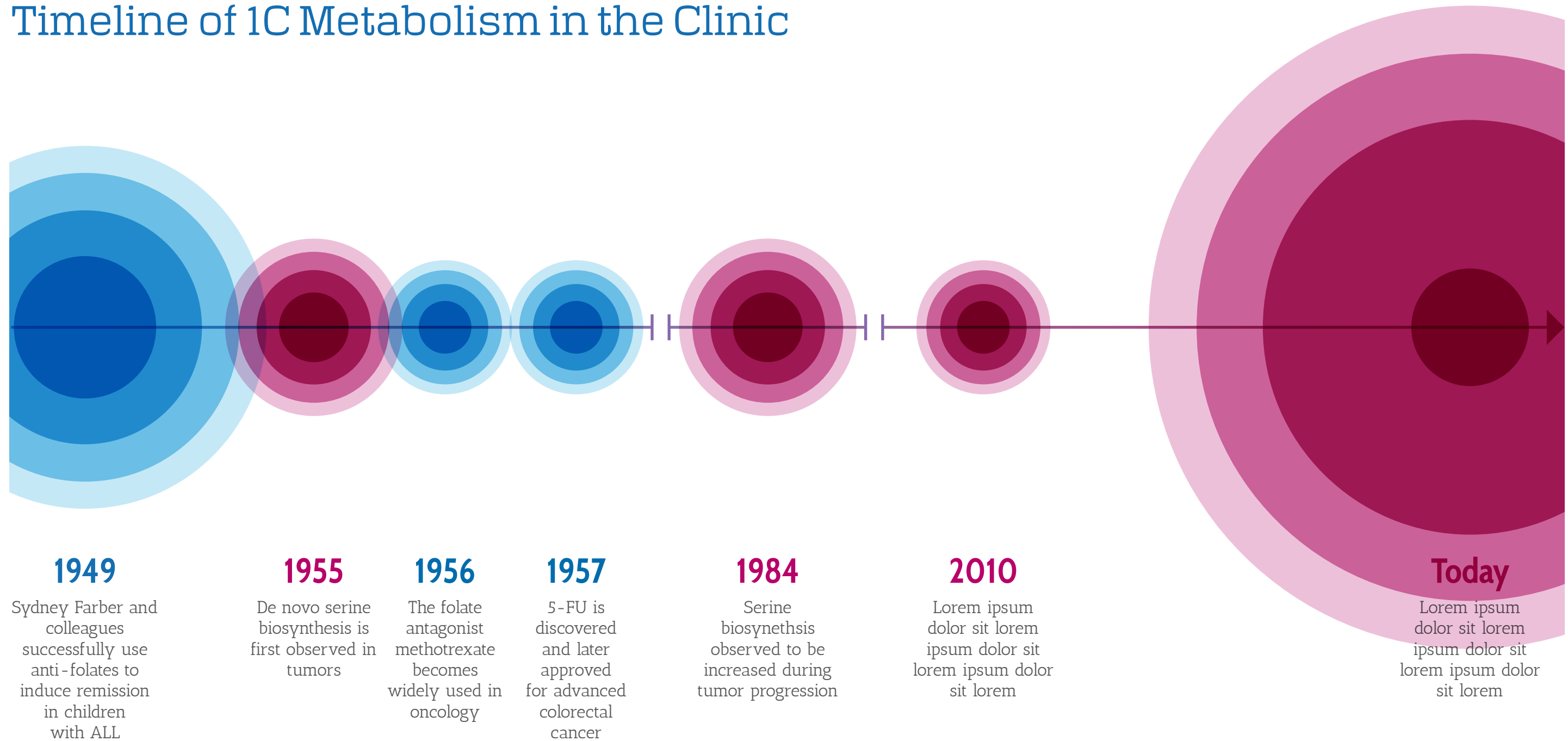


# Timeline of 1C Metabolism in the Clinic



Clinical success • Yet understanding of 1C metabolism inhibitors has lagged

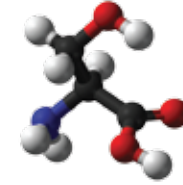
## Timeline of 1C Metabolism in the Clinic



**1949**  
Sydney Farber and colleagues successfully use anti-folates to induce remission in children with ALL



**1956**  
The folate antagonist methotrexate becomes widely used in oncology



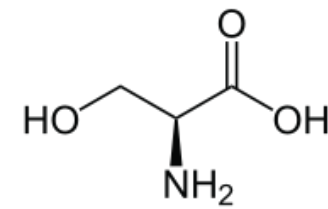
**1984**  
Serine biosynthesis observed to be increased during tumor progression



**1998**  
Raltitrexed (thymidylate synthase inhibitor) approved



**2008**  
Pemetrexed approved, reaches > \$2.7B sales by 2013



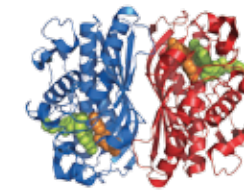
**1955**  
De novo serine biosynthesis is first observed in tumors



**1957**  
5-FU is discovered and later approved for advanced colorectal cancer



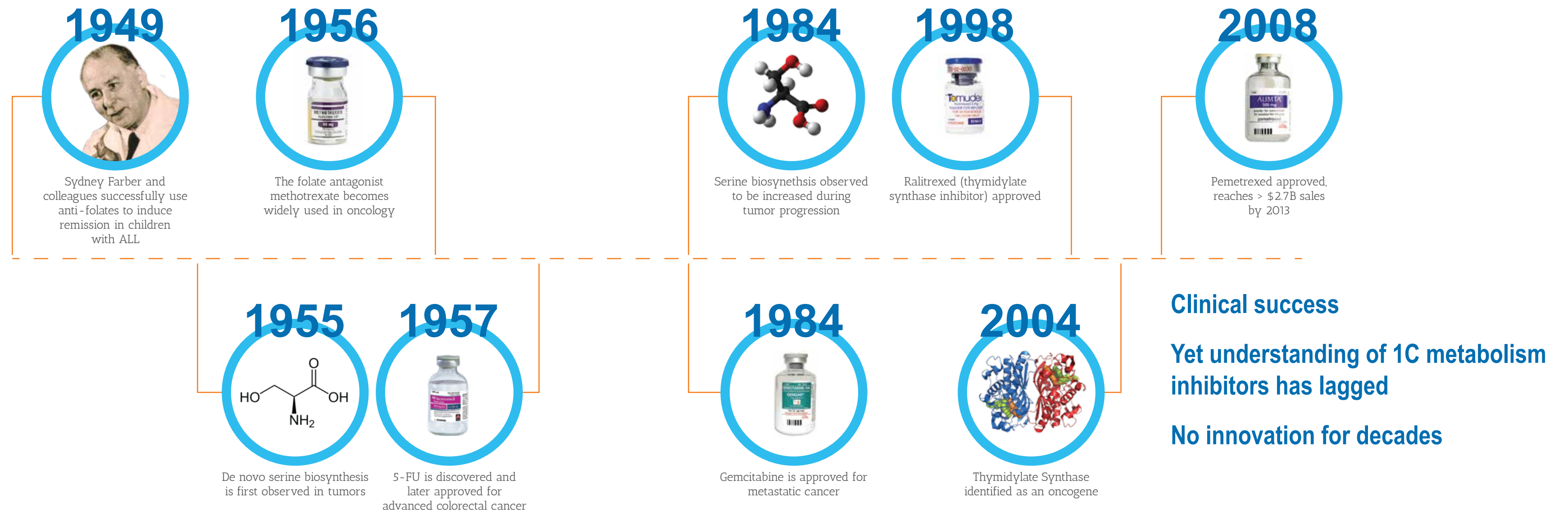
**1984**  
Gemcitabine is approved for metastatic cancer



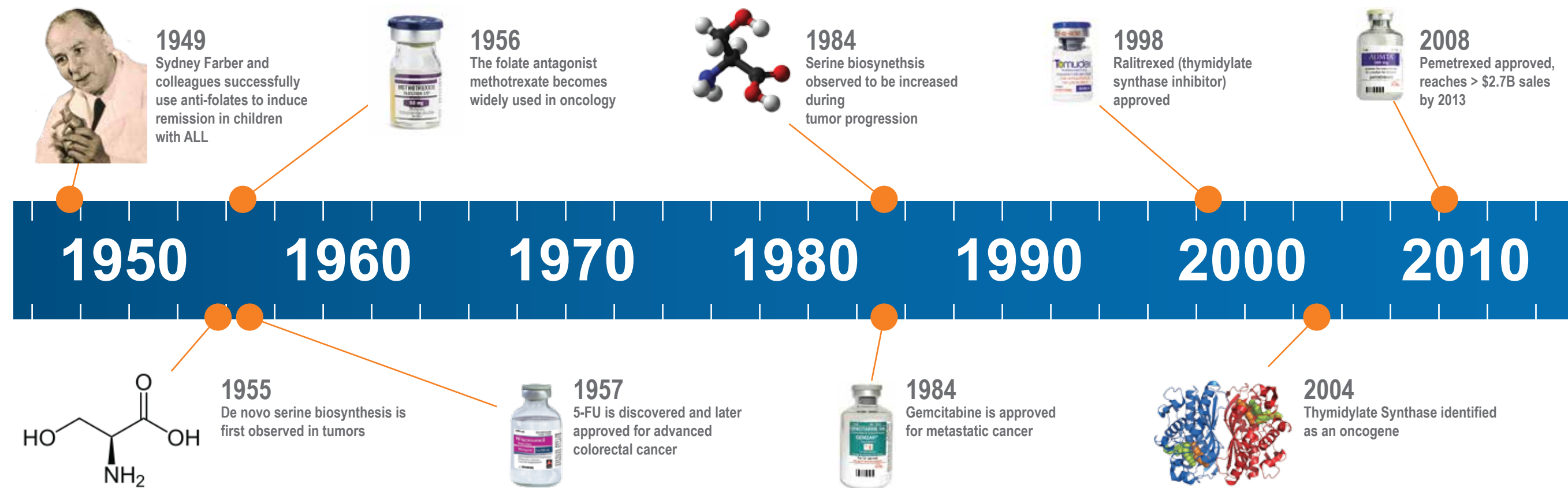
**2004**  
Thymidylate Synthase identified as an oncogene

**Clinical success**  
Yet understanding of 1C metabolism inhibitors has lagged  
No innovation for decades

## Timeline of 1C Metabolism in the Clinic



## Timeline of 1C Metabolism in the Clinic



**Clinical success**  
**Yet understanding of 1C metabolism inhibitors has lagged**  
**No innovation for decades**