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International Centre for Genetic Engineering and Biotechnology (ICGEB)

Research, industry and innovation in life sciences

Trieste

Adriatic sea

ICGEB

International Centre for Genetic Engineering and Biotechnology

An International Organisation in the United Nations System

80+ Signatory States, 60+ Member States, 3 Components:
Trieste (Italy) - New Delhi (India) - CapeTown (South Africa)

History of Biotechnology

- ✓ 1953 - double helical structure of DNA published in *Nature* by Watson and Crick*
- ✓ 1980 - the U.S. patent for cloning genes is awarded to Cohen and Boyer
- ✓ First biotech companies formed:

  1976 - Genentech

  1978 - Biogen

  1980 - Amgen

  1981 - Immunex

  1981 - Chiron

  1981 - Genzyme

World's 10 bestselling prescription drugs made $75bn last year

Majority of bestsellers are created by biological processes rather than chemically synthesised and several are used as cancer medicines

Rank in 2013 (in 2012)	Product	Company	Therapeutic category	2013 sales ($US m)	2012 sales ($US m)
1 (1)	Humira	AbbVie	Other anti-rheumatics	10,659	9,616
2 (2)	Enbrel	Pfizer/Amgen	Other anti-rheumatics	8,776	8,496
3 (4)	Remicade	Johnson & Johnson/ Merck & Co	Other anti-rheumatics	8,386	7,990
4 (3)	Seretide/Advair	GlaxoSmithKline	Other bronchodilators	8,251	7,634
5 (6)	Lantus	Sanofi	Anti-diabetics	7,592	7,155
6 (5)	Rituxan	Roche	Anti-neoplastic MAbs	7,503	6,377
7 (9)	Avastin	Roche	Anti-neoplastic MAbs	6,751	6,282
8 (7)	Herceptin	Roche	Anti-neoplastic MAbs	6,562	6,253
9 (8)	Crestor	AstraZeneca	Anti-hyperlipidaemics	5,622	6,149
10 (10)	Abilify	Otsuka Holdings	Anti-psychotics	5,500	5,304

Humira (adalimumab) – Monoclonal antibody against TNFalpha

Enbrel (etanercept) – Fusion between the p75 TNFalpha receptor and an Ig

Remicade (infliximab) – Monoclonal antibody against TNFalpha

Seretide/Advair – Salmeterol and fluticasone

Lantus – insulin glargine

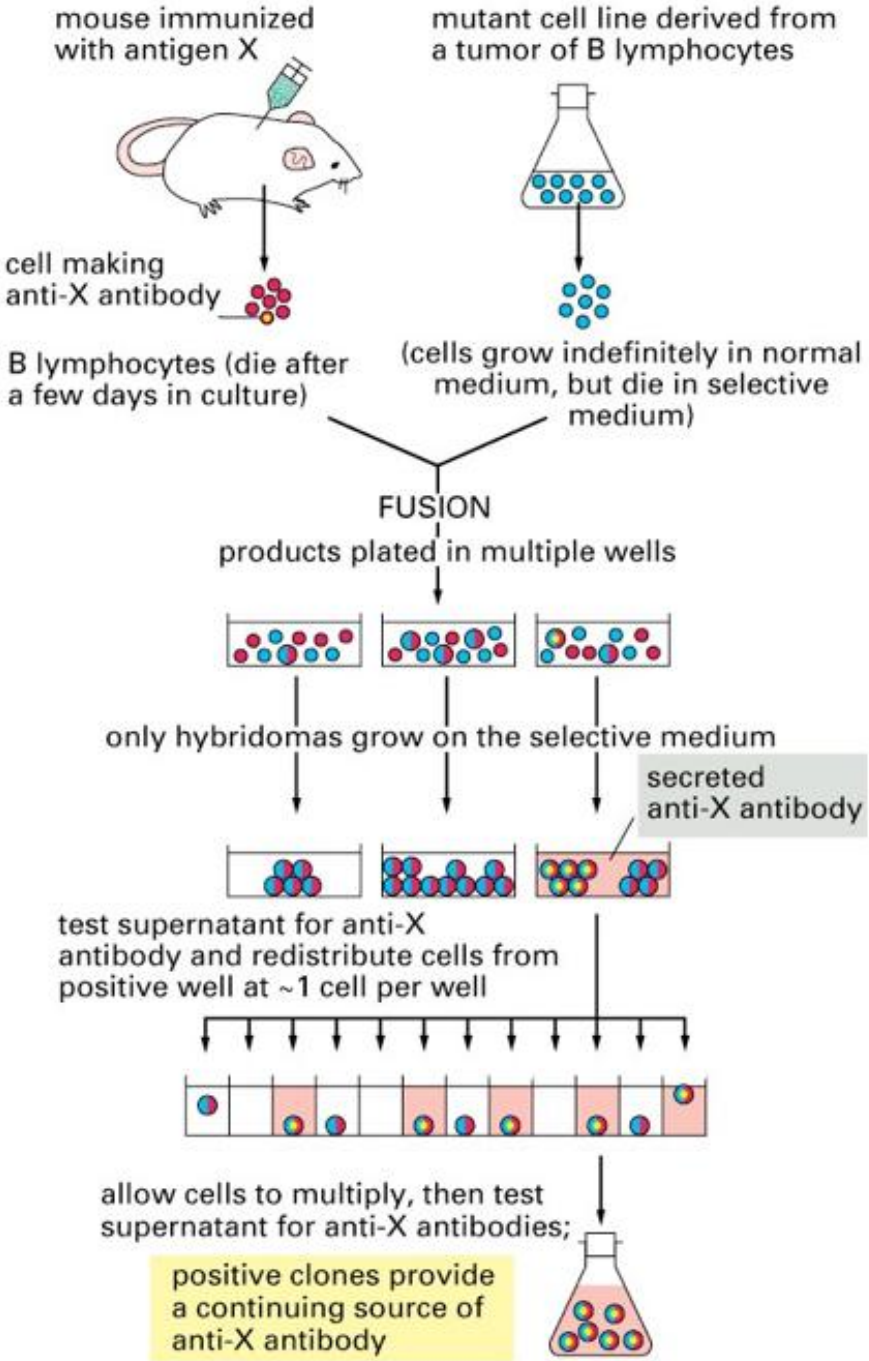
Rituxan (rituximab) – monoclonal antibody against B cell CD20

Avastin - monoclonal antibody against VEGF-A

Herceptin (trastuzumab) – monoclonal antibody against HER2/neu

Crestor (rosuvastatina) - statin

Abilifty (aripiprazolo) – schizophrenia and bipolar disorders



Hybridoma Cell Lines Provide a Permanent Source of Monoclonal Antibodies

nature International weekly journal of science

Letters to Nature

Nature **256**, 495-497 (7 August 1975) | doi:10.1038/256495a0; Accepted 26 June 1975

Continuous cultures of fused cells secreting antibody of predefined specificity

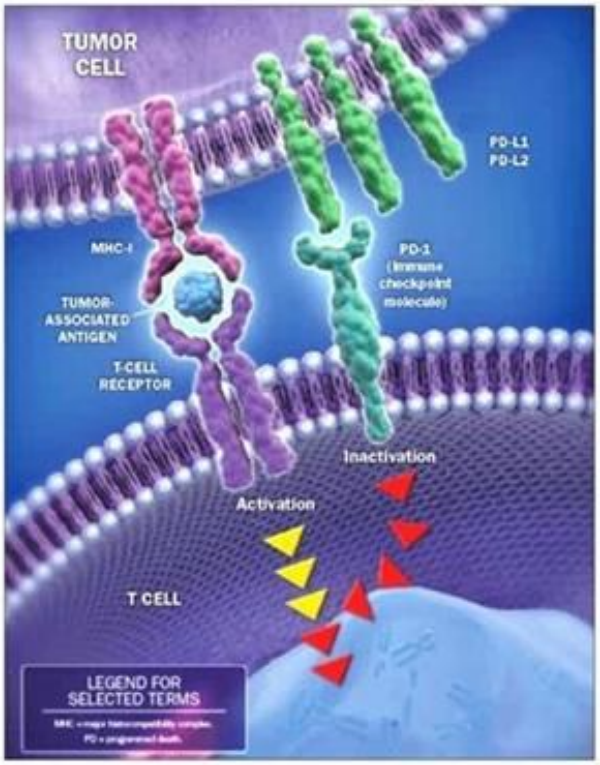
G. KÖHLER & C. MILSTEIN

1. MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK

Top

THE manufacture of predefined specific antibodies by means of permanent tissue culture cell lines is of general interest. There are at present a considerable number of permanent cultures of myeloma cells[1,2] and screening procedures have been used to reveal antibody activity in some of them. This, however, is not a satisfactory source of monoclonal antibodies of predefined specificity. We describe here the derivation of a number of tissue culture cell lines which secrete anti-sheep red blood cell (SRBC) antibodies. The cell lines are made by fusion of a mouse myeloma and mouse spleen cells from an immunised donor. To understand the expression and interactions of the Ig chains from the parental lines, fusion experiments between two known mouse myeloma lines were carried out.

PD-1 Pathway and Immune Surveillance



- PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells[1]
- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function[1]
- Expression of PD-L1 on tumor cells and macrophages can suppress immune surveillance and permit neoplastic growth[2]
- The anti-PD-1 antibody pembrolizumab has demonstrated clinical activity in multiple tumor types[3-9] and is approved in several countries for advanced melanoma

1. Keir ME et al. *Annu Rev Immunol*. 2008;26:677-704. 2. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-64. 3. Ribas A et al. *J Clin Oncol*. 2014;32(suppl 5):abstr LBA9000. 4. Rizvi N et al. *J Clin Oncol*. 2014;32(suppl 5): abstr 8007. 5. Garon EB et al. *J Clin Oncol*. 2014;32(suppl 5):abstr 8020. 6. Seiwert TY et al. *J Clin Oncol*. 2014;32(suppl 5):abstr 6011. 7. Plimack E et al. Abstr. LBA23. Presented at 2014 ESMO Congress, September 26-30, Madrid, Spain. 8. Moskowitz CH et al. *Blood*. 2014;124(21):abstr 290. 9. Nanda R et al. Abstract 1349 (S1-09) presented at SABCS 2014, Dec 9-13, San Antonio, TX.

pembrolizumab (Keytruda), Merck
nivolumab (Opdivo),Bristol-Myers-Squibb

Biopharmaceuticals

- Peptide hormones
- Enzymes
- Cytokines and peptides
- Vaccines
- Monoclonal antibodies
- Nucleic acids (cDNAs, RNAs)
- Cell therapies

Adoptive cell transfer as personalized immunotherapy for human cancer

REVIEW

Disease Models & Mechanisms (2015) doi:10.1242/dmm.018036

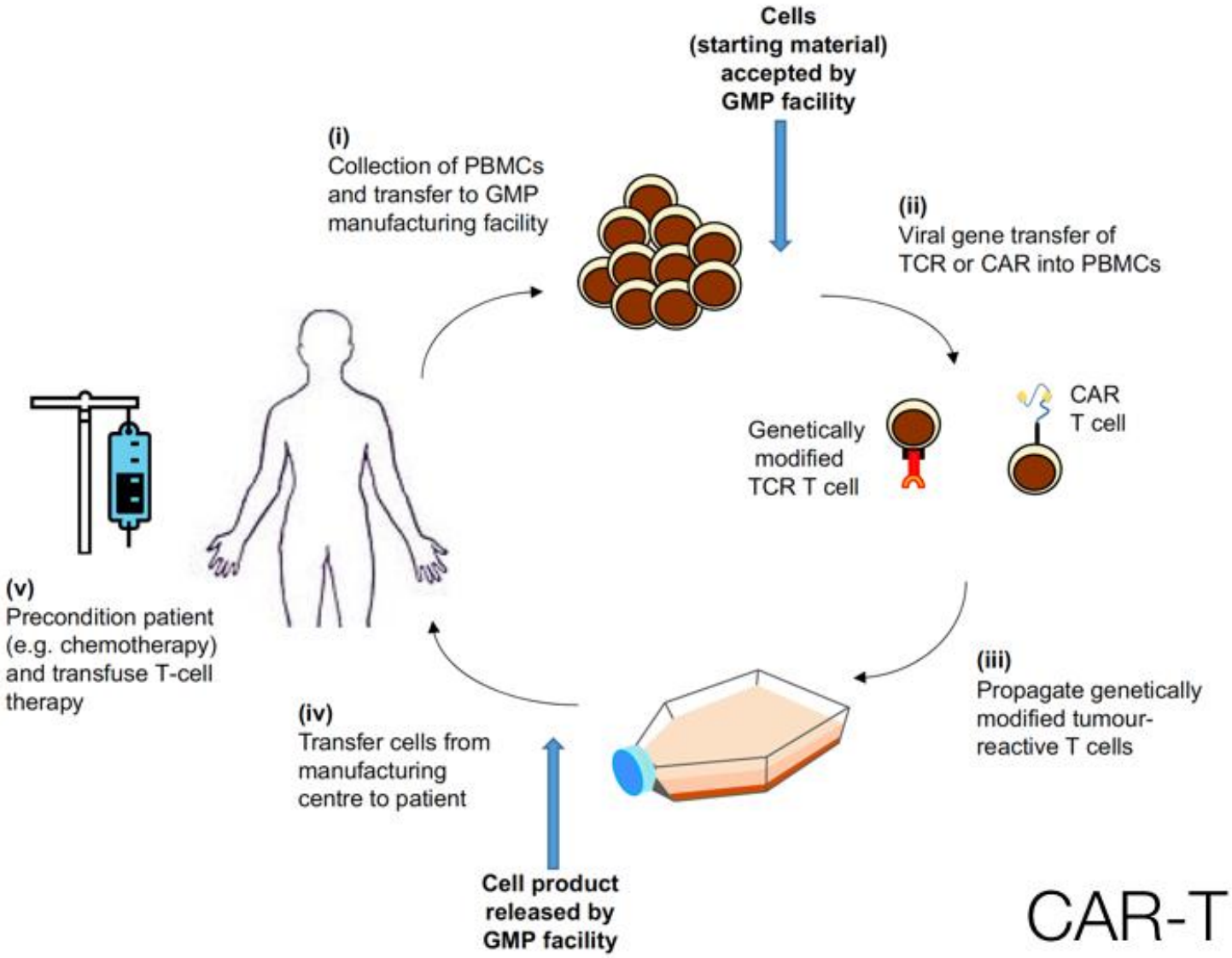


Fig. 6. Manufacturing and delivery pipeline of genetically modified T-cell therapies. (i) T cells are harvested from a patient and sent to a good manufacturing practices (GMP) manufacturing facility, which might not be local to the treating hospital. Cells that pass acceptance criteria are genetically engineered (ii) with either a new T cell receptor (TCR) or a receptor based on a recognition sequence of an antibody [chimeric antigen receptor (CAR)], combined with T-cell co-stimulatory sequences. After a brief period of *in vitro* expansion and passing of product-specific release criteria (iii), the T-cell product must be returned to the correct patient (iv). The patient can undergo conditioning regimens prior to infusion of the genetically modified T-cell product (v). The complexity of this multi-step process in the manufacture and delivery of T-cell immunotherapies poses several economic and regulatory issues, which represent a challenge for the improvement and accessibility of such therapies. PBMC, peripheral blood mononuclear cell.

CAR-T immunotherapy

Clinical trials for siRNAs therapeutics

Table 1
Current examples of clinical trials for siRNA therapeutics with number of patients, type of RNA therapeutics and target disease (Davidson and McCray, 2011; Watts and Corey, 2010).

Drug name	Target disease	Target gene	Phase	Company	Patients
Alicaforsen	Crohn's disease	ICAM-1	III	Isis Pharmaceuticals	150
Atu027	Advanced solid tumors	PKN3	I	Silence Therapeutics AG	33
Bevasiranib	Diabetic macular edema Macular degeneration	VEGF	II	Opko health, Inc.	48
CALAA-01	Solid tumor	M2 subunit of ribo-nucleotide reductase	I	Calando pharmaceuticals	36
I5NP	Injury of kidney Acute renal failure Delayed graft function, Other complication of Kidney transplant	p53	I I, II	Quark Pharmaceuticals	16
ISIS104838	Rheumatoid arthritis	TNF-a	II	Isis Pharmaceuticals	160
PF-04523655	Choroidal neovascularization Diabetic macular edema Diabetic retinopathy	RTP801	II	Quark Pharmaceuticals	184
QPI-1007	Optic atrophy, Non-arteritic anterior, Ischemic optic neuropathy	Caspase 2	I	Quark Pharmaceuticals	66
siRNA-EphA2-DOPC	Advanced cancer	EphA2	I	M.D. Anderson Cancer Center	40
SPC2996	Chronic lymphocytic leukemia	Bcl-2	I,II	Santaris Pharma A/S	46
SPC3649 (miravirsen)	Hepatitis C	miR-122	II	Santaris Pharma A/S	38
SYL040012	Glaucoma, Ocular hypertension	β2 adrenergic receptor	I	Sylentis, S.A	30
SYL1001	Ocular pain dry eye	TrpV1	I	Sylentis, S.A	30
TD101	Pachyonychia congenita	Keratin 6A (N171K mutantation)	I	Pachyonychia Congeita Projcet	1
TKM-080301	Primary or secondary liver cancer	PLK-1	I	National Cancer Institute	42
ALN-RSV01	Respiratory syncytial virus infections	RSV (viral nucleocapsid)	II	Alnylam	24
Withdrawn drugs					
PRO-040201	Hypercholesterolemia Potential for immune stimulation to interfere with further dose escalation	APOB	I	Tekmira Pharmaceuticals Corporation	23
AGN211745	Age-related macular degeneration, Choroidal neovascularization The study was terminated early due to company decision (non-safety related).	VEGFR1	II	Allergan	138
Bevasiranib	Age-relatedmacular degeneration This study has been withdrawn prior to enrollment. (Study never initiated)	VEGF	III	Opko Health, Inc.	

The pressing need to develop novel therapeutics for highly prevalent degenerative disorders

Ischemic cardiomyopathy and heart failure (HF)

15 million HF patients worldwide; 50% of patients with HF die within 4 years

Neurodegeneration

30% of people over 80 years develop Alzheimer disease, and 1-3% of those over 65 years of age develop Parkinson's disease

Diabetes mellitus

>170 million people affected worldwide. Both Type 1 (autoimmune) and Type 2 (due to insulin resistance) diabetes are eventually determined by β-cell loss

Retinal degeneration

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness, mostly affecting people over the age of 50. Prevalence of 30% in people over age 75

Presbycusis (Age-related hearing loss)

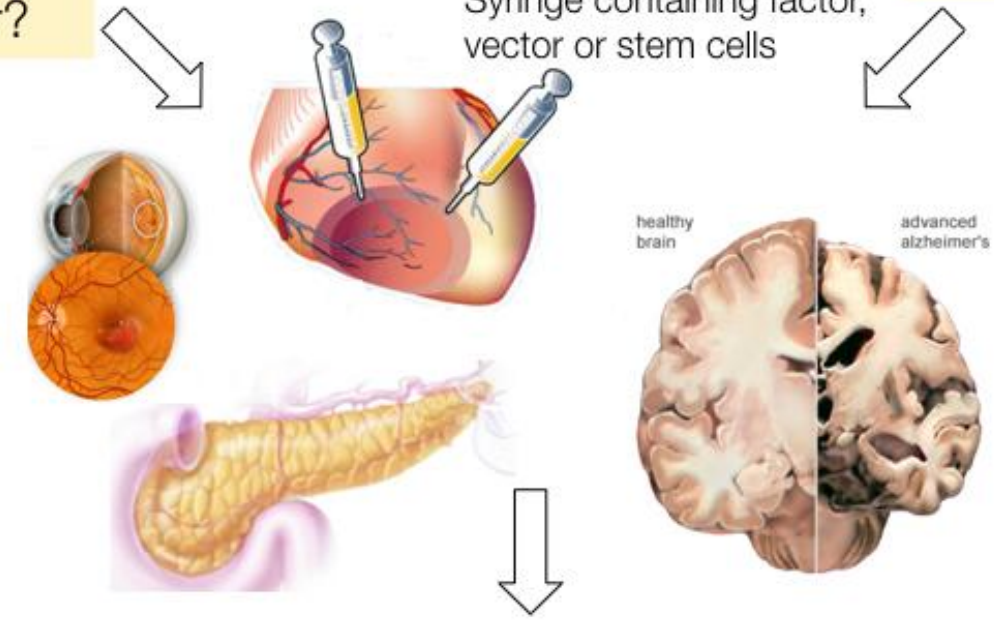
Due to degeneration of hair cells of the cochlea and giant stereociliary cells. Affects >50% people over age 75

Biotherapeutics for degenerative conditions

Synthetic peptides or **recombinant proteins**

Gene Therapy
Protein-coding cDNA, siRNA, miRNA, miRNA inhibitor. Which vector?

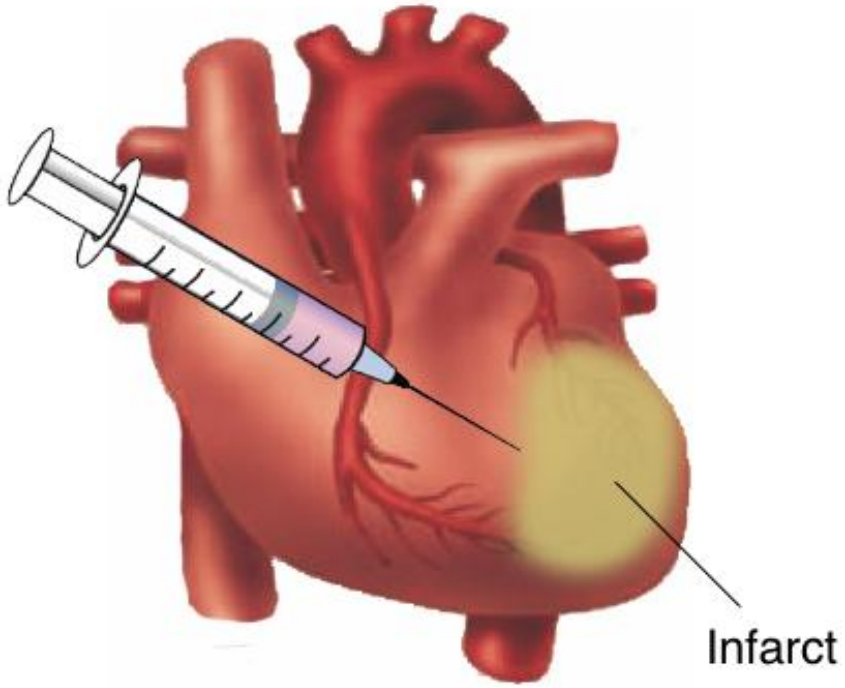
Cell Therapy
Stem cell? Source?



Tissue protection
Improved function
Regeneration

The holy grail of cardiac regeneration

The problem

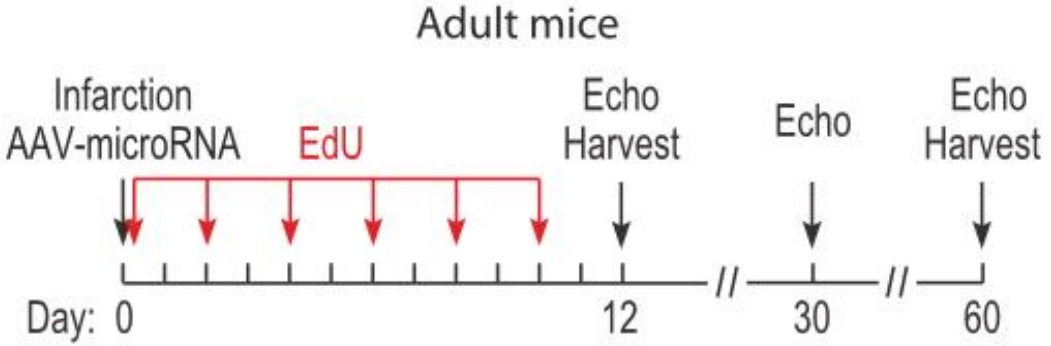


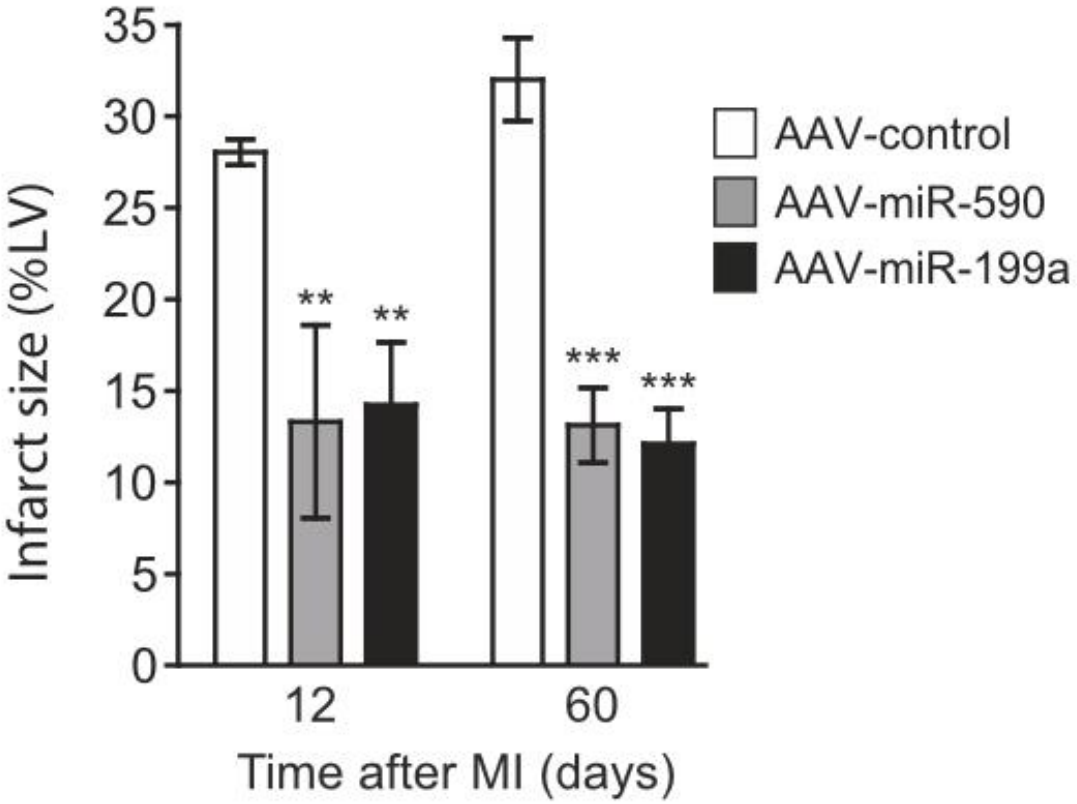
2-4 billion cardiomyocytes are lost from the left ventricle during myocardial infarction

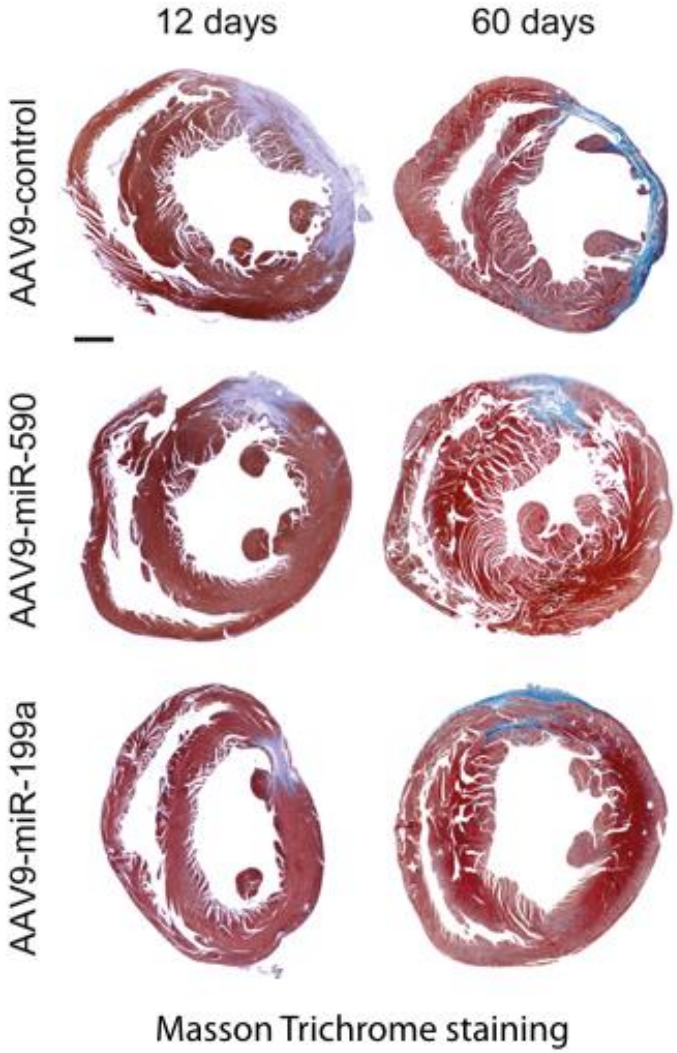
miR-590 and miR-199a markedly reduce infarct size


Serena Zacchigna


Matteo Dal Ferro



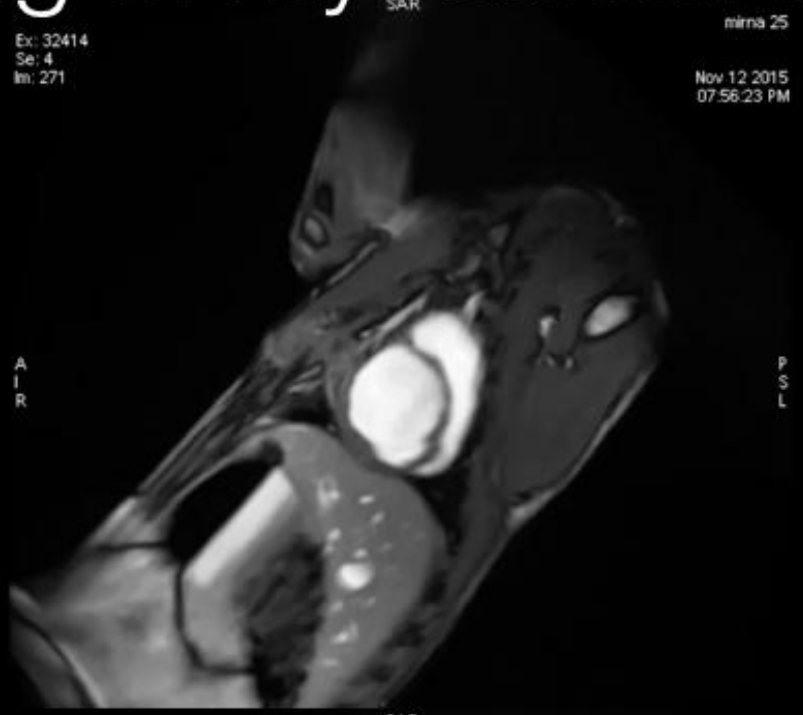




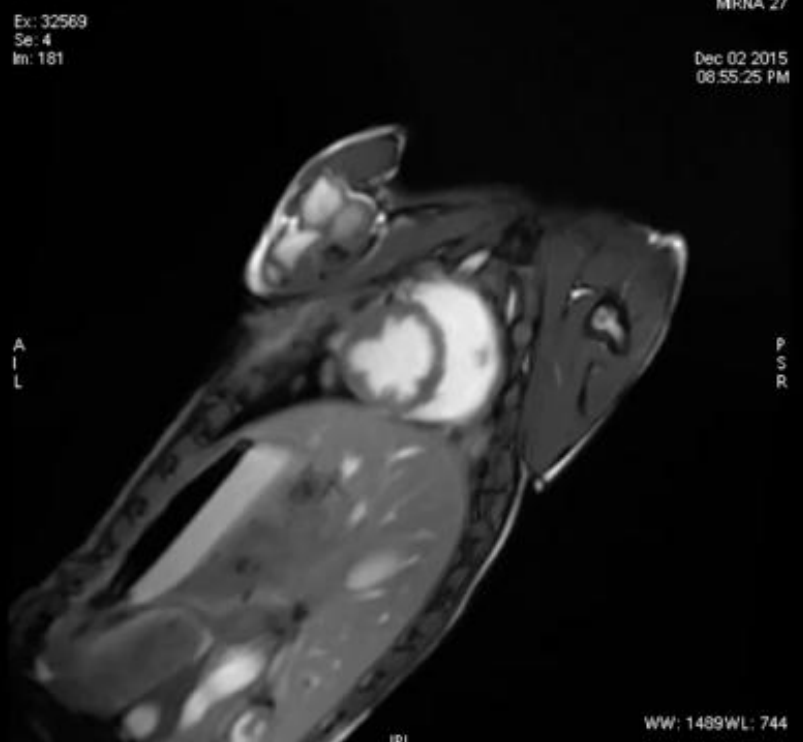
Masson Trichrome staining

Eulalio et al. 2012. Nature 492, 376

Healing of myocardial infarct in pigs

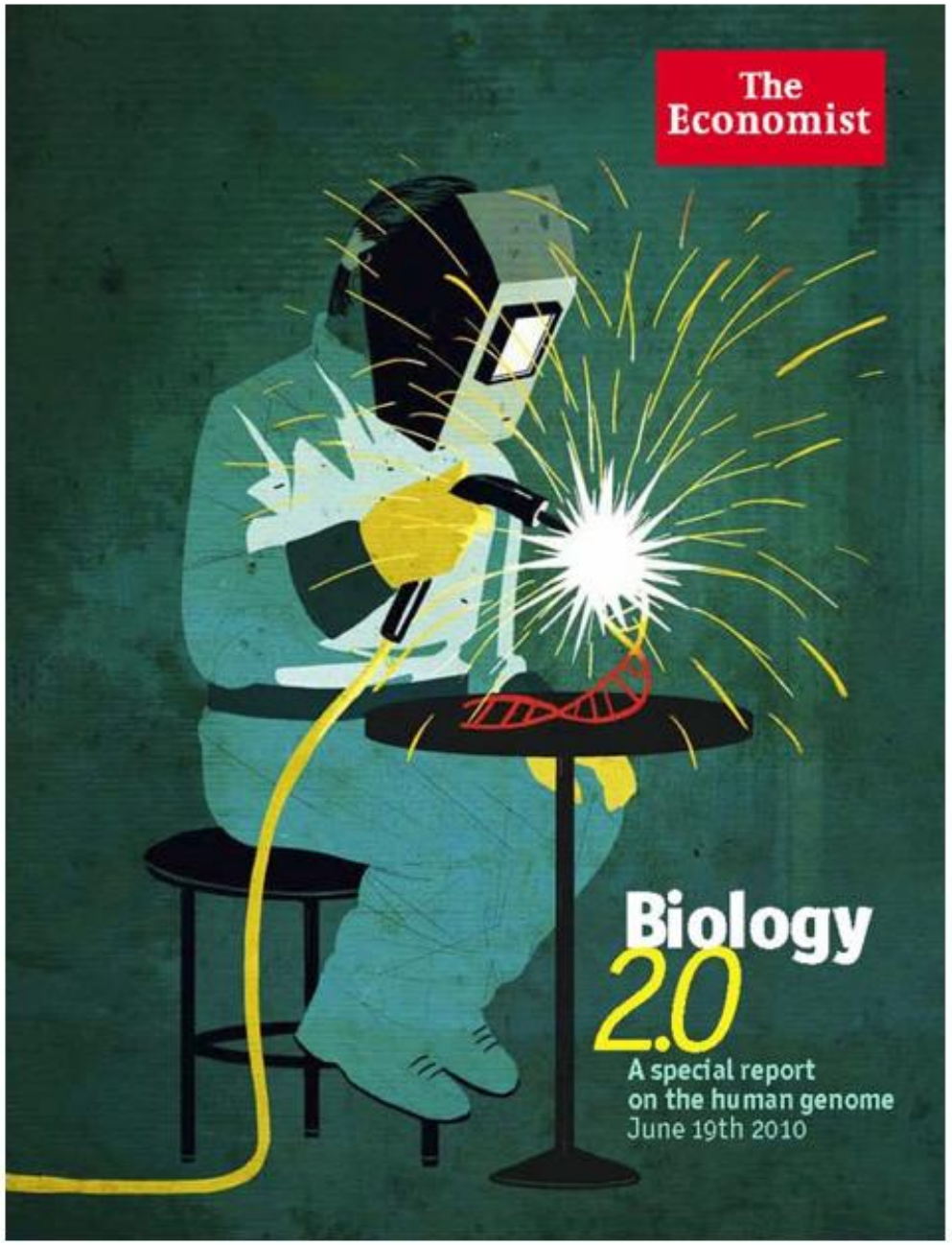


Infarct
Control

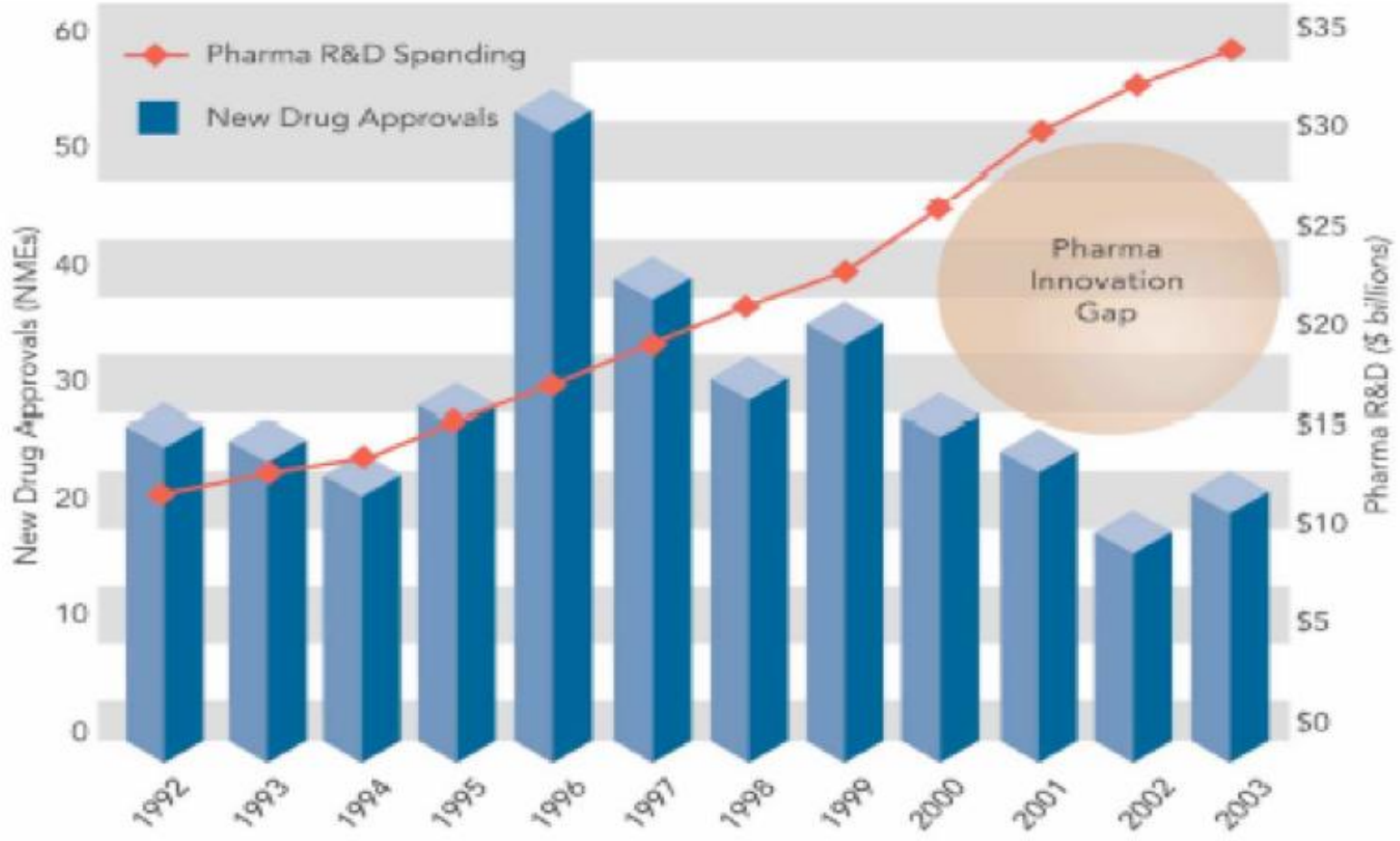


Infarct
miR-199a

Business model for the new bio-technologies?



Innovation gap for traditional drugs



Burrill & Co

Big companies like small molecules, small companies like big molecules.

Judah Folkman

atorvastatin

Molecular weight

= 558 Daltons

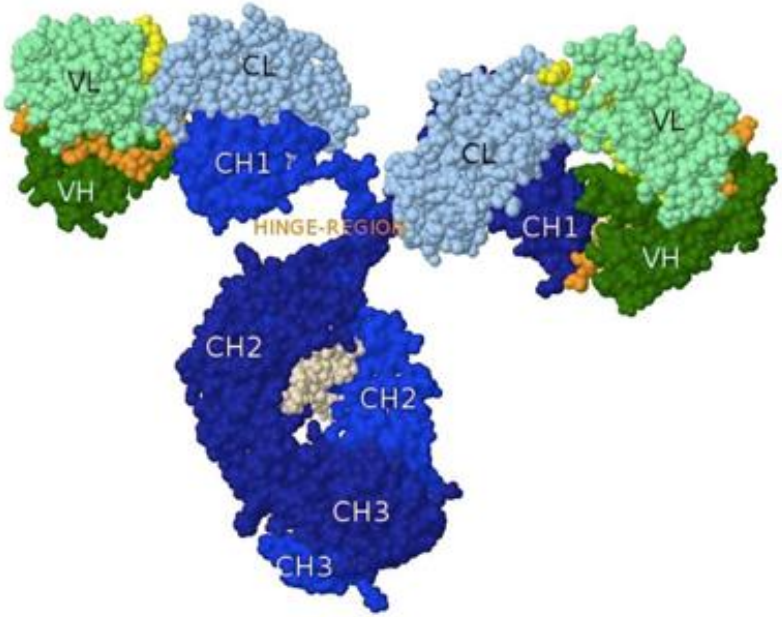
0 amino acids

Interferon-alpha

Molecular weight

= 19,625 Daltons

~165 amino acids



Antibody (IgG)

Molecular weight

= 150,000 Daltons

~1,300 amino acids

Source: http://www.path.cam.ac.uk/~mrc7/mikeimages.html

Biotech Companies are Entrepreneurial

- ✓ Founded by an individual or perhaps a small group, usually scientists
- ✓ Technology obtained from tech transfer
- ✓ Angel or Venture capital backed
- ✓ High risk

Sorting the wheat from the chaff

Only 1 drug of every 5,000 is commercialized (most drugs fail!)

It costs over $1M

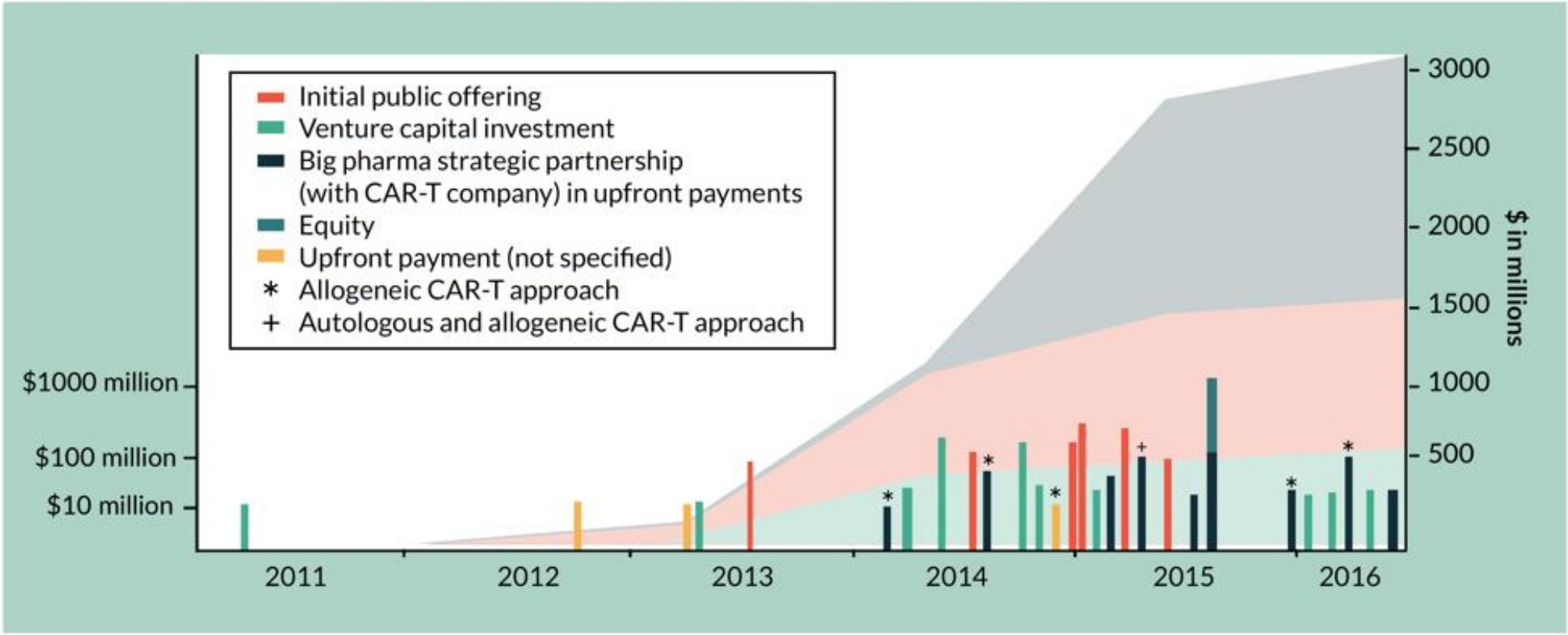
And takes over 12 years

2/3 of all drugs that make it to the market do not recover R&D expenses

Who is going to pay?

Companies developing CAR-T products

CAR-T companies: venture investments, initial public offerings and pharmaceutical partnerships.



Beginning in 2011 with Kite Pharma, venture capitalists have invested in six companies developing CAR-T therapeutics. Total venture capital (VC) dollars have reached over $600 million as of September 1st 2016 (see Table 1 for details). The six companies funded, the majority of which are developing autologous CAR-T therapies, completed initial public offerings totaling nearly $1 billion (see Table 2 for details). Since the first Big Pharma strategic partnership in the CAR-T space between Novartis and the University of Pennsylvania in 2012, seven other Big Pharma companies have followed suit, placing bets of at least $1.5 billion in upfront payments, the majority for allogeneic approaches marked by asterisks (see Table 3 for details).

Includes only VC funding for companies involved in CAR-T program(s) at the time of investment. For example, VC funding of Bluebird Bio occurred prior to their CAR-T programs, while the company had only a gene therapy focus. These investments are not included. See Table 1 for details.

Includes only initial public offerings where the company had a CAR-T focus at the time of going public. See Table 2 for details.

Includes only strategic partnerships where Big Pharma companies invest in and obtain rights to CAR-T therapeutic programs. Not included, for example, is the Roche and Genentech partnership with Kite Pharma in March 2016 to combine Kite's CAR-T technology with Roche or Genentech's small molecules. See Supplementary Table 1 for other deals like this. Payments are upfront only, see Table 3 for additional details on milestone, royalties and other terms.

Sources: Company press releases, Nelsen Biomedical Analysis.

Cell & Gene Therapy Insights
Published: Oct 3 2016

Financing: a Critical Path

3 F's (friends, family, fools)
Public Grants
Angel investors
Venture capital
Partnering
Public offering (institutions)
Merger/acquisitions

Capital Financing Needs

Company Stage	Private investment
Proof of Concept	$25,000 – $100,000
Pre-seed	$50,000 – $500,000
Seed	$150,000 – $2 million
Early-stage	$1 million – $5 million
Expansion-stage	Up to $10 million

COUNTRIES WITH ATTRACTIVE GOVERNMENT SUPPORT FOR STARTUPS

Singapore

$48M

pumped into six venture capital funds

United Kingdom

50%

income tax relief on investments up to **£100,000**

Chile

$40,000

equity free grants

Finland

$145M

through grants and loans

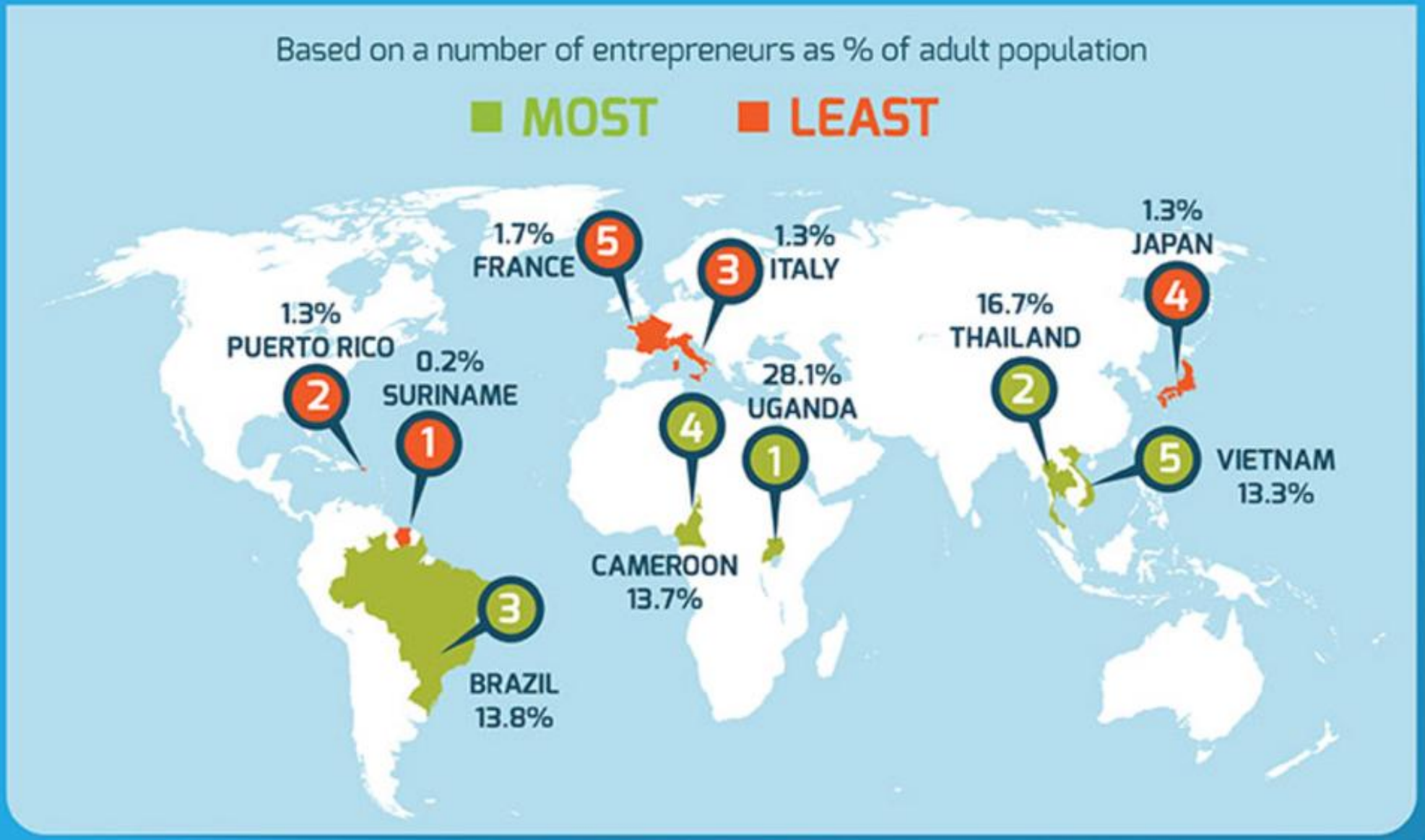
Israel

$450M

for seed funding and R&D projects

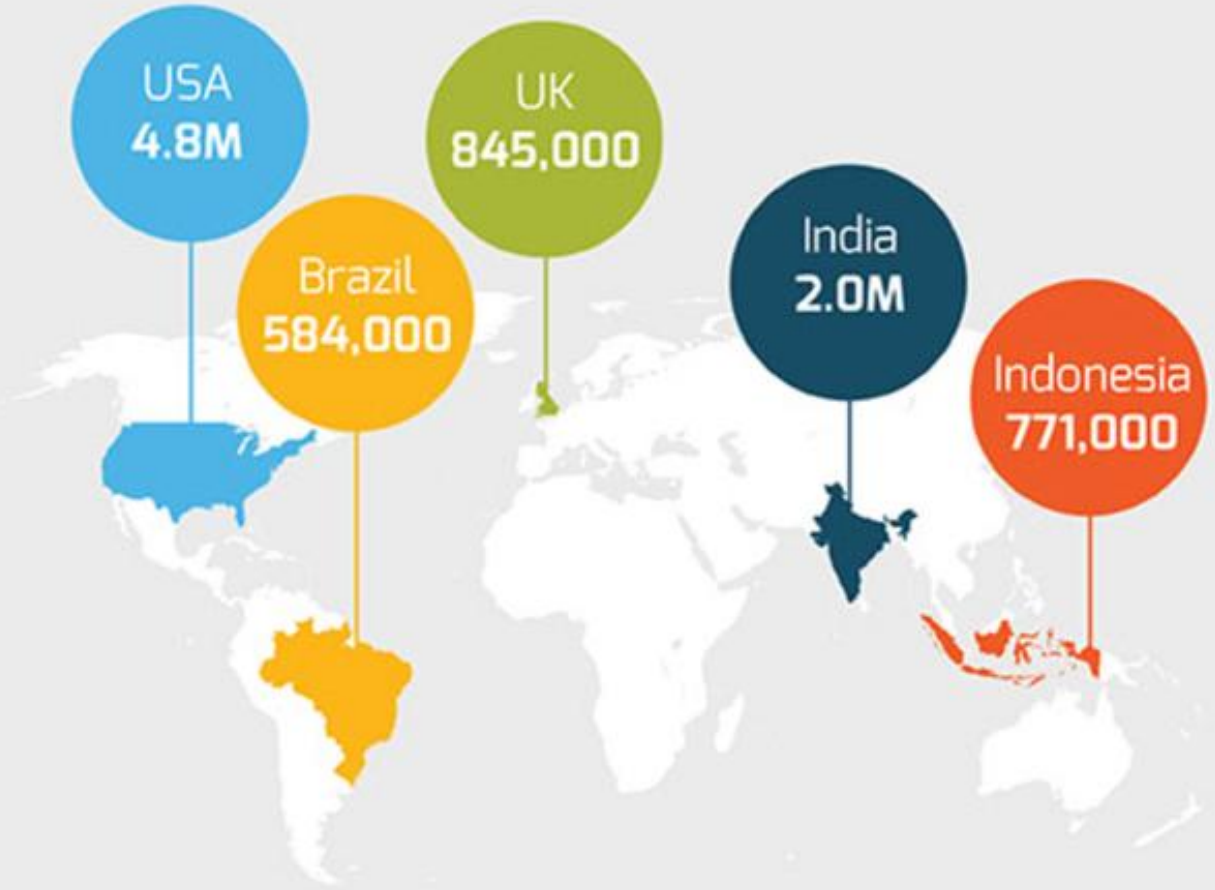
Source: Coupofy Infographic 2015

WHAT COUNTRIES ARE THE MOST AND LEAST ENTREPRENEURIAL IN THE WORLD?



Source: Coupofy Infographic 2015

THE COUNTRIES WITH THE **HIGHEST NUMBER OF STARTUPS**



There are as many startups in Nigeria as in Germany.

Canada has **10%** of the US startups.

Indonesia has twice as many startups as Italy.

Source: Coupofy Infographic 2015

How to promote start-up development

- IP consultancy (freedom to operate)
- Patent office
- Business development
- Initial economic support to startups
- Bridge to Angels and VCs
- Bridge to large pharmacompanies


Thanks!
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