

What is Erythropoietin?

Protein Hormone that Stimulates Red Blood Cell Production

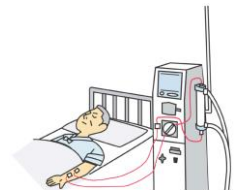
Deterioration of kidney function and anemia



- The kidneys serve a variety of functions, including the production of urine and the excretion of waste products as well as the production of **erythropoietin**, a hormone that stimulates the production of red blood cells.
- The kidneys regulate erythropoietin secretion in response to blood oxygen levels. **When kidney function declines, the kidneys' ability to secrete erythropoietin also declines.**
- The reduced erythropoietin secretion inhibits production of red blood cells, **causing symptoms of anemia.**
- Symptoms of anemia include fatigue, palpitations, shortness of breath, headache, dizziness, cramps and fainting.

Treatment of anemia prior to the erythropoietin drug

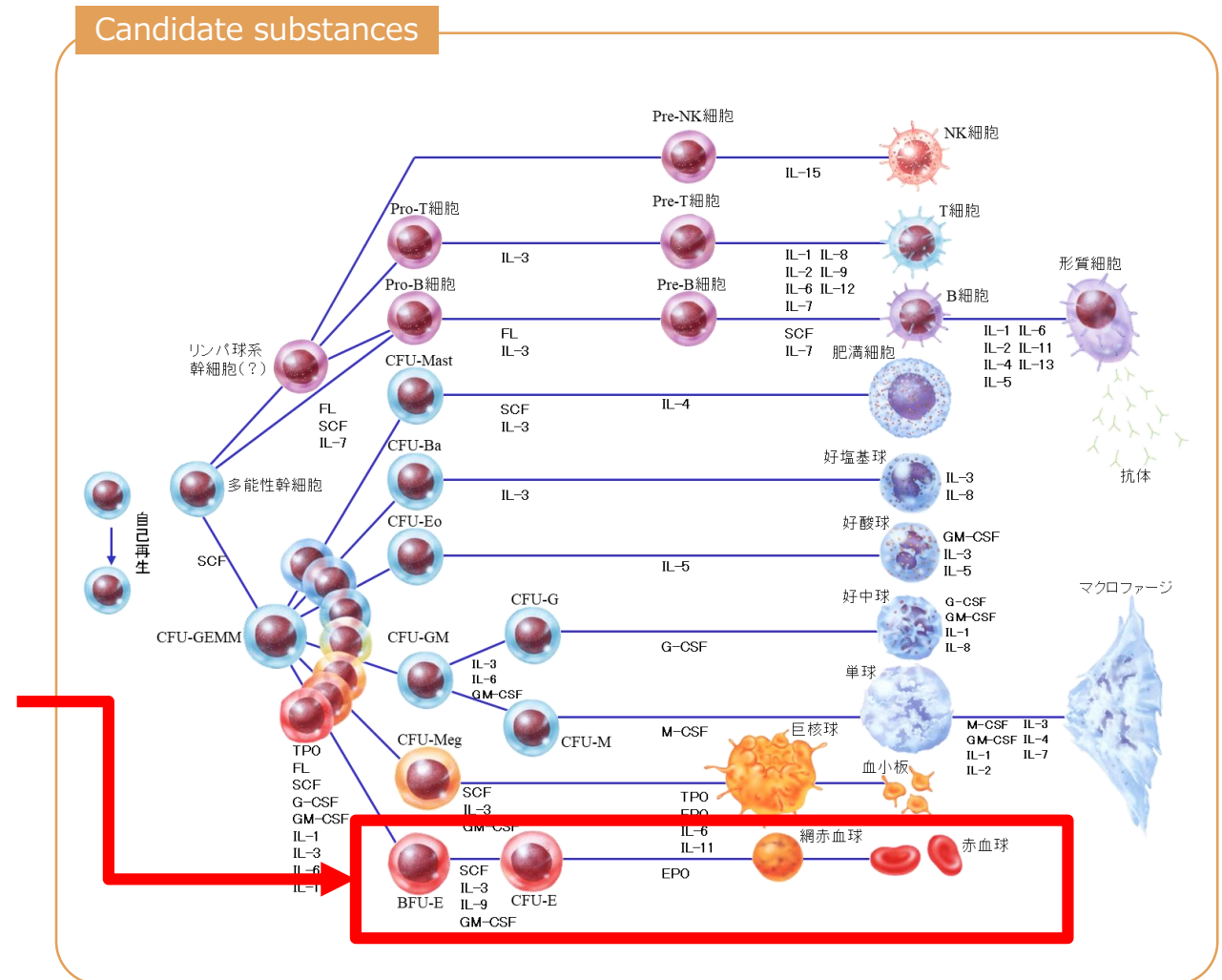
- Before the advent of erythropoietin as a drug in the 1980s, **patients with kidney failure were given blood transfusions to treat their anemia.**
- Patients with chronic renal failure **required regular blood transfusions.**
- Repeated transfusions at times saw a higher risk of **adverse events such as transfusion-derived iron deposition and hepatitis virus infection.**
- In recent years, the frequency of blood transfusions to dialysis patients has **fallen dramatically.**



Development of Erythropoietin (EPO)

Kirin's First Biologic

- In the 1970s, Kirin Brewery (now Kirin Holdings) announced a policy of diversification and began **studying applications of biotechnology based on fermentation and brewing technologies.**
- Over a decade later, Kirin Brewery embarked on a **biologics business leveraging genetic recombination technology.**
- **EPO** was selected as one of the first research subjects among several other candidates under consideration because of its clear mechanism of action and ability to address clear patient needs.



Development of erythropoietin

Development of erythropoietin (EPO) at Kirin

1980s

- Hypothesis formulated in the 1980s
The hormone involved in hematopoiesis (erythropoietin (EPO)) is made by the kidneys; if the kidney function deteriorates, EPO will no longer be produced and anemia will develop
- In-house research on EPO begins in order to prove the hypothesis
Decreased EPO production is confirmed as a cause of anemia
- Partnership with Amgen starts in 1984 (Kirin-Amgen, Inc. established)
Research and development on EPO continues
- Human erythropoietin successfully isolated and cloned in 1985*

1990s

- 1990: Human erythropoietin (genetically recombinant) approved in Japan; EPO formulation with the same structural characteristics and immunological/ biological properties as human EPO (derived from urine) launched.

*Lin FK, Suggs S, Lin CH, et al. Cloning and expression of the human erythropoietin gene. Proc Natl Acad Sci USA. 1985; 82: 7580-7584

Development of erythropoietin

U.S.-based Amgen Inc.

→ About Amgen

- Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics.
- This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.



▲ U.S.-based Amgen Inc.

Development of Erythropoietin (EPO)

Mass Production with the Roller Bottle Method

→ In 1993, Kirin Brewery filed an **application to expand the indications** for erythropoietin (EPO), which had been approved for the treatment of renal anemia in patients on dialysis to include chronic renal failure before dialysis and anemia in premature infants, among other conditions. However, there was a concern that if these applications were approved, the use of active pharmaceutical ingredients would increase dramatically and that it would be **highly difficult to ensure the supply with the existing production capacity**.

- Construction of an EPO API building on the premises of the Takasaki Plant proceeded, and a **fully automated roller bottle system for animal cell mass culture** was in place by February 1995.
- The new **roller bottle system** consisted of a culture rack for culturing cells, a filling and harvesting unit for filling, exchanging, washing, and collecting culture media, and an automatic system for loading/unloading and transferring roller bottles that connected the culture rack with the filling and harvesting unit. This allowed use of 8,000 roller bottles to perform a series of tasks aseptically and automatically.
- This **quadrupled Kirin Brewery's EPO production capacity**.



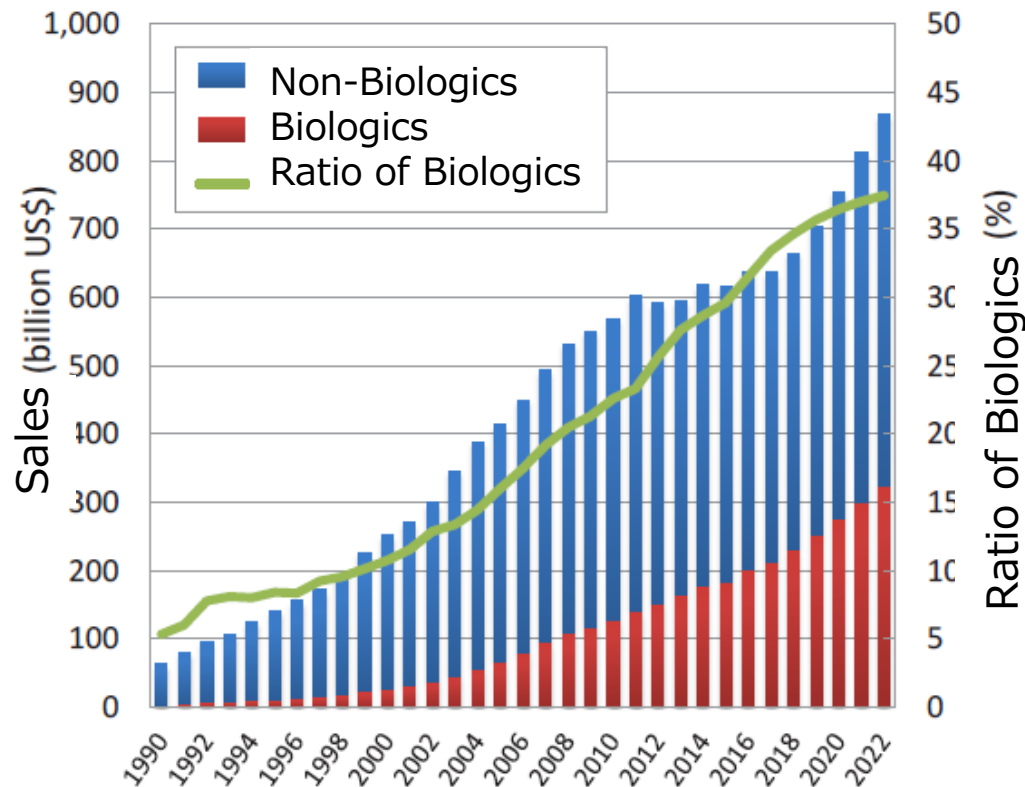
*EPO is currently manufactured with cutting-edge technology and no longer with a roller bottle process.

▲ Roller bottle system
(Original bottle system)

Kirin's Foresight and Strategy

The Growing Biologics Market

Global biologics market trends



Source: Research "Challenges for the Biopharmaceutical Industry and Proposals for Further Development" Policy Research Paper Series No. 71, Office of Pharmaceutical Industry Research

- When Kirin Brewery first started looking at biologics, the number of biologics on the market was negligible; in recent years, however, the ratio accounted for by biologics has exceeded 35%.
- Kirin Brewery was among the first companies to predict that biologics have the potential to prove highly effective in treating diseases for which no other treatment was available or which could not be treated effectively. Kirin Brewery thus embarked on a biologics business entailing the application of biotechnology based on fermentation and brewing technologies.

Kirin's foresight

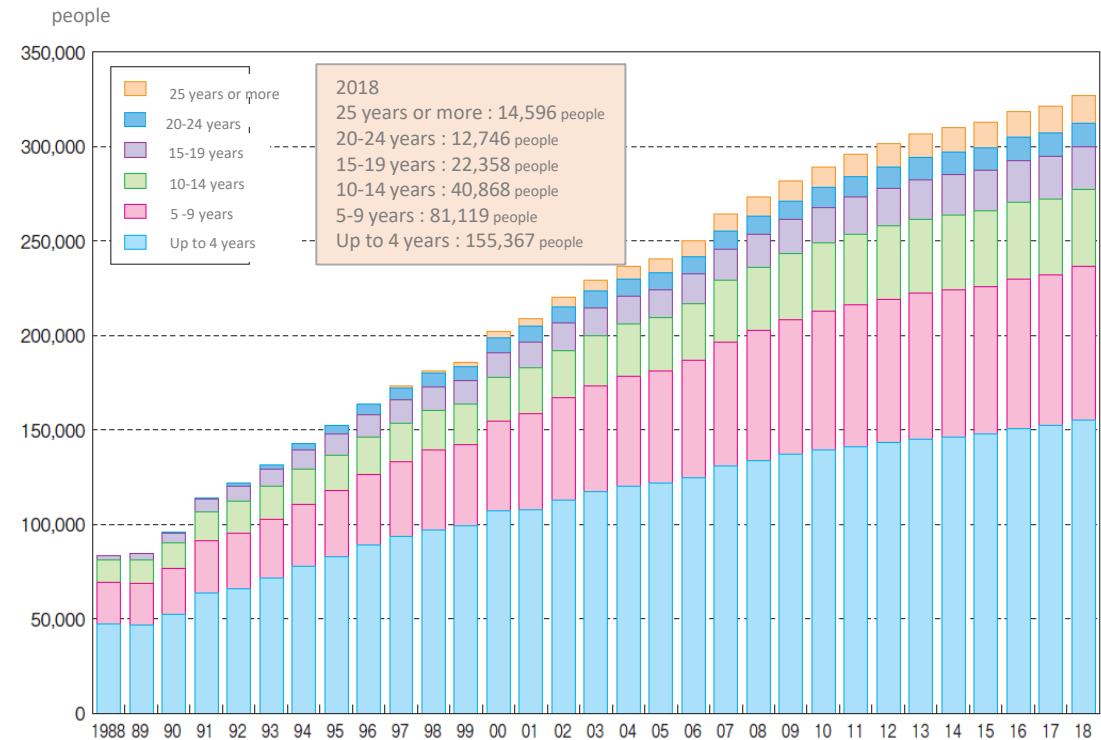
Many lives saved by EPO biopharmaceutical.

Previously unable to continue treatment over the long term with conventional blood transfusions



The discovery of erythropoietin's function and the launch of its formulation are now saving more lives by **enabling long-term dialysis treatment**

Chronic dialysis patients: trends in distribution of dialysis history



Source: "Current Status of Chronic Dialysis Therapy in Japan (as of December 31, 2018)" The Japanese Society for Dialysis Therapy

Current treatment of renal anemia

From next-generation therapeutics to a new stage

- In recent years, **long-acting** erythropoietin and drugs that stimulate erythropoietin secretion through **oral administration** have emerged, providing more treatment options
- Other drugs aimed at **improving deteriorated kidney function** are also being developed in Japan and abroad



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