REGULATION OF VERTEBRATE NEURON DEATH IN DEVELOPMENT AND NEURODEGENERATION:

ROLE OF TRANSCRIPTION

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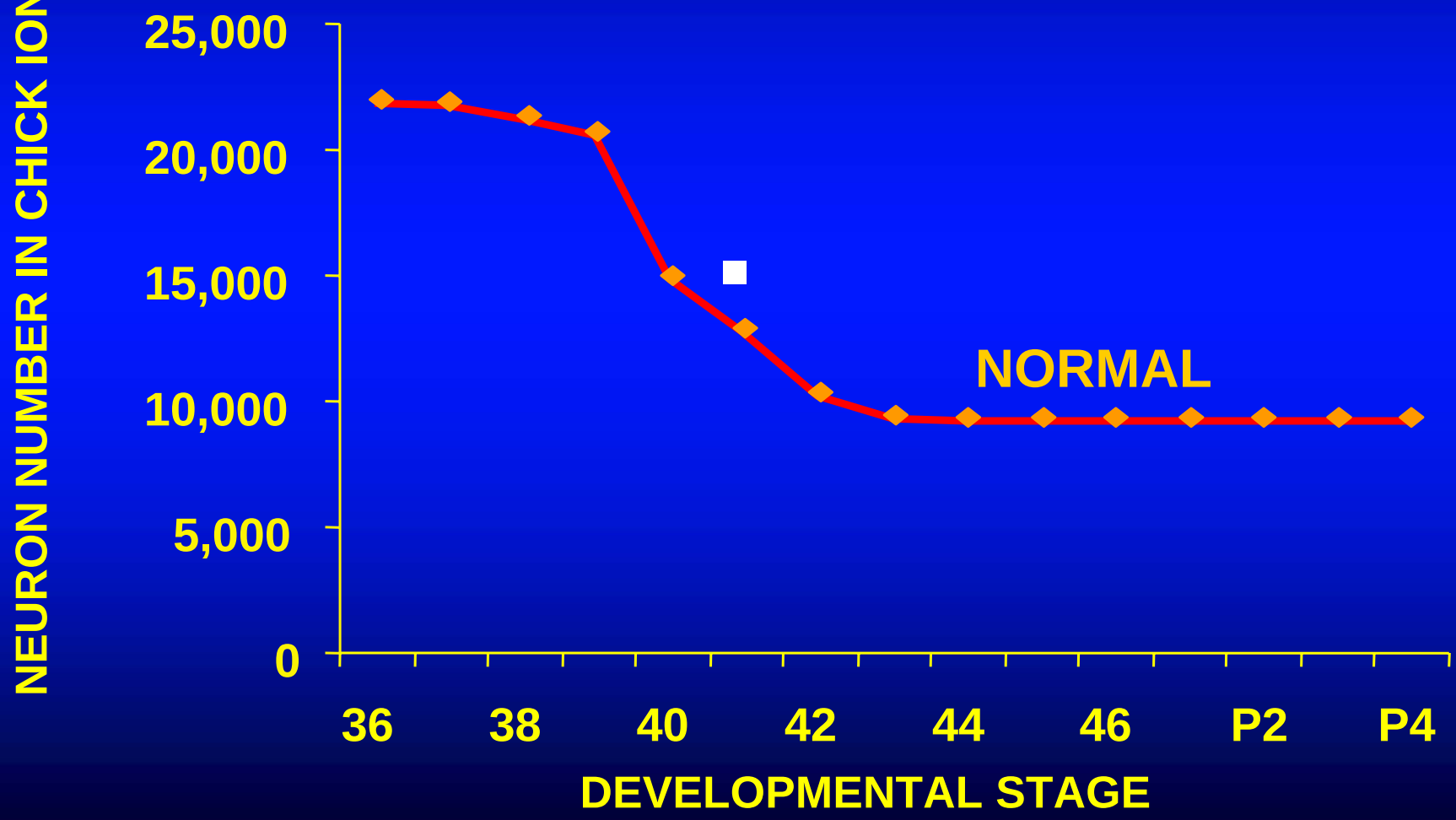
MASSIVE LOSS OF NEURONS DURING VERTEBRATE DEVELOPMENT HAS BEEN LONG KNOWN

- BEARD (1889) - LOSS OF NEURONAL POPULATIONS IN FISH (ROHON-BEARD NEURONS)

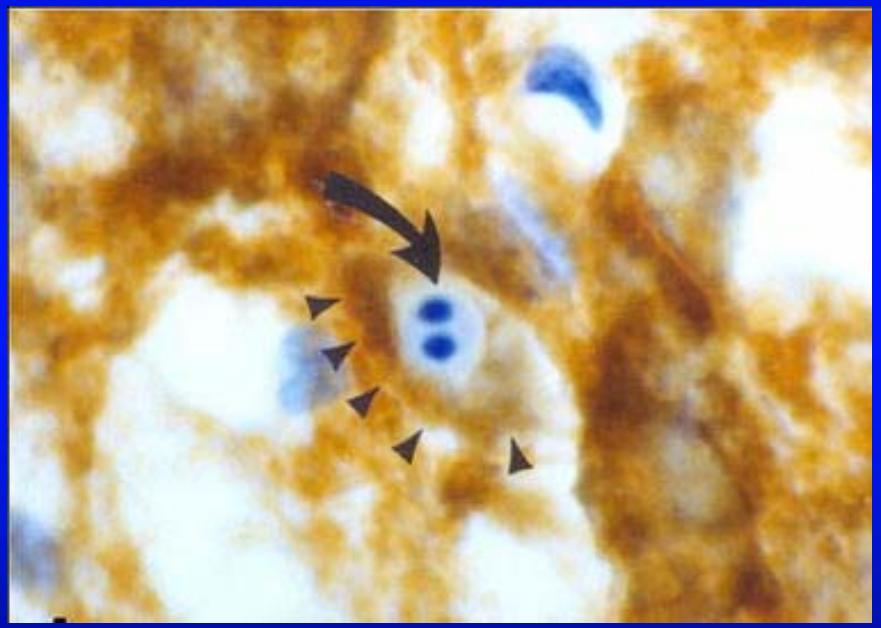
- COLLIN (1906) - DEATH OF MANY SENSORY AND MOTOR NEURONS IN THE CHICK EMBRYO

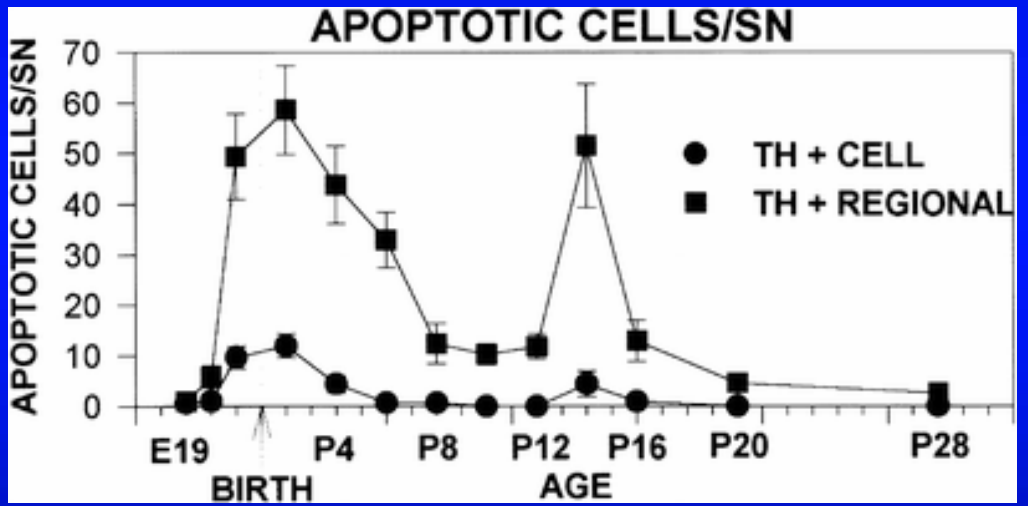
APPROXIMATELY 50% OF POST-MITOTIC NEURONS DIE DURING NORMAL DEVELOPMENT



Clarke, Rogers & Cowan J. Comp. Neurol. 167: 125 (1976)

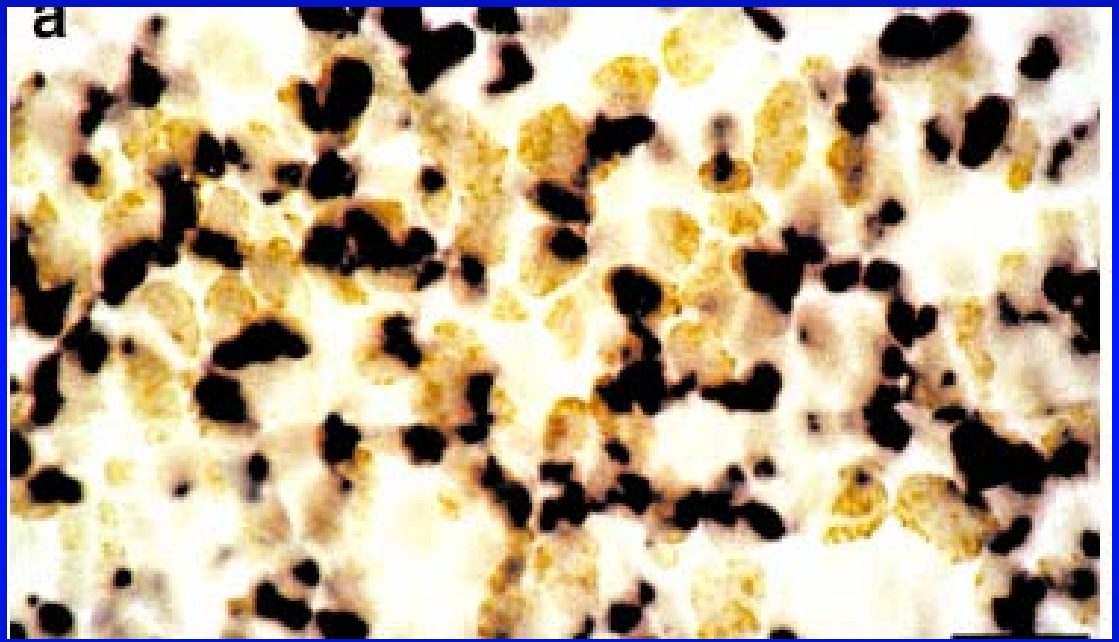
APOPTOTIC NEURONAL DEATH IN DEVELOPING SUBSTANTIA NIGRA





R. Burke Cell Tiss Res (2004)

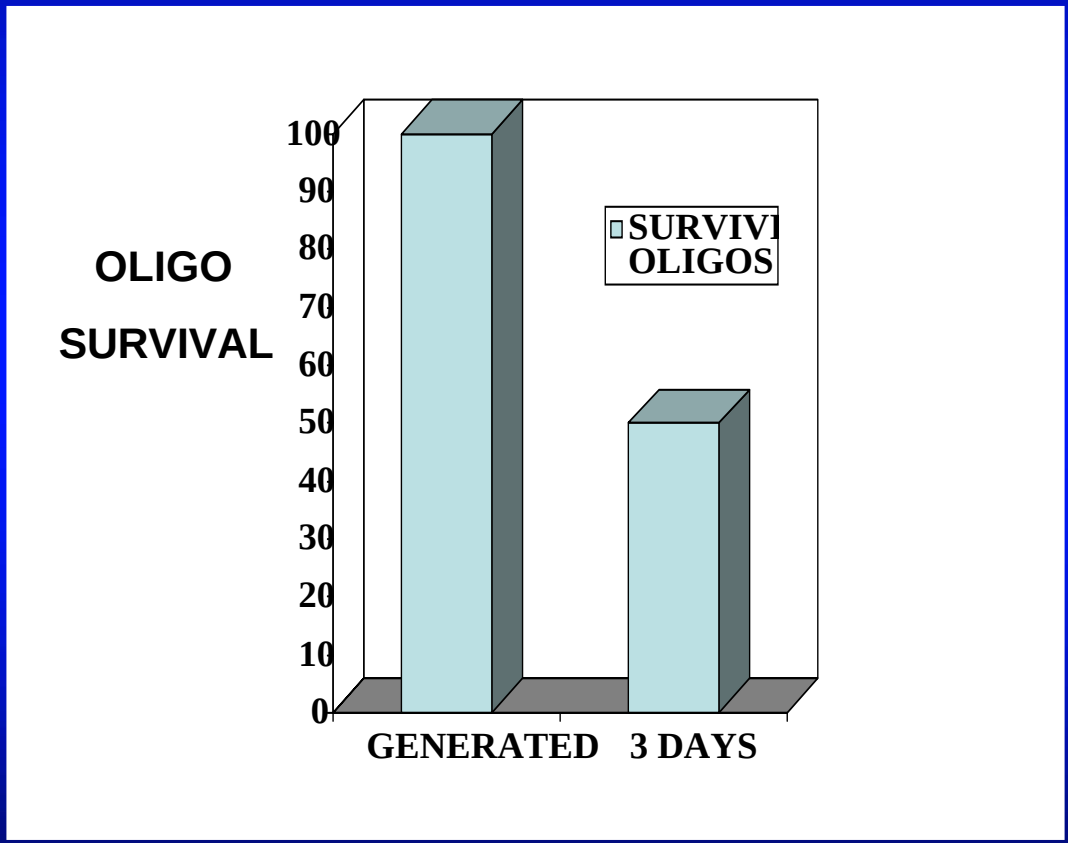
DEATH OF PROLIFERATING VZ CELLS IN E14 MOUSE CEREBRUM



Tan = BrDU; Purple = ISEL/dying

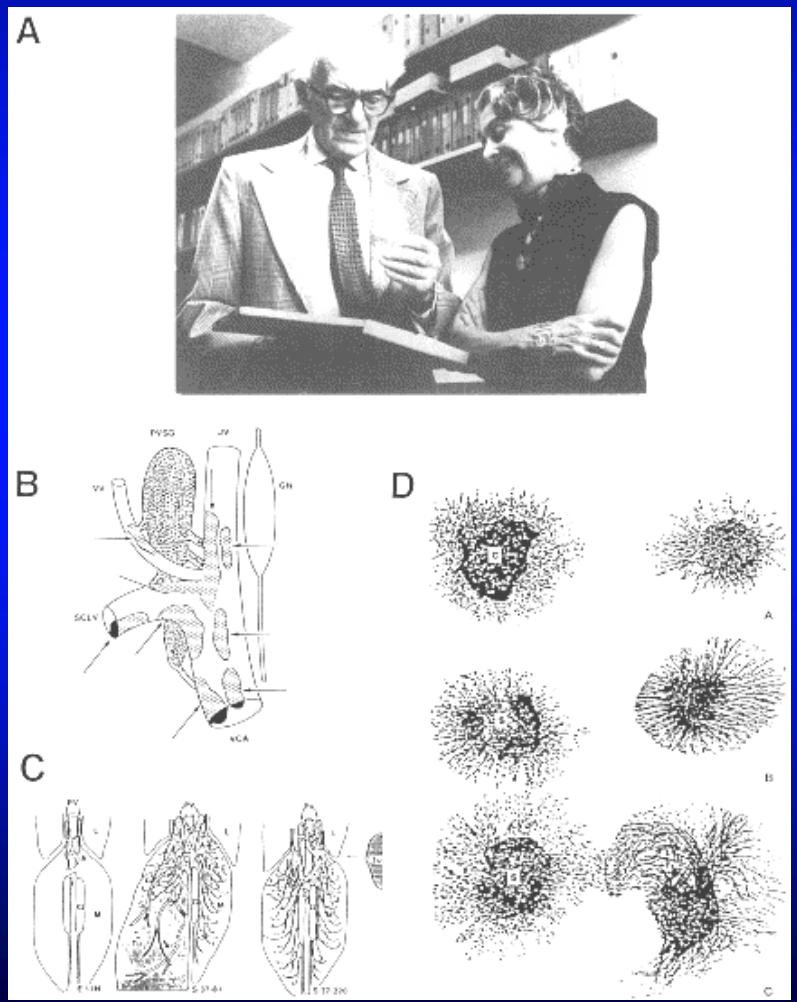
Blaschke et al J Comp Neurol 1998

REGULATED DEVELOPMENTAL DEATH OF OLIGODENDROCYTES

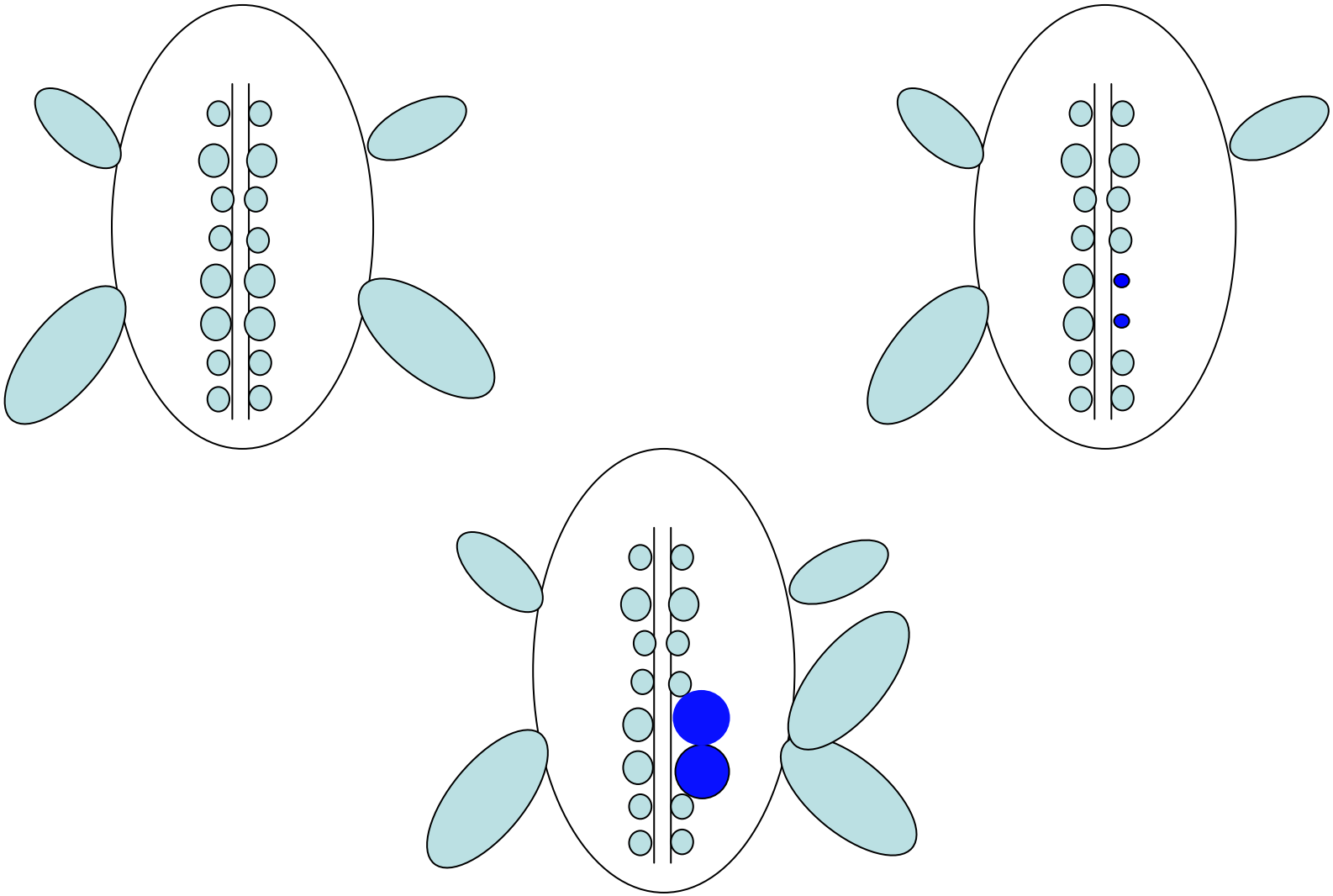


FROM Barres and Raff, Journal of Cell Biology, Volume 147, Number 6, December 13, 1999 1123-1128

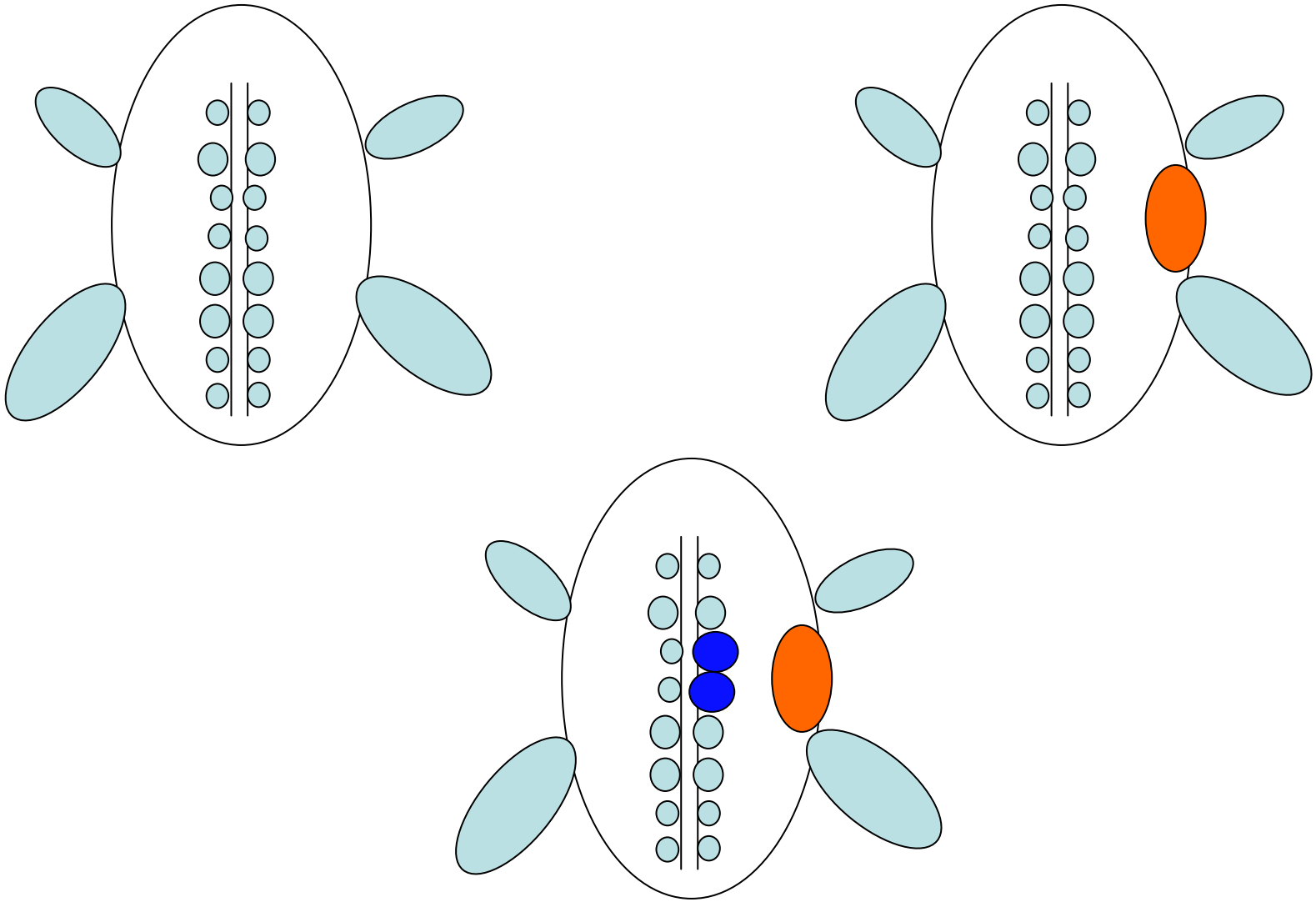
VIKTOR HAMBURGER AND RITA LEVI-MONTALCINI AND THE BEGINNING OF THE NEUROTROPHIC THEORY OF DEVELOPMENTAL NEURON DEATH IN VERTEBRATES



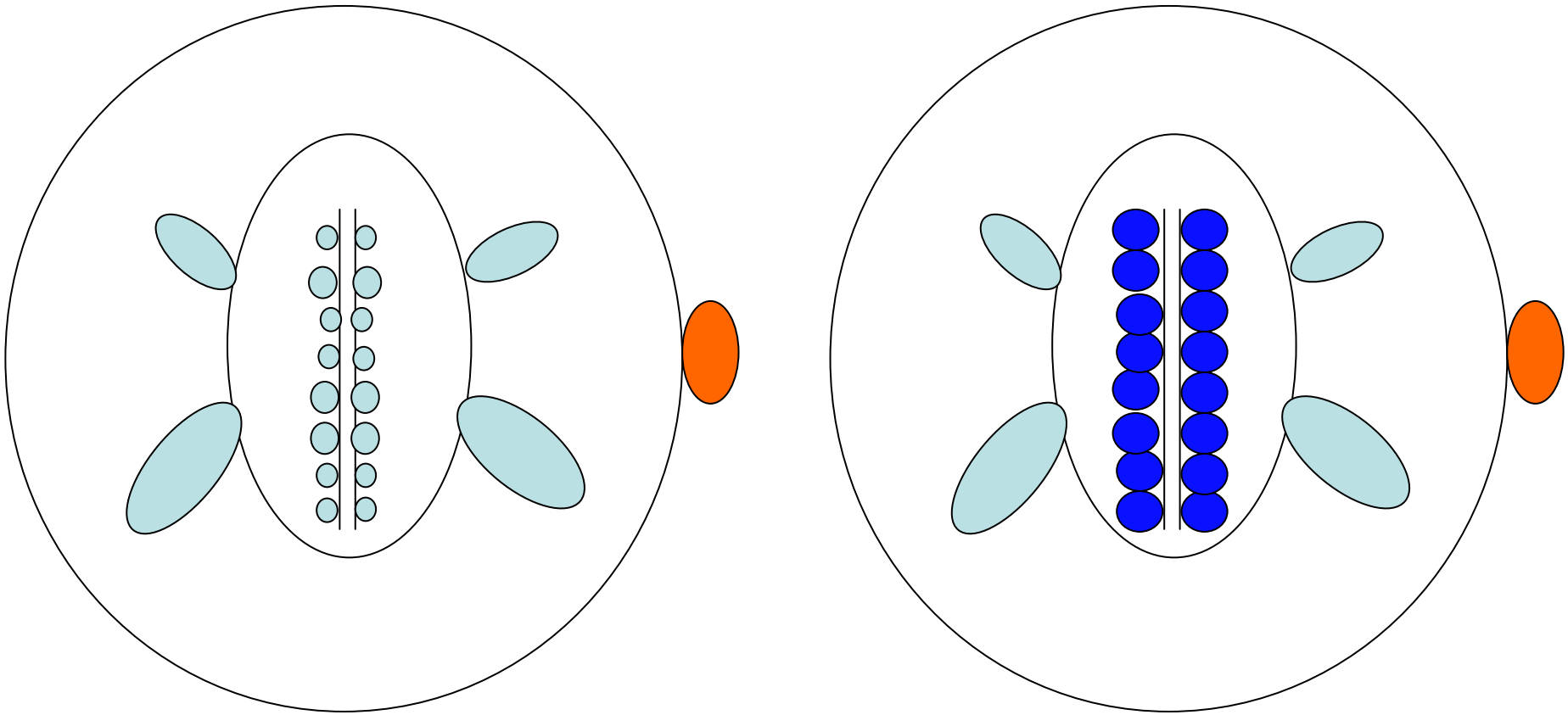
VICTOR HAMBURGER AND THE NOTION THAT PERIPHERAL TARGETS REGULATE NEURONAL CELL DEATH



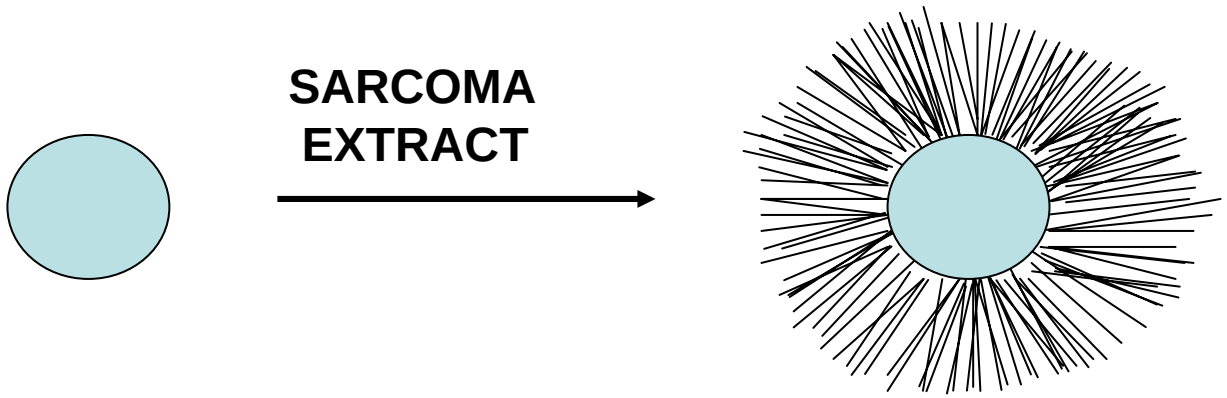
ELMER BEUKER AND THE EFFECTS OF SARCOMA 180 ON NEURONAL SURVIVAL



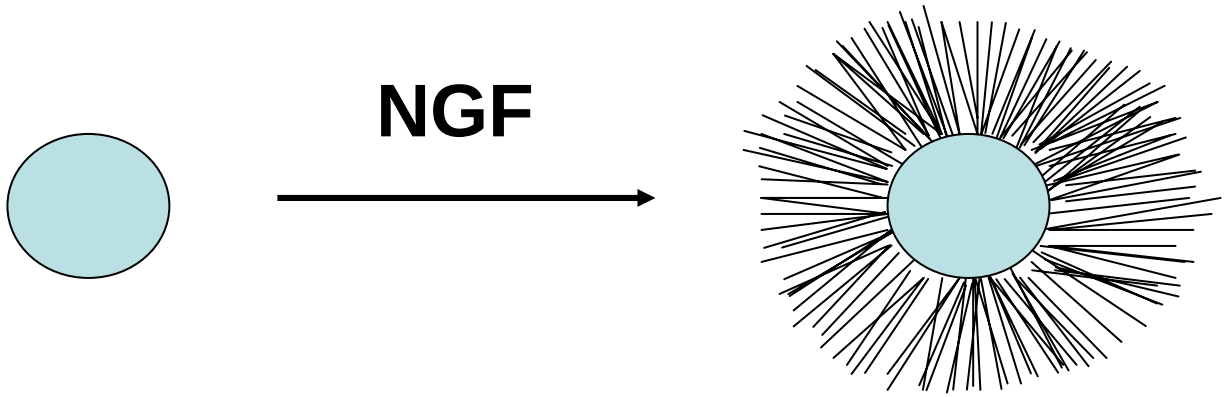
LEVI-MONTALCINI AND THE DISCOVERY OF A DIFFUSIBLE SURVIVAL-PROMOTING ACTIVITY



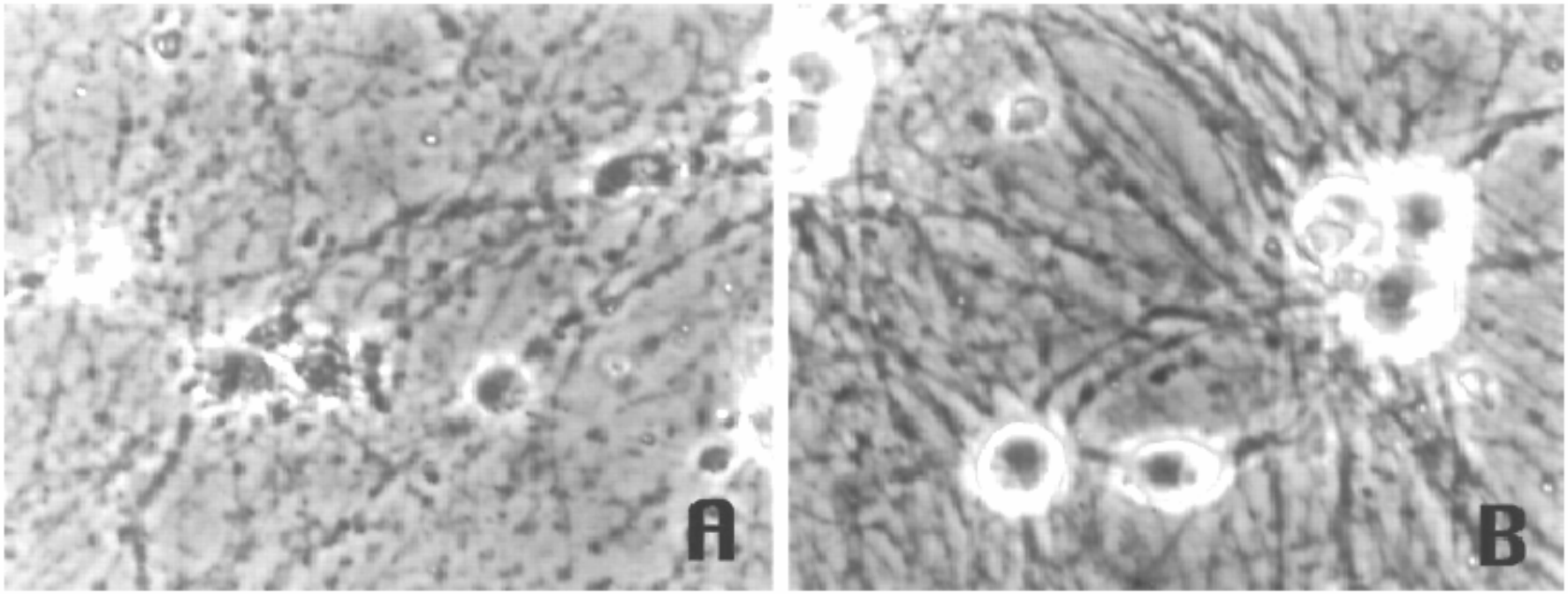
LEVI-MONTALCINI AND HAMBURGER DISCOVER A SOLUBLE NERVE-GROWTH PROMOTING ACTIVITY (NGF) IN EXTRACTS OF SARCOMA 180



PURIFIED NGF PROMOTES NEURON SURVIVAL IN VITRO



NGF PROMOTES SYMPATHETIC & SENSORY NEURON SURVIVAL IN VITRO



-NGF

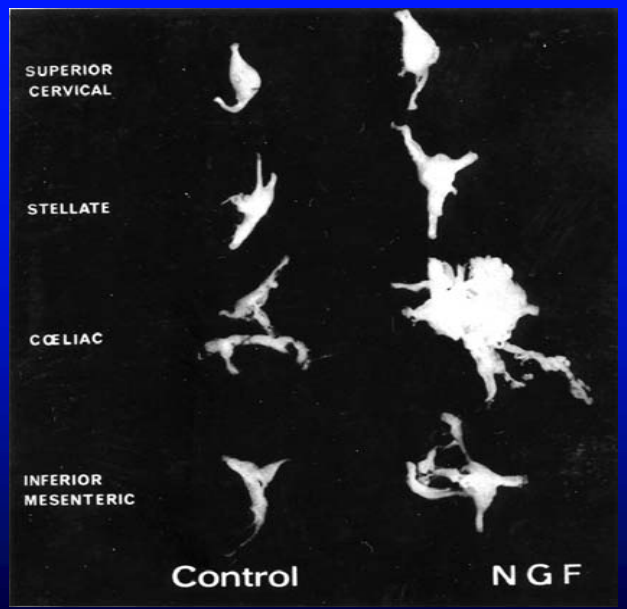
+NGF

EVIDENCE FOR THE ROLE OF GROWTH FACTORS IN REGULATING DEVELOPMENTAL NEURONAL DEATH IN VIVO

1. INJECTION OF NEW BORN MICE WITH NGF ANTIBODIES YIELDS "IMMUNOSYMPATHECTOMY"

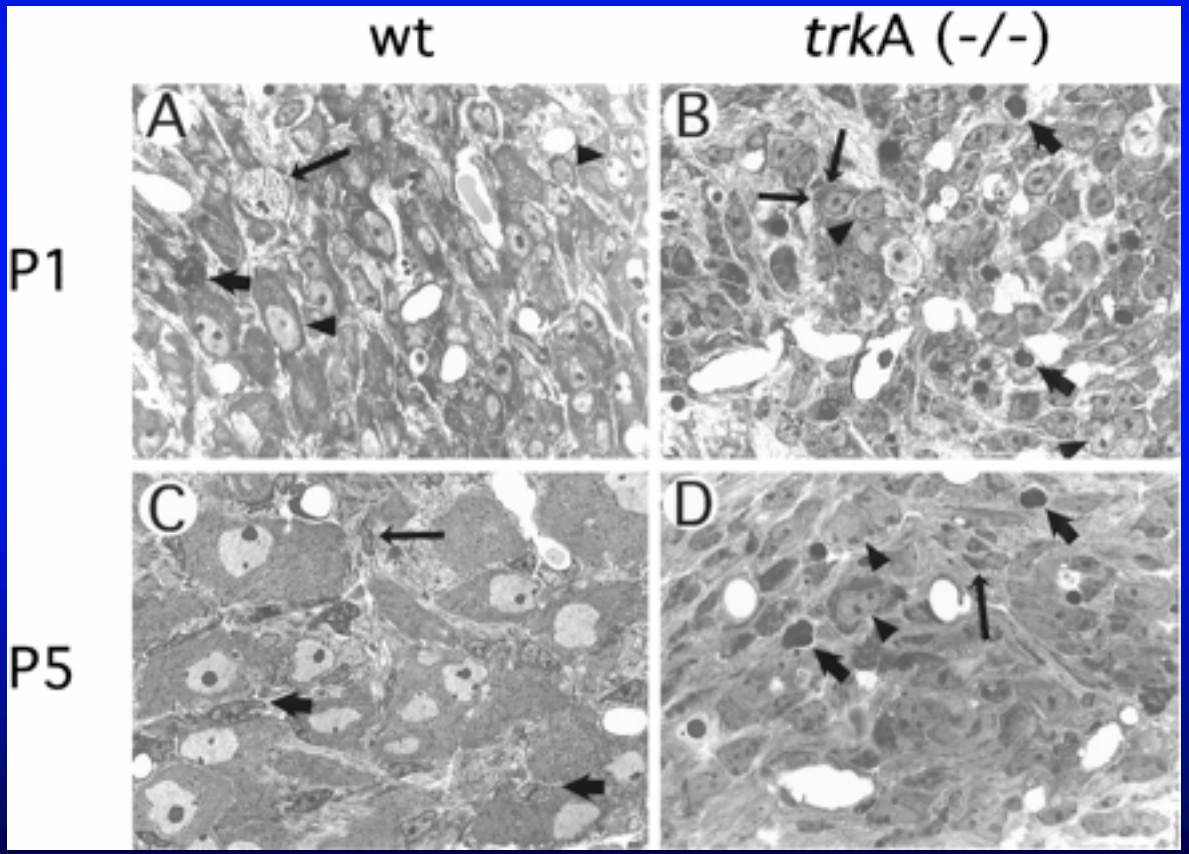
   MOTHERS AUTOIMMUNIZED AGAINST NGF PRODUCE OFFSPRING WITH MANY FEWER DORSAL ROOT GANGLIONIC NEURONS

2. SUPPLY OF EXOGENOUS NGF BLOCKS DEVELOPMENTAL CELL DEATH OF SYMPATHETIC NEURONS



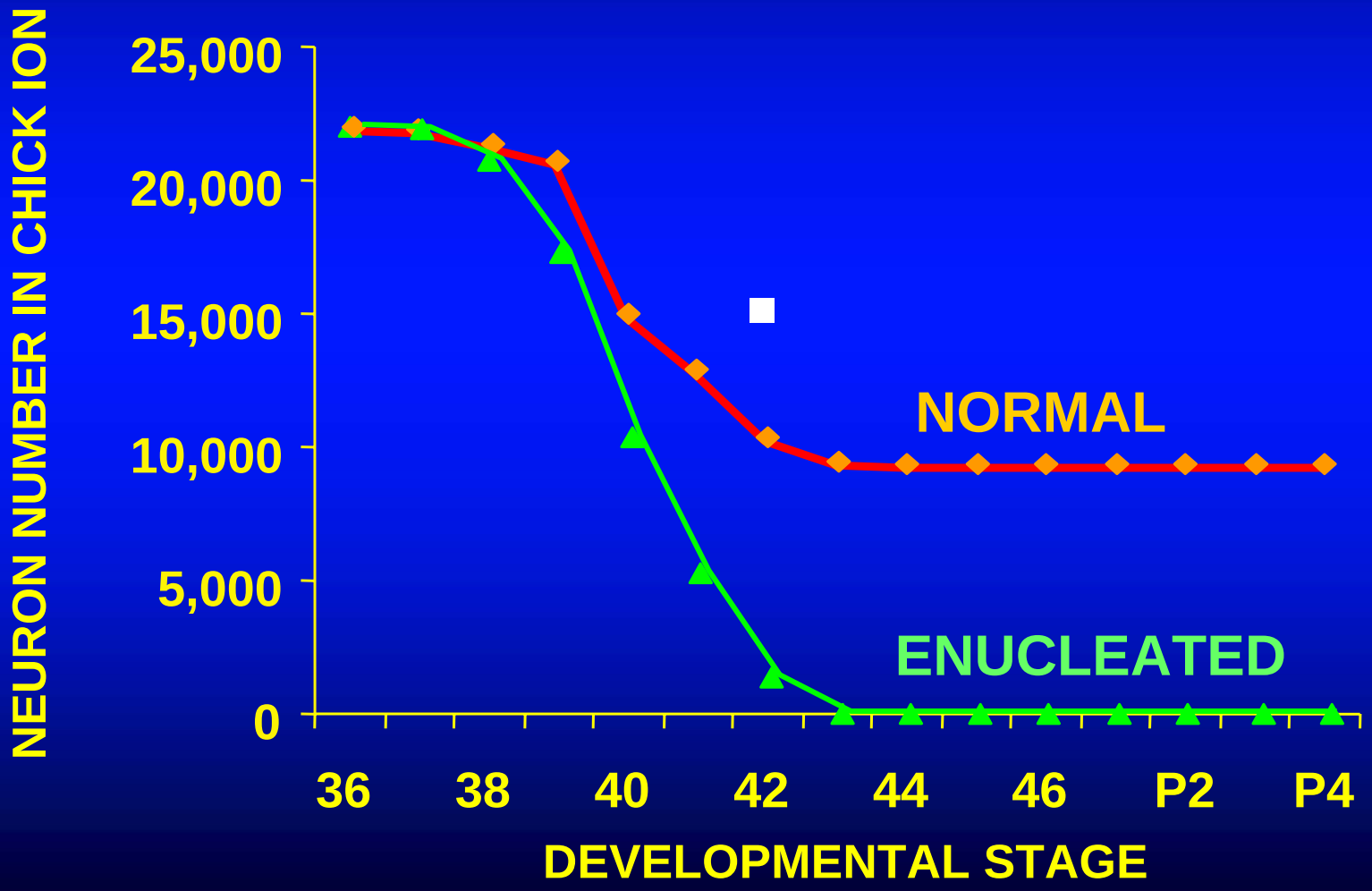
EVIDENCE FOR THE ROLE OF GROWTH FACTORS IN REGULATING DEVELOPMENTAL NEURONAL DEATH IN VIVO

MICE NULL FOR NGF OR ITS RECEPTORS SHOW EXCESS NEURONAL DEATH.



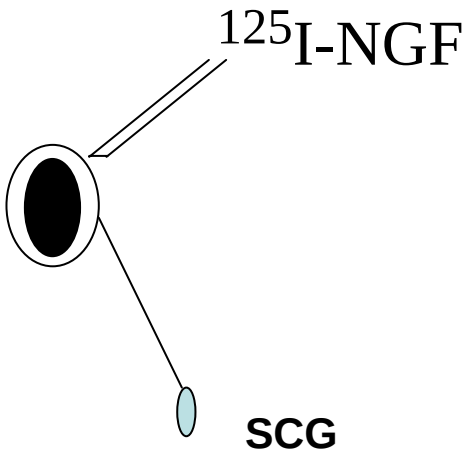
Fagin et al. J Neurosci (1996)

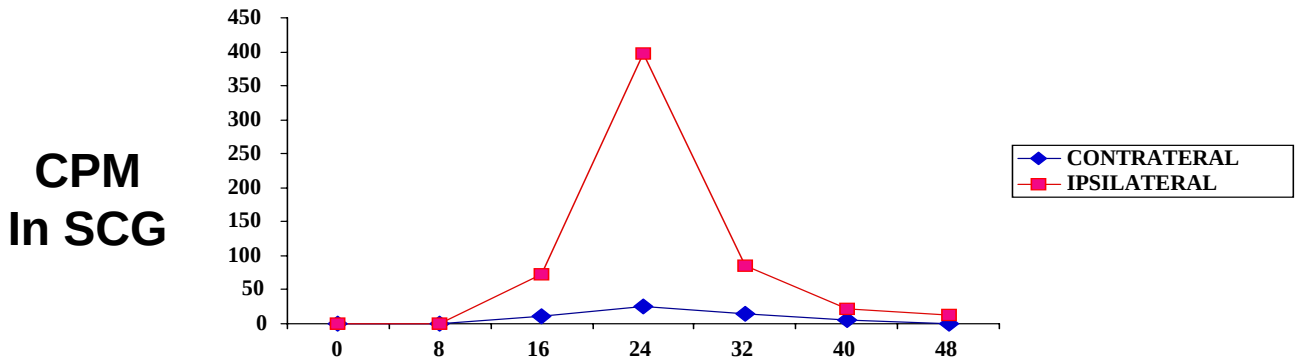
NORMAL DEVELOPMENTAL NEURONAL DEATH OCCURS AND IS REGULATED BY TARGET DERIVED TROPHIC FACTORS



Clarke, Rogers & Cowan J. Comp. Neurol. 167: 125 (1976)

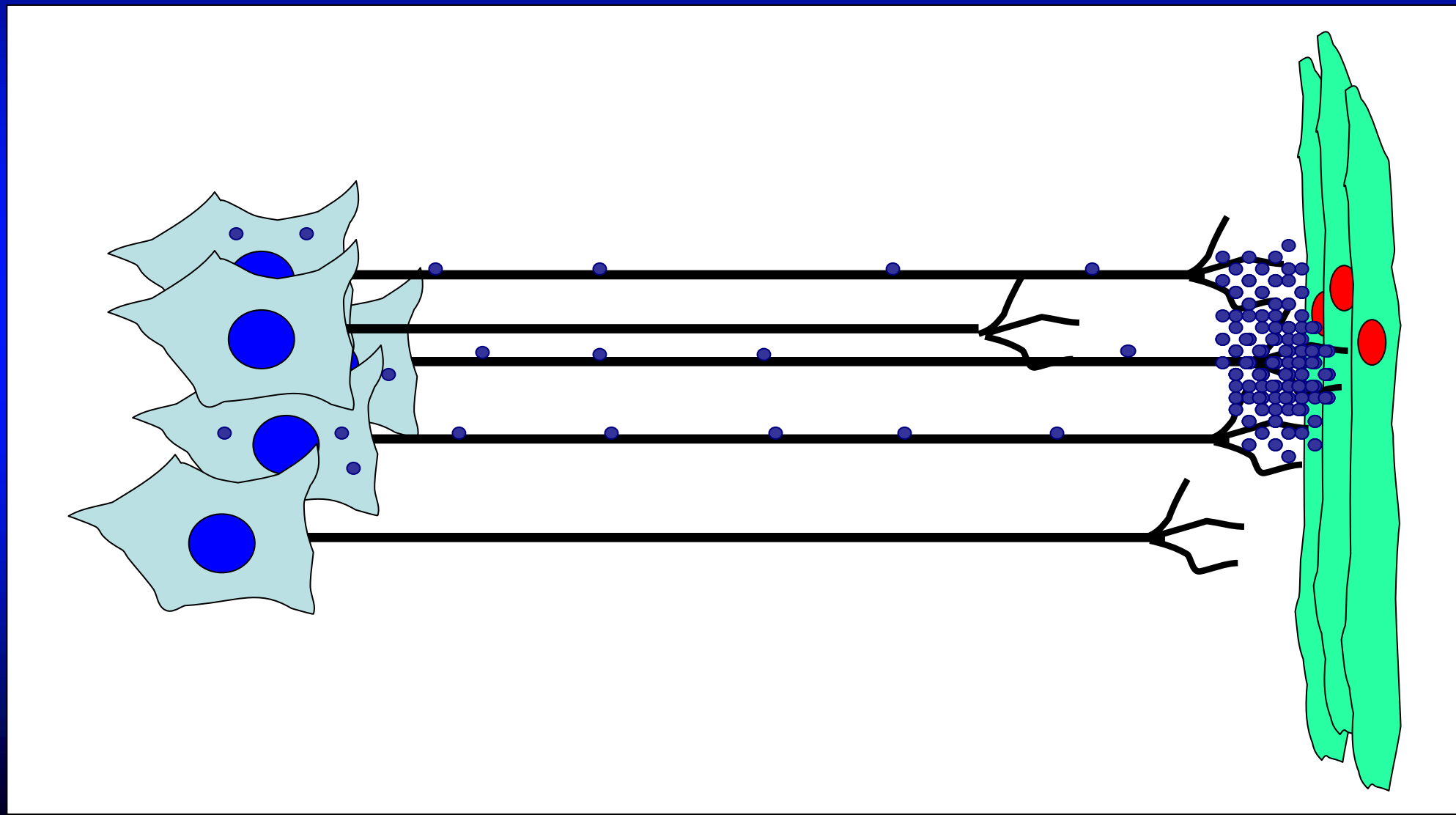
RETROGRADE TRANSPORT OF NEUROTROPHINS FROM TARGETS



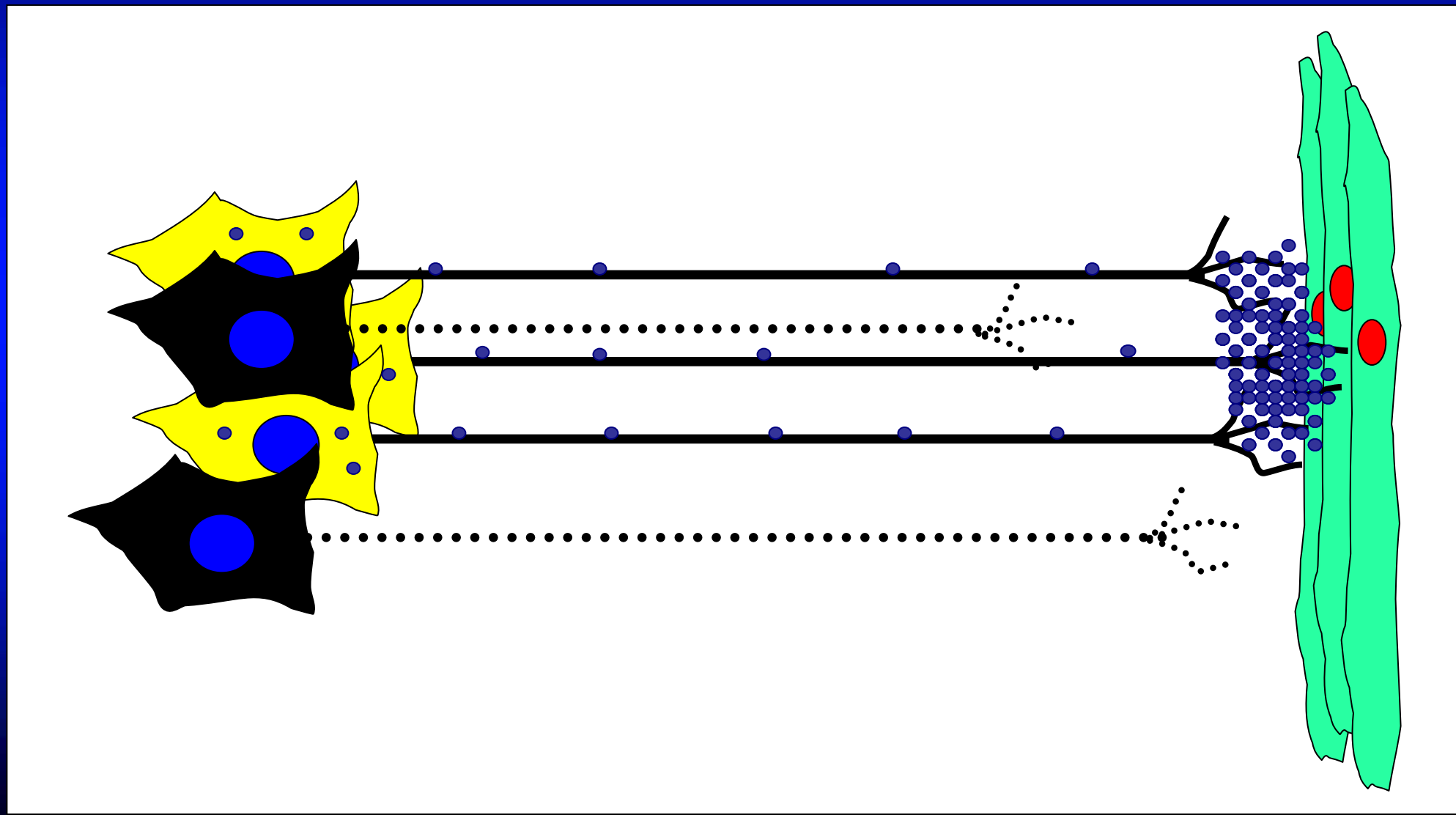


Ian Hendry & Hans Thoenen

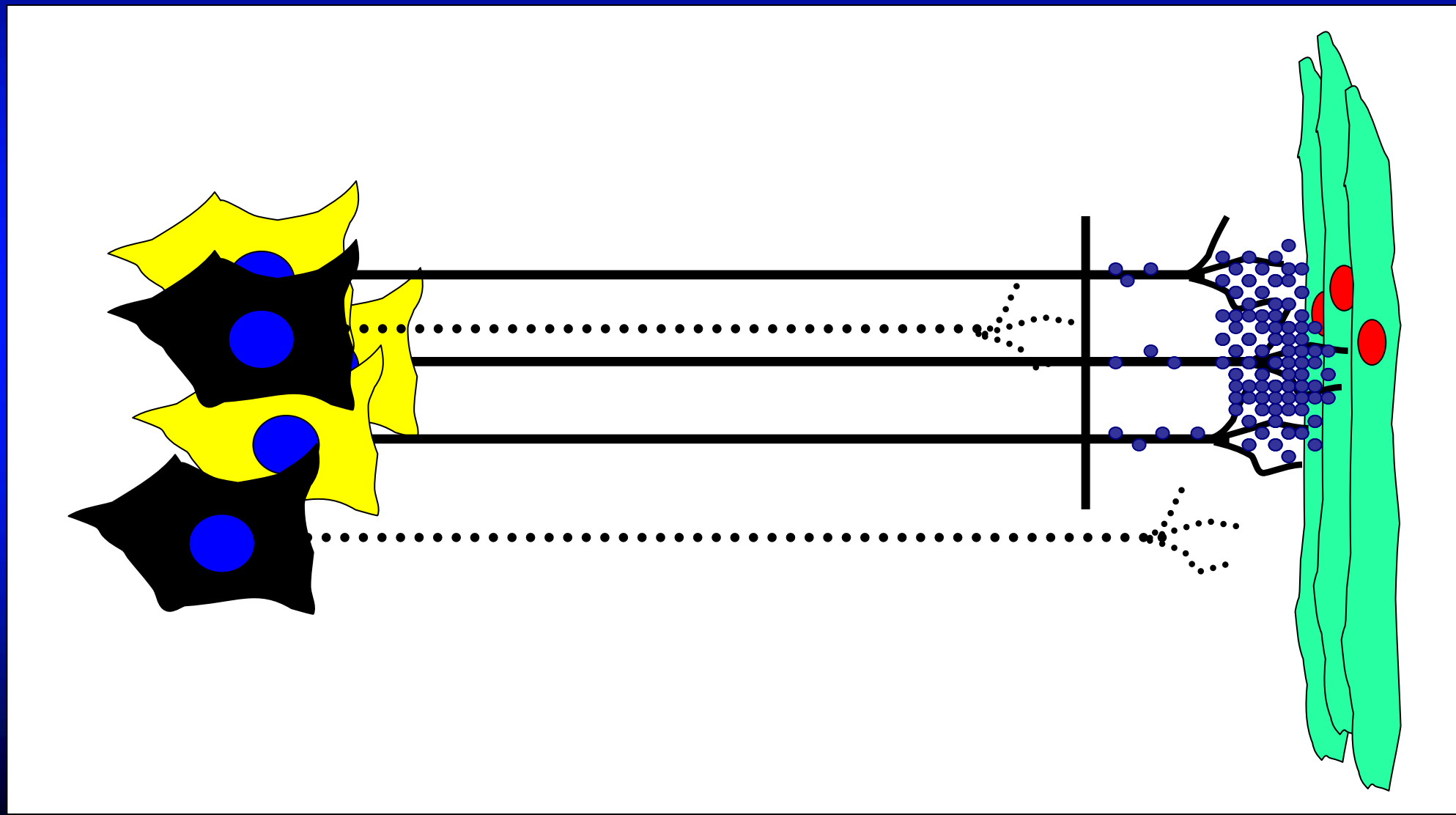
NEURONAL SURVIVAL AS REGULATED BY COMPETITION FOR TARGET-SUPPLIED TROPHIC FACTOR



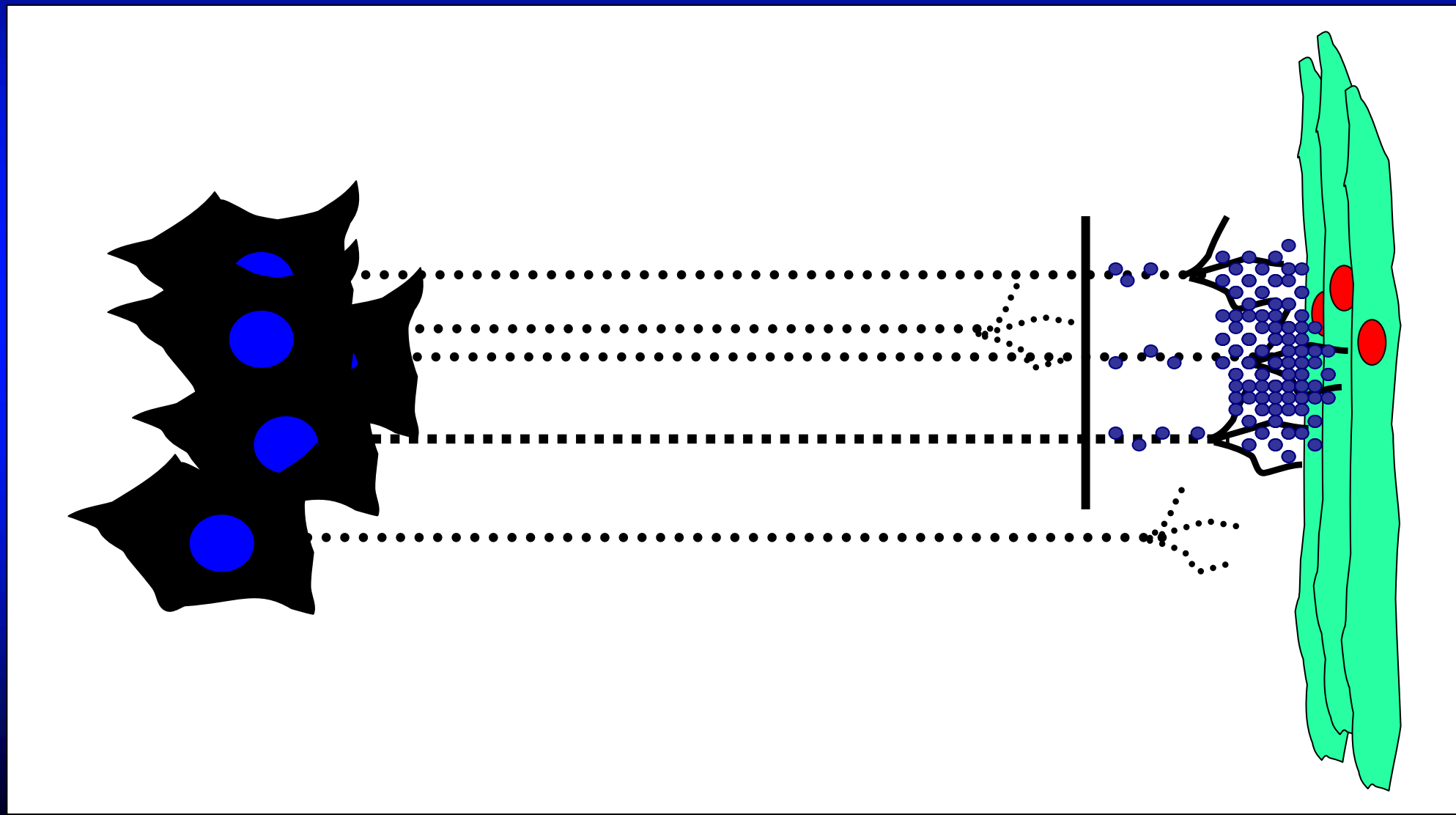
NEURONAL SURVIVAL AS REGULATED BY COMPETITION FOR TARGET-SUPPLIED TROPHIC FACTOR



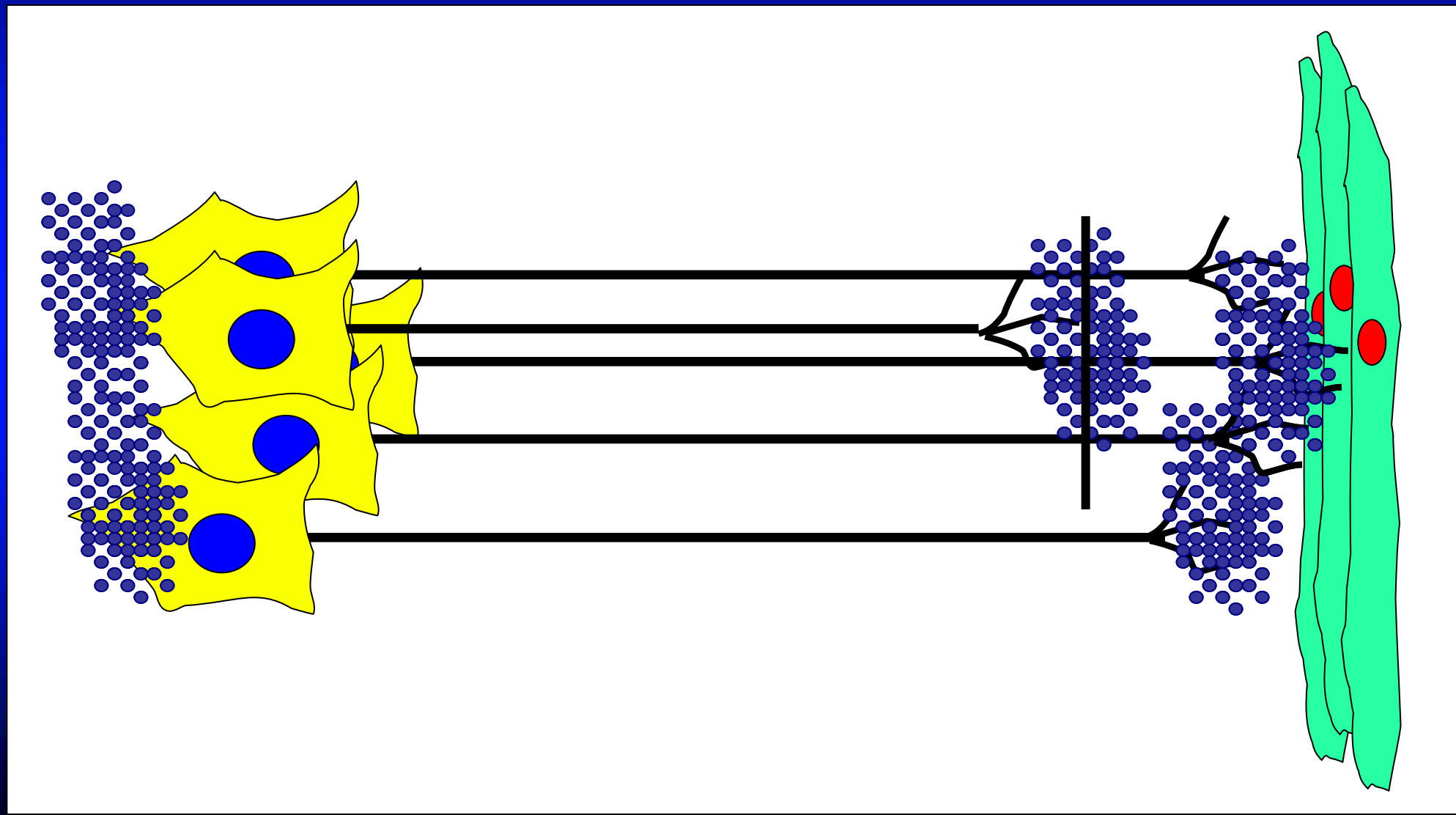
NEURONAL SURVIVAL AS REGULATED BY COMPETITION FOR TARGET-SUPPLIED TROPHIC FACTOR



NEURONAL SURVIVAL AS REGULATED BY COMPETITION FOR TARGET-SUPPLIED TROPHIC FACTOR



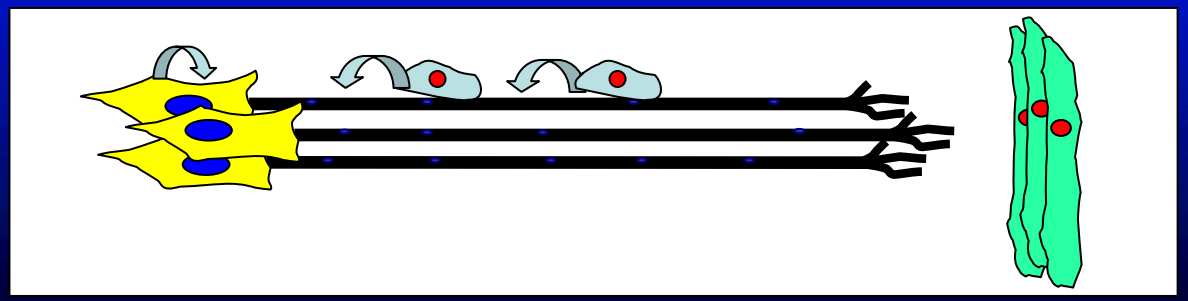
NEURONAL SURVIVAL AS REGULATED BY COMPETITION FOR TARGET-SUPPLIED TROPHIC FACTOR



ALL TROPHIC SUPPORT DURING DEVELOPMENT IS NOT NECESSARILY TARGET DERIVED - WHAT KEEPS NEURONS ALIVE BEFORE THEY INTERACT WITH THEIR TARGETS?

AUTOCRINE LOOPS -NEURONS CAN MAKE THEIR OWN NEUROTROPHIC FACTORS (CORTICAL NEURONS; BDNF)

TISSUE EN ROUTE TO TARGET MAY PROVIDE TROPHIC FACTORS (SUCH AS NT3 AND BDNF)



GROWTH FACTORS THAT CAN MAINTAIN SURVIVAL OF SELECT NEURONAL POPULATIONS

NEUROTROPHINS
- NGF
- BDNF
- NT3
- NT4/5

EGF FAMILY
- EGF
- TGFα
- NEUREGULINS

FGF FAMILY

INSULIN & IGFs

TGFβ SUPERFAMILY
- TGFβ
- BMPs
- GDNF
- ARTEMIN
- NURTURIN
- PERSEPHIN

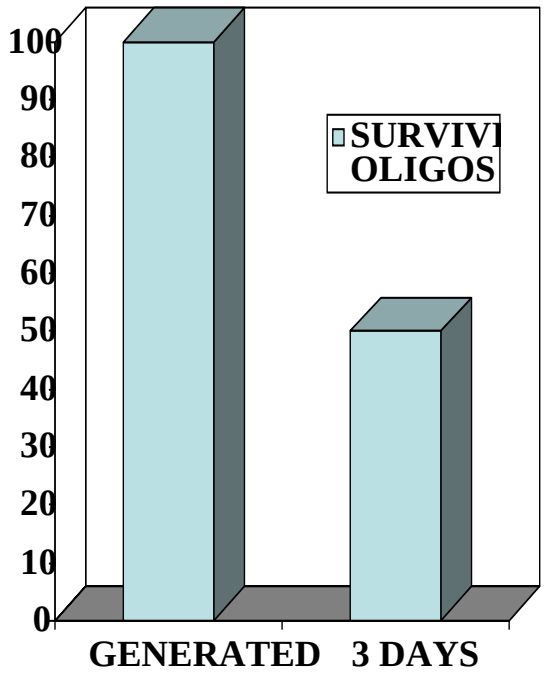
CYTOKINES
- CNTF
- LIF
- INTERLEUKINS

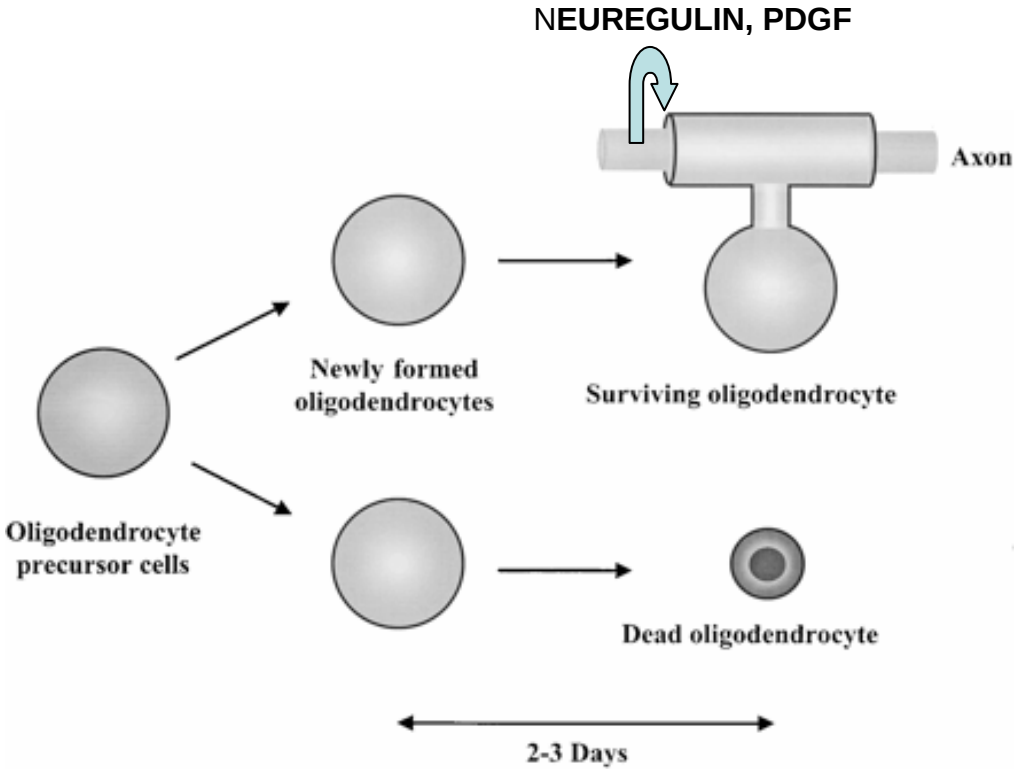
PDGF

HGF FAMILY
- HGF
- MSP

NEUROPEPTIDES
- PACAP
- VIP

REGULATED DEVELOPMENTAL DEATH OF OLIGODENDROCYTES



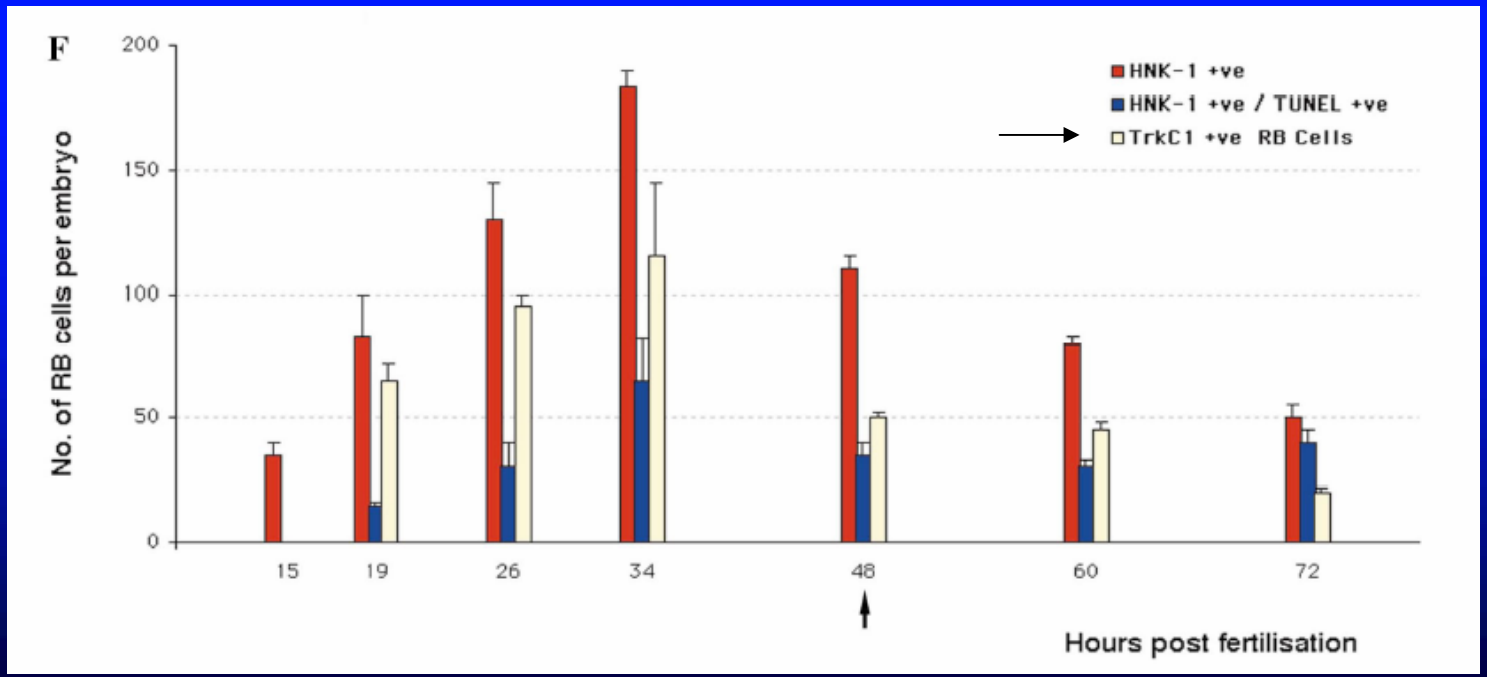


FROM Barres and Raff, Journal of Cell Biology, Volume 147, Number 6, December 13, 1999 1123-1128

WHY DOES CELL DEATH OCCUR IN VERTEBRATE NEURODEVELOPMENT?

REMOVAL OF NEURONS WITH TRANSIENT FUNCTIONS

ROHON-BEARD CELLS - LOSS IN ZEBRA FISH

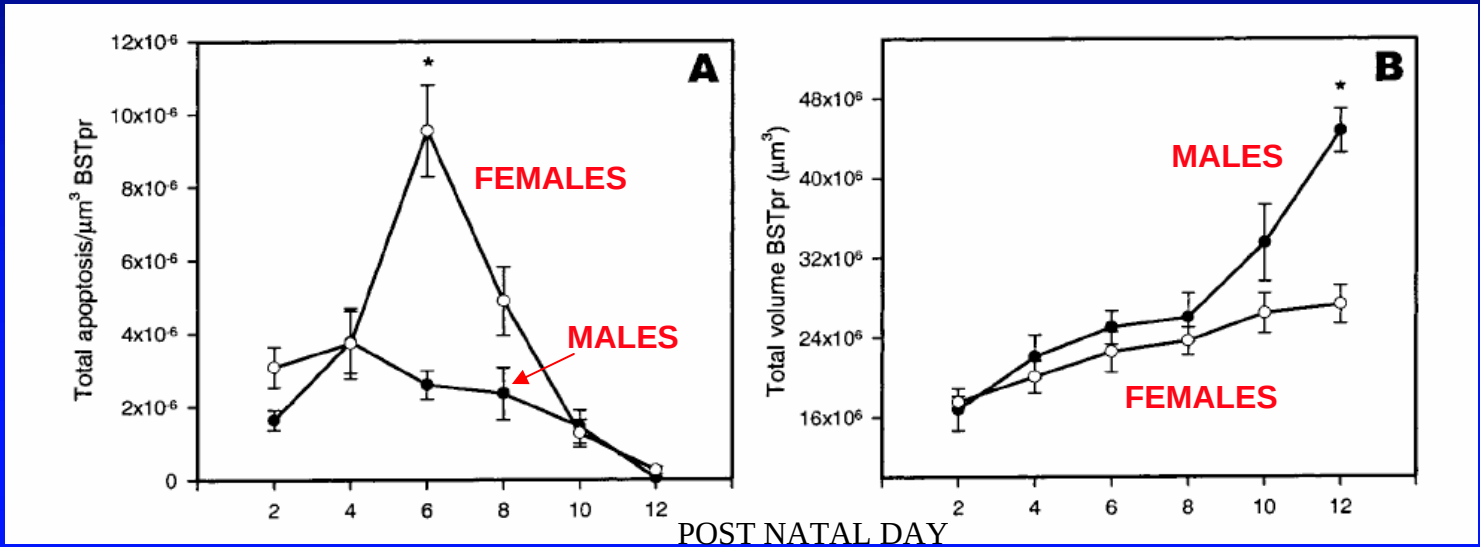


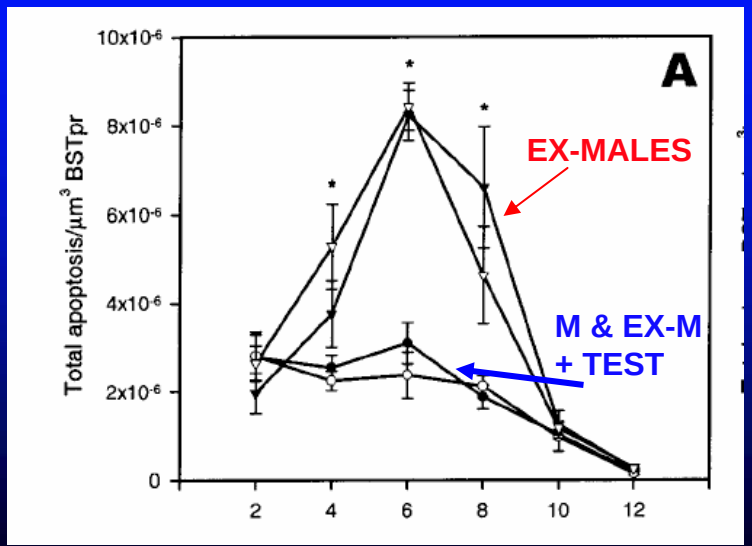
Williams et al. Dev Biol (2000)

WHY DOES CELL DEATH OCCUR IN VERTEBRATE NEURODEVELOPMENT?

CREATION OF SEXUALLY DIMORPHIC STRUCTURES

SEXUALLY DIMORPHIC NEURON DEATH IN RAT BSTpr - REGULATION BY TESTOSTERONE



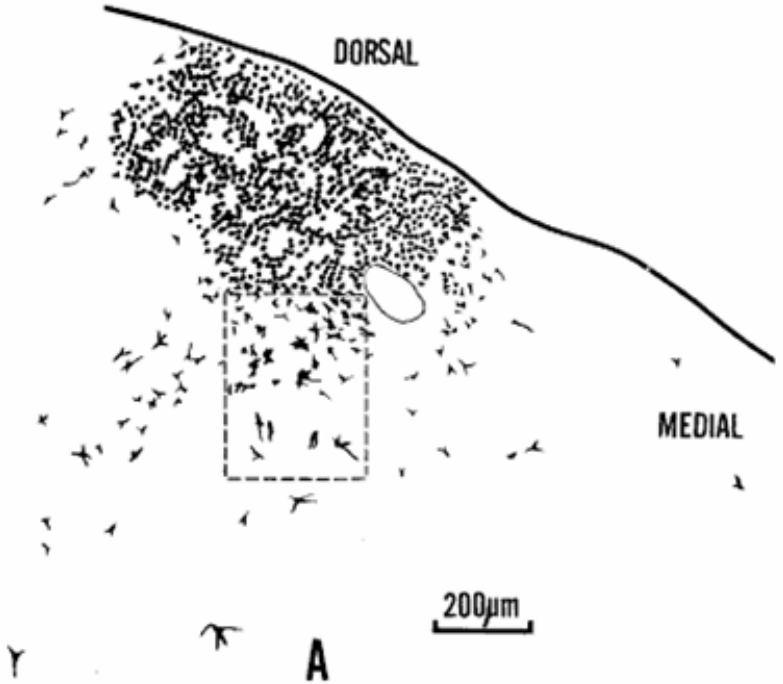


BSTpr =Principal nucleus of the Bed nucleus of the striatus terminalis

Chung et al. J Neurbiol (2000)

WHY DOES CELL DEATH OCCUR IN VERTEBRATE NEURODEVELOPMENT?

ELIMINATION OF ECTOPIC NEURONS



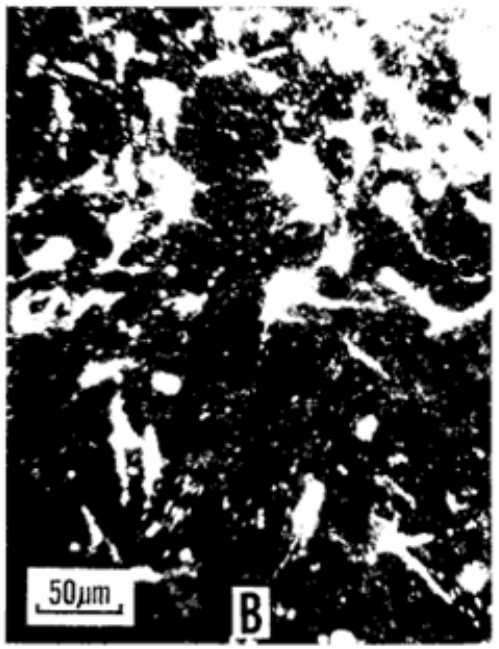
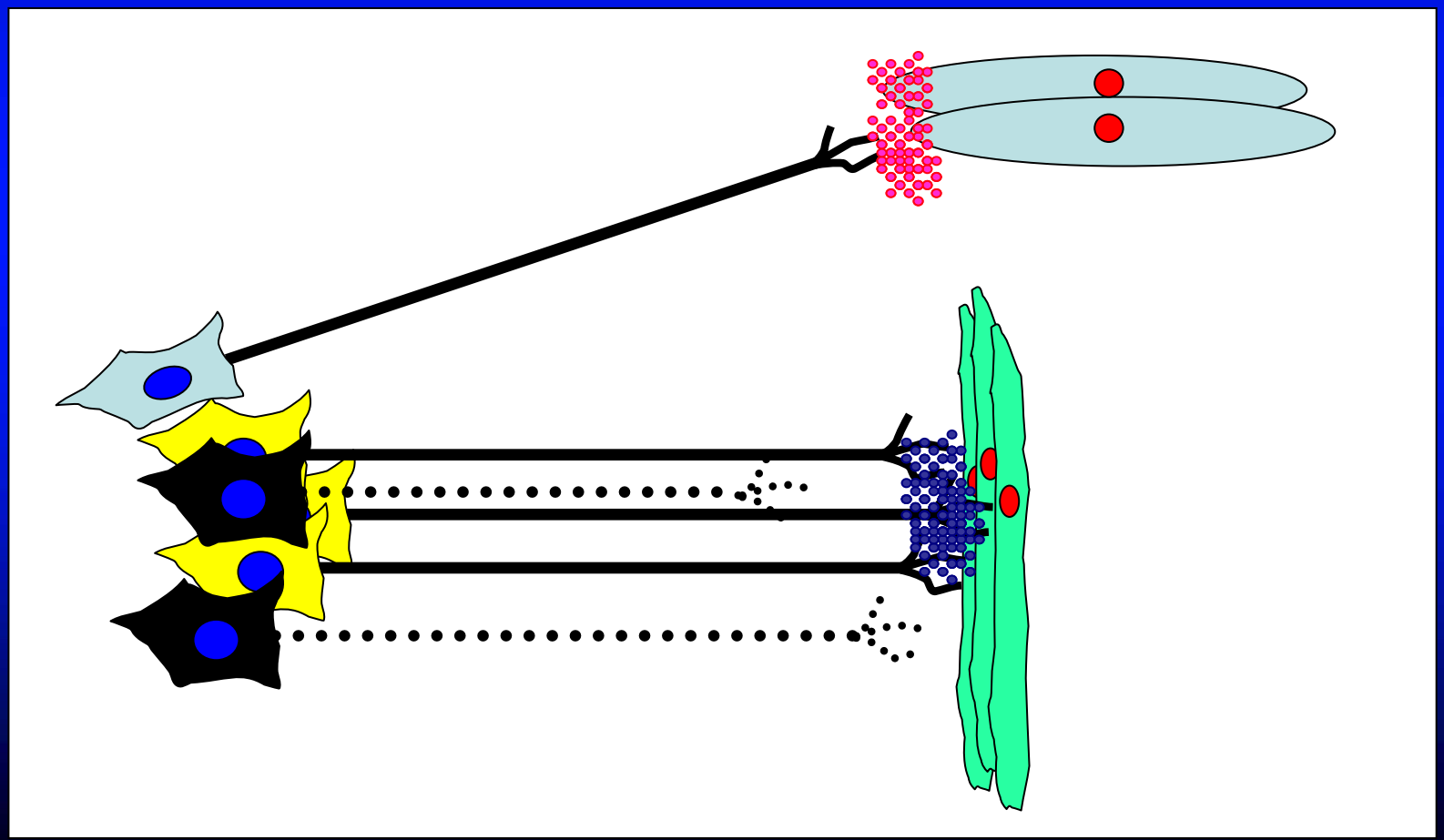


FIG. 2. (A) A camera lucida drawing of the labeled cells in the region of the ION in a 15-day-old embryo which was injected with HRP (in the contralateral eye). No attempt has been made to reproduce the form of the cells in the ION proper (since these were traced under bright-field optics from a Nissl-stained preparation); however, the appearance of the ectopic neurons ventral to the nucleus has been as accurately represented as possible, having been traced under dark-field illumination. (B) A dark-field photomicrograph of a group of ectopic neurons in the area outlined in (A).

WHY DOES CELL DEATH OCCUR IN VERTEBRATE NEURODEVELOPMENT?

ELIMINATION OF NEURONS WITH ECTOPIC PROJECTIONS

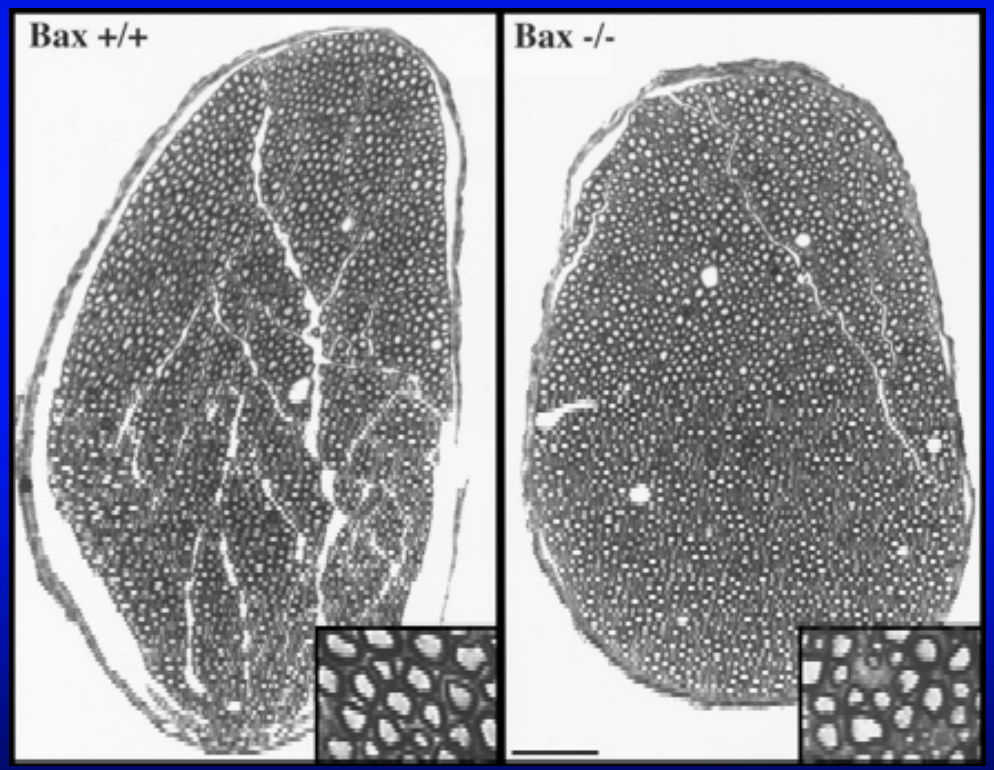


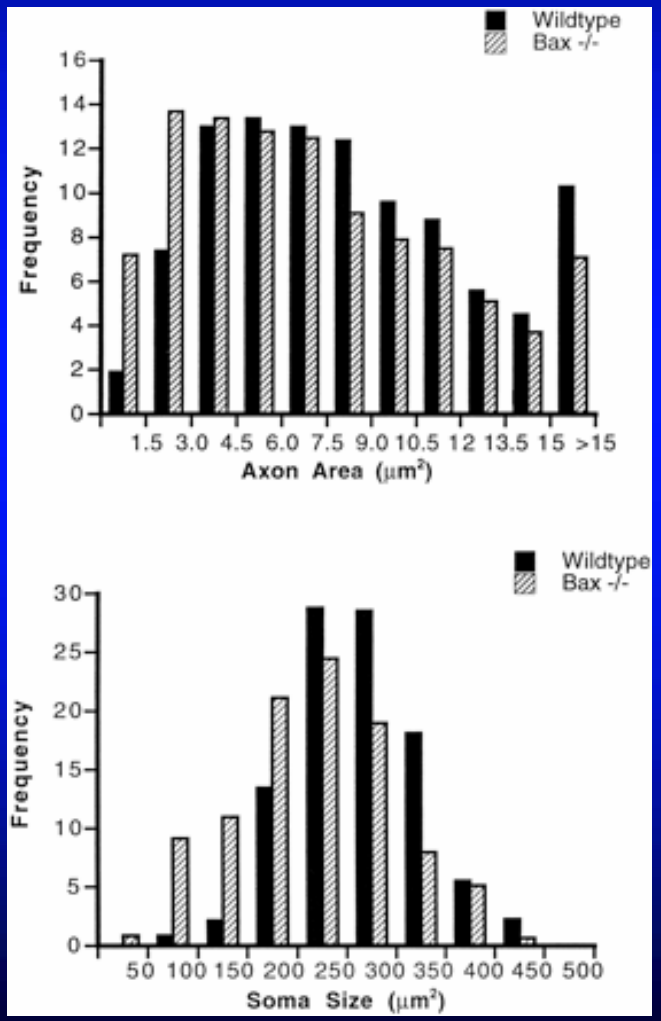
WHY DOES CELL DEATH OCCUR IN VERTEBRATE NEURODEVELOPMENT?

"SYSTEMS MATCHING: CREATION OF OPTIMAL LEVELS OF INNERVATION BETWEEN INTERCONNECTED GROUPS OF NEURONS AND BETWEEN NEURONS AND THEIR NON-NEURONAL TARGETS" (Buss and Oppenheim Anat Sci Int, 2004)

WHAT HAPPENS IF DEVELOPMENTAL NEURON CELL DEATH IS ABSENT?

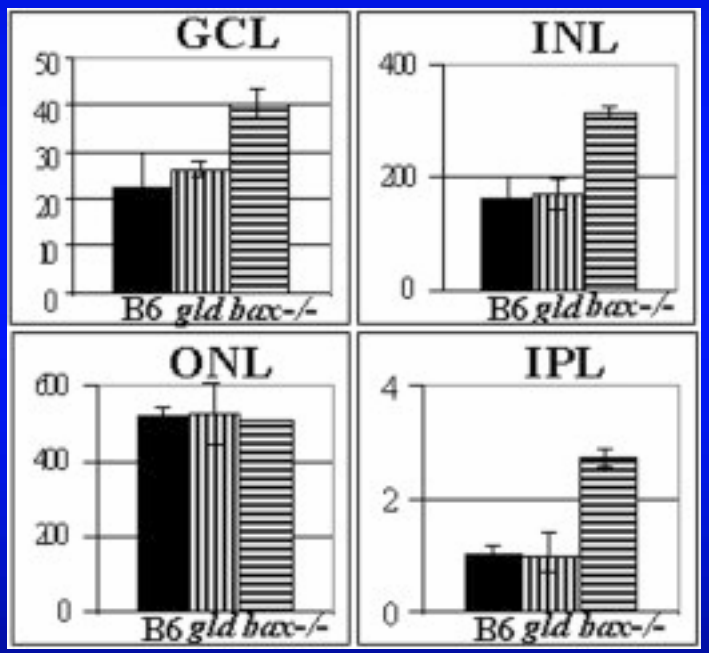
IN ABSENCE OF NORMAL DEVELOPMENTAL CELL DEATH MOST EXCESS NEURONS BECOME ATROPHIC: EXAMPLE OF FACIAL NERVE



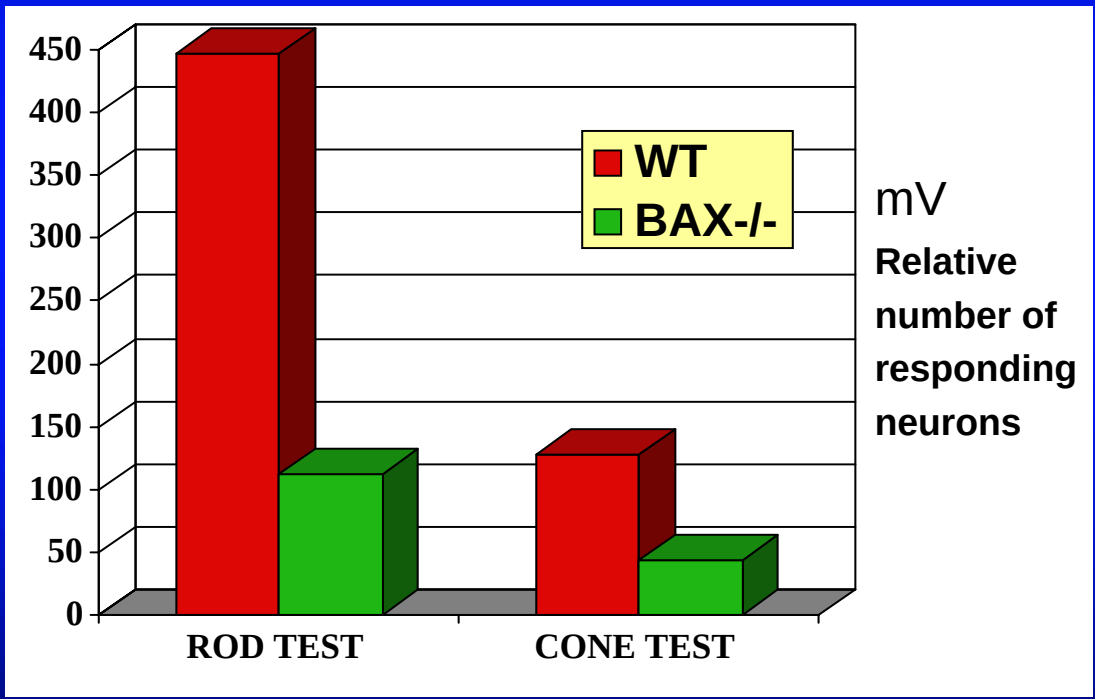


White et al. J Neurosci 1998

RETINAL NEURON RESPONSES TO LIGHT CHANGE IN ABSENCE OF NORMAL DEVELOPMENTAL CELL DEATH



GCL=ganglion cell layer
INL=inner nuclear layer
ONL=outer nuclear layer
IPL=inner plexiform layer

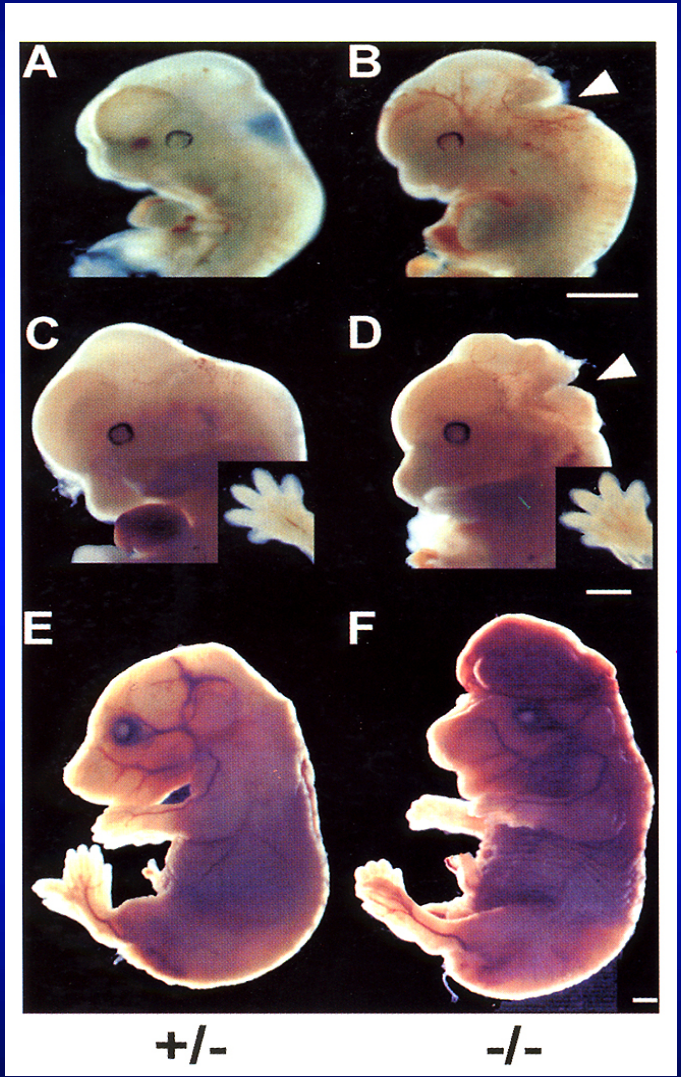


(Péquignot et al. Dev Dyn 2003

WHY DOES CELL DEATH OCCUR IN VERTEBRATE NEURODEVELOPMENT?

PREVENT OVER-PRODUCTION OF NEUROPROGENITOR CELLS TO GENERATE PROPER SIZED BRAIN

EMBRYOGENIC DEFECTS IN A MOUSE LACKING CASPASE-9



From: Kuida et al Cell:94: 325-337, 1998

WHY DOES CELL DEATH OCCUR IN NEURODEVELOPMENT?

ELIMINATION OF CELLS WITH DAMAGED DNA OR WITH OTHER DEFECTS

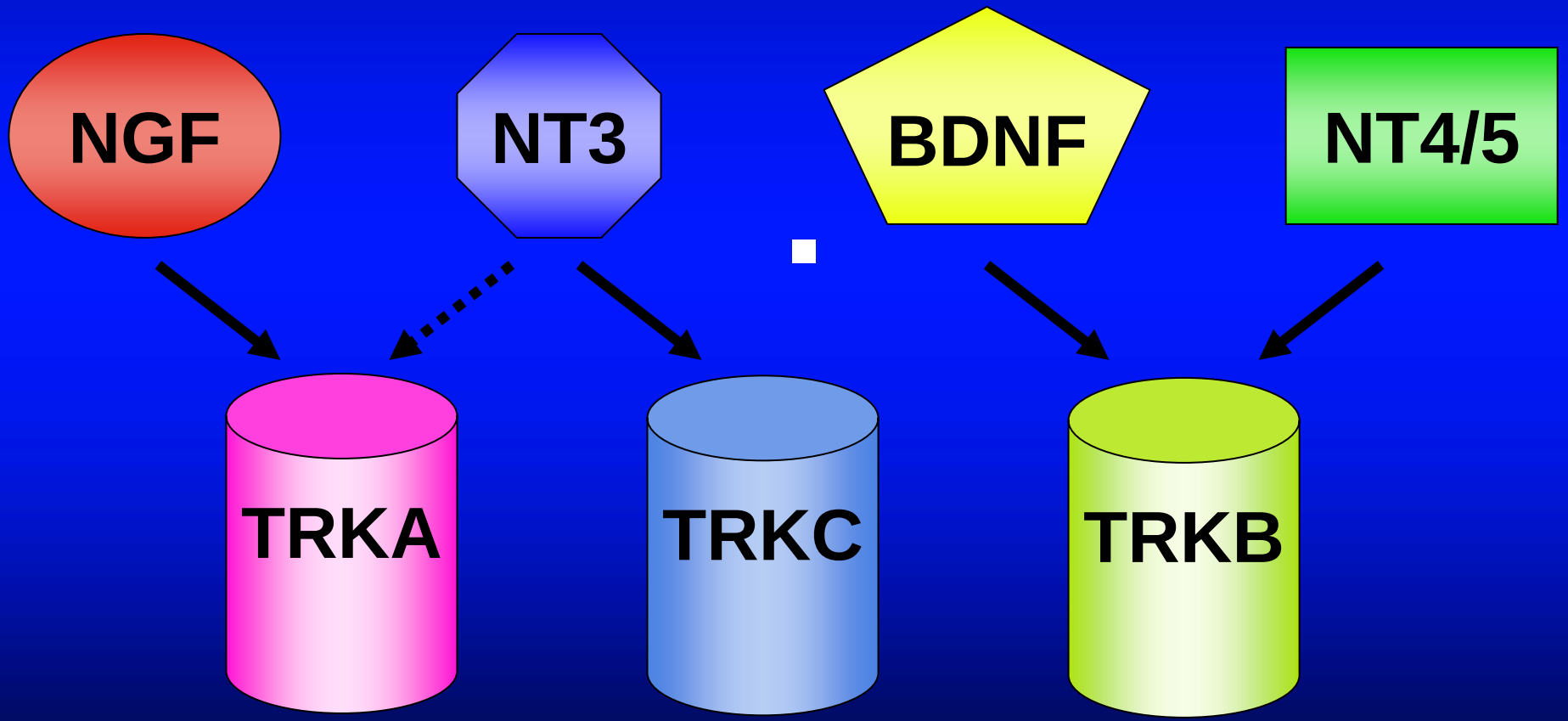
WHY DOES CELL DEATH OCCUR IN VERTEBRATE NEURODEVELOPMENT?

“A MEANS OF EVOLUTIONARY CHANGE: ADAPTIVE CHANGES IN THE ONTOGENETIC DEATH AND SURVIVAL OF CELLS IN REPSPONSE TO GENETIC MUTATION (E.G. THE PRODUCTION OF EXCESS NEURONS COULD BE USED FOR THE INNERVATION OF NEW TARGETS MADE AVAILABLE BY THE EVOLUTION OF LIMBS)”

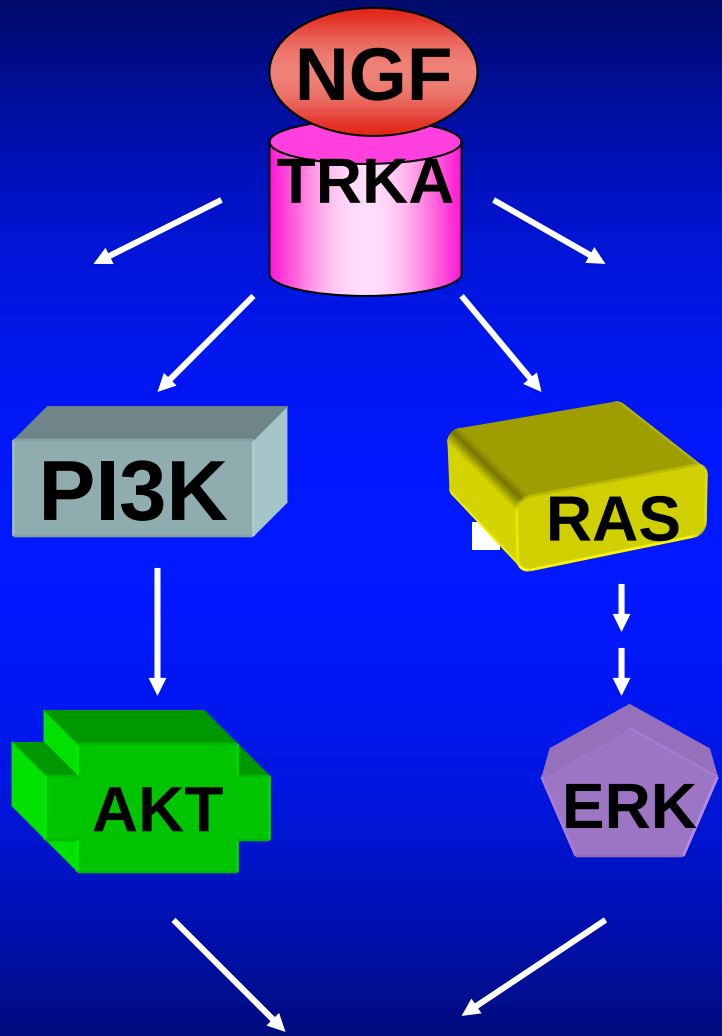
(Buss and Oppenheim Anat Sci Int, 2004)

WHAT ARE THE MECHANISMS BY WHICH NEURON SURVIVAL AND DEATH ARE REGULATED DURING VERTEBRATE DEVELOPMENT?

SPECIFICITY OF NEUROTROPHIN FAMILY RECEPTOR BINDING



TRK SIGNALING AND PROMOTION OF NEURON SURVIVAL



WORTMANNIN
LY2942002
D/N PI3K

ACT-PI3K

D/N AKT

ACT-AKT

D/N-RAS

ACT-RAS

PD98059
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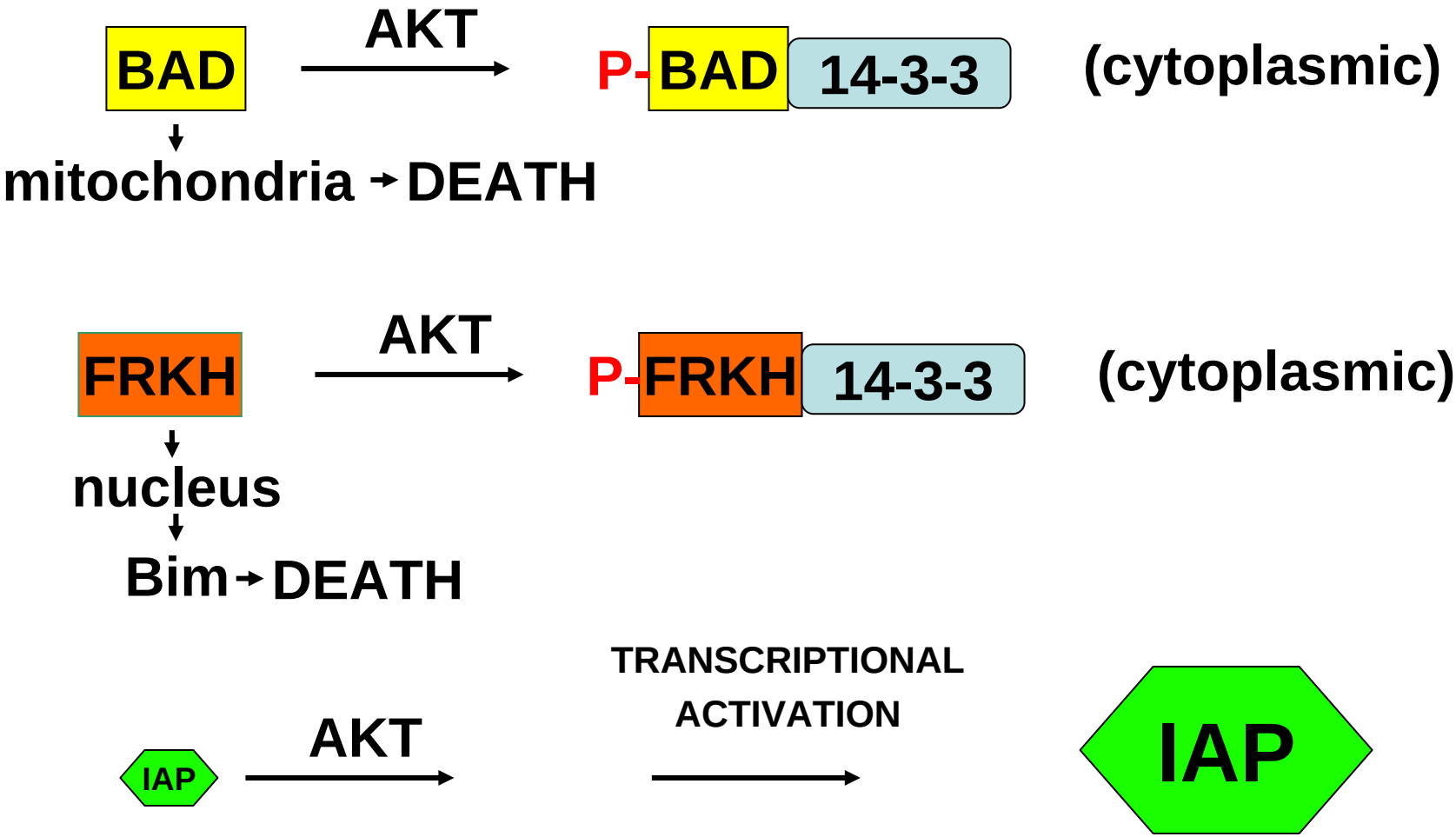
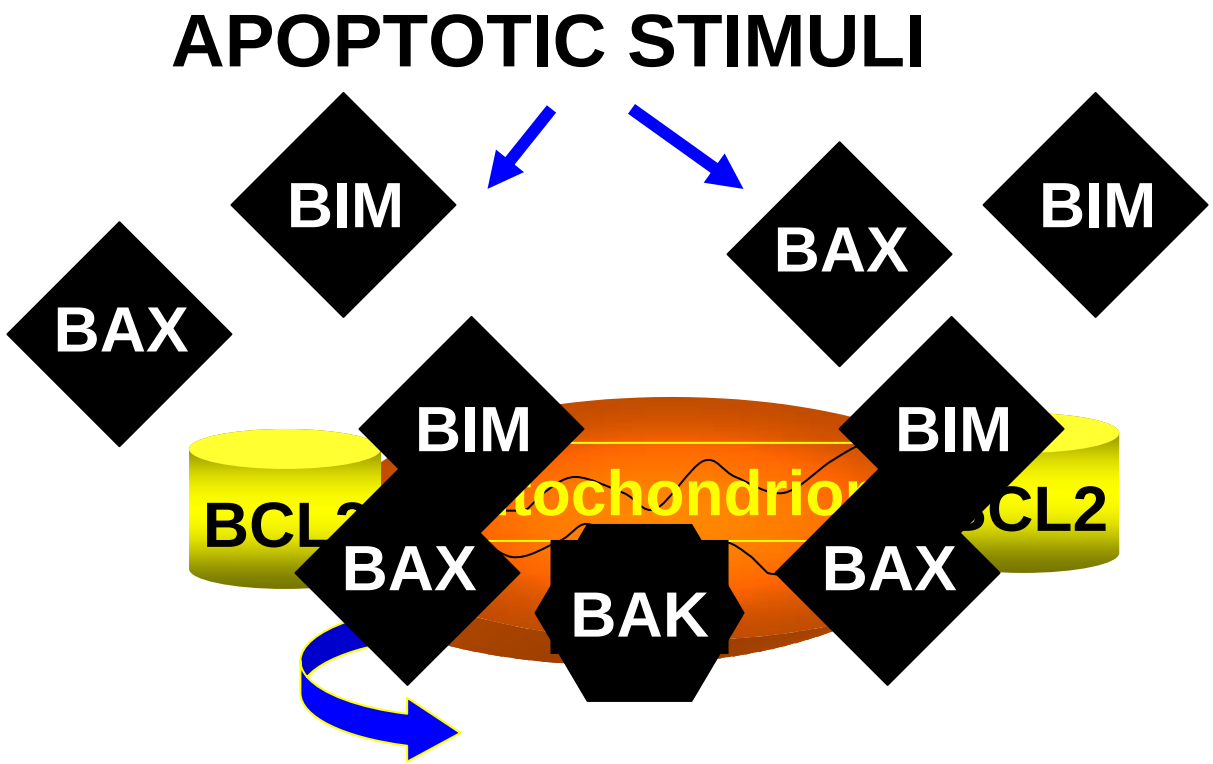
DEATH IN SOME PARADIGMS

SURVIVAL

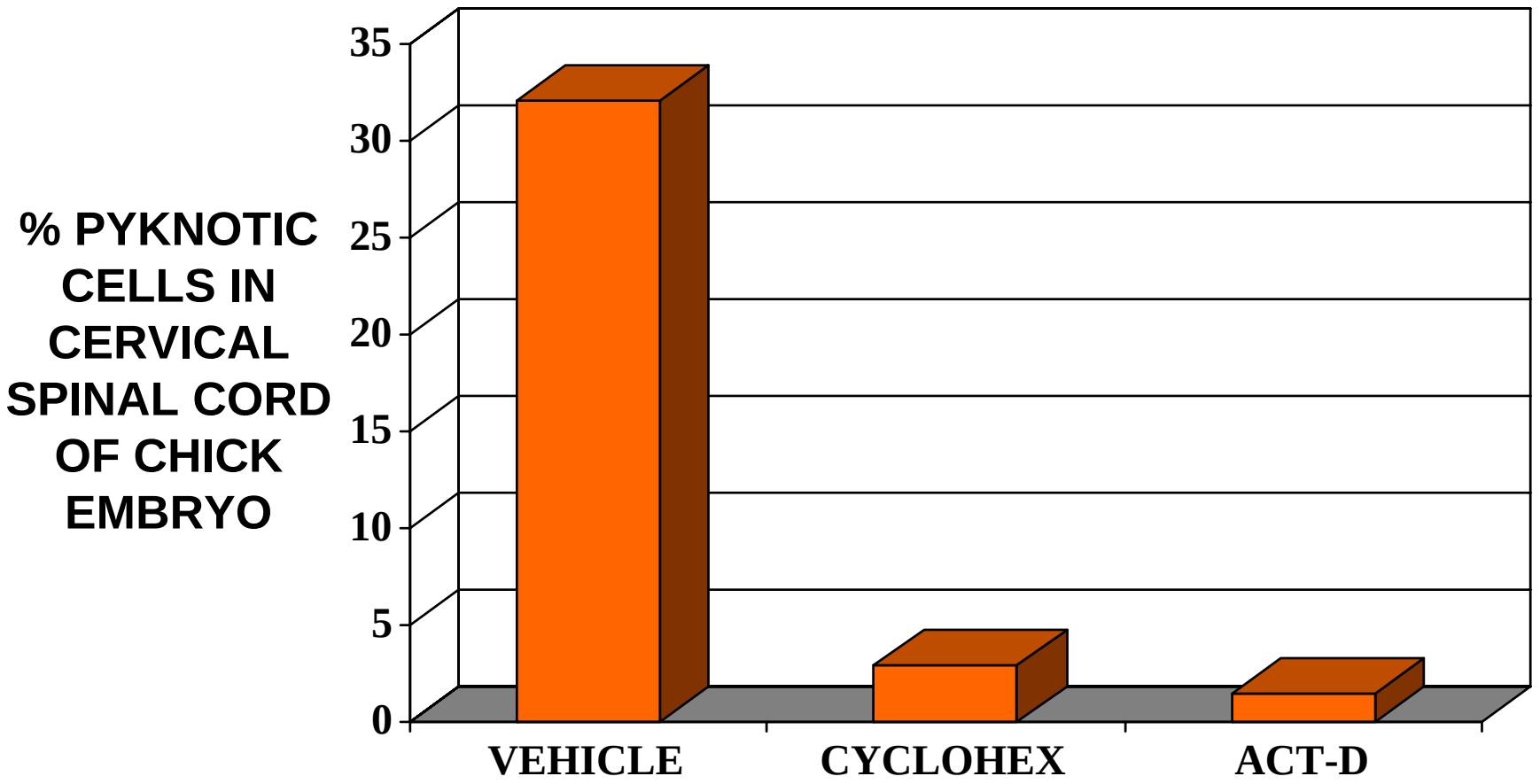
EXAMPLES OF HOW AKT PROMOTES SURVIVAL



MITOCHONDRIA AND APOPTOTIC DEATH

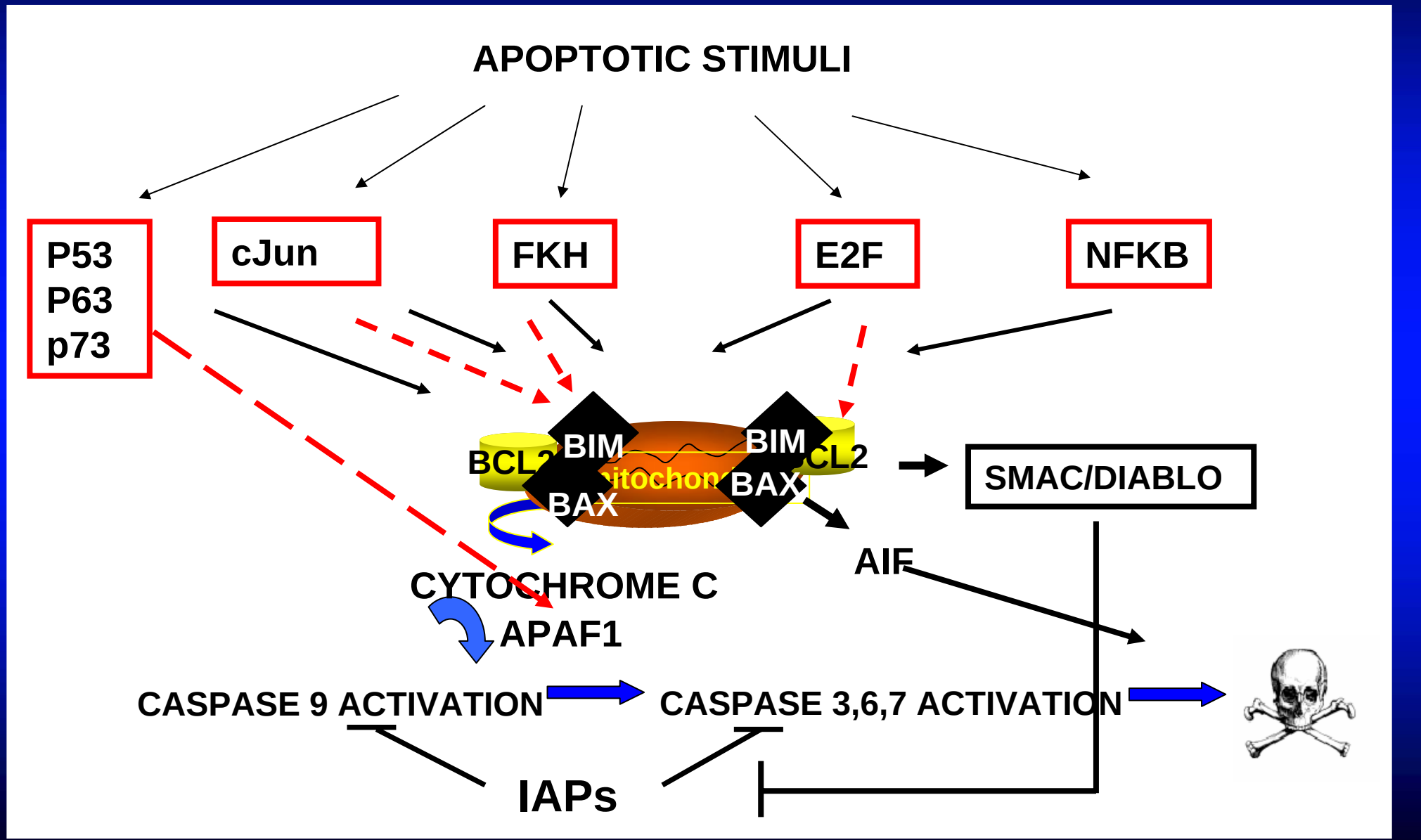


DEVELOPMENTAL NEURON CELL DEATH IN VERTEBRATES REQUIRES MACROMOLECULAR SYNTHESIS

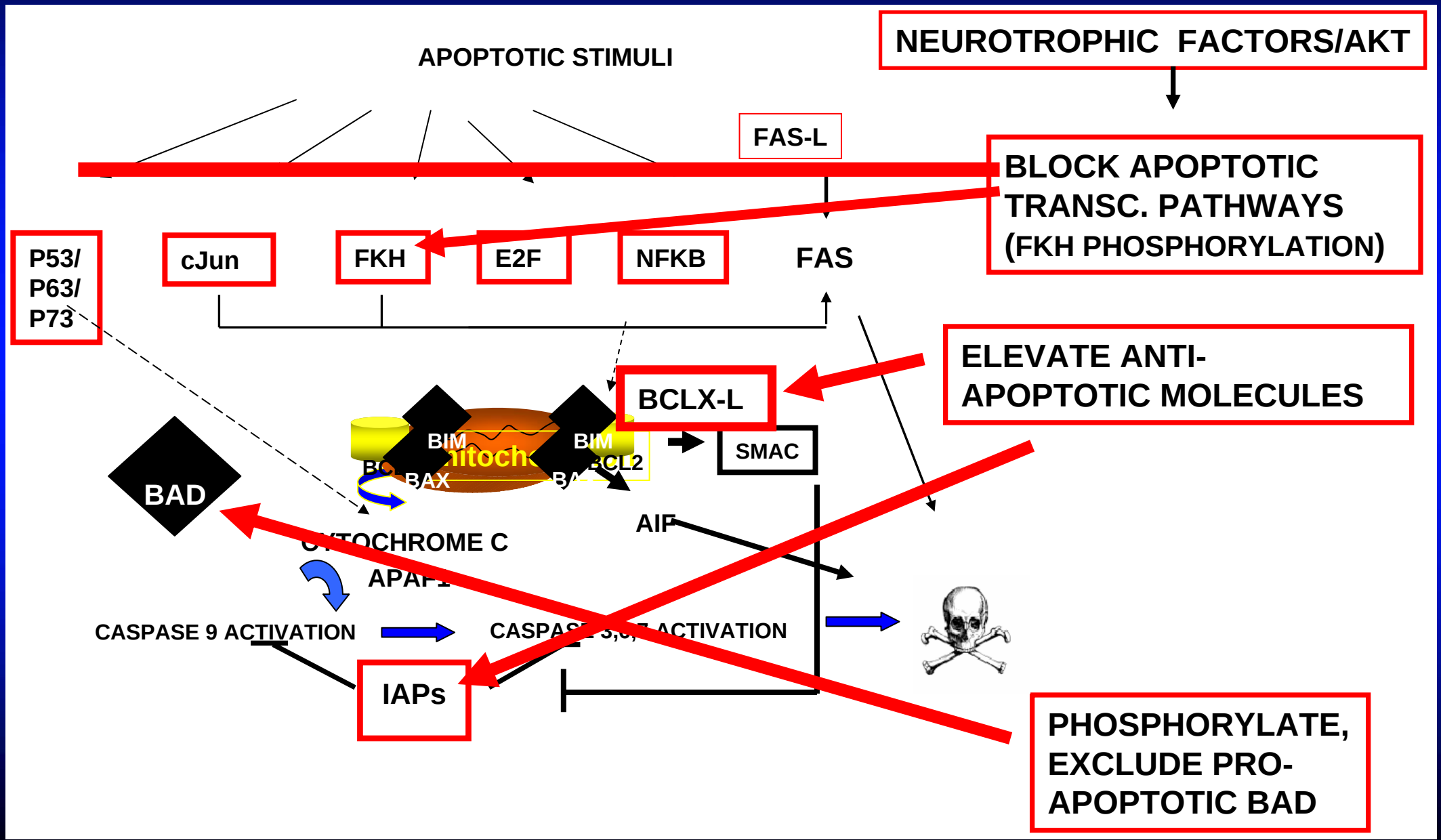


Plotted from data in: Yaginuma et al. J Neurosci 1996

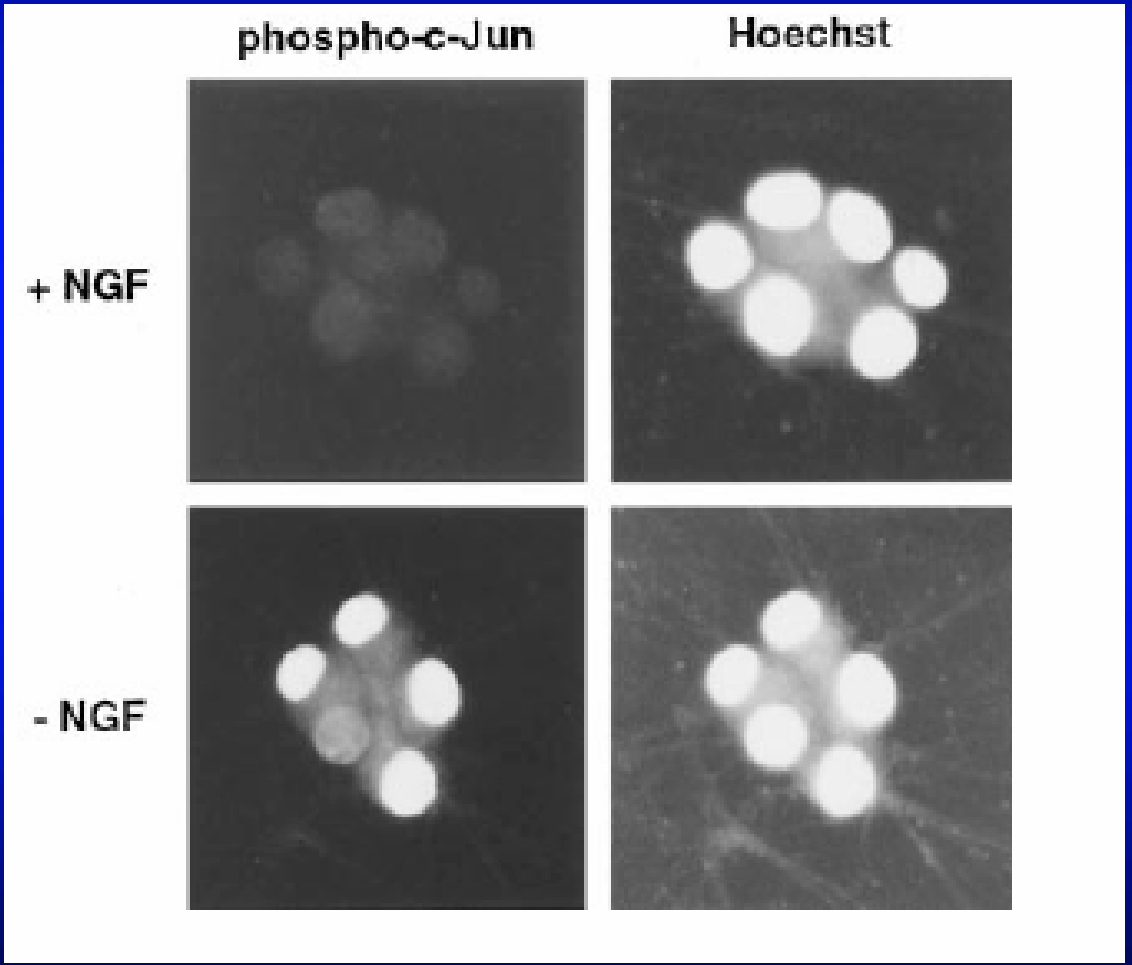
TRANSCRIPTIONAL REGULATION OF APOPTOTIC DEATH



AKT BLOCKS DEATH AT MULTIPLE LEVELS OF THE APOPTOTIC MECHANISM



C-JUN IS PHOSPHORYLATED/ACTIVATED IN NGF-DEPRIVED NEURONS

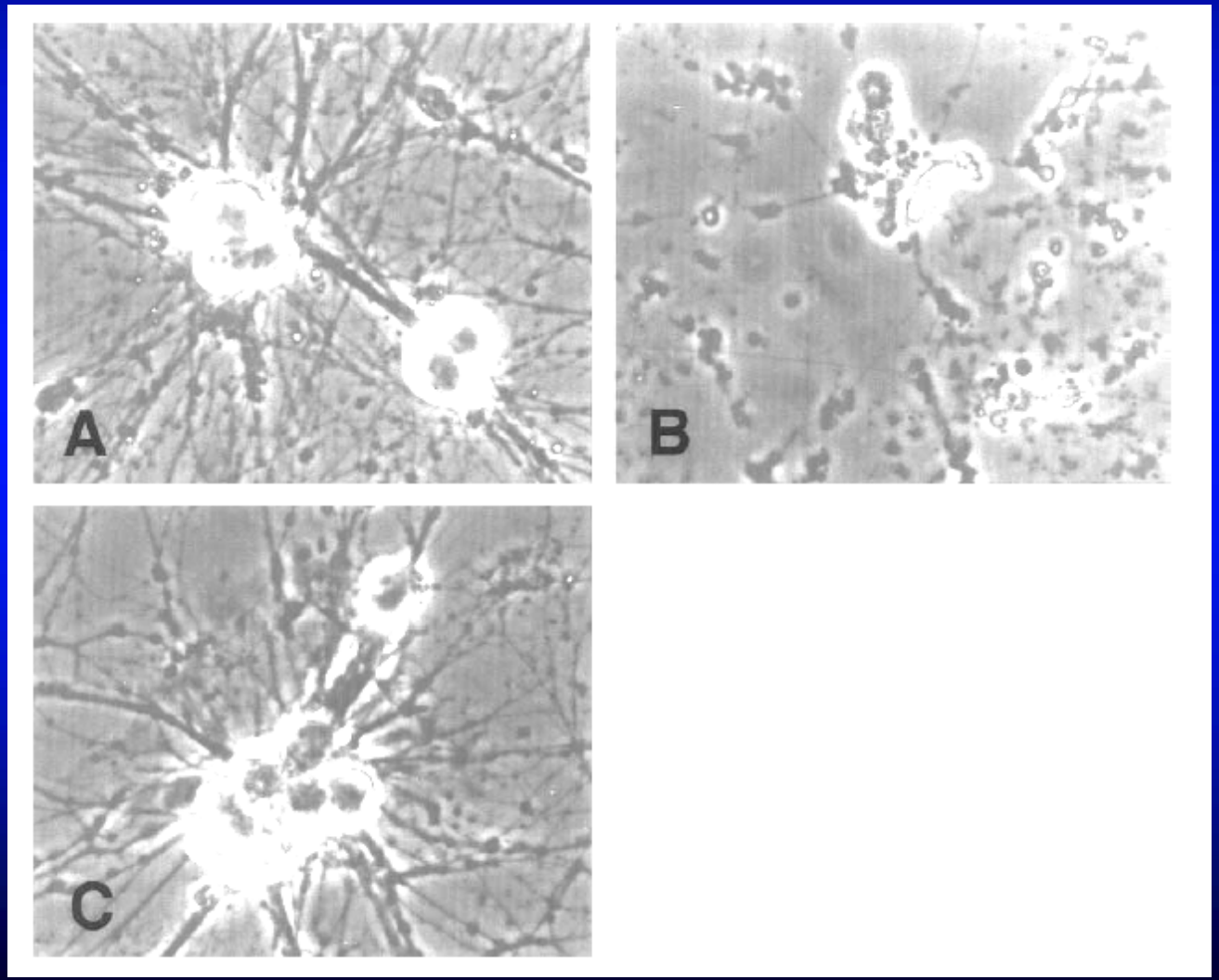


Eilers et al. J Neurosci 1998

BLOCKING JNK ACTIVATION BLOCKS NEURON DEATH CAUSED BY NGF DEPRIVATION

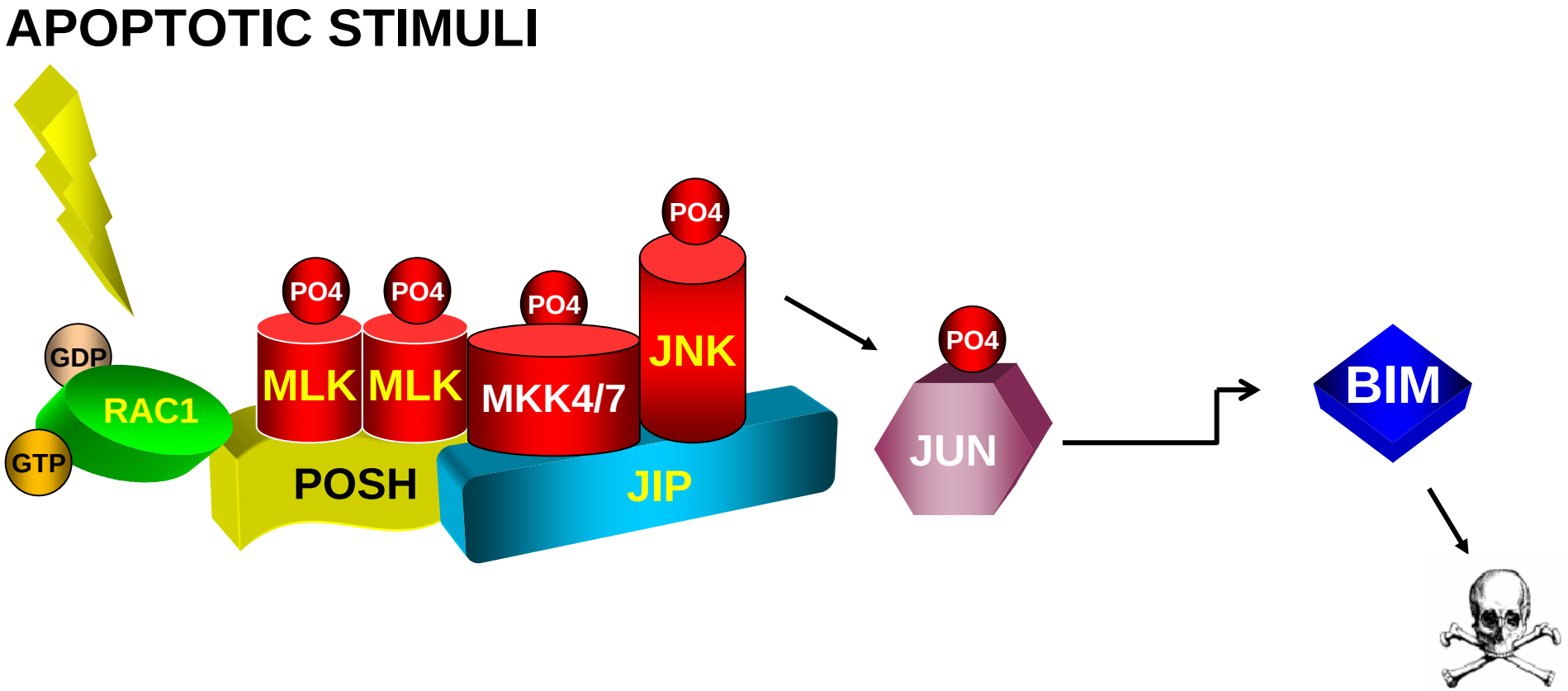
+NGF

-NGF

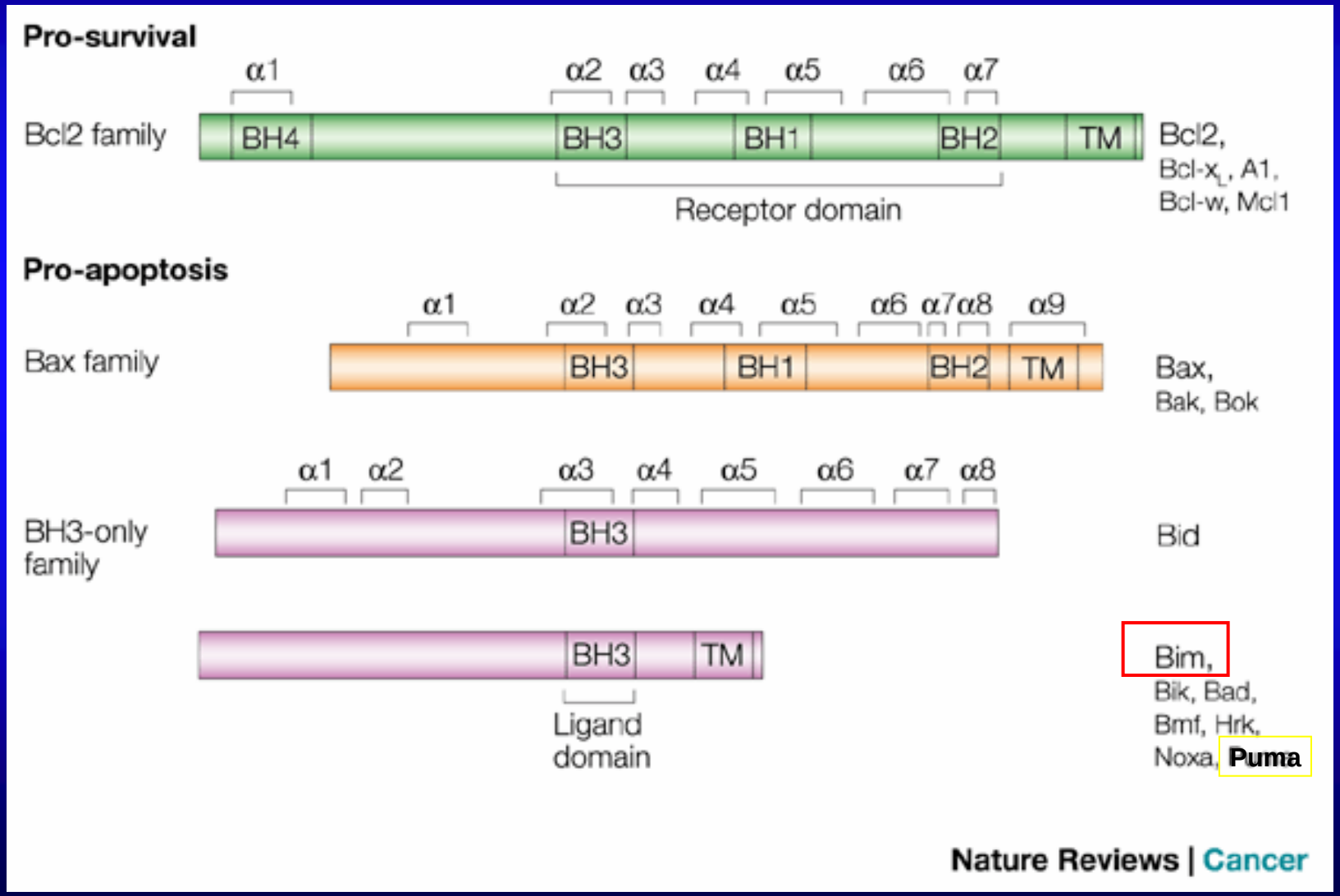


-NGF
+CEP1347

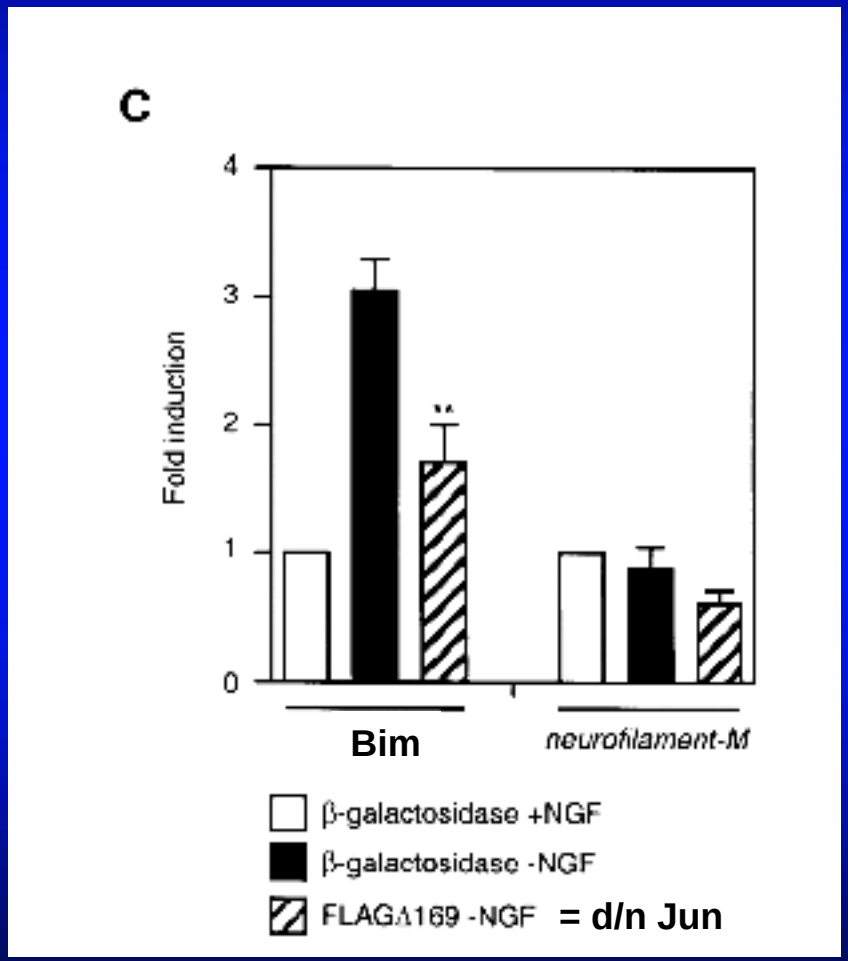
DEATH SIGNALING BY THE JNK PATHWAY IN NEURON DEATH

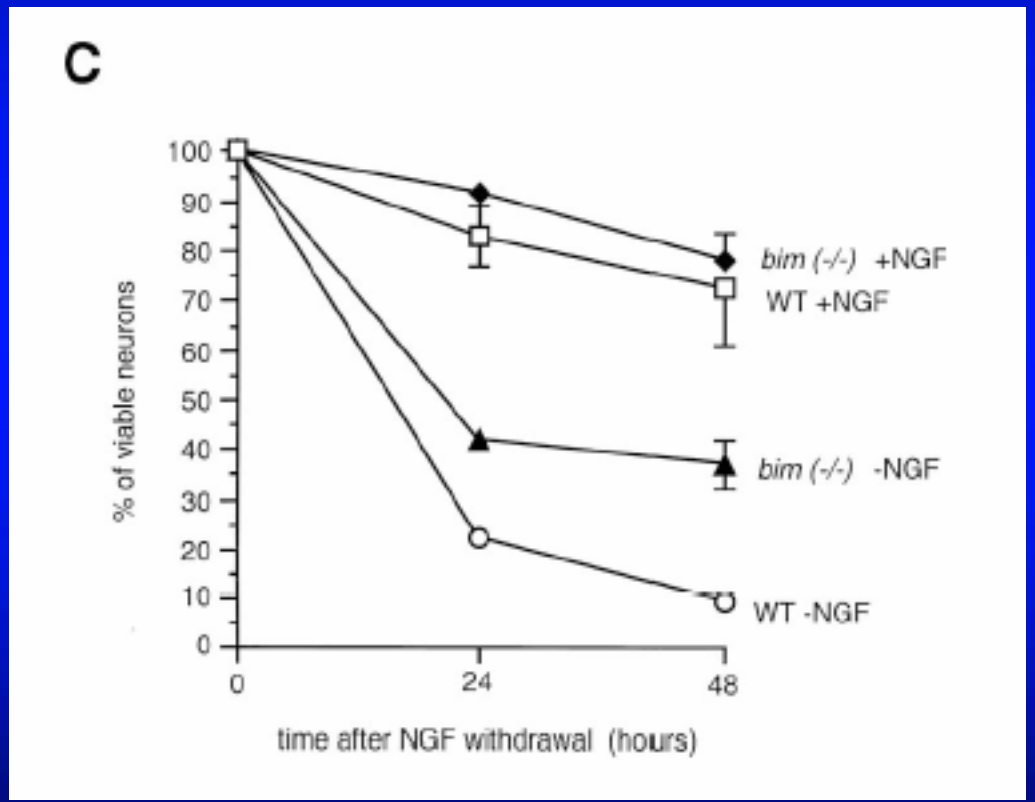


BIM IS A PRO-APOPTOTIC MEMBER OF THE BCL2 FAMILY



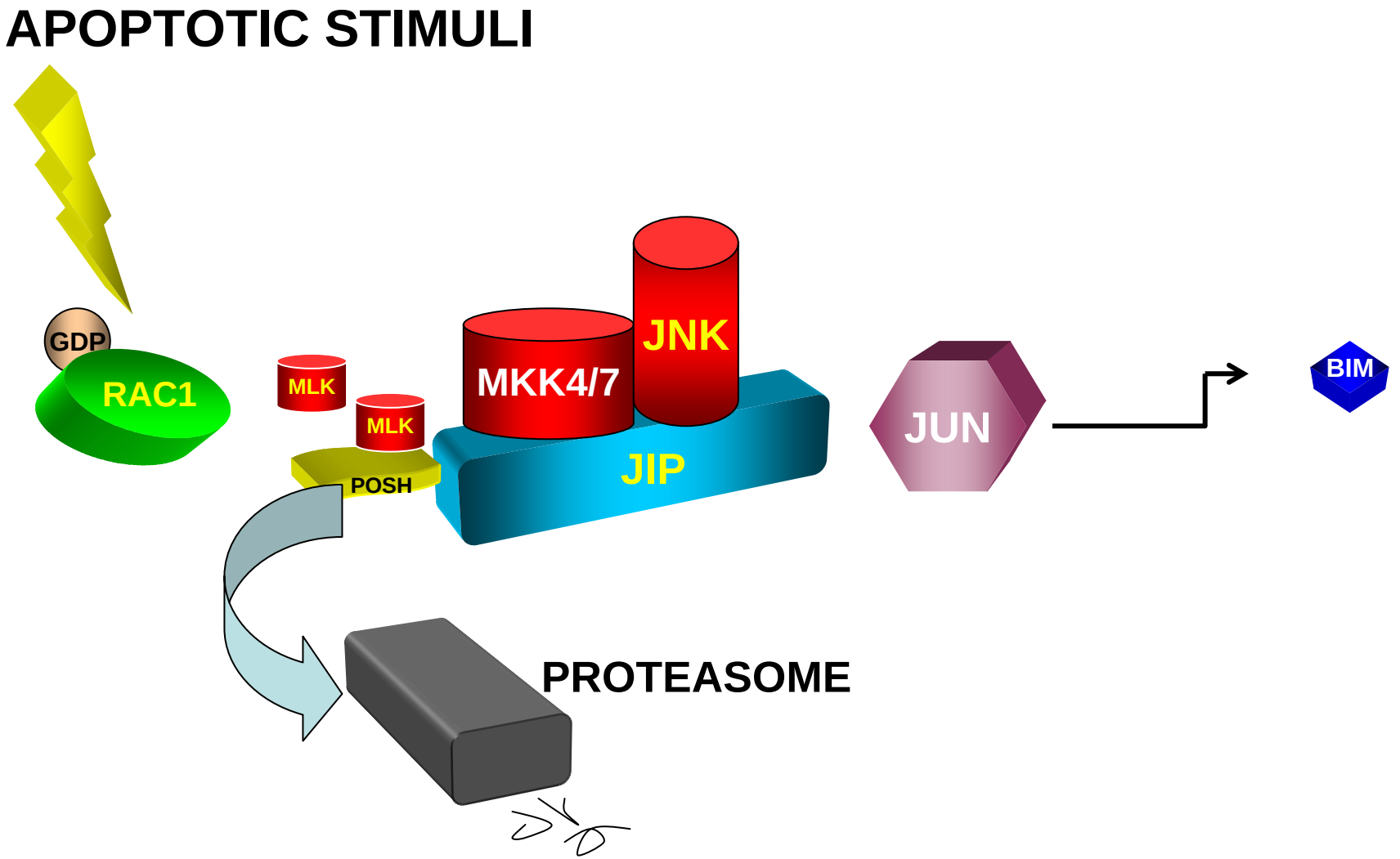
BIM IS UPREGULATED BY NGF DEPRIVATION, PARTLY VIA THE JNK PATHWAY AND CONTRIBUTES TO NEURON DEATH



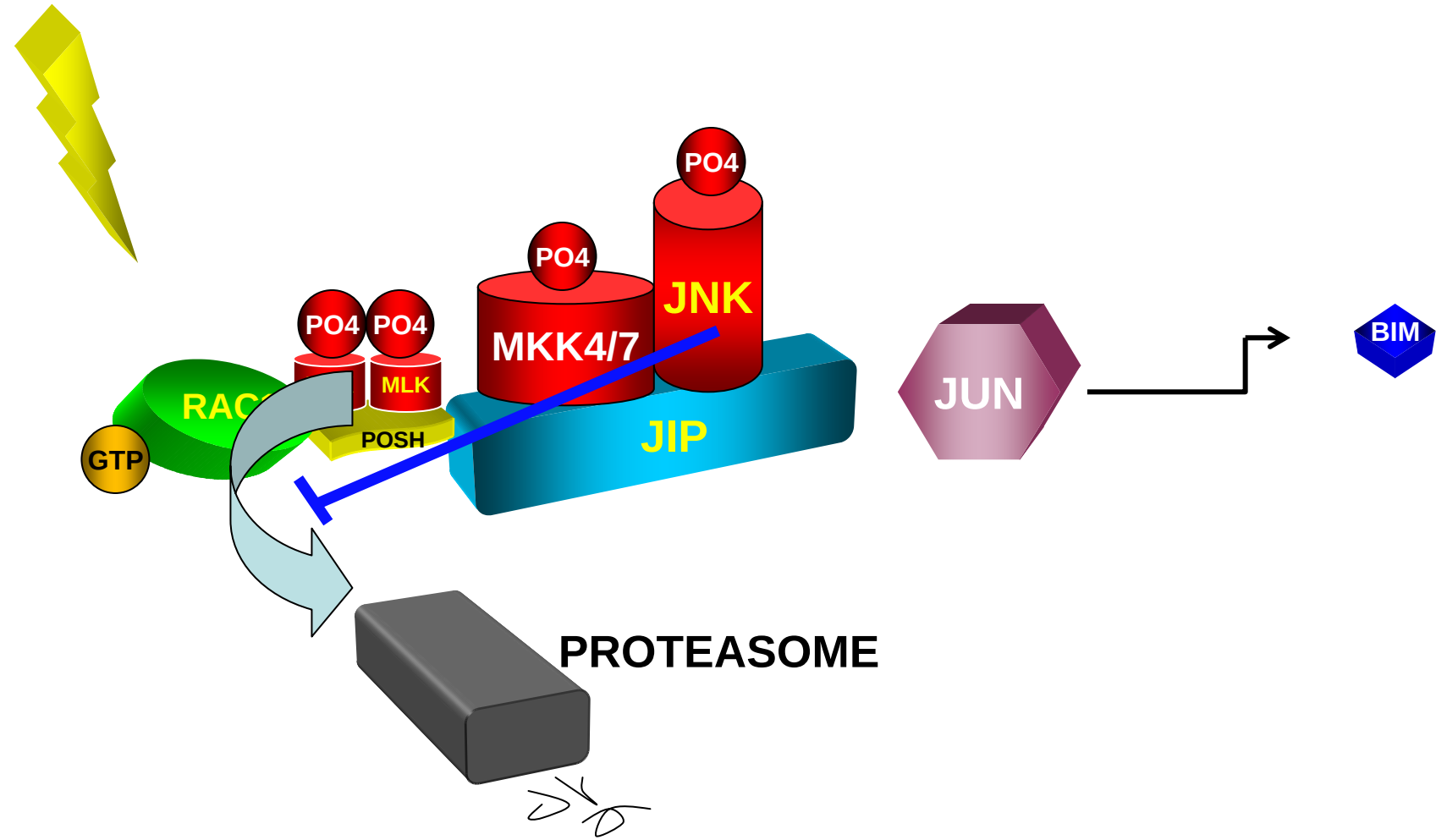


Whitfield et al Neuron 2001

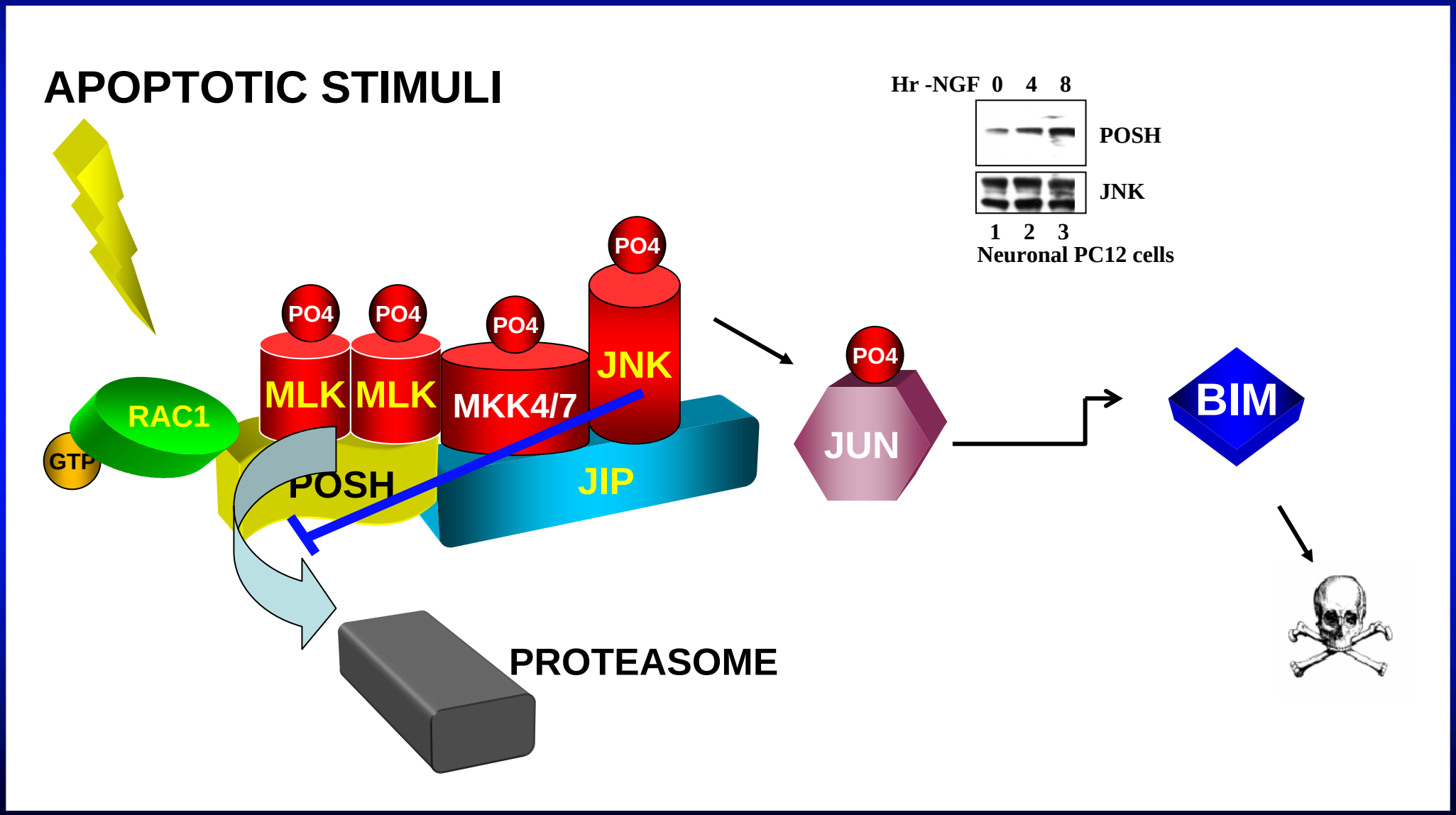
MLKS AND POSH ARE DEGRADED IN VIABLE NEURONS



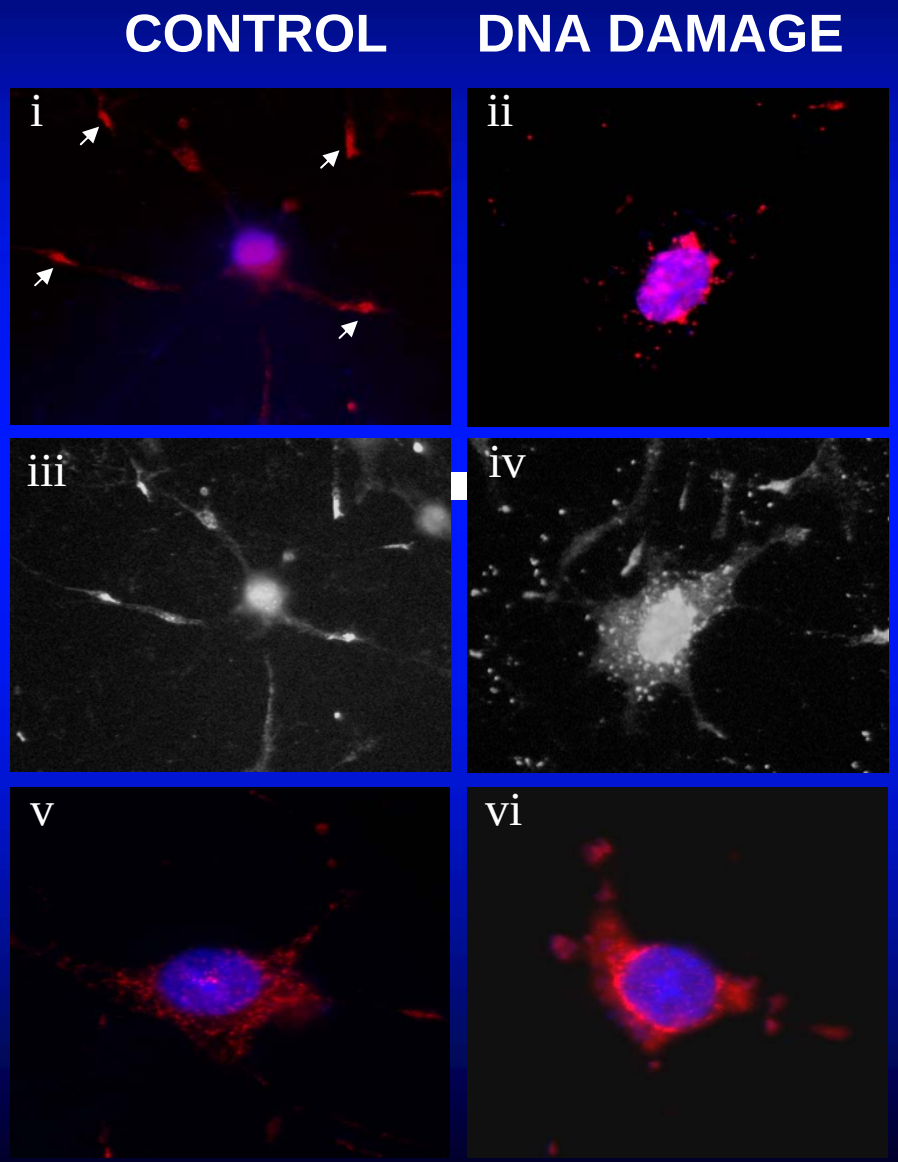
MLKS AND POSH ARE STABILIZED BY A FEEDBACK LOOP MECHANISM IN RESPONSE TO APOPTOTIC STIMULI



DEATH SIGNALING BY THE JNK PATHWAY IN NEURON DEATH

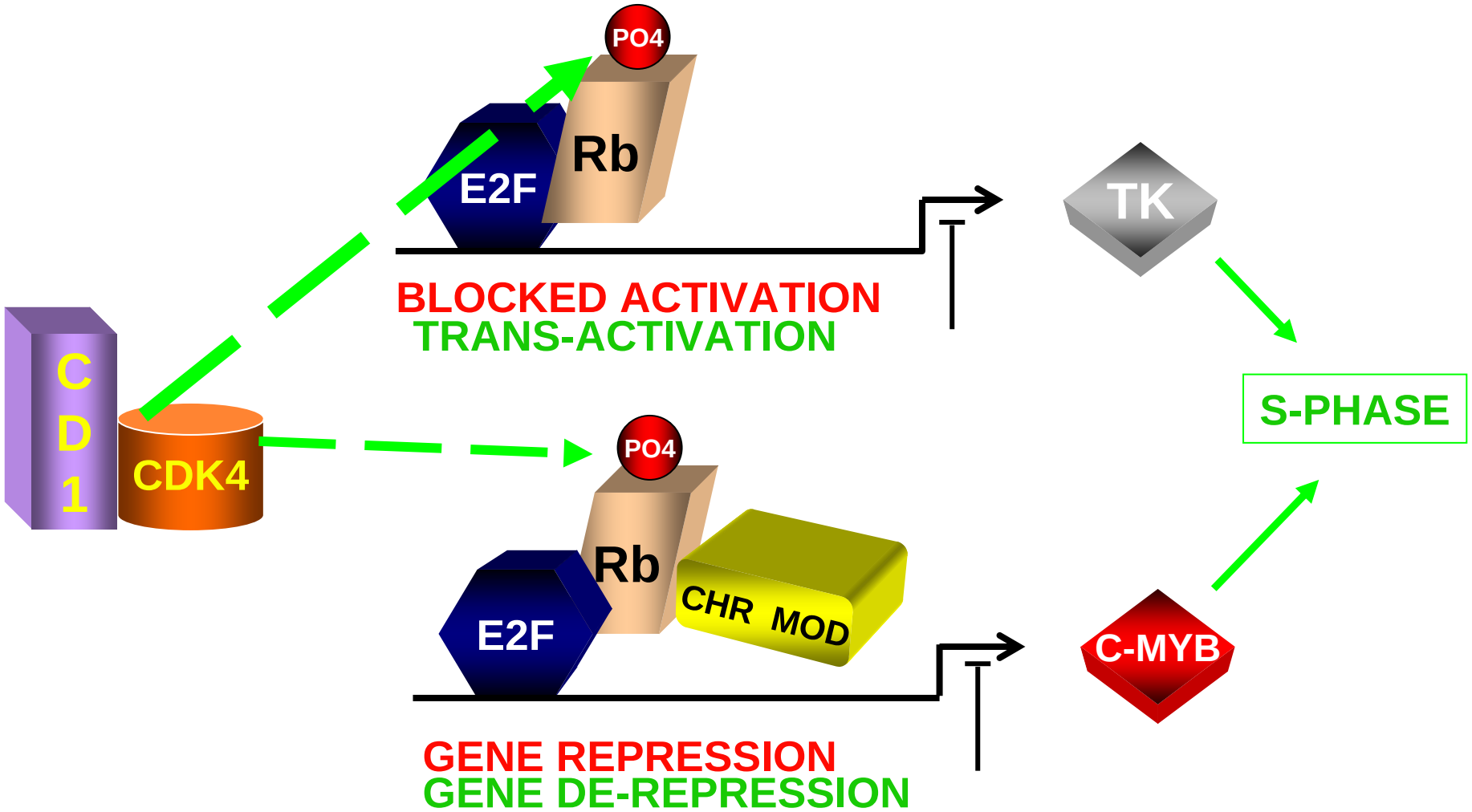


JIP AND POSH RELOCALIZE IN RESPONSE TO APOPTOTIC STIMULI

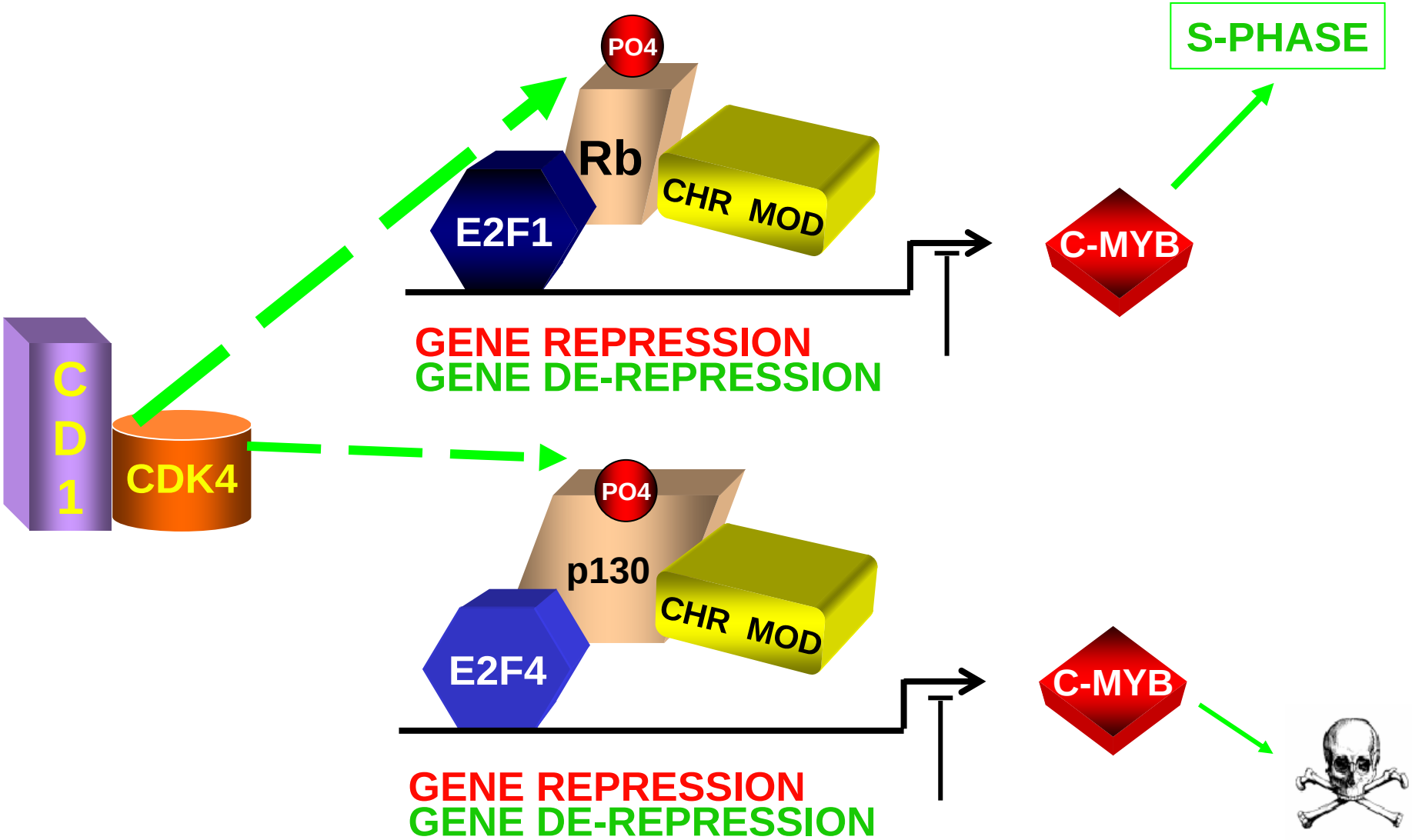


CELL CYCLE MOLECULES MEDIATE NEURON CELL DEATH EVOKED BY LOSS OF TROPHIC SUPPORT

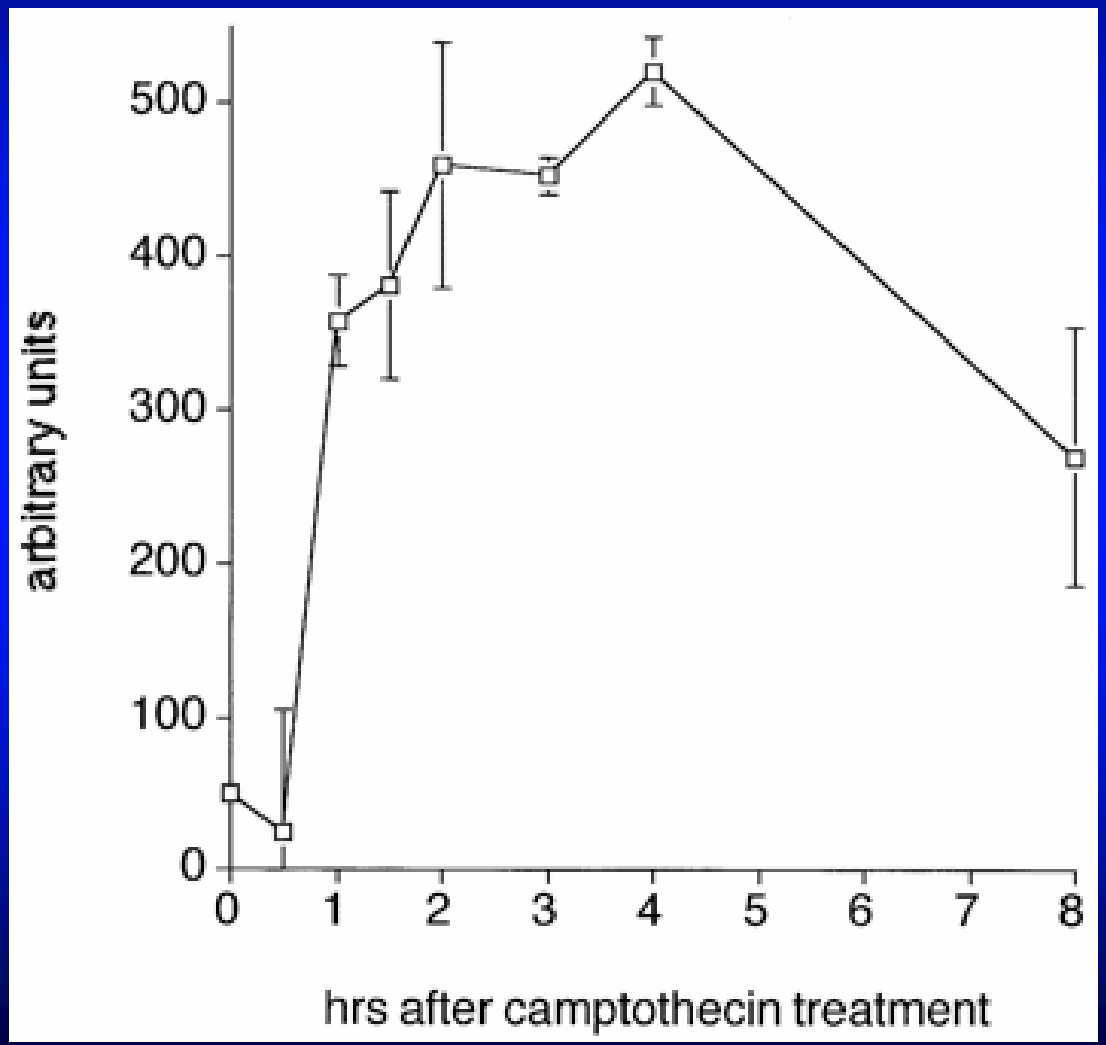
E2F REGULATES CELL PROLIFERATION



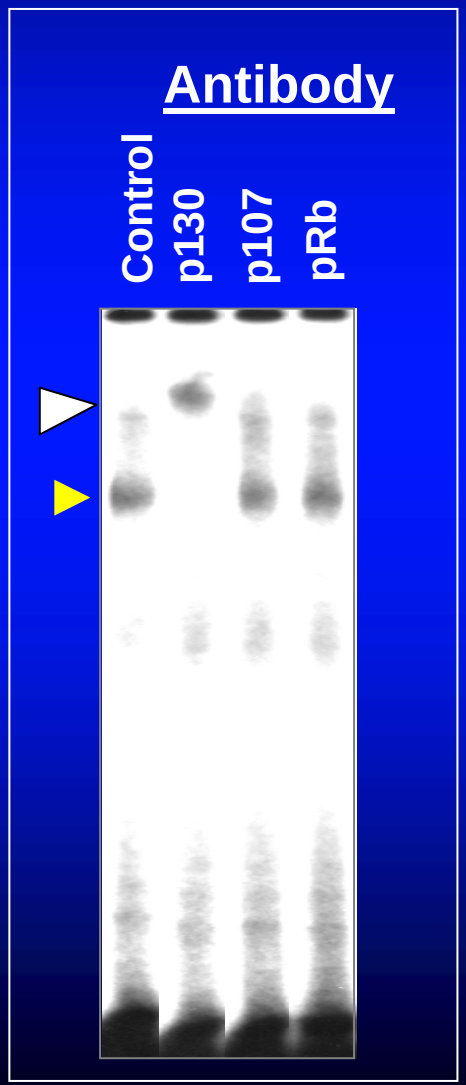
E2F REGULATES CELL PROLIFERATION & NEURON DEATH

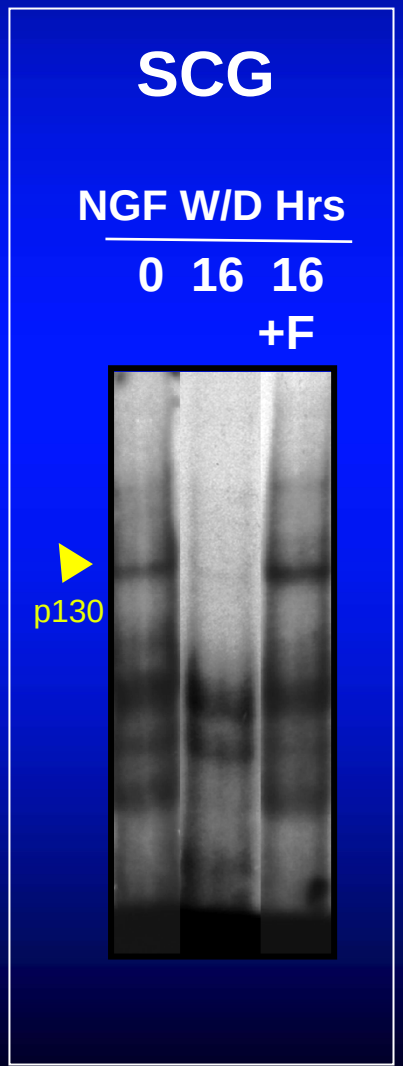


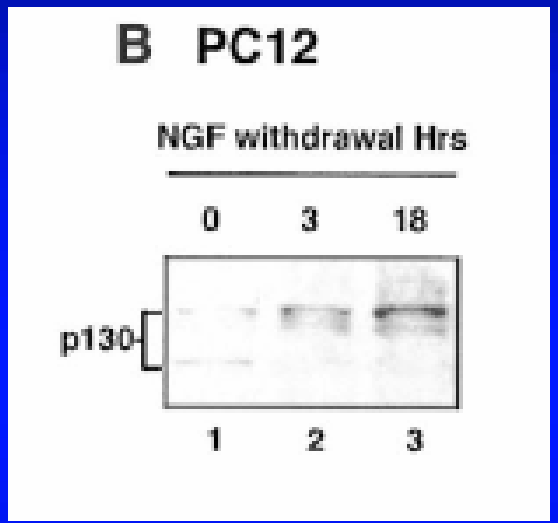
APOPTOTIC STIMULI ACTIVATE CDK4/6 IN NEURONS

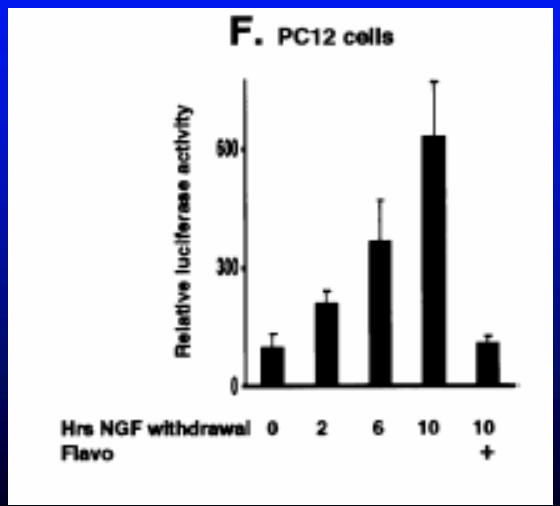


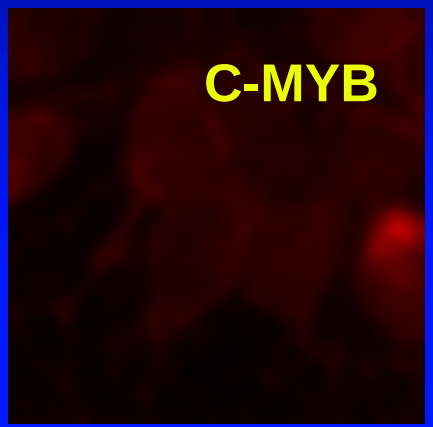
p130 IS THE MAJOR E2F PARTER ON CHROMATIN IN NEURONS, IS PHOSPHORYLATED AND LOST WITH NGF DEPRIVATION, RESULTING IN MYB DE-REPRESSION AND UP-REGULATION



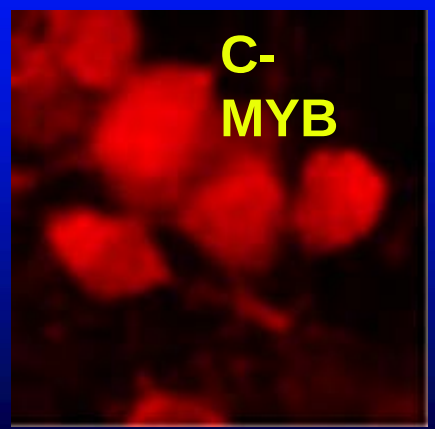






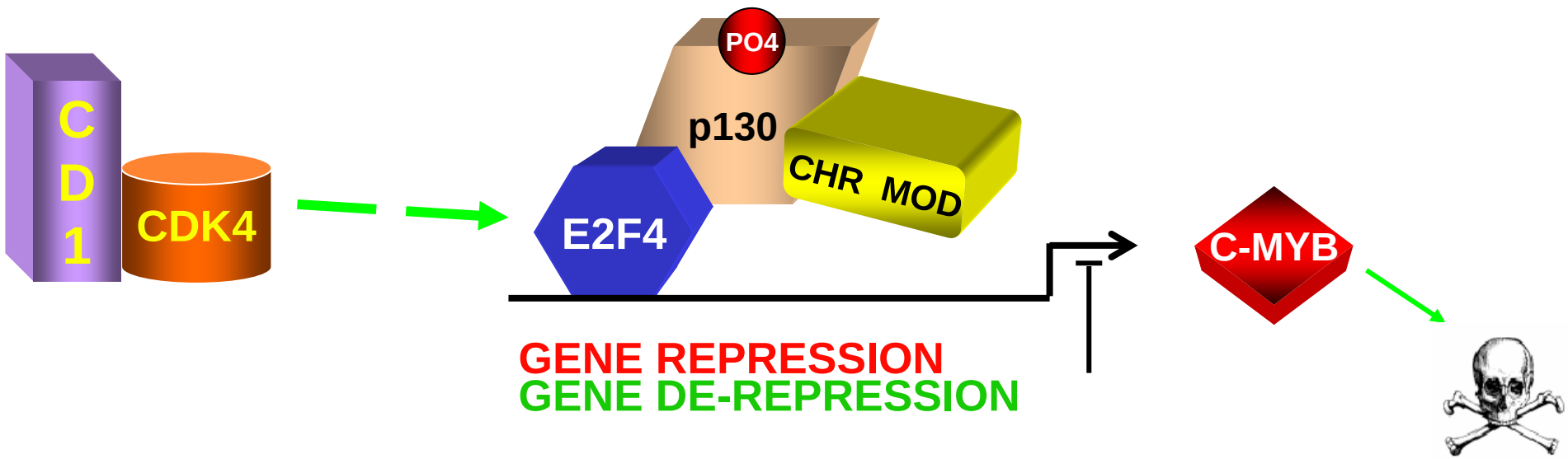


+NGF

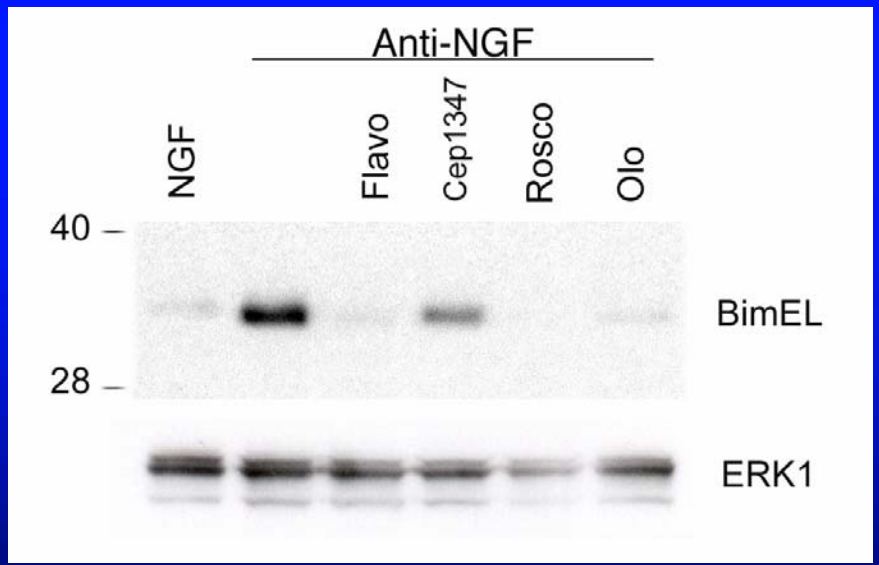


-NGF

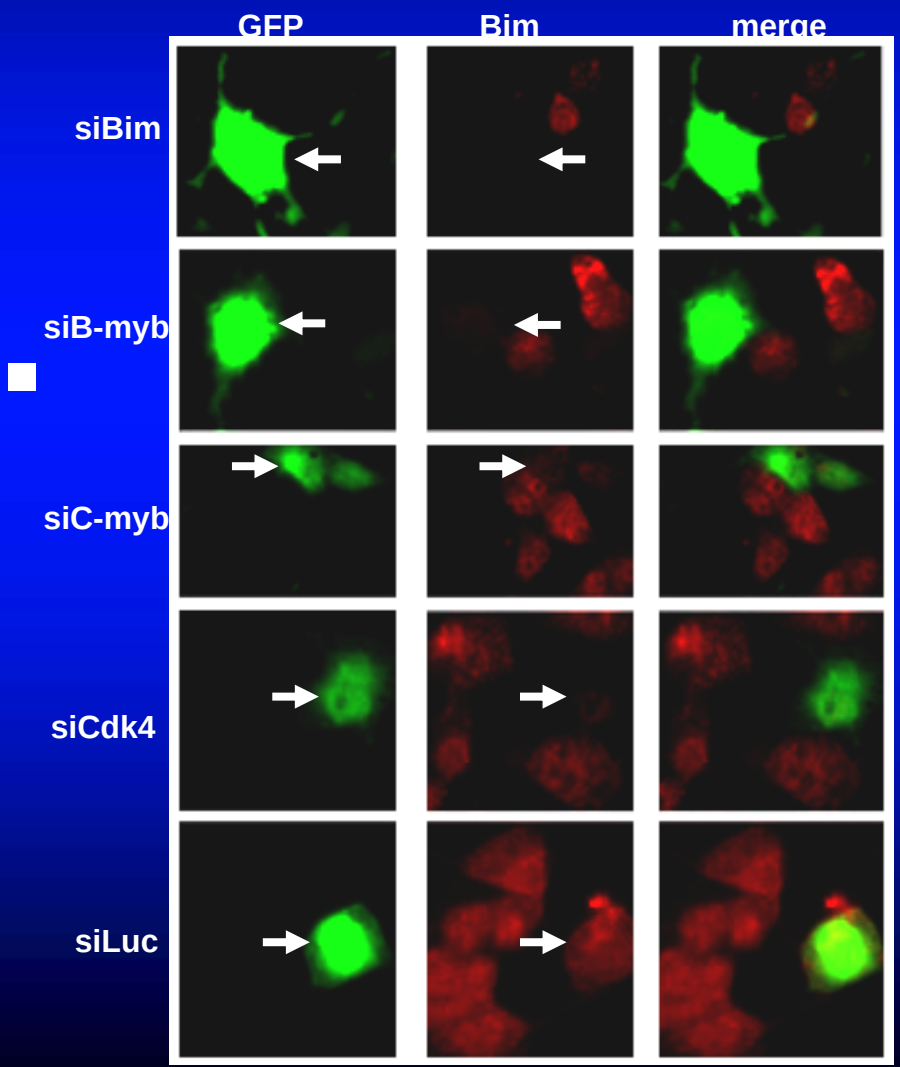
E2F REGULATES CELL PROLIFERATION & NEURON DEATH



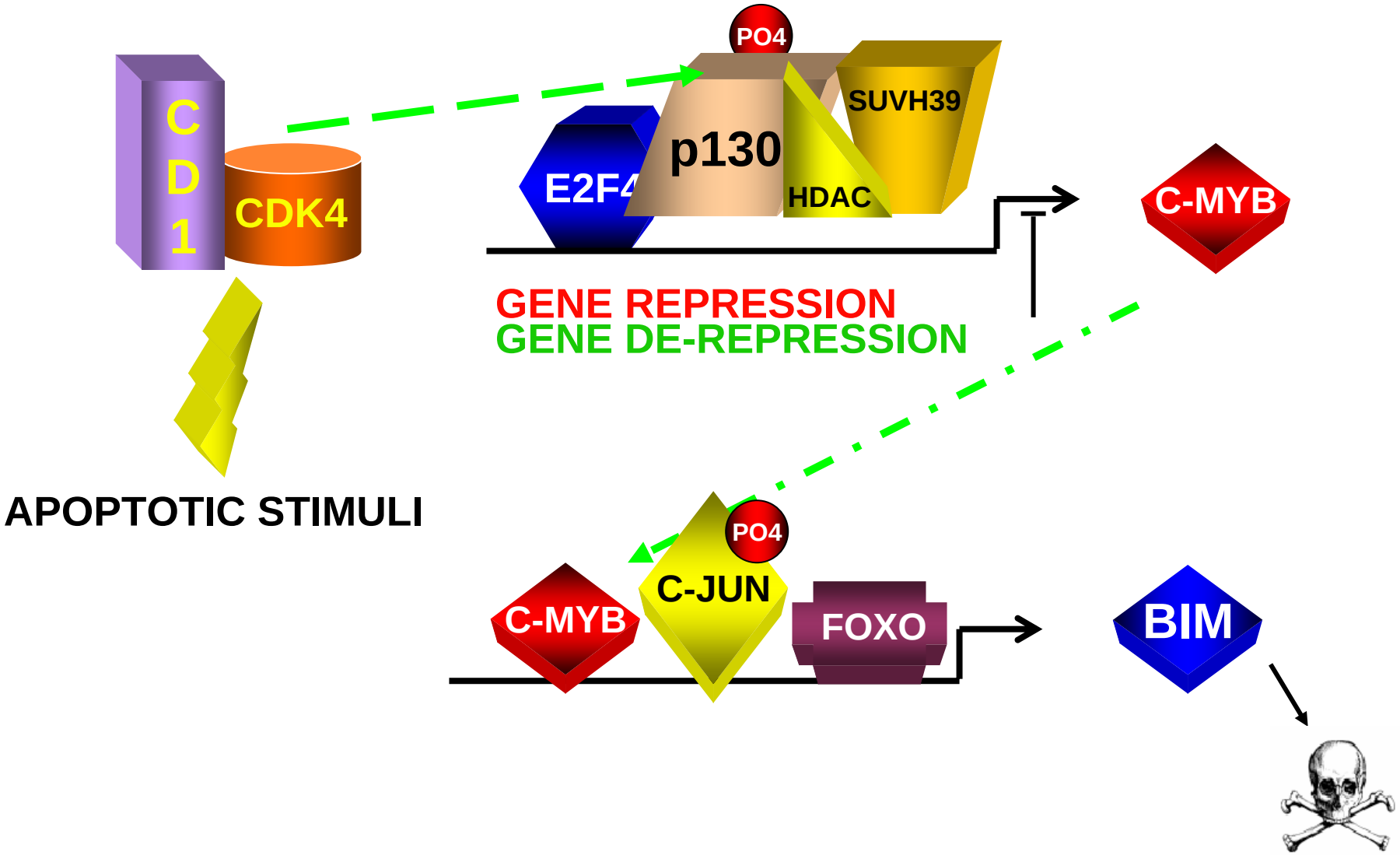
THE E2F PATHWAY LEADS TO BIM UPREGULATION VIA CDK4 AND MYB



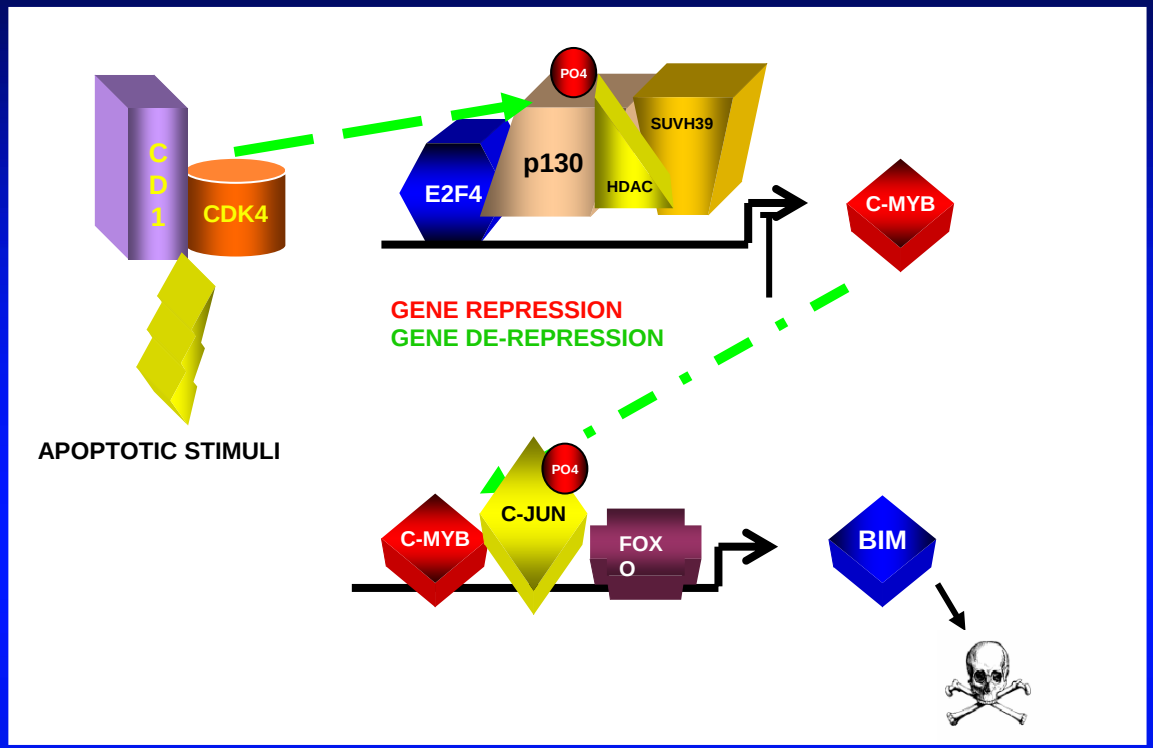
A. Neuronal PC12 cells

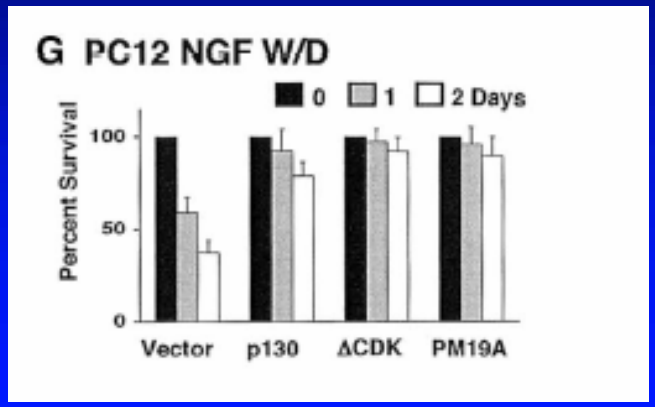


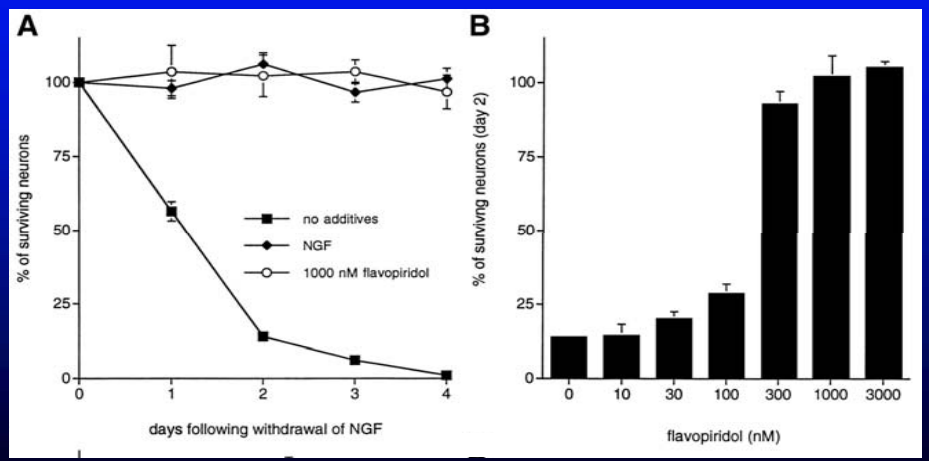
E2F AND NEURON CELL DEATH

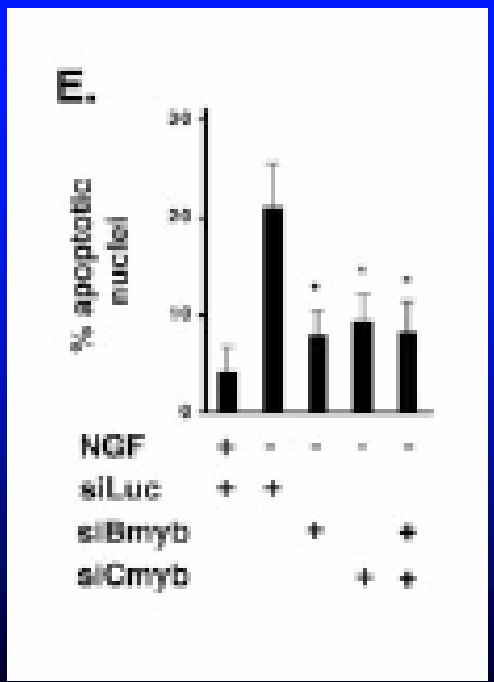


THE CDK4-E2F-p130-MYB-BIM PATHWAY OF NEURON CELL DEATH

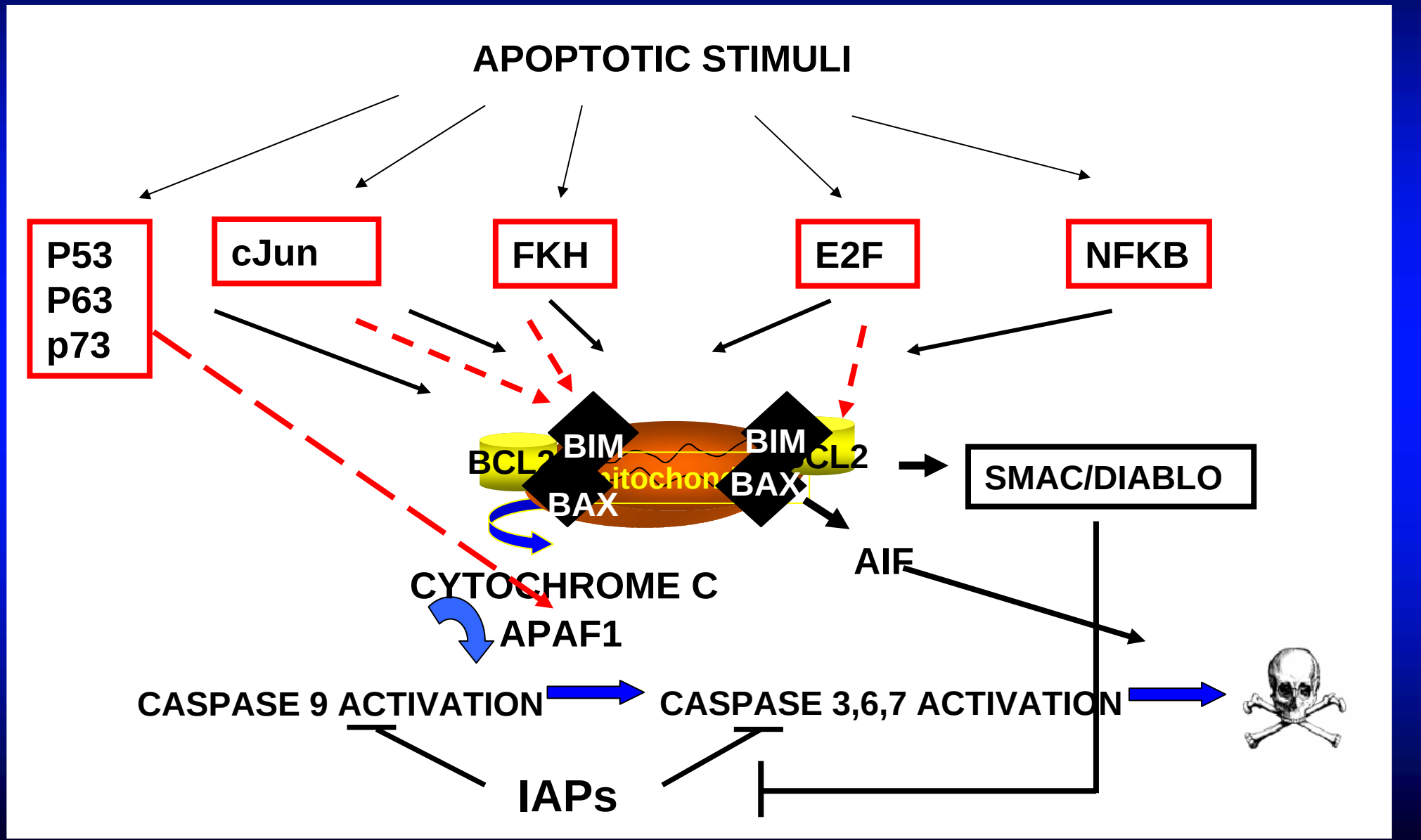








TRANSCRIPTIONAL REGULATION OF APOPTOTIC DEATH



- THERE IS MASSIVE DEATH OF NEURONS, NEUROPROGENITORS AND OLIGODENDROGLIA IN NORMAL VERTEBRATE DEVELOPMENT

- THIS IS LARGELY REGULATED BY ACCESS TO LIMITING SUPPLIES OF EXOGENOUS SURVIVAL-PROMOTING TROPHIC FACTORS

- SURVIVAL IS PROMOTED LARGELY BY ACTIVATION OF AKT AS WELL AS OF ERKS AND INVOLVES BLOCKADE OF DEATH PATHWAYS AT MULTIPLE POINTS

- DEVELOPMENTAL NEURON DEATH IS TRANSCRIPTION DEPENDENT

- INDUCTION OF DEATH INVOLVES MULTIPLE PRO-APOTOTIC SIGNALING PATHWAYS, SOME OF WHICH CONVERGE ON INDUCTION OF BH3-DOMAIN PROTEINS