

Ways and steps of drug discovery

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*12th International Conference on Thalassaemia and the Haemoglobinopathies, and 14th TIF
Antalya, 11-14 May, 2011*

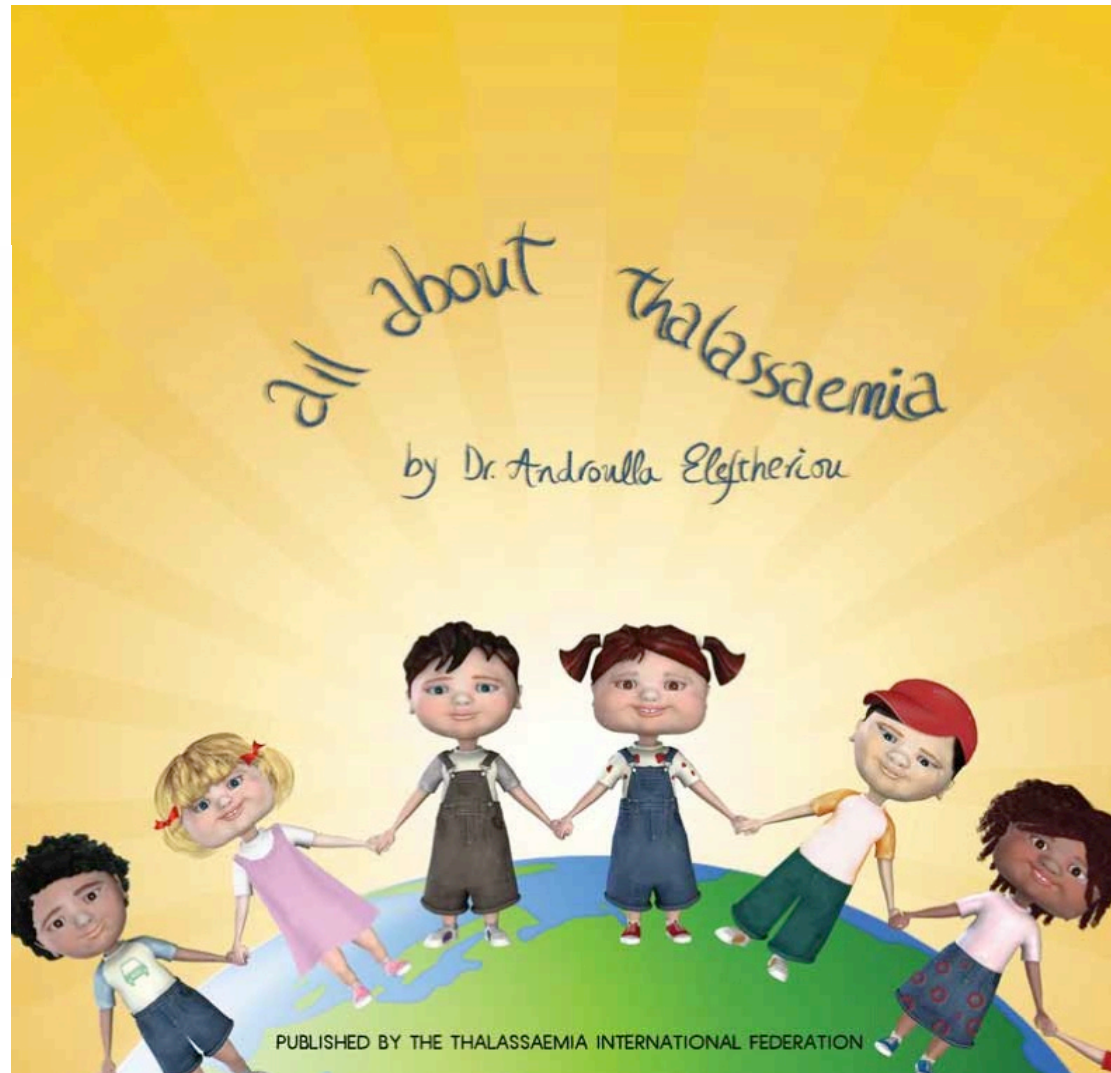
What do I know about thalassaemia ?

Thalassaemia Cartoon for Young Children

ALL ABOUT THALASSAEMIA

By Dr Androulla Eleftheriou

Thalassaemia International Federation
2011



Alkan 2011

What do I know about drug discovery ?

~30 years of experience



(CIBA)-Novartis
Basel, Switzerland



(HMR)-Aventis
New Jersey



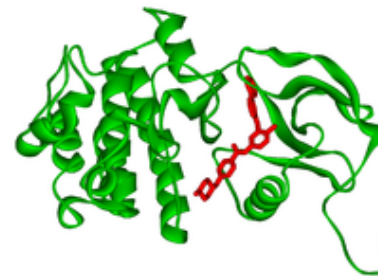
3M Pharma.
St-Paul, MN

Agenda

- **Classical Drug Discovery Process**
 - Lessons learned
- **Thalassemia Treatment**
 - Standard and novel treatments

Different Ways of Drug Discovery

- ***Serendipity*** (e.g. *Desferal*)
- **Folk medicine** (e.g. Aspirin)
- **Whole animal screen** (e.g. Cyclosporin)
- **Cellular screen** (e.g. Many)
- **Molecular screen** (e.g. Glivec)

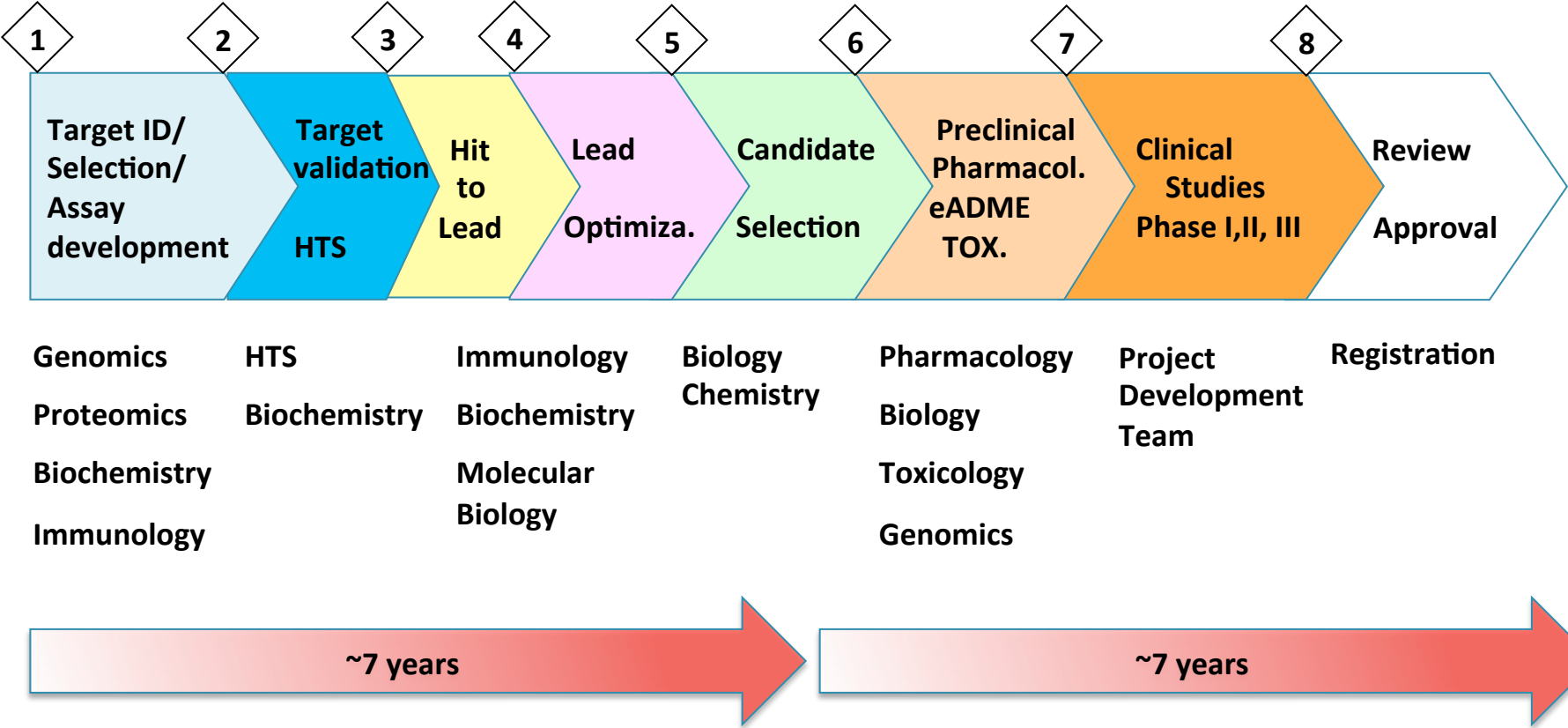


In CML, the tyrosine kinase enzyme ABL is stuck in its activated form; imatinib binds to the site of the enzyme

Drug discovery problems

- **Why it takes too LONG**
- **Why it is so RARE**
- **Why it is very EXPENSIVE**
- **Why more INVESTMENT NOT MORE DRUGS**

Classical drug discovery steps



Most clinical trials are designated as phase I, II,

- **In Phase I** clinical trials, researchers test a new drug or treatment in a small group of people **(20-80)** for the first time (safety, dosage range, and identify side effects).
- **In Phase II** clinical trials, the study drug or treatment is given to a larger group of people **(100-300)** (if it is effective-POC-and to further evaluate its safety).

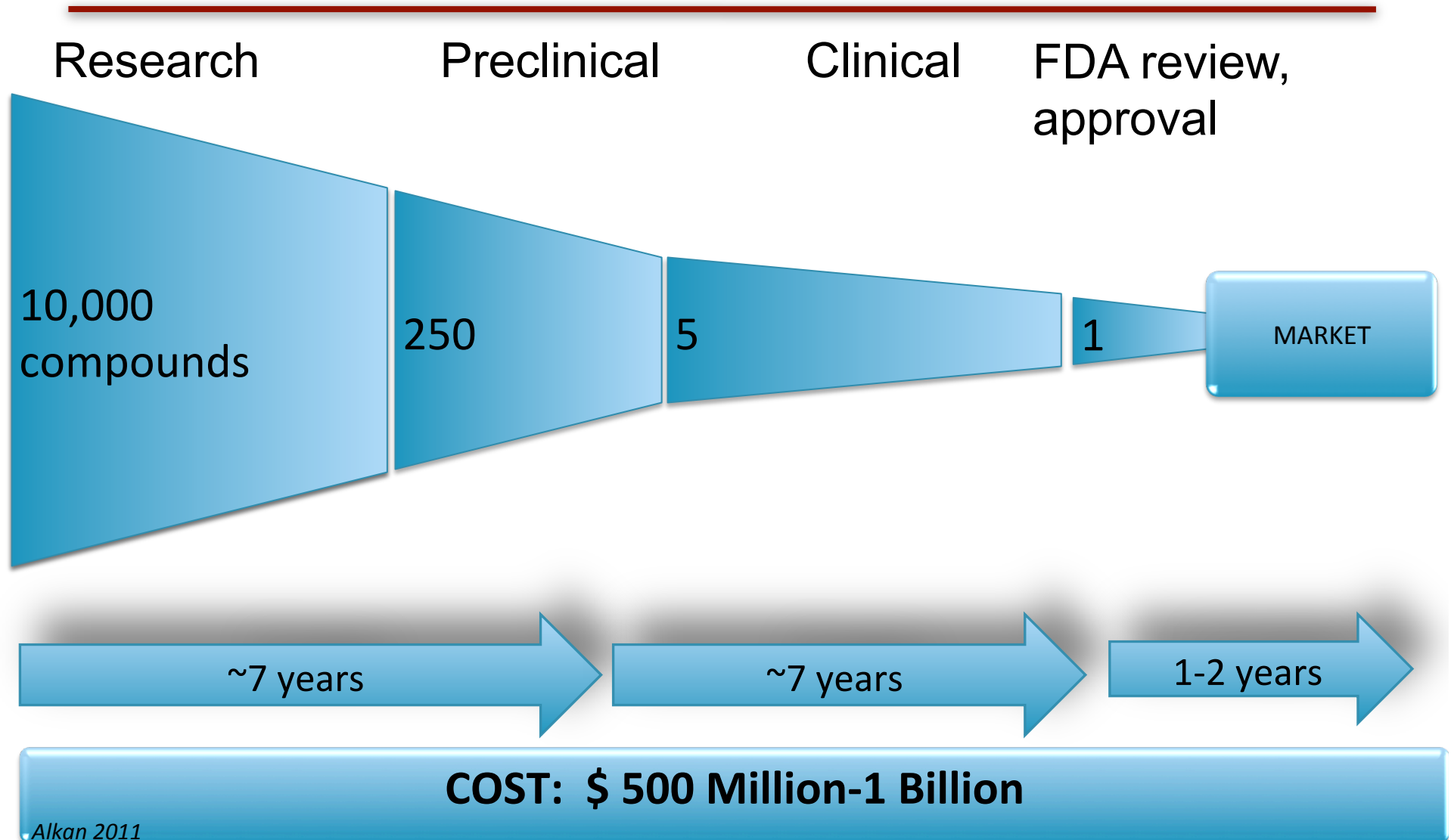
These phases are defined by the Food and Drug Administration in the Code of Federal Regulations.

Most clinical trials are designated as phase III, IV

- **In Phase III** studies, the study drug or treatment is given to large groups of people (1,000-3,000) (confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely).
- **In Phase IV** studies, the post marketing studies (delineate additional information including the drug's risks, benefits, and optimal use).

These phases are defined by the Food and Drug Administration in the Code of Federal Regulations.

Drug discovery & development



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- **Thalassemia Treatment**
 - Standard and novel treatments

How are thalassemia's treated?

Standard Treatments

- **Blood Transfusions**

- Takes 1 to 4 hours.
- Red blood cells live only for ~120 days.
- Repeat: 2 to 4 weeks

- **Iron Chelation Therapy**

- Deferoxamine is a liquid medicine/portable pump/mildly painful. vision and hearing problems.
- Deferasirox is a pill taken once daily. Side effects: headache, nausea vomiting, diarrhea, joint pain, and fatigue

- **Folic Acid Supplements**

- B vitamin that helps build healthy red blood cells

Other Treatments

1. Blood and marrow stem cell transplant

- To prevent problems, the donor's stem cells should match yours as closely as possible (HLA tissue typing)
- Difficult to find a good donor match
- Risky procedure

http://www.nhlbi.nih.gov/health/dci/Diseases/bmsct/bmsct_what.html

Frittoli MC, et al. Hum Gene Ther. 2011 Apr;22(4):507

Other Treatments

2-Inserting normal Hb gene into BM stem cells cont.

- Major changes since the incidents of leukemia development in X-SCID patients **after retroviral** gene therapy
- A relative clonal dominance was detected two years after genetically modified stem cells transfer using **lentiviral vectors**
- Most advanced vector systems **does not have enough safety**
- **Additional features need to be studied:**
 - chromatin insulators,
 - co-transduction of a suicidal gene,
 - conditional expression of the transgene,
 - targeted transduction,
 - cell type-specific expression, targeted local administration,
 - splitting of the viral genome, site specific insertion of retroviral vector

Other Treatments

3. Trigger a person's fetal hemoglobin

- Embryonic, fetal, and adult Hb are sequentially expressed
- Understanding the **loss** of fetal globin expression and **activation** of adult globin expression could potentially lead to new therapeutic approaches.
- HbF could significantly ameliorate the clinical manifestations of β -thalassemia.

Wilber A, Nienhuis AW, Persons DA. Blood. 2011 Feb 14

What is new in iron chelation therapy?

- **Over 40 years, dramatic improvements in survival of thalassemia major patients is mainly due to improved iron chelators.**

- *parenteral deferoxamine (1970's)*

- *oral deferiprone (1999's)*

- *oral deferasirox (exjade, 2005's)*

- **Chelators differ strikingly in side-effect profile, cost, efficacy etc.**

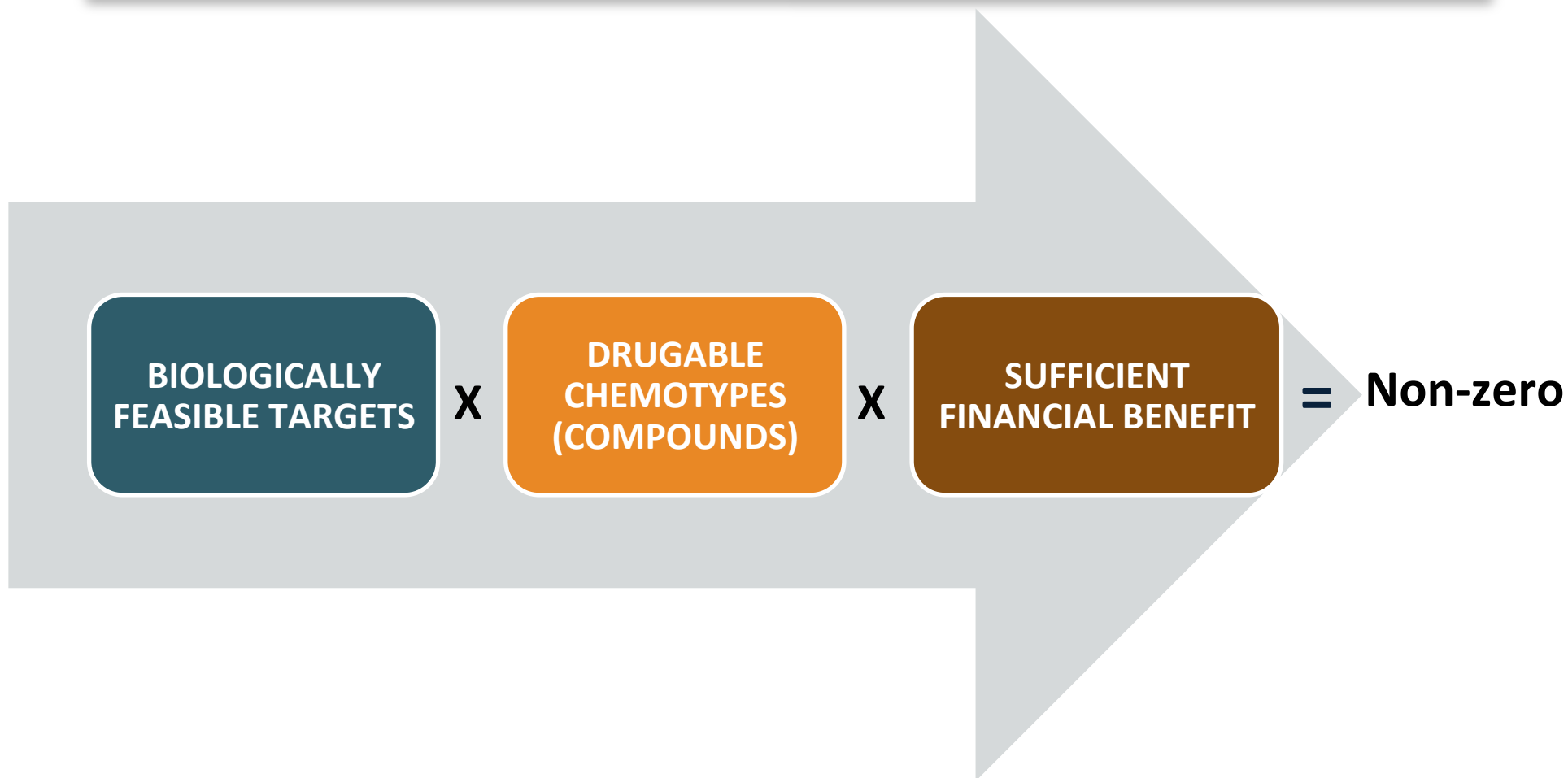
- **Clinical trials suffers from the lack of head-to head comparison**

- (Neufeld EJ. Hematology Am Soc Hematol Educ Program;2010:451)*

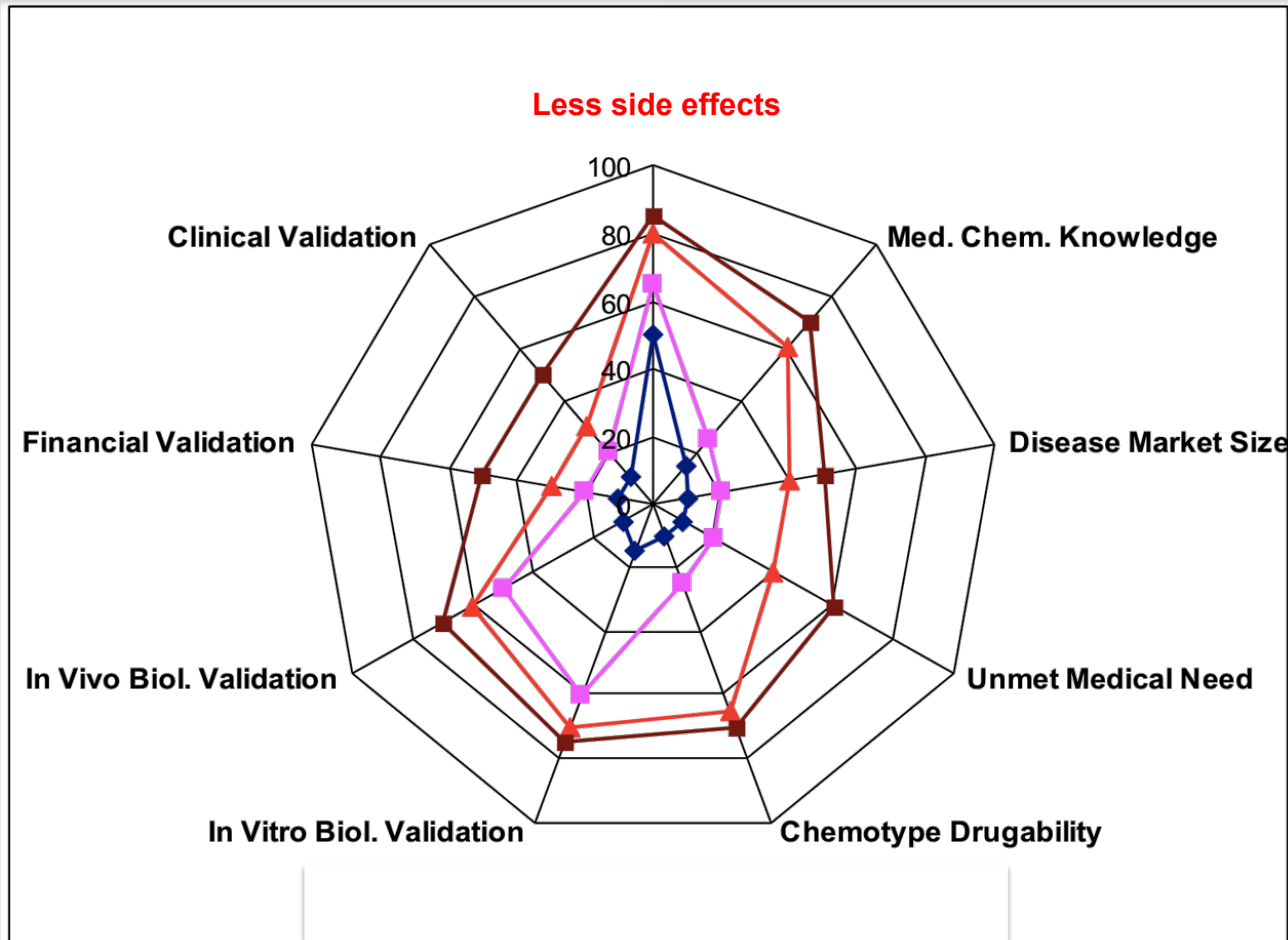
- **Development of new iron chelators is needed**

- (Heli H, et al. Expert Opin Ther Pat. 2011 Mar 30)*

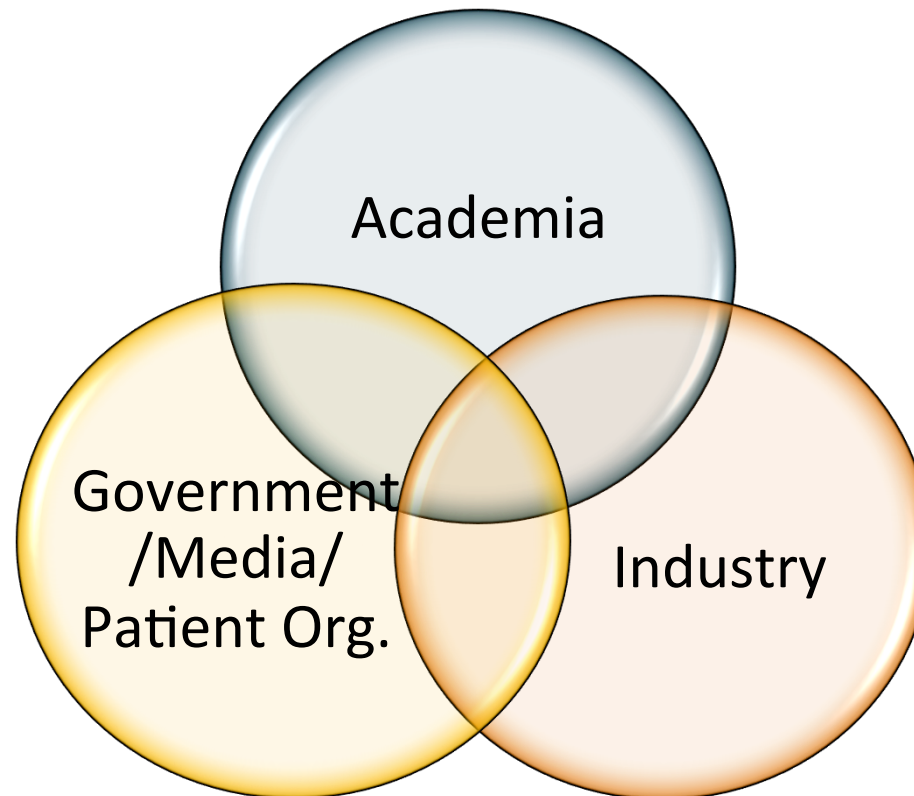
Non-zero sum of drug discovery



Drug development: spider diagram



Essential communications for drug discovery



NIH encourages translational collaboration with industry

M. Wadman; brought together 439 government researchers and officials, and senior industry executives to brainstorm with the academic clinicians, NRDD, Mar. 2010

Summary

➤ Classical Drug Discovery Process

- New drug discovery: Time consuming, rare and expensive

Experience is one thing you can't get for nothing... O. Wilde

➤ Thalassemia Treatment

- New gene delivery methods/New chelators needed

Imagination is more important than knowledge...A. Einstein

Drug Discovery

**Thank You
&
Prof. Duran Canatan !**



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