

# Alkaline phosphatase: An old enzyme newly discovered as a medicine

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## ABSTRACT

Alkaline phosphatase (AP), a non-toxic natural compound (enzyme) has a great potential to replace or avoid the use of various drugs, in particular anti-inflammatory drugs (e.g. used during surgery and to reduce arthritis) and antibiotics applied to farm animals, which both have serious negative effects on the environment. Promising studies are being performed to demonstrate the possibility to avoid complications after major surgery (thereby eliminating the need to use harmful drugs for many years) and the reduction of antibiotics use in piglets.

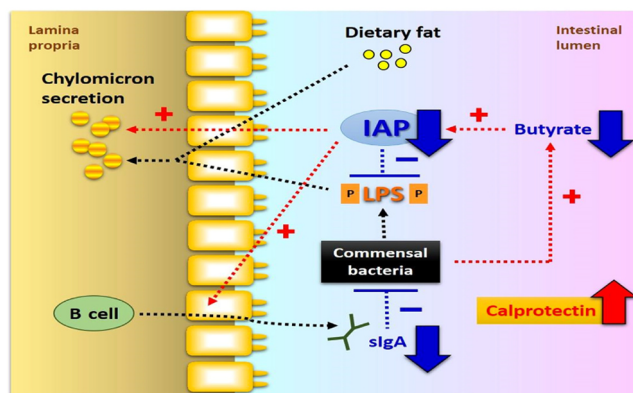
## 1. Introduction

The use of natural compounds to prevent and cure diseases has been a common practice for many centuries. Yet in the past 100 years, chemical alternatives have become dominant due to their versatility and more or less superior effectiveness. A disadvantage of this development is that several classes of synthetic drugs are very persistent (non-degradable), leaving harmful residues in the environment (soils and surface waters). While there is a trend to search for natural compounds to replace synthetic drugs, sufficient effectiveness remains a problem, as well as the side effects (or even toxic nature) of many natural compounds.

A promising, non-toxic natural compound is alkaline phosphatase (AP). This is an endogenous enzyme, present in all mammals and commonly known for its use in diagnostics. In the past 20 years, its potential use as a drug has been studied in various animals, showing promising results (Melo, 2016; Liu, 2016; Sulaiman and Hamarneh, 2014). The attractive feature of AP, besides its safety and biodegradability, is that it has a major function in the protection of membrane integrity against inflammation-triggering moieties (Lalles, 2014). Important sub-functions are e.g.:

- Regulation of bicarbonate secretion and duodenal surface pH (Mizumori, 2009)
- Modulation of intestinal long chain fatty acids (LCFA) absorption (Matthew, 2011)
- Detoxification of lipopolysaccharides (LPS, produced by bacteria in the gut), resulting in reduced intestinal and systemic inflammation (Poelstra, 1997)

- Regulation of microbial communities and their translocation across the gut barrier (Malo, 2014)
- Dephosphorylation of ATP released from damaged tissue (Rezende, 1994)



Due to these functions, extra supply of AP is a promising way to prevent (the onset of) acute inflammations and reduce chronic, low-grade systemic inflammations.

Alloksys Life Sciences BV has worked on in the past years on the use of AP during major surgery, to prevent complications (such as kidney failure) resulting from release of inflammatory compounds during and after operations (due to ischemic conditions). A phase 2a clinical study with 52 patients indicated the potential of AP to reduce complications after cardio-surgery (Kats, 2009). A phase 2b/3 clinical study with

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1.250 patients is now under way, as part of the Meduwa project, to further proof the benefits of the use of AP during cardio-surgery, which is known to often lead to serious complications. These complications, besides causing much patient discomfort, lead to the use of large amounts of various (persistent) drugs for many years.

AMRIF BV, on the other hand, focusses on the reduction of chronic, low-grade systemic inflammations which are thought to contribute to conditions such as diabetes, neuro-degenerative diseases and obesity. As part of the Meduwa project, a study is being performed by AMRIF to reduce the use of antibiotics in piglets. Disturbance of the intestinal barrier system, associated with indigestion and diarrhea, is a common disease condition. It frequently occurs in piglets during weaning at the change from fluid- to fast food feeding, which is the period in life that the epithelial expression of AP is relatively low. Antibiotic treatment is often applied, leading to antibiotic resistance and the environmental concerns mentioned above. AMRIF is therefore developing an AP-based pharmaceutical for piglets to overcome this post weaning syndrome.

## 2. Methods

The phase 2b/3 clinical trials in cardio-thoracic surgery is performed by Alloksys Life Sciences by administering (parenterally) bovine intestinal AP (bRESCAP) to 1.250 patients, in more than 6 hospitals worldwide, during and after their surgery. Besides observing their health condition following surgery for 30 days, the effect of bRESCAP on inflammation and other biochemical parameters is being monitored.

The animal study to reduce the use of antibiotics is performed by AMRIF by developing AP-containing capsules which can be taken orally by piglets after birth and during their weaning. Methods are developed to obtain stable AP formulations which can be used in capsules which protect the AP from adverse stomach conditions and release the AP in the intestines. After showing increased intestinal AP levels in healthy piglets, the effect of AP on the birth diarrhea and weaning diarrhea will be studied in groups of piglets which suffer from increased levels of birth diarrhea and weaning diarrhea.

## 3. Results/discussion

The phase 2b/3 clinical trials in cardio-thoracic surgery are being performed (started in 2017), with patients being treated in various hospitals in different countries. Early 2020 a first indication of the success of the study will be obtained (expected result is a clear reduction in kidney failure)

For the piglet study, a stable AP formulation has been developed, which can now be further processed into entero-stable capsules. It is expected that the first results of the use in piglets are obtained early 2019.

## 4. Conclusions

While the two studies are still under way, it has been clear that there is a great interest in the use of AP in cardio-surgery, as demonstrated by the willingness of many hospitals, all over the world, to join the phase 2b/3 study. The same applies to the pig-farmers which are very interested to perform the study on birth and weaning diarrhea. They feel under increased pressure to improve piglet health and growth without the use of antibiotics or other drugs.

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