The Search for Better Chagas Drugs: Discovery Research Efforts

Frederick S. Buckner
University of Washington
Department of Medicine
October 2, 2009

Drug development pipeline for Chagas disease

Discovery	Preclinical	Clinical	Available to patients
• Screening • Lead series • Lead optimization	• DMPK studies • Tox studies • IND submission	• Phase I • Phase II • Phase III	• Benznidazole • Nifurtimox

Drug development pipeline for Chagas disease

Discovery	Preclinical	**Clinical**	Available to patients
• Screening • Lead series • Lead optimization	• DMPK studies • Tox studies • IND submission	• Phase I • Phase II • Phase III	• Benznidazole • Nifurtimox

Cysteine protease inhibitors
- Sandler Center (UCSF)

Pediatric formulation of Benznidazole
- DNDi (Brazil)

- BENEFIT Trial

Drug development pipeline for Chagas disease

Discovery	Preclinical	**Clinical**	Available to patients
• Screening • Lead series • Lead optimization	• DMPK studies • Tox studies • IND submission	• Phase I • Phase II • Phase III	• Benznidazole • Nifurtimox

Clinical trial with an azole antifungal drug?

- Posaconazole?
- Ravuconazole or Ravuconazole prodrug (E1224)?

Drug development pipeline for Chagas disease

Discovery

- Screening
- Lead series
- Lead optimization

Preclinical

- DMPK studies
- Tox studies
- IND submission

Clinical

- Phase I
- Phase II
- Phase III

Available to patients

- Benznidazole
- Nifurtimox

Drug development pipeline for Chagas disease

Discovery	Preclinical	Clinical	Available to patients
• Screening • Lead series • Lead optimization	• DMPK studies • Tox studies • IND submission	• Phase I • Phase II • Phase III	• Benznidazole • Nifurtimox

Novel sterol 14-demethylase inhibitors (University of Washington)

Drug development pipeline for Chagas disease

Discovery	Preclinical	Clinical	Available to patients
• Screening • Lead series • Lead optimization	• DMPK studies • Tox studies • IND submission	• Phase I • Phase II • Phase III	• Benznidazole • Nifurtimox

DNA topoisomerase inhibitors
Transialidase inhibitors
Trypanothione reductase inhibitors
Farnesyl pyrophosphate synthase inhibitors
Bioinorganics

Drug development pipeline for Chagas disease

Discovery	Preclinical	Clinical	Available to patients
• **Screening** • Lead series • Lead optimization	• DMPK studies • Tox studies • IND submission	• Phase I • Phase II • Phase III	• Benznidazole • Nifurtimox

Natural products libraries
Diverse synthetic libraries
Focused chemical libraries

Lack of access and funding are limiting progress

“Repurposing” compounds for Chagas disease

- Ergosterol biosynthesis inhibitors
  - Azole antifungals
  - Allylamines (terbinafine)
- Amiodarone
- Screen of FDA approved drug on *T. cruzi*
  - Antihistamines
  - SSRIs
  - Etc.

Combination Chemotherapy for Chagas Disease

- Benznidazole + ?
- Azole drug + ?
- FDA approved drug A + B

Synergy matrix of 24 compounds on *T. cruzi*

Proportion of Observed to Maximum Inhibition

Comp \ Test	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1		-0.04	-0.04	0.41	-0.13	-0.16	0.46	0.00	0.43	-0.19	0.61	-0.10	0.12	-0.32	-0.08	-0.13	0.04		0.15	0.11	-0.09		0.14	-0.19
2	0.22			-0.01	-0.26	0.06	0.24	0.31	0.57	0.42	0.31	0.46	0.05		0.37	0.05	0.07		-0.03	0.55	-0.06		0.42	-0.18
3	0.11	0.20		0.11	0.04	-0.16	0.41	0.00	-0.06	-0.28	0.19	0.29	-0.07	-0.27	-0.36	-0.15	-0.08		-0.06	0.32	-0.39		0.11	-0.33
4		-0.05	0.00		0.02	0.06	0.75	0.14	0.44	-0.11	0.83				0.06	0.53	0.30		0.11	0.14	0.27		0.10	0.00
5	0.16	-0.01	0.13	0.14		0.07			-0.14	-0.21	-0.04	0.09	-0.10	-0.05	-0.09	-0.08	-0.15			-0.06			-0.07	-0.19
6	0.15	0.29	-0.11	0.14	0.13		0.61	0.13	0.35	-0.01	0.27	0.36	-0.12	-0.27	-0.06	-0.02	-0.18		-0.05	0.26	-0.53		0.14	-0.29
7		0.82	0.85	0.89		0.82		0.88	0.89	0.42	0.88	0.81	0.49	-0.14	0.43	0.42	0.25		0.80		0.87		0.75	0.10
8		0.36	-0.15	-0.08	-0.04	-0.22	0.63		0.26	-0.09	0.32	0.48	0.09	-0.01	0.06	0.06	0.04		0.00		-0.44		0.24	-0.28
9	0.46	0.66	0.49	0.53		0.44	0.84	0.54		0.69	0.88	0.91			0.67	0.20	0.58		0.51	0.52			0.56	-0.10
10	0.03	0.45	0.11	0.03		0.02		-0.09	0.43		0.34	0.60	0.15	0.06	0.47	0.22	-0.13		0.04	0.42	-0.29	0.11	0.34	0.01
11	0.64	0.38	0.50	0.81		0.23	0.82	0.37	0.83	0.34		0.07	0.42	-0.27	0.39	0.19	0.33	-0.24	-0.18	0.36	0.19	0.61	0.44	-0.09
12	0.00	0.53	0.50	0.06		0.42		0.57		0.74	0.54				0.75	0.52	0.33		0.02	0.63			0.66	-0.03
13								0.15	0.24	-0.01	0.33	-0.14		-0.35	0.00		0.38		0.21	0.31	-0.12	0.13	0.30	-0.12
14	-0.16	0.02	0.05			-0.12		0.01		0.07	0.00		0.06				0.10		-0.05	0.07			0.05	-0.15
15	-0.13	0.33	-0.06	-0.03	-0.05	-0.22	0.23	-0.08	0.40	0.26	0.52	0.75	0.11	-0.11		0.09	-0.39		-0.22				0.31	-0.19
16	-0.20	-0.01	-0.07	0.31	-0.12		0.27	-0.05	0.31	0.17	0.14	0.36	0.05	-0.01	0.24		-0.17		0.08	0.24			0.15	-0.17
17	0.04	0.10	0.02	0.42	-0.05	-0.01	0.09		0.45	0.02	0.20	0.17	0.13	-0.14	-0.24	-0.29			-0.39	0.28	0.07		0.22	-0.16
18							0.12					-0.37												
19	0.15	-0.01	-0.28	0.12	0.07	-0.08	0.85	0.01	0.47	-0.25	0.18	0.05	0.11		-0.30	0.09	-0.07			0.01	-0.06		-0.19	-0.19
20	0.13		0.29	0.15	0.27	0.38	0.27							-0.04			0.27		0.11		-0.37		0.63	-0.14
21	-0.27		-0.67	0.23		-0.47	0.83	-0.18			-0.36		-0.11	-0.41			-0.11	-0.37	-0.26	-0.47		-0.14	0.03	-0.18
22	0.29	-0.10		0.56	-0.33	-0.23	0.78	-0.09	0.43	0.05	0.64	0.16	0.09	-0.12	-0.08	-0.15								
23	0.02	0.22	0.15	0.05	0.23	0.17		0.17	0.65	0.43	0.50	0.60	0.10		0.33	0.10	0.31		-0.09		-0.23			-0.06
24	-0.15	-0.33	-0.14	-0.08	-0.13	0.02	0.16	0.01	-0.19	0.00	-0.08	-0.10	-0.09	-0.23		-0.24	-0.05		-0.23	-0.11	-0.11		-0.14	

9/24/2009

Green: "synergistic"
Red: "antagonistic"
White: not done

The challenges for Chagas drug R & D

- Limited resources means only a few “shots on goal”

- Focus on: What’s the cheapest, fastest way to make safe, effective drugs available to patients?