Will there be a new golden age of drug discovery?

RSC-SCI Advances in Synthesis and Medicinal Chemistry

Welwyn Garden City, May 1, 2012

David Brown PhD, FRSC

Alchemy Biomedical Consulting Ltd, Cambridge, UK

Will there be a new golden age of drug discovery?

I welcome your views

at the end of this presentation

Quickly, what went wrong?

Pre mid1980's: Observation led; phenotypic screening
- whole animal, tissue or cell

From 1988: Hypothesis led; protein screening
- invention of FPLC allowed isolation of proteins

Mid 1990's: Human genome 'screening'
- massive increase in potential targets

The age of target-based drug discovery

But...

Relatively few ‘first in class’ new medicines per year from 1999 to 2011 have been developed from the new target-based drug discovery approach:-

6-7 per year (67% small molecules, 33% biologics)

“Despite the emphasis on target-based drug discovery, phenotypic screening still produced the majority of ‘first in class’ small-molecule medicines”.

- *phenotypic approaches gave 28*
- *target-based approaches gave 17*

David Swinney, Nature Reviews Drug Discovery, 507, July 2011

Pharma made rapid switch from 'observation-led' to 'hypothesis-led' with no evidence it would work

Observation-led

(Main paradigm before mid 1980's)

- **Chemist supplies compounds; biologist screens vs tissues, cells or animals**
- **Biologist selects 'actives' giving phenotype of interest**
- **Identify mechanism if possible (but not essential)**
- **Projects always started with a lead compound and an effect of interest in a physiological system**

Hypothesis-led

(Main paradigm from early 1990's)

- **Biochemist screens compounds on purified protein**
- **'Hits' are assessed in functional assay for in vitro efficacy**
- **Phenotype is assessed in animal model of disease**
- **Project has several steps to a lead with an effect of interest in a physiological system**

Examples

Observation-led

(Main paradigm before mid 1980's)

- Phenotype: a plant reduces fever
    - Then find the active entity (eg aspirin)
    - Then find the mechanism (aspirin inhibits COX)
- Next generation drugs from Hypothesis-led research

Hypothesis-led

Examples

Observation-led

Hypothesis-led

(Main paradigm from early 1990's)

- cGMP PDE assay (initially for hypertension, then angina, then…)
  - Find sildenafil / Viagra
  - Clinical trials in angina (find efficacy in erectile dysfunction! Same mechanism)

Both approaches have serious weaknesses

Observation-led

(Main paradig[illegible] before mid 1980's)

- Screen [illegible]pounds vs tissues [illegible] or animals

WEAKNESSES

- Finding the mechanism rare or late
  - relevance to man / efficacy risk
  - mechanism - based toxicity risk
- Leads may interact with several targets
  - non-mechanism-based toxicity risk
- No mechanistic assay
  - SAR complex for chemists to optimize

Hypothesis-led

Both approaches have serious weaknesses

Observation-led

Hypothesis-led

(Main paradigm from early 1990's)

- Screen compounds on purified protein

WEAKNESSES

- Targets selected may have poor disease linkage ('unvalidated')
  - high failure rate downstream in Research phase or in Clinical trials
- Lead identification less successful and more costly than expected
- Ability to predict 'off-target' effects poorer than expected

These weaknesses lead to problems

Observation-led

Problems

Drug / target interaction not explicit

Low throughput

Disease models critical

Hypothesis-led

These weaknesses lead to problems

Observation-led

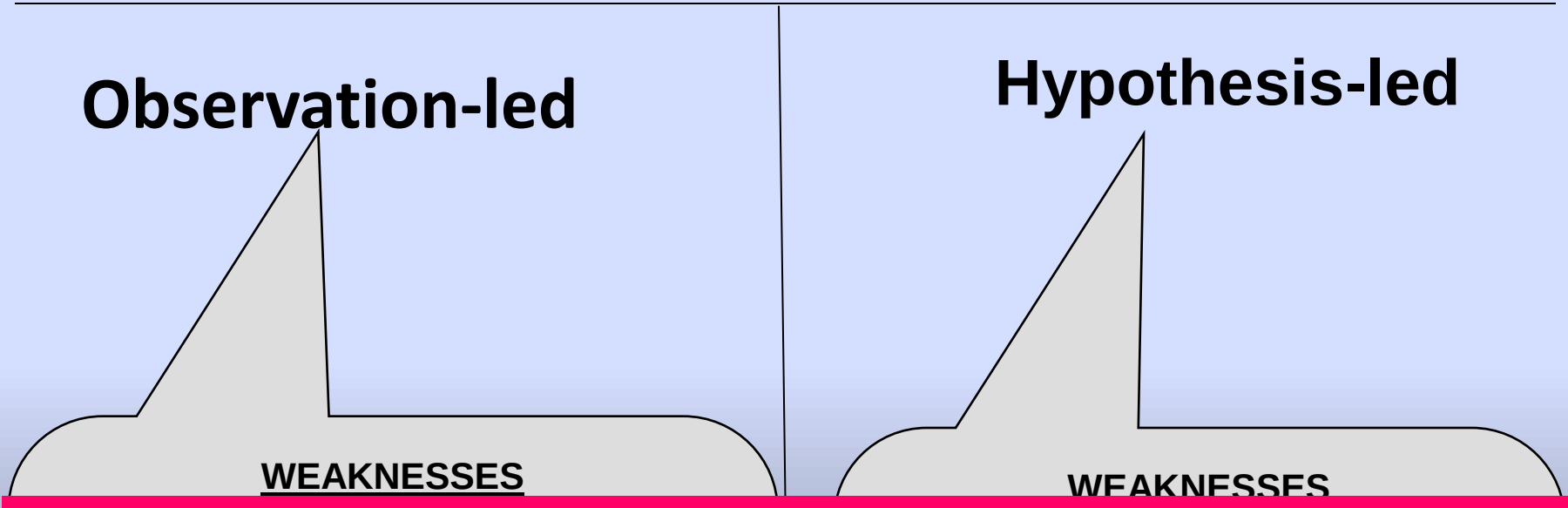
Hypothesis-led

Problems

‘Drug / target’ interaction not ‘drug / organism’

‘Physiology’ is eliminated until late in the process

Companies more often working on the same targets



Have unsolved problems with both approaches held back productivity?

And medicinal chemistry went astray too

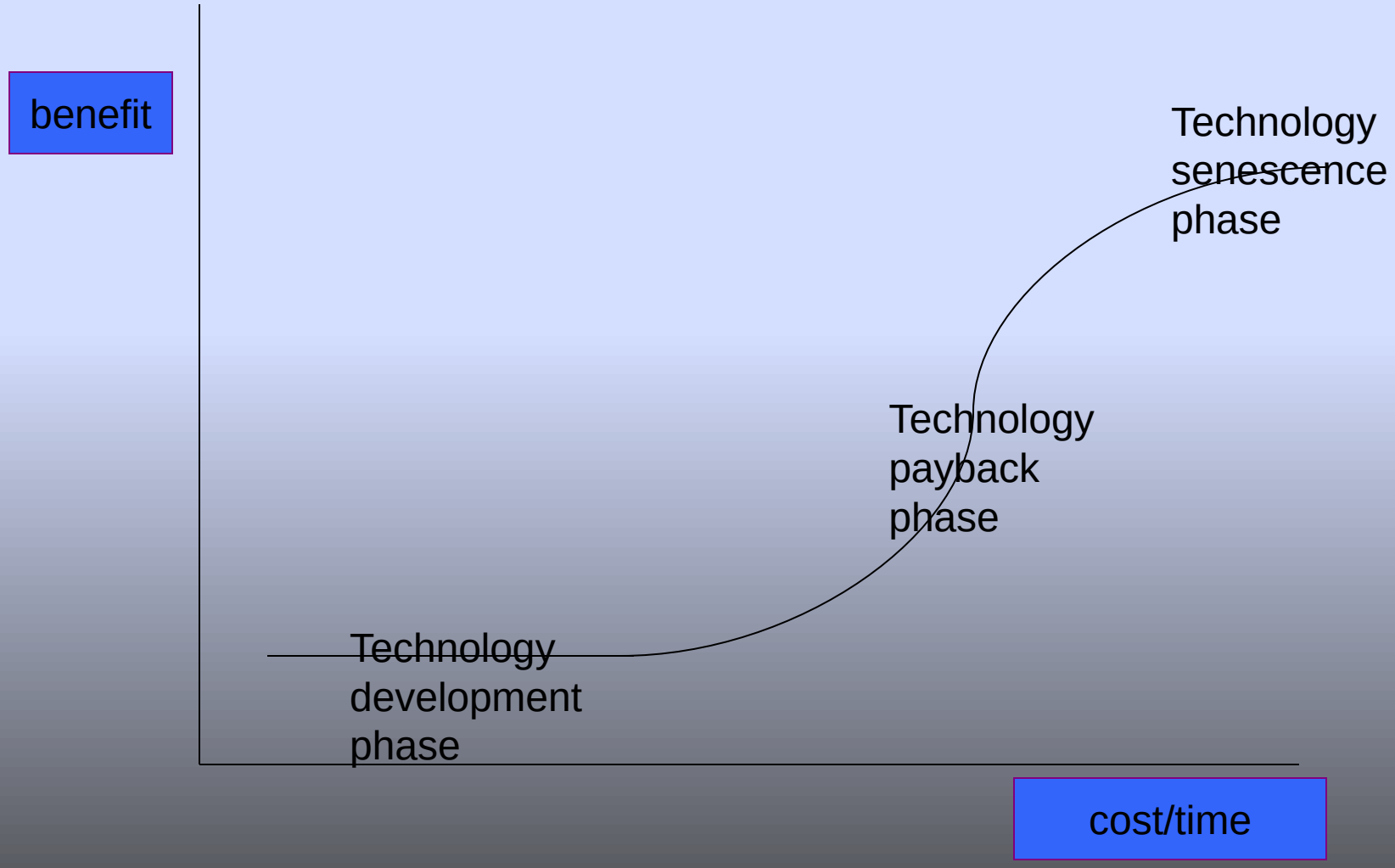
- HTS drove chemistry direction
  - Quantity not quality; simpler chemistry, poorer molecules
  - Companies bought from the same suppliers
    - Duplication not diversity; similar molecules in similar screens across the entire industry. Systemic failure
- 'Industrialisation':Essential drug discovery skills lost?
  - Do today's med chemists understand the total R&D process?
  - Did we forget the Mckinsey concept of 'T-shaped people'?

The timing was wrong

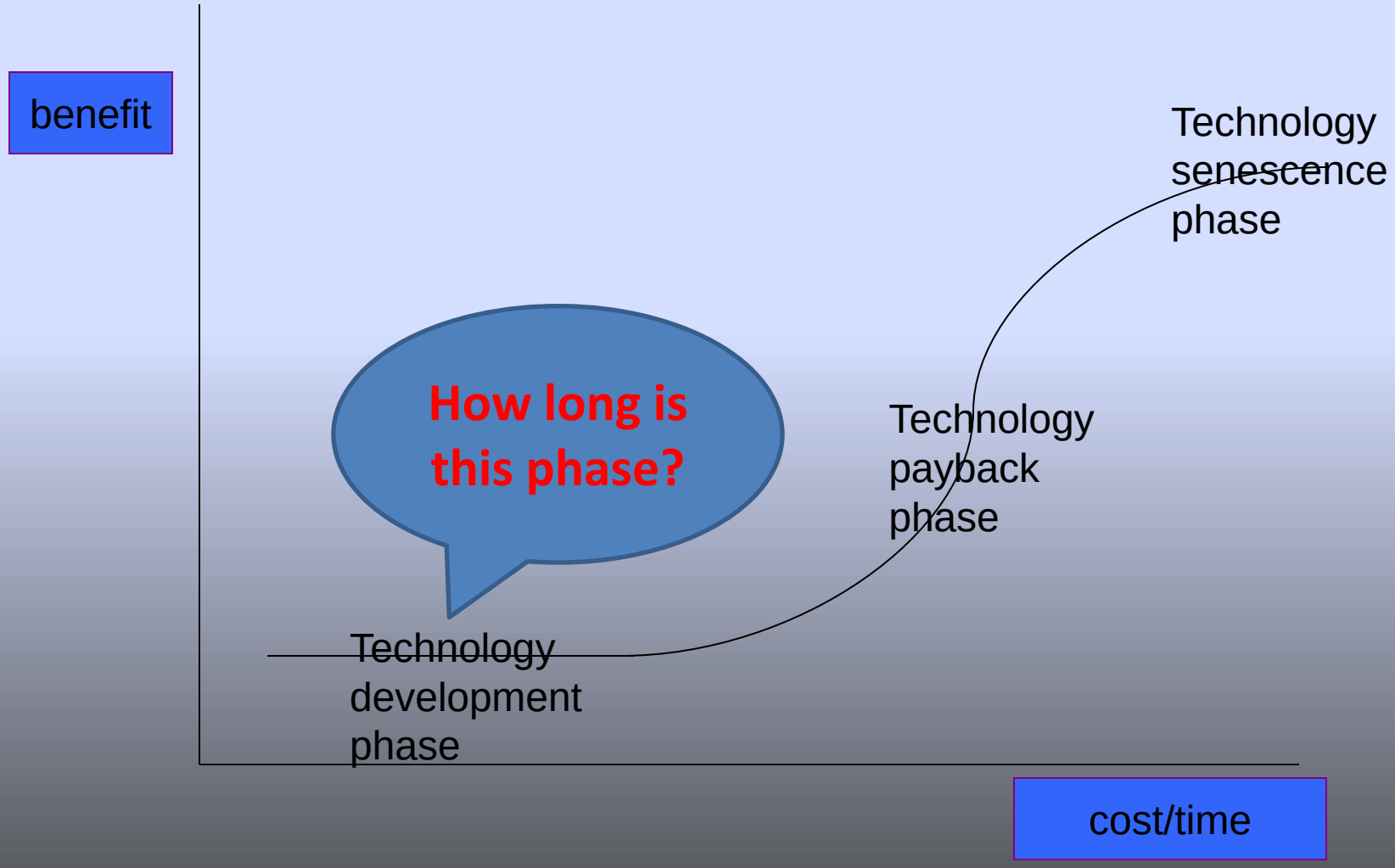
Our industry jumped on the hypothesis-driven target based approach prematurely, with no evidence it would work.

KEY QUESTION:
How long does it take for a new technology to mature and pay back?
- There is good research on this question across many industries

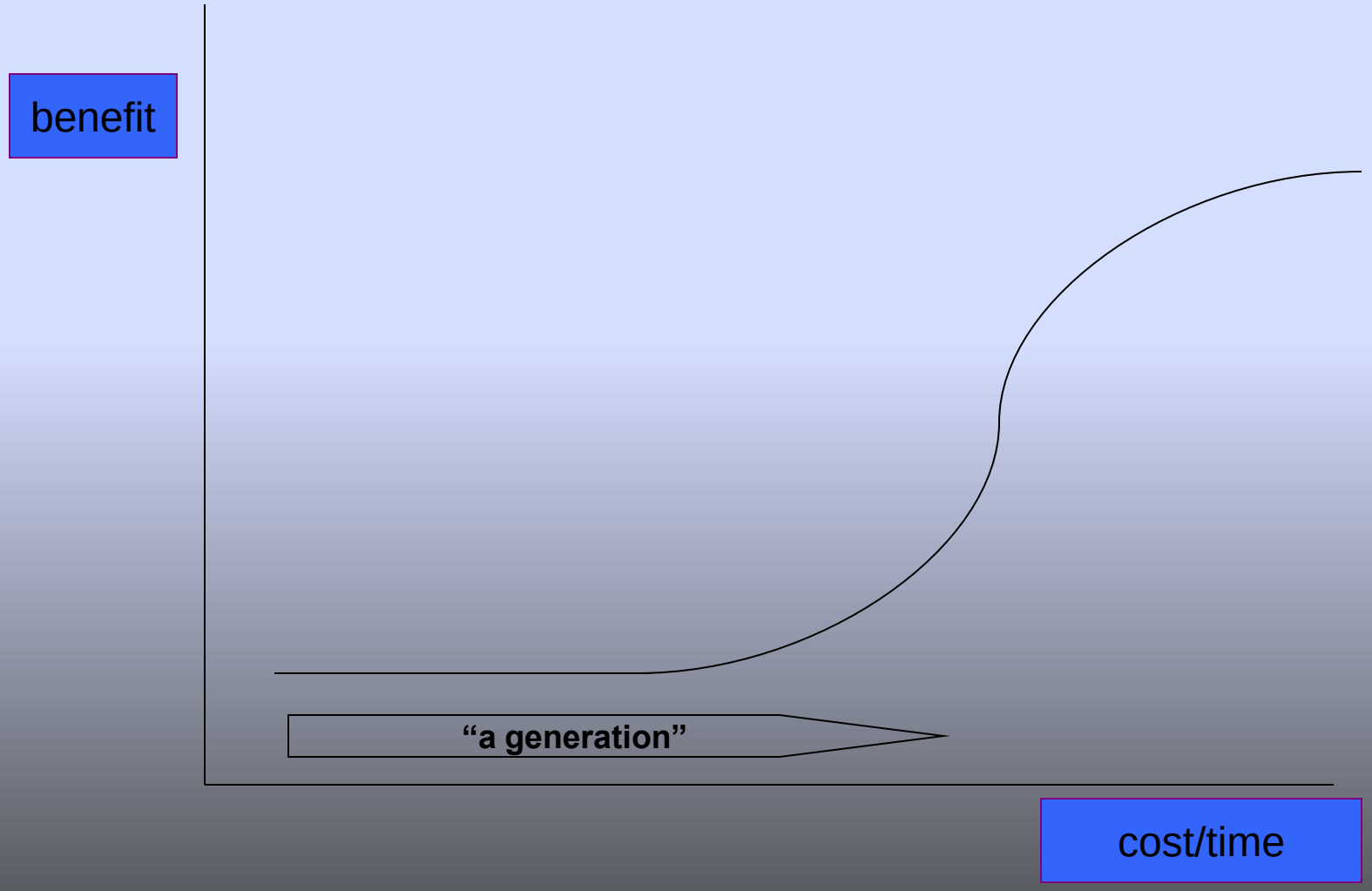
S-curve of technology investment



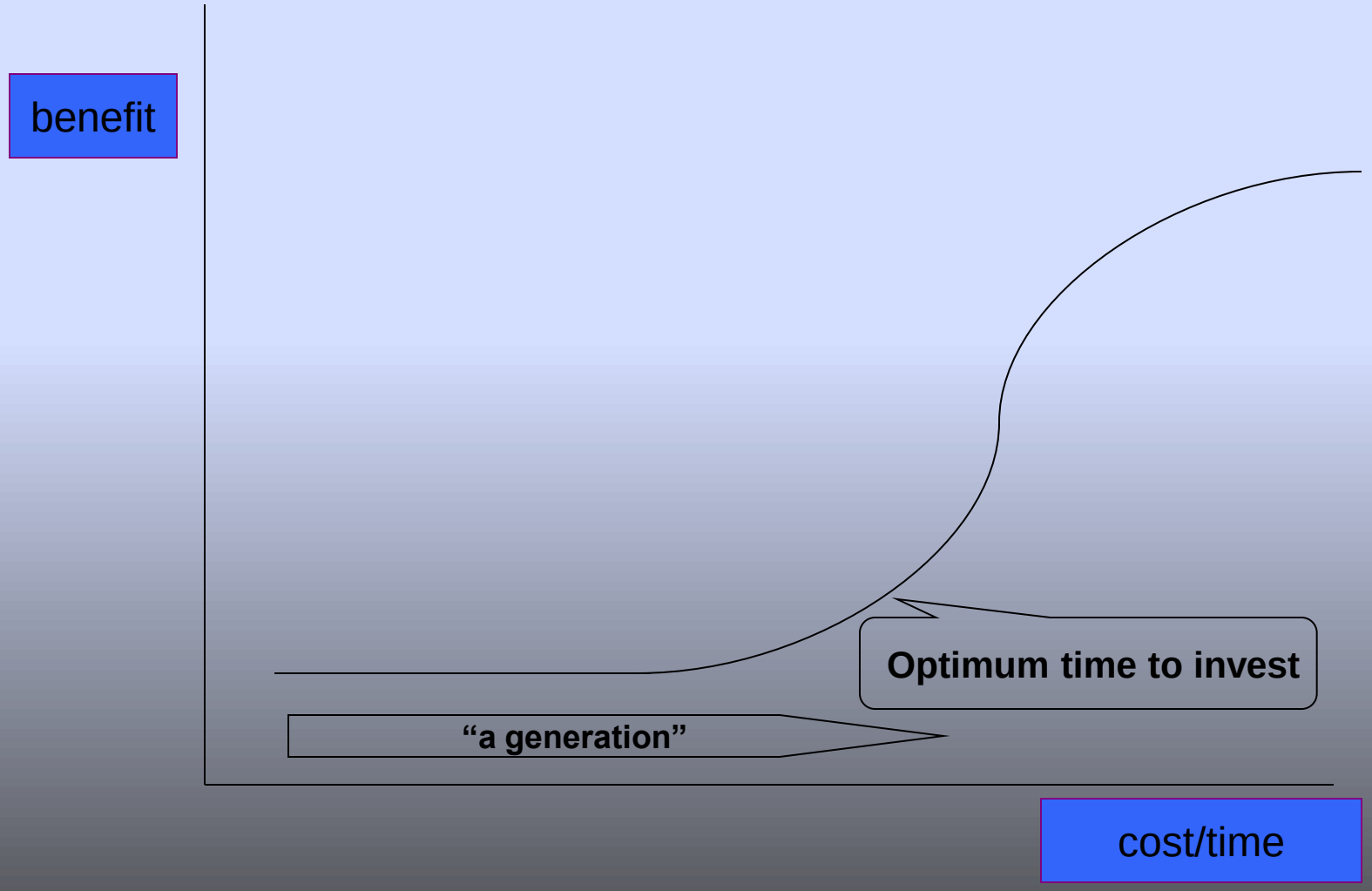
S-curve of technology investment



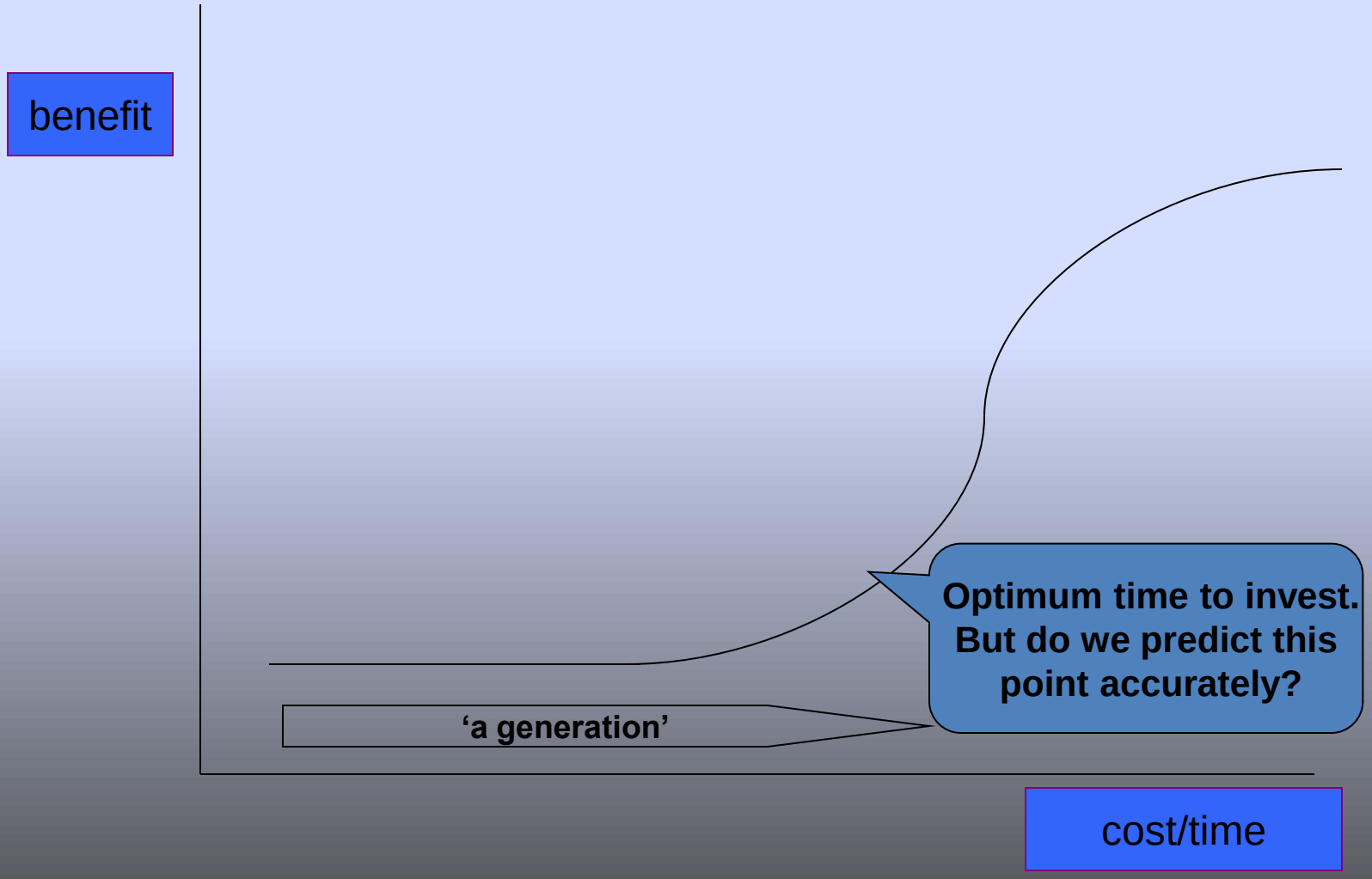
S-curve of technology investment



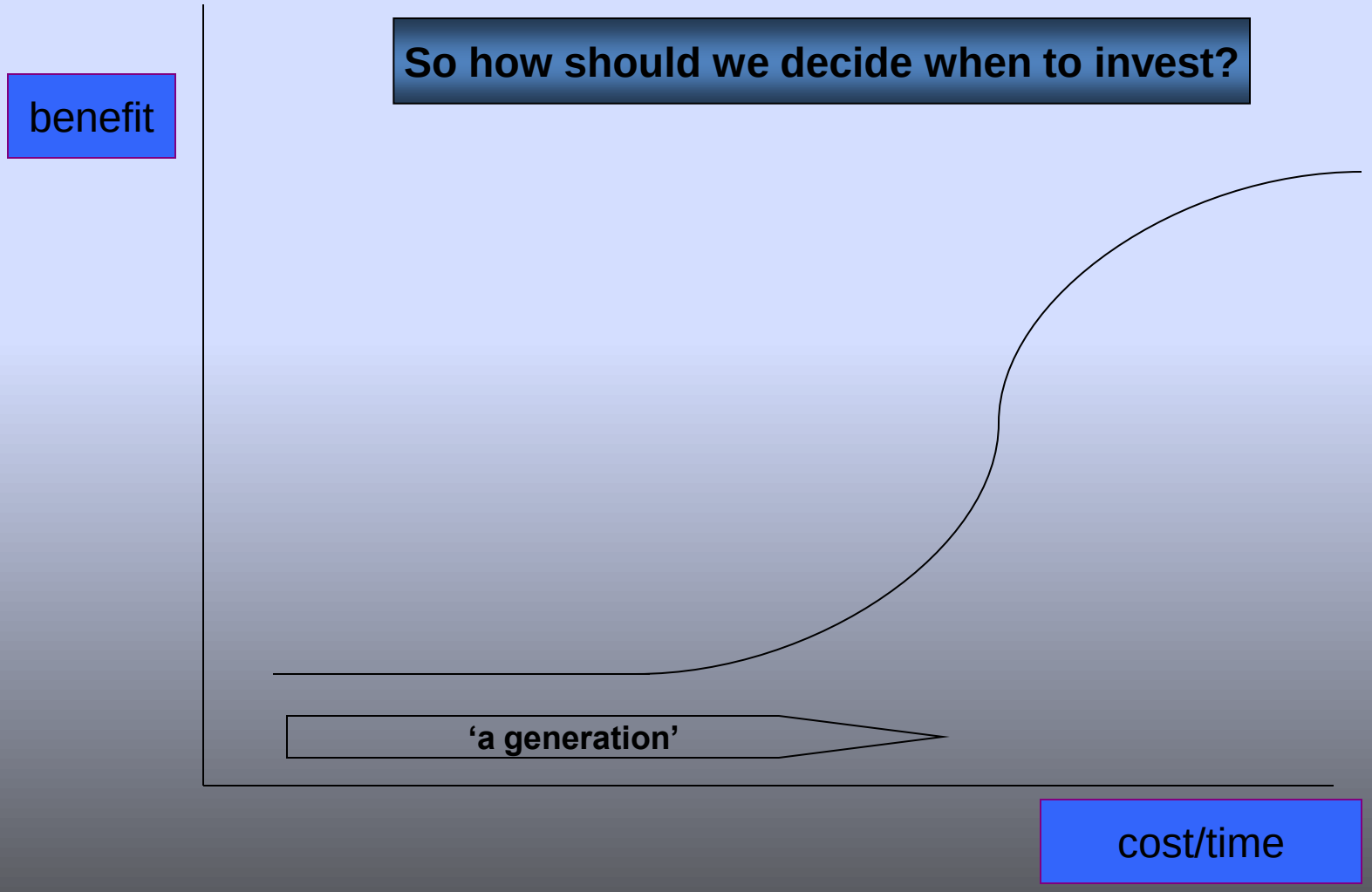
S-curve of technology investment



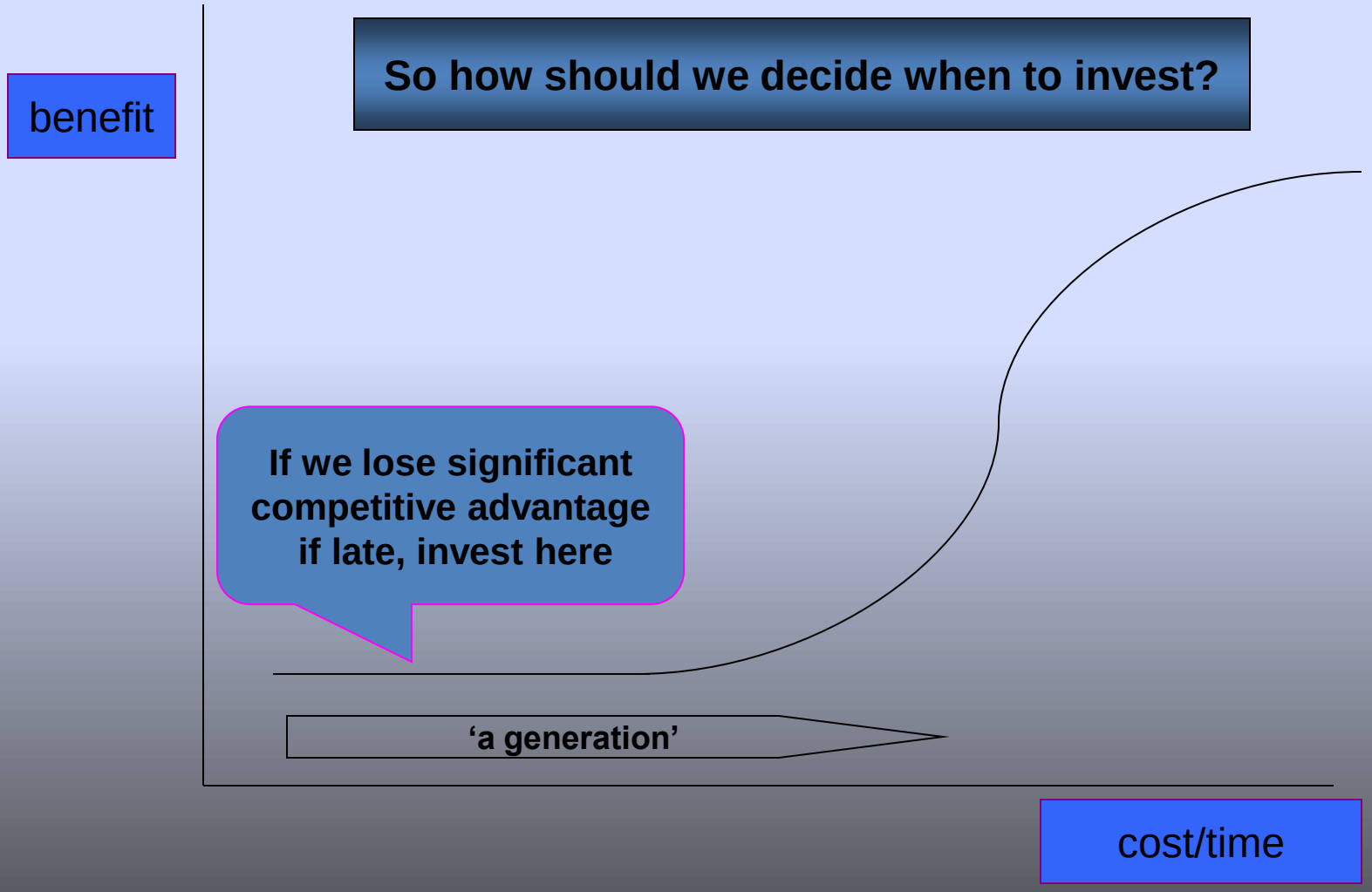
S-curve of technology investment



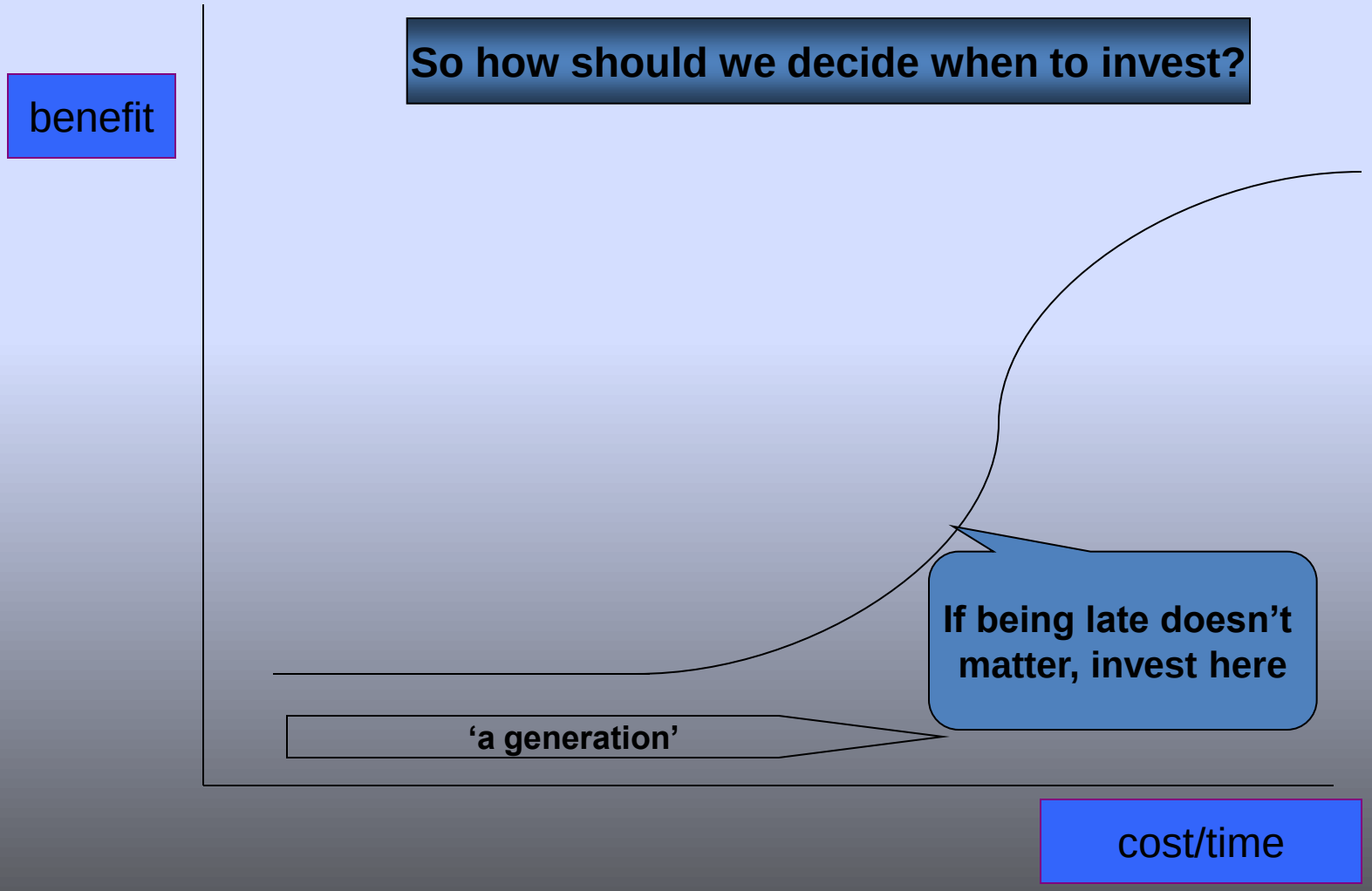
S-curve of technology investment



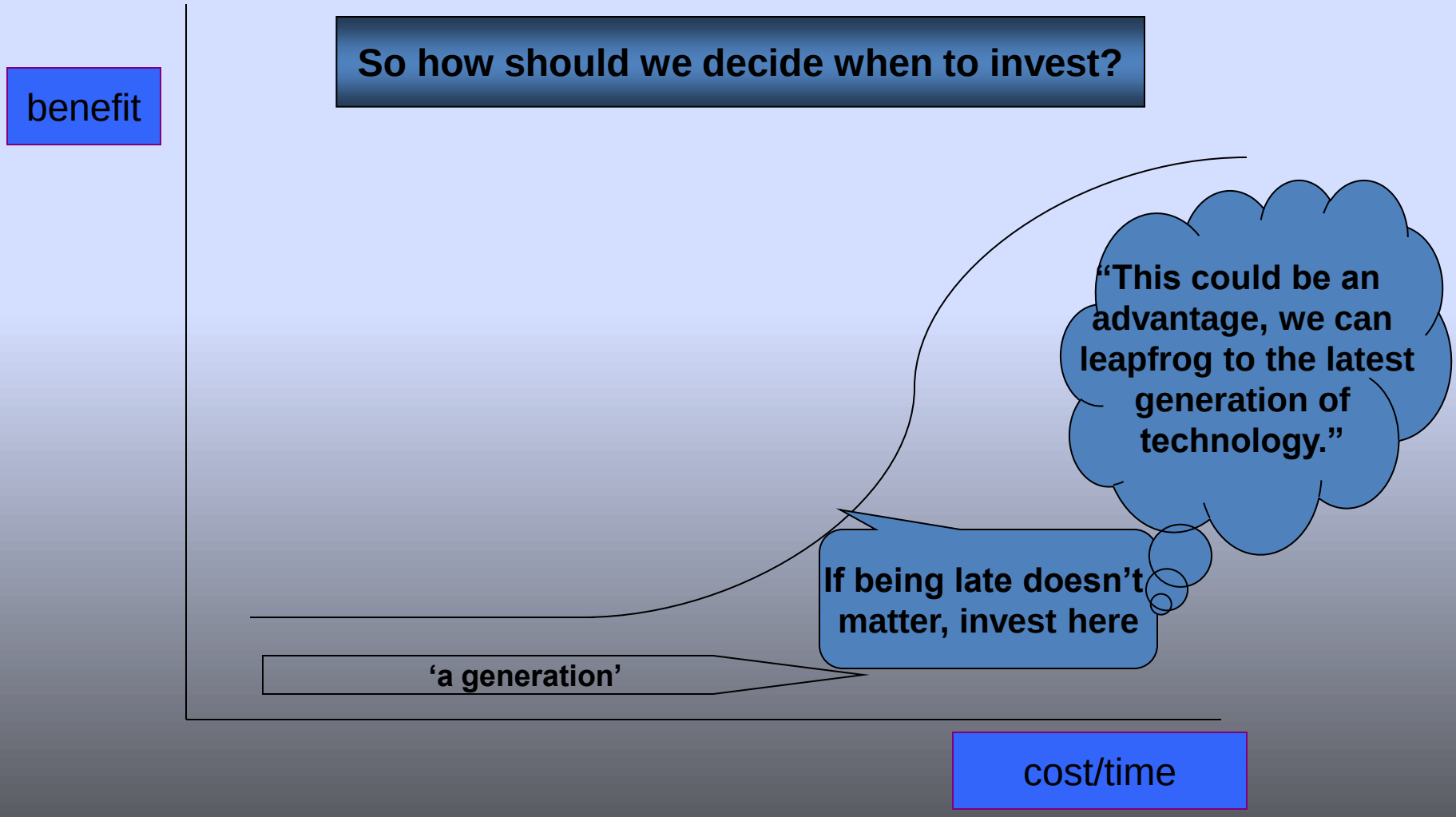
S-curve of technology investment



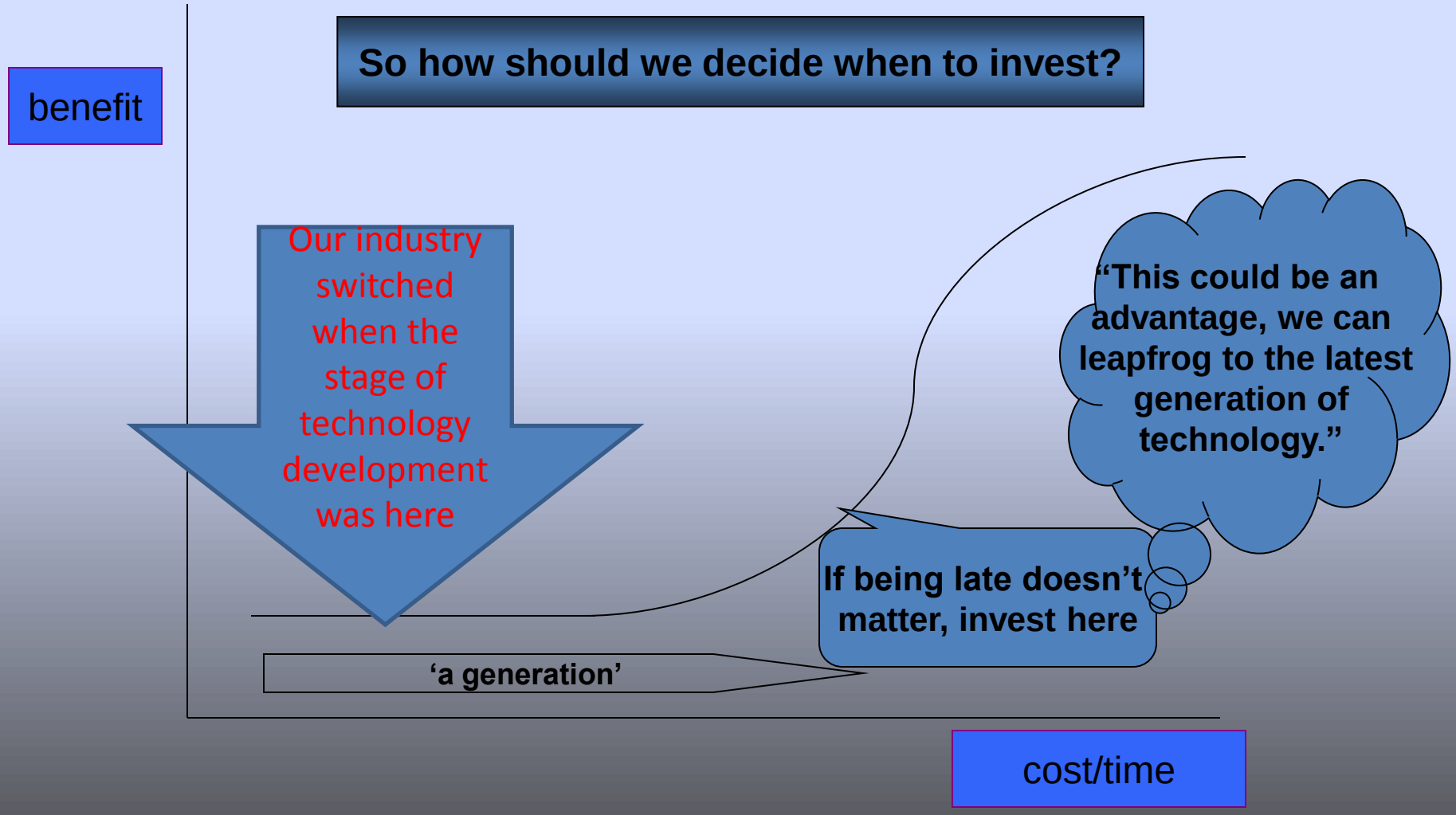
S-curve of technology investment



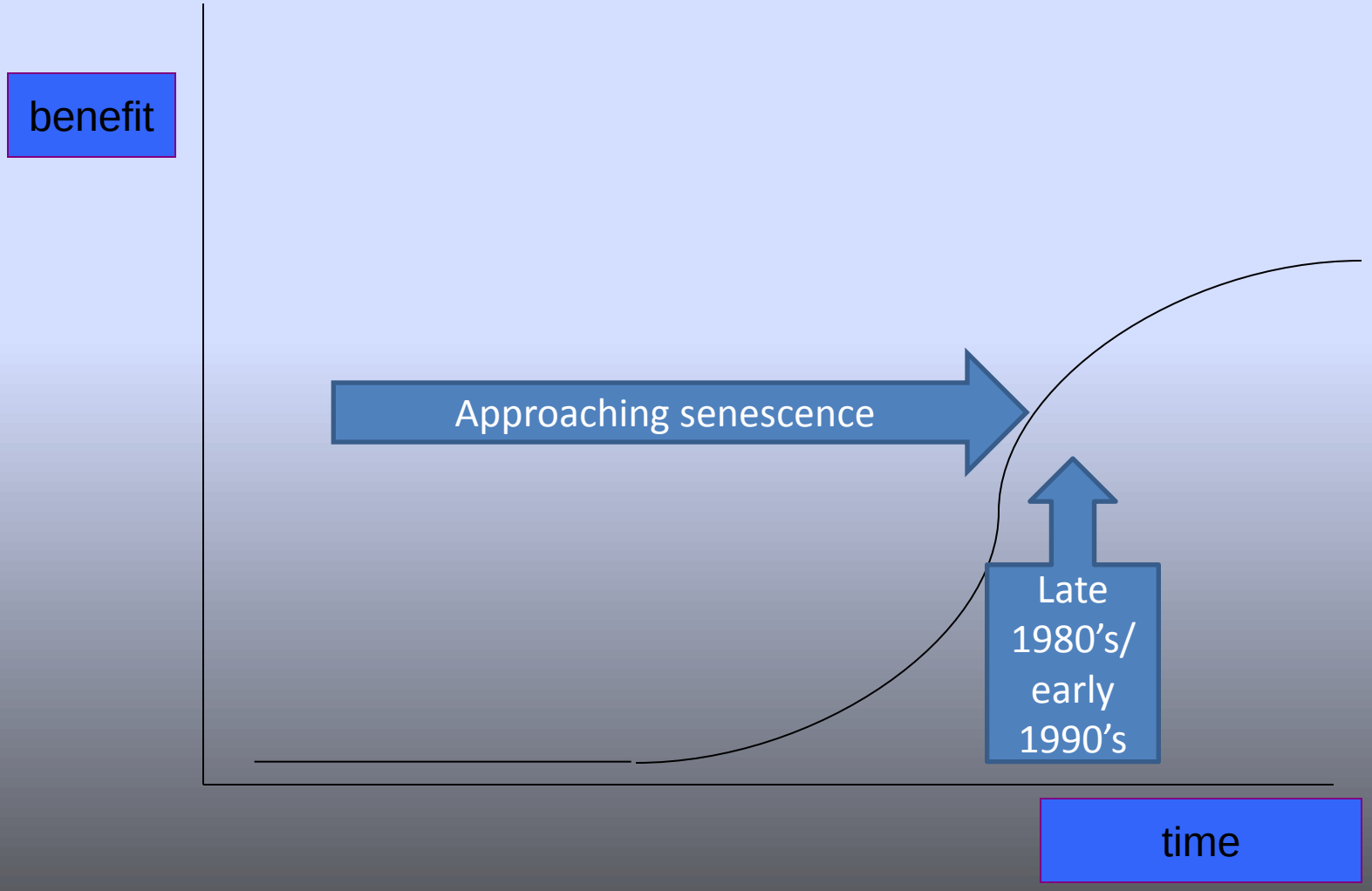
S-curve of technology investment



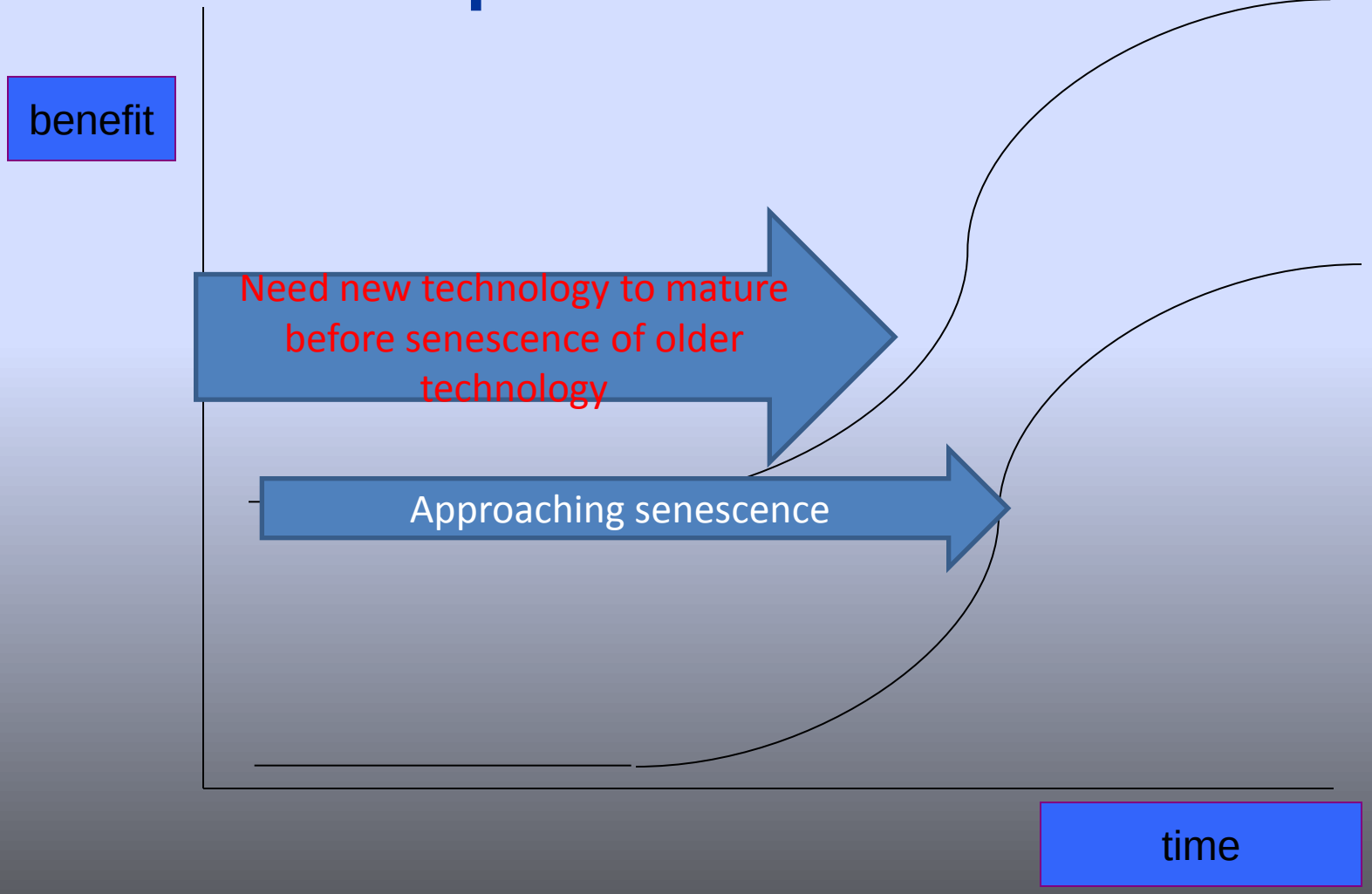
Key point: The timing was wrong



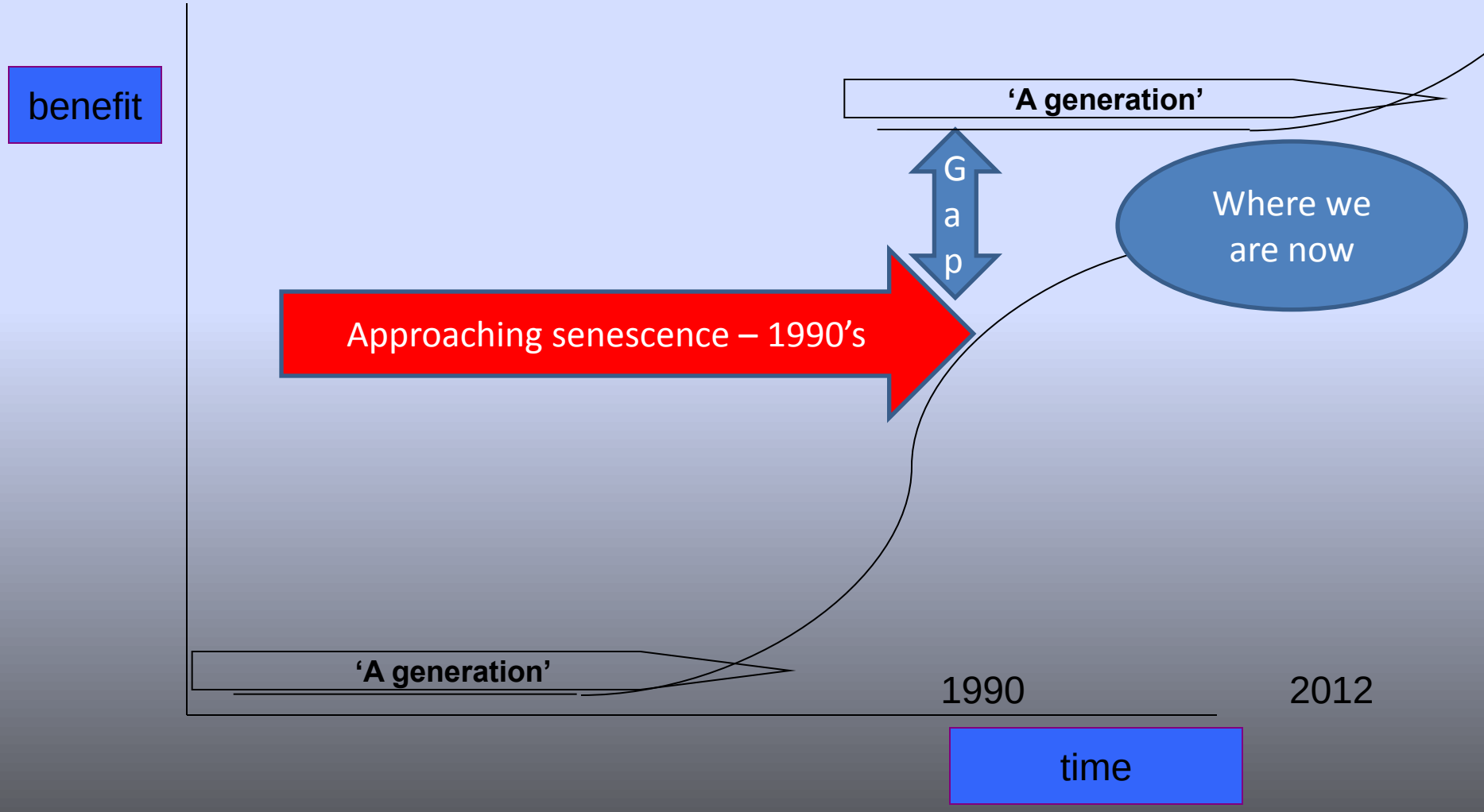
Timing: The situation around year 1990



For any industry, new overlapping waves of S-curves are required to secure the future



But this is what *actually* happened: the next S-curve was years behind



The outcome

"On average studies have shown that if you spend a dollar on research and development it will return 70 cents.“

Chris Viehbacher, CEO Sanofi

Consolidation of the Pharma

1980

33

Merck
Schering-Plough
Hoffman
Roche
Genentech
Hoechst Roussel
Marion
Merrill Dow
RhonePoulenc
Sanofi
Synthelabo
Squibb
Meyers
Bristol
DuPont Pharma
Sandoz
Geigy
Ciba
Glaxo
Wellcome
French
Kline
Smith
Beecham PLC
Pfizer
Parke-Davis
Warner Lambert
Monsanto
Upjohn
Pharmacia
A.H. Robbins
Amer. Cyanamid
AHP

Pharma in 80's

20

LaRoche
Syntex
Genentech
Hoechst
Sanofi-Synthelabo
RhonePoulenc
& Fisons
Marion Merrill
Dow
Squibb
Bristol-Meyers
DuPont Pharma
Sandoz
Ciba-Geigy
French
Beecham PLC
SmithKline
Pfizer
Warner Lambert
Monsanto
Pharmacia Upjohn
Amer. Cyanamid
AHP

10

Hoechst
Roussel
RhonePoulenc
& Fisons
Sanofi-Synthelabo
Bristol-Myers
Squibb
Beecham PLC
GlaxoWellcome
SmithKlineFrench
Pfizer
Pharmacia
AHP (Wyeth)

8

Hoffman
LaRoche
Genentech
Aventis
Sanofi-Synthelabo
GlaxoWellcome
SmithKline
Beecham
Wyeth
Pfizer

7 Pharma

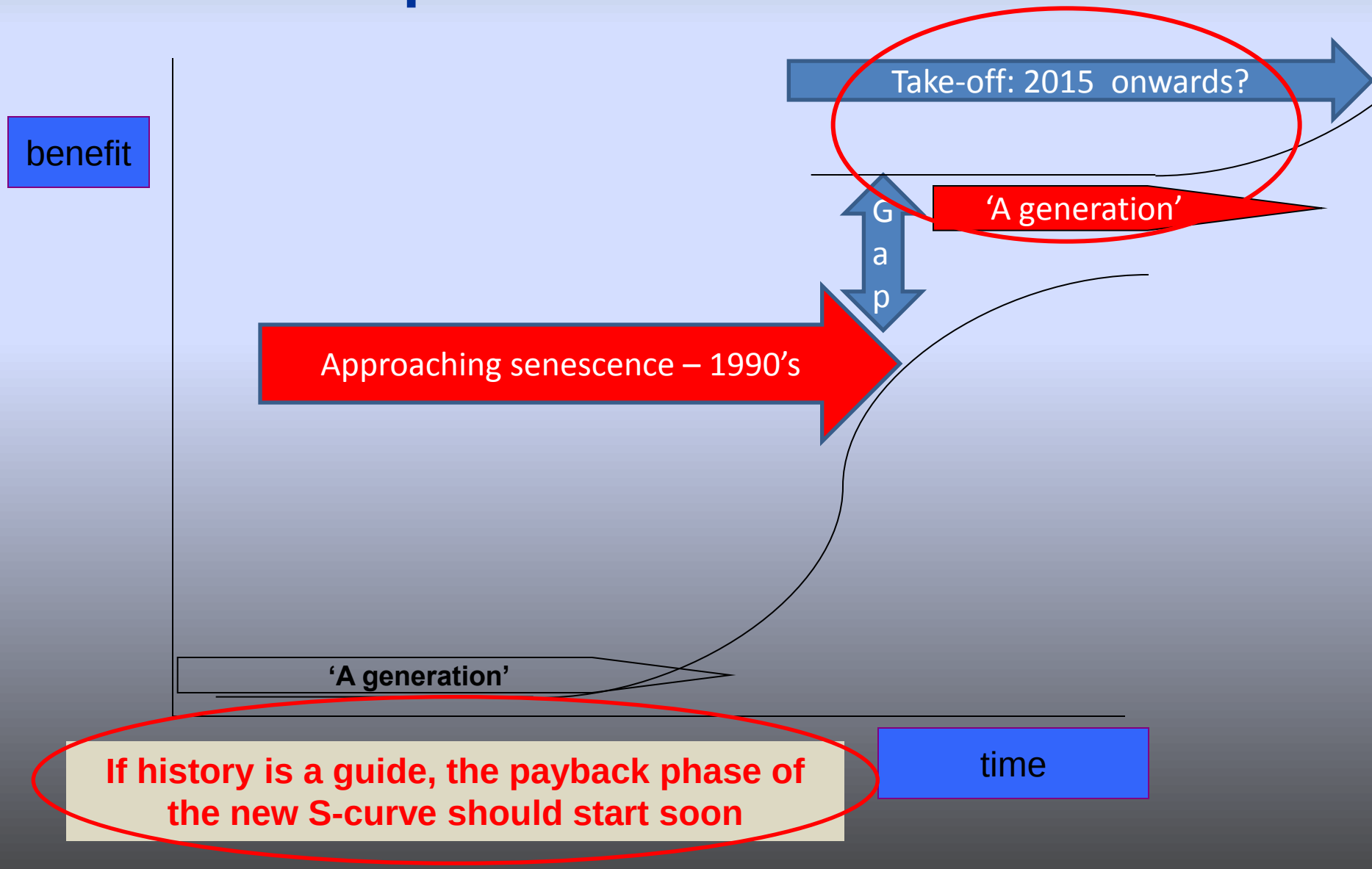
Merck
Roche
Sanofi-Aventis
Bristol-Myers
Squibb
Novartis
Glaxo
SmithKline
Pfizer

7 Companies

2010

Is there any reason to be hopeful?

We are now 15-20 years into development of the new S-curve



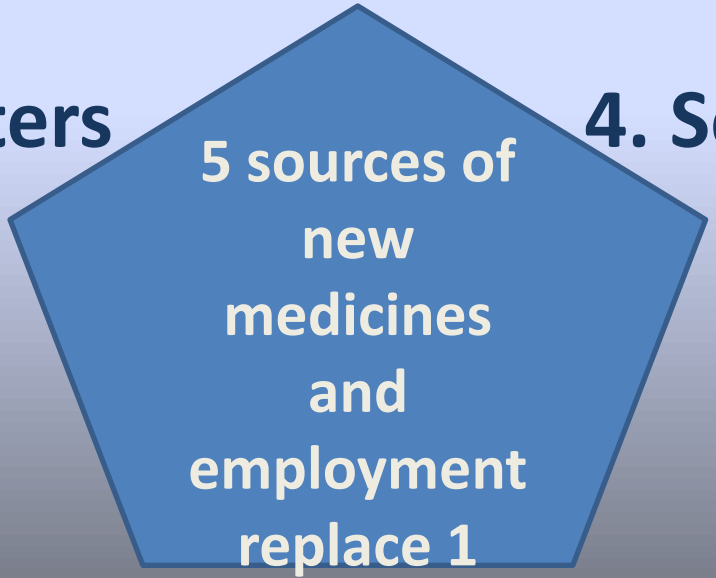
But the shape of the industry will be very different during the next wave

Is this the new shape of the industry?

1. Pharma

2. Biotech clusters

4. Service providers



3. Public sector

5.Charities/Foundations

1. A few large pharmas
   - Clinical / Manufacturing / Sales / Services as *primary* focus'; drug discovery but out-source heavily
   - Mostly western; will Asia follow the same path?

Which direction for traditional Pharma?

- Pharma splitting into 2 clubs
    1. Research intensive
    2. Diversifying

- Importance of size not clear. Ability to manage size an issue – requires true excellence in management.

- New skill sets valued
  - In-licensing skills required/need to improve.
    - GSK: 65% Phase 3's in-licensed. Was 0% in my early career
  - Partnering skills (most fail). Careers in themselves.

2. Many biotech clusters - the ‘new pharma’
   - Platform, discovery, early clinical, medtech
   - Location will matter more than it did for ‘self-contained’ pharma
   - *More stable!*

3. Public sector

- Commoditisation of drug discovery
- Universities, research councils, NIH in USA
- Excellence in biology, but not med chem

Another career option

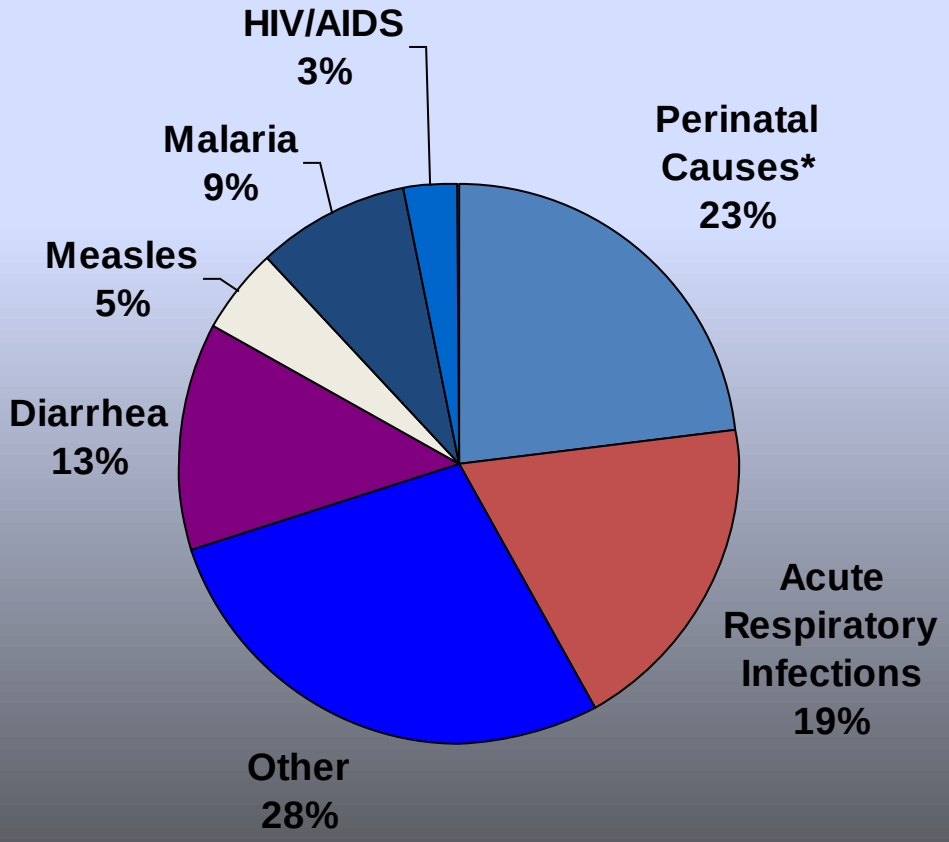
4. Charities

- In the UK, medical charities account for one third of all public expenditure on medical and health research.
    - Wellcome Trust
    - Medical Research Council Technologies
    - Cancer Research UK
- Act as both funders and R&D centres
- Global Health too – next slides

Causes of Child Mortality Worldwide

- Almost **11 million children under age 5 die each year**, according to UNICEF
- Nearly one-third of children's deaths due to **acute respiratory infections** or **diarrhea**
- **Malnutrition** associated with roughly one-half of all children's deaths in less developed countries, according to WHO

98 percent of deaths of children occur in the developing world



* Perinatal causes include infections, birth injury, asphyxia, and problems relating to premature births. Source: World Health Organization, Evidence and Information for Policy Program, 2001.

New partners for drug development:
The new R & D landscape for neglected diseases

R&D Funders

Gates Foundation, NIH, Wellcome Trust, etc

Pharma

GSK (Tres Cantos): malaria, TB

Novartis Institute(Singapore): TB, dengue, malaria

AstraZeneca (Bangalore): TB

Sanofi-aventis: malaria

Otsuka (Japan): TB

Product Development Partnerships

iOWH, TBAlliance, MMV, DNDi, IAVI, etc

Biotechs

Immtech, Zentaris, Amyris, Romark, Hollis-Eden

Global Fund

Purchase of drugs for Malaria, TB, HIV

Pharma & PDPs working together

Emerging model

Pharma in subsidized partnerships with PDPs

PDPs funded by public sources and Foundations eg Gates Foundation

NGOs, DC's, Pharma, PDPs

WHO policy making role


Stop TB Partnership
FIND
DIAGNOSTICS
President's Emergency Plan for AIDS Relief
(PEPFAR)
SECURE THE FUTURE
Initiative on Public-Private
Partnerships for Heal
Concept
Foundation
Accelerating
Access Initiative
RBM
ROLL BACK MALARIA
Global Alliance to Eliminate Leprosy
(GAEL)
Venture
APOC
AFUTUREFREEOFLF
Global Alliance
gain
Global Alliance for
Improved Nutrition
2020
THE RIGHT TO SIGHT
iavi
International AIDS
Vaccine Initiative
GAVI
ALLIANCE
CLINTON
FOUNDATION
MTCT
PLUS
ACHAP
Global Polio
Eradication Initiative
GLOBAL ALLIANCE FOR
TB DRUG DEVELOPMENT
International
Trachoma
Initiative
GBC
DIFLUCAN
PARTNERSHIP
Children's
Vaccine
Program
Global
Health
Council
EMVI
The European Malaria Vaccine
Initiative
Hope for African
Children Initiative
MECTIZAN
DONATION
PROGRAM
NetMark
Public-Private Partnersh
Global Campaign
FOR MICROBICIDES
Schistosomiasis Control Initiative
The
Micronutrient
Initiative
Pediatric DENGUE
VACCINE INITIATIVE

5. Service companies

- CRO’s ....and engage in their own drug discovery
- major employers
- deep sources of skills

All 5 are tending to locate in one type of area.. biotech clusters

These centres are of critical importance to the future

The Cambridge cluster

An example of ‘the new pharma’

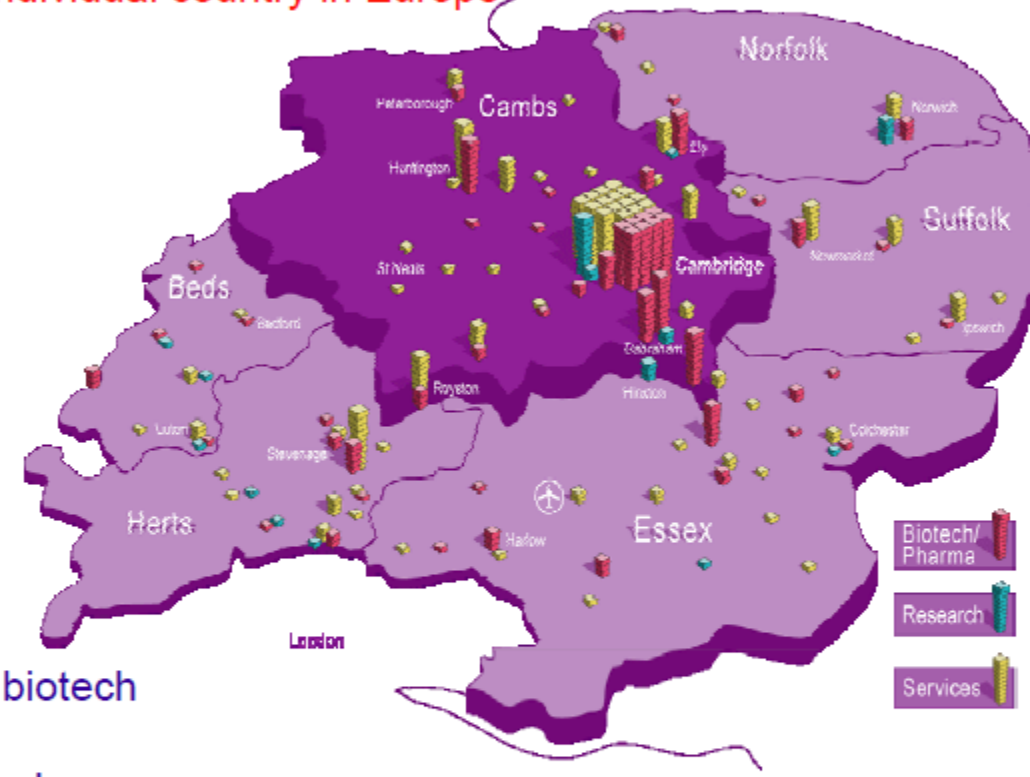
N.B. The Cambridge – London corridor is becoming a mega-cluster

The Cambridge Biotechnology Cluster

Courtesy of ERBI

Biotech companies in the region have over 75 products in the clinic, more than any other individual country in Europe

235 biotech companies
360 specialist service providers
30 research institutes and universities
20 multi-nationals in pharmaceuticals, agribio and food
4 leading hospitals.
100 organisations which take a strong interest in the biotech



One third of the UK's top 20 LSE quoted biotech companies
One fifth of Europe's top 50 publicly quoted companies
33% of UK's biotech and 10% of all Europe's biotech companies.

13,000 people employed directly related to biotechnology businesses
30,000 people employed in life sciences, biote
relevant pharma and research

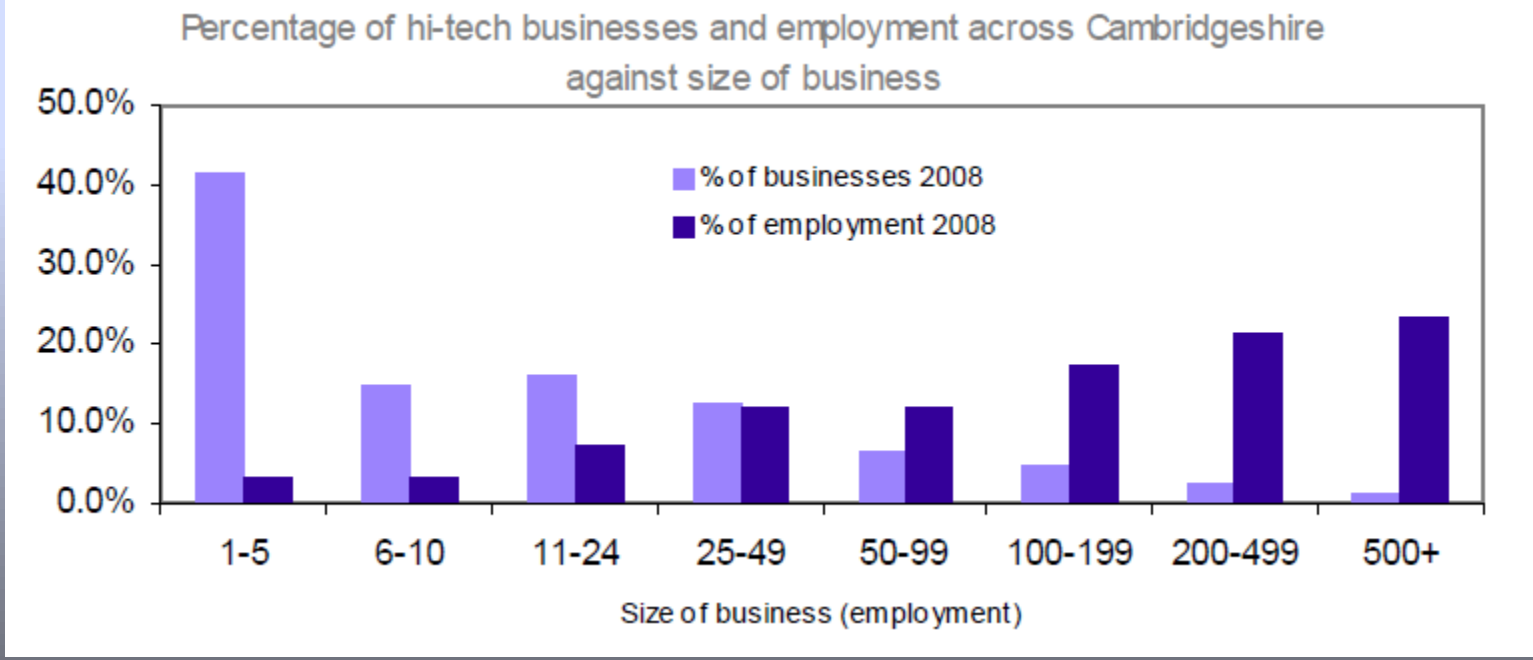
More than 3,500 students and 350 research groups within life sciences

14 Nobel prize winners in medicine and chemistry.

The Cambridge environment

- Babraham Institute
- Sanger Institute
- EBI
- MRC-LMB
- Addenbrookes Hospital
- CIMR
- Cambridge CRI
- Gurdon Institute
- Cambridge University
- Cambridge Science Park
- Granta Park
- Great Chesterford

Across Cambridgeshire around 75% of hi-tech companies employ 24 or fewer staff.



New small companies create net employment, large companies destroy it

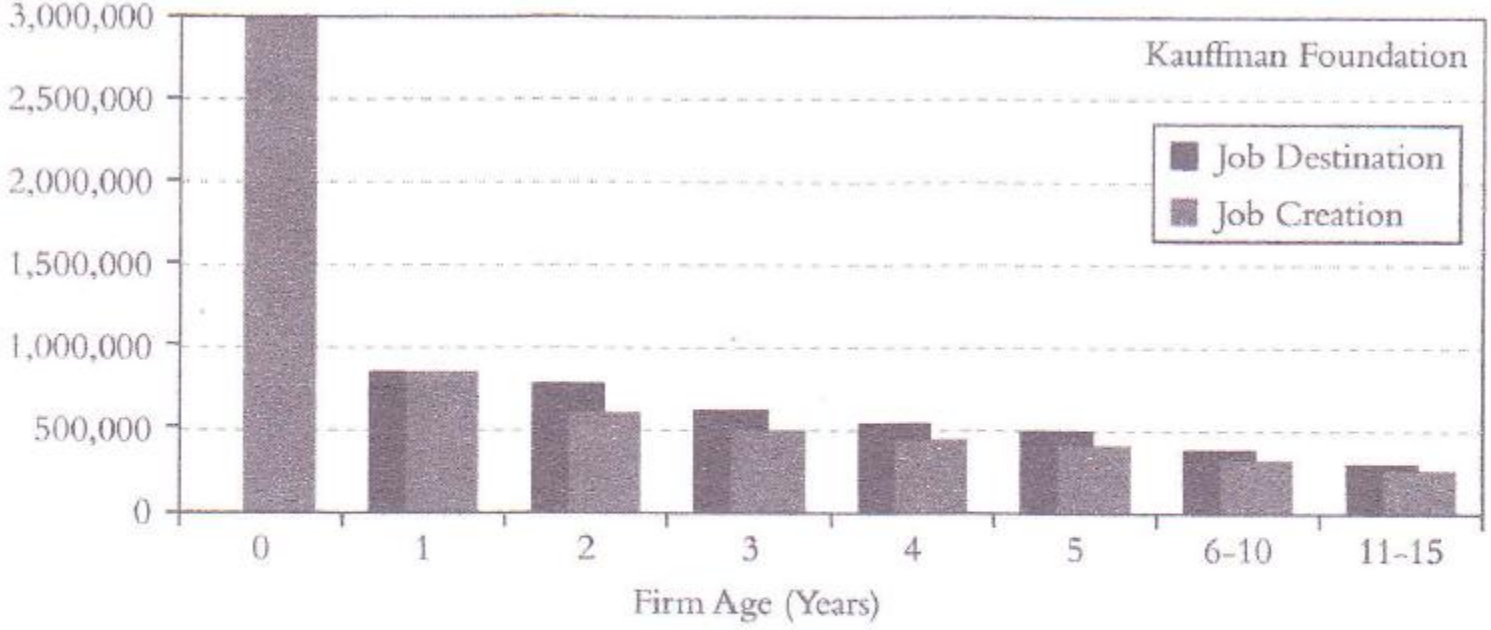


Figure 3.2 Job Creation and Loss by Firm Age (average per year, by year-group, 1992–2005)

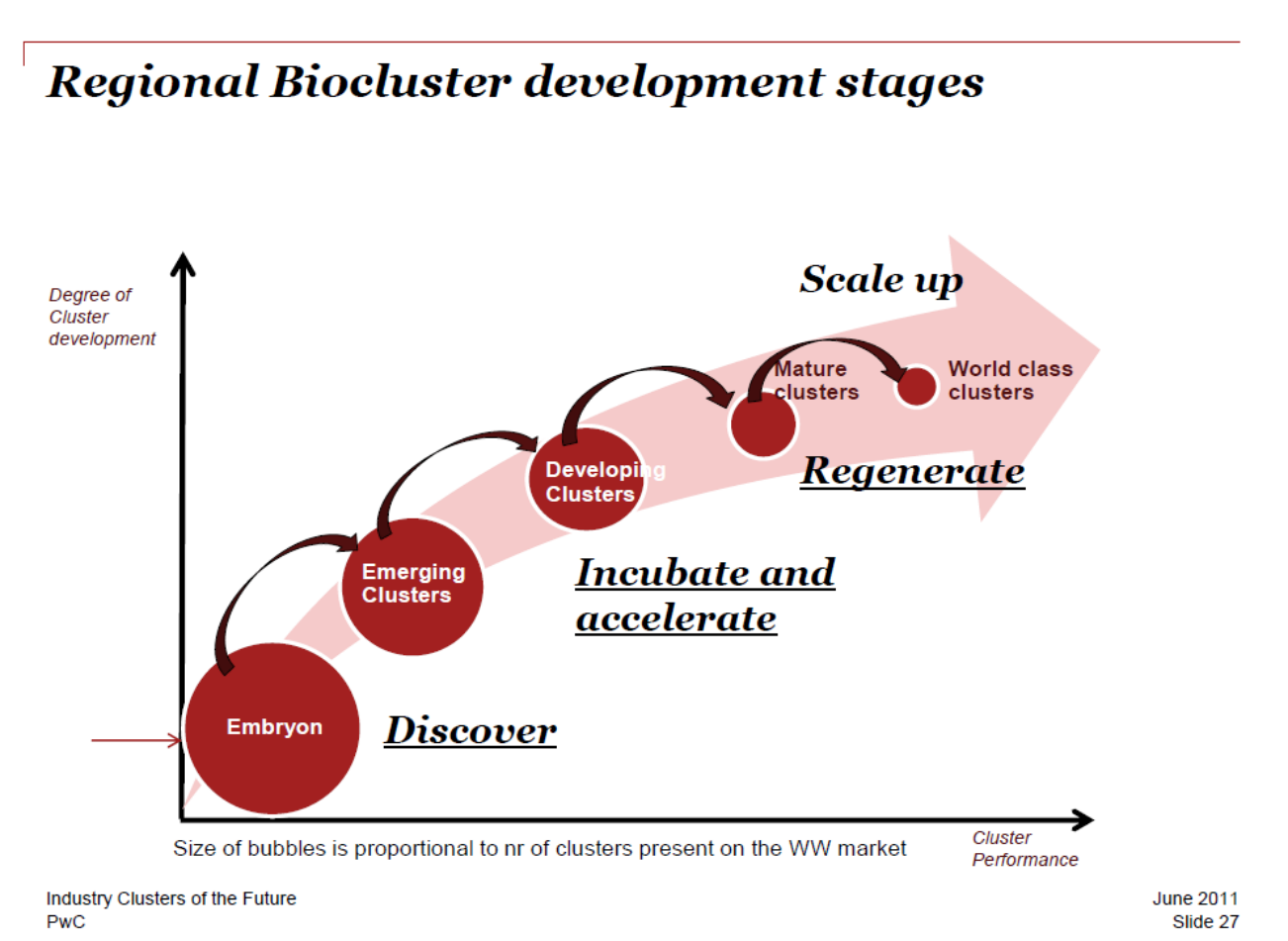
40 year development pathway of the Cambridge Cluster

Date:	1971	1981	1991	2001	2011	2021?
Hi-tech jobs:	20,200	25,100	34,900	46,200	???	???
	Scientific Instruments	Scientific Instruments	Scientific Instruments	Scientific Instruments		
		Computing	Computing	Computing	Computing	Computing
		Software	Software	Software	Software	Software
			Telecoms	Telecoms	Telecoms	Telecoms
			Wireless communications		Wireless communications	
			Biosciences	Biosciences	Biosciences	Biosciences

+ Renewable energy ?
+ Cleantech ?
+ Nanomaterials ?
+ Medical engineering ?
etc

Across the UK we have clusters at several stages of development

PwC / European Union 12/2010



"We can all choose freedom over a job"

Luke Johnson, Financial Times, March 13, 2012

- Can everyone be an entrepreneur?
- Work IQ survey: 65% of 1,000 respondents claimed they wanted to be an entrepreneur:

  - not one wanted to be a corporate executive.

- "Technology has transformed the opportunities for micro-business.
  - Thanks to mobile communications and tablet computers, operating an enterprise part-time wherever you are is a much more realistic option than ever before.

Letter to the Financial Times, April 2012 (extracts)

Sir,

As innovators, entrepreneurs and investors in the life sciences we welcome the Government's support for this high-growth sector.

Our industry comprises more than 5,000 companies employing more than 70,000 people and with a combined value of more than £50 billion in market cap.

We believe the UK has the research base, entrepreneurial skills and venture finance necessary to be a leading hub of global biomedicine. Many of the world's drugs, devices and diagnostics have been discovered here.

Some talk as if the UK's bio-pharma sector is in decline. It is not. Increasing investor confidence and well-informed government policies are combining to boost growth.

etc

So...
...will there be a new golden age of drug discovery?

Thank you

Q&A