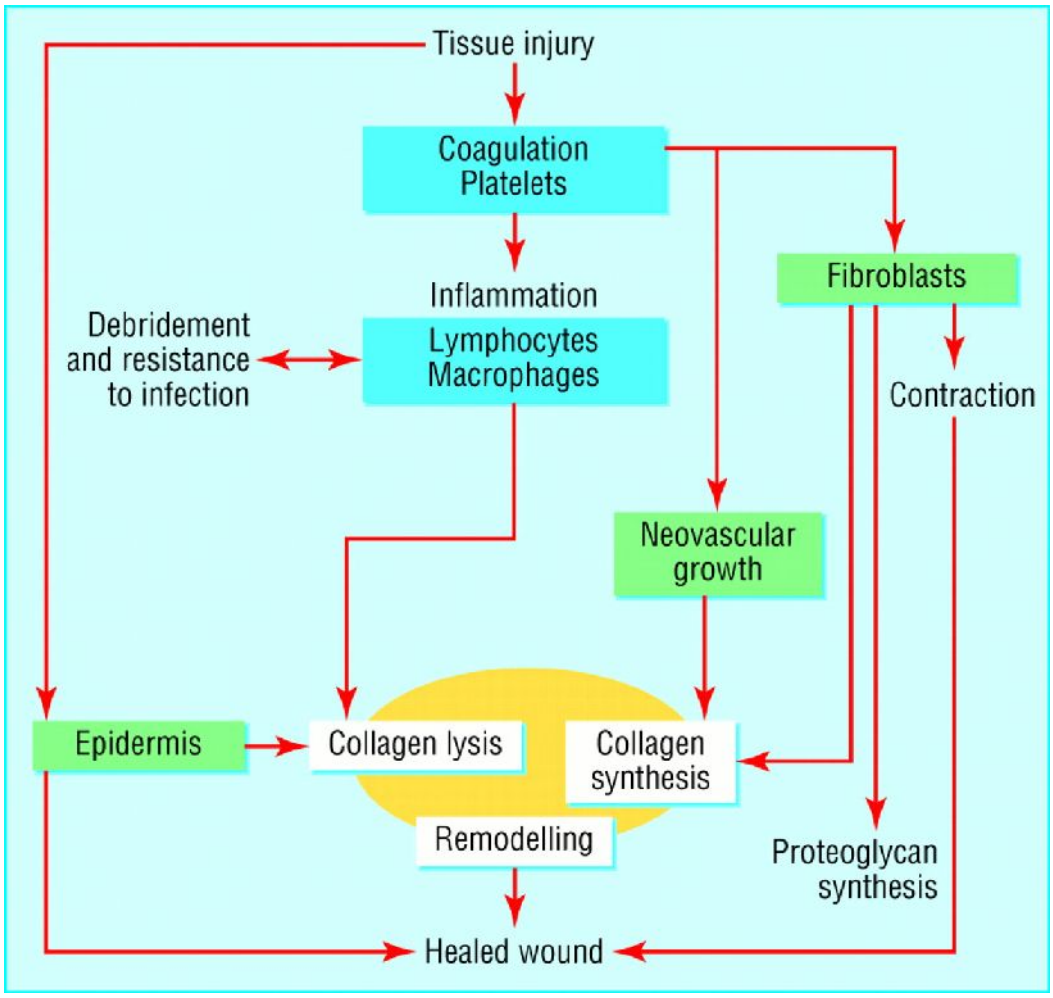
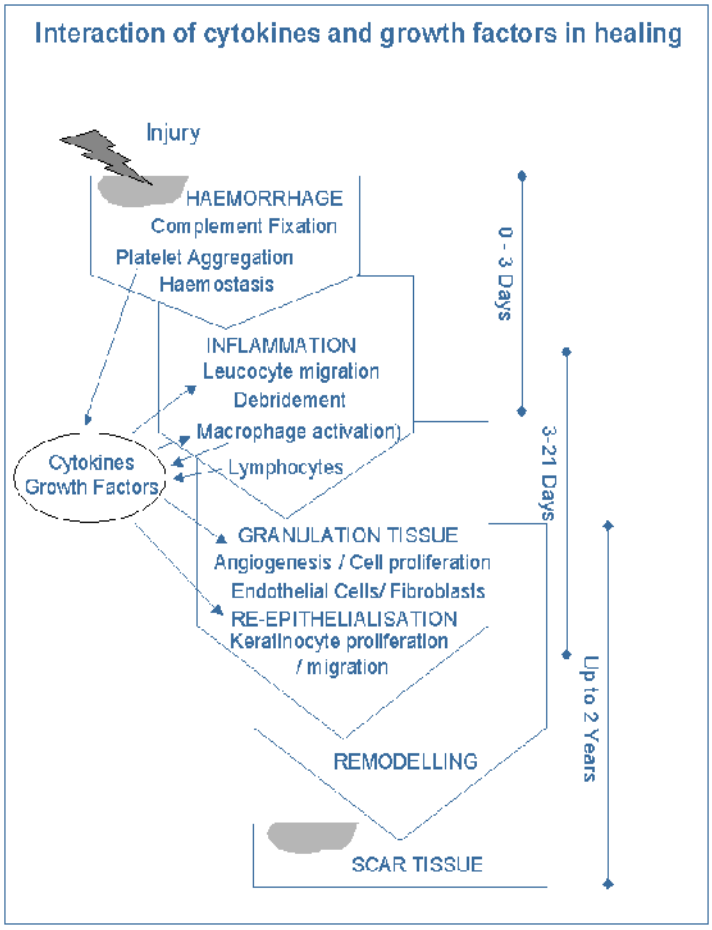
THE BIOLOGY OF PLATELET-GEL THERAPY

The synopsis of normal healing includes a well known sequence of coordinated phases. The unique process leading to healing is ontologically partitioned in three sequential phases: inflammation, proliferation, remodeling



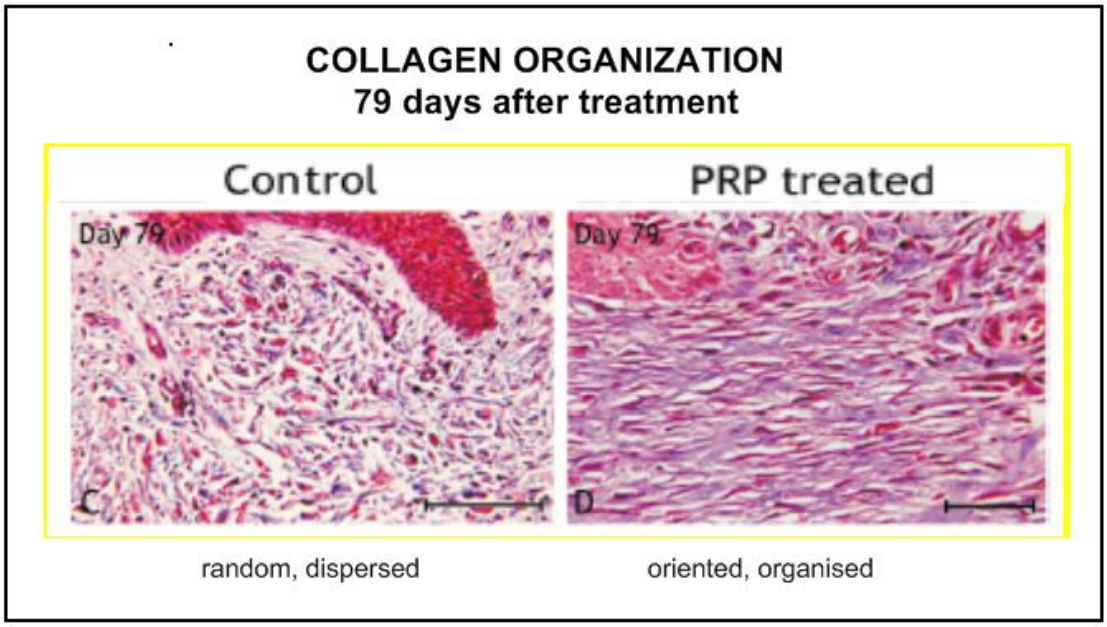
(Figures from:Harding et al. Healing chronic wounds. BMJ 2002;324:160-3).



The platelet gel restores the inflammatory phase and sustains the proliferation phase eliciting several processes:

- the major components of the platelet gel, platelets and fibrin polymers, provide a unique natural provisional matrix (scaffold for cell migration)
- platelets provide the chemotactic and proliferation-inducing factors leading to the formation of the granulation tissue
- the bactericidal action of platelet gel, achieved through platelet-derived kinocidins and other bactericidal proteins, precedes that of incoming (chemoattracted) polymorphonuclear cells and phagocytes
- platelets and plasma from the platelet gel restore a paraphysiologic environment and buffer the eventually occurring pH alteration
- the platelet gel modulates the proteolytic activity of matrix metalloprotases (MMPs): first providing large amount of fibrin and, later, inducing fibroblasts (through CTGF) to produce MMPs as required for neoangiongenesis.

Albeit remodelling takes long to be accomplished, there are convincing evidences (see figure) that platelet gel improves tissue remodelling many weeks after the treatment.



The principal actions of the major platelet-derived factors are quite well known. Nevertheless, one must recognise that a process which includes inflammation; local immune activity; incoming and proliferation of cells; cell differentiation relevant to complex tissue organisation; extracellular matrix deposition and its organisation in a physiologic texture; long term tissue remodelling and inhibition of hyperproliferative scars, is much too complex for simply being the cumulative summation (Σ) of the activity of each single growth factor. Reality is by far much more complex.
To get the best harmonised results, in a symphony-playing orchestra, synchronisation of hundred instruments playing (or pausing) is mandatory. In wound healing, the platelet gel-derived factors do behave and work alike. Complexity of “tuning” is shortly summarised in the table and in the figure reported below. Clinical outcome obtained with platelet gel is hardly imaginable with combinations of conventional medications, also with so-called advanced medications.

In the table.
Some of the factors delivered from the platelet gel. Diversity of actions, convergent results:

FACTOR	ACTION
PDGF-A,AB,B	Chemotactic, mitogenic
Connective tissue GF (CTGF)	Collagen synthesis, angiogenic
CTAP-3 connective tissue-activating protein-3	Chemotactic, mitogenic
Basic-FGF	Wide-spectrum cell growth stimulator
TGF-β1 and TGF-β2	Modulation (inhibition) of EGF, PDGF, bFGF
Platelet-derived angiogenic factor (PDAF)	Angiogenesis
Early pregnancy factor (EPF)	Survival factor for many cells
Epithelial growth inhibitor (EGI)	Modulate (inhibit) epithelial cell growth
Keratinocyte growth factor (KGF)	Potent growth factor for keratinocyte proliferation
Insulin-like GF (IGF)	Mitogenesis; matrix synthesis by bone cells
IGFBP-3	Negative regulator of cell growth
VEGF	Mitogenenic for vascular endothelial cells
Fibroblast-derived endothelial cell GF (f-ECGF)	Supports the growth of endothelial cells
Hepatocyte GF (HGF)	Migration and proliferation of endothelial cells
Human collagenase inhibitor	Modulation of collagenase and some MMPs
Fibronectin	Regulation of cell migration and differentiation
Vitronectin	Prevention of thrombin degradation
Thrombospondin	Extracellular matrix driving cell
Platelet microbicidal protein-1 (PMP-1)	Antimicrobial kinocidin
Thrombin-induced platelet microbicidal protein-1	Antimicrobial kinocidin
Platelet basic protein-PBP (CXCL7)	Antimicrobial kinocidin
Thrombocidin-1 and 2 (TC1; TC2)	Antibacterial proteins
Serotonin	Chemotactic for neutrophils; vascular permeability
Cathepsin - IL8 converting enzyme	Chemotactic for neutrophils
Somatostatin (SST)	Modulator of immune activities
RANTES	Chemotaxis inflammatory cells; activation of K cells
Annexin 11	Mediator of cell–cell adhesion
Ca^{++}; Mg^{++}; Zn^{++}	Proactivators of protein and enzyme function
Metalloprotease MMP-1, -2, -9, -13	Remodelling of collagenous extracellular matrix
Collagenase	Analogous to matrix metalloproteinases
ADAMTS-13	Metalloprotease multimer cliving
Superoxide dismutase (SOD)	Inhibitor of growth factor-induced responses
α1-α2 anti-thypsin	Protease inhibitor
α2-macroglobulin	Inhibitor of proteases
HMGB1 (amphiregulin)	signal transduction protein; angioblast migration

Cross-talk among cells orchestrated by platelet-derived factors. Complex network leading to **TISSUE REPAIR**