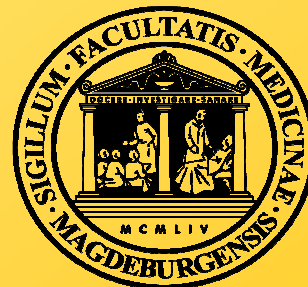


Molekulare Ursachen unerwünschter Wirkungen bei der Chemotherapie

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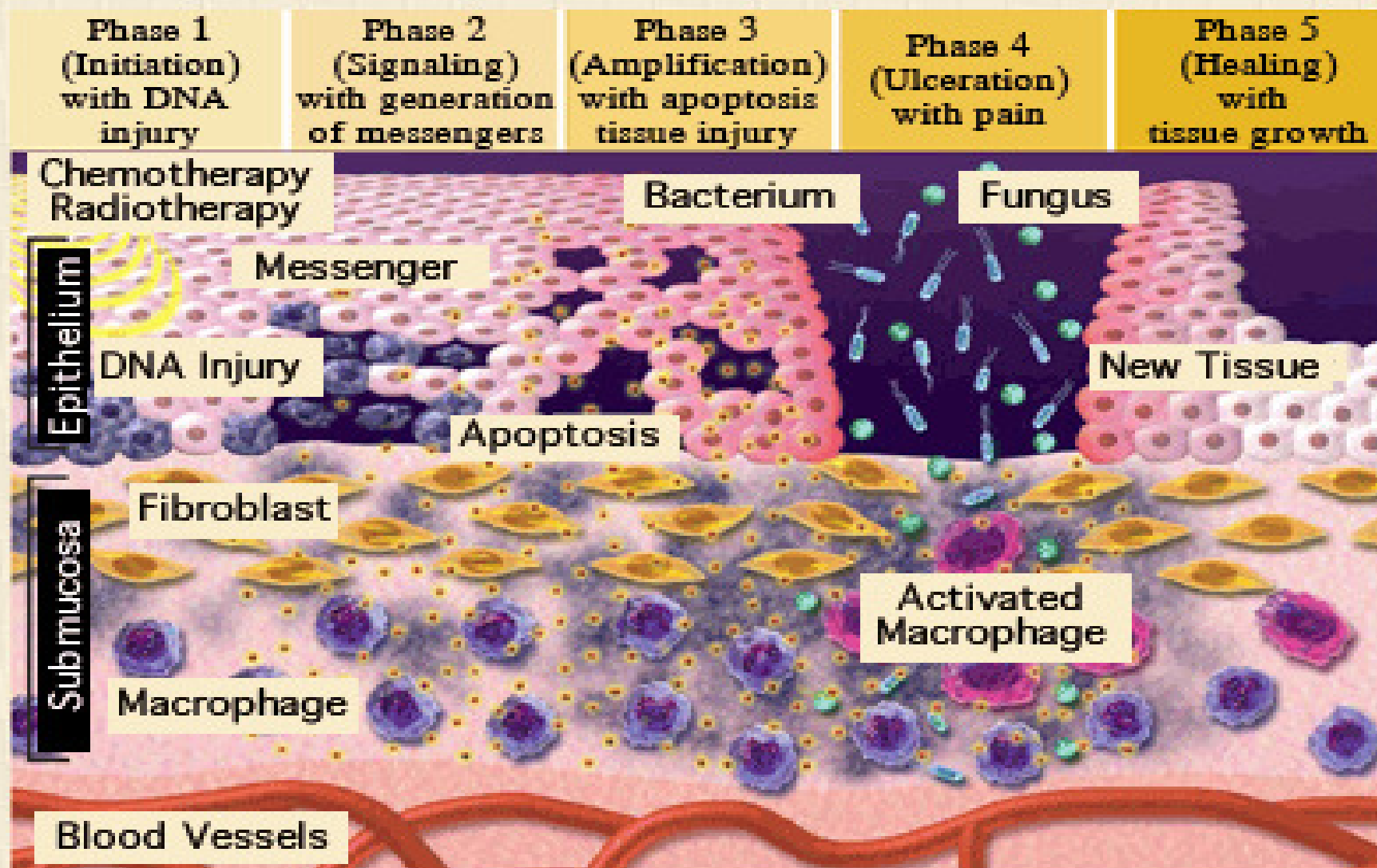
Klinik für Frauenheilkunde und Geburtshilfe



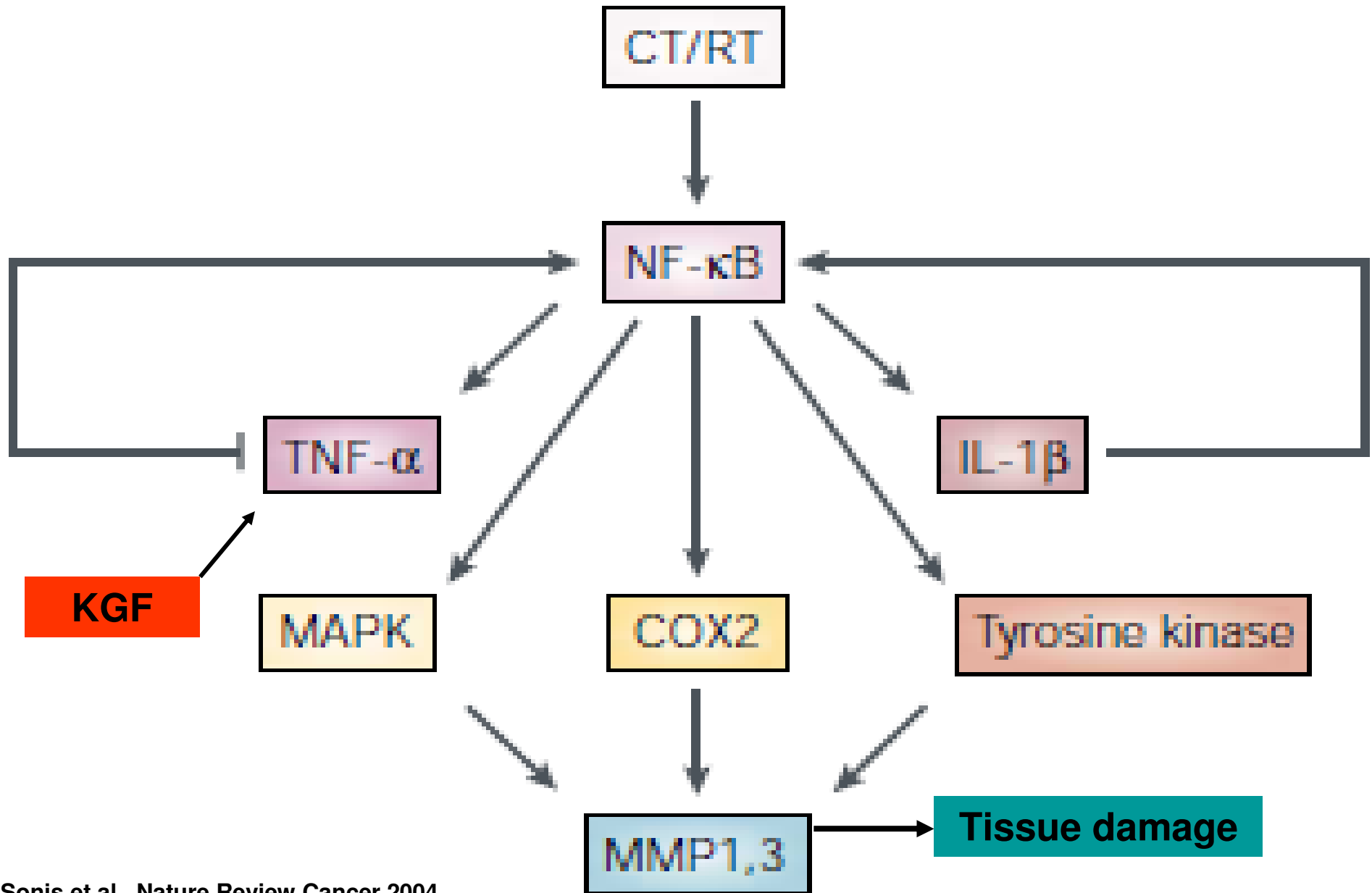
Molekulare Ursachen unerwünschter Wirkungen bei der Chemotherapie

1. Mukokutane Toxizitäten
 - Mukositis (valides biol. Modell → Prototyp einer zielgerichteten Supportivtherapie)
 - Hand-Fuss-Syndrom (HFS)
2. Periphere Polyneuropathie (PNP)
3. LV-Dysfunktion

The 5 Phases of Mucositis



Phase 2 – Signaling



Palifermin (recomb. KGF): the first targeted approach in supportive care

keratinocyte growth factor (KGF) = fibroblast growth factor (FGF 7)

↓
Ligandenbindung

Aktivierung des TK-Rezeptors → downstream signalling

↓
Downregulation von TNF α → NF- κ B

↓
Damage response/protection against mucositis

Pathophysiology of PPE

Extravasation of PLD from deeper microcapillaries (H+F)



active transport by sweat
(high number of eccrine glands)



penetration into stratum corneum



accumulation



COX 2

free radicals



inflammatory reaction

Tubulin targeted drugs

Taxanes

Vinca alkaloids

Epothilone analogues

-Ixabepilone

-Sagopilone

-Patupilone

nab-Paclitaxel

Eribulin

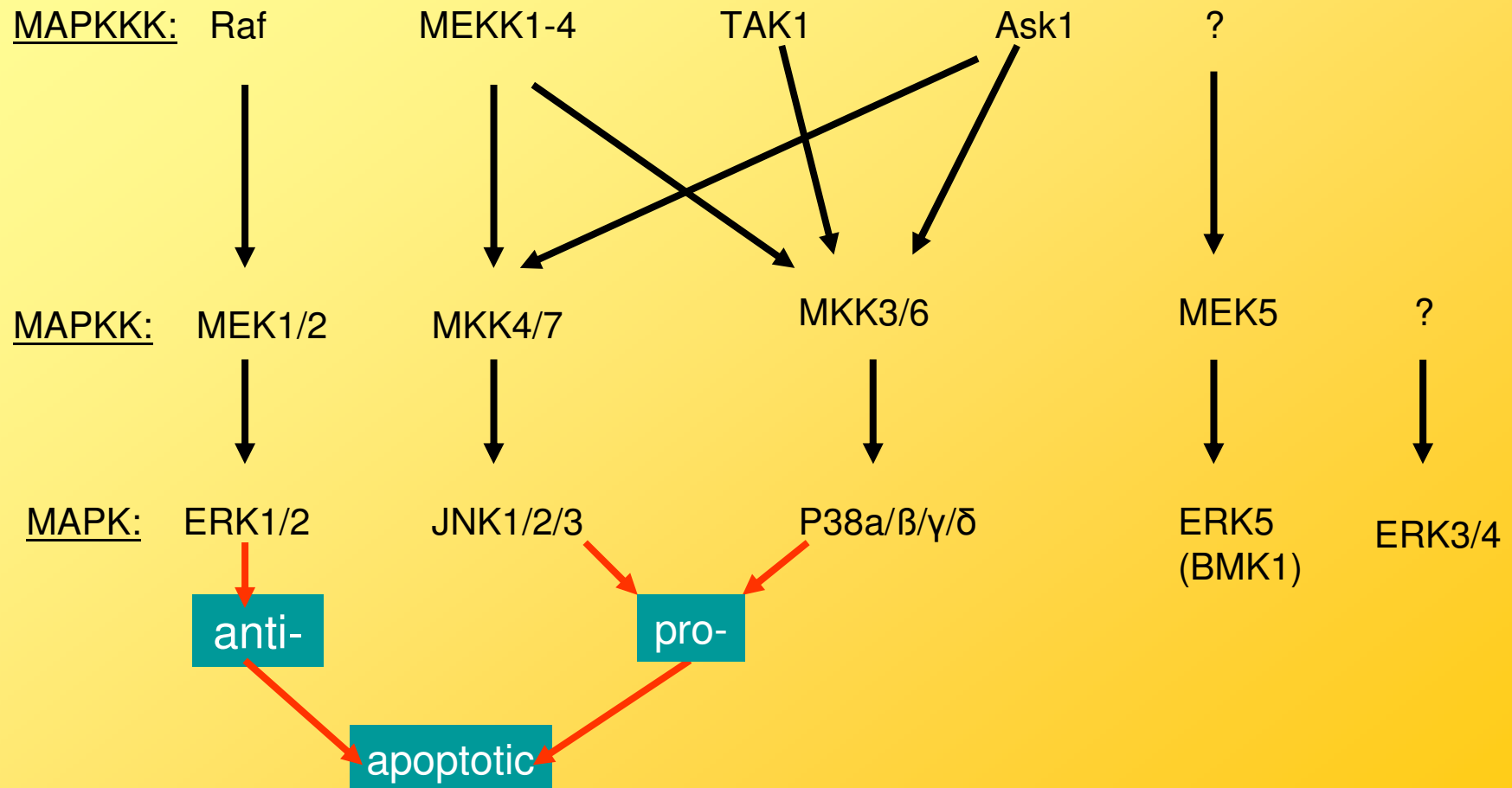
Chemotherapy-induced peripheral neuropathy (CIPN) – epigenetic aspects and therapeutic implications

- CIPN is correlated with a decrease of Nerve Growth Factor (NGF) circulating levels (Cavaletti et al., 2002)
- NGF exerts a strong trophic effects on dorsal root ganglia (DRG) neurons and serves as a protective agent for CIPN (Apfel et al., 1991 – 1999)
- Acetyl-L-Carnitin (ALC) has shown to enhance cell response to NGF and to modulate tubulin activity via histone acetylation
- ALC is a natural compound that is involved in the regulation of cellular levels of acety-CoA (Pisano et al., CCR 2003)

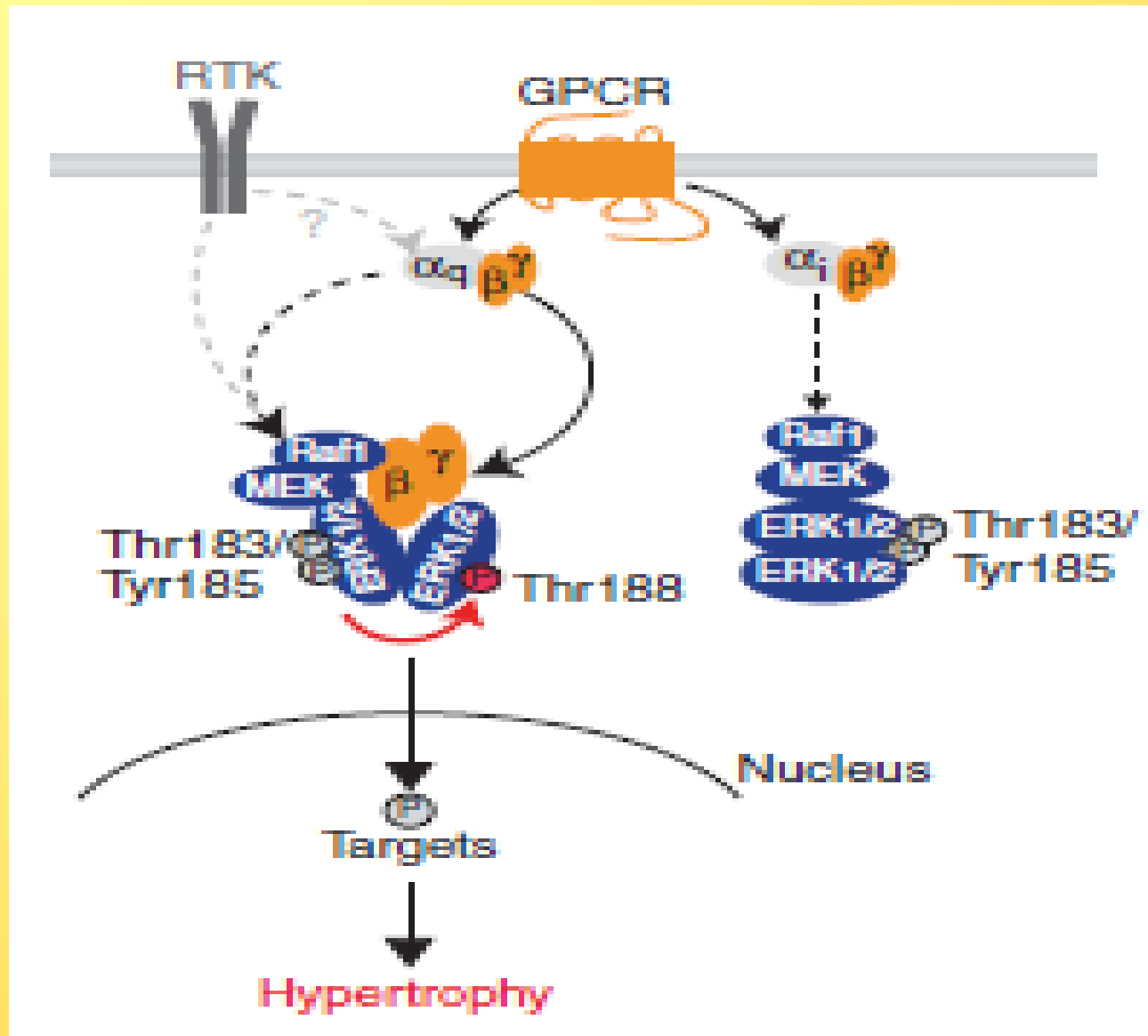
CDDP / Paclitaxel – based
neurotoxicity:
pilotstudies (Acetyl - L – Carnitine)

Reference	pts	Response	Schedule
Bianchi, Eur J Cancer 2005	25	60 % (sensory) 92 % (motor)	1 g tid (oral) for 8 weeks
Maestri, Tumori 2005	27	73 % (≥ 1 WHO grade)	1 g/ die (i.v.) ≥ 10 days

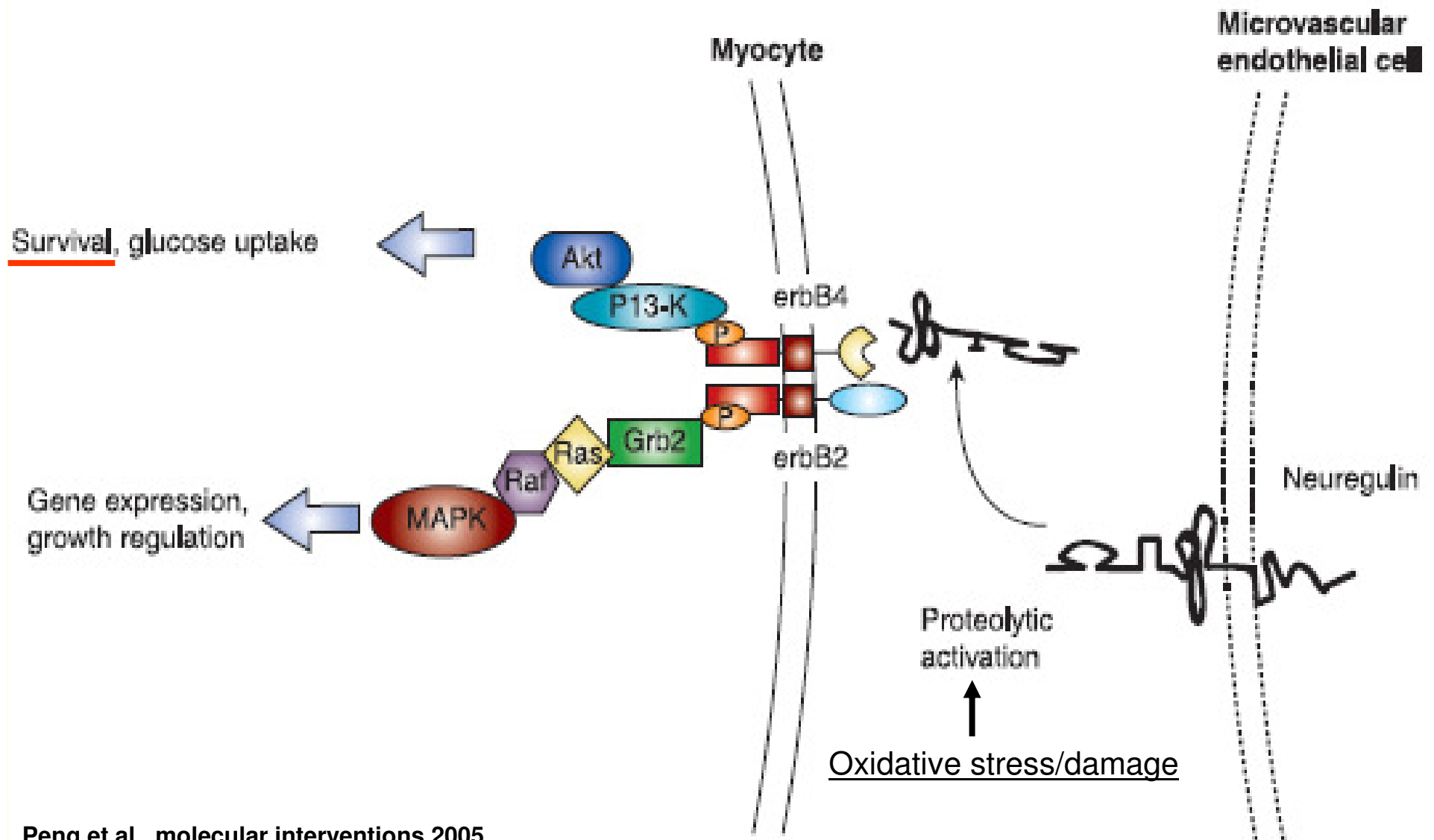
STRESS signaling pathways that modulate cardiac myocyte apoptosis



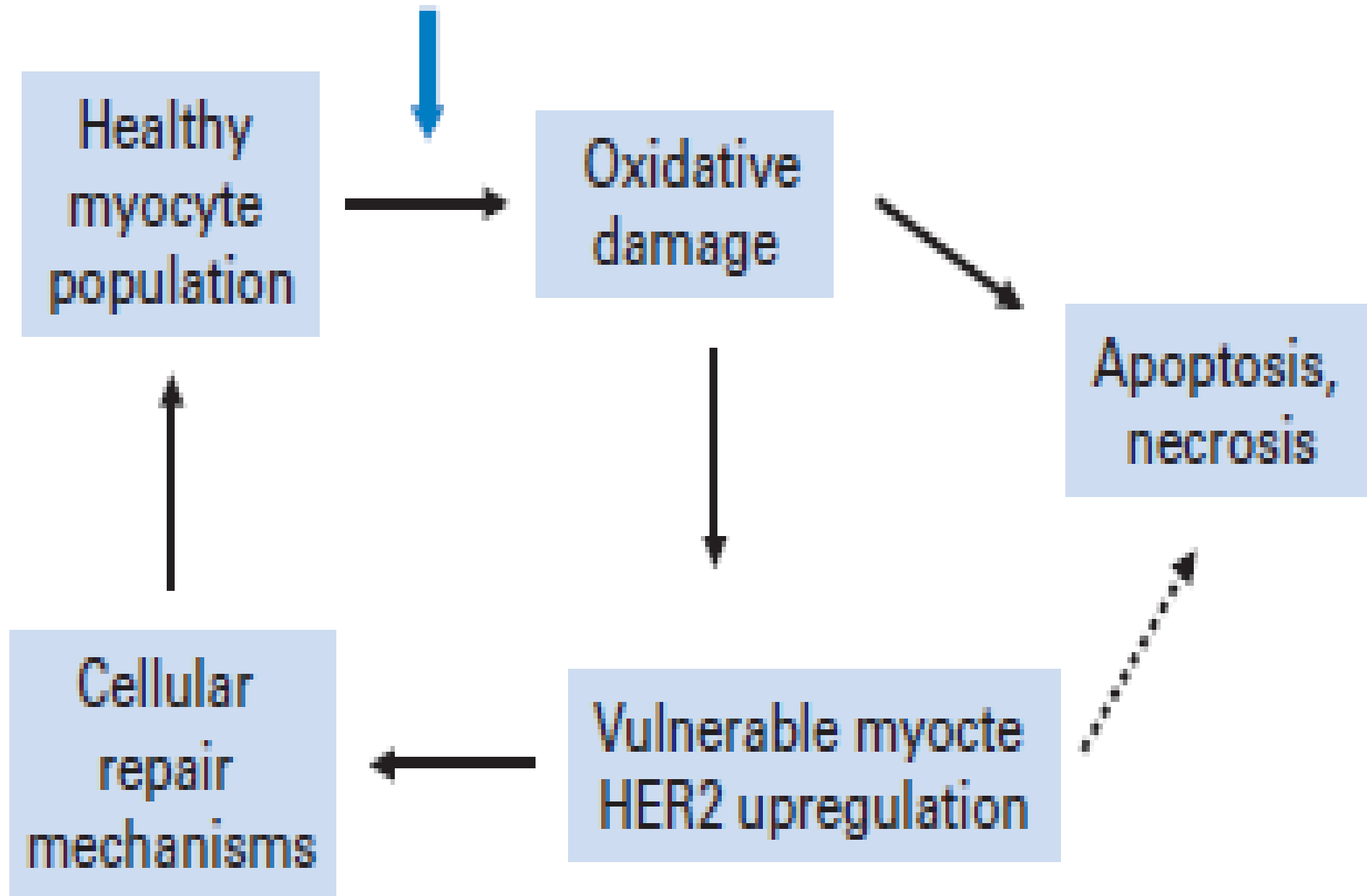
A new type of ERK1/2 autophosphorylation causes cardiac hypertrophy



The Cardiotoxicology of Anthracycline Chemotherapeutics: TRANSLATING MOLECULAR MECHANISM INTO PREVENTATIVE MEDICINE



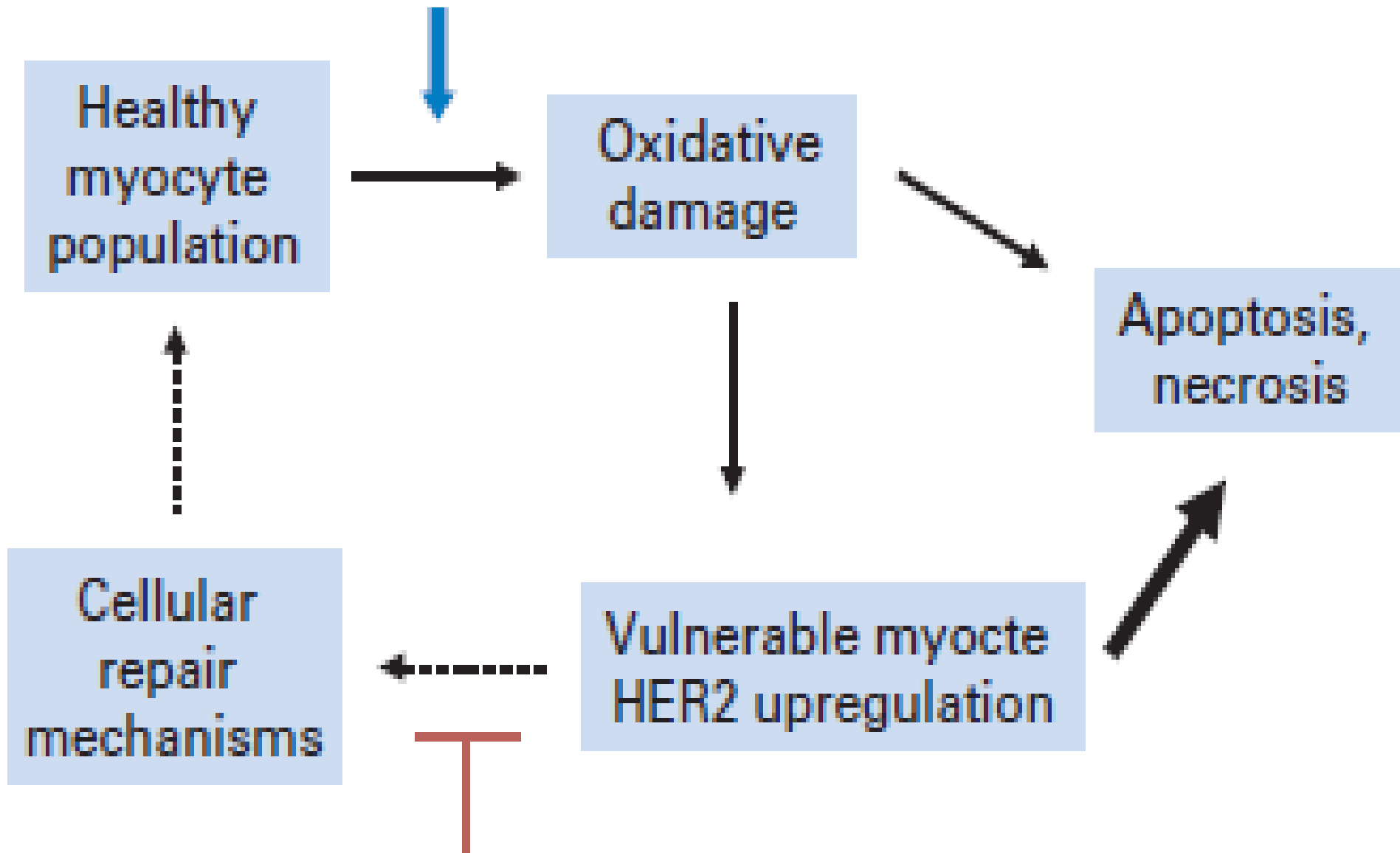
Anthracycline



Troponin I (TNI) provides insight into cardiotoxicity and the anthracycline-trastuzumab interaction

- Troponin I (TNI) seems to be an early predictor of major adverse cardiac events
- patients with elevated TNI serum levels early after anthracycline (A) preexposure were more likely to develop irreversible(!) trastuzumab (T) -induced cardiotoxicity
- further data have to clarify: Is TNI a helpful marker to select patients with an increased cardiac risk associated with a sequential A-T regimen?

Anthracycline



Trastuzumab