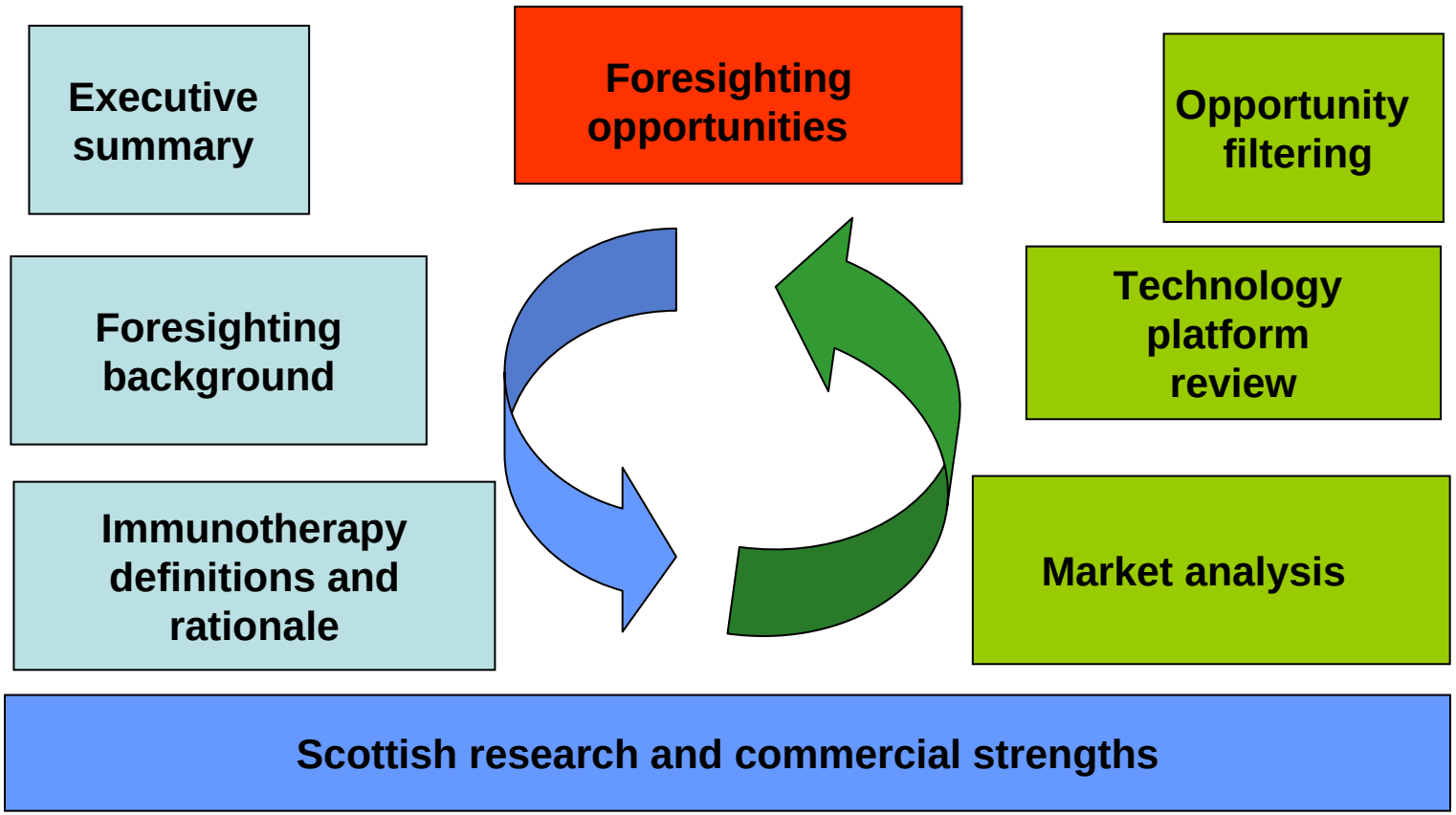
Immunotherapy

Environmental Scan

ITI Life Sciences

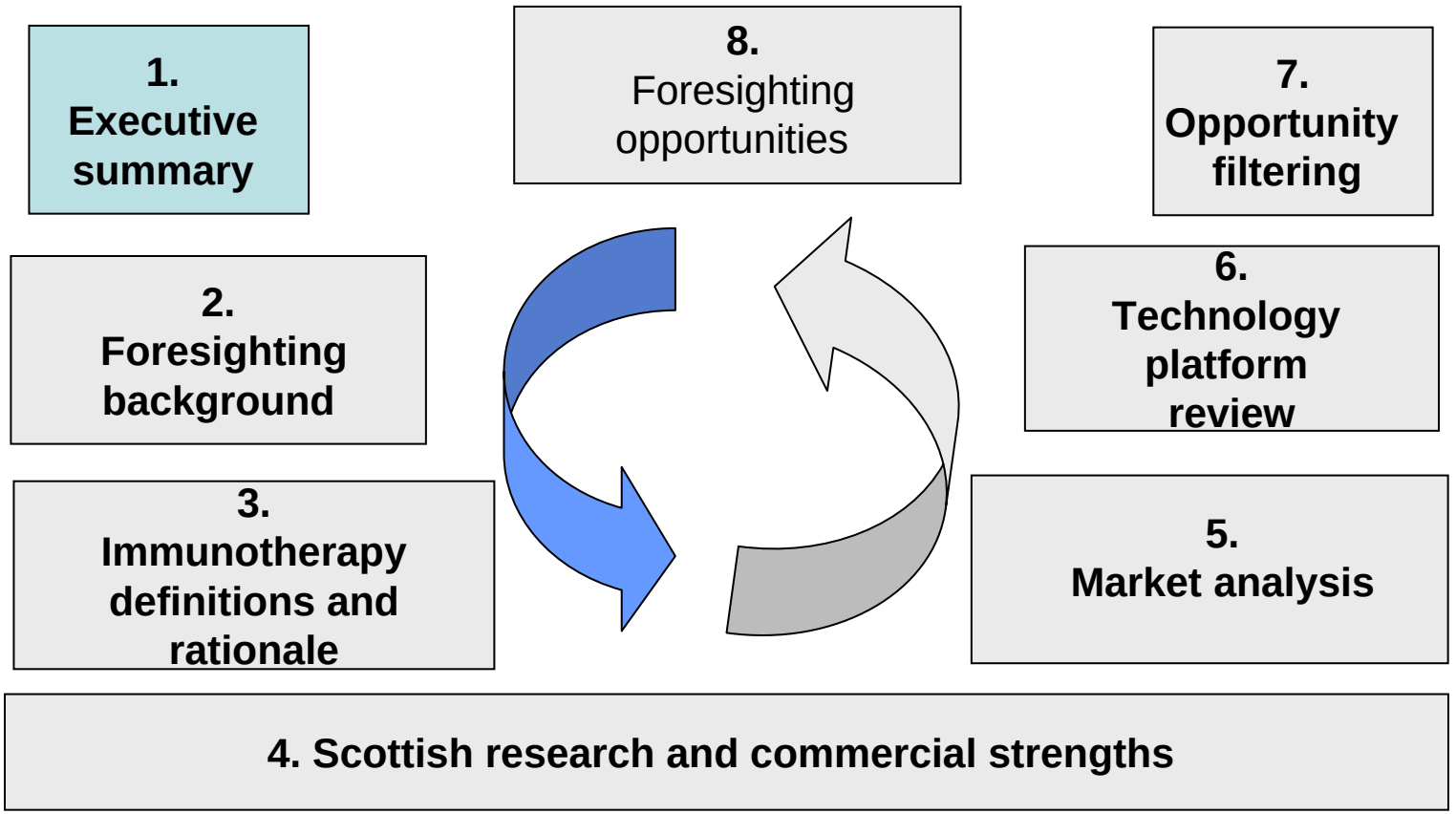
August 2009

Report Structure



Key:
Background and description **Analysis** **Conclusion**

Part 1: Executive Summary



Immunotherapy Executive Summary 1

- Multiple fundamental research advances have described details of immune-system function at cellular, molecular and genomic levels.
- New molecular targets and mechanisms have been identified from this research, in particular major receptors and related pathways (such as CTLA-4, B7 and CD28), which control T-cell function.
- Parallel development and/or industrial scale-up of new (RNA, TCR) and existing (monoclonal) classes of therapeutic molecules has been possible.
- There is now a greatly improved ability to isolate, identify and manipulate key immune effector cells.
- Quantum improvements in conventional prophylactic vaccines have been seen, which can be applied wholly or in part to novel immunotherapy:
  - vaccine development technologies
  - vaccine production technologies
  - novel adjuvants.

Immunotherapy Executive Summary 2

- In recent years, the range of diseases and conditions in which an immune, or autoimmune, component has been implicated has greatly expanded.
- In parallel, the technological ability to develop new immunotherapies, and as crucially, to produce them in commercial quantities, has greatly increased.
- This has been driven largely, but not exclusively, by rapid advances in traditional vaccine technologies and the coming of age of antibodies as a mainstream therapeutic modality.
- Cell-based therapies, T-cell receptor therapy and siRNA are on a similar trajectory to monoclonals and are all readily applicable to immune therapy.
- The major Pharma and biotech companies are investing heavily in both applied research and infrastructure to support immunotherapy production.
- The range of pathologies in which there is an immune component and/or unmet clinical needs is widening.
- The research and platform technologies are progressing rapidly.

Immunotherapy Executive Summary 3

- Increasing knowledge of the science of the immune system is creating opportunities for immunotherapy that reach beyond conventional vaccines for infectious diseases of childhood.
- A survey of leading-edge science revealed a rapidly moving field with therapeutic modalities of potentially wide future application to diseases such as:
  - cancer
  - chronic illnesses, e.g. hypertension and diabetes
  - degenerative diseases such as Alzheimer's
  - autoimmune diseases, e.g. multiple sclerosis and inflammatory bowel disease.

Executive Summary 4

- The research base in Scotland is highly competitive in the key cognate areas of immunology and infection, and also in several of the key emerging application areas of novel immunotherapy, most notably cancer, cardiovascular disease and diabetes.

- There is well-developed translational research and clinical trials capability in Scotland, which can be applied to evaluation of new therapies.

- There is small but significant group of companies based in, or having a presence within, Scotland with capability in immunotherapy technologies.

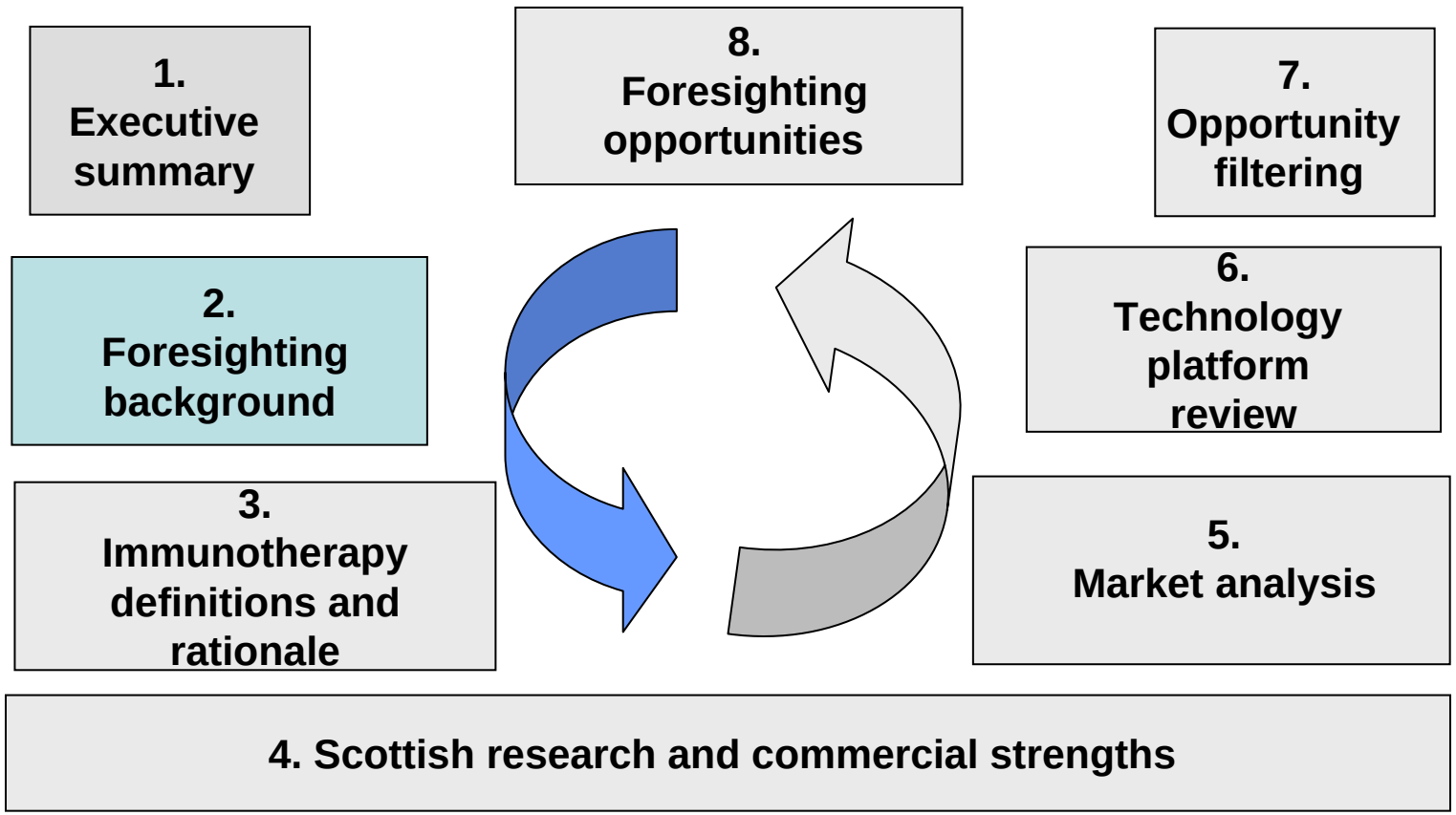
- The Scottish company base is particularly strong in biological manufacturing processes which are relevant to immunotherapy.

- **The basic premise of this survey is that the renaissance in conventional vaccines will act as a technological and business springboard for new interventions collectively enabling a new wave of Immunotherapy products.**

Immunotherapy Executive Summary 5

- There are multiple potential market opportunities in the rapidly growing immunotherapy market space. These include interventions directed at modulating the immune response to enhance disease elimination or to suppress autoimmune responses.
- A first-pass filtering exercise based primarily on market size and perceived technical difficulty yielded a discrete short-list of potential market opportunities for novel immunotherapeutic approaches to:
  - human-acquired infections, in particular of implants
  - fungal infections
  - elimination of minimal residual disease in major cancers
  - hypertension
  - food allergies and bowel autoimmune disease
  - rheumatoid arthritis
  - allergic rhinitis (hayfever).

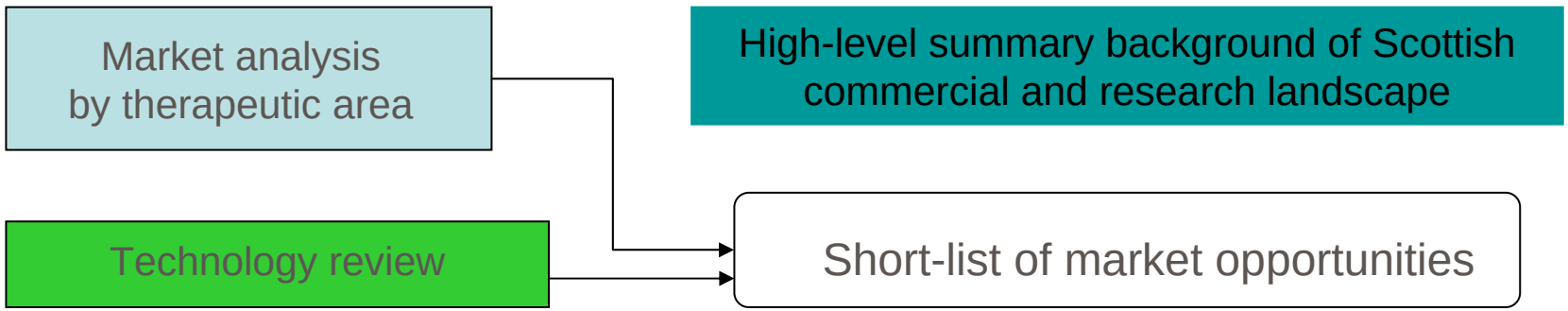
Part 2: Foresighting Background



E-scan Deliverables

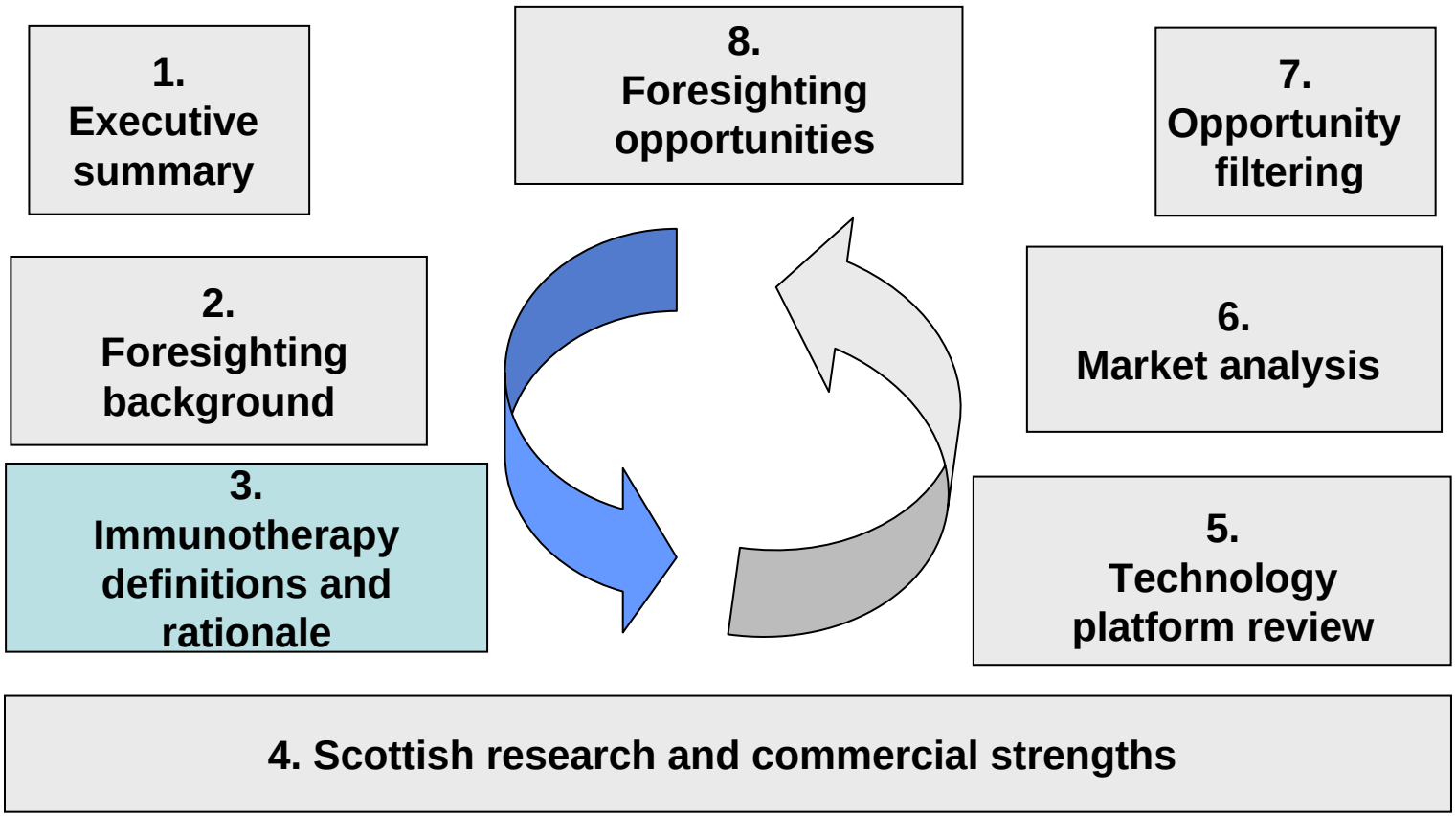
- The goal of this environmental scan is to provide a market and technology background for immunotherapy: placing the emerging immunotherapy market in the wider context of the traditional vaccine, biologicals and pharmaceuticals markets.
  - A broad-based market survey by disease indication.
  - Relating disease sector to technology platforms at a high level.
  - Selective case studies and High-level review of Scottish strengths.
  - Preliminary opportunity mapping for full foresighting.
- This background market analysis and the potential opportunities can be exploited by:
  - ITI LifeSciences
  - SE Network
  - Academic research partners
  - Scottish SMEs, spinout companies and strategic partners.

E-Scan Survey Process



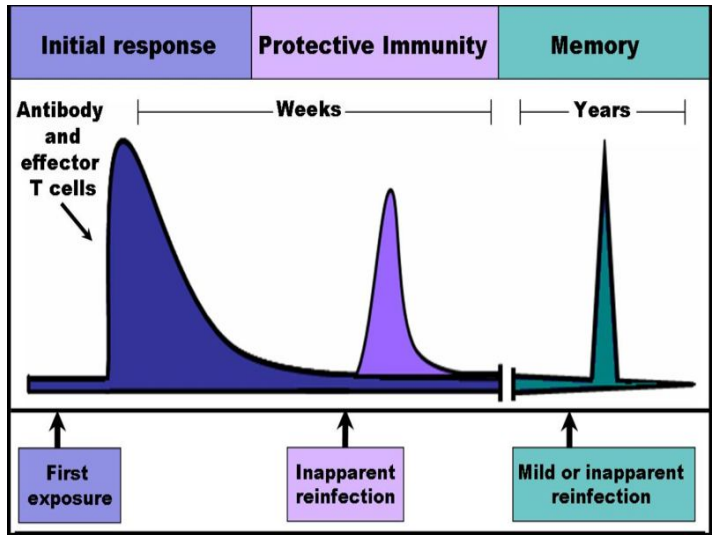
- We based our analysis on a science and technology survey on two dimensions: disease areas and technology platforms.
- US patient numbers and current market costs were used to assess commercial opportunity by specific disease states
- This E-scan is focused more heavily on market opportunity identification as opposed to a review of specific platform technologies.
- The endpoint generated was a short-list of market opportunities perceived to be tractable.
- These specific market opportunities will be investigated in more detail within future foresighting exercises and linked to specific Scottish capabilities.

Part 3: The Case for Immunotherapy



Immunotherapy: Innate and adaptive immunity

- The distinction between the adaptive and innate immune systems is critical to therapy.
- **Innate immunity** is short lived and non-specific, therefore any therapy targeted against it or using components solely from it (e.g. anti-inflammatory drugs) will be short lived.
- Selective manipulation of specific components of the **adaptive immune system** (e.g. monoclonal antibodies, TCRs or cell therapies) can also yield very effective but temporary therapy.
- The adaptive immune response offers a unique potential property to any new immunotherapy: the possibility of long-term protection through generating memory T cells.
- Although this is best demonstrated with traditional prophylactic vaccines, it could also apply to certain new therapeutic vaccines and adaptive cell therapies.

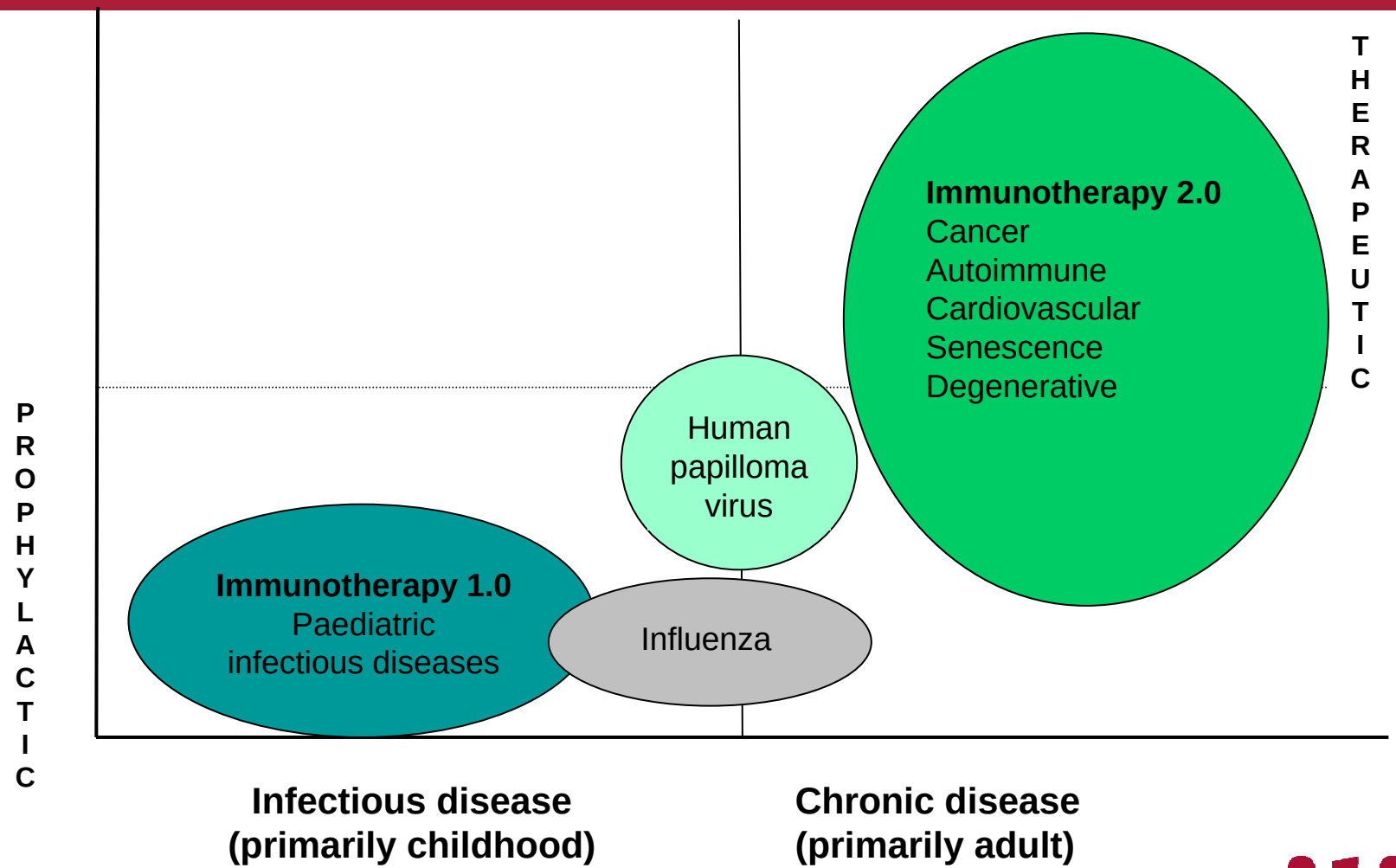


Short-term therapies	Long-lasting therapies
Monoclonals	Vaccines
Small molecules	Adaptive T cells

Immunotherapy: Definition and Scope

- Immunotherapy can be defined broadly as a set of clinical interventions aimed at countering disease by modulating a patient's immune system using both conventional small molecule approaches and tools derived from the immune system itself.
- These tools include: antibodies, receptor fusion proteins, vaccines and specific immune system effector cells.
- These and other therapeutic options stem from major medical advances in the last 10–15 years and are being applied to an increasingly wide range of disease states.
- The therapeutic benefits can be accrued in two ways:
  - prophylactic interventions prior to disease, as typified by paediatric vaccines, which seek to prevent infection in the immunised patient. This can be thought if as Immunotherapy 1.0
  - therapeutic interventions, which seek to inhibit or modulate existing disease progression e.g. adoptive cell therapy, which is broadly described in this report as Immunotherapy 2.0

Immunotherapy 1.0 > Immunotherapy 2.0
A market and technical evolution towards Chronic Disease



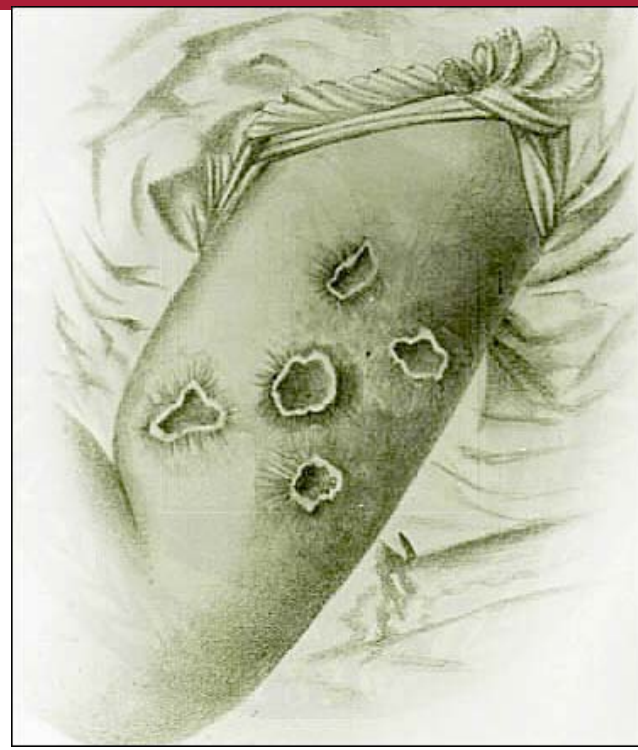
Immunotherapy 1.0 and 2.0

- The term “Immunotherapy 2.0” is useful shorthand to denote the post-genomic era and a period of rapid progress in basic immunology.
- These are both driving further rapid progress in both conventional vaccines and novel immunotherapy.
- **Immunotherapy 1.0 (1798–2000):**
  - traditional paediatric vaccines
  - slow development and production technologies.
- **Immunotherapy 2.0 (after ~2000):**
  - post-genomic era and incorporating related fundamental advances in immunology
  - exploiting new production technologies
  - focusing on treating chronic disease in adults.

Immunotherapy 1.0 (1798–2000)

Immunotherapy 1.0 is characterised by:

- A relatively crude pre-genomic understanding of the immune system.
- Relatively slow and crude production methodologies, such as egg-based methods.
- A slow clinical trials process.
- A heavy focus on infectious disease and childhood illnesses.
- Low-cost, low-margin products as governments are the principal customers.
- An Intense concentration of industry in 5-6 large companies driven by the need to achieve economies of scale necessary to be competitive.
- Researchers and clinicians that were able apply this limited knowledge to great effect, producing a range of highly effective paediatric prophylactic vaccines.
- Collectively, these represent one of the most important and cost-effective contributions to public health.



Immunotherapy 2.0 (~2000 onwards)

Immunotherapy 2.0 can be characterised by:

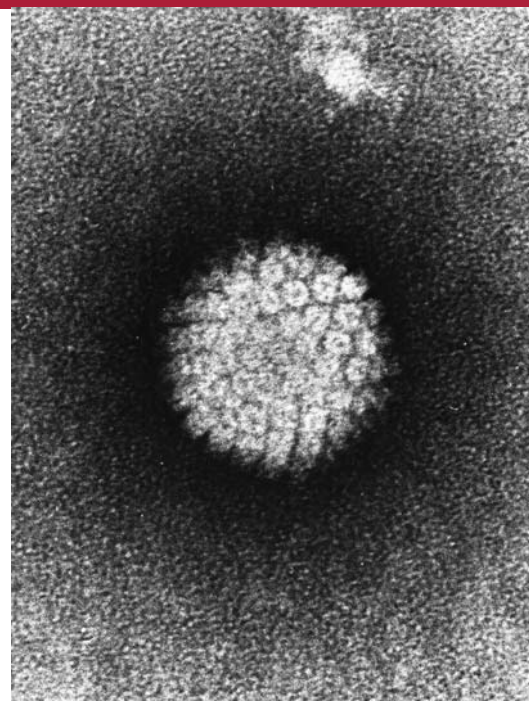
- A much deeper understanding of the immune system driven partly by genomics but also by advances in defining regulatory immune cell types, receptors and signalling pathways.
- The ability to leverage this greater level of knowledge to produce effective prophylactic and therapeutic interventions directed at a much wider range of chronic adult diseases.
- Much faster production methodologies of cell culture for molecular components of immunotherapy and the increasing use of cells as therapy.
- Still a relatively slow, highly regulated clinical trials process: although somewhat faster for therapeutic interventions.
- A clear focus on chronic neoplastic, autoimmune and degenerative disease in adults.

Immunotherapy 2.0 … continued

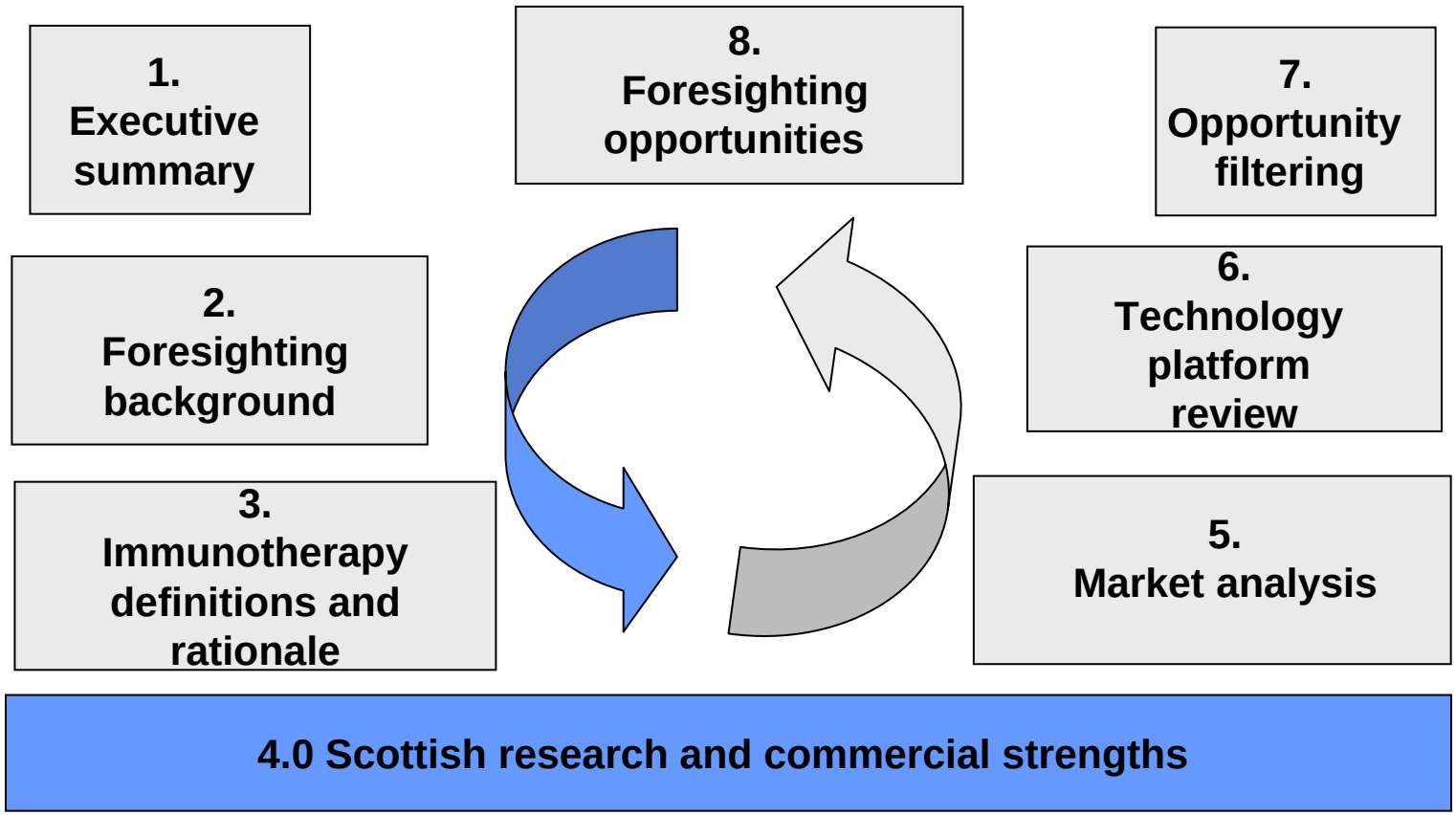
- There will more opportunities for new entrants with novel platform technologies, although strategic partnerships with Big Pharma will still probably be required for clinical trials and production.
- There will be extensive opportunities for novel immunotherapy to be used in combination with other therapeutic modes, such as surgery, radiotherapy and small molecules.
- Novel therapies to both monitor and maintain immune function in an ageing population will become increasingly important, as will reformulations of existing immunotherapy for elderly patients.
- The much higher cost and profit margin commanded by human papilloma virus (HPV) vaccines will serve as a model for effective immunotherapy for other chronic adult diseases.
- The market size for products successfully addressing chronic disease in adults have potential to be an order of magnitude (or more) than traditional vaccines.

Human Papilloma Virus (HPV) Vaccines: Changing the Landscape

- Strains of HPV are responsible for nearly 3000 cases of cervical cancer and more than 100,000 diagnosed cases of anogenital warts annually in the UK.
- The recent launch of new vaccines in this sector profoundly changed the vaccine industry as these vaccines were:
  - high-value blockbuster products: Gardasil – the HPV vaccine produced by Merck – had 2008 sales of $1.4bn
  - directed against an infectious virus: the clinical effect is to prevent adult neoplastic disease.
- HPV vaccines can be thought of as a highly profitable transitional and pioneering product leading the way for further Immunotherapy 2.0 related products targeting chronic diseases.



Part 4: Scottish Commercial and Research



Scottish Academic Research Strengths

- The academic research strength in immunological sciences is well established within the life sciences and medical research departments of the major Scottish universities.
- This strength in depth is somewhat masked by the vagaries of the Research assessment exercise system.
- In 2009, only Glasgow University amongst Scottish institutions submitted its immunology researchers under the “Infection and Immunity” heading.
- The strength of Glasgow University lies in the breadth of coverage across all branches of immunological sciences.
- However, significant research groups also reside in other major centres such as Dundee (cell signalling) Edinburgh (macrophage and T-cell autoimmunity), Veterinary (Moredun) and Aberdeen (Regulatory T cells).
- These specific areas of interest map well onto most of the technology platforms reviewed below as do specialist interest groups in infectious disease and biofilms.

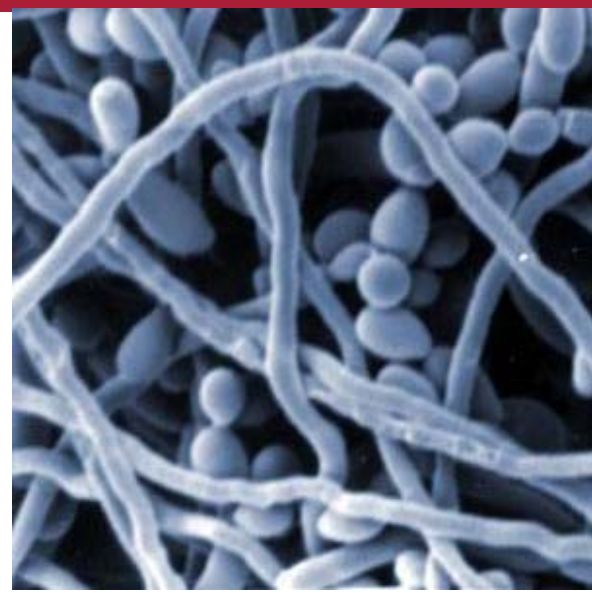
Scottish Infection Research Network (SIRN)

Scottish Infection Research Network

- Launched in August 2007: designed to increase the quality of research and contribute towards the prevention and control of healthcare-associated infections.
- Comprises a formal steering group and an informal network.

Biofilm Research in Scotland

- Dundee University:
  - College of Life Sciences: genetics of bacterial biofilm development
- University of Glasgow:
  - Dental School: biofilms in prosthetic joints, mucosal fungal infections
  - Microbiology: *Candida* biofilms
- Heriot-Watt University: biofilms in marine bacteria.



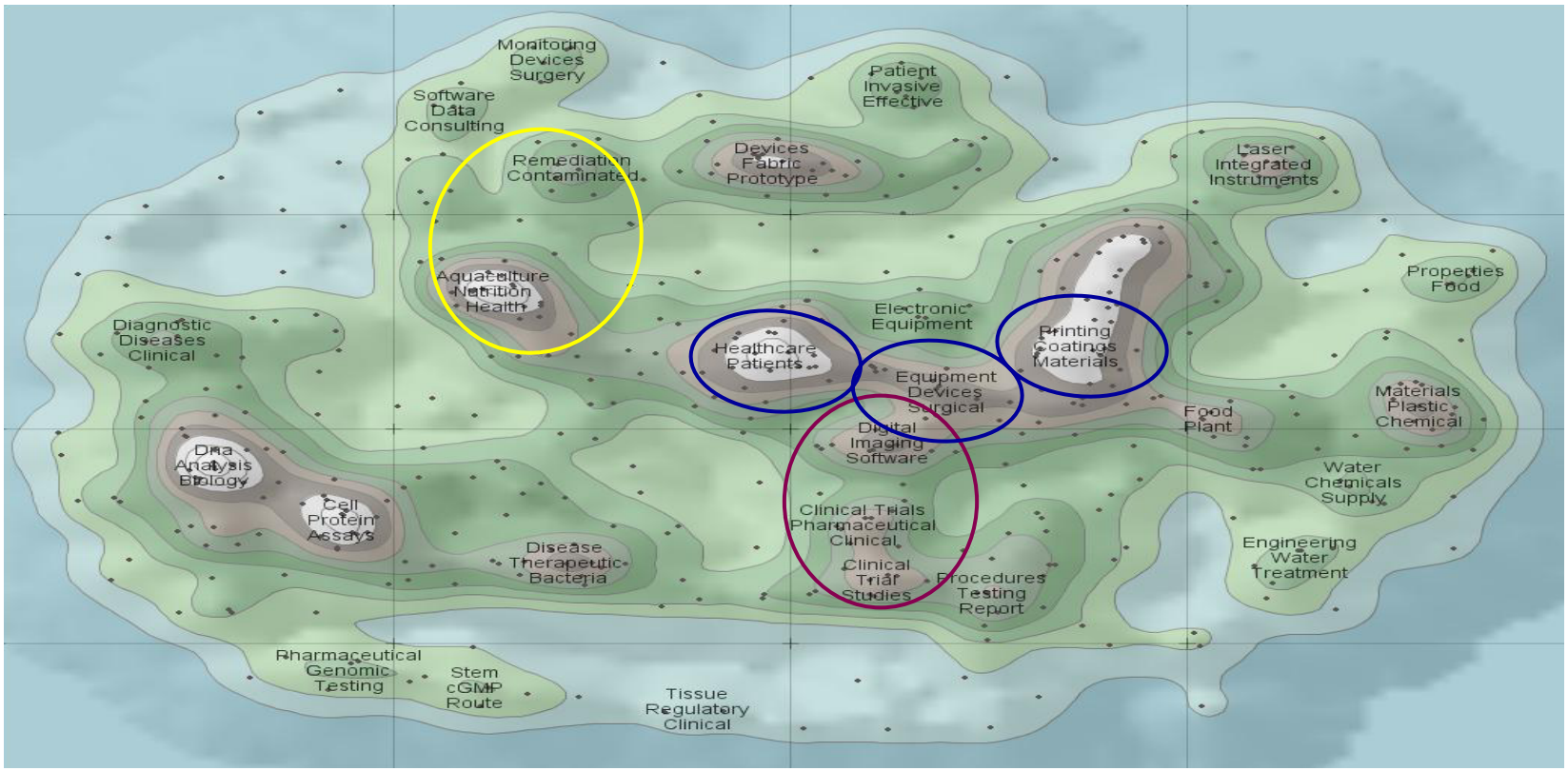
Biofilm structure in *Candida albicans* (EM). Julia M Douglas, University of Glasgow

Scottish Commercial Landscape
Companies with Vaccine/Immunotherapy Interests

- There is a small but robust group of companies in Scotland with interests and capabilities in the vaccine and immunotherapy sector (see next two slides).
- Most of this group are cGMP and CRO companies that provide services supporting the manufacture, testing and trials of vaccines as part of their overall service offering.
- This group of companies includes, among others, Accuro Biologics, Angel Biotech, Bio-Best, Bio-outsource, Diosynth Pharma, Vitrology and Xstalbio,
- In addition to this group of smaller companies, several larger companies (Charles River, Geron and Invitrogen) maintain a presence in Scotland, thus offering a further route to relevant expertise and resources.
- Scotland also has a good academic and commercial structure for supporting clinical trials, in particular in cancer, which is highly relevant to immunotherapy (slide 27).

Reading the Scottish Commercialisation Landscape map

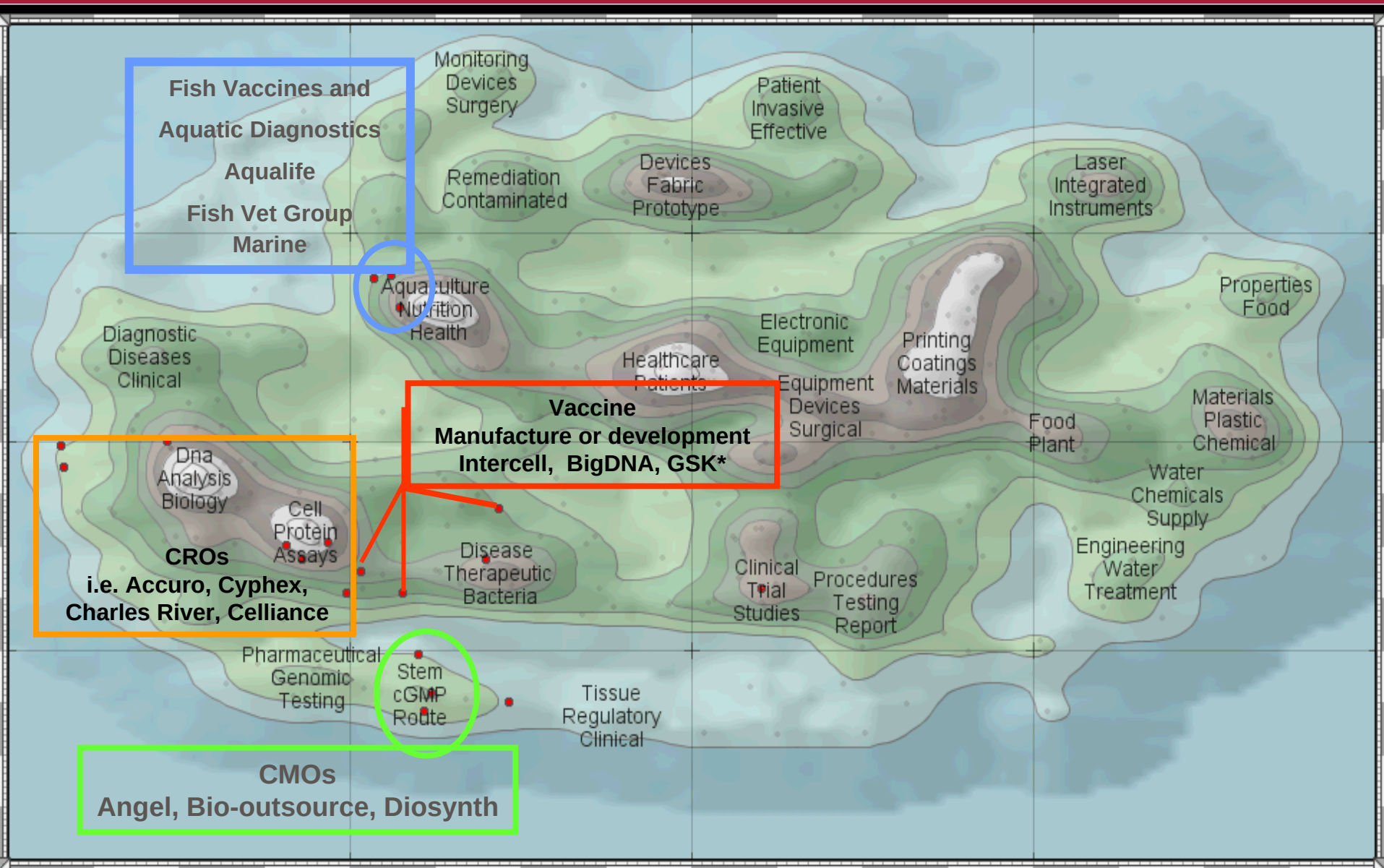
- The landscape is displayed as a series of keyword “mountain tops” and “valleys” with the higher mountains representing the increased frequency of the keyword. Collections of keywords or themes that share common elements are represented geographically close together. Each dot represents a company.



- It is also important to note that those companies serving related markets (e.g. Chemical Sciences) do not appear as separate islands or discrete peaks on the map thus illustrating the synergies across sectors and the potential for novel cross-sector clusters to be generated. In this example groups of related companies operating in the electronics (Blue), clinical (red) and water quality (yellow) sectors are highlighted.

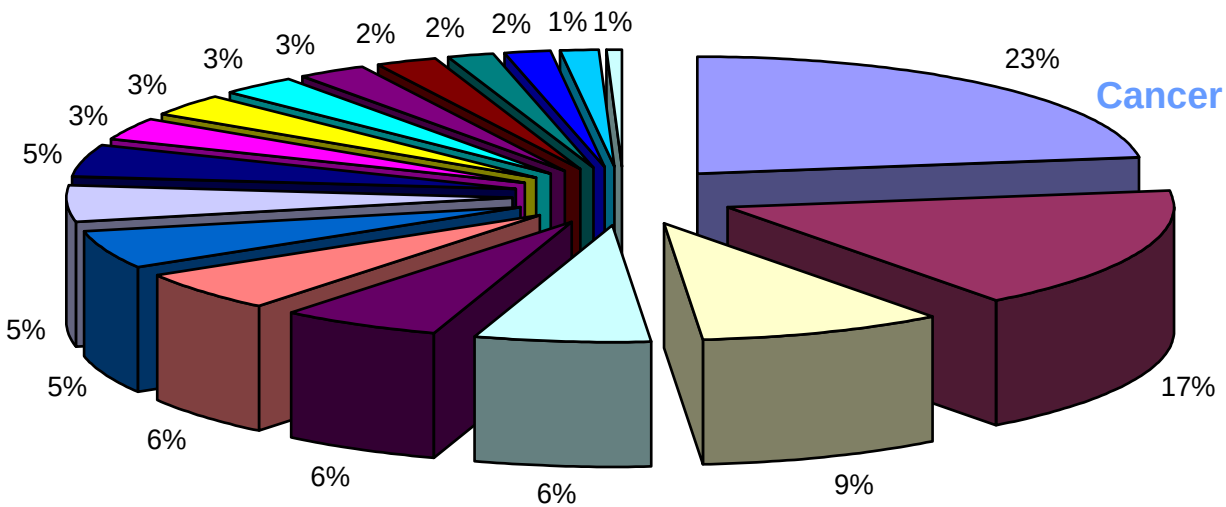
Scottish Commercial Landscape by Activity

Companies operative in Scotland with listed vaccine interests.



Clinical Trials Expertise in Scotland

- Analysis of clinical trials in Scotland shows particular strengths in cancer, cardiovascular and diabetes with additional presence in inflammatory and immune systems.
- This capability is highly applicable to future immunotherapy projects.



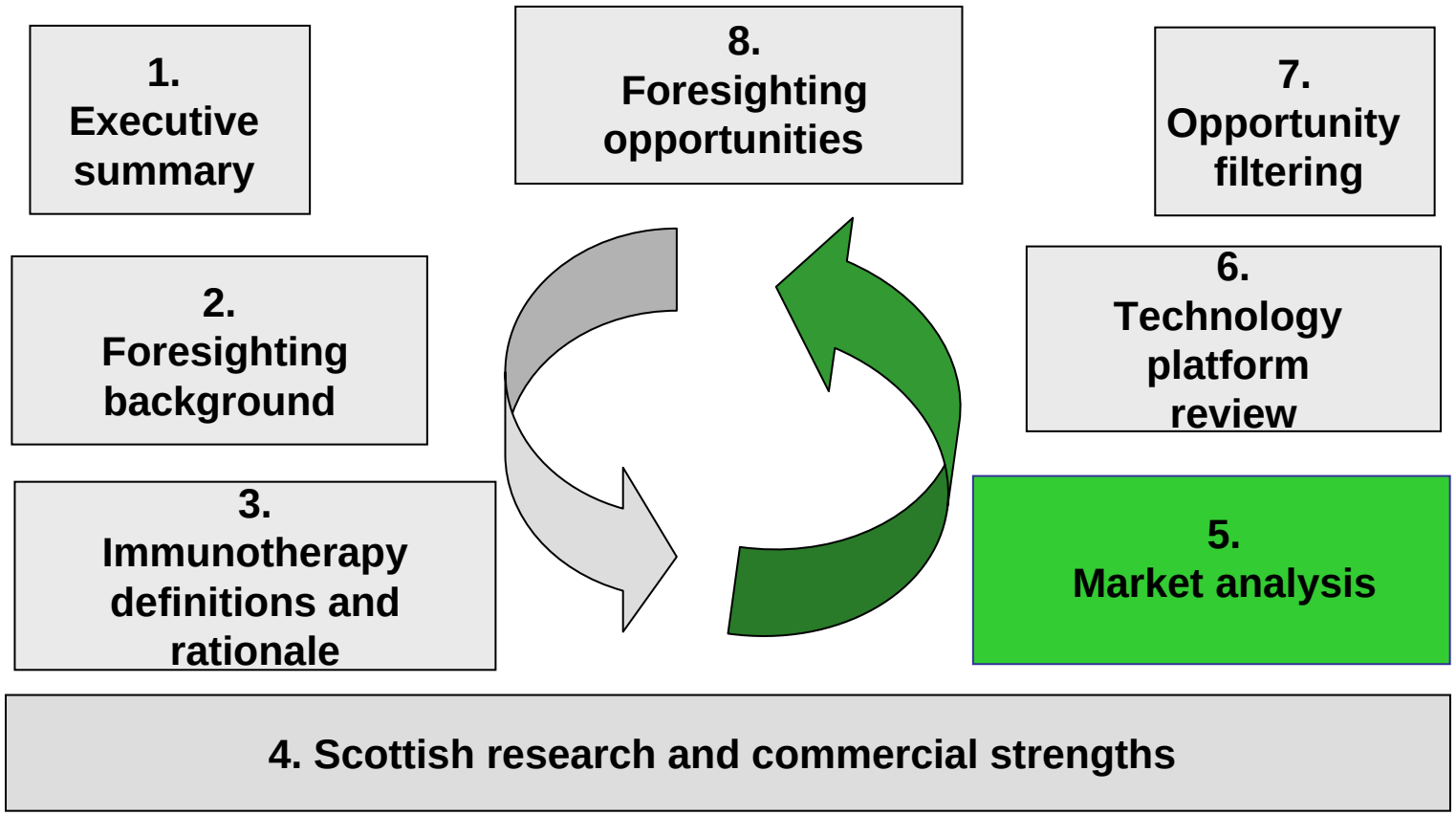
- Cancer
- Cardiovascular
- Metabolic and Endocrine
- Neurological
- Musculoskeletal
- Skin
- Renal and Urogenital
- Oral and Gastrointestinal
- Respiratory
- Blood
- Reproductive Health and Childbirth
- Inflammatory and Immune Systems
- Stroke
- Other
- Infection
- Mental Health
- Eye
- Injuries, Accidents & Congenital

Source: Scottish Enterprise. Commercial clinical trials in Scotland 2004–2006 categorised by UKCRN therapeutic areas according to PI department. 'General health relevance' and 'unclassified' studies not included; 'cardiovascular' might include some studies that could have been classed under 'stroke'

Scottish Commercial Landscape:
Companies with Vaccine/Immunotherapy Interests

- Several companies have the capability of vaccine production or development in Scotland.
- Intercell (Austria) has a significant presence in Livingston. Intercell's plant specialises in Encephalitis vaccines and the company has just launched in the European travellers' market with Novartis. Intercell is regarded as one of the rising players in the industry, particularly in the area of adjuvants.
- GlaxoSmithKline*, one of the five major vaccine companies has a significant specialist chemistry manufacturing site in Irvine.
- BigDNA is an Scottish start-up with a leading position in the exploitation of bacteriophage as a delivery mode for novel vaccines.
- There is a further grouping of CRO and cGMP companies with vaccine development and capability is Scotland.
- A small but important group of companies serves the fish-farming and aquaculture sector such as Aquatic Diagnostics Ltd.
- This small but significant company cluster and capability, strengths provides a commercial foundation for new initiatives in immunotherapy.
- This is strongly complemented by academic research strengths and clinical trials capabilities.

Part 5a: Market Analysis



Purpose of Market Survey

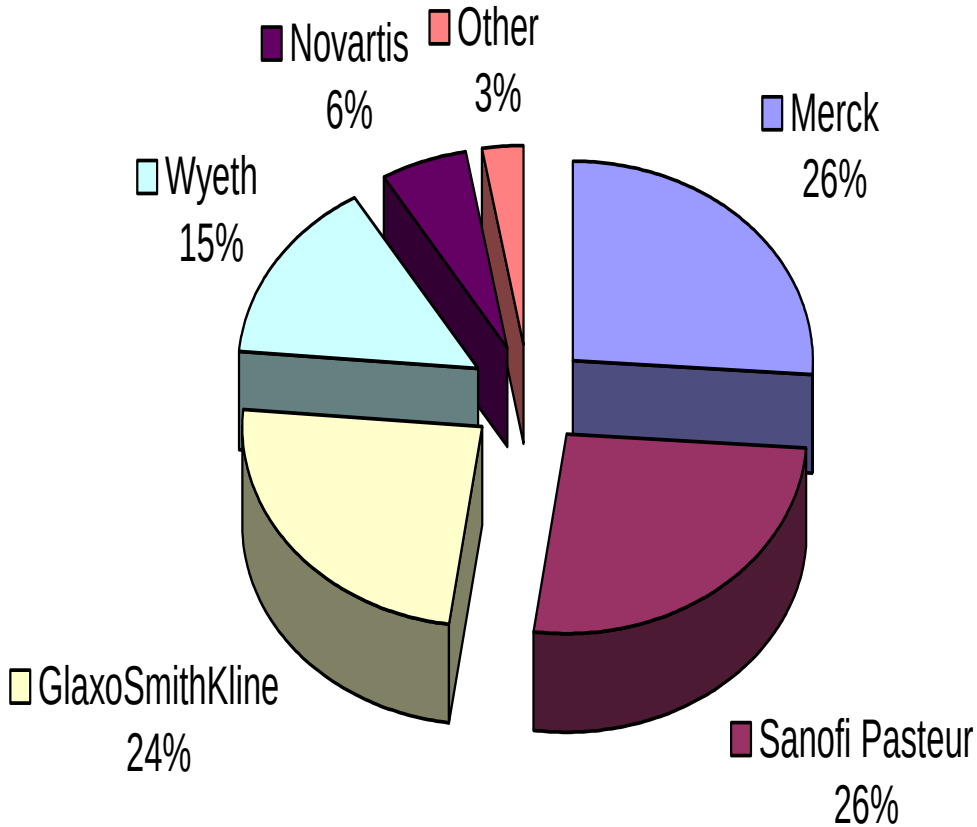
- This section provides some background information on the conventional vaccines market.

- It reviews some of the regulatory and technical risks associated with the vaccines and immunotherapy sectors in general.

- It reviews the potential market for new immunotherapies by a systematic review of therapeutic areas.

Conventional Vaccines Market

- The world vaccines market is dominated by five companies: Merck, GlaxoSmithKline (GSK), Sanofi Pasteur, Wyeth and Novartis.
- The four largest had vaccine sales exceeding $2bn each in 2007.
- It is expected that, by 2012, the vaccines arms of companies like GSK, Sanofi-Aventis, Merck and Wyeth will constitute more than 10% of sales.
- The conventional vaccines market is projected to expand from $10bn (2007) to over $20bn (2012).
- This market growth is driven primarily by new vaccines such as HPV and also extremely rapid growth for conventional vaccines in developing economies.



Vaccines market share 2007 (source: Kalorama)

Company Landscape and primary business roles

Market Tiers	Example Companies	Role
Tier 1 Big Pharma with vaccine divisions	Wyeth (Pfizer), GSK, Sanofi Pasteur, Novartis, Merck	Route to market acquisition Strategic partners
Tier 2 ($0.5 > $5bn) Mid-sized vaccine Mid-sized immunotherapy	Crucell, Acambis, Intercell*, Elan, Dendreon	Acquisition targets Technology license partners
Tier 3 Market cap (<$200 million) Small/start-up VC and private investment immunotherapy	Oncothyreon, Immunocellular Therapeutics, Argos Therapeutics, Nabi Pharmaceuticals, Athera	High risk /high reward Source of innovation Links to basic research institutions

Risk and Regulatory Background

- Vaccines have always been controversial and have aroused suspicion from the earliest days, when widespread resistance to vaccination on the grounds of perceived risk and individual liberty coincided with major campaigns by national governments to eradicate common infectious diseases.

- These issues remain to this day, with widespread distrust of MMR vaccines resulting in reduced vaccination rates. The reduction of so called “herd immunity” results in increasing incidence of measles in both the UK and US.

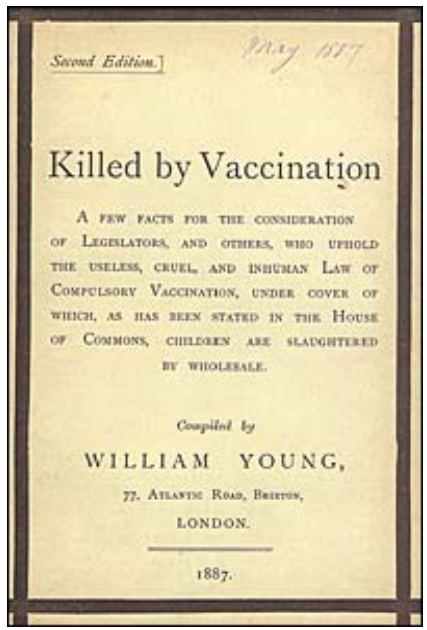
BBC News

Study backs safety of MMR vaccine. A UK study of more than 5,000 children has ruled out any link between the MMR vaccine and autism, researchers say.

The Medical Research Council team could find no evidence of autism associated with the triple vaccine.

The MMR controversy was first sparked after a small-scale study published in *The Lancet* in 1998 by Dr Andrew Wakefield suggested a link.

The new study, appearing in the same journal, follows numerous others disproving any such link.


Second Edition.

May 1887

Killed by Vaccination

A FEW FACTS FOR THE CONSIDERATION OF LEGISLATORS, AND OTHERS, WHO UPHOLD THE USELESS, CRUEL, AND INHUMAN LAW OF COMPULSORY VACCINATION, UNDER COVER OF WHICH, AS HAS BEEN STATED IN THE HOUSE OF COMMONS, CHILDREN ARE SLAUGHTERED BY WHOLESALE.

Compiled by

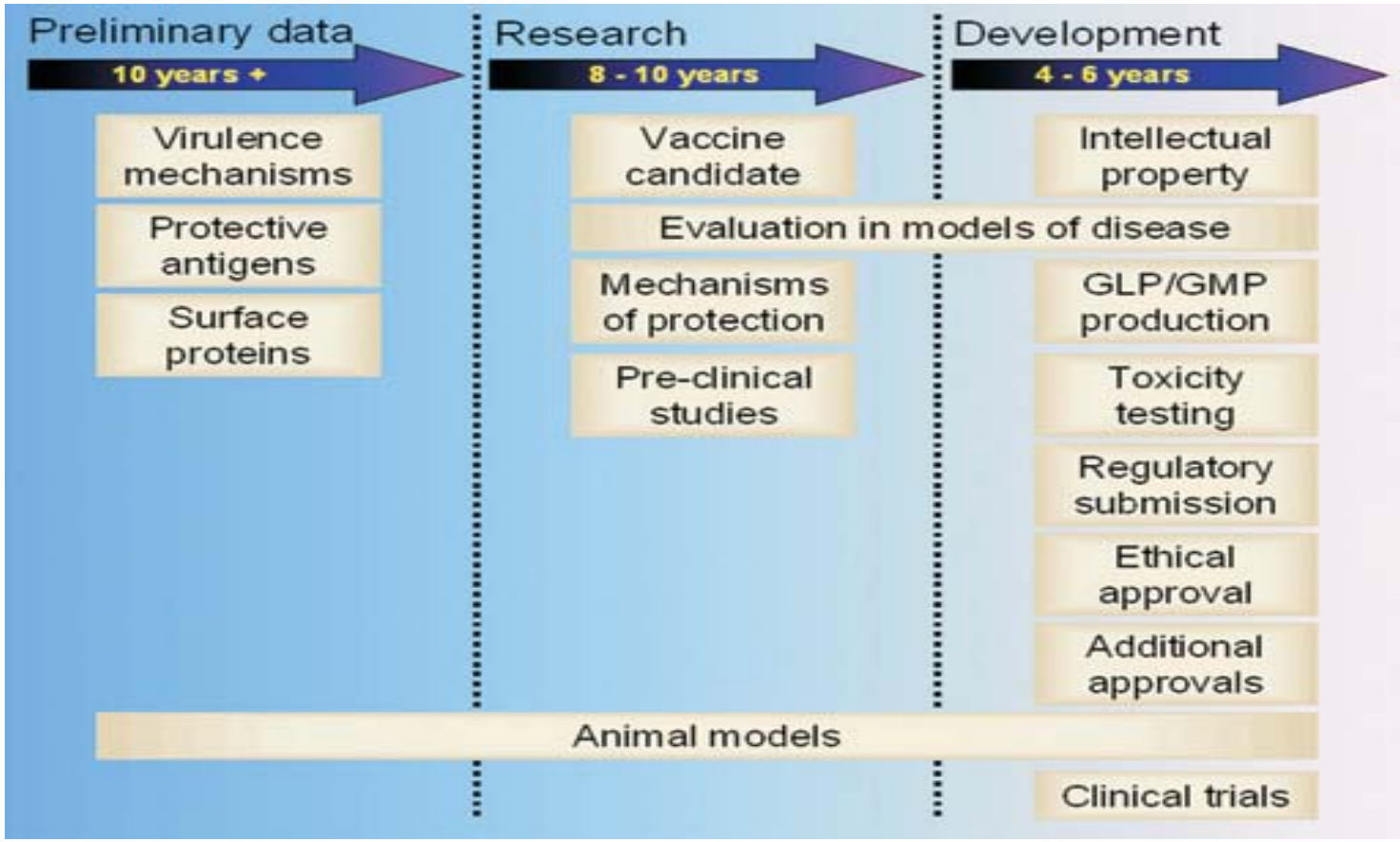
WILLIAM YOUNG,

77, ATLANTIC ROAD, BRIXTON,

LONDON.

1887.

Time to Market: Vaccine Development Cycle



Source: Healy *Microbiologist* (March 2006)

Regulatory Background and Technical Risk: I

- Vaccines remain exceptionally tightly regulated and slow-to-market: the cost is comparable to drugs and is estimated to be between $500 and $800 million.*
- By its very nature, establishing the efficacy of a new prophylactic vaccine requires long-term trials to monitor the altered incidence rates between vaccinated groups and controls.
- Such trials can take considerably longer than clinical trials of drugs, where the clinical end-point and efficacy can generally be determined more quickly.
- As vaccines are largely purchased and delivered under compulsory mandate by national governments and given to a generally healthy recipient there is an intense focus on establishing safety.
- There is a highly conservative approach to new product introduction, as witnessed, for example, by the retention of old adjuvants (such as alum) long after their introduction.
- Modulation of a biological system as important as the immune system can have wide-ranging effects: from tolerable levels of local inflammation to temporary fever to much more serious adverse reactions.
- These effects can be compounded further in those diseases where recipient has a dysfunctional immune system

*Source. Plotkin, S.A. Vaccines: past, present and future. *NatureMedicine* (2005), **11**(4), p. S5-S11.

Regulatory Background and Technical Risk: II
Northwick Park: TeGenero Trial

- The high profile case of TeGenero's immunotherapy TGN1412 and its near fatal effects on healthy volunteers in the Northwick Park Trial (2006) was a landmark study and led to the temporary suspension of all immunotherapy "first in man" studies.

- TGN1412 a CD28 agonist was intended for the treatment of leukemia, multiple sclerosis (MS) and rheumatoid arthritis (RA).

- TGN1412 developed a systemic inflammatory response called a cytokine storm within 90 minutes of infusion was caused by the ligation of CD28 on human cells.

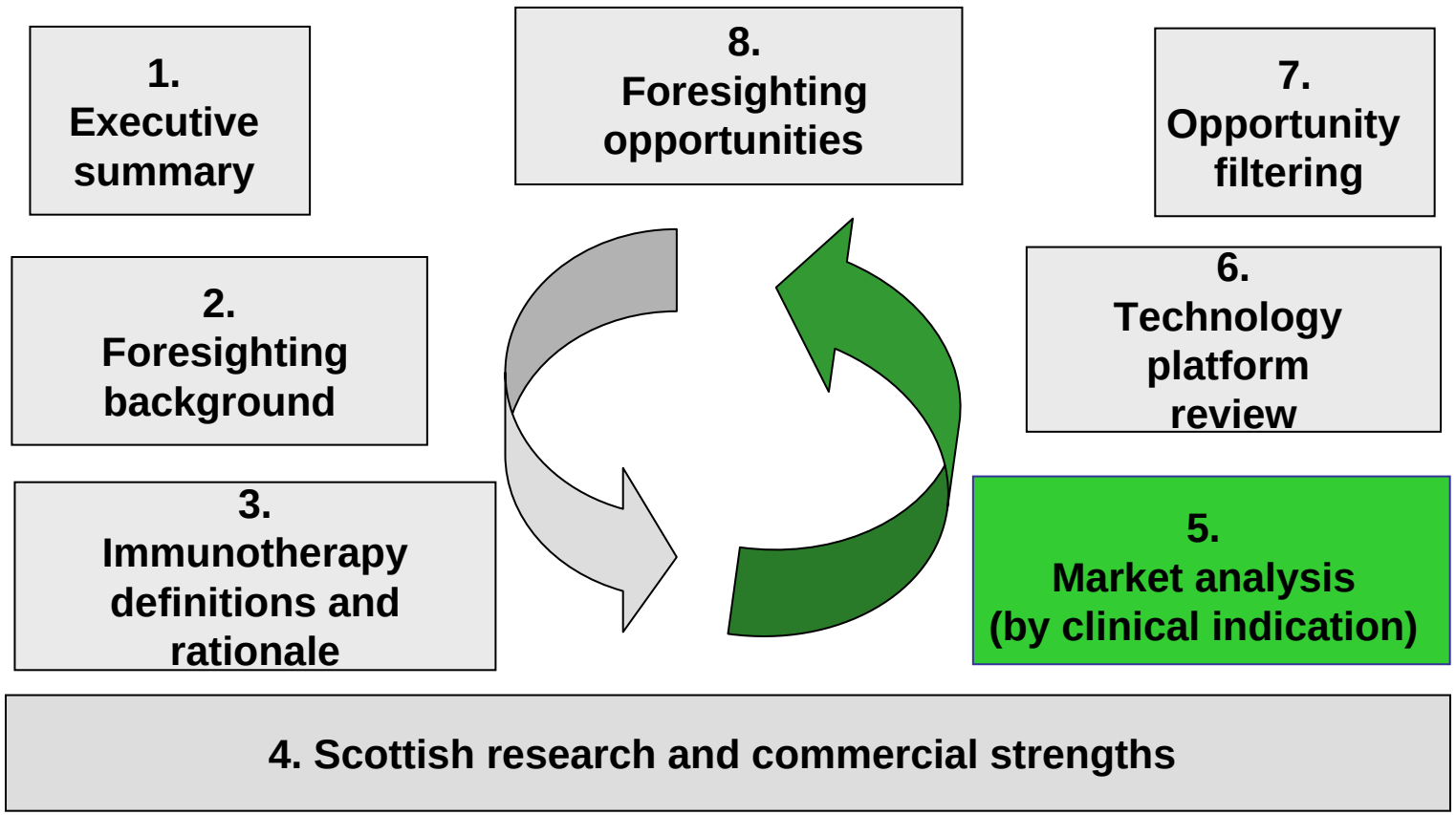
- The study prompted major review of trial and *in vitro* testing guidelines by MHRA, EMEA and other regulatory authorities.

- How to design experiments *in vitro* to predict the effects of a targeted immunotherapeutic *in vivo* remains a fundamental question for drug developers.

Regulatory Background: TeGenero Impact

- The TeGenero trial showed the potential dangers of novel immunotherapy products directed at key newly described immune effector mechanisms. It also highlighted indirectly how specific and powerful such new targeted therapies can be.
- There has been significant attrition at phase III trials of the first wave of therapeutic cancer vaccines directed at tumour markers. This is due primarily to the emergent state of this sector and key gaps in scientific knowledge.
- Nonetheless, steady progress towards new products, such as Provenge a prostate cancer therapy, and increased fundamental knowledge, such as the importance of immune suppression by regulatory T cells in the tumour micro-environment, is highlighting the promise of such new approaches.
- The overall picture is one characteristic of regulatory development in all newly emerging therapeutic fields: a slow, difficult evolution of the field with high-profile events that regulators react to by tightening procedures.
- The overall Clinical and Regulatory risk for new immunotherapies remains to be determined. Humanised monoclonal antibody therapies provide an encouraging model in terms of both regulatory process and successful market acceptance.

Part 5b: Systematic Review of Market Sectors



Market review by clinical indication

- The purpose of this section is to review and briefly summarise key aspects and the estimated potential market of disease that could be treated using immunotherapy.
- We classified diseases potentially treatable by emerging immunotherapy methods into two groups:
  1. conditions requiring potentiation of the immune system: malignancies, infections and other less obvious candidates
  2. conditions requiring inhibition of the immune system: allergies, autoimmune diseases* and other conditions involving chronic inflammation.

**Note*: an autoimmune component is suspected but not proven in many diseases. This report includes only those conditions that are generally agreed to have a significant autoimmune component.

Therapeutic Areas: Review

A. Immune system potentiation

- Adventitious infections
- Healthcare Associated Infections
- Implant Associated Infections
- Cancer
- Hypertension
- Atherosclerosis
- Alzheimer's and other 'foldopathies'
- Substance abuse
- CNS Trauma
- Immunosenescence (thymic shrinkage)
- Infectious disease

B. Immune system inhibition

- Gastro-Intestine allergy
- Airway Allergy
- Skin Allergy
- Transplantation Biology
- Stroke
- Inflammatory Bowel Disease
- Rheumatoid Arthritis
- Psoriasis
- CNS trauma
- Immunosenescence (inflammation)
- Other autoimmune disease

Characteristics of Therapeutic Areas (TAs)

- For each TA, we identified an approximate market size:
  - ‘headline’ numbers were taken from published reports in the US market
  - account was also taken of US patient numbers – annual incidence or prevalence as appropriate
  - market size estimates therefore represent only a rough guide for just this purpose. It is not strictly comparable between disease indications and, without further validation, could not be used at this stage to support financial modelling
- Therapeutic areas were also graded according to our view of “unmet clinical need” which encompassed:
  - absence of a cure for chronic diseases
  - acute conditions with high health or economic impact
  - unsatisfactory current treatment for either type.

Sub-sector Analysis Process

- The relative market opportunities polarise into two categories:
  1. a small group of several very large opportunities associated with common chronic and degenerative diseases, such as major cancers, Alzheimer's, brain trauma all of which are greater than $10 Billion.
  2. a more varied group of other indications which lie in the $1–10bn range.
- For each sub-sector, a brief commentary is attached relating to the opportunity and the relative level of innovation required to develop a new product.
- Where appropriate, specific and potentially relevant platform technologies are identified.
- Where appropriate, selective case studies are described.
- The end point is a short-list of prospective opportunities categorised by unmet clinical need, perceived innovation requirement and market size.

Sub-sector Analysis Process … continued

- A review of the major potential platform technologies and cellular targets relevant to enabling any immunotherapy was carried out in parallel with this market opportunity review.
- The relevance of specific platforms or cell targets, at a very broad level, is captured in the adjacent blue bar inserted in relevant slides in the body of the market survey.
- Listed technologies are of relevance to the particular clinical opportunity under discussion:
  - blue indicates links to traditional vaccine technologies as in Immunotherapy 1.0
  - green indicates links to traditional vaccine technologies as in Immunotherapy 2.0
  - black indicates the relevance of alternative non-immunotherapeutic approaches, such as small molecules, existing therapies or opportunities for better diagnostics
  - greyed-out or deleted titles indicate lack of relevance.

Relevant platforms

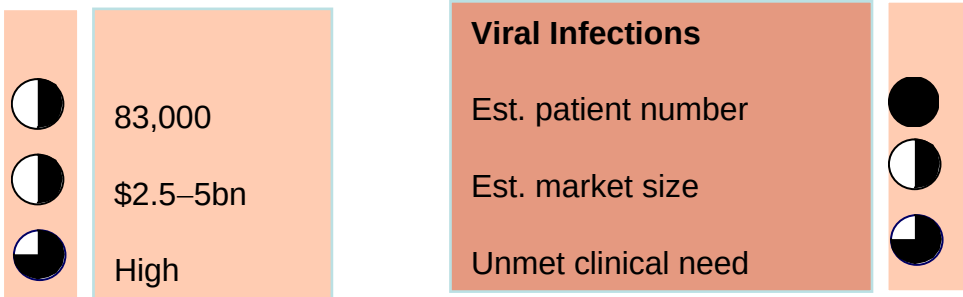
- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - *Dendritic cells*
  - *T-reg cells*
  - *Other T cells*
  - *B cells*
  - *NK cells*
  - *Microglial cells*
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Diseases treated by Immune Potentiation

- Adventitious infections
- Healthcare Associated Infections
- Implant Associated Infections
- Cancer
- Hypertension
- Atherosclerosis
- Alzheimer's and other 'foldopathies'
- Substance abuse
- CNS Trauma
- Immunosenescence (thymic shrinkage)

Fungal and viral Infections

Fungal Infection		Viral Infections	
Est. patient number	83,000	Est. patient number	>1 million
Est. market size	$2.5–5bn	Est. market size	$2.5–5bn
Unmet clinical need	High	Unmet clinical need	High



- Treating adventitious fungal and viral infections represents a significant growing niche market with clear unmet need where current methods are ineffective.
- A common example is invasive aspergillosis in patients with leukaemia, especially those undergoing stem-cell transplants.
- A major technical challenge is that many of these patients are immuno-suppressed.
- There is also a growing market for treatments of adventitious viral infections in immuno-compromised patients, especially stem-cell patients.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Healthcare-associated Infections (HAIs)

Healthcare-associated infections (all)		
Est. patient number		2,100,000
Est. market size		$5.5–11.0bn
Unmet clinical need		High

Implant-associated infections		
Est. patient number		1,000,000
Est. market size		$3.6–6.0bn
Unmet clinical need		High and growing

- HAIs are a recognised source of concern in advanced healthcare systems; implant-associated infections account for a high proportion of the cost of treatment for HAI's.
- HAIs constitute a significant risk to patients and, by extending stay in hospital, represent an increasing drain on resources.
- The increasing emergence of multiple antibiotic resistance within bacteria such as *Clostridium difficile* reduces efficacy of the main therapeutic option, namely antibiotics.
- This has prompted a return to traditional public measures, such as increasing hygiene measures in wards via sprays and hand washing, which has been partially effective.

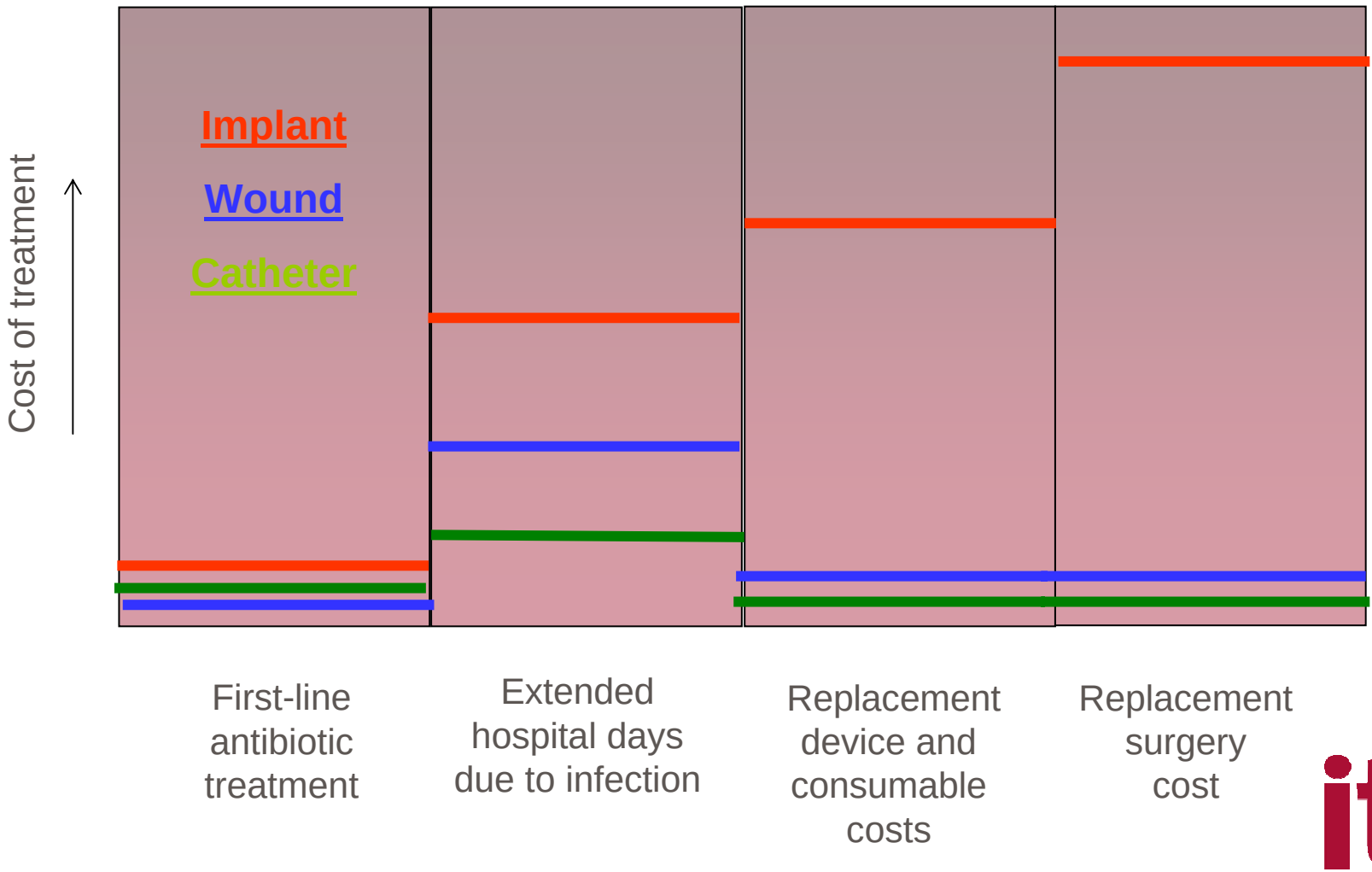
Healthcare-associated Infections (HAIs) … continued

- This combination of increased rates of bacterial infection and reduced antibacterial resistance opens up a classic opportunity for conventional vaccines.
- However, this is complicated by the fact that HAIs are caused by a broad spectrum of microbes, the specific treatment of which varies according to the type of treatment, wound, catheter infection or implant and immune status of patient.
- This general market opportunity is beginning to be addressed by vaccine companies (e.g. Acambis) developing traditional vaccine against specific HAI-associated infections.
- However, a universal prophylactic pre-surgery vaccine would most likely need to be a cocktail vaccine against several leading organisms.
- It will take some time to identify relevant strains of bacteria, develop a cocktail and prove its safety and efficacy.
- The generally elderly demographic for such therapies will impose additional challenges for clinical trials.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Hospital-acquired Infections (HAIs): Indicative Segregation by Cost



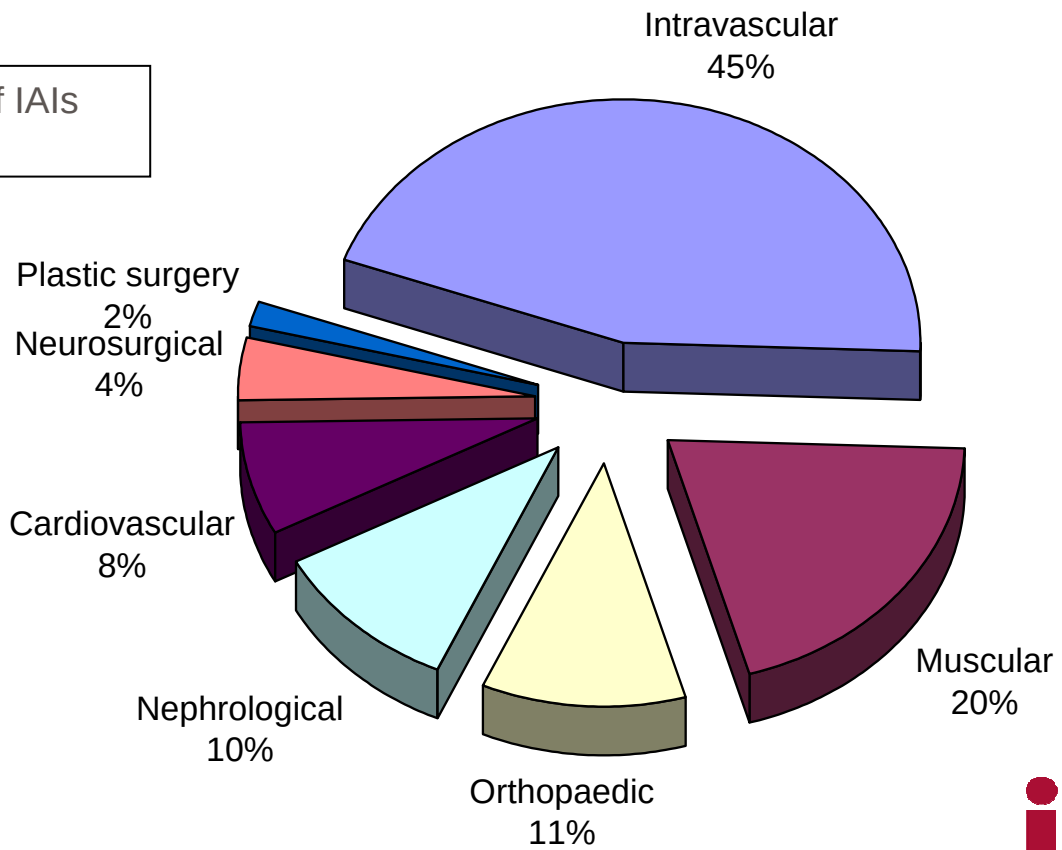
Implant-associated Infections (IAIs)

- The leading source of costs is the “intravascular” category – mostly venous and arterial catheters – these procedures are too short term for immunotherapy to be relevant (see slide 48) :
  - dialysis and urinary catheters are in the “nephrological” category
  - “muscular” (hernia meshes) and “orthopaedic” (spinal, joint and fracture implants) are sizeable opportunities.
- Prophylaxis is currently achieved by sterile technique and careful sterilization of the implant:
  - the presence of foreign material greatly increases the risk of infection
  - prophylactic antibiotics can be given at the time of implant.
- Future methods being developed include:
  - implants made of material that exudes antibiotics, either as a peri-operative bolus or long-term elution
  - coating the implant with biologicals or other substances designed to enhance natural mechanisms of fighting infection.

Implant-associated Infections (IAIs)

- A rough calculation shows annual costs of IAIs could be as much as $4.7bn in the US ($11.9bn worldwide).

Breakdown of cost of IAIs (US)



Implant-associated Infections

- There are two main factors which determine the size of this market, an increasing demand for surgery and post operative infection rates
  - There is a long term and general increase in the number of implant associated surgeries due to an ageing population.
  - longer lifespan requires repeated replacement of (for example) hip implants for reasons of wear again leading to increased cases of revisional surgery and opportunity for infection.
  - Obesity in the developed world increases musculoskeletal stress and therefore increases both requirements for implants and failure rates once installed. Surgical replacement is comparable cost to the original implant procedure.
  - Increasing sophistication and personalization of implants increases cost of replacement.
  - Reported Implant infection rates vary from
    - 2% for the orthopaedic, urological and plastic surgery sectors.
    - 3.5% for high value cardiovascular implants.
    - 15% for neurological implants.

Implant-associated Infections

- Typical implants (orthopaedic and cardiac) are a high-value market as they:
  - have high value in terms of cost and clinical impact
  - carry a very high surgical delivery cost
  - generate even higher replacement implant and surgery cost and increased morbidity if subject to intractable infection
  - are often difficult to diagnose.
- Treatment by conventional means is difficult because of antibiotic resistance and the biofilm nature of infection on the implant surface. This is compounded by a poor immune response at the non-vascularised surface of the implant.
- Novel interventions could be directed at the patient's immune system (adaptive or innate), the infectious organism itself, the implant surface or some combination of these.
- Any effective intervention, including prophylactic vaccines, could command a significant price given the high cost of implant failure.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Cancer: Market Estimates of the Four Major Cancers

Cancer	*Breast*	*Lung*	*Colon*	*Prostate*
Est. patient number	184,000	215,000	108,000	186,000
Est. market size	$1.8–7.0bn	$9.6bn	$8.4bn	$3.4bn
Unmet clinical need	High	High	High	High

- The overall market for innovative cancer therapies is forecast to grow significantly over the next 5 years, increasing from $22.0bn in 2006 to $47.3bn in 2011.*
- There is already a strong and increasing acceptance of novel therapeutics derived from exploiting and manipulating the immune system:
  - monoclonal cancer therapies account for approximately half of all cancer therapeutics by value and are currently the fastest growing market segment. Projected sales (2007) were $1bn, driven by products such as Rituxan, Avastin, Humira and Erbitux
  - newly launched anti-HPV vaccines, (e.g. Gardasil) which protect against cervical cancer, have rapidly established themselves as blockbuster cancer vaccine products
  - after years of research and failed trials, new therapeutic anti-cancer vaccines, led by Sipuleucel, are beginning to emerge successfully through the trials and FDA approval process.

*Source: The cancer vaccine roller coaster *Nat. Biotech.* (2009), **27**, 129-139

Future technology drivers for cancer immunotherapy

- The recent and rapid increase in fundamental knowledge of immune system function and targets, in particular of regulatory T (T-reg) cells, will open up a whole new set of immunotherapy targets accessible to:
  - new generations of monoclonal therapies
  - novel small molecules
  - RNA-based interventions
  - new therapeutic vaccines including novel adjuvants.
- The ability to identify, isolate and manipulate immune cells, T cells and others such as dendritic cells will increasingly be used to develop cell-based therapies for cancer.
- This will synergise strongly with recent breakthroughs in T-cell receptor technologies, which ultimately may have the potential to rival monoclonals as a new therapeutic platform technology.
- The huge success of HPV vaccines, and the more recent successful progress of Sipuleucel and other therapeutic vaccines, will change perception of the business and regulatory risks associated with cancer immunotherapy and vaccines.

Cancer: Vaccines in Late-stage Trials

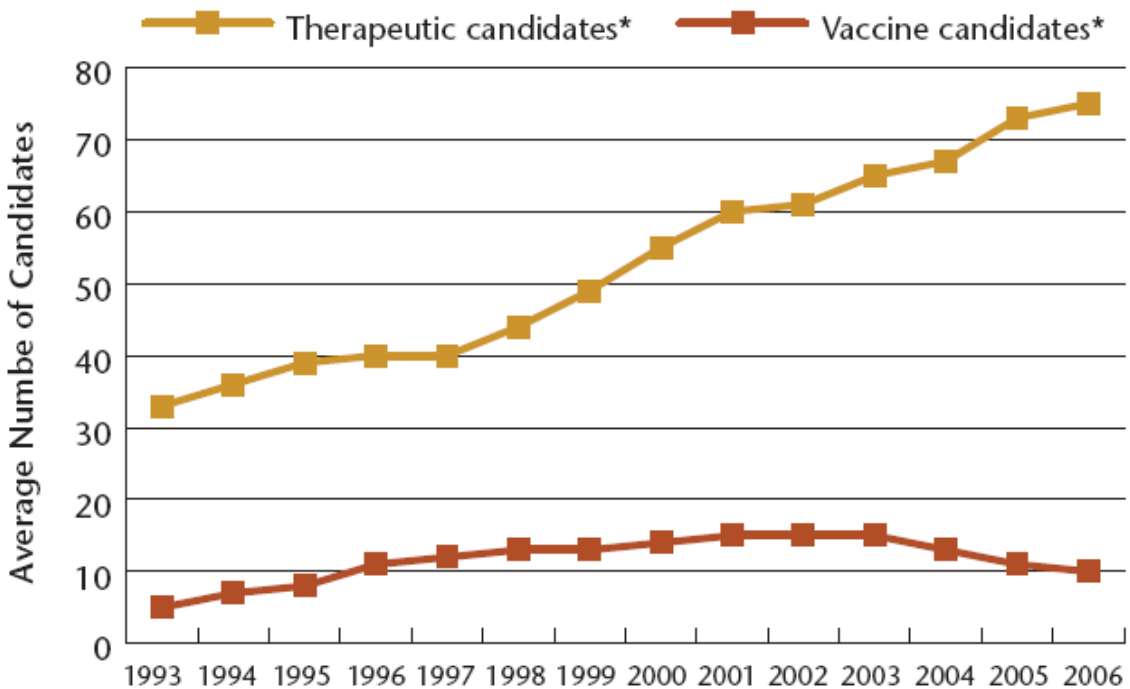
- A recent review charted the competitive landscape in cancer vaccines.*
- It described 28 cancer vaccines in late clinical trials (phase II or III) from 23 companies.

Type	Vaccines in late clinical trials	Companies	Indication B L C P	Indication: other
Whole-cell-based autologous cells (personalised)	11	8	1 1 1 2	Melanoma (2), AML, bladder, glioblastoma, ovarian, leukaemia
Whole-cell-based allogeneic tumour cells (off-the-shelf)	4	3	- 1 - 1	Pancreatic, leukaemia
Unique antigen-based (personalised): purified peptide or protein	2	2	- - - -	Glioma, renal, mantle-cell carcinoma, Hodgkin's lymphoma
Shared antigen (off-the-shelf) purified protein or peptide	11	10	2 3 1 -	Melanoma (2), glioblastoma, pancreatic, renal

*Source: The cancer vaccine roller coaster *Nat. Biotech.* (2009), **27**, 129-139

Cancer: Therapeutic Vaccines and Therapies

- The effectiveness of monoclonal antibodies accounts for much of the recent growth in new cancer therapeutic candidates.
- This may account in part for the tailing off of novel cancer vaccines trials which have reduced in recent years.

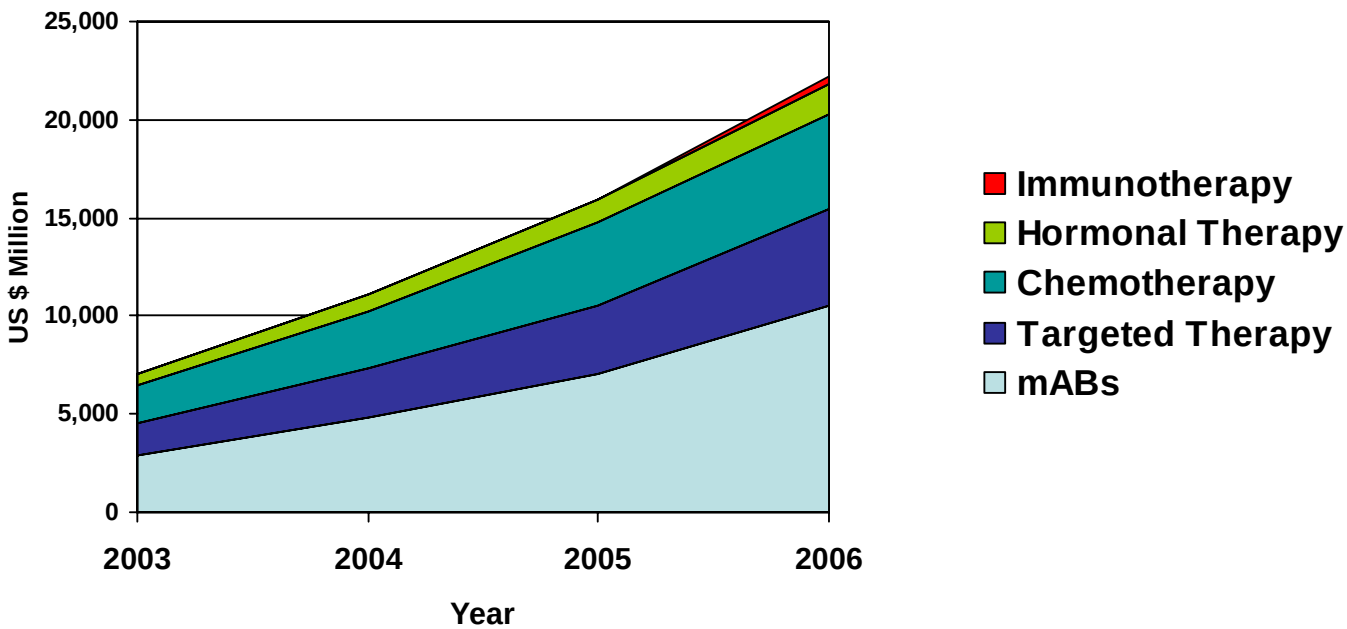


* 4-year moving average

Source: Tufts Center for the Study of Drug Development

Growth in the Cancer Therapy Market (US)

- Monoclonal antibody derived therapies are now single largest category of cancer therapies, making up around 50% of sales.
- Immunotherapy sales are just beginning to register in this market.



Source : Frost and Sullivan

Case Study: Dendreon's Prostate Cancer Vaccine

- US scientists have determined that Sipuleucel-T, a prostate cancer immunotherapy drug, significantly prolongs survival in men with advanced prostate cancer (metastatic, hormone-resistant prostate cancer; HRPC).
- A phase III trial showed that Sipuleucel-T (Provenge) improved survival in men with metastatic disease.
- The Seattle-based Dendreon Corp., claims that, compared with placebo, sipuleucel-T extends median survival by 4.1 months and improves 3-year survival by 38%.
- This is a whole cell-based, patient-specific therapy induced by incubation of dendritic cells and antigen-presenting cells with fusion of protein of prostatic acid phosphatase and GM-CSF.
- The therapy breaks tolerance to prostatic acid phosphatases.
- It is a landmark study, being the first active cellular immunotherapy shown in a phase III clinical trial to benefit patients.
- Potential leading product in opening up therapeutic cancer market.

Cancer: Summary

- Immunotherapy approaches to cancer are many and varied:
  - currently dominated by a pipeline of biologicals (mABs)
  - numerous “cancer vaccines” in late trials.

- To date most cancer therapeutic vaccine trials have concentrated on established disease, where potential effectiveness is limited by late stage of disease and results highly sensitive to clinical endpoint chose for the trial.
- *“Well over 50% of common cancers can be treated into a state of minimal residual disease. What we lose patients to … is the inability to eliminate that residual component”* (Levitsky*)
- It is increasingly recognised that current trials and industry that focus on such late-stage established cancers are missing a major long-term opportunity: namely technologies that monitor and eliminate **minimal residual disease**.
- This represents a strategic unmet clinical need and commercial opportunity for new technologies and trial design.

Source : *Goldman, Nature Biotechnology 27, 129 - 139 (2009)

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Hypertension

Hypertension		
Est. patient number		~85,000,000 [P]
Est. market size		$54bn
Unmet clinical need		High

- Hypertension is one of the largest and most profitable markets in the worldwide pharmaceutical sector with sales of $52bn (2007):
  - dominated by angiotensin II blockers (ARBs), calcium-channel blockers (CCB), ACE inhibitors and β-blockers
  - Norvasc is a CCB and the largest-selling single drug in this category.
- The main advantage of the vaccine approach is that it could removes the need for frequent doses of drugs for life as most therapeutic compounds have a half-life of less than 24hrs.
- This half-life limitation inherent in existing methods, coupled with failures in compliance, results in sub-optimal control of blood pressure in approximately 25% of patients.
- Vaccine trials directed against angiotensin II have shown safety and are well tolerated.

Hypertension – Cytos Biotechnology AG

- Cytos is the market leader in hypertension vaccine approaches directed against angiotensin II targets.
- In March 2009 it suffered a setback in the development of its hypertension vaccine CYT006-AngQb leading to a re-structuring of activity.
- The study was a double-blind, placebo-controlled clinical trial in 69 patients with mild-to-moderate hypertension designed to explore the safety, tolerability and efficacy of a modified treatment regimen.
- The study results showed that the vaccine was safe and well tolerated, but the new treatment regimen failed to induce a significant reduction of the ambulatory blood pressure.
- The company is analysing the data in detail to understand the reasons for this negative outcome, particularly in the light of an earlier phase IIa trial that showed a clinically relevant and significant reduction of blood pressure.

Source: www.cytos.com

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
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  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Atherosclerosis

Atherosclerosis		
Est. patient number		14,000,000 [P]
Est. market size		$15bn
Unmet clinical need		High

- Atherosclerosis involves chronic inflammation in the walls of arteries, and is associated with the accumulation of macrophages and low-density lipoproteins (LDLs), leading to the formation of multiple plaques within the arteries. Atherosclerotic plaques may eventually result in heart attacks or stroke due to obstruction of the blood supply.

- Atherosclerosis may continue at a sub-clinical level for decades before resulting, without warning, in a life-changing event such as stroke or heart attack. Therefore, methods to diagnose sub-clinical atherosclerosis and to prevent its progression to the point at which the risk of a fatal or crippling event is increased would be a major advance.

- The mechanism by which plaques form is believed to be the result of LDLs being oxidised by oxygen free radicals, which then damage the artery wall. Repair of artery wall damage involves recruitment of macrophages to absorb the oxidised LDL.

Atherosclerosis …vaccines

- The various approaches to developing an atherosclerosis prophylactic vaccine have each been directed against specific steps in the development of the plaques. These have included targeting:
  - cholesterol transfer enzyme proteins (CTEP) to modulate HDL/LDL balance and inhibit formation of the plaques.
  - Microsomal triglyceride transfer protein (MTP)
  - ApoB1000 and other inflammatory epitopes that are involved in initiating or maintaining the inflammatory response, which is a key element in plaque formation.
- Although there has been some success in animal models, these approaches are still at a very early stage of development and the latter approach will be dependent on advances in understanding more fully the activity of natural regulator T cells in plaques.
- The two companies most active in this sector have been Avant Immunotherapeutics and Aegerion Pharmaceuticals with phase 2 clinical trials completed.

Atherosclerosis … continued

- Immunotherapeutic approaches to the modulation of atherosclerosis have been reported to show promise in animal models.
- T lymphocytes appear to enhance inflammation in atherosclerotic plaques and are thought to contribute to atherosclerotic lesion progression, and it seems that regulatory T cells are important in limiting pro-atherogenic T-cell responses.
- Full understanding of how pro-atherogenic T cells are activated and regulated might lead to therapies based on T cell modulation.
- It seems that both pathogenic effector T-cell responses and regulatory T cells are influenced by similar sets of co-stimulators and co-inhibitors, which may complicate the development of immunotherapeutic approaches for atherosclerotic disease.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Neurodegenerative disorders
(‘foldopathies’ pathologies due to protein misfolding)

Alzheimer’s disease		
Est. patient number		400,000
Est. market size		$76bn
Unmet clinical need		High

Creuzfeldt–Jakob disease (CJD)		
Est. patient number		3
Est. market size	??	N/A
Unmet clinical need	??	High and growing

- Protection of patients, especially the elderly, from the effects of Alzheimer’s disease (AD) would have widespread social and health benefits.
- The high cost of care for AD creates an attractive market for a therapy; other foldopathies also have unmet needs for therapy.
- Antibodies against the AD protein tangles have bad side effects in humans and it is likely that a more sophisticated approach is needed – as well as a solution to getting antibodies across the blood–brain barrier.

Competitive R&D Field: Alzheimer's Vaccines: Selected Companies with Trials

- Elan Pharmaceuticals is market leader:
  - first preclinical vaccine was halted due to recipients developing meningo-encephalitis due to aberrant cytotoxic T cells
  - follow-up study (Southampton University) showed clearance of amyloid plaques
  - new formulated vaccine ACC-001 developed to minimise toxicity underway along with humanised antibody based treatment
  - Johnston &Johnston (through a newly formed company) will acquire all the assets and rights of Elan related to its Alzheimer's Immunotherapy Program investing $1bn.
- GSK also has vaccine development activity in this areas using a novel adjuvant Protollin, a proteosome-based adjuvant composed of purified outer membrane proteins of *Neisseria meningitidis* and lipopolysaccharide with glatiramer acetate.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
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  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Substance Abuse

Nicotine		
Est. patient number		44,500,000 [P]
Est. market size		$5bn?
Unmet clinical need		Low–medium

Banned drugs		
Est. patient number		170,000–1,000,000
Est. market size		$0.2–1.0bn
Unmet clinical need		High

- Vaccination to help reduce dependency on nicotine or drugs of abuse would have obvious attractions potentially replacing or complementing more expensive, and only partially effective, replacement treatments (e.g. nicotine patches, methadone) and behavioural modification treatments.
- Current immunotherapy approaches rely on antibodies that bind the drug and stop it crossing the blood–brain barrier.
- Several companies most notably Cyto Biotechnology, Nabi Biotechnology and Celtic Pharma working on this type of treatments with Phase 1 &2 clinical trial.
- Assuming the approach works each will address a large market.

Case Study: First Smoking Cessation Vaccine to Market?

- Nabi Biopharmaceuticals (Nasdaq: NABI) announced it has reached agreement with the US FDA on a Special Protocol Assessment (SPA) for a pivotal phase III clinical trial of NicVAX(r) (nicotine conjugate vaccine).
- NicVAX(r) is designed to stimulate the immune system to produce antibodies that bind to nicotine. A nicotine molecule attached to an antibody is too large to cross the blood–brain barrier.
- NicVAX(r) blocks nicotine from reaching its receptors in the brain and prevents the highly addictive pleasure sensation experienced by smokers and users of nicotine products.
- Anti-nicotine antibodies act as a mechanism to help quit smoking in the short and long terms to avoid relapse.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
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  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Immunosenescence

Market comment
Declining effectiveness of the immune system with age could contribute to the development of a number of indications that occur more frequently in old age – hence the “cost” could be vast, although by the same token it is impossible to estimate until the effect is characterised more fully.

- Ageing causes changes in the immune system, which in general make it less effective.
- Therapies designed to slow down or reverse these changes could have beneficial effects on rates of disease in the elderly.
- But the ramifications of interventions designed to support immune function in old age are unknown: a naïve approach could easily backfire.
- Despite the highly favourable demographics, this market is likely to be difficult to enter technically as understanding is rudimentary.

CNS Trauma

CNS trauma		*Stroke*		*Spinal cord injury*		*Traumatic brain injury (TBI)*
Est. patient number		500–700,000		11,000		1,500,000
Est. market size		$3.6bn		$10 bn		$56.3bn
Unmet clinical need		High		High		High

- Acute CNS trauma and ischaemic events in the brain (such as strokes) are accompanied by local activation of immune system cells – called microglial cells – making it possible that immunotherapy could be used to limit neuronal damage.
- However, neuronal damage occurs rapidly following trauma or stroke, and immunotherapeutic approaches probably would almost certainly have to be rapid-acting to be of use in CNS trauma indications.
- No good treatments are available: the cost per patient is high.
- Immunotherapy might have limitations in the treatment of traumatic brain injury (TBI) and stroke, in which rapid onset of action is required.

Relevant platforms

- Prophylactic vaccines
- Adjuvants
- *Therapeutic vaccines*
- *Monoclonals*
- ***New biologics***
- ***Cell therapy***
  - *Dendritic cells*
  - *T-reg cells*
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- Novel antibiotics
- **Diagnostics**
- **Small molecules**

Immune Inhibition

Allergy & Autoimmune Disease

Allergies and Autoimmune Disease

- This group of diseases represents a continuum of essentially inappropriately severe immune response directed against common environmental agents (allergens) or – more seriously – against markers of the host cells.
- Allergies are commonly mediated by an IgE response on mucosal surfaces exposed to the air (skin, eyes, nose throat and lung) or the gut (food allergies).
- Autoimmune disease can be directed at any tissue in the body and can be initiated and maintained by dysfunction in the cellular and humoral arms of the immune response; the influence of regulatory T cells is becoming increasingly implicated.
- Given the breadth of mechanisms in these diseases, and the centrality of regaining immune suppression, a wide range of potential platform technologies can be deployed, particularly in autoimmune disease.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
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Allergic Disease

- Allergic diseases such as asthma, rhinitis and eczema are increasing in prevalence and are reported to affect 15–25% of the population in countries such as the UK and the US.
- Specific immunotherapy is said to be potentially beneficial in treating allergic rhinitis, mild to moderate asthma, and anaphylaxis caused by bee and wasp venom.
- Advantages of specific immunotherapy: long-term, antigen-specific, protective immune effect. It is the only treatment that offers the possibility of reducing the risk of asthma development in children with allergic rhinitis.
- Disadvantages of specific immunotherapy: potentially severe side effects, which have precluded its widespread use.

Summary: Allergies – GI Tract

Food allergies including EGIDs		
Est. patient number		12,000,000 [P]
Est. market size		$3.9bn
Unmet clinical need		Medium

- The GI tract is continually exposed to foreign proteins in the diet. The majority of these are tolerated through suppression of cellular or humoral responses (a process known as oral tolerance).
- However, in approximately 6% of children and 4% of adults in the US, tolerance to a given dietary antigen either is not established or breaks down, resulting in food hypersensitivity, which may induce life-threatening reactions.
- In the US, food-induced anaphylaxis is said to be the most common reason for anaphylactic reactions seen in the emergency department. At present, avoidance of the allergenic food is the only method of preventing such reactions:
  - the (US) market for food-allergy and intolerance products is expected to reach $3.9bn in 2009 (Source: Packaged Facts)
  - the market for gluten-free foods and drinks is expected to hit $1.3bn by 2010, up from $700 million in 2006 (Source: Mintel).

Allergies: GI Tract – EGIDs

- The EGIDs (Eosinophilia-related GastroIntestinal Disorders) are a spectrum of inflammatory diseases characterised by GI symptoms and eosinophilic infiltration of the GI tract. Immune-mediated reactions to food allergens appear to drive the inflammation in a sub-set of patients.
- There are currently no EU/US medications specifically approved for use in EGIDs, which is a major obstacle in the care of these patients and highlights the need for new therapeutic approaches.
- Proposed immunotherapeutic approaches include antibody approaches, namely monoclonal antibodies against anti-IgE (omalizumab) and anti-IL-5 (SCH55700/reslizumab and mepolizumab).
- Similarities between the pathogenesis of asthma and atopic dermatitis and the pathogenesis of EGIDs imply that biologic therapeutics suggested for asthma management (see below) might have potential in EGID immunotherapy.
- Further understanding of the early events in EGID pathogenesis is needed to support the development of preventive and disease treatments.

Allergies: GI Tract … continued

- Development of oral tolerance appears to involve various antigen-presenting cells, including dendritic cells, signalling by regulatory T cells and deletion of lymphocytes.
- Increased understanding of these mechanisms may shift the focus of food allergy treatment and prevention toward induction of tolerance.
- Immunotherapeutic options currently under investigation include:
  - anti-IgE therapy
  - peptide immunotherapy
  - mutated protein immunotherapy
  - DNA immunisation
  - immunisation with immuno-stimulatory sequences linked to allergens.
- Data from early-phase clinical trials suggest both sub-lingual and oral immunotherapy routes are effective in reducing sensitivity to allergens.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Allergies: Airway

Allergic rhinitis		
Est. patient number		>50,000,000
Est. market size		$5.9bn
Unmet clinical need		Low–medium

Asthma		
Est. patient number		22,000,000
Est. market size		$12.7bn
Unmet clinical need		Medium

- Allergic rhinitis/conjunctivitis (hayfever) is extremely common affecting up to 25% of some populations.
- Most patients can be treated with conventional pharmacotherapy on an “as needed” symptomatic basis.
- However, allergen immunotherapy may be useful for patients with severe disease and is said to improve symptoms to a greater extent than pharmacotherapy.
- Unlike pharmacotherapy, allergen immunotherapy provides clinical benefits such as long-term disease remission, prevention of new atopic sensitisations and a reduction in disease progression from rhinitis to asthma.

Allergies: Airway … continued

- Specific immunotherapy for allergic rhinitis uses standardised allergen products usually administered via the subcutaneous route of administration (SCIT).
- Recently, the sub-lingual immunotherapy route (SLIT) has also been investigated. A long-term effect up to 12 years after discontinuation of SCIT has been reported and efficacy and safety of SLIT in pollen allergic rhinoconjunctivitis have been demonstrated in adults.
- SLIT also has the potential for preventing the development of asthma in children with allergic rhinoconjunctivitis.
- Other possible immunotherapy approaches to allergic rhinitis include using anti-IgE antibodies to reduce serum levels of free IgE and/or interfere with IgE binding to low-affinity receptors and hence to inhibit the amplification of the Th(2)-type response.
- Treatment of allergic rhinitis with anti-IgE is said to be safe and to reduce specific symptoms. Furthermore, the combination of omalizumab with specific immunotherapy might increase not only efficacy but also safety in some patients.

Allergies: Airway … continued

- IgE is also responsible for activation of allergic reactions in allergic asthma and is important in the development and persistence of airway inflammation.
- Omalizumab may be of benefit and is thought to work by non-specifically inhibiting the IgE-mediated inflammatory cascade. It is FDA approved for adults and adolescents with moderate-to-severe persistent allergic asthma.
- SLIT also might be effective in treating allergic asthma.
- As noted above, allergic rhinitis might progress to asthma, and allergic rhinitis prevention/management might therefore also prevent asthma.

- Emerging results on B-cell switching suggest a potential route to treatment of rhinitis and asthma.
- Recent (2005) evidence that class switch recombination (CSR) occurs locally in the nasal mucosa in allergic rhinitis offers the prospect of modulation of this process to control IgE-expressing cells.
- The discovery (2007) of CSR in the bronchial mucosa of patients with atopic and non-atopic asthma suggests that this mechanism could also be a target for treatment of asthma.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Summary: Allergies – Skin

Skin allergies (e.g. atopic dermatitis)		
Est. patient number		27,000,000 [P]
Est. market size		$0.9–3.6bn
Unmet clinical need		Medium

- A number of approaches are being examined for skin allergies: there are effective current treatments but they have undesirable side effects.
- Atopic dermatitis (eczema) is a common inflammatory skin disease associated with elevated serum IgE levels.
- It may be treated by immuno-suppressants such as cyclosporine A, tacrolimus and pimecrolimus.
- Other suggested treatment strategies include various monoclonal antibodies (e.g. anti-CD11a, anti-TNF-α, anti-IgE or anti-CD20 antibodies), specific immunotherapy and leukotriene receptor antagonists.
- None of these is as yet as effective as cyclosporine A, but the limitations of cyclosporine A (e.g. side effects) is driving the search for alternatives, in particular B-cell-directed therapies.

Relevant platforms

- Prophylactic vaccines
- Adjuvants
- *Therapeutic vaccines*
- ***Monoclonals***
- *New biologics*
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- Novel antibiotics
- Diagnostics
- **Small molecules**

Allergies: Insect Venom

Anaphylactic reaction to venom (risk)		
Est. patient number		9,000,000 [P]
Est. market size		$0.9bn
Unmet clinical need		Low

- Some individuals are hypersensitive to insect venoms such as bee-sting venom.
- So-called prophylactic venom immunotherapy (VIT), is said to be the only effective means of prevention of serious allergic reactions to bee and wasp stings in sensitised individuals.
- Many people may require VIT treatment lasting 3 years or more, indicating scope for the development of more rapidly acting venom immunotherapy.
- This is a good example of a field in which niche strengths may justify investment in developing IP for a therapy.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Immune Inhibition

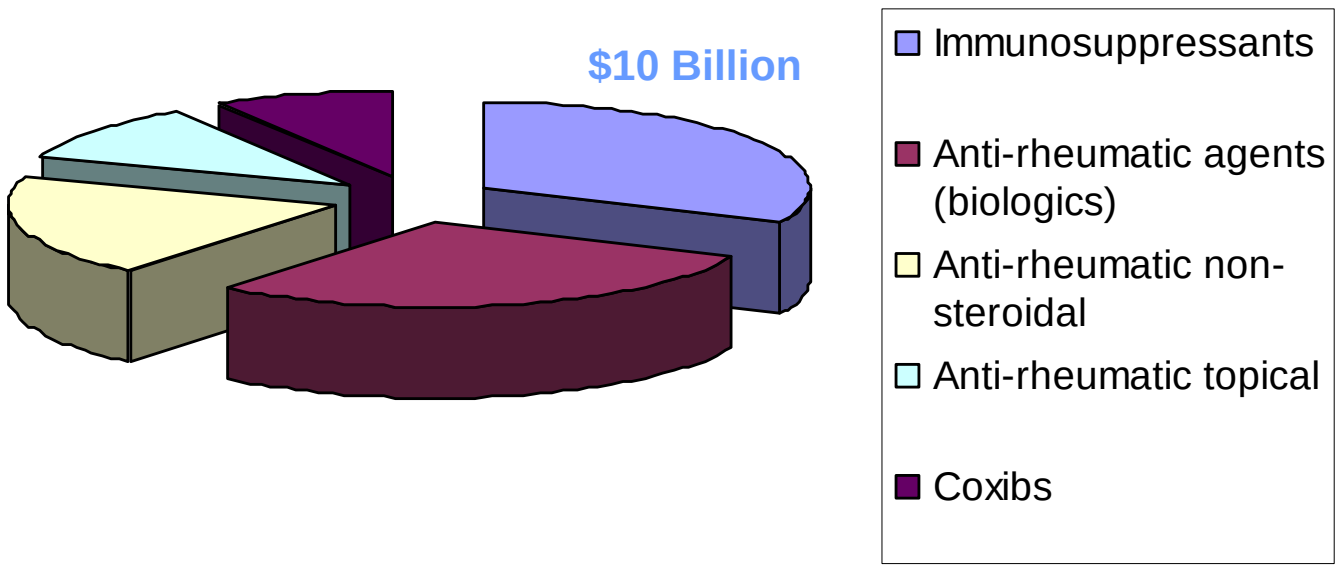
Auto-immune Disease

Autoimmune Disease

- Autoimmune disease is a very fast-growing market segment driven by:
  - an older population in which immune dysfunction correlates strongly with ageing
  - an emerging younger population where lifestyle, environmental and dietary changes appear to increase incidence.
- Autoimmune disease covers a wide range of diseases characterised by:
  - the particular elements, or control mechanisms, of the dysfunctional immune system (i.e. cellular T-cell antibody/B cells)
  - the tissues primarily affected (e.g. joints, skin, gut).
- Current therapeutic intervention relies primarily on biologics, specialist and anti-inflammatory drugs.
- This is a natural market for new immunotherapy, which can displace existing therapies or meet outstanding unmet needs.

Autoimmune Disease … continued

Global autoimmune drug market by drug class
Overall Market $28 Billion 2007



Source : Business Insights

Autoimmune Disease: Joints and Connective Tissue

Rheumatoid arthritis (RA)	
Est. patient number	72,000
Est. market size	$3.6bn
Unmet clinical need	Medium

Systemic lupus erythematosus (SLE)	
Est. patient number	22,180
Est. market size	$650+ million
Unmet clinical need	Medium–high

- Rheumatoid arthritis (RA, autoimmune arthritis) is a chronic inflammatory disorder affecting about 1% of the world's population. It can involve many tissues and organs, but especially the joints, where it results in an inflammatory synovitis and destruction of articular cartilage.
- There is no cure for RA and treatment, which is aimed at slowing disease progression and alleviating symptoms (e.g. pain), includes anti-inflammatories, immuno-suppressants and analgesics. These often have significant unwanted side effects.
- Systemic lupus erythematosus (SLE) is a chronic autoimmune connective- tissue disease that can affect the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system. It is frequently associated with auto-antibodies against nucleic acids and proteins in the cell nucleus, and is mainly treated with corticosteroids and immuno-suppressants such as methotrexate.
- These and related diseases are poorly served by existing medication.

Autoimmune Disease: Rheumatoid Arthritis

- Large world market: £11.6bn in 2007
- Could grow to $27bn by 2015:
  - ageing population is driver in developed countries
  - may be related to adoption of ‘westernised’ life style: potential growth in developing countries
- Traditional small-molecule treatments include NSAIDs, glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate.
- Biologicals (monoclonal antibodies; MAbs) are already important:
  - anti-TNF-α
  - antibodies against CD20+ B cells
  - antibodies targeting IL-1
- Strong competition from existing biological in development:
  - RA was the third most frequent target for biologicals (not necessarily all MAbs) in the late-stage pipeline in 2006, behind cancer and blood disorders.

Source: Research and Markets

Autoimmune Disease: Rheumatoid Arthritis

- The precise cause of RA is not clear, but autoimmunity seems to be a fundamental feature of its pathology as it is thought that RA is a T-cell-mediated autoimmune disease.
- Strategies to modulate T-cell function, such as co-stimulation blockade, might therefore be effective treatments for RA.

- Dendritic cells (DCs) may be of particular interest, having been implicated in RA pathogenesis, and immuno-modulated or tolerogenic dendritic cells are said to have been used as tools to ameliorate experimental arthritis by down-regulating the autoimmune response.
- However, the specific roles of DC sub-sets in human RA are not yet known. Further work in this field may allow the manipulation of dendritic cells for RA immunotherapy.

- Other proposed approaches are based on modulation of pro-inflammatory signalling. In addition, interference with NFκB signalling pathways, and the use of monoclonal antibody therapies to target interleukin (IL)-17 may be of interest.

Relevant platforms

- Prophylactic vaccines
- Adjuvants
- *Therapeutic vaccines*
- *Monoclonals*
- *New biologics*
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- Novel antibiotics
- Diagnostics
- **Small molecules**

Autoimmune Disease: Systemic lupus erythematosus (SLE)

- For SLE, new drugs based on modulation of the immune system activation pathways relevant to SLE pathogenesis, rather than on global suppression of the immune system, are currently being developed.
- In particular, B cells – thought to be key players in SLE pathogenesis – may be a key therapeutic target.
- Immunotherapeutic approaches for SLE could therefore include methods focusing on B-cell depletion, B-cell tolerance, co-stimulatory signals and cytokines that affect B-cell survival and activation.
- Other anti-cytokine approaches relevant to B-cell inhibition include blockers of IL-10, IL-6, IFN-α and the B-cell activity factor belonging to the tumour necrosis factor family (BAFF), which is thought to be involved in aberrant survival of B cells directed to the self.
- B-cell-depleting therapies with the monoclonal antibodies rituximab and epratuzumab are said to have shown good therapeutic results.

Relevant platforms

- Prophylactic vaccines
- Adjuvants
- *Therapeutic vaccines*
- *Monoclonals*
- *New biologics*
- ***Cell therapy***
  - *Dendritic cells*
  - *T-reg cells*
  - *Other T cells*
  - ***B cells***
  - *NK cells*
  - *Microglial cells*
- Novel antibiotics
- Diagnostics
- **Small molecules**

Summary: Autoimmune Disease – CNS/Neuromuscular

Multiple sclerosis (MS)	
Est. patient number	10,000 [P]
Est. market size	$0.5bn
Unmet clinical need	Medium

Other CNS autoimmune	
Est. patient number	11,500 [P]
Est. market size	N/k
Unmet clinical need	High

- Scientific knowledge of the role of the immune system in pathogenesis of MS is advancing rapidly with a rich set of medium-term approaches and the opportunity to gain deeper understanding.

- Notoriously, there is ‘no cure’ for MS: even these advanced drugs are only partially effective and their ability to attenuate the more progressive phases of the disease is doubtful. Therefore, there is a need to develop improved treatments for MS.

- The other CNS autoimmune diseases are rare, related to MS or have a rapid onset, which makes them less attractive.

Autoimmune Disease: CNS/Neuromuscular

- One of the most common CNS-associated autoimmune disorders is multiple sclerosis (MS), which involves chronic inflammation of the CNS apparently mediated by autoreactive effector T cells that penetrate the blood–brain barrier and become activated within the CNS.
- Immunotherapeutic treatments may include
  - immunomodulatory drugs interferon beta and glatiramer acetate,
  - Immunosuppressants such as mitoxantrone.
  - Anti-T cell vaccines OpexaTherapeutics (Phase 2).
- More recently, natalizumab, a monoclonal antibody against α4 integrin, has been approved by the US Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) on the basis of its higher efficacy than the available treatments and its good safety profile.

Relevant platforms

- Prophylactic vaccines
- Adjuvants
- ***Therapeutic vaccines***
- *Monoclonals*
- *New biologics*
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- Novel antibiotics
- Diagnostics
- **Small molecules**

Autoimmune Disease: Metabolic/Endocrine

Type 1 diabetes (T1D)		
Est. patient number		60,000
Est. market size		$1.6bn
Unmet clinical need		High

- Type 1 diabetes (insulin-dependent diabetes mellitus, juvenile diabetes, T1D) is a chronic autoimmune disease in which the insulin-producing beta cells of the pancreas are destroyed, resulting in hyperglycaemia and a host of other metabolic changes.
- T1D patients depend on insulin replacement therapy, but this is not a cure and is inconvenient.
- A cure would require prevention or reversal of the destruction of the beta cells themselves. Accordingly, there are attempts to develop therapies that effectively prevent and/or treat T1D in the clinic, in particular immunotherapy.
- Improved capabilities to predict onset of T1D at an early stage have also contributed to interest in a prophylactic immunotherapeutic strategy.

Autoimmune Disease: Metabolic/Endocrine … continued

- It is suggested that defects in the number and activity of regulatory T (T-reg) cells might be causally related to the development of T1D. Furthermore, it is said that increasing the number of T-regs by adoptive transfer can be used to prevent T1D and even to treat established T1D.
- Specific strategies for employing β-cell-specific T-regs include *ex vivo* expansion of natural T-regs specific for β-cells prior to reinfusion, and *ex vivo* conversion of naïve or activated T cells specific for β-cell antigens to T-regs, by genetic manipulation or by specific cytokine combinations.
- Both of these approaches are said to be successful in treating even established diabetes in animal models.
- It has been suggested that T-regs recognising β-cell antigens are more efficient in treating the disease than polyspecific T-regs, and that they result in a tissue-specific immunotolerance without compromising the general immuno-competence of the patient.

Autoimmune Disease: Metabolic/Endocrine … continued

- Vaccination with self-antigen, to promote self-antigen-specific tolerance rather than to mediate an immune response, may be able to prevent development of T1D. This type of strategy, although effective in animal models, has not so far been demonstrated to be effective in humans.
- Some suggest that multiple strategies aimed at modulation of both central and peripheral immunity must be considered for a realistic prospect of preventing T1D.
- Recently, it has been suggested that autoimmune diabetes and perhaps even T2D might be triggered by *Enterobacter* infections, raising the possibility of an *Enterobacter* vaccine to prevent diabetes.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Autoimmune Disease: Metabolic/Endocrine … continued

Other diseases (Addison's, Graves', Hashimoto's)		
Est. patient number		45,500
Est. market size		N/k
Unmet clinical need		High

- Graves' disease is an autoimmune disease in which antibodies against the receptor for thyroid-stimulating hormone (TSH) are activated. These antibodies bind to the TSH receptor and chronically stimulate it, causing hyperthyroidism.
- Treatments include anti-thyroid drugs, thyroidectomy and treatment with radioactive iodine. There is a clear need for improved therapeutic strategies.
- The recent development of an animal model of Graves' disease may enable investigation of immune intervention strategies, including modulation of the auto-reactive B- and T-cell players in the autoimmune process.

Relevant platforms

- Prophylactic vaccines
- Adjuvants
- *Therapeutic vaccines*
- *Monoclonals*
- *New biologics*
- *Cell therapy*
  - *Dendritic cells*
  - *T-reg cells*
  - *Other T cells*
  - *B cells*
  - *NK cells*
  - *Microglial cells*
- Novel antibiotics
- Diagnostics
- **Small molecules**

Autoimmune Disease: Metabolic/Endocrine … continued

- **Other (rare) metabolic diseases with a less well-characterised autoimmune component may be targets for new immunotherapy such as induction of tolerance by a vaccine:**
  - Addison's disease: some types are caused by destruction of the adrenal cortex due to auto-antibodies, e.g. against the enzyme 21-hydroxylase.
  - Hashimoto's disease: T cells attack the thyroid and involve auto-antibodies against various proteins such as thyroglobulin. Current treatment is limited to daily thyroid hormone replacement for life.
  - Pernicious anaemia (B12 deficiency): may involve autoantibodies against gastric parietal cells. Current treatment may just be lifelong B12 replacement by injection.

Autoimmune Disease: Skin

Psoriasis	
Est. patient number	1,800,000
Est. market size	$3.6bn
Unmet clinical need	Medium

Alopecia	
Est. patient number	300,000
Est. market size	$375million
Unmet clinical need	Medium

- These conditions are already treated with immuno-suppressants, but these are associated with adverse side effects.
- Existing immunotherapies for psoriasis have quite major limitations.
- However, despite the autoimmune causation of these diseases, there is not an obvious route for prophylaxis.
- Microbial involvement in triggering psoriasis is not ruled out.
- **Although a promising area for application of better immunotherapy, this is likely to be long term given the current state of knowledge.**

Relevant platforms

- Prophylactic vaccines
- Adjuvants
- *Therapeutic vaccines*
- *Monoclonals*
- *New biologics*
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- Novel antibiotics
- Diagnostics
- **Small molecules**

Autoimmune Disease: GI Tract

IBD	
Est. patient number	53,000
Est. market size	$20bn
Unmet clinical need	Medium–high

Coeliac disease	
Est. patient number	2,280
Est. market size	$1.7bn
Unmet clinical need	High

- Crohn's disease and ulcerative colitis are the most common forms of a group of disorders collectively termed inflammatory bowel disease (IBD).
- Although there are fewer patients with coeliac disease than IBD, this market is boosted by the high cost of gluten-free foods and beverages; for IBD, 30% of costs arise from the 2% worst affected.
- These are chronic inflammatory disorders of the bowel. There does not seem to be a cure and treatments aim to control symptoms/ sustain remission. Patients can be treated with corticosteroids or immuno-suppressants, intravenous Remicade or even surgery.
- There is a obvious unmet need but it is not clear what proportion of current treatment costs a new immunotherapy would intercept and immunotherapy concepts are early stage.

Autoimmune Disease: GI Tract IBD

- IBD may involve a hyper-reactive immune response in the gut wall directed against the commensal intestinal bacterial flora mediated by CD4+ T cells, or an immune response to the gut wall itself.

- Chemokines seem to play a central role in recruiting inflammatory cells to the inflamed bowel of IBD patients, suggesting that the chemokine/receptor system may be a source of targets for new therapeutic approaches for IBD.

- Knocking out IL-23 may reduce bowel inflammation in animal models, and some research suggests that the Th17 group of T cells are unregulated in IBD, implying that development of methods to modulate this group of CD4+ lymphocytes might modulate IBD.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Autoimmune Disease: GI Tract Coeliac disease

- Coeliac disease is an autoimmune disorder of the small intestine occurring in genetically susceptible individuals, triggered by gluten and related substances.
- Pathophysiology is complex, but may involve antibodies to the enzyme tissue transglutaminase and T-cell-mediated inflammation, which disrupts the structure and function of the small-bowel mucosa.
- Although gluten-free diets are an effective treatment for coeliac disease (except in a few rare cases who need steroids or immunosuppressants), these can be awkward and inconvenient to comply with.
- Some researchers suggest that IBD is a consequence of the immune system having no conventional intestinal parasites to attack. This has led to suggestions that immunotherapy comprising ingestion of gut parasite material might treat or even prevent IBD.
- There is a demand for alternative treatment options, which have been suggested to include different forms of immunotherapy.

Relevant platforms

- **Prophylactic vaccines**
- **Adjuvants**
- ***Therapeutic vaccines***
- ***Monoclonals***
- ***New biologics***
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
  - ***Other T cells***
  - ***B cells***
  - ***NK cells***
  - ***Microglial cells***
- **Novel antibiotics**
- **Diagnostics**
- **Small molecules**

Autoimmune Disease: Other

Market comment
The other autoimmune diseases screened are characterised by being rare and therefore having small patient populations

- This group includes:
  - EBA (skin)
  - anti-phospholipid antibody syndrome (APS)
  - Autoimmune haemolytic anaemia
  - Idiopathic thrombocytopenic purpura
  - Goodpasture's syndrome
  - Sjögren's syndrome.
- A strategy to exploit these would depend on 'orphan indication' status or exceptionally high re-imbursement per patient for other reasons.
- Nevertheless, the existence of such a niche cannot be ruled out.

Transplantation related therapies

Transplants		
Est. patient number		21,000
Est. market size		N/k
Unmet clinical need		Medium-High

- Currently, most approaches to ensuring that organ transplants and tissue grafts are not rejected rely on broadly immunosuppressive approaches. These agents are associated with side effects and also variable efficacy due to pharmacogenetic factors (enzyme polymorphisms).
- This opens up the possibility of more sophisticated approaches through modulation of the immune system. These could exploit Treg and Dendritic cells to more effectively ensure transplant survival.
- These opportunities in conventional transplants also have potential in regenerative medicine as well.
- There is increasing evidence that the immune privilege of embryonic derived stem cells is not absolute. This implies that successful application of regenerative medicine may require either low level immuno-suppression, tissue matching or a mixture of both.

Relevant platforms

- Prophylactic vaccines
- Adjuvants
- *Therapeutic vaccines*
- *Monoclonals*
- *New biologics*
- ***Cell therapy***
  - ***Dendritic cells***
  - ***T-reg cells***
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  - *B cells*
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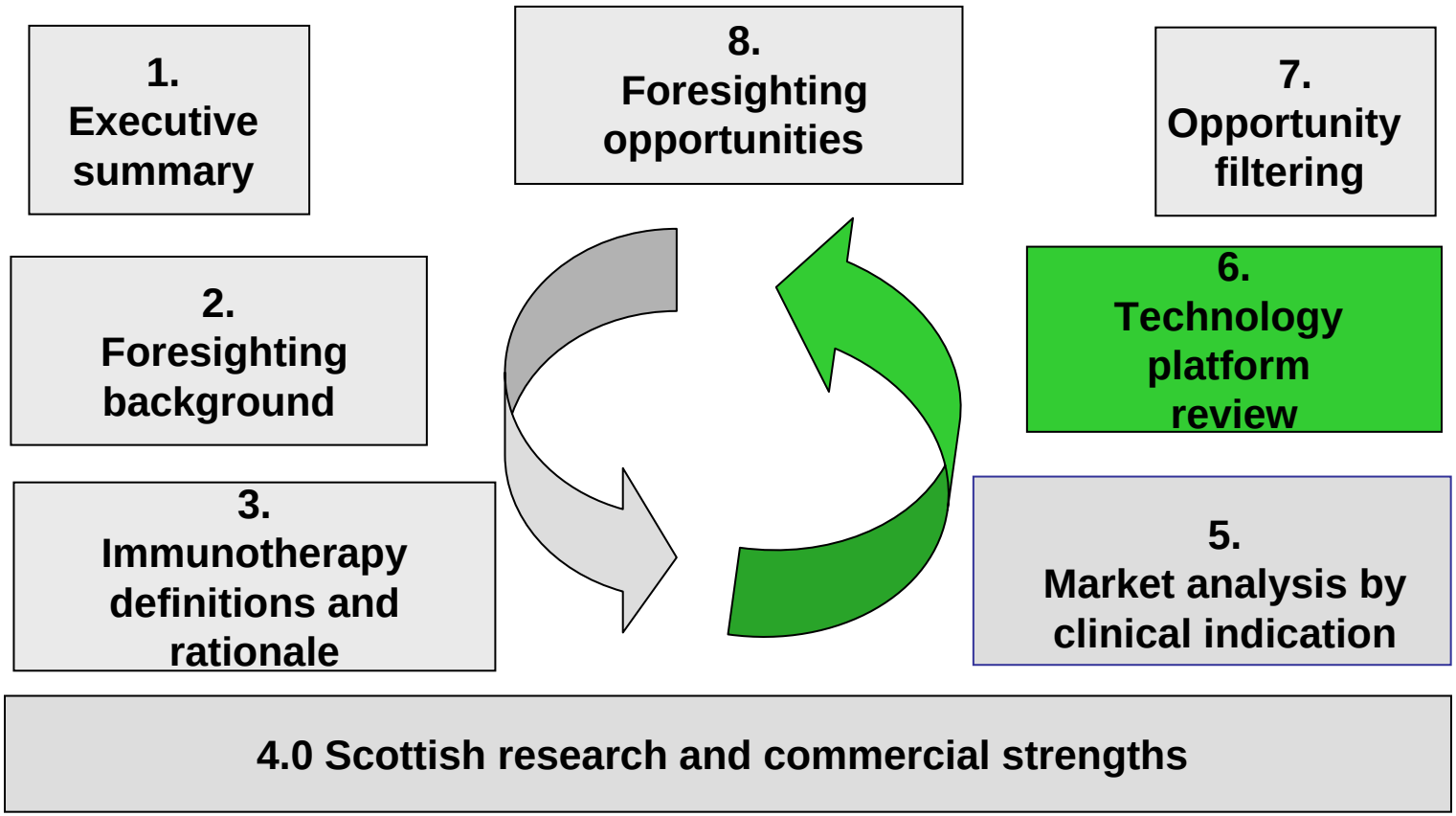
  - *Microglial cells*
- Novel antibiotics
- Diagnostics
- **Small molecules**

Part 6: Review of Technology



Technology Review and Process

- We have reviewed the technology field relevant to each disease indication for evidence of emerging technology platforms.
- These split into cellular-based platforms and a diverse group of non-cellular-based technologies relevant to immunotherapy.
- The status of each multiple relevant technology platform is summarised briefly here (it has been extracted from a more detailed review, which is available on request).
- These platforms were characterised by the ability to up- or down-regulate the immune response.
- The platforms were then mapped onto clinical application areas.

Conventional Immunotherapy Platforms: Relevance to Immune Modulation Treatment Approaches

Technology area	A. Conditions requiring potentiation	B. Conditions requiring inhibition
Monoclonal antibodies	Adventitious infections, cancer, hypertension, foldopathies, substance abuse	Allergies, autoimmune disease, transplants, atherosclerosis, CNS trauma
Diagnostics / monitoring	Adventitious infections, cancer	Allergies, autoimmune disease, transplants
Sub-unit vaccines, adjuvants and delivery systems	Adventitious infections, cancer, hypertension, foldopathies, substance abuse	Allergies, autoimmune disease
Personalised therapy	Cancer	Autoimmune disease
Combination approaches	Adventitious infections, cancer	Allergies, autoimmune disease

Monoclonal Antibodies (mAbs):
The Most Successful Therapeutic Immunotherapy derived Platform

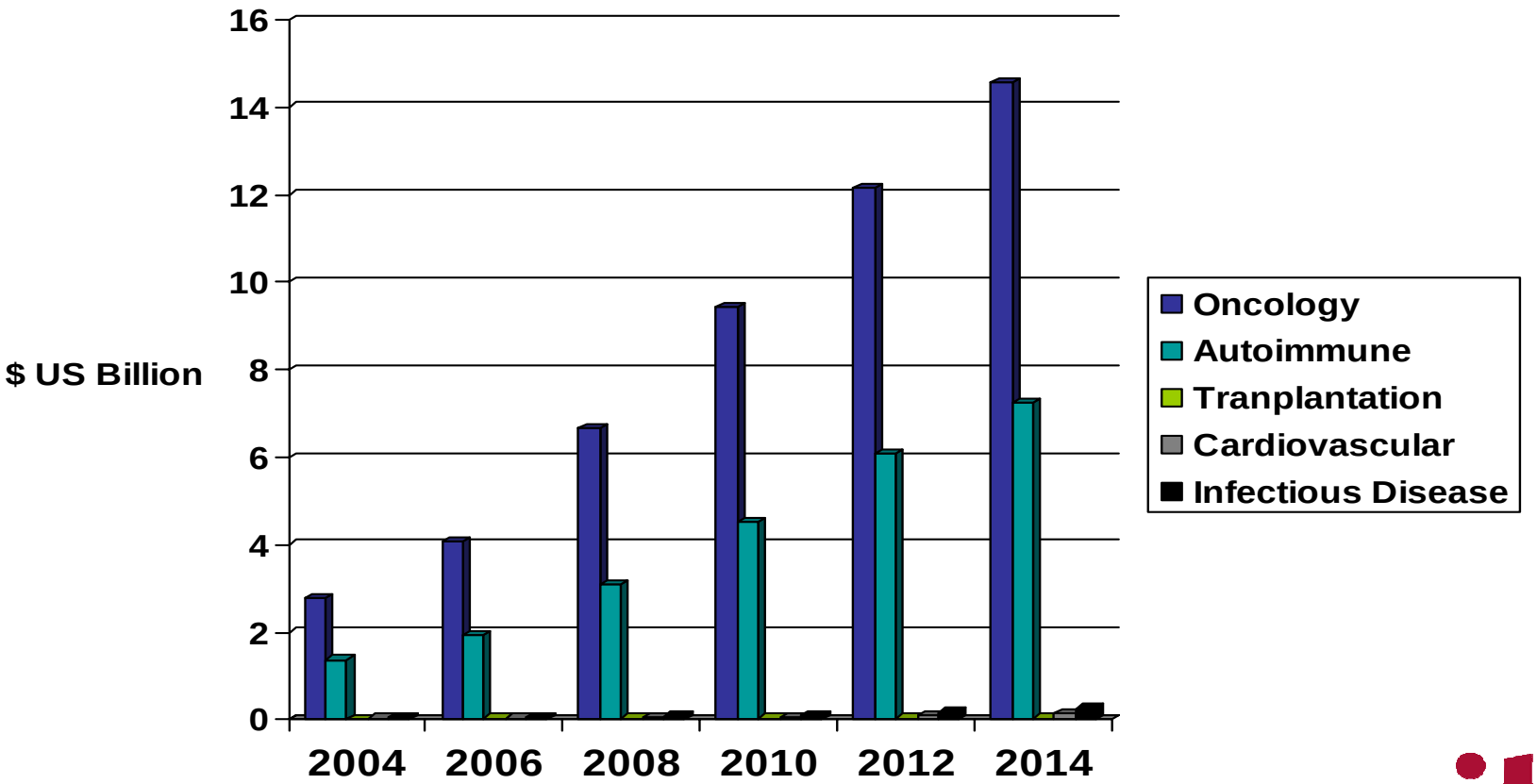
- mAbs have become a highly successful new therapeutic modality in the last 10 years and are now directed at a whole range of therapeuitic targets, most notably in cancer. The principles and practice of use of mAbs are now well established.
- Antibody-based products can be made in a variety of forms (fully human, humanised, xenogeneic, full-length or fragment) and in a variety of ways (phage display, engineered animals).
- Antibody-based products can be co-opted for a variety of functions: activation of signalling by receptor binding, signalling blockade by binding to receptors or by sequestering ligands, intracellular or extracellular action.
- Relative disadvantages include:
  - potentially competitive complex IP in the area
  - costly and complex procedures associated with production, quality control, storage and administration of a biological (as compared with a small molecule).

Monoclonal Antibodies (mAbs):
The Most Successful Therapeutic Immunotherapy derived Platform

The key advantages of mAbs

- A relatively well-understood and usually specific mode of action.
- A well-established regulatory pathway, the relatively high chances of regulatory approval relative to small molecules.
- Relatively straightforward production methods.
- An antibody approach may be used to relatively rapidly prove the principle of a therapeutic strategy prior to embarking on a small molecule search.
- Versatility: there is substantial precedent in targeting other therapeutic entities via the specificity of the antibody moiety.
- mAbs are a key platform technology that is finding increasingly widespread applicability is treating a range of diseases with an immune or autoimmune component.
- There are still widespread opportunities for further exploitation of mAbs in immunotherapy applications in such areas as transplantation.

Monoclonal Antibodies (mAbs): Market Size : indications and projections (Europe)



Source Frost and Sullivan

Diagnostic and Monitoring Technologies

- Technical advances, together with new insights into molecular immunology, have changed typical immune monitoring assays from the formerly used bulk assays, such as cell proliferation or cytotoxicity assays, towards more sophisticated single-cell assays, multiplex profiling and signalling molecule detection.
- A variety of cellular platform technologies are used including microscopy and flow cytometry and novel combinations such as Ellispot and Tetramer T cell assays.
- Improved diagnostics/monitoring technologies and/or new biomarkers could have significant impact on the potential of immunotherapy.
- There is a need for improved techniques for immune response monitoring in general, and particularly for T-cell function, in light of the greater prominence of vaccines to elicit T-cell responses, adoptive T-cell therapy and small-molecule and monoclonal therapies directed at T-reg and other T cells.
- Early-stage disease detection allows for the timely application of an immunotherapy before the onset of an immunological disorder. Examples include:
  - improved the ability to identify individuals at risk of T1D; it is suggested that children with a 6-year risk of disease higher than 90% can be identified due to an ongoing immune process
  - biomarker and antibody profiling for early-stage cancer detection, monitoring of interventions and re-occurring disease.

Vaccines, Adjuvants and Delivery Systems

Vaccine technology is evolving continuously, with significant developments in:

- Protein, peptides and sub-unit vaccines, particularly those directed against cytokines as a more cost-effective alternative to anti-cytokine monoclonal therapies.
- Autoantigenic so-called “negative vaccination” using self-antigens to promote tolerance in diseases such RA and T1D.
- Synthetic immunogens such as synthetic long peptides, which mimic tumour antigens.
- DNA and viral particle vaccines, which have tremendous potential advantages in terms of cost and ease of manufacture.
- Novel viral vectors such as Sendai recombinant pox virus and Salmonella.
- Virus-like particle vaccines, which retain the key immunological features of the virus (such as repetitive immunogenic surface molecules) but lack the genomic material necessary for replication. These can be manufactured recombinantly and modified by conjugation and gene fusion, thus greatly extending their potential range of use from microbial pathogens to chronic diseases.
- Oncolytic viruses that kill tumour cells by intracellular replication and stimulation of the innate immune response.

Vaccine Production technologies

- Conventional vaccine production technology has relied heavily on fertilized hens' eggs, to produce infected allantoic fluid. Typically an extracted virus is purified from this fluid inactivated and treated to produce a whole virus, split or subunit vaccine.
- The major weakness of egg based production, which is still widely used, is the time take for production typically six-months which limits responsiveness to new threats.
- In recent years there has been a large scale switch to cell based production using insect and mammalian cell lines. These techniques allow much faster scale up of manufacture and reduce both time to product (6-8 weeks) and cost.
- Another are of innovation is the increasing use of fully self enclosed disposable systems developed by companies such as Novavax.
- The use of plants as an efficient and low cost alternate production technology is also receiving significant attention and investment by companies notably Medicago Inc.
- BigDNA based in Edinburgh is exploiting Bacteriophage as a further alternate vehicle for vaccine production.

Adjuvants

- There is a clearly defined need for better potentiators of humoral, cellular and mucosal immunity, and for a greater understanding of the mechanisms of innate immunity that have opened up multiple new avenues for novel adjuvant development including:
  - exploitation of Toll-like receptors as targets
  - exploitation C-type lectins as targets
  - use of unmethylated cytosine-phosphate-guanine (CpG) motifs.
- Alum is well established as the standard traditional – almost default – adjuvant but, although cost effective and cheap better alternatives are sought.
- This is an area of intense commercial interest and partnership, notably between Intercell and Wyeth licensing the IC31, which stimulates innate immunity through the TLR9 receptor, leading to maturation and activation of antigen-presenting cells and efficient antigen presentation.
- GSKs recent acquisition of Corixa, in a deal valued at $330 million, which gave them control over their MPL adjuvant, underlines the increasing importance of novel adjuvant technologies.

Personalised Approaches

- Personalised medicine may be applicable to immunotherapy.
- Areas in which research might produce general advances in personalised immunotherapy include:
  - genomic research, particularly when linked to data regarding clinical outcomes and drug responses
  - theranostic strategies, including antigen–autoantibody microarrays, serological analysis of antigens by recombinant cDNA expression, cloning, serological proteome analysis and autoantibody-mediated identification of antigens
  - personalised vaccines, developed according to the immune response expected in the context of a given genotype.

Combination Approaches

- Combining immunotherapy with other therapeutic modalities has the potential to lead to synergies and, in some cases, might ‘rescue’ an approach that failed clinical trials as a monotherapy.
- Research in this field might allow failed monotherapies to be licensed cheaply and repackaged as a combination therapy.
- Areas where more than one immunotherapy approach has been used in combination, or has been suggested, include:
  - adventitious infections, particularly anti-fungals
  - persistent infections, e.g. hepatitis, HIV
  - substance abuse, e.g. nicotine
  - cancer.

Immune System Cell Types as Targets and Potential Technology Platforms

- In effect, the immune system is an interactive hierarchy of specialised cells that maintains immune function.
- This offers two distinct modes of therapeutic intervention relevant to this review:
  1. The specialist cell **as a platform** technology: the specialist cell is isolated, manipulated and returned to the patient. Dendritic cell vaccines are an example of this approach.
  2. The specific immune cell type acts **as a target** for selective up- or down-regulation by small molecules, vaccines, biologics or molecular intervention.
- Specificity is the key and either approach can yield new immuno-therapies.

Immune System Cell Types as Targets/Platforms

Technology	A. Conditions requiring potentiation	B. Conditions requiring inhibition
Dendritic cells	Adventitious infections, cancer, immunosenescence (thymic shrinking)	Allergies, autoimmune disease, transplants
Regulatory T cells	Adventitious infections, cancer, foldopathies, immunosenescence (thymic shrinking)	Allergies, autoimmune disease, transplants, atherosclerosis, CNS trauma, immunosenescence (inflammation)
Other T cells	Adventitious infections, cancer, foldopathies, immunosenescence (thymic shrinking)	Allergies, autoimmune disease, atherosclerosis, CNS trauma, immunosenescence (inflammation)
B cells	Cancer	Allergies, autoimmune disease
NK cells	Adventitious infections, cancer	Autoimmune disease
Microglial cells	Foldopathies	CNS trauma

Dendritic Cells : Clinical Potential

- Dendritic Cells are key antigen-presenting cells (APCs) that reside in peripheral tissues, where they sample antigens and process them for presentation to immune effector cells. The interact and modulate a wide variety of cells including:
  - all classes of lymphocyte: T, B, NK cells
  - T-cell function: Th1/Th2/Th17, regulatory T cells, peripheral T-cell deletion.
- Their ability to induce and coordinate T-cell immunity suggests that therapeutic modulation of their activity might contribute to the treatment of disorders with an immune component.

Therapeutic Use of Dendritic Cells (DCs)

- **Recent examples where DCs have been used in therapeutic setting:**
- Persistent infections:
  - *ex vivo* conditioned DCs give complete and durable protection against infection in a murine model of leishmaniasis
  - DC approaches may be used to augment T-cell immunity to HIV infection. Recent clinical trials are said to involve administering DCs loaded *ex vivo* with HIV antigen preparations to HIV-infected patients. DC-mediated therapy has also been suggested for T1D
  - the immunoregulatory properties of DCs are said to offer the potential of donor-specific control of graft rejection after organ transplantation
  - attempts to understand DC functions in RA might enable modulation of DC functions to allow for immunotherapy by down-regulating the autoimmune response.
- Cancer: there is significant interest in the immunotherapeutic potential of antigen-pulsed DC for the treatment of cancer.

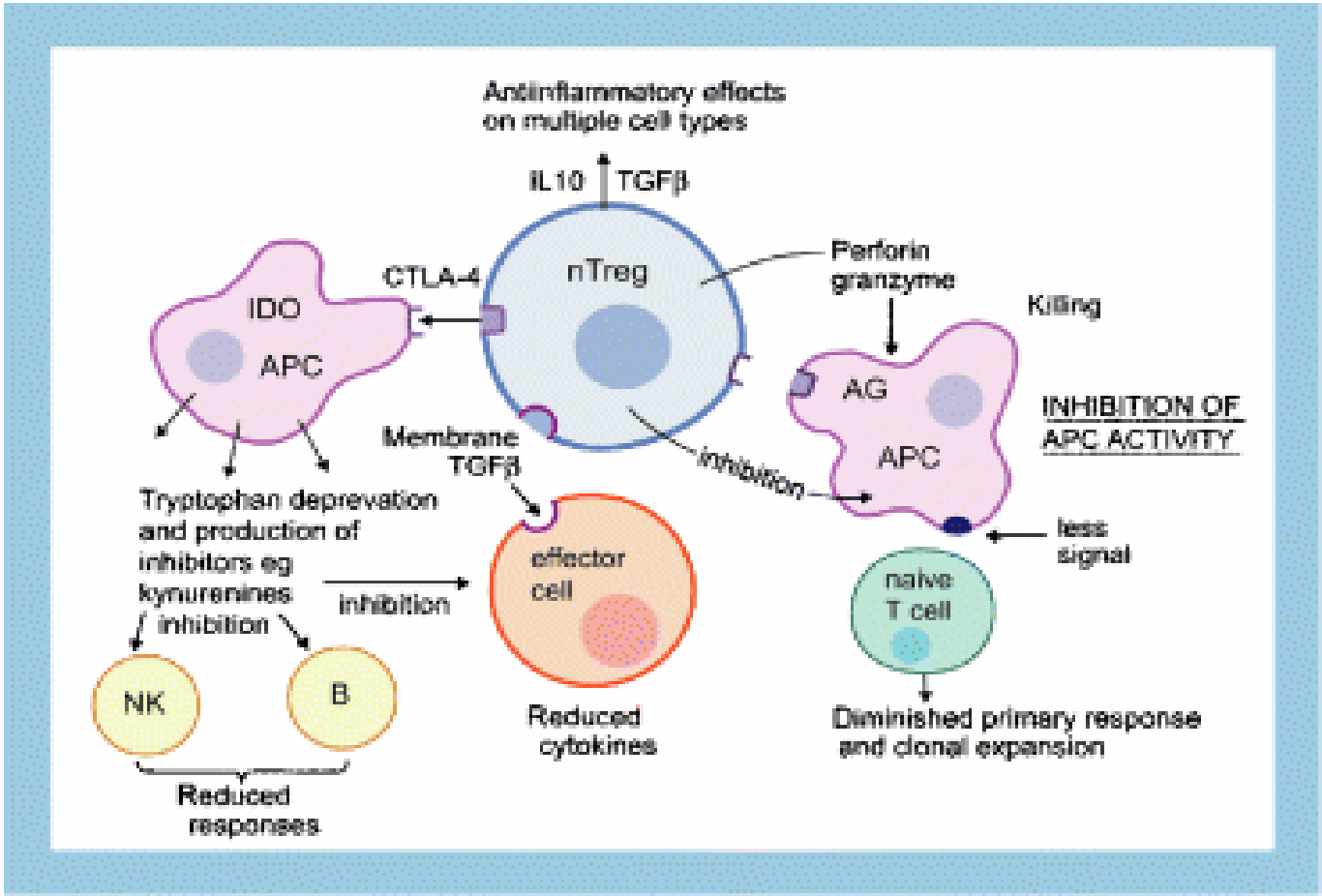
Cellular Target/Platform: Regulator T cells (T-reg)
Primary Mediators of Immune Suppression

- Following the seminal work of the Sakaguchi group in the mid-1990s, the central importance of T-reg cells in preventing autoimmune disease has been widely recognised and represents a major new target for autoimmune therapies.
- Research, mainly from *in vitro* studies, has revealed that T-reg can exert suppressive effects against multiple cell types involved in immunity and inflammation, including:
  - induction plus the effector and memory function of CD4+ and CD8+ T cells
  - the inhibition of proliferation, immunoglobulin production and class switching of B cells
  - the inhibition of NK and NK T-cell cytotoxicity
  - the function and maturation of dendritic cells
  - effects on the function and survival of neutrophils.
- Therefore, selective induction and/or expansion has the potential to inhibit unwanted immune responses across a wide spectrum of diseases, most obviously in allergy and autoimmunity but also transplantation medicine and in inflammation.

T-regulatory Cells: Monitoring Opportunities

- There seems to be a need for methods and markers for the identification/ purification/expansion of polyclonal and antigen-specific T-reg cells for adoptive immunotherapy.
- Elevated CD4(+) T-reg cells seem to be associated with various types of cancer and are thought to contribute to the suppression of anti-tumour immunity.
- Less is known about CD8(+) T-reg cells and their detrimental effects on immunotherapy directed towards cancer; more information in this field may suggest new therapeutic approaches.

Breadth of Treg mediated Suppression Mechanisms



Source: *Journal of Internal Medicine* (2007) **262**. © 2007 Blackwell Publishing Ltd

T Cells: Key Effector and Memory Targets

- The basis of T-cell immune responses is the specific recognition of an immunogenic peptide epitope by a T-cell receptor, resulting in antigen-dependent activation of the T cells that leads to clonal expansion and differentiation into effector and memory T cells.
- These effector and memory functions place T cells right at the centre of the immune response. Specific potential cellular targets include:
  - modulation of major B7/CD28 and B7/CTLA-4 co-stimulatory and co-inhibitory axis which is a major determinant of T-cell function
  - altered peptide ligands can act as modulators of immune responses
  - control of novel helper T (Th) cell sub-sets such as IL-17-producing Th cells (Th17 cells)
  - indirect modulation of DC function through $V\gamma9V\delta2$ T-cell activation by small molecules
  - inhibition of pro-atherogenic T cells
  - improved methods for generating anti-tumour T cells, including T-cell receptor methods.

T Cells: Clinical Potential

- **Therapeutic interventions that up- or down-regulate T-cell function have potentially wide-ranging clinical application in the following:**
- Autoimmune disease:
  - T-cell-depleting strategies are suggested to be of use in vasculitis
  - co-stimulation blockade is said to be an effective treatment for RA
  - T1D vaccines target autoreactive CD8+ T cells
  - immune regulation by T-cell vaccination (TCV) through injecting attenuated form of myelin-reactive T cells selected and expanded from each MS donor appears to induce protective immunity.
- Persistent infections:
  - adoptive immunotherapy involving the transfer of autologous virus-reactive T lymphocytes is said to be effective in the eradication of virally infected cells.
  - adoptive transfer of donor-derived virus-specific T cells can reconstitute anti-viral immunity in recipients and be effective both in preventing and treating cytomegalovirus, Epstein–Barr virus and adenovirus infection.

T Cells: Clinical Potential … continued

- Atherosclerosis:
  - T lymphocytes enhance inflammation in atherosclerotic plaques and contribute to lesion progression and remodelling. It is suggested that this action could be modulated by manipulating T-cell co-stimulatory and co-inhibitory pathways including both the B7/CD28 (B7-1/2, ICOS, and PDL-1/2) and the TNF/TNF receptor (CD40, OX40, and CD137) families.
- Acute or neurodegenerative CNS disorders:
  - T cells that recognise CNS antigens are needed to activate resident immune cells and to recruit blood-borne monocytes, which may act to restore homeostasis and facilitate repair. It has been suggested that vaccination strategies could recruit such T cells.

T Cells: Clinical Potential in cancer

- Adoptive immunotherapy involving the transfer of autologous tumour-reactive T lymphocytes may have a potential role in the therapy of cancer. For example, adoptive transfer of antigen-specific T-cells has shown therapeutic successes in the treatment of tumours in patients with metastatic melanoma.
- CD4+ Th cells can enhance anti-tumour cytotoxic T-lymphocyte (CTL) responses by enhancing clonal expansion at the tumour site, preventing activation-induced cell death and functioning as antigen-presenting cells.
- CD137 is a surface co-stimulatory glycoprotein present on activated T lymphocytes. Artificial stimulation of this molecule with monoclonal antibodies or other agonists is said to augment the cellular immune response against tumours to a greater extent than the membrane-bound natural ligand. An anti-CD137 agonistic monoclonal antibody is said to have entered phase II clinical trials.

T Cells: Clinical Potential in cancer

- It may be possible to augment T-cell-mediated immunity by blocking inhibitory signals that suppress T-cell function. CTLA-4 is a key negative regulator of T-cell activation. CTLA-4 blockade using anti-CTLA-4 monoclonal antibodies potentiates the T-cell response against tumours and is said to demonstrate good efficacy and tolerability in cancer patients.
- Activated Vγ9Vδ2 T cells can kill most tumour cells because of recognition by T-cell and NK receptors. Intentional activation of γδ T cells *in vivo* by aminobisphosphonates may represent a promising mechanism for cancer immunotherapy. Several phase I–II trials are said to be investigating the activity of zoledronic acid plus IL-2 in solid tumours.

B Cells

- The opportunities for B cells as a potential platform technology stem primarily from the prospect of inhibiting inappropriate antibody production, which contributes to a variety of autoimmune disease states.
- Inappropriate antibody production is increasingly implicated in a range of autoimmune disease states.
- B cells are said to be key players in the pathogenesis of SLE, and strategies for the therapy of SLE have been suggested to include B-cell depletion, B-cell tolerance, co-stimulatory signals and cytokines that affect B-cell survival and activation.
- Similarly, B-cell-depleting therapies with the monoclonal antibodies rituximab and epratuzumab have shown good therapeutic results, as have studies targeting co-stimulatory pathways such as B7-CD28.
- B-cell-depleting strategies and directed interventions are also suggested to be of use in vasculitis and atopic dermatitis.
- Potentially, B-cell-mediated tolerance may be of use in autoimmune arthritis.

NK Cells

- NK cells are cytotoxic lymphocytes that play a role in the rejection of tumours and virally infected cells. They are activated by cytokines and by antibodies bound to cells, and have various other activating and inhibiting receptors including:
  - C-type lectin receptors
  - KIRs (killer cell immunoglobulin-like receptors)
  - LIRs (leukocyte inhibitory receptors).
- In theory, NK-cell activity could be modulated by manipulating any of the above.
- Pharmacological activation of invariant natural killer T (iNKT) cells in the presence of antigenic proteins can positively modulate dendritic cells and B cells, and enhance antigen-specific B- and T-cell responses.
- For treating cancer, it seems that NK recognition of human tumours may be effected or enhanced by treatments based on immuno-modulatory agents that affect NK cells; adoptive transfer of NK cells may also have potential.

Microglial Cells

- Microglial cells are the main type of immune cell in the CNS. They act in the absence of antibodies, which do not usually cross the blood–brain barrier.
- Microglial cells have a very wide variety of actions, including phagocytosis, cytotoxicity, antigen presentation, promotion of repair and extracellular signalling, by which they influence neurons, astrocytes, other microglia, and T cells, e.g. during the promotion of inflammation.
- Controlled immuno-modulation of microglial activity could contribute to immunotherapy for many disorders of the nervous system.

Summary: Clinical Application vs. Platform Mapping

Disease Mapped Against Cell and Monoclonal Platforms

Market	Dendritic cells	T-regs	Other T cells	B Cells	NK cells	Micro Glial	Monoclonal
Hospital infections			Y				
Adventitial			Y				Y
Persistent	Y	Y	Y		Y		Y
Cancer	Y	Y	Y	Y	Y		
Hypertension							
Alzheimer's		Y	Y	Y	Y		Y
Immuno-senescence	Y	Y	Y				
Substance abuse							Y
Infectious disease							

Market	Dendritic cells	T-regs	Other T cells	B Cells	NK cells	Micro Glial	Monoclonal
Allergies	Y	Y	Y	Y			Y
Autoimmune			Y				Y
Transplants	Y	Y			Y		Y
Atherosclerosis		Y	Y				Y
CNS/Trauma		Y	Y			Y	Y
Senescence inflammaging		Y	Y				

Activated

Immune activity required

Inhibited

Summary: Clinical Application vs. Platform Mapping

Disease Mapped Against Diagnostics, Vaccines and Other Platforms

Market	Diagnostics monitoring	Vaccines adjuvants	Personal therapy	Combination therapies
Hospital infections		Y		
Adventitious infections	Y	Y		Y
Persistant infections	Y	Y		Y
Cancer	Y	Y	Y	Y
Hypertension		Y		
Alzheimer's		Y		
Immuno-senescence				

Market	Diagnostics monitoring	Vaccines adjuvants	Personal therapy	Combination therapies
Allergies	Y		Y	Y
Autoimmune	Y	Y	Y	Y
Transplants	Y			
Atherosclerosis	Y			
CNS/Trauma				
Senescence inflammaging		Y	Y	

Activated

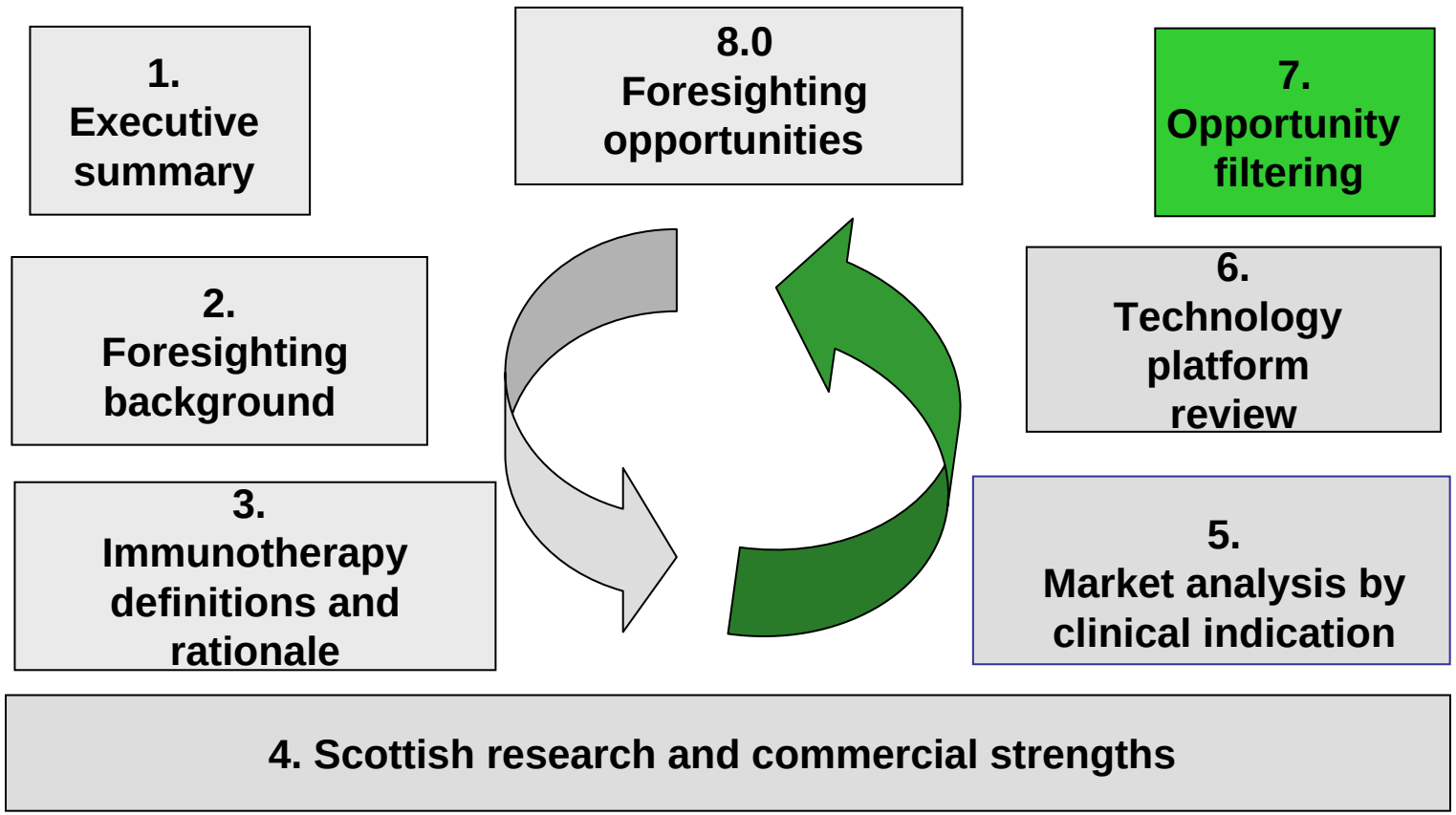
Immune activity required

Inhibited

Summary

- The two slides above summarise the relevance of all technology platforms both cellular and conventional to the disease indications surveyed.
- It is clear that most of the specific platform technologies reviewed , for example regulatory T cells, have potential relevance to multiple disease indications.
- This will be of particular relevance in further Foresighting where the possibility of leveraging a technology platform developed from its initial market into other adjacent markets would be an important selection criteria.
- The primary selection criteria in this survey, as described in the next section, is a clearly defined market and unmet need.

Part 7: Opportunity Filtering



Opportunity Filtering and Ranking

- This section describes the process of Opportunity Filtering and Ranking process used to generate a short list of accessible market opportunities which may be candidates for further Foresighting.

- The basis of this ranking exercise was based on three principal criteria:

  1. estimated market size
  2. unmet clinical need
  3. perceived technical difficulty.

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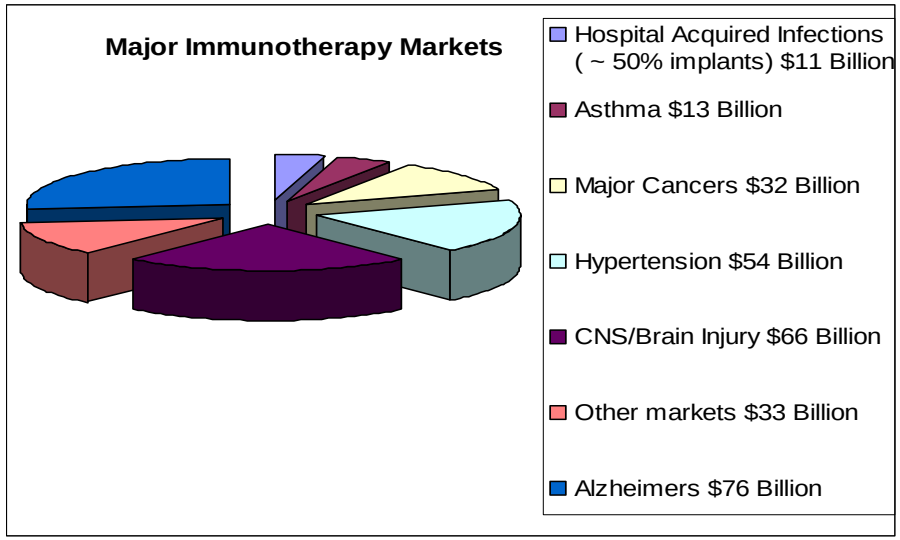
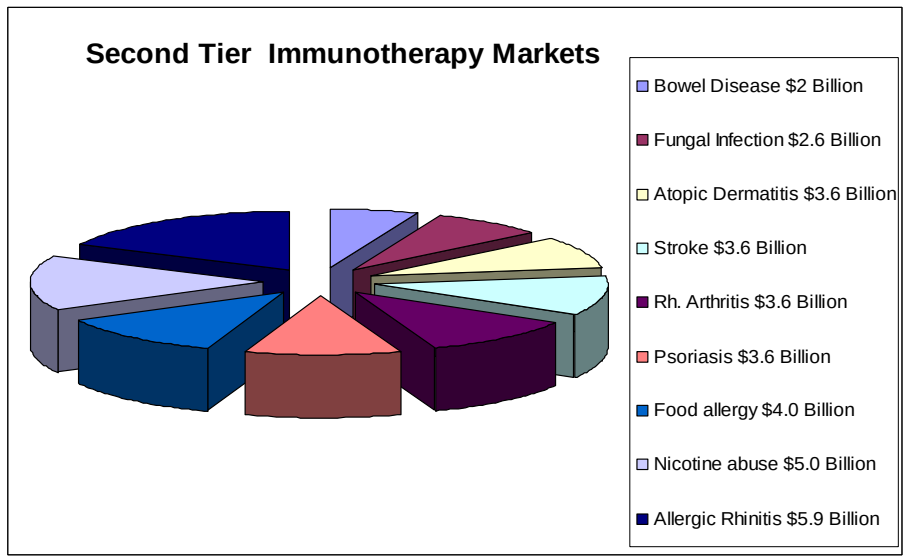
Market Opportunities Ranked by Cost of Treatment

The biggest US markets, by cost of treatment,

- Alzheimer's: $76bn
- SCI/TBI: $66bn
- Hypertension: $54bn
- Breast, lung, colon, prostate cancer: ($2–10bn for each type of cancer)
- Asthma: $13bn
- HAIs: up to $11bn p.a. in US (>50% IAIs)
- Allergic rhinitis: $5.9bn
- Nicotine/drugs of abuse: ~ $5bn
- Food allergy: ~ $4bn
- Stroke: $3.6bn
- RA: $3.6bn
- Psoriasis: $3.6bn
- Atopic dermatitis: $3bn
- Fungal infections: $2.6bn in 1998
- IBD: $2bn

* Market size indications are approximate and low patient numbers do not necessarily denote a small market by value.





Market Opportunities: Selective Exclusions

- On the basis of technical difficulty:
  - Stroke
  - SCI/TBI.
- On the basis of relatively advanced competition:
  - Alzheimer's
  - nicotine abuse.
- On the basis of an apparently low percentage of patients suitable for immunotherapy:
  - asthma
  - atopic dermatitis
  - psoriasis.

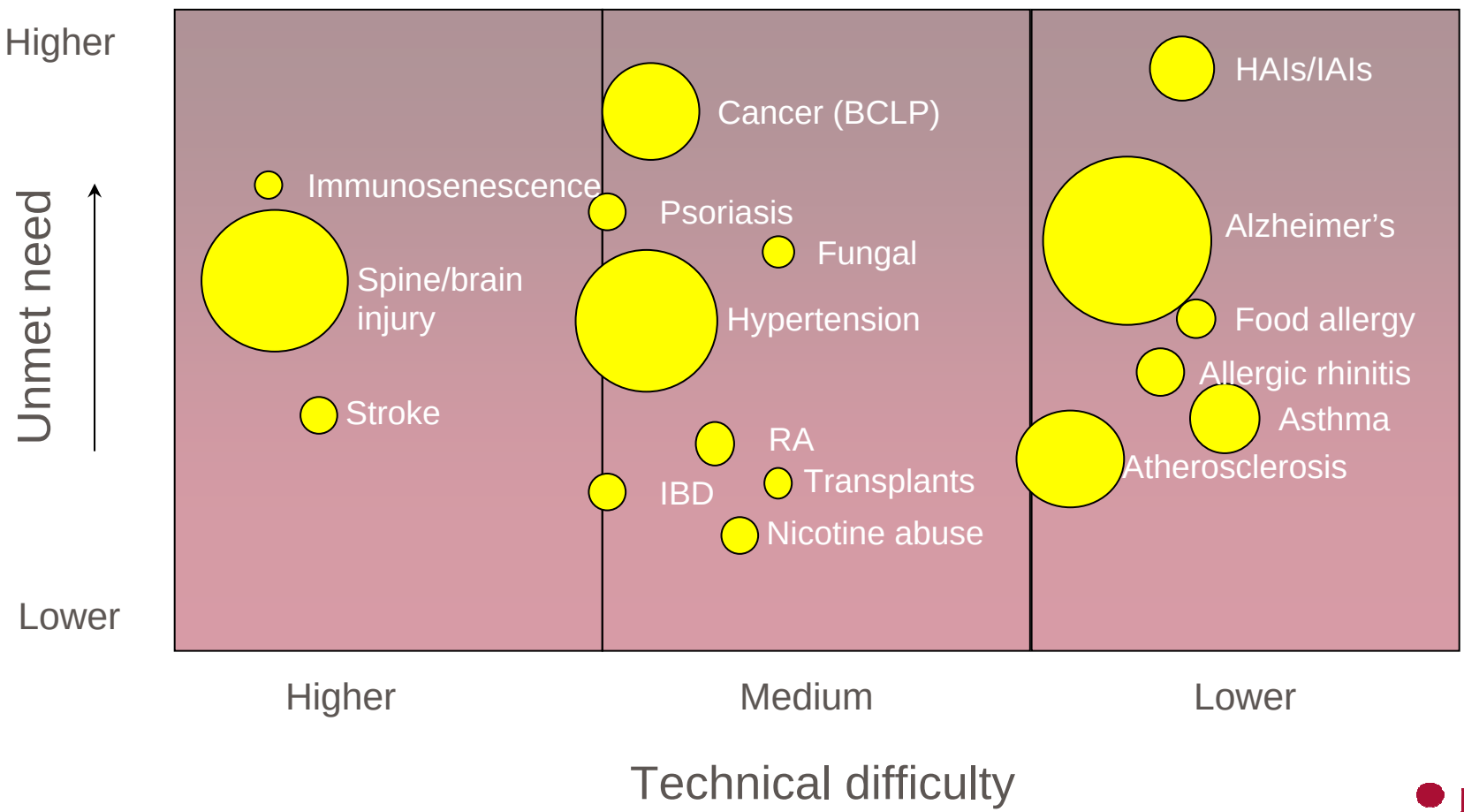
Market Opportunities Filtered by Perceived Technical Difficulty

Indication	Level of innovation required
Alzheimer's	Intermediate difficulty
SCI/TBI	Very High difficulty
Hypertension	Intermediate difficulty
Cancer	Intermediate difficulty
Asthma	Lower difficulty
HAI/IAI	Lower difficulty
Allergic rhinitis	Lower difficulty
Nicotine & drugs of abuse	Lower difficulty
Food allergy	Lower difficulty
Stroke	Very High difficulty
Rheumatoid Arthritis	Intermediate difficulty
Psoriasis	Intermediate difficulty
Atopic Dermatitis	Intermediate difficulty
Fungal	Intermediate difficulty
IBD	Intermediate difficulty

Definition of Technical Difficulty

- High: research is still at a very basic or fundamental level and long-term consolidation of the field and/or unforeseen disruptive breakthrough technologies are required to advance.
- Intermediate: R&D is at or near the “proof-of-concept” level, where there is a clear concept backed by scientific data and insight and a practical route to demonstration at prototype level.
- Lower: there are clearly identifiable technological solutions, either recently emerged or transferable from other fields of use, and market advantage derives from their rapid adaptation adoption or novel combination.

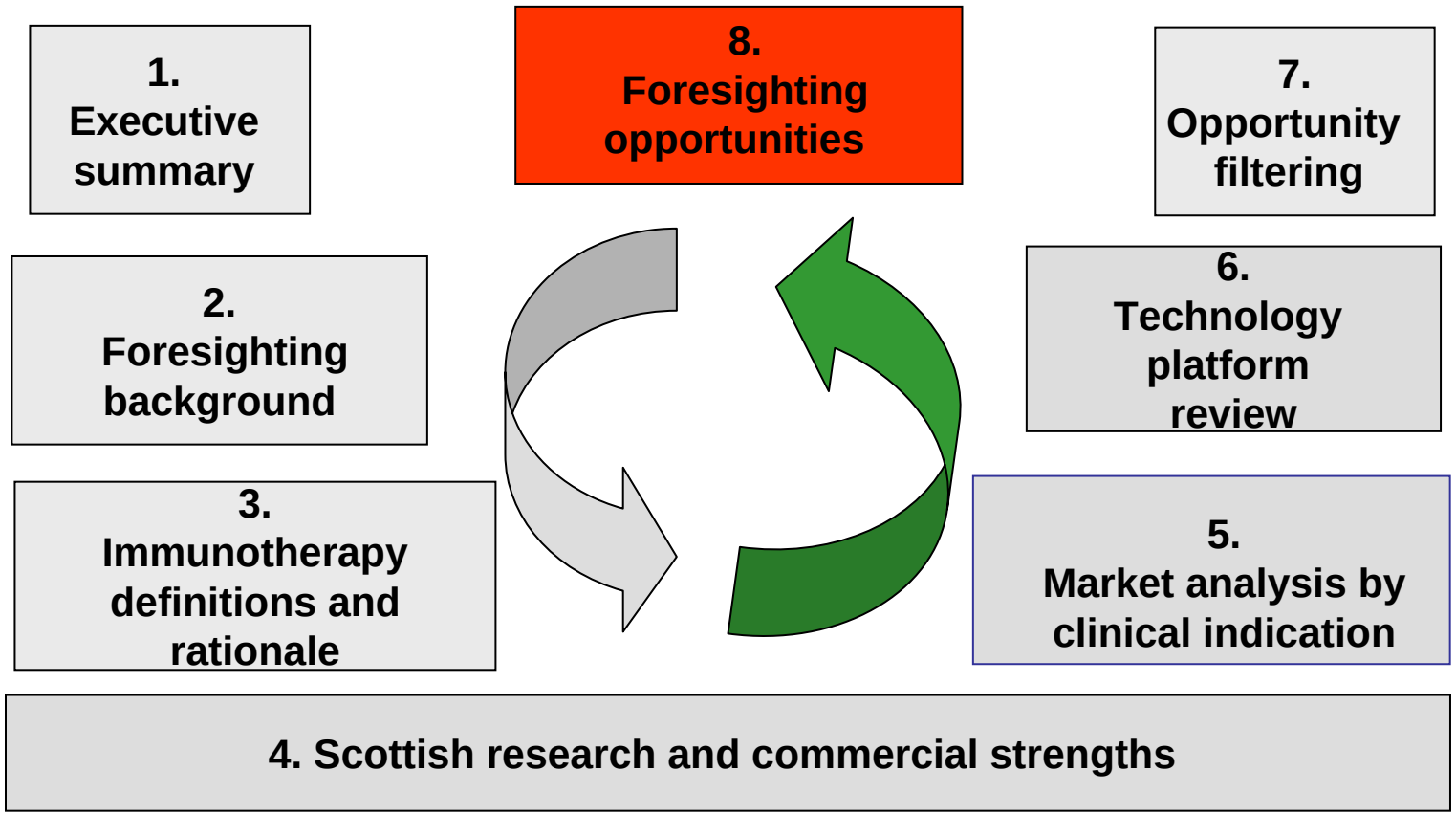
Shortlist of diseases and relative US market size



Initial Shortlist of Opportunities

Condition	US market value ($bn)	Technical difficulty	Competitive environment (provisional estimate)
HAI/IAIs	11	Lower	Low competition Unrecognised Opportunity
Fungal	2.6	Intermediate	Low competition from immunotherapies
Cancer	2–10 each	Intermediate	High competition from small mols/mAB Emerging market for immunotherapy
Hypertension	54	Intermediate	High competition Pharma
Food allergy	4	Lower	Relatively low competition
Allergic rhinitis	5.9	Lower	High competition from antihistamines Low from alternative
Inflammatory bowel disease	2	Intermediate	Medium competition
Rheumatoid arthritis	3.6	Intermediate	High–medium competition Pharma

Part 8: Potential Foresighting Opportunities



General E-scan Conclusions

- There are multiple potential market opportunities in the rapidly developing immunotherapy market space. These include interventions directed at modulating immune response to enhance disease elimination or to suppress autoimmune responses.
- A first-pass filtering exercise, primarily on the basis of market size and perceived technical difficulty, yielded a discrete short-list of potential market opportunities for novel immunotherapeutic approaches to:
  - human-acquired infections in particular of implants
  - fungal infections
  - elimination of minimal residual disease in major cancers
  - hypertension
  - food allergies and bowel autoimmune disease.
  - rheumatoid arthritis
  - allergic rhinitis (hayfever)

Foresighting: Next Steps

- Dissemination of market survey and E-scan and, where appropriate, associated background documents with Scottish commercial academic and governmental networks.
- Further detailed investigation of candidate opportunities identified in this market survey and E-scan and/or new opportunities identified by reaction to this document.
- Workshop of key immunology and immunotherapy research and commercial leaders in Scotland.
- Short-list of one or two leading opportunities that might warrant more detailed market and technical foresighting.
- Matching of any opportunity emerging from foresighting to appropriate SE/ITI programs of support.

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Glossary of terms and abbreviations

- Adjuvant : and agent that enhances the immunological effect of other agents (most notably vaccines) while having few if any direct effects itself.
- CRO : Contract research Organisation
- CNS : Central Nervous System
- Foldopathies : pathologies where the underlying cause is due to protein misfolding
- GMP : Good manufacturing processes
- LDL : low density lipoproteins
- mAB : monoclonal antibodies
- MMR Vaccine : Mumps, Measles and Rubella Vaccine
- Immunosenescence : the gradual deterioration of the immune system associated with ageing.
- siRNA : silencing RNA
- TBA : Traumatic Brain Injury
- TCR : T cell receptor
- Th(1) response – T Helper cell response which stimulates cellular response
- Th(2) response – T Helper cell response which stimulates humoral response