Ron Franklin

A Potted (& Selected)History of LY170053

1982 -Project team formed in Erl Wood

1986 -IND submitted in U.S.

1987 -*May* '87 Human volunteers dosed (some SGPT (ALT) elevations)

September '87 1st patients dosed in Europe

^{14}C-study done in humans; no parent plasma concentrations measured because of assay sensitivity: urine showed some parent & lots of unidentified metabolites

ZY 148 459

A Potted (& Selected)History of LY170053[cont'd]

1990 -*July* '90 RBF appointed to Team
Recommendation of more ^{14}C material for human and animal studies e.g , bioavailability studies in dogs, studies for Japan etc. etc

1991-*June* '91 Rec'd ^{14}C-LY170053
August '91 Bioavailability expts in dogs with ^{14}C material started and completed in September; some urine sent to Clinic--
start of continuing collaboration
October '91 ^{14}C- study #2 carried out in humans (gc/ms assay)

1992-*January* '92 C- study #3 carried out in humans
February '92 Concerns about missing raw data from original preclinical ADME (Tox QA pay a visit)

ZY 148 460

ADME Responsibilities from 1990 to present

Clinical	*Preclinical*	*In vitro*
1990/1		
Obermeyer	Sullivan et al	-
Rubin/Mattiuz	Franklin et al.	
Kassahun/Mattiuz	Gillespie/Murphy	-
-	Pohland et al	-
1994		Wrighton/Ring

ZY 148 461

Preclinical ADME Responsibilities

- single dose PK with ^{14}C
- mass balance studies
- biliary secretion
- enterohepatic recirculation
- site & extent of absorption (portal vs. systemic)
- toxicokinetics
- tissue distribution (single & multiple)
- plasma protein binding
- bioavailability
- plasma metabolite profiling (rat,dog and mouse)
- urinary metabolite profiling, isolation and identification of metabolites (Kassahun and Mattiuz)

ZY 148 462

Overview of Preclinical ADME of LY170053

- Compound was well absorbed from small intestine and colon
- Substantial first-pass effect (portal vs. systemic)
- Bioavailability of LY170053 in the rat was 47%
- Plasma levels of LY170053 were lower than those of total metabolites
- Plasma metabolites included:
  Rat: 2-CH_2OH, N-oxide, N-desmethyl-, 7-OH and 7-OH-glucuronide

  Dog: 2-CH_2OH, N-oxide, N-desmethyl-, 7-OH-

  Mouse: 2-CH_2OH, N-desmethyl-, GSH conjugates

Overview of Preclinical ADME of LY170053
[cont'd]

- Single dose tissue distribution:
  96 hours - liver (0.62%), kidneys (0.07%), blood (0.04%), testes (0.02%), jejunum (0.01% of dose)

- 21 day tissue distribution:
  tissues with highest conc. - thyroid, kidneys, liver
  linear increase in tissues over time
  168 hours after last dose, only 0.4% dose found in collected matrices
  protracted t1/2 of radioactivity esp. blood, thyroid

- Plasma half-time of radiocarbon exceeded that of LY170053, for example:

Rat	30 h vs. 3 h
Dog	25 h vs. 6-8 h
Monkey	98 h vs. 3-5 h

- Between 40-60% of radiocarbon was secreted into bile

- Enterohepatic recirculation accounted for 35% of dose

- Majority of radiocarbon was eliminated *via* feces

- Major urinary metabolites differed with species

ZY 148 464

A staid schizophrenic named Struther
When told of the death of his brother,
Said: "Yes, I am sad.
It makes me feel bad,
But then, I still have each other."