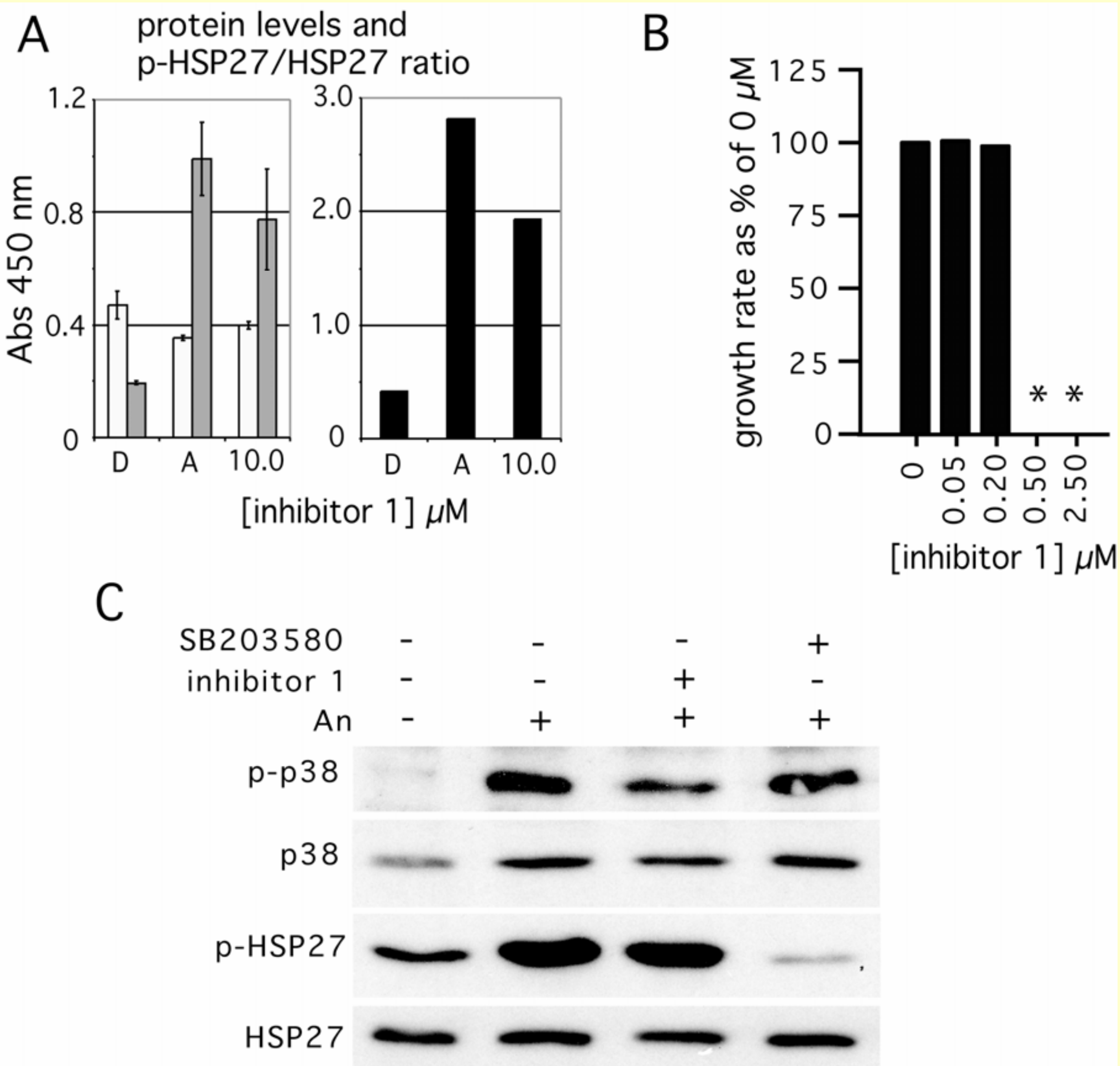
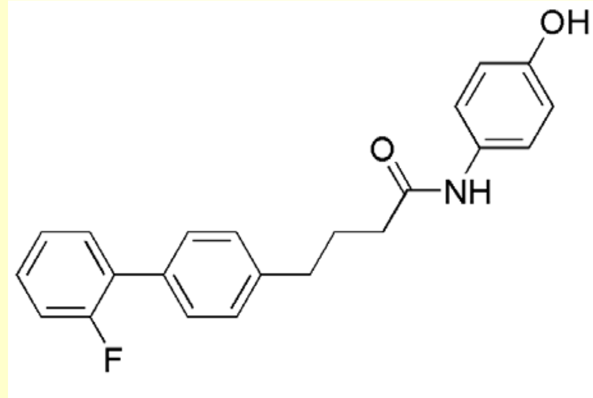
MK2 INHIBITORS IN WS CELLS





CMPD 1

>200 nM, cell growth stops

At 10 μM, minimal effect on p-HSP27/HSP27 (see **A**) as compared to SB203580 (see **C**)

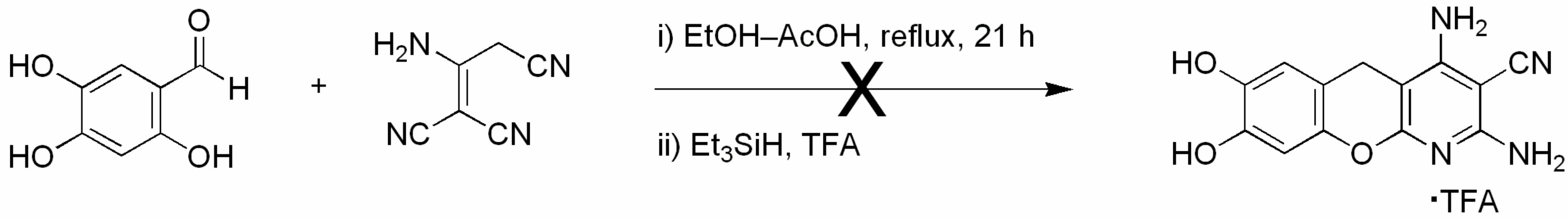
>25 μM, cell death occurs

FAILED IN CELL STUDIES

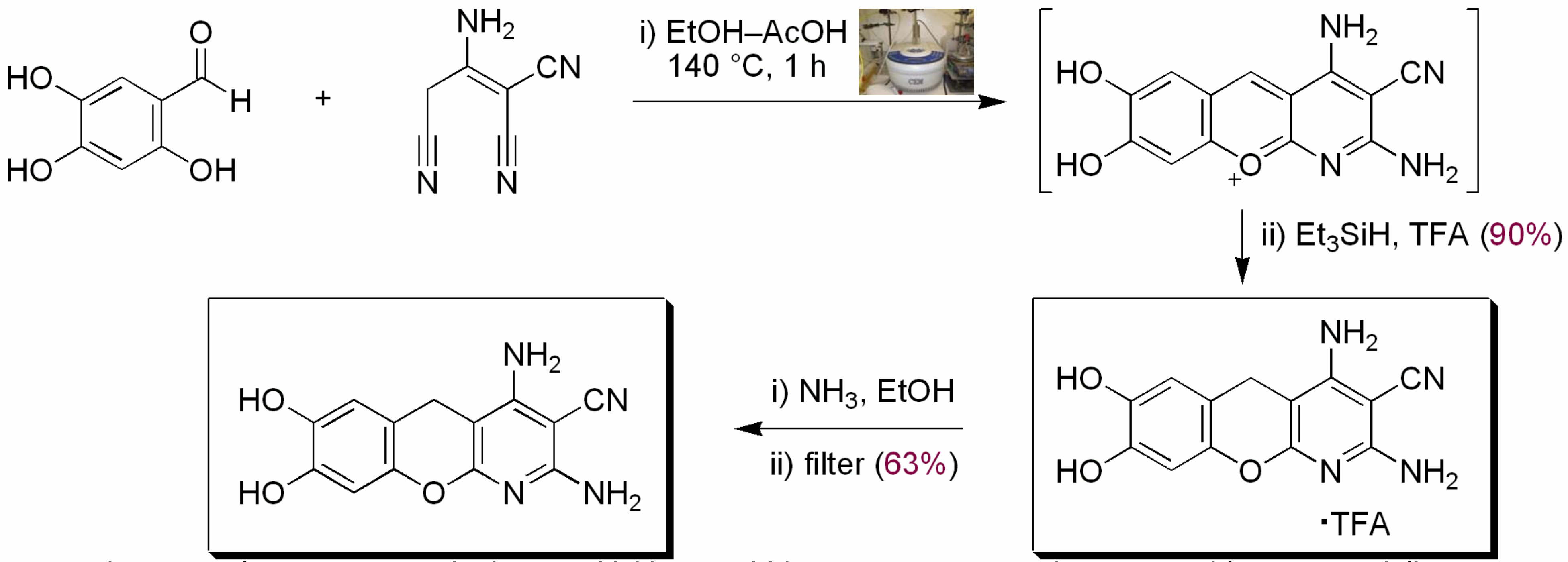
Davis, T.; Bagley, M. C.; Murziani, P.; Rokicki, M.; Widdowson, C. S.; Zayed, J. M.; Bachler, M. A.; Kipling, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6832–6835.

Synthesis of Alternative 'MK2 Inhibitors'

Conductive Heating:

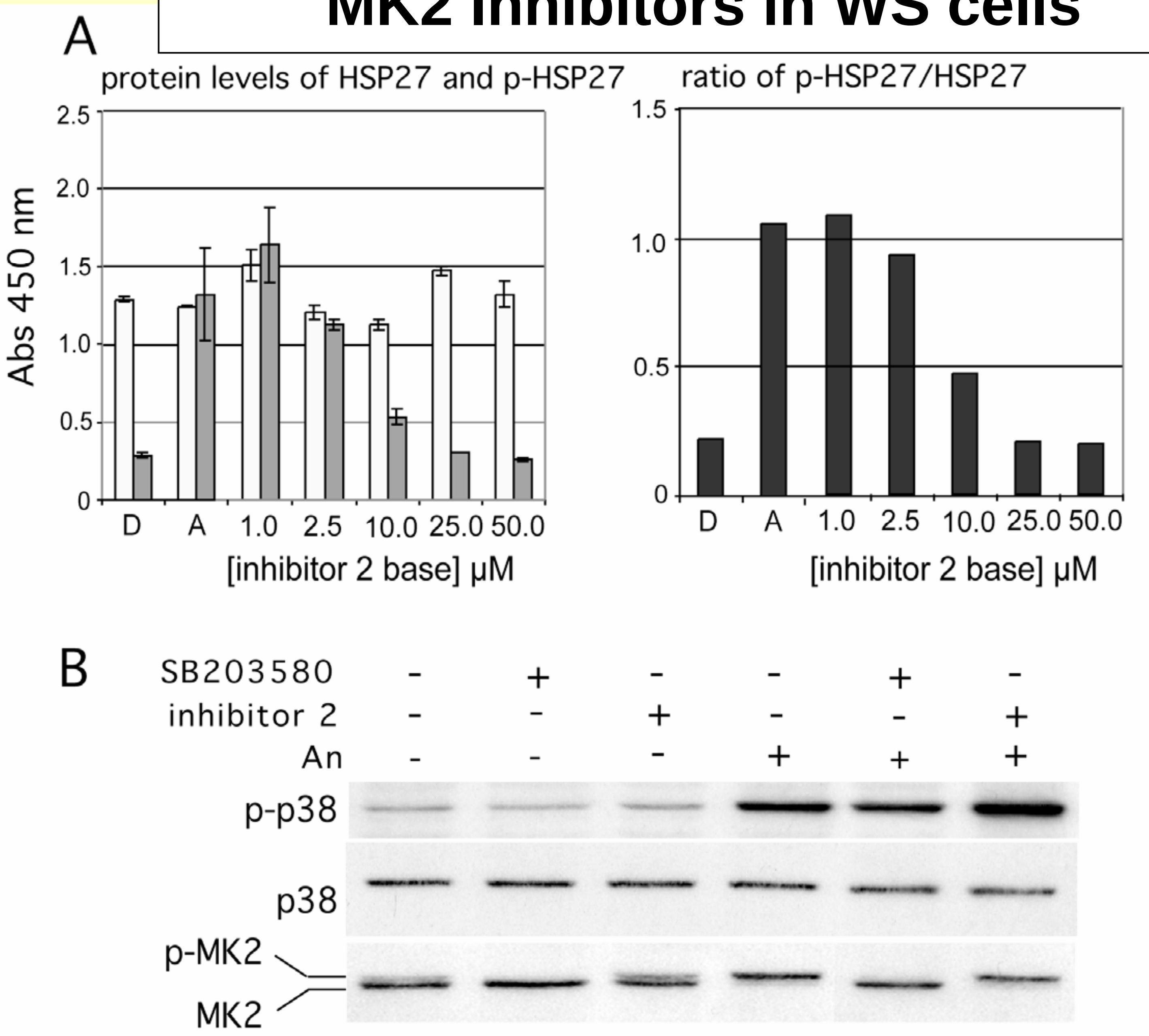


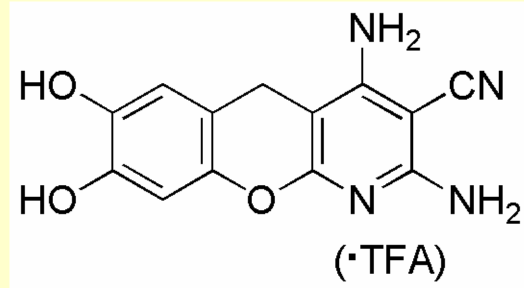
Microwave Heating:



Davis, T.; Bagley, M. C.; Murziani, P.; Rokicki, M.; Widdowson, C. S.; Zayed, J. M.; Bachler, M. A.; Kipling, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6832–6835.

MK2 Inhibitors in WS cells

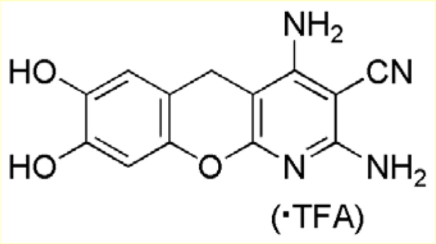




- Inhibits at >2.5 μM
- Maximal inhibition at >25 μM
- IC_{50} between 2.5 and 10 μM
- Doesn't inhibit the phosphorylation of MK2, *cf* SB203580

MK2 INHIBITION CONFIRMED

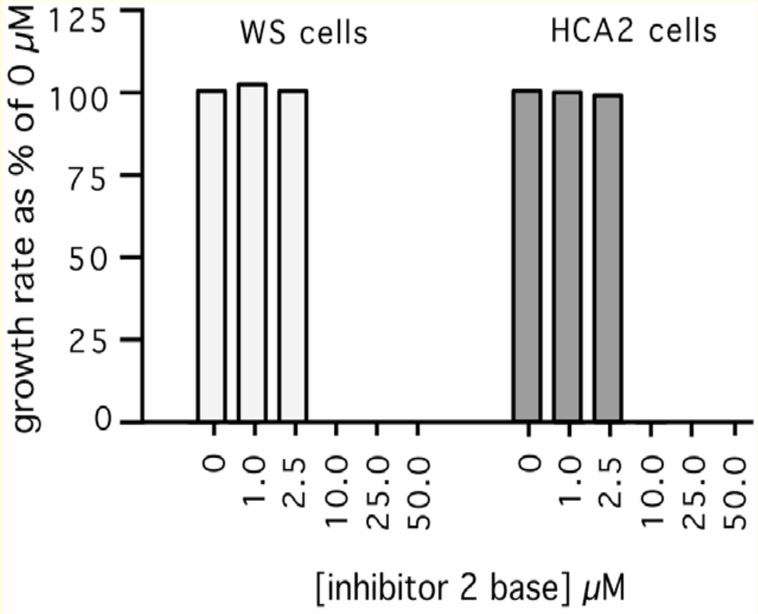
Treating age-related disease: can we manipulate the main risk factor?



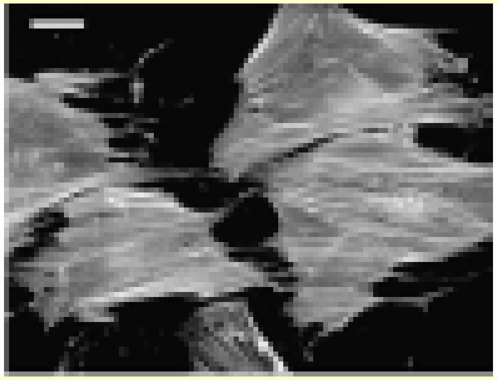
Little effect on growth rate at <2.5 μM

Cells senesce at >2.5 μM which is <[IC50]

cells undergo a dramatic morphological change at 10 μM



WS control cells



WS cells treated with 25 μM inhibitor

Davis, T.; Bagley, M. C.; Murziani, P.; Rokicki, M.; Widdowson, C. S.; Zayed, J. M.; Bachler, M. A.; Kipling, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6832–6835.

Summary of the story so far

Can we intervene in accelerated ageing in WS?

Yes!

Will this lead to a clinical treatment?

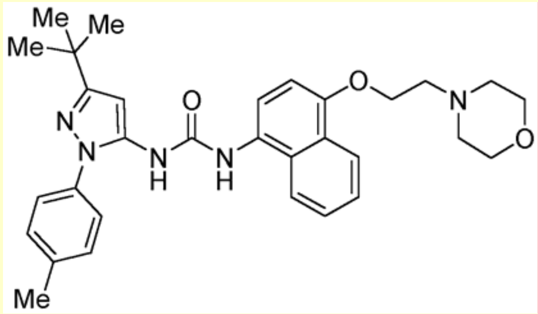
Maybe…..

Can we intervene in the other clinical symptoms of this syndrome?

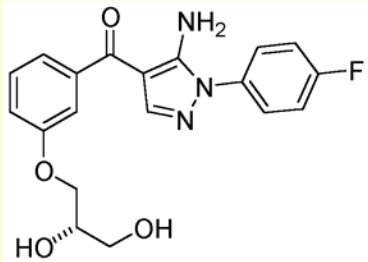
Maybe…..

Can we intervene in ageing in you and I?

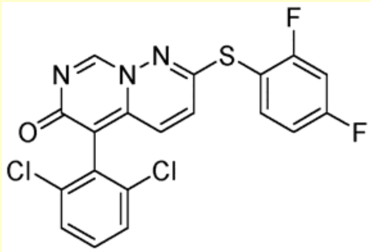
No not yet, but we are gathering evidence that the senescence of somatic cells may be a causal agent of normal ageing



BIRB 796

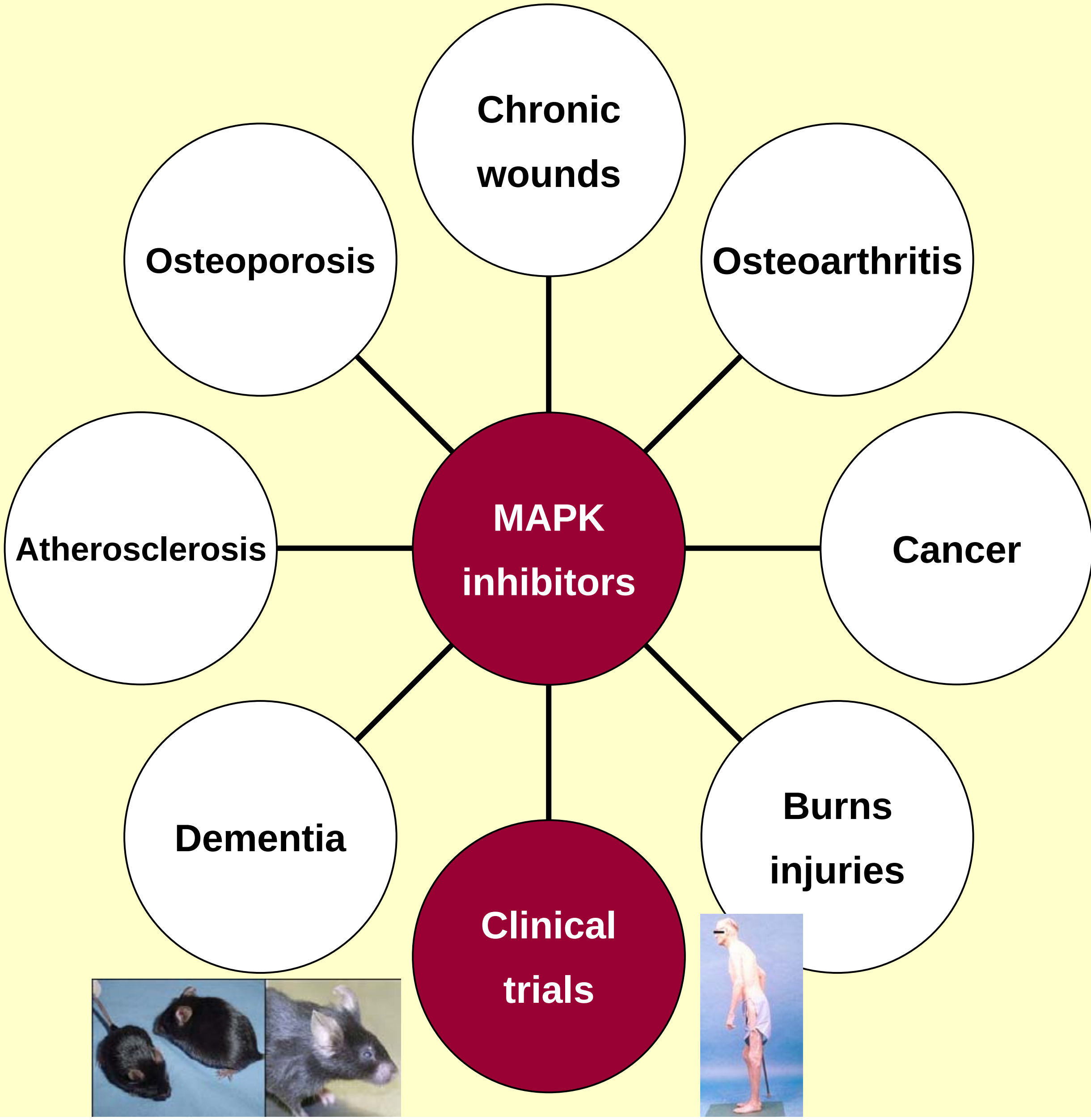


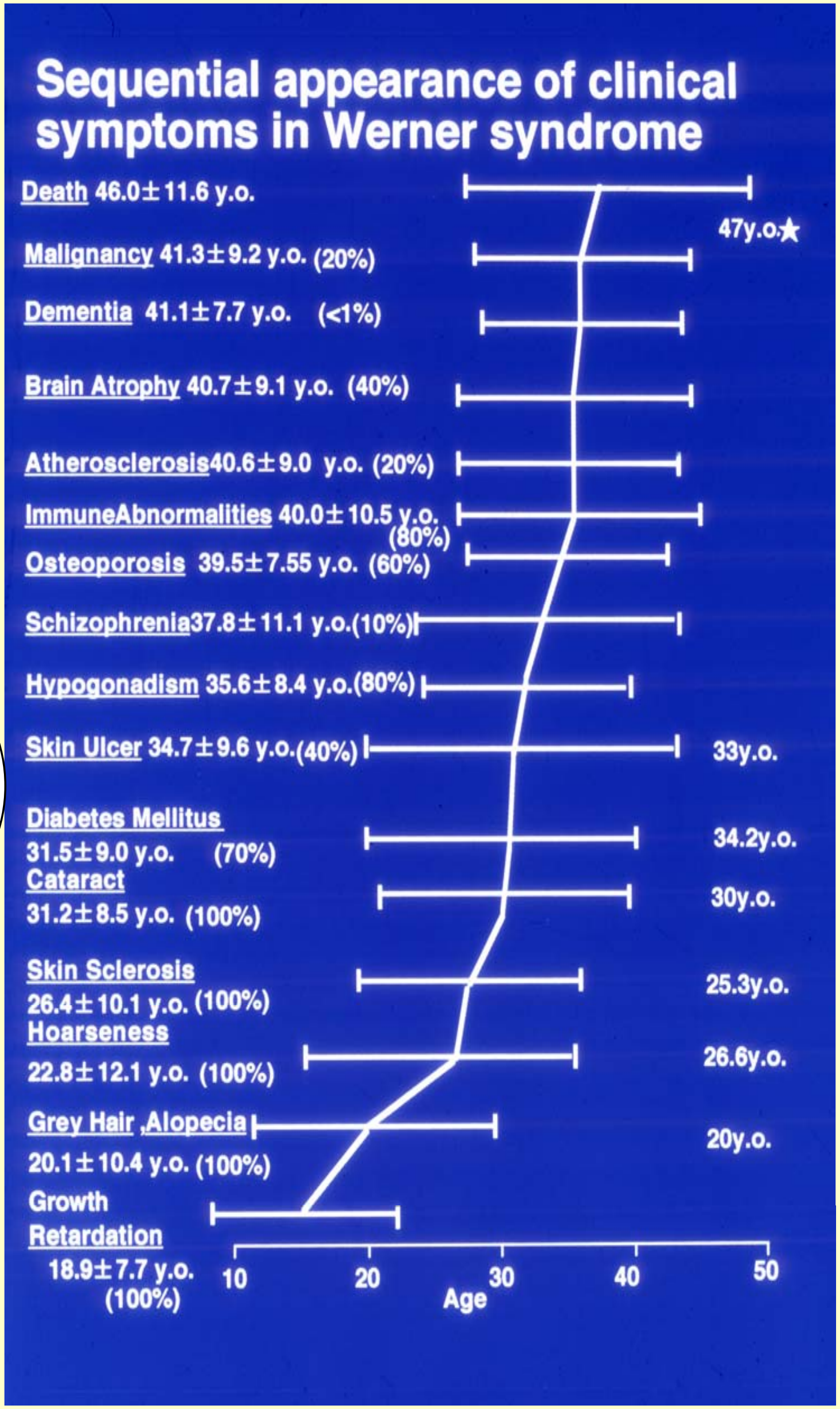
RO3201195



VX-745

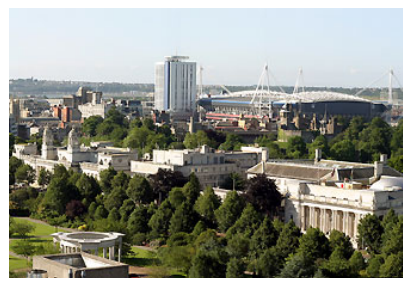
Long term opportunities





Acknowledgements

Co-workers	*Funding*
M. Caterina Lubinu	**BBSRC**
Zhifan Lin	EPSRC
Dr. Matt Dix	SPARC
Eleanor Merritt	Pfizer Ltd.
Vincenzo Fusillo	The Nuffield Foundation
Caz Widdowson	GB-China Educational Trust
Paola Murziani	RiboTargets Ltd. (Vernalis)
Dr Chris Mason	Henry-Lester Trust
Dr Robin Wood	Wellcome Trust
Dr Michal Rokicki	AstraZeneca
Prof David Kipling	The Royal Society
Dr Terry Davis	CEM UK Ltd
Prof Makoto Goto	**Anglo-Japanese Partnering Award**



Biotage

coleg meddygaeth cymru wales college of medicine