Cyclosporine

$\Leftrightarrow \text{C}_{62}\text{H}_{111}\text{N}_{11}\text{O}_{12}$

$\Leftrightarrow$ cyclo-($\text{L-Alanyl-D-alanyl- N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3}$
hydroxy-$\text{N,4-dimethyl-L-2-amino-6-octenoyl-L-a-amino-butyl-L-N}$
methyl-$\text{L-leucyl-L-valyl-N-methyl-L-leucyl}$)

Thea Lotz
Corinna Martin
Markus Müller
Martin Müller
Structure:

Cyclosporine is a cyclic peptide, made of eleven amino acids. It doesn't have any C- or N terminus. In particular, the peptide has two unusual amino acids: (4R)-4-[(E)-but-2-enyle]-4-methyle-L-threonine (Bmt), that is synthesized intracellular in an enzyme catalyzed reaction, and (L)-α-amino-butyric acid (Abu). Both of them are found in nearly no other organisms. The circle also contains a D-alanine, made of L-alanine by a racemase that is normally found only in bacteria cells. For the immune suppressive functionality, the relevant parts are the long chain of Bmt and its surrounding amino acids.

Historical facts about Cyclosporine:

Cyclosporine is extracted from the sac fungi Tolypocladium inflatum and Cylindrocarpon lucidum. Tolypocladium inflatum was discovered in Oberurgl in Tirol in 1957 and tested by the company Sandoz (today Novartis) in Basel on antibiotic or inhibition effects in 1971. Tolypocladium inflatum constrains other fungi in their growth and causes a specific aborization in their growing. After many years of research they found amongst thousands of substances of the raw material only few specimens of the effective combination: Cyclosporine. They chemically analyzed Cyclosporine, but didn’t find any antibiotic effect. In 1975 its structure was cleared up with chemical and radiographic additives.

Some years later it was discovered by accident that Cyclosporine has an immunosuppressive effect while they tested the substance on mice that had had kidney transplantations. They showed a increased rate of living after the addition of Cyclosporine. Both Dr. Jean-Francois Borel and Dr. Hartmann Staehlin were included in the discovery of Cyclosporine. Dr. Jean-Francois Borel said about the unique property which hampers only cells of the immune defense mechanism:

-When you compare the immune answer with biting dogs, then Cyclosporine is the muzzle who hinders special cells of the immune defense system to bite without killing them."
In 1976 the biological characteristics of Cyclosporine were published for the first time and more analyses at the Cambridge University of Great Britain conducted by Roy Calne followed. At first Cyclosporine was given oral in capsules. It didn’t work, since the blood was not receptive of the substance. Giving a solution consisting of Cyclosporine and olive oil solved the problem. Firstly there were made tests on dogs with transplanted kidneys and it was again noticed an increased number of living patients. In 1978 Cyclosporine was given to a human for the first time. In 1982 it was licensed as ‘Sandimmun’. Until today the doctors succeeded in transplanting more than 500,000 kidneys, using Cyclosporine as an immune suppressive.

Since 1994 Cyclosporine is given in a homogenous solution which makes the reception faster and more efficient.

It hasn’t been discovered yet, what exactly Cyclosporine does in the metabolic system of the fungus Tolypocladium inflatum.

**Synthesis:**

The fungus is cultivated via fermentation until today. Complete or part synthesis have proven too expensive. The enzyme catalyzing the synthesis is ‘Cyclosporine-Synthase’. The starting amino acid for the circle building is D-Ala; the amino groups are methylised in the end.

**Mechanism:**

The active agent cyclosporine inhibits blood cells, the so-called T helper cells which are part of the immune defense. The T helper cells recognize exogenous substances caring for their removal from the organism. It is important to control them in transplantation medicine to prevent rejection of a transplanted organ. Administration of cyclosporine inhibits the body’s defense reaction.

The mechanism of action of cyclosporine can be described roughly as an inhibition of the DNA-transcription factor, which would cause an activation of T helper cells.

If a T helper cell comes upon an exogenous substance, a cascade of reactions is triggered activating the T helper cells.

In the cytoplasm the enzyme calcineurin binds to the gene-transcription factor NF-AT dephosphorylating it. Thus the transcription factor can get into the nucleus. There it specifically activates the transcription of diverse cytokines (proteins which initiate or adjust cell growth and cellular differentiation) and cell-surface-receptors (especially Interleukin-2).

If these gene-sections are expressed, the resulting activation of T helper cells starts removal of the exogenous substances.
Cyclosporine comes into action directly in the first step of the chain reaction: it ties down to calcineurin so that the dephosphorylation cannot take place. Like this the genes that are necessary for the immune reaction cannot be realized.

However cyclosporine inhibits only inactive T helper cells. Once a T helper cell is activated, cyclosporine can barely influence it.

Through the inhibition of the T helper cells indirectly also B-Lymphocytes and T killer cells are inhibited, since they can only be activated by the T helper cells. Though, cyclosporine does not have an impact on Macrophages and other cells in the human body. This implies an increased specificity simplifying the dosage scheme.

The inhibition of calcineurin is reversible; as soon as the concentration of cyclosporine in the cells decreases, the immune defense can proceed normally again.

**Areas of application:**

Primary Cyclosporine is used after organ transplants to prevent the rejection of the foreign tissue.

Cyclosporine is also used to fight off inflammations, which are caused by the immune system, like Uveitis, Neurodermatitis or Rheumatoid Arthritis.

In that case Cyclosporine is only used when all other medications show no effect.
Another unproven area of application is the usage of Cyclosporine for type 1 Diabetes, which is also caused by the immune system.

**Side effects:**

The major side effect of Cyclosporine is the arterial hypertension which is closely linked to a kidney failure. This effect occurs at 80 percent of the patients and is known as nephrotoxicity. The main reason for the nephrotoxicity is the retention of the Na+ level which causes an increased water-resorption so that the volume blood plasma rises. Studies have shown that a low sodium diet can help to improve the arterial hypertension. Other side effects are hyperlipidemia, tremor and headache which occurred at 10% of the patients. Much rarer side effects are cramps, gastrointestinal problems, tiredness and liver damages (about 1% of the patients). At less than 0.1% of the patients caused the taking of Cyclosporine states of confusion, visual disorders and comatose states.

**Conclusion:**

Cyclosporine has long been irreplaceable concerning transplantations. But by now, there are some other agents, which have a similar efficiency rate but fewer side effects.
Sources:

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by Thea Lotz, Corinna Martin, Markus Müller, Martin Müller
TU Darmstadt
Bc. of Science Biomolecular Engineering