Signalling via growth factors

Learning objectives

-to develop an understanding of growth factors

-to develop an understanding of how cells respond to growth factors

-to examine how growth factor signalling can go awry and lead to pathological conditions.

-to explore how modern rational drug design is capitalising on all of our understanding of growth factor signalling to treat disease.

What do cells and tissues need do for the body to achieve homeostasis?

-right number of cells

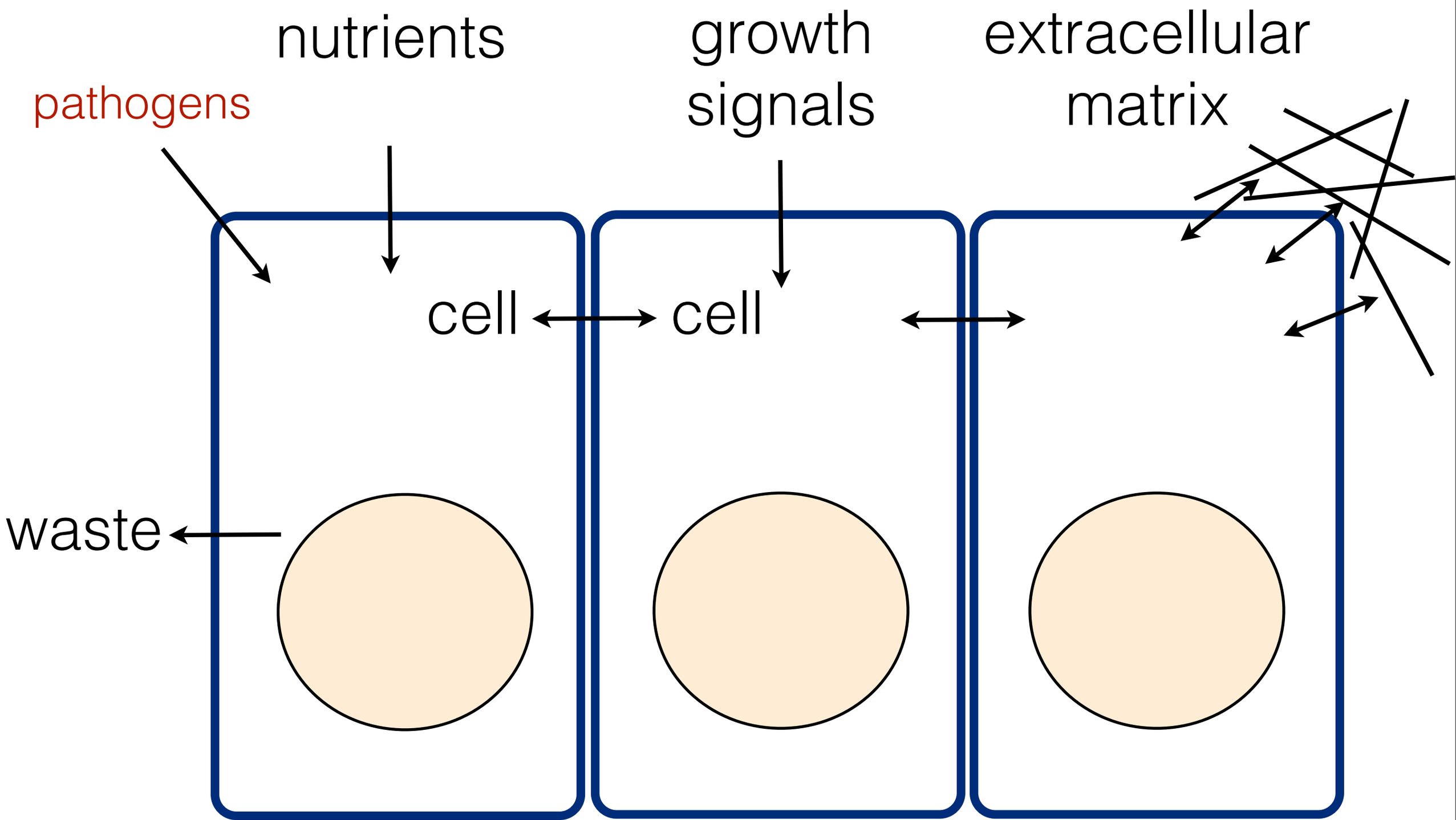
-doing the right thing

-at the right time

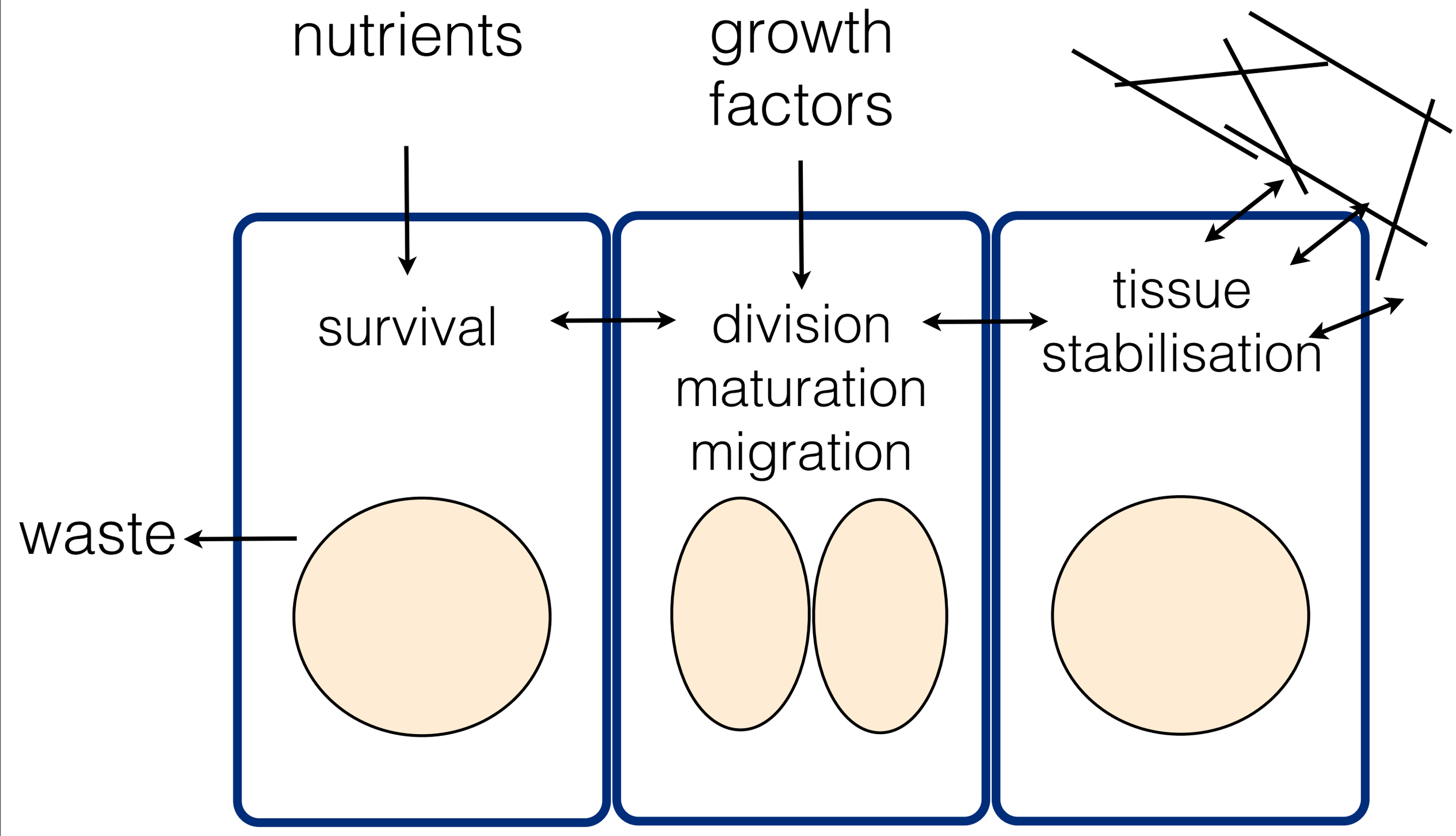
-in the right place

-able to cope with change

Cellular interactions with the environment



Cellular interactions with the environment



Growth factors

-usually soluble factors

-can be transported throughout the body rapidly

-bind specific receptors, usually expressed on restricted cell types.

- induce proliferation

-may also influence other processes such as differentiation, migration, maturation or specific functions.

Types of Growth Factors (GF)

Originally identified in blood production:

*Interleukins (IL)

*Colony stimulating factors (CSF)

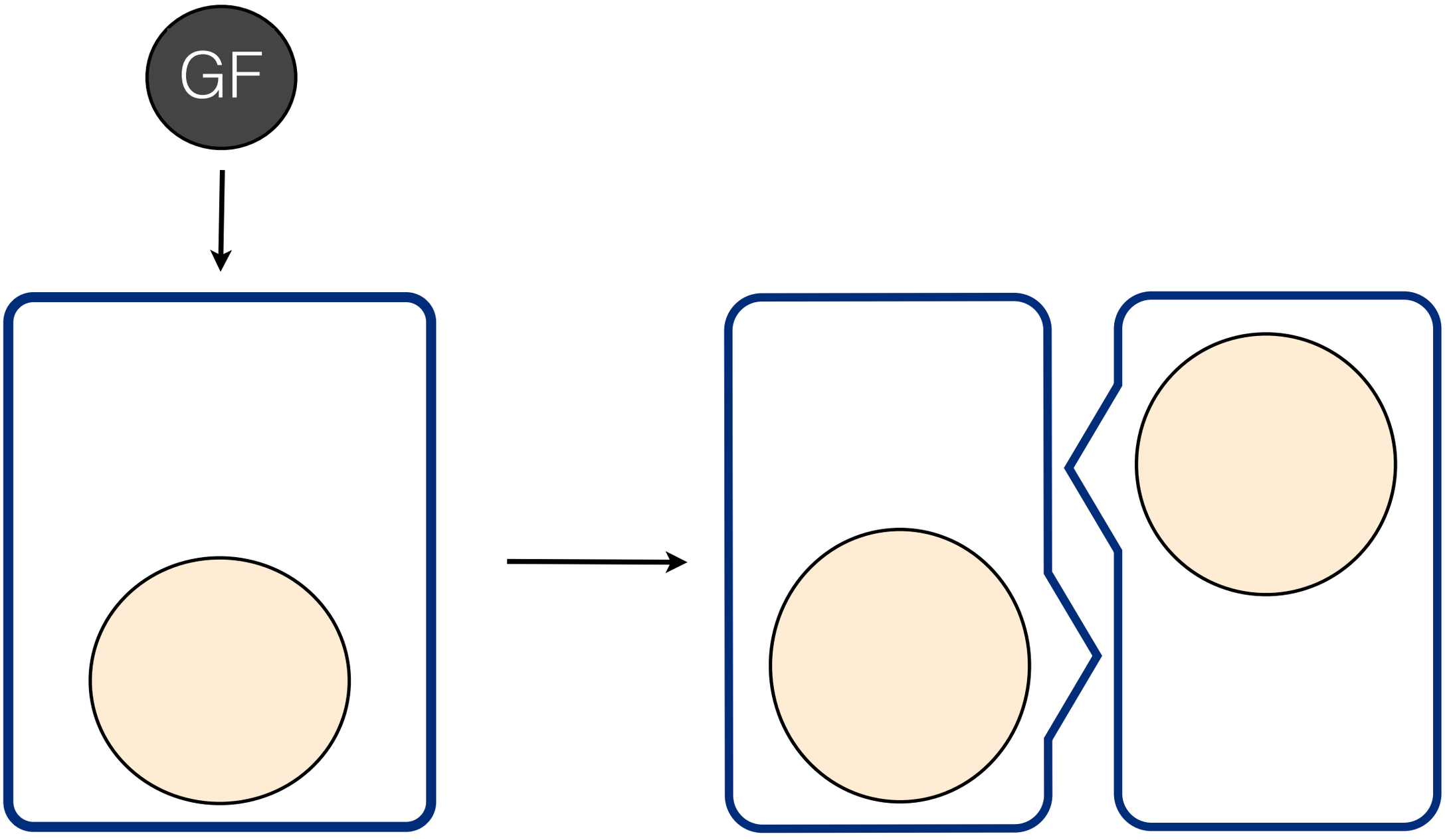
*Chemokines: show a similar sequence and play roles in chemotaxis.

Many others discovered in different tissues e.g.:

*Fibroblast growth factors (FGF)
*Hepatocyte growth factor (HGF)
*Epidermal growth factor (EGF)
*Neurotrophic factors
*Vascular endothelial growth factor (VEGF)
*Transforming growth factor-beta
*Some hormones such as insulin-like growth factor or erythropoietin
(except steroid hormones)

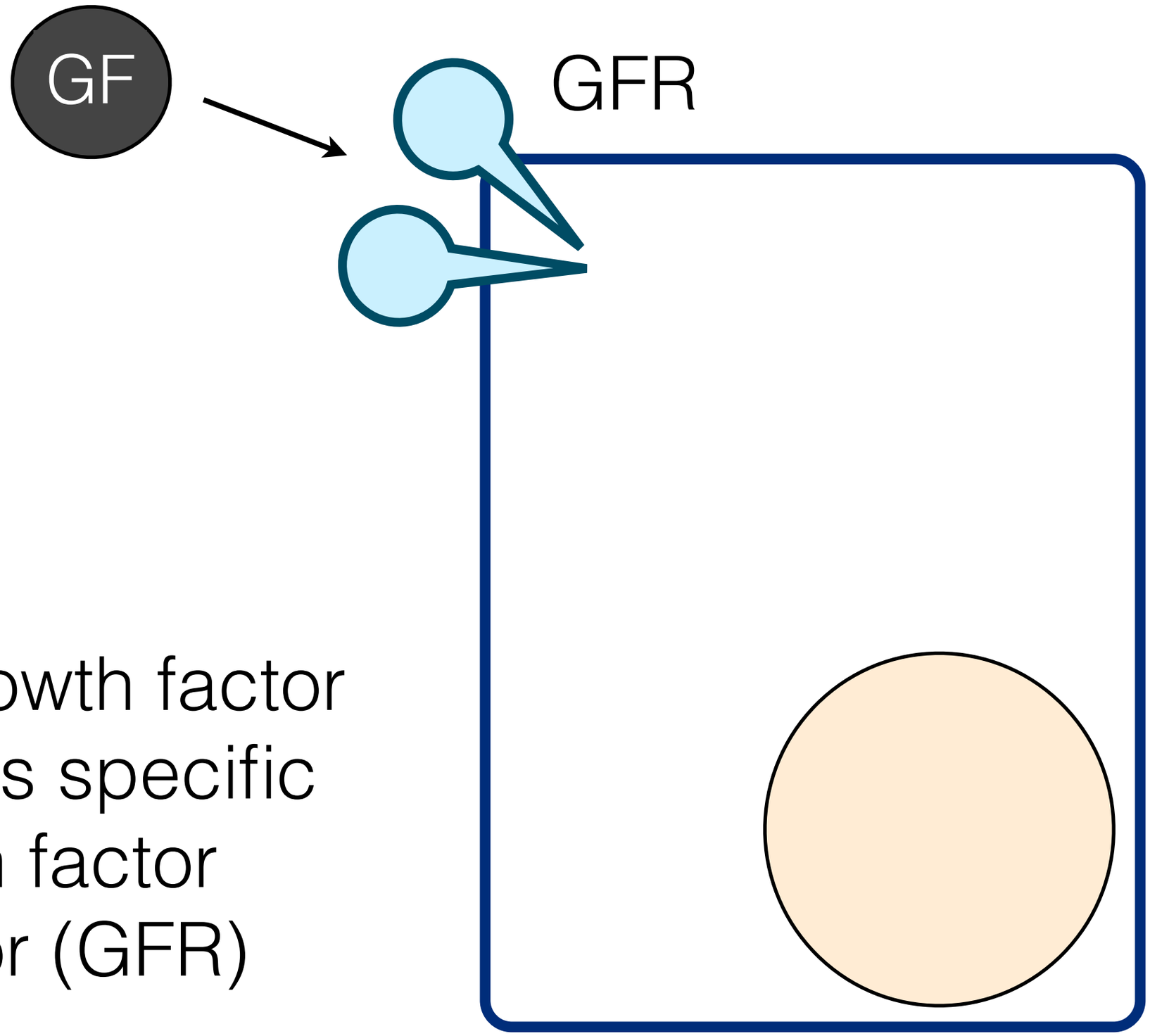
Signalling via growth factor receptors

how does an external signal such as a growth factor induce an internal signal inside a cell?



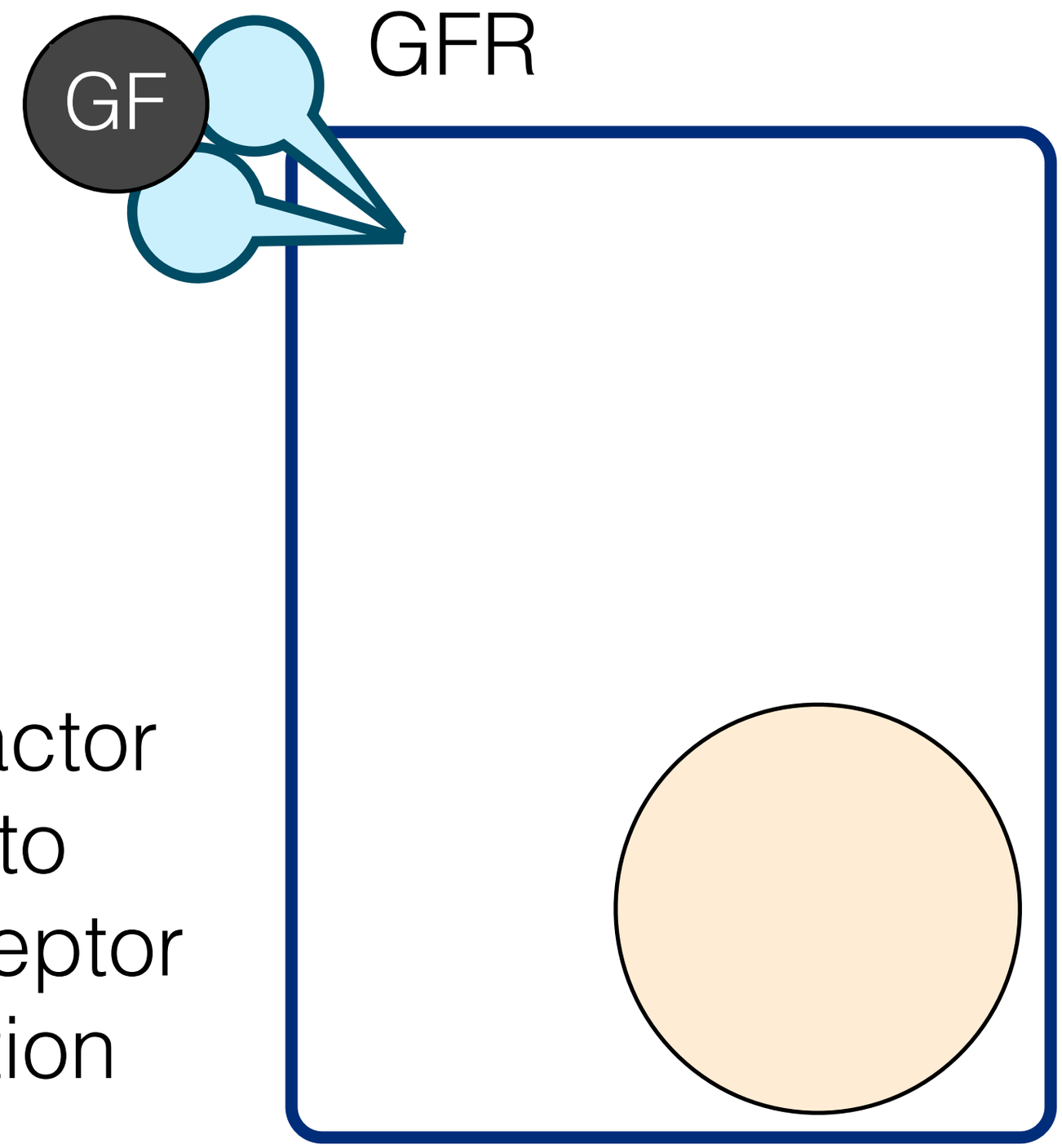
Signalling via growth factor receptors

Step 1: growth factor (GF) binds specific growth factor receptor (GFR)



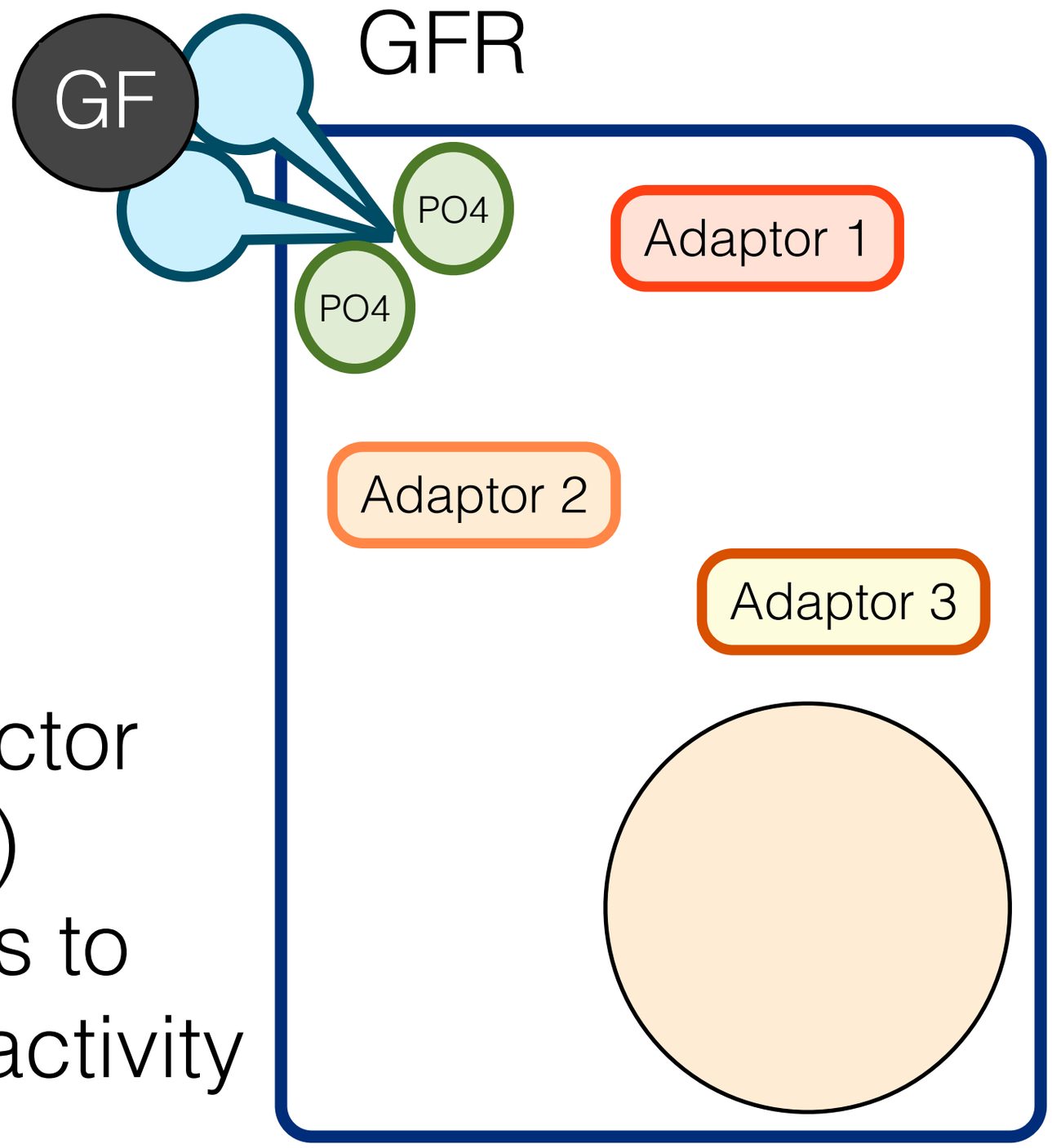
Signalling via growth factor receptors

Step 2: growth factor binding leads to growth factor receptor (GFR) dimerisation



Signalling via growth factor receptors

Step 3: Growth factor receptor (GFR) dimerisation leads to activation of kinase activity



Receptor tyrosine kinase (RTK) activity

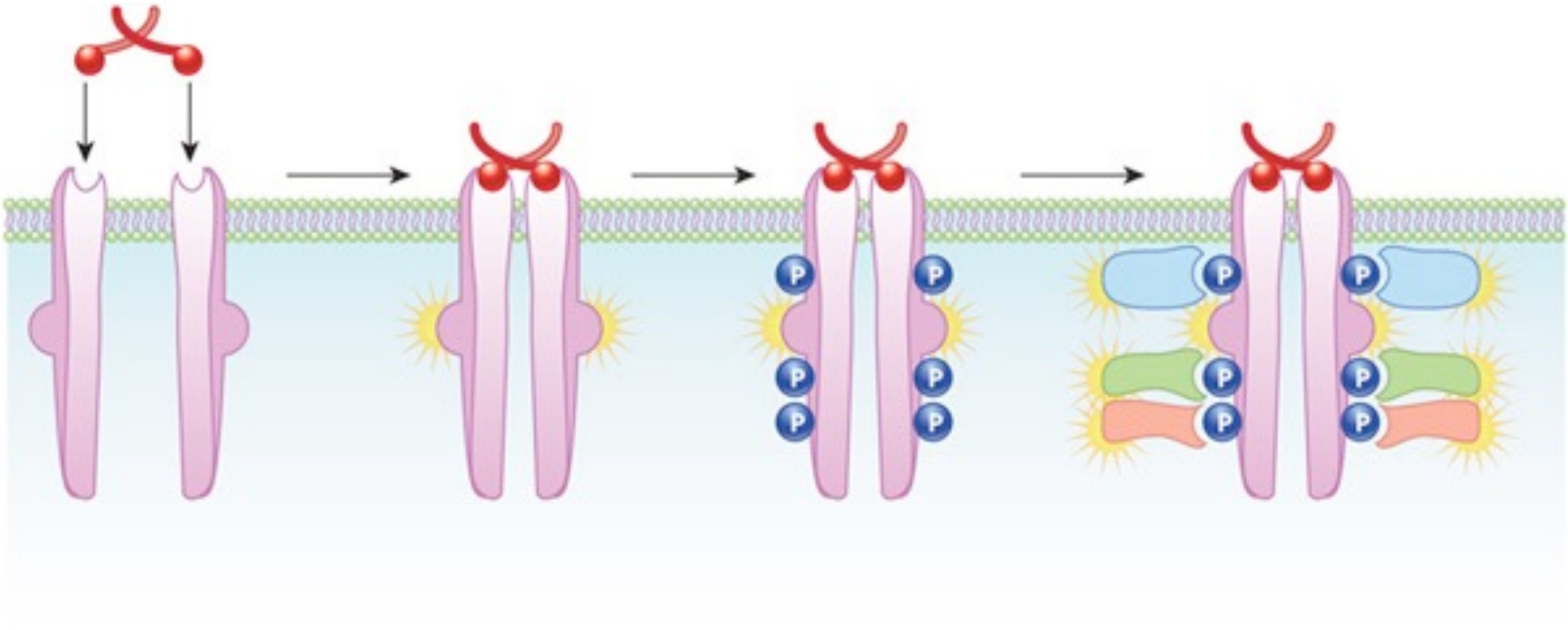


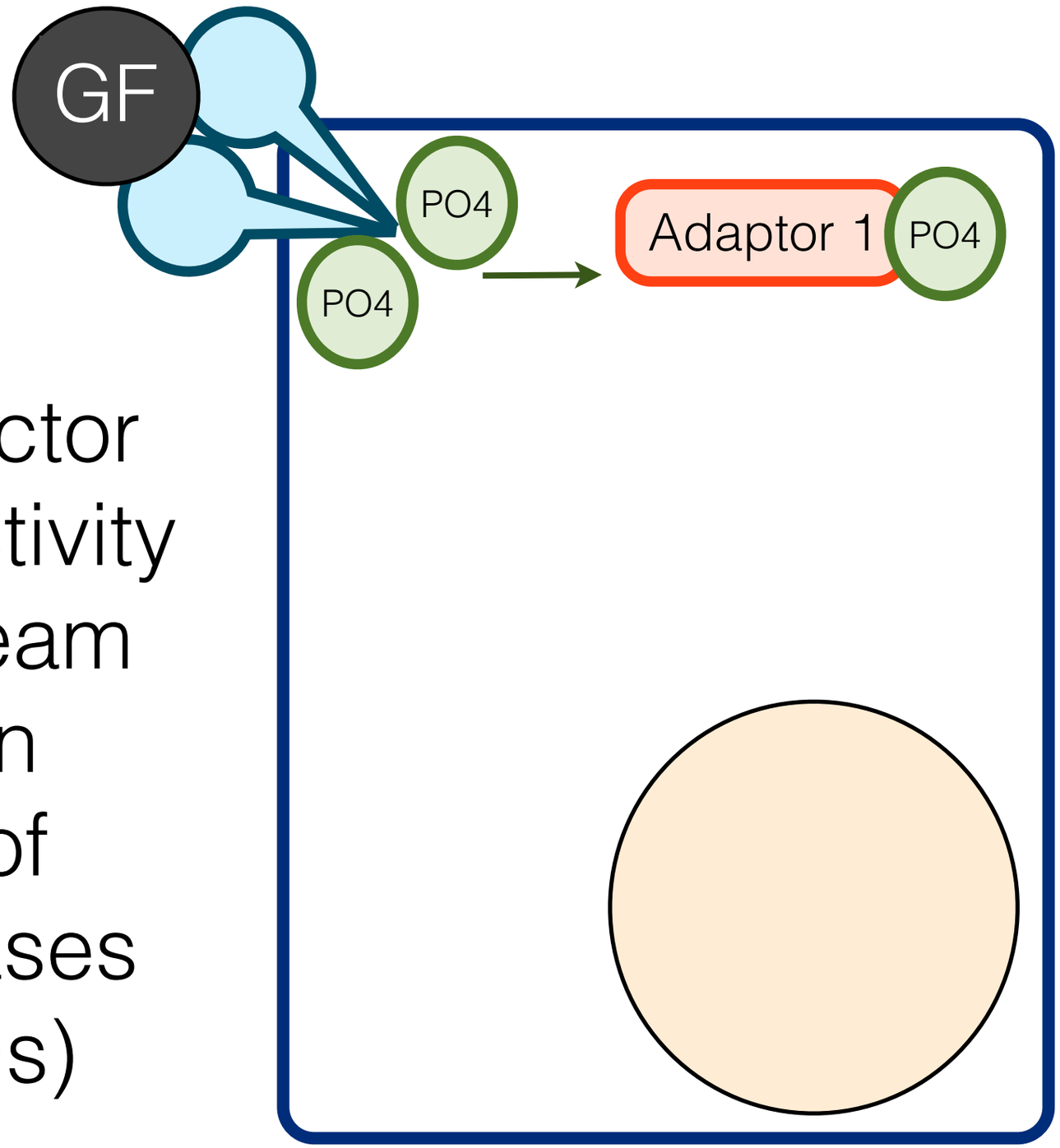
Figure 1: RTK activation involves the joining together and phosphorylation of proteins.

On the left, an unactivated RTK receptor (pink) encounters a ligand (red).
Upon binding, the receptor forms a complex of proteins that phosphorylate each other.
In turn, this phosphorylation affects other proteins in the cell that change gene transcription (not shown).

http://www.nature.com/scitable/topicpage/rtk-14050230

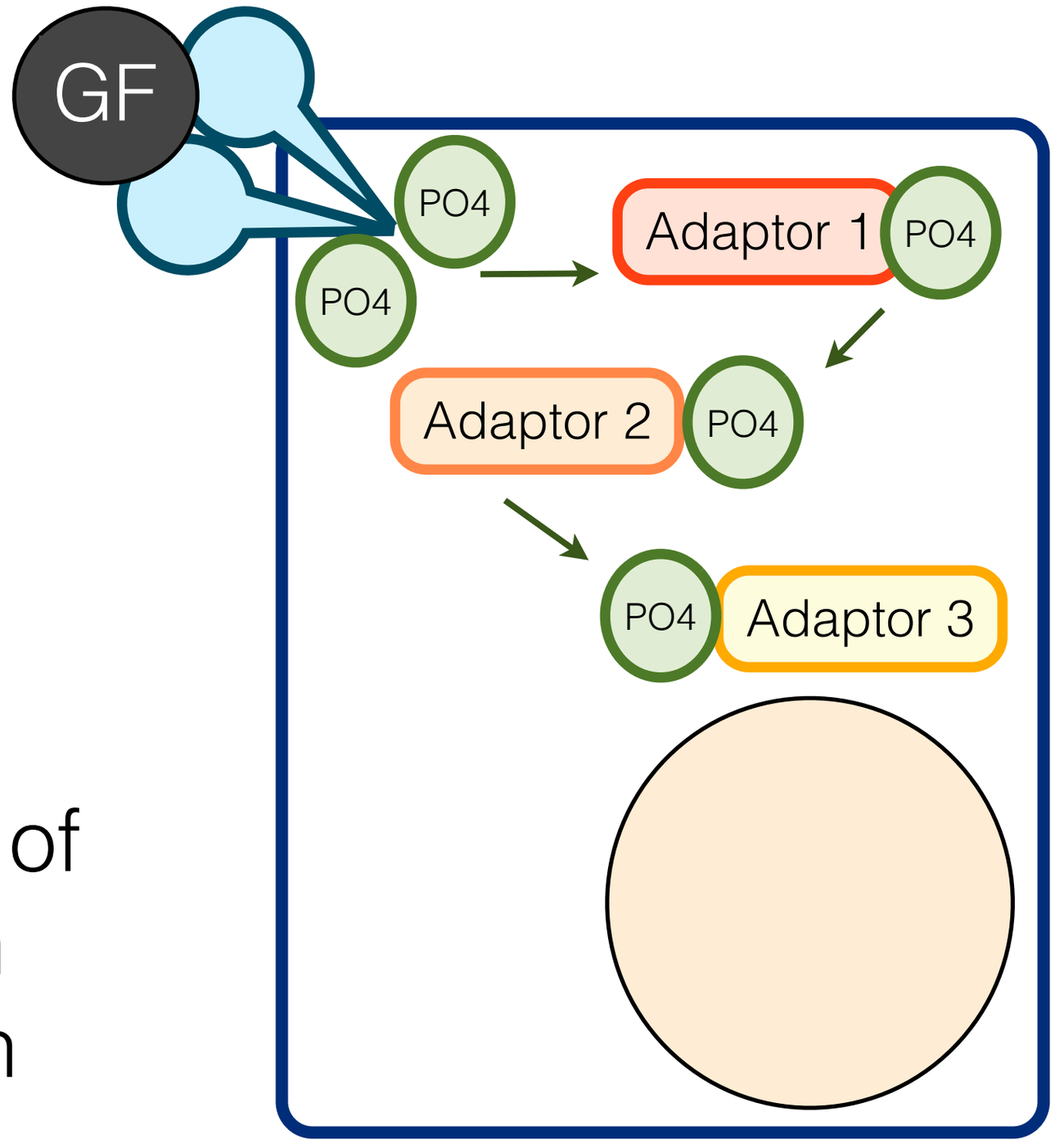
Signalling via growth factor receptors

Step 4: Growth factor receptor kinase activity induces downstream phosphorylation and activation of non-receptor kinases (adaptor proteins)



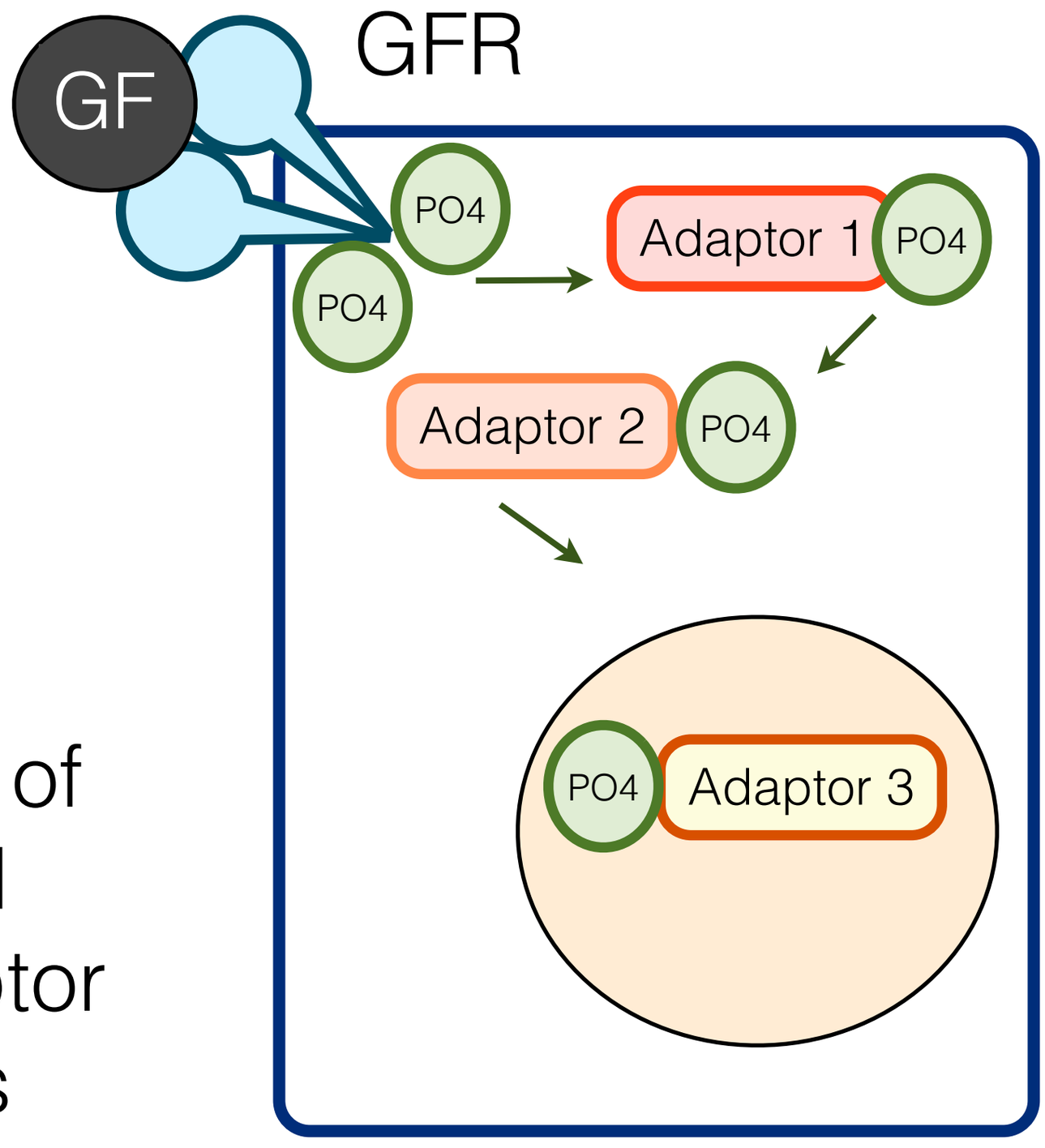
Signalling via growth factor receptors

Step 5: Cascade of adaptor protein phosphorylation



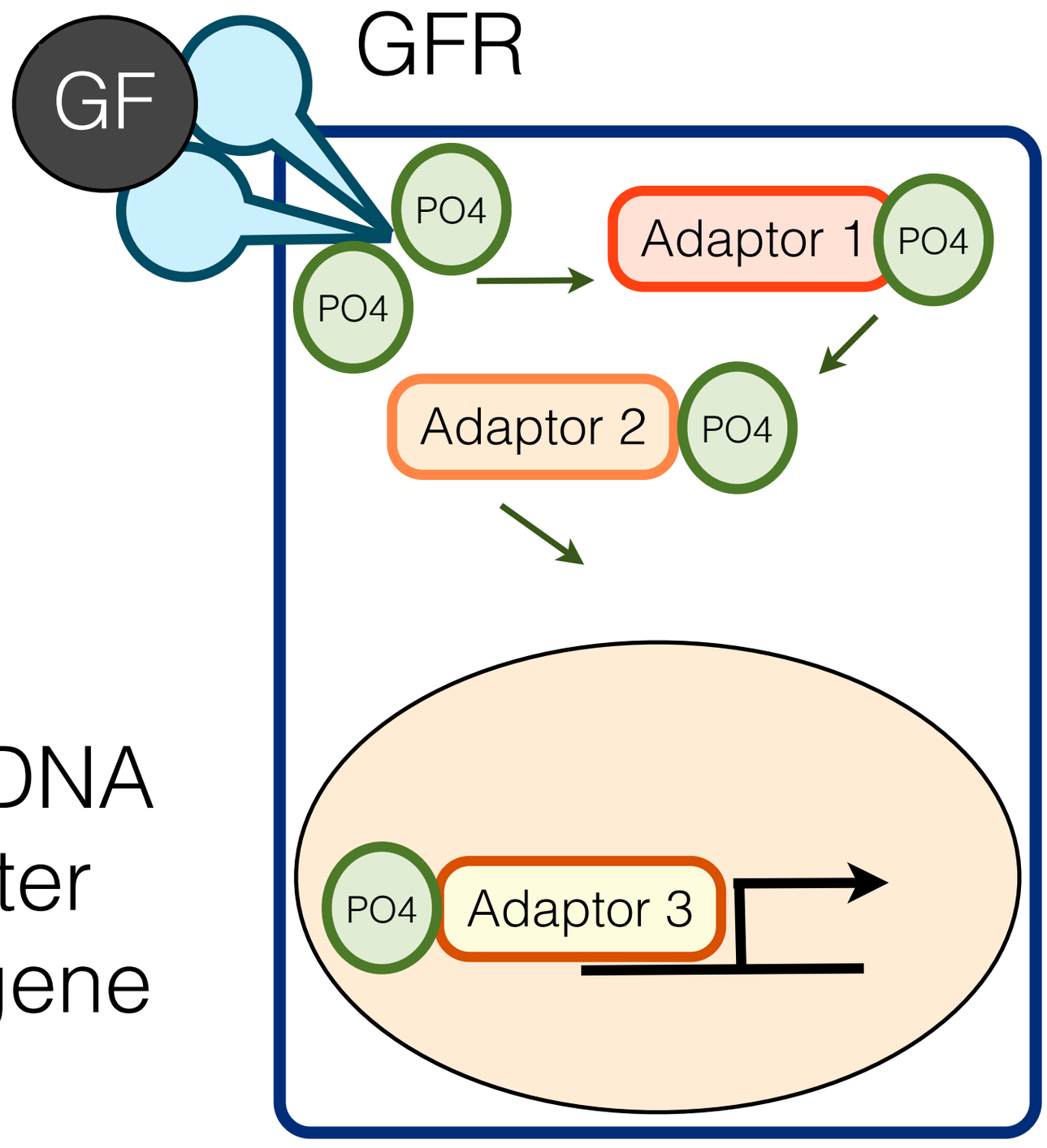
Signalling via growth factor receptors

Step 6: Migration of phosphorylated downstream adaptor into the nucleus



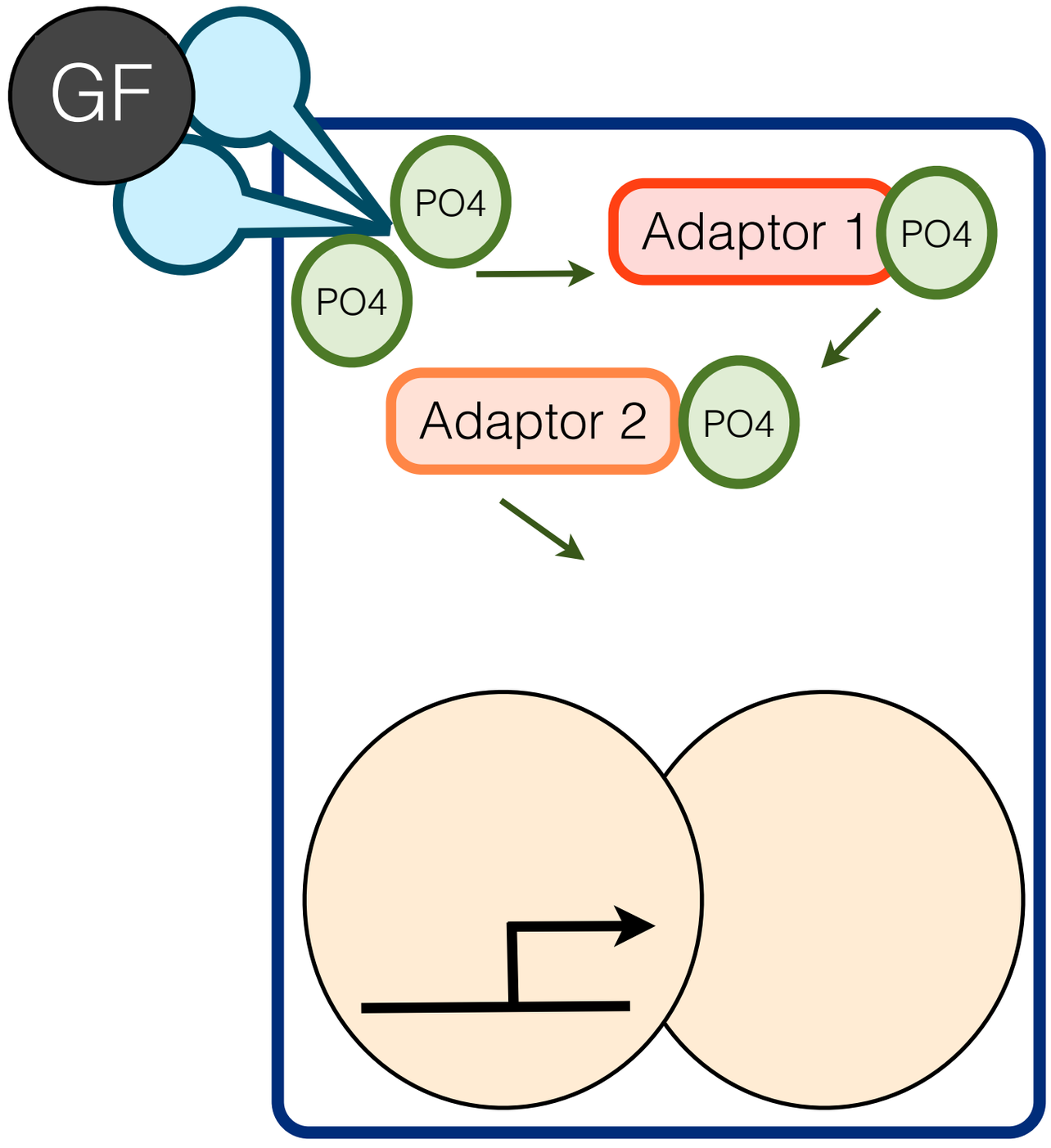
Signalling via growth factor receptors

Step 7: Binding to DNA at specific promoter regions to induce gene expression



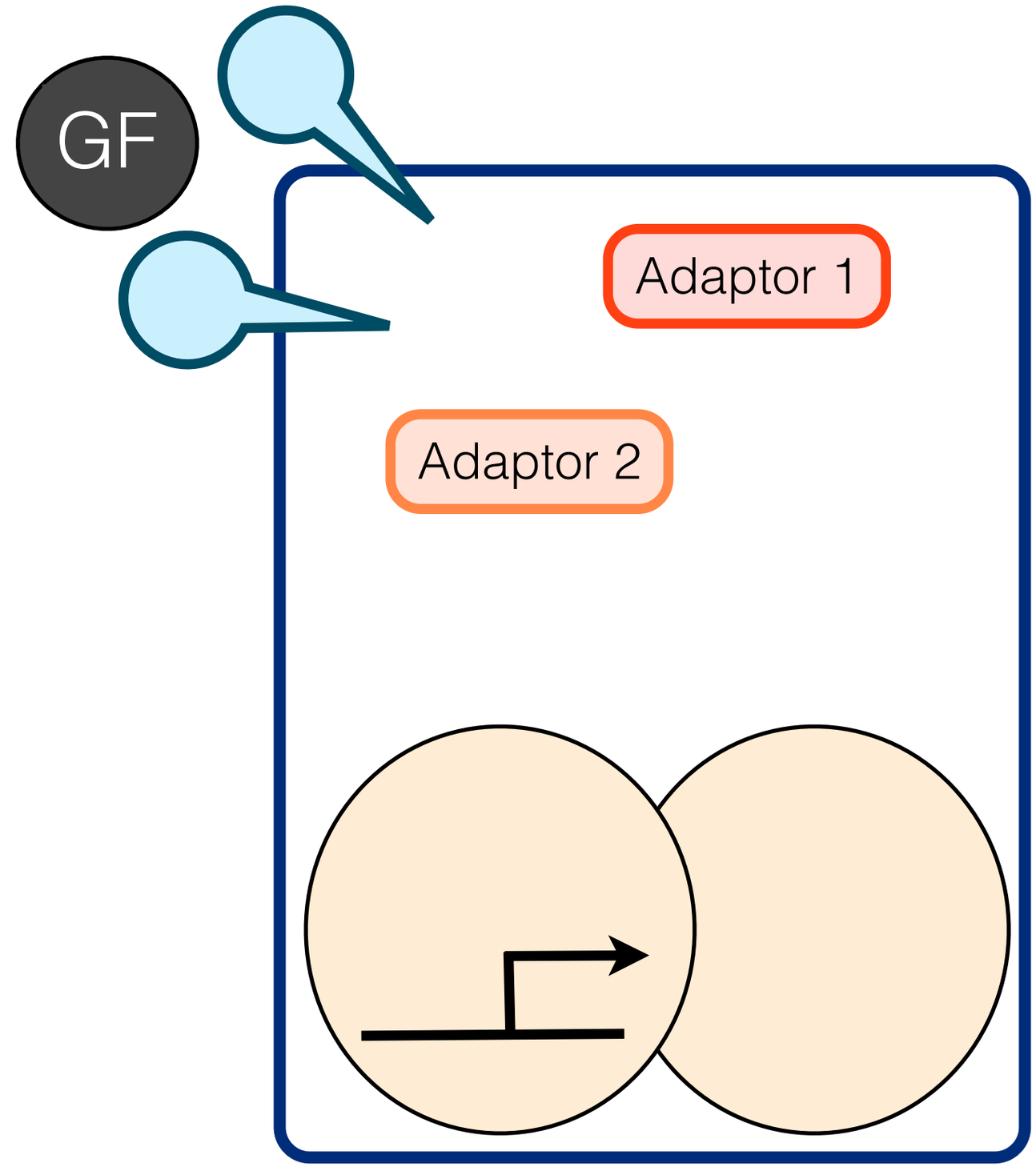
Signalling via growth factor receptors

Step 8: Induction of cell proliferation gene expression leads to cell division

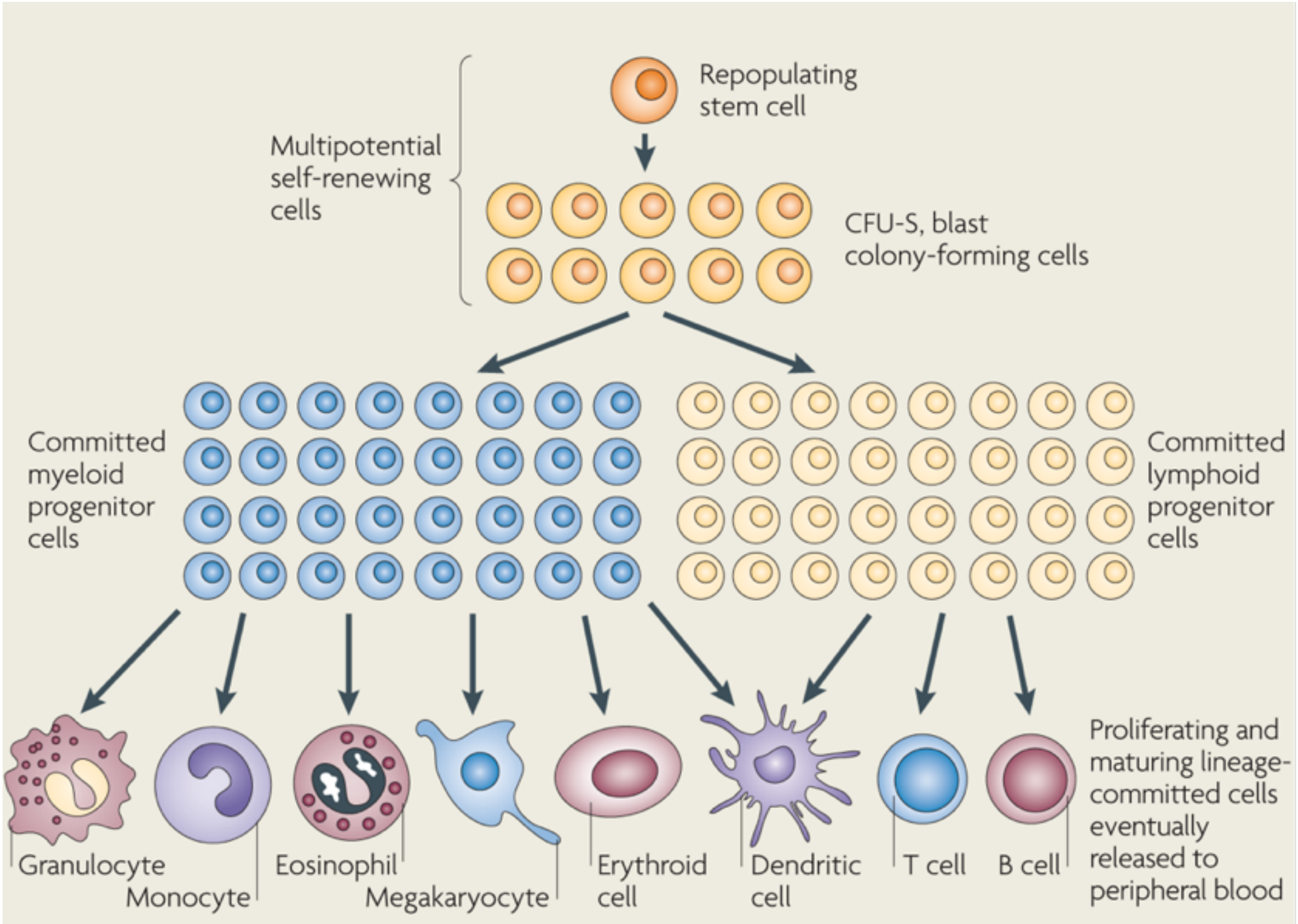


Signalling via growth factor receptors

Step 9: Induction of signalling suppression

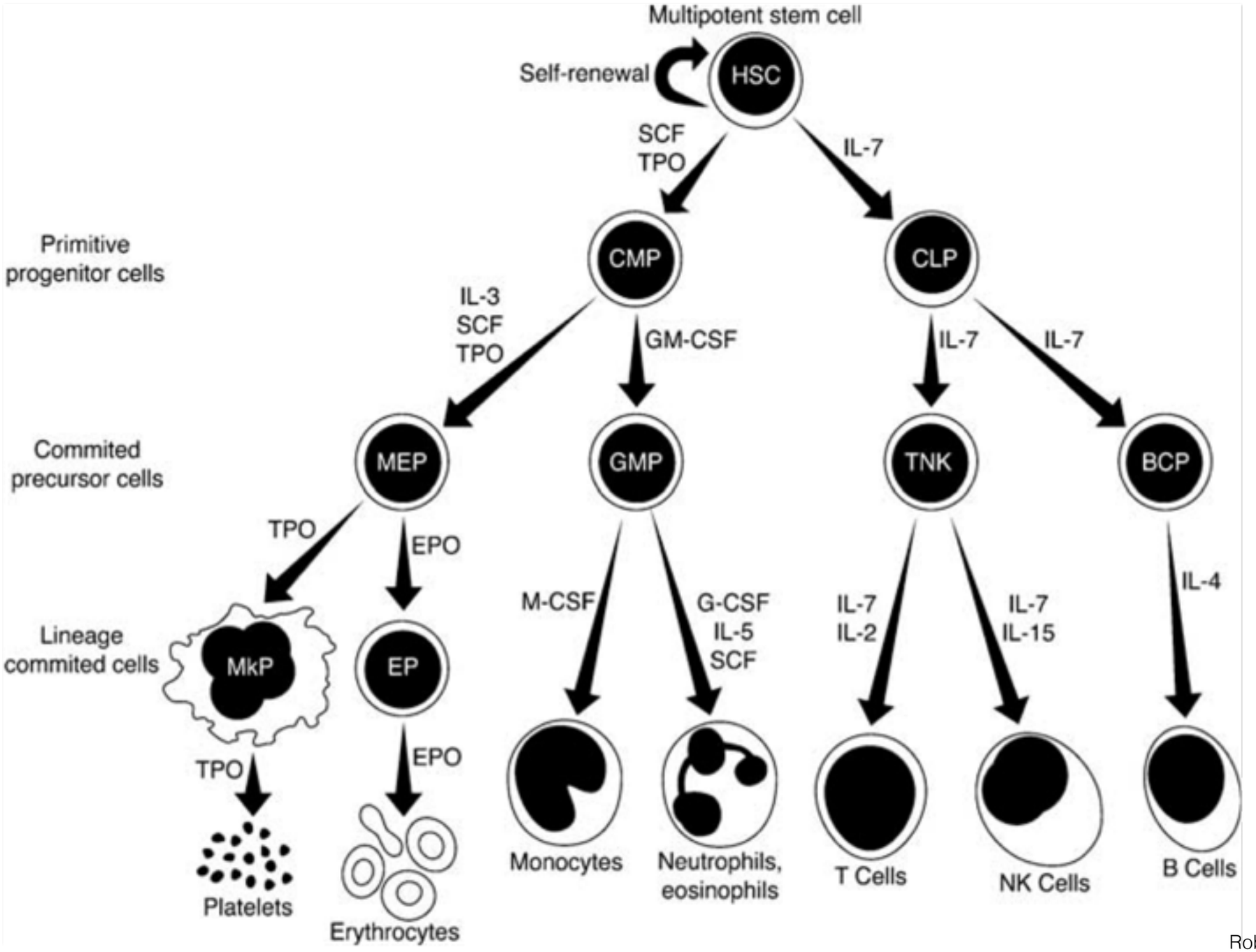


Haematopoietic hierarchy



Metcalf, Nat. Rev. Cancer, 2010, Vol 10 pp 425

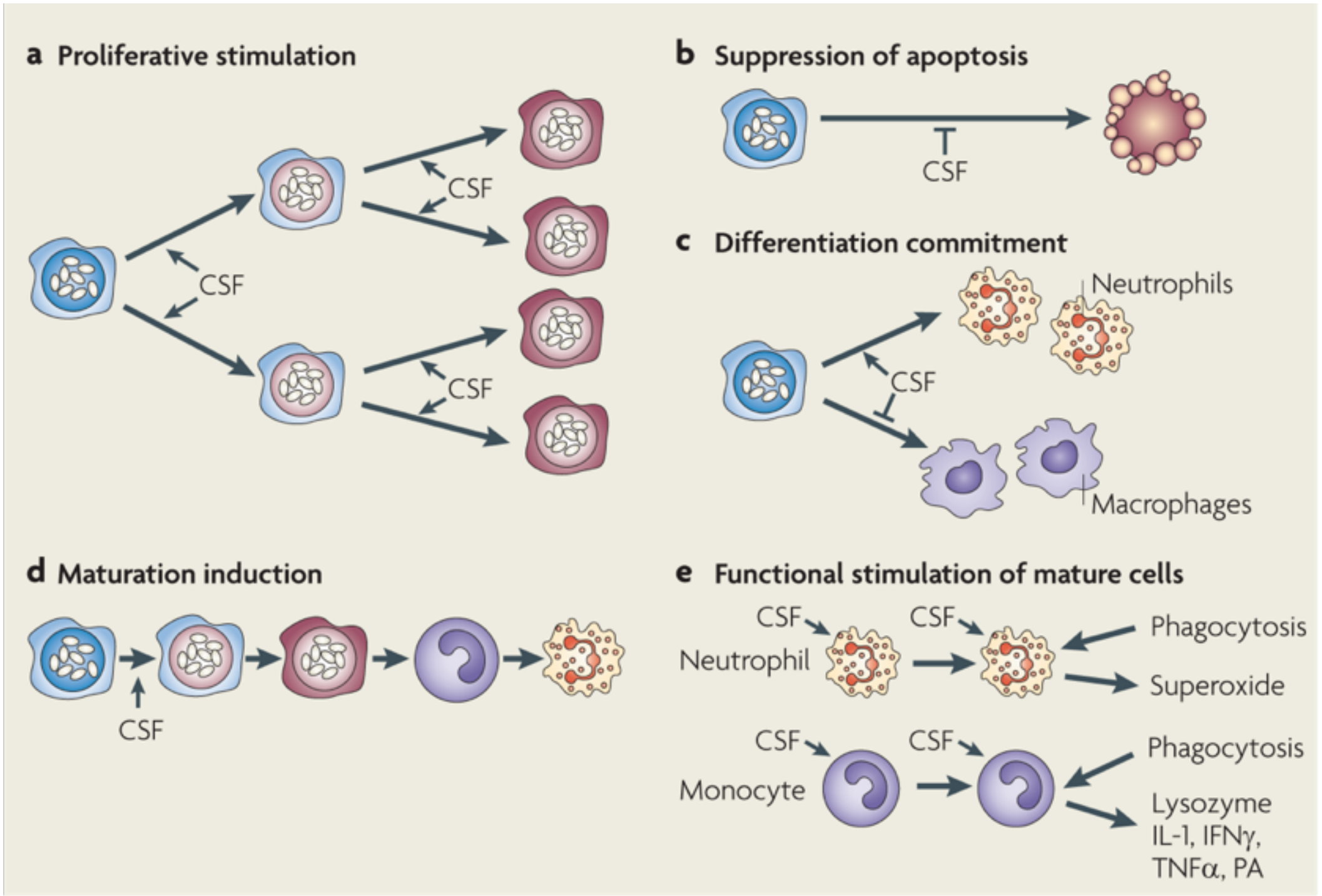
Growth factors in blood cell production



Robb, Oncogene (2007) 26, 6715–6723

IL=Interleukins Tpo=thrombopoietin Epo=Erythropoietin

Growth factors can play a range of roles in blood production



Metcalf, Nat. Rev. Cancer, 2010, Vol 10 pp 425

http://www.wehi.edu.au/education/wehitv/colony_stimulating_factor_csf-1/

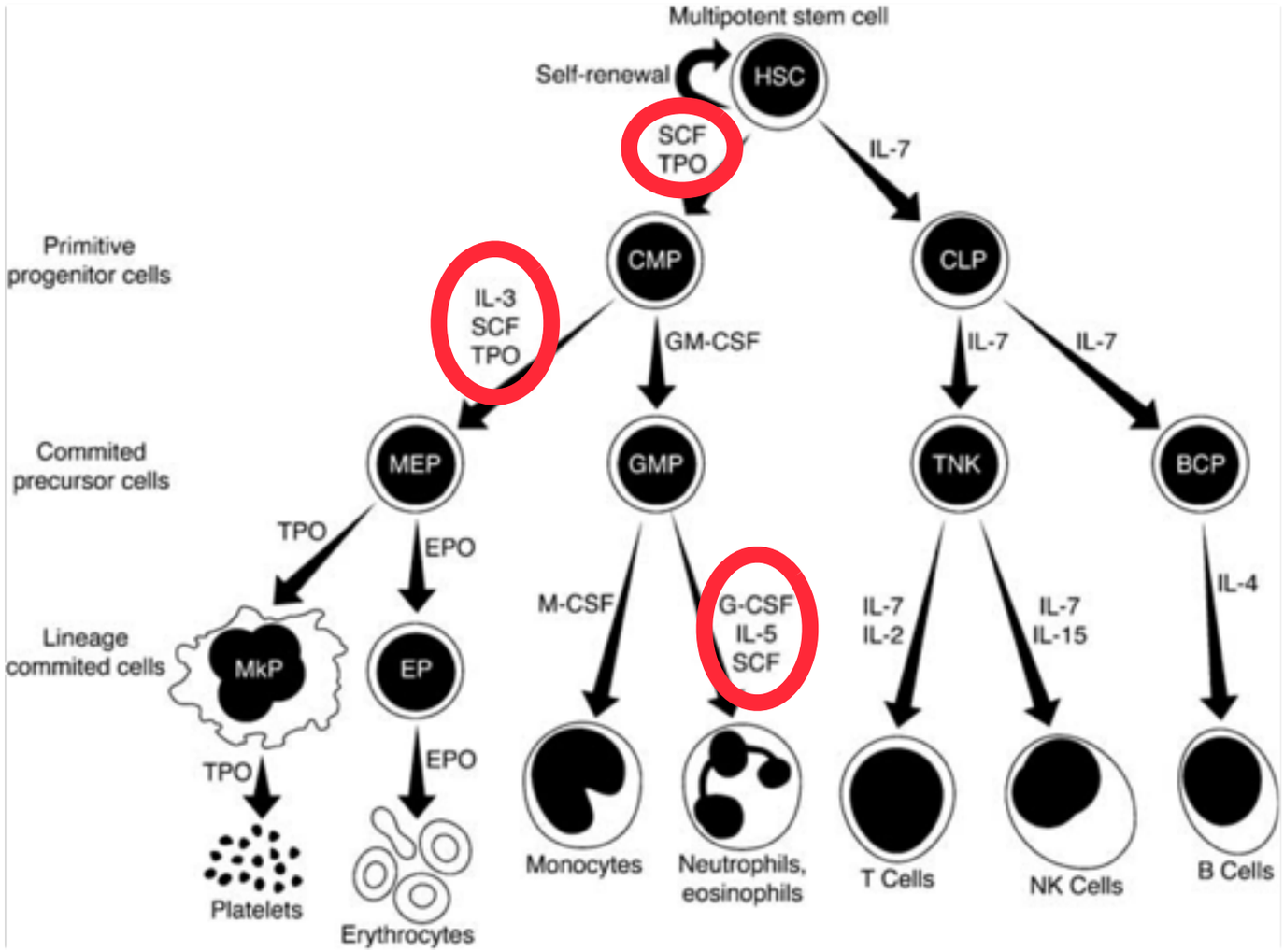
Stem cell factor (SCF)

*Different blood cell types require distinct growth factors during their maturation.

*HSC need the growth factor SCF (stem cell factor) to survive

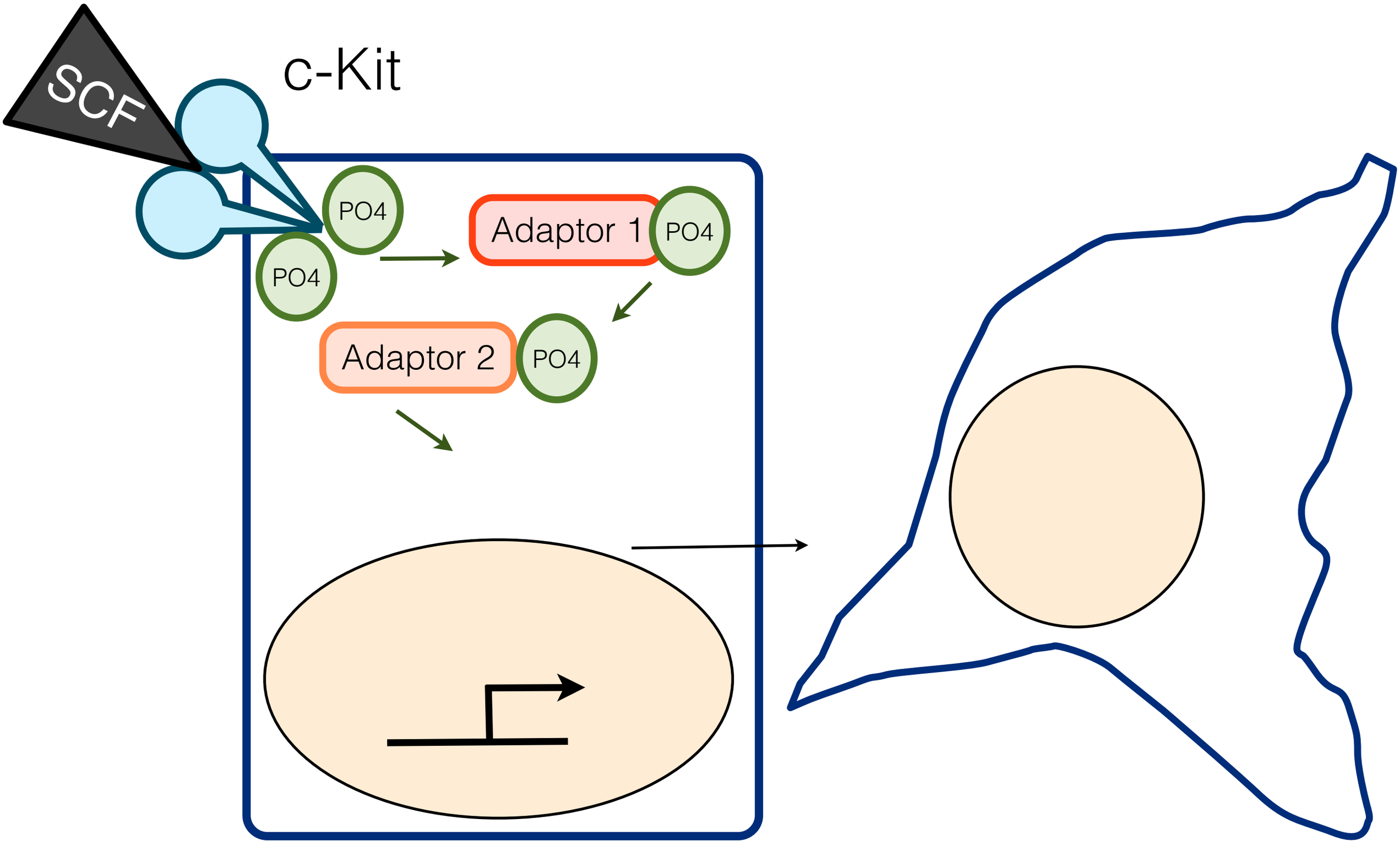
*SCF knockout mice die in utero

*Binds to a surface receptor tyrosine kinase on HSC named c-kit.



Robb, Oncogene (2007) 26, 6715–6723

Growth factors can induce migration

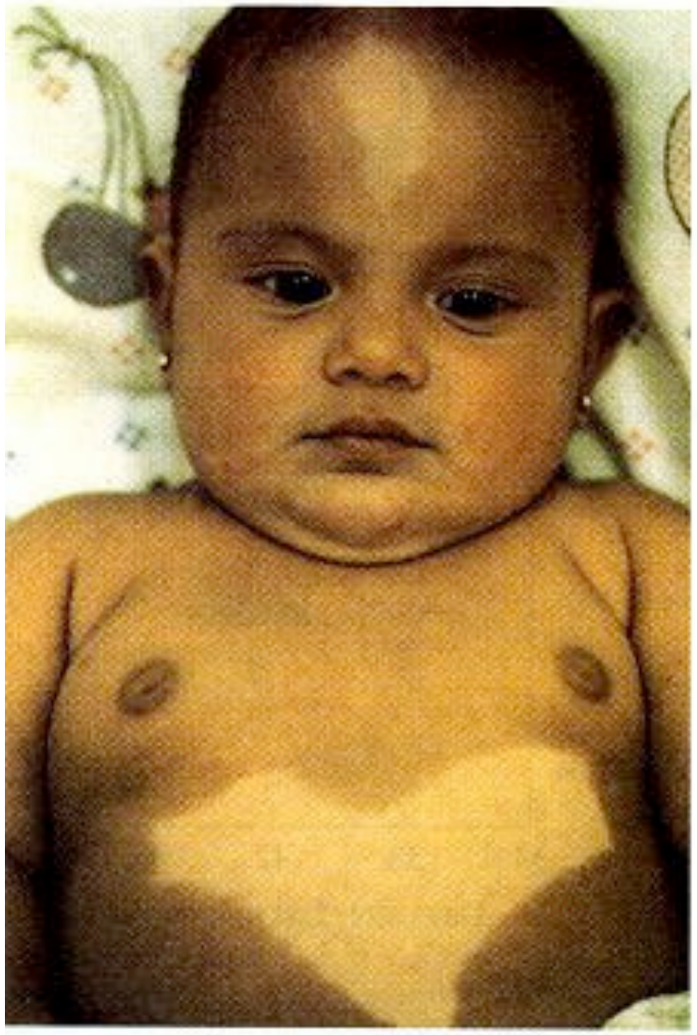


Stem cell factor, c-Kit and Piebaldism

*Melanocytes fail to migrate completely to the ventral midline leaving part of the body unpigmented.

*this migration is regulated by SCF binding to c-Kit

*Mutations in SCF or c-Kit genes can lead to piebaldism



(A)

(B)

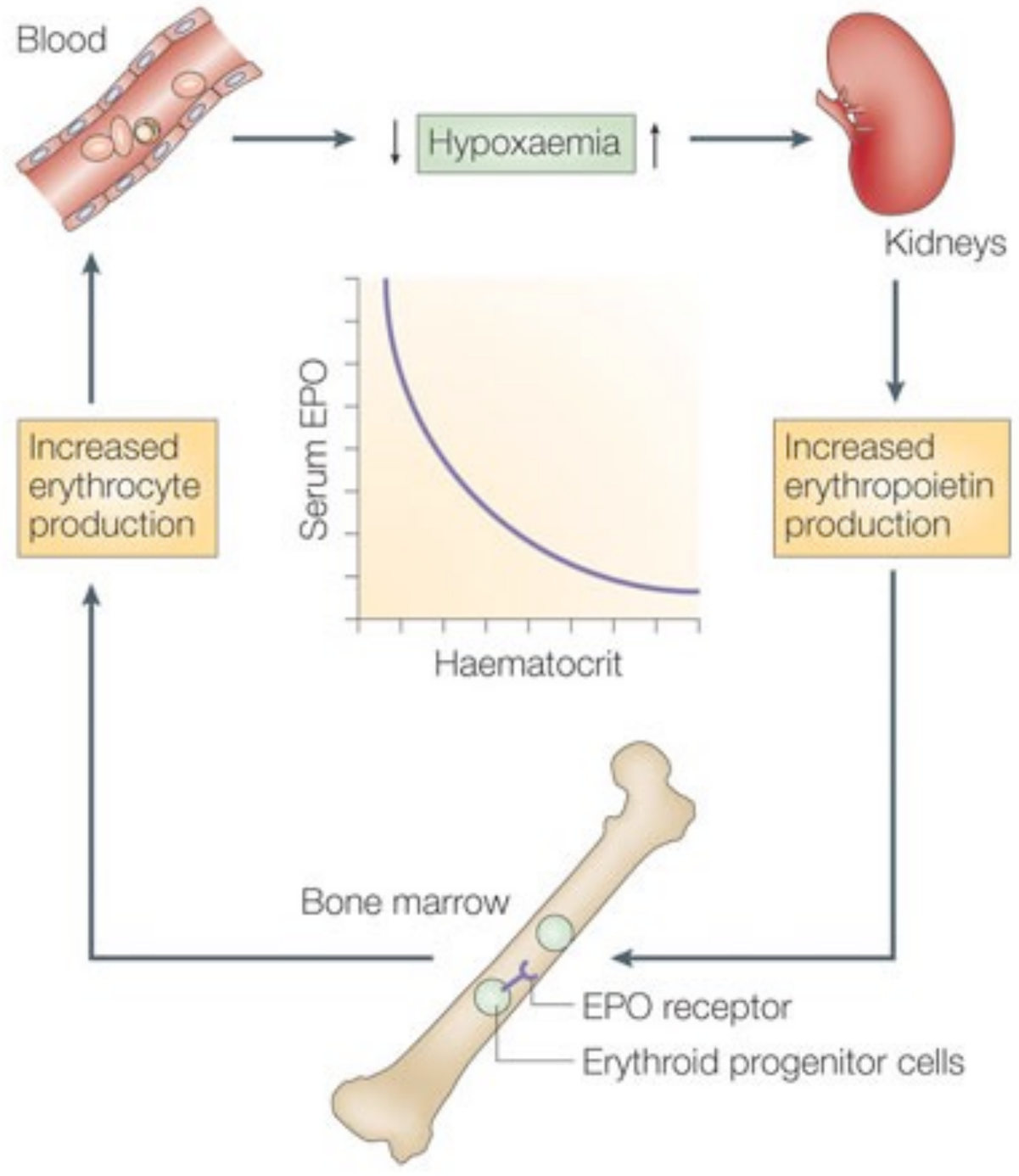
Developmental Biology. 6th edition.
Gilbert SF.
Sunderland (MA): Sinauer Associates; 2000.

Erythropoietin: the hormone that regulates RBC number

*Erythropoietin (Epo) is hormone that acts as a growth factor for the erythroid lineage.

*Essential for the expansion of erythroid progenitors.

*Produced endothelial cells of the peritubular capillaries of the adult kidney.

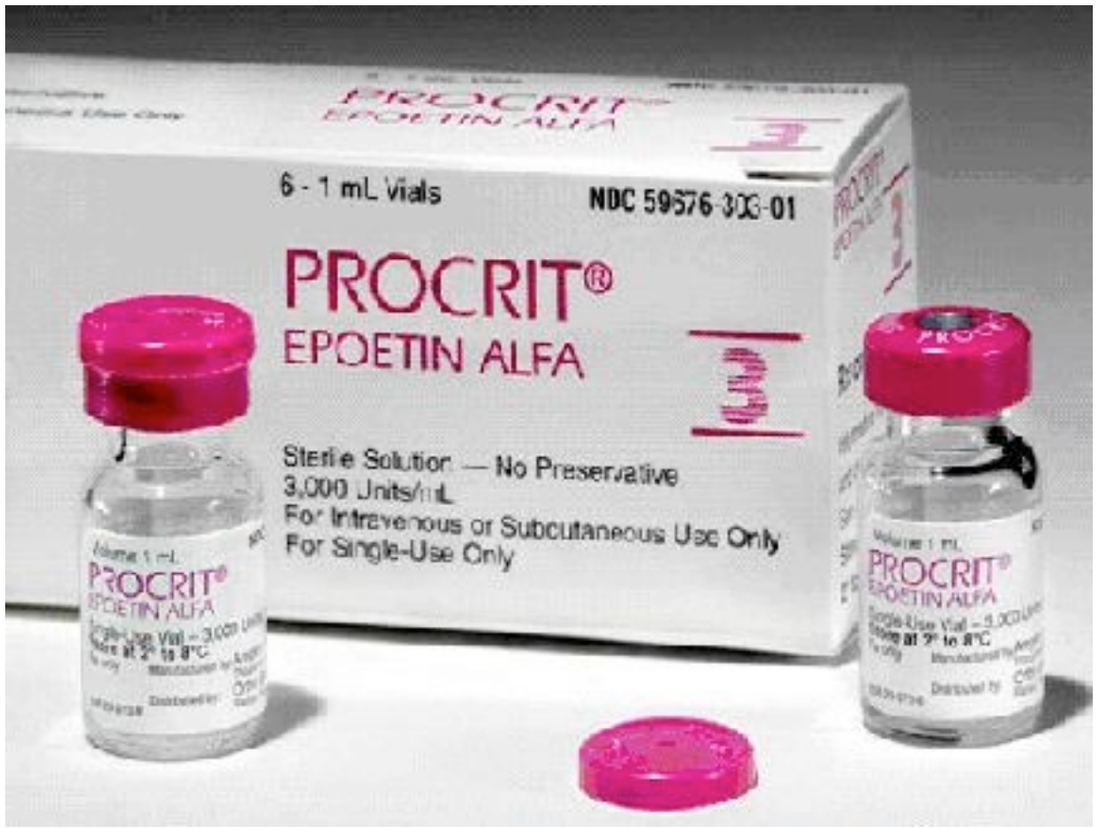


Uses of erythropoietin (Epo)

*Widely used to treat anaemia following surgery or chemotherapy.

*Commercially produced forms of Epo generated
~$9 billion in sales in 2006.

*Widely used as a “doping” drug in sports.

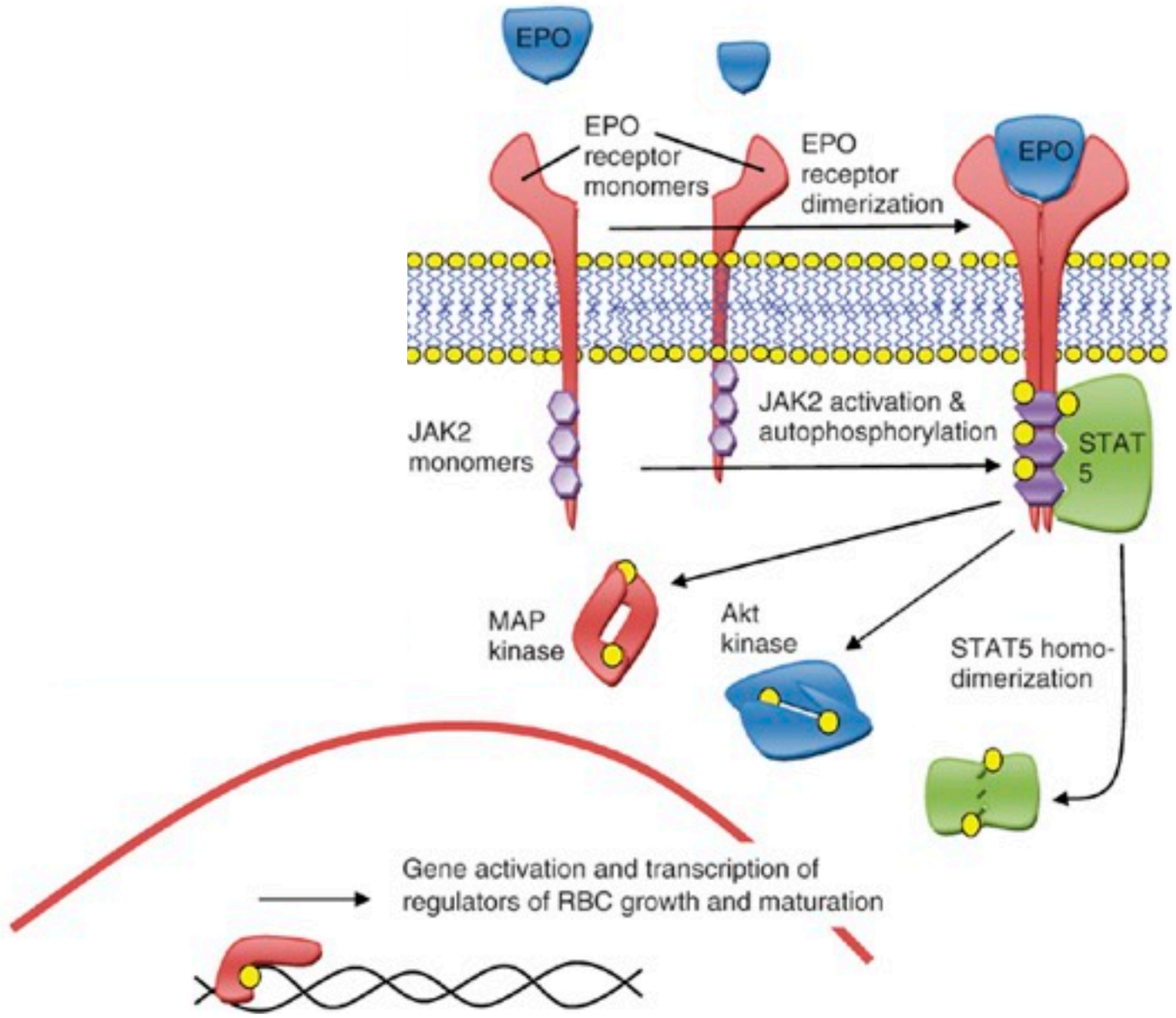


Erythropoietin signalling

*Epo binds to a cell-surface receptor EpoR

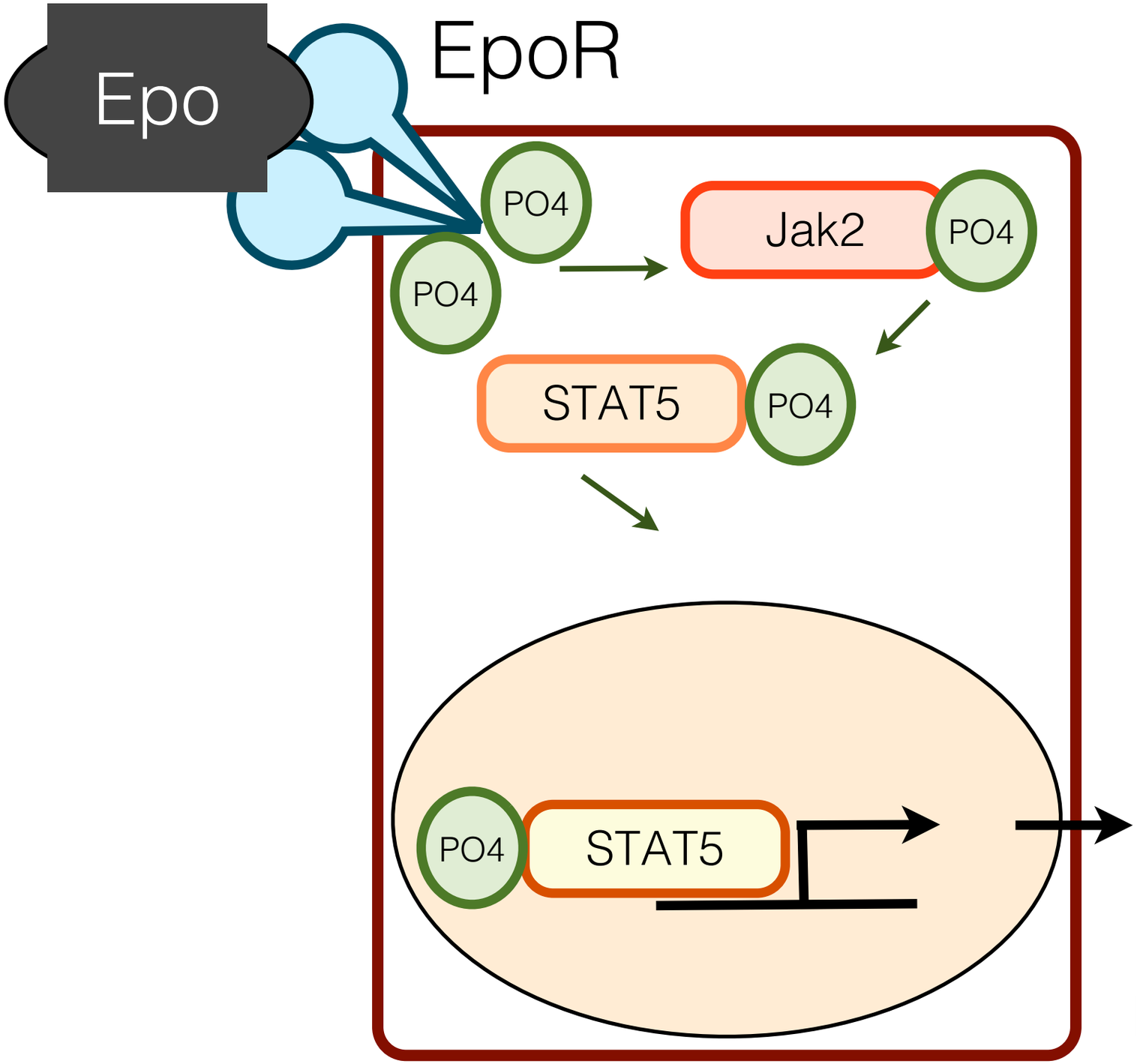
*Janus Kinase-2 (Jak2) is phosphorylated following Epo--EpoR binding.

*Jak2 phosphorylates STAT5a which then translocates to the nucleus to induce gene expression.



M M Patnaik and A Tefferi Leukemia 23, 834-844 (May 2009)

I'm anaemic!
Not enough oxygen in my blood stream



make more
red blood cells

Polycythaemia vera

*Myeloproliferative disorder or neoplasms

*Excessive production of erythrocytes.

*Haematocrit significantly increased.

*Patients often suffer from or even die from cardiovascular disease such as strokes.

*Blood flow becomes viscous from too many red blood cells in the circulation.

*Splenomegaly is very common.

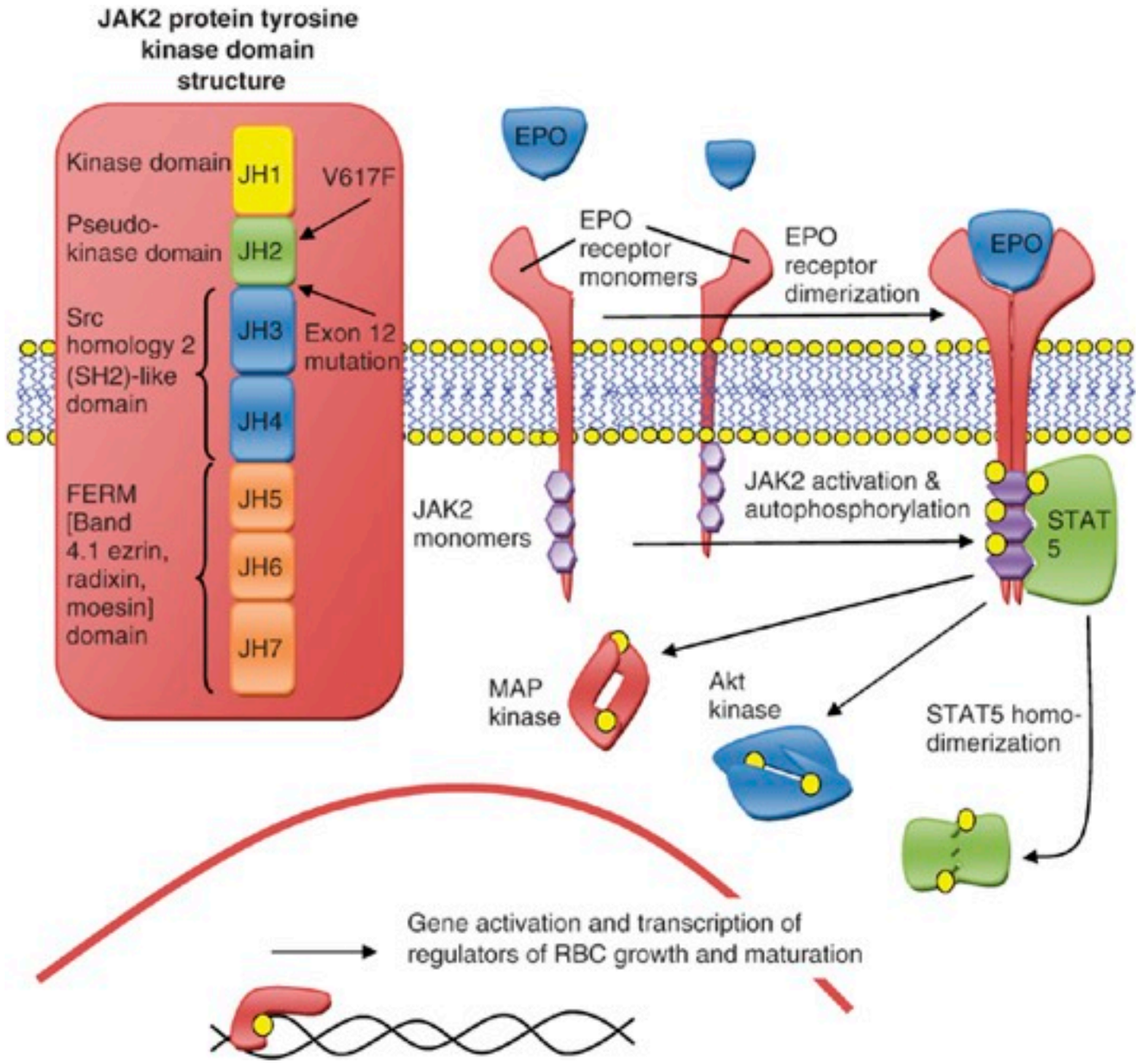
*Generally occurs in older patients (70~75 years old)

*Often leads to myeloid leukaemia

Jak2 mutations cause Polycythaemia vera

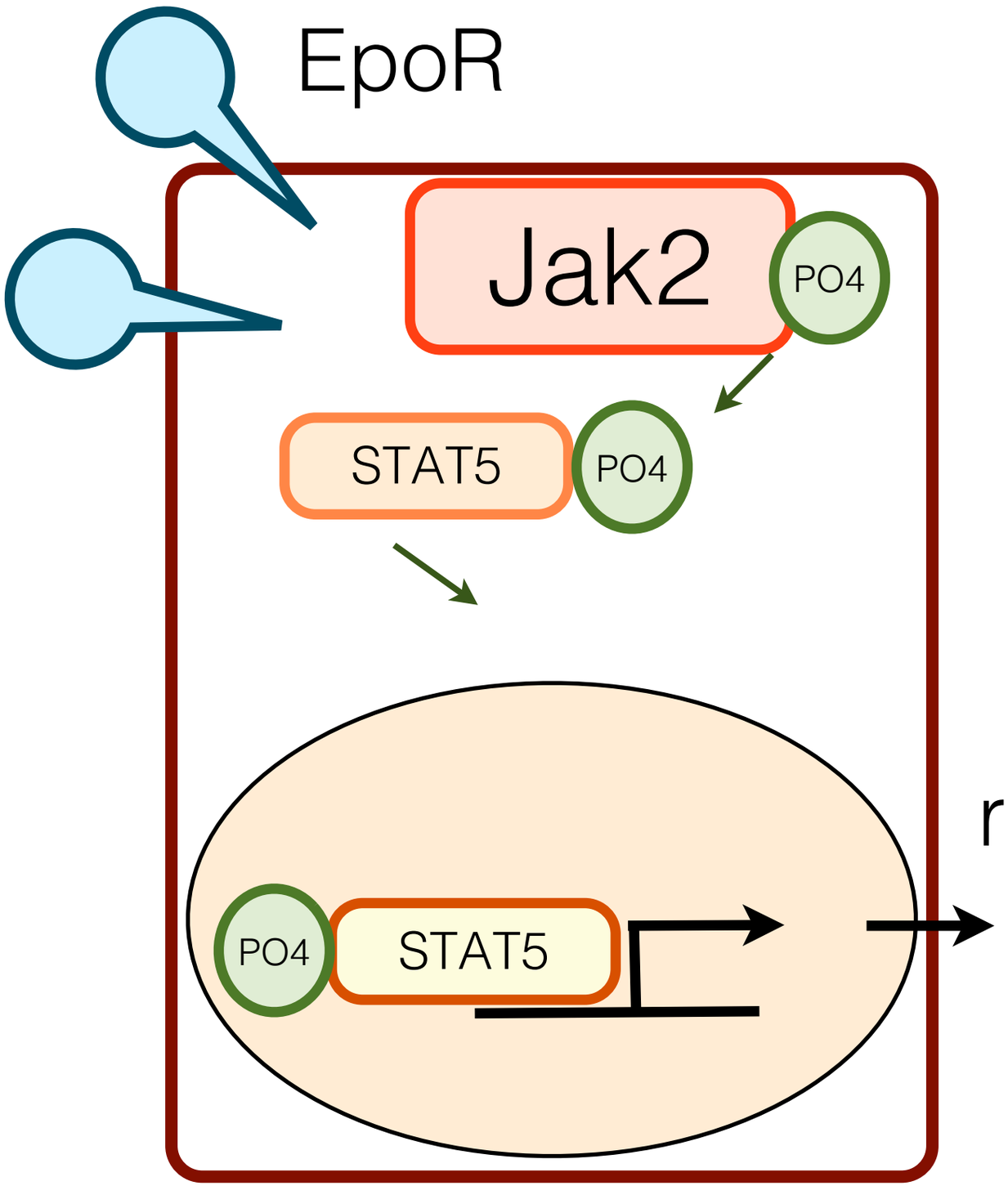
*Jak2 mutations in exon 12 lead to constitutive activation of the EpoR.

*Constant proliferation signal leads to excessive production of RBCs



M M Patnaik and A Tefferi Leukemia 23, 834-844 (May 2009)

Polycythaemia vera



make more
red blood cells

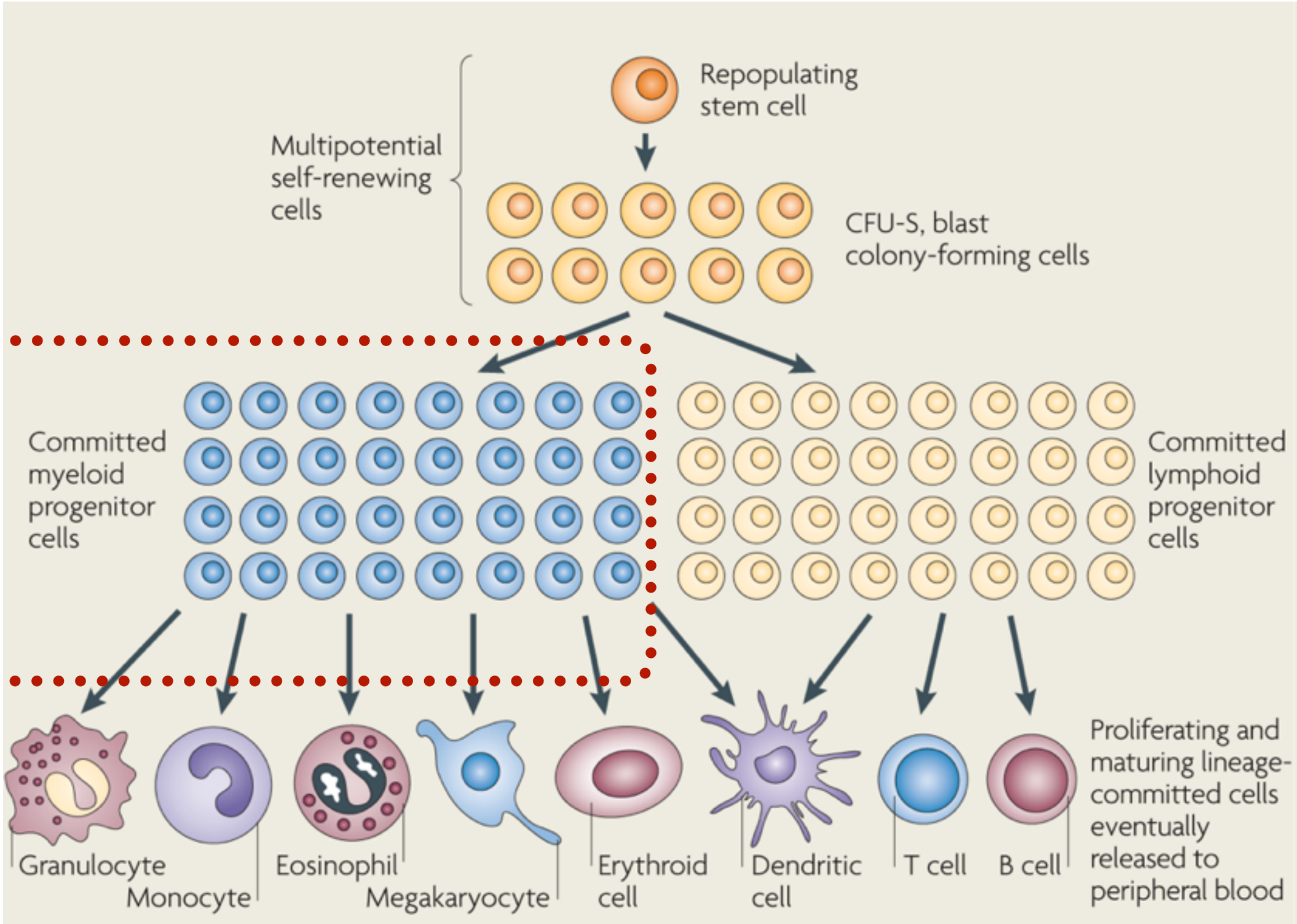
too many!!!

Treatment of polycythaemia vera

*Bleed the patient.

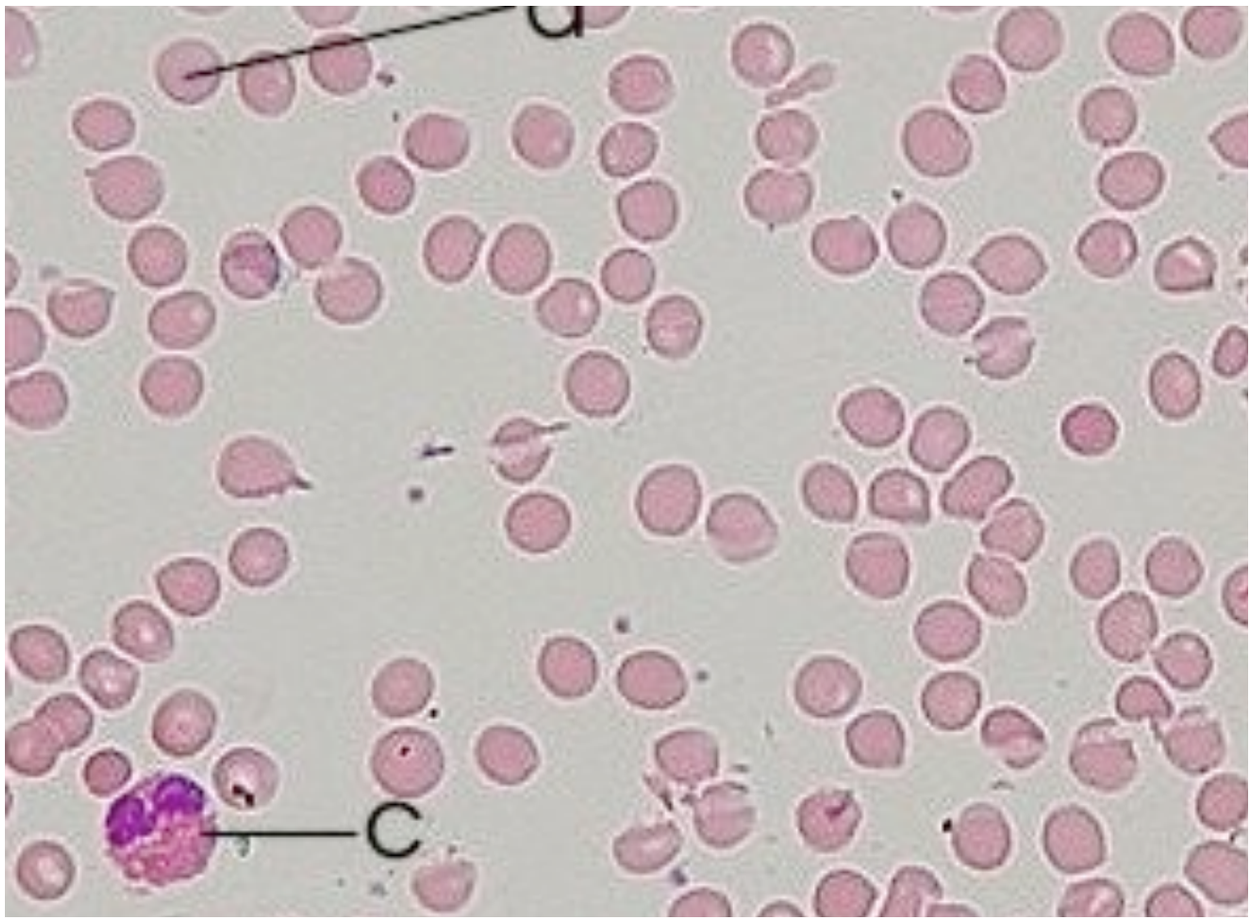
*Specific Jak2 inhibitors have proven very useful in reducing the amount of RBCs produced in Polycythaemia vera patients.

Chronic myeloid leukaemia



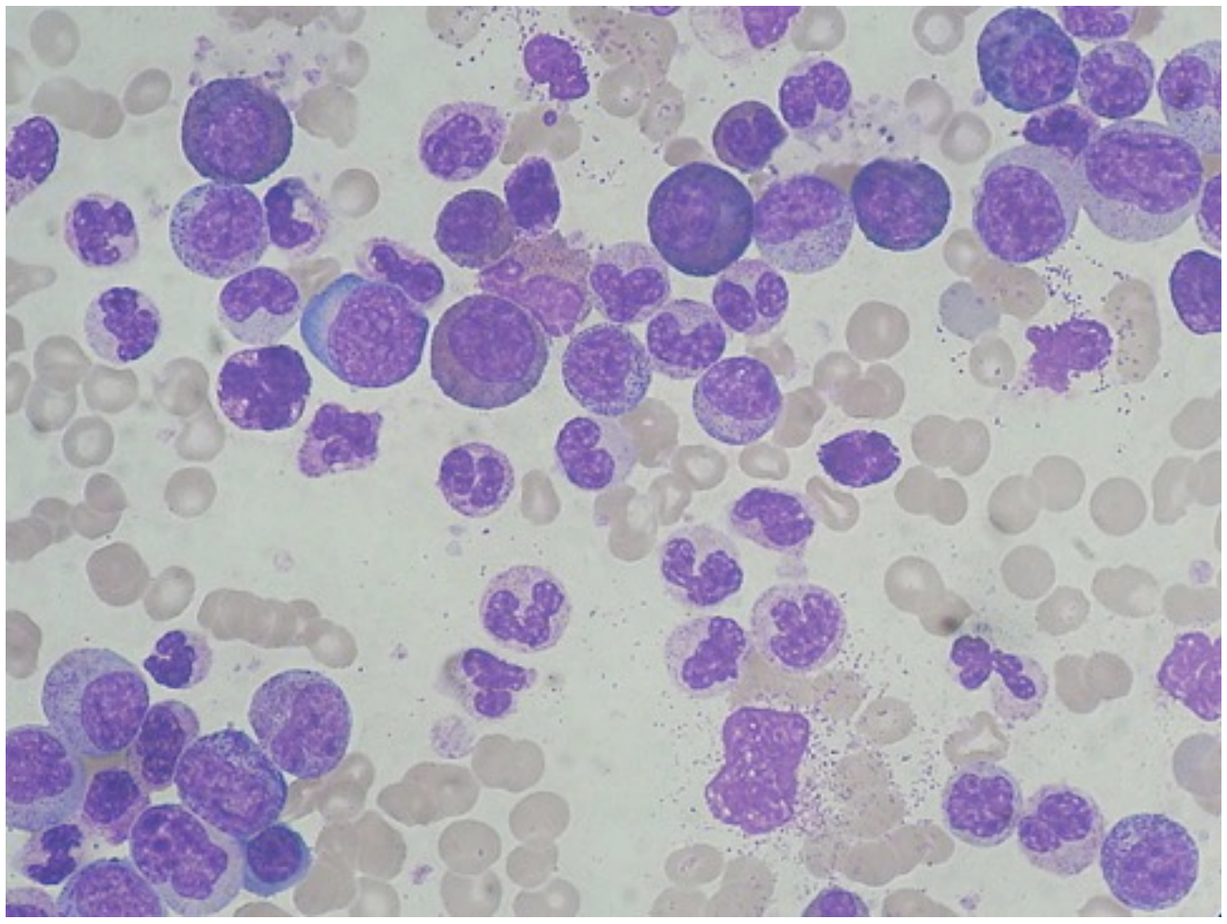
Chronic myeloid leukaemia

Normal human blood



Department of Histology, Jagiellonian University Medical College

Blood from CML patient



Paulo Henrique Orlandi Mourao

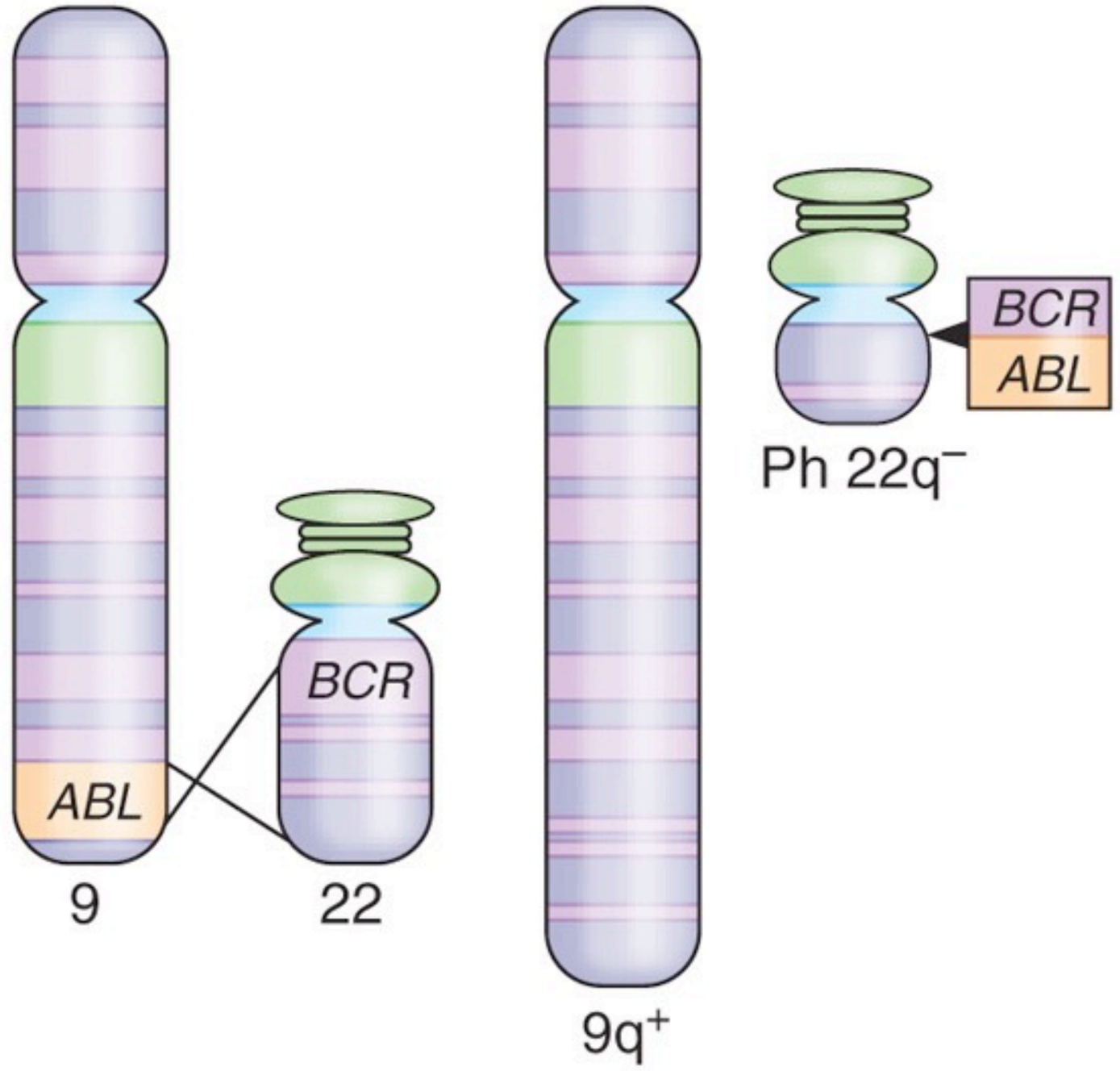
The Philadelphia chromosome and Bcr-Abl

*Translocation between chromosomes 9 and 22

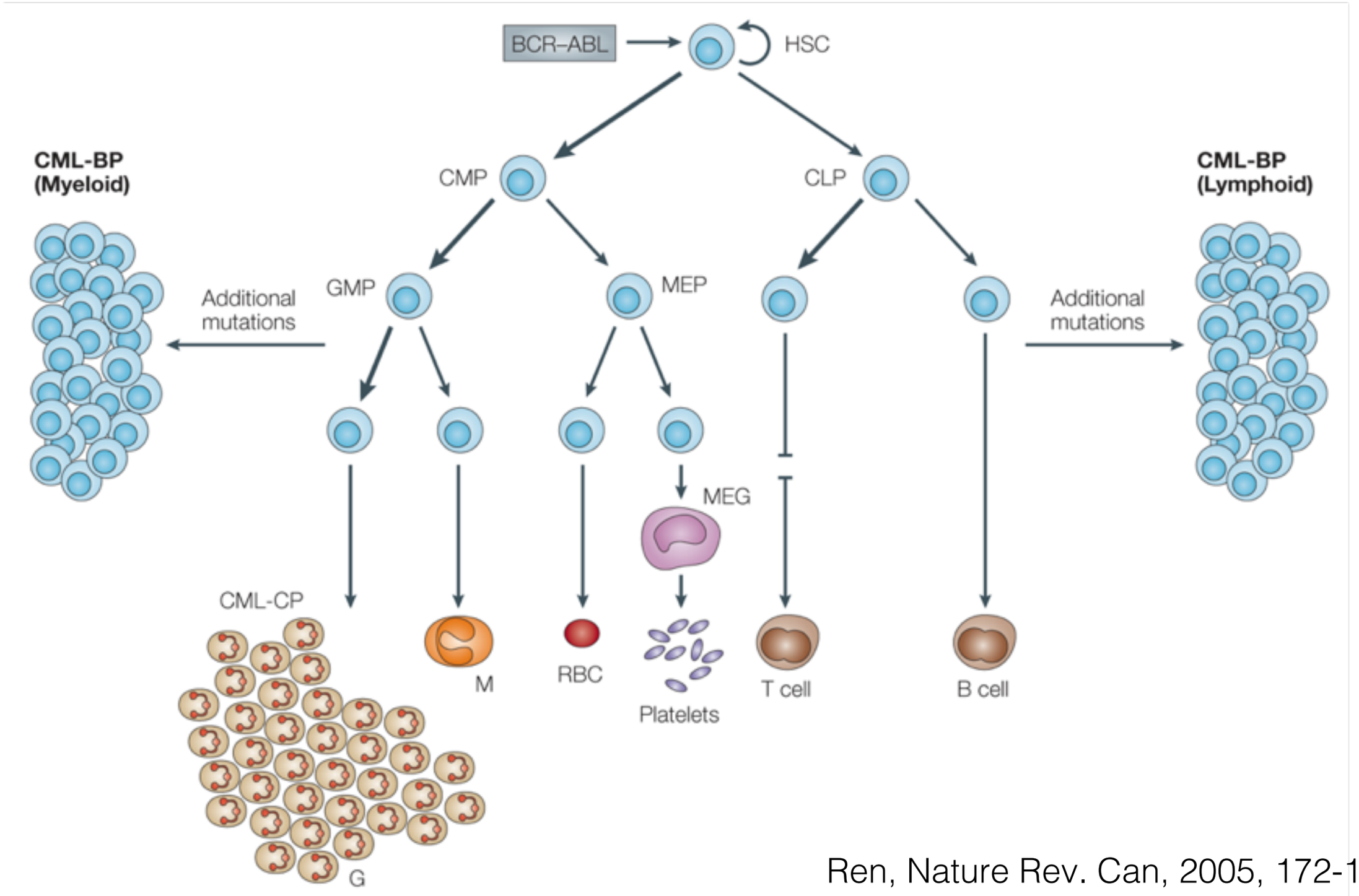
*Results in a fusion protein termed BCR-Abl.

*Blocks myeloid differentiation in the progenitor stage.

Progenitors expand enormously.



Chronic myeloid leukaemia



Ren, Nature Rev. Can, 2005, 172-183

Bcr-Abl

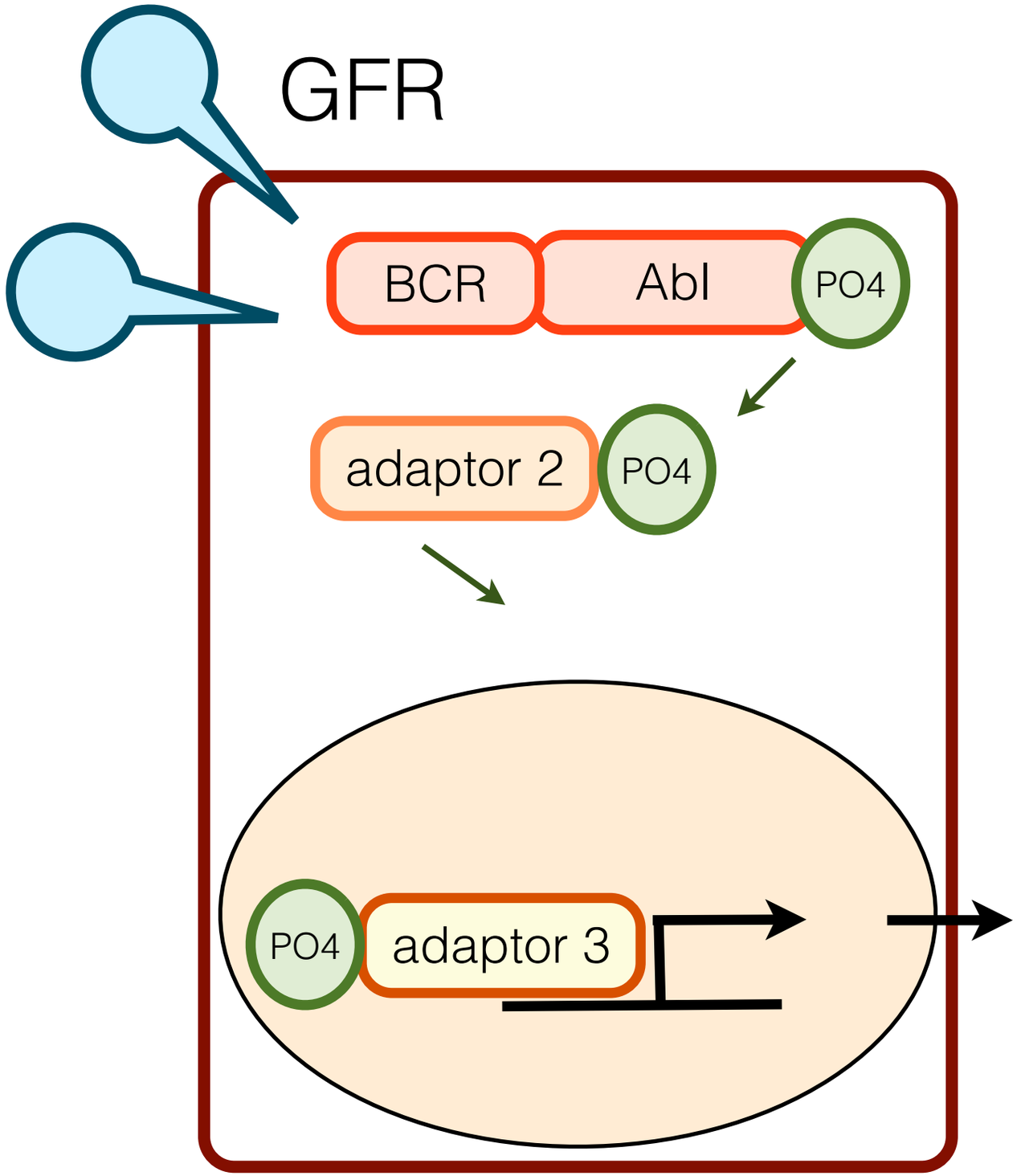
*Bcr: Breakpoint cluster region protein

*Abl: Non-receptor tyrosine kinase

Abl transmits signals, from growth factor receptors from the cytoplasm to the nucleus.

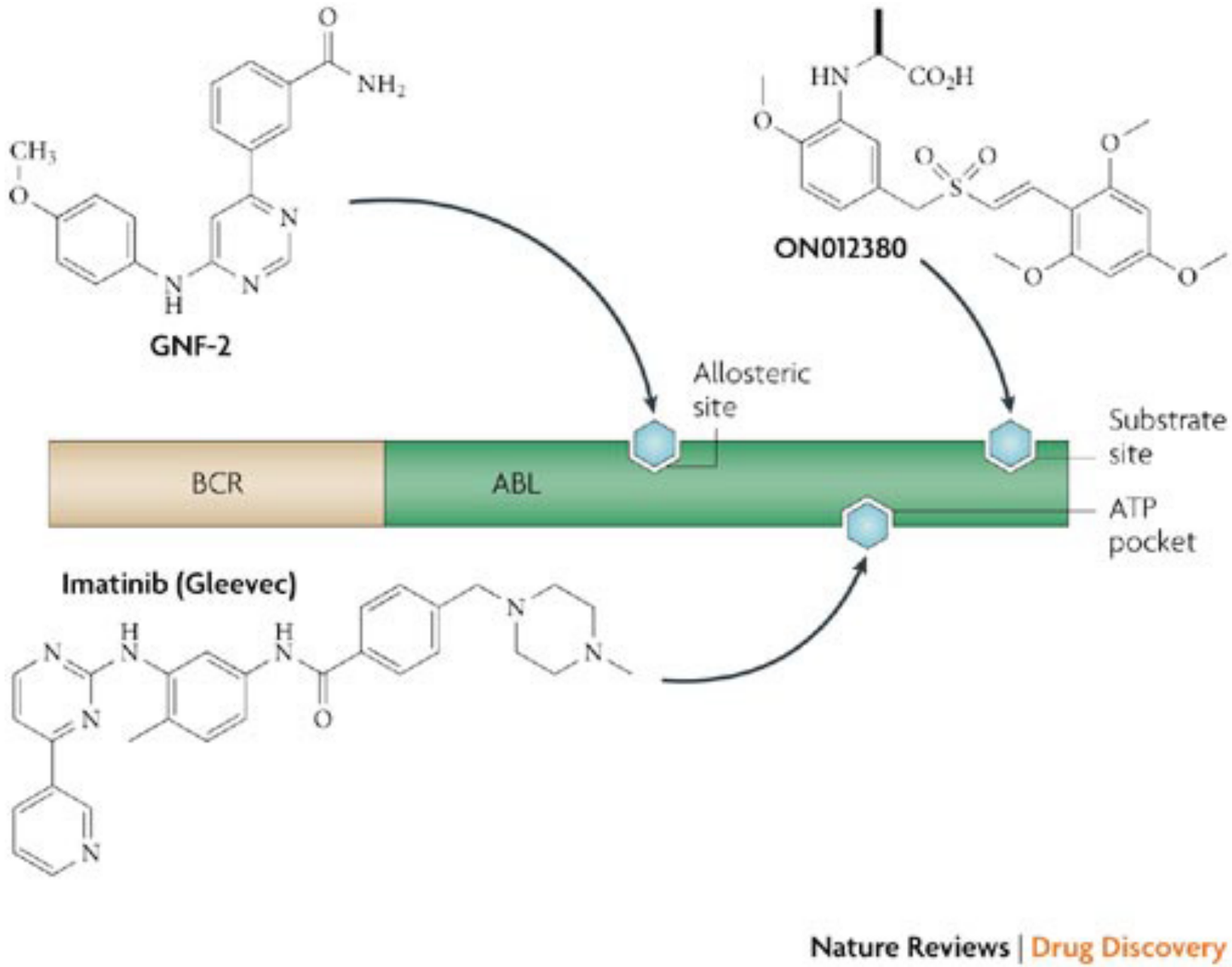
*The BCR-Abl results in constitutive activation of the Abl kinase.

BCR-Abl: a new fusion on all the time



make more blood progenitor cells= leukaemia

Glivec designed to block Bcr-Abl function



Flying under the radar: the new wave of BCR–ABL inhibitors

Alfonso Quintás-Cardama, Hagop Kantarjian & Jorge Cortes

Nature Reviews Drug Discovery 6, 834-848 (October 2007)

Imatinib/Glivec treatment of CML

*"rational drug design"- predicted inhibiter of Src kinases such as Abl.

*Functionally tested to inhibit Abl activity as well as other tyrosine kinases with Src homology domains.

*Previous remission rate for CML was ~%20.

*Treatment of CML patients with early stage CML showed dramatic success ("53 of 54 patients...showed complete haematological recovery").

*Development of resistance in some CML patients.

http://www.youtube.com/watch?NR=1&feature=endscreen&v=7ZMVQ1Vbb7Y

The SCF receptor c-kit

*SCF binds to a surface receptor tyrosine kinase on HSC named c-kit.

*c-kit is important in a range of stem cell populations throughout the body-melanocytes, GI epithelium.

*The drug Glivec inhibits Src domains in c-kit-used for treating c-kit(+) gastrointestinal stromal tumours
(median survival alone ~12 months
median survival+Glivec 4.8 years)