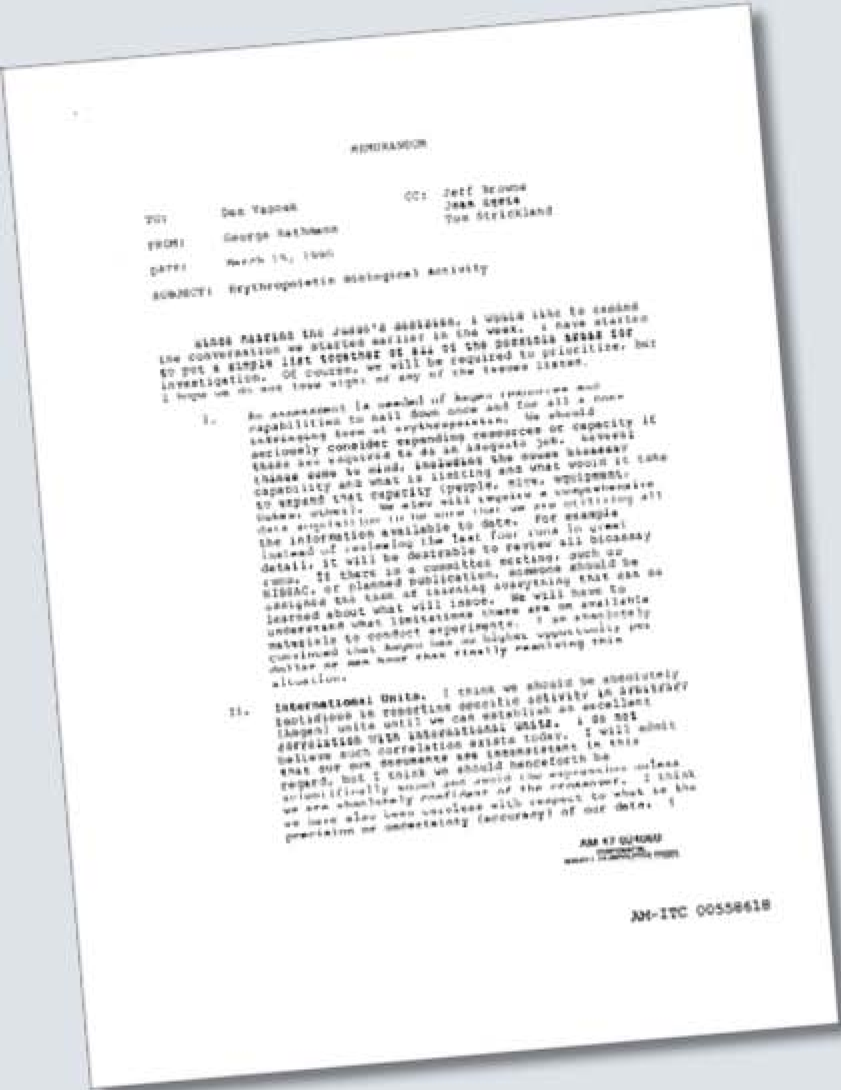
- Goldwasser's purified EPO was the key;
- Techniques like Maniatis made cloning of the EPO gene obvious;
- EPO producing cell lines were available prior to Lin patents: Gayliss / Shouval / Fisher;
- Once you the EPO gene, it was fully expected that one could make an in vivo biologically active protein;
- Lin admitted that in vivo biological activity was expected;
- CHO cells were freely available before Lin's invention;
- Amgen already had 17 years of EPO patent protection with its now expired '008 patent;
- Amgen's recombinant EPO is not new because its structure is the same as natural EPO in the body;
- Before Lin, Baron/Goldwasser clinical trial using natural EPO showed that it worked in patients;
- Amgen did not even know the structure of EPO when it filed its patents - Amgen thought it was 166aa when in fact it is 165aa;
- Amgen also did not know how to describe its claims to RIA - too many different standards, too many non-EPO fragments detected by RIA;
- Amgen claimed too much - it claimed EPO made in millions of vertebrate cells when it only knew how to do it in 1 type of cell;
- Amgen did not teach how to make purified EPO for use in a pharmaceutical composition

Amgen Admits that Units are "Arbitrary" and Do Not Correlate to International Standards


MEMORANDUM

TO: Dan Vapnek

FROM: George Rathmann

DATE: March 15, 1990

SUBJECT: Erythropoietin biological activity

AM-ITC 00558618

March 15, 1990

Memo from Rathman to Vapnek

"I think we should be absolutely fastidious in reporting specific activity in arbitrary (Amgen) units until we can establish an excellent correlation with international units. **I do not believe such correlation exists today. I will admit that our own documents are inconsistent in this regard...**

...I think we have also been careless with respect to what is the precision or uncertainty (accuracy) of our data...

... It is absolutely imperative that we learn as early as possible what the international (NICSAC) committee that is conducting round robin studies is finding. My prediction is that the information will be absolute chaos."

AM-ITC 00558618

History of the Lin Patents

EPO Producing Cell Lines Were Available Prior To Lin Patents

1982 | **1983**

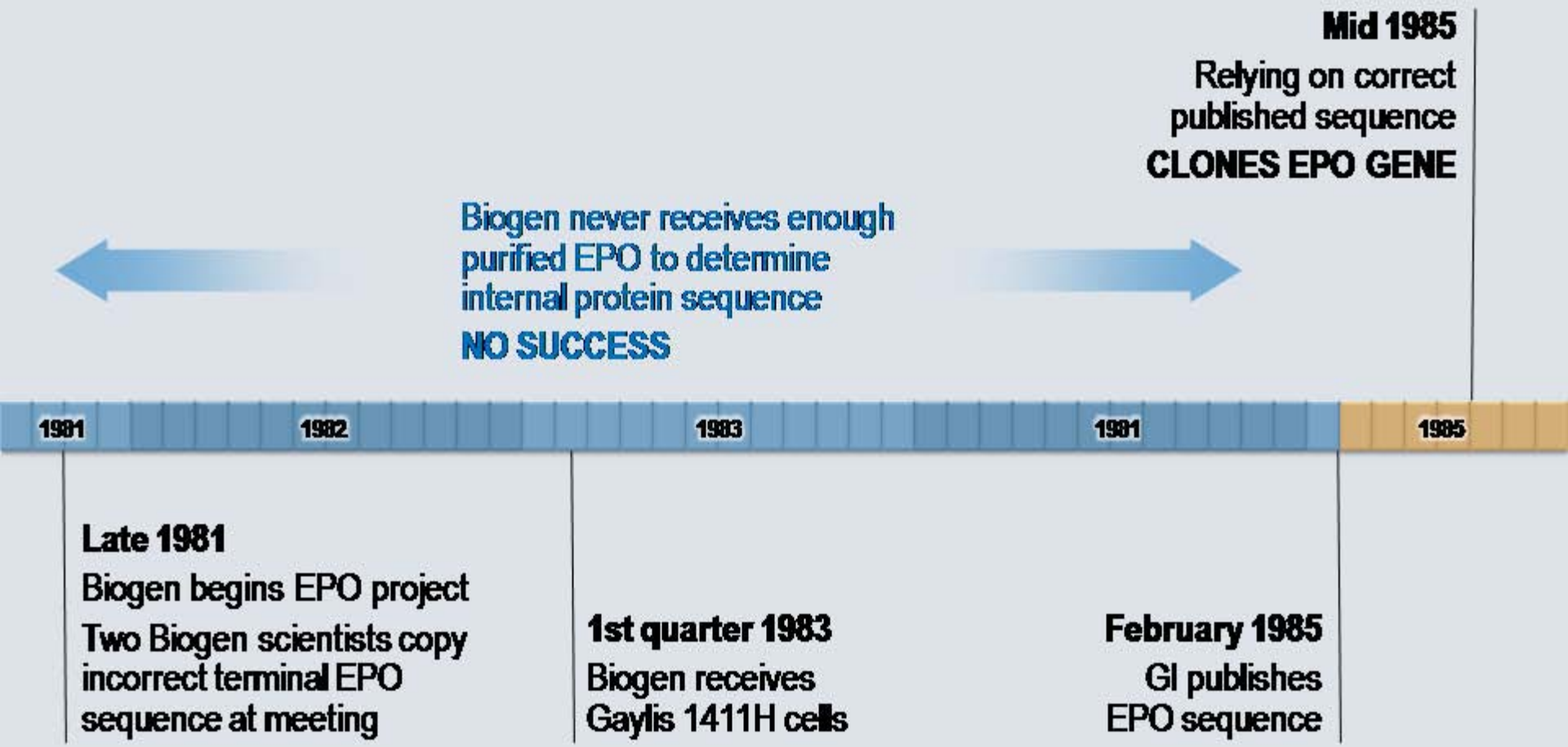
November 30, 1982 - Ascensao and Gayfiss publish 1411-H Cell line, Ascensao et al, Amer Fed Clin Res. Abstract, 1982

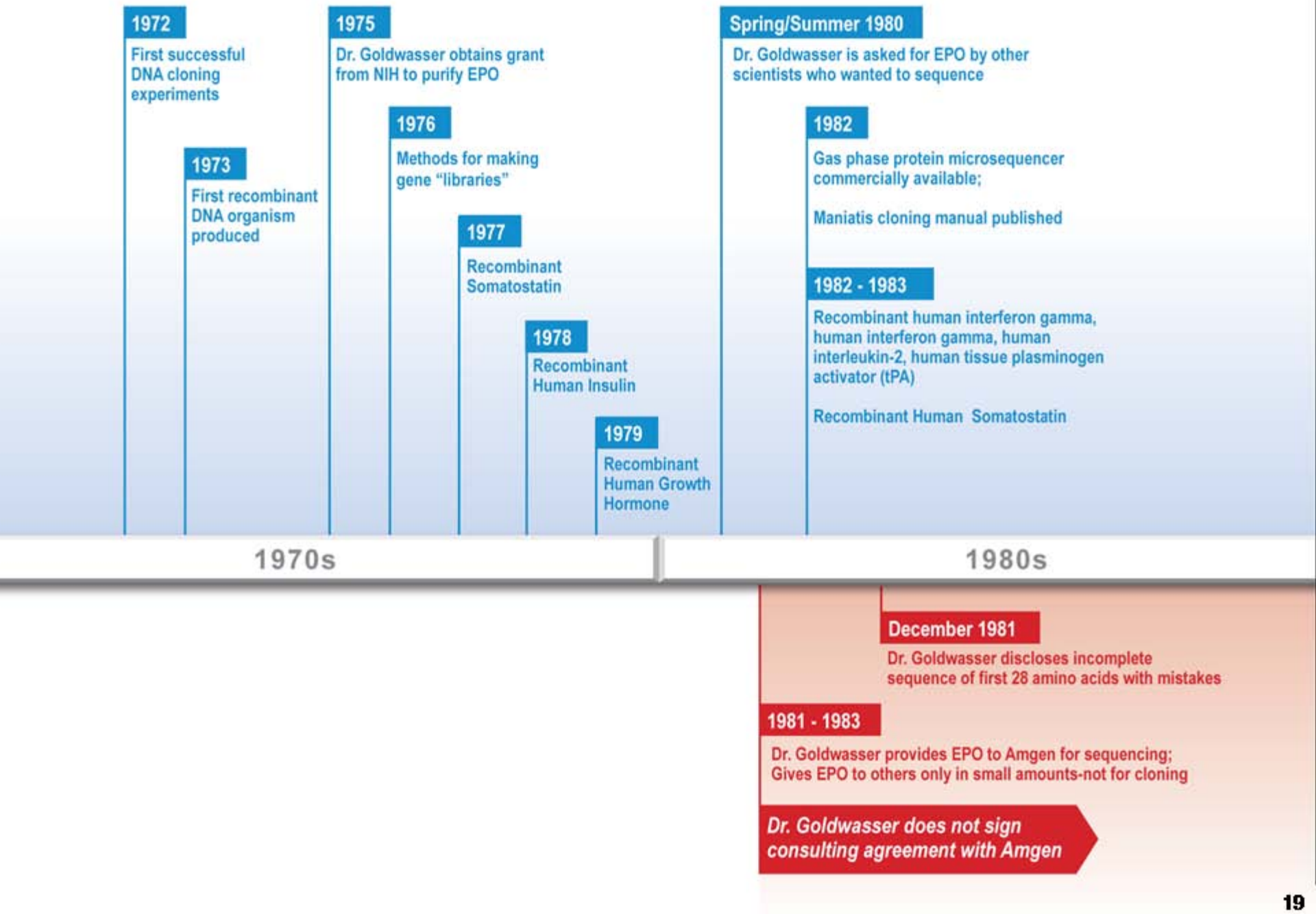
April 1983 -Sherwood and Shouval publish renal carcinoma cell lines, Sherwood et al., Clinical Res. (1983).

August 1983 -Katsuoka and Fisher publish renal carcinoma cells, Katsuoka et al, Gann, 74(4): 534-541 (1983)

December 13, 1983 - Amgen files first Lin application

EPO Producing Cell Lines Were Available Prior To Lin Patents




1972
First successful DNA cloning experiments
1973
First recombinant DNA organism produced
1975
Dr. Goldwasser obtains grant from NIH to purify EPO
1976
Methods for making gene "libraries"
1977
Recombinant Somatostatin
1978
Recombinant Human Insulin
1979
Recombinant Human Growth Hormone
Spring/Summer 1980
Dr. Goldwasser is asked for EPO by other scientists who wanted to sequence
1982
Gas phase protein microsequencer commercially available;
Maniatis cloning manual published
1982 - 1983
Recombinant human interferon gamma, human interferon gamma, human interleukin-2, human tissue plasminogen activator (tPA)
Recombinant Human Somatostatin
1970s
1980s
December 1981
Dr. Goldwasser discloses incomplete sequence of first 28 amino acids with mistakes
1981 - 1983
Dr. Goldwasser provides EPO to Amgen for sequencing; Gives EPO to others only in small amounts-not for cloning
Dr. Goldwasser does not sign consulting agreement with Amgen

Chronology of '008 and Continuation Patents

'008 Patents and Patents-in-suit all share the same specification