

# Evidence based formulation proves to exquisitely relieve pain and inflammation when applied topically

Observations made on the pain relieving capacity of Polyactil on sports lesions in professional soccer players, led to the development of Bioactil, the leading formulation for topical pain relief and of inflammation.

During a study done in a professional soccer team of Costa Rica a decade ago, athletes reported intense relief of pain and inflammation when Polyactil was applied to the lesion and then cooling the lesion with ice applied on the affected area for about 10 mins. This pain relief was not well understood at that moment. However it was clear that Polyactil could resolve these closed lesions more rapidly than known methods adopted for many decades and for the intervention group of the study treated with Polyactil, plus resolution of the lesion with no fibrotic sequelae at ultrasound examination.

One of the positive control groups was treated with inhibitors of cyclooxygenase-2 or COX-2. This group did not have the same favorable outcome as the Polyactil group did.

Since then the resolution phase of inflammation has been uncovered and studied extensively and it has become clear that for damaged tissues to produce Lipoxins and Resolvins, which pro-actively promote resolution of inflammation and possibly regenerative healing, the inducible COX-2 enzyme is essential. Resolution is a local process at the site of injury occurring via transcellular sequential biosynthesis which generates autocrine and paracrine lipid mediators from arachidonic acid released by action of lipoxygenases on the plasma membrane and subsequently metabolized by the COXs isoforms. Downstream in the sequence, it switches strategically at some point to generation of lipoxins from arachidonic acid and resolvins from essential polyunsaturated fatty acids, rather than prostaglandins and leukotrienes as in the preceding inflammatory phase <sup>1)</sup>. Although inhibitors of COX-2 are still used in clinical practice they are held now responsible for disrupting endogenous resolution mechanisms <sup>2)</sup>. For the above described switch to occur it has been shown that a second paradoxical peak of COX-2 expression, 350% more intensive than the one during the inflammatory phase, sub-enters and coinciding fully with the production of resolution mediators <sup>3)4)</sup>. Other researchers have shown that COX-2 inhibitors reduce the production of key local lipid mediators, leading to deficits in inflammation resolution <sup>5)</sup>. It was found in an early study using a rat inflammation model (pleurisy) that the COX-2 inhibitor NS-398 reduced inflammation at 2 hours but enhanced inflammation at 48 hours. Therefore it is well proven that COX-2 essentially contributes to resolving inflammation and that its inhibition is a harmful intervention and in the longer term it is pronociceptive.

## Inflammatory pain

Pain from inflammation is induced by inflammatory mediators released after tissue insults and subsequent hypoxic injury microenvironments that follow. Nociceptor terminals (bidirectional signaling units) express receptors for all inflammatory mediators. Activation of these receptors causes hyperactivity of key transduction molecules, such as transient receptor potential subtype V1 (TRPV1) and A1 (TRPA1) and conduction molecules such as sodium channels Nav1.7/1.8/1.9. As a result, the sensitivity and excitability of nociceptors are increased, via activation of protein kinases, such as

protein kinase A (PKA), protein kinase C (PKC), and mitogen-activated protein kinases (MAPKs). This can be called a peripheral sensitization of pain (excitation thresholds drops). It is generally believed that inflammatory pain is driven by peripheral sensitization within primary sensory neurons in the dorsal root ganglion (DRG) <sup>6)7)</sup>

Tissue injury-triggered hyperactivity of nociceptors will lead to increased release of neurotransmitters (e.g., glutamate) and neuromodulators [eg. substance P, enkephalins; neurokinin; serotonin and brain-derived neurotrophic factor (BDNF)] from nociceptor central terminals in the spinal cord, causing hyperactivity of postsynaptic dorsal horn neurons and sensitization. Neurotransmission during prolonged nociceptor excitation reaches beyond the DRGs and is able of establishing postsynaptic sensitization escalating pain to a more advanced and complex form of central sensitization <sup>8)</sup>. Activation of the N-methyl-D-aspartate receptor NMDAR plays an essential role in the induction and maintenance of central sensitization also called [spinal cord synaptic plasticity](#) <sup>9)</sup>. Tissue injury-induced spinal cord synaptic plasticity also is important for maintaining persistent pain and generating secondary pain outside the initial injury site (Ji et al., 2003)(Dubner & Ruda, 1992) Central sensitization contributes importantly to the development and maintenance of inflammatory pain (Ji et al., 2003) <sup>10)</sup>. Long-term potentiation (LTP) in the spinal cord <sup>11)</sup> is a unique form of central sensitization for persistent pain development. The complexity of neurotransmission and sensitization of inflammatory pain suggests that a reductionist intervention directed to inhibit one or two of the transmitters involved, either peripherally or centrally, is destined to fail.

## Analgesic Effect of Resolution Mediators

Other studies have established that resolution mediators had a profound analgesic effect on the pain caused by inflammation and spinal cord synaptic plasticity in mice by inhibition of transient receptor potential channels TRPs in the nm range. Members of the Resolvin family inhibited TRPs as follows: RvD2 was found to be a remarkably potent inhibitor of TRPV1 (IC<sub>50</sub> = 0.1 nm) and TRPA1 (IC<sub>50</sub> = 2 nm) in primary sensory neurons, whereas RvE1 and RvD1 selectively inhibited TRPV1 (IC<sub>50</sub> = 1 nm) and TRPA1 (IC<sub>50</sub> = 9 nm), respectively <sup>12)13)</sup>. Transient receptor potential vanilloid 1 (TRPV1) and ankyryn 1 (TRPA1) are two critical types of TRP channels that are strongly implicated in the genesis of inflammatory pain <sup>14)15)</sup>. Activation of TRPV1 and TRPA1 can enhance inflammatory pain not only via well demonstrated peripheral sensitization <sup>16)17)18)</sup> but also via central sensitization, by increasing glutamate release from primary afferent terminals to enhance synaptic transmission <sup>19)</sup>

So the experimental success in reducing inflammatory pain is appealing and illustrative though the detailed signaling mechanisms of RvD2 in pain relief remain unclear. Therefore inflammatory pain relief by topical application of Polyactil becomes very enlightening since it is resolution-driven and by correlation quite well defined as antagonistic to TRPV1 and TRPA1. Thus the marked relief of pain that can be observed while inflammation is gradually reduced by Polyactil can be equated to the action of RvD2; not quite dissimilar to both facets of inflammation that lead into resolution and relief of inflammatory pain.

### Analgesic Enhancement by Cold

Polyactil's potentiation by application of cold which enhances its analgesic effect is even more revealing. Six of the 28 TRP channels from the three distinct TRP family subtypes are activated by temperature (TRPV1-4, TRPM8 and TRPA1), and are expressed in sensory neurons or in skin keratinocyte cells, which are peripheral targets of these nerves <sup>20)</sup>. At the same time clinical evidence

suggests that cold does enhance the resolution effect of Polyactil since if used together with cold, inflammation subsides sooner. The latter fact confirms how complex is the physiology of the sensory system and the pathophysiology of pain. But it must be conceded for this purpose that an agonistic effect is being exerted on TRPM8 by cold and not an inhibitory one. Indeed, most cold-sensitive neurons respond to menthol and display a thermal activation threshold of  $\sim 25^{\circ}\text{C}$ . TRPM8 is a cold and menthol-sensitive channel whose physiological characteristics match those of native cold currents and TRPM8-deficient mice show a very substantial loss of menthol and cold-evoked responses at the cellular or nerve fiber level. Likewise, these animals display severe deficits in cold-evoked behavioral responses<sup>21)</sup> (Bautista et al., 2007)<sup>22)23)</sup> over a wide range of temperatures spanning 30 to  $10^{\circ}\text{C}$ . Activation of TRPM8 by icilin is reported to produce analgesia by activating central inhibitory pathways<sup>24)</sup> The agonistic action of menthol has been extensively studied. TRPM8 permits the channeling of charged ions, usually calcium or potassium ions, to flow through cellular membranes to which it is attached when temperatures drop at or below  $26 \pm 2^{\circ}\text{C}$ <sup>25)</sup> When temperatures fall below this region, the TRPM8 channel allows for membrane currents to increase at the peripheral nerve endings of cold-specific non-nociceptive afferents (A delta fibers) resulting in cold perception (Sarria & Gu, 2010)<sup>26)</sup>. At those same temperatures, an associated intracellular increase in calcium ions is observed across the calcium permeable TRPM8 channel (Sarria & Gu, 2010). The literature shows that menthol acts within the presynaptic regions where TRPM8 channels are prevalent and the somatic sensory synapses connect primary afferent fibers and dorsal horn neurons in the spinal cord to the central nervous system (CNS).

In view of opposite actions exerted on TRPs that can have a beneficial effect, both on inflammation and inflammatory pain, addition of 3% menthol was thought to complement quite effectively Polyactil's effect on inflammation and pain, while making the application of cold inherent to every single treatment. Thus a combined targeted effect on TRPs could be obtained by simply applying the new formulation to the affected area. It was conceived as a proof-of-concept formulation, which indeed it has proven exhaustively to be exquisitely effective for pain relief in wide human usage. Further studies can be planned to demonstrate the molecular effects of the dual effect exerted by Bioactil in resolving inflammation and relieving inflammatory pain.

## Healing Underground

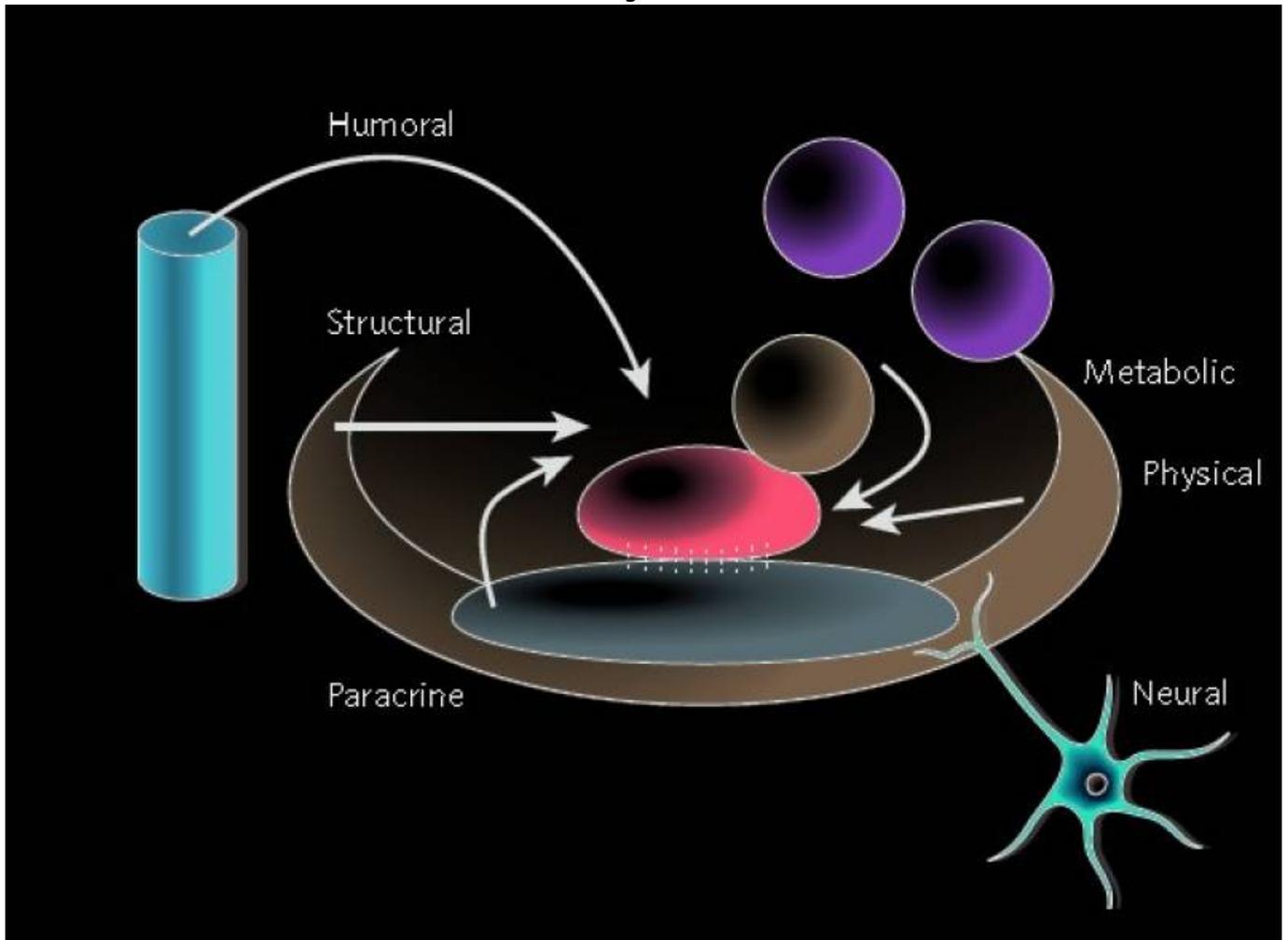
It is not fully clear to many that serious healing disorders can take place under the skin. Blunt injury can cause serious damage even if the skin will not suffer breaks in its continuity. This is particularly true if muscle is compromised.

A ruptured muscle will simply regenerate if is not unduly affected by inflammation and if the natural conditions under which it habitually thrives can be preserved. This has been adequately reviewed elsewhere<sup>27)28)</sup>. Muscle has almost inexhaustible resources to repair itself, but modern medicine has not been successful in controlling inflammation without compromising the switch during wound healing required to trigger resolution and the up-to-now total disregard in controlling the microenvironment of the wound (See ref. n° 3 and 4). This is further complicated by the fact that the varied community of therapists intervening on these lesions has not achieved thorough knowledge of the muscle regeneration perspectives and continues to consider the process as a repair<sup>29)30)</sup>. Very frequently trauma involving a muscle lesion will result in the formation of a scar with fibrous tissue sub-entering in place of the normal restoration of newly formed functional muscle fibers.

This outcome for lesions in the limbs compromising agonistic musculature becomes sensibly critical in view of the fact that the scar will not hold for athletes returning to performance and re-injury will

occur. For very high performance cases a scar can mean incapacitation.

Therefore muscle injury is a mayor problem most of the time treated lightly. Or when treated seriously (however non-surgically), using extrinsic growth hormones and/or stem cell therapies, the inflammatory conditions of the injured site strongly counteract the cellular, molecular and metabolic events which orchestrate fully satisfactory outcomes(Domiziana Costamagna, Paola Costelli, Maurilio Sampaolesi, and Fabio Penna (2015))<sup>31)32)33)</sup>. In other words stem cells need a special microenvironment in order for them to function Fig 1.



environment that participate in regulating the system of a stem cell in its tissue state are depicted<sup>34)</sup>.

It is now very well accepted that stem or progenitor cells need a specific microenvironment for them to be up-regulated and then differentiate. It has been proposed that an approach which will modulate the stem cell niche microenvironment is a more sensible proposition, since the already existing stem cells in the target area will do the regenerative work and bring back fully functional tissue to the site<sup>35)</sup>. No need of extrinsic cells or of growth hormones. Given the huge intrinsic regenerative potential of skeletal muscle this seems to be the right clue for begetting optimal healing.

But the caveat is the modulation of inflammation.

## Mastering Inflammation

There is no acceptable method to control inflammation despite the enormous research that has been done on it. This is especially true if the lipid mediated resolution phase is to be conducted to a state of functional restitution. Very simply it can't be denied that if it starts it must somehow come to an end.

However it is not whatever end since fibrosis will be unavoidable if inflammation does not resolve within special and favorable microenvironment conditions.

Just by trying to calm inflammatory pain the auspicious end can be abrogated. An ongoing debate that has lasted over 3 decades has not clarified whether using COX-1 and COX-2 inhibitors will or will not blunt in the long term the resolution phase of inflammation with intensification of fibrosis in wound healing<sup>36)</sup>. This is particularly relevant in muscle regeneration where scar formation is not desirable.

Participation in the debate is not a scope of this text. The intervention proposed here has the advantage of treating pain and at the same time correcting the abnormal microenvironment of a muscular lesion favoring consequently healing and regeneration of muscle fibers. Therefore it is a new and comprehensive type of intervention which can be used through the whole process of healing and abbreviating it<sup>37)</sup>. In addition it is topical and pain relief is strong which will intensify during the span of a single application and accumulate during successive ones with no side effects. Therefore it is in a new class of pharmaceutical forms and supersedes conventional treatment without being incompatible with it.

In the study of Ref. n° 37 the shortest evolution was of the group using Polyactil and a COX-2 inhibitor shortening the evolution 32% with respect to the placebo group; a >week (7.5 days) gained and returning to performance in 14.8 days. So without the aim of entering the NSAIDs debate, it must be considered that there are at least 100 lipid resolution mediators and that NSAIDs may have also other incompletely understood effects besides the widely known of inhibiting prostaglandin formation. These are mediated by the inhibition of certain transcription factors such as NF- $\kappa$ B and AP-1<sup>38)</sup> and shunting of mobilized free arachidonic acid (AA) substrate via parallel enzymatic pathways<sup>39)</sup>. However the former effects are observed only at doses much higher than therapeutic. □□□□ □□

## Bioactil and microenvironments

As demonstrated in the study of ref. n° Bioactil has powerful pain relieving effect in sport lesions and favors muscle regeneration. In view of the compounded effect it can be theorized that this is due to the actions of resolving mediators of inflammation. It also shortens the evolution to 16.9 days.

The formulation has acid/base and redox buffering capacities keeping physiological pH and mild stimulatory oxidative conditions +118mV necessary for stem cell up-regulation ( Lane, S. W., Williams, D. A., & Watt, F. M. (2014)). Polyactil has been widely tested in all types of open wound healing showing excellent results in reactivating chronic wounds and healing them in absence of infection and without the use of antibiotics. So the balance exerted by the redox couple and doing the redox buffering seems to have optimal balance for wound healing and infection control. Much of these features apply also for Bioactil in closed wounds as is the case in sports lesions.

Although the study showed remarkable effects when used in combination with a COX-2 inhibitor shortening evolution in 2.1 additional days a word of caution is necessary since most of the long term studies of the use of NSAIDs in muscle lesions tend to agree that they blunt the protein synthesis machinery and the recruitment of myogenic stem (satellite) cells<sup>40)</sup>.

Also the study was conducted in very young individuals so that further studies would be necessary in older individuals in order to corroborate if the combination is a safe proposal. In such studies lipid mediator profiles should be included in the methodology to ascertain what has been theorized in this paper.

Finally inflammation can be dealt with in all its complexity and so that it can proceed to favorable resolution.

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[https://erp.redplusalus.com/do/doku/!admin/doku.php?id=pain\\_relief](https://erp.redplusalus.com/do/doku/!admin/doku.php?id=pain_relief)

Last update: **2018/09/01 15:46**

