

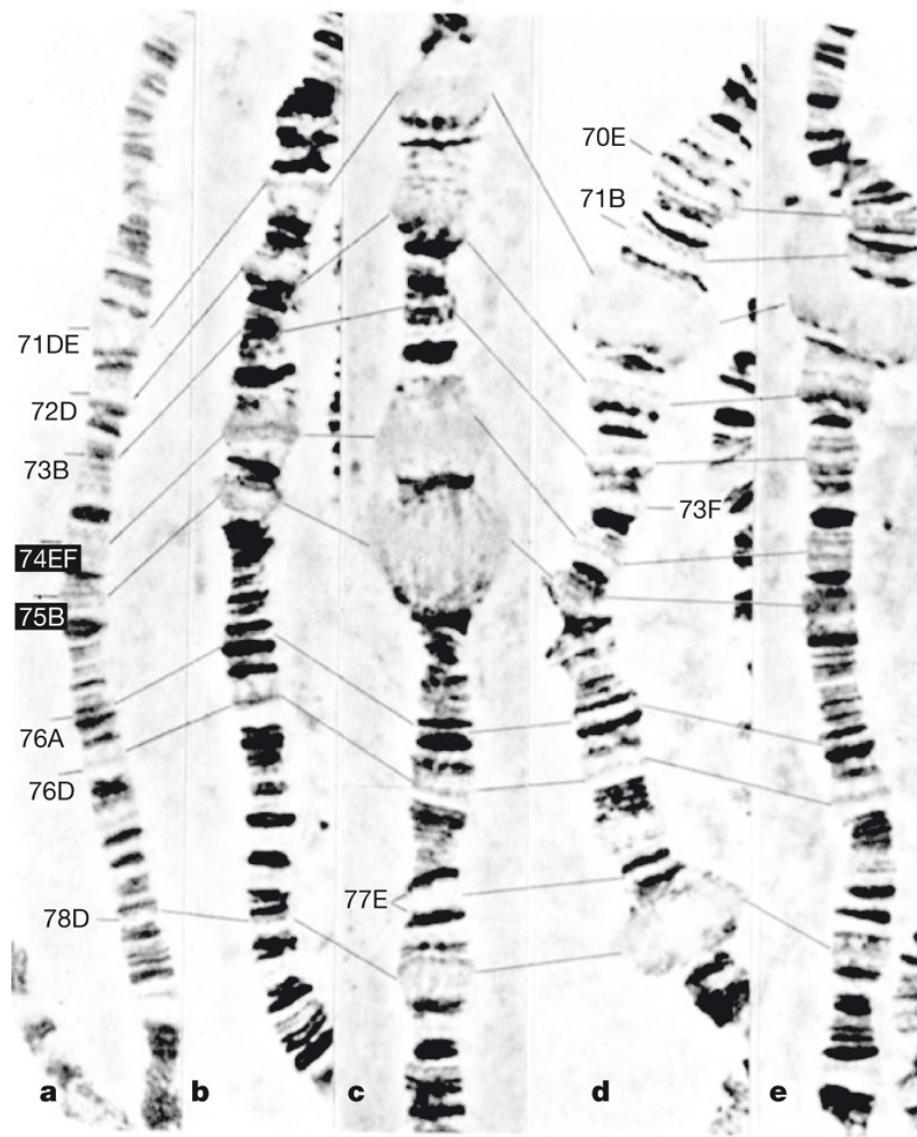
1. Znaczenie i miejsce badań stresu komórkowego w nowoczesnej biologii

- 2. Różne czynniki stresogenne prowadzą do podobnej odpowiedzi komórki**
- 3. Rodziny oraz przedstawiciele genów i białek stresowych**
- 4. Reakcja stresu komórkowego rozpoczyna się na poziomie transkrypcji**
- 5. HSFs (*heat shock factors*) i poszukiwania molekularnego termometru**
- 6. Struktura i funkcja klasycznych białek stresowych (HSPs) - I**
- 7. Struktura i funkcja klasycznych białek stresowych (HSPs) - II**
- 8. Współczesne poglądy na molekularny mechanizm apoptozy**
- 9. Inne drogi zaprogramowanej śmierci komórki**
- 10. Rozpoznanie i fagocytoza komórki apoptotycznej**
- 11. Białka stresowe w komórkach nowotworowych – ciemna strona cytoprotekcji**
- 12. Pozakomórkowe funkcje HSPs - I**
- 13. Pozakomórkowe funkcje HSPs - II**
- 14. Białka stresowe w układzie odpornościowym**

Drosophila melanogaster



Puffing patterns on giant chromosomes



Ritossa F.M.

'A new puffing pattern induced by a
temperature shock and DNP
in *Drosophila*'

Experientia 18: 571-573 (1962)

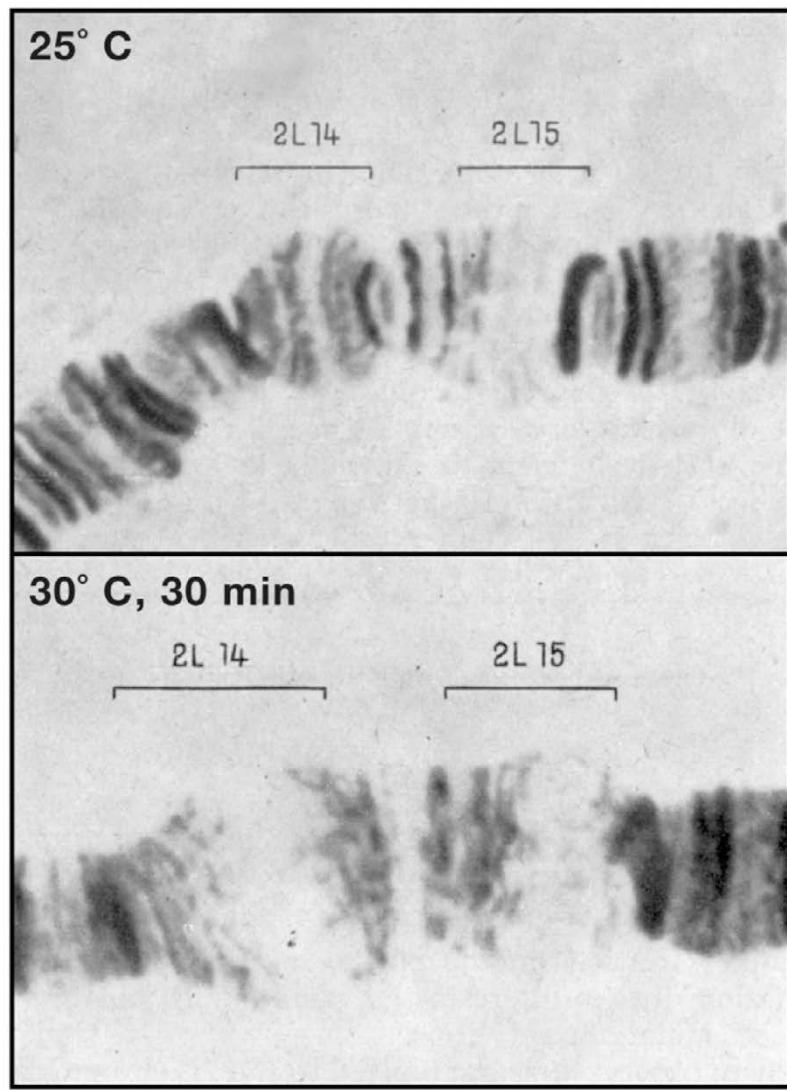


Figure 2. A Transcriptional Response to Heat Stress

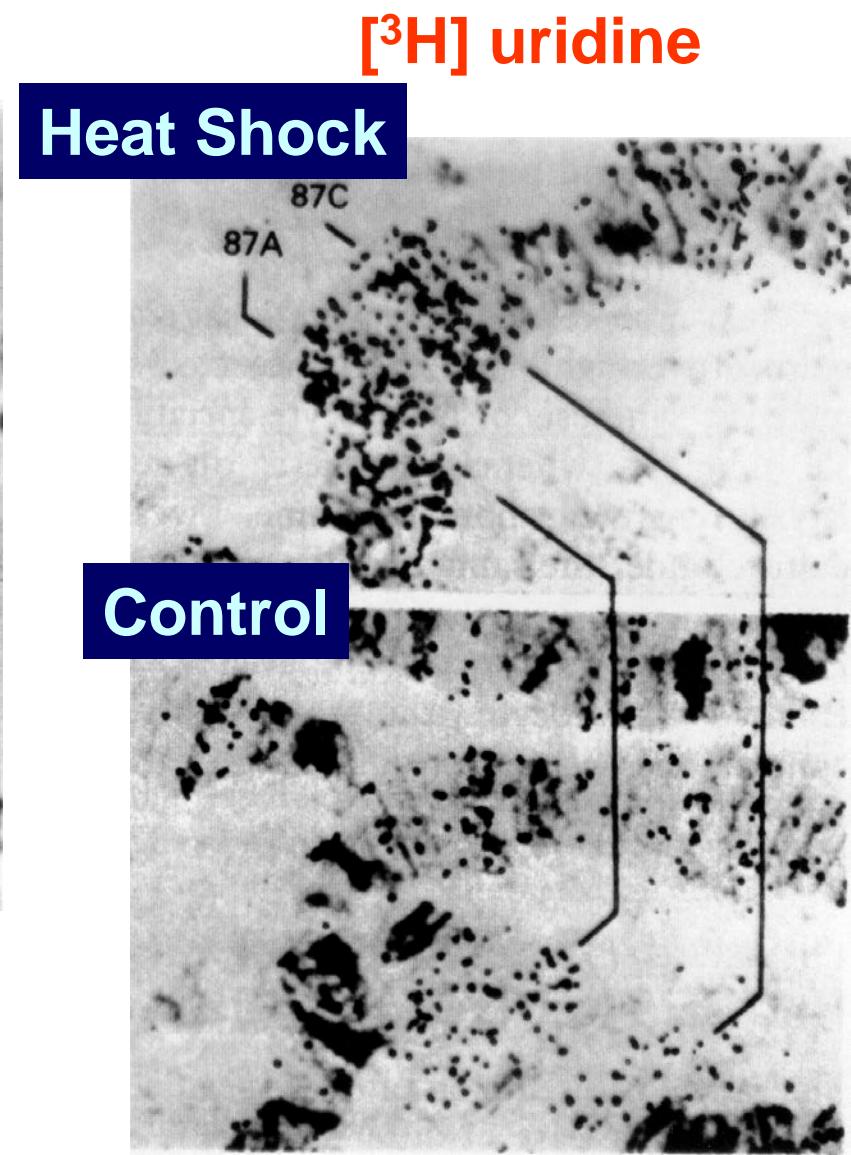
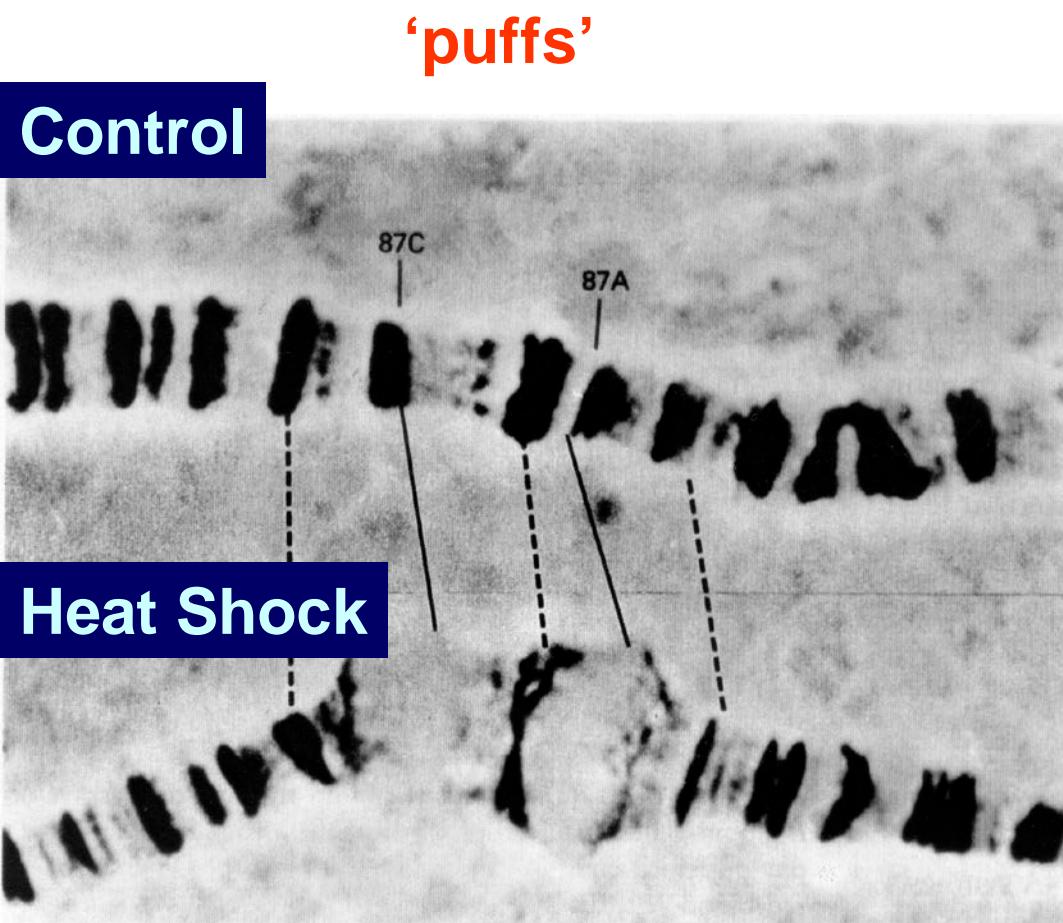
Drosophila busckii salivary gland chromosome spreads, showing “puffing” of two regions following temperature shift of larvae from 25°C (top) to 30°C for 30 min (bottom) (from Ritossa, 1962).

...his discovery was initially rejected because, in the words of a prominent journal editor, “it was irrelevant to the scientific community”

An aerial photograph of the Cold Spring Harbor Laboratory complex. In the foreground, several modern laboratory buildings with colorful facades (red, orange, yellow, green) and multiple chimneys are nestled among trees. A large parking lot filled with cars is visible. In the background, a large body of water (the harbor) is dotted with numerous small boats and yachts. The surrounding land is covered in dense green trees.

Cold Spring Harbor Laboratory

Szok cieplny powoduje silny wzrost aktywności transkrypcyjnej chromatyny



Ashburner M., and Bonner J.J. 1979, Cell
Bonner J.J., and Pardue M.L. 1976, Cell

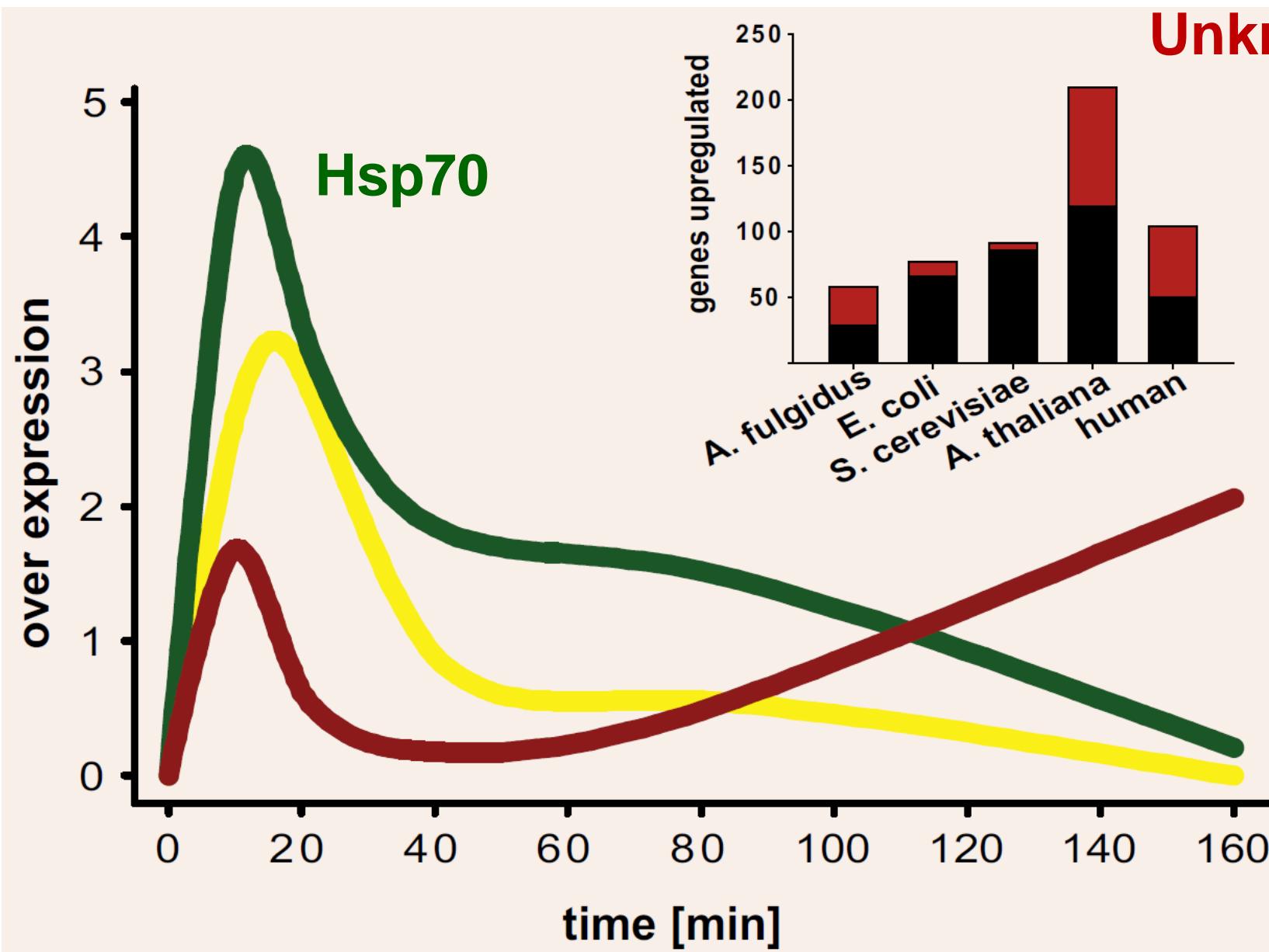


**Szok cieplny powoduje gwałtowną
syntezę grupy białek nazwanej
białkami szoku cieplnego**

(*Heat Shock Proteins*) HSP



Unknown



**Jak w warunkach cytotoksycznych
komórka może zwiększać syntezę białek?**

Jak regulowana jest ekspresja genów?

Czynniki transkrypcyjne

Szok cieplny powoduje aktywację czynnika transkrypcyjnego

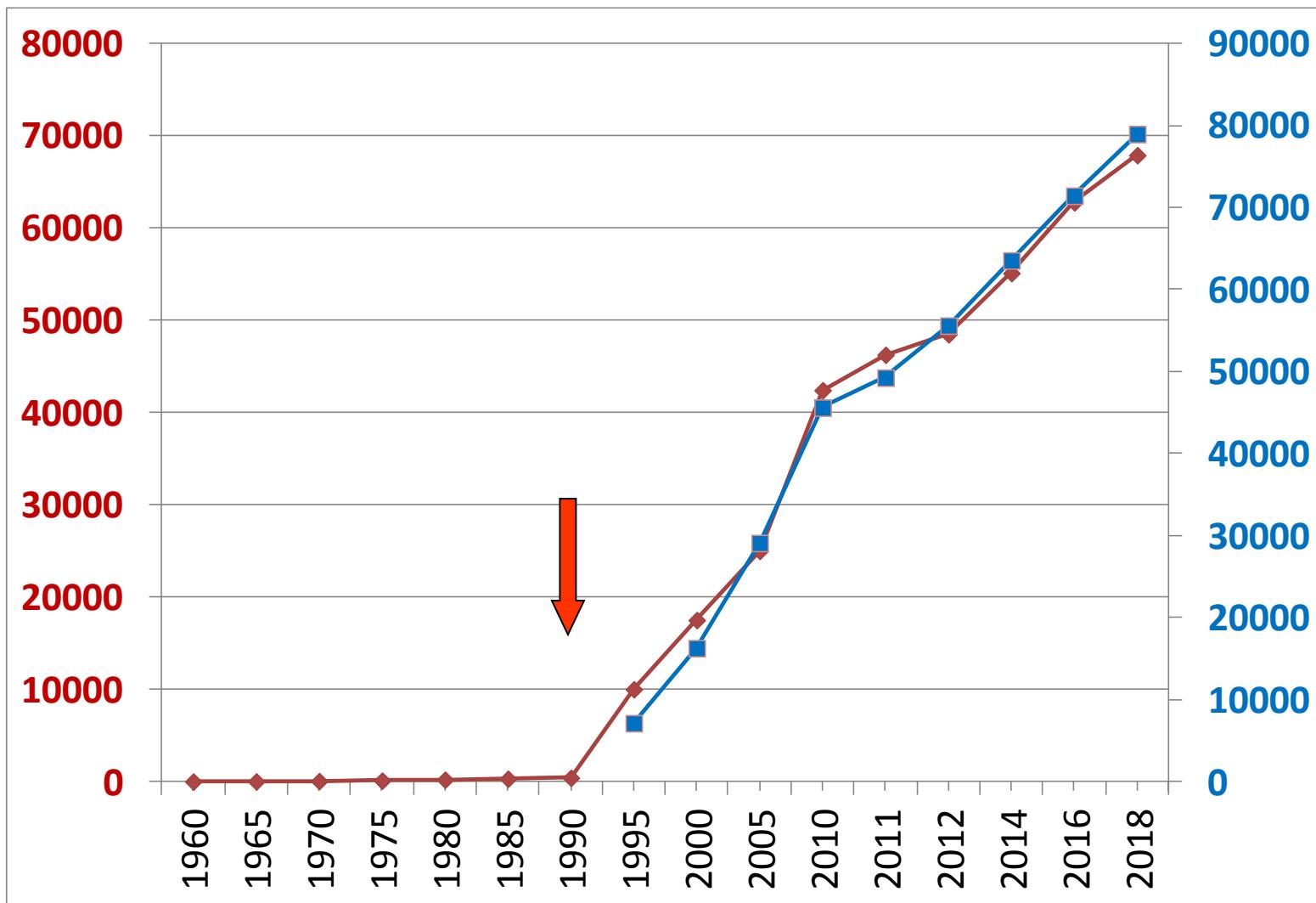
HSF (*Heat Shock Factor*)

wiązającego się w promotorach *hsp* do elementu regulacyjnego

HSE (*Heat Shock Element*)

Co HSP robią w komórce?

Przyrost liczby publikacji zawierających słowa kluczowe „heat shock” lub „chaperone”



HSP chronią komórkę przed skutkami działania stresu

Heat Shock Is Lethal to Fibroblasts Microinjected with Antibodies Against hsp70

KARL T. RIABOWOL,* LEE A. MIZZEN,† WILLIAM J. WELCH†

Synthesis of a small group of highly conserved proteins in response to elevated temperature and other agents that induce stress is a universal feature of prokaryotic and eukaryotic cells. Although correlative evidence suggests that these proteins play a role in enhancing survival during and after stress, there is no direct evidence to support this in mammalian cells. To assess the role of the most highly conserved heat shock protein (hsp) family during heat shock, affinity-purified monoclonal antibodies to hsp70 were introduced into fibroblasts by needle microinjection. In addition to impairing the heat-induced translocation of hsp70 proteins into the nucleus after mild heat shock treatment, injected cells were unable to survive a brief incubation at 45°C. Cells injected with control antibodies survived a similar heat shock. These results indicate that functional hsp70 is required for survival of these cells during and after thermal stress.

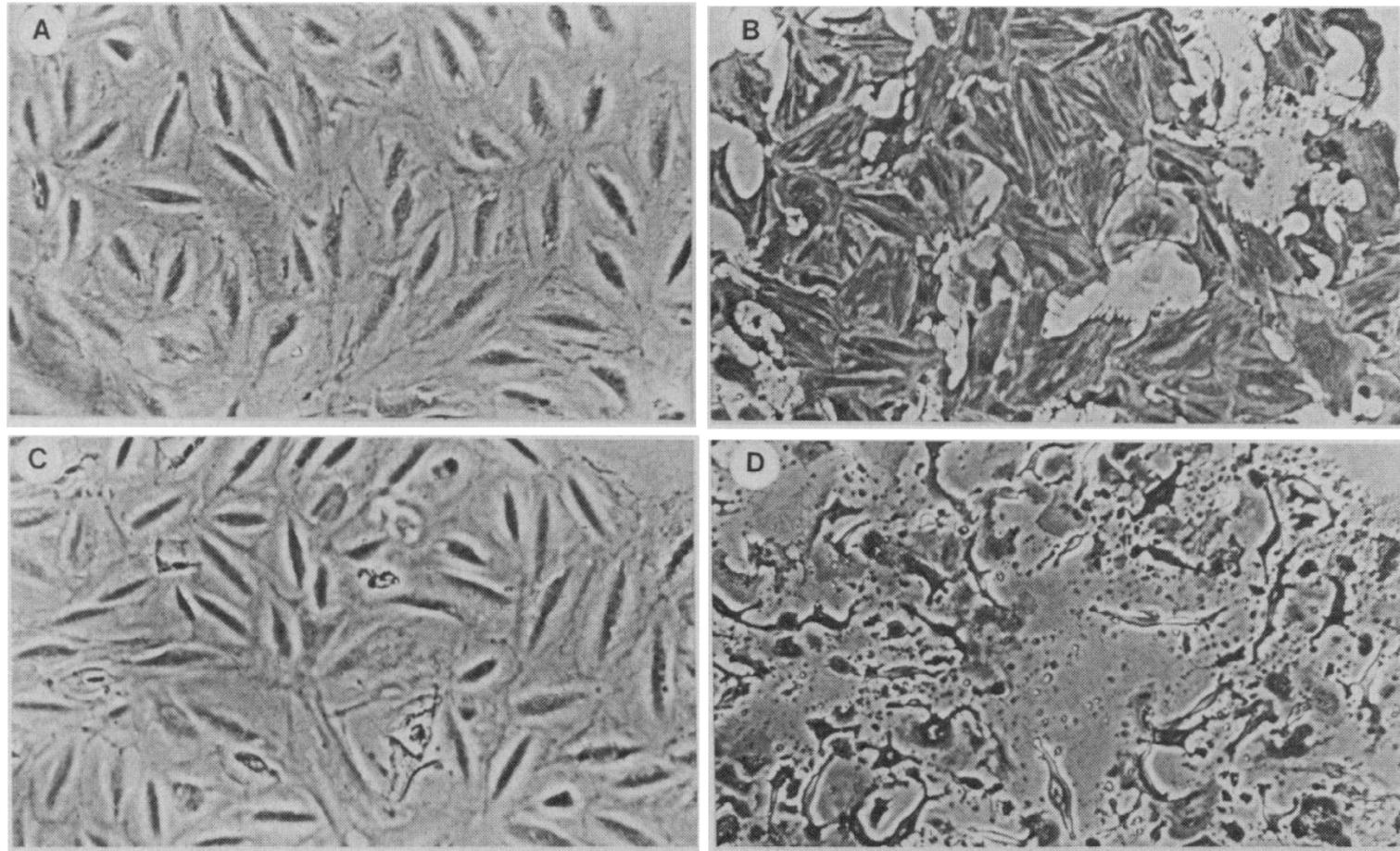


Fig. 2. Heat shock treatment is lethal to fibroblasts microinjected with hsp70 antibodies. Fields of REF-52 (rat embryo fibroblast) cells were injected with control goat antibodies against chicken IgG or hsp70 antibodies at a concentration of 5 mg/ml. After incubation at 37°C for 2 hours, phase contrast micrographs were taken of cells injected with (**A**) control or (**C**) hsp70 antibodies. The same cells were heat shocked at 45°C for 30 min, returned to 37°C, and further incubated for 24 hours. The cells were then stained for 10 min in 0.2% Trypan blue (w/v in phosphate-buffered saline), and fixed and stained with either goat antibodies against rabbit IgG (for the nonspecific control and antibodies to Fos and Ras) or goat antibodies against mouse IgG (for the antibodies to hsp70, actin, tubulin, and the C subunit of cAMP-dependent protein kinase) (19, 27). Goat antibodies against IgGs were conjugated with horseradish peroxidase to identify injected cells. (**B**) Cells injected with the nonspecific control antibodies, and (**D**) cells injected with hsp70 antibodies 24 hours after the heat shock treatment.

**HSP należą do białek
opiekuńczych
*(Molecular Chaperones)***

The E. coli dnaK gene product, the hsp70 homolog, can reactivate heat-inactivated RNA polymerase in an ATP hydrolysis-dependent manner

Skowyra D, Georgopoulos C, Zylacz M.
Cell. 1990 Sep 7;62(5):939-44.

Maciej Żylicz



<https://www.iimcb.gov.pl/en/research/laboratories/10-department-of-molecular-biology-zylicz-laboratory>

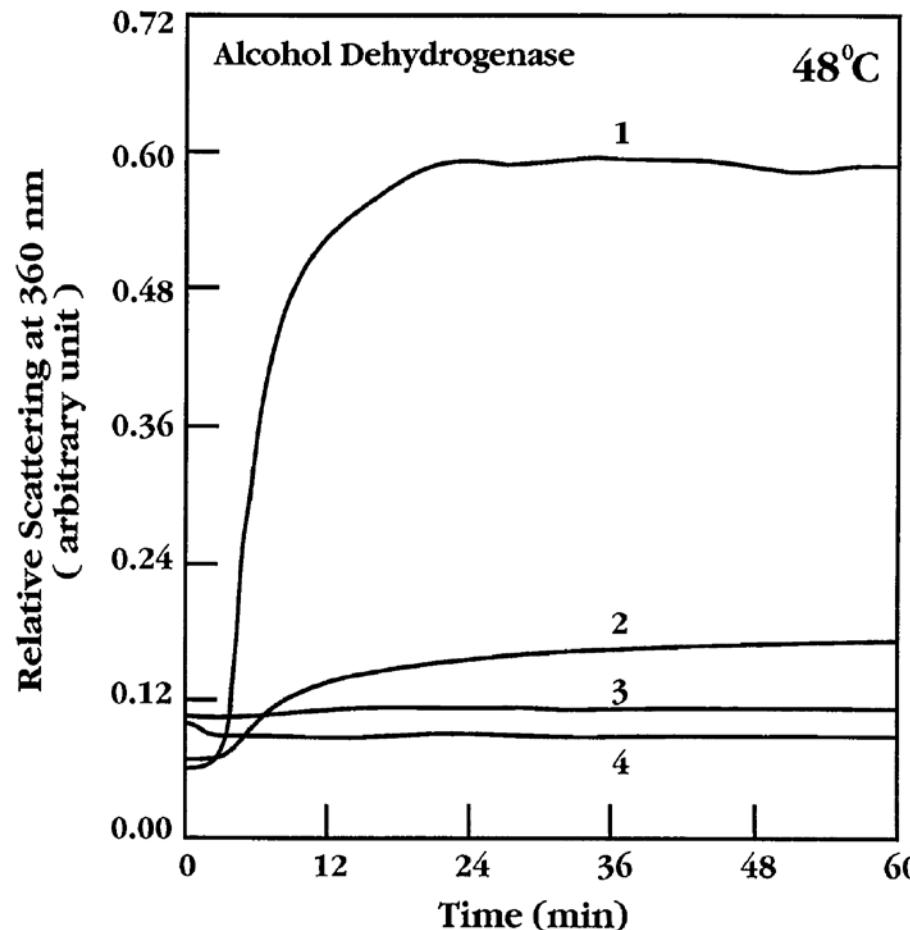


FIG. 1. Aggregation of alcohol dehydrogenase at 48°C in the absence and presence of α -crystallin. In each experiment, 0.13 mg of alcohol dehydrogenase (horse liver) in 50 mM sodium phosphate (pH 7) was used with the following additions: Curves 1, none; 2, plus 0.04 mg of α -crystallin; 3, plus 0.12 mg of α -crystallin; 4, plus 0.55 mg of α -crystallin. The final volume of each reaction mixture was 0.4 ml and the pathlength was 10 mm.

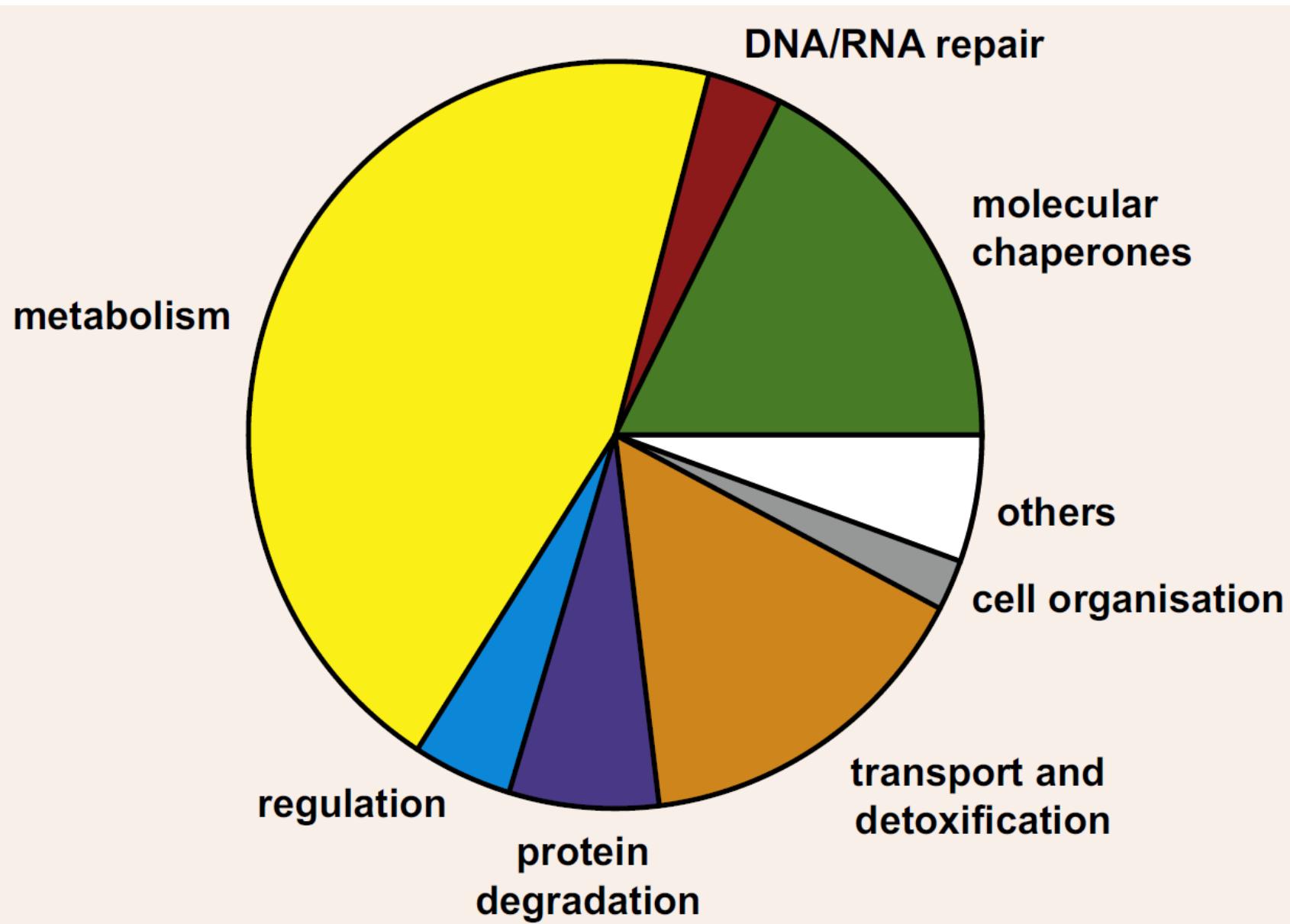
Białka szoku cieplnego

versus

Białka opiekuńcze (*chaperone proteins*)



Functional classes of proteins upregulated during the heat shock response



**HSPs chronią komórki nowotworowe
przed skutkami działania cytostatyków,
hipertermii i promieniowania**

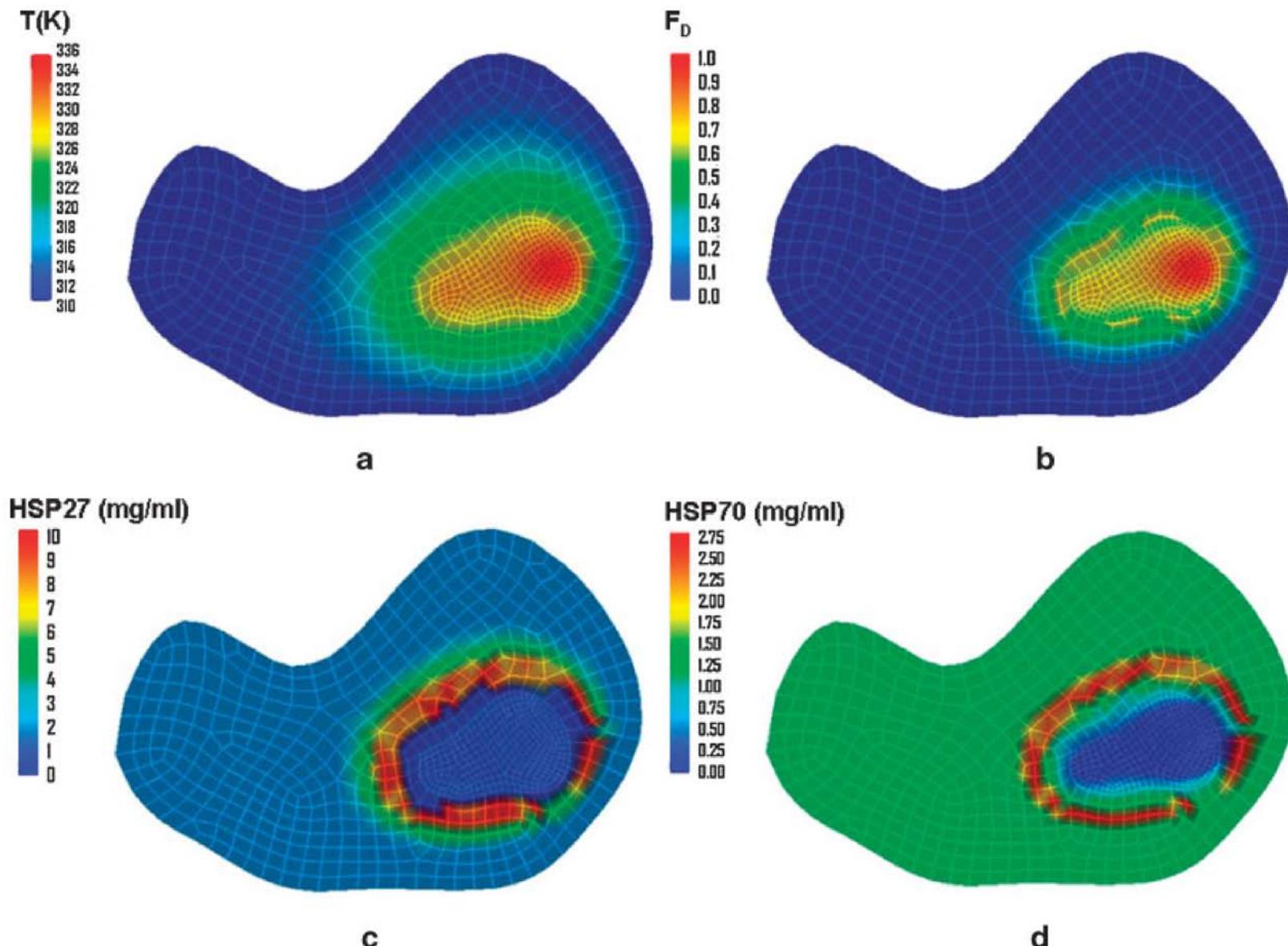


Fig. 6. Therapy outcome based on HSP expression-based optimization for an initial guess of $P_1 = 1.0$ W and $P_2 = 0.5$ W depicting (a) temperature, (b) injury fraction, (c) HSP27, and (d) HSP70 distribution following therapy.



HSPs hamują apoptozę



Hsp27 negatively regulates cell death by interacting with cytochrome c

Jean-Marie Bruey*, Cécile Ducasse†, Philippe Bonniaud*, Luigi Ravagnan‡, Santos A. Susin‡, Chantal Diaz-Latoud†, Sandeep Gurbuxani*, André-Patrick Arrigo†, Guido Kroemer‡, Eric Solary* and Carmen Garrido*§

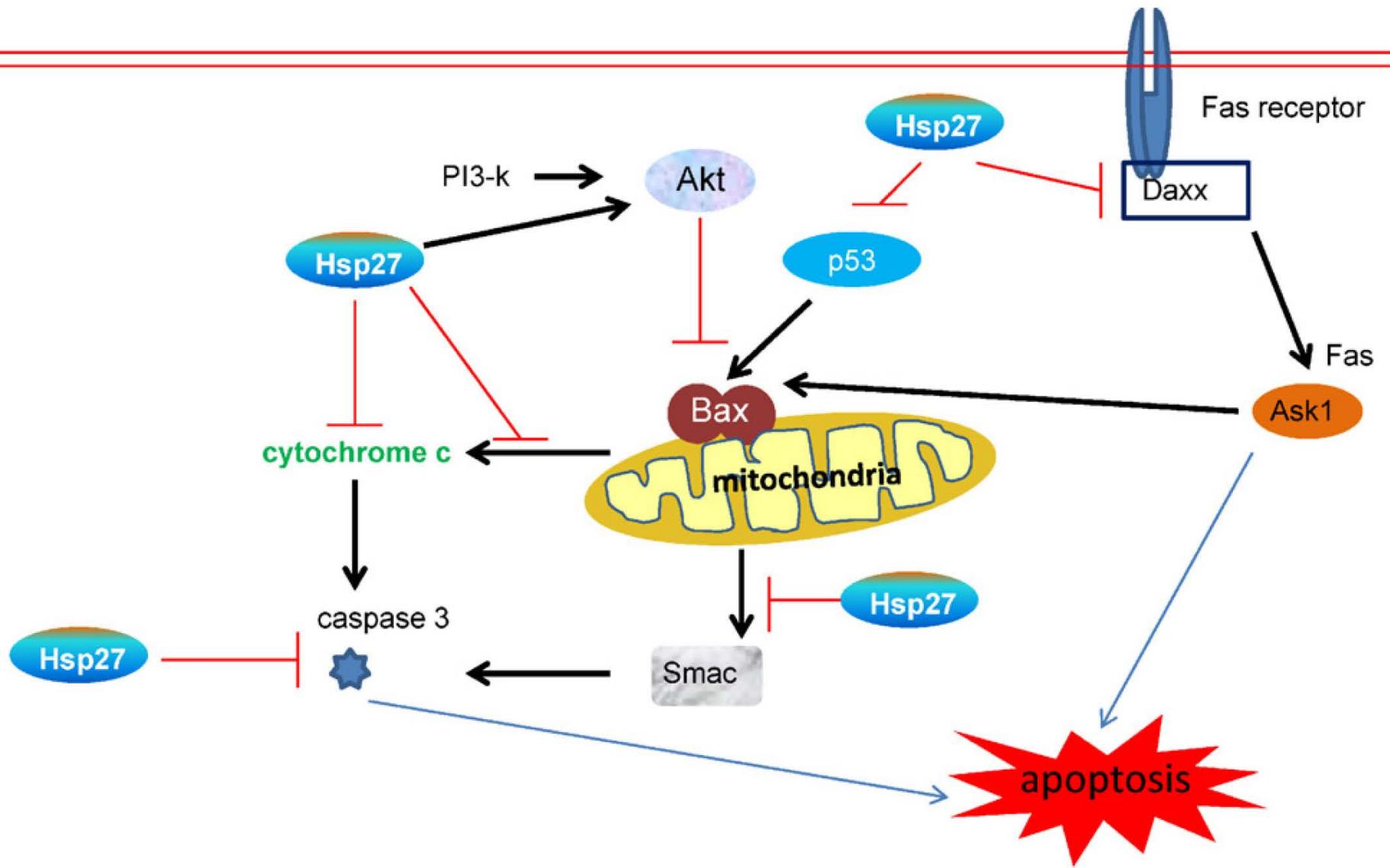
*INSERM U-517, Faculty of Medicine and Pharmacy, 7 Boulevard Jeanne d'Arc, 21033 Dijon, France

†Stress Laboratory, CNRS UMR-5534, 69622 Villeurbanne, France

‡CNRS UMR 1599, Institute Gustave Roussy, 94805 Villejuif, France

§e-mail: cgarrido@u-bourgogne.fr

Mammalian cells respond to stress by accumulating or activating a set of highly conserved proteins known as heat-shock proteins (HSPs). Several of these proteins interfere negatively with apoptosis. We show that the small HSP known as Hsp27 inhibits cytochrome-c-mediated activation of caspases in the cytosol. Hsp27 does not interfere with granzyme-B-induced activation of caspases, nor with apoptosis-inducing factor-mediated, caspase-independent, nuclear changes. Hsp27 binds to cytochrome c released from the mitochondria to the cytosol and prevents cytochrome-c-mediated interaction of Apaf-1 with pro-caspase-9. Thus, Hsp27 interferes specifically with the mitochondrial pathway of caspase-dependent cell death.

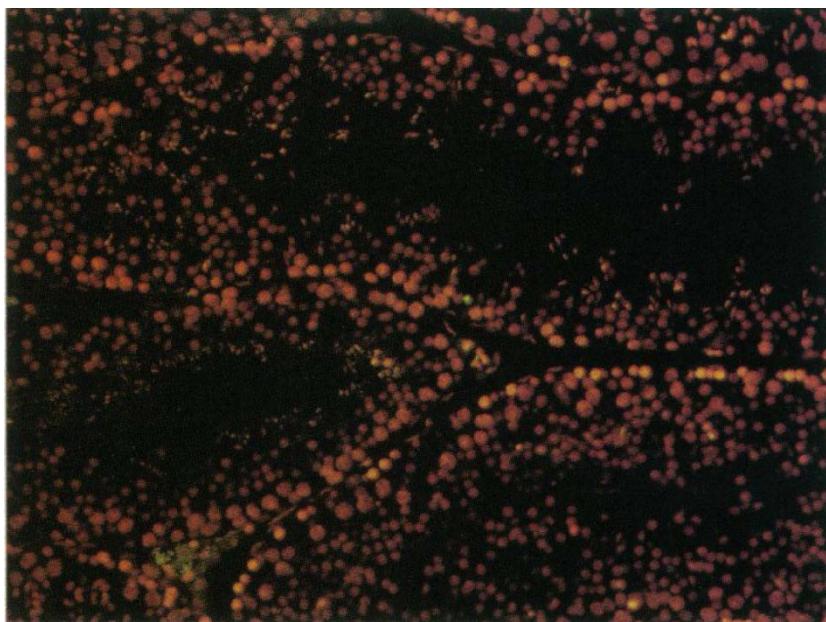


Delecje HSPs są letalne

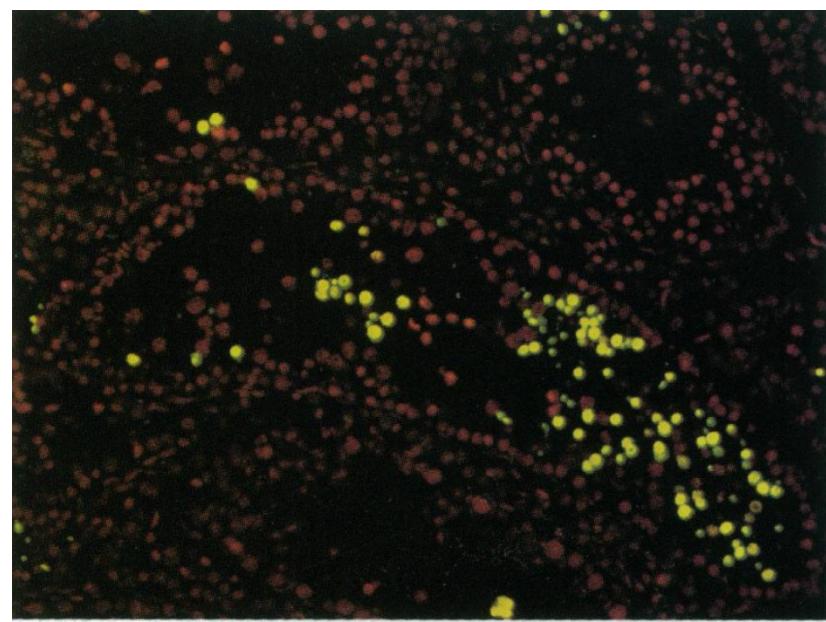


Targeted gene disruption of Hsp70-2 results in failed meiosis, germ cell apoptosis (TUNEL), and male infertility

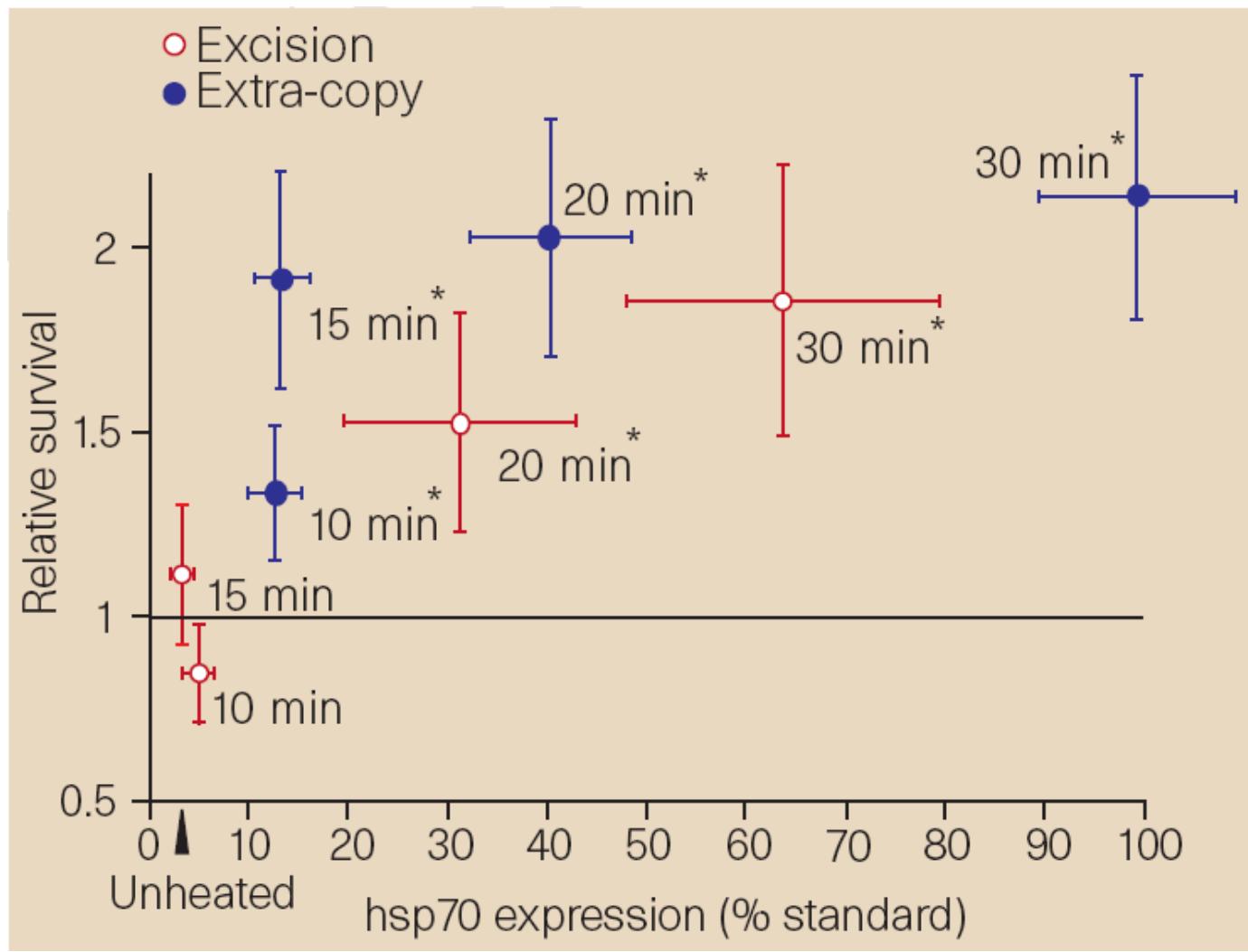
$+/+$



$-/-$

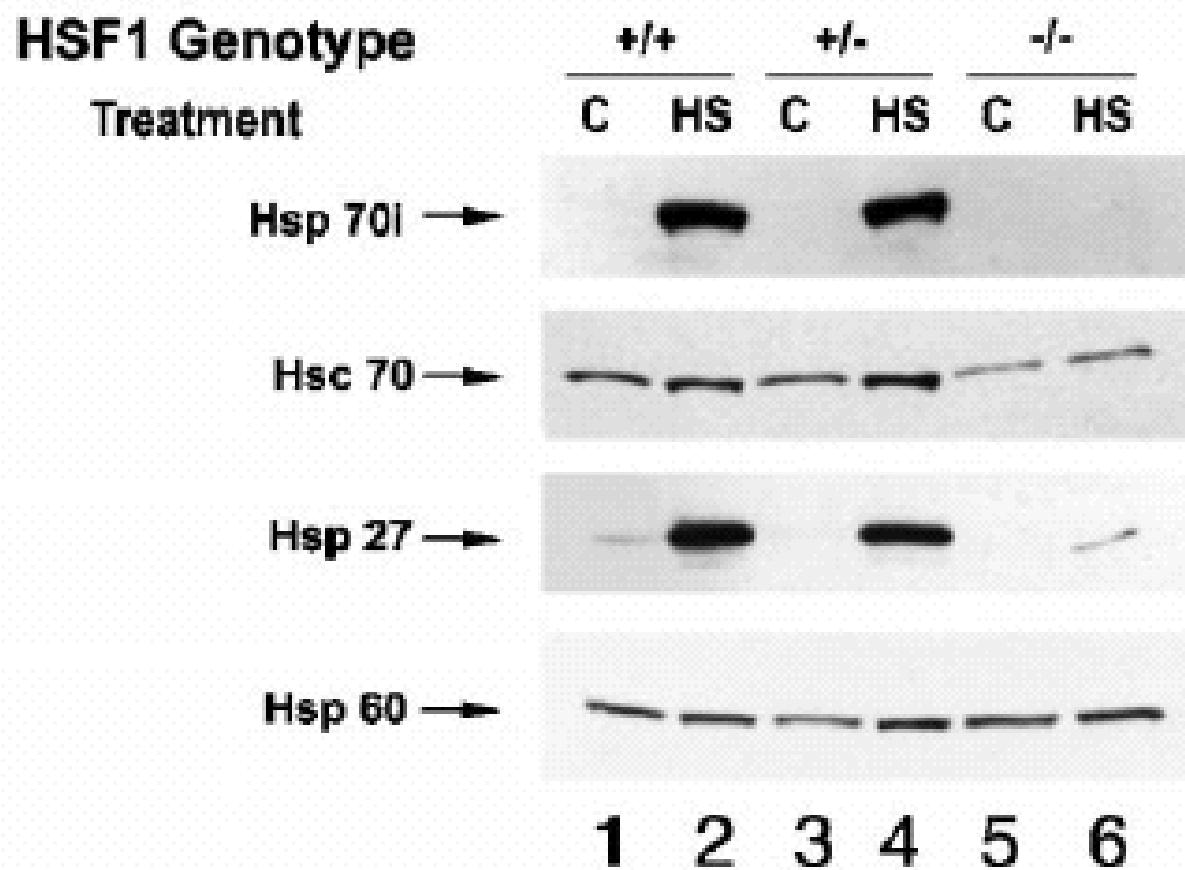


**Ekspresja HSP koreluje
z długością życia**

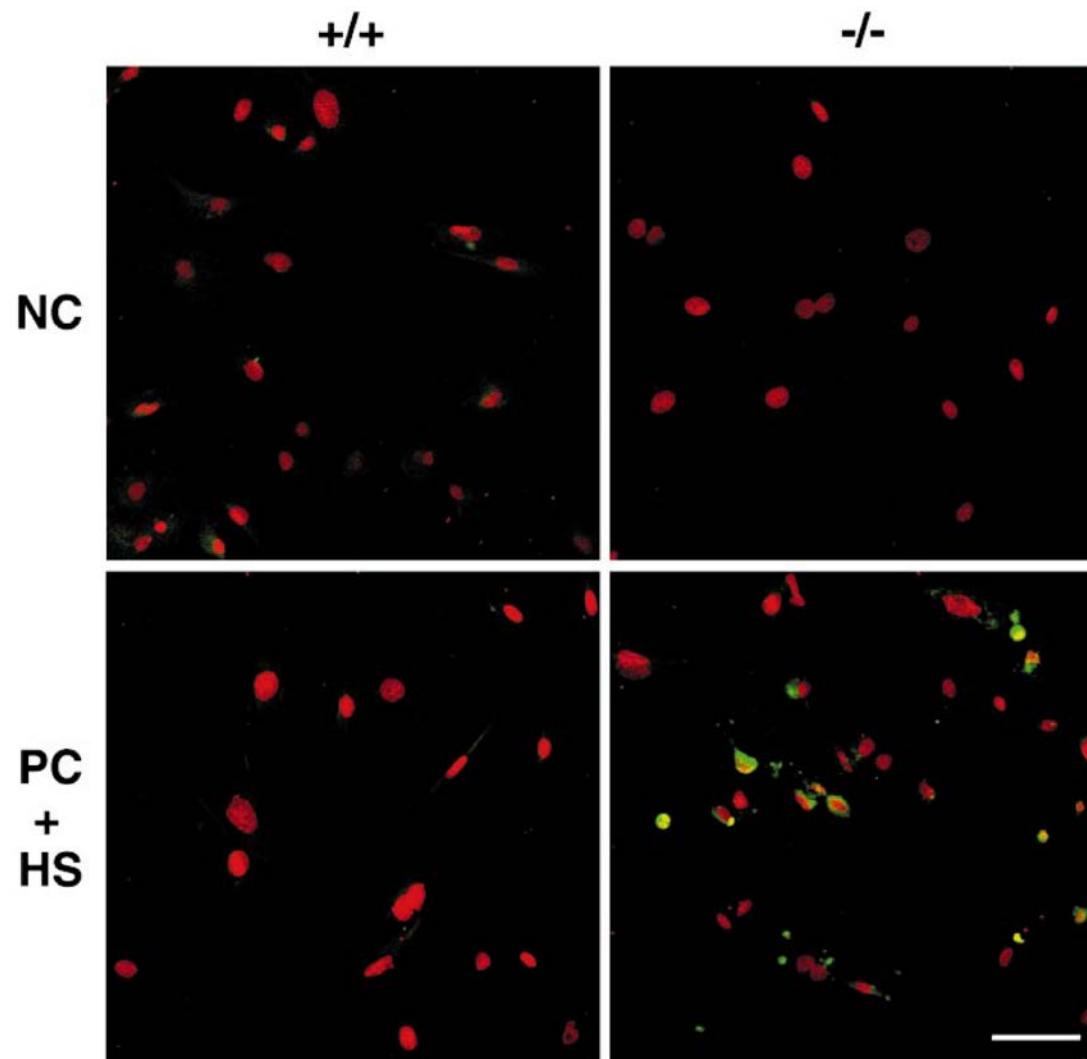


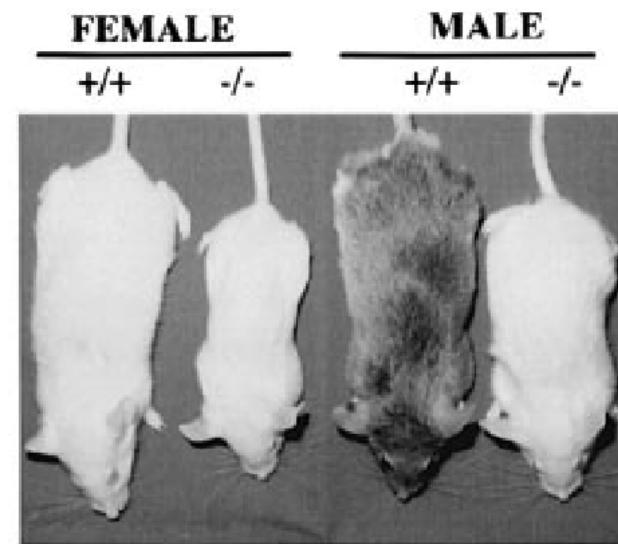
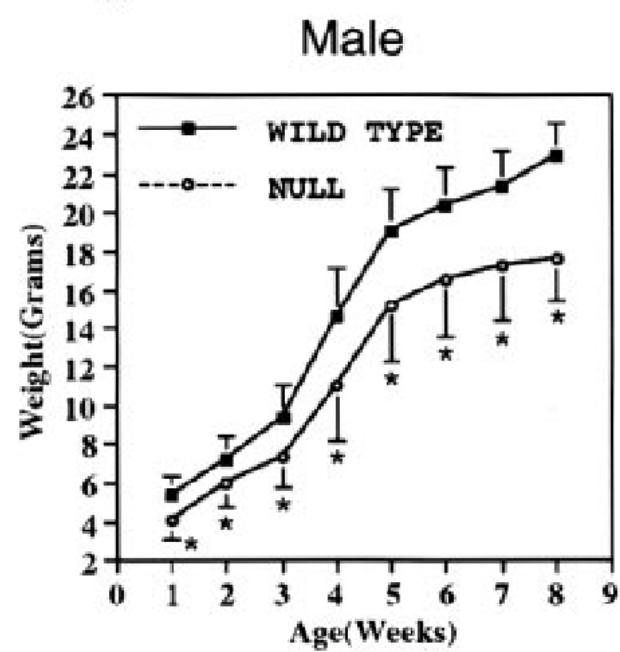
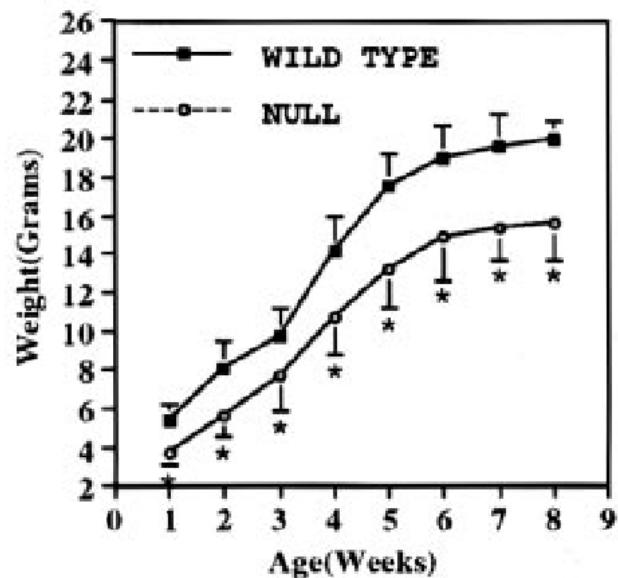
Delecje HSF są letalne

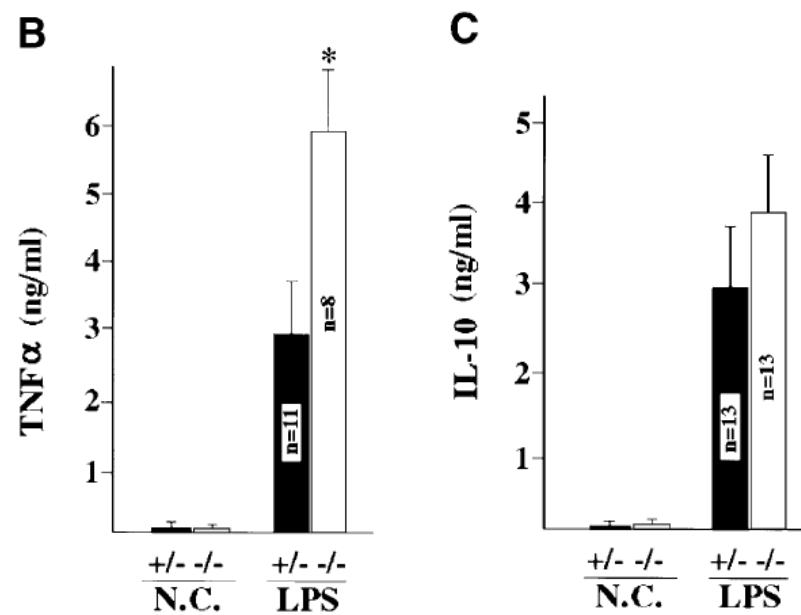
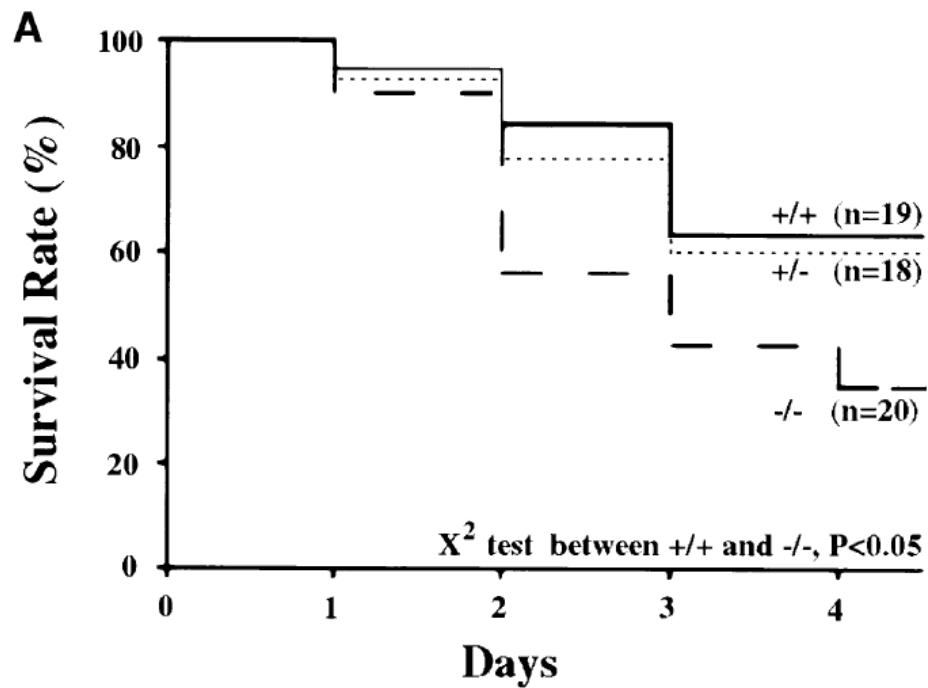
Expression of HSPs



Apoptosis (TUNEL)



**A****C129-Hsf1****B****C****Female**



Heat Shock Factor 1 Is a Powerful Multifaceted Modifier of Carcinogenesis

Chengkai Dai,¹ Luke Whitesell,¹ Arlin B. Rogers,³ and Susan Lindquist^{1,2,*}

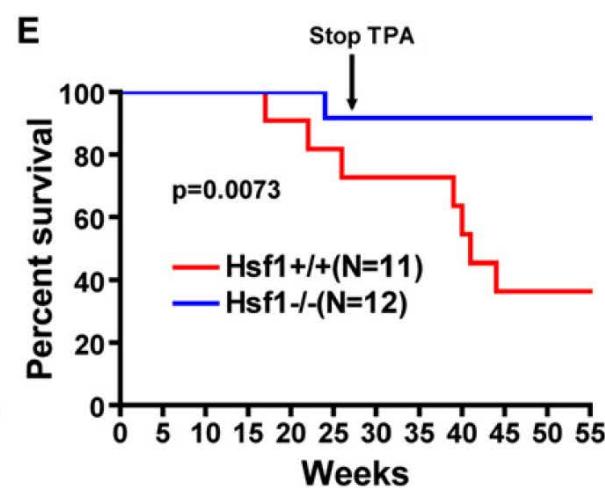
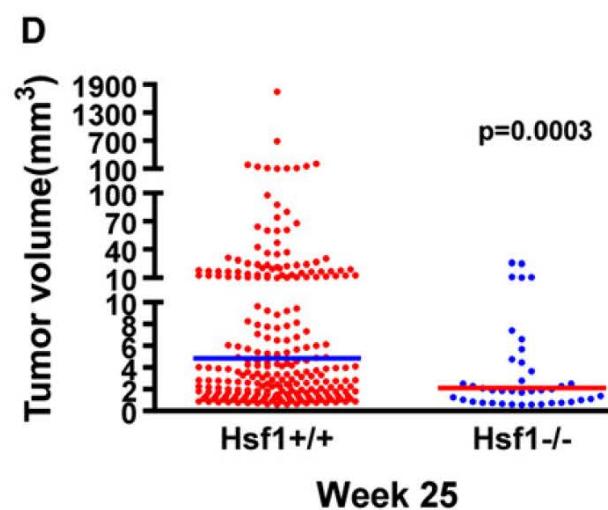
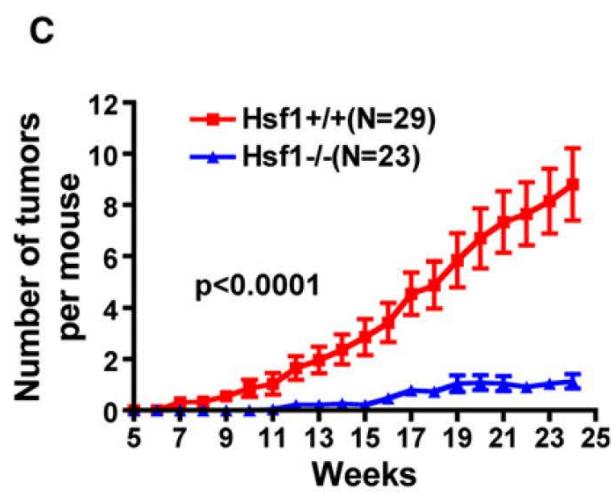
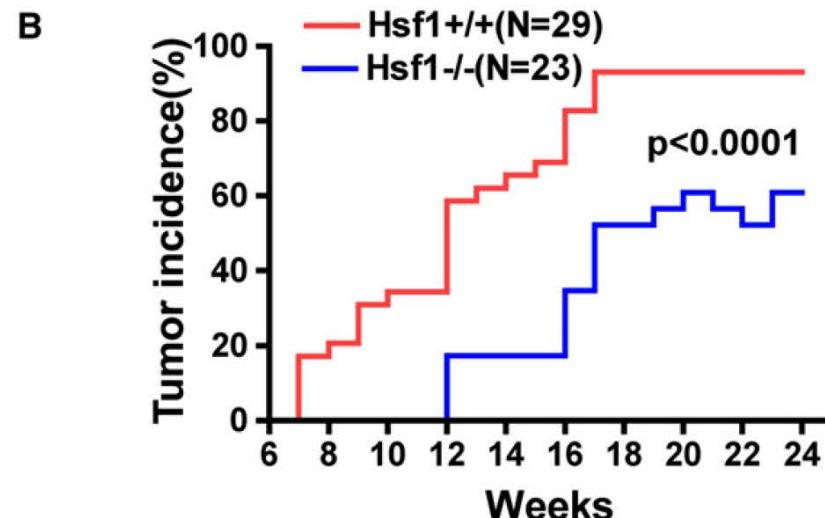
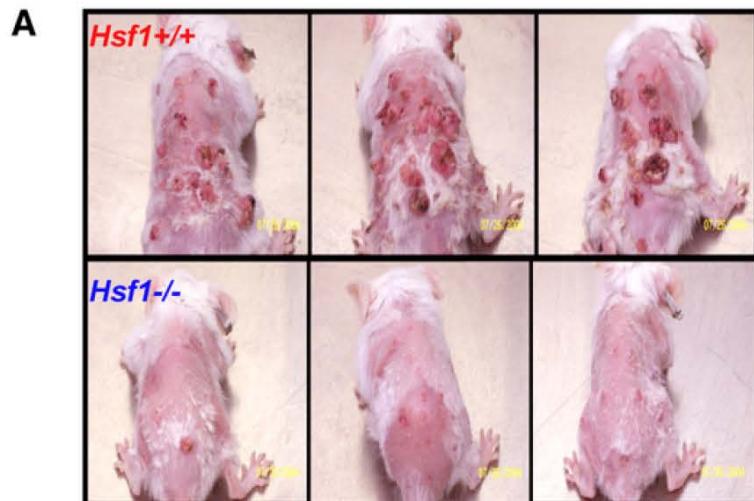
¹Whitehead Institute for Biomedical Research, Cambridge, MA 02142, USA

²Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA

³Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

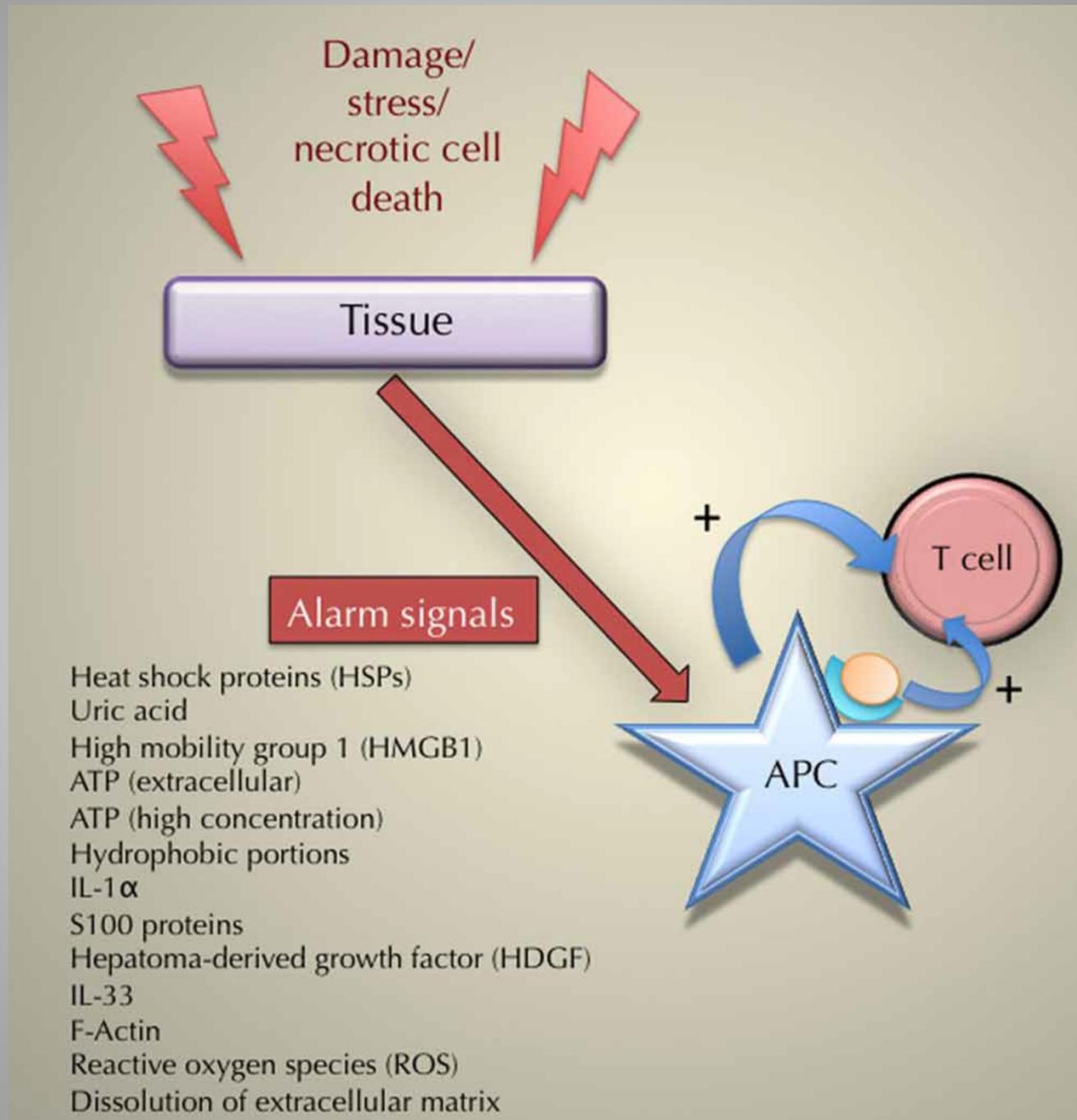
*Correspondence: lindquist_admin@wi.mit.edu

DOI 10.1016/j.cell.2007.07.020



**Czy HSPs mogą funkcjonować
poza komórką?**

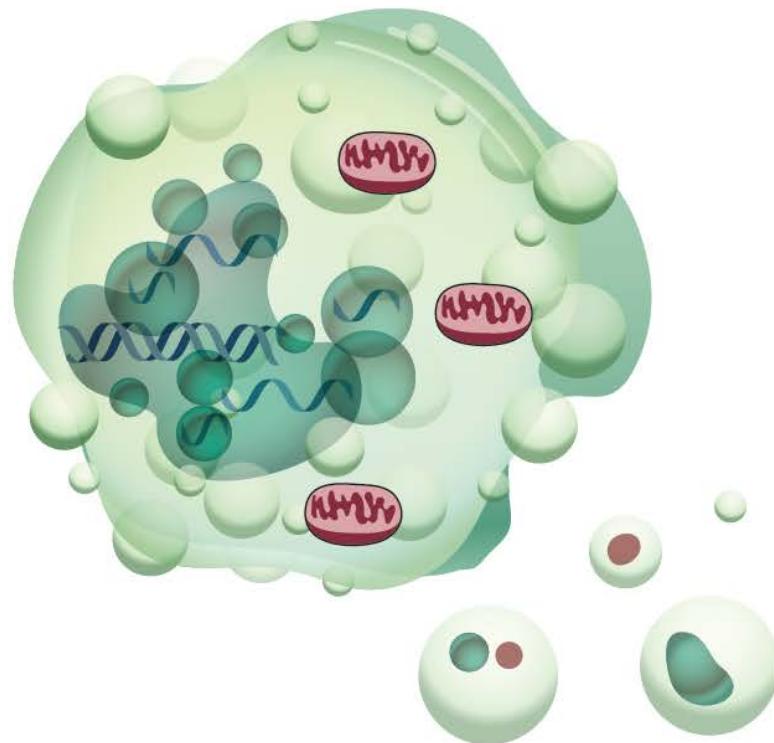
Danger Theory



**Danger signals =
Damage-associated molecular
patterns (DAMPs)**

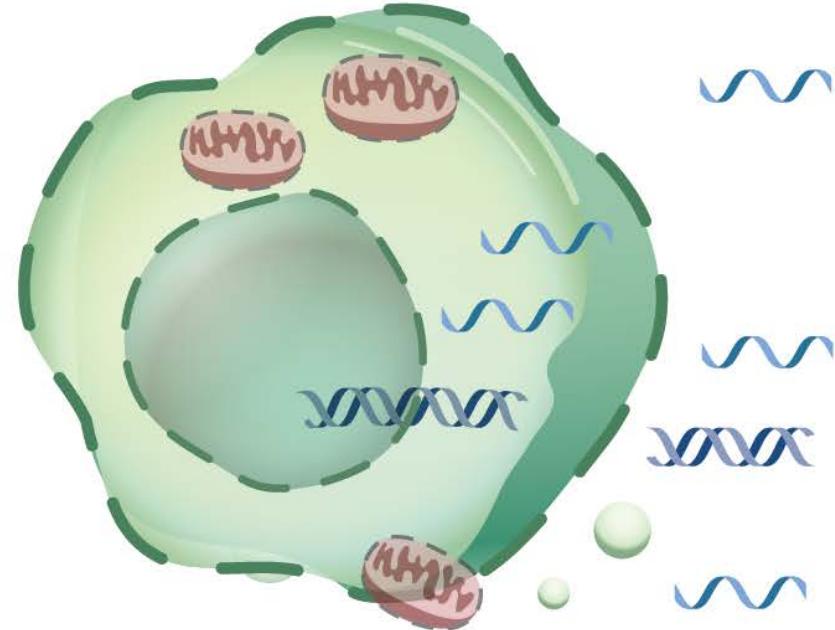
**b**

Apoptosis



Limited DAMP release
Weak inducer of inflammation

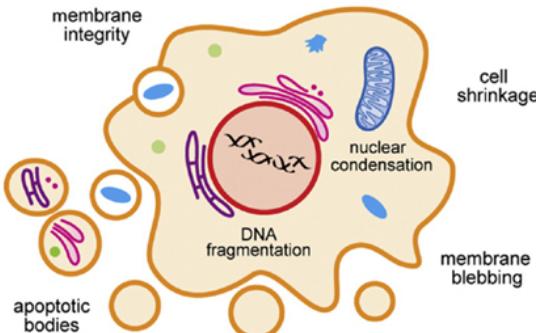
Necroptosis



Massive DAMP release
Strong inducer of inflammation

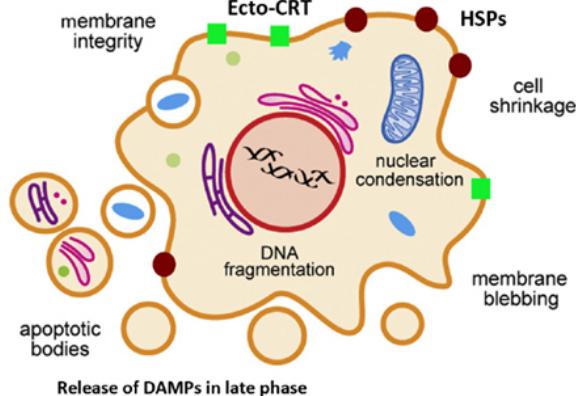
Immunogenic Cell Death (ICD)

non-immunogenic apoptosis

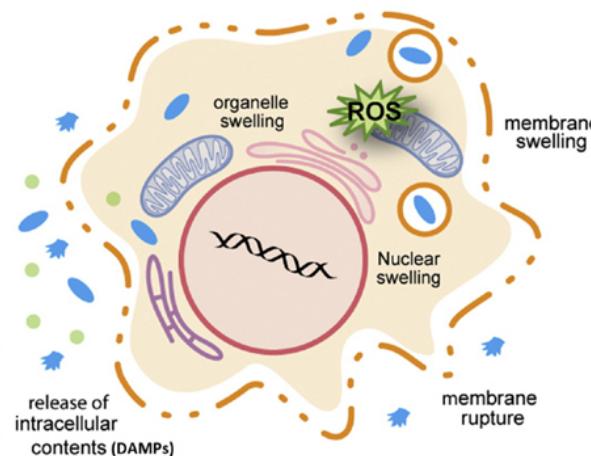


Non-immunogenic cell death mode

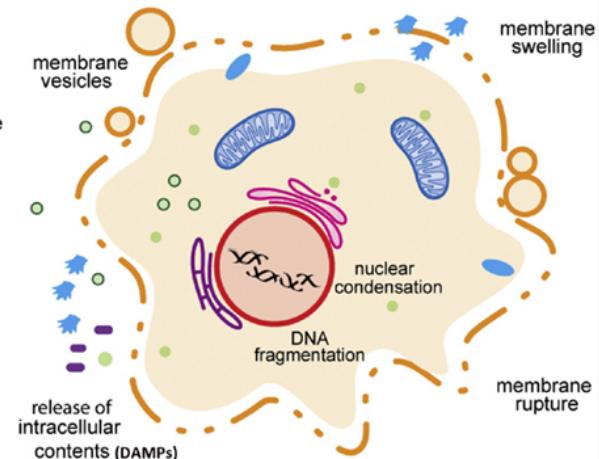
immunogenic apoptosis



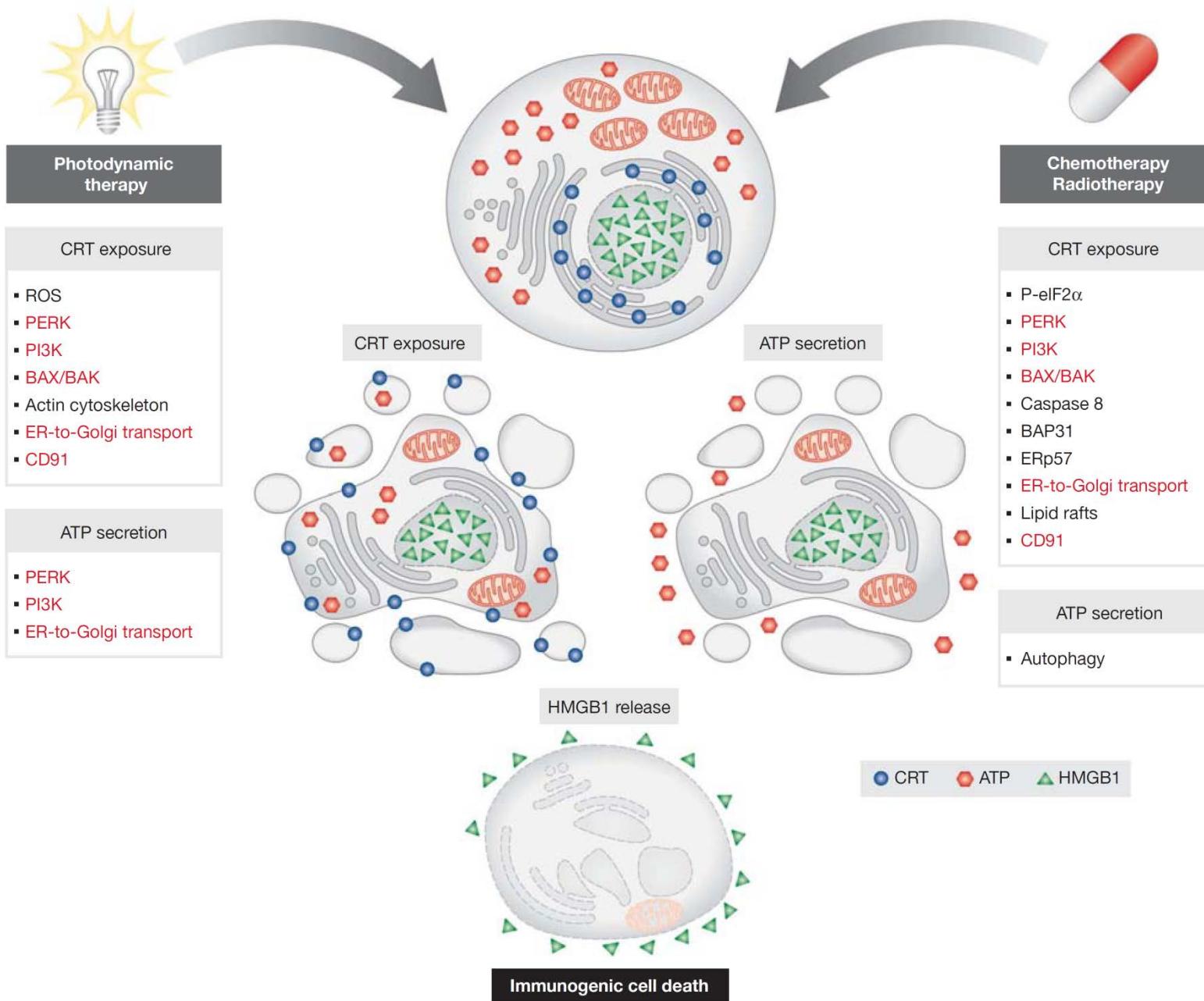
necrosis



pyroptosis



ICD and cancer



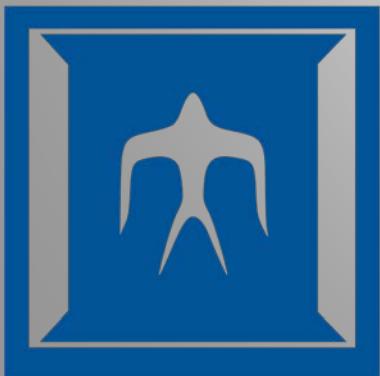
Autophagy

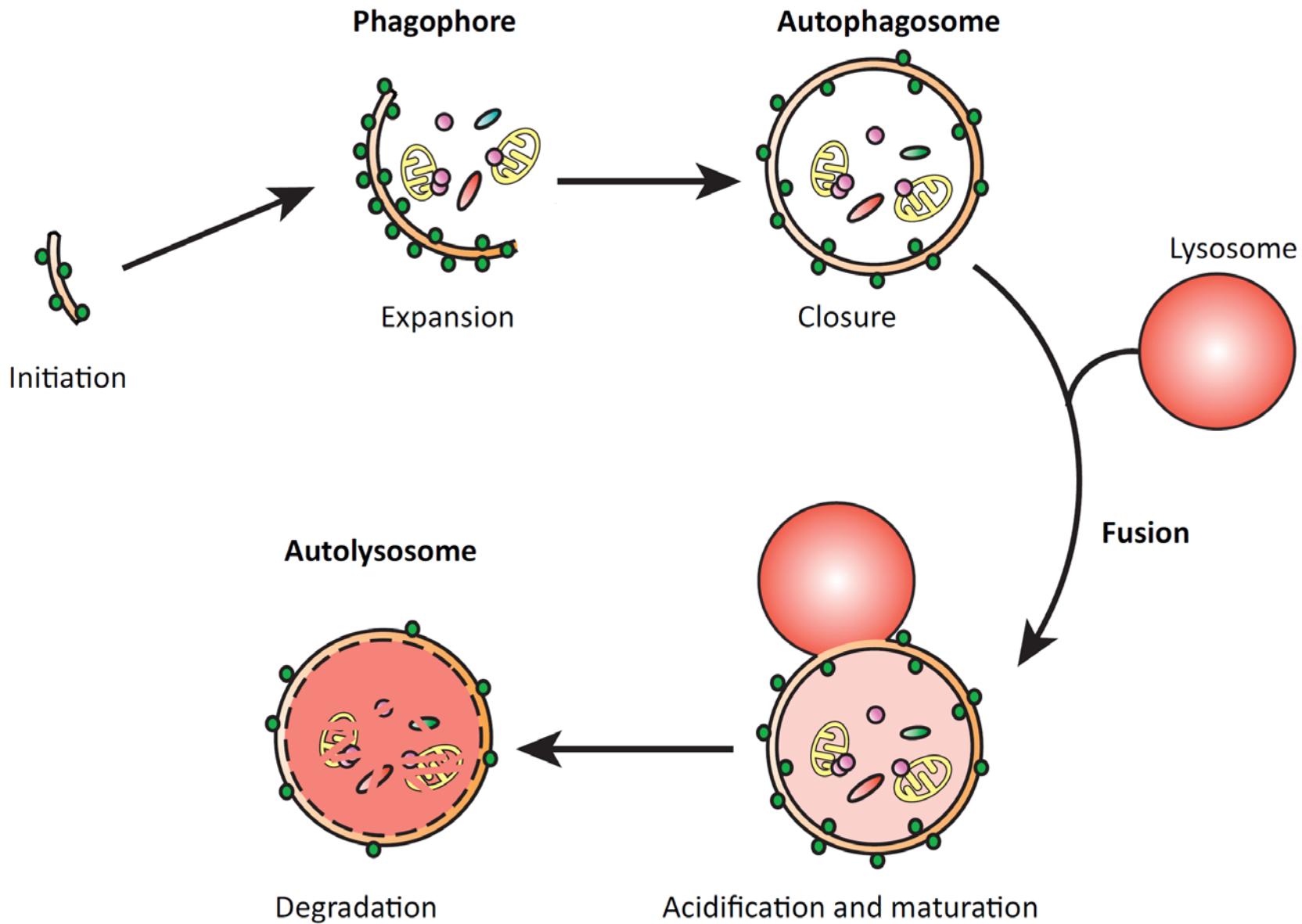
Nobel' 2016 Yoshinori Ohsumi

"for his discoveries of mechanisms for autophagy"

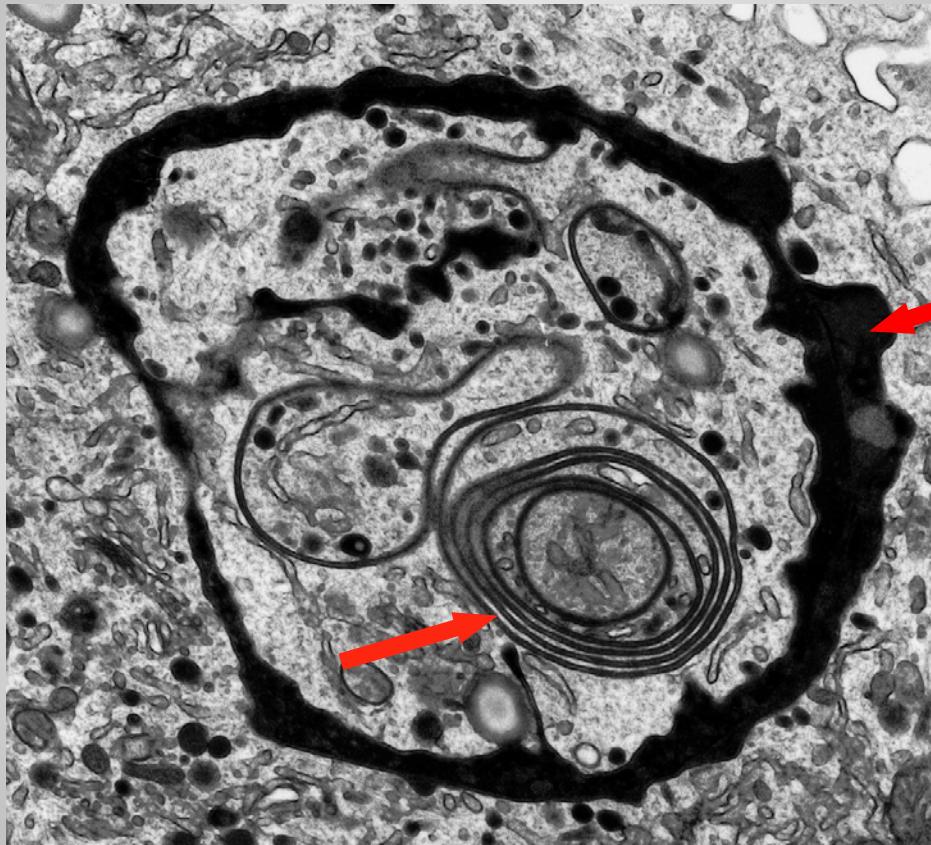


Tokyo Institute of Technology



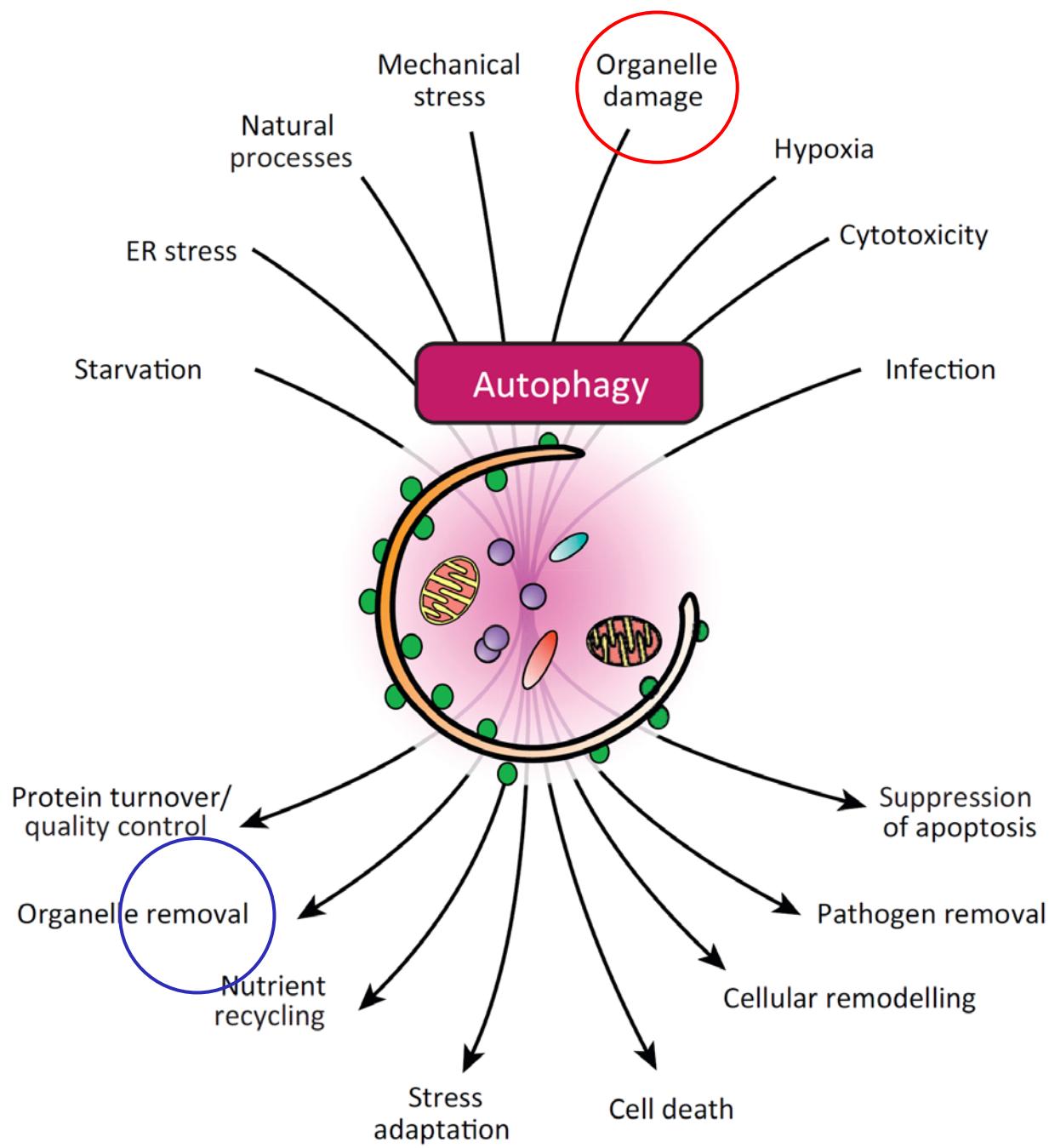


Autofagiczny neutrofil pochłonięty przez makrofaga



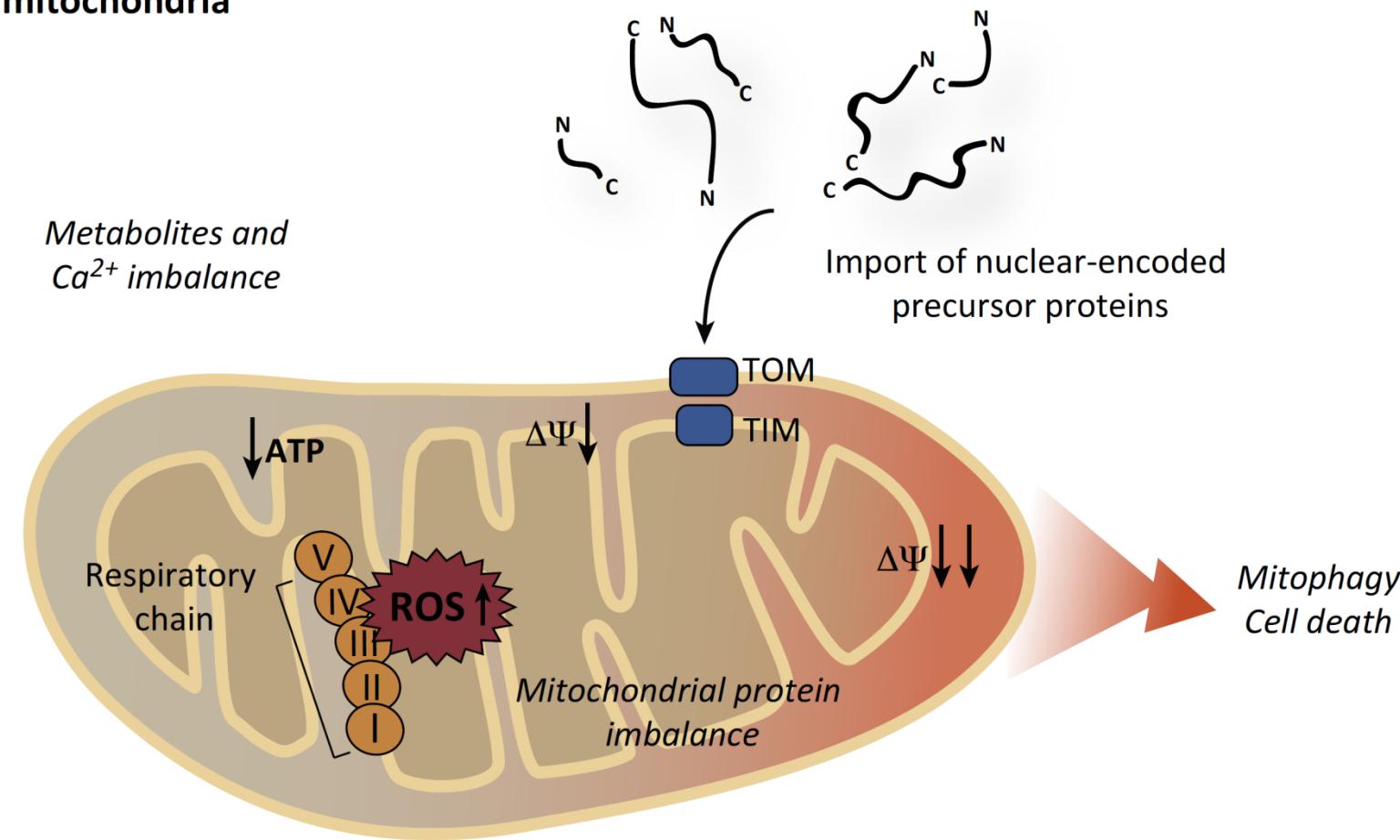
Fagosom typowy dla komórki nekrotycznej

Wyraźne cechy autofagii



Defective mitochondria

Accumulation of precursor proteins



$\text{ATP} \downarrow$ Activation of signaling pathways

$\text{ROS} \uparrow$ Signaling and oxidative damage

$\Delta\Psi \downarrow$ Inhibition of transport processes

October 1st 2018

Cancer immunotherapy

sweeps Nobel for medicine

Tasuku Honjo and James Allison

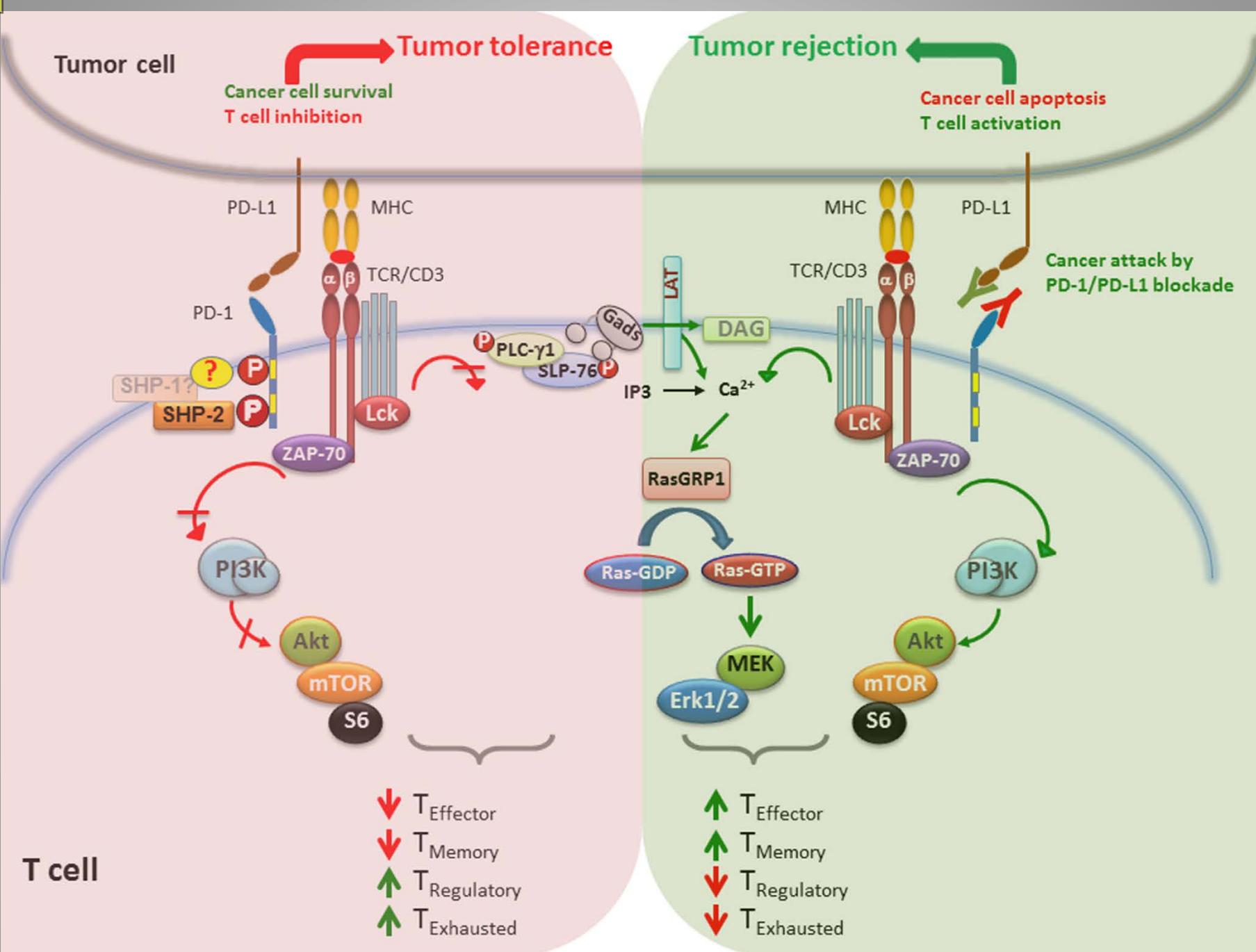


京都大学
KYOTO UNIVERSITY

THE UNIVERSITY OF TEXAS
MD Anderson
~~Cancer~~ Center
Making Cancer History®

PD-1 PD-L1

Checkpoint inhibitor therapy



OPDIVO™ (nivolumab)

INJECTION FOR INTRAVENOUS USE 10 mg/mL



Bristol-Myers Squibb

[All News](#)[Consumer](#)[Pro](#)[New Drugs](#)[Pipeline](#)[Clinical Trials](#)[FDA Alerts](#)[More ▾](#)

FDA Approves Opdivo (nivolumab) for Certain Patients with Previously Treated Small Cell Lung Cancer



PRINCETON, N.J.--(BUSINESS WIRE)--August 17, 2018 -- Bristol-Myers Squibb Company (NYSE: BMY) today announced that **Opdivo (nivolumab)** received approval from the U.S. Food and Drug Administration (FDA) as the first and only Immuno-Oncology treatment option for patients with metastatic **small cell lung cancer (SCLC)** whose cancer has progressed after platinum-based chemotherapy and at least one other line of therapy.¹ Approval for this indication has been granted under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.¹