Emerging Drug Targets Environmental Scan December 2006

Life Sciences SCOTLAND

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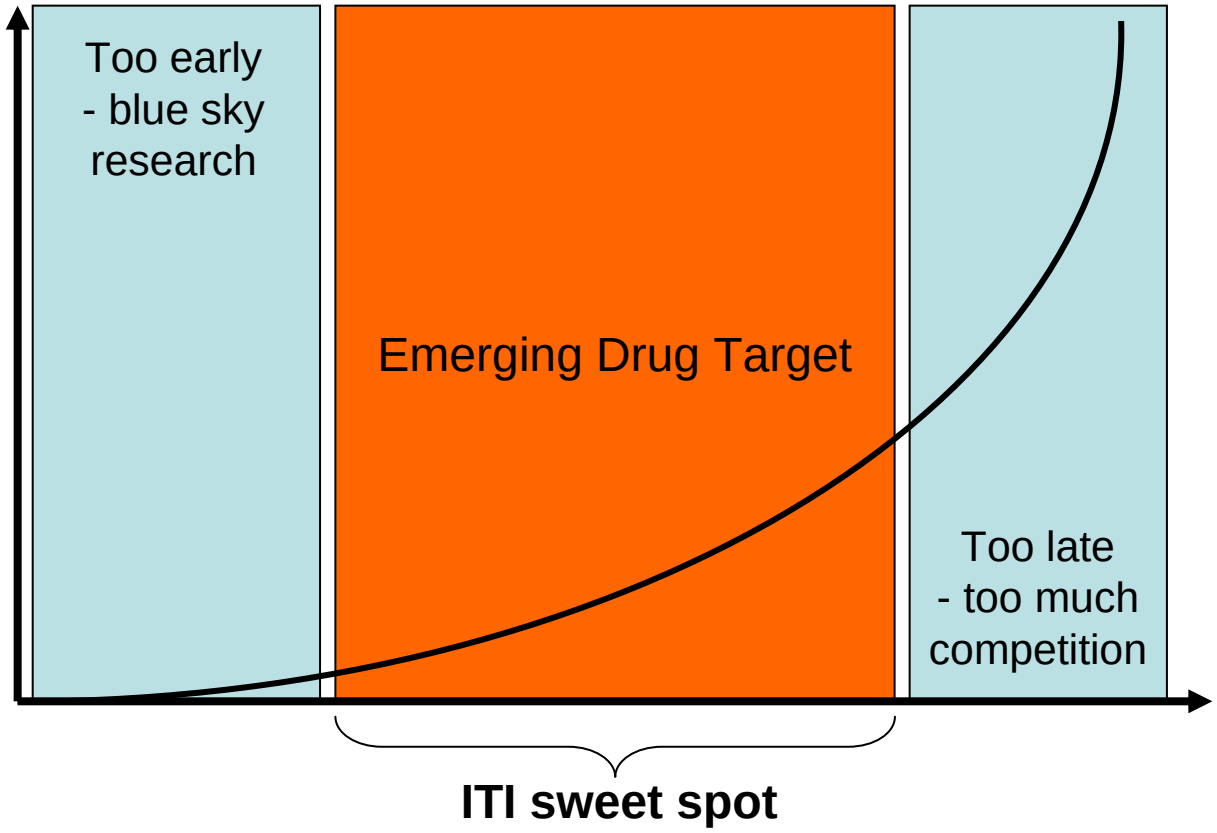
Executive Summary

- Changing market conditions have recently led to an increased number of licensing deals for early stage (preclinical / PI) lead compounds
- Opportunities therefore exist to identify key emerging drug targets of the future and develop the necessary therapeutic lead compounds and supporting technologies that may generate valuable IP and assets required to fully exploit these key targets
- Dialogue with Key Opinion Leaders, Pharma Licensing Directors, Pharma and Biotech R&D Executives, Life Sciences Venture Capital groups and Drug Identification Service Providers identified 11 key drug target classes that were anticipated to play major roles in drug discovery in the future
- Trends analysis of publication and patenting rates across these target classes was used to narrow down the targets and identify early signs of emerging areas of research
- Further stratification of these target classes allowed initial identification of waves of increased interest in novel technologies and targets, allowing us to predict what areas may translate into emerging drug targets of the future
- The results of this initial analysis allowed us to identify four emerging drug target classes that merit further analysis.
- The first two, Nuclear Receptors and Kinases are partially established target classes that still offer opportunities for additional exploitation, perhaps of subsets of the target class
- The other two are true emerging targets that have not yet been exploited in the drug discovery arena, namely Ubiquitin Ligases and miRNA and offer exciting new opportunities

What do mean by emerging drug target?

- Target lifecycle – broad definition!
- Impossible to be more specific - Target and Therapeutic Area dependent



Why look at this space now ?

Changing times within Pharma …

- Dearth of compounds in pipelines
- Many me-too compounds
- Lack of late stage (PII-PIII) licensing candidates available to fill pipeline
  - Increasing competition / auction for what late stage deals are available
  - *"Five years ago two-thirds of candidates would have only one or two companies looking to license them, while none would have attracted more than five competitors. Now nearly half of the high quality Phase III candidates have between five and eight bidders, while none have fewer than three,"* ***Merv Turner, Senior VP of Worldwide Licensing, Merck & Co. Inc***
- Increasing competition for late stage clinical assets is forcing the pharmaceutical industry to reach out to the venture capital community as a source of deals
  - Pharmas hosting orientation days with VCs exploring how they might interact symbiotically
- Licensing deals moving towards earlier stage products (Preclinical-PI candidates)
  - Licensor giving away more at earlier stages than previously witnessed
  - Broad terms often including Pharma company paying R&D costs on top of milestones
  - Critically many deals also allow co-promotion
  - *Pharma " told us that they were feeling a competitive pinch and that most of the late stage compounds that are available have been shopped around, so they are now being forced to look at opportunities that have yet to reach the clinic, and that there is a market for early stage companies,"* ***Nessan Bermingham of Atlas Venture in London.***

Conclusion: Lead molecules/series against novel, validated targets are an increasingly valuable commodity and can be outlicensed at much earlier stages of development than in the past

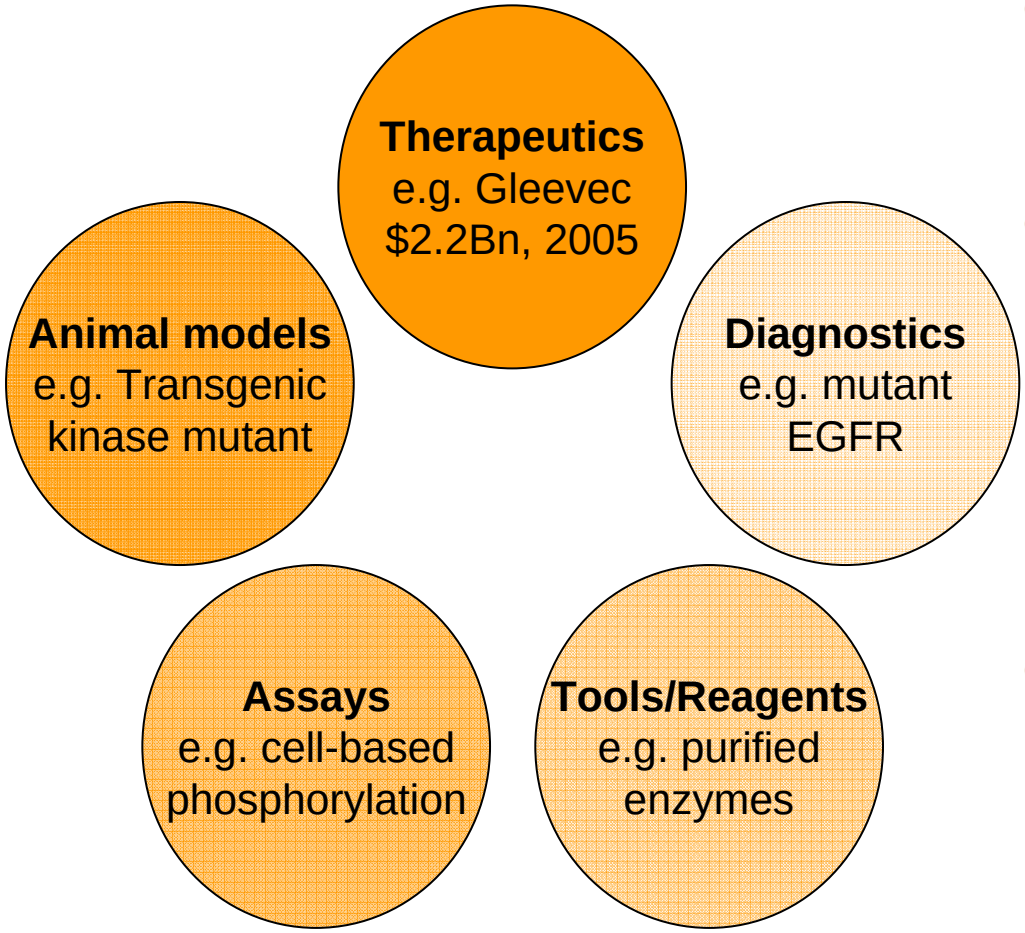
Increasing Deal Flow for Early Stage Leads

Market appetite for novel leads/preclinical/early stage clinical compounds is high (last 12 months):

- EPIX Pharmaceuticals and GlaxoSmithKline
  - GPCR inhibitors - 4 compounds, most advanced in early-stage clinical development
  - $35MM upfront, $1.2BN milestone payments, tiered double-digit royalties, co-promotion rights in US
- SGX Pharma and Novartis
  - BCR-ABL inhibitors - lead compound
  - $25MM upfront, $515MM milestone payments, minimum 2 years R&D funding & royalties
- Astex and Novartis
  - CDK inhibitors - 2 compounds, preclinical and Phase I
  - $25MM upfront, $520MM milestone payments, R&D funding & double digit royalties
- Astex and AZ
  - PKB/Akt inhibitors – lead discovery
  - $5MM upfront, $275MM milestone payments, R&D funding & double digit royalties
- Kai Pharma and Daiichi
  - PKCδ inhibitors – rights to Phase I compound in 2 indications
  - $320MM upfront and milestone payments, R&D funding & royalties
- PIramed and Genentech
  - PI-3 kinase inhibitors
  - $230MM upfront and milestone payments, R&D funding & royalties

All of this leads us to believe that there is a strong shift in the market towards earlier stage licensing deals and therefore opportunities exist to identify key emerging drug targets and develop therapeutic lead compounds and supporting technologies

Multiple Commercial Opportunities



- Identification of future emerging drug targets presents multiple opportunities for commercial exploitation along the way
- For example:
  - Novel assays that support hit identification;
  - Novel animal models that support *in vivo* target validation and proof of concept;
  - Novel diagnostic biomarkers for measuring drug efficacy, disease progression, toxicity etc
- Accurate predictions of emerging targets will allow ITI-Life Sciences to match future funded programmes to areas of increasing interest to the Biotech / Pharma community

Potential drug target class identification

Where to start….how do we try and identify areas/targets that may be of increasing interest to the Pharma/Biotech communities in the future?

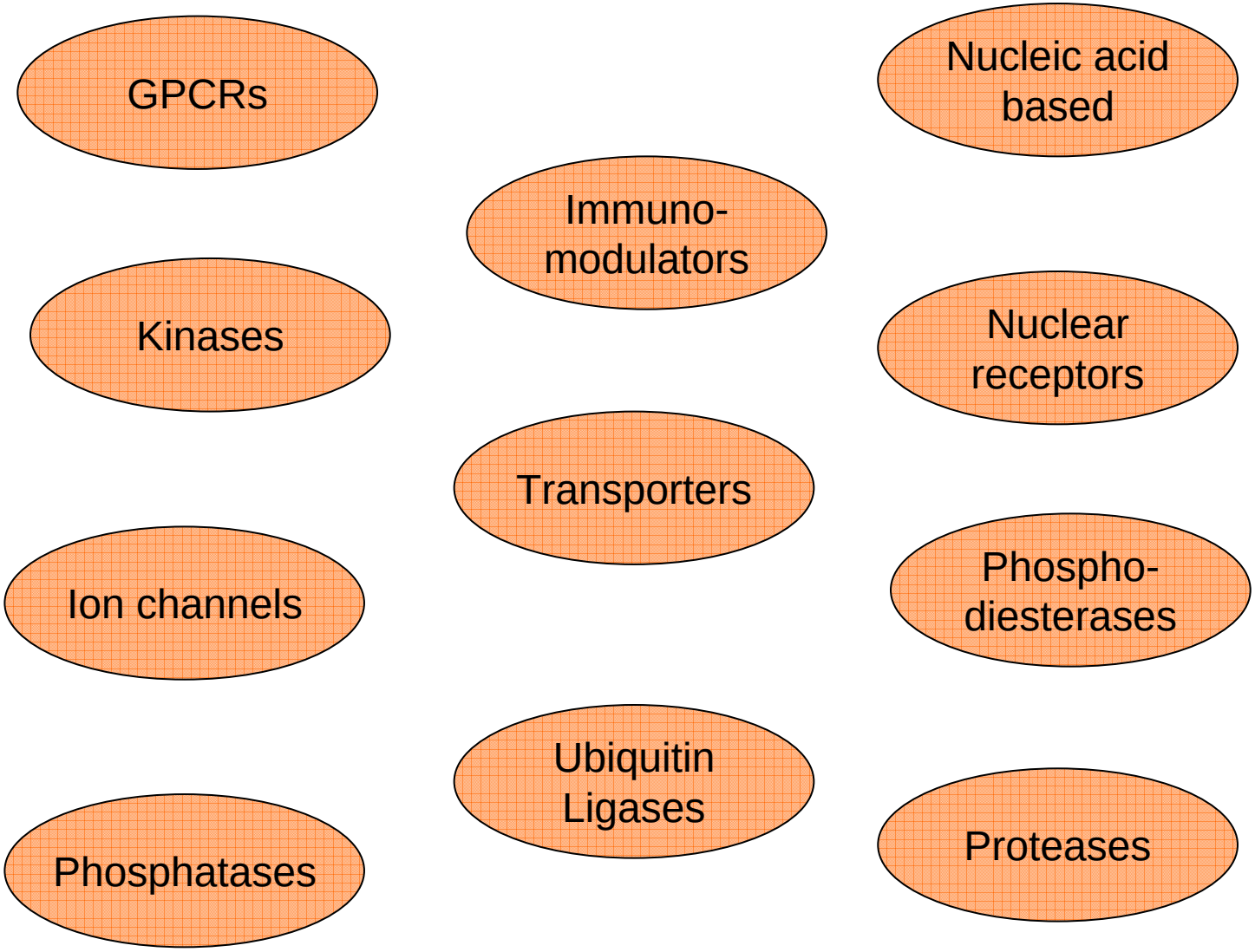
Utilise personal and Scientific Advisory Group networks to initiate dialogue with:

- Key opinion leaders – industrial and academic
- Pharma Licensing Directors
- Pharma and Biotech R&D Group Leaders
- Life Sciences Venture Capital groups
- Drug identification Service Providers

- Killer Question: What are the key drug target classes of the future ?

- The answers were collated and the most cited target classes were identified
  - The classes ranged from well established drug targets with multiple marketed products to much more speculative targets (see next page)

Most Cited Target Classes



Methods of analysis

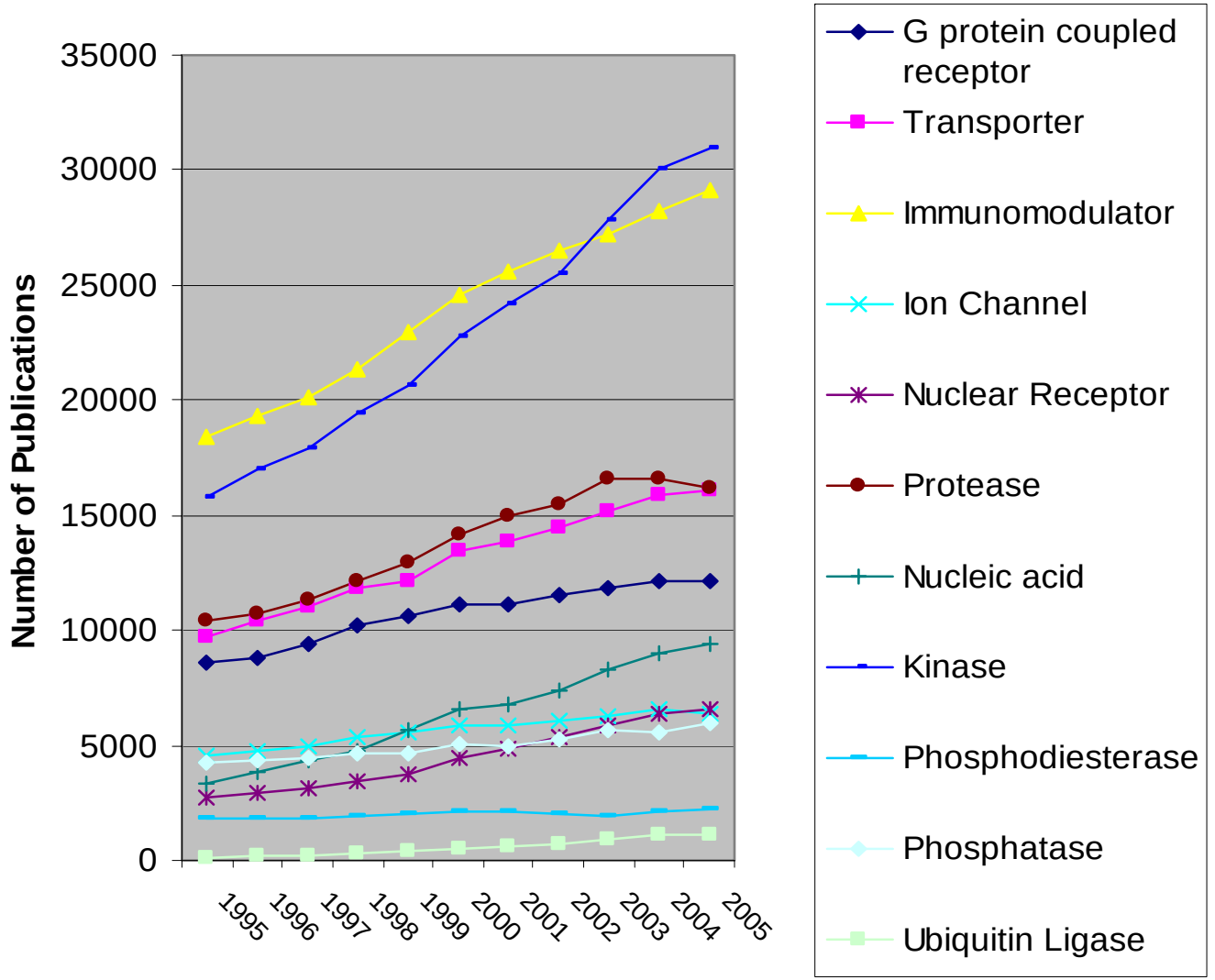
- How do you analyse such a huge field ???
- There's no right or wrong way to accomplish this
- In depth analysis of all potential molecular drug targets within each class is impossible
- In depth analysis of major classes of potential drug targets is improbable
- Analysis of trends across the major classes of drug targets is achievable in the first instance, using search terms that utilise as many of the individual targets within each class as possible, for example for
  - Immunomodulators, search on Cytokines, Chemokines, TGF, Interleukins, Toll, Toll-like receptor, Interferons, TNF
  - Nucleic Acid-based, search gene therapy, gene delivery, antisense, aptamer, ribozyme, RNAi, miRNA
- Look for early signs of emerging areas of research
  - Publications
  - Patents
- Narrowing down the haystack……triage target classes down to a manageable size, prior to more in depth analysis

Publications analysis

- The lifeblood of scientific research
- One of the earliest trends measurable

- Aim : Quantify publication sizes and rates to identify publication trends across the identified 11 target classes

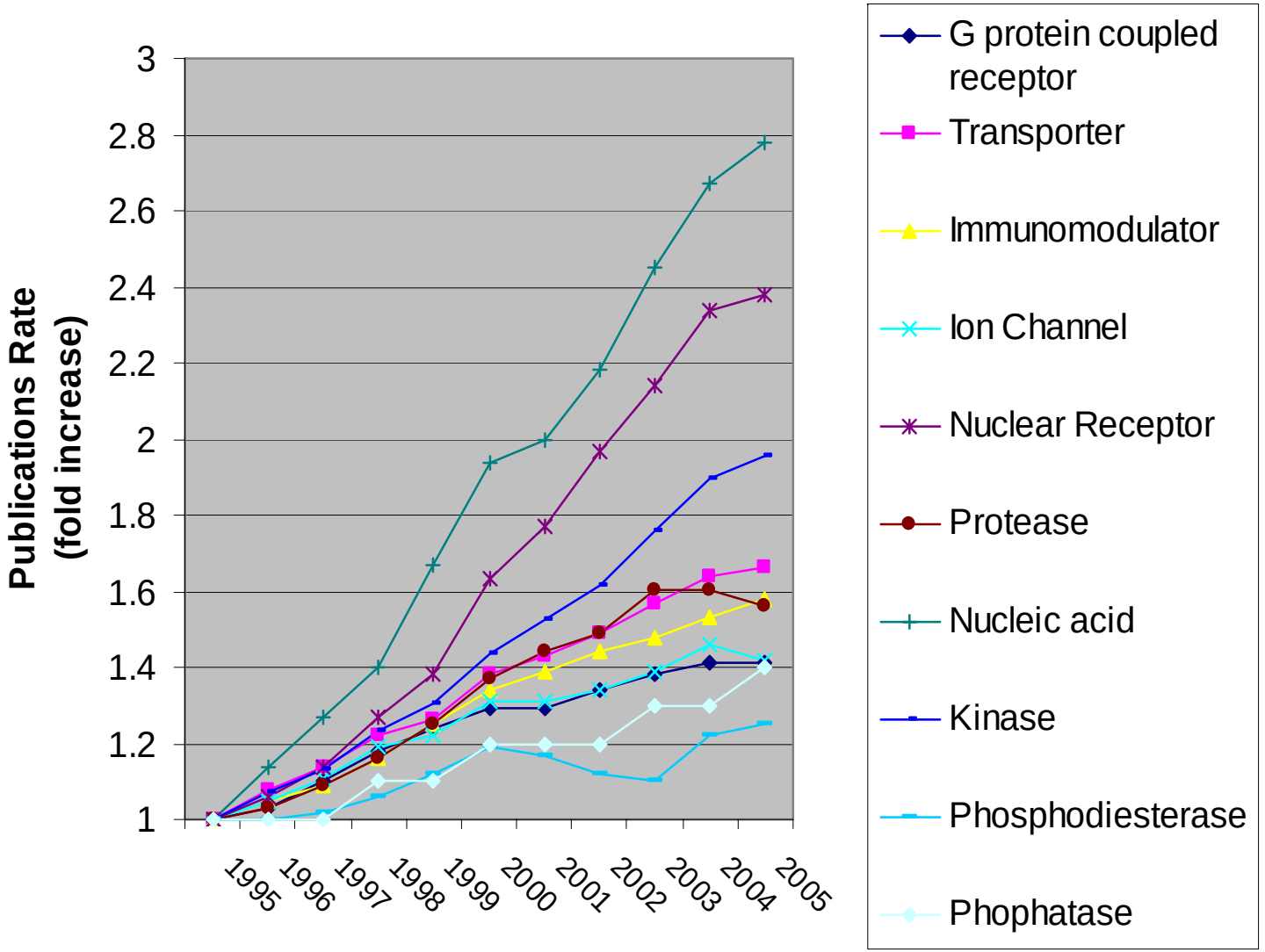
Target Classes: Publications (1995-2005)



Target Classes: Publications (1995-2005)

- Kinase and Immunomodulators research produce the greatest number of scientific publications per year, whilst Ubiquitin Ligases produce the least
- Is this good or bad (lots of interest versus lots of competition)?
- More important for trend analysis is the rate of increase in publications over time – slope of graph
- Utilise the above analysis to delineate areas of increasing publication rates and project this to future interests in target classes

Target Classes:
Annual Fold Increase in Publications (1995-2005)



√ Nuclear Receptor

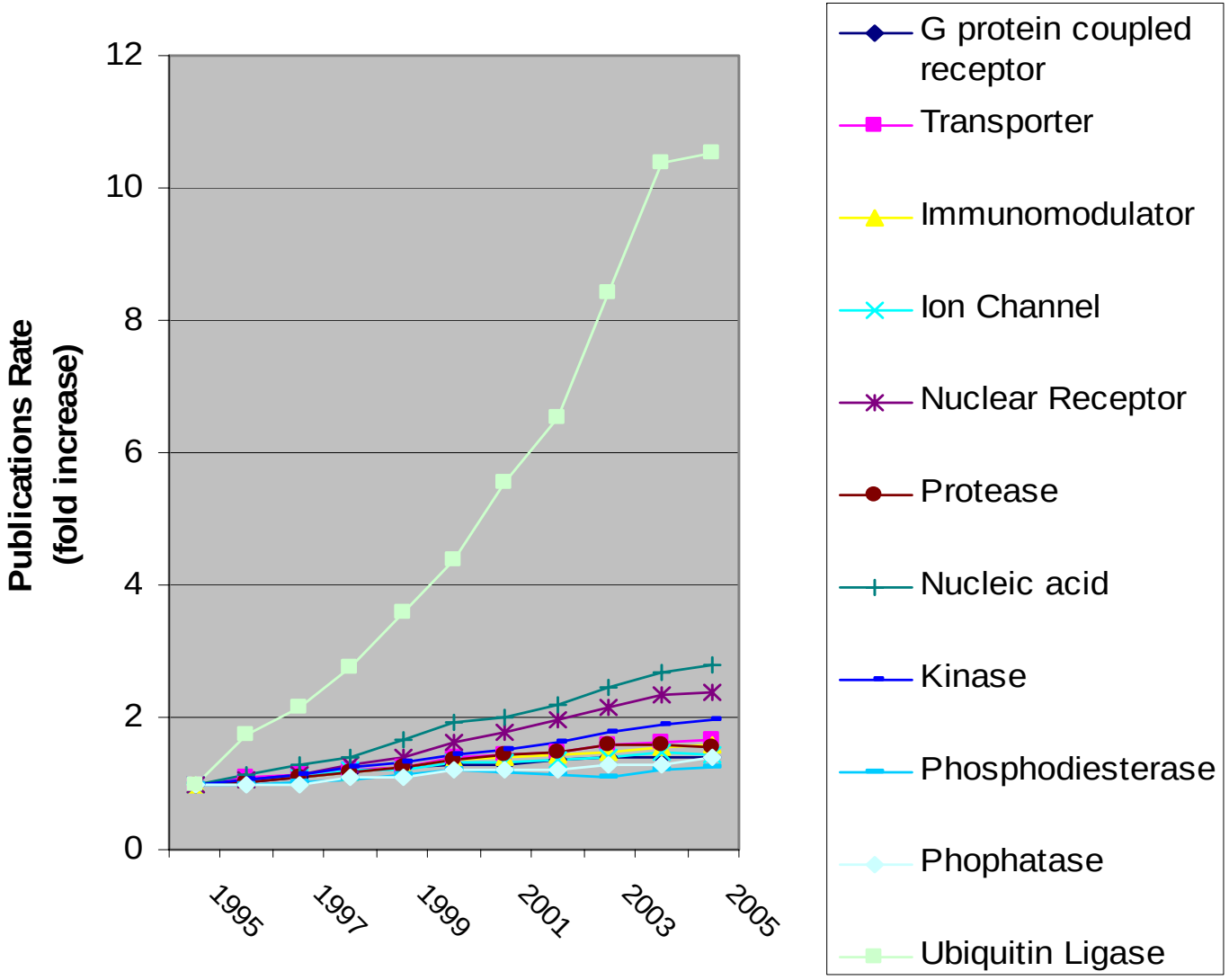
√ Nucleic acid

√ Kinase

Target Classes: Annual Fold Increase in Publications (1995-2005)

- Publication trend analysis of the top 10 drug target classes, suggests nucleic acid-based, nuclear receptors and kinases are the drug target classes with the greatest increase in publication rate at 2.8, 2.4 and 2 fold respectively
- However, this analysis has deliberately left out one of the identified target classes due to its flattening effect on the other 10 target classes …

Target Classes: Annual Fold Increase in Publications (1995-2005)



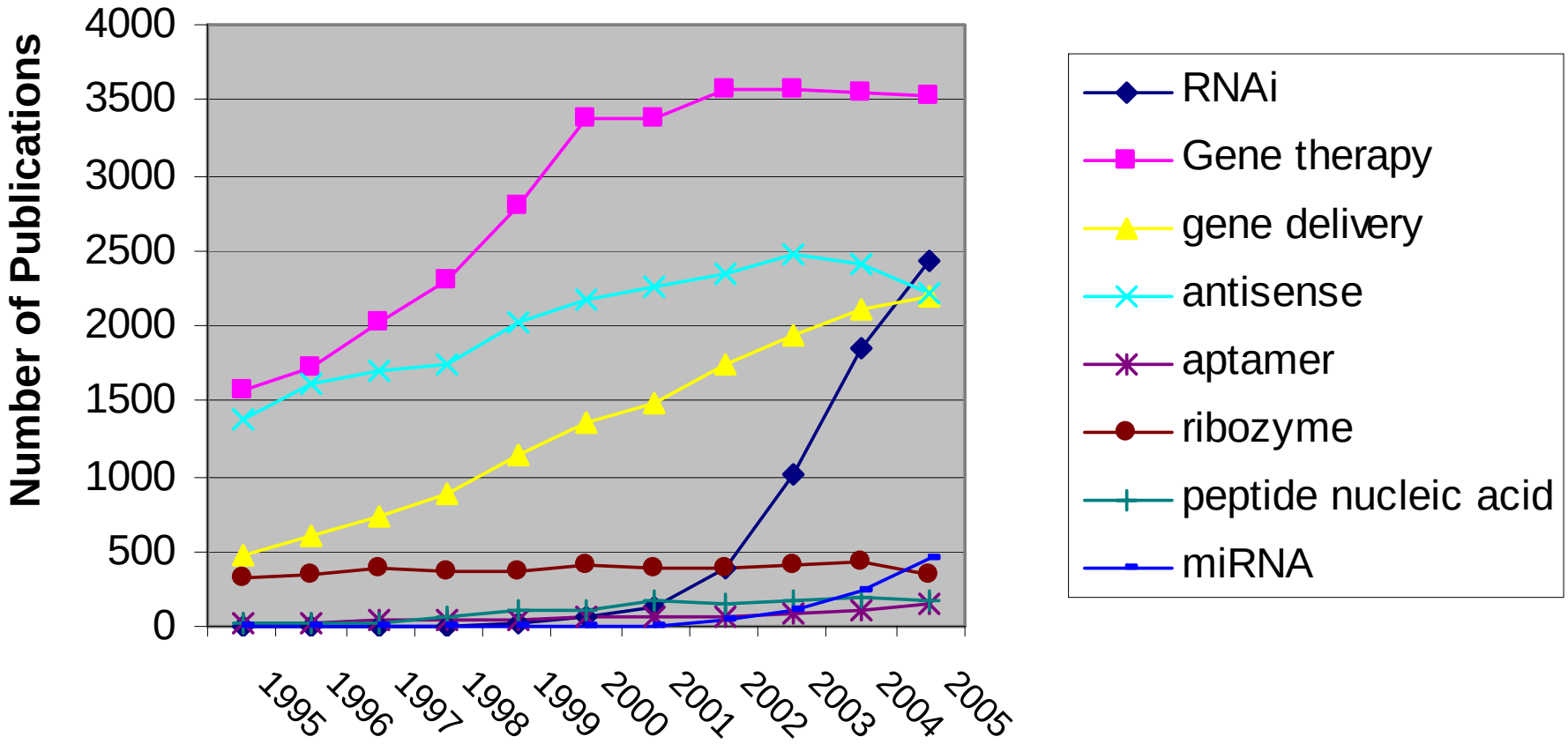
Target Classes: Analysis of Publications – Conclusions (1)

- Ubiquitin Ligases show a 10.5 fold increase in publication rates over the past decade
- This is between three and five fold greater than the next most prominent target classes (nucleic acid-based, nuclear receptors and kinases) with respect to publication trend analysis
- Results suggest that these four target classes are of increasing importance

- Additional data can also be mined from these analysis by breaking down some of the larger target classes into sub-topics and searching on these, for example Nucleic-acid based targets

Breakdown of components within Nucleic acids

- The Nucleic acid-based targets search can be further broken down to sub-searches and analysed for trends within each of these components:



Target Classes: Analysis of Publications – Conclusions (2)

- Historically, gene therapy and gene delivery were the primary drivers of publication growth within the nucleic acid-based target class
- More recently RNAi has been driving the increased publication rates in this area
- Looking to the future there may be initial indications that miRNA may be about to drive a new wave of future publications and may be a technology/therapeutic to look out for in the future
- Therefore, mining of sub-target classes may also unearth potential areas of future interest

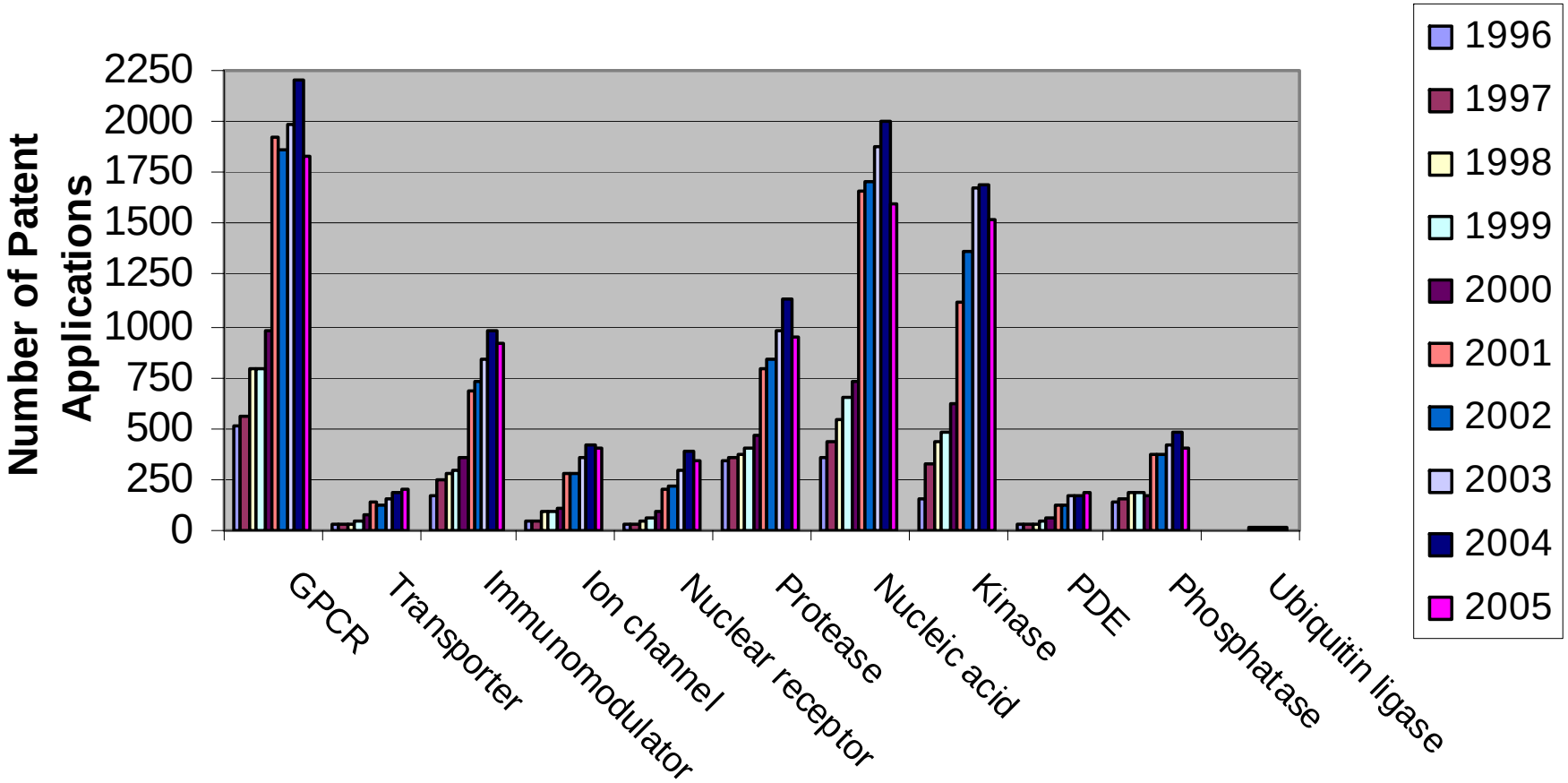
Justification for use of analysis of publications

- Is this kind of analysis useful in unearthing technologies and emerging drug targets and guiding future investments?
  - Example – RNAi - discovered by Andrew Fire and Craig Mello in 1998 (Nobel prize for Medicine in 2006)
  - Early increased interest in RNAi technology (as shown on slide 18) led to Ribozyme Pharmaceuticals deciding to change its focus from ribozymes (flat line on previous slide) to RNAi
  - In order to kick start this change in emphasis, they bought a portfolio of RNAi patents from Massachusetts Medical School in 2003
  - At the same time, they changed their name to Sirna and raised money on the back of the RNAi patents and the progression of their lead candidate for the wet form of age related macular degeneration (AMD)
  - On 30th Oct 2006, Merck announced that it was acquiring Sirna for $1.1Bn, a 100% premium on their current stock price
- Using this publication trend analysis, increasing trends in RNAi could be picked up as early as 2001-2002.
- Considered investment at this early stage, similar to Sirna, is likely to have paid large dividends.
- Using the current stratification analysis of the nucleic acid based targets, the very recent increased interest in miRNA may be the precursor to the next peak of interest within this target class

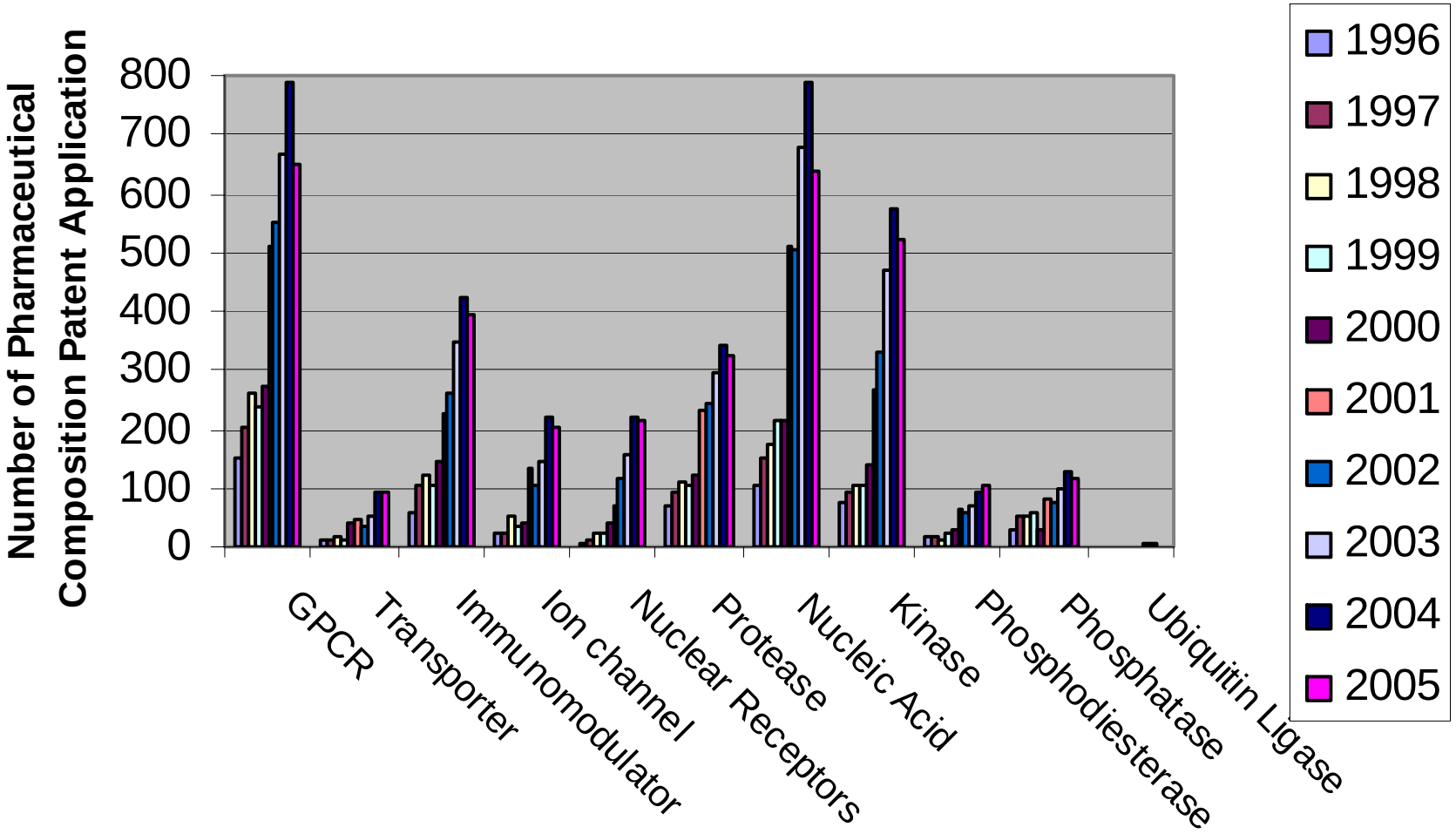
Patent Analysis

- A vision of what people are thinking will be important for the future and hence worth protecting
- A link between the academic and commercial sectors
- Analysis broken into 2 distinct patent searches:
  - General patent applications
    - All patent applications for given target class
  - Pharmaceutical composition patent applications
    - Patent applications limited to those involving pharmaceutical compositions i.e.. novel chemical entities that modulate a given target class
    - “hits” from this search are more likely to be on targets that are at a slightly more advanced stage of development

Target Classes: Patent Applications (1996-2005)



Target Classes: Pharmaceutical Patent Applications (1995-2005)

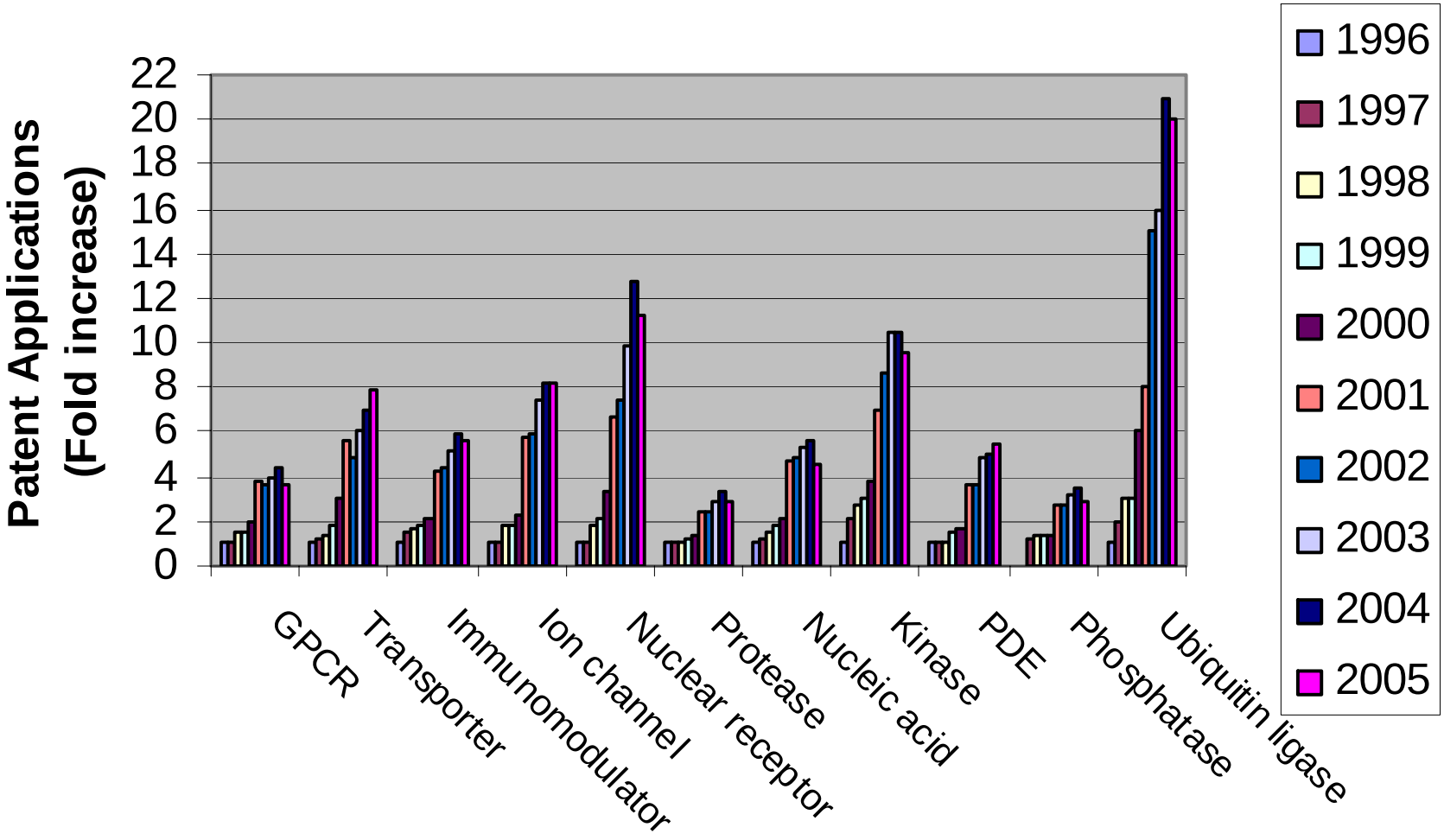


Target class: Patent Applications

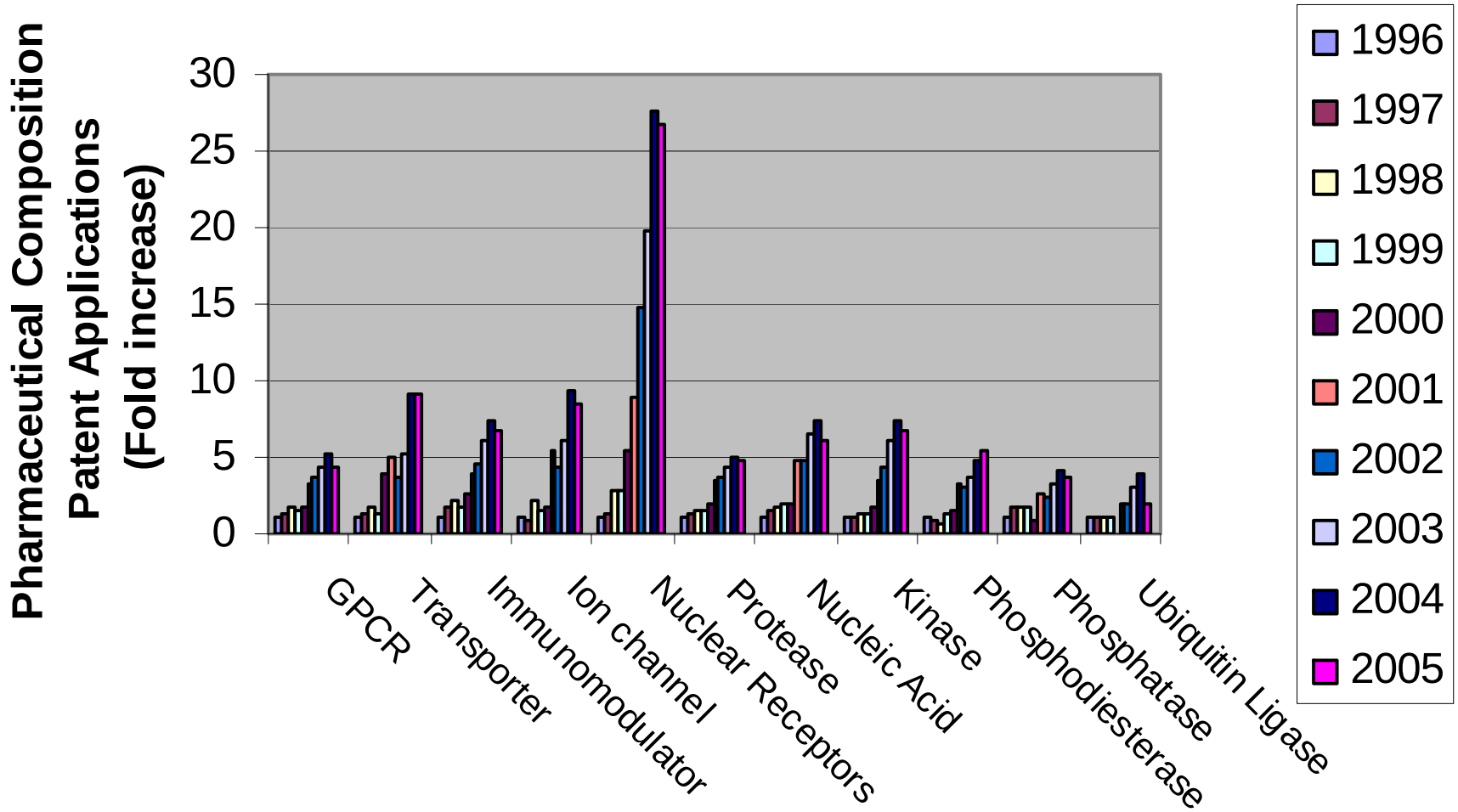
- Quantitation of patent applications and pharmaceutical composition patent applications show similar patterns of results
- GPCR, Nucleic acid-based and Kinases target classes show the highest level of patent activity across both patent searches
- Out of all the target classes analysed, Ubiquitin ligases have the least patent coverage in both searches

- What about patent trends analysis over time to delineate areas of increasing interest?

Target Classes:
Fold Increase in Patent Applications (1996-2005)



Target Classes:
Fold Increase in Pharmaceutical Patent Applications (1996-2005)



Target Classes: Analysis of Patents - Conclusions

- GPCRs, Kinases and Nucleic acid based targets generate the highest number of patents
- Ubiquitin ligases have the lowest number of patents

- Trends analysis of general patent activity and specific pharmaceutical composition patent activity show very distinct profiles over time for specific target classes
  - Ubiquitin ligases, nuclear receptors and kinases show the highest rate of increase in general patent activity, suggesting these target classes are of increasing interest, whereas proteases and phosphatases show the lowest rate of increase
  - When the rate of increase in pharmaceutical composition patents are analysed however, nuclear receptors show by far the greatest rate of increase, suggesting that this target class is of increasing interest, particularly at later stages of development

Overall Conclusions

Taking into account the results from both the publications and patents trend analysis, three target classes stand out as being of interest as we proceed into more in depth analysis:

1. Nuclear Receptors
   - Intermediate number of publications (6,500) but increasing at an elevated rate (2.4 fold)
   - Intermediate number of patent applications but large increase in rate of general patent activity (13 fold) and largest increase in rate of pharmaceutical composition specific patents (27 fold)
   - Target class is of increasing interest but likely to be at advanced stage of target development

2. Kinases
   - Highest number of publications (31,000) and increasing at elevated rate (2 fold)
   - High number of patent applications with a large increase in rate of general patent activity (11 fold) and intermediate increase in pharmaceutical composition specific patents (7 fold)
   - Popular target class but still showing signs of increasing interest. Potential opportunities may be identified within a subset of this target class

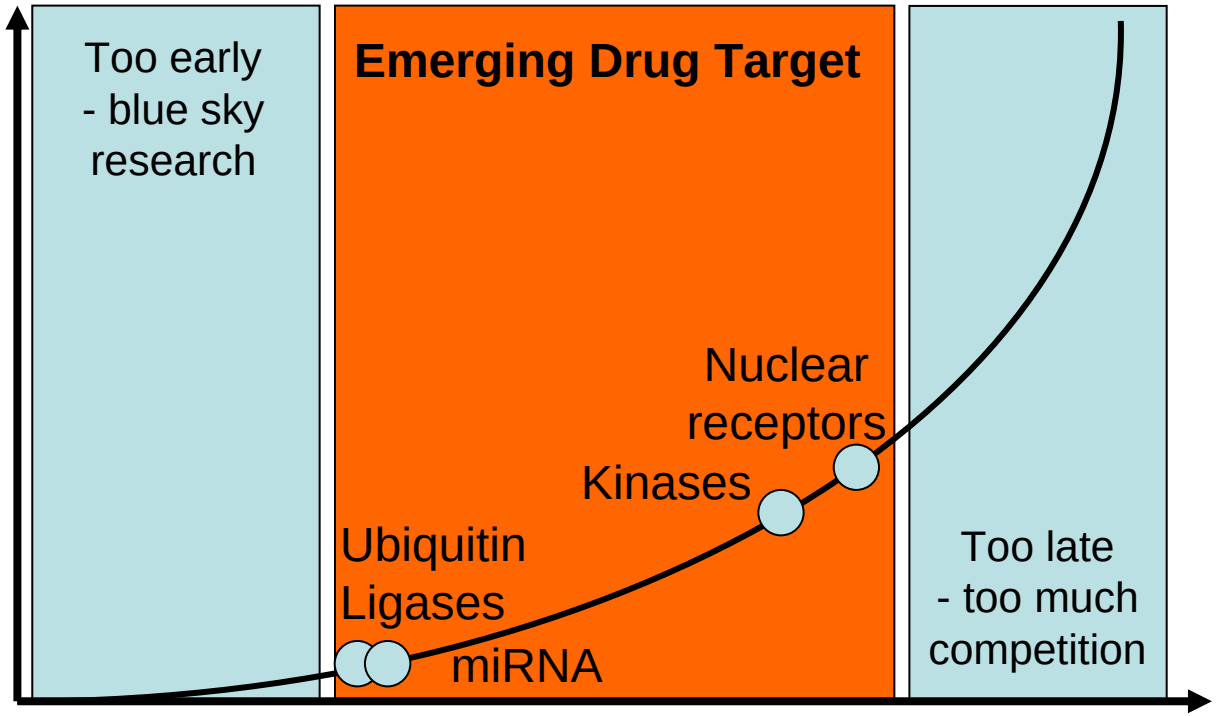
3. Ubiquitin Ligases
   - Lowest number of publications (1,000) but increasing at highest rate (10.5 fold)
   - Lowest number of patent applications but largest increase in rate of general patent activity (21 fold), but smallest increase in rate of pharmaceutical composition specific patents (4 fold)
   - Very early stage targets that have been identified but not yet exploited. Lots of opportunities for Foreground IP generation

In addition, initial stratification of the nucleic acid based target class suggests that miRNA may also be an additional early stage specific target class/technology that requires further in depth analysis.

All four areas may be advanced to the next stage of our process, In Depth Analysis, where additional filters will be applied to narrow down the potential opportunities

Emerging drug targets lifecycle

- Based on this initial analysis, the previously mentioned target classes all fall within our definition of the Emerging Drug Target field
- Ubiquitin ligases and miRNA occupy an early stage opportunity, whereas Kinases and Nuclear Receptors both offer later stage opportunities that would require further definition



Next steps …

- Ubiquitin Ligases, miRNA, Nuclear Receptors and Kinases have been identified as potential target classes from this initial analysis and warrant progression to the next stage of our process, In Depth Analysis
- This is an *Ongoing process* and this Environmental Scan is the precursor to a more in depth Foresighting report which will be released in March 2007
- Further analysis will include:
  - An in depth investigation of a selected target class including a breakdown of the drivers, challenges and competition within the area
  - Additional stratification to identify potential opportunities within the selected class
  - Scottish fit
- ITI-LS would like to engage with people with ideas for additional novel target *classes* (not individual molecules) as well as those involved in the identified target classes
- To ensure that our Foresighting is as comprehensive and rigorous as possible, and to determine if and where opportunities lie within the identified areas, we would very much welcome dialogue with our Members.
- To arrange a discussion, please contact us at
  - foresighting@itilifesciences.com or Tel: 01382 568060